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STUDIES TOWARD THE TOTAL SYNTHESIS OF (±)-AGELASIMINE A AND ITS ANALOGS, AND DEVELOPMENT OF THE TANDEM OXY-COPE/ENE/CLAISEN REACTION

By

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A Thesis Submitted to the School of Graduate Studies and Research In Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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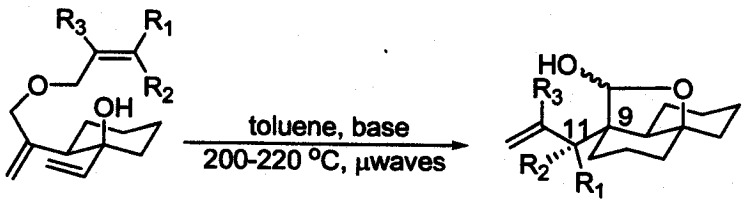
LIST OF ABBREVIATIONS

AcO	acetate
BBN	borabicyclo[3.3.1]nonane
Bn	benzyl
Bu	butyl
Cat.	catalyst
COSY	correlation spectroscopy
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DME	1,2-dimethoxyethane
DIBAL-H	diisobutylaluminumhydride
DMA	N,N-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
E^+	electrophile
Et	ethyl
equiv	equivalents
GC	gas chromatography
GC/MS	gas chromatography/mass spectrometry
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrum
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamine
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethyl
mp	melting point

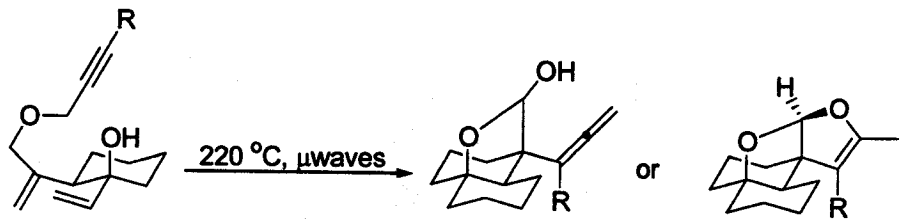
ms	molecular sieves
NMO	N-methylmorpholine oxide
NOE	nuclear Overhauser enhancement
NOESY	nuclear Overhauser effect spectroscopy
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
ppm	parts per million
Py	pyridine
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofurane
THP	tetrohydropyrane
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMDA	N,N,N',N'-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
p-TsOH	*p*-toluenesulfonic acid
Ts	*p*-toluenesulfonyl

ABSTRACT

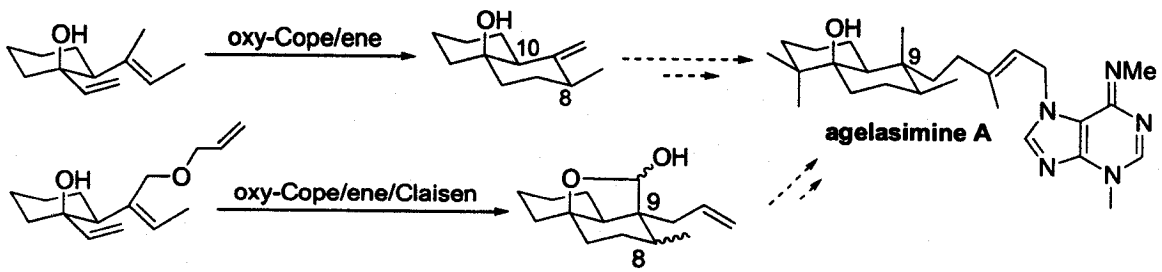
The discovery and development of a novel tandem oxy-Cope/ene/Claisen reaction is described. The strategy allows for highly diastereoselective formation of *trans*-decalins having a quaternary carbon center at C9. Depending on the substitution pattern of the terminal olefin of the starting 1,2-divinylcyclohexanol an additional tertiary or quaternary carbon center can be introduced at C11.



The oxy-Cope/ene/Claisen reaction of 1,2-divinylcyclohexanol propargyl ethers provides decalines possessing an allene moiety.

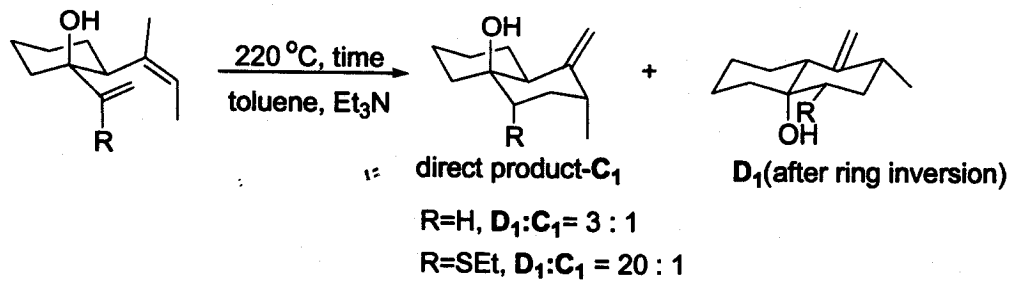


An approach toward the total synthesis of (±)-agelasimine A, a clerodane-related diterpene isolated from orange sponge *Agelas mauritiana*, via the oxy-Cope/ene and the oxy-Cope/ene/Claisen reaction has been investigated.



The factors affecting the selectivity at C8 during the oxy-Cope/ene reaction have been studied in detail. Control over the selectivity at C8 can be achieved by either increasing the

energy difference between transition states of the ene-reaction or changing the electronic properties of the substituent α to the carbonyl.

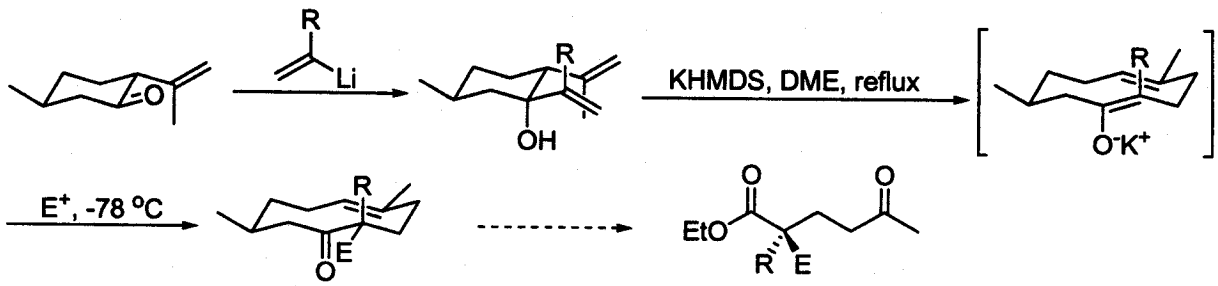


direct product-C_1 D_1(after ring inversion)

R=H, D_1:C_1= 3 : 1

R=SEt, D_1:C_1 = 20 : 1

The new approach toward formation of the quaternary carbon centers via an anionic oxy-Cope/alkylation reaction is also described. The anionic oxy-Cope reaction affords the macrocyclic enolate, which geometry is predetermined by the stereochemistry of the starting material and a chair-like transition state of the oxy-Cope reaction. The conformation of the macrocycle provides excellent means for controlling facial approach of the electrophile in the following alkylation step. Cleavage of the resulting macrocyclic ketone would afford a chiral ester bearing a quaternary carbon center α to a carbonyl.



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ITHAKA

``As you set out for Ithaka
hope your road is a long one,
full of adventure, full of discovery.
Laistrygonians, Cyclops,
angry Poseidon - don't be afraid of them:
you'll never find things like that one on your way
as long as you keep your thoughts raised high,
as long as a rare excitement
stirs your spirit and your body.
Laistrygonians, Cyclops,
wild Poseidon - you won't encounter them
unless you bring them along inside your soul,
unless your soul sets them up in front of you.

Hope your road is a long one.
May there be many summer mornings when,
with what pleasure, what joy,
you enter harbours you're seeing for the first time;
may you stop at Phoenician trading stations
to buy fine things,
mother of pearl and coral, amber and ebony,
sensual perfumes of every kind -
as many sensual perfumes as you can;
and may you visit many Egyptian cities
to learn and go on learning from their scholars.

Keep Ithaka always in your mind.
Arriving there is what you're destined for.
But don't hurry the journey at all.
Better if it lasts for years,
so you're old by the time you reach the island,
wealthy with all you've gained on the way,
not expecting Ithaka to make you rich.

Ithaka gave you the marvellous journey.
Without her you wouldn't have set out.
She has nothing left to give you now.
And if you find her poor, Ithaka won't have fooled you.
Wise as you will have become, so full of experience,
you'll have understood by then what these Ithakas mean.``

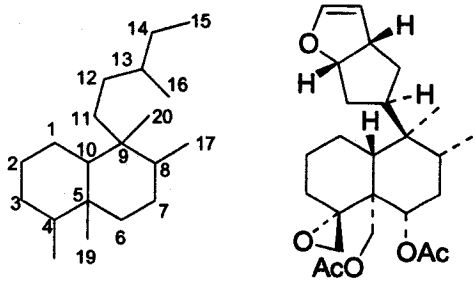
Constantine P. Cavafy

``To my family.....``

Chapter 1 Introduction

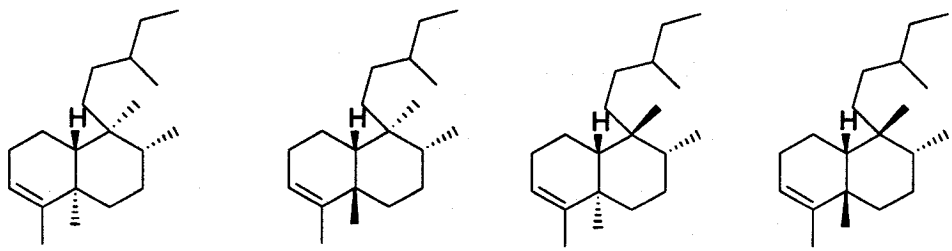
1.1 Clerodane diterpenes

Diterpenes possessing a carbon skeleton **1.1** as shown in Figure 1.1 belong to the clerodane family, which has been named after clerodin **1.2**, an antifeedant isolated from Verbenaceae plants.[1] More then a thousand compounds from this family have been isolated, mostly from higher plants, marine sponges and microorganisms. A distinct structural feature of the clerodanes is a presence of four contiguous chiral centers C5-C10-C9-C8 on the decalin core with a quaternary carbon center at C9 and a center at C4 usually sp^2 hybridized. There are four structural types of clerodanes (*trans-trans, trans-cis, cis-cis, cis-trans*), which are distinguished by the relationship between the stereocenters at the ring junction and the methyl groups at C8 and C9 as shown in Figure 1.2.



1.1 **1.2**

Figure 1.1 Clerodane skeleton

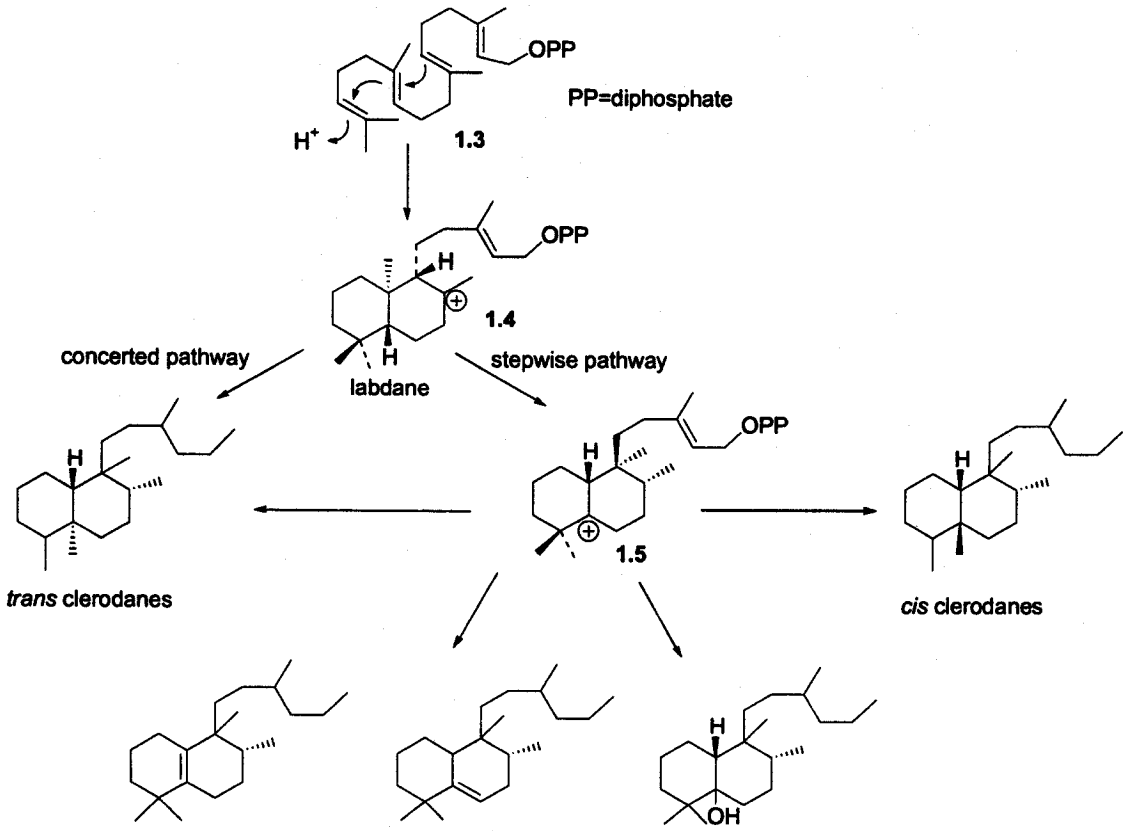


trans-cis *cis-cis* *trans-trans* *cis-trans*

Figure 1.2 Structural types of clerodanes

[1] Merrit, A.T.; Ley, S.V. *Nat. Prod. Rep.* **1992**, *1*, 243.

The biosynthesis of clerodanes involves a rearrangement of labdane skeleton **1.4**, which originates from geranylgeranyldiphosphate **1.3** as illustrated in Scheme 1.1. While concerted hydride and methyl group migration leads to *trans*-clerodanes, the stepwise process gives intermediate carbocation **1.5**. The latter can undergo migration of the methyl to afford either *cis* or *trans* clerodanes. This intermediate can also react via other pathways such as elimination of the proton, or nucleophilic attack by water.



Scheme 1.1 Biosynthesis of clerodanes

A few compounds with the partially rearranged labdane skeleton, such as marine products ambiol B,[2] agelasimine A and B[3] and plant products chettaphanines[4] have been isolated and

[2] a) Walker, R.P.; Faulkner, D.J. *J. Org. Chem.* **1981**, *46*, 1098. b) Walker, R.P.; Rosser, R.M.; Faulkner, D.J.; Bass, L. S.; He, C. H.; Clardy, J. *J. Org. Chem.* **1984**, *49*, 5160.
[3] Fathi-Afshar, R.; Allen, T.M. *Can. J. Chem.* **1988**, *66*, 45.
[4] a) Sato, A.; Kurabayashi, M.; Nagahori, H.; Ogiso, A.; Mishima, H. *Tetrahedron Lett.* **1970**, *11*, 1095. b) Sato, A.; Kurabayashi, M.; Ogiso, A.; Mishima, H. *Tetrahedron Lett.* **1971**, *12*, 838.

characterized (Figure 1.3). This provides strong evidence for the proposed biosynthetic mechanism. There are also a number of compounds structurally related to clerodanes, such as dysidiolide (Figure 1.3), the marine sponge metabolite that exhibits significant anticancer activity.[5] Many clerodanes exhibit antifeedant and insecticidal activities.[6] In addition, cytotoxic,[7] anti-peptic-ulcer,[8] psychotropic[9] and antimicrobal[10] activity have also been reported.

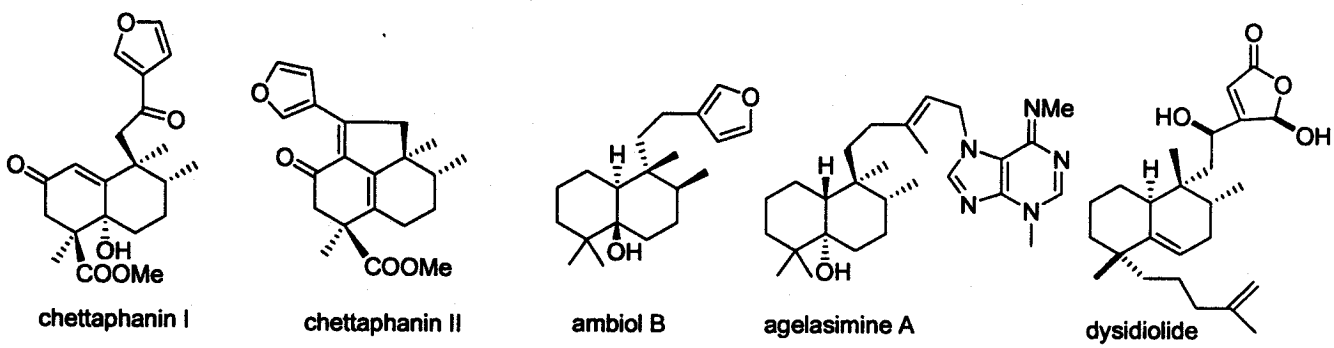


Figure 1.3 Various clerodane related diterpenes

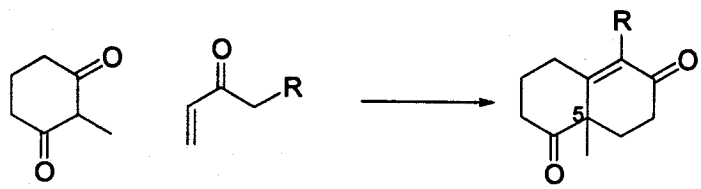
1.2 Synthesis of clerodanes and related diterpenes

The major challenge in the synthesis of clerodanes is the stereoselective construction of four contiguous stereocenters C5-C10-C9-C8. Several synthetic strategies have been developed since early 1970's. A recent comprehensive review by Tokorayama provides a detailed classification of these methods based on the sequence in which the four stereocenters are

[5] Gunasekera, S.P.; McCarthy, P.J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759.
[6] a) Kubo, I.; Lee, Y.W.; Balogh-Nair, V.; Nakanishi, K.; Chapya, A.J. *J. Chem. Soc. Chem. Commun.* **1976**, *22*, 949. b) Kubo, I.; Klocke, J.A.; Miura, I.; Fukuyama, Y. *J. Chem. Soc. Chem. Commun.* **1982**, *11*, 618.
[7] Koike, K.; Cordell, G.A., Farnsworth, N.R.; Freer, A.A.; Gilmore, C.J.; Sim, G.A. *Tetrahedron*, **1980**, *36*, 1167.
[8] Kitazawa, E.; Ogiso, A.; Takahashi, S.; Sato, A.; Kurabayashi, M.; Kuwano, H.; Hata, T.; Tamura, C. *Tetrahedron Lett.* **1979**, *19*, 1117.
[9] Valdes III, L.J.; Butler, W.M.; Hatfield, G.M.; Paul, A.G.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 4716.
[10] Andersen, N.R.; Rasmussen, P.R. *Tetrahedron Lett.* **1984**, *25*, 465.

installed.[11] Although the presence of the quaternary center at C9 and the methyl group at C8 are characteristic of the clerodane skeletone, the C5 and C10 stereocenters are intrinsic to *trans* and *cis* decalin systems found in a vast number of polyterpenoids. Thus, it is not surprising that the methods employed in the synthesis of clerodanes are those traditionally applied for the construction of *trans* and *cis* decalins. Some of the classical synthetic approaches include Robinson and other aldol related annulations and inter- and intramolecular Diels-Alder reaction.[12]

The Robinson annulation has been extensively exploited in the synthesis of terpenoids and steroids. It generally provides an unsaturated decalin, which can be further transformed to *cis* or *trans* decalin. The Wieland-Miescher (W-M) type diketones are readily available in racemic and enantiomerically pure forms via the Robinson annulation of the 2-methyl-1,3-cyclohexanedione and corresponding α,β-unsaturated ketone as shown in Scheme 1.2.

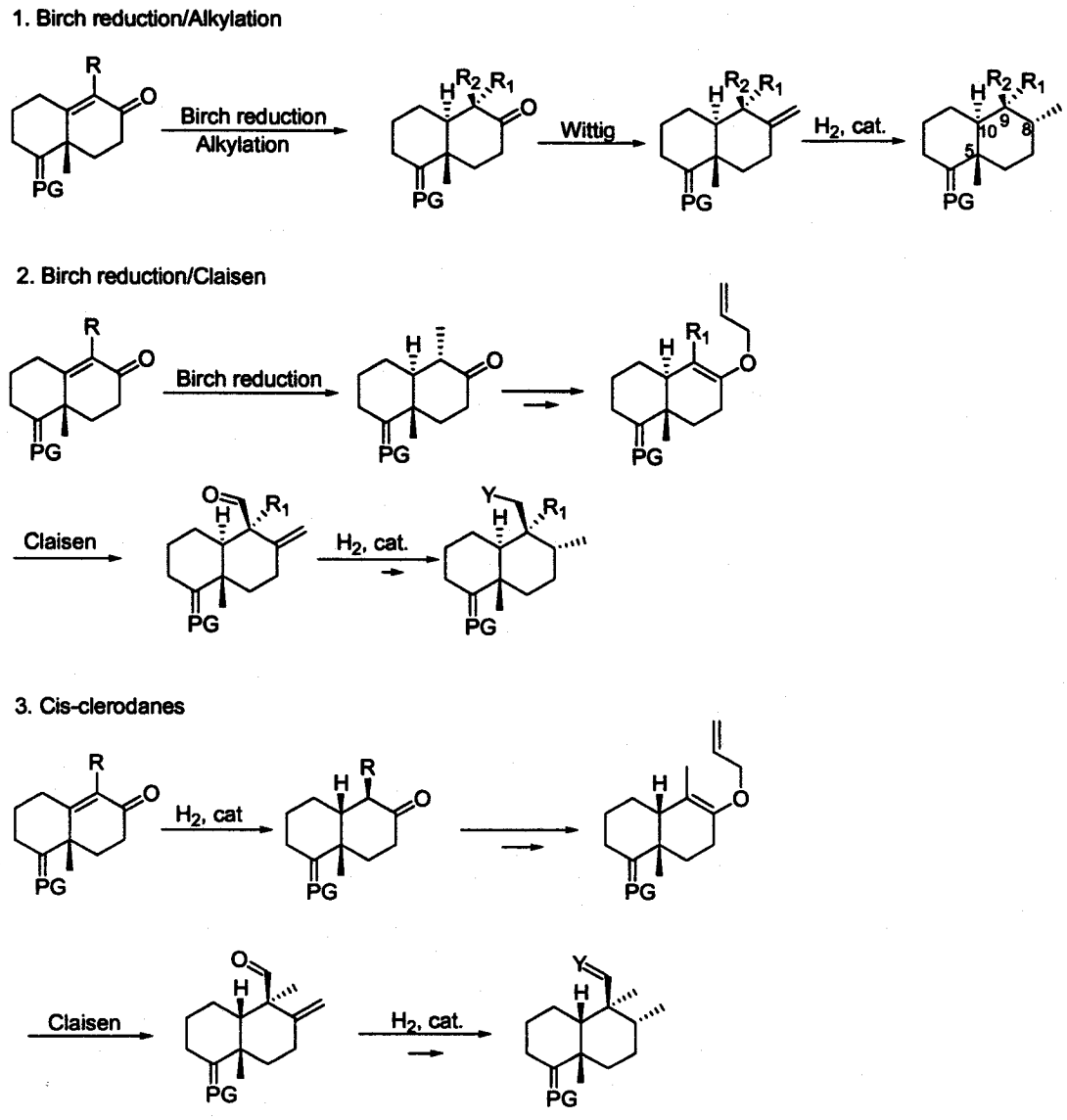


Scheme 1.2 Wieland-Miescher ketones

W-M diketones are common starting materials for synthesis of diterpenes. Only the stereocenter at C5 is initially present. The remaining centers have to be introduced in a stepwise process. The synthesis usually begins by protecting the non-conjugated keto-group. Reduction of the alkene then follows, which, depending on the conditions, can afford either *trans* (Birch reduction) or *cis* (catalytic hydrogenation) ring junction, thus introducing the

[11] a) Tokoroyama, T. *Synthesis* **2000**, *5*, 611. For earlier review see b) Tokoroyama, T. *J. Synth. Org. Chem. (Jpn)* **1993**, *51*, 1164.
[12] For reviews see a) Varner, M.; Grossman, R.G. *Tetrahedron* **1999**, *55*, 13867. b) Ho, T.L. In *Carbocycle Construction in Terpene Synthesis*; VCH: Weinheim, 1988.

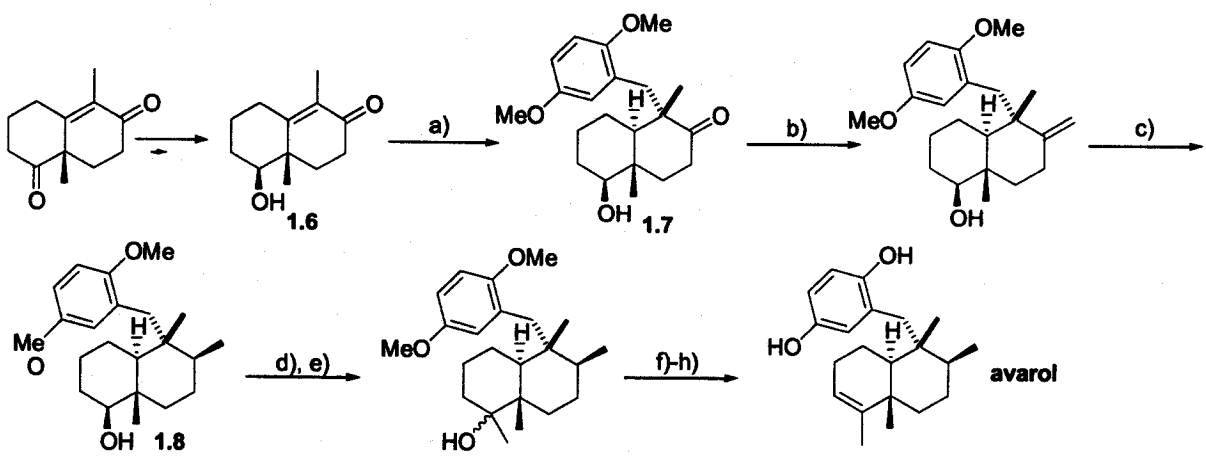
stereocenter at C10 as shown in Scheme 1.3. When W-M ketone is applied to the synthesis of clerodanes, the quaternary carbon center at C9 is installed either by alkylation of the enolate generated in the Birch reduction or via a Claisen rearrangement. Finally, the methyl group at C8 is introduced via catalytic hydrogenation of the exocyclic methylene obtained either from the olefination of the ketone or via the Claisen rearrangement (Scheme 1.3).



Scheme 1.3 Application of W-M diketones toward a synthesis of clerodanes

One of the first examples of using W-M ketone toward the synthesis of clerodanes was that of a clerodane related sesquiterpenoid, (±)-avarol, reported by Sarma *et al.* in 1982 as shown

in Scheme 1.4.[13] (±)-Avarol belongs to the *trans-cis* clerodane structural type (see Figure 1.2), since it has a *trans*-decalin core and the methyl groups at C9 and C8 are *cis* to each other and to the C5 center at the ring junction. The synthesis began from the Birch reduction of **1.6** followed by the alkylation of the enolate generated *in situ* to afford decalin ketone **1.7** with the quaternary center at C9 and a *trans*-ring-junction as shown in Scheme 1.4. Wittig olefination of ketone **1.7** generated exo-cyclic double bond, which was then reduced using H_2/Pd/C to give **1.8** as a 5.6:1 mixture of epimers at C8 center. The total synthesis was competed in 8 steps starting from **1.6**.



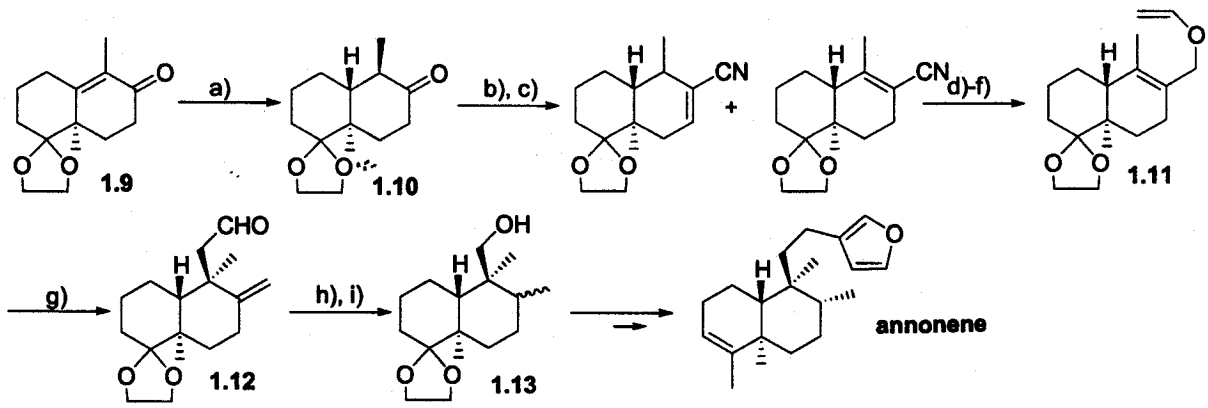
a) Li-NH_3,THF, 2.5-dimethoxybenzylbromide, 75%; b) CH_2=PPh_3, DMSO, 80 °C, 40 h, 85%; c) H_2, 10% Pd/C, EtOH, 75%; d) PCC, CH_2Cl_2, 90%; e) MeLi, Et_2O, 90%; f) $POCl_3$, Py, 95%; g) $RhCl_3$, EtOH, 80%; h) *n*-BuSLi, HMPA, 80%.

Scheme 1.4 Total synthesis of avarol

In the total synthesis of (±)-annonene the *trans* ring junction was first secured via the Birch reduction of acetal-protected W-M ketone **1.9** as shown in Scheme 1.5.[14] Decalin **1.10** was then transformed to allyl enol ether **1.11**. The thermally induced Claisen rearrangement of **1.11** afforded product **1.12** with a quaternary carbon center at C9 as a major diastereomer (dr

[13] Sarma, A.S.; Chattopadhyay, P. *J. Org. Chem.* **1982**, *47*, 1727.
[14] Takahashi, S.; Kusumi, T.; Kakisawa, H. *Chem. Lett.* **1979**, 515.

5.6:1). Further hydrogenation of the exo-cyclic methylene gave **1.13** as a 1:1 mixture of epimers at C8.

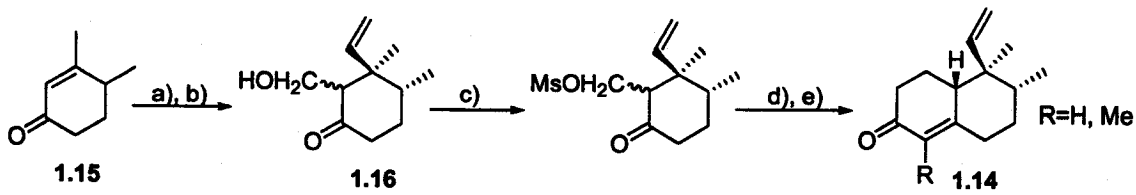


a) Li-NH_3; b) KCN, AcOH; c) $SOCl_2$, Py, 84% over 2 steps, dr=1:1; d) DIBAL-H e) $NaBH_4$, 60%; f) $EtOCH{=}CH_2$, $Hg(OAc)_2$, 73%; g) 200 °C/decaline, 70%; h) $NaBH_4$; i) H_2/Pd-C, 84% over 2 steps, 1:1 mixture of epimers at C8

Scheme 1.5 Total synthesis of annonene

Methods employing cyclohexanones with both quaternary and tertiary centers installed prior annulation step can be an alternative to W-M diketones. Tokoroyama *et al.* developed a general method toward construction of *cis* and *trans* clerodanes using unsaturated decalin **1.14** as a common precursor (Scheme 1.6).[15] Contrary to the W-M ketone, **1.14** already possessed stereocenters at C10, C9 and C8. The quaternary carbon center was introduced via conjugated addition of vinyl cuprate to cyclohexanone **1.15**. Quenching the reaction with formaldehyde afforded ketone **1.16** in which all three stereocenters were present. The subsequent condensation reaction followed by decarboxylation and dehydration provided decalin **1.14**. The enantioselective version of this approach was also developed.[16]

[15] Tokoroyama, T.; Fujimori, K.; Shimizu, T.; Yamagiwa, Y.; Moden, M.; Iio, H. *Tetrahedron* **1988**, *44*, 6607.
[16] Iio, H.; Monden, M,; Okada, K.; Tokoroyama, T. *J. Chem. Soc., Chem. Commum.* **1987**, *5*, 358.



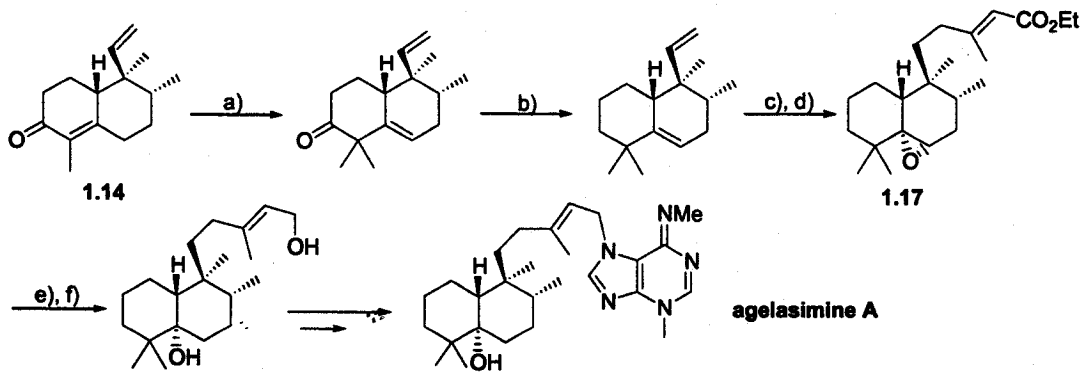
a) CH_2=CHMgBr, CuI·*n*-Bu_3P, THF; b) CH_2O, 66% over 2 steps; c) MsCl, Et_3N, CH_2Cl_2, 93%; d) $CH_3COCH_2CO_2Me$ or $C_2H_5COCH_2CO_2Me$, MeONa, MeOH, benzene, heat; e) 2 M HCl, MeOH, heat, 79% over 2 steps.

Scheme 1.6 Synthesis of Tokoroyama intermediate

The applicability of the strategy was demonstrated by a number of total syntheses.[17] For example, Ohba *et al.* employed both racemic and chiral versions of the Tokoroyama method for the synthesis of agelasimine A (Scheme 1.7).[18] As already mentioned before, biosynthetically agelasimine is a product of the partial rearrangement of the labdane skeleton in which cation **1.4** (see Scheme 1.1 in the beginning of the chapter) is quenched with water before the last migration of the methyl occurs. As a result, a tertiary alcohol is formed at the ring junction (C5), whereas geminal dimethyls at C4 are preserved. In order to install these two functionalities, decalin **1.14** was treated with potassium *tert*-butoxide to generate dienolate which was then alkylated to afford geminal dimethyls at C4. The carbonyl group was then reduced to the methylene using a Wolf-Kishner procedure. Epoxidation of the angular double bond followed by epoxide opening generated *trans*-decalin **1.17** with the tertiary alcohol at the ring junction.

[17] a) Iio, H.; Matsumoto, Y.; Shimikoata, K.; Shibata, K.; Tokoroyama, T. *J. Chem. Soc. Perkin 1* **1989**, *7*, 1360. b) Ihara, M.; Katsumata, A.; Egashira, M.; Suzuki, S.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 5560.

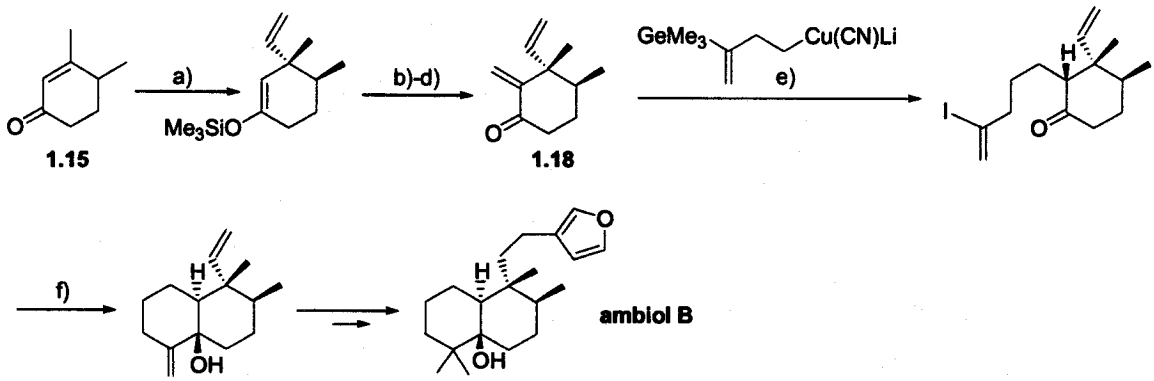
[18] a) Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem. Soc.* **1996**, *118*, 8250. b) Ohba, M.; Iizuka, K.; Ishibashi, H.; Fujii, T. Tetrahedron, **1997**, *53*, 16977.



a) MeI, *t*-BuOK, *t*-BuOH, reflux, 30 min, 85%; b) 80% aq. $NH_2NH_2.H_2O$, KOH, diethylene glycol, 130 °C, 1h, 190 °C, 3 h, 84%; c) 1. 9-BBN, THF, reflux, 2 h; 2. $Pd(dppf)Cl_2$, Cs_2CO_3, Ph_3As, THF-H_2O-DMF, rt, 3 h, 67%; d) *m*-CPBA, CH_2Cl_2, 0 °C, 2 h, 82%; e) DIBAL-H, CH_2Cl_2, -78 °C, 1 h, 88%; f) $LiAlH_4$, THF, reflux, 4 h, 70%.

Scheme 1.7 Total synthesis of agelasimine A

A slightly modified precursor **1.18** was used by Piers *et al.* in the synthesis of ambiol B, as shown in Scheme 1.8.[19] In this case the tertiary alcohol at the ring junction (C5) was installed via intramolecular alkylation of the ketone with the vinyl lithium species.



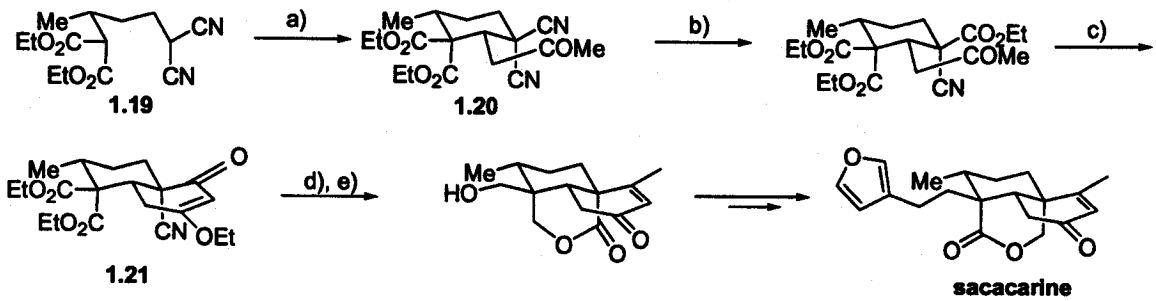
a) CH_2=CH_2MgBr, $CuBr{\cdot}Me_2S$, TMSCl, 90%; b) MeLi; c) $[Me_2N{=}CH_2]^+I^-$, 84% over 2 steps; e) 1. TMSCl; 2. I_2, 42%; f) *n*-BuLi, 88%.

Scheme 1.8 Total synthesis of ambiol B

Grossman *et al.* have recently reported the total synthesis of clerodane diterpene (±)-sacacarin using the double annulation strategy (Scheme 1.9).[20] Double Michael addition of **1.19** and 3-butyn-2-one generated *in situ* from 4-trimethylsilyl-3-butyn-2-one afforded

[19] Piers, E.; Marais, P.C. *J. Chem. Soc., Chem. Commun.* **1989,** *17,* 1222.
[20] Grossman, R.; Rasne, R.M. *Org. Lett.* **2001,** *3,* 4027.

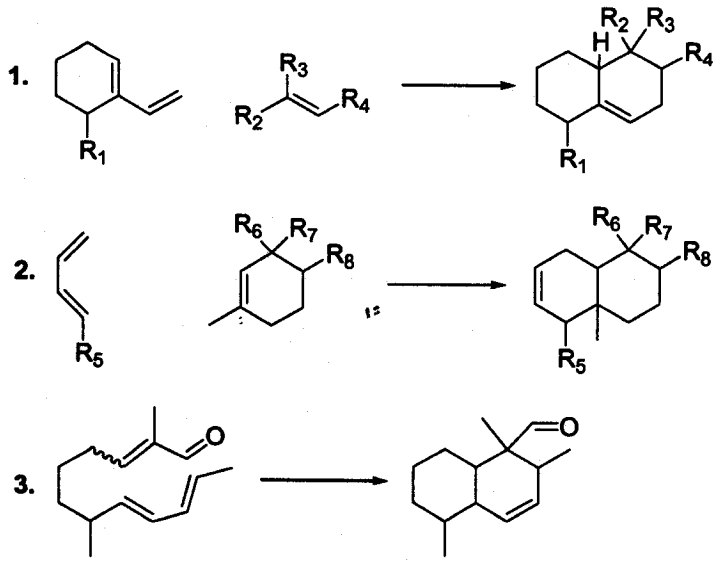
highly substituted cyclohexane **1.20** (dr=5:1). The latter possessed all four stereocenters required for the future C5-C10-C9-C8 network of the clerodane skeleton, although two quaternary centers had to be further desymmetrized. Thus, **1.20** was transformed via hydrolysis of the less hindered cyano group followed by Dieckmann condensation and enol etherification to *trans*-decalin **1.21**. The synthesis of the natural product was completed in four additional steps.



a) $Me_3SiC{\equiv}CCOMe$, 15 mol % $KF{\cdot}2H_2O$, *t*-BuOH, rt. 66% (60:1 dr); b) EtOH, HCl_{dry}, $HCl_{aq.,\ con}$, DME, 99%; c) NaOEt, EtOH, reflux; $TsOH_{cat}$, EtOH, bezene-H_2O, reflux, 90%; d) MeLi, THF, -78 °C; TMSCl; $LiAlH_4$, 0 °C; e) HCl_{con}, reflux, 62%.

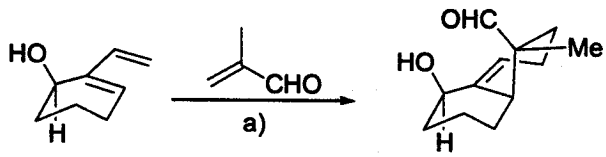
Scheme 1.9 Total synthesis of (±)-sacacarine

Inter- and intramolecular Diels-Alder reactions have been successfully applied to the synthesis of both *trans*- and *cis*-diterpenes. Depending on the substitution pattern of the diene and dienophile, various functionalities can be introduced on the decalin ring including the quaternary carbon center at C9 and the methyl at C8 as depicted in Scheme 1.10. Type 1 Diels-Alder reactions afford decalins with sp^2-hybridized carbon at C5, which can be further transformed to *trans*- or *cis*-decalin. When cyclohexene is used as a dienophile (type 2), *cis*-decalins are obtained, which can be isomerized to provide the more stable *trans*-isomer. Intramolecular Diels-Alder reaction can provide both *cis*- and *trans*-decalins depending on geometry of the dienophile part of the molecule. In all cases controlling π-facial selectivity remains a significant challenge.



Scheme 1.10 Diels-Alder reactions in the synthesis of diterpenes

Barriault *et al.* have reported a highly diastereoselective synthesis of decalins using type 1 Diels-Alder reaction of dienes with tertiary and secondary alcohols as shown in Scheme 1.11.[21] A temporary magnesium alkoxide tether was applied for controlling facial selectivity.



a) Et_3N, $MgBr_2 \cdot OEt_2$, CH_2Cl_2, 78%, dr>25:1.

Scheme 1.11 Synthesis of decalines using hydroxy-directed Diels-Alder reaction

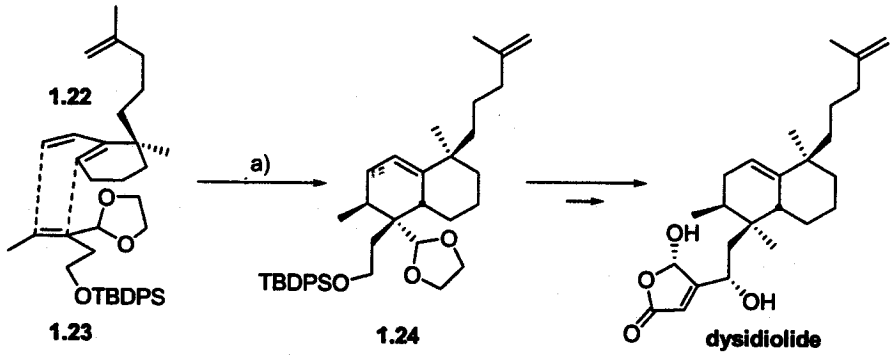
Remarkably, four out of seven reported total syntheses of clerodane related sesquiterpene dysidiolide utilized the Diels-Alder reaction for construction of the decalin core.[22]

Danishefsky *et al.* envisioned formation of the decalin framework via intermolecular Diels-Alder reaction (type 1, Scheme 1.10) using diene **1.22** and activated dienophile **1.23** as

[21] Barriault, L.; Thomas, J.D.O.; Clement, R. *J. Org. Chem.* **2003**, *68*, 2317.

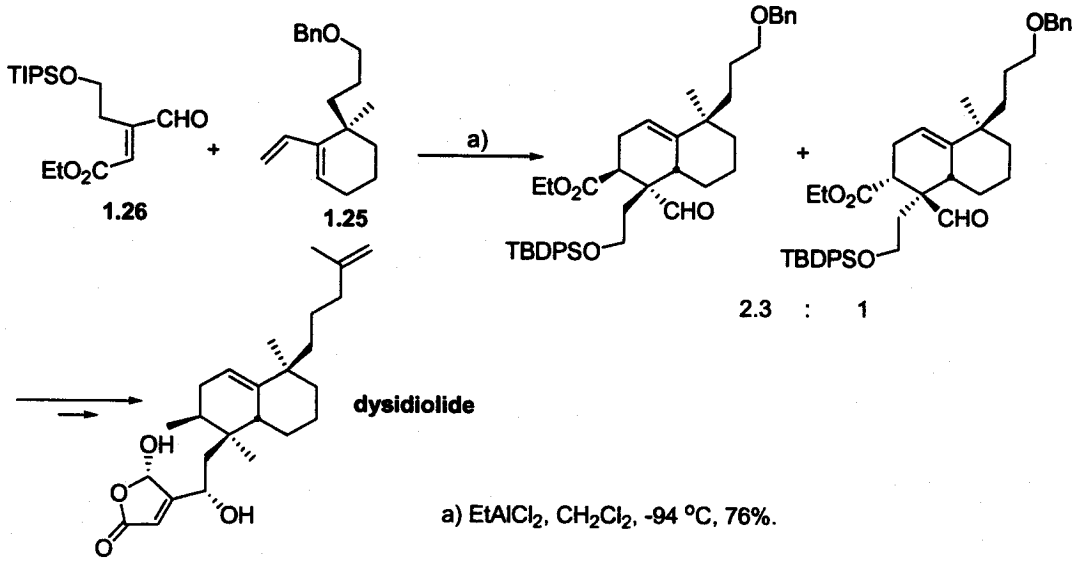
[22] For the syntheses employing approaches other then the Diels-Alder strategy see a) Corey, E.J.; Roberts, B.E. *J. Am. Chem. Soc.* **1997**, *119*, 12425. b) Piers, E.; Caille, S.; Chen, G. *Org. Lett.* **2000**, *2*, 2483. c) Demeke, D.; Forsyth, C.J. *Org. Lett.* **2000**, *2*, 3177. For one more synthesis using the Diels-Alder reaction see: Jung, M.E.; Nishimura, N. *Org. Lett.* **2001**, *3*, 2113.

shown in Scheme 1.12.[23] *Endo* addition of the dienophile occurred from the face anti to the large side chain to give adduct **1.24**.



Scheme 1.12 Diels-Alder reaction in Danishefsky's total synthesis of dysidiolide

Boukouvalas and co-workers performed an intermolecular Diels-Alder reaction using diene **1.25,** which is similar to **1.22**, and dienophile **1.26** to synthesize the decalin core of dysidiolide.[24] In this case a 2.3:1 mixture of diastereomers was obtained (Scheme 1.13).



Scheme 1.13 Diels-Alder reaction in Boukouvalas total synthesis of dysidiolide

Yamada *et al.* chose a slightly different approach toward the dysidiolide core by using the intramolecular Diels-Alder reaction of **1.27** as illustrated in Scheme 1.14.[25] In this case, the facial attack was directed by the stereochemistry of the tethered dienophile moiety.

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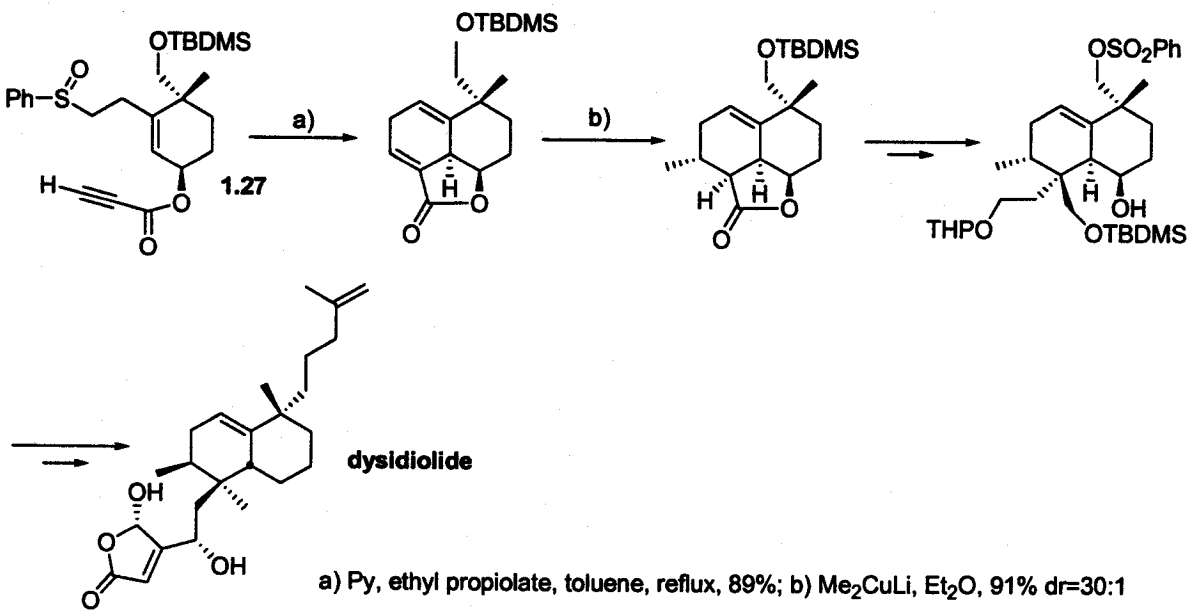
[23] Mgnuson, S.R.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. *J. Am. Chem. Soc.* **1998**, *120,* 1615.
[24] Boukouvalas, J.; Cheng, Y-X.; Robichaud, J. *J. Org. Chem.* **1998**, *63,* 228.

The total synthesis of (±) teucvine reported by Liu and co-workers demonstrates an application of type 2 Diels-Alder reaction (Scheme 1.10) to generating a core of the natural product (Scheme 1.15).[26] The cycloaddition reaction using diene **1.28** and *trans*-2.4-pentadien-1-ol as a dienophile afforded a 11:1 diastereomeric mixture of decalines **1.30** and **1.29** respectively. Compound **1.30** was transformed to (±) teucvine in nine steps.



Scheme 1.14 Diels-Alder reaction in Yamada's total synthesis of dysidiolide

Fallis and co-workers have recently described an example of a type 3 (Scheme 1.10) intramolecular Diels-Alder reaction for the construction of *cis*-decalins.[27] *Cis*-isopropylidene acetal group installed on the side chain was employed to restrict its flexibility and direct the facial attack of the dienophile as illustrated in Scheme 1.16.

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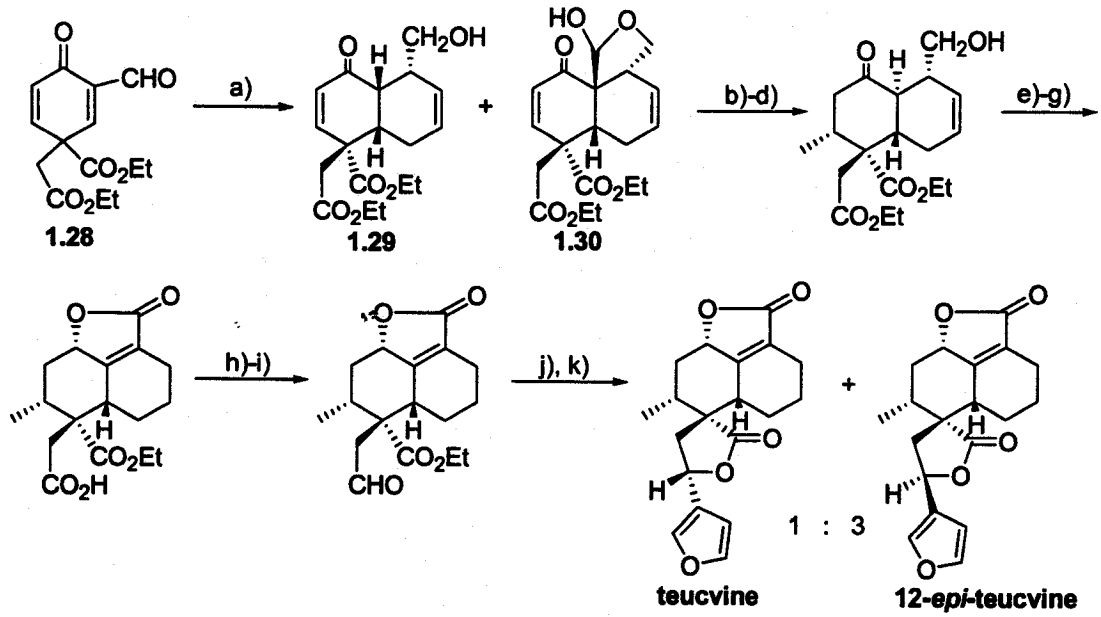
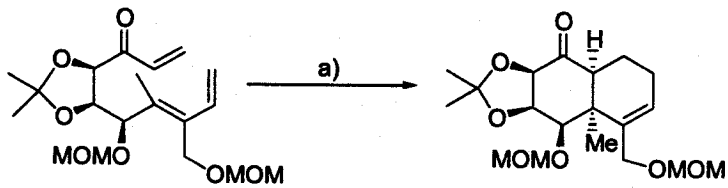
[25] Miyaoka, H.; Kajiwara, Y.; Hara, Y.; Yamada, Y. *J. Org. Chem.* **2001**, *66*, 1429.
[26] Liu, H.-J.; Zhu, J.-L.; Chen I.-C.; Jankowaska, R.; Han, Y.; Shia, K.-S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1851.
[27] Melekhov, A.; Forgione, P.; Legoupy, S.; Fallis, A.G. *Org. Lett.* **2000**, *2*, 2793.



a) $ZnCl_2$, *trans*-2,4-pentadien-1-ol, CH_2Cl_2, 0 °C, 1 h, 90% (**1.30:1.29**=11:1); b) Ac_2O, Py, cat. DMAP, rt, 10 h, 90%; c), $(CH_3)_2CuLi$, Et_2O, 0 °C, 0.5 h, 82%; d) NaOH, EtOH, H_2O, rt, 10 h, 90%; e) H_2 (60 psi), 10% Pd/C, EtOAc, rt, 6 h, 89%; f) Jones reagent, acetone, 0 °C, 1 h, 90%; g) *p*-TsOH, benzene, reflux, 5 h, 85%; h) $(COCl)_2$, benzene, reflux, 10 min; i) $LiAl(t\text{-}BuO)_3H$, THF, -40 °C, 1 h, 70% over 2 steps; j) 3-lithiofurane, Et_2O, -78 °C, 20 min; k) LiH, THF, rt, 10 h, 45% over 2 steps, dr =1:3.

Scheme 1.15 Total synthesis of (±)-teucvine



a) Dess-Martin periodinane, CH_2Cl_2, 21 °C, 60 h, or 40 °C, 4 h, 87%

Scheme 1.16 Construction of *cis*-decalines via a type 3 Diels-Alder reaction

1.3 Conclusion

To the best of our knowledge since the last reviews in the area of decalin synthesis no conceptually new methods have been developed. The classical methods briefly described in this chapter often require each stereogenic center of the target molecule to be separately installed. Moreover, the lack of selectivity at C9 and C8 centers is frequently encountered during the total synthesis of clerodane related diterpenes. In Chapter 2 we will demonstrate our novel tandem oxy-Cope/ene/Claisen strategy that has been developed to generate *trans*-

diterpenes possessing a quaternary carbon center at C9. We will also show the application of this strategy toward the synthesis of clerodane related diterpene (±)-agelasimine A and its analogs.

Chapter 2 Studies toward the total synthesis of (±)-agelasimine A and development of the oxy-Cope/ene/Claisen reaction

2.1 General Introduction

The rapid construction of complex polycyclic molecules in a highly stereoselective fashion remains a synthetic challenge. Processes, combining two or more reactions in one step, so called tandem reactions, can be an efficient solution to this problem.[1] Many tandem reactions reported in literature have found their application in a total synthesis of various natural products.[2]

In the past five years the main objective of the Barriault group has been the development of new tandem strategies for construction of multiple carbon-carbon bonds to generate in a few steps polycyclic terpene structures with high stereochemical complexity. The first methodology studied was a tandem oxy-Cope/transannular ene reaction. This reaction was originally observed by Sutherland as an undesired side reaction of an oxy-Cope rearrangement.[3] Later, Paquette[4] and Rajagopalan[5] also reported that in some cases an anionic oxy-Cope reaction would give a side product resulting from an ene-reaction.

In our lab the tandem oxy-Cope/ene reaction has been developed as a strategy for the construction of *trans*-decalins with a tertiary alcohol at the ring junction. It has been shown by Warrington and Barriault that thermally induced rearrangement of *trans*-1,2-divinylcyclohexanols produces bi- and tricyclic structures **2.2** in a highly diastereoselective

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[1] For reviews see: a) Ho, T.-L.; *Tandem Organic Reactions*; Wiley; New York, **1992**. b) Bunce, R.A. *Tetrahedron*, **1995**, *51*, 13103. c) Parson, P.J.; Penkett, C.S.; Shell, A.J. *Chem. Rev.* **1996**, *96*, 195. d) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *J. Chem. Soc. Chem. Commun.* **2003**, *5*, 551.

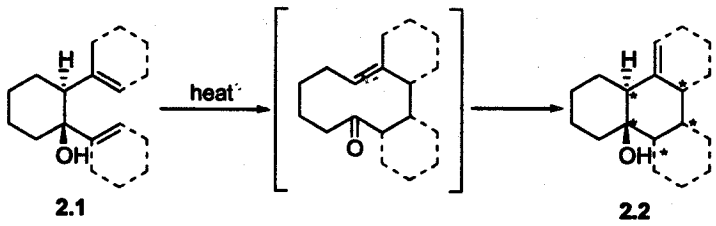
[2] For example see: a) Belanger, G.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 285. b) Li, C.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 10484. c) Bell, R.P.L.; Wijnberg, J. B.P.A.; De Groot, A. *J. Org. Chem.* **2001**, *66*, 2350.

[3] Chorlton, A.P.; Morris, G.A.; Sutherland, J.K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1205.

[4] Paquette, L. A.; Nakatani, S.; Zydowsky, T.M.; Edmondson, S.D.; Sun, Q.-L.; Skerlj, R. *J. Org. Chem.* **1999**, *64*, 3244.

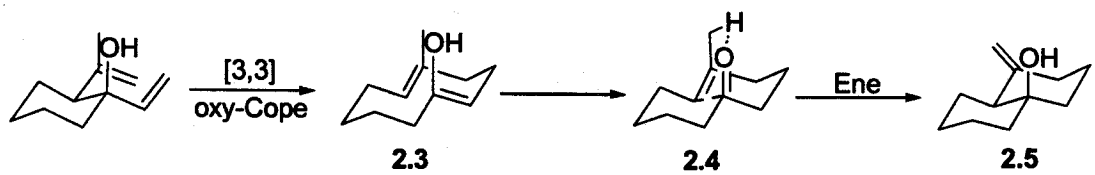
[5] Rajagopalan, K.; Janardhanam, S.; Balakumar, A. *J. Org. Chem.* **1993**, *58*, 5482.

fashion as a result of two-step process as illustrated in Scheme 2.1.[6] The *trans* stereochemistry of a decalin core of the product originates from a *trans* relationship of the vinyl groups on the cyclohexanol **2.1**.



Scheme 2.1 Generation of bi- and tricyclic structures via oxy-Cope-/ene reaction

The first step of this sequence is an oxy-Cope rearrangement generating 10-membered ring enol **2.3**, which can rapidly tautomerize to give macrocyclic ketone **2.4**. The ketone is properly aligned with a methyl group across the ring to undergo a transannular ene-reaction to yield **2.5** as illustrated in step 3 of Scheme 2.2.

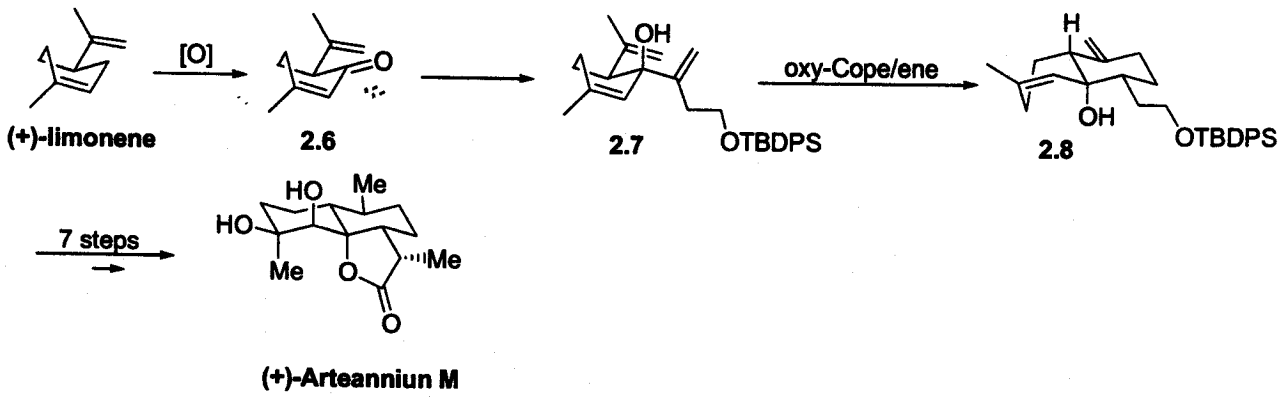


Scheme 2.2 Mechanism of the tandem oxy-Cope/ene reaction

The applicability of this new methodology was first demonstrated in our lab by Dan Deon's total synthesis of (+)-Arteannium M,[7] a natural product isolated form *Artemisia annula L.*, where the tandem oxy-Cope/ene reaction was used to construct the core of the natural product as illustrated in Scheme 2.3. The simple procedure for the generation of **2.8** involved heating 1,2-divinylcyclohexanol **2.7** at 220 °C in toluene in the presence of DBU in a sealed tube. The product was obtained in good yield (55-60%), excellent diastereoselectivity

[6] Warrington, J. M.; Yap, G.P.A.; Barriault, L. *Org. Lett.* **2000**, *2*, 663.
[7] Barriault, L.; Deon, D.H. *Org. Lett.* **2001**, *3*, 1925.

(dr>25:1) and good enantioselectivity (ee=78%). The total synthesis was completed in only 9 steps with an overall yield of 14.1% starting from **2.6** available from (+)-limonene.



(+)-Arteanniun M

Scheme 2.3 Total synthesis of (+)-Arteanniun M from (+)-limonene

The next step in illustrating the synthetic versatility of the tandem oxy-Cope/ene methodology was demonstrating its use in the synthesis of a different family of diterpenes. Thus, the synthesis of (±)-agelasimine A was embarked upon.

2.2 Entry to the total synthesis of (±)-agelasimine A via the oxy-Cope/ene strategy

2.2.1 Introduction

Agelasimine A (Figure 2.1) is a novel nonquaternary adenine-related diterpene isolated from the orange sponge *Agelas mauritiana* by Fathi-Ashfar and Allen in 1988.[8] Its biological activities include cytotoxicity, inhibition of adenosine transfer into rabbit erythrocytes, Ca^{2+}-channel antagonistic action and α_1 adrenergic blockade.[9] The structure of agelasimine A features a *trans*-decalin core with a tertiary alcohol at ring junction (C5 position). It bears four contiguous chiral centers C5-C10-C9-C8, including a quaternary carbon center at C9

[8] Fathi-Afshar, R.; Allen, T.M. *Can. J. Chem.* **1988**, *66*, 45.
[9] Fathi-Afshar, R.; Allen, T.M.; Krueger, C.A.; Cook, D.A.; Clanachan, A.S.; Vriend, R.; Baer, H.P.; Cass, C.E. *Can J. Physiol. Pharmacol.* **1989**, *67*, 276.

and a tertiary center at C8, a feature characteristic of the clerodane family as well as a side chain attached to a modified adenine base. It also has geminal methyls at C4. The presence of four adjacent stereocenters, one of which is a quaternary carbon center, along with its interesting biological properties makes agelasimine an appealing synthetic target.

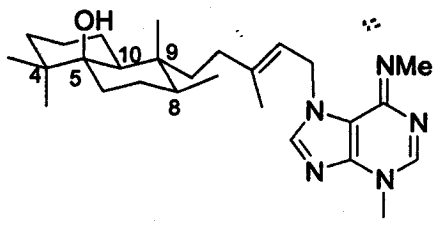
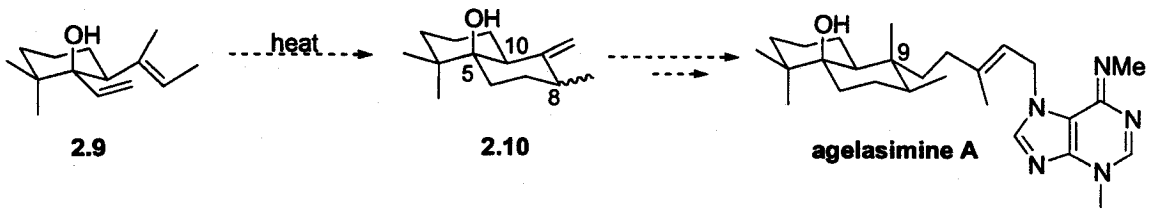


Figure 2.1 Agelasimine A

Ohba *et al.* have previously reported the total synthesis of agelasimine A in racemic and enantiomerically pure forms.[10] Their synthetic approach was to generate the bicyclic core via an aldol reaction, which took 11 steps to achieve (see Chapter 1, Scheme 1.7). Although efficient in accomplishing the goal, the strategy required each stereogenic center to be separately installed.

We have envisioned that our oxy-Cope/ene tandem strategy will generate *trans*-decalin core **2.10** of agelasimine A with three (C5, C10 and C8) chiral centers in only one step from **2.9** as depicted in Scheme 2.4.



Scheme 2.4 Synthesis of a *trans*-decalin core of agelasimine A using the tandem oxy-Cope/ene reaction

[10] a) Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem. Soc.* **1996**, *118*, 8250. b) Ohba, M.; Iizuka, K.; Ishibashi, H.; Fujii, T. Tetrahedron, **1997**, *53*, 16977.

The two main challenges of the oxy-Cope/ene strategy that needed to be investigated were installation of a quaternary center at C9 and ensuring a *syn* relation of the methyl group at C8 to the tertiary alcohol at C5.

Before embarking on the synthesis of the natural product, model studies were performed on (±)-dihydroagelasimine A, an analog of agelasimine A without geminal methyls at C4 (Figure 2.2).

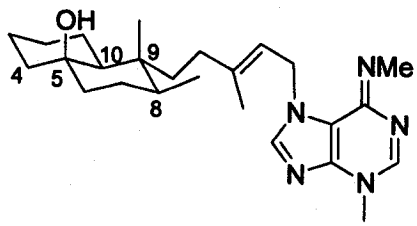
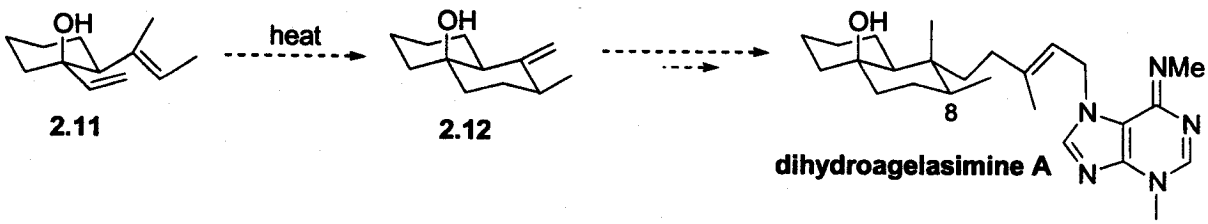


Figure 2.2 Dihydroagelasimine A

In order to generate the core of dihydroagelasimine A **2.12** via the tandem oxy-Cope/ene reaction we had to start from 1,2-divynilcyclohexanol **2.11** as shown in Scheme 2.5.

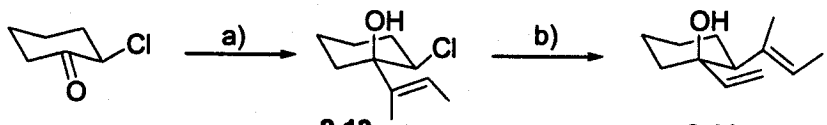


Scheme 2.5 Tandem oxy-Cope/ene approach toward dihydroagelasimine A

2.2.3 Results and Discussion

The synthesis of the substrate for the tandem oxy-Cope/ene step began by the alkylation of commercially available 1-chloro-2-cyclohexanone with the vinyl lithium species generated via metal-halogen exchange at –78 °C from *trans*-2-bromobutene to give chlorohydrin **2.13** in 76% yield (Scheme 2.6). Deprotonation of **2.13** with vinylmagnesium bromide induced

[1,2]-migration of the butene group followed by a nucleophilic attack on the resulting ketone to generate the desired tertiary alcohol **2.11** in 50% yield.

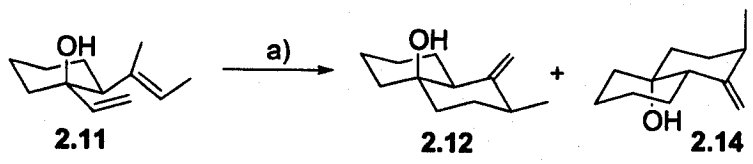


2.13 **2.11**

a) *trans*-2-bromobutene, *t*-BuLi, -78 °C, 76%; b) vinylmagnesium bromide, reflux, THF, 50% over 2 steps

Scheme 2.6 Synthesis of the starting material for the oxy-Cope/ene step

After heating in toluene at 220 °C **2.11** rearranged via the tandem oxy-Cope/ene mechanism previously described in Scheme 2.2 to give a core of dihydroagelasimine A, disappointingly as an inseparable 3.2:1 mixture of diastereomers at C8, **2.12** and **2.14** respectively (Scheme 2.7). The position of the methyl at C8 was assigned based on the NOESY and NOE difference data. When the methyl was *syn* to the alcohol (decaline **2.12**), a strong correlation was observed between H_A and the protons of the methyl (Figure 2.3). On contrary, in the case of decaline **2.14**, the NOE effect was observed for H_A and H_G. Unfortunately, we were not able to obtain the full network of NOE interactions for compound **2.14** since only few protons could be individually irradiated. The proton H_G in compound **2.14** was assigned based on its correlation with the methyl group observed in COSY experiment. Interestingly, heating the reaction in a sealed tube using a wax bath required 3 d for the reaction to go to completion whereas using the microwave oven reduced the reaction time to 1 h. Nevertheless, the results were identical; they demonstrated the capacity of oxy-Cope/ene reaction to generate a biterpene core in only 3 steps starting from commercially available 2-chlorocyclohexanone. They also revealed the first pitfall of our strategy, namely lack of selectivity at C8. (Detailed investigations on the selectivity at C8 will be presented in Chapter 3).



a) toluene, DBU, 220 °C, 70%, dr=3.2:1 in the μwave -1 h, in the sealed tube -3 d

Scheme 2.7 The tandem oxy-Cope/ene reaction of **2.11**

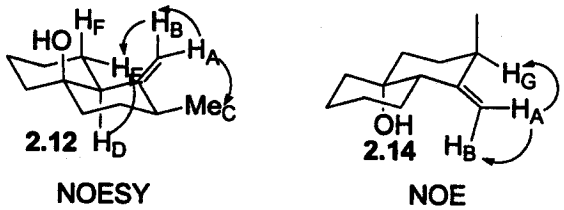
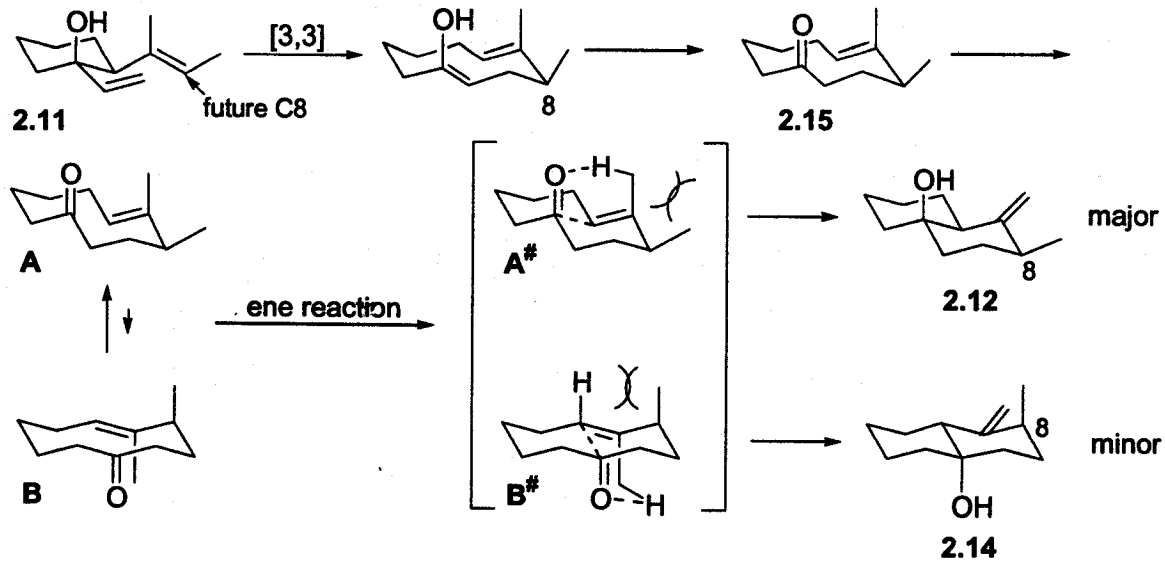


Figure 2.3 NOESY and NOE correlations for **2.12** and **2.14**

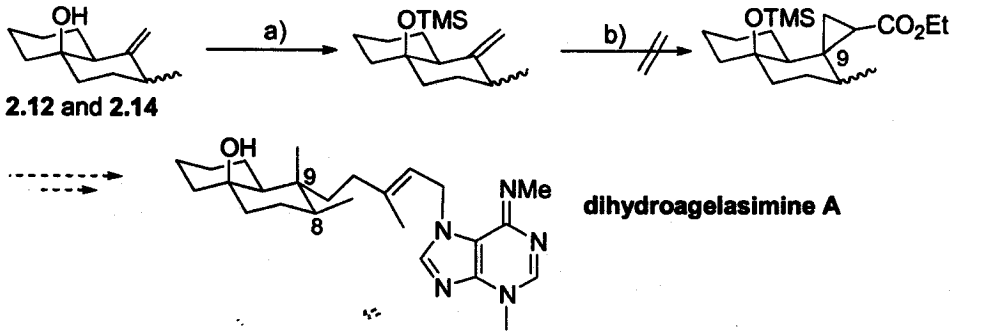
Formation of the two diastereomers can be rationalized by the mechanism depicted in Scheme 2.8. The oxy-Cope rearrangement of **2.11** results, after tautomerization, in macrocyclic ketone **2.15**. The ketone can then undergo either a ring inversion to conformer **B** followed by the ene-reaction generating compound **2.14** or proceed directly through the ene-reaction to give **2.12**, which is the desired product (the methyl at C8 is equatorial and *syn* to the alcohol at C5).

Applying Curtin-Hammett principle to our model we may anticipate that the product ratio will be determined based exclusively on the difference in energies of transition states $\mathbf{A}^{\#}$ and $\mathbf{B}^{\#}$. Transition state $\mathbf{A}^{\#}$ (the methyl at C8 is equatorial) is expected to be lower in energy than transition state $\mathbf{B}^{\#}$, thus resulting in formation of desired product **2.12** as a major product.



Scheme 2.8 Proposed mechanism for the formation of the diastereomers

In spite of the low diastereoselectivity of the tandem oxy-Cope/ene reaction of **2.11** we then decided to continue the synthesis and attempt to install the next key feature – quaternary carbon center at C9. One would envision that cyclopropanation of the exo-cyclic double bond followed by reductive cleavage would provide the desired quaternary center (Scheme 2.9). Thus, the tertiary alcohols of inseparable **2.12** and **2.14** were protected with TMS group and subjected to various cyclopropanation conditions. Unfortunately, using ethyl diazoacetate in the presence of catalytic amounts of rhodium diacetate dimer, palladium acetate or copper salts as a catalyst led to the formation of complex mixtures and decomposition.



Scheme 2.9 Attempt to install the quaternary carbon center at C9 via cyclopropanation

It was obvious that a strategy toward dihydroagelasimine A needed revision, since in the course of the model studies two major problems were encountered, i.e. how to install a quaternary carbon center at C9 and how to control the selectivity at C8. On the other hand developing a new general method to install a quaternary center at C9 would provide an access to a variety of clerodanes possessing a quaternary carbon center at C9. Thus the original approach was abandoned and search for a new general method was undertaken.

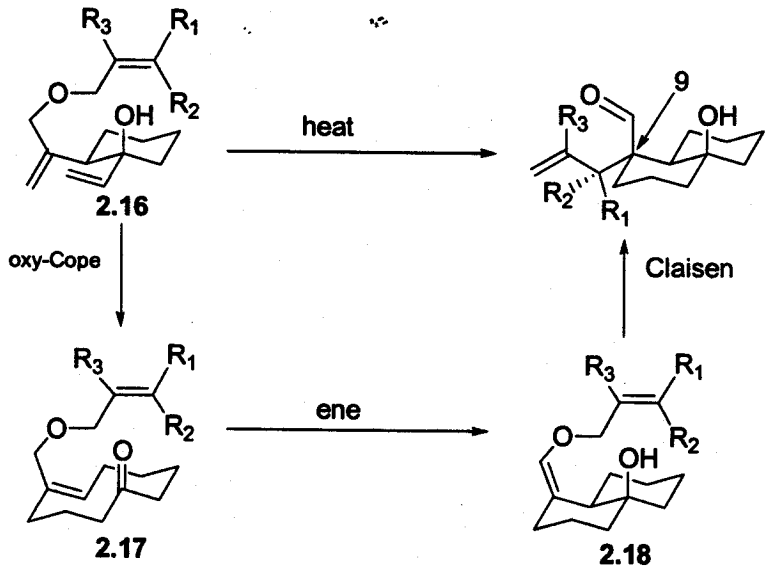
2.3 Development of a tandem Oxy-Cope/ene/Claisen reaction

2.3.1 Introduction

Stereoselective synthesis of quaternary carbon centers remains a significant challenge to synthetic chemist. Although a vast number of methods have been reported, there is still a great need in developing general strategies toward construction of quaternary centers, in particular in diterpene synthesis.[11]

[11] For reviews on quaternary centers see a) Martin, S.F. *Tetrahedron* **1980**, *36*, 419. b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. c) Corey, E.J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *110*, 402. d) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1688. e) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105.

We envisioned that adding a Claisen rearrangement step to a tandem oxy-Cope/ene sequence could provide an easy access to diterpenes with a quaternary carbon center at C9. Thus we proposed a new synthetic method based on a tandem oxy-Cope/ene/Claisen reaction sequence (Scheme 2.10).



Scheme 2.10 A proposed tandem oxy-Cope/ene/Claisen reaction

First, a thermal oxy-Cope reaction of **2.16** would produce, after tautomerization, macrocyclic ketone **2.17**. The ketone would then undergo the tansannular ene-reaction to afford enol ether **2.18** properly set up to undergo the third tandem step, a Claisen rearrangement, to generate a desired quaternary carbon center at C9. A Claisen rearrangement would be expected to proceed via chair-like TS with the facial attack *anti* to the bridgehead alcohol. This would result in the formation of the aldehyde *syn* to the alcohol with potential for further hemiacetal formation.

2.3.2. Results and discussion[12]

[12] Barriault, L.; Denissova, I. *Org. Lett.* **2002**, *4*, 1371.

The simplest model studied was the rearrangement of allyl ether **2.21,** easily prepared via etherification of diol **2.20** (Scheme 2.11). The diol was obtained in 62% yield (based on recovery of the starting material) via allylic oxidation of **2.19** with SeO_2.[13] The etherification with allyl bromide afforded **2.21** in 73% yield. The latter was then dissolved in toluene and DBU (2 equiv) in the quartz cell equipped with a carboflon™.[14] The solution was degassed with argon for 30 min, sealed and heated at 220 °C for 1 h in a CEM microwave.[15] After 1 h there was no starting material present as indicated by TLC. Moreover, ^{1}H NMR (300 MHz) and GC-MS studies on the crude reaction mixture revealed the presence of only two diastereomeric (anomeric position) lactols **2.22.** No peak corresponding to the free aldehyde was observed. This evidence confirmed our initial assumption about the Claisen rearrangement occurring anti to the bridgehead alcohol. In order to determine the precise diastereomeric ratio of the cascade process, the crude lactol mixture was oxidized with TPAP to give lactone **2.23** in 70% yield as a sole diastereomer (dr>25:1) according to ^{1}H NMR (300 MHz) and GC-MS of the crude. It is noteworthy that the initial experiment was performed on a rather small scale (20-50 mg) and showed great diastereoselectivity (dr>25:1). Interestingly, two years after the results were published the same reaction was performed on >1 g scale. To our dismay, formation of a side product, aldehyde **2.24** was observed in 9% yield

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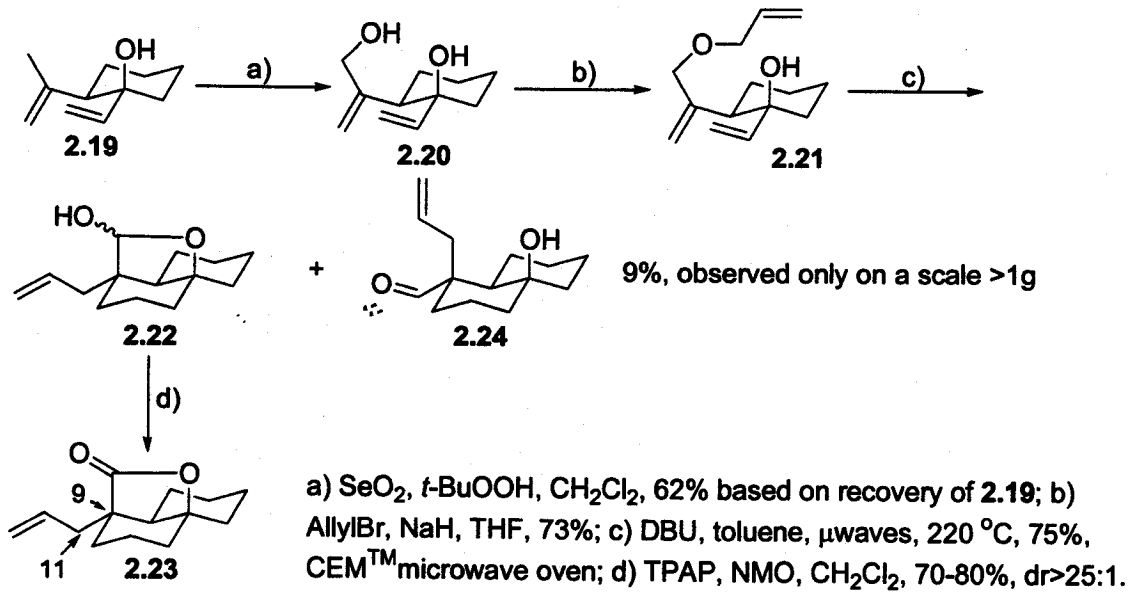
[13] Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2001**, *123*, 3369.

[14] Carboflon™ is a chemically inert fluoropolymer filled with carbon black, a strong microwave absorber. It transfers generated heat to non-polar solvents, which do not absorb microwaves, thus providing necessary energy for a reaction.

[15] For review on Microwaves in Organic Synthesis see: a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, *9*, 1213. b) Loupy, A.; Perreux, L. *Tetrahedron* **2001**, *57*, 9199.



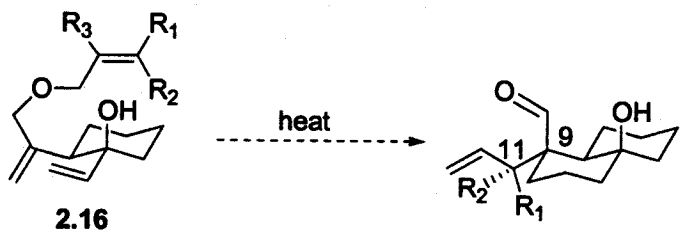
Scheme 2.11 Diastereoselective formation of the *trans*-decalin with a quaternary carbon center at C9

Formation of aldehyde **2.24** was attributed to the Claisen rearrangement occurring from the face *syn* to the bridgehead alcohol. The following rationalization has been proposed: An oxy-Cope/ene/Claisen reaction performed in the microwave in non-polar solvent such as toluene normally requires use of a carboflon™ as a heat conductor; that is assuming that substrate does not absorb microwaves itself. When an oxy-Cope/ene/reaction is carried on a scale of 20-50 mg, reaction concentration is extremely low (0.01-0.007 M), since 12-15 mL of toluene is always used due to the instrument design. Then microwaves are mostly absorbed by a carboflon™ transferring heat further to the reaction mixture. Even if a substrate partially absorbed microwaves, the excess energy would likely be dissipated in the surrounding solvent. However, scaling up (~1 g) significantly increases reaction concentration (up to 1 M). Now, the situation is changed dramatically. Extra energy received by molecules absorbing microwaves cannot be efficiently dissipated in the solvent; instead it is likely to be transferred to the neighboring molecules or used by original molecule-receptor. Thus energy supplied to these molecules is much higher than the energy, which can

be obtained by just heating at 220 °C. An excess of energy can be used by the molecules to populate higher energy conformational states, thus increasing a number of possible events that could occur in the course of the tandem reaction and during the Claisen rearrangement in particular. All this would eventually lead to general loss of selectivity for example allowing one of decaline rings to adopt boat-like conformation in which the Claisen attack *syn* to the alcohol is less hindered.

2.3.2.1 Synthesis of decalines with tertiary and quaternary carbon centers at C11

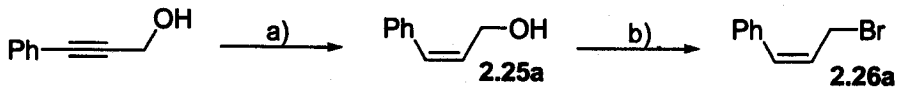
One could envision that, depending on the substitution pattern of allyl ether **2.16**, additional tertiary or quaternary carbon centers could be introduced at C11, the center adjacent to C9 (Scheme 2.12).



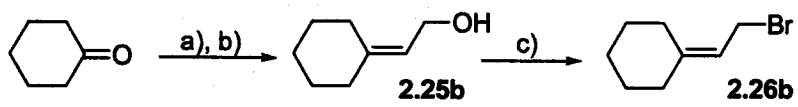
2.16

Scheme 2.12 Installation of an asymmetric center at C11 via the oxy-Cope/ene/Claisen reaction

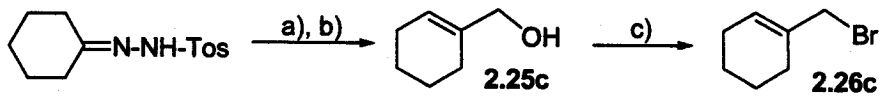
In order to investigate the scope of the oxy-Cope/ene/Claisen reaction allyl ethers with various degree of substitution at the terminal double bond were prepared via etherification of diol **2.20** with the corresponding allyl halides (Table 2-1). All allyl halides except for commercially available cinnamyl chloride **2.26e** and 1-bromo-3-methyl-but-2-ene **2.26f** (Scheme 12.4) were prepared from the corresponding alcohols via bromination with CBr_4/Ph_3P in CH_2Cl_2 (Scheme 2.13 and 2.14). Due to their instability on the silica gel allyl bromides were used in the etherification reaction without purification.



a) Lindlar cat./H_2, quinoline, hexanes, 67%; b) CBr_4, Ph_3P, CH_2Cl_2, 10 min, rt, c) CBr_4, Ph_3P, CH_2Cl_2, 10 min, rt.

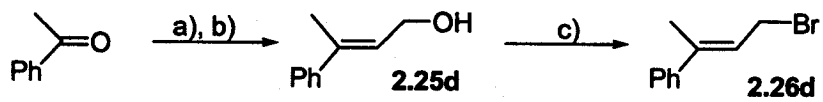


a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C b) DIBAL-H, THF, -78 °C, 67% over 2 steps, c) CBr_4, Ph_3P, CH_2Cl_2, 10 min, rt.



a) 4 eq. *t*-BuLi, TMDA, 5 h, then DMF, 75% b) DIBAL-H, THF, -78 °C, 42%, c) CBr_4, Ph_3P, CH_2Cl_2, 10 min, rt.

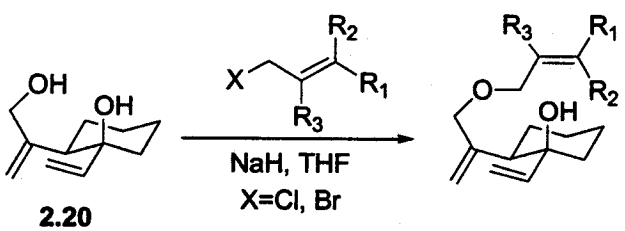
Scheme 2.13 Synthesis of allyl bromides



a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 62%; b) DIBAL-H, THF, -78 °C, 64%; c) CBr_4, Ph_3P, CH_2Cl_2, 10 min, rt.

Scheme 2.14 Synthesis of allyl bromides, contd.

Table 2-1 Preparation of substrates for the oxy-Cope/ene/Claisen reaction

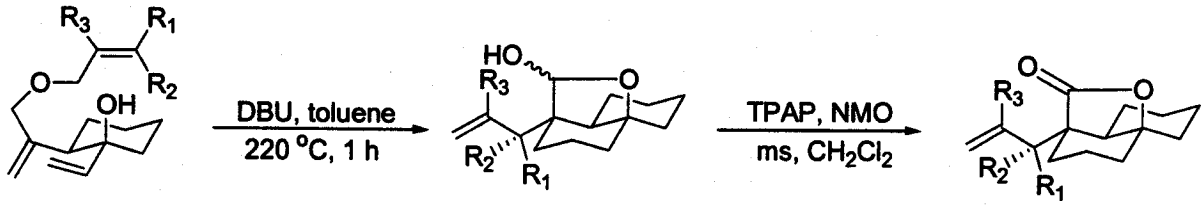


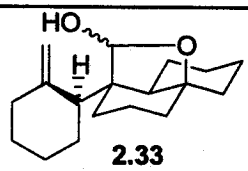
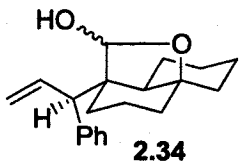
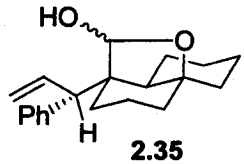
Entry	Allyl bromide	R_1	R_2	R_3	Product	Yield, %
1	**2.26b**	$R_1, R_3 = -(CH_2)_4-$, $R_2=H$			**2.27**	68
2	**2.26e**	Ph	H	H	**2.28**	80

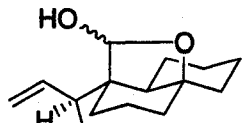
3	**2.26a**	H	Ph	H	**2.29**	60
4	**2.26f**	CH_3	CH_3	H	**2.30**	73
5	**2.26d**	Ph	CH_3	H	**2.31**	73
6	**2.26c**	R_1, R_2 = -$(CH_2)_4$-		H	**2.32**	70

Allyl ethers (**2.27-2.29**) were dissolved in toluene and 3-10 equiv of DBU in a quartz tube, degassed with argon for at least 30 min and irradiated at 220 °C for 1 h in a microwave reactor. In order to determine a diastereomeric ratio, the crude mixture of lactols was oxidized with TPAP. The results are summarized in the Table 2-2.

Table 2-2 Synthesis of decalines with tertiary centers at C11



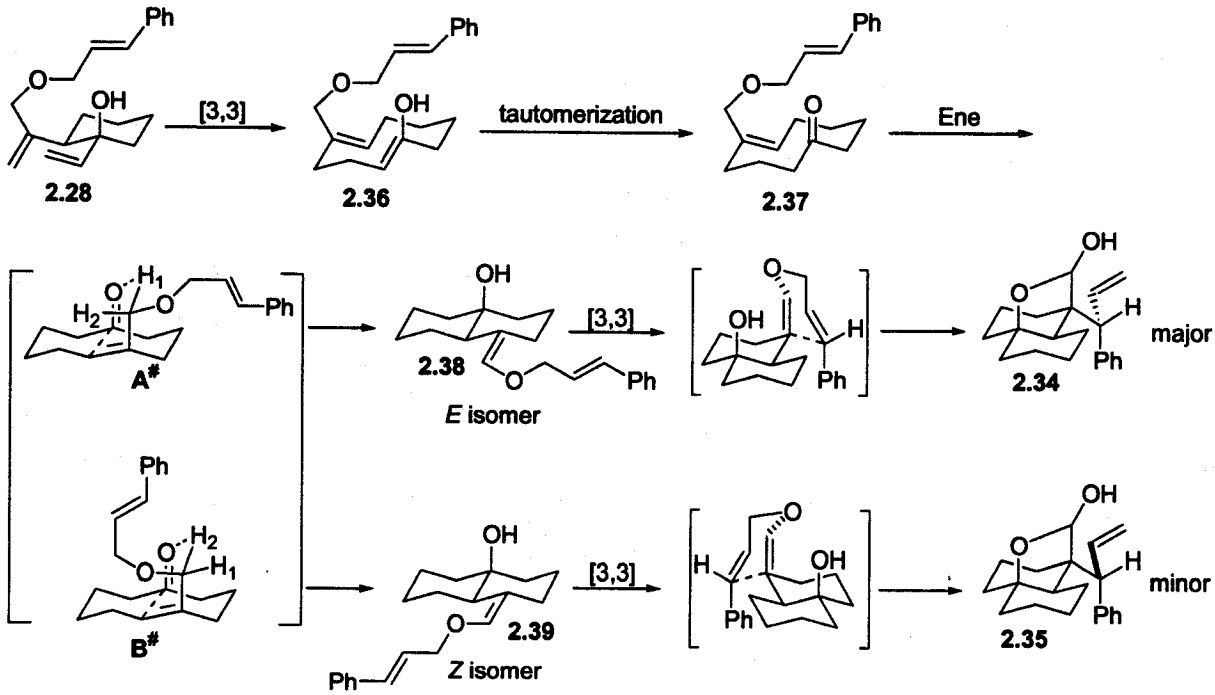
Entry	Allyl ether	Product	Yield, % [a]	Lactone	dr [b]
1	**2.27**	 **2.33**	60	**2.33a**	25:1
2	**2.28**	 **2.34** and  **2.35**	90 [c]	**2.34a** and **2.35a**	2:1

3	**2.29**	 **2.35** and  **2.34**	70 [c]	**2.35a** and **2.34a**	1:1

[a] Isolated yields of the lactols. [b] Diastereomeric ratios were determined by 300 MHz ^{1}H NMR of the crude mixture of the corresponding lactones. [c] Combined yields.

We were pleased to observe that irradiation of **2.27** (entry 1) produced a mixture of lactols **2.33**, which upon oxidation gave the corresponding lactone **2.33a** with tertiary center at C11 as a single diastereomer. The relative stereochemistry of the tertiary center (R configuration) was determined by X-ray crystallography (Appendix 1). Surprisingly, after heating allyl ether **2.29** in the microwave followed by oxidation of the crude reaction mixture with TPAP, a mixture of two diastereomeric lactones **2.34a** and **2.35b** was obtained in 2:1 ratio. Thus, replacing phenyl group for an alkyl chain resulted in loss of selectivity. Formation of two diastereomeric lactones **2.35a** and **2.34a** as a 1:1 mixture was also observed after the oxy-Cope/ene/Claisen reaction of **2.29** followed by TPAP oxidation of a crude mixture of lactols (entry 3). These observations can be rationalized by the mechanism shown in Scheme 2.15. First, the oxy-Cope rearrangement of **2.28** produces enol **2.36**, which then rapidly tautomerizes to afford ketone **2.37**. The latter is ready to undergo a tansannular-ene reaction. Assuming that the ene-reaction proceeds via chair-like transition state and therefore 10-membered ring macrocycle adopts chair-chair like conformation, two conformations, $\mathbf{A}^{\#}$ and $\mathbf{B}^{\#}$, are possible. The difference between $\mathbf{A}^{\#}$ and $\mathbf{B}^{\#}$ lies in which hydrogen is being abstracted in the course of the ene-reaction. When H_1 is being abstracted (transition state $\mathbf{A}^{\#}$), alkoxy group occupies a pseudo equatorial position, whereas abstraction of H_2 (transition state $\mathbf{B}^{\#}$) places the same alkoxy group in a pseudo axial position thus creating unfavorable 1,3-diaxial interactions with the macrocycle ring and raising the energy of

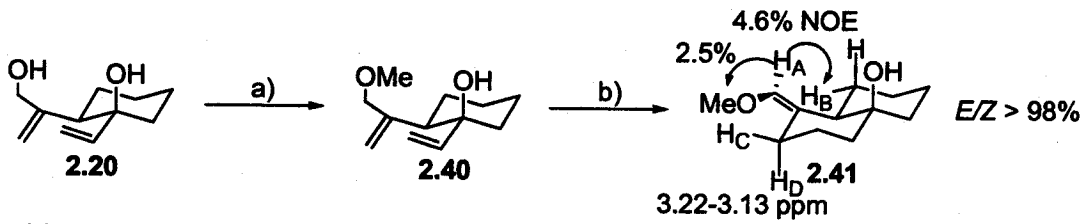
conformer B. This should make $A^{\#}$ a dominant transition state and yield *E* enol ether **2.38**. Finally, the Claisen rearrangement proceeding via chair-like transition state gives lactol **2.34**, which is, in fact, the major product of the tandem reaction. However if the energy difference between **A** and **B** were not significant, formation of both, *E* **(2.38)** and *Z* **(2.39)** enol ethers could be possible. In that case, both diastereomers **2.34** and **2.35** should be obtained.



Scheme 2.15 Proposed mechanism of the tandem oxy-Cope/ene/Claisen reaction

To determine which geometry results from the ene-reaction, the following experiment was performed. A primary alcohol in diol **2.20** was protected with MeI, therefore eliminating the possibility of the Claisen rearrangement. Resulting ether **2.40** was heated at 220 °C for 1 h to give only one isomer **2.41** according to ^{1}H NMR (300 MHz) of the crude reaction mixture (Scheme 2.16). The *E* geometry of the enol ether was confirmed by NOE experiment (For more details see Appendix 2, Table 9). The position of proton H_A was unambiguously

assigned based on its chemical shift value (5.49 ppm, 500 MHz, C_6D_6). Upon irradiation of proton H_A in NOE difference experiment, NOE was observed for a methyl group (2.5%) as well as a proton at 1.35-1.28 ppm (4.9%). In case of *E*-enol ether one would expect to see the correlation between H_A and proton H_B. Whereas for *Z*-enol ether a correlation between H_A and H_C would be detected. A multiplet at 3.12-3.07 ppm (^{1}H NMR, 500 MHz) was assigned as proton H_D. Its chemical shift matched with the one expected for allylic proton and according to the HMQC data it 1.35-1.28 ppm neither in COSY nor NOE difference experiments. Described observations allowed us to assign a proton at 1.32 ppm as H_B and therefore establish the geometry of the enol ether **2.41** as *E*. Exclusive formation of *E* enol ether supports our hypothesis of $\mathbf{A}^{\#}$ being the only transition state for the ene-reaction, but does not explain loss of diastereoselectivity in entry 2 (Table 2-2).

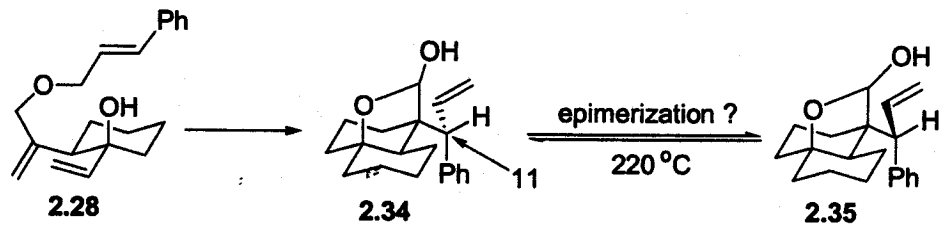


Scheme 2.16 Formation of *E* enol ether

The use of DBU as a proton scavenger in the tandem oxy-Cope/ene/Claisen reaction originated from the oxy-Cope/ene project. Its presence led to higher yields and less degradation.[16] Since DBU is quite a strong base ($pK_{protonated\ base}$ ~12), it could potentially abstract an acidic proton in the starting material or product at 220 °C. This could lead to loss of selectivity. In our system, the proton at C11 in **2.34** being next to the phenyl and vinyl groups might be acidic enough to be deprotonated with DBU upon formation of the lactol. Thus appearance of the second minor diastereomer could be attributed to epimerization

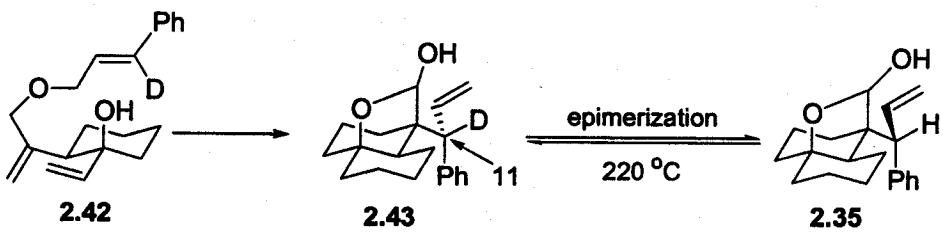
[16] Deon, D.H.; MSc Thesis, University of Ottawa, **2001**.

(Scheme 2.17). Intriguingly, changing from DBU to much weaker base Et_3N gave the same diastereomeric ratio of 2:1.



Scheme 2.17 Possible epimerization of the oxy-Cope/ene/Claisen product

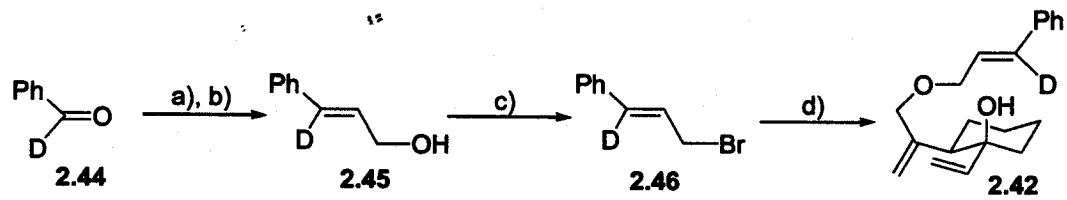
In order to get a better insight into the real mechanism studies with deuterated allyl ether **2.42** were initiated. The rearrangement of **2.42** would result in lactol **2.43** featuring a deuterium atom at C11. If deuterium were to be removed from the tertiary center at C11 by a base, the reverse protonation would result in formation of the minor isomer **2.35** having now hydrogen instead of deuterium atom at C11 (Scheme 2.18). Therefore, the loss of deuterium would be observed and could be detected by ^1H NMR due to the difference in their magnetogyric ratios (as a result the resonance frequency for ^1H is always 6.6 times as large as that for ^2H)



Scheme 2.18 Proposed studies with deuterated allyl ether

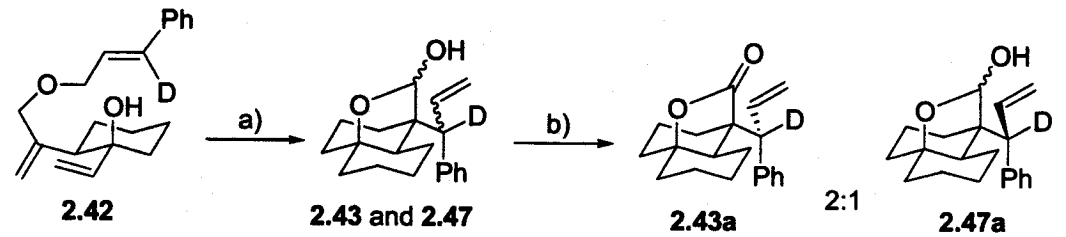
Deuterated allyl bromide **2.46** was first prepared from commercially available α-deuterated benzaldehyde **2.44** using Horner-Wadsworth-Emmons protocol followed by DIBAL reduction and allylic bromination of the alcohol **2.45** (Scheme 2.19). It was used without purification in the etherification of diol **2.20** to give desired allyl ether **2.42** in 25% yield (not optimized). The allyl ether was heated in toluene with Et_3N (3 equiv) at 220 °C for 1 h in the

microwave to yield again a mixture of diastereomers **2.43** and **2.47** (Scheme 2.20). The crude mixture was further oxidized with TPAP to afford a 2:1 mixture of lactones **2.43a** and **2.47a**. However, no loss of deuterium was observed according to ^{1}H NMR thereby ruling out a possible epimerization with a base.



a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C b) DIBAL-H, THF, -78 °C, 25% over 2 steps; c) CBr_4, Ph_3P, CH_2Cl_2, 10 min, rt, use crude in the next step; d) **2.20**, NaH, THF, 26%.

Scheme 2.19 Preparation of deuterated allyl bromide

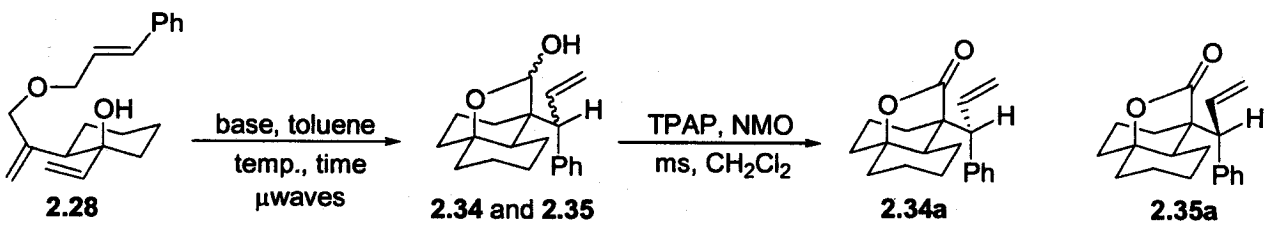


a) 1 h, 220 °C, μwaves, Et_3N; b) ms, TPAP, NMO, CH_2Cl_2, 44% over 2 steps.

Scheme 2.20 The tandem oxy-Cope/ene/Claisen rearrangement of deuterated allyl ether

Interestingly, performing oxy-Cope/ene/Claisen reaction on **2.28** at different temperatures clearly demonstrated that diastereomeric outcome of the reaction is temperature dependent (Table 2-3).

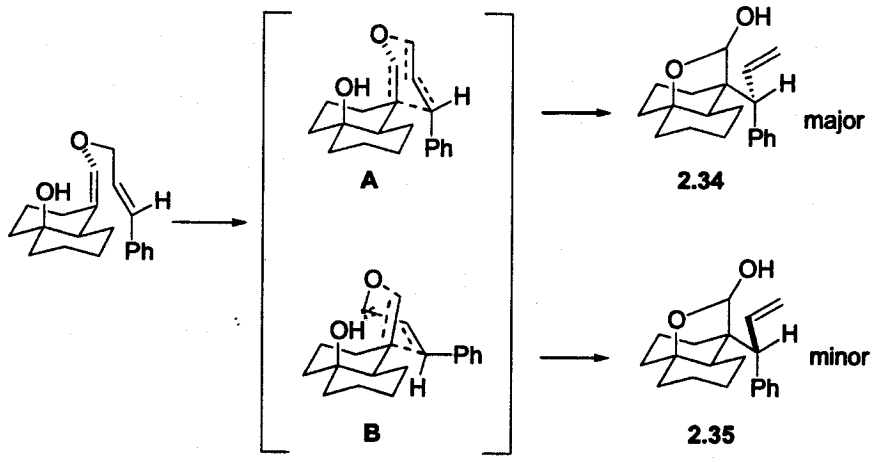
Table 2-3 Temperature dependence of the oxy-Cope/ene/Claisen rearrangement of **2.28**



Entry	Base	Temperature, °C	Yield, % [a]	dr (**2.34a** : **2.35a**) [b]
1	Et_3N	220	44	2:1
2	None	220	N/A	2:1
3	None	200	40	11:1
4	None	180	55	13:1
5	None	160	Trace	N/A

[a] Yield of the lactone mixture over 2 steps [b] Diastereomeric ratios were determined by 300 MHz ^{1}H NMR of a crude mixture of lactones. [c] We have originally reported that the oxy-Cope/ene/Claisen rearrangement of **2.28** at 220 °C occurs with a high diastereoselectivity (dr>25:1), however, this result has been found irreproducible.

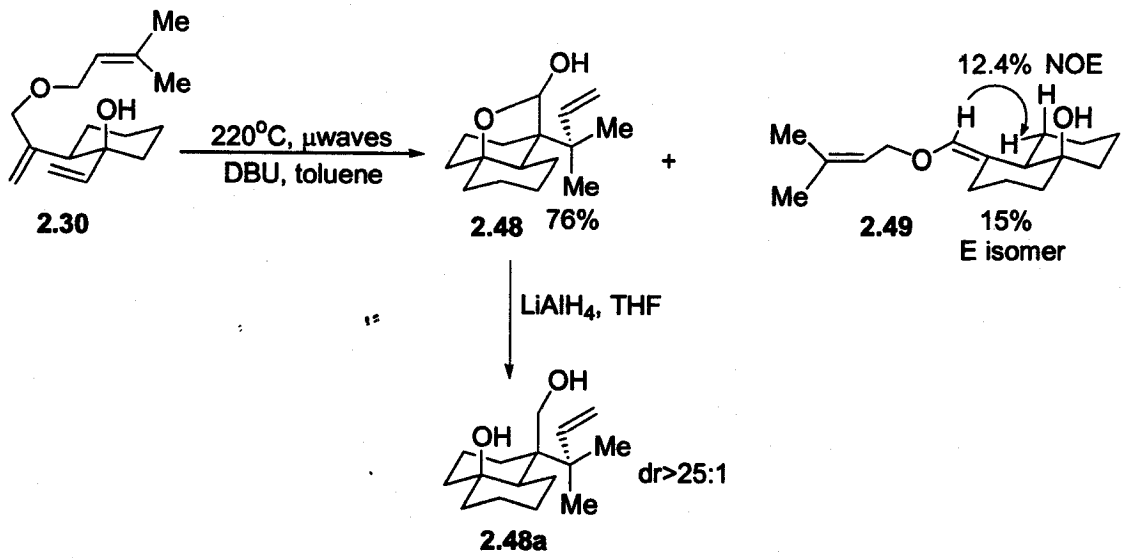
At 220 °C the diastereoselectivity of the tandem reaction remained poor regardless of the presence of the base (entries 1 and 2). However, decreasing the reaction temperature to 200 °C gave a ratio of 11:1 (entry 3) thereby significantly improving the selectivity. The further progress in diastereoselectivity (now 13:1 ratio) was achieved when the temperature was lowered to 180 °C (entry 4). Finally, at 160 °C no reaction or only trace of the product was observed after prolonged heating in the microwave, thereby outlining a temperature barrier for the oxy-Cope reaction. This temperature dependant behaviour suggests that there is a competing pathway for the Claisen reaction at 220 °C. The Claisen rearrangement can occur via chair-like transition state **A** to afford lactol **2.34** (major product) or through higher energy boat-like transition state **B** resulting in the formation of minor isomer **2.35** (Scheme 2.21).



Scheme 2.21 Two possible transition states for the Claisen rearrangement step in the tandem reaction of **2.28**

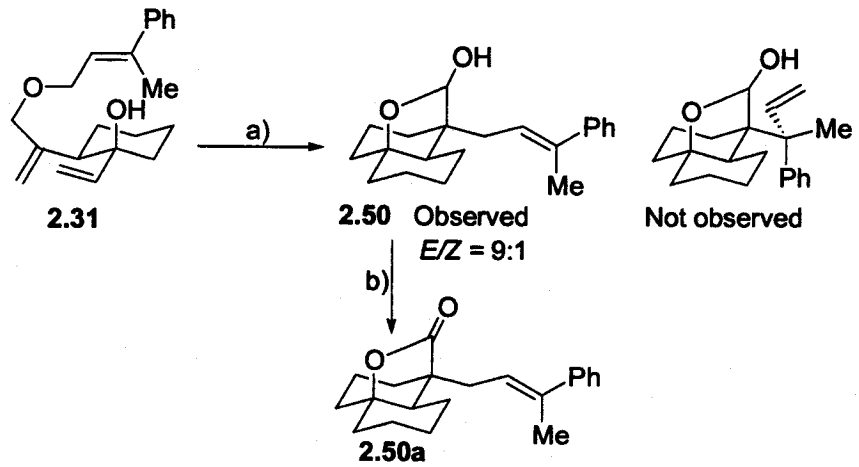
Encouraged by our success in generation of decalines with a tertiary center at C11, we then investigated the synthesis of decalines with a quaternary carbon center at C11.

To our satisfaction, when allyl ether **2.30** was subjected to standard reaction conditions (toluene, DBU, 220 °C, microwave, 1 h) desired lactol **2.48** bearing two adjacent quaternary carbon centers at C11 and C9 was isolated (dr>25:1, determined after reduction with $LiAlH_4$) in 76% yield (Scheme 2.22). Interestingly, *E* enol ether **2.49** (*E/Z* > 98%) was also formed as a side product in 15% yield. (Assignment of the geometry of enol ether **2.49** was done using the same arguments as for compound **2.41**). Prolonged exposure of **2.49** to heat resulted in degradation products.



Scheme 2.22 Formation of decaline with two adjacent quaternary carbon centers

The next step was to attempt a synthesis of decalines with an asymmetric quaternary center. Contrary to expectations, heating allyl ether **2.31** in the microwave afforded a 1,3 shift product **2.50** as a single diastereomer at C9 (dr>25:1)[17] (Scheme 2.23). Moreover, partial isomerization of the double bond was observed (*E/Z*= 9:1)

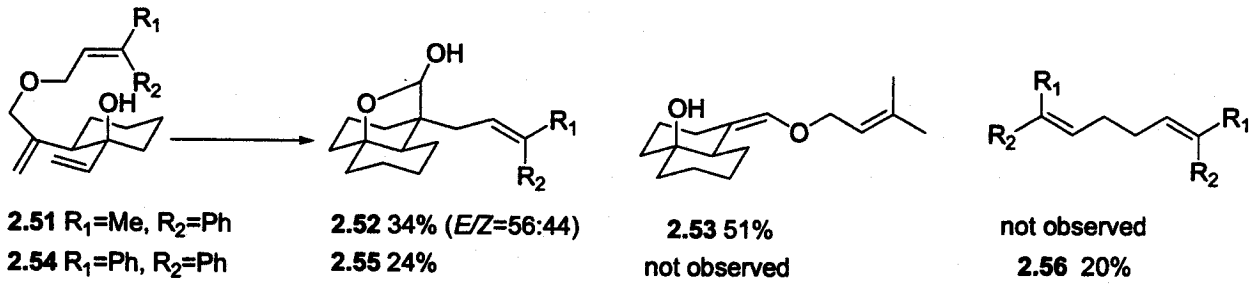


a) DBU, toluene, 220 °C, 1 h, μwaves; b) TPAP, NMO, ms, CH_2Cl_2, 51% over 2 steps.

Scheme 2.23 Formation of 1,3-shift product

[17] Diastereomeric ratio was determined after the oxidation of lactol to corresponding lactone **2.50a**

Later on Julie Frand (MSc student in our lab) demonstrated that irradiation of allyl ether **2.51** gave similar results (Scheme 2.24).[18] Heating of this substrate in the microwave resulted in the formation of 1,3 shift product **2.52** (*E/Z* = 56:44) in 34% yield. As in the case of irradiation of allyl ether **2.30** in which formation of enol ether was observed (Scheme 2.22), enol ether **2.53** was also isolated in 51% yield. Remarkably, irradiations of **2.54** afforded 1,3 shift product **2.55** and dimer **2.56** in 24% and 20% yield respectively.



2.51 R_1=Me, R_2=Ph
2.54 R_1=Ph, R_2=Ph

2.52 34% (*E/Z*=56:44)
2.55 24%

2.53 51%
not observed

not observed
2.56 20%

Scheme 2.24 Results of Julie Farand

Isomerization of the double bond as well as formation of the dimer points to a possibility of radical mechanism involved in the tandem process. Thus formation of an oxaallyl-allyl radical pair **A** in the course of the Claisen rearrangement was postulated (Scheme 2.25). This mechanism is also supported by literature examples.[19] Gajewski has previously demonstrated that the chair-like transition state for the Claisen rearrangement resembles the oxaallyl-allyl radical pair, particularly, in the presence of radical stabilizing substituents. In our case, phenyl groups can act as radical stabilizers. Thereby formation of the oxaallyl-allyl radical pair can lead via consequent recombination to 3,3-, 1,3- or dimer products. Sterically demanding substituents increase the activation energy of the Claisen rearrangement, favoring the alternative 1,3 shift.

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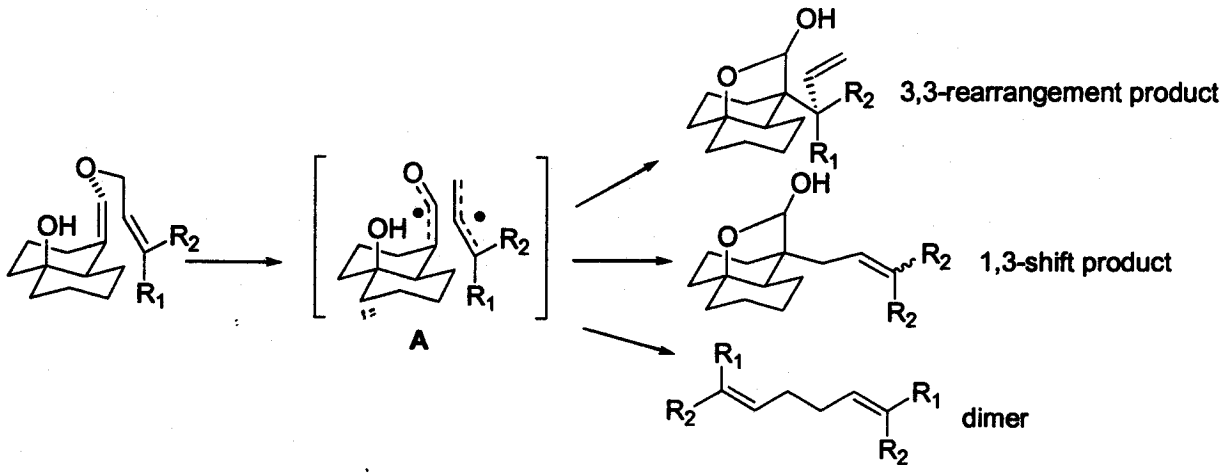
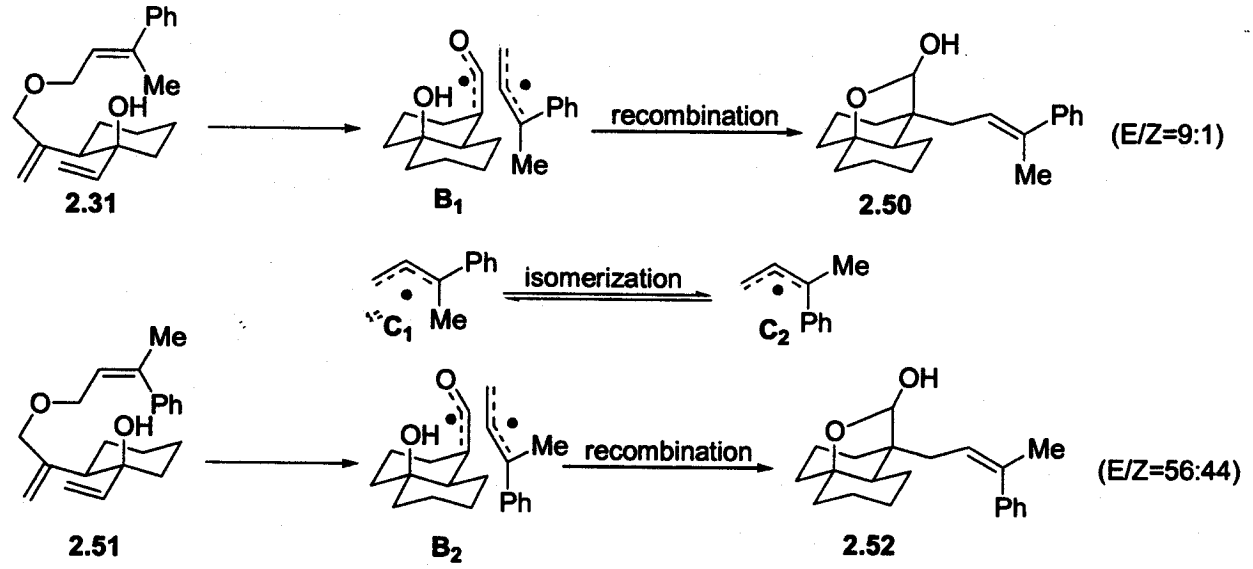
[18] Farand, J.A.; Denissova, I.; Barriault, L. *Heterocycles* **2004**, *62*, 735.
[19] a) Gajewski, J.J.; Conrad, N.D. *J. Am. Chem. Soc.* **1979**, *101*, 2747. b) Barluenga, J. A.; Liz, R.; Bayod, M. *J. Org. Chem.* **1987**, *52*, 5190. c) Gajewski, J.J. *Acc. Chem. Res.* **1997**, *30*, 219 and references therein.



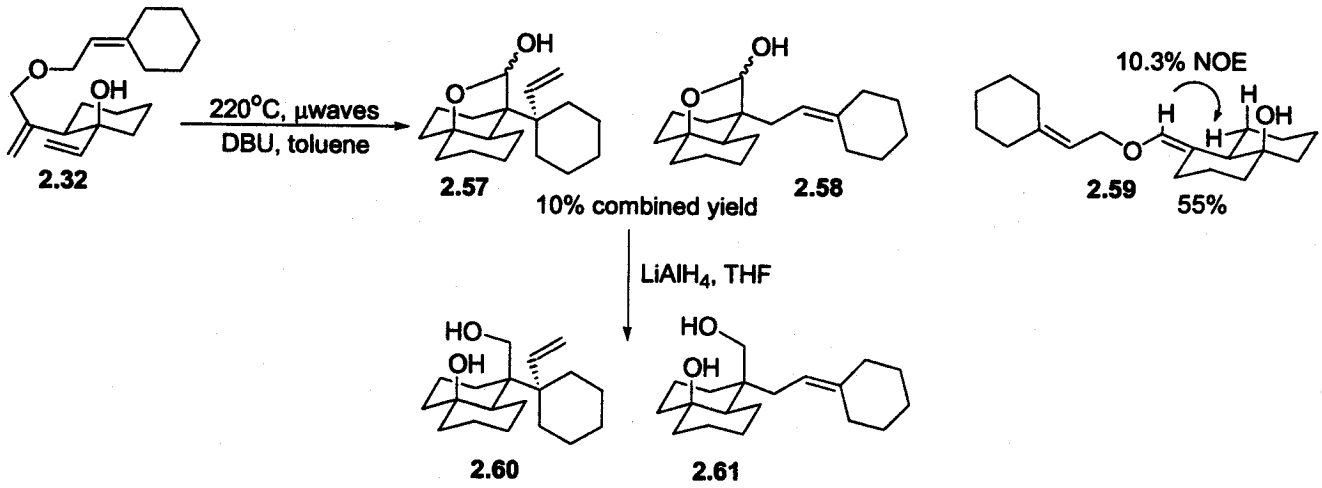
Scheme 2.25 Claisen rearrangement proceeding via an oxaallyl-allyl radical pair

According to the Curtin-Hammett principle and assuming that allyl ethers **2.31** (Scheme 2.26) and **2.51** generate the oxaallyl–allyl radical pairs $\mathbf{B_1}$ and $\mathbf{B_2}$, if isomerization equilibrium of the allyl components $\mathbf{C_1}$ and $\mathbf{C_2}$ is fast, allyl ether should form products **2.50** and **2.52** with identical *E/Z* ratio. The difference in ratios demonstrates that the recombination rate of the radical pair competes with the allyl radical isomerization rate.

An attempt to generate a decalin with asymmetric quaternary carbon centers at C9 and C11 from allyl ether **2.32** was not successful (Scheme 2.27). Formation of a complex mixture of products was observed. *E* enol ether **2.59** was isolated in 55% yield along with a mixture of desired 3,3-product (**2.57**) and 1,3-shift product (**2.58**) in 10% yield. A mixture of **2.57** and **2.58** was reduced by $LiAlH_4$ to afford diols **2.60** and **2.61** in a 1:1.4 ratio. Their structures were tentatively assigned based on spectroscopic data of the mixture, since we were unable to isolate individual compounds.



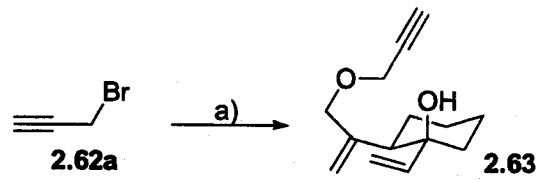
Scheme 2.26 Formation of the oxaallyl-allyl radical pairs in the case of **2.31** and **2.52**



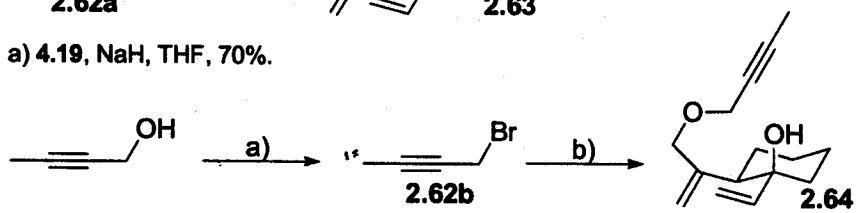
Scheme 2.27 Microwave reaction of allyl ether **2.32**

2.3.2.2 Propargyl ether series

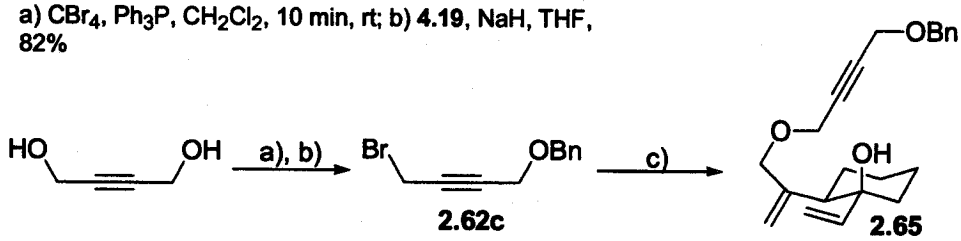
The new tandem oxy-Cope/ene/Claisen reaction gave excellent results in case of propargyl ether series. Ethers **2.63**, **2.64**, and **2.65** were prepared from the corresponding propargyl bromides **2.62a-c** (Scheme 2.28) and heated in the microwave under standard conditions (toluene, DBU, 1h, 220 °C or 210 °C) (Table 2-4).



a) **4.19**, NaH, THF, 70%.



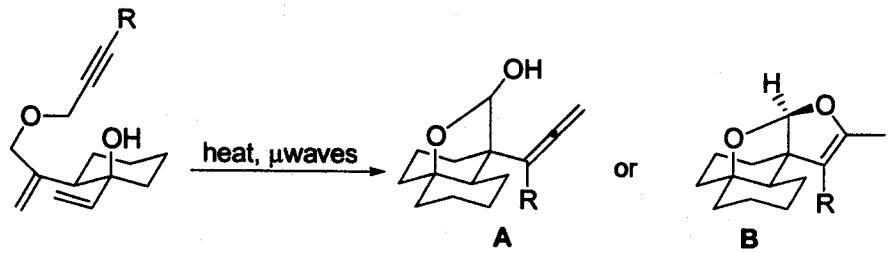
a) CBr_4, Ph_3P, CH_2Cl_2, 10 min, rt; b) **4.19**, NaH, THF, 82%



a) NaH, BnBr, THF; b) CBr_4, Ph_3P, CH_2Cl_2, 10 min, rt; c) **4.20**, NaH, THF, 81%.

Scheme 2.28 Preparation of propargyl ethers

Table 2-4 Oxy-Cope/ene/Claisen reaction of propargyl ethers

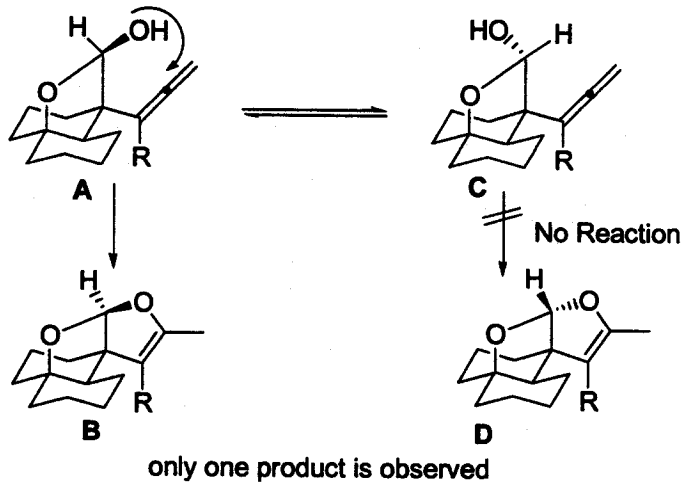


Entry	Substrate	R	Temp., °C	Time, min	Product	Yield, % [a]	Ratio
1	**2.63**	H	220	60	**2.66(A)**	98	25:1 [b]
2	**2.64**	Me	210	50	**2.67(A)**	68	25:1 [b]
3	**2.65**	CH_2OBn	220	60	**2.68(B)**	81	25:1

[a] Isolated yields. [b] Diastereomeric ratios were determined after TPAP oxidation to the corresponding lactones

Depending on the substituents on the propargyl group, either compound **A** or **B** was isolated. In the case of R being electron-donating group such as H or CH_3 (entries 1 and 2) only formation of allene **A** was observed in 98% and 68% yields and great diastereomeric ratios.

When R was an electron-withdrawing group such as CH_2OBn (entry 3) tetracyclic acetal **B** was obtained in 81% yield as a single diastereomer (dr>25:1). Formation of tetracyclic acetal **B** can be explained via attack of the lactol hydroxyl group on the allene (Scheme 2.29). Interestingly, only one isomer is formed since lactol **C** is not able to cyclize to acetal **D** due to geometrical reason. Thereby, the equilibrium is completely shifted toward lactol **A**.



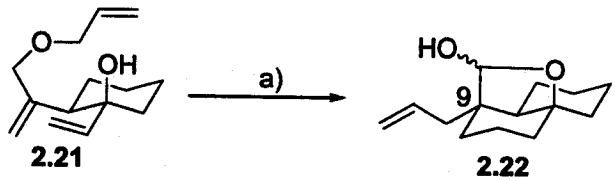
Scheme 2.29 Mechanism of formation of tetracyclic acetal **B**

2.3.3. Conclusion.

The tandem oxy-Cope/ene/Claisen reaction is a powerful method to generate *trans*-decalines with a quaternary carbon center at C9. It can be used to install a tertiary and quaternary carbon center at C11. However, restrictions apply:1) Sterically demanding substituents on the double bond increase the activation energy of the Claisen rearrangement, therefore favoring the alternative 1,3 shift. 2) Claisen rearrangement can pass through a boat-like transition state at high internal temperatures, thereby resulting in loss of diastereoselectivity.

2.4 Application of the oxy-Cope/ene/Claisen reaction to the synthesis of (±)-dihydroagelasimine A

We have previously demonstrated (Section 2.3.2) that the oxy-Cope/ene/Claisen reaction can generate decaline **2.22** with a quaternary carbon center at C9 in only one step from allyl ether **2.21** as illustrated on Scheme 2.30.

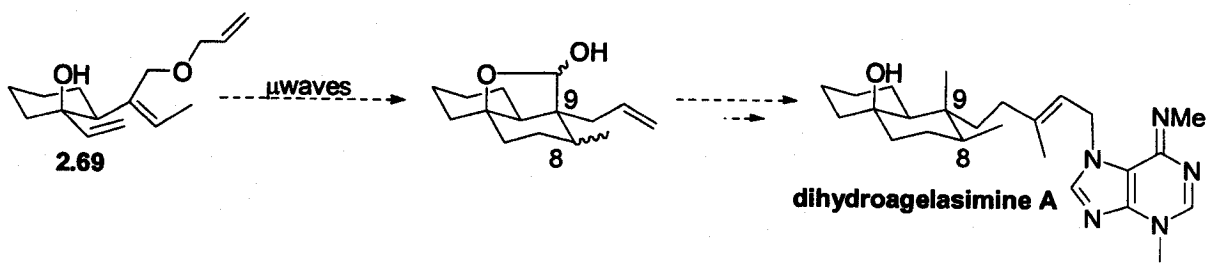


2.21 **2.22**

a) DBU, toluene, μwaves, 220 °C, 75%

Scheme 2.30 Formation of decaline **2.22** with a quaternary carbon center at C9

With this new powerful tool we returned to the total synthesis of dihydroagelasimine A. The first challenge was to establish whether introduction of substitution at C-8 would have any impact on diastereoselectivity of the oxy-Cope/ene/Claisen reaction (Scheme 2.31).



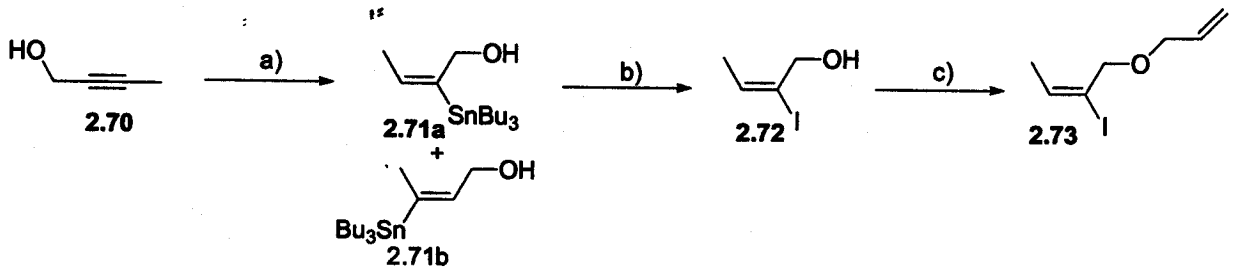
2.69 **dihydroagelasimine A**

Scheme 2.31 Application of the tandem oxy-Cope/ene/Claisen reaction to the synthesis of dihydroagelasimine A

In order to synthesize precursor **2.69** for the tandem reaction several synthetic approaches were investigated. It was envisioned that the large allyl ether side chain could be prepared separately and then attached to a cyclohexane core.

Synthesis of the side chain began with hydrostannylation of 2-butyne-1-ol **2.70** in the presence of palladium (0) catalyst in toluene to afford desired regioisomer **2.71** as a major

product in 70% yield (Scheme 2.32).[20] Tin-iodine exchange in CH_2Cl_2 produced unstable vinyl iodide **2.72** in 89%.[21] The latter was deprotonated with NaH, followed by addition of freshly distilled allyl bromide and refluxed for 3 h to give allylated product **2.74** in 50-70% yield.[22]



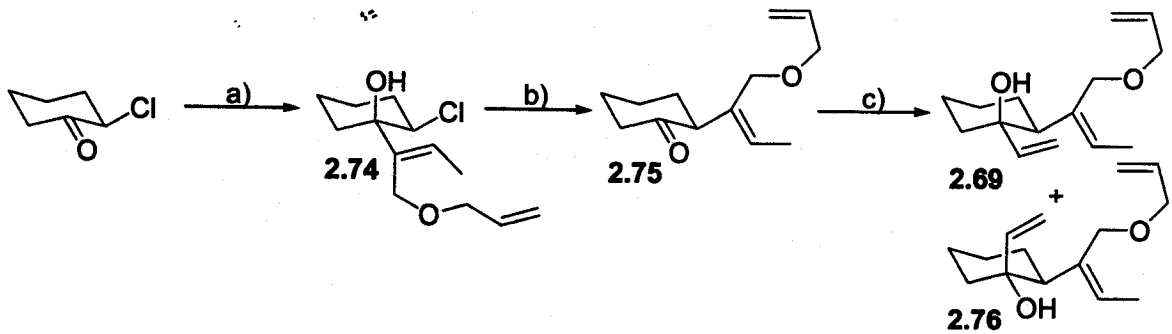
a) $Pd(Ph_3)$, *n*-Bu_3SnH, toluene, 70% of **2.71a** and 10% of **2.71b**; b) CH_2Cl_2, I_2, 89%; c) NaH, THF, 70 %.

Scheme 2.32 Synthesis of the side chain

The 1,2-rearrangement method was first considered for attaching the side chain to a cyclohexane core (as described in Section 2.2.3, Scheme 2.6). Alkylation of commercial 1-chloro-2-cyclohexanone with the vinyl lithium species (generated via metal-halogen exchange of **2.73** with *t*-BuLi at –100 °C for 1 h) gave chlorohydrine **2.74** (Scheme 2.33). It was then deprotonated with excess of vinylmagnesium bromide (3 equiv) to induce [1,2]-rearrangement followed by alkylation. Unfortunately this procedure was inefficient, since a mixture of the intermediate ketone **2.75** and vinyl alcohol **2.69** was always isolated. Thus the strategy was slightly modified. Only 1 equiv of vinylmagnesium bromide was added to chlorohydrine **2.74** affording ketone **2.75** after 1 h of reflux in THF. The product was isolated, purified and treated with vinylmagnesium bromide at rt. The reaction went to completion giving a mixture diastereomers **2.69** and **2.76** in 56% and 12% yields

[20] Miyake, H.; Yamamura, K. *Chem. Lett.* **1989**, 981.
[21] Decomposition was evident when **2.73** was stored in the freezer for more than two days.
[22] The iodide was found to be quite volatile and difficult to handle, but stored for more than six months without degradation.

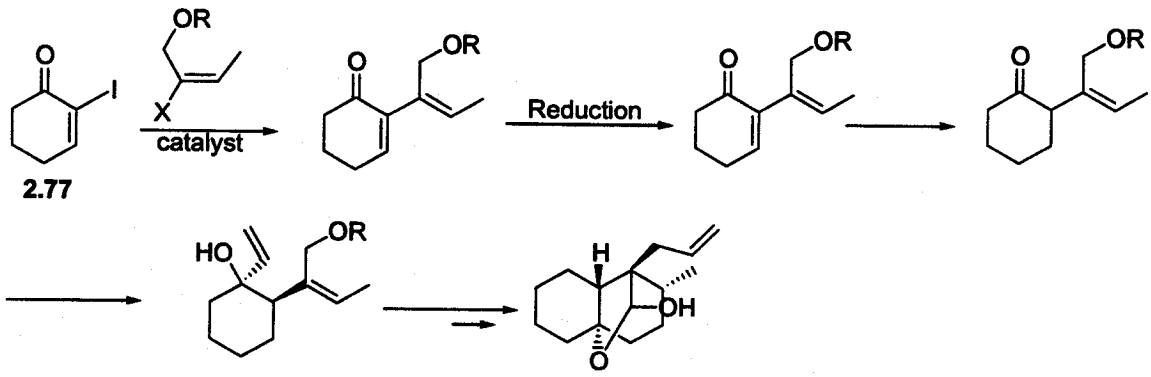
respectively. Formation of diastereomers can be attributed to attack of vinyl anion from both faces of the ketone with preferred mode of attack being anti to the large side chain. Attempts to increase selectivity by decreasing reaction temperature to –78 °C, 0 °C or 10 °C were not successful, giving mainly starting material.



a) **2.73**, *t*-BuLi, Et_2O, -90 °C, 45%; b) vinylmagnesium bromide, THF, reflux, 2 h, 68%; c) vinylmagnesium bromide, THF, rt, 56% of **2.70** and 12% of **2.76**.

Scheme 2.33 Synthesis of allyl ether **2.69**

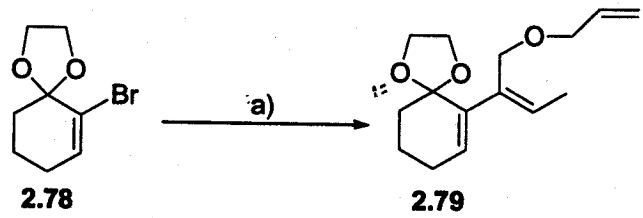
Due to the low yield of the overall process (17% yield over 3 steps) other coupling strategies were also explored, such as Stille or Negishi coupling with iodoenone **2.77** followed by reduction of the conjugated double bond (Scheme 2.34).



Scheme 2.34 Proposed synthesis of **2.69** via metal catalyzed coupling reaction

Unfortunately, Negishi coupling with protected bromo-enone **2.78** resulted in only 26% yield of coupling product **2.79** and was not reproducible. While Stille coupling worked well

with simple vinyl stannanes and several examples were reported in our lab,[23] the presence of extra functionalities on the vinyl stannane compound seemed to decrease its reactivity dramatically resulting in no reaction.

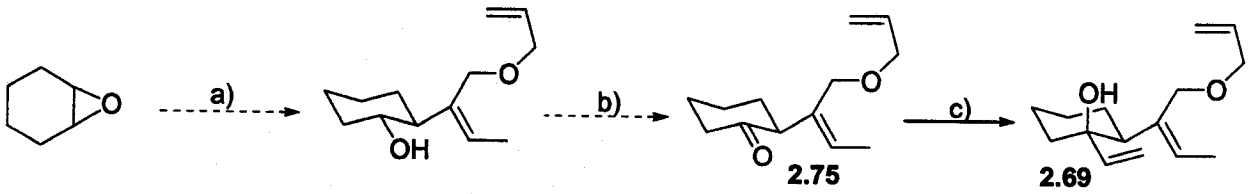


2.78 **2.79**

a) 2 equiv of *t*-BuLi, THF then $ZnBr_2$ then **2.73** and $Pd(Ph_3P)_4$, 26%.

Scheme 2.35 Approach using Negishi coupling

Finally, the epoxide opening strategy was undertaken. A three-step sequence starting from cyclohexene oxide opening with vinyl cuprate generated from vinyl iodide **2.73**, followed by oxidation of the alcohol and vinylmagnesium bromide addition to the ketone was expected to afford desired substrate **2.69** (Scheme 2.36).



2.75 **2.69**

a) **2.73**, *t*-BuLi, Et_2O, Cu (I) catalyst; b) [O], c) vinylmagnesium bromide, THF, rt.

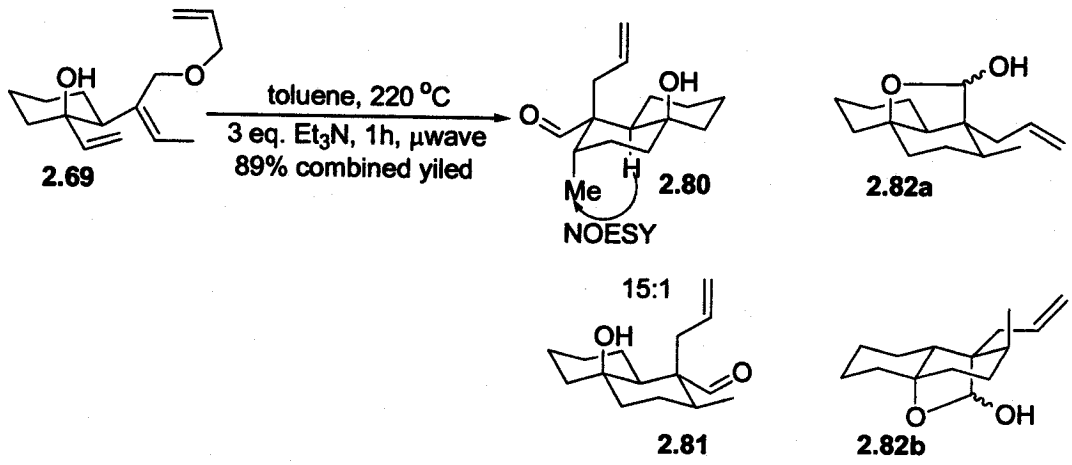
Scheme 2.36 Epoxide-opening strategy

A number of protocols employing cuprates of different order were investigated. Unfortunately, formation of the desired product was never observed. Since most of the conditions required prolonged stirring at –40 to –20 °C, β-elimination could likely be an alternative reaction pathway.[24]

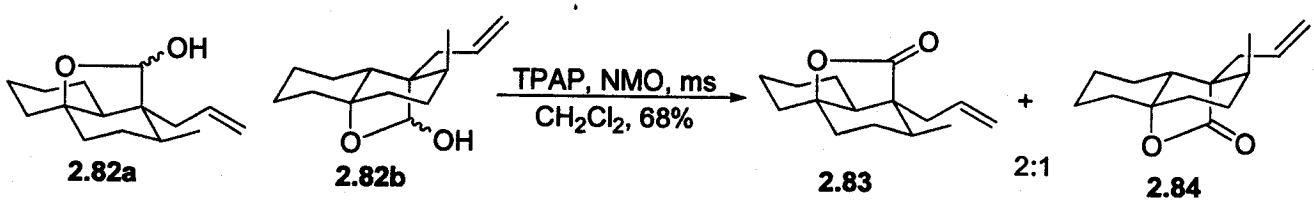
Since all our attempts to optimize the strategy were unsuccessful, we returned to the original approach for generating **2.69**. The latter was subjected to the oxy-Cope/ene/Claisen reaction

[23] Thomas, J.D.O.; MSc Thesis, University of Ottawa, **2002.**
[24] Alexakis, A.; Mangeney, J.F.; Normant, J.F. *Tetrahedron Lett.* **1985**, *26*, 4197.

in the microwave (Scheme 2.37). After heating at 220 °C for 1 h all starting material was consumed according to TLC. The ^{1}H NMR spectrum of the crude reaction mixture was quite complex, indicating a presence of more than two products. Also, a peak at 9 ppm characteristic to an aldehyde was observed. Purification by flash chromatography led to the isolation of two products, the less polar being indeed an inseparable 15:1 mixture of aldehydes **2.80** and **2.81** (47% yield). The more polar spot (41% yield) was found to be a mixture of four lactols **2.82a-b**, which upon oxidation with TPAP afforded a 2:1 mixture of lactone **2.83** and **2.84** (Scheme 2.38). Relative stereochemistry of aldehyde **2.80** was assigned based on a NOESY correlation.



Scheme 2.37 The oxy-Cope/ene/Claisen reaction of **2.69**



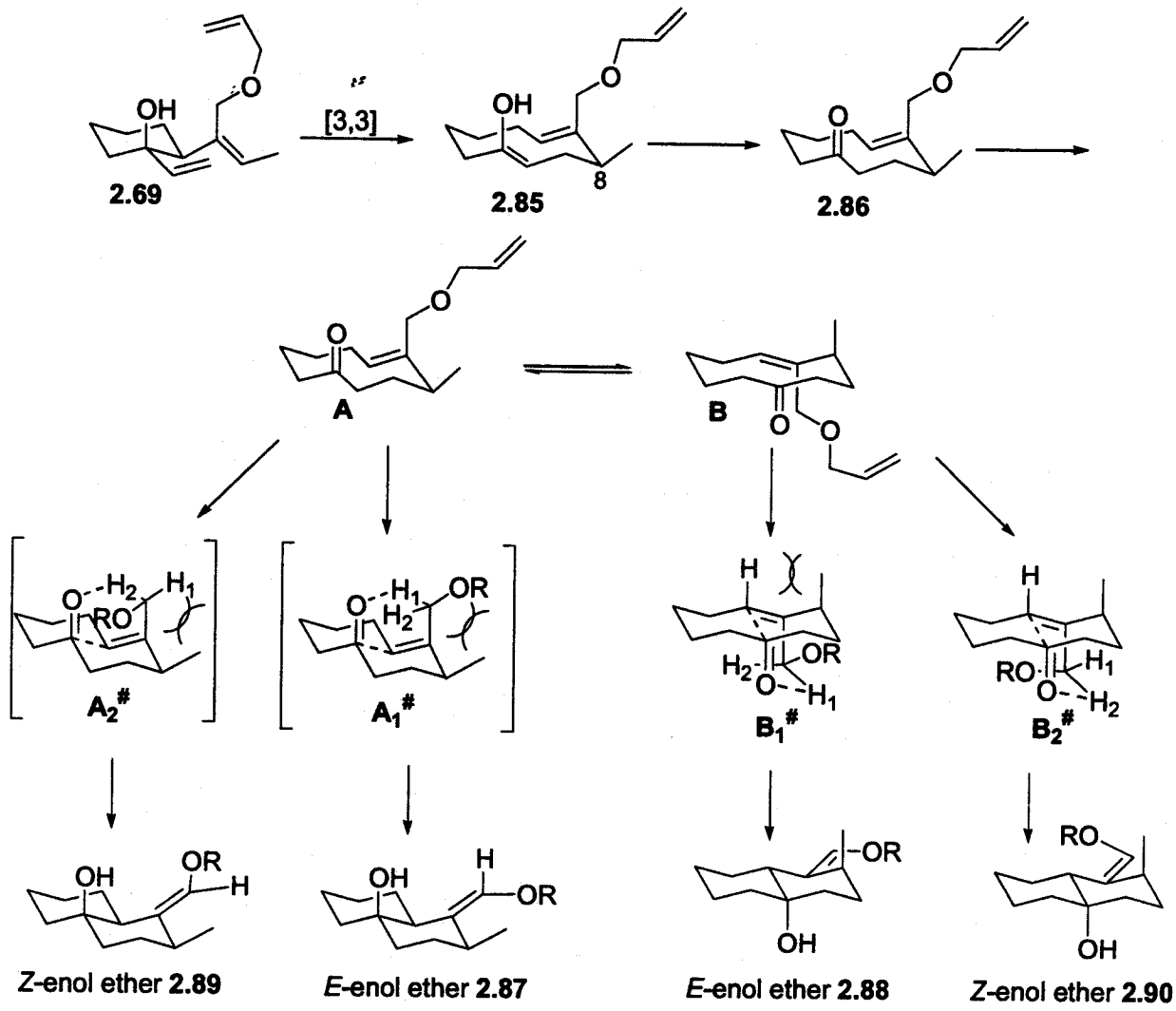
Scheme 2.38 TPAP oxidation of lactols **2.82a** and **2.82b**

In order to rationalize complete loss of selectivity with the addition of the methyl group at C8 a stepwise mechanism of the tandem oxy-Cope/ene/Claisen reaction was thoroughly investigated. As illustrated in Scheme 2.39, the oxy-Cope reaction of **2.69** generates enol

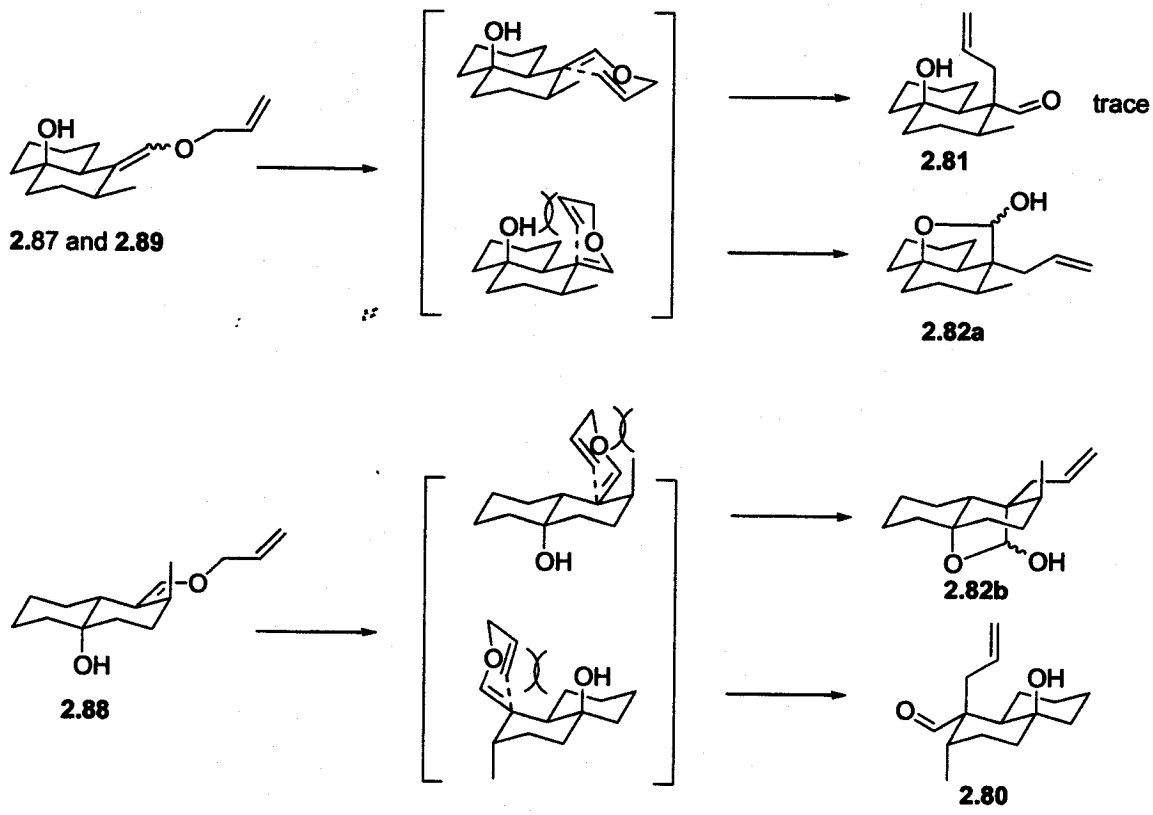
2.85, which then tautomerizes to afford macrocyclic ketone **2.86**. In the latter the equatorial position of methyl at C8 is inherited from the original *cis*-geometry of the vinyl group in the starting material. Ketone **2.86** can either directly proceed to the ene-reaction or first undergo a ring inversion to conformer **B** followed by the ene-reaction. Two transition states should be considered for each of the ene-reactions depending on the proton being abstracted.[25] Abstraction of H_1 (transition states $\mathbf{A_1}^{\#}$ and $\mathbf{B_1}^{\#}$) should lead to formation of *E*-enol ethers **2.87** and **2.88** respectively. When H_2 is being abstracted (transition states $\mathbf{A_2}^{\#}$ and $\mathbf{B_2}^{\#}$), *Z*-enol ethers **2.89** and **2.90** should be generated. In transition state $\mathbf{A_1}^{\#}$, the alkoxy group occupies a lower energy pseudo equatorial position, whereas in transition state $\mathbf{A_2}^{\#}$ the alkoxy group is pseudo axial and develops 1,3-diaxial interactions with the macrocycle ring. However, in $\mathbf{A_1}^{\#}$, there is a destabilizing *syn* pentane interaction between the methyl at C8 and the alkoxy group. Thus, the difference in energy between transition state $\mathbf{A_1}^{\#}$ and transition state $\mathbf{A_2}^{\#}$ becomes less significant and formation of both *E* and *Z* enol ethers is expected. It will not affect, however, the outcome of the subsequent Claisen rearrangement since there is no chiral center at C11 present in the final product. Transition state $\mathbf{B_1}^{\#}$ does not exhibit a *syn* pentane interaction between the methyl at C8 and the alkoxy group and should be favored over $\mathbf{B_2}^{\#}$, resulting in *E*-enol ether **2.88**. The successive Claisen rearrangement can occur from the face either *anti* or *syn* to the alcohol. Since only a trace of aldehyde **2.81** (Scheme 2.37) was detected, it can be concluded that the Claisen rearrangement for enol ethers **2.87** and **2.89** occurs almost exclusively from the face *anti* to the alcohol to avoid steric repulsions, affording lactol **2.82a** (Scheme 2.40). In case of enol ether **2.88** one has to discriminate between attacks *anti* to the alcohol or *anti* to the axial

[25] Again, we assume that Curtin-Hammet principle applies to this case, i.e. a product ration is only dependant on the difference in energies of the corresponding transition states

methyl at C8 with no real preference for either two, since both transition states should have similar energies. This results in formation of both lactol **2.82b** and aldehyde **2.80**.



Scheme 2.39 Proposed mechanism for the oxy-Cope/ene/Claisen reaction of **2.69**. The oxy-Cope/ene part



Scheme 2.40 Proposed mechanism for the oxy-Cope/ene/Claisen reaction of **2.69**. The Claisen part

2.5 Conclusion

Unfortunately, selectivity of the ene-reaction and the Claisen rearrangement step are both affected by the presence of substituent at C8. Ross MacLean (MSc student in our lab) obtained similar results in the course of his attempts toward the total synthesis of natural product Rosane, when substrate containing the allyl group at C8 was employed.[26] Significant effort was also made in our lab to install the functionality at C8 after the oxy-Cope/ene/Claisen reaction, however without major success.

A different approach was taken in the course of our studies. It was proposed that control over the macrocycle ring inversion could be gained by installing extra substituents on the ring,

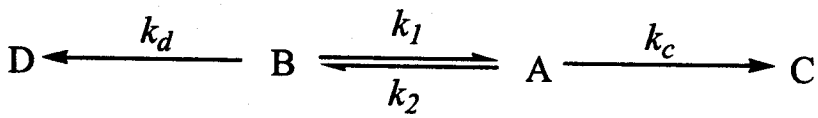
[26] MacLean, P.R.; MSc Thesis, Unversity of Ottawa, **2003**.

thus changing the steric component. This led to the new model studies, which are described in Chapter 3.

Chapter 3 Control of the selectivity at C8

3.1 Background

As we demonstrated in Chapter 2, the loss of selectivity at C8 during both oxy-Cope/ene and oxy-Cope/ene/Claisen tandem reactions originates from the ene-reaction step, in which the starting material, 10-membered ring ketone, can adopt a number of conformations. The reactivity of the system in which many conformers exist in equilibrium is directly related to their conformations. Thus both reaction rates and product ratios may depend on the ratio of the conformers in their ground states as well as the conformation of the corresponding transition states. The general kinetic scheme (Figure 3.1) is applied to describe a system with several reactive conformers.[1]



Three situations that should be considered are listed below:

1. k_1,~k_2 >> k_d and k_c - *Curtin-Hammettt principle* [2]

$$[C]/[D]=e^{-\Delta G^{\ddagger}/RT} \text{ or } \Delta G^{\ddagger}=-RT\ln[C]/[D]$$

2. k_c, k_d >> k_1 and k_2 – *B/A ratio remains constant during the reaction*

D/C ratio reflects B/A ratio

3. k_c, k_d ~ k_1 and k_2 – *equilibrium is not maintained, complex kinetics*

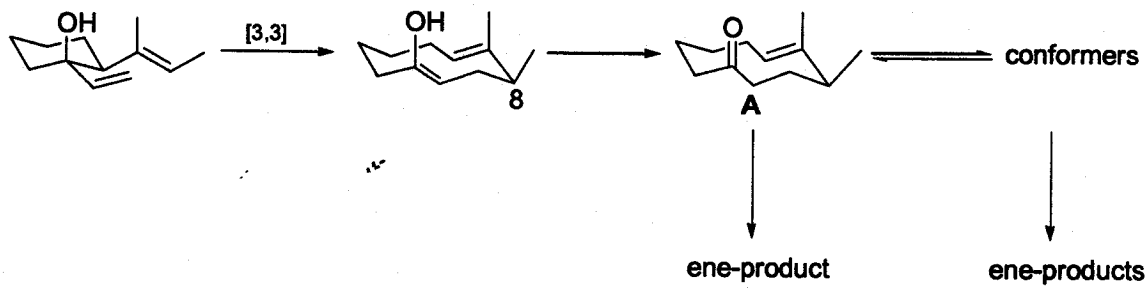
Figure 3.1 General kinetic scheme for two reactants in equilibrium

Returning to the oxy-Cope/ene reaction and concentrating on the ene-step, we should take into account that conformer **A**, which is a direct result of the chair-like transition state of the

[1] For more details see Eliel, E.L.; Wilen, S.H.; Doyle, M.P. In *Basic Organic Stereochemistry*, John Wiley & Sons, Inc.: New York, **2001**, *10-4*, 407 and references cited therein.

[2] a) Curtin, D.Y. *Rec. Chem. Prog.* **1954**, *15*, 111. b) Winstein, S.; Holness, N.J. *J. Am. Chem. Soc.* **1955**, *77*, 5562. c) Hammettt, L.P. In *Physical Organic Chemistry*, McGraw-Hill: New York, **1970**, *5*.d) Seeman, J.I. *Chem. Rev.* **1983**, *83*, 83.

oxy-Cope reaction, can undergo a ring inversion prior the ene reaction to give more than one stable conformer as shown in Scheme 3.1.



Scheme 3.1 Preliminary analysis of the oxy-Cope/ene reaction

To simplify matters we should again consider the case when the rate constants for the ring inversion are much higher than the reaction rates of the ene-reactions of all possible conformers. Thus we can apply Curtin-Hammett principle (case 1, Figure 3.1) and rationalize the product ratio based solely on the energies of the transition states in going from the macrocycle ketone conformers to the ene-products.[3]

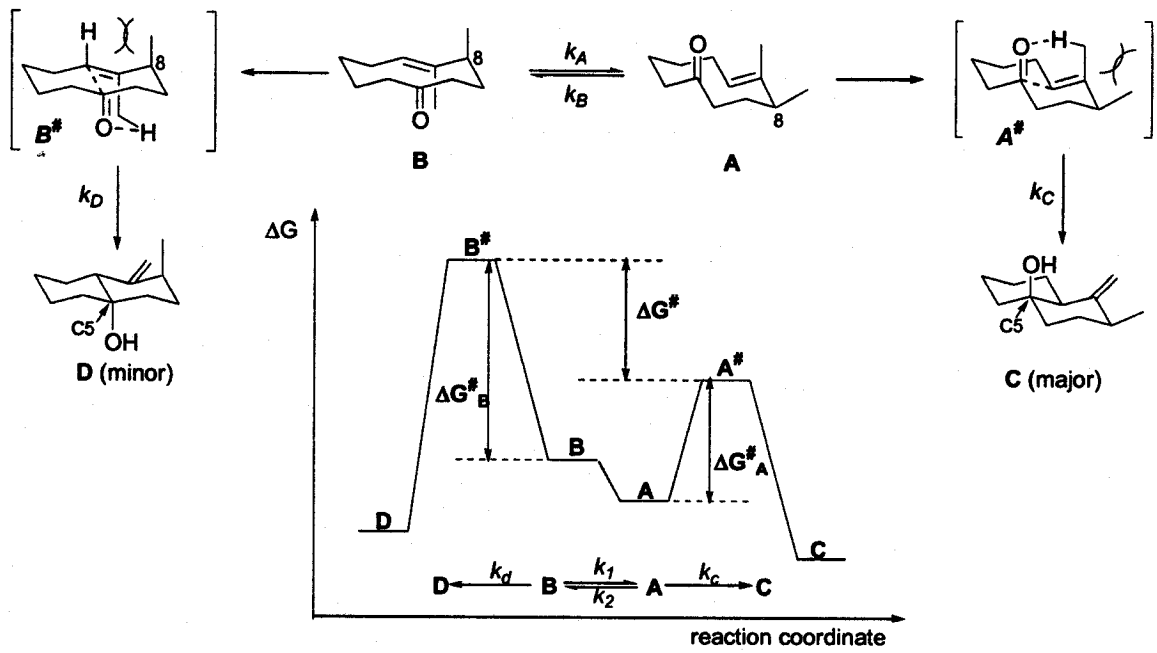
10-membered ring macrocycles can adopt more than two conformations, with the most stable one being a boat-chair-boat (BCB) conformation not a chair-chair-chair (CCC) conformation (Figure 3.2).[4]

Figure 3.2 The most stable conformation for a saturated 10-membered macrocycle

However, not all conformations of the macrocycle can give the ene-products for two reasons. First, the methyl group on the double bond and the ketone group and have to align for further proton abstraction. Second, the ene-reaction has to proceed via chair-like transition state. Therefore due to geometrical constraints, only a few of the possible

[3] For similar example see: Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1979**, *18*, 1623.
[4] Kolossvary, I.; Guida, W.C. *J. Am. Chem. Soc.* **1993**, *115*, 2107.

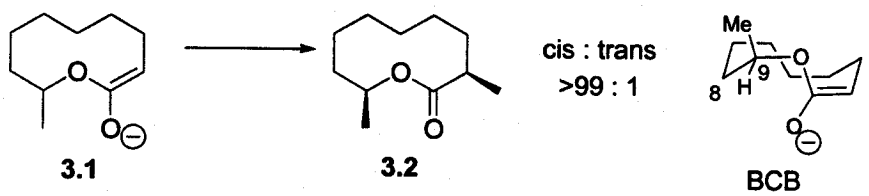
conformers can reach the transition state of the ene-reaction. AM1 semi-empirical calculations that we have performed using Spartan software show that the energy of the transition state for the ene-reaction is minimized when the macrocyclic ketone is in CCC conformation. Now we can assume that conformers **A** and **B** are the only reactive conformers out of all possible ones (Scheme 3.2). Thus conformer **A** will convert to product **C** via transition state $\mathbf{A}^{\#}$ whereas conformer **B** will give product **D** via transition state $\mathbf{B}^{\#}$. As we previously demonstrated (see Scheme 2.7, Chapter 2), the experimental **C/D** ratio was 3.2:1 (at 220 °C). This ratio is consistent with 1.14 kcal/mol energy difference between transition state $\mathbf{A}^{\#}$ (lower in energy) and transition state $\mathbf{B}^{\#}$ at the reaction temperature of 493 K (220 °C).



Scheme 3.2 Conformational and kinetic analysis of the ene reaction of macrocycle conformers **A** and **B**

To increase the **C/D** ratio at a particular temperature one would have to increase the energy difference between $\mathbf{A}^{\#}$ and $\mathbf{B}^{\#}$. For example, to get a ratio of 10:1 at 493 K, the $\Delta\mathbf{G}^{\#}$ would have to be ~2.5 kcal/mol.

W.C. Still *et al.* previously demonstrated by studying medium- and large-ring organic molecules that conformational properties of macrocycles determine the stereochemical outcome of their chemical reactions.[5] This is directly related to the fact that macrocycles are most likely to adopt a conformation in which all transannular nonbonding repulsions are minimized. As already mentioned above, in the case of saturated 10-membered rings BCB conformation is the most stable one. Moreover, the pseudo A-values for a substituent on the macrocycle depend not only on the size of a given substituent but also on which site of the macrocycle this substituent is located. For some sites the energy difference between pseudo equatorial and pseudo axial substitution is so high, that the latter becomes forbidden. Most importantly, W.C. Still has shown that in some cases having a single remote substituent on the macrocycle can provide an effective control over asymmetric induction in the course of a reaction. For example, alkylation of macrocyclic enolate **3.1** under kinetic conditions gave macrocycle **3.2** as a single diastereomer (dr>99:1) (Scheme 3.2), which was in agreement with results of molecular mechanics calculations. The latter demonstrated that BCB was the most stable conformation of the 10-membered enolate and axial substitution was preferred for the methyl at C9 position. Thus, formation of only *cis*-isomer was observed after nucleophilic attack.



3.1 **3.2** BCB

Scheme 3.3 Control over asymmetric induction by a single substituent on a 10-membered macrocycle

[5] Still, W.C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

Based on our kinetic and conformational analysis of the ene-reaction step in the oxy-Cope/ene sequence discussed above (Scheme 3.2), we proposed installing a remote chirality on the macrocyclic ketone to improve the ratio of the ene-products and therefore increasing selectivity at C8. When choosing a proper substituent for the remote stereochemical control, we had to consider its further applicability in the total synthesis of agelasimine. Two factors were taken into account: **1.** In the total synthesis of (±)-agelasimine it was necessary to install geminal dimethyls at C4 (Figure3.3). At the time neither oxy-Cope/ene nor oxy-Cope/ene/Claisen reactions had been performed in our lab with this functionality present on the substrate. Thus its impact on the selectivity outcome of the tandem processes remained unknown and required further investigation. **2.** Extra substituents, if they were not present on the natural product, would have to be easily removable after the oxy-Cope/ene step.

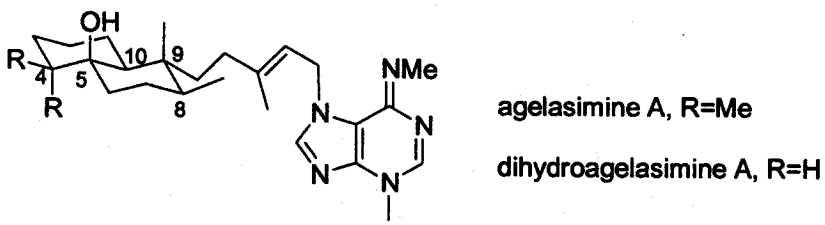


Figure 3.3 Agelasimine A and dihydroagelasimine A

Based on the above-mentioned criteria an "ideal substrate" for our model studies on the oxy-Cope/ene reaction was designed. As shown in Figure 3.4 this substrate contained geminal dimethyls and axial alkoxy group, which could be removed later in the synthesis.

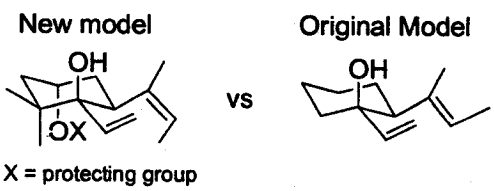
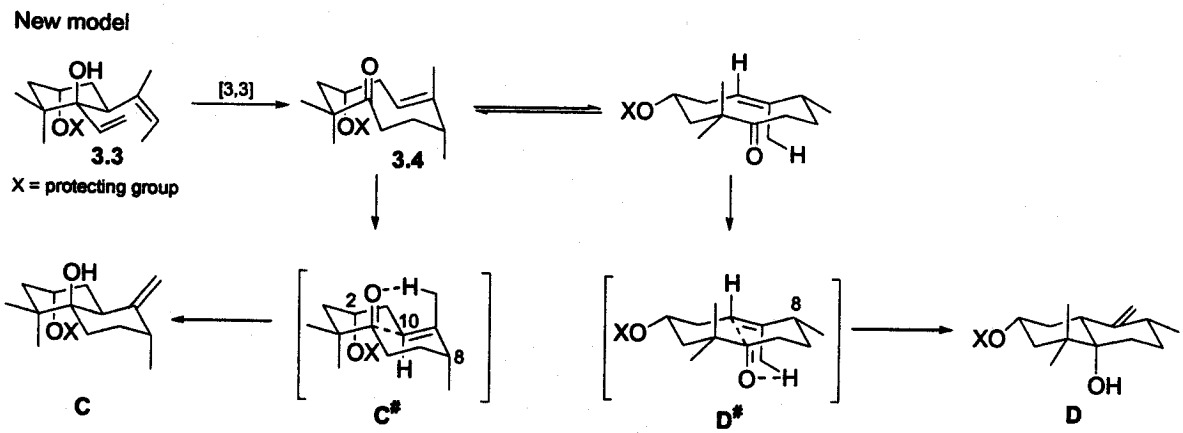


Figure 3.4 Ideal substrate for the model studies on the selectivity at C8 in the oxy-Cope/ene reaction

In addition, the geometry of the butenyl group was changed to *trans* (compare to the *cis* geometry in the original model).

As illustrated in Scheme 3.4, the oxy-Cope reaction of 1,2-divinylcyclohexanol **3.3** followed by tautomerization would generate macrocyclic ketone **3.4**. Once again, assuming that relative stabilities of the conformational isomers of the macrocycle do not contribute to a product ratio (Curtin-Hammett principle), we would only have to account for stabilities of the conformers relevant to the transition state of the ene-reaction.

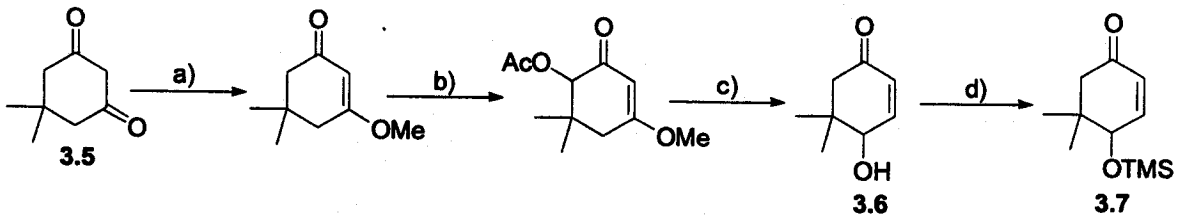


Scheme 3.4 Proposed mechanism of the oxy-Cope/ene reaction of **3.3**

In this regard, two conformers $\mathbf{C}^{\#}$ and $\mathbf{D}^{\#}$ should be considered. In conformer $\mathbf{C}^{\#}$ the methyl at C8 as well as the alkoxy group at C2 occupy axial positions creating unfavorable 1,3-diaxial interactions with hydrogen at C10 and one of the geminal methyls. Inversion of macrocycle **3.4** will lead to transition state $\mathbf{D}^{\#}$ in which the methyl and the alkoxy are in equatorial positions, thus making it preferred over $\mathbf{C}^{\#}$. The ene-reaction would then produce **D** as a major product, with the methyl at C8 *syn* to the bridgehead alcohol exactly as in the natural product. It was expected that the presence of an alkoxy group on the macrocycle would increase $\Delta G^{\#}$ ($\Delta G^{\#}=\Delta G^{\#}_{C}-\Delta G^{\#}_{D}$) so that only product **D** is formed.

3.2 Results and Discussion

In planning the synthesis of substrate for model studies, 1,4 addition to conjugated ketone **3.7** was chosen to install the butenyl moiety. The synthesis of ketone **3.6** from 5,5-dimethyl-cyclohexanedione **3.5** was previously reported in the literature.[6] This procedure was further optimized and allowed for convenient generation of up to 10 g of **3.6**. The latter was protected with TMSCl to afford ketone **3.7** in good yield.



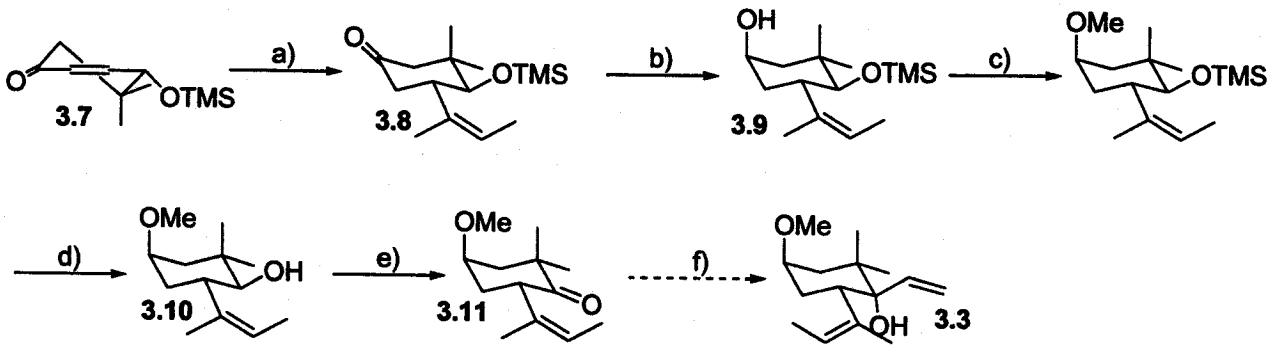
a) $(MeO)_3CH$, MeOH, H_2SO_4, 93%; b) $Mn(OAc)_3$, benzene, reflux, 48h, 91%; c) $LiAlH_4$, reflux, Et_2O, 70%; d) TMSCl, imidazole, THF, 82%.

Scheme 3.5 Synthesis of the starting material **3.7** for the model studies

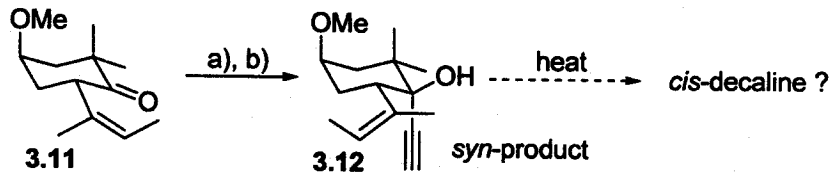
A convenient protocol was established for the 1,4 conjugate addition on ketone **3.7**. The vinyl lithium species generated from *cis*-2-bromo-but-2-ene via metal-halogen exchange with *t*-BuLi in deoxygenated Et_2O at –78 °C was canulated to a suspension of copper (I) cyanide (0.5 equiv) in Et_2O to give the corresponding cuprate reagent(Scheme 3.5). Addition of **3.7** to the cuprate solution at –78 °C followed by NH_4OH/NaCl work up provided **3.8** in yields varying from 80 to 98% depending on the reaction scale. Ketone **3.8** was then reduced with L-selectride to afford axial alcohol **3.9** in 60% yield, resulting from an equatorial attack of the reducing agent on the carbonyl group. The free alcohol was deprotonated with KH and trapped with methyl iodide followed by removal of TMS group from the second alcohol to give **3.10** in 85% yield over two steps. Alcohol **3.10** was oxidized with TPAP to ketone **3.11**, thus placing us only one step away from desired compound **3.3**. Unfortunately, all our

[6] Demir, A.S.; Sayrac, T.; Watt, D.S. *Synthesis*, **1990**, *12*, 1119.

attempts to alkylate ketone **3.11** with vinylmagnesium bromide were unsuccessful, probably due to the axial substituents hindering approach to the carbonyl. Surprisingly, when vinylmagnesium bromide was replaced with a smaller nucleophile, lithium TMS-acetylene, only *syn*-product **3.12** was obtained. The relative stereochemistry of **3.12** was assigned from the NOE experiment, as illustrated in Figure 3.5. (For more details see Appendix 2, Table 1)



a) *cis*-2-bromo-but-2-ene, *t*-BuLi, Et_2O, CuCN, -78 °C, 91%; b) L-selectride, THF, -78 °C, 60%; c) MeI, KH, THF; d) TBAF, THF, 85% over 2 steps; e) TPAP, NMO, CH_2Cl_2, ms, 80%.



a) TMS-acetylene, *n*-BuLi, THF, -78 °C; b) TBAF, THF, 88% over 2 steps

Scheme 3.6 Synthesis of the precursor for model studies

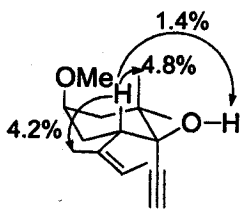
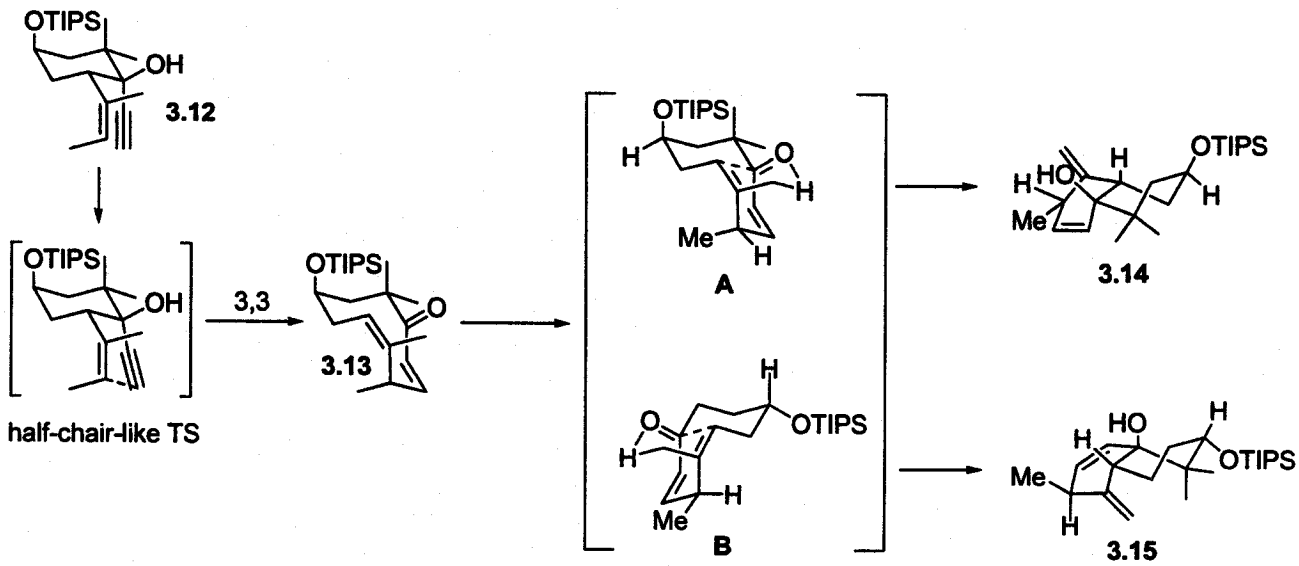


Figure 3.5 NOE correlations for **3.12**

It was not obvious what would be the stereochemical outcome of the oxy-Cope/ene reaction of **3.12.** Assuming that the oxy-Cope rearrangement would proceed via half chair-like

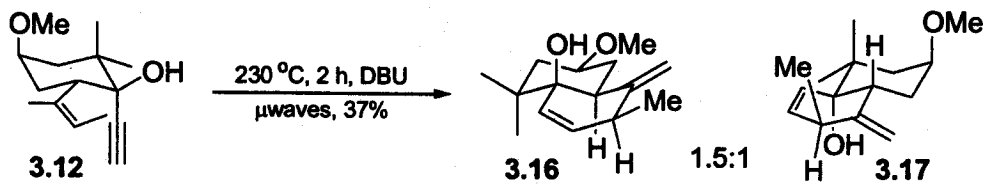
transition state one would expect to obtain macrocyclic ketone **3.13** with a *Z* double bond (the bond which participates in the ene-reaction) as illustrated in Scheme 3.7. This ketone could give rise to two *cis*-decaline diastereomers **3.14** and **3.15** formed via two different transition states **A** and **B**. If the Curtin-Hammettt principle applied, the energy difference between these transition states would determine the ratio of the products **3.14** and **3.15**.



Scheme 3.7 Expected outcome of the oxy-Cope/ene reaction of **3.12**

To establish what the stereochemistry of the oxy-Cope/ene products would be, substrate **3.12** was dissolved in toluene followed by addition of Et_3N (3 equiv). The resulting solution was deoxygenated with argon, sealed and heated in the microwave. Remarkably, the reaction required higher temperature (230 °C) and longer time (2 h) to proceed than in the case of *trans*-1,2-divynylcyclohexanoles (compare to 200-220 °C, 1h). The ^1H NMR spectrum of the crude reaction mixture showed a 1.5:1 mixture of diastereomers and starting material (<5%) was also detected by GC. Interestingly, using DBU (12 equiv) instead of Et_3N improved the yield and suppressed product decomposition. Separation by flash chromatography afforded two products **3.16** and **3.17** in 27% and 10% yields respectively (2.7:1 ratio) (Scheme 3.8).

Partial loss of one of the products was attributed to its instability on the silica gel; basifying silica gel with Et_3N did not improve the yield. Contrary to our expectations, the diastereomers **3.16** and **3.17** were found to be *trans*-decalines. The relative stereochemistry was assigned based on 2D NMR data including COSY, NOESY and HMQC (Figure 3.6, see also Appendix 2, Table 2 and 3).



Scheme 3.8 Oxy-Cope/ene reaction of **3.12**

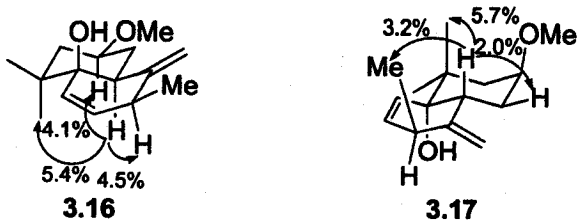
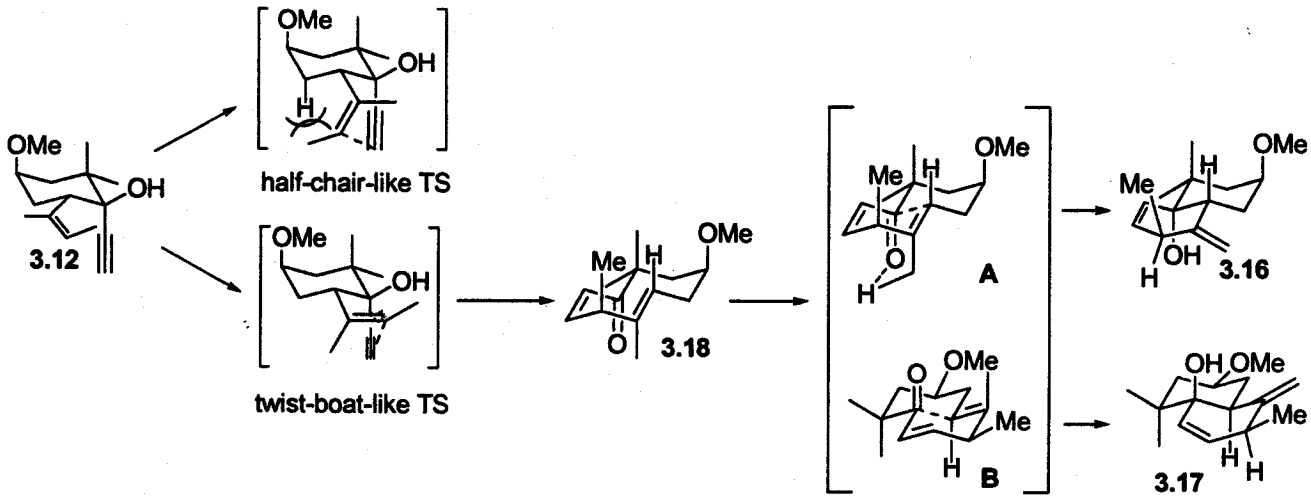


Figure 3.6 Some NOE correlations for **3.16** and **3.17**

Our original prediction of *cis*-decaline formation was based on the assumption that the oxy-Cope rearrangement of **3.12** occurs via the half-chair-like transition state. However, closer examination of this transition state indicates that there is a strong interaction between one of the methyls of the butenyl moiety and the cyclohexane ring as depicted in Scheme 3.9. Alternatively, the oxy-Cope reaction can pass through a twist-boat-like transition state to give macrocyclic ketone **3.18** with an *E* double bond (the bond further participating in the ene-reaction). Two diastereomers **3.16** and **3.17** are formed as a result of the ene-reaction occurring via transition state **A** and **B** respectively. The ratio of 1.5:1 indicates that there is no sufficient energy difference between the two transition states (1.5:1 ratio corresponds to a $\Delta G^{\#}$ of 0.4 kcal/mol when calculated for 503 K)

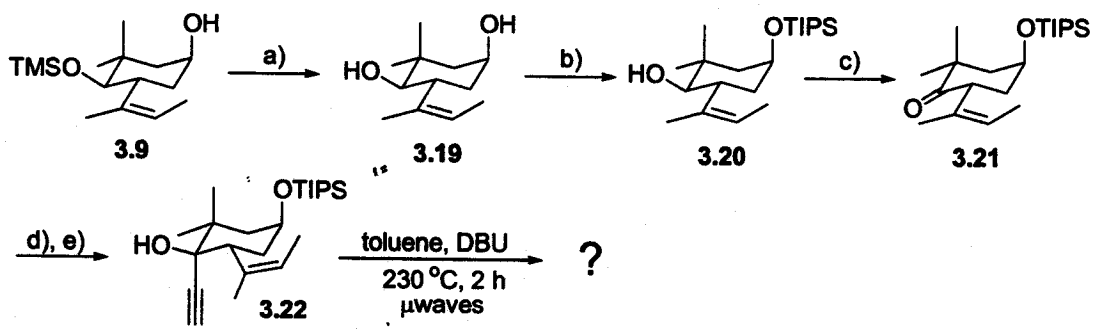


Scheme 3.9 Proposed mechanism of the tandem oxy-Cope/ene reaction of **3.12**

To investigate if the ratio can be improved by simply changing the size of the protecting group on the alcohol, the original procedure was slightly modified to prepare divinyl alcohol **3.22** having its secondary alcohol protected with a large TIPS group (Scheme 3.10).

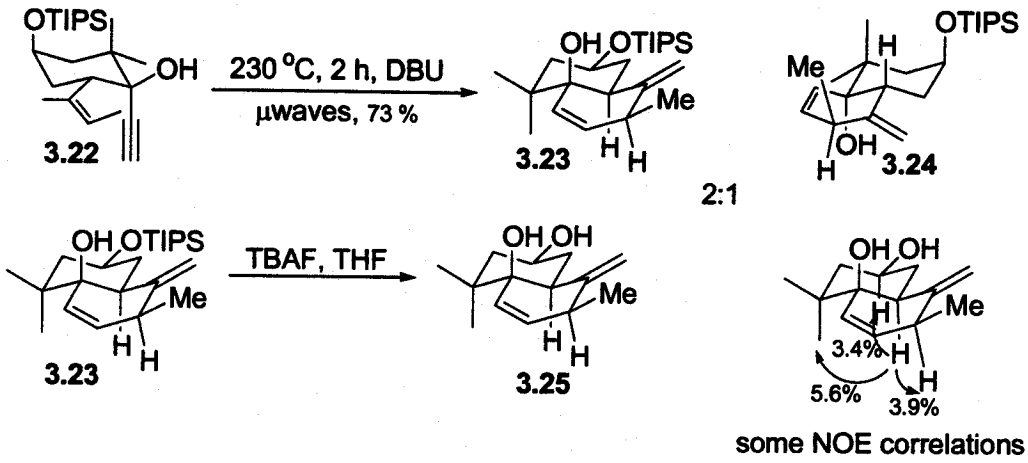
When subjected to the same experimental conditions (toluene, 10 equiv of DBU, 230 °C, 2 h) in the microwave both substrates rearranged to give 2:1 ratio of diastereomers (Scheme 3.11).[7] Multiple purification of the mixture containing TIPS protected diastereomers afforded **3.23** contaminated with non-polar impurities in 33% yield and a mixture of **3.23** and **3.24** in 40% yield. Compound **3.23** was treated with TBAF to give diol **3.25**, which was easily purified by flash chromatography. Full stereochemical assignment of **3.25** was achieved based on 2D NMR data (See Appendix 2, Table 4). Unfortunately, we were unable to isolate **3.24** from the mixture. Thus the stereochemistry of this product was assigned by analogy with methyl-protected compound **3.17**. It appears that the size of the substituent on the oxygen does not affect the ratio. However this preliminary conclusion can only be made for the case of *cis*-1,2-vinyl alkynyl cyclohexanols.

[7] Ratios were determined by GC and ^{1}H NMR of the crude reaction mixture



a) TBAF, THF, 100%; b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C; 75% c) TPAP, ms, NMO, CH_2Cl_2, 65%; d) TMS-acetylene, *n*-BuLi, THF, -78 °C; e) TBAF, THF, rt., 58% over 2 steps.

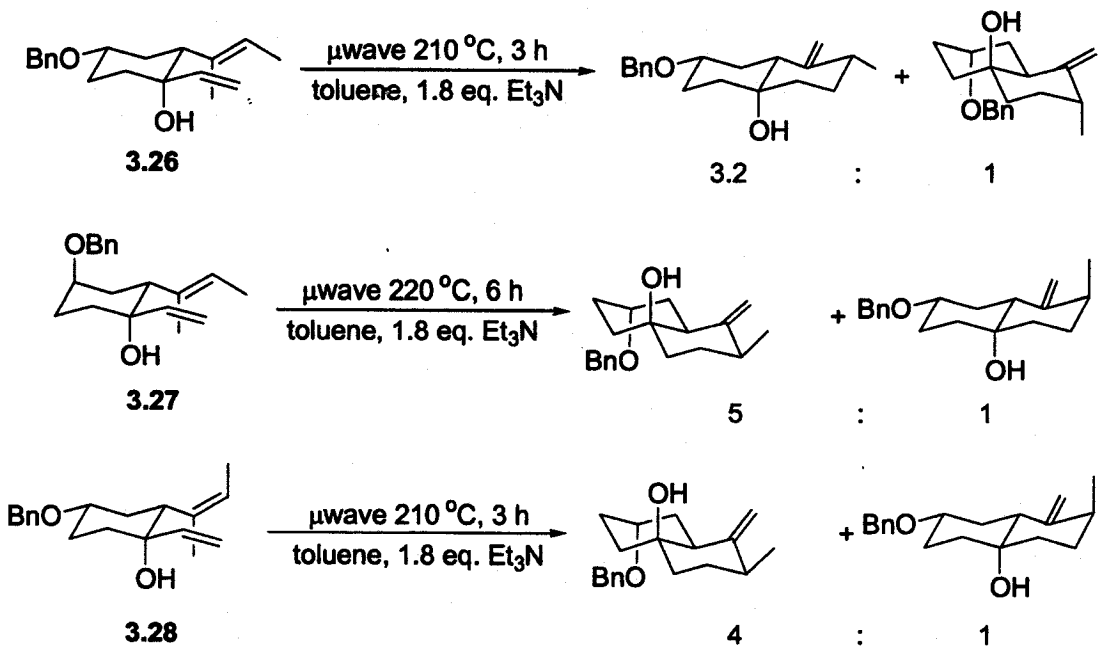
Scheme 3.10 Preparation of **3.22**



Scheme 3.11 The oxy-Cope/ene reaction of **3.22**

Since we were unable to prepare *trans*-1,2-divinylcyclohexanol while having geminal methyls on the ring, we decided to study the influence of a remote alkoxy group on the oxy-Cope/ene reaction using more simple substrates. During her summer project Nathalie Goulet prepared and tested three compounds (**3.26-3.28**) having either an axial or an equatorial benzyloxy group or a different geometry of the butenyl group as shown in Scheme 3.12. In all cases the oxy-Cope/ene reaction produced mixtures of products. The highest ratio (5:1)

was observed in the case of **3.27**. The diastereoselectivity of these reactions can also be rationalized using the Curtin-Hammett principle.



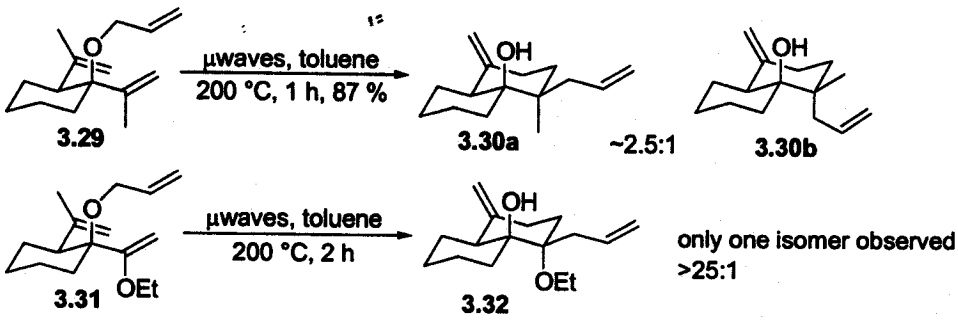
Scheme 3.12 Natalie Goulet results

We can therefore conclude that the remote alkoxy substituent at C2 does not provide adequate energy difference between macrocycle conformations of the ene-reaction transition states such that only one product is formed.

3.3 Influence of the electronic factors on the selectivity at C8

Our previous attempts to control the selectivity of the ene-reaction step in the tandem oxy-Cope/ene sequence were based exclusively on altering the steric factors of the system. A different approach was chosen based on the results obtained by Effiette Sauer during her

studies on an oxy-Cope/Claisen/ene reaction.[8] She observed that heating allyl ether **3.29** at 200 °C for 1 h in the microwave gave a 2.5:1 mixture of diastereomers **3.30a** and **3.30b**, whereas heating **3.31** under the same conditions provided decaline **3.32** as a single product as depicted in Scheme 3.13.

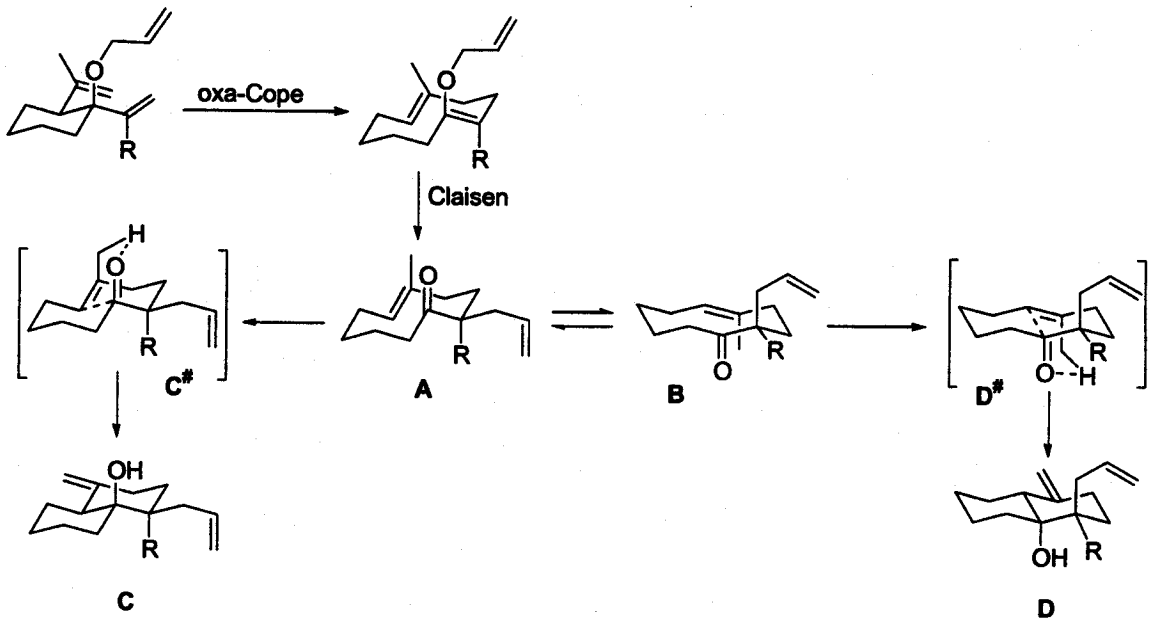


Scheme 3.13 Oxy-Cope/Claisen/ene reaction

The reaction mechanism is shown in Scheme 3.14. The oxy-Cope reaction of the allyl ether gives 10-membered ring enol ether, which then undergoes the Claisen rearrangement to generate macrocyclic ketone **A**. Assuming that conformer **A** is in rapid equilibrium with conformer **B**, two products **C** and **D** can be obtained from the ene-reaction in a ratio dependant only on the energy difference between transition states from **A** to **C** and **B** to **D**. The 2.5:1 ratio, observed in the case of **3.29** (R=Me), corresponds to 0.86 kcal energy difference (calculated for 473K, 200 °C) between transition states $\mathbf{C}^{\#}$ and $\mathbf{D}^{\#}$. The value seems to be reasonable since in $\mathbf{C}^{\#}$ the allyl group occupies equatorial position and the methyl group is axial, whereas in $\mathbf{D}^{\#}$ it is a reverse. However, it is unlikely that changing from the methyl group to the ethoxy (smaller A value then the methyl: A_{Me}=1.74 kcal/mol, A_{OEt}=0.65 kcal/mol) would raise the energy difference between $\mathbf{C}^{\#}$ and $\mathbf{D}^{\#}$ up to 3.14 kcal/mol, the value accounting for the 25:1 ratio. This ratio cannot be explained using the Curtin-Hammett principle. One could rationalize the high selectivity assuming that the ene-

[8] Sauer, E. L. O.; Barriault, L. *J. Am. Chem Soc.* **2004**, *in press*.

reaction is competing with equilibrium between **A** and **B**. Then the ratio of the products should reflect the **A/B** ratio (case 2, Figure 3.1). Since **B** is not initially present in the reaction mixture, **A** can convert to the ene-product before undergoing a ring-inversion to **B**, thus forming **C** exclusively. The ethoxy-group does not change the steric factors but contributes to the rate enhancement of the ene-reaction. This is supported by the fact, that the electron withdrawing groups α to the carbonyl accelerate ene-reactions.[9]

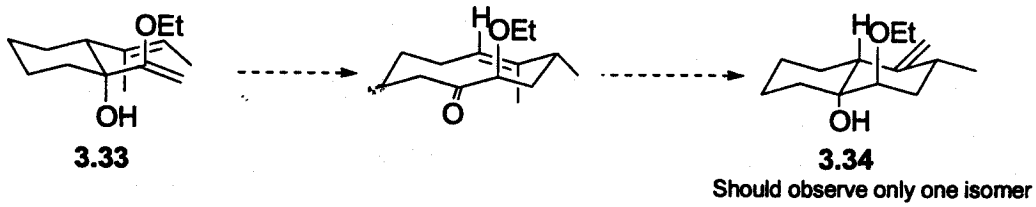


Scheme 3.14 Proposed mechanism for the Oxy-Cope/Claisen/ene reaction

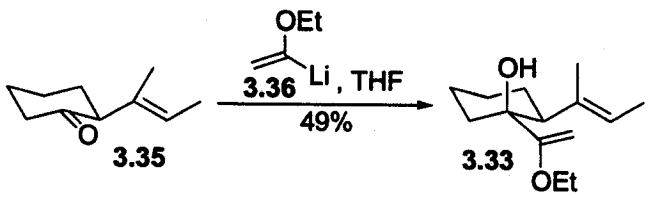
As we learnt from the observations made by Effiette Sauer, the presence of ethoxy group α to the carbonyl accelerates the ene-reaction thus eliminating the macrocycle inversion and formation of the second diastereomer. We then envisioned that the oxy-Cope/ene reaction of 1,2-divinylcyclohexanol **3.33** in the microwave would result in exclusive formation of decaline **3.34**, in which the methyl group at C8 would be equatorial and *syn* to the bridgehead alcohol as illustrated in Scheme 3.15. Substrate **3.33** was prepared in 49% yield

[9] a) Sinder, B.B. In *Comprehensive Organic Synthesis, Combining C-C π bond*; Paquette, L.A., Ed.; Pergamon Press: Oxford, **1991**; Vol. 5; Chapter 1.1. b) Sinder, B.B. In *Comprehensive Organic Synthesis, addition to C-X π bond*; Heathcock, C.H., Ed.; Pergamon Press: Oxford, **1991**; Vol. 2; Chapter 2.1.

via alkylation of ketone **3.35** with vinyl lithium species **3.36** in THF as shown in Scheme 3.16.



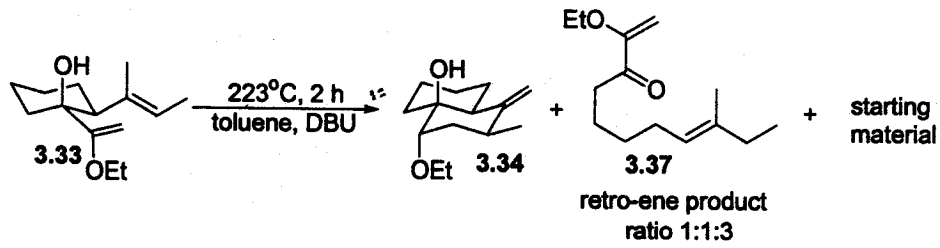
Scheme 3.15 Proposed outcome for the oxy-Cope/ene reaction of **3.33**



Scheme 3.16 Preparation of **3.33**

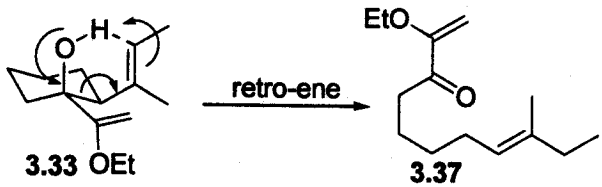
Heating **3.33** in toluene with Et_3N (3 equiv) at 210 °C for 2 h gave only starting material. The temperature was increased to 220 °C, however, after heating for 2 h the oxy-Cope/ene reaction did not go to completion. ^1H NMR of the crude reaction mixture indicated the presence of desired decaline **3.34** as a single diastereomer along with decomposition products and the starting material. In agreement with earlier observations, using DBU instead of Et_3N eliminated decomposition, although it did not affect the rate of the reaction as shown in Scheme 3.17. Heating **3.33** in toluene in the presence of DBU for 2 h at 223 °C afforded the desired product **3.34**, an unknown side product and a starting material in a 1:1:3 ratios (detected by ^1H NMR). Purification by flash chromatography allowed for separation of **3.34** in 18% yield and an inseparable mixture of the starting material and the side product in 70% yield. The relative stereochemistry of **3.34** was assigned based on the 2-D NMR experiments (Figure 3.7). The first evidence of the axial position of the ethoxy substituent

was given by two small J values (2.3 Hz) of the adjacent proton H_A. Strong correlation between H_B and the protons of the methyl group was observed from NOESY experiment.



Scheme 3.17 Oxy-Cope/ene reaction of **3.33**

The side product **3.37** was believed to be a result of the retro-ene reaction of the starting material (Scheme 3.18).



Scheme 3.18 Explanation of formation of the side product

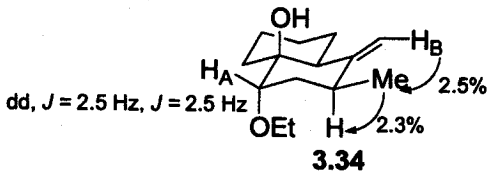


Figure 3.7 NOE correlations for **3.34**

Jeff Warrington and Daniel Deon (Barriault's laboratory) have previously reported formation of retro-ene products when substrates with an electron rich double bond attached to the tertiary alcohol were used for the oxy-Cope/ene reaction.[10, 11] Their observation can be applied to our case since oxy-Cope/ene substrate **3.33** has an electron rich vinyl ether group.

[10] Warrington, J. M.; Yap, G.P.A.; Barriault, L. *Org. Lett.* **2000**, *2*, 663.
[11] Deon, D.H.; M.Sc. Thesis, University of Ottawa, **2001**.

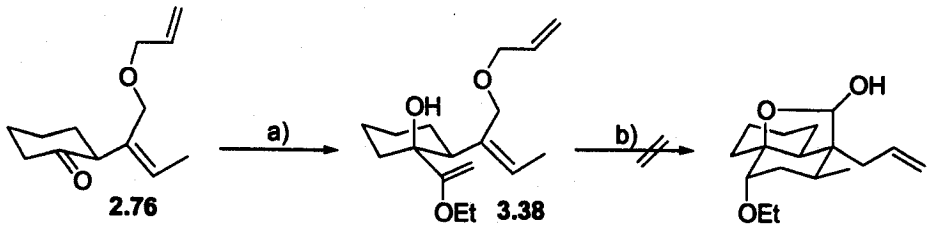
The mixture of the starting material and the retro-ene product was resubmitted to heating in the microwave at 230 °C. After prolonged exposure (6 h, 230 °C) all starting material reacted. Unfortunately, we mostly observed degradation and only traces of the desired product were isolated (<1 mg). It was also possible to isolate retro-ene product **3.37** (<1 mg) and prove its structure by ^{1}H NMR (300 MHz).

We were pleased to find out that the oxy-Cope/ene reaction of **3.33** led to formation of the single decaline. Interestingly, it appeared to be a much more energetically demanding process than in the case of the substrate without the ethoxy group. Paquette *et al.* have recently demonstrated that the presence of ether substituent on the 1,5-diene decreases the reactivity of the oxy-Cope reaction.[12] Thus, in the case of the tandem oxy-Cope/ene sequence, the ethoxy group plays a dual role by increasing the activation energy of the oxy-Cope step due to the electron donation to the double bond and decreasing the activation energy of the following ene-reaction because of its electron-withdrawing properties. Although the low yield of the oxy-Cope/ene reaction of **3.33** and the formation of the side product make its application in the total synthesis impractical, the results demonstrate that exceptionally high selectivity can be achieved during the ene-reaction of the macrocyclic ketone by changing the electronic nature of the substituent α to the carbonyl.

Also, the oxy-Cope/ene/Claisen reaction was attempted with a substrate having the ethoxy group on the double bond. Unfortunately, after heating **3.38** at 230 °C for 4 h only degradation was observed (Scheme 3.19).

---

[12] a) Paquette, L.A.; Haeffner, F.; Houk, K.N.; Reddy, Y.R. *J. Am. Chem. Soc.* **1999**, *121*, 11880. b) Paquette, L.A.; Reddy, Y.R.; Haeffner, F.; Houk, K.N. *J. Am. Chem. Soc.* **2000**, *122*, 740.

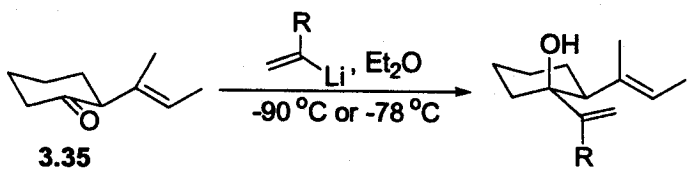


a) **3.36**, THF, 0 °C to -78 °C, 32%; b) toluene, 3 equiv Et_3N, 4 h, 230 °C.

Scheme 3.19 Attempted oxy-Cope/ene/Claisen reaction of 3.38

3.4 Control of the selectivity at C8 by adding substituent at C6 of the macrocyclic ketone

We have noticed before that the presence of a phenyl group on 1,5-diene systems significantly accelerates an anionic oxy-Cope reaction (see Chapter 5). We then decided to investigate how a replacement of the ethoxy by the phenyl group would affect the course of the thermal oxy-Cope/ene reaction and how it would change electronic and steric factors contributing to the selectivity of the ene-step. It was also interesting to make a comparison with a case where the ethoxy group is replaced by a methyl. 1,2-divinylcyclohexanols **3.39** and **3.40** were prepared via alkylation of ketone **3.35** with a corresponding vinyl lithium species (Scheme 3.20).

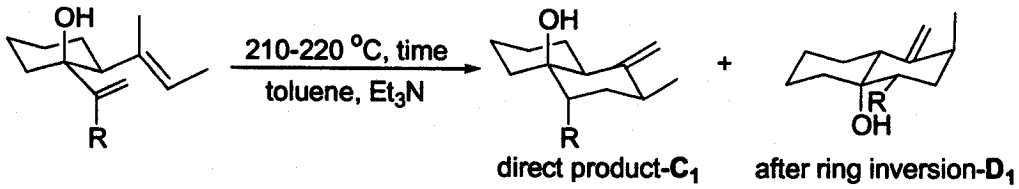


3.39 R=Me, 57%
3.40 R=Ph, 82%

Scheme 3.20 Preparation of 1,2-divinylcyclohexanols **3.39** and **3.40**

The substrates were heated in the microwave to afford the oxy-Cope/ene products. The results are shown in Table 3.1.

Table 3-1 Oxy-Cope/ene reaction of the substrates with a substituent at C6 obtained from ketone **3.35**



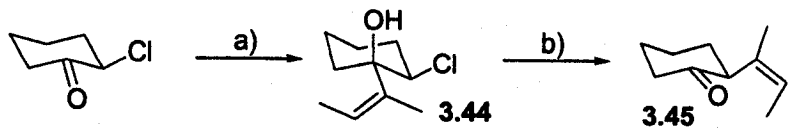
direct product-C_1 after ring inversion-D_1

Entry	Substrate	R	Time, h	Product [d]	dr (D_1 : C_1) [b]	Yield, % [c]
1	**2.11** [a]	H	1	**2.12(C_1)** and **2.14(D_1)**	1:3	70
2	**3.39**	Me	2	**3.41(C_1)** and **3.42(D_1)** [e]	3.4:1	77
3	**3.40**	Ph	1	**3.43(D_1)**	>25:1	93

[a] Preparation and the oxy-Cope/ene reaction of this substrate was discussed in Chapter 2. [b] Diastereomeric ratios were determined by 300 MHz ^{1}H NMR and GC of the crude reaction mixtures. [c] Combined isolated yields. [d] Relative stereochemistry was assigned based on 2D NMR (see Appendix) [e] Relative stereochemistry of **3.42** was assigned based on the proposed mechanism of the reaction.

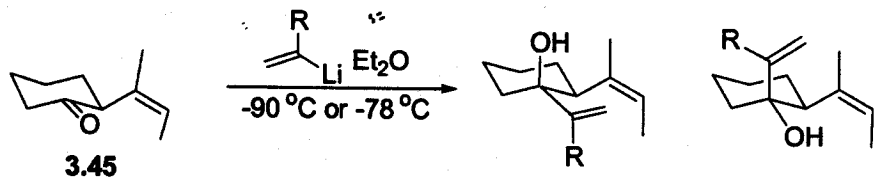
As we have already seen before in Chapter 2, in the case of R=H (entry 1) the oxy-Cope/ene reaction (1 h, 220 °C) affords a 3:1 mixture of **2.12(C_1)** and **2.14(D_1)**. Interestingly, the replacement of H by a methyl group (entry 2) gave a mixture of **3.42(D_1)** and **3.41(C_1)** in a 3.4:1 ratio respectively. Remarkably, the exclusive formation of product **3.43(D_1)** (93% yield) was observed in entry 3 (R=Ph).

To complete our investigation, ketone **3.45** was prepared from 2-chloro-1-cyclohexanone in two steps in 51% overall yield as illustrated in Scheme 3.20. The ketone was alkylated with three different vinyl lithium species to give *trans*-1,2-divinylcyclohexanols **3.46**, **3.47** and **3.48** in 56%, 72% and 40% yields respectively (Scheme 3.21). In the case of R=SEt, formation of *cis*-1,2-divinylcyclohexanol was also detected by ^{1}H NMR.



a) *cis*-2-bromo-2-butene, *t*-BuLi, -78 °C, 65%; b) vinylmagnesium bromide, THF, reflux, 79%.

Scheme 3.21 Preparation of ketone **3.45**

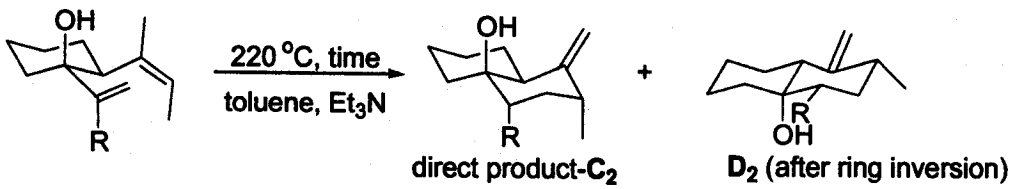


3.46 R=H, 56% n/d
3.47 R=Ph, 72% n/d
3.48 R=SEt, 40% 2.7%

Scheme 3.22 Synthesis of substrates for the oxy-Cope/ene reaction via alkylation of ketone **3.45**

Substrates (**3.46-3.48**) were heated in the microwave oven to give the corresponding oxy-Cope/ene products. The results are summarized in Table 3-2.

Table 3-2 Oxy-Cope/ene reaction of the substrates with a substituent at C6 obtained from ketone **3.45**



direct product-C_2 D_2 (after ring inversion)

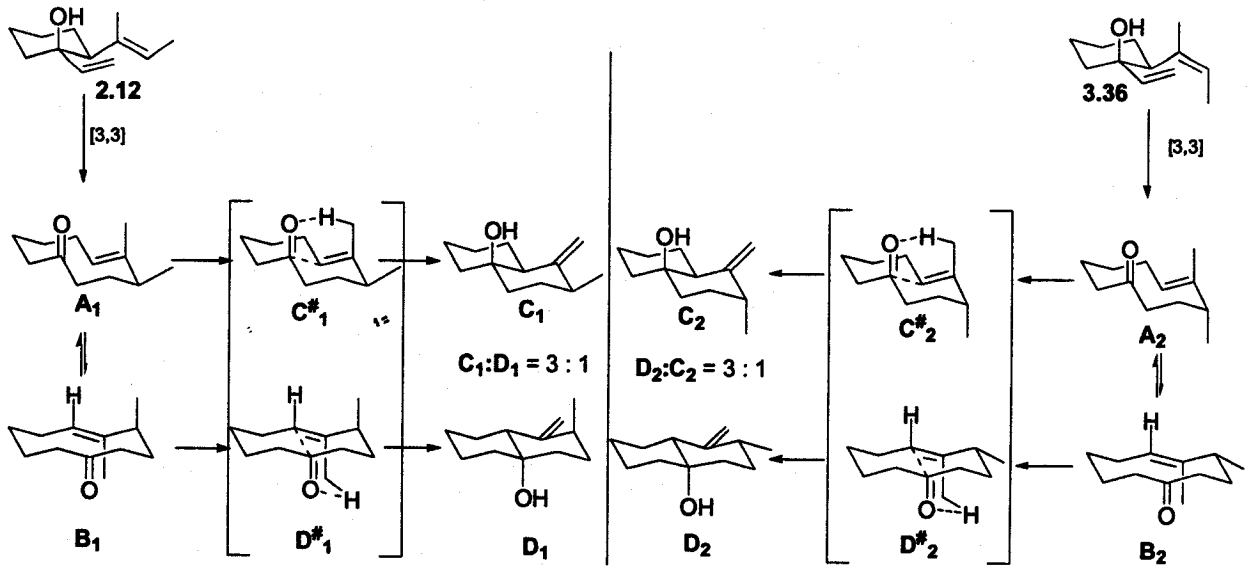
Entry	Substrate	R	Time, h	Product	dr (D_2 : C_2) [a]	Yield, % [b]
1	**3.46**	H	1	**3.49 (C_2) and 3.50 (D_2)**	3:1	60
2	**3.47**	Ph	3	**3.51 (D_2)**	>25:1	64
3	**3.48**	SEt	3	**3.52 (D_2)**	20:1	81

[a] Diastereomeric ratios were determined by 300 MHz ^{1}H NMR and CG of the crude reaction mixtures. [b] Isolated yields.

Interestingly, the oxy-Cope/ene reaction of **3.47** (R=Ph, entry 2) required heating for 3 h at 220 °C. Product **3.51(D_2)** was obtained in good yield (64%) and excellent diastereoselectivity. A similar result was obtained in the case of R=SEt (entry 3). Heating **3.48** for 3 h at 220 °C afforded product **3.52(D_2)** in 81% yield (dr=20:1).

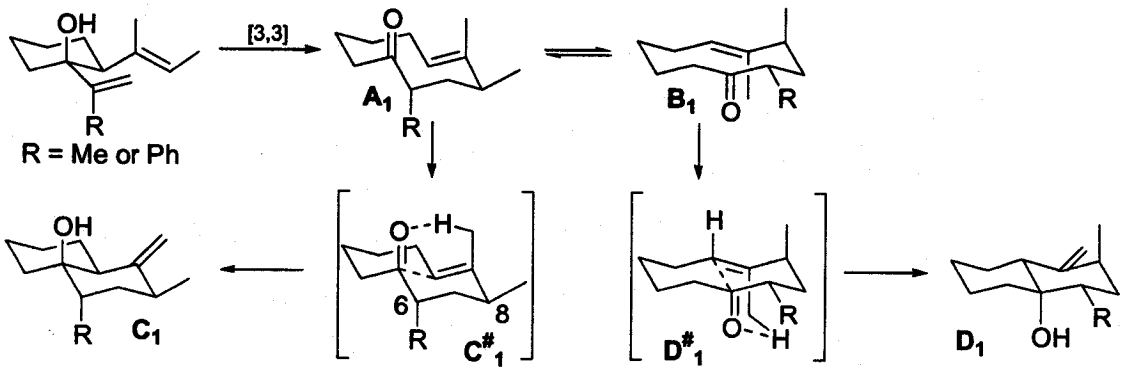
The oxy-Cope/ene reaction of **3.46** (R=H, entry 1) resulted in formation of a 3:1 mixture of products **3.49** (C_2) and **3.50** (D_2). After comparing product **3.50**(D_2) in Table 3-2 to product **2.12**(C_1) in Table 3-1 it becomes obvious that they are identical with the exception of being enantiomers. The same conclusion applies to product **3.49**(C_2) from Table 3-2 and product **2.14**(D_1) from Table 3-1. Moreover, the ratio of D_1/C_1 obtained in entry 1 of Table 3-1 and the ratio of C_2/D_2 obtained in entry 1 of Table 3-2 are identical. This important observation provides an experimental justification to the use of the Curtin-Hammett principle in explaining the mechanism of the oxy-Cope/ene reaction. Detailed rationalization to this observation is provided below.

As shown on the right-hand side of Scheme 3.22, the oxy-Cope rearrangement of **3.46** gives directly macrocyclic ketone A_2. This ketone is a mirror image of ketone B_1 (the left-hand side of the Scheme) obtained via a ring inversion of macrocycle A_1. A_2 can either react to give the ene-product C_2 (via transition state $C^{\#}_2$), which is a mirror image of product D_1, or undergo ring inversion to afford B_2 (mirror image of A_1). The ene-reaction of B_2 generates D_2 (a mirror image of C_1) via transition state $D^{\#}_2$. Therefore identical products (with the exception that they are enantiomers) can be obtained from both right- and left-hand side reactions. The ene-product generated prior to the ring inversion on the left-hand side corresponds to the ene-product obtained after the ring inversion on the right-hand side. If we again assume that macrocyclic conformers A_2 and B_2 and A_1 and B_1 are in rapid equilibrium and the rates of the ene-reactions of all the conformers are at least 10 times slower (Curtin-Hammett principle), then the ratio of the products is determined based only on $\Delta G^{\#} = \Delta G^{\#}_{C1} - \Delta G^{\#}_{D1}$, which equals $\Delta G^{\#} = \Delta G^{\#}_{D2} - \Delta G^{\#}_{C2}$. Therefore the ratio of the products on the right-hand side should be exactly the same as the ratio of the products on the left-hand side.



Scheme 3.23 Proposed mechanism for the oxy-Cope/ene reaction of **2.12** and **3.36**

Returning to the results obtained in entries 2 and 3 of both tables, we can now rationalize the observed ratios based only on the energy differences of the transition states of the ene-reaction. As illustrated in Scheme 2.23, the oxy-Cope rearrangement of 1,2-divinylcyclohexanol affords macrocyclic ketone $\mathbf{A_1}$. The latter can either undergo the ene-reaction via transition state $\mathbf{C^{\#}_1}$ to give product $\mathbf{C_1}$ or undergo ring inversion followed by the ene-reaction via transition state $\mathbf{D^{\#}_1}$ to generate product $\mathbf{D_1}$.

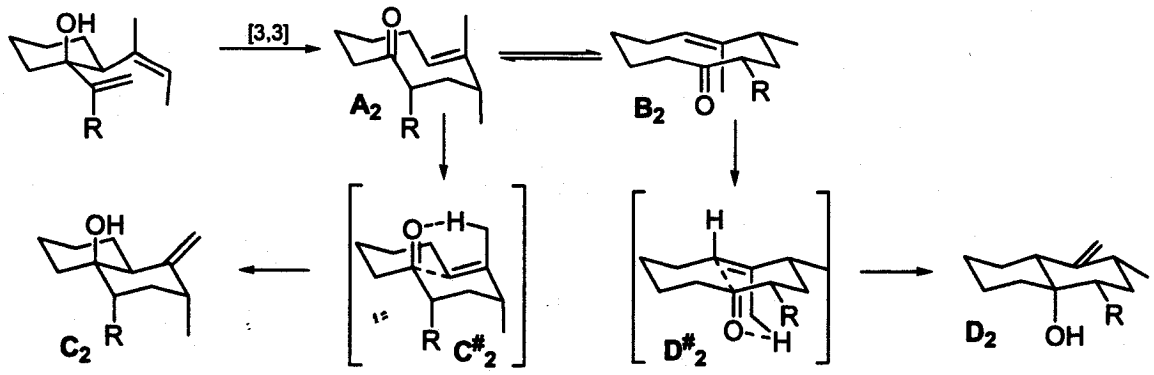


Scheme 3.24 Proposed mechanism of the oxy-Cope/ene reaction of **3.39** and **3.40**

When R=Me (entry 2, Table 3-1), in transition state $\mathbf{C^{\#}_1}$ the methyl at C8 occupies equatorial position and the methyl at C6 is axial. Inversion of the macrocycle $\mathbf{A_1}$ to $\mathbf{B_1}$ will give

transition state $\mathbf{D^{\#}_1}$ in which the methyl at C8 is now axial and the methyl at C6 becomes equatorial. The observed 3:1 ratio of $\mathbf{D_1/C_1}$ corresponds to 1.1 kcal/mol (calculated for 493 K or 220 °C) difference between $\Delta\mathbf{G^{\#}_{C1}}$ and $\Delta\mathbf{G^{\#}_{D1}}$. This value indicates that the methyl at the position C8 contributes less to the stability of the transition state than the methyl at the position C6. It can be easily explained by the fact that in $\mathbf{C^{\#}_1}$ the equatorial methyl at C8 develops pseudo-guache interactions with the methyl participating in the ene-reaction. Thus the energy of the equatorial methyl becomes closer to the energy of the methyl at C8 in axial position (transition state $\mathbf{D^{\#}_1}$). When the phenyl group replaces the methyl at C6 (entry 3, table 3-1), the $\mathbf{D_1/C_1}$ ratio becomes greater than 25:1, which corresponds to the greater than 3.08 kcal/mol (calculated for 483 K or 210 °C) energy difference between $\mathbf{C^{\#}_1}$ and $\mathbf{D^{\#}_1}$. This increase of the energy difference between transition states can be attributed to the much larger size of the phenyl group compared to the methyl group. (The A value of a phenyl group is 2.8 kcal/mol; the A value of a methyl is 1.74 kcal/mol).

Scheme 3.24 illustrates the mechanism of the oxy-Cope/ene reaction responsible for the formation of the products $\mathbf{C_2}$ and $\mathbf{D_2}$ (Table 3-2, entries 2 and 3). Again, the oxy-Cope reaction of **3.47** or **3.48** generates macrocyclic ketone $\mathbf{A_2}$, which is either converted to ene-product $\mathbf{C_2}$ via transition state $\mathbf{C^{\#}_2}$, or undergoes the ring inversion to $\mathbf{B_2}$, followed by the ene-reaction via transition state $\mathbf{D^{\#}_2}$ to give $\mathbf{D_2}$. The ratio of greater than 25:1 in entry 2 (R=Ph) and 20:1 in entry 1 (R=SEt) suggest that in both cases the energy difference between $\mathbf{C^{\#}_2}$ and $\mathbf{D^{\#}_2}$ is greater than 3.14 kcal/mol and 2.92 kcal/mol (calculated for 493 K or 220 °C) respectively. Examination of transition state $\mathbf{C^{\#}_2}$ reveals strong 1,3 diaxial interactions between R group at C6 and the methyl at C8, explaining the large energy difference between $\mathbf{D^{\#}_2}$ and $\mathbf{C^{\#}_2}$.



Scheme 3.25 Explanation of diastereoselective outcome of the oxy-Cope/ene reaction of **3.47** and **3.48**

AM1 semi-empirical calculations using Spartan software were performed to estimate the energy differences between transition states of the ene-reactions in the case of R=Me (entry 1, Table 3-2). As shown in Figure 3.8, $\Delta G^{\#}$ between $C^{\#}_1$ and $D^{\#}_1$ was found to be 1.7 kcal/mol, which would give the 5.7:1 ratio of the products (calculated for 493 K or 220 °C). This result was consistent with the experimentally obtained 3:1 ratio.

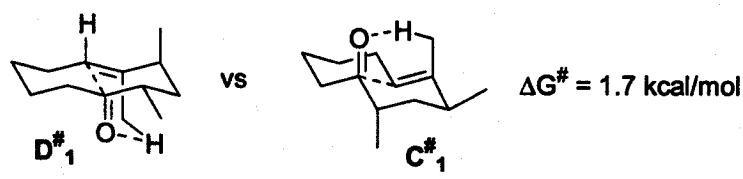


Figure 3.8 Results of AM1 semi-empirical calculation for $\Delta G^{\#}$ between $D^{\#}_1$ and $C^{\#}_1$

3.5 Conclusion

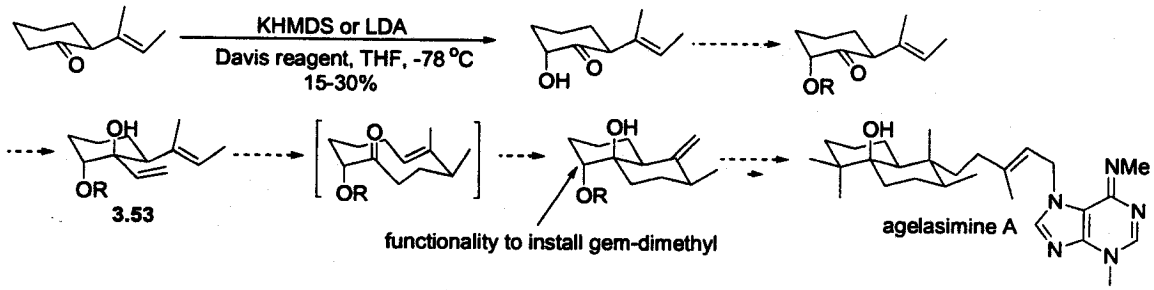
We have found that introducing substituents of different nature on the macrocycle at C6 (α to the carbonyl) can control the selectivity of the ene-reaction step of the oxy-Cope/ene sequence and therefore selectivity at C8. It has been demonstrated that having an electron-withdrawing substituent (OEt) α to the carbonyl accelerates the ene-reaction, thus making the impact of the macrocycle ring inversion on the selectivity of the ene-reaction negligible. We have also shown that in the case where the ring inversion is much faster than the ene-

reaction (i.e. the Curtin-Hammett principle applies), excellent selectivity can be achieved by increasing the energy difference between transition states of the ene-reaction.

These results open a new perspective for the application of the oxy-Cope/ene and eventually the oxy-Cope/ene/Claisen strategy in the total synthesis of agelasimine A and other diterpenes having a substituent at C8.

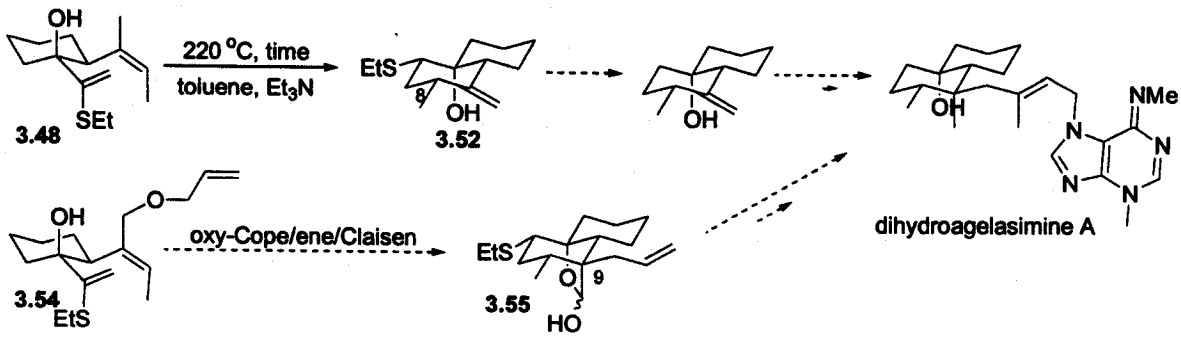
3.6. Future perspectives

As previously demonstrated, while having ethoxy group next to a tertiary alcohol on a 1,5 diene system accelerated the ene-reaction. It also increased the activation energy of the oxy-Cope step, resulting in low yield of the oxy-Cope/ene sequence. To overcome this disadvantage a new approach has recently been proposed as shown in Scheme 3.26. The oxy-Cope/ene reaction of **3.53** is expected to give only one isomer, since the macrocyclic ketone generated in the course of the oxy-Cope step possesses an electron-withdrawing (alkoxy) group α to a carbonyl. However, this alkoxy group is not a part of a 1,5-diene system of **3.53**, therefore its presence should not affect the rate of the oxy-Cope rearrangement. Importantly, the group can further be transformed to the geminal dimethyls, which are present on the natural product.



Scheme 3.26 New approach to agelasimine A

Another strategy that needs to be explored is illustrated in Scheme 3.27. As we already know the oxy-Cope/ene reaction of **3.48** gives decaline **3.52** in which the methyl at C8 and the tertiary alcohol are *syn* to each other. One could envision that removal of SEt would give a core of dihydroagelasimine with the methyl at C8 in the right position. Similarly, the oxy-Cope/ene/Claisen reaction of **3.54** should generate compound **3.55**, which has not only the methyl at C8 but also the quaternary carbon center at C9 with the desired stereochemistry.



Scheme 3.27 New approach to dihydroagelasimine A

Chapter 4 Synthesis of (±)-agelasimine A analogues

4.1 Introduction

A natural product with known biological activity is often altered by introducing new and modifying existing functional groups.[1] This is done in the hopes of improving the biological activity and providing information about structure-activity relationship. A highly active analogue may also be obtained from a biosynthetic precursor, for example, taxotere®, which is the structurally related to taxol®. In some situations however the desired chemical modifications cannot be achieved. In addition, the biosynthetic precursor may not be readily available for technical or stability reasons.

Danishefsky *et al.* have introduced the concept of diverted total synthesis, where desired structural modifications are incorporated into advanced intermediates.[2] The goal of this approach is to prepare analogues, which are less structurally complex than the natural product, but have similar or improved biological activity. This new strategy is currently being implemented for the discovery of new biologically active molecules.[3]

As discussed in Chapter 2 agelasimine A is a natural product that exhibits significant *in vitro* cytotoxicity against L1210 leukemia cells (ED_{50}=2.1 nM) and acts as a smooth muscle relaxant.[4] As we have previously demonstrated, the core of agelasimine A, lactol **4.1,** without geminal dimethyls at C4 and the methyl group at C8 can be generated via our new tandem oxy-Cope/ene/Claisen strategy in only 6 steps starting from commercially available cyclohexene oxide (Scheme 4.1). We were interested in determining whether the presence of

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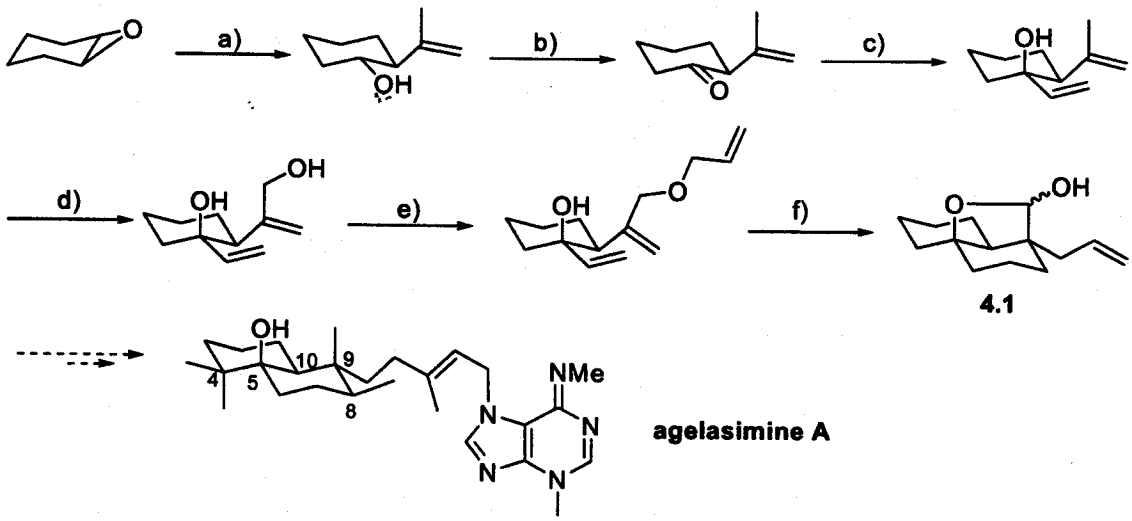
[1] For the recent review see: Tietze, L.F.; Bell, H.P.; Chandrasekhar, S. *Angew. Chem, Int. Ed.* **2003**, *42*, 3996 and references therein.

[2] Njardarson, J.T.; Gaul, C.; Shan, D.; Huang, X.-Y., Danishefsky, S.J. *J. Am. Chem. Soc.* **2004**, *126*, 1038.

[3] For earlier examples see: a) Wender, P.A., Hegde, S.G.; Hubbard, R.D.; Zhang, L.; Mooberry, S.L. *Org. Lett.* **2003**, *5*, 3507. b) Wender, P.A.; Baryza, J.L.; Bennett, C.E.; Bi, C.; Brenner, S.E.; Clarke, M.O.; Horan, J.C.; Kan, C.; Lacote, E.; Lippa, B.; Nell, P.G., Turner, T.M. *J. Am. Chem. Soc.* **2002**, *124*, 13648.

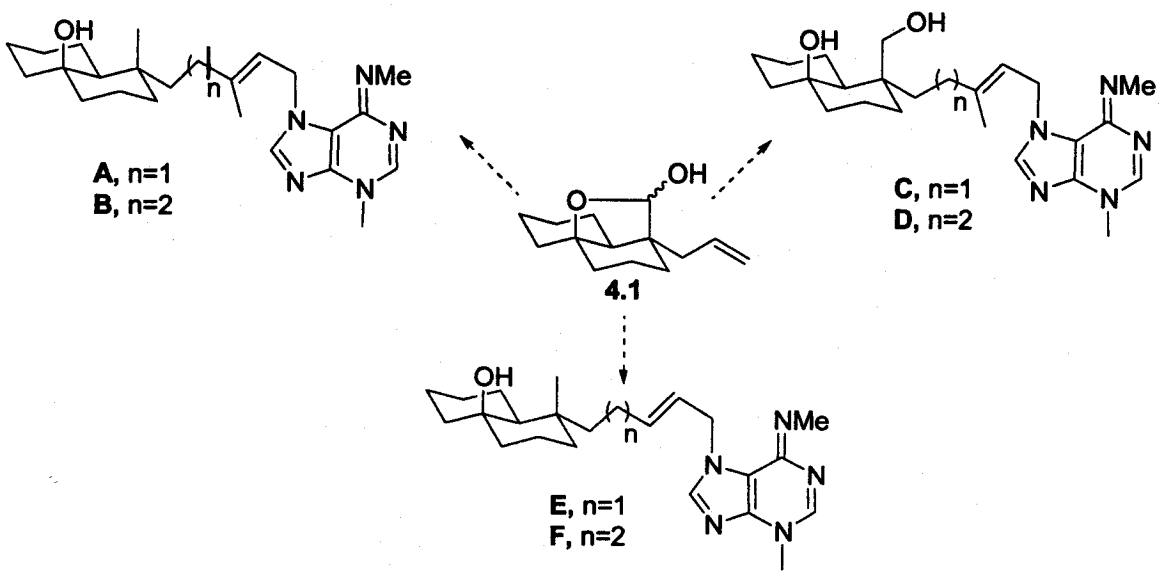
[4] Fathi-Afshar, R.; Allen, T.M.; Krueger, C.A.; Cook, D.A.; Clanachan, A.S.; Vriend, R.; Baer, H.P.; Cass, C.E. *Can J. Physiol. Pharmacol.* **1989**, *67*, 276.

geminal dimethyls or the methyl at C8 and the length of the side chain contribute to these activities. We have envisioned that analogues **A-F** can be synthesized from a common intermediate, lactol **4.1**, as illustrated in Scheme 4.2.



a) isopropenylmagnesium bromide, THF, CuBr·DMS, -40 °C; b) Swern oxidation, 90% over 2 steps; c) vinylmagnesium bromide, THF, 60%; d) SeO_2, *t*-BuOOH, CH_2Cl_2, 62% based on the recovery of the starting material; e) allyl bromide, NaH, THF, 70%; f) toluene, Et_3N, 220 °C, 1 h, μwaves, 80%.

Scheme 4-1 Synthesis of the core of (±)-agelasimine A

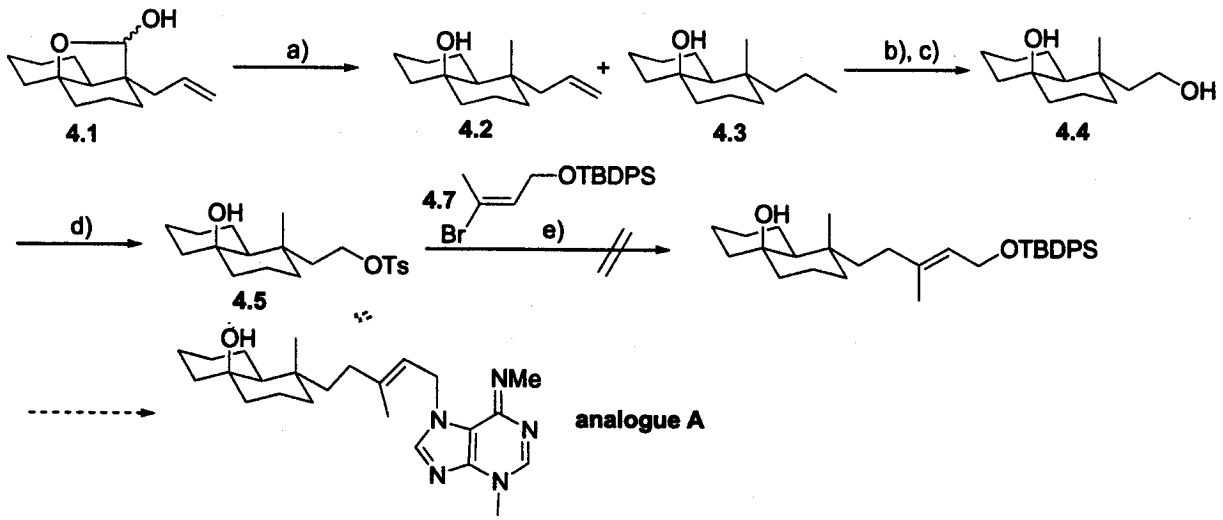


Scheme 4-2 Proposed analogues of (±)-agelasimine A

4.2 Studies toward analogue A

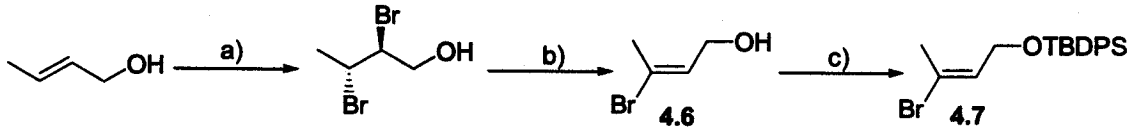
The synthesis of analogue **A** was initially attempted. The installation of the side chain began by a Wolf-Kischner reduction of the lactol **4.1** as shown in Scheme 4.3. Heating **4.1** in diethyleneglycol in the presence of K_2CO_3 and $NH_2NH_2 \cdot H_2O$ at 150 °C for 12 h afforded inseparable 15:1 mixture of desired product **4.2** and side-product **4.3** with a reduced allyl group in 50-55% combined yield. Ozonolysis of the allyl group followed by $LiAlH_4$ reduction provided diol **4.4** in 82% yield over two steps and allowed for separation of compound **4.3**. Tosylation of diol **4.4** using freshly recrystallized TsCl, Et_3N and catalytic amount of DMAP in CH_2Cl_2 gave mono-tosylate **4.5** in 90% yield. It was envisioned that the S_{N2} displacement of the tosyl group with vinyl cuprate generated from vinyl bromide **4.7** would install the rest of the carbon side chain. Vinyl bromide **4.7** was prepared in three steps starting from crotyl alcohol (Scheme 4.4).[5] Attempts to perform the S_{N2} reaction using substrate **4.5** with unprotected tertiary alcohol were unsuccessful.

[5] Vinyl bromide **4.6** was prepared according to procedure reported by: Corey, E.J.; Bock, M.G.; Kozikowski, A.P.; Rama Rao, A.V.; Floyd, D.; Lipshutz, B. *Tetrahedron Lett.* **1978**, *19*, 1051.



a) $NH_2NH_2{\cdot}H_2O$, K_2CO_3, diethylene glycole, 50-55%, 15:1; b) O_3, CH_2Cl_2, -78 °C, DMS c) $LiAlH_4$, THF, rt, 82% over 2 steps; d) TsCl, CH_2Cl_2, Et_3N, DMAP, 90%; e) **4.6**, CuI, *t*-BuLi, Et_2O or THF, no reaction.

Scheme 4-3 First attempt toward analogue A



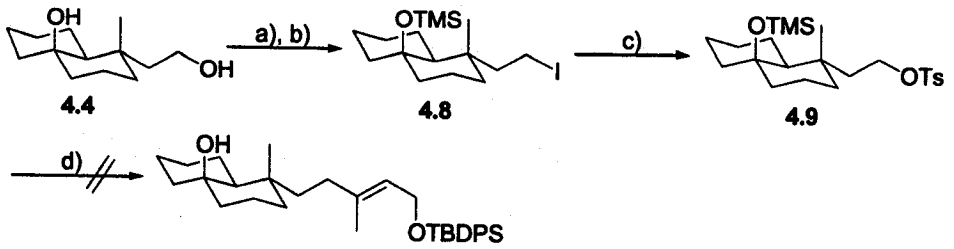
a) Br_2, $CHCl_3$; b) LDA, HMPA, THF, -78°C, 37% over 2 steps; c) TBDPSCl, THF, imidazole, 87%.

Scheme 4-4 Synthesis of vinyl bromide **4.7**

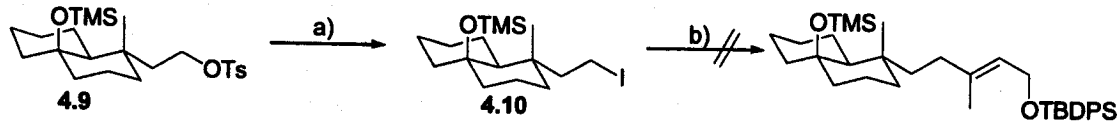
Treating diol **4.4** with 4 equiv of TMSCl and 2.2 equiv of KHMDS in THF at –78 °C followed by a basic work up and deprotection of the primary alcohol using K_2CO_3 in MeOH afforded compound **4.8** with protected tertiary alcohol in 81% (Scheme 4.5). The mono-protected diol was treated with TsCl to give **4.9** in 65% yield. The S_{N2} displacement of the tosyl group using the mixed cuprate was attempted.[6] Unfortunately, no desired product was observed.

We then proposed to perform S_{N2} displacement using a substrate with a better leaving group (e.g. bromide or iodide). Iodide **4.10** was prepared from **4.9** in 67% yield (Scheme 4.5). However, no reaction was observed upon addition of the iodide to the vinyl cuprate solution.

[6] Boeckman, R.K.; Ramaiah, M. Jr. *J. Org. Chem.* **1977**, *42*, 1581. See also: Corey, E.J.; Floyd, D.; Lipshutz, B.H. *J. Org. Chem.* **1978**, *43*, 3418.



a) TMSCl, KHMDS, THF, -78 °C; b) K_2CO_3, MeOH, 81% over 2 steps; c) TsCl, Et_3N, DMAP, CH_2Cl_2, 65%; d) **4.7**, *t*-BuLi, CuI, 3,3-dimethyl-1-butyne, THF, *n*-BuLi

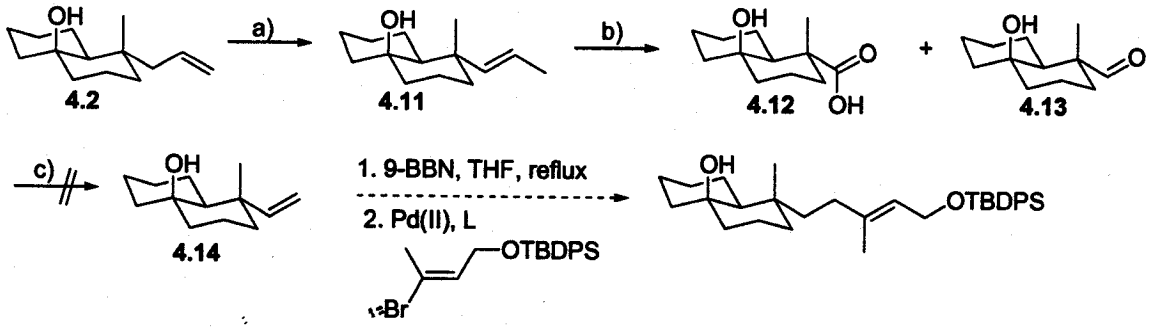


a) NaI, acetone, rt, 3 d, 67%; b) **4.7**, *t*-BuLi, CuI,THFor Et_2O, no reaction.

Scheme 4-5 Attempts to extend the side chain

Installation of the side chain using Suzuki coupling conditions, developed by Ohba *et al.* in the course of their synthesis of agelasimine A,[7] was also attempted as shown in Scheme 4.6. In order to prepare substrate **4.14** for the Suzuki coupling it was necessary to transform the allyl chain into the vinyl group. The isomerization of the double bond of **4.2** using ruthenium catalyst gave an inseparable 15:1 mixture of **4.11** and **4.2** in 92% yield. We expected that ozonolysis of **4.11** followed by reductive work up and the Wittig reaction would result in formation of **4.14**. Unexpectedly, the ozonolysis gave a mixture of acid **4.12** and aldehyde **4.13** in 43% and 32% yields respectively. Changing the ozonolysis conditions did not suppress acid formation. Attempts to obtain **4.14** via Wittig olefination of **4.13** were unsuccessful, probably due to the presence of a free tertiary alcohol on the substrate.

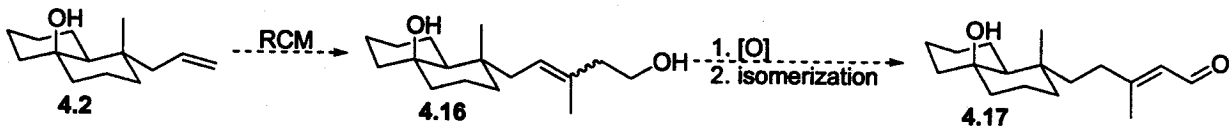
[7] a) Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem. Soc.* **1996**, *118*, 8250. b) Ohba, M.; Iizuka, K.; Ishibashi, H.; Fujii, T. Tetrahedron, **1997**, *53*, 16977.



a) $RuCl_2(PPh_3)_2$, DIPEA, toluene, reflux, 92%; b) O_3, CH_2Cl_2, -78 °C, DMS, 43% of **4.12** and 32% of **4.13**; c) $Ph_3P^+CH_3I^-$, KHMDS, THF, 0 °C to rt, no reaction.

Scheme 4-6 Attempt to install the side chain using the Suzuki coupling

We then envisioned that the cross-coupling metathesis of decaline **4.2** and a corresponding alkene would give product **4.16**. The latter was expected to generate aldehyde **4.17** upon oxidation followed by migration of the double bond a shown in Scheme 4.7.



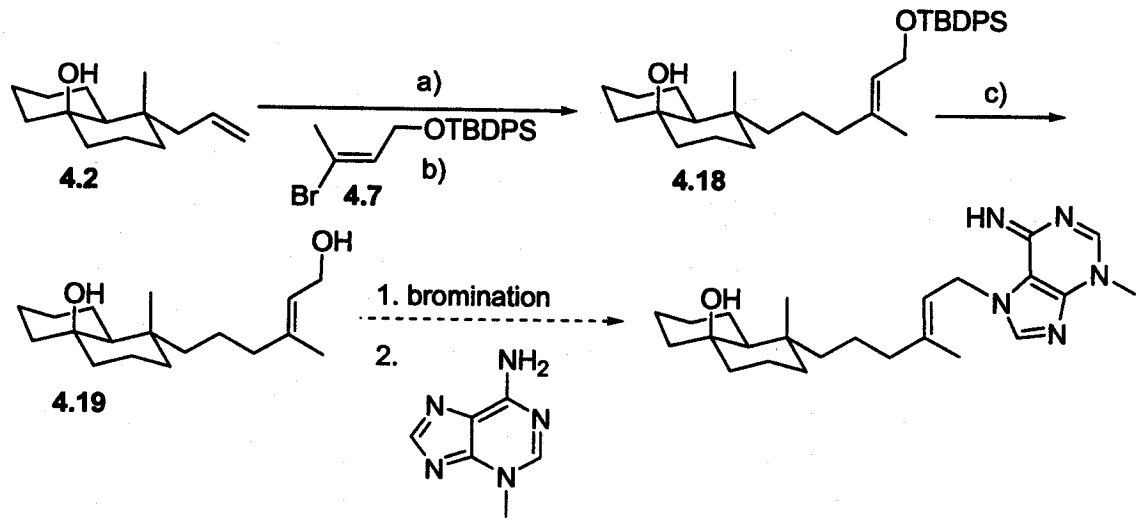
Scheme 4-7 Installation of the side chain using cross-coupling metathesis

However, an attempt to perform the cross coupling resulted only in dimerization of decaline **4.2**. The dimerization can be attributed to the difference in the degree of substitution of two coupling partners.

4.3. Studies toward analogue B

The synthesis of analogue **B** was carried parallel to the synthesis of **A**. It began with the Suzuki cross coupling between decaline **4.2** and vinyl bromide **4.7** (Scheme 4.8). Hydroboration of **4.2** with 9-BBN in THF under refluxing conditions afforded the corresponding 9-alkyl-9-BBN derivative, which was then added to a solution of **4.7**,

$Pd(dppf)Cl_2$,[8] $AsPh_3$, Cs_2CO_3 and H_2O in DMF. After stirring the reaction mixture at rt for 3-5 h the expected coupling product **4.18** was obtained in 50-65% yields. The removal of TBDPS group with TBAF gave alcohol **4.19** in 70-80% yields. At this stage, all attempts to brominate the resulting primary alcohol in a presence of a free tertiary alcohol with either CBr_4/Ph_3P or PBr_3 and to use crude allyl bromide in a consequent coupling with 3-methyl adenine[9] in DMA of DMF failed. Protection of the tertiary alcohol was then undertaken. We were unable to install the TMS group using the method employed in the synthesis of analogue A (TMSCl, KHMDS, THF, -78 °C).



a) 9-BBN, THF, reflux, 1.3 h; b) **4.7**, $Pd(pddf)Cl_2$, Cs_2CO_3, $AsPh_3$, DMF, H_2O, 50-65%; c) TBAF, THF, 70-80%;

Scheme 4-8 Attempted synthesis of analogue B using the Suzuki cross coupling

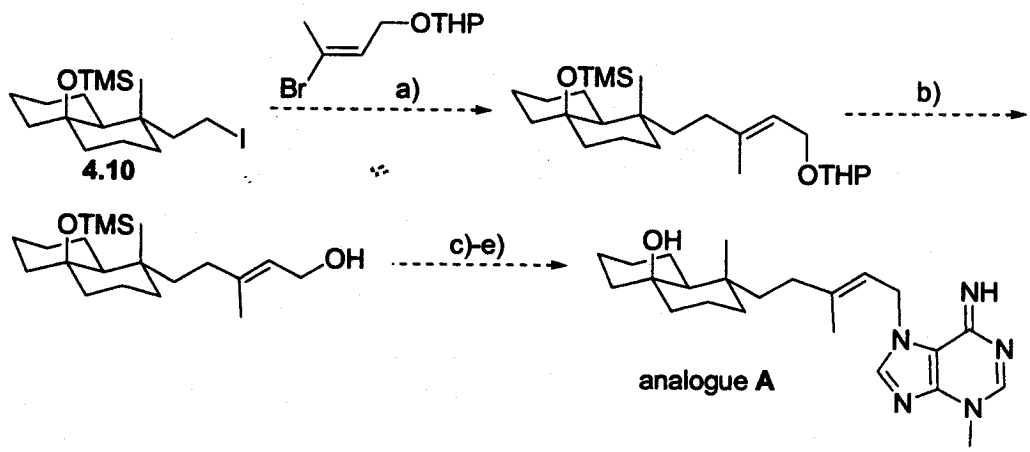
4.4 Conclusion and future perspectives

Unfortunately, due to the time constraint we were unable to complete the analogue syntheses. We have established, however, that protection of the tertiary alcohol is required prior the modification of the side chain and coupling with 3-methyladenine. A modified

[8] $Pd(pddf)Cl_2$ was prepared from $Pd(CH_3CN)_2Cl_2$ according to procedure by: Hayashi, T.; Konishi, M.; Kobori, Y. Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158. For preparation of $Pd(CH_3CN)_2Cl_2$ see: Hartley, F.R.; Murray, S.G.; McAuliffe, C.A. *Inorg. Chem.* **1979**, *18*, 1394.

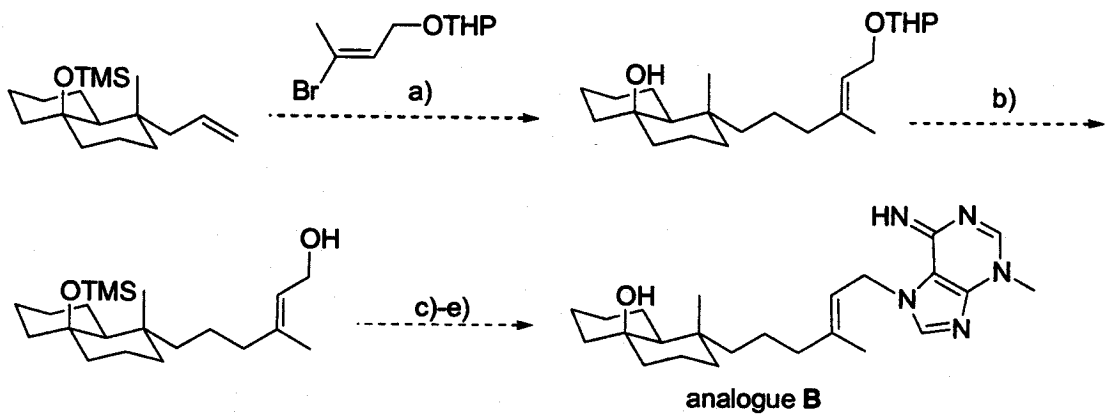
[9] Jones, J.W.; Robins, R.K. *J. Am. Chem. Soc.* **1962**, *84*, 1914.

approach toward analogues **A** and **B** is illustrated in Schemes 4.9 and 4.10 respectively. The synthesis of the analogues will be continued in the nearest future.



a) Nigishi coupling; b) removal of THP; c) bromination; d) coupling with 3-methyl adenine; e) removal of TMS.

Scheme 4-9 Modified approach toward analogue **A**



a) Suzuki coupling; b) removal of THP; c) bromination; d) coupling with 3-methyl adenine; e) removal of TMS.

Scheme 4-10 Modified approach toward analogue **A**

Chapter 5 Anionic oxy-Cope reaction – a new approach toward generation of quaternary carbon centers

5.1 Background

Alkylation of tetrasubstituted enolates is a method commonly used to generate quaternary carbon centers α to a carbonyl. Formation of the enolate in a stereoselective fashion and control of the facial selectivity of the consequent electrophilic attack are two major challenges associated with this strategy. A majority of the methods reported in literature combine traditional approaches to enolate formation (removal of acidic proton α to a carbonyl with a base) with a use of a chiral auxiliary.[1] Although presence of a chiral auxiliary allows for efficient diastereoselective and enantioselective induction, removal of chiral auxiliary can pose a problem. In many cases harsh conditions are required resulting in low yields.

We have envisioned that the anionic oxy-Cope reaction of 1,2 divinylcyclohexanols **5.1** and **5.6** could be used as a new approach toward construction of quaternary carbon centers based on a stereoselective enolate formation/electrophilic addition as illustrated in Schemes 5.1 and 5.2. The anionic oxy-Cope reaction of **5.1** will generate 10-membered ring *E*-enolate **5.2**. The geometry of this enolate is predetermined by a stereochemistry of the starting material and a chair-like transition state of the oxy-Cope reaction. The conformation of the macrocyclic enolate provides excellent means for controlling facial approach of the electrophile, since one face of the π-system is severely hindered by the ring.[2] Trapping the

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[1] For example see a) Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146. b) Sundararaman, P.; Schultz, A.G. *Tetrahedron Lett.* **1984**, *25*, 4591. c) Manthorpe, J. M.; Gleason, J.L. *J. Am. Chem. Soc.* **2001**, *123*, 2091.

[2] For examples of an asymmetric induction in macrocycles see: b) Still, W.C. *J. Am. Chem. Soc.* **1977**, *99*, 4186. c) Still, W.C. *J. Am. Chem. Soc.* **1979**, *101*, 2493. d) Still, W. *Curr. Trends Org. Synth., Proc. 4th Znt.*

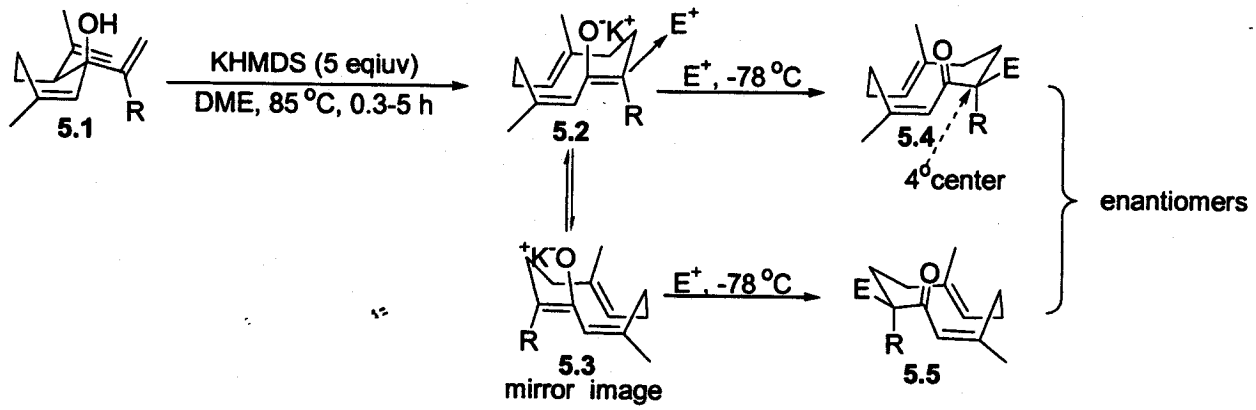
macrocyclic enolate with a source of a carbon electrophile under conditions favoring C-alkylation should result in formation of macrocyclic ketone **5.4** bearing a quaternary carbon center α to the carbonyl. It was previously shown that the anionic oxy-Cope reaction of enantiomerically pure **5.1** (when R=Ph) results in complete racemization.[3] This is because macrocyclic enolate **5.2** generated from the anionic oxy-Cope reaction does not have any chiral centers as shown in Scheme 5.1, but instead possesses so-called planar chirality.[4] Chiral plane can be described as a planar arrangement of at least four centers (atoms) with a fifth center outside of this plane. Therefore information about chirality is coded in the conformation of the macrocycle (conformation is treated as a topographic property of the macrocycle).[5] The ring inversion of the enolate **5.2** gives its mirror image, macrocycle **5.3**. If the barrier of inversion is low and the alkylation is the rate-determining step, then the mixture of enantiomers **5.4** and **5.5** is obtained in the end of the reaction.

Conf. **1983**, 233. e) Still, W.C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625. f) Still, W. C.; Novack, V.J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. g) Still, W.C.; Romero, A.G. *J. Am. Chem. Soc.* **1986**, *108*, 2105.

[3] Gauvreau, D.; M.Sc. Thesis, University of Ottawa, **2003**.

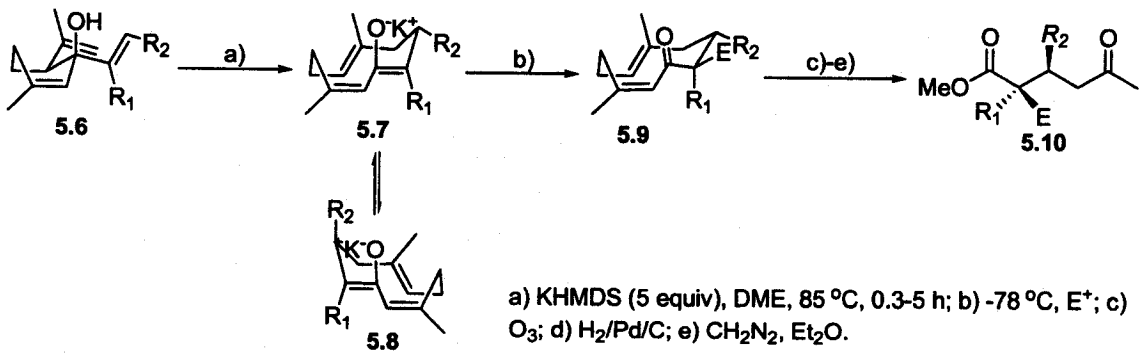
[4] a) Nubbemeyer, U. *Eur. J. Org. Chem.* **2001**, 1801. b) Münich, W.; Sudau, A.; Nubbemeyer, U. *Chem. Eur. J.* **2001**, *7*, 611.

[5] For more examples of how a macrocyclic bias provides the selectivity see: a) Vedejs, E.; Gapinski, D.M. *J. Am. Chem. Soc.* **1983**, *105*, 5058. b) Vedejs, E.; Dolphin, J.M.; Mastalerz, H. *J. Am. Chem. Soc.* **1983**, *105*, 127. c) Schreiber, S.L.; Hawley, R.C. *Tetrahedron Lett.* **1986**, *26*, 2205. d) Schreiber, S.L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106. e) Vedejs, E.; Dent, W.H.; Gapinski, D.M.; McClure, C.K. *J. Am. Chem. Soc.* **1987**, *109*, 5437. f) Paterson, I.; Rawson, D.J. *Tetrahedron Lett.* **1989**, *30*, 7463. g) Mulzer, J. ; Kirstein, H.M.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 910. h) Neeland, E.; Ounsworth, J.P.; Sims, R.J.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 35. i) Keller, T.H.; Weiler, L. *J. Am. Chem. Soc.* **1990**, *112*, 450. j) Keller, T.H.; Weiler, L. *Tetrahedron Lett.* **1990**, *31*, 6307. k) Graham, R.J.; Weiler, L. *Tetrahedron Lett.* **1991**, *32*, 1027. l) Neeland, E.D.; Ounsworth, J.P.; Sims, R.J.; Weiler, L. *J. Org. Chem.* **1994**, *59*, 7383. m) Weiler, L.; Clyne, D.S. *Tetrahedron* **2000**, *56*, 1281.



Scheme 5.1 Proposed formation of quaternary centers via an oxy-Cope/alkylation reaction

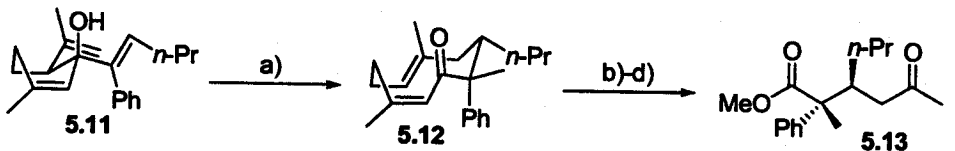
However, the racemization cannot occur when the oxy-Cope reaction is performed with substrates having two substituents on the vinyl group next to the alcohol (Scheme 5.2). In this case the anionic oxy-Cope reaction of **5.6** will generate macrocyclic enolate **5.7** with a chiral center on the ring. Inversion of this enolate will give diastereomeric enolate **5.8**, which is not a mirror image of **5.7**. Trapping **5.7** with an electrophile should generate macrocyclic ketone **5.9** having a quaternary carbon center adjacent to a tertiary center. One can envision that cleavage of the macrocycle will provide ketoester **5.10**, which can be used as a building block in a synthesis of natural and non-natural products.



Scheme 5.2 Anionic oxy-Cope/alkylation reaction of **5.6**

It was shown in our laboratory by Danny Gauvreau that treating 1,2-divinylcyclohexanol **5.11** with 5 equiv of KHMDS in DME followed by 1.5 h reflux initiated the anionic oxy-

Cope reaction (Scheme 3).[3] Quenching the reaction with MeI at-78 °C afforded 10-membered ring ketone **5.12** bearing two contiguous chiral centers including the quaternary carbon center α to the carbonyl (determined by 1H NMR of the reaction mixture) (Scheme 5.3). Ozonolysis of the crude reaction mixture followed by hydrogenation and diazomethane treatment resulted in formation of ketoester **5.13** as a single diastereomer in 13% yield starting from the 1,2-divinylcyclohexanol. Encouraged by the excellent diastereoselectivity of the quaternary carbon center formation in the oxy-Cope/alkylation sequence we then proceeded to explore a scope of the new methodology.



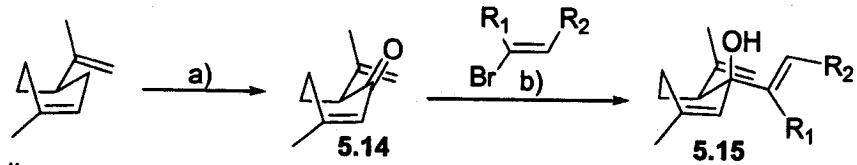
a) KHMDS (5 equiv), DME, 85 °C, 1.5 h, quench with MeI at -78 °C; b) O_3, c) H_2/Pd/C d) CH_2N_2, Et_2O. 13% over 4 steps.

Scheme 5.3 Results of Danny Gauvreau

5.2 Results and Discussion

5.2.1 Preparation of 1,2-divinylcyclohexanols

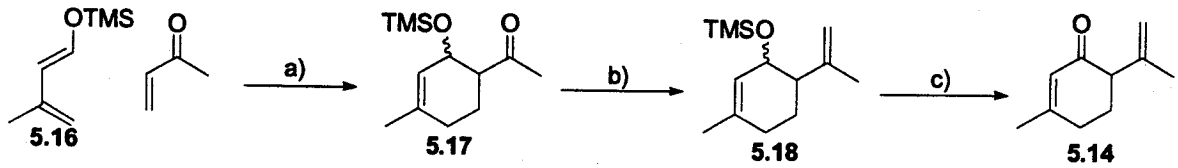
The substrates **5.15** for the anionic oxy-Cope reaction can be easily obtained in either racemic or enantiomerically pure forms by alkylation of isopiperitenone **5.14** as shown in Scheme 5.4. The procedure used in our lab to prepare optically active ketone **5.14** involves oxidation of (+) or (-)-limonene with CrO_3·2Py complex. Although the oxidation provides a rapid access to the enantiomerically pure substrate, it is a low yielding process (the isolated yields are 10-13%). Furthermore, at least 5.5 equiv of CrO_3·2Py is required for oxidation to occur. In order to prepare (±)-isopiperitenone a 1:1 mixture of (+)- and (-)-limonene is prepared and oxidized.



a) $CrO_3 \cdot 2Py$, CH_2Cl_2, 13%; b) *t*-BuLi, Et_2O, -90 °C or -78 °C.

Scheme 5.4 Preparation of the substrates for the anionic oxy-Cope reaction

A different approach to the synthesis of (±)-isopiperitenone **5.14** was chosen in the course of our studies. It was found in literature that the Diels-Alder reaction of diene **5.16**[6] with methylvinyl ketone, followed by the Wittig reaction and Jones oxidation affords the desired ketone **5.14** in 56-64% overall yield as depicted in Scheme 5.5.[7] This procedure is also effective on larger scale, e.g. 3-5 g (Compare to oxidation of limonene, where to obtain 5 g of the product one has to use 500 g of $CrO_3 \cdot 2Py$).

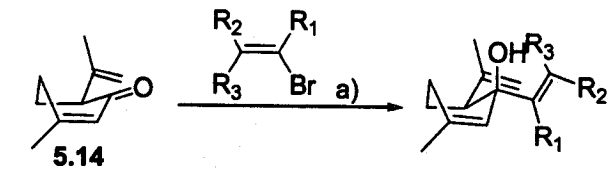


a) heat, 74-76%; b) $P^+Ph_3CH_3I^-$, *t*-BuLi, THF, -78 °C; c) Jones reagent, Et_2O, 71% over 2 steps.

Scheme 5.5 Synthesis of **5.14** using a Diels-Alder strategy

A number of racemic and enantiomerically pure 1,2-divinycyclohexanols were synthesized by the alkylation of **5.14** with the corresponding lithium species generated in *situ* via metal-halogen exchange from the vinyl halides as shown in Scheme 5.6.

[6] For preparation of this diene see: South, M.S.; Liebeskind, L.S. *J. Org. Chem.* **1982**, *47*, 3815.
[7] Friedrick, D.; Bohlmann, F. *Tetrahedron* **1988**, *44*, 13697.



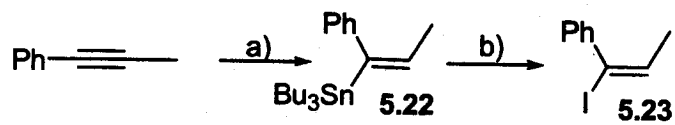
5.14
(+) or racemic

a) *t*-BuLi, Et_2O, -78 °C or -90 °C

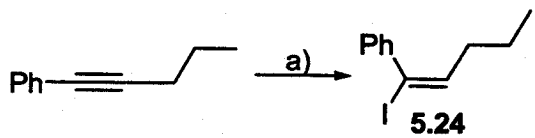
(+)-5.11 R_1=Ph, R_2=i-Pr, R_3=H, 60%
5.19 R_1=Ph, R_2=H, R_3=H %, 85%
(+)-5.20 R_1=Me, R_2=H, R_3=Me, 81%
5.21 R_1=Ph, R_2=Me, R_3=H, 60%

Scheme 5.6 Preparation of 1,2-divinylcyclohexanols via alkylation of **5.14**

Vinyl halides that were not commercially available were prepared from the alkynes as illustrated in Scheme 5.7. All vinyl halides were found to be light sensitive and could not be stored in the freezer longer than for a few days. Interestingly, attempts to prepare vinyl iodide **5.23** using the same procedure[8] as for **5.24** gave a mixture of *E* and *Z* isomers. Instead, a two-step procedure involving hydrostannylation[9] followed by the tin-iodine exchange was employed. Using vinyl-stannane **5.22** directly to generate vinyl lithium species for alkylation of ketone **5.14** gave a mixture of products.



a) Bu_3SnH, $PdCl_2(PPh_3)_2$, 53%; b) I_2, CH_2Cl_2, 63%



a) 9-I-BBN, CH_2Cl_2, then AcOH, then NaOH and H_2O_2, 83%

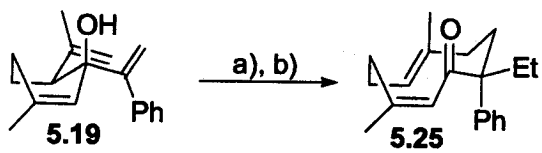
Scheme 5.7 Synthesis of vinyl iodides

[8] Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.
[9] Zhang, H.X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

5.2.2 Generation of quaternary centers

The anionic oxy-Cope reaction of (+)-**5.11** was attempted using reaction conditions (5 equiv of KHMDS, DME, 1.5 h of reflux, addition of MeI at –78 °C), which were previously established by Danny Gauvreau for the same substrate in its racemic form. To our disappointment the result was found irreproducible. Attempts to modify reaction conditions by varying a solvent, reaction temperature and electrophile were unsuccessful.

In order to ensure that lack of consistency in our results was not due to a quality of reagents, we performed the anionic oxy-Cope/alkylation reaction on 1,2-divinylcyclohexanol **5.19**.[10] When subjected to the same conditions (5 equiv of KHMDS, DME, reflux) **5.19** reacted smoothly after 40 min according to TLC. The reaction mixture was then cooled to –78 °C followed by addition of freshly distilled EtI, stirred for 2 h at –78 °C and quenched. Purification by flash chromatography afforded desired macrocyclic ketone **5.25** with quaternary carbon center α to the carbonyl in 98% yield (Scheme 5.8).



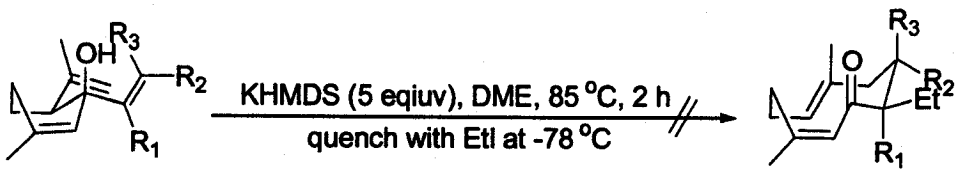
5.19 **5.25**

a) KHMDS (5 eqiuv), DME, 85 °C, 2h; b) quench with EtI at -78 °C, 98%.

Scheme 5.8 Anionic oxy-Cope /alkylation reaction of **5.19**

Having demonstrated that the anionic oxy-Cope/alkylation reaction works well in case of **5.19** we then investigated the reaction of 1,2-divinylcyclohexanols **5.20** and **5.21** (Scheme 5.9).

[10] It was previously reported by Danny Gauvreau that the anionic oxy-Cope of **5.19** occurs smoothly giving the corresponding macrocyclic ketone in 78% yield.



(+)-5.20 R_1=Me, R_2=H, R_3=Me
5.21 R_1=Ph, R_2=Me, R_3=H

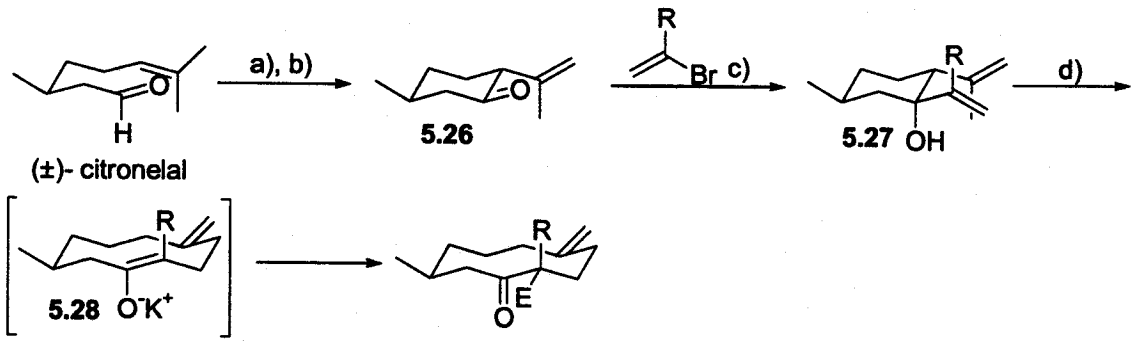
Scheme 5.9 Attempted anionic oxy-Cope/alkylation reaction of substrates (+)-**5.20** and (±)-**5.21**

After refluxing for 1 h in DME the anionic oxy-Cope reaction of (+)-**5.21** gave only the starting material, prolonged periods of heating led to complete decomposition. This result is consistent with that of substrate (+)-**5.11** having the propyl group at C1 position of the 1,5-diene. All attempts to initiate the anionic oxy-Cope reaction of **5.21** (entry 2) using different conditions, i.e. base, solvent, reaction time and temperature were unsuccessful.

Based on our results, it appears that adding a second substituent on the vinyl group decreases the rate of the oxy-Cope reaction. Moreover, when the substrate possesses an alkyl group is at C1 position of the 1,5-diene system (cases of **5.11** and **5.21**), the oxy-Cope reaction does not occur.

As previously discussed, racemization of the enolate generated in the course of the anionic oxy-Cope reaction of 1,2-divinylcyclohexanols **5.1** and **5.6** (Schemes 5.1 and 5.2) can be avoided if a chiral center is present. In the case of compounds (+)-**5.11**, (+)-**5.20** and **5.21** this chiral center originates from a substituent at C1 of the 1,5-diene fragment. However, the presence of a substituent at C1 decreases the reactivity of these substrates. Thus we proposed to implement a substrate for the anionic oxy-Cope reaction in which a chiral center is present prior the enolate formation but is not a part of 1,5-diene moiety.

Ketone **5.26** is readily available in two steps from citronellal in 42% yield (Scheme 5.10).[11] Alkylation of the ketone should afford 1,2-divinylcyclohexanols **5.27**, the anionic oxy-Cope reaction of which will generate macrocyclic enolate **5.28** having a chiral center. If the enolate ring inversion occurs, it will give diastereomeric macrocycle. However, no racemization is possible in this case via the ring inversion. The next step was to investigate whether the anionic oxy-Cope/alkylation reaction of **5.27** can be used to generate a quaternary carbon center. In order to establish the reaction conditions all studies were done using racemic material.

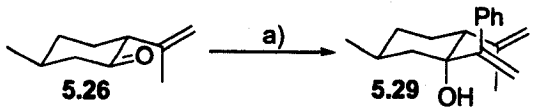


a) $SnCl_4$, CH_2Cl_2, -78 °C, 70%; b) Jones reagent, Et_2O, 60%. c) *t*-BuLi, Et_2O or THF, -90 or -78 °C; d) KHMDS, DME, reflux, then quench with E^+ at -78 °C.

Scheme 5.10 New substrate for the anionic oxy-Cope/alkylation reaction prepared from citronelal

Initially, (±)-1,2-divinylcyclohexanol **5.29** was prepared via alkylation of ketone **5.26** with α-lithium styrene (obtained from α-bromostyrene via metal halogen exchange) in 73% yield (Scheme 5.11).

[11] a) Corey, E.J.; Ensley, H.E.; Suggs, J.W. *J. Org. Chem.* **1976**, *41*, 380. b) Buschmann, H.; Scharf, H-D. *Synthesis* **1988**, *10*, 827.

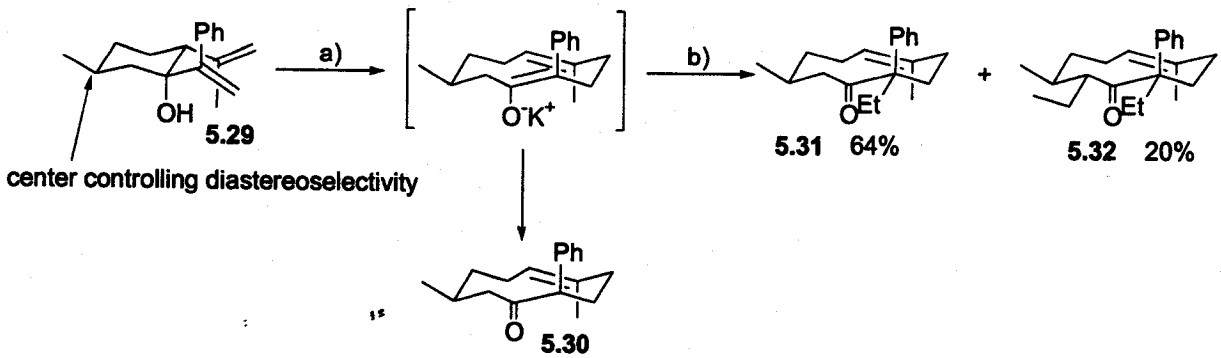


5.26 5.29

a) α-bromostyrene, *t*-BuLi, Et_2O, -90 °C, 75%

Scheme 5.11 Preparation of **5.29**

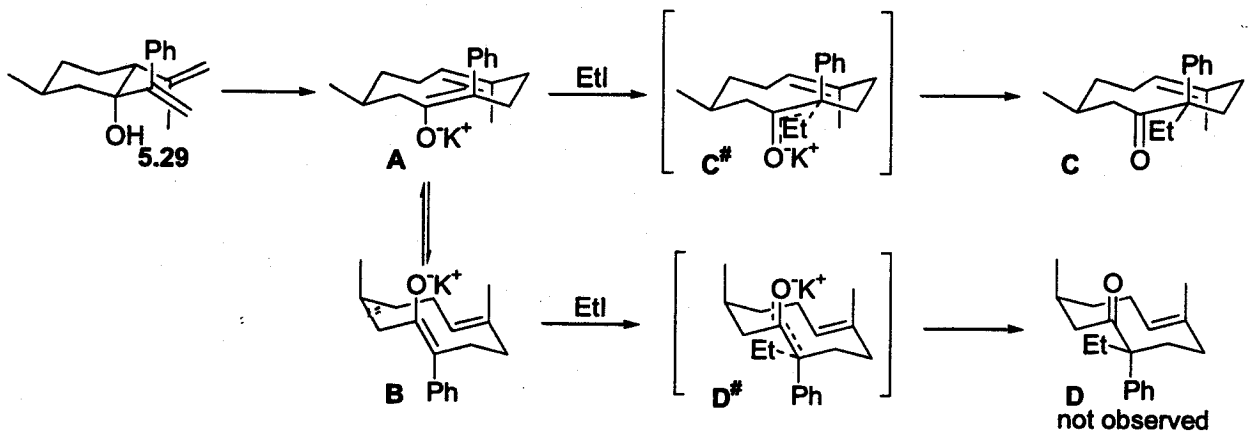
The 1,2-divinylcyclohexanol was treated with 5 equiv of KHMDS in DME at 25 °C and heated to 90 °C. Monitoring the reaction by TLC indicated that after 15 min the starting material was consumed. Cooling the reaction mixture to –78 °C and stirring for 2 h after adding EtI afforded macrocycle **5.31** as a single diastereomer in 64% yield (dr>25:1, detected by ^{1}H NMR). However, double alkylated product **5.32** was also isolated in 20% yield (Scheme 5.12). Formation of the side product was explained by the deprotonation of generated ketone **5.31** with excess of KHMDS followed by a second alkylation with EtI. An attempt to decrease the reaction time led to the isolation of the oxy-Cope product, macrocyclic ketone **5.30**. Christiane Grise (honors project) has been able to improve the ratio of the monoalkylated to the double alkylated product from 2.5:1 to 5.7:1 by decreasing the amount of base and EtI. However, the yield of **2.31** decreased to 48%. Further optimization of the reaction yield is currently under investigation. Relative stereochemistry of **5.31** and **5.32** was tentatively assigned based on the proposed mechanism of the reaction (see Scheme 5.13). We expect to obtain a solid proof of the relative stereochemistry of the quaternary center once the conditions for the macrocycle cleavage are established and cyclic 6-membered derivative can be prepared.



a) KHMDS (5 equiv), DME, 85 °C, 15 min, then quench with EtI at -78 °C.

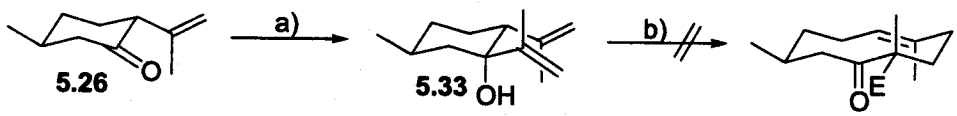
Scheme 5.12 Anionic oxy-Cope/alkylation reaction of **5.29**

Our result demonstrated that high diastereoselectivity in formation of the quaternary carbon center could be achieved by using a remote chiral center. This is rationalized by the mechanism depicted in Scheme 5.13. The anionic oxy-Cope rearrangement of **5.29** generates macrocyclic enolate **A**. The enolate can then either undergo ring inversion to macrocycle **B** followed by the alkylation with EtI to give product **D** or proceed directly to the alkylation step to afford **C**. Assuming that the Curtin-Hemmett principle applies to this case, we can determine the product ratio based solely on the energy difference between transition states $\mathbf{C}^{\#}$ (from **A** to **C**) and $\mathbf{D}^{\#}$ (from **B** to **D**). Transition state $\mathbf{C}^{\#}$ has the methyl group pseudo-equatorial, whereas in transition state $\mathbf{D}^{\#}$ this methyl is in the pseudo-axial position, thereby developing steric interactions with the ring. Thus transition state $\mathbf{C}^{\#}$ should be lower in energy than $\mathbf{D}^{\#}$ favoring formation of product **C**. The observed **C/D** ratio of 25:1 corresponds to a 1.3 kcal/mol (calculated for 195 K= -78 °C) energy difference between transition states $\mathbf{C}^{\#}$ and $\mathbf{D}^{\#}$.



Scheme 5.13 Proposed mechanism for the anionic oxy-Cope/alkylation reaction of **5.29**

In order to investigate how the replacement of the phenyl group with an alkyl substituent affects the reactivity of the anionic oxy-Cope reaction, 1,2-divinylcyclohexanol **5.33** was prepared and subjected to the established anionic oxy-Cope/alkylation conditions (Scheme 5.14). Unfortunately, no reaction was observed. The attempts to modify the reaction conditions (base, solvent, reaction temperature) were unsuccessful. Further work needs to be done on determining the reaction conditions suitable for the substrates with alkyl substituents on the vinyl moiety.



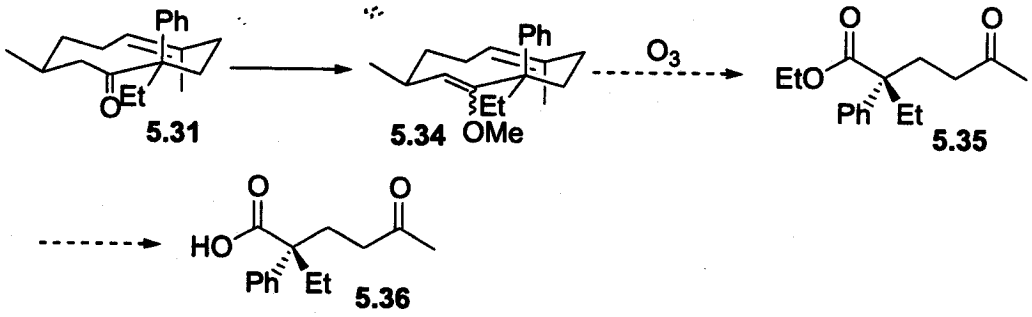
a) isopropenyl magnesium bromide, $CeCl_3$, THF, 0 °C to rt, 92% b) KHMDS, DME, reflux then E^+.

Scheme 5.14 Studies on 1,2-divinylcyclohexanol **2.53**

5.3 Future perspectives

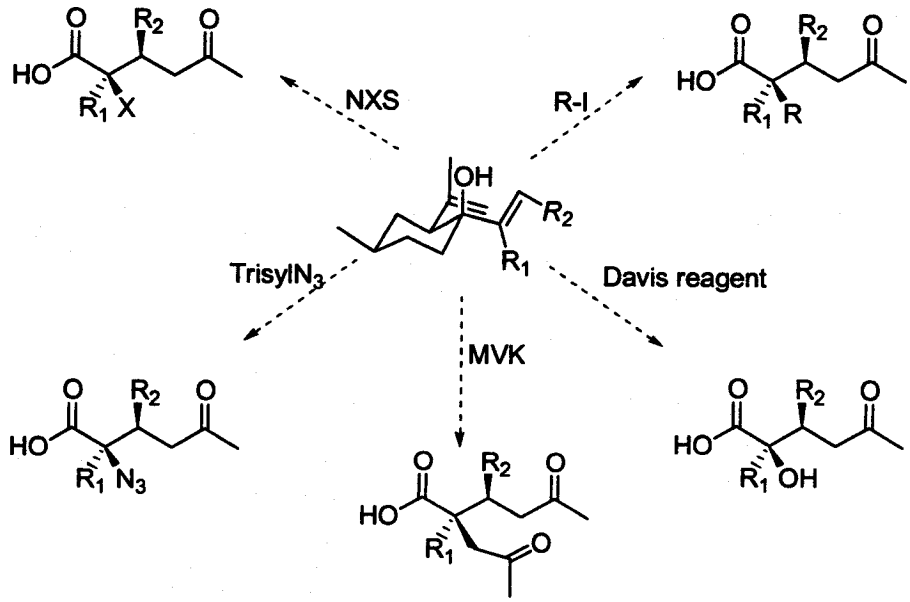
Starting from enantiomerically pure citronellal would lead to formation of enantiomerically pure macrocyclic ketone **5.31** with the quaternary carbon center α to the carbonyl. Cleavage

of the macrocycle would afford a chiral ester **5.35** as illustrated in Scheme 5.15. The preliminary results obtained by Christiane Grise show that this could be achieved via formation of methyl enolate **5.34** followed by the ozonolysis and reductive work up. The hydrolysis of the ester would provide chiral acid **5.36.**



Scheme 5.15 Preparation of a chiral acid with a quaternary carbon center

Once the anionic oxy-Cope/alkylation reaction and the macrocyclic cleavage conditions are optimized, the method could be extended to a number of carbon as well as oxygen and nitrogen electrophiles as shown in Scheme 5.16. The use of nitrogen electrophile could potentially lead to a formation of chiral amino acids.



Scheme 5.16 Future perspectives

Chapter 6 Experimental

6.1 General

All reactions were carried out under dry N_2 or argon atmospheres in flame-dried glassware or sealed tubes equipped with a magnetic bar and a rubber septum, unless otherwise indicated. THF, Et_2O and DME were freshly distilled from sodium/benzophenone. Toluene, CH_2Cl_2 and Et_3N were freshly distilled from CaH_2. The other commercially available reagents were used without purification, unless otherwise indicated.

Reactions were monitored by TLC analysis of aliquots using aluminum and glass sheets pre-coated (0.2 and 0.25 mm layer thickness respectively) with silica gel 60 F_{254} (E. Merck). Flash chromatography was carried out on Silicycle silica gel (0.35-0.75 mm, 60 Å pore size). TLC plates were viewed under UV light and stained with *p*-anisaldehyde or phosphomolybdic acid staining solution. GC (Agilent 6890 Series) was equipped with a crosslinked 5% PH ME siloxane column (30m × 0.32 mm, 0.25 μm film). ^1H spectra were recorded on Bruker Avance 300 MHz and Bruker Avance 500 MHz spectrometers, ^{13}C NMR spectra were recorded at 75 MHz and 125 MHz . IR spectra were recorded on a Bomen Michaelson 100 FTIR spectrometer. HRMS spectra were obtained on a Kratos Analytical Concept instrument. Melting points were recorded on a Gallenkamp Melting Point Apparatus P 1106G. X-ray crystallographs were performed on a Bruker AX SMART 1k CCD diffractometer.

Microwave reactions were conducted in a CEM Model ESP-1500 Plus oven equipped with a pressure monitoring device and an EST-300 Plus fibre optic temperature probe. All experiments were performed in a quartz tube previously washed with an aqueous 2-propanol/NaOH solution.

Trans-2-bromo-butene (IUPAC nomenclature) and *cis*-2-bromo-butene (IUPAC nomenclature) were purchased from Aldrich under the names of *cis*-2-bromo-butene and *trans*-2-bromo-butene respectively.

6.2 Experimental for Chapter 2

6.2.1 General procedures

A. Tandem oxy-Cope/ene/Claisen reaction in the microwave: A solution of an allyl ether (0.10 mmol) in 12-15 mL of toluene in a quartz tube (previously washed with an aqueous 2-propanol/NaOH solution) equipped with a carboflon™ was added freshly distilled DBU[1] (0.50-1.00 mmol). The resulting solution was deoxygenated with argon for 0.5 h, sealed and heated in the CEM microwave at 220 °C for 1 h. The reaction was then cooled to rt. The solution was transferred to a round-bottom flask and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (20 % EtOAc in hexanes) afforded a corresponding lactol.

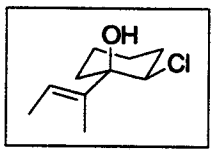
B. Oxidation with TPAP: To a solution of a lactol (0.10 mmol) in CH_2Cl_2 (1 mL) were added molecular sieves (4Å, 50 mg per 0.10 mmol), NMO (0.15 mmol) and TPAP. Resulting black mixture was left stirring for 4-6 h, and then it was filtered through a short pad of silica gel. The silica gel was rinsed with 50 mL of 10 % MeOH in EtOAc solution. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (10 % EtOAc in hexanes) on silica gel to yield a corresponding lactone.

C. Preparation of allyl bromides: To a solution of an allyl alcohol (1.0 mmol) in 10 mL of CH_2Cl_2 was added CBr_4 (1.25 mmol). To a resulting mixture was transferred by cannula a solution of Ph_3P (1.50 mmol) in 5 mL of CH_2Cl_2. After stirring for 10 min the reaction

[1] In the later studies DBU was replaced with Et_3N (3-5 equiv)

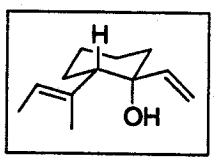
mixture was concentrated under reduced pressure and diluted with 50 mL of hexanes to induce a precipitation of triphenylphosphine oxide. The precipitate was filtered through Celite and the filtrate was concentrated under reduced pressure. The last two steps were repeated two more times to ensure that most of triphenylphosphine oxide was removed. The residue containing allyl bromide was used in the allylation of diol **2.20** without further purification.

6.2.2 Spectroscopic data



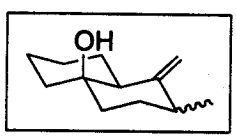
2-Chloro-1- (1-methyl-propenyl)-cyclohexanol (2.13)

To a solution of a *trans*-2 bromo-2-butene (0.15 mL, 1.50 mmol) in Et_2O (5 mL) at –78 °C was added *t*-BuLi (1.65 mL, 1.7 M in pentane, 2.80 mmol). The mixture was stirred for 2 h at –78 °C. Then a solution of 1-chloro-cyclohexan-2-one (132 mg, 1.00 mmol) in Et_2O (2 mL) was transferred by cannula to the lithiated compound at –78 °C. The reaction was completed in 20 min after addition of the ketone. It was quenched with H_2O and extracted with Et_2O 3 x 10 mL. The combined organic extracts were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (7% EtOAc in hexanes) gave chloroalcohol **2.13** (143 mg, 76%) as a yellowish oil. IR (cm^{-1}, neat) 3570 (m), 3482 (bm), 2939 (s), 2850 (m), 1447 (m), 988 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.74-5.67 (m, 1H), 4.35-4.15 (m, 1H), 2.07-1.93 (m, 3H), 1.79-1.52 (m, 10H), 1.51-1.38 (m, 1H), 1.34-1.18 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 134.0 (C_4), 119.0 (CH), 76.8 (C_4), 66.4 (CH), 36.6 (CH_2), 32.7 (CH_2), 26.7 (CH_2), 21.0 (CH_2), 13.7 (CH_3), 12.8 (CH_3); HRMS (E1), m/z (M^+) calculated for $C_{10}H_{17}OCl$ 188.0968, found 188.0953.



2-(1-Methyl-propenyl)-1-vinyl-cyclohexanol (2.11)

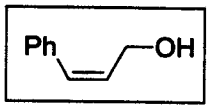
To a solution of chloroalcohol **2.13** (62 mg, 0.33 mmol) in THF (5 mL) at rt was added vinylmagnesium bromide (0.66 mL, 1.5 M in THF, 0.99 mmol). The reaction mixture was refluxed for 3 h. It was then cooled to rt and quenched with a saturated aqueous solution of NH_4Cl. The mixture was extracted with Et_2O 3 x 15 mL. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (8% EtOAc in hexanes) to afford product **2.11** (34.5 mg, 58%) as a yellow oil. IR (cm^{-1}, neat) 3549 (m), 3479 (m), 2933 (s), 2859 (m), 1640 (w), 1447 (m), 970 (m), 915 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.86 (dd, J = 10.7 Hz, J = 17.2 Hz, 1H), 5.24 (q, J = 6.2 Hz, 1H), 5.10 (dd, J = 1.5 Hz, J = 17.2 Hz, 1H), 4.91 (dd, J = 1.4 Hz, J = 10.7 Hz, 1H), 2.00 (dd, J = 3.2 Hz, J = 12.6 Hz, 1H), 1.80-1.35 (m, 14H), 1.28-1.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 147.2 (CH), 138.8 (C_4), 120.5 (CH), 110.6 (CH_2), 73.5 (C_4), 54.3 (CH), 38.3 (CH_2), 27.4 (CH_2), 26.7 (CH_2), 21.7 (CH), 19.6 (CH_3), 13.8 (CH_3); HRMS (E1), m/z (M^+) calculated for $C_{12}H_{20}O$ 180.1514, found 180.1503.



2-Methyl-1-methylene-octahydro-naphthalen-4a-ols (2.12 and 2.14)

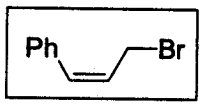
The microwave induced oxy-Cope/ene reaction (procedure A) of **2.11** (30 mg, 0.17 mmol) afforded an inseparable 3.2:1 mixture of diastereomers **2.12** and **2.14** respectively (21 mg, 70%). The ratio was determined from ^1H NMR spectrum by integrating the proton at 4.09 ppm and calibrating the integral for one. Reagents and quantities: DBU (0.13 mL, 0.84 mmol), toluene (12 mL). ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 4.09 (dd, J = 1.6

Hz, J = 1.6 Hz, 1H, **2.14**), 4.84 (bs, 1H, **2.12**), 4.70 (bs, 1H, **2.12**), 4.57 (dd, J = 1.9 Hz, J = 1.9 Hz, 1H, **2.14**), 2.58 (q, J = 6.7 Hz, 1H, **2.14**), 2.22 (m, 1H, **2.14**), 2.03-1.20 (m, 28H, **2.12** and **2.14**), 1.09 (d, J = 7.0 Hz, 3H, **2.14**), 1.05 (d, J = 6.6 Hz, 3 H, **2.12**); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 154.7, 154.1, 108.7, 106.0, 72.4, 72.3, 50.4, 44.3, 40.3, 39.0, 38.9, 38.8, 35.0, 33.1, 29.2, 26.4, 26.3, 24.5, 24.2, 21.7, 21.6, 19.1, 18.7.



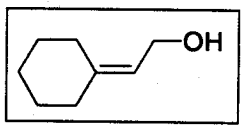
Z-3-Phenyl-prop-2-en-1-ol (2.25a)

To a solution of 3-phenyl-prop-2-yne-1-ol (315 mg, 2.38 mmol) in 10 mL of hexanes was added Lindlar catalyst (32 mg, 10% w/w), followed by addition of quinoline (0.03 mL). The mixture was stirred under H_2 (1 atm) for 20 h at rt. The mixture was concentrated and purified by flash chromatography on silica gel (40% EtOAc in hexanes) to give allyl alcohol **2.25a** (210 mg, 67%). The spectroscopic data was in accord with that reported by Charette *et al.*[2]



(Z)-1-bromo-3-phenyl-prop-2-en (2.26a)

Bromination of allyl alcohol **2.25a** (180 mg, 1.34 mmol) according to procedure C afforded **2.26a** as a yellow oil. Crude oil was used for the etherification of diol **2.20** without purification. Reagents and quantities: CBr_4 (556 mg, 1.68 mmol), Ph_3P (527 mg, 2.01 mmol), CH_2Cl_2 (10 mL).



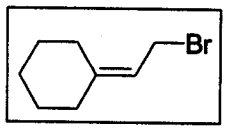
2-Cyclohexylidene-ethanol (2.25b)

1. To a suspension of NaH (1.44 g, 0.036 mol, 60% in oil) in 50 mL of

[2] Charette, A.B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168-12175.

THF at 0 °C was added dropwise triethylphosphonoacetate (4 mL, 0.020 mol). The mixture was stirred for 40 min at 0 °C, then cyclohexanone (1.1 mL, 0.010 mmol) was added dropwise. The reaction was stirred overnight at rt and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Resulting crude oil was used in the next step without further purification.

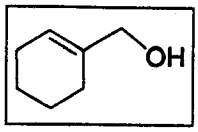
2. To a solution of ester (1.680 g, 0.010 mol) in 100 mL of THF at –78 °C was added dropwise a solution of DIBAL-H (20 mL, 1.5 M in toluene, 0.030 mol). The contents were stirred for 2 hours at –78 °C and then slowly transferred by cannula to a stirred mixture of hexanes/Et_2O/saturated aqueous solution of tartaric acid (1:1:1) at 0 °C. The resulting emulsion was stirred for 2.5 h and diluted with H_2O and Et_2O. The aqueous phase was extracted with Et_2O 5 x 100 mL. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (30% EtOAc in hexanes) afforded **2.25b** (916 mg, 73% over 2 steps) as a clear oil. The spectroscopic data was in accord with that reported by Sabol *et al.*[3]



(2-Bromo-ethylidene)-cyclohexane (2.26b)

Bromination of allyl alcohol **2.25b** (916 mg, 7.27 mmol) according to procedure C afforded **2.27b** as a yellow oil. Crude oil was used for the etherification of diol **2.20** without purification. Reagents and quantities: CBr_4 (3.000 g, 9.09 mmol), Ph_3P (2.860 g, 10.91 mmol), CH_2Cl_2 (50 mL).

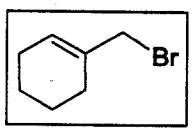
[3] Sabol, J.S.; Cregge, R.J. *Tetrahedron Lett.* **1990**, *31*, 27.



Cyclohex-1-enyl-methanol (2.25c)

1. To a solution of cyclohexanone tosyl hydrazone (9.580 g, 0.036 mol) in freshly distilled TMEDA (50 mL) at –78 °C was added *n*-BuLi (57 mL, 2.5 M in pentane, 0.14 mmol). After stirring for 2 h at –78 °C the mixture was warmed to rt and stirred for 3 h followed by addition of freshly distilled DMF (3.5 mL, 45.00 mmol). The resulting mixture was then stirred for 1 h at rt and quenched with H_2O. The aqueous phase was extracted with Et_2O 5 x 50 mL. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (15% Et_2O in hexanes) afforded aldehyde (3.00 g, 75%) as a yellow oil.

2. To a solution of cyclohex-1-enecarbaldehyde (3.000 g, 0.027 mol) in 200 mL of THF at –78 °C was added dropwise a solution of DIBAL-H (27 mL, 1.5 M in toluene, 0.041 mol). The contents were stirred for 2 hours at –78 °C and then slowly transferred by cannula to a stirred mixture of hexanes/Et_2O/saturated aqueous solution of tartaric acid (1:1:1) at 0 °C. The resulting emulsion was stirred for 2.5 h and diluted with H_2O and Et_2O. The aqueous phase was extracted with Et_2O 5 x 200 mL. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (40% EtOAc in hexanes) afforded **2.25c** (1.235 g, 42%) as a clear oil. The spectroscopic data was in accord with that reported in literature.[4]

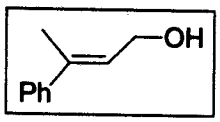


1-Bromomethyl-cyclohexene (2.26c)

Bromination of allyl alcohol **2.25c** (877 mg, 7.80 mmol) according to

[4] Baldwin, J. E.; Burrell, R. C. *J. Org. Chem.* **1999**, *64*, 3567-3571.

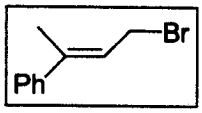
procedure C afforded **2.26c** as an orange oil. Crude oil was used for the etherification of diol **2.20** without purification. Reagents and quantities: CBr_4 (3.237 g, 9.75 mmol), Ph_3P (3.068 g, 11.70 mmol), CH_2Cl_2 (50 mL).



3-Phenyl-but-2-en-1-ol (2.25d)

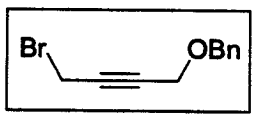
1. To a suspension of NaH (1.152 g, 0.029 mol, 60% in oil) in 50 mL of THF at 0 °C was added dropwise triethylphosphonoacetate (3.2 mL, 0.016 mol). The mixture was stirred for 40 min at 0 °C, then acetophenone (1.0 mL, 0.008 mol) was added dropwise. The reaction was stirred overnight at rt and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 50 mL. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15 % EtOAc in hexanes) afforded ethyl (*E*)-3-phenylbut-2-enoate (940 mg, 62%).

2. To a solution of ethyl (*E*)-3-phenylbut-2-enoate (335 mg, 0.010 mol) in 100 mL of THF at –78 °C was added dropwise a solution of DIBAL-H (20 mL, 1.5 M in toluene, 0.030 mol). The contents were stirred for 2 hours at –78 °C and then slowly transferred by cannula to a stirred mixture of hexanes/Et_2O/saturated aqueous solution of tartaric acid (1:1:1) at 0 °C. The resulting emulsion was stirred for 2.5 h and diluted with H_2O and Et_2O. The aqueous phase was extracted with Et_2O 5 x 100 mL. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (30% EtOAc in hexanes) afforded **2.25d** (165 mg, 64%) as a clear oil. The spectroscopic data was in accord with that reported in literature.[2]



(1-Bromo-3-phenyl-but-2-ene) (2.26d)

Bromination of allyl alcohol **2.25d** (304 mg, 2.08 mmol) according to procedure C afforded **2.26d** as a yellow oil. Crude oil was used for the etherification of diol **2.20** without purification. Reagents and quantities: CBr_4 (864 mg, 2.60 mmol), Ph_3P (818 mg, 3.12 mmol), CH_2Cl_2 (20 mL).



1-bromo-4-*O*-Benzyl-2-butyne (2.62c)

1. To a solution of but-2-yne-1,4-diol (5.00 g, 58.00 mmol) in 50 mL of THF was added NaH (232 mg, 5.80 mmol, 60% in oil) 0 °C. The resulting mixture was stirred for 5 min followed by addition of freshly distilled benzyl bromide (0.69 mL, 5.80 mmol). The reaction mixture was stirred for 4 h at rt and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 50 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (30% EtOAc in hexanes) afforded 1-*O*-benzyl-2-butyne-1,4-diol (728 mg, 71%) as a yellow oil. The spectroscopic data were in accord with those reported in literature.[5]

2. Bromination of 1-*O*-benzyl-2-butyne-1,4-diol (364 mg, 2.07 mmol) according to procedure C afforded **2.62c** as a yellow oil. Crude oil was used for the etherification of diol **2.20** without purification. Reagents and quantities: CBr_4 (857 mg, 2.59 mmol), Ph_3P (814 mg, 3.11 mmol), CH_2Cl_2 (20 mL).

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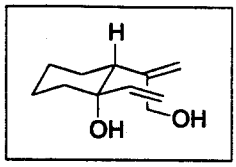
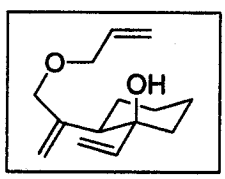
[5] Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem*, **2003**, *68*, 3702.



2-(1-Hydroxymethyl-vinyl)-1-vinyl-cyclohexanol (2.20)

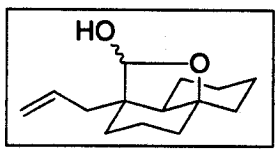
To a solution of 1,2-divinylcyclohexanol **2.19** (6.53 g, 0.04 mol) in 300 mL of CH_2Cl_2 was added SeO_2 (1.99 g, 0.02 mol) and *t*-BuOOH (18.5 mL, 70% in H_2O, 0.16 mol). The mixture was stirred for 24 h and diluted with CH_2Cl_2 (300 mL). The combined organic fractions were washed with H_2O 1 x 400 mL, a saturated aqueous solution of $NaHCO_3$ 2 x 500 mL, H_2O 1 x 400 mL and brine x 400 mL, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (20% EtOAc in hexanes then 40% EtOAc in hexanes) afforded diol **2.20** (3.308 g, 47% or 62% based on the recovery of **2.19**) as a white solid. IR (cm^{-1}, neat) 3310 (br), 3201 (br), 3073 (m), 3010 (m), 2978 (m), 2934 (s), 2855 (s), 1638 (m), 1448 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.83 (dd, J =10.7 Hz, J =17.2 Hz, 1 H), 5.14 (d, J =17.2 Hz, 1H), 5.03 (s, 1H), 4.96 (d, J =10.7 Hz, 1H), 4.86 (s, 1H), 4.03 (d, J_{AB} =12.5, 1H), 3.90 (d, J_{BA} =12.5 Hz, 1H), 3.46 (bs, 2H), 2.21 (dd, J =3.1 Hz, J =12.8 Hz, 1H), 1.92-1.19 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 149.8 (C_4), 146.4 (CH), 116.7 (CH_2), 111.7 (CH_2), 73.3 (C_4), 65.1 (CH_2), 52.4 (CH), 38.7 (CH_2), 27.2 (CH_2), 26.4 (CH_2), 21.5 (CH_2); HRMS (EI), m/z (M^+-H_2O) calculated for $C_{11}H_{16}O$ 164.1247, found 164.1223; mp = 77.9-80.1 °C.



2-(1-Allyloxymethyl-vinyl)-1-vinyl-cyclohexanol (2.21)

To a suspension of NaH (1.590 g, 0.039 mol, 60% in oil) in THF (180 mL) was transferred by cannula a solution of diol **2.20** (3.308 g, 0.018 mol) in 10 mL of THF at 0 °C. The resulting mixture was stirred for 5 min followed by addition of freshly distilled allyl bromide (1.9 mL, 0.022 mol). The reaction was stirred overnight and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase

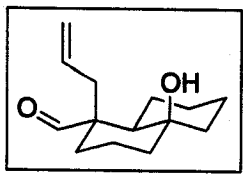
was extracted with Et_2O 3 x 150 mL. The combined organic extracts were dried over MgSO4 and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **2.21** (2.713 g, 68%) as a yellowish oil. Note: diallylated product (1.033 g, 22%) was also isolated as a yellowish oil. IR (cm^{-1}, neat) 3411 (m), 3083 (w), 2932 (s), 2855 (m), 1640 (w), 1445 (m), 1413 (m), 1067 (s), 974 (m), 916 (s); ^1H NMR (500 MHz, $CDCl_3$), δ_{ppm} 5.91-5.81 (m, 2H), 5.26 (dddd, J = 1.7 Hz, J = 1.7 Hz, J = 1.7 Hz, J = 17.2 Hz, 1H), 5.19-5.15 (m, 2H), 5.06-5.05 (m, 1H), 4.97 (d, J = 1.9 Hz, 1H), 4.94 (dd, J = 1.0 Hz, J = 10.6 Hz, 1H), 4.03-3.96 (m, 2H), 3.86 (dddd, J_{AX} = 1.4 Hz, J_{AY} = 1.4 Hz, J_{AM} = 5.8 Hz, J_{AB} = 12.7 Hz, 1H), 3.73-3.70 (m, 1H), 3.57 (d, J = 2.3 Hz, 1H), 2.25 (dd, J = 3.4 Hz, J = 12.8 Hz, 1H), 1.85 (ddd, J = 3.6 Hz, J = 12.9 Hz, J = 16.4 Hz, 1H), 1.80-1.65 (m, 2H), 1.62 –.59 (m, 1H), 1.53-1.48 (m, 1H), 1.43-1.37 (m, 2H), 1.31-1.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 146.5 (CH), 146.2 (C4), 133.9 (CH), 118.0 (CH_2), 117.5 (CH_2), 111.0 (CH_2), 72.6 (C4), 72.2 (CH_2), 70.9 (CH_2), 65.8 (CH_2), 52.0 (CH), 38.4 (CH_2), 26.8 (CH_2), 26.2 (CH_2); HRMS (EI), m/z (M^+-H_2O) calculated for $C_{14}H_{19}O$ 204.1514; found 204.1504.



7-Allyl-11-oxa-tricyclo[5.3.2.01,6]dodecan-12-ol (2.22), mixture of anomers

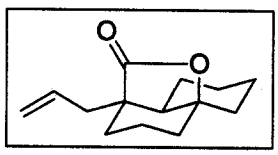
1. The microwave induced oxy-Cope/ene/Claisen rearrangement (procedure A) of **2.21** (80 mg, 0.36 mmol) afforded **2.22** (60 mg, 75%) as a white solid. Reagents and quantities: DBU (0.11 mL, 7.20 mmol), toluene (12 mL). **2.** The microwave reaction (procedure A) of **2.21** (2.713 g, 0.012 mol) in the presence of Et_3N (0.16 mL, 0.001 mol) in 15 mL of toluene gave lactol **2.22** (2.164 g, 80%) and aldehyde **2.24** (0.248 g, 9%).

^{1}H NMR (300MHz, $CDCl_3$), δ_{ppm} 5.84-5.68 (m, 1H), 5.32 (s) and 5.08-4.98 (m) give 1H, 3.46-3.42 (m) and 3.37-3.22 (m) give 1H, 2.31 (dd, J = 7.4 Hz, J = 14.0 Hz, 1H), 2.23-2.08 (m, 1H), 2.05-1.97 (m, 1H), 1.88-0.81(m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 136.0, 135.3, 117.4, 104.5, 102.2, 84.1, 82.7, 50.8, 50.4, 49.4, 48.9, 39.6, 39.0, 37.1, 35.8, 34.9, 34.5, 31.5, 25.3, 24.9, 24.2, 23.9, 21.9, 19.8.



1-Allyl-4a-hydroxy-decahydro-naphthalene-1-carbaldehyde (2.24)

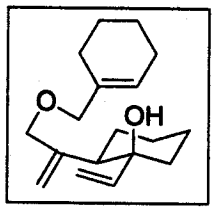
IR (cm^{-1}, neat) 3523 (bm), 2931 (s), 2854 (m), 1719 (s); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 9.15 (d, J = 1.1 Hz, 1H), 5.92 (m, 1H), 5.18-5.12 (m, 1H), 5.06-5.02 (m, 1H); 3.09-3.01 (m, 1H), 2.65-2.58 (m, 1H), 1.82-1.62 (m, 3H), 1.49-0.89 (m, 12 H), 0.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 205.5 (C_4), 136.6 (CH), 117.3 (CH_2), 70.2 (C_4), 52.3 (C_4), 44.9 (CH), 42.2 (CH_2), 40.4 (CH_2), 31.9 (CH_2), 29.1(CH_2), 26.9 (CH_2), 23.0 (CH_2), 21.7 (CH_2), 16.3 (CH_2); HRMS (E1), m/z (M^+- H·) calculated for $C_{14}H_{21}O_2$ 221.1541, found 221.1537.



7-Allyl-11-oxa-tricyclo[5.3.2.01,6]dodecan-12-one (2.23)

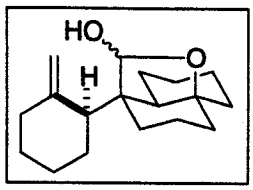
The oxidation (procedure B) of lactol **2.22** (28 mg, 0.13 mmol) gave lactone **2.23** (20 mg, 70%) as a white solid. Reagents and quantities: molecular sieves (65 mg), TPAP (2 mg, 5% mol), NMO (22 mg, 0.20 mmol). IR (cm^{-1}, neat) 2932 (s), 2859 (w), 1767 (s); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.79-5.65 (m, 1H), 5.12-5.06 (m, 2H), 2.36-2.24 (m, 2H), 2.02-1.99 (m, 1H), 1.79-0.81 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 180.7 (C_4), 133.5 (CH), 118.7 (CH_2), 83.5 (C_4), 52.6 (C_4), 49.6 (CH), 36.0 (CH_2), 35.3 (CH_2), 33.6

(CH_2), 32.3 (CH_2), 24.7 (CH_2), 24.2 (CH_2), 21.2 (CH_2), 19.8 (CH_2); HRMS (E1), m/z (M^+) calculated for $C_{14}H_{20}O_2$ 220.1463; found 220.1485; mp = 35.6-38.8 °C.



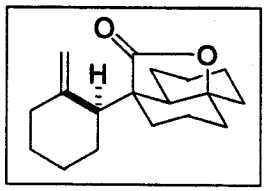
2-[1-(Cyclohex-1-enylmethoxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.27)

To a suspension of NaH (50 mg, 1.25 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol **2.20** (103 mg, 0.56 mmol) at rt. The resulting mixture was stirred for 3 min followed by addition of solution of allyl bromide **2.26c** (200 mg, 1.13 mmol) in 1 mL of THF. The reaction was left stirring overnight at rt. It was quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 20 mL. The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford product **2.27** (106 mg, 68%) as a yellow oil. IR (cm^{-1}, neat) 3403 (m), 2929 (s), 2856 (s), 1638 (w), 1443 (m), 1055 (m), 915 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.8 (dd, J = 10.6 Hz, J = 17.2 Hz, 1H), 5.65-5.64 (m, 1H), 5.17 (dd, J = 1.7Hz, J = 17.1 Hz, 1H), 5.05-5.04 (m, 1H), 4.94 (dd, J = 1.7 Hz, J = 10.6 Hz, 1H), 4.95-4.95 (m, 1H), 3.98-3.62 (m, 5H), 2.26 (dd, J = 3.2 Hz, J = 12.8 Hz, 1H), 2.03-1.16 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 146.9 (C4), 146.6 (CH), 134.5 (C4), 125.9 (CH), 118.5 (CH_2), 113.2 (CH_2), 75.3 (CH_2), 72.9 (C4), 71.9 (CH_2), 52.5 (CH), 38.6 (CH_2), 27.1 (CH_2), 25.6 (CH_2), 26.4 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 21.6 (CH_2); HRMS (EI), m/z (M^+ - H_2O) calculated for $C_{18}H_{26}O$ 258.1983, found 258.19927.



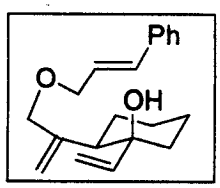
7-(2-Methylene-cyclohexyl)-11-oxa-tricyclo[5.3.2.0^{1,6}]dodecan-12-ol (2.33), (mixture of anomers)

The microwave induced oxy-Cope/ene/Claisen rearrangement (procedure A) of **2.27** (50 mg, 0.18 mmol) gave lactol **2.33** (30 mg, 60%) as a white solid. Reagents and quantities: DBU (0.27 mL, 1.80 mmol), toluene (12 mL). ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.55 (d, J = 3.0 Hz) and 5.12 (d, J = 4.1 Hz) give 1H, 4.82 (s) and 4.80 (s) give 1H, 4.64 (s) and 4.71 (s) give 1H, 2.50-2.40 (m, 2H), 2.27-1.04 (m, 23H).



7-(2-Methylene-cyclohexyl)-11-oxa-tricyclo[5.3.2.0^{1,6}]dodecan-12-one (2.33a)

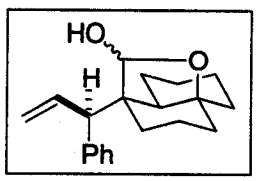
The oxidation (procedure B) of lactol **2.33** (30 mg, 0.11 mmol) afforded lactone **2.33a** (19 mg, 63%) as a white solid. Reagents and quantities: molecular sieves (55 mg), TPAP (2 mg, 5% mol), NMO (20 mg, 0.17 mmol). IR (cm^{-1}, neat) 2930 (s), 2855 (m), 1766 (s), 1648 (w), 1445 (w); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 4.88 (s, 1H), 4.73 (s, 1H), 2.37-2.25 (m, 2H), 2.11-1.02 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 179.5 (C_4), 148.9 (C_4), 107.7 (CH_2), 82.5(C_4), 56.4 (C_4), 52.3 (CH), 48.1 (CH), 39.9 (CH_2), 36.8 (CH_2), 33.8 (CH_2), 33.5 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 28.1 (CH_2), 25.9 (CH_2), 24.5 (CH_2), 22.2 (CH_2), 21.3 (CH_2); HRMS (EI), m/z (M^+) calculated for $C_{18}H_{26}O_2$ 274.1933, found 274.1915; mp = 98.0-101.2 °C.



2-[1-(*E*-3-Phenyl-allyloxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.28)

To a suspension of NaH (90 mg, 2.20 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol **2.20** (100 mg, 0.55 mol) in 1

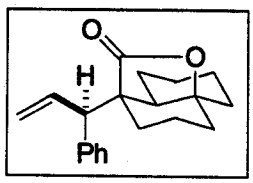
mL of THF at rt. The resulting mixture was stirred for 5 min followed by addition of cinnamyl chloride **2.26e** (0.15 mL, 1.10 mmol) and NaI (8 mg, 0.06 mmol). The reaction mixture was stirred overnight and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 20 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **2.28** (132 mg, 80%) as a yellow oil. IR (cm^{-1}, neat) 3403 (m), 2931 (s), 2854 (m), 1618 (s), 1447 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.38-7.20 (m, 5H), 6.58 (d, J = 16.6 Hz, 1H), 6.34 (ddd, J_{MA} = 6.1 Hz, J_{MB} = 6.1 Hz, J = 16.6 Hz 1H), 5.86 (dd, J = 10.6 Hz, J = 17.2 Hz, 1H), 5.20 (dd, J = 1.8 Hz, J = 17.2 Hz, 1H), 5.10 (bs, 1H), 5.01 (d, J = 1.9 Hz, 1H), 4.97 (dd, J = 1.8 Hz, J = 10.6 Hz, 1H), 4.16 (ddd, J_{AM} = 6.0 Hz, J_{AX} = 1.4 Hz, J_{AB} = 12.6 Hz, 1H), 4.09-4.01 (m, 2H), 3.77 (d, J_{AB} = 12.0 Hz, 1H), 3.61 (s, 1H), 2.26 (dd, J = 3.2 Hz, J = 12.0 Hz, 1H), 1.94-1.19 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 147.0 (C4), 146.5 (CH), 137.2 (C4), 132.9 (CH), 128.5 (CH) x 2, 127.7 (CH), 126.5 (CH) x 2, 125.13 (CH), 118.1 (CH_2), 111.1 (CH_2), 73.0 (C4), 72.0 (CH_2), 70.5 (CH_2), 51.9 (CH), 38.3 (CH_2), 26.8 (CH_2), 26.1 (CH_2), 21.2 (CH_2); HRMS (EI), m/z (M^+-$C_9H_{10}O$) calculated for $C_{11}H_{16}O$ 164.1201; found 164.1199.



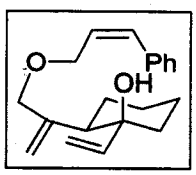
7-(1-Phenyl-allyl)-1,1-oxatricyclo[5.3.2.0^{1,6}]dodecadecan-12-ol (2.34) (mixture of anomers)

The microwave induced oxy-Cope/ene/Claisen reaction (procedure A) of allyl ether **2.28** (80 mg, 0.27 mmol) afforded **2.34** (50 mg, 63%) as a white solid and **2.35** (22 mg, 28%) as a white solid. Reagents and quantities: DBU (0.3 mL, 1.80 mmol), toluene (12 mL). ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.36-7.24 (m, 5H), 6.47-6.42 (m) and 6.38-6.14

(m) give 1H, 5.51 (d, J = 4.5 Hz) and 5.25 (d, J = 3.0 Hz, 1H), 5.13-4.93 (m, 2H), 4.11 (d, J = 7.1 Hz) and 3.62 (d, J = 9.3 Hz) give 1H, 3.34 (d, J = 4.6 Hz) and 3.30 (d, J = 3.3 Hz) give 1H, 2.50-0.81 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 142.1, 141.8, 140.0, 139.8, 130.8, 129.6, 128.5, 128.3, 127.9, 126.6, 117.3, 115.9, 104.0, 101.8, 84.3, 82.7, 54.8, 53.0, 51.3, 51.2, 49.3, 49.1, 39.7, 38.8, 35.2, 34.9, 31.0, 29.2, 25.3, 25.2, 25.1, 23.7, 21.8, 21.8, 20.1, 20.0

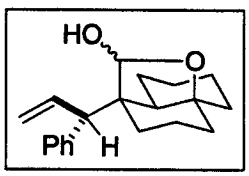


7-(1-Phenyl-allyl)-11-oxa-tricyclo[5.3.2.0^{1,6}]dodecan-12-one (2.34a) The oxidation (procedure B) of lactol **2.34** (25 mg, 0.08 mmol) afforded lactone **2.34a** (20 mg, 80%) as a white solid. Reagents and quantities: molecular sieves (42 mg), TPAP (2 mg, 5% mol), NMO (15 mg, 0.12 mmol). IR (cm^{-1}, neat) 3077 (w), 3022 (w), 2932 (m), 2858 (w), 1764 (s), 1634 (w), 1596 (w), 1448 (m); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 6.71-6.61 (m, 1H), 5.13 (d, J = 9.9 Hz, 1H), 4.64 (d, J = 17.3 Hz, 1H), 3.79-3.78 (d, J = 4.7 Hz, 1H), 2.19-2.12 (m, 1H), 2.02-0.79 (m, 19H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 179.0 (C_4), 140.7 (C_4), 139.6 (CH), 130.5 (CH), 130.5 (CH), 128.6 (CH), 128.6 (CH), 127.0 (CH), 117.3 (CH_2), 82.9 (C_4), 56.2 (C_4), 51.3 (CH), 50.0 (CH), 36.3 (CH_2), 33.9 (CH_2), 30.0 (CH_2), 24.6 (CH_2), 24.3 (CH_2), 21.1 (CH_2), 20.4 (CH_2); HRMS (EI), m/z (M^+) calculated for $C_{20}H_{24}O_2$ 296.1776, found 296.1778.



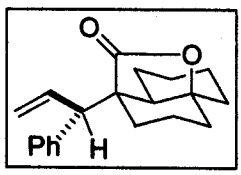
2-[1-(*Z*-3-Phenyl-allyloxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.29) To a suspension of NaH (50 mg, 1.25 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol **2.20** (103 mg, 0.57 mol) in 1 mL of THF at rt. The resulting mixture was stirred for 5 min followed by addition of allyl

bromide **2.26a** (263 mg, 1.34 mmol). The reaction mixture was stirred for 3 h at rt and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 20 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether **2.29** (97 mg, 60%) as a yellow oil. IR (cm^{-1}, neat) 3407 (bm), 3084 (w), 3027 (w), 2931 (s), 2855 (s), 1782 (w), 1733 (w), 1447 (m), 1071 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.35-7.15 (m, 5H), 6.60 (d, J = 11.8 Hz, 1H), 5.91-5.77 (m, 2H), 5.15 (dd, J = 1.3 Hz, J = 17.2 Hz, 1H), 5.02 (s, 1H), 4.95 (s, 1H), 4.89 (dd, J = 1.2 Hz, J = 10.7 Hz, 1H), 4.30-4.24 (m, 1H), 4.19-4.08 (m, 1H), 4.02 (d, J_{AB} = 11.6 Hz, 1H), 3.72 (d, J_{BA} = 11.7 Hz, 1H), 3.60 (d, J = 2.0 Hz, 1H), 2.25 (dd, J = 3.1 Hz, J = 12.9 Hz, 1H), 1.91- 1.19 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 146.8 (CH), 146.4 (C_4), 136.9 (C_4), 132.3 (CH), 129.1 (CH) x 2, 128.6 (CH) x 2, 128.5 (CH), 127.6 (CH), 118.5 (CH_2), 111.4 (CH_2), 73.0 (C_4), 72.8 (CH_2), 67.1 (CH_2), 52.2 (CH), 38.7 (CH_2), 27.1 (CH_2), 26.5 (CH_2), 21.6 (CH_2); HRMS (EI), m/z (M^+) calculated for $C_{20}H_{26}O_2$ 298.1933, observed degradation.



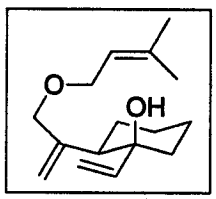
7-(1-Phenyl-allyl)-1,1-oxatricyclo[5.3.2.0^{1,6}]dodecadecan-12-ol (2.35) (mixture of anomers)

^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.37-7.12 (m, 5H), 6.35-6.17 (m, 1H), 5.54 (d, J = 4.7 Hz) and 4.78 (d, J = 3.4 Hz) give 1H, 5.14-5.04 (m, 2H), 4.07 (d, J = 9.1 Hz) and 3.59 (d, J = 8.5 Hz) give 1H, 2.77 (d, J = 3.5 Hz, 1H), 2.15-1.00 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 142.7, 141.8, 138.7, 138.0, 131.0, 129.7, 128.5, 128.0, 126.9, 126.3, 117.5, 117.3, 103.3, 101.7, 84.2, 82.1, 54.7, 53.0, 51.3, 49.4, 48.2, 39.8, 38.9, 35.1, 35.0, 29.3, 27.1, 25.4, 25.2, 24.4, 23.0, 22.0, 21.9, 19.8, 19.7.



7-(1-Phenyl-allyl)-11-oxa-tricyclo[5.3.2.01,6]dodecan-12-one (2.35a)

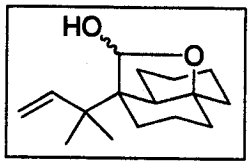
The oxidation (procedure B) of lactol **2.35** (20 mg, 0.07 mmol) afforded lactone **2.35a** (18 mg, 90%) as a white solid. Reagents and quantities: molecular sieves (34 mg), TPAP (1 mg, 5% mol), NMO (12 mg, 0.11 mmol). IR (cm^{-1}, neat) 2934 (s), 2861 (m), 1767 (s), 1634 (w), 1602 (w), 1446 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.33-7.20 (m, 5H), 6.21 (ddd, J = 7.2 Hz, J = 10.4 Hz, J = 17.3 Hz, 1H), 5.05-5.00 (m, 1H), 4.92-4.85 (m, 1H), 3.78 (d, J = 7.1 Hz, 1 H), 2.09-1.95 (m, 3H), 1.74–1.11 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 179.1 (C_4), 140.2 (C_4), 139.3(CH), 130.6 (CH) x 2, 128.5 (CH) x 2, 127.1 (CH), 116.9 (CH_2), 82.7 (C_4), 56.7 (C_4), 53.0 (CH), 51.4 (CH), 36.2 (CH_2), 34.0 (CH_2), 32.3 (CH_2), 26.9 (CH_2), 24.6 (CH_2), 21.3 (CH_2), 19.8 (CH_2) ; HRMS (EI), m/z (M^+) calculated for $C_{20}H_{24}O_2$ 296.1776, found 296.1782.



2-[1-(3-Methyl-but-2-enyloxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.30)

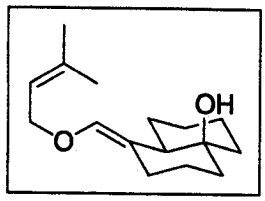
To a suspension of NaH (48 mg, 1.21 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol **2.20** (100 mg, 0.55 mmol) at rt. The resulting mixture was stirred for 3 min followed by addition of 1-bromo-3-methyl-but-2-ene (0.127 mL, 1.10 mmol). The reaction was refluxed for 2 h. The mixture was then cooled to rt and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 20 mL. The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded product **2.30** (100 mg, 73%) as a yellow oil. IR (cm^{-1}, neat) 3727 (w),

3399 (m), 2931 (s), 2857 (m), 1675 (w), 1638 (w), 1445 (w), 1063 (m), 974 (w); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.82 (dd, J = 10.6 Hz, J = 17.2 Hz, 1H), 5.32-5.26 (m, 1H), 5.13 (dd, J = 1.7 Hz, J = 17.2 Hz, 1H), 5.04-5.04 (m, 1H), 4.95-4.91 (m, 2H), 3.99-3.82 (m, 4H), 3.68 (d, J = 11.5, 1H), 2.26 (dd, J = 3.3 Hz, J = 12.9 Hz, 1H), 1.86- 1.22 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 146.9 (C4), 146.6 (CH), 137.8 (C4), 120.6 (CH), 118.5 (CH_2), 111.3 (CH_2), 72.9 (CH_2), 72.2 (C4), 67.0 (CH_2), 52.5 (CH_2), 38.6 (CH_2), 27.0 (CH_2), 26.5 (CH_2), 26.1 (CH_3), 21.6 (CH_2), 18.5 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{16}H_{26}O_2$, observed degradation.



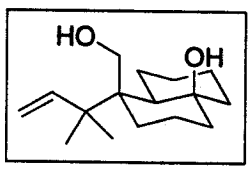
7-(1,1-Dimethyl-allyl)-11-oxa-tricyclo[5.3.2.0^{1,6}]dodecan-12-ol (2.48) (mixture of anomers)

The microwave induced oxy-Cope/ene/Claisen reaction (procedure A) of **2.30** (100 mg, 0.40 mmol) at 200 °C gave lactol **2.48** (76 mg, 76%) as a clear oil and enol ether **2.49** (15 mg, 15%) as a clear oil. Reagents and quantities: DBU (0.3 mL, 2.00 mmol), toluene (12 mL). Purification by flash chromatography on silica gel (10% EtOAc in hexanes, then 20% EtOAc in hexanes) ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 6.12 (dd, J = 10.6 Hz, J = 18.2 Hz, 1H), 5.82 (d, J = 5.0 Hz, 1H), 4.94-4.91 (m, 1H), 4.87-4.86 (m, 1H), 3.86 (d, J = 5.0 Hz, 1H), 2.26-2.02 (m, 2H), 1.81-0.83 (m, 19H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 148.2, 110.7, 110.0, 103.2, 101.0, 83.3, 82.3, 77.8, 77.6, 77.4, 77.0, 53.7, 50.8, 49.6, 40.8, 40.5, 39.8, 39.7, 35.9, 35.7, 33.4, 32.0, 29.0, 28.1, 25.8, 25.7, 25.5, 25.0, 23.0, 22.1, 21.8, 20.4, 14.5.



1-(3-Methyl-but-2-enyloxymethylene)-octahydro-naphthalen-4a-ol (2.49)

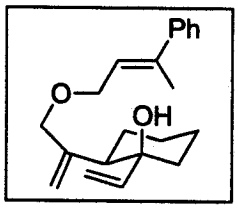
IR (cm^{-1}, neat) 3547 (w), 3474 (w), 2928 (s), 2857 (m), 1672 (m), 1446 (m), 1154 (s), 1088 (w); ^{1}HMR (300 MHz, $CDCl_3$), δ_{ppm} 5.69 (s, 1H), 5.35-5.27 (m, 1H), 4.35 (d, J = 6.9 Hz, 2H) 2.87-2.82 (m, 1H), 1.95-1.89 (m, 1H), 1.75-1.20 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 139.9 (CH), 136.8 (C_4), 121.6 (CH), 118.8 (C_4), 70.8 (C_4), 68.4 (CH_2), 47.4 (CH), 40.5 (CH_2), 38.8 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 25.7 (CH_3), 23.9 (CH_2), 23.1 (CH_2), 21.8 (CH_2), 18.0 (CH_3); HRMS (EI), m/z (M^+-$C_5H_{10}O$) calculated for $C_{11}H_{16}O$ 164.1201; found 164.1175.



1-(1,1-Dimethyl-allyl)-1-hydroxymethyl-octahydro-naphthalen-4a-ol (2.48a)

To a solution of lactol **2.48** (38 mg, 0.15 mmol) in 2 mL of THF was carefully added $LiAlH_4$ (11 mg, 0.30 mmol) at –78 °C. After 10 min a dry-ice/isopropanol bath was removed and the mixture was stirred at 0 °C for 5 h. It was quenched by a dropwise addition of 2 mL of 1.0 M aqueous solution of sodium tartrate. The resulting emulsion was stirred for 10 h until it became almost clear and the phases separated. The aqueous phase was extracted with EtOAc 5 x 5 mL. The combined fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (40 % EtOAc in hexanes) on silica gel afforded diol **2.48a** (30 mg, 79%) as a white solid. IR (cm^{-1}, neat) 3226 (s), 2970 (m), 2930 (s), 2846 (m), 1632 (w), 1449 (m), 1410 (m), 1055 (s); ^{1}HMR (300 MHz, $CDCl_3$), δ_{ppm} 6.01 (dd, J = 10.6 Hz, J = 17.7, 1H), 4.92-4.87 (m, 2H), 3.89 (d, J = 1.1 Hz, 1H), 3.58 (d, J = 11.1 Hz, 1H), 3.28-3.23 (m, 2H), 2.01-1.16 (m, 15H), 1.01 (s, 3H),

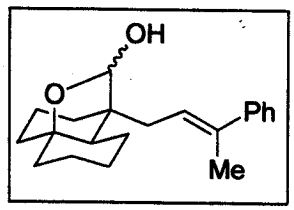
0.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 147.5 (CH), 111.2 (CH_2), 71.5 (C4), 65.8 (CH_2), 47.8 (CH), 44.6 (C4), 43.8 (C4), 42.3 (CH_2), 40.5 (CH_2), 32.0 (CH_2), 27.5 (CH_2), 25.8 (CH_3), 24.3 (CH_2), 24.3 (CH_3), 22.0 (CH_2), 20.2 (CH_2); HRMS (EI), m/z (M^+- H_2O) calculated for $C_{16}H_{26}O$ 234.1984, found 234.1947; mp = 140.0-143.0 °C.



2-[1-(3-Phenyl-but-2-enyloxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.31)

To a suspension of NaH (45 mg, 1.14 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol **2.20** (94 mg, 0.52 mmol) at rt. The resulting mixture was stirred for 3 min followed by addition of allyl bromide **2.26b** (220 mg, 1.04 mmol) in 3 mL of THF. The reaction was stirred overnight and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 20 mL. The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford product **2.31** (119 mg, 73%) as a yellow oil. IR (cm^{-1}, neat) 3560 (w), 3399 (m), 3081 (w), 3058 (w), 3027 (w), 2979 (w), 2931 (s), 2857 (s), 1639 (m), 1598 (w), 1576 (w), 1494 (m), 1445 (m), 1402 (m), 1381 (m), 1285 (w), 1270 (w), 1049 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.41-7.26 (m, 5H), 5.90-5.82 (m, 2H), 5.20 (dd, J = 1.7 Hz, J = 17.2 Hz, 1H), 5.11-5.10 (m, 1H), 5.01 –4.98 (m, 1H), 4.97 (dd, J = 1.7 Hz, J = 10.6 Hz, 1H), 4.20 (ddd, J_{AX} = 0.8 Hz, J_{AM} = 6.3 Hz, J_{AB} = 12.3 Hz, 1H), 4.13-4.06 (m, 2H), 3.77 (dd, J_{AX} = 0.5 Hz, J_{AB} = 11.6 Hz, 1H), 3.71 (d, J = 2.3 Hz, 1H), 2.30 (dd, J = 3.3 Hz, J = 12.7 Hz, 1H), 2.05-2.04 (m, 3H), 1.92-1.25 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 146.9 (CH), 146.6 (C4), 143.1 (C4), 139.1 (C4), 128.6 (CH) x 2, 127.6 (CH), 126.2 (CH) x 2,

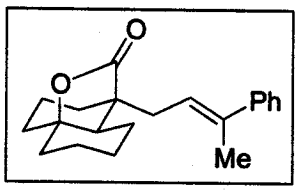
123.8 (CH), 118.6 (CH_2), 113.9 (CH_2), 72.9 (C_4), 72.5 (CH_2), 67.4 (CH_2), 52.4 (CH), 38.7 (CH_2), 27.2 (CH_2), 26.6 (CH_2), 21.6 (CH_2), 16.6 (CH_3); HRMS (EI), m/z (M^+-H_2O) calculated 294.2029 for ($C_{21}H_{26}O$), found 294.1998.



7-(3-Phenyl-but-2-enyl)-11-oxa-tricyclo[5.3.2.01,6]dodecan-12-ol

(2.50) (mixture of the anomers)

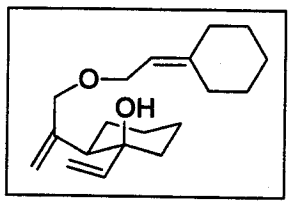
The microwave reaction (procedure A) of **2.31** (71 mg, 0.38 mmol) afforded lactol **2.50**. Reagents and quantities: DBU (0.3 mL, 2.00 mmol), toluene (15 mL). The crude lactol was oxidized to lactone **2.50a** without further purification.



7-(3-Phenyl-but-2-enyl)-11-oxa-tricyclo[5.3.2.$0^{1,6}$]dodecan-12-one

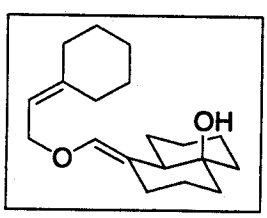
mixture *E/Z* (89:11) (2.50a)

The oxidation (procedure B) of lactol **2.50** (43 mg, 0.14 mmol) afforded lactone **2.50a** (22 mg, 51%) as a yellowish oil. Reagents and quantities: molecular sieves (69 mg), TPAP (3 mg, 5% mol), NMO (24 mg, 0.21 mmol). IR (cm^{-1}, neat) 2922 (m), 2858 (w), 1769 (s), 1692 (m), 1641 (m), 1538 (m), 1447 (m), 1093 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.59-7.22 (m, 5H), 5.67-5.66 (m, 1H), 2.51 (dd, J = 8.0 Hz, J = 15.5 Hz, 1H), 2.40 (dd, J = 15.5 Hz, J = 6.5 Hz, 1H), 2.05-2.01 (m, 4H), 1.86-0.80 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 180.9 (C_4), 144.2 (C_4), 138.2 (C_4), 128.6 (CH) x 2, 127.3 (CH), 126.1 (CH), 126.1 (CH), 122.7 (CH), 83.6 (C_4), 53.5 (C_4), 49.5 (CH), 36.0 (CH_2), 33.6 (CH_2), 32.5 (CH_2), 30.2 (CH_2), 24.8 (CH_2), 24.2 (CH_2), 21.2 (CH_2), 19.9 (CH_2), 16.7 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{21}H_{26}O_2$ 310.1933, found 310.1926.



2-[1-(2-Cyclohexylidene-ethoxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.32)

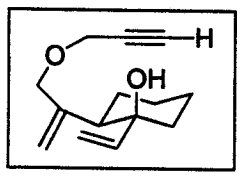
To a suspension of NaH (56 mg, 1.28 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol **2.20** (115 mg, 0.63 mmol) in 2 mL of THF at rt. The resulting mixture was stirred for 3 min followed by addition of allyl bromide **2.26b** solution (438 mg, 2.32 mmol) in THF (3 mL). The solution was stirred overnight and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 20 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc in hexanes) afforded **2.32** (128 mg, 70%) as a yellowish oil. IR (cm^{-1}, neat) 3395 (bm), 2930 (s), 2854 (m), 1668 (w), 1637 (w), 1445 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.63 (dd, J = 10.6 Hz, J = 17.2 Hz, 1H), 5.26-5.20 (m, 1H), 5.16 (dd, J = 1.7 Hz, J = 17.2 Hz, 1H), 5.04-5.03 (m, 1H), 4.94-4.93 (m, 1H), 4.91 (dd, J = 1.7 Hz, J = 10.7 Hz, 1H), 4.00-3.65 (m, 5H), 2.26 (dd, J = 3.3 Hz, J = 12.8 Hz, 1H), 2.13-2.08 (m, 4H), 1.86-1.21 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 147 (C_4), 146.7 (CH), 145.8 (C_4), 118.4 (CH_2), 117.2 (CH), 113.0 (CH_2), 72.9 (C_4), 72.0 (CH_2), 66.1 (CH_2), 52.5 (CH), 38.7 (CH_2), 37.4 (CH_2), 29.4 (CH_2), 28.8 (CH_2), 28.1 (CH_2), 27.0 (CH_2), 27.0 (CH_2), 26.6 (CH_2), 21.6 (CH_2); HRMS (EI), m/z (M^+-H_2O) calculated for $C_{19}H_{28}O$ 272.2140, found 272.2152.



1-(2-Cyclohexylidene-ethoxymethylene)-octahydro-naphthalen-4a-ol (2.59)

^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.69 (s, 1H), 5.26 (tdd, J = 1.1 Hz,

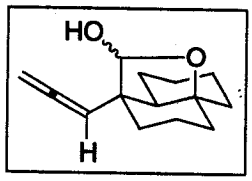
J = 1.1 Hz, J = 7.1 Hz, 1H), 4.21 (d, J = 7.0 Hz, 2H), 2.86-2.82 (m, 1H), 2.18-2.10 (m, 4H), 1.94-1.89 (m, 1H), 1.77-1.16 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 146.1 (C_4), 139.8 (CH), 118.3 (C_4), 117.4 (CH), 71.3 (CH), 67.9 (CH_2), 47.5 (CH), 40.3 (CH_2), 38.4 (CH_2), 37.4 (CH_2), 29.5 (CH_2), 28.8 (CH_2), 28.1 (CH_2), 27.0 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 23.7 (CH_2), 22.92 (CH_2), 21.7 (CH_2).



2-(1-Prop-2-ynyloxymethyl-vinyl)-1-vinyl-cyclohexanol (2.63)

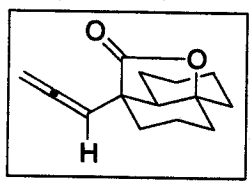
To a suspension of NaH (48 mg, 1.14 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol **2.20** (100 mg, 0.55 mmol) at rt. The resulting mixture was stirred for 3 min followed by addition of propargyl bromide **2.62a** (0.92 mL, 0.82 mmol) and NaI (8 mg, 0.05 mmol). The reaction was refluxed for 5 h, cooled to rt and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 20 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15% EtOAc in hexanes) afforded product **2.63** (85 mg, 70%) as a yellow oil. IR (cm^{-1}, neat) 3425 (m), 3084(w), 2930 (s), 2858 (m), 1782 (w), 1640 (w), 1447 (m), 1068 (m); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.83 (dd, J = 10.6 Hz, J = 17.2 Hz, 1H), 5.16 (dd, J = 2.0 Hz, J = 10.6 Hz, 1H), 5.19-5.10 (m, 1H), 5.02-5.01 (m, 1H), 4.94 (dd, J = 10.6 Hz, J = 2.0 Hz, 1H), 4.14-3.98 (m, 3H), 3.84 (dd, J = 3.3 Hz, J = 12.9 Hz, 1H), 2.96 (s, 1H), 2.41 (dd, J = 2.4 Hz, J = 2.4 Hz, 1H), 2.24 (dd, J = 3.3 Hz, J = 12.9 Hz, 1H), 1.89-1.19 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 146.7 (C_4), 146.0 (CH), 118.3 (CH_2), 111.1 (CH_2), 79.5 (C_4), 75.2 (C_4), 73.0 (C_4), 72.2 (CH_2), 57.1 (CH_2), 51.4 (CH), 38.6 (CH_2), 27.2 (CH_2), 26.5

(CH_2), 21.5 (CH_2); HRMS (EI), m/z (M^+-C_3H_4O) calculated for $C_{11}H_{16}O$ 164.1201, found 164.1195.



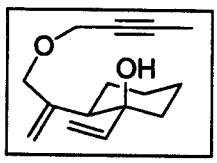
7-Propa-1,2-dienyl-11-oxa-tricyclo[5.3.2.01,6]dodecan-12-ol (2.66) (mixture of anomers)

The microwave reaction (procedure A) of **2.63** (42 mg, 0.18 mmol) afforded lactol **2.66** (41 mg, 98%) as a clear oil. Reagents and quantities: DBU (0.15 mL, 1.00 mmol), toluene (12 mL). ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.53-5.49 (m, 1H), 5.13-5.05 (m, 1H), 4.74 (dd, J = 3.9 Hz, J = 6.6 Hz, 2H), 3.56 (d, J = 5.2 Hz) and 3.42 (d, J = 5.2 Hz) give 1H, 2.33-2.15 (m, 1H), 2.09-0.80 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 208.5, 208.4, 102.8, 102.2, 91.8, 91.5, 84.5, 82.8, 77.8, 77.59, 77.4, 77.0, 76.9, 76.7, 52.9, 51.6, 50.3, 49.5, 39.4, 38.9, 34.8, 34.3, 34.3, 32.9, 25.3, 25.0, 24.4, 21.9, 20.0, 19.8.



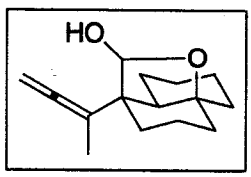
7-Propa-1,2-dienyl-11-oxa-tricyclo[5.3.2.0^{1,6}]dodecan-12-one (2.66a)

The oxidation (procedure B) of lactol **2.67** (40 mg, 0.18 mmol) afforded lactone **2.66a** (31 mg, 78%) as a yellowish oil. Reagents and quantities: molecular sieves (91 mg), TPAP (3 mg), NMO (32 mg, 0.27 mmol). IR (cm^{-1}, neat) 2934 (s), 2859 (m), 1956 (w), 1772 (s); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.32 (dd, J = 6.8 Hz, J = 6.8 Hz, 1H), 4.89-4.78 (m, 2H), 2.04-1.98 (m, 1H), 1.92-0.83 (m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 209.3 (C_4), 179.1 (C_4), 89.4 (CH), 83.8 (C_4), 78.0 (CH_2), 53.3 (C_4), 51.7 (CH), 35.9 (CH_2), 33.5 (CH_2), 33.2 (CH_2), 25.5 (CH_2), 24.2 (CH_2), 21.1 (CH_2), 19.8 (CH_2); HRMS (EI), m/z (M^+) calculated for $C_{14}H_{18}O_2$ 218.1307, found 218.1316.



2-(1-But-2-ynyloxymethyl-vinyl)-1-vinyl-cyclohexanol (2.64)

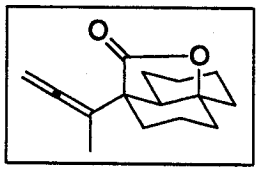
To a suspension of NaH (50 mg, 1.25 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol **2.20** (100 mg, 0.55 mmol) at rt. The resulting mixture was stirred for 3 min followed by adding solution of 1-bromo-2-butyne **2.62b** (110 mg, 0.83 mmol). The reaction was stirred overnight and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 20 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15% EtOAc in hexanes) afforded product **2.64** (105 mg, 82%) as a yellow oil. IR (cm^{-1}, neat) 3423 (m), 3082 (w), 2931 (s), 2856 (m), 1780 (w), 1639 (w); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.84 (dd, J = 10.6 Hz, J = 17.2 Hz, 1H), 5.18 (dd, J = 1.6 Hz, J = 17.2 Hz, 1H), 5.10-5.09 (m, 1H), 5.00-4.99 (m, 1H), 4.95 (dd, J = 1.6 Hz, J = 10.6 Hz, 1H), 4.11-3.79 (m, 4H), 3.18 (d, J = 2.2 Hz, 1H), 2.2 (dd, J = 3.3 Hz, J = 12.9 Hz, 1H), 1.83 (dd, J = 2.3 Hz, J = 2.3 Hz, 3H), 1.81-1.22 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 146.8 (C_4), 146.2 (CH), 118.3 (CH_2), 111.4 (CH_2), 83.3 (C_4), 74.9 (C_4), 73.0 (C_4), 72.0 (CH_2), 57.8 (CH_2), 51.6 (CH), 38.6 (CH_2), 27.2 (CH_2), 26.5 (CH_2), 21.6 (CH_2), 4.0 (CH_3); HRMS (EI), m/z (M^+-C_4H_6O) calculated 164.1200 for $C_{11}H_{16}O$, found 164.1192.



7-(1-Methyl-propa-1,2-dienyl)-11-oxa-tricyclo[5.3.2.0^{1,6}]dodecan-12-ol (2.67)

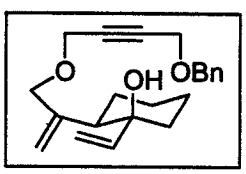
The microwave reaction (procedure A) of **2.64** (40 mg, 0.17 mmol) afforded lactol **2.67** (27 mg, 68%) as a clear oil. Reagents and quantities: DBU (0.20 mL,

1.34 mmol), toluene (12 mL). IR (cm^{-1}, neat) 3393 (m), 2931 (s), 2857 (m), 1963 (w), 1445 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.59 (d, J = 5.0 Hz, 1H), 4.68-4.59 (m, 2H), 3.06 (d, J = 5.6 Hz, 1H), 2.33-2.20 (m, 1H), 1.83-1.07 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 206.4 (C_4), 102.6 (CH), 98.7 (C_4), 82.4 (C_4), 75.1 (CH_2), 52.5 (C_4), 50.7 (CH), 38.9 (CH_2), 34.8 (CH_2), 31.3 (CH_2), 29.9 (CH_2), 24.8 (CH_2), 21.9 (CH_2), 20.1 (CH_2), 16.1 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{15}H_{22}O_2$ 234.1619, found 234.1605.



1.7-(1-Methyl-propa-1,2-dienyl)-11-oxa-tricyclo[5.3.2.01,6]dodecan-12-one (2.67a)

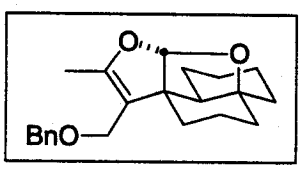
The oxidation (procedure B) of lactol **2.67** (27 mg, 0.12 mmol) afforded lactone **2.67a** (22 mg, 81%) as a yellow oil. Reagents and quantities: molecular sieves (58 mg), TPAP (2 mg, 5% mol), NMO (20 mg, 0.18 mmol). IR (cm^{-1}, neat) 2931 (s), 2858 (m), 1958 (w), 1771 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 4.78- 4.63 (m, 2H), 2.02-1.97 (m, 1H), 1.86-0.80 (m, 17H) ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 207.8 (C_4), 177.3 (C_4), 95.8 (C_4), 82.6 (C_4), 76.0 (CH_2), 56.4 (C_4), 50.7 (CH), 36.1 (CH_2), 33.6 (CH_2), 32.8 (CH_2), 25.5 (CH_2), 24.3 (CH_2), 21.2 (CH_2), 20.0 (CH_2), 16.6 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{15}H_{20}O_2$ 232.1463, found 232.1452.



2-[1-(4-Benzyloxy-but-2-ynyloxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.65)

To a suspension of NaH (53 mg, 1.33 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol **2.20** (110 mg, 0.60 mmol) at rt. The resulting mixture was stirred for 3 min followed by addition of allyl bromide **2.62c** (217 mg,

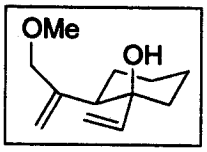
0.91 mmol) solution in 2 mL of THF. The reaction was stirred overnight and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 20 mL. The combined organic extracts were dried over $MgSO_4$, $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15% EtOAc in hexanes) afforded product **2.65** (167 mg, 81%) as a yellow oil. IR (cm^{-1}, neat) 3567(w), 3444(m), 3084(w), 3065(w), 3030(w), 3005(w), 2932 (s), 2855 (s), 1950 (w), 1828 (w), 1639 (w), 1496 (w), 1445 (m), 1387 (m), 1349 (s), 1120 (s), 918 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.35-7.24 (m, 5H), 5.85 (dd, J = 17.2 Hz, J = 10.6 Hz, 1H), 5.18 (dd, J = 17.2 Hz, J = 1.6 Hz, 1H), 5.12-511 (m, 1H), 5.03-5.02 (m, 1H), 4.96 (dd, J = 1.6 Hz, J = 10.6 Hz, 1H), 4.58 (s, 2H), 4.17-4.11 (m, 4H), 4.08 (dd, J = 0.1 Hz, J = 12.2 Hz, 1H), 3.84 (dd, J = 0.5 Hz, J = 12.1 Hz, 1H), 3.03-3.02 (m, 1H), 2.25 (dd, J = 3.3 Hz, J = 12.8 Hz, 1H), 1.87-1.23 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 146.7 (CH), 146.1 (C_4), 137.7 (C_4), 128.8 (4 CH), 128.3 (CH), 118.3 (CH_2), 114.7 (CH_2), 83.1 (C_4), 82.4 (C_4), 73.0 (C_4), 73.02 (C_4), 72.3 (CH_2), 72.0 (CH_2), 57.7 (CH_2), 57.5 (CH_2), 51.5 (CH), 38.7 (CH_2), 27.3 (CH_2), 26.5 (CH_2), 21.6 (CH_2); HRMS (EI), m/z (M^+ - $C_{11}H_{12}O_2$) calculated 164.1201; found 164.1413.



Tetracyclic acetal (2.68)

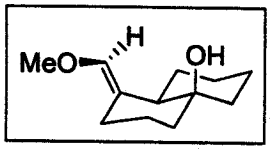
The microwave induced oxy-Cope/ene/Claisen reaction (procedure A) of **2.65** (102 mg, 0.45 mmol) afforded acetal **2.68** (83 mg, 81%) as a white solid. Reagents and quantities: DBU (0.30 mL, 2.00 mmol), toluene (15 mL). IR (cm^{-1}, neat) 2924 (s), 2857 (m), 1679 (m), 1599 (w), 1448 (m); ^1HMR (300 MHz, $CDCl_3$), δ_{ppm} 7.36-7.26 (m, 5H), 5.73 (s, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.43 (d, J = 12.0 Hz, 1H), 3.99 (d, J = 11.8 Hz, 1H), 3.90 (d, J = 11.8 Hz, 1H), 1.95-1.90 (m, 1H), 1.77 (s, 3H), 1.71-

0.83 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 152.4 (C_4), 139.0 (C_4), 128.7 (CH) x 2, 127.9 (CH) x 3, 112.8 (CH), 108.5 (C_4), 89.4 (C_4), 72.1 (CH_2), 64.6 (CH_2), 61.5 (C_4), 50.9 (CH), 39.2 (CH_2), 33.9 (CH_2), 31.4 (CH_2), 25.3 (CH_2), 24.3 (CH_2), 21.6 (CH_2), 19.7 (CH_2), 12.0 (CH_3); HRMS (EI), m/z (M^+-C_7H_8O) calculated for $C_{15}H_{20}O_2$ 232.1462, found 232.1443; mp = 72.6-74.9 °C.



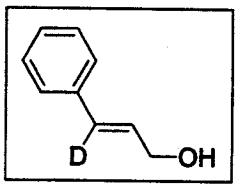
2-(1-Methoxymethyl-vinyl)-1-vinyl-cyclohexanol (2.40)

To a suspension of NaH (21 mg, 0.53 mmol, 60% in oil) in 5 mL of THF was transferred by cannula a solution of diol **2.20** (43 mg, 0.24 mmol) in 0.5 mL of THF at 0 °C. The resulting mixture was stirred for 5 min followed by addition of freshly distilled MeI (0.02 mL, 0.36 mmol). The reaction mixture was stirred overnight and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 10 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5% EtOAc in hexanes) afforded methyl ether **2.40** (20 mg, 43%) as a yellowish oil. Note: dimethylated product was also detected by GCMS. ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.84 (dd, J = 10.7 Hz, J = 17.2 Hz, 1H), 5.17 (dd, J = 1.7 Hz, J = 17.2 Hz, 1H), 5.06-5.05 (m, 1H), 4.98 (s, 1H), 4.96 (dd, J = 10.7 Hz, J = 1.7 Hz, 1H), 4.00 (dd, J = 1.0 Hz, J = 11.6 Hz, 1H), 3.64 (d, J = 2.3 Hz, 1H), 3.61 (dd, J = 0.6 Hz, J = 11.6 Hz, 1H), 3.28 (s, 3H), 2.26 (dd, J = 3.3 Hz, J = 11.3 Hz, 1H), 1.92-1.20 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 146.9 (CH), 146.3 (C_4), 118.6 (CH_2), 111.4 (CH_2), 75.0 (CH_2), 72.9 (C_4), 58.1 (CH), 52.4 (CH_3), 38.7 (CH_2), 27.1 (CH_2), 26.5 (CH_2), 21.6 (CH_2); GC/MS, m/z (M^+-H_2O) calculated for $C_{12}H_{18}O$ 178, found 178.



1-Methoxymethylene-octahydronaphthalen-4a-ol (2.41)

The microwave reaction of **2.40** (procedure A) at 210 °C (20 mg, 0.10 mmol) afforded enol ether **2.41** (14 mg, 70%) as a yellow oil. Reagents and quantaties: DBU (0.20 mL, 1.3 mmol), toluene (12 mL), flash chromatography on silica gel (15% EtOAc in hexanes). IR (cm^{-1}, neat) 3559 (w), 3478 (w), 2928 (s), 2852 (m), 1680 (w); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.52 (d, J = 1.5 Hz, 1H), 3.20-3.13 (m, 1H), 3.18 (s, 3H), 1.93-1.15 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 141.5 (CH), 118.3 (C_4), 70.8 (C_4), 59.1 (CH_3), 47.5 (CH), 40.4 (CH_2), 38.8 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 23.8 (CH_2), 23.0 (CH_2), 21.8 (CH_2); GC/MS, m/z (M^+) calculated for $C_{12}H_{20}O_2$ 196.15, found 196.00.

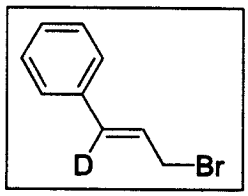


3-Deutero-(*E*)-3-phenyl-prop-2-en-1-ol (2.45)

1. To a suspension of NaH (708 mg, 17.77 mmol, 60% in oil) in 20 mL of THF at 0 °C was added dropwise triethylphosphonoacetate (1.95 mL, 9.84 mmol). The mixture was stirred for 40 min at 0 °C, then α-deuterobezaldehyde (0.5 mL, 4.92 mmol) was added dropwise. The reaction was stirred overnight and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 50 mL. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Resulting crude oil was used in the next step without further purification.

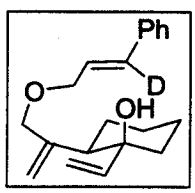
2. To a solution of ethyl 3-deutero-(*E*)-3-phenylprop-2-enoate (575 mg, 4.92 mmol) in 40 mL of THF at –78 °C was added dropwise a solution of DIBAL-H (9.80 mL, 1.5 M in toluene 14.76 mmol). The contents were stirred for 2 hours at –78 °C and then slowly

transferred by cannula to a stirred mixture of hexanes/Et_2O/saturated aqueous solution of tartaric acid (1:1:1). The resulting emulsion was stirred for 2.5 h and diluted with H_2O and Et_2O. The aqueous phase was extracted with Et_2O 5 x 30 mL. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (40% EtOAc in hexanes) afforded allyl alcohol **2.45** (163.5 mg, 25 % over 2 steps) as a yellowish solid. IR (cm^{-1}, neat) 3332 (bs), 3080 (w), 3058 (w), 3032 (m), 2918 (m), 2861 (m), 1708 (w), 1642 (w), 1598 (w), 1576 (w), 1493 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.39-7.19 (m, 5H), 6.38-6.33 (m, 1H), 4.32 (d, J = 5.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 136.9 (C_4), 128.7 (CH) x 3, 128.7 (CH), 128.1 (CH), 126.8 (CH) x 2, 64.1 (CH_2); HRMS (E1), m/z (M^+) calculated for C_9H_9DO 135.0793, found 135.0788.



1-Bromo-3-deutero-(*E*)-3-phenyl-prop-2-ene (2.46)

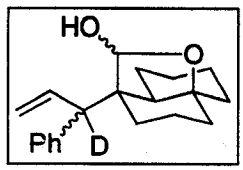
To a solution of allyl alcohol **2.45** (163 mg, 1.22 mmol) in 10 mL of CH_2Cl_2 was added CBr_4 (506 mg, 1.53 mmol) followed by a cannulation of a solution of PPh_3 (480 mg, 1.83 mmol) in 2 mL of CH_2Cl_2. The mixture was stirred for 10 min and then concentrated under reduced pressure. The rest of the solvent was removed with a vacuum pump. The crude solidifying oil was used for the etherification of diol **2.20** without further purification.



2-[1-(3-Deutero-*E*-3-Phenyl-allyloxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.42)

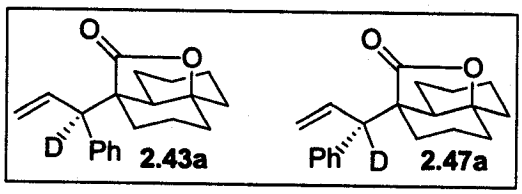
To a suspension of NaH (90 mg, 2.20 mmol, 60% in oil) in 10 mL of THF

was slowly transferred by cannula a solution of diol 2.20 (100 mg, 0.55 mmol) in 1 mL of THF. The mixture was stirred for 5 min followed by addition of a solution of allyl bromide (240 mg, 1.22 mmol) in 5 mL of THF and NaI (8 mg, 0.06 mmol). The reaction was stirred overnight and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 20 mL. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel (10 % EtOAc in hexanes) to afford 2.42 (43 mg, 26%) as a yellow oil. IR (cm^{-1}, neat) 3401 (s), 3084 (w), 3059 (w), 3023 (w), 2932 (s), 2855 (s), 1779 (w), 1642 (w), 1494 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.43-7.20 (m, 5H), 6.26-6.22 (m, 1H), 5.86 (dd, J = 10.6 Hz, J = 17.2 Hz, 1H), 5.20 (d, J = 17.2 Hz, 1H), 5.10 (s, 1H), 5.01 (s, 1H), 4.97 (d, J = 10.7 Hz, 1H), 4.16 (dd, J_{AX} = 6.2 Hz, J_{AB} = 12.6 Hz, 1H), 4.04(dd, J_{BX} = 8.1 Hz, J_{AB} = 12.6 Hz, 1H), 4.05 (d, J_{AB} = 12.5 Hz, 1H), 3.78 (d, J_{AB} = 12.0 Hz, 1H), 3.64 (s, 1H), 2.28 (dd, J = 3.0 Hz, J = 12.7 Hz, 1H), 1.94-1.20 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 146.9 (CH), 146.5 (C_4), 136.8 (C_4), 128.9 (CH) x 3, 128.2 (CH), 126.9 (CH) x 2, 125.4 (CH), 118.6 (CH_2), 11.5 (CH_2), 73.0 (C_4), 72.4 (CH_2), 70.9 (CH_2), 52.3 (CH), 38.7 (CH_2), 27.2 (CH_2), 26.5 (CH_2), 21.6 (CH_2); HRMS (EI), m/z (M^+) calculated for $C_{20}H_{25}DO_2$ 299.1995, observed degradation.



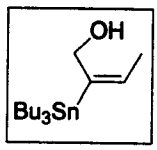
2.43 (anomeric mixture) and **2.47 (anomeric mixture)**

The microwave induced oxy-Cope/ene/Claisen reaction (procedure A) of allyl ether **2.42** (15 mg, 0.05 mmol) afforded a mixture of lactols **2.43** and **2.47**. Reagents and quantities: Et_3N (0.03 mL, 0.21 mmol), toluene (11 mL). The crude mixture of lactols was used in the oxidation with TPAP without further purification.



Mixture of lactones (2.43a and 2.47a)

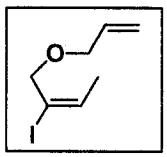
The oxidation (procedure B) of the crude mixture of lactols **2.43** and **2.47** (15 mg, 0.05 mmol) afforded a 2:1 mixture of lactones **2.43a** and **2.47a** respectively (6.6 mg, 44% over 2 steps) as a white solid. Reagents and quantities: molecular sieves (25 mg), TPAP (1 mg, 5% mol), NMO (9 mg, 0.18 mmol). ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 6.66 (dd, J = 10.5 Hz; J = 17.2 Hz, 1H, **2.43a**), 6.20 (dd, J = 10.6 Hz, J = 17.4 Hz, 1H, **2.47a**), 5.13 (dd, J = 1.6 Hz; J = 10.5 Hz, 1H, **2.43a**), 5.03 (dd, J = 1.5 Hz, J = 10.3 Hz, 1H, **2.47a**), 4.89 (dd, J = 1.6 Hz, J = 17.1 Hz, 1H, **2.47a**), 4.65 (dd, J = 1.6 Hz; J = 17.3 Hz, 1H, **2.43a**), 2.18-0.81 (m, 40H, **2.43a** and **2.47a**); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 179.8, 140.7, 140.2, 139.6, 139.3, 130.5, 130.4, 128.6, 128.5, 127.1, 127.0, 117.3, 116.9, 82.9, 82.7, 56.6, 56.2, 56.1, 51.3, 36.3, 36.2, 34.0, 33.9, 32.2, 30.1, 30.0, 26.8, 24.6, 24.6, 24.3, 21.3, 21.1, 20.4, 19.8.



2-Tributylstannanyl-but-2-en-1-ol (2.71a)

To a solution of $Pd(PPh_3)_4$ (323 mg, 0.28 mmol) in 10 mL of toluene was added but-2-yne-1-ol **2.70** (1.07 mL, 14.00 mmol) and stirred for 2 min at rt. Bu_3SnH (4.2 mL, 15.20 mmol) was then added dropwise. After an abrupt change of reaction color additional 0.1 equivalent of Bu_3SnH (0.38 mL, 1.40 mmol) was introduced into the mixture. The solution was stirred for 10 min and concentrated under reduced pressure. Crude oil was initially passed through a short pad of silica gel in order remove Pd catalyst. Purification by flash chromatography on silica gel (5% EtOAc in hexanes) afforded **2.71a** (3.537 g, 70%) as

a clear oil, regioisomer **2.71b** was also isolated (0.500 g, 10%). The spectroscopic data was in accord with that reported in literature.[6]



1-Allyloxy-2-iodo-but-2-ene (2.73)

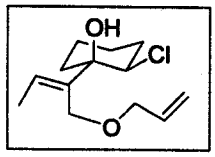
1. Preapration of 2-iodo-but-2-en-1-ol **(2.72)**

To a solution of **2.71a** (2.000 g, 5.54 mmol) in 40 mL of CH_2Cl_2 was added in portions I_2 (1.56 g, 6.09 mmol). After addition was completed and an iodine color maintained, reaction mixture was stirred for 10 min and quenched with a saturated aqueous solution of Na_2SO_3. The aqueous phase was extracted with CH_2Cl_2 3 x 50 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under atmospheric pressure. Purification by flash chromatography on silica gel (20% Et_2O in pentane) afforded **2.72** (890 mg, 81%) as a yellow oil. **Caution: vinyl iodide is volatile and light sensitive!!!**

2. To a suspension of NaH (277 mg, 6.95 mmol, 60% in oil) in THF (10mL) at rt was transferred by cannula a solution of 2-iodo-but-2-en-1-ol **2.72** (1.146 g, 5.79 mmol) in THF (5 mL). The mixture was stirred for 3 min. Allyl bromide (0.5 mL, 6.37 mmol) was then added and the solution was refluxed for 3h. The reaction was then cooled to rt and quenched with a saturated aqueous solution of NH_4Cl followed by extraction with Et_2O 3 x 15 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. **Caution: resulting iodide is volatile!!!** Purification by flash chromatography on silica gel (5% Et_2O in petroleum ether) afforded **2.73** (910 mg, 66% yield) as a yellow oil. IR (cm^{-1}, neat) 3079 (w), 2924 (s), 2854 (s), 1646 (w), 1633 (w), 1456 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 6.46 (qt, J = 7.2 Hz, J = 0.9 Hz, 1H), 5.92 (dddd, J = 5.7 Hz, J= 5.7 Hz,

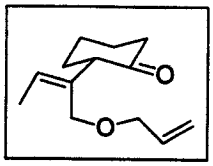
[6] Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768.

J = 10.4 Hz, J = 17.2 Hz, 1H), 5.32-5.25 (m, 1H), 5.22-5.17 (m, 1H), 4.12 (s, 2H), 3.95 (ddd, J = 1.4 Hz, J = 1.4 Hz, J = 5.7 Hz, 2H), 1.71 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 140.1 (CH), 134.8 (CH), 118.1 (CH_2), 99.1 (C_4), 71.0 (CH_2), 70.7 (CH_2), 17.3 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_7H_{11}OI$ 237.9855, found 237.9878.



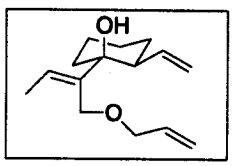
1-(1-Allyloxymethyl-propenyl)-2-chloro-cyclohexanol (2.74)

To a solution of vinyl iodide **2.73** (540 mg, 2.27 mmol) in Et_2O (10 mL) at –100 °C was added a solution of *t*-BuLi (2.45 mL, 1.7 M in pentane, 12.49 mmol). The reaction mixture was stirred for 1 h at –100 °C. Then a solution of 1-chloro-2-cyclohexanone (100 mg, 0.78 mmol) in Et_2O (1 mL) was cooled to –100 °C and transferred by cannula to the lithiated compound. The solution was allowed to warm to –60 °C, then cooled to –100 °C and quenched with H_2O. The aqueous layer was extracted with Et_2O 3 x 20 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel (12% EtOAc in hexanes) to afford product **2.74** (83 mg, 45%) as a colorless oil. IR (cm^{-1}, neat) 3495 (br), 3079 (w), 2938 (s), 2860 (s), 1647 (w), 1447 (m); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.97-5.84 (m, 2H), 5.30-5.23 (m, 1H), 5.19-5.14 (m, 1H), 4.23 (dd, J = 6.2 Hz, J = 10.2 Hz, 1H), 4.15 (d, J_{AB} = 11.5 Hz, 1H), 4.07 (d, J_{BA} = 11.5 Hz, 1H), 4.02-3.89 (m, 2H), 2.78 (d, J = 1.8 Hz, 1H), 2.10-1.95 (m, 2H), 1.82-1.49 (m, 7H), 1.47-1.41 (m, 1H), 1.35-1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 140.7(C_4), 135.0 (CH), 125.6 (CH), 117.6 (CH_2), 76.6 (C_4), 71.3 (CH_2), 67.4 (CH), 65.0 (CH_2), 39.2 (CH_2), 33.0 (CH_2), 25.6 (CH_2), 21.1 (CH_2), 13.9 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{13}H_{21}O_2Cl$ 244.1230, found 244.1230.



2-(1-Allyloxymethyl-vinyl)-cyclohexanone (2.75)

To a solution of chlorohydrine **2.74** (83 mg, 0.34 mmol) in THF (6 mL) at rt was added vinylmagnesium bromide (0.38 mL, 0.9 M in THF, 0.34 mmol). The solution was refluxed for 2 h, cooled to rt and quenched with a saturated aqueous solution of NH_4Cl. The mixture was extracted with Et_2O 3 x 10 mL. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to afford ketone **2.75** (48 mg, 68%) as a colorless oil. IR (cm^{-1}, neat) 3084 (w), 2950 (m), 2864 (m), 1707 (s), 1639 (w), 1453 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.94-5.81 (m, 1H), 5.44 (q, J = 6.9 Hz, 1H), 5.26-5.12 (m, 2H), 4.05 (d, J_{AB} = 11.4 Hz, 1H), 3.95-3.83 (m, 3H), 3.17 (dd, J = 4.7 Hz, J =11.7 Hz, 1H), 2.43-2.27 (m, 2H), 2.08-1.96 (m, 2H), 1.92-1.63 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 212.3 (C_4), 135.3 (C_4), 135.2 (CH), 126.2 (CH), 117.4 (CH_2), 71.4 (CH_2), 67.1 (CH_2), 56.2 (CH), 42.3 (CH_2), 32.4 (CH_2), 28.1 (CH_2), 25.7 (CH_2), 13.9 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{13}H_{20}O_2$ 208.1464, found 208.1443.



2-(1-Allyloxymethyl-vinyl)-1-vinyl-cyclohexanol (2.69)

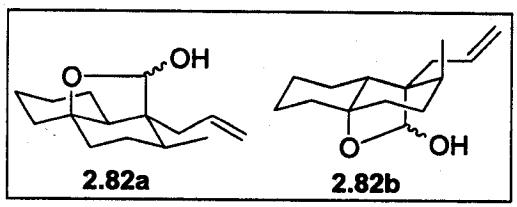
Procedure A (from chlorohydrine 2.74)

To a solution of **2.74** (61.7 mg, 0.33 mmol) in THF (5 mL) at rt was added vinylmagnesium bromide (0.65 mL, 1.5 M in THF, 0.99 mmol). The reaction mixture was refluxed for 3 h, cooled to rt and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 10 mL. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by

flash chromatography on silica gel (8% EtOAc in hexanes) to afford product **2. 69** (34.5 mg, 58%) as a clear oil.

Procedure B (from ketone 2.75)

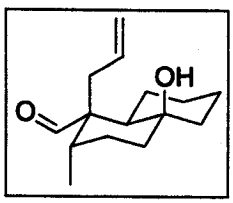
To a solution of **2.75** (25 mg, 0.12 mmol) in THF (2 mL) at 0 °C was added a solution of vinylmagnesium bromide (0:27 mL, 0.9 M in THF, 0.24 mmol). The solution was stirred for 1.5 h at 0 °C and quenched with a saturated aqueous solution of NH_4Cl. The mixture was extracted with Et_2O 3 x 5 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15% EtOAc in hexanes) afforded desired product **2.69** (16 mg, 56%) as a clear oil. *Syn* isomer (3.4 mg, 12%) was also isolated as a clear oil. IR (cm^{-1}, neat) 3411 (br), 3083 (w), 2932 (s), 2856 (m), 1642 (w), 1445 (m), 1401 (m), 1171 (w), 1057 (s), 975 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.95 (m, 2H), 5.52 (q, J = 6.7 Hz, 1H), 5.30-5.11 (m, 3H), 4.90 (dd, J = 1.8 Hz, J = 10.7 Hz, 1H), 4.14-3.95 (m, 3H), 3.89-3.78 (m, 2H), 2.20 (dd, J = 2.9 Hz, J = 12.5 Hz, 1H), 1.94-1.19 (m, 8H), 1.65 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 147.5 (CH), 136.6 (C_4), 134.3 (CH), 129.8 (CH), 117.9 (CH_2), 111.0 (CH_2), 73.4 (C_4), 72.1 (CH), 64.5 (CH_2), 55.3 (CH), 38.9 (CH_2), 27.0 (CH_2), 26.8 (CH_2), 21.8 (CH_2), 13.9 (CH_3); HRMS (EI), m/z (M^+-H_2O) calculated for $C_{15}H_{22}O$ 218.1672, found 218.1706.



2.82a **2.82b**

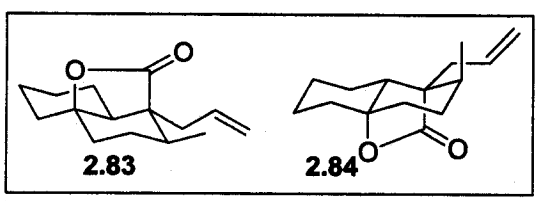
7-Allyl-8-methyl-11-oxa-tricyclo[5.3.2.0^{1,6}]dodecan-12-ols (2.82a) (anomeric mixture) and (2.82b) (anomeric mixture)

The microwave reaction (procedure A) of **2.69** (13 mg, 0.06 mmol) gave a mixture of lactols **2.82a** and **2.82b** (6.1 mg, 47%) and (76 mg, 76%) as a clear oil and 15:1 mixture of aldehydes **2.80** and **2.81** (5.4 mg, 41%) as a clear oil. Reagents and quantities: Et_3N (0.03 mL, 0.18 mmol), toluene (12 mL). In order to determine the diastereomeric ratio the mixture of lactols was oxidized with TPAP to corresponding lactones **3.83** and **3.84**.



1-Allyl-4a-hydroxy-2-methyl-decahydro-naphthalene-1-carbaldehyde (2.80)

IR (cm^{-1}, neat) 3511 (bm), 3077 (w), 2929 (s), 2861 (m), 2712 (w), 1713 (s), 1640 (w); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 9.46 (s, 1H), 6.00-5.86 (m, 1H), 5.12-5.03 (m, 2H), 2.96 (dd, J = 8.4 Hz, J = 14.7 Hz, 1H), 2.54 (dd, J = 6.8 Hz, J = 14.8 Hz, 1H), 2.21-2.09 (m, 2H), 1.88 (dd, J = 2.5 Hz, J = 11.8 Hz, 1H), 1.82-1.19 (m, 12H), 0.91 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 207.7 (C_4), 135.8 (CH), 118.1 (CH_2), 71.4 (C_4), 53.8 (C_4), 42.3 (CH_2), 40.2 (CH), 35.2 (CH_2), 34.2 (CH_2), 31.4 (CH), 27.1 (CH_2), 23.9 (CH_2), 23.7 (CH_2), 22.1 (CH_2), 15.4 (CH_3); HRMS (EI), m/z (M^+-H_2O) calculated for $C_{15}H_{22}O$ 218.1671, found 218.1681.

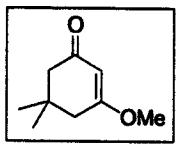


Mixture of lactones 2.83 and 2.84

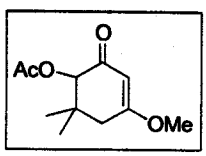
The oxidation (procedure B) of a mixture of lactols **2.82a** and **2.82b** (6.1 mg, 0.03 mmol) afforded a 2.2:1 mixture of lactones **2.83** and **2.84** (4 mg, 68%) as a white solid. Reagents and quantities: molecular sieves (13 mg), TPAP (1 mg, 10% mol), NMO (5 mg, 0.05 mmol). ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 6.11-6.14 (m, 1H, **2.83**), 5.73-5.59 (m, 1H, **2.84**), 5.20-

5.02 (m, 4H, **2.83** and **2.84**), 2.59-2.48 (m, 1H, **2.84**), 2.46-2.38 (m, 1H, **2.83**), 2.24-2.16 (m, 1H, **2.84**), 2.73-0.83 (m, 39H, **2.83** and **2.84**); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 181.6, 179.1, 134.9, 133.2, 118.8, 117.5, 83.8, 83.2, 55.8, 55.1, 49.5, 45.0, 36.6, 34.9, 34.1, 33.7, 33.5, 32.8, 31.1, 30.1, 29.4, 27.0, 25.2, 25.0, 24.6, 24.4, 24.2, 21.2, 16.6, 13.9.

6.3. Spectroscopic data for Chapter 3



3-Methoxy-5,5-dimethyl-cyclohex-2-enone was prepared according to procedure reported in literature[7]: to a solution of 5,5-dimethyl-cyclohexane-1,3-dione (2.000 g, 0.014 mol) in 78 mL of MeOH was added 1 mL of concentrated H_2SO_4. The mixture was refluxed for 2 h, and concentrated under reduced pressure. To the concentrate was added a saturated aqueous solution of $NaHCO_3$ until pH=8. The mixture was extracted with CH_2Cl_2 3 x 100 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (45% EtOAc in hexanes) gave 3-methoxy-5,5-dimethyl-cyclohex-2-enone (1.960 g, 93%) as a yellow solid.

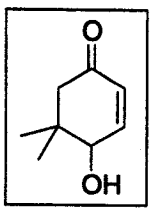


4-methoxy-6,6-dimethyl-2-oxo-cyclohex-3-enyl acetate[8]

A suspension of $Mn(OAc)_3 \cdot 2H_2O$ (12.86 g, 0.048 mol) in 200 mL of benzene was refluxed using a Dean-Stark trap for 2 h. The mixture was the cooled to rt, followed by addition of 3-methoxy-5,5-dimethyl-cyclohex-2-enone (1.84 g, 0.012 mol). The resulting suspension was refluxed (Dean-Stark trap) for 2 d, cooled and diluted with EtOAc (200 mL). The aqueous phase was extracted with EtOAc 2 x 200 mL.

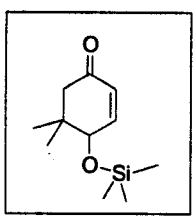
[7] Quesada, M. L.; Schlessinger, R. H.; Parsons, W. H. *J. Org. Chem.* **1978**, *43*, 3968.
[8] Demir, A.S.; Sayrac, T.; Watt, D.S. *Synthesis*, **1990**, *12*, 1119.

The combined organic extracts were washed with 1 N HCl x 400 mL, a saturated aqueous solution of $NaHCO_3$ x 400 mL and with brine x 400 mL, dried over $MgSO_4$ and concentrated under reduced pressure. Purification on flash chromatography (30% EtOAc in hexanes) afforded 4-methoxy-6,6-dimethyl-2-oxo-cyclohex-3-enyl acetate (2.33 g, 91%) as a yellow oil.



4-Hydroxy-5,5-dimethyl-cyclohex-2-enone (3.6)

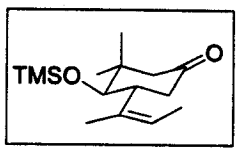
To a suspension of $LiAlH_4$ (6.00 g, 0.154 mol) in 300 mL of Et_2O at rt was transferred by cannula a solution of 4-methoxy-6,6-dimethyl-2-oxo-cyclohex-3-enyl acetate (16.49 g, 0.077 mol) in 20 mL of Et_2O. The mixture was stirred at rt for 30 min and then refluxed for 3 h. The reaction was cooled to 0 °C and quenched by a dropwise addition of H_2O (100 mL) **(H_2O must be added very carefully)** followed by addition of a 10% aqueous solution of H_2SO_4. The suspension was stirred for 3 h at rt. The aqueous phase was extracted with EtOAc 3 x 300 mL. The combined organic fractions were washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil (7.58 g) was used for protection with TMSCl without further purification. The spectroscopic data was in accord with that reported in literature.[8]



5,5-Dimethyl-4-trimethylsilanyloxy-cyclohex-2-enone (3.7)

To a solution of crude ketone **3.6** (0.054 mol, 7.58 g) in 200 mL of THF was added imidazole (0.065 mL, 4.66 g) followed by addition of TMSCl (8.2 mL, 0.065 mol). Formation of a white precipitate was observed almost immediately. The mixture was stirred for 2 h at rt, then the reaction was quenched by addition of a

saturated aqueous solution of NaCl. The aqueous phase was extracted three times with EtOAc 3 x 200 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (20% EtOAc in hexanes) afforded product **3.7** (9.387 g, 82 %) as yellow crystals. IR (cm^{-1}, neat) 3045 (w), 2961 (s), 2904 (m), 2978 (m), 2827 (w), 1680 (s), 1461 (m), 888 (s), 837 (s); ^1H NMR (300 MHz, $CDCl_3$), δ ppm 6.59 (dd, J = 2.4 Hz, J = 10.2 Hz, 1H), 5.91 (ddd, J = 1.1 Hz, J = 1.1. Hz, J = 9.1 Hz, 1H), 4.20 (dd, J = 2.2 Hz, J = 2.2 Hz, 1H), 2.33 (dd, J_{AX} = 1.1 Hz, J_{AB} = 16.2 Hz, 1H), 2.21 (dd, J_{BX} = 0.5 Hz, J_{BA} = 16.2 Hz, 1H), 1.01 (s, 3H), 0.91 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 199.6 (C_4), 152.4 (CH), 128.8 (CH), 75.0 (CH), 50.7 (CH_2), 40.3 (C_4), 28.1 (CH_3), 20.5 (CH_3), 0.5 (CH_3) x 3; HRMS (EI), m/z (M^+) calculated for $C_{11}H_{20}O_2Si$ 212.1283, observed degradation, no M^+ detected.



3,3-Dimethyl-5-(1-methyl-propenyl)-4-trimethylsilanyloxy-cyclohexanone (3.8)

The reaction was preformed under argon. Et_2O was degassed with argon for at least 0.5 h.

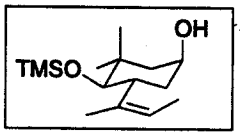
Procedure for a scale up: To a –78 °C solution of 2-*cis*-bromobutene (2.7 mL, 0.03 mol) in 60 mL of Et_2O was added a solution of *t*-BuLi (31 mL, 1.64 M in pentane, 50.84 mmol) over 10 min under argon. The resulting solution was stirred for 2 h at –78 °C. A separate flame-dried flask was charged with copper (I) cyanide (1.209 g, 13.49 mmol) and dried with a heat-gun under vacuum for approximately 40 sec. The flask was then filled with argon (**Caution: copper cyanide is a fine powder, letting argon in the evacuated flask should be done slowly and with a lot of care, otherwise all the powder ends up on the septum and the**

flask joint). Then 60 mL of Et_2O was added to the flask with the copper salt and the resulting suspension was cooled to –78 °C. A solution of vinyl lithium at –78 °C was transferred by cannula into the copper cyanide and the mixture was stirred for 10 min at –78 °C. The dry-ice bath was removed and the reaction mixture was stirred for additional 10 min, during which time it became slightly yellow. Solution was then cooled to –78 °C and a solution of ketone **3.7** (1.500 g, 6.70 mmol) in 5 mL of Et_2O was transferred by cannula into the flask under argon. The mixture was stirred for additional 30 min at –78 °C and then quenched with a solution of NH_4OH/NaCl (prepared by mixing an aqueous solution of NaOH with a saturated aqueous solution of NH_4Cl until pH 8-9) at –78 °C. The bath was then removed and the mixture was left stirring for 1 h. The product was extracted with EtOAc 3 x 200 mL. The combined organic fractions were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (20% EtOAc in hexanes) afforded product **3.8** (1.760 g, 98%) as a yellow oil.

The yields varied from 80 to 98 % depending on the scale of the reaction.

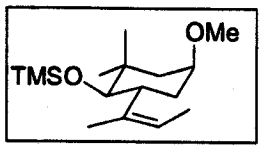
In order to perform this reaction on a small scale for each step of cuprate formation the time is reduced to 2-3 min of stirring. Formation of vinyl lithium species takes around 2 h at –78 °C. IR (neat, cm^{-1}) 2955 (s), 2872 (m), 1725 (s), 1474 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.34-5.32 (m, 1H), 3.70 (d, J = 10.3 Hz, 1H), 3.10 (ddd, J = 4.6 Hz, J = 10.3 Hz, J = 13.5 Hz, 1H), 2.41-2.28 (m, 2H), 2.12-2.06 (m, 2H), 1.65—1.64 (m, 3H), 1.54 (dq, J = 1.4 Hz, J = 6.8 Hz, 3H), 1.00 (s, 3H), 0.88 (s, 3H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 210.7 (C_4), 133.5 (C_4), 124.4 (CH), 78.3 (CH), 53.5 (CH_2), 43.8 (CH_2), 41.5 (CH), 40.0

(C_4), 30.2 (CH_3), 19.5 (CH_3), 18.8 (CH_3), 13.1 (CH_3), 0.83 (CH_3) x 3; HRMS (EI), m/z (M^+) calculated for $C_{15}H_{28}O_2Si$ 268.1859, found 268.1862.



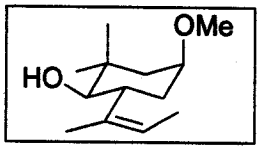
3,3-Dimethyl-5-(1-methyl-propenyl)-4-trimethylsilanyloxy-cyclohexanol (3.9)

To a solution of ketone **3.8** (854 mg, 3.18 mmol) in 30 mL of THF was added L-selectride (6.4 mL, 1.0 M in THF, 6.36 mmol) at –78 °C. The mixture was stirred for 1.5 h at –78 °C and then quenched with a saturated aqueous solution of NH_4Cl. The dry-ice bath was removed and the mixture was left stirring for 2 h at rt. The aqueous phase was extracted with EtOAc 4 x 50 mL. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc in hexanes) on silica gel afforded alcohol **3.9** (515 mg, 60%) as a white solid. IR (neat, cm^{-1}) 3377 (bs), 2964 (s), 2919 (s), 2868 (m), 1438 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.32-5.25 (m, 1H), 4.07 (bs, 1H), 3.27 (d, J = 10.4 Hz, 1H), 3.14 (ddd, J = 4.5 Hz, J = 10.8 Hz, J = 10.8 Hz, 1H), 1.69-1.52 (m, 9H), 1.38 (dd, J = 3.4 Hz, J = 14.7 Hz, 1H), 1.12 (s, 3H), 0.88 (s, 3H), 0.1 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 135.7 (C_4), 123.0 (CH), 80.4 (CH), 67.5 (CH), 45.5 (CH_2), 37.3 (CH_2), 36.8 (CH), 35.4 (CH), 31.9 (CH_3), 22.4 (CH_3), 19.8 (CH_3), 13.6 (CH_3), 1.2 (CH_3) x 3; HRMS (EI), m/z (M+) calculated for $C_{15}H_{30}O_2Si$ 270.2015, found 270.2020; mp= 66.6-67.2 °C.



[4-Methoxy-2,2-dimethyl-6-(1-methyl-propenyl)-cyclohexyloxy]-trimethyl-silane (3.10a)

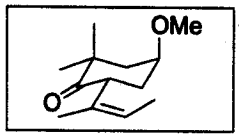
Potassium hydride (190 mg, 35 wt% in mineral oil, 3.33 mmol) was first purified from oil by washing with dry hexanes three times and drying under vacuum. To its suspension in 10 mL of THF was transferred by cannula a solution of alcohol **3.9** (300 mg, 1.11 mmol) in 2 mL of THF at rt, followed by addition of MeI (0.11 mL, 1.67 mmol) freshly distilled from CaH_2. The reaction was completed after 15 min. It was then quenched with a saturated aqueous solution of NH_4Cl, followed by extraction with EtOAc 3 x 15 mL. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was used in the next step without further purification.



4-Methoxy-2,2-dimethyl-6-(1-methyl-propenyl)-cyclohexanol (3.10)

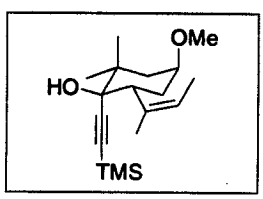
To a solution of crude **3.10a** (235 mg, 1.11 mmol) in 20 mL of THF was added TBAF (2.2 mL, 1.0 M in THF, 2.22 mmol) at rt. The reaction was completed after 1.5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (10% EtOAc in hexanes) on silica gel to afford **3.10** (199 mg, 85% yield over 2 steps) as a clear oil. IR (neat, cm^{-1}) 3487 (bm), 2967 (s), 2909 (s), 2864 (s), 2829 (m), 1461 (m), 1367 (m), 1095 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.31-5.45 (m, 1H), 3.47-3.43 (m, 1H), 3.27 (s, 3H), 3.18 (d, J = 10.7 Hz, 1H), 3.03 (ddd, J = 3.3 Hz, J = 10.7 Hz, J = 12.2 Hz, 1H), 1.86 (ddd, J = 2.7 Hz, J = 2.7 Hz, J = 14.8 Hz, 1H), 1.74 (ddd, J = 3.0 Hz, J = 6.1 Hz, J = 14.1 Hz, 1H), 1.63-1.62 (m, 6H), 1.56- 1.46 (m, 2H), 1.21 (dd, J = 3.4 Hz, J = 14.8 Hz, 1H), 1.09 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 135.6 (C_4), 124.4

(CH), 78.0 (CH), 76.2 (CH), 56.2 (CH), 41.3 (CH_2), 35.8 (CH_3), 35.8 (C_4), 33.8 (CH_2), 30.9 (CH_3), 20.6 (CH_3), 19.0 (CH_3), 13.5 (CH_3); HRMS (EI), m/z (M+) calculated for $C_{13}H_{24}O_2$ 212.1776, found 212.1774.



4-Methoxy-2,2-dimethyl-6-(1-methyl-propenyl)-cyclohexanone (3.11)

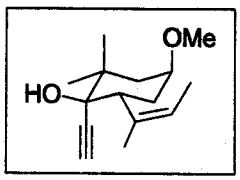
To a solution of alcohol **3.10** (0.80 mmol, 169 mg) in 8 mL of CH_2Cl_2 was added 4Å molecular sieves (400 mg, 500 mg per 1 mmol), NMO (140 mg, 1.20 mmol) and TPAP (14 mg, 0.04 mmol). The resulting black mixture was stirred for 3 h at rt, then it was filtered through a short pad of silica gel. The silica gel pad was rinsed with 100 mL of 10 % MeOH in EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (10 % EtOAc in hexanes) on silica gel to yield product **3.11** (148 mg, 88%) as a clear oil. IR (neat, cm^{-1}) 2961 (m), 2934 (m), 2876 (m), 2823 (w), 1709 (s), 1466 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.45 (m, 1H), 4.07 (dd, J = 5.2 Hz, J = 13.6 Hz, 1H), 3.67-3.64 (m, 1H), 3.38 (s, 3H), 2.17-2.07 (m, 2H), 2.02-1.92 (m, 1H), 1.70-1.63 (m, 4H), 1.49 (dq, J = 1.5 Hz, J = 6.8 Hz, 3H), 1.23 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 215.0 (C_4), 133.4 (C_4), 122.7 (CH), 75.3 (CH), 56.4 (CH), 45.5 (C_4), 43.2 (CH_2), 42.4 (CH_3), 35.4 (CH_3), 28.6 (CH_3), 26.7 (CH_3), 20.8 (CH_3), 13.5 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{13}H_{22}O_2$ 210.1620, found 210.1611.



4-Methoxy-2,2-dimethyl-6-(1-methyl-propenyl)-1-trimethylsilanylethynyl-cyclohexanol (3.12a)

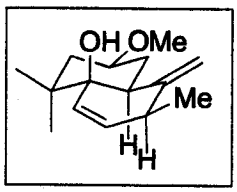
To a solution of trimethylsilyl acetylene (0.40 mL, 2.82 mmol) in 7

mL of THF at –78 °C was added *n*-BuLi (1.04 mL, 2.0 M in pentane, 2.11 mmol). After stirring for 20 min at –78 °C a solution of ketone **3.11** (148 mg, 0.70 mmol) in 1 mL of THF was transferred by cannula into the flask. The reaction mixture was stirred for additional 30 min and quenched with a saturated aqueous solution of NH_4Cl at –78 °C, warmed to rt and extracted with Et_2O 3 x 10 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude oil was used in the next step without further purification.



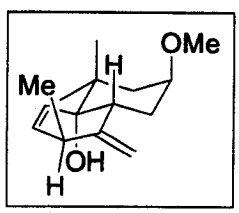
1-Ethynyl-4-methoxy-2,2-dimethyl-6-(1-methyl-propenyl)-cyclohexanol (3.12)

To a solution of crude **3.12a** (165 mg, 0.70 mmol) in 7 mL of THF was added TBAF (1.1 mL, 1.0 M in THF, 1.1 mmol). The mixture was stirred for 15 min, then concentrated under reduced pressure and purified by flash chromatography on silica gel (15% EtOAc in hexanes) to afford product **3.12** (144 mg, 87% over 2 steps) as a white solid. IR (cm^{-1}, neat) 3547 (bm), 3304 (m), 2973 (s), 2926 (s), 2824 (m), 2361 (w), 1734 (w), 1457 (m), 1092 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.60-5.57 (m, 1H), 3.51-3.49 (m, 1H), 3.39 (dd, J = 2.9 Hz, J = 13.1 Hz, 1H), 3.27 (s, 3H), 2.45 (s, 1H), 2.35 (s, 1H), 2.06 (ddd, J = 3.3 Hz, J = 14.1 Hz, J = 14.1 Hz, 1H), 1.86-1.74 (m, 5H), 1.65-1.57 (m, 4H), 1.24 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 134.8 (C_4), 126.0 (CH), 86.4 (C_4), 76.2 (C_4), 76.1 (CH), 75.5 (C_4), 56.2 (CH), 39.7 (CH_2), 39.5 (C_4), 37.3 (CH_3), 32.7 (CH_2), 27.1 (CH_3), 22.1 (CH_3), 21.5 (CH_3), 14.2 (CH_3); HRMS (EI), m/z (M^+– CH_3·) calculated for $C_{14}H_{21}O_2$ 221.1541, found 221.1540; mp = 59.6-62.6 °C.



2-Methoxy-4,4,7-trimethyl-8-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (3.16)

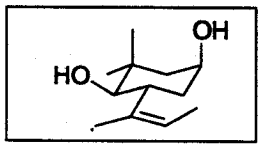
To a solution of alcohol **3.12** (13 mg, 0.06 mmol) in toluene (12 mL) in a microwave cell was added DBU (0.1 mL, 0.67 mmol). The solution was degassed using argon for 30 min and heated in the microwave oven for 2 h at 230 °C. Reaction was monitored by CG. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford two products **3.16** (3.5 mg, 27%) as a white solid and **3.17** (1.3 mg, 10%) as a clear oil. IR (neat, cm^{-1}) 3430 (bm), 2961 (s), 2887 (m), 1463 (m), 1079 (s); ^1H NMR (300 MHz, C_6D_6), δ_{ppm} 5.77 (dd, J = 3.0 Hz, J = 9.9 Hz, 1H), 5.36 (dd, J = 2.0 Hz, J = 9.8 Hz, 1H), 4.72-4.70 (m, 2H), 3.36-3.23 (m, 1H), 3.23 (s, 3H), 2.54-2.52 (m, 1H), 2.34-2.29 (m, 1H), 2.05 (dd, J = 12.2 Hz, J = 12.2 Hz, 1H), 1.91-1.84 (m, 2H), 1.67-1.62 (m, 1H), 1.17 (s, 3H), 1.0 (s, 1H), 0.90 (d, J = 7.1 Hz, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6), δ_{ppm} 151.3 (C_4), 135.6 (CH), 130.5 (CH), 106.6 (CH_2), 76.3 (CH), 74.3 (C_4), 55.6 (CH_3), 43.6 (CH), 41.6 (CH_2), 38.1 (CH_2), 38.1 (C_4), 30.0 (CH_2), 25.0 (CH_3), 24.3 (CH_3), 17.4 (CH_3); HRMS (EI), m/z (M+) calculated for $C_{15}H_{24}O_2$ 236.1776, found 236.1772.



2-Methoxy-4,4,7-trimethyl-8-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (3.17)

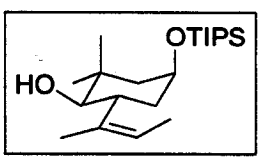
IR (neat, cm^{-1}) 3485 (bm), 2921 (s), 2872(m), 1455 (m), 1087 (s); ^1H NMR (500 MHz, C_6D_6), δ_{ppm} 5.95 (d, J = 10.2 Hz, 1H), 5.62 (dd, J = 4.3 Hz, J = 9.9 Hz, 1H), 4.94 (bs, 1H), 4.81 (dd, J = 1.5 Hz, J = 1.6 Hz, 1H), 3.53 (dddd, J= 2.1 Hz, J = 2.1 Hz, J = 4.0 Hz, J = 4 Hz, 1H), 3.29-3.26 (m, 1H), 3.19 (s, 3H), 2.75-2.70 (m, 1H), 2.01 (ddd, J

= 3.7 Hz, J = 13.4 Hz, J = 13.4 Hz, 1H), 1.95-1.87 (m, 2H), 1.70 (ddd, J = 2.3 Hz, J = 2.3 Hz, J = 14.4 Hz, 1H), 1.38 (s, 3H), 1.28 (s, 3H), 1.17 (s, 1H), 1.12 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6), δ_{ppm} 152.3 (C_4), 134.5 (CH), 130.2 (CH), 108.7 (CH_2), 76.6 (CH), 74.9 (C_4), 55.7 (CH_3), 40.2 (CH), 37.6 (CH_2), 37.0 (C_4), 34.4 (CH), 27.8 (CH_2), 25.6 (CH_3), 25.3 (CH_3), 21.1 (CH_3); HRMS (EI), m/z (M+) calculated for $C_{15}H_{24}O_2$ 236.1776, found 236.1766.



2,2-Dimethyl-6-(1-methyl-propenyl)-cyclohexane-1,4-diol (3.19)

To a solution of **3.9** (309 mg, 1.14 mmol) in 15 mL of THF was added TBAF (1.26 mL, 1.0 M in THF, 1.26 mmol). The mixture was stirred overnight and concentrated under reduced pressure. Purification by flash chromatography on silica gel (60% EtOAc in hexanes) afforded diol 3.19 (226 mg, 100%) as a white solid. IR (neat, cm^{-1}) 3432 (bs), 2921 (s), 2872 (s), 1453 (m), 1059 (s), 1024 (s); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.51-5.47 (m, 1H), 4.12-4.10 (m, 1H), 3.22-3.11 (m, 2H), 1.70-1.40 (m, 11H), 1.44 (s, 1H), 1.17 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 135.4 (C_4), 124.6 (CH), 78.0 (CH), 67.5 (CH), 45.7 (CH_2), 36.8 (CH_2), 35.6 (C_4), 35.4 (CH), 30.9 (CH_3), 21.6 (CH_3), 19.1 (CH_3), 13.5 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{12}H_{22}O_2$ 198.1620, found 198.1584.

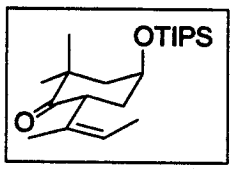


2,2-Dimethyl-6-(1-methyl-propenyl)-4-triisopropylsilanyloxy-cyclohexanol (3.20)[9]

To a solution of diol **3.19** (128 mg, 0.65 mmol) in CH_2Cl_2 (8 mL) at –

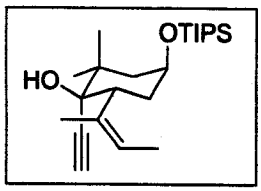
[9] Nathalie Goulet (summer student) assisted in preparation of this compound

78 °C was added 2,6-lutidine (0.60 mL, 5.18 mmol) followed by addition of TIPSOTf (0.69 mL, 2.56 mmol). The solution was stirred for 1 h and quenched with a saturated aqueous solution of $NaHCO_3$ at –78 °C. The mixture was extracted with CH_2Cl_2 3 x 10 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pure hexanes, then 15% EtOAc in hexanes) afforded product **3.20** contaminated with TIPSOH. Alcohol **3.20** was oxidized to ketone **3.21** without further purification.



2,2-Dimethyl-6-(1-methyl-propenyl)-4-triisopropylsilanyloxy-cyclohexanone (3.21)[9]

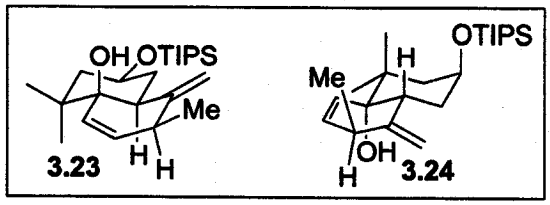
To a solution of alcohol **3.20** (206 mg, 0.58 mmol) in CH_2Cl_2 (1 mL) was added 4Å molecular sieves (291 mg, 500 mg per 1 mmol), NMO (103 mg, 0.87 mmol) and TPAP (45 mg, 2% mol). The resulting black mixture was stirred for 14 h, then it was filtered through a short pad of silica gel. The silica gel was rinsed with 100 mL of 10 % CH_3OH in EtOAc solution. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc in hexanes) on silica gel to yield ketone **3.21** (134 mg, 65%) as a white solid. IR (neat, cm^{-1}) 2927 (s), 2867 (s), 1711 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.44-5.37 (m, 1H), 4.36-4.82 (m, 2H), 2.77 (m, 3H), 1.74 (dd, J = 3.4 Hz, J = 14.2 Hz, 1H), 1.65-1.63 (m, 3H), 1.50 (dq, J = 1.5 Hz, J = 6.8 Hz, 3H), 1.41 (s, 3H), 1.10-1.05 (m, 21H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 215.4 (C_4), 133.7 (C_4), 122.4 (CH), 67.3 (CH), 47.8 (CH_2), 45.7 (C_4), 41.9 (CH), 40.1 (CH_2), 29.5 (CH_3), 26.9 (CH_3), 20.8 (CH_3), 18.5 (CH_3) x 6, 13.4 (CH_3), 12.6 (CH) x 3; HRMS (EI), m/z (M^+) calculated for $C_{21}H_{40}O_2Si$ 352.2798, found 352.2789.



1-Ethynyl-2,2-dimethyl-6-(1-methyl-propenyl)-4-triisopropylsilanyloxy-cyclohexanol (3.22)[9]

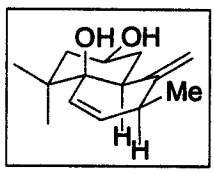
1. To a solution of trimethylsilyl acetylene (0.18 mL, 1.24 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (0.36 mL, 2.6 M in pentane, 0.93 mmol). After stirring for 20 min at –78 °C a solution of ketone **3.21** (110 mg, 0.31 mmol) in THF (1 mL) was transferred by cannula and the reaction mixture was stirred for additional 30 min. It was then quenched with a saturated aqueous solution of NH_4Cl at –78 °C, warmed up to rt and extracted with Et_2O 3 x 10 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude oil was used in the next step without further purification.

2. To a solution of unpurified product from part **1** (139 mg, 0.31 mmol) in THF (5 mL) was added a solution of TBAF (0.34 mL, 1.0 M in THF, 0.34 mmol). The mixture was stirred for 15 min, then concentrated under reduced pressure and purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford **3.22** (69 mg, 58% over 2 steps) as a white solid. IR (neat, cm^{-1}) 3563 (w), 3314 (m), 2947 (s), 2869 (s), 1466 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.59 (q, J = 6.5 Hz, 1H), 4.18-4.17 (m, 1H), 3.58 (dd, J = 2.6 Hz, J = 12.9 Hz, 1H), 2.44 (s, 1H), 2.33 (s, 1H), 2.15 (ddd, J = 2.9 Hz, J = 13.4 Hz, J = 13.4 Hz, 1H), 1.85 (s, 3H), 1.74-1.58 (m, 6H), 1.32 (s, 3H), 1.09 (s, 3H), 1.04 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 135.1 (C_4), 126.3 (CH), 86.5 (C_4), 76.1 (C_4), 75.4 (CH), 67.8 (CH), 44.7 (CH_2), 39.6 (C_4), 37.4 (CH), 37.3 (CH_2), 27.6 (CH_3), 23.2 (CH_3), 21.4 (CH_3), 18.5 (CH_3) x 6, 13.9 (CH_3), 12.6 (CH_3) x 3; HRMS (EI), m/z (M^+) calculated for $C_{23}H_{42}O_2Si$ 378.2954, found 378.2933; mp = 58.0-59.8 °C.



4,4,7-Trimethyl-8-methylene-2-triisopropylsilanyloxy-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ols (3.23) and (3.24)

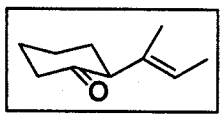
To a solution of alcohol **3.22** (30 mg, 0.08 mmol) in toluene (12 mL) in a microwave cell was added DBU (0.12 mL, 0.70 mmol). The solution was degassed using argon for 30 min and heated in the microwave oven for 2 h at 230 °C. Reaction was monitored by CG. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford **3.23** (10 mg, 33%) contaminated with non-polar impurities and a mixture of **3.23** and **3.24** (12 mg, 40%). Compound **3.23** was treated with TBAF to afford diol **3.25**, which was easily purified.



4,4,7-Trimethyl-8-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalene-2,4a-diol (3.25)

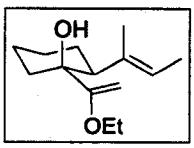
To a solution of decaline **3.24** (10 mg, 0.03 mmol) in 0.5 mL of THF was added TBAF (0.03 mL, 1.0 M in THF, 0.03 mmol). The mixture was stirred overnight and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pure hexanes to remove non-polar impurities then 50% EtOAc in hexanes) afforded diol **3.25** (3 mg, 60%) as a white solid. IR (neat, cm^{-1}) 3335 (s), 3258 (s), 2949 (s), 2921 (s), 2865 (s), 1469 (m), 1092 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.84 (dd, J = 2.9 Hz, J = 9.7 Hz, 1H), 5.45 (dd, J = 2.0 Hz, J = 9.7 Hz, 1H), 4.84 (s, 1H), 4.79 (b, 1H), 3.78-3.72 (m, 1H), 2.60-2.58 (m, 1H), 2.40-2.37 (m, 1H), 1.94 (dd, J = 12.0 Hz, J = 12.0 Hz, 1H), 1.82 (ddd, J = 12.3 Hz, J = 12.3 Hz, J = 12.3 Hz, 1H), 1.74-1.72 (m, 1H), 1.50-1.37 (m, 3H), 1.23 (s,

3H), 1.00 (d, J = 7.0 Hz, 3 H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 151.3 (C_4), 135.6 (CH), 130.4 (CH), 106.5 (CH_2), 74.0 (C_4), 67.1 (CH), 45.1 (CH), 43.7 (CH), 38.3 (C_4), 38.0 (CH_2), 33.8 (CH_2), 24.9 (CH_3), 24.0 (CH_3), 17.4 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{14}H_{22}O_2$ 222.1620, found 222.1610.



2-(1-Methyl-propenyl)-cyclohexanone (3.35)

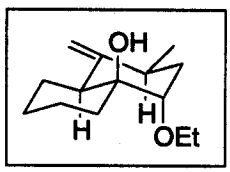
To solution of chloroalcohol **2.13** (196 mg, 1.04 mmol) in THF (10 mL) at rt was added vinylmagnesium bromide (1.16 mL, 0.9 M in THF, 1.04 mmol). The solution was refluxed for 50 min, cooled to rt and quenched with a saturated aqueous solution of NH_4Cl. The mixture was extracted with Et_2O 3 x 30 mL. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (8% EtOAc in hexanes) to afford product (128 mg, 81%) as a yellow oil. IR (cm^{-1}, neat) 2934 (m), 2862 (m), 1710 (s), 1448 (m); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.23-5.15 (m, 1H), 2.90 (dd, J = 5.3 Hz, J = 11.6 Hz, 1H), 2.41-2.20 (m, 2H), 2.05-1.56 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 212.2 (C_4), 134.3 (C_4), 121.8 (CH), 60.6 (CH), 42.6 (CH_2), 32.6 (CH_2), 27.9 (CH_2), 25.4 (CH_2), 15.0 (CH_3), 13.8 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{10}H_{16}O_4$ 152.1201, found 152.1189.



1-(1-Ethoxy-vinyl)-2-(1-methyl-propenyl)-cyclohexanol (3.33)

To a mixture of THF (0.1 mL) and ethyl vinyl ether (0.38 mL, 3.94 mmol) at –78 °C was added dropwise (over 5 min) a solution of *t*-BuLi (1.16 mL, 1.7 M in pentane, 1.97 mmol). The solution was stirred for 5 min at –78 °C. It was then warmed to 0 °C (a dry-ice/isopropanol bath was replaced with an ice bath), stirred for 45 min at 0 °C and re-cooled

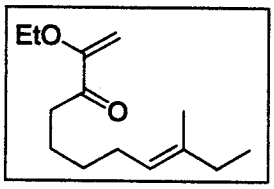
to –78 °C. Ketone **3.35** (30 mg, 0.20 mmol) was dissolved in THF (1 mL) and transferred by cannula to the solution of the lithiated compound at –78 °C. The reaction mixture was stirred for 40 min and quenched with H_2O at –78 °C. The mixture was extracted with Et_2O 3 x 5 mL. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc in hexanes) on silica gel to give product (20 mg, 45%) as a colorless oil. IR (cm^{-1}, neat) 3541(m, sharp), 2978 (m), 2931 (s), 2859 (m), 1654 (m), 1608 (m); ^1H NMR (300 MHz, C_6D_6), δ_{ppm} 5.28 (q, J = 6.4 Hz, 1H), 4.49-4.48 (m, 1H), 3.84 (s, 1H), 3.44-3.29 (m, 2H), 2.60 (dd, J = 3.4 Hz, J = 13.2 Hz, 1H), 2.08-1.77 (m, 5H), 1.72-1.65 (m, 1H), 1.65 (s, 3H), 1.59-1.44 (m, 5H), 1.37-1.17 (m, 1H), 1.05 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6), δ_{ppm} 168.7 (C_4), 139.0 (C_4), 120.0 (CH), 79.3 (CH_2), 74.2 (C_4), 62.7 (CH_2), 51.1 (CH), 37.1 (CH_2), 27.6 (CH_2), 26.7 (CH_2), 21.8 (CH_2), 17.9 (CH_3), 14.6 (CH_3), 13.6 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{14}H_{24}O_2$ 224.1776, found 224.1760.



4-Ethoxy-2-methyl-1-methylene-octahydro-naphthalen-4a-ol (3.34)

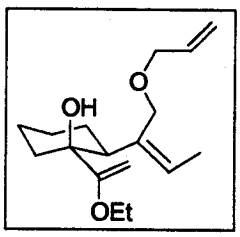
To a solution of alcohol **3.33** (27 mg, 0.12 mmol) in toluene (10 mL) in a microwave cell was added DBU (0.18 mL, 1.20 mmol). The solution was degassed using argon for 30 min and heated in the microwave oven for 2 h at 223 °C. Reaction was monitored by 300 MHz ^1H NMR. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford **3.34** (4.8 mg, 18%) as a yellowish oil and an inseparable 3:1 mixture of the starting material and retro-ene product **3.37** (20 mg). IR (cm^{-1}, neat) 3564 (bm), 2929 (s), 2864 (s), 1639 (m), 1448 (m), 1094 (s); ^1H NMR (300 MHz, C_6D_6), δ_{ppm} 4.80 (s, 1H), 4.70

(s, 1H), 3.40-3.35 (m, 1H), 3.15-3.09 (m, 1H), 3.00 (dd, J = 2.5 Hz, J = 2.5 Hz, 1H), 2.52-2.43 (m, 1H), 2.09-2.04 (m, 1H), 1.81-1.16 (m, 11H), 1.05 (t, J = 6.9 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6), δ_{ppm} 154.6 (C_4), 106.0 (CH_2), 81.8 (CH), 74.4 (CH), 65.1 (CH_2), 44.8 (CH), 36.2 (CH_2), 33.8 (CH_2), 32.5 (CH), 26.1 (CH_2), 24.4 (CH_2), 21.7 (CH_2), 18.3 (CH_3), 15.9 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{14}H_{24}O_2$ 224.1776, found 224.1758.



2-Ethoxy-9-methyl-undeca-1,8-dien-3-one (3.37)

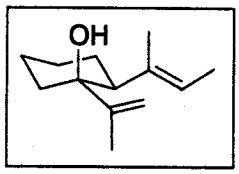
^{1}H NMR (500 MHz, C_6D_6), δ_{ppm} 5.45 (d, J = 2.0 Hz, 1H), 5.24-5.20 (m, 1H), 4.09 (d, J = 2.0 Hz, 1H), 3.34 (q, J = 7.0 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 2.11-2.04 (m, 4H), 1.74 (s, 3H), 1.45-1.40 (m, 4H), 1.08 (t, J = 7.0 Hz, 3H), 1.02 (t, J = 7.6 Hz, 3H).



2-(1-Allyloxymethyl-propenyl)-1-(1-ethoxy-vinyl)-cyclohexanol (3.38)

To a mixture of ethyl vinyl ether (0.21 mL, 2.20 mmol) in THF (0.05 mL) at –78 °C was added dropwise (over 5 min) a solution of *t*-BuLi (0.65 mL, 1.7 M in pentane, 1.10 mmol). The solution was stirred for 5 min at –78 °C. The mixture was warmed to 0 °C (a dry-ice/isopropanol bath was replaced with an ice bath), stirred for 45 min at 0 °C and re-cooled to –78 °C. Ketone **3.33** (23 mg, 0.11 mmol) was dissolved in THF (1 mL) and transferred by cannula to the solution of the lithiated compound at –78 °C. The reaction mixture was stirred for 40 min and quenched with H_2O at –78 °C. The mixture was extracted with Et_2O 3 x 5 mL. The combined organic layers were

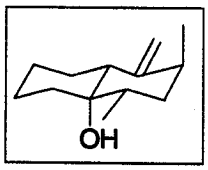
dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc in hexanes) on silica gel to give desired product **3.38** (10 mg, 32%) as a colorless oil. IR (cm^{-1}, neat) 3401 (m), 2981 (m), 2927 (s), 2857 (m), 1652 (m), 1612 (m), 1447 (m), 1067 (s); ^1H NMR (300 MHz, C_6D_6), δ_{ppm} 5.84-5.72 (m, 1H), 5.62 (q, J = 7.0 Hz, 1H), 5.23-5.18 (m, 1H), 5.03-4.99 (m, 1H), 4.75-4.75 (m, 1H), 4.54 (s, 1H), 3.97-3.94 (m, 2H), 3.82 (dddd, J_{AX} = 1.6 Hz, J_{AY} = 1.6 Hz, J_{AM} = 5.1 Hz, J_{AB} = 12.9 Hz, 1H), 3.72 (dd, J_{AB} = 11.2 Hz, 1H), 3.64 (dddd, J_{AX} = 1.4 Hz, J_{AY} = 1.14 Hz, J_{AM} = 5.5 Hz, J_{AB} = 12.8 Hz, 1H), 3.54-3.34 (m, 2H), 2.96 (dd, J = 3.0 Hz, 12.9 Hz, 1H), 2.16-1.98 (m, 4H), 1.81-1.77 (m, 1H), 1.57-1.27 (m, 6H), 1.10 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6), δ_{ppm} 169.3 (C_4), 136.9 (C_4), 134.7 (CH), 127.8 (CH), 116.9 (CH_2), 79.9 (CH_2), 75.0 (C_4), 71.0 (CH_2), 64.4 (CH_2), 62.7 (CH_2), 57.2 (CH), 37.4 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 22.0 (CH_2), 14.8 (CH_3), 13.7 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{17}H_{28}O_3$ 280.2038, found 280.2060.



1-Isopropenyl-2-(1-methyl-propenyl)-cyclohexanol (3.39)

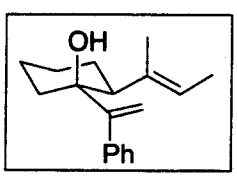
To a solution of 2-bromopropene (0.09 mL, 1.05 mmol) in THF (5 mL) at –78 °C was added dropwise a solution of *t*-BuLi (1.16 mL, 1.7 M in pentane, 1.95 mmol). The resulting mixture was stirred for 1 h at –78 °C. Then a solution of ketone **3.35** (40 mg, 0.26 mmol) in THF (0.5 mL) was transferred by cannula. The mixture was stirred for 1 h at –78 °C and quenched with H_2O. The aqueous phase was extracted with Et_2O 3 x 10 mL. The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5 % EtOAc in hexanes) afforded product **3.39** (44 mg, 86%) as a yellow oil. IR (cm^{-1}, neat)

3545 (m), 2931 (s), 2850 (s), 1441 (m); ^{1}H NMR (300 MHz, C_6D_6), δ_{ppm} 5.27-5.21 (m, 1H), 5.10-5.09 (m, 1H), 4.80-4.79 (m, 1H), 2.12 (dd, J = 3.3 Hz, J = 12.7 Hz, 1H), 1.92-1.65 (m, 8H), 1.58-1.33 (m, 9H), 0.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 151.8 (C_4), 139.0 (C_4), 120.1 (CH), 109.5 (CH_2), 76.2 (C_4), 52.3 (CH), 37.7 (CH_2), 27.9 (CH_2), 26.8 (CH_2), 21.8 (CH_2), 20.1 (CH_3), 16.7 (CH_3), 13.5 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{13}H_{22}O$ 194.1671, found 194.1659.



2-Methyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (3.41)

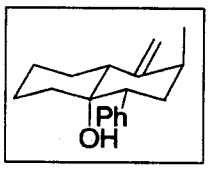
To a solution of alcohol **3.39** (44 mg, 0.23 mmol) in toluene (12 mL) in a microwave cell was added Et_3N (0.16 mL, 1.15 mmol). The resulting solution was degassed using argon for 30 min and heated in the microwave oven for 2 h at 220 °C. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford **3.41** (22 mg, 50%) as a clear oil and an inseparable mixture of **3.41** and **3.42** (12 mg, 27%). IR (cm^{-1}, neat) 3571 (m), 2931 (s), 2853 (s), 1460 (m); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 4.89-4.89 (m, 1H), 4.58 (dd, J = 1.8 Hz, J = 1.8 Hz, 1H), 2.59-2.51 (m, 1H), 2.20-2.14 (m, 1H), 1.98-1.91 (m, 1H), 1.80-1.65 (m, 2H), 1.60-1.41 (m, 5H), 1.35-1.06 (m, 7H), 0.81(d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 154.4 (C_4), 108.9 (CH_2), 73.8 (C_4), 44.6 (CH), 39.1 (CH), 38.7 (CH_2), 36.3 (CH), 35.6 (CH_2), 26.2 (CH_2), 24.5 (CH_2), 21.9 (CH_2), 19.9 (CH_3), 14.8 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{13}H_{22}O$ 194.1671, found 194.1676.



2-(1-Methyl-propenyl)-1-(1-phenyl-vinyl)-cyclohexanol (3.40)

To a solution of α-bromostyrene (0.34 mL, 2.63 mmol) in Et_2O (10 mL)

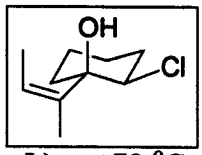
at –90 °C was added dropwise a solution of *t*-BuLi (2.9 mL, 1.7 M in pentane, 4.93 mmol). The resulting solution was stirred for 1 h 20 min at –90 °C (a reaction flask was covered with aluminum foil to protect it from light). Then a solution of ketone **3.35** (100 mg, 0.67 mmol) in Et_2O (1 mL) was transferred by cannula and the mixture was warmed to –60 °C. The solution was cooled to –90 °C and quenched with H_2O. The aqueous phase was extracted with Et_2O 3 x 20 mL. The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pure hexanes then 5 % EtOAc in hexanes) afforded product **3.40** (138 mg, 82%) as a yellow oil. IR (cm^{-1}, neat) 3564 (bm), 3080 (m), 3054 (m), 3021 (m), 2932 (s), 2858 (m), 1949 (w), 1877 (w), 1816 (w), 1598 (w), 1573 (w), 1492 (m), 1443 (m), 980 (m), 775 (m), 702 (s); ^1H NMR (300 MHz, C_6D_6), δ_{ppm} 7.30-7.27 (m, 2H), 7.18-7.06 (m, 3H), 5.39-5.33 (m, 2H), 5.02 (d, J = 1.7 Hz, 1H), 2.25 (dd, J = 3.4 Hz, J = 12.6 Hz, 1H), 1.96 (ddd, J = 3.5 Hz, J = 13.0 Hz, J = 16.5 Hz, 1H), 1.73-1.72 (m, 3H), 1.70-1.31 (m, 10H), 1.22 (s, 1H); ^{13}C NMR (75 MHz, C_6D_6), δ_{ppm} 157.8 (C_4), 142.5 (C_4), 138.7 (C_4), 129.2 (CH) x 2, 127.8 (CH) x 2, 127.1 (CH), 121.5 (CH), 114.1 (CH_2), 76.8 (C_4), 53.8 (CH), 40.9 (CH_2), 28.5 (CH_2), 26.5 (CH_2), 21.9 (CH_2), 16.4 (CH_3), 13.5 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{18}H_{24}O$ 256.1827, found 256.1827.



2-Methyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (3.43)

To a solution of alcohol **3.40** (70 mg, 0.27 mmol) in toluene (12 mL) in a microwave cell was added Et_3N (0.19 mL, 1.35 mmol). The solution was degassed using argon for 30 min and heated in the microwave oven for 1 h at 210 °C. The solvent was removed under reduced pressure and the residue was purified by flash

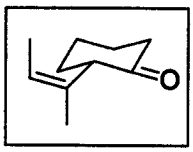
chromatography on silica gel (5% EtOAc in hexanes) to afford **3.43** (65 mg, 93%) as a clear oil. IR (cm^{-1}, neat) 3555 (m), 3083 (m), 3060 (m), 3025 (m), 2931 (s), 2894 (m), 2858 (m), 1937 (w), 1861 (w), 1801 (w), 1641 (m), 1494 (m), 1452 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.30-7.15 (m, 5H), 4.89-4.87 (m, 1H), 4.61 (dd, J = 1.9 Hz, J = 1.9 Hz, 1H), 2.67 (dd, J = 3.7 Hz, J = 13.6 Hz, 1H), 2.53-2.44 (m, 1H), 2.24-2.14 (m, 2H), 1.67-1.36 (m, 6H), 1.29-1.11 (m, 3H), 1.08 (d, J = 7.2 Hz, 3H), 1.03-0.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 153.9 (C_4), 142.6 (C_4), 128.3 (CH) x 2, 126.8 (CH) x 2, 126.8 (CH), 109.3 (CH_2), 73.9 (C_4), 49.3 (CH), 45.0 (CH), 39.1 (CH), 37.2 (CH_2), 36.9 (CH_2), 26.2 (CH_2), 24.5 (CH_2), 21.7 (CH_2), 19.8 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{18}H_{24}O$ 256.1827, found 256.1846.



2-Chloro-1-(1-methyl-propenyl)-cyclohexanol (3.44)

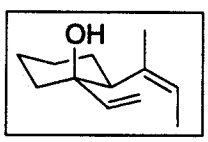
To a solution of *cis* -2 bromo-2-butene (0.46 mL, 4.55 mmol) in Et_2O (20 mL) at –78 °C was added *t*-BuLi (4.70 mL, 1.8 M in pentane, 8.48 mmol). The mixture was stirred for 2 h at –78 °C. A solution of 1-chloro-cyclohexan-2-one (400 mg, 3.03 mmol) in Et_2O (2 mL) was then transferred by cannula to the lithiated compound at –78 °C. The reaction was completed in 20 min after addition of the ketone. The mixture was quenched with H_2O and extracted with Et_2O 3 x 20 mL. The combined organic extracts were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (5% EtOAc in hexanes) gave product (330 mg, 58%) as a colorless oil. IR (cm^{-1}, neat) 3576 (s), 2969 (s), 2941 (s), 2864 (s), 2736 (w), 1446 (s), 1069 (s), 987 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.37-5.30 (m, 1H), 4.19 (dd, J = 4.9 Hz, J = 11.6 Hz, 1H), 2.19-2.17 (m, 1H), 2.07-1.89 (m, 3H), 1.82-1.79 (m, 3H), 1.71-1.39 (m, 7H), 1.32-1.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 139.7 (C_4), 123.9 (CH), 77.1 (C_4), 67.9 (CH), 35.7

(CH_2), 32.3 (CH_2), 26.5 (CH_2), 22.7 (CH_3), 20.6 (CH_2), 15.3 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{10}H_{17}OCl$ 188.0968, found 188.0953.



2-(1-Methyl-propenyl)-cyclohexanone (3.45)

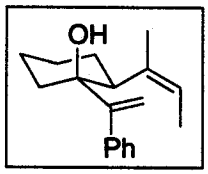
To solution of chloroalcohol **3.44** (50 mg, 0.27 mmol) in THF (3 mL) at rt was added vinylmagnesium bromide (0.3 mL, 0.9 M in THF, 0.27 mmol). The solution was refluxed for 1 h, cooled to rt and quenched with a saturated aqueous solution of NH_4Cl. The mixture was extracted with Et_2O 3 x 10 mL. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc in hexanes) on silica gel to afford ketone **3.45** (25 mg, 62%) as a yellow oil. **Note: the compound is volatile.** IR (cm^{-1}, neat) 2935 (s), 2863 (m), 1710 (s), 1449 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.44-5.37 (m, 1H), 3.34 (dd, J = 5.6 Hz, J = 11.6 Hz, 1H), 2.46-2.40 (m, 1H), 2.35-2.21 (m, 1H), 2.11-2.02 (m, 1H), 1.98-1.64 (m, 8H), 1.49-1.46 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 210.8 (C_4), 133.9 (C_4), 122.5 (CH), 52.1 (CH), 42.6 (CH_2), 32.0 (CH_2), 27.4 (CH_2), 25.6 (CH_2), 21.1 (CH_3), 13.6 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{10}H_{16}O$ 152.1201, found 152.1194.



2-(1-Methyl-propenyl)-1-vinyl-cyclohexanol (3.46)

To a solution of ketone **3.45** (50 mg, 0.33 mmol) in 5 mL of THF was added vinylmagnesium bromide (1.50 mL, 0.9 M in THF, 1.35 mmol) at 0 °C. The solution was stirred for 3 h at rt and then quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O 3 x 5 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography

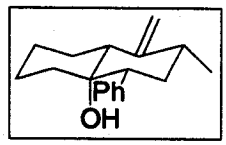
on silica gel (8% EtOAc in hexanes) afforded product **3.46** (28.6 mg, 48%, dr=20:1) as a clear oil. **Note: due to a high volatility of the compound the solvent could not be removed completely.** IR (cm^{-1}, neat) 3489 (bm), 2932 (s), 2859 (s), 1448 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.88 (dd, J = 10.8 Hz, J = 17.3 Hz, 1H), 5.26-5.12 (m, 2H), 4.95 (dd, J = 1.3 Hz, J = 10.8 Hz, 1H), 2.47 (dd, J = 3.2 Hz, 12.7 Hz, 1H), 1.93-1.45 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 145.9 (CH), 138.0 (C_4), 120.9 (CH), 111.0 (CH_2), 75.4 (C_4), 46.1 (CH), 39.7 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 22.3 (CH_2), 21.8 (CH_3), 13.9 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{12}H_{20}O$ 180.1514, found 180.1533.



2-(1-Methyl-propenyl)-1-(1-phenyl-vinyl)-cyclohexanol (3.47)

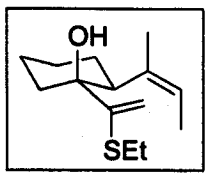
To a solution of α-bromostyrene (0.17 mL, 1.32 mmol) in Et_2O (5 mL) at –90 °C was added dropwise a solution of *t*-BuLi (1.45 mL, 1.7 M in pentane, 2.47 mmol). The resulting mixture was stirred for 1 h 20 min at –90 °C (a reaction flask was covered with aluminum foil to protect it from light). Then a solution of ketone **3.45** (50 mg, 0.33 mmol) in Et_2O (1 mL) was transferred by cannula and the mixture was warmed to –60 °C. The solution was re-cooled to –90 °C and quenched with H_2O. The aqueous phase was extracted with Et_2O 3 x 10 mL. The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pure hexane then 5 % EtOAc in hexanes) afforded product **3.47** (61 mg, 72%) as a yellow oil. IR (cm^{-1}, neat) 3594 (bm), 3981 (w), 3053 (w), 3029 (w), 2929 (s), 2857 (s), 1949 (w), 1892 (w), 1828 (w), 1749 (w), 1690 (w), 1625 (w), 1598 (w), 1573 (w); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.30 (m, 2H), 7.12-7.08 (m, 3H), 5.42 (d, J = 1.8 Hz, 1H), 5.25-5.18 (m, 1H), 4.98 (d, J = 1.8 Hz, 1H), 2.64 (dd, J = 3.5 Hz, J

= 12.7 Hz, 1H), 2.03-1.86 (m, 4H), 1.73-1.52 (m, 3H), 1.47-1.25 (m, 6H), 1.15-1.03 (m, 1H), 1.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 157.7 (C_4), 142.1 (C_4), 140.1 (C_4), 129.6 (CH) x 2, 127.8 (CH) x 2, 127.2 (CH), 120.7 (CH), 113.7 (CH_2), 77.0 (C_4), 44.9 (CH), 41.0 (CH_2), 27.7 (CH_2), 26.4 (CH_2), 22.7 (CH_3), 21.8 (CH_2), 13.5 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{18}H_{24}O$ 256.1827, found 256.1831.



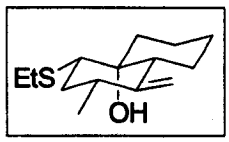
2-Methyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (3.51)

To a solution of alcohol **3.47** (25 mg, 0.08 mmol) in toluene (12 mL) in a microwave cell was added Et_3N (0.06 mL, 0.40 mmol). The solution was degassed using argon for 30 min and heated in the microwave oven for 3 h at 220 °C. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford **3.51** (16 mg, 643%) as a yellowish oil. IR (cm^{-1}, neat) 3553 (m), 3087 (m), 3060 (m), 3026 (m), 2931 (s), 2855 (s), 1945 (w), 1876 (w), 1802 (w), 1727 (w), 1643 (m), 1494 (m), 982 (m); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.25-7.11 (m, 5H), 4.84 (d, J = 1.1 Hz, 1H), 4.71 (s, 1H), 2.37 (dd, J = 4.7 Hz, J = 12.1 Hz, 1H), 1.96-1.86 (m, 1H), 1.82-1.77 (m, 1H), 1.68-1.39 (m, 7H), 1.29-1.21 (m, 1H), 1.15-1.05 (m, 2H), 1.01-0.91 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6), δ_{ppm} 153.9 (C_4), 142.8 (C_4), 128.2 (CH) x 2, 128.0 (CH) x 2, 126.6 (CH), 106.2 (CH_2), 73.3 (C_4), 55.2 (CH), 50.6 (CH), 40.7 (CH_2), 38.7 (CH), 37.1 (CH_2), 26.2 (CH_2), 24.8 (CH_2), 21.7 (CH_2), 18.3 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{18}H_{24}O$ 256.1827, found 256.1818.



1-(1-Ethylsulfanyl-vinyl)-2-(1-methyl-propenyl)-cyclohexanol (3.48)

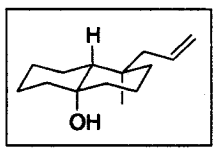
To a mixture of THF (0.17 mL) and ethylsulfanylethene (0.67 mL, 6.60 mmol) at –78 °C was added dropwise (over 5 min) a solution of *t*-BuLi (1.90 mL, 1.7 M in pentane, 3.30 mmol). The solution was stirred for 5 min at –78 °C. It was then warmed to 0 °C (a dry-ice/isopropanol bath was replaced with an ice bath), stirred for 45 min at 0 °C and re-cooled to –78 °C. Ketone **3.45** (50 mg, 0.33 mmol) was dissolved in THF (0.5 mL) and transferred by cannula to a solution of the lithiated compound at –78 °C. The reaction mixture was stirred for 40 min and quenched with H_2O at –78 °C. The mixture was extracted with Et_2O 3 x 5 mL. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc in hexanes) on silica gel pretreated with Et_3N to give product **3.48** (27 mg, 34%) as a colorless oil and a 2:1 mixture of **3.48** and the *syn*-diastereomer (6.6 mg, 8%). IR (cm^{-1}, neat) 3496 (bm), 2930 (s), 2858 (s), 1598 (m), 1448 (m); ^1H NMR (500 MHz, C_6D_6), δ_{ppm} 5.56 (s, 1H), 5.41-5.37 (m, 1H), 4.79 (s, 1H), 3.08 (dd, J = 3.4 Hz, J = 12.7 Hz, 1H), 2.55-2.44 (m, 2H), 2.17-2.04 (m, 4H), 1.82-1.67 (m, 5H), 1.57-1.40 (m, 3H), 1.39-1.31 (m, 3H), 1.14 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6), δ_{ppm} 153.7 (C_4), 138.5 (C_4), 120.9 (CH), 104.4 (CH_2), 78.0 (C_4), 45.2 (CH), 40.4 (CH_2), 27.3 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 22.3 (CH_3), 21.9 (CH_2), 13.8 (CH_3), 13.0 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{14}H_{24}OS$ 240.1548, found 240.1537.



4-Ethylsulfanyl-2-methyl-1-methylene-octahydro-naphthalen-4a-ol (3.52)

To a solution of alcohol **3.48** (13 mg, 0.05 mmol) in toluene (12 mL) in a microwave cell was added Et_3N (0.03 mL, 0.22 mmol). The solution was degassed using argon for 30 min and heated in the microwave oven for 3 h at 220 °C. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford **3.43** (11 mg, 81%) as a clear oil. IR (cm^{-1}, neat) 3524 (bm), 2931 (s), 2854 (s), 1644 (m), 1449 (m); ^1H NMR (500 MHz, C_6D_6), δ_{ppm} 4.77 (s, 1H), 4.69 (s, 1H), 2.54-2.50 (m, 1H), 2.41-2.29 (m, 3H), 1.93 (ddd, J = 4.0 Hz, J = 4.0 Hz, J = 13.0 Hz, 1H), 1.84-1.79 (m, 1H), 1.74-1.57 (m, 4H), 1.54-1.45 (m, 3H), 1.25 (s, 1H), 1.13-1.08 (m, 4H), 0.99-0.92 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6), δ_{ppm} 152.6 (C_4), 105.8 (CH_2), 74.2 (C_4), 55.4 (CH), 50.4 (CH), 41.6 (CH_2), 38.7 (CH), 37.5 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 24.9 (CH_2), 21.8 (CH_2), 18.0 (CH_3), 15.5 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{14}H_{24}OS$ 240.1548, found 240.1534.

6.4. Spectroscopic data for Chapter 4

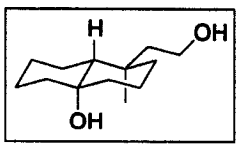


1-Allyl-1-methyl-octahydro-naphthalen-4a-ol (4.2)

To a solution of lactol **4.1** (720 mg, 3.24 mmol) in 32 mL of diethylenglycole was added K_2CO_3 (3.58 g, 25.92 mmol) followed by addition of $NH_2NH_2 \cdot H_2O$ (0.786 mL, 16.2 mmol). The flask was then equipped with a condenser and immersed into a wax bath preheated to 150 °C. The reaction mixture was left stirring for 12 h at 150 °C. Then it was cooled to rt and poured into an Erlenmeyer flask containing 320 mL of distilled H_2O. The resulting milky solution was extracted five times with Et_2O. The

combined organic extracts were concentrated under reduced pressure. Purification by flash chromatography on silica gel (5 % EtOAc in hexanes) yielded deoxygenated product **4.2** (387 mg, 57 % yield) as a clear oil.

The yields vary from 43% to 57%. In some cases reduction of a double bond was observed as a side reaction, resulting in an inseparable mixture of **4.2** and **4.3**, with the ratios ranging from 4:1 to 15:1. IR (cm^{-1}, neat) 3490 (brm), 3073 (m), 3000 (m), 2930 (s), 2865 (s), 2850 (s), 1637 (m), 1446 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.84-5.72 (m, 1H), 5.02-4.93 (m, 2H), 2.03-1.72 (m, 4H), 1.59-1.02 (m, 12H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 135.6 (CH), 117.3 (CH_2), 71.9 (C_4), 49.2 (CH), 47.8 (CH_2), 42.2 (CH_2), 41.1 (CH_2), 38.3 (CH_2), 36.3 (C_4), 27.1 (CH_2), 22.1 (CH_2), 21.7 (CH_3), 21.2 (CH_2), 15.5 (CH_2); HRMS (EI), m/z (M^+-H_2O) calculated for $C_{14}H_{22}$ 190.1722, found 190.1720.

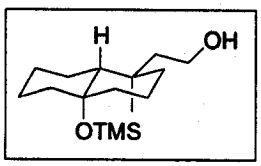


1-(2-Hydroxy-ethyl)-1-methyl-octahydro-naphthalen-4a-ol (4.4)

A. Ozonolysis: A solution of **4.2** (190 mg, 0.91 mmol) in 10 mL of CH_2Cl_2 in a round-bottom flask was saturated with oxygen at rt. The contents were then cooled to –78 °C and bubbled with ozone. After 15 min the color of the reaction turned gray-blue and bubbling was discontinued, followed by immediate addition of DMS (0.25 mL, 4.57 mmol) at –78 °C. The reaction mixture was stirred for 10 min at –78 °C, warmed to rt and stirred for 0.5 h. The solution was concentrated under reduced pressure and used for the reduction without further purification.

B. $LiAlH_4$ Reduction: To a solution of a crude oil from part **A** in 10 mL of THF was carefully added $LiAlH_4$ (78 mg, 2.74 mmol) at –78 °C. After 10 min the dry-ice/isopropanol bath was removed and the mixture was left stirring at rt overnight. It was quenched by a

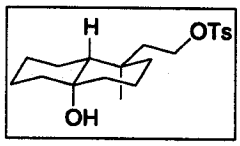
dropwise addition of 10 mL of a 1.0 M aqueous solution of sodium tartrate. The resulting emulsion was left stirring for 10 h until it became almost clear and the phases separated. The aqueous phase was extracted with EtOAc 5 x 20 mL. The combined fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (40 % EtOAc in hexanes) on silica gel afforded product **4.4** (158 mg, 82% yield over 2 steps) as a white solid. IR (cm^{-1}, neat) 3606 (w), 3382 (bs), 2930 (s), 2850 (s), 2668 (w), 1448 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 3.65 (t, J = 8.1Hz, 2H), 1.86-1.70 (m, 2H), 1.63-1.16 (m, 16H), 1.02-0.98 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 71.8 (C_4), 59.6 (CH_2), 50.3 (CH), 46.2 (CH_2), 42.3 (CH_2), 41.0 (CH_2), 38.8 (CH_2), 35.5 (C_4), 27.3 (CH_2), 22.0 (CH_2), 21.9 (CH_2), 20.6 (CH_3), 18.2(CH_2); HRMS (EI), m/z (M^+) calculated for $C_{13}H_{24}O_2$ 212.1777, found 212.1797; mp=114.7-116.1 °C



2-(1-Methyl-4a-trimethylsilanyloxy-decahydro-naphthalen-1-yl)-ethanol (4.8)

To a solution of crude **4.4** (66 mg, 0.31 mmol) in 5 mL of THF at –78 °C was added TMSCl (0.16 mL, 1.24 mmol) freshly distilled over CaH_2, followed by addition of solid KHMDS (155 mg, 0.78 mmol). The resulting solution was stirred for 3 h during which time it slightly warmed up (to –50 °C). The reaction was monitored by TLC and quenched with a saturated aqueous solution of $NaHCO_3$ when no starting material and only trace of mono-protected product were observed. The aqueous phase was extracted with Et_2O 3 x 10 mL. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting yellowish oil was dissolved in 3 mL of MeOH, followed by addition of K_2CO_3 (47 mg, 0.34 mmol). The mixture was stirred for 10-15 min,

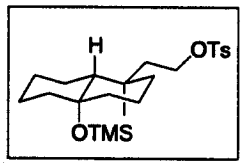
quenched with brine and extracted with CH_2Cl_2 3 x 10 mL. Purification by flash chromatography on silica gel (40 % EtOAc in hexanes) afforded product **4.8** (33 mg, 37% over 4 steps) as a clear oil. IR (cm^{-1}, neat) 3526 (bm), 2936 (s), 2853 (m), 1514 (w), 1447 (m), 1057 (s), 1032 (s), 836 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 3.63 (t, J = 7.9 Hz, 2H), 1.85-1.09 (m, 19H), 0.91 (s, 3H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 75.8 (C_4), 59.6 (CH_2), 52.2 (CH), 46.5 (CH_2), 41.5 (CH_2), 40.6 (CH_2), 38.9 (CH_2), 35.5 (C_4), 27.6 (CH_2), 22.4 (CH_2), 21.9 (CH_3), 20.8 (CH_2), 18.5 (CH_2), 2.9 (CH_3) x 3; HRMS (EI), m/z (M^+) calculated for $C_{16}H_{32}O_2Si$ 284.2172, found 284.2177.



Toluene-4-sulfonic acid 2-(4a-hydroxy-1-methyl-decahydro-naphthalen-1-yl)-ethyl ester (4.5)

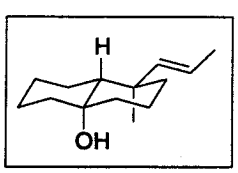
To a mixture of diol **4.4** (20 mg, 0.09 mmol), Et_3N (0.04mL, 0.28 mmol) and DMAP (2 mg, 10% mol) in 1 mL of CH_2Cl_2 was added TsCl (27 mg, 0.14 mmol), freshly recrystallized from benzene. The resulting solution was stirred at rt for 2 h and quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 3 x 5 mL. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc in hexanes) on silica gel afforded product **4.5** (31 mg, 90% yield) as a clear oil. IR (cm^{-1}, neat) 3551 (w), 2929 (s), 2854 (m), 1721 (s), 1598 (w), 1451 (w), 948 (s), 815 (m), 665 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.77 (d, J = 8.1 Hz, 2H), 7.33 (d, J =8.1 Hz, 2H), 4.04 (t, J = 7.4 Hz, 2H), 2.43 (s, 3H), 2.39-0.98 (m, 17H), 0.92 (s, 3H), 0.92-0.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 145.1 (C_4), 133.5 (C_4), 130.2 (CH) x 2, 128.3 (CH) x 2, 71.7 (C_4), 68.1 (CH_2), 51.4 (CH), 42.3 (CH_2), 41.9 (CH_2), 40.9 (CH_2), 38.5 (CH_2), 35.5 (C_4), 27.1 (CH_2), 22.0 (CH_2),

21.9 (CH_3), 21.9 (CH_2), 21.8 (CH_3), 18.0 (CH_2) HRMS (EI), m/z (M^+) calculated for $C_{20}H_{30}O_4S$ 366.1865, found 366.1877.



Toluene-4-sulfonic acid 2-(1-methyl-4a-trimethylsilanyloxy-decahydro-naphthalen-1-yl)-ethyl ester (4.9)

To a solution of **4.8** (16 mg, 0.06 mmol) and pyridine (0.02 mL, 0.17 mmol) in 1 mL of CH_2Cl_2 was added TsCl (16 mg, 0.09 mmol) at rt. The mixture was stirred for 2 h, followed by addition of more pyridine (0.02 mL, 0.17 mmol) and TsCl (16 mg, 0.09 mmol). After 5 h the reaction was quenched with a saturated aqueous solution of $NaHCO_3$. It was extracted with CH_2Cl_2 3 x 5 mL. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography on silica gel (15% EtOAc in hexanes) yielded product **4.9** (10 mg, 65%) as a clear oil. IR (cm^{-1}, neat) 2935 (s), 2858 (m), 1917 (w), 1729 (w), 1596 (w), 1447 (m), 1059 (s), 1033 (s), 952 (s), 906 (m), 837 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.77 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 4.02 (t, J = 7.5 Hz, 2H), 2.43 (s, 3H), 1.74-0.99 (m, 15H), 0.92-0.85 (m, 4H), 0.71 (dd, J = 2.7 Hz, J = 11.9 Hz, 1H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 145.0 (C_4), 133.6 (C_4), 130.2 (CH) x 2, 128.3 (CH) x 2, 75.6 (C_4), 68.3 (CH_2), 51.4 (CH), 41.7 (CH_2), 41.4 (CH_2), 40.4 (CH_2), 38.6 (CH_2), 35.5 (C_4), 27.4 (CH_2), 22.2 (CH_2), 22.0 (CH_3), 21.8 (CH_2), 20.6 (CH_3), 18.3 (CH_2), 2.9 (CH_3) x 3; HRMS (EI), m/z (M^+) calculated for $C_{23}H_{38}O_4SSi$ 438.2260, found 438.2271.

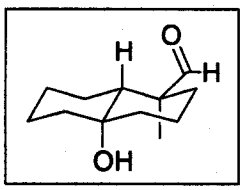


1-Methyl-1-propenyl-octahydro-naphthalen-4a-ol (4.11)

To a solution of **4.2** (130 mg, 0.63 mmol) in 6 mL of toluene in a sealed

tube was added $RuCl_2(PPh_3)_2$ (45 mg, 0.06 mmol) and diisopropylethylamine (0.82 ml, 5.04 mmol). The sealed tube was immersed into a preheated to 145 °C wax bath and stirred for 18.5 h. It was then concentrated and purified by flash chromatography on silica gel (5% EtOAc in hexanes) to give an inseparable 20:1 mixture of **4.11** and **4.2** (120 mg, 92% yield) as a white solid.

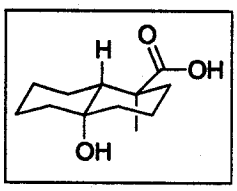
^1H NMR is the only way to monitor a reaction progress since TLC results and retention times of product and starting material (CG) coincide. IR (cm^{-1}, neat) 3473 (m), 3026 (w), 2997 (w), 2977 (s), 2848 (m), 1445 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.32-5.13 (m, 2H), 1.88-1.12 (m, 19H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 144.1 (CH), 121.2 (CH), 71.6 (C_4), 50.6 (CH), 42.3 (CH_2), 41.0 (CH_2), 40.9 (CH_2), 39.1 (C_4), 27.3 (CH_2), 22.7 (CH_2), 22.2 (CH_2), 18.6 (CH_3), 18.3 (CH_2), 18.2 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{14}H_{24}O$ 208.1827, found 208.1804.



4a-Hydroxy-1-methyl-decahydro-naphthalene-1-carbaldehyde (4.13)

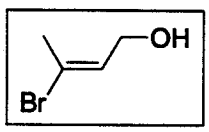
A solution of **4.11** (20 mg, 0.10 mmol) in 2 mL of CH_2Cl_2 in a round-bottom flask was saturated with oxygen at rt. The contents were then cooled to –78 °C and bubbled with ozone. After 10 min a flow of ozone was discontinued, followed by bubbling of argon for 10 min and addition of DMS (0.04 mL, 0.48 mmol) at –78 °C. The reaction mixture was stirred for 10 min at –78 °C, warmed to rt and stirred for 0.5 h under argon. The solution was concentrated under reduced pressure and purified by flash chromatography on silica gel (20 % EtOAc in hexanes) to afford aldehyde **4.13** (6.1 mg, 32%) as a clear oil and acid **4.14** (8.7 mg, 43%) as a white solid. IR (cm^{-1}, neat) 3529 (m), 2930 (s), 2853 (s), 2965

(w), 1719 (s), 1448 (m), 951 (s); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 9.25 (s, 1H), 1.95-1.06 (m, 19H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 207.2 (C_4), 70.7 (C_4), 49.8 (C_4), 44.8 (CH), 42.0 (CH_2), 40.4 (CH_2), 33.3 (CH_2), 26.8 (CH_2), 24.2 (CH_2), 21.9 (CH_2), 16.9 (CH_2), 14.5 (CH_3); HRMS (EI), m/z calculated for $C_{12}H_{20}O_2$ 196.1443, found 196.1458.



4a-Hydroxy-1-methyl-decahydro-naphthalene-1-carboxylic acid (4.12)

IR (cm^{-1}, neat) 3422 (bm), 2930 (s), 2856 (m), 1694 (s), 1445 (m), 1166 (m), 948 (m); ^{1}H NMR (300 MHz, $CDCl_3$), δ_{ppm} 1.91-1.64 (m, 5H), 1.58-1.22 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 185.6 (C_4), 71.3 (C_4), 47.0 (C_4), 46.9 (CH), 42.1 (CH_2), 40.4 (CH_2), 37.7 (CH_2), 26.9 (CH_2), 24.4 (CH_2), 21.9 (CH_2), 17.7 (CH_2), 16.4 (CH_3); HRMS (EI), m/z calculated for $C_{12}H_{20}O_3$ 212.1412, found 212.1417; mp= 137-140 °C.

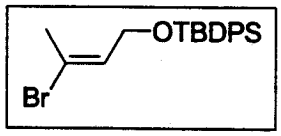


***E*-3-Bromo-but-2-en-1-ol (4.6)**

1. To a solution of crotyl alcohol (2 mL, 0.023 mol) in 115 mL of $CHCl_3$ at –10 °C (acetone-ice bath) was added dropwise Br_2 (1.17 mL, 0.023 mol). After stirring for 1.5 h the reaction was quenched with a saturated aqueous solution of Na_2SO_3. The aqueous phase was extracted with CH_2Cl_2 3 x 10 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The brominated crotyl alcohol was used in the next step without purification.

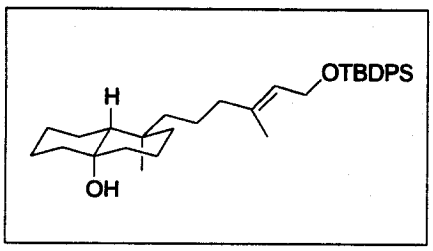
2. To a solution of DIPA (8.38 mL, 0.06 mol) in 80 mL of THF at –78 °C was added dropwise *n*-BuLi (20 mL, 1.7 M in pentane, 0.05 mol) followed by addition of HMPA (2 mL, 0.01 mol), freshly distilled twice over CaH_2. A solution of the brominated crotyl alcohol

(4.64 g, 0.02 mol) in 20 mL of THF was then added to the reaction mixture with a syringe pump over 1.5 h. After stirring for additional 1 h the reaction was quenched with H_2O at –78 °C. The aqueous phase was extracted with EtOAc 4 x 100 mL. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (20% EtOAc in hexanes) afforded **4.6** (1.27 g, 37% over 2 steps) as a yellow oil. The spectroscopic data was in accord with that reported in literature.[10]



***E*-(3-Bromo-but-2-enyloxy)-*tert*-butyl-diphenyl-silane (4.7)**

To a solution of **4.6** (131 mg, 0.87 mmol) in 5 mL of THF was added imidazole (178 mg, 2.62 mmol) followed by addition of TBDPSCl (0.34 mL, 1.31 mmol). Formation of white precipitate was immediately observed. The mixture was stirred for 1 h at rt and quenched with brine. The aqueous phase was extracted with Et_2O 3 x 10 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5% EtOAc in hexanes) gave **4.7** (294 mg, 87 %) as a yellowish oil.[11]



1-[6-(tert-Butyl-diphenyl-silanyloxy)-4-methyl-hex-4-enyl]-1-methyl-octahydro-naphthalen-4a-ol (4.19)

This reaction was performed using procedure developed by Ohba *et al.*[12] To a solution of 9-BBN-dimer (35 mg,

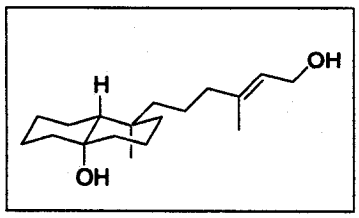
[10] Corey, E.J.; Bock, M.G.; Kozikowski, A.P.; Rama Rao, A.V.; Floyd, D.; Lipshutz, B. *Tetrahedron Lett.* **1978**, *19*, 1051.

[11] Corey, E.J.; Kania, R.S. *J. Am. Chem. Soc.* **1996**, *118*, 1229.

[12] a) Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem. Soc.* **1996**, *118*, 8250. b) Ohba, M.; Iizuka, K.; Ishibashi, H.; Fujii, T. Tetrahedron, **1997**, *53*, 16977.

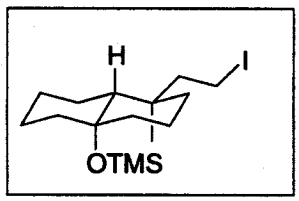
0.14 mmol) in 0.3 mL of THF was added dropwise a solution of **4.2** (20 mg, 0.10 mmol) in 0.12 mL of THF and the mixture was refluxed for 1h 20 min. In a separate flask were placed Cs_2CO_3 (56 mg, 0.17 mmol), 10% mol of $Pd(dppf)Cl_2$[13] (7 mg), 10% mol of Ph_3As (3 mg), vinyl bromide **4.7** (52 mg, 0.13 mmol), DMF (0.24 mL) and H_2O (0.02 mL, 12 equiv mol). To this mixture was transferred by cannula the THF solution of the borane at rt. Resulting red suspension was stirred for 3 h and poured into H_2O (1 mL). The aqueous phase was extracted with Et_2O 3 x 3 mL. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15% EtOAc in hexanes) afforded product **4.19** (236 mg, 48%) as a clear oil. Yields varied from 48% to 65%. IR (cm^{-1}, neat) 3578 (w), 3490 (w), 3071 (w), 3049 (w), 2997 (w), 2932 (s), 1960 (w), 1897 (w), 1822 (w), 1669 (w), 1589 (w), 1472 (m), 1462 (m), 1428 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.69- 7.66 (m, 4H), 7.43-7.33 (m, 6H), 5.34 (t, J = 6.3 Hz, 1H), 4.20 (d, J = 6.3 Hz, 2H), 1.91-1.86 (m, 2H), 1.83-1.73 (m, 2H), 1.58-1.03 (m, 21H), 1.03 (s, 9H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 137.7 (C_4), 136.0 (CH) x 4, 134.4 (C_4) x 2, 129.7 (CH) x 4, 127.9 (CH) x 2, 124.3 (CH), 72.0 (C_4), 61.5 (CH_2), 49.7 (CH), 43.1 (CH_2), 42.3 (CH_2), 41.1 (CH_2), 40.6 (CH_2), 38.2 (CH_2), 35.6 (C_4), 27.3 (CH_2), 27.2 (CH_3) x 3, 22.1 (CH_2), 21.8 (CH_2), 21.3 (CH_2), 21.1 (CH), 19.6 (C_4), 18.3 (CH_2), 16.6 (CH_3); HRMS (EI), m/z (M^+-C_4H_9) calculated for $C_{30}H_{41}O_2Si$ 461.2876, found 461.2849.

[13] $Pd(pddf)Cl_2$ was prepared from $Pd(CH_3CN)_2Cl_2$ according to procedure by: Hayashi, T.; Konishi, M.; Kobori, Y. Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158. For preparation of $Pd(CH_3CN)_2Cl_2$ see: Hartley, F.R.; Murray, S.G.; McAuliffe, C.A. *Inorg. Chem.* **1979**, *18*, 1394.



1-(6-Hydroxy-4-methyl-hex-4-enyl)-1-methyl-octahydro-naphthalen-4a-ol (4.20)

To a solution of **4.19** (202 mg, 0.39 mmol) in 5 mL of THF was added TBAF (0.39 mmol, 1.0 M solution in THF, 0.39 mL). The reaction mixture was stirred for 2 h and then concentrated under reduced pressure. Flash chromatography on silica gel (50% EtOAc in hexanes) afforded **4.20** (77 mg, 82%) as a clear oil, which eventually solidified in the freezer. IR (cm^{-1}, neat) 3380 (bs), 2933 (s), 2865 (s), 2848 (s), 1447 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 5.52 (t, J = 6.7 Hz, 1H), 4.10 (d, J = 6.7 Hz, 2H), 1.90 (t, J = 7.5 Hz, 2H), 1.85-1.71 (m, 2H), 1.61 (s, 3H), 1.61-0.94 (m, 19H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 40.2 (C_4), 123.7 (CH), 72.0 (C_4), 59.7 (CH_2), 49.4 (CH), 43.2 (CH_2), 42.3 (CH_2), 41.0 (CH_2), 40.7 (CH_2), 38.1 (CH_2), 35.7 (C_4), 27.3 (CH_2), 22.1 (CH_2), 21.8 (CH_2), 21.5 (CH_2), 21.2 (CH_3), 18.26 (CH_2), 16.6 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{18}H_{32}O_2$ 280.2402, found 280.2386.

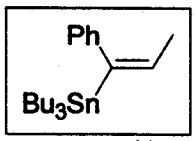


[1-(2-Iodo-ethyl)-1-methyl-octahydro-naphthalen-4a-yloxy]-trimethyl-silane (4.10)

To a solution of **4.9** (27 mg, 0.07 mmol) in acetone (2 mL) was added NaI (131 mg, 0.88 mmol). The mixture was stirred for 3 d. The white precipitate was then removed by filtering through celite. The obtained filtrate was concentrated under reduced pressure. Purification by flash chromatography on silica gel (5% EtOAc in hexanes) afforded **4.10** (32 mg, 67%) as a yellowish oil. IR (cm^{-1}, neat) 2935 (s), 2851 (m), 1446 (m), 1260 (m), 1059 (s), 1029 (s), 836 (s); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 3.18-3.02 (m, 2H), 1.93-1.10 (m, 16H), 0.89-0.81 (m, 4H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 75.3

(C_4), 51.0 (CH), 49.0 (CH_2), 41.1 (CH_2), 40.1 (CH_2), 38.7 (C_4), 37.5 (CH_2), 27.2 (CH_2), 21.9 (CH_2), 21.5 (CH_2), 19.8 (CH_3), 17.9 (CH_2), 2.5 (CH_3) x 3, 2.1 (CH_2); HRMS (EI), m/z (M^+) calculated for $C_{16}H_{31}OSiI$ 394.1189, found 394.1174.

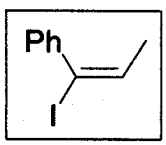
6.5. Spectroscopic data for Chapter 5



Tributyl-(1-phenyl-propenyl)-stannane (5.22)

Vinyl stannane **5.22** was prepared according to a procedure reported in literature.[14]

To a suspension of $PdCl_2(PPh_3)_2$ (56 mg, 0.08 mmol) in 12 mL of THF was added 1-phenyl-1-propyne (0.50 mL, 3.90 mmol). The mixture was stirred for 2 min followed by dropwise addition of Bu_3SnH (0.11 mL, 4.68 mmol) upon which the color of reaction mixture changed form green to dark brown. The solution was stirred for 10 min and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pure hexanes) afforded tributyl-(1-phenyl-propenyl)-stannane **5.22** (848 mg, 53%) as a yellowish oil. The spectroscopic data was in accord with that reported in the original paper.

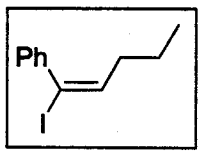


(1-Iodo-propenyl)-benzene (5.23)

To a solution of vinyl stannane **5.22** (640 mg, 1.57 mmol) in 10 mL of CH_2Cl_2 was added in portions I_2 (164 mg, 1.57 mmol). The mixture was stirred for 10 min and quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 2 x 20 mL. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure **(Note: the compound is light and temperature sensitive, the flask must be protected from light)**. Purification by flash chromatography on

[14] Zhang, H.X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

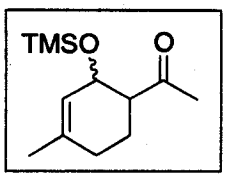
silica gel (pure hexanes) afforded vinyl iodide **2.23** (242 mg, 63%). The spectroscopic data was in accord with that eported in the literature.[15]



1-Iodo-1-phenyl-1-pentene (5.24)

Vinyl iodide **5.24** was prepared using a procedure reported by Suzuki *et al.*[16]

To a solution of B-I-9-BBN (7.5 mL, 1 M in CH_2Cl_2, 7.50 mmol) in 60 mL of CH_2Cl_2 at 0 °C was added dropwise 1-phenyl-1-pentyne (1 mL, 0.06 mmol). The mixture was warmed to rt over 15 h. The reaction was quenched with 7.5 mL of AcOH and stirred for 1 h, then a 3 N aqueous solution of NaOH (90 mL) and a 30% aqueous solution of H_2O_2 were slowly added at 0 °C. The emulsion was stirred for 30 min at 0 °C. The aqueous phase was extracted with CH_2Cl_2 3 x 60 mL. The combined organic extracts were washed with H_2O, a saturated aqueous solution of $NaHCO_3$ and again H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded vinyl iodide **5.24** (1.398 g, 83%) as a yellow oil.

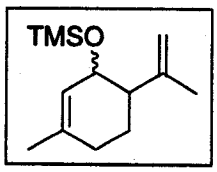


1-(4-Methyl-2-trimethylsilanyloxy-cyclohex-3-enyl)-ethanone (5.17)

To a solution of diene **5.16** (4.22 g, 0.027 mol) in 3 mL of toluene was added methyl vinyl ketone (2.5 mL, 0.030 mol) previously dried over $CaCl_2$ and distilled under reduced pressure. The mixture was refluxed for 26 h, cooled to rt and concentrated under reduced pressure. Purification by flash chromatography on silica gel

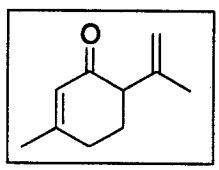
[15] Gao, Y.; Harada, K.; Hata, T.; Urabe, H.; Sato, F. *J. Org. Chem.* **1995**, *60*, 290-291.
[16] Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.

pretreated with Et_3N (10% EtOAc in hexanes) afforded product **5.17** (4.48 g, 76%) as a yellow oil. The spectroscopic data was in accord with that reported in literature.[17]



(6-Isopropenyl-3-methyl-cyclohex-2-enyloxy)-trimethyl-silane (5.18)

To a suspension of $Ph_3P^+CH_3I^-$ (18.85 g, 0.047 mol) in 60 mL at –78 °C was added dropwise *n*-BuLi (11.2 mL, 2.6 M in pentane, 0.030 mol). The reaction was stirred for 1 h at –78 °C, then a dry-ice bath was removed and the mixture was stirred for 40 min at rt. The suspension was cooled to –78 °C and a solution of **5.17** (2.61 g, 0.012 mol) in 5 mL of THF was transferred by cannula and stirred for 30 min at –78 °C. The bath was removed and the mixture was stirred overnight. The reaction was quenched with a 1:1 mixture of Et_2O/H_2O (300 mL). The aqueous fraction was extracted with Et_2O x 100 mL. The combined organic extracts were diluted with hexanes, filtered through a pad of Celite and concentrated under reduced pressure. The crude mixture was used for the oxidation without further purification.

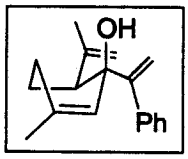


6-Isopropenyl-3-methyl-cyclohex-2-enone (5.14)

To a solution of crude **5.18** (2.64 g, 0.012 mol) in 50 mL of Et_2O at 0 °C was added dropwise Jones reagent (8 mL, 2.16 M, 0.018 mmol). The mixture was stirred at room temperature for 2 h and quenched with H_2O. The aqueous layer was extracted with Et_2O 3 x 100 mL. The combined organic layers were washed with a 5 % aqueous solution of KOH x 50 mL and brine x 50 mL, dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (10 % EtOAc in hexanes)

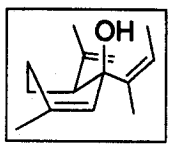
[17] Friedrick, D.; Bohlmann, F. *Tetrahedron* **1988**, *44*, 13697.

afforded **5.14** (1.48 g, 71%) as a yellow oil. The spectroscopic data was in accord with that reported in literature.[17]



6-Isopropenyl-3-methyl-1-(1-phenyl-vinyl)-cyclohex-2-enol (5.19)

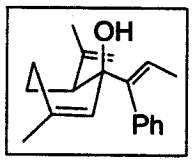
To a solution of α-bromostyrene (0.16 mL, 1.20 mmol) in 5 mL of Et_2O at –90 °C was added a solution of *t*-BuLi (1.80 mL, 1.3 M in pentane, 2.40 mmol). The mixture was stirred for 45 min at –90 °C. A solution of ketone **5.14** (100 mg, 0.67 mmol) in 2 mL of Et_2O was transferred by cannula and the mixture was warmed to –78 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with EtOAc 3 x 10 mL. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The spectroscopic data was identical to that previously reported in our lab.



(+) 6-Isopropenyl-3-methyl-1-(1-methyl-propenyl)-cyclohex-2-enol (5.20)

To a solution of *cis*-2-bromobutene (0.34 mL, 3.34 mmol) in Et_2O (17 mL) at –78 °C was added dropwise a solution of *t*-BuLi (3.73 mL, 1.7 M in pentane, 6.35 mmol). The mixture was stirred for 2 h at –78 °C, then a solution of ketone (+)-**5.14** (250 mg, 1.67 mmol) in Et_2O (2 mL) was transferred by cannula to the solution of the lithiated compound. The resulting mixture was stirred for 15 min followed by quenching with H_2O at –78 °C. The mixture was extracted with Et_2O 3 x 20 mL. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc in hexanes) on silica gel pretreated with Et_3N to give product **5.20** (278 mg, 81%) as a yellowish oil. IR (cm^{-1}, neat) 3546 (bm), 3086 (w), 2969 (s), 2931

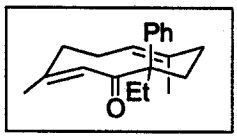
(s), 2869 (s), 2852 (m), 1639 (m), 1459 (m), 1068 (m), 956 (s); ^{1}H NMR (300 MHz, C_6D_6), δ_{ppm} 5.43-5.42 (m, 1H), 5.33 (qq, J = 1.4 Hz, J = 7.3 Hz, 1H), 4.95-4.93 (m, 1H), 4.87-4.86 (m, 1H), 2.37-2.32 (m, 1H), 1.90-1.71 (m, 9H), 3.30 (dq, J = 1.4 Hz, J = 7.3 Hz, 3H), 1.49 (bs, 3H), 1.43-1.35 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6), δ_{ppm} 147.7 (C_4), 142.3 (C_4), 135.2 (C_4), 129.8 (CH), 120.1 (CH), 113.1 (CH_2), 74.4 (C_4), 49.7 (CH), 31.1 (CH_2), 24.7 (CH_2), 23.9 (CH_3), 23.7 (CH_3), 23.3 (CH_3), 14.9 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{14}H_{22}O$ 206.1671, found 206.1684; $[\alpha]_D^2$ = +31.2.



6-Isopropenyl-3-methyl-1-(1-phenyl-propenyl)-cyclohex-2-enol (5.21)

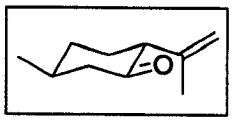
To a solution of *E*-1-iodo-1-phenyl-1-propene **2.23** (242 mg, 0.99 mmol) in Et_2O (5 mL) at –90 °C was added dropwise a solution of *t*-BuLi (1.02 mL, 1.7 M in pentane, 1.74 mmol). The resulting solution was stirred for 1 h at –90 °C (a reaction flask was covered with aluminum foil to protect it from light). Then a solution of ketone **5.14** (37 mg, 0.25 mmol) in Et_2O (1 mL) at –90 °C was transferred by cannula and the mixture was gradually warmed to –60 °C. The solution was cooled to –90 °C and quenched with H_2O. The aqueous phase was extracted with Et_2O 3 x 10 mL. The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5 % EtOAc in hexanes) afforded product **5.21** (40 mg, 61%) as a yellow oil. IR (cm^{-1}, neat) 3524 (m), 2307 (m), 3053 (m), 2929 (s), 2859 (s), 1950 (w), 1885 (w), 1808 (w), 1667 (w), 1636 (m), 1599 (w), 1492 (m), 1440 (s), 1075 (s); ^{1}H NMR (300 MHz, C_6D_6), δ_{ppm} 7.31-7.29 (m, 2H), 7.21-7.15 (m, 2H), 7.11-7.02 (m, 1H), 6.22 (q, J = 6.9 Hz, 1H), 5.51 (bs, 1H), 4.98-4.96 (m, 2H), 2.35 (dd, J = 2.9 Hz, J = 11.8 Hz, 1H), 1.86-1.73 (m, 4H), 1.68-1.42 (m, 10H); ^{13}C NMR (75

MHz, C_6D_6), δ_{ppm} 147.3 (C_4), 147.3 (C_4), 139.9 (C_4), 136.7 (C_4), 130.7 (CH) x 2, 129.6 (CH), 127.8 (CH) x 2, 126.8 (CH), 122.6 (CH), 113.5 (CH_2), 75.3 (C_4), 48.6 (CH), 30.4 (CH_2), 25.3 (CH_2), 23.9 (CH_3), 23.5 (CH_3), 15.1 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{19}H_{24}O$ 268.1827, found 268.1824.



10-Ethyl-3,7-dimethyl-10-phenyl-cyclodeca-2,6-dienone (5.25)

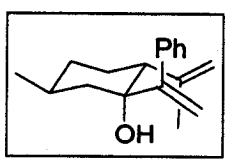
To a solution of alcohol **5.19** (15 mg, 0.06 mmol) in DME (2 mL) was transferred by cannula a solution of KHMDS (59 mg, 0.30 mmol) in DME (1 mL) at rt. The resulting yellow solution was heated (oil bath, 90 °C) for 40 min. During the reflux, the reaction color changed to red-orange. The solution was then cooled to –78 °C **(Note: the condenser was left on the flask)** followed by addition of EtI (0.02 mL, 0.30 mmol) freshly distilled form CaH_2. The solution was stirred for 2 h at –78 °C and quenched with a saturated aqueous solution of NH_4Cl at –78 °C. The mixture was extracted with Et_2O 3 x 5 mL. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2% EtOAc in hexanes) to give ketone **5.25** (16.4 mg, 98%) as a yellow oil. IR (cm^{-1}, neat) 3055 (w), 3020 (w), 2965 (s), 2935 (s), 2872 (m), 1677 (s), 1619 (s), 1493 (w), 1444 (m); ^1H NMR (300 MHz, $CDCl_3$), δ_{ppm} 7.32-7.17 (m, 5H), 5.65 (s, 1H), 4.87 (m, 1H), 3.30 (ddd, J = 4.5 Hz, J = 12.3 Hz, J = 12.3 Hz, 1H), 2.38-1.76 (m, 9H), 1.69 (s, 3H), 1.45 (s, 3H), 0.48 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, C DCl_3), δ_{ppm} 206.5 (C_4), 149.5 (C_4), 142.7 (C_4), 139.2 (C_4), 128.8 (CH) x 2, 127.2 (CH) x 2, 126.9 (CH) x 2, 126.3 (CH), 58.0 (C_4), 35.0 (CH_2), 30.8 (CH_2), 30.3 (CH_2), 26.6 (CH_2), 26.1 (CH_2), 25.9 (CH_3), 16.2 (CH_3), 7.6 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{20}H_{26}O$ 282.1984, found 282.1987.



2-isopropenyl-5-methyl-cyclohexanone (5.26)

1. To a suspension of (±)-citronelal (2.94 g, 13.80 mmol) and dried molecular sieves (3.2 mm, 1.38 g) in 150 mL of CH_2Cl_2 was added dropwise a solution of $SnCl_4$ (1.38 mL, 1 M in CH_2Cl_2, 1.38 mmol). The mixture was stirred for 1 h at –78 °C and quenched with a saturated aqueous solution of NH_4Cl. The resulting emulsion was stirred for 1 h at rt. The aqueous phase was extracted with CH_2Cl_2 4 x 200 mL. Purification by flash chromatography on silica gel (15% EtOAc in hexanes) afforded a mixture of axial and equatorial alcohols (1.48 g, 70% combined yield).

2. To a solution of a diasteremeric mixture of alcohols from part 1 (5.20 g, 33.7 mmol) in 100 mL of Et_2O at 0 °C was added dropwise Jones reagent (23.0 mL, 3.0 M, 67.4 mmol). The reaction was stirred at room temperature for 5 min, then 3.0 mL of Jones reagent (8.9 mmol) were added. The mixture was stirred at rt for 3 hours and quenched with H_2O. The aqueous layer was extracted with Et_2O 3 x 150 mL. The combined organic layers were washed with a 5 % aqueous solution of KOH x 70 mL and brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (5 to 10 % EtOAc in hexanes) afforded **5.26** (2.58 g, 50%, a yellow oil) as a single diastereomer. The spectroscopic data was identical to that reported in literature.[18]

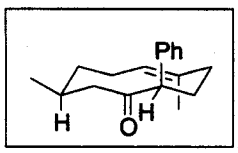


2-Isopropenyl-5-methyl-1-(1-phenyl-vinyl)-cyclohexanol (5.29)

To a solution of α-bromostyrene (0.34 mL, 2.64 mmol) in Et_2O (10 mL) at –90 °C was added dropwise a solution of *t*-BuLi (2.5 mL, 1.7 M in pentane, 4.21 mmol). The resulting mixture was stirred for 1 h 20 min at –90 °C (a reaction

[18] a) Corey, E.J.; Ensley, H.E.; Suggs, J.W. *J. Org. Chem.* **1976**, *41*, 380. b) Buschmann, H.; Scharf, H-D. *Synthesis* **1988**, *10*, 827.

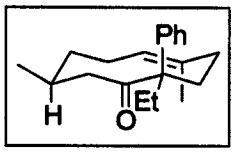
flask was covered with aluminum foil to protect it from light). A solution of ketone **5.29** (100 mg, 0.66 mmol) in Et_2O (1 mL) was transferred by cannula and the mixture was warmed to –60 °C. The solution was then cooled to –90 °C and quenched with H_2O. The aqueous phase was extracted with Et_2O 3 x10 mL. The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5 % EtOAc in hexanes) afforded product **5.30** (122.5 mg, 73%) as a yellow oil. IR (cm^{-1}, neat) 3561 (bm), 3476 (bm), 3079 (w), 2984 (s), 2924 (s), 2867 (w), 2843 (w), 1636 (m), 1597 (w), 1571 (w), 1491 (m), 1454 (m), 1441 (m); ^1H NMR (300 MHz, C_6D_6), δ_{ppm} 7.35-7.32 (m, 2H), 7.17-7.05 (m, 3H), 5.34 (d, J = 1.6 Hz, 1H), 5.03 (d, J = 1.6 Hz, 1H), 4.93-4.91 (m, 2H), 2.25 (dd, J = 3.5 Hz, J = 12.9 Hz, 1H), 2.00-1.69 (m, 5H), 1.64-1.44 (m, 3H), 1.32-1.23 (m, 2H), 0.80-0.66 (m, 1H), 0.76 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6), δ_{ppm} 157.4 (C_4), 148.4 (C_4), 142.4 (C_4), 129.3 (CH) x2, 127.6 (CH) x2, 127.3 (CH), 114.3 (CH_2), 113.5 (CH_2), 76.8 (C_4), 51.5 (CH), 49.4 (CH_2), 35.1 (CH_2), 28.8 (CH_2), 27.8 (CH_3), 23.9 (CH_3), 22.5 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{18}H_{24}O$ 256.1827, found 256.1831.



5,9-Dimethyl-2-phenyl-cyclodec-5-enone (5.30)

Compound **5.30** was isolated as a side product during the studies on the oxy-Cope/alkylation reaction of alcohol **5.29**. IR (cm^{-1}, neat) 2947 (m), 2928 (m), 1692 (s), 1595 (w), 1492 (m), 1454 (m), 1433 (m), 1418 (m), 1096 (m); ^1H NMR (300 MHz, C_6D_6), δ_{ppm} 7.28-7.26 (m, 2H), 7.23-7.01 (m, 3H), 5.03-5.00 (m, 1H), 3.29-3.25 (m, 1H), 2.85 (ddd, J = 3.4 Hz, J = 12.8 Hz, J = 16.3 Hz, 1H), 2.32-2.23 (m, 1H), 2.19-2.01 (m, 2H), 1.97-1.77 (m, 4H), 1.61-1.49 (m, 5H), 1.07-0.84 (m, 1H), 0.64 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75

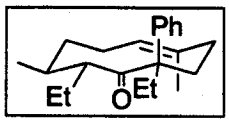
MHz, C_6D_6), δ_{ppm} 205.7 (C_4), 141.0 (C_4), 138.6 (C_4), 129.0 (CH) x 2, 128.4 (CH) x 2, 127.1 (CH), 126.6 (CH), 61.4 (CH), 52.3 (CH_2), 41.4 (CH_2), 38.3 (CH_2), 35.6 (CH_2), 28.9 (CH), 27.9 (CH_2), 24.8 (CH_3), 16.3 (CH_3); HRMS (EI), m/z (M^+) calculated for $C_{18}H_{24}O$ 256.1827, observed degradation, no M^+ detected.



2-Ethyl-5,9-dimethyl-2-phenyl-cyclodec-5-enone (5.31)

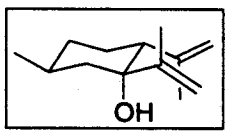
To a solution of alcohol **5.29** (157 mg, 0.61 mmol) in DME (5 mL) was transferred by cannula a solution of KHMDS (245 mg, 1.22 mmol) in DME (5 mL) at rt. The resulting yellow solution was heated in the oil bath at 90 °C for 15 min. During the reflux, the reaction color changed to orange. The reaction flask was then cooled to –78 °C followed by addition of EtI (0.06 mL, 0.73 mmol) freshly distilled from CaH_2. The solution was stirred for 2 hours at –78 °C and quenched with H_2O at –78 °C. The aqueous phase was extracted with Et_2O 3 x 10 mL. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to give **5.31** (83 mg, 48 %) as a yellow oil, dialkylated compound **5.32** (9.1 mg, 5%) as a yellow oil and their 1:1 mixture (16.2 mg) in combined yield of 62 %. IR (cm^{-1}, neat) 3085 (w), 3059 (w), 3024 (w), 2952 (s), 2929 (s), 2867 (m), 1954 (w), 1866 (w), 1801 (w), 1696 (s), 1598 (w), 1498 (w), 1445 (m); ^1H NMR (300 MHz, C_6D_6), δ_{ppm} 7.23-7.20 (m, 2H), 7.14-7.11 (m, 2H), 7.05-7.01 (m, 1H), 5.12-5.10 (m, 1H), 2.98-2.85 (m, 2H), 2.27-1.81 (m, 8H), 1.62-1.60 (m, 4H), 1.15-0.88 (m, 2H), 0.78 (d, J = 7.1 Hz, 3H), 0.57 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6), δ_{ppm} 208.8 (C_4), 144.7 (C_4), 137.7 (C_4), 128.4 (CH) x 2, 128.0 (CH) x 2, 127.0 (CH), 126.4 (CH), 57.0 (C_4), 47.8 (CH_2), 38.2 (CH_2), 35.8 (CH_2), 33.0 (CH_2), 28.0 (CH), 27.9 (CH_2), 25.2

(CH_3), 25.2 (CH_2), 16.5 (CH_3), 8.2 (CH_3); HRMS (E1), m/z (M^+) calculated for $C_{20}H_{28}O$ 284.2140, observed degradation, no M^+ detected.



2,10-Diethyl-5,9-dimethyl-2-phenyl-cyclodec-5-enone (5.32)

IR (cm^{-1}, neat) 3093 (w), 3056 (w), 3020 (w), 2970 (s), 2936 (s), 2880 (m), 2859 (m), 1941 (w), 1877 (w), 1838 (w), 1806 (w), 1690 (s), 1598 (w), 1580 (w), 1498 (w), 1475 (m), 1445 (m); ^1H NMR (300 MHz, C_6D_6), δ_{ppm} 7.56-7.54 (m, 2H), 7.15-7.12 (m, 2H), 7.04-6.97 (m, 1H), 5.33-5.28 (m, 1H), 3.16-3.02 (m, 1H), 2.74-2.65 (m, 1H), 2.42-2.02 (m, 6H), 1.93-1.83 (m, 1H), 1.75-1.61 (m, 4H), 1.55-1.47 (m, 1H), 1.55-1.47 (m, 1H), 1.44-1.26 (m, 2H), 1.25-1.11 (m, 1H), 0.86-0.77 (m, 6H), 0.19 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ_{ppm} 211.9 (C_4), 142.5 (C_4), 138.8 (C_4), 128.2 (CH) x 2, 128.1 (CH) x 2, 126.3 (CH), 125.8 (CH), 56.9 (C_4), 53.2 (CH), 36.8 (CH_2), 36.1 (CH_2), 32.0 (CH), 29.9 (CH_3), 23.0 (CH_2), 22.0 (CH_2), 21.0 (CH_2), 18.7 (CH_2), 17.1 (CH_3), 14.5 (CH_3), 8.7 (CH_3); HRMS (E1), m/z (M^+) degradation observed, no M^+ detected.



1,2-Diisopropenyl-5-methyl-cyclohexanol (5.33)

Anhydrous $CeCl_3$ (210 mg, 0.85 mmol) was suspended in 4 mL THF and stirred for 1 h. A solution of ketone **5.26** in 1 mL of THF pre-cooled to 0 °C was transferred by cannula into the suspension and cooled to 0 °C. Isopropenyl magnesium bromide (4 mL, 2.0 M solution in THF, 2.00 mmol) was added slowly and the reaction was allowed to warm to rt. After 3 h the reaction was quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with EtOAc 3 x 5 mL. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography

(2% EtOAc in hexanes) on silica gel afforded compound **5.33** (76 mg, 92 %) as a colorless oil. The spectroscopic data was identical to that previously reported in our lab.[19]

[19] Sauer, E. L. O.; Barriault, L. *J. Am. Chem Soc.* **2004**, *in press.*

CLAIMS TO ORIGINAL RESEARCH

1. Solved two major challenges encountered during the synthesis of (±)-agelasimine A: formation of the quaternary center at C9 and control of the selectivity at C8.

2. Developed the novel highly diastereoselective tandem oxy-Cope/ene/Claisen reaction as a general method for construction of *trans*-decalines with a quaternary center at C9.

3. Studied in detail the scope and limitations of the new tandem process.

4. Investigated the effect of substituents on the diastereoselectivity of the oxy-Cope/ene reaction.

5. Developed a new approach toward the quaternary centers via the anionic oxy-Cope/alkylation reaction.

PUBLICATIONS AND PRESENTATIONS

1. Farand, J.A.; Denissova, I.; Barriault, L. "Microwave Assisted Pericyclic Reactions In Cascade To Construct Decalin Frameworks Possessing Quaternary Centers, Scope And Limitations" *Heterocycles*, **2004**, *62*, 735.

2. Barriault, L.; Denissova, I. "Highly Diastereoselective Synthesis Of Decalin Sceletons with Quaternary Carbon Centers Via The Tandem Oxy-Cope/Ene/Claisen Reaction" *Org. Lett.* **2002**, *4*, 1371.

3. Denissova, I.; Farand, J.; Gauvreau, D.; Barriault, L. "Asymmetric Synthesis Of Quaternary Centers" The 39th IUPAC Congress and 86th Conference of the Canadian Society for Chemistry, August 2003, Ottawa, Canada, poster presentation.

4. Denissova, I.; Barriault, L. "Highly Diastereoselective Synthesis Of Decalin Sceletons With Quaternary Carbon Centers Via The Oxy-Cope/Ene/Claisen Reaction" Ottawa-Carleton Chemistry Institute Conference, May 2002, Ottawa, Canada, oral presentation.

5. Denissova, I.; Barriault, L. "Highly Diastereoselective Synthesis Of Quaternary Centers Via The Tandem Oxy-Cope/Ene/Claisen Reaction" 223rd American Chemical Society National Meeting, Orlando, USA, April 2002, oral presentation.

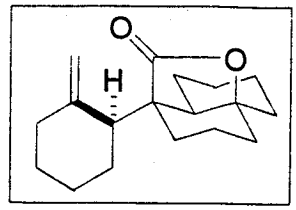
6. Denissova, I.; Barriault, L. "Highly Diastereoselective Synthesis Of Quaternary Centers Via The Tandem Oxy-Cope/Ene/Claisen Reaction" 12th Quebec-Ontario Minisymposium in Synthesis and Bioorganic Chemistry, November 2001, Sherbrooke, Quebec, Canada, oral presentation.

7. Denissova, I.; Barriault, L. "Investigations Toward The Tandem Claisen/Transanular Ene Reaction. Studies Toward The Total Synthesis of (±)-4,4-Dihydroagelasimine A Using Tandem Oxy-Cope/Ene Reaction Strategy" 84th CSC Conference and Exhibition, May 2001, Montreal, Canada, poster presentation.

8. Denissova, I.; Barriault, L. "Studies Toward The Total Synthesis Of (±)-Agelasimine A. Development Of The Tandem Oxy-Cope/Ene/Claisen Reaction" Ottawa-Carleton Chemistry Institute Conference, May 2001, Ottawa, Canada, poster presentation.

Appendix 1

X-Ray Data


O
O
H

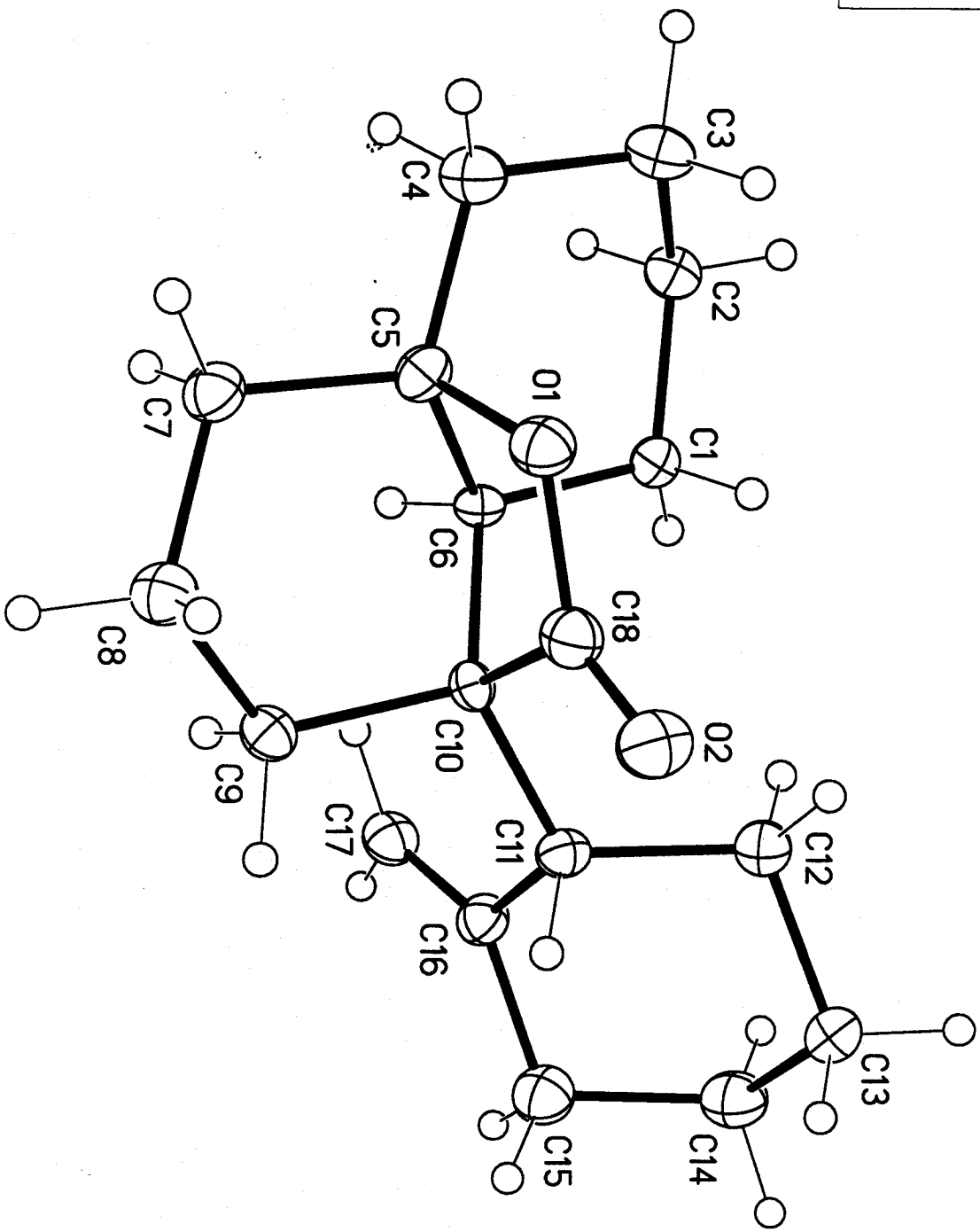

C3
C4
C2
C5
O1
C7
C1
C6
C8
C18
O2
C10
C9
C17
C11
C12
C16
C13
C15
C14

Table 1. Crystal data and structure refinement for lb005.

Identification code	lb005
Empirical formula	C20 H24 O2
Formula weight	296.39
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 10.693(3) A alpha = 90 deg. b = 9.296(3) A beta = 101.88(2) deg. c = 16.278(5) A gamma = 90 deg.
Volume	1583.5(8) A^3
Z, Calculated density	4, 1.243 Mg/m^3
Absorption coefficient	0.078 mm^-1
F(000)	640
Crystal size	0.1 x 0.1 x 0.1 mm
Theta range for data collection	2.10 to 23.25 deg.
Limiting indices	-10<=h<=11, 0<=k<=10, 0<=l<=18
Reflections collected / unique	4486 / 2142 [R(int) = 0.0472]
Completeness to theta = 23.25	94.3 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2142 / 0 / 199
Goodness-of-fit on F^2	1.010
Final R indices [I>2sigma(I)]	R1 = 0.0482, wR2 = 0.0979
R indices (all data)	R1 = 0.0975, wR2 = 0.1112
Largest diff. peak and hole	0.165 and -0.223 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for lb005.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	6901(2)	9839(2)	3403(1)	41(1)
O(2)	7218(2)	10838(2)	2217(1)	30(1)
C(1)	6537(3)	10014(3)	2658(2)	29(1)
C(2)	5330(3)	9445(3)	2065(2)	24(1)
C(3)	4294(3)	10622(3)	1998(2)	30(1)
C(4)	4798(3)	12139(3)	1900(2)	35(1)
C(5)	5624(3)	12170(3)	1239(2)	34(1)
C(6)	6542(3)	10896(3)	1328(2)	27(1)
C(7)	5836(3)	9442(3)	1238(2)	23(1)
C(8)	6747(3)	8188(3)	1181(2)	31(1)
C(9)	7627(3)	8437(3)	559(2)	35(1)
C(10)	8412(3)	9804(3)	790(2)	39(1)
C(11)	7535(3)	11095(3)	793(2)	33(1)
C(12)	4882(3)	7967(3)	2358(2)	27(1)
C(13)	4518(3)	8074(3)	3209(2)	36(1)
C(14)	3865(3)	7136(4)	3533(2)	50(1)
C(15)	2563(3)	7754(3)	1560(2)	36(1)
C(16)	1625(3)	7099(4)	958(2)	46(1)
C(17)	1912(4)	5950(4)	492(2)	51(1)
C(18)	3145(4)	5436(4)	649(2)	51(1)
C(19)	4089(3)	6076(3)	1248(2)	37(1)
C(20)	3828(3)	7269(3)	1701(2)	29(1)

Table 3. Bond lengths [A] and angles [deg] for lb005.

O(1)-C(1)	1.207(3)
O(2)-C(1)	1.358(3)
O(2)-C(6)	1.480(3)
C(1)-C(2)	1.538(4)
C(2)-C(3)	1.545(4)
C(2)-C(7)	1.551(4)
C(2)-C(12)	1.562(4)
C(3)-C(4)	1.529(4)
C(4)-C(5)	1.527(4)
C(5)-C(6)	1.526(4)
C(6)-C(11)	1.517(4)
C(6)-C(7)	1.541(4)
C(7)-C(8)	1.534(4)
C(8)-C(9)	1.536(4)
C(9)-C(10)	1.526(4)
C(10)-C(11)	1.524(4)
C(12)-C(13)	1.518(4)
C(12)-C(20)	1.529(4)
C(13)-C(14)	1.296(4)
C(15)-C(16)	1.390(4)
C(15)-C(20)	1.400(4)
C(16)-C(17)	1.381(5)
C(17)-C(18)	1.376(5)
C(18)-C(19)	1.384(4)
C(19)-C(20)	1.392(4)

C(1)-O(2)-C(6)	109.3(2)
O(1)-C(1)-O(2)	120.7(3)
O(1)-C(1)-C(2)	129.7(3)
O(2)-C(1)-C(2)	109.6(2)
C(1)-C(2)-C(3)	107.3(2)
C(1)-C(2)-C(7)	98.5(2)
C(3)-C(2)-C(7)	108.2(2)
C(1)-C(2)-C(12)	112.5(2)
C(3)-C(2)-C(12)	112.6(2)
C(7)-C(2)-C(12)	116.5(2)
C(4)-C(3)-C(2)	113.4(2)
C(5)-C(4)-C(3)	111.0(2)
C(4)-C(5)-C(6)	111.9(2)
O(2)-C(6)-C(11)	108.0(2)
O(2)-C(6)-C(5)	107.3(2)
C(11)-C(6)-C(5)	111.3(2)
O(2)-C(6)-C(7)	101.1(2)
C(11)-C(6)-C(7)	116.1(2)
C(5)-C(6)-C(7)	112.2(2)
C(8)-C(7)-C(6)	111.6(2)
C(8)-C(7)-C(2)	113.1(2)
C(6)-C(7)-C(2)	99.6(2)
C(7)-C(8)-C(9)	114.1(2)
C(10)-C(9)-C(8)	110.1(2)
C(11)-C(10)-C(9)	110.4(2)
C(6)-C(11)-C(10)	114.2(2)
C(13)-C(12)-C(20)	112.1(2)
C(13)-C(12)-C(2)	111.9(2)
C(20)-C(12)-C(2)	112.8(2)
C(14)-C(13)-C(12)	126.0(3)

C(16)-C(15)-C(20)	120.5(3)
C(17)-C(16)-C(15)	121.1(3)
C(18)-C(17)-C(16)	118.6(3)
C(17)-C(18)-C(19)	120.9(3)
C(18)-C(19)-C(20)	121.3(3)
C(19)-C(20)-C(15)	117.5(3)
C(19)-C(20)-C(12)	120.6(3)
C(15)-C(20)-C(12)	121.8(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1b005.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	50(2)	44(1)	25(1)	0(1)	0(1)	-5(1)
O(2)	31(1)	31(1)	27(1)	1(1)	4(1)	-7(1)
C(1)	35(2)	24(2)	30(2)	-3(2)	10(2)	2(2)
C(2)	26(2)	23(2)	24(2)	-1(1)	4(1)	-1(2)
C(3)	30(2)	30(2)	33(2)	2(1)	10(2)	6(2)
C(4)	36(2)	24(2)	48(2)	2(2)	11(2)	8(2)
C(5)	34(2)	23(2)	44(2)	3(2)	8(2)	1(2)
C(6)	30(2)	29(2)	21(2)	3(1)	3(1)	-5(2)
C(7)	23(2)	24(2)	22(2)	1(1)	4(1)	0(2)
C(8)	30(2)	30(2)	34(2)	0(2)	13(2)	0(2)
C(9)	33(2)	37(2)	37(2)	-2(2)	16(2)	2(2)
C(10)	28(2)	48(2)	44(2)	2(2)	17(2)	-5(2)
C(11)	31(2)	37(2)	32(2)	5(2)	7(2)	-9(2)
C(12)	27(2)	24(2)	31(2)	4(1)	10(1)	3(2)
C(13)	38(2)	39(2)	32(2)	1(2)	12(2)	-4(2)
C(14)	46(2)	66(3)	42(2)	4(2)	18(2)	-12(2)
C(15)	36(2)	37(2)	37(2)	6(2)	12(2)	-7(2)
C(16)	37(2)	55(3)	44(2)	14(2)	2(2)	-12(2)
C(17)	62(3)	53(3)	32(2)	5(2)	-4(2)	-30(2)
C(18)	70(3)	36(2)	47(2)	-10(2)	11(2)	-19(2)
C(19)	43(2)	25(2)	44(2)	2(2)	14(2)	-8(2)
C(20)	33(2)	25(2)	31(2)	6(2)	10(2)	-7(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for lb005.

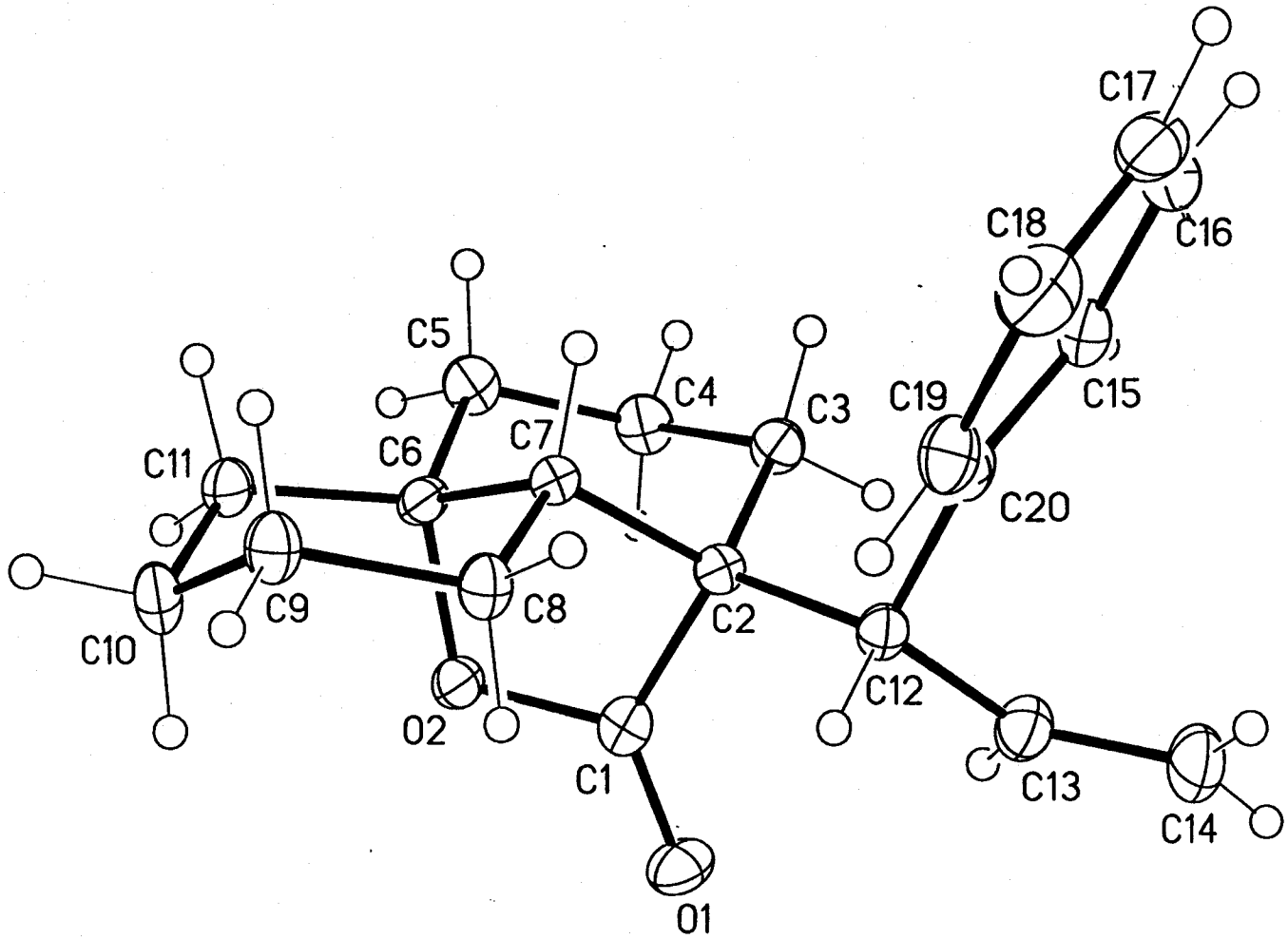
	x	y	z	U(eq)
H(3A)	3606	10411	1515	37
H(3B)	3929	10591	2503	37
H(4A)	4077	12801	1736	42
H(4B)	5305	12464	2440	42
H(5A)	6115	13067	1293	40
H(5B)	5070	12152	678	40
H(7A)	5118	9450	745	28
H(8A)	6240	7318	1014	37
H(8B)	7276	8015	1740	37
H(9A)	8202	7613	570	42
H(9B)	7113	8526	-11	42
H(10A)	8964	9692	1347	46
H(10B)	8959	9965	384	46
H(11A)	8058	11937	997	40
H(11B)	7094	11295	214	40
H(12A)	5629	7315	2430	32
H(13A)	4793	8897	3532	43
H(14A)	3570	6295	3234	60
H(14B)	3685	7295	4067	60
H(15A)	2345	8529	1874	43
H(16A)	781	7444	867	56
H(17A)	1278	5526	76	61
H(18A)	3350	4640	346	61
H(19A)	4921	5698	1350	44

Table 6. Torsion angles [deg] for lb005.

C(6)-O(2)-C(1)-O(1)	-178.7(3)
C(6)-O(2)-C(1)-C(2)	0.5(3)
O(1)-C(1)-C(2)-C(3)	94.2(4)
O(2)-C(1)-C(2)-C(3)	-84.8(3)
O(1)-C(1)-C(2)-C(7)	-153.5(3)
O(2)-C(1)-C(2)-C(7)	27.4(3)
O(1)-C(1)-C(2)-C(12)	-30.2(4)
O(2)-C(1)-C(2)-C(12)	150.8(2)
C(1)-C(2)-C(3)-C(4)	43.2(3)
C(7)-C(2)-C(3)-C(4)	-62.2(3)
C(12)-C(2)-C(3)-C(4)	167.5(2)
C(2)-C(3)-C(4)-C(5)	46.6(3)
C(3)-C(4)-C(5)-C(6)	-43.9(3)
C(1)-O(2)-C(6)-C(11)	-150.9(2)
C(1)-O(2)-C(6)-C(5)	89.0(3)
C(1)-O(2)-C(6)-C(7)	-28.6(3)
C(4)-C(5)-C(6)-O(2)	-50.4(3)
C(4)-C(5)-C(6)-C(11)	-168.3(2)
C(4)-C(5)-C(6)-C(7)	59.7(3)
O(2)-C(6)-C(7)-C(8)	-75.5(3)
C(11)-C(6)-C(7)-C(8)	40.9(3)
C(5)-C(6)-C(7)-C(8)	170.5(2)
O(2)-C(6)-C(7)-C(2)	44.2(2)
C(11)-C(6)-C(7)-C(2)	160.6(2)
C(5)-C(6)-C(7)-C(2)	-69.8(3)
C(1)-C(2)-C(7)-C(8)	76.0(3)
C(3)-C(2)-C(7)-C(8)	-172.5(2)
C(12)-C(2)-C(7)-C(8)	-44.4(3)
C(1)-C(2)-C(7)-C(6)	-42.6(2)
C(3)-C(2)-C(7)-C(6)	68.9(3)
C(12)-C(2)-C(7)-C(6)	-163.0(2)
C(6)-C(7)-C(8)-C(9)	-47.4(3)
C(2)-C(7)-C(8)-C(9)	-158.8(2)
C(7)-C(8)-C(9)-C(10)	57.2(3)
C(8)-C(9)-C(10)-C(11)	-58.2(3)
O(2)-C(6)-C(11)-C(10)	67.7(3)
C(5)-C(6)-C(11)-C(10)	-174.8(2)
C(7)-C(6)-C(11)-C(10)	-44.8(3)
C(9)-C(10)-C(11)-C(6)	52.8(3)
C(1)-C(2)-C(12)-C(13)	62.3(3)
C(3)-C(2)-C(12)-C(13)	-59.1(3)
C(7)-C(2)-C(12)-C(13)	175.0(2)
C(1)-C(2)-C(12)-C(20)	-170.1(2)
C(3)-C(2)-C(12)-C(20)	68.4(3)
C(7)-C(2)-C(12)-C(20)	-57.5(3)
C(20)-C(12)-C(13)-C(14)	36.3(4)
C(2)-C(12)-C(13)-C(14)	164.2(3)
C(20)-C(15)-C(16)-C(17)	0.7(5)
C(15)-C(16)-C(17)-C(18)	1.6(5)
C(16)-C(17)-C(18)-C(19)	-1.5(5)
C(17)-C(18)-C(19)-C(20)	-0.9(5)
C(18)-C(19)-C(20)-C(15)	3.1(4)
C(18)-C(19)-C(20)-C(12)	-179.8(3)
C(16)-C(15)-C(20)-C(19)	-3.0(4)
C(16)-C(15)-C(20)-C(12)	180.0(3)
C(13)-C(12)-C(20)-C(19)	-125.4(3)

C(2)-C(12)-C(20)-C(19)	107.2(3)
C(13)-C(12)-C(20)-C(15)	51.5(4)
C(2)-C(12)-C(20)-C(15)	-75.9(3)

Symmetry transformations used to generate equivalent atoms:


C17
C18
C16
C5
C4
C3
C19
C15
C11
C6
C7
C20
C9
C8
C2
C10
C12
O2
C1
C13
C14
O1

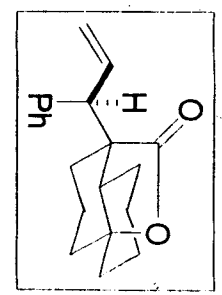

Ph
H
O
O

Table 1. Crystal data and structure refinement for lb006.

Identification code	lb006
Empirical formula	C18 H27 O2
Formula weight	275.40
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 9.7798(8) A alpha = 90 deg. b = 10.9953(8) A beta = 100.36(2) deg c = 14.1118(9) A gamma = 90 deg.
Volume	1492.72(19) A^3
Z, Calculated density	4, 1.225 Mg/m^3
Absorption coefficient	0.077 mm^-1
F(000)	604
Crystal size	0.1 x 0.1 x 0.1 mm
Theta range for data collection	2.12 to 20.81 deg.
Limiting indices	-9<=h<=9, 0<=k<=10, 0<=l<=14
Reflections collected / unique	4196 / 1559 [R(int) = 0.0723]
Completeness to theta = 20.81	100.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1559 / 0 / 181
Goodness-of-fit on F^2	1.033
Final R indices [I>2sigma(I)]	R1 = 0.0471, wR2 = 0.1379
R indices (all data)	R1 = 0.0520, wR2 = 0.1447
Largest diff. peak and hole	0.144 and -0.276 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for lb006.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	-4559(2)	-3259(2)	79(2)	33(1)
O(2)	-3454(2)	-3314(2)	1607(2)	43(1)
C(1)	-3284(3)	-956(3)	-501(2)	28(1)
C(2)	-4383(3)	-490(3)	-1344(2)	34(1)
C(3)	-5688(3)	-1308(3)	-1379(2)	38(1)
C(4)	-5348(3)	-2608(3)	-1575(2)	37(1)
C(5)	-4142(3)	-3127(3)	-876(2)	29(1)
C(6)	-2858(3)	-2260(3)	-621(2)	22(1)
C(7)	-3727(3)	-4364(3)	-1202(2)	33(1)
C(8)	-2707(3)	-5005(3)	-408(2)	35(1)
C(9)	-1572(3)	-4126(3)	65(2)	28(1)
C(10)	-2148(3)	-2884(3)	310(2)	22(1)
C(11)	-1022(3)	-2252(3)	1066(2)	28(1)
C(12)	-1432(3)	-1078(3)	1539(2)	32(1)
C(13)	-369(3)	-792(3)	2464(2)	35(1)
C(14)	1078(4)	-633(3)	2201(3)	44(1)
C(15)	1487(3)	-1740(3)	1653(2)	41(1)
C(16)	386(3)	-2005(3)	777(2)	31(1)
C(17)	642(3)	-1948(3)	-75(2)	34(1)
C(18)	-3436(3)	-3155(3)	791(3)	34(1)

Table 3. Bond lengths [A] and angles [deg] for lb006.

O(1)-C(18)	1.354(4)
O(1)-C(5)	1.483(4)
O(2)-C(18)	1.168(4)
C(1)-C(6)	1.511(4)
C(1)-C(2)	1.540(4)
C(2)-C(3)	1.555(5)
C(3)-C(4)	1.504(5)
C(4)-C(5)	1.507(4)
C(5)-C(7)	1.514(4)
C(5)-C(6)	1.566(4)
C(6)-C(10)	1.533(4)
C(7)-C(8)	1.531(4)
C(8)-C(9)	1.531(4)
C(9)-C(10)	1.539(4)
C(10)-C(11)	1.554(4)
C(10)-C(18)	1.564(5)
C(11)-C(16)	1.530(4)
C(11)-C(12)	1.538(4)
C(12)-C(13)	1.548(4)
C(13)-C(14)	1.536(5)
C(14)-C(15)	1.533(5)
C(15)-C(16)	1.514(5)
C(16)-C(17)	1.274(4)

C(18)-O(1)-C(5)	110.4(2)
C(6)-C(1)-C(2)	113.4(2)
C(1)-C(2)-C(3)	106.6(3)
C(4)-C(3)-C(2)	110.4(3)
C(3)-C(4)-C(5)	114.4(3)
O(1)-C(5)-C(4)	108.7(2)
O(1)-C(5)-C(7)	108.7(2)
C(4)-C(5)-C(7)	111.3(3)
O(1)-C(5)-C(6)	101.0(2)
C(4)-C(5)-C(6)	114.9(3)
C(7)-C(5)-C(6)	111.7(2)
C(1)-C(6)-C(10)	114.9(2)
C(1)-C(6)-C(5)	112.2(2)
C(10)-C(6)-C(5)	98.4(2)
C(5)-C(7)-C(8)	111.5(3)
C(7)-C(8)-C(9)	110.8(3)
C(8)-C(9)-C(10)	113.1(2)
C(9)-C(10)-C(6)	109.5(2)
C(9)-C(10)-C(11)	108.0(2)
C(6)-C(10)-C(11)	123.0(2)
C(9)-C(10)-C(18)	106.5(2)
C(6)-C(10)-C(18)	100.4(2)
C(11)-C(10)-C(18)	108.2(2)
C(16)-C(11)-C(12)	106.5(2)
C(16)-C(11)-C(10)	117.2(2)
C(12)-C(11)-C(10)	117.8(2)
C(11)-C(12)-C(13)	110.4(3)
C(14)-C(13)-C(12)	109.1(3)
C(15)-C(14)-C(13)	111.5(3)
C(16)-C(15)-C(14)	110.7(3)
C(17)-C(16)-C(15)	122.0(3)
C(17)-C(16)-C(11)	126.8(3)

C(15)-C(16)-C(11)	111.0(3)
O(2)-C(18)-O(1)	124.5(3)
O(2)-C(18)-C(10)	127.8(3)
O(1)-C(18)-C(10)	107.6(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for lb006.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	30(1)	33(1)	34(1)	1(1)	4(1)	-2(1)
O(2)	41(2)	48(2)	39(2)	0(1)	5(1)	-1(1)
C(1)	28(2)	27(2)	28(2)	-3(1)	5(1)	-1(1)
C(2)	35(2)	35(2)	33(2)	0(2)	4(2)	5(2)
C(3)	29(2)	44(2)	40(2)	3(2)	2(2)	0(2)
C(4)	34(2)	38(2)	38(2)	3(2)	4(2)	-1(2)
C(5)	32(2)	28(2)	26(2)	-2(1)	5(1)	-3(1)
C(6)	19(2)	27(2)	21(2)	2(1)	2(1)	-1(1)
C(7)	33(2)	33(2)	34(2)	-3(2)	4(2)	-5(2)
C(8)	34(2)	33(2)	39(2)	0(2)	5(2)	-3(2)
C(9)	29(2)	26(2)	29(2)	2(1)	6(1)	1(1)
C(10)	21(2)	22(2)	24(2)	0(1)	8(1)	0(1)
C(11)	27(2)	30(2)	25(2)	2(1)	2(1)	-1(1)
C(12)	31(2)	34(2)	33(2)	-1(2)	6(1)	-1(2)
C(13)	37(2)	38(2)	30(2)	-3(2)	5(2)	0(2)
C(14)	40(2)	47(2)	41(2)	1(2)	1(2)	-3(2)
C(15)	38(2)	43(2)	44(2)	-1(2)	7(2)	-2(2)
C(16)	33(2)	30(2)	29(2)	-1(2)	4(2)	-2(2)
C(17)	26(2)	37(2)	39(2)	0(2)	6(2)	-2(2)
C(18)	32(2)	30(2)	38(2)	1(2)	2(2)	1(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for lb006.

	x	y	z	U(eq)
H(1A)	-2459	-437	-439	33
H(1B)	-3656	-886	97	33
H(2A)	-4033	-548	-1951	41
H(2B)	-4612	361	-1240	41
H(3A)	-6014	-1257	-763	46
H(3B)	-6435	-1018	-1887	46
H(4A)	-5139	-2662	-2227	45
H(4B)	-6172	-3109	-1556	45
H(6A)	-2265	-2316	-1118	27
H(7A)	-3297	-4269	-1773	40
H(7B)	-4560	-4869	-1381	40
H(8A)	-2278	-5694	-685	42
H(8B)	-3210	-5321	80	42
H(9A)	-908	-4001	-370	33
H(9B)	-1068	-4496	658	33
H(11A)	-817	-2843	1602	33
H(12A)	-2359	-1174	1700	39
H(12B)	-1464	-400	1085	39
H(13A)	-639	-45	2761	42
H(13B)	-351	-1458	2928	42
H(14A)	1082	96	1802	53
H(14B)	1765	-517	2791	53
H(15A)	2378	-1583	1450	50
H(15B)	1602	-2450	2079	50
H(17A)	1536	-1737	-176	41
H(17B)	-64	-2118	-605	41

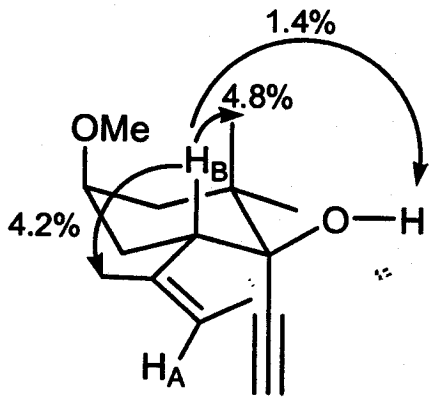
Table 6. Torsion angles [deg] for lb006.

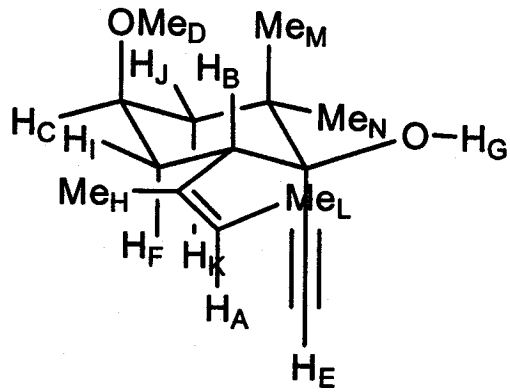
C(6)-C(1)-C(2)-C(3)	61.1(3)
C(1)-C(2)-C(3)-C(4)	-62.1(3)
C(2)-C(3)-C(4)-C(5)	55.2(4)
C(18)-O(1)-C(5)-C(4)	-151.1(3)
C(18)-O(1)-C(5)-C(7)	87.7(3)
C(18)-O(1)-C(5)-C(6)	-29.9(3)
C(3)-C(4)-C(5)-O(1)	68.8(3)
C(3)-C(4)-C(5)-C(7)	-171.6(3)
C(3)-C(4)-C(5)-C(6)	-43.4(4)
C(2)-C(1)-C(6)-C(10)	-161.4(2)
C(2)-C(1)-C(6)-C(5)	-50.2(3)
O(1)-C(5)-C(6)-C(1)	-76.8(3)
C(4)-C(5)-C(6)-C(1)	39.9(3)
C(7)-C(5)-C(6)-C(1)	167.8(2)
O(1)-C(5)-C(6)-C(10)	44.5(2)
C(4)-C(5)-C(6)-C(10)	161.2(3)
C(7)-C(5)-C(6)-C(10)	-70.9(3)
O(1)-C(5)-C(7)-C(8)	-49.1(3)
C(4)-C(5)-C(7)-C(8)	-168.8(3)
C(6)-C(5)-C(7)-C(8)	61.4(3)
C(5)-C(7)-C(8)-C(9)	-44.8(3)
C(7)-C(8)-C(9)-C(10)	45.8(3)
C(8)-C(9)-C(10)-C(6)	-62.3(3)
C(8)-C(9)-C(10)-C(11)	161.5(3)
C(8)-C(9)-C(10)-C(18)	45.5(3)
C(1)-C(6)-C(10)-C(9)	-171.4(2)
C(5)-C(6)-C(10)-C(9)	69.3(3)
C(1)-C(6)-C(10)-C(11)	-43.2(4)
C(5)-C(6)-C(10)-C(11)	-162.4(3)
C(1)-C(6)-C(10)-C(18)	76.7(3)
C(5)-C(6)-C(10)-C(18)	-42.5(3)
C(9)-C(10)-C(11)-C(16)	59.7(3)
C(6)-C(10)-C(11)-C(16)	-69.2(4)
C(18)-C(10)-C(11)-C(16)	174.7(3)
C(9)-C(10)-C(11)-C(12)	-171.1(2)
C(6)-C(10)-C(11)-C(12)	60.0(4)
C(18)-C(10)-C(11)-C(12)	-56.2(3)
C(16)-C(11)-C(12)-C(13)	-62.8(3)
C(10)-C(11)-C(12)-C(13)	163.2(3)
C(11)-C(12)-C(13)-C(14)	59.7(3)
C(12)-C(13)-C(14)-C(15)	-54.5(4)
C(13)-C(14)-C(15)-C(16)	54.5(4)
C(14)-C(15)-C(16)-C(17)	117.3(3)
C(14)-C(15)-C(16)-C(11)	-59.0(4)
C(12)-C(11)-C(16)-C(17)	-113.8(4)
C(10)-C(11)-C(16)-C(17)	20.6(5)
C(12)-C(11)-C(16)-C(15)	62.4(3)
C(10)-C(11)-C(16)-C(15)	-163.3(3)
C(5)-O(1)-C(18)-O(2)	-173.9(3)
C(5)-O(1)-C(18)-C(10)	2.2(3)
C(9)-C(10)-C(18)-O(2)	88.8(4)
C(6)-C(10)-C(18)-O(2)	-157.1(3)
C(11)-C(10)-C(18)-O(2)	-27.1(4)
C(9)-C(10)-C(18)-O(1)	-87.1(3)
C(6)-C(10)-C(18)-O(1)	27.0(3)
C(11)-C(10)-C(18)-O(1)	157.0(2)

Appendix 2

2D and NOE NMR Data

Table 1 2D and NOE NMR data for **3.12**



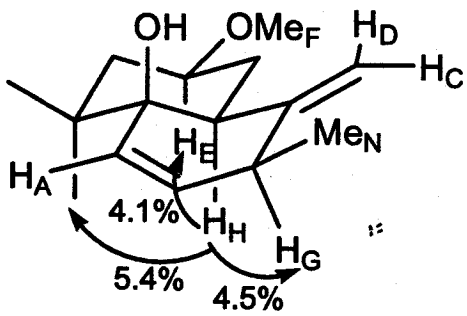


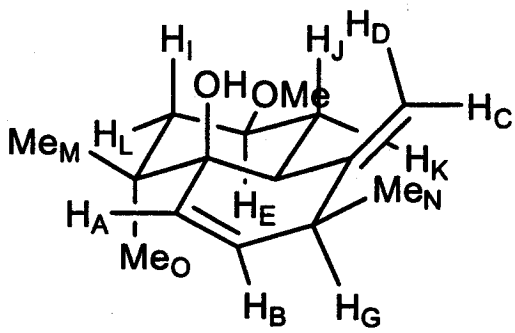
NOE difference data	
Irradiated proton	Correlation, (%)
A	H (1.6), L (2.4)
B	G [a] (1.4), H (4.2), M (4.8)

[a] Chemical shift of a hydroxy proton (G) was determined by addition of D_2O

COSY data	
Proton	Correlation
B	F, I
C	F, I, J, K
A	L, H
F	I, B, C
I	F, J, C
J	K, I, C
K	I, C
M	N
H	L, A
L	A, H

Table 2 2D and NOE NMR data for **3.16** (Chapter 3, Scheme 3.8)

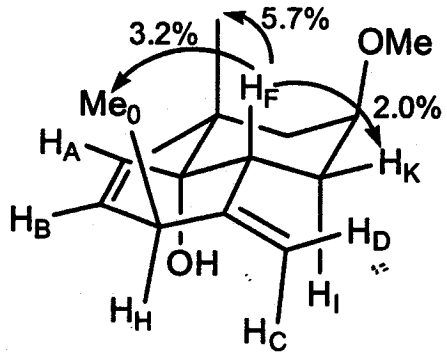


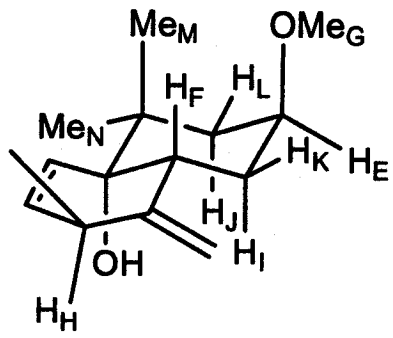


NOE difference data	
Irradiated proton	Correlation, (%)
C	D (8.5), N (5.3)
F	E (0.7)
N	G (2.6), C (2.4), B (1.5)
B	A (6.5), G (3.4)
A	B (4.6), M (5.6), O (2.6)
E	F (2.3), H (4.1), K (3.2), L (3.2), O (3.0)
H	G (4.5), E (4.1), K (2.6), O (5.4)
G	B (2.8), H (5.0), N (5.2)

HMQC data		COSY data	
^{13}C	Proton correlation	Proton	Correlation
106.6	C, D	A	B, G
55.6 (CH_3)	F	B	A, G
41.6	I, L	C and D	G, H
30.0	J, K	I	L, E, O
25.0 (CH_3)	M	E	I, L, J, K
24.2 (CH_3)	O	G	N, C, D, A, B
17.4 (CH_3)	N	H	J, K, C, D

Table 3 2D and NOE data for **3.17** (Chapter 3, Scheme 3.8)



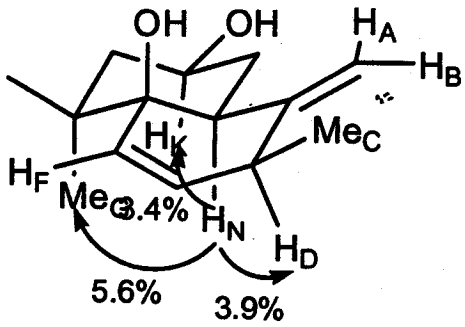


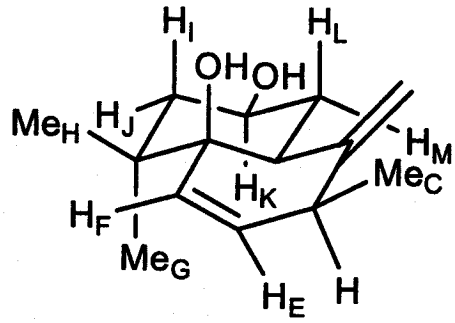
NOE difference data	
Irradiated proton	Correlation, (%)
O	H (1.7), F (1.0), B (0.5)
H	B (3.6), C (3.4), O (4.5)
G	E (1.1), K (0.8), L (0.5), M (0.4)
F	K (2.0), M (5.7), O (3.2)
E	G (2.5), K (2.0), I (3.5), J (6.0)
D	C (12.7), I (3.7), K (3.0)
C	D (13.8), H (3.5)
B	A (4.3), H (3.2), O (1.9)
A	B (3.9), M (2.3), N (5.2)

COSY	
Proton	Correlation
A	B
B	A, H
C	D, F
D	C, F
E	I, J, K, L
F	C, D, I, K
H	O, B
I	K, E, F
J	L, M, E

K	L (small), I, E, F

Table 4 2D and NOE NMR data for **3.25** (Chapter 3, Scheme 3.11)

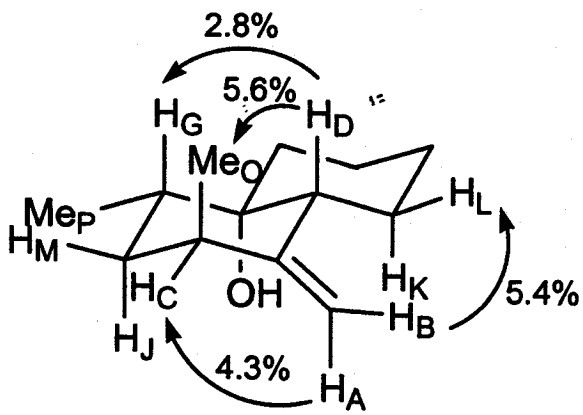




NOESY		COSY	
Proton	Observed correlation	Proton	Correlation
F	E, G, H	K	J, I, M, L
E	F, C	F	E, D
B	C, A	E	D, F
A	L, M, B	B	N, D
K	G, M, J, N	K	L, M, J, I
D	N, C	D	C, B, E, F
N	K, M, G, D	N	M, L, D, G, K
I	H, J	I	K, H, G
		M	J (small), N, K, L
		L	M, N, K

NOE difference data	
Irradiated proton	Correlation, (%)
E	F (4.6), D (2.4), C (2.3)
D	E (1.6), B (0.4), N (3.5), C (4.4)
N	D (3.9), M (1.8), G (5.6), K (3.4)
K	N (2.9), M (2.4), J (2.0), G (2.5)
C	D (1.6), B (1.5), E (1.0)

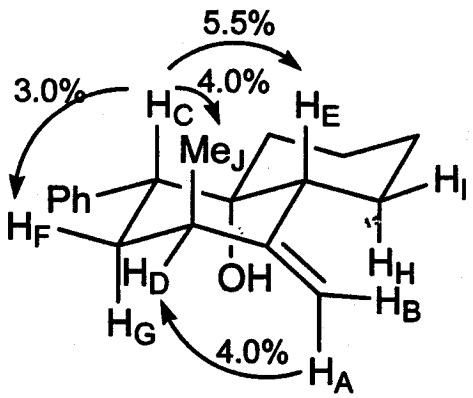
Table 5 COSY and NOE NMR data for **3.42** (Chapter 3, Table 3-1)



NOE difference data	
Irradiated proton	Correlation, (%)
D	O (5.6), L (2.4), G (2.8)
B	L (5.4), A (12.8)
C	A (4.9), O (4.5), M (1.4), J (2.8)
A	B (14.1), C (4.3)

COSY	
Proton	Observed correlation
O	C
P	G
A	B, D
B	A, D

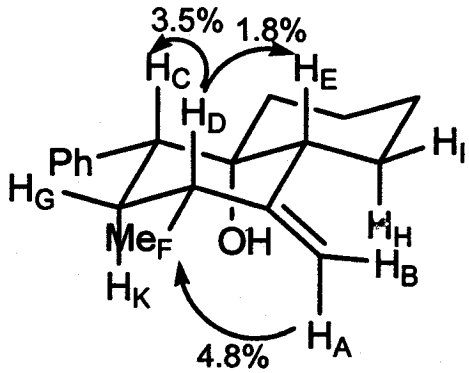
Table 6 NOE data for **3.43** (Chapter 3, Table 3-1)



NOE difference data	
Irradiated proton	Correlation, (%)
D	A (5.6), F (4.0), G (2.6), J (4.0)
C	E (5.5), J (3.9), F (3.0), phenyl protons (5.9)
A	B (2.9), D (4.5)
B	A (13.8), I (6.3)

HMQC	Proton correlation
49.3 (CH)	C
45.0 (CH)	E
39.1 (CH)	D
37.2 (CH_2)	F+G

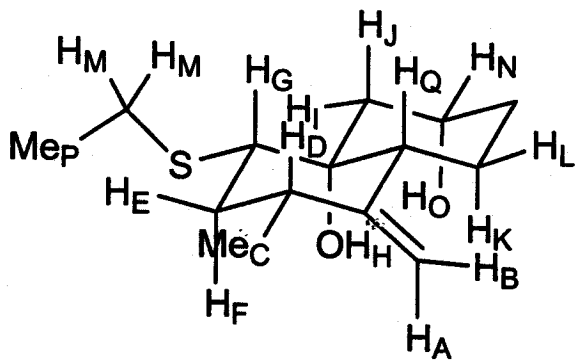
Table 7 COSYand NOE NMR data for **3.51** (Chapter 3, Table 3-2)



NOE difference data	
Irradiated proton	Correlation, (%)
D	C (3.5), E (1.8), F (3.7)
B	A (13.8), I (6.7)
A	B (11.3), F (4.8)
D	E (1.8), C (3.5), F (3.7)
E	C (5.3), I (3.3)

COSY	
Proton	Observed correlation
A	E (small)
B	E
D	F, G, K
C	G, K

Table 8 COSY and NOE NMR data for **3.52** (Chapter 3, Table 32)

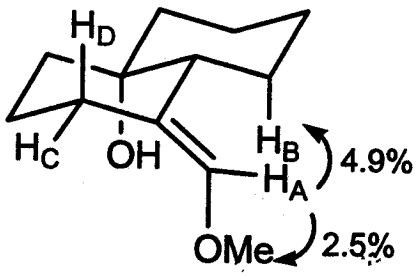


NOE difference data	
Irradiated proton	Correlation, (%)
A	B (11.0), C (5.1)
B	A (12.0), K (3.8), L (2.6)
C [a]	A (5.0), F (7.0), E (6.0), D (5.3)
D	G (3.6), E (2.6), C (3.9), Q (2.5)
E	F (14.0), G (2.9), C (2.0)
I	M (1.3), N (2.0), O (2.0), H (1.0), J (17.0)
J	I (8.0), G (5.0)

[a] Me group was irradiated together with proton H_J

COSY	
Proton	Observed correlation
I	J, O, N
M	P
G	E, F, P
E	F, D
D	F, E, C

Table 9 NOE difference, COSY and HMQC data for **2.41** (See Chapter 2)

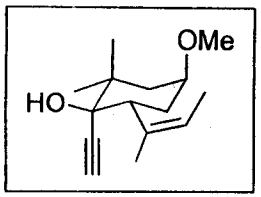


Chemical Shift for some protons, (500 MHz, C_6D_6), δ_{ppm}:

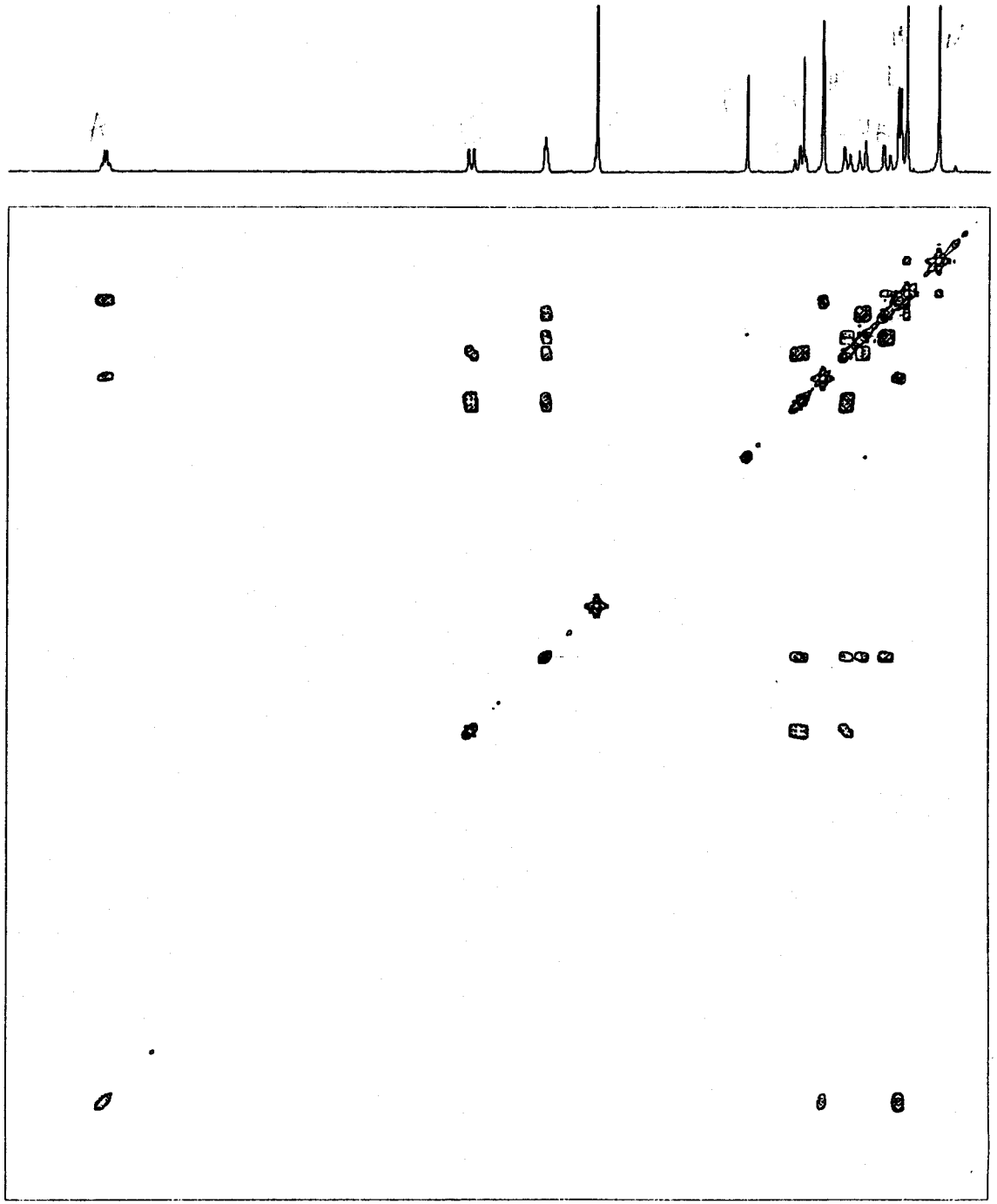
H_A 5.49 (d, J = 1.5 Hz), H_B 1.28-1.35 (m), H_C 1.52-1.48 (m), H_D 3.12-3.07 (m)

NOE difference data	
Irradiated proton	Correlation, (%)
A	B (4.9), Me (2.5)
Me and D together	A (1.0), C (1.8)

HMQC data		COSY data	
^{13}C (125 MHz, C_6D_6)	Proton correlation	Proton	Correlation
141.8	A (CH)	Me	none
118.7	C_4	D	C
71.1	C_4		
59.4	CH_3 at 3.15 ppm		
47.5	CH		
47.5	CH_2		
40.8	CH_2		
26.9	C and D		
26.7	CH_2		
24.1	CH_2		
23.3	CH_2		
22.1	CH_2		



1H COSY



Current Data Parameters

NAME	irina_test
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20040318
Time	19.47
INSTRUM	AV500WB
PROBHD	5 mm BBI 1H-BB
PULPROG	cosygpqf
TD	1024
SOLVENT	CDCl3
NS	8
DS	0
SWH	2357.424 Hz
FIDRES	2.311938 Hz
AQ	0.2183188 sec
RG	2896
DW	211.200 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	1.00000000 sec
d13	0.00000400 sec
D16	0.00010000 sec
IN0	0.00042240 sec
MCREST	0.00000000 sec
MCWRK	1.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P0	10.50 usec
P1	10.50 usec
PL1	3.00 dB
SFO1	500.1318028 MHz

====== GRADIENT CHANNEL =====

GPNAM1	SINE100
GPNAM2	SINE100
GPX1	0.00 %
GPX2	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPZ1	10.00 %
GPZ2	10.00 %
P16	1000.00 usec

F1 - Acquisition parameters

ND0	1
TD	256
SFO1	500.1318 MHz
FIDRES	9.247751 Hz
SW	4.734 ppm

F2 - Processing parameters

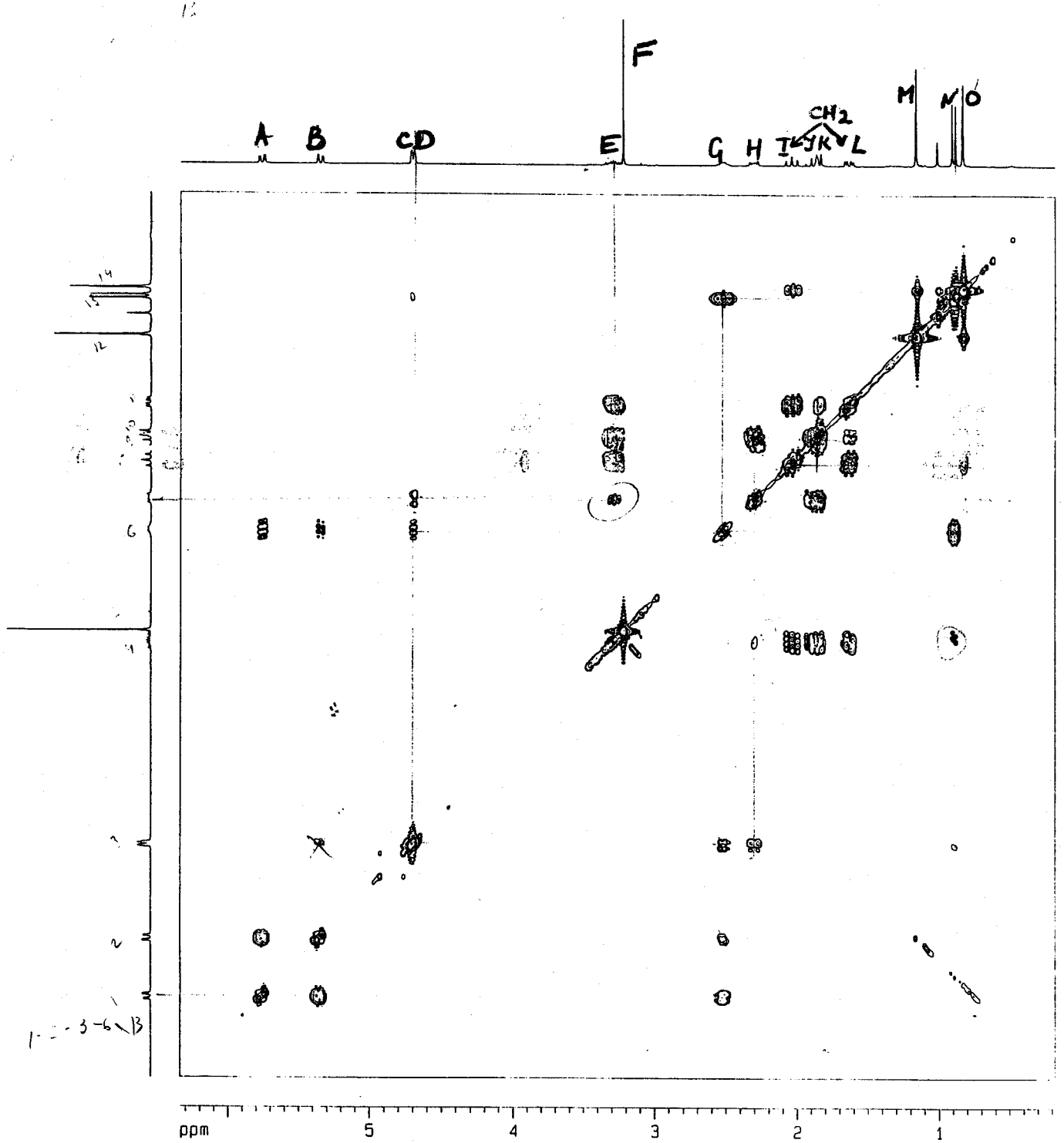
SI	1024
SF	500.1300049 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

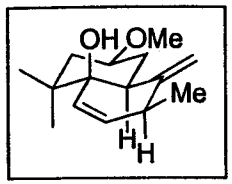
F1 - Processing parameters

SI	1024
MC2	QF
SF	500.1300049 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	5.962 ppm
F2LO	2981.62 Hz
F2PHI	1.228 ppm
F2HI	614.20 Hz
F1PLO	5.962 ppm
F1LO	2981.62 Hz
F1PHI	1.228 ppm
F1HI	614.20 Hz
F2PPMCM	0.31557 ppm/cm
F2HZCM	157.82628 Hz/cm
F1PPMCM	0.31557 ppm/cm





1H COSY

Current Data Parameters

NAME	irina_I
EXPNO	11
PROCNO	1

F2 - Acquisition Parameters

Date_	20030223
Time	4 21
INSTRUM	av300
PROBHD	5 mm ONP 1H/1
PULPROG	cosy45gpqf
TD	1024
SOLVENT	~~CDCl3~~ C_6D_6
NS	48
DS	0
SWH	1849 112 Hz
FIDRES	1 805774 Hz
AQ	0 2769396 sec
RG	5160 6
DW	270 400 usec
DE	6 00 usec
TE	300 0 K
d0	0 00000300 sec
D1	1 00000 0 sec
d13	0 0000 sec
D16	0 00010000 sec
IN0	0 sec
MCREST	0 sec
MCWRK	1 00000000 sec

CHANNEL f1

NUC1	1H
p0	4 88 usec
P1	9 75 usec
PL1	-3 00 dB
SFO1	300 1309788 MHz

GRADIENT CHANNEL

GPNAM1	sine 100
GPNAM2	sine 100
GPX1	0 00 %
GPX2	0 00 %
GPY1	0 00 %
GPY2	0 00 %
GPZ1	10 00 %
GPZ2	10 00 %
P16	1000 00 usec

F1 - Acquisition parameters

MDD	1
TD	256
SFO1	300 131 MHz
FIDRES	7 223095 Hz
SW	6 161 ppm

F2 - Processing parameters

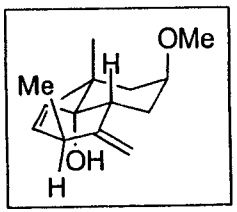
SI	1024
SF	300 1300000 MHz
WDW	SINE
SSB	0
LB	0 00 Hz
GB	0
PC	1 00

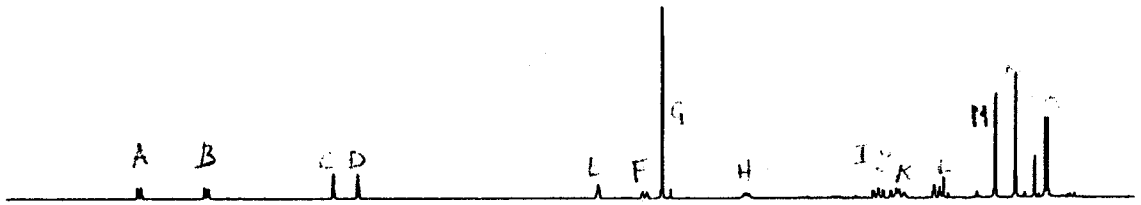
F1 - Processing parameters

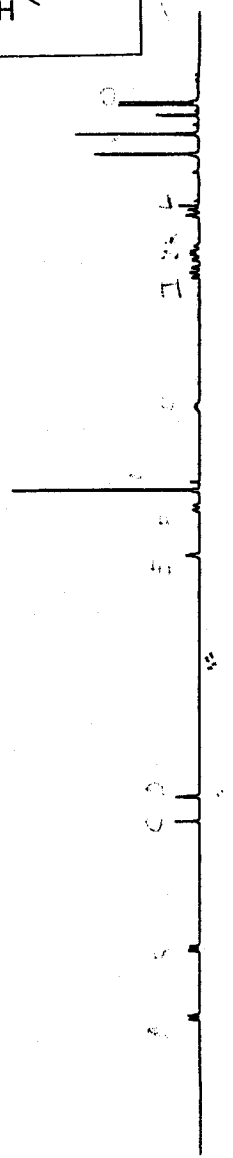
SI	1024
MC2	QF
SF	300 1300000 MHz
WDW	SINE
SSB	0
LB	0 00 Hz
GB	0

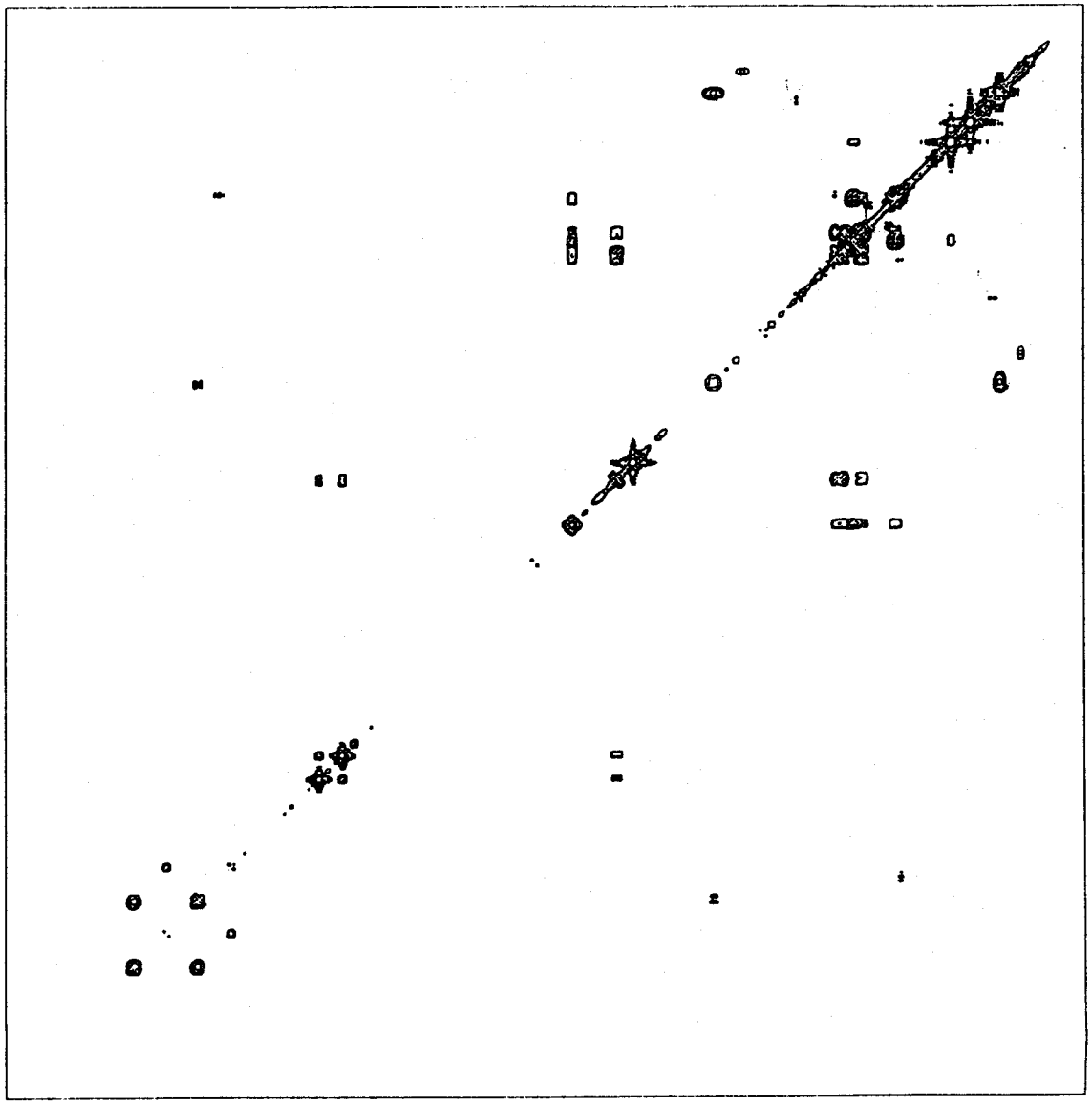
2D NMR plot parameters

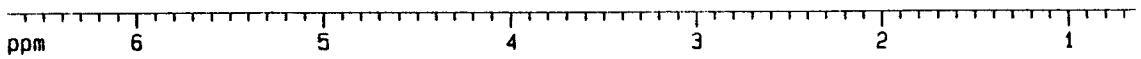
CX2	15 00 cm
CX1	15 00 cm
F2PLO	6 342 ppm
F2LO	1903 38 Hz
F2PHI	0 181 ppm
F2HI	54 27 Hz
F1PLO	6 342 ppm
F1LO	1903 38 Hz
F1PHI	0 181 ppm
F1HI	54 27 Hz
F2PPMCM	0 41074 ppm/cm
F2HZCM	123 27417 Hz/cm
F1PPMCM	0 41074 ppm/cm
F1HZCM	123 27417 Hz/cm

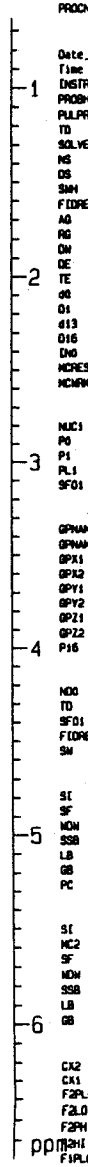












1H COSY

Current Data Parameters

NAME	irina_β-44min
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20040301
Time	19.38
INSTRUM	AV500MB
PROBHD	5 mm BBI 1H-BB
PULPROG	cosygpqf
TD	1024
SOLVENT	C6D6
NS	32
DS	0
SWH	3033.980 Hz
FIDRES	2.962872 Hz
AQ	0.1688052 sec
RG	512
DW	164.800 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	1.00000000 sec
d13	0.00000400 sec
D16	0.00010000 sec
DW0	0.00032960 sec
MCREST	0.00000000 sec
MCWRK	1.00000000 sec

-------- CHANNEL f1 --------

NUC1	1H
P0	10.50 usec
P1	10.50 usec
PL1	3.00 dB
SFO1	500.1318389 MHz

------ GRADIENT CHANNEL -----

GPNAM1	SINE100
GPNAM2	SINE100
GPX1	0.00 %
GPX2	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPZ1	10.00 %
GPZ2	10.00 %
P16	1000.00 usec

F1 - Acquisition parameters

NDO	1
TD	256
SFO1	500.1318 MHz
FIDRES	11.851485 Hz
SW	6.085 ppm

F2 - Processing parameters

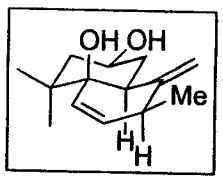
SI	1024
SF	500.1300049 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

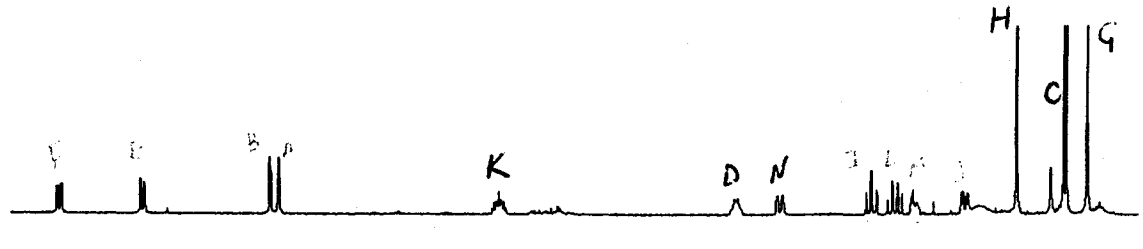
F1 - Processing parameters

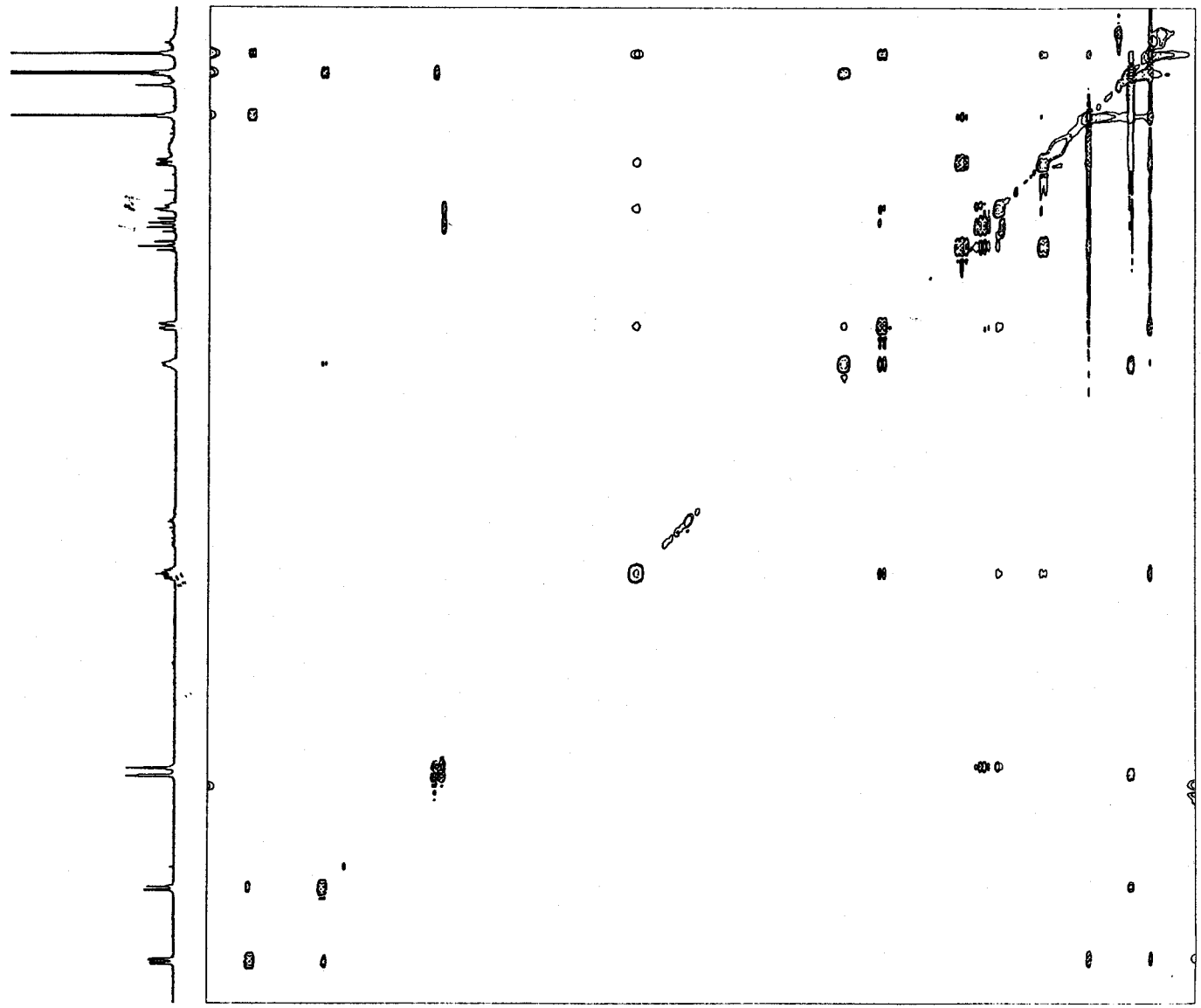
SI	1024
MC2	QF
SF	500.1300049 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	6.695 ppm
F2LO	3349.07 Hz
F2PHI	0.630 ppm
F2HI	315.09 Hz
F1PLO	6.695 ppm
F1LO	3349.07 Hz
F1PHI	0.630 ppm
F1HI	315.09 Hz
F2PPMCM	0.40443 ppm/cm
F2HZCM	202.26538 Hz/cm
F1PPMCM	0.40443 ppm/cm







1H NOESY/EXSY

Current Data Parameters

NAME	prina_β-76repeat
EXPNO	110
PROCNO	2

F2 - Acquisition Parameters

Date_	20040416
Time	0.09
INSTRUM	AV500NB
PROBHD	5 mm BBI 1H-BB
PULPROG	noesygppn
TD	1024
SOLVENT	H2O+D2O
NS	32
DS	2
SWH	2717.391 Hz
FIDRES	2.653702 Hz
AQ	0.1884660 sec
RG	90.51
DW	184.000 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	1.70000005 sec
D8	1.60000002 sec
D16	0.00010000 sec
d20	0.79850001 sec
IN0	0.00036800 sec
MCREST	0.00000000 sec
MCWRK	1.70000005 sec

-------- CHANNEL f1 --------

NUC1	1H
P1	10.50 usec
P2	21.00 usec
PL1	3.00 dB
SFO1	500.1316909 MHz

------ GRADIENT CHANNEL -----

GPNAM1	SINE100
GPNAM2	SINE100
GPX1	0.00 %
GPX2	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPZ1	40.00 %
GPZ2	-40.00 %
P16	1000.00 usec

F1 - Acquisition parameters

ND0	1
TD	256
SFO1	500.1317 MHz
FIDRES	10.614810 Hz
SW	5.433 ppm

F2 - Processing parameters

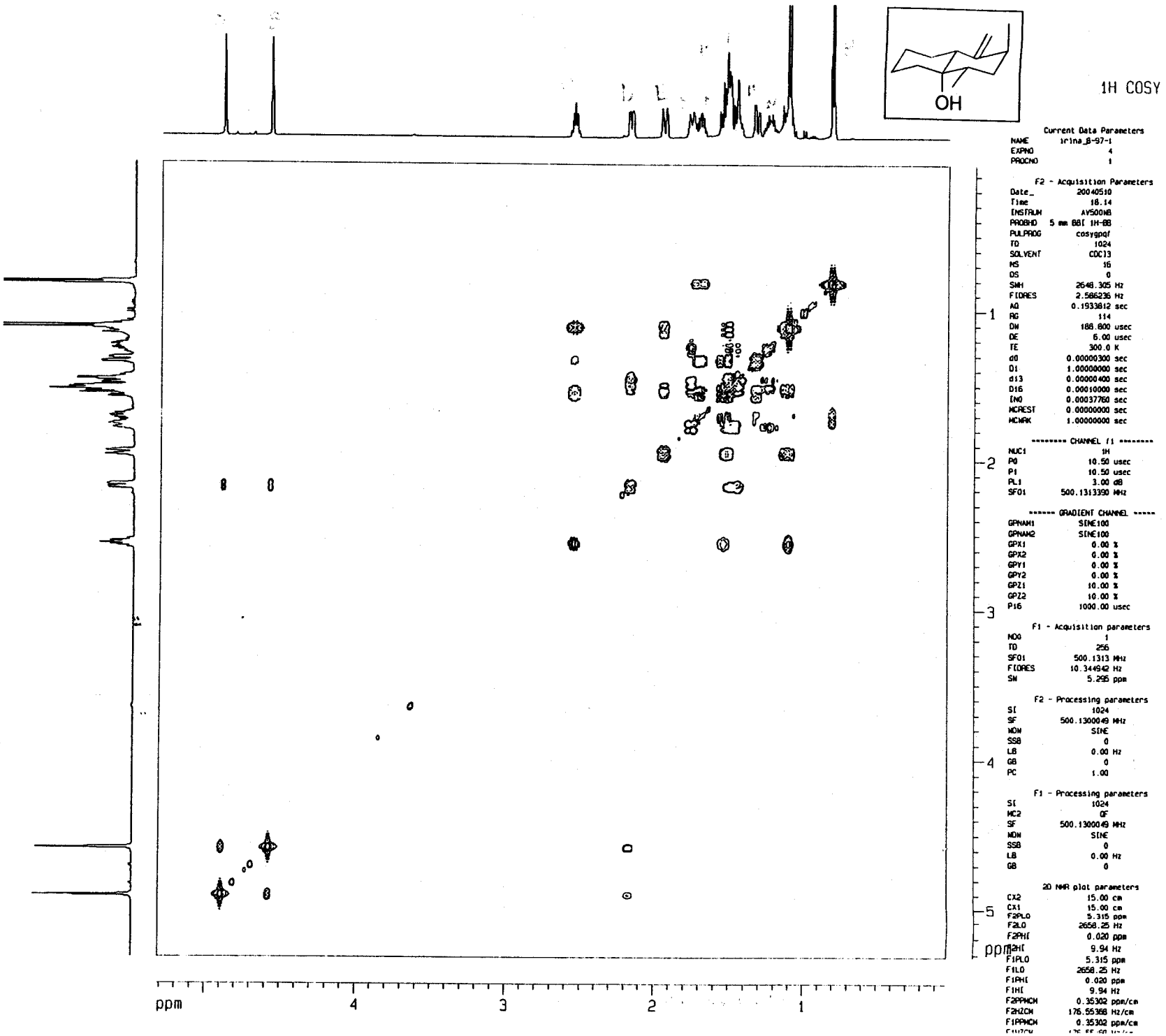
SI	1024
SF	500.1300049 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	1024
MC2	TPPI
SF	500.1300049 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	6.088 ppm
F2LO	3044.70 Hz
F2PHI	0.654 ppm
F2HI	327.31 Hz
F1PLO	6.088 ppm
F1LO	3044.70 Hz
F1PHI	0.654 ppm
F1HI	327.31 Hz
F2PPMCM	0.36222 ppm/cm
F2HZCM	181.15942 Hz/cm
F1PPMCM	0.36222 ppm/cm
F1HZCM	181.15942 Hz/cm



Current Data Parameters

NAME	ircina_8-97-1
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20040510
Time	18.14
INSTRUM	AV500NB
PROBHD	5 mm BBI 1H-BB
PULPROG	cosygpqf
TD	1024
SOLVENT	CDCl3
NS	16
DS	0
SWH	2648.305 Hz
FIDRES	2.586236 Hz
AQ	0.1933812 sec
RG	114
DW	188.800 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	1.00000000 sec
d13	0.00000400 sec
D16	0.00010000 sec
IN0	0.00037760 sec
MCREST	0.00000000 sec
MCWRK	1.00000000 sec

-------- CHANNEL f1 --------

NUC1	1H
P0	10.50 usec
P1	10.50 usec
PL1	3.00 dB
SFO1	500.1313390 MHz

------ GRADIENT CHANNEL -----

GPNAM1	SINE100
GPNAM2	SINE100
GPX1	0.00 %
GPX2	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPZ1	10.00 %
GPZ2	10.00 %
P16	1000.00 usec

F1 - Acquisition parameters

ND0	1
TD	256
SFO1	500.1313 MHz
FIDRES	10.344942 Hz
SW	5.295 ppm

F2 - Processing parameters

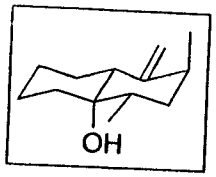
SI	1024
SF	500.1300049 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

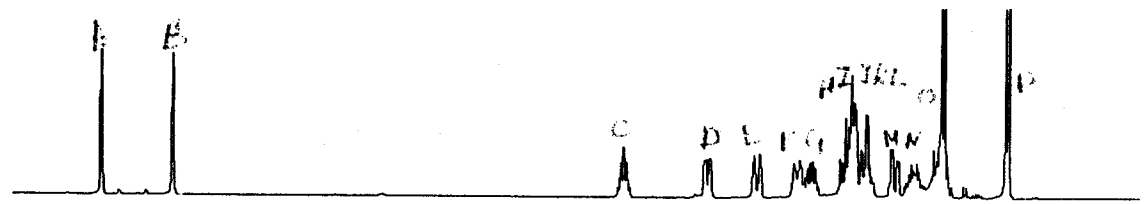
F1 - Processing parameters

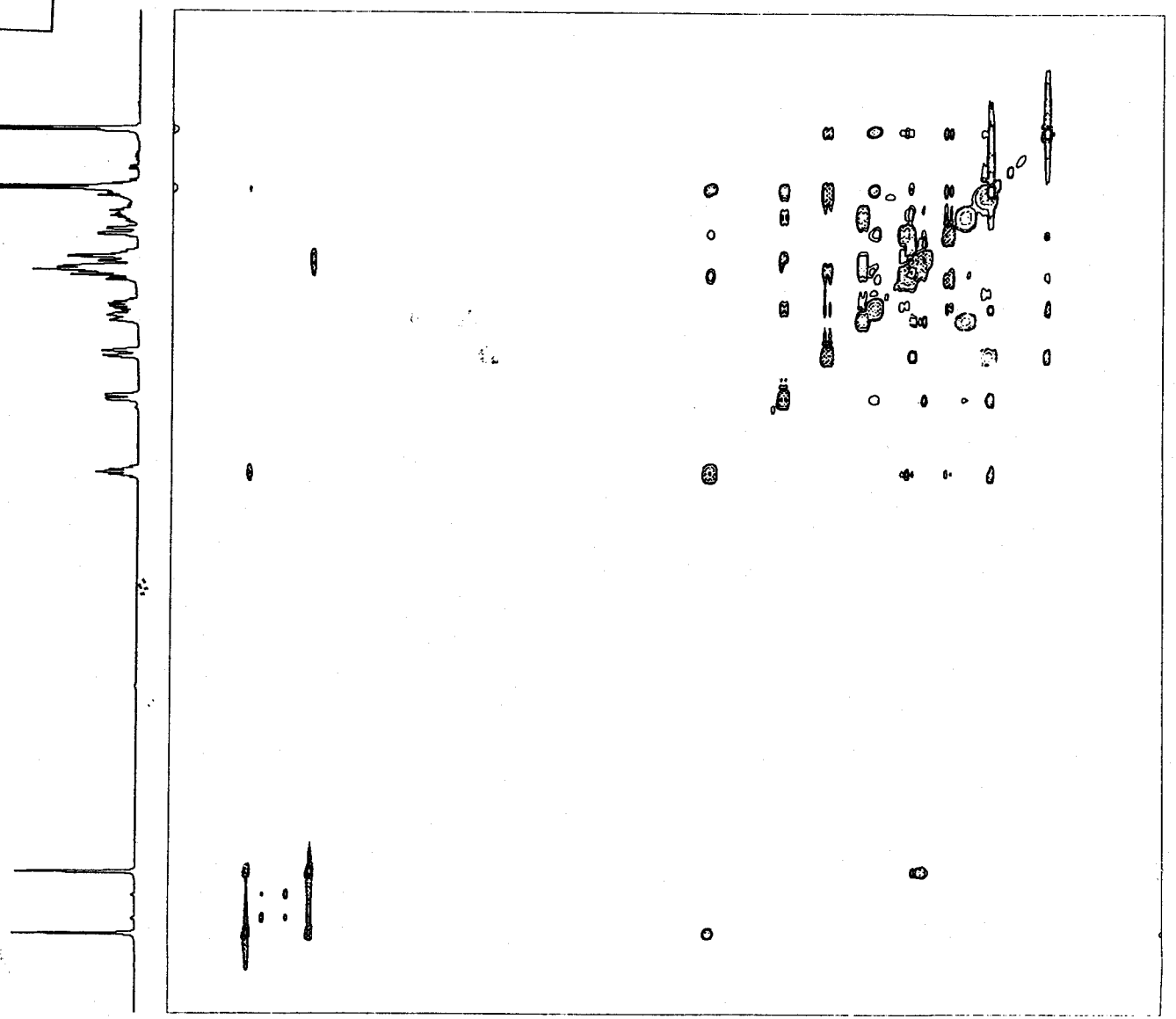
SI	1024
MC2	QF
SF	500.1300049 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	5.315 ppm
F2LO	2658.25 Hz
F2PHI	0.020 ppm
F2HI	9.94 Hz
F1PLO	5.315 ppm
F1LO	2658.25 Hz
F1PHI	0.020 ppm
F1HI	9.94 Hz
F2PPMCM	0.35302 ppm/cm
F2HZCM	176.55368 Hz/cm
F1PPMCM	0.35302 ppm/cm







1H NOESY/EXSY

Current Data Parameters

NAME	irina_β-97-1
EXPNO	5
PROCNO	100

F2 - Acquisition Parameters

Date_	20040510
Time	20.52
INSTRUM	AV500MB
PROBHD	5 mm BBI 1H-BB
PULPROG	noesygppn
TD	1024
SOLVENT	CDCl3
NS	32
DS	2
SWH	2540.650 Hz
FIDRES	2.481104 Hz
AQ	0.2015732 sec
RG	90.51
DW	196.800 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	2.00000000 sec
D8	1.79999995 sec
D16	0.00010000 sec
d20	0.89889997 sec
DW0	0.00039360 sec
MCREST	0.00000000 sec
MCWRK	2.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	10.50 usec
P2	21.00 usec
PL1	3.00 dB
SFO1	500.1313810 MHz

====== GRADIENT CHANNEL =====

GPNAM1	SINE100
GPNAM2	SINE100
GPX1	0.00 %
GPX2	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPZ1	40.00 %
GPZ2	-40.00 %
P16	1000.00 usec

F1 - Acquisition parameters

ND0	1
TD	256
SFO1	500.1314 MHz
FIDRES	9.924416 Hz
SW	5.080 ppm

F2 - Processing parameters

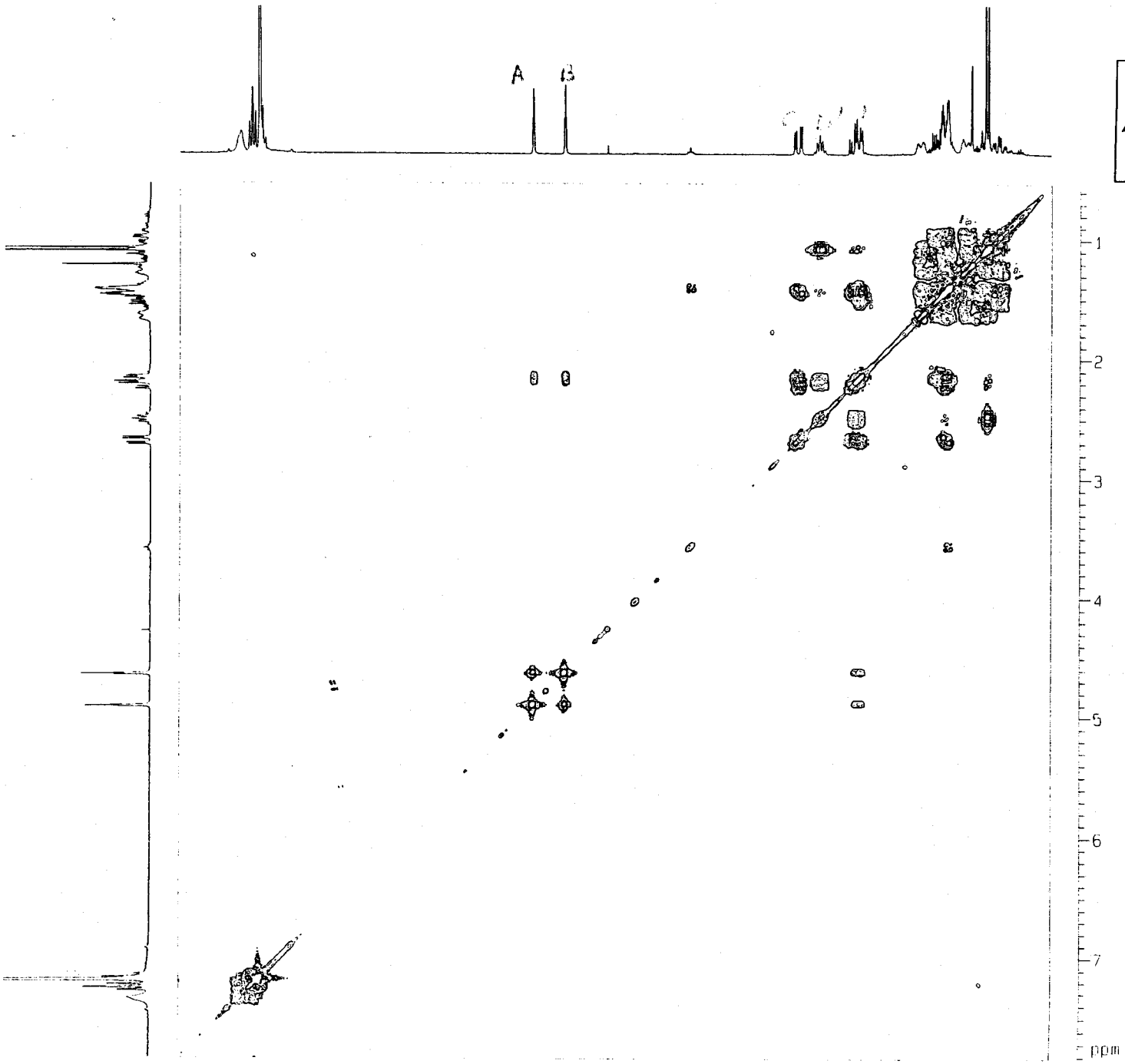
SI	1024
SF	500.1300049 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

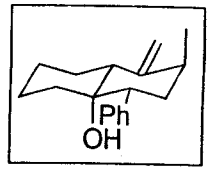
F1 - Processing parameters

SI	1024
MC2	TPPI
SF	500.1300049 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	5.292 ppm
F2LO	2646.46 Hz
F2PHI	0.212 ppm
F2HI	105.81 Hz
F1PLO	5.292 ppm
F1LO	2646.46 Hz
F1PHI	0.212 ppm
F1HI	105.81 Hz
F2PPMCM	0.33867 ppm/cm
F2HZCM	169.37669 Hz/cm
F1PPMCM	0.33867 ppm/cm





1H COSY

Current Data Parameters

NAME	irina_8-3pure
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20040205
Time	22 01
INSTRUM	av500
PROBHD	5 mm QNP 1H/1
PULPROG	cosy45gpqf
TD	1024
SOLVENT	CDCl3
NS	32
DS	0
SWH	2185 315 Hz
FIDRES	2 134096 Hz
AQ	0 2343412 sec
RG	5160 E
DW	228 800 usec
DE	6 00 usec
TE	300 0 K
d0	0 00000300 sec
D1	1 00000000 sec
d13	0 00000400 sec
D16	0 00010000 sec
in0	0 00045760 sec
MCREST	0 00000000 sec
MCWRK	1 00000000 sec

---------- CHANNEL f1 ----------

NUC1	1H
p0	5 25 usec
P1	10 50 usec
PL1	-3 00 dB
SFO1	300 1312521 MHz

---------- GRADIENT CHANNEL ----------

GPNAM1	sine.100
GPNAM2	sine.100
GPX1	0 00 %
GPX2	0 00 %
GPY1	0 00 %
GPY2	0 00 %
GPZ1	10 00 %
GPZ2	10 00 %
P16	1000 00 usec

F1 - Acquisition parameters

ND0	1
TD	256
SFO1	300 1313 MHz
FIDRES	6 536386 Hz
SW	7 281 ppm

F2 - Processing parameters

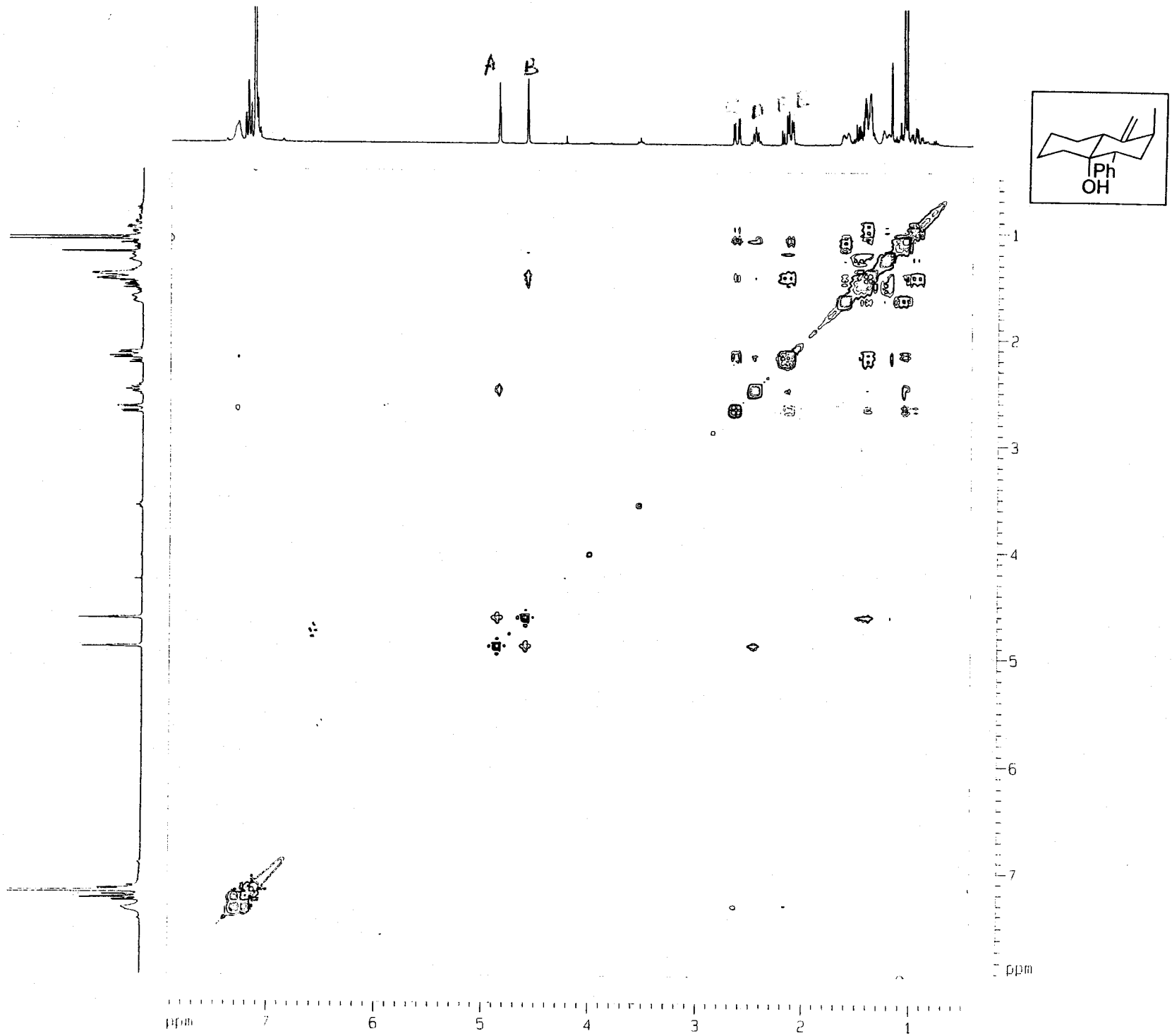
SI	1024
SF	300 1300000 MHz
WDW	SINE
SSB	0
LB	0 00 Hz
GB	0
PC	1 00

F1 - Processing parameters

SI	1024
MC2	QF
SF	300 1300000 MHz
WDW	SINE
SSB	0
LB	0 00 Hz
GB	0

2D NMR plot parameters

CX2	15 00 cm
CX1	15 00 cm
F2PLO	7 812 ppm
F2LO	2344 72 Hz
F2PHI	0 531 ppm
F2HI	159 40 Hz
F1PLO	7 812 ppm
F1LO	2344 72 Hz
F1PHI	0 531 ppm
F1HI	159 40 Hz
F2PPMCM	0 46542 ppm/cm
F2HZCM	149 68765 Hz/cm
F1PPMCM	0 46542 ppm/cm



1H NOESY

Current Data Parameters

NAME	irina_8-39pure
EXPNO	3
PROCNO	2

F2 - Acquisition Parameters

Date_	20040206
Time	1 00
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	noesyetgp
TD	1024
SOLVENT	CDCl3
NS	32
DS	8
SWH	2248 201 Hz
FIDRES	2 195509 Hz
AQ	0 2277876 sec
RG	7298 2
DW	222 400 usec
DE	6 00 usec
TE	300 0 K
d0	0 00000300 sec
D1	1 00000000 sec
D8	1 00000000 sec
d11	0 03000000 sec
D16	0 00010000 sec
DELTA	0 00110300 sec
DELTA1	0 00110800 sec
d20	0 00344480 sec
MCREST	0 00000000 sec
MCWRK	0 00750000 sec
STSCNT	128
TAU	0 00890000 sec

********** CHANNEL f1 **********

NUC1	1H
P1	10 50 usec
p2	21 00 usec
PL1	-3 00 dB
SFO1	300 1312556 MHz

********** GRADIENT CHANNEL **********

GPNAM1	sine 100
GPNAM2	sine 100
GPNAM3	sine 100
GPX1	0 00 %
GPX2	0 00 %
GPX3	0 00 %
GPY1	0 00 %
GPY2	0 00 %
GPY3	0 00 %
GPZ1	30 00 %
GPZ2	50 00 %
GPZ3	30 00 %
P16	1000 00 usec

F1 - Acquisition parameters

ND0	1
TD	256
SFO1	300 1313 MHz
FIDRES	8 782037 Hz
SW	7 491 ppm

F2 - Processing parameters

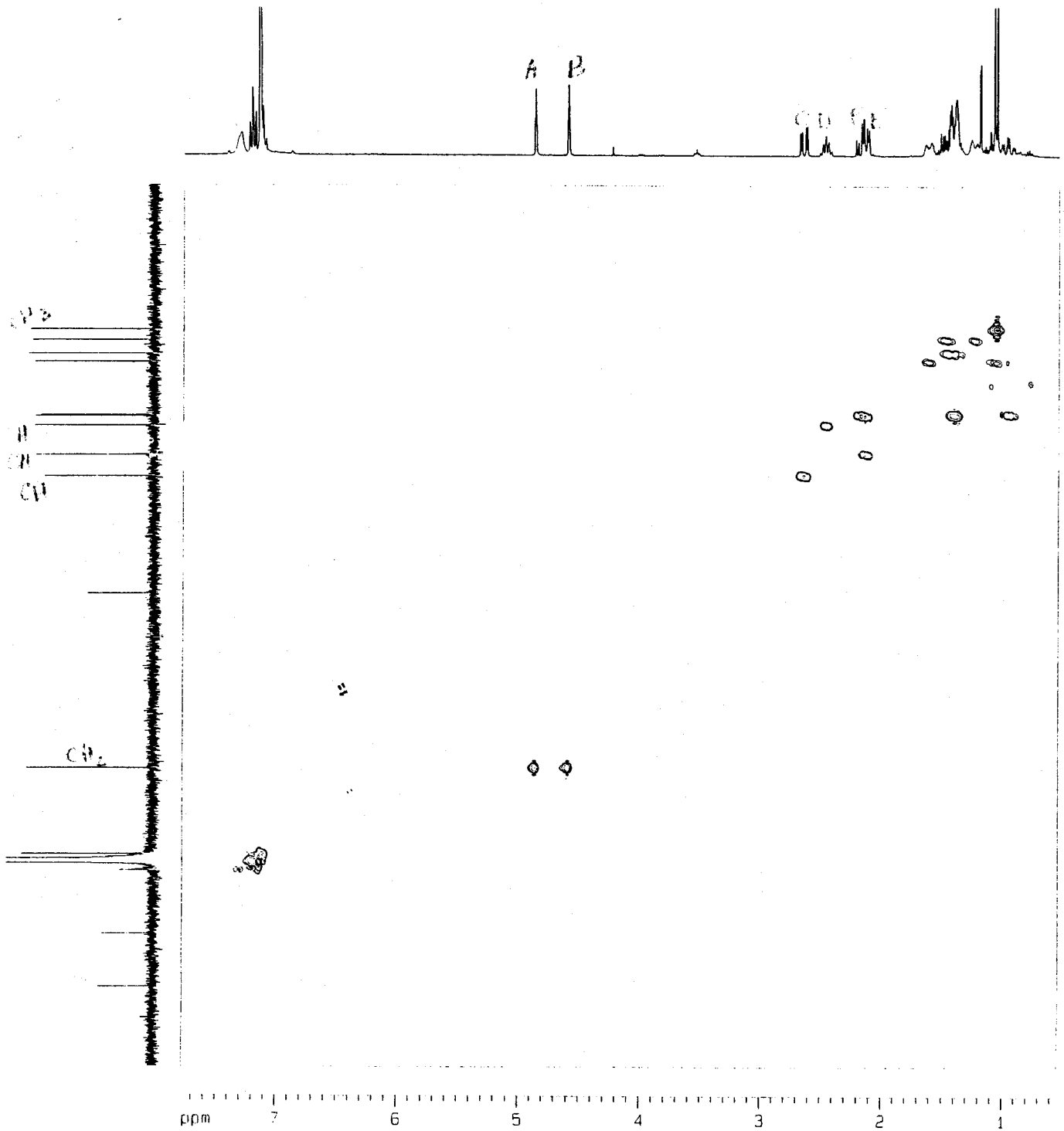
SI	1024
SF	300 1300000 MHz
WDW	QSINE
SSB	2
LB	0 00 Hz
GB	0
PC	1 00

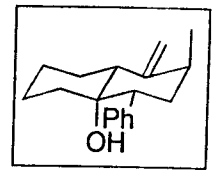
F1 - Processing parameters

SI	1024
MC2	echo-antiecho
SF	300 1300000 MHz
WDW	QSINE
SSB	2
LB	0 00 Hz
GB	0

2D NMR plot parameters

CX2	15 00 cm
CY1	15 00 cm
F2PLO	7 930 ppm
F2LO	2379 94 Hz
F2PHI	0 439 ppm
F2HI	131 74 Hz
F1PLO	7 930 ppm
F1LO	2379 94 Hz
F1PHI	0 439 ppm
F1HI	131 74 Hz
F2PPMCM	0 49938 ppm/cm
F2HZCM	149 88010 Hz/cm





1H 13C HMQC

Current Data Parameters

NAME	irina_8-39pure
EXPNO	7
PROCNO	1

F2 - Acquisition Parameters

Date_	20040207
Time	22 20
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	inv4gpqf
TD	1024
SOLVENT	CDCl3
NS	112
DS	2
SWH	2170 139 Hz
FIDRES	2 119276 Hz
AQ	0 2359796 sec
RG	13004
DW	230 400 usec
DE	6 00 usec
TE	300 0 K
CNST2	145 0000000
d0	0 00000300 sec
D1	1 00000000 sec
d2	0 00344828 sec
d12	0 00002000 sec
d13	0 00000400 sec
D16	0 00010000 sec
d20	0 00242428 sec
TN0	0 00003688 sec
MCREST	0 70000000
MCWRK	1 60000000 sec

********** CHANNEL f1 **********

NUC1	1H
P1	10 50 us
p2	21 0 usec
PL1	1 00 dB
SFO1	300 1312483 MHz

********** CHANNEL f2 **********

CPDPRG2	garp
NUC2	13C
P3	5 00 usec
PCPD2	70 00 usec
PL2	-6 00 dB
PL12	16 92 dB
SFO2	75 4737564 MHz

********** GRADIENT CHANNEL **********

GPNAM1	sine.100
GPNAM2	sine.100
GPNAM3	sine.100
GPX1	0 00 %
GPX2	0 00 %
GPX3	0 00 %
GPY1	0 00 %
GPY2	0 00 %
GPY3	0 00 %
GPZ1	50 00 %
GPZ2	30 00 %
GPZ3	40 10 %
P16	1000 00 usec

F1 - Acquisition parameters

ND0	2
TD	256
SFO1	75 47376 MHz
FIDRES	53 074047 Hz
SW	198 022 ppm

F2 - Processing parameters

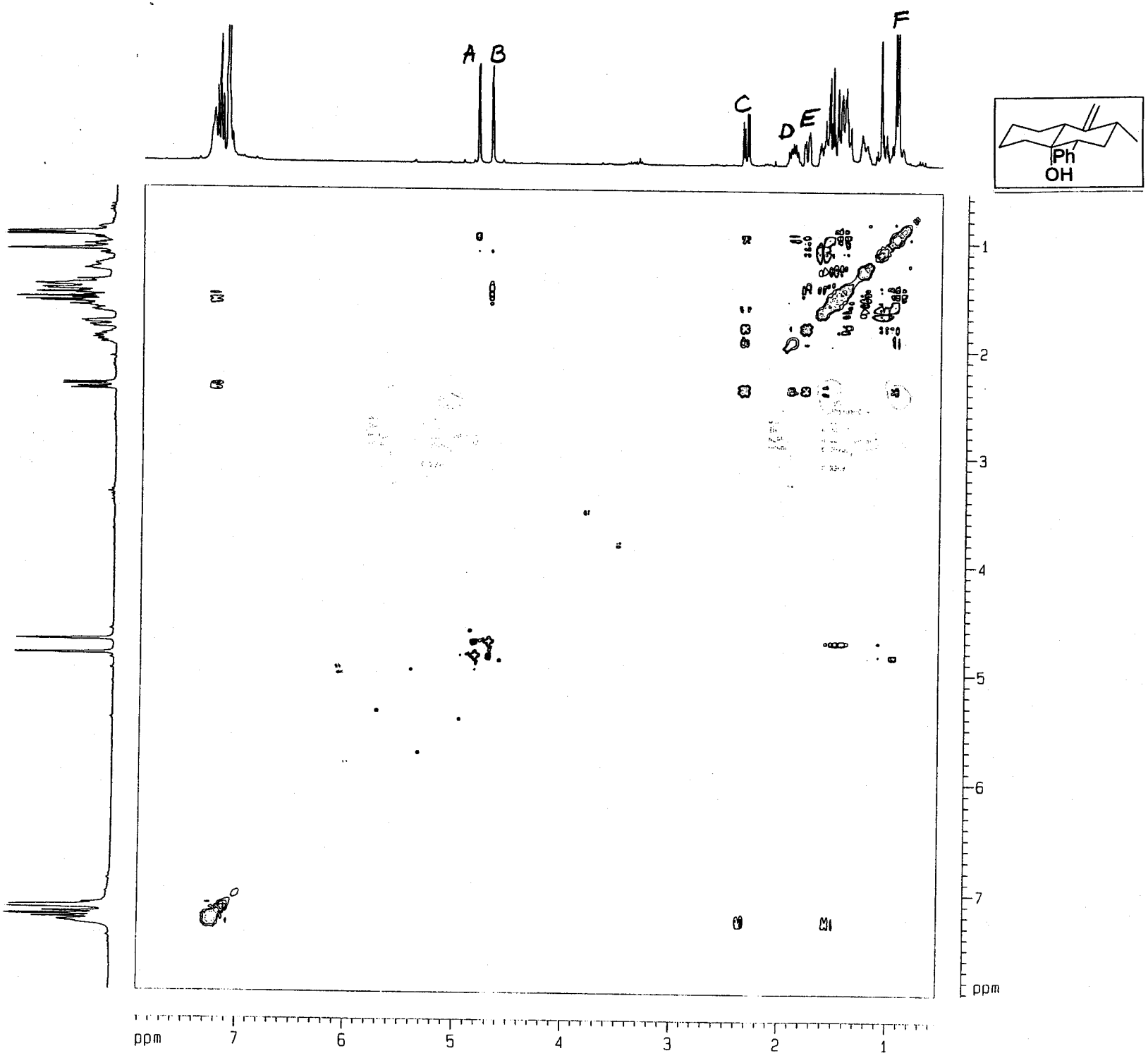
SI	512
SF	300 1300000 MHz
WDW	SINE
SSB	0
LB	0 00 Hz
GB	0
PC	1 00

F1 - Processing parameters

SI	512
MC2	QF
SF	75 4677190 MHz
WDW	SINE
SSB	0
LB	0 00 Hz
GB	0

2D NMR plot parameters

CX2	15 00 cm
CX1	15 00 cm
F2PLO	7 774 ppm
F2LO	2333 35 Hz
F2PHI	0 544 ppm
F2HI	163 21 Hz
F1PLO	170 018 ppm
F1LO	12636 88 Hz
F1PHI	10 613 ppm
F1HI	796 08 Hz
F2PPMCM	0 48204 ppm/cm
F2HZCM	144 67542 Hz/cm
F1PPMCM	12 80244 ppm/cm
F1HZCM	960 18311 Hz/cm



1H NOESY

Current Data Parameters

NA	irina_8-48purif
PR	3
	2

F2 - Acquisition Parameters

Date_	20040214
Time	2.27
INSTRUM	av300
PROBHD	5 mm GNP 1H/1
PULPROG	noesyetgp
TD	1024
SOLVENT	CDCl3
NS	32
DS	8
SWH	2216.312 Hz
FIDRES	2.164367 Hz
AQ	0.2310644 sec
RG	7298.2
DW	225.600 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	1.00000000 sec
D8	1.00000000 sec
d11	0.03000000 sec
D16	0.00010000 sec
DELTA	0.00110300 sec
DELTA1	0.00110800 sec
IN0	0.00045120 sec
MCREST	0.00000000 sec
MCWRK	0.00750000 sec
STSI	128
TAU	0.99830000 sec

CHANNEL f1

NUC1	1H
P1	10.50 usec
p2	21.00 usec
PL1	-3.00 dB
SFO1	300.1312686 MHz

GRADIENT CHANNEL

GPNAM1	sine.100
GPNAM2	sine.100
GPNAM3	sine.100
GPX1	0.00 %
GPX2	0.00 %
GPX3	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPY3	0.00 %
GPZ1	30.00 %
GPZ2	50.00 %
GPZ3	30.00 %
P16	1000.00 usec

F1 - Acquisition parameters

ND0	1
TD	256
SFO1	300.1313 MHz
FIDRES	8.657468 Hz
SW	7.384 ppm

F2 - Processing parameters

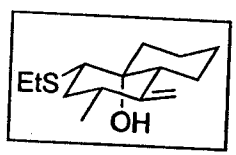
SI	1024
SF	300.1300000 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

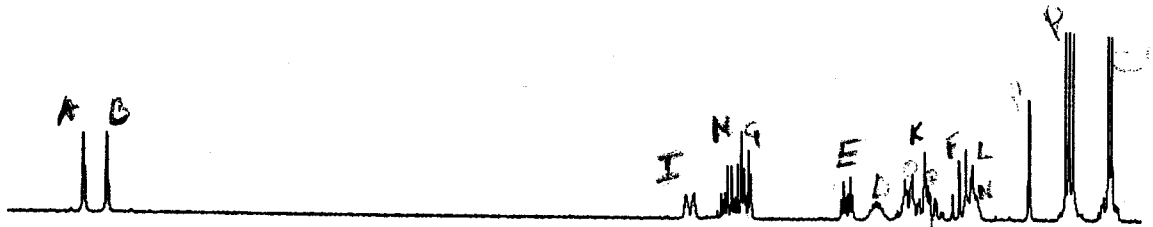
F1 - Processing parameters

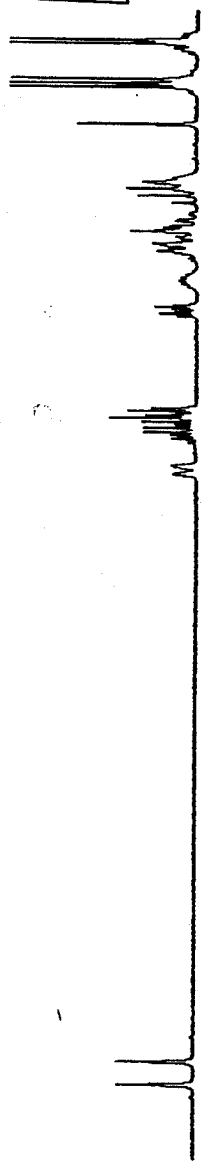
SI	1024
MC2	echo-antiecho
SF	300.1300000 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

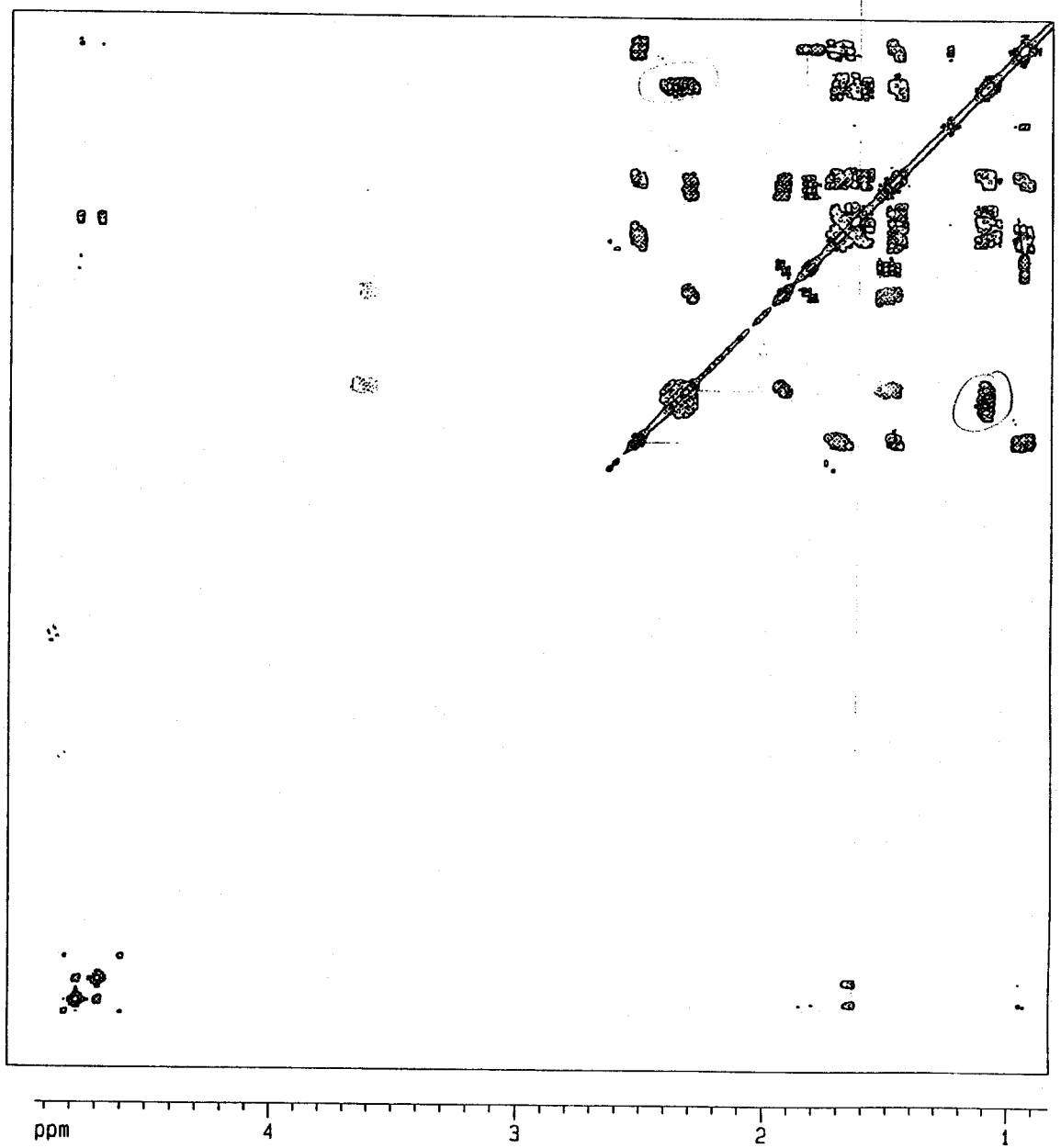
2D NMR plot parameters

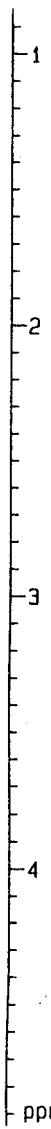
CX2	15.00 cm
CX1	15.00 cm
F2PLO	7.919 ppm
F2LO	2376.72 Hz
F2PHI	0.534 ppm
F2HI	160.41 Hz
F1PLO	7.919 ppm
F1LO	2376.72 Hz
F1PHI	0.534 ppm
F1HI	160.41 Hz
F2PPMCM	0.49230 ppm/cm
F2HZCM	147.75414 Hz/cm
F1PPMCM	0.49230 ppm/cm
F1HZCM	147.75414 Hz/cm











1H COSY

Current Data Parameters

NAME	irina_B-09-1
EXPNO	3
PROCNO	1

F2 - Acquisition Parameters

Date_	20040331
Time	19.22
INSTRUM	AV500NB
PROBHD	5 mm BBI 1H-BB
PULPROG	cosygpqf
TD	1024
SOLVENT	CDCl3
NS	16
DS	0
SWH	2111.487 Hz
FIDRES	2.061999 Hz
AQ	0.2425332 sec
RG	5161
DW	236.800 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	1.00000000 sec
d13	0.00000400 sec
D16	0.00010000 sec
IN0	0.00047360 sec
MCREST	0.00000000 sec
MCWRK	1.00000000 sec

--------- CHANNEL f1 ---------

NUC1	1H
P0	10.50 usec
P1	10.50 usec
PL1	3.00 dB
SFO1	500.1314761 MHz

------ GRADIENT CHANNEL -----

GPNAM1	SINE100
GPNAM2	SINE100
GPX1	0.00 %
GPX2	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPZ1	10.00 %
GPZ2	10.00 %
P16	1000.00 usec

F1 - Acquisition parameters

NDO	1
TD	256
SFO1	500.1315 MHz
FIDRES	8.247994 Hz
SW	4.222 ppm

F2 - Processing parameters

SI	1024
SF	500.1300629 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

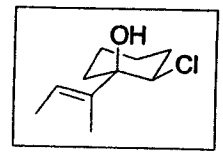
SI	1024
MC2	QF
SF	500.1300603 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

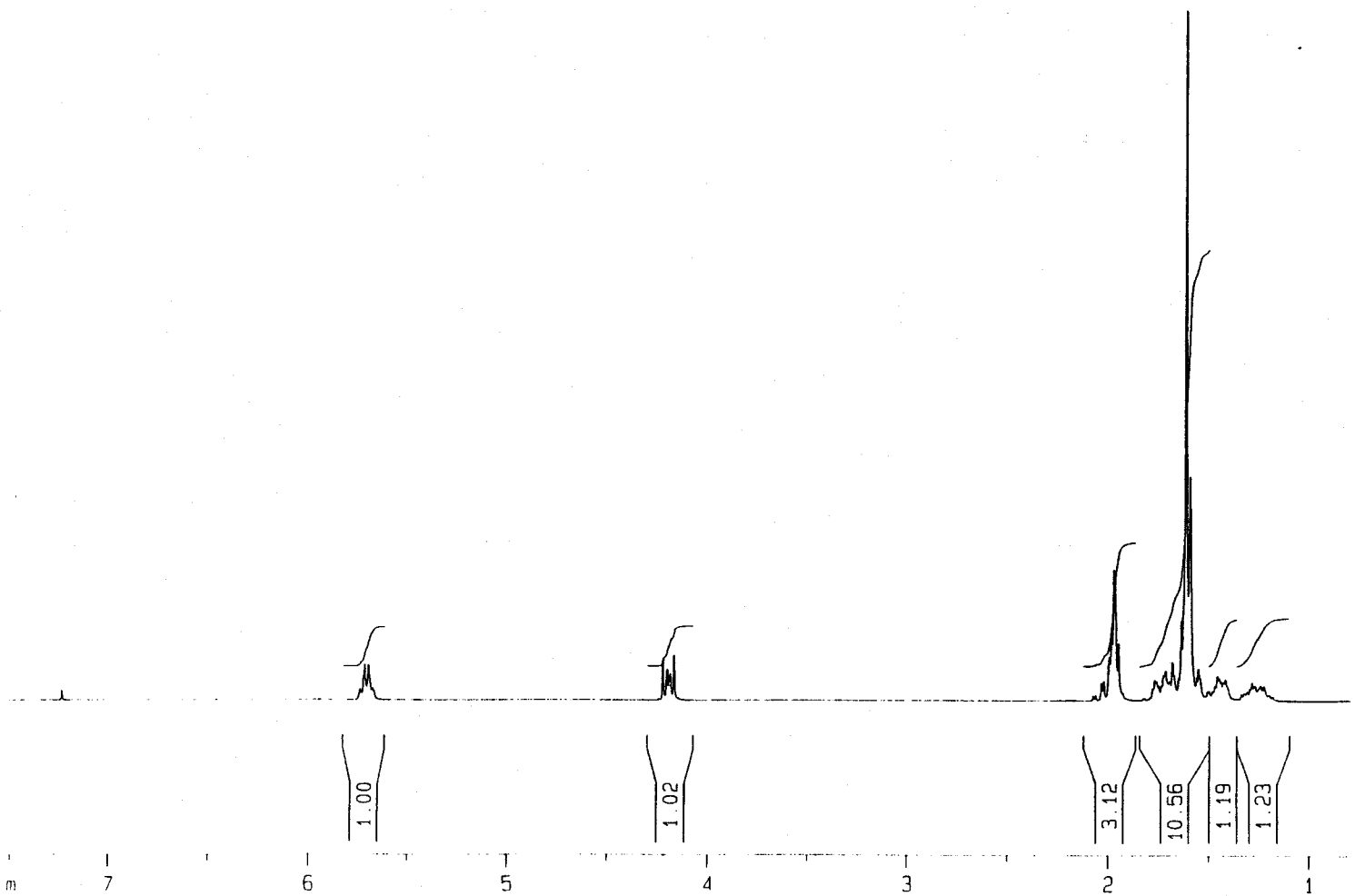
2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	5.053 ppm
F2LO	2526.98 Hz
F2PHI	0.831 ppm
F2HI	415.49 Hz
F1PLO	5.053 ppm
F1LO	2526.98 Hz
F1PHI	0.831 ppm
F1HI	415.49 Hz
F2PPMCM	0.28145 ppm/cm
F2HZCM	140.76579 Hz/cm
F1PPMCM	0.28145 ppm/cm

Appendix 3

^{1}H NMR Spectra





Current Data Parameters

NAME	irina_7-74
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20030825
Time	15.18
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	45.3
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

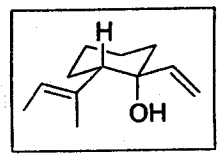
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

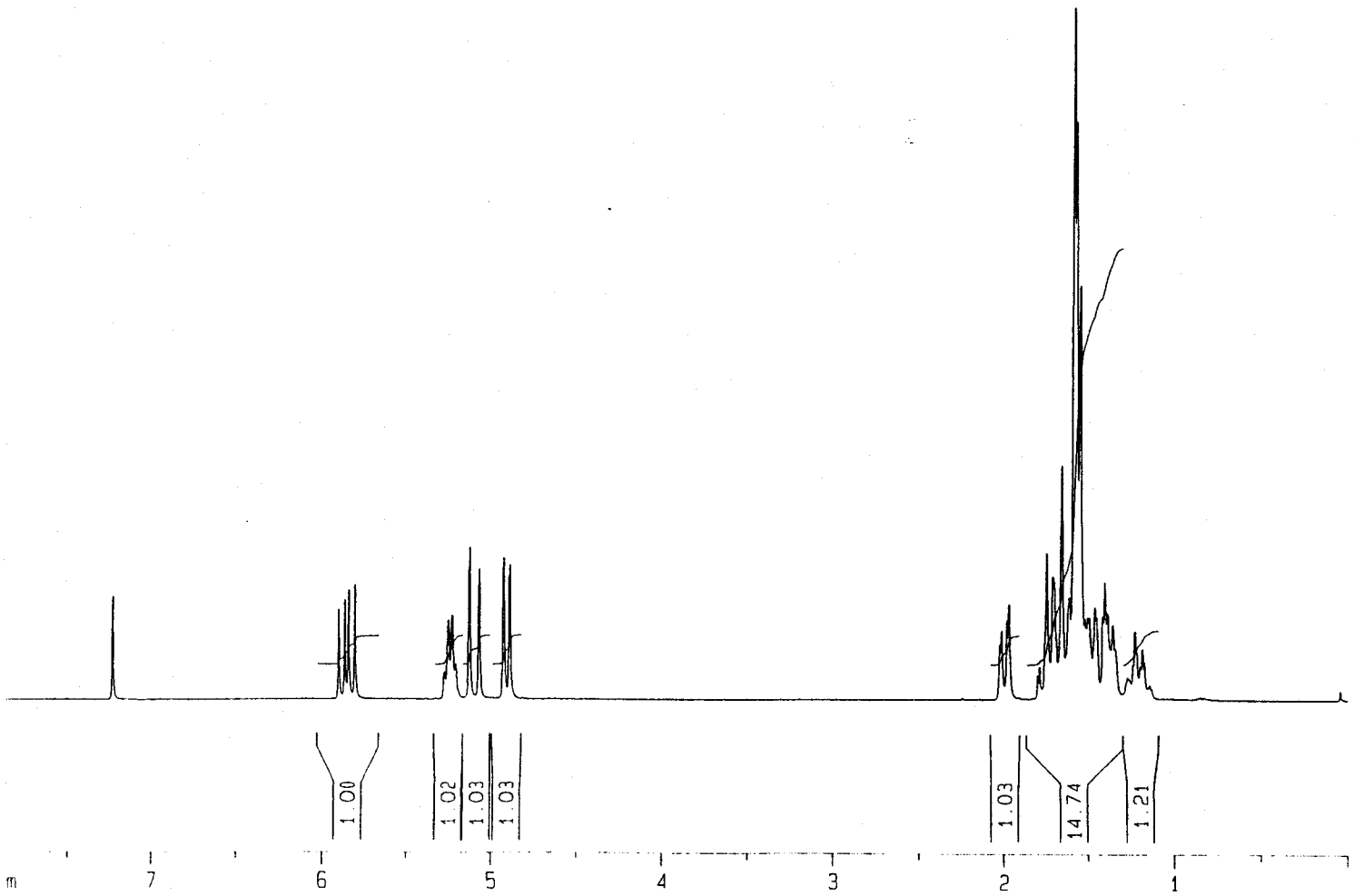
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	7.639 ppm
F1	2292.57 Hz
F2P	0.791 ppm
F2	237.52 Hz
PPMCM	0.34236 ppm/cm
HZCM	102.75206 Hz/cm





Current Data Parameters

NAME	irina_13dec
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20031213
Time	19.04
INSTRUM	av300
PROBHD	5 mm GNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	181
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

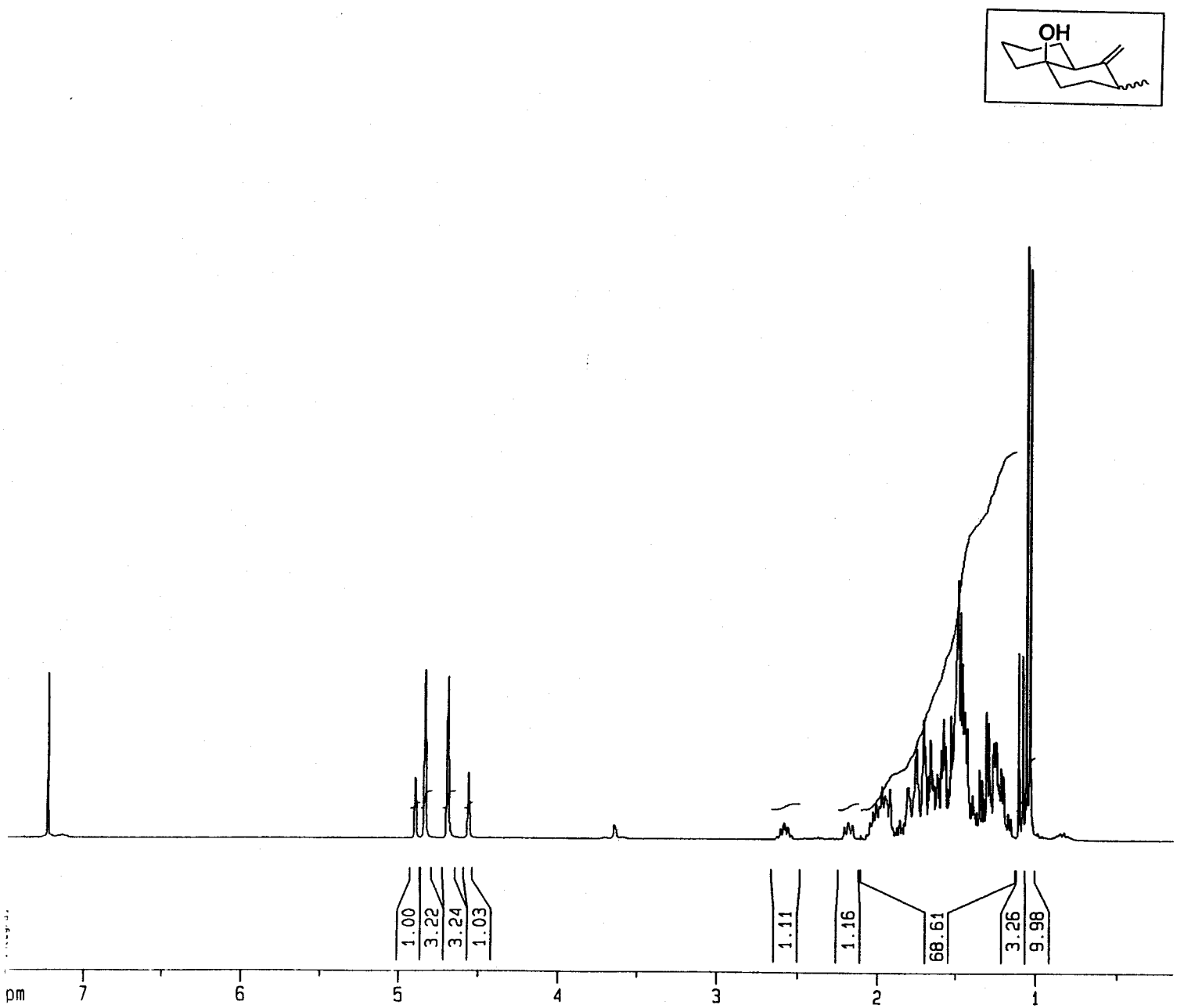
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

F2 - Processing parameters

SI	65536
SF	300.1300001 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm



Current Data Parameters

NAME	irina_8-67-p
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040511
Time	14.34
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	13
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	181
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

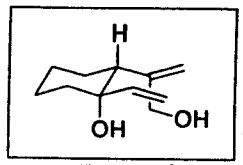
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

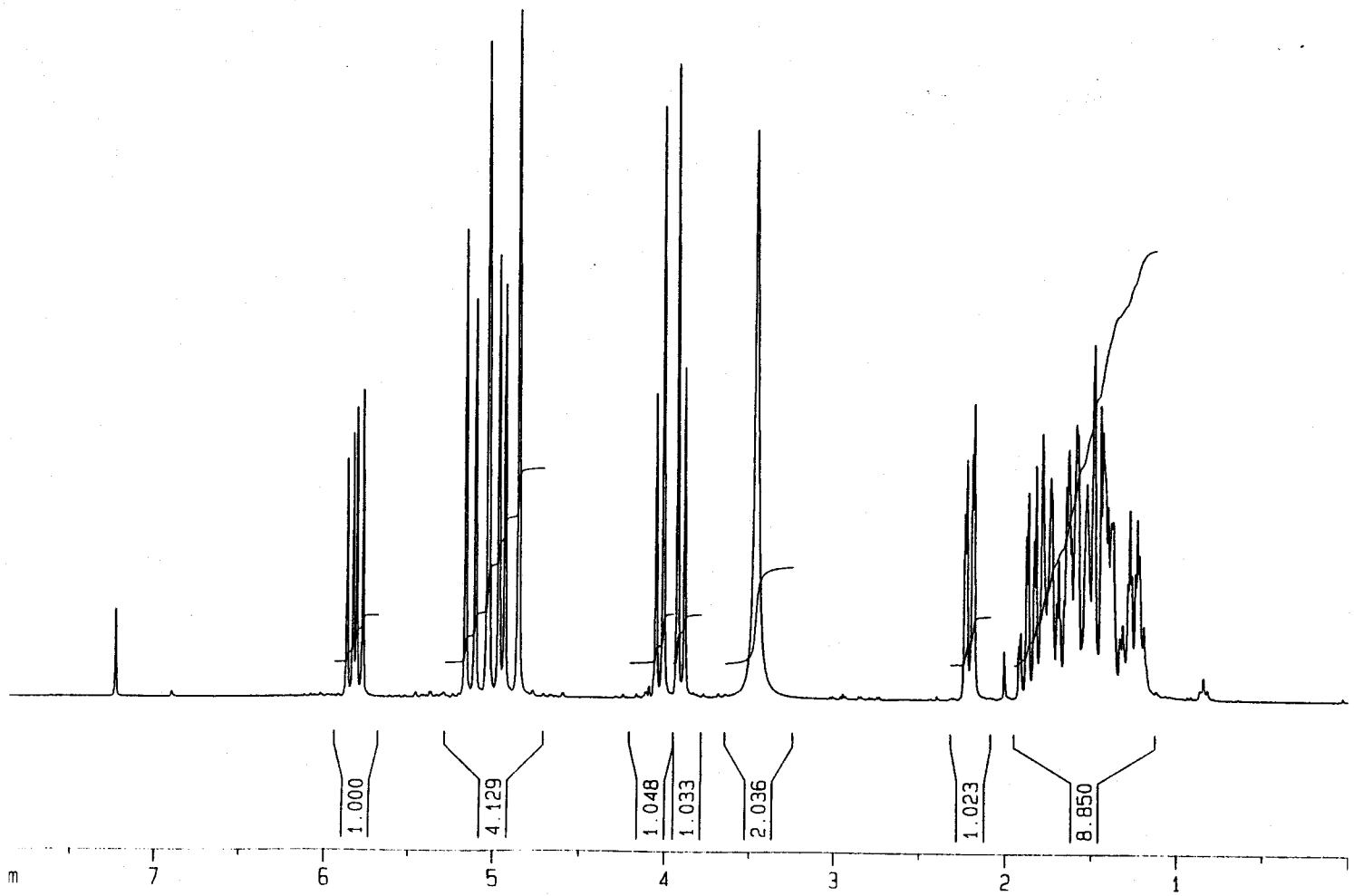
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	7.558 ppm
F1	2268.48 Hz
F2P	0.145 ppm
F2	43.50 Hz
PPMCM	0.37067 ppm/cm
HZCM	111.24892 Hz/cm





Current Data Parameters

NAME	irina_diol
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20031117
Time	17.31
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	80.6
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

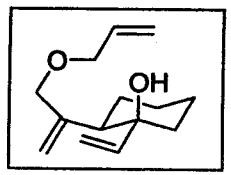
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

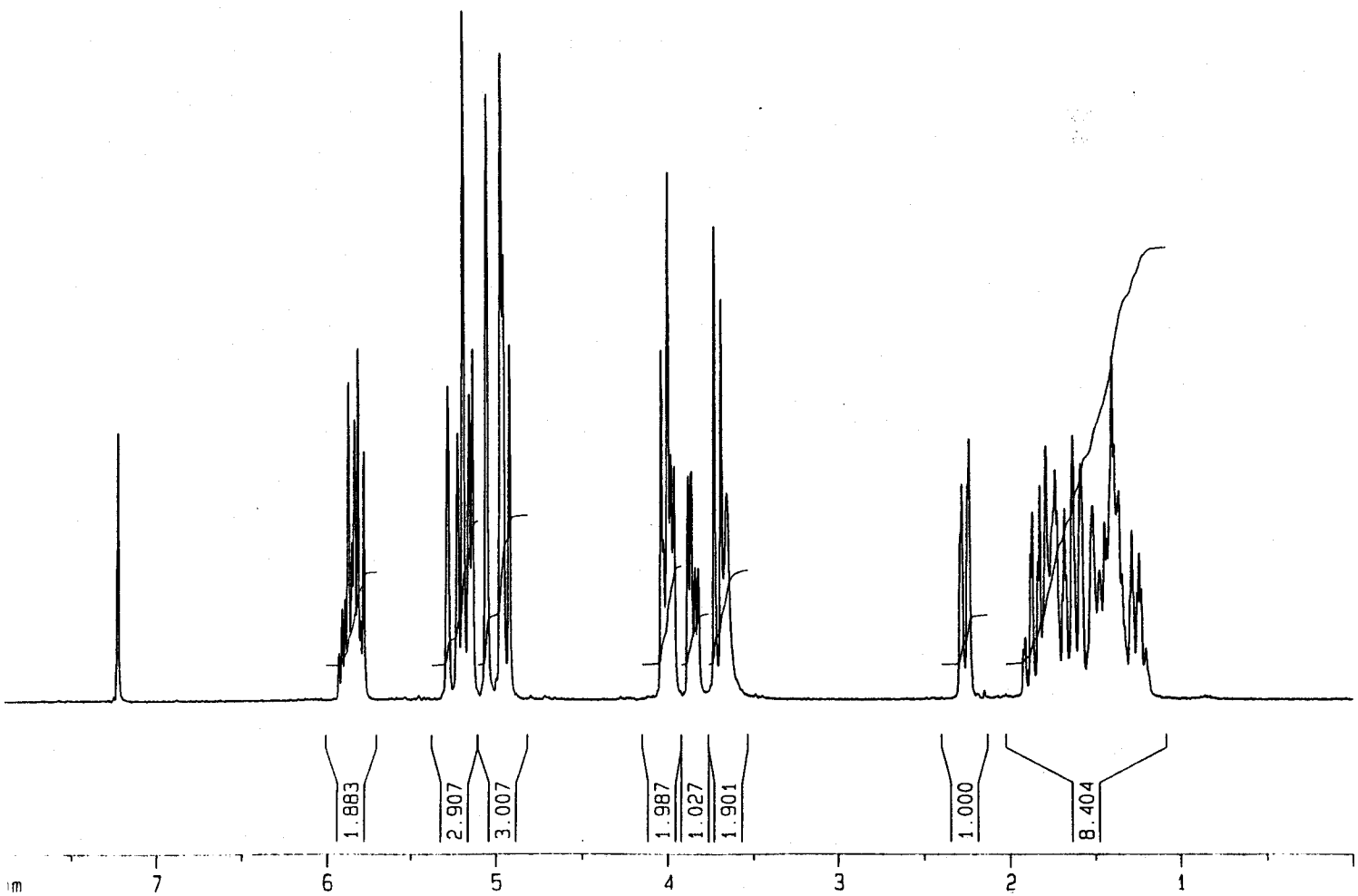
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





Current Data Parameters

NAME	irina_7-140
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20031120
Time	12.02
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	203.2
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

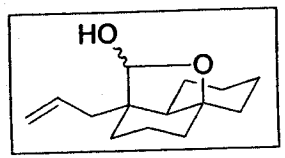
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

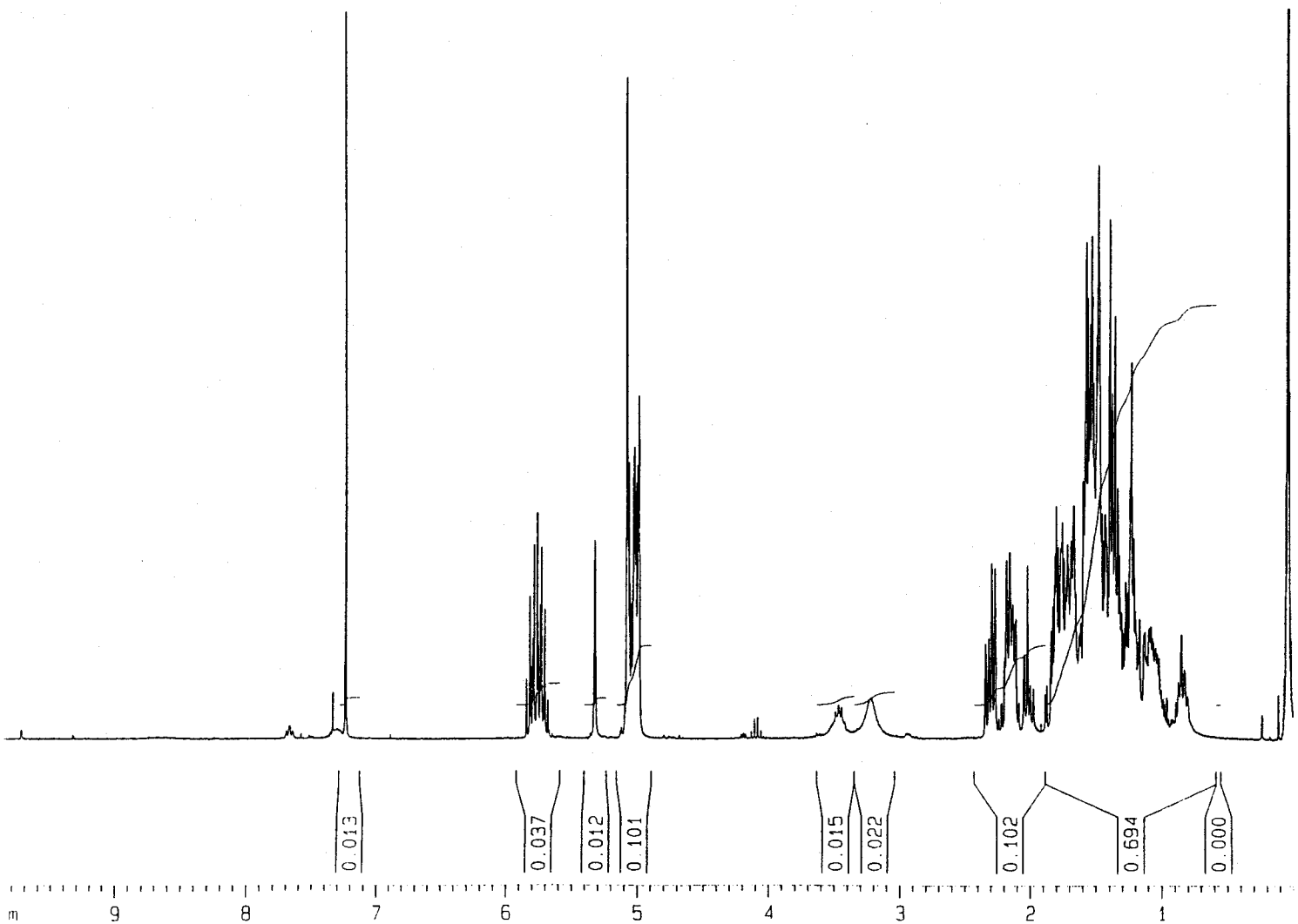
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





Current Data Parameters

NAME	irina_2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010124
Time	19.44
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	203.2
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

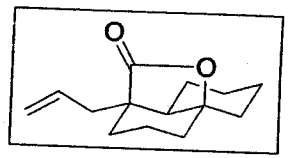
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

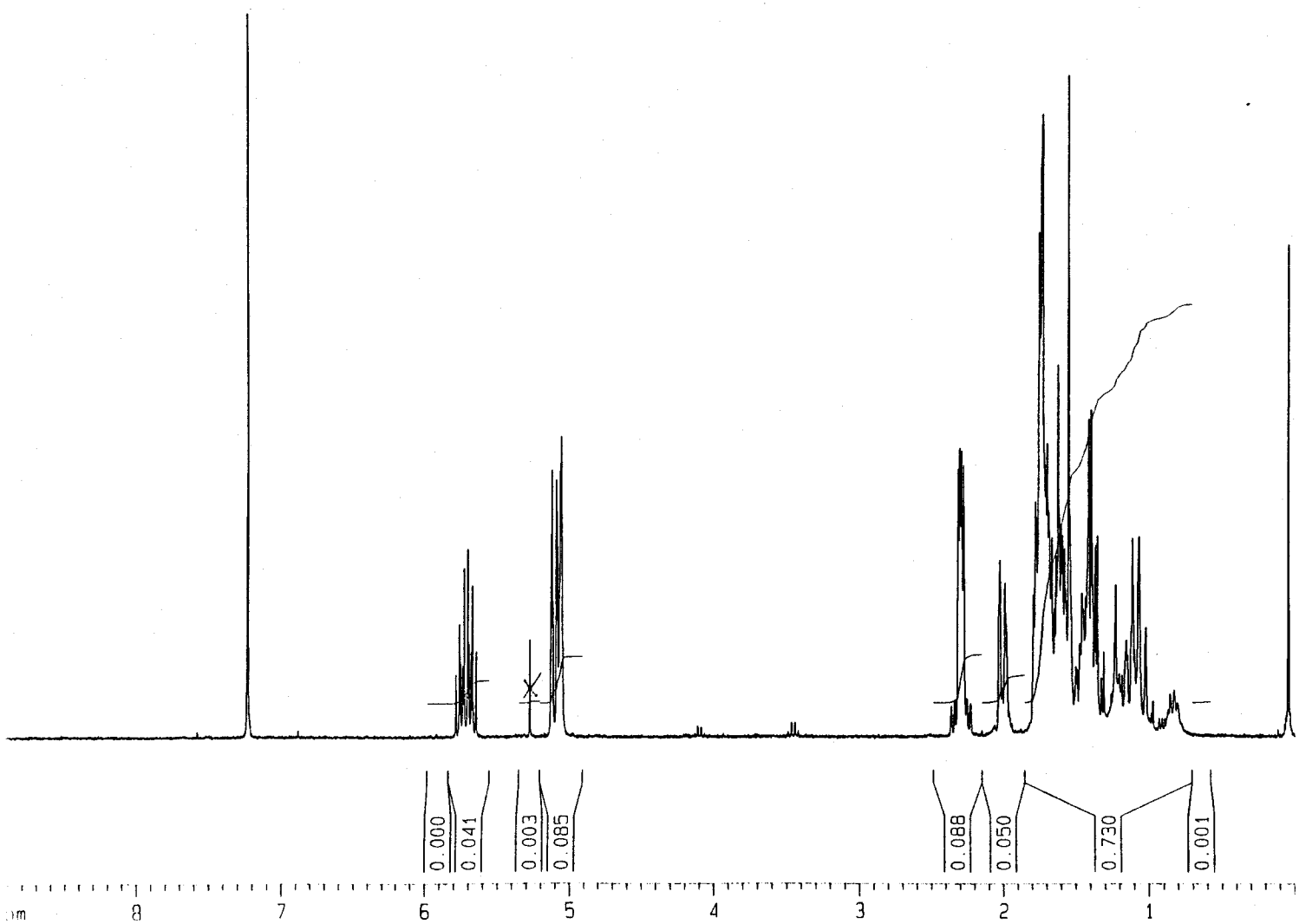
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.50000 ppm/cm
HZCM	150.06500 Hz/cm





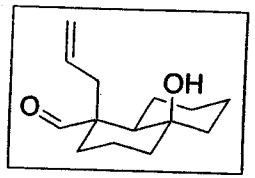
Current Data Parameters
NAME irina_20
EXPNO 1
PROCNO 1

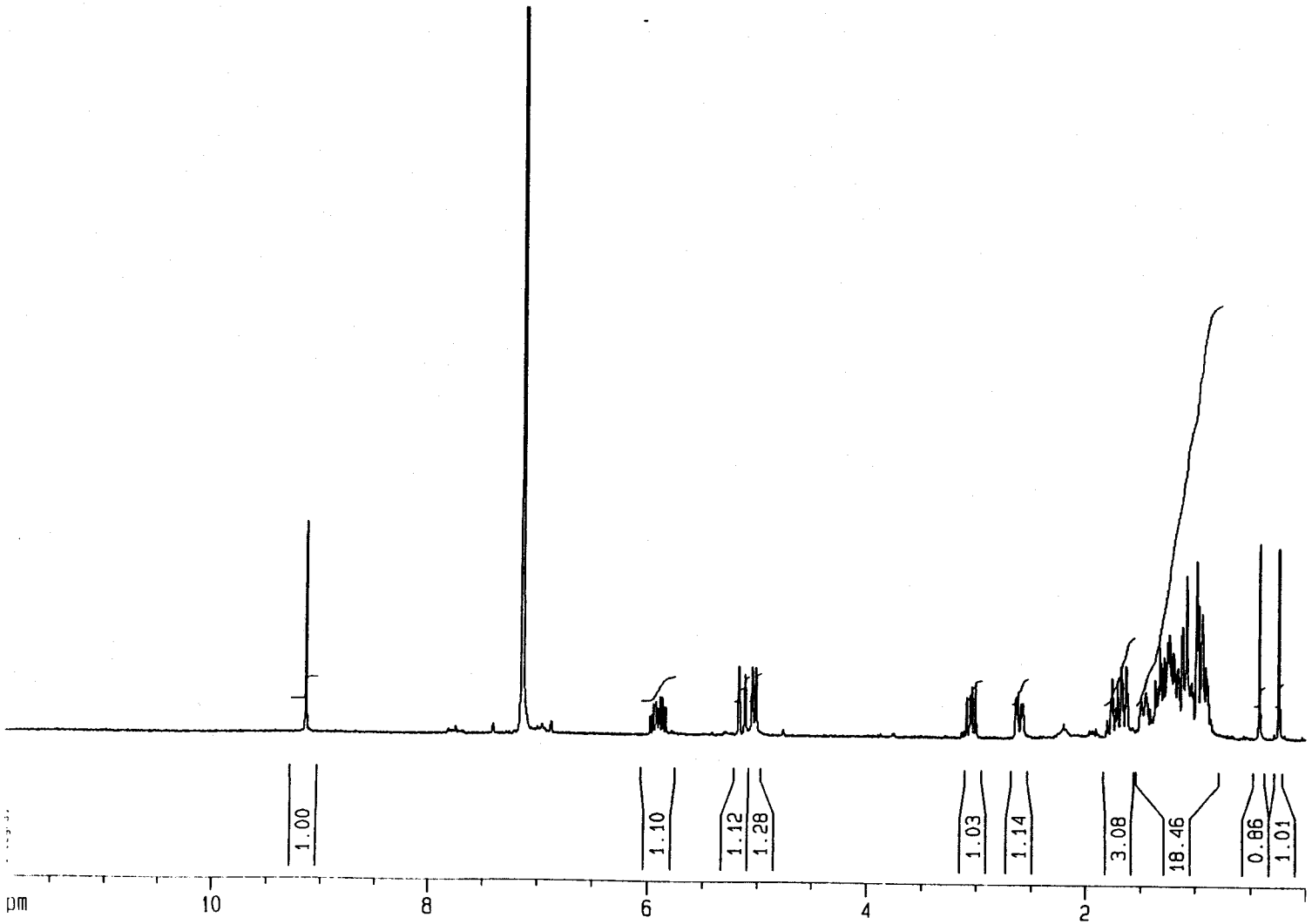
F2 - Acquisition Parameters
Date_ 20010131
Time 18.33
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 512
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 9.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 9.000 ppm
F1 2701.17 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.45000 ppm/cm
HZCM 135.05850 Hz/cm





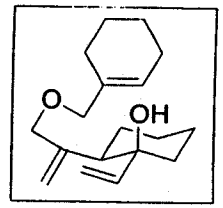
Current Data Parameters
NAME irina_7-167-top
EXPNO 1
PROCNO 1

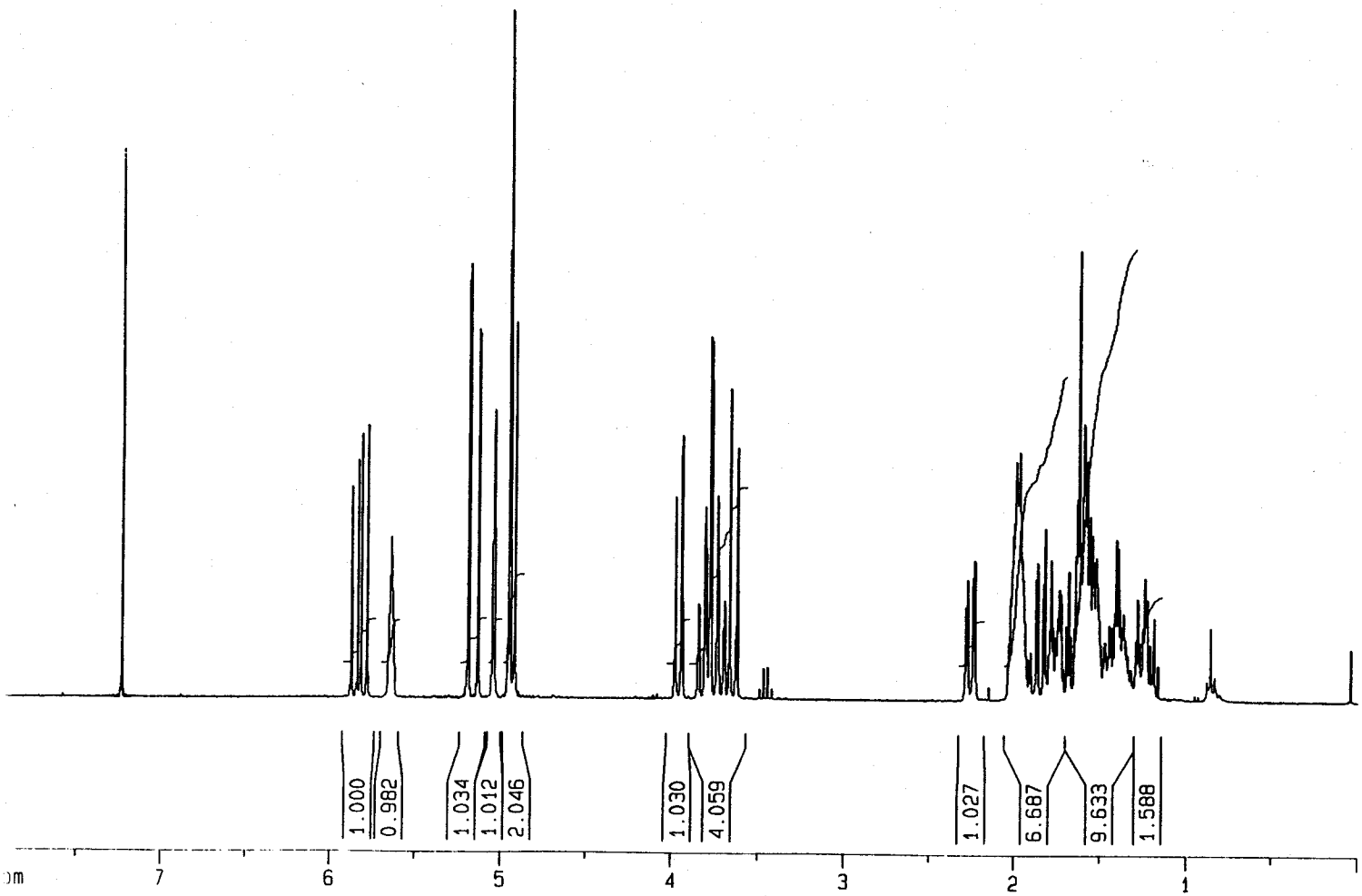
F2 - Acquisition Parameters
Date_ 20040511
Time 16.25
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 406.4
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 30.00 cm
F1P 12.000 ppm
F1 3601.56 Hz
F2P -0.000 ppm
F2 -0.00 Hz
PPMCM 0.60000 ppm/cm
HZCM 180.07800 Hz/cm





Current Data Parameters

NAME	irina_hex
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010714
Time	16.14
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	203.2
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

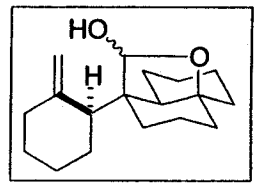
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm

SEP 2 8 2001



Current Data Parameters

NAME	irina_523
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

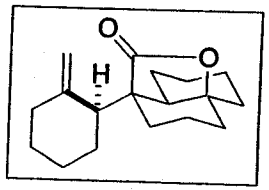
Date	20010928
Time	2.18
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	512
NUCLEUS	1H
HL1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	88.8 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	0

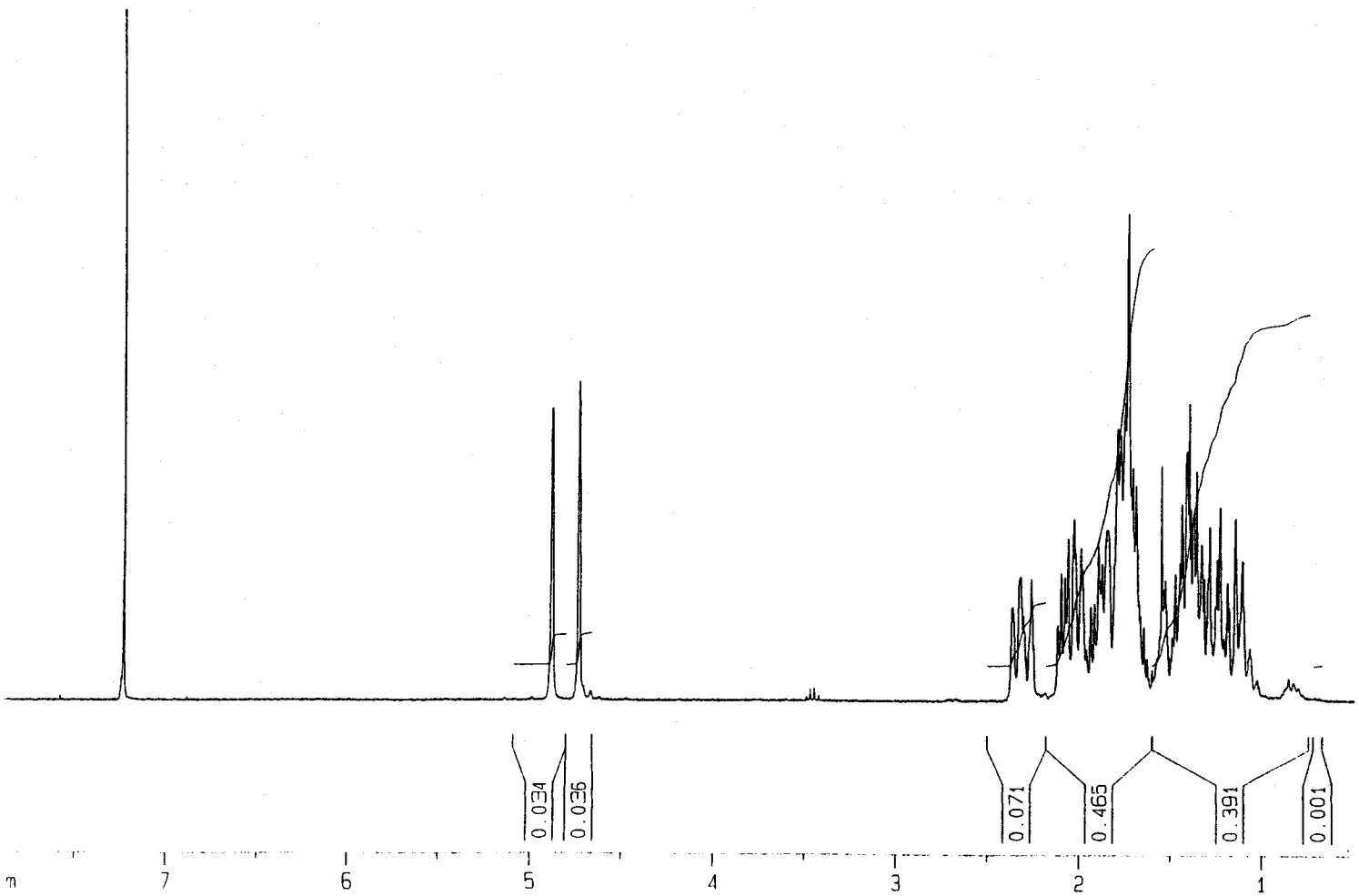
F1 - Processing parameters

SI	32768
MC2	QF
SF	500.1354307 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0

1D NMR plot parameters

CX	22.00 cm
F1P	10.000 ppm
F1	5001.35 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.45455 ppm/
HZCM	227.33429 Hz/





Current Data Parameters

NAME	irina_101
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010531
Time	10.16
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	456.1
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

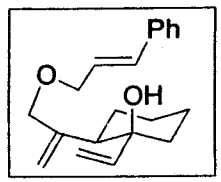
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

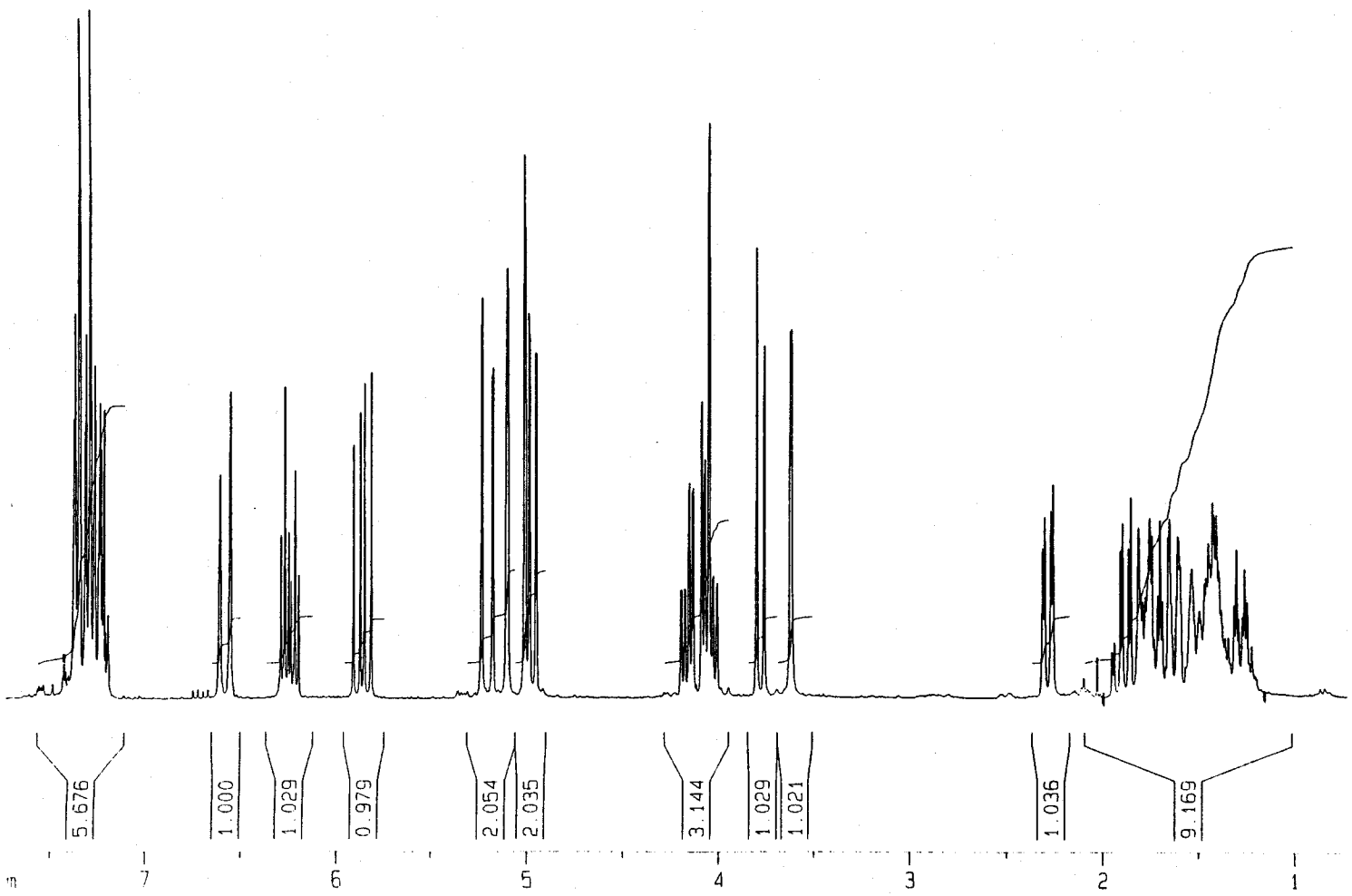
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.500 ppm
F2	150.07 Hz
PPMCM	0.37500 ppm/cm
HZCM	112.54875 Hz/cm





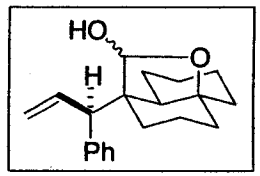
Current Data Parameters
NAME test123
EXPNO 1
PROCNO 1

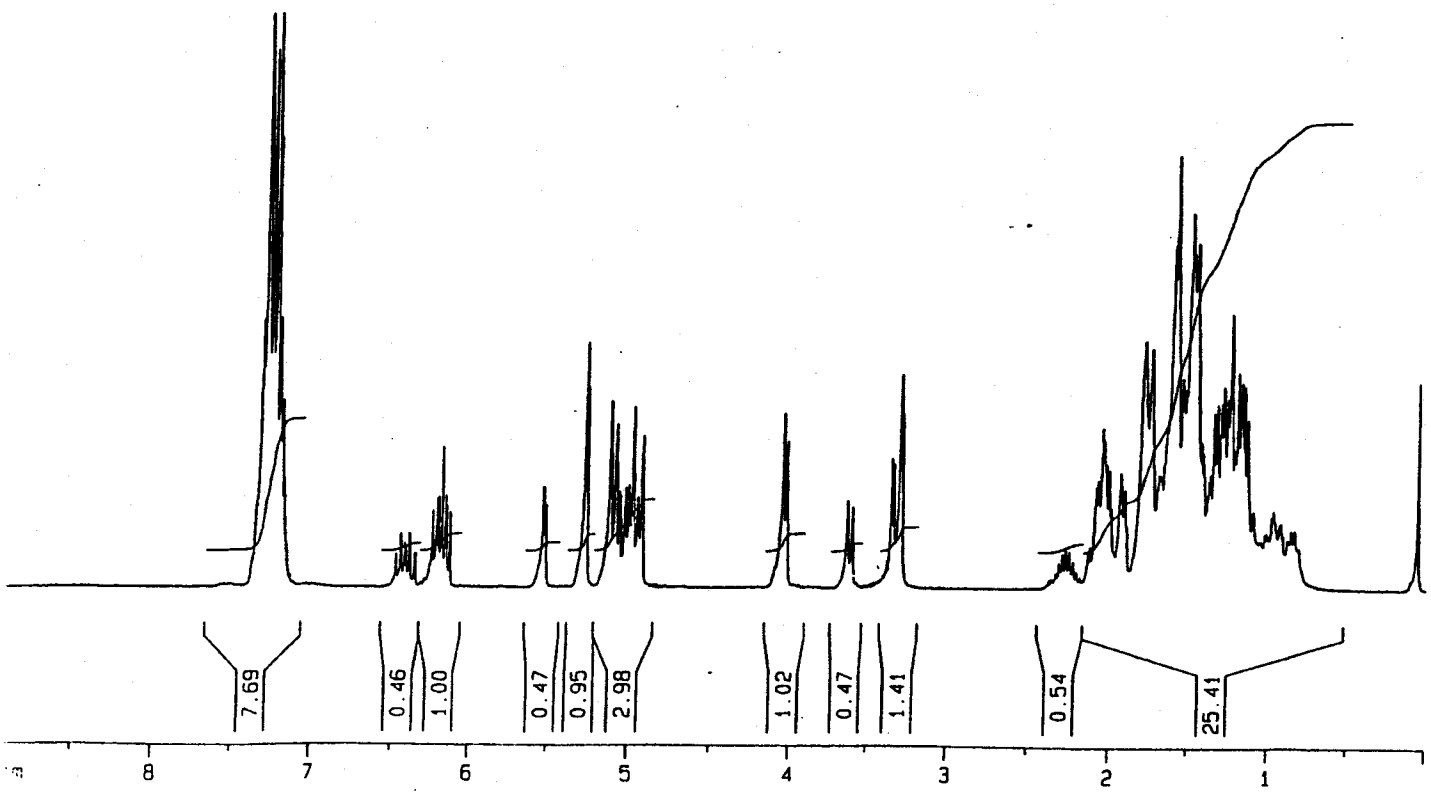
F2 - Acquisition Parameters
Date_ 20020131
Time 20.34
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 101.6
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 11.00 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 7.852 ppm
F1 2356.51 Hz
F2P 0.723 ppm
F2 217.01 Hz
PPMCM 0.35643 ppm/cm
HZCM 106.97475 Hz/cm





Current Data Parameters

NAME	irina_trans
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20020122
Time	12.27
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	143.7
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

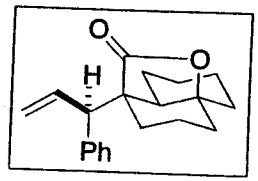
NUC1	1H
P1	11.00 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

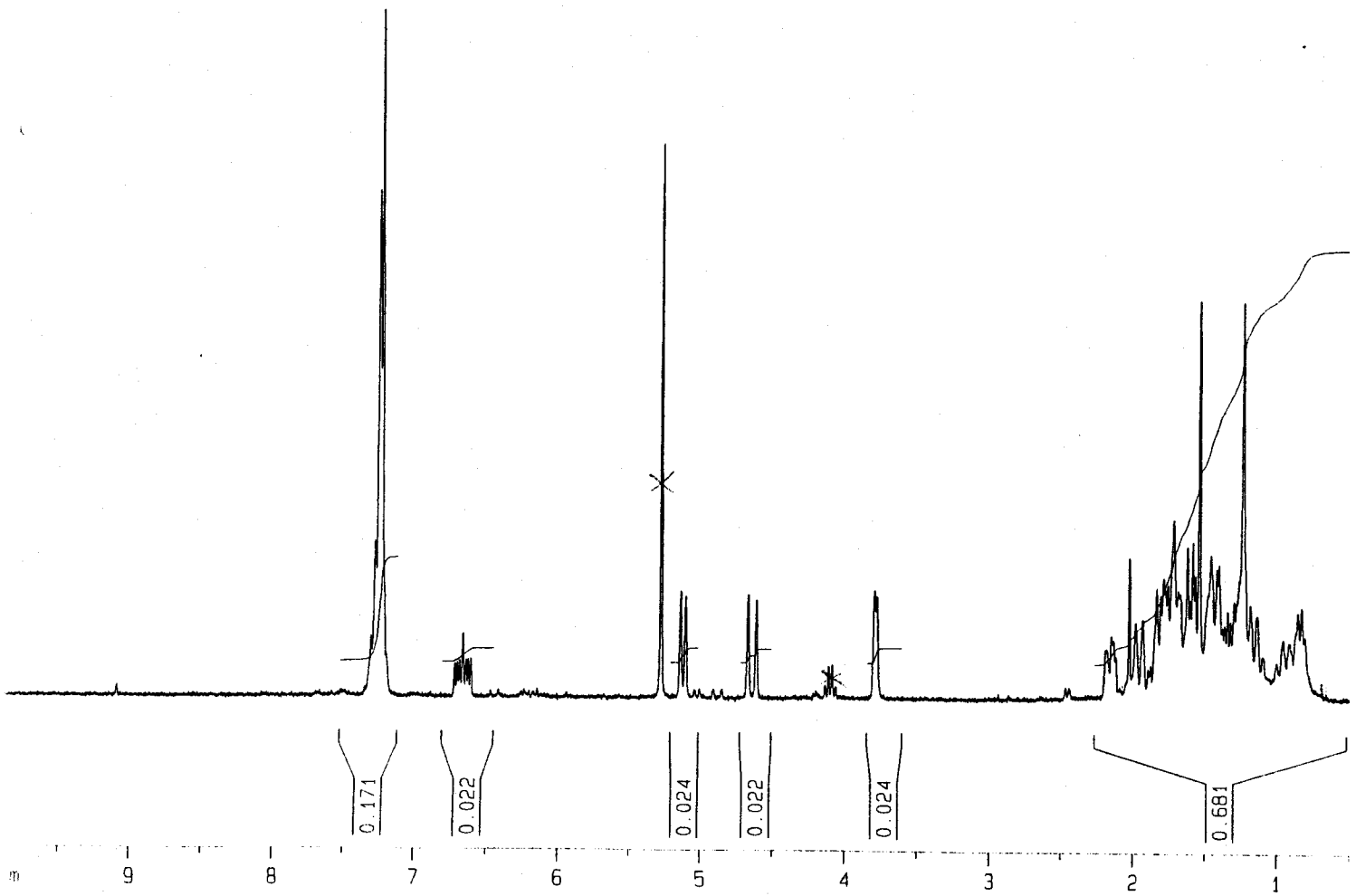
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	8.00 cm
F1P	9.000 ppm
F1	2701.17 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.45000 ppm/cm
HZCM	135.05852 Hz/cm





Current Data Parameters

NAME	irina_16
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010426
Time	18.31
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	724.1
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

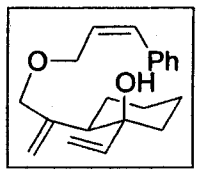
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

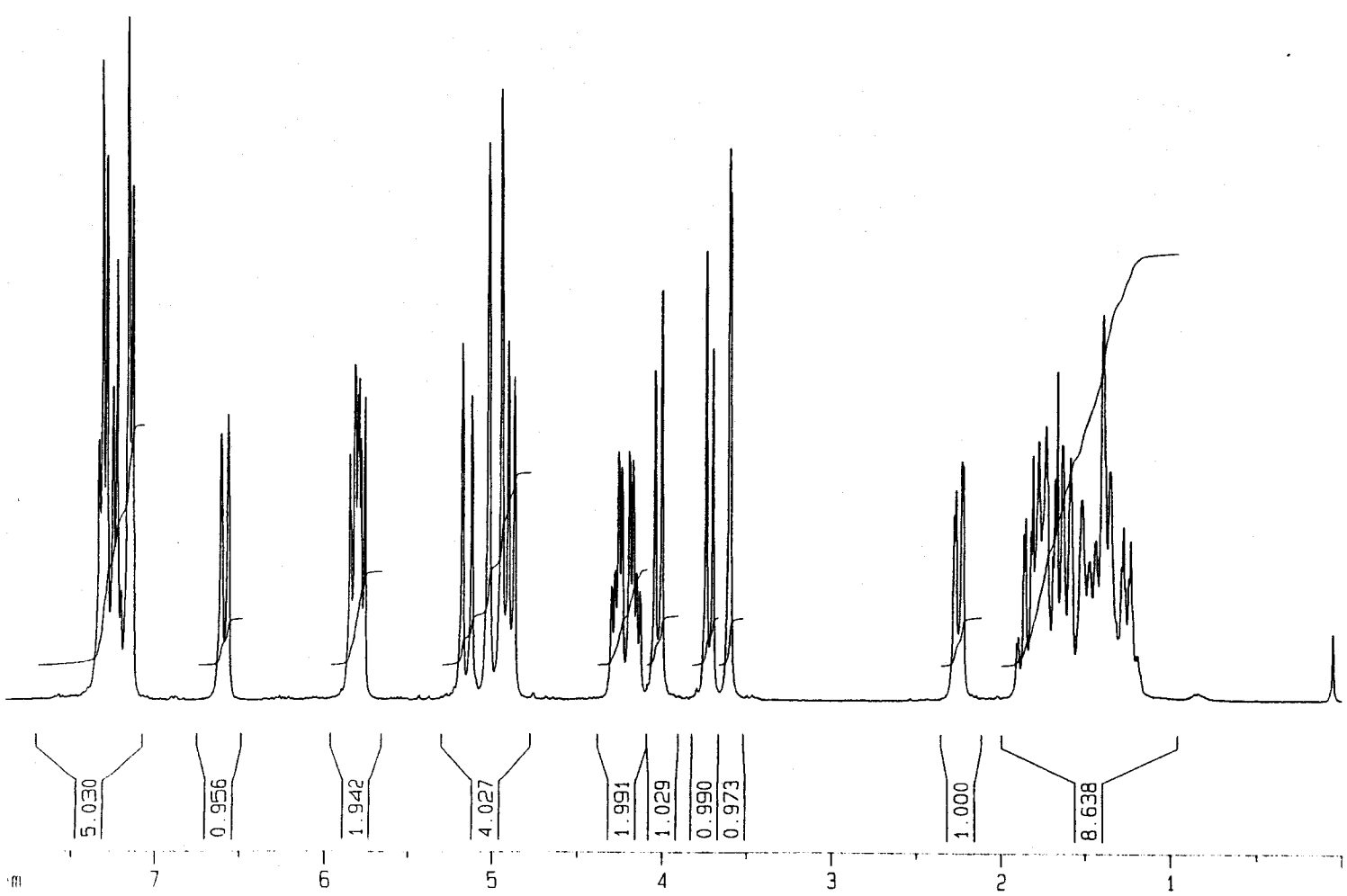
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	0.500 ppm
F2	150.06 Hz
PPMCM	0.47500 ppm/cm
HZCM	142.56175 Hz/cm





Current Data Parameters

NAME	irina_cis
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20020111
Time	14.06
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	128
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

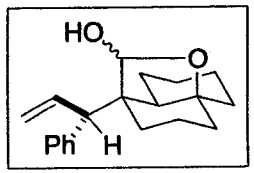
NUC1	1H
P1	11.00 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

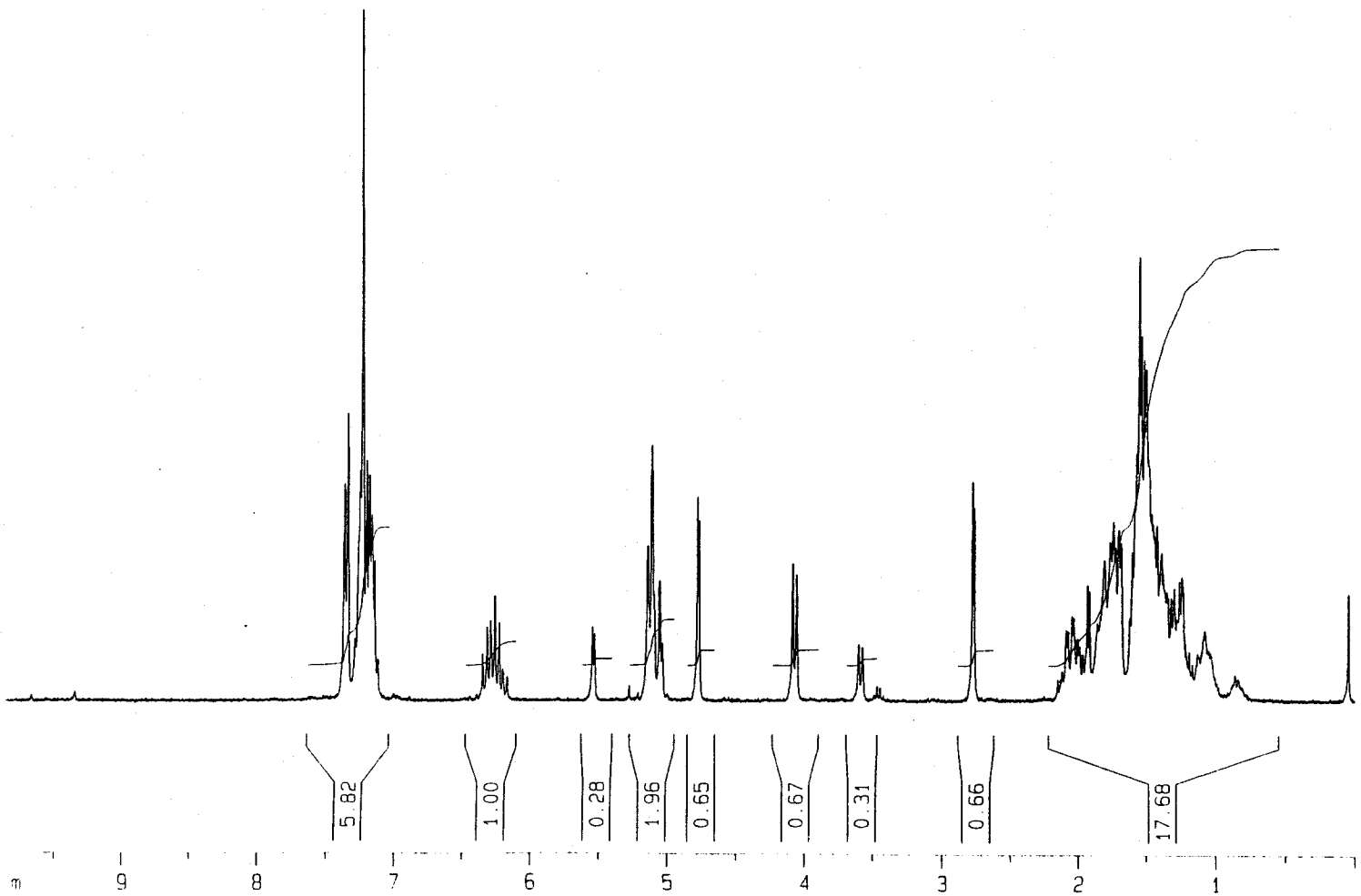
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





Current Data Parameters

NAME	irina_552a
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20020115
Time	13.29
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	456.1
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

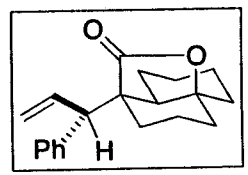
NUC1	1H
P1	11.00 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

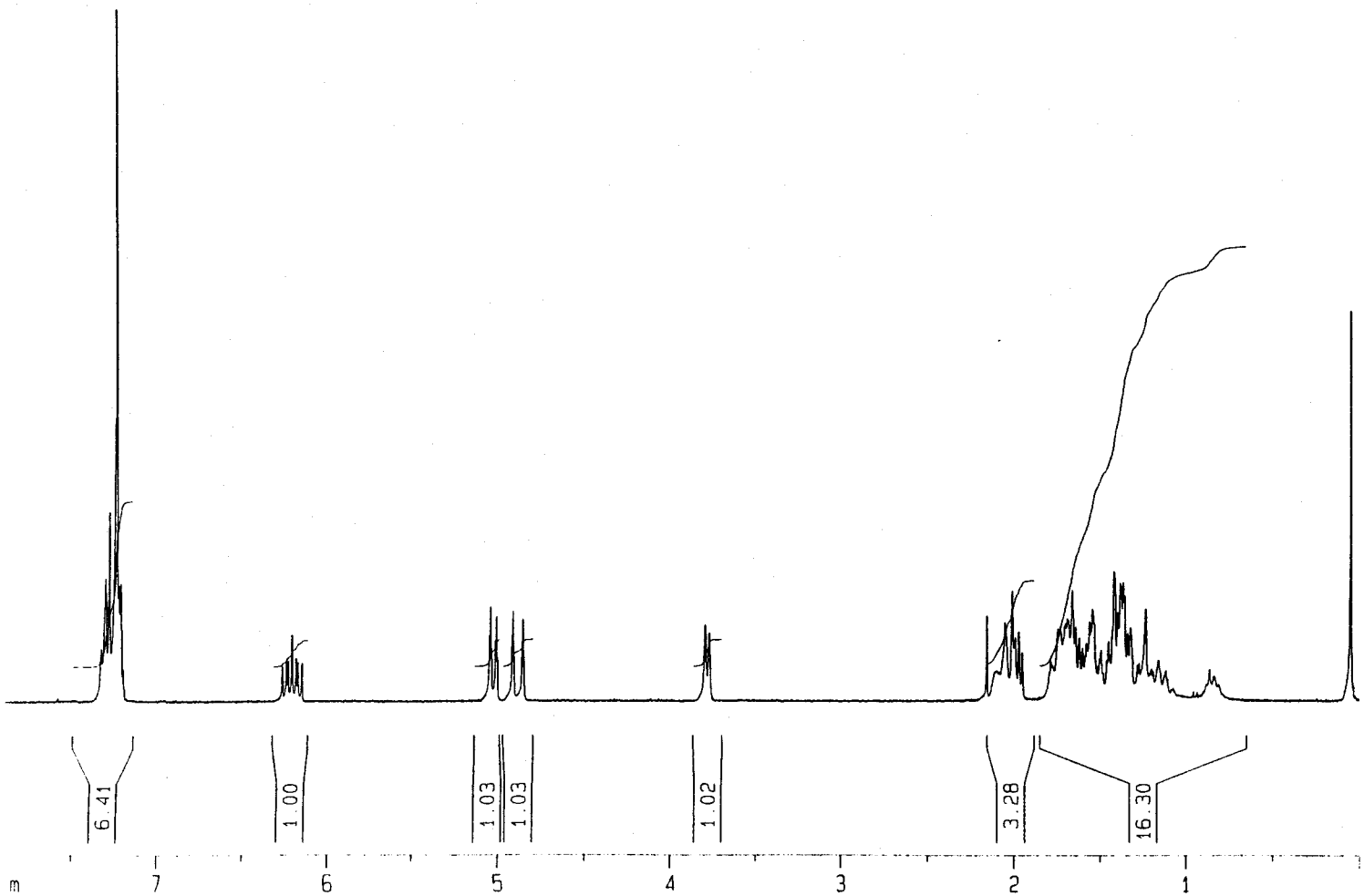
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.50000 ppm/cm
HZCM	150.06500 Hz/cm





Current Data Parameters

NAME	irina_553
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20020117
Time	18.29
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	724.1
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

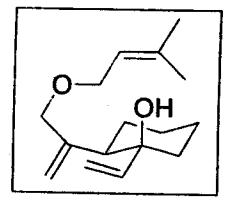
NUC1	1H
P1	11.00 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

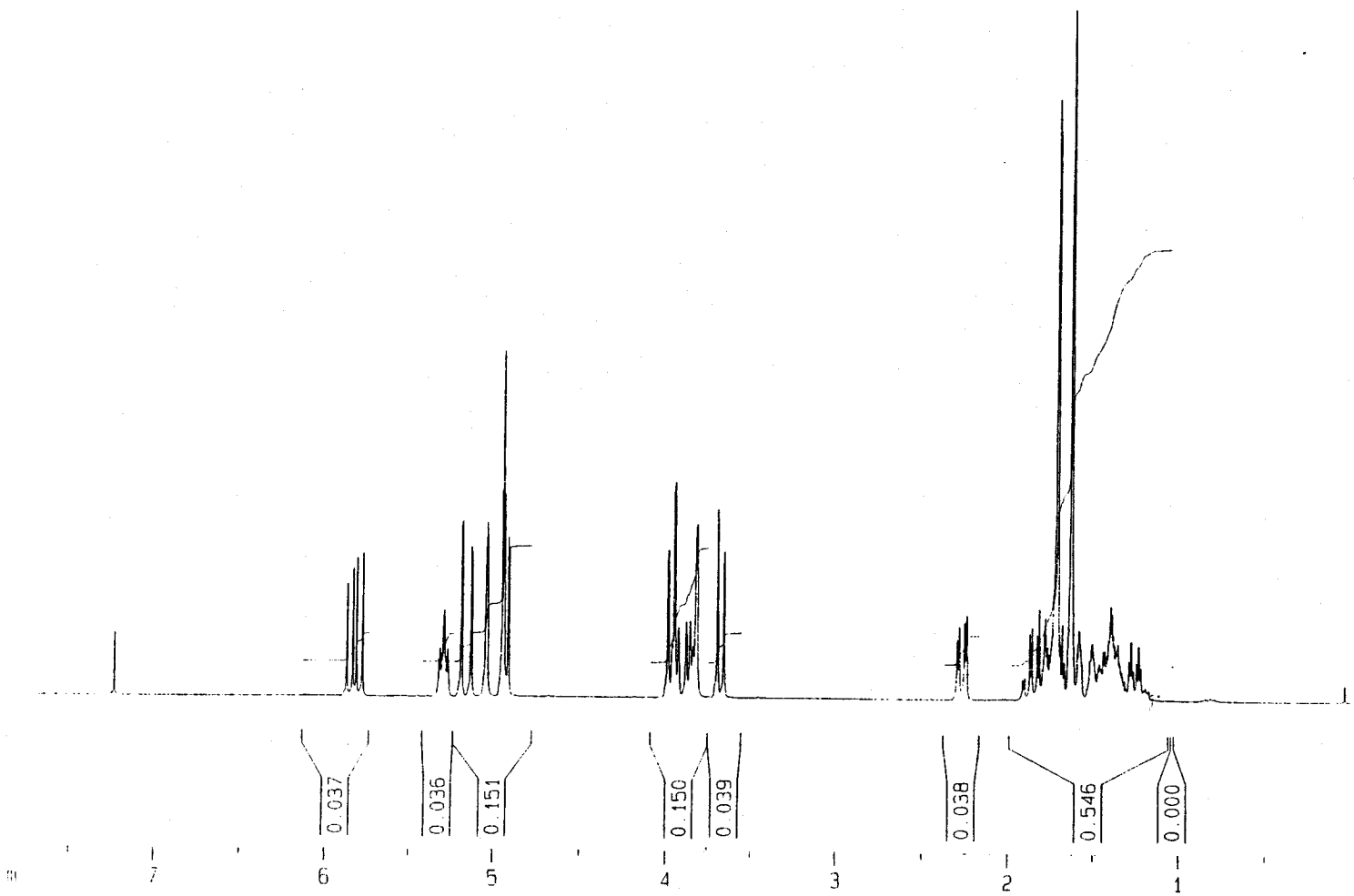
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





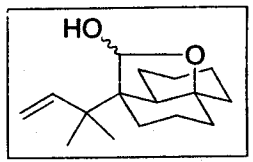
Current Data Parameters
NAME [illegible]
EXPNO 1
PROCNO 1

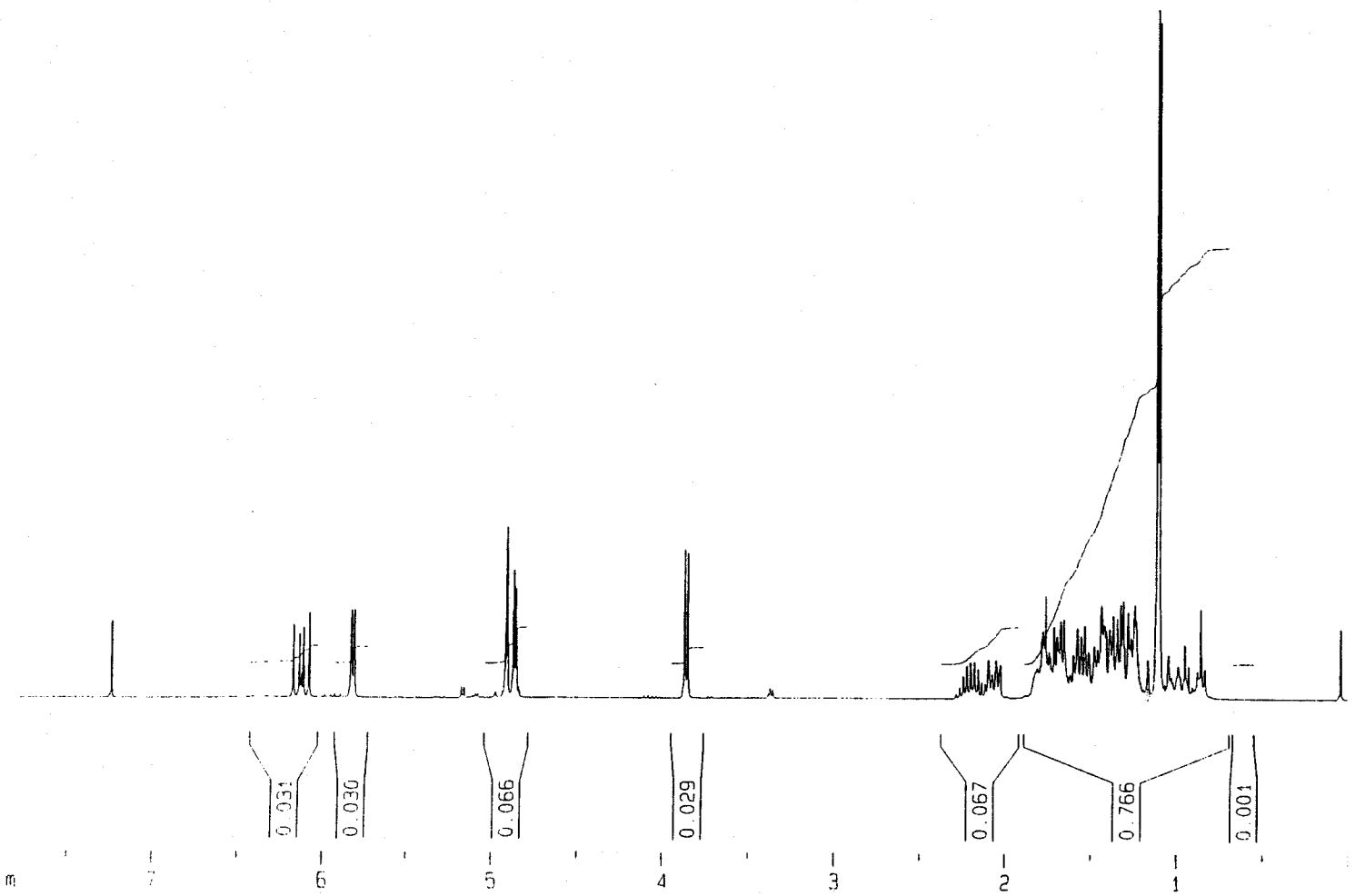
F2 - Acquisition Parameters
Date_ 20010811
Time 13.20
INSTRUM av300
PROBHD 5 mm QNP 1H_1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.155407 Hz
AQ 3.0228980 sec
RG 90.5
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 9.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.03 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm





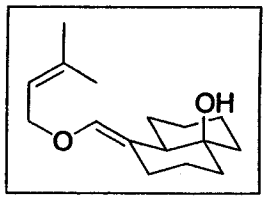
Current Data Parameters
NAME prima_189
EXPNO 1
PROCNO 1

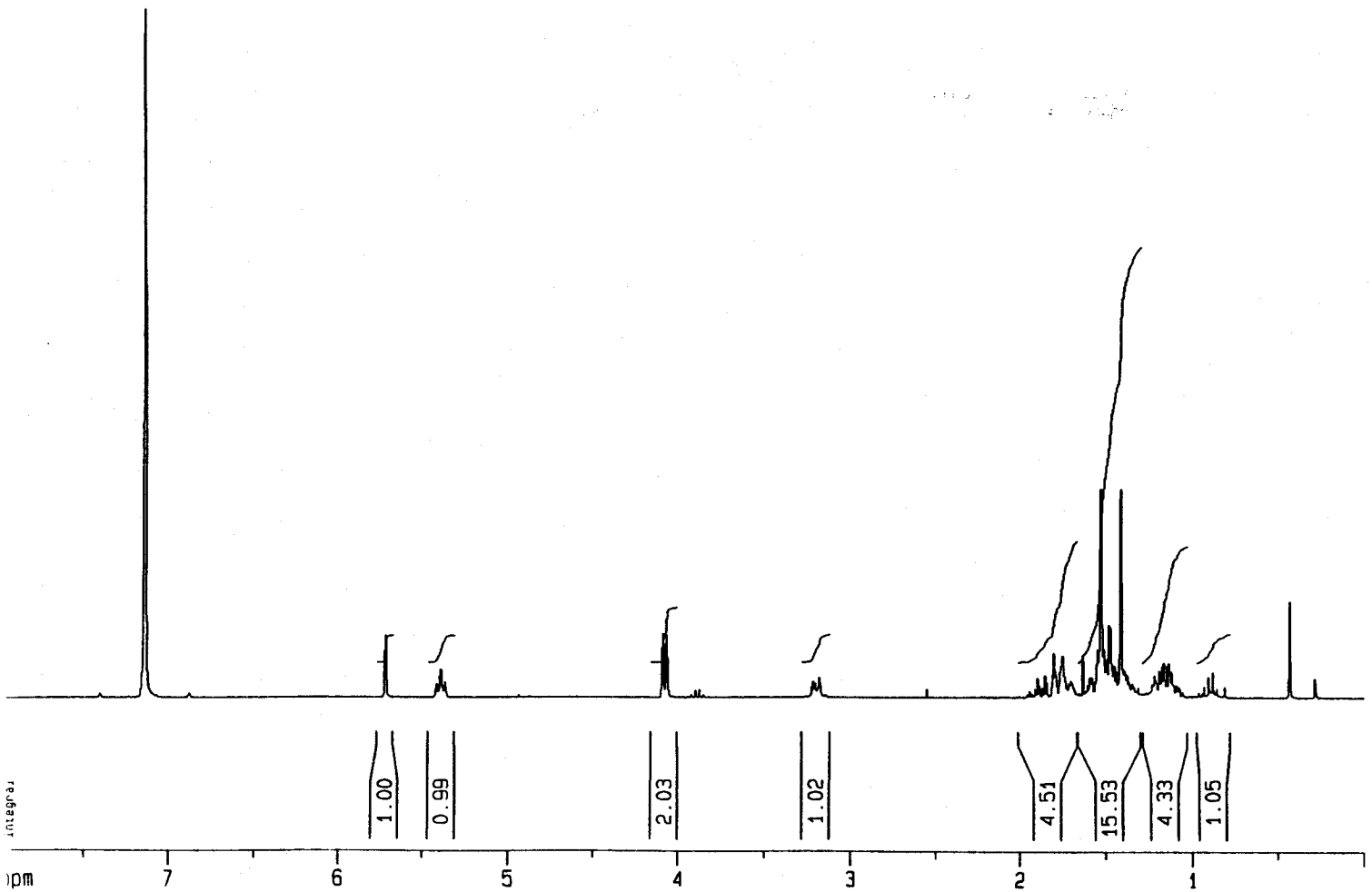
F2 - Acquisition Parameters
Date 20010817
Time 14.17
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 49720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 114
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 9.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm





Current Data Parameters

NAME	irina_eepure
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040531
Time	21.49
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	C6D6
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	406.4
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

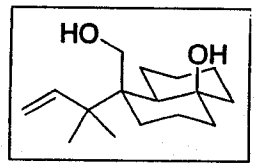
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

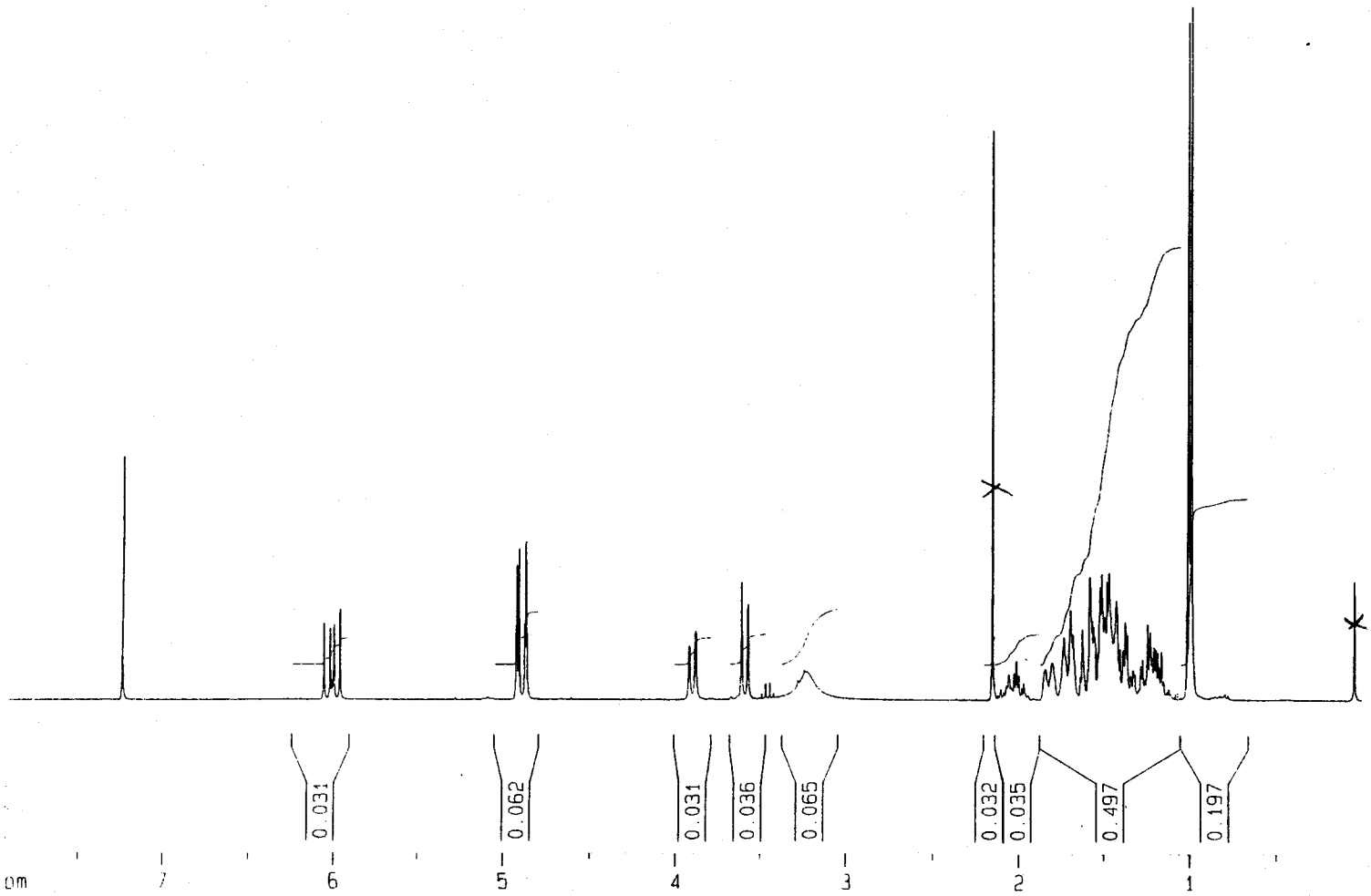
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





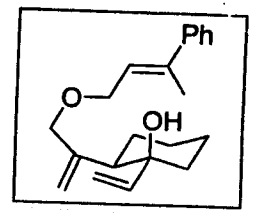
Current Data Parameters
NAME irina_499
EXPNO 1
PROCNO 1

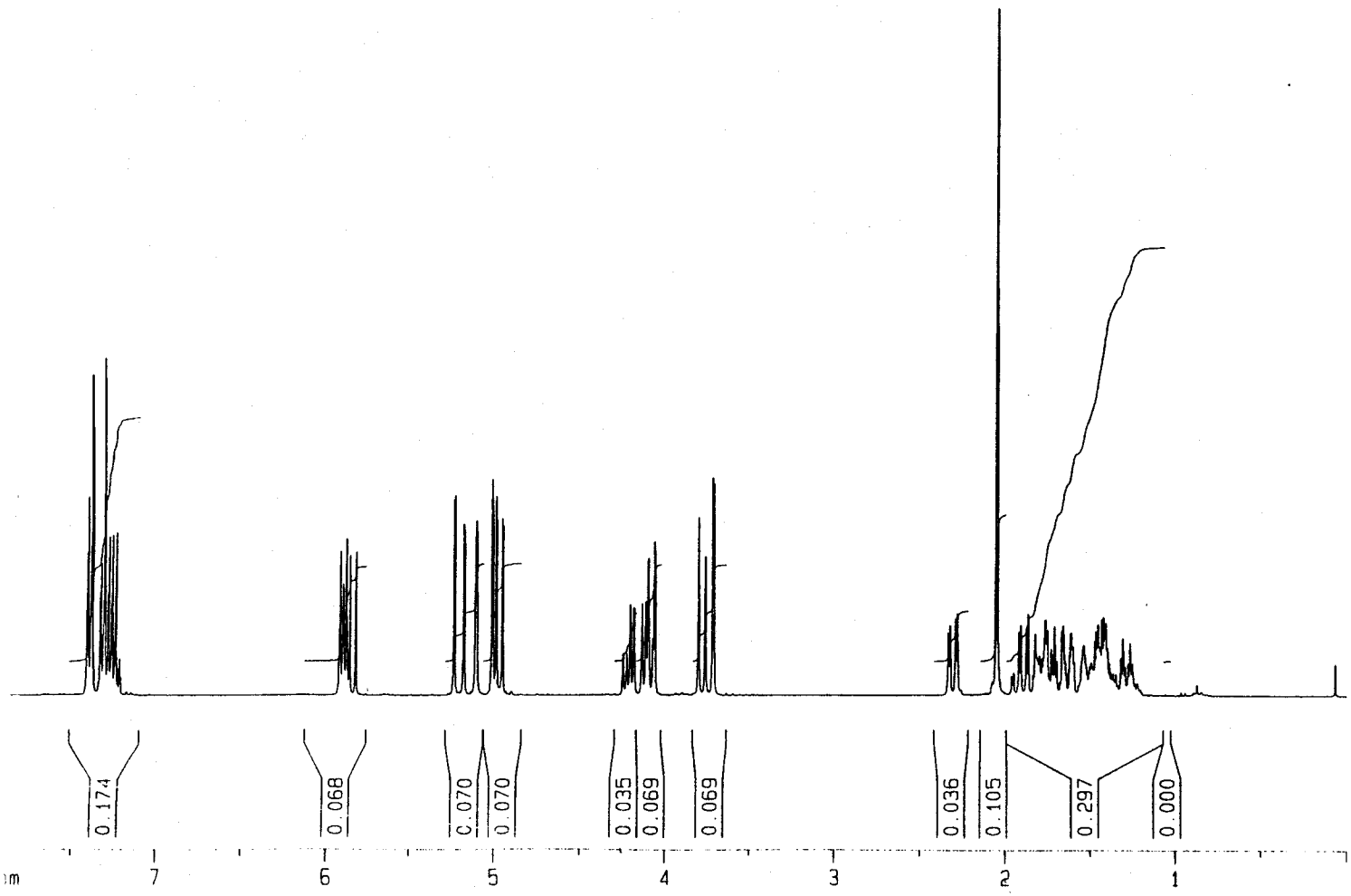
F2 - Acquisition Parameters
Date_ 20010816
Time 11.17
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 362
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 9.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm





Current Data Parameters

NAME	irina_453
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010704
Time	19.36
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	80.6
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

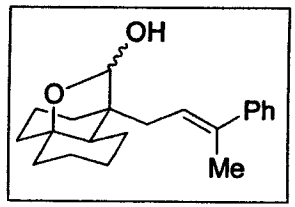
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

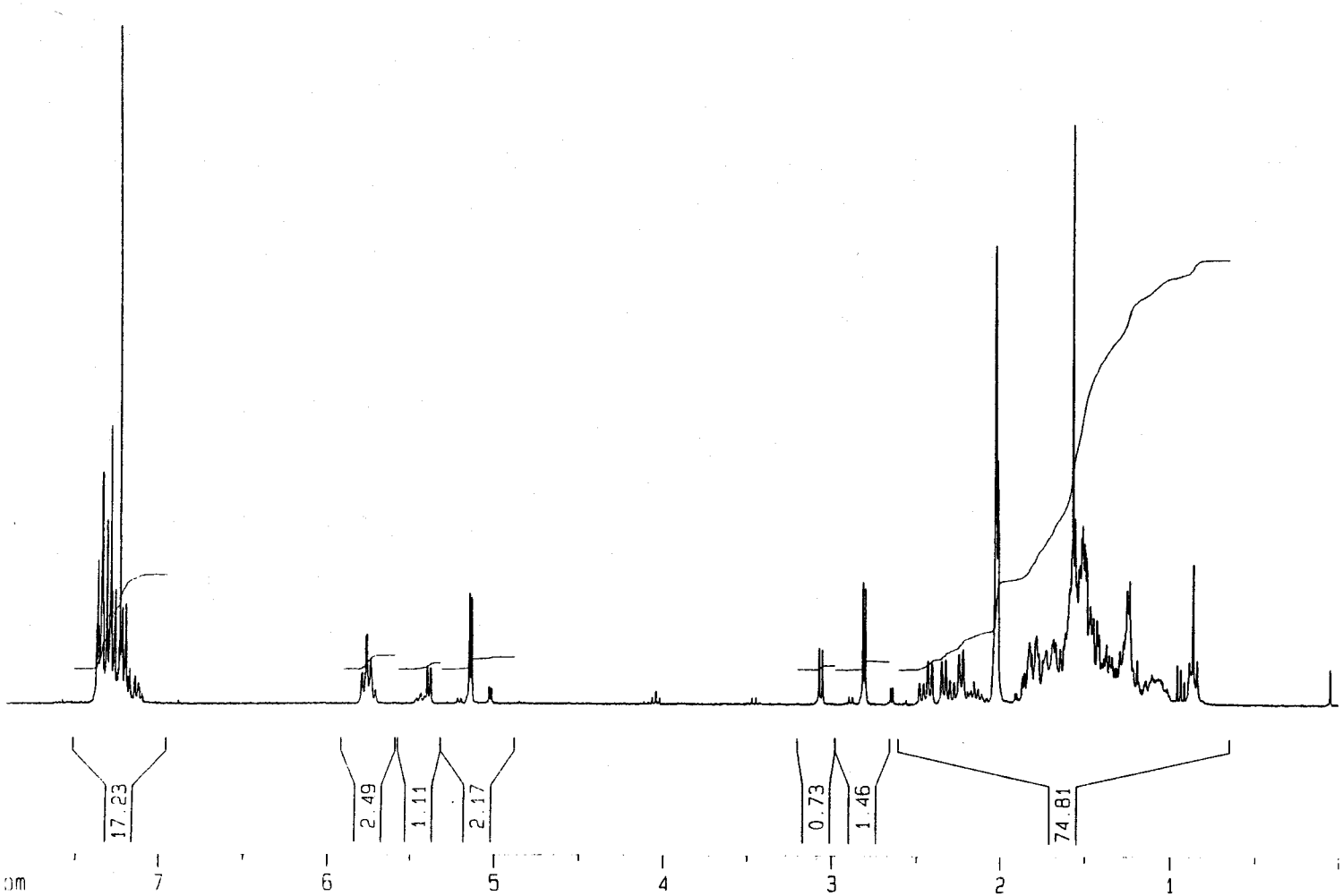
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





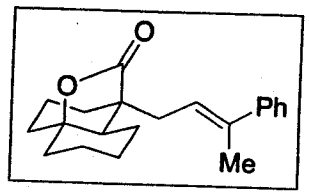

```
Current Data Parameters
NAME                  irina_486
EXPNO                         1
PROCNO                        1

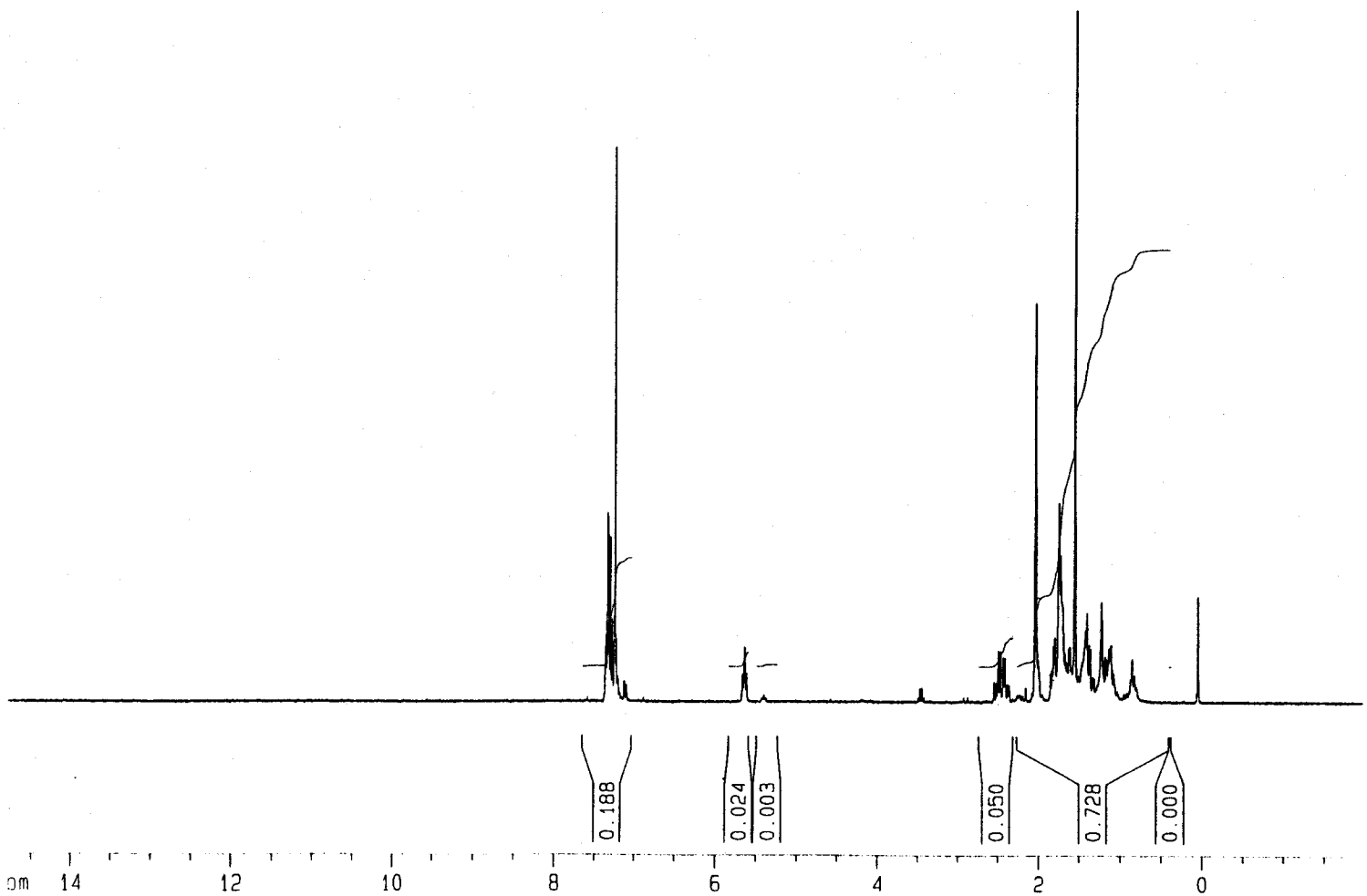
F2 - Acquisition Parameters
Date_              20010811
Time                    17.25
INSTRUM                 av300
PROBHD    5 mm QNP  1H/1
PULPROG                 zg30
TD                     30720
SOLVENT                CDCl3
NS                        16
DS                         0
SWH                5081.301 Hz
FIDRES             0.165407 Hz
AQ                 3.0228980 sec
RG                       512
DW                  98.400 usec
DE                   6.00 usec
TE                   300.0 K
D1                 1.00000000 sec

============ CHANNEL f1 ============
NUC1                      1H
P1                    9.50 usec
PL1                  -3.00 dB
SFO1           300.1319477 MHz

F2 - Processing parameters
SI                        65536
SF             300.1300000 MHz
WDW                       EM
SSB                        0
LB                      0.10 Hz
GB                         0
PC                      1.00

1D NMR plot parameters
CX                     20.00 cm
CY                     10.00 cm
F1P                    8.000 ppm
F1                  2401.04 Hz
F2P                    0.000 ppm
F2                     0.00 Hz
PPMCM                0.40000 ppm/cm
HZCM               120.05200 Hz/cm
```





Current Data Parameters

NAME	irina_lact
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010716
Time	14.37
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	812.7
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

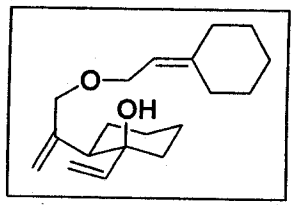
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

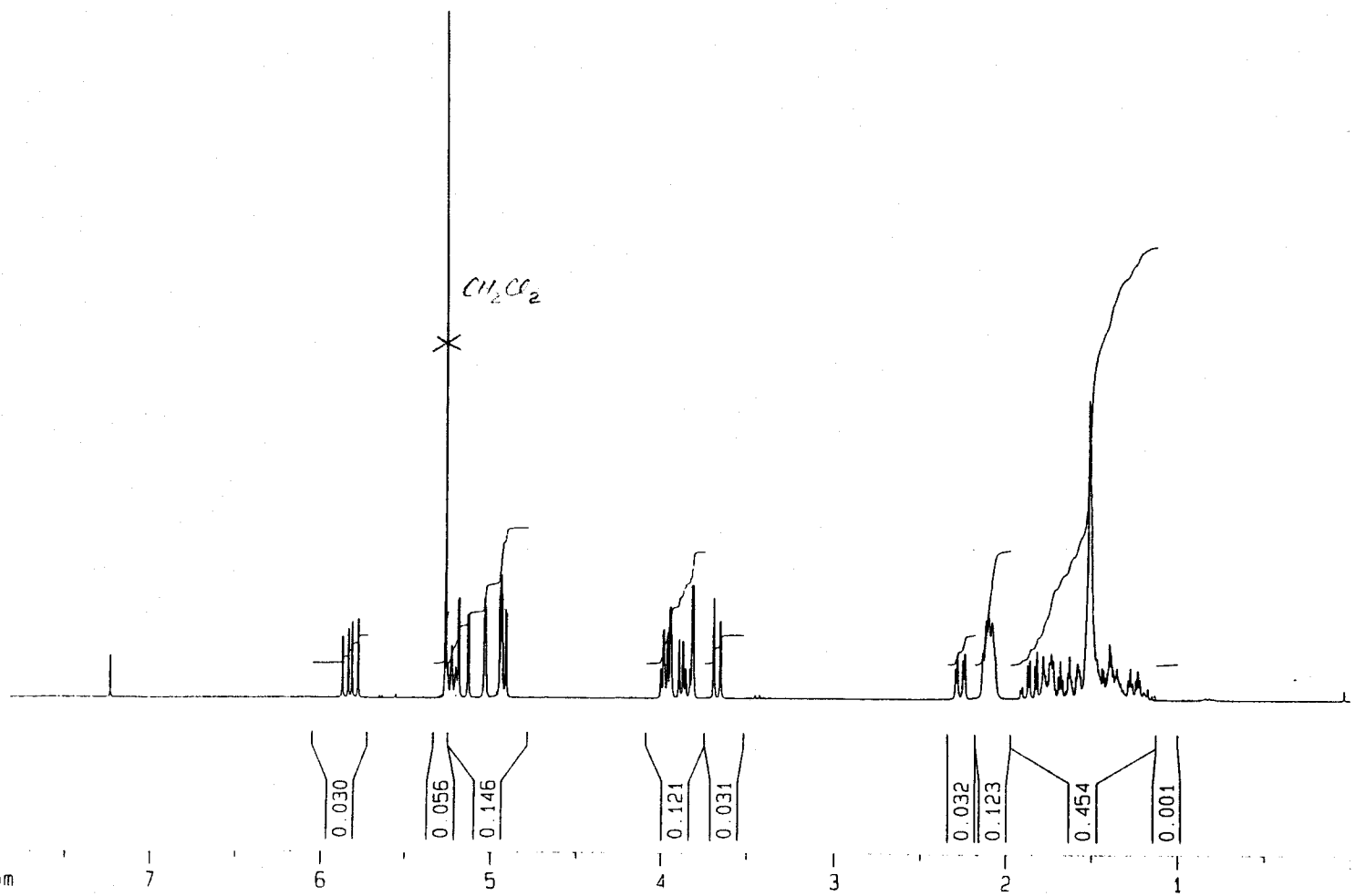
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	14.955 ppm
F1	4488.36 Hz
F2P	-1.976 ppm
F2	-592.94 Hz
PPMCM	0.84652 ppm/cm
HZCM	254.06503 Hz/cm





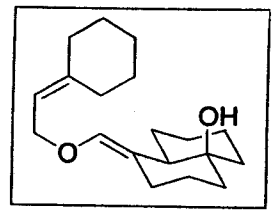
Current Data Parameters
NAME irina_479I
EXPNO 1
PROCNO 1

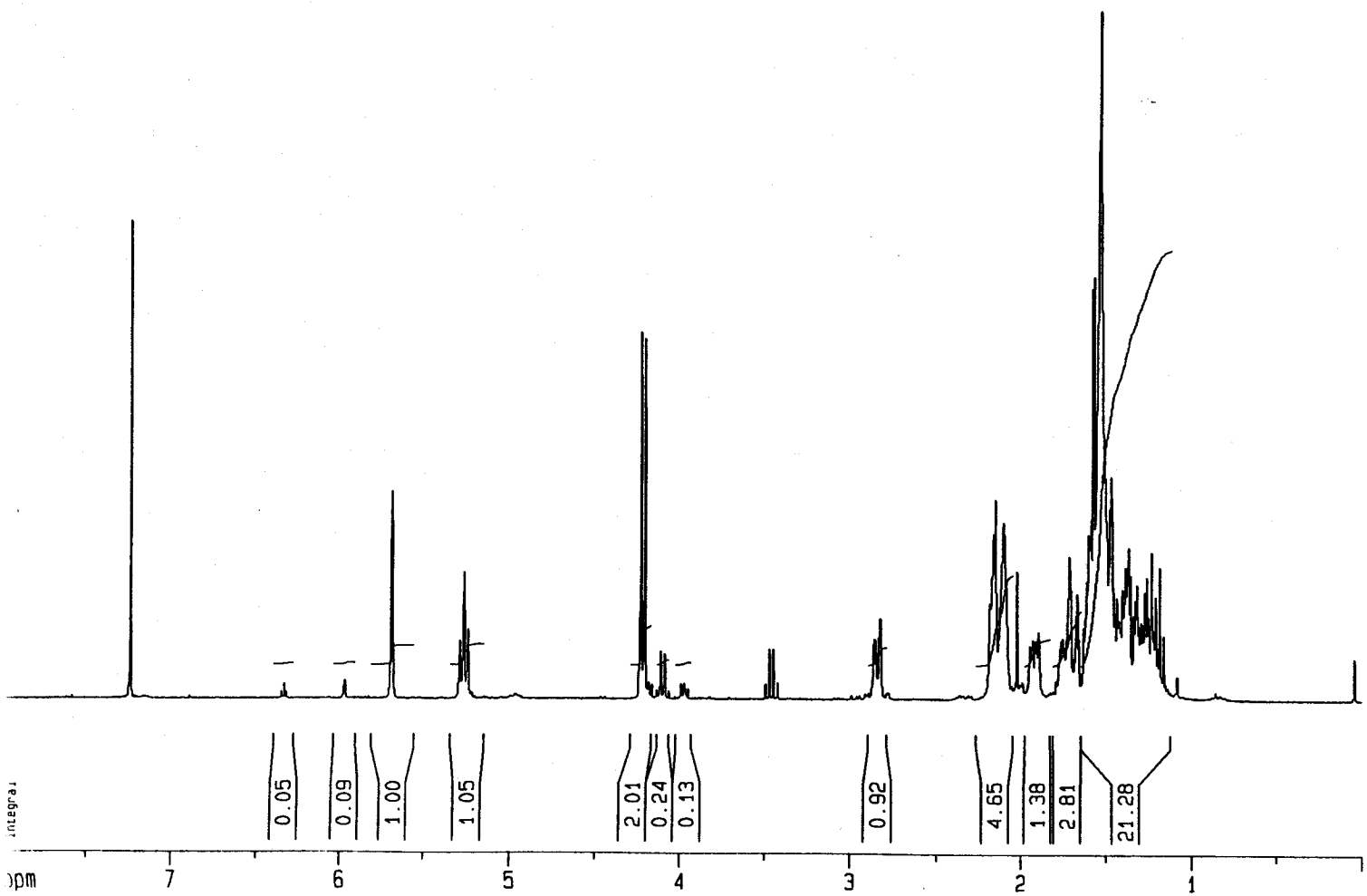
F2 - Acquisition Parameters
Date_ 20010802
Time 17.31
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 80.6
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

============ CHANNEL f1 =============
NUC1 1H
P1 9.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm





Current Data Parameters

NAME	irina_475
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010725
Time	16.42
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	256
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

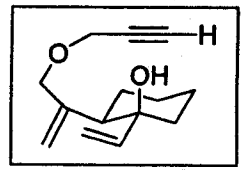
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

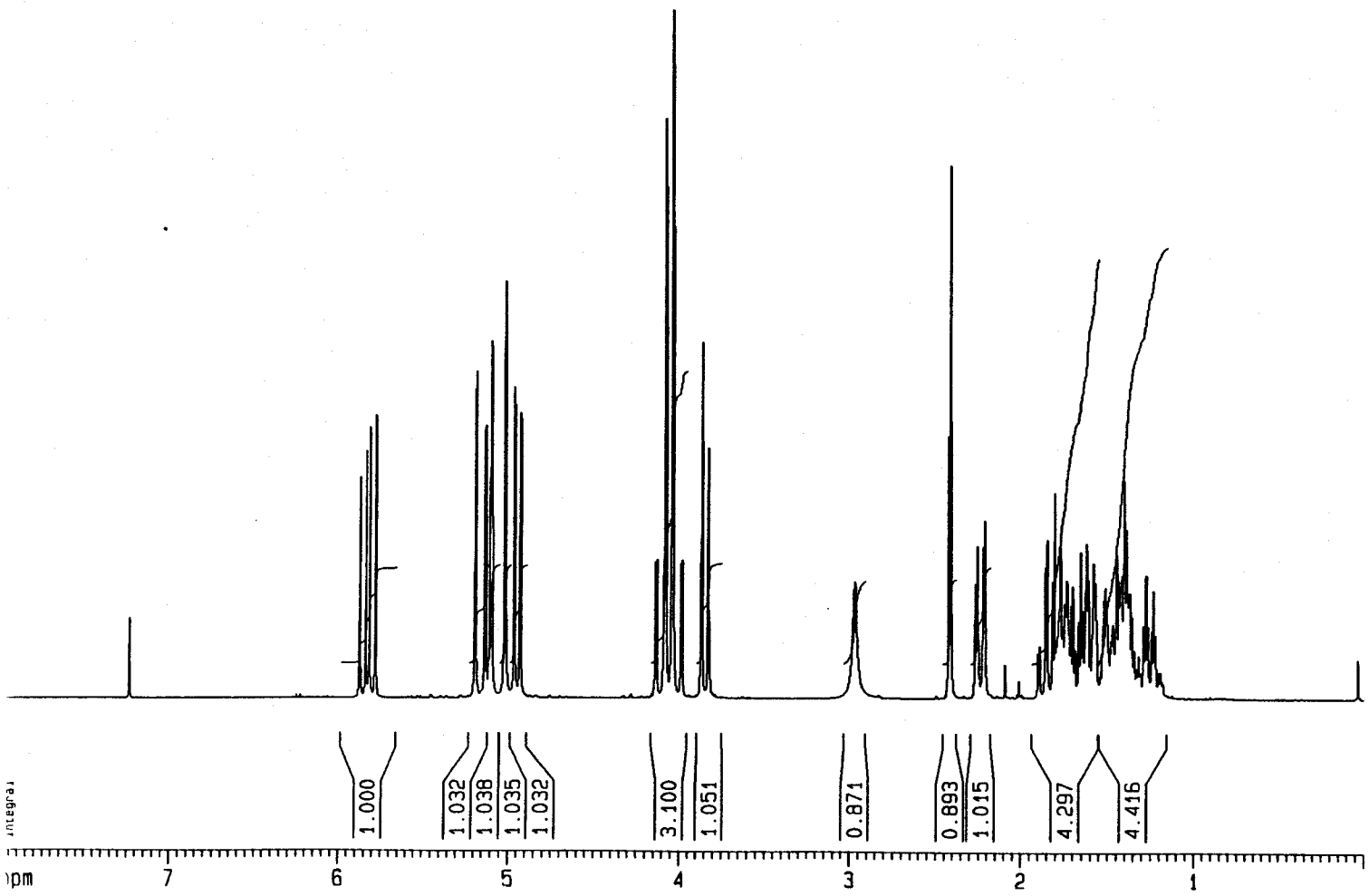
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





Current Data Parameters

NAME	irina_17
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010427
Time	18.17
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	90.5
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

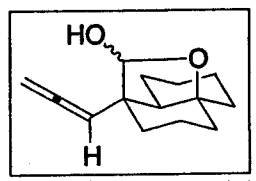
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

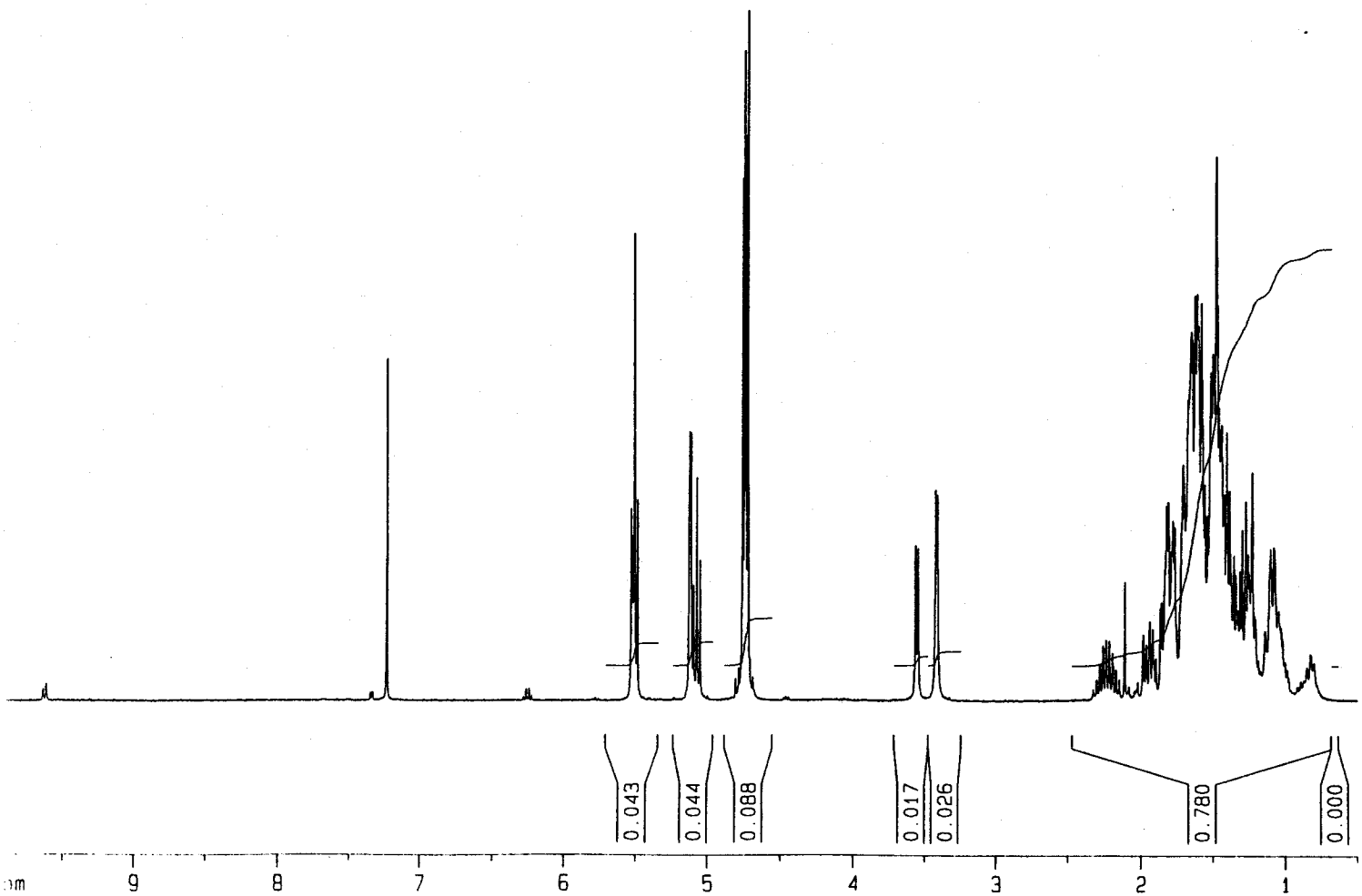
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





Current Data Parameters

NAME	irina_18
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010430
Time	18.34
INSTRUM	av300
PROBHD	5 mm GNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	228.1
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

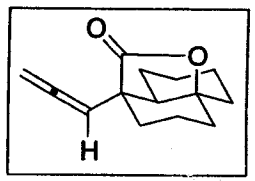
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

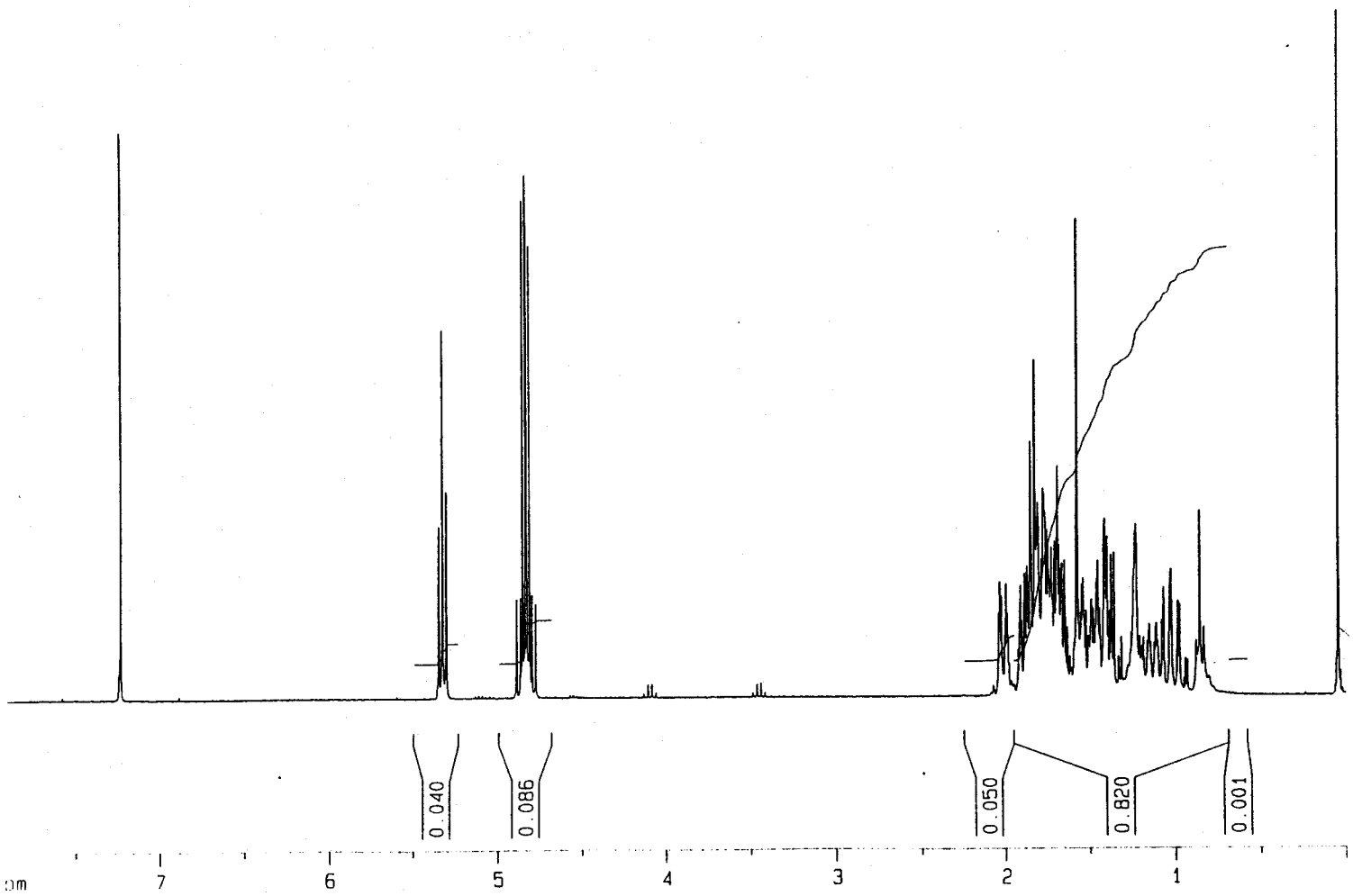
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	0.500 ppm
F2	150.06 Hz
PPMCM	0.47500 ppm/cm
HZCM	142.56175 Hz/cm





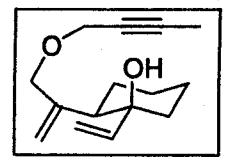
Current Data Parameters
NAME irina_501
EXPNO 1
PROCNO 1

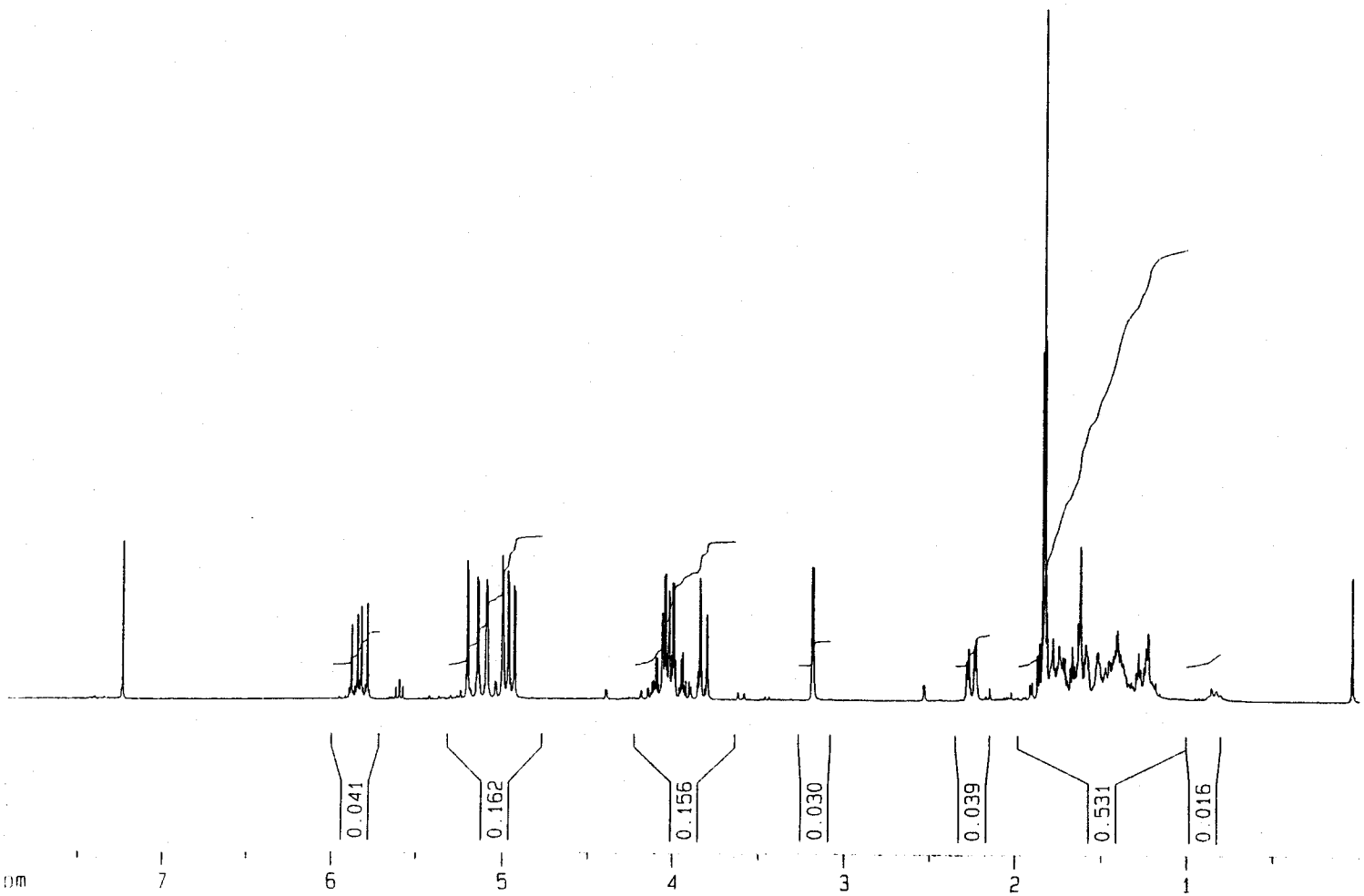
F2 - Acquisition Parameters
Date_ 20010714
Time 18.28
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 362
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 9.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm





Current Data Parameters

NAME	irina_488
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010812
Time	17.21
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	228.1
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

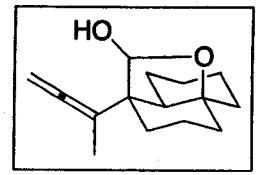
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

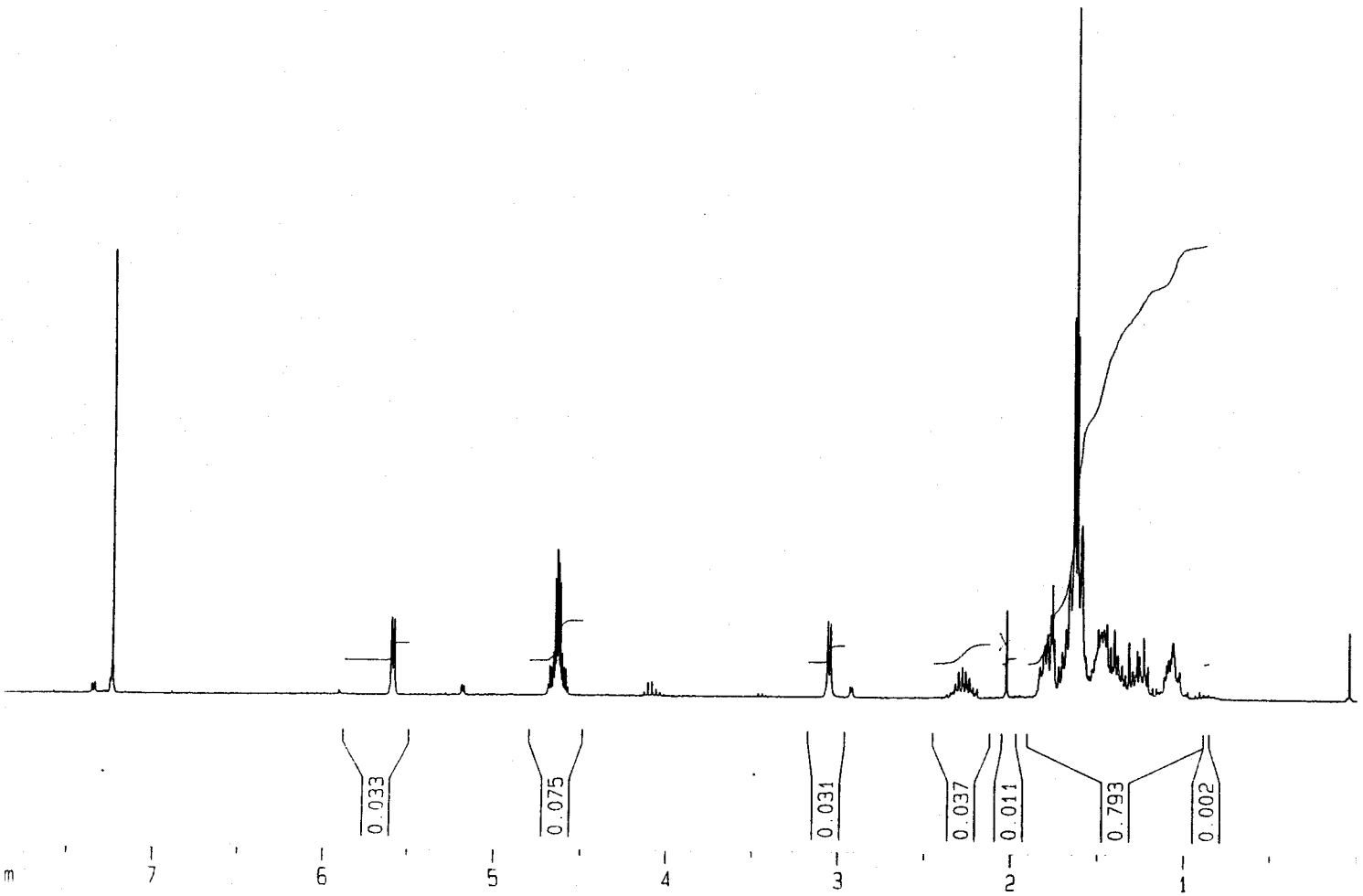
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





Current Data Parameters

NAME	irina_491
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010814
Time	11.20
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	512
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

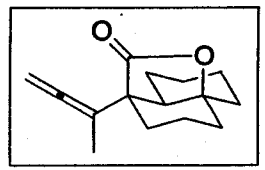
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

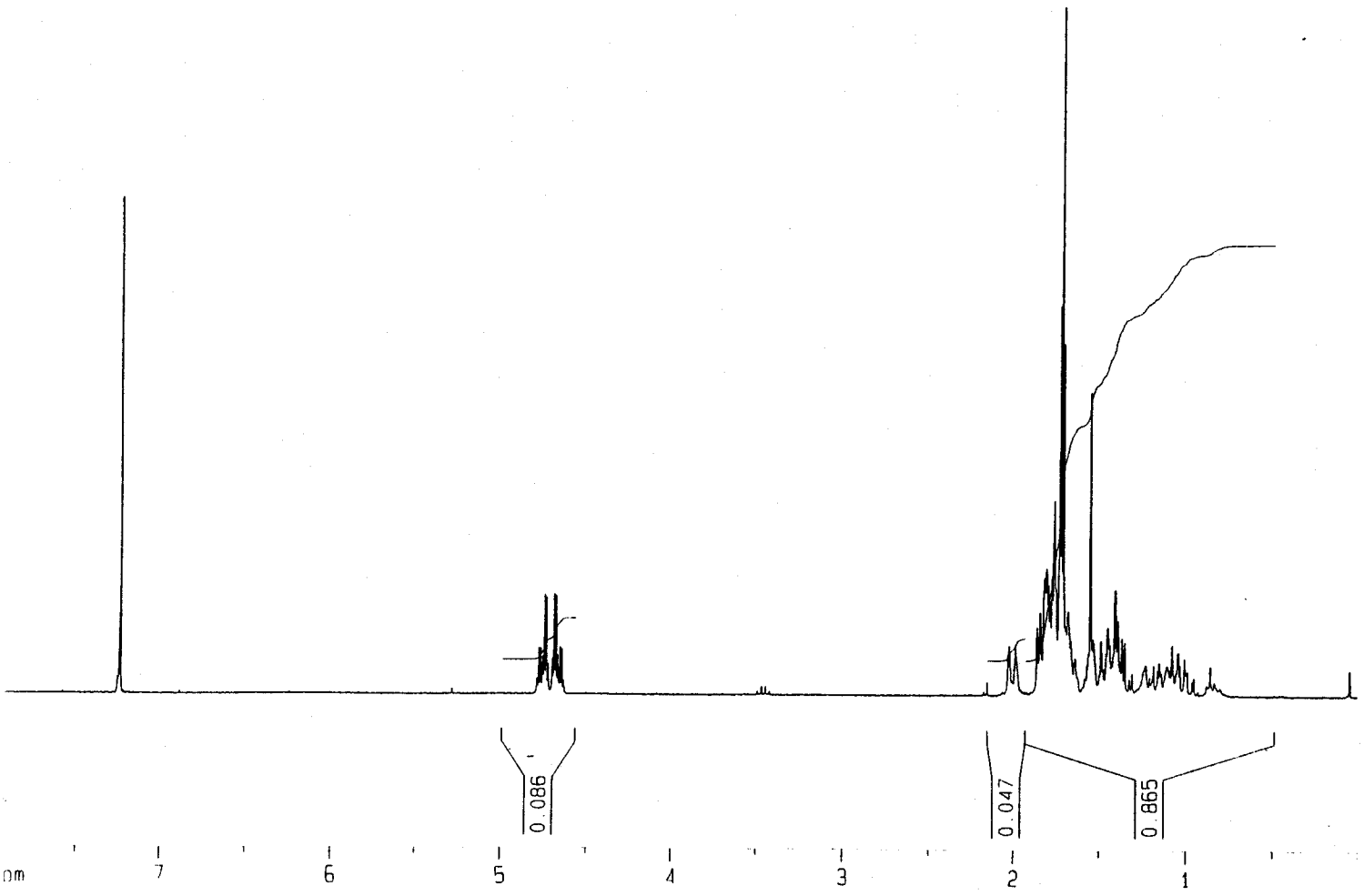
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





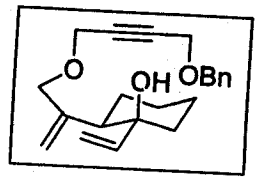
Current Data Parameters
NAME irina_494
EXPNO 1
PROCNO 1

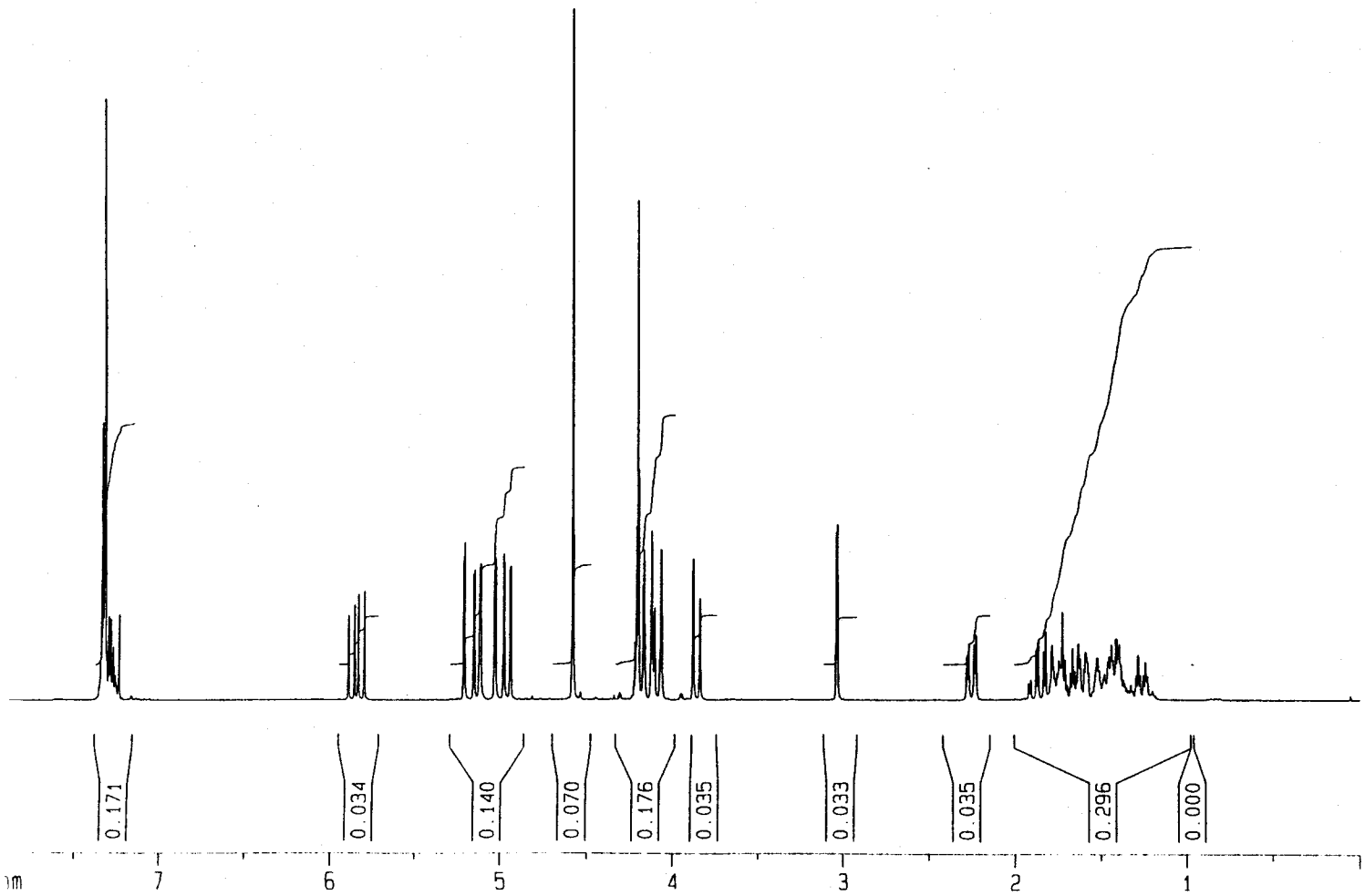
F2 - Acquisition Parameters
Date_ 20010816
Time 12.37
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 724.1
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 9.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm





Current Data Parameters

NAME	irina_455
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010706
Time	13.22
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	90.5
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

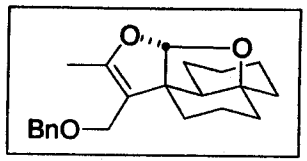
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

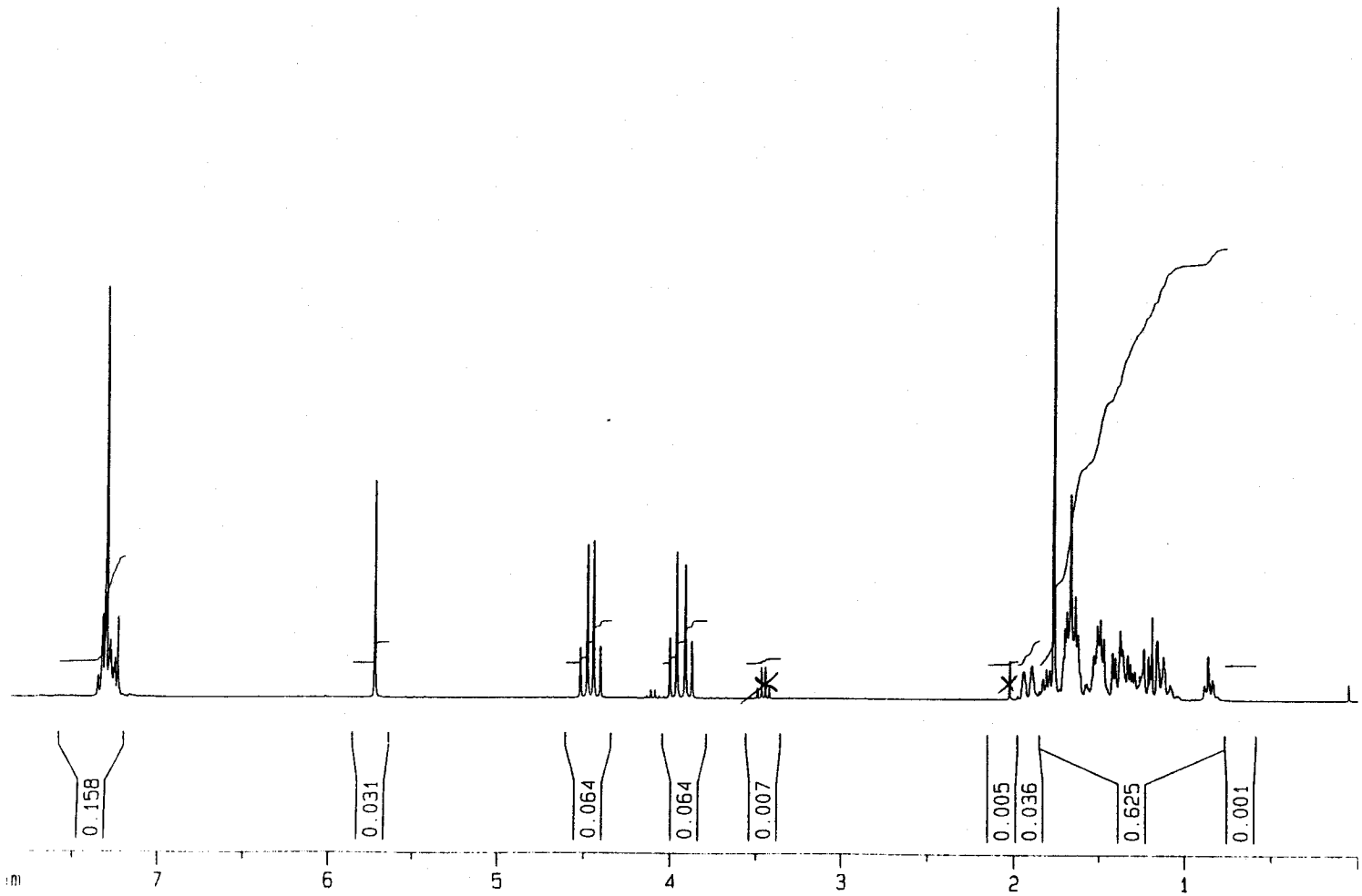
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





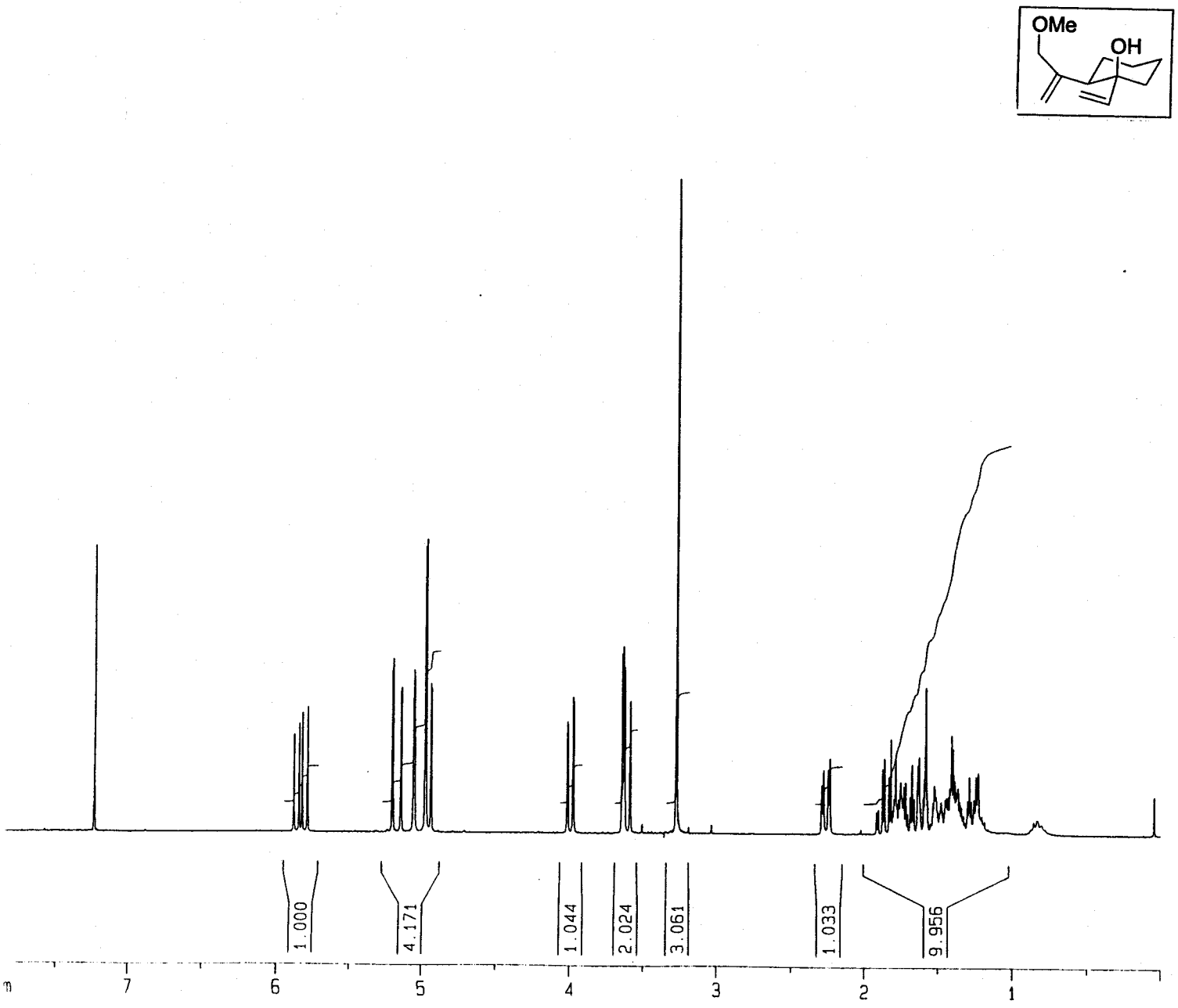
Current Data Parameters
NAME irina_460
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20010708
Time 18.48
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 128
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 9.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm



Current Data Parameters

NAME	irina_methyl
EXPNO	3
PROCNO	1

F2 - Acquisition Parameters

Date_	20020107
Time	15.36
INSTRUM	av300
PROBHD	5 mm GNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	406.4
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

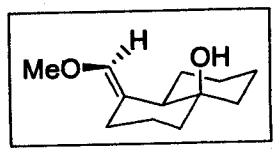
NUC1	1H
P1	11.00 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

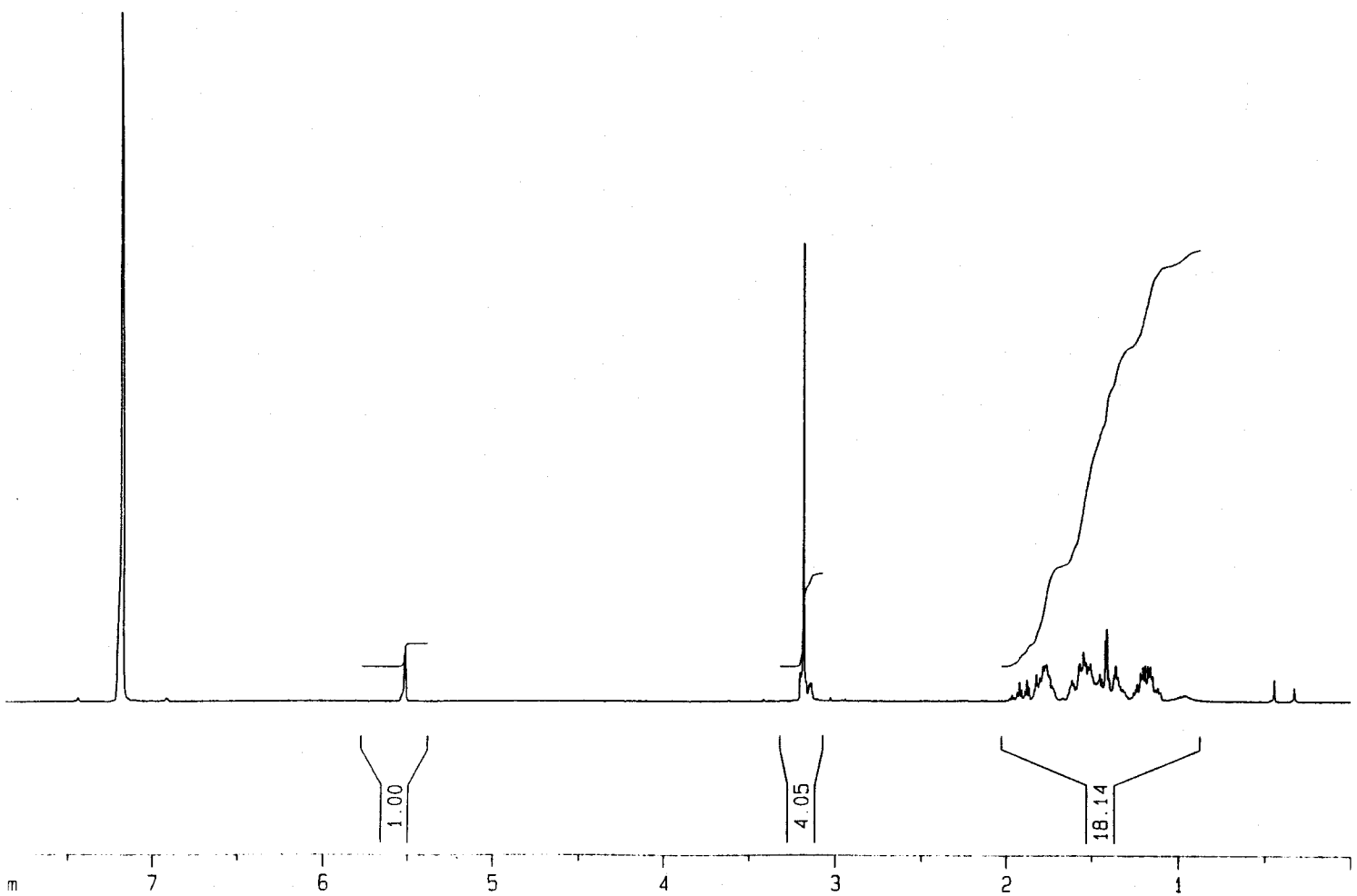
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	30.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





Current Data Parameters

NAME	irina_methox
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20020131
Time	13.00
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	~~CDCl3~~ C_6D_6
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	574.7
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

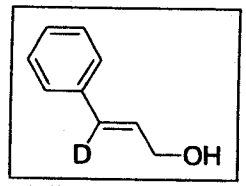
NUC1	1H
P1	11.00 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

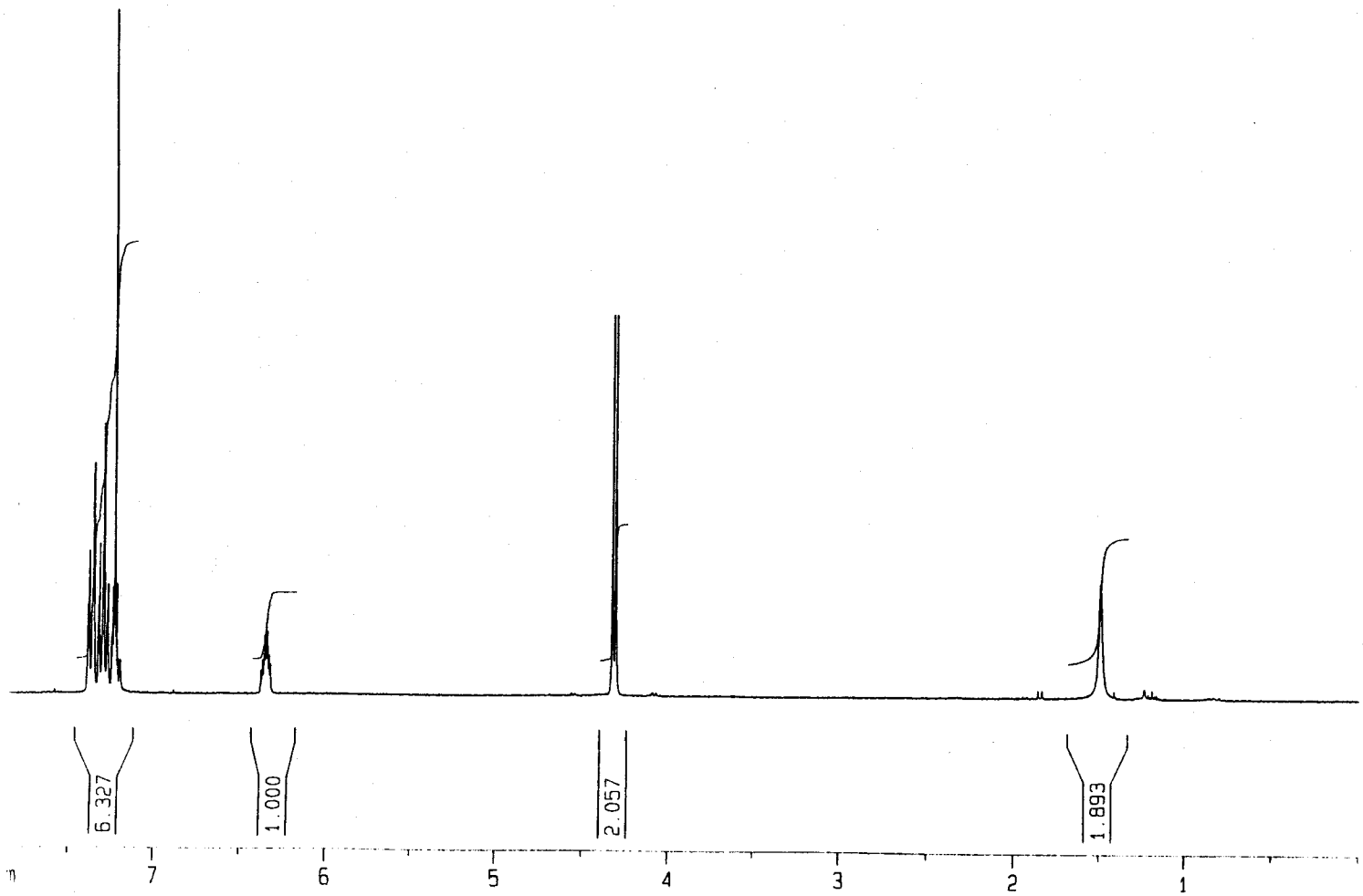
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





Current Data Parameters

NAME	irina_7-78
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20030827
Time	15.27
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	1024
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

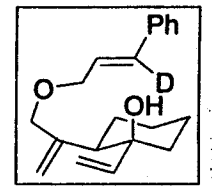
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

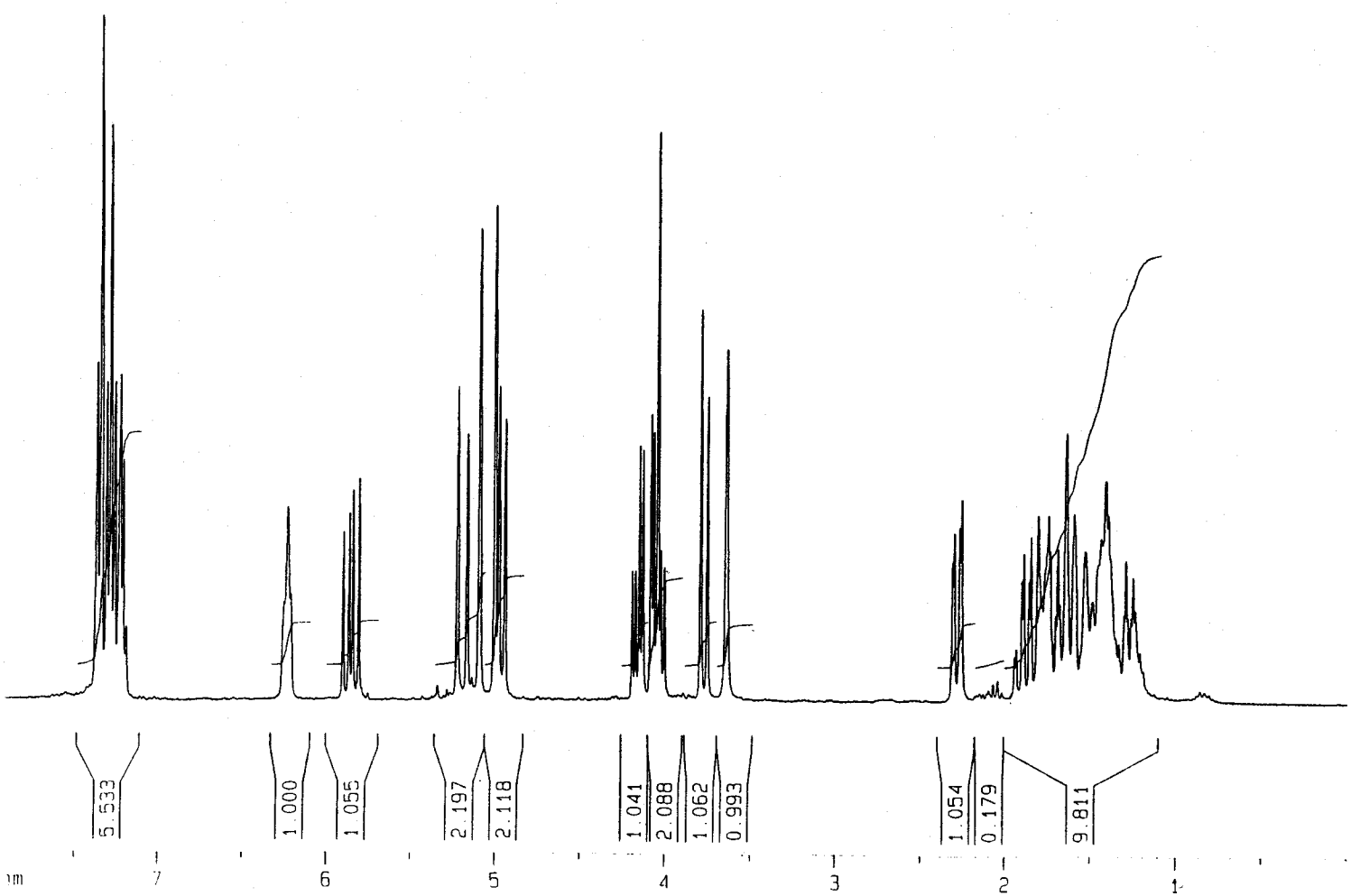
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





Current Data Parameters

NAME	irina_7-83
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20030828
Time	12.52
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	161.3
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

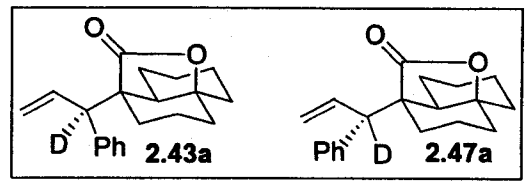
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

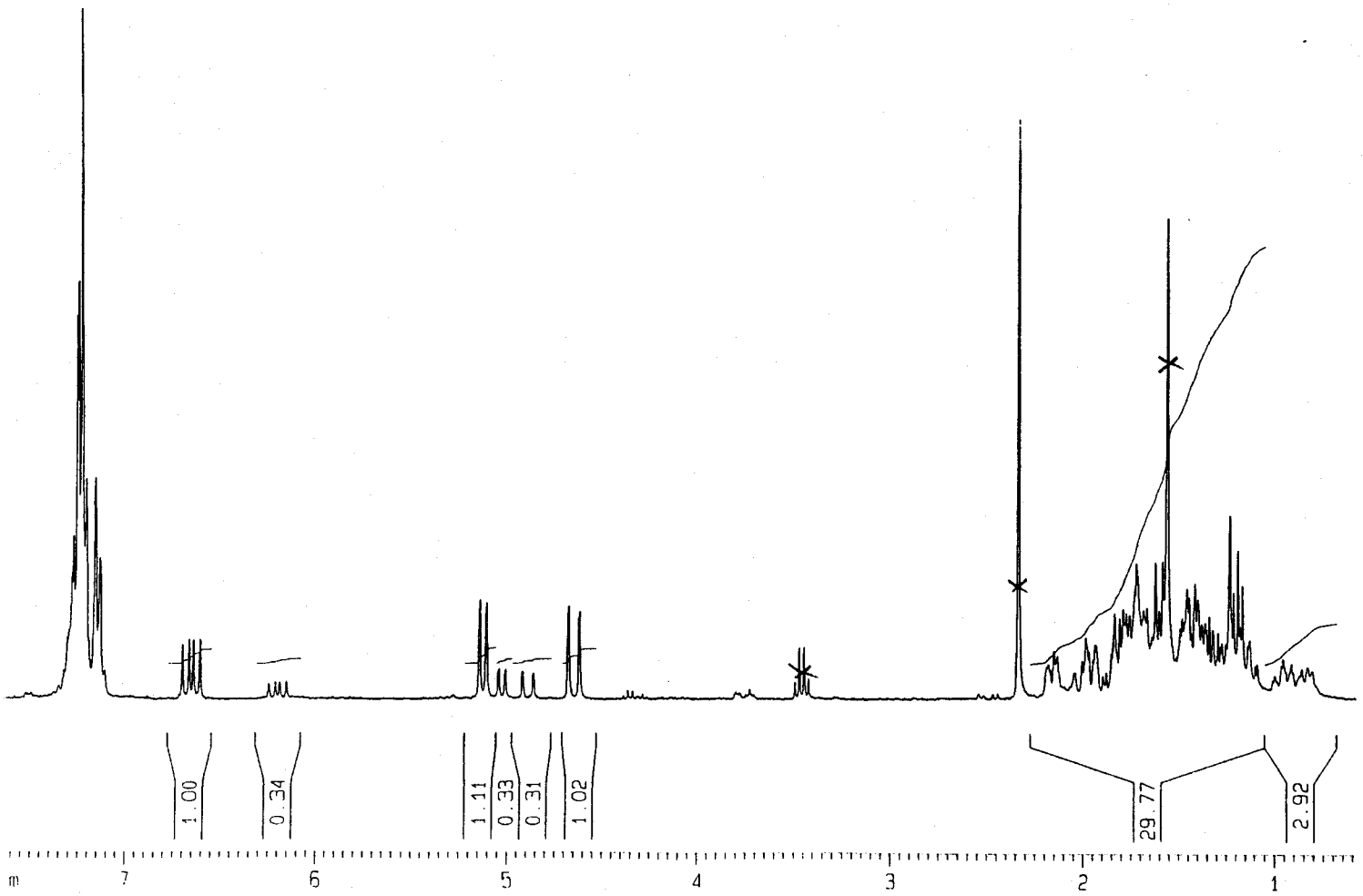
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





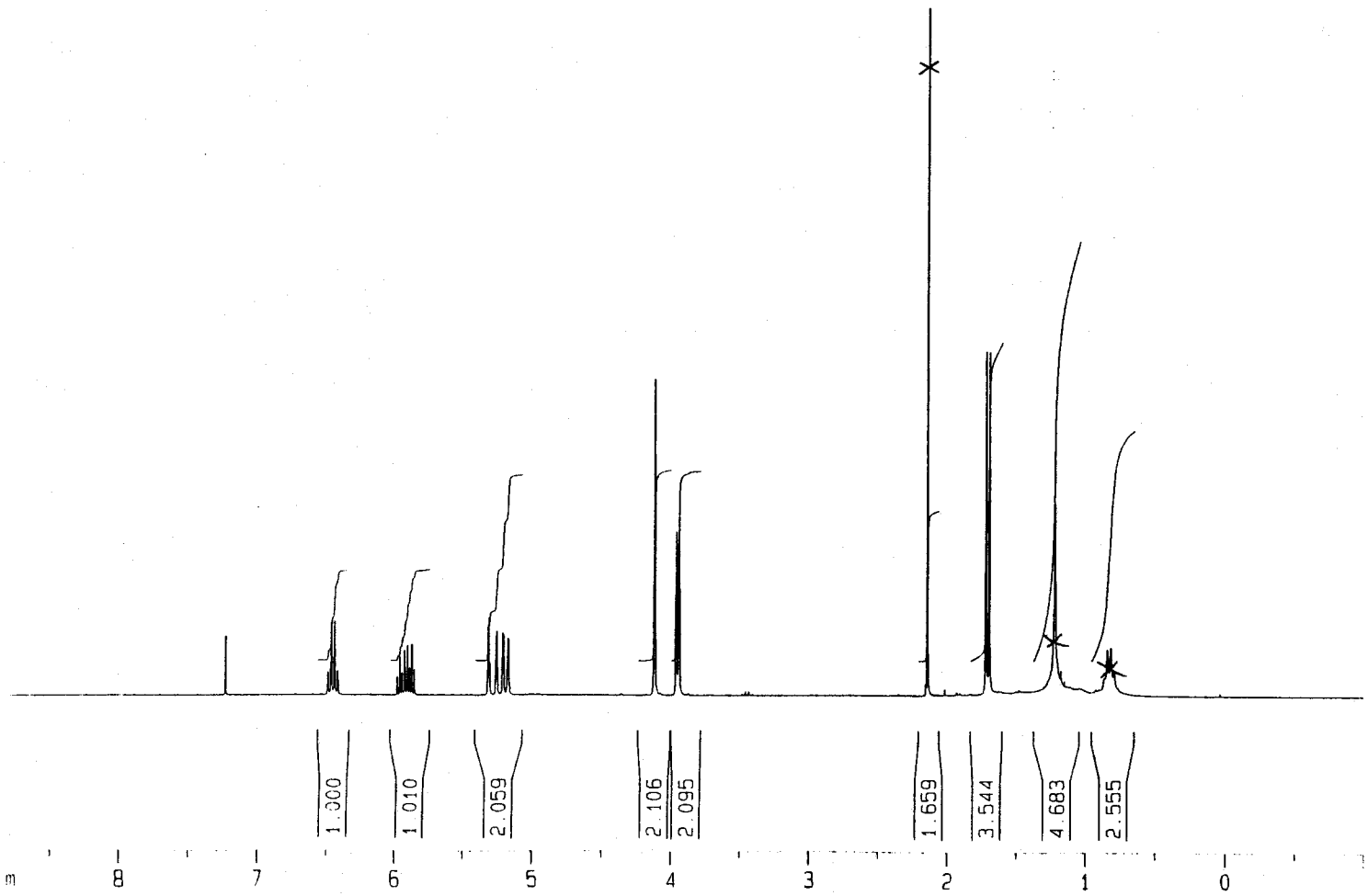
Current Data Parameters
NAME irina_7-87(2nd
EXPNO 1
PROCNO 1

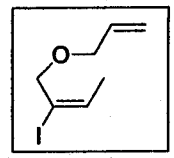
F2 - Acquisition Parameters
Date_ 20030903
Time 15.29
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 362
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 7.732 ppm
F1 2320.72 Hz
F2P 0.580 ppm
F2 174.18 Hz
PPMCM 0.35760 ppm/cm
HZCM 107.32664 Hz/cm





Current Data Parameters

NAME	effie-ira
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20030131
Time	12.07
INSTRUM	av300
PROBHD	5 mm GNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	5
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	128
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

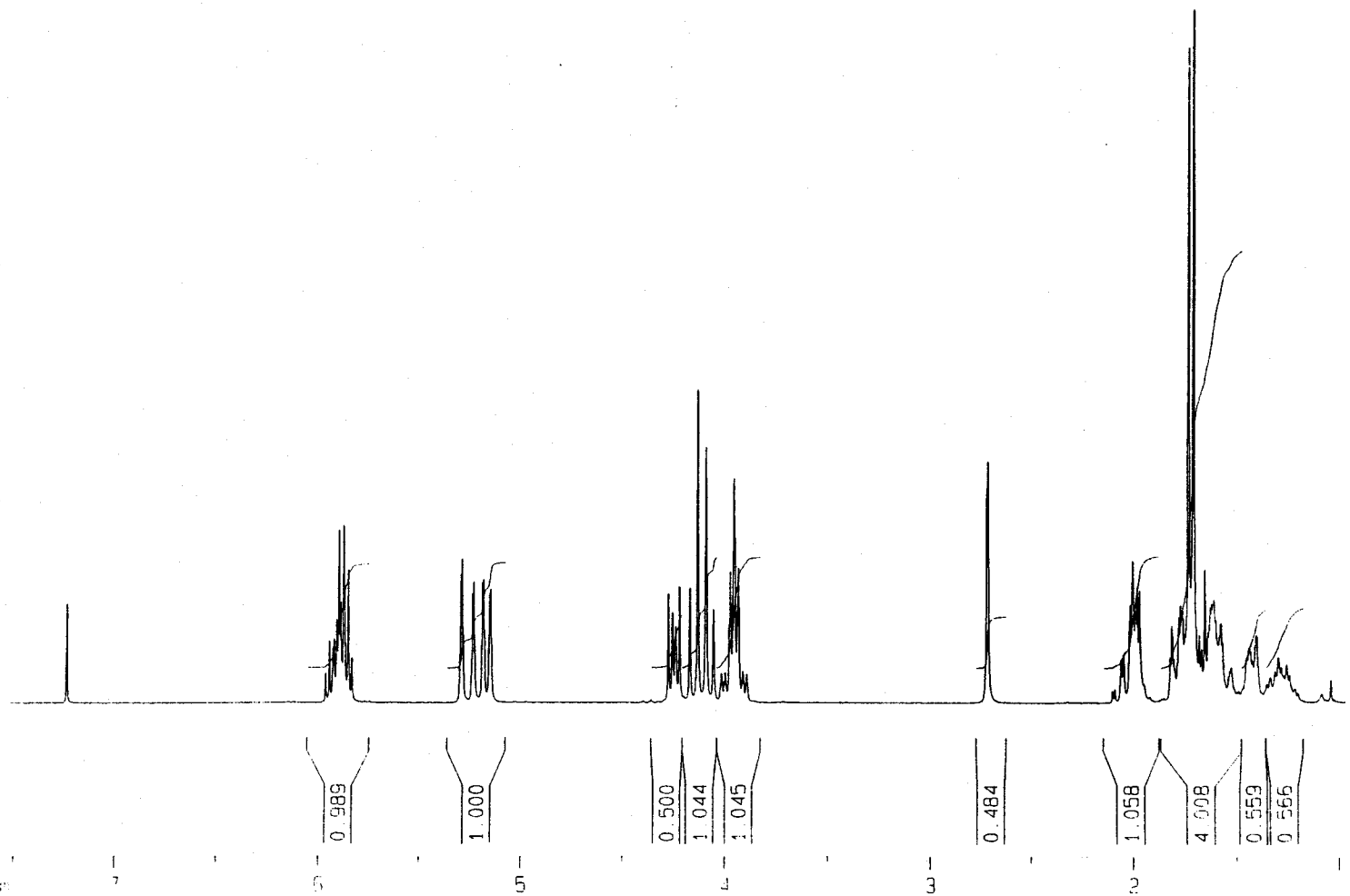
NUC1	1H
P1	9.75 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

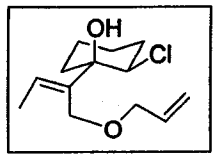
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	9.000 ppm
F1	2701.17 Hz
F2P	-1.000 ppm
F2	-300.13 Hz
PPMCM	0.50000 ppm/cm
HZCM	150.06500 Hz/cm





Current Data Parameters

NAME	irina_7-94
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20030929
Time	12.14
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	128
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

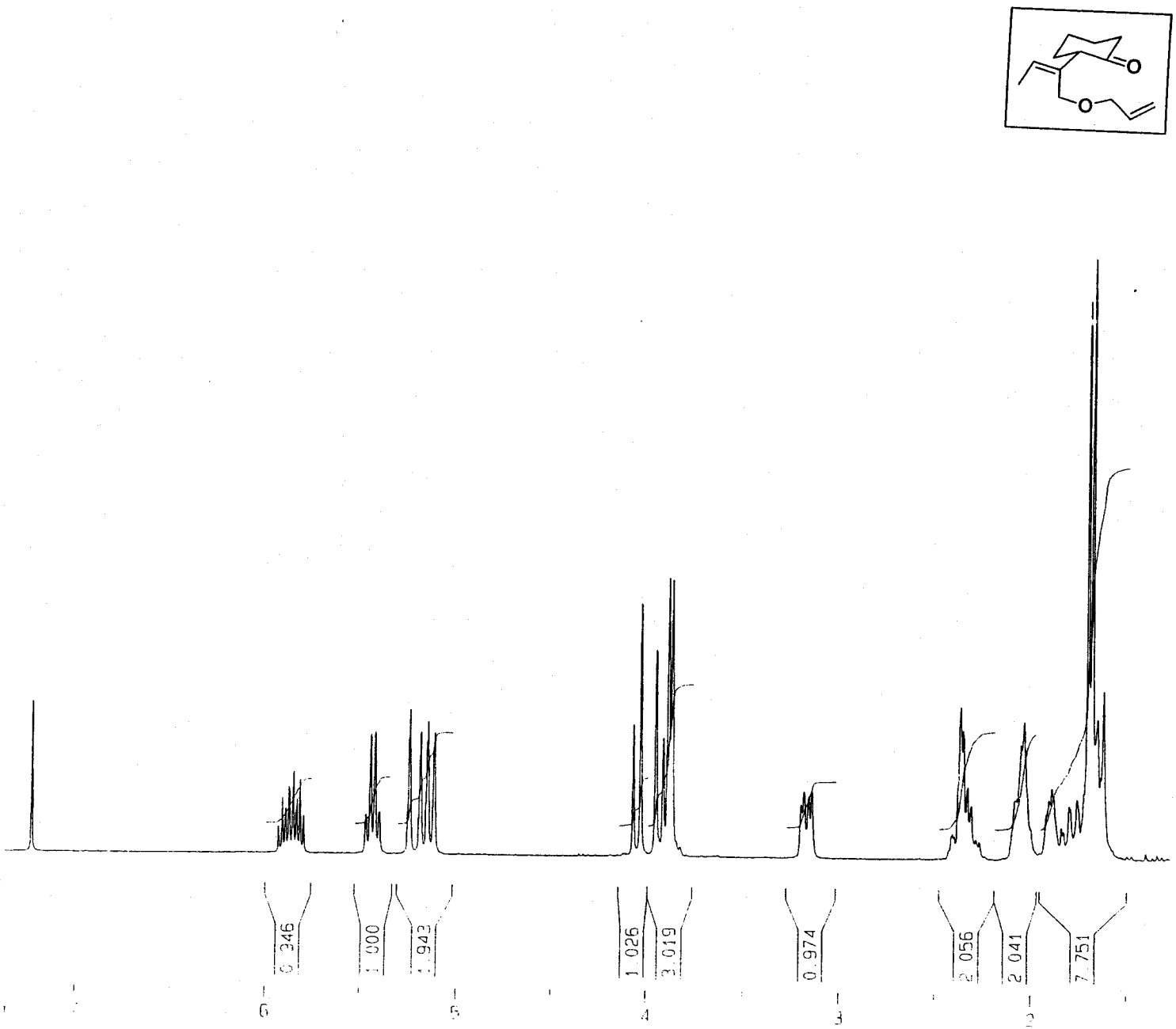
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	7.686 ppm
F1	2306.72 Hz
F2P	0.969 ppm
F2	290.77 Hz
PPMCM	0.33585 ppm/cm
HZCM	100.79755 Hz/cm



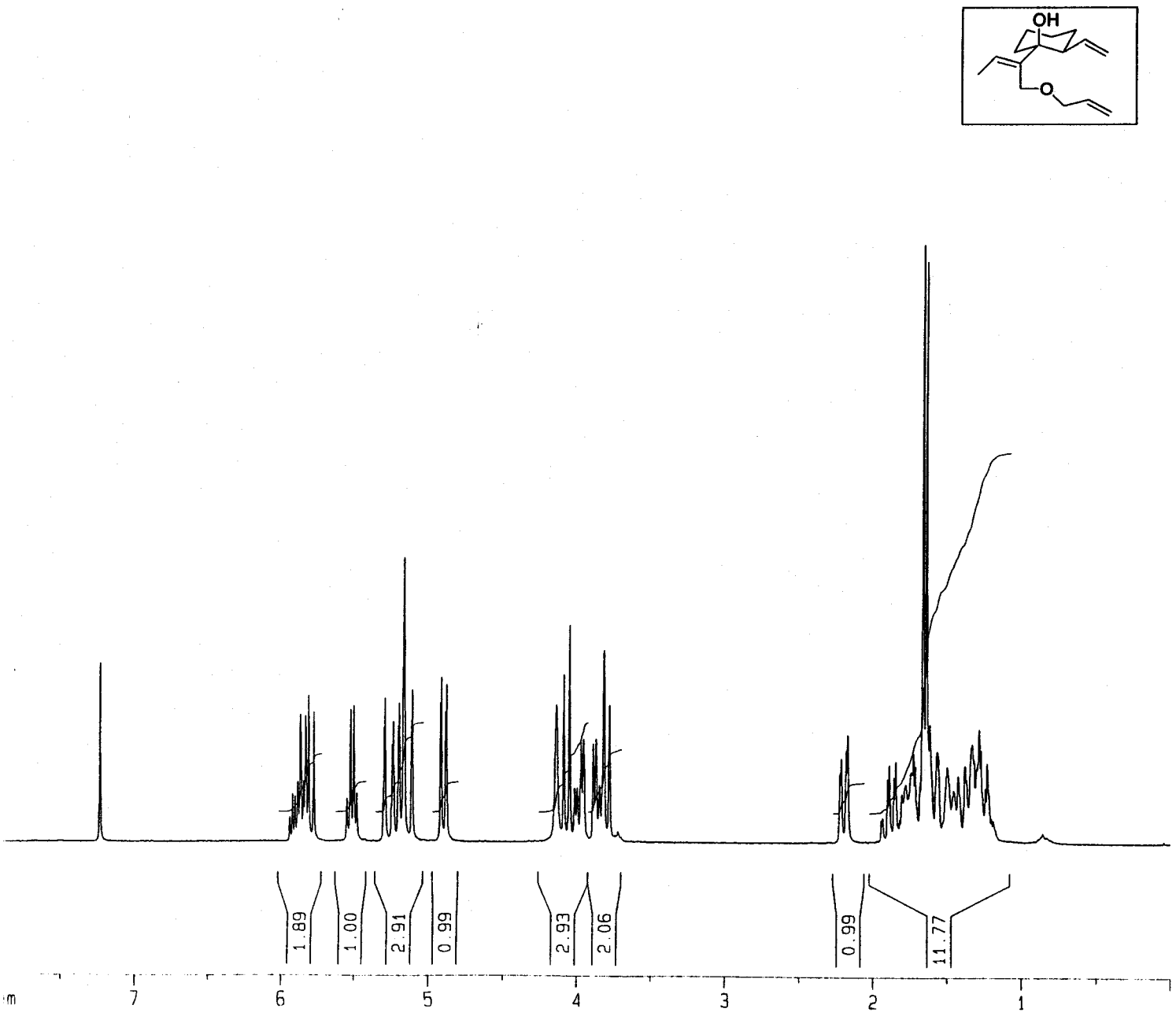
Current Data Parameters
NAME irina_7-95
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20030929
Time 18.56
INSTRUM av300
PROBHD 5 mm GNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 228.1
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 7.502 ppm
F1 2251.49 Hz
F2P 1.268 ppm
F2 380.52 Hz
PPMCM 0.31169 ppm/cm
HZCM 93.54841 Hz/cm



Current Data Parameters

NAME	irina_7-100
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20031007
Time	10.14
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	256
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

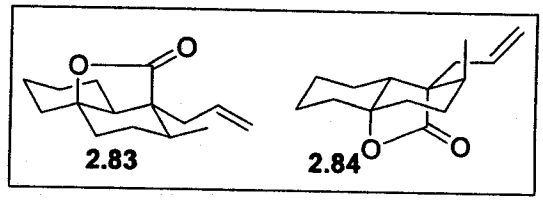
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm



Current Data Parameters
NAME irina_7-122-repeat 112
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters

Date_	20040513
Time	5.57
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	32
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	574.7
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

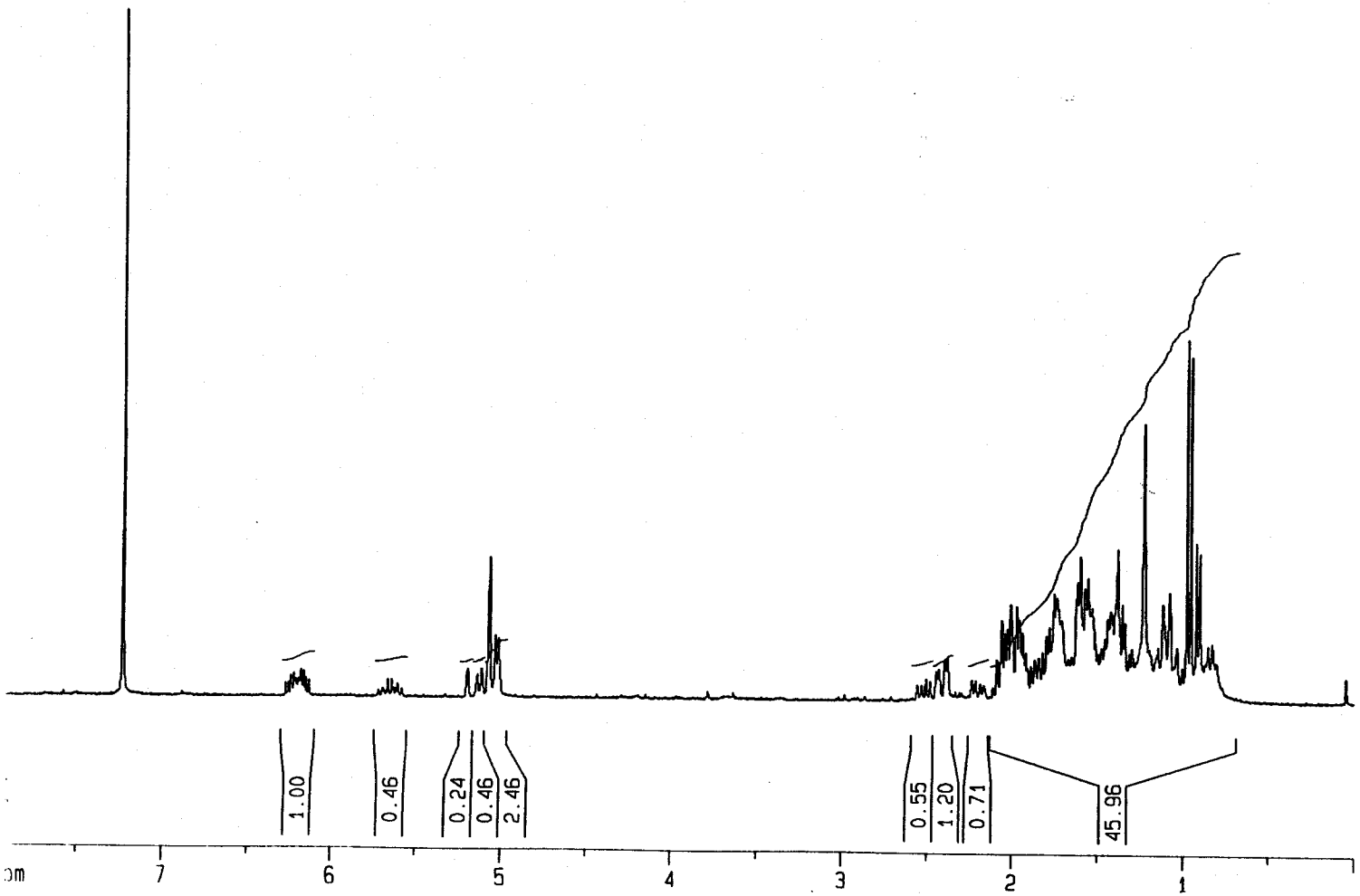
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

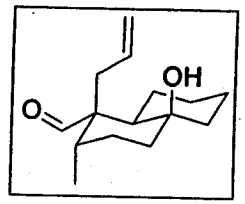
F2 - Processing parameters

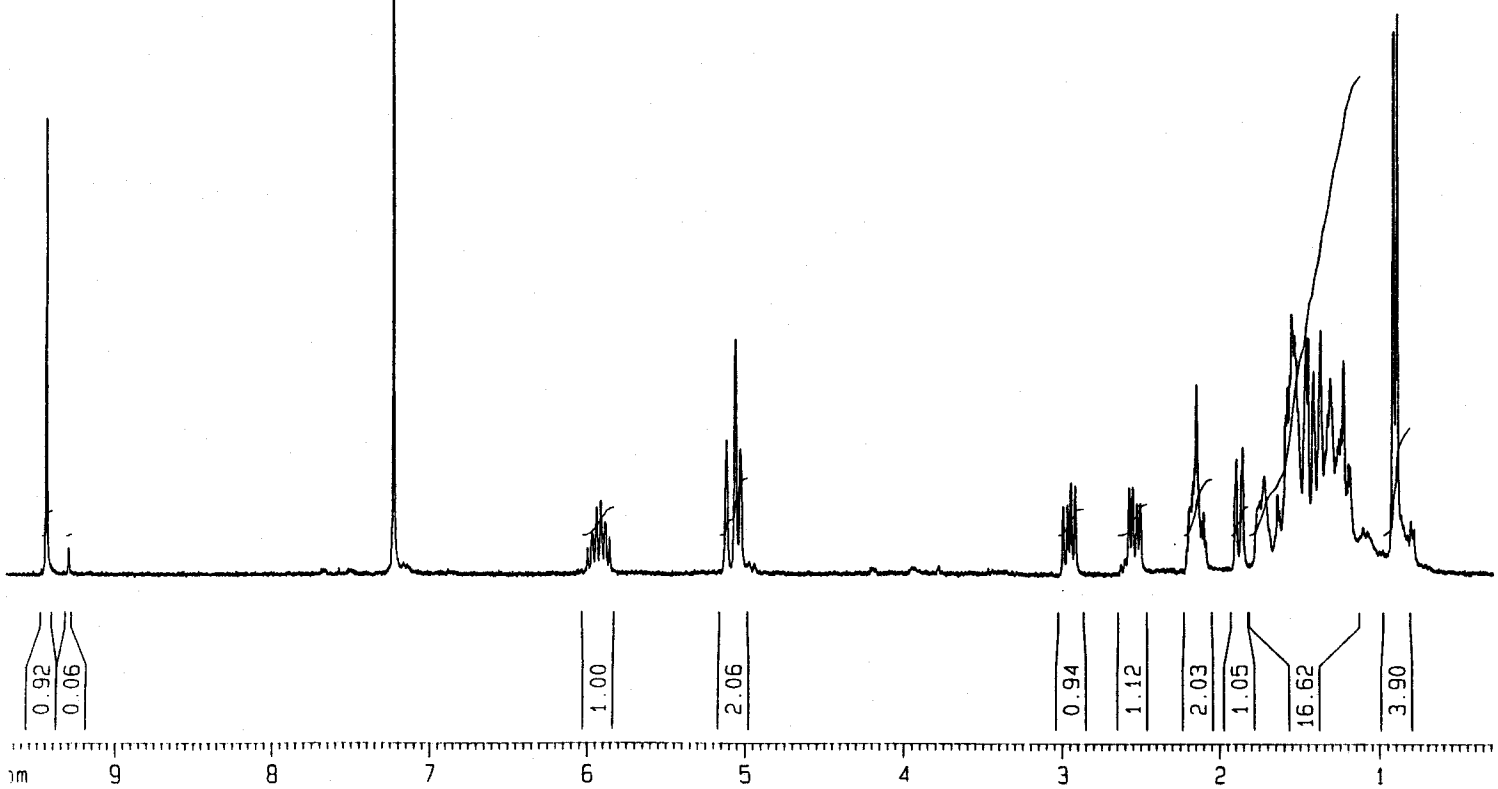
SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm







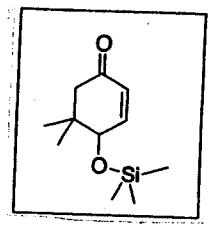
Current Data Parameters
NAME irina_7-105(a)
EXPNO 2
PROCNO 1

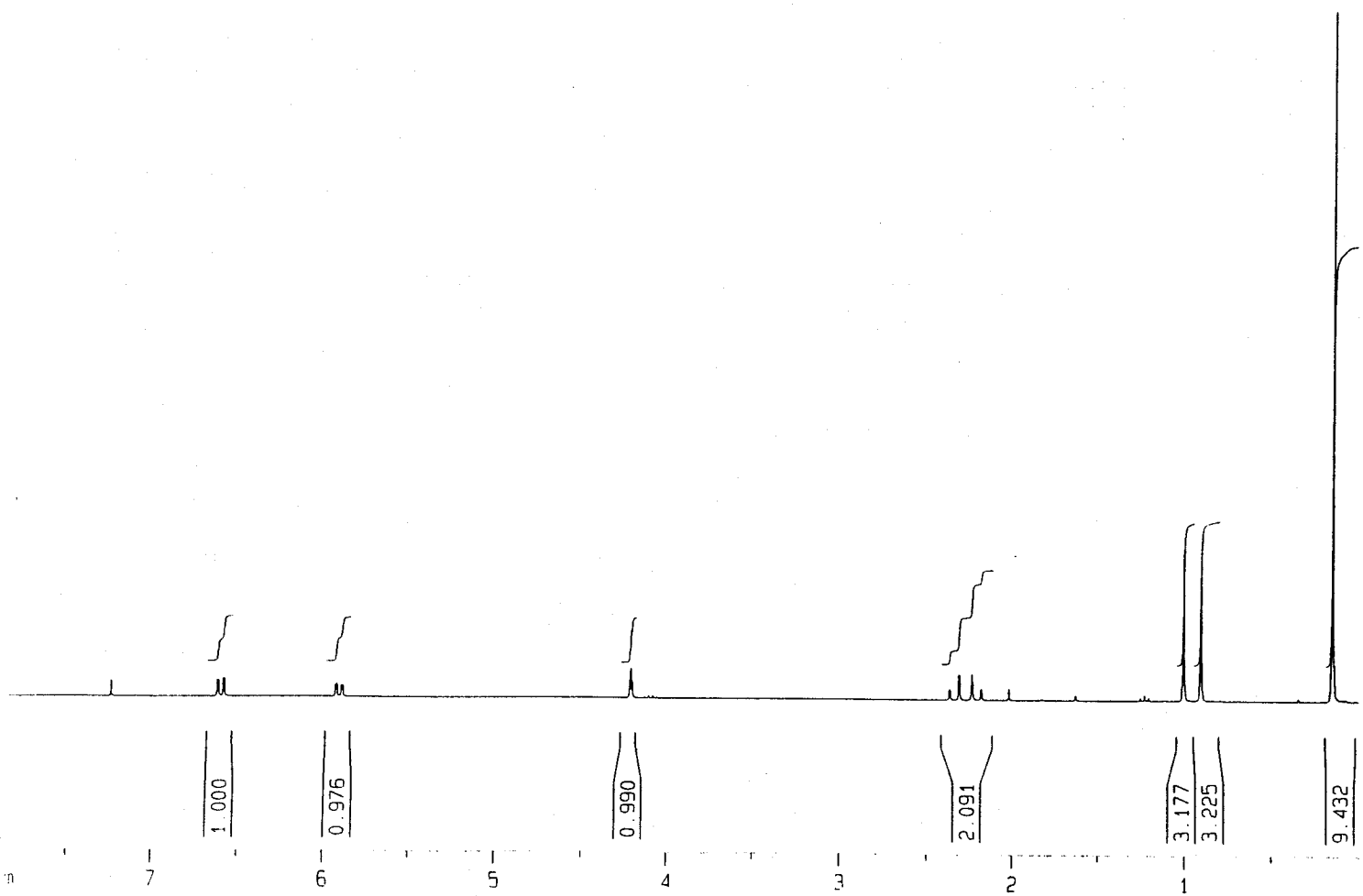
F2 - Acquisition Parameters
Date_ 20031027
Time 22.12
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 645.1
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 9.800 ppm
F1 2941.36 Hz
F2P 0.285 ppm
F2 85.63 Hz
PPMCM 0.47575 ppm/cm
HZCM 142.78653 Hz/cm





Current Data Parameters

NAME	irina_sm
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20020914
Time	18.54
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	203.2
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

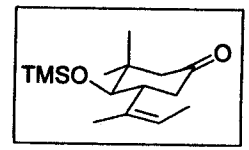
NUC1	1H
P1	9.75 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm



Current Data Parameters

NAME	irina_711
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20020919
Time	19.06
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	181
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

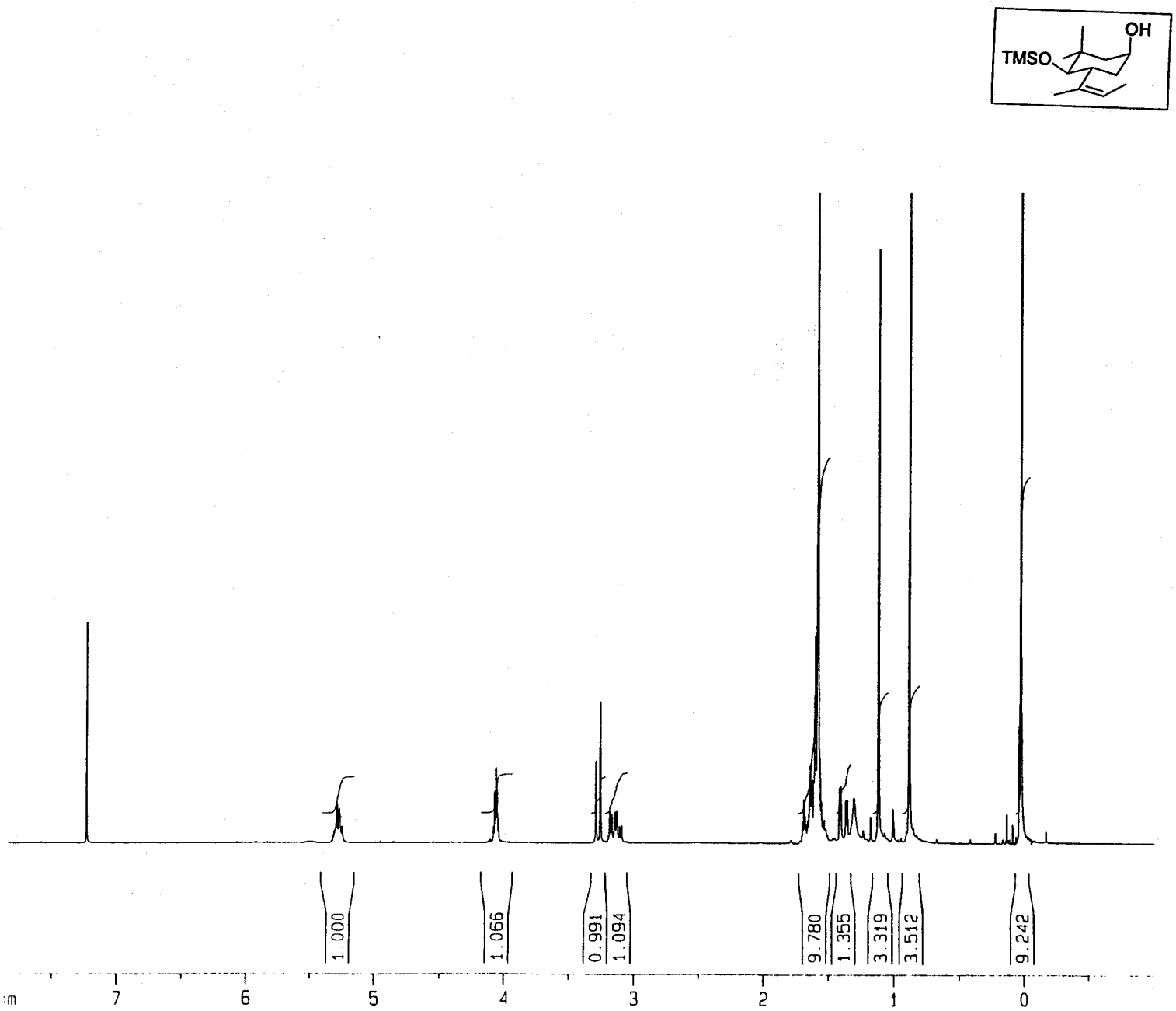
NUC1	1H
P1	9.75 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	-0.500 ppm
F2	-150.06 Hz
PPMCM	0.42500 ppm/cm
HZCM	127.55524 Hz/cm



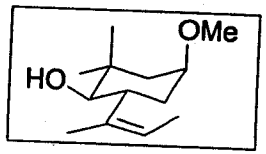
Current Data Parameters
NAME irina_axial1
EXPNO 1
PROCNO 1

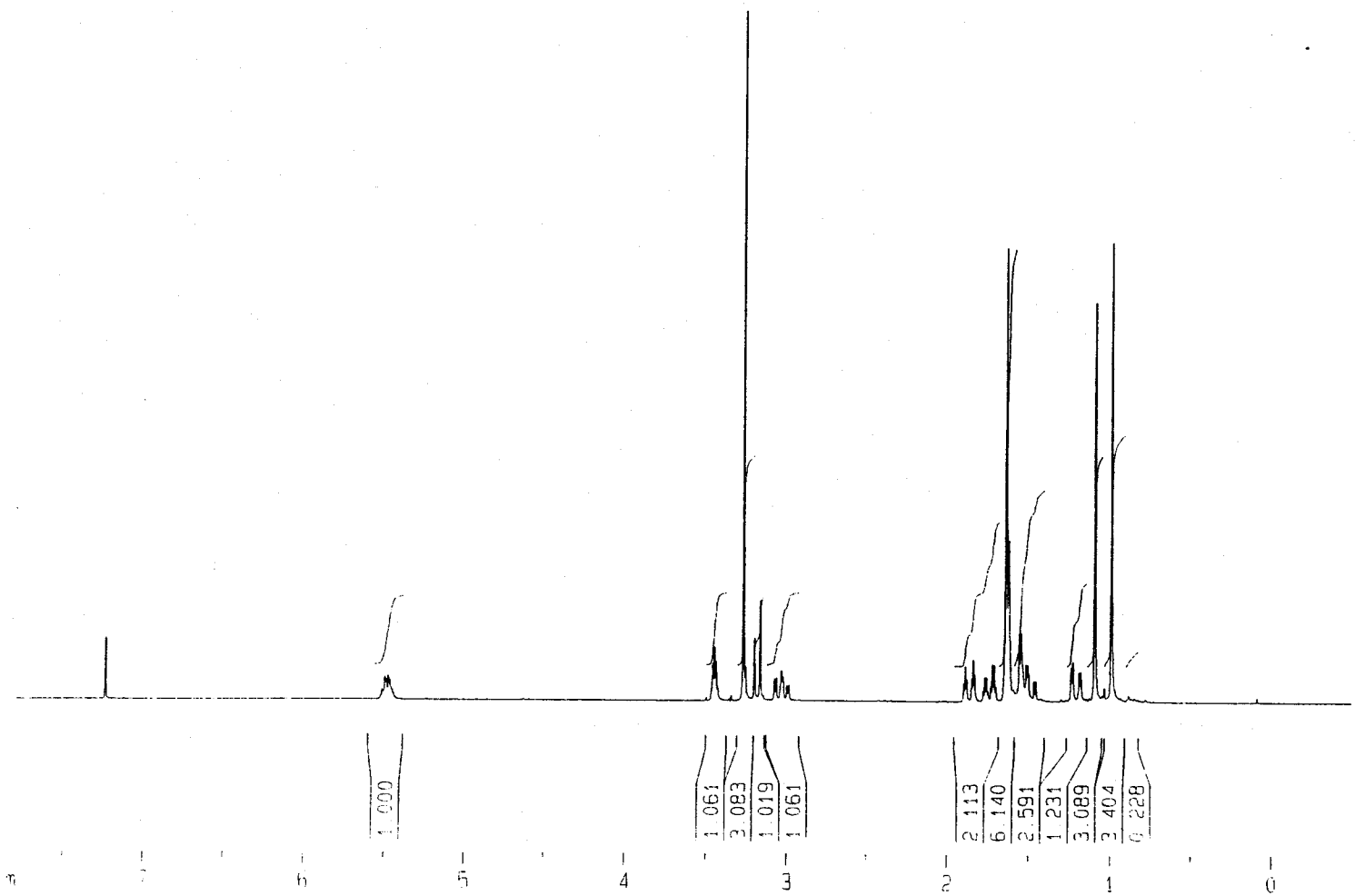
F2 - Acquisition Parameters
Date_ 20040126
Time 19.03
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 287.4
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 50.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P -1.000 ppm
F2 -300.13 Hz
PPMCM 0.45000 ppm/cm
HZCM 135.05850 Hz/cm





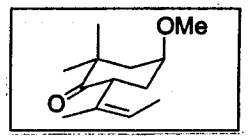
Current Data Parameters
NAME irina_716
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20020926
Time 19.30
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 228.1
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 9.75 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P -0.500 ppm
F2 -150.06 Hz
PPMCM 0.42500 ppm/cm
HZCM 127.55524 Hz/cm



Current Data Parameters

NAME	irina717
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20020928
Time	15.45
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	724.1
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

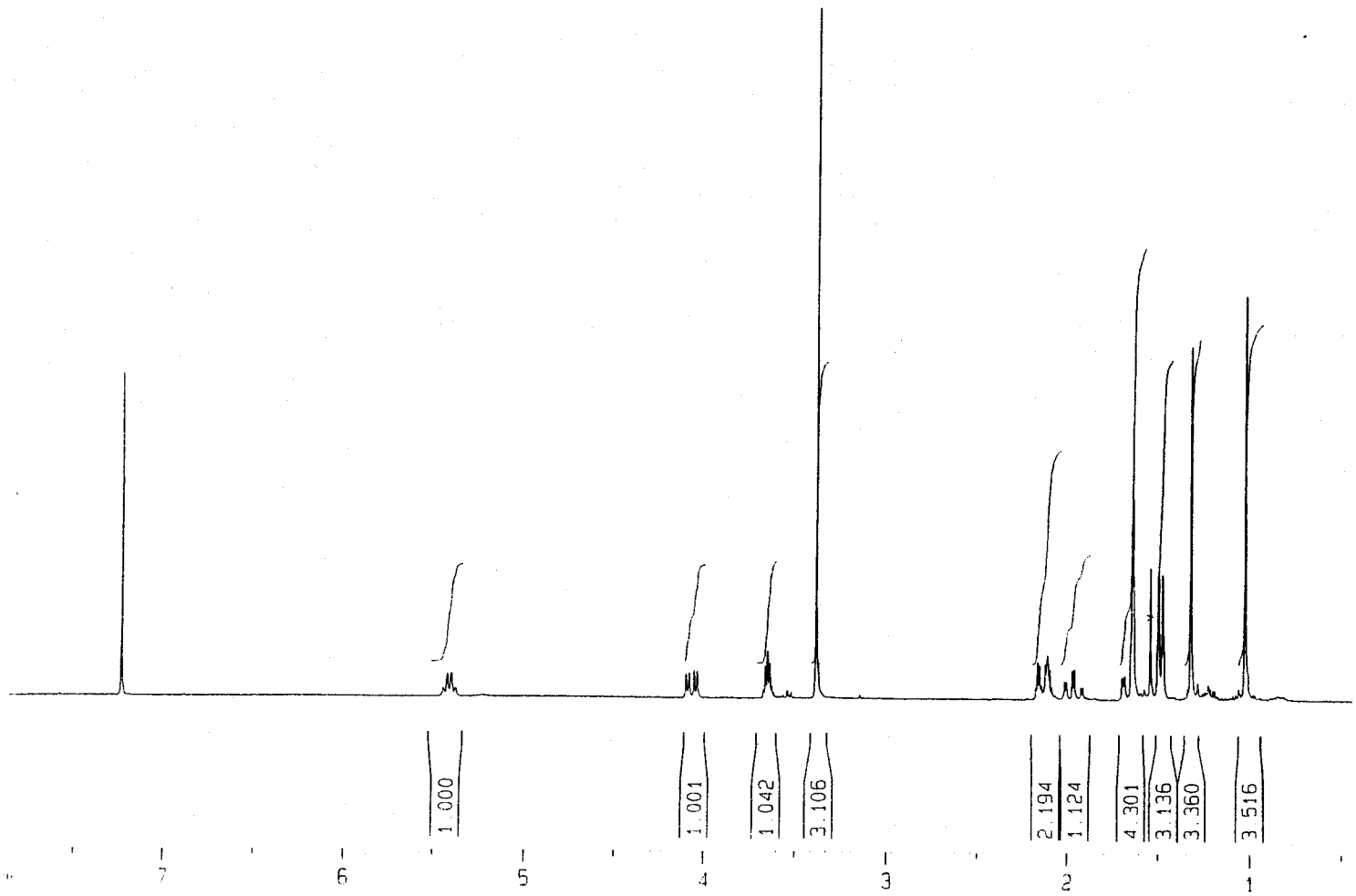
NUC1	1H
P1	9.75 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

F2 - Processing parameters

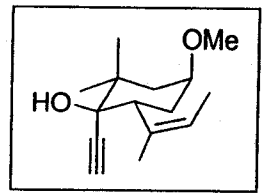
SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

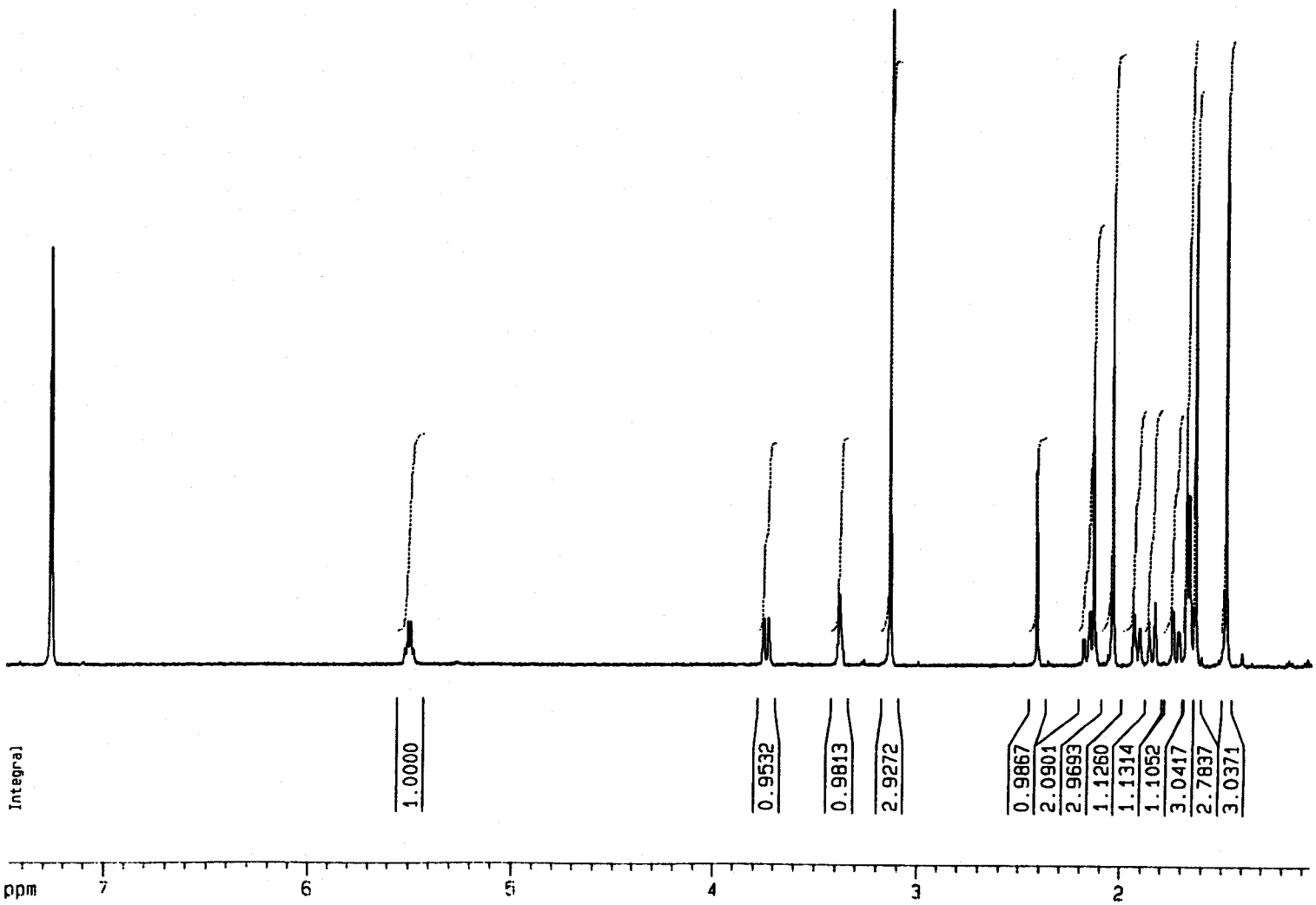
1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.025 ppm
F1	2408.42 Hz
F2P	0.440 ppm
F2	131.99 Hz
PPMCM	0.37924 ppm/cm
HZCM	113.82114 Hz/cm



1H NMR





Current Data Parameters

NAME	irina_test
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040318
Time	19.32
INSTRUM	AV500NB
PROBHD	5 mm BBI 1H-BB
PULPROG	zg30
TD	65536
SOLVENT	~~Acetone~~ C_6D_6
NS	8
DS	0
SWH	7440.476 Hz
FIDRES	0.113533 Hz
AQ	4.4040694 sec
RG	912.3
DW	67.200 usec
DE	6.00 usec
TE	300.0 K
D1	0.01000000 sec

======== CHANNEL f1 ========

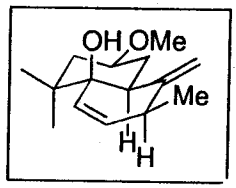
NUC1	1H
P1	10.50 usec
PL1	3.00 dB
SFO1	500.1327766 MHz

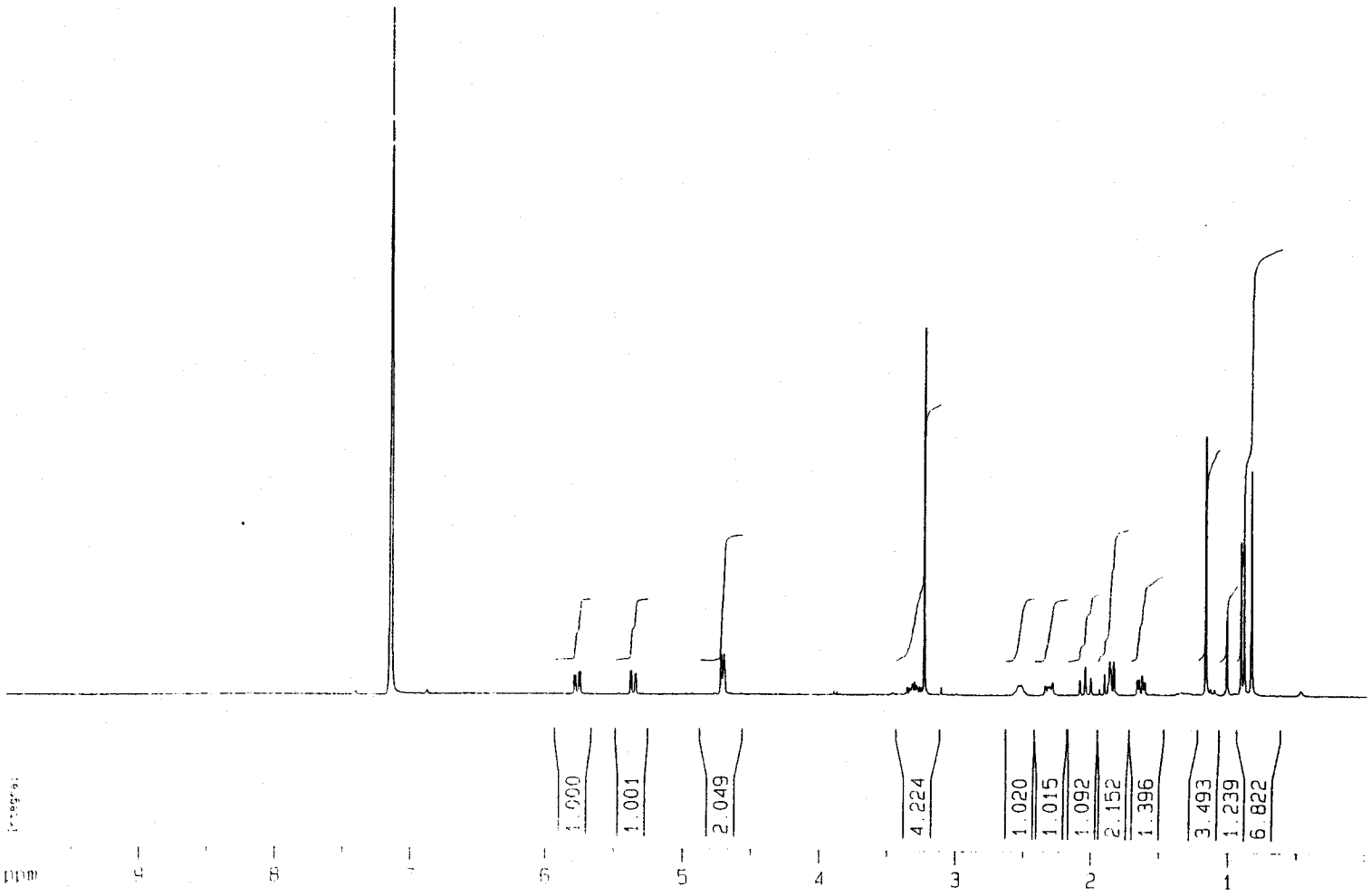
F2 - Processing parameters

SI	65536
SF	500.1300049 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	7.487 ppm
F1	3744.46 Hz
F2P	1.058 ppm
F2	529.20 Hz
PPMCM	0.32144 ppm/cm
HZCM	160.76323 Hz/cm





Current Data Parameters
NAME irina_I
EXPNO 1
PROCNO 1

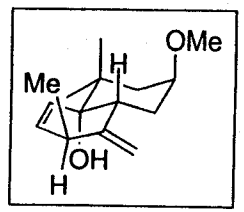
F2 - Acquisition Parameters
Date_ 20030219
Time 20.09
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT ~~CDCl3~~ C_6D_6
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 362
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 9.75 usec
PL1 -3.00 dB
SF01 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 10.000 ppm
F1 3001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.50000 ppm/cm
HZCM 150.06500 Hz/cm

1H NMR



Current Data Parameters

NAME	irina_8-44min
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040301
Time	19.33
INSTRUM	AV500WB
PROBHD	5 mm BBI 1H-BB
PULPROG	zg30
TD	65536
SOLVENT	~~Acetone~~ C_6D_6
NS	16
DS	0
SWH	7440.476 Hz
FIDRES	0.113533 Hz
AQ	4.4040694 sec
RG	203.2
DW	67.200 usec
DE	6.00 usec
TE	300.0 K
D1	0.01000000 sec

======== CHANNEL f1 ========

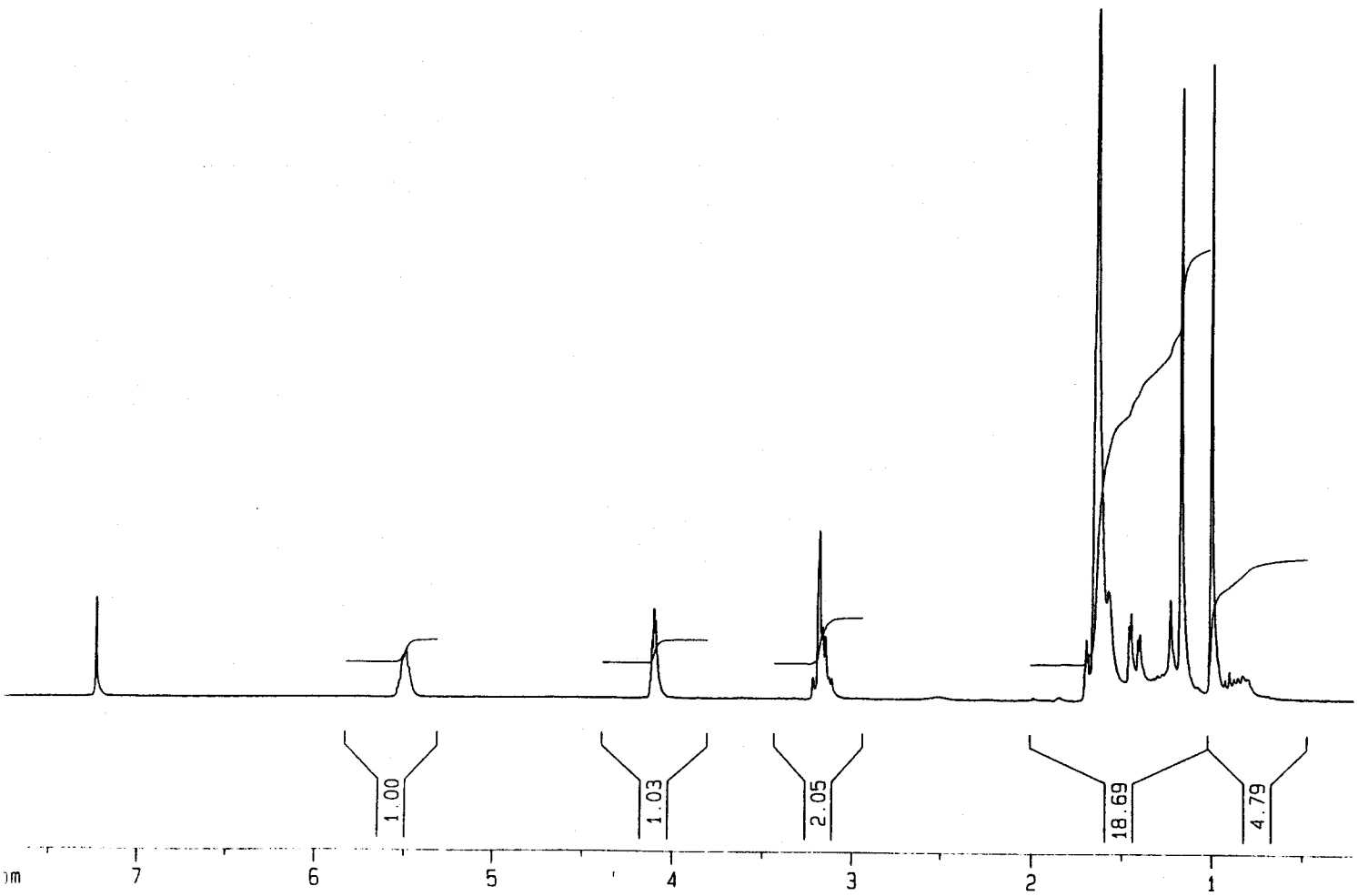
NUC1	1H
P1	10.50 usec
PL1	3.00 dB
SFO1	500.1327766 MHz

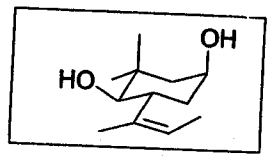
F2 - Processing parameters

SI	65536
SF	500.1300049 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	40.00 cm
F1P	8.000 ppm
F1	4001.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	200.05200 Hz/cm





Current Data Parameters

NAME	ng_7
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20030513
Time	17.13
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	287.4
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

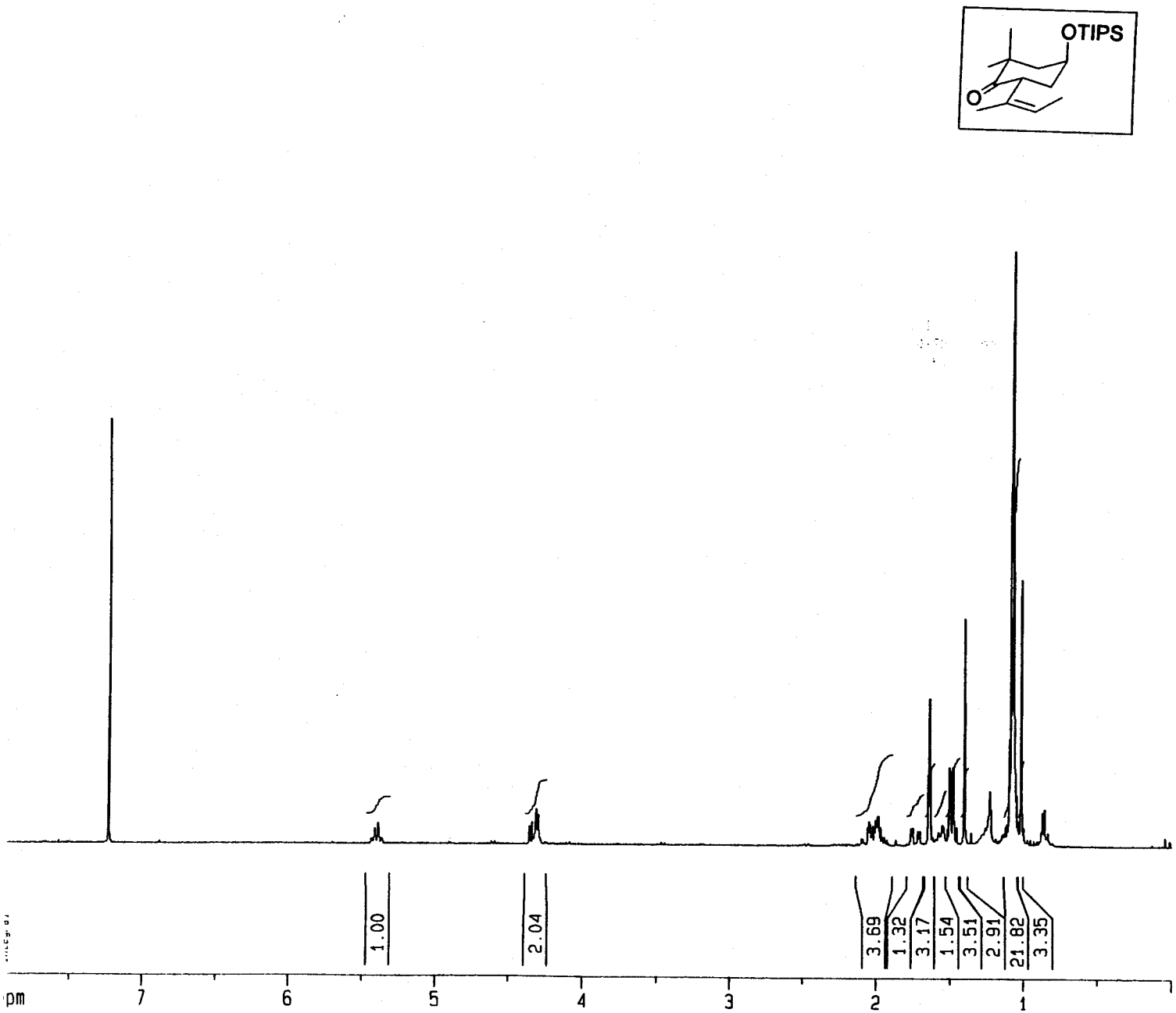
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	7.843 ppm
F1	2353.81 Hz
F2P	0.216 ppm
F2	64.88 Hz
PPMCM	0.38132 ppm/cm
HZCM	114.44675 Hz/cm



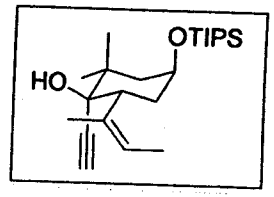
Current Data Parameters
NAME irina_TIPSka
EXPNO 1
PROCNO 1

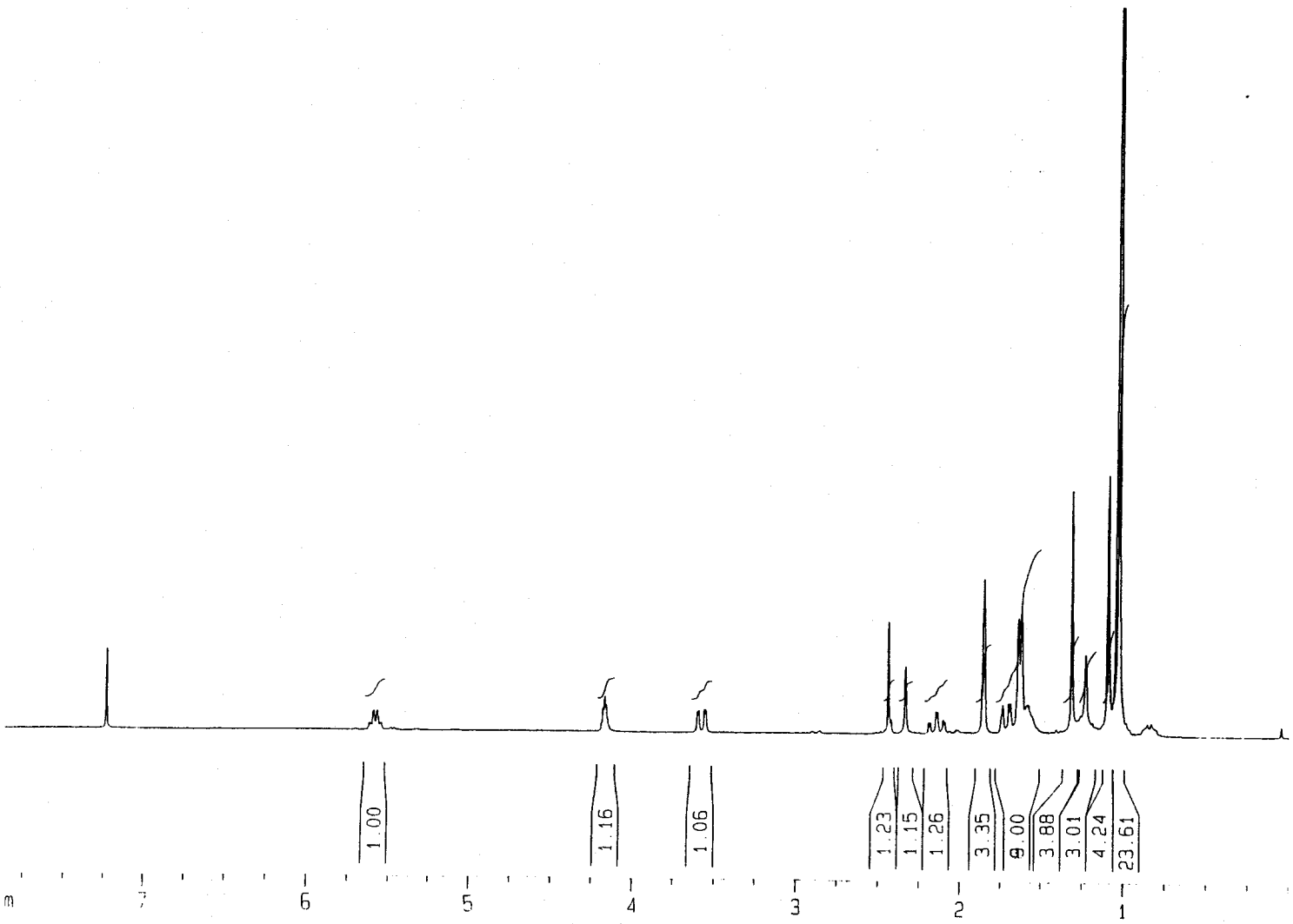
F2 - Acquisition Parameters
Date_ 20040531
Time 20.35
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 574.7
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm





Current Data Parameters

NAME	irina_TIPS
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040229
Time	20.29
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	203.2
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

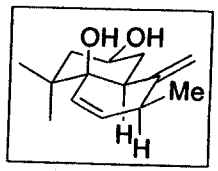
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	20.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm

1H NMR



Current Data Parameters

NAME	irina_8-76repeat
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040415
Time	20.58
INSTRUM	AV500WB
PROBHD	5 mm BBI 1H-BB
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	16
DS	0
SWH	7440.476 Hz
FIDRES	0.113533 Hz
AQ	4.4040694 sec
RG	143.7
DW	67.200 usec
DE	6.00 usec
TE	300.0 K
D1	0.01000000 sec

======== CHANNEL f1 ========

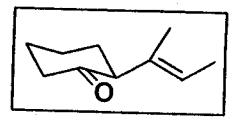
NUC1	1H
P1	10.50 usec
PL1	3.00 dB
SFO1	500.1327766 MHz

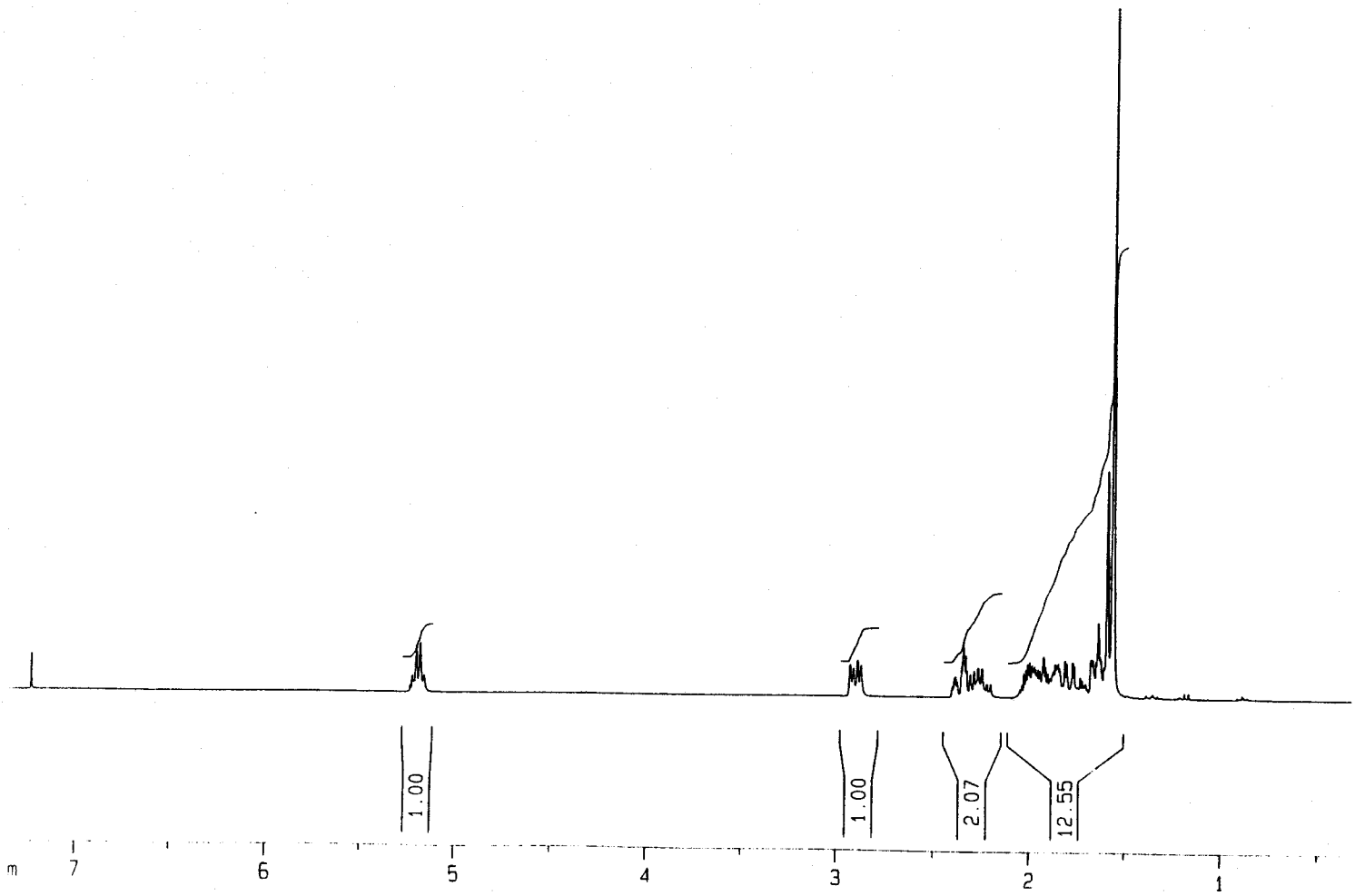
F2 - Processing parameters

SI	65536
SF	500.1300049 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	200.00 cm
F1P	8.000 ppm
F1	4001.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	200.05200 Hz/cm





Current Data Parameters

NAME	irina_7-75
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20030826
Time	15.42
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	80.6
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

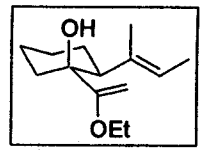
F2 - Processing parameters

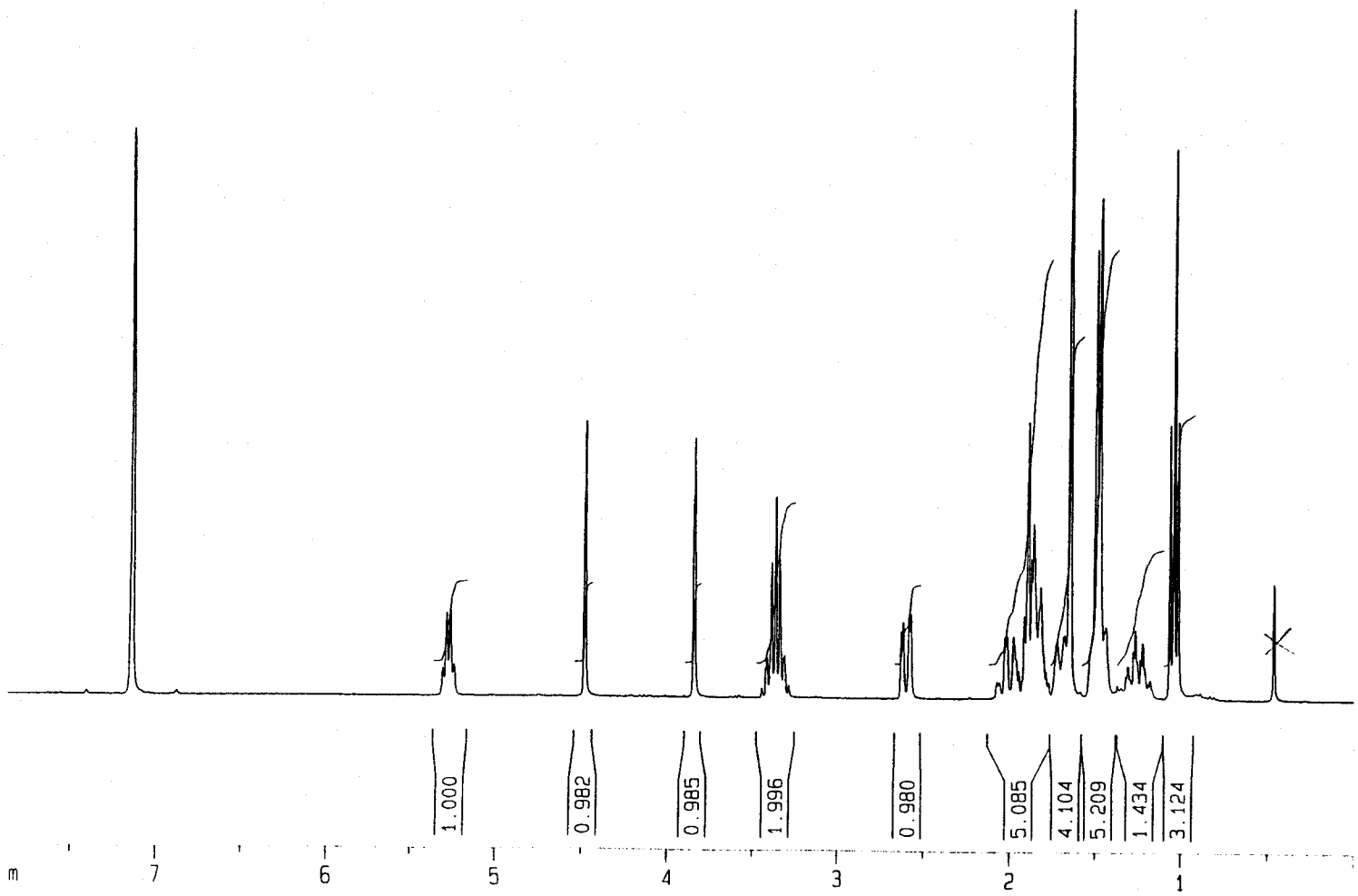
SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	7.474 ppm
F1	2243.30 Hz
F2P	0.322 ppm
F2	96.77 Hz
PPMCM	0.35760 ppm/cm
HZCM	107.32664 Hz/cm

C_6D_6





Current Data Parameters

NAME	irina_7-88
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20030904
Time	13.00
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	~~CDCl3~~ C_6D_6
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	228.1
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

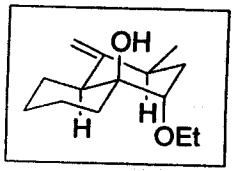
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

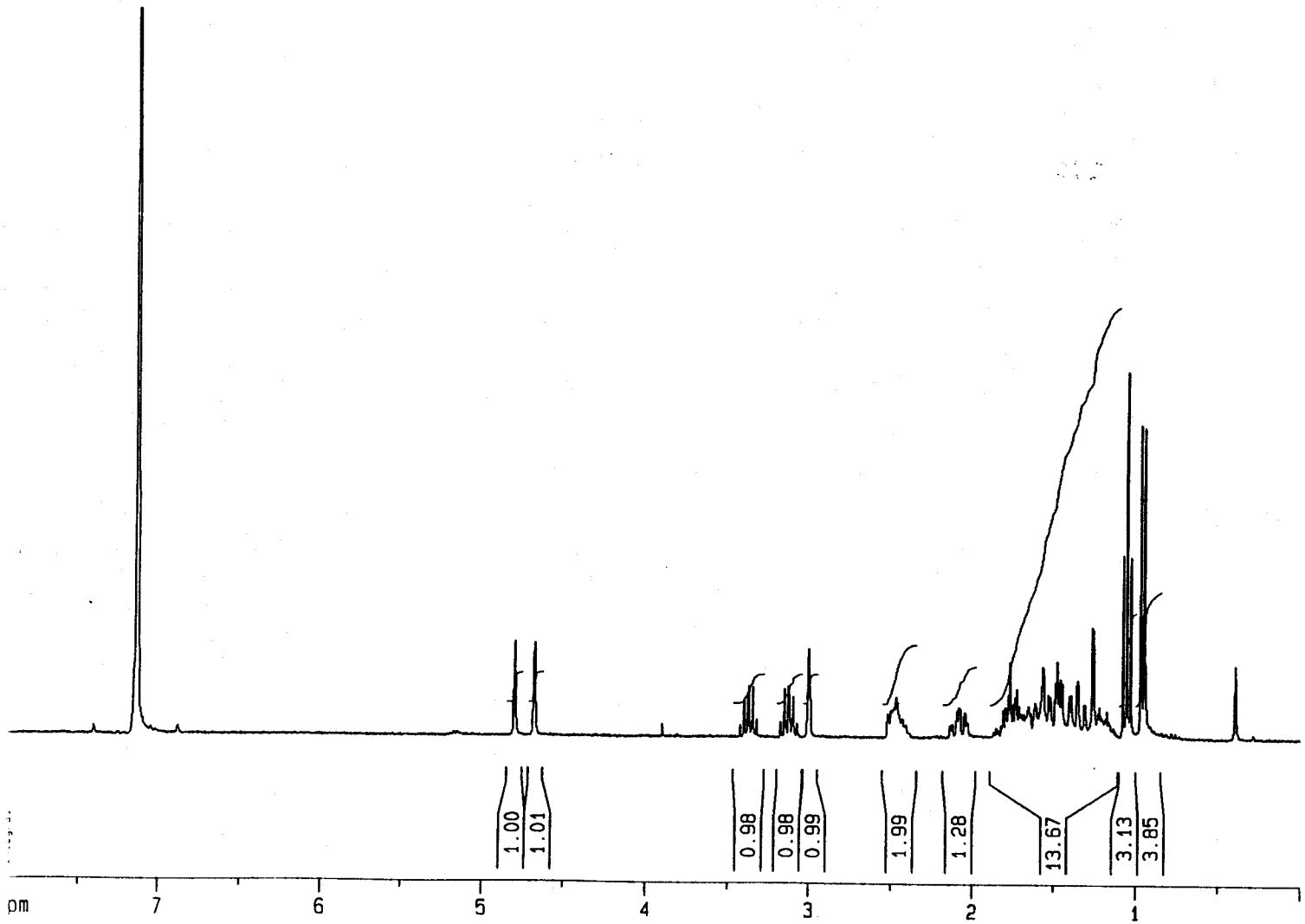
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





Current Data Parameters
NAME irina_june6e
EXPNO 1
PROCNO 1

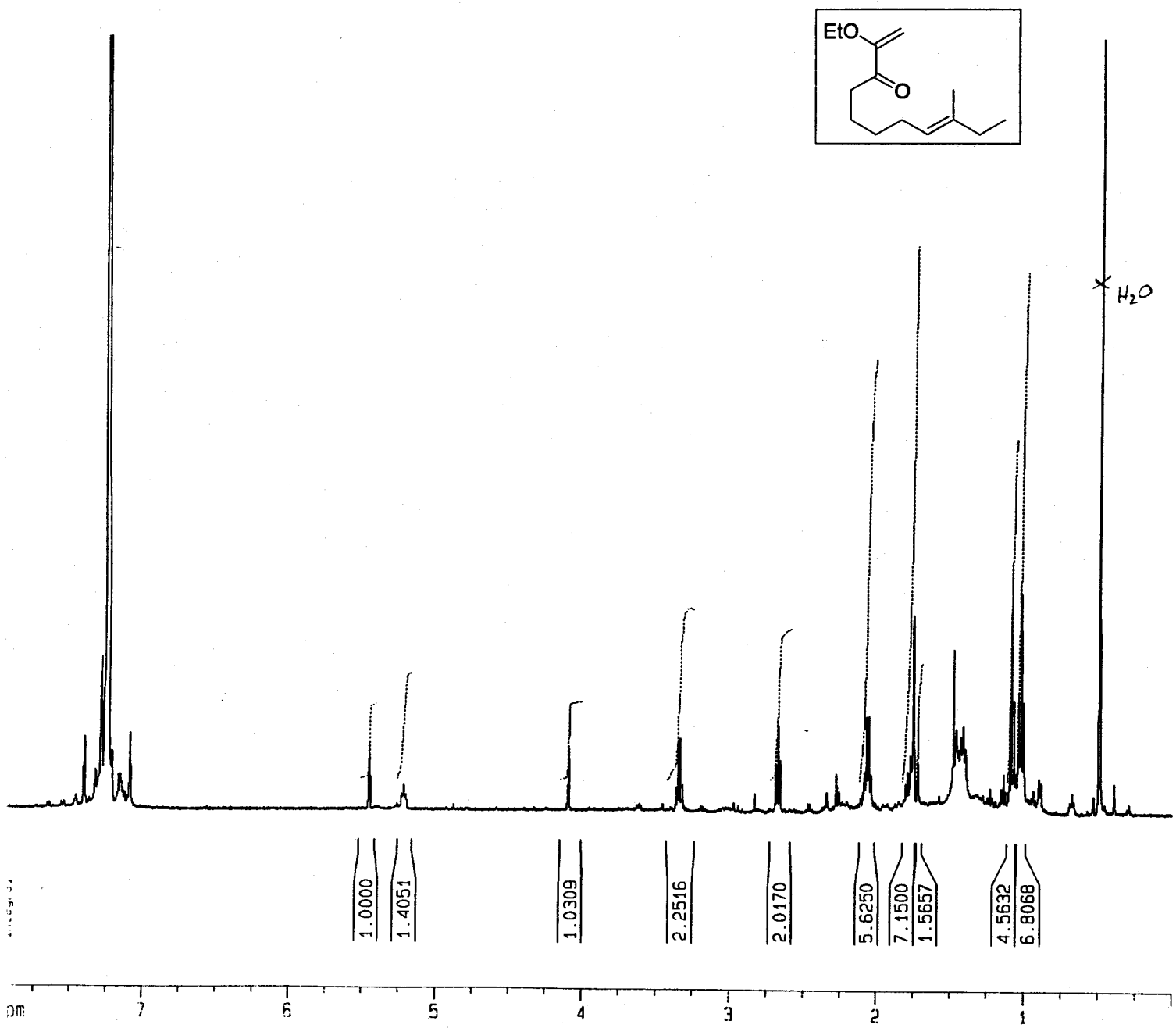
F2 - Acquisition Parameters
Date_ 20040606
Time 17.10
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 574.7
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 20.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm

1H NMR



Current Data Parameters

NAME	irina_retro-ene
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040530
Time	11.58
INSTRUM	AV500WB
PROBHD	5 mm TBO BB/1H
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	512
DS	0
SWH	7440.476 Hz
FIDRES	0.113533 Hz
AQ	4.4040694 sec
RG	203.2
DW	67.200 usec
DE	6.00 usec
TE	300.0 K
D1	0.01000000 sec

======== CHANNEL f1 ========

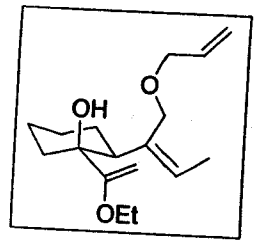
NUC1	1H
P1	14.00 usec
PL1	0.00 dB
SFO1	500.1327766 MHz

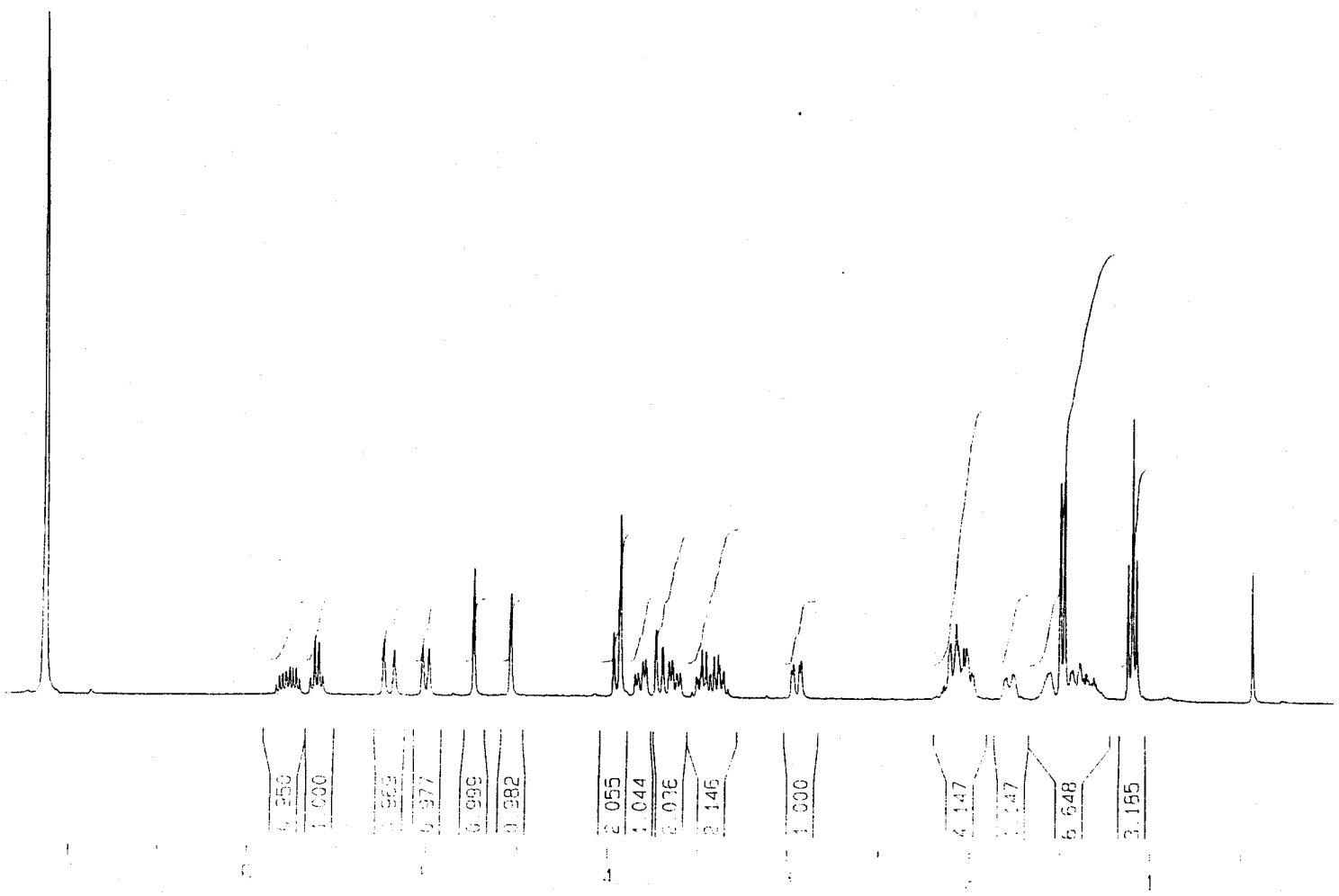
F2 - Processing parameters

SI	65536
SF	500.1300049 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	200.00 cm
F1P	8.000 ppm
F1	4001.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	200.05200 Hz/cm





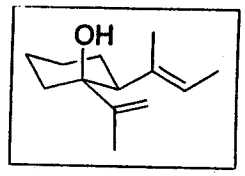
Current Data Parameters
NAME irina_7-96
EXPNO 1
PROCNO 1

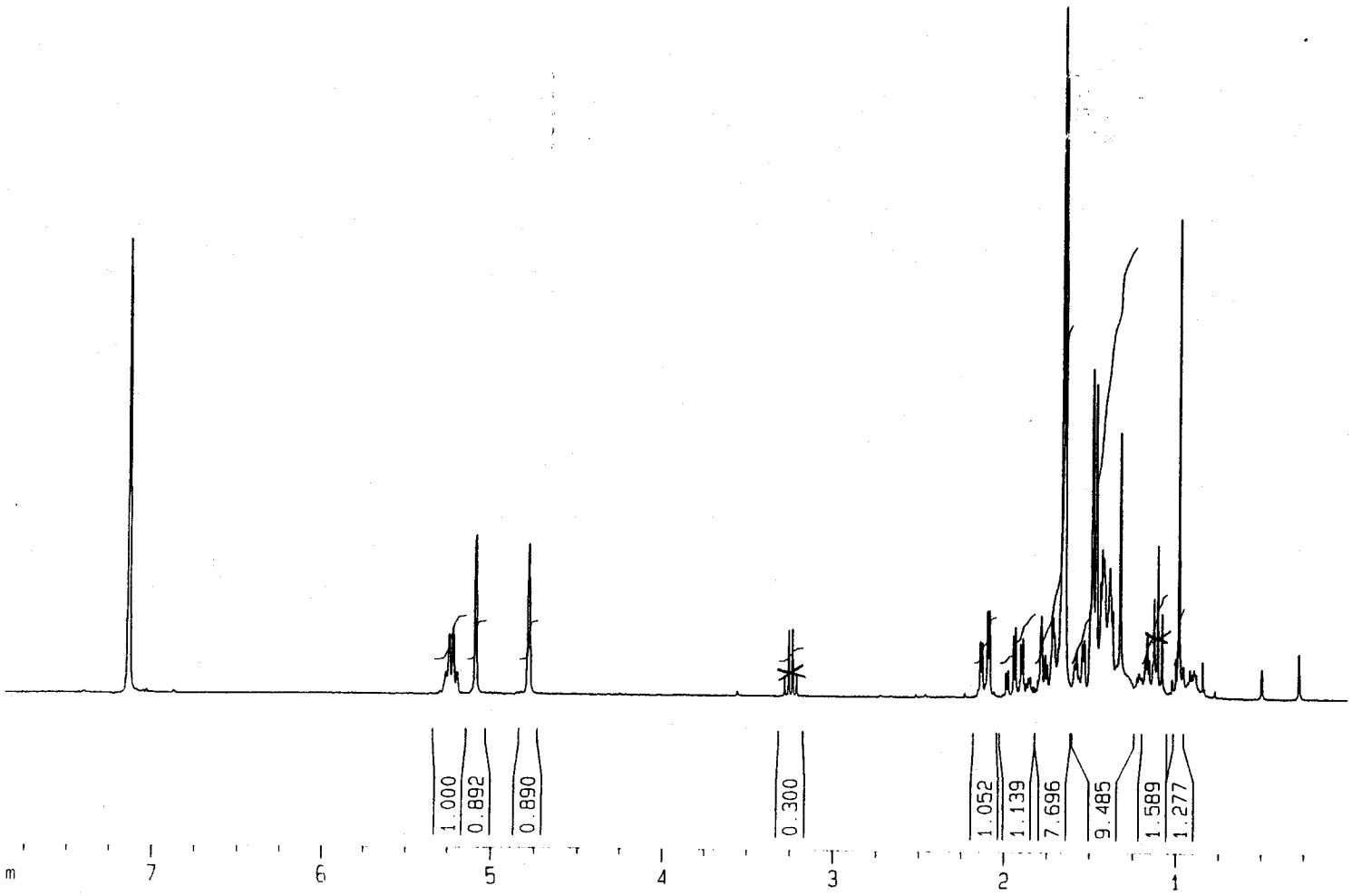
F2 - Acquisition Parameters
Date_ 20030930
Time 14.48
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 406.4
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SF01 300.1319437 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1H NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P [illegible] ppm
F1 [illegible] Hz
F2P [illegible] ppm
F2 0.00 Hz
PPMCM 0.47500 ppm/cm
HZCM [illegible] Hz/cm





Current Data Parameters

NAME	irina_8-57
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20040224
Time	11.09
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	C6D6
NS	1
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	128
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

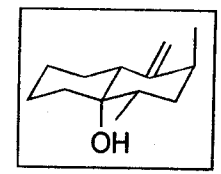
F2 - Processing parameters

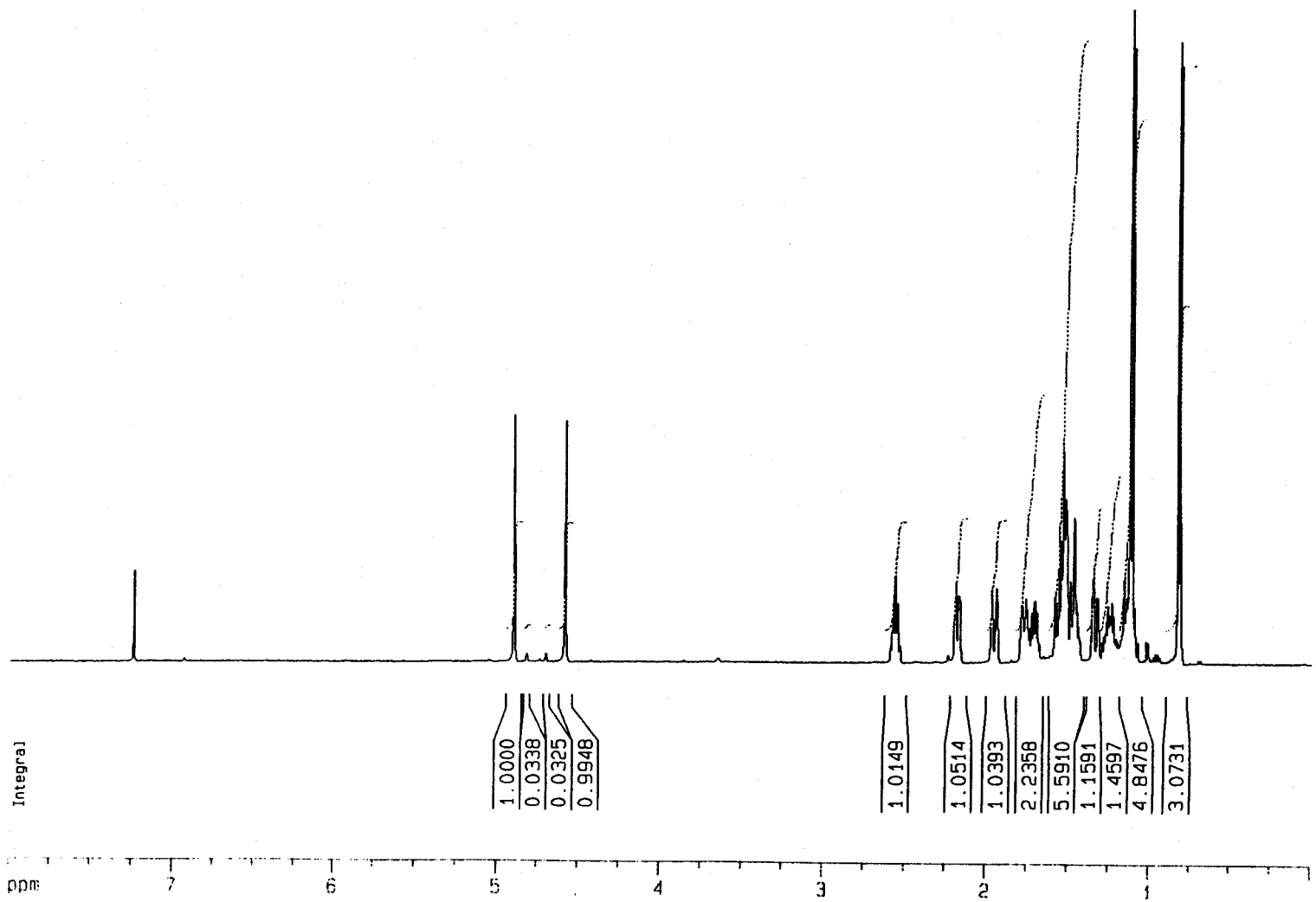
SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm

1H NMR





Current Data Parameters

NAME	irina_8-97-1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040510
Time	18.01
INSTRUM	AV500WB
PROBHD	5 mm BBI 1H-BB
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	1
DS	0
SWH	7440.476 Hz
FIDRES	0.113533 Hz
AQ	4.4040694 sec
RG	25.4
DW	67.200 usec
DE	6.00 usec
TE	300.0 K
D1	0.01000000 sec

======== CHANNEL f1 ========

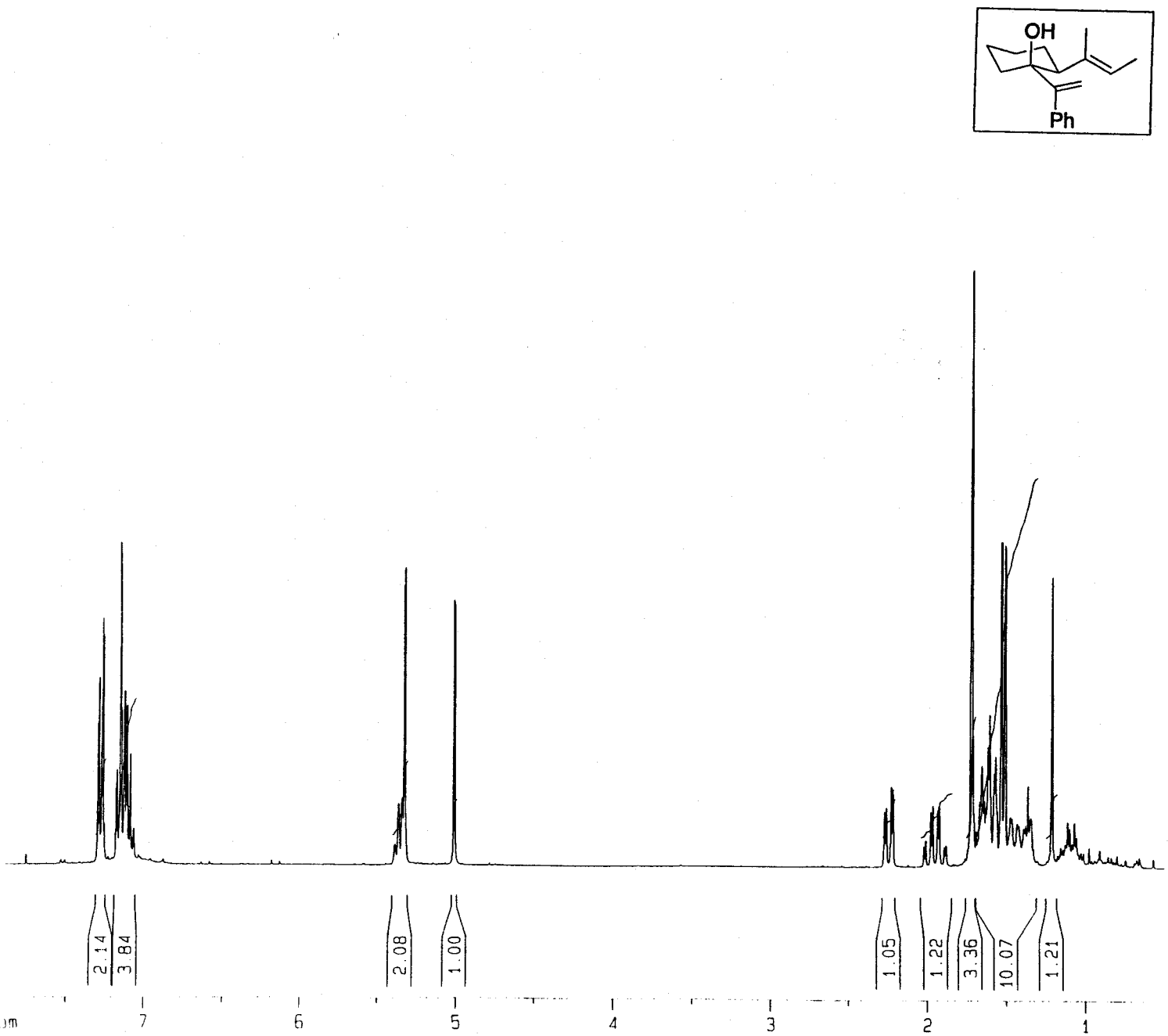
NUC1	1H
P1	10.50 usec
PL1	3.00 dB
SFO1	500.1327766 MHz

F2 - Processing parameters

SI	65536
SF	500.1300049 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	4001.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	200.05200 Hz/cm



Current Data Parameters

NAME	irina_8-52
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040218
Time	19.49
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	45.3
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

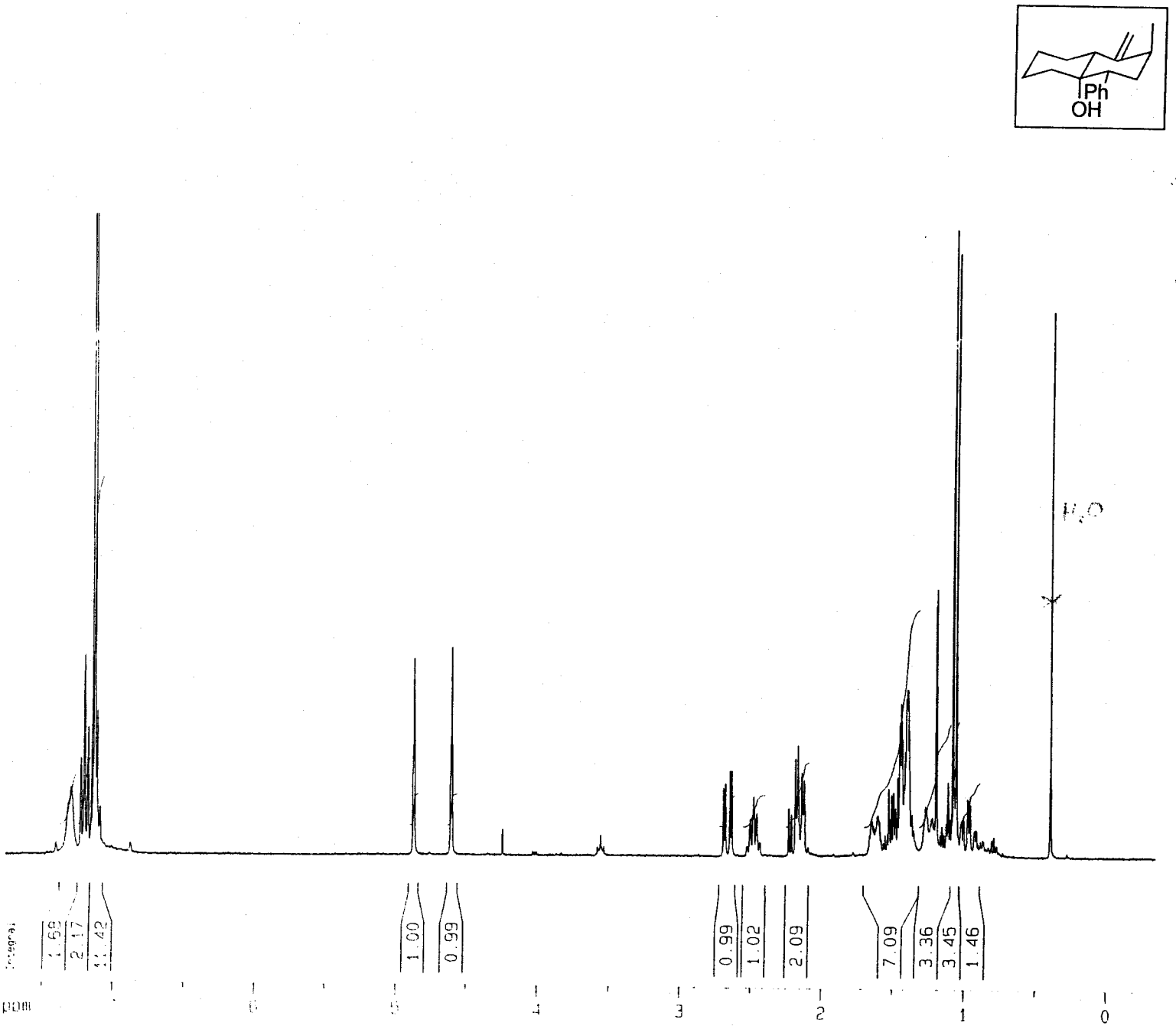
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.500 ppm
F2	150.07 Hz
PPMCM	0.37500 ppm/cm
HZCM	112.54875 Hz/cm



Current Data Parameters

NAME	irina_8-39pure
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040205
Time	21.52
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	512
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

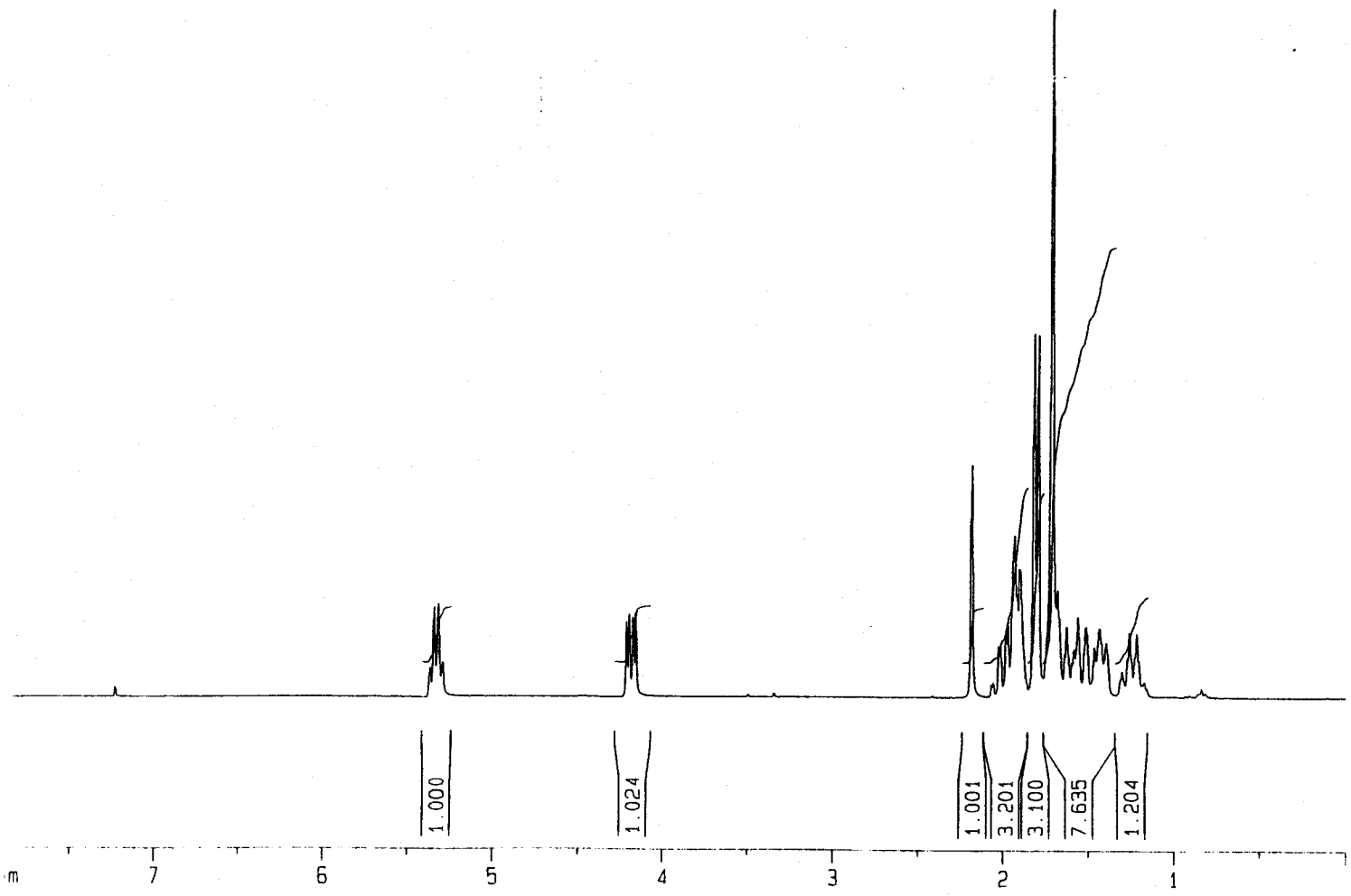
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

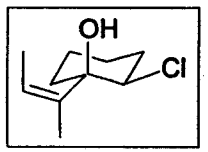
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	30.00 cm
F1P	7.774 ppm
F1	2333.35 Hz
F2P	-0.338 ppm
F2	-101.44 Hz
PPMCM	0.40562 ppm/cm
HZCM	121.73951 Hz/cm





Current Data Parameters

NAME	irina_8-43
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040210
Time	17.14
INSTRUM	av300
PROBHD	5 mm GNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	15
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	28.5
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

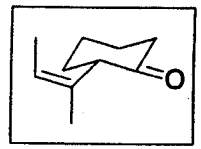
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

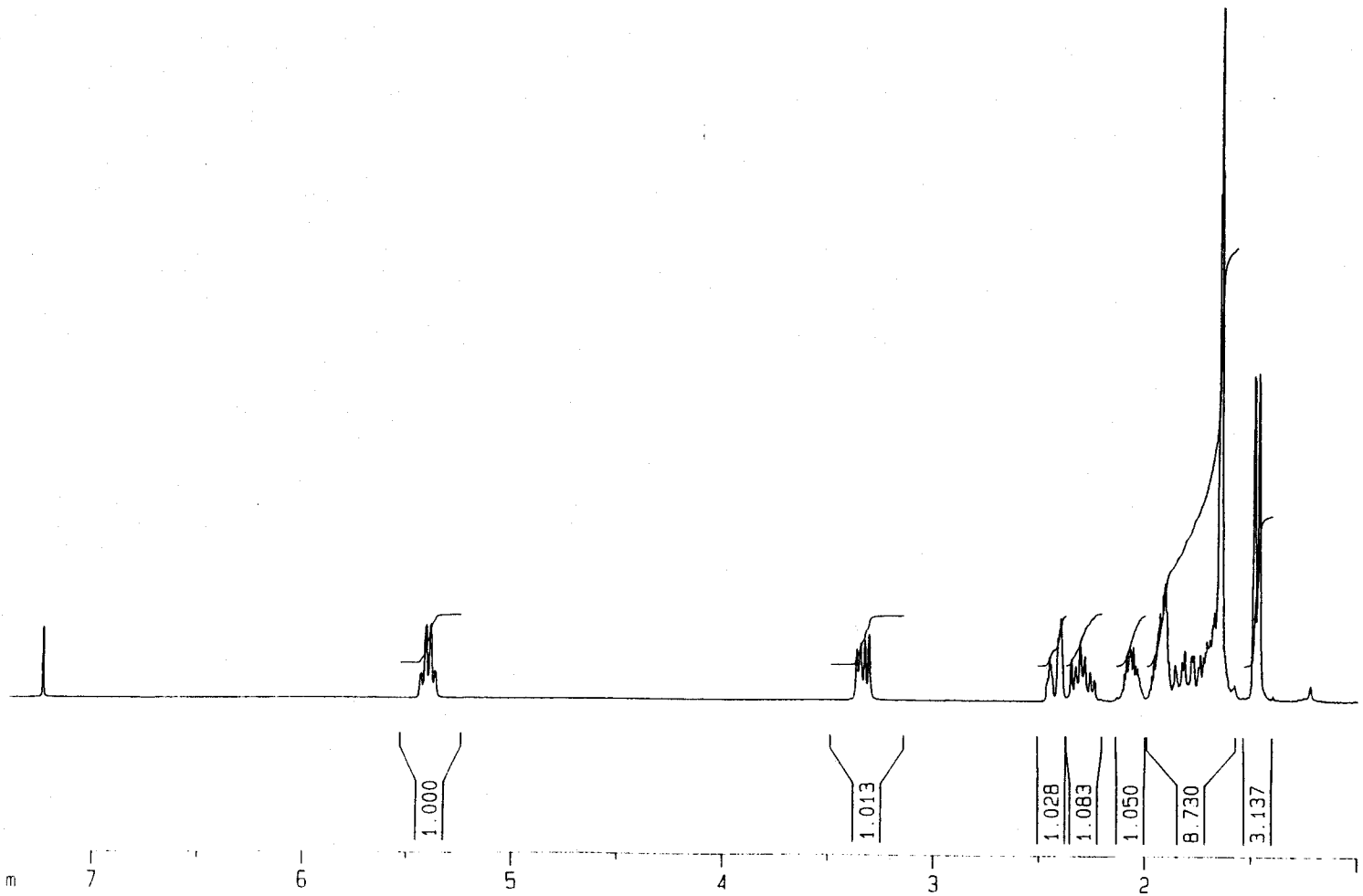
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





Current Data Parameters

NAME	irina_8-45
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040211
Time	22.10
INSTRUM	av300
PROBHD	5 mm GNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	143.7
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

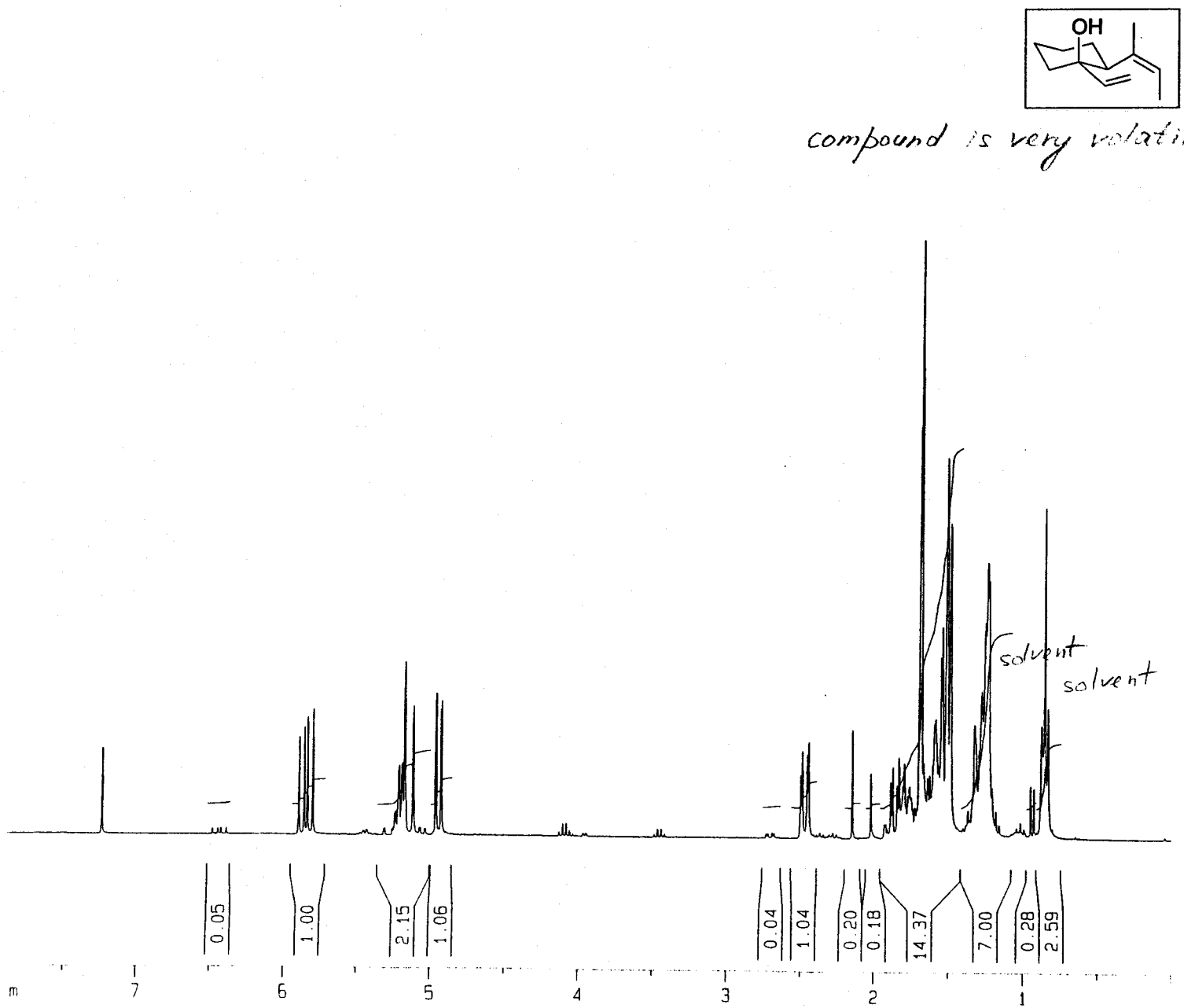
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	7.523 ppm
F1	2257.89 Hz
F2P	0.997 ppm
F2	299.25 Hz
PPMCM	0.32630 ppm/cm
HZCM	97.93180 Hz/cm



Current Data Parameters

NAME	irina_8-55
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040225
Time	15.20
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	101.6
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

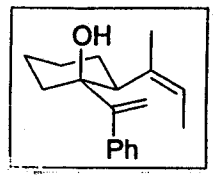
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

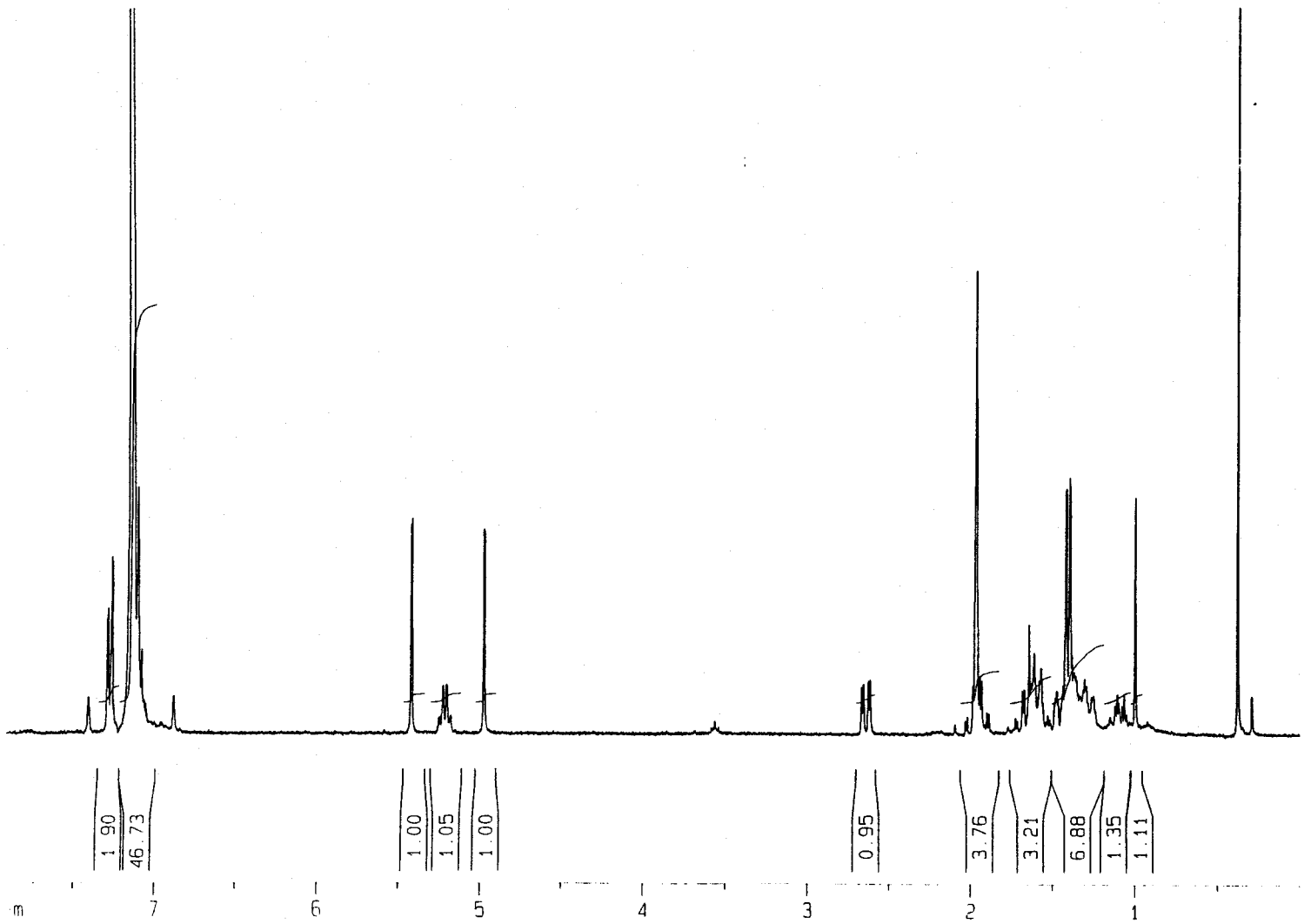
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





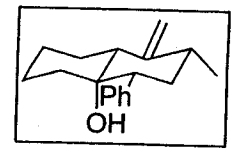
Current Data Parameters
NAME irina_8-54pure
EXPNO 5
PROCNO 1

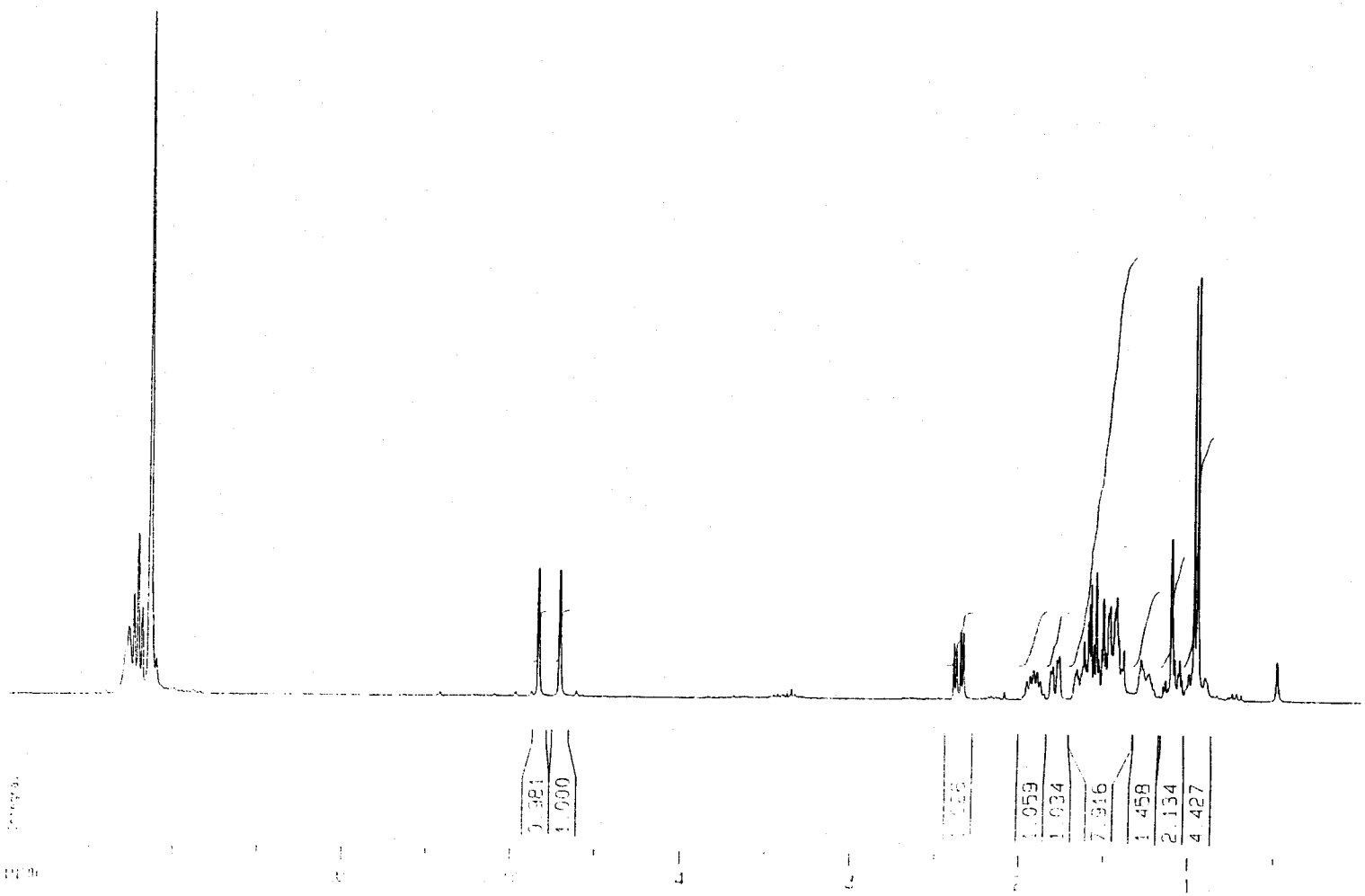
F2 - Acquisition Parameters
Date_ 20040224
Time 16.02
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 48
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 645.1
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 100.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm





Current Data Parameters
NAME irina_8-58pure
EXPNO 1
PROCNO 1

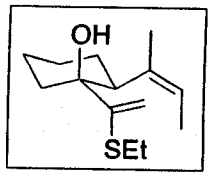
F2 - Acquisition Parameters
Date_ 20040302
Time 15.19
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CHCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 256
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

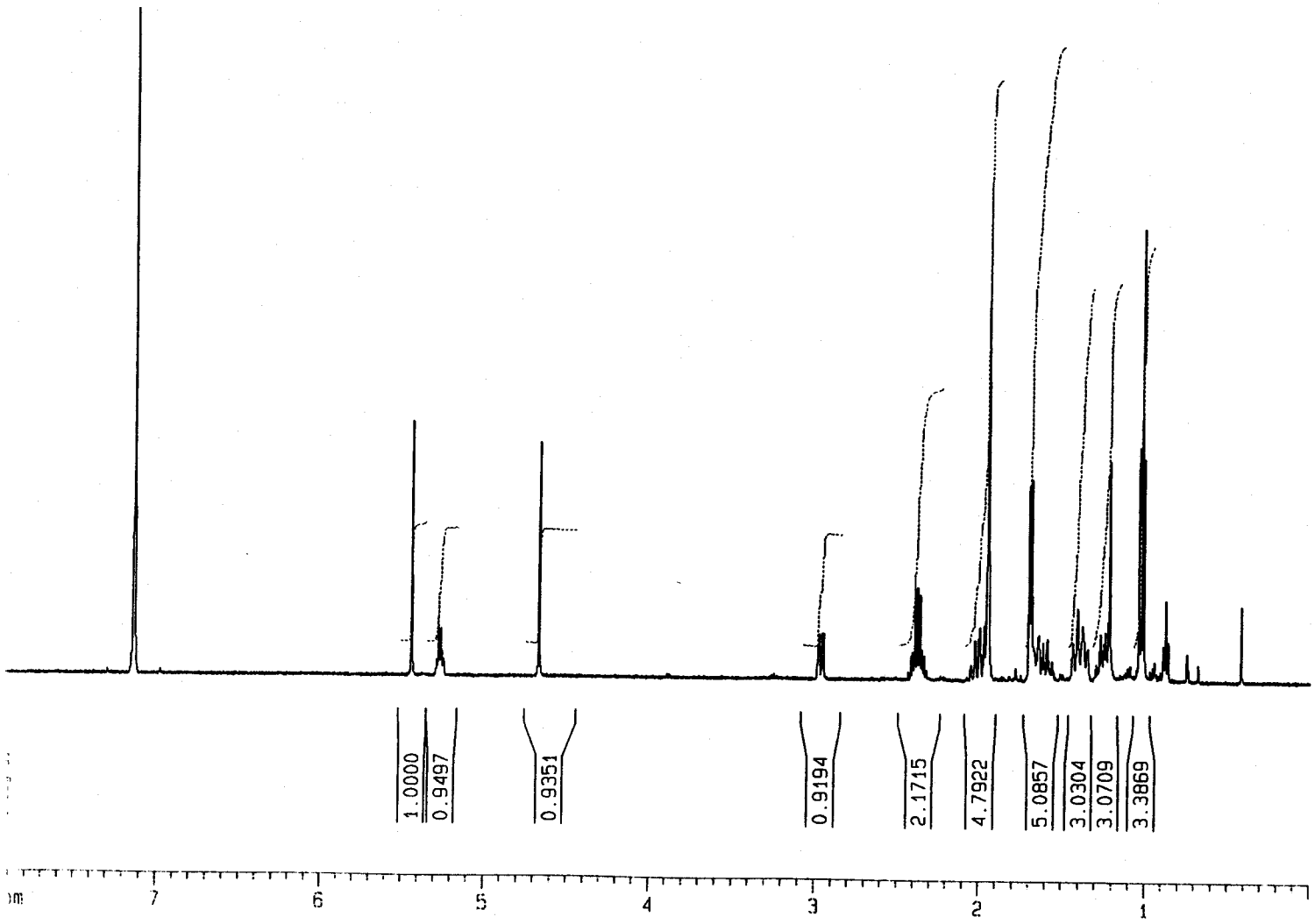
======== CHANNEL f1 ========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm

1H NMR





Current Data Parameters

NAME	irina_8-86
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040329
Time	16.53
INSTRUM	AV500WB
PROBHD	5 mm BBI 1H-BB
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	32
DS	0
SWH	7440.476 Hz
FIDRES	0.113533 Hz
AQ	4.4040694 sec
RG	1149
DW	67.200 usec
DE	6.00 usec
TE	300.0 K
D1	0.01000000 sec

======== CHANNEL f1 ========

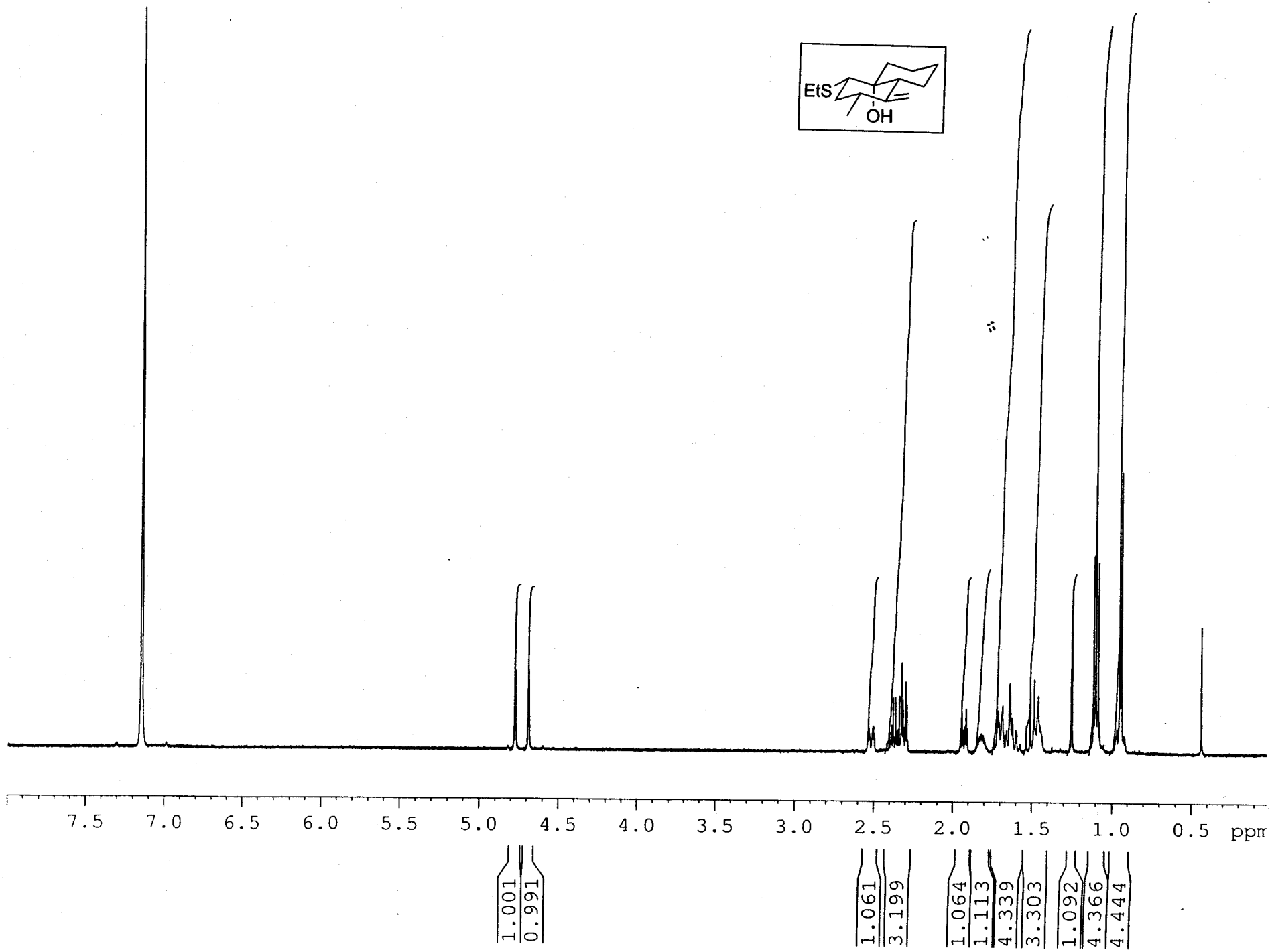
NUC1	1H
P1	10.50 usec
PL1	3.00 dB
SFO1	500.1327766 MHz

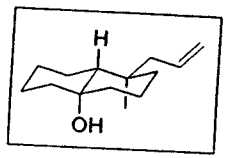
F2 - Processing parameters

SI	65536
SF	500.1300626 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	4001.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	200.05203 Hz/cm


EtS
OH
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.001
0.991
1.061
3.199
1.064
1.113
4.339
3.303
1.092
4.366
4.444



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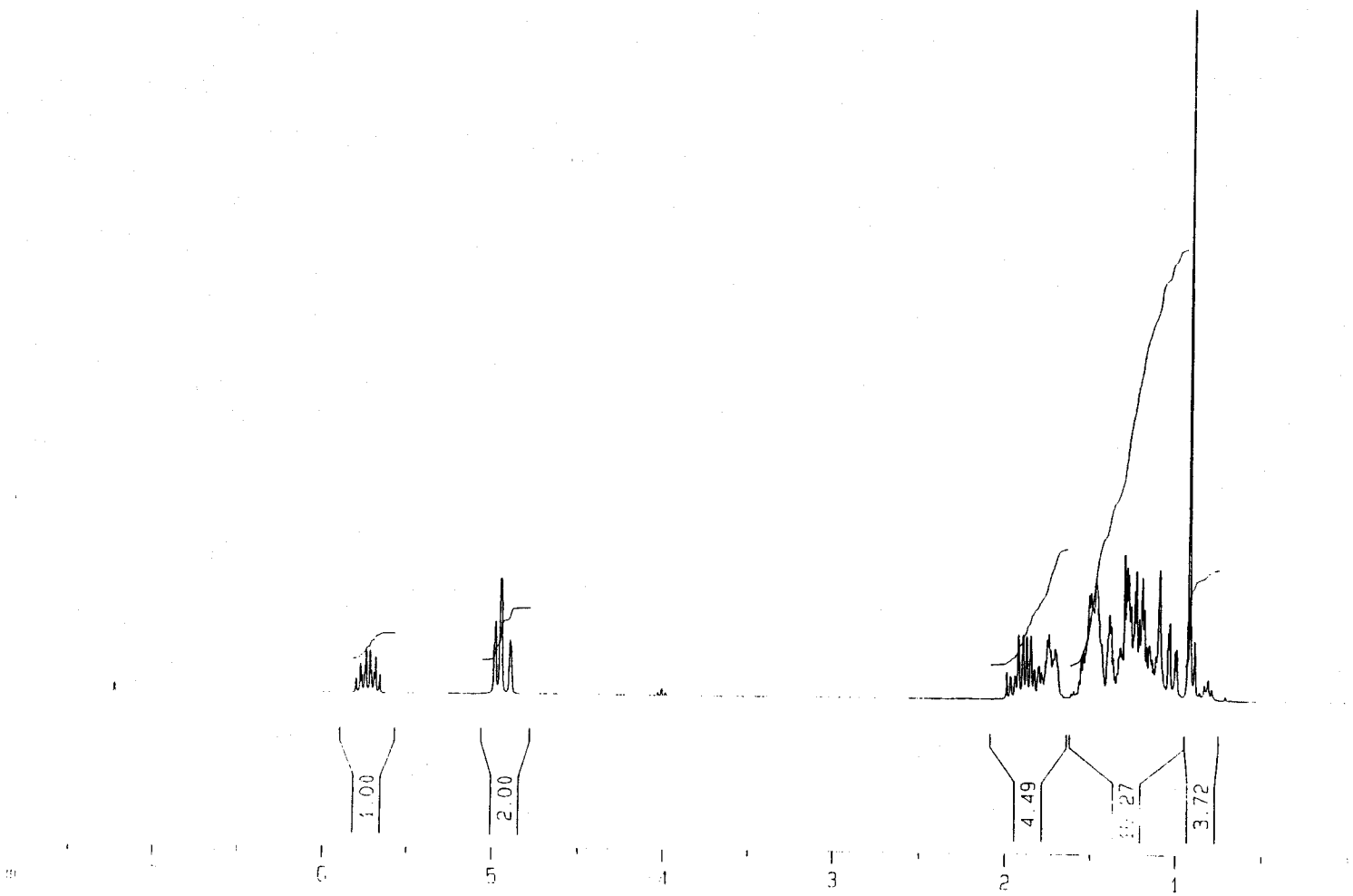
Current Data Parameters
NAME irina_WKred
EXPNO 1
PROCNO 1

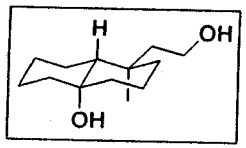
F2 - Acquisition Parameters
Date_ 20031213
Time 15 15
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 15
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0208990 sec
RG [illegible]
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

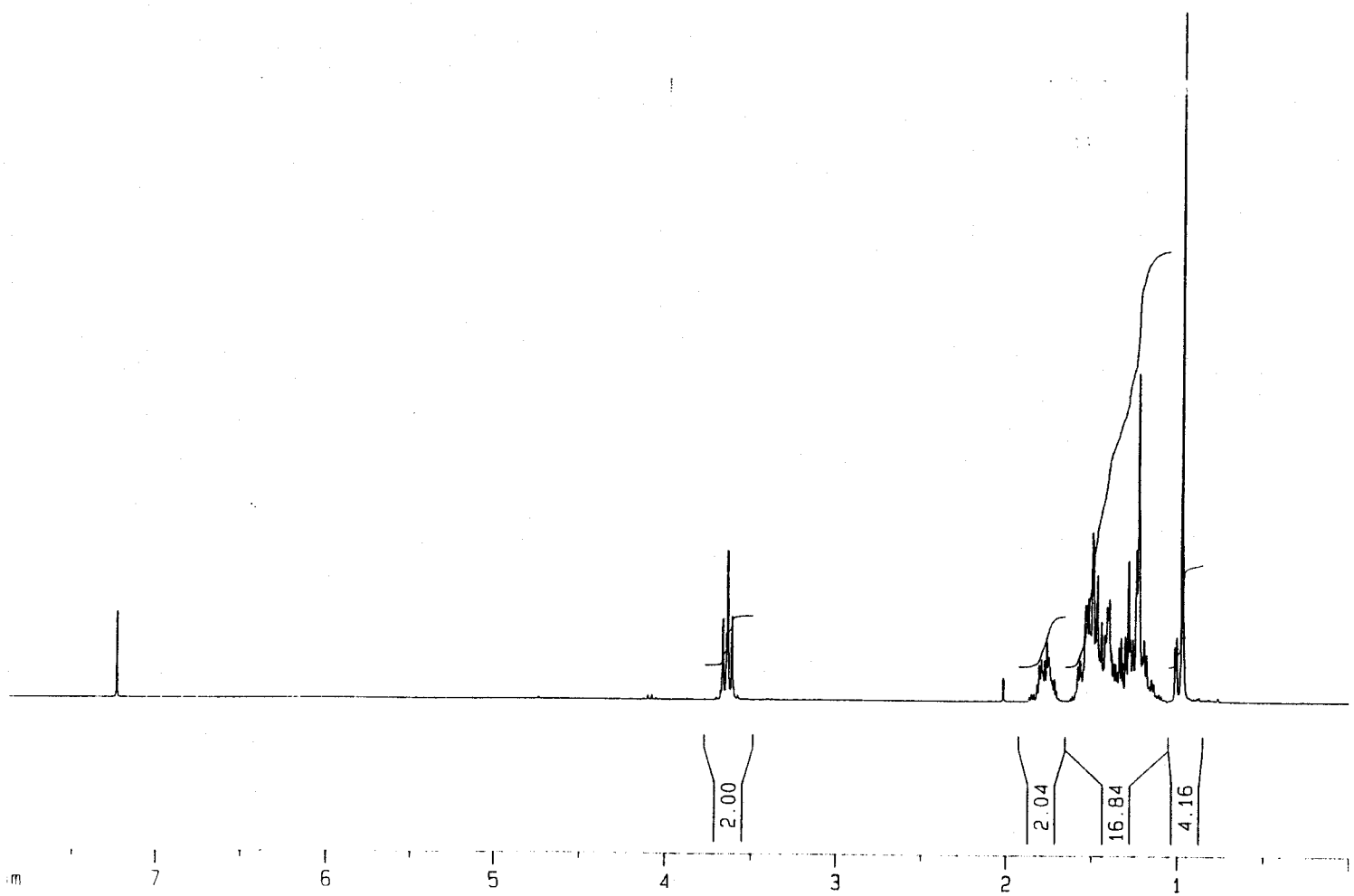
========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 6.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm







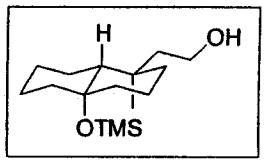
Current Data Parameters
NAME irina_7-149
EXPNO 1
PROCNO 1

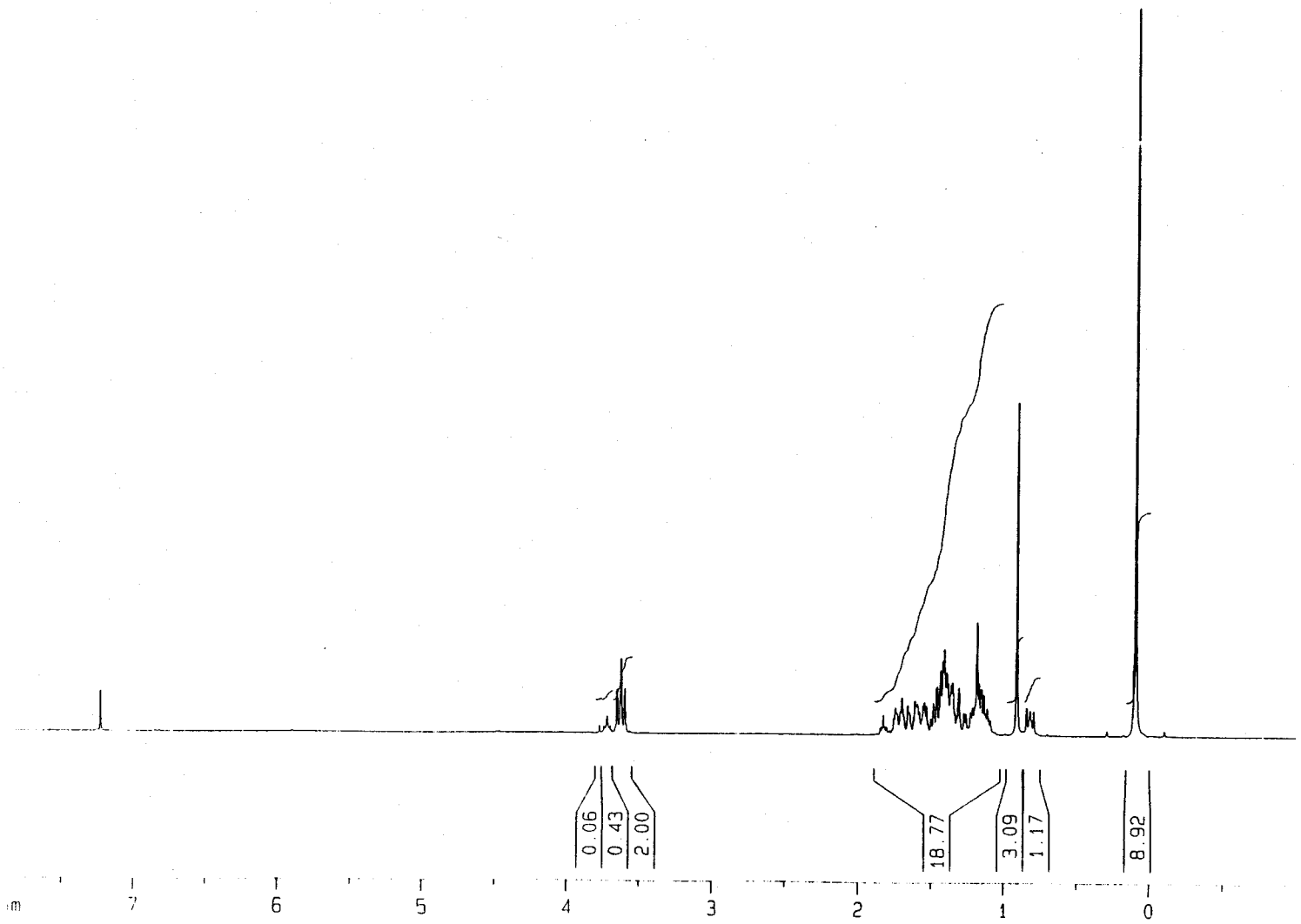
F2 - Acquisition Parameters
Date_ 20031126
Time 12.49
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG [illegible]
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm





Current Data Parameters

NAME	irina_8-15
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040119
Time	21.51
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	128
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

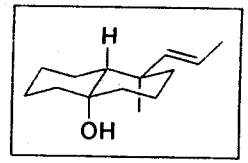
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

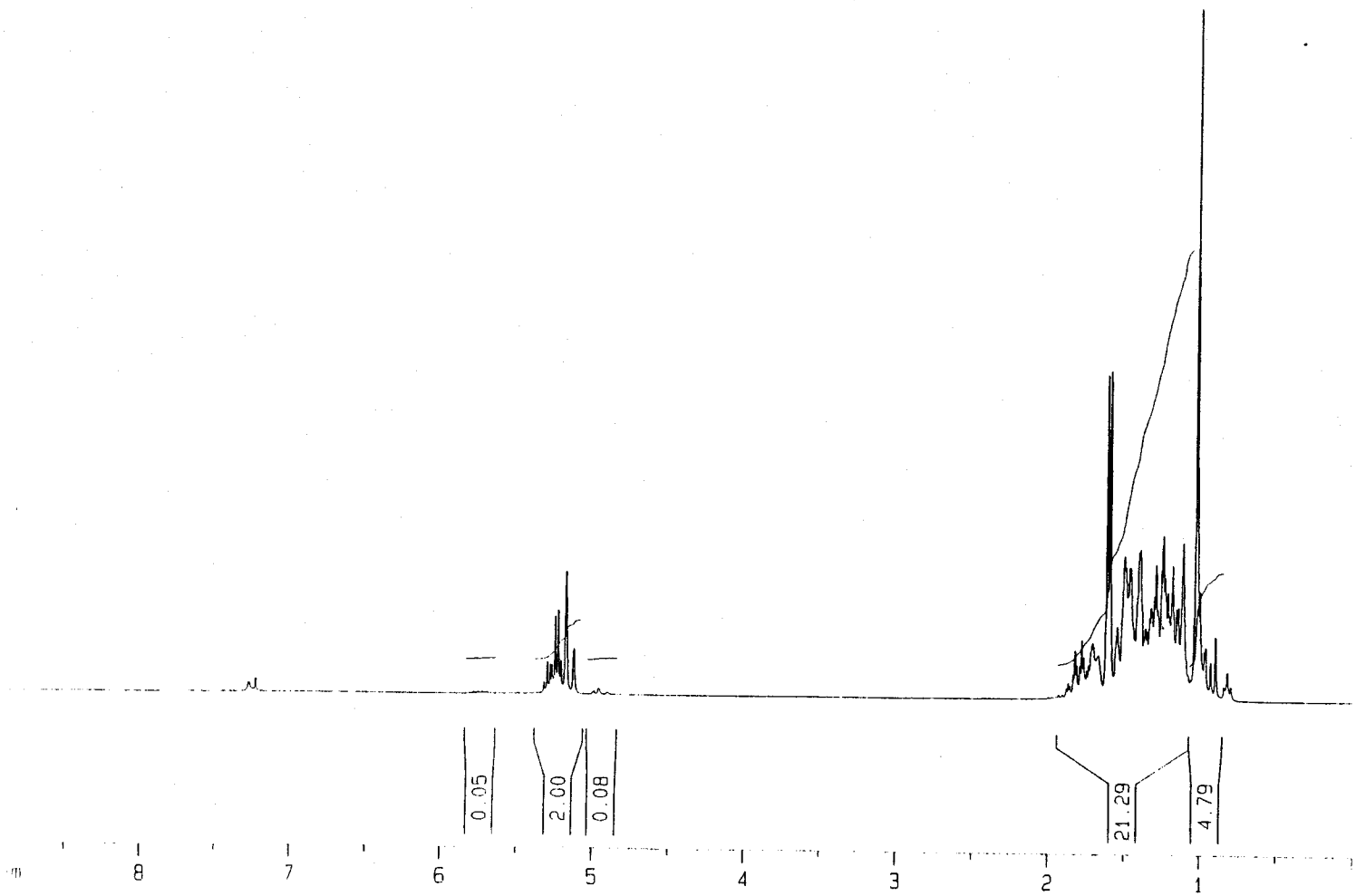
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	20.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	-1.000 ppm
F2	-300.13 Hz
PPMCM	0.45000 ppm/cm
HZCM	135.05850 Hz/cm





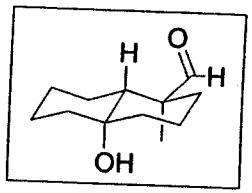
Current Data Parameters
NAME irina_7-172
EXPNO 1
PROCNO 1

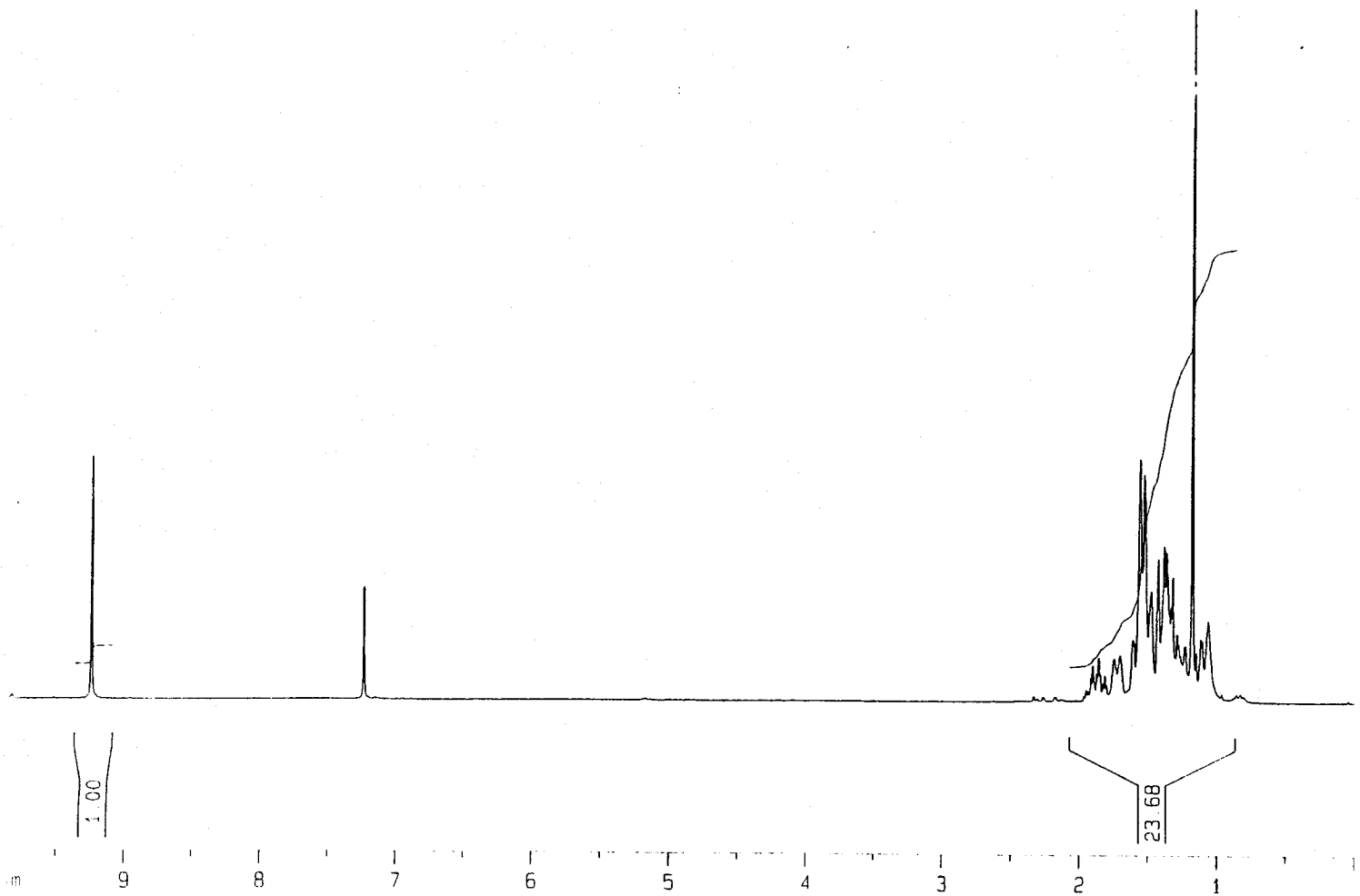
F2 - Acquisition Parameters
Date_ 20031215
Time 12.57
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 28.5
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 9.000 ppm
F1 2701.17 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.45000 ppm/cm
HZCM 135.05850 Hz/cm





Current Data Parameters

NAME	irina_7-174
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20031215
Time	17.46
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	287.4
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

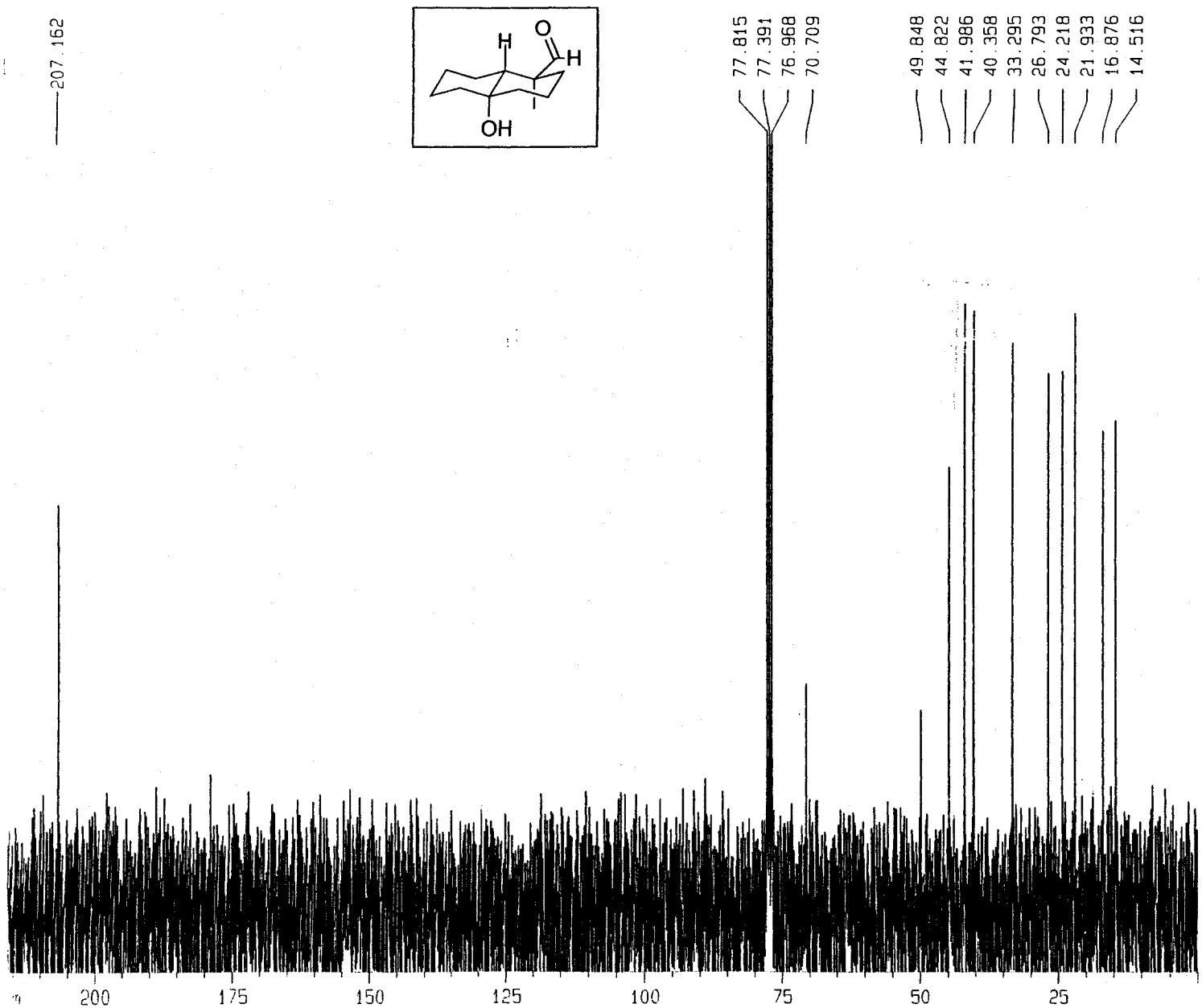
F2 - Processing parameters

SI	65536
SF	300.1299996 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.50000 ppm/cm
HZCM	150.06500 Hz/cm

13C with proton decoupling



Current Data Parameters

NAME	irina_7-174
EXPNO	3
PROCNO	1

F2 - Acquisition Parameters

Date_	20031215
Time	17.53
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	52
DS	0
SWH	17985.611 Hz
FIDRES	0.548877 Hz
AQ	0.9110004 sec
RG	1625.5
DW	27.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

========== CHANNEL f1 ==========

NUC1	13C
P1	5.00 usec
PL1	-6.00 dB
SFO1	75.4752653 MHz

========== CHANNEL f2 ==========

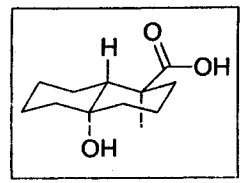
CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-3.00 dB
PL12	13.48 dB
PL13	15.63 dB
SFO2	300.1314860 MHz

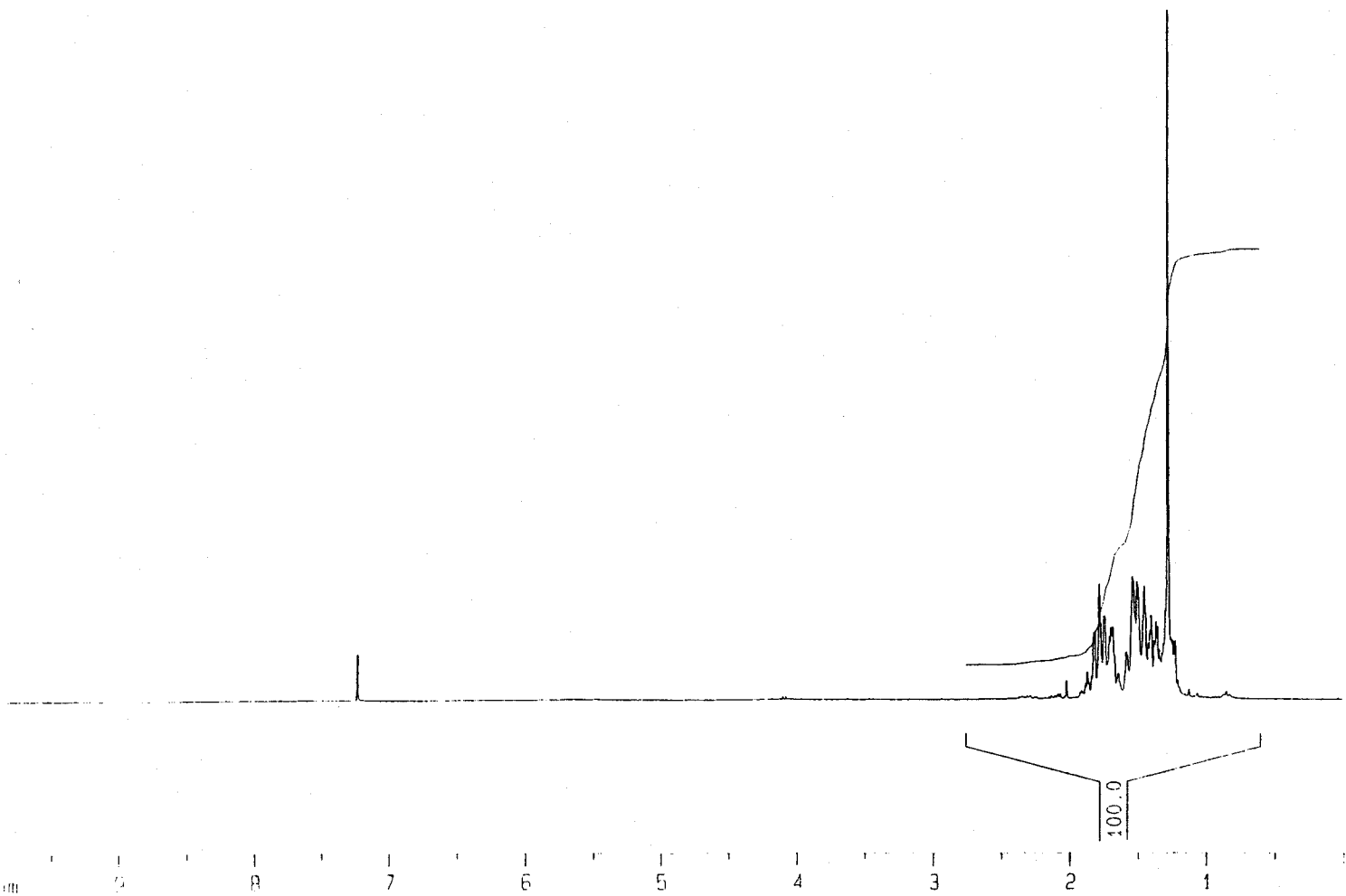
F2 - Processing parameters

SI	65536
SF	75.4677190 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	16602.90 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	11.00000 ppm/cm
HZCM	830.14490 Hz/cm



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Current Data Parameters
NAME        irina_7-174(2)
EXPNO                    1
PROCNO                   1

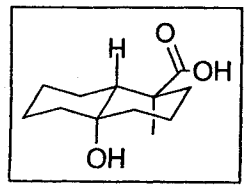
F2 - Acquisition Parameters
Date_             20031215
Time                 21.22
INSTRUM              av300
PROBHD   5 mm QNP  1H/1
PULPROG              zg30
TD                  30720
SOLVENT             CDCl3
NS                     16
DS                      0
SWH               5081.301 Hz
FIDRES            0.165437 Hz
AQ                3.0228980 sec
RG                    114
DW                 98.400 usec
DE                  6.00 usec
TE                 300.0 K
D1                1.00000000 sec

========== CHANNEL f1 ==========
NUC1                   1H
P1                  10.50 usec
PL1                 -3.00 dB
SF01          300.1319477 MHz

F2 - Processing parameters
SI                  65536
SF          300.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.10 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  20.00 cm
CY                  10.00 cm
F1P                10.000 ppm
F1                3001.30 Hz
F2P                 0.000 ppm
F2                  0.00 Hz
PPMCM              0.50000 ppm/cm
HZCM             150.06500 Hz/cm
```

13C with proton decoupling



185.564

77.822
77.400
76.976
71.260

46.984
46.873
42.140
40.339
37.735
26.861
24.413
21.937
17.673
16.408

200
175
150
125
100
75
50
25

Current Data Parameters
NAME irina_7-174(2)
EXPNO 2
PROCNO 1

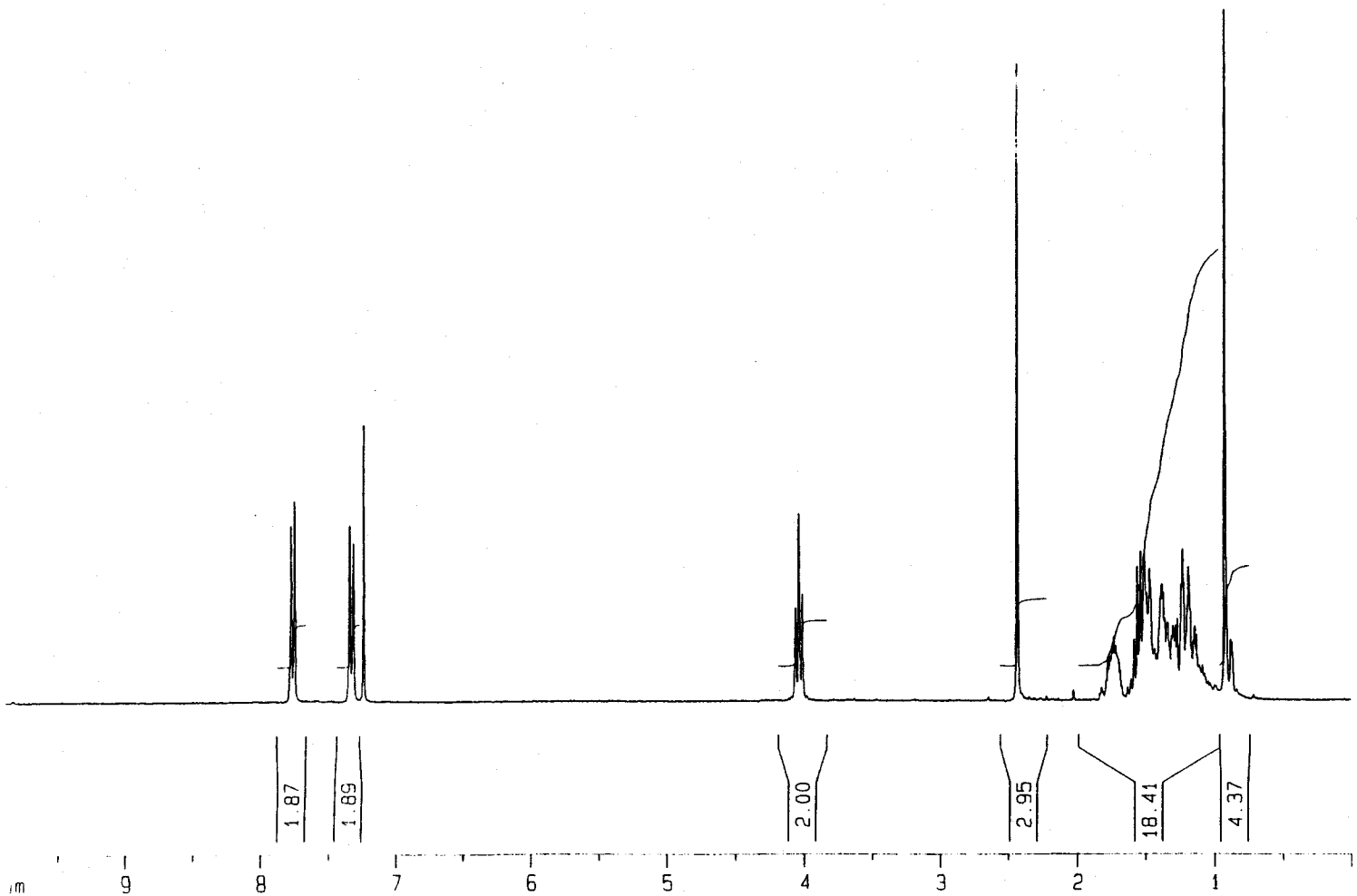
F2 - Acquisition Parameters
Date_ 20031215
Time 21.24
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 83
DS 0
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 2896.3
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

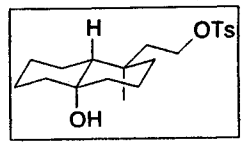
========== CHANNEL f1 ==========
NUC1 13C
P1 5.00 usec
PL1 -6.00 dB
SFO1 75.4752653 MHz

========== CHANNEL f2 ==========
CPDPRG2 waltz16
NUC2 1H
PCPD2 70.00 usec
PL2 -3.00 dB
PL12 13.48 dB
PL13 15.63 dB
SFO2 300.1314860 MHz

F2 - Processing parameters
SI 65536
SF 75.4677190 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 220.000 ppm
F1 16602.90 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 11.00000 ppm/cm
HZCM 830.14490 Hz/cm





Current Data Parameters

NAME	irina_7-150
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20031127
Time	19.27
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5091.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	456.1
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

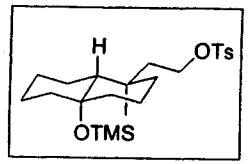
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

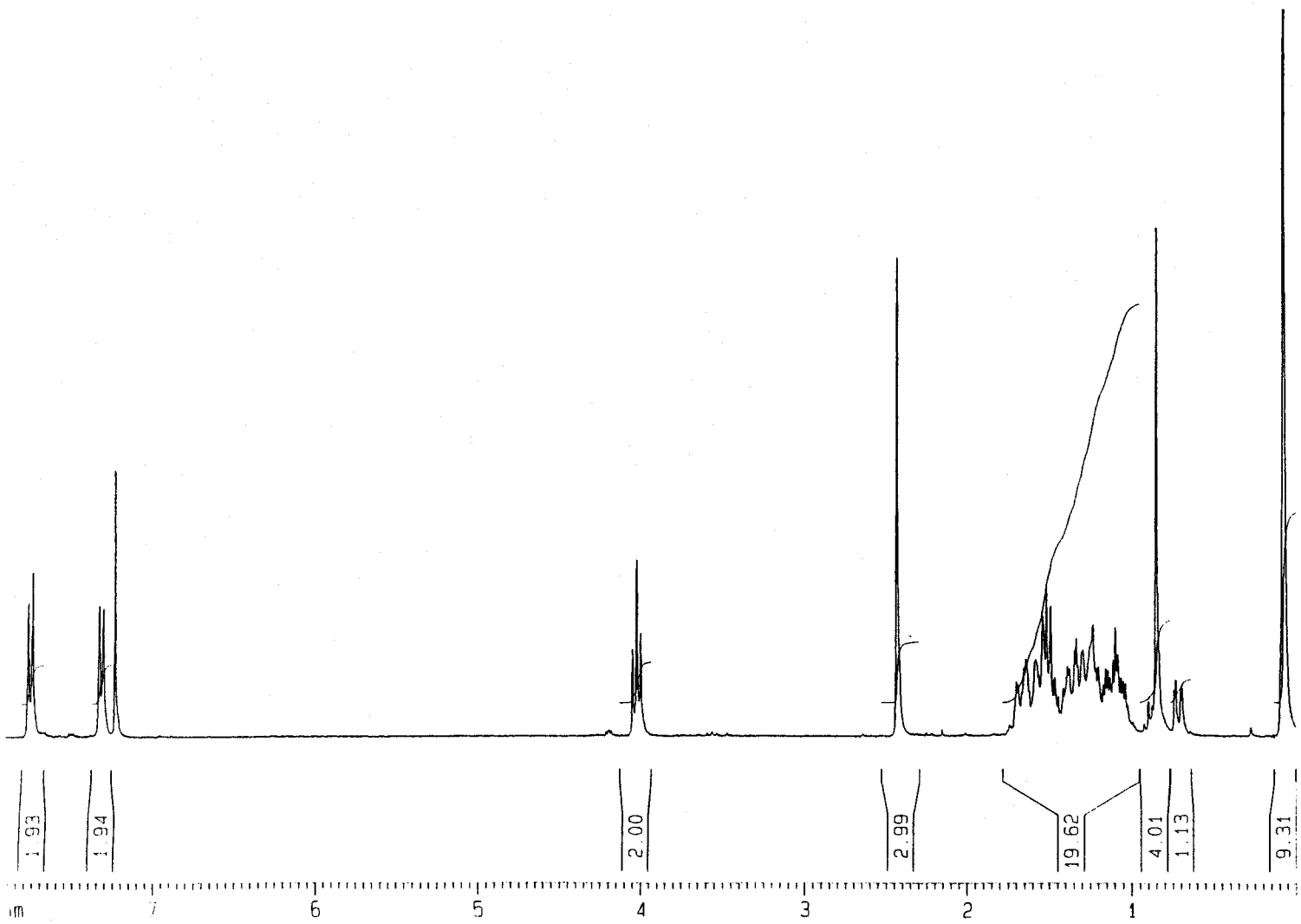
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.50000 ppm/cm
HZCM	150.06500 Hz/cm





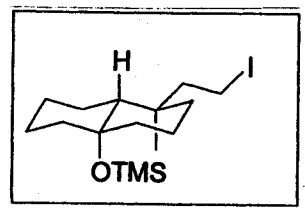
Current Data Parameters
NAME irina_7-155
EXPNO 1
PROCNO 1

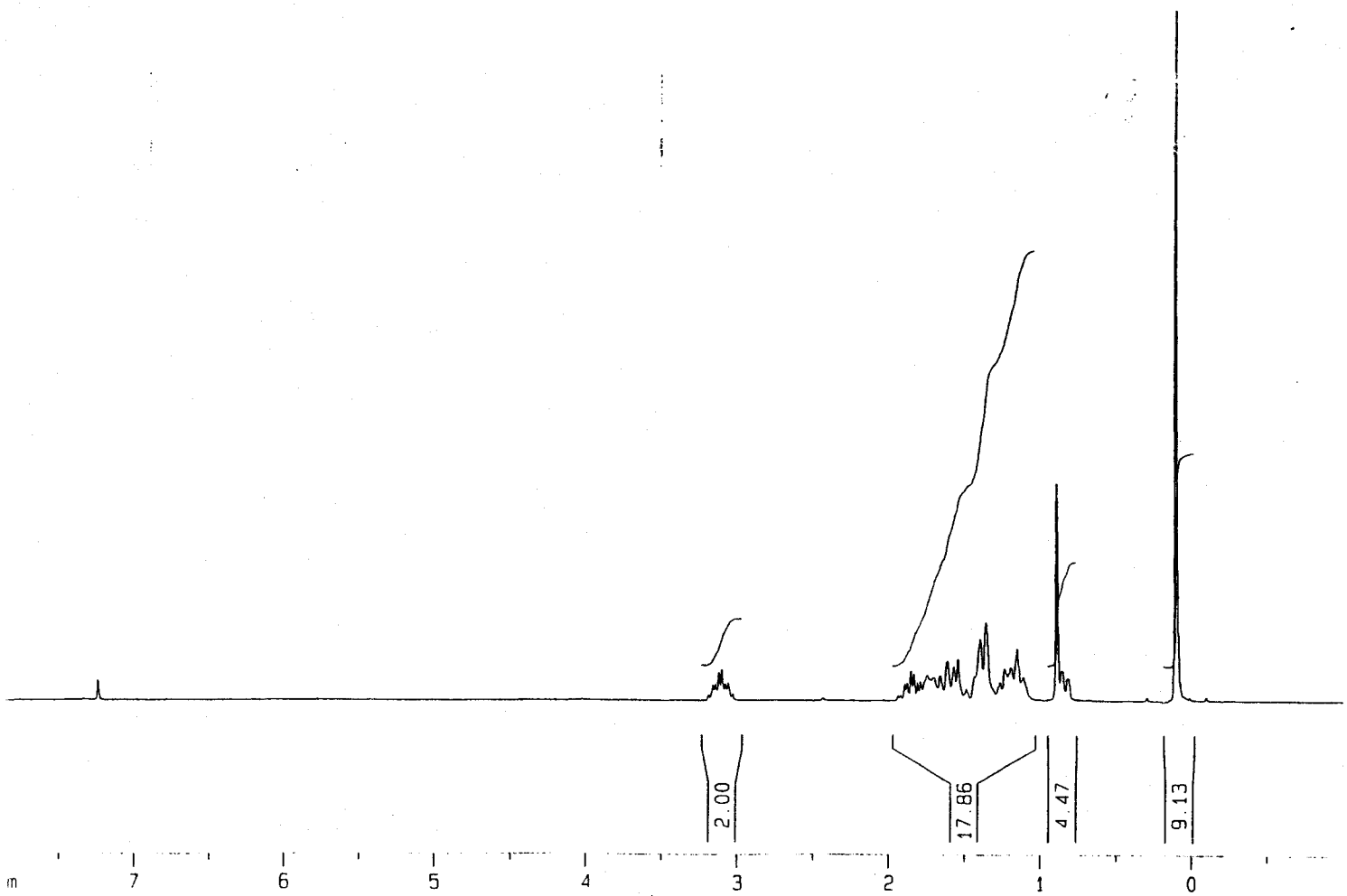
F2 - Acquisition Parameters
Date_ 20031203
Time 14.47
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228990 sec
RG 362
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SF01 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 30.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm





Current Data Parameters

NAME	irina_8-72
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040315
Time	8.54
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	7
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	128
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

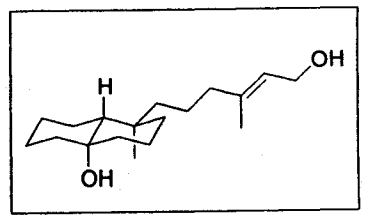
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

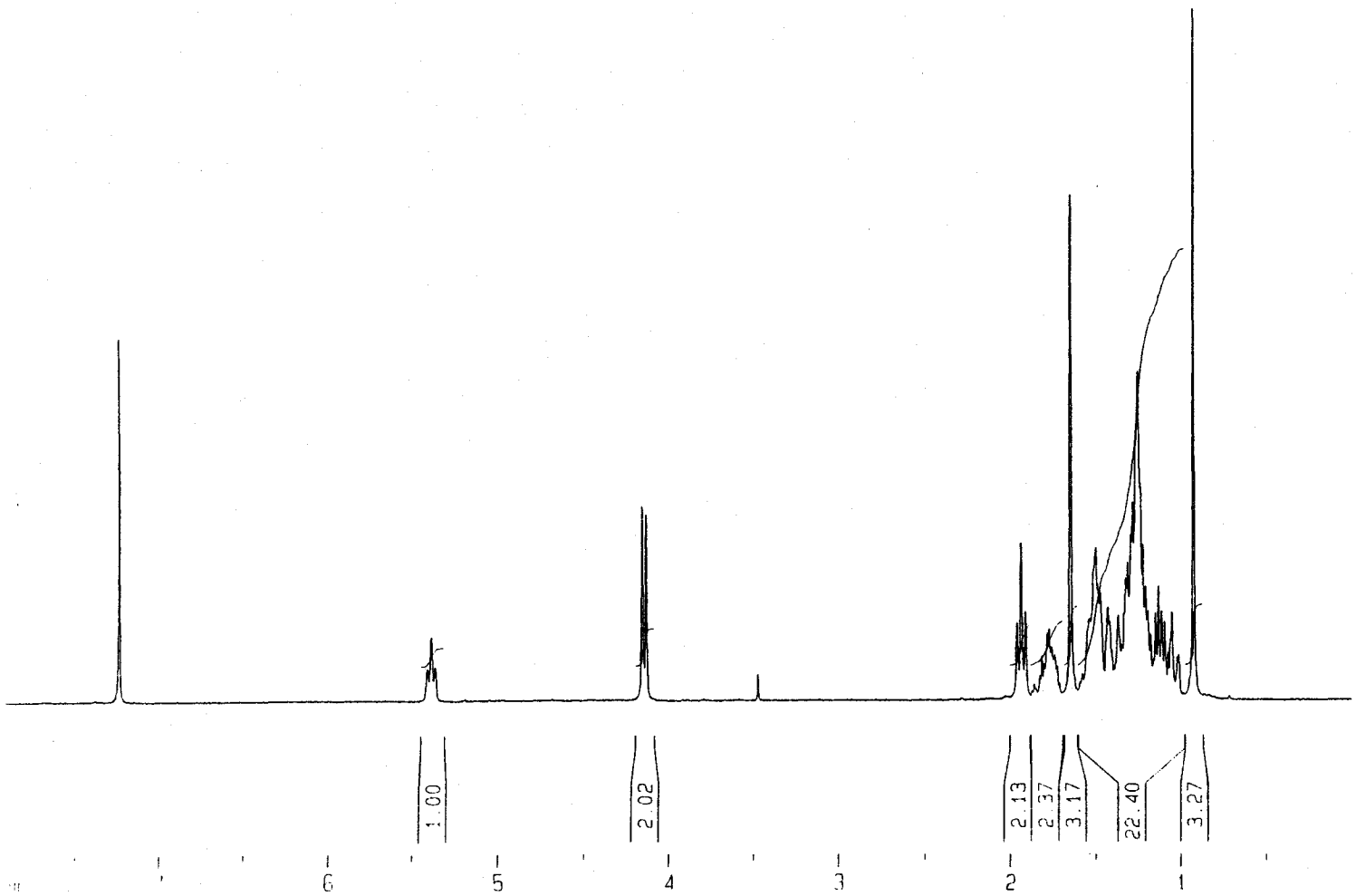
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	-1.000 ppm
F2	-300.13 Hz
PPMCM	0.45000 ppm/cm
HZCM	135.05850 Hz/cm





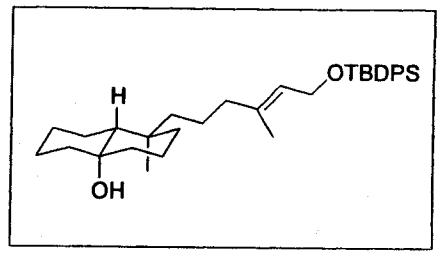
Current Data Parameters
NAME irina_diol
EXPNO 1
PROCNO 1

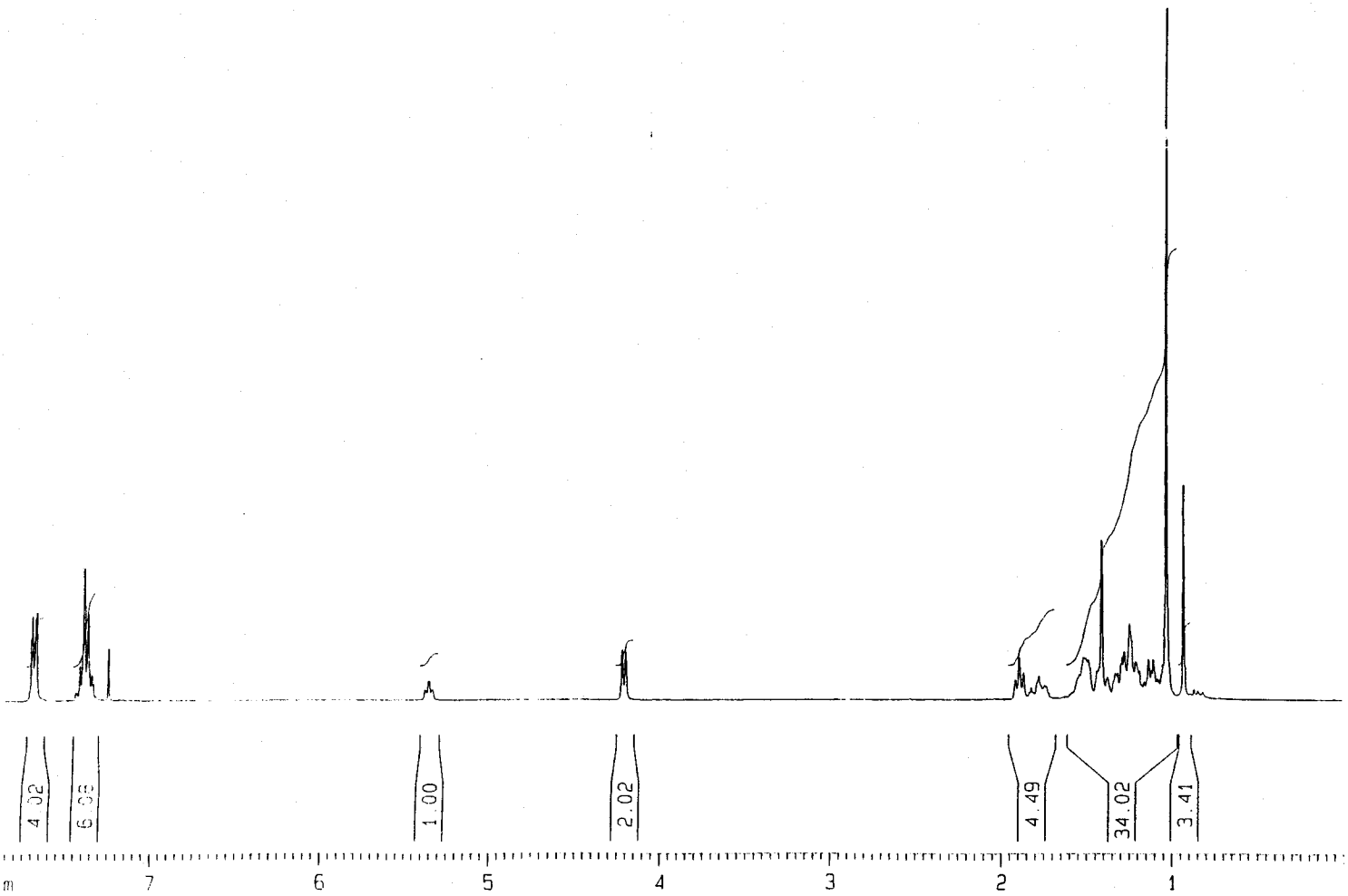
F2 - Acquisition Parameters
Date_ 20040302
Time 19.59
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 456.1
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm





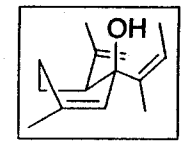

```
Current Data Parameters
NAME                  irina_8-9
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_              20040109
Time                    16.19
INSTRUM                 av300
PROBHD    5 mm QNP  1H/1
PULPROG                 zg30
TD                     30720
SOLVENT                 CDCl3
NS                         16
DS                          0
SWH                5081.301 Hz
FIDRES             0.165407 Hz
AQ                 3.0228980 sec
RG                     161.3
DW                    98.400 usec
DE                     6.00 usec
TE                     300.0 K
D1                 1.00000000 sec

========== CHANNEL f1 ========
NUC1                       1H
P1                      10.50 usec
PL1                     -3.00 dB
SFO1               300.1319477 MHz

F2 - Processing parameters
SI                        65536
SF                 300.1299999 MHz
WDW                          EM
SSB                           0
LB                         0.10 Hz
GB                            0
PC                         1.00

1D NMR plot parameters
CX                        20.00 cm
CY                        10.00 cm
F1P                       8.000 ppm
F1                     2401.04 Hz
F2P                       0.000 ppm
F2                         0.00 Hz
PPMCM                  0.40000 ppm/cm
HZCM                 120.05200 Hz/cm
```



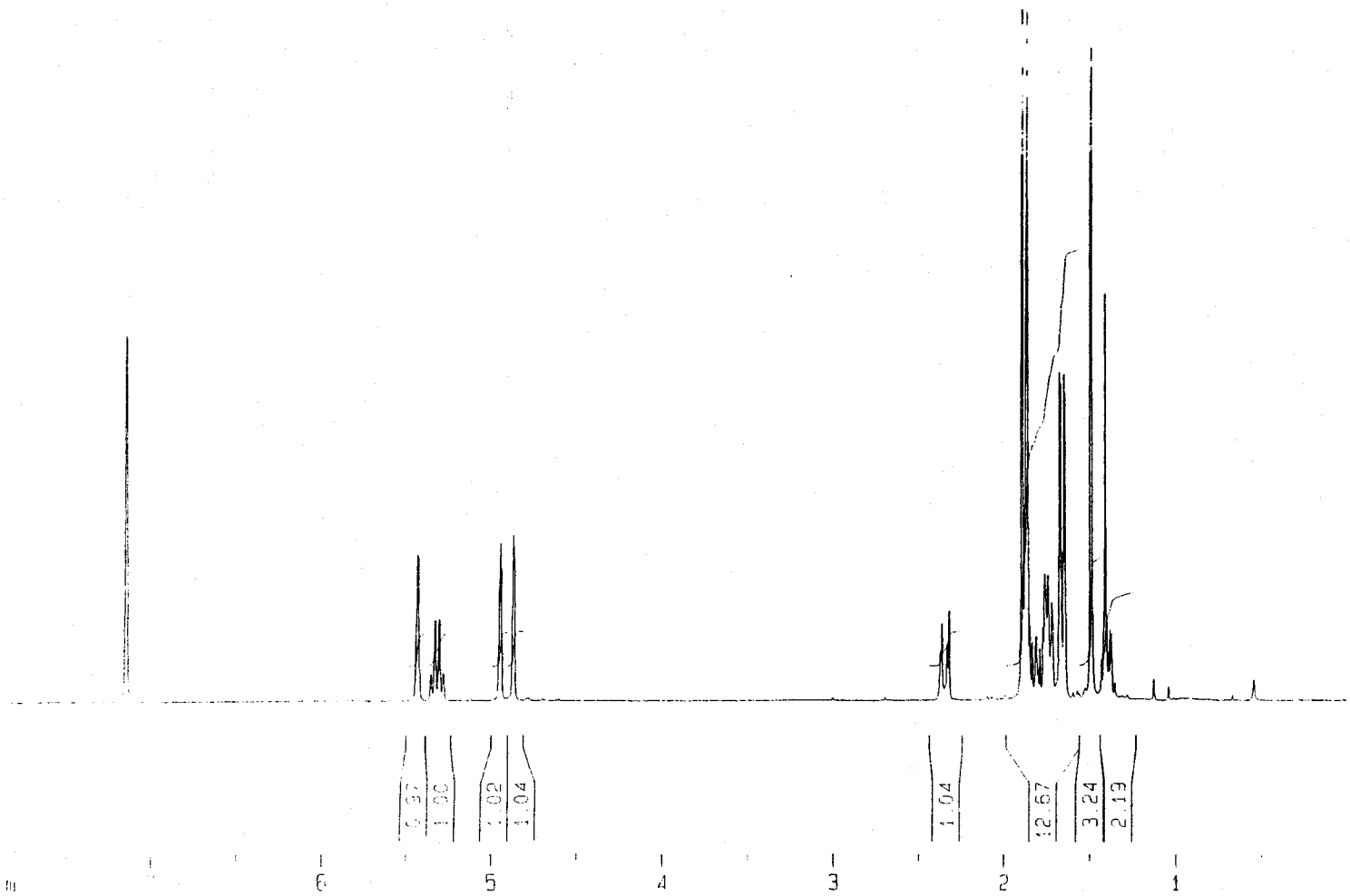
Current Data Parameters
NAME [illegible]
EXPNO 1
PROCNO 1

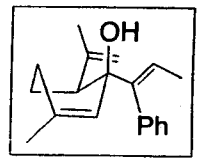
F2 - Acquisition Parameters
Date_ 20030305
Time 20 47
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH [illegible] 301 Hz
FIDRES [illegible] 540 Hz
AQ 3.0[illegible]080 sec
RG 114
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

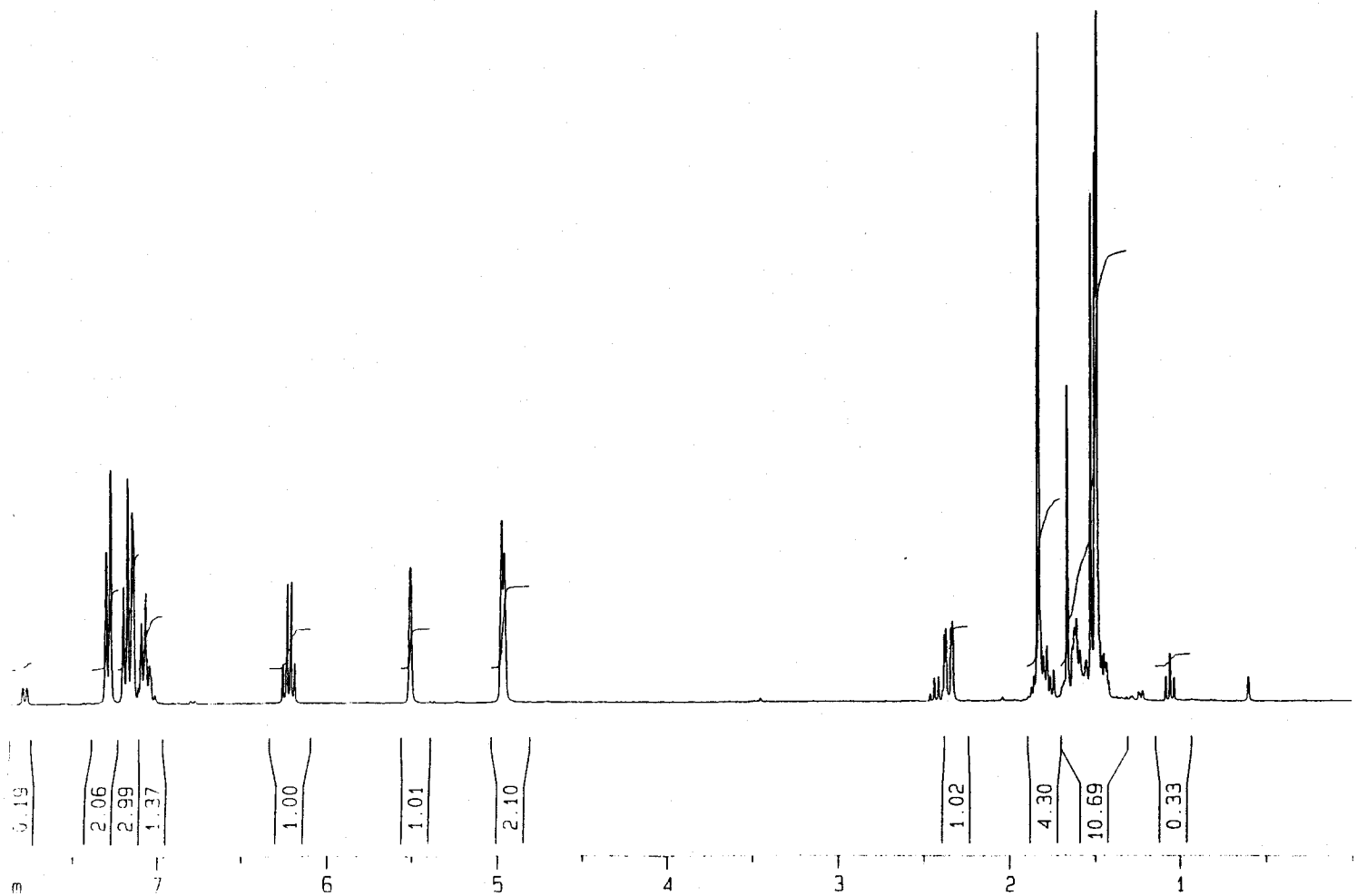
========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.01 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm







Current Data Parameters

NAME	irina_real7-68
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20030802
Time	16.06
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	90.5
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

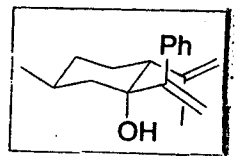
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

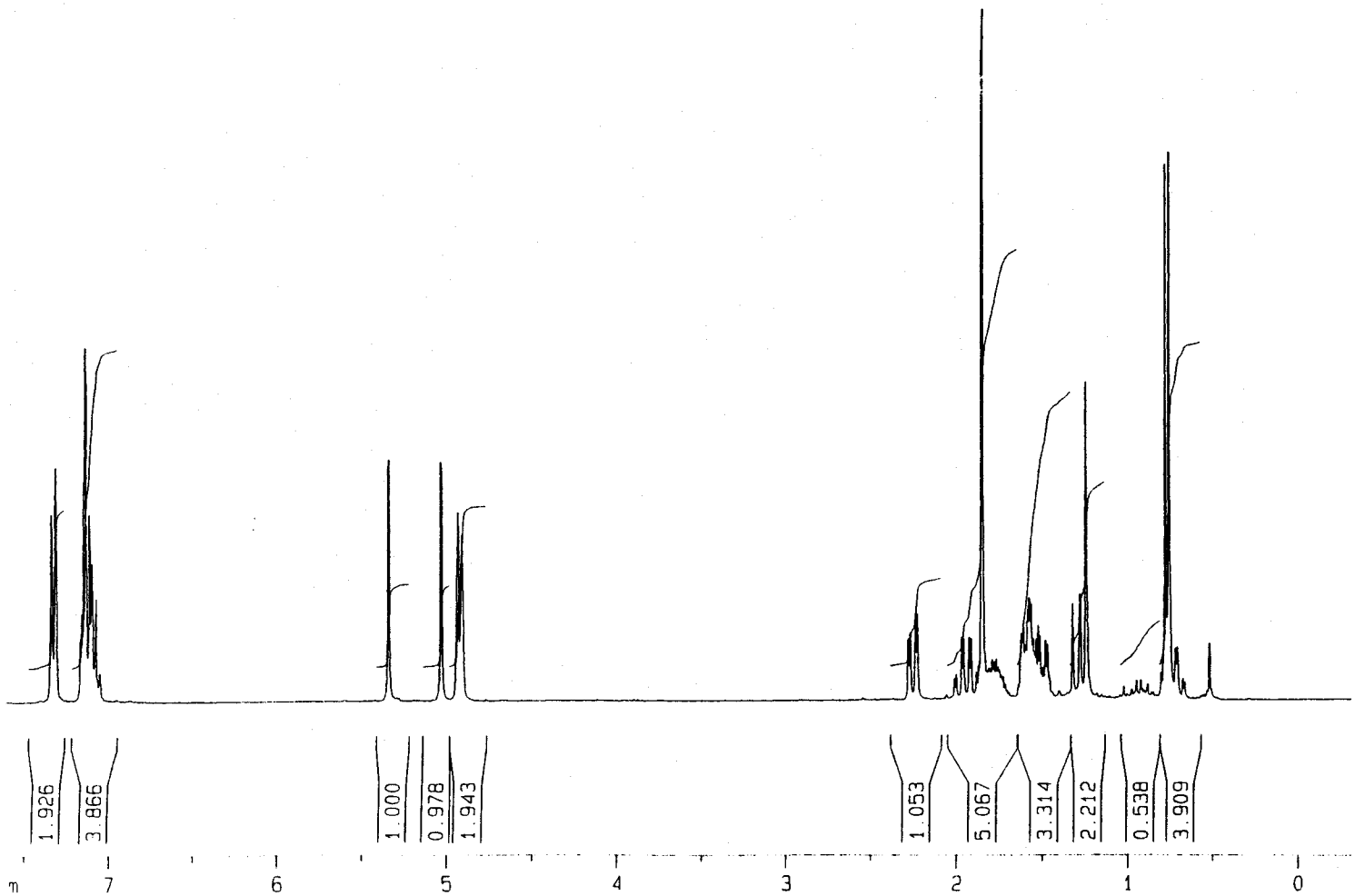
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm





Current Data Parameters

NAME	irina_7-63
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20030731
Time	13.56
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	C6D6
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	90.5
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

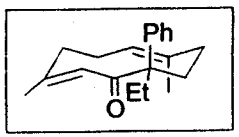
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

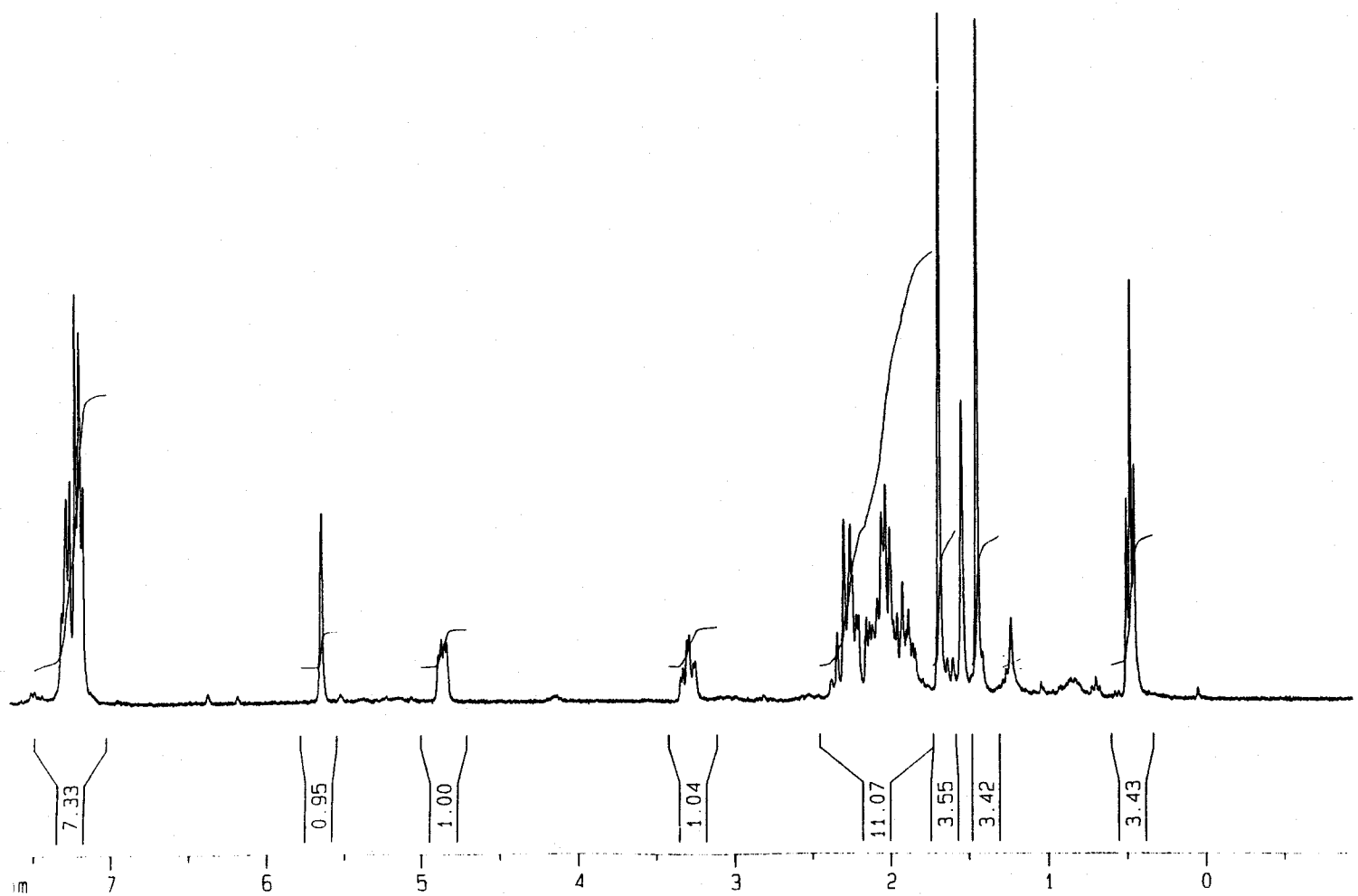
F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	7.734 ppm
F1	2321.12 Hz
F2P	-0.317 ppm
F2	-95.06 Hz
PPMCM	0.40252 ppm/cm
HZCM	120.80903 Hz/cm





Current Data Parameters

NAME	irina_7-46
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20030710
Time	18.27
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	456.1
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

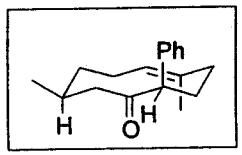
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

F2 - Processing parameters

SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	7.758 ppm
F1	2328.27 Hz
F2P	-0.937 ppm
F2	-281.25 Hz
PPMCM	0.43473 ppm/cm
HZCM	130.47565 Hz/cm



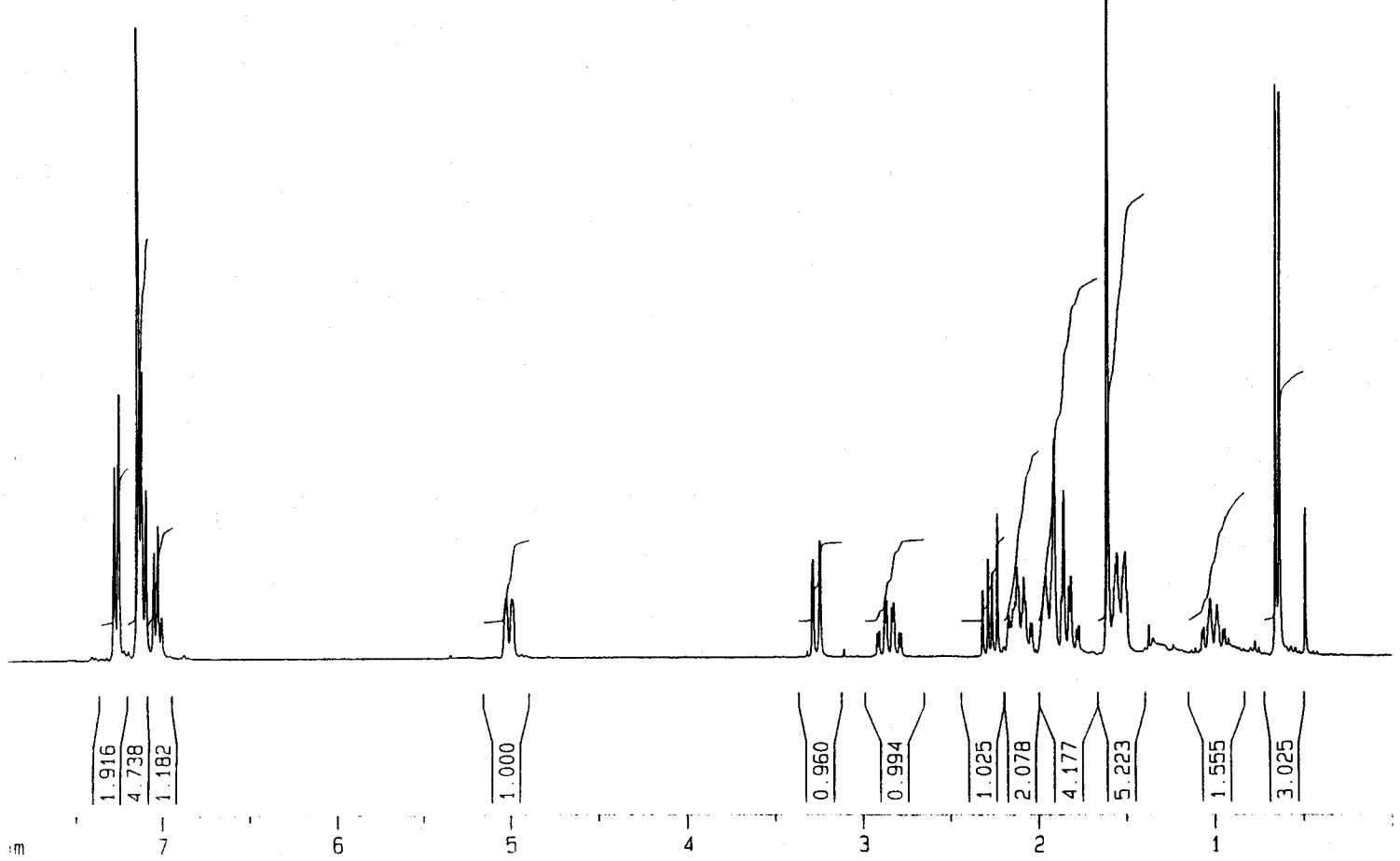
Current Data Parameters
NAME irina_7-65(1stproduct)
EXPNO 1
PROCNO 1

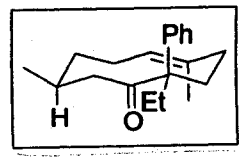
F2 - Acquisition Parameters
Date_ 20030731
Time 20.27
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT ~~CDCl3~~ C_6D_6
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 228.1
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

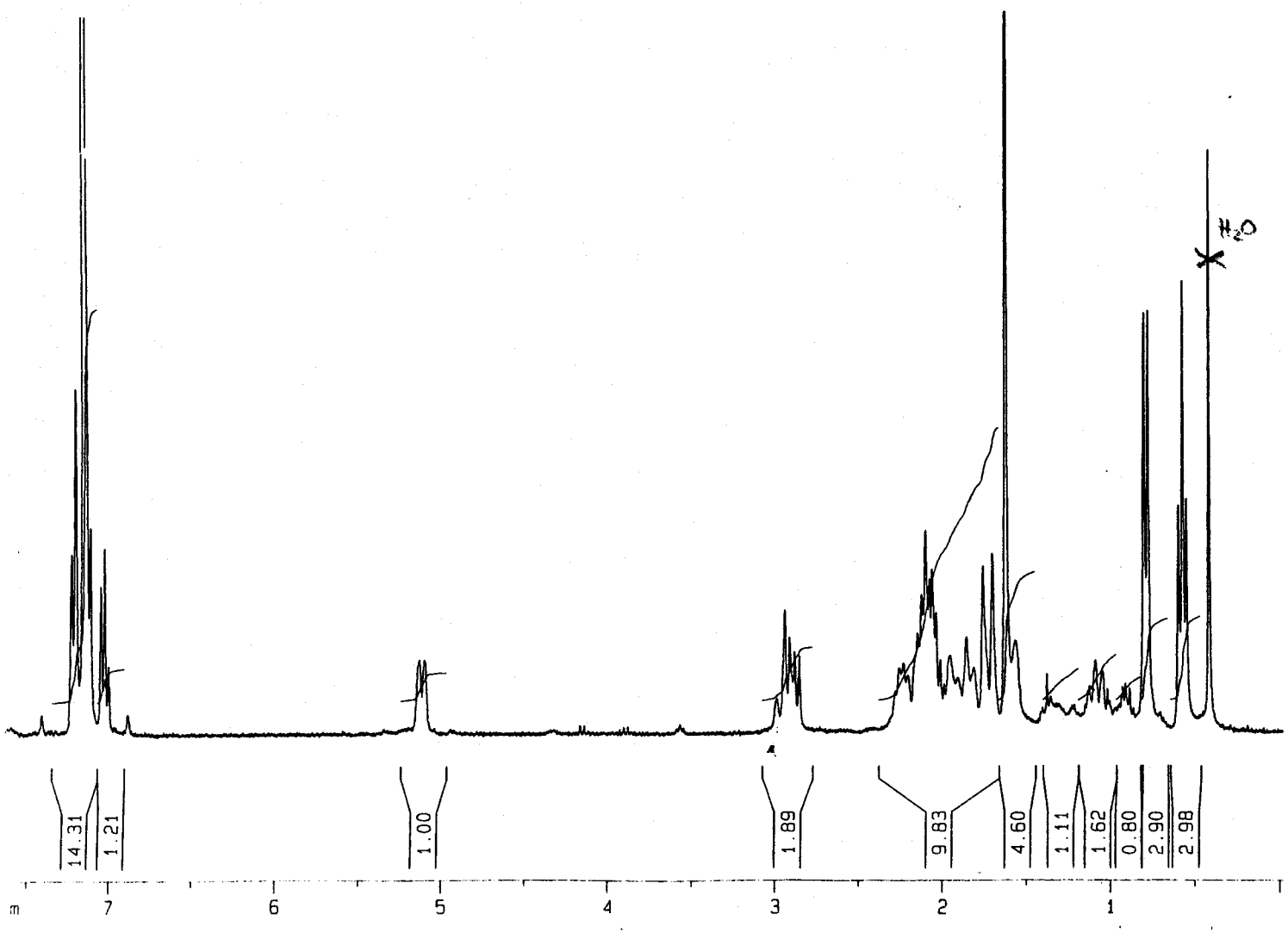
========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 120.05200 Hz/cm







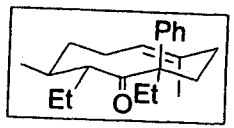
Current Data Parameters
NAME irina_7-68(2nd
EXPNO 1
PROCNO 1

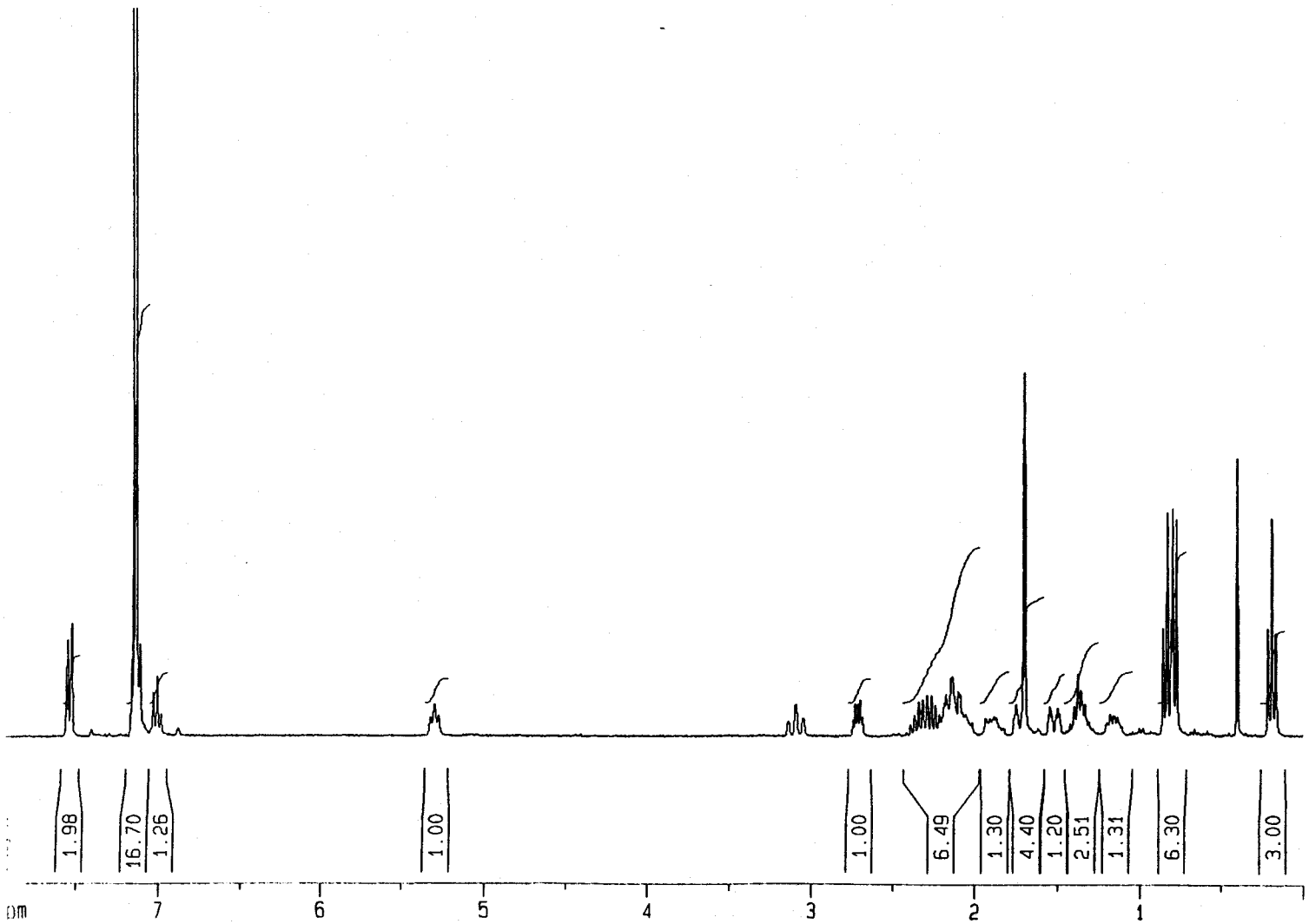
F2 - Acquisition Parameters
Date_ 20030802
Time 12.46
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT ~~CDCl3~~ C_6D_6
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 512
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 50.00 cm
F1P 7.734 ppm
F1 2321.12 Hz
F2P -0.024 ppm
F2 -7.20 Hz
PPMCM 0.38789 ppm/cm
HZCM 116.41597 Hz/cm





Current Data Parameters

NAME	irina_7-68
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20030802
Time	12.37
INSTRUM	av300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	30720
SOLVENT	~~CDCl3~~ C_6D_6
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	574.7
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

F2 - Processing parameters

SI	65536
SF	300.1299995 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	20.00 cm
F1P	8.000 ppm
F1	2401.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.40000 ppm/cm
HZCM	120.05200 Hz/cm