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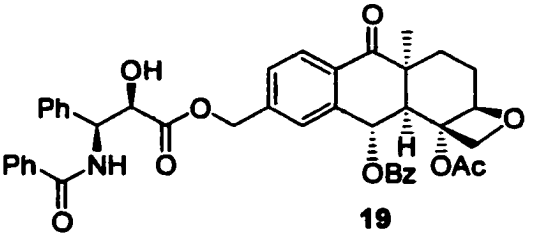
Abstract

Studies towards the synthesis of Taxol® mimics **19** and **20** are described. The strategy involved two sequential Diels-Alder reactions to form the ABC ring system. The synthesis of aromatic analogue **19** was abandoned due to the lack of regioselectivity and low yields in the Diels-Alder reaction. More progress was made in the synthesis of norbornane analogue **20**. *In situ* oxidation of methyl-2,5-dihydroxybenzoate, followed by cycloadditions with 2-triisopropylsilyl-1,3-butadiene and cyclopentadiene, respectively, gave the tetracyclic skeleton **56** in good yield. Further manipulations afforded compounds **69**, **71**, and **73**, which were subsequently sent for biological testing with the hopes that they will display Taxol-like effects on microtubules.

A sequential carbomagnesiation-palladium (0) coupling reaction was investigated. Treatment of a propargyl alcohol with vinyl magnesium chloride generated a magnesium-chelate intermediate, which was capable of undergoing a palladium-catalyzed cross coupling with aryl halides. The reaction was used in a stereoselective three-step synthesis of new analogues (**99** and **100**) of the breast cancer drug tamoxifen (**74**).



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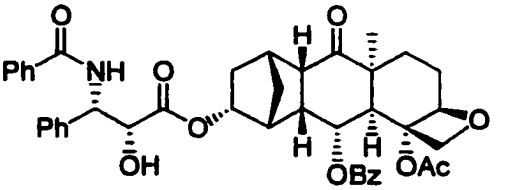

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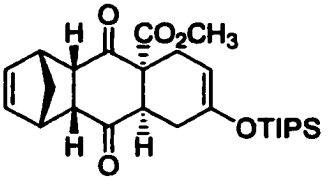

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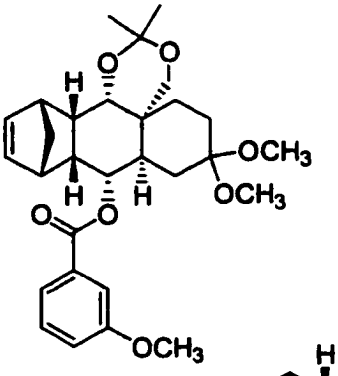

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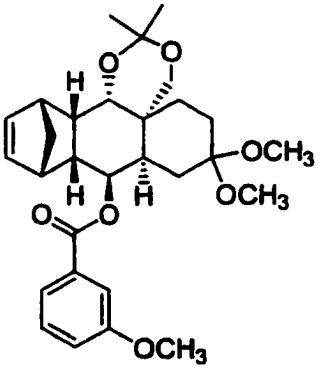

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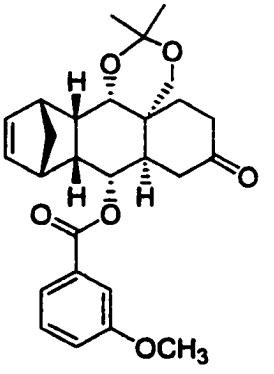

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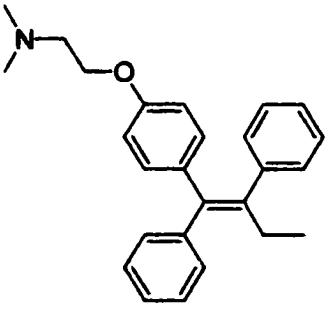
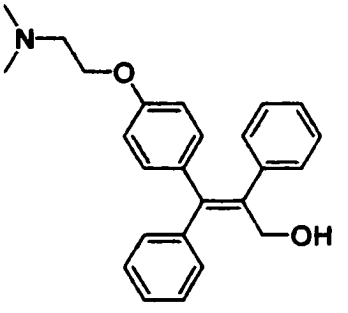


74 tamoxifen



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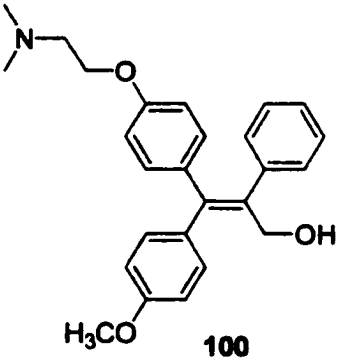

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List of Schemes

List of Abbreviations

Ac	acetyl
acac	acetylacetonate
aq	aqueous
[BMIM]BF_4	1-butyl-3-methylimidazolium tetrafluoroborate
bp	boiling point
Bz	benzoyl
calcd	calculated
cat.	catalytic
m-CPBA	*meta*-chloroperoxybenzoic acid
d	doublet
dd	doublet of doublets
dt	doublet of triplets
dba	dibenzylideneacetone
DCC	dicyclohexylcarbodiimide
DMAP	*N,N'*-dimethyl-4-aminopyridine
EDG	electron-donating group
eq.	equivalents
EWG	elecron-withdrawing group
FDA	Food and Drug Administration (US)
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectroscopy
IR	infrared
J	doupling constant
KHMDS	potassium hexamethyldisilzazide
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M^+	molecular ion

mp	melting point
MOM	methyoxymethyl
MS (CI)	mass spectrum by chemical ionization
MS (EI)	mass spectrum by electron impact
NCI	National Cancer Institute
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
PMB	*para*-methoxybenzyl
ppm	parts per million
py	pyridine
q	quartet
R	alkyl
rt	room temperature
s	singlet
SERM	selective estrogen receptor modulator
t	triplet
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl (toluenesulfonyl)

1 Introduction - Synthesis of Taxoid Mimics

1.1 General Background

Cancer, a disease characterized by uncontrolled growth and spread of abnormal cells, is the second leading cause of death in Canada exceeded only by heart disease.[1] One in three Canadians will be diagnosed with cancer in their lifetime.[2] An estimated 136,900 new cases of cancer and 66,200 deaths from cancer will occur in Canada in 2002 and given current trends, the incidence of cancer is expected to increase by 70% by the year 2015. However, with improved screening tests, availability of comprehensive information, and better treatment, more than half of all people with cancer will survive the disease.

Breast cancer is the most frequently diagnosed cancer in women accounting for about 30% of all new cancer cases each year. In 2002, an estimated 20,500 Canadian women will be diagnosed with breast cancer and 5,400 will die of it. Ovarian cancer is one of the most lethal cancers, often not diagnosed until late stage, and is the fifth leading cause of cancer deaths among Canadian women. Widespread screening and early detection have improved the prognosis of women who develop these cancers. Possible treatments include surgery, radiation, and/or chemotherapy. Researchers, however, continue to learn more about what causes cancer and are exploring new ways to prevent, detect, diagnose, and treat these diseases.

A major breakthrough in the treatment of cancer came with the discovery of Taxol® (**1**, Figure 1), a complex polyoxygenated alkaloid isolated from the Pacific Yew.[3,4] Interest in Taxol® was triggered by its unique mechanism of action and its excellent clinical activity against ovarian and breast cancers. It has become the largest selling anticancer drug of all time, with sales of over $1.5 billion in 1999.[5] However, more efficient and selective drugs are still to be synthesized to treat and cure cancer. The purpose of this research is to develop

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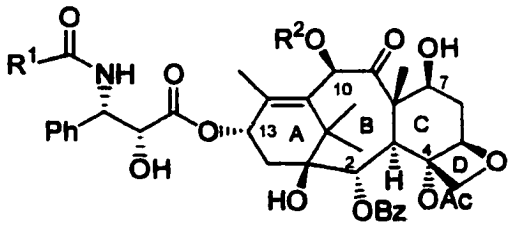
[1] Health Canada: www.hc-sc.gc.ca/pphb-dgspsp/dsol-smed/ (select cancer button). Updated January 21, 2002.
[2] Statistics appearing in this thesis were obtained from Canadian Cancer Statistics: www.cancer.ca/english/index.asp/ (select research/statistics button). Updated August 12, 2002.
[3] (a) Wani M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325; (b) Taxol® was named by its discoverers in 1971. The name is now a registered trademark of Bristol-Meyers Squibb, who applied it to their formulation of the drug. The generic name is paclitaxel.
[4] For a recent review on Taxol® see: Kingston, D. G. I. *Chem. Commun.* **2001**, *10*, 867.
[5] Thayer, A. M. *Chem. Eng. News.* **2000**, *78*, 20.

a short route to Taxol® mimics with the hope of generating facile access to potentially more potent molecules.



1 Taxol $R^1 = Ph$, $R^2 = Ac$
2 Taxotere $R^1 = t\text{-BuO}$, $R^2 = H$

Figure 1: Structures of Taxol® and Taxotere®.

1.2 History of the Development of Taxol® as a Therapeutic Agent

The Pacific Yew (*Taxus brevifolia)* grows in the oldest forests of the Pacific Northwest of North America. Native Americans once recognized its unique qualities and used its bark as a disinfectant, an abortifacient, and even as a medicine for healing skin cancer.[6] In the early 1960s, the National Cancer Institute (NCI) began an ongoing program to screen thousands of plant species for antineoplastic activity. It was in these forests, in 1962, that botanist Arthur Barclay collected samples of the stem and bark of the Pacific Yew for chemical and biological studies. These samples, along with many others, were extracted and tested for bioactivity, and in 1964 an extract from the bark was found to be cytotoxic to leukemia cells. The samples were subsequently sent by the NCI to Drs. M. C. Wani and Moroe Wall, chemists at the Research Triangle Institute in North Carolina, who isolated and identified the active ingredient in Pacific Yew tree bark as Taxol® in 1971.[3a]

Despite its novel molecular architecture and its very good anticancer activity, further development of Taxol® as a drug was delayed for nearly a decade for a couple of reasons. First, it was poorly soluble in water, and would therefore be a difficult drug to formulate for administration by the normal route of injection. Second, it would be very difficult to supply the substance in adequate quantities for clinical use. It was isolated initially in a yield of 0.014% from the bark the Pacific Yew, a relatively uncommon and slow-growing tree. As

[6] Nicolaou, K. C.; Guy, R. K. *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 2079.

well, it was believed that Taxol® was simply another microtubule-destabilizing agent like other drugs on the market.

Fortunately, additional testing was carried out in some newly developed *in vivo* bioassays that were introduced by the NCI. Taxol® showed excellent activity in these assays, with promising activity against breast cancer and melanoma. It was on this basis that Taxol® was selected as a development candidate in 1977. The solubility problem was then successfully overcome with a formulation in ethanol and Cremaphor EL, a polyethoxylated castor oil.

Interest in Taxol® as a drug candidate was significantly increased when Horwitz and coworkers reported in 1979 that Taxol® had a unique mechanism of action, in that it promoted the irreversible assembly of tubulin into microtubules.[7] The tubulin-microtubule equilibrium is crucial to the mitotic process and other antimitotic agents such as the anticancer drugs vinblastine (Velban™) and vincristine (Oncovin™), as well as podophyllotoxin and colchicine, were known to act as spindle poisons by preventing the assembly of tubulin into microtubules. Taxol® was the first compound known to act as a promoter of microtubule assembly and this discovery greatly enhanced interest in its development.

Taxol® went into Phase I clinical trials in 1984 and into Phase II trials in 1985. Further development of the drug for commercial use was assigned to Bristol-Myers Squibb and in 1992 the Food and Drug Administration approved Taxol® for treatment of ovarian cancer. Approval for treatment of breast cancer followed in 1994. Today, Taxol® is used for treatment of ovarian and breast cancers (either as a single agent or in combination with other drugs such as cisplatin), and also for treatment of non-small-cell lung cancer, small-cell lung cancer, squamous cancers of the head and neck, and various other cancers.[8] Its semisynthetic analogue, Taxotere® (2), developed by Rhone-Poulenc Rorer, has an activity similar to Taxol® and was approved for treatment of breast cancer in 1995.[9]

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[7] Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature.* **1979**, *277*, 665.
[8] Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 726.
[9] Guénard, D.; Guéritte-Voegelin, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160.

1.3 Taxol® Supply

Large-scale clinical trials of Taxol® were initially hampered by the relatively low supply of the drug. At the time, Taxol® was obtained by a tedious extraction from the bark of the Pacific Yew. To obtain one kilogram of Taxol®, 10,000 kilograms of bark were required, which, in turn, required the sacrifice of 3,000 trees.[10] Because of the relatively large amount of Taxol® needed to treat a patient (up to two grams), this one kilogram would treat only 500 patients. The Pacific Yew is a relatively uncommon and slow-growing conifer and is an important habitat for endangered species, such as the spotted owl and other birds. Thus, the large-scale logging required to supply Taxol® to the clinical market raised serious environmental concerns. It was obvious that the Pacific Yew bark was not a sustainable resource for the production of Taxol®.

Possible solutions to the supply problem included isolation of Taxol® from a renewable resource such as yew needles, semisynthesis of Taxol® from other taxoids, bioproduction through plant tissue cultures, production through fungal cultures, and biosynthesis.[11]

The breakthrough to the problem came in 1980 when Potier's group discovered that needles of the European Yew, *Taxus baccata*, contained substantial amounts of 10-deacetylbaccatin III (**3**) and smaller amounts of baccatin III (**4**), which were identified as readily accessible starting materials for the semisynthesis of anticancer taxanes (Figure 2).[12] Holton then discovered an efficient semisynthesis of Taxol® from protected baccatin III (**5**) and β-lactam **6** (Scheme 1).[13] This process was patented and licensed to Bristol-Myers Squibb in 1992. Extraction of precursor **3** from the European Yew needles, a renewable resource, followed by a short synthetic sequence allows the company to produce enough Taxol® to meet the current demand. However, the method is laborious and low yielding, hence the high price of the drug.

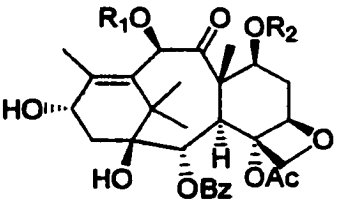
---

[10] Nicolaou, K. C.; Dai, W-M; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15.

[11] Suffness, M. in *Taxane Anticancer Agents: Basic Science and Current Status;* Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995; pp 1-13.

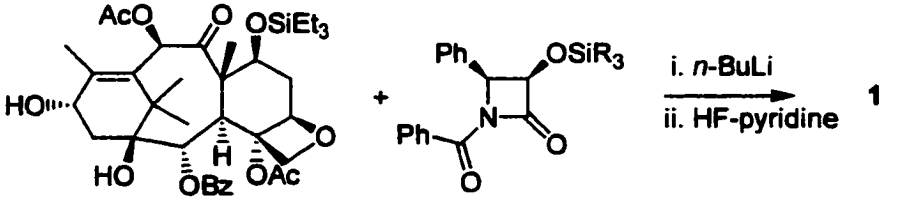
[12] Senilh, S.; Blechert, S.; Colin, M.; Guénard, D.; Picot, F.; Potier, P.; Varenne, P. J. *J. Nat. Prod.* **1984**, *47*, 131.

[13] Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. in *Taxane Anticancer Agents: Basic Science and Current Status;* Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995; pp 288-301.



3 10-deacetylbaccatin III $R_1 = R_2 = H$
4 baccatin III $R_1 = Ac$, $R_2 = H$

Figure 2: Structures of 10-deacetylbaccatin III and baccatin III.



5 **6**

Scheme 1: Semisynthesis of Taxol®.

1.4 Taxol® Syntheses

As mentioned above, Taxol® is commercially synthesized by acylation of a protected baccatin III with a β-lactam. However, chemists had been interested in the compound much earlier than this discovery. Intrigued by its extremely challenging structure and its therapeutic potential, 30 or so research groups from around the world began working on the total synthesis of Taxol® prior to the FDA's approval of the drug.

The total synthesis of Taxol® represents an enormous challenge to the ingenuity and creativity of the synthetic organic chemist. The most obvious challenge is the synthesis of the central eight-membered B ring. Such rings are difficult to form due to both entropic and enthalpic factors. The C ring is *trans*-fused with an angular methyl group and the A ring includes a bridgehead alkene, which is formally forbidden by Bredt's rule. In addition, a high degree of oxygenation has to be introduced in a manner that allows for differential protection of five alkoxy groups. To date, six groups have published the total synthesis of

Taxol® using a variety of approaches.[14] In all cases, the method is aimed at the synthesis of the tricyclic ABC taxane core followed by coupling of the side chain in a manner similar to that used in the semisynthesis of Taxol®.

Although these syntheses represented major accomplishments in the field of synthetic organic chemistry, none is viable on an industrial scale. The disadvantages and difficulties present with semisynthesis and total synthesis, such as low overall yield, could be overcome by using Taxol® mimics. These mimics would ideally be less complex molecules that are easier to synthesize and possess a bioactivity similar to Taxol®. In order to design potential Taxol® mimics, knowledge of the chemical functionalities required for biological activity is necessary.

1.5 Structure-Activity Relationships

In terms of structure-activity relationships, Taxol® can be divided into three main areas: the northern hemisphere, the southern hemisphere and the side chain (Figure 3). The northern hemisphere of Taxol® includes carbons 6 to 12, with oxygen functionalities at C7, C9 and C10. In general, changes at these positions do not have a significant impact on the activity of Taxol®.[15]

---

[14] (a) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature*, **1994**, *367*, 630; (b) Holton, R. A.; Somoza, C.; Kim, H.–B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597; (c) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.*, **1996**, *118*, 2843; (d) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floerancig, P. E.; Glass, T. E.; Granicher, C.; Houze, J. B.; Janichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Muhlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2755; (e) Kusama, H; Hara, R.; Kawahara, T.; Nishimori, T.; Kashima, N.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811; (f) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121.

[15] Kingston, D. G. I. In *Taxane Anticancer Agents: Basic Science and Current Status;* Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995; p 204.

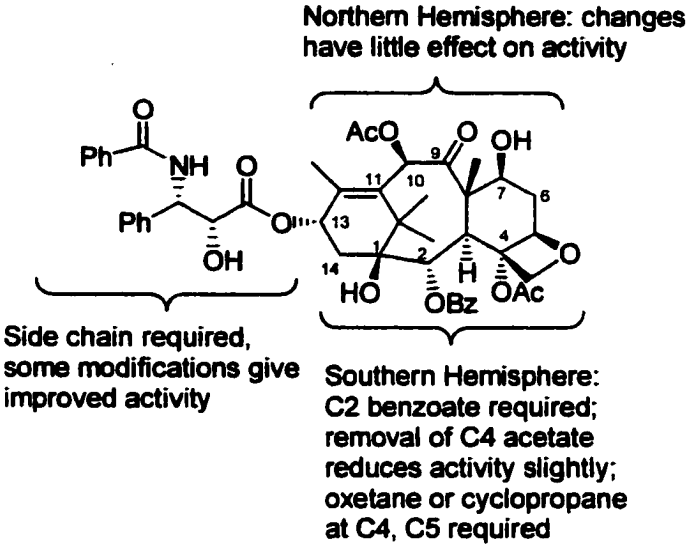


Figure 3: Structure activity relationships of Taxol®.

In contrast, changes to the southern hemisphere, comprising C14 and C1 to C5, have a dramatic effect on the activity of Taxol®. The oxetane ring has been thought to be essential for activity since opening of the ring almost always leads to loss of activity.[16] The four-membered ring is believed to rigidify the Taxol® core giving a favourable conformation for activity. As well, the oxetane oxygen is thought to participate in hydrogen bonding with the tubulin protein. However, recent studies by Snyder's group, using a minireceptor model of the binding site for Taxol® on tubulin, have indicated that although the oxetane ring is capable of making a positive contribution to the bioactivity of Taxol® analogues, it is not necessary for Taxol® analogue bioactivity.[17]

The C4 acetate function is necessary for activity since deoxygenation results in an inactive product.[18] The C2 benzoate is also important for activity. Many analogues have been synthesized with substituted benzoyl groups and it is interesting to note that *m*-substituted analogues are more potent than the corresponding *p*-substituted analogues. For example, 2-

[16] Magri, N. F.; Kingston, D. G. I. *J. Org. Chem.* **1986**, *51*, 797.
[17] Wang, M.; Cornett, B.; Nettles, J.; Liotta, D. C.; Snyder, J. P. *J. Org. Chem.* **2000**, *65*, 1059.
[18] Chordia, M. D.; Chaudhary, A. G.; Kingston, D. G. I.; Jiang, Y. Q.; Hamel, E. *Tetrahedron Lett.* **1994**, *35*, 6843.

p-azidobenzoyltaxol is essentially inactive, while 2-*m*-azidobenzoyltaxol is almost an order of magnitude more active than Taxol®. [19]

It is generally agreed that the side chain is required for activity. One of the early observations in Taxol® structure-activity relationship investigations was that removal of the C13 side chain to give baccatin III completely abolished its antimitotic and antimicrotubule activity.[20] However, recent reports on studies performed with baccatin III have led to a confusing role of the side chain. Recent studies by Bane's group have shown that baccatin III can indeed mimic Taxol®'s effects of the properties of microbutubules.[21] As well, Kingston found that 2-*m*-azido baccatin III, a Taxol analogue lacking the C13 side chain, but with a *m*-azido benzoyl group at the C2 position, was significantly active as a promoter of tubulin polymerization.[22] These results suggest that the C13 side chain is not an absolute requirement for biological activity in a taxane molecule. Many modifications of the side chain have been investigated and it has been shown that a *tert*-butoxycarbonyl group on the nitrogen (Taxotere®, **2**) enhances activity.

1.6 Natural Taxol® Mimics

For many years Taxol® was the only compound known to promote the assembly of tubulin into microtubules. Recently, several other natural products have been discovered that share Taxol's mechanism of action. These include epothilones A (**7**) and B (**8**),[23] eleutherobin (**9**)[24] and discodermolide (**10**)[25] (Figure 4). Although their chemical structures are unique, they are all similar to Taxol® in their biological function. Attempts have been made to identify a common pharmacophore of these Taxol® mimics, particularly between Taxol® and the

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[19] Chaudhary, A. G.; Gharpure, M. M.; Rimoldi, J. M.; Chordia, M. D.; Gunatilaka, A. A. L.; Kingston, D. G. I. *J. Am. Chem. Soc.* **1994**, *116*, 4097.
[20] Parness, J.; Kingston, D. G. I.; Powell, R. G.; Harracksingh, C.; Horwitz, S. B. *Biochem. Biophys. Res. Commun.* **1982**, *105*, 1082.
[21] Chatterjee, S. K.; Barron, D. M.; Vos, S.; Bane, S. *Biochemistry* **2001**, *40*, 6964.
[22] He, L.; Prakash, J. G.; Kingston, D. G. I.; Shen, H.-J.; Orr, G. A.; Horwitz, S. B. *Biochemistry* **2000**, *39*, 3972.
[23] Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325.
[24] Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744.
[25] Haar, E. ter; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243.

epothilones.[26] One model proposes that the thiazole side chain of the epothilones corresponds to the C2 benzoyl group of Taxol® and the macrolide system overlaps with the taxane ring system.[22]

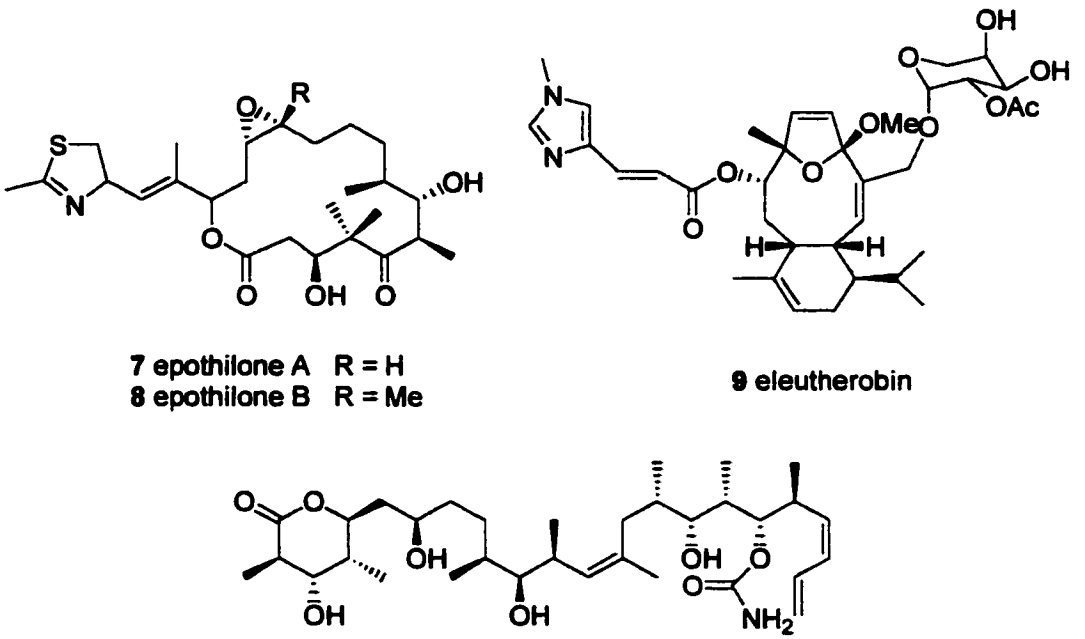

Figure 4: Structures of epothilones A and B, eleutherobin and discodermolide.

1.7 Novel Taxol® Mimics

One research interest in the Fallis group is the design and synthesis of novel Taxol® analogues. Molecular modeling has been used to ensure that the spatial shape of the analogues is similar to that of Taxol® (Figure 5).[27] By maintaining the same basic shape and by having some of the functionalities required for activity, the molecules should behave similarly to Taxol® with respect to the microtubule binding site.

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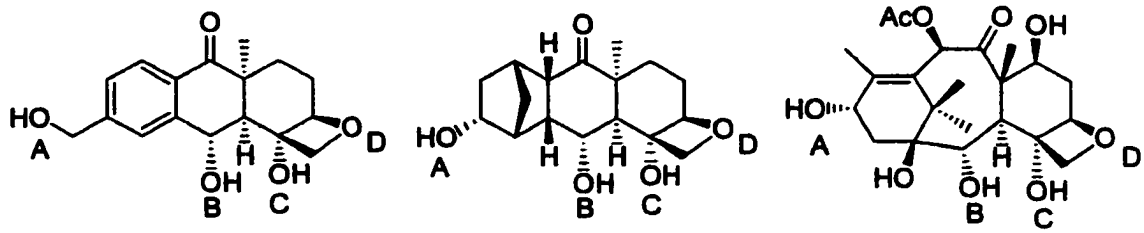
[26] (a) Ojima, I.; Lin, S.; Inoue, T., Miller, M. L.; Borella, C. P.; Geng, X.; Walsh, J. J. *J. Am. Chem. Soc.* **2000**, *122*, 5343; (b) He, L.; Prakash, J. G.; Kingston, D. G. I.; Shen, H.-J.; Orr, G. A.; Horwitz, S. B. *Biochemistry* **2000**, *39*, 3972; (c) Wang, M.; Xia, X.; Kim, Y.; Hwang, D.; Jansen, J. M.; Botta, M.; Liotta, D. C.; Snyder, J. P. *Org. Lett.* **1999**, *1*, 43.

[27] Nicole Mackintosh, M.Sc. Thesis, 1998, University of Ottawa.



15	16	17 Hydroxytaxol
A-B 5.04 Å	A-B 2.50 Å	A-B 5.16 Å
A-C 5.71 Å	A-C 5.95 Å	A-C 5.54 Å
A-D 8.62 Å	A-D 7.54 Å	A-D 8.16 Å
B-C 2.80 Å	B-C 3.87 Å	B-C 2.76 Å
B-D 4.51 Å	B-D 5.65 Å	B-D 3.92 Å
C-D 3.10 Å	C-D 3.10 Å	C-D 3.08 Å

Figure 5: Comparison of important oxygen separation distances.[28]

Two novel taxoid analogues (**15** and **16**) and a Taxol® model (**17**) were simplified for molecular modeling purposes; that is, the side chain, the C2 benzoate, and the C4 acetate were substituted with hydroxyl groups due to limitations of the software. The lowest energy conformations of the compounds were found and the key oxygen distances were measured (Figure 5). A CH_2 spacer was incorporated in the side chain of aromatic analogue **15** as it provides increased flexibility of the side chain and allows the molecule to attain the general shape of Taxol®. Models suggested that the *cis* B-C ring junction is nearly as good as the *trans* geometry found in nature. The similarity in the oxygen separation distances between the target analogues (**15** and **16**) and **17** indicated that the analogues' key functionalities possessed similar spatial arrangements to those found in Taxol® and therefore confirmed the suitability of the compounds as promising Taxol® mimics.

[28] Molecular modeling studies were conducted using MOPAC and MM2 programs within CAChe Editor, version 3.7, supplied from CAChe Scientific Inc.

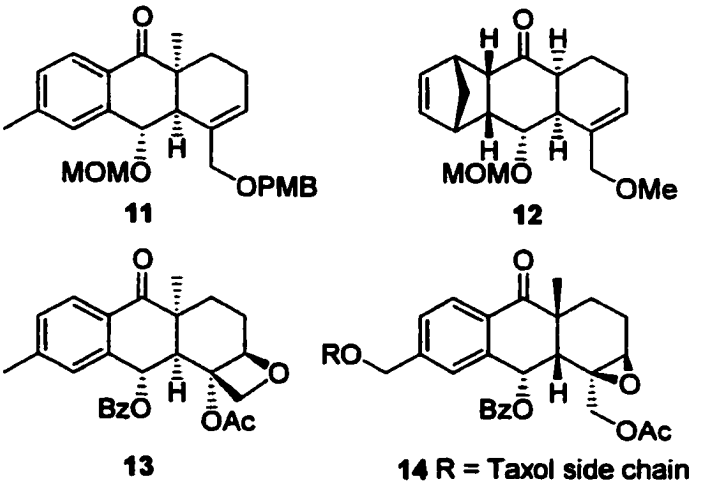
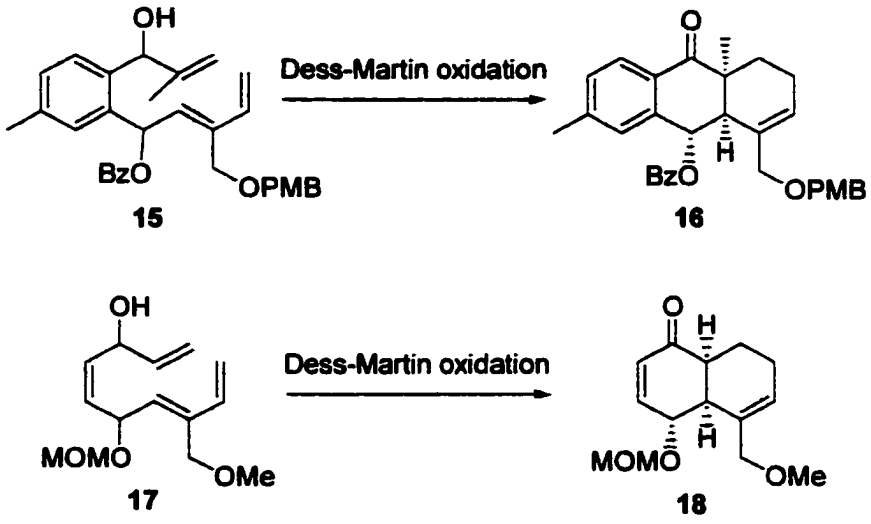


Figure 6: Previously prepared taxoid models and analogues.

Previous group members have synthesized a number of taxoid models and analogues (Figure 6). Compounds **11-14** were synthesized as part of a cycloaddition study in which the key step was an intramolecular tether controlled Diels-Alder reaction using a planar control group (either an aromatic ring or a *cis* alkene) (Scheme 2).[29] Although these planar control groups had a dramatic influence on the ease of cyclization and provided useful functionality for subsequent manipulations, the syntheses required seven to eight steps to reach the Diels-Alder precursors, **15** and **17** (Scheme 2).

[29] (a) Millan, D. S.; Pham, T. T.; Lavers, J. A.; Fallis, A. G. *Tetrahedron Lett.* **1997**, *38*, 795; (b) Martin, C.; Mackintosh, N.; Lamb, N.; Fallis, A. G. *Org. Lett.* **2001**, *3*, 1021.



Scheme 2: Planar tether-controlled cycloadditions.

1.8 Research Objectives

Since the long range goal of this work was to develop facile access to Taxol® mimics that would be effective for cancer chemotherapy, a shorter synthesis was desired. The main objective of this research was to synthesize analogues **19** and **20** using a shorter route to the multicyclic core (Figure 7).

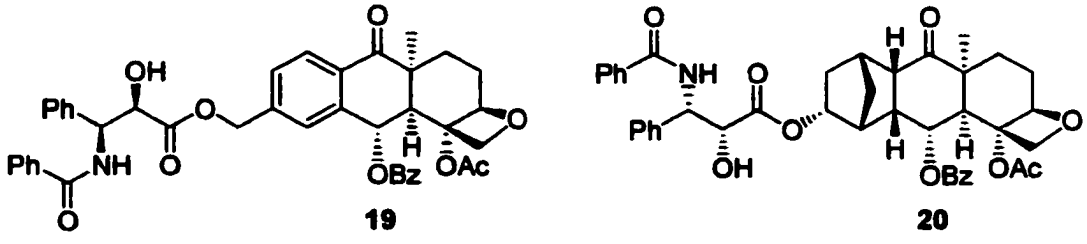
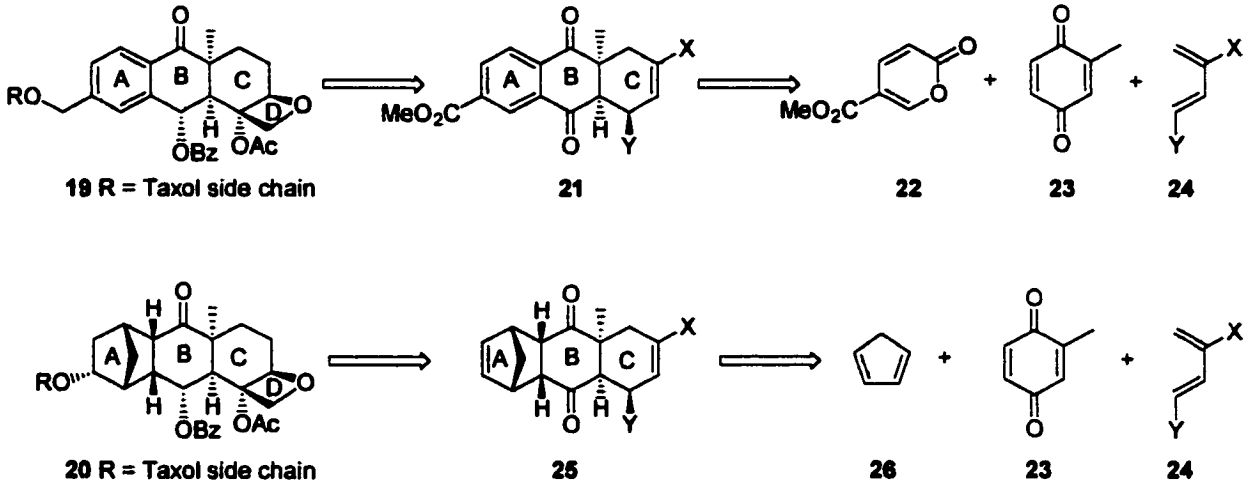


Figure 7: Structures of synthetic targets **19** and **20**.

1.8.1 Retrosynthetic Plan

The new strategy uses two sequential intermolecular Diels-Alder cycloadditions as a short route to analogues **19** and **20** (Scheme 3). The AB ring system in **21** can be prepared by the Diels-Alder reaction of substituted pyrone **22** and methyl-1,4-benzoquinone (**23**).

Cycloaddition with a substituted butadiene (**24**) will provide the C ring. In norbornane analogue **20**, the AB tricyclic ring system can be synthesized by the Diels-Alder reaction of cyclopentadiene (**26**) and methyl-1,4-benzoquinone (**23**). Again, addition of a substituted butadiene (**24**) should provide the C ring of **25**. Further elaboration will allow attachment of the requisite functional groups.



Scheme 3: Retrosynthetic plan for the synthesis of taxoid analogues **19** and **20**.

1.8.2 Diels-Alder Chemistry

The Diels-Alder reaction is one of the most powerful transformations in modern synthetic chemistry. The pericyclic reaction has had elegant applications in the total synthesis of many complex natural products.[30] Discovered in 1928 by Diels and Alder, this [4+2] cycloaddition is a useful method for the synthesis of simple and complex ring systems.[31] The reaction of a diene and a dienophile results in the formation of two new σ bonds, with the introduction of up to four new stereogenic centers. With the use of chiral catalysts, complete stereochemical control of the centers can be achieved.[32]

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[30] For a recent review on the Diels-Alder reaction in total synthesis see: Nicolaou, K. C.; Snyder, S. A.; Montagnon T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668.
[31] Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.
[32] For a recent review on catalytic enantioselective Diels-Alder reactions see: Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650.

For the reaction to occur, the diene must adopt an *s-cis* conformation. This allows for the correct overlap of molecular orbitals. The diene and dienophile approach one another in approximately parallel planes allowing for an interaction between the LUMO of the dienophile and the HOMO of the diene as shown in Figure 8.

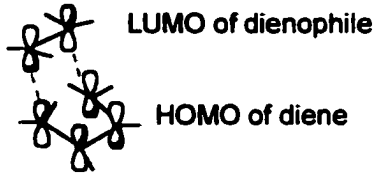


Figure 8: Interaction of LUMO of dienophile with HOMO of diene.

The reaction is accelerated when the diene has an electon-donating substituent and the dienophile an electon-withdrawing substituent. The electronic substituents have the effect of making the $HOMO_{diene}$-$LUMO_{dienophile}$ energy gap smaller and therefore increasing the reaction rate. An inverse electron demand Diels-Alder can also occur in which an electron-poor diene reacts with an electron-rich dienophile.

For an unsymmetrical dienophile, there are two possible stereochemical orientations with respect to the diene: *endo* and *exo*. In the *endo* transition state, the substituent on the dienophile is oriented toward the π orbitals of the diene. In the *exo* transition state, the substituent on the dienophile is oriented away from the diene's π system. When the dienophile has an unsaturated substituent, such as a carbonyl group, a secondary orbital overlap observed in the *endo* orientation stabilizes the transition state and favours the *endo* product over the *exo* product (Figure 9).

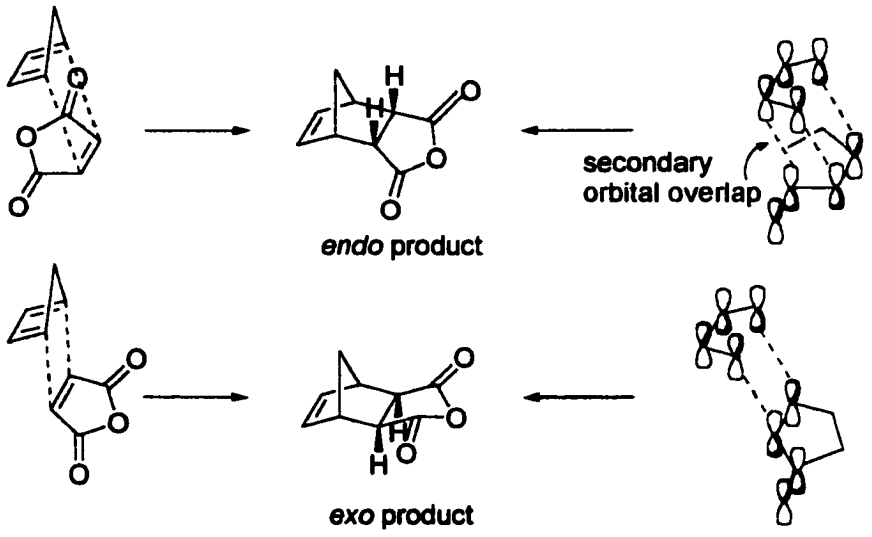


Figure 9: *Endo* and *exo* addition in a Diels-Alder reaction.

When both the diene and dienophile are unsymmetrical, two regioisomers can result. With 1-substituted dienes, the *ortho* product is generally preferred over the *meta* product and with 2-substituted dienes, the *para* product is preferred (Figure 10).

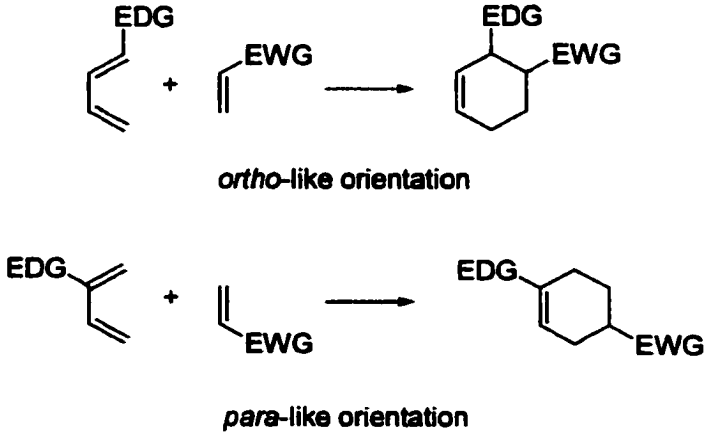


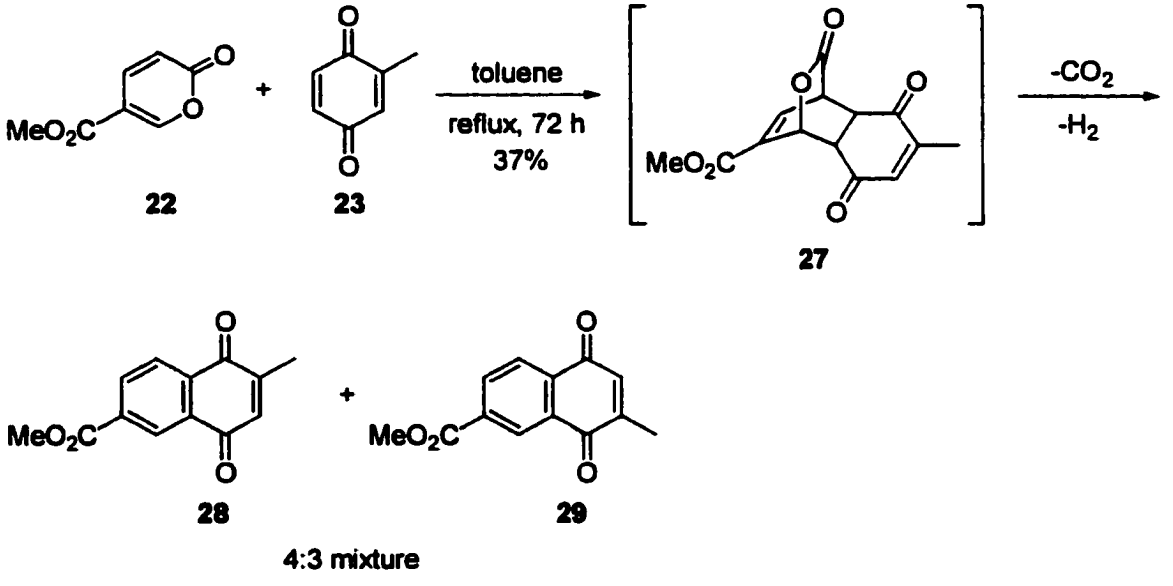
Figure 10: Regioselectivity of Diels-Alder cycloadditon reactions.

The Diels-Alder reaction allows for the rapid assembly of highly functionalized ring systems and is therefore a useful method for the preparation of taxoid analogues **19** and **20**. In addition, varying the diene and dienophile can easily lead to a large number of new analogues.

2 Results and Discussion – Taxoid Mimics

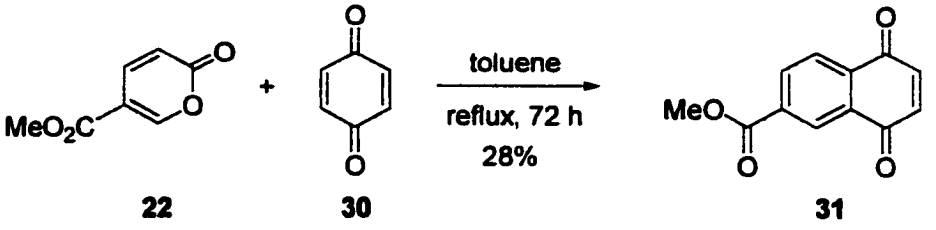
2.1 Attempts at synthesizing an aromatic analogue

The strategy for synthesizing analogue **19**, an aromatic taxoid mimic, is outlined in Scheme 3. Although the approach seemed simple and straightforward on paper, it proved to be more troublesome than initially thought. To start, the Diels-Alder reaction of methyl coumalate (**22**) and methyl-1,4-benzoquine (**23**) yielded a mixture of regioisomers in approximately a 4:3 ratio following *in situ* CO_2 extrusion and aromatization (Scheme 4). Attempts to separate **28** and **29** by flash chromatography, crystallization, and HPLC failed.



Scheme 4: Diels-Alder reaction of methyl coumalate and methyl-1,4-benzoquinone.

To overcome the regioselectivity problem, 1,4-benzoquinone (**30**), a symmetrical dienophile, was chosen. It was anticipated that the angular methyl group could be added later in the synthesis. Aromatic adduct **31** was obtained in 28% yield after heating at reflux in toluene for three days (Scheme 5). This reaction, as well as the corresponding reaction with methyl-1,4-benzoquinone (**23**), was very sluggish. Even after six days of reflux, starting material remained.



22 30 31

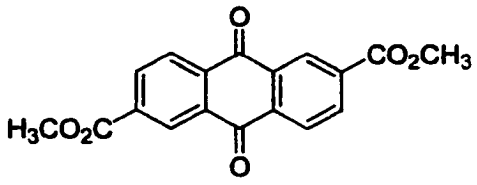
Scheme 5: Diels-Alder reaction of methyl coumalate and 1,4-benzoquinone.

Because 2-pyrone dienes have some aromatic character, they undergo Diels-Alder cycloadditions less easily than do most cyclic conjugated dienes.[33] To increase the rate of the reaction, various conditions were attempted (Table 1). When the reaction was performed at a higher temperature, diadduct **32** formed as a minor product (entry 2). Using a Lewis acid catalyst, such as diethylaluminum chloride, gave no reaction (entry 3). As well, performing the reaction in an autoclave under pressure (68 atm) did not improve the yield (entry 4).

Table 1: Diels-Alder conditions for 1,4-benzoquinone and methyl coumalate.

Entry	Conditions	Result
1	toluene, reflux, 72 h	28% **31**
2	xylene, reflux, 48 h	29% monoadduct **31** + 6% diadduct **32**
3	Et_2AlCl (1.1 eq.), -78 °C to rt, 24 h	no reaction
4	toluene, 68 atm, 100 °C, 72 h	22% **31**
5	[BMIM]BF_4, 80 °C, 72 h	29% **31**

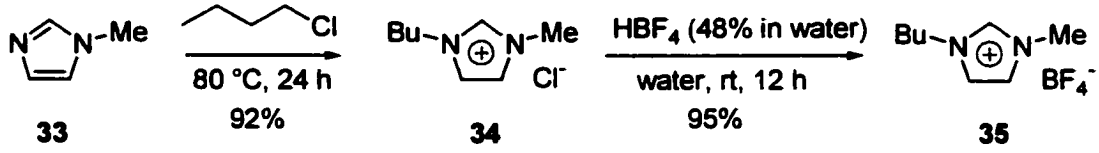
[33] For a review on Diels-Alder cycloadditions of 2-pyrones and 2-pyridones see: Afarinkia, K.; Vinander, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111.



32

Recently, ionic liquids have received attention as alternative solvents for a number of reactions, including the Diels-Alder reaction.[34] Room temperature ionic liquids are a new class of liquids that are composed entirely of ions. They therefore provide a solvent environment that is quite unlike any other at room temperature. Recent studies have shown that ionic liquids such as 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF_4, **35**) can increase the rate of the Diels-Alder reaction.[35]

[BMIM]BF_4 was easily prepared by quarternization of 1-methylimidazole (**33**) with 1-chlorobutane followed by exchange of the chloride anion with the tetrafluoroborate anion (Scheme 6).[36]



33 **34** **35**

Scheme 6: Preparation of 1-butyl-3-methylimidazolium tetrafluoroborate (**35**).

Unfortunately, using [BMIM]BF_4 as a solvent for the Diels-Alder reaction of methyl coumalate (**22**) and 1,4-benzoquinone (**30**) did not improve the yield (Table 1, entry 5). The product (**31**) was extracted from the ionic liquid with diethyl ether, purified by chromatography, and obtained in 29% yield.

The best conditions for the reaction were the initial conditions of heating the reactants at reflux in toluene for three days (Table 1, entry 1). Although the yield was low, most of

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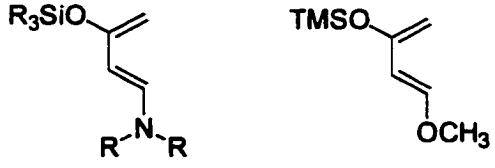
[34] For reviews on ionic liquids see: (a) Wassersheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772; (b) Welton, T. *Chem. Rev.* **1999**, 2071.

[35] (a) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, *1*, 23; (b) Fisher, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793.

[36] Handy, S. T.; Zhang, X. *Org. Lett.* **2001**, *3*, 233.

starting material **22** could be recovered and reused. With adduct **31** in hand, the next step in the synthesis involved a second Diels-Alder reaction to install the C ring.

Around the same time as this work, Dr. Viresh Rawal from the University of Chicago visited the University of Ottawa and presented a lecture on a new class of dienes and their use in Diels-Alder reactions. 1-Amino-3-siloxy-1,3-butadienes (**36**) are a novel class of heteroatom-containing dienes with several useful properties.[37] They readily undergo [4 + 2] cycloadditions with a wide range of electron-deficient dienophiles. The reactions occur under mild conditions affording the cycloadducts in high yields and with high regioselectivity. Elimination of the amino group can be accomplished under acidic conditions leading to the formation of enones. Asymmetric induction is also possible by using a chiral amine. As a result of the higher nucleophilicity of the nitrogen atom, amino-siloxy dienes are more reactive than the corresponding alkoxy-siloxy dienes (e.g. Danishefsky's diene, **37**).



36 **37**

Figure 11: Structures of 1-amino-3-siloxy-1,3-butadienes and Danishefsky's diene.

1-Diethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene (**40**) was prepared by first reacting diethylamine with acetylacetaldehyde dimethylacetal (**38**) to afford **39** (Scheme 7).[38] Deprotonation with potassium hexamethyldisilazide followed by silylation with *tert*-butyldimethylsilyl chloride afforded the diene in 80% overall yield.

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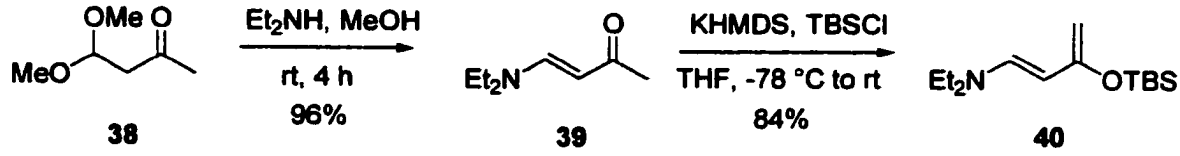
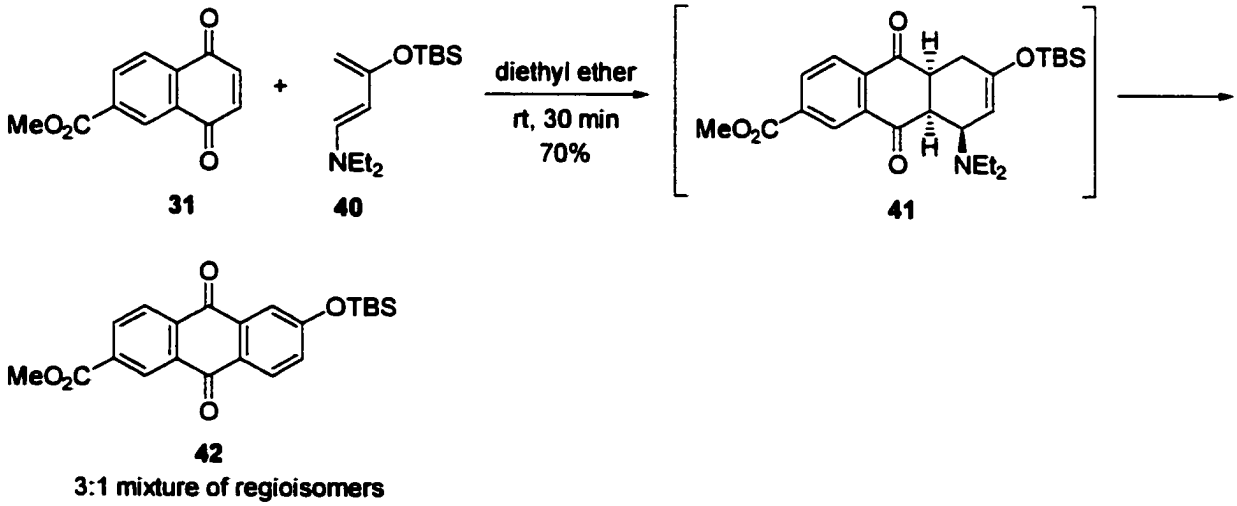
[37] (a) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039; (b) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562; (c) Janey, J. M.; Iwama, T.; Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **2000**, *65*, 9059.

[38] Kozmin, S. A.; He, S.; Rawal, V. H. *Org. Synth.* **2000**, *78*,



Scheme 7: Preparation of 1-diethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene (**40**).

Unfortunately, the Diels-Alder reaction of diene **40** and quinone **31** gave an aromatized product (**42**) as a 3:1 mixture of regioisomers (Scheme 8). It was believed that aromatization (and oxidation) likely occurred during flash chromatography. The acidity of the silica gel was apparently sufficient to promote elimination of the amino group without hydrolysis of the silyl enol ether. Pre-treatment of the silica gel with triethylamine helped prevent aromatization. However, the reaction product, **41**, was difficult to handle and purify. A closer look at Rawal's work revealed that the dienophiles used in cycloadditions with aminosiloxy dienes were substituted to prevent aromatization. 1,4-Quinone adducts synthesized from various 1-heterosubstituted dienes (including Danishefsky's diene) are known to readily aromatize and are difficult to handle (unless at least one of the fusion substituents is a non-hydrogen angular group).[39]

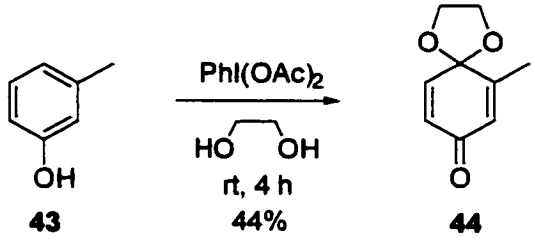


Scheme 8: Diels-Alder reaction of quinone **31** and diene **40**.

[39] Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammil, R. B.; McCurry, P. M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

To overcome the aromatization and regioselectivity problems, it was decided to mask one of the ketones in the quinone as a ketal.[40] There are a number of potential advantages of 1,4-quinone monoketals over the corresponding quinones. The first is that the monoketals would provide adducts that do not undergo facile aromatization. Secondly, higher regioselctivity is possible with masked quinones. As well, monoketals provide adducts in which one of the two carbonyls of the 1,4-quinone is already protected, simplifying the task of further selective transformations. A recent study by Corey's group has shown that achiral 1,4-quinone monoketals work well as dienophiles in enantioselective Diels-Alder reactions catalyzed by a chiral Ti(IV) Lewis acid.[40a]

Ketal **44** was prepared by a literature procedure for the oxidative *p*-ketalization of phenols using the reaction of *m*-cresol (**43**) with iodobenzene diacetate in ethylene glycol (Scheme 9).[41]



43 44% **44**

Scheme 9: Preparation of monoketal **44**.

Various conditions were attempted for the Diels-Alder reaction of methyl coumalate with monoketal **44**, but with little success (Table 2). The ketal was now less reactive than the corresponding 1,4-quinone. Heating at reflux in toluene gave no reaction (entry 1). Heating the reaction at 155 °C neat gave 2% of the desired aromatic adduct and 9% of its regioisomer along with a complex mixture of decomposed material (entry 2). Using a Lewis acid catalyst gave no reaction (entry 3). Performing the reaction in a mixture of lithium perchlorate in ether (5.0 M), a solvent system known to increase reactivity in the Diels-Alder reaction through a high internal pressure and the Lewis acidic nature of the lithium ion,[42] resulted in

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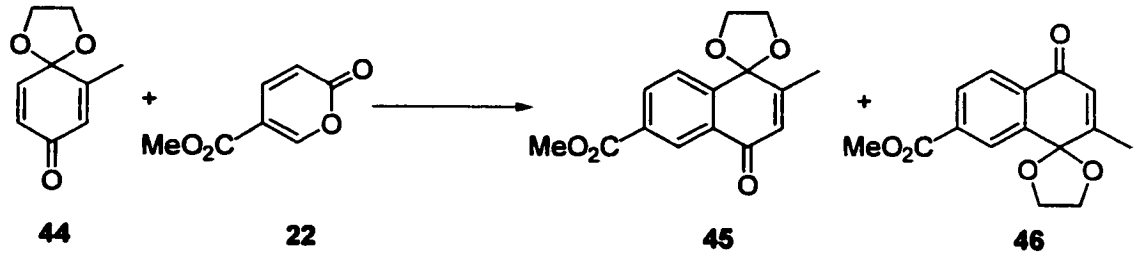
[40] For examples of masked *p*-benzoquinones as dienophiles in the Diels-Alder reaction see: (a) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559; (b) March, P.; Figueredo, M.; Josep, F.; Rodriguez, S. *Tetrahedron*, **2000**, *56*, 3603; (c) Carreno, M. C.; Farina, F.; Galan, A.; Ruano, J. L. G. *J. Chem. Research.* **1979**, 296.

[41] Rose, P. A.; Lei, B.; Shaw, A. C.; Walker-Simmons, M. K.; Napper, S.; Quail, J. W.; Abrams, S. R. *Can. J. Chem.* **1996**, *74*, 1836.

[42] Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4594.

deketalization and produced a mixture of the 1,4-quinone adducts (**28** and **29**) in low yield (entry 4).



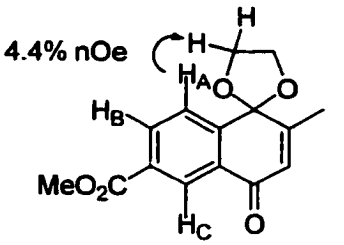
44 **22** **45** **46**

Scheme 10: Diels-Alder reaction of monoketal **44** and methyl coumalate.

Table 2: Conditions for the Diels-Alder reaction of monoketal 44 and methyl coumalate.

Entry	Conditions	Result
1	toluene, reflux, 24 h	No reaction
2	neat, 155 °C, 48 h	2% **45** 9% **46**
3	Et_2AlCl (1.1 eq.), CH_2Cl_2, rt, 24 h	No reaction
4	$LiClO_4$, ether, rt, 24 h	13% (1:1 mixture of **28** and **29**)

The structures of **45** and **46** were elucidated by NMR spectroscopy. The aromatic protons in **45** were assigned based on their splitting patterns and coupling constants. In a nOe difference experiment, irradiation of H_A generated a nOe at the methylene protons, while irradiation of H_C did not (Figure 12).

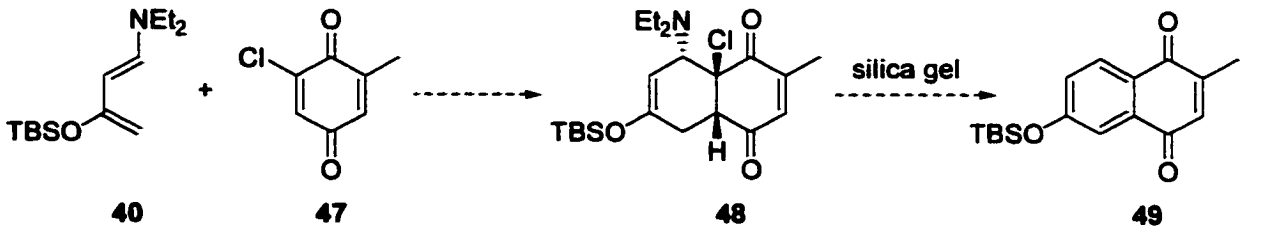


45

Figure 12: nOe observed in **45**.

The main reason for the poor regiocontrol in the Diels-Alder reactions was the electronic compatibility of the 2-pyrone diene with the dienophile. Methyl coumalate has a very electron-withdrawing group in the 5-position making the diene electron deficient. The dienophile counterpart, the quinone or monoketal, is not electronically compatible (i.e. electron rich) which makes prediction of the regiochemical outcome difficult.

A possible solution takes advantage of the facile elimination of the amino group of Rawal's diene that occurs during aromatization of the cycloadduct (Scheme 11). Introduction of a halogen onto the quinone dienophile is an effective way of controlling the regiochemistry in the Diels-Alder reaction.[43] The nucleophilic end of the electron rich Rawal's diene will add to the unsubstituted carbon on the activated side of quinone **47**. Aromatization of the resulting adduct (**48**) should occur readily on exposure to silica gel and air to afford **49**.[43b]



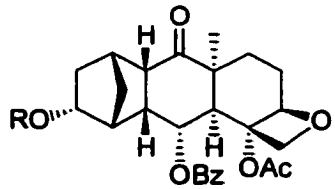
40 **47** **48** **49**

Scheme 11: Potential synthesis of the aromatic system using a haloquinone.

[43] (a) Savard, J.; Brassard, P. *Tetrahedron*, **1984**, *40*, 1984; (b) Boisvert, L.; Brassard, P. *J. Org. Chem.* **1988**, *53*, 4052; (c) Kelly, T. R.; Xu, W.; Ma, Z.; Li, Q.; Bhushan, V. *J. Am. Chem. Soc.* **1993**, *115*, 5843.

2.2 A Norbornane Analogue

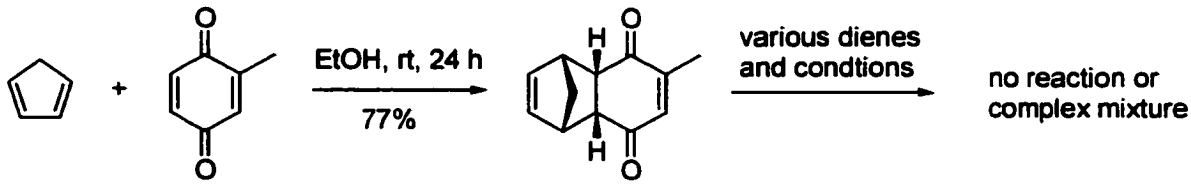
At this point, we decided to abandon the aromatic analogue and concentrate on norbornane analogue **20**.



20

2.2.1 Preliminary Work

Preliminary work on the synthesis of **20** was carried out by Dr. Nancy Lamb.[44] The general strategy is shown in Scheme 3. Unfortunately, the cycloaddition of various dienes with **50** gave either no reaction or a complex mixture of products (Scheme 12). The low reactivity of **50** as a dienophile is known.[45] Furthermore, **50** is susceptible to undergo a retro-Diels-Alder reaction at temperatures above 135 °C.[44]



26 **23** **50**

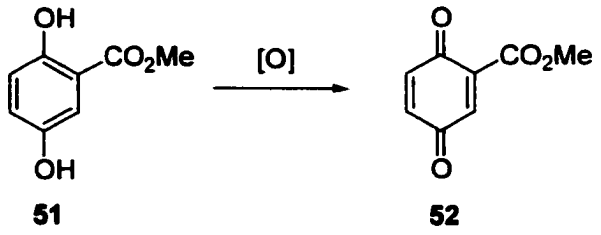
Scheme 12: Preliminary work on the norbornane analogue.

2.2.2 Using an Activated 1,4-Benzoquinone

Since **50** was not very reactive in the Diels-Alder reaction, it was decided to use a more reactive dienophile, one bearing an electron-withdrawing group. 2-Carbomethoxy-1,4-benzoquinone (**52**) is an unstable dienophile, but can be generated *in situ* by oxidation of

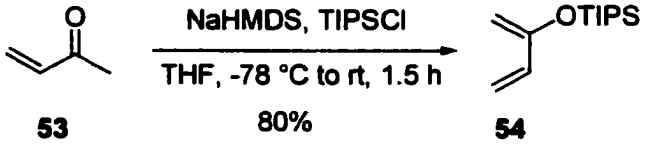
[44] Lamb, N. Progress Report, 2002, University of Ottawa.
[45] Srivastava, S.; Marchand, A. P.; Vidyasagar, V.; Flippen-Anderson, J. L.; Gilardi, R.; George, C.; Zachwieja, Z.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 247.

methyl 2,5-dihydroxybenzoate (**51**) (Scheme 13). The methyl ester could later be converted to an acid, which would hopefully aid with complexation and solubility of the analogue.



Scheme 13: Preparation of 2-carbomethoxy-1,4-benzoquinone (**52**).

2-Triisopropyl-1,3-butadiene (**54**) was chosen as the diene since it would provide oxygen functionality in the correct position on the analogue and since it is a robust diene. Several procedures were used to prepare 2-triisopropyl-1,3-butadiene (**54**) from methyl vinyl ketone (**53**), which included using triethylamine and LDA as bases. The best conditions used sodium hexamethyldisilazide in THF in a procedure similar to that used for the preparation of Rawal's diene (Scheme 14).

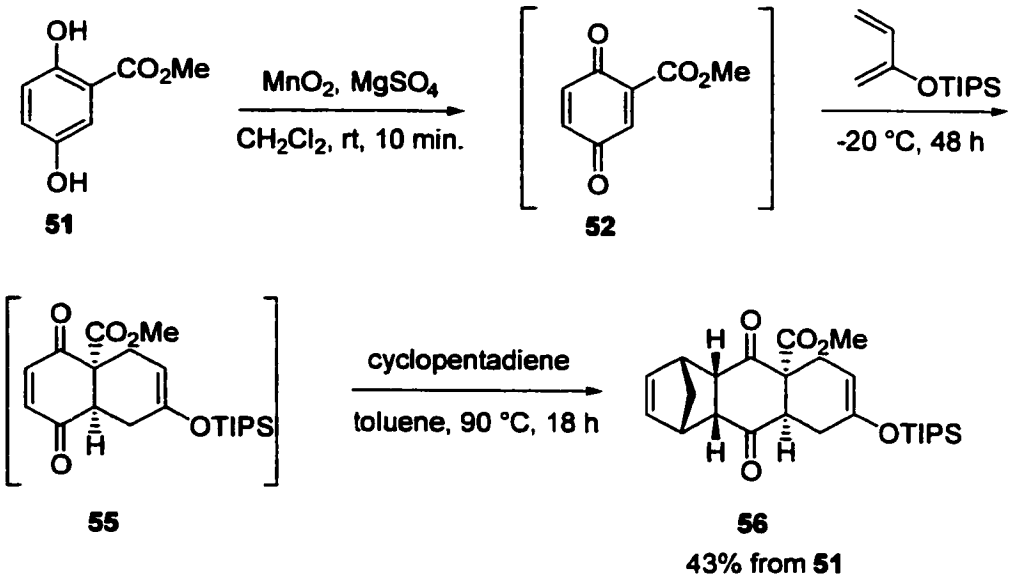


Scheme 14: Synthesis of 2-triisopropyl-1,3-butadiene.

2-Carbomethoxy-1,4-benzoquinone (**52**) was generated *in situ* by oxidation of methyl 2,5-dihydroxybenzoate (**51**) using manganese (IV) dioxide (Scheme 15).[46] The diene, **54**, was then added to the mixture at –78 °C and the reaction was kept in a –20 °C freezer and monitored by TLC until the reaction was complete (ca. 2 days). The low temperature was required, as a mixture of regioisomers formed when the reaction was performed at room temperature. The product, **55**, could be isolated and purified by chromatography. However, after removal of excess manganese dioxide by filtration and concentration of the filtrate, the crude material could be used in the next reaction. Addition of cyclopentadiene gave the

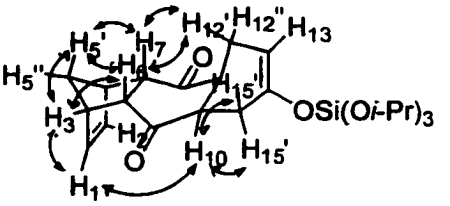
[46] Brimble, M. A.; Elliott, R. J. R. *Tetrahedron*, **1997**, *53*, 7715.

desired tetracyclic core, **56**, in 43% overall yield for the three steps. The reaction was conducted at 90 °C, as at higher temperatures the competing retro Diels-Alder occurred, affording a mixture of product **56** and intermediate **55**.



Scheme 15: Synthesis of the tetracyclic core **56**.

The structure of **56** was elucidated by NMR spectroscopy. A COSY experiment confirmed the regiochemistry of the first cycloaddition: the triisopropylsiloxy group was *para* to the carbomethoxy group as predicted by frontier molecular orbital theory. The cycloaddition of cyclopentadiene with **55** occurred through intermediacy of an *endo* transition state at the less hindered face of the molecule. This was evident from the NOESY spectrum of **56**, which indicated correlations between H_6 and $H_{5'}$, $H_{12'}$, and correlations between H_7 and $H_{5'}$, $H_{12'}$ (Figure 3).



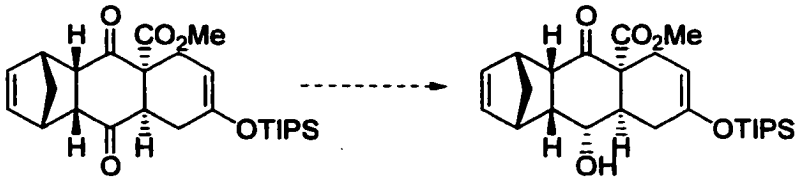
Proton	Correlations
H_1	H_2, H_3, H_{10}
H_3	H_1, $H_{5'}$, H_6
$H_{5'}$	H_3, H_4, $H_{5''}$, H_6, H_7
H_6	H_3, H_5, H_7, $H_{12'}$
H_7	H_4, H_5, H_6, $H_{12'}$
H_{10}	H_1, $H_{15'}$, $H_{15''}$
$H_{12'}$	H_6, H_7, $H_{12''}$, H_{13}

Figure 13: Correlations observed in the NOESY spectrum of **56**.

2.2.3 Reductions of the "northern" ketone and the ester

The next step was to regio- and stereoselectively reduce diketone **56** to alcohol **57** (Scheme 16). No reaction was observed in the Meerwin-Pondorf-Verley reduction using aluminum tri-*tert*-butoxide and *sec*-butanol in benzene.[47] When lithium tri-*tert*-butoxyaluminum hydride was used as the reducing agent, a 4:1 mixture of keto-alcohols was obtained. Recrystallization from ethyl acetate provided the major product as a crystalline solid in 54% yield. It was assumed that the major product was structure **57** based on NMR evidence and the sterics of the reaction. Lithium tri-*tert*-butoxyaluminum hydride is a bulky hydride donor and was expected to reduce the less hindered ketone from the less hindered face of the molecule.

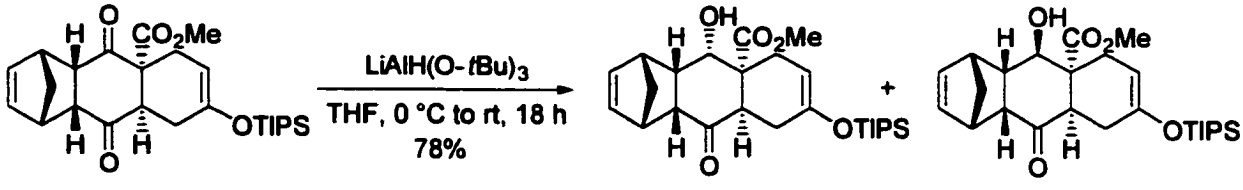
[47] Bach, G.; Capitaine, J.; Engel, C. R. *Can. J. Chem.* **1968**, *46*, 733.



56 57

Scheme 16: Expected reduction product of diketone **56**.

X-ray quality crystals were grown from slow evaporation of ethyl acetate. Crystallographic data revealed that the compound was not the expected product, **57**, but alcohol **58** (Figure 14). Contrary to the initial prediction, the reduction had taken place at the more hindered ketone (Scheme 17). The reducing agent presumably coordinated to the nearby ester and the "northern" ketone, delivering the hydride to the top face of the molecule to give **58** as the major product. The minor product was confirmed by NMR spectroscopy to be epimeric alcohol **59**.



56 58 59

4:1 (58:59)

Scheme 17: Reduction of diketone **56**.

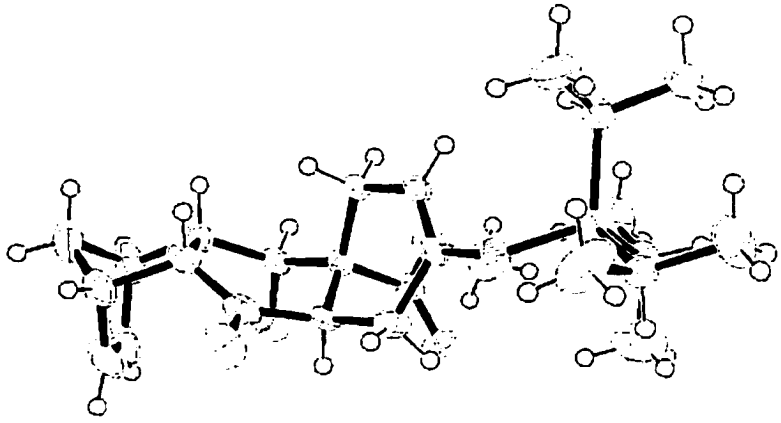
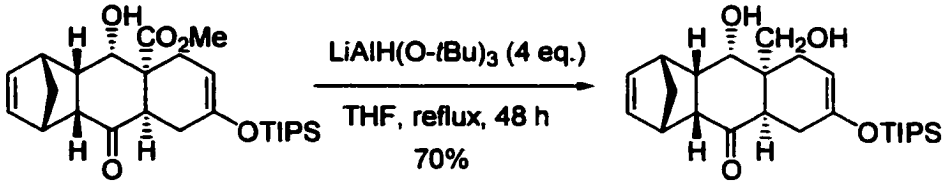


Figure 14: X-ray crystal structure of **58**.[48]

The "southern" ketone in **58** was surprisingly unreactive towards a variety of reducing conditions, including using $NaBH_4$ in various solvents. When an excess of $LiAlH(O\text{-}t\text{Bu})_3$ was used in refluxing THF, the major product was diol **60** (Scheme 18). The ester had unexpectedly been reduced instead of the ketone. However, this product was useful since the diol could be protected as an acetonide prior to the manipulation of other functional groups.



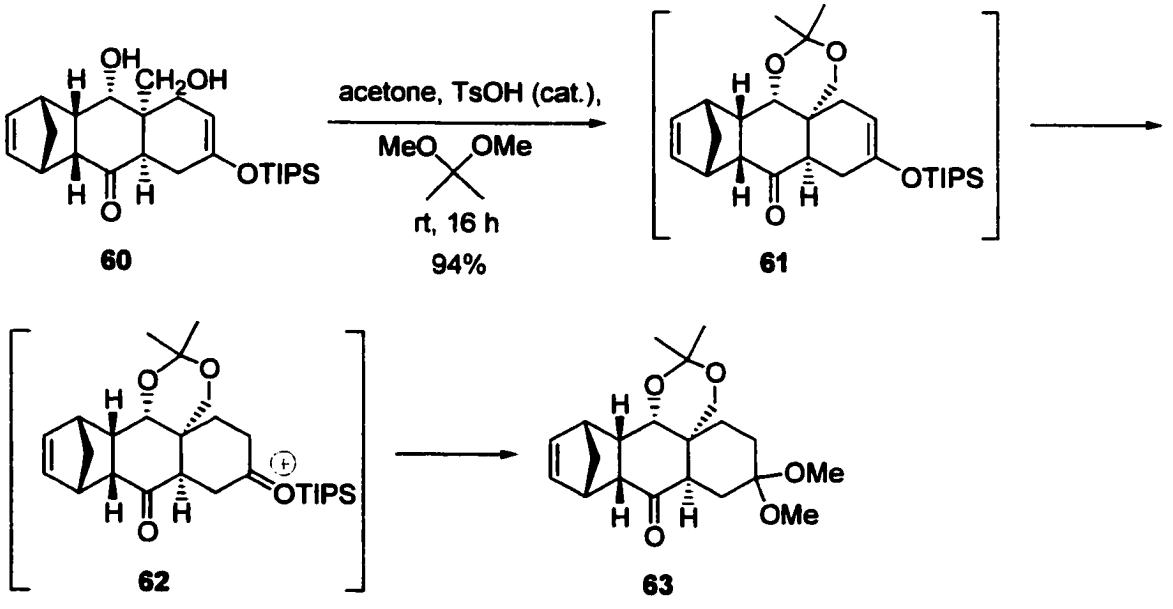
58 **60**

Scheme 18: Reduction of ester **58**.

[48] See Appendix A for X-ray crystallographic data.

2.2.4 Formation of 63 *via* a one-pot diol protection-silyl enol ether hydrolysis-ketone acetylization sequence

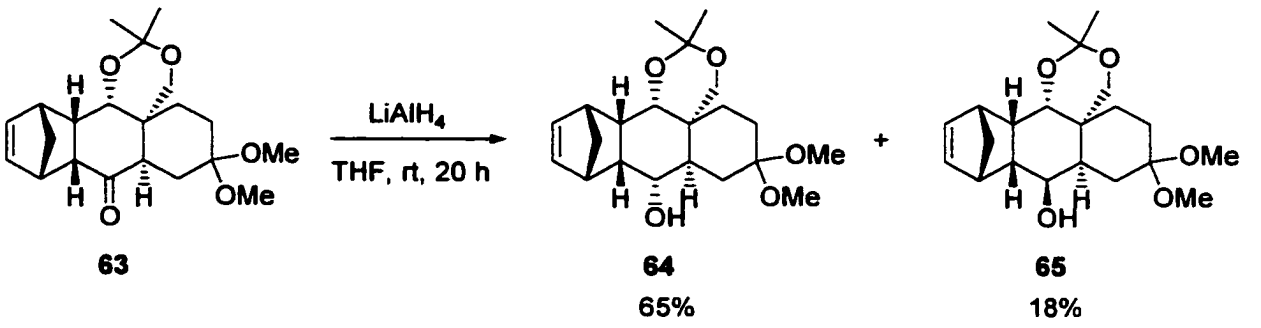
When **60** was treated with acetone, 2,2-dimethoxypropane, and a catalytic amount of *p*-toluenesulfonic acid, not only did the acetonide form, but the silyl enol ether was hydrolysed and the resulting ketone, **62**, reacted with methanol formed in the reaction to give **63** in 94% yield (Scheme 19). This was fantastic as it allowed protection of the diol and the resulting ketone in one step.



Scheme 19: Protection of diol **60**.

2.2.5 Reduction of the "southern" ketone

The "southern" ketone in **63** was ultimately stereoselectively reduced using $LiAlH_4$ (Scheme 20). The reaction gave approximately a 4:1 mixture of diastereomers (**64** and **65**), which were easily separated by chromatography. The major product was the desired alcohol, **64**, obtained in 65% yield. Its structure was elucidated by NMR spectroscopy and later confirmed by X-ray crystallographic analysis (Figure 14).



Scheme 20: Reduction of ketone **63**.

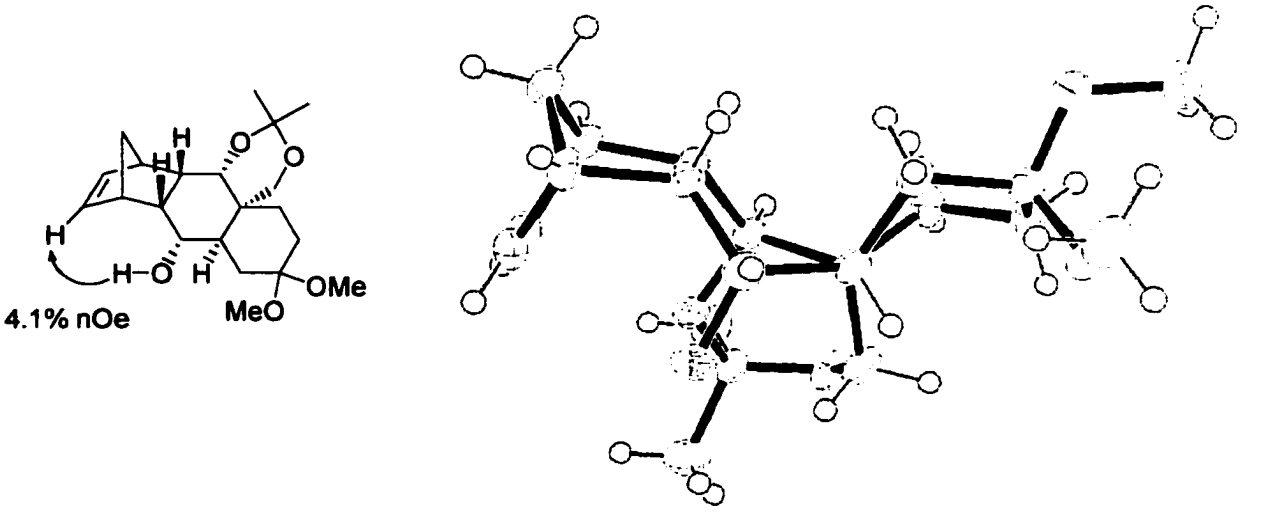
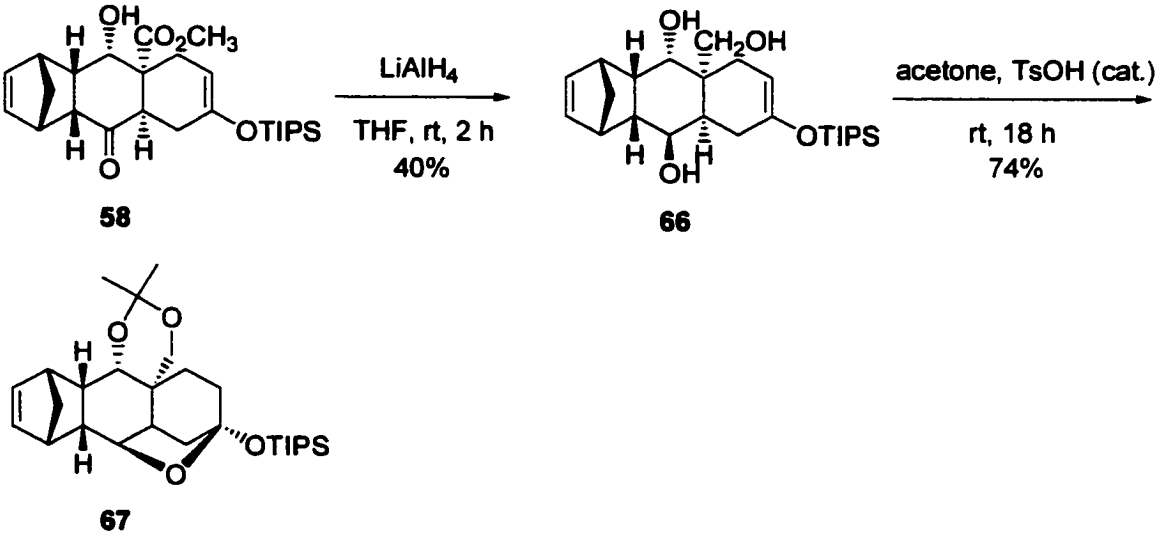


Figure 15: X-ray crystal structure of alcohol **64**.[49]

Reduction of **58** using $LiAlH_4$ was also carried out, since simultaneous reduction of the ester and ketone avoided a second reduction step (Scheme 21).[50] A triol, **66**, was obtained in 40% yield. However, the stereochemistry of the newly formed secondary alcohol was uncertain. When **66** was treated with acetone and *p*-toluenesulfonic acid, the acetonide formed and a cyclization also took place to generate a highly-strained, multicyclic product, **67** (Figure 16). The structure of **67** confirmed that alcohol **66** had the undesired

[49] See Appendix B for X-ray crystallographic data.
[50] This work was done by Dr. N. Lamb.

stereochemistry. The reducing agent presumably coordinated to the "northern" alcohol and delivered the hydride to the bottom face of the molecule.



Scheme 21: Reduction of alcohol **58** using $LiAlH_4$.

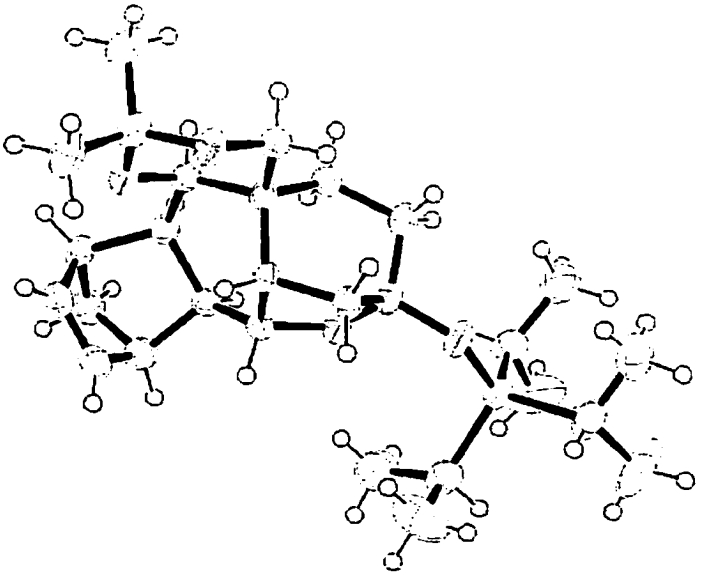


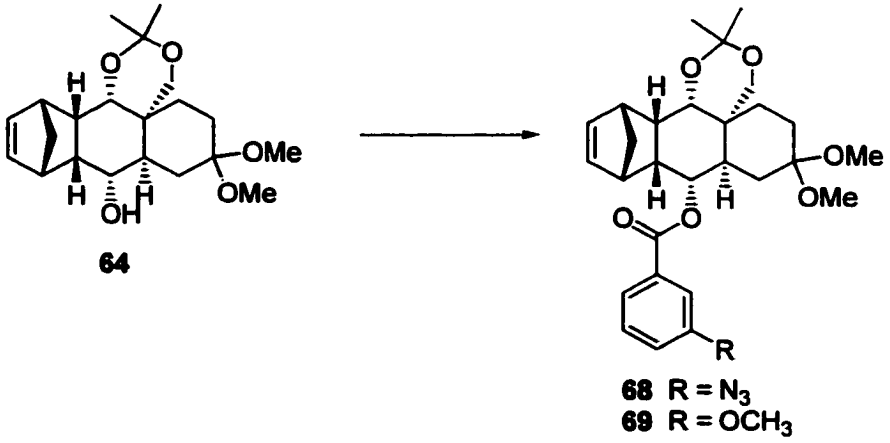
Figure 16: X-ray crystal structure of **67**.[51]

[51] See Appendix C for X-ray crystallographic data.

2.2.6 Introduction of the C2 benzoate

The next step was to introduce the requisite benzoyl group at C2 (Scheme 22). As mentioned in the introduction, some *m*-substituted benzoyl analogues are more cytotoxic than Taxol® and have greater activity in promoting tubulin assembly.[19] In particular, having an azido-substituted benzoate gives a molecule that is an order of magnitude more active than Taxol®. Other *m*-substituents that lead to improved activity are OCH_3, Cl, and CN.

The benzoylation of **64** proved to be more challenging than initially anticipated (Table 3). The first attempt involved treating the alcohol with *m*-azidobenzoic acid, DCC, and DMAP at room temperature (entry 1). No reaction was observed under these conditions. The reaction of **64** with 3-methoxybenzoylchloride, Et_3N, and DMAP also failed (entry 2). Performing the same reaction using NaH as the base to generate higher nucleophilicity gave no results at room temperature or at 60 °C (entry 3). It was obvious from the crystal structure that the alcohol was very sterically hindered; however, it was surprising that the reaction with NaH did not work. Assuming that the solubility of NaH was an issue, *n*-BuLi was chosen as the base in a final attempt (entry 4). Adding *n*-BuLi to the alcohol at –78 °C produced a white cloudy solution not observed when NaH was used. Addition of the acid chloride at 0 °C immediately changed the solution from cloudy to clear. The reaction was complete after 2 h at room temperature and gave high yields of the *m*-azidobenzoyl and *m*-methoxybenzoyl compounds (**68** and **69**).

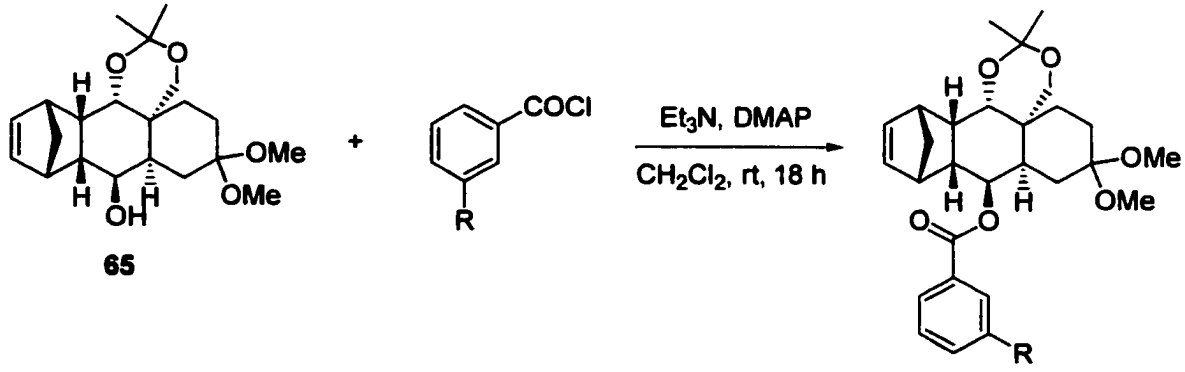


Scheme 22: Benzoylation of alcohol **64**.

Table 3: Conditions for the benzoylation of **64**.

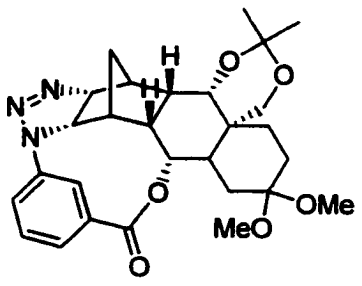
Entry	Conditions	Results
1	*m*-azidobenzoic acid, DCC, DMAP, CH_2Cl_2, rt, 24 h	no reaction
2	*m*-methoxybenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, rt, 24 h	no reaction
3	i. NaH, THF, 0 °C, 1 h ii. *m*-methoxybenzoyl chloride, rt and 60 °C	no reaction
4	i. *n*-BuLi, THF, -78 °C, 30 min. ii. acid chloride, 0 °C to rt, 2 h.	**68** R = N_3, 86% **69** R = OCH_3, 94%

Since it is not known how the molecules will behave at the microtubule binding site, epimeric alcohol, **65**, was also benzoylated (Scheme 23). This reaction proceeded smoothly under milder conditions, as the alcohol is less hindered than in the case of alcohol **64**.



Scheme 23: Benzoylation of **65**.

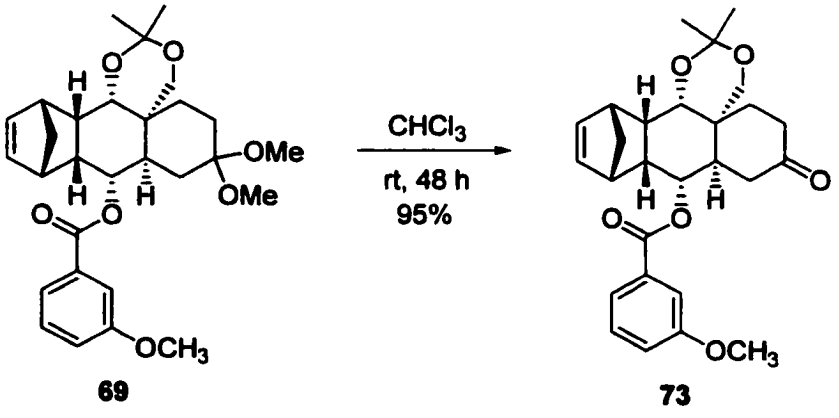
Unfortunately the azido derivatives **68** and **70** decomposed over time. The compounds may have been light sensitive (although attempts were made to protect the compounds from light) or perhaps the azido group underwent an intramolecular 1,3-dipolar cycloaddition with the alkene in the norbornene system to produce an unstable compound (**72**).



72

2.2.7 Selective removal of the dimethoxyketal

Contrary to the azido derivatives, the methoxy derivatives **69** and **71** were quite stable. The next step involved selective deprotection of the ketal. It was found that the dimethylketal was readily hydrolysed in deuterated chloroform, while the acetonide remained intact. When **69** was stirred for 48 h in slightly acidic chloroform, ketone **73** was obtained in 95% yield (Scheme 24).



69 **73**

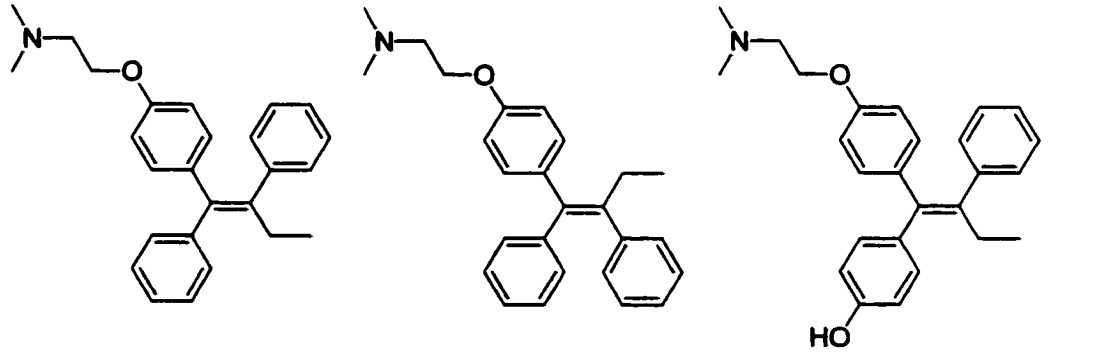
Scheme 24: Deprotection of ketal **69**.

At this point we decided to send a few of the molecules for biological testing. Compounds **69**, **71**, and **73** are being tested for their effects on microtubule assembly and stability *in vitro*. Subsequent modification of the structures will be influenced by the biological results.

3 Introduction - Synthesis of Tamoxifen Mimics *via* a New Carbomagnesiation-Palladium Coupling Reaction

3.1 Tamoxifen As a Selective Estrogen Receptor Modulator

Estrogens are known to play a predominant role in breast cancer development and growth. Antiestrogens work by blocking the interaction of estrogens with their specific receptor and therefore interefere with, or even prevent, the proliferation of cancer cells. Tamoxifen (Nolvadex®, **74**, Figure 17), an antiestrogen first described by Harper and Walpole in 1966,[52] has been used for nearly 20 years for the treatment of estrogen-sensitive breast cancer and has recently been approved by the FDA for chemoprevention of the disease.[53] In addition to blocking the effect of estrogen on breast tissue, tamoxifen acts like a weak estrogen in other body systems. Tamoxifen is thus called a selective estrogen receptor modulator (SERM). SERMs selectively stimulate or inhibit the estrogen receptors of different target tissues. Since tamoxifen mimics the action of estrogen in other tissues, women who take tamoxifen share some of the beneficial effects of taking estrogen replacement therapy, such as a decreased risk of osteoporosis and lower cholesterol levels.



74 tamoxifen **75** (*E*)-tamoxifen **76** (Z)-4-hydroxytamoxifen

Figure 17: Structures of tamoxifen (**74**), (*E*)-tamoxifen (**75**) and (*Z*)-4-hydroxytamoxifen (**76**).

[52] Harper, M. J. K.; Walpole, A. L. *Nature (London)*. **1966**, *212*, 87.
[53] Jordan, V. C. *J. Steroid Biochem. Mol. Biol.* **2000**, *74*, 269.

(*Z*)-4-Hydroxytamoxifen **76** is the active metabolite of tamoxifen having a much higher binding affinity for the estrogen receptor.[54] In contrast to the Z isomer, the E isomer of tamoxifen **75**, usually referred to as *cis*-tamoxifen, has no clinical uses and is not only antiestrogenic, but in rats is a full estrogen agonist.[55]

Several strategies have been used for the synthesis of tamoxifen and 4-hydroxytamoxifen, the majority of which result in the generation of a mixture of geometrical isomers, separable only by fractional crystallization techniques or by HPLC.[56] To date, there have been two stereoselective syntheses of (*Z*)-tamoxifen that employ a carbometallation strategy.[57]

In the first, phenyl(trimethylsilyl)acetylene was carbometallated with diethylaluminum chloride-titanocene dichloride to give an organometallic intermediate which was then quenched with N-bromosuccinimide (Scheme 25).[57a] A phenyl group then replaced the bromine by a palladium-catalyzed coupling with phenylzinc chloride. The trimethylsilyl group was substituted with bromine and the resulting vinyl bromide was coupled with a (*p*-methoxyphenyl)zinc reagent to give the ethyl triaryl olefin, **81**. The methoxyaryl compound was then transformed into (*Z*)-tamoxifen. The overall yield over 6 steps was 30%.

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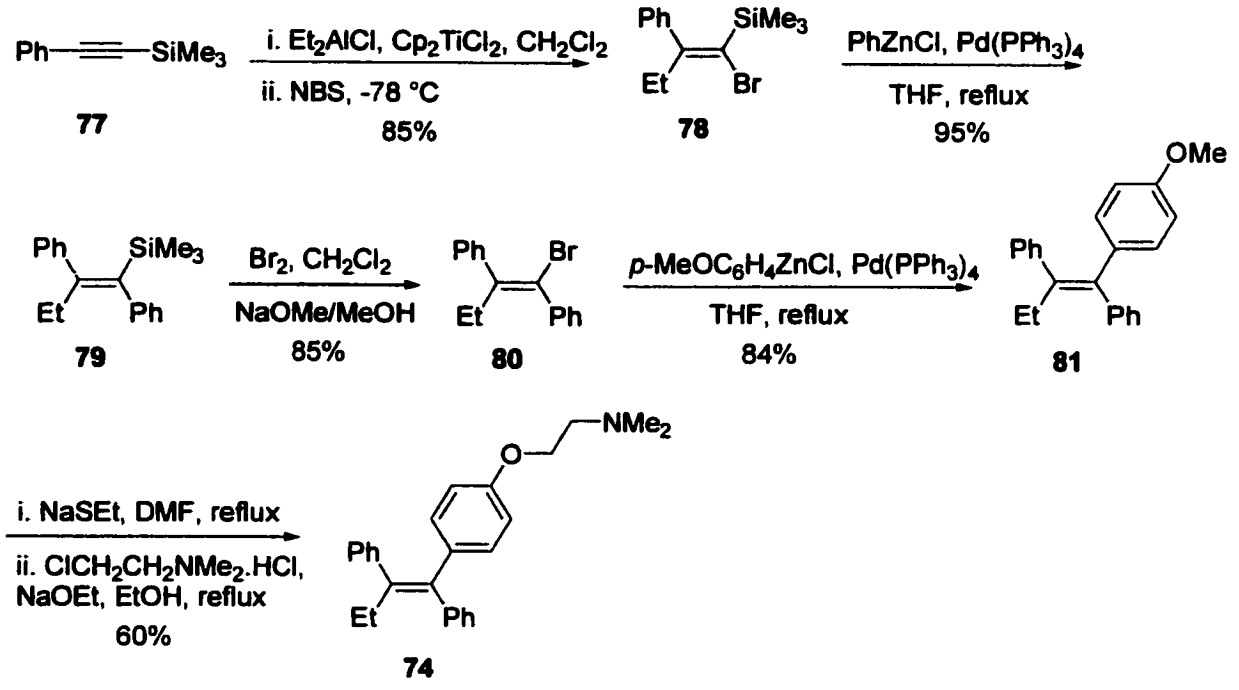
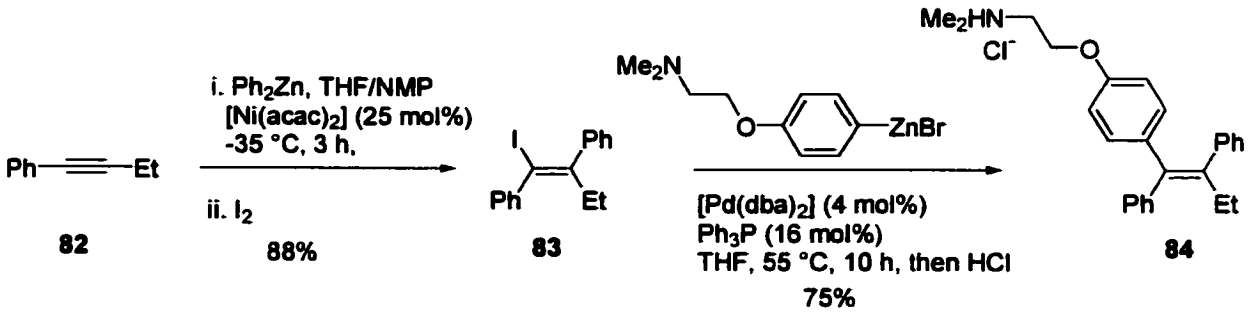
[54] Katznellenbogen, B. S.; Carlson, K. E.; Katzenellenbogen, B. S. *J. Steroid Biochem.* **1985**, *22*, 589.
[55] Jordan, V. C.; Haldeman, B.; Allen, K. E. *Endocrinology* **1981**, *108*, 1353.
[56] (a) McCague, R. *J. Chem. Res., Synop.* **1986**, 58; (b) Potter, G. A.; McCague, R. *J. Org. Chem.* **1990**, *55*, 6184; (c) Olier-Reuchet, C.; Aitken, D. J.; Bucourt, R.; Husson, H. P. *Tetrahedron Lett.* **1995**, *36*, 8221; (d) Gauthier, S.; Mailhot, J.; Labrie, F. *J. Org. Chem.* **1996**, *61*, 3890; (e) Detsi, A.; Koufaki, M.; Calogeropoulou T. *J. Org. Chem.* **2002**, *67*, 4300.
[57] (a) Miller, R. B.; Al-Hassan, R. I.; *J. Org. Chem.* **1985**, *50*, 2121; (b) Knochel, P.; Studemann, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 93.



Scheme 25: Stereospecific synthesis of (Z)-tamoxifen *via* a carbometallation of alkynylsilanes.

The second synthesis involved a nickel-catalyzed carbozincation of alkynes (Scheme 26).[57b] This *syn* selective method afforded (Z)-tamoxifen hydrochloride in two steps. The addition of diphenylzinc to 1-phenyl-1-butyne (**82**) followed by an iodine quench gave the pure (Z)-alkene **83** in 88% yield. A subsequent palladium-catalyzed cross coupling with the arylzinc bromide afforded (*Z*)-tamoxifen hydrochloride in 75% yield (66% over two steps).



Scheme 26: Synthesis of (*Z*)-tamoxifen hydrochloride using a nickel-catalyzed carbozincation of alkynes.

A number of tamoxifen analogues and other SERMs have been synthesized (Figure 18).[58] Most of the SERMs to date share a number of structural features. A key requirement for activity consists of two aryl groups separated by two atoms (often a stilbene type arrangement). Additionally, compounds typically bear a third phenyl group containing a 4-aminoethoxy substituted phenyl moiety. It is believed that the molecules function by binding to the receptor through their stilbene-like cores and projecting the third phenyl group that contains the 4-aminoethoxy group into a region of space that corresponds to the 11 position of an estratriene nucleus (*i.e.* estrone or estradiol).[59]

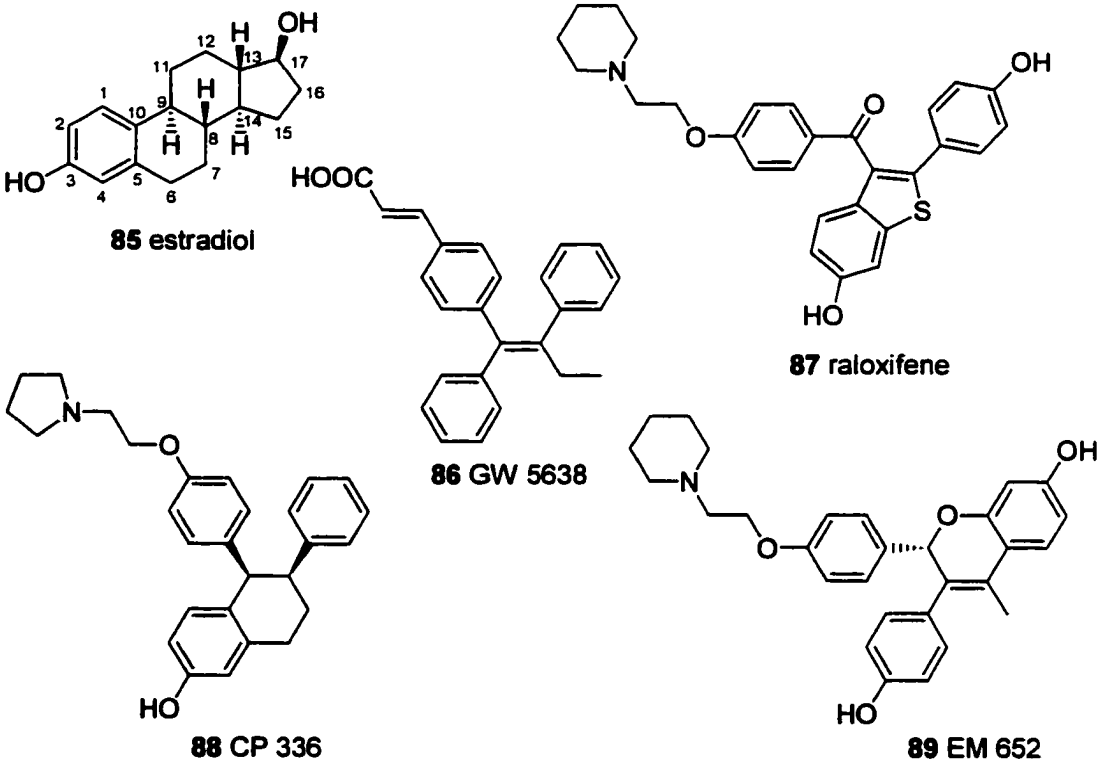


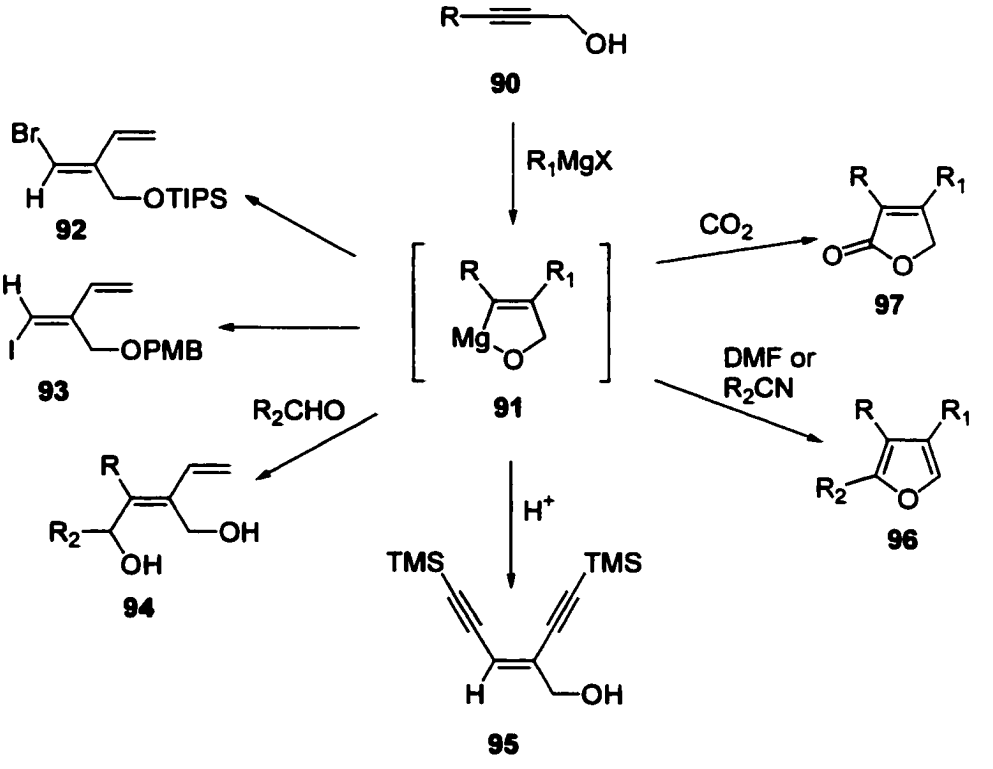
Figure 18: Structures of estradiol and novel SERMs.

[58] (a) Foster, A. B.; Jarman, M.; Leung, O. T.; McCague, R.; Leclercq, G.; Devleeschouwer, N. *J. Med.Chem.* **1985**, *28*, 1491; (b) McCague, R.; Leclercq, G.; Jordan, V. C. *J. Med. Chem.* **1988**, *31*, 1285; (c) Gauthier, S.; Caron, B.; Clouthier, J.; Dory, Y. L.; Favre, A.; Larouche, D.; Mailhot, J.; Oeullet, C.; Schwerdtfeger, A.; Leblanc, G.; Martel, C.; Simard, J.; Merand, Y.; Belanger, A.; Labrie, C.; Labrie F. *J. Med. Chem.* **1997**, *40*, 2117; (d) Davies, H. M. L.; Nagashima, T.; Klino, J. L. *Org. Lett.* **2000**, *2*, 823; (e) Miller, C. P.; Collini, M. D.; Tran, B. D.; Harris, H. A.; Kharode, Y. P.; Marzolf, J. T.; Moran, R. A.; Henderson, R. A.; Bender, R. H. W.; Unwalla, R. J.; Greenberger, L. M.; Yardley, J. P.; Abou-Gharbia, M. A.; Lyttle, C. R.; Komm, B. S. *J. Med. Chem.* **2001**, *44*, 1654.

[59] Bouhoute, A.; Leclercq, G. *Biochem. Pharmacol.* **1994**, *47*, 748.

3.2 Magnesium-Mediated Carbometallation of Propargyl Alcohols

Our lab has developed several procedures for the magnesium-mediated carbometallation of propargyl alcohols (Scheme 27).[60] The reaction is believed to proceed *via* the magnesium chelate intermediate **91** (or a closely related species). The intermediate can then react with a variety of electrophiles providing access to a number of unsaturated systems that can be used for a variety of synthetic applications. The reaction has been used to prepare stereodefined halodienes (**92**, **93**), dihydroxydienes (**94**), enediyne alcohols (**95**), substituted furans (**96**), and furanones (**97**). Further applications of the products include synthesis of the Taxol® AB ring system and tether-controlled intramolecular Diels-Alder reactions.

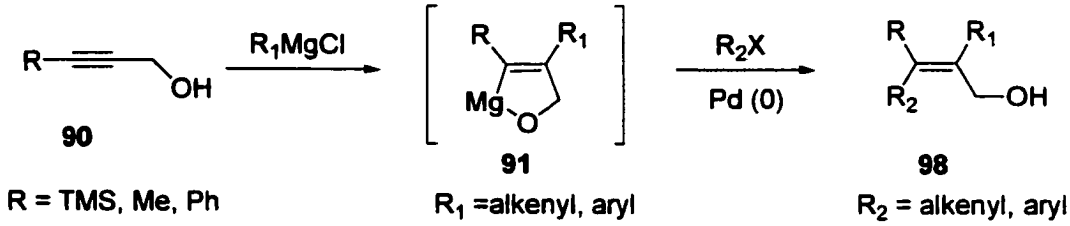


Scheme 27: Magnesium-mediated carbometallation of propargyl alcohols.

[60] (a) Wong, T.; Tjepkema, M. W.; Audrain, H.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.* **1996**, *37*, 755; (b) Forgione, P.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 11; (c) Forgione, P.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 17.

3.3 Research Objectives

To further investigate the carbomagnesiation reaction and to expand the number of targets that can be synthesized by this route, we wanted to know if the magnesium chelate intermediate **91** could directly undergo a palladium-catalyzed cross coupling reaction. It was anticipated that an aryl or alkenylpalladium halide complex would transmetallate with the magnesium chelate intermediate providing a number of additional useful unsaturated compounds (Scheme 28).



90

R = TMS, Me, Ph

91

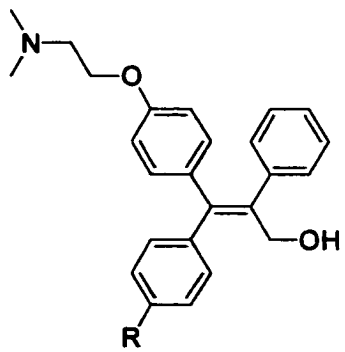
R_1 =alkenyl, aryl

98

R_2 = alkenyl, aryl

Scheme 28: Sequential carbomagnesation/palladium coupling reaction.

One potential use of this method is the synthesis of new analogues of the antiestrogen tamoxifen. Carbometallation of a phenylpropargyl alcohol with a phenyl Grignard reagent followed by a palladium-catalyzed cross coupling with an aryl iodide should provide a facile and stereoselective route to new analogues. These would differ from other known compounds, as they will have a methyl alcohol instead of an ethyl group (Figure 19).



R = H (**99**), R = OCH_3 (**100**), R = OH (**101**)

Figure 19: Structures of new tamoxifen analogues (**99-101**).

3.3.1 Carbometallation Chemistry

Reactions which result in the addition of the carbon-metal bond of an organometallic across a carbon-carbon multiple bond, giving a new organometallic in which the newly formed carbon-metal bond can be used for further synthetic transformations (such as protonation, nucleophilic attack, or transmetallation) are called carbometallation reactions.[61] A number of regioselective and stereoselective additions of organometallics to alkynes have been reported and reviewed.[62] Reactions of alkynes containing an allylic or homoallylic heteroatom are the most widely reported. In general, oxygen is the most useful heteroatom, usually as a free alcohol.

Organomagnesium compounds have been a versatile reagent in carbon-carbon bond forming reactions. Although Grignard reagents do not add easily to non-functionalised triple bonds, the reactions are feasible with transition metal catalysis or with functionalised triple bonds.[63] In the past, Grignard reagents other than allylic Grignards did not add easily to alkynols. However, in the presence of 10% copper (I) iodide most Grignard reagents, with the exception of vinyl Grignards, now undergo addition under mild conditions.[64]

A few examples of additions of vinyl magnesium reagents to propargyl alcohols are known and generally the yields are low.[65] In contrast to earlier reports, our lab has found that metal salts are not required with vinyl Grignards and in most cases yields are improved by conducting the reaction in a refluxing mixture of cyclohexane and THF (3:2).

The addition of organomagnesium compounds to alkynols is a regiocontrolled *anti*-carbometallation. A close analogy is the *anti*-hydroalumination of propargyl alcohols with $LiAlH_4$ or Red-Al, which are considered to involve intermediates like **103** (Figure 20).[66]

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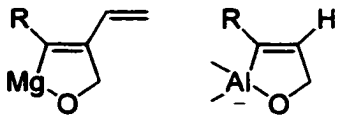
[61] Negishi, E.; Van Horn, D. *J. Am. Chem. Soc.* **1978**, *100*, 2252.
[62] For reviews see: (a) Normant, J. F.; Alexakis, A. *Synthesis.* **1981**, 841; (b) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333; (c) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 38; (d) Knochel, P. in Comprehensive Organometallic Chemistry II; Able, E. W.; Stone, F. G. A.; Wilkinson, G. Eds.; Pergamon Press: Oxford, 1995; Vol. 11, p. 159; (e) Knochel, P. in Comprehensive Organic Synthesis; Trost, B. M.; Fleming, I.; Eds.; Pergamon Press: Oxford, 1991; Vol. 4. p. 865-911; (f) Negishi, E.; Konkakov, D. Y. *Chem. Rev.* **1996**, *96*, 417; (g) Marek, I. *J. Chem. Soc., Perkin Trans. I.* **1999**, 535.
[63] (a) Richey, H. G.; Rothman, A. M. *Tetrahedron Lett.* **1968**, 1457; (b) Hill, E. A. *J. Organomet. Chem.* **1975**, 123; (c) Crandall, J. K.; Battioni, P.; Wehlacz, J. T.; Bindra, R. *J. Am. Chem. Soc.* **1975**, *97*, 7171.
[64] Jousseaume, B.; Duboudin, J. G. *J. Organomet. Chem.* **1975**, 1; (b) Jousseaume, B.; Duboudin, J. G. *J. Organomet. Chem.* **1979**, 1.
[65] Von Rein, F. W.; Richey, H. G. *Tetrahedron Lett.* **1971**, 3777.
[66] Marshall, J. A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 863.

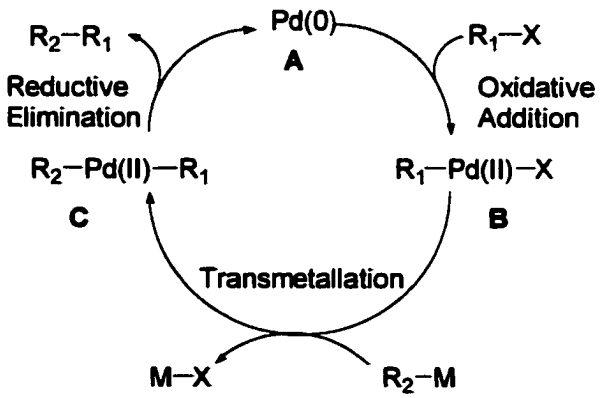


102 **103**

Figure 20: Intermediates in carbomagnesation and hydroalumination reactions of propargyl alcohols.

3.3.2 Palladium-Catalyzed Cross Coupling Reactions

In 1972, Kumada's and Corriu's groups independently reported the cross-coupling reaction of Grignard reagents with aryl and alkenyl halides using nickel complexes as catalysts.[67] The catalytic cycle, which involves oxidative addition, transmetallation, and reductive elimination steps has become a prototype for the more practical palladium – catalyzed cross coupling reaction (Scheme 26). The reactions proceed smoothly with a variety of organometallic reagents containing B, Mg, Li, Sn, Al, and Zn as the metal. Typically, aryl, alkenyl, and alkyl halides and pseudohalides (such as triflates) are used for coupling with aryl, alkenyl, alkynyl, and alkylmetal compounds.[68] The reactivity of the organohalides is in the following order: I > triflate > Br >>> Cl.



Scheme 29: Basic catalytic cycle for palladium-catalyzed cross coupling reactions.

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[67] (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374; (b) Corriu, R. J. P.; Masse, J. P. *Chem. Commun.* **1972**, 144.

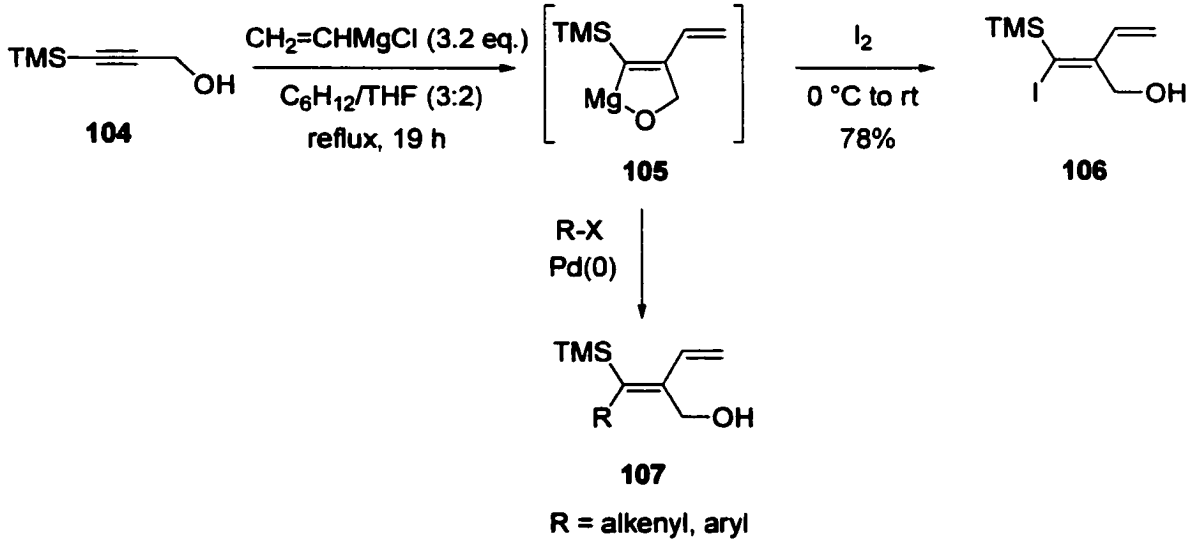
[68] Tsuji, J. *Transition Metal Reagents and Catalysts. Innovations in Organic Synthesis;* John Wiley & Sons, Ltd: New York, 2000; p 56.

Since organomagnesium compounds are known to undergo palladium-catalyzed cross coupling reactions with aryl and alkenyl halides, it seemed likely that transmetallation of the organopalladium complex **B** with magnesium chelate intermediate **91** would occur readily. Reductive elimination of **C** would then yield the coupling product **98** and regenerate the palladium (0) species.

4 Results and Discussion – Tamoxifen Mimics

4.1 Initial Studies

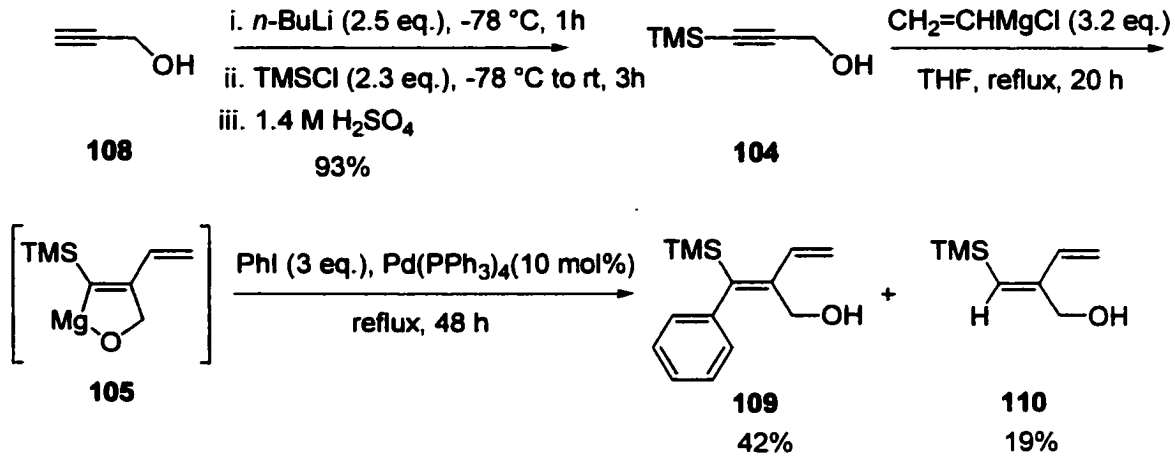
The addition of vinyl magnesium chloride to trimethylsilyl propargyl alcohol (**104**) followed by condensation with elecrophiles has been used to prepare synthetically useful dienes (e.g. **106**) in our lab (Scheme 30). It was anticipated that the magnesium chelate **105** could undergo a palladium-catalyzed cross coupling reaction with aryl and alkenyl halides to afford additional useful dienes (**107**).



Scheme 30: Preparation of useful dienes using magnesium-mediated carbometallation of an alkynol.

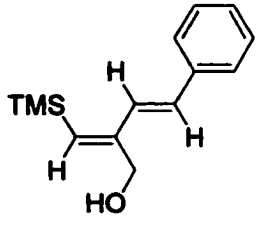
Previous occupants of our lab had examined this coupling reaction without success. Using better conditions, the reaction was successful on the first attempt. Trimethylsilyl propargyl alcohol **104** was initially prepared in high yield from propargyl alcohol (Scheme 31). Addition of vinyl magnesium chloride afforded intermediate **105**, which was reacted with iodobenzene in the presence of 10 mol% tetrakistriphenylphosphine palladium. The reaction was heated at reflux for 48 h affording the target molecule **109** in 42% yield and the proton-quench product **110** in 19% yield. The reaction was difficult to monitor by TLC as **109** and **110** had similar R_f values. Attempts were made to drive the reaction to completion (longer

reaction times and increased amount of catalyst) but with little improvement. As well, reagents and glassware were thoroughly dried prior to use and reactions were performed under an inert atmosphere of nitrogen.



Scheme 31: Synthesis of diene **109** *via* a new carbomagnesiation-palladium coupling reaction.

A possible side product (**111**) could have formed if the monosubstituted alkenyl group had inserted into the arylpalladium iodide complex (Heck reaction). Fortunately, this product was not observed. The transmetallation reaction apparently occurs faster than the insertion reaction.



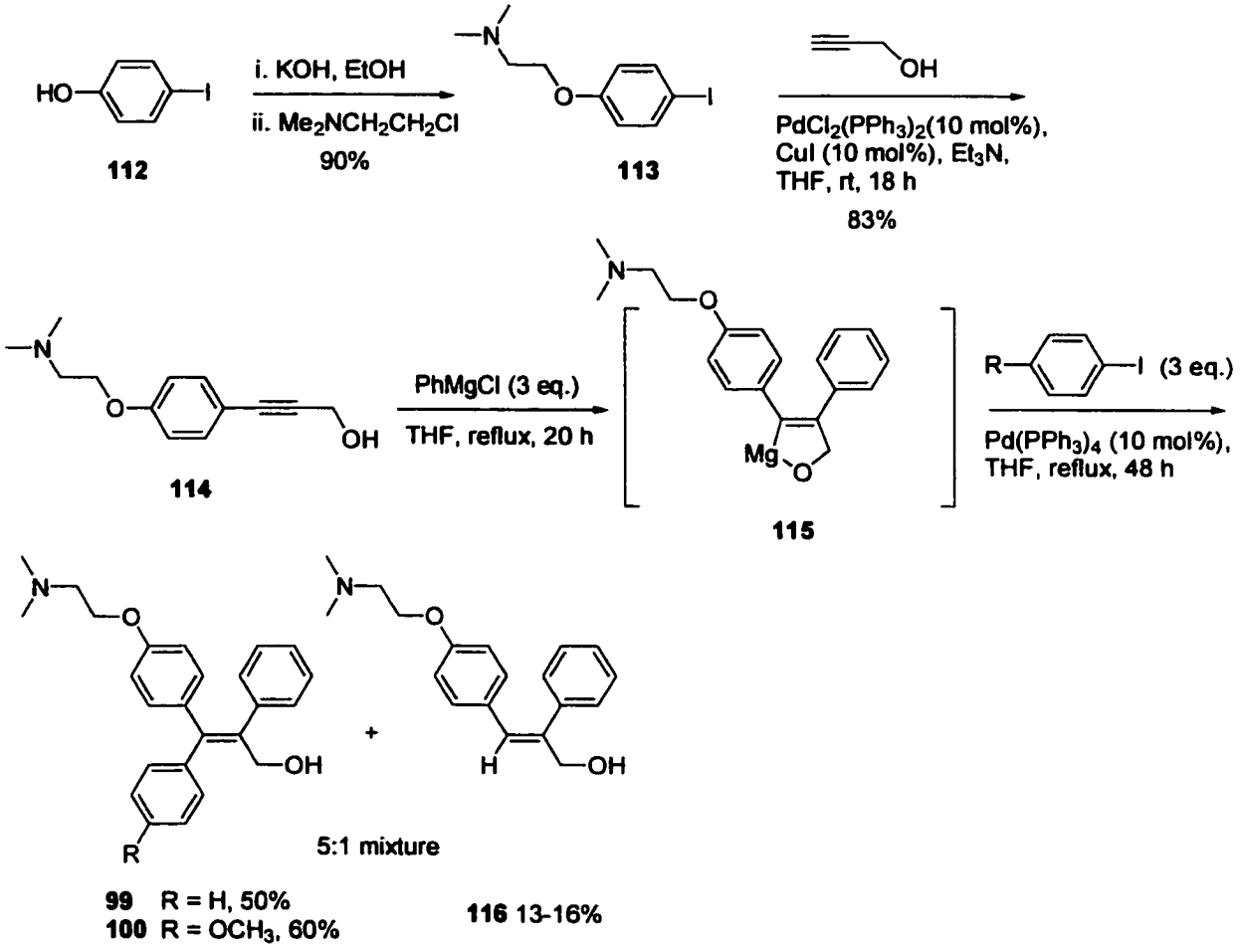
111

4.2 Synthesis of Tamoxifen Analogues

Keeping in line with our interest in the synthesis of cancer chemotherapeutic agents, this new multi-component coupling reaction was applied in a three-step stereoselective synthesis of tamoxifen analogues.

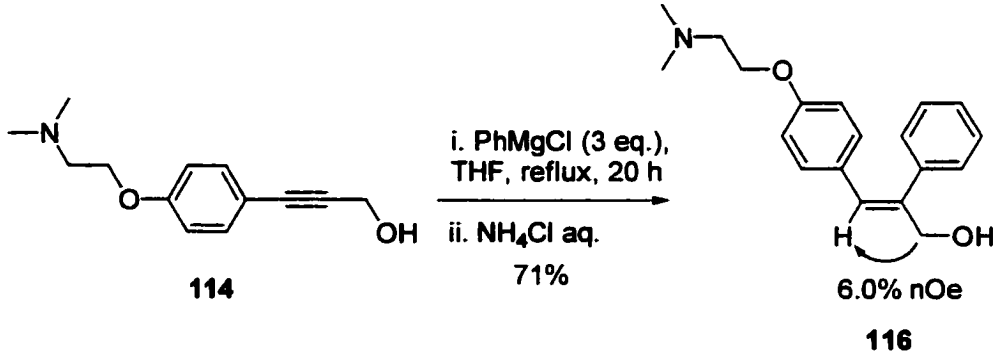
In the first step, 4-iodophenol (**112**) was deprotonated and alkylated with dimethylaminoethyl chloride according to a literature procedure (Scheme 28).[69] A Sonogashira coupling reaction of aryl iodide **113** with propargyl alcohol afforded alkynol **114** in 83% yield. Addition of phenylmagnesium chloride gave the magnesium chelate intermediate **115**, which then underwent the palladium-catalyzed cross coupling reaction with iodobenzene to produce the desired analogue, **99**, in 50% yield and the proton-quench product, **116**, in 13% yield. An analogous reaction using 4-iodoanisole gave the methoxy analogue, **100**, in 60% yield and **116** in 16% yield. Again the reactions were difficult to monitor by TLC as the intermediate and the products had similar R_f values. Unfortunately, purification of the products by chromatography and HPLC has been unsuccessful.

[69] Hunter, D. H.; Ponce, Y. Z. *Can. J. Chem.* **1984**, *62*, 2015.



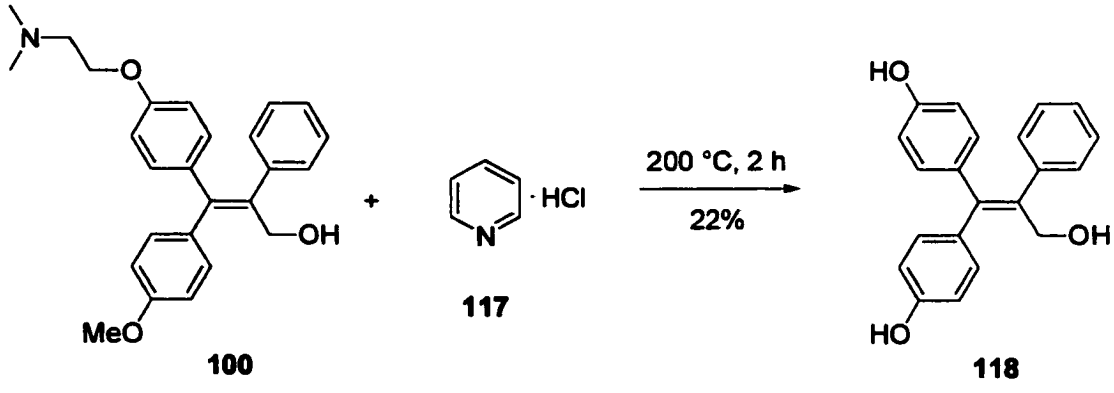
Scheme 32: Synthesis of tamoxifen analogues *via* a carbomagnesiation-palladium coupling reaction.

To properly characterize **116**, chelate **115** was quenched with a proton source to give the product in 71% yield (Scheme 33). In an nOe difference experiment, irradiation of the methylene protons generated a nOe at the alkenyl proton, confirming that the addition of phenylmagnesium chloride was a regiocontrolled *anti*-carbometallation.



Scheme 33: Synthesis of intermediate **116**.

Attempts were made to cleave the aryl methyl ether in **100** to prepare hydroxy analogue **101**, which would hopefully be separable from the proton-quench product, **116**. Pyridine hydrochloride has been reported to cleave the methyl ether of a tamoxifen analogue while leaving the dimethylaminoethyl group intact.[58b] However, when this reaction was performed on **100**, both the methyl ether and the *N,N*-dimethylaminoethyl ether were cleaved (Scheme 34).



Scheme 34: Cleavage of the methyl ether and the dimethylaminoethyl ether functionalities in **100**.

5 Conclusions

Studies toward the synthesis of novel taxoid analogues **19** and **20** were described. It was anticipated that the multicylcic core of the analogues could be synthesized using a shorter route than in previous studies. By employing two sequential intermolecular Diels-Alder reactions to form the ABC ring system and attaching functionalities useful for activity, we would hopefully generate facile access to new analogues.

Due to problems with regioselectivity and aromatization in the synthesis of **19**, we decided to focus on norbornane analogue **20**. An efficient route to the tetracyclic skeleton, **56**, was developed, which involved three sequential reactions (an oxidation and two cycloadditions). The "northern" ketone and the methyl ester were then reduced using $LiAlH(O\text{-}t\text{Bu})_3$ to give diol **60**. A one-pot diol protection-silyl enol ether hydrolysis-ketone acetylization sequence afforded acetonide **63**. The "southern" ketone was then reduced stereoselectively using $LiAlH_4$ affording alcohol **64** as the major product.

The biologically important *m*-substituted benzoyl group was next introduced. *Meta*-methoxybenzoyl and *m*–azidobenzoyl derivatives of alcohols **64** and **65** (the minor product from the $LiAlH_4$ reduction) were synthesized in high yield. Unfortunately, the azido derivatives slowly decomposed. The ketal in *m*-methoxybenzoate **69** was then removed to allow future attachment of the oxetane ring. At this point, several of the compounds were sent for biological testing. Further elaboration of the analogues will be influenced by the biological results.

A new carbomagnesiation-palladium coupling reaction of propargyl alcohols was investigated for the regio- and stereocontrolled synthesis of tetrasubstituted olefins. Treatment of propargyl alcohol **104** with vinyl magnesium chloride generated chelate **105**, which then underwent a palladium-catalyzed cross coupling reaction with iodobenzene to afford diene **109**. The reaction was applied in a stereoselective, three-step synthesis of new analogues of the antiestrogen tamoxifen.

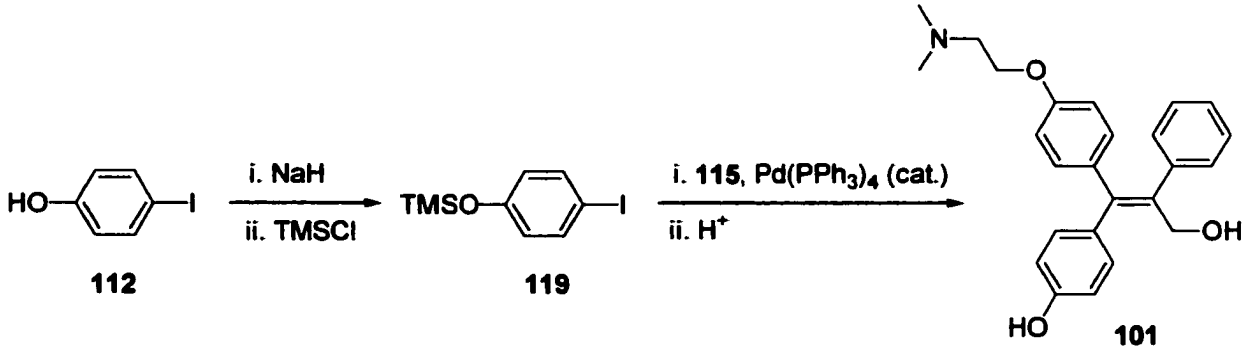
5.1 Future Work – Taxoid Mimics

Ideally, the synthetic taxane mimics should contain the C4 acetate, the oxetane ring, and Taxol® side chain, in addition to the C2 benzoate. Due to difficulties in functionalising **73**, future work may involve the synthesis of a similar molecule that would either contain or allow easier installation of these groups.

5.2 Future Work – Tamoxifen Mimics

Future work involves optimizing the reaction conditions of the carbomagnesiation-palladium coupling reaction to avoid mixtures of the desired products and the proton-quench products. Possible solutions to drive the reaction to completion include using a higher boiling solvent, using a more reactive catalyst, or adding a co-catalyst such as a zinc salt. To extend the versatility of the carbomagnesiation-palladium coupling reaction, the coupling of alkenyl halides with the magnesium chelate intermediate could be investigated.

To avoid the troublesome cleavage of the methyl ether in tamoxifen analogue **100**, 4-iodophenoxytrimethylsilane (**119**) could be used in the coupling reaction with magnesium chelate **115** (Scheme 35). The silyl group would be removed from the coupling product upon work-up to provide **101**.



112 119 101

Scheme 35: Proposed synthesis of hydroxy analogue **101**.

6 Experimental

General Experimental

All non-aqueous reactions were performed under a positive pressure of dry nitrogen in flame-dried glassware using dry solvents. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone. Dichloromethane, toluene, triethylamine and methyl vinyl ketone were distilled from calcium hydride. Standard inert atmosphere techniques were employed in handling air and moisture sensitive reagents. All starting material was purchased from Aldrich Chemical Company and used without further purification unless otherwise stated.

Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel sheets coated with silica gel 60 F_{254} (E. Merck). TLC spots were visualized under ultraviolet light and developed by heating the plate after treatment with a 5% solution of ammonium molybdate in 10% aqueous sulphuric acid. Room temperature corresponds to 21 °C. Anhydrous magnesium sulfate ($MgSO_4$) was used to dry solutions in organic solvents. Excess solvents were removed *in vacuo* at pressures obtained by a water or air aspirator connected to a Büchi rotary evaporator. Trace solvents were removed on a vacuum pump. Product purification by flash chromatography was performed with E. Merck Silica Gel 60 (230-400 mesh). Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30-60 °C.

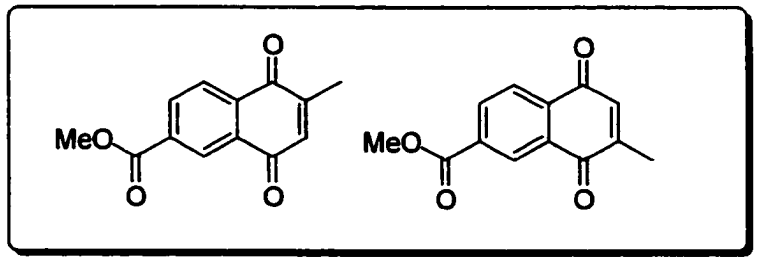
Melting points were determined with a Thomas-Hoover Unit melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained as neat thin films or as a solution of the sample in $CDCl_3$ or $CHCl_3$ in a sodium chloride solution cell. All IR spectra were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR).

^1H NMR (300 or 500 MHz) and C^{13} NMR (75 or 125 MHz) were run on a Bruker AMX300 spectrometer or Brucker AMX500 spectrometer. Chemical shifts are reported downfield from tetramethylsilane (δ scale) in ppm. ^1H NMR data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet), coupling constants (Hz), and integration. Low resolution mass spectroscopy (MS), using either electron impact (EI) or chemical ionization (CI), was performed on a V.G. Micromass 7070 HS mass

spectrometer with an electron beam energy of 70 eV (for EI). High resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam energy of 70 eV.

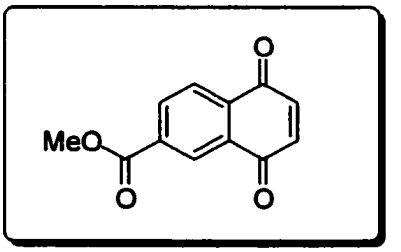
Compounds were named using ACD/I-Lab Web service (ACD/IUPAC Name 6.04).

Methyl 5- and 6-methyl-5,8-dioxo-5,8-dihydronaphthalene-2-carboxylate (28 and 29)



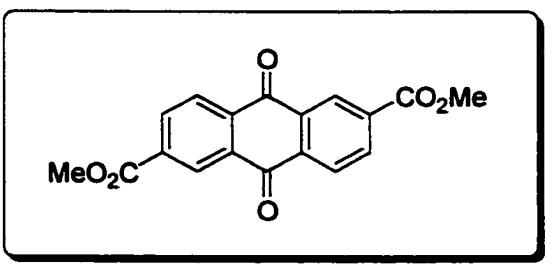
Methyl coumalate (7.68 g, 49.8 mmol) was added to a solution of methyl-1,4-benzoquinone (6.15 g, 50.4 mmol) in toluene (200 mL). The reaction was stirred at reflux for 72 h. The solution was concentrated and purified by flash chromatography (ethyl acetate/hexanes 1:4) to give a 4:3 mixture of regioisomers **28** and **29** as a yellow solid (4.24 g, 37%). mp 109-127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) first isomer: δ 8.67 (d, J = 1.6 Hz, 1H), 8.31 (dd, J = 8.0, 1.7 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 6.85 (q, J = 1.6 Hz, 1H), 3.95 (s, 3H), 2.19 (d, J = 1.5 Hz, 3H); second isomer: δ 8.63 (d, J = 1.7 Hz, 1H), 8.31 (dd, J = 8.0, 1.7 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 6.87 (q, J = 1.6 Hz, 1H), 3.94 (s, 3H), 2.18 (d, J = 1.5 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 184.8, 184.5, 184.1, 183.9, 165.4, 165.3, 148.7, 148.4, 135.9, 135.7, 134.72, 134.70, 134.67, 134.6, 134.5, 134.1, 134.0, 132.2, 132.1, 127.8, 127.4, 126.7, 126.3, 52.6, 16.44, 16.37; IR ($CHCl_3$) ν = 3022, 1727, 1669, 1626, 1607, 1522, 1478, 1427, 1263, 1213, 1017, 928 cm^{-1}; MS (EI) *m/z* (relative intensity) 230 (M^+, 100), 199 (75), 171 (61), 143 (32), 115 (75), 103 (37), 75 (63); HRMS (EI) *m/z* calcd for $C_{13}H_{10}O_4$ (M^+) 230.05791, found 230.05875.

Methyl 5,8-dioxo-5,8-dihydronaphthatlene-2-carboxylate (31)



Methyl coumalate (4.44 g, 28.8 mmol) was added to a solution of 1,4-benzoquinone (4.60 g, 42.6 mmol) in toluene (100 mL). The reaction was heated at reflux and stirred for 72 h. The reaction was concentrated and purification by flash chromatography (ethyl acetate/hexanes 1:4) afforded of the title compound as a yellow solid (1.75 g, 28%). mp 96-97 °C (lit. mp 94-95 °C)[70]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, J = 1.6 Hz, 1H), 8.40 (dd, J = 8.1, 1.7 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 1.9 Hz, 2H), 3.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 184.3, 165.5, 139.2, 138.9, 135.2, 134.6, 132.1, 129.0, 127.9, 126.9, 53.0; IR ($CHCl_3$) ν = 3029, 2953, 1728, 1673, 1607, 1439, 1313, 1256, 1150 cm^{-1}; MS (EI) *m/z* (relative intensity) 216 (M^+, 68), 185 (100), 162 (6), 143 (3), 129 (9), 101 (11), 75 (13); HRMS (EI) *m/z* calcd for $C_{12}H_8O_4$ (M^+) 216.04226, found 216.04182. ^{1}H NMR spectrum of this sample was in good agreement with that reported for this compound.[70]

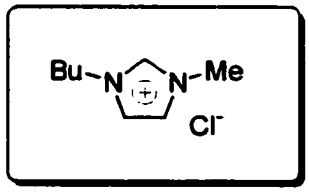
Dimethyl 9,10-dioxo-9,10-dihydroanthracene-2,6-dicarboxylate (32)



[70] Gust, D.; Moore, T. A.; Moore, A. L.; Seely, G.; Liddell, P.; Barrett, D.; Harding, L. O.; Ma, X. C.; Lee, S. -J.; Gao, F. *Tetrahedron.* **1989**, *45*, 4867.

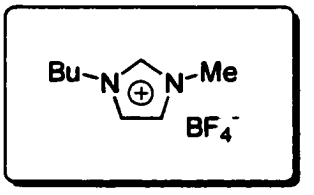
mp 183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (d, J = 1.3 Hz, 2H), 8.40 (m, 4H), 4.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.4, 181.8, 165.7, 136.2, 135.8, 135.2, 133.8, 129.2, 128.1, 53.2; IR ($CHCl_3$) ν = 3021, 2400, 1727, 1680, 1522, 1477, 1425, 1213, 928 cm^{-1}; MS (EI) *m/z* (relative intensity) 324 (38), 293 (100), 279 (3), 265 (15), 237 (4), 209 (8), 178 (4), 150 (8), 131 (12), 117 (4), 98 (2), 75 (6); HRMS (EI) *m/z* calcd for $C_{18}H_{12}O_6$ (M^+) 324.06339, found 324.06294.

1-Butyl-3-methylimidazolium chloride (34)



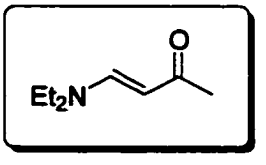
The compound was prepared according to the procedure described in Ref. 36. A mixture of 1-methylimidazole (30.0 mL, 0.376 mol) and 1-chlorobutane (50.0 mL, 0.610 mol) was stirred at 75-85 °C for 24 h. After the reaction time, the mixture became biphasic with a clear and colourless top layer and a yellow viscous bottom layer. The upper layer was decanted and the bottom layer was washed with ethyl acetate (3 × 50 mL). The remaining ethyl acetate was removed by drying on a vacuum line overnight. The product was obtained as a white solid (60.0 g, 92%). ^{1}H NMR (300 MHz, acetone-d_6) δ 10.77 (s, 1H), 8.07 (s, 1H), 7.98 (s, 1H), 4.46 (t, J = 7.2 Hz, 2H), 4.10 (s, 3H), 1.90 (m, 2H), 1.34 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 138.7, 123.9, 122.7, 49.2, 35.9, 30.1, 19.5, 13.3. ^{1}H NMR and ^{13}C NMR spectra of this sample were in good agreement with that reported for this compound.[36]

1-Butyl-3-methylimidazolium tetrafluoroborate (35)



The compound was prepared according to the procedure described in Ref. 36. 1-Butyl-3-methylimidazolium chloride (12.7 g, 0.0728 mmol) was dissolved in water (100 mL) and 48% aqueous tetrafluoroboric acid (9.2 mL, 0.0728 mmol) was added dropwise *via* a dropping funnel over 15 min. The reaction was stirred for an additional 12 h at rt and was then extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was washed with water (20 mL aliquots) until the aqueous washes were no longer acidic. The ionic liquid was dried on a vacuum line overnight at 80 °C to afford a pale yellow liquid (15.1 g, 95%) that was used without further purification. ^{1}H NMR (300 MHz, acetone-d_6) δ 9.04 (s, 1H), 7.71 (s, 1H), 7.66 (s, 1H), 4.31 (t, J = 7.2 Hz, 2H), 4.00 (s, 3H), 1.88 (m, 2H), 1.35 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 137.0, 124.2, 122.8, 49.6, 36.0, 30.2, 19.4, 13.2. ^{1}H NMR and ^{13}C NMR spectra of this sample were in good agreement with that reported for this compound.[36]

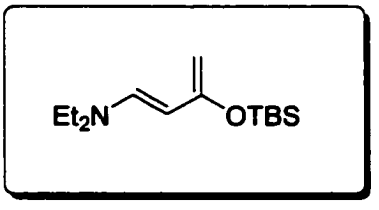
4-Diethylamino-3-buten-2-one (40)



The compound was prepared according to the procedure described in Ref. 38. A solution of diethylamine (20.0 mL, 0.192 mol) in methanol (95 mL) was added to a flask containing freshly distilled acetylacetaldehyde dimethylacetal (bp 73-75 °C, 15 mm Hg). The resulting yellow solution was stirred at rt for 4 h and then concentrated. Purification by vacuum

distillation (bp 121-122 °C, 1 mm Hg) afforded the desired product as a yellow oil (23.02 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) 7.41 (d, J = 13.0 Hz, 1H), 5.04 (d, J = 12.8 Hz, 1H), 3.16 (q, J = 6.8 Hz, 4H), 2.03 (s, 3H), 1.11 (t, 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 195.1, 150.6, 96.0, 50.2, 42.4, 28.4, 14.6, 11.3; HRMS (EI) *m/z* calcd for $C_8H_{15}NO$ (M^+) 141.11536, found 141.11590. ^{1}H and ^{13}C NMR spectra of this sample were in good agreement with those reported for this compound.[38]

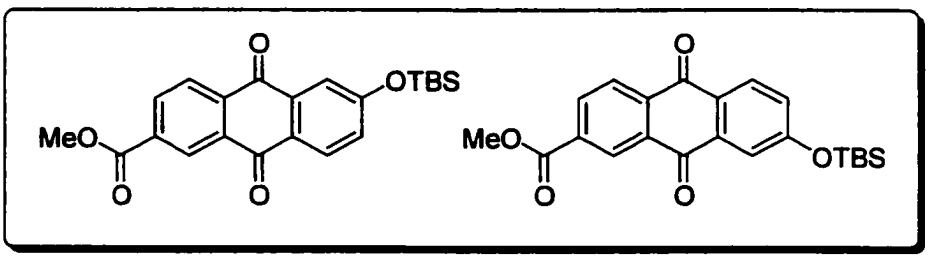
1-Diethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene (40)



The compound was prepared according to the procedure described in Ref. 38. A dry, 500 mL 3-necked round bottom flask was equipped with a pressure equalizing dropping funnel, a large egg-shaped magnetic stirring bar and a nitrogen/vacuum adapter. The apparatus was evacuated and flushed with nitrogen (3×). The flask was charged with potassium hexamethyldisilazide (100.0 mL, 0.0500 mol, 0.5 M in toluene) and was cooled to –78 °C, causing a viscous, yellow-white suspension to form. A solution of 4-diethylamino-3-buten-2-one in dry THF (25 mL) was added to the suspension *via* a dropping funnel over 20 min. The clear orange solution was stirred for 2 h at –78 °C. A solution of *tert*-butyldimethylchlorosilane (8.10 g, 0.0537 mol) in THF (25 mL) was added over 5 min. *via* a dropping funnel. The cooling bath was removed and the reaction was allowed to reach rt. The reaction was stirred for 1.5 h. The reaction mixture was poured into a 500 mL Erlenmeyer flask containing 400 mL of dry diethyl ether. The suspension was allowed to stand for 30 min. and then suction filtered through a pad of flame-dried Celite (30 g) packed in a 350 mL sintered glass filter funnel having a C-porous frit. The filtrate was concentrated. The resulting dark orange oil, containing the diene and hexamethyldisilazane, was subjected to vacuum distillation (bp 110-111 °C, 1 mm Hg) to afford the diene as an orange oil (10.56

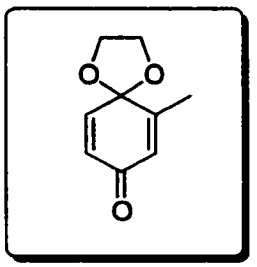
g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (d, J = 13.4 Hz, 1H), 4.77 (d, J = 13.4 Hz, 1H), 3.85 (s, 1H), 3.77 (s, 1H), 3.03 (q, J = 7.3 Hz, 4H), 1.07 (t, J = 7.1 Hz, 6H), 0.96 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 138.7, 94.1, 85.1, 45.7, 26.3, 18.3, 13.5, -4.2; HRMS (EI) *m/z* calcd for $C_{14}H_{29}NOSi$ (M^+) 255.20184, found 255.20122. ^{1}H and ^{13}C NMR spectra of this sample were in good agreement with those reported for this compound.[38]

Methyl 6- and 7-(*tert*-butyldimethylsiloxy)-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate (42a and b)



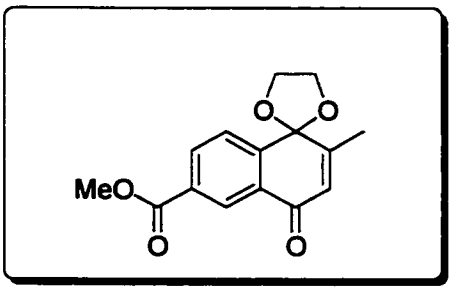
1-Diethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene (92 mg, 0.36 mmol) was added to a solution of **32** (81 mg, 0.37 mmol) in dry diethyl ether (3.5 mL). The reaction was stirred at rt for 30 min. and then concentrated. Purification by flash chromatography (ethyl acetate/hexanes 1:4) yielded a 3:1 mixture of regioisomers **42a** and **42b** as a yellow oil (99 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) first isomer: δ 8.89 (d, J = 1.6 Hz, 1H), 8.39 (dd, J = 8.0, 1.7 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 2.6 Hz, 1H), 7.20 (dd, J = 8.5, 2.6 Hz, 1H), 3.99 (s, 3H), 1.00 (s, 9H), 0.99 (s, 6H); second isomer: δ 8.90 (d, J = 1.6 Hz, 1H), 8.38 (dd, J = 7.9, 1.7 Hz, 1H), 8.33 (d, J = 8.1 Hz, 1H), 8.24 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 2.6 Hz, 1H), 7.22 (dd, J = 8.5, 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 182.6, 182.3, 181.5, 181.3, 165.5, 161.6, 161.5, 136.3, 136.2, 135.5, 135.4, 135.1, 134.7, 134.5, 134.1, 133.7, 133.6, 130.1, 130.0, 128.5, 128.4, 127.5, 127.4, 127.3, 126.2, 126.1, 117.6, 117.5, 52.7, 25.5, 18.2, -4.4; IR ($CHCl_3$) ν = 3019, 2400, 1727, 1676, 1592, 1476, 1425, 1291, 929 cm^{-1}; MS (EI) *m/z* (relative intensity) 396 (M^+, 5), 339 (100), 312 (3), 280 (7), 209 (2), 182 (34), 105 (12), 73 (7); HRMS (EI) *m/z* calcd for $C_{22}H_{24}O_5Si$ (M^+) 396.13930, found 396.13950.

6-Methyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (44)



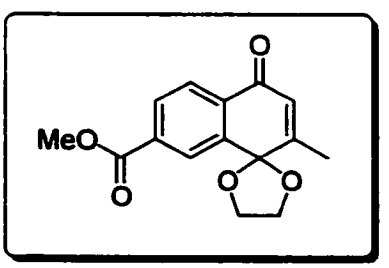
The compound was prepared according to the procedure described in Ref. 41. A suspension of iodobenzene diacetate (6.41 g, 19.9 mmol) in hexane (40 mL) was cooled to 0 °C. A solution of *m*-cresol (1.03 g, 9.56 mmol) in anhydrous ethylene glycol (7.00 mL, 126 mmol) was added to the suspension over 15 min. *via* a dropping funnel. The cooling bath was removed and the mixture was stirred for 4 h at rt. The reaction was quenched with water (75 mL). The two phases were separated and the aqueous phase was extracted with diethyl ether (3 × 75 mL). The organic extracts were combined and washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried, filtered, and concentrated. Purification of the orange residue by flash chromatography (ethyl acetate/hexanes 5:95) afforded the product as an orange oil (0.70 g, 44%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.60 (d, J = 10.1 Hz, 1H), 6.04 (dd, J = 10.1, 2.2 Hz, 1H), 5.99 (dd, J = 2.2, 1.5 Hz, 1H), 4.14 (s, 4H), 1.90 (d, J = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.4, 155.1, 134.0, 128.0, 127.5, 99.6, 66.3, 16.7; HRMS (EI) *m/z* calcd for $C_9H_{10}O_3$ (M^+) 166.06300, found 166.06366. ^1H and ^{13}C NMR spectra of this sample were in good agreement with those reported for this compound.[41]

Methyl 2'-methyl-4'oxo-4'H-spiro[1,3-dioxolane-2,1'-naphthalene]-6'-carboxylate (45)



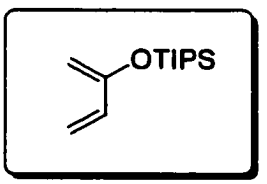
A mixture of methyl coumalate (0.419 g, 2.72 mmol) and 2-methyl-4,4-ethylenedioxycyclohexa-2,5-dienone (0.300 g, 1.81 mmol) was heated to 150 °C and stirred for 72 h. The reaction was cooled to rt and purification by flash chromatography (triethylamine/ethyl acetate/hexanes 5/20/75) afforded the title compound **45** as a white solid (11 mg, 2%) and regioisomer **46** as a white solid (44 mg, 9%). Title compound: mp 128-130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 1.8 Hz, 1H), 8.21 (dd, J = 8.2, 1.9 Hz, 1H), 7.57 (dd, J = 8.2, 0.3 Hz, 1H), 6.27 (d, J = 1.4 Hz, 1H), 4.39-4.46 (m, 2H), 4.30-4.35 (m, 2H), 3.92 (s, 3H), 2.07 (d, J = 1.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9, 166.0, 157.1, 146.9, 133.3, 130.9, 130.6, 128.8, 127.7, 125.9, 102.2, 67.1, 52.4, 29.7, 17.6; IR ($CHCl_3$) ν = 3020, 2400, 1724, 1675, 1476, 1424, 1269, 1098, 929 cm^{-1}; MS (EI) *m/z* (relative intensity) 274 (M^+, 89), 259 (39), 246 (91), 231 (20), 215 (40), 190 (100), 171 (79), 115 (38), 103 (28), 89 (8), 77 (13); HRMS (EI) *m/z* calcd for $C_{15}H_{14}O_5$ (M^+) 274.08413, found 274.08327.

Methyl 2'-methyl-4'-oxo-4'H-spiro[1,3-dioxolane-2,1'-naphthalene]-7'-carboxylate (46)



mp 146-148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 8.14 (s, 1H), 8.07 (s, 2H), 6.26 (d, J = 1.2 Hz, 1H), 4.44-4.50 (m, 2H), 4.28-4.34 (m, 2H), 3.93 (s, 3H), 2.08 (d, J = 1.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.1, 166.1, 157.8, 143.1, 133.7, 133.3, 129.7, 128.7, 127.2, 126.5, 102.2, 67.1, 52.5, 17.7; IR ($CHCl_3$) ν = 3020, 1724, 1672, 1653, 1477, 1438, 1287, 1178, 1075, 928 cm^{-1}; MS (EI) *m/z* (relative intensity) 274 (M^+, 40), 259 (29), 246 (78), 231 (12), 206 (76), 190 (100), 171 (51), 143 (23), 127 (33), 115 (48), 103 (31), 89 (10), 77 (12); HRMS (EI) *m/z* calcd for $C_{15}H_{14}O_5$ (M^+) 274.08413, found 274.08400.

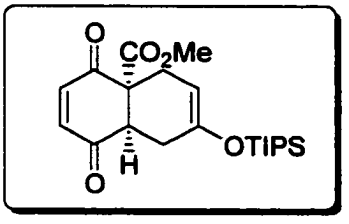
1-Triisopropylsiloxy-1,3-butadiene (54)



The procedure for the preparation of **54** was adapted from Ref. 38. A dry, 500 mL 3-necked round bottom flask was equipped with a pressure equalizing dropping funnel, a stirring bar and a nitrogen/vacuum adapter. The apparatus was evacuated and flushed with nitrogen (3×). The flask was charged with sodium hexamethyldisilazide (50.0 mL, 0.0500 mol, 1.0 M in THF) and the flask was cooled to –78 °C, causing a viscous, orange suspension to form. A solution of distilled methyl vinyl ketone (bp 81 °C) (4.00 mL, 0.0480 mol) in THF (25 mL) was added to the suspension *via* a dropping funnel over 30 min. The clear orange solution was stirred for 1 h at –78 °C. A solution of triisopropylsilyl chloride (12.00 mL, 0.0580 mol) in THF (25 mL) was added over 5 min. *via* a dropping funnel. The reaction was allowed to reach rt and stirred for 1.5 h. The reaction mixture was poured into a 500 mL Erlenmeyer flask containing 200 mL of dry diethyl ether. The suspension was allowed to stand for 30 min. and then suction filtered through a pad of Celite in a sintered glass filter funnel. The filtrate was concentrated. The resulting dark orange oil was subjected to fractional distillation (65-69 °C, 1 mm Hg) to yield the diene as a colourless oil (8.75 g, 80%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.17 (dd, J = 16.9, 10.5 Hz, 1H), 5.53 (dd, J = 16.9, 1.9 Hz, 1H),

5.07 (dd, J = 10.5, 1.9 Hz, 1H), 4.32 (s, 1H), 4.26 (s, 1H), 1.19-1.26 (m, 3H), 1.10 (s, 18H); ^{13}C NMR (125 MHz, C_6D_6) δ 155.4, 134.9, 114.3, 95.0, 18.0, 12.8; HRMS (EI) *m/z* calcd for $C_{13}H_{26}OSi$ (M^+) 226.17529, found 226.17499. ^{1}H NMR spectrum of this sample was in good agreement with that reported for this compound.[71]

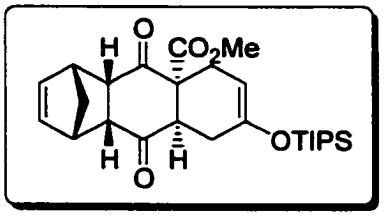
Methyl (4a*R, 8a*R**)-1,4-dioxo-7-[(triisopropylsilyl)oxy]-1,5,8,8a-tetrahydro-naphthalene-4a(4H)-carboxylate (55)**



Manganese dioxide (<5 micron activated) (9.912 g, 112.9 mmol) and anhydrous magnesium sulfate (2 g) were added to a solution of methyl-2,5-dihydroxybenzoate (1.489 g, 8.855 mmol) in dry CH_2Cl_2 (50 mL). The solution was stirred for 10 min. at rt and then cooled to –78 °C. 1-Triisopropylsilyloxy-1,3-butadiene was added and the reaction was stirred at –78 °C for 1 h. The flask was then placed in a –20 °C freezer. The reaction was complete after 2 days at –20 °C as indicated by TLC. The mixture was filtered through a pad of silica gel and the orange filtrate was concentrated. The crude product could be used for the next reaction. Purification by flash chromatography (1:3 ether/petroleum ether) afforded the title compound as an orange oil (0.179 g, 51%). ^{1}H NMR (500 MHz, C_6D_6) δ 5.99 (d, J = 10.4 Hz, 1H), 5.92 (d, J = 10.3 Hz, 1H), 4.76 (m, 1H), 3.52 (ddd, J = 6.6, 4.5, 1.2 Hz, 1H), 3.29 (s, 3H), 2.74 (m, 1H), 2.59 (m, 1H), 2.42 (ddd, J = 16.9, 5.1, 2.9 Hz, 1H), 2.22 (m, 1H), 1.07 (s, 21H); ^{13}C NMR (500 MHz, C_6D_6) δ 196.2 195.8, 170.4, 148.9, 139.6, 137.6, 99.9, 60.5, 52.9, 49.4, 28.1, 27.8, 18.5, 13.3; IR (neat) ν = 2946, 2867, 1736, 1686, 1606, 1465, 1370 cm^{-1}; MS (EI) *m/z* (relative intensity) 392 (M^+, 9), 360 (16), 333 (18), 317 (100), 289 (9), 219 (2), 162 (3), 145 (12), 89 (5); HRMS (EI) *m/z* calcd for $C_{21}H_{32}O_5Si$ (M^+) 392.20190, found 392.20359.

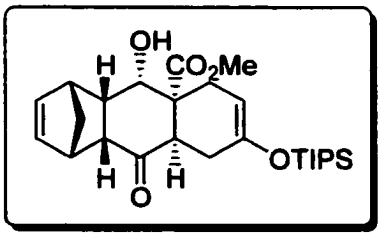
[71] Vedejs, E.; Eberlein, T. H.; Mazur, D. J.; McClure, C. K.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.* **1986**, *51*, 1556.

Methyl (1*R, 2*S**, 4*R**, 9*R**, 11*R**, 12*S**)- 3,10-dioxo-7-[(triisopropylsilyl)oxy]tetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-6,13-diene-4-carboxylate (56)**



Cyclopentadiene (5.00 mL, 60.9 mol), distilled from dicyclopentadiene (bp 40 °C), was added to a solution of crude **55** (3.47 g, 8.86 mmol) in toluene. The reaction was heated to 90 °C and stirred for 18 h. The reaction was cooled to rt and concentrated. Purification by flash chromatography (ether/petroleum ether 1:3) afforded the desired product as a white solid (1.75 g, 43% from methyl-2,5-dihydroxybenzoate). mp 99-101 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 6.13 (dd, *J*= 5.7, 2.9 Hz, 1H), 5.67 (dd, *J*= 5.6, 2.9 Hz, 1H), 4.83 (d, *J* = 5.6 Hz, 1H), 3.43 (s, 3H), 3.24 (br s, 1H), 3.13 (d, *J* = 17.4 Hz, 1H), 3.06 (br s, 1H), 2.98 (m, 1H), 2.80 (m, 1H), 2.70 (dd, *J*= 9.7, 3.9 Hz, 1H), 2.52 (dd, *J*= 9.7, 3.6 Hz, 1H), 2.25 (m, 1H), 2.06 (m, 1H), 1.06-1.15 (m, 22H), 0.76 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 207.0, 206.6, 170.5, 149.9, 138.7, 135.2, 99.2, 61.4, 52.6, 51.5, 50.7, 50.0, 49.3, 47.9, 47.5, 27.1, 26.8, 18.5, 13.4; IR ($CHCl_3$) ν = 2947, 2868, 1737, 1704, 1671, 1463, 1368, 1221 cm^{-1}; MS (EI) *m/z* (relative intensity) 458 (M^+, 1), 392 (29), 360 (26), 333 (22), 317 (100), 289 (11), 261 (4), 219 (2), 115 (6), 66 (22); HRMS (EI) *m/z* calcd for $C_{26}H_{38}O_5Si$ (M^+) 458.24885, found 458.24705.

Methyl (1*R, 2*S**, 3*S**, 4*R**, 9*R**, 11*R**, 12*S**)-3-hydroxy-10-oxo-7-[(triisopropylsilyl)oxy]tetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-6,13-diene-4-carboxylate (58)**

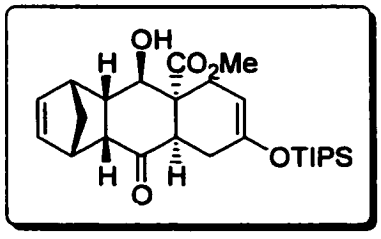


Lithium tri-*tert*-butoxyaluminohydride (8.417 g, 33.10 mmol) was added to a solution of **56** (8.416 g, 18.38 mmol) in dry THF (200 mL) at 0 °C. The reaction was warmed to rt and stirred for 18 h. The reaction was quenched by slow addition of saturated aqueous NH_4Cl (50 mL) and the resulting precipitate was removed by suction filtration through Celite. The filtrate was poured into a separatory funnel and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with brine (1 × 100 mL), dried, filtered, and concentrated. Purification by flash chromatography (ether/petroleum ether 1:1) afforded a 4:1 mixture of diastereomers (5.92 g, 78%). Recrystallization from ethyl acetate afforded the major isomer as a white solid (4.55 g, 54%). mp 149-151 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 6.06 (dd, *J*= 5.5, 3.0 Hz, 1H), 5.99 (dd, *J*= 5.6, 3.0 Hz, 1H), 4.85 (d, *J*= 5.6 Hz, 1H), 4.14 (d, *J*= 7.0 Hz, 1H), 3.38 (s, 3H), 3.27 (br s, 1H), 3.22 (d, *J*= 17.4 Hz, 1H), 2.70-2.81 (m, 3H), 2.58 (dd, *J*= 16.9, 5.7 Hz, 1H), 2.32-2.40 (m, 2H), 2.08 (m, 1H), 1.57 (broad s, OH), 1.24 (m, 1H), 1.09-1.16 (m, 21H), 0.91 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 212.3, 176.1, 152.1, 138.7, 135.9, 101.0, 72.5, 53.2, 53.0, 51.9, 51.2, 48.1, 47.6, 45.4, 45.1, 30.3, 28.7, 19.6, 14.4; IR (film) ν = 3479, 2949, 2871, 1734, 1687, 1456, 1430, 1365, 1242, 1178 cm^{-1}; MS (EI) *m/z* (relative intensity) 460 (M^+, 25), 417 (9), 394 (53), 376 (16), 351 (100), 319 (59), 301 (29), 281 (40), 253 (27), 157 (13), 115 (23), 75 (35), 66 (24); HRMS (EI) *m/z* calcd for $C_{26}H_{40}O_5Si$ (M^+) 460.26450, found 460.26386.

Crystal size 0.18 × 0.15 × 0.05 mm^3, monoclinic, space group P2(1), scan range 1.59 < θ <

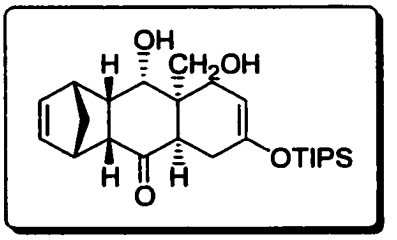
28.50 °, a = 12.829 (4), b = 7.247 (3), c = 27.482 (9) Å, α = 90 °, β = 93.91 °, γ = 90 °, V = 2549.3 Å^3, Z = 4, ρ_{calc} = 1.198 g/cm^3, u = 0.125 mm^{-1}, 3794 unique reflections at –80 °C, of which 7297 were taken as observed [$I_0 > 2.00\sigma(I)$], R = 0.0476, R_w = 0.1213.

Methyl (1*R, 2*S**, 3*R**, 4*R**, 9*R**, 11*R**, 12*S**)-3-hydroxy-10-oxo-7-[(triisopropylsilyl)oxy]tetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-6,13-diene-4-carboxylate (59)**



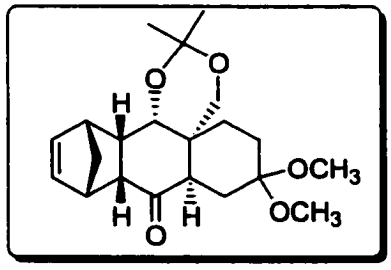
Spectral properties of minor isomer **59**: ^{1}H NMR (500 MHz, C_6D_6) δ 6.06 (dd, J_1 = 5.7 Hz, J_2 = 3.0 Hz, 1H), 5.94 (dd, J_1 = 5.7 Hz, J_2 = 3.0 Hz, 1H), 4.81 (m, 1H), 3.77 (dd, J = 8.5, 3.7 Hz, 1H), 3.23 (s, 3H), 2.2-3.4 (m, 10H), 1.28 (dt, J = 8.4, 1.8 Hz, 1H), 1.09 (m, 21H), 0.90 (d, J = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.8, 171.9, 150.6, 138.0, 136.0, 100.4, 71.3, 59.3, 52.2, 51.7, 50.0, 48.5, 46.4, 46.0, 43.2, 31.9, 28.5, 18.6, 13.4; IR (film) ν = 3464, 1738, 1693 cm^{-1}; MS (EI) *m/z* (relative intensity) 460 (M$^+$, 18), 417 (57), 394 (29), 351 (100), 319 953), 311 (43), 281 (37), 201 (38), 185 (43), 131 (37), 115 (31), 103 (57), 75 (87), 66 (43); HRMS (EI) *m/z* calcd for $C_{26}H_{40}O_5Si$ (M$^+$) 460.26450, found 460.26181.

(1*S, 2*R**, 4*R**, 9*S**, 10*S**, 11*S**, 12*R**)-10-Hydroxy-9-(hydroxymethyl)-6-[(triisopropylsilyl)oxy]tetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-6,13-dien-3-one (60)**



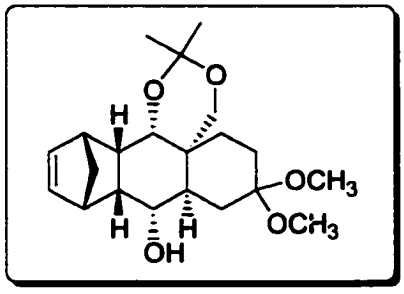
Lithium tri-*tert*-butoxyaluminohydride (0.169, 0.665 mmol) was added to a solution of **58** (0.116 g, 0.252 mmol) in dry THF (10 mL). The reaction was heated at reflux and stirred for 48 h. The reaction was cooled to rt and quenched with saturated aqueous NH_4Cl (5 mL). The solution was stirred for 30 min. and the resulting white precipitate was removed by suction filtration through Celite. The filtrate was poured into a separatory funnel and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (1 × 5 mL), dried, filtered, and concentrated. Purification by flash chromatography (ether/petroleum ether 1:1) afforded the title compound as a yellow oil (76 mg, 70%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.23 (dd, *J* = 5.2, 2.5 Hz, 1H), 6.07 (dd, *J* = 5.2, 2.5 Hz, 1H), 4.72 (m, 1H), 3.95 (d, *J* = 5.9 Hz, 1H), 3.72 (d, *J* = 11 Hz, 1H), 3.51 (d, *J* = 11 Hz, 1H), 3.39 (br s, 1H), 3.24 (br s, OH), 3.10 (d, *J* = 17.3 Hz, 1H), 2.90 (br s, OH), 2.81 (br s, 1H), 2.45-2.51 (m, 2H), 2.34-2.40 (m, 2H), 1.91 (d, *J* = 17.5 Hz, 1H), 1.46 (d, *J* = 17.5 Hz, 1H), 1.33 (d, *J* = 8.1 Hz, 1H), 1.15 (m, 21 H), 0.99 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 213.7, 150.5, 138.0, 134.0, 99.9, 74.3, 69.1, 51.2, 50.2, 46.9, 46.4, 44.7, 43.1, 41.4, 28.1, 27.2, 18.6, 13.4; IR (neat) ν = 3409, 2943, 2867, 1673, 1464, 1366, 1204 cm^{-1}; MS (EI) *m/z* (relative intensity) 432 (M^+, 26), 414 (10), 389 (81), 366 (47), 323 (64), 305 (25), 265 (22), 235 (30), 207 (12), 162 (22), 103 (70), 66 (60), 59 (100); HRMS (EI) *m/z* calcd for $C_{25}H_{40}O_4Si$ (M^+) 432.26959, found 432.26979.

(1*R, 2*S**, 3*S**, 8*S**, 13*R**, 15*R**, 16*S**)-11,11-dimethoxy-5,5-dimethyl-4,6-dioxapentacyclo[14.2.1.$0^{2,15}$.$0^{3,8}$.$0^{8,13}$]nonadec-17-en-14-one (63)**



Para-toluenesulfonic acid (0.3 mg, 0.002 mmol) and 2,2-dimethoxypropane (1.00 mL, 8.13 mmol) were added to a solution of **60** (44 mg, 0.10 mmol) in acetone (0.5 mL). The reaction was stirred at rt for 16 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (0.5 mL) and the acetone was removed by evaporation. The residue was diluted with ether and the phases were separated. The organic phase was washed with brine (1 × 2 mL), dried, filtered, and concentrated. Purification by flash chromatography (ether/petroleum ether 1:1) afforded **63** as a white solid (36 mg, 94%). mp 176-178 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 6.28 (dd, J= 5.5, 3.0 Hz, 1H), 6.13 (dd, J= 5.0, 3.0 Hz, 1H), 3.64-3.68 (m, 2H), 3.46 (br s, 1H), 3.17 (d, J = 11.7 Hz, 1H), 2.96 (s, 3H), 2.93 (s, 3H), 2.86-2.92 (m, 2H), 2.79 (m, 1H), 2.72 (br s, 1H), 2.51 (m, 1H), 1.66-1.72 (m, 2H), 1.54 (dd, J = 7.0, 14.3 Hz, 1H), 1.41 (m, 1H), 1.26 (s, 3H), 1.20 (s, 3H), 1.02-1.09 (m, 2H), 0.77 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 212.2, 136.9, 133.9, 100.2, 98.9, 72.0, 66.9, 50.2, 49.7, 47.8, 47.7, 46.0, 45.1, 42.6, 42.5, 36.5, 31.3, 30.0, 27.9, 25.8, 19.0; IR ($CHCl_3$) ν = 3017, 2962, 2871,1693, 1455, 1384, 1247, 1104 cm^{-1}; MS (EI) *m/z* (relative intensity) 362 (M^+, 1), 330 (7), 304 (40), 272 (26), 244 (10), 206 (15), 175 (20), 123 (100), 101 (41), 66 (66), 59 (6); HRMS (EI) *m/z* calcd for $C_{21}H_{30}O_5$ (M^+) 362.20933, found 362.20768.

(1*R, 2*S**, 3*S**, 8*S**, 13*R**, 14*R**, 15*R**, 16*S**)-11,11-dimethoxy-5,5-dimethyl-4,6-dioxapentacyclo[14.2.1.$0^{2,15}$.$0^{3,8}$.$0^{8,13}$]nonadec-17-en-14-ol (64)**

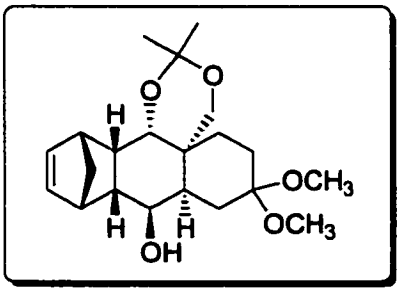


Lithium aluminum hydride (0.547 g, 14.4 mmol) was added to a solution of ketone **63** (1.217 g, 3.362 mmol) in dry THF (50 mL) at 0 °C. The reaction was warmed to rt and stirred for 18 h. The reaction was quenched by slow addition of saturated aqueous potassium sodium tartrate at 0 °C until bubbling ceased. The resulting phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with water (1 × 10 mL), dried, filtered, and concentrated. Purification by flash chromatography (ether/petroleum ether 1:1) afforded the desired product **64** as a white solid (0.326 g, 65%) and a more polar diastereomer **65** as a white solid (0.092 g, 18%). mp 119-121 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 6.39 (dd, *J* = 5.4, 3.2 Hz, 1H), 6.05 (dd, *J* = 5.4, 3.1 Hz, 1H), 3.87 (ddd,, *J* = 12.2, 3.8, 2.7 Hz, 1H), 3.79 (d, *J* = 11.6 Hz, 1H), 3.58 (d, *J* = 12.3 Hz, 1H), 3.49 (d, *J* = 4.5 Hz, 1H), 3.38 (d, *J* = 11.6 Hz, 1H), 3.03 (s, 3H), 2.96 (s, 3H), 2.84 (br s, 1H), 2.64 (br s, 1H), 2.11-2.18 (m, 2H), 1.99 (ddd, *J* = 13.8, 3.7, 2.7 Hz, 1H), 1.67-1.73 (m, 2H), 1.48-1.54 (m, 1H), 1.44 (dt, *J* = 7.7, 1.8 Hz, 1H), 1.32-1.39 (m, 2H), 1.23 (s, 3H), 1.20-1.23 (m, 1H), 1.17 (s, 3H), 1.14 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 135.2, 134.1, 102.3, 100.2, 73.2, 73.0, 68.0, 52.3, 48.0, 47.7, 46.6, 46.5, 41.8, 40.6, 39.8, 38.3, 34.8, 29.8, 27.8, 26. 0, 22.0; IR ($CHCl_3$) ν = 3439, 3019, 2964, 1456, 1383, 1227cm^{-1}; MS (EI) *m/z* (relative intensity) 332 (M^+-OCH_3, 1), 288 (4), 274 (11), 243 (8), 209 (9), 177 (16), 151 (54), 123 (100), 91 (73), 79 (49), 66 (83); HRMS (EI) *m/z* calcd for $C_{20}H_{29}O_4$ (M^+ - OCH_3) 333.20656, found 333.20807.

Crystal size 0.20 × 0.20 × 0.20 mm^3, monoclinic, space group P2(1), scan range 1.39 < θ <

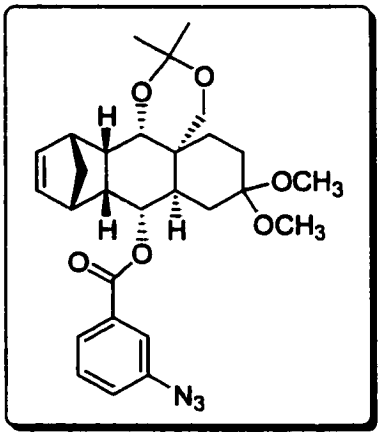
28.50 °, a = 17.291 (4), b = 6.4765 (3), c = 18.337 (9) Å, $\alpha = 90$ °, $\beta = 110.558$ °, $\gamma = 90$ °, $V = 1922.8$ Å^3, $Z = 4$, $\rho_{calc} = 1.259$ g/cm^3, $u = 0.088$ mm^{-1}, 4550 unique reflections at –80 °C, of which 16434 were taken as observed [$I_0 > 2.00\sigma(I)$], $R = 0.0462$, $R_w = 0.1262$.

(1*R, 2*S**, 3*S**, 8*S**, 13*R**, 14*S**, 15*R**, 16*S**)-11,11-dimethoxy-5,5-dimethyl-4,6-dioxapentacyclo[14.2.1.$0^{2,15}$.$0^{3,8}$.$0^{8,13}$]nonadec-17-en-14-ol (65)**



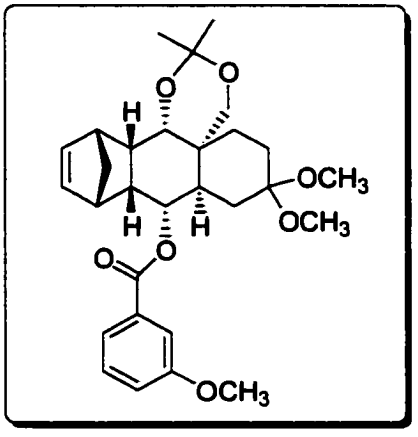
More polar diastereomer **65**: mp 70-72 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 6.24 (dd, $J = 5.6$, 3.0 Hz, 1H), 6.06 (dd, $J = 5.5$, 3.0 Hz, 1H), 3.88 (dd, $J = 11.3$, 6.3 Hz, 1H), 3.64 (d, $J = 11.3$ Hz, 1H), 3.41 (d, $J = 5.2$ Hz, 1H), 3.29 (d, $J = 11.3$, 1H), 3.06 (s, 3H), 3.05 (s, 3H), 3.03 (br s, 1H), 2.67 (br s, 1H), 2.08-2.19 (m, 3H), 1.99-2.04 (m, 1H), 1.66-1.74 (m, 3H), 1.56 (m, 1H), 1.48 (m, 1H), 1.31-1.38 (m, 2H), 1.30 (s, 3H), 1.21 (s, 3H), 1.17-1.23 (m, 1H), 1.06-1.12 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) 139.4, 130.5, 102.3, 99.0, 73.0, 70.1, 67.9, 51.1, 48.1, 47.7, 46.9, 44.9, 43.3, 41.4, 39.5, 37.9, 29.6, 28.6, 28.3, 27.4, 20.9; IR (film) $\nu = 3426$, 3075, 3055, 2958, 2866, 1458, 1380, 1228 cm^{-1}; MS (EI) *m/z* (relative intensity) 332 (M^+-OCH_3), 317 (3), 274 (32), 259 (7), 203 (21), 153 (45), 123 (100), 91 (69), 79 (42), 66 (84), 43 (65); HRMS (EI) *m/z* calcd for $C_{20}H_{29}O_4$ (M^+ - OCH_3) 333.20656, found 333.20250.

(1*R, 2*S**, 3*S**, 8*S**, 13*R**, 14*R**, 15*R**, 16*S**)-11,11-Dimethoxy-5,5-dimethyl-4,6-dioxapentacyclo[14.2.1.$0^{2,15}$.$0^{3,8}$.$0^{8,13}$]nonadec-17-en-14-yl 3-azidobenzoate (68)**



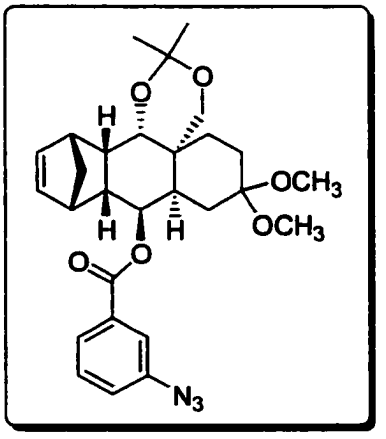
n-Butyllithium (150 μL, 0.38 mmol, 2.5 M in hexanes) was slowly added to a solution of **64** (0.105 g, 0.288 mmol) in dry THF (2 mL) at –78 °C. The cloudy white solution was stirred for 30 min. at –78 °C. The flask was covered with aluminum foil to protect the reaction from light. The solution was warmed to 0 °C and 3-azidobenzoyl chloride (69 mg, 0.38 mmol) was added. The reaction was warmed to rt and stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and the resulting phases were separated. The aqueous phase was extracted with diethyl ether (3 × 5 mL) and the combined organic extracts were dried, filtered, and concentrated. Purification by flash chromatography (petroleum ether followed by ether/petroleum ether 1:1) afforded the desired product as a yellow oil (0.103 mg, 86%), which slowly decomposed. ^{1}H NMR (300 MHz, C_6D_6) δ 8.01 (s, 1H), 7.98 (s, 1H), 6.88 (dd, J = 12.7 Hz, 1H), 6.70 (m, 1H), 6.29 (dd, J = 9.0, 5.0 Hz, 1H), 6.07 (dd, J = 8.9, 4.2 Hz, 1H), 5.88 (dd, J = 12.4 Hz, 1H), 3.58 (d, J =12.9 Hz, 1H), 3.35 (m, 2H), 3.01 (s, 3H), 2.96 (s, 3H), 2.92-3.06 (m, 1H), 2.80-2.87 (m, 2H), 2.43 (m, 1H), 2.19 (m, 1H), 2.08 (m, 1H), 1.77 (m, 1H), 1.36 (s, 3H), 1.29 (s, 3H), 1.22-1.51 (m, 5H), 1.07 (d, J = 12.6 Hz, 1H); ^{13}C NMR (75 MHz, C_6D_6) 165.3, 140.9, 136.9, 133.5, 130.1, 127.8, 126.5, 123.3, 120.7, 100.2, 99.5, 74.6, 72.3, 64.9, 51.0, 47.5, 47.3, 47.1, 46.7, 41.6, 40.1, 38.6, 36.0, 31.4, 28.3, 27.7, 26.5, 21.4; IR ($CHCl_3$) 2950, 2931, 2862, 2119, 1714, 1584, 1460, 1369, 1294, 1150 cm^{-1}; too unstable for MS.

(1*R, 2*S**, 3*S**, 8*S**, 13*R**, 14*R**, 15*R**, 16*S**)-11,11-Dimethoxy-5,5-dimethyl-4,6-dioxapentacyclo[14.2.1.$0^{2,15}$.$0^{3,8}$.$0^{8,13}$]nonadec-17-en-14-yl 3-methoxybenzoate (69)**



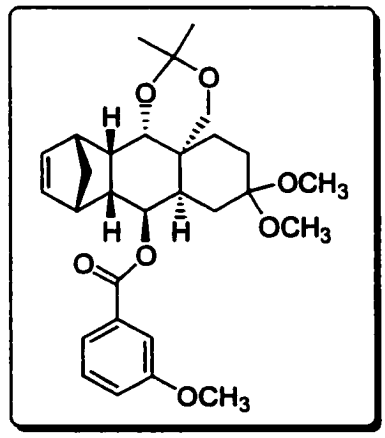
n-Butyllithium (80 μL, 0.20 mmol, 2.5 M in hexane) was slowly added to a solution of **64** (62 mg, 0.17 mmol) in dry THF (2 mL) at –78 °C. The cloudy white solution was stirred for 30 min. at –78 °C. The reaction was warmed to 0 °C and 3-methoxybenzoyl chloride (29 μL, 0.21 mmol) was added. The solution became clear and colourless. The reaction was warmed to rt and stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and the resulting phases were separated. The aqueous phase was extracted with diethyl ether (3 × 5 mL) and the combined organic extracts were dried, filtered, and concentrated. Purification by flash chromatography (petroleum ether followed by ether/petroleum ether 1:3) afforded the desired product as a white solid (79 mg, 94%). mp 60-62 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 7.95-7.97 (m, 2H), 7.07 (dd, J = 8.2 Hz, 1H), 6.88 (m, 1H), 6.24 (dd, J = 5.4, 3.0 Hz, 1H), 6.13 (dd, J = 5.4, 3.0 Hz, 1H), 5.92 (dd, J = 8.2 Hz, 1H), 3.60 (d, J = 8.2 Hz, 1H), 3.40 (m, 2H), 3.30 (s, 3H), 3.02 (s, 3H), 2.94 (s, 3H), 2.90-2.93 (m, 2H), 2.85 (br s, 1H), 2.49 (m, 1H), 2.16-2.21 (m, 2H), 1.78 (m, 1H), 1.35 (s, 3H), 1.30-1.45 (m, 5H), 1.29 (s, 3H), 1.06 (d, J = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 166.1, 160.2, 137.0, 133.6, 133.2, 129.7, 122.5, 119.3, 114.9, 99.9, 99.4, 73.8, 72.2, 64.6, 54.8, 50.5, 47.4, 47.2, 46.8, 41.7, 40.2, 38.8, 35.9, 30.7, 28.3, 27.3, 26.4, 21.6; IR ($CHCl_3$) ν = 3008, 2963, 2942, 1705, 1602, 1465, 1381, 1213 cm^{-1}; MS (CI) *m/z* 498 (M^+), 467 (M^+-OCH_3), 409 (M^+-$OC(CH_3)_2$), 332 (M^+-$COPhOCH_3$).

(1*R, 2*S**, 3*S**, 8*S**, 13*R**, 14*S**, 15*R**, 16*S**)-11,11-Dimethoxy-5,5-dimethyl-4,6-dioxapentacyclo[14.2.1.$0^{2,15}$.$0^{3,8}$.$0^{8,13}$]nonadec-17-en-14-yl 3-azidobenzoate (70)**



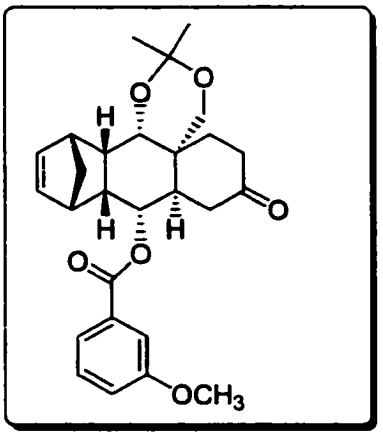
Triethylamine (65 μL, 0.47 mmol), DMAP (18 mg, 0.15 mmol) and 3-azidobenzoyl chloride (56 mg, 0.31 mmol) were added to a solution of **65** (54 mg, 0.15 mmol) in CH_2Cl_2 (2 mL). The reaction was protected from light and stirred at rt for 18 h. Saturated aqueous NH_4Cl (2 mL) was added to the reaction and the resulting phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried, filtered, and concentrated. Purification by flash chromatography (ether/petroleum ether 1:3) afforded the desired compound as a clear and colourless oil (70 mg, 92%) which slowly decomposed. ^{1}H NMR (300 MHz) 7.90 (m, 2H), 6.84 (dd, 1H, 8.4 Hz), 6.68 (m, 1H), 6.26 (dd, 1H, J = 5.5, 3.0 Hz), 6.15 (dd, 1H, J = 5.5, 3.0 Hz), 5.62 (dd, 1H, J = 11.9, 5.9 Hz), 3.92 (d, 1H, J = 11.4 Hz), 3.42 (d, 1H, J = 4.6 Hz), 3.31 (d, 1H, J = 11.4 Hz), 3.05 (s, 3H), 2.88 (s, 3H), 2.82 (br s, 1H), 2.67 (br s, 1H), 2.33-2.51 (m, 2H), 2.10-2.24 (m, 2H), 1.20-2.24 (m, 2H), 1.70 (m, 1H), 1.50 (m, 1H), 1.43 (s, 3H), 1.27-1.39 (m, 2H), 1.21 (s, 3H), 1.16 (d, 1H, 8.3 Hz); ^{13}C NMR (75 MHz, C_6D_6) 164.6, 140.9, 139.2, 133.3, 130.1, 130.0, 126.1, 123.2, 120.3, 101.6, 98.7, 75.2, 72.4, 67.4, 50.7, 47.7, 47.3, 46.4, 44.6, 41.3, 39.5, 39.4, 35.1, 29.5, 28.8, 28.2, 26.8, 20.4; IR ($CHCl_3$) ν = 2955, 2929, 2859, 2118, 1713, 1584, 1461, 1371, 1294, 1262, 1152 cm^{-1}; too unstable for MS.

(1*R, 2*S**, 3*S**, 8*S**, 13*R**, 14*S**, 15*R**, 16*S**)-11,11-Dimethoxy-5,5-dimethyl-4,6-dioxapentacyclo[14.2.1.$0^{2,15}$.$0^{3,8}$.$0^{8,13}$]nonadec-17-en-14-yl 3-methoxybenzoate (71)**



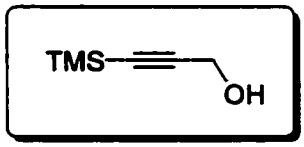
Triethylamine (50 μL, 0.36 mmol), DMAP (30 mg, 0.25 mmol) and 3-methoxybenzoyl chloride (50 μL, 0.36 mmol) were added to a solution of **65** (44 mg, 0.12 mmol) in CH_2Cl_2 (2 mL). The reaction was stirred at rt for 18 h. Saturated aqueous NH_4Cl (2 mL) was added to the reaction and the resulting phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried, filtered, and concentrated. Purification by flash chromatography (petroleum ether followed by ether/petroleum ether 1:3) afforded the desired compound as a clear and colourless oil (55 mg, 92%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.89 (m, 2H), 7.03 (dd, 1H, 8.2 Hz), 6.85 (m, 1H), 6.27 (dd, J = 5.6, 3.0 Hz, 1H), 6.09 (dd, J = 5.6, 3.0 Hz, 1H), 5.65 (dd, J = 12.2, 5.8 Hz, 1H), 3.93 (d, J = 11.4 Hz, 1H), 3.44 (d, J = 5.0 Hz, 1H), 3.32 (d, J = 11.4 Hz, 1H), 3.25 (s, 3H), 3.03 (s, 3H), 2.87 (br s, 1H), 2.86 (s, 3H), 2.68 (br s, 1H), 2.42-2.50 (m, 2H), 2.19-2.25 (m, 2H), 1.68-1.74 (m, 2H), 1.45-1.53 (m, 2H), 1.43 (s, 3H), 1.32-1.42 (m, 2H), 1.22 (s, 3H), 1.18 (d, J = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 165.4, 160.2, 139.0, 133.0, 130.0, 129.7, 127.8, 122.1, 119.3, 114.6, 101.7, 98.7, 74.6, 72.4, 67.4, 54.8, 50.6, 47.1, 46.4, 44.5, 41.3, 39.6, 39.5, 35.1, 29.5, 28.7, 28.8, 26.8, 20.4; IR ($CHCl_3$) ν = 2964, 2940 2869, 1711, 1588, 1464, 1382, 1280, 1229 cm^{-1}; MS (CI) *m/z* 498 (M^+), 467 (M^+-OCH_3), 409 (M^+-$OC(CH_3)_2$), 332 (M^+-$COPhOCH_3$).

(1*R, 2*S**, 3*S**, 8*S**, 13*R**, 14*R**, 15*R**, 16*S**)-5,5-Dimethyl-11-oxo-4,6-dioxapentacyclo[14.2.1.$0^{2,15}$.$0^{3,8}$.$0^{8,13}$]nonadec-17-en-14-yl 3-methyoxybenzoate (73)**



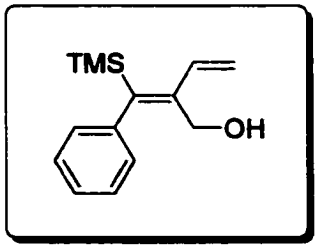
Ketal **69** (29 mg, 0.058 mmol) was dissolved in chloroform (3 mL) and stirred at room temperature for 48 h. The solution was concentrated and purification by flash chromatography (ether/petroleum ether 1:1) afforded the desired compound as a white foam (25 mg, 95%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.86-7.89 (m, 2H), 7.08 (dd, 8.0 Hz, 1H), 6.92 (m, 1H), 6.32 (dd, J = 5.4, 3.0 Hz, 1H), 6.12 (dd, J = 5.4, 2.9 Hz, 1H), 5.22 (dd, J = 10.4, 8.8 Hz, 1H), 3.50 (d, J = 9.0 Hz, 1H), 3.36 (d, J = 11.7 Hz, 1H), 3.30 (d, 3H), 3.23 (d, J = 11.7 Hz, 1H), 2.88 (br s, 1H), 2.79 (br s, 1H), 2.74-2.77 (m, 1H), 2.33-2.38 (m, 2H), 2.18 (m, 1H), 2.09 (dd, J = 16.8, 5.8 Hz, 1H), 1.95 (dd, J = 15.7, 4.6 Hz, 1H) 1.81-1.89 (m, 1H), 1.34 (s, 3H), 1.25-1.38 (m, 3H), 1.27 (s, 3H), 1.02 (d, J = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) 207.7, 166.4, 160.7, 139.1, 132.4, 130.1, 122.8, 122.8, 120.0, 115.2, 100.1, 74.2, 70.9, 65.5, 55.2, 50.0, 47.6, 47.2, 42.4, 40.3, 40.1, 38.9, 36.8, 36.6, 28.0, 26.9, 21.8; IR ($CHCl_3$) ν = 2967, 2940, 2872, 1714, 1601, 1588, 1488, 1466, 1381, 1280, 1230 cm^{-1}; MS (EI) *m/z* (relative intensity) 452 (M^+, 0.2), 394 (4), 300 (1), 243 (12), 177 (4), 135 (100), 107 (18), 66 (24), 43 (13); HRMS (EI) *m/z* calcd for $C_{24}H_{26}O_5$ (M^+ - $OC(CH_3)_2$), 394.17800, found 394.17811.

3-(Trimethylsilanyl)prop-2-yn-1-ol (104)



The compound was prepared according to the procedure described in Ref. 72. *n*-Butyllithium (50.0 mL, 0.125 mol, 2.5 M in hexanes) was added over 30 min. *via* a dropping funnel to a cold solution (-78 °C) of propargyl alcohol (3.00 mL, 0.0515 mol) in dry THF. The cloudy white solution was stirred at –78 °C for 40 min. Trimethylsilyl chloride (15.0 mL, 0.118 mol) was added over 5 min. *via* a dropping funnel. The reaction was warmed to rt and stirred for 3 h. The solution was cooled to 0 °C and 1.4 M H_2SO_4 (66 mL) was added over 45 min. via a dropping funnel. The yellow solution was stirred at 0 °C for 20 min. The phases were separated and the aqueous phase was extracted with ether (3 × 50 mL). The organic extracts were combined, washed with saturated aqueous NaCl (100 mL), dried, filtered, and concentrated. Purification by vacuum distillation afforded the desired product as a yellow oil (6.12 g, 93%). bp 62-65 °C, 10 mm Hg (lit. bp 71 °C, 15 mm Hg);[72] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (s, 2 H), 1.64 (s, 1H), 0.16 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.1, 91.1, 52.0, 0.1. ^{1}H NMR spectrum of this sample was in good agreement with that reported for this compound.[72]

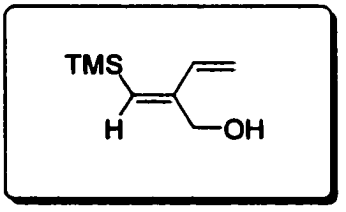
(2*E*)-2-[Phenyl(trimethylsilyl)methylene]-but-3-en-1-ol (109)



[72] Spyroudis, S. P. *J. Org. Chem.* **1986**, *51*, 3453.

Vinylmagnesium chloride (4.00 mL, 6.40 mmol, 1.6 M in THF) was slowly added to a solution of 3-(trimethylsilanyl)prop-2-yn-1-ol (0.259 g, 2.02 mmol) in dry THF (5 mL) at room temperature. The reaction was heated at reflux for 20 h. The solution was cooled to rt and degassed for 20 min. by bubbling through a stream of nitrogen. In a separate flask, iodobenzene (0.68 mL, 6.06 mmol) in dry THF (5 mL) was degassed for 10 min. Tetrakis(triphenylphosphine) palladium (0.230 g, 0.202 mmol) was added to the iodobenzene solution and degassed for 10 min. This solution was cannulated to the carbomagnesiation intermediate at rt. The reaction was heated to reflux and stirred for 48 h. The reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with ether (3 × 15 mL) and the combined organic extracts were dried, filtered, and concentrated. Purification by flash chromatography (petroleum ether followed by ether/petroleum ether 1:3) afforded 0.254 g of a mixture of the desired product **109** (42%) and the proton-quench product **110** (19%). ^{1}H NMR (300 MHz, C_6D_6) δ 6.97-7.15 (m, 3H), 6.76-6.87 (m, 3H), 5.59 (dd, J = 17.3, 0.6 Hz, 1H), 5.19 (dd, J = 11.1, 0.6 Hz, 1H), 4.04 (s, 2H), 1.37 (br s, 1H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 152.8, 148.4, 147.8, 144.2, 136.8, 136.1, 125.9, 116.7, 59.8, 0.5; IR ($CDCl_3$); ν = 3451, 3019, 2955, 1596, 1408, 1249 cm^{-1}; MS (EI) *m/z* (relative intensity) 232 (M^+, 9), 217 (36), 199 (57), 183 (34), 159 (26), 141 (100), 115 (69), 91 (37), 73 (77), 45 (42); HRMS (EI) *m/z* calcd for $C_{14}H_{20}OSi$ (M^+) 232.12834, found 232.12698.

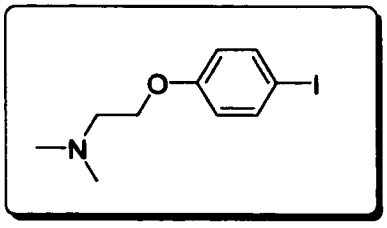
(2*E*)-2-Trimethylsilylmethylene-but-3-en-1-ol (110)



^{1}H NMR (500 MHz, C_6D_6) δ 6.66 (dd, J = 18.1, 11.2 Hz, 1H), 5.96 (s, 1H), 5.11 (d, J = 18.1 Hz, 1H), 4.98 (dt, J = 11.2, 1.2 Hz, 1H), 4.12 (s, 1H), 1.42 (br s, 1H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 152.7, 135.9, 128.8, 114.5, 64.0, 0.3.[73]

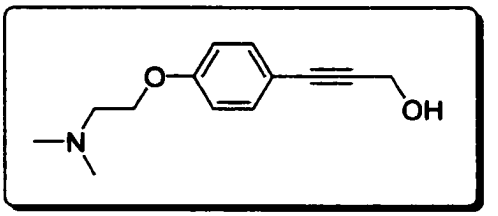
[73] Dr. P. Forgione, Ph.D. Thesis, 2001, University of Ottawa.

_N_-[2-(4-Iodophenoxy)ethyl]-_N_,_N_-dimethylamine (113)



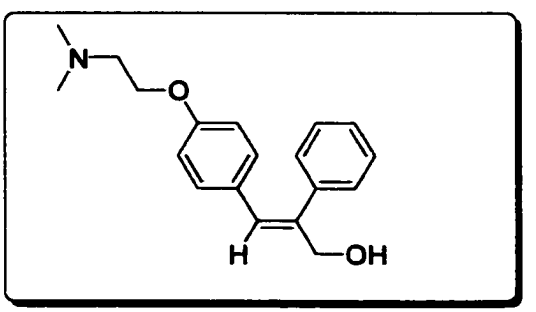
The compound was prepared according to the procedure described in Ref. 69. Potassium hydroxide (0.770 g, 13.7 mmol) was added to a solution of 4-iodophenol (3.03 g, 13.6 mmol) in 99% ethanol (15 mL) at room temperature. The reaction was stirred for 30 min. Evaporation of the solvent afforded the 4-iodophenoxide salt as a yellow oil. Sodium hydroxide (0.683 g, 17.1 mmol) in water (2 mL) was added to a cold solution (0 °C) of 2-dimethylaminoethylchloride hydrochloride (2.00 g, 13.9 mmol) in water (4 mL). The reaction mixture was saturated with solid NaCl and extracted with toluene (5 × 5 mL). The combined toluene extracts were dried over KOH pellets. The dried toluene solution was added to the 4-iodophenoxide salt and refluxed overnight. The reaction was cooled to rt and filtered. The filtrate was washed with saturated aqueous NaOH (4 × 15 mL) and brine (10 mL). The organic phase was dried, filtered, and concentrated to give the desired product as a brown oil which was used without further purification (3.55 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J= 9.0 Hz, 2H), 6.67 (d, J = 9.0 Hz, 2H), 4.00 (t, J = 5.6 Hz, 2H), 2.70 (t, J = 5.6 Hz, 2H), 2.31 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 138.5, 117.3, 83.2, 66.4, 58.5, 46.2; HRMS (EI) m/z calcd for $C_{10}H_{14}INO$ (M^+) 291.01201, found 291.00999. ^{1}H NMR spectrum of this sample was in good agreement with that reported for this compound.[69]

3-{4-[2-(Dimethylamino)ethoxy]phenyl}prop-2-yn-1-ol (114)



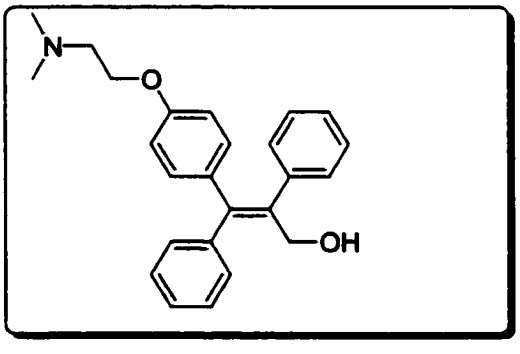
A solution of copper iodide (66 mg, 0.35 mmol) and dichlorobis(triphenylphosphine) palladium chloride (0.238 g, 0.335 mmol) in dry THF (10 mL) was degassed by bubbling through a stream of nitrogen for 15 min. Aryl iodide **113** (1.085 g, 3.729 mmol) was added at room temperature and the solution was degassed for 15 min. Triethylamine (5 mL, 35.9 mmol) was added and the solution was degassed for an additional 15 min. Propargyl alcohol (0.20 mL, 3.4 mmol) was then added and the reaction immediately turned from cloudy orange to dark brown. The reaction was stirred overnight at room temperature. The solution was then filtered through a pad of silica gel. The filtrate was concentrated and purified by flash chromatography (ethyl acetate followed by methanol/triethylamine/ethyl acetate 1:1:98) to give a brown solid (0.675 g, 83%). mp 106-108 °C; ^{1}H NMR (300 MHz, acetone-d_6); 7.32 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 4.36 (s, 2H), 4.09 (t, J = 5.8 Hz, 2H), 3.69 (br s, 1H), 2.67 (t, J = 5.8 Hz, 2H), 2.26 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ 159.4, 133.2, 115.5, 114.9, 87.8, 84.0, 66.7, 58.3, 50.5, 45.6; IR ($CDCl_3$) ν = 3612, 2943, 2872, 2827, 2775, 1603, 1506, 1461, 1236, 1172, 1026 cm^{-1}; MS (EI) *m/z* (relative intensity) 219 (13), 186 (1), 162 (2), 131 (3), 102 (5), 72 (41), 58 (100), 42 (29); HRMS (EI) *m/z* calcd for $C_{13}H_{17}NO_2$ (M^+) 219.12593, found 219.12601.

(2*E*)-3-{4-[2-(Dimethylamino)ethoxy]phenyl}-2-phenylprop-2-en-1-ol (116)



Phenylmagnesium chloride (0.90 mL, 1.80 mmol, 2.0 M in THF) was slowly added to a solution of 3-[4-(2-dimethylamino-ethoxy)-phenyl]-prop-2-yn-1-ol (0.157 g, 0.716 mmol) in dry THF (5 mL) at rt. The reaction was heated at reflux for 24 h. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) and stirred for 20 min. at room temperature. The resulting phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried, filtered, and concentrated. Purification by flash chromatography (ethyl acetate followed by methanol/triethylamine/ethyl acetate 1:1:98) afforded the title compound as a white solid (0.151 g, 71%). mp 126-128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.30 (m, 5H), 6.87 (d, 8.5 Hz, 2H), 6.62 (d, J = 8.6 Hz, 2H), 6.59 (s, 1H), 4.39 (s, 2H), 3.97 (t, J = 5.6 Hz, 2H), 2.80 (br s, 1H), 2.68 (t, J = 5.5 Hz, 2H), 2.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 157.9, 140.1, 139.3, 130.8, 129.6, 129.2, 127.8, 126.2, 114.4, 68.9, 66.0, 58.5, 46.1; IR ($CDCl_3$) ν = 3606, 2951, 2867, 2819, 2776, 1604, 1508, 1469, 1242, 1174, 1080 cm^{-1}; MS (EI) *m/z* (relative intensity) 297 (M^+, 3), 264 (0.3), 208 (3), 178 (6), 84 (7), 72 (53), 58 (100), 42 (16); HRMS (EI) *m/z* calcd for $C_{19}H_{23}NO_2$ (M^+) 297.17288, found 297.17085.

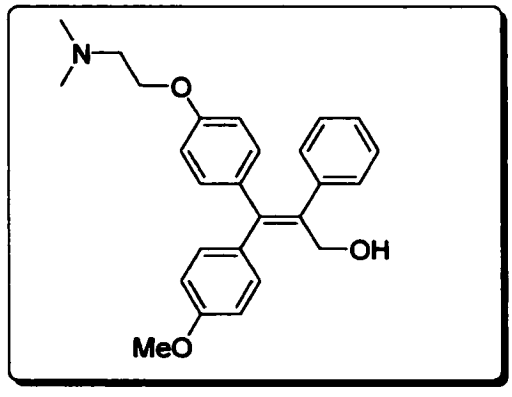
(2*E*)-3-{4-[2-(Dimethylamino)ethoxy]phenyl}-2,3-diphenylprop-2-en-1-ol (99)



Phenylmagnesium chloride (1.50 mL, 3.00 mmol, 2.0 M in THF) was slowly added to a solution of **114** (0.200 g, 0.911 mmol) in dry THF (5 mL) at rt. The reaction was heated at reflux for 24 h. The solution was cooled to rt and degassed by bubbling through a stream of nitrogen for 20 min. In a separate flask, iodobenzene (0.40 mL, 3.6 mmol) in dry THF (5

mL) was degassed for 10 min. Tetrakis(triphenylphosphine) palladium (0.108 g, 0.0932 mmol) was added to the iodobenzene solution and degassed for 10 min. This solution was cannulated to the carbomagnesiation intermediate at rt. The reaction was heated to reflux and stirred for 72 h. The reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried, filtered, and concentrated. Purification by flash chromatography (ethyl acetate followed by methanol/triethylamine/ethyl acetate 1:1:98) afforded 0.205 g of a mixture of the desired product **99** (50%) and **116** (13%) as a yellow solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.24-7.32 (m, 5 H), 7.07-7.20 (m, 5H), 6.79 (d, J = 8.7 Hz, 2H), 6.56 (d, J = 8.7 Hz, 2H), 4.40 (s, 2H), 3.89 (t, 5.5 Hz, 2H), 2.76 (br s, 1H), 2.60 (t, J = 5.5 Hz, 2H), 2.23 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 157.6, 142.9, 142.6, 141.2, 138.2, 135.1, 132.3, 130.3, 130.2, 128.6, 128.5, 127.6, 127.0, 113.9, 66.0, 65.3, 58.5, 46.2; IR ($CDCl_3$) ν = 3601, 3060, 2950, 2878, 2833, 2780, 2247, 1606, 1508, 1467, 1443, 1371, 1243, 1177, 1030 cm^{-1}; MS (EI) *m/z* (relative intensity) 373 (M^+, 10), 343 (0.3), 297 (4), 252 (1), 226 (0.3), 191 (1), 165 (4), 133 (1), 105 (4), 72 (47), 58 (100); HRMS (EI) *m/z* calcd for $C_{25}H_{27}NO_2$ (M^+) 373.20418, found 373.20794.

(2*Z*)-3-{4-[2-(Dimethylamino)ethoxy]phenyl}-3-(4-methoxyphenyl)-2-phenylprop-2-en-1-ol (100)



Phenylmagnesium chloride (1.50 mL, 3.00 mmol, 2.0 M in THF) was slowly added to a solution of 3-[4-(2-dimethylamino-ethoxy)-phenyl]-prop-2-yn-1-ol (0.209 g, 0.953 mmol) in

dry THF (5 mL) at rt. The reaction was heated at reflux for 24 h. The solution was cooled to rt and degassed by bubbling through a stream of nitrogen for 20 min. In a separate flask, 4-iodoanisole (0.891 g, 3.81 mmol) in dry THF (5 mL) was degassed for 10 min. Tetrakis(triphenylphosphine) palladium (0.112 g, 0.0970 mmol) was added to the 4-iodoanisole solution and degassed for 10 min. This solution was cannulated to the carbomagnesiation intermediate at rt. The reaction was heated to reflux and stirred for 72 h. The reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried, filtered, and concentrated. Purification by flash chromatography (ethyl acetate followed by methanol/triethylamine/ethyl acetate 1:1:98) afforded 0.276 g of a mixture of the desired product **100** (60%) and **116** (16%) as a yellow solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.24 (d, 2 H), 7.06-7.31 (m, 5H), 6.86 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.56 (d, J = 8.8 Hz, 2H), 4.43 (s, 2H), 3.89 (t, 5.8 Hz, 2H), 3.79 (s, 3H), 2.60 (t, J = 5.5 Hz, 2H), 2.53 (br s, 1H), 2.23 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 157.6, 142.6, 141.5, 137.6, 135.4, 135.4, 132.4, 131.5, 130.4, 129.1, 128.6, 126.9, 113.8, 66.0, 65.5, 58.6, 55.6, 46.2; IR ($CDCl_3$) ν = 3602, 3060, 2951, 2878, 2833, 2780, 2248, 1606, 1573, 1508, 1467, 1442, 1371, 1243, 1177, 1030 cm^{-1}; MS (EI) *m/z* (relative intensity) 403 (14), 373 (2), 344 (0.2), 297 (3), 265 (0.3), 239 (1), 196 (1), 165 (1), 133 (1), 105 (3), 72 (36), 58 (100); HRMS (EI) *m/z* calcd for $C_{26}H_{29}NO_3$ (M^+) 403.21474, found 403.21269.

Claims to Original Research

1. Developed an efficient route to the tetracyclic skeleton of taxoid analogue **20** using two sequential Diels-Alder reactions.

2. Developed an efficient one-pot diol protection-enol ether hydrolysis ketone acetylization sequence.

3. Submitted compounds **69**, **71**, and **73** for biological testing to assess their cytotoxicity.

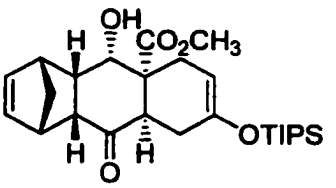
4. Developed a new carbomagnesiation-palladium coupling reaction of propargyl alcohols for the regio- and stereocontrolled synthesis of tetrasubstituted olefins.

5. Completed a stereoselective three-step synthesis of new tamoxifen analogues **99** and **100**.

Appendices

Appendix A

X-Ray Crystallographic Data for Compound **58**



58

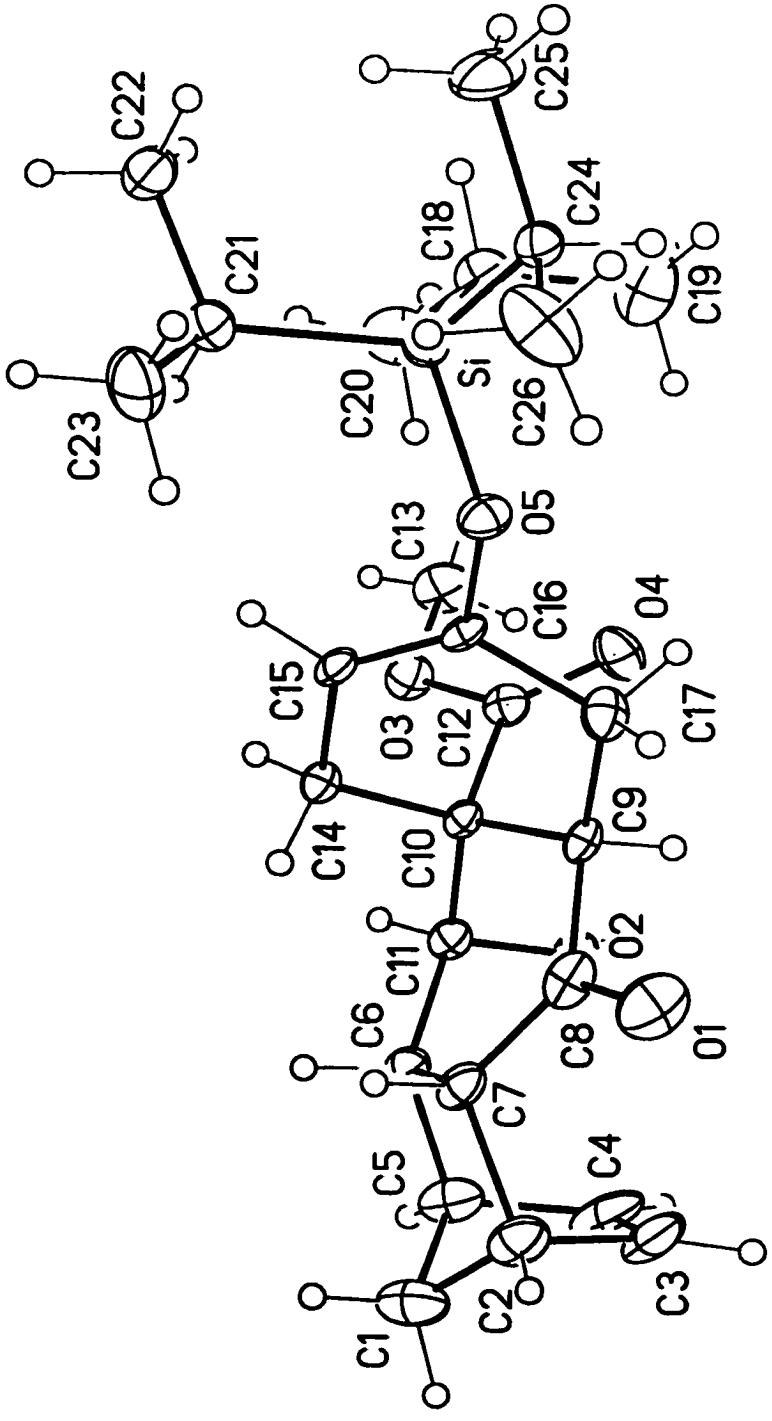

C22
C25
C21
C18
C24
C19
C23
C20
Si
C26
C13
O5
C16
O4
C15
O3
C12
C17
C14
C10
C9
C11
O2
C6
C8
O1
C7
C5
C4
C2
C3
C1

Table 1. Crystal data and structure refinement for af2001.

Identification code	af2001
Empirical formula	C26 H39 O5 Si
Formula weight	459.66
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 12.829(4) A alpha = 90 deg. b = 7.247(3) A beta = 93.91(3) deg. c = 27.482(9) A gamma = 90 deg.
Volume	2549.3(15) A^3
Z, Calculated density	4, 1.198 Mg/m^3
Absorption coefficient	0.125 mm^-1
F(000)	996
Crystal size	0.18 x 0.15 x 0.05 mm
Theta range for data collection	1.59 to 28.50 deg.
Limiting indices	-16<=h<=16, 0<=k<=9, 0<=l<=17
Reflections collected / unique	7297 / 3794 [R(int) = 0.0274]
Completeness to theta = 28.50	58.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000000 and 0.907748
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3794 / 0 / 289
Goodness-of-fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0476, wR2 = 0.1213
R indices (all data)	R1 = 0.0672, wR2 = 0.1318
Largest diff. peak and hole	0.513 and -0.224 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for af2001.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Si	7247(1)	6498(1)	610(1)	30(1)
O(1)	9142(2)	8052(3)	2804(1)	58(1)
O(2)	6364(1)	11662(2)	2985(1)	35(1)
O(3)	5396(1)	11896(2)	1826(1)	37(1)
O(4)	5422(1)	9003(2)	2121(1)	44(1)
O(5)	7788(1)	6855(2)	1175(1)	33(1)
C(1)	9455(2)	13590(5)	3420(2)	57(1)
C(2)	9525(2)	11497(4)	3343(1)	47(1)
C(3)	8750(2)	10836(5)	3697(1)	58(1)
C(4)	7995(2)	12089(6)	3695(1)	59(1)
C(5)	8243(2)	13612(5)	3349(1)	48(1)
C(6)	8110(2)	12870(4)	2814(1)	31(1)
C(7)	8954(2)	11306(4)	2817(1)	36(1)
C(8)	8593(2)	9383(4)	2687(1)	36(1)
C(9)	7532(2)	9063(3)	2411(1)	28(1)
C(10)	7019(2)	10864(3)	2206(1)	25(1)
C(11)	6993(2)	12337(3)	2613(1)	28(1)
C(12)	5865(2)	10439(3)	2043(1)	30(1)
C(13)	4280(2)	11723(4)	1698(1)	50(1)
C(14)	7580(2)	11565(3)	1764(1)	27(1)
C(15)	7718(2)	10049(3)	1398(1)	27(1)
C(16)	7682(2)	8268(3)	1511(1)	26(1)
C(17)	7567(2)	7545(3)	2016(1)	36(1)
C(18)	5775(2)	6648(4)	604(1)	39(1)
C(19)	5328(2)	5330(5)	976(2)	69(1)
C(20)	5358(2)	8610(4)	672(2)	58(1)
C(21)	7706(2)	8240(3)	160(1)	37(1)
C(22)	7153(3)	8124(4)	-355(1)	50(1)
C(23)	8891(2)	8286(5)	128(2)	60(1)
C(24)	7659(2)	4061(3)	487(1)	34(1)
C(25)	7370(4)	3473(4)	-41(2)	77(2)
C(26)	8811(2)	3658(4)	631(2)	66(1)

Table 3. Bond lengths [A] and angles [deg] for af2001.

Si-O(5)	1.676(2)
Si-C(24)	1.881(3)
Si-C(21)	1.891(3)
Si-C(18)	1.891(2)
O(1)-C(8)	1.225(3)
O(2)-C(11)	1.432(3)
O(3)-C(12)	1.335(3)
O(3)-C(13)	1.456(3)
O(4)-C(12)	1.213(3)
O(5)-C(16)	1.393(3)
C(1)-C(2)	1.535(5)
C(1)-C(5)	1.555(4)
C(2)-C(3)	1.515(5)
C(2)-C(7)	1.582(4)
C(3)-C(4)	1.327(5)
C(4)-C(5)	1.505(5)
C(5)-C(6)	1.563(4)
C(6)-C(11)	1.549(3)
C(6)-C(7)	1.567(3)
C(7)-C(8)	1.504(4)
C(8)-C(9)	1.530(3)
C(9)-C(17)	1.548(4)
C(9)-C(10)	1.550(3)
C(10)-C(14)	1.539(4)
C(10)-C(11)	1.548(4)
C(10)-C(12)	1.548(3)
C(14)-C(15)	1.509(4)
C(15)-C(16)	1.330(3)
C(16)-C(17)	1.500(4)
C(18)-C(20)	1.535(4)
C(18)-C(19)	1.538(4)
C(21)-C(23)	1.529(4)
C(21)-C(22)	1.541(4)
C(24)-C(26)	1.531(4)
C(24)-C(25)	1.534(5)
O(5)-Si-C(24)	101.99(11)
O(5)-Si-C(21)	112.03(11)
C(24)-Si-C(21)	113.91(14)
O(5)-Si-C(18)	110.51(13)
C(24)-Si-C(18)	110.21(12)
C(21)-Si-C(18)	108.12(13)
C(12)-O(3)-C(13)	116.5(2)
C(16)-O(5)-Si	132.47(16)
C(2)-C(1)-C(5)	93.4(2)
C(3)-C(2)-C(1)	100.2(3)
C(3)-C(2)-C(7)	106.1(2)
C(1)-C(2)-C(7)	100.6(2)
C(4)-C(3)-C(2)	106.9(3)
C(3)-C(4)-C(5)	108.6(3)
C(4)-C(5)-C(1)	99.5(3)
C(4)-C(5)-C(6)	109.1(3)
C(1)-C(5)-C(6)	99.1(2)
C(11)-C(6)-C(5)	117.4(2)
C(11)-C(6)-C(7)	116.3(2)
C(5)-C(6)-C(7)	102.3(2)

C(8)-C(7)-C(6)	117.86(19)
C(8)-C(7)-C(2)	114.4(2)
C(6)-C(7)-C(2)	102.6(2)
O(1)-C(8)-C(7)	120.3(2)
O(1)-C(8)-C(9)	119.2(3)
C(7)-C(8)-C(9)	120.5(2)
C(8)-C(9)-C(17)	112.8(2)
C(8)-C(9)-C(10)	113.21(19)
C(17)-C(9)-C(10)	112.1(2)
C(14)-C(10)-C(11)	112.12(19)
C(14)-C(10)-C(12)	109.0(2)
C(11)-C(10)-C(12)	106.22(18)
C(14)-C(10)-C(9)	110.76(19)
C(11)-C(10)-C(9)	110.3(2)
C(12)-C(10)-C(9)	108.16(18)
O(2)-C(11)-C(10)	108.74(19)
O(2)-C(11)-C(6)	112.5(2)
C(10)-C(11)-C(6)	111.41(19)
O(4)-C(12)-O(3)	123.7(2)
O(4)-C(12)-C(10)	124.8(2)
O(3)-C(12)-C(10)	111.44(19)
C(15)-C(14)-C(10)	111.6(2)
C(16)-C(15)-C(14)	122.9(3)
C(15)-C(16)-O(5)	123.5(3)
C(15)-C(16)-C(17)	124.3(3)
O(5)-C(16)-C(17)	112.2(2)
C(16)-C(17)-C(9)	114.1(2)
C(20)-C(18)-C(19)	110.2(3)
C(20)-C(18)-Si	114.12(19)
C(19)-C(18)-Si	112.06(19)
C(23)-C(21)-C(22)	110.3(3)
C(23)-C(21)-Si	114.0(2)
C(22)-C(21)-Si	114.82(19)
C(26)-C(24)-C(25)	111.0(3)
C(26)-C(24)-Si	114.26(18)
C(25)-C(24)-Si	112.23(19)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for af2001. 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
Si	31(1)	28(1)	32(1)	0(1)	4(1)	0(1)
O(1)	51(1)	59(1)	61(2)	6(1)	-4(1)	25(1)
O(2)	31(1)	47(1)	28(2)	3(1)	10(1)	4(1)
O(3)	27(1)	45(1)	39(2)	5(1)	-1(1)	3(1)
O(4)	31(1)	43(1)	58(2)	2(1)	5(1)	-9(1)
O(5)	39(1)	33(1)	26(2)	-5(1)	1(1)	6(1)
C(1)	43(2)	83(2)	44(3)	-15(2)	-8(2)	-6(2)
C(2)	28(1)	76(2)	35(3)	6(2)	-2(1)	2(1)
C(3)	46(2)	96(3)	30(3)	17(2)	-7(2)	1(2)
C(4)	41(2)	116(3)	20(3)	-3(2)	1(2)	6(2)
C(5)	40(1)	70(2)	31(3)	-11(2)	-1(1)	5(1)
C(6)	30(1)	41(1)	22(3)	0(1)	2(1)	-1(1)
C(7)	26(1)	52(2)	30(3)	7(1)	4(1)	2(1)
C(8)	31(1)	50(2)	28(3)	9(1)	10(1)	12(1)
C(9)	33(1)	32(1)	21(3)	6(1)	8(1)	3(1)
C(10)	25(1)	29(1)	20(3)	2(1)	4(1)	1(1)
C(11)	27(1)	34(1)	22(3)	1(1)	2(1)	3(1)
C(12)	29(1)	38(1)	24(3)	-3(1)	5(1)	1(1)
C(13)	25(1)	69(2)	55(3)	-1(2)	-2(1)	6(1)
C(14)	29(1)	29(1)	22(3)	2(1)	4(1)	0(1)
C(15)	29(1)	35(1)	19(3)	1(1)	4(1)	-1(1)
C(16)	27(1)	34(1)	18(3)	-3(1)	4(1)	3(1)
C(17)	44(1)	29(1)	34(3)	3(1)	11(1)	5(1)
C(18)	32(1)	50(2)	34(3)	1(1)	2(1)	3(1)
C(19)	34(1)	96(3)	78(4)	29(2)	14(2)	2(2)
C(20)	39(1)	63(2)	72(4)	-12(2)	-4(2)	15(1)
C(21)	49(1)	32(1)	29(3)	-1(1)	4(1)	-3(1)
C(22)	71(2)	42(2)	36(3)	2(2)	4(2)	-2(1)
C(23)	52(2)	63(2)	64(4)	13(2)	12(2)	-16(1)
C(24)	43(1)	27(1)	32(3)	-2(1)	4(1)	-1(1)
C(25)	152(4)	34(2)	43(4)	-10(2)	-15(3)	15(2)
C(26)	44(2)	39(2)	116(4)	-14(2)	16(2)	6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for af2001.

	x	y	z	U(eq)
H(1A)	9791	14300	3170	69
H(1B)	9719	13980	3747	69
H(2A)	10233	10955	3385	56
H(3A)	8796	9746	3883	69
H(4A)	7405	12034	3879	71
H(5A)	7907	14815	3407	57
H(6A)	8349	13864	2601	37
H(7A)	9464	11666	2580	43
H(9A)	7065	8590	2655	34
H(11A)	6653	13457	2470	33
H(13A)	4024	12846	1540	75
H(13B)	3917	11518	1992	75
H(13C)	4156	10688	1478	75
H(14A)	7174	12572	1607	32
H(14B)	8267	12056	1876	32
H(15A)	7834	10379	1075	33
H(17A)	8153	6716	2104	43
H(17B)	6923	6816	2015	43
H(18A)	5498	6232	277	46
H(19A)	4572	5422	954	103
H(19B)	5599	5664	1302	103
H(19C)	5531	4074	906	103
H(20A)	4600	8584	656	87
H(20B)	5588	9402	416	87
H(20C)	5621	9084	987	87
H(21A)	7518	9462	289	44
H(22A)	7425	9073	-560	75
H(22B)	6408	8304	-334	75
H(22C)	7277	6920	-494	75
H(23A)	9072	9235	-100	89
H(23B)	9129	7096	18	89
H(23C)	9226	8555	448	89
H(24A)	7250	3261	695	40
H(25A)	7580	2202	-86	115
H(25B)	7727	4262	-262	115
H(25C)	6621	3584	-110	115
H(26A)	8960	2374	564	99
H(26B)	8954	3901	976	99
H(26C)	9248	4443	444	99

Table 6. Torsion angles [deg] for af2001.

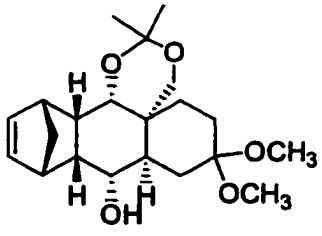
C(24)-Si-O(5)-C(16)	-170.2(2)
C(21)-Si-O(5)-C(16)	67.6(2)
C(18)-Si-O(5)-C(16)	-53.0(2)
C(5)-C(1)-C(2)-C(3)	-50.8(3)
C(5)-C(1)-C(2)-C(7)	57.9(3)
C(1)-C(2)-C(3)-C(4)	34.4(3)
C(7)-C(2)-C(3)-C(4)	-69.8(3)
C(2)-C(3)-C(4)-C(5)	-0.5(4)
C(3)-C(4)-C(5)-C(1)	-33.0(4)
C(3)-C(4)-C(5)-C(6)	70.2(3)
C(2)-C(1)-C(5)-C(4)	50.1(3)
C(2)-C(1)-C(5)-C(6)	-61.2(3)
C(4)-C(5)-C(6)-C(11)	66.3(3)
C(1)-C(5)-C(6)-C(11)	169.8(2)
C(4)-C(5)-C(6)-C(7)	-62.4(2)
C(1)-C(5)-C(6)-C(7)	41.1(3)
C(11)-C(6)-C(7)-C(8)	-7.6(4)
C(5)-C(6)-C(7)-C(8)	121.7(3)
C(11)-C(6)-C(7)-C(2)	-134.3(3)
C(5)-C(6)-C(7)-C(2)	-4.9(3)
C(3)-C(2)-C(7)-C(8)	-58.3(3)
C(1)-C(2)-C(7)-C(8)	-162.3(2)
C(3)-C(2)-C(7)-C(6)	70.6(3)
C(1)-C(2)-C(7)-C(6)	-33.5(3)
C(6)-C(7)-C(8)-O(1)	-160.6(3)
C(2)-C(7)-C(8)-O(1)	-39.9(4)
C(6)-C(7)-C(8)-C(9)	18.9(4)
C(2)-C(7)-C(8)-C(9)	139.6(3)
O(1)-C(8)-C(9)-C(17)	-40.9(4)
C(7)-C(8)-C(9)-C(17)	139.6(3)
O(1)-C(8)-C(9)-C(10)	-169.5(3)
C(7)-C(8)-C(9)-C(10)	11.0(4)
C(8)-C(9)-C(10)-C(14)	73.4(3)
C(17)-C(9)-C(10)-C(14)	-55.7(3)
C(8)-C(9)-C(10)-C(11)	-51.4(3)
C(17)-C(9)-C(10)-C(11)	179.58(18)
C(8)-C(9)-C(10)-C(12)	-167.2(2)
C(17)-C(9)-C(10)-C(12)	63.8(3)
C(14)-C(10)-C(11)-O(2)	173.71(17)
C(12)-C(10)-C(11)-O(2)	54.7(2)
C(9)-C(10)-C(11)-O(2)	-62.3(2)
C(14)-C(10)-C(11)-C(6)	-61.7(3)
C(12)-C(10)-C(11)-C(6)	179.3(2)
C(9)-C(10)-C(11)-C(6)	62.2(3)
C(5)-C(6)-C(11)-O(2)	-31.4(3)
C(7)-C(6)-C(11)-O(2)	90.2(3)
C(5)-C(6)-C(11)-C(10)	-153.9(2)
C(7)-C(6)-C(11)-C(10)	-32.2(3)
C(13)-O(3)-C(12)-O(4)	2.3(4)
C(13)-O(3)-C(12)-C(10)	-174.3(2)
C(14)-C(10)-C(12)-O(4)	129.0(3)
C(11)-C(10)-C(12)-O(4)	-110.0(3)
C(9)-C(10)-C(12)-O(4)	8.4(4)
C(14)-C(10)-C(12)-O(3)	-54.5(3)
C(11)-C(10)-C(12)-O(3)	66.5(3)
C(9)-C(10)-C(12)-O(3)	-175.0(2)

C(11)-C(10)-C(14)-C(15)	173.00(18)
C(12)-C(10)-C(14)-C(15)	-69.7(2)
C(9)-C(10)-C(14)-C(15)	49.3(3)
C(10)-C(14)-C(15)-C(16)	-20.6(3)
C(14)-C(15)-C(16)-O(5)	178.77(18)
C(14)-C(15)-C(16)-C(17)	-3.8(3)
Si-O(5)-C(16)-C(15)	-46.9(3)
Si-O(5)-C(16)-C(17)	135.4(2)
C(15)-C(16)-C(17)-C(9)	-2.2(3)
O(5)-C(16)-C(17)-C(9)	175.51(18)
C(8)-C(9)-C(17)-C(16)	-97.3(3)
C(10)-C(9)-C(17)-C(16)	31.9(3)
O(5)-Si-C(18)-C(20)	71.4(3)
C(24)-Si-C(18)-C(20)	-176.7(2)
C(21)-Si-C(18)-C(20)	-51.6(3)
O(5)-Si-C(18)-C(19)	-54.7(3)
C(24)-Si-C(18)-C(19)	57.2(3)
C(21)-Si-C(18)-C(19)	-177.7(2)
O(5)-Si-C(21)-C(23)	57.5(3)
C(24)-Si-C(21)-C(23)	-57.6(3)
C(18)-Si-C(21)-C(23)	179.5(2)
O(5)-Si-C(21)-C(22)	-173.81(19)
C(24)-Si-C(21)-C(22)	71.1(2)
C(18)-Si-C(21)-C(22)	-51.8(2)
O(5)-Si-C(24)-C(26)	-45.3(3)
C(21)-Si-C(24)-C(26)	75.6(3)
C(18)-Si-C(24)-C(26)	-162.7(2)
O(5)-Si-C(24)-C(25)	-172.8(2)
C(21)-Si-C(24)-C(25)	-51.9(3)
C(18)-Si-C(24)-C(25)	69.8(3)

Symmetry transformations used to generate equivalent atoms:

Appendix B

X-Ray Crystallographic Data for Compound **64**



64

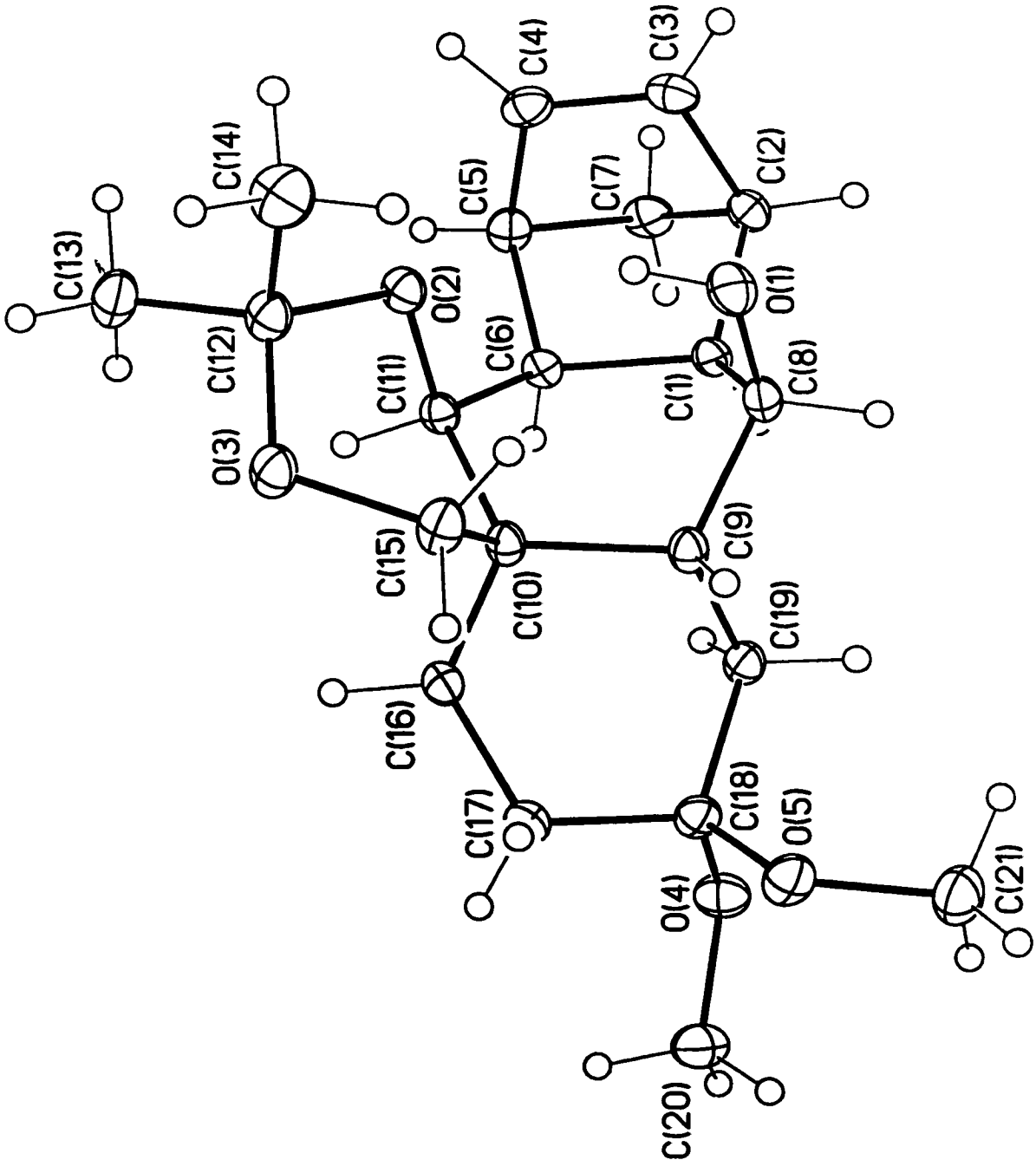

C(4)
C(3)
C(14)
C(5)
C(7)
C(2)
C(13)
O(2)
O(1)
C(12)
C(6)
C(11)
C(1)
C(8)
O(3)
C(15)
C(9)
C(10)
C(19)
C(16)
C(17)
C(18)
O(5)
O(4)
C(21)
C(20)

Table 1. Crystal data and structure refinement for af2005.

Identification code	af2005
Empirical formula	C21 H32 O5
Formula weight	364.47
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 17.291(2) A alpha = 90 deg. b = 6.4765(7) A beta = 110.558(2) deg c = 18.337(2) A gamma = 90 deg.
Volume	1922.8(4) A^3
Z, Calculated density	4, 1.259 Mg/m^3
Absorption coefficient	0.088 mm^-1
F(000)	792
Crystal size	0.20 x 0.20 x 0.20 mm
Theta range for data collection	1.39 to 28.50 deg.
Limiting indices	-23<=h<=21, 0<=k<=8, 0<=l<=24
Reflections collected / unique	16434 / 4550 [R(int) = 0.0259]
Completeness to theta = 28.50	93.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000000 and 0.919356
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4550 / 0 / 235
Goodness-of-fit on F^2	1.018
Final R indices [I>2sigma(I)]	R1 = 0.0462, wR2 = 0.1185
R indices (all data)	R1 = 0.0577, wR2 = 0.1262
Largest diff. peak and hole	0.298 and -0.231 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for af2005.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	4500(1)	4132(2)	2586(1)	32(1)
O(2)	3783(1)	8134(2)	2186(1)	26(1)
O(3)	3412(1)	8396(2)	825(1)	33(1)
O(4)	7225(1)	7330(2)	1442(1)	36(1)
O(5)	6345(1)	4585(2)	837(1)	33(1)
C(1)	5610(1)	6575(2)	3327(1)	24(1)
C(2)	5487(1)	6343(2)	4133(1)	30(1)
C(3)	4569(1)	6254(3)	4005(1)	33(1)
C(4)	4251(1)	8118(3)	3765(1)	31(1)
C(5)	4945(1)	9507(2)	3725(1)	28(1)
C(6)	5223(1)	8751(2)	3036(1)	23(1)
C(7)	5666(1)	8607(3)	4421(1)	32(1)
C(8)	5318(1)	4877(2)	2713(1)	26(1)
C(9)	5409(1)	5664(2)	1947(1)	25(1)
C(10)	4846(1)	7583(2)	1597(1)	24(1)
C(11)	4587(1)	8853(2)	2202(1)	22(1)
C(12)	3124(1)	8618(2)	1465(1)	29(1)
C(13)	2843(1)	10851(3)	1449(1)	38(1)
C(14)	2435(1)	7090(3)	1403(1)	42(1)
C(15)	4034(1)	6816(2)	979(1)	31(1)
C(16)	5291(1)	9061(2)	1210(1)	30(1)
C(17)	5729(1)	7878(3)	739(1)	35(1)
C(18)	6417(1)	6461(2)	1265(1)	28(1)
C(19)	6318(1)	6109(2)	2053(1)	27(1)
C(20)	7487(1)	7598(3)	784(1)	41(1)
C(21)	6959(1)	3048(3)	1191(1)	43(1)

Table 3. Bond lengths [A] and angles [deg] for af2005.

O(1)-C(8)	1.4343(18)
O(2)-C(12)	1.4449(16)
O(2)-C(11)	1.4552(16)
O(3)-C(12)	1.4325(17)
O(3)-C(15)	1.4392(17)
O(4)-C(18)	1.4338(18)
O(4)-C(20)	1.4385(18)
O(5)-C(18)	1.4278(18)
O(5)-C(21)	1.434(2)
C(1)-C(8)	1.5278(19)
C(1)-C(2)	1.5720(18)
C(1)-C(6)	1.5713(19)
C(2)-C(3)	1.522(2)
C(2)-C(7)	1.552(2)
C(3)-C(4)	1.336(2)
C(4)-C(5)	1.523(2)
C(5)-C(7)	1.551(2)
C(5)-C(6)	1.5790(18)
C(6)-C(11)	1.5406(18)
C(8)-C(9)	1.5519(19)
C(9)-C(19)	1.542(2)
C(9)-C(10)	1.5696(18)
C(10)-C(15)	1.5447(19)
C(10)-C(16)	1.547(2)
C(10)-C(11)	1.5678(18)
C(12)-C(14)	1.522(2)
C(12)-C(13)	1.523(2)
C(16)-C(17)	1.538(2)
C(17)-C(18)	1.544(2)
C(18)-C(19)	1.5318(19)

C(12)-O(2)-C(11)	112.97(10)
C(12)-O(3)-C(15)	111.24(11)
C(18)-O(4)-C(20)	115.20(12)
C(18)-O(5)-C(21)	115.70(11)
C(8)-C(1)-C(2)	120.39(12)
C(8)-C(1)-C(6)	113.85(10)
C(2)-C(1)-C(6)	102.85(11)
C(3)-C(2)-C(7)	99.21(12)
C(3)-C(2)-C(1)	109.69(11)
C(7)-C(2)-C(1)	98.83(11)
C(4)-C(3)-C(2)	107.69(14)
C(3)-C(4)-C(5)	107.99(13)
C(4)-C(5)-C(7)	99.07(12)
C(4)-C(5)-C(6)	108.83(11)
C(7)-C(5)-C(6)	99.13(11)
C(11)-C(6)-C(1)	116.49(11)
C(11)-C(6)-C(5)	117.94(11)
C(1)-C(6)-C(5)	102.71(10)
C(5)-C(7)-C(2)	93.93(11)
O(1)-C(8)-C(1)	114.40(11)
O(1)-C(8)-C(9)	111.81(11)
C(1)-C(8)-C(9)	108.57(11)
C(19)-C(9)-C(8)	111.68(11)
C(19)-C(9)-C(10)	111.22(11)
C(8)-C(9)-C(10)	112.63(11)

C(15)-C(10)-C(16)	109.37(11)
C(15)-C(10)-C(11)	106.03(11)
C(16)-C(10)-C(11)	108.18(11)
C(15)-C(10)-C(9)	108.57(11)
C(16)-C(10)-C(9)	109.93(11)
C(11)-C(10)-C(9)	114.62(10)
O(2)-C(11)-C(6)	110.55(10)
O(2)-C(11)-C(10)	109.01(10)
C(6)-C(11)-C(10)	113.43(11)
O(3)-C(12)-O(2)	109.74(11)
O(3)-C(12)-C(14)	111.18(12)
O(2)-C(12)-C(14)	105.83(12)
O(3)-C(12)-C(13)	106.30(12)
O(2)-C(12)-C(13)	111.52(12)
C(14)-C(12)-C(13)	112.32(13)
O(3)-C(15)-C(10)	109.82(12)
C(17)-C(16)-C(10)	111.84(13)
C(16)-C(17)-C(18)	111.66(12)
O(5)-C(18)-O(4)	110.41(11)
O(5)-C(18)-C(19)	112.02(12)
O(4)-C(18)-C(19)	105.59(11)
O(5)-C(18)-C(17)	105.26(11)
O(4)-C(18)-C(17)	112.57(13)
C(19)-C(18)-C(17)	111.14(11)
C(18)-C(19)-C(9)	110.86(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for af2005. 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)	35(1)	24(1)	37(1)	1(1)	11(1)	-4(1)
O(2)	23(1)	29(1)	21(1)	1(1)	3(1)	0(1)
O(3)	32(1)	40(1)	21(1)	0(1)	3(1)	11(1)
O(4)	35(1)	44(1)	28(1)	-4(1)	12(1)	-5(1)
O(5)	34(1)	36(1)	26(1)	-7(1)	7(1)	5(1)
C(1)	24(1)	27(1)	19(1)	3(1)	6(1)	2(1)
C(2)	32(1)	36(1)	20(1)	6(1)	8(1)	6(1)
C(3)	36(1)	39(1)	27(1)	3(1)	15(1)	-3(1)
C(4)	28(1)	41(1)	24(1)	-3(1)	11(1)	1(1)
C(5)	33(1)	28(1)	22(1)	-5(1)	8(1)	1(1)
C(6)	24(1)	22(1)	20(1)	-2(1)	6(1)	-2(1)
C(7)	31(1)	43(1)	19(1)	-3(1)	6(1)	-1(1)
C(8)	30(1)	21(1)	26(1)	2(1)	8(1)	4(1)
C(9)	29(1)	21(1)	20(1)	-1(1)	6(1)	5(1)
C(10)	28(1)	22(1)	19(1)	-1(1)	5(1)	4(1)
C(11)	25(1)	21(1)	19(1)	0(1)	5(1)	1(1)
C(12)	25(1)	34(1)	22(1)	-1(1)	2(1)	3(1)
C(13)	35(1)	40(1)	34(1)	1(1)	7(1)	13(1)
C(14)	29(1)	51(1)	38(1)	-2(1)	2(1)	-6(1)
C(15)	31(1)	35(1)	21(1)	-6(1)	1(1)	8(1)
C(16)	37(1)	30(1)	26(1)	7(1)	14(1)	9(1)
C(17)	38(1)	44(1)	24(1)	8(1)	13(1)	13(1)
C(18)	29(1)	33(1)	21(1)	-3(1)	8(1)	3(1)
C(19)	28(1)	31(1)	20(1)	0(1)	6(1)	7(1)
C(20)	43(1)	46(1)	40(1)	-1(1)	23(1)	-1(1)
C(21)	50(1)	34(1)	42(1)	-2(1)	15(1)	9(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for af2005.

	x	y	z	U(eq)
H(1A)	4169	5107	2457	48
H(1B)	6212	6718	3446	29
H(2A)	5833	5280	4486	35
H(3A)	4279	5096	4081	39
H(4A)	3695	8504	3643	37
H(5A)	4850	11010	3745	34
H(6A)	5687	9656	3043	27
H(7A)	5599	8839	4924	38
H(7B)	6209	9095	4439	38
H(8A)	5700	3694	2897	31
H(9A)	5221	4535	1561	29
H(11A)	4529	10317	2036	27
H(13A)	3304	11766	1506	56
H(13B)	2642	11081	1874	56
H(13C)	2403	11127	958	56
H(14A)	2646	5693	1430	63
H(14B)	1987	7287	910	63
H(14C)	2234	7317	1828	63
H(15A)	4130	6471	497	37
H(15B)	3845	5566	1167	37
H(16A)	4886	10012	864	37
H(16B)	5697	9882	1613	37
H(17A)	5969	8868	474	42
H(17B)	5324	7042	340	42
H(19A)	6506	7337	2380	33
H(19B)	6662	4940	2319	33
H(20A)	8036	8194	957	61
H(20B)	7105	8511	408	61
H(20C)	7495	6268	544	61
H(21A)	6859	1841	858	64
H(21B)	6932	2663	1693	64
H(21C)	7503	3600	1263	64

Table 6. Torsion angles [deg] for af2005.

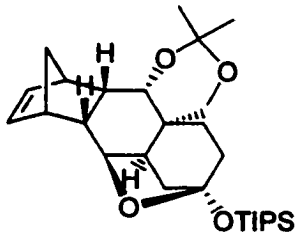
C(8)-C(1)-C(2)-C(3)	-63.07(17)
C(6)-C(1)-C(2)-C(3)	64.86(14)
C(8)-C(1)-C(2)-C(7)	-166.23(12)
C(6)-C(1)-C(2)-C(7)	-38.31(13)
C(7)-C(2)-C(3)-C(4)	33.92(14)
C(1)-C(2)-C(3)-C(4)	-68.98(16)
C(2)-C(3)-C(4)-C(5)	0.03(16)
C(3)-C(4)-C(5)-C(7)	-33.98(15)
C(3)-C(4)-C(5)-C(6)	68.98(15)
C(8)-C(1)-C(6)-C(11)	2.62(17)
C(2)-C(1)-C(6)-C(11)	-129.31(12)
C(8)-C(1)-C(6)-C(5)	133.08(12)
C(2)-C(1)-C(6)-C(5)	1.16(13)
C(4)-C(5)-C(6)-C(11)	63.10(15)
C(7)-C(5)-C(6)-C(11)	166.01(12)
C(4)-C(5)-C(6)-C(1)	-66.47(13)
C(7)-C(5)-C(6)-C(1)	36.44(13)
C(4)-C(5)-C(7)-C(2)	51.12(12)
C(6)-C(5)-C(7)-C(2)	-59.77(12)
C(3)-C(2)-C(7)-C(5)	-51.22(12)
C(1)-C(2)-C(7)-C(5)	60.54(12)
C(2)-C(1)-C(8)-O(1)	46.54(17)
C(6)-C(1)-C(8)-O(1)	-76.23(15)
C(2)-C(1)-C(8)-C(9)	172.17(11)
C(6)-C(1)-C(8)-C(9)	49.41(15)
O(1)-C(8)-C(9)-C(19)	-170.12(11)
C(1)-C(8)-C(9)-C(19)	62.75(14)
O(1)-C(8)-C(9)-C(10)	63.89(15)
C(1)-C(8)-C(9)-C(10)	-63.24(14)
C(19)-C(9)-C(10)-C(15)	138.43(12)
C(8)-C(9)-C(10)-C(15)	-95.34(13)
C(19)-C(9)-C(10)-C(16)	18.83(15)
C(8)-C(9)-C(10)-C(16)	145.07(12)
C(19)-C(9)-C(10)-C(11)	-103.26(13)
C(8)-C(9)-C(10)-C(11)	22.98(16)
C(12)-O(2)-C(11)-C(6)	167.02(11)
C(12)-O(2)-C(11)-C(10)	-67.65(13)
C(1)-C(6)-C(11)-O(2)	79.90(14)
C(5)-C(6)-C(11)-O(2)	-42.94(15)
C(1)-C(6)-C(11)-C(10)	-42.88(16)
C(5)-C(6)-C(11)-C(10)	-165.73(11)
C(15)-C(10)-C(11)-O(2)	25.10(14)
C(16)-C(10)-C(11)-O(2)	142.32(11)
C(9)-C(10)-C(11)-O(2)	-94.64(13)
C(15)-C(10)-C(11)-C(6)	148.73(12)
C(16)-C(10)-C(11)-C(6)	-94.05(13)
C(9)-C(10)-C(11)-C(6)	28.99(16)
C(15)-O(3)-C(12)-O(2)	31.16(16)
C(15)-O(3)-C(12)-C(14)	-85.58(15)
C(15)-O(3)-C(12)-C(13)	151.89(12)
C(11)-O(2)-C(12)-O(3)	37.64(15)
C(11)-O(2)-C(12)-C(14)	157.69(12)
C(11)-O(2)-C(12)-C(13)	-79.88(14)
C(12)-O(3)-C(15)-C(10)	-72.19(15)
C(16)-C(10)-C(15)-O(3)	-78.01(14)
C(11)-C(10)-C(15)-O(3)	38.42(15)

C(9)-C(10)-C(15)-O(3)	162.04(11)
C(15)-C(10)-C(16)-C(17)	-77.09(14)
C(11)-C(10)-C(16)-C(17)	167.86(11)
C(9)-C(10)-C(16)-C(17)	42.02(15)
C(10)-C(16)-C(17)-C(18)	-62.85(17)
C(21)-O(5)-C(18)-O(4)	54.64(16)
C(21)-O(5)-C(18)-C(19)	-62.73(16)
C(21)-O(5)-C(18)-C(17)	176.37(13)
C(20)-O(4)-C(18)-O(5)	52.69(17)
C(20)-O(4)-C(18)-C(19)	173.96(13)
C(20)-O(4)-C(18)-C(17)	-64.61(16)
C(16)-C(17)-C(18)-O(5)	138.32(13)
C(16)-C(17)-C(18)-O(4)	-101.36(15)
C(16)-C(17)-C(18)-C(19)	16.84(19)
O(5)-C(18)-C(19)-C(9)	-73.20(14)
O(4)-C(18)-C(19)-C(9)	166.57(11)
C(17)-C(18)-C(19)-C(9)	44.23(16)
C(8)-C(9)-C(19)-C(18)	168.62(11)
C(10)-C(9)-C(19)-C(18)	-64.61(14)

Symmetry transformations used to generate equivalent atoms:

Appendix C

X-Ray Crystallographic Data for Compound **67**



67

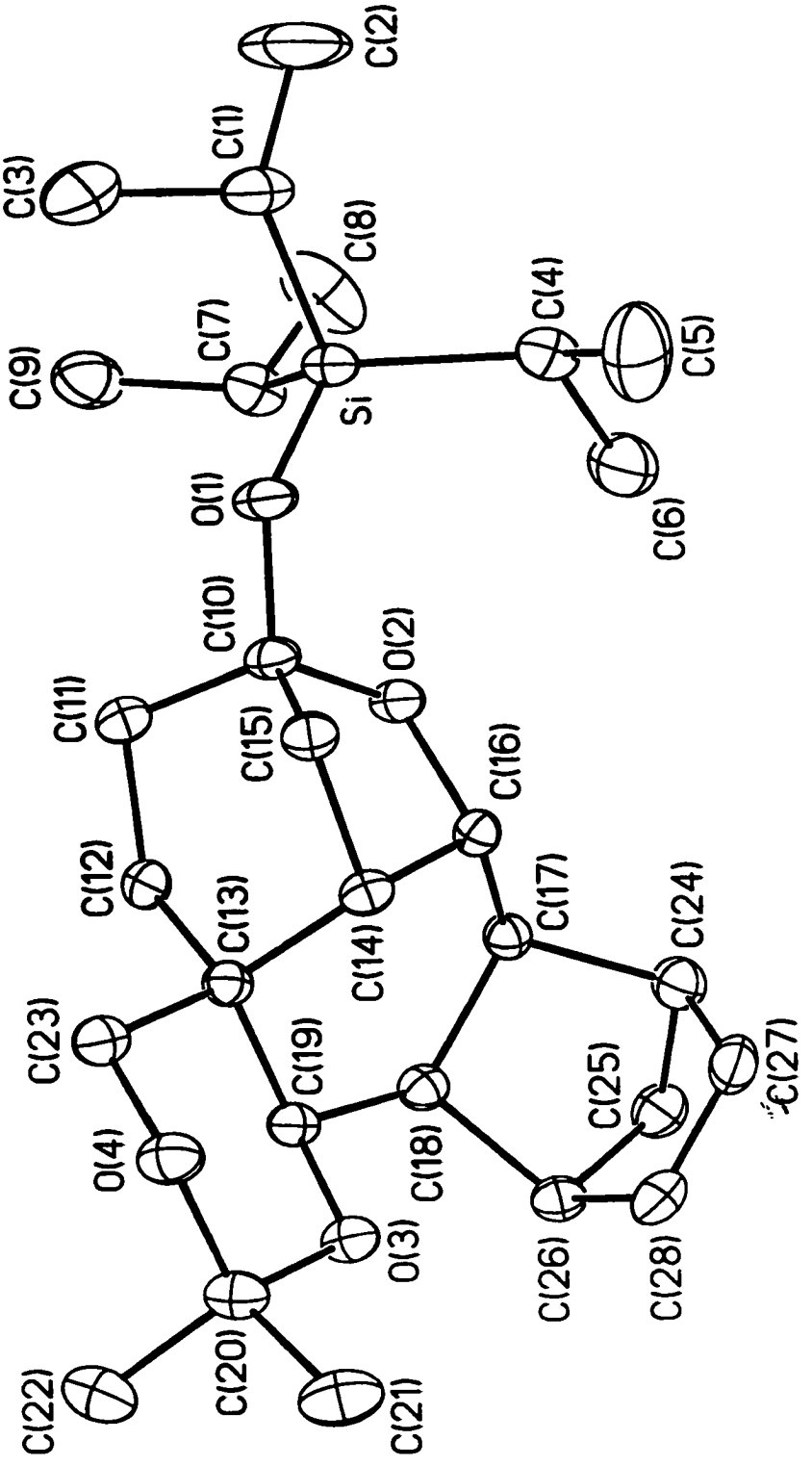

C(2)
C(1)
C(3)
C(8)
C(7)
C(4)
C(9)
Si
C(5)
O(1)
C(6)
C(10)
O(2)
C(11)
C(15)
C(16)
C(12)
C(13)
C(14)
C(17)
C(24)
C(23)
C(19)
C(25)
C(27)
O(4)
C(18)
O(3)
C(26)
C(28)
C(22)
C(20)
C(21)

Table 1. Crystal data and structure refinement for af2003.

Identification code	af2003
Empirical formula	C28 H46 O4 Si
Formula weight	474.74
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 27.085(7) A alpha = 90 deg. b = 8.887(2) A beta = 99.278(5) deg. c = 23.472(7) A gamma = 90 deg.
Volume	5576(3) A^3
Z, Calculated density	8, 1.131 Mg/m^3
Absorption coefficient	0.113 mm^-1
F(000)	2080
Crystal size	0.10 x 0.10 x 0.10 mm
Theta range for data collection	2.13 to 20.82 deg.
Limiting indices	-26<=h<=26, 0<=k<=8, 0<=l<=23
Reflections collected / unique	7853 / 2855 [R(int) = 0.0275]
Completeness to theta = 20.82	98.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000000 and 0.881946
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2855 / 0 / 298
Goodness-of-fit on F^2	1.008
Final R indices [I>2sigma(I)]	R1 = 0.0409, wR2 = 0.0997
R indices (all data)	R1 = 0.0572, wR2 = 0.1106
Largest diff. peak and hole	0.200 and -0.277 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for af2003.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Si	3145(1)	2980(1)	1432(1)	36(1)
O(1)	3607(1)	3530(2)	1093(1)	41(1)
O(2)	4245(1)	1846(2)	1473(1)	33(1)
O(3)	5913(1)	1818(2)	884(1)	34(1)
O(4)	5584(1)	3783(2)	264(1)	38(1)
C(1)	2603(1)	4044(4)	1001(2)	56(1)
C(2)	2103(1)	3825(6)	1194(2)	120(2)
C(3)	2702(1)	5701(4)	896(2)	81(1)
C(4)	2996(1)	898(4)	1355(1)	51(1)
C(5)	2938(2)	368(5)	725(2)	92(1)
C(6)	3347(1)	-198(4)	1746(2)	79(1)
C(7)	3290(1)	3484(4)	2227(1)	49(1)
C(8)	2909(2)	2810(5)	2587(2)	93(2)
C(9)	3349(1)	5187(4)	2351(2)	65(1)
C(10)	4126(1)	3233(3)	1155(1)	33(1)
C(11)	4433(1)	4497(3)	1485(1)	39(1)
C(12)	4991(1)	4016(3)	1628(1)	35(1)
C(13)	5194(1)	3233(3)	1118(1)	30(1)
C(14)	4795(1)	2152(3)	789(1)	28(1)
C(15)	4298(1)	2961(3)	578(1)	34(1)
C(16)	4617(1)	1009(3)	1205(1)	30(1)
C(17)	5016(1)	335(3)	1675(1)	31(1)
C(18)	5571(1)	949(3)	1725(1)	31(1)
C(19)	5670(1)	2329(3)	1356(1)	31(1)
C(20)	6028(1)	2949(3)	489(1)	37(1)
C(21)	6166(1)	2088(4)	-23(1)	51(1)
C(22)	6454(1)	3993(4)	759(1)	52(1)
C(23)	5347(1)	4445(3)	712(1)	38(1)
C(24)	5091(1)	-1411(3)	1611(1)	42(1)
C(25)	5606(1)	-1637(4)	1997(1)	47(1)
C(26)	5875(1)	-524(3)	1641(1)	37(1)
C(27)	5234(1)	-1666(3)	1020(1)	44(1)
C(28)	5698(1)	-1137(3)	1036(1)	42(1)

Table 3. Bond lengths [A] and angles [deg] for af2003.

Si-O(1)	1.661(2)
Si-C(1)	1.895(3)
Si-C(4)	1.897(3)
Si-C(7)	1.899(3)
O(1)-C(10)	1.414(3)
O(2)-C(10)	1.450(3)
O(2)-C(16)	1.473(3)
O(3)-C(20)	1.437(3)
O(3)-C(19)	1.449(3)
O(4)-C(20)	1.439(3)
O(4)-C(23)	1.443(3)
C(1)-C(2)	1.508(5)
C(1)-C(3)	1.524(5)
C(4)-C(5)	1.538(5)
C(4)-C(6)	1.552(5)
C(7)-C(9)	1.544(5)
C(7)-C(8)	1.555(5)
C(10)-C(15)	1.521(4)
C(10)-C(11)	1.532(4)
C(11)-C(12)	1.553(4)
C(12)-C(13)	1.560(4)
C(13)-C(23)	1.538(4)
C(13)-C(19)	1.544(4)
C(13)-C(14)	1.557(4)
C(14)-C(15)	1.535(4)
C(14)-C(16)	1.538(4)
C(16)-C(17)	1.535(4)
C(17)-C(24)	1.575(4)
C(17)-C(18)	1.587(4)
C(18)-C(19)	1.550(4)
C(18)-C(26)	1.575(4)
C(20)-C(21)	1.521(4)
C(20)-C(22)	1.534(4)
C(24)-C(27)	1.517(4)
C(24)-C(25)	1.548(4)
C(25)-C(26)	1.550(4)
C(26)-C(28)	1.524(4)
C(27)-C(28)	1.338(4)
O(1)-Si-C(1)	100.18(13)
O(1)-Si-C(4)	114.05(13)
C(1)-Si-C(4)	107.55(15)
O(1)-Si-C(7)	110.47(13)
C(1)-Si-C(7)	115.20(16)
C(4)-Si-C(7)	109.25(15)
C(10)-O(1)-Si	135.08(18)
C(10)-O(2)-C(16)	108.61(19)
C(20)-O(3)-C(19)	116.6(2)
C(20)-O(4)-C(23)	112.7(2)
C(2)-C(1)-C(3)	111.3(3)
C(2)-C(1)-Si	115.6(3)
C(3)-C(1)-Si	115.3(2)
C(5)-C(4)-C(6)	109.5(3)
C(5)-C(4)-Si	112.1(3)
C(6)-C(4)-Si	117.1(2)
C(9)-C(7)-C(8)	109.4(3)

C(9)-C(7)-Si	114.5(2)
C(8)-C(7)-Si	113.2(2)
O(1)-C(10)-O(2)	110.3(2)
O(1)-C(10)-C(15)	112.3(2)
O(2)-C(10)-C(15)	104.5(2)
O(1)-C(10)-C(11)	111.4(2)
O(2)-C(10)-C(11)	107.8(2)
C(15)-C(10)-C(11)	110.4(2)
C(10)-C(11)-C(12)	109.6(2)
C(11)-C(12)-C(13)	114.2(2)
C(23)-C(13)-C(19)	107.2(2)
C(23)-C(13)-C(14)	111.1(2)
C(19)-C(13)-C(14)	109.4(2)
C(23)-C(13)-C(12)	109.0(2)
C(19)-C(13)-C(12)	109.4(2)
C(14)-C(13)-C(12)	110.6(2)
C(15)-C(14)-C(16)	99.6(2)
C(15)-C(14)-C(13)	112.0(2)
C(16)-C(14)-C(13)	110.9(2)
C(10)-C(15)-C(14)	99.5(2)
O(2)-C(16)-C(17)	109.9(2)
O(2)-C(16)-C(14)	104.1(2)
C(17)-C(16)-C(14)	117.3(2)
C(16)-C(17)-C(24)	113.7(2)
C(16)-C(17)-C(18)	117.9(2)
C(24)-C(17)-C(18)	102.1(2)
C(19)-C(18)-C(26)	116.6(2)
C(19)-C(18)-C(17)	118.5(2)
C(26)-C(18)-C(17)	102.3(2)
O(3)-C(19)-C(13)	109.9(2)
O(3)-C(19)-C(18)	108.6(2)
C(13)-C(19)-C(18)	113.9(2)
O(3)-C(20)-O(4)	109.9(2)
O(3)-C(20)-C(21)	105.4(2)
O(4)-C(20)-C(21)	105.5(2)
O(3)-C(20)-C(22)	112.5(2)
O(4)-C(20)-C(22)	111.6(2)
C(21)-C(20)-C(22)	111.5(2)
O(4)-C(23)-C(13)	111.2(2)
C(27)-C(24)-C(25)	100.2(2)
C(27)-C(24)-C(17)	106.9(2)
C(25)-C(24)-C(17)	101.0(2)
C(24)-C(25)-C(26)	93.4(2)
C(28)-C(26)-C(25)	99.7(2)
C(28)-C(26)-C(18)	108.8(2)
C(25)-C(26)-C(18)	99.3(2)
C(28)-C(27)-C(24)	107.3(3)
C(27)-C(28)-C(26)	107.8(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for af2003. 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
Si	26(1)	42(1)	41(1)	1(1)	5(1)	3(1)
O(1)	25(1)	48(1)	49(1)	10(1)	10(1)	9(1)
O(2)	28(1)	37(1)	36(1)	6(1)	8(1)	4(1)
O(3)	30(1)	39(1)	35(1)	3(1)	9(1)	6(1)
O(4)	33(1)	46(1)	38(1)	8(1)	11(1)	6(1)
C(1)	31(2)	63(3)	72(2)	5(2)	3(2)	8(2)
C(2)	31(2)	148(5)	183(5)	63(4)	19(3)	19(3)
C(3)	56(3)	66(3)	116(4)	20(3)	-2(2)	18(2)
C(4)	39(2)	53(2)	60(2)	0(2)	10(2)	-3(2)
C(5)	131(4)	66(3)	85(3)	-27(2)	34(3)	-14(3)
C(6)	59(3)	55(3)	120(4)	25(2)	1(2)	-3(2)
C(7)	40(2)	59(2)	48(2)	-3(2)	9(2)	-5(2)
C(8)	98(3)	134(4)	53(3)	-16(3)	27(2)	-54(3)
C(9)	49(2)	77(3)	71(3)	-23(2)	16(2)	-1(2)
C(10)	25(2)	37(2)	37(2)	5(2)	4(1)	6(2)
C(11)	35(2)	40(2)	45(2)	-4(2)	13(2)	5(2)
C(12)	34(2)	32(2)	39(2)	-6(2)	8(1)	-1(2)
C(13)	27(2)	32(2)	32(2)	1(1)	7(1)	1(1)
C(14)	27(2)	33(2)	25(2)	0(1)	5(1)	5(1)
C(15)	29(2)	37(2)	34(2)	2(2)	2(1)	3(2)
C(16)	30(2)	29(2)	32(2)	-3(1)	5(1)	1(1)
C(17)	30(2)	31(2)	32(2)	1(1)	4(1)	0(1)
C(18)	29(2)	34(2)	29(2)	-1(1)	1(1)	2(1)
C(19)	25(2)	37(2)	30(2)	-3(1)	5(1)	0(1)
C(20)	28(2)	47(2)	37(2)	4(2)	6(2)	4(2)
C(21)	42(2)	72(3)	41(2)	3(2)	15(2)	13(2)
C(22)	38(2)	65(2)	54(2)	8(2)	11(2)	-7(2)
C(23)	32(2)	37(2)	47(2)	3(2)	9(2)	3(2)
C(24)	39(2)	34(2)	52(2)	8(2)	4(2)	0(2)
C(25)	44(2)	37(2)	57(2)	10(2)	3(2)	10(2)
C(26)	28(2)	39(2)	43(2)	2(2)	0(1)	5(2)
C(27)	44(2)	30(2)	55(2)	-7(2)	-1(2)	5(2)
C(28)	44(2)	35(2)	47(2)	-3(2)	8(2)	13(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for af2003.

	x	y	z	U(eq)
H(1A)	2561	3582	613	67
H(2A)	1850	4390	943	181
H(2B)	2121	4179	1588	181
H(2C)	2017	2765	1175	181
H(3A)	2406	6150	673	121
H(3B)	2980	5790	684	121
H(3C)	2783	6218	1263	121
H(4A)	2662	776	1470	61
H(5A)	2862	-700	705	138
H(5B)	3247	549	577	138
H(5C)	2668	920	494	138
H(6A)	3234	-1224	1666	119
H(6B)	3339	36	2148	119
H(6C)	3685	-89	1667	119
H(7A)	3618	3020	2377	59
H(8A)	3003	3098	2989	140
H(8B)	2910	1722	2556	140
H(8C)	2577	3190	2442	140
H(9A)	3424	5350	2764	98
H(9B)	3040	5699	2196	98
H(9C)	3619	5581	2170	98
H(11A)	4304	4712	1844	47
H(11B)	4404	5415	1251	47
H(12A)	5030	3327	1958	42
H(12B)	5194	4910	1743	42
H(14A)	4922	1639	467	34
H(15A)	4349	3906	380	40
H(15B)	4064	2321	324	40
H(16A)	4444	175	974	36
H(17A)	4904	509	2051	37
H(18A)	5673	1252	2133	38
H(19A)	5904	3010	1601	37
H(21A)	5890	1442	-184	77
H(21B)	6461	1479	104	77
H(21C)	6236	2794	-315	77
H(22A)	6357	4505	1089	78
H(22B)	6520	4729	476	78
H(22C)	6753	3403	883	78
H(23A)	5050	5006	536	46
H(23B)	5579	5155	936	46
H(24A)	4816	-2051	1706	51
H(25A)	5731	-2669	1987	56
H(25B)	5610	-1308	2396	56
H(26A)	6242	-451	1758	45
H(27A)	5033	-2113	700	53
H(28A)	5882	-1142	729	50

Table 6. Torsion angles [deg] for af2003.

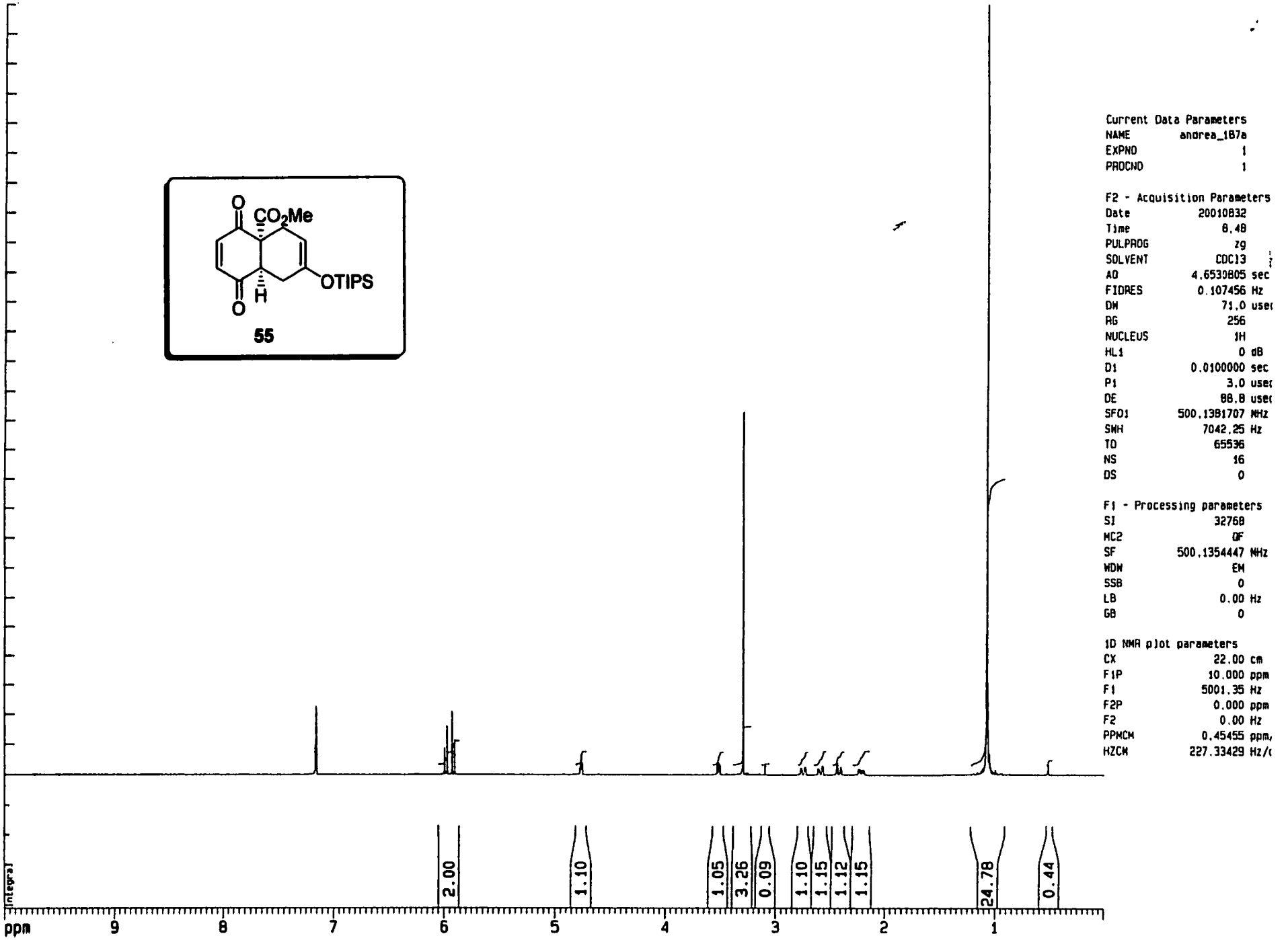
C(1)-Si-O(1)-C(10)	-180.0(3)
C(4)-Si-O(1)-C(10)	-65.4(3)
C(7)-Si-O(1)-C(10)	58.1(3)
O(1)-Si-C(1)-C(2)	-179.5(3)
C(4)-Si-C(1)-C(2)	61.0(4)
C(7)-Si-C(1)-C(2)	-61.0(4)
O(1)-Si-C(1)-C(3)	-47.3(3)
C(4)-Si-C(1)-C(3)	-166.7(3)
C(7)-Si-C(1)-C(3)	71.2(3)
O(1)-Si-C(4)-C(5)	-48.8(3)
C(1)-Si-C(4)-C(5)	61.3(3)
C(7)-Si-C(4)-C(5)	-173.0(3)
O(1)-Si-C(4)-C(6)	79.0(3)
C(1)-Si-C(4)-C(6)	-170.9(3)
C(7)-Si-C(4)-C(6)	-45.2(3)
O(1)-Si-C(7)-C(9)	61.6(3)
C(1)-Si-C(7)-C(9)	-51.0(3)
C(4)-Si-C(7)-C(9)	-172.2(2)
O(1)-Si-C(7)-C(8)	-172.1(3)
C(1)-Si-C(7)-C(8)	75.3(3)
C(4)-Si-C(7)-C(8)	-45.8(3)
Si-O(1)-C(10)-O(2)	20.5(4)
Si-O(1)-C(10)-C(15)	136.5(2)
Si-O(1)-C(10)-C(11)	-99.2(3)
C(16)-O(2)-C(10)-O(1)	139.5(2)
C(16)-O(2)-C(10)-C(15)	18.7(3)
C(16)-O(2)-C(10)-C(11)	-98.7(2)
O(1)-C(10)-C(11)-C(12)	171.2(2)
O(2)-C(10)-C(11)-C(12)	50.1(3)
C(15)-C(10)-C(11)-C(12)	-63.4(3)
C(10)-C(11)-C(12)-C(13)	43.5(3)
C(11)-C(12)-C(13)-C(23)	82.7(3)
C(11)-C(12)-C(13)-C(19)	-160.4(2)
C(11)-C(12)-C(13)-C(14)	-39.8(3)
C(23)-C(13)-C(14)-C(15)	-65.9(3)
C(19)-C(13)-C(14)-C(15)	175.9(2)
C(12)-C(13)-C(14)-C(15)	55.4(3)
C(23)-C(13)-C(14)-C(16)	-176.2(2)
C(19)-C(13)-C(14)-C(16)	65.7(3)
C(12)-C(13)-C(14)-C(16)	-54.9(3)
O(1)-C(10)-C(15)-C(14)	-161.0(2)
O(2)-C(10)-C(15)-C(14)	-41.5(3)
C(11)-C(10)-C(15)-C(14)	74.2(3)
C(16)-C(14)-C(15)-C(10)	47.3(2)
C(13)-C(14)-C(15)-C(10)	-70.0(3)
C(10)-O(2)-C(16)-C(17)	138.3(2)
C(10)-O(2)-C(16)-C(14)	11.9(3)
C(15)-C(14)-C(16)-O(2)	-37.1(2)
C(13)-C(14)-C(16)-O(2)	81.0(2)
C(15)-C(14)-C(16)-C(17)	-158.6(2)
C(13)-C(14)-C(16)-C(17)	-40.5(3)
O(2)-C(16)-C(17)-C(24)	126.3(2)
C(14)-C(16)-C(17)-C(24)	-115.2(3)
O(2)-C(16)-C(17)-C(18)	-114.2(2)
C(14)-C(16)-C(17)-C(18)	4.3(4)
C(16)-C(17)-C(18)-C(19)	7.9(4)

C(24)-C(17)-C(18)-C(19)	133.3(2)
C(16)-C(17)-C(18)-C(26)	-121.8(3)
C(24)-C(17)-C(18)-C(26)	3.6(3)
C(20)-O(3)-C(19)-C(13)	54.0(3)
C(20)-O(3)-C(19)-C(18)	179.2(2)
C(23)-C(13)-C(19)-O(3)	-51.8(3)
C(14)-C(13)-C(19)-O(3)	68.8(3)
C(12)-C(13)-C(19)-O(3)	-169.9(2)
C(23)-C(13)-C(19)-C(18)	-174.0(2)
C(14)-C(13)-C(19)-C(18)	-53.4(3)
C(12)-C(13)-C(19)-C(18)	67.9(3)
C(26)-C(18)-C(19)-O(3)	17.2(3)
C(17)-C(18)-C(19)-O(3)	-105.6(3)
C(26)-C(18)-C(19)-C(13)	140.1(2)
C(17)-C(18)-C(19)-C(13)	17.3(3)
C(19)-O(3)-C(20)-O(4)	-54.5(3)
C(19)-O(3)-C(20)-C(21)	-167.7(2)
C(19)-O(3)-C(20)-C(22)	70.6(3)
C(23)-O(4)-C(20)-O(3)	55.8(3)
C(23)-O(4)-C(20)-C(21)	169.0(2)
C(23)-O(4)-C(20)-C(22)	-69.7(3)
C(20)-O(4)-C(23)-C(13)	-59.6(3)
C(19)-C(13)-C(23)-O(4)	56.0(3)
C(14)-C(13)-C(23)-O(4)	-63.5(3)
C(12)-C(13)-C(23)-O(4)	174.3(2)
C(16)-C(17)-C(24)-C(27)	58.1(3)
C(18)-C(17)-C(24)-C(27)	-70.0(3)
C(16)-C(17)-C(24)-C(25)	162.4(2)
C(18)-C(17)-C(24)-C(25)	34.3(3)
C(27)-C(24)-C(25)-C(26)	50.9(3)
C(17)-C(24)-C(25)-C(26)	-58.7(2)
C(24)-C(25)-C(26)-C(28)	-50.4(3)
C(24)-C(25)-C(26)-C(18)	60.6(2)
C(19)-C(18)-C(26)-C(28)	-67.4(3)
C(17)-C(18)-C(26)-C(28)	63.5(3)
C(19)-C(18)-C(26)-C(25)	-171.1(2)
C(17)-C(18)-C(26)-C(25)	-40.2(3)
C(25)-C(24)-C(27)-C(28)	-34.0(3)
C(17)-C(24)-C(27)-C(28)	70.8(3)
C(24)-C(27)-C(28)-C(26)	0.2(3)
C(25)-C(26)-C(28)-C(27)	33.6(3)
C(18)-C(26)-C(28)-C(27)	-69.9(3)

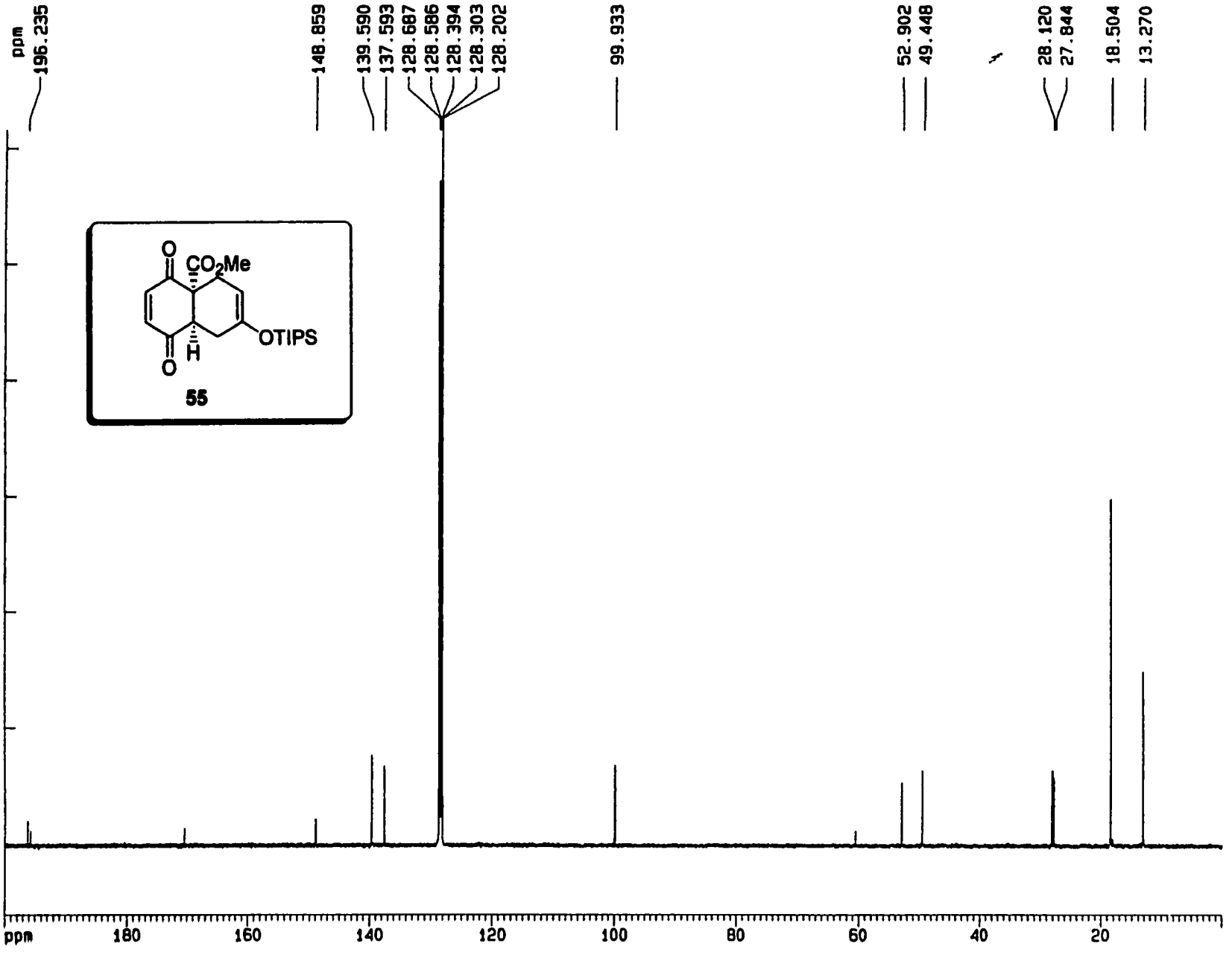
Symmetry transformations used to generate equivalent atoms:

Appendix D

Selected NMR Spectra



^{1}H NMR spectrum (500 MHz, C_6D_6) of **55**.



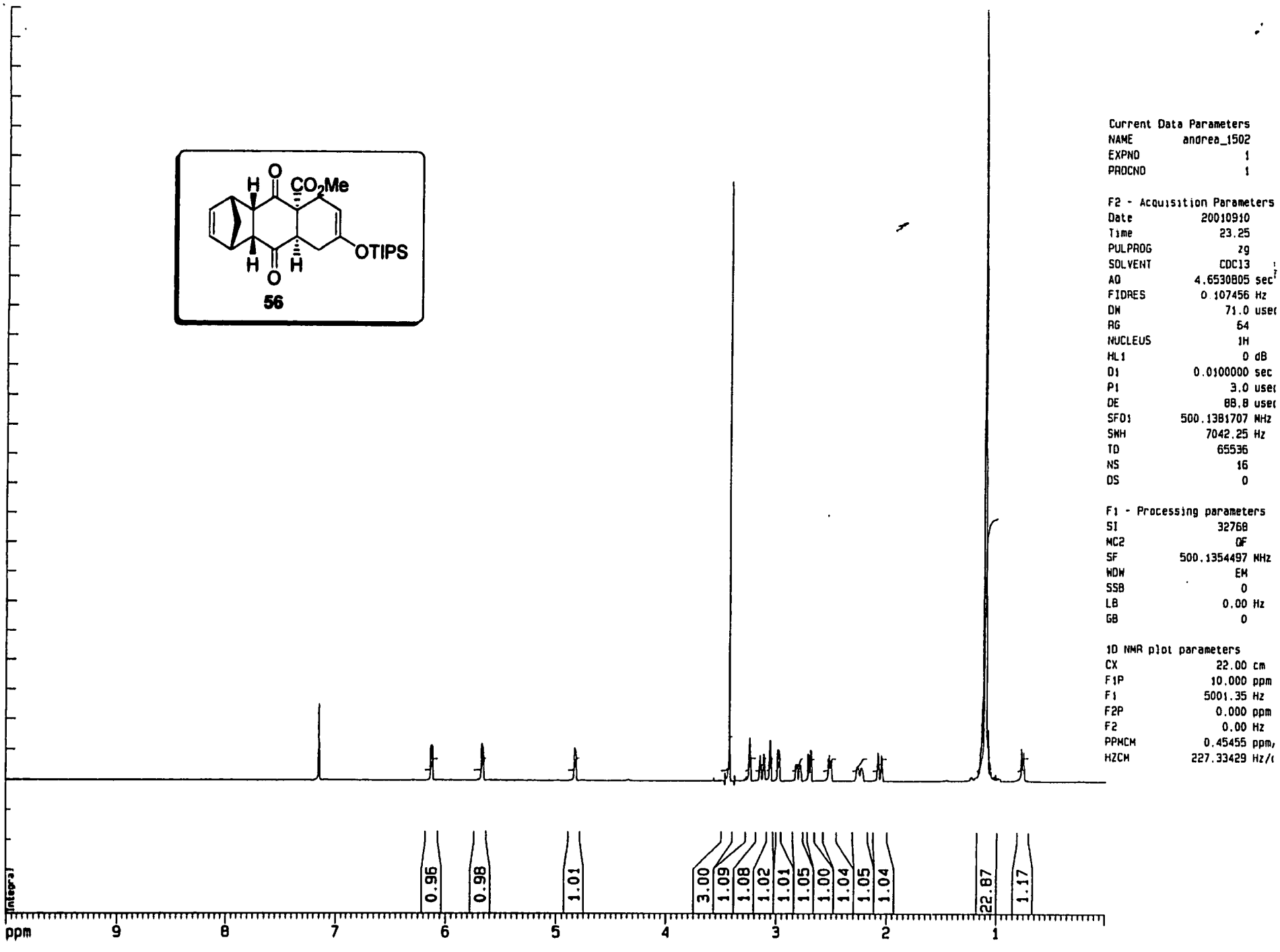
Current Data Parameters
NAME andrea_187a
EXPNO 4
PROCNO 1

F2 - Acquisition Parame
Date 20010832
Time 11.25
PULPROG zgdc
SOLVENT CDCl3
AQ 0.8519880
FIDRES 0.586877
DW 13.0
RG 32768
NUCLEUS 13C
D11 0.0300000
P31 70.0
S2 22
HL1 22
D1 1.0000000
P1 5.0
DE 18.6
SFO1 125.7724464
SWH 38461.54
TD 65536
NS 1024
DS 0

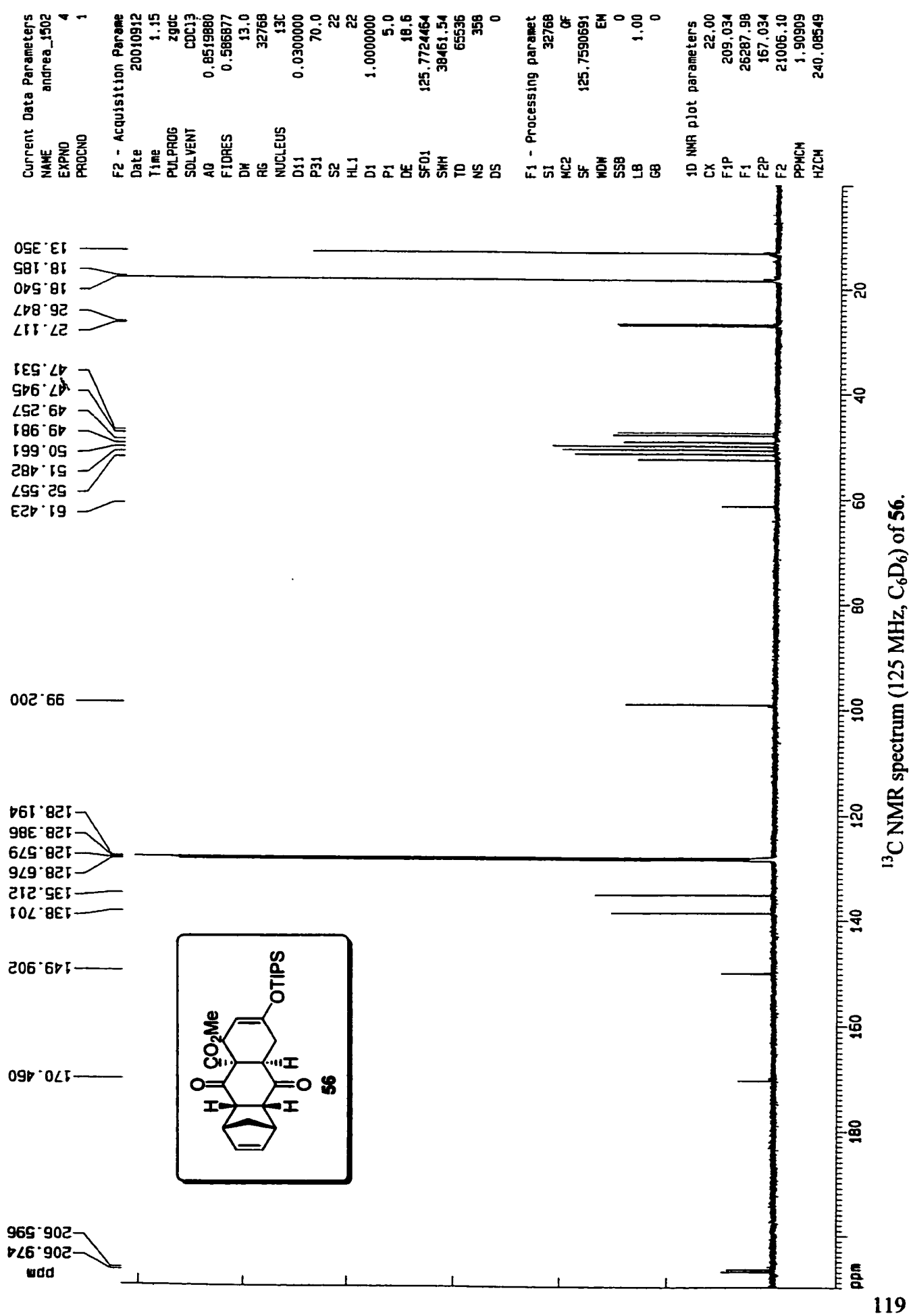
F1 - Processing paramet
SI 32768
WC2 QF
SF 125.7590679
WDW EM
SSB 0
LB 1.00
GB 0

1D NMR plot parameters
CX 22.00
F1P 200.000
F1 25151.81
F2P 0.000
F2 0.00
PPMCM 9.09091
HZCM 1143.26428

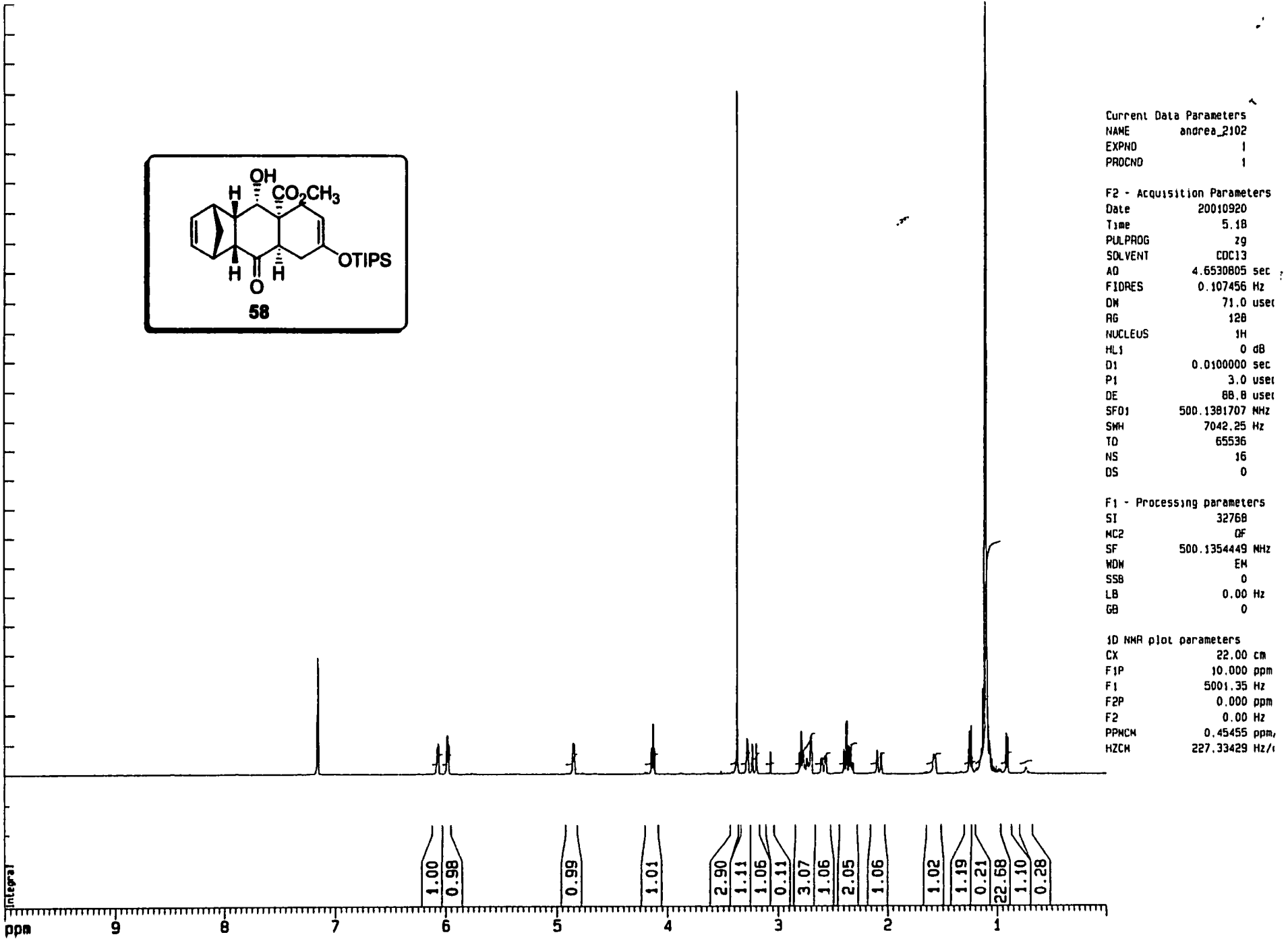
^{13}C NMR spectrum (125 MHz, C_6D_6) of **55**.



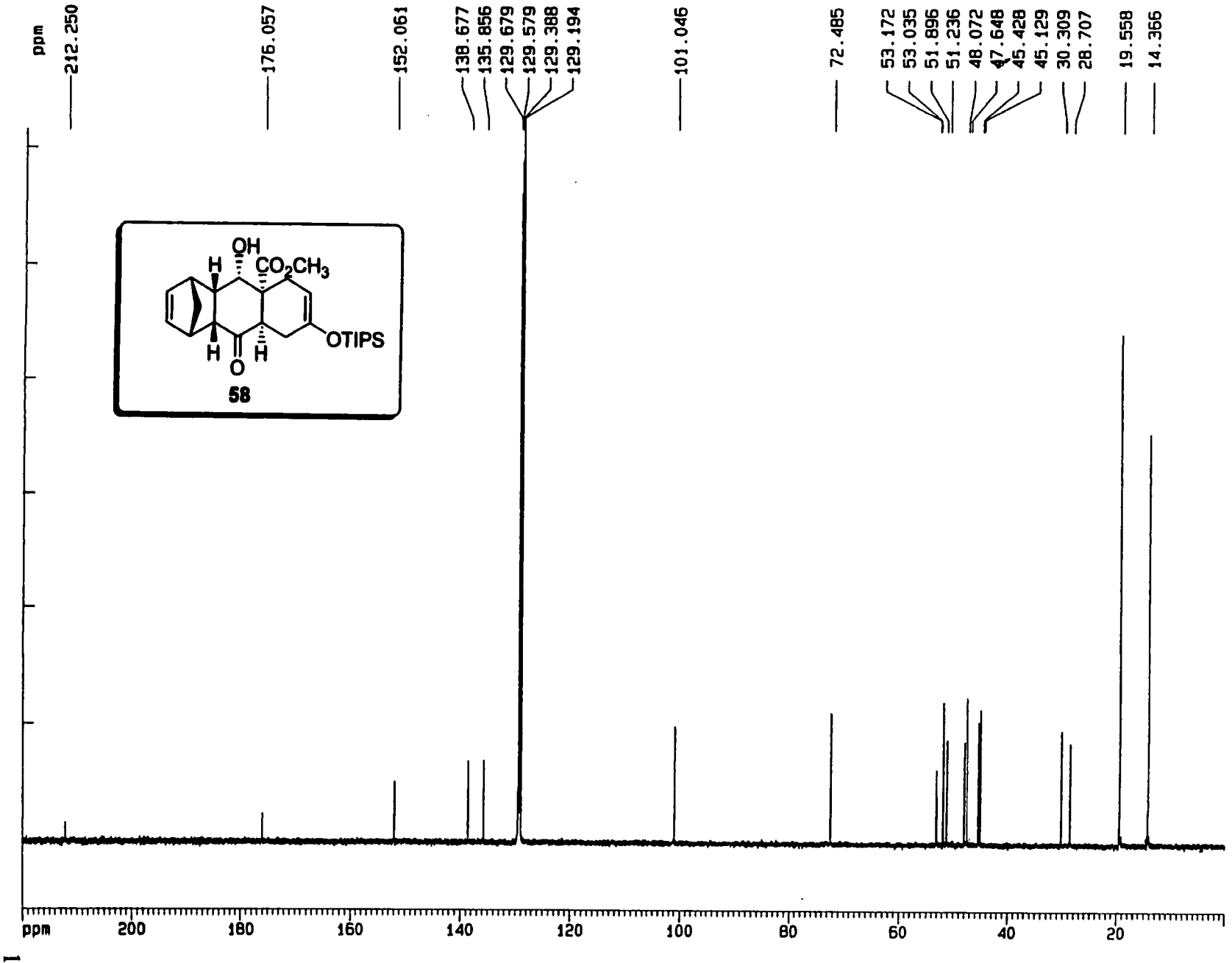
^{1}H NMR spectrum (500 MHz, C_6D_6) of **56**.



^{13}C NMR spectrum (125 MHz, C_6D_6) of **56**.



^{1}H NMR spectrum (500 MHz, C_6D_6) of **58**.



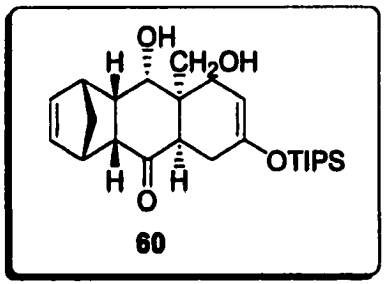
Current Data Parameters
NAME andrea_2102
EXPNO 4
PROCNO 1

F2 - Acquisition Parame
Date 20010920
Time 6.43
PULPROG zgdc
SOLVENT CDCl3
AQ 0.8519880
FIDRES 0.586877
DW 13.0
RG 32768
NUCLEUS 13C
D11 0.0300000
P31 70.0
S2 22
HL1 22
D1 1.0000000
P1 5.0
DE 18.6
SFO1 125.7724464
SWH 38461.54
TD 65536
NS 443
DS 0

F1 - Processing paramet
SI 32768
WC2 QF
SF 125.7589433
WDW EM
SSB 0
LB 1.00
GB 0

1D NMR plot parameters
CX 22.00
F1P 220.000
F1 27666.97
F2P 0.000
F2 0.00
PPMCM 10.00000
HZCM 1257.58936

^{13}C NMR spectrum (125 MHz, C_6D_6) of **58**.



60

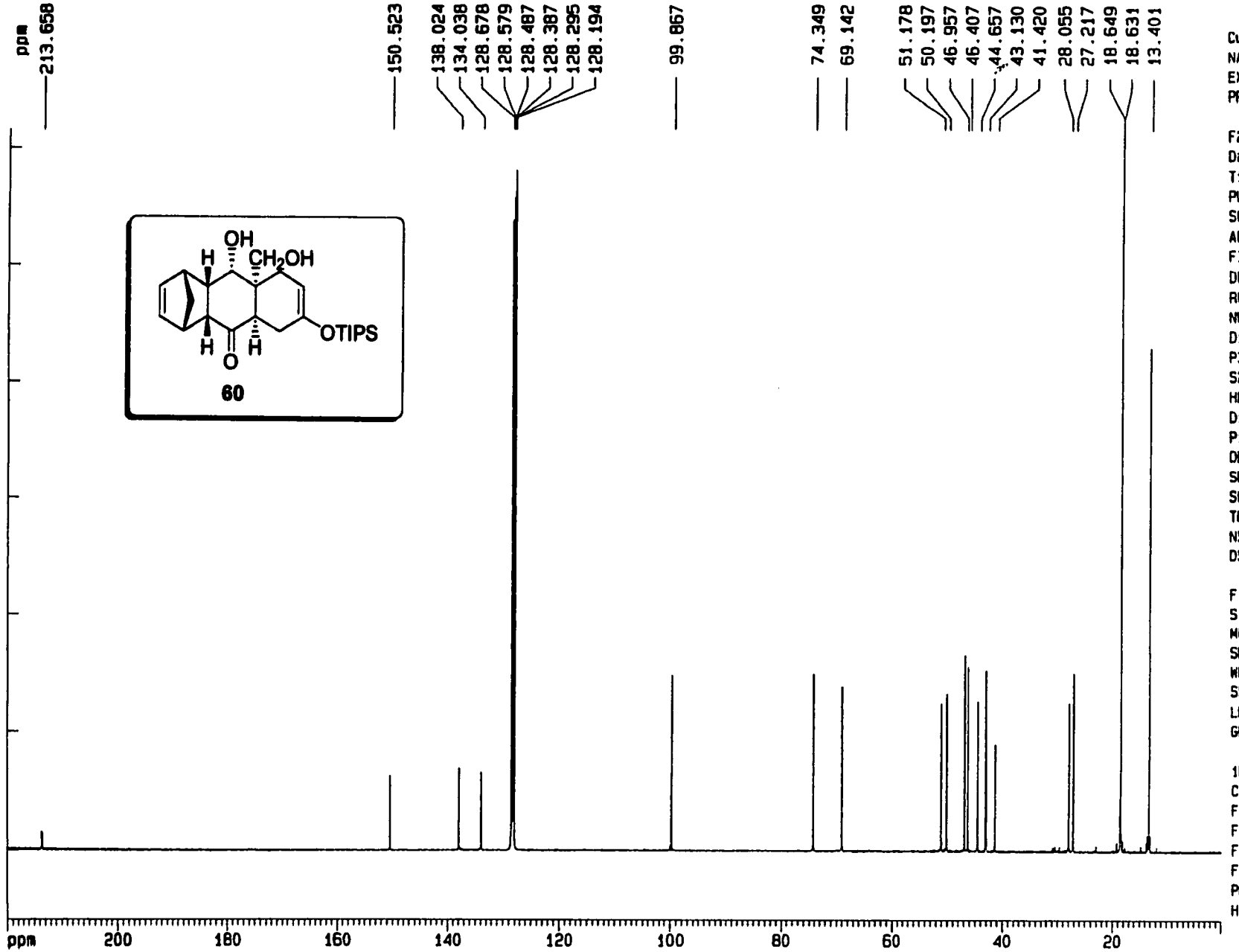
Current Data Parameters
NAME andrea_55.02
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 20011120
Time 22.14
PULPROG zg
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 usec
RG 64
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 500.1354445 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/

^{1}H NMR spectrum (500 MHz, C_6D_6) of **60**.



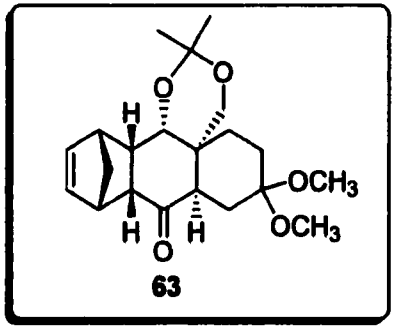
Current Data Parameters
NAME andrea_55-02
EXPNO 4
PROCNO 1

F2 - Acquisition Parame
Date 20011120
Time 5.20
PULPROG zgdc
SOLVENT CDCl3
AQ 0.8519880
FIDRES 0.586877
DW 13.0
RG 32768
NUCLEUS 13C
D11 0.0300000
P31 70.0
S2 22
HL1 22
D1 1.0000000
P1 5.0
DE 18.6
SFO1 125.7724464
SWH 38461.54
TD 65536
NS 8192
DS 0

F1 - Processing paramet
SI 32768
WC2 QF
SF 125.7590691
WDW EM
SSB 0
LB 1.00
GB 0

1D NMR plot parameters
CX 22.00
F1P 52.400
F1 6589.78
F2P 26.113
F2 3283.92
PPMCM 1.19487
HZCM 150.26622

^{13}C NMR spectrum (125 MHz, C_6D_6) of **60**.



63

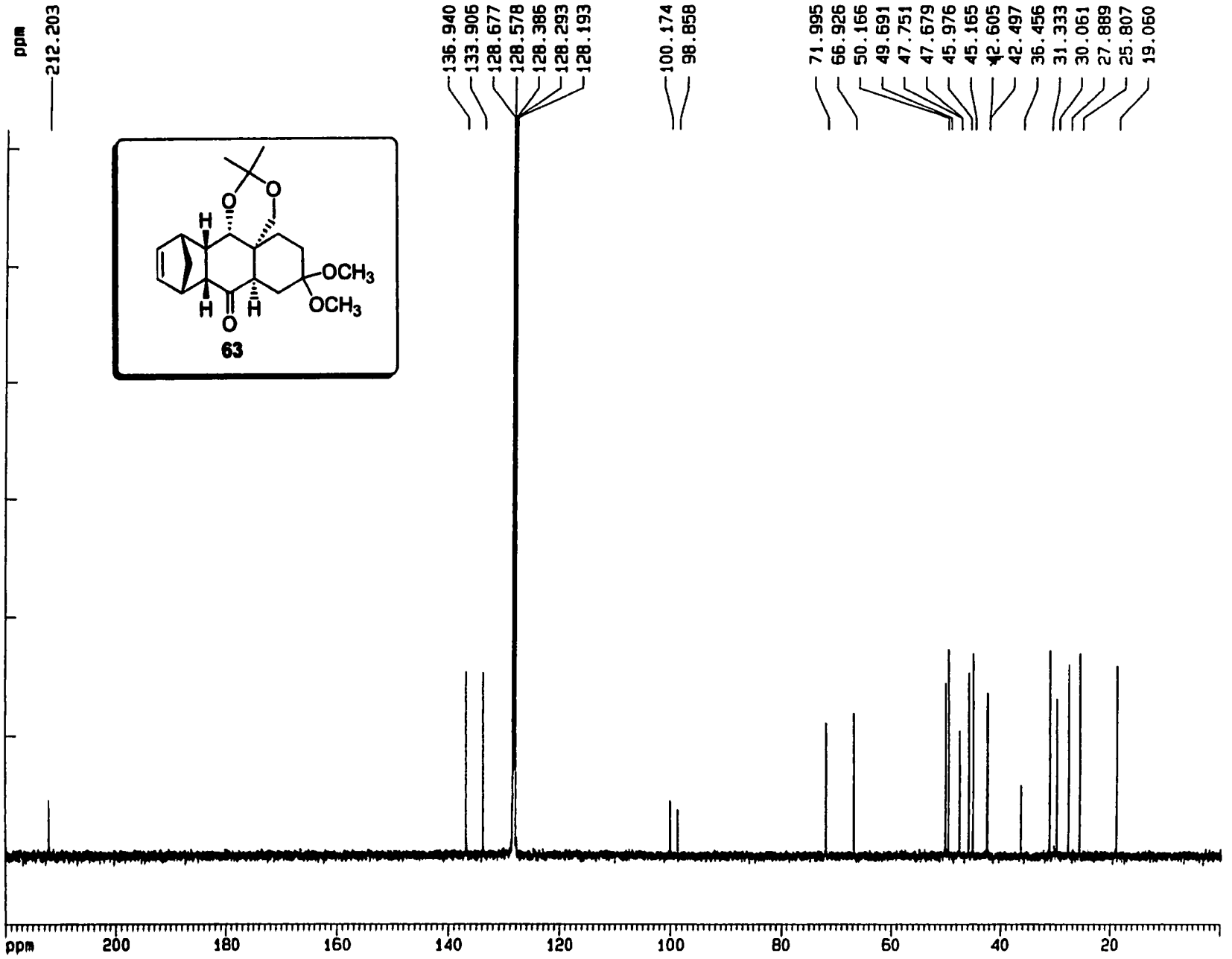
Current Data Parameters
NAME andrea_57.02
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 20011122
Time 16.27
PULPROG zg
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 use
RG 256
NUCLEUS 1H
HL1 0 dB
D1 0.0100000 sec
P1 3.0 use
DE 88.8 use
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0

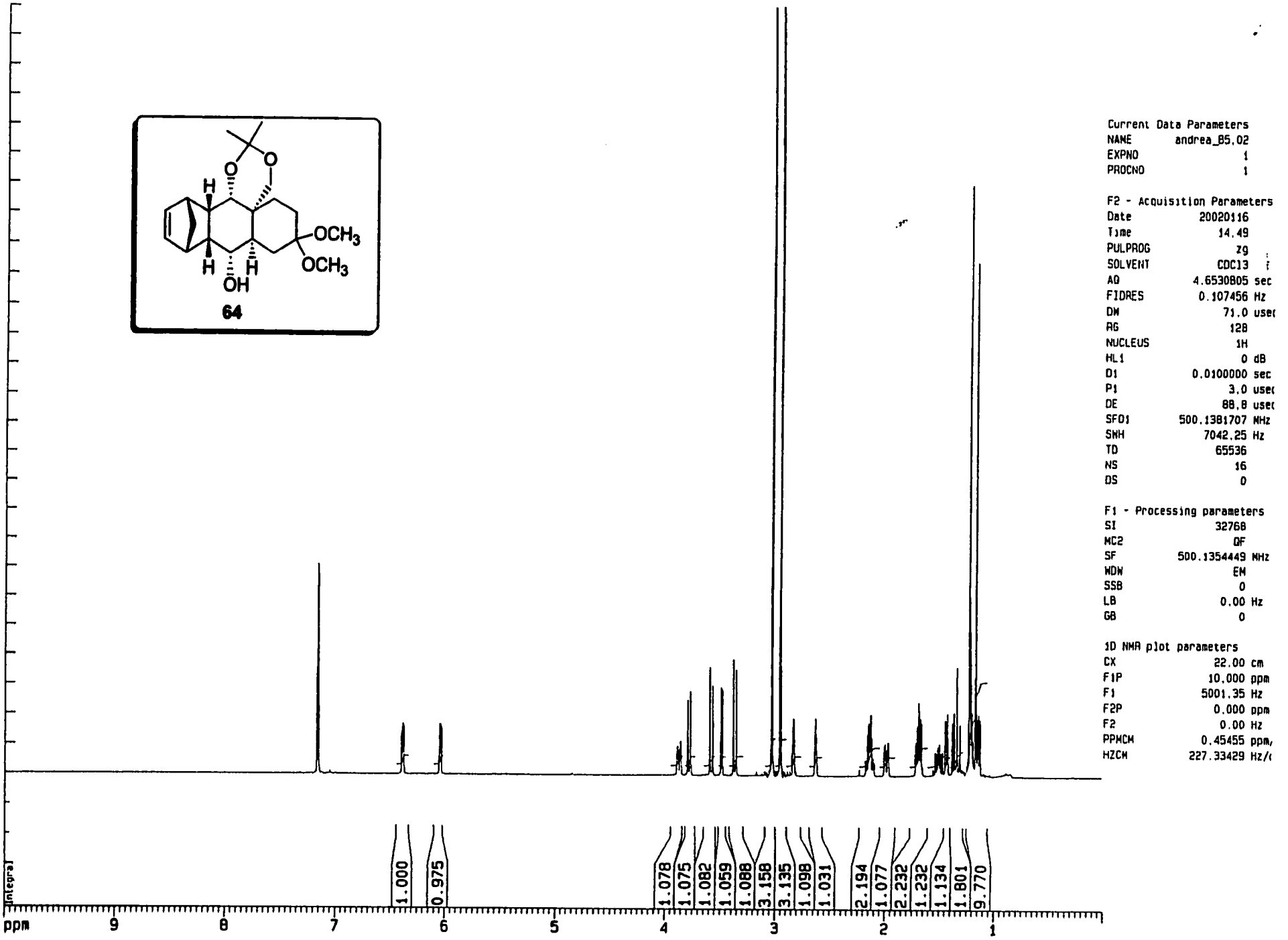
F1 - Processing parameters
SI 32768
WC2 QF
SF 500.1354447 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0

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/

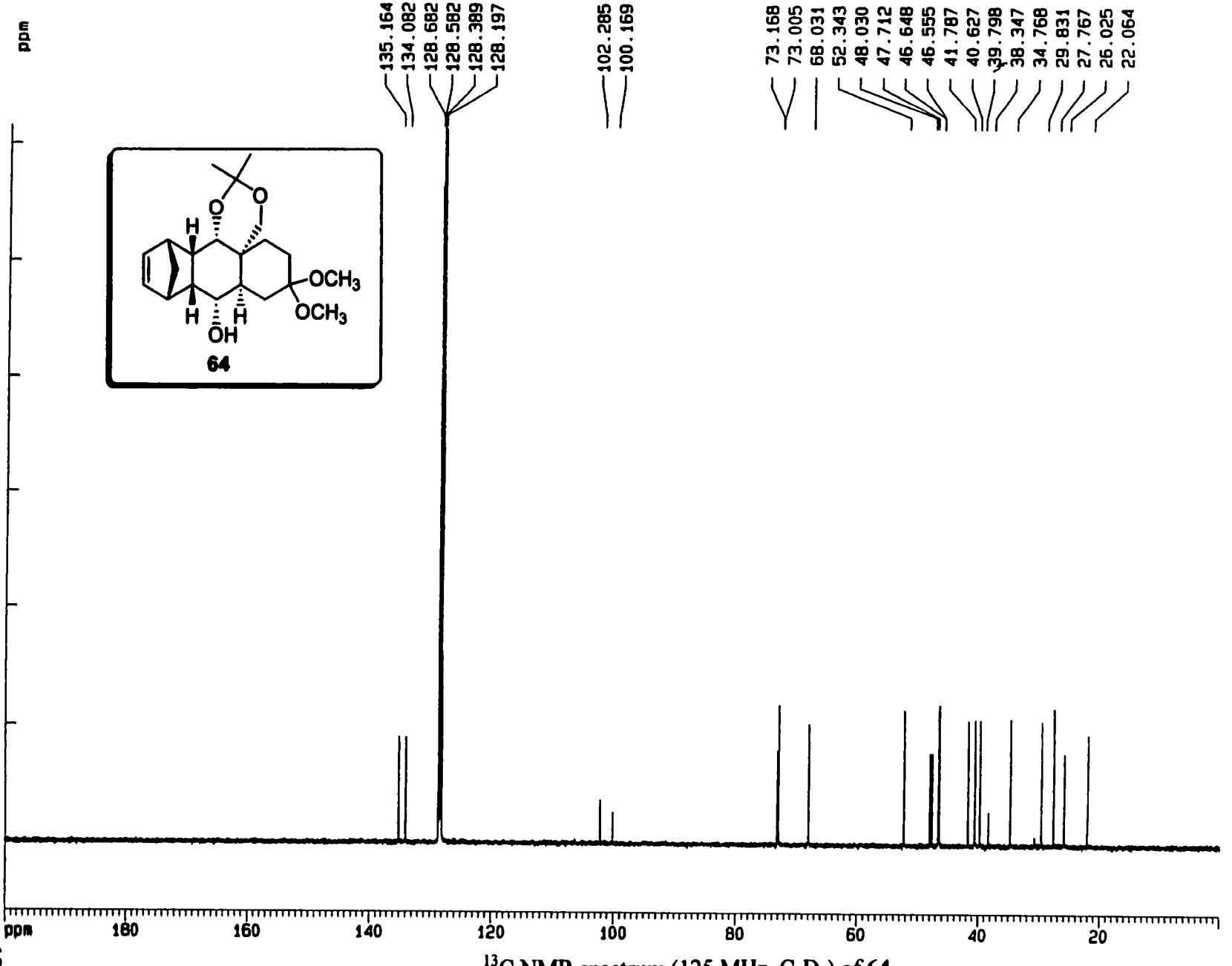
^{1}H NMR spectrum (500 MHz, C_6D_6) of **63**.



^{13}C NMR spectrum (125 MHz, C_6D_6) of **63**.



^{1}H NMR spectrum (500 MHz, C_6D_6) of **64**.



Current Data Parameters

NAME	andrea_85.02
EXPNO	4
PROCNO	1

F2 - Acquisition Parame

Date	20020116
Time	17.03
PULPROG	zgdc
SOLVENT	CDCl3
AQ	0.8519880
FIDRES	0.586877
DW	13.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	18.6
SFO1	125.7724464
SWH	38461.54
TD	65536
NS	690
DS	0

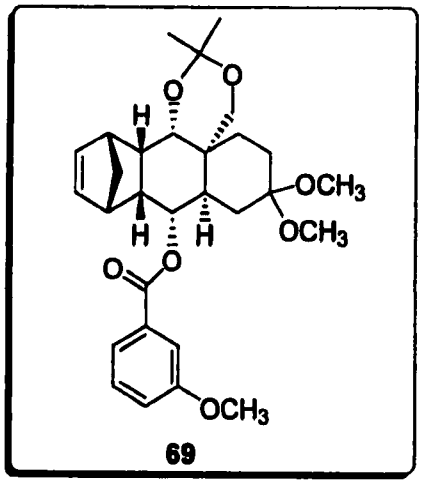
F1 - Processing paramet

SI	32768
MC2	GF
SF	125.7590691
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	136.469
F1	17162.25
F2P	98.001
F2	12324.49
PPMCM	1.74857
HZCM	219.89825

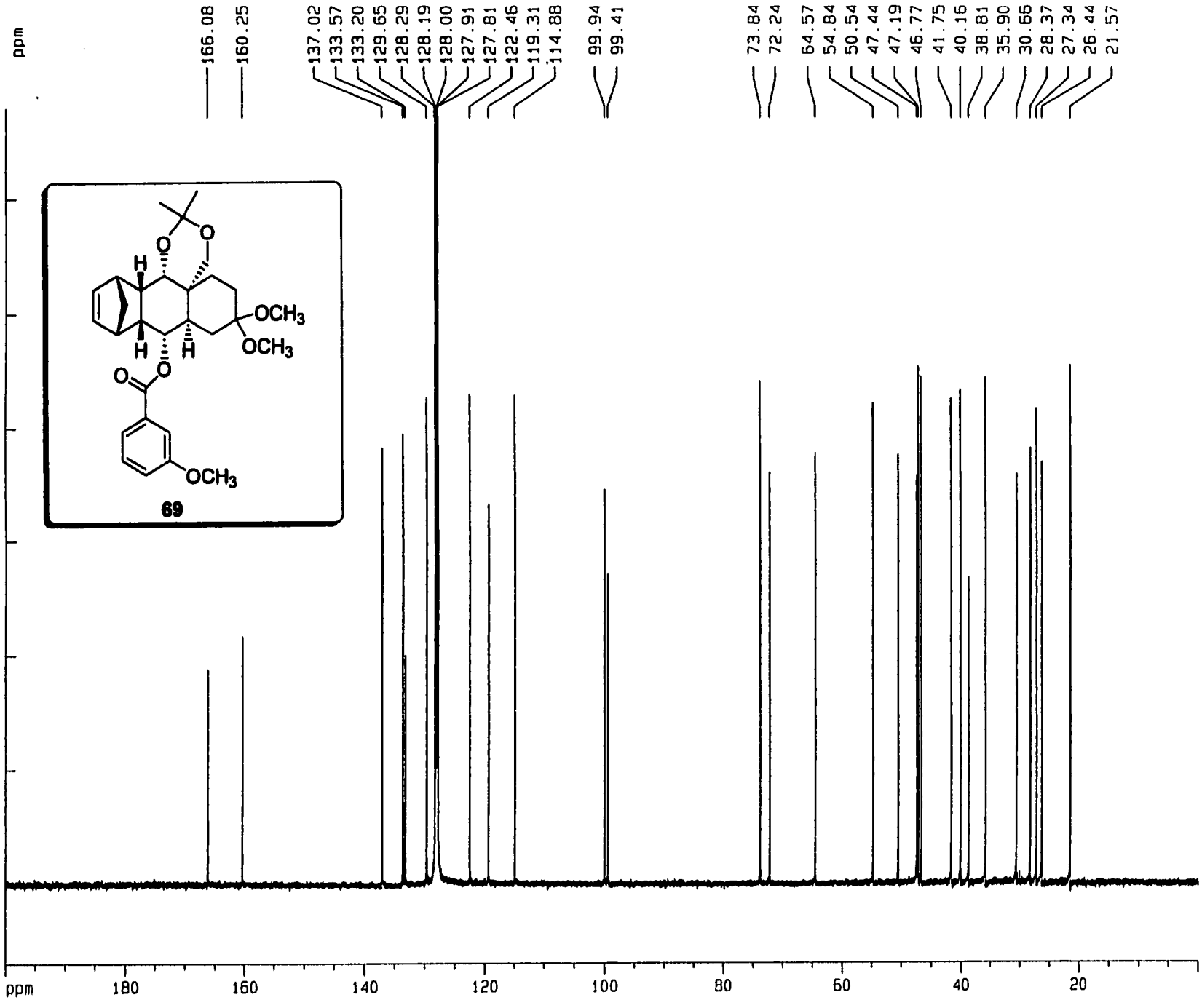
^{13}C NMR spectrum (125 MHz, C_6D_6) of **64**.



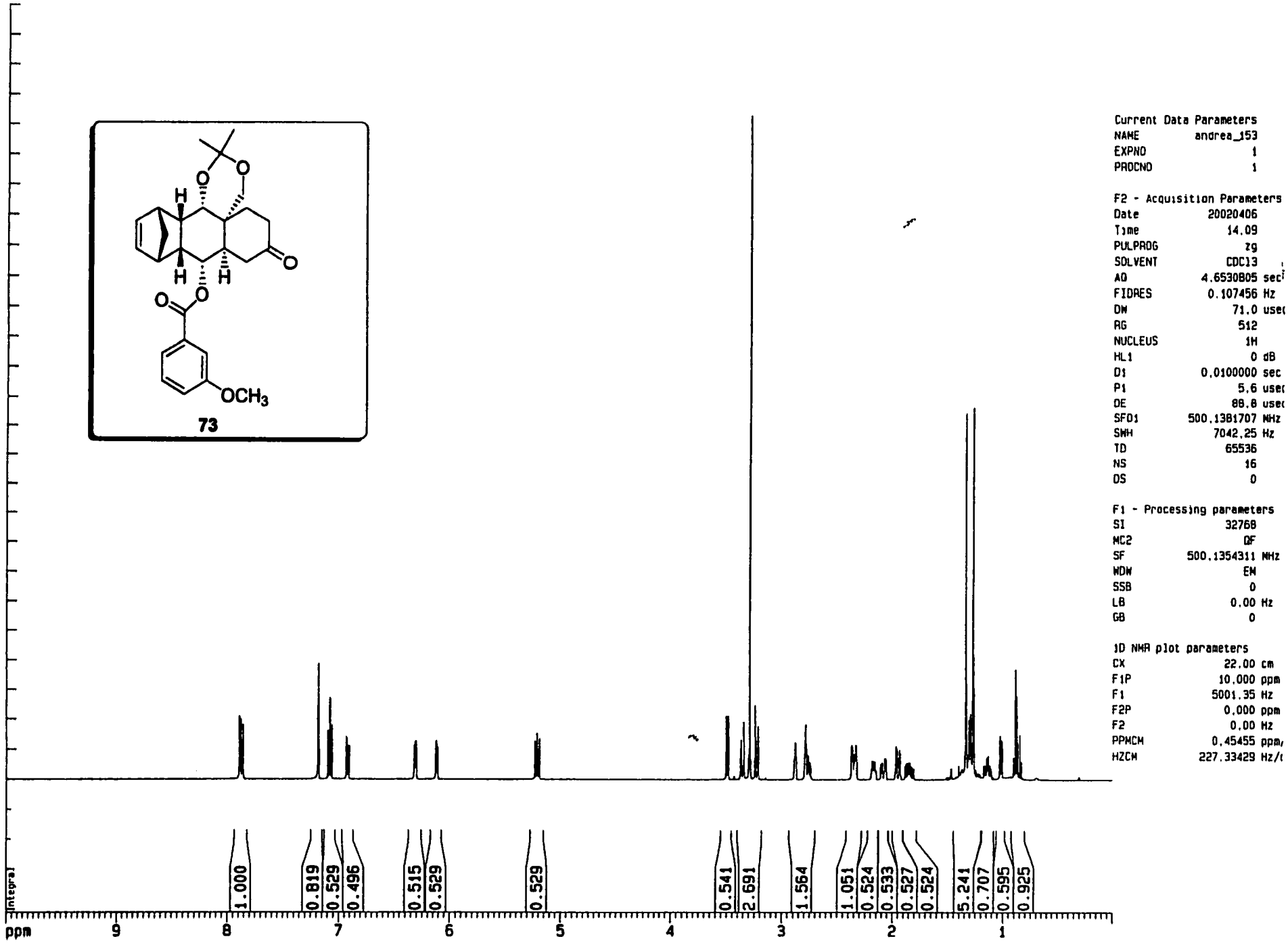
69


```
Current Data Parameters
NAME          andrea_13702
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20020323
Time                  14.37
INSTRUM             amx500
PROBHD
PULPROG                 zg
TD                   65536
SOLVENT              COCl3
NS                      16
DS                       0
SWH              7042.247 Hz
FIDRES           0.107456 Hz
AQ               4.6531062 sec
RG                     128
DW                71.000 usec
DE                88.75 usec
TE                300.0 K

F2 - Processing parameters
SI                   32768
SF          500.1354495 MHz
WDW                     EM
SSB                      0
LB                0.00 Hz
GB                       0
PC                    1.00

1D NMR plot parameters
CX                22.00 cm
CY                10.00 cm
F1P              10.000 ppm
F1               5001.35 Hz
F2P               0.000 ppm
F2                0.00 Hz
PPMCM          0.45455 ppm/cm
HZCM          227.33429 Hz/cm
```

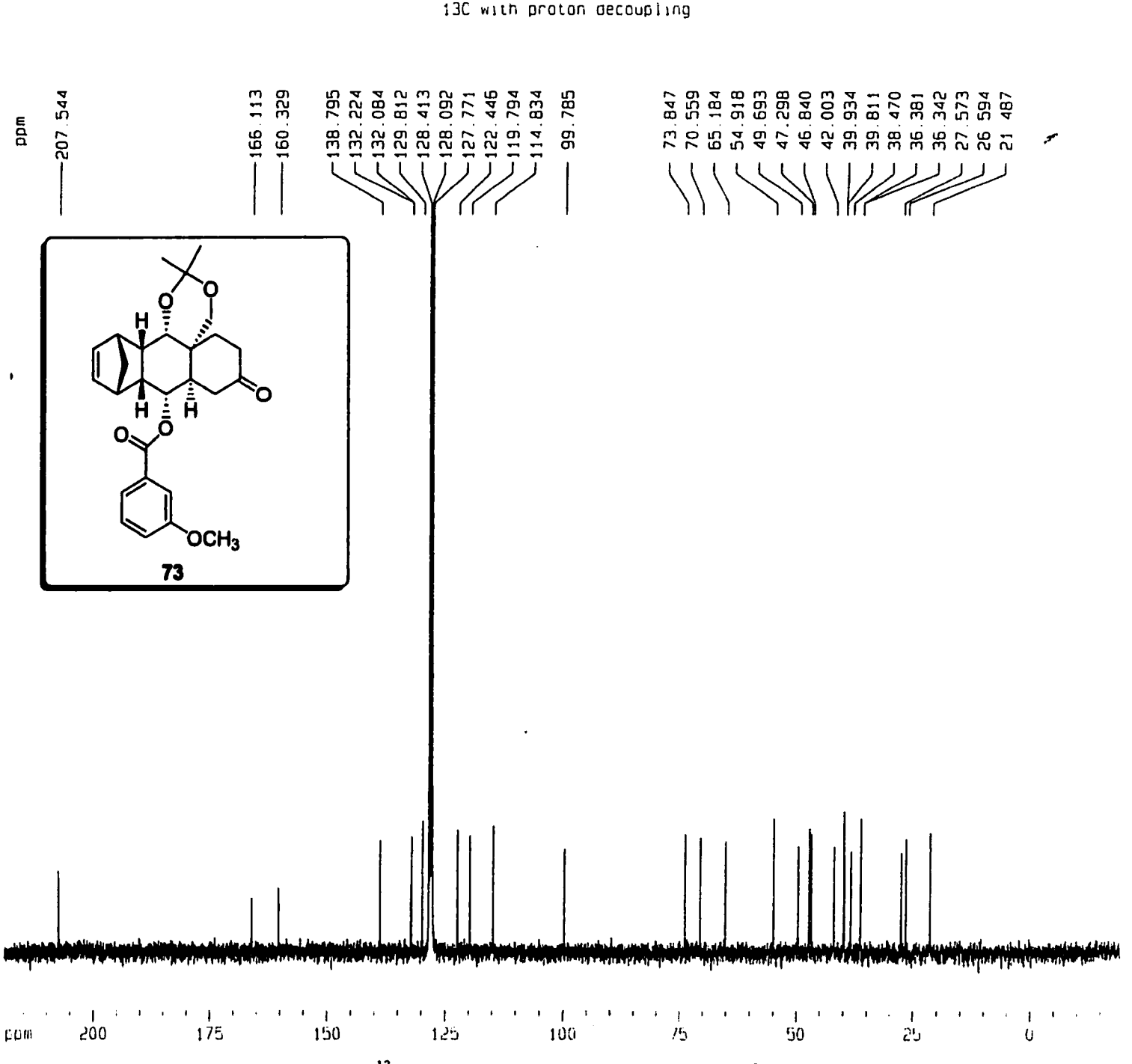
^{1}H NMR spectrum (500 MHz, C_6D_6) of **69**.



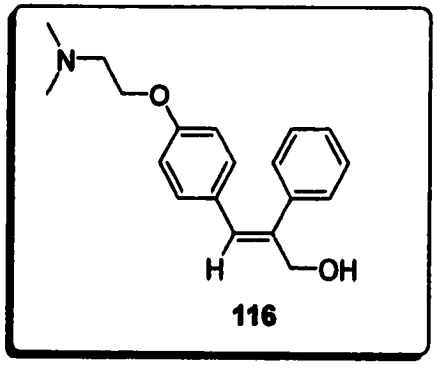
^{13}C NMR spectrum (125 MHz, C_6D_6) of **69**.



^{1}H NMR spectrum (500 MHz, C_6D_6) of **73**.



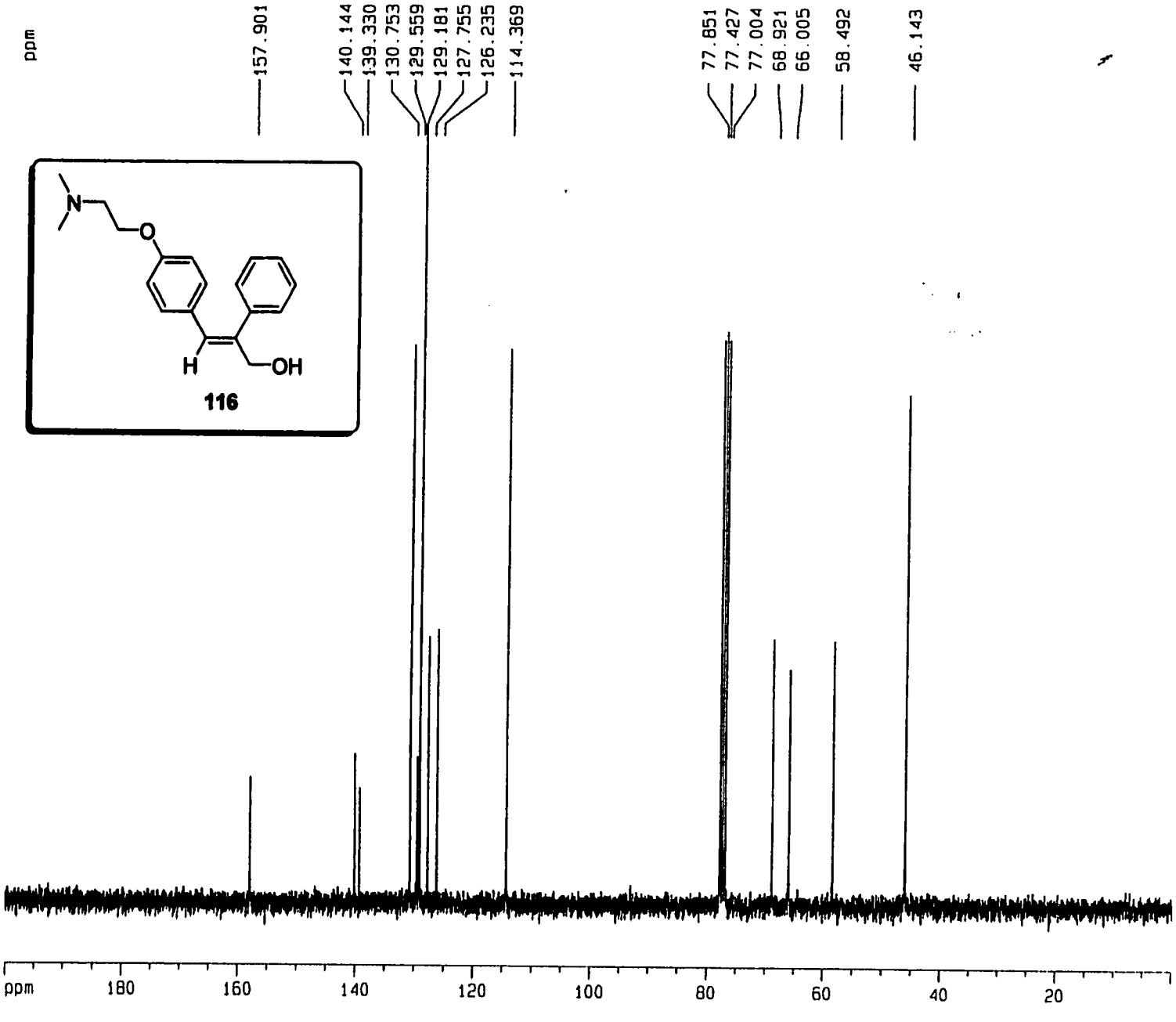
^{13}C NMR spectrum (125 MHz, C_6D_6) of **73**.



116

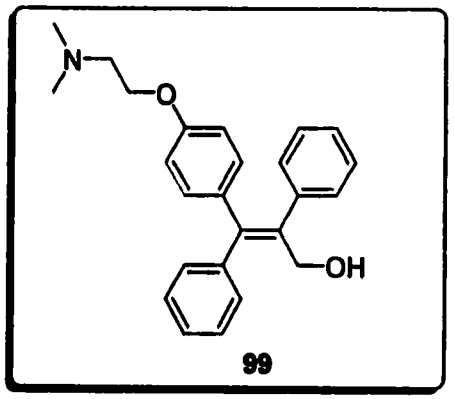
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **116**.

```
Current Data Parameters
NAME                  AP_175_02
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20020523
Time                      14.44
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                          181
DW                  98.400 usec
DE                   6.00 usec
TE                   300.0 K
D1                 1.00000000 sec

============ CHANNEL f1 ========
NUC1                         1H
P1                   15.00 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
```



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **116**.

```
Current Data Parameters
NAME                  AP_175_02
EXPNO                         4
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20020523
Time                      15.13
INSTRUM                   av300
PROBHD     5 mm QNP  1H/1
PULPROG                 zgpg30
TD                        32768
SOLVENT                   CDCl3
NS                          256
DS                            0
SWH                17985.611 Hz
FIDRES              0.548877 Hz
AQ                  0.9110004 sec
RG                       5792.6
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                        5.10 usec
PL1                      -6.00 dB
SFO1               75.4752653 MHz

========== CHANNEL f2 =========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                    70.00 usec
PL2                      -3.00 dB
PL12                     10.38 dB
PL13                     13.90 dB
SFO2              300.1314850 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                       12.50 cm
F1P                     200.000 ppm
F1                    15093.54 Hz
F2P                       0.000 ppm
F2                        0.00 Hz
PPMCM                10.00000 ppm/cm
HZCM                754.67719 Hz/cm
```



99

Current Data Parameters
NAME AP_191
EXPNO 1
PROCNO 1

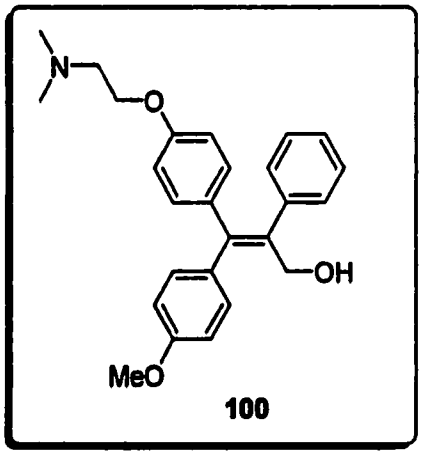
F2 - Acquisition Parameters
Date_ 20020607
Time 14.45
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 45.3
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

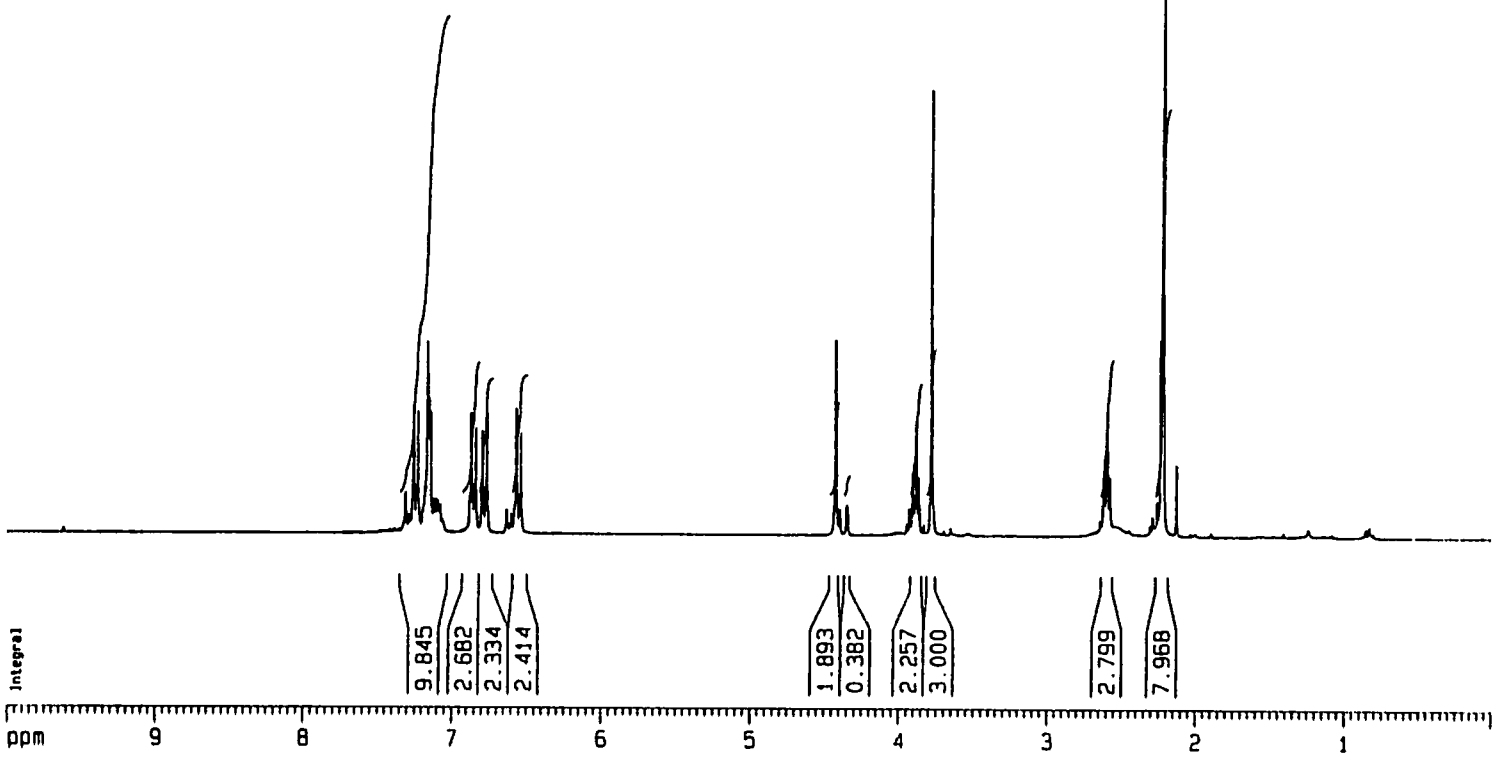
========== CHANNEL f1 =======
NUC1 1H
P1 20.00 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

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 15.00 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

^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **99**.






```
Current Data Parameters
NAME                  AP_189
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_              20020607
Time                  11.11
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                   20.00 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
```

^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **100**.