INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

ProQuest Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

UMI®

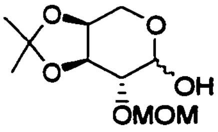
Université d'Ottawa • University of Ottawa

0-612-66181-4

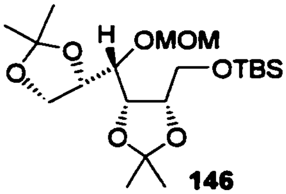
Abstract

Taxol® **1a**, a very important drug used in cancer chemotherapy, has been synthesized by several groups. However these syntheses are long and there is still the need for a short and efficient route that would allow the production of this compound in larger amount.

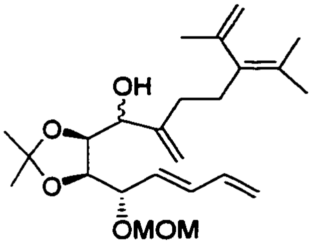
The route proposed by our group toward a simplified model compound **78** implied a double Diels-Alder strategy and started from readily available protected (L)-arabinose **118** or (D)-guluno-γ-lactone **146**. Conversion of **118** to **164**, followed by Diels-Alder reaction led to the stereoselective construction of **165**. Deprotection of the isopropylidene acetal tether group and oxidative cleavage gave compounds **172a** and **173a**. We were able to ultimately get to compound **189**. Despite precedents in the literature the second Diels-Alder cycloaddition required for the construction of rings A and B failed.



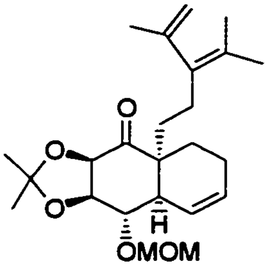
118



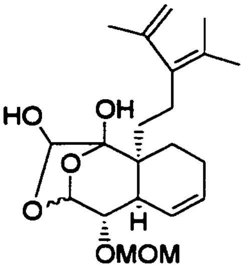
146



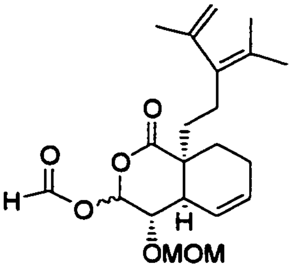
164



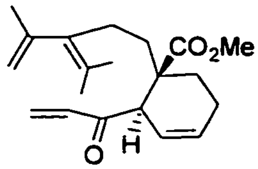
165



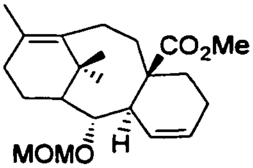
172a



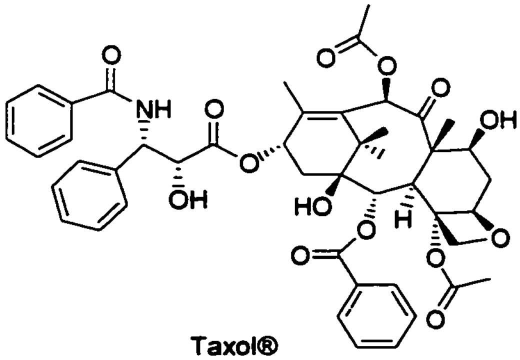
173a



189



78



Taxol®
1a

Résumé

Le Taxol® **1a** est un médicament utilisé pour le traitement de nombreux cancers. Sa synthèse totale a déja été décrite par de nombreux groupes mais les synthèses sont longues et une route plus efficace et plus courte est nécessaire pour le produire en plus grande quantité et obtenir des analogues.

La stratégie de synthèse proposée par notre groupe repose sur l'utilisation de deux réactions de Diels-Alder successives pour former le système ABC **78** du Taxol®. La synthèse utilise des produits de départ facilement accessible comme des dérivés de l' arabinose **118** ou de la (D)-guluno-γ-lactone **146**. L' hémiacetal **118** est transformé en triene **164** puis soumis a une première réaction de Diels-Alder pour donner stéréoselectivement la décaline **165**. La déprotection de l'acétonide suivie d'une oxydation permet l'obtention des composés **172a** et **173a** qui furent transformés en précurseur **189** pour la deuxieme cycloaddition de Diels-Alder. En dépit d'exemples similaires décrits dans la littérature, la cycloaddition pour former les cycles A et B n'a pas lieu.

Acknowledgements

First and foremost I would like to express my gratitude to my supervisor Dr. Alex G. Fallis for giving me the opportunity to work on a challenging project under his direction and to come to Canada. It has been a wonderful experience.

I would also like to acknowledge the following people for their help or for simply being there when I needed it:

Thank to Dr. Pete Wilson, Dr. Simon Woo and Dr. Stéphanie Legoupy for the many discussions we had on the construction of the taxane ring system. Their help relating to the matter of chemistry was invaluable. A special thank to Dr. Alain Laurent, Shawn Collins and Matt Heuft who proofread this manuscript many times and for their sound advice. I would also like to thank Poonam Tauh, Irina Brinza, Tanya Rietveld, Dr. Stéphanie Legoupy, Dr. Catherine Martin and Dr. Nadine Thery for our lengthy philosophical discussions.

Special thanks to the other group members, Shawn Collins, Pat Forgione, Nicole Mackintosh my old buddies from the first years in the lab. Dr. Alexey Melekhov, Dr. MayLing Lee and Dr. Stephen Graham for their assistance and their valuable knowledge of chemistry, Matt Heuft, Beth Husk, Rana Ibrahim, Nidia Villalva, Jenny Tiffin and Andrea Penwell for their welcome in Canada. Thanks as well to our foreigner team, Helen Clark, Gonzalo Cosa, Nadine, Alain, Catherine, Thierry, Francois, Karine, Odile, Ditte and Nadia for our many non-chemistry activities, our wine and cheese parties.

I would like to thank Dr Glenn Facey, Mr. Raj Capoor for their efforts in conducting the high field NMR. Thanks to the support staff, always helpful, Annette, Monic, Linda and Lise.

Enfin, cette page serait incomplète sans mentionner le support de ma famille, mes parents, toujours présents pendant ces longues années d'étude qui arrivent finalement à leur terme. Merci de tout cœur.

“All men by nature desire knowledge”
Aristotle (384-322 BC)

Table of Contents

List of Figures

List of Schemes

List of Tables

List of Abbreviations

Ac	acetyl
Anal. Calcd.	elemental analysis calculated
aq	aqueous
Ar	aryl
Bn	benzyl
BOM	benzyloxymethyl
Bp	boiling point
Bu	butyl
Bu_3SnH	tributyltin hydride
n-Bu	butyl
n-BuLi	*n*-Butyllithium
t-Bu	tertiary-butyl
t-BuOK	potassium tertiary-butoxide
t-BuLi	tert-Butyllithium
Bz	benzoyl
cat.	catalytic
cf.	compare
COSY	H^1-H^1 NMR correlation spectroscopy
m-CPBA	*meta*-chloroperoxybenzoic acid
Δ	heat
d	doublet
dd	doublet of doublets
dt	doublet of triplets
DABCO	1,4-diazabicyclo[2.2.2]octane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dec.	decomposition
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	N,N'-dimethyl-4-aminopyridine
DME	1,2-dimethoxyethane
DMF	N,N'-dimethylformamide
DMP	Dess Martin periodinane
DMS	dimethylsulfide

DMSO	dimethylsulfoxide
ee	enantiomeric excess
eq.	equivalent(s)
E.I.	electron impact
Et	ethyl
Ether, Et_2O	diethylether
EtOAc	ethyl acetate
Et_3N	triethylamine
EtOH	ethanol
g	gram(s)
GC	gas-liquid chromatography
GC/MS	gas-liquid chromatography-mass spectrometry
h	hour
HRMS	high resolution mass spectrum
Hz	Hertz
Im	imidazole
IMDA	intramolecular Diels-Alder
i-Pr	isopropyl
IR	infra red
J	coupling constant
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperide
M^+	molecular ion (mass spectroscopy) or metal cation
Me	methyl
MeOH	methanol
mg	milligram(s)
min	minute
mm Hg	millimeters of mercury
mmol	millimole(s)
mol	mole(s)
mp	melting point
MHz	megahertz
MOM	methoxymethyl
Ms	methanesulfonyl
MS (CI)	mass spectrum by chemical ionization

MS (EI)	mass spectrum by electronic impact
NIS	N-iodosuccinimide
NMR	nuclear magnetic resonance
Nu^-	nucleophile
obs.	observed
Ph	phenyl
PMB	*para*-methoxybenzyl
PPh_3	triphenylphosphine
ppm	parts per million
Pr	propyl
py	pyridine
q	quartet
R	alkyl group
rt	room temperature
s	singlet
t	Triplet
t-BuLi	*t*-Butyllithium
TBAF	tetra-*n*-butylammonium fluoride
TBS	tertiary-butyl dimethylsilyl
TBDPS/TPS	tertiary-butyl diphenylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
triflate	trifluoromethanesulfonate
Troc	2,2,2-trichloroethoxycarbonyl
TS	transition state
Ts	*para*-toluenesulfonyl
p-TsOH	*para*-toluenesulfonic acid

CHAPTER 1

1 Chapter 1

1.1 INTRODUCTION

Cancer remains a major cause of mortality in our industrialised countries, despite adequate treatment when diagnosed early. While in the 60's heart diseases were responsible for twice as many deaths as cancer, currently cancer kills more people than heart disease. It was estimated that 65,000 Canadians died from cancer in 2000[1]. With an estimated 5,400 deaths and 1,500 deaths among Canadian women, breast cancer and ovarian cancer are amongst the most deadly forms of the disease. The incidence of breast cancer among women rose steadily over the past 30 years largely due to the fact that better screening programs are in place. Concurrently, the mortality rates have declined slightly thanks to better treatment and early diagnosis. Ovarian cancer is one of the most lethal cancers, often diagnosed in a late stage, and is the fifth most diagnosed cancer (after lung, breast, prostate and colorectal).[2] Widely spread screening and early detection have improved the prognosis when women develop those cancers, however the mortality rate is still too high to be considered satisfactory. A cure to the disease is still to be found.

About thirty years ago a great breakthrough in the treatment of cancer was announced with the discovery of Taxol® **1a**, a new natural antineoplastic agent.[3] Three other natural product families with similar anticancer activity have been discovered recently: the epothilones **2a,b**, eleutherobin **3** and discodermolide **4** (Figure 1-1). Those antitumor agents share a set of common features, in particular a new and original mechanism of action.[4] They show a significant improvement on previous alkaloids used to treat cancer, and a new pathway to fight the disease. Amongst these, Taxol® is the most advanced in terms of development and is already on the market to treat breast cancer and ovarian cancer. [5]

---

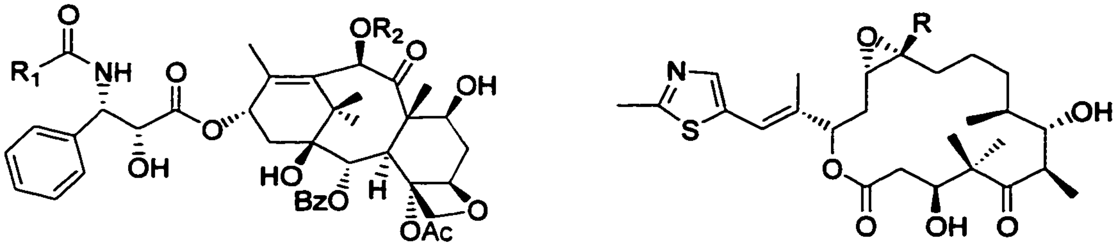
[1] Canadian Cancer Statistics: www.cancer.ca/stats2000/

[2] Health Canada: www.hc-sc.gc.ca/

[3] Wani M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.*, **1971**, *93*, 2325.

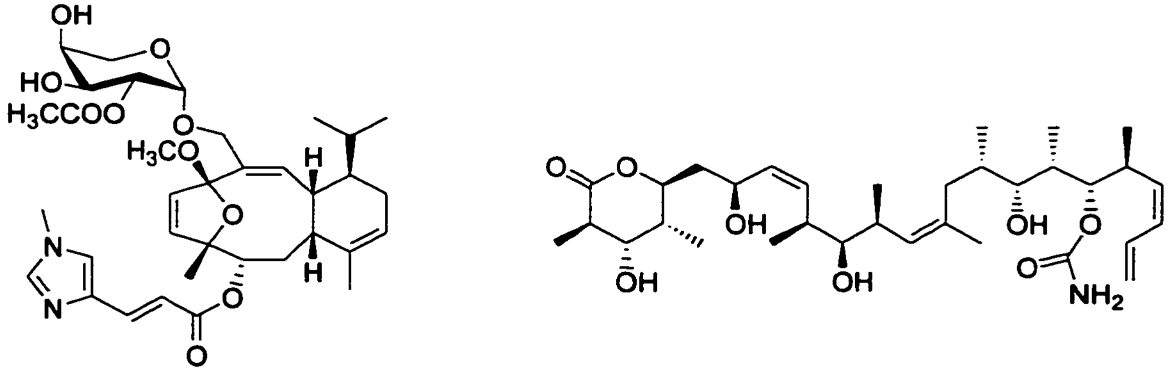
[4] Jordon, M. A.; Wilson, L. in *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M. Eds; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995; Chap.10; pp138-151.

[5] (a) Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *Natl. Cancer Inst.*, **1990**, *82*, 1247. (b) McGuire, W. P.; Rowinsky, E. K.; Rosenshein, N.B.; Grumbine, F. C.; Ettinger, D. S.; Armstrong, D. K.; Donehower, R. C. *Ann. Intern. Med.*, **1989**, *111*, 273.



1a Taxol R_1 = Ph, R_2 = Ac
1b Taxotere R_1 = *t*-BuO, R_2 = H

2a Epothilone A R = H
2b Epothilone B R = CH_3



3 Eleutherobin

4 Discodermolide

Figure 1-1: New antineoplastic agents.

Taxol® triggered a lot of interest following its discovery due to its exceptional activity on resistant types of cancer. However more efficient and selective drugs are still to be synthesized to treat and cure cancer. The purpose of this research is to develop an efficient and short route towards the Taxol® skeleton, hence providing an easy route for its production and a facile access to potentially more potent analogues.

1.2 HISTORY[6]

Taxol® is a natural product extracted from the yew tree whose toxicity has been known since antiquity when Romans used it as a poison. The ancients exploited its biological activity, using it as an anticoagulant and as a tranquillizer. It was used also for its cardiotonic and expectorant properties.[7] More recently it has been studied for its cytotoxic effect.

---

[6] Wall, M. E.; Wani, M. C. in *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M. Eds; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995; Chap. 2; pp 18-30.

[7] Guénard, D.; Guéritte-Voegelein, F.; Potier, P.; Denia, J. N.; Greene, A. *La Recherche*, **1990**, *226*, 1427.

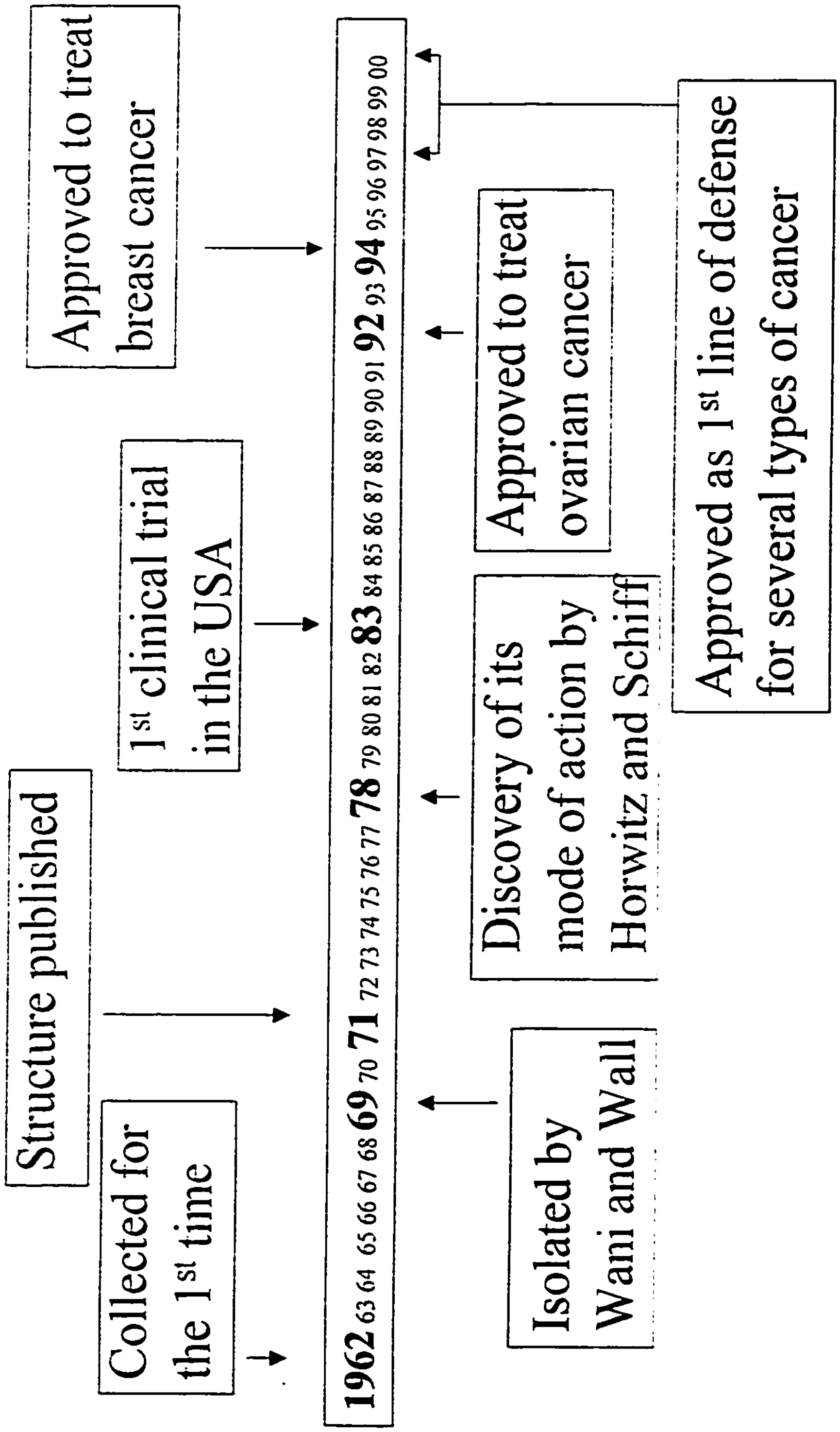


Figure 1-2: Timeline of Taxol®.

Its rediscovery dates from forty years ago. In the late 50's, a large program of exploration of our environment was initiated by the American National Cancer Institute (NCI) to identify natural substances with anticancer activity (Figure 1-2). In 1962, American botanist A. Barkley collected samples of the Pacific yew tree (*Taxus brevifolia*). C. Wani and L. Wall observed that an extract of the inner bark killed leukaemic cells in vitro. Wani and Wall were able to isolate the molecule responsible for the biological activity in 1966 and named it Taxol®. Its structure was reported in 1971.[3] Several years later, two biologists in New York City, S. B. Horwitz and P. Schiff published their study on the mechanism of action of Taxol®.[8] They showed that Taxol® follows a totally different pathway than those known so far, bringing new hope in the fight against cancer. Clinical studies started soon afterward and led to the approval of Taxol® by the FDA for the treatment of refractory ovarian cancer in 1992 and metastatic breast cancer in 1994.[5] Taxotere®, a very efficient analogue of Taxol® was approved for treatment of breast cancer in 1995. Today Taxol® is not only used for treatment of ovarian and breast cancers but also for treatment of some small cell lung cancers, squamous cancers of the neck and head and AIDS related Kaposis syndrome.[9] It has become the best-selling anti-cancer drug in history, with commercial sales of over $1 billion in 1998.[10]

1.3 BIOLOGY[11]

Taxol® is the lead compound of a new series of antitumor agents promoting the assembly of microtubules. It targets a protein, the tubulin, required for the formation of the mitotic spindle, an essential element involved in mitosis. In contrast to previous drugs (colchicines, vinblastine) known to poison the cell by inhibiting the assembly of tubulins into microtubules, Taxol® inhibits the reverse natural process of depolymerisation. By binding to the microtubules, Taxol® makes the structure extremely stable altering the tubulin-microtubule polymerisation dynamics. The microtubules are important cytoskeletal components involved in the regulation of cell proliferation, differentiation and apoptosis (programmed death). Therefore disruption of the tubule-microtubule dynamics of polymerisation causes disorganisation in the cell. At first level, the stabilization of the microtubules results in the

---

[8] Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature*, **1979**, *277*, 665.

[9] (a) Forastriere, A. A. *Semin. Oncol. Suppl. 3*, **1993**, *20*, 56. (b) Ettinger, D.S. *Semin. Oncol. Suppl. 3*, **1993**, *20*, 46. (c) Bristol-Myers-Squibb website: www.bms.com; March 2001.

[10] Kingston, D. G. I. *J. Nat. Prod.*, **2000**, *63*, 726.

[11] For a review see Nicolaou, K.C.; Dai, W-M.; Guy, R.K. *Angew. Chem. Int. Ed. Engl*, **1994**, *33*, 15.

sequestration of the tubulin required to form the spindle and in the formation of bundles of non functional microtubules. As a consequence it fails to form a normal mitotic apparatus, which causes the cell division process to halt between the metaphase and anaphase (Figure 1-3).

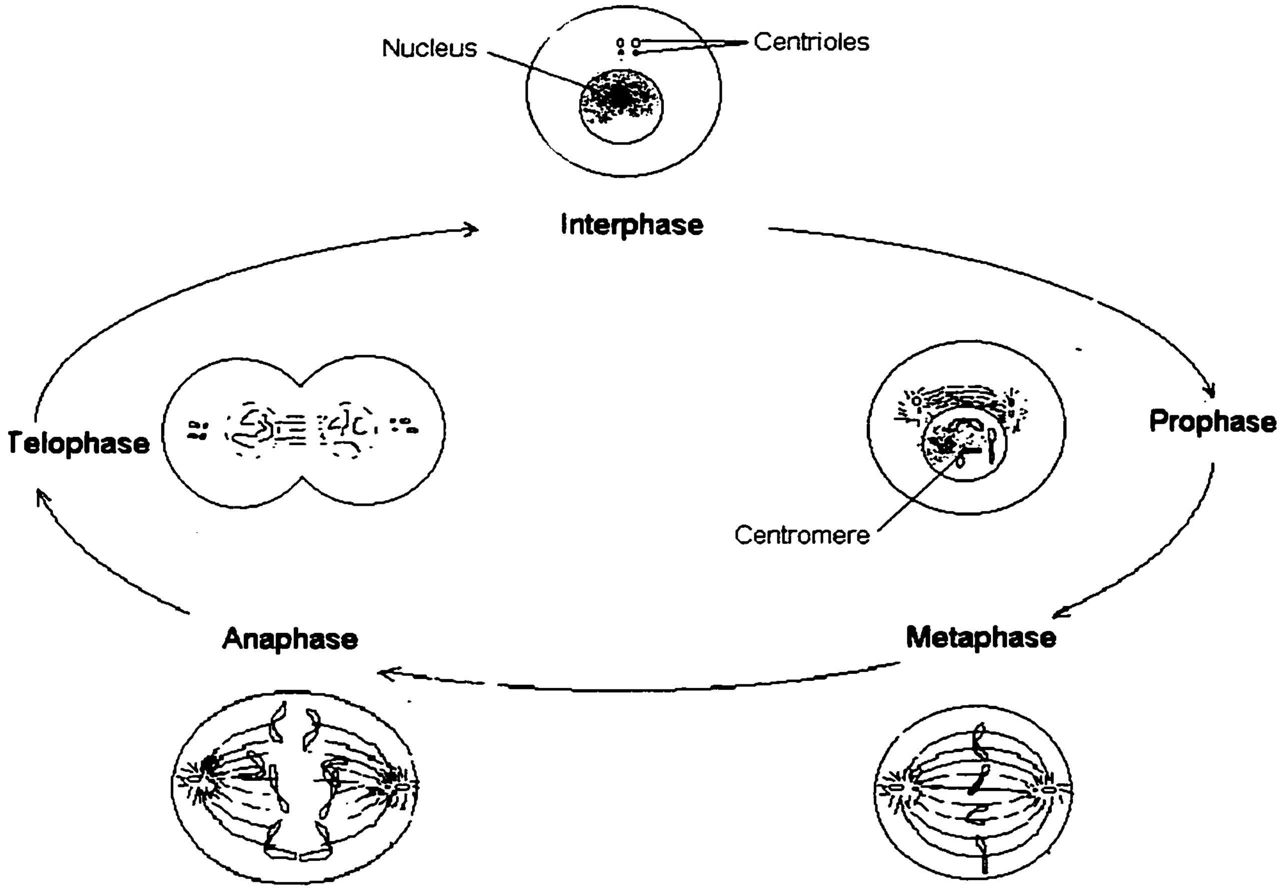


Figure 1-3: The cell cycle.[12]

Taxol® as well as other antimicrotubules agents induces apoptosis by disorganizing the microtubules structure acting at a different level of the apoptotic signal transduction pathways. It acts in particular on a family of genes (bcl-2) involved in the regulation of apoptotic signal.[13]

---

[12] Adapted from J. J. Baker and G. E. Allen, *The Study of Biology*, Addison-Wesley Publishing Company, Don Mills, Onatrio, 1982.

[13] Wang, L. G.; Liu, X. M.; Kreis, W.; Budman D. R. *Cancer Chemother. Pharmacol.*, **1999**, *44*, 355.

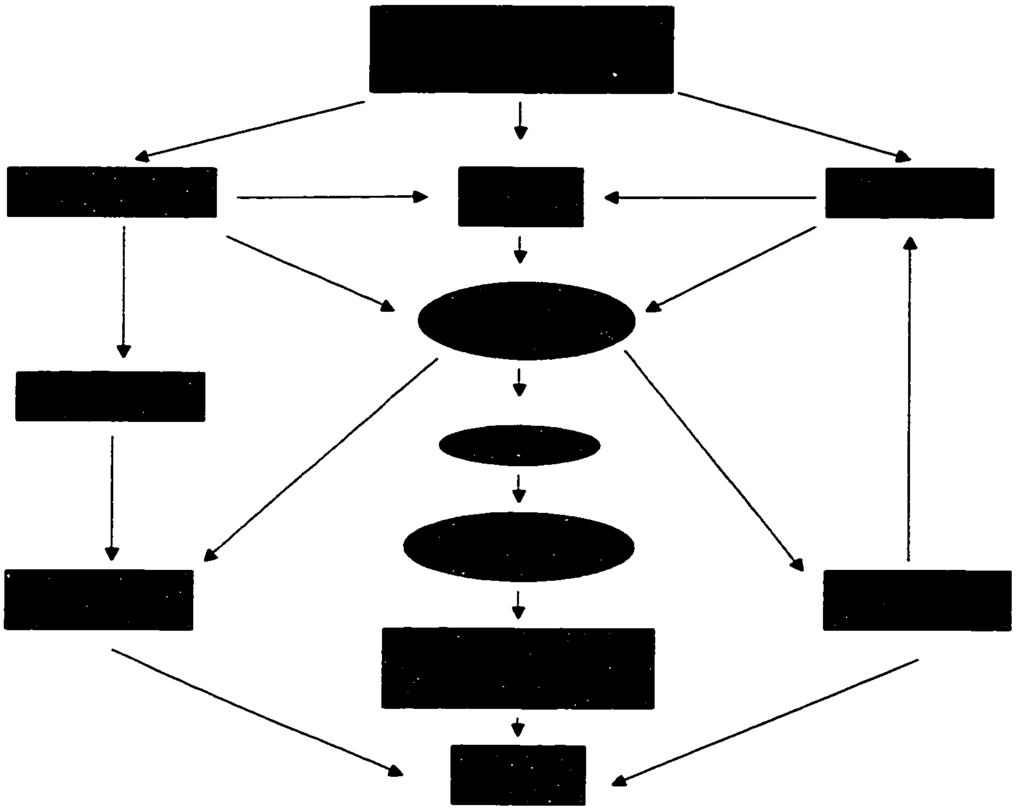


Figure 1-4: The effect of antimicrotubule agents on signal transduction pathways.[13]

As a major effect of the disruption of the microtubular architecture by Taxol®, the bcl-2 genes responsible for an antiapoptotic effect are inactivated through phosphorylation. Concomitant raf-1 and PKA (Protein Kinase A) activation and inhibition of MAP kinases (Microtubule Associated Protein) participate in a complex activation of the apoptotic pathway (Figure 1-4). Alteration of those protein activities are directly or indirectly responsible for bcl-2 phosphorylation, stabilization or expression of genes p53 and p21, a family of genes upstream of apoptosis, which lead to apoptosis.

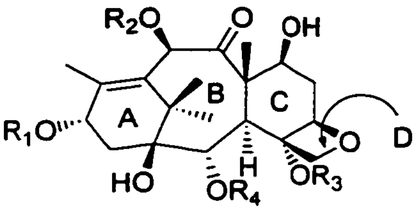
As cancerous cells divide more frequently than normal cells, Taxol® acts essentially on anarchically dividing tumor cells. However other fast dividing cells (like blood cells, intestinal cells) will be touched as well therefore inducing unwanted side effects, weakening the immune system or killing nervous cells, causing nausea and baldness.

Although Taxol® presents the two major advantages of having a unique and original mechanism of action and a totally different structure, it is not perfect. While incredibly efficient it has many side effects. Moreover, it is not water-soluble which lowers its bioavailability, increasing the dose required for treatment. A carrier, Cremephor®,[9c] has to be used increasing the risk of allergic reactions upon delivery of the drug. A solution to all this would be a more hydrosoluble analogue with better specifity and higher selectivity. In order to find such a perfect match the compound has to be produced in large quantity, which brings us to the last problem associated with Taxol®: its supply.

1.4 TAXOL® STRUCTURE

1.4.1 CHEMICAL/PHYSICAL PROPERTIES

Taxol® also named paclitaxel, is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9 g/mol. It has a tetracyclic ABCD core with a dense highly oxygenated pattern and an aminoacid side chain (Figure 1-5).



5

Figure 1-5: Taxane core.

The chemical name of this polyoxygenated diterpene is 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate-2-benzoate-13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

1.4.2 STRUCTURE ACTIVITY RELATIONSHIP (SAR) STUDIES[11]

In order to design analogues of paclitaxel, knowledge of the chemical elements required for the biological activity is necessary.[14,15]

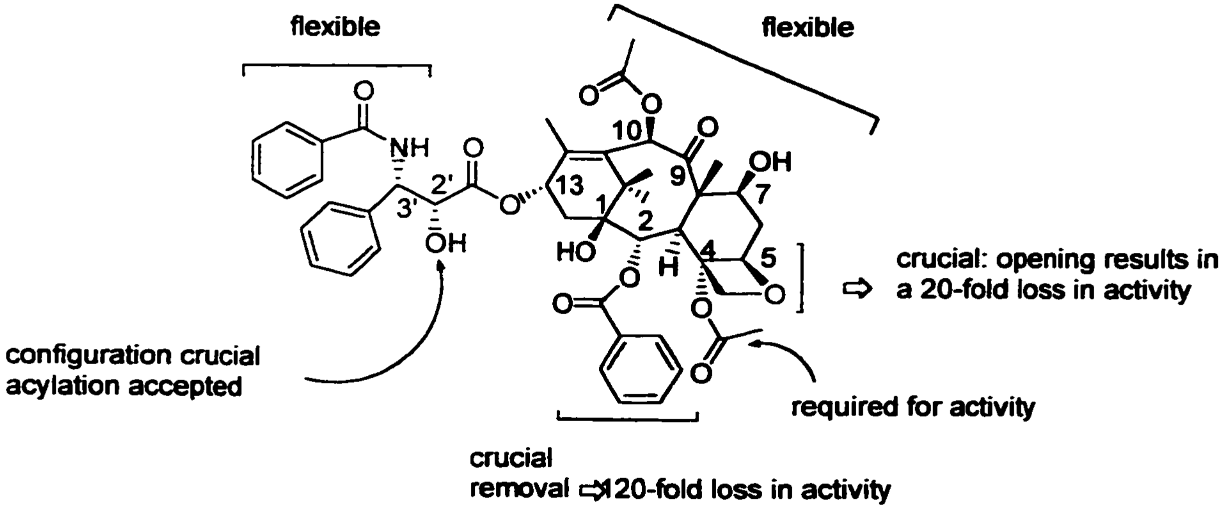


Figure 1-6: Required functionalities for biological activity.

Structure Activities Relationships (SAR) studies showed that the presence of the Taxol® side-chain is essential for activity. [16] On this lateral chain, the 3' amine must be protected. A *tert*-butoxycarbonyl group (Taxotere®) is more efficient than the benzyloxy protecting group. The configuration at the C-2' is very important for the bioactivity, but the hydroxyl group can be acylated or left free.

The rigid core bearing the side-chain and the other substituents is equally thought to be important. However not all substituents have the same importance for the activity of the molecule. Substituents on the "Northern Hemisphere" of the molecule have a small influence on the activity of Taxol®. The 7-OH can be eliminated altogether and a free or acetylated 10-hydroxyl group does not affect the activity significantly. The ketone at C-9 can be reduced. Both resulting stereoisomers of the alcohol improved the activity slightly.

---

[14] Wang, M.; Xia, X.; Kim, Y.; Hwang, D.; Jansen, J. M.; Botta, M.; Liotta, D. C.; Snyder, J. P. *Org Lett.*, **1999**, *1*, 43.

[15] Hiriguchi, T.; Oritani, T.; Cheng, Q. *Tetrahedron*, **2000**, *56*, 1667.

[16] Kingston, D. C. I. *Pharmac. Therap.*, **1991**, *52*, 1.

More important are the substituents on the "Southern Hemisphere" with the exception of the 1-OH. 1-Deoxy analogues of Taxol® were tested and demonstrated that it is not necessary for the activity.[17] Removal of the acetate at the C-4 position reduces the activity as well as the replacement of the benzoyloxy group by a non-aromatic protecting group. However certain substitutions of the aromatic ring brought improvement.

The oxetane ring has been thought to be very important for the biological activity of Taxol®. The oxetane oxygen is expected to participate in the binding process by hydrogen bonding. Another hypothesis is that the four membered ring brings rigidity to the Taxol® core therefore enforcing a favourable conformation leading to activity. Recent studies have shown, that elimination of the D ring altogether does not significantly change the protein binding property of the molecule.[18] Taxol® analogues with oxetane surrogate (3-membered ring or double bond) are predicted to maintain the structural stiffness therefore enabling the protein polymerisation to take place.

In summary, the four structural features regarded as being responsible for the biological activity of Taxol® are:

1. C-13 side-chain
2. esters at C-2 and C-4
3. core of the molecule or ABC ring system
4. oxetane ring

1.5 SOURCE OF TAXOL®

1.5.1 NATURAL SUPPLY-HEMISYNTHESES

For many years the drug has been extracted from the inner bark harvested from yew trees thus condemning them to die. The tedious extraction of Taxol® from the Pacific yew tree was not a sustainable resource for the drug. Only 1 kg of product was obtained from 25,000 lb of dried bark or the bark of 2,500 yew trees. This quantity in turn will treat only 500 patients

---

[17] Liang, J.; Shen, Y-C.; Long, B. H.; Fairchild, C. R.; Johnston, K. A.; Chordia, M. D.; Jagtap, P. G.; Kingston, D. G. I. *J. Org. Chem.*, **1999**, *64*, 1814.

[18] Wang, M.; Cornett, B.; Nettles, J.; Liotta, D. C.; Snyder, J. P. *J. Org. Chem.*, **2000**, *65*, 1059.

causing a conscious, environmental and financial dilemma.[19] If Taxol® bioactivity allowed even larger applications than shown to date, the demand for Taxol® may exceed 300 kg or 750 000 trees per year. Agronomists, horticulturists, botanists and biologists tried to find a way around that limitation by exploring hydroponic cultures, plant cell cultures, biosynthesis, genetic engineering and fermentation procedures.[20] The solution came from the discovery of a precursor to the Taxol® structure, the 10-deacetylbaccatin III **6** present in extracts from the leaves of the European yew trees (*Taxus baccata*). [21] A simple method was then developed to attach the side chain to the skeleton and the first semisynthesis of Taxol® was achieved and patented in 1986 (Scheme 1-1).[22] At some point during these studies Potier *et al.*, discovered another active molecule named Taxotere® which is now synthesized following a similar process.[23]

---

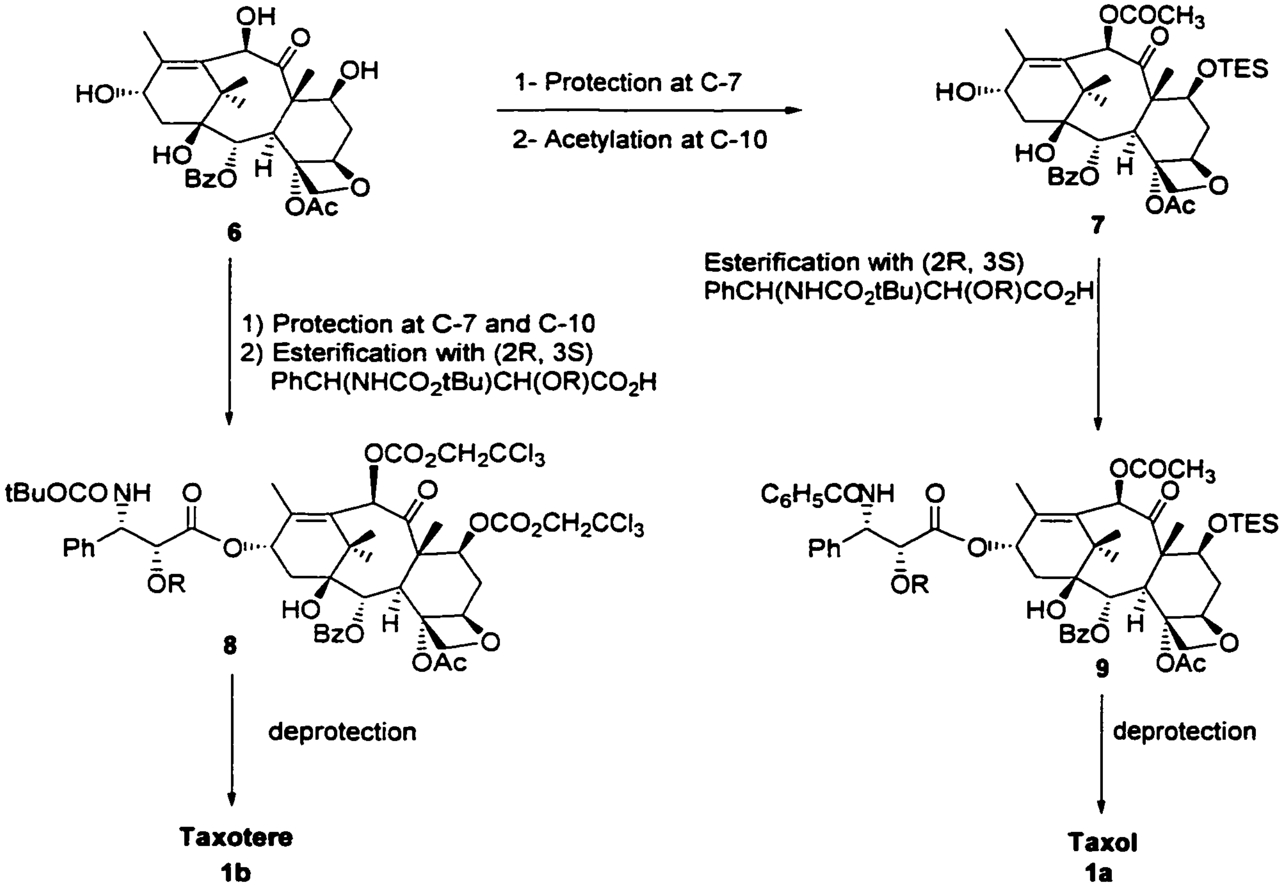
[19] Cragg, G. M.; Snader, K. M. *Cancer Cells*, **1990**, *3*, 233.

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

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

[22] (a) Colin, M.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. Eur. Pat. Appl. EP 253,738 (Cl.C07D305/14), 20 Jan 1988, *Chem. Abstr.* **1988**, *109*, 22762w. (b) Colin, M.; Guénard, D.; Guéritte-Voegelein, F. ; Potier, P. Eur. Pat. Appl. EP 253,739 (Cl.C07D305/14), 20 Jan 1988, *Chem. Abstr.* **1988**, *109*, 22763x.

[23] Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.*,**1993**, *26*, 160.



Scheme 1-1: Semisyntheses of Taxol® and Taxotere®.

At the same time, on the other side of the Atlantic Ocean, other semisyntheses were developed and the production of Taxol® and Taxotere® is now well established from a natural renewable source.[24] Extraction of the precursor from the needles harvested from the European Yew tree and a short synthetic sequence allows the production of Taxol® on a relatively large scale and provides sufficient amount for treatment. Until now those compounds are produced following a similar pathway patented by Holton (Taxol®) and licensed to Bristol-Myers Squibb and Rhône-Poulenc (Taxotere®). The method however is laborious and low yielding hence the high price of the drug. Taxol® remains prohibitively expensive for its wide scale use to be implemented in the fight against cancer. Thus a total synthesis of Taxol® will improve our knowledge of those drugs and allow the development of simpler and better analogues as it was done for natural structures like penicillins and

---

[24] (a) Denis, J.-N.; Greene, A.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier P. *J. Am. Chem. Soc.*, **1988**, *110*, 5917. (b) Ref 8. (c) Holton, R. A. 1991, U.S. Patent, 5,015,744. (d) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jagasinghi, L. R. *J. Org. Chem.*, **1991**, *56*, 1681.

tetracyclins in which the therapeutic utility has been improved by chemists. These include compounds that are not accessible from the natural product.

1.5.2 TOTAL SYNTHESES

Many chemists are intrigued by the unique structure of Taxol®. Its tetracyclic core with its highly oxygenated dense pattern and characteristic side chain is a challenge to any organic chemist. There are currently over 30 groups in the world that are working on the synthesis of taxanes.

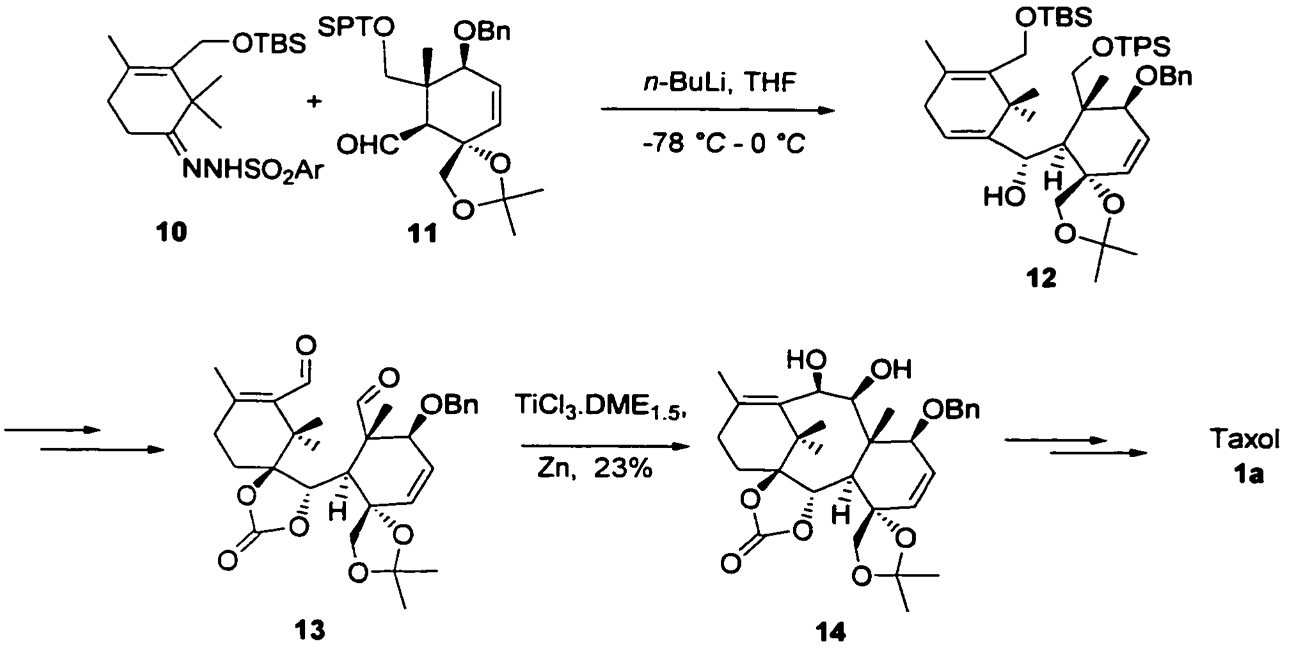
To date six groups have been able to achieve the total synthesis of this complex polyoxygenated diterpene. In all cases the method is aimed at the synthesis of the tricyclic ABC taxane core which is then coupled with the side chain in a similar fashion to the semisynthesis of Taxol® or Taxotere®.

1.5.2.1 Nicolaou's synthesis (A+C→AC→ABC)

Nicolaou devised a convergent sequence in which fully functionalised A ring **10** and C- ring **11** fragments were constructed separately and brought together to form the 8-membered B ring *via* a McMurry pinacol coupling, leaving the attachment of the side chain and the formation of the oxetane D ring for the final stages of the synthesis.[25] Nicolaou's synthesis has the advantage to be flexible, allowing the synthesis of a wide range of taxoids. However, the final yield is low.

---

[25] (a) Nicolaou, K.C.; Nantermet, P.G.; Ueno, H.; Guy, R.K.; Couladouros, E.A.; Sorensen, E.J. *J. Am. Chem. Soc.*, **1995**, *117*, 624. (b) Nicolaou, K.C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E.J.; Claiborne, C.F.; Guy, R.K.; Hwang, C.-K.; Nakada, M.; Nantermet, P.G. *J. Am. Chem. Soc.*, **1995**, *117*, 634. (c) Nicolaou, K.C.; Yang, Z.; Liu, J.-J.; Nantermet, P.; Claiborne, C.F.; Renaud, J.; Guy, R.K.; Shibayama, K. *J. Am. Chem. Soc.*, **1995**, *117*, 645. (d) Nicolaou, K.C.; Ueno, H.; Liu, J.-J.; Nantermet, P.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.*, **1995**, *117*, 653.

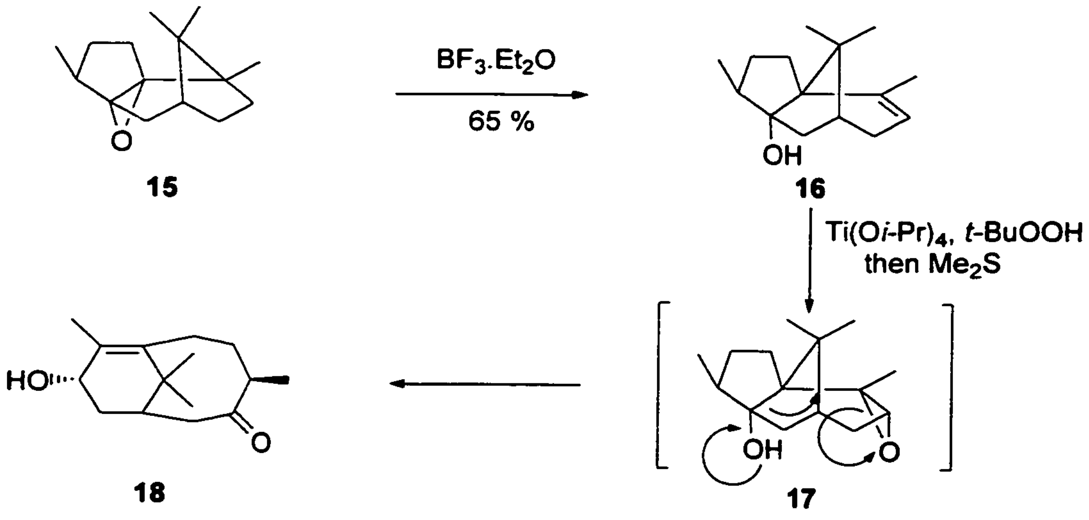


Scheme 1-2: Nicolaou's synthesis.

The Shapiro coupling reaction of the vinyl lithium reagent generated from the sulphonylhydrazone **10** with aldehyde **11** proceeded under standard conditions to give allylic alcohol **12** as a single diastereoisomer in 82% yield (Scheme 1-2). Directed epoxidation of the A ring followed by regioselective ring opening of the epoxide group and exposure of the resulting diol to excess KH and phosgene resulted in the formation of a cyclic carbonate intermediate as a protecting group of the diol. Further deprotection and oxidation of the *tert*-butylsilyl ether afforded dialdehyde **13** in good yield over 5 steps. B-ring closure occurs *via* a McMurry reaction mediated by $TiCl_3.(DME)_{1.5}$ and activated by Zn at 70 °C. Expected vicinal diol **14** was obtained in 23% yield as a mixture of compounds. Chemical resolution of **14** led to the enantiomerically pure diol which was then submitted to the final steps of the synthesis. The oxetane formation, oxygenation of ring A and introduction of the side chain proceeded without major problems to give Taxol®.

1.5.2.2 Holton's synthesis (A→AB→ABC)

Holton's approach to the total synthesis of Taxol®[26] is based on the synthesis of the taxane core from camphor using his previously developed epoxidation-fragmentation sequence (Scheme 1-3).[27]



Scheme 1-3: Epoxidation fragmentation of β-patchoulene oxide.

The tertiary alcohol **16** obtained from commercially available β-patchoulene oxide gives the bicyclic structure **18** similar to the AB ring system of Taxol® *via* fragmentation after epoxidation of the trisubstituted olefin.

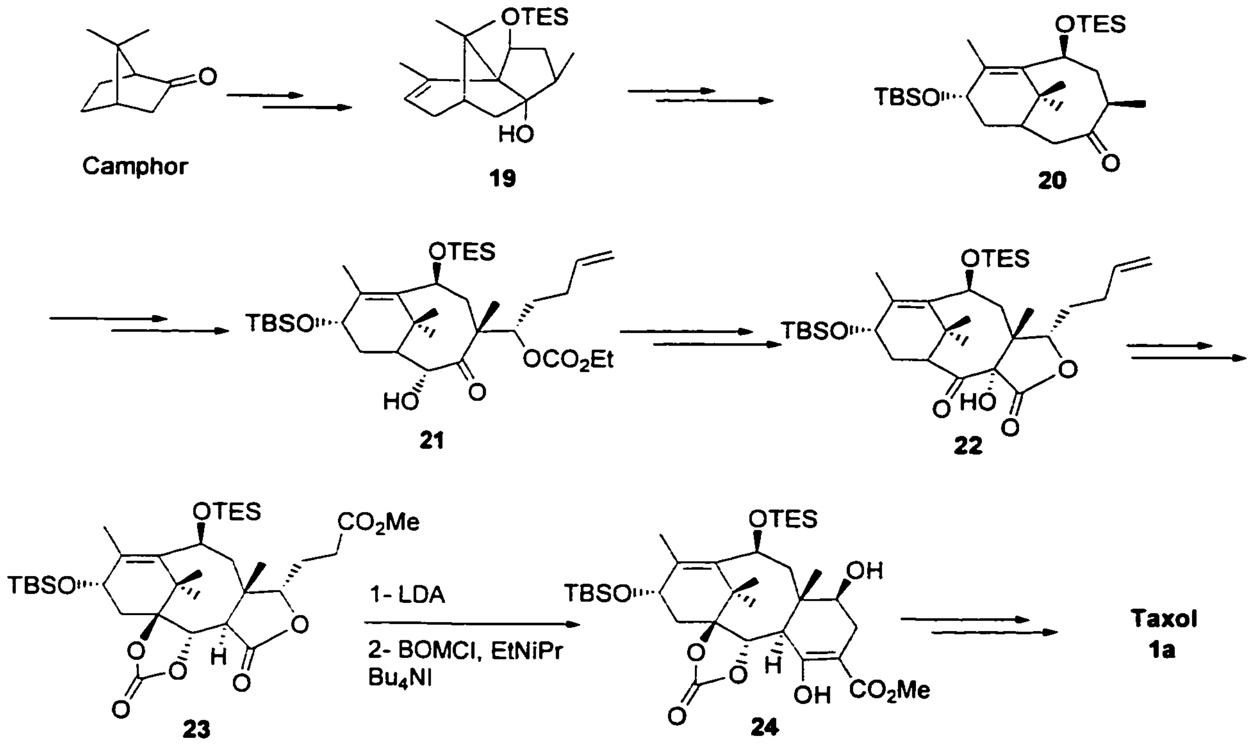
In the total synthesis, intermediate **19** obtained from camphor was epoxidized and treated with a Lewis acid to induce the rearrangement yielding the AB ring system **20** in 93 % (Scheme 1-4). Aldol condensation of **20** with 4-pentenal followed by protection of the resulting alcohol and hydroxylation at C-2 yielded hydroxycarbonate **21**. Reduction of the ketone gave a triol converted to another carbonate intermediate. Oxidation at the C-2 followed by treatment with LTMP afforded hydroxylactone **22** in 90 % yield *via* a

---

[26] (a) 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. (b) Holton, R. A.; Kim, H.-B.; Somoza, C.; 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*, 1599.

[27] (a) Holton, R. A. *J. Am. Chem. Soc.*, **1984**, *106*, 5731. (b) Holton, R. A.; Kennedy, R. M. *Tetrahedron Lett.*, **1984**, *25*, 4455.

rearrangement similar to the Chan rearrangement.[28] Appropriate functional group manipulations afforded lactone carbonate **23**.



Scheme 1-4: Holton's synthesis.

Completion of the C ring was achieved taking this intermediate through the oxidative cleavage of the terminal olefin to give the required ester to perform the Dieckmann cyclization and yielded the enol ester **24**. Taxol® was obtained from deprotected alcohol **19** in 4-5% yield.

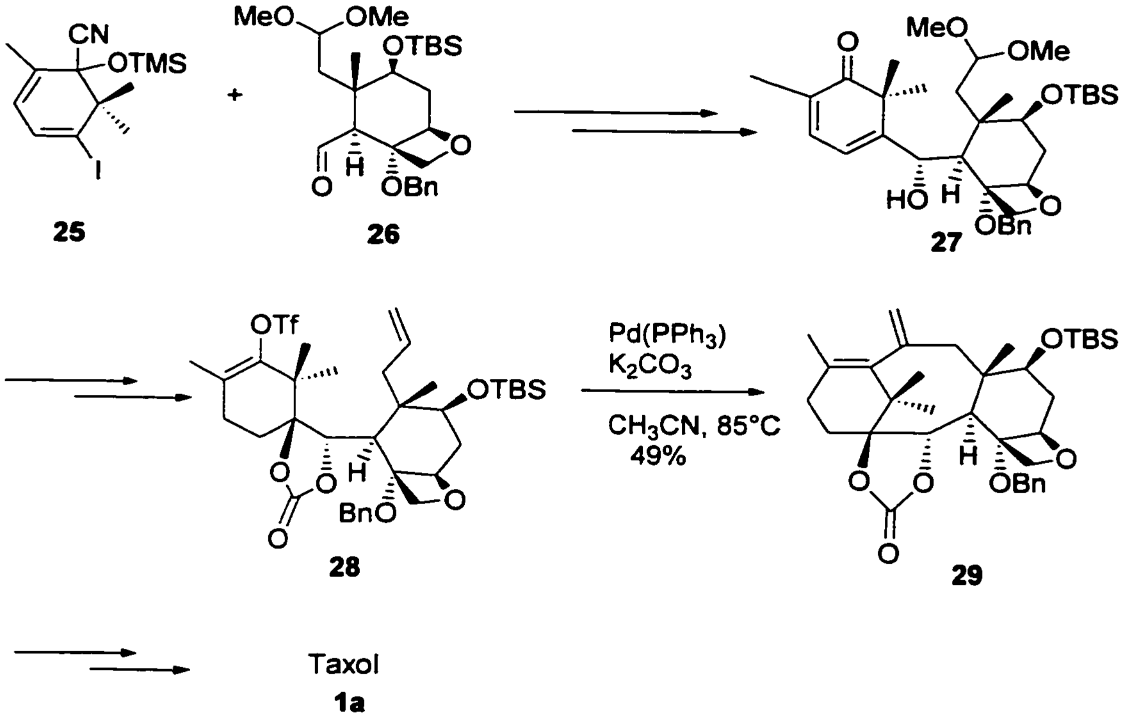
1.5.2.3 Danishefsky's synthesis (A+CD→ACD→ABCD)

In his total synthesis of Taxol®, Danishefsky coupled A ring and C ring substructures. The D ring was installed from the beginning on the C ring subunit and was carried along through the synthesis. Ring closure via Heck coupling at the C-9, C-10 position provided the 8-membered B ring giving rise to the tetracyclic structure of Taxol®.[29]

---

[28] Lee, S. D.; Chan, T. H.; Kwon, K. S. *Tetrahedron Lett.*, **1984**, *25*, 3399.

[29] 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.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.*, **1996**, *118*, 2843.



Scheme 1-5: Danishefsky's synthesis.

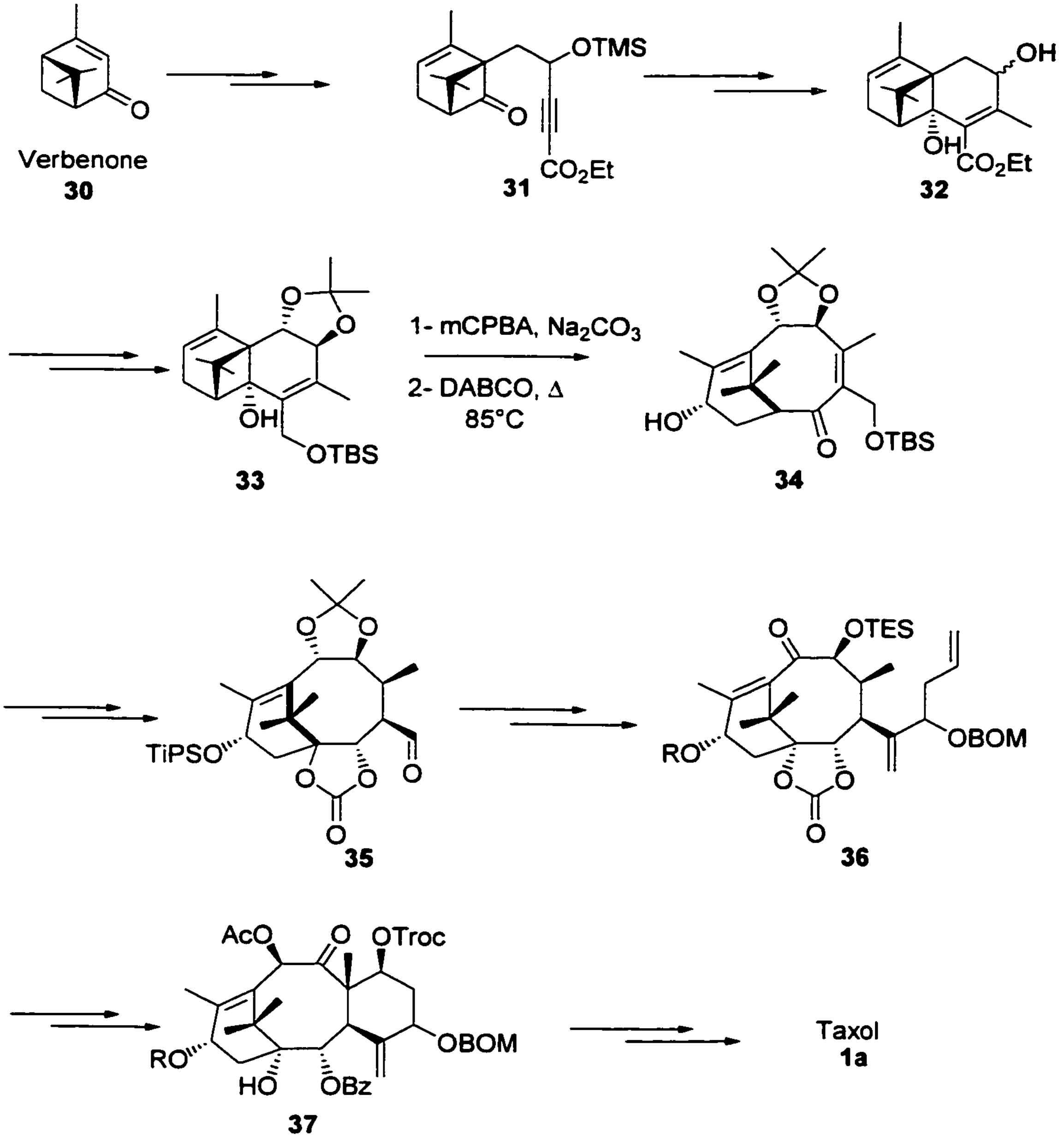
Coupling of aldehyde **26** and the lithium derivative of the iodo cyclohexadiene **25** gave rise to the single carbinol **27** after deprotection of the C-11 ketone. Formation of the cyclic carbonate at the C-1, C-2 position, enolization of the ketone to give the enol triflate followed by formation of the olefin upon Wittig olefination of the hidden aldehyde provided substrate **28**. The intramolecular Heck reaction proceeded smoothly to give the 8-membered B ring **29** from the A and C attached rings. Further functionalization and attachment of the side chain ultimately gave Taxol®.

1.5.2.4 Wender's synthesis (A→ AB→ ABC)

Wender's strategy relies on the recognition that the A ring could be supplied from pinene, an abundant natural product.[30] Functionalization of the compound would then lead to a bicyclic system which upon epoxidation-fragmentation provided the AB ring system.

---

[30] (a) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floerancig, P. E.; Glass, T. E.; Gränicher, C.; Houze, J. B.; Jänichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, 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. (b) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floerancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.*, **1997**, *119*, 2757.



Scheme 1-6: Wender's synthesis.

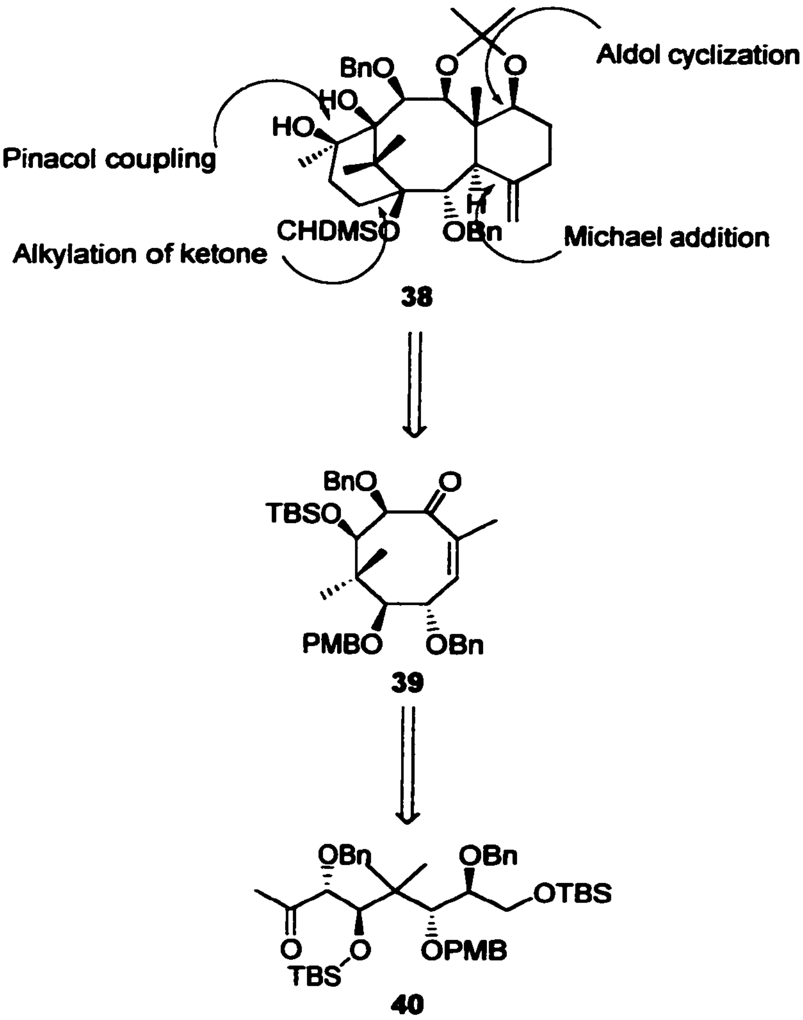
Verbenone **30**, the air oxidation product of pinene, was used as its dienolate to introduce the alkynyl chain. Photochemical rearrangement of the verbenone followed by addition of lithium ethyl propiolate led to the chrysanthenone derivative **31** (Scheme 1-6). Conjugated addition of methyl cuprate to the triple bond followed by cyclization of the intermediate yielded compound **32** with a masked taxane B ring in the form of a bicyclo[4.2.0]-octene subunit. Further functional modifications led to **33**. B ring **34** was then revealed in its expected form by a chemoselective epoxidation of the trisubstituted alkene followed by DABCO induced fragmentation and *in situ* protection of the generated alcohol at C-13. Introduction of the C-1 hydroxyl of Taxol®, stereoselective reduction of the C-2 ketone and protection of the diol with a carbonate followed by deprotection of the primary alcohol and oxidation provided compound **35**. The C ring was then installed by addition of the lateral chain on the aldehyde and inversion of configuration at C-10 *via* a series of regioselective protection-oxidation-reductions to yield the precursor **36**. Oxidation of the terminal olefin and the key aldol cyclization proceeded to give a mixture of epimers at the C-7. The undesired minor epimer can be converted into the required isomer by interconversion when treated with $NaHCO_3$ in MeOH and compound **37** is obtained after *in situ* protection of the C-7 hydroxyl with Troc. Introduction of the oxetane and the side chain led to Taxol® in 37 steps overall from verbenone.

1.5.2.5 Mukaiyama's synthesis (B→ BC → ABC)

Mukaiyama's strategy adopted a totally different route from the previously mentioned syntheses. The synthesis of the skeleton of Taxol® starts from the chiral B ring unit **39**, obtained from the optically active linear polyether **40**. The A and C rings are installed onto this framework by successive stereoselective Michael addition, intramolecular aldol reaction, stereoselective homoallylation and intramolecular pinacol coupling cyclization (Scheme 1-7).[31] The final product was obtained in 59 steps.

---

[31] (a) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Sakoh, H.; Tani, Y.; Hasegawa, M.; Saitoh, K. *Proc. Japan Acad. Ser. B*, **1997**, *73*, 95. (b) 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.



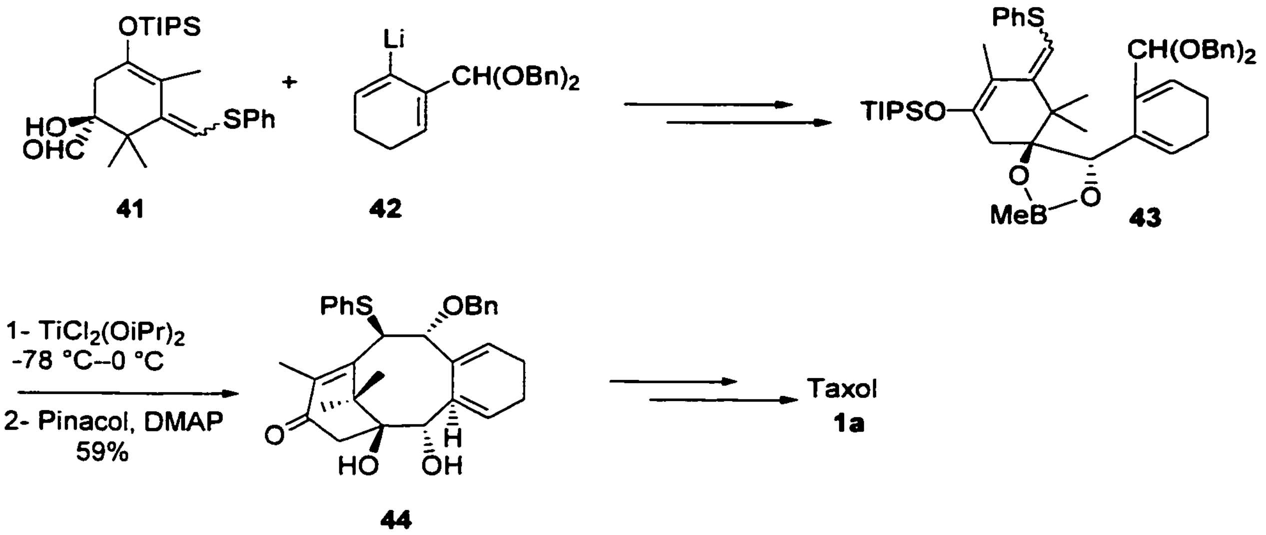
Scheme 1-7: Mukaiyama's retrosynthetic scheme.

1.5.2.6 Kuwajima's synthesis (A → AC → ABC)

Kuwajima's route proceeds similarly to Danishefsky and Holton by coupling the A and C precursor units of Taxol® followed by cyclization to form ring B.[32]

---

[32] Kuwajima, I.; Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H. *J. Am. Chem. Soc.*, **1998**, 120, 12980.



Scheme 1-8: Kuwajima's synthesis.

Addition of lithiated species **42** to the hydroxyaldehyde **41** under magnesium chelate stereocontrolled conditions followed by protection of the resulting vicinal diol gave **43** (Scheme 1-8). The B ring cyclization was induced with $Ti(Cl)_2(OiPr)_2$ and afforded compound **44**. Subsequent appropriate functionalizations led to Taxol® in 46 steps from the aldehyde.

Of these six total syntheses of Taxol®, none is viable on a large industrial scale. Some even required more than 60 steps to obtain the product. More approaches to Taxol® have been published but will not be discussed here. In accordance with our project to use Diels-Alder reactions to build the core of Taxol®, only studies using Diels-Alder strategies to build the tricyclic system will be reviewed.

1.6 DIELS-ALDER STRATEGIES IN THE TAXOIDS SYNTHESES

Several groups have investigated the synthesis of the taxane core using a Diels-Alder reaction. Nicolaou *et al.* have developed the synthesis of both the A and C ring synthons *via* a Diels-Alder cycloaddition. We will discuss here the efforts made by different groups to achieve the tricyclic taxane core using a Diels-Alder cycloaddition as a key step.

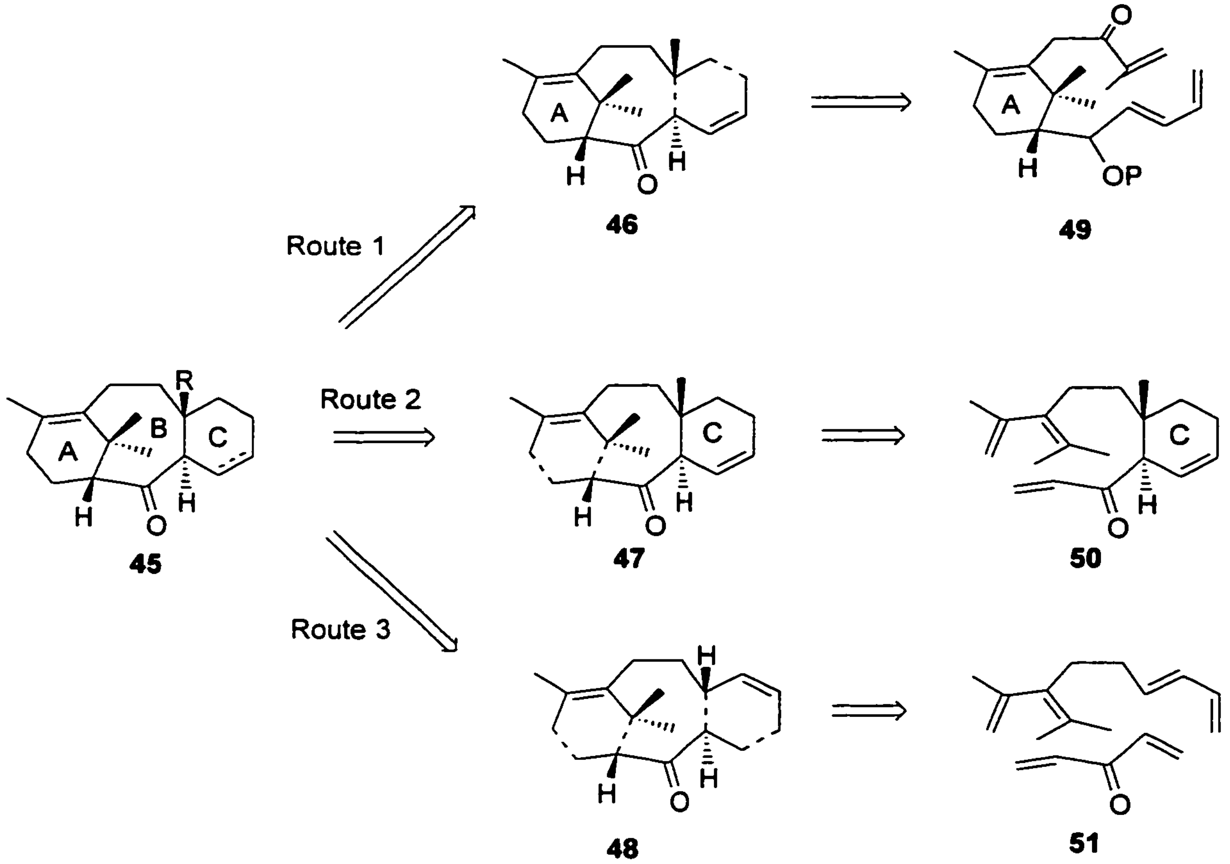


Figure 1-7: Diels-Alder approaches to the ABC ring system.

Several strategies can be used (Figure 1.7). The ABC ring system can be built from an A ring subunit (route 1) or the reverse strategy can be used, were a ring C synthon is the starting material (route 2). Alternatively a tandem Diels-Alder sequence has been reported (route 3).

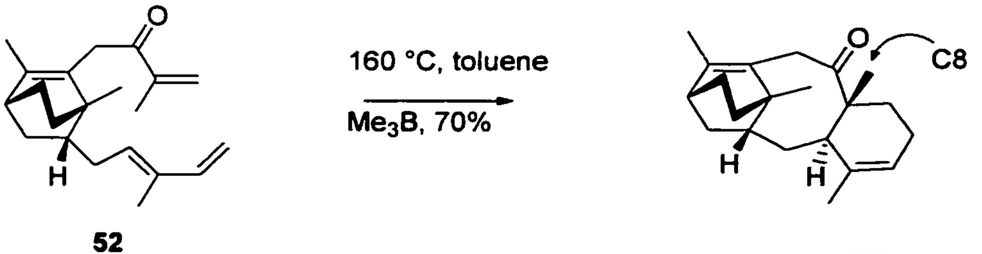
1.6.1 LEFT TO RIGHT SYNTHESES (FROM THE A RING TOWARDS THE C RING).

1.6.1.1 Sakan's and Craven's approach[33]

Sakan and Craven reported the formation of the ABC ring system of the taxane nucleus from a suitable precursor utilizing an Intramolecular Diels-Alder reaction (IMDA).

---

[33] (a) Sakan, K.; Smith, D. A.; Babirad, S. A.; Fronczek, F. R.; Houk, K. N. *J. Org. Chem.*, **1991**, *56*, 2311. (b) Sakan, K.; Craven, B. M. *J. Am. Chem. Soc.*, **1983**, *105*, 3732.



52

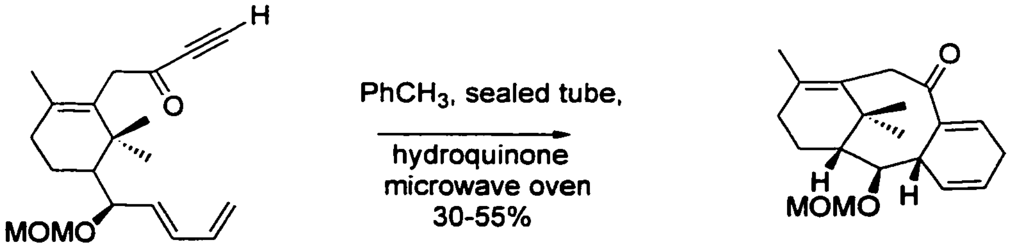
4:1 **53a:53b**
53b epimer of **53a** at C8

Scheme 1-9: IMDA cycloaddition of bicyclo[2.2.2]octane tethered compound (52).

The C ring was built starting with the bicyclo[2.2.2]octene A ring **52** designed to attain maximum entropic assistance for the cycloaddition. The rigidity imparted by the structure locks the A ring in a boat conformation therefore positioning the diene and dienophile in close proximity and allowing for a proper alignement. Consequently the reaction occurs at 160 °C under thermal conditions or at room temperature when a Lewis acid was used. Unexpectedly, the strereoselectivity of the reaction is reversed when a Lewis acid was used and the cis epimer of **53a** at C-8 was obtained.

1.6.1.2 Fallis' approach[34]

Previous work by the Fallis team had targeted the synthesis of the ABC ring system starting with a functionalised A ring and achieving the BC ring system via a Diels-Alder cycloaddition.



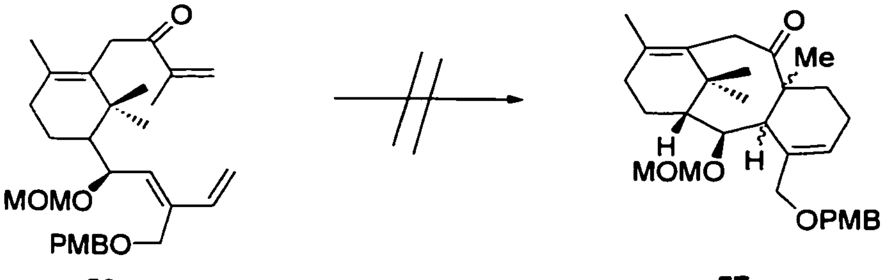
54 **55**

Scheme 1-10: IMDA cycloaddition of A ring tethered compound (54).

---

[34] (a) Fallis, A. G.; Lu, Y.-F. *Can. J. Chem.*, **1995**, *73*, 2239. (b) Lu, Y-F.; Fallis, A. G. *Tetrahedron Lett.*, **1993**, *34*, 3367. (c) Tjepkema, M.; Wong, T.; Wilson, P. D.; Fallis, A. G. *Can. J. Chem.*, **1997**, *38*, 1542. (b) Lu, Y-F.; Fallis, A. G. *Tetrahedron Lett.*, **1993**, *77*, 3367.

Cycloaddition of compound **54** proceeds in toluene with microwave activation. The reaction yields compound **55** in low yield and with the wrong relative stereochemistry at C-1,C-3. Other examples showed that a substituent on the diene inhibits the reaction (Scheme 1-11).



56 **57**

Scheme 1-11: Influence of substituents on IMDA cycloaddition.

More investigation showed that bulky protecting groups on the C2 alcohol and on the diene increase the steric hindrance in the transition state and the reaction fails to occur.

1.6.2 RIGHT TO LEFT SYNTHESES (FROM THE C RING TOWARDS THE A RING).

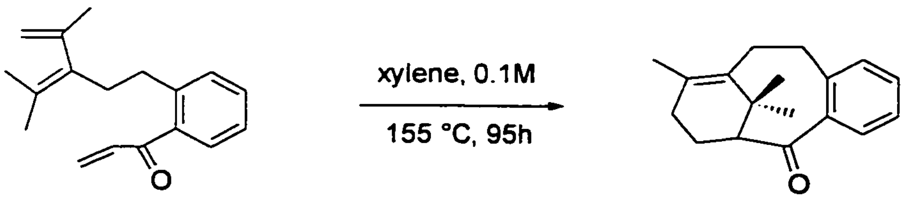
The use of intramolecular Diels-Alder reactions as a route to establish the AB subunit of taxanes has been studied by various groups as described in the following section.

1.6.2.1 Shea's studies[35]

The feasibility of the method was first demonstrated by Shea *et al.*[35a]. Using a phenyl ring as a planar tether control they were able to achieve the cyclization of compound **58** at 155 °C (Scheme 1-12).

---

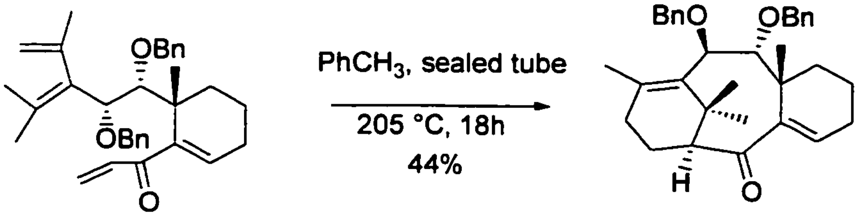
[35] (a) Shea, K. J.; Davies, P. D. *Angew. Chem. Int. Ed. Engl*, **1983**, *22*, 419. (b) Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.*, **1986**, *108*, 4953. (c) Jackson, R. W.; Higby, R. G.; Shea, K. J. *Tetrahedron Lett.*, **1992**, *33*, 4695. (d) Shea, K. J.; Haffner, C. D. *Tetrahedron Lett.*, **1988**, *29*, 1967. (e) Jackson, R. W.; Shea, K. J. *Tetrahedron Lett.*, **1994**, *35*, 1317.



58 **59**

Scheme 1-12: IMDA cycloaddition of phenyl tethered compound (58).

Shea also demonstrated that compounds with a C-8, C-9 and C-10 substituted upper side chain still cyclize, however, the reaction requires higher temperatures and lower yields were observed. The introduction of substituents affects the stereochemical outcome of the reaction and reversed stereochemistry is achieved at C-1 giving the C-1 epimer **61** of the natural baccatin (Scheme 1-13).

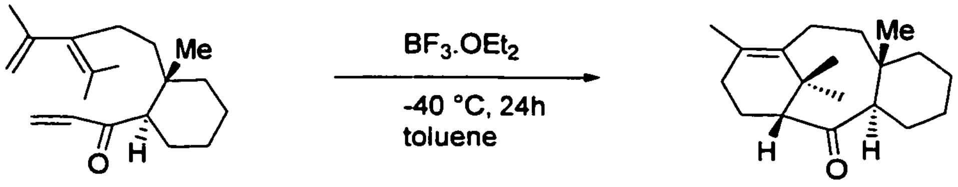


60 **61**

Scheme 1-13: Influence of the stereochemistry of substituents on IMDA cycloaddition.

1.6.2.2 Jenkins approach[36]

In the absence of a substituent at C-9 or C-10, Jenkins *et al.* demonstrated that the cycloaddition proceeded readily with a Lewis acid and the proper stereochemistry was obtained at the C-1 (Scheme 1-14).



62 **63**

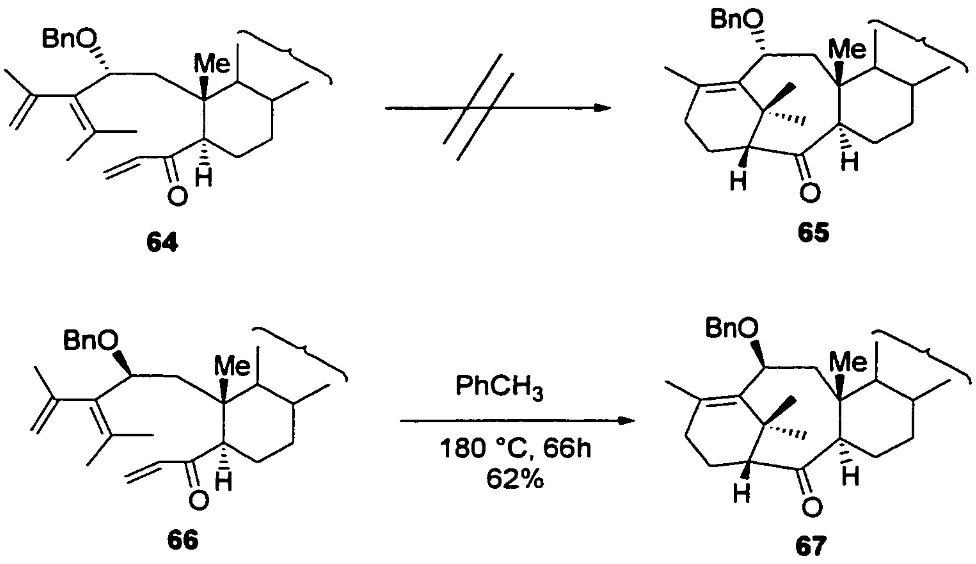
Scheme 1-14: IMDA cycloaddition of cyclohexane tethered compound (62).

---

[36] Bonnert, R. V.; Jenkins, P.R. *J. Chem. Soc., Perkin Trans 1*, **1989**, 413.

1.6.2.3 Danishefsky approach[37]

Danishefsky's attempts at IMDA demonstrated that the stereochemistry of the substituent plays an important role in the outcome of the reaction.



Scheme 1-15: Effect of the stereochemistry on IMDA reactions.

Compound **64** failed to react under any of the conditions tested, however its epimer at C-10 **66** reacts at 180 °C to give the cycloadduct **67** in 62% yield with the correct stereochemistry at C-1 and C-3. More studies on the effect of substitution on the C ring have showed that in presence of a Lewis acid the reaction proceeds to give the expected diastereoisomers.[38]

1.6.2.4 Winkler's approach[39]

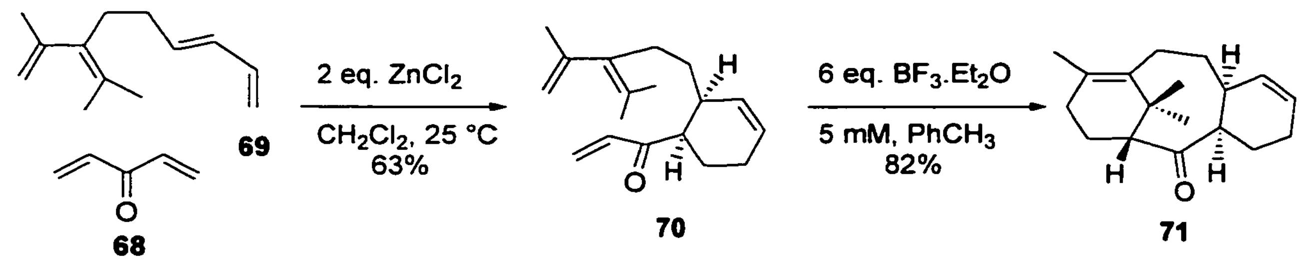
In this case both A and C rings of the taxane ring system are prepared via Diels-Alder cycloaddition reactions. The ABC ring system is obtained in a two-step sequence.

---

[37] (a) Danishefsky, S. J.; Kim, I. J.; Park, T. K. *Tetrahedron Lett.*, **1995**, *36*, 1015. (b) Danishefsky, S. J.; Kim, I. J.; Park, T. K.; De Gala, S.*Tetrahedron Lett.*, **1995**, *36*, 1019.

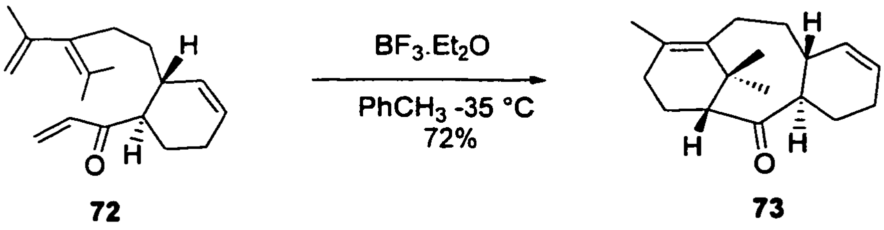
[38] (a) Rubenstein, S. M.; Williams, R. M. *J. Org. Chem.*, **1995**, *60*, 7215. (b) Vazquez, A.; Williams, R. M. *J. Org. Chem.*, **2000**, *65*, 7865.

[39] Kim, H. S.; Kim, S.; Winkler, J. D. *Tetrahedron Lett.*, **1995**, *36*, 687.



Scheme 1-16: Double Diels-Alder reactions sequence.

Intermolecular Diels-Alder cycloaddition of **68** and **69** proceeds regioselectively *via* zinc chloride catalysis affording **70** in 63% yield. Subsequent intramolecular Diels-Alder cyclization occurs *via* boron trifluoroborate catalysis to give compound **71** with a relative trans stereochemistry between C-1 and C-3 (Scheme 1-16).[39]



Scheme 1-17: Influence of the stereochemistry at the bridge on the IMDA reaction.

Winkler probed the effect of the stereochemistry of substituents at C-8 on the cycloaddition as it is believed that the stereochemical information is transmitted across the framework from the C ring to the A ring during the cycloaddition. As a result the trans bridged C ring **72** was built and submitted to cyclization. Diels-Alder reaction of **72** leads to the exclusive formation of **73** with the right relative trans stereochemistry between C-1 and C-3 (Scheme 1-17).[40]

These studies established that both cis and trans bridged compounds lead to the critical C-1, C-3 stereochemical relationship required for the synthesis of taxane. In most cases described above for the synthesis of the ABC ring system, the intramolecular Diels-Alder cycloaddition to build the multicyclic structure takes place easily. This improvement can be linked to the presence of a cyclic entity, which brings the diene and the dienophile in close proximity, thus allowing the proper alignment of the reactive species for the transition state.

---

[40] Kim, H. S.; Kim, S.; Ando, K.; Hark, K. N.; Winkler, J. D. *J. Org. Chem.*, **1997**, *62*, 2957.

This tether control proved to have an effect on the energy of activation on the reaction. The constraint in mobility brought to the reactive units helps to overcome entropic difficulties associated with the reaction between two free species.

1.6.3 TETHER CONTROL

In order to achieve the necessary control of stereoselectivity required to synthesize natural, active compounds, a temporary tether control group can be introduced in the molecule which will be removed later in the synthesis. Therefore, the products from an overall intermolecular reaction can be accessed exploiting the intramolecularity achieved by the tether control. A good choice of a tether group will not only enable the reaction to occur intramolecularly, but also limit the flexibility, providing the rigidity required for the reaction to take place. It will promote a dominant transition state and can induce asymmetry when chiral.

Many tether groups have been reported in the literature such as isopropylidene acetals[41], chiral auxiliaries[42] and planar moiety such as aromatic rings[43]. Metals have also been used for their coordination or complexation properties with the use of Lewis acids[44], magnesium chelation[45] and chiral copper complexes[46].

The use of a Carbon-Metal or Carbon-Metalloid bond as a tether control group is of particular interest, since the C-M bond in the product can be subsequently transformed. Various metalloid groups can be used but silicon-tethered groups[47] have been more widely reviewed. The tether control enables predictable control of stereochemistry in many reactions such as pericyclic reactions (ene reaction)[48], in free radical reactions[49], and metal insertion[50]. Their use in intramolecular Diels-Alder reactions[51] has been extensively studied.

---

[41] Fallis A.G. *Acc Chem. Res.*, **1999**, *32*, 464-474.

[42] (a) Chapman, K. T.; Bisaha, J.; Evans, D. A. *J. Am. Chem. Soc.*, **1984**, *106*, 4261. (b) Oppolzer, W.; Seletsky, B. M.; Bernardinelli, G. *Tetrahedron Lett.*, **1994**, *35*, 3509.

[43] Millan, S.; Pham, T.; Lavers, J.; Fallis, A. G. *Tetrahedron Lett.*, **1997**, *38*, 795.

[44] Bertozzi, F.; Olsson, R.; Frejd, T. *Org. Lett.*, **2000**, *2*, 1283.

[45] Fleming, F. F.; Wang, Q.; Steward, O. W. *Org. Lett.*, **2000**, *2*, 1477.

[46] Evans, D. A.; Johnson, J. S. *J. Org. Chem.*, **1997**, *62*, 786.

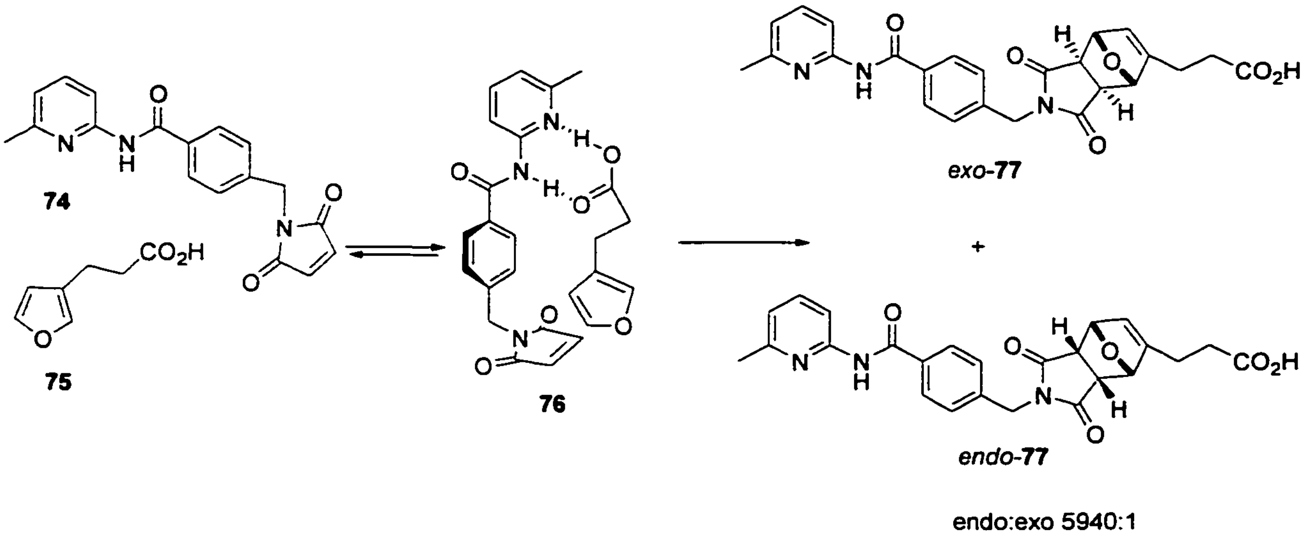
[47] (a) Fensterbank, L.; Malacria, M.; Sieburth, S.M. *Synthesis*, **1997**, 813. (b) Bols, M.; Skrydstrup, T. *Chem. Rev.*, **1995**, *95*, 1253.

[48] Robertson, J.; Middleton, D.S.; O'Connor, G.; Sardharwala, T. *Tetrahedron Lett.*, **1998**, *39*, 669.

[49] (a) Friestad, G. K. *Org. Lett.*, **1999**, *1*, 1499. (b) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Iton, K. *J. Org. Chem.*, **1983**, *49*, 2298.

[50] Kablean, S. N.; Marsden, S. P.; Craig, A. M. *Tetrahedron Lett.*, **1998**, *39*, 5109.

A planar moiety such as an aromatic ring have been shown to facilitate the cyclization by entropically favoring the reaction compared to their intermolecular counterparts.[43] Kinetic studies and molecular mechanics calculations were conducted in order to quantify the accelerating and stereocontrol effects of complexation of the diene and the dienophile in the Diels-Alder cycloaddition (Scheme 1-18).[52]



Scheme 1-18: Effects of the complexation of diene and dienophile on the IMDA cycloaddition.

Diels-Alder cycloaddition of complex **76** at 30 °C in $CDCl_3$ was followed by NMR and compared to a control reaction. The recognition mediated reaction showed a dramatic increase in stereoselectivity and a modest rate acceleration proving the superiority of the intramolecular reaction versus the intermolecular cycloaddition.

The role of chiral tether groups in Diels-Alder cycloadditions and their influence on the stereoselectivity was investigated by Shea.[53] The method used a silylacetal as a disposable tether and allowed good stereocontrol and an enantiomerically pure product was obtained. More studies showed that the use of a chiral isopropylidene acetal improved the selectivity of the reaction.[54]

The idea of using a temporary tether control group lead to a new strategy using the Diels-Alder reaction for the synthesis of Taxol® implemented in our group.

---

[51] Gillard, J. W.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R.; Fortin, R. *Tetrahedron Lett.*, **1991**, *32*, 1145.

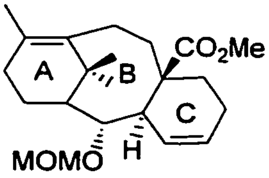
[52] Robertson, A.; Spencer, N.; Philp, D. *Tetrahedron*, **1999**, *55*, 11365.

[53] Gauthier, D. R. Jr.; Shea, K. J. *Tetrahedron Lett.*, **1994**, *35*, 7311.

[54] Wong, T.; Wilson, P. D.; Woo, S.; Fallis, A. G. *Tetrahedron Lett.*, **1997**, *38*, 7045.

1.7 RESEARCH OBJECTIVES

Our target molecule was designed according to the SAR studies mentioned previously.



78

Figure 1-8: Simplified structure.

Requirements 2 and 3 were incorporated in the molecule (Figure 1-8). The ABC ring system is present as well as the alcohol in position 2. This alcohol might be protected appropriately in later steps. The Taxol® side-chain can be added following procedures already described by Nicolaou or Kingston. The absence of the four membered ring oxetane is a problem. Recent computational studies by Snyder *et al.* investigated the consequences of the absence or the opening of the oxetane on the activity. Fortunately they concluded that the D ring is not necessary to carry the activity. Its replacement by an epoxide or a double bond should not change the bioactivity. In our case the double bond on the C ring could be functionalized to the epoxide or kept as it is. Attachment of the side-chain to the core represented here would then give analogues of Taxol® (Figure 1-9).

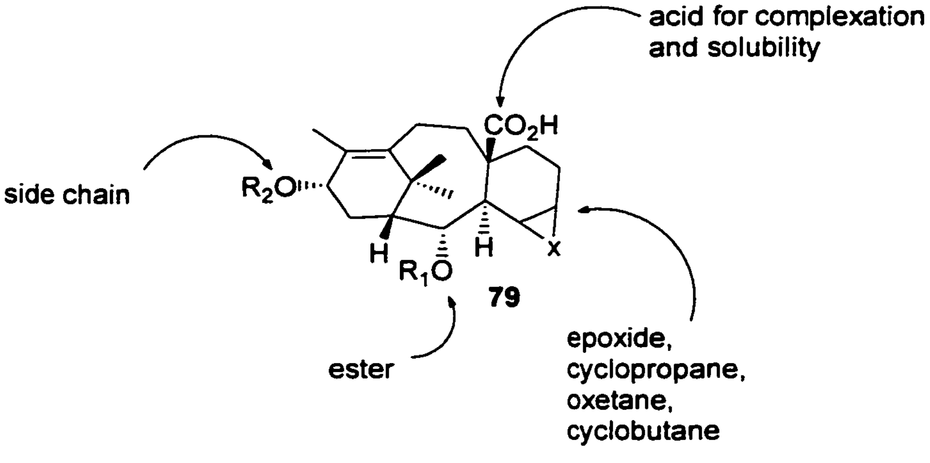
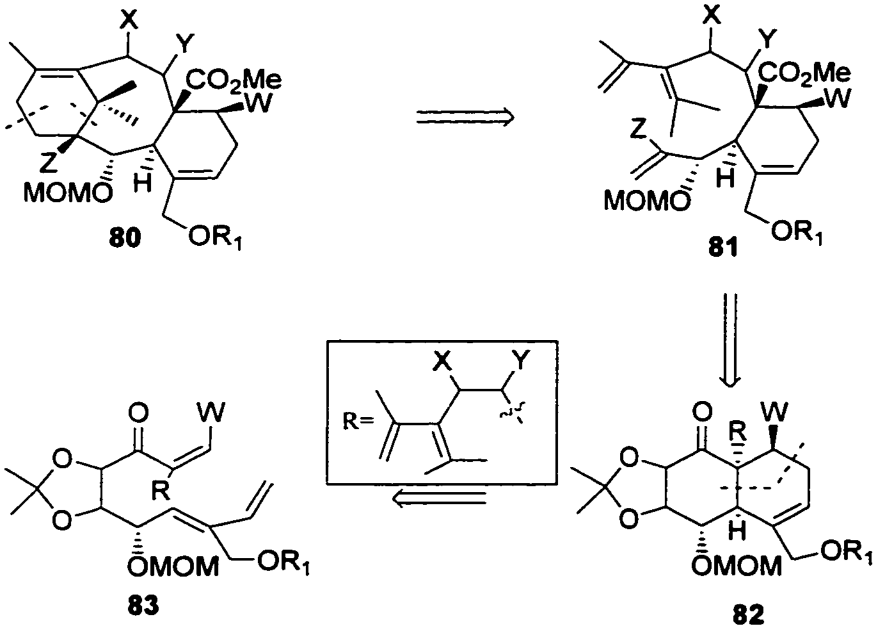


Figure 1-9: Possible analogues of Taxol®.

1.7.1 RETROSYNTHETIC PLAN TO PREPARE THE TAXANE NUCLEUS

The retrosynthesis of the taxane nucleus was designed to involve a double intramolecular Diels-Alder sequence using a temporary tether control.

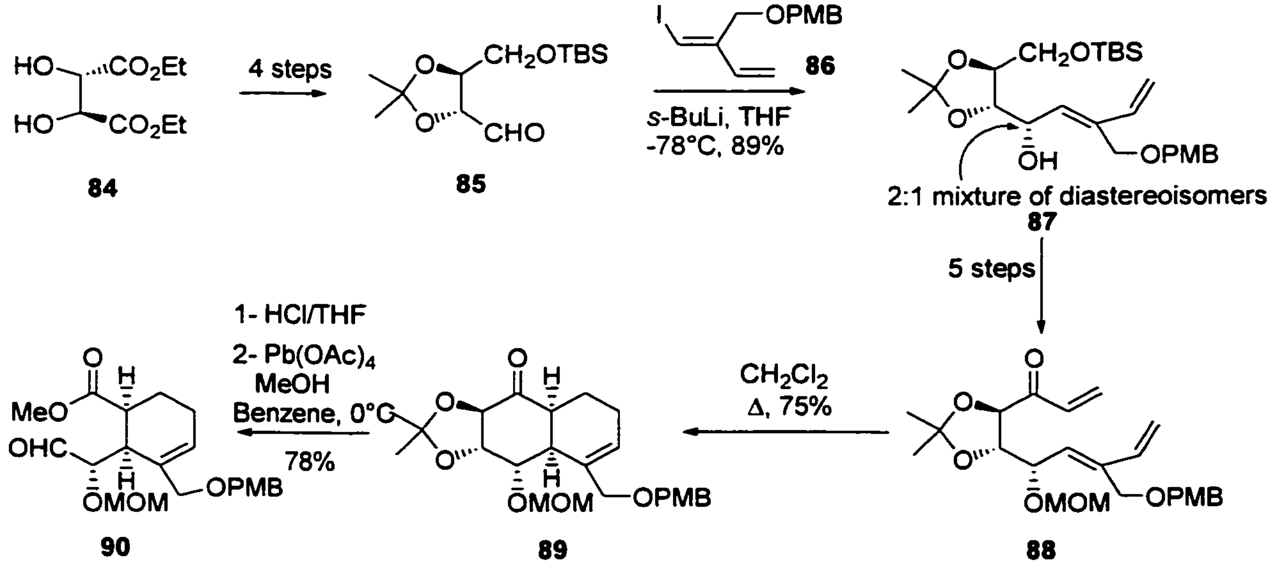


Scheme 1-19: Retrosynthetic strategy.

Removal of the D ring oxetane and the side chain of Taxol® leaves the simpler tricyclic structure **80**. Double disconnection between C-13, C-14 and C-1, C-17 in ring A suggests **81** as a precursor to an intramolecular Diels-Alder. The structure may contain all oxygen substituents but for convenience a model lacking a substituent on the diene chain will be studied (X, Y = H). As mentioned before, the oxygen functionalities on the upper part of Taxol® are not required for activity and study of a simpler system seems more prudent. The methyl ester present is thought to be a possible way to facilitate the intramolecular cyclization by chelating the oxygens present in the molecule. In addition, it provides a handle for remote functionalization and improved solubility *via* an acid salt. Compound **81** is obtained from cleavage of the protected diol present in decalin **82**. A second disconnection on the C ring between C-3, C-8 and C-6, C-7 of the decalin system affords the triene **83**. This bicyclic compound results from the intramolecular Diels-Alder cycloaddition of that precursor. Triene **83** has been designed so that the diene and the dienophile are maintained in close proximity due to the presence of the isopropylidene protecting group used as a disposable control group, which is removed later to give rise to the precursor for the second Diels-Alder reaction. The stereochemistry at the carbon centers bearing the protected diol is set by the starting material.

1.7.2 PREVIOUS STUDIES

In previous studies conducted in the group, diethyltartrate **84** was chosen as the starting material. Protection of the diol with an isopropylidene acetal followed by reduction of the diester to its diol and selective protection and oxidation led to aldehyde **85**.[55] The tether group has a syn configuration coming from the natural stereochemistry of the starting material. The lithium species of the iododiene **86** was added to the aldehyde to give diene **87** as a 2:1 mixture of diastereoisomers. The major diastereoisomer was separated and further deprotection and funtionalization afforded triene **88** with the diene and the dienophile in place for the Diels-Alder reaction.[54]

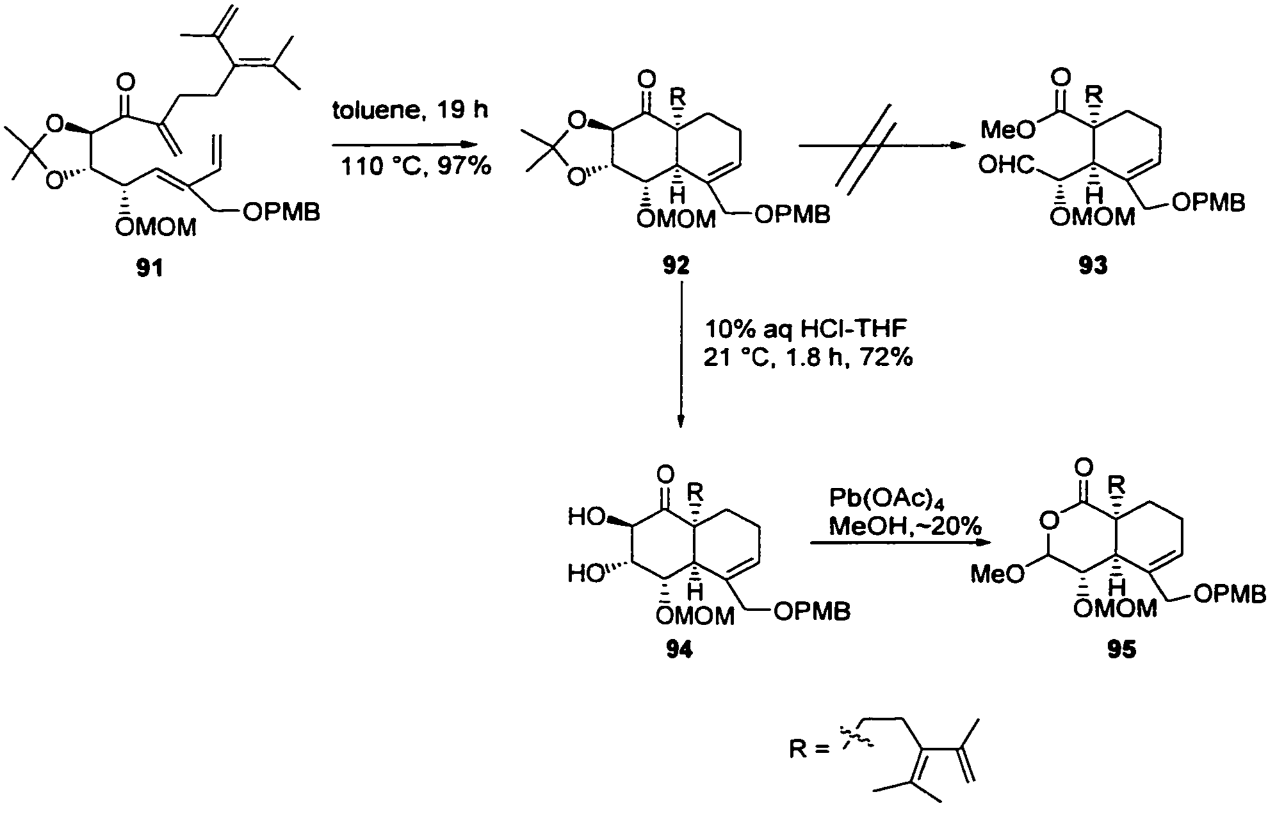


Scheme 1-20: Double Diels-Alder strategy with the trans acetal.

---

[55] Lida, H.; Yamazaki, N.; Kinayashi, C. *J. Org. Chem.*, **1987**, *52*, 3337.

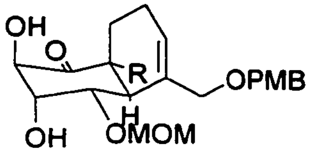
A simpler model with no substituent on the dienophile was studied first. The cyclization of compound **88** proceeded in good yield using thermal conditions and decalin **89** was obtained. Removal of the tether group by deprotection of the acetonide followed by oxidative cleavage of the resulting diol afforded the aldehydoester **90** in 78% yield.



Scheme 1-21: Deprotection and oxidative cleavage of the trans acetal (92).

In contrast, the presence of the diene side chain, on compound **91**, proved to be troublesome. The intramolecular Diels-Alder cycloaddition took place in toluene at high temperature and gave the decalin system **92** in 97% yield. Subsequent acid hydrolysis using standard conditions gave the expected diol **94**. Unfortunately, in contrast to the model study, the oxidative cleavage of this trans diol with lead tetraacetate in methanol was troublesome and did not generate the required ester-aldehyde **93**. Instead, a low yield (~20%) of the acetal-lactone **95** resulted from the capture of the intermediate aldehyde by the carboxylic acid and methanol. This diol was inert to treatment with sodium metaperiodate and related reagents, even at elevated temperatures.

It is well established that the ease and rate of lead tetraacetate glycol cleavage is dependent on the structure and stereochemistry of the substrate.[56] In this case it appears, that this lack of reactivity is a consequence of the preferred conformation of **94**, in which the methoxymethyl ether and the diene substituent (R) adopt equatorial positions to minimize their stereochemical interactions. This places the adjacent hydroxyl groups in a diaxial orientation as illustrated in Figure 1-10. Thus reagents that require a cyclic intermediate prior to bond cleavage will not be effective. The cleavage of the diol with lead tetraacetate or related reagents requires a 5-membered ring transition state which is difficult to attain with the preferred conformation of the decalin system **96**.



96

Figure 1-10: Preferred conformation of the decalin.

Oxidation of **94** to the triketone was not a clean reaction and reduction of the ketone in **94** with sodium borohydride to the triol followed by cleavage experiments was also unsatisfactory. Systematic epimerization of one center appeared problematic and thus alternative approaches had to be devised to improve the ring cleavage reaction.

1.7.3 A FRESH START

Avoidance of the problems linked with the trans (syn) acetal required a new strategy. The best alternative, for an easier removal of the tether group, was to use a 'cis-tartrate' precursor, with an *anti* configuration of the diol, for the cycloaddition. Applying the same sequence to the cis diethyltartrate would lead the cis diol, which should then be able to undergo the desired cleavage reaction. However the use of (L)-arabinose allows us to solve the lack of selectivity during the addition of the iododiene. The C-2 center would then have the appropriate stereochemistry inherent to Taxol®. Moreover, parallel research including

---

[56] (a) Criegee, R.; Hoger, E.; Huber, G.; Kruck, P.; Marktscheffel, F.; Schellenbergerger, H. *Liebigs Ann.* **1956**, *81*, 599. (b) Bunton, C. A.; Carr, M. D. *J. Chem. Soc.* **1963**, 770. (c) Moriconi, E. J.; Wallenberger, F. T.; O'Connor, W. F. *J. Am. Chem. Soc.* **1958**, *80*, 656.

this thesis has shown that the use of the cis isopropylidene acetal to facilitate Diels-Alder reaction gives better results than the trans acetonide.[57]

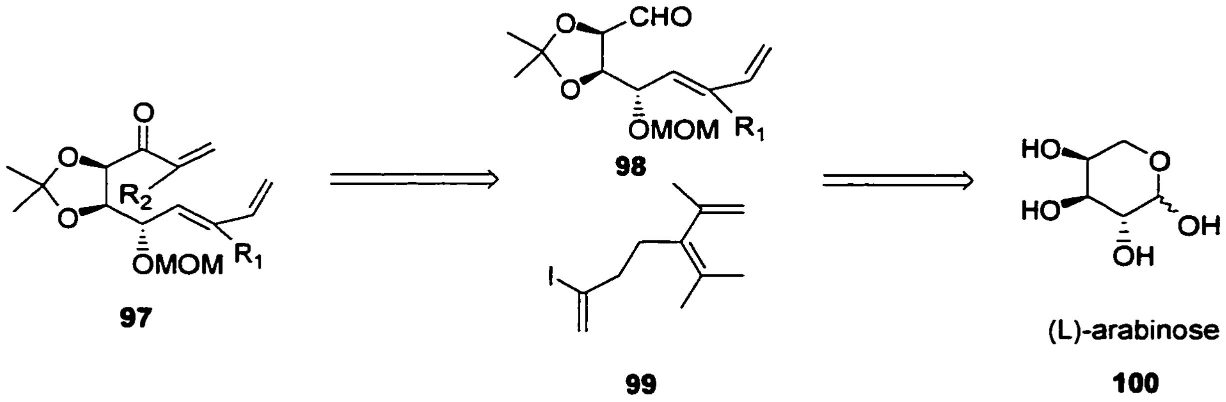


Figure 1-11: New retrosynthetic strategy for the decalin system.

(L)-arabinose is a readily available starting material with all the required stereogenic centers. It should allow the direct formation of the requisite cis isopropylidene acetal and carry the right stereochemistry at C-2 for the taxane benzoate. Functional group transformations will lead to the aldehydodiene **98**. Addition of the lithium derivative of the iodotriene **99** onto the aldehyde will give the expected triene **97** following the known procedure used in previous studies.

---

[57] Melekhov, A.; Forgione, P.; Legoupy, S.; Fallis, A. G. *Org. Lett.*, **2000**, 2, 2793.

RESULTS AND DISCUSSION

2 Chapter 2

Preparation of the taxane core

The double Diels-Alder strategy studied previously failed presumably because of the stereochemistry of the isopropylidene tether group. However, the strategy still possesses great utility and a simple inversion of one of the chiral centers should allow one to overcome the problem encountered with the oxidative cleavage of the trans (syn) diol. Initial investigations focused on the use of a 4-carbon synthon similar to the trans isopropylidene aldehyde **82**.

2.1 STARTING WITH A 4-CARBON ALDEHYDE BUILDING BLOCK

An identical strategy to the one described in Scheme 1-19 was developed where the trans (syn) isopropylidene was replaced by a cis (anti) isopropylidene (Figure 2-1).

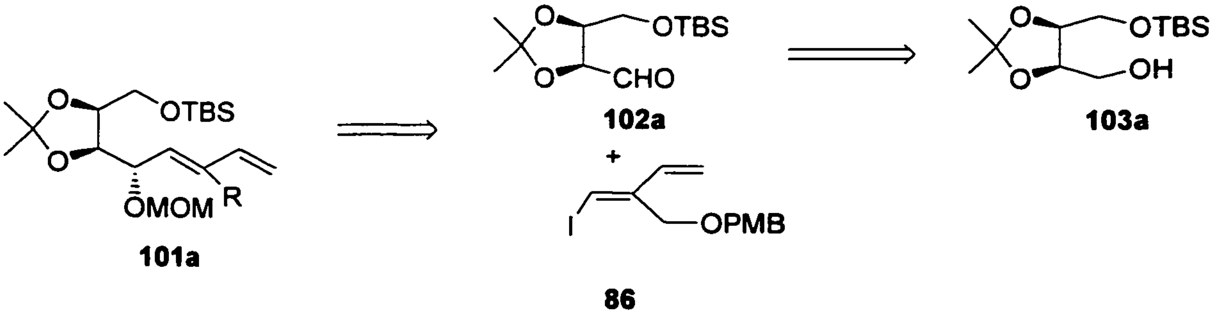
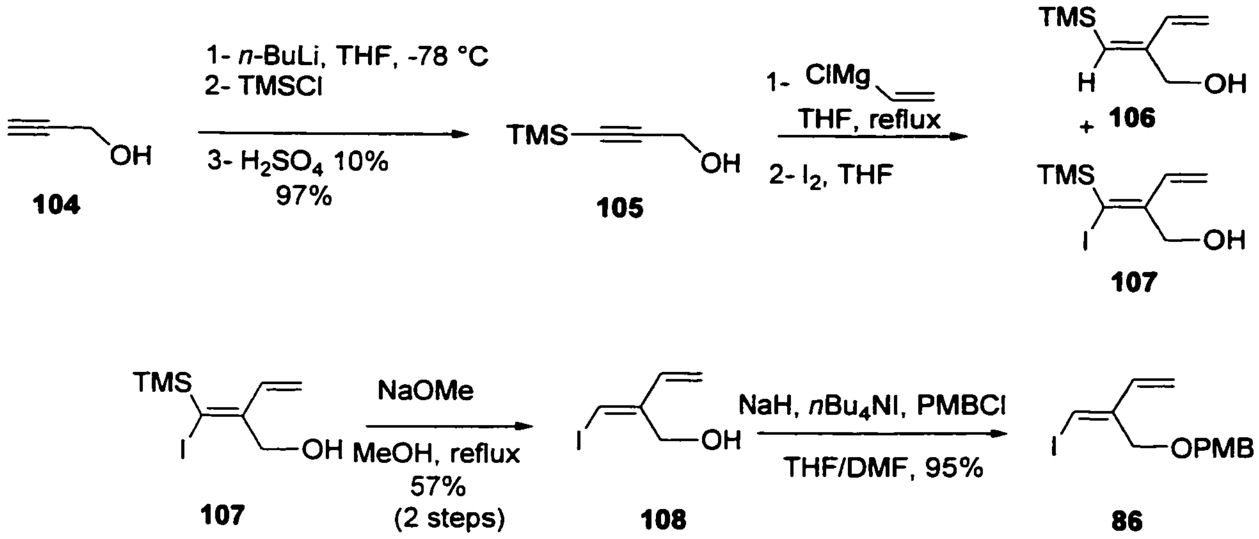


Figure 2-1: Retrosynthetic scheme to the 4-carbon building block.

The retrosynthetic analysis of our first approach to compound **101a** is outlined above. Disconnection of the disubstituted double bond leads to the chiral aldehyde **102a** and iododiene **86**. The iododiene is the identical unit that has been used for the synthesis of the trans acetal protected decalin **89** while the aldehyde resulted from the oxidation of the alcohol precursor **103a** whose synthesis has been developed previously in our laboratory for other purposes.

2.1.1 SYNTHESIS OF THE IODODIENE

The iododiene is a common building block used in different projects in the Fallis laboratory. It was prepared as previously described by Dr. T. Wong (Scheme 2-1).[58]



Scheme 2-1: Synthesis of the iododiene (86).

Deprotonation of propargylic alcohol with 2 equivalents of butyllithium followed by addition of trimethylsilylchloride yielded the desired alcohol in 97% yield. Addition of vinylmagnesium chloride to the trimethylsilylpropargylic alcohol **105** followed by treatment with iodine gave a mixture of the required (Z) diene **107** and a byproduct **106** with the ratio shifting with each trial. The iododiene **107** was purified and desilylated using sodium methoxide in methanol at reflux. Subsequent protection of the allylic alcohol **108** under standard conditions afforded iododiene **86** in 95% yield.

2.1.2 SYNTHESES OF THE CIS ISOPROPYLIDENE ACETAL

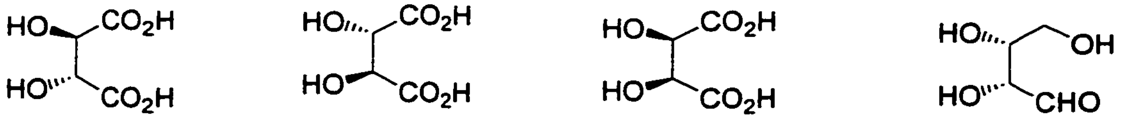
Several approaches were considered to synthesize aldehyde **102**. These are described in the following section.

---

[58] (a) Dr. T. Wong, Final Research Report, 1996, University of Ottawa. (b) Wong, T.; Tjepkema, M. W.; Audrain, H.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.*, **1996**, *37*, 755.

2.1.2.1 From but-2-en-1,4-diol

While enantiomerically pure trans isopropylidene aldehyde **85** was synthesized from (L)-diethyltartrate using a literature procedure,[55] the cis equivalent of this compound is a meso species which does not allow a facile selective functionalisation and resolution (Figure 2-2). In addition, derivatives of the meso tartaric acid are not commercially available and the most closely related species is the very expensive (D)-erythrose.



(L)-tartaric acid natural | (D)-tartaric acid | meso tartaric acid | (D)-erythrose

Figure 2-2: Commercially available chiral 4-carbon building blocks.

In order to obtain our cis aldehyde derivative a new strategy was devised (Figure 2-3).

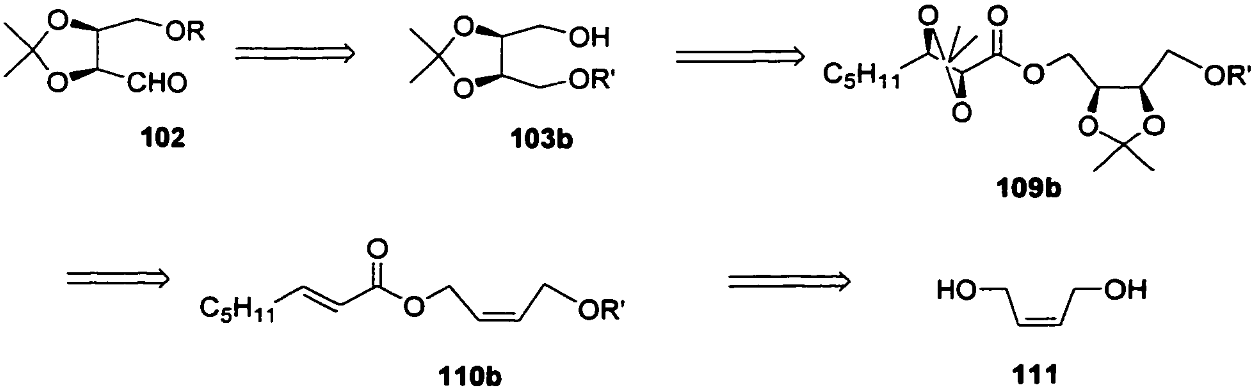
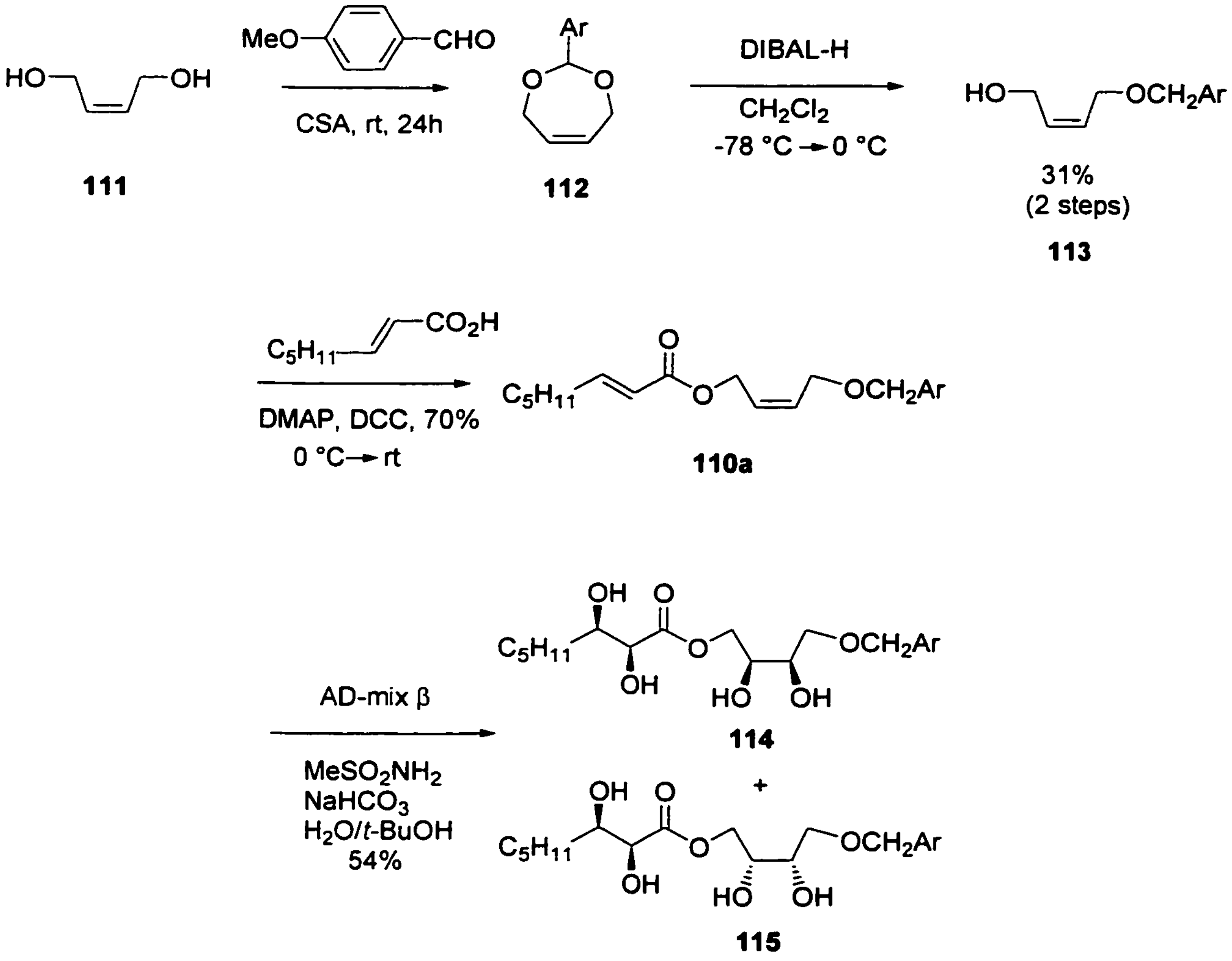


Figure 2-3: Retrosynthetic scheme towards aldehyde (102).

Aldehyde **102** can be obtained from the corresponding alcohol through a protection-deprotection sequence of **103b**, itself resulting from the hydrolysis of diacetonide ester **109b**. Protected diol **109b** could be obtained via asymmetric dihydroxylation of the unsaturated compound **110b**. Cleavage of the ester bond and deprotection arrives at the commercially available butenediol **111**.

The asymmetric dihydroxylation of a cis olefin is known not to proceed with good selectivity while the trans disubstituted olefin can be dihydroxylated with excellent enantiomeric excess. Using this difference in reactivity Merlic *et al.* showed that the octenoic acid can be used as an achiral auxiliary.[59] Dihydroxylation of the cis olefin portion of a derivative of unsaturated ester **110b**, where R' = Bn gave a 3:2 mixture of enantiomeric diols while dihydroxylation of the (E) olefin portion of the molecule proceeds in excellent enantiomeric excess with AD mix-β, giving a mixture of two diastereomers separable by purification. This method was applied to our ester.



Scheme 2-2: Use of an achiral auxiliary towards the synthesis of aldehyde (102).

---

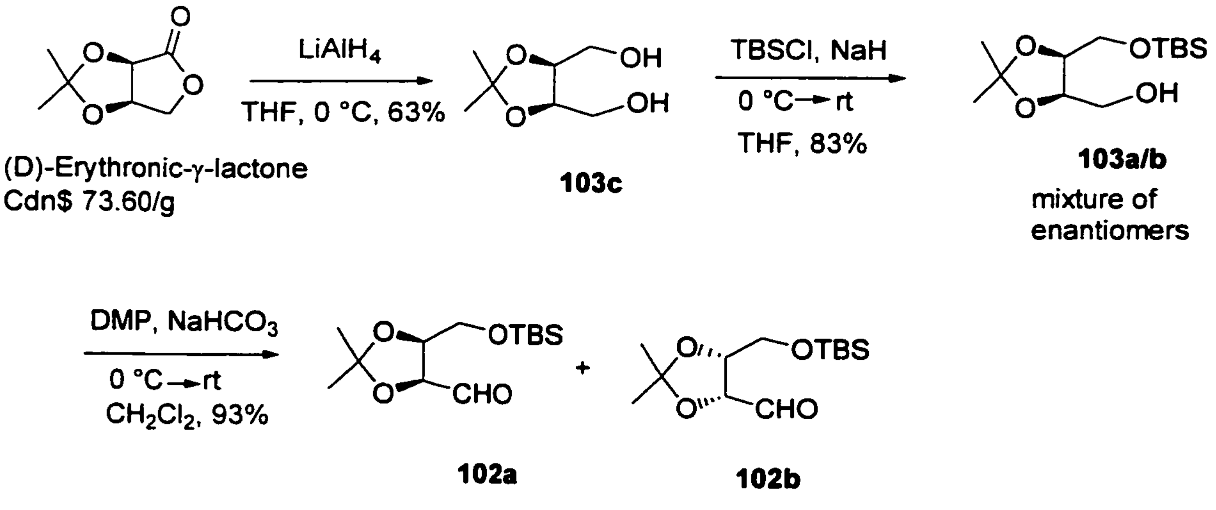
[59] Pauly, M. E.; Pringle, W. C.; Merlic, C. A. Department of Chemistry and Biochemistry, University of California, Los Angeles, unpublished results.

Selective monoprotection of butenediol **111** was obtained *via* formation of the cyclic acetal **112** using anisaldehyde and a catalytic amount of camphor sulfonic acid followed by reduction of the hemiacetal to the monoprotected diol **113** with DIBAL-H. The reaction has been reported to give a good yield of monoprotected compound[60] however when scaled up our yield diminished to 31%. Condensation of (*E*)-octenoic acid with alcohol **113** proceeded in good yield using DCC as a dehydrating agent and catalytic amount of DMAP. Asymmetric dihydroxylation of our unsaturated ester with AD mix β in presence of methylsulfonamide resulted in a mixture of two diastereoisomers with only one identified after crystallization.

However the difficulties in scaling up the protection, the loss in product during the dihydroxylation and more importantly, quality results in parallel studies led us to give up this route.

2.1.2.2 From D-erythronolactone

(D)-Erythronic-γ-lactone is commercially available but it is very expensive. However, it can be easily obtained in 3 steps from the readily available isoascorbic acid by oxidative cleavage and protection of the cis diol with an isopropylidene acetal.[61] The synthesis of the lactone was scaled up to one hundred grams by coworkers.[62]



Scheme 2-3: Synthesis of (102) from (D)-erythronic-γ-lactone.

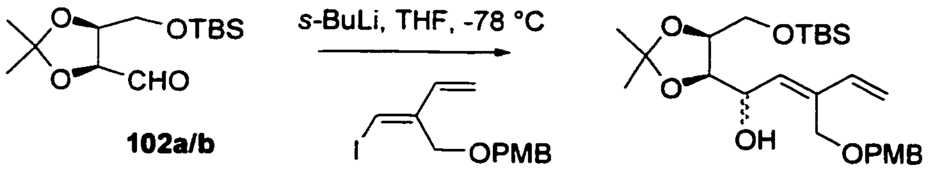
---

[60] Jodi Lavers, M. Sc. Thesis, 1998, University of Ottawa.
[61] (a) Cohen, N.; Banner, B. L.; Loprest, R. J.; Wong, F.; Rosenberger, M.; Liu, Y.-Y.; Thom, F.; Liebman, A. A. *J. Am. Chem. Soc.*, **1983**, *105*, 3661. (b) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.*, **1996**, *61*, 7217.
[62] Dr. P. Forgione, Ph.D. Thesis, 2001, University of Ottawa.

Enantiomerically pure D-erythronolactone was reduced to the meso diol compound **103c**. Selective monoprotection of the diol with sodium hydride and TBSCl afforded a mixture of enantiomeric alcohols in 83% yield. The mixture was taken through the next step and the free alcohol was oxidized with Dess Martin's periodinane to give aldehydes **102a** and **102b** in 93% yield.

2.1.3 COUPLING OF ALDEHYDE AND IODODIENE

The coupling of the aldehyde **102** with the lithiated derivative of the iododiene **86** did not give good results (Scheme 2-4). The reaction produced a 34% yield in a 2:3 diastereomeric mixture.



102a/b

86

mixture of diastereomers
101b

Scheme 2-4: Addition of iododiene (86) to aldehyde (102).

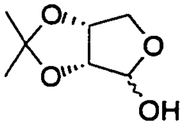
The reactivity of the cis and the trans isopropylidene acetals proved to be different. While the trans isopropylidene aldehyde **85** reacted with the iododiene in good yield under standard conditions (Scheme 1-19) and Grignard reagent added readily to the enantiomerically pure cis lactol derivative **116a**,[62] it was shown that its enantiomer **116b** does not react with the iododiene under the same conditions (Figure 2-4).[63] Therefore our racemic mixture of aldehydes **102a/b**, derivatives of compounds **116a** and **116b**, will probably reflect the results mentioned above in the lack of reactivity of the cis acetal-aldehyde towards the addition of the iododiene **86**, probably due to the change in stereochemistry α to the reacting center.

In both the synthesis we tried to develop, both enantiomers of aldehyde **102** are obtained. Starting with the butenediol, both enantiomeric diols and consequently aldehydes would be

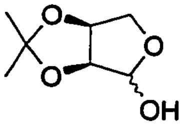
---

[63] Dr. S. Woo, Final Research Report, 1999, University of Ottawa.

obtained after hydrolysis of the ester if the route was carried on. As for the synthesis *via* the erythronolactone, the use of a meso intermediate means that a racemic mixture of aldehydes is formed. Therefore, a complex mixture of diastereomers would be obtained from the addition of the lithium derivative of the iododiene onto the racemic mixture of aldehyde **102**.



116a

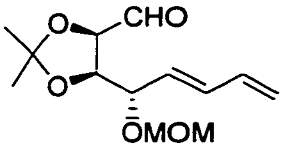


116b

Figure 2-4: Cis lactol (116)

In the end this route for the synthesis of the aldehyde **102** was abandoned and a novel strategy using a 5-carbon synthon was developed.

2.2 FORMATION OF THE DIENEALDEHYDE (117)



117

Figure 2-5: Dienealdehyde.

The enantiopure dienealdehyde **117** is a key unit for the synthesis of the taxane core. This compound can be obtained by functional manipulation of a starting material carrying the required oxygens and chiral carbon centers. A readily available source is desirable keeping in mind that the synthesis requires multiple steps. Two possible choices were envisaged. The first synthesis was developed to take advantage of a readily available enantiomerically pure starting material such as (L)-arabinose. A second synthesis began with (D)-guluno-γ-lactone.

2.2.1 STARTING WITH (L)-ARABINOSE

Carbohydrates are extensively used for the total synthesis of chiral complex molecules due to their many advantages.[64] Carbohydrates represent an unparalled source of enantiomerically pure starting materials of known absolute configuration. They are inexpensive compounds obtained from renewable sources and therefore can be use in large scale syntheses without supply difficulties. For this same reason, poor yields in the first steps of the process may be acceptable and chiral centers are usually preserved with great care. Consequently, the carbohydrate configuration can be used to provide excellent control of stereochemistry during functional group manipulations and discarded later on. They are easy to derivatize to provide useful synthons for highly oxygenated compounds with predetermined stereochemistry. In addition they show great potential and versatility for providing compounds with little resemblance to the parent sugar derivative but with excellent stereocontrol achieved without the use of expensive chiral auxiliaries. In our case, three stereogenic centers are required in the diene we are seeking to synthesize and can be provided by a natural aldose: (L)-arabinose. (L)-arabinose is obtained from a plant gum and costs approximately $ 1.32/g. [65]

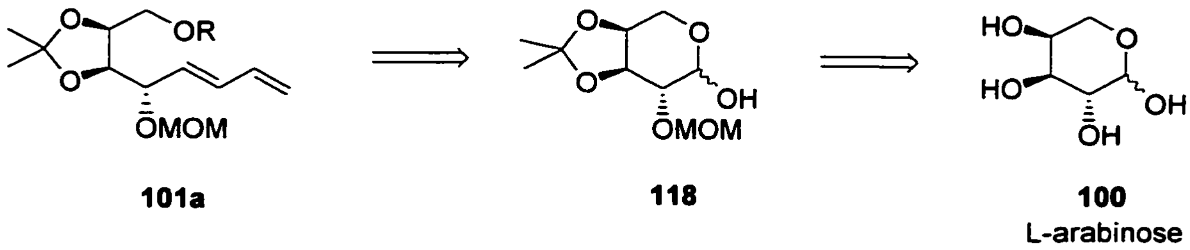


Figure 2-6: Retrosynthetic analysis of diene (101a).

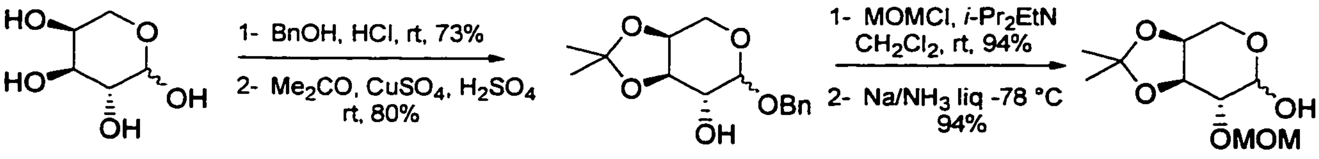
In the retrosynthesis presented in Figure 2-6, the required dienealdehyde **117** is an oxidized derivative of alcoholdiene **101a** This compound was formed by functionalization of the protected aldose **118**. Several steps are necessary to get to the protected hemiacetal form of the pentose from (L)-arabinose.

---

[64] Bols, M. *Carbohydrate Building Blocks;* John Wiley & Sons, Inc.**1996**, Chap.1.
[65] Aldrich® catalog, 1999-2000.

2.2.1.1 Synthesis of required hemiacetal (118)

The availability of both enantiomeric forms of arabinose, combined with simple protection of the different hydroxyl groups makes them an attractive starting material for the synthesis of highly functionalized chiral compounds. According to the retrosynthetic scheme detailed previously (Figure 2-6), the anomeric alcohol has to remain free for further manipulation and the cis vicinal alcohol has to be protected with an isopropylidene acetal that will be used as a tether control group. The synthesis of aldose derivatives unsubstituted at the anomeric alcohol involves a multistep sequence in which the reduced carbon has to be initially masked. Those conditions dictated in which order the protection had to be accomplished and what groups had to be used to allow for selective deprotection (Scheme 2-5).



100 **119** **118**

Scheme 2-5: Protection of (L)-arabinose.

By taking advantage of the different chemical properties of the hydroxyl groups, the anomeric alcohol was protected first. When unprotected C-1 alcohols have to be synthesized, a methyl ether group is usually used and selectively cleaved later by acidic hydrolysis in presence of other ethers. With the presence of the acetal in the molecule, it is impossible to use the methylether protecting group and (L)-arabinose was protected first with a benzylether group, followed by the formation of the cis acetonide to eventually provide the tether group. The remaining free secondary alcohol was then protected as a methoxymethylether. The first two steps have been described for the synthesis of benzyl-3,4-O-isopropylidene-β-D-arabinopyranoside from (D)-arabinose.[66] The hydroxyl group at C-1 is more nucleophilic than the other secondary alcohol, therefore the benzylether derivative was obtained exclusively from condensation of benzyl chloride formed *in situ* from benzyl alcohol and hydrochloric acid gas onto the arabinose. The furanoside was then condensed with acetone in the presence of anhydrous copper sulfate and a catalytic amount of sulfuric

---

[66] (a) Whistler and Wolfrom. *Methods in Carbohyd. Chemistry*, **1963**, *vol 2*, 386. (b) Ballou, C. E. *J. Am. Chem. Soc.*, **1957**, *79*, 165.

acid to give the cis isopropylidene **119** selectively. The methoxymethylether was then formed by reacting the last free alcohol with MOMCl and diisopropylethylamine and to yield the fully protected aldose in 94%.[67]

Several methods are known for debenzylation, such as acid induced cleavage, hydrogenolysis and metal reduction. The first one was not available to us with the presence of an acid sensitive isopropylidene protecting group in the molecule. However both hydrogenolysis and alkali metal-ammonia reduction were attempted. The hydrogenolysis of the benzoyl ether could be conducted with various platinum, rhodium, palladium and nickel catalysts but Raney nickel is cheaper and less delicate. Catalytic hydrogenation of the fully protected carbohydrate using Raney Nickel at ordinary pressure and temperature led to mixed results. Hydrogenation with commercially available W-2 Raney Nickel in ethanol 99% at room temperature led to the expected product **118** in 52% yield after two days at room temperature. Use of a more reactive W-4 Raney Nickel, made following the procedure developed by Pavlic and Adkins,[68] gave only poor results (21%)[69]. In an attempt to improve the yield of the reaction, the reductive elimination of the benzyl group was carried out with sodium metal in liquid ammonia at -78 °C.[70] This metal reduction was rapid with complete disappearance of the substrate after 20 min. and in excellent yield (94%). The overall yield to get to compound **118** was quite good, 51% over 4 steps, which is noteworthy because several hundreds of grams had to be synthesized.

Several routes can then be envisaged to form the diene. Many syntheses of complex molecules with biological activity require the formation of a double bond with excellent stereoselectivity. Various methods exist for the preparation of these alkenes but a standard route is the alkenation of a carbonyl to give a double bond via a Wittig-like reaction. This method has the advantage of providing olefins with both regio- and stereocontrol and is a simple, convenient, and efficient route.

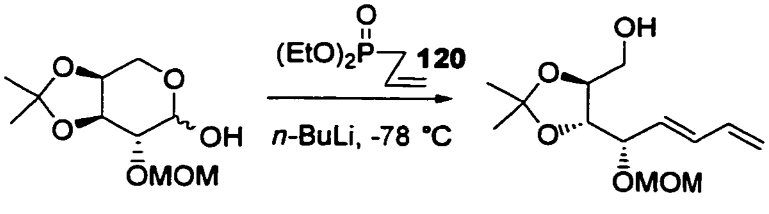
---

[67] Shinkai, I.; Volante, R. P.; Reamer, R. A.; Ryan, K. M.; Askin, D. *Tetrahedron Lett.*, **1988**, *29*, 277.
[68] (a) Pavlic, A. A.; Adkins, H. *J. Am. Chem. Soc.*, **1946**, *68*, 1471. (b) Pavlic, A. A.; Adkins, H. *Ibid.*, **1947**, *69*, 3039.
[69] Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu O. *Tetrahedron*, **1986**, *42*, 3021.
[70] Philips, K. D.; Zemlicka, J.; Horwitz, J. P. *Carbohyd. Res.*, **1973**, *30*, 281.

2.2.1.2 Formation of the diene

The direct construction of the conjugated diene in one step was designed using a Horner-Wadsworth-Emmons reaction (Scheme 2-6). The formation of a conjugated 1,3-diene *via* condensation of a stabilized allylphosphonate onto an aldehyde is well described in the synthesis of polyene containing natural products such as retinoic acid[71], fatty acids[72], vitamin D[73] and leukotrienes[74]. Moreover, the use of phosphoryl-stabilized carbanions over phosphonium ylides has the additional advantages of giving water-soluble phosphates as byproducts of the reaction, facilitating the isolation and purification of the products, in addition to increase reactivity. A careful choice of the reaction conditions will afford either (*E*)- or (*Z*)-alkenes.

In order to get the selectivity required for the formation of the (*E*) double bond, allyldiethylphosphonate **120** was used to introduce the diene portion onto the masked aldehyde (Scheme 2-6).



Scheme 2-6: Addition of allylphosphonate (120) to hemiacetal (118).

The phosphonate species **120** was prepared from the commercially available allylbromide, by the well-established Arbuzov phosphonylation.[75] Standard conditions for the condensation of the carbanion species resulting from the deprotonation of **120** with *n*-BuLi were shown to give **121** in 77% yield[76] but the reaction only worked on a small scale and all attempts at scaling up lead to a reduction in yield. This was disappointing and frustrating as insufficient material could be generated for further progress.

---

[71] Dominguez, B.; Iglesias, B ; De Lera, A. R. *J. Org. Chem.*, **1998**, *63*, 4135.
[72] Rotherham, L. W.; Semple, J. E. *J. Org. Chem.*, **1998**, *63*, 6667.
[73] Sesteko, J. P.; Mourino, A.; Sarandeses, L. A. *Org. Lett.*, **1999**, *1*, 1005.
[74] Petasis, N. A.; Seitz, S. P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.*, **1981**, 1195.
[75] Bhattacharya, A. K.; Thyagarjan, G. *Chem. Rev.*, **1981**, *81*, 415.
[76] Dr. Pete Wilson, Final Research Report, 1998, University of Ottawa.

Various conditions used to get to the expected compound **121** using the diethylphosphonate **120** are summarized in Table 2.1.

Entry	Equivalent of phosphonate	Base (eq.)	Solvent	Temperature (° C)	Reaction time	Yield (%)
1	2.5	*n*-BuLi[a] (2.3)	THF	rt	42 h[d]	34
2	2.4	*n*-BuLi[a] (2.2)	THF	rt 35° C	16 h + 2 h	18
3	4.4	*n*-BuLi[a] (4.2)	THF	rt	2 h	traces product+ polar mixture
4	6.4	*n*-BuLi[a] (6.2)	THF	rt	2 h	polar mixture
5	2.5	*n*-BuLi[b] (2.3)	DMF	rt	44 h	SM + polar mixture
6	1.4	*n*-BuLi[c] (1.5)	THF	rt reflux	24 h + 8 h	SM
7	2.5	*t*-BuOK (2.5)	Toluene/ DME	rt then reflux	2 h + 2 h	black gum

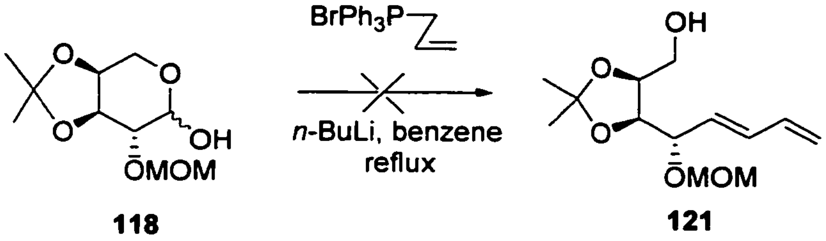
(a) Addition of *n*-BuLi to phosphonate then addition of the acetal at -78 °C. (b) Addition of *n*-BuLi then acetal at -50 °C. (c) 1.1 eq of NaH was added to the acetal before addition of the solution of phosphonate anion. (d) On small scale a 77% yield was obtained.

Table 2-1: Horner-Wadsworth-Emmons conditions.

Standard conditions with addition of the hemiacetal to a solution of 2.3 equivalents of the phosphoryl-stabilized reagent at low temperature (-78 °C) was attempted on a larger scale (Entry 1). The best yield obtained was 34% in spite of several attempts. The temperature of the reaction was then raised to 35 °C with no improvement in yield (Entry 2). An increased amount of phosphonate species (Entry 3 and 4) and a change to a more polar solvent (Entry 5) led to an unidentified polar mixture. Treatment of the lactol with sodium hydride prior to the addition of the reagent yielded only starting material (Entry 6). Under salt-free conditions a black gum was obtained (Entry 7). Last, the phosphoryl stabilized species was allowed to stir at 0 °C for 30 min. after the addition of the butyllithium then cooled back down to -78 °C before addition of the acetal solution and gave only traces of product by TLC. A reversal in the order of the addition was attempted too, with addition of the phosphoryl-stabilized reagent to the solution of acetal at -78 °C with no improvement. In each case a change in color of the reaction mixture, which turned from colorless to orange, characteristic of the formation of the anion in the Wittig chemistry occurred. Thus the formation of the reactive carbanionic species is not expected to be a problem.

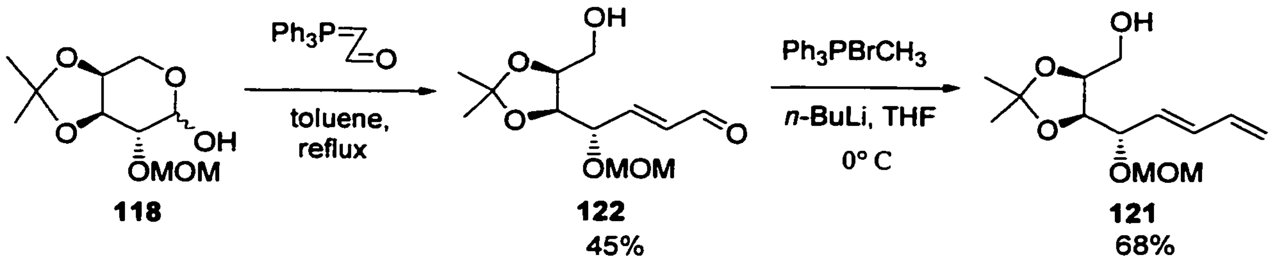
The use of 2 equivalents of the carbanion seemed to give the best result while too many equivalents led only to the more polar unidentified mixture of compounds. Heating did not improve the yield of the reaction but increased its rate. The best yield was obtained on a small scale. Unfortunately the reaction could not be scaled up and was not reproducible in spite of several attempts.

In an attempt to install the diene portion on our lactol the allytriphenylphosphonium bromide was condensed with the closed form of the (L)-arabinose (Scheme 2-7). The reaction failed to give any product but the condensation of such semi-stabilized ylide like allylphosphoranes rarely shows remarkable stereoselectivity in the formation of the double bond and is known to stop at the addition of the carbanion to the carbonyl, short of the elimination step.



Scheme 2-7: Addition of an allylphosphorane to hemiacetal (118).

More research on the reactivity of these lactols has shown that stabilized ylides react to give the olefin in good to excellent yields. Finally a two-step sequence was developed to get to the conjugated diene using two consecutive Wittig reactions (Scheme 2-8).



Scheme 2-8: Formation of diene (121) *via* double Wittig reactions.

Lactol **118** was condensed with stabilized (triphenylphosphoranylidene)acetaldehyde to give the conjugated aldehyde **122** in 45% yield with the correct geometry of the double bond.[77] In spite of long reaction time 46% of starting material was recovered. Subsequent addition of the isolated product onto the lithium derivative of the methyltriphenylphosphonium salt resulted in the formation of the expected dienol **121** in 68% yield. The overall yield of those two steps is only 30% and a better route is still required.

Previous studies of the condensation of triphenylphosphinecarboxylatemethylene onto ribolactol, allolactol, and arabinolactol have shown that the selectivity of the outcoming double bound is influenced by the C4-hydroxyl group stereochemistry.[78]

However, fewer reports described the condensation of a phosphonate onto carbohydrate-derived lactols. The reactivity of the lactol is dependent on the amount of free aldehyde in equilibrium with the closed form of the aldose (Figure 2-7).

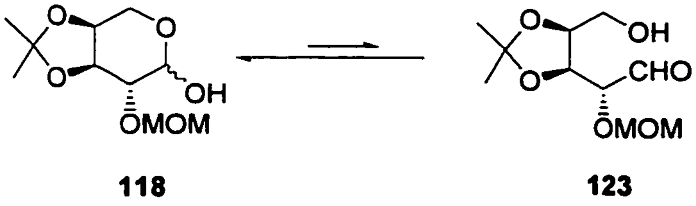


Figure 2-7: Hemiacetal-aldehyde equilibrium.

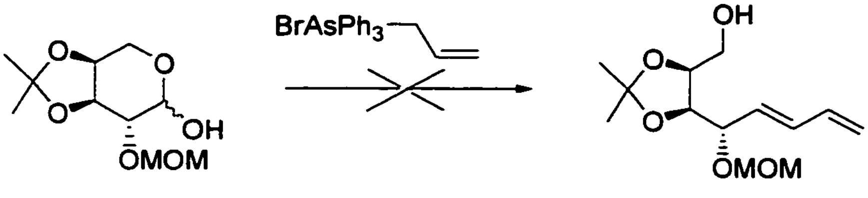
The disapearance of the aldehyde present in the solution should drive the equilibrium to the right, hence providing more of the reactive species. However, in our case the condensation

---

[77] (a) Deng, Y.; Salomon, R. G. *J. Org. Chem.*, **1998**, *63*, 7789. (b) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.*, **1982**, *47*, 1373.

[78] Wilcox, C. S. *Tetrahedron Lett.*, **1988**, *29*, 6823.

does not occur. This may be explained by a lack of reactivity of the phosphorus stabilized species or the aldehyde. Seeking to assess the potential of other reagents to react with the aldehyde, we looked at the possibility of using arsonium ylides. Stabilized arsonium ylides have been reported to be more reactive than the corresponding phosphonium ylides.[79] Recent studies have shown that stabilized arsonium ylides react readily with protected or semi-protected pyranose or furanose derivatives to give the expected (*E*) alkene in good yield. [80]



118 **121**

Scheme 2-9: Addition of an arsonium ylide to hemiacetal (118).

Allyltriphenylarsonium bromide was synthesized by heating triphenylarsonium and allylbromide at reflux.[81] Treatment of the resulting salt with butyllithium at -40 °C followed by addition of the lactol failed to give the expected product (Scheme 2-9).

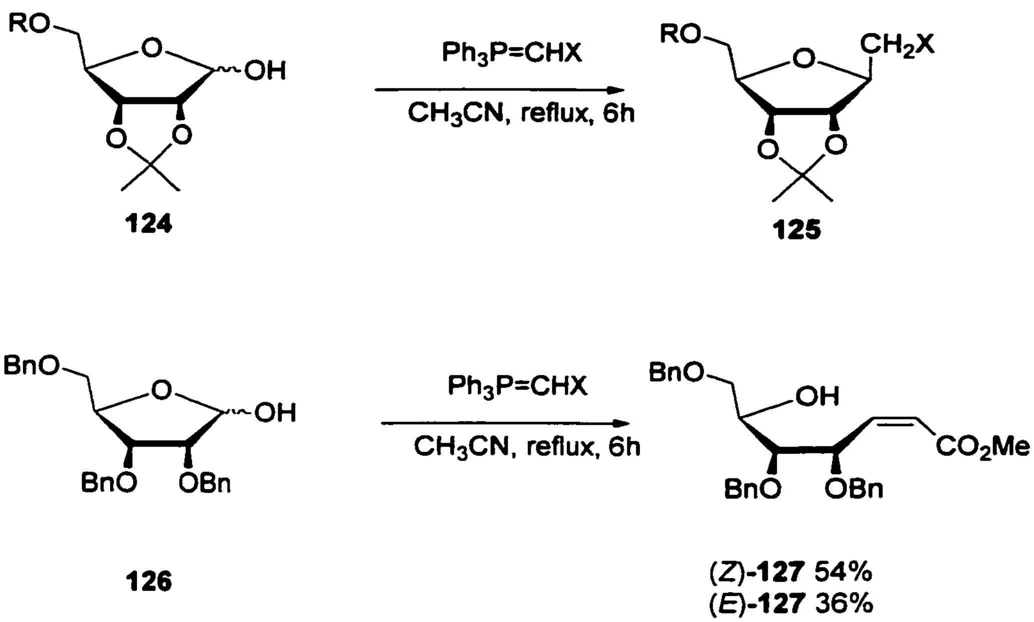
The ylide carbanion as a weak base should help in the hemiacetal ring opening process to give the free aldehyde. However, it has been shown that in the case of carbohydrates used as the carbonyl species, the protective group influences the result of the reaction.

---

[79] Aitken, R. A.; Blake, A. J.; Gosney, I.; Gould, R. O.; Lloyd, D.; Ormiston, R. A. *J. Chem. Soc. Perkin Trans I*, **1998**, *11*, 1801.

[80] Lievre, C. et al *Carbohydr. Res.*, **1997**, *303*, 1.

[81] Raizada, M. S.; Srivastava, T. N. *J. Indian Chem. Soc.*, **1996**, *73*, 646.



124

125

126

(*Z*)-**127** 54%
(*E*)-**127** 36%

Scheme 2-10: Influence of the protective groups on the reactivity of hemiacetals.

In the presence of an acetonide protecting group on the reactive lactol, the condensation of the stabilized ylide leads to a C-glycoside resulting from the Wittig reaction followed by a Michael addition (Scheme 2-10). When the acetonide protecting group is replaced by benzyl groups, a mixture of (*Z*) and (*E*) olefins was obtained under the same reaction conditions showing that the constraint brought by the isopropylidene increases the probability of having the aldehyde in its closed form.[82]

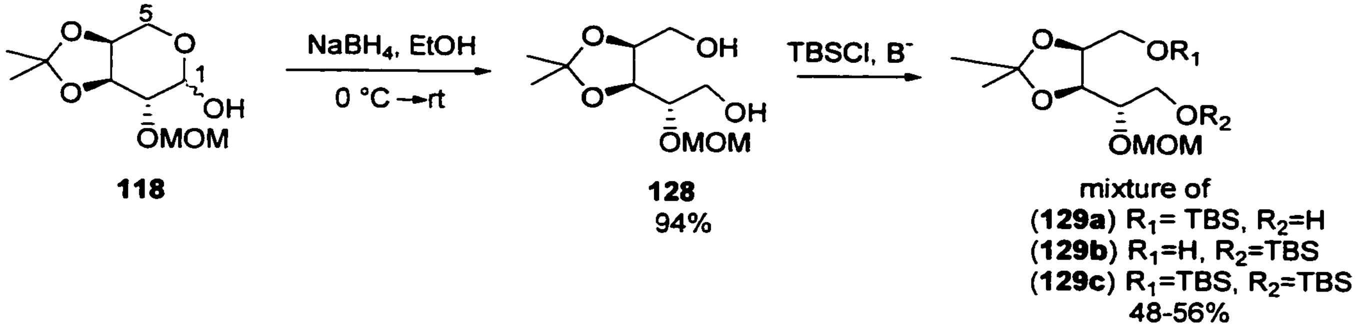
Therefore, better access to the carbonyl species was required. It appeared that the problem resulted from a near non-existent concentration of free aldehyde in solution due to the strain induced by the cis isopropylidene. The synthesis of the free aldehyde was designed *via* a totally different route, with the expectation that this would solve the problems outlined above.

2.2.1.3 An alternative to the free aldehyde

Various other routes towards the free aldehyde **123** were tried using the material in hand. A first attempt to gauge the reactivity of the hemiacetal through its open form was made. Diverse attempts to differentiate the hydroxyl groups on C-1 and C-5 led to mixed results (Scheme 2-11).

---

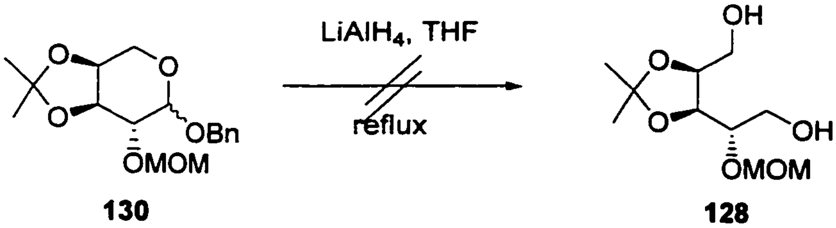
[82] Moffat, G. *J. Am. Chem. Soc.*, **1975**, *97*, 4602.



Scheme 2-11: Reduction and protection of hemiacetal (118).

The lactol was reduced to the diol **128** in 93% yield using sodium borohydride in ethanol. The two primary alcohols generated by the reaction have different environments resulting from different substitution in the α position. By choosing a bulky protecting group we hoped to see a slightly different reactivity of each alcohol to provide some selectivity during the protection step.

Addition of one equivalent of tertbutyldimethylsilylchloride to the alcohol **128** in presence of one equivalent of NaH in THF gave 56% of a 1:1 mixture of both monoprotected alcohols **129a** and **129b**. Under standard protection conditions with imidazole as the base in dichloromethane afforded a similar 1:1 mixture of regioisomers **129a** and **129b** in 48% as well as 11% of diprotected alcohol **129c**.



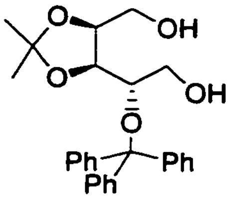
Scheme 2-12: Attempt at a one-pot deprotection-reduction of protected hemiacetal (130).

Due to the existence of a protocol for the deprotection of a benzylether and reduction of the resulting lactol in one step,[83] **130** was submitted to the vigorous reduction conditions with

---

[83] Kutney, J. P.; Abdurahman, N.; Gletsos, C.; Le Quesne, P.; Piers, E. ; Vlattas, I. *J. Am. Chem. Soc.*, **1970**, *92*, 1727.

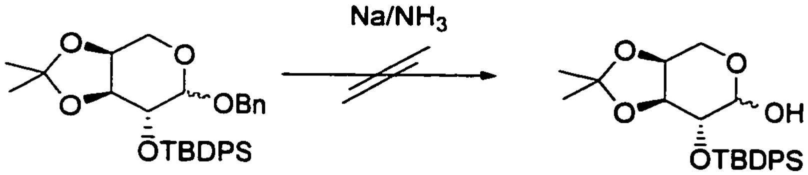
LAH in THF at reflux for 4 days (Scheme 2-12). Under these conditions only the starting material was recovered.



131

Figure 2-8: Increase of steric hindrance with a trityl protecting group.

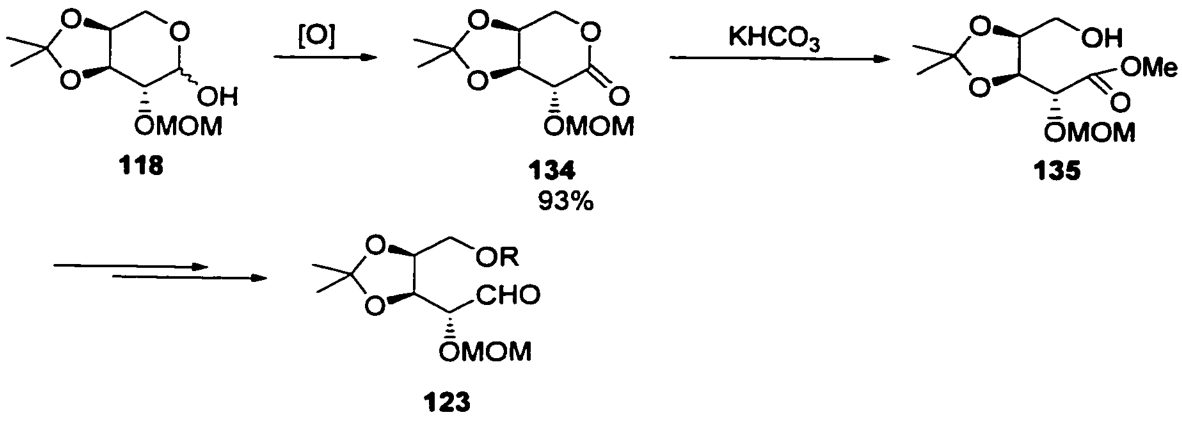
It appears that no selectivity can be achieved due to minimal difference in the primary hydroxyl group environments. However, molecular modeling of compound **131** where the MOM group has been replaced by a bulky trityl group showed that the alcohol next to it may be far less accessible to a reagent that the other alcohol (Figure 2-8). A more selective protection is then expected due to an increase in steric hindrance in the vicinity of the C-1 alcohol.



132 **133**

Scheme 2-13: Attempt at deprotecting (132).

Exploration of this hypothesis using a tertbutyldiphenylsilylether as protecting group was undertaken (Scheme 2-13). Compound **132** was made available due to previous research conducted in the group.[76] Deprotection of the benzylether group on the anomeric carbon *via* a Birch reduction should provide the lactol derivative. To our surprise these conditions led to degradation of the product. The silyl ether seemed to be sensitive to the reduction conditions employed. This route was not pursued further; however, another attempt at protecting the aldehyde was made (Scheme 2-14).



Scheme 2-14: Attempt at differenciating C-1 and C-5 on hemiacetal (118).

Hemiacetal **118** was oxidized to the lactone **134**, which could then be opened to give a compound with a methylester and free alcohol **135**. Further protection of the alcohol and reduction of the ester to the aldehyde would provide desired aldehyde **123** ready to undergo a Horner-Wadworth-Emmons reaction.

Standard oxidation of the lactol **118** with Dess-Martin periodinane in the presence of sodium bicarbonate gave the expected lactone in 52% yield after 16 h at room temperature (Table 2-2). The use of *N*-iodosuccinimide or potassium permanganate led to decomposition. Eventually the lactone was obtained in excellent yield (93%) using Fetizon's reagent in benzene at reflux for 3 h.[84] This lactone was then submitted to basic hydrolysis in presence of freshly made sodium methanolate in methanol. Unfortunately the reaction resulted only in degradation, however 9% of the expected compound was isolated when potassium bicarbonate[85] was used and the starting material was recovered in 21% yield.

Oxidant	Yield
$KMnO_4/Na_2CO_3$ in H_2O at rt	decomposition
DMP/$NaHCO_3$ in CH_2Cl_2	52%
NIS, *n*Bu_4NI in CH_2Cl_2	decomposition
Ag_2CO_3/Celite® in benzene at reflux	**93%**

Table 2-2: Oxidation of lactol (118).

---

[84] (a) Balogh, V.; Fetizon, M.; Golfier, M. *J. Org. Chem.*, **1971**, *36*, 1339. (b) Fetizon, M.; Golfier, M.; Louis, J. M. *Tetrahedron*, **1975**, *31*, 171.

[85] Pan, J.; Camell, A.; Bouchard, H.; Lesage, L.; Hanessian, S. *J. Org. Chem.*, **1997**, *62*, 465.

The results were not good enough to pursue further and this route was abandoned.

All attempts at forming the free aldehyde from the protected arabinose hemiacetal failed and a new route towards the synthesis of this aldehyde was designed. In order to provide the right stereochemical elements and the numerous oxygen functionalities from the beginning, (D)-gulunolactone was chosen.

2.2.2 STARTING WITH (D)-GULUNOLACTONE

Both enantiomeric forms of gulunolactone are readily available and can be easily protected using different combinations of protecting groups. In order to have the correct strereochemistry, (D)-gulunolactone was used in our synthesis.

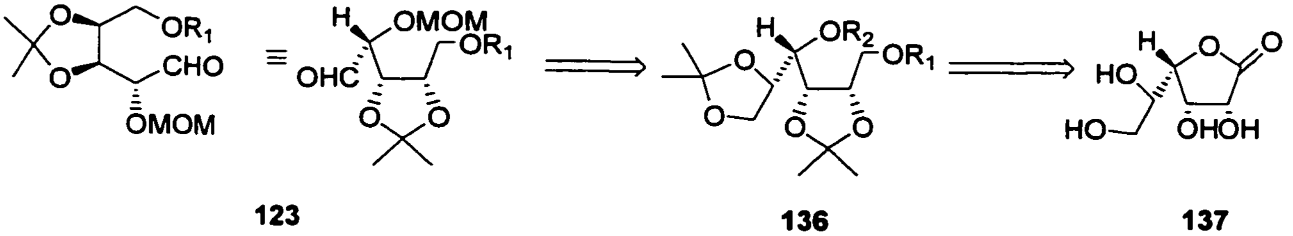


Figure 2-9: Retrosynthetic analysis of free aldehyde (123).

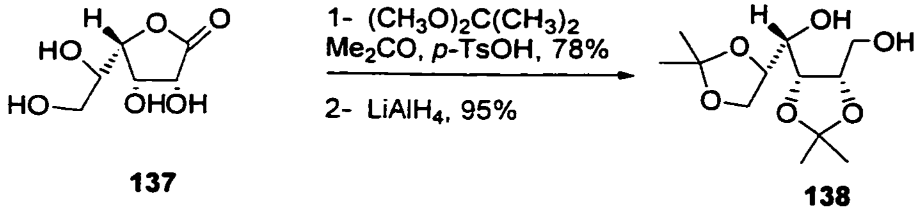
In our retrosynthetic scheme the required aldehyde **123**, identical to the aldehyde form of the arabinose derivative, was obtained from the selective deprotection and oxidative cleavage of the terminal vicinal diol **136**. This diol itself results from a sequence of protection-deprotection steps after reduction of the natural (D)-gulunolactone **137** (Figure 2-9).

The (D)-gulunolactone was first converted into 2,3:5,6-di-O-isopropylidene-D-gulunolactone with acetone/dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid (Scheme 2-15).[86] Other methods such as acetone in presence of copper sulfate or acetone with catalytic amounts of sulfuric acid gave modest yields of the expected protected

---

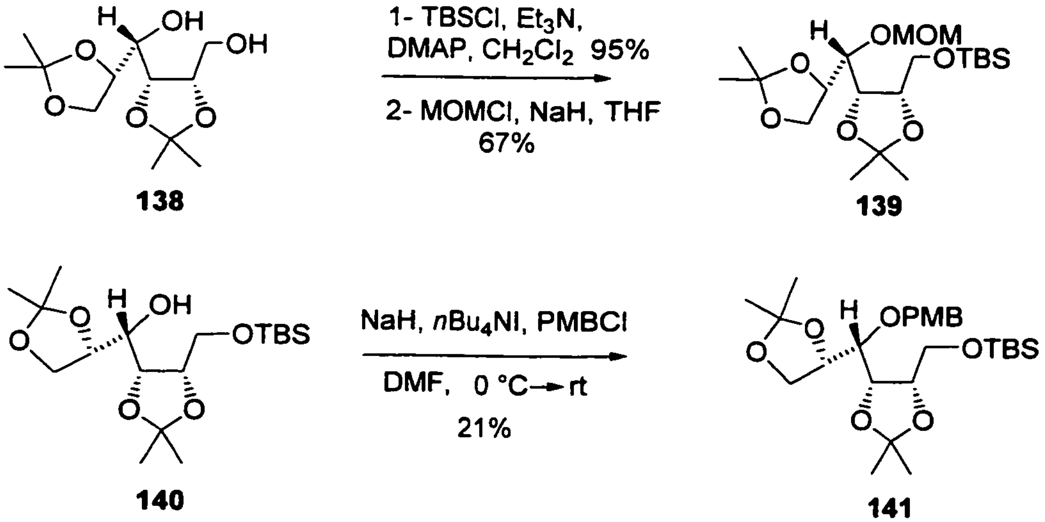
[86] Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron*, **1989**, *45*, 319.

acetal (8% and 48% respectively).[87] The lactone was then reduced to diol **138** in 95% yield using LAH.[86]



Scheme 2-15: Protection and reduction of lactone (133).

The secondary alcohol has to be protected in order to stop the oxidative cleavage at the first vicinal diol and keep the right number of carbon atoms in the molecule. Therefore, a sequence was designed to protect the primary alcohol then the secondary alcohol with protective groups stable to the cleavage conditions.



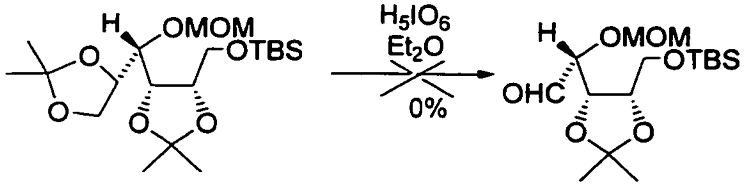
Scheme 2-16: Selective protection of diol (134).

Protection of diol **138** with one equivalent of TBSCl in the presence of triethylamine and a catalytic amount of DMAP afforded the monoprotected alcohol in 95% (Scheme 2-16). Standard conditions to protect the secondary free alcohol using MOMCl and i-Pr_2NEt failed to give the expected compound **135** in good yield. The best yield (28%) was obtained in methylene chloride with two equivalents of MOMCl and four equivalents of the amine.

---

[87] Kohn, P.; Kohn, B. D.; Lerner, L. M. *J. Org. Chem.*, **1968**, *33*, 1780.

Without solvent the yield was enhanced to 46%. Different solvents (ether, THF, DMF) and various bases (KH and NaH) were tried. The use of sodium hydride solved the problem, however an excess had to be used (4 equivalents of NaH and 6 equivalents of MOMCl) and the yield was only 67%. Protection with another group was attempted. Deprotonation of the secondary alcohol with NaH in the presence of a catalytic amount of tetrabutylammonium iodide and installation of the paramethoxybenzyl group proceeded in only 21%. Selective deprotection of the terminal isopropylidene was attempted with 2M and 4M HCl, but only starting material was recovered.[88]



139 **142**

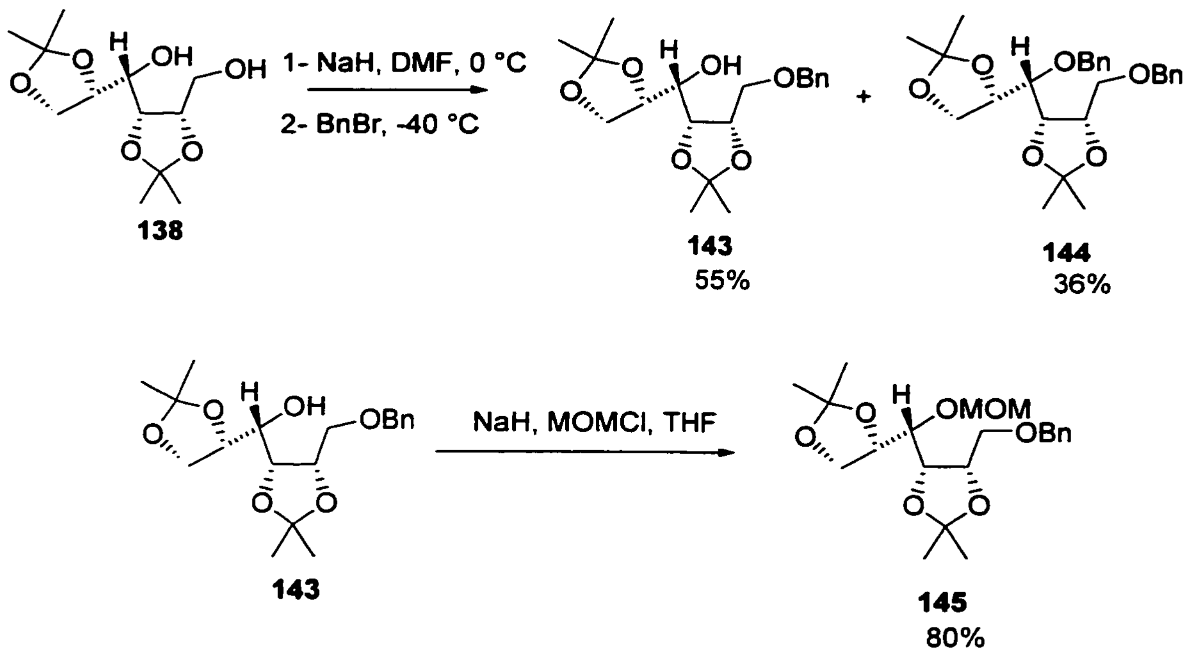
Scheme 2-17: Deprotection and oxidative cleavage of the terminal isopropylidene acetal in the tertbutyldimethylsilylether protected alcohol.

Periodic acid was then added to our fully protected compound **139** to effect a one-pot selective deprotection and oxidative cleavage (Scheme 2-17). In spite of previous examples where a tertbutyldimethylsilylether protecting group had been shown to be stable to such conditions, the reaction led to decomposition.[89]

---

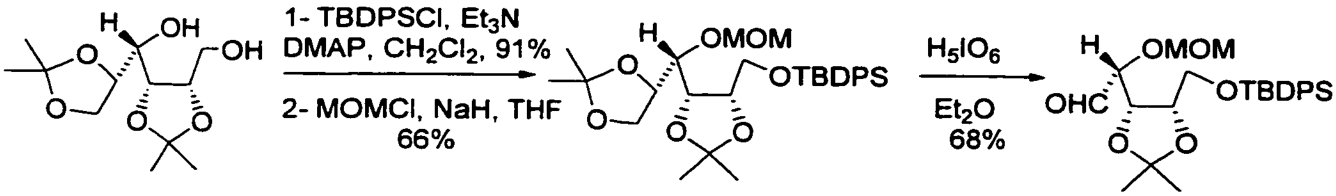
[88] Yoshimura, Y.; Kitano, K.; Yamada, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.*, **1997**, *62*, 3140.

[89] Wu, W-L.; Wu, Y-L. *J. Org. Chem.*, **1993**, *58*, 3586.



Scheme 2-18: Selective protection with a benzylether group.

A benzylether group was chosen to replace the sensitive silyl ether. It should give a better result, since the benzyl ether is stable to the acid/oxidant conditions and can still be deprotected selectively. Monoprotection of the diol using 1.1 equivalent of benzylbromide in presence of NaH was attempted (Scheme 2-18). Unfortunately a mixture of both monoprotected and diprotected alcohols **143** and **144** were obtained. Protection of the secondary alcohol with a methoxymethylether gave the expected compound **145** in 80% yield, proving that previously, the alcohol was too hindered to react. However the yields are still too low to produce the compound in large quantities. A bigger and more stable protecting group has to be used to effect the selective monoprotection in good yield. Tertbutyldiphenylsilylethers are less sensitive than tertbutyldimethylsilylether to acidic conditions and were employed to protect our primary alcohol.

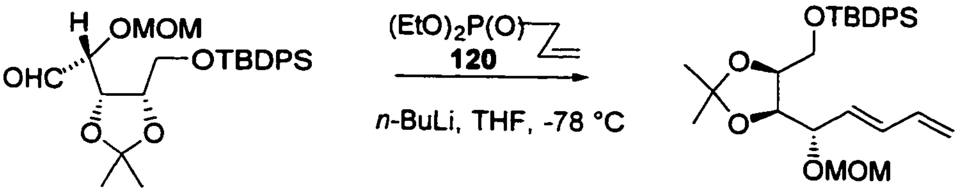


138 **146** **147**

Scheme 2-19: Synthesis of the tertbutyldiphenylsilylether derivative and oxidative cleavage.

Selective protection of the primary alcohol with TBDPSCl in the presence of triethylamine was achieved in excellent yield (Scheme 2-19). Protection of the secondary alcohol with a MOM group required the harsh conditions seen previously. The fully protected compound **146** was obtained in 60% (over 2 steps). Selective deprotection followed by oxidative cleavage was then carried out using periodic acid in ether.[90] The reaction proceeded smoothly to give aldehyde **147** in 68%.

With the free aldehyde in hand, we proceeded to test diene formation *via* a Horner-Wadsworth-Emmons reaction. Applying the standard conditions used previously, (Entry 1, Table 1-1) to our aldehyde, gave similar mixed results.



147 **148** 10%

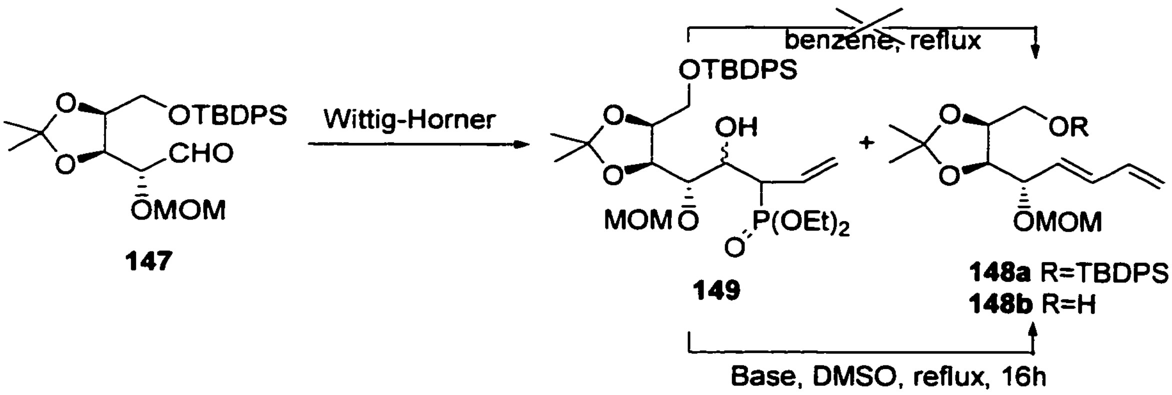
Scheme 2-20: Addition of allylphosphonate (120) to aldehyde (143).

The aldehyde was added to the reagent formed *in situ* by the addition of *n*-BuLi at -78 °C to the phosphonate. The starting material had been totally consumed after 4 h but a more polar complex mixture was formed in addition to the expected product **148**. As observed in the previous attempts on the hemiacetal, the mixture showed the signal of both the arabinose/gulunolactone derivative and of the phosphoryl reagent but was different from the starting materials. Suspecting that the addition of phosphoryl-stabilized species on the

---

[90] Li, Y-L.; Sun, X-L.; Wu, Y-L. *Tetrahedron*, **1994**, *50*, 10727.

aldehyde has taken place but not the elimination, we might have a diastereomeric mixture of **149**. In the case of difficult Wittig condensations, it has been shown that the use of heat or the addition of a base helped the elimination and afforded the product in good yield.



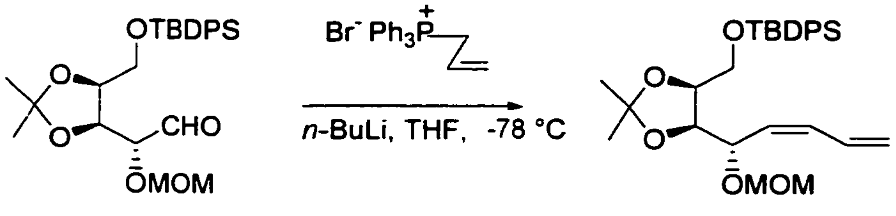
Scheme 2-21: Conversion of the unidentified mixture into the diene.

The unidentified mixture was thus submitted to a reflux of 4 h in benzene to no avail (Scheme 2-21). Therefore different kinds of base were added to the mixture in DMSO in an attempt to force the elimination (Table 2-3).

Equivalents of phosphonate	Equivalents of n-BuLi	Diene (%)	Base	Conversion yield (%)	R
3.6	3.6	10			
1.3	1.3	8	K_2CO_3	16	TBDPS
1.2	1.2	6	CsF	9	H

Table 2-3: Horner-Wadsworth-Emmons conditions.

Although the Horner-Wadsworth-Emmons reaction on the aldehyde gave poor yields regardless of the number of equivalent of phosphonate used, some conversion of the unidentified polar mixture to the diene was obtained when treated with a weak base. The unidentified mixture was treated with one equivalent of potassium carbonate in DMSO and refluxed for 20 h. Up to 16% of diene **148a** was recovered from elimination of hydroxyphosphonate proving that part of the mixture at least contains the non-collapsed compound **149**. The use of the weaker base cesium fluoride under identical conditions afforded the expected deprotected diene **148b** in 9% yield. A closer look into the literature related to Horner-Wadsworth-Emmons reactions shows that allylphosphoryl species condensed on lactols are usually substituted by an electon withdrawing group or in the case of a simple allylphosphonate the reaction is applied to free aldehyde and non-oxygenated substrates. The failure of the phosphonate **120** to condense with either the lactol or the free aldehyde might be explained by the presence of the numerous co-ordinating oxygen atoms in the molecule. The influence of oxygenated groups located in α or β to the reactive carbonyl species often leads to a reversed stereoselectivity at the double bond.[91]



147

(*Z*)-148a
30%

Scheme 2-22: Addition of an allylphosphorane to aldehyde (143).

Addition of a semi-stabilized ylide to the free aldehyde gave 30% of the conjugated diene (Scheme 2-22). The reaction gave a better yield than with the phosphonate but with the wrong (*Z*) stereochemistry at the double bond.

The need for a better method to synthesize diene **148** prompted us to investigate the reactivity of the carbonyl towards an organometallic reagent.

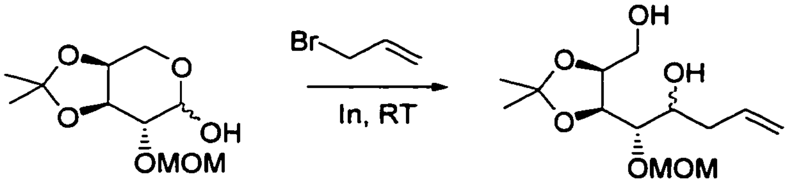
2.2.3 SYNTHESIS OF THE CONJUGATED DIENE

2.2.3.1 Indium chemistry

---

[91] Reitz, A. B.; Maryanoff, B. E. *Chem. Rev.*, **1989**, *89*, 863.

The study of indium reagents to mediate or catalyze organic reactions is a relatively new area in organometallic chemistry. Of particular interest is the use of indium reagents to mediate Barbier-type reactions in water.[92] When compared to magnesium, zinc or tin, indium has the lowest first ionization potential and unlike them is not sensitive to boiling water or alkali and does not oxidize readily in air. Allylation reactions with indium in water proceed smoothly at room temperature without any promoter, unlike zinc and tin promoted allylations. Indium can be used stoichiometrically as a metal or catalytically as indium chloride in combination with aluminium or zinc metal. One of the most developed uses for indium chemistry is the formation of carbon-carbon bonds in water soluble compounds such as carbohydrates, making it applicable to unprotected sugars. The advantages of this chemistry are numerous. The reaction can be carried out in protic solvents, water in particular, eliminating the handling and disposal of anhydrous and flammable solvents. The experimental protocol is straightforward and applicable on large scale. Good regio- and stereoselectivity can be achieved when either the carbohydrate or the indium reagent are substituted. The use of unprotected carbohydrates shorten the synthesis, bypassing the tedious protection-deprotection sequence often required for allylation under acidic conditions. In short, indium mediated allylations proceed under mild conditions, afford excellent yields, are cost-effective, and provided a 'perfect fit' to work with our derivatized arabinose and the polar diol resulting from the allylation.



118

150

Scheme 2-23: Addition of allylindium onto hemiacetal (118).

To evaluate this method, allylation of the lactol was attempted with allylbromide and indium metal in protic solvents (Table 2-4). In water, the addition reaction evolved to decomposition, while in a 1:1 mixture of water and ethanol the decomposition process was slow and some starting material was recovered. The hypothesis for the failure of the allylation reaction is that hydrogen bromide was generated as a byproduct and proceeded to cleave the acid

---

[92] Li, C. J.; Chan, T. H. *Tetrahedron Lett.*, **1991**, *32*, 7017.

sensitive isopropylidene acetal. Allylation of ketones in the presence of a dimethyl acetal was reported to be possible under such mild conditions[93] but our cis isopropylidene acetal proved to be too sensitive. The use of a non protic solvent solved the problem and in DMF[94] as well as in THF the reaction proceeded in good yield, 77% and 72% respectively, to give a 1:1 mixture of diastereoisomers. The loss of product and yield were due to problems encountered during purification, as the indium salts present in the crude mixture were slightly soluble in ether.

R	Allylbromide (eq.)	Indium (eq.)	Solvent	Yield (%)
H	5.6	2.1	H_2O	decomposition
H	3.1	2	H_2O/EtOH	decomposition + SM (50%)
H	4.3	2.1	DMF	77
H	4.2	2.1	THF	72
$CH=CH_2$	3.1	2.1	DMF	96

Table 2-4: Allylation conditions with allylbromide and indium.

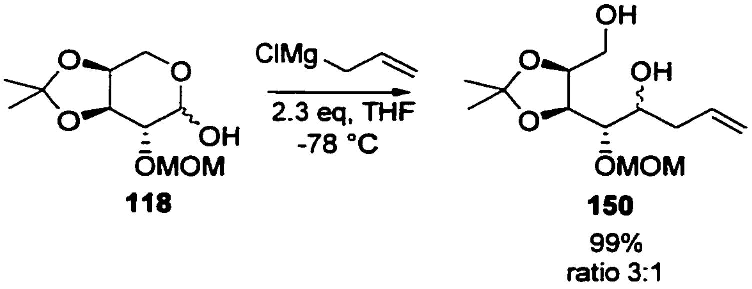
No real stereoselectivity was observed in these cases. The use of a Grignard reagent was investigated next to see whether better yields can be obtained.

2.2.3.2 Use of a Grignard reagent

Allylmagnesium chloride was the Grignard reagent of choice in this synthesis. Addition of 2.3 equivalents of allymagnesium chloride to lactol **118** afforded a 3:1 diastereomeric mixture of allylic diols **150** in excellent yield (95%).

---

[93] Li, C. J.; Chan, T. H. *Tetrahedron Lett.*, **1991**, *32*, 7017.
[94] Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.*, **1988**, *53*, 1831.



Scheme 2-24: Addition of allylmagnesium chloride to hemiacetal (118).

The difference in the ratio of diastereomers between the Barbier type reaction with indium and the addition of the Grignard reagent might be explained by a difference in the way each metal coordinates to the lactol and its many oxygenated substituants. According to Cram's chelate model, the presence of a strongly coordinating hydroxyl group in the α position relative to the acetal leads to a product where the stereochemistry is preferentially syn (Figure 2-10). On the other hand when the hemiacetal is substituted in the β position by an hydroxyl group, then the expected stereochemistry is anti. Weaker coordinating agents like ether have less influence on the selectivity of the addition. However the presence of alkoxy substituents in α and β positions as well as in γ position on the lactol prevents any prediction of stereoselectivity for the product.

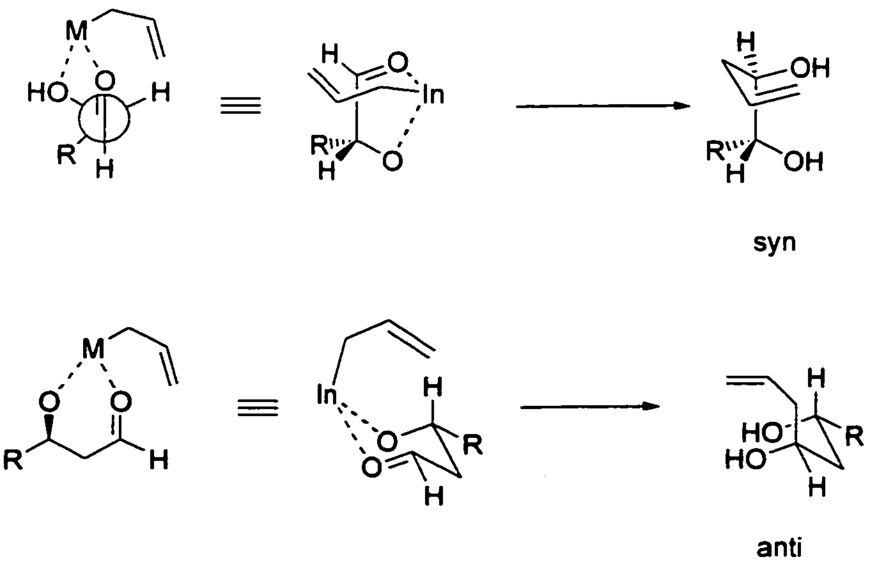
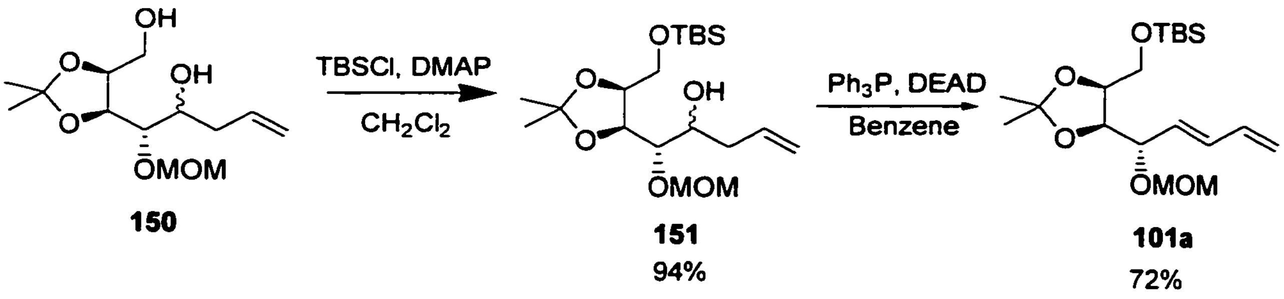


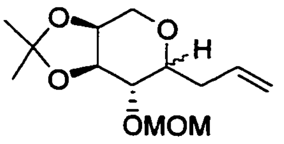
Figure 2-10: Cram's chelate model for the allylation of oxygen bearing substrates.

Dehydration of the allylic alcohol **150** to diene **101a** was straightforward. The primary alcohol was protected as a tertbutylsilylether using standard conditions (Scheme 2-25). Several reagents were used to try to dehydrate the allylic alcohol and form the conjugated double bond.



Scheme 2-25: Dehydration of allylic alcohol (150).

A two-step sequence requiring the formation of the mesylate intermediate was attempted but protection of the secondary alcohol with MsCl under standard conditions (MsCl, Pyr, DMAP) failed to proceed. However the diene was obtained in high yield using Mitsunobu conditions. A similar attempt on the unprotected diol led to cyclization to compound **152**.

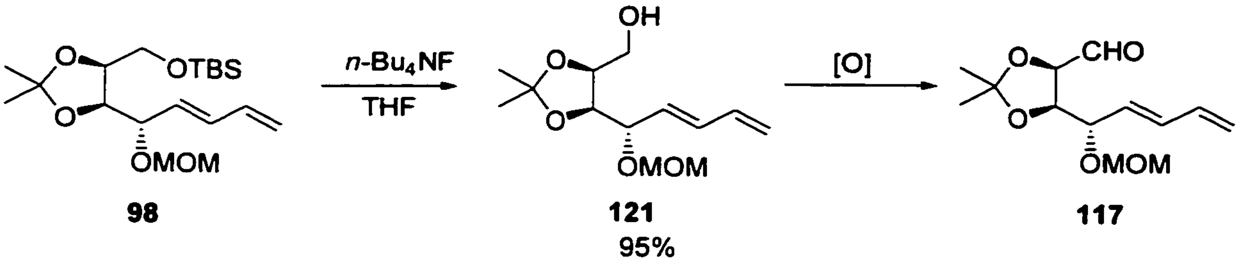


152

Figure 2-11: Cyclization of unprotected diol (150).

A difference in the rate of the elimination was observed between the two diastereomers with the less polar and major one reacting faster. However in the preparation of larger quantities of compound **101a**, the diastereomers were not separated.

In order to get the required aldehyde **117**, the primary alcohol must be deprotected and oxidized. Deprotection was carried out with tetrabutylammonium fluoride and afforded the free alcohol in excellent yields (>95%) (Scheme 2-26).



Scheme 2-26: Deprotection and oxidation of the primary alcohol (98).

Various conditions were tried in order to oxidize alcohol **121** into aldehyde **117** (Table 2-5).

Entry	Oxidant	Yield (%)
1	DMSO, ClCOCOCl, Et_3N	48-80
2	Dess-Martin's Periodinane	38
3	IBX	32-70
4	PCC	60

Table 2-5: Oxidation conditions.

Aldehyde **117** is sensitive to purification on silica gel. The best yield was obtained with a Swern oxidation, although the purity of the crude product varied between reactions (Entry 1). However, on a larger scale the best yield was 55%. Oxidations with DMP[95] and IBX[96] were very easy to conduct. However, DMP afforded the aldehyde in only 38% yield. Upon oxidation with the DMP precursor, IBX, significant improvement was achieved, but unfortunately the method was not reproducible. The use of Collins reagent gave the expected product in reliable and reproducible yields.[97] Pyridinium chlorochromate was easy to use and the reaction could be scaled up to 3 grams.

---

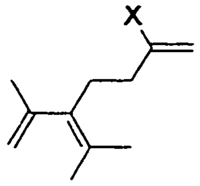
[95] Liu, L.; Ireland, R. E. *J. Org. Chem.*, **1993**, *58*, 2899. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.*, **1983**, *48*, 4156.

[96] (a) Frigerio, M.; Sputore, S.; Santagostino, M. *J. Org. Chem.*, **1998**, *64*, 4537. (b) Frigerio, M.; Sputore, S.; Santagostino, M.; Palmisano, G. *J. Org. Chem.*, **1995**, *60*, 7272.

[97] (a) Akashi, K. Sharpless, K. B. *J. Am. Chem. Soc.*, **1975**, *97*, 8927. (b) Rodehorst, R.; Ratcliffe, R. *J. Org. Chem.*, **1970**, *35*, 4000. (c) Hess, W. W.; Frank, F. J.; Collins, J. C. *Tetrahedron Lett.*, **1968**, *9*, 3363.

In any case, the aldehyde was sensitive to air and could not be stored very long even frozen in benzene. In addition a very clean compound is essential for the coupling step.

2.3 SYNTHESIS OF THE SIDE CHAIN



99a X = I
99b X = Br

Figure 2-12: Triene derivatives.

The diene necessary for the second Diels-Alder reactions, required for the synthesis of the AB ring was derived from triene **99** and is a key building block for our approach of Taxol® derivatives (Figure 2-12). The synthesis of iodotriene **99a** was developed by Dr. Tim Wong using tin chemistry.[58a]

2.3.1 SYNTHESIS OF IODOTRIENE (99a)

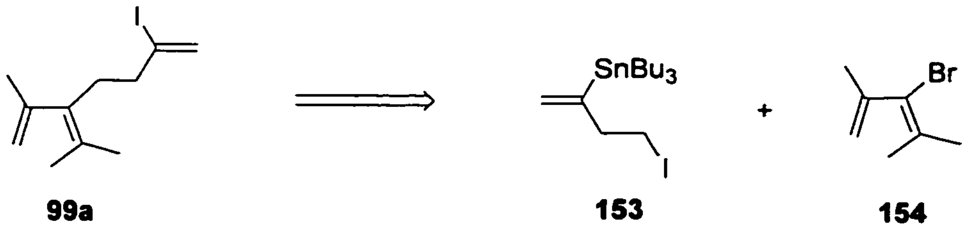
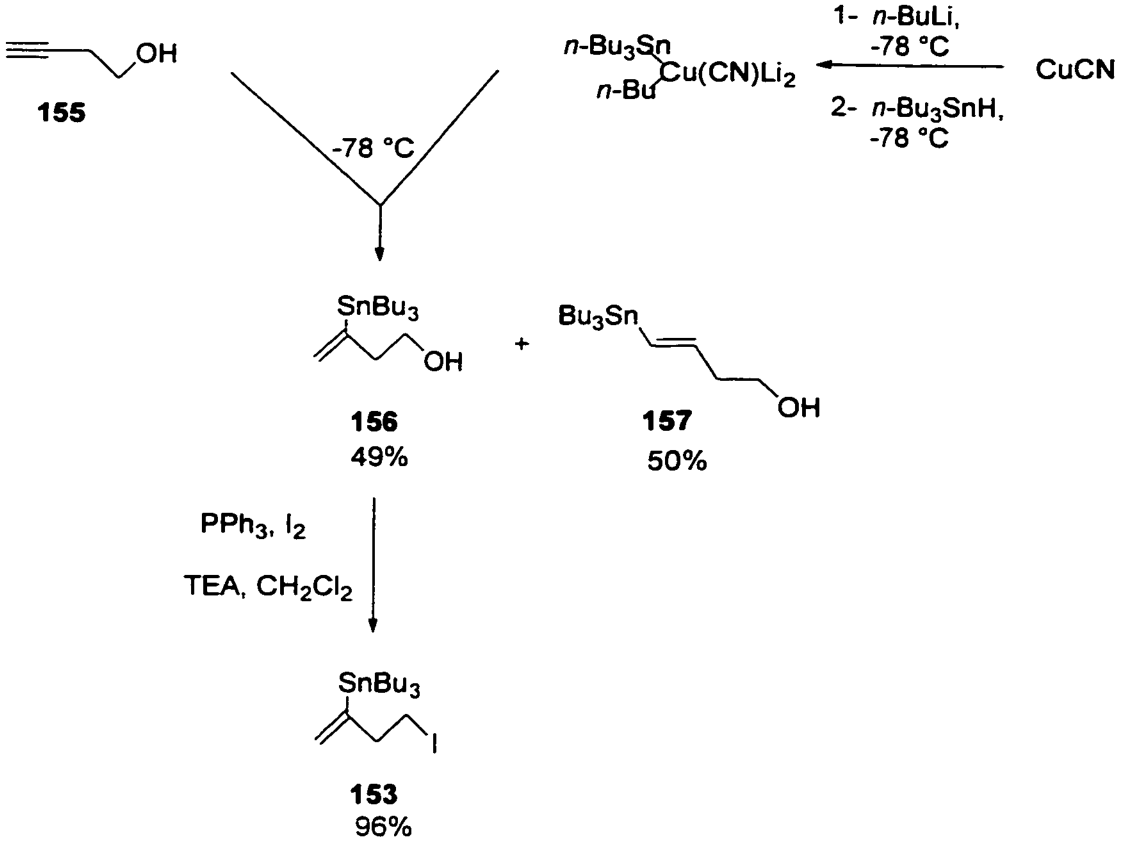


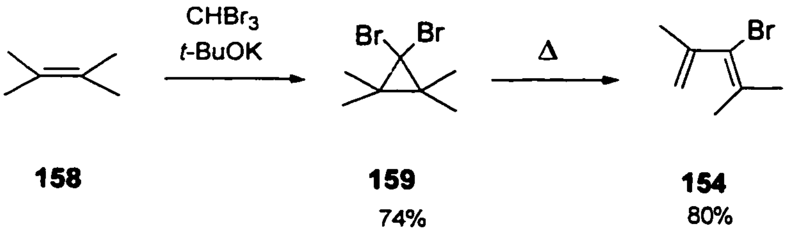
Figure 2-13: Retrosynthetic approach to the iodotriene (99a).

The synthesis of iodotriene **99a** involved the regioselective coupling of the organometallic species **153** and diene **154** (Figure 2-13).



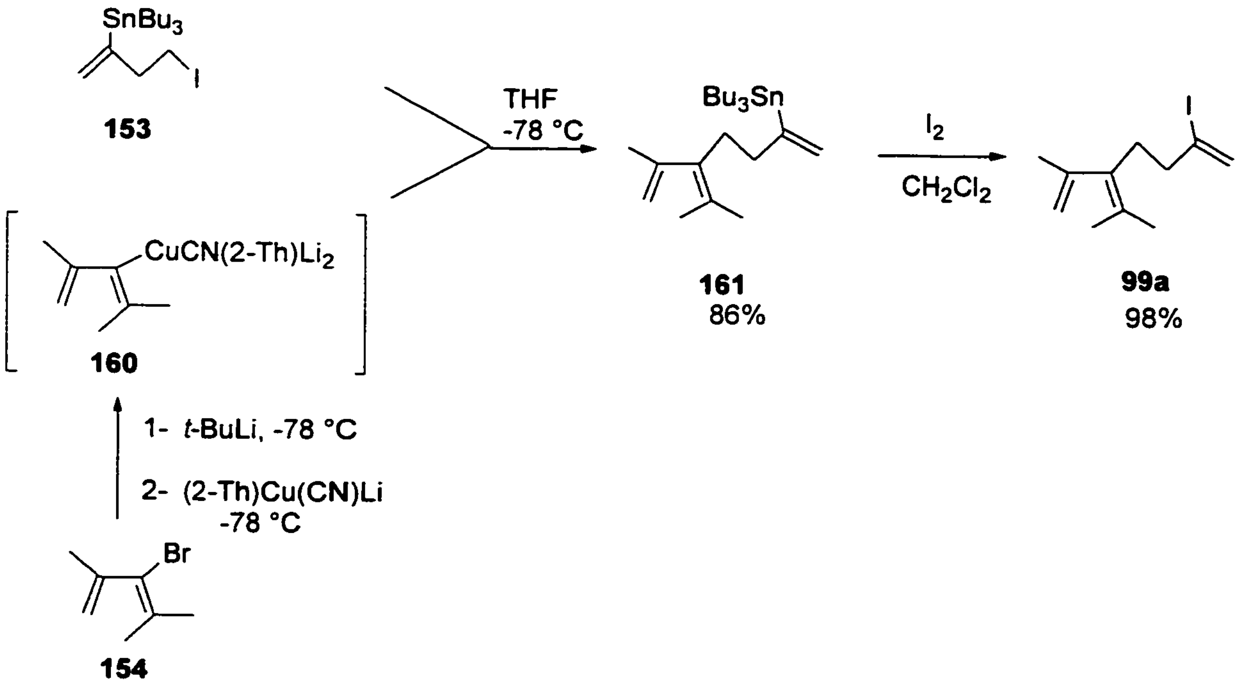
Scheme 2-27: Synthesis of the iodostannane species (153).

Hydrostannation of the homopropargylic alcohol *via* transmetallation with organocuprate reagent gave a mixture of regioisomers which were difficult to separate and the required α-substituted compound **156** was obtained in only 49% yield after separation. Iodination of the alcohol gave a 96% yield of expected iodostannane **153** (Scheme 2-27).



Scheme 2-28: Synthesis of the bromodiene.

The synthesis of bromodiene **154** was improved in the laboratory by Dr. Wilson.[76] Formation of dibromocyclopropane **159** by addition of bromoform to 2,3-dimethylbut-2-ene in basic solution is well known (Scheme 2-28). Heating of this species has been reported to give bromodiene **154**. However every attempt at heating compound **159** following the literature procedure just led to decomposition.[98] Cracking of the solid cyclopropyldibromide **158** with a propane torch was required to obtain the bromodiene as a colorless liquid in good yield while slow heating led to decomposition.



Scheme 2-29: Coupling of the bromodiene and the iodostannane species.

Reactive heterocuprate **160** was then formed by metal metal exchange between the lithium derivative of bromodiene formed *in situ* and a commercially available thienylcyanocuprate. The resulting cuprate intermediate **160** was then coupled with the iodostannane **153** to give stannane derivative **161** in good yield *via* transfer of the diene ligand. Iodination of the vinylstannane with solid iodine in methylene chloride led to the expected iodotriene **99a** in 98%. The overall yield of this sequence is 39%. Due to the mixture of regioisomers in the first step a significant amount of product was lost. In addition to bad yields, the use of toxic reagents (tin, copper cyanide) undesirable on a large scale makes this route a poor candidate for scale up. Moreover, the final compound is very unstable and decomposes immediately on standing after purification. It is often contaminated by tin residue and the pure product is difficult to obtain.

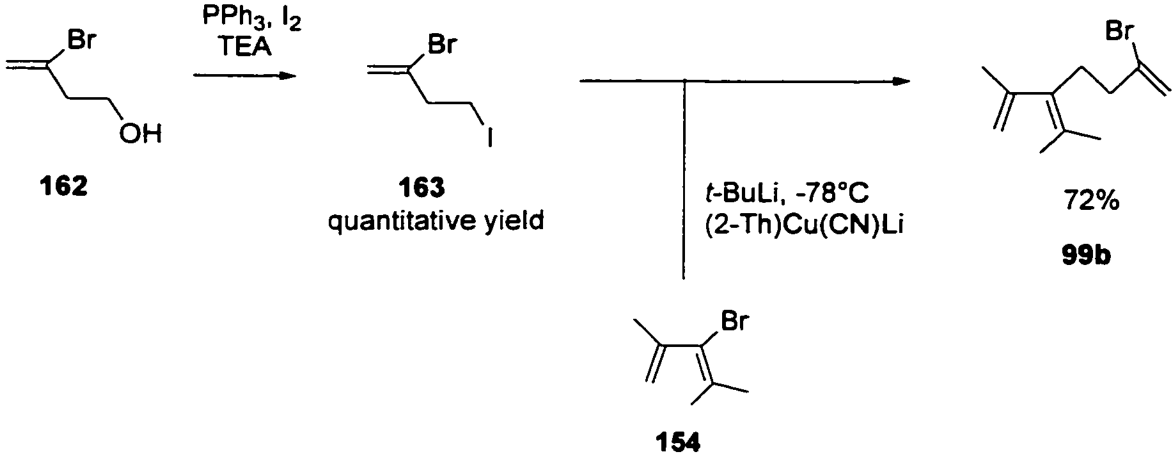
---

[98] Sandler, S. R. *J. Org. Chem.*, **1967**, *32*, 3876.

Keeping in mind that large quantities of the compound would be required for the synthesis, another approach to this fragment was developed.

2.3.2 SYNTHESIS OF BROMOTRIENE (99b)

In parallel studies, explored by Dr. S. Woo, the coupling of an appropriate alkyne fragment with the bromodiene before regioselective hydroxylation were examined but no desired product was observed. Alcohol **162** was now commercially available, thus a new, more convenient route using this compound was developed (Scheme 2-30).



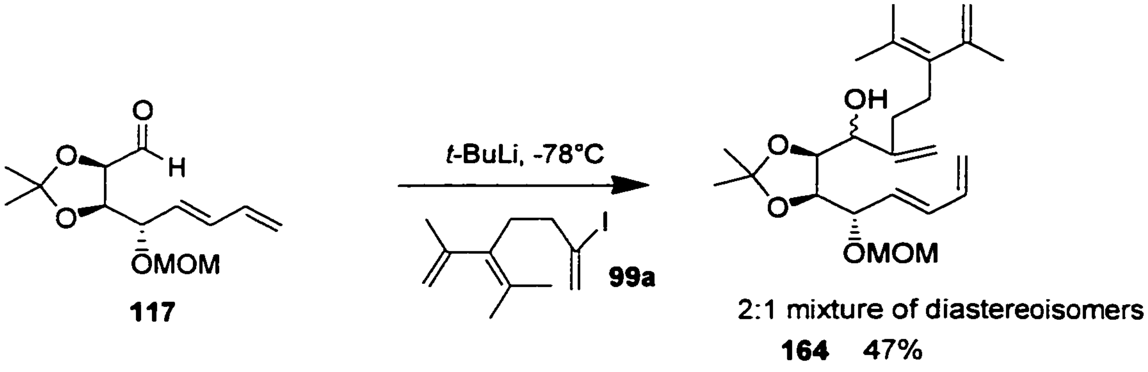
Scheme 2-30: Synthesis of bromotriene (99b).

Bromoiodobutene **163** was synthesized from **162**. Addition of the dienecuprate derivative formed *in situ* to fragment **163** proceeded regioselectively to give the expected bromotriene in 72% yield. Attempted copper catalyzed coupling of the tosylate derivative of **162** with the Grignard derivative of **154** gave a low yield. The organocuprate is very oxygen sensitive and the quality of the commercial reagent was very uneven. Consequently it was generated *in situ* and used immediately in order to achieve good and reproducible yields. The bromotriene possesses the advantage of being more stable than the iodotriene and it can be purified by distillation (bp 70-80 °C, 1mm Hg). The pure colorless oil can be kept for a reasonable time (several weeks) in the freezer before use. This is a priceless improvement as the coupling step with the aldehyde is very sensitive to impurities.

2.4 SYNTHESIS OF THE FUNCTIONALIZED DECALIN

2.4.1 COUPLING OF THE ALDEHYDE AND THE SIDE CHAIN

With our two fragments in hand, coupling was attempted using standard conditions.

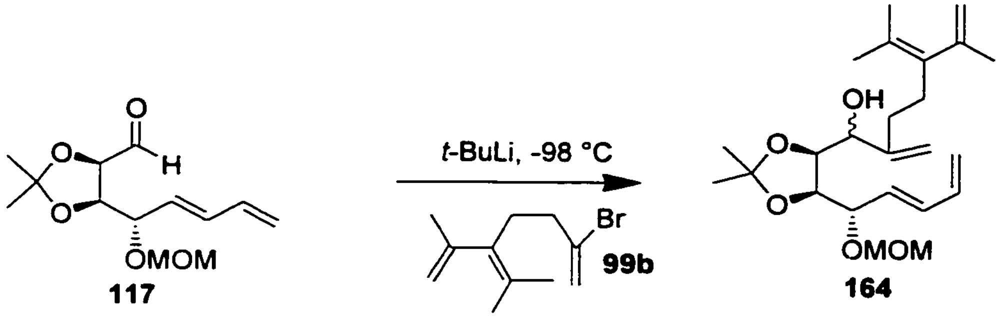


Scheme 2-31: Coupling of the iodotriene and aldehyde (117).

Halogen-metal exchange at -78 °C formed the lithiated triene to which the pure aldehyde was added (Scheme 2-31). The reaction was rapid and was quenched after 15 min at -78 °C then 15 min at 0 °C. A 2:1 mixture of diastereoisomers was obtained in only 47% yield despite repurification of the starting materials to eliminate the degradation product. Increasing the temperature or the reaction time did not bring any improvement. Addition of cerium chloride, prepared following the improved procedure by Dimitrov, to the mixture gave slightly lower yield.[99] The low yields were attributed to the labile iodotriene which compelled us to seek a more convenient fragment. Addition of the triene stannane species **161** to similar aldehydes has been studied previously in the laboratory and failed to give good results. Therefore, the synthesis of bromodiene **99b** was developed as shown previously and coupling with the aldehyde was attempted.

---

[99] Kostova, K.; Genov, M.; Dimitrov, V. *Tetrahedron Lett.*, **1996**, *37*, 6787.



3:1 mixture of diastereoisomers
79%

Scheme 2-32: Coupling of the bromotriene and aldehyde (117).

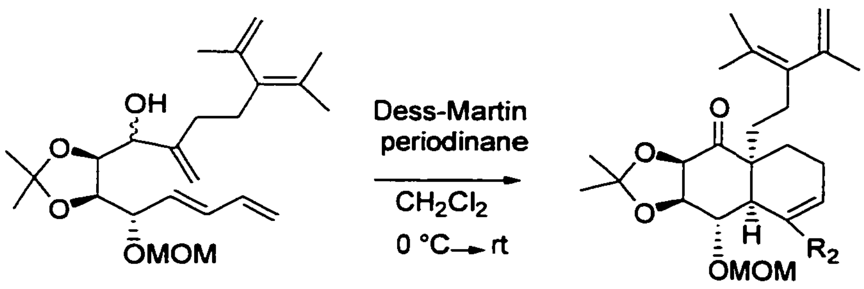
Bromine is known to be less reactive towards halogen-metal exchange than iodine, thus, the temperature of the coupling reaction was lowered in order to avoid competitive reaction such as elimination. Fortunately the reaction proceeded cleanly and consistently at - 98 °C as well as at - 110 °C and allylic alcohol **164** was obtained as a 1:1 mixture in 79% yield. Addition of a stoichiometric amount of cerium chloride to the carbonyl species following the 'reverse addition procedure' described by Imamoto yielded no significant improvement (81%).[100]

2.4.2 SYNTHESIS OF THE C RING

An oxidation and subsequent Diels-Alder reaction were expected to give the decalin system with good stereoselectivity due to the chiral tether control of the isopropylidene acetal. First the allylic alcohol must be oxidized to activate the dienophile and facilitate the Diels-Alder reaction required for the formation of the decaline. Alcohol **164** was exposed to various standard oxidants. While Swern oxidation gave mixed results with only 16% of product, the Dess-Martin's periodinane afforded 81 % of the same product, which to our delight was identified as decalin system **165**. Oxidation of the allylic alcohol yielded the decalin in one step and excellent overall yield (Scheme 2-33).

---

[100] Takiyama, N.; Nakamura, K.; Hatajima, T.; Kimiya, Y.; Imamoto, T. *J. Am. Chem. Soc.*, **1989**, 93, 2325.

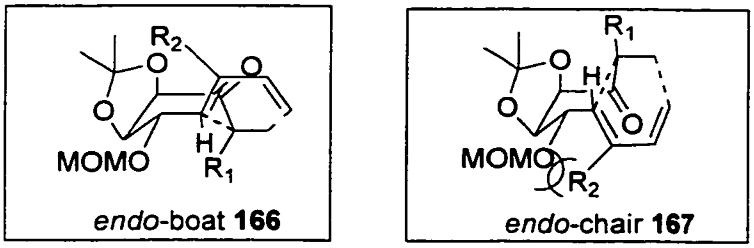


164

165
R_2 = H, 81%

Scheme 2-33: Diels-Alder cycloaddition.

The cycloaddition proceeded readily at room temperature and in 1.75 h. Only one diastereomer was obtained and no ketone intermediate was isolated. The improvement brought by the cis isopropylidene acetal over its trans derivative is obvious. The cis tether group allowed the cycloaddition to take place *in situ* while the trans isopropylidene afforded only the allylketone and had to be submitted to more vigourous conditions to induce the cycloaddition (toluene, 19h, 110 °C).[101] The difference in reactivity of both cis and trans isopropylidene derivatives, studied in this laboratory, attests to the powerful activation properties linked with the stereochemistry of the substituents.[57] The activation is the result of a strong conformational bias brought by the tether control group.



endo-boat **166**

endo-chair **167**

Figure 2-14: *endo* transition states.

Reports on intramolecular Diels-Alder reactions of decatrieneone show that the *endo* addition of a tethered dienophile to the diene leads to a *cis*-fused ring system.[102] More

---

[101] Woo, S.; Legoupy, S.; Parra, S.; Fallis, A. G. *Org. Lett.*, **1999**, *1*, 1013.

[102] Reviews: (a) Fallis, A. G. *Can. J. Chem.*, **1984**, *62*, 183. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.*, **1980**, *80*, 63. (c) Roush, W. R. in *Comprehensive Organic Synthesis*; B. M. Trost, Ed.; Pergamon Press: Oxford, 1991; Vol 5, pp 513-550. (d) Ciganek, B. *Org. React.*, **1984**, *32*, 1. (e) Craig, D. *Chem. Soc. Rev.*, **1987**, *16*, 187.

studies confirmed a strong preference of the cycloaddition for an *endo* transition state.[103] Recent investigations by Kurth *et al.* [104] on the remote stereocontrol of a C-3 substituent confirmed the *endo* and boat directing effect observed by Roush in these systems. From those results we can predict the stereochemistry of the fused system using the transition states drawn in Figure 2-14. The conformation (chair or boat) of the tether group and its substituents will determine the selectivity of the reaction. Four *endo* transitions states are available for the cycloaddition of the ketone of **164**. Amongst those four, two have the MOM protecting group in an axial position, increasing the destabilization of the transition states, and the two others (**166**, **167**) are more stable with the substituents in equatorial positions. The endo-chair-**167** conformation presents a 1,3-allylic interaction, which may destabilize the transition state. The endo-boat-**166** has no such effect and accounts for the cis stereochemistry observed in **165** and established by an X ray crystal structure of **173b** a derivative of compound **165**, in another series (R_2= $CH=CH_2$), synthesized later in the synthesis.

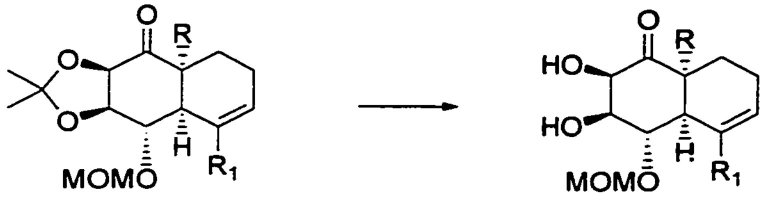
2.5 DEPROTECTION OF THE ACETAL

Despite literature precedent, simple reactions such as acetal hydrolysis and oxidative cleavage of the resulting diol are often unreliable in the complex highly substituted molecules encountered during a total synthesis. For example, Arseniyadis *et al.* have described interesting cascade reactions that arise from lead tetraacetate oxidations of unsaturated bicyclic diols.[105]

Acetonide hydrolysis is usually facile, as observed in the miniminally substituted trans series (**89** to **90**), however, for the cis isomers (**165a** R_1 = H, **165b** R_1 = $CH=CH_2$), this reaction proved particularly troublesome and several established methods failed to generate diol **168** or caused decomposition (Table 2-6). Attempted deprotections were carried out in both series but results in the b series (from **165b** to **175b**) were obtained by Dr. Legoupy and Dr. Lee.[106]

---

[103] Roush, W. R. in *Advances in Cycloaddition*, vol. 2; Curran, D. P., Ed.; Jai Press: Greenwich, CT, 1990; pp 91-146.
[104] Kim, P.; Nantz, M. H.; Olmstead, M. M.; Kurth, M. J. *Org. Lett.*, **2000**, *2*, 1831.
[105] (a) Arseniyadis, S.; Brondi Alves, R.; Yashunsky, D. V.; Wang, Q.; Potier, P. *Tetrahedron Lett.*,**1995**, *36*, 1027. (b) Arseniyadis, S.; Toupet, L.; Yashunsky, D. V.; Wang, Q.; Potier, P. *Tetrahedron Lett.*, **1995**, *36*, 8783.
[106] (a) Dr. Legoupy, Final Research Report, 1998, University of Ottawa. (b) Dr. Lee, Final Research Report, 1999, University of Ottawa.



165a, 165b **168a, 168b**

a R_1 = H
b R_1 = CH=CH_2

R_1	Reagent	Solvent	Temperature	Result
CH=CH_2	HCl 10%	THF	rt	diol 40%
	HCl 10%	THF	60 °C	decomposition
	HCl 40%	THF	rt	decomposition
	$FeCl_3/SiO_2$	acetone	rt	starting material
	$FeCl_3/SiO_2$	$CHCl_3$	rt	starting material
	Dowex® 50X4-400	MeOH	rt	starting material
	H_5IO_6	dry ether	rt	decomposition
	CF_3CO_2H	THF/H_2O 4:1	rt	starting material
	pTsOH	CH_2Cl_2/H_2O 4:1	rt	starting material
	CF_3SO_3H	**THF**	**rt**	**diol 68%**
H	I_2	MeOH	45 °C	decomposition
	thiourea	$EtOH/H_2O$	reflux	starting material
	CF_3SO_3H	ethyleneglycoldimethylether	rt	diol 10%
	CF_3SO_3H	**THF**	**rt**	**diol 57%**

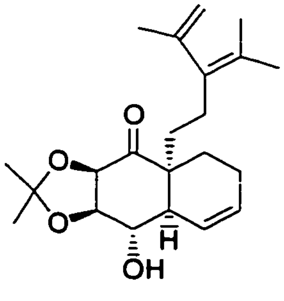
Table 2-6: Deprotection of the cis isopropylidene acetal in both series.

These included mild procedures such as ferric chloride on silica gel in acetone,[107] transacetalization with I_2/MeOH,[108] use of thiourea in a 1:1 mixture of $EtOH/H_2O$,[109] various acidic methods, Dowex 50X4-400 in methanol,[110] trifluoroacetic acid in THF/H_2O, para-

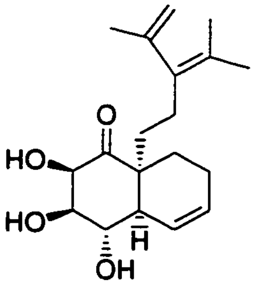
---

[107] Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahm, C. S. *J. Org. Chem.*, **1986**, *51*, 404.
[108] Nugent, T. C.; Hudlicky, T. *J. Org. Chem.*, **1998**, *63*, 510.
[109] Majundar, S.; Bhattacharjya, A. *J. Org. Chem.*, **1999**, *64*, 5682.
[110] Ho, P. T. *Tetrahedron Lett.*, **1978**, *19*, 1623.

toluenesulfonic acid in CH_2Cl_2/H_2O as well as aqueous hydrochloric acid THF solutions greater than 10% concentration. Diol **168b** could be prepared in 40% yield when exposed to aqueous 10% HCl in THF at 21 °C for 2 hours or more efficiently in 68% yield by portion wise addition of a 10% trifluorosulfonic acid solution at room temperature over 2 hours. However, trace quantities of the bicyclic triol from hydrolysis of the MOM group were also present. With ethylene glycol dimethylether as solvent, deprotection of **165a** was faster and was completed after 1 h but more decomposition occured and side product **169** was obtained in 20% yield, while the expected diol **168a** was obtained in 14% yield. Deprotection of **165a** in THF with an aqueous 10% trifluorosulfonic acid proceeded in medium yield (57%) over several hours and gave the triol **170** as a byproduct.



169



170

Figure 2-15: Byproducts of the acidic deprotection.

Periodic acid in ether has been developed to deprotect acetals and cleave a vicinal diol in one step,[111] but this procedure also failed.

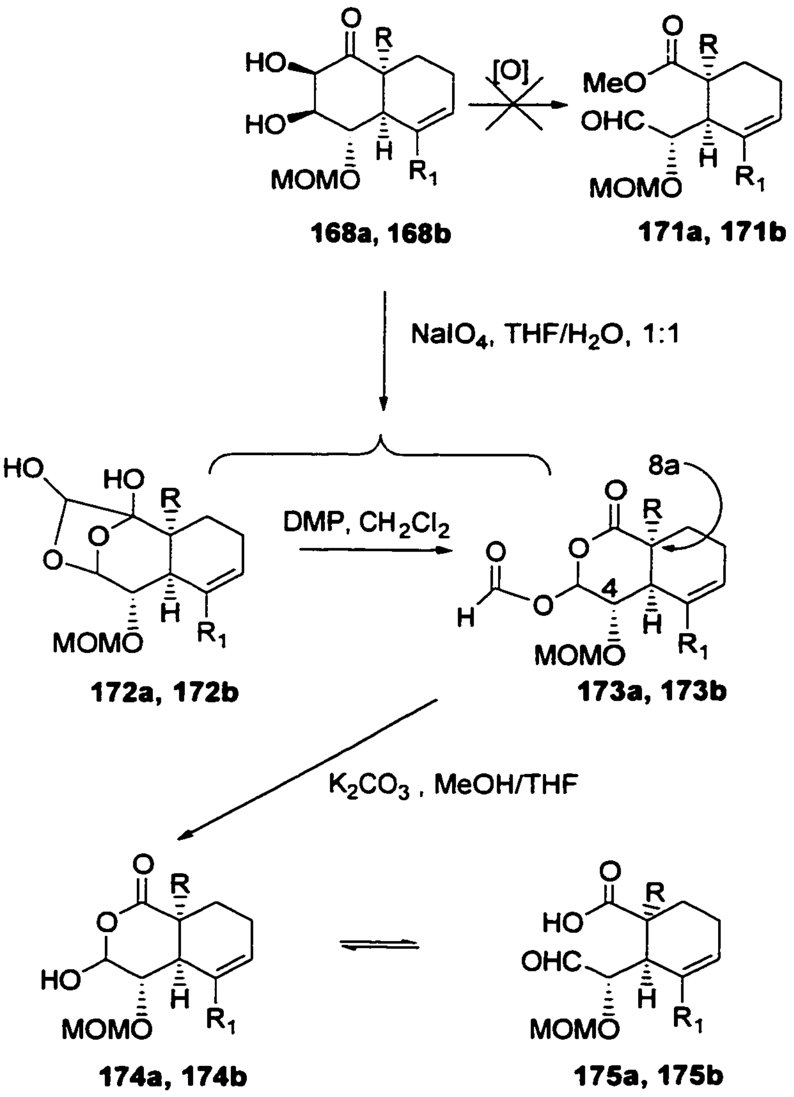
2.6 CLEAVAGE OF THE DIOL

It was anticipated, that lead tetraacetate oxidative cleavage of the diols **168** to the aldehyde-esters **171** should now be straightforward, in view of the cis orientation of the adjacent hydroxyl groups and increased reaction rate that should result. However, no aldehyde could be detected under the conditions employed for **168** above, nor when sodium periodate was used as the oxidant. Instead, the periodate mediated reaction initially afforded a mixture of two compounds in which the cyclohexanol carbon atom was retained (Scheme 2-34).

---

[111] Wu, W. L.; Wu, Y. L. *Tetrahedron Lett.*, **1993**, *21*, 4665.

Spectral analysis and subsequent chemical manipulation established their structures as the hemiacetal **172a, 172b** and the formate-lactone **173a, 173b** respectively.



a $R_1 = H$, **b** $R_1 = CH{=}CH_2$
$R = CH_2CH_2\text{-}(CMe{=}CH_2){=}CMe_2$

Scheme 2-34: Deprotection-oxidative cleavage sequence to acidaldehyde (175).

X-ray crystal analysis of compound **173b** established the all C4-C4a-C8a cis relationship and absolute stereochemistry of the stereogenic centers (Figure 2-16) with retention of configuration at C-4.

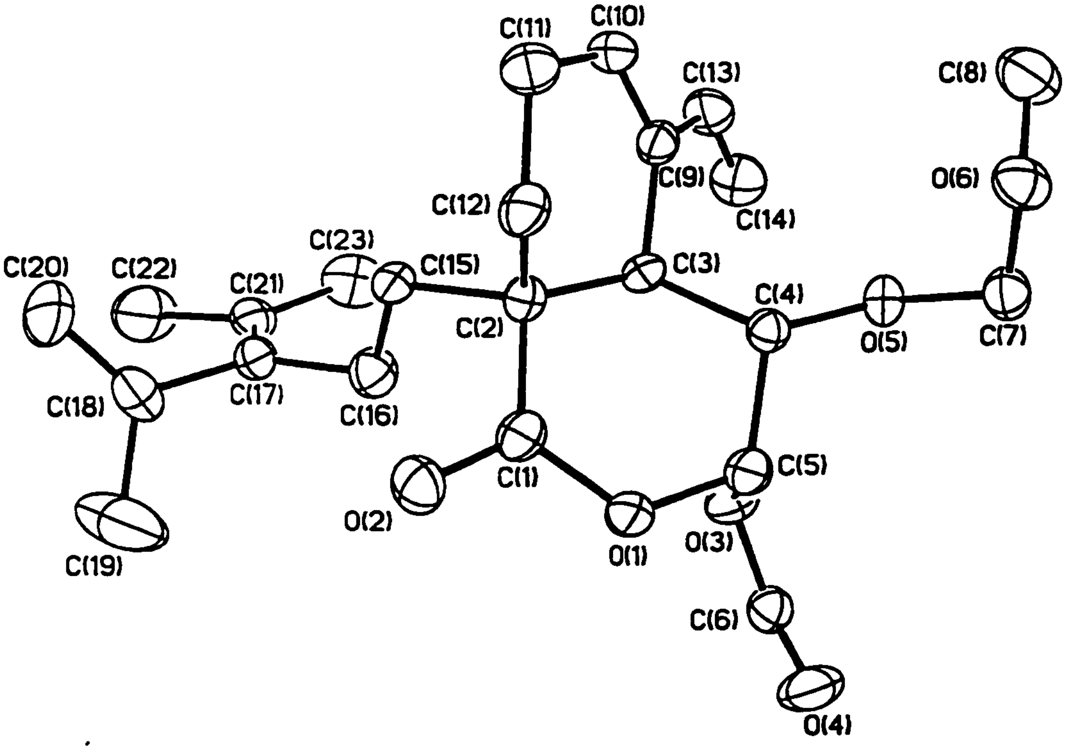


Figure 2-16: X-ray crystal structure of (173b).

Further experimentation established a different but reliable method in each case to control the product distribution as summarized in Table 2-7. The solvent exerts an important influence on these transformations. For diol **168a** the use of lead tetraacetate in dichloromethane containing sodium carbonate provided a 3:7 ratio of **172a** and **173a** respectively (Entry a). In contrast, for **168b** the best conditions with lead tetraacetate required a solvent mixture of tert-butyl alcohol and benzene but gave the formate-lactone **173b** as the sole product (Entry d). The use of this bulky alcohol thus inhibited the formation of the compound related to **95** observed above. Treatment of **168a** with sodium metaperiodate in THF/H_2O (Entry b) afforded a 90% yield of **172a** and **173a** but the ratio 9:1 was reversed compared to Entry a. The best and simplest procedure for the synthesis of **173a** was based on the use of the silica-gel supported metaperiodate reagent developed by Zhong and Shing[112] in which the prepared powder was added to a stirred dichloromethane solution containing the diol **168a** and the reaction was worked up, after 30 minutes, by filtration to provide the formate in 99% yield. This material is of sufficient purity to be used directly in the next step (Entry c). Compound **172b** was obtained as the major product (97%, (9:1) when **168b** was treated with sodium metaperiodate in aqueous THF solution (Entry e), while the use of methanol/THF solvent mixtures was deleterious.

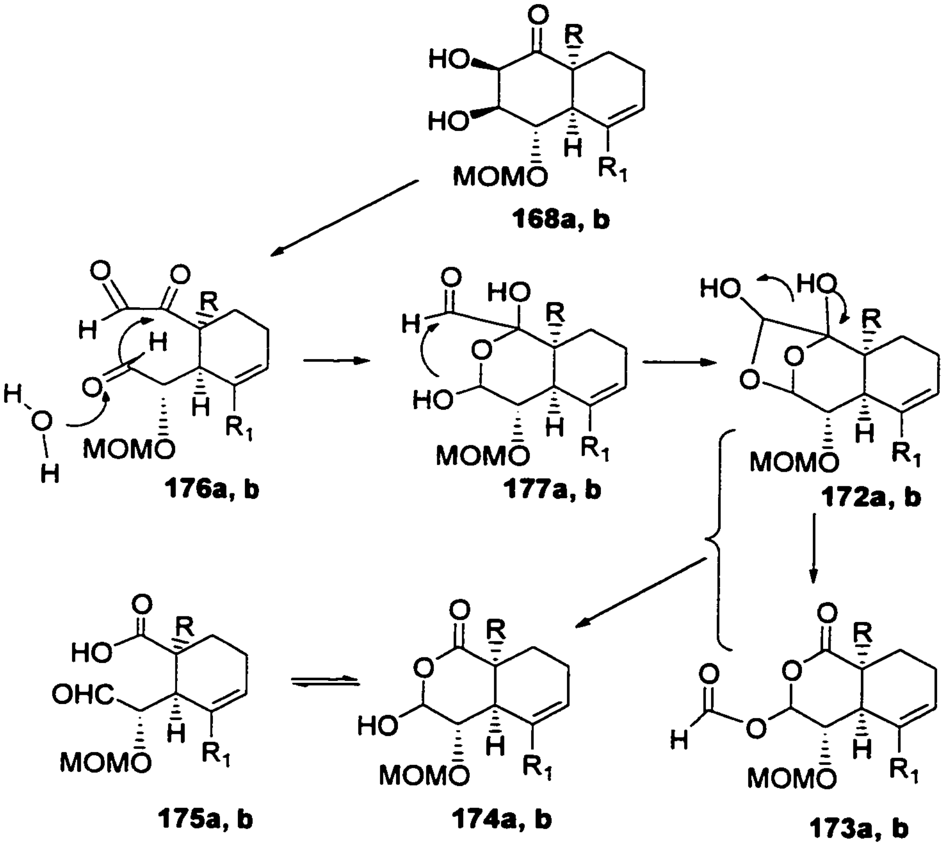
---

[112] Zhong, Y-L; Shing, T. K. M. *J. Org. Chem.*, **1997**, *62*, 2622.

entry	substrate	oxidants (conditions)	product (yield, ratio)
a	**168a**	$Pb(OAc)_4$ Na_2CO_3, CH_2Cl_2	**172a,173a** (75%, 3:7)
b	**168a**	$NaIO_4$ THF/H_2O 1:1	**172a,173a** (96%, 9:1)
c	**168a**	$NaIO_4/SiO_2$ CH_2Cl_2	**173a** (99%)
d	**168b**	$Pb(OAc)_4$ t-BuOH/C_6H_6	**173b** (62%)
e	**168b**	$NaIO_4$ THF/H_2O	**172b,173b** (97%, 9:1)
f	**168b**	$NaIO_4$ THF/MeOH	starting material
g	**168b**	HIO_4 THF/MeOH	complex mixture

Table 2-7: Oxidative cleavage of decalin diols (168a) and (168b).

Treatment of **173** with aqueous potassium carbonate solution afforded an equilibrium mixture of the hemiacetal **174** and the acid **175** in 83% yield.



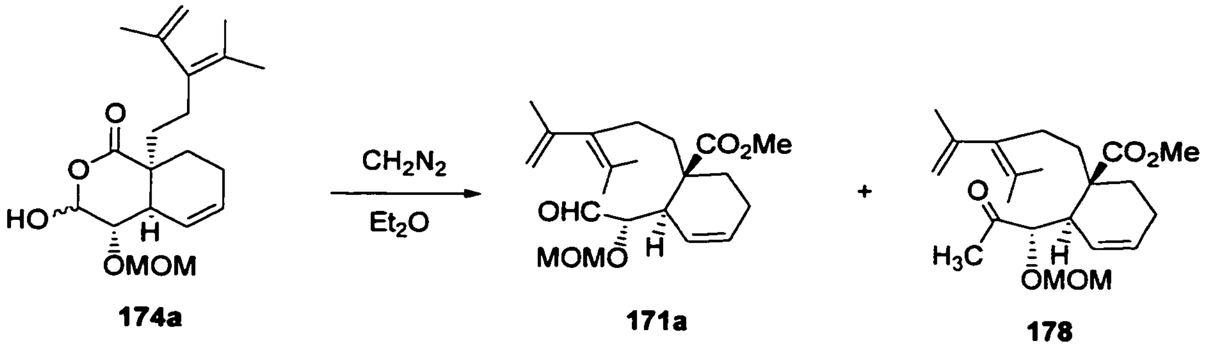
R = CH_2CH_2-(CMe=CH_2)=CMe_2

a R_1 = H, **b** R_1 = CH=CH_2

Scheme 2-35: Proposed mechanism for the oxidative behaviour of diols (168).

The formation of compound **172** can be explained by addition of water onto the dicarbonyl formed during the oxidative cleavage, followed by a tandem attack of the hydroxyl oxygens onto the free carbonyls. The intermediate **176** was very sensitive to any trace of moisture. Scheme 2-35 outlines a mechanistic rationalization for the oxidative behavior of diols **168**. The initial oxidative cleavage afforded the tricarbonyl species **176**. However, instead of undergoing further oxidation to the aldehyde **175** and formation of the acetal-lactone **174**, addition of water and cyclization to **177** was the dominant pathway. Subsequent ring closure provided the bridged ring diol **172**, which underwent further oxidative cleavage to generate the formate-lactone **173**. As noted above, aqueous carbonate hydrolysis afforded an equilibrium mixture of **175** and **174** in which the carboxylic acid was captured by esterification.

The products, ester-aldehydes related to **171**, contain appropriate functionality for subsequent transformation into the Diels-Alder precursors related to **81**.



Scheme 2-36: Synthesis of aldehydo-ester (171a).

Compound **174a** was reacted directly with ethereal diazomethane to afford the desired methyl esters **171a** in 60% yield (Scheme 2-36). The methyl ketone **178** was characterized as a side product of the esterification. Thus, this sequence provided the requisite substituted cyclohexenes with the functionality required for installation of an appropriate dieneophile.

In conclusion, a four step sequence has been developed to perform the transformation of decalin **165a** to Diels-Alder precursor **171a** via a facile and efficient vicinal diol cleavage.

2.7 FORMATION OF THE DIELS-ALDER PRECURSOR

2.7.1 DINITRILE COMPOUND

The synthesis of a first dienophile activated by two nitrile groups was undertaken. In our molecule the diene and dienophile are brought together *via* a cyclohexene permanent link. The conformational constraint imposed by the tether allows for controlling both the regio- and stereoselectivity of the cycloaddition. Shea *et al.* has reported that in some case the constraint brought by tether group can override the usual regiochemical pattern and results in a reverse regiochemistry.[113] (Figure 2-17).

---

[113] Gauthier Jr., D. R.; Shea, K. J. *Tetrahedron Lett.*, **1990**, *31*, 5885.

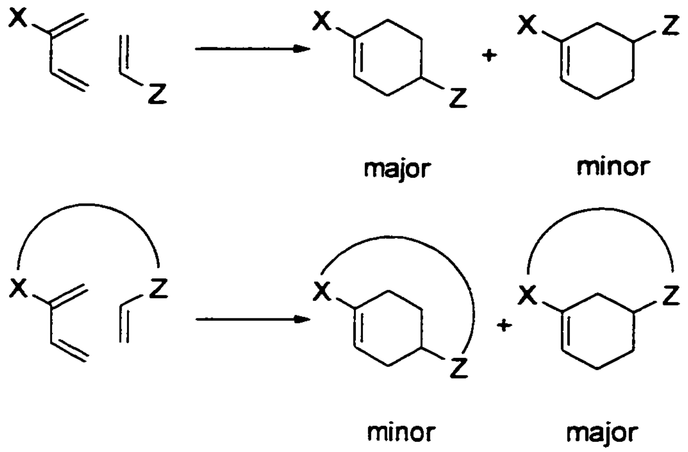
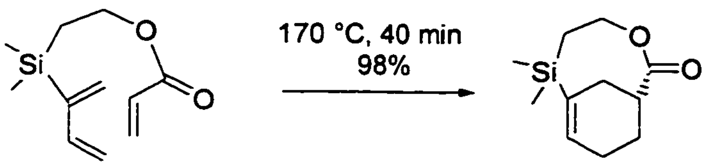


Figure 2-17: Regiochemical patterns of intra- and intermolecular Diels-Alder reactions.

The mechanical constraint imposed by the tether was shown to bias the cycloaddition reaction to some degree and in the case of a 5-atom tether control, the intrinsic regiochemical preferences of the Diels-Alder reaction was completely reversed (Scheme 2-37).[114]



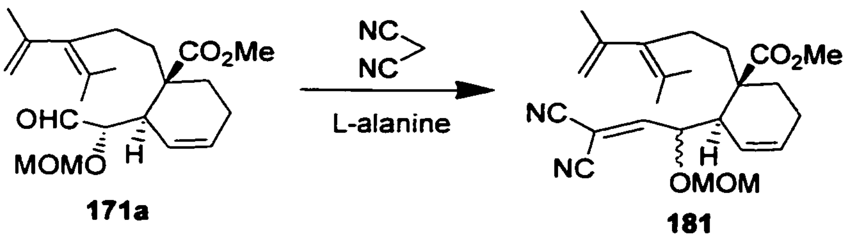
179 **180**

Scheme 2-37: Diels-Alder cycloaddition leading to a reversed regiochemistry.

In order to retain the key stereocenter at C-2 in the final compound, the dienophile can only be activated on the other side of the double bond and the MOM group must be left intact. A disubstituted double bond with two nitriles was expected to be strongly activated towards Diels-Alder reactions.

---

[114] Staab, A. J.; Zandi, K. S.; Shea, K. J. *Tetrahedron Lett.*, **1991**, *32*, 2715.



Scheme 2-38: Synthesis of the dinitrile activated precursor for the Diels-Alder reaction.

Knoevenagel condensation of malonitrile onto aldehyde **171a** gave the expected triene **181** in 13% yield as well as a diastereoisomer as a byproduct (Scheme 2-38). Under the basic conditions used, epimerisation is likely to occur at the α position of the carbonyl and the utilization of a weak base like alanine did not allow the synthesis of the triene in good yield. The reaction was not optimized and the next step, the Diels-Alder cycloaddition, was attempted on a small scale.

According to the electronic effect known to induce the regioselectivity in Diels-Alder cycloaddition,[115] the diene and the dienophile are not ideally set to react. However by analogy with the results mentioned above, a reverse addition might be possible due to the geometrical constraint brought by the tether.

The cycloaddition was investigated under various conditions (Table 2-8).

Concentration (M)	Solvent	Temperature (°C)	Reaction Time
	neat	110 then 135	1h then 3h
0.012	toluene[a]	170	
0.0076	toluene[a]	205	4 days
0.0126	water	reflux	24h
	water[b]	110	10 min

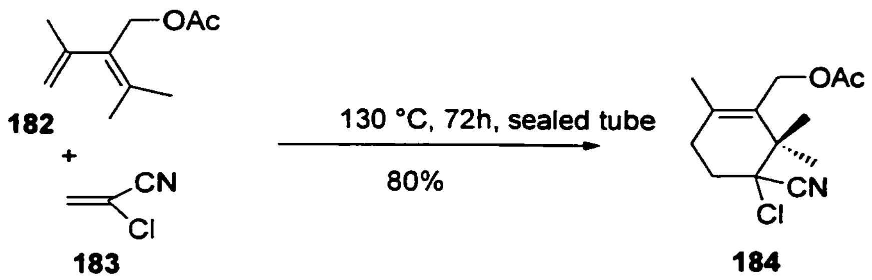
a- The reaction is performed in a sealed tube. b- The reaction was performed in an open vessel in a microwave.

Table 2-8: Diels Alder conditions.

---

[115] Fringuelli, F.; Taticchi, A. in *Dienes in the Diels-Alder Reaction*; John Wiley & Sons, Inc.; 1990; Chap. 1; pp13-16.

The cycloaddition was attempted neat at 110-135 °C. Only starting material was recovered. The material was dissolved in toluene and heated at 170 or 205 °C in a sealed tube to no avail. Changes in the nature of the solvent have been reported to have a moderate effect on the Diels-Alder reaction, however Breslow *et al.* have demonstrated that the rate of cycloadditions performed in water can be subjected to dramatic acceleration.[116] Therefore the reaction was performed in water at reflux for 24 h, to no avail. The next attempt used microwave activation. Pericyclic reactions can be carried out with dramatic enhancement in yield and a reduction in reaction time. Intermolecular,[117] intramolecular[118] and hetero Diels-Alder[119] reactions have been shown to benefit from microwave activation. Thus, the material was heated at 110 °C in an open vessel for 10 min, using water as a microwave active solvent. Unfortunately these conditions failed to give any product. In parallel with the preceding attempts, the starting material was recovered.



Scheme 2-39: Synthesis of Taxol® A ring *via* Diels-Alder reaction.

The addition of chloroacrylonitrile onto a derivative of diene **153** to build the A ring in Nicolaou's synthesis is a good example of the natural expected regiochemistry (Scheme 2-39).[25a] The intermolecular cycloaddition afforded only one regioisomer in 80% yield due to the regiocontrol induced by the electronic effects.

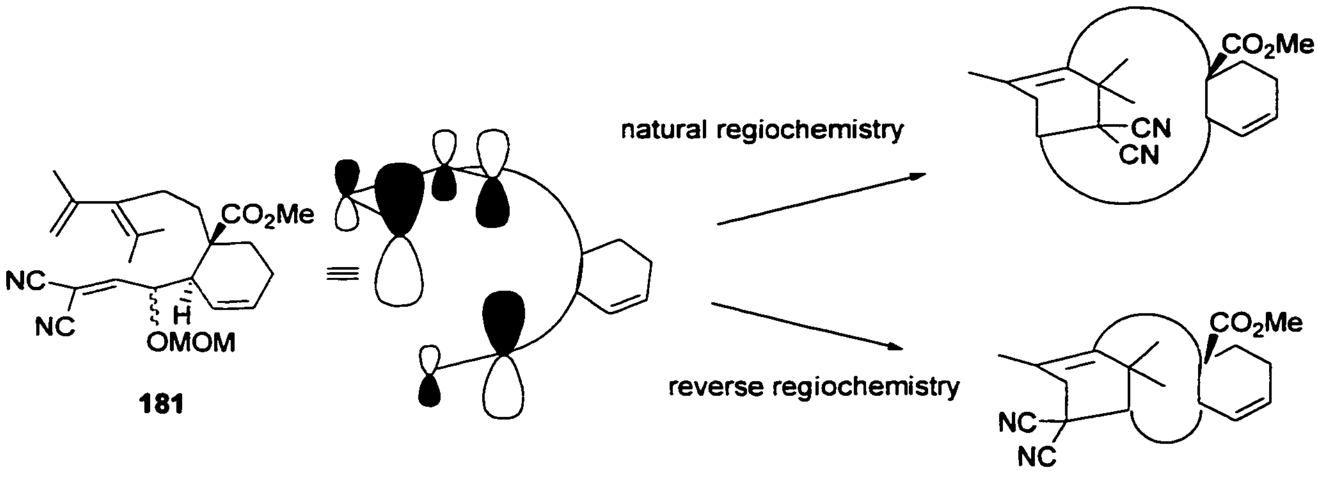
---

[116] Breslow, R. *Acc. Chem. Res.*, **1991**, *24*, 150.

[117] Bray, T. L.; Duncan, S. M.; Giguere, R. J.; Majetich, G. *Tetrahedron Lett.*, **1986**, 27, 4945.

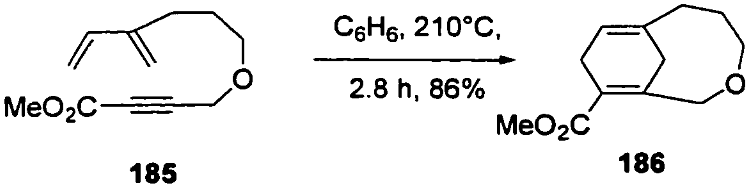
[118] (a) Lei, B.; Fallis, A. G. *J. Am. Chem. Soc.*, **1990**, *112*, 4609. (b) Lei, B.; Fallis, A. G. *J. Org. Chem.*, **1993**, *58*, 2186.

[119] Stambouli, A.; Chastrette, M.; Soufiaoui, M. *Tetrahedron Lett.*, **1991**, *32*, 1723.



Scheme 2-40: Diels-Alder cycloaddition of (181).

As shown in Scheme 2-40, the natural regiochemistry of the Diels-Alder cycloaddition is not easily available with compound **181**. The constraint brought by the tether as well as the steric hindrance of the gem dimethyl and the gem dinitrile makes it impossible for the diene and dienophile to align properly for the reaction to take place. However, the possible cycloaddition with reverse regiochemistry that would be induced by the tether did not occur either with compound **181**. A closer look at the orbitals involved in the reaction (LUMO of the dienophile and HOMO of the diene) showed that in addition to being bulky, the gem dimethyl on the diene is strongly activating the conjugated diene so the reactive orbitals have very different size and the size are apparently not similar enough to allow a reversed addition. The same can be said for the activation of the dienophile with the two nitrile groups.

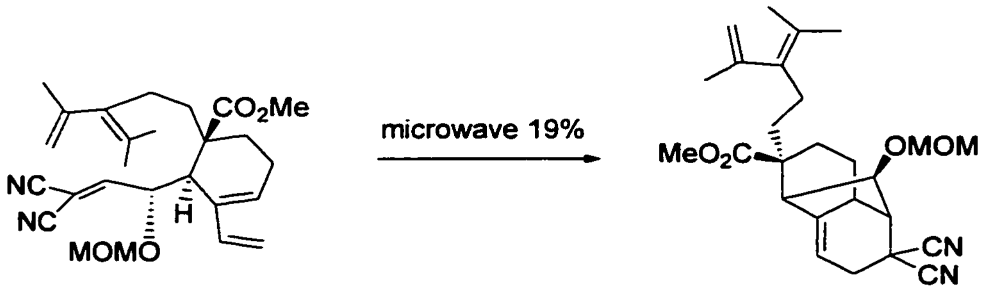


Scheme 2-41: Intramolecular Diels-Alder reaction of the nor methyl diene (185).

However it is known in the case of the nor methyl system that an ester activated dienophile afforded the strained system illustrated in Scheme 2-41.[120]

---

[120] Coper, D. K.; England, W. P.; Ziller, J. W.; Lease, T. G. *Tetrahedron Lett.*, **1990**, *31*, 6843.



187 **188**

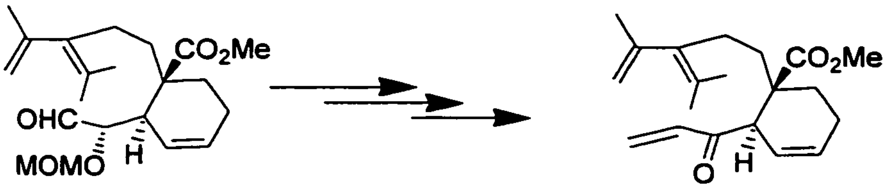
Scheme 2-42: Regioselectivity in intramolecular Diels-Alder.

In addition, the unexpected reactivity of compound **187**, similar to our triene **181**, showed that the electronic effects of the diene and dienophile overcome the steric effect and the dienophile would rather cyclize onto the less substituted diene in spite of the resulting strain in the resulting molecule (Scheme 2-42).[106b]

Therefore, as the molecule was not properly activated towards cycloaddition and the steric hindrance presented by the substituents prevented the reverse addition, another course was taken.

2.7.2 1,3-DIENONE

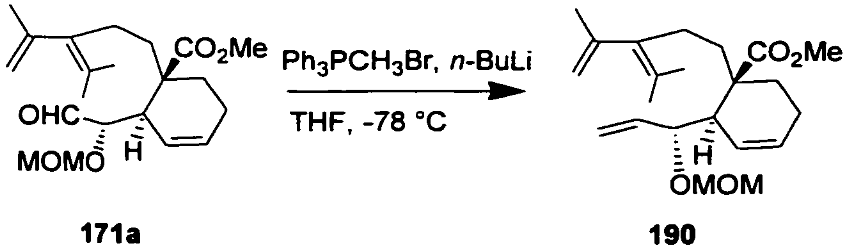
Ultimately the stereochemical center bearing the MOM ether was sacrificed to activate the dienophile with an α ketone. Thus, compound **189** resembles the species **62**, **66** and **72** which have been reported to undergo Diels-Alder reaction quite easily.



171a **189**

Figure 2-18: A new Diels-Alder precursor.

Aldehyde **171a** was transformed into the alkene intermediate **190**. Subsequent deprotection of the MOM ether followed by oxidation of the resulting alcohol would lead to the Diels-Alder precursor **189**. However, if the condensation of triphenylphosphine methylene onto the aldehyde led the expected alkene **190** in good yield (Scheme 2-43), the deprotection of the alcohol proved to be a problem.

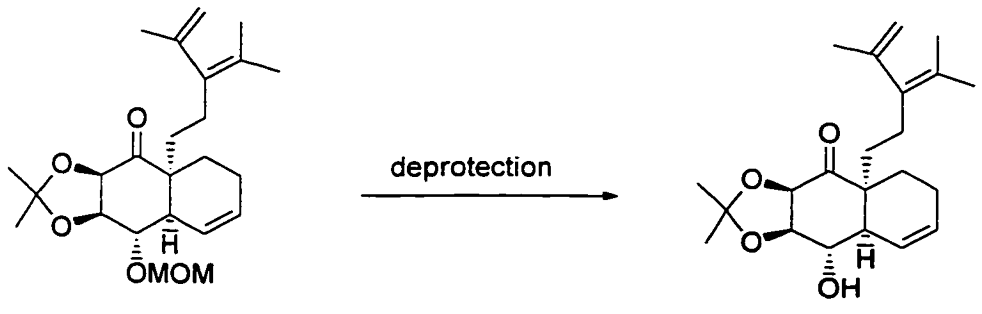


171a **190**

44%

Scheme 2-43: Formation of the dienophile.

Deprotection of the methoxymethyl ether was attempted first with hydrochloric acid 6N but lead to decomposition with some starting material left.[121] Due to the small quantities of product available at this stage, less drastic conditions were investigated on a derivative **165** (Table 2-9). Note that the competitive deprotection of the isopropylidene (if it ever occurs) is not a problem as ultimately this protecting group will not be present in the compound to deprotect.



165 **169**

Scheme 2-44: Selective deprotection of the MOM group in the decaline (165).

---

[121] Durandetta, J. L.; Munavu, R. ; Meyers, A. I. *J. Org. Chem.*, **1975**, *40*, 2025.

Entry	Reagent	Solvent	Temperature	Result
a	$Ph_3C^+BF_4^-$	CH_2Cl_2	rt	decomposition
b	TMSBr (4 eq) molecular sieves 4Å	CH_2Cl_2	-30 °C to rt	decomposition
c	TMSBr (4 eq) molecular sieves 4Å	CH_2Cl_2	-30 °C to 0 °C	decomposition + starting material
d	TMS_2/I_2	CH_2Cl_2	40 °C to reflux	traces of product
e	Me_2SiCl_2/*n*-Bu_4NBr molecular sieves 4Å	CH_2Cl_2	0 °C to rt	20%
f	**$BF_3.OEt_2$, $(CH_3)_2S$**	**CH_2Cl_2**	**0 °C**	**29%**

Table 2-9: MOM deprotection conditions.

Deprotection of the methyloxymethyl ether group with trityl tetrafluoroborate at room temperature gave decomposition (Entry a).[122] The use of mild reagent bromotrimethylsilane in large excess (4 equivalents) at –30 °C then 0 °C led to decomposition with some starting material (Entry b).[123] With a longer warming time to room temperature total decomposition occurred (Entry c). Attempted dealkylation with iodotrimethylsilane generated *in situ* from hexamethyldisilane and iodine yielded traces of product (Entry d).[124] Ether cleavage by exposure to tetrabutylammonium bromide and an excess of dichlorodimethylsilane at 0 °C provided the expected deprotected alcohol in 20% yield (Entry e),[125] but the best yield was obtained by treatment of the ether with trifluoroboron etherate and dimethylsulfide at 0 °C (Entry f).[126]

The best result was applied to our Diels-Alder derivative.

---

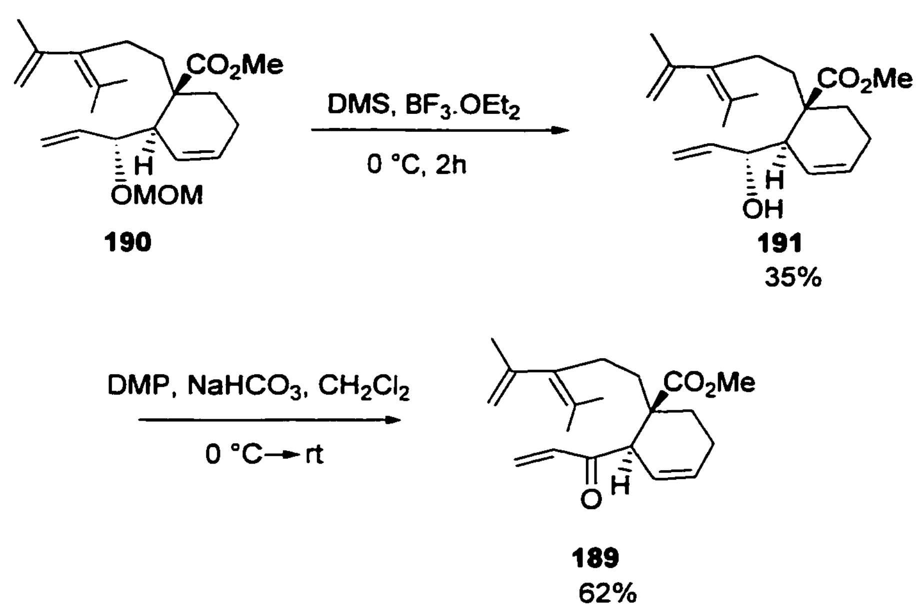
[122] Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.*, **1978**, *100*, 2933.

[123] Ishihara, J.; Tomita, K.; Ogawa, S. ; Tadano, K. *J. Org. Chem.*, **1992**, *57*, 3789.

[124] Shirahata, A.; Sasaki, K. ; Hosomi, A.; Sakurai, I. *Synthesis*, **1979**, 740.

[125] Liu, W.; Ghosh, A. K. *J. Org. Chem.*, **1997**, *62*, 7908.

[126] Sinha, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.*, **1999**, *64*, 2381.



Scheme 2-45: Deprotection and oxidation of (190) to form activated dienophile (189).

Treatment of **190** with 3.2 equivalents of trifluoroborate and a large excess of dimethylsulfide in methylene chloride gave the expected deprotected alcohol **191** in 35% yield. Subsequent oxidation under mild conditions using Dess Martin's Periodinane reagent afforded the Diels-Alder precursor **189** in 62% yield.

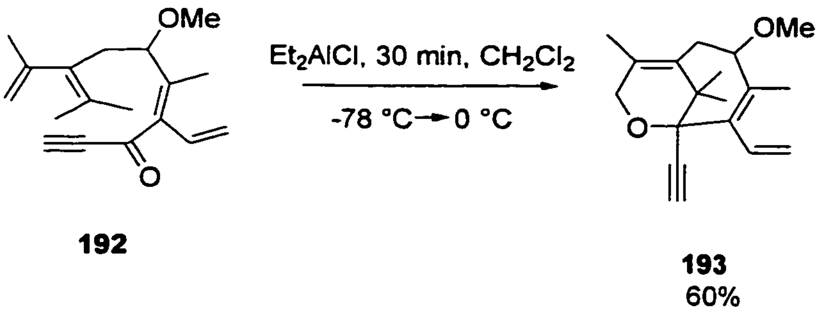
2.8 DIELS-ALDER REACTION

2.8.1 HETERO DIELS-ALDER

Ketone **178** was submitted to Diels-Alder conditions in order to see if any hetero Diels-Alder reaction would take place. Such reaction have been shown to occur in similar system to build the AB ring system of Taxol (Scheme 2-46).[127]

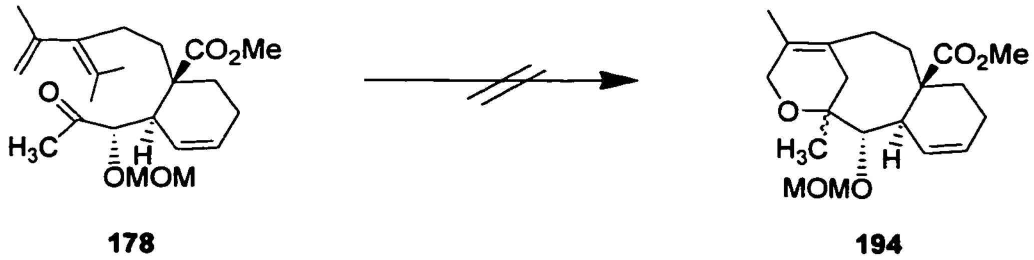
---

[127] Dr. A. Laurent, Final Research Report, 2001, University of Ottawa.



Scheme 2-46: Hetero Diels-Alder reaction preferred over Diels-Alder reaction with the alkyne dienophile.

In order to induce the cycloaddition, 1.1 equivalent of diethylaluminium chloride was added to the ketone **178** in THF at -78 °C. No reaction took place, even after warming up to room temperature. The starting material was then submitted to thermal activation (Table 2-10).



Scheme 2-47: Attempted hetero Diels-Alder reaction.

Temperature (°C)	Time of reaction	Pressure
180[a]	2 days	unknown
210[a]	4 days	unknown
210[b]	15 min	133 PSI
210[b]	30 min	133 PSI

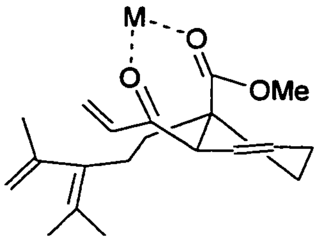
a- The reaction was done in a sealed tube.
b- The reaction took place in a microwave.

Table 2-10: Thermal activation of the hetero Diels-Alder.

Compound **178** was dissolved in dry toluene and heated to 180 °C then 210 °C in a sealed tube for a long period of time under dilute conditions. In both cases the starting material was recovered and used for the next experiment, to extend the total heating time. The pressure in the sealed tube was not known. For better control of the temperature and the pressure the reaction was attempted under microwave activation. It has been reported that microwave accelerated the process when the reaction was slow to occur under conventional heating. The sample was solubilized in dry toluene and placed in a closed vessel with a carboflon bar used as a microwave active component to absorb the waves and heat the solution. The mixture was heated for small amounts of time and controlled by TLC after each experiment. The temperature and pressure were monitored at any time and a graph temperature/pressure vs time was available for each experiment. (See appendix A). Unfortunately in each case the starting material was recovered, the hetero Diels-Alder did not take place. The superheating effect of the microwave activation and the high pressure effect did not lead to any product formation.

2.8.2 DIELS-ALDER REACTION

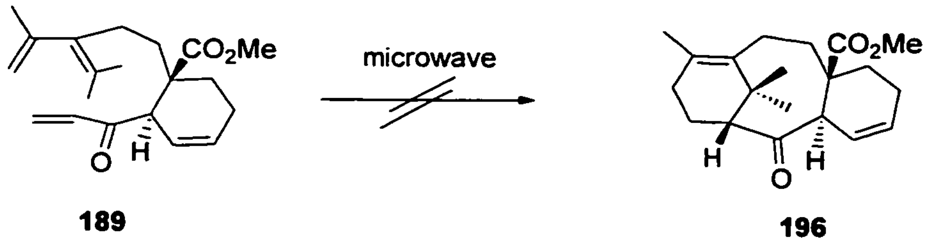
In order to effect the Diels-Alder cycloaddition, triene **189** was treated with $BF_3.OEt_2$. Identical conditions were employed to induce the cycloaddition of **72** in 72% yield. However, treatment of **189** with up to 9 equivalents of $BF_3.OEt_2$ in toluene at -78°C did not yield any product. As no reaction occurred, the mixture was allowed to warm to room temperature and was left to stir for 4 days to no avail. No product was detected by TLC or by ^1H NMR but the starting material was recovered. It might be possible that in this case both the ketone and the methyl ester can coordinate with the Lewis acid, resulting in a separation of the diene and dienophile instead of a better overlapping.



195

Figure 2-19: Possible conformation of the Diels-Alder precursor when a Lewis acid is used.

In a final attempt at constructing the ABC ring system, triene **189** was submitted to microwave activation (Scheme 2-48).



Scheme 2-48: Diels-Alder cycloaddition of (182).

Entry	Temperature (°C)	Time of reaction	Pressure
a	200	30 min	100 PSI
b	210	15 min	133 PSI
c	200	1 h	100 PSI

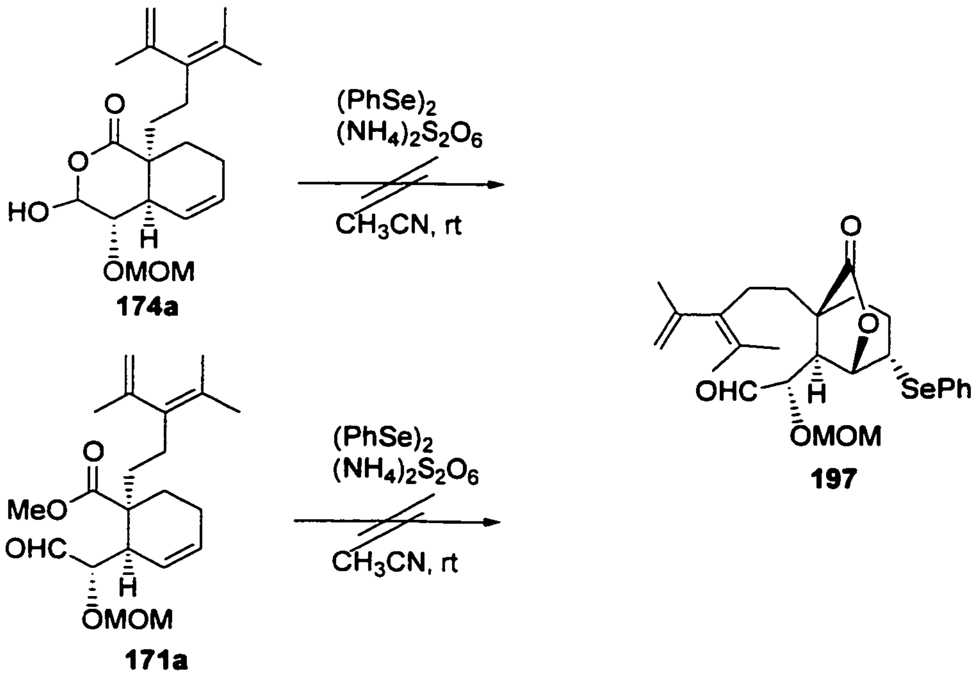
Table 2-11: Microwave activation of the Diels-Alder reaction.

After heating of a solution of 5 mg of **189** in dry degased toluene for 5 min then 30 min at 200 °C under 100 PSI (100 PSI or 6.8 atm), only starting material can be seen on TLC (Entry a). Higher temperature (210 °C) and pressure (133 PSI or 9 atm) for 15 min. led to a mixture which after purification yielded traces of starting material (0.5 mg, 10%) and a major product (3 mgs) along with traces of unidentified byproducts (Entry b). An attempt at characterizing the major product showed that the ester and the double bonds have disappeared, the molecule was broken down. The small sample of **189**, recovered from previous attempts, was submitted again to microwave activation but at lower temperature for a longer time to no avail (Entry c).

With such a small quantity of product, few experiments could be attempted and conventional heating was bypassed for microwave irradiation with the hope that superheating of an already high boiling solvent and an increase pressure would combined to effect the reaction. However, neither superheating nor microwave effect could force the cycloaddition to occur. By comparison with the Diels-Alder reactions reported on similar system, compound **189** possesses a methyl ester that can coordinate with the Lewis acid used in the first attempt and prevent the required overlapping of the diene and dienophile for the cycloaddition to occur. In order to improve the chance of cyclisations a few transformations could be performed on compound **189**.

The presence of the methyl ester and the trans stereochemistry between the diene and the dienophile are not convenient for the cycloaddition. To address this problem, the ester was removed.

One possibility was to tie the ester in an environment away from the diene and dienophile. In order to facilitate the Diels-Alder reaction, an intramolecular lactonization reaction was attempted on the lactol, hoping it would allow a better overlap of the diene and the dienophile without the ester intervening. Iodolactonization is common and has been used to effect syn dihydroxylation on the most hindered face of the substrate.[128] However, the reported yield for such reactions are typically mediocre for 5 and 6-membered rings (60-70%). On the other hand, selenolactonization can be done under mild conditions and in good yields, using a phenylselenium cation.[129] Moreover, the installation of a phenylseleno group would allow direct further selective transformation of the molecule and provide a handle for the formation of the oxetane D ring.



Scheme 2-49: Attempts at selenolactonization.

Selenolactonization attempts on compound **174a** and aldehydoester **171a** failed (Scheme 2-49). Another possibility to get rid of the methyl ester is to replace it by a methyl group, which

---

[128] Clausen, R. P.; Bols, M. *J. Org. Chem.*, **2000**, *65*, 2797.

[129] Balducci, R.; Bartoli, D.; Tingoli, M.; Testaferri, L. ; Tiecco, M. *J. Org. Chem.*, **1990**, *55*, 429.

would give a compound very similar to **62** and more likely to undergo the cycloaddition. However, this would severely curtailed the attractive features of this group to make a soluble salt and Barton photolysis for remote functionalization.[130]

An alternative solution would be to effect the migration of the cyclohexene double bond to form the conjugated flat system more reactive towards the Diels-Alder reaction. However, the lack of material prevented us from doing further research and the project was stopped at this stage, but, the possibilities remain for future work.

2.9 CONCLUSION

The studies towards the synthesis of Taxol® analogs, using a double Diels-Alder strategy, have been described. The transformation of carbohydrates into complex targets that only resemble the starting material was achieved. Starting with (L)-arabinose or (D)-guluno-γ-lactone, compounds such as polyfunctionalized decalin **165** and the Diels-Alder precursor **191** were synthesized. The starting materials are cheap and the synthesis can be scaled up. The route to compounds **181** and **189** described here has been optimized up to the diol deprotection with an overall 14% yield for 11 steps.

We have established that *cis*-isopropylidene acetals **164** derived from (L)-arabinose are superior to the trans isomer for inducing the overlap required for facile cyclization to give decalin **165**. In addition, the reaction rate is increased, and lower temperatures may be employed. Oxidation of alcohol **164** led directly to the formation of the highly functionalized decadienone **165** with excellent stereoselectivity. Only one diastereomer was obtained and the resulting bicyclic compound carries five consecutive stereogenic centers. Up to this point, the synthesis is very efficient, without loss of product due to the formation of diastereomers or epimerization.

However, the following steps have not been optimized and the loss in material increased exponentially starting at the diol deprotection. Despite reports in the literature of facile hydrolysis of the acetonide protecting group, this reaction proved to be particularly troublesome for our product and resulted in an incomplete reaction or loss of product. The

---

[130] Beaton, I. M.; Barton, D. H. R. *J. Am. Chem. Soc.*, **1961**, *83*, 4083.

oxidative cleavage of the cis diol under standard conditions led to an unexpected result but, a direct oxidative sequence for the controlled cleavage of vicinal decalin diols has been developed using a dry loaded $NaIO_4$ on silica gel. Subsequent functional group manipulations afforded trienes **181** and **189**, which are precursors for the second Diels-Alder. Attempted cyclization to form the ABC ring system of Taxol® failed to occur under the conditions tested but the lack of product prevented us from doing further experiments. Future work may prove that the cycloaddition is feasible.

EXPERIMENTAL

Chapter 3

General Experimental

Melting points were determined with a Thomas-Hoover Unit melting point apparatus and are uncorrected.Infrared (IR) spectra were obtained either as neat thin films or as a thin film of a carbon tetrachloride solution of the compound on sodium chloride discs. All IR spectra were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR) (internal calibration).

Proton Magnetic Resonance spectra (^{1}H NMR) were measured at either 200 MHz with a Varian Gemini spectrometer or at 500 MHz with a Brucker AMX500 spectrometer in the stated solvent. Carbon Magnetic Resonance spectra (^{13}C NMR) were measured at either 50 MHz with a Varian Gemini spectrometer or at 125 MHz with a Brucker AMX500 spectrometer in the stated solvent. All chemical shifts are reported downfield from tetramethylsilane (δ scale) in ppm.

Low resolution mass spectroscopy (MS) using either electron impact (E.I.), or chemical ionization (CI) mode was performed on a V.G. Micromass 7070 HS mass spectrometer with an electron beam energy of 70 eV (for E.I.). High Resolution Mass Spectroscopy (HRMS) was performed on a Kratos Concept-IIA mass spectrometer with an electron beam energy of 70 eV.

Microanalyses were conducted by M-H-W Laboratories, Phoenix, AZ, USA.

Deviation of polarized light was measured on a Perkin-Elmer polarimeter 241 with a sodium lamp at 589 nm in dry MeOH unless otherwise stated.

Commercial aluminium sheets coated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck) were used for analytical Thin Layer Chromatography (TLC). TLC spots were visualized with UV light (254 nm), iodine vapour, and/or heating the plate after treatment with either a 5% solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v) or a 20% solution of phosphomolybdic acid in ethanol.

Product purification by conventional and flash chromatography was performed with E. Merck Silica Gel 60 (70-230 or 230-400 mesh, respectively).

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 aspirator or air aspirator connected to a Büchi rotary evaporator. Trace solvents were removed on a vacuum pump.

Reaction run at room temperature indicates 21 °C.

All non aqueous reactions were performed under a nitrogen atmosphere in flame dried glassware in dry solvents, unless otherwise stated.

Solvents and Reagents

Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30-60 °C. Anhydrous tetrahydrofuran and ether were distilled from sodium/benzophenone. Dichloromethane, toluene, benzene, triethylamine and diisopropylethylamine were distilled from calcium hydride. Unless otherwise stated, all starting material were purchased from Aldrich Chemical Company and used without prior purification.

Intramolecular Diels-Alder Cycloadditions

1. Thermally induced cycloaddition

The starting material was dissolved in anhydrous toluene and transferred *via* a canula into a thick glass tube (70 mL) equipped with a stirring bar. The solution was degazed (vacuum down and filled with argon *3). The septum was replaced by a screw cap and the tube was hermetically closed. The solution was then heated at the required temperature with either a wax bath or a Kugelrohr. Reading of the temperature and the pressure was not available using this apparatus.

2. Microwave induced cycloaddition

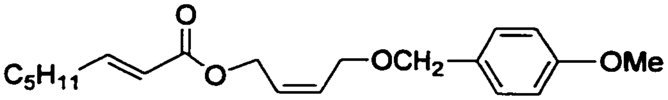
Microwave heating was achieved using a CEM Mars X reactor, equipped with a magnetron emitting at a frequency of 2.455 GHz. Temperature control and/or pressure control allow for power modulation from 300 to 1200 Watts to reach the temperature or pressure goal. The oven functions as a multimode applicator. Temperature measurement was carried out with a

EST-300 Plus optical fiber thermometer and a pressure probe read the pressure inside the vessel at any given time.

The starting material (1 to 5 mg) was placed in the thick glass vessel adapted to microwave use and dissolved in anhydrous toluene (10-15 mL). The vessel was equipped with a carboflon (t° <200 °C) or a glass coated carboflon (t° >200 °C), placed in the insulated recipient and holder, and closed with the appropriate plastic cap. The solution was degazed (vacuum down and filled with argon *3), equipped with a temperature and pressure probes and placed in the microwave. The program was then run under temperature and pressure control allowing for a 20 min ramp to the temperature to hold. A graph of the conditions used is available in appendix A.

Compounds were named following the nomenclature rules used in Beilstein Information System applying the IUPAC rules.

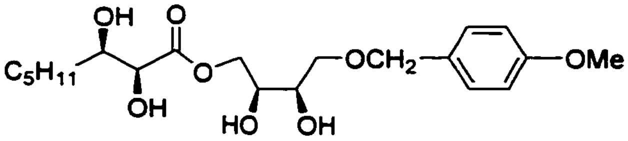
Oct-2-enoic acid 4-(4-methoxy-benzyloxy)-but-2-enyl ester (110)

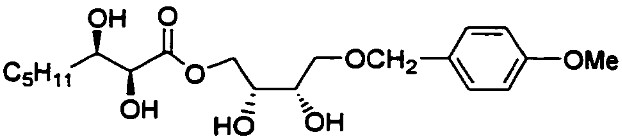


A solution of alcohol **113** (7.00 g, 33.7 mmol) in CH_2Cl_2 (15 mL) and a solution of DCC (7.25 g, 35.1 mmol) in CH_2Cl_2 (20 mL) were simultaneously added to a cold solution (0 °C) of *trans* octenoic acid (6.5 mL, 34.5 mmol) and DMAP (0.416 g, 3.40 mmol) in CH_2Cl_2 (90 mL). The solution was allowed to stir at 0 °C for 1.5 h then at room temperature for 6 h. The suspension was filtered through a pad of Celite®, washed with dichloromethane and concentrated. The crude yellow oil was purified twice by flash chromatography (25:75, ether/petroleum ether) after dry loading and gave the product as a slightly yellow oil (7.78, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.96 (dt, *J* = 15.7, 7.1 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.81-5.76 (m, 2H), 5.73-5.69 (m, 1H), 4.66 (dd, *J* = 6.7, 0.8 Hz, 2H), 4.42 (s, 2H), 4.09 (dd, *J* = 6.7, 0.8 Hz, 2H), 3.76 (s, 3H), 2.16 (qd, *J* = 7.2, 1.6 Hz, 2H), 1.44-1.41 (m, 2H), 1.30-1.25 (m, 4H), 0.86 (t, *J* = 6.9 Hz, 3H). ^{13}C (125 MHz, $CDCl_3$) δ 166.3, 159.2, 149.9, 130.8, 130.1, 129.3, 126.7, 120.8, 113.8, 72.0, 65.3, 60.0, 55.2, 32.1, 31.2, 27.6, 22.3, 13.8. IR (neat) 3031, 3000, 2930, 2858, 1721, 1654, 1613, 1514 cm^{-1}. Anal. Calcd. for $C_{20}H_{28}O_4$ (332.44): C, 72.26; H, 8.49. Found: C, 72.30; H, 8.57.

2,3-Dihydroxy-octanoic acid 4-benzyloxy-2,3-dihydroxy-butyl ester (114)/(115)

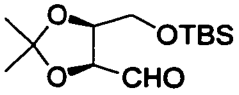




Methanesulfonamide (0.143 g, 1.47 mmol) was added to the yellow solution of sodium bicarbonate (0.297 g, 3.53 mmol) and AD Mix β (1.650 g, ~2 eq) in a 1:1 mixture of *t*-BuOH/H_2O (14 mL). The solution was cooled to 0 °C and a solution of diene **110** (0.195 g, 0.59 mmol) in a 1:1 mixture of *t*-BuOH/H_2O (6 mL) was added. The mixture was vigorously stirred at 5 °C for 24 h then quenched with portions of Na_2SO_3 (1.780g) and extracted with AcOEt, then CH_2Cl_2, dried and concentrated. The crude was recrystallized from hexane/AcOEt (2:1) and gave a fluffy white solid (0.125 g, 54%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.7 (br s, 1H), 4.58 (dd, *J* = 8.2, 2.8 Hz, 1H), 4.47 (s, 2H), 4.28 (dd, *J* = 8.3, 5.2 Hz, 1H), 4.16 (d, *J* = 1.8 Hz, 1H), 3.92-3.91 (m, 2H), 3.79 (s, 3H), 3.78-3.66 (m, 1H), 3.64-3.59 (m, 2H), 3.15 (br s, 1H), 2.7 (br s, 1H), 2.3 (br s, 1H), 1.59-1.58 (m, 2H), 1.32-1.27 (m, 6H), 0.89 (t, 3H). IR (neat) 3395, 3028, 2934, 1732, 1612 cm^{-1}.

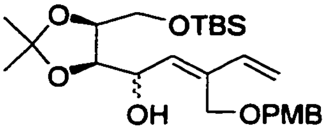
5*S**-(tert-Butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolane-4*R**-carbaldehyde (102)



Dess Martin's reagent (1.834 g, 4.33 mmol) was added portion wise to the cold suspension of alcohol **103** (1.095 g, 3.96 mmol) and sodium bicarbonate (1.668 g, 19.9 mmol) in dichloromethane (20 mL). The white mixture was allowed to stir at room temperature for 24 h then the mixture was quenched with $NaHCO_3$:Na_2SO_3 (100 mL, 1:1), extracted with CH_2Cl_2, washed with brine, dried and concentrated. The crude colorless oil was purified by chromatography (20:80, ether/petroleum ether) to give the expected product (1.008 g, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (d, *J* = 2.1 Hz, 1H), 4.46-4.43 (m, 1H), 4.39 (dd, *J* = 7.9, 2.1 Hz, 1H), 3.75 (dd, *J* = 11.4, 3.9 Hz, 1H), 3.67 (dd, *J* = 11.4, 2.8 Hz, 1H), 1.54 (s, 3H), 1.35 (s, 3H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C (125 MHz, $CDCl_3$) δ 200.1, 110.5, 80.8, 79.7, 60.5, 26.8, 25.6 (3H), 24.9, 18.1, -5.6, -5.7. IR (neat) 2931, 2888, 2858, 1727 cm^{-1}. MS (EI) *m/z* 259 (M^+ -CH_3). HREIMS *m/e* calcd for $C_{13}H_{26}O_4Si$ (M^+ -CH_3) 259.1366, found 259.1329.

1*RS*-[5*S-(tert-Butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4*R**-yl]-3-(4-methoxy-benzyloxymethyl)-penta-2,4-dien-1-ol (101b)**

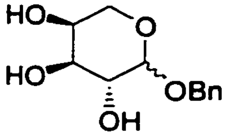


A solution of iododiene **86** (0.866 g, 2.63 mmol) in THF (10 mL) was added to a cold solution (-78 °C) of *s*-BuLi 1.3M (3.2 mL, 4.16 mmol) in THF (10 mL). The yellow solution turned to brown then orange and was allowed to stir at -78 °C for 15 min. A solution of aldehyde **102** (0.509 g, 1.86 mmol) in THF (8 mL) was added at -78 °C. The mixture turned yellow and was allowed to stir at -78 °C for 15 min then at room temperature for 1.5 h. The yellow solution was quenched by addition of aqueous Na_2SO_3. The mixture was extracted with ether, washed with brine, dried, filtered and concentrated. The crude orange oil was purified by chromatography (20:80, ether/petroleum ether) and gave a 2:3 mixture of diastereoisomers (0.319 g, 34%).

Diastereoisomer #1: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2 (d, *J* = 8.4 Hz, 2H), 6.8 (d, *J* = 8.4 Hz, 2H), 6.32 (dd, *J* = 16.6, 12 Hz, 1H), 5.74 (d, *J* = 8 Hz, 1H), 5.42 (d, *J* = 16.6 Hz, 1H), 5.08 (d, *J* = 12 Hz, 1H), 4.6 (m, 1H), 4.4-4.0 (m, 5H), 3.8-3.6 (m+s, 5H), 3.0 (m, 1H), 1.4 (s, 3H), 1.3 (s, 3H), 0.8 (s, 9H), 0.0 (s, 6H).

Diastereoisomer #2: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2 (d, *J* = 8.4 Hz, 2H), 6.8 (d, *J* = 8.4 Hz, 2H), 6.28 (dd, *J* = 16.8, 11.0 Hz, 1H), 5.82 (d, *J* = 9.2 Hz, 1H), 5.30 (d, *J* = 16.8 Hz, 1H), 5.08 (d, *J* = 11.0 Hz, 1H), 4.7-4.6 (m, 1H), 4.5-4.0 (m, 5H), 3.9-3.6 (m+s, 4H), 3.3 (m, 1H), 2.5 (br. s., 1H), 1.4 (s, 3H), 1.3 (s, 3H), 0.8 (s, 9H), 0.0 (s, 6H).

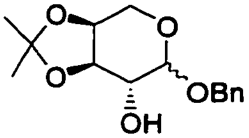
(L)-Benzyl arabinopyranoside



A mixture of (L)-arabinose (40.56 g, 0.270 mol) and benzyl alcohol (200 mL, 1.93 mol) was cooled in an ice-salt bath and HCl (g) was bubbled into the suspension reaction. The suspension turned yellow. The mixture was stirred overnight and ether (300 mL) was slowly added to the continuously stirred suspension. The mixture was left 5 h at 5 °C to crystallize. The product was filtered, washed with diethyl ether then air-dried by suction 4 h. The combined crops were recrystallized from EtOH and to give a pure white powder (47.33 g, 73 %). mp = 168-169 °C (Lit. 169-171 °C).
^{1}H NMR (200 MHz, CD_3OD) δ 7.32-7.18 (m, 5H), 4.62 (dd, J = 11.9, 1.7 Hz, 1H), 4.42 (dd, J = 11.9, 1.8 Hz, 1H), 3.78-3.67 (m, 4H), 3.48 (dt, J = 12.5, 2.0 Hz, 1H), 3.22-3.17 (m, 4H).

The hydrogen chloride gas was generated by the slow addition of concentrated sulfuric acid (40 mL) on a mixture of ammonium chloride (30 g, 181 mmol) and concentrated hydrochloric acid (30 mL).[131]

(L)-Benzyl 3,4-O-isopropylidene-arabinopyranoside (119)



A suspension of (L)-benzyl arabinopyranoside (30.1 g, 125 mmol), anhydrous cupric sulfate (64.4 g, 409 mmol) and concentrated H_2SO_4 (2 mL) in 1 L of dry acetone was stirred for 20 h at room temperature. The solution was then neutralized with concentrated ammonium hydroxide and turned to blue. The resulting precipitate was filtered, washed with acetone

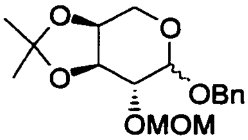
---

[131] Vogel, A. in *Textbook of Practical Organic Chemistry*; Longman Scientific & Technical; 4th edition; 1978; Chap. 2; p 297.

and the filtrate was concentrated to give a colourless syrup. The compound was recrystallized from ether and afforded **119** as a white powder (28.06 g, 80%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 4.90 (d, *J* = 3.5 Hz, 1H), 4.76 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.18 (m, 2H), 3.94 (m, 2H), 3.77 (m, 1H), 1.50 (s, 3H), 1.33 (s, 3H), ^{13}C (50 MHz, $CDCl_3$) δ 136.9, 128.5 (2C), 127.9 (2C), 109.1, 96.9, 75.9, 72.9, 69.9, 69.6, 65.8, 59.7, 27.8, 25.9.

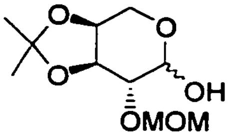
(L)-Benzyl 3,4-O-isopropylidene-2-O-methoxymethyloxy-arabinopyranoside (130)



Distilled diisopropylethylamine (12.5 mL, 71.8 mmol) was added to a cold solution (0 °C) of (L)-Benzyl 3,4-O-isopropylidene-arabinopyranoside (15.1 g, 53.9 mmol) in methylene chloride (100 mL). Methoxychloromethane (5.30 mL, 69.8 mmol) was then slowly added and generated white fumes. The mixture was allowed to stir overnight at room temperature and turned to an orange-brown solution. The solution was washed once with aq. sodium bicarbonate and the aqueous layer was extracted with methylene chloride. The organic extracts were dried, filtered and concentrated to give an orange oil. The crude product was purified by flash-chromatography (75:25 to 50:50, petroleum ether/ether) to give a pure colourless oil (16.41 g, 94 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 4.95 (d, *J* = 3 Hz, 1H), 4.77 (d, *J* = 6.7 Hz, 1H), 4.73 (d, *J* = 12 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.30 (dd, *J* = 8.0, 5.57 Hz, 1H), 4.21 (m, 1H), 3.95 (m, 2H), 3.72 (dd, *J* = 8.0, 3.4 Hz, 1H), 3.27 (s, 3H), 1.52 (s, 3H), 1.33 (s, 3H), ^{13}C (50 MHz, $CDCl_3$) δ 137.0, 128.4 (2C), 127.9 (2C), 127.8, 108.8, 96.6, 96.5, 75.7, 74.7, 73.5, 69.3, 58.8, 55.2, 28.1, 26.3.

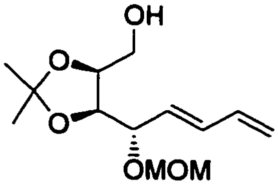
(L)-3,4-O-Isopropylidene-2-methoxymethyloxy-arabinose (118)



Sodium metal (4.95 g, 21.5 mmol) was added portion wise to liquid ammonia (250 mL) at -78 °C until the solution remained blue. A sample of 1-O-benzyl-3,4-O-isopropylidene-2-O-methoxymethyl-(L)-arabinopyranoside (31.96 g, 98.6 mmol) in dry ether (40 mL) was slowly added *via* a syringe. The reaction was quenched after 20 min at -78 °C with aq. ammonium chloride until the blue colour disappeared. The ammonia was allowed to evaporate at room temperature and the residue was extracted with hot ethyl acetate. The crude product was purified by flash-chromatography (90:10, ether/petroleum ether) and gave a mixture of diastereoisomers of the expected product as a white oily solid (21.70 g, 94 %). mp = 81-82 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.17 (s, 1H), 4.80 (d, *J* = 6.6 Hz, 1H'), 4.78 (d, *J* = 6.7 Hz, 1H), 4.73 (d, *J* = 6.5 Hz, 1H'), 4.70 (d, *J* = 6.7 Hz, 1H), 4.55 (m, 1H'), 4.29 (t, *J* = 6.1 Hz, 1H), 4.24 (m, 1H'), 4.19-4.17 (m, 1H+1H'), 4.12 (dd, *J* = 13.1, 3.1 Hz, 1H), 4.07 (d, *J* = 2.8 Hz, 1H'), 3.85 (dd, *J* = 13.1, 1.8 Hz, 1H), 3.77-3.74 (m, 1H+1H'), 3.72 (dd, *J* = 6.7, 3.2 Hz, 1H), 3.54 (t, *J* = 6.8 Hz, 1H'), 3.39 (s, 3H'), 3.37 (s, 3H), 1.49 (s, 3H'), 1.48 (s, 3H), 1.31 (s, 3H+3H'). ^{13}C (125 MHz, $CDCl_3$) δ 109.1, 96.7, 91.3, 75.5, 74.4, 72.7, 59.7, 55.6, 27.7, 25.9 + 109.9, 96.8, 95.5, 77.2, 76.7, 72.9, 62.6, 55.6, 27.6, 25.9. IR (neat) 3405, 2942 cm^{-1}. MS (EI) *m/z* 219 (M^+ -CH_3).

[5*S*-(1*S*-Methoxymethoxy-penta-2*E*,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-yl]-methanol (121)



Wittig-Horner reaction:

n-Butyllithium (0.43 mL, 1.075 mmol, 2.5M) was added slowly to a cold solution (-78 °C) of phosphonate **120** (0.205 g, 1.15 mmol) in dry THF (3 mL). The mixture was allowed to stir at -78 °C for 0.5 h. A cold solution (-78 °C) of 1-hydroxy-3,4-O-isopropylidene-2-O-methoxymethyloxy-(L)-arabinopyranoside **118** (0.108 g, 0.46 mmol) in dry THF (2 mL) was transferred *via* a canula to the cold solution (-78 °C) of the ylide. The mixture was warmed and stirred at room temperature (21 °C) for 42 h. Aqueous saturated $NaHCO_3$ was added to the brown solution and the aqueous layer was extracted with Et_2O. The resulting orange oil was purified by flash-chromatography (90:10, ether/petroleum ether) to give a colourless oil (41 mg, 34%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32-6.28 (m, 2H), 5.57 (q, *J* = 14.6, 8.1 Hz, 1H), 5.25 (d, *J* = 15 Hz, 1H), 5.15 (d, *J* = 9.9 Hz, 1H), 4.68 (d, *J* = 6.6 Hz, 1H), 4.59 (d, *J* = 6.6 Hz, 1H), 4.24-4.24-4.01 (m, 3H), 3.75-3.66 (m, 2H), 3.36 (s, 3H), 2.50 (br. s., 1H), 1.46 (s, 3H), 1.36 (s, 3H). ^{13}C (125 MHz, $CDCl_3$) δ 136.4, 135.6, 128.9, 119.3, 108.7, 93.6, 78.7, 77.4, 74.8, 61.3, 55.6, 27.6, 25.3. IR (neat) 3366, 2984, 1604 cm^{-1}. MS (EI) *m/z*: 258 (M^+).

From Wittig reaction on compound **122**:

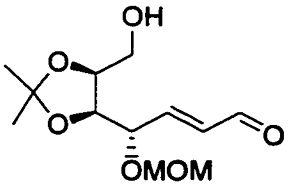
n-Butyllithium 2.27M (0.40 mL, 0.908 mmol,) was added slowly to a cold suspension (0 °C) of triphenylphosphonium bromide (0.333 g, 0.930 mmol) in dry THF (10 mL). The mixture was allowed to stir at 0 °C for 10 min. A solution of 4-(5*S*-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-4*S*-methoxymethoxy-but-2-enal **122** (0.112 g, 0.431 mmol) in dry THF (2 mL) was transferred *via* a canula to the cold solution (0 °C) of the ylide. The mixture was warmed and stirred at room temperature (21 °C) for 1.3 h. Aqueous saturated NH_4Cl was added to the orange solution and the aqueous layer was extracted with Et_2O. The resulting orange oil was purified by flash-chromatography (30:70, ether/petroleum ether) to give a colourless oil identified as **121** (0.076 g, 68%).

Deprotection of compound **101a**:

TBAF (34 mL, 34 mmol, 1M) was added to the cold solution (0 °C) of **101a** (12.497 g, 33.6 mmol) in THF (250 mL). The solution turned yellow and was allowed to stir at room temperature for 2 h. Aqueous saturated $NaHCO_3$ was added to the solution and the aqueous layer was extracted with Et_2O. The organic layer was dried, filtered and concentrated. The crude yellow oil was purified by flash-chromatography (50:50, ether/petroleum ether) to give compound **121** (8.40 g, 96 %). $[\alpha]_D^{22.5}$ +43.08 degrees (c = 4.83 10^{-2} g/mL, MeOH).

^1H NMR (500 MHz, benzene-d^6) δ 6.22-6.12 (m, 2H), 5.61-5.55 (m, 1H), 5.04 (dd, *J* = 16.0, 0.8 Hz, 1H), 4.95 (dd, *J* = 8.8, 1.8 Hz, 1H), 4.59 (d, *J* = 6.6 Hz, 1H), 4.46 (d, *J* = 6.6 Hz, 1H), 4.31 (t, *J* = 7.1 Hz, 1H), 4.12 (t, *J* = 6.4 Hz, 1H), 4.0 (m, 1H), 3.74-3.64 (m, 2H), 3.17 (s, 3H), 2.12 (br. s., 1H), 1.44 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (125 MHz, benzene-d^6) δ 136.4, 135.8, 130.1, 118.7, 108.6, 94.2, 79.5, 78.2, 74.8, 61.7, 55.5, 27.8, 25.6. IR (neat) 3460, 2940, 1604 cm^{-1}. MS (EI) *m/z* 243 (M^+ $-CH_3$). HREIMS *m/e* calcd for $C_{12}H_{19}O_5$ (M^+ $-CH_3$) 243.1233, found 243.1230. Anal. Calcd. for $C_{13}H_{22}O_5$ (258.15): C, 60.45; H, 8.58. Found: C, 60.60; H, 8.70.

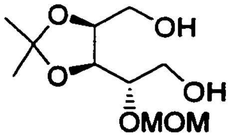
4-(5*S*-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-4*S*-methoxymethoxy-but-2-enal (122)



(Triphenylphosphoranylidene)acetaldehyde (0.929 g, 3.05 mmol) was added to a cold solution (0 °C) of hemiacetal **118** (0.302 g, 1.29 mmol) in toluene (15 mL). The mixture was allowed to stir at room temperature for 16 h then refluxed for 3 h. The brown mixture was vacuum down and the brown residue was purified by flash-chromatography (90:10, ether/petroleum ether) to give a colourless oil (0.150 g, 45%).

^1H NMR (200 MHz, $CDCl_3$) δ 9.5 (s, 1H), 6.96-6.82 (m. 1H), 6.37-6.09 (m, 2H), 4.85 (d, *J* = Hz, 1H), 4.6 (d, *J* = Hz, 1H), 4.3-4.0 (m, 2H), 3.8-3.6 (m, 2H), 3.4 (s, 3H), 1.5 (s, 3H), 1.3 (s, 3H). IR (neat) 3360, 2921, 2858, 2827, 1722, 1678.

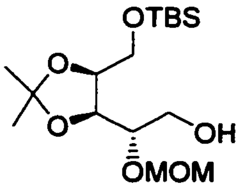
2-(5*S*-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-2*S*-methoxymethoxy-ethanol (128)



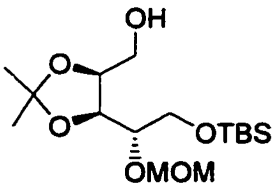
Sodium borohydride (0.028 g, 0.71 mmol) was slowly added to a solution of 1-hydroxy-3,4-O-isopropylidene-2-O-methoxymethyl-(L)-arabinopyranoside (0.113 g, 0.48 mmol) in 99% ethanol (5 mL). The mixture was cooled at 0 °C and stirred for 2.5 h. The excess of sodium borohydride was neutralized with acetic acid (~ 3 drops), and the mixture was purified by chromatography (95:5, dichloromethane/MeOH) after dry loading. The pure product was obtained as a colourless oil (10.5 mg, 93%). $[\alpha]_D^{30.5}$ -42.33 degrees (c = 1.52 10^{-2} g/mL, MeOH).

^{1}H NMR (500MHz, $CDCl_3$) δ 4.74 (s, 2H), 4.22 (t, *J* = 6.9, 6.0 Hz, 1H), 4.15 (q, *J* = 11.7, 5.9 Hz, 1H), 3.76-3.73 (m, 1H), 3.68-3.59 (m, 4H), 3.38 (s, 3H), 1.42 (s, 3H), 1.31 (s, 3H). ^{13}C (125 MHz, $CDCl_3$) δ 108.5, 96.9, 78.1, 77.3, 77.1, 63.5, 61.3, 55.8, 27.6, 25.3. IR (neat) 3391, 2933 cm^{-1}. MS (EI) *m/z* 221 (M^+ -CH_3). HREIMS *m/e* calcd for $C_9H_{17}O_6$ (M^+ -CH_3) 221.1025, found 221.1041.

2-[5*S*-(tert-Butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-yl]-2*S*-methoxymethoxy-ethanol (129a) / {5*S*-[2-(tert-Butyl-dimethyl-silanyloxy)-1*S*-methoxymethoxy-ethyl]-2,2-dimethyl-[1,3]dioxolan-4*R*-yl}-methanol (129b)



125a



125b

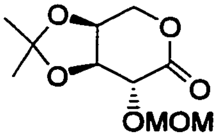
A solution of diol **128** (59 mg, 0.252 mmol) in dry THF (3 mL) was added dropwise *via* a syringe to a cold suspension (0 °C) of sodium hydride (7 mg, 0.3 mmol) in dry THF (2 mL). The addition was followed by gas evolution. The mixture was allowed to warm and stir at room temperature for 0.5 h. The solution turned to light yellow. A solution of terbutyldimethylsilyl chloride (42 mg, 0.279 mmol) in dry THF (2 mL) was then added to the cold mixture (0 °C) and the mixture was allowed to stir at room temperature for 2 h. It was poured onto a mixture of ice-water (3-5 mL), the aqueous layer was extracted with ether, the combined organic extracts were washed with an aq. solution of NaCl, dried, filtered and concentrated. The crude greasy product was purified by chromatography (55:45, ether/petroleum ether) after dry loading. A 1:1 mixture of both monoprotected alcohols **129a/b** was obtained (44 mg, 50%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.80-4.74 (m, 4H), 4.30-4.08 (m, 4H), 3.92-3.52 (m, 12H), 3.42 (s, 3H), 3.38 (s, 3H), 1.46 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 0.87 (s, 18H), 0.05 (s, 12H).

A solution of terbutyldimethylsilyl chloride (0.142 g, 0.939 mmol) in dry dichloromethane (5 mL) was added drop wise to a cold solution (0 °C) of diol **128** (0.197 g, 0.833 mmol) and imidazole (0.086 g, 1.26 mmol) in dry dichloromethane (5 mL). The mixture turned to milky white before the end of the addition. It was allowed to stir 0.5 h at 0 °C then 6.8 h at room temperature. The mixture was then diluted with ether and washed with an aqueous solution of saturated ammonium chloride. The organic layer was dried, filtered and concentrated. The crude colorless oil was purified by chromatography (55:45, ether/petroleum Ether) after dry loading. A 1:1 mixture of both monoprotected alcohols **129a/b** was obtained as a colourless oil (0.137g, 47%) with diprotected alcohol **129c** (0.044 g, 11%) as a byproduct.

Diprotected diol **129c** : ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79-4.74 (m, 2H), 4.29 (t, J = 6.2 Hz, 1H), 4.11-4.08 (m, 1H), 3.84-3.71 (m, 4H), 3.64-60 (m, 1H), 3.37 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.04 (s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.9, 96.7, 77.5, 76.8, 75.7, 63.6, 62.3, 55.5, 27.6, 25.9, 25.8, 25.5, 18.2, -5.46, -5.49, -5.50, -5.54.

7S-Methoxymethoxy-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyran-6-one (134)



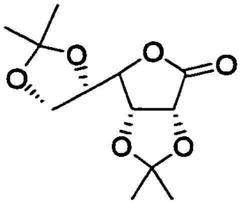
Preparation of Fetizon's oxidant (0.57 g = 1 mmol Ag_2CO_3):

Celite® (4.98 g) was washed with a solution of MeOH/conc. HCl (100 mL, 90:10) then with distilled water until pH = 5-6. The Celite® was dried at 125°C for 1.5 h and overnight at room temperature. The dried Celite® was added to a solution of silver nitrate (8.296 g, 48.8 mmol) in distilled water (35 mL). A solution of sodium carbonate (2.543 g, 23.9 mmol) in distilled water (25 mL) was added to the previous brown suspension. After 10 min of stirring at room temperature the suspension turned to yellow and was filtered and concentrated. The resulting yellow-green powder was freed from the residual water by concentration of the benzene-water azeotrope just before using.

Oxidation

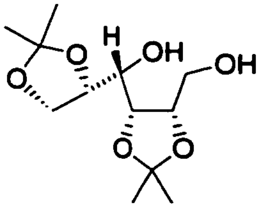
A suspension of the Ag_2CO_3/Celite® (11.28 g, 19.8 mmol), prepared as described above, in dry benzene (50 mL) was added to a solution of 1-hydroxy-3,4-O-isopropylidene-2-O-methoxymethyl-(L)-arabinopyranoside (0.258 g, 1.10 mmol) in dry benzene (5 mL). The resulting yellow suspension was refluxed for 3 h and quickly turned to black. The black mixture was then cooled, filtered, washed with dichloromethane and concentrated. The resulting yellow oil was purified by chromatography (90:10, ether/petroleum ether). The pure product was obtained as a lightly yellow oil (0.211 g, 82%).
^1H NMR (500 MHz, $CDCl_3$) δ 4.77(d, *J* = 6.6 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.62 (q, *J* = 12.1, 2.8 Hz, 1H), 4.52-4.48 (m, 2H), 4.31 (d, *J* = 3.7 Hz, 1H), 4.27 (q, *J* = 12.1, 3.5 Hz, 1H), 3.38 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H). ^{13}C (125 MHz, $CDCl_3$) δ 167.9, 110.7, 96.1, 75.2, 73.0, 71.0, 67.2, 56.1, 26.1, 24.1. IR (neat) 2947, 1762 cm^{-1}. MS (EI) *m/z* 232 (M^+), 217 (M^+ -CH_3). HREIMS *m/e* calcd for $C_{10}H_{16}O_6$ (M^+) 232.0947, found 232.0947.

(D)-2,3-5,6-Di-O-isopropylideneguluno-γ-lactone



2,2-methoxypropane (7.4 mL, 60.2 mmol) was added to the white suspension of the (D)-gulunolactone (2.416 g, 13.6 mmol) in acetone (80 mL). p-TsOH was then added to the white suspension and the mixture was allowed to stir at room temperature for 44 h. The suspension turned to a colorless solution, which was quenched with an excess of solid $NaHCO_3$. The solvent was removed under vacuum. The residue was dissolved in methylene chloride, washed with H_2O and the organic extract gave a fluffy white solid after the solvent was removed. The crude compound was recrystallized with ethyl acetate to yield the protected compound (2.748 g, 78%) as a white crystal. mp = 150-152 °C (litt. 151-153 °C). ^{1}H NMR (500 MHz, benzene d^6) δ 4.39-4.34 (m, 1H), 4.05 (d, *J* = 5.4 Hz, 1H), 3.94 (dd, *J* = 8.6, 6.7 Hz, 1H), 3.66-3.61 (m, 2H), 3.44 (dd, *J* = 8.6, 6.7 Hz, 1H), 1.43 (d, *J* = 0.4 Hz, 3H), 1.25 (d, *J* = 0.5 Hz, 3H), 1.19 (d, *J* = 0.3 Hz, 3H), 1.01 (d, *J* = 0.5 Hz, 3H). ^{13}C (125 MHz, benzene d^6) δ 172.5, 114.1, 110.3, 80.4, 76.1, 75.9, 75.7, 65.3, 27.0, 26.5, 25.8, 25.4. IR (CCl_4) 2994, 1802 cm^{-1}.

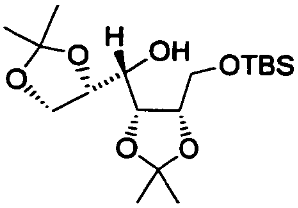
(2,2-Dimethyl-[1,3]dioxolan-4*R*-yl)-(5*S*-hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-methan-1*S*-ol (138)



$LiAlH_4$ (0.363 g, 9.07 mmol) was added portion wise to a cold solution (0 °C) of the protected lactone (2.010 g, 7.79 mmol) in dry THF (50 mL). The grey mixture was allowed to warm to room temperature and stir for 19 h. Quenching at 0 °C with excess AcOEt, 0.36 mL of H_2O, 0.36 mL of NaOH 15% and 1.08 mL of H_2O afforded the crude product as a yellow oil. Recrystallization from ether/pentane gave the required compound as a white powder (1.913 g, 95%). mp = 74-75 °C.

^{1}H NMR (500 MHz, benzene d^6) δ 4.22-4.18 (m, 1H), 3.99-3.95 (m, 1H), 3.91 (dd, *J* = 6.7, 2.63 Hz, 1H), 3.84-3.78 (m, 2H), 3.73-3.72 (m, 1H), 3.65-3.60 (m, 2H), 3.04 (d, *J* = 5.0 Hz, 1H), 2.63 (br. s., 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.26 (d, *J* = 0.4 Hz, 3H), 1.21 (d, *J* = 0.3 Hz, 3H). ^{13}C (125 MHz, benzene d^6) δ 109.5, 108.4, 78.1, 77.4, 76.6, 69.4, 66.1, 61.5, 27.2, 26.7, 25.5, 25.2. IR (neat) 3496 (br), 2989, 2935, 1376, 1224, 1062 cm^{-1}. MS (EI) *m/z* 247 (M^+ -CH_3). HREIMS *m/e* calcd for $C_{11}H_{19}O_6$ (M^+-CH_3) 247.1182, found 247.1201. Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95: H, 8.45. Found: C, 54.86: H, 8.28.

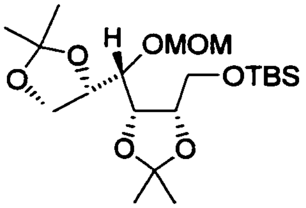
[5*S*-(tert-Butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-yl]-(2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-methan-1*S*-ol (140)



DMAP (0.405 g, 3.31 mmol) and freshly distilled Et_3N (3.50 mL, 25.1 mmol) were added slowly to the cold solution (0 °C) of diol **138** (3.479 g, 13.3 mmol) in dry methylene chloride (25 mL). After 5 min TBSCl (4.161 g, 26.78 mmol) was added and the solution was allowed to warm and stir at room temperature for 18 h. The milky suspension was quenched with aqueous NH_4Cl sat'd, extracted with methylene chloride then AcOEt to give a yellow oil. The crude product was purified by chromatography (75:25 petroleum ether/ether) and yielded the expected product as a slightly yellow oil (4.719 g, 95%). $[\alpha]^{20}_D$ +25.03 degrees (c = 8.75x 10^{-3} g/mL, $CHCl_3$).

^{1}H NMR (500 MHz, benzene d^6) δ 4.35-4.31 (m, 1H), 4.19-4.15 (m, 1H), 4.12 (dd, *J* = 6.6, 2.9 Hz, 1H), 3.99-3.90 (m, 3H), 3.88-3.85 (m, 1H), 3.80 (dd, *J* = 10.5, 4.5 Hz, 1H), 2.78 (d, *J* = 5.8 Hz, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.30 (d, *J* = 0.3 Hz, 3H), 1.23 (d, *J* = 0.3 Hz, 3H), 0.91 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C (125 MHz, benzene d^6) δ 109.4, 108.5, 77.9, 77.5, 77.1, 69.2, 66.2, 62.6, 27.2, 26.8, 25.9 (3C), 25.7, 25.2, 18.4, -5.4, -5.5. IR (neat) 3994, 2986, 2940, 2859, 1467, 1376, 1254, 1088 cm^{-1}. MS (EI) *m/z* 361 (M^+ -CH_3). HREIMS *m/e* calcd for $C_{17}H_{33}O_6Si$ (M^+-CH_3) 361.1999, found 361.2053. Anal. Calcd for $C_{18}H_{36}O_6Si$: C, 57.41: H, 9.64. Found: C, 57.51: H, 9.67.

tert-Butyl-{5*S*-[(2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-methoxymethoxy-methyl]-2,2-dimethyl-[1,3]dioxolan-4*S*-ylmethoxy}-dimethyl-silane (139)

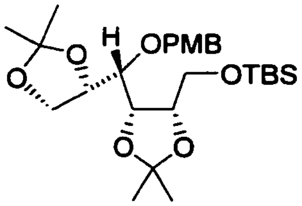


A solution of alcohol **140** (1.241 g, 3.30 mmol) in dry THF (7 mL) was added *via* a canula to the suspension of NaH (0.547 g, 13.69 mmol), previously washed with pentane, in dry THF (2 mL). The white suspension was allowed to stir at room temperature for 25 min then cooled to 0 °C for 15 min. MOMCl (0.75 mL, 9.87 mmol) was then added and the mixture was allowed to warm up and stir at room temperature overnight. The white suspension was quenched with aqueous $NaHCO_3$ sat'd, extracted with methylene chloride then AcOEt, dried and concentrated to give a colorless oil. The crude product was purified by chromatography with a gradient of eluant (90:10—75:25 petroleum ether/ether) and yielded the expected product as a colorless oil (0.924 g, 67%). $[\alpha]^{20}_D$ -41.77 degrees (c = 9.76x 10^{-3} g/mL, $CHCl_3$).

^1H NMR (500 MHz, benzene d^6) δ 5.06 (d, *J* = 6.7 Hz, 1H), 4.78 (d, *J* = 6.7 Hz, 1H), 4.60-4.54 (m, 2H), 4.28-4.25 (m, 1H), 4.13 (dd, *J* = 7.9, 6.9 Hz, 1H), 4.05 (dd, *J* = 7.9, 6.8 Hz, 1H), 4.02 (dd, *J* = 7.0, 3.8 Hz, 1H), 3.93 (dd, *J* = 10.5, 7.6 Hz, 1H), 3.73 (dd, *J* = 10.5, 4.3 Hz, 1H), 3.24 (s, 3H), 1.51 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H), 0.90 (s, 9H), 0.0 (s, 6H). ^{13}C (125 MHz, benzene d^6) δ 109.6, 108.3, 97.9, 78.3, 77.9, 76.7, 75.3, 66.3, 62.7, 55.8, 27.9, 26.6, 26.0 (3C), 25.8, 25.7, 18.4, -5.4, -5.5. IR (neat) 2925, 1466, 1374, 1235, 1087 cm^{-1}. MS (EI) *m/z* 405 (M^+ -CH_3). HREIMS *m/e* calcd for $C_{19}H_{37}O_7Si$ (M^+-CH_3)

405.2309, found 405.2310. Anal. Calcd for $C_{20}H_{40}O_6Si$ (420.62): C, 57.11: H, 9.58. Found: C, 57.12: H, 9.65.

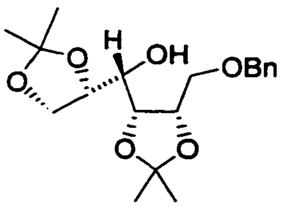
tert-Butyl-{5*S*-[(2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-(4*S*-methoxy-benzyloxy)-methyl]-2,2-dimethyl-[1,3]dioxolan-4*S*-ylmethoxy}-dimethyl-silane (141)



A solution of alcohol **140** (0.214 g, 0.57 mmol) in DMF (2 mL) was added *via* a canula to the suspension of NaH (0.034 g, 0.85 mmol), previously washed with pentane, in DMF (1 mL) at 0 °C. *n* -Bu_4NI (0.018 g, 0.047 mmol) and PMBCl (0.10 mL, 0.74 mmol) were added and the mixture was allowed to warm up and stir at room temperature protected by an aluminium foil for 20 h. The white suspension was diluted with ether, extracted with ether, washed with brine, dried and concentrated to give a yellow oil. The crude product was purified by chromatography (90:10 petroleum ether/ether) and gave the expected product as a colorless oil (0.058 g, 21%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.72 (d, *J* = 2.9 Hz, 2H), 4.38-4.34 (m, 1H), 4.31 (t, *J* = 5.9 Hz, 1H), 4.17-4.14 (m, 1H), 3.91 (dd, *J* = 7.9, 6.5 Hz, 1H), 3.78 (s, 3H), 3.78-3.73 (m, 2H), 3.68-3.62 (m, 2H), 1.43 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H). ^{13}C (125 MHz, $CDCl_3$) δ 159.0, 130.9, 129.4 (2C), 113.6 (2C), 109.3, 108.5, 77.9, 77.6, 76.6, 75.6, 73.0, 65.9, 62.4, 55.2, 27.6, 26.4, 25.8 (3C), 25.6 (2C), 18.2, -5.3, -5.4. IR (neat) 2933, 1614, 1514 cm^{-1}.

(5*S*-Benzyloxymethyl-2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-(2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-methan-1*S*-ol (143)



A solution of diol **138** (0.101 g, 0.38 mmol) in DMF (1.5 mL) was added *via* a canula to the suspension of NaH (0.0187 g, 0.47 mmol), previously washed with pentane, in DMF (0.5 mL) at 0 °C. The resulting yellow solution was allowed to warm up and stir at room temperature for 0.5 h then cooled to -40 °C for 15 min and BnBr (0.05 mL, 0.42 mmol) was added. The mixture was stirred at -40 °C for 2.6 h then quenched with aqueous NH_4Cl sat'd, extracted with ether then AcOEt, washed with brine, dried and concentrated. The crude product was purified by chromatography with a gradient of eluant (30:70—90:10 ether/petroleum ether) and yielded the expected product **143** (0.075 g, 55%) and the diprotected compound **144** (0.062 g, 36%).

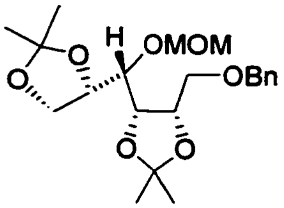
Monoprotected compound **143**

^{1}H NMR (500 MHz, benzene d^6) δ 7.21-7.19 (m, 2H), 7.15-7.11 (m, 2H), 7.07-7.04 (m, 1H), 4.30-4.21 (m, 4H), 4.07 (dd, *J* = 6.6, 3.3 Hz, 1H), 3.86 (dd, *J* = 8.0, 7.2 Hz, 1H), 3.80 (dd, *J* = 8.0, 6.6 Hz, 1H), 3.73 (dd, *J* =9.8, 6.7 Hz, 1H), 3.62 (dd, *J* = 9.8, 4.9 Hz, 1H), 2.685 (d, *J* = 5.7 Hz, 1H), 1.44 (s, 3H), 1.39 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H). ^{13}C (125 MHz, benzene d^6) δ 138.5, 129.1 (2C), 128.7, 128.6 (2C), 109.4, 108.6, 77.4, 77.2, 76.4, 73.6, 69.6, 69.3, 66.1, 27.3, 26.7, 25.7, 25.2. IR (neat) 3489, 3031, 2985 cm^{-1}. MS (EI) *m/z* 337 (M^+-CH_3). HREIMS *m/e* calcd for $C_{18}H_{25}O_6$ (M^+-CH_3) 337.1651, found 337.1635. Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H,8.01. Found: C, 65.00; H, 8.11.

Diprotected compound **144**

^{1}H NMR (500 MHz, benzene d^6) δ 7.34-7.23 (m, 10H), 4.79 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 11.9 Hz, 1H), 4.39-4.34 (m, 2H), 4.32-4.28 (m, 1H), 4.25 (t, *J* = 5.3 Hz, 1H), 4.87 (dd, *J* = 7.9, 6.6 Hz, 1H), 3.75 (t, *J* = 7.9 Hz, 1H), 3.62-3.55 (m, 2H), 3.53 (t, *J* = 5.1 Hz, 1H), 1.47 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H). ^{13}C (125 MHz, benzene d^6) δ 138.7, 137.7, 128.3 (2C), 128.1 (2C), 127.8 (2C), 127.7, 127.6 (2C), 127.3, 109.3, 108.8, 77.3, 76.6, 76.0, 73.4, 73.1, 69.1, 65.9, 27.3, 26.4, 25.5, 25.4. IR (neat) 3030, 2985, 1496, 1454 cm^{-1}.

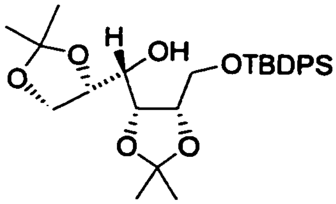
1*S*-[(5*S*-Benzyloxymethyl-2,2-dimethyl-[1,3]dioxolan-4*R*-yl]-[(2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-methoxymethoxy]-methane (145)



A solution of alcohol **143** (0.098 g, 0.28 mmol) in dry THF (3 mL) was added *via* a canula to the suspension of NaH (0.049 g, 1.23 mmol), previously washed with pentane, in dry THF (1 mL). The white suspension was allowed to stir at room temperature for 0.5 h then cooled to 0 °C and MOMCl (0.063 mL, 0.83 mmol) was added. The mixture was allowed to warm up and stir at room temperature overnight. The white suspension was quenched with aqueous $NaHCO_3$ sat'd, extracted with ether, dried and concentrated to give a colorless oil. The crude product was purified by chromatography (70:30 petroleum ether/ether) and yielded the expected product as a colorless oil (0.088 g, 80%).

^{1}H NMR (500 MHz, benzene d^6) δ 7.19-7.05 (m, 5H), 5.05 (d, J = 6.7 Hz, 1H), 4.75 (d, J = 6.7 Hz, 1H), 4.54 (dd, J = 15.6, 7.1 Hz, 1H), 4.48 (ddd, J = 7.2, 7.1, 6.9 Hz, 1H), 4.36 (ddd, J = 7.5, 5.6, 4.5 Hz, 1H), 4.22 (d, J = 11.5 Hz, 1H), 4.18 (d, J = 11.5 Hz, 1H), 4.04 (dd, J = 7.9, 6.9 Hz, 1H), 3.90-3.86 (m, 2H), 3.67 (dd, J = 9.7, 7.5 Hz, 1H), 3.49 (dd, J = 9.7, 4.5 Hz, 1H), 3.23 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H). ^{13}C (125 MHz, benzene d^6) δ 138.5, 128.6, 128.3, 127.9, 109.6, 108.5, 97.8, 78.3, 76.6, 76.1, 75.3, 73.4, 69.5, 66.3, 55.9, 27.9, 26.6, 25.8, 25.7.

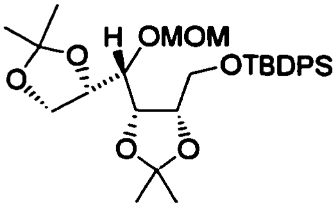
[5*S*-(tert-Butyl-diphenyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-yl]-(2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-methan-1*S*-ol



DMAP (0.005 g, 0.041 mmol) and freshly distilled Et_3N (0.1 mL, 0.72 mmol) were added slowly to the solution of the diol **138** (0.120 g, 0.46 mmol) in dry methylene chloride (2.5 mL). The mixture was cooled to 0 °C, TBDPSCl (0.15 mL, 0.57 mmol) was then added and the solution was allowed to warm and stir at room temperature for 42 h. The reaction was quenched with aqueous NH_4Cl sat'd, extracted with ether, dried and concentrated. The crude product was purified by chromatography (50:50 petroleum ether/ether) and afforded the expected product as a colorless oil (0.209 g, 91%). $[\alpha]^{20}_{D}$ +9.53 degrees (c = 5.6x 10^{-2} g/mL, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H), 7.43-7.36 (m, 6H), 4.29-25 (m, 1H), 4.13 (dd, J = 6.3, 3.3 Hz, 1H), 4.05-3.97 (m, 2H), 3.91 (dd, J = 7.9, 4.5 Hz, 1H), 3.86-3.78 (m, 2H), 2.66 (d, J = 5.8 Hz, 1H), 1.43 (s, 6H), 1.36 (s, 3H), 1.33 (s, 3H), 1.65 (s, 9H). ^{13}C (125 MHz, $CDCl_3$) δ 135.5 (4C), 132.9, 129.8 (2C), 127.7 (4C), 109.4, 108.6, 77.1, 76.8, 76.7, 69.4, 65.9, 62.7, 27.1, 26.8 (3C), 26.5, 25.3, 25.0. IR (neat) 3487, 3072, 2934, 1590 cm^{-1}. MS (EI) *m/z* 485 (M^+-CH_3). HREIMS *m/e* calcd for $C_{27}H_{37}O_6$ Si (M^+-CH_3) 485.2360, found 485.2357.

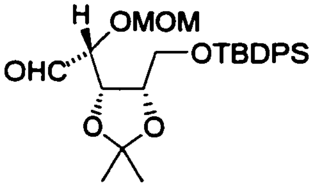
tert-Butyl-{5*S*-[(2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-methoxymethoxy-methyl]-2,2-dimethyl-[1,3]dioxolan-4*R*-ylmethoxy}-diphenyl-silane (146)



A solution of alcohol (1.393 g, 2.7 mmol) in dry THF (7mL) was added *via* a canula to the suspension of NaH (0.917 g, 22.9 mmol), previously washed with pentane, in dry THF (8 mL). The grey suspension was allowed to stir at room temperature for 1 h. MOMCl (1.3 mL, 17.1 mmol) was then added at 0°C and the mixture was allowed to warm up and stir at room temperature for 24 h. The suspension was quenched with aqueous $NaHCO_3$ sat'd, extracted with methylene chloride then AcOEt, dried and concentrated to give a colorless oil. The crude product was purified by chromatography with a gradient of eluant (25:75—50:50 ether/petroleum ether) to yield the expected product (1.011 g, 66%).

^{1}H NMR (500 MHz, benzene d^6) δ 7.78-7.76 (m, 4H), 7.22-7.19 (m, 6H), 4.97 (d, *J* = 6.6 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.58-4.56 (m, 1H), 4.49-4.48 (m, 2H), 4.12-4.06 (m, 2H), 4.03 (dd, *J* = 6.6, 4.1 Hz, 1H), 3.97-3.92 (m, 2H), 3.17 (s, 3H), 1.49 (s, 3H), 1.42 (s,3H), 1.32 (s, 3H), 1.26 (s, 3H), 1.15 (s, 9H). ^{13}C (125 MHz, benzene d^6) δ 136.0 (4C), 135.9 (6C), 133.7, 133.6, 109.5, 108.5, 97.7, 78.1, 78.0, 76.6, 75.5, 66.3, 63.7, 55.8, 27.7, 27.1 (3C), 26.6, 25.7 (2C), 19.4. IR (neat) 2939, 1590, 1465, 1376, 1129 cm^{-1}. MS (EI) *m/z* 529 (M^+ -CH_3). HREIMS *m/e* calcd for $C_{29}H_{41}O_7Si$ (M^+ -CH_3) 529.2623, found 529.2641. Anal. Calcd for $C_{30}H_{44}O_7Si$: C, 66.14: H, 8.14. Found: C, 65.92: H, 8.04.

[5*S*-(tert-Butyl-diphenyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-yl]-2*R*-methoxymethoxy-acetaldehyde (147)



A solution of the alcohol **146** (0.096 g, 0.176 mmol)in dry ether (15 mL) was added *via* a canula to a suspension of periodic acid (0.127 g, 0.56 mmol) in dry ether (15 mL, results in a 0.1N solution) at room temperature. After 1.5 h the mixture turned to a slightly pink solution. The mixture was quenched with aqueous $NaHCO_3$ sat'd and solid $NaHCO_3$, extracted with ether, dried and concentrated to give aldehyde **147** (0.057 g, 68%,) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.3 Hz, 1H), 7.64 (td, *J* = 8.1, 1.5 Hz, 4H), 7.44-7.35 (m, 6H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.61 (dd, *J* = 6.7 Hz, 1H), 4.45 (dd, *J* = 6.2, 5.2 Hz, 1H), 4.35-4.22 (m, 1H), 4.18 (dd, *J* = 5.1, 1.3 Hz, 1H), 3.84-3.77 (m, 2H), 3.35 (s, 3H), 1.44

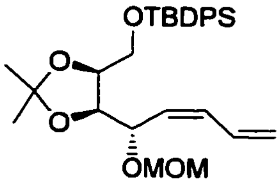
(s, 6H), 1.32 (s, 3H), 1.05 (s, 9H). ^{13}C (125 MHz, $CDCl_3$) δ 201.1, 135.6 (4C), 133.0, 132.9, 129.8 (2C), 127.7 (4C), 109.1, 97.4, 81.2, 76.9, 76.5, 62.5, 56.0, 26.8 (3C), 26.7, 25.2, 19.1. IR (neat) 3072, 2934, 2897, 2859, 1738 cm^{-1}. MS (EI) *m/z* 457 (M^+ -CH_3). HREIMS *m/e* calcd for $C_{25}H_{33}O_6Si$ (M^+ -CH_3) 457.2047, found 457.1983.

tert-Butyl-[5*S*-(1*S*-methoxymethoxy-penta-2*E*,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-ylmethoxy]-diphenyl-silane ((*E*)-148a)

n-BuLi (0.29 mL, 2.12 M) was added to a cold solution (-78 °C) of phosphonate (0.109 g, 0.61 mmol) in dry THF (3 mL). A solution of aldehyde **147** (0.080 g, 0.169 mmol) in dry THF (3 mL) was transferred *via* a canula to the cold solution after 15 min. The resulting yellow mixture was allowed to stir 0.5 h at -78 °C then at room temperature for 4 h. The mixture was quenched with aqueous $NaHCO_3$ sat'd, extracted with ether, dried and concentrated. The crude yellow oil was purified by chromatography with (30:70 ether/petroleum ether) and yielded 8% (0.007 g) of the expected product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4H), 7.42-7.34 (m, 6H), 6.26-6.19 (m, 1H), 6.15-6.10 (m, 1H), 5.54 (dd, *J* = 15.3, 7.9 Hz, 1H), 5.13 (d, *J* = 16.5 Hz, 1H), 5.09 (d, *J* = 10.1 Hz, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 4.57 (d, *J* = 6.6 Hz, 1H), 4.35 (t, *J* = 7.4 Hz, 1H), 4.18-4.13 (m, 2H), 3.85 (dd, *J* = 11.1, 4.2 Hz, 1H), 3.70 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.30 (s, 3H), 1.47 (s, 3H), 1.36 (s, 3H), 1.06 (s, 9H). ^{13}C (125 MHz, $CDCl_3$) δ 135.9, 135.7 (4C), 135.4, 133.3, 129.7, 129.4, 127.7 (4C), 118.6, 108.6, 99.7, 79.3, 77.7, 74.0, 65.8, 55.5, 27.3, 26.9 (3C), 25.5, 19.2. IR (neat) 3064, 2985, 1497 cm^{-1}. MS (EI) *m/z* 481 `(M^+ -CH_3). HREIMS *m/e* calcd for $C_{28}H_{37}O_5Si$ (M^+ -CH_3) 481.2411, found 481.2422.

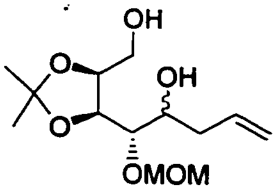
tert-Butyl-[5*S*-(1*S*-methoxymethoxy-penta-2*Z*,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-ylmethoxy]-diphenyl-silane ((*Z*)-148a)



n-Butyllithium 2.04M (0.15 mL, 3.06 mmol,) was added slowly to a cold suspension (-78 °C) of triphenylphosphonium bromide (0.123 g, 0.322 mmol) in dry THF (5 mL). The mixture was allowed to stir at -78 °C for 0.5 h. A solution of aldehyde **147** (0.112 g, 0.431 mmol) in dry THF (2 mL) was transferred *via* a canula to the brown cold solution (-78 °C) of the ylide. The mixture turned bright yellow ,was allow to warm and stir at room temperature (21 °C) for 22 h. Aqueous saturated NH_4Cl was added and the aqueous layer was extracted with Et_2O. The resulting oil was purified by flash-chromatography (30:70, ether/petroleum ether) to give **148a** (0.039 g, 30%) as a colourless oil.

^1H NMR (200 MHz, benzene d^6) δ 7.8-7.6 (m, 4H), 7.7.2-7.1 (m, 6H), 6.7-6.5 (m, 1H), 5.9 (t, *J* = 9.6 Hz, 1H), 5.15 (t, *J* = 9.6 Hz, 1H), 4.95 (d, *J* = 16 Hz, 1H), 4.88 (d, *J* = 10 Hz, 1H), 4.78-4.69 (m, 1H), 4.55 (d, *J* = 6.4 Hz, 1H), 4.40 (d, *J* = 6.5 Hz, 1H), 4.2-4.1 (m, 2H), 3.9 (m, 2H), 3.1 (s, 3H), 1.5 (s, 3H), 1.25 (s, 3H), 1.1 (s, 9H).

1-(5*S*-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4*R*-yl)-1*S*-methoxymethoxy-pent-4-en-2*RS*-ol (150)



Addition of allylindiumbromide species:

Indium (0.389 g, 3.39 mmol) was added portion wise to a cold (0 °C) solution of acetal **118** (0.382 g, 1.63 mmol) and allylbromide (0.61 mL, 7.05 mmol) in DMF (0.6 mL) in a small vial. The grey suspension was allowed to stir vigorously at room temperature (21 °C) for 48 h in a closed vial. The white suspension was then diluted with methylene chloride and the resulting solution was poured onto Et_2O. The resulting slurry was filtered on silica, washed with Et_2O and the filtrate was concentrated. The crude product was purified by flash-chromatography (75:25, ether/petroleum ether) and gave two diastereoisomers (1:1) of the expected diol **150** (0.345 g, 76%).

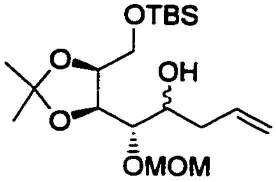
Addition of allylmagnesiumchloride:

A solution of allylmagnesium chloride (37.0 mL, 40.7 mmol, 1.10 M) was added drop wise to a cold solution (-78 °C) of lactol **118** (4.128 g, 17.6 mmol) in THF (50 mL). The mixture was allowed to warm and stir at room temperature overnight. The brown thick solution was quenched with aq. ammonium chloride, extracted with ether, washed with brine, dried and concentrated. The crude product was purified by chromatography (98:2 to 95:5, CH_2Cl_2/ MeOH) and yielded compound **150** as a 3:1 mixture of diastereoisomers (4.878 g, 99%).

Diatereoisomer #1: $[\alpha]_D^{30.5}$ -55.51 degrees (c = 4.02 10^{-2} g/mL, MeOH). ^1H NMR (500 MHz, $CDCl_3$) δ 5.85-5.82 (m, 1H), 5.14-5.10 (m, 2H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.25 (dd, *J* = 7.8, 5.7 Hz, 1H), 4.19 (dd, *J* = 11.8, 5.9 Hz, 1H), 3.73 (dd, *J* = 7.8, 5.4 Hz, 1H), 3.68 (dd, *J* = 11.1, 5.9 Hz, 1H), 3.65-3.58 (m, 2H), 3.41 (s, 3H), 2.75 (br.s., 2H), 2.50-2.40 (m, 1H), 2.25-2.22 (m, 1H), 1.43 (s, 3H), 1.33 (s, 3H). ^{13}C (125 MHz, benzene-d^6) δ 135.5, 117.6, 107.7, 98.0, 79.6, 78.8, 77.9, 72.4, 61.7, 55.9, 38.7, 28.1, 25.6. IR (neat) 3399, 2951 cm^{-1}. MS (EI) *m/z* 261 (M^+ -CH_3).

Diatereoisomer #2: $[\alpha]_D^{30.5}$ -67.96 degrees (c = 1.90 10^{-2} g/mL, MeOH). ^1H NMR (500 MHz, $CDCl_3$) δ 5.82-5.77 (m, 1H), 5.12-5.06 (m, 2H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.42 (dd, *J* = 8.3, 5.7 Hz, 1H), 4.15-4.13 (m, 1H), 3.68 (dd, *J* = 8.3, 2.1 Hz, 1H), 3.62-3.53 (m, 3H), 3.39 (s, 3H), 2.65 (br.s., 2H), 2.35-2.28 (m, 2H), 1.41 (s, 3H), 1.31 (s, 3H). ^{13}C (125 MHz, $CDCl_3$) δ 134.4, 118.0, 108.3, 97.4, 77.2, 77.1, 76.2, 71.0, 61.4, 56.2, 38.5, 27.9, 25.4. MS (EI) *m/z* 261 (M^+ -CH_3). IR (neat) 3423 (br), 3077, 2937 cm^{-1}. HRMS (EI) *m/e* calcd for $C_{12}H_{21}O_6$ (M^+ -CH_3) 261.1338, found 261.1353.

1-[5*S*-(tert-Butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-yl]-1*S*-methoxymethoxy-pent-4-en-2*RS*-ol (151)

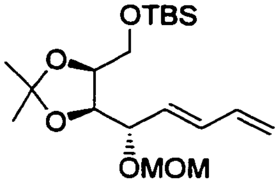


DMAP (8.779 g, 71.1 mmol) and TBSCl (11.031 g, 70.9 mmol) were added to a cold solution (0 °C) of both diastereoisomers of alcohol **150** (17.782 g, 64.4 mmol) in dry methylene chloride (300 mL). The mixture was allowed to warm and stir at room temperature for 21 h. The resulting white suspension was diluted with methylene chloride, washed with water then aq. ammonium chloride, dried and concentrated to give a colorless oil. The product was purified by chromatography (50:50, ether/petroleum ether) to give a 3:1 mixture of two diastereoisomers (23.60 g, 94%).

Diatereoisomer #1: $[\alpha]_D^{30.5}$ -55.72 degrees (c = 13.3 10^{-2} g/mL, MeOH). ^{1}H NMR (500 MHz, benzene-d^6) δ 6.09-6.04 (m, 1H), 5.17 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.10 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.98 (d, *J* = 6.7 Hz, 1H), 4.69 (d, *J* = 6.7 Hz, 1H), 4.37-4.34 (m, 1H), 4.31-4.27 (m, 1H), 4.02-3.99 (m, 1H), 3.90-3.87 (m, 2H), 3.70 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.17 (s, 3H), 3.09 (d, *J* = 9.2 Hz, 1H), 2.60-2.58 (m., 1H), 2.44-2.41 (m, 1H), 1.41 (s, 3H), 1.26 (s, 3H), 0.91 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C (125 MHz, benzene-d^6) δ 136.0, 117.1, 107.8, 97.9, 79.5, 79.4, 78.0, 72.37, 63.0, 55.8, 39.0, 28.0, 26.1 (3C), 25.6, 18.5, -5.4, -5.5. IR (neat) 3459 (br), 2940 cm^{-1}. Anal. Calcd for $C_{19}H_{38}SiO_6$ (390.59): C, 58.43; H, 9.81. Found: C, 58.60; H, 9.61.

Diatereoisomer #2: $[\alpha]_D^{30.5}$ -50.90 degrees (c = 1.65 10^{-2} g/mL, MeOH). ^{1}H NMR (500 MHz, benzene-d^6) δ 6.09-6.01 (m, 1H), 5.19-5.14 (m, 1H), 5.11-5.08 (m, 1H), 5.06 (d, *J* = 6.7 Hz, 1H), 4.68 (dd, *J* = 8.1, 5.6 Hz, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.19-4.16 (m, 1H), 3.96 (dd, *J* = 8.1, 2.4 Hz, 1H), 3.92-3.88 (m, 1H), 3.78(dd, *J* = 10.7, 7.2 Hz, 1H), 3.59 (dd, *J* = 10.7, 4.0 Hz, 1H), 3.19 (s, 3H), 2.65 (d, *J* = 8.4 Hz, 1H), 2.52-2.45 (m., 2H), 1.40 (s, 3H), 1.27 (s, 3H), 0.89 (s, 9H), 0.00 (s, 6H). ^{13}C (500 MHz, benzene-d^6) δ 135.8, 117.1, 108.1, 97.8, 78.4, 77.7, 77.5, 71.4, 62.9, 55.9, 39.3, 28.0, 26.1, 25.6, 18.5, -5.3, -5.4. IR (neat) 3452 (br), 3077, 2942. MS (EI) *m/z* 375 (M^+-CH_3). Anal. Calcd for $C_{19}H_{38}SiO_6$ (390.59): C, 58.43; H, 9.81. Found: C, 58.60; H, 9.78.

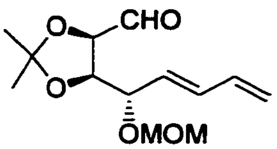
tert-Butyl-[5*S*-(1*S*-methoxymethoxy-penta-2*E*,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-ylmethoxy]-dimethyl-silane (98)



DEAD (10.0 mL, 60.3 mmol) was added to a cold solution (0 °C) of alcohol **151** (7.799 g, 19.9 mmol) and triphenylphosphine (15.730 g, 59.9 mmol) in dry benzene (75 mL). The orange-red mixture was allowed to stir at 0 °C for 2 h then at room temperature for 2.5 h. The mixture was then concentrated and gave a red oil. The crude was purified by chromatography (20:80, petroleum ether/CH_2Cl_2) and gave a pink oil (5.360 g, 72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37-6.21 (m, 2H), 5.73 (dd, *J* = 15.3, 7.2 Hz, 1H), 5.08 (dd, *J* = 16.3, 1.0 Hz, 1H), 4.96 (dd, *J* = 9.8, 1.1 Hz, 1H), 4.66 (d, *J* = 6.6 Hz, 1H), 4.62 (d, *J* = 6.6 Hz, 1H), 4.45 (t, *J* = 7.1 Hz, 1H), 4.13 (t, *J* = 6.2 Hz, 1H), 4.06 (q, *J* = 5.4 Hz, 1H), 3.87 (dd, *J* = 10.8, 5.2 Hz, 1H), 3.74 (dd, *J* = 10.8, 5.3 Hz, 1H), 3.25 (s, 3H), 1.47 (s, 3H), 1.27 (s, 3H), 0.93 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 135.1, 129.5, 118.4, 108.3, 93.6, 79.3, 77.7, 73.7, 62.3, 55.3, 27.4, 25.9 (3C), 25.4, 18.2, -0.1 (2C). IR (neat) 2940, 1605 cm^{-1}. Anal. Calcd for $C_{19}H_{36}SiO_5$ (390.59): C, 61.25; H, 9.74. Found: C, 61.12; H, 9.59.

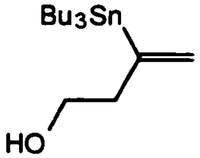
5*R*-(1*S*-Methoxymethoxy-penta-2*E*,4-dienyl)-2,2-dimethyl-[1,3]dioxolane-4*R*-carbaldehyde (117)



Oxalyl chloride (1.65 mL, 18.9 mmol) was added to a cold solution (-78 °C) of DMSO (3.40 mL, 47.5 mmol) in dry CH_2Cl_2 (100 mL). After 5 min a solution of alcohol (4.016 g, 15.5 mmol) in CH_2Cl_2 (10 mL) was transferred *via* a canula onto the cold cloudy solution. The mixture was allowed to stir at -78 °C for 1 h then triethylamine (13.5 mL, 96.8 mmol) was added and the mixture was allowed to warm and stir at room temperature for 45 min. The mixture was diluted with CH_2Cl_2 and quenched with aqueous NH_4Cl. The aqueous layer was extracted with ether, washed with brine, dried, filtered and concentrated. The crude yellow oil was purified by flash-chromatography (30:70-50:50, ether/petroleum ether) to give a slightly yellow oil (3.199 g, 80%). $[\alpha]_D^{23}$ +138.94 degrees (c = 2.29 10^{-2} g/mL, $CDCl_3$).

^1H NMR (500 MHz, $CDCl_3$) δ 9.65 (d, J = 2.4 Hz, 1H), 6.33-6.24 (m, 2H), 5.65 (dd, J= 14.9, 8.6 Hz, 1H), 5.23 (dd, J = 16.4, 2.1 Hz, 1H), 5.13 (dd, J= 9.9, 1.9 Hz, 1H), 4.60 (d, J = 6.6 Hz, 1H), 4.46 (d, J = 6.6 Hz, 1H), 4.42 (dd, J = 7.7, 3.9 Hz, 1H), 4.36 (dd, J = 7.7, 2.4 Hz, 1H), 4.11 (dd, J = 8.5, 3.9 Hz, 1H), 3.31 (s, 3H), 1.57 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 136.1, 135.7, 128.4, 119.1, 111.0, 94.1, 81.7, 80.8, 73.9, 56.2, 26.7, 25.1. IR (neat) 3088, 2988, 2845, 2833, 1731 (s),1604 cm^{-1}. MS (EI) *m/z* 256 (M^+), 241 (M^+ -CH_3). HREIMS *m/e* calcd for $C_{13}H_{20}O_5$ (M^+) 256.1311, found 256.1239. Unstable product for EA.

3-(Tri-n-butylstannyl)-3-buten-1-ol (156)[132]



n-Butyllithium 2.4 M (14.0 mL, 33.6 mmol) was added to a cold stirred suspension (-78 °C) of dry copper cyanide (1.50 g, 16.7 mmol) in dry THF (100 mL). The resulting yellow mixture

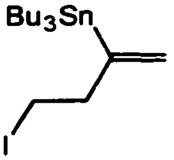
---

[132] Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tet. Letters*, **1989**, *30*, 2065.

was allowed to stir 5 min at room temperature until the solid CuCN disappeared. Tributyltin hydride (9.0 mL, 33.5 mmol) was added to the cold mixture (-78 °C) which was then stirred at room temperature for 20 min. 3-Butyn-1-ol (1.1 mL, 14.5 mmol) was slowly added over 1 min to the deeper yellow-brown mixture at -78 °C and the resulting brown mixture was allowed to stir for 1 h. A saturated aqueous solution of NH_4OH/NH_4Cl (1:9) was added and the mixture was stirred at room temperature under air atmosphere until the solid residue was dissolved to give a deep blue aqueous solution. The layers were separated and the aqueous layer was extracted with ether, the organic extracts were washed with brine, dried with Na_2SO_4 and evaporated. Flash-chromatography of the residual oil (90:10-80:20, petrole ether/ether) yielded the product (1.987 g, 38%) as a colourless oil.

^1H NMR (200 MHz, $CDCl_3$) δ 5.80 (dt, J = 3, 1.5 Hz, 1H), 5.29 (dm, J = 3 Hz, 1H), 3.63 (q, J = 7 Hz, 2H), 2.52 (t, J = 7 Hz, 2H), 1.58-1.40 (m, 6H), 1.38 (br. s., 1H), 1.35-1.27 (m, 12H), 0.94-0.75 (m, 15H).

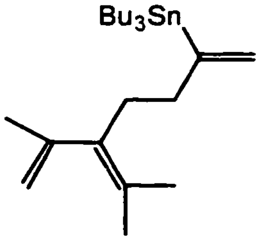
4-Iodo-2-(tri-n-butylstannyl)-2-butene (153)



Iodine (2.69 g, 10.59 mmol) was added to a stirred solution of triphenylphosphine (2.845 g, 10.84 mmol) in dry dichloromethane (60 mL) at room temperature. Freshly distilled triethylamine (1.5 mL, 10.8 mmol) and a solution 3-(tri-n-butylstannyl)-3-buten-1-ol **156** (3.128 g, 8.67 mmol) in dry dichloromethane (20 mL) were added 10 min later to the previous orange solution. The mixture was allowed to stir in the dark for another 5 h at room temperature and then poured into magnetically stirred petroleum ether. The resulting slurry was filtered through a column of Florisil® eluted with petroleum ether and the combined eluates were evaporated giving the product as a colourless oil with a quantitative yield.

^1H NMR (200 MHz, $CDCl_3$) δ 5.75-5.68 (m, $^3J_{Sn-H}$ = 130 Hz, 1H), 5.26-5.22 (m, $^3J_{Sn-H}$ = 56 Hz, 1H),3.15 (t, J = 7 Hz, 2H), 2.78 (t, J = 7 Hz, $^3J_{Sn-H}$ = 40 Hz, 2H), 1.70-1.20 (m, 12H), 1.8-0.70 (m, 15H). ^{13}C (50 MHz, $CDCl_3$) δ 153.5, 127.2, 45.1, 29.1, 27.4, 13.7, 9.6, 4.9. IR (neat) 1459, 1376, 1248, 1168, 1074, 919, 871, 671 cm^{-1}. HREIMS *m/e* calcd for $C_{12}H_{24}SnI$ (M^+- *n*-Bu) 414.9946, found 414.9977.

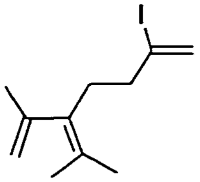
2-Methyl-3-(1-methylethylenyl)-6-(tri-n-butylstannyl)-hepta-2,6-diene (160)



Tert-butyllithium 1.58M (19 mL, 30.0 mmol) in pentane was added to a cold and stirred dry THF (20 mL). After 10 min a solution of 3-bromo-2,4-dimethylpenta-2,4-diene (2.58 g, 14.7 mmol) in dry THF (6 mL) was added slowly to the yellow solution. The mixture was then stirred at -78 °C for 20 min before the commercially available solution of lithium (2-thienyl)cyanocuprate (60 mL, 15 mmol) in THF was added through a dropping funnel. The resulting brown mixture was stirred at -78 °C for another 15 min before a solution of 4-iodo-2-(tri-n-butylstannyl)-2-butene (3.470 g, 7.38 mmol) in dry THF (6 mL) was added. After another 15 min at room temperature the mixture was allowed to stir in the dark and at room temperature for 63 h. The mixture was quenched with a saturated aqueous solution of NH_4OH/NH_4Cl (1:9) and allowed to stir at room temperature until the solution turned to blue. The aqueous layer was extracted with ether, the combined organic fractions were washed with brine, dried, filtered and evaporated. Chromatography of the residual yellow oil yielded 86% of the expected product (2.662 g).

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.69-5.67 (m, $^3J_{Sn\text{-}H}$ = 141 Hz, 1H), 5.10-5.08 (m, $^3J_{Sn\text{-}H}$ = 64 Hz, 1H), 4.92-4.89 (m, 1H), 4.56-4.53 (m, 1H), 2.18-2.15 (m, 2H), 2.12-2.07 (m, 2H), 1.75 (dd, *J* = 1.4, 1 Hz, 3H), 1.66 (s, 3H), 1.65 (s, 3H), 1.50-1.44 (m, 6H), 1.34-1.25 (m, 6H), 0.96-0.81 (m, 1H). ^{13}C (50 MHz, $CDCl_3$) δ 155.5, 146.5, 136.4, 125.0, 124.5, 113.0, 40.0, 31.9, 29.2, 27.5, 22.8, 21.7, 19.5, 13.7, 9.6. IR (neat) 1631, 1453, 1374, 1074, 912, 894, 670 cm^{-1}. HREIMS *m/e* calcd for $C_{19}H_{35}Sn$ (M^+- *n*-Bu) 383.1763, found 383.1770. Anal. Calcd for $C_{23}H_{44}Sn$: C, 62.89; H, 10.10. Found: C, 63.22; H, 10.36.

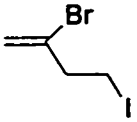
2-Iodo-5-isopropenyl-6-methyl-hepta-1,5-diene (99a)



Iodine (3.340 g, 13.16 mmol) was added to a solution of stannane **160** (5.53 g, 13.11 mmol) in CH_2Cl_2 (90 mL). The resulting black solution was allowed to stir at room temperature for 12 min then quenched with a 1M aqueous solution of $Na_2S_2O_3$ (70 mL). After 15 min at room temperature aqueous KF 2M (85 mL) was added to the colorless solution. The resulting emulsion was allowed to stir for 1 h then extracted with CH_2Cl_2, washed with brine, dried and concentrated. The crude yellow oil was purified by flash-chromatography (100%, petroleum ether) and gave the expected iodotriene (3.545 g, 98%) as a colorless oil.

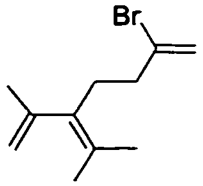
^{1}H NMR (200 MHz, $CDCl_3$) δ 6.00-5.95 (m, 1H), 5.65 (d, *J* = 1.5 Hz, 1H), 4.96-4.88 (m, 1H), 4.56-4.50 (m, 1H), 2.46-2.22 (m, 4H), 1.75 (s, 3H), 1.69 (s, 3H), 1.65 (s, 3H). ^{13}C (50 MHz, $CDCl_3$) δ 145.9, 134.5, 126.6, 125.1, 113.7, 112.2, 44.3, 30.9, 22.6, 21.8, 19.8. IR (neat) 1619, 1440, 1372, 1191, 1117, 893 cm^{-1}. HREIMS *m/e* calcd for $C_{11}H_{17}I$ (M+) 276.0376, found 276.0375.

2-Bromo-4-iodo-1-butene (163)



Iodine (9.662 g, 38.1 mmol) was added to a cold solution (0 °C) of PPh_3 (9.962 g, 37.9 mmol) in CH_2Cl_2 (100 mL). The mixture turned to a clear yellow. After 10 min. triethylamine (5.5 mL, 39.4 mmol) and bromoalcohol (3.2 mL, 31.6 mmol) were added to the cold solution. The mixture was allowed to stir at RT under an aluminum foil for 5 H. It was then poured onto vigorously stirred petroleum ether. The resulting yellow slurry was filtered on Florisil, then concentrated. The crude cloudy white oil was purified by chromatography (100% petroleum ether) and gave the expected product (8.084 g, 98%) as a colorless oil.
^1H NMR (200 MHz, $CDCl_3$) δ 5.66 (s, 1H), 5.54 (s, 1H), 3.32 (t, J = 6.9 Hz, 2H), 2.70 (t, J = 6.9 Hz, 2H).

2-Bromo-5-isopropenyl-6-methyl-hepta-1,5-diene (99b)



A solution of freshly distilled bromodiene **154** (6.479 g, 37.0 mmol) in 6 ml of dry THF was transferred into THF (100 mL) in a dry 3-neck round bottom flask under strong flow of Ar. The mixture was cooled down to -78 °C then *tert*-butyllithium 0.98M (51 mL, 50.0 mmol) was added to the cold solution which turned yellow then colorless again. The mixture was then stirred at -78 °C for 10 min and purged 3 times before the new commercially available solution of lithium (2-thienyl)cyanocuprate (100 mL, 25 mmol) in THF was added.[133] The light yellow-brown mixture was stirred at -78 °C for another 15 min then a solution of 2-bromo-4-iodo-1-butene (6.50 g, 24.9 mmol) in dry THF (5 mL) was added. The resulting orange-brown mixture was allowed to stir in the dark and at room temperature for 14 h. The mixture was quenched with saturated aqueous solution of NH_4Cl/NH_4OH (9:1, 100 mL). The aqueous layer was extracted with petroleum ether, the combined organic fractions were washed with brine, dried and evaporated. Chromatography (100% petroleum ether) of the

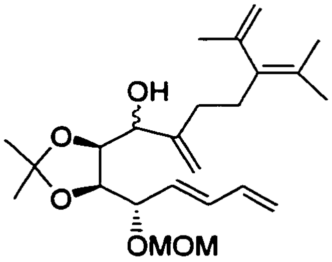
---

[133] The commercially available cuprate was not reliable and often gave lower yield. Therefore, the cuprate was made *in situ* following the procedure developed by R. J. K. Taylor in *OrganoCopper Reagents: A practical approach*, Oxford University Press, 1994, pp113, Ed. Harwood L. M.and Moody C. J.

residual colorless oil yielded 99% of the expected product (5.651 g). The bromotriene **99b** can be purified by distillation (70-80 °C, 1 mm Hg).

^{1}H NMR (200 MHz, CDCl$_3$) δ 5.53 (d, *J* =1.1 Hz, 1H), 5.34 (d, *J* =1.6 Hz, 1H), 4.94 (m, 1H), 4.54 (m, 1H), 2.42-2.33 (m, 4H), 1.75 (s, 3H), 1.68 (s, 3H), 1.65 (s, 3H). MS (EI) *m/z* (M$^+$) 230 and 228.

5-Isopropenyl-1*RS*-[5*S*-(1*S*-methoxymethoxy-penta-2*E*,4-dienyl)-2,2-dimethyl-[1,3]dioxolan-4*R*-yl]-6-methyl-2-methylene-hept-5-en-1-ol (164)

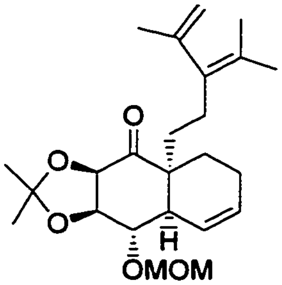


t-BuLi 1.70 M (12.5 mL, 21.2 mmol) was added to cold THF (140mL, -98 °C). A solution of freshly distilled bromotriene (3.272 g, 14.3 mmol) in THF (10 mL) was transferred *via* a canula onto the cloudy yellow solution. The solution turned clear yellow and was allowed to stir at -98 °C for 10 min. A solution of aldehyde (2.596 g, 10.1 mmol) in THF (10 mL) was added at -98 °C. The yellow mixture was allowed to warm a little and checked in TLC every 5 min. After 15 min the yellow solution was quenched at -60 °C by addition of aqueous NH$_4$Cl. The mixture was warmed up and extracted with ether, washed with brine, dried filtered and concentrated. The crude yellow oil was purified by chromatography (10:90-30:70, ether/petroleum ether) and gave two diastereoisomers (3.252 g, 79%).

Diastereoisomer #1: $[\alpha]_D^{22}$ +70.34 degrees (c = 1.38 10^{-2} g/mL, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.39-6.25 (m, 2H), 5.82 (dd, *J* = 14.9, 8.1 Hz, 1H), 5.24 (d, *J* = 17.1 Hz, 1H), 5.14-5.11 (m, 2H), 5.00 (d, *J* = 1.1 Hz, 1H), 4.90-4.89 (m, 1H), 4.71 (d, *J* = 6.4 Hz, 1H), 4.61 (d, *J* = 6.4 Hz, 1H), 4.55 (d, *J* = 1.8 Hz, 1H), 4.47 (dd, *J* = 9.3, 3.6 Hz, 1H), 4.43 (dd, *J* = 8.1, 4.1 Hz, 1H), 4.29 (dd, *J* = 5.8, 4.3 Hz, 1H), 4.19 (dd, *J* = 9.3, 5.9 Hz, 1H), 3.43 (d, *J* = 3.7 Hz, 1H), 3.38 (s, 3H), 2.28-2.10 (m, 4H), 1.75 (s, 3H), 1.67 (s, 3H), 1.65 (s, 3H), 1.40 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) 149.9, 146.5, 136.3, 135.9, 135.7, 129.6, 125.2, 118.6, 113.0, 111.9, 108.7, 94.2, 79.4, 78.8, 76.4, 72.0, 55.9, 30.6, 30.0, 26.8, 25.1, 22.7, 21.6, 19.5. IR (neat) 3467, 3075, 2985, 2934, 1647, 1604 cm^{-1}. MS (EI) *m/z* 391 (M^+ -CH_3). HREIMS *m/e* calcd for $C_{23}H_{35}O_5$ (M^+-CH_3) 391.2485, found 391.2458. Anal. Calcd for $C_{24}H_{38}O_5$ (406.27): C, 70.90; H, 9.42. Found: C, 70.87; H, 9.49.

Diastereoisomer #2: $[\alpha]_D^{22}$ +43.43 degrees (c = 3.08 10^{-2} g/mL, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39-6.28 (m, 2H), 5.62 (dd, *J* = 14.6, 8.6 Hz, 1H), 5.27 (dd, *J* = 16.8, 1.7 Hz, 1H), 5.16 (dd, *J* = 9.4, 1.7 Hz, 1H), 5.10 (s, 1H), 4.98 (s, 1H), 4.89 (dd, *J* = 2.7, 1.4 Hz, 1H), 4.74 (d, *J* = 6.7 Hz, 1H), 4.62 (d, *J* = 6.7 Hz, 1H), 4.53-4.50 (m, 2H), 4.26-4.22 (m, 2H), 4.16 (dd, *J* = 6.7, 2.2 Hz, 1H), 3.39 (s, 3H), 2.69 (d, *J* = 6.6 Hz, 1H), 2.25-2.17 (m, 2H), 2.12-2.06 (m, 1H), 1.98-1.91 (m, 1H), 1.73 (s, 3H), 1.64 (s, 6H), 1.54 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 149.0, 146.3, 136.7, 136.0, 135.6, 128.9, 125.3, 119.4, 113.1, 110.8, 108.5, 93.6, 79.3, 77.2, 74.1, 71.5, 55.7, 31.4, 29.9, 26.5, 24.7, 22.7, 21.6, 19.5. IR (neat) 3579, 3078, 2987, 2932, 1549 cm^{-1}. MS (EI) *m/z* 406 (M^+), 391 (M^+ -CH_3). HREIMS *m/e* calcd for $C_{23}H_{35}O_5$ (M^+-CH_3) 391.2485, found 391.2514. Anal. Calcd for $C_{24}H_{38}O_5$ (406.27): C, 70.90; H, 9.42. Found: C, 71.14; H, 9.23.

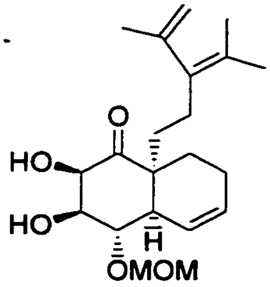
4a-(3-Isopropenyl-4-methyl-pent-3-enyl)-9*S*-methoxymethoxy-2,2-dimethyl-4a*S*,5,6,8a*R*,9,9a-hexahydro-3aH-naphtho[2,3-d][1,3]dioxol-4-one (165)



Dess Martin's reagent (5.30 g, 12.5 mmol) was added to the cold (0 °C) solution of alcohol (3.386 g, 8.34 mmol) in CH_2Cl_2 (100 mL). The white mixture was allowed to stir at room temperature for 1.75 h then the mixture was quenched with $NaHCO_3$:Na_2SO_3 (50 mL, 1:1), extracted with CH_2Cl_2, washed with brine, dried and concentrated. The crude yellow oil was purified by chromatography (20:80, ether/petroleum ether) to give the expected product (2.728 g, 81%). $[\alpha]_D^{20}$ -124.5 degrees (c = 1.47 10^{-2} g/mL, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82-5.79 (m, 1H), 5.73-5.70 (m, 1H), 4.85 (m, 1H), 4.83 (d, *J* = 6.5 Hz, 1H), 4.75 (d, *J* = 8.7 Hz, 1H), 4.63 (d, *J* = 6.5 Hz, 1H), 4.54 (dd, *J* = 8.6, 6.6 Hz, 1H), 4.46 (m, 1H), 3.46 (dd, *J* = 11.6, 6.5 Hz, 1H), 3.34 (s, 3H), 2.42-2.40 (m, 1H), 2.07-1.95 (m, 4H), 1.83 (td, *J* = 13.1, 3.7 Hz, 1H), 1.71 (td, *J* = 13.7, 4.7 Hz, 1H), 1.66 (s, 3H), 1.59 (s, 3H), 1.56 (s, 3H), 1.46 (s, 3H), 1.41-1.3 (m, 1H), 1.35 (s, 3H), 1.30,(td, *J* = 13.5, 3.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.5, 146.1, 135.2, 128.1, 125.6, 124.6, 113.2, 111.3, 95.5, 82.1, 77.6, 76.9, 55.7, 47.4, 42.9, 33.5, 26.9, 25.4, 24.9, 22.6, 22.2, 21.6, 21.1, 19.4. IR (neat) 3074, 3035, 2980, 2920, 1729, 1630 cm^{-1}. MS (EI) *m/z* 389 (M^+ - CH_3). HREIMS *m/e* calcd for $C_{23}H_{33}O_5$ (M^+ -CH_3) 389.2329, found 389.2313.

2*R*,3*S*-Dihydroxy-8a*S*-(3-isopropenyl-4-methyl-pent-3-enyl)-4*S*-methoxymethoxy-3,4,4a*R*,7,8,8a-hexahydro-2H-naphthalen-1-one (168a)

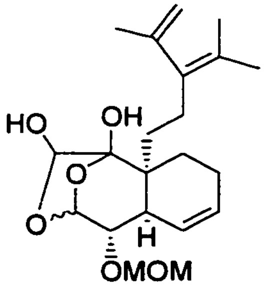


A solution of 10% CF_3SO_3H in water (55 mL) was added drop wise and in 3 times to the cold solution (0 °C) of decalin (1.106 g, 2.74 mmol) in THF (50 mL). The reaction mixture was stirred at room temperature for 20 hr. The mixture was neutralized by the addition of solid $NaHCO_3$ at 0 °C. Ether was then added, and the aqueous layer was extracted with ether. The combined organic phases were washed with saturated $NaHCO_3$, brine, dried, filtered and concentrated. Flash-chromatography (ether/petroleum ether) provided diol **168a** (0.578g, 58%) as a slightly yellow oil. $[\alpha]_D^{23}$ -95.78 degrees (c = 1.95 10^{-2} g/mL, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69-5.65 (m, 1H), 5.59-5.56 (m, 1H), 4.87-4.85 (m, 1H), 4.75 (d, *J*= 6.8 Hz, 1H), 4.71 (d, *J*= 6.8 Hz, 1H), 4.61 (t, *J*= 4.1 Hz, 1H), 4.47-4.46 (m, 1H), 4.33-4.31 (m, 1H), 3.87 (dd, *J*= 5.3, 3.2 Hz, 1H), 3.81 (d, *J*= 3.8 Hz, 1H), 3.38 (s, 3H), 2.76-2.75 (m, 1H), 2.59 (d, *J*= 2.5 Hz, 1H), 2.16-1.92 (m, 5H), 1.78-1.70 (m, 1H), 1.67 (s, 3H), 1.62-

1.56 (m, 1H), 1.59 (s, 3H), 1.56 (s, 3H), 1.52-1.46 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 146.1, 135.3, 127.0, 126.8, 125.6, 113.2, 96.0, 80.1, 75.6, 72.7, 55.8, 48.2, 44.1, 36.6, 26.2, 25.1, 22.6, 21.6, 21.5, 19.3. IR (neat) 3448, 3067, 3031, 2920, 1716 cm^{-1}. MS (EI) *m/z* 364 (M^+). HRMS (EI) found *m/z* calcd for $C_{21}H_{32}O_5$ $(M)^+$ 364.2251, found 364.2249. Anal. Calcd for $C_{21}H_{32}O_5$ (364.22): C, 69.20; H, 8.85. Found: C, 69.07, H, 8.66.

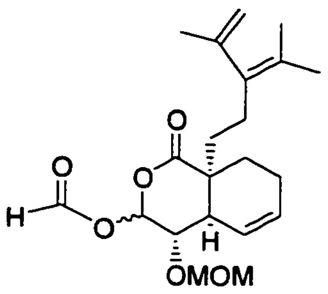
2*S*-(3-Isopropenyl-4-methyl-pent-3-enyl)-8*S*-methoxymethoxy-10,12-dioxa-tricyclo[7.2.1.02,7]dodec-5-ene-1*RS*,11*RS*-diol (172a)



$NaIO_4$ (0.670 g, 3.13 mmol) was added portionwise to the clear solution of the diol (0.290 g, 0.797 mmol) in THF:H_2O (1:1, 5 mL) at room temperature. The solution turned yellow then milky white. The course of reaction was monitored by TLC (15 min). Water was added and the mixture was extracted with methylene chloride, dried, filtered and concentrated (benzene azeotrope). Chromatography (50:50-75:25, ether/petroleum ether) afforded a 9:1 mixture of bilactol **172a** and formyl **173a** (0.293 g, 96%).

Bilactol **172a**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.76-5.69 (m, 2H), 5.46 (d, *J* = 1.6 Hz, 1H), 5.36 (d, *J* = 5.7 Hz, 1H), 4.86 (dd, *J* = 2.7 Hz, 1H), 4.65 (d, *J* = 6.9 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 1H), 4.48 (dd, *J* = 2.5, 0.7 Hz, 1H), 4.11 (s, 1H), 3.37 (s, 3H), 3.36-3.33 (m, 1H), 3.27 (d, *J* = 5.8 Hz, 1H), 2.46 (td, *J* = 13.4, 4.4 Hz, 1H), 2.15-2.07 (m, 2H), 2.03 (td, *J* = 13.4, 4.5 Hz, 1H), 1.95 (dd, *J* = 13.9, 5.5 Hz, 1H), 1.88-1.84 (m, 1H), 1.82-1.79 (m, 1H), 1.71 (s, 3H), 1.69-1.63 (m, 1H), 1.61 (s, 6H), 1.23-1.14 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 136.8, 127.7, 125.8, 124.7, 112.9, 106.0, 99.8, 97.3, 90.6, 80.6, 55.5, 41.0, 39.7, 31.8, 25.8, 22.6, 21.9, 21.6, 19.7, 19.4. IR (neat) 3427, 3073, 3028, 2913, 1630 cm^{-1}. MS *m/z* 362 (M^+ - H_2O). HREIMS (EI) *m/e* calcd for $C_{25}H_{30}O_2$ (M^+ -H_2O) 362.2247, found 362.2241.

Formic acid 8a*S*-(3-isopropenyl-4-methyl-pent-3-enyl)-4*S*-methoxymethoxy-1-oxo-3*RS*,4,4a*R*,7,8,8a-hexahydro-1H-isochromen-3-yl ester (173a)



Preparation of the oxidant (1.16 10^{-3} mol $NaIO_4$/g SiO_2):

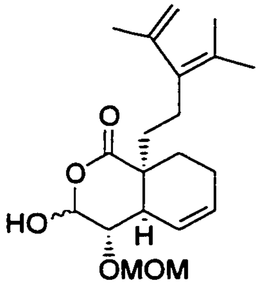
$NaIO_4$ (3.567 g) was solubilized in hot water (7 mL). SiO_2 60 mesh (14.3 g) was then added to the vigorously stirred hot solution. The white powder was allowed to stir and cool down to room temperature for 30 min.

Oxidation of diol (**168a**):

The silica-$NaIO_4$ powder was added to the solution of diol (0.759 g, 2.08 mmol) in CH_2Cl_2 (25 mL). The mixture was allowed to stir at room temperature under air and turned yellow. The reaction was followed by TLC and after 45 min the reaction was completed. The mixture was filtered through a sintered glass funnel and washed with CH_2Cl_2. The filtrate was concentrated and gave the expected product (0.778 g, 99%) clean in ^{1}HNMR.

^{1}H NMR (500MHz, $CDCl_3$) δ 8.15 (d, *J* = 0.69 Hz, 1H), 6.61 (d, *J* = 2.7, 1H), 5.87-5.84 (m, 1H), 5.74-5.70 (m, 1H), 4.89-4.87 (m, 1H), 4.70-4.66 (m, 2H), 4.51-4.50 (m, 1H), 3.86 (dd, *J* = 11.3, 2.7 Hz, 1H), 3.35 (s, 3H), 2.89 (dd, *J* = 11.3, 4.2 Hz, 1H), 2.19-1.99 (m, 4H), 1.88-1.70 (m, 3H), 1.71 (s, 3H), 1.63-1.57 (m, 1H), 1.63 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 158.5, 146.0, 135.4, 128.3, 126.0, 124.2, 113.3, 97.0, 89.4, 73.9, 56.1, 45.2, 34.4, 33.1, 30.8, 25.8, 22.5, 21.7, 21.4, 19.4. IR (neat) 3074, 3036, 2929, 2859, 1746, 1630 cm^{-1}. MS *m/z* 378 (M^+). HREIMS *m/e* calcd for $C_{21}H_{30}O_6$ (M^+) 378.2043, found 378.2039. Anal. Calcd for $C_{21}H_{30}O_6$ (378.20): C, 66.65; H, 7.99. Found: C, 66.46;H, 7.99.

3*RS*-Hydroxy-8a*S*-(3-isopropenyl-4-methyl-pent-3-enyl)-4*S*-methoxymethoxy-3,4,4a*R*,7,8,8a-hexahydro-isochromen-1-one (174a)

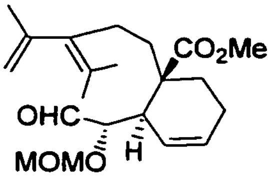


A solution of saturated K_2CO_3 in dry MeOH was added portion wise to the yellow solution of crude formate **173a** (0.081 g) in THF (10 mL). The mixture turned a darker yellow and the reaction was complete after 0.5 h. The reaction mixture was diluted with water (2 mL) and extracted with Et_2O. The combined organic phases were dried, filtered and concentrated. Flash-chromatography (50:50, ether/petroleum ether) yielded the expected product (0.073 g, 51 % over 3 steps).

Diastereoisomer #1: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90-5.86 (m, 1H), 5.66-5.63 (m, 1H), 5.52 (d, *J* = 4.1 Hz, 1H), 4.88-4.87 (m, 1H), 4.79 (br. s., 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.50 (dd, *J* = 2.6, 0.8 Hz, 1H), 3.87 (t, *J* = 3.8 Hz, 1H), 3.36 (s, 3H), 2.84-2.83 (m, 1H), 2.17-1.55 (m, 17H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 146.0, 135.5, 129.6, 125.7, 123.9, 113.3, 96.5, 96.2, 73.7, 55.7, 44.6, 36.3, 35.5, 30.3, 25.6, 22.5, 21.7, 21.6, 19.4. IR (neat) 3349, 3021, 2920, 1704 cm^{-1}.

Diastereoisomer #2: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87-5.84 (m, 1H), 5.68-5.65 (m, 1H), 5.535-5.530 (m, 1H), 5.25 (d, *J* = 5.9 Hz, 1H), 4.85 (dd, *J* = 2.7, 1.4 Hz, 1H), 4.73 (s, 2H), 4.48-4.47 (m, 1H), 3.73 (dd, *J* = Hz, 1H), 3.41 (s, 3H), 2.97-2.95 (m, 1H), 2.19-1.99 (m, 4H), 1.91-1.85 (m, 1H), 1.78-1.67 (m, 5H), 1.65-1.57 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 146.3, 135.8, 128.7, 125.6, 125.1, 113.1, 97.1, 93.7, 77.3, 56.0, 44.8, 35.4, 34.5, 30.8, 25.7, 22.5, 21.7, 21.6, 19.4. IR (neat) 3368, 3075, 3035, 2927, 2859, 1710, 1630 cm^{-1}. MS *m/z* 350 (M$^+$). HREIMS *m/e* calcd for $C_{20}H_{30}O_5$ (M$^+$) 350.2094, found 350.2088.

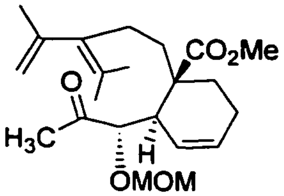
1*S*-(3-Isopropenyl-4-methyl-pent-3-enyl)-2*R*-(1*S*-methoxymethoxy-2-oxo-ethyl)-cyclohex-3-enecarboxylic acid methyl ester (171a)



A solution of freshly prepared diazomethane from *N*-nitrosomethylurea was added dropwise to a solution of crude compound **174a** (0.768 g, 2.22 mmol) in dry ether (5 mL) at 0° C until the yellow color of the diazomethane reamined. The mixture was stirred at 0 °C for 15 min then at room temperature until the yellow colour disappeared. The solvent was removed. Chromatography (20:80-50:50 ether/petroleum ether) provided compound **171a** (0.245 g, 31%) as a light yellow oil.

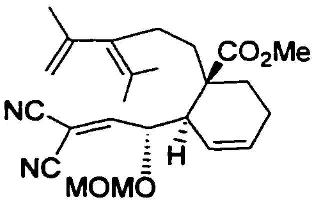
$[\alpha]^{24}_{D}$ -107.89 degrees. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (s, 1H), 5.88-5.85 (m, 1H), 5.38-5.34 (m, 1H), 4.89-4.86 (m, 1H), 4.66 (d, *J*= 6.9 Hz, 1H), 4.55 (d, *J*= 6.9 Hz, 1H), 4.49-4.48 (m, 1H), 3.85-3.84 (m, 1H), 3.69 (s, 3H), 3.36 (s, 3H), 2.63 (s, 1H), 2.15-1.81 (m, 5H), 1.76-1.66 (m, 5H), 1.60, (s, 3H), 1.58, (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 176.4, 146.1, 135.5, 130.1, 125.5, 121.9, 113.2, 97.7, 84.4, 56.5, 51.5, 47.5, 44.9, 34.1, 26.2, 22.5, 22.1, 21.7, 21.6 19.3. IR ($CHCl_3$) 3076, 3032, 2950, 2855, 2836, 1778, 1733, 1630 cm^{-1}. Unstable to HRMS and EA.

Byproduct **178**:



^{1}H NMR (500 MHz, CDCl$_3$) δ 5.86-5.85 (m, 1H), 5.29-5.26 (m, 1H), 4.87 (br. s, 1H), 4.53 (d, *J* = 6.9 Hz, 1H), 4.48-4.47 (d+s, 2H), 4.03 (d, *J* = 2.3 Hz, 1H), 3.72 (s, 3H), 3.31 (s, 3H), 2.50 (br. s, 1H), 2.15-2.09 (m+s, 5H), 2.02-1.80 (m, 3H), 1.74-1.68 (m, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.58-1.52 (m, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 208.4, 176.5, 146.1, 135.5, 130.0, 125.4, 121.6, 113.2, 97.3, 84.0, 56.8, 51.4, 47.9, 44.5, 34.5, 26.9, 26.2, 22.5, 21.71, 21.68, 21.6, 19.3. IR (neat) 3078, 3026, 2949, 1731 cm^{-1}. MS *m/z* 378 (M$^+$). HREIMS *m/e* calcd for $C_{22}H_{34}O_5$ (M$^+$) 378.2407, found 378.2392.

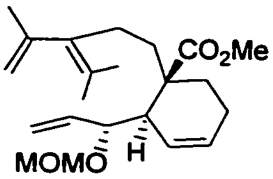
2*R*-(3,3-Dicyano-1*RS*-methoxymethoxy-allyl)-1*S*-(3-isopropenyl-4-methyl-pent-3-enyl)-cyclohex-3-enecarboxylic acid methyl ester (181)



Malonitrile (0.581 g, 8.80 mmol) and L-alanine (0.099 g, 0.111 mmol) were added to a cold solution (0 °C) of aldehyde **171a** (0.203 g, 0.056 mmol) in EtOH 95% (8 mL). The solution was allowed to stir at room temperature for 22 h, filtered on silica, washed with ether. The filtrate was dried and concentrated. The crude product was purified by flash-chromatography (30:70, ether/petroleum ether) after dry loading and gave the expected product (0.035 g, 15%).

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.84 (d, *J* = 12.4 Hz, 1H), 6.03 (d, *J* = 10.1 Hz, 1H), 5.77 (d, *J* = 10.1 Hz, 2H), 4.97 (d, *J* = 12.4 Hz, 1H), 4.89 (s, 1H), 4.87 (s, 1H), 4.51 (d, *J* = 1.6 Hz, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.69-2.66 (m, 1H), 2.43 (m, 1H), 2.04-1.91 (m, 3H), 1.70 (s, 1H), 1.60 (s, 3H), 1.59 (s, 3H), 1.60-1.47 (m, 3H), 1.36 (td, *J* = 13.5, 2.6 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 174.7, 150.1, 146.0, 136.6, 135.4, 125.8, 123.7, 113.7, 113.4, 99.0, 96.4, 76.7, 56.3, 51.9, 47.0, 44.4, 40.4, 38.6, 29.5, 25.7, 22.9, 22.5, 21.7, 19.4. IR (neat) 3069, 2961, 2253, 1733, 1696, 1654 cm^{-1}. MS (ES) *m/z* 413 (M$^+$+1).

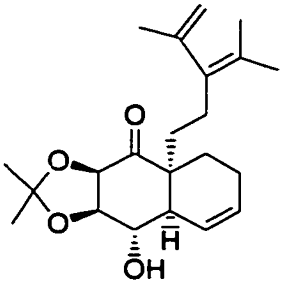
1*S*-(3-Isopropenyl-4-methyl-pent-3-enyl)-2*R*-(1*S*-methoxymethoxy-allyl)-cyclohex-3-enecarboxylic acid methyl ester (190)



n-BuLi (0.24 mL, 5.76 mmol, 2.4M) was added to the cold suspension (0 °C) of phosphonate (0.201 g, 5.61 mmol) in THF (5 mL). After 5 min a solution of aldehyde (0.167 g, 4.60 mmol) in THF (5 mL) was added to the yellow solution. The mixture was allowed to warm and stir at room temperature for 1.25 h. Aqueous ammonium chloride was added, the mixture was extracted with ether, dry, filtered and concentrated. The yellow crude oil was purified by flash-chromatography (10:90-30:70, ether/petroleum ether) to give compound **190** (0.073 g, 44%).

^{1}H NMR (500 MHz, benzene-d^6) δ 5.78-5.71 (m, 3H), 5.13 (dd, *J* = 17.3, 1.1 Hz, 1H), 5.0 (dt, *J* = 10.4, 0.8 Hz, 1H), 4.96-4.95 (m, 1H), 4.67 (d+s, *J* = 6.8 Hz, 2H), 4.42 (d, *J* = 6.7 Hz, 1H), 4.26 (dd, *J* = 7.4, 3.4 Hz, 1H), 3.44 (s, 3H), 3.27 (s, 3H), 2.55-2.49 (m, 1H), 2.41 (d, *J* = 2.4 Hz, 1H), 2.17 (dd, *J* = 13.9, 9.7 Hz, 1H), 2.07-1.94 (m, 5H), 1.82-1.77 (m, 1H), 1.74 (d, *J* = 0.7 Hz, 3H), 1.69 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (125 MHz, benzene-d^6) δ 176.3, 146.7, 137.9, 136.5, 128.3, 125.4, 124.7, 117.1, 113.5, 94.5, 79.2, 56.1, 50.7, 49.0, 48.2, 35.1, 26.8, 22.7, 22.6, 22.5, 21.9, 19.4. IR (neat) 3082, 2935, 2850, 1735, 1637 cm^{-1}. MS *m/z* 362 (M$^+$). HREIMS *m/e* calcd for $C_{22}H_{34}O_4$ (M)$^+$ 362.2458, found 362.2574.

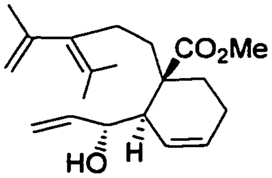
9S-Hydroxy-4aS-(3-isopropenyl-4-methyl-pent-3-enyl)-2,2-dimethyl-4a,5,6,8a*R*,9,9a-hexahydro-3aH-naphtho[2,3-d][1,3]dioxol-4-one (169)



$BF_3.OEt_2$ (0.060 mL, 0.473 mmol) and dimethylsulfide (0.9 mL, 12.2 mmol) were added to a cold solution (0 °C) of decalin (0.051 g, 0.126 mmol) in CH_2Cl_2 (1 mL). The yellow solution was allowed to stir at 0 °C for 30 min. $NaHCO_3$ solid was added and the suspension was filtered on a pad of silica, dried and concentrated. The crude product was purified by flash-chromatography (20:80, ether/petroleum ether) and gave **169** (0.013 g, 29%).

$[\alpha]_D^{20}$ -156.65 degrees (c = 1.5 10^{-2} g/mL, MeOH). ^1H NMR (500 MHz, $CDCl_3$) δ 5.91-5.88 (m, 1H), 5.74-5.70 (m, 1H), 4.86-4.84 (m, 1H), 4.76 (d, *J* = 9.0 Hz, 1H), 4.51 (dd, *J* = 9.0, 7.3 Hz, 1H), 4.46-4.45 (m, 1H), 3.40 (dd, *J* = 11.6, 7.3 Hz, 1H), 2.44 (br s, 1H), 2.33-2.30 (m, 1H), 2.14-1.96 (m, 4H), 1.82 (td, *J* = 13.2, 3.8Hz, 1H), 1.70 (td, *J* = 13.8, 4.8 Hz, 1H), 1.66 (s, 3H), 1.59 (s, 3H), 1.56 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H), 1.35-1.29 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.5, 146.1, 135.2, 129.6, 125.7, 123.4, 113.3, 111.5, 82.0, 77.0, 75.1, 47.6, 43.5, 33.7, 26.9, 25.3 24.9, 22.6, 22.5, 21.6, 21.2, 19.5. IR (neat) 3449, 3034, 2922, 1726, 1633 cm^{-1}. MS *m/z* 345 (M^+ -CH_3). HREIMS *m/e* calcd for $C_{21}H_{32}O_4$ (M^+ - CH_3) 345.2067, found 345.2065.

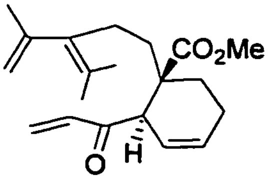
2*R*-(1*S*-Hydroxy-allyl)-1*S*-(3-isopropenyl-4-methyl-pent-3-enyl)-cyclohex-3-enecarboxylic acid methyl ester (191)



Dimethylsulfide (1 mL, 13.6 mmol) and boron trifluoride etherate (0.060 mL, 0.473 mmol) were added to the cold solution (0 °C) of protected alcohol **190** (0.053 mg, 0.146 mmol) in ether (2 mL). The yellow solution was allowed to stir at 0 °C for 2 h then quenched with $NaHCO_3$ solid and a drop of water. The mixture was dried, vacuum down and purified by flash-chromatography (30:70, ether/petroleum ether) to give 16.3 mgs of the expected alcohol (35%).

^1H NMR (500 MHz, $CDCl_3$) δ 5.95-5.92 (m, 1H), 5.90-5.83 (m, 1H), 5.54-5.50 (m, 1H), 5.21 (dt, *J* = 17.2, 1.7 Hz, 1H), 5.1 (dt, *J* = 10.6, 1.7 Hz, 1H), 4.88-4.87 (m, 1H), 4.51-4.50 (m, 1H), 4.12 (br. s, 1H), 3.71 (s, 3H), 2.30-2.23 (m, 1H), 2.22-2.19 (m, 1H), 2.15-2.09 (m, 1H), 2.01-1.95 (m, 3H), 1.83-1.76 (m, 2H), 1.70 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.73-1.59 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 146.2, 140.5, 135.7, 131.0, 125.4, 122.2, 113.9, 113.2, 72.1, 51.5, 48.4, 34.5, 26.0, 23.1, 22.5, 22.1, 22.0, 21.7, 19.3. IR (neat) 3511, 3075, 3026, 2917, 1772, 1734, 1630 cm^{-1}. MS (CI) *m/z* 319 (M^++1).

2*R*-Acryloyl-1*S*-(3-isopropenyl-4-methyl-pent-3-enyl)-cyclohex-3-enecarboxylic acid methyl ester (189)



Dess Martin's reagent (24 mg, 0.057 mmol) and sodium hydrogenocarbonate (4 mg, 0.047 mmol) were added to the cold (0 °C) solution of alcohol (16.5 mg, 0.052 mmol) in CH_2Cl_2 (2 mL). The white mixture was allowed to stir at room temperature for 1.75 h then the mixture was quenched with $NaHCO_3$:Na_2SO_3 (2 mL, 1:1), extracted with CH_2Cl_2, washed with brine, dried and concentrated. The crude yellow oil was purified by chromatography (20:80, ether/petroleum ether) to give the expected product (10.2 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (dd, *J* = 17.4, 10.5 Hz, 1H), 6.24 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.83-5.81 (m, 1H), 5.75 (dd, *J* = 10.5, 1.3 Hz, 1H), 5.67-5.63 (m, 1H), 4.88-4.87 (m, 1H), 4.50-4.49 (m, 1H), 3.60 (s, 3H), 3.58-3.56 (m, 1H), 2.21-1.94 (m, 5H), 1.86 (td, *J* = 13.2, 4.3 Hz, 1H), 1.69 (m, 3H), 1.68-1.63 (m, 1H), 1.62 (s, 3H), 1.58 (s, 3H), 1.45-1.39 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 176.7, 146.2, 135.7, 135.3, 130.3, 128.2, 125.5, 121.0, 113.2, 53.9, 51.4, 45.6, 33.4, 25.5, 22.6, 22.4, 22.0, 21.7, 19.4. IR (neat) 3025, 2921, 1738, 1701, 1456 cm^{-1}. MS *m/z* 316 (M^+). HREIMS *m/e* calcd for $C_{20}H_{28}O_3$ (M^+) 316.2039, found 316.2042.

Claim to Original Research

1. Developed an effective stereospecific route for the synthesis of decalin 4a-(3-Isopropenyl-4-methyl-pent-3-enyl)-9*S*-methoxymethoxy-2,2-dimethyl-4a*S*,5,6,8a*R*,9,9a-hexahydro-3aH-naphtho[2,3-d][1,3]dioxol-4-one **165** *via* a tether controlled cycloaddition.

2. Established that cis isopropylidene acetals derived from (L)-arabinose are superior to the trans isomer for inducing the overlap required for facile cyclization and for synthesis of highly substituted decadienones

3. Developed a direct oxidative sequence for the controlled cleavage of vicinal decalin diols

4. Improved knowledge and understanding of the preparation of the triene building block.

5. Preparation of substituted C rings as precursors to Diels-Alder cycloadditions to form the Taxol® ABC ring system.

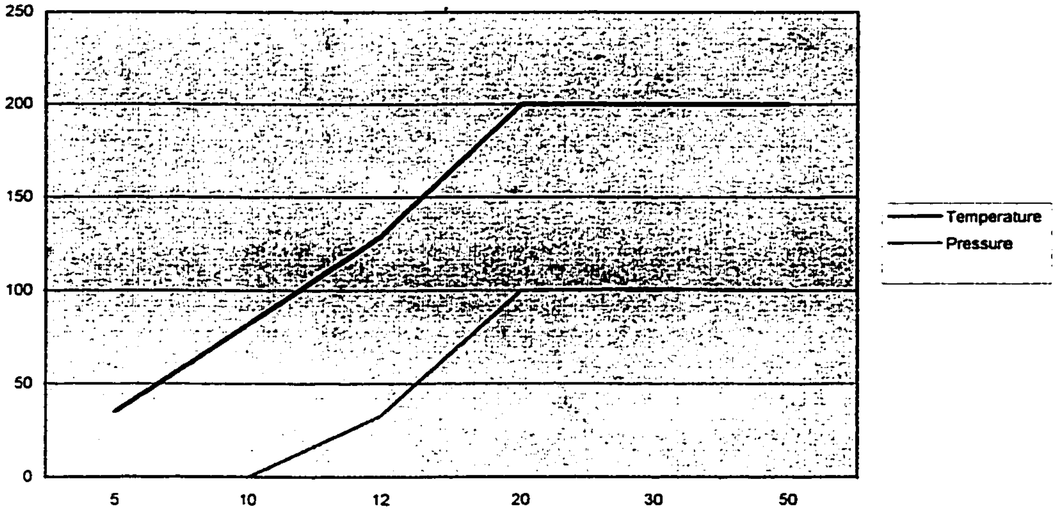
6. Publications:

    - S. Woo, S. Legoupy, S. Parra and A. G. Fallis, "A Diene Transmissive Diels-Alder Strategy for Oxygenated Nor-Steroid and Triterpenoid Skeletons", *Organic Letters*, **1999**, *1*, 1013.
    - S. Parra, S. Legoupy, M.-L. Lee and A. G. Fallis, "Acetal Hydrolysis and Oxidative Cleavage of Decaline Diols", *Organic Letters*, **2001**, submitted.

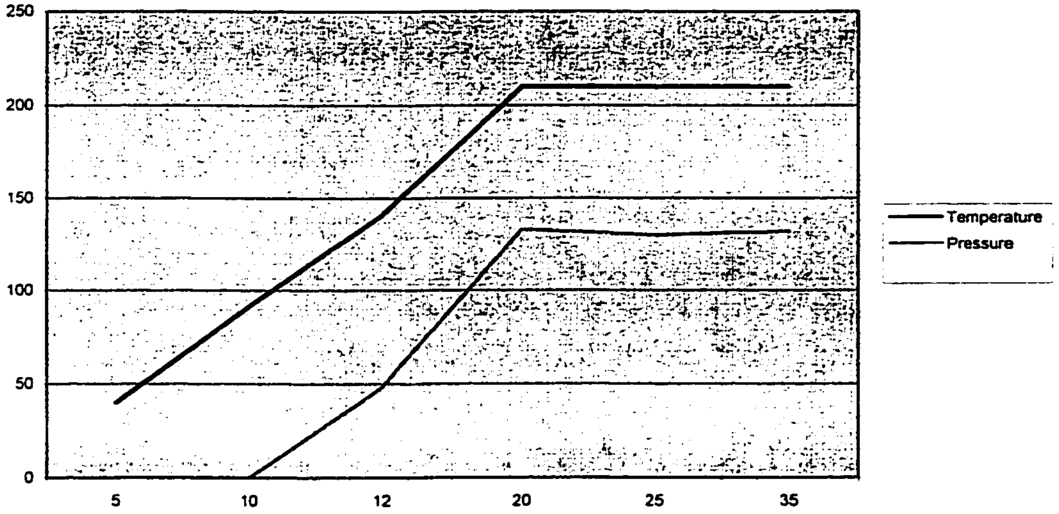
APPENDICES

Appendix A

Program 1 : 200 °C for 30 min

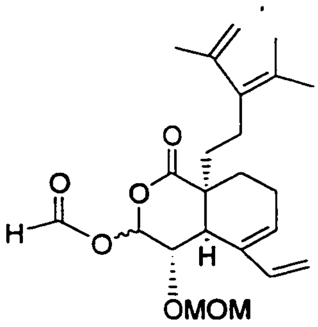


Program 2: 210 °C for 15 min



Appendix B

X Ray crystallographic data for compound **173b**



173b

Table 1. Crystal data and structure refinement for af008.

Identification code	af008
Empirical formula	C23 H32 O6
Formula weight	404.49
Temperature	238(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 11.433(6) A alpha = 90 deg. b = 7.769(4) A beta = 109.475(9) deg. c = 13.484(7) A gamma = 90 deg.
Volume	1129(1) A^3
Z, Calculated density	2, 1.190 Mg/m^3
Absorption coefficient	0.085 mm^-1
F(000)	436
Crystal size	0.4 x 0.1 x 0.05 mm
Theta range for data collection	1.60 to 21.97 deg.
Limiting indices	-12<=h<=11, -8<=k<=8, 0<=l<=14
Reflections collected / unique	8813 / 2744 [R(int) = 0.0521]
Completeness to theta = 21.97	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2744 / 1 / 263
Goodness-of-fit on F^2	1.098
Final R indices [I>2sigma(I)]	R1 = 0.0421, wR2 = 0.0899
R indices (all data)	R1 = 0.0537, wR2 = 0.0938
Absolute structure parameter	-0.2(14)
Extinction coefficient	0.029(3)
Largest diff. peak and hole	0.144 and -0.150 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for af008.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	6311(2)	9660(3)	425(2)	45(1)
O(2)	6926(2)	7015(3)	486(2)	59(1)
O(3)	7187(2)	12344(3)	908(2)	44(1)
O(4)	6143(3)	13255(4)	-742(2)	66(1)
O(5)	6114(2)	12668(3)	2458(2)	41(1)
O(6)	4392(2)	12153(4)	2988(2)	53(1)
C(1)	6899(3)	8280(5)	993(3)	41(1)
C(2)	7448(3)	8325(4)	2195(2)	34(1)
C(3)	7478(3)	10157(4)	2655(2)	33(1)
C(4)	6241(3)	11021(4)	2034(3)	35(1)
C(5)	6181(3)	11256(4)	907(3)	40(1)
C(6)	7014(4)	13305(5)	29(3)	47(1)
C(7)	4860(3)	13085(5)	2317(3)	50(1)
C(8)	4974(3)	12586(6)	4057(3)	70(1)
C(9)	7759(3)	10107(4)	3832(3)	40(1)
C(10)	7505(3)	8711(5)	4310(3)	51(1)
C(11)	7006(3)	7046(5)	3773(3)	54(1)
C(12)	6605(3)	7137(4)	2576(3)	44(1)
C(13)	8421(3)	11551(5)	4482(3)	52(1)
C(14)	8887(3)	12919(5)	4173(3)	59(1)
C(15)	8757(3)	7549(5)	2492(3)	39(1)
C(16)	9624(3)	8396(5)	1991(3)	50(1)
C(17)	10845(3)	7471(5)	2221(3)	46(1)
C(18)	10775(4)	5769(6)	1693(4)	66(1)
C(19)	10453(6)	5803(8)	548(4)	128(2)
C(20)	10914(6)	4282(6)	2223(5)	121(2)
C(21)	11918(3)	8125(5)	2860(3)	52(1)
C(22)	13159(3)	7273(8)	3034(4)	92(2)
C(23)	12036(4)	9788(6)	3462(4)	76(1)

Table 3. Bond lengths [A] and angles [deg] for af008.

O(1)-C(1)	1.358(4)
O(1)-C(5)	1.431(4)
O(2)-C(1)	1.204(4)
O(3)-C(6)	1.358(4)
O(3)-C(5)	1.427(4)
O(4)-C(6)	1.176(4)
O(5)-C(7)	1.420(4)
O(5)-C(4)	1.429(4)
O(6)-C(7)	1.397(4)
O(6)-C(8)	1.412(4)
C(1)-C(2)	1.530(5)
C(2)-C(15)	1.538(4)
C(2)-C(12)	1.541(4)
C(2)-C(3)	1.549(4)
C(3)-C(9)	1.510(5)
C(3)-C(4)	1.537(5)
C(4)-C(5)	1.510(5)
C(9)-C(10)	1.342(5)
C(9)-C(13)	1.469(5)
C(10)-C(11)	1.500(5)
C(11)-C(12)	1.524(5)
C(13)-C(14)	1.318(5)
C(15)-C(16)	1.522(5)
C(16)-C(17)	1.507(5)
C(17)-C(21)	1.342(5)
C(17)-C(18)	1.492(6)
C(18)-C(20)	1.340(6)
C(18)-C(19)	1.463(6)
C(21)-C(23)	1.508(5)
C(21)-C(22)	1.511(5)

C(1)-O(1)-C(5)	122.4(3)
C(6)-O(3)-C(5)	116.2(3)
C(7)-O(5)-C(4)	112.5(2)
C(7)-O(6)-C(8)	112.7(3)
O(2)-C(1)-O(1)	115.2(3)
O(2)-C(1)-C(2)	122.7(3)
O(1)-C(1)-C(2)	122.0(3)
C(1)-C(2)-C(15)	106.7(3)
C(1)-C(2)-C(12)	105.0(3)
C(15)-C(2)-C(12)	109.9(3)
C(1)-C(2)-C(3)	113.1(3)
C(15)-C(2)-C(3)	111.5(2)
C(12)-C(2)-C(3)	110.4(3)
C(9)-C(3)-C(4)	114.7(3)
C(9)-C(3)-C(2)	111.5(3)
C(4)-C(3)-C(2)	106.8(3)
O(5)-C(4)-C(5)	108.5(3)
O(5)-C(4)-C(3)	111.7(3)
C(5)-C(4)-C(3)	109.1(3)
O(3)-C(5)-O(1)	108.0(3)
O(3)-C(5)-C(4)	107.7(3)
O(1)-C(5)-C(4)	112.0(3)
O(4)-C(6)-O(3)	125.9(4)
O(6)-C(7)-O(5)	112.5(3)
C(10)-C(9)-C(13)	118.8(4)

C(10)-C(9)-C(3)	121.4(3)
C(13)-C(9)-C(3)	119.6(3)
C(9)-C(10)-C(11)	125.0(3)
C(10)-C(11)-C(12)	113.7(3)
C(11)-C(12)-C(2)	112.4(3)
C(14)-C(13)-C(9)	127.5(4)
C(16)-C(15)-C(2)	115.8(3)
C(17)-C(16)-C(15)	113.5(3)
C(21)-C(17)-C(18)	122.3(3)
C(21)-C(17)-C(16)	122.5(3)
C(18)-C(17)-C(16)	115.2(3)
C(20)-C(18)-C(19)	121.4(5)
C(20)-C(18)-C(17)	122.1(4)
C(19)-C(18)-C(17)	116.3(4)
C(17)-C(21)-C(23)	124.7(3)
C(17)-C(21)-C(22)	123.0(4)
C(23)-C(21)-C(22)	112.3(4)

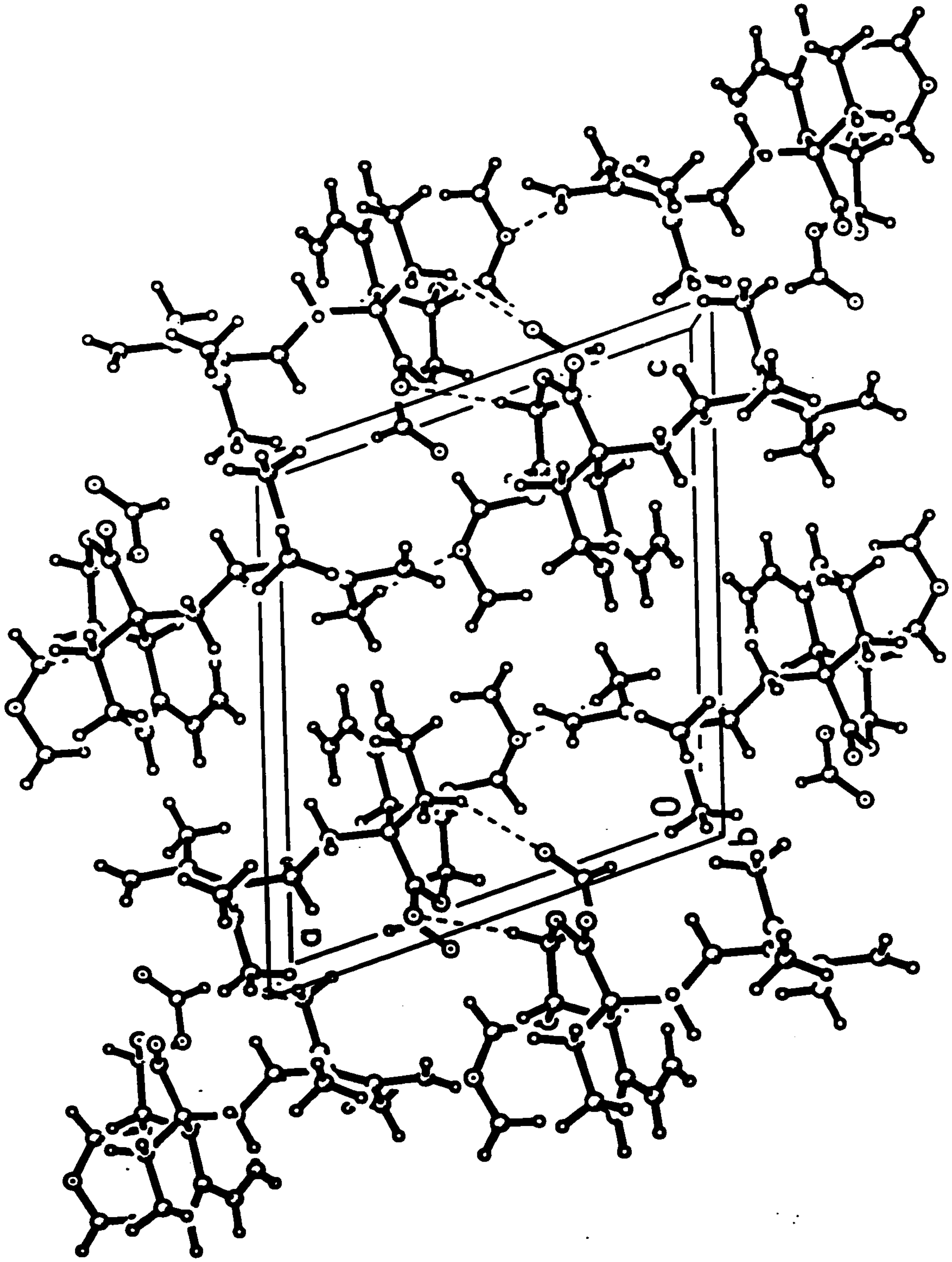
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for af008. 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)	52(2)	42(2)	37(2)	-2(1)	11(1)	4(1)
O(2)	69(2)	47(2)	52(2)	-16(2)	9(1)	10(2)
O(3)	44(1)	45(2)	42(2)	8(1)	12(1)	-2(1)
O(4)	70(2)	79(2)	44(2)	20(2)	12(2)	8(2)
O(5)	34(1)	34(1)	54(2)	-2(1)	16(1)	3(1)
O(6)	44(1)	65(2)	56(2)	0(2)	23(1)	-5(1)
C(1)	33(2)	41(2)	46(2)	3(2)	9(2)	1(2)
C(2)	32(2)	28(2)	41(2)	-1(2)	9(2)	1(2)
C(3)	32(2)	32(2)	31(2)	3(2)	6(2)	-2(2)
C(4)	37(2)	29(2)	37(2)	-3(2)	12(2)	2(2)
C(5)	33(2)	42(2)	42(3)	1(2)	10(2)	3(2)
C(6)	57(2)	37(2)	53(3)	6(2)	26(2)	8(2)
C(7)	44(2)	50(2)	58(3)	1(2)	21(2)	8(2)
C(8)	66(2)	91(3)	56(3)	-8(3)	26(2)	2(3)
C(9)	39(2)	39(2)	39(3)	0(2)	9(2)	7(2)
C(10)	56(2)	61(3)	36(2)	8(2)	18(2)	12(2)
C(11)	62(2)	44(2)	65(3)	11(2)	35(2)	-2(2)
C(12)	43(2)	32(2)	57(3)	5(2)	17(2)	0(2)
C(13)	48(2)	63(3)	39(3)	-8(2)	7(2)	6(2)
C(14)	59(2)	56(3)	54(3)	-17(2)	8(2)	-7(2)
C(15)	44(2)	35(2)	36(2)	3(2)	10(2)	9(2)
C(16)	42(2)	54(2)	60(3)	5(2)	24(2)	8(2)
C(17)	46(2)	50(2)	47(2)	6(2)	21(2)	10(2)
C(18)	79(3)	64(3)	64(3)	-12(3)	37(3)	10(2)
C(19)	219(7)	108(5)	82(5)	-27(4)	84(5)	-49(5)
C(20)	213(7)	55(3)	89(5)	0(3)	40(4)	52(4)
C(21)	43(2)	69(3)	49(2)	6(2)	24(2)	9(2)
C(22)	57(3)	134(5)	85(3)	15(4)	21(2)	29(3)
C(23)	65(3)	86(3)	78(4)	-2(3)	26(2)	-16(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for af008.

	x	y	z	U(eq)
H(3A)	8152	10807	2516	39
H(4A)	5548	10271	2053	41
H(5A)	5384	11805	498	48
H(6A)	7648	14082	37	57
H(7A)	4799	14318	2446	60
H(7B)	4351	12851	1586	60
H(8A)	4605	11925	4487	105
H(8B)	4864	13804	4155	105
H(8C)	5852	12325	4263	105
H(10A)	7652	8782	5037	61
H(11A)	6292	6697	3975	64
H(11B)	7644	6156	4022	64
H(12A)	5750	7561	2300	53
H(12B)	6620	5977	2296	53
H(13A)	8523	11492	5203	62
H(14A)	8812	13048	3462	71
H(14B)	9294	13767	4665	71
H(15A)	9145	7610	3258	47
H(15B)	8678	6329	2296	47
H(16A)	9209	8441	1228	60
H(16B)	9784	9582	2247	60
H(19A)	10437	4636	288	192
H(19B)	11067	6470	362	192
H(19C)	9642	6324	236	192
H(20A)	10804	3230	1858	146
H(20B)	11121	4290	2958	146
H(22A)	13038	6213	2632	139
H(22B)	13548	7018	3776	139
H(22C)	13687	8042	2806	139
H(23A)	11219	10274	3340	114
H(23B)	12537	10593	3227	114
H(23C)	12430	9566	4208	114


c
0
b
a

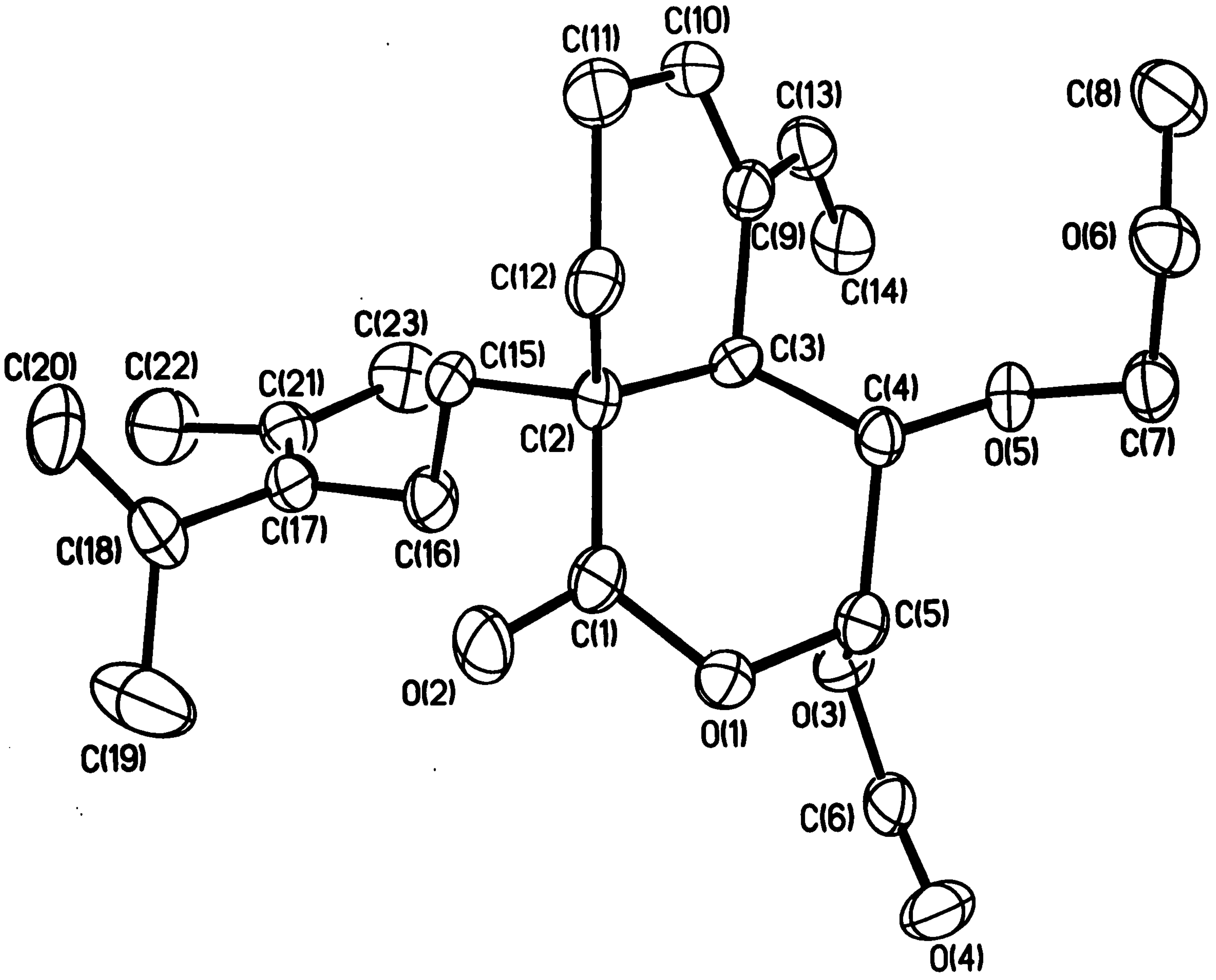

C(11)
C(10)
C(13)
C(8)
C(9)
O(6)
C(12)
C(14)
C(23)
C(15)
C(3)
C(20)
C(22)
C(21)
C(4)
C(2)
O(5)
C(7)
C(18)
C(17)
C(16)
C(1)
C(5)
O(2)
O(1)
O(3)
C(19)
C(6)
O(4)

Table 6. Observed and calculated structure factors for af008

h	k	l	10Fo	10Fc	10s
0	-8	0	97	100	6
1	-8	0	40	46	8
2	-8	0	35	44	10
1	-7	0	118	122	4
2	-7	0	131	131	6
3	-7	0	55	59	6
4	-7	0	76	73	5
5	-7	0	6	13	5
0	-6	0	43	35	12
1	-6	0	28	28	10
2	-6	0	162	163	4
3	-6	0	65	59	6
4	-6	0	184	188	4
5	-6	0	88	91	4
6	-6	0	49	45	6
7	-6	0	71	67	5
1	-5	0	147	148	3
2	-5	0	104	101	3
3	-5	0	205	195	3
4	-5	0	90	92	4
5	-5	0	200	189	4
6	-5	0	38	35	10
7	-5	0	24	26	23
8	-5	0	0	9	1
0	-4	0	302	296	7
1	-4	0	144	146	2
2	-4	0	84	89	2
3	-4	0	60	62	3
4	-4	0	43	39	5
5	-4	0	92	90	3
6	-4	0	78	76	4
7	-4	0	54	62	7
8	-4	0	70	66	5
9	-4	0	75	71	7
1	-3	0	193	195	3
2	-3	0	233	233	3
3	-3	0	99	99	2
4	-3	0	65	65	3
5	-3	0	92	80	3
6	-3	0	44	43	5
7	-3	0	98	94	2
8	-3	0	68	68	4
9	-3	0	51	45	5
10	-3	0	44	43	5
0	-2	0	981	939	22
1	-2	0	425	428	5
2	-2	0	53	52	3
3	-2	0	172	167	2
4	-2	0	234	215	3
5	-2	0	321	330	3
6	-2	0	87	90	2
7	-2	0	170	177	2
8	-2	0	93	88	2
9	-2	0	38	43	5
10	-2	0	87	87	3
11	-2	0	33	32	7
1	-1	0	479	465	6
2	-1	0	83	82	2
3	-1	0	252	255	4
4	-1	0	150	152	3
5	-1	0	243	247	4
6	-1	0	248	244	4
7	-1	0	207	211	4
8	-1	0	79	73	4
9	-1	0	136	137	4
10	-1	0	134	136	5
11	-1	0	65	72	5
1	0	0	335	335	7
2	0	0	439	451	10
3	0	0	359	377	6
4	0	0	137	142	2
5	0	0	165	187	3
6	0	0	110	113	2
7	0	0	60	65	4
8	0	0	81	87	4
9	0	0	86	88	4
10	0	0	60	60	4
11	0	0	13	3	12
1	1	0	454	465	6
2	1	0	82	82	2
3	1	0	252	255	3
4	1	0	154	151	2
5	1	0	253	247	3
6	1	0	248	244	3
7	1	0	204	211	4
8	1	0	80	73	4
9	1	0	136	137	4
10	1	0	130	136	4
11	1	0	72	72	4
0	2	0	1076	939	24
1	2	0	421	428	5
2	2	0	53	52	4
3	2	0	173	167	2
4	2	0	224	215	3
5	2	0	338	330	4
6	2	0	90	91	3
7	2	0	177	177	6
8	2	0	97	88	6
9	2	0	37	43	11
10	2	0	91	87	6
11	2	0	30	32	17
1	3	0	199	195	3
2	3	0	219	233	13
3	3	0	96	99	2
4	3	0	65	65	3
5	3	0	83	80	3
6	3	0	45	43	5
7	3	0	96	94	6
8	3	0	66	68	7
9	3	0	45	45	9
10	3	0	51	43	9
0	4	0	297	296	7
1	4	0	148	146	3
2	4	0	87	89	3
3	4	0	62	62	4
4	4	0	41	39	6
5	4	0	98	90	3
6	4	0	77	76	3
7	4	0	57	62	9
8	4	0	74	66	6
9	4	0	73	71	7
1	5	0	154	148	4
2	5	0	101	101	4
3	5	0	197	195	4
4	5	0	89	92	3
5	5	0	187	189	3
6	5	0	38	35	7
7	5	0	23	26	22
8	5	0	0	9	1
0	6	0	43	35	20
1	6	0	34	28	18
2	6	0	162	163	4
3	6	0	58	59	8
4	6	0	180	188	3
5	6	0	88	91	3
6	6	0	51	45	5
7	6	0	71	67	5
1	7	0	123	122	4
2	7	0	136	131	4
3	7	0	57	59	7
4	7	0	74	73	5
5	7	0	0	13	1
0	8	0	91	100	7
1	8	0	49	46	8
2	8	0	45	44	9
-2	-8	1	15	20	15
-1	-8	1	39	44	9
0	-8	1	95	95	4
1	-8	1	47	48	8
-6	-7	1	17	25	16
-5	-7	1	81	73	4
-4	-7	1	11	9	11
-3	-7	1	99	100	4
-2	-7	1	89	88	4
-1	-7	1	40	40	9
0	-7	1	147	153	3
1	-7	1	153	149	4
2	-7	1	12	16	11
3	-7	1	98	95	4
4	-7	1	11	19	11
5	-7	1	70	70	5
-7	-6	1	0	16	1
-6	-6	1	66	69	5
-5	-6	1	172	161	4
-4	-6	1	101	97	4
-3	-6	1	122	125	4
-2	-6	1	74	69	4
-1	-6	1	112	112	3
0	-6	1	40	43	6
1	-6	1	118	118	4
2	-6	1	87	91	4
3	-6	1	153	156	4
4	-6	1	87	82	5
5	-6	1	87	84	4
6	-6	1	7	16	7
7	-6	1	79	71	5
-9	-5	1	68	72	5
-8	-5	1	71	69	4
-7	-5	1	111	105	4
-6	-5	1	184	181	4
-5	-5	1	97	101	4
-4	-5	1	147	145	3
-3	-5	1	103	104	3
-2	-5	1	67	60	3
-1	-5	1	156	157	3
0	-5	1	111	112	3
1	-5	1	116	116	3
2	-5	1	168	172	3
3	-5	1	82	80	5
4	-5	1	130	126	4
5	-5	1	37	27	11
6	-5	1	49	46	7
7	-5	1	27	25	12
8	-5	1	37	28	9
-10	-4	1	57	56	6
-9	-4	1	53	61	6
-8	-4	1	67	68	5
-7	-4	1	157	153	4
-6	-4	1	21	19	21
-5	-4	1	75	79	3
-4	-4	1	38	37	6
-3	-4	1	52	50	4
-2	-4	1	65	70	3
-1	-4	1	63	65	3
0	-4	1	105	108	3
1	-4	1	91	86	2
2	-4	1	115	116	2
3	-4	1	58	60	3
4	-4	1	51	41	6
5	-4	1	106	108	4
6	-4	1	25	24	24
7	-4	1	39	39	9
8	-4	1	14	17	14
9	-4	1	10	5	10
-10	-3	1	12	13	11
-9	-3	1	57	56	4
-8	-3	1	71	76	3
-7	-3	1	83	76	3
-6	-3	1	122	118	3
-5	-3	1	212	208	3
-4	-3	1	117	114	2
-3	-3	1	103	105	2
-2	-3	1	191	195	3
-1	-3	1	164	167	2
0	-3	1	74	69	3
1	-3	1	239	232	3
2	-3	1	203	198	3
3	-3	1	21	28	10
4	-3	1	155	156	2
5	-3	1	74	73	3
6	-3	1	43	42	4
7	-3	1	54	57	5
8	-3	1	16	14	15
9	-3	1	39	37	6
10	-3	1	56	53	4
-11	-2	1	64	69	4
-10	-2	1	53	50	4
-9	-2	1	17	23	17
-8	-2	1	157	151	2
-7	-2	1	129	129	2
-6	-2	1	147	144	2
-5	-2	1	213	210	2
-4	-2	1	204	203	2
-3	-2	1	92	93	2
-2	-2	1	501	496	6
-1	-2	1	203	197	3
0	-2	1	40	42	8
1	-2	1	282	285	5
2	-2	1	227	238	3
3	-2	1	144	146	2
4	-2	1	360	366	4
5	-2	1	242	232	3
6	-2	1	76	74	2
7	-2	1	65	44	4
8	-2	1	25	23	9
9	-2	1	18	14	17
10	-2	1	52	56	4
-11	-1	1	64	58	4
-10	-1	1	94	86	4
-9	-1	1	65	65	5
-8	-1	1	155	149	4
-7	-1	1	76	79	4
-6	-1	1	33	38	8
-5	-1	1	390	394	6
-4	-1	1	226	232	4
-3	-1	1	456	479	5
-2	-1	1	431	457	4
0	-1	1	444	457	7
1	-1	1	598	631	7
2	-1	1	770	771	13
3	-1	1	387	380	6
4	-1	1	46	44	4
5	-1	1	270	274	5
6	-1	1	165	169	3
7	-1	1	120	127	3
8	-1	1	91	90	4
9	-1	1	96	87	3
10	-1	1	75	74	4
-11	0	1	0	9	1
-10	0	1	28	35	9
-9	0	1	273	273	7
-8	0	1	152	148	5
-7	0	1	213	224	10
-6	0	1	74	75	3
-5	0	1	79	79	3
-4	0	1	458	450	8
-3	0	1	1084	1084	18
-2	0	1	505	524	8
-1	0	1	827	745	14
0	0	1	345	342	8
1	0	1	302	347	5
2	0	1	325	322	5
3	0	1	457	483	7
4	0	1	20	14	9
5	0	1	142	153	2
6	0	1	48	47	4
7	0	1	171	165	4
8	0	1	107	113	3
9	0	1	43	48	6
10	0	1	57	55	5
11	0	1	50	50	6
-11	1	1	70	58	4
-10	1	1	92	86	4
-9	1	1	66	65	5
-8	1	1	154	149	4
-7	1	1	75	79	4
-6	1	1	31	38	5
-5	1	1	417	394	5
-4	1	1	244	232	3
-3	1	1	489	479	6
-2	1	1	455	457	6
-1	1	1	435	433	7
0	1	1	447	457	6
1	1	1	650	631	11
2	1	1	784	771	10
3	1	1	380	380	5
4	1	1	46	44	3
5	1	1	279	274	5
6	1	1	175	169	3
7	1	1	122	127	3
8	1	1	90	90	4
9	1	1	79	87	4
10	1	1	56	74	6
-11	2	1	70	69	6
-10	2	1	49	50	8
-9	2	1	13	23	13
-8	2	1	164	151	6
-7	2	1	126	129	5
-6	2	1	150	144	2
-5	2	1	215	210	3
-4	2	1	210	203	3
-3	2	1	94	93	2
-2	2	1	505	496	7
-1	2	1	196	197	3
0	2	1	39	42	5
1	2	1	272	285	4
2	2	1	231	238	3
3	2	1	149	146	2
4	2	1	365	366	5
5	2	1	234	232	4
6	2	1	80	74	3
7	2	1	37	44	11
8	2	1	13	23	12
9	2	1	0	14	1
10	2	1	62	56	7
-10	3	1	0	13	1
-9	3	1	61	56	7
-8	3	1	69	76	7
-7	3	1	77	76	6
-6	3	1	118	118	2
-5	3	1	217	208	3
-4	3	1	118	114	2
-3	3	1	97	105	2
-2	3	1	192	195	4
-1	3	1	169	167	3
0	3	1	77	69	3
1	3	1	233	232	4
2	3	1	191	197	11
3	3	1	21	28	13
4	3	1	155	156	2
5	3	1	75	73	3
6	3	1	39	42	5
7	3	1	58	57	8
8	3	1	19	14	19
9	3	1	46	37	9
10	3	1	60	54	8
-10	4	1	52	56	9
-9	4	1	58	61	7
-8	4	1	62	68	7
-7	4	1	156	153	6
-6	4	1	24	19	14
-5	4	1	83	79	3
-4	4	1	44	37	6
-3	4	1	49	51	4
-2	4	1	69	70	3
-1	4	1	70	65	3
0	4	1	104	108	3
1	4	1	94	86	4
2	4	1	115	116	3
3	4	1	60	61	3
4	4	1	44	41	5
5	4	1	105	108	3
6	4	1	27	24	9
7	4	1	33	39	15
8	4	1	16	17	16
9	4	1	0	5	1
-9	5	1	69	72	7
-8	5	1	69	69	7
-7	5	1	100	105	4
-6	5	1	186	181	3
-5	5	1	96	101	3
-4	5	1	148	145	3
-3	5	1	108	104	3
-2	5	1	61	60	5
-1	5	1	165	157	4
0	5	1	112	112	4
1	5	1	124	116	4
2	5	1	181	172	4
3	5	1	81	80	4
4	5	1	130	126	3
5	5	1	21	27	21
6	5	1	47	46	5
7	5	1	33	25	13
8	5	1	47	28	9
-7	6	1	30	16	12
-6	6	1	70	69	4
-5	6	1	163	161	3
-4	6	1	98	97	3
-3	6	1	123	125	3
-2	6	1	69	68	7
-1	6	1	119	112	4
0	6	1	45	43	11
1	6	1	119	117	4
2	6	1	89	92	5
3	6	1	158	156	4
4	6	1	82	82	5
5	6	1	84	84	3
6	6	1	3	17	2
7	6	1	73	71	7
-6	7	1	29	25	10
-5	7	1	75	73	4
-4	7	1	8	9	8
-3	7	1	98	100	4
-2	7	1	85	88	5
-1	7	1	36	40	14
0	7	1	157	153	4
1	7	1	152	149	4
2	7	1	29	16	16
3	7	1	100	95	4
4	7	1	17	19	16
5	7	1	76	70	5
-2	8	1	29	20	20
-1	8	1	46	44	9
0	8	1	99	95	5
1	8	1	42	48	10

Table 6. Observed and calculated structure factors for af008

h	k	l	10Fo	10Fc	10s
-2	-8	2	32	25	13
-1	-8	2	70	73	5
0	-8	2	27	25	17
1	-8	2	27	34	11
-6	-7	2	40	34	9
-5	-7	2	20	16	20
-4	-7	2	34	36	11
-3	-7	2	55	61	6
-2	-7	2	136	132	4
-1	-7	2	48	48	5
0	-7	2	96	94	3
1	-7	2	30	20	15
2	-7	2	66	67	5
3	-7	2	85	84	5
4	-7	2	42	38	8
5	-7	2	45	43	7
-8	-6	2	0	7	1
-7	-6	2	54	43	6
-6	-6	2	77	73	4
-5	-6	2	51	45	7
-4	-6	2	242	238	5
-3	-6	2	58	58	4
-2	-6	2	63	65	4
-1	-6	2	50	44	5
0	-6	2	101	105	3
1	-6	2	52	49	8
2	-6	2	71	69	6
3	-6	2	71	74	5
4	-6	2	124	119	4
5	-6	2	0	2	1
6	-6	2	76	74	4
-9	-5	2	36	38	9
-8	-5	2	80	80	4
-7	-5	2	111	112	4
-6	-5	2	92	93	4
-5	-5	2	183	187	3
-4	-5	2	75	76	4
-3	-5	2	183	185	3
-2	-5	2	43	40	5
-1	-5	2	82	83	3
0	-5	2	38	35	9
1	-5	2	124	123	4
2	-5	2	170	165	4
3	-5	2	86	84	4
4	-5	2	63	63	5
5	-5	2	36	34	11
6	-5	2	123	126	4
7	-5	2	32	30	10
8	-5	2	8	14	7
-10	-4	2	12	19	12
-9	-4	2	77	79	4
-8	-4	2	114	113	4
-7	-4	2	58	60	4
-6	-4	2	111	111	3
-5	-4	2	51	46	5
-4	-4	2	110	110	3
-3	-4	2	164	162	3
-2	-4	2	50	49	4
-1	-4	2	91	101	2
0	-4	2	264	261	4
1	-4	2	63	56	3
2	-4	2	81	85	2
3	-4	2	52	54	6
4	-4	2	57	55	6
5	-4	2	61	65	6
6	-4	2	10	7	9
7	-4	2	82	83	4
8	-4	2	32	37	9
9	-4	2	60	59	5
-10	-3	2	60	59	4
-9	-3	2	47	51	4
-8	-3	2	89	92	3
-7	-3	2	40	43	6
-6	-3	2	79	79	3
-5	-3	2	58	58	3
-4	-3	2	184	179	3
-3	-3	2	128	131	2
-2	-3	2	187	183	3
-1	-3	2	164	163	2
0	-3	2	295	295	5
1	-3	2	79	78	2
2	-3	2	220	216	3
3	-3	2	165	166	2
4	-3	2	198	193	3
5	-3	2	60	63	5
6	-3	2	79	77	3
7	-3	2	61	59	4
8	-3	2	25	27	11
9	-3	2	73	74	3
-11	-2	2	38	37	5
-10	-2	2	36	34	5
-9	-2	2	83	79	3
-8	-2	2	51	45	4
-7	-2	2	124	126	2
-6	-2	2	109	112	2
-5	-2	2	310	317	3
-4	-2	2	270	246	4
-3	-2	2	324	327	4
-2	-2	2	426	428	5
-1	-2	2	227	236	3
0	-2	2	253	256	4
1	-2	2	318	322	5
2	-2	2	256	265	4
3	-2	2	201	192	2
4	-2	2	276	267	3
5	-2	2	41	38	3
6	-2	2	83	83	2
7	-2	2	154	153	2
8	-2	2	0	5	1
9	-2	2	42	40	5
10	-2	2	35	40	7
-11	-1	2	28	20	12
-10	-1	2	65	68	5
-9	-1	2	93	100	4
-8	-1	2	60	61	5
-7	-1	2	94	93	3
-6	-1	2	213	236	4
-5	-1	2	197	229	12
-4	-1	2	378	383	4
-3	-1	2	429	462	10
-2	-1	2	254	258	3
-1	-1	2	387	405	5
0	-1	2	231	244	3
1	-1	2	282	315	4
2	-1	2	493	496	8
3	-1	2	209	208	4
4	-1	2	145	154	3
5	-1	2	136	132	3
6	-1	2	133	136	3
7	-1	2	18	13	17
8	-1	2	60	66	5
9	-1	2	132	125	4
10	-1	2	27	31	27
-11	0	2	51	60	5
-10	0	2	57	55	5
-9	0	2	24	29	23
-8	0	2	71	75	4
-7	0	2	37	47	7
-6	0	2	160	152	3
-5	0	2	12	1	12
-4	0	2	59	64	2
-3	0	2	399	372	7
-2	0	2	312	302	5
-1	0	2	256	244	6
0	0	2	539	538	9
1	0	2	97	105	3
2	0	2	688	689	11
3	0	2	47	52	4
4	0	2	77	68	2
5	0	2	84	85	2
6	0	2	84	79	2
7	0	2	186	180	4
8	0	2	41	42	7
9	0	2	50	58	5
10	0	2	0	9	1
-11	1	2	26	21	13
-10	1	2	71	68	5
-9	1	2	96	100	4
-8	1	2	58	61	6
-7	1	2	92	93	4
-6	1	2	229	236	3
-5	1	2	244	229	3
-4	1	2	385	383	5
-3	1	2	480	462	6
-2	1	2	247	258	3
-1	1	2	394	405	5
0	1	2	234	244	3
1	1	2	325	316	7
2	1	2	510	496	7
3	1	2	206	208	3
4	1	2	151	154	2
5	1	2	130	132	3
6	1	2	134	136	3
7	1	2	24	13	13
8	1	2	51	66	5
9	1	2	125	125	3
10	1	2	28	31	11
-11	2	2	41	37	11
-10	2	2	32	34	14
-9	2	2	79	79	7
-8	2	2	45	45	11
-7	2	2	120	126	5
-6	2	2	111	112	2
-5	2	2	310	317	4
-4	2	2	260	246	3
-3	2	2	313	327	4
-2	2	2	430	428	6
-1	2	2	234	236	3
0	2	2	258	256	3
1	2	2	331	322	5
2	2	2	264	266	3
3	2	2	193	192	3
4	2	2	281	267	5
5	2	2	44	38	5
6	2	2	82	83	3
7	2	2	158	153	4
8	2	2	0	5	1
9	2	2	45	40	9
10	2	2	43	40	11
-10	3	2	55	59	7
-9	3	2	37	51	11
-8	3	2	94	92	6
-7	3	2	46	43	10
-6	3	2	79	79	3
-5	3	2	58	57	4
-4	3	2	185	179	3
-3	3	2	126	131	2
-2	3	2	181	183	3
-1	3	2	160	162	2
0	3	2	300	295	4
1	3	2	81	78	3
2	3	2	204	216	15
3	3	2	167	166	3
4	3	2	193	193	3
5	3	2	54	63	3
6	3	2	81	77	4
7	3	2	58	59	8
8	3	2	23	27	22
9	3	2	72	74	6
-10	4	2	16	20	15
-9	4	2	85	79	6
-8	4	2	105	113	6
-7	4	2	63	60	5
-6	4	2	117	111	3
-5	4	2	54	47	5
-4	4	2	104	109	3
-3	4	2	162	162	3
-2	4	2	54	49	4
-1	4	2	100	101	2
0	4	2	255	261	4
1	4	2	63	56	4
2	4	2	78	85	4
3	4	2	53	53	4
4	4	2	53	55	4
5	4	2	66	65	3
6	4	2	10	7	9
7	4	2	75	83	6
8	4	2	30	37	15
9	4	2	65	59	7
-9	5	2	37	38	12
-8	5	2	78	80	6
-7	5	2	111	112	4
-6	5	2	91	93	3
-5	5	2	187	187	3
-4	5	2	73	76	4
-3	5	2	194	185	3
-2	5	2	38	40	7
-1	5	2	86	84	4
0	5	2	37	35	10
1	5	2	123	123	4
2	5	2	171	165	4
3	5	2	79	84	4
4	5	2	63	63	4
5	5	2	36	33	7
6	5	2	125	126	3
7	5	2	41	30	12
8	5	2	0	14	1
-8	6	2	13	7	12
-7	6	2	53	43	6
-6	6	2	82	73	3
-5	6	2	42	45	6
-4	6	2	240	238	5
-3	6	2	59	58	5
-2	6	2	62	65	7
-1	6	2	53	44	8
0	6	2	107	105	4
1	6	2	67	50	7
2	6	2	66	69	6
3	6	2	73	74	5
4	6	2	120	119	4
5	6	2	14	2	14
6	6	2	72	74	3
-6	7	2	37	34	7
-5	7	2	12	16	12
-4	7	2	32	36	9
-3	7	2	58	61	7
-2	7	2	135	132	4
-1	7	2	38	48	11
0	7	2	100	94	4
1	7	2	20	20	20
2	7	2	63	67	6
3	7	2	84	84	4
4	7	2	33	38	11
5	7	2	43	43	8
-2	8	2	22	25	21
-1	8	2	76	73	6
0	8	2	26	25	26
1	8	2	32	33	14
-6	-7	3	12	19	12
-5	-7	3	117	115	4
-4	-7	3	20	29	19
-3	-7	3	33	33	10
-2	-7	3	42	28	6
-1	-7	3	92	92	3
0	-7	3	75	72	3
1	-7	3	13	17	12
2	-7	3	0	8	1
3	-7	3	42	40	9
4	-7	3	31	26	14
-8	-6	3	51	53	7
-7	-6	3	80	78	4
-6	-6	3	58	52	7
-5	-6	3	135	137	4
-4	-6	3	17	18	16
-3	-6	3	68	67	4
-2	-6	3	31	27	9
-1	-6	3	74	72	4
0	-6	3	82	81	3
1	-6	3	41	33	10
2	-6	3	76	73	5
3	-6	3	56	61	7
4	-6	3	62	63	5
5	-6	3	92	91	4
6	-6	3	16	25	16
-9	-5	3	43	50	7
-8	-5	3	35	41	9
-7	-5	3	151	150	4
-6	-5	3	145	143	3
-5	-5	3	204	198	3
-4	-5	3	56	58	5
-3	-5	3	89	91	3
-2	-5	3	58	64	4
-1	-5	3	141	140	3
0	-5	3	2	4	2
1	-5	3	98	101	4
2	-5	3	77	70	4
3	-5	3	31	30	14
4	-5	3	96	100	4
5	-5	3	100	102	4
6	-5	3	19	19	18
7	-5	3	28	18	13
-10	-4	3	19	28	18
-9	-4	3	57	59	6
-8	-4	3	104	102	3
-7	-4	3	100	104	3
-6	-4	3	67	70	4
-5	-4	3	71	65	4
-4	-4	3	100	95	3
-3	-4	3	56	49	3
-2	-4	3	194	187	3
-1	-4	3	245	269	18
0	-4	3	276	273	5
1	-4	3	82	80	2
2	-4	3	112	117	3
3	-4	3	143	141	3
4	-4	3	63	64	5
5	-4	3	90	88	4
6	-4	3	17	22	17
7	-4	3	66	68	5
8	-4	3	63	64	4
-11	-3	3	45	41	5
-10	-3	3	53	59	3
-9	-3	3	105	112	3
-8	-3	3	49	44	5
-7	-3	3	65	61	4
-6	-3	3	54	56	4
-5	-3	3	295	292	4
-4	-3	3	119	117	2
-3	-3	3	74	70	3
-2	-3	3	172	183	9
-1	-3	3	504	493	7
0	-3	3	284	285	5
1	-3	3	269	264	4
2	-3	3	102	100	3
3	-3	3	100	99	3
4	-3	3	23	25	18
5	-3	3	58	59	3
6	-3	3	57	63	4
7	-3	3	28	29	10
8	-3	3	72	70	3
9	-3	3	32	34	7
-11	-2	3	44	41	4
-10	-2	3	51	54	3
-9	-2	3	125	129	3
-8	-2	3	183	187	2
-7	-2	3	100	94	2
-6	-2	3	328	324	3
-5	-2	3	349	350	5
-4	-2	3	213	332	49
-3	-2	3	299	342	6
-2	-2	3	260	263	3
-1	-2	3	284	309	4
0	-2	3	26	35	5
1	-2	3	67	68	3
2	-2	3	166	164	3
3	-2	3	133	132	2
4	-2	3	148	145	2
5	-2	3	61	66	2
6	-2	3	169	156	2
7	-2	3	165	163	3
8	-2	3	74	75	3
9	-2	3	64	62	4
-11	-1	3	67	66	4
-10	-1	3	39	40	6
-9	-1	3	40	62	8
-8	-1	3	34	38	8
-7	-1	3	133	133	3
-6	-1	3	123	119	3
-5	-1	3	156	159	2
-4	-1	3	202	207	2
-3	-1	3	446	464	6
-2	-1	3	189	188	2
-1	-1	3	620	624	8
0	-1	3	203	216	3
1	-1	3	335	347	4
3	-1	3	74	67	2
4	-1	3	122	119	3
5	-1	3	189	193	3
6	-1	3	12	17	12
7	-1	3	32	30	9
8	-1	3	40	43	7
9	-1	3	40	37	11
10	-1	3	52	48	9
-11	0	3	42	43	7
-10	0	3	87	84	4
-9	0	3	241	233	5
-8	0	3	44	53	7
-7	0	3	94	100	3
-6	0	3	368	395	6
-5	0	3	37	35	3
-4	0	3	71	81	3
-3	0	3	319	306	5
-2	0	3	475	466	8
-1	0	3	823	773	20
0	0	3	299	303	5
1	0	3	107	114	4
2	0	3	229	237	5
3	0	3	75	75	3
4	0	3	181	169	3
5	0	3	74	64	2
6	0	3	117	121	2
7	0	3	132	131	3
8	0	3	108	100	4
9	0	3	34	38	8
10	0	3	19	18	19

Table 6. Observed and calculated structure factors for af008

h	k	l	10Fo	10Fc	10s
-11	1	3	65	66	4
-10	1	3	48	41	6
-9	1	3	69	62	5
-8	1	3	46	38	8
-7	1	3	148	133	4
-6	1	3	113	119	2
-5	1	3	160	159	3
-4	1	3	196	207	3
-3	1	3	458	464	7
-2	1	3	188	188	3
-1	1	3	626	624	10
0	1	3	208	217	3
1	1	3	343	347	6
2	1	3	128	117	3
3	1	3	59	67	2
4	1	3	126	119	4
5	1	3	185	193	4
6	1	3	22	17	10
7	1	3	31	30	10
8	1	3	43	44	6
9	1	3	40	37	6
10	1	3	46	48	6
-11	2	3	44	41	10
-10	2	3	48	54	9
-9	2	3	121	129	6
-8	2	3	180	187	6
-7	2	3	99	94	6
-6	2	3	343	324	4
-5	2	3	346	350	4
-4	2	3	340	332	4
-3	2	3	344	341	4
-2	2	3	241	263	20
-1	2	3	309	310	4
0	2	3	34	35	4
1	2	3	71	68	3
2	2	3	163	164	4
3	2	3	138	133	3
4	2	3	150	145	3
5	2	3	67	66	4
6	2	3	162	156	3
7	2	3	173	163	4
8	2	3	79	75	4
9	2	3	74	62	7
-11	3	3	44	41	10
-10	3	3	54	59	7
-9	3	3	107	112	6
-8	3	3	53	44	10
-7	3	3	65	61	7
-6	3	3	58	56	4
-5	3	3	292	292	4
-4	3	3	113	118	2
-3	3	3	79	70	3
-2	3	3	182	183	3
-1	3	3	507	493	7
0	3	3	293	285	4
1	3	3	276	264	5
2	3	3	99	99	3
3	3	3	103	99	2
4	3	3	11	25	11
5	3	3	63	59	5
6	3	3	61	63	5
7	3	3	16	29	16
8	3	3	70	70	6
9	3	3	29	34	28
-10	4	3	25	28	25
-9	4	3	55	59	7
-8	4	3	106	102	6
-7	4	3	97	104	4
-6	4	3	61	70	4
-5	4	3	71	65	3
-4	4	3	98	95	3
-3	4	3	49	49	5
-2	4	3	191	187	3
-1	4	3	280	269	4
0	4	3	295	274	5
1	4	3	82	80	4
2	4	3	116	117	3
3	4	3	136	141	3
4	4	3	63	64	3
5	4	3	89	88	3
6	4	3	9	22	8
7	4	3	69	68	7
8	4	3	57	64	9
-9	5	3	43	50	9
-8	5	3	37	41	11
-7	5	3	147	150	4
-6	5	3	147	143	3
-5	5	3	196	198	3
-4	5	3	57	58	5
-3	5	3	89	91	3
-2	5	3	65	64	4
-1	5	3	147	140	3
0	5	3	0	4	1
1	5	3	100	101	4
2	5	3	76	70	4
3	5	3	30	31	12
4	5	3	97	100	4
5	5	3	98	101	3
6	5	3	23	19	11
7	5	3	21	18	21
-8	6	3	53	53	9
-7	6	3	77	78	4
-6	6	3	46	52	6
-5	6	3	133	137	3
-4	6	3	4	18	3
-3	6	3	69	67	4
-2	6	3	31	27	18
-1	6	3	70	72	6
0	6	3	84	81	5
1	6	3	33	33	14
2	6	3	73	73	5
3	6	3	64	61	6
4	6	3	56	63	5
5	6	3	93	91	4
6	6	3	29	24	12
-6	7	3	0	19	1
-5	7	3	113	115	3
-4	7	3	17	29	16
-3	7	3	33	33	13
-2	7	3	36	28	12
-1	7	3	96	92	4
0	7	3	85	72	5
1	7	3	0	17	1
2	7	3	5	8	4
3	7	3	34	39	11
4	7	3	16	26	16
-6	-7	4	96	97	4
-5	-7	4	0	9	1
-4	-7	4	78	82	4
-3	-7	4	63	62	4
-2	-7	4	66	71	3
-1	-7	4	43	39	5
0	-7	4	76	82	3
1	-7	4	50	46	4
2	-7	4	34	23	11
3	-7	4	58	56	7
-8	-6	4	25	31	21
-7	-6	4	23	20	23
-6	-6	4	24	27	23
-5	-6	4	25	21	13
-4	-6	4	122	124	3
-3	-6	4	60	55	4
-2	-6	4	64	65	4
-1	-6	4	30	29	8
0	-6	4	46	43	5
1	-6	4	65	66	4
2	-6	4	99	104	4
3	-6	4	22	17	22
4	-6	4	108	101	4
5	-6	4	66	69	5
-9	-5	4	31	37	11
-8	-5	4	65	64	5
-7	-5	4	54	53	5
-6	-5	4	89	90	3
-5	-5	4	99	102	3
-4	-5	4	63	62	4
-3	-5	4	35	35	7
-2	-5	4	85	81	3
-1	-5	4	114	116	3
0	-5	4	112	109	3
1	-5	4	85	86	4
2	-5	4	27	31	19
3	-5	4	74	72	5
4	-5	4	17	24	17
5	-5	4	57	56	6
6	-5	4	57	53	5
7	-5	4	81	81	4
-10	-4	4	41	36	7
-9	-4	4	69	69	3
-8	-4	4	51	54	5
-7	-4	4	45	42	6
-6	-4	4	116	108	3
-5	-4	4	23	22	22
-4	-4	4	338	331	5
-3	-4	4	129	126	2
-2	-4	4	174	172	3
-1	-4	4	216	211	3
0	-4	4	63	61	3
1	-4	4	197	188	4
2	-4	4	46	43	6
3	-4	4	44	41	7
4	-4	4	83	84	4
5	-4	4	56	44	6
6	-4	4	74	77	4
7	-4	4	61	63	5
8	-4	4	60	58	5
-11	-3	4	75	77	3
-10	-3	4	101	104	3
-9	-3	4	93	91	3
-8	-3	4	52	44	5
-7	-3	4	35	34	7
-6	-3	4	94	92	3
-5	-3	4	122	117	3
-4	-3	4	85	129	14
-3	-3	4	167	167	3
-2	-3	4	292	300	5
-1	-3	4	266	259	5
0	-3	4	45	49	4
1	-3	4	16	18	16
2	-3	4	68	65	3
3	-3	4	100	97	3
4	-3	4	30	30	11
5	-3	4	65	61	3
6	-3	4	129	127	3
7	-3	4	38	35	6
8	-3	4	6	7	6
-11	-2	4	67	64	3
-10	-2	4	45	45	4
-9	-2	4	114	112	2
-8	-2	4	45	51	4
-6	-2	4	70	74	3
-5	-2	4	128	121	2
-4	-2	4	300	292	4
-3	-2	4	125	122	2
-2	-2	4	66	63	2
-1	-2	4	145	139	2
0	-2	4	217	208	3
1	-2	4	119	124	3
2	-2	4	65	67	3
3	-2	4	234	246	3
4	-2	4	21	19	10
5	-2	4	119	121	2
6	-2	4	96	96	3
7	-2	4	34	33	7
8	-2	4	26	27	10
9	-2	4	39	44	6
-11	-1	4	89	85	6
-10	-1	4	140	139	4
-9	-1	4	121	118	4
-8	-1	4	55	50	5
-7	-1	4	184	175	3
-6	-1	4	191	194	2
-5	-1	4	49	44	2
-4	-1	4	341	335	4
-3	-1	4	85	89	2
-2	-1	4	93	94	2
-1	-1	4	132	135	2
0	-1	4	260	278	3
1	-1	4	226	223	5
2	-1	4	65	75	4
3	-1	4	4	33	4
4	-1	4	187	184	3
5	-1	4	45	49	5
6	-1	4	215	220	4
7	-1	4	35	30	8
8	-1	4	23	23	23
9	-1	4	88	88	6
-12	0	4	56	66	5
-11	0	4	18	2	18
-10	0	4	23	15	23
-9	0	4	48	40	6
-8	0	4	128	128	3
-7	0	4	0	1	1
-6	0	4	160	153	2
-5	0	4	102	97	3
-4	0	4	548	537	9
-3	0	4	139	144	5
-2	0	4	229	233	4
-1	0	4	174	183	3
0	0	4	446	452	7
1	0	4	173	178	3
2	0	4	0	20	1
3	0	4	37	38	7
4	0	4	130	126	3
5	0	4	24	27	10
6	0	4	90	82	3
7	0	4	2	2	2
8	0	4	26	26	12
9	0	4	49	49	6
-11	1	4	94	85	4
-10	1	4	139	139	4
-9	1	4	119	118	4
-8	1	4	54	50	6
-7	1	4	185	175	4
-6	1	4	193	194	3
-5	1	4	51	44	4
-4	1	4	342	335	6
-3	1	4	82	89	3
-2	1	4	84	94	9
-1	1	4	129	135	3
0	1	4	271	277	4
1	1	4	223	223	3
2	1	4	75	75	3
3	1	4	40	33	6
4	1	4	176	184	11
5	1	4	42	49	5
6	1	4	223	220	3
7	1	4	25	30	14
8	1	4	21	23	20
9	1	4	84	88	4
-11	2	4	58	64	8
-10	2	4	44	45	10
-9	2	4	123	112	7
-8	2	4	48	51	12
-7	2	4	174	164	6
-6	2	4	77	74	2
-5	2	4	124	121	2
-4	2	4	294	292	4
-3	2	4	122	122	2
-2	2	4	66	63	2
-1	2	4	137	139	2
0	2	4	230	208	4
1	2	4	123	124	2
2	2	4	60	67	2
3	2	4	256	246	6
4	2	4	14	19	14
5	2	4	121	120	3
6	2	4	97	97	3
7	2	4	38	33	9
8	2	4	32	28	9
9	2	4	11	44	11
-11	3	4	79	77	7
-10	3	4	104	104	6
-9	3	4	97	91	6
-8	3	4	52	44	9
-7	3	4	30	34	10
-6	3	4	92	92	3
-5	3	4	123	117	2
-4	3	4	132	129	2
-3	3	4	169	167	3
-2	3	4	303	300	4
-1	3	4	263	259	4
0	3	4	49	49	3
1	3	4	7	18	7
2	3	4	66	65	4
3	3	4	102	97	5
4	3	4	34	30	16
5	3	4	58	61	6
6	3	4	131	127	4
7	3	4	29	35	17
8	3	4	15	7	15
-10	4	4	35	36	12
-9	4	4	78	69	6
-8	4	4	56	54	8
-7	4	4	41	42	7
-6	4	4	110	108	3
-5	4	4	22	22	13
-4	4	4	334	331	4
-3	4	4	127	126	2
-2	4	4	180	172	3
-1	4	4	220	211	3
0	4	4	61	61	5
1	4	4	193	188	4
2	4	4	48	43	7
3	4	4	28	41	9
4	4	4	87	83	6
5	4	4	53	44	9
6	4	4	74	77	4
7	4	4	64	63	7
8	4	4	56	58	8
-9	5	4	27	37	27
-8	5	4	65	64	6
-7	5	4	52	53	5
-6	5	4	82	90	3
-5	5	4	98	102	3
-4	5	4	58	62	4
-3	5	4	33	35	8
-2	5	4	79	81	3
-1	5	4	113	116	4
0	5	4	111	109	4
1	5	4	86	86	4
2	5	4	31	31	13
3	5	4	76	72	4
4	5	4	15	24	14
5	5	4	62	55	6
6	5	4	47	53	8
-8	6	4	43	31	10
-7	6	4	20	20	20
-6	6	4	19	26	19
-5	6	4	29	21	9
-4	6	4	121	124	3
-3	6	4	58	55	7
-2	6	4	70	65	6
-1	6	4	27	29	24
0	6	4	39	43	11
1	6	4	61	66	5
2	6	4	98	104	4
3	6	4	18	17	18
4	6	4	98	101	4
5	6	4	71	69	4
-6	7	4	102	97	3
-5	7	4	0	9	1
-4	7	4	81	82	5
-3	7	4	61	62	6
-2	7	4	70	71	6
-1	7	4	34	39	11
0	7	4	79	82	7
1	7	4	51	46	7
2	7	4	25	23	24
3	7	4	58	56	6
-5	-7	5	56	57	6
-4	-7	5	68	68	3
-3	-7	5	103	109	3
-2	-7	5	27	7	10
-1	-7	5	54	56	4
0	-7	5	74	73	3
1	-7	5	59	63	4
2	-7	5	35	38	7
-8	-6	5	0	7	1
-7	-6	5	60	59	5
-6	-6	5	61	60	4
-5	-6	5	41	43	6
-4	-6	5	68	67	4
-3	-6	5	103	108	3
-2	-6	5	89	90	4
-1	-6	5	15	18	15
0	-6	5	37	31	6
1	-6	5	36	33	7
2	-6	5	26	25	18
3	-6	5	63	62	5
4	-6	5	87	87	4
5	-6	5	65	63	5
-9	-5	5	18	15	17
-8	-5	5	23	17	14
-7	-5	5	84	78	3
-6	-5	5	46	47	6
-5	-5	5	97	97	3
-4	-5	5	114	118	3
-3	-5	5	114	115	4
-2	-5	5	0	9	1
-1	-5	5	45	45	5
0	-5	5	37	35	7
1	-5	5	53	54	5
2	-5	5	68	67	6
3	-5	5	56	56	6
4	-5	5	149	153	4
5	-5	5	21	18	20
6	-5	5	139	140	4
-10	-4	5	61	54	4
-9	-4	5	19	16	18
-8	-4	5	13	5	13
-7	-4	5	115	108	3
-6	-4	5	14	2	14
-5	-4	5	158	154	5
-4	-4	5	72	102	10

Table 6. Observed and calculated structure factors for af008

h	k	l	10Fo	10Fc	10s
-3	-4	5	135	137	5
-2	-4	5	181	188	10
-1	-4	5	96	106	3
0	-4	5	88	91	3
1	-4	5	126	126	3
2	-4	5	112	119	3
3	-4	5	20	18	20
4	-4	5	67	64	5
5	-4	5	45	45	7
6	-4	5	59	62	5
7	-4	5	90	87	4
-11	-3	5	61	65	4
-10	-3	5	53	51	5
-9	-3	5	86	88	3
-8	-3	5	31	32	8
-7	-3	5	38	46	5
-6	-3	5	41	45	5
-5	-3	5	235	236	3
-4	-3	5	109	107	2
-3	-3	5	253	250	3
-2	-3	5	119	118	2
-1	-3	5	186	184	3
0	-3	5	24	16	10
1	-3	5	135	141	7
2	-3	5	81	83	3
3	-3	5	165	167	3
4	-3	5	106	117	3
5	-3	5	48	47	4
6	-3	5	84	88	3
7	-3	5	42	35	5
8	-3	5	60	61	4
-11	-2	5	29	34	6
-10	-2	5	58	85	5
-9	-2	5	63	66	3
-8	-2	5	42	50	4
-7	-2	5	129	128	3
-6	-2	5	149	144	3
-5	-2	5	179	181	3
-4	-2	5	143	136	2
-3	-2	5	160	158	2
-2	-2	5	166	164	2
-1	-2	5	90	87	2
0	-2	5	169	168	2
1	-2	5	159	163	3
2	-2	5	89	86	2
3	-2	5	86	91	3
4	-2	5	113	118	2
5	-2	5	119	125	2
6	-2	5	76	73	3
7	-2	5	33	29	7
8	-2	5	91	78	3
-11	-1	5	50	58	3
-10	-1	5	113	115	2
-9	-1	5	173	168	2
-8	-1	5	98	96	2
-7	-1	5	0	8	1
-6	-1	5	101	102	2
-5	-1	5	128	133	2
-4	-1	5	161	165	2
-3	-1	5	214	212	3
-2	-1	5	225	229	3
-1	-1	5	254	254	3
0	-1	5	117	120	1
1	-1	5	183	176	3
2	-1	5	114	120	4
3	-1	5	261	249	6
4	-1	5	0	42	1
5	-1	5	54	56	7
6	-1	5	128	131	3
7	-1	5	23	15	23
8	-1	5	105	103	5
9	-1	5	68	61	7
-12	0	5	16	5	15
-11	0	5	13	11	12
-10	0	5	0	2	1
-9	0	5	107	108	4
-8	0	5	104	101	4
-7	0	5	38	45	4
-6	0	5	52	50	3
-5	0	5	12	4	12
-4	0	5	91	87	3
-3	0	5	10	19	10
-2	0	5	386	361	10
-1	0	5	300	296	5
0	0	5	188	180	3
1	0	5	653	633	11
2	0	5	0	3	1
3	0	5	102	100	4
4	0	5	105	105	4
5	0	5	155	147	3
6	0	5	43	33	5
7	0	5	150	151	3
8	0	5	103	109	3
9	0	5	37	50	11
-11	1	5	56	58	8
-10	1	5	116	115	6
-9	1	5	168	168	6
-8	1	5	104	96	6
-7	1	5	0	8	1
-6	1	5	102	102	3
-5	1	5	132	132	3
-4	1	5	148	165	3
-3	1	5	202	212	4
-2	1	5	230	229	4
-1	1	5	269	254	5
0	1	5	120	120	3
1	1	5	180	176	2
2	1	5	118	120	2
3	1	5	264	249	4
4	1	5	41	42	6
5	1	5	41	56	5
6	1	5	132	131	3
7	1	5	15	15	14
8	1	5	98	103	3
9	1	5	58	61	5
-11	2	5	40	34	12
-10	2	5	91	85	6
-9	2	5	63	66	9
-8	2	5	40	50	13
-7	2	5	131	128	6
-6	2	5	149	144	3
-5	2	5	172	181	3
-4	2	5	131	136	3
-3	2	5	156	158	3
-2	2	5	165	164	3
-1	2	5	92	87	3
0	2	5	165	168	3
1	2	5	154	163	3
2	2	5	83	86	2
3	2	5	98	91	5
4	2	5	126	118	5
5	2	5	129	125	5
6	2	5	69	73	4
7	2	5	31	29	9
8	2	5	46	78	10
-11	3	5	58	65	8
-10	3	5	42	51	11
-9	3	5	91	88	6
-8	3	5	39	32	15
-7	3	5	40	46	5
-6	3	5	45	45	4
-5	3	5	234	236	3
-4	3	5	100	106	2
-3	3	5	236	250	14
-2	3	5	122	118	2
-1	3	5	189	184	3
0	3	5	24	16	8
1	3	5	146	141	5
2	3	5	93	83	5
3	3	5	169	167	5
4	3	5	117	117	5
5	3	5	50	48	10
6	3	5	93	88	6
7	3	5	50	35	9
8	3	5	62	61	8
-10	4	5	51	54	8
-9	4	5	30	16	17
-8	4	5	12	5	11
-7	4	5	105	108	3
-6	4	5	13	2	12
-5	4	5	155	154	3
-4	4	5	99	102	3
-3	4	5	137	137	3
-2	4	5	194	188	3
-1	4	5	108	106	2
0	4	5	92	91	4
1	4	5	132	125	3
2	4	5	115	119	4
3	4	5	10	18	10
4	4	5	71	64	7
5	4	5	51	45	9
6	4	5	68	62	6
-9	5	5	21	15	21
-8	5	5	17	17	16
-7	5	5	86	78	4
-6	5	5	46	47	5
-5	5	5	93	97	3
-4	5	5	120	118	4
-3	5	5	124	115	3
-2	5	5	10	9	9
-1	5	5	43	45	8
0	5	5	39	35	10
1	5	5	55	54	7
2	5	5	64	67	6
3	5	5	59	56	5
4	5	5	157	153	6
5	5	5	24	18	24
6	5	5	148	140	5
-8	6	5	9	7	9
-7	6	5	57	59	5
-6	6	5	53	60	5
-5	6	5	45	43	5
-4	6	5	67	67	5
-3	6	5	108	108	4
-2	6	5	87	90	4
-1	6	5	19	18	18
0	6	5	32	31	11
1	6	5	28	33	13
2	6	5	23	25	19
3	6	5	62	62	5
4	6	5	72	87	6
5	6	5	66	63	7
-5	7	5	52	57	6
-4	7	5	73	68	5
-3	7	5	106	109	4
-2	7	5	0	7	1
-1	7	5	62	56	6
0	7	5	75	73	5
1	7	5	60	63	5
2	7	5	35	38	9
-5	-7	6	14	20	14
-4	-7	6	47	48	7
-3	-7	6	72	73	3
-2	-7	6	40	47	6
-1	-7	6	86	89	3
0	-7	6	78	77	3
1	-7	6	54	57	4
-7	-6	6	76	68	5
-6	-6	6	77	77	5
-5	-6	6	82	81	3
-4	-6	6	95	98	3
-3	-6	6	20	20	19
-2	-6	6	71	75	3
-1	-6	6	34	31	7
0	-6	6	30	28	7
1	-6	6	39	45	6
2	-6	6	94	96	3
3	-6	6	43	45	8
4	-6	6	51	50	6
-9	-5	6	33	36	11
-8	-5	6	43	45	8
-7	-5	6	83	77	4
-6	-5	6	80	79	4
-5	-5	6	30	44	8
-4	-5	6	27	33	8
-3	-5	6	94	100	4
-2	-5	6	69	75	4
-1	-5	6	74	76	3
0	-5	6	58	64	4
1	-5	6	112	109	3
2	-5	6	42	50	8
3	-5	6	116	118	4
4	-5	6	53	45	6
5	-5	6	113	111	4
-10	-4	6	32	57	11
-9	-4	6	48	46	5
-8	-4	6	90	81	3
-7	-4	6	72	73	3
-6	-4	6	78	79	4
-5	-4	6	141	132	3
-4	-4	6	93	92	3
-3	-4	6	86	90	3
-2	-4	6	191	185	3
-1	-4	6	98	102	3
0	-4	6	130	135	3
1	-4	6	37	46	6
2	-4	6	114	117	3
3	-4	6	28	25	14
4	-4	6	51	51	6
5	-4	6	43	40	7
6	-4	6	83	80	4
-11	-3	6	25	28	24
-10	-3	6	58	57	4
-9	-3	6	24	27	10
-8	-3	6	38	35	7
-7	-3	6	47	40	5
-6	-3	6	86	82	3
-5	-3	6	51	53	4
-4	-3	6	20	26	19
-3	-3	6	133	136	2
-2	-3	6	110	106	2
-1	-3	6	138	138	2
0	-3	6	214	214	3
1	-3	6	96	93	2
2	-3	6	47	48	5
3	-3	6	13	29	12
4	-3	6	58	56	5
5	-3	6	94	96	3
6	-3	6	134	134	3
7	-3	6	78	76	3
-11	-2	6	27	27	8
-10	-2	6	128	127	2
-9	-2	6	122	129	3
-8	-2	6	155	159	3
-7	-2	6	64	66	3
-6	-2	6	102	96	2
-5	-2	6	48	47	3
-4	-2	6	143	142	2
-3	-2	6	105	102	2
-2	-2	6	224	225	3
-1	-2	6	64	65	2
0	-2	6	338	346	4
1	-2	6	131	134	2
2	-2	6	65	67	2
3	-2	6	52	59	3
4	-2	6	98	99	3
5	-2	6	105	107	2
6	-2	6	108	104	3
7	-2	6	53	49	4
8	-2	6	0	5	1
-11	-1	6	57	61	3
-10	-1	6	137	137	2
-9	-1	6	30	27	6
-8	-1	6	85	83	2
-7	-1	6	79	81	2
-6	-1	6	36	32	5
-5	-1	6	72	65	3
-4	-1	6	133	129	2
-3	-1	6	403	399	7
-2	-1	6	78	73	3
-1	-1	6	266	266	3
0	-1	6	210	209	2
1	-1	6	66	56	3
2	-1	6	53	54	5
3	-1	6	89	87	4
4	-1	6	107	102	5
6	-1	6	134	138	5
7	-1	6	145	155	5
8	-1	6	83	75	6
-11	0	6	31	31	11
-10	0	6	84	81	4
-9	0	6	101	93	4
-8	0	6	255	252	5
-7	0	6	56	52	3
-6	0	6	0	4	1
-5	0	6	72	70	2
-4	0	6	163	144	3
-3	0	6	9	11	8
-2	0	6	476	452	12
-1	0	6	0	13	1
0	0	6	624	626	10
1	0	6	400	387	7
2	0	6	149	163	3
3	0	6	72	60	5
4	0	6	40	43	7
5	0	6	53	65	6
6	0	6	70	73	4
7	0	6	27	26	17
8	0	6	123	118	5
-11	1	6	57	61	9
-10	1	6	128	137	6
-9	1	6	31	27	31
-8	1	6	84	83	7
-7	1	6	77	81	4
-6	1	6	35	32	7
-5	1	6	70	66	3
-4	1	6	122	129	3
-3	1	6	415	399	10
-2	1	6	78	73	3
-1	1	6	272	266	5
0	1	6	221	209	4
1	1	6	61	56	2
2	1	6	57	54	3
3	1	6	89	88	2
4	1	6	114	102	3
5	1	6	138	139	3
6	1	6	117	138	15
7	1	6	150	155	5
8	1	6	74	75	5
-11	2	6	35	27	16
-10	2	6	123	127	6
-9	2	6	130	128	6
-8	2	6	157	159	6
-7	2	6	63	66	4
-6	2	6	99	96	3
-5	2	6	50	47	5
-4	2	6	142	142	3
-3	2	6	99	102	13
-2	2	6	235	225	4
-1	2	6	69	65	4
0	2	6	362	346	6
1	2	6	139	134	3
2	2	6	76	67	7
3	2	6	66	59	9
4	2	6	105	99	6
5	2	6	125	107	6
6	2	6	114	104	5
-11	3	6	28	28	22
-10	3	6	61	57	7
-9	3	6	33	26	14
-8	3	6	40	35	13
-7	3	6	44	40	6
-6	3	6	87	82	3
-5	3	6	55	53	5
-4	3	6	8	26	7
-3	3	6	139	136	3
-2	3	6	112	106	3
-1	3	6	136	139	3
0	3	6	205	214	6
1	3	6	99	93	5
2	3	6	53	48	9
3	3	6	25	29	25
4	3	6	65	56	8
5	3	6	102	96	6
6	3	6	136	134	5
-10	4	6	56	57	8
-9	4	6	49	46	8
-8	4	6	83	81	6
-7	4	6	72	74	3
-6	4	6	82	79	3
-5	4	6	129	132	3
-4	4	6	89	92	3
-3	4	6	88	90	3
-2	4	6	192	185	3
-1	4	6	101	102	4
0	4	6	136	135	4
1	4	6	50	46	11
2	4	6	114	117	6
3	4	6	32	25	26
4	4	6	52	51	10
5	4	6	42	40	11
6	4	6	89	80	6
-9	5	6	33	35	14
-8	5	6	46	45	8
-7	5	6	80	77	3
-6	5	6	74	79	3
-5	5	6	45	44	5
-4	5	6	33	33	7
-3	5	6	101	101	4
-2	5	6	71	75	5
-1	5	6	82	76	5
0	5	6	65	64	6
1	5	6	115	109	4
2	5	6	42	50	13
3	5	6	111	118	6
4	5	6	47	45	10
5	5	6	109	111	6
-7	6	6	76	68	4
-6	6	6	78	77	3
-5	6	6	82	81	4
-4	6	6	97	98	4
-3	6	6	19	20	19
-2	6	6	76	75	4
-1	6	6	28	31	15
0	6	6	31	28	12

Table 6. Observed and calculated structure factors for af008

h	k	l	10Fo	10Fc	10s
1	6	6	40	45	8
2	6	6	95	96	4
3	6	6	47	45	10
4	6	6	54	50	9
-5	7	6	0	20	1
-4	7	6	42	48	8
-3	7	6	67	73	5
-2	7	6	43	47	8
-1	7	6	84	90	4
0	7	6	79	77	6
1	7	6	46	57	7
-3	-7	7	10	10	10
-2	-7	7	42	49	7
-1	-7	7	85	90	4
-7	-6	7	16	9	15
-6	-6	7	14	24	14
-5	-6	7	22	47	18
-4	-6	7	27	43	11
-3	-6	7	42	65	7
-2	-6	7	0	13	1
-1	-6	7	33	32	9
0	-6	7	34	33	8
1	-6	7	89	93	4
2	-6	7	30	34	9
3	-6	7	53	54	5
-9	-5	7	85	82	5
-8	-5	7	41	39	10
-7	-5	7	64	71	5
-6	-5	7	81	90	5
-5	-5	7	57	60	6
-4	-5	7	57	57	6
-3	-5	7	27	18	14
-2	-5	7	59	60	5
-1	-5	7	29	31	12
0	-5	7	92	95	3
1	-5	7	85	88	4
2	-5	7	145	146	3
3	-5	7	69	65	4
4	-5	7	63	59	5
5	-5	7	59	54	5
-10	-4	7	35	42	10
-9	-4	7	0	19	1
-8	-4	7	88	89	4
-7	-4	7	42	42	9
-6	-4	7	36	33	13
-5	-4	7	124	127	4
-4	-4	7	84	83	4
-3	-4	7	24	25	21
-2	-4	7	112	108	3
-1	-4	7	144	150	3
0	-4	7	17	12	16
1	-4	7	145	149	3
2	-4	7	90	92	3
3	-4	7	41	58	7
4	-4	7	21	19	21
5	-4	7	24	25	16
6	-4	7	16	21	16
-10	-3	7	49	49	7
-9	-3	7	95	93	4
-8	-3	7	48	38	8
-7	-3	7	63	63	6
-6	-3	7	22	17	22
-5	-3	7	83	77	4
-4	-3	7	130	125	3
-3	-3	7	90	91	3
-2	-3	7	25	25	9
-1	-3	7	97	95	2
0	-3	7	53	55	4
1	-3	7	91	95	3
2	-3	7	67	71	3
3	-3	7	115	115	3
4	-3	7	56	58	4
5	-3	7	87	91	2
6	-3	7	51	44	4
-11	-2	7	33	36	10
-10	-2	7	62	65	5
-9	-2	7	95	88	5
-8	-2	7	12	15	11
-7	-2	7	71	64	5
-6	-2	7	53	46	7
-5	-2	7	108	105	3
-4	-2	7	40	40	7
-3	-2	7	29	31	9
-2	-2	7	186	184	3
-1	-2	7	108	110	2
0	-2	7	21	25	9
1	-2	7	97	92	2
2	-2	7	197	205	2
3	-2	7	172	182	2
4	-2	7	79	75	3
5	-2	7	130	132	2
6	-2	7	76	80	3
7	-2	7	21	16	14
-11	-1	7	44	42	4
-10	-1	7	23	26	10
-9	-1	7	101	99	3
-8	-1	7	63	63	3
-7	-1	7	218	213	3
-6	-1	7	97	91	2
-5	-1	7	63	60	3
-4	-1	7	156	153	3
-3	-1	7	259	259	4
-2	-1	7	138	134	3
-1	-1	7	174	173	2
0	-1	7	80	84	1
1	-1	7	59	57	3
2	-1	7	155	150	3
3	-1	7	80	78	4
4	-1	7	120	124	5
5	-1	7	26	28	25
7	-1	7	44	34	9
-11	0	7	0	10	1
-10	0	7	14	4	13
-9	0	7	47	47	6
-8	0	7	93	84	4
-7	0	7	10	6	10
-6	0	7	13	18	12
-5	0	7	47	40	4
-4	0	7	141	131	3
-3	0	7	284	269	8
-2	0	7	65	69	6
-1	0	7	297	285	5
0	0	7	184	195	3
1	0	7	198	193	4
2	0	7	0	1	1
3	0	7	112	109	3
4	0	7	41	34	8
5	0	7	73	71	4
6	0	7	56	58	6
-11	1	7	45	42	10
-10	1	7	26	26	26
-9	1	7	98	99	6
-8	1	7	56	63	11
-7	1	7	220	212	4
-6	1	7	85	91	3
-5	1	7	59	60	4
-4	1	7	158	153	3
-3	1	7	267	259	5
-2	1	7	143	134	3
-1	1	7	190	173	4
0	1	7	89	84	3
1	1	7	62	58	3
2	1	7	155	150	2
3	1	7	79	78	3
4	1	7	126	124	3
5	1	7	31	28	11
6	1	7	96	94	3
7	1	7	11	34	11
-11	2	7	28	36	26
-10	2	7	58	64	8
-9	2	7	86	88	6
-8	2	7	30	15	30
-7	2	7	63	64	4
-6	2	7	47	46	6
-5	2	7	102	105	3
-4	2	7	39	41	9
-3	2	7	23	31	22
-2	2	7	183	184	4
-1	2	7	113	110	3
0	2	7	22	25	16
1	2	7	101	92	5
2	2	7	212	205	6
3	2	7	207	182	6
4	2	7	86	75	7
5	2	7	152	132	6
6	2	7	89	80	6
-10	3	7	41	49	11
-9	3	7	94	93	6
-8	3	7	47	39	10
-7	3	7	63	63	5
-6	3	7	15	17	15
-5	3	7	77	77	4
-4	3	7	124	124	3
-3	3	7	92	91	3
-2	3	7	25	25	14
-1	3	7	106	95	5
0	3	7	54	55	10
1	3	7	99	95	6
2	3	7	72	71	7
3	3	7	122	115	6
4	3	7	62	58	9
5	3	7	98	91	6
6	3	7	49	44	10
-10	4	7	35	42	13
-9	4	7	24	19	24
-8	4	7	88	89	6
-7	4	7	47	42	6
-6	4	7	26	33	15
-5	4	7	125	127	4
-4	4	7	78	83	9
-3	4	7	21	25	21
-2	4	7	111	108	6
-1	4	7	140	150	6
0	4	7	21	12	20
1	4	7	148	149	6
2	4	7	91	92	6
3	4	7	71	58	7
4	4	7	0	19	1
5	4	7	0	25	1
6	4	7	34	21	16
-8	5	7	47	39	9
-7	5	7	70	71	3
-6	5	7	90	90	3
-5	5	7	58	60	4
-4	5	7	56	57	6
-3	5	7	24	19	24
-2	5	7	63	60	6
-1	5	7	31	31	14
0	5	7	98	95	6
1	5	7	98	88	6
2	5	7	148	146	6
3	5	7	74	65	7
4	5	7	70	59	7
5	5	7	57	54	8
-7	6	7	14	9	13
-6	6	7	28	24	13
-5	6	7	47	47	6
-4	6	7	42	43	7
-3	6	7	68	65	5
-2	6	7	0	13	1
-1	6	7	30	32	12
0	6	7	27	33	13
1	6	7	95	92	4
2	6	7	39	34	13
3	6	7	52	54	9
-3	7	7	24	11	21
-2	7	7	48	49	7
-6	-6	8	19	32	19
-5	-6	8	42	42	8
-4	-6	8	101	99	4
-3	-6	8	49	50	6
-2	-6	8	20	14	20
-1	-6	8	8	22	7
0	-6	8	15	7	15
1	-6	8	19	23	19
2	-6	8	61	66	5
-8	-5	8	15	12	15
-7	-5	8	112	119	4
-6	-5	8	65	61	5
-5	-5	8	122	130	4
-4	-5	8	102	103	4
-3	-5	8	74	75	4
-2	-5	8	59	64	5
-1	-5	8	0	21	1
0	-5	8	39	35	7
1	-5	8	55	56	5
2	-5	8	89	93	4
3	-5	8	77	85	10
4	-5	8	48	50	10
-9	-4	8	48	44	8
-8	-4	8	132	125	4
-7	-4	8	68	65	5
-6	-4	8	142	138	4
-5	-4	8	110	109	4
-4	-4	8	102	101	4
-3	-4	8	64	54	5
-2	-4	8	73	69	5
-1	-4	8	78	78	4
0	-4	8	126	125	3
1	-4	8	155	146	4
2	-4	8	40	39	7
3	-4	8	35	27	8
4	-4	8	22	13	21
5	-4	8	20	23	19
-10	-3	8	49	51	7
-9	-3	8	44	34	8
-8	-3	8	141	136	4
-7	-3	8	100	97	4
-6	-3	8	34	28	13
-5	-3	8	57	58	5
-4	-3	8	147	146	3
-3	-3	8	90	88	3
-2	-3	8	113	115	3
-1	-3	8	57	52	5
0	-3	8	178	183	4
1	-3	8	102	105	3
2	-3	8	190	187	4
3	-3	8	183	195	3
4	-3	8	75	72	3
5	-3	8	51	49	5
6	-3	8	61	66	4
-11	-2	8	24	15	24
-10	-2	8	94	95	4
-9	-2	8	56	54	6
-8	-2	8	103	99	4
-7	-2	8	121	108	4
-6	-2	8	57	58	6
-5	-2	8	30	23	13
-4	-2	8	205	204	4
-3	-2	8	175	175	3
-2	-2	8	69	72	3
-1	-2	8	127	130	3
0	-2	8	45	46	5
1	-2	8	138	137	3
2	-2	8	84	84	2
3	-2	8	138	152	2
4	-2	8	53	57	3
5	-2	8	79	85	3
6	-2	8	50	50	4
-11	-1	8	46	39	12
-10	-1	8	25	25	25
-9	-1	8	58	57	11
-8	-1	8	37	38	20
-7	-1	8	41	34	8
-6	-1	8	60	57	5
-5	-1	8	114	111	3
-4	-1	8	75	74	3
-3	-1	8	171	174	3
-2	-1	8	61	62	3
-1	-1	8	52	58	3
0	-1	8	56	62	3
1	-1	8	64	63	3
2	-1	8	139	145	3
3	-1	8	37	29	7
4	-1	8	61	60	6
5	-1	8	107	105	5
6	-1	8	63	64	6
7	-1	8	20	4	20
-11	0	8	33	40	17
-10	0	8	42	45	14
-9	0	8	21	2	20
-8	0	8	179	168	7
-7	0	8	51	57	5
-6	0	8	6	2	6
-5	0	8	27	24	26
-4	0	8	48	50	11
-3	0	8	58	59	8
-2	0	8	164	164	5
-1	0	8	23	24	9
0	0	8	92	84	3
1	0	8	27	27	9
2	0	8	21	27	16
3	0	8	24	22	13
4	0	8	55	53	4
5	0	8	56	53	5
6	0	8	0	12	1
7	0	8	33	37	13
-11	1	8	37	39	15
-10	1	8	30	25	20
-9	1	8	53	57	10
-8	1	8	39	38	18
-7	1	8	35	34	8
-6	1	8	55	57	5
-5	1	8	108	111	3
-4	1	8	76	74	3
-3	1	8	183	174	4
-2	1	8	61	62	4
-1	1	8	63	59	4
0	1	8	61	62	4
1	1	8	67	63	3
2	1	8	147	145	3
3	1	8	31	29	10
4	1	8	61	60	4
5	1	8	103	105	3
6	1	8	65	64	5
7	1	8	9	4	8
-11	2	8	4	15	4
-10	2	8	97	95	6
-9	2	8	58	54	9
-8	2	8	103	99	6
-7	2	8	104	108	3
-6	2	8	59	58	5
-5	2	8	26	23	20
-4	2	8	153	204	11
-3	2	8	175	175	4
-2	2	8	69	72	4
-1	2	8	130	130	3
0	2	8	41	46	12
1	2	8	130	138	5
2	2	8	98	84	6
3	2	8	177	152	6
4	2	8	64	57	11
5	2	8	85	85	6
6	2	8	68	50	9
-10	3	8	49	51	9
-9	3	8	45	34	9
-8	3	8	133	136	6
-7	3	8	95	97	4
-6	3	8	26	28	16
-5	3	8	60	58	5
-4	3	8	132	146	10
-3	3	8	94	88	4
-2	3	8	122	115	4
-1	3	8	70	52	9
0	3	8	183	183	6
1	3	8	118	105	7
2	3	8	209	187	7
3	3	8	208	195	6
4	3	8	84	72	6
5	3	8	51	49	10
6	3	8	73	66	7
-9	4	8	48	44	10
-8	4	8	123	125	6
-7	4	8	73	64	4
-6	4	8	136	138	4
-5	4	8	108	109	3
-4	4	8	103	101	4
-3	4	8	65	54	8
-2	4	8	63	69	10
-1	4	8	77	78	7
0	4	8	130	124	6
1	4	8	148	146	6
2	4	8	32	39	24
3	4	8	28	27	28
4	4	8	15	13	15
5	4	8	31	23	20
-8	5	8	15	12	14
-7	5	8	116	119	4
-6	5	8	67	61	4
-5	5	8	127	130	5
-4	5	8	105	103	6
-3	5	8	78	75	7
-2	5	8	58	64	9
-1	5	8	0	21	1
0	5	8	28	35	28
1	5	8	64	56	8
2	5	8	93	93	6
3	5	8	100	85	6
4	5	8	57	50	9
-6	6	8	32	32	10
-5	6	8	32	42	9
-4	6	8	101	99	4
-3	6	8	45	50	7
-2	6	8	18	14	17
-1	6	8	19	22	19
0	6	8	7	7	7
1	6	8	22	23	22
2	6	8	66	67	8
-5	-6	9	50	52	6
-4	-6	9	36	37	9
-3	-6	9	44	47	7
-2	-6	9	38	42	8
-1	-6	9	9	9	9
0	-6	9	47	51	7
-7	-5	9	56	56	6

Table 6. Observed and calculated structure factors for af008

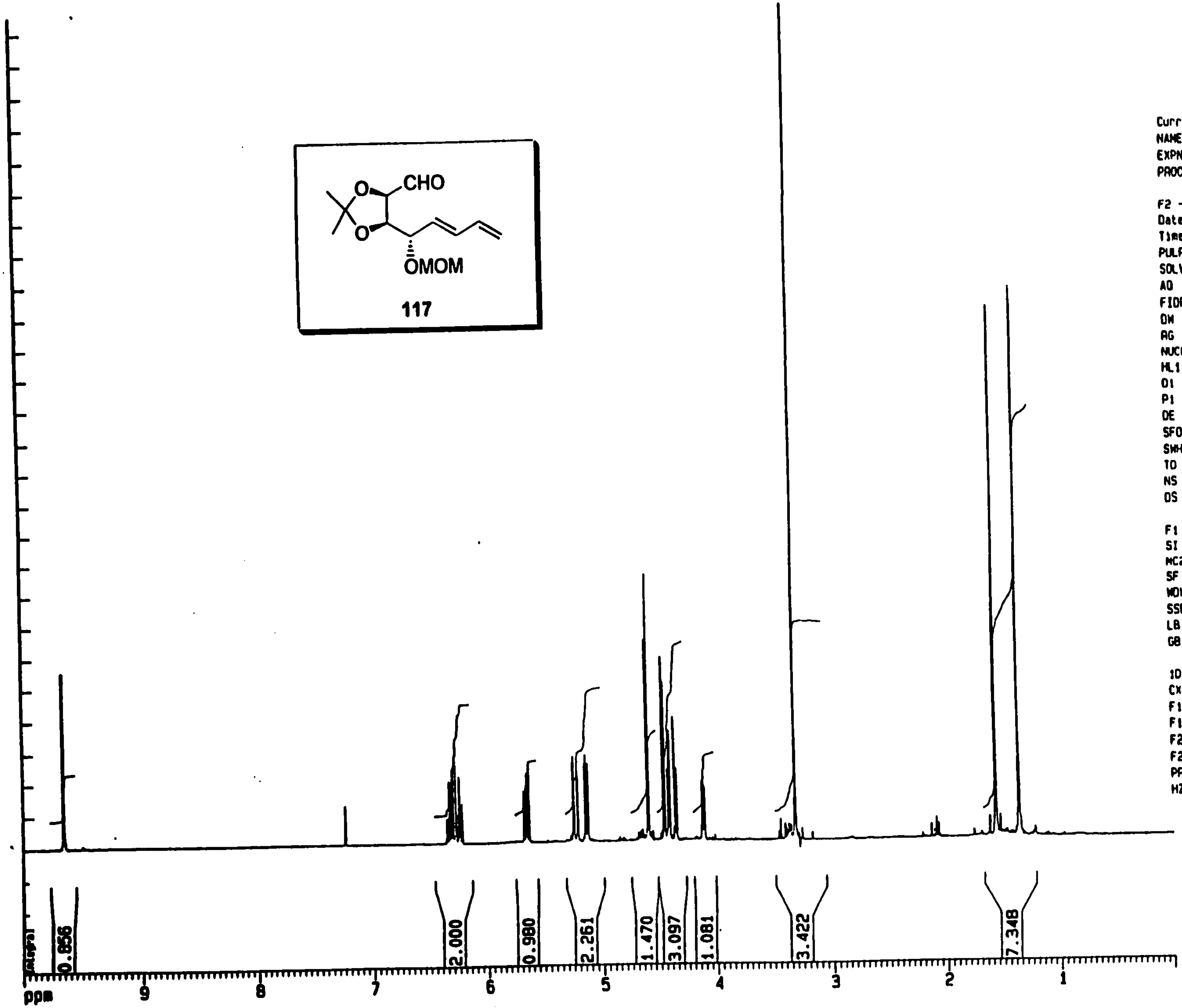
h	k	l	10Fo	10Fc	10s
-6	-5	9	82	84	4
-5	-5	9	67	65	4
-4	-5	9	18	24	17
-3	-5	9	0	10	1
-2	-5	9	28	27	10
-1	-5	9	62	57	5
0	-5	9	86	86	4
1	-5	9	56	51	6
2	-5	9	59	55	5
-9	-4	9	53	46	11
-8	-4	9	48	38	12
-7	-4	9	111	107	6
-6	-4	9	65	71	5
-5	-4	9	73	74	4
-4	-4	9	84	83	4
-3	-4	9	147	152	4
-2	-4	9	183	178	4
-1	-4	9	83	89	4
0	-4	9	97	94	4
1	-4	9	170	169	4
2	-4	9	18	12	17
3	-4	9	56	59	5
4	-4	9	35	36	9
-10	-3	9	37	33	15
-9	-3	9	121	120	7
-8	-3	9	49	43	12
-7	-3	9	83	85	8
-6	-3	9	91	79	8
-5	-3	9	230	222	7
-4	-3	9	30	27	12
-3	-3	9	172	171	4
-2	-3	9	76	76	4
-1	-3	9	268	275	5
0	-3	9	213	216	4
1	-3	9	142	145	4
2	-3	9	73	71	4
3	-3	9	55	52	5
4	-3	9	107	107	4
5	-3	9	61	62	7
-10	-2	9	91	92	7
-9	-2	9	28	22	27
-8	-2	9	96	86	7
-7	-2	9	135	125	7
-6	-2	9	173	178	6
-5	-2	9	76	70	8
-4	-2	9	193	201	6
-3	-2	9	88	80	6
-2	-2	9	70	71	7
-1	-2	9	30	33	9
0	-2	9	120	125	3
1	-2	9	58	58	4
2	-2	9	126	129	3
3	-2	9	117	120	3
4	-2	9	70	66	4
5	-2	9	124	129	5
-11	-1	9	30	25	29
-10	-1	9	17	17	17
-9	-1	9	113	111	7
-8	-1	9	52	50	12
-7	-1	9	48	49	14
-6	-1	9	106	97	7
-5	-1	9	76	75	7
-4	-1	9	87	85	7
-3	-1	9	78	67	6
-2	-1	9	91	92	6
-1	-1	9	79	75	6
0	-1	9	74	80	6
1	-1	9	67	64	3
2	-1	9	45	46	5
3	-1	9	60	56	4
4	-1	9	19	17	19
5	-1	9	97	100	3
6	-1	9	36	29	12
-11	0	9	38	34	15
-10	0	9	39	28	15
-9	0	9	0	15	1
-8	0	9	69	75	10
-7	0	9	63	59	5
-6	0	9	22	25	22
-5	0	9	0	10	1
-4	0	9	61	65	8
-3	0	9	141	150	5
-2	0	9	94	90	5
-1	0	9	27	28	19
0	0	9	0	7	1
1	0	9	109	115	5
2	0	9	73	71	3
3	0	9	22	28	14
4	0	9	40	32	6
5	0	9	80	78	4
6	0	9	0	2	1
-11	1	9	16	25	15
-10	1	9	23	17	22
-9	1	9	109	111	6
-8	1	9	52	50	11
-7	1	9	45	49	7
-6	1	9	92	97	4
-5	1	9	79	75	4
-4	1	9	88	84	4
-3	1	9	73	67	4
-2	1	9	105	92	4
-1	1	9	84	75	4
0	1	9	85	80	4
1	1	9	61	64	5
2	1	9	55	46	12
3	1	9	64	56	4
4	1	9	16	17	16
5	1	9	101	100	4
6	1	9	33	29	12
-10	2	9	98	92	6
-9	2	9	31	22	17
-8	2	9	89	86	6
-7	2	9	121	125	4
-6	2	9	170	178	6
-5	2	9	76	70	5
-4	2	9	196	202	4
-3	2	9	86	80	4
-2	2	9	77	71	4
-1	2	9	33	33	10
0	2	9	130	125	6
1	2	9	57	58	9
2	2	9	133	129	6
3	2	9	128	120	6
4	2	9	71	66	8
5	2	9	142	129	6
-10	3	9	34	33	14
-9	3	9	123	120	6
-8	3	9	44	43	10
-7	3	9	83	85	4
-6	3	9	74	79	4
-5	3	9	224	222	4
-4	3	9	21	27	21
-3	3	9	171	171	4
-2	3	9	79	76	7
-1	3	9	274	275	7
0	3	9	227	216	7
1	3	9	142	145	6
2	3	9	77	71	9
3	3	9	56	51	11
4	3	9	112	107	6
5	3	9	55	62	10
-9	4	9	44	46	10
-8	4	9	38	37	10
-7	4	9	108	107	3
-6	4	9	64	71	4
-5	4	9	71	74	4
-4	4	9	88	83	6
-3	4	9	143	152	6
-2	4	9	190	178	6
-1	4	9	90	89	7
0	4	9	102	94	6
1	4	9	181	169	6
2	4	9	16	12	16
3	4	9	57	59	10
4	4	9	33	36	21
-7	5	9	58	56	5
-6	5	9	87	84	5
-5	5	9	14	65	13
-4	5	9	8	24	8
-3	5	9	0	10	1
-2	5	9	28	27	28
-1	5	9	51	57	11
0	5	9	95	86	6
1	5	9	54	51	10
2	5	9	60	55	9
-5	6	9	52	52	9
-4	6	9	36	37	15
-3	6	9	35	47	14
-2	6	9	31	42	21
-1	6	9	18	9	17
0	6	9	44	51	12
-6	-5	10	48	45	11
-5	-5	10	32	28	17
-4	-5	10	44	52	10
-3	-5	10	0	17	1
-2	-5	10	33	38	13
-1	-5	10	50	45	6
0	-5	10	52	51	5
1	-5	10	23	25	22
-8	-4	10	81	81	8
-7	-4	10	31	10	30
-6	-4	10	67	67	9
-5	-4	10	36	27	15
-4	-4	10	127	126	6
-3	-4	10	132	139	6
-2	-4	10	75	78	6
-1	-4	10	119	120	6
0	-4	10	91	96	6
1	-4	10	62	69	4
2	-4	10	61	52	4
3	-4	10	45	46	6
-9	-3	10	81	80	8
-8	-3	10	59	55	10
-7	-3	10	58	55	10
-6	-3	10	37	33	19
-5	-3	10	88	86	7
-4	-3	10	227	229	7
-3	-3	10	69	74	8
-2	-3	10	207	209	7
-1	-3	10	69	69	7
0	-3	10	0	23	1
1	-3	10	71	73	6
2	-3	10	95	94	6
3	-3	10	43	36	6
4	-3	10	48	44	6
-10	-2	10	15	34	14
-9	-2	10	50	46	11
-8	-2	10	138	135	7
-7	-2	10	127	120	7
-6	-2	10	58	66	9
-5	-2	10	115	99	7
-4	-2	10	201	203	6
-3	-2	10	97	89	6
-2	-2	10	48	50	10
-1	-2	10	59	64	8
0	-2	10	82	82	6
1	-2	10	159	163	6
2	-2	10	73	78	6
3	-2	10	41	39	10
4	-2	10	28	31	20
-10	-1	10	39	35	13
-9	-1	10	38	38	15
-8	-1	10	50	53	12
-7	-1	10	57	47	11
-6	-1	10	38	38	19
-5	-1	10	76	79	7
-4	-1	10	37	35	19
-3	-1	10	100	104	6
-2	-1	10	31	31	18
-1	-1	10	41	46	11
0	-1	10	44	40	9
1	-1	10	102	109	5
2	-1	10	73	75	6
3	-1	10	28	28	19
-10	0	10	50	50	10
-9	0	10	42	28	14
-8	0	10	101	100	7
-7	0	10	104	104	4
-6	0	10	100	96	7
-5	0	10	8	10	8
-4	0	10	170	158	6
-3	0	10	48	50	11
-2	0	10	16	21	15
-1	0	10	69	75	6
0	0	10	20	16	20
1	0	10	15	18	14
2	0	10	0	5	1
3	0	10	80	70	7
4	0	10	39	36	22
5	0	10	51	42	16
-10	1	10	38	35	16
-9	1	10	35	38	17
-8	1	10	53	53	12
-7	1	10	45	47	7
-6	1	10	36	38	9
-5	1	10	80	79	4
-4	1	10	39	35	8
-3	1	10	107	104	4
-2	1	10	36	31	11
-1	1	10	40	46	9
0	1	10	47	40	7
1	1	10	125	109	7
2	1	10	80	75	7
3	1	10	36	28	19
4	1	10	111	99	6
5	1	10	55	45	12
-10	2	10	20	35	19
-9	2	10	44	46	10
-8	2	10	138	135	6
-7	2	10	118	120	4
-6	2	10	71	65	5
-5	2	10	100	99	3
-4	2	10	188	203	4
-3	2	10	92	89	4
-2	2	10	46	51	7
-1	2	10	66	64	9
0	2	10	93	82	7
1	2	10	175	163	6
2	2	10	75	78	6
3	2	10	35	39	18
4	2	10	39	31	19
-9	3	10	76	80	6
-8	3	10	62	55	7
-7	3	10	54	55	5
-6	3	10	33	33	10
-5	3	10	75	86	4
-4	3	10	237	229	5
-3	3	10	82	74	6
-2	3	10	218	209	6
-1	3	10	76	69	7
0	3	10	28	23	27
1	3	10	80	73	7
2	3	10	103	94	6
3	3	10	44	36	16
4	3	10	41	44	15
-8	4	10	75	81	6
-7	4	10	17	11	16
-6	4	10	67	67	4
-5	4	10	0	27	1
-4	4	10	134	126	6
-3	4	10	130	139	6
-2	4	10	80	78	7
-1	4	10	119	120	6
0	4	10	99	96	6
1	4	10	70	69	9
2	4	10	56	52	11
3	4	10	46	46	14
-6	5	10	52	45	9
-5	5	10	29	28	17
-4	5	10	53	52	8
-3	5	10	21	17	21
-2	5	10	27	38	27
-1	5	10	49	45	11
0	5	10	58	51	9
1	5	10	25	25	24
-4	-5	11	56	53	8
-3	-5	11	49	56	9
-2	-5	11	25	19	24
-7	-4	11	15	22	14
-6	-4	11	33	29	29
-5	-4	11	28	26	28
-4	-4	11	121	118	6
-3	-4	11	92	96	6
-1	-4	11	68	67	7
0	-4	11	45	43	11
1	-4	11	18	23	17
-8	-3	11	46	38	13
-7	-3	11	90	93	6
-6	-3	11	35	38	18
-5	-3	11	85	77	7
-4	-3	11	6	17	6
-3	-3	11	125	124	6
-2	-3	11	19	7	18
-1	-3	11	22	26	22
0	-3	11	56	51	8
1	-3	11	22	20	22
2	-3	11	37	32	11
-9	-2	11	43	46	13
-8	-2	11	127	127	6
-7	-2	11	39	34	16
-6	-2	11	87	92	6
-5	-2	11	0	21	1
-4	-2	11	101	101	7
-3	-2	11	153	151	6
-2	-2	11	35	36	15
-1	-2	11	68	67	7
0	-2	11	47	46	9
1	-2	11	80	79	6
2	-2	11	49	48	9
3	-2	11	19	29	19
-10	-1	11	112	102	7
-9	-1	11	68	75	8
-8	-1	11	77	75	8
-7	-1	11	53	56	10
-6	-1	11	63	63	10
-5	-1	11	29	30	29
-4	-1	11	74	65	8
-3	-1	11	68	64	7
-2	-1	11	55	65	9
-1	-1	11	56	58	8
0	-1	11	33	33	15
1	-1	11	98	109	5
2	-1	11	49	51	8
-10	0	11	35	33	35
-9	0	11	35	30	15
-8	0	11	64	72	9
-7	0	11	59	56	5
-6	0	11	89	88	7
-5	0	11	0	11	1
-4	0	11	37	42	15
-3	0	11	55	51	10
-2	0	11	88	92	6
-1	0	11	42	33	10
0	0	11	12	0	11
1	0	11	5	3	5
2	0	11	139	120	6
3	0	11	7	10	7
4	0	11	38	29	34
-10	1	11	107	102	6
-9	1	11	73	75	7
-8	1	11	75	75	7
-7	1	11	54	56	5
-6	1	11	59	64	5
-5	1	11	12	30	11
-4	1	11	68	65	5
-3	1	11	67	64	5
-2	1	11	73	65	5
-1	1	11	66	58	6
0	1	11	22	33	22
1	1	11	120	109	6
2	1	11	51	51	11
3	1	11	51	44	12
-9	2	11	48	46	10
-8	2	11	130	127	6
-7	2	11	36	34	9
-6	2	11	97	92	4
-5	2	11	9	21	8
-4	2	11	93	101	3
-3	2	11	151	151	4
-2	2	11	36	36	16
-1	2	11	67	67	8
0	2	11	42	46	15
1	2	11	80	79	6
2	2	11	53	48	11
3	2	11	31	29	31
-8	3	11	33	38	13
-7	3	11	85	93	4
-6	3	11	40	38	8
-5	3	11	78	77	4
-4	3	11	27	17	26
-3	3	11	123	124	5
-2	3	11	8	7	7
-1	3	11	28	26	28
0	3	11	58	51	10
1	3	11	25	20	25
2	3	11	40	32	17
-7	4	11	32	22	15
-6	4	11	26	29	25
-5	4	11	14	26	13
-4	4	11	115	118	6
-3	4	11	85	96	6
-2	4	11	69	78	7
-1	4	11	65	67	8
0	4	11	49	43	11
1	4	11	25	23	24
-4	5	11	64	53	8
-3	5	11	56	56	9
-2	5	11	0	19	1
-5	-4	12	47	58	10
-4	-4	12	82	80	7
-3	-4	12	30	27	17
-2	-4	12	31	33	16
-1	-4	12	51	41	8
-7	-3	12	0	12	1
-6	-3	12	69	74	8

Table 6. Observed and calculated structure factors for af008

h	k	l	10Fo	10Fc	10s
-5	-3	12	22	20	21
-4	-3	12	16	27	16
-3	-3	12	32	36	16
-2	-3	12	85	92	6
-1	-3	12	58	67	8
0	-3	12	36	33	14
1	-3	12	12	21	12
-8	-2	12	142	131	7
-7	-2	12	77	70	8
-6	-2	12	45	43	12
-5	-2	12	32	40	19
-4	-2	12	86	86	7
-3	-2	12	27	17	27
-2	-2	12	3	5	3
-1	-2	12	75	69	6
0	-2	12	61	70	7
1	-2	12	18	21	18
-9	-1	12	62	71	9
-8	-1	12	76	77	7
-7	-1	12	0	6	1
-6	-1	12	90	82	7
-5	-1	12	42	53	12
-4	-1	12	20	26	19
-3	-1	12	65	58	7
-2	-1	12	143	139	6
-1	-1	12	79	85	6
0	-1	12	60	62	7
1	-1	12	40	45	10
-9	0	12	66	60	9
-8	0	12	53	56	9
-7	0	12	10	6	10
-6	0	12	0	6	1
-5	0	12	92	96	6
-4	0	12	70	75	7
-3	0	12	53	53	10
-2	0	12	24	26	23
-1	0	12	83	86	6
0	0	12	29	10	29
1	0	12	60	55	11
2	0	12	13	21	13
-9	1	12	84	71	8
-8	1	12	68	77	7
-7	1	12	10	6	10
-6	1	12	79	82	4
-5	1	12	45	53	6
-4	1	12	31	26	10
-3	1	12	61	58	5
-2	1	12	146	139	6
-1	1	12	94	85	6
0	1	12	71	62	9
1	1	12	50	46	12
2	1	12	46	51	14
-8	2	12	140	131	6
-7	2	12	82	70	4
-6	2	12	41	43	6
-5	2	12	34	40	7
-4	2	12	87	86	5
-3	2	12	19	17	18
-2	2	12	12	5	12
-1	2	12	76	69	7
0	2	12	81	70	7
1	2	12	16	21	16
-7	3	12	24	12	16
-6	3	12	76	74	6
-5	3	12	0	20	1
-4	3	12	19	27	19
-3	3	12	39	36	12
-2	3	12	89	92	6
-1	3	12	56	67	8
0	3	12	32	33	21
1	3	12	21	21	20
-5	4	12	46	58	10
-4	4	12	75	80	7
-3	4	12	18	27	18
-2	4	12	29	33	28
-1	4	12	53	41	11
-5	-3	13	71	64	8
-4	-3	13	42	43	13
-3	-3	13	45	40	11
-2	-3	13	20	14	19
-7	-2	13	48	44	12
-6	-2	13	33	37	19
-5	-2	13	41	45	12
-4	-2	13	0	11	1
-3	-2	13	24	21	23
-2	-2	13	8	8	7
-1	-2	13	100	108	6
-8	-1	13	70	60	8
-7	-1	13	49	53	12
-6	-1	13	20	6	19
-5	-1	13	32	30	15
-4	-1	13	115	116	6
-3	-1	13	27	25	27
-2	-1	13	82	84	6
-1	-1	13	33	32	14
0	-1	13	55	61	7
-8	0	13	32	39	20
-7	0	13	32	38	9
-6	0	13	0	11	1
-5	0	13	20	19	20
-4	0	13	9	4	9
-3	0	13	55	65	6
-2	0	13	18	30	17
-1	0	13	72	60	8
0	0	13	35	22	20
-8	1	13	71	60	7
-7	1	13	45	53	6
-6	1	13	0	6	1
-5	1	13	26	30	12
-4	1	13	119	116	4
-3	1	13	30	25	16
-2	1	13	87	84	6
-1	1	13	29	32	28
0	1	13	60	61	10
-7	2	13	52	44	6
-6	2	13	36	37	7
-5	2	13	34	45	9
-4	2	13	0	11	1
-3	2	13	8	21	7
-2	2	13	13	8	12
-1	2	13	108	108	6
-5	3	13	60	65	8
-4	3	13	25	43	25
-3	3	13	40	40	11
-2	3	13	0	14	1
-5	-1	14	36	37	12
-4	-1	14	40	38	13
-3	-1	14	32	40	21
-5	0	14	29	31	11
-4	0	14	42	51	6
-3	0	14	43	50	7
-5	1	14	37	37	8
-4	1	14	43	38	10
-3	1	14	29	40	21

Appendix C

Reproduction of the ^{1}H NMR and ^{13}C NMR Spectra of Selected Compounds

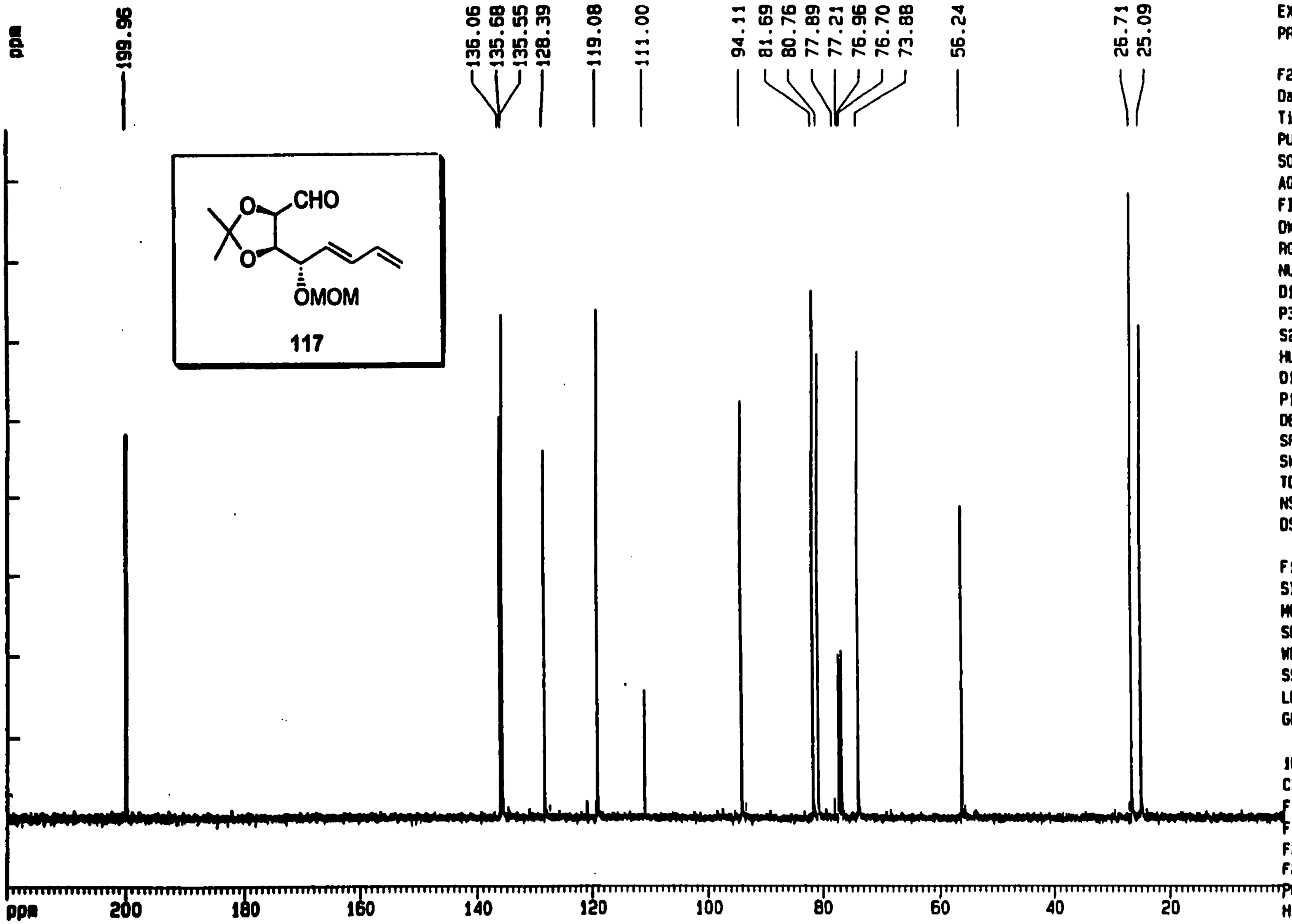


Current Data Parameters	
NAME	stepp_smp226
EXPNO	1
PROCNO	1

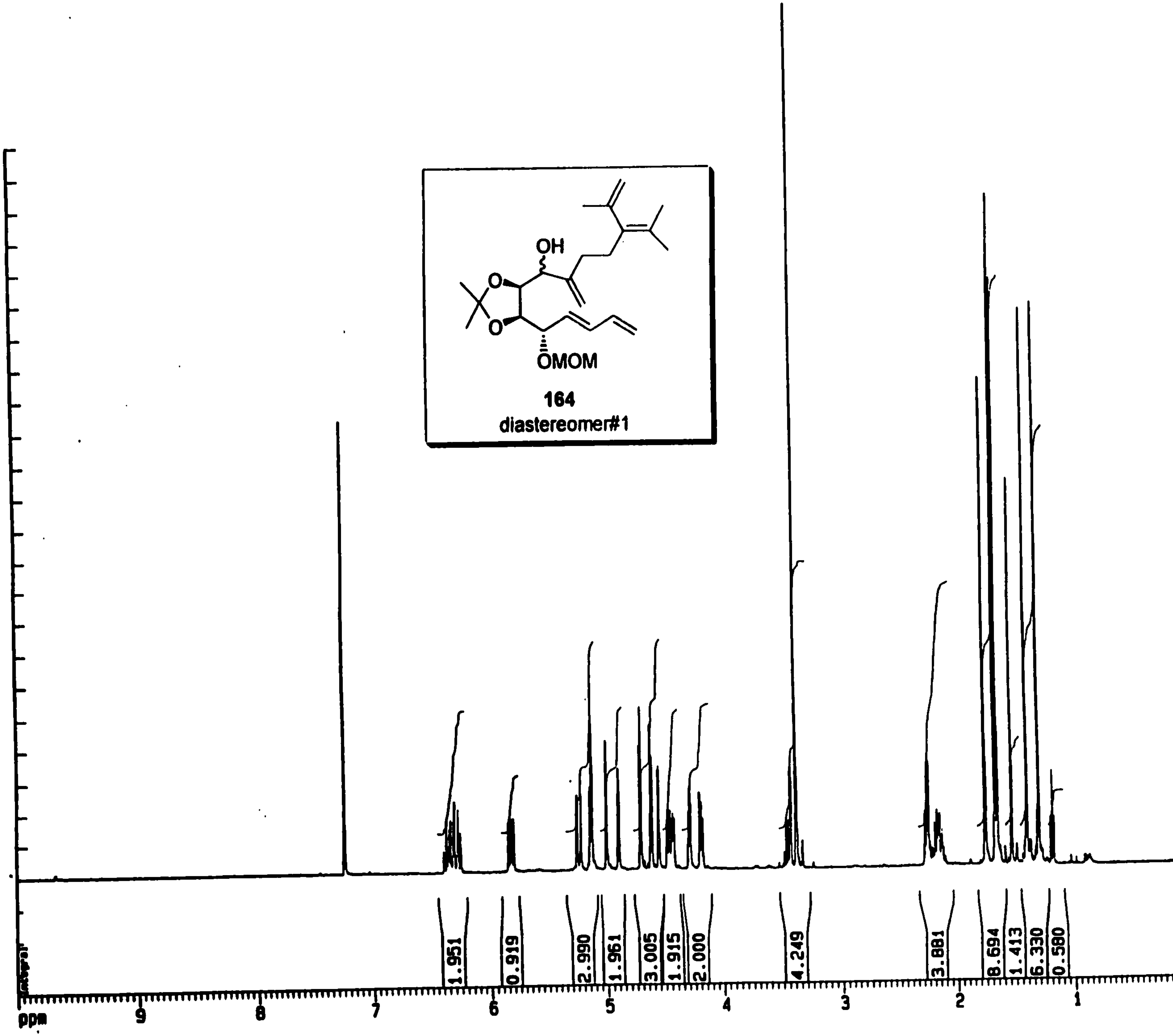
F2 - Acquisition Parameters	
Date	980805
Time	9.45
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	256
NUCLEUS	1H
HL1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	88.8 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	0

F1 - Processing parameters	
SI	32768
MC2	QF
SF	500.1354311 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/c

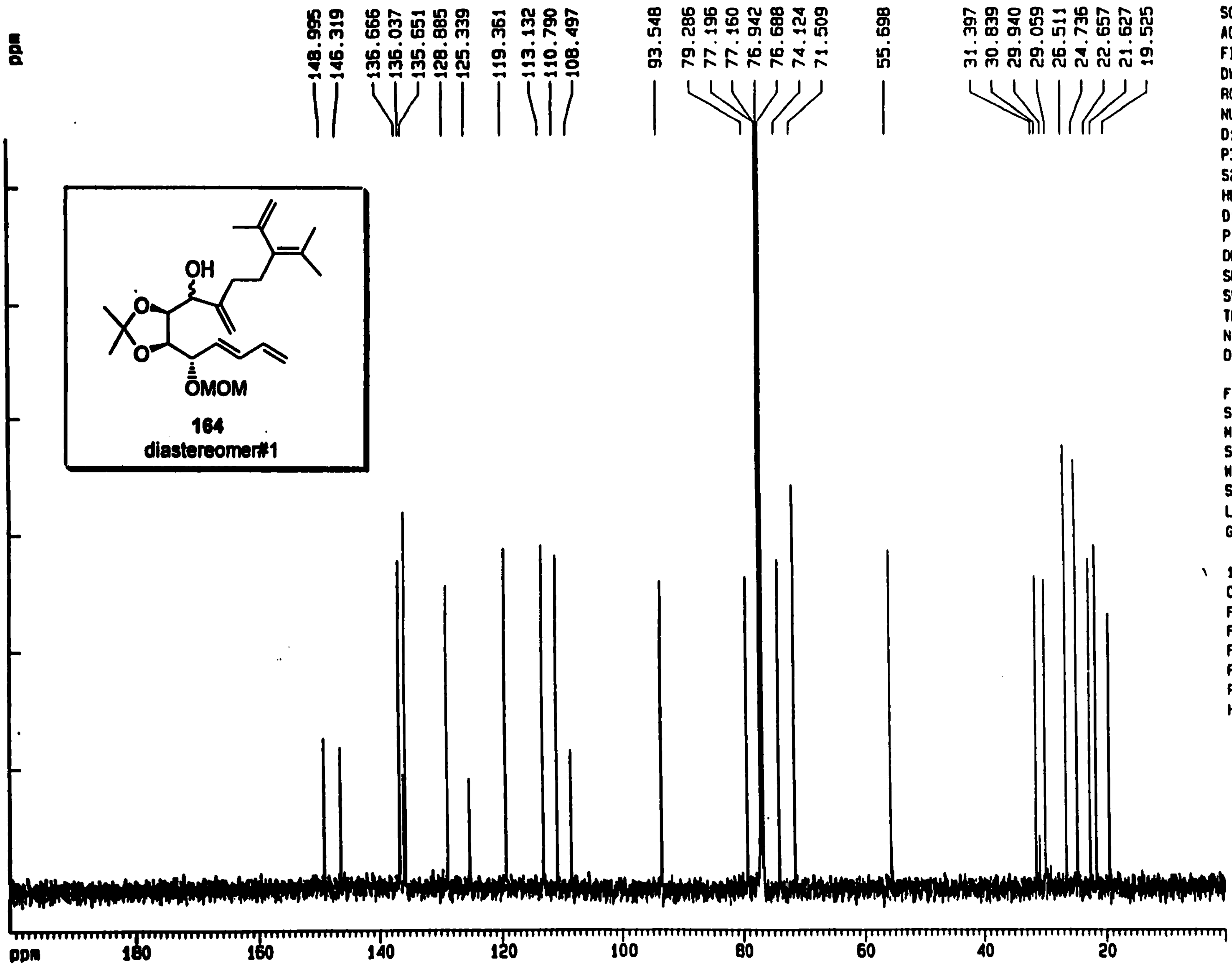


```
Current Data Parameters
NAME        stepp_smp226
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parame
Date              980805
Time               10.37
PULPROG             zgdc
SOLVENT            CDCl3
AQ             1.0485960
FIDRES          0.476837
DW                  16.0
RG                 32768
NUCLEUS              13C
D11            0.0300000
P31                 70.0
S2                    22
HL1                   22
D1             1.0000000
P1                   5.0
DE                  20.0
SFO1         125.7724464
SWH             31250.00
TD                 65536
NS                  1305
DS                     0

F1 - Processing paramet
SI                 32768
MC2                   QF
SF           125.7591571
WDW                   EM
SSB                    0
LB                  1.00
GB                     0

1D NMR plot parameters
CX                 22.00
F1P              139.141
F1              17498.23
F2P               51.456
F2               6471.04
PPMCM            3.98568
HZCM           501.23575
```



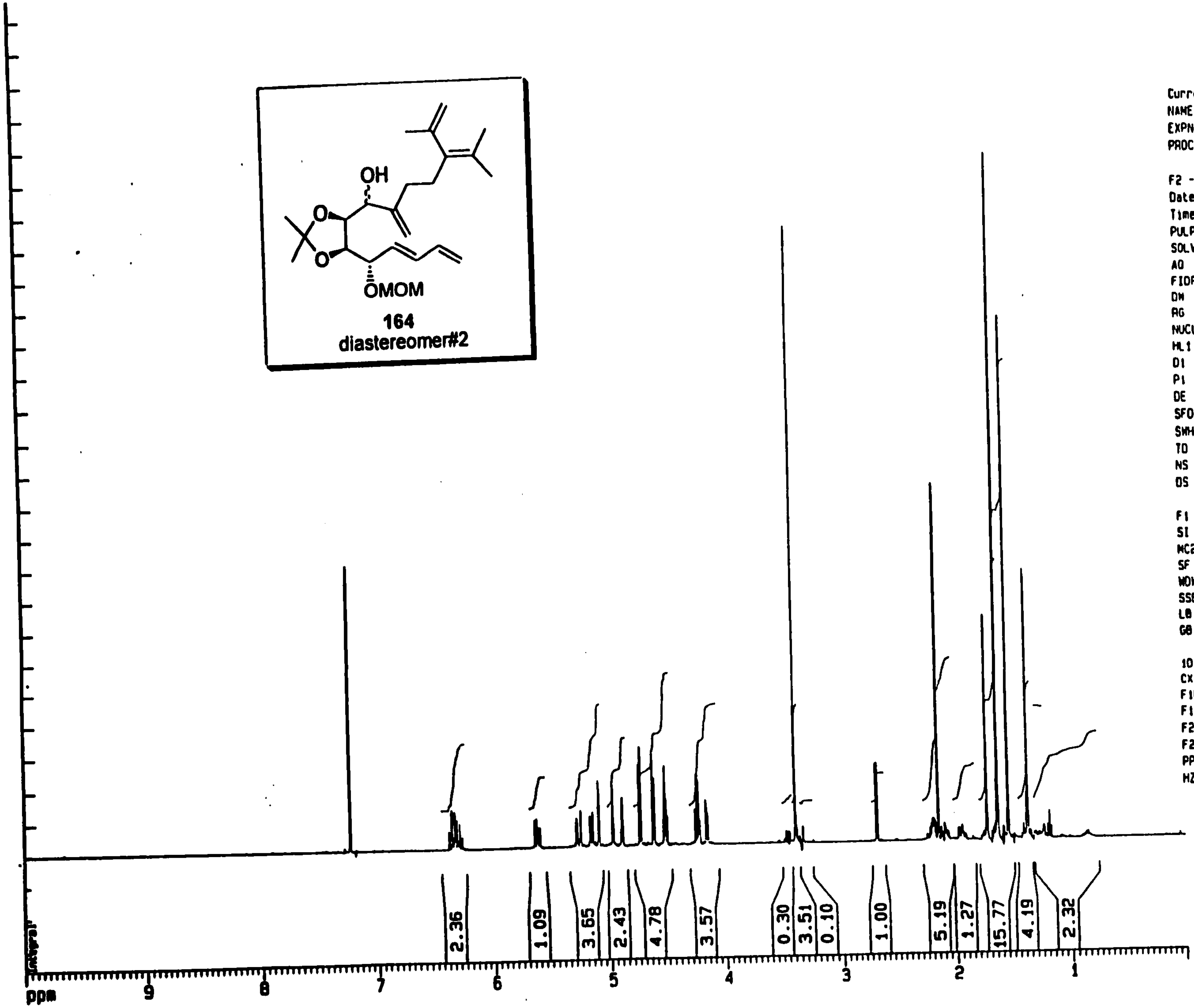
164
diastereomer#1

```
Current Data Parameters
NAME           step_3551
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date              990506
Time               17.04
PULPROG               zg
SOLVENT            CDCl3
AQ          4.6530805 sec
FIDRES      0 107456 Hz
DW             71.0 usec
RG                  2048
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       500.1354311 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/c
```



164
diastereomer#1

```
Current Data Parameters
NAME            steph_3552
EXPNO                    4
PROCNO                   1

F2 - Acquisition Parame
Date                990512
Time                  0.48
PULPROG               zgdc
SOLVENT              CDC13
AQ               1.0485960
FIDRES            0.476837
DW                    16.0
RG                   32768
NUCLEUS                13C
D11              0.0300000
P31                   70.0
S2                      22
HL1                     22
D1               1.0000000
P1                     5.0
DE                    20.0
SFO1           125.7724464
SWH               31250.00
TD                   65536
NS                   10240
DS                       0

F1 - Processing paramet
SI                   32768
MC2                     QF
SF             125.7591571
WDW                     EM
SSB                      0
LB                    1.00
GB                       0

1D NMR plot parameters
CX                   22.00
F1P                152.019
F1                19117.78
F2P                 91.686
F2                11530.41
PPMCM              2.74239
HZCM             344.88040
```



Current Data Parameters

NAME	stepn_3552
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

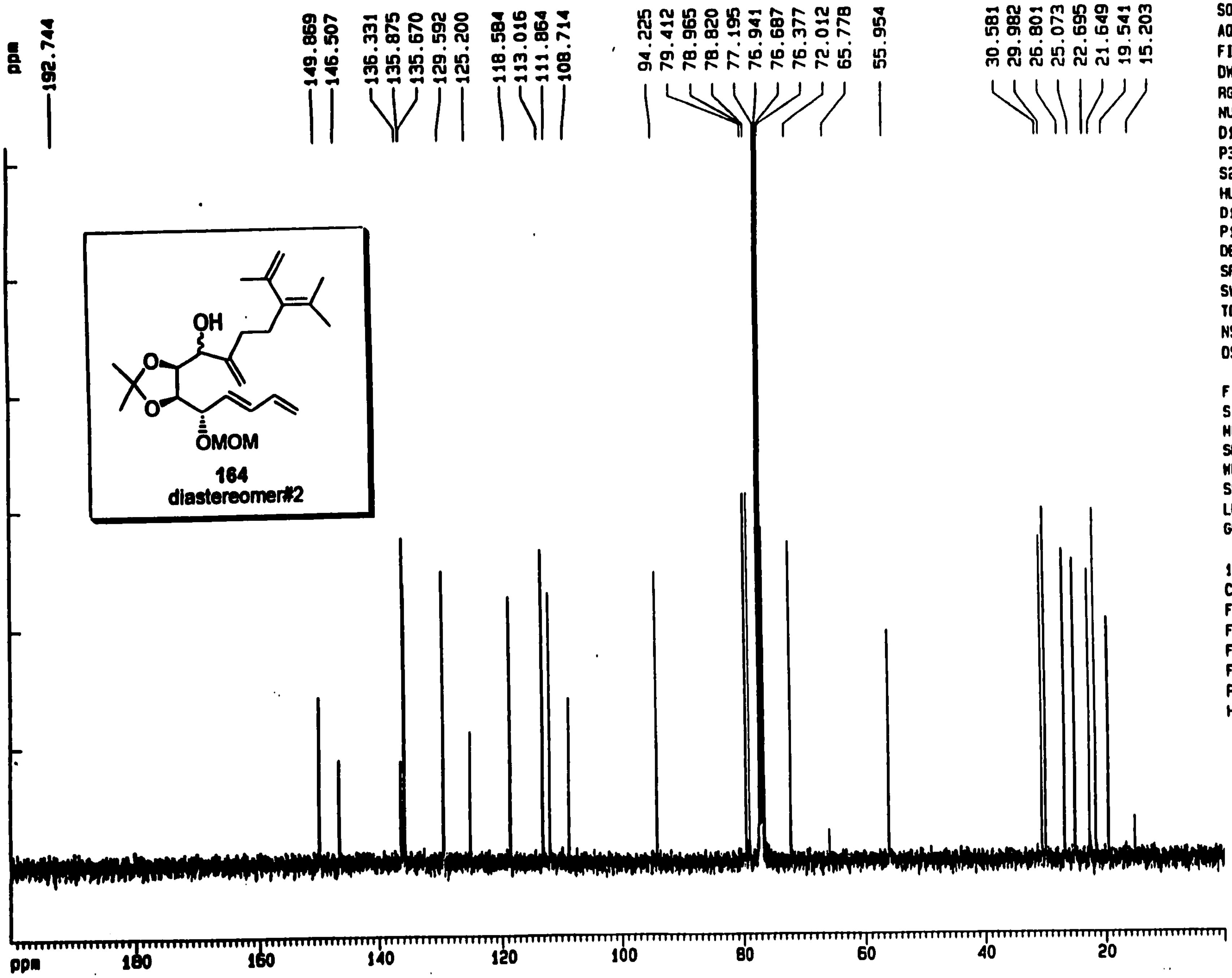
Date	990511
Time	18.34
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	1024
NUCLEUS	1H
HL1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	88.8 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	0

F1 - Processing parameters

SI	32768
MC2	QF
SF	500.1354311 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0

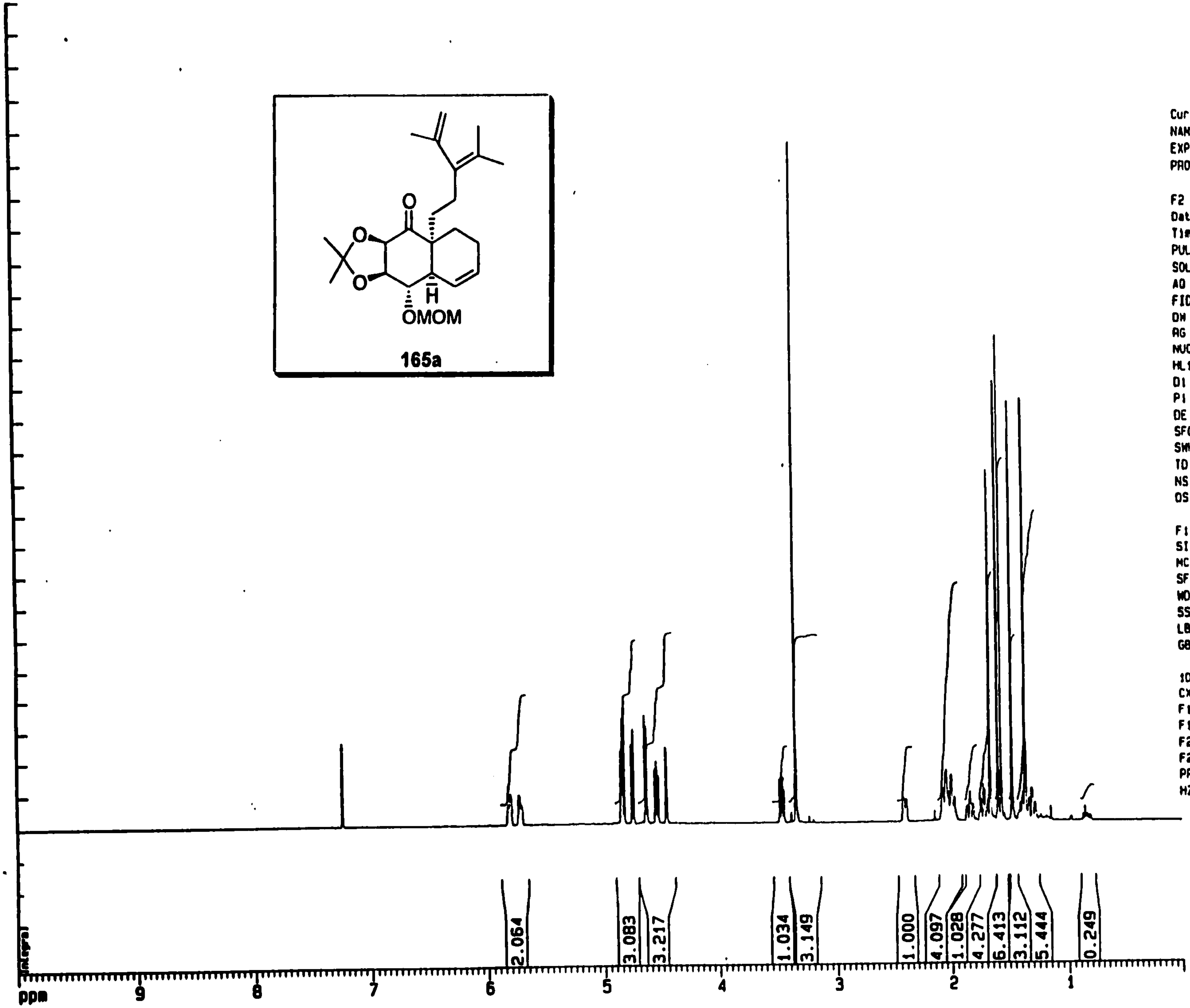
1D NMR plot parameters

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/

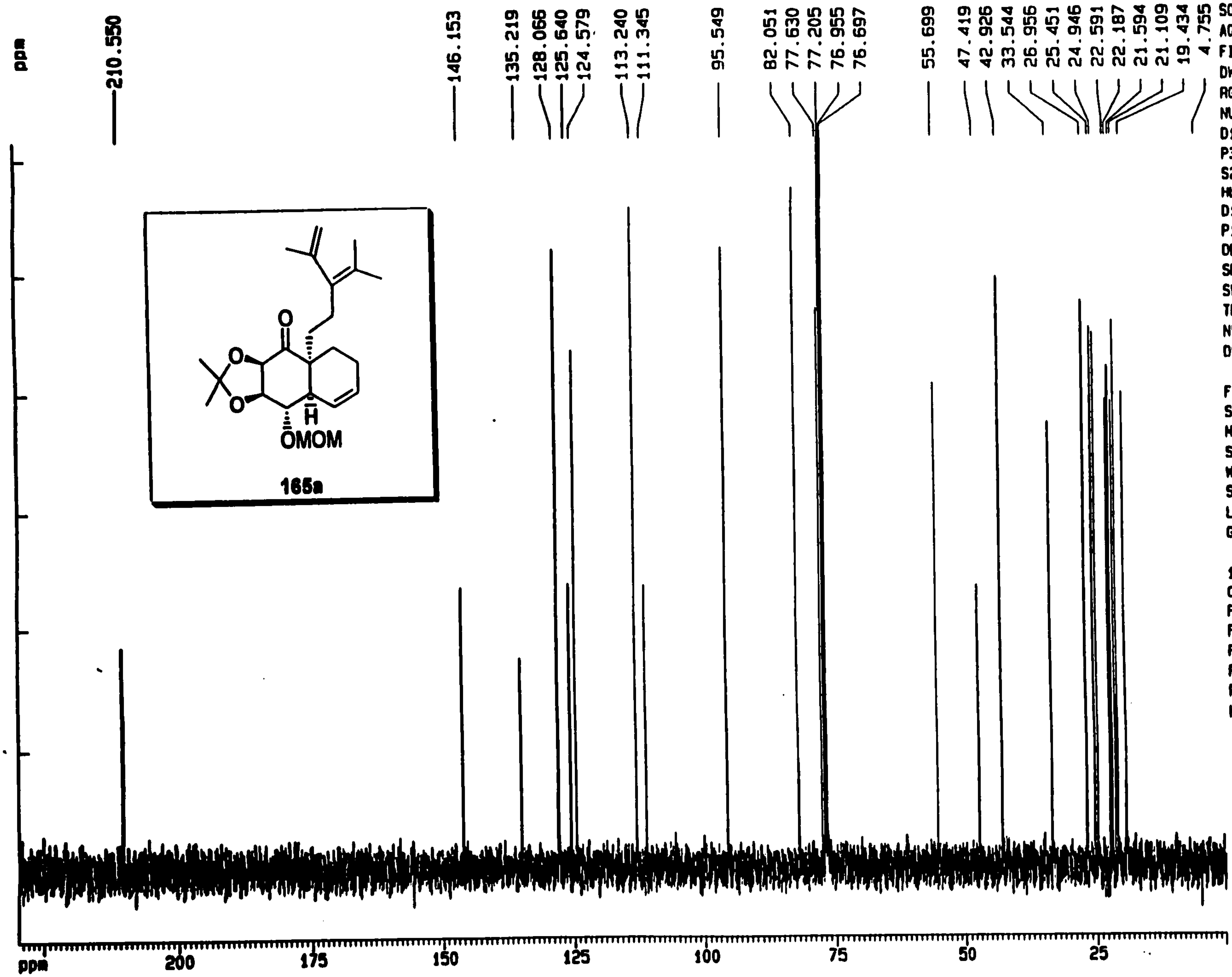


164
diastereomer#2

```
Current Data Parameters
NAME          step_3551
EXPNO                 4
PROCNO                1

F2 - Acquisition Parame
Date             990506
Time              19.58
PULPROG            zgdc
SOLVENT           CDCl3
AQ            1.0485960
FIDRES         0.476837
DW                 16.0
RG                32768
NUCLEUS             13C
D11           0.0300000
P31                70.0
S2                   22
HL1                  22
D1            1.0000000
P1                  5.0
DE                 20.0
SFO1        125.7724464
SWH            31250.00
TD                65536
NS                12288
DS                    0

F1 - Processing paramet
SI                32768
MC2                  QF
SF          125.7591571
WDW                  EM
SSB                   0
LB                 1.00
GB                    0

1D NMR plot parameters
CX                22.00
F1P             200.000
F1             25151.83
F2P               0.000
F2                 0.00
PPMCM           9.09091
HZCM         1143.26501
```

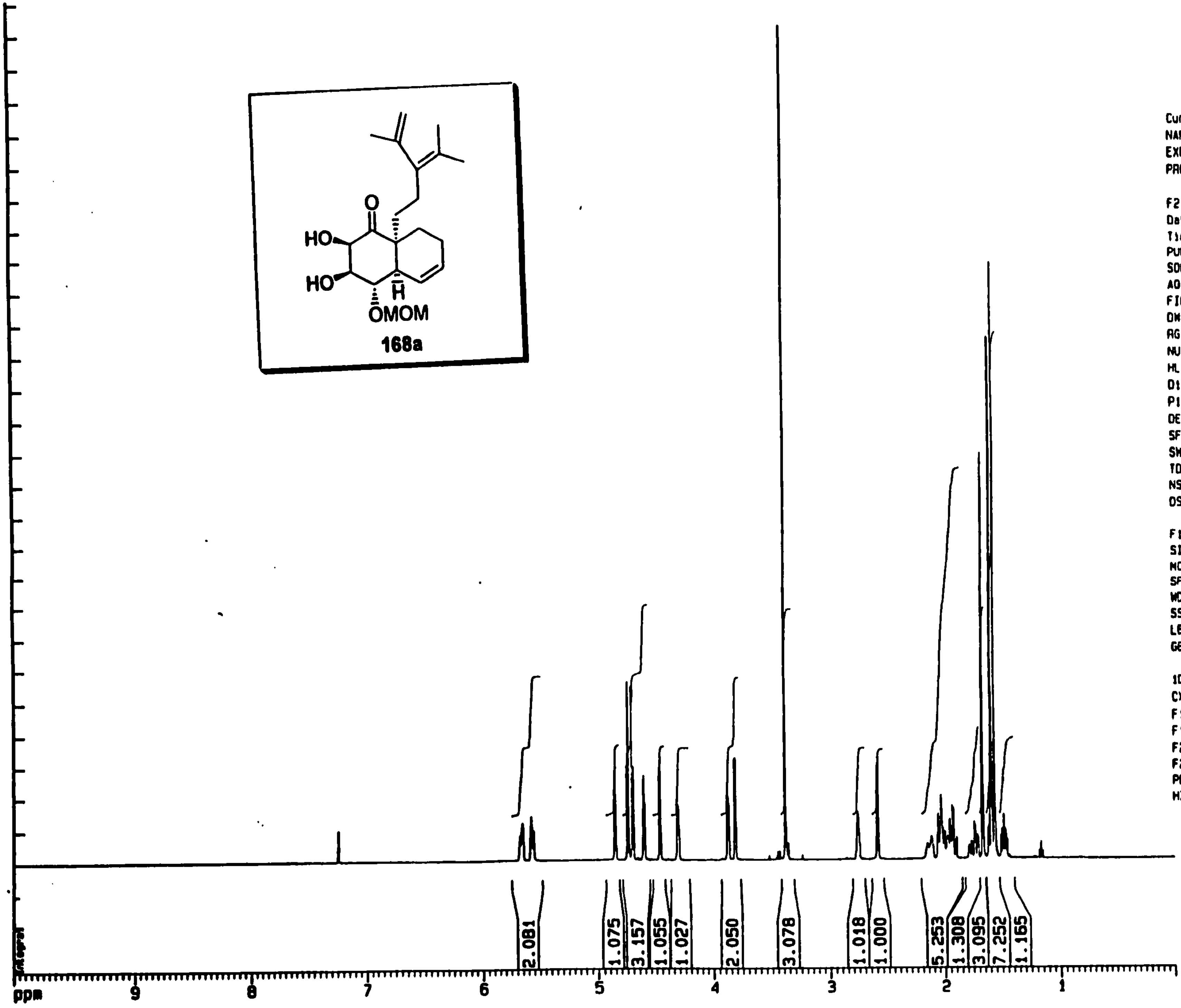


```
Current Data Parameters
NAME           step_357
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date             990513
Time              15.06
PULPROG              zg
SOLVENT           CDCl3
AD         4.6530805 sec
FIDRES      0.107456 Hz
DW             71.0 usec
RG                  512
NUCLEUS              1H
HL1                0 dB
D1         0.0100000 sec
P1              3.0 usec
DE             88.8 usec
SFO1    500.1381707 MHz
SWH          7042.25 Hz
TD                65536
NS                   16
DS                    0

F1 - Processing parameters
SI                32768
MC2                  QF
SF      500.1354311 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/
```

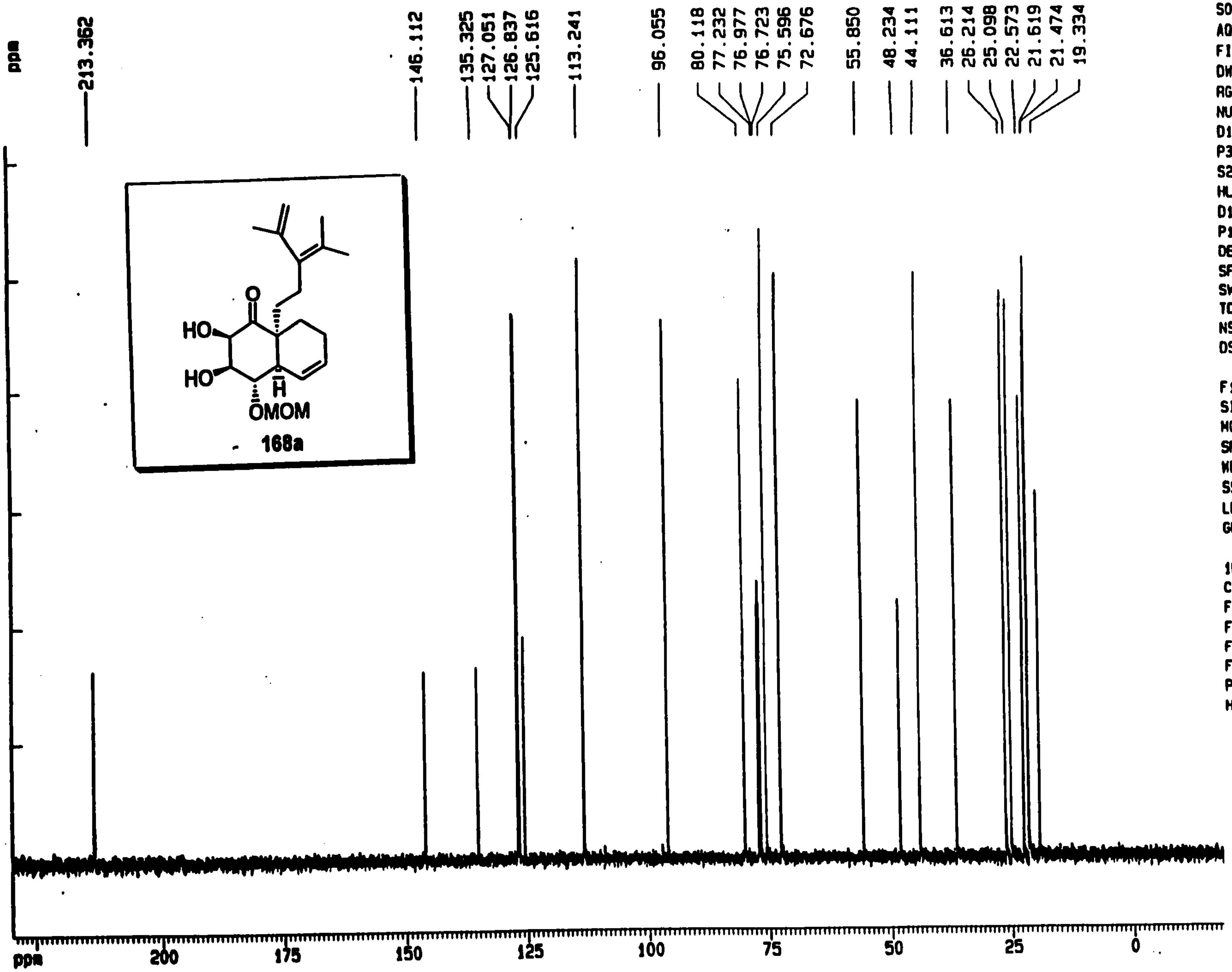


165a

```
Current Data Parameters
NAME             step_357
EXPNO                   4
PROCNO                  1

F2 - Acquisition Parame
Date               990513
Time                16.12
PULPROG              zgdc
SOLVENT             CDC13
AQ              1.0485960
FIDRES           0.476837
DW                   16.0
RG                  32768
NUCLEUS               13C
D11             0.0300000
P31                  70.0
S2                     22
HL1                    22
D1              1.0000000
P1                    5.0
DE                   20.0
SFO1          125.7724464
SWH              31250.00
TD                  65536
NS                    488
DS                      0

F1 - Processing paramet
SI                  32768
MC2                    QF
SF            125.7591571
WDW                    EM
SSB                     0
LB                   1.00
GB                      0

1D NMR plot parameters
CX                  22.00
F1P               149.092
F1               18749.65
F2P                74.273
F2                9340.49
PPMCM             3.40086
HZCM            427.68930
```

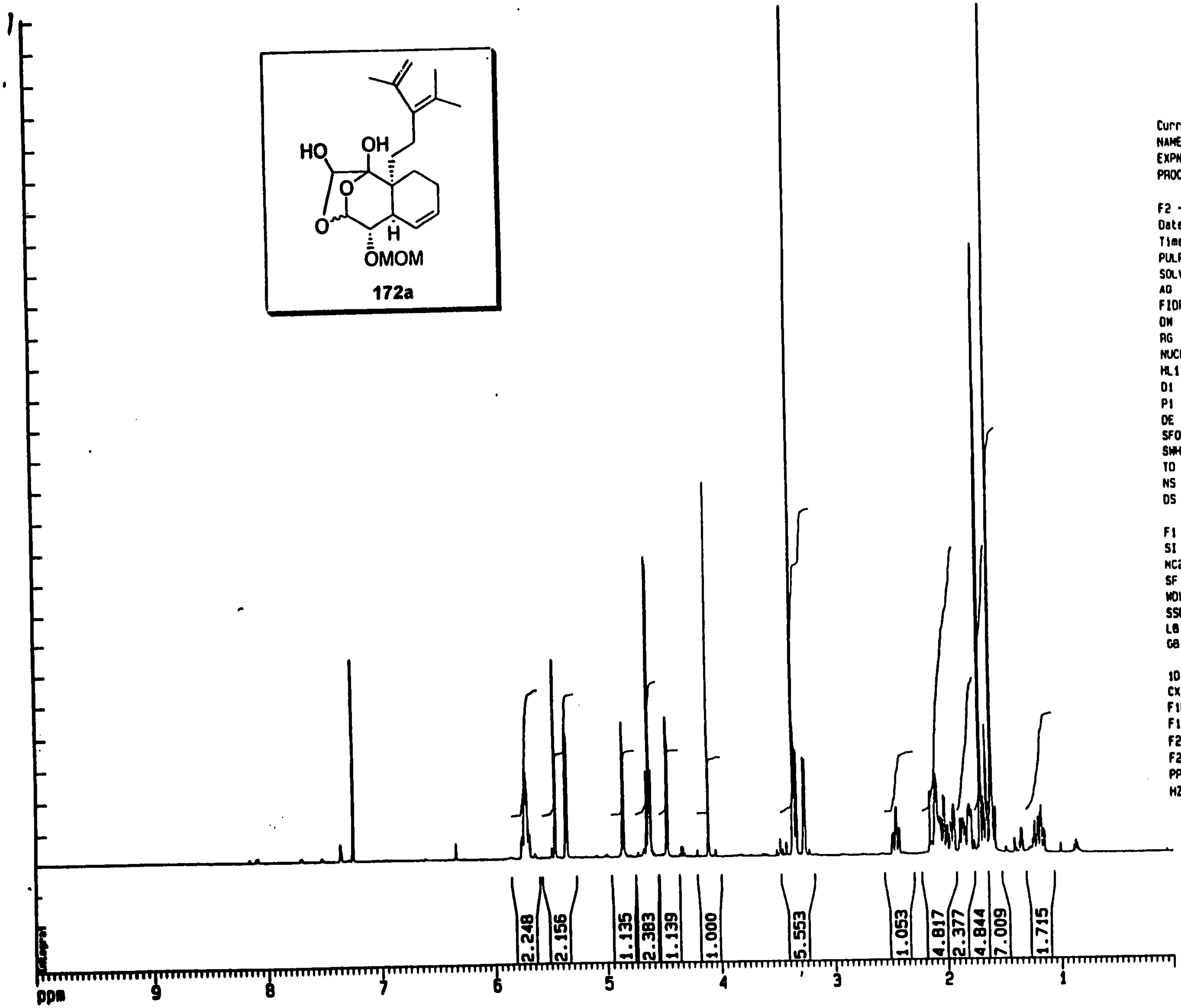

168a

```
Current Data Parameters
NAME          step_4142
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date             990827
Time              16.42
PULPROG              zg
SOLVENT           CDCl3
AQ         4.6530805 sec
FIDRES      0.107456 Hz
DW             71.0 usec
RG                  128
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       500.1354311 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/c
```



168a

Current Data Parameters	
NAME	step_4142
EXPNO	3
PROCNO	1
F2 - Acquisition Parame	
Date	990827
Time	17.13
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	385
DS	0
F1 - Processing paramet	
SI	32768
MC2	QF
SF	125.7591571
WDW	EM
SSB	0
LB	1.00
GB	0
1D NMR plot parameters	
CX	22.00
F1P	229.918
F1	28914.29
F2P	-18.573
F2	-2335.70
PPMCM	11.29504
HZCM	1420.45435



172a

Current Data Parameters

NAME	step_36522
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

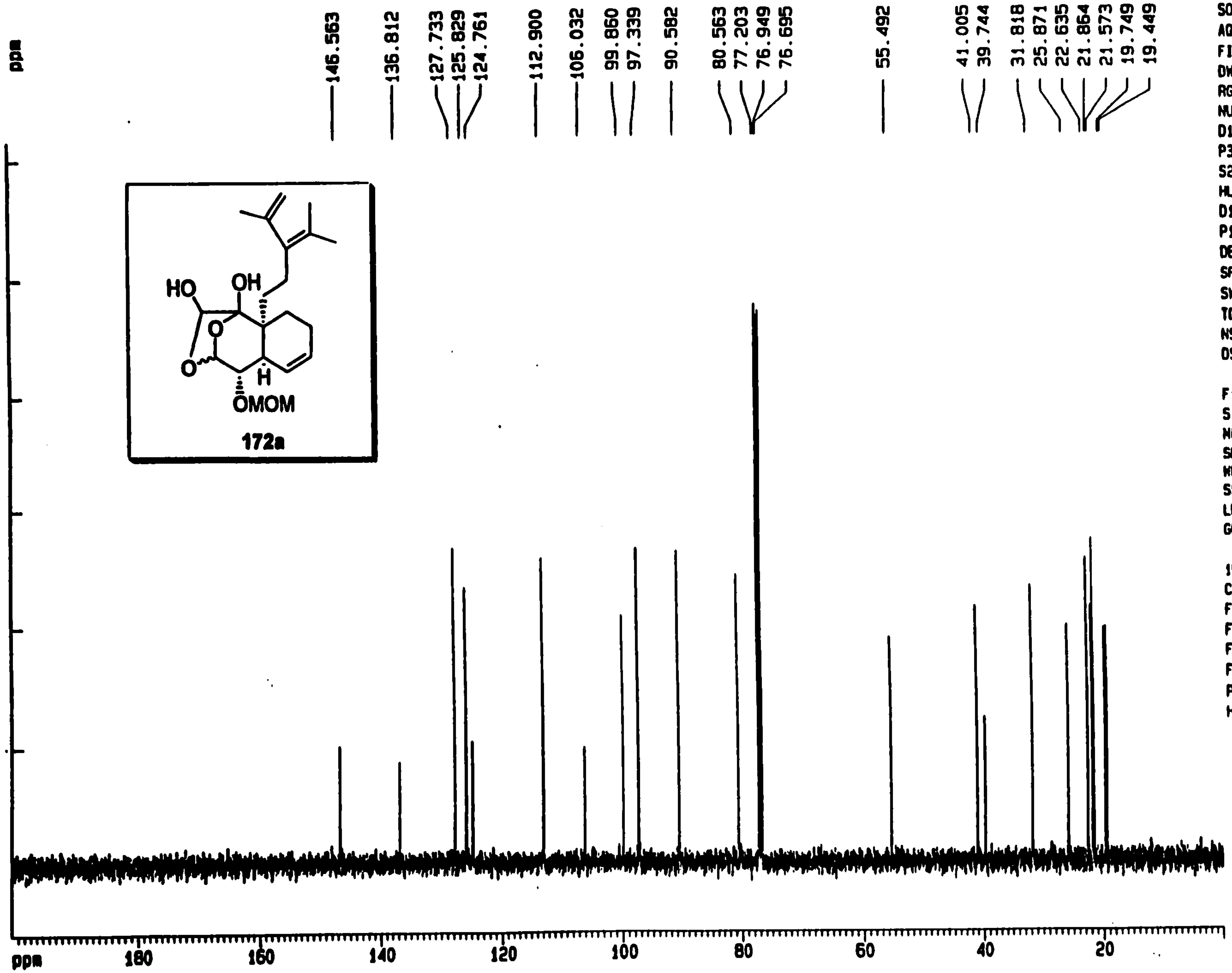
Date	990521
Time	10.40
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	512
NUCLEUS	1H
HL1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	88.8 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	0

F1 - Processing parameters

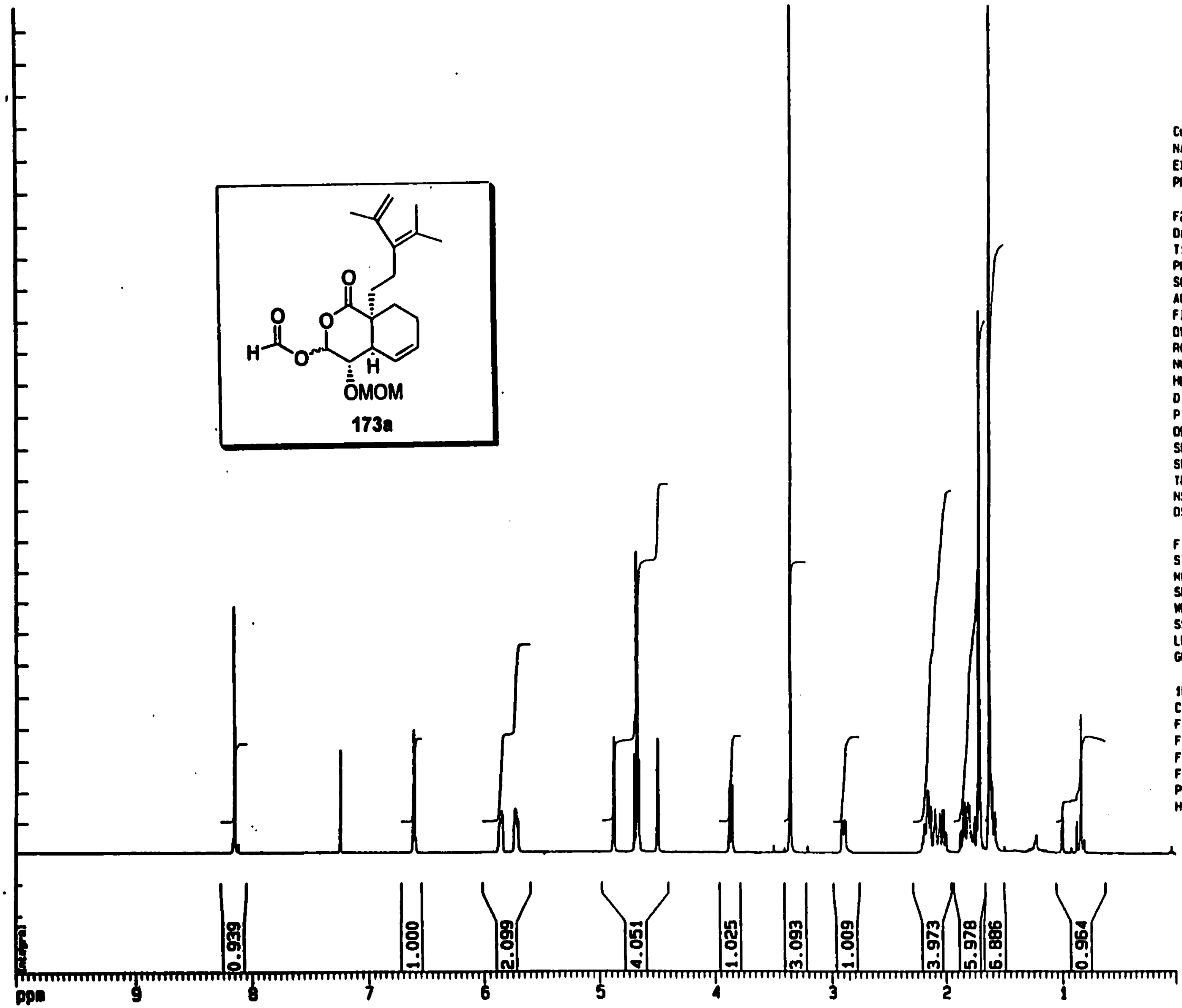
SI	32768
MC2	QF
SF	500.1354311 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0

1D NMR plot parameters

CX	22.00 cm
F1P	5.967 ppm
F1	2984.10 Hz
F2P	3.150 ppm
F2	1575.61 Hz
PPMCM	0.12801 ppm/
HZCM	64.02254 Hz/

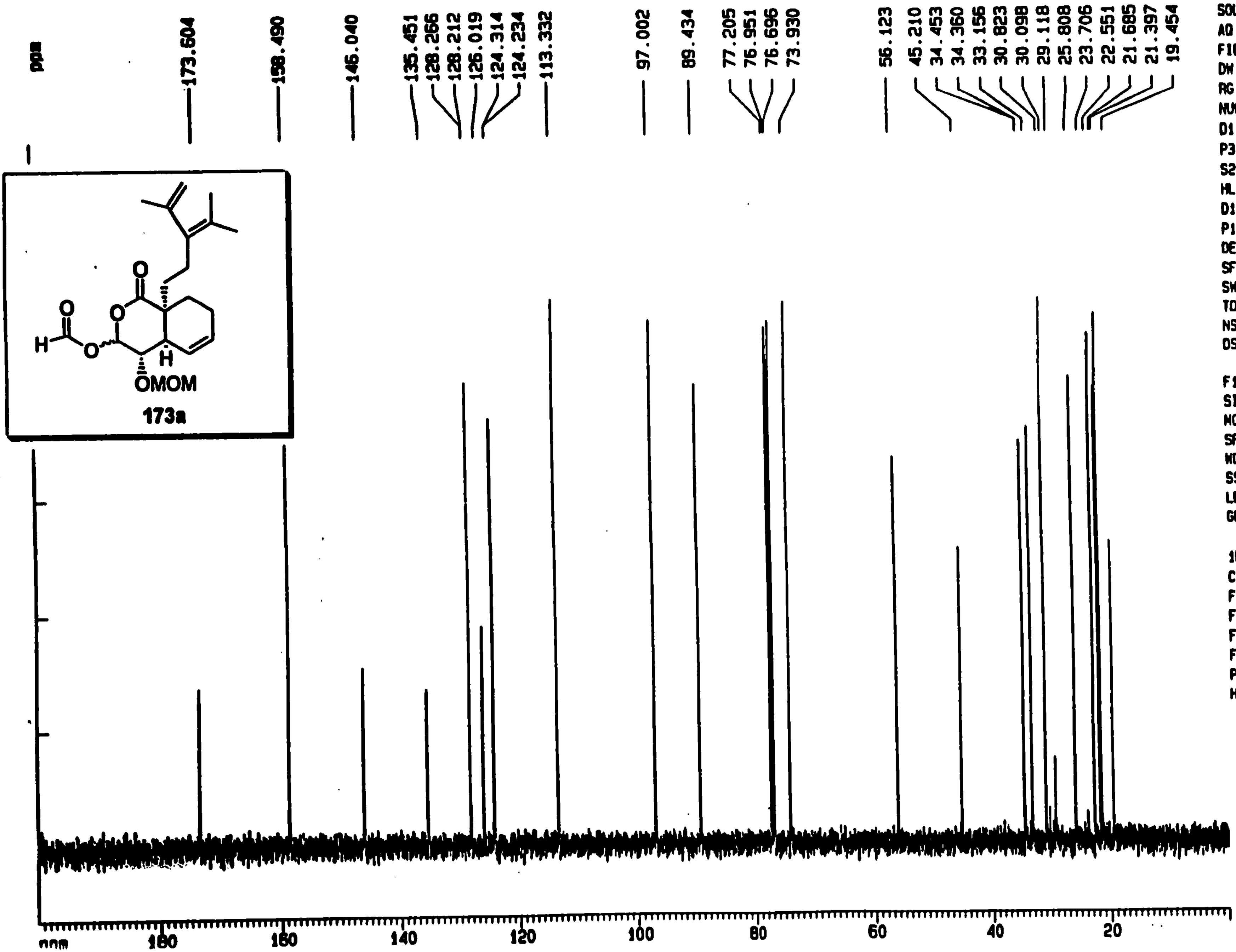


Current Data Parameters	
NAME	step_36522
EXPNO	4
PROCNO	1
F2 - Acquisition Parame	
Date	990521
Time	11.41
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	601
DS	0
F1 - Processing paramet	
SI	32768
MC2	QF
SF	125.7591571
WDW	EM
SSB	0
LB	1.00
GB	0
1D NMR plot parameters	
CX	22.00
F1P	150.119
F1	18878.81
F2P	88.836
F2	11171.95
PPMCM	2.78558
HZCM	350.31158



173a

```
Current Data Parameters
NAME            step_637
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date            20001116
Time                2.11
PULPROG               zg
SOLVENT            CDCl3
AQ          4.6530805 sec
FIDRES       0.107456 Hz
DW              71.0 usec
RG                  1024
NUCLEUS               1H
HL1                 0 dB
DI          0.0100000 sec
P1               3.0 usec
DE              88.8 usec
SFO1     500.1381707 MHz
SWH           7042.25 Hz
TD                 65536
NS                     8
DS                     0

F1 - Processing parameters
SI                 32768
MC2                   QF
SF       500.1354311 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/cm
HZCM      227.33429 Hz/cm
```



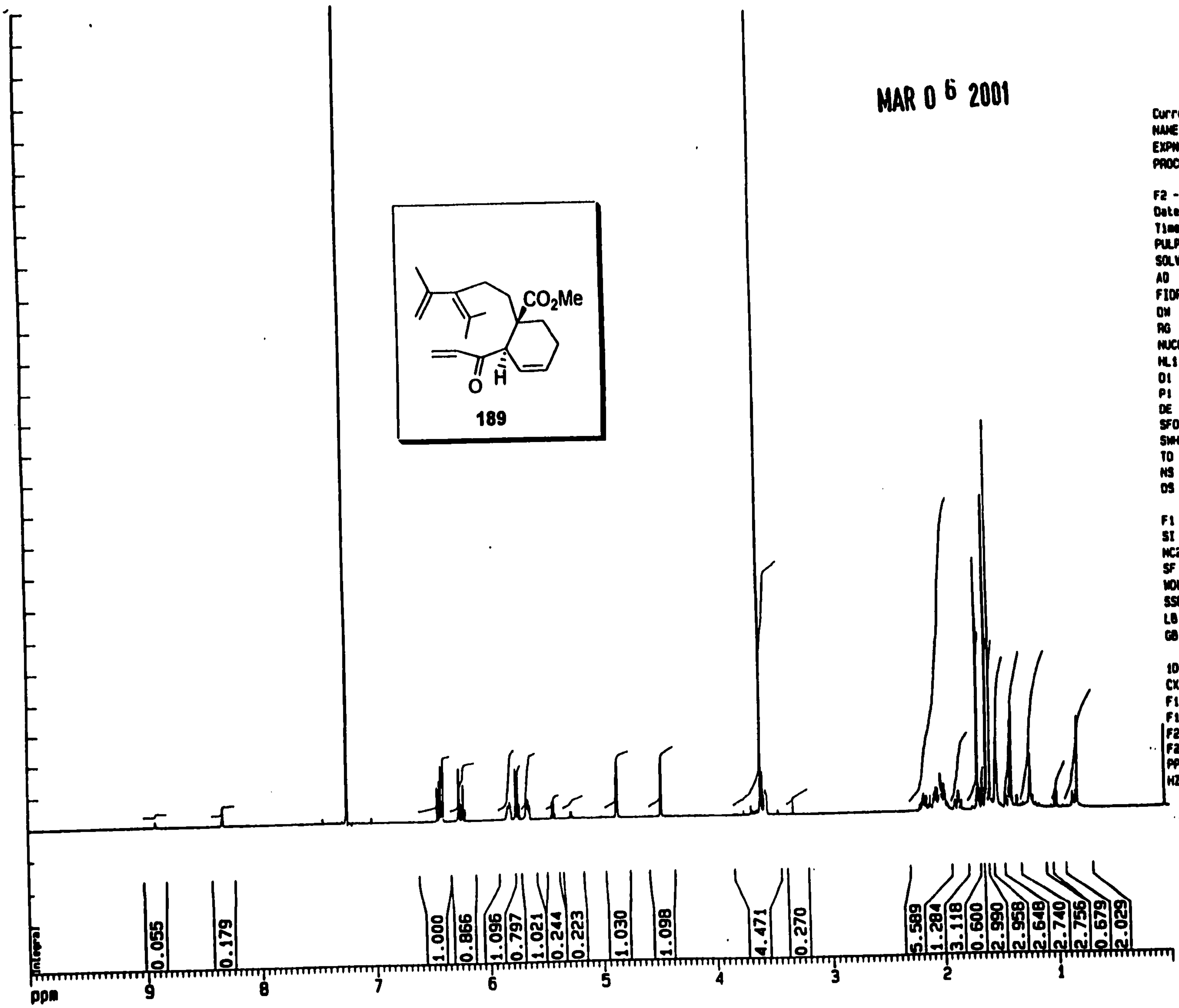
Current Data Parameters	
NAME	step_637
EXPNO	4
PROCNO	1

F2 - Acquisition Parame	
Date	20001116
Time	3.09
PULPROG	zgdc
SOLVENT	CDC13
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	561
DS	0

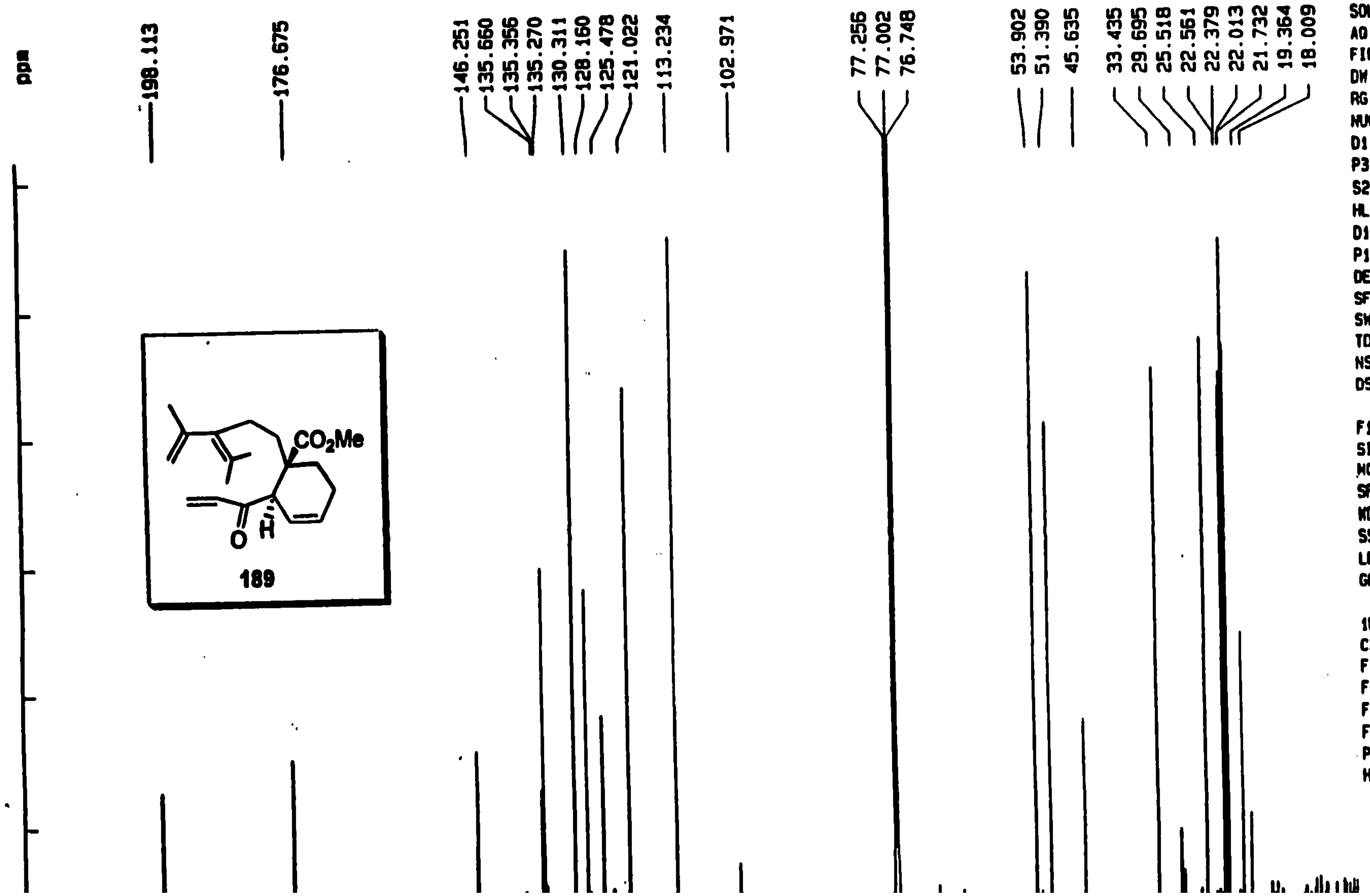
F1 - Processing paramet	
SI	32768
MC2	QF
SF	125.7591571
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters	
CX	22.00
F1P	177.011
F1	22260.81
F2P	86.437
F2	10870.21
PPMCM	4.11703
HZCM	517.75446

MAR 0 6 2001



```
Current Data Parameters
NAME          steph_6682
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date            20010300
Time               13.54
PULPROG               zg
SOLVENT            CDCl3
AQ          4.6530805 sec
FIDRES       0.107456 Hz
DW               71.0 usec
RG                  2048
NUCLEUS               1H
PL1                 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         500.1354311 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/
```



189

```
Current Data Parameters
NAME          steph_6682
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parame
Date            20010300
Time               19.33
PULPROG             zgdc
SOLVENT            CDCl3
AQ             1.0485960
FIDRES          0.476837
DW                  16.0
RG                 32768
NUCLEUS              13C
D11            0.0300000
P31                 70.0
S2                    22
HL1                   22
D1             1.0000000
P1                   5.0
DE                  20.0
SFO1         125.7724464
SWH             31250.00
TD                 65536
NS                 12288
DS                     0

F1 - Processing paramet
SI                 32768
MC2                   QF
SF           125.7591485
WDW                   EM
SSB                    0
LB                  1.00
GB                     0

1D NMR plot parameters
CX                 22.00
F1P              220.000
F1              27667.01
F2P                0.000
F2                  0.00
PPMCM           10.00000
HZCM          1257.59143
```