THE TOTAL SYNTHESIS OF (±)-β-PANASINSENE

by

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Department of CHEMISTRY

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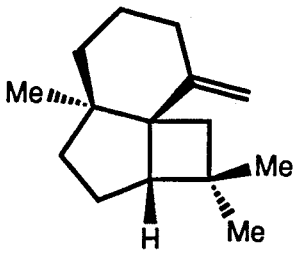
ABSTRACT

This thesis describes a total synthesis of the sesquiterpenoid (±)-β-panasinsene (**31**).

Two different routes for the synthesis of a bicyclic enone of general structure **74** were investigated. An unsuccessful attempt to generate a synthetically useful enone **74** employed the Pauson-Khand cyclization of an enyne **75** (R= Me; XX= $S(CH_2)_3S$ or MeS, *p*-$MeC_6H_4SO_2$). A second approach, which was based on the Weiss-Cook condensation of glyoxal (**44**) with dimethyl 3-oxoglutarate (**45**) led to the production of the dione **43**, which was converted, *via* several steps, into the enone **159**.

The enone **159** was subjected to a methylenecyclohexane annulation sequence. Thus, copper (I)-catalyzed conjugate addition of the Grignard reagent **7** to **159**, followed by intramolecular alkylation of the resultant chloro keto ester, provided the tricyclic intermediate **171**. Sequential reduction of the keto function in **171**, deoxygenation of the resultant hydroxyl function, and hydrolysis of the ketal moiety gave rise to the keto ester **182**. Subjection of **182** to a photochemical Wolff ring contraction reaction sequence provided a mixture of the diesters **200** and **201**. Alkylation of the mixture of **200** and **201** with methyl iodide, followed by a reduction-oxidation sequence, gave the dialdehyde **217**. Wolff-Kishner reduction of **217** resulted in the simultaneous deoxygenation of both of the carbonyl groups and successfully completed the synthesis of (±)-β-panasinsene (**31**).



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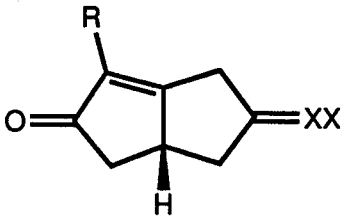

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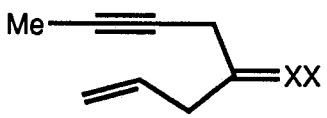

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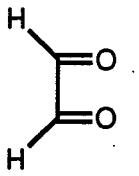

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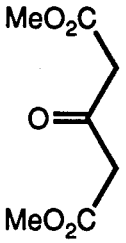

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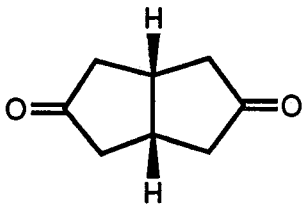

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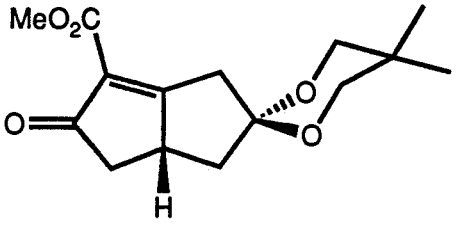

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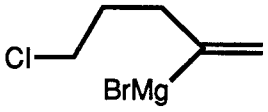

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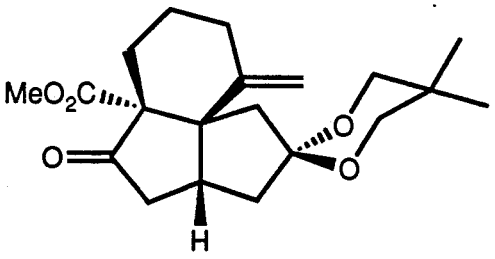

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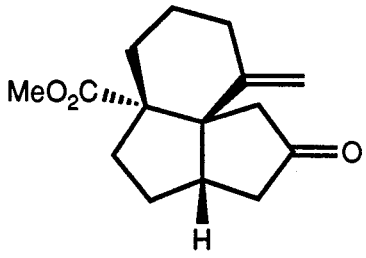

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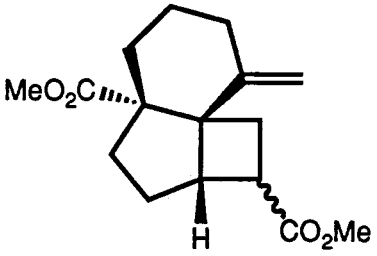

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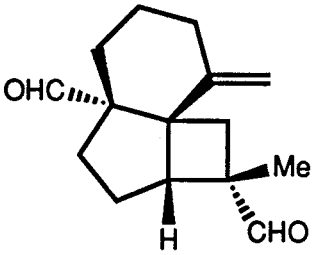

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LIST OF ABBREVIATIONS

Ac	Acetyl
AIBN	2,2'-azobisisobutyronitrile
APT	attached proton test
aq	aqueous
br	broad
b.p.	boiling point
n-Bu	*normal*-butyl
t-Bu	*tertiary*-butyl
cat	catalyst, catalytic
COSY	correlation spectroscopy
d	doublet
DEG	diethylene glycol
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMSO	dimethyl sulfoxide
E^+	electrophile
equiv	equivalents
Et	ethyl
g	grams
glc	gas-liquid chromatography
h	hour(s)
HETCOR	heteronuclear correlation spectroscopy
HMPA	hexamethylphosphoramide
Hz	hertz
ir	infrared

LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
lit.	literature
m	multiplet
M	molar
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mmol	millimole(s)
mol	mole(s)
m.p.	melting point
Ms	methanesulfonyl
MS	mass spectrum (low resolution)
m/z	mass to charge ratio
N	normal
NMO	*N*-methylmorpholine *N*-oxide
nmr	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
Nu:	nucleophile
p	page
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
PTC	phenoxythiocarbonyl
Pyr	pyridine

q	quartet
quant	quantitative
rel. int.	relative intensity
r t	room temperature
s	singlet (nmr); strong (ir)
t	triplet
TBDMS	*tertiary*-butyldimethylsilyl
T f	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
t l c	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	tetramethylsilane
TMS-	trimethylsilyl
p-Tol	*para*-tolyl
p-Ts	*para*-toluenesulfonyl
v	very
w	weak

ACKNOWLEDGEMENTS

This thesis would have been impossible were it not for the input, in various different ways, of many people.

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I. INTRODUCTION

1.1. The Rationale.

The synthesis of biologically useful, theoretically interesting, and stereochemically or structurally challenging molecules has provided the basis for much of the research in synthetic organic chemistry. Presently, the trend seems to be towards the study of "substances and reactions relevant to life"[1] which means that inhibitors for important enzymes or receptors[2] are becoming key target molecules. The enantiomeric purity of a biologically active product that has been made synthetically in a laboratory can have major implications in biological systems especially if one enantiomer exhibits undesirable activity. Though in recent years there has been a greater emphasis placed on the synthesis of enantiomerically pure compounds as compared to the synthesis of racemic mixtures, the synthesis of racemic mixtures is still informative. However, the successful synthesis of any molecule, in a racemic or an enantiomerically pure form, depends largely on the chemist's ability to analyze the target in a logical retrosynthetic* manner,[3] and to develop a feasible synthetic route for its preparation. Despite careful retrosynthetic analysis, the actual implementation of any route may be unsuccessful due either to the

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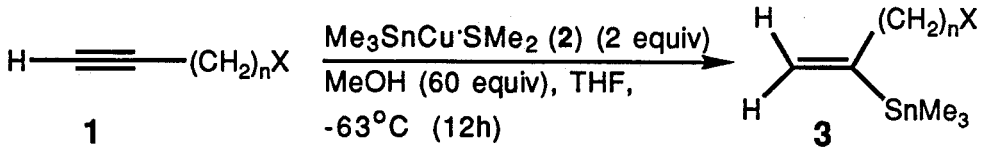
* Retrosynthetic (or antithetic) analysis is a technique that has been developed in order to transform the structure of the synthetic target into a logical sequence of progressively simpler structures which finally leads to simple or commercially available chemicals. Each step in the retrosynthetic direction (a transform) corresponds to a chemical reaction in the synthetic direction.[3]

failure of a particular reaction or due to the lack of procedures for carrying out the desired transformation. Consequently, alternative routes must be envisaged in advance, particularly for reactions that may be synthetically challenging. In cases where the implementation of a route has failed, other options must be explored or new methods must be found in order to circumvent the obstruction.

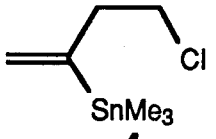
One of the currently fruitful areas of research with regard to developing new reactions is organometallic chemistry. From an organic chemist's point of view, an important test of the utility of a particular organometallic reagent is its applicability to the solution of a given synthetic organic chemical problem.

The use of organotin reagents in organic synthesis has been explored by many research groups including our own.[4] In 1983, it was first reported that ω-substituted 1-alkynes (**1**) undergo a regioselective reaction with (trimethylstannyl)copper (I)-dimethyl sulfide complex (**2**) in the presence of 60 equivalents of methanol (THF, -63°C) to give the corresponding 2-trimethylstannyl-1-alkenes (**3**) in a good yields (equation I-1).[5] Functional groups tolerated in the reaction are halides, hydroxyls, and trialkylsilyl or tetrahydropyranyl ethers. Subsequent research has demonstrated that the 2-trimethylstannyl-1-alkene reagents **4**[6] and **5**[7] can by transmetallation with methyllithium be converted into the corresponding lithio species, which can then be transformed into the corresponding Grignard or organocopper reagents. For example, 5-chloro-2-trimethylstannyl-1-pentene (**5**) was reacted with methyllithium (THF, -78°C, 15 min) to make the vinyllithium species



1 3 (I-1)

n = 1-4
X= Cl, OH, OTHP, OTBDMS



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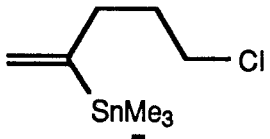
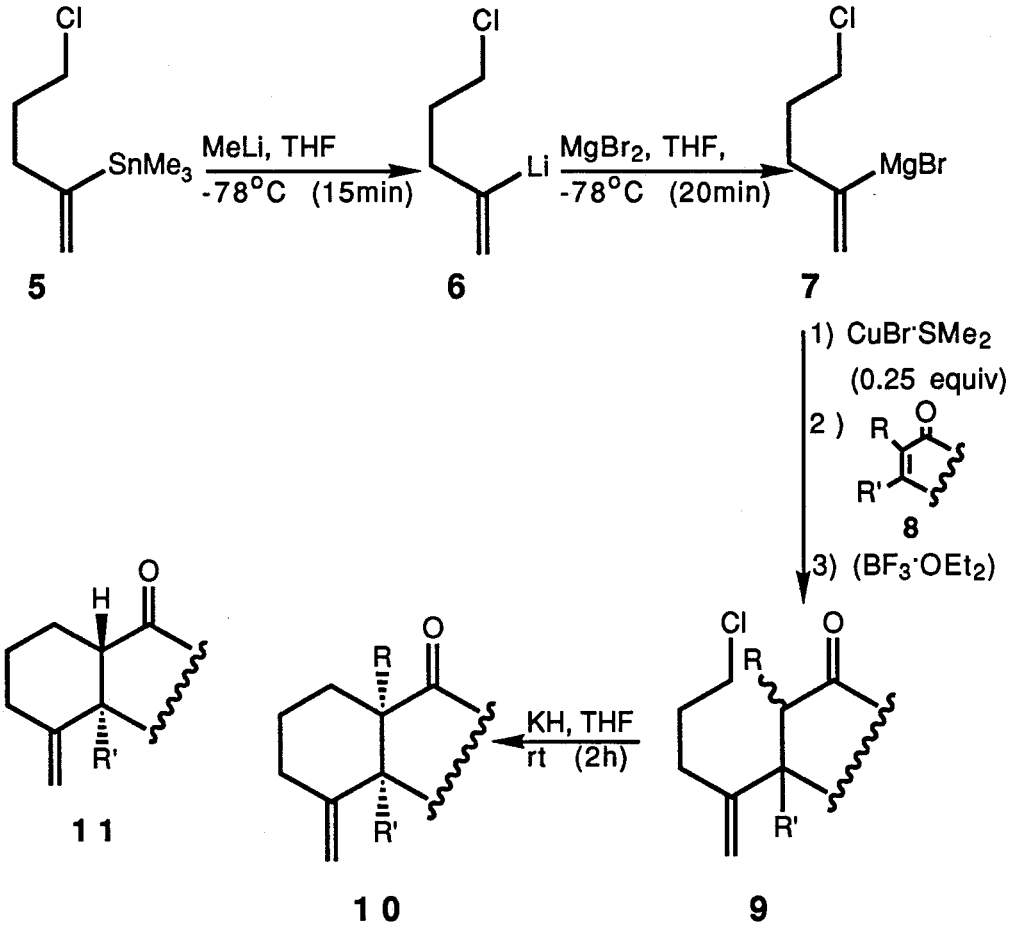


5

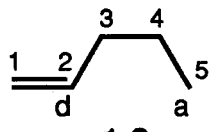
6.[7] Treatment of **6** with anhydrous magnesium bromide produced the Grignard reagent **7**, which was found to undergo a copper (I)-catalyzed ($CuBr{\cdot}SMe_2$, 0.25 equiv) conjugate addition reaction to enones of general structure **8**. In the cases of enones with a trisubstituted double bond, (e.g. **8**, R or R'=Me), boron trifluoride etherate was added as an additional catalyst to improve the efficiency of the conjugate addition. The chloro ketones **9** were cyclized with potassium hydride (THF, room temperature, 2 hours) to give exclusively the *cis*-fused bicyclic products (**10**) for cases where subsequent equilibration was impossible (R=Me). If equilibration of the bicyclic product was possible (R=H), then varying amounts of the *trans*-fused bicyclic ketone (**11**) were also obtained as the minor component of the product mixture (Scheme I-1).[7] The overall process described above demonstrates the utilization of the chloro vinylstannane **5** as a bifunctional conjunctive reagent* in which the two reactive sites have been selectively, sequentially deployed. In these reactions, **5** serves as

* A bifunctional conjunctive reagent is a reagent with two reactive sites which is incorporated in whole or in part into a substrate molecule to increase its structural complexity.[8]

the synthetic equivalent of the 1-pentene donor[2],acceptor[5]-synthon (d^2,a^5-synthon) **12**. The overall result of the sequence of reactions, in which **8** is converted into **10** and/or **11**, is the annulation of a methylenecyclohexane unit onto a cyclic enone.



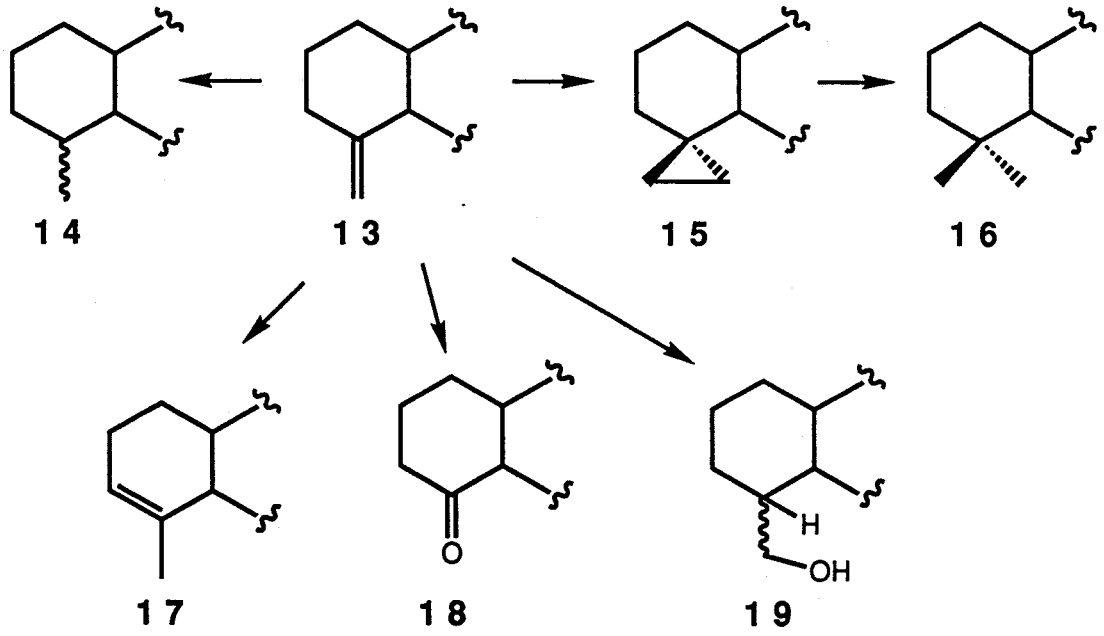
Scheme I-1



12

The methylenecyclohexane annulation process is an important tool in natural products synthesis because the methylenecyclohexane

ring and derivatives thereof (part structures **13**, **14**, **16-19**, Scheme I-2) are common in terpenoid natural products. Thus, the olefinic function in the methylenecyclohexane annulated product (**13**) may be hydrogenated to give the corresponding methyl group present in **14** or it may be cyclopropanated to give **15**. The cyclopropyl ring in **15** may then be hydrogenolyzed to give the *gem*-dimethyl group found in **16**. An acid-catalyzed double bond isomerization in **13** would provide **17**. Alternatively, the methylene group may be cleaved to give the ketone **18**, or hydroxylated to give **19**.

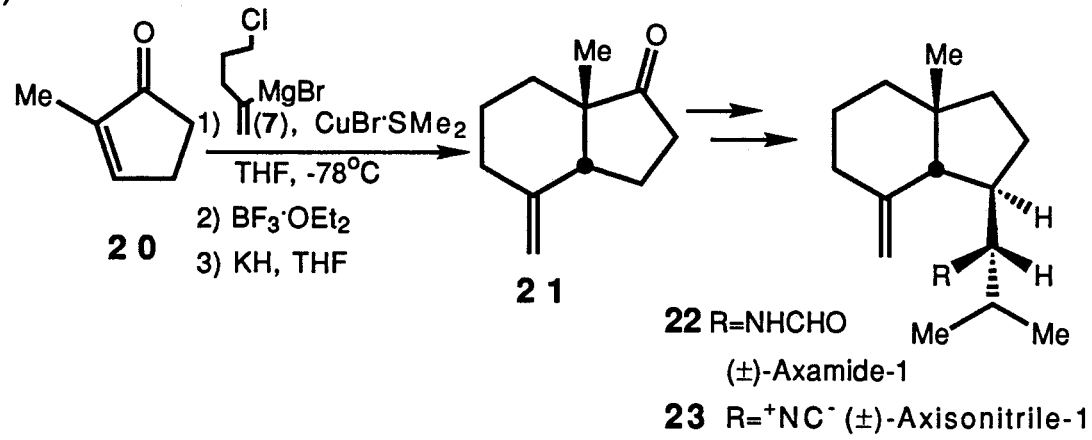


Scheme I-2

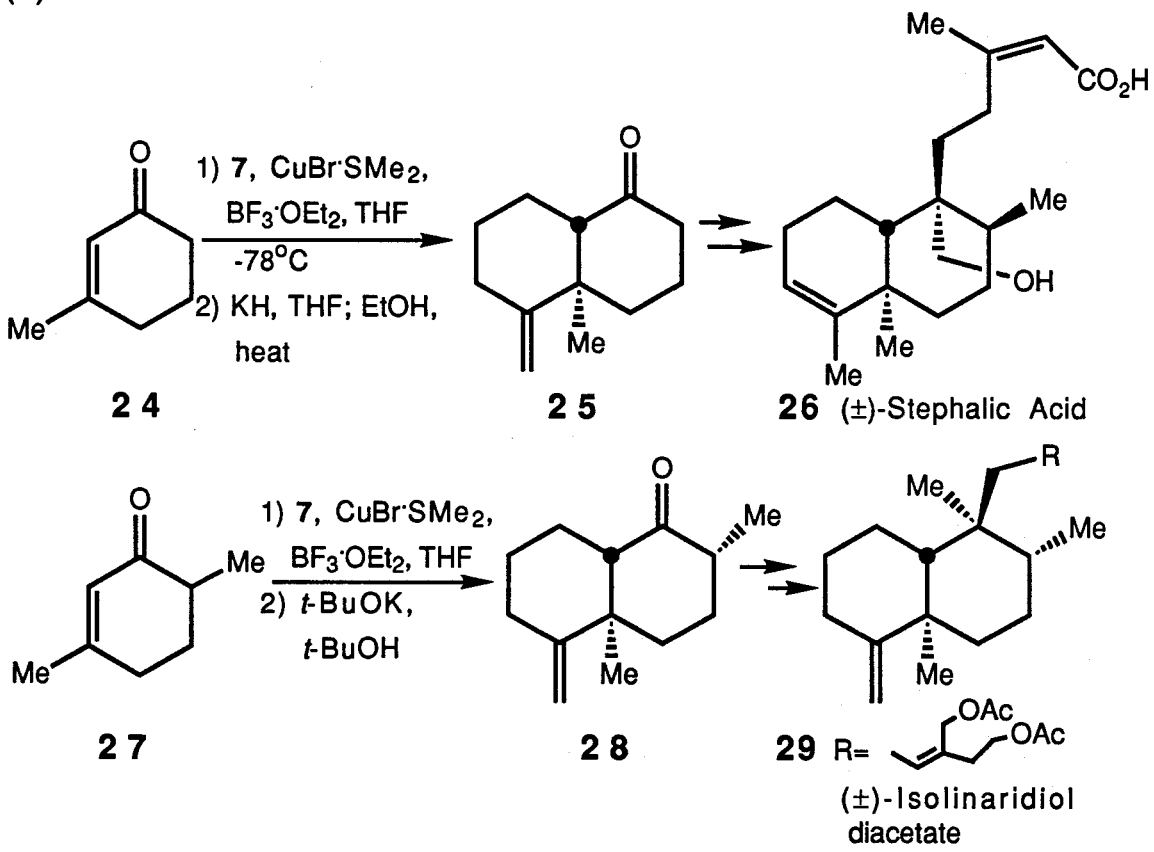
The annulation procedure has been used in the syntheses of natural products with the bicyclic axane[9] and clerodane skeletons[10,11] and has also been employed in the total synthesis of the sesterterpenoid (±)-palauolide[12] (Scheme I-3). Each of these

syntheses involved the annulation of the methylenecyclohexane unit onto a cyclic enone with a trisubstituted double bond. Thus, in the synthesis of the axane skeleton, conjugate addition to the cyclopentenone **20** of the Grignard reagent **7** (derived from the vinylstannane **5**) was catalyzed by copper (I) bromide-dimethyl sulfide complex and boron trifluoride etherate. The resultant chloro ketone was cyclized as described earlier to give only the *cis*-fused bicyclic ketone **21**, which was then transformed via a series of reactions into (±)-axamide-1 (**22**) and (±)-axisonitrile-1 (**23**). In a similar manner, conjugate addition of the Grignard reagent **7** to the cyclohexenone **24**, followed by cyclization of the resultant chloroketone, gave a mixture of the *cis*- and *trans*-fused bicyclic ketones in which the *cis*-fused product predominated. The mixture was converted by equilibration (KH/EtOH) to another mixture in which the *trans*-fused product (**25**) was the major component. Subsequent reactions converted the bicyclic ketone **25** into (±)-stephalic acid (**26**). A different cyclohexenone (**27**) was used for the syntheses of the clerodane (±)-isolinaridiol diacetate (**29**) and the sesterterpenoid (±)-palauolide (**30**), but a similar conjugate addition/ cyclization sequence led to the formation of a mixture of the *cis*- and *trans*-fused bicyclic ketones in which the *cis*-fused compound predominated. Equilibration (*t*-BuOK/*t*-BuOH) of the mixture led to the formation of another mixture in which the *trans*-fused product (**28**) was the major component. The bicyclic ketone **28** then was converted into (±)-isolinaridiol diacetate (**29**) and (±)-palauolide (**30**).

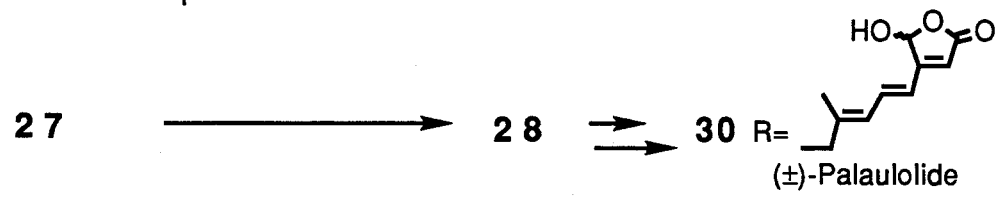
(a) Axanes[9]



(b) Clerodanes[10,11]

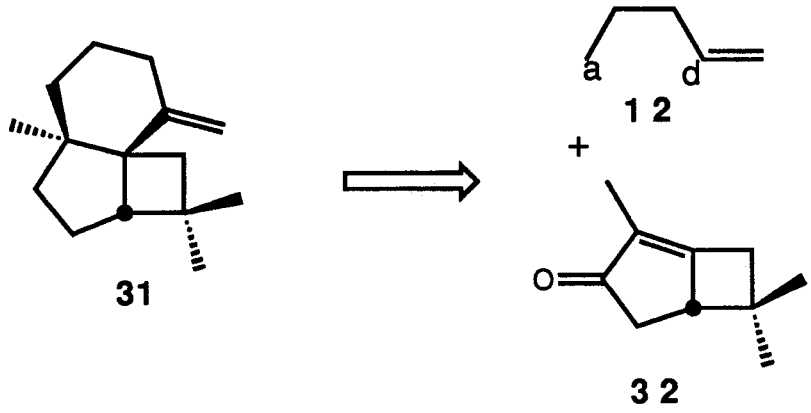


(c) A Sesterterpene[12]



Scheme I-3

1.2. The Problem.



(I-2)

The angularly fused tricyclic sesquiterpene (-)-β-panasinsene (**31**), isolated by Yoshihara and Hirose in 1975,[13] attracted our attention due to (a) its novel structure, and (b) the presence of a methylenecyclohexane ring *cis*-fused to a substituted bicyclo-[3.2.0]heptane unit. It seemed reasonable to assume that the methylenecyclohexane annulation protocol (*vide supra*, pp. 2-4) utilizing the copper (I)-catalyzed conjugate addition of the Grignard reagent **7** could be extended from the use of monocyclic enone substrates having a trisubstituted double bond (**20**, **24**, **27**) to the use of a bicyclic enone substrate having a tetrasubstituted double bond. If the methylenecyclohexane unit present in (-)-β-panasinsene (**31**) is disconnected and the remaining bicyclic portion is suitably functionalized, an enone such as **32** with a tetrasubstituted double bond results (equation I-2). Preparation of an enone similar to **32**, or its synthetic equivalent, then would be a key part of a possible synthesis of (±)-β-panasinsene (**31**).

The strategy we wished to employ in the synthesis of (±)-β-panasinsene (**31**), which would have the methylenecyclohexane annulation as a key sequence, differs significantly from those of the two previously reported approaches (*vide infra*, p. 18).

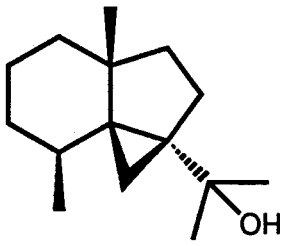
1.3. Angularly Fused Terpenoids.

The carbon skeleton of (-)-β-panasinsene (**31**) is an example of one of a variety of angularly fused skeletons found in terpenoid natural products. A few of the ring size combinations found in terpenoids are depicted in Scheme I-4. The unifying feature of the skeletons is the presence of a bridged spirane arrangement of rings[14] such that three variously sized carbocyclic rings share a common carbon atom.

The synthesis of angularly fused terpenoids has been approached by a number of different methods which fall into three main categories. In effect, the strategies may be divided according to whether a monocyclic substrate is utilized for a two ring annulation, a bicyclic substrate is employed for a one ring annulation, or a monocyclic substrate is subjected to two sequential one ring annulations. The approach chosen depends, of course, on how the retrosynthetic analysis was performed on the target, particularly with respect to which rings were found to be strategic for preservation and which were found to be strategic for disconnection. General factors to be considered in the antithetical analysis include the sizes of the rings, the connectivities and

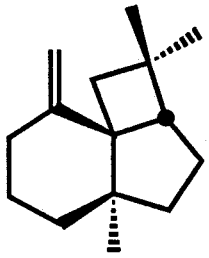
stereorelationships between the rings, the functional groups present and the availability of suitable precursors.[3]

3-5-6



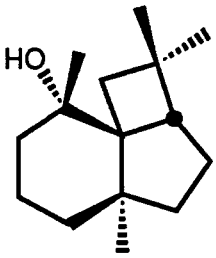
33 Cycloeudesmol[15]

4-5-6



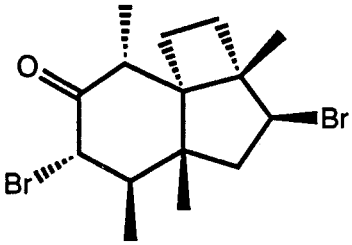
31 β-Panasinsene[13]

4-5-6



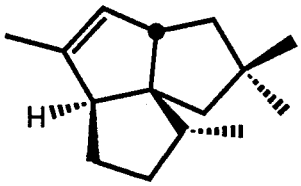
34 Panasinsanol B[16]

4-5-6



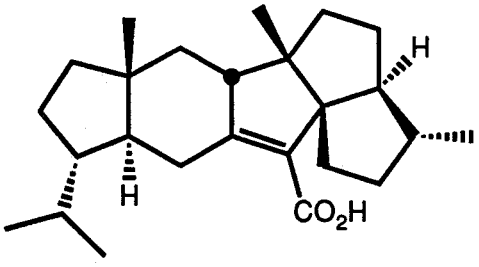
35 Perforatone[17]

5-5-5



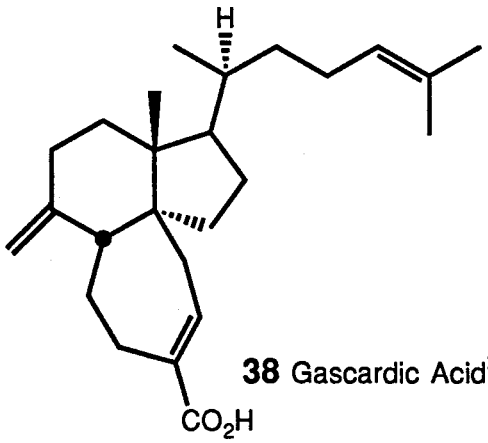
36 Pentalenene[18]

5-5-5



37 Retigeranic Acid[19]

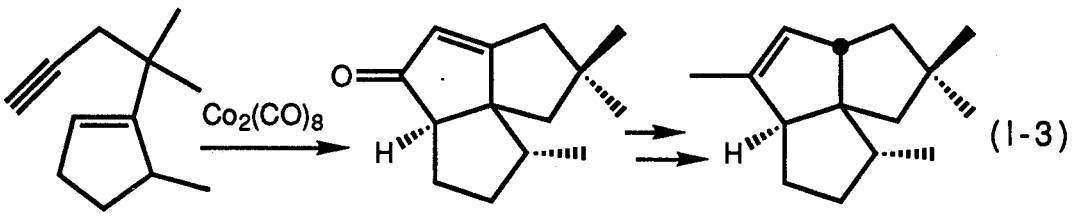
5-6-7



38 Gascardic Acid[20]

Scheme I-4

In the first synthetic approach, a tricyclic framework is assembled in one step from a monocyclic precursor having an appropriately substituted side chain (or side chains) which can undergo a cycloaddition reaction such as a carbene insertion, a 2+2 cycloaddition, or a 2+2+1 cycloaddition. Two examples of this approach involve the syntheses of the terpenoids pentalenene **36** and retigeranic acid **37**. The key step in Schore and Rowley's synthesis[21] of (±)-pentalenene (**36**) was the octacarbonyldicobalt catalyzed 2+2+1 cyclization of the enyne **39** (Pauson-Khand cyclization,[22] *vide infra*, p. 26) to make the angularly fused tricyclic enone **40**. The enone **40** then was converted into **36** by a series of chemical reactions (equation I-3).

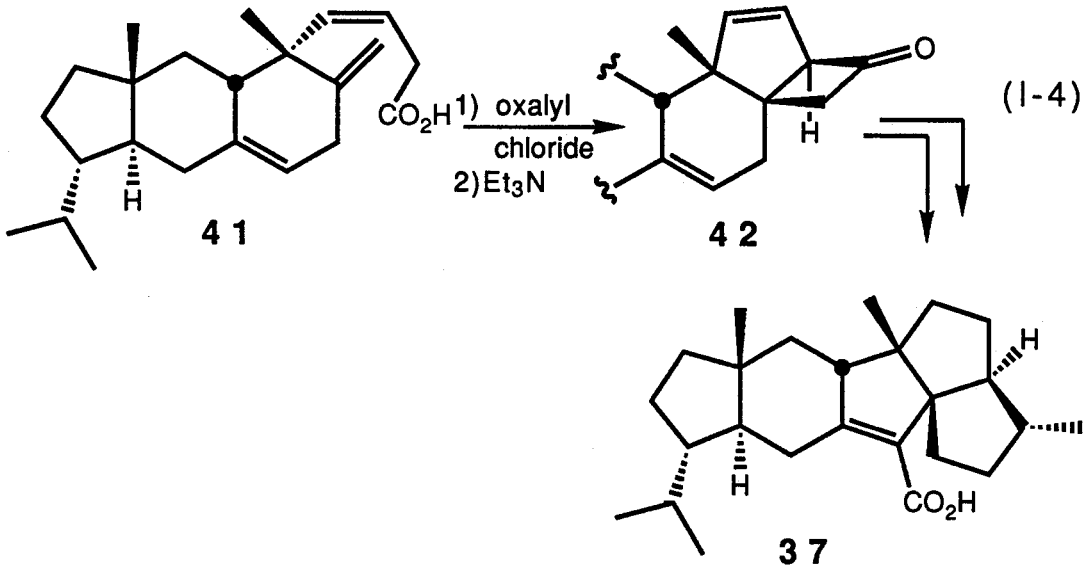


(I-3)

39 **40** **36**

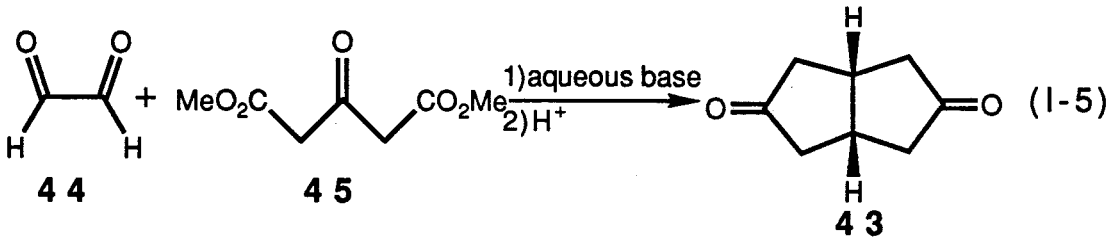
In Corey's synthesis[23] of (±)-retigeranic acid (**37**) the key step in assembling the angularly fused triquinane portion of the target was a 2+2 cycloaddition reaction. Thus, the carboxylic acid function in **41** was converted into the corresponding ketene which underwent an intramolecular 2+2 cyclization to give **42**. Ring expansion of the four membered ring, ring contraction of the six membered ring, and suitable functional group manipulations served to convert **42** into the racemic natural product **37** (equation I-4). Corey's synthesis of

37 illustrates the fact that rings of sizes differing from those in the final product may be assembled initially due to the existence of a convenient route for their preparation and then, provided the appropriate methods exist, suitable ring expansions/contractions may be employed to create the desired ring size. The approach in which a two ring annulation onto a monocyclic substrate is performed was also used for the previous syntheses of *β*-panasinsene (*vide infra*, p. 18).



(I-4)

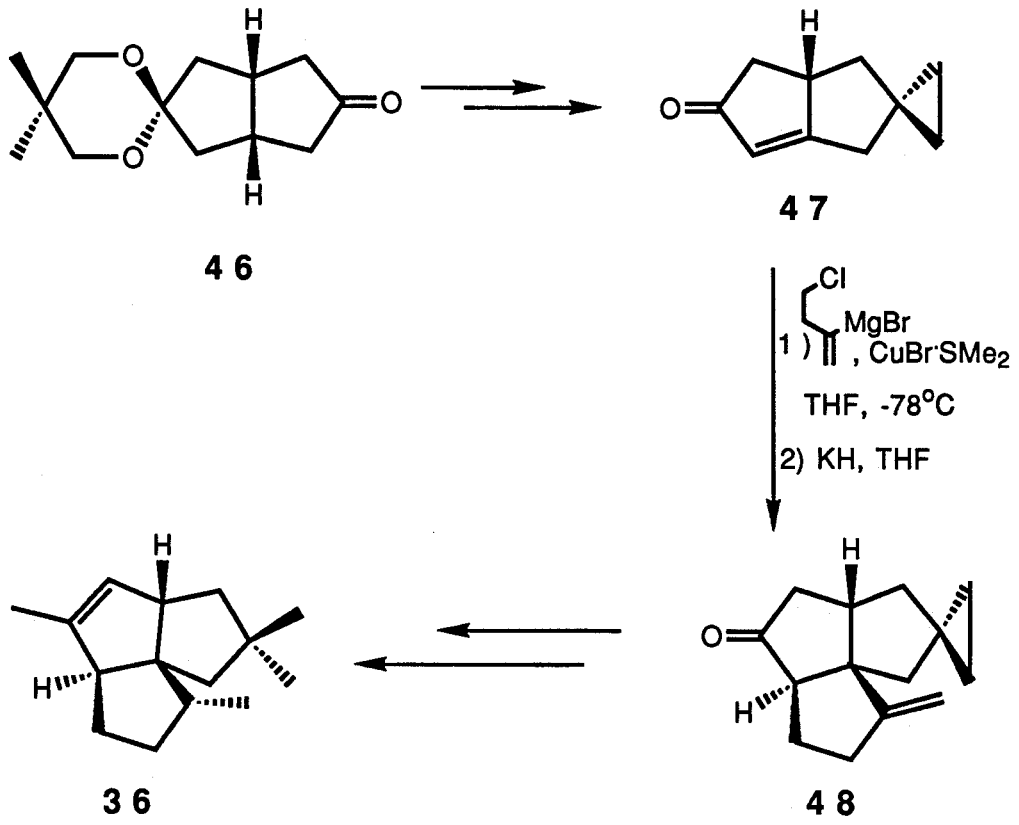
A second approach to the synthesis of angularly fused terpenoids involves the annulation of a bicyclic substrate to produce the required tricyclic skeleton. An example of this approach is a synthesis of pentalenene (**36**) different from that discussed above. Thus, the key skeleton-assembling step in the synthesis of (±)-pentalenene by Piers and Karunaratne[24] was a methylenecyclopentane annulation reaction on the tricyclic enone **47**. The enone **47** was derived from the dione **43**, which, in turn, was prepared from



44 45 43

acyclic precursors *via* the Weiss-Cook condensation[25] of glyoxal (**44**) with the keto diester **45** (equation I-5, and *vide infra*, p. 55). Monoketalization of the dione **43** yielded **46**, which was subjected to a series of chemical manipulations to furnish the enone **47**. The enone intermediate **47** underwent the methylenecyclopentane annulation to provide the tetracyclic ketone (**48**) which was transformed by standard means into (±)-pentalenene (**36**) (Scheme I-5). The above described approach, in which the third ring is annulated onto a bicyclic substrate to make a tricyclic skeleton, is the one we chose to use for the synthesis of β-panasinsene (**31**).

The sequential assembly of the rings making up the tricyclic framework is a third approach that has been employed to achieve the synthesis of angularly fused terpenoids. The Boeckman synthesis[20] of gascardic acid (**38**) exemplifies this third approach. A one-pot annulation of the six-membered ring onto the enone **20** was performed *via* conjugate addition of cuprate reagent **49**, trapping of the resultant enolate anion with the enone **50**, and a subsequent base-catalyzed aldol condensation to provide the key intermediate **51** (Scheme I-6). Introduction of a functionalized two carbon unit at the β-carbon of the α,β-unsaturated ketone function in **51** was a key objective in their synthesis. However, compound **51** proved to

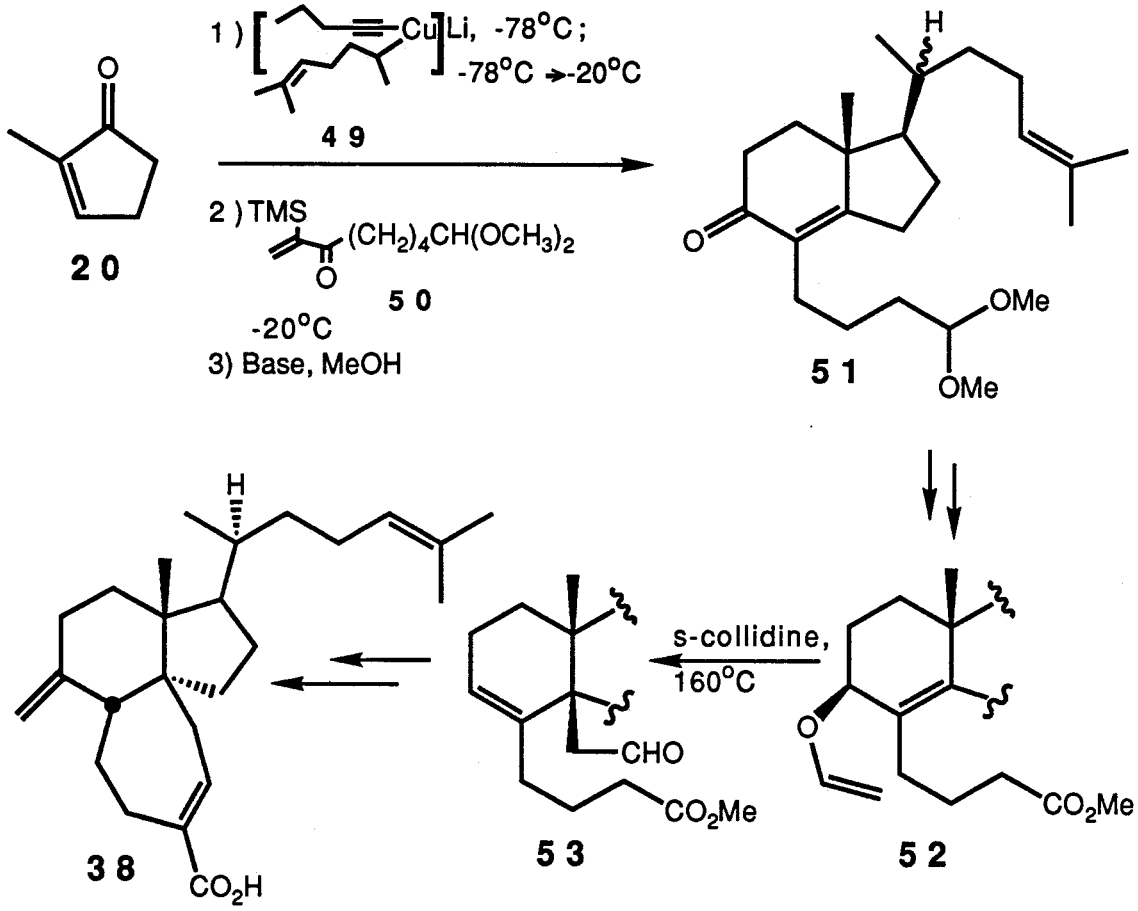


Scheme I-5

be quite unreactive towards conjugate additions reactions. Therefore, compound **51** was converted into the vinyl ether **52** which subjected to a Claisen rearrangement to provide **53**. Intermediate **53** then was transformed into gascardic acid (**38**) *via* a series of standard chemical reactions which included an intramolecular cyclization to form the 7-membered ring. It is of interest to note (for future reference) that steric congestion contributed to the lack of reactivity towards conjugate addition reactions of the bicyclic enone **51**.

The examples chosen above, while illustrative of the different approaches to the synthesis of angularly fused terpenoids, also were chosen to demonstrate applications of reactions or strategies

studied as a part of the research reported herein. Thus, the Pauson-Khand cyclization, the Weiss-Cook condensation, a ring contraction, and a conjugate addition to a tetrasubstituted enone will be discussed in greater detail at suitable points in the thesis.



Scheme I-6

1.4. Isolation and Structural Elucidation of β-Panasinsene (31).

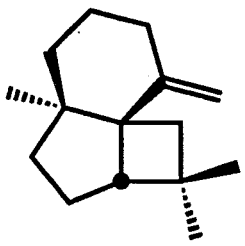
In 1975 Yoshihara and Hirose[13] reported their isolation of the new sesquiterpene hydrocarbon, β-panasinsene (**31**), from the

neutral portion of the volatile oil extract of the roots and rootlets of both fresh and commercial dried ginseng (*Panax ginseng* C.A. Meyer) from Japan and commercial dried ginseng rootlets from Korea.

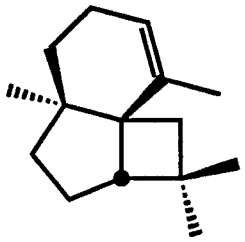
The molecular weight of **31** was found to be 204. Signals for three tertiary methyl groups and an exocyclic methylene group were found in the ^{1}H nmr spectrum at δ 0.74 (s, 3H), 0.86 (s, 3H), 1.08 (s, 3H), 4.78 (d, 1H, J = 2 Hz) and 4.84 (d, 1H, J = 2 Hz). Absorptions at 1365 and 1360 cm^{-1} in the ir spectrum indicated that two of the methyl groups were geminal. Catalytic hydrogenation of **31** gave two dihydro derivatives which were identical with two derivatives obtained by the catalytic hydrogenation of the endocyclic double bond isomer, α-panasinsene (**54**) (also isolated at the same time). Further confirmation of the structure of β-panasinsene (**31**) was obtained by ozonolysis of **31** to give the known ketone (**55**), an intermediate in Parker's synthesis of neoclovene (**56**).[26] It was found too, that **31**, when treated with concentrated sulfuric acid in diethyl ether, rearranged to give α-panasinsene (**54**), α-neoclovene (**56**), and β-neoclovene (**57**). It was known that caryophyllene (**58**) is isomerized to α-neoclovene (**56**) upon treatment with concentrated sulfuric acid and Parker had postulated a cation with the panasinsene framework as an intermediate.[27] Therefore, based on the spectroscopic evidence and the chemical behavior of the compound, the structure of β-panasinsene (**31**) was established.

The roots and rootlets of ginseng (*jen-shen*) have been used in Chinese medicine for centuries, mention of *jen-shen* having been made in Chinese pharmaceutical works with traditions dating to the

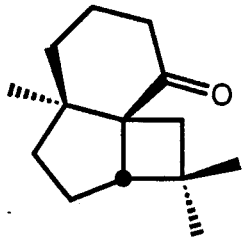
later Han period.* [28] Ginseng is still claimed to be a wonder remedy with anti-fatigue, anti-diabetic, anti-stress, and central nervous system stimulant and sedative properties. However, which components are responsible for which properties is still being investigated. As yet, the biological activity of β-panasinsene (**31**) is unknown.[29]



31



54



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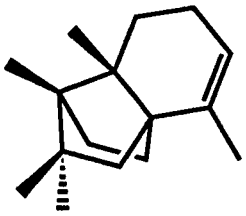

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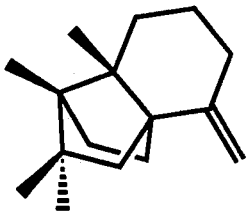

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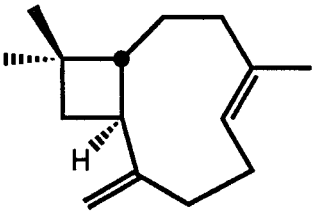

58

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* The Han dynasty was in power 206 B.C.-250 A.D. in China. The entry[25] for *jen-shen*, purported to date to about that time is: "taste: sweet; [thermoinfluence:] slightly cold. Controls the filling of the five depots. Pacifies the spirit; fixes the *hun-* and *p'o* souls. Ends fright and agitation. Expels evil influences. Clears the eyes. Opens the heart and benefits one's wisdom. Consumed over a long time, it takes the material weight from the body and extends one's years of life. Other names are 'man's bit' and 'demon's cover'."

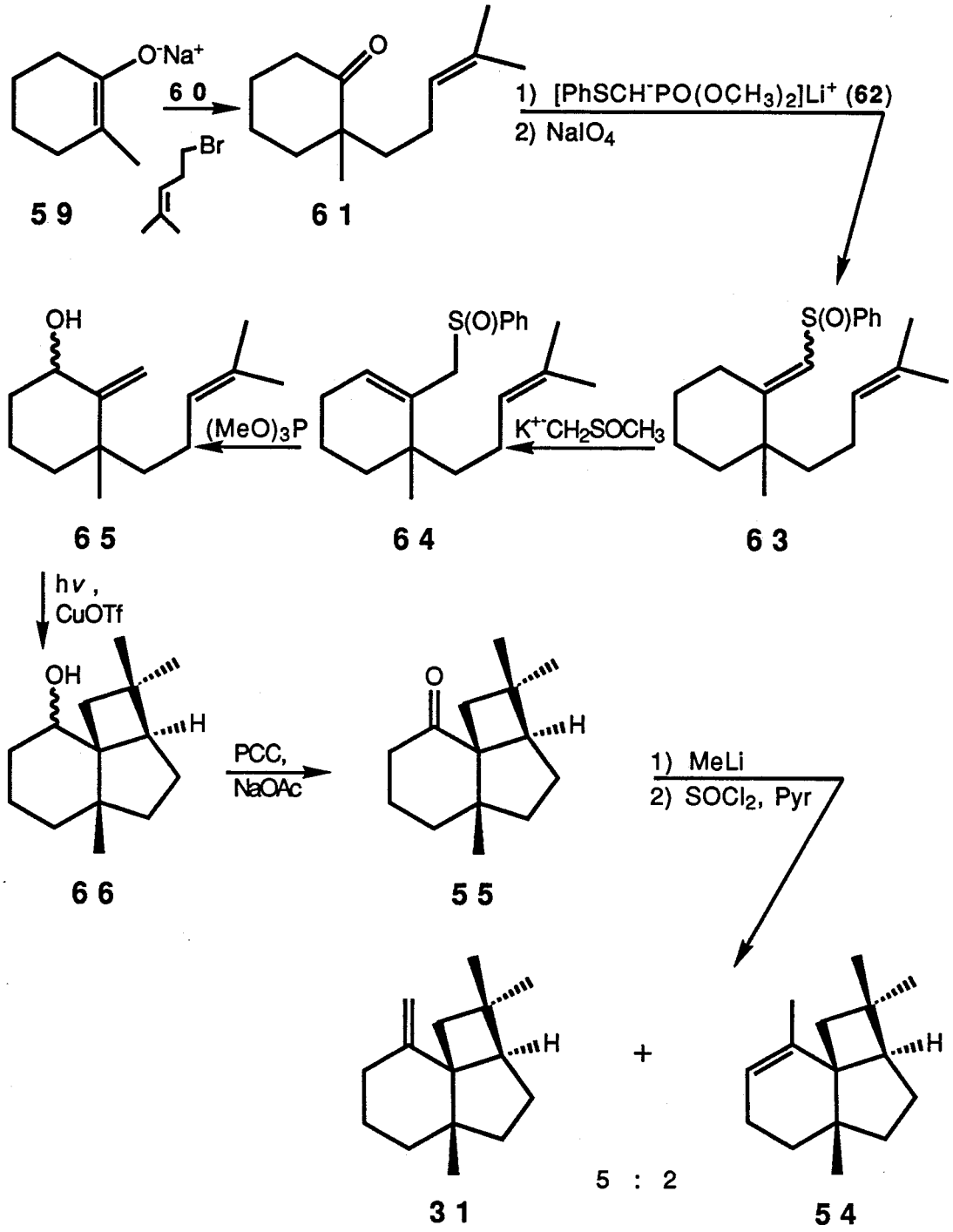
1.5. Previous Syntheses of β-Panasinsene (31).

β-Panasinsene (**31**) has been synthesized twice previously, by McMurry and Choy in 1980[30] and by Johnson and Meanwell in 1981.[31] Both syntheses, as mentioned earlier, made use of the same general approach. Thus, the two research groups introduced an unsaturated side chain onto a cyclohexanone and performed a photochemical 2+2 cycloaddition reaction to assemble the tricyclic carbon framework. The details of the syntheses differ as outlined in the following description of their routes.

1.5.1. McMurry and Choy's Synthesis of Racemic α- and β-Panasinsene (**54** and **31**).

The McMurry and Choy synthesis[30] of the panasinsenes (**54** and **31**) commenced with the alkylation of the sodium enolate of 2-methylcyclohexanone (**59**) with 1-bromo-4-methyl-3-pentene (**60**) to give **61** (Scheme I-7). Compound **61** was treated with the lithio salt of dimethyl phenylthiomethylphosphonate (**62**) to give a 9:1 mixture of vinyl sulfides which were oxidized with $NaIO_4$ to the corresponding sulfoxides (**63**). Deconjugation of the sulfoxides with dimsyl potassium provided the allyl sulfoxides **64**. Treatment of **64** with trimethylphosphite provided a mixture of the key diene alcohols (**65**). Photolysis of **65** in diethyl ether in the presence of copper (I) triflate gave the 2+2 cycloaddition product (**66**) as a mixture of epimeric alcohols which were oxidized to the ketone (**55**). Ketone **55** was reacted with methyllithium and the resulting

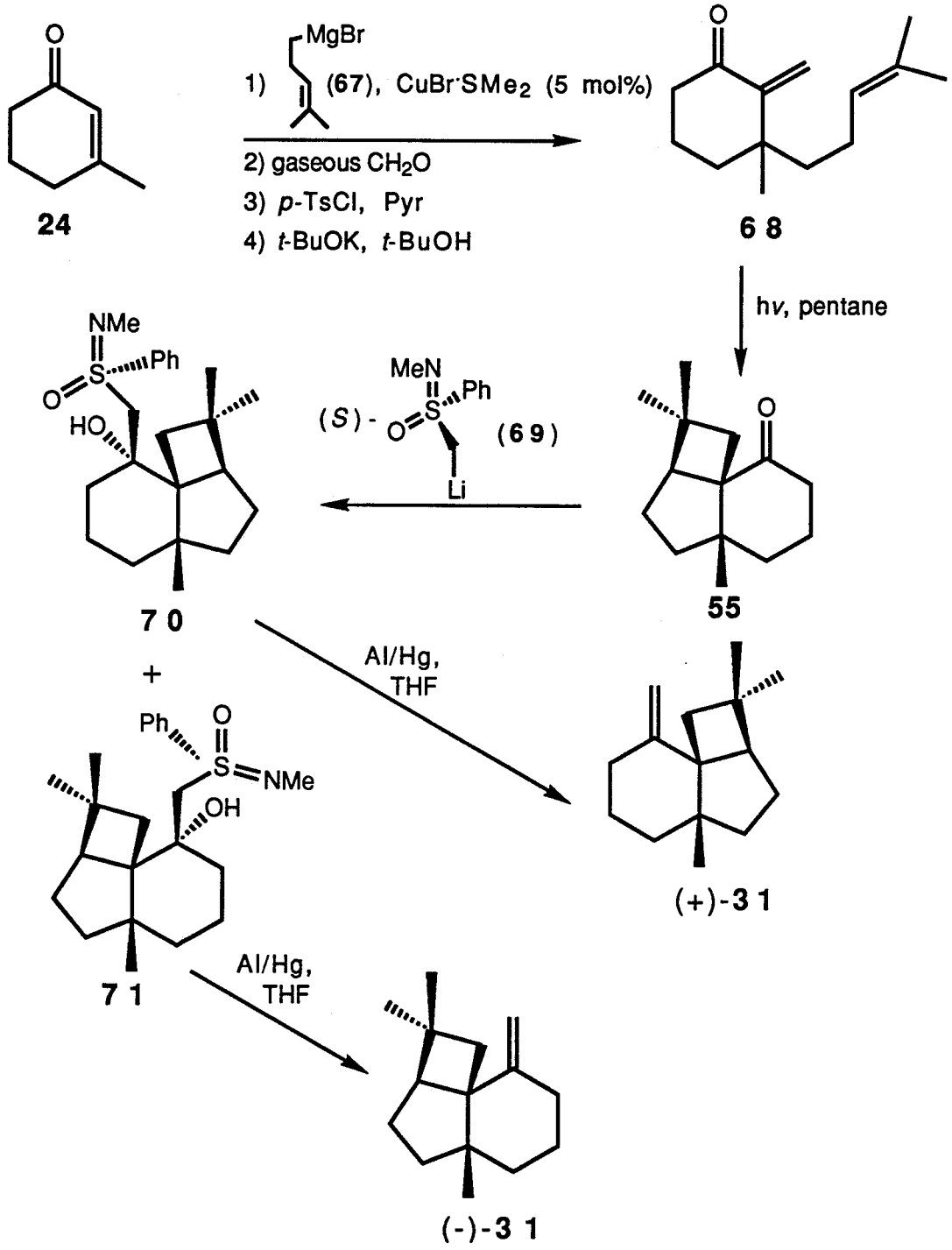
alcohols were dehydrated to provide synthetic racemic α- and β-panasinsene (**54** and **31**).



Scheme I-7

1.5.2. Johnson and Meanwell's Synthesis of (-)-β-Panasinsene and Its Enantiomer ((-)- and (+)-**31**).

Johnson and Meanwell began their synthesis[31] of (-)-β-panasinsene ((-)-**31**) with the copper (I)-catalyzed conjugate addition of 4-methyl-3-pentenylmagnesium bromide (**67**) to 3-methyl-2-cyclohexen-1-one (**24**) (Scheme I-8). The enolate anion intermediate was trapped with formaldehyde and the resultant mixture of keto alcohols was converted to the corresponding keto tosylate mixture. The tosylates were subjected to a base-catalyzed elimination reaction to provide the enone **68**. Photolysis of **68** in pentane provided racemic **55** by means of a 2+2 cycloaddition of the alkene functional group and the double bond of the enone. Resolution of the enantiomers occurred by reaction of the carbonyl function in **55** with (*S*)-(*N*-methylphenylsulfonimidoyl)methyllithium **69** to provide a mixture of diastereomers (**70** and **71**). The diastereomers were transformed separately into (+)- and (-)-β-panasinsene ((+)-**31** and (-)-**31**), respectively, by treatment with aluminum amalgam and acetic acid in wet THF.


MgBr
1) (67), CuBr·SMe2 (5 mol%)
2) gaseous CH2O
3) p-TsCl, Pyr
4) t-BuOK, t-BuOH
24
68
hν, pentane
NMe
Ph
HO
MeN
Ph
(S) -
(69)
Li
55
70
+
71
Al/Hg, THF
(+)-31
Ph
NMe
OH
Al/Hg, THF
(-)-31

Scheme I-8

II. DISCUSSION

Total Synthesis of (±)-β-Panasinsene 31.

2.1. Retrosynthetic Analysis.

Our retrosynthetic analysis of (±)-β-panasinsene **31** was guided by two main strategies, namely: (a) the application of the methylenecyclohexane annulation transform described earlier (pp. 2-4) and (b) the utilization of the bicyclic enone **74** as a key intermediate. The bicyclic enone **74** represents an important branch point in the analysis since it may be derived from a variety of precursors. The exact structure of the enone (i.e., the nature of R and XX) would depend on the route chosen for its synthesis.

Suitable retrosynthetic functionalization of (±)-β-panasinsene (**31**),* followed by a carbon-carbon bond disconnection and the Wolff rearrangement transform would "convert" **31** into the tricyclic ring-expanded ketone **72** (Scheme D-1). The R group in ketone **72** was expected to be either a methyl group as is present in the natural product or a methoxycarbonyl moiety. There is ample precedent for the synthetic conversion of a methoxycarbonyl function into a methyl group.[32]

Retrosynthetic functional group manipulations and a functional group introduction would transform **72** into the ketone **73**, in which XX is a carbonyl equivalent. Application of the methylenecyclo-

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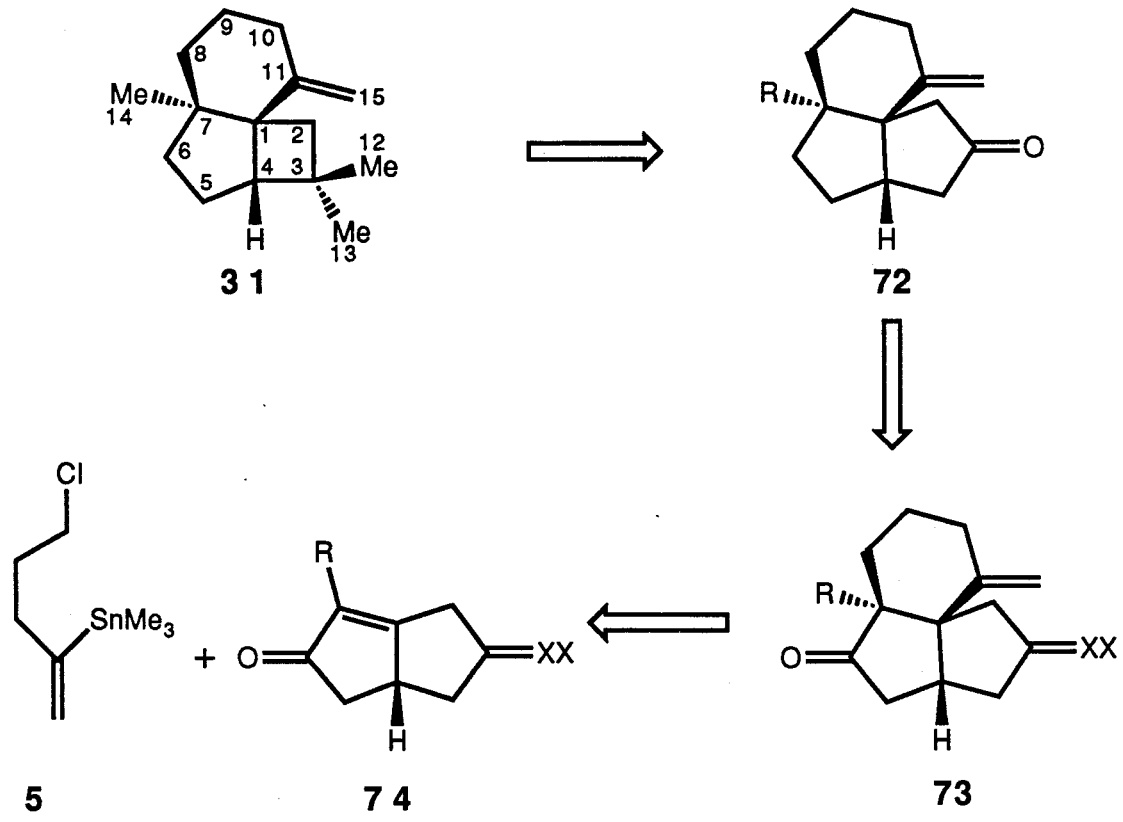
* The numbering scheme utilized for (±)-β-panasinsene (**31**) is analagous to the one used by Iwabuchi and coworkers[16] for panasinsanols A and B.



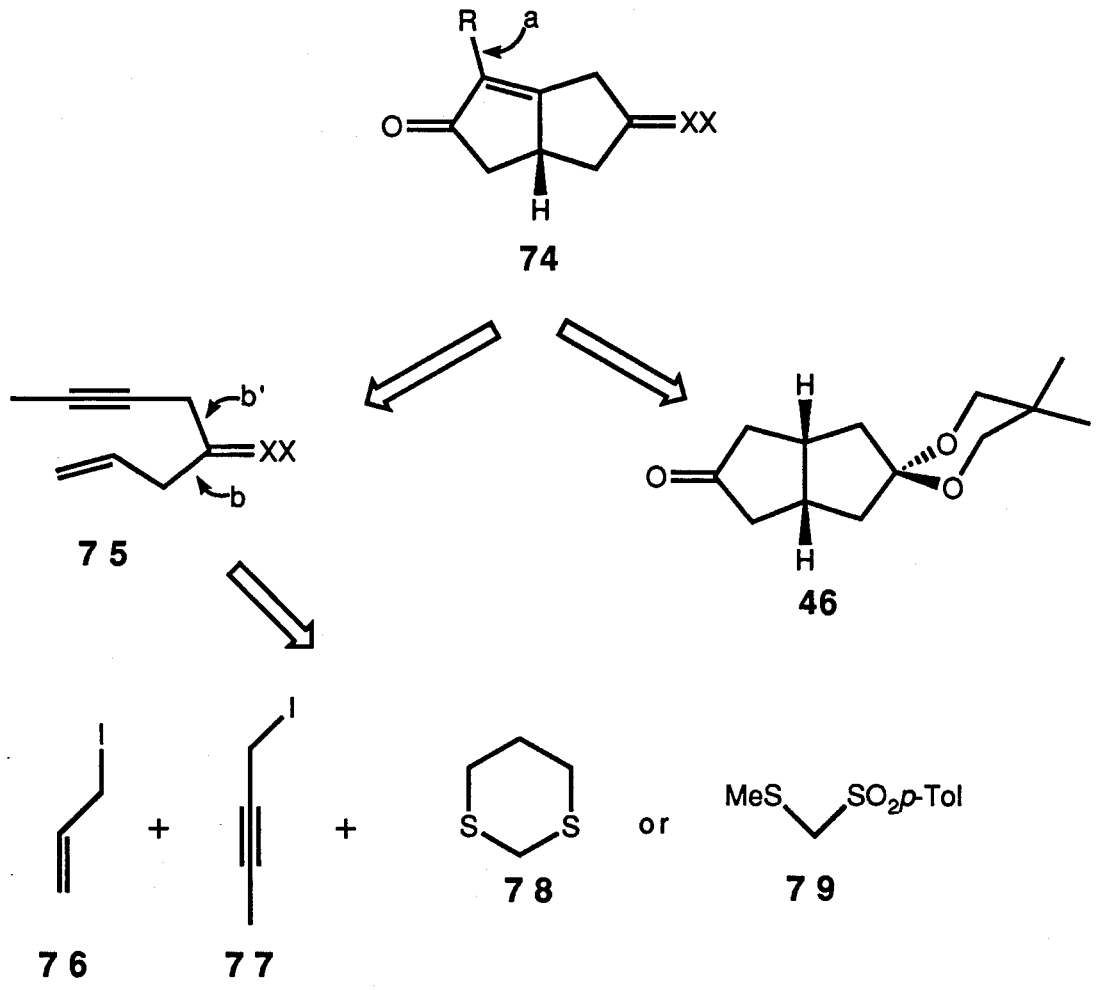
Scheme D-1

hexane annulation transform to **73** would yield two fragments, the vinylstannane **5** and the key bicyclic enone **74** (Scheme D-1). It is well documented in the literature that conjugate additions of cuprate reagents to bicyclo[3.3.0]oct-1-en-3-ones occur on the convex face of the enone to give *cis*-fused diquinanes.[33] The preference for the formation of *cis*-fused diquinanes is probably due to (a) the fact that *trans*-fused diquinanes are more strained than the *cis*-fused isomers[34] and (b) the likelihood that the transition state for the reaction has some product-like character.[35] Consequently, the transition state leading to the formation of the *cis*-fused product will be of lower energy than that leading to the *trans*-fused adduct, and the *cis*-fused diquinane will be formed

preferentially. As outlined in the Introduction (pp. 2-4), cyclization of the keto chloride intermediate in the methylenecyclohexane annulation sequence gives the *cis*-fused annulated product when further equilibration is impossible. Thus, provided that the R group was already installed on the enone double bond, the methylenecyclohexane annulation would be expected to give rise to a product with the desired relative stereochemistry at the three chiral centers (C-1, C-4 and C-7) of β-panasinsene (**31**).

Retrosynthetic analysis of the important enone **74** was approached in two different ways (Scheme D-2). In the case where R is a methyl group, utilization of the Pauson-Khand cyclization transform would lead to the linear enyne **75**. The enyne **75** can be disconnected retrosynthetically in a number of ways. For example, disconnection of both bonds α- to the C=XX function (bonds b and b') in enyne **75** would produce fragments which may be envisaged as **76**, **77** and **78** or **79**. In theory, the enyne **75** could be assembled synthetically by the sequential alkylation of an anion derived from **78** or **79** with the alkylating agents **76** and **77**. Utilization of **78** or **79** to prepare the enyne **75** would mean that, at an appropriate stage in the synthesis, it would be necessary to transform the dithioketal derived functions (i.e., XX=1,3-dithianyl or XX=MeS, SO_2p-Tol) into a carbonyl function (XX=O) in order to provide the tricyclic ketone **72** desired for the Wolff rearrangement reaction. The proposed alkylations of **78** and **79** followed by the hydrolysis of the dithioketal derived functions to a carbonyl group are consistent with the previously reported use of **78**[36] and **79**[37] as masked acyl anion equivalents.

In the case where R is a methoxycarbonyl group, retrosynthetic removal of the double bond and a disconnection of the carbon-methoxycarbonyl bond (bond a) in the enone **74** would provide the known keto ketal **46**.[24,38] In the synthetic direction, the reactions are a methoxycarbonylation and a dehydrogenation, respectively, both of which are known processes.

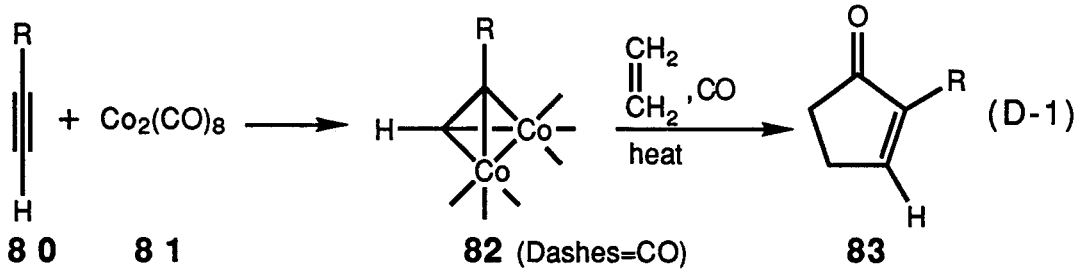


Scheme D-2

2.2. An Approach to the Synthesis of (±)-β-Panasinsene (31) *via* the Use of the Pauson-Khand Reaction.

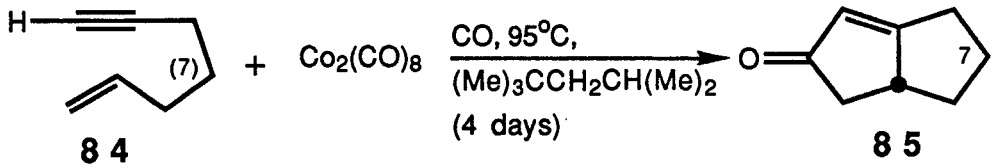
2.2.1. Background.

The Pauson-Khand reaction is a formal 2+2+1 cycloaddition reaction of a hexacarbonyldicobalt alkyne complex with an alkene. During the reaction, one of the carbon monoxide ligands of the complex is used, and the product generated is a substituted cyclopentenone.[22,39] An example using the generalized alkyne **80** and ethylene is illustrative (equation D-1). The alkyne reacts with octacarbonyldicobalt **81** to give the hexacarbonyldicobalt complex **82**. Heating the complex with ethylene produces the cyclopentenone **83**.

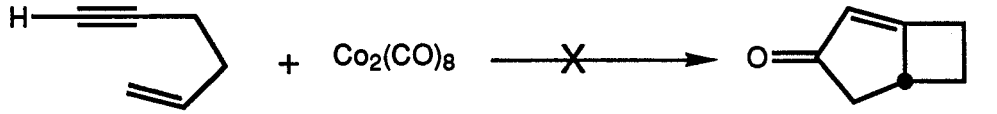


80 **81** **82** (Dashes=CO) **83**

The intramolecular version of the Pauson-Khand reaction was first reported by Croudace and Schore in 1981.[40] They found that cyclization of hept-1-en-6-yne (**84**) at 95°C (4 days) produced bicyclo[3.3.0]oct-1-en-3-one (**85**) in 31% yield (equation D-2). In contrast, the attempted cyclization of hex-1-en-5-yne (**86**) to give



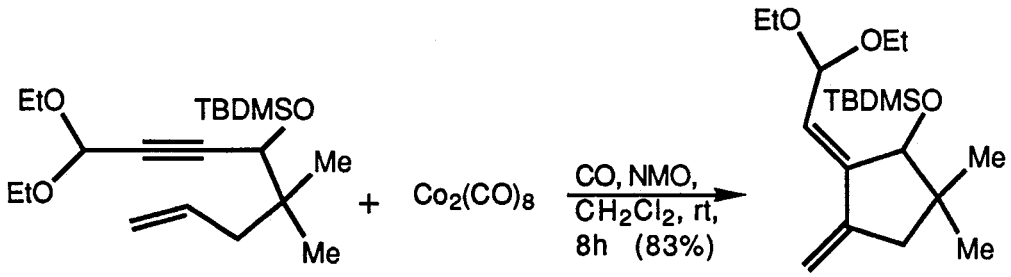
84 **85** (D-2)



86 **87** (D-3)

bicyclo[3.2.0]hept-1-en-3-one (**87**) yielded only products from alkyne trimerization (equation D-3).

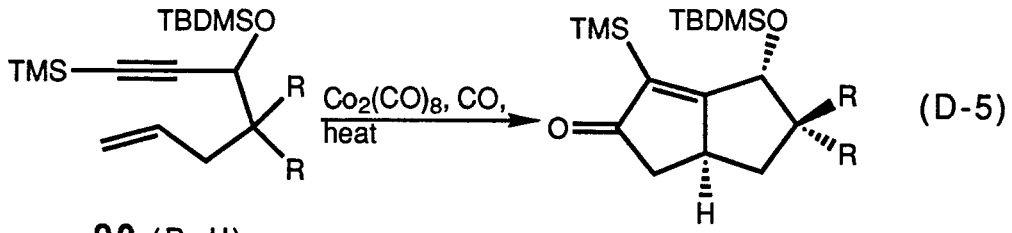
Various substituents may be tolerated on the alkyne and alkene functional groups. However, electron-withdrawing groups on the olefin (CHO, COR, CO_2R, or CN)[41] or on the alkyne moiety (CO_2R,[39b] $CH(OEt)_2$[42]) are detrimental to the cyclization due to the formation of dienes *via* a hydrogen migration. This is illustrated by the cyclization of the enyne **88** to give the diene **89** (equation D-4).[42] The presence of electron-donating groups on the alkene moiety (OC(O)R or OR)[43] or on the alkyne function (OR[44] or SR[45]) may be beneficial.



88 NMO=*N*-methylmorpholine *N*-oxide **89** (D-4)

The Pauson-Khand cyclization reactions of enynes to give bicyclo[3.3.0]oct-1-en-3-ones have been studied to determine the effects on the cyclization of various substituents on the carbon chain linking the alkene and alkyne functions. The yields, reaction times and diastereoselectivities were affected. Some of the results, relevant to our attempted synthesis of (±)-β-panasinsene (**31**), are presented in the following discussion. It may be noted that C-7 refers to the position on the carbon chain which becomes C-7 in the bicyclo[3.3.0]oct-1-en-3-one produced in the reaction (see equation D-2).

The yields of cyclizations of enynes with substituents on the carbon chain linking the alkene and alkyne functions are generally better than those of the less substituted cases, and the reaction times are usually shorter. Thus, for example, cyclization of the



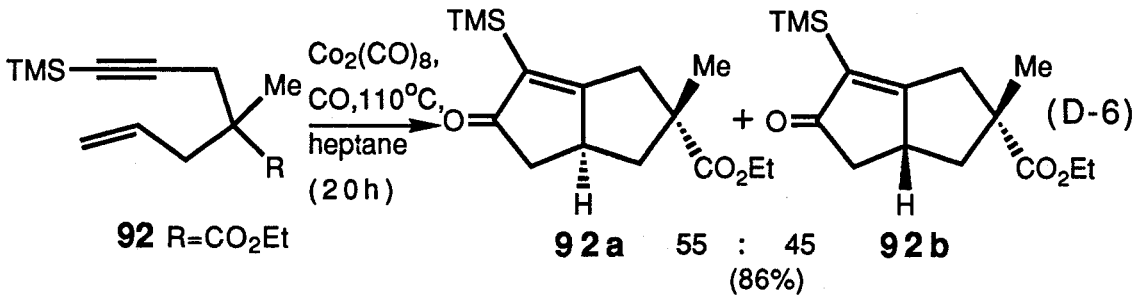
90 (R=H)
91 (R=Me)

90a (14%)
91a (78%)

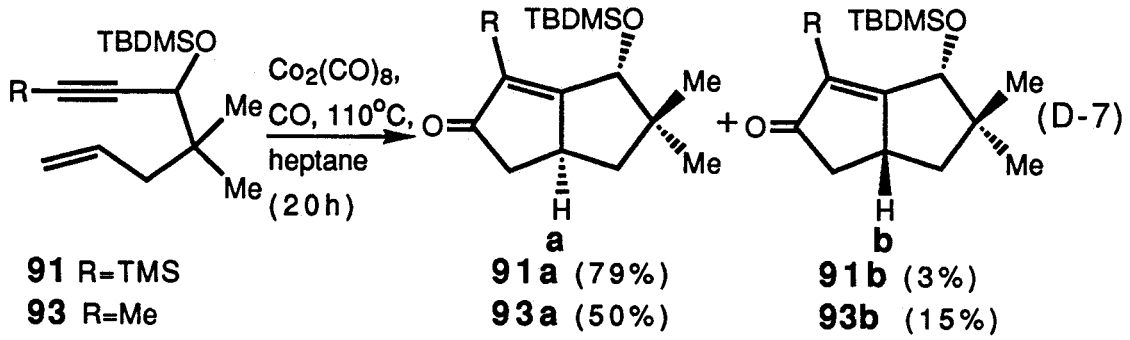
(D-5)

enyne **90** occurred in only 14% yield, while cyclization of the enyne **91** with the additional *gem*-dimethyl substitution, occurred in 78% yield (equation D-5).[46] In addition, the cyclization of the enyne **91** (equation D-5) was complete in 20 hours, a decrease in reaction time when compared with the cyclization of the enyne **84** (4 days) (equation D-2). Good yields are also obtained with enynes in which

the carbon chain between the alkene and alkyne functional groups is substituted only in the homopropargylic (C-7) position. Cyclization of the enyne **92** to give a mixture of **92a** and **92b** in 86% yield after 20 hours is a pertinent example (equation D-6).[47] The improved yields for the cyclizations of the enynes **91** and **92** (equations D-5 and D-6) when compared with the enyne **84** (equation D-2) were proposed[46,47] to be due to the more favorable enthalpy and entropy of the reaction (Thorpe-Ingold effect).[48]



The diastereoselectivities of the cyclizations of the enynes **91** and **92** differ significantly.[47] Thus, the cyclization of the enyne **91** gives rise to a very high selectivity in favor of the enone **91a**, while cyclization of enyne **92** leads to virtually no selectivity. The results are as would be expected based on the steric effects of 1,3- versus 1,4-pseudo diaxial interactions in the transition states (*vide infra*). Further confirmation of the importance of steric effects to the diastereoselectivity in the cyclization may be obtained by comparing the results of the cyclizations of enynes **91** and **93** (equation D-7).[47,49] The trimethylsilyl (TMS) group is more sterically bulky than the methyl group. As expected, the cyclization



91 R=TMS
93 R=Me

91a (79%)
93a (50%)

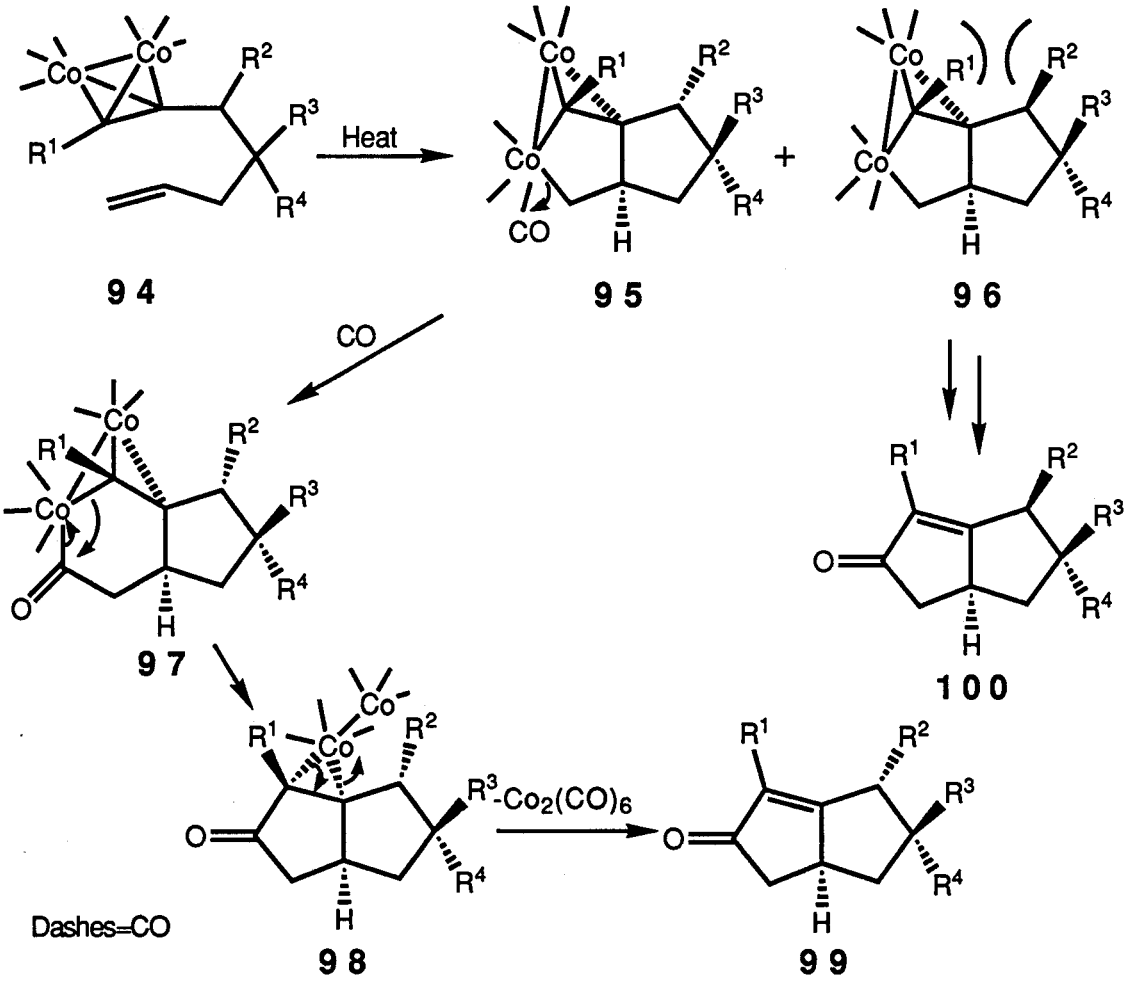
91b (3%)
93b (15%)

reaction of the enyne **91** gave rise to a diastereoselectivity greater than that of the enyne **93** (79:3 versus 50:15).

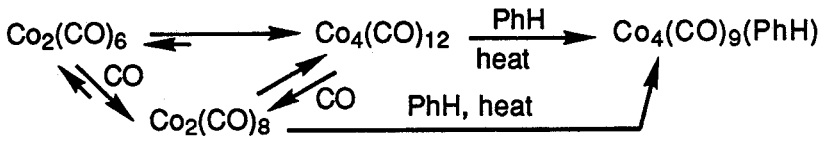
The working hypotheses for the mechanism of the Pauson-Khand cyclization as proposed by Magnus[50] and Schore[51] invoke the same types of intermediates,* but the Magnus mechanism was developed to rationalize the stereoselectivity of the intramolecular reaction of various enynes including **91** and **93** (equation D-7). Thus, according to the Magnus proposal (Scheme D-3), alkene insertion into the internal C-Co bond of the hexacarbonyldicobalt complex **94** leads to the formation of two cobaltabicyclooctanes **95** and **96**. Both metallocycles are likely to be *cis*-fused. In the transition state leading to metallocycle **95**, the steric interactions between R^1 and R^2 are minimized, but in the corresponding transition state for the metallocycle **96** there is a severe 1,3-pseudo diaxial interaction between R^1 and R^2. Consequently, the pathway for the formation of **96** and thus, of the enone **100** is disfavored, particularly in the case of sterically bulky R^1 groups. For the metallocycle **95**, insertion of a carbon monoxide ligand into the indicated C-Co bond gives rise to the acyl-Co complex **97**. Migration of the other C-Co bond to the

* None of the various intermediates have, as yet, been isolated.

adjacent electrophilic carbonyl group produces **98**. The reductive elimination of the cobalt carbonyl residue (likely $Co_2(CO)_6$) in **98** leads to the formation of the enone **99**. The exact identity of the cobalt residue initially eliminated is uncertain,[52] but in isooctane $[Co_4(CO)_{12}]$[53] has been isolated and in aromatic solvents, such as benzene, $[Co_4(CO)_9(PhH)]$[54] has been found (Scheme D-4).



Scheme D-3



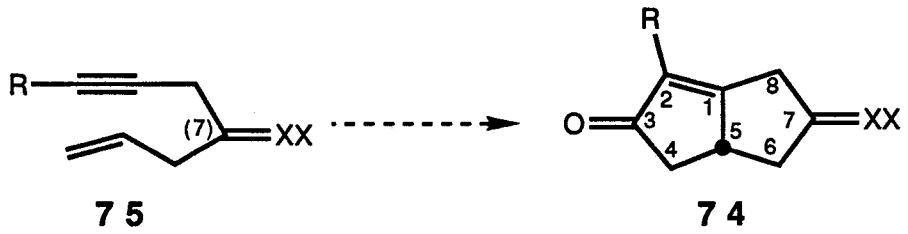
Scheme D-4

In cases with substituents only at C-7 (i.e., R^2=H for enyne **94**), the steric interactions are less significant than those described above. Thus, the main steric interactions are a 1,4-pseudo diaxial interaction between R^1 and R^3 or R^4 and an interaction between the metallocycle methylene and R^3 or R^4. Understandably, the effects are smaller than for 1,3- or 1,2-pseudo diaxial arrangements of substituents. Reduced steric interactions would lead then to a reduced diastereoselectivity as is observed in the cyclization of the enyne **92** (equation D-6) when compared with enynes **91** or **93** (equation D-7).

2.2.2. Approach to the Synthesis of (±)-β-Panasinsene (**31**).

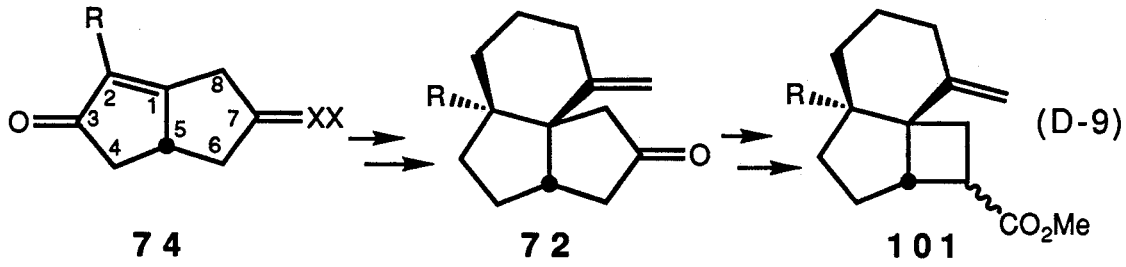
The inter- and intramolecular Pauson-Khand cyclizations have been used in the syntheses of a variety of natural products and natural product precursors.[55,21,46,47,49] It seemed that the cyclization would provide a viable approach to the preparation of a bicyclic enone **74** which was a desired intermediate in the synthesis of (±)-β-panasinsene (**31**). In one step a successful Pauson-Khand reaction would transform an appropriately substituted enyne **75** into

the enone **74** (equation D-8) needed for the key methylenecyclohexane annulation sequence (pp. 2-4).



75 **74** (D-8)

According to the synthetic plan, the enyne **75** would have a methyl group on the alkyne function and would have a suitable functional group at C-7. The function at C-7 would serve a two-fold purpose. In the first place, by analogy to the examples given earlier (equations D-5 and D-6 compared with equation D-2), it was hoped that the presence of substitution at C-7 would contribute to an acceptable reaction yield and reaction time for the cyclization. Secondly, the moiety at C-7 was to be used as a "handle" for future functional group manipulations at that position. Therefore, the nature of the functional group at C-7 was important. Given that a future step in the planned synthetic sequence (equation D-9) called for a carbonyl group at the position corresponding to C-7, the XX moiety on the enyne **75** would have to be transformable into a carbonyl group. Also, the viability of the synthetic plan depended on the stability of the XX moiety to the reaction conditions encountered before it was to be converted into a carbonyl group.



74 **72** **101**

Potential functionalities at C-7 of the enyne **75**, in terms of future usefulness in the synthesis, would include oxygenated groups (XX=OR, H, or XX=2,2-dimethylpropan-1,3-dioxy) or dithioketal derived groups (XX=1,3-dithianyl, or XX=SMe, SO_2p-Tol). To date, there have been no reports of dithioketal derived moieties being employed as C-7 substituents of enynes subjected to the Pauson-Khand cyclization.* If such groups were viable options, they would further expand the versatility of the cyclization due to the fact that the hydrolysis of dithioketal derived functions yields the corresponding carbonyl group,[36,37] while desulfurization of the 1,3-dithianyl group with Raney nickel provides a methylene group.[36a] Thus, the dithioketal derived functions (1,3-dithianyl and SMe, SO_2p-Tol) at C-7 of enyne **75** were investigated with a view to their utility in the synthesis of (±)-β-panasinsene (**31**).

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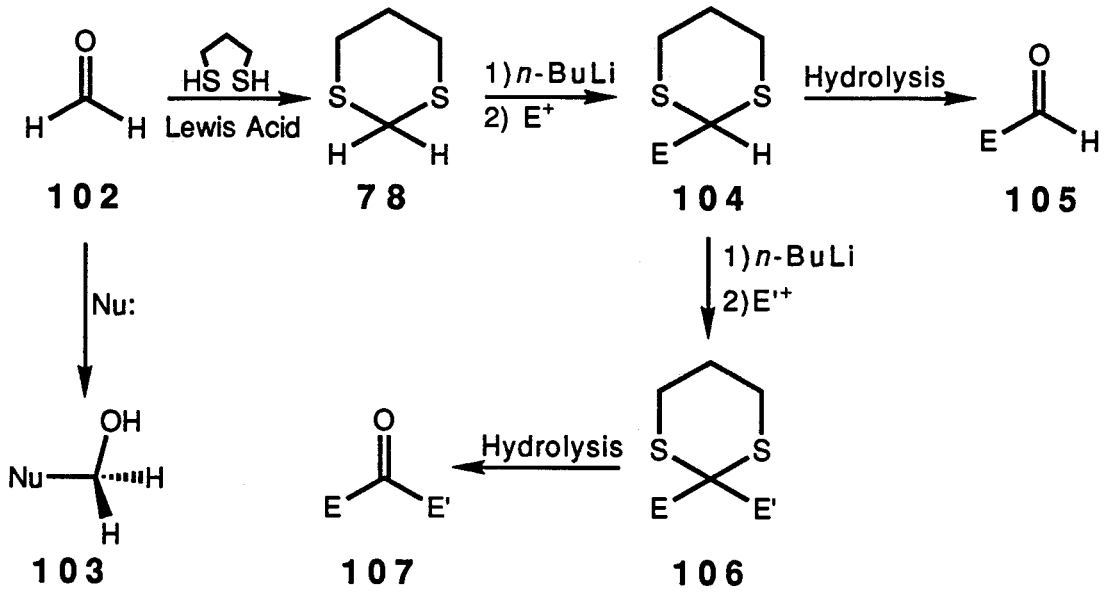
* In the intermolecular Pauson-Khand reaction, a methylthioether tethered to the olefin function by a carbon chain has been used to enhance the regioselectivity of the reaction.[56]

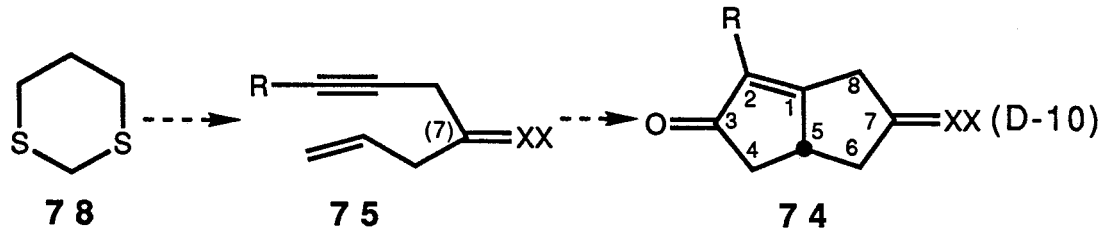
2.2.2.1. The 1,3-Dithianyl Function at C-7.

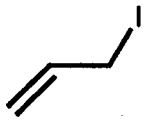
The ability to reversibly invert (*umpolung*)[57] the normal reactivity of an acyl carbon atom is a powerful tool in organic synthesis.[36b-c,58] Thus, while acyl groups are generally attacked at the electrophilic carbon by nucleophiles (for example, **102** gives **103**, Scheme D-5), an *umpolung* causing group on the acyl carbon permits the atom to function as a nucleophile.[57] For example, conversion of formaldehyde (**102**) into 1,3-dithiane (**78**) followed by deprotonation of **78** with *n*-butyllithium produces a nucleophilic anion. Treatment of the anion with an electrophile (E^+) provides **104**. The dithianyl group of **104** then may be hydrolyzed to produce the aldehyde **105** or further deprotonated and reacted with an electrophile to give **106**. Hydrolysis of the dithiane function in **106** generates the ketone **107** (Scheme D-5). A variety of electrophiles, including alkyl halides, carbonyl compounds, small ring ethers and acylating reagents, may be employed to transform compound **78** into **104** or compound **104** into **106**.[59] The hydrolysis reactions (transformation of **104** and **106** into **105** and **107**, respectively) most commonly are performed with mercuric salts or with *N*-halosuccinimides.[36c] The overall result of the reaction of the anion of either **78** or **104** with an electrophile followed by hydrolysis of the dithiane function in the product is a nucleophilic acylation of the electrophile.



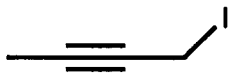
Scheme D-5

We wished to exploit the reactivity of 1,3-dithiane (**78**) to prepare an enyne **75** on which to perform a Pauson-Khand cyclization to generate the corresponding enone **74** (equation D-10; XX=1,3-dithianyl). Then, at an appropriate stage in the planned synthesis of (±)-*β*-panasinsene (**31**), the dithianyl function would be hydrolyzed to regenerate a carbonyl function. The proposed reactions of **78** with allyl iodide (**76**) and with 1-iodo-2-butyne (**77**) appeared to be similar to alkylations reported earlier,[59] but in practice (*vide infra*) turned out to be somewhat problematic.



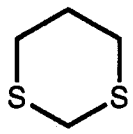


76



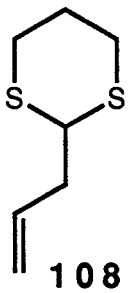
77

To the best of our knowledge, the alkylation of 1,3-dithiane (**78**) with allyl iodide (**76**) has not been reported in the literature. However, the product of the reaction, 2-allyl-1,3-dithiane (**108**), is known.[60] Using a procedure similar to that reported for the alkylations of dithiane,[59a] a THF solution of commercially available 1,3-dithiane (**78**) was treated with *n*-butyllithium at ~-25°C to form the dithiane anion. The solution of the anion was cooled to -78°C and allyl iodide (**76**) was added quickly. Workup of the reaction mixture and purification of the product led to the isolation of 2-allyl-1,3-dithiane (**108**) in 63-73% yield (equation D-11).



78

1) *n*-BuLi (1.1 equiv), THF
-25 - -30°C (1.5h)
2) Allyl iodide (**76**, 1.1 equiv),
-78°C (2.5h);
-78 → 0°C (1.5h)



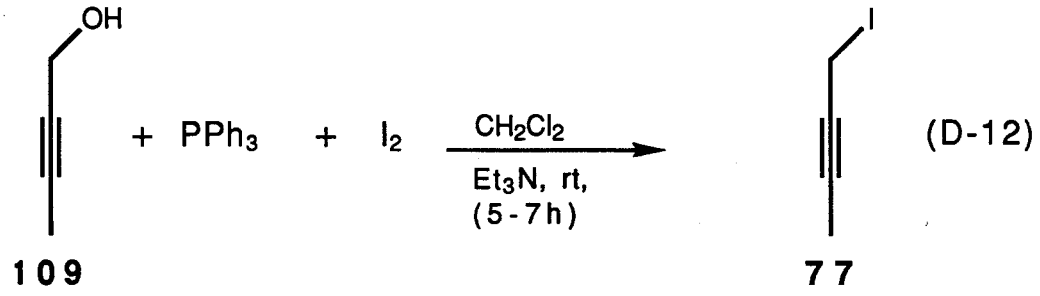
108

(D-11)

The ir spectrum (neat) of 2-allyl-1,3-dithiane **108** exhibited absorptions due to the mono-substituted alkene at 3077 (w), 1640 (m), 991 (s), and 920 (vs) cm^{-1}.[61] In the ^1H nmr spectrum (400 MHz, $CDCl_3$), signals were found for the -SC<u>H</u>S- at δ 4.10 (t, 1H, J = 7 Hz) and for the olefinic hydrogens at 5.11-5.19 (m, 2H, CH=C<u>H</u>$_2$), and at

5.82-5.92 (m, 1H, C<u>H</u>=CH_2).* The exact mass of the molecular ion was found to be 160.0374 which is consistent with a molecular formula of $C_7H_{12}S_2$.

The second alkylating agent for the preparation of the enyne **75**, the iodide **77**, was synthesized from the corresponding alcohol (**109**) using a modification of a known procedure.[62] Thus, a dichloromethane solution of the commercially available alcohol **109** was treated with triphenylphosphine diiodide (1.1 equiv) in the presence of triethylamine (1.1 equiv) to give the iodide **77** (equation D-12). The ir spectrum of the iodide **77** exhibited an alkyne C≡C stretch at 2235 cm^{-1}, while the ^1H nmr spectrum (300 MHz, $CDCl_3$) showed signals for the methyl group at δ 1.83 (t, 3H, J = 3 Hz) and for the methylene group at 3.68 (q, 2H, J = 3 Hz).



109 **77**

In order to prepare the enyne **75**, a THF solution of 2-allyl-1,3-dithiane (**108**) was treated first with *n*-butyllithium (1.1 equiv) at ~-25-30°C (~3 hours) to form the anion and then with 1-iodo-2-butyne **77** (~1.2 equiv) to perform the alkylation. The desired alkyne

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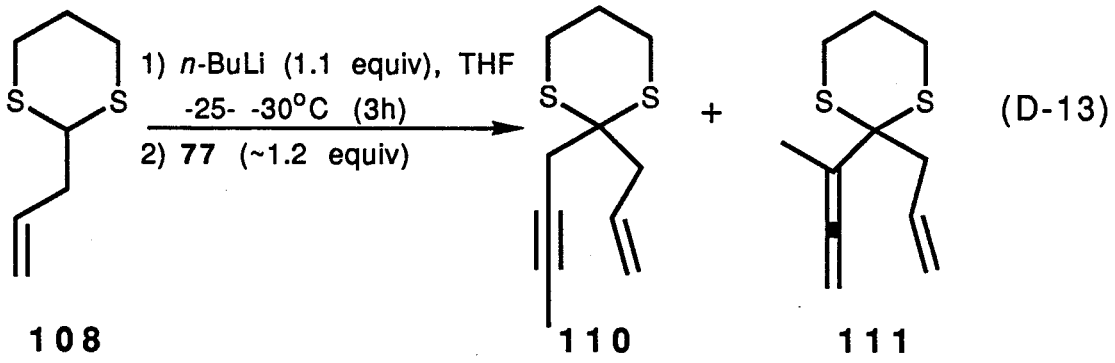
* The signals due to the allylic methylene appeared at δ 2.52 (tt, 2H, J = 7, 1 Hz), while the dithiane methylene hydrogens appeared as multiplets at 1.80-1.92 (1H), 2.08-2.16 (1H) and 2.80-2.94 (4H). According to the literature,[60] the nmr signals for **108** are as follows: δ 1.6-3.0 (m, 8H), 4.1 (t, 1H, J= 6.6 Hz, -SCHS-) and 4.9-6.7 (m, 3H, -CH=CH_2).

110 (an oil) and the allene isomer **111** (an oil) were formed in approximately equal amounts (ratio, 1:1.2, respectively, GLC analysis) (equation D-13). The isolated yield of each isomer was generally 12-18% because the two isomers were difficult to separate from each other and from other by-products of the reaction.*



108 **110** **111**

The ^{1}H nmr spectrum (400 MHz, $CDCl_3$) of the alkyne **110** exhibited signals for the acetylenic methyl group at δ 1.84 (t, 3H, J = ~2 Hz) and for the olefinic hydrogens at 5.17-5.25 (m, 2H) and 5.87-5.97 (m, 1H).** In the ir spectrum (neat) the alkyne C≡C stretch occurred at 2235 (w) cm^{-1}, while the alkene C=C stretch was at 1638 (m) cm^{-1}. The exact mass of the molecular ion was found to be 212.0697 which is consistent with the molecular formula of $C_{11}H_{16}S_2$.

The structure of the allene **111** was consistent with the ^{1}H nmr, ir and low resolution mass spectral data. Thus, in the ^{1}H nmr

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* The purification procedure was not further optimized since the approach was ultimately abandoned.

**Other hydrogen signals in the ^{1}H nmr spectrum appeared at δ 1.90-2.06 (m, 2H) and 2.76-2.93 (m, 8H). In the ir other absorptions due to the alkene were at 3076 (m), 991 (m), 920 (s) cm^{-1}.

spectrum (400 MHz, $CDCl_3$), the allene **111** exhibited signals for the allenic methyl group at δ 1.82 (t, 3H, J = ~2 Hz), for the allenic hydrogens at 4.88 (q, 2H, J = ~2 Hz) and for the olefinic hydrogens at 5.13-5.20 (m, 2H), 5.79-5.90 (m, 1H).* The ir spectrum of the allene **111** showed an allenic C=C stretch at 1953 (vs) cm^{-1} and an olefinic C=C stretch at 1639 (s) cm^{-1}. In the low resolution mass spectrum the molecular ion was observed at 212 mass units (13%).

The presence of allenes as by-products in the reactions of nucleophiles with propargylic alkylating reagents (and conversely, the presence of acetylenic by-products in similar reactions) is a persistent problem.[63,64] It is known that the alkyne/allene ratio in the product can be influenced by a variety of factors which include: the solvent, the temperature, the structure of the propargylic substrate and the structure of the nucleophile.[65] Thus, for example, in the reaction of a Grignard reagent with **112** (equation D-14), the acetylene/allene ratio in the product mixture generally was larger at higher temperatures and smaller in less polar solvents.[65c] In contrast, similar reactions (using 1,4-dichloro-2-butyne) of alkyllithium reagents tended to give the opposite results in that raising the temperature led to a higher proportion of the allene in the product mixture.[65d] Also, different products have been obtained depending on the nucleophile employed.[65a,65d] Thus, in the reaction of methyllithium with **112** (X,Y=Cl) the product was mainly the allene **114** (R=Me, Y=Cl), while the same reaction with

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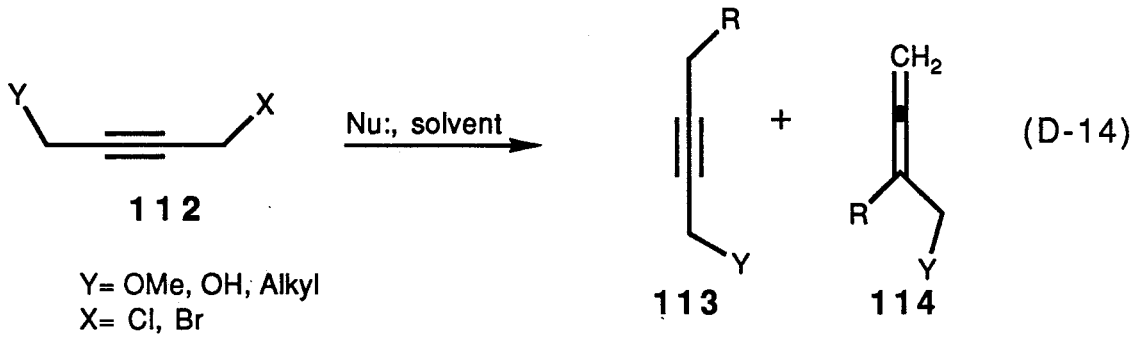
* Other hydrogen signals in the ^1H nmr spectrum were found at δ 1.84-1.96 (m, 1H), 2.01-2.09 (m, 1H), 2.64-2.72 (m, 4H), 2.92-3.00 (m, 2H). In the ir spectrum, other absorptions appeared at 3076 (s), 995 (vs), 917 (vs), 847 (vs) cm^{-1}.

methylmagnesium bromide gave mainly the acetylene **113** (R=Me, Y=Cl).[65d]



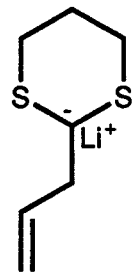
112

Y= OMe, OH, Alkyl
X= Cl, Br
Nu:= RMgBr

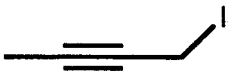
113 **114**

(D-14)

In our hands, various modifications in the reaction conditions for the alkylation of the lithio anion of 2-allyl-1,3-dithiane (**113**) with 1-iodo-2-butyne (**77**) were made and included the following: (a) changing the solvent (THF, DME), (b) varying the temperature (-78°C, ~-25°C), or (c) using an additive (none, HMPA). However, results similar to or worse than those described above were obtained. In addition, modifying the alkylating reagent **77** by replacing the methyl group with the more bulky triisopropylsilyl (TIPS) group[66] to give the iodide **116** did not improve the outcome of the reaction. The option of changing the structure of the nucleophile remained to be explored, but first the feasibility of the Pauson-Khand cyclization reaction of an enyne with a dithioketal function at C-7 needed to be established.



115



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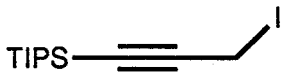

116

The enyne **110** was subjected to Pauson-Khand cyclization conditions similar to those reported by Magnus.[46] Thus, the deep-red hexacarbonyldicobalt alkyne complex **117** was formed by reacting the alkyne function in enyne **110** with octacarbonyldicobalt (1.1 equiv) (Scheme D-6). Purification of the crude product mixture by rapid chromatography on a Florisil column gave the complex **117** in 68-78% yield. The ir spectrum (KBr) of the complex exhibited carbonyl absorptions at 2087 (m), 2045 (s), and 2016 (s) cm^{-1}.*

The hexacarbonyldicobalt complex **117**, dissolved in heptane and sealed in a resealable tube under a carbon monoxide atmosphere, was heated at 90-100°C for 14-18 hours. The yield of the purified enone **118** (a pale yellow oil) was ~50% based on the enyne (or 70-80%, based on the isolated complex). The yield and reaction time were comparable to those reported previously (compare with equation D-7).

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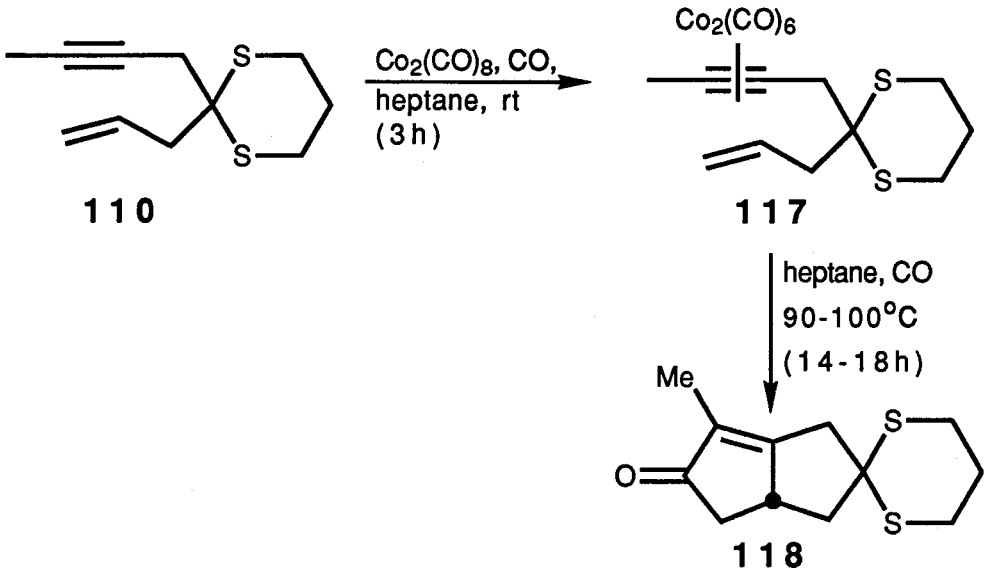
* The absorptions due to the organic moiety were very weak in comparison with the carbonyl absorptions. Absorptions (br, vw) due to the olefinic group appeared at 967 and 931 cm^{-1}, while the absorption due to the Co-C was at 519 cm^{-1}. There was no octacarbonyldicobalt present as evidenced by the lack of an absorption at 1864 cm^{-1} due to bridging carbonyl ligands.[43]



110 **117** **118**

Scheme D-6

The structure of the enone **118** was confirmed by the ir, nmr and high resolution mass spectral data. Thus, the ir spectrum of the enone **118** exhibited absorptions at 1707 (vs) and 1672 (vs) cm^{-1} which are characteristic of a conjugated cyclopentenone.[61] In the ^1H nmr spectrum (300 MHz, $CDCl_3$; traces of impurities present), the vinylic methyl group appeared at δ 1.73 (br s, 3H) and the angular hydrogen appeared at 3.25-3.39 (m, 1H).* In the high resolution mass spectrum the exact mass was found to be 240.0644, which is consistent with the molecular formula, $C_{12}H_{16}OS_2$.

The Pauson-Khand cyclization of enyne **110** occurred with an acceptable yield in a reasonable length of time and the enone **118** was isolable. However, the overall route was synthetically mediocre due to the practical difficulties involved in the synthesis

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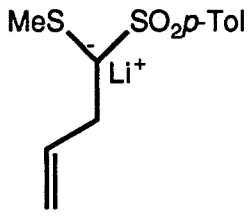
* Further spectral data also was observed. Other absorptions in the ir appeared at 1413 (s), 1310 (s), 1050 (m), 936 (w), 906 (w) and 667 (w) cm^{-1}. In the ^1H nmr spectrum, signals due to the other hydrogens appeared at δ 1.58 (t, 1H, J = 12 Hz), 2.06-2.17 (m, 3H), 2.70 (dd, 1H, J = 17, ~6 Hz) and 2.83-3.20 (m, 7H).

of the enyne **110**. The problems included: (a) the low yield in the alkylation reaction with 1-iodo-2-butyne **77** and (b) the difficulty in separating the desired alkylated product **110** from the allene isomer **111** (equation D-13). Thus, it was decided to modify the dithioketal function and use an oxidized dithioketal derivative, the methylthio-*p*-toluenesulfonyl function. It was expected that the more reactive anion (**119**) would show different (preferably more desirable) behavior in the alkylation reaction with the alkyne **77**.

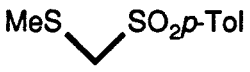


119

2.2.2.2. The Methylthio-*p*-toluenesulfonyl Function at C-7.

Several dithioacetal[36c] *S*-monosulfoxides[67,68] or *S,S*-dioxides,[69] including methylthiomethyl *p*-tolyl sulfone (**79**),[37] have been used as masked carbonyl anion equivalents. However, ketone synthesis *via* the oxidized dithioacetal reagents, **120-122**, may be accompanied by problems such as: (a) competative alkylation on a monoactivated alkyl group instead of at the doubly activated methylene position;[37c] (b) little or no dialkylation;[68a] or (c) difficulties in the hydrolysis of the oxidized dithioketal function to generate the carbonyl group.[68a] In contrast, for sulfone **79**, site-selective deprotonation of the

methylene group occurs with a variety of bases* and produces an anion which may be reacted with electrophiles such as aldehydes,[37c,71] esters,[37c,72] α,β-unsaturated carbonyl compounds[71] and alkyl halides.[37b,37c] The dithioacetal *S,S*-dioxide function in the adducts so formed may be hydrolyzed to give an aldehyde carbonyl group or again treated with a base to form the α-anion. Reaction of the anion with a second electrophile followed by hydrolysis of the methylthio *p*-toluenesulfonyl function produces a ketone. The hydrolysis of the methylthio *p*-toluenesulfonyl group generally has been performed photochemically[37b] or using acidic conditions.[37b,37c,71a,73]



79

120[67]

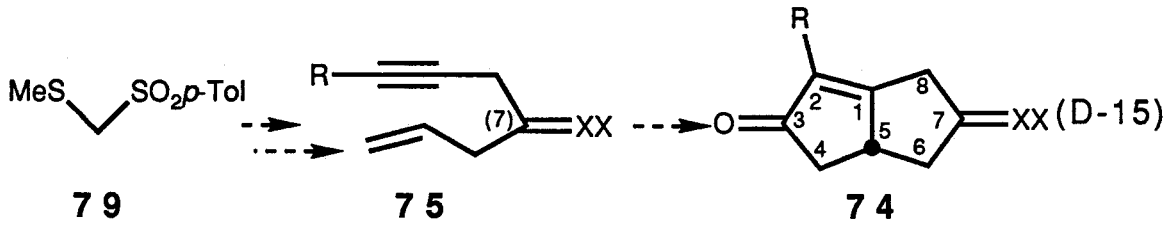
121[69]

122[68]

It appeared that methylthiomethyl p-tolyl sulfone (**79**) was a viable carbonyl anion equivalent and could be used in our strategy to prepare the enone **74** *via* the Pauson-Khand cyclization of an enyne **75** (equation D-15; XX=SMe, SO_2p-Tol). As was the case for 1,3-dithiane (**78**) described earlier, the sulfone **79** was alkylated with allyl iodide (**76**) and 1-iodo-2-butyne (**77**) to prepare the desired enyne.

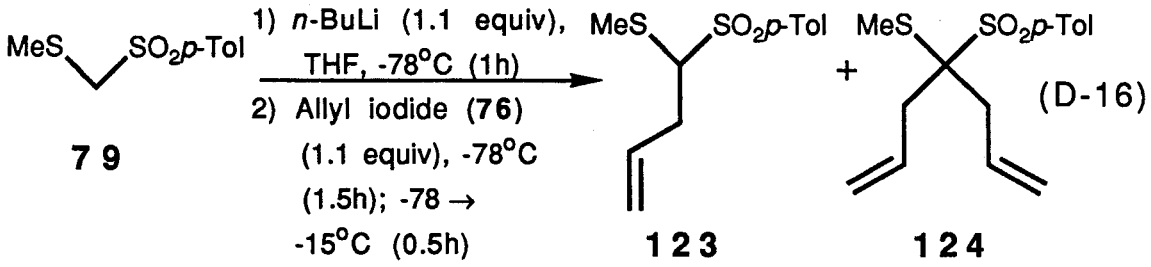
---

* Bases used include: 50% aqueous NaOH-toluene/trioctylmethylammonium chloride;[37b,37c] NaH-DMF;[70] NaH-THF;[37c] K_2CO_3-*i*-PrOH;[37c] and *n*-BuLi-THF.[71]



Methylthiomethyl *p*-tolyl sulfone (**79**) (also available from the Aldrich Chemical Co.), was prepared and recrystallized according to the procedure reported by Ogura and coworkers.[74] The product thus obtained exhibited m.p. 83.5-85°C (lit. 82-83°C[74]) and ^{1}H nmr data in accord with the reported data.

A cold (-78°C) THF solution of the sulfone **79** was deprotonated with *n*-butyllithium and the resultant anion was treated with allyl iodide (**76**) (equation D-16). The purified monoalkylated material (**123**) was obtained as a white solid (crude m.p. 37-38°C) in ~70-75% yield. The amount of the dialkylated product **124** obtained and that of the starting sulfone **79** recovered varied depending on the scale of the reaction and the number of equivalents of allyl iodide (**76**) used. Thus, in our hands, for a small scale reaction (~2 mmol of **79**) 1.1 equivalents of allyl iodide were found to give **124** and **79** each in ~10% yield. However, in a large scale reaction (~10 mmol of **79**), four equivalents of allyl iodide (**76**) were needed to obtain a similar result. Other conditions generally led to the formation of either **124** or **79** in larger amounts.



79 **123** **124**

In the ^{1}H nmr spectrum (300 MHz, $CDCl_3$) of 1-methylthio-1-*p*-toluenesulfonylbut-3-ene (**123**) signals for the two methyl groups were displayed at δ 2.24 (s, 3H) and 2.44 (s, 3H), while the signals for the three olefinic hydrogens were at 5.16-5.20 (m, 2H) and 5.73-5.87 (m, 1H).* In the low resolution mass spectrum, the molecular ion peak at *m/z* = 256 ($C_{12}H_{16}O_2S_2$) was very small (0.3%), while the base peak (101) corresponded to the loss of the *p*-toluenesulfonyl fragment, $C_7H_7O_2S$ (*m/z*=155).

The structure of the diallylated sulfone **124** was readily deduced from its ^{1}H nmr spectrum (300 MHz, $CDCl_3$). Thus, the expected signals for the two methyl groups (s, 3H each) were at δ 2.25 and 2.36, while the signals for the olefinic hydrogens appeared at 5.12-5.20 (m, 4H) and 5.85-6.00 (m, 2H).** In the ir spectrum absorptions due to the C=C stretch and the sulfone asymmetric and symmetric S=O stretches were displayed at 1639, 1302 and 1147 cm^{-1}, respectively.[61] In the low resolution mass spectrum, the molecular ion appeared at *m/z* = 296 (0.3%) and a major fragment

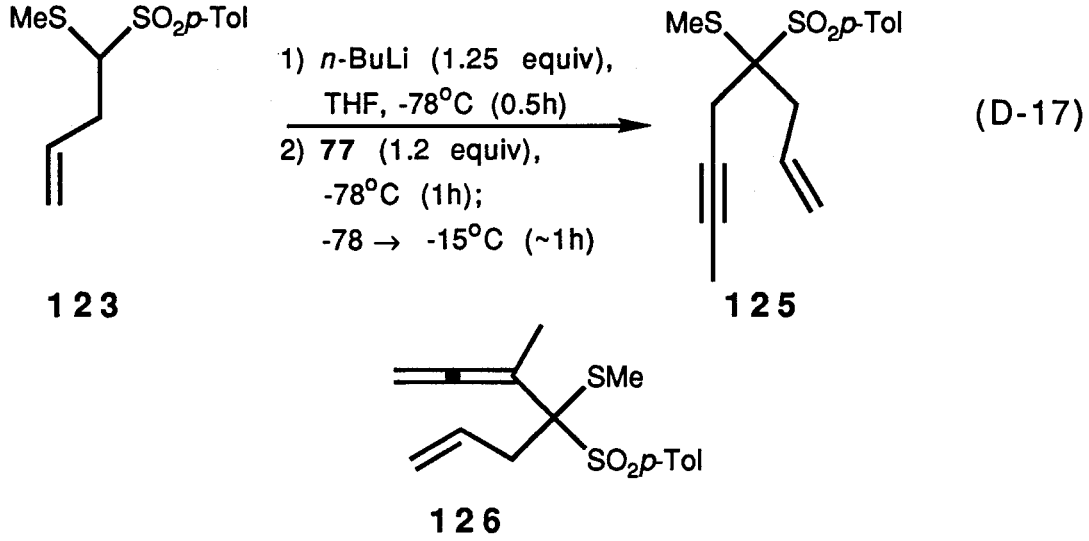
---

* Other aliphatic hydrogen signals in the ^{1}H nmr spectrum of **123** appeared at δ 2.24-2.34 (m, 1H), 2.91-3.00 (m, 1H) and 3.71 (dd, 1H, *J* = 11, ~4 Hz), while the aromatic hydrogens were at 7.36 (d, 2H, *J* = 8 Hz) and 7.84 (d, 2H, *J* = 8 Hz).

** The ^{1}H nmr signals for the remaining hydrogens of **124** were displayed at δ 2.60-2.81 (m, 4H), 7.33 (d, 2H,*J* = 8 Hz) and 7.84 (d, 2H, *J* = 8 Hz).

corresponding to the loss of the *p*-toluenesulfonyl moiety ($C_7H_7O_2S$) was observed at 141 (32%).

The enyne **125** was prepared by treating a cold (-78°C) THF solution of the sulfone **123** with *n*-butyllithium and alkylating the resultant anion with 1-iodo-2-butyne (**77**) (equation D-17). The isolated, purified 4-methylthio-4-*p*-toluenesulfonyloct-1-en-6-yne (**125**) was obtained as a pale yellow oil in 79-86% yield. Gratifyingly, none of the corresponding allene **126** was detected.



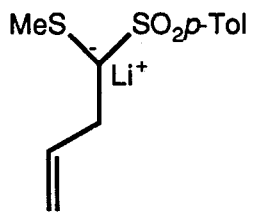
123 **125** **126** (D-17)

The presence in the ^1H nmr spectrum (300 MHz, $CDCl_3$) of a new methyl signal at δ 1.70 (t, 3H, J = ~2Hz) for the acetylenic methyl group and signals for two other methyl groups (s, 3H, each) at 2.31 and 2.45, as well as the other expected signals,* indicated that the desired compound (**125**) had been prepared. The ir spectrum (neat), displayed absorptions due to the olefin C=C stretch at 1639, the

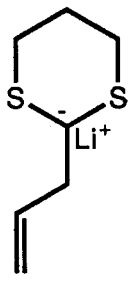
* Other hydrogen signals appeared at δ 2.71-2.94 (m, 4H), 5.19-5.28 (m, 2H), 5.88-6.01 (m, 1H), 7.35 (d, 2H, J = 8 Hz) and 7.87 (d, 2H, J = 8Hz).

alkyne C≡C stretch at 2236 (very weak), and the sulfone S=O asymmetric and symmetric stretches (strong) at ~1302 and 1144 cm^{-1}, respectively.[61] The molecular ion peak in the low resolution mass spectrum was at *m/z* = 308 mass units, consistent with the molecular formula, $C_{16}H_{20}O_2S_2$.

Though similar reaction conditions were utilized, the results of the alkylation of the lithio anions of sulfone **123** and dithiane **109** with the iodide **77** were quite different. Thus, for the anion **119** only the desired S_N2 reaction was observed, while for the anion **115**, both S_N2 and S_N2' reactions occurred. The differences in the behaviors of the anions **119** and **115** are likely due to differences in the anion structure. As mentioned earlier, reactions of Grignard and organolithium reagents with propargylic substrates tend to give complementary results, but the provenance of this behavior is not fully understood.[63a,65a,65d] However, our results confirm that the structure of the nucleophile also plays an important role in the outcome of the reaction of a nucleophile with a propargylic halide.



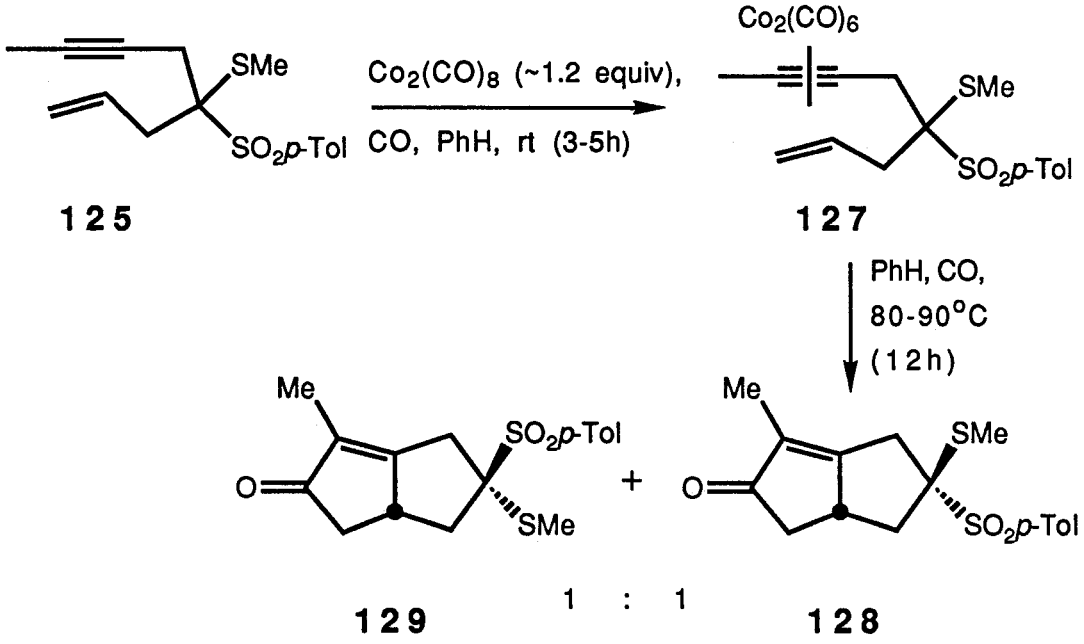
119



115

The enyne **125** was subjected to the Pauson-Khand cyclization reaction (Scheme D-7). Cyclization of the enyne in this case can give rise to a mixture of diastereomers, but based on the results reported in the literature[47] and decribed earlier (equation D-6), the diastereoselectivity was expected to be minimal. The enyne **125** was treated with octacarbonyldicobalt (~1.2 equiv) in benzene. After chromatography of the crude product on Florisil, the hexacarbonyldicobalt alkyne complex **127** was isolated as a deep red oil in 80-90% yield. The complex was dissolved in benzene, and the resultant solution was sealed in a resealable tube under a carbon monoxide atmosphere and then was heated at 80-90°C. The mixture of diastereomers **128** and **129** (ratio ~1:1, ^{1}H nmr analysis) was formed in 46-54% yield based on the isolated complex **127**, or in 37-49% yield based on the starting material (enyne **125**). The yield for the cyclization of enyne **125** was a bit lower than that of the previous example (enyne **110**, Scheme D-6), but the reaction also occurred somewhat more rapidly (5-12 hours *versus* 14-18 hours).

The two diastereomers **128** and **129** could be separated by careful flash column chromatography or could be partially separated by fractional recystallization from dichloromethane-pentane. The relative stereochemistries of the two compounds were not determined. Using the above solvent system, the less polar diastereomer (**A**) crystallized first from mixtures of both compounds. Pure **A** was recrystallized from diethyl ether-dichoromethane (3:1) to produce prisms that exhibited m.p. 146.5-148.5°C. The ^{1}H nmr spectrum (300 MHz, $CDCl_3$) of **A** displayed the expected three singlets (3H each) for the methyl groups at δ 1.71 (br



Scheme D-7

s, allylic Me), 2.34 and 2.48. The signal due to the angular hydrogen appeared as a broad multiplet at δ ~3.28-3.40 (overlapped with a doublet at 3.45) and the aromatic hydrogens resonated at 7.39 (d, 2H, J = 8 Hz) and 7.90 (d, 2H, J = 8 Hz)*. In the ^{13}C nmr spectrum (75 MHz, $CDCl_3$), fifteen signals were observed due to the fact that two pairs of aromatic carbon atoms were magnetically equivalent (see figure 1). The signals for the three methyl groups were at δ 8.6, 14.5 and 21.7, while the angular methine carbon resonated at 42.30.** The data was in accord with what one would expect for one of the bicyclic enone diastereomers.

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* The signals for the other hydrogens appeared at δ 1.54 (dd, 1H, J = 14, 11 Hz),2.07 (dd, 1H, J = 18, 3 Hz), 2.66-2.74 (m, 2H), 3.05 (dd, 1H, J = 14, 9 Hz) and 3.45 (d, 1H, J = 18 Hz).

** The ^{13}C signals for the three methylene groups appeared at δ 35.8, 40.0 and 41.99; those for the six quaternary carbons were at 76.6, 131.20, 134.1, 145.4, 174.5, 209.0 (carbonyl); and those for the aromatic methynes were at 129.3 (2CH) and 130.94 (2CH).

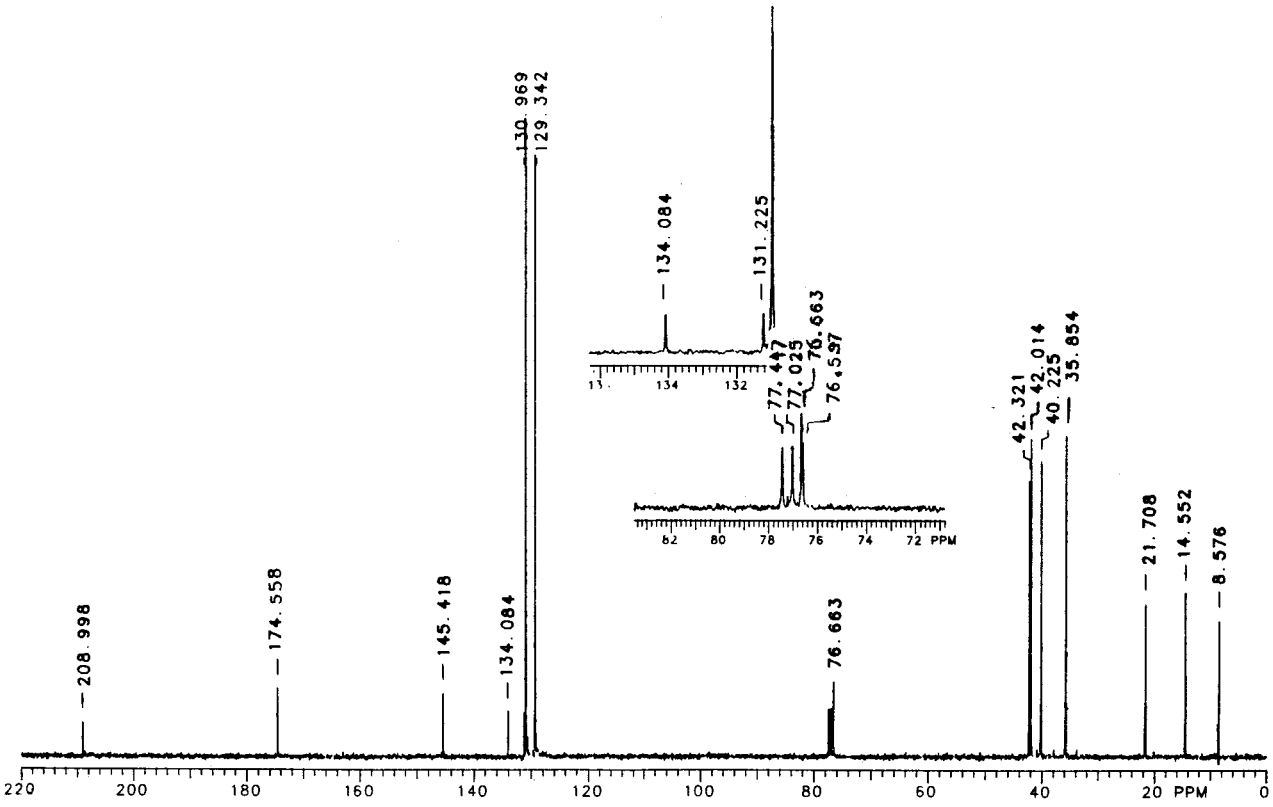
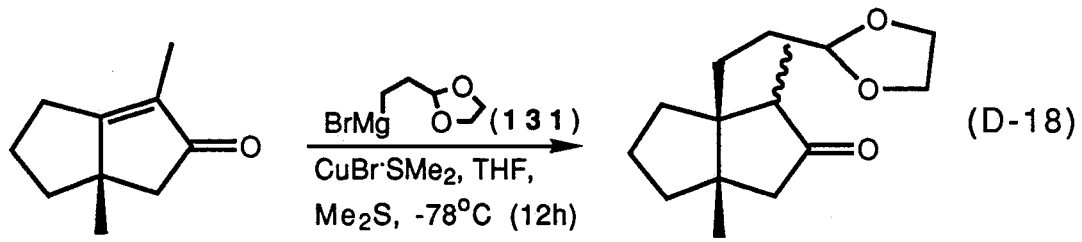


Figure 1. The 75 MHz broad band decoupled ^{13}C nmr spectrum of the enone diastereomer **A**.

The diastereomer **B** was recrystallized from acetone/pentane and exhibited m.p. 149.5-152°C. In the ^{1}H nmr spectrum (300 MHz, $CDCl_3$) of diastereomer **B** there were some slight differences from that of **A**. Thus, the signals for the three methyl groups (3H each) appeared at δ 1.72 (br s, allylic Me), 2.36 and 2.47, while the angular hydrogen appeared at δ ~3.21-3.34 and the aromatic hydrogens resonated at 7.37 (d, 2H, J = 8 Hz) and 7.83 (d, 2H, J = 8 Hz).*

* The signals for the other hydrogens appeared at δ 2.09-2.20 (m, 3H), 2.63-2.76 (m, 2H) and 3.50 (d, 1H, J = 19 Hz).

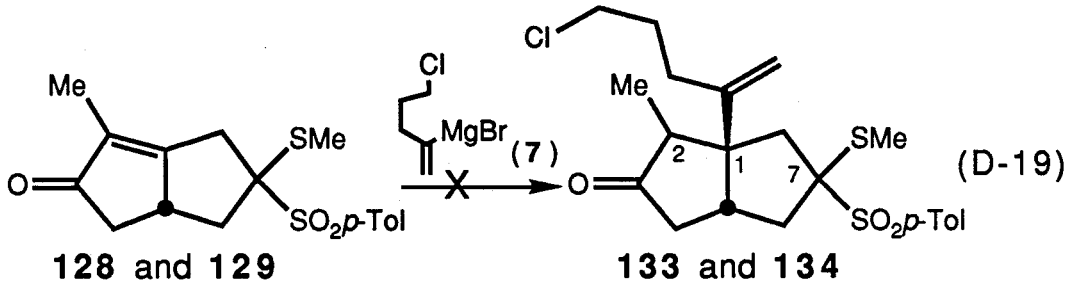
With the enones **128** and **129** in hand, the key methylenecyclohexane annulation was investigated. It was expected that the reaction might be sluggish based on the results presented in the Introduction (pp. 2-4). However, it was anticipated that the reaction would be possible, since copper (I)-catalyzed conjugate additions have been performed on enones with tetrasubstituted double bonds. Thus, for example, Paquette and Han[75] found that the diquinane enone **130** reacted with the Grignard reagent **131** in the presence of a copper (I) salt to give the adduct **132** in 68% yield (equation D-18), but the reaction took 12 hours at -78°C.



130 **132** (D-18)

The attempts to perform the copper (I)-catalyzed conjugate addition of the Grignard reagent **7** on the enones **128** and **129** were frustrated by the lack of solubility of the enones in THF, the solvent normally used in our laboratories[7] for the reaction. The enones were soluble in hexamethylphosphoramide (HMPA), an additive sometimes used along with trimethylsilyl chloride to improve sluggish conjugate addition reactions of Grignard reagents[76] (copper (I) catalysis) or of stoichiometric organocopper reagents.[77] However, the amount of HMPA required to dissolve the enones was such that the polarity of the reaction solvent mixture would be significantly

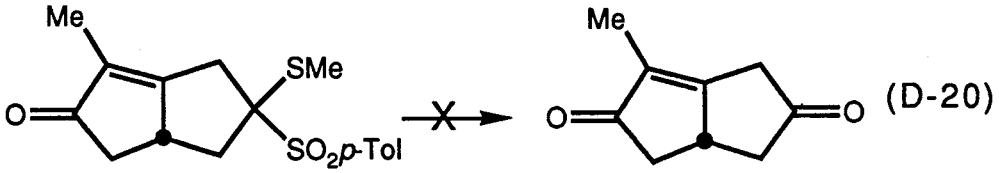
increased. It is known that 1,4-additions of cuprates to enones occur more readily in less polar solvents[78] (diethyl ether, dimethyl sulfide, hydrocarbons) and that HMPA (in the absence of trimethylsilyl chloride) retards the 1,4-additions.[77,78a] Not unexpectedly, the desired conjugate addition reaction of **7** to the enones **128** and **129** in a THF-HMPA solvent mixture (~24% v/v HMPA) was unsuccessful. The reaction in the presence of TMSCl (2 equiv relative to the enones) also failed (equation D-19).



128 and **129** **133** and **134** (D-19)

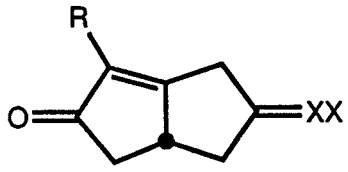
Alkylated methylthiomethyl *p*-tolyl sulfones were reported to undergo a facile hydrolysis of the thioether sulfone function to give the corresponding carbonyl compounds using a variety of mild reaction conditions.[37b,37c,71a,73] Therefore, it was decided to hydrolyze the thioether sulfone function in **128** and **129** to the keto function in the enone **135**. The reactivities of the two carbonyl groups in the enone **135** would be different, thus permitting the protection of the saturated ketone in the presence of the unsaturated one. It was envisaged that the saturated ketone would be reduced to the alcohol and protected as an ether. The hydrolysis reaction was attempted under several of the reported conditions (concentrated HCl/MeOH,[37b,69] $CuCl_2$·silica gel/CH_2Cl_2[73a] and

$CuCl_2/H_2O/MeOH$[73b]), but mixtures of products resulted and the attempt was abandoned (equation D-20).



128 and **129** **135**

In summary, our use of the Pauson-Khand reaction to prepare the important bicyclic enone **74** (see Scheme D-1) on which we wished to carry out the methylenecyclohexane annulation was discontinued due to the unanticipated difficulties encountered which included; the poor yields in the alkylation of the 2-allyl-1,3-dithiane (**109**) with the propargylic iodide **77**; the low solubilities of the enones **128** and **129** in THF; and the mixtures of products obtained in the attempted unmasking of the ketone carbonyl in the same enones. However, it was gratifying to find that the Pauson-Khand cyclization could be done with dithioketal derived functions at C-7 and that the yields and reaction times were comparable to the previously reported examples.

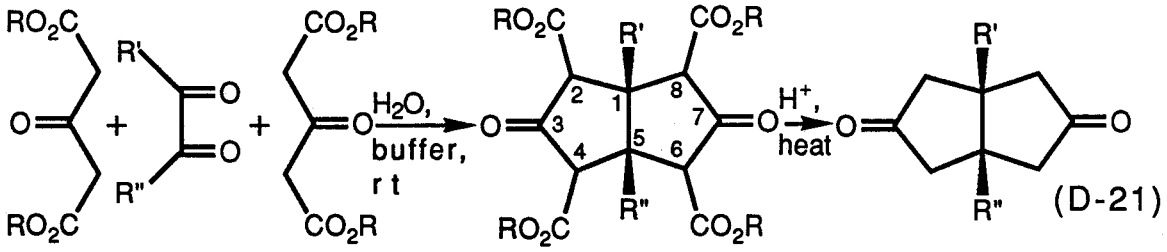


74

2.3. The Synthesis of (±)-β-Panasinsene (31) *via* the Weiss-Cook Condensation Reaction.

2.3.1. Background.

The Weiss-Cook condensation, which has been described as a 3-component (A+B+B or 2+3+3) coupling reaction,[79] has proved useful in the synthesis of many natural and non-natural polyquinanes.[25] The reaction of a dialkyl 3-oxoglutarate (**136**) (2 equiv) with a 1,2-dicarbonyl compound **137** in the presence of a base catalyst (or less commonly, an acid catalyst) produces, in high yield, a tetraalkyl *cis*-bicyclo[3.3.0]octane-3,7-dione-2,4,6,8-tetracarboxylate **138**. Heating the tetraester **138** with acid leads to the hydrolysis of the ester functions. The β-keto acid groups thus formed undergo a spontaneous decarboxylation to generate the dione **139** (equation D-21).

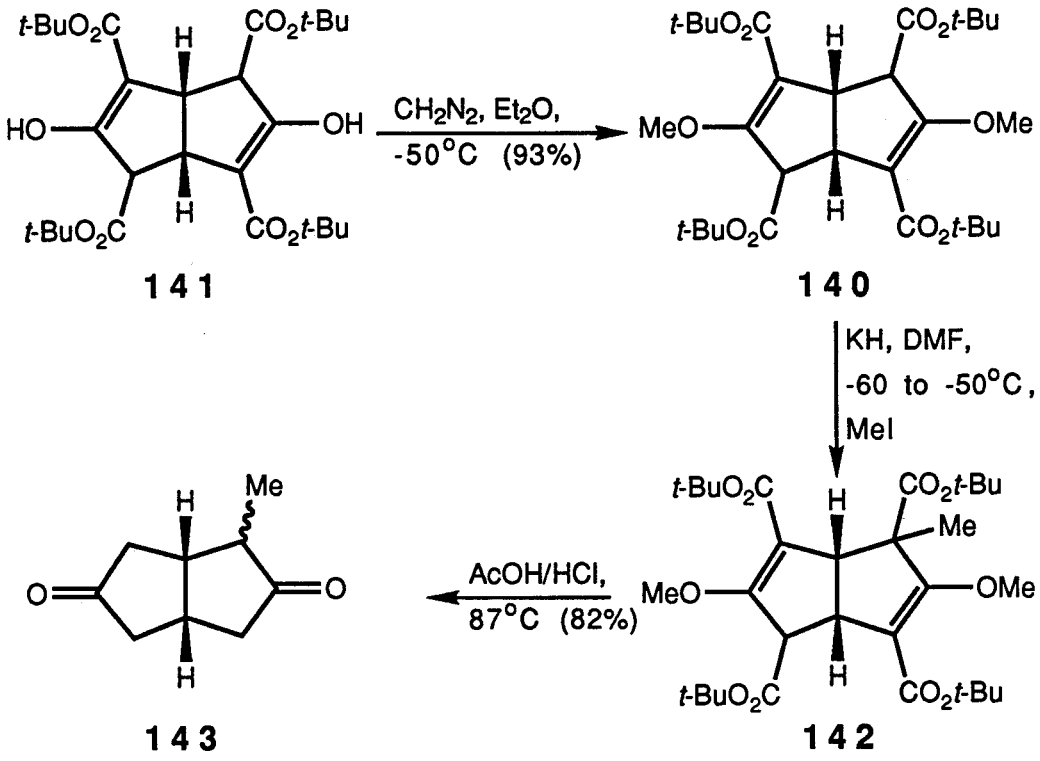


136 **137** **136** **138** **139**

Many different tetraester and dione compounds (**138** and **139**) may be produced *via* the Weiss-Cook condensation.[25] The identities of the R groups in **138** are determined by the ester of 3-oxoglutarate which is employed; normally, R is either a methyl or a

t-butyl group. The structure of the dicarbonyl compound utilized determines the nature of the R' and R" groups of **138** and **139**; R' and R" may be hydrogens, alkyl groups or aryl groups and may be either the same or different. Thus, glyoxal (**44**, R'=R"=H), α-keto aldehydes (R', R"=H, alkyl/aryl), and acyclic or cyclic α-diketones (R', R"=alkyl/aryl) may be utilized with the proviso that the bicyclic product may not be formed if very sterically bulky groups are used (*vide infra*).[80] Also, dicarbonyl compounds with limited solubility in the usual aqueous solvents (i.e., R', R"=large alicyclic group) may be employed if the reaction is performed in organic solvents.[81]

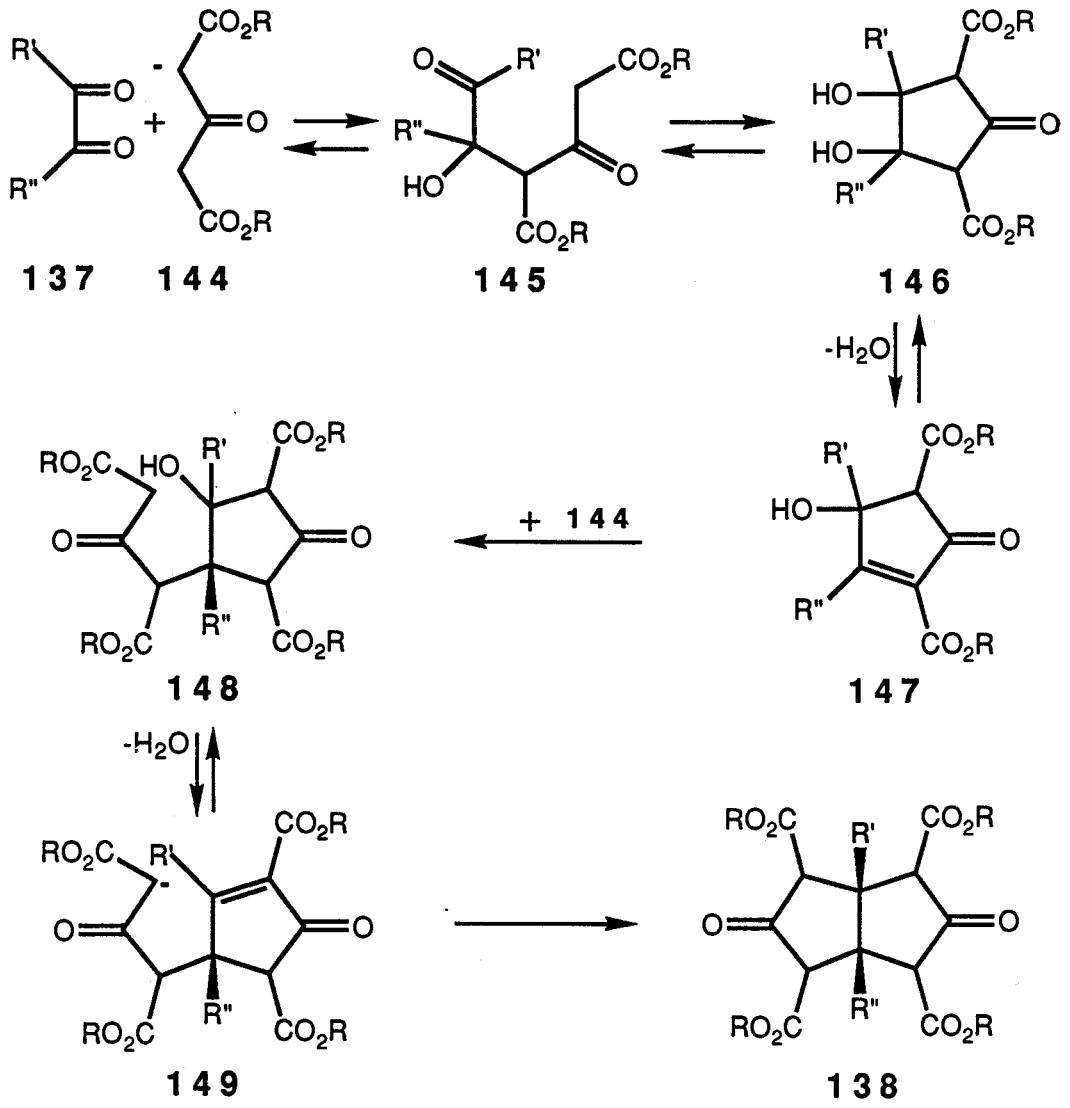
The utility of the Weiss-Cook condensation is due in part to the fact that both the tetraester intermediate **138** and the bicyclic dione **139** are rich in functional groups, which permit further synthetic manipulations of the molecule. Different functional groups at the 1- and 5-positions may be introduced by varying the structure of the initial dicarbonyl compound **137** and then by performing suitable synthetic manipulations on the R' and R" groups. Additional functional groups may be added selectively[25] at the 2-, 4-, 6- and 8-positions by standard alkylation procedures or at the 3- and 7-positions *via* carbonyl group reactions. It is possible to introduce groups regioselectively at the 2- and 6- or the 2- and 8-positions of the bisenol ether of the tetraester (e.g., **140**) or of the dione **139**.[25] Also, as exemplified in Scheme D-8, selective monoalkylations[82] using potassium hydride and an electrophile (MeI, EtI, allyl iodide, etc.) have been performed on the bisenol ethers of tetra-*t*-butyltetraester intermediates such as **140**.[82b] Subsequent



Scheme D-8

hydrolysis and decarboxylation of the ester functions of the alkylated material,**142**, would provide the monoalkylated dione **143**.

One restriction on the versatility of the Weiss-Cook condensation reaction to produce diquinanes is that only the *cis*-bicyclo[3.3.0]octane-3,7-dione stereoisomer is produced. The preference for the formation of the *cis* isomer is reasonable since the presently accepted mechanism[83] for the reaction is based on a series of equilibria (Scheme D-9). Also, Boyd and coworkers[34] have calculated that the *trans* isomer of bicyclo[3.3.0]octane is ~6.5 kcal/mole less stable than the *cis* isomer. Thus, even in the unlikely event that any of the *trans* isomer were to be formed during the reaction, it would rapidly undergo a reverse reaction and eventually



Scheme D-9

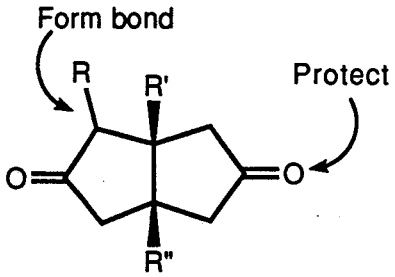
would be transformed into the thermodynamically more stable *cis* isomer.

The proposed mechanism[83a,83b] for the Weiss-Cook condensation is thought to proceed as depicted in Scheme D-9. An aldol condensation of one molecule of the mono-anion of the dialkyl 3-oxoglutarate (**144**) with one carbonyl group of a molecule of the dicarbonyl compound **137** produces the hydroxy dione **145**. A second

aldol reaction may generate the diol **146** which loses a molecule of water to produce the enone **147** (or possibly the dehydration may occur before the second aldol reaction and circumvent the diol **146**). Michael addition of a second molecule of the anion **144** to the enone **147** gives the hydroxy dione **148**. Loss of a molecule of water from **148** to give the enone **149**, followed by a second Michael addition leads to the formation of the tetraester **138**. If appropriate R' and R" groups are used (e.g. R'=R"=*c*-hexyl),[80c] the enone intermediate **147** may be isolated as the reaction is sensitive to steric effects caused by the R' and R" groups.[80]

2.3.2. Application of the Weiss-Cook Condensation Reaction to the Synthesis of (±)-β-Panasinsene (**31**).

2.3.2.1. Preparation of an enone **74**.



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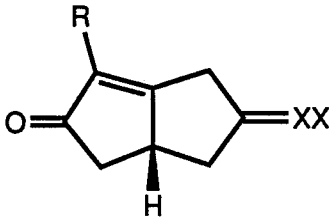
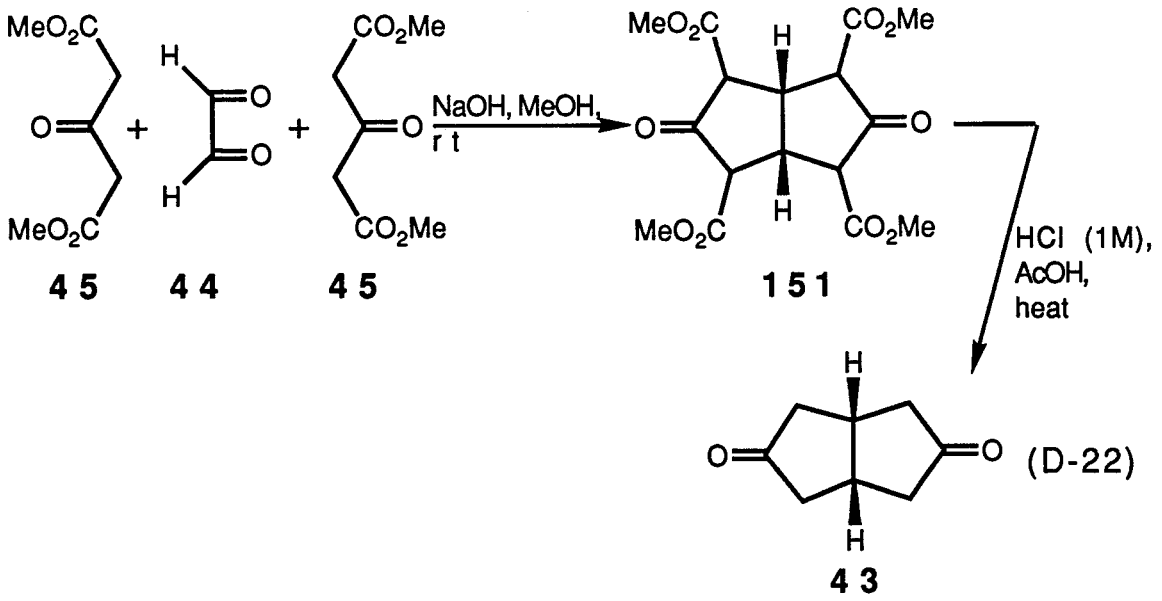


74

If the Weiss-Cook approach were to be employed for the preparation of the key enone **74** in the synthesis of β-panasinsene (**31**), then the R' and R" groups in the dione **150** would be hydrogens. Furthermore, one of the two keto functions of the dione **150** would

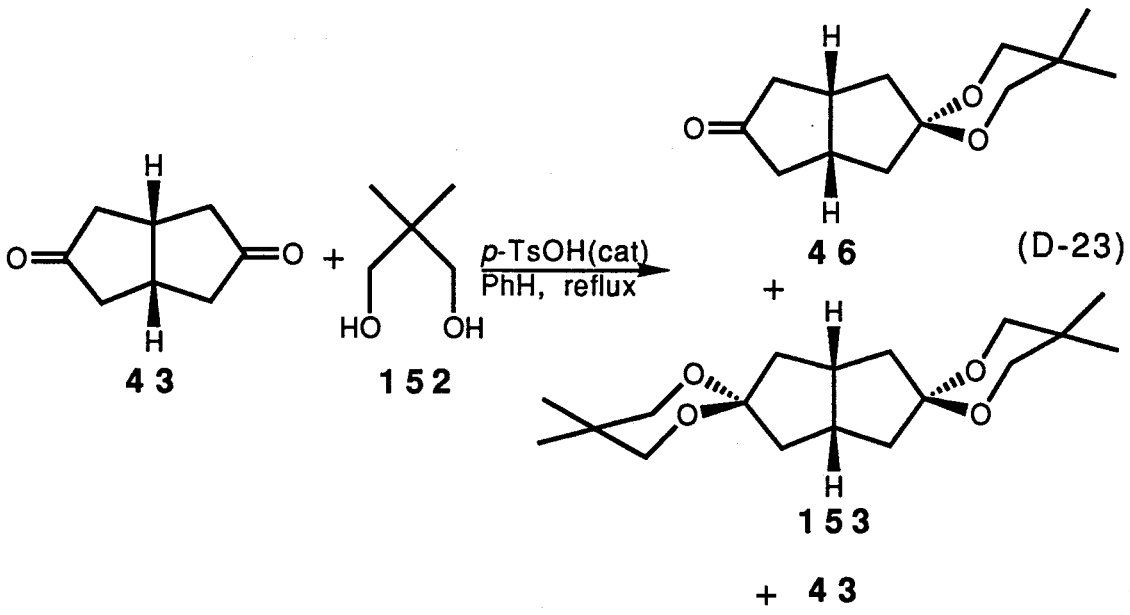
need to be protected to permit differentiation between the two carbonyls, and an appropriate R group would have to be introduced before the enone double bond was installed. With regard to the identity of the R group, it was thought that preparation of an enone **74** with R=methoxycarbonyl would provide several advantages (*vide infra*) in comparison with the preparation of an enone having the ultimately desired R=methyl. Thus, a synthetic sequence utilizing the monoalkylation (MeI) of the bisenol ether tetra-*t*-butyl-tetraester intermediate **140** to generate the methylated dione **143** (Scheme D-8) was not considered.

Synthetically, a base-catalyzed Weiss-Cook condensation using glyoxal **44** and dimethyl 3-oxoglutarate **45**, followed by an acid-catalyzed hydrolysis/ decarboxylation of the tetraester intermediate (**151**) provided the known dione **43** (equation D-22).[84]

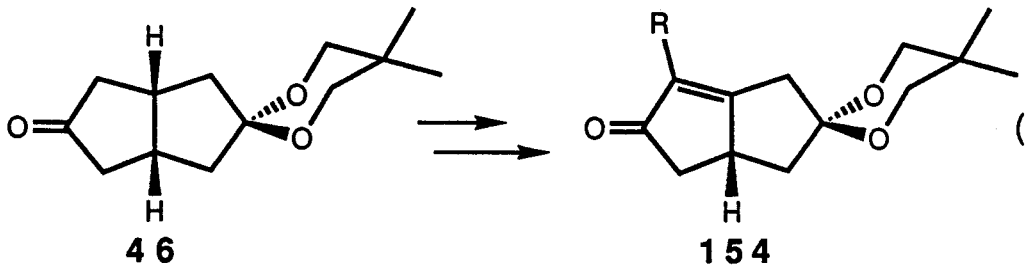


Selective protection of one of the carbonyl functions in **43** to give the keto ketal **46** was achieved *via* an acid catalyzed reaction

of **43** with 2,2-dimethyl-1,3-propanediol (**152**) by the method reported by Moss and Piers (equation D-23).[38,85] Preparation of **46** usually involves a tedious chromatographic separation of **46** from the diketal **153** and the dione **43**. However, the purification was simplified by loading the sample as a solid adsorbed on Celite onto the silica gel column and successively eluting compounds **153**, **46** and **43** with diethyl ether-petroleum ether (2:1), diethyl ether-ethyl acetate (9:1) and ethyl acetate (neat), respectively. The purified keto ketal exhibited m.p. 46.5-47.5°C (literature[85] m.p. 48°C).

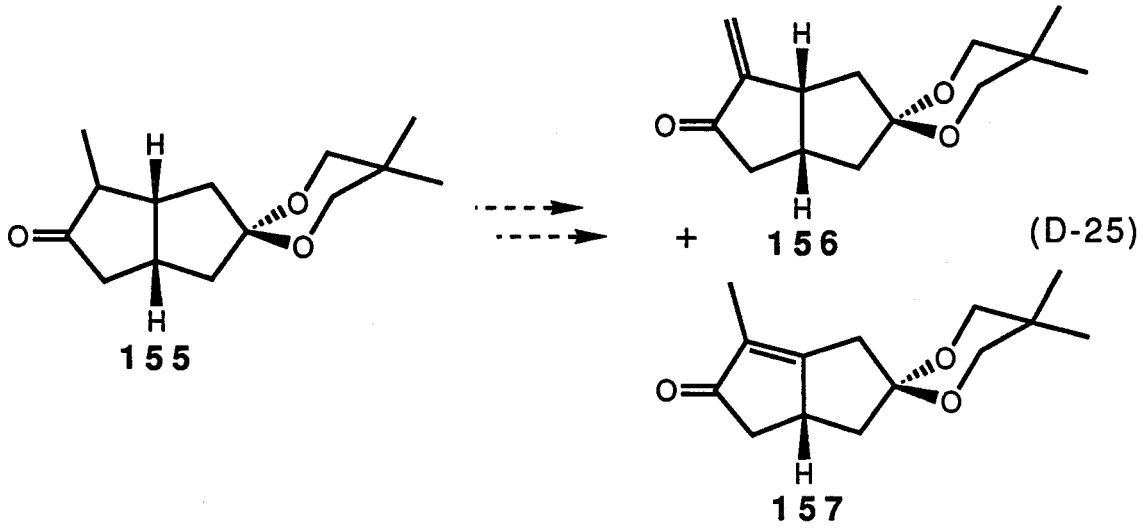


In order to transform the keto ketal **46** into the desired enone **154**, it was necessary to introduce an appropriate R group and the enone double bond (equation D-24). Depending on the identity of the R group, formation of the double bond and the proposed conjugate addition reaction could be more or less expedited. If R were a methyl group, as is found in β-panasinsene (**31**), then in the formal



46 **154** (D-24)

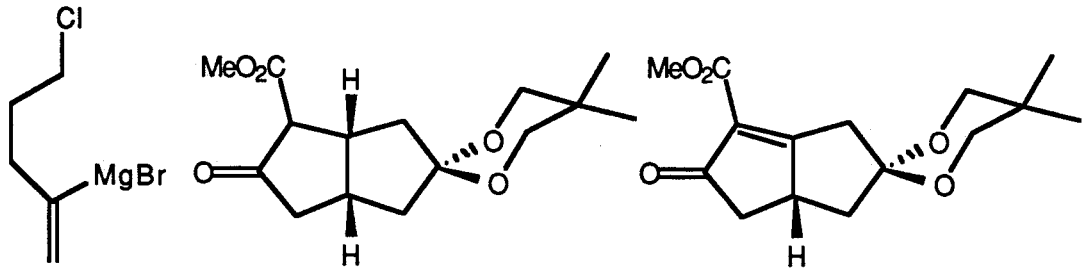
dehydrogenation step to generate enone **154**, the double bond theoretically could end up either exo- or endo- to the 5-membered ring (**156** or **157**, respectively, equation D-25). Due to the strain involved in introducing two new sp^2 centers into the five-membered ring to give **157**, it was difficult to predict, *a priori*, whether or not the elimination of the selenoxide derived from **155** would generate the endo isomer **157** as the major product; however, others have noted the predominance of the endo isomer[86] for a variety of bicyclic lactones and 2,3-dialkylated cyclopentanones. Another, less serious problem, was that the presence of the methyl group on the enone double bond would deactivate[87] the enone **157** towards the key copper (I)-catalyzed conjugate addition reaction of the Grignard



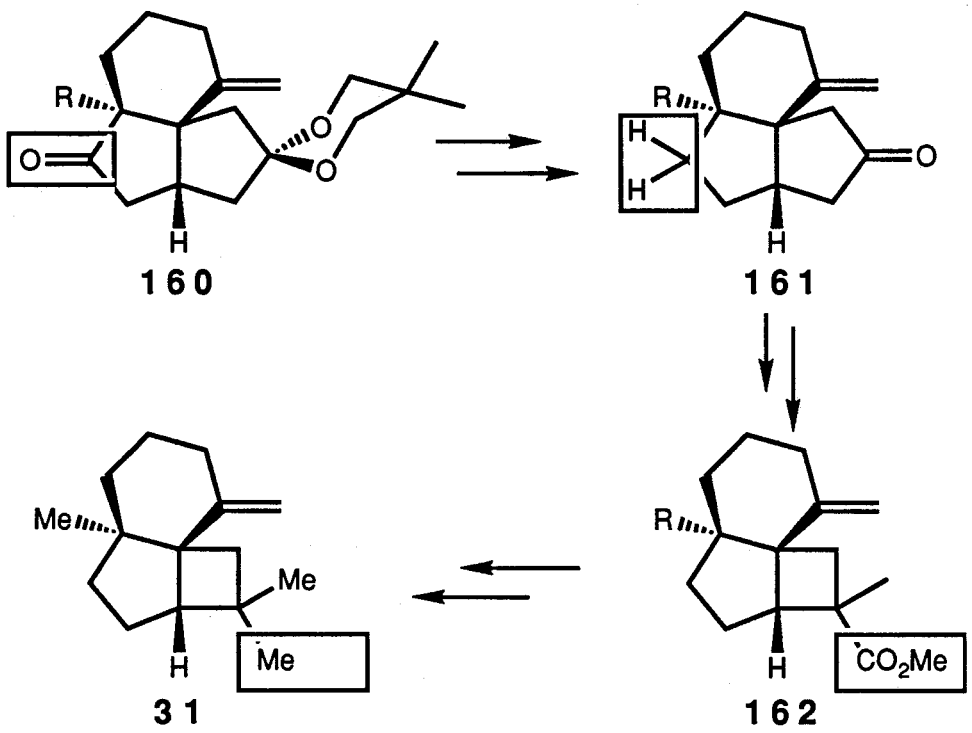
155 **156** (D-25)

157

reagent **7**. On the other hand, if R were the methoxycarbonyl function, there would be no possibility of the formation of an enone with an exocyclic double bond from the keto ester **158**. In addition, the enone **159** would be activated[78a] towards conjugate addition reactions. A disadvantage of utilizing R=methoxycarbonyl was that at some stage during the synthesis, the methoxycarbonyl group would have to be deoxygenated to generate the corresponding methyl group. However, deoxygenation reactions were already planned at two stages of the synthesis (between **160** and **161** and between **162** and **31**, relevant positions indicated, Scheme D-10), so it was expected that at either point a double deoxygenation could be done. Consequently, it was decided that a methoxycarbonyl group rather than a methyl group would be employed as the R group in the synthesis of an enone **74** and that its deoxygenation would be performed in tandem with the deoxygenation of either the keto or the ester functions in **160** or **162**, respectively.



7 **158** **159**



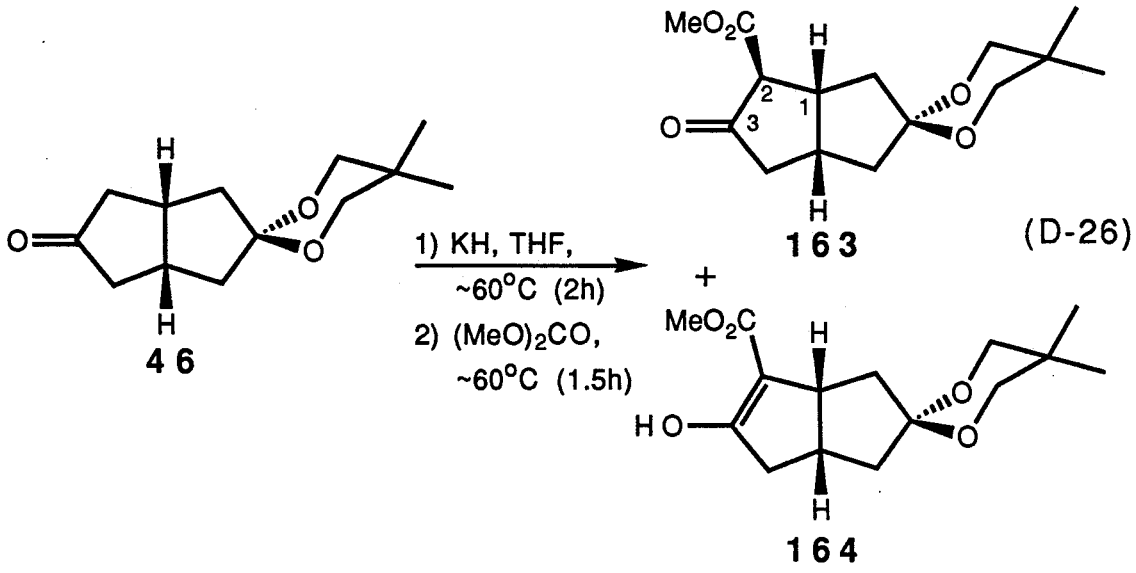
Scheme D-10

The keto ester ketal **158** (actually as a mixture of **163** and **164**) was prepared *via* a modification of the procedure reported by Deslongchamps and coworkers.[88] Thus, a THF solution of the keto ketal **46** was treated with potassium hydride, and the enolate anion thus generated was allowed to react with dimethyl carbonate to form, in ~93% yield, an ~1.5:1 mixture (^{1}H nmr analysis) of the keto ester **163** and its ester enol tautomer **164** (equation D-26). Due to the fact that the mixture of **163** and **164** was not stable to purification by flash chromatography, this material was not rigorously purified.

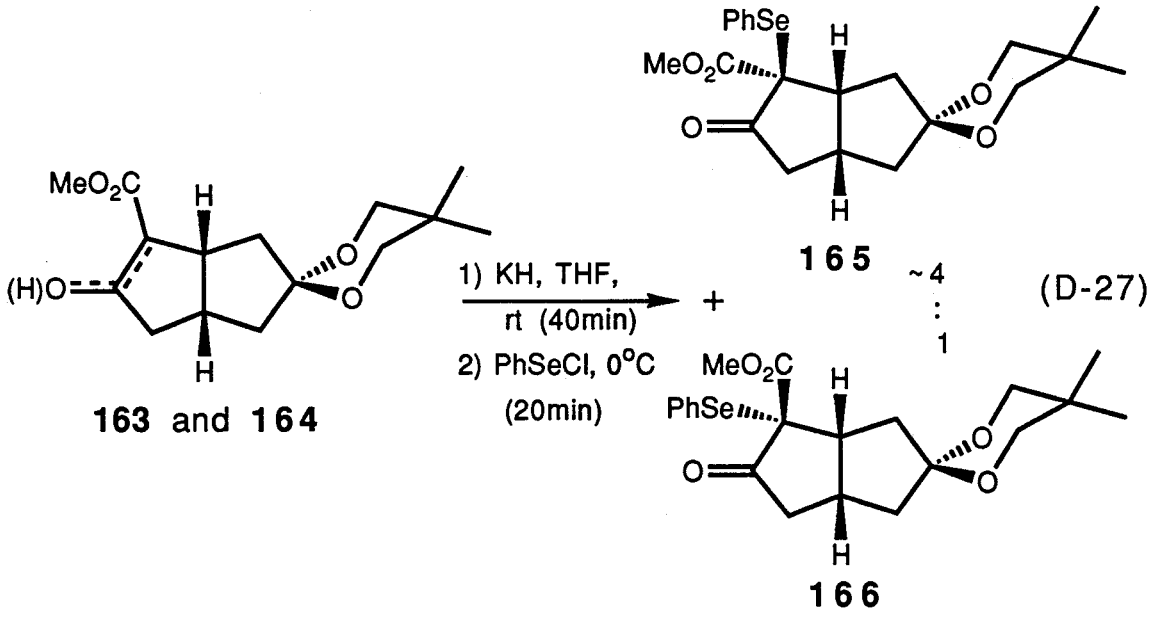
The stereochemistry of the keto ester **163** was not proven, but was assumed to be that shown based on the following reasoning. Excess base present during the reaction would remove the proton

between the keto and ester functions to generate the corresponding enolate. During the workup of the reaction, protonation of the enolate would give a mixture of **163** and the epimer at C-2. Equilibration of the mixture *via* the enol tautomer **164** would lead to the methoxycarbonyl group preferentially being on the sterically less congested, convex face[89] of the molecule.

In the ^1H nmr spectrum of the crude mixture, the signals due to the methoxycarbonyl functions of **163** and **164** were displayed as singlets at δ 3.73 and 3.75, respectively, while the signal for the enol O<u>H</u> of **164** was displayed at 10.35. In the high resolution mass spectrum, the exact mass of the molecular ion of the mixture (**163** and **164**) was found to be 282.1459, which is consistent with the molecular formula $C_{15}H_{22}O_5$. Signals for fragments corresponding to the loss of MeOH (M^+-32) and the loss of the methoxycarbonyl group (M^+-59) were also observed in the low resolution mass spectrum. Such signals were displayed by many of the other methoxycarbonyl containing intermediates which were prepared.



In order to generate the enone **159**, a modification of the selenoxide syn elimination procedure developed by Reich and coworkers[90] was employed. The required selenide was prepared by treating a THF solution of a mixture of the keto ester **163** and its enol tautomer **164** with potassium hydride (1.3 equiv) and allowing the resultant enolate anion to react with benzeneselenenyl chloride (1.35 equiv) at 0°C. An ~4:1 mixture (^{1}H nmr analysis, using the ratio of the signals of the methoxy groups) of the epimeric selenides **165** and **166** was obtained in 86% yield.

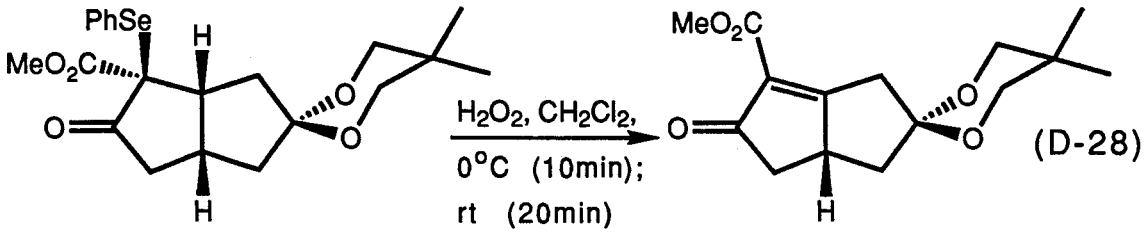


(D-27)

The two epimers **165** and **166** could be distinguished readily by three main signals in the ^{1}H nmr spectra of the mixture. Thus, the signals for the tertiary methyl groups of the major epimer **165** appeared at δ 0.89 and 0.97, while those of the minor epimer **166** were at 0.92 and 0.99. The resonances due to the methoxycarbonyl functions were at δ 3.71 and 3.51, respectively. Also, signals for

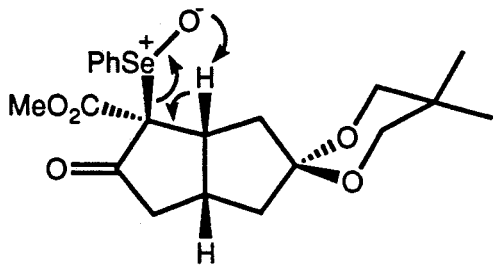
aromatic hydrogens at δ 7.53-7.57 and 7.63-7.65 were characteristic of **165** and **166**, respectively. A small amount of the minor epimer (**166**) was obtained in pure form and the expected molecular formula, $C_{21}H_{26}O_5{}^{80}Se$, was confirmed by the presence of an ion with a mass of 438.0940 mass units in the high resolution mass spectrum.

The oxidation of the mixture of the selenides **165** and **166** to the corresponding selenoxides had to be done with care as 2-alkoxycarbonyl-2-cyclopenten-1-ones are sensitive to base catalyzed epoxidation by hydrogen peroxide.[90] In the case of **165** and **166**, only the major epimer **165** would be able to undergo the normal selenoxide syn elimination.[91] However, because compounds **165** and **166** could not be separated by chromatography (silica gel), the minor epimer **166** was also present during the oxidation to give the corresponding selenoxide. Thus, a dichloromethane solution of the mixture of the epimeric selenides was treated with 15% aqueous hydrogen peroxide (2.1 equiv) at 0°C (10 min) and room temperature (20 min) (equation D-28). A ^1H nmr spectrum of the crude product indicated unexpectedly that the product obtained was quite pure with just traces of aromatic compounds present.

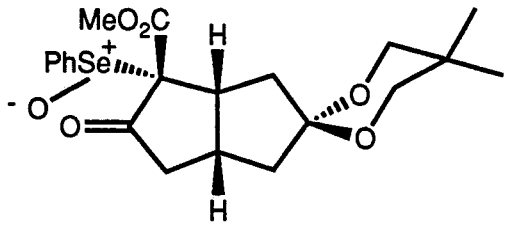


165 **159** (D-28)

A control experiment was done to try to determine the fate of the minor selenide epimer **166**. Thus, a sample of **166** with less than 5% of the major epimer **165** present (^{1}H nmr analysis), but which contained some other impurities, was oxidized using our normal procedure. A ^{1}H nmr spectrum of the crude product showed the presence in the mixture of the enone **159** and small amounts of other compounds having aromatic, methoxycarbonyl and/or ketal functions present. The presence of enone **159** was surprising given that the normal syn elimination[91] (as shown in formula **167**) of the selenoxide cannot occur in compound **168**. There have been reports in the literature of the selenoxide elimination occurring in cases where the selenoxide and the β–proton were anti to each other in the starting material used for the reaction (for example, *trans*-2-(phenylselenenyl)-3-alkylcyclopentanones).[92] However, in such cases, there was a proton α- to the selenoxide function. Thus, it was believed that an *in situ* epimerization of the selenoxide function generated occurred to give the syn arrangement of the selenoxide and the β-proton and that then the normal elimination reaction took place. In the case of the selenoxide **168**, a simple epimerization is impossible, so a more complex process may be occurring. However, the mixture that was obtained from the oxidation of **166** was not

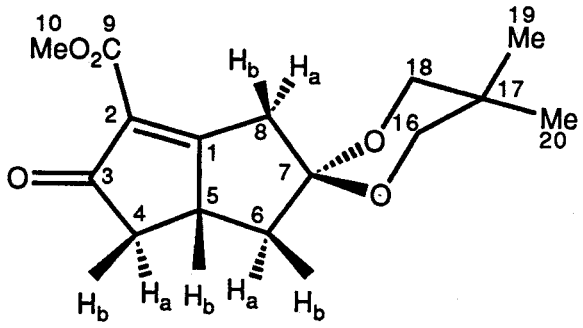


167



168

characterized further. The results of the oxidation of the selenide **166** indicated that the presence of **166** during the oxidation/ selenoxide elimination reaction of the major selenide epimer (**165**) would not be a significant problem.



159

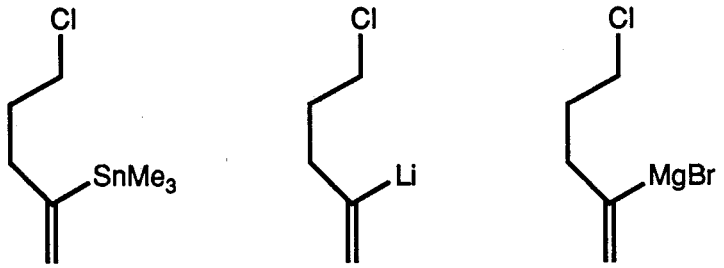
The enone **159** obtained from the selenoxide elimination was not stable to flash chromatography, so it was characterized without rigorous purification. In the ^{1}H nmr spectrum, the signals for all the hydrogens of **159** were assigned based on decoupling experiments and on the observations[93] that in bicyclo[3.3.0]octanones, hydrogens on the convex face are deshielded relative to those on the concave face and vicinal *cis* couplings between hydrogens α- to a keto function and the angular hydrogen are larger than the corresponding trans couplings. Thus, the multiplet for the angular hydrogen (H-5b) at δ 3.14-3.26 was coupled with the indicated coupling constants to the signals at 2.25 (J = 4.0 Hz, H-4a), 2.79 (J = 6.5 Hz, H-4b), 1.48 (J = 12.5 Hz, H-6a) and 2.70 (J = 8.0 Hz, H-6b). The geminal couplings for H-4a and H-4b and for H-6a and H-6b were 18.0 Hz and 12.5 Hz, respectively. The signal for the hydrogens at the 8-position was a broad singlet at 3.30 (2H). The methyl ester signal was at δ

3.85, while the resonances due to the tertiary methyl groups were at 0.94 and 1.09 (s, 3H each). Two carbonyl absorptions were observed at 1750 and 1719 cm^{-1} in the ir spectrum and were due, respectively, to the cyclopentenone and ester carbonyl stretches.[61] The molecular formula, $C_{15}H_{20}O_5$, was consistent with the ion found at 280.1311 in the high resolution mass spectrum.

The key enone intermediate **159**, representative of the generalized structure **74**, (see p. 60) was one of the subtargets in the synthesis of (±)-β-panasinsene (**31**). Also, the enone **159** appeared to be more suitable for the key methylenecyclohexane annulation sequence than the previously synthesized enones **128** and **129** (Scheme D-7, p. 51) had proved to be.

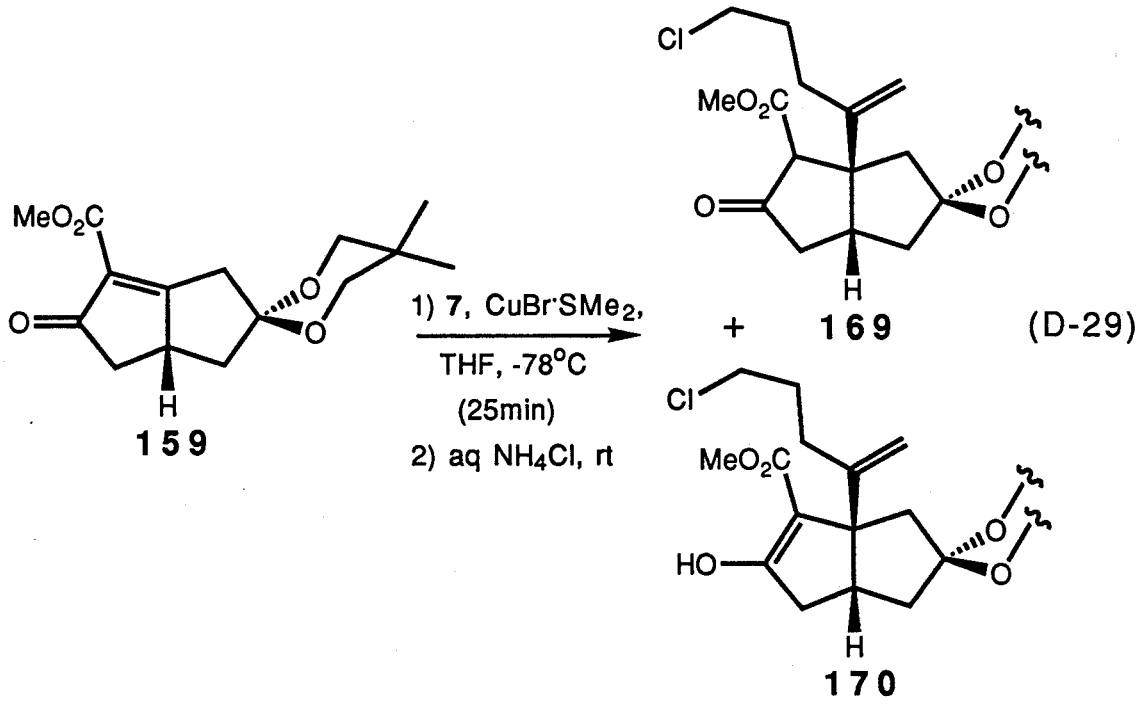
2.3.2.2. Methylenecyclohexane Annulation on the Enone **159**.

The vinylstannane **5**, prepared by a modification[10b] of previously reported procedures,[5] was dissolved in THF and transmetallated at -78°C with a solution of methyllithium. The resulting vinyllithium species **6** was transformed into the corresponding Grignard reagent **7** by the addition of solid magnesium bromide etherate. The successive addition of the copper (I) bromide-dimethyl sulfide catalyst (0.25 equiv) and a THF solution of the enone **159** gave an orange suspension which was stirred at -78°C for 25 minutes. After an appropriate workup, a mixture of the keto ester chloride **169** and its enol tautomer **170** was obtained in 94% yield (equation D-29). It was gratifying and not unexpected to find that the enone **159** was



5 **6** **7**

very reactive towards the conjugate addition reaction of the Grignard reagent **7**. As seen earlier, similar reactions of enones having tri- or tetrasubstituted double bonds were more sluggish and required either longer reaction times (see equation D-18) or the presence of additives (see Schemes I-1 and I-3).

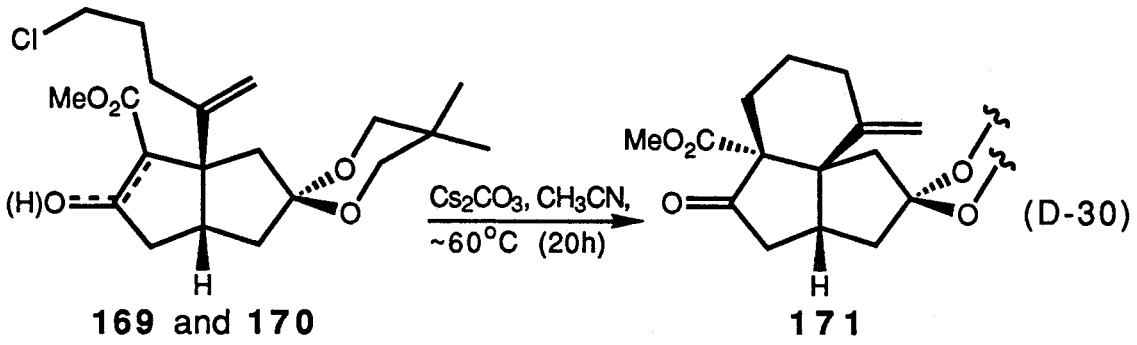


(D-29)

The crude product mixture of **169** and **170** was not stable to purification by flash chromatography. Therefore, apart from a rapid filtration through a short silica gel column to remove inorganic and

very polar organic material, it was characterized without purification. A strong absorption characteristic of an enolized β-dicarbonyl group[61] was displayed at 1657 cm^{-1} in the ir spectrum. The keto and ester carbonyl stretches at 1754 and 1722 cm^{-1} were relatively weak, which indicated that the enol tautomer **170** predominated. The ^1H nmr spectrum ($CDCl_3$) also indicated that the enol **170** was the predominant component of the mixture. Thus, the signal for the enol OH (br s at δ 10.79) integrated for ~1 hydrogen. That the conjugate addition had been performed was further confirmed by the presence in the ^1H nmr spectrum of signals due to the hydrogens α- to the chloride (part of a multiplet at δ 3.42-3.62) and due to the olefinic hydrogens at δ 4.74 and 4.82 (s, 1H each).

With the keto ester mixture **169/170** in hand, the second step in the methylenecyclohexane annulation, namely the cyclization of the keto chloride to obtain a tricyclic ketone, was performed. Surprisingly, the cyclization was problematic and, before success was achieved, a variety of methods were tested (i.e., KH/THF/45°C; K_2CO_3/ acetone/ 50°C;[94] K_2CO_3/ 2-butanone/ 80°C; K_2CO_3/ 3-pentanone/ ~100°C; one-pot conjugate addition/ cyclizations in the presence of HMPA[95]). Ultimately, it was found that the cyclization of the crude keto ester chloride **169/170** worked best in hot (~60°C) acetonitrile using cesium carbonate[96] (5 equiv) as the base (equation D-30). The product thus generated was more pure and was produced in a better yield than that obtained from the other procedures. After chromatographic purification and a recrystallization, the tricyclic keto ester ketal **171** was obtained as colorless crystals in 64% yield and exhibited m.p. 127.5-128.5°C.



169 and **170** **171**

The tricyclic keto ester ketal **171** was further characterized by ir spectroscopy, mass spectrometry (high and low resolution), an elemental analysis, and nmr spectroscopy (^{1}H and ^{13}C, one and two[97] dimensional experiments). Thus, in the ir spectrum, very strong absorptions were observed at 1745 and 1723 cm^{-1} due to the keto and ester carbonyl stretches, respectively, and at 1115 cm^{-1} due to the ketal C-O bonds. Weak absorptions due to the exocyclic olefinic methylene appeared at 1637 and 893 cm^{-1}. The high resolution mass spectrum indicated that the molecular ion had a mass of 348.1929 mass units which is consistent with the molecular formula, $C_{20}H_{28}O_5$. In the low resolution mass spectrum, fragments corresponding to the loss of MeO (M^+-31) and CO_2Me (M^+-59) were observed. The analytical data also was in keeping with the formula.

The ^{1}H nmr spectrum of **171** (see figure 2) showed the expected three singlets (3H, each) due to the tertiary methyl groups (Me-19 and Me-20)* at δ 0.91 and 1.01, and to the methoxycarbonyl group (Me-14') at 3.74. The signals due to the two olefinic hydrogens were found at δ 5.01 (H-15b) and 5.07 (H-15a) and were, respectively, a

* Note: The numbering system employed is based on the numbering scheme used for β-panasinsene (see Scheme D-1, compound **31**). Thus, the position numbered C(H)-13 in the various tricyclic intermediates synthesized ultimately becomes the corresponding methyl group (Me-13) in the synthetic β-panasinsene (**31**).

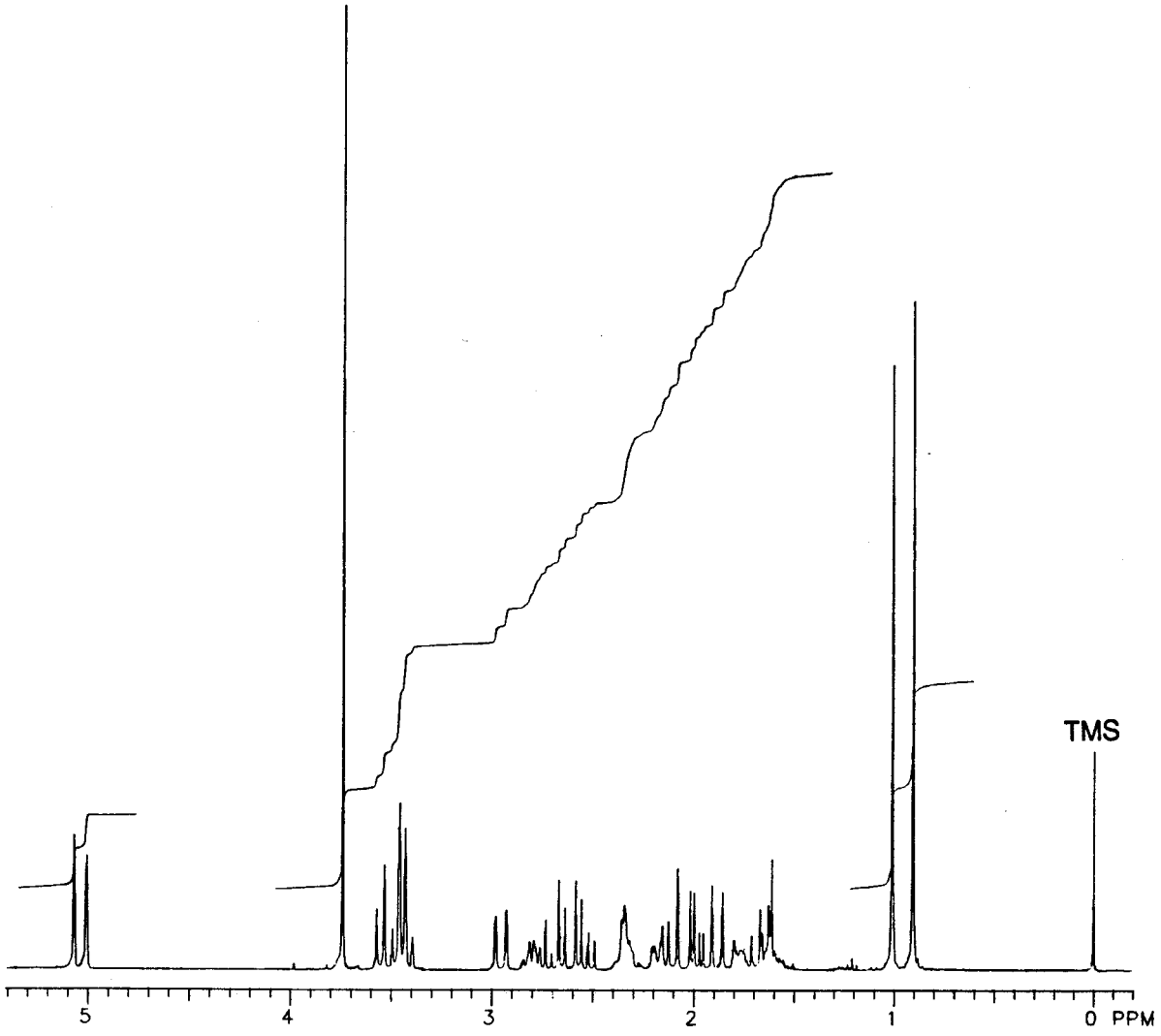
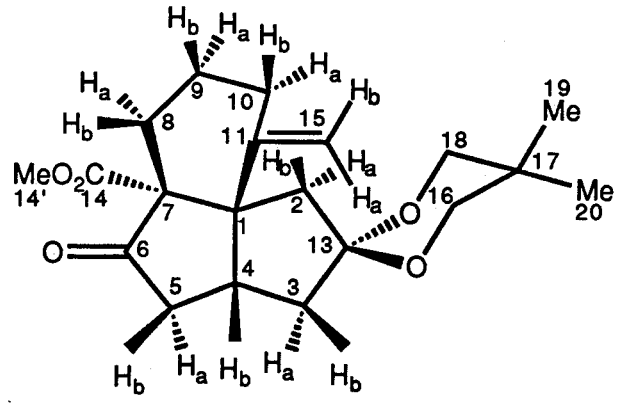


Figure 2. The 300 MHz ^{1}H nmr spectrum of the keto ester ketal **171**.

doublet (J = 1.0 Hz) and a singlet. The methine hydrogen (H-4b) appeared as a multiplet at δ 2.76-2.84 (1H). The remaining aliphatic hydrogen signals also were displayed in the spectrum and are listed together with the COSY (^{1}H-^{1}H COrrelation Spectroscopy) correlations in Table 2.



171

From a ^{13}C nmr APT (Attached Proton Test) experiment performed on **171**, the signals for the carbons corresponding to the methyl and methine groups could be assigned as follows; δ 22.23 and 22.32, the tertiary methyl groups ($\underline{C}H_3$-19 and $\underline{C}H_3$-20); 52.1, the methyl ester ($\underline{C}H_3$-14'); and 38.65, the methine ($\underline{C}H$-4). Some of the signals due to the other carbons could be assigned based on their chemical shifts. Thus, the signal for the olefinic methylene ($\underline{C}H_2$-15) resonated at δ 112.7; the signal for the quaternary olefinic carbon (C-11) was at 145.1; and the signals for the keto (C-6) and ester (C-14) carbonyl groups were at 211.8 and 170.5, respectively. The rest of the carbon signals along with the HETCOR (^1H-^{13}C, HETeronuclear Shift CORrelation) correlations are listed in Table 1.

Based on the HETCOR and COSY data, all the hydrogen signals in the ^1H nmr spectrum and most of the carbon signals in the ^{13}C nmr spectrum could be reasonably assigned. Thus, a HETCOR experiment (see figure 3) confirmed the above ^1H and ^{13}C assignments and permitted the determination of the pairs of geminal hydrogens. For example, the carbon signal at δ 42.8 ($\underline{C}H_2$-2) correlated with hydrogen signals at 1.88 (d, 1H, J = 16.0 Hz, H-2a) and 2.95 (br d, 1H,

J = 16.0 Hz, H-2b); the carbon signal at 38.74 ($\underline{C}H_2$-3) correlated with hydrogen signals at 1.96 (distorted dd, 1H, J = 14.0, 6.0 Hz, H-3a) and 2.10 (distorted d, 1H, J = 14.0 Hz, H-3b); and the carbon signal at 32.4 ($\underline{C}H_2$-10) correlated with only the 2-hydrogen multiplet at 2.26-2.39 (H-10a and H-10b). The other pairs of geminal hydrogens were assigned in a similar manner, but the determination of which pair was at which position was based on the observed COSY correlations.

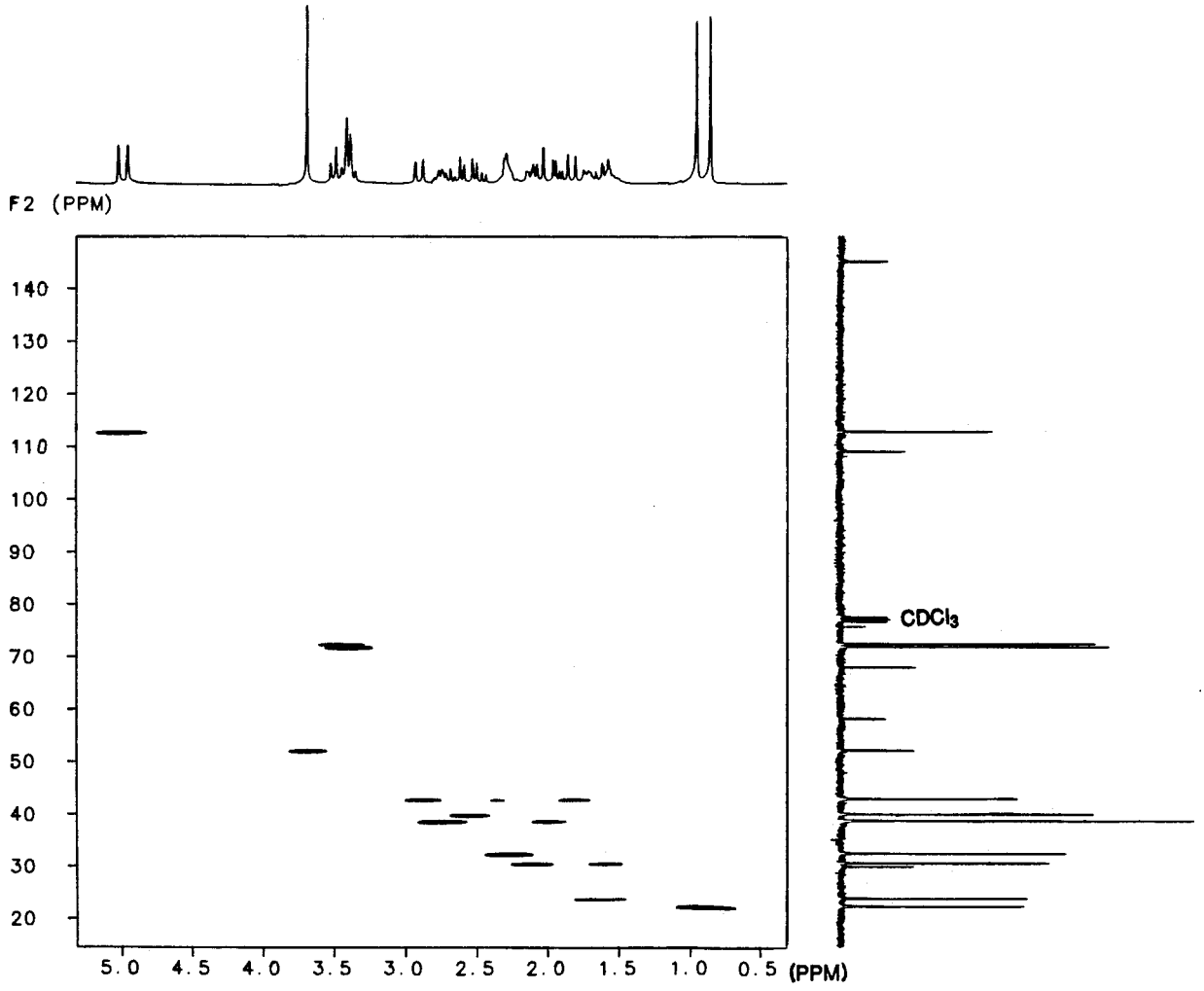
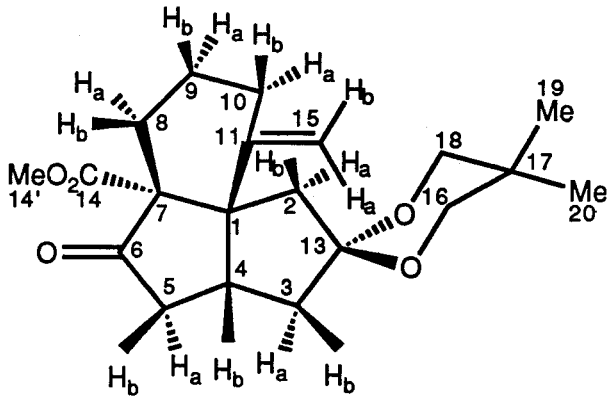


Figure 3. The 75 MHz HETCOR spectrum of the keto ketal ester **171**.

Table 1: The 75 MHz HETCOR Data for the Keto Ester Ketal **171**.



171

Position (C-x)	^{13}C (75 MHz) δ ppm	^{1}H (300 MHz) δ ppm (H-x)
1	58.2[a]	- -
2	42.8	1.88 (2a); 2.95 (2b)
3	38.74	1.96 (3a); 2.10 (3b)
4	38.65	2.76-2.84 (4b)
5	39.9	2.54 (5a or 5b); 2.69 (5b or 5a)
6	211.8	- -
7	68.0[a]	- -
8	30.6	1.54-1.71 (8a or 8b); 2.15-2.21 (8b or 8a)
9	23.8	1.72-1.80 (9a or 9b); 1.54-1.71 (9b or 9a)
10	32.4	2.26-2.39 (10a and 10b)
11	145.1	- -
13	109.0	- -
14	170.5	- -
14'	52.1	3.74 (3H-14')
15	112.7	5.07 (15a); 5.01 (15b)
16/18	71.8/72.4	3.40-3.57 (2H-16/2H-18)
17	30.0	- -
19/20	22.23/22.32	0.91/1.01 (3H-19/3H-20)

a. Assignments may be interchanged.

In the COSY spectrum of the keto ester ketal **171** (see figure 4), the spin system of the six-membered ring was separable from interrelated ones of the two five-membered rings. Thus, key entry points into the two main spin systems were the signals for the olefinic hydrogens at δ 5.01 (d, 1H, J = 1.0 Hz, H-15b) and 5.07 (s, 1H, H-15a) which showed correlations in the six-membered ring system and the signal for the methine hydrogen at 2.76-2.84 (m, 1H, H-4b) which led into the five-membered ring systems. The process followed in making the assignments of the hydrogen positions by use of the COSY correlations is exemplified for the five-membered ring systems. The signal for the methine hydrogen (H-4b) at δ 2.76-2.84 showed strong correlations (large cross peaks) to the distorted doublets at 1.96 (1H), 2.54 (1H), 2.69 (1H) and weaker correlations to the signals at 2.10 (distorted d, 1H) and at 2.95 (br d, 1H). From the HETCOR results (see Table 1), the signals (a) at δ 2.95 and 1.88, (b) at 1.96 and 2.10 and (c) at 2.54 and 2.64 were due to pairs of geminal hydrogens. Since the signal at δ 2.95 also showed a weak correlation to the signal for the olefinic hydrogen at 5.07 (H-15a), it seemed reasonable to assign the signal at 2.95 to H-2b and thus, the one at 1.88 to H-2a. The signals at δ 2.54 and 2.64 were then assigned to the hydrogens at position 5, α- to the ketone carbonyl, while the signals at 1.96 and 2.10 were assigned to H-3a and H-3b, respectively, α- to the ketal function with the assignment of the a- and b-hydrogens based largely on reported observations of the magnitudes of relevant coupling constants in other systems.[93] The pairs of geminal hydrogens on the six-membered ring were assigned

to the appropriate positions starting from the cross peaks shown by the two olefinic hydrogens at δ 5.01 (H-15b) and 5.07 (H-15a).

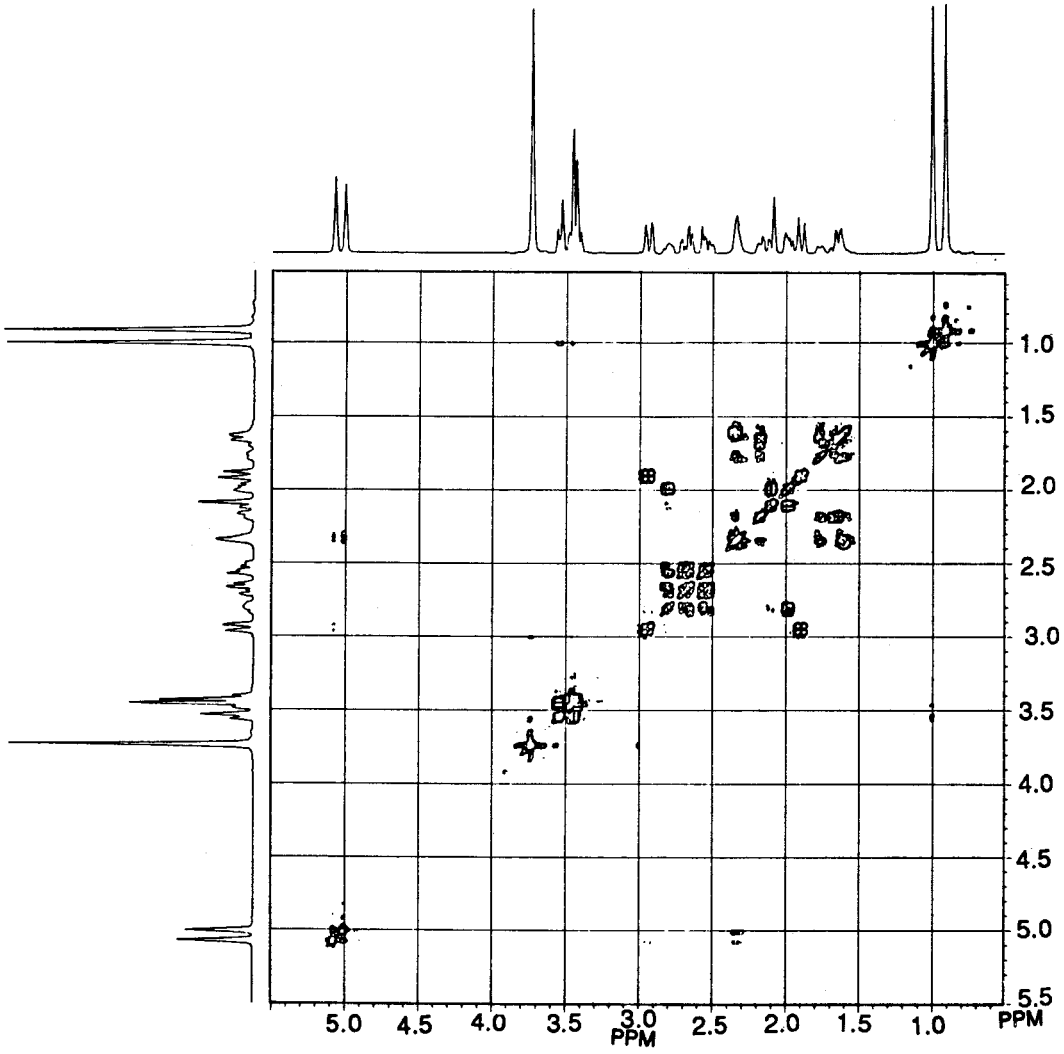
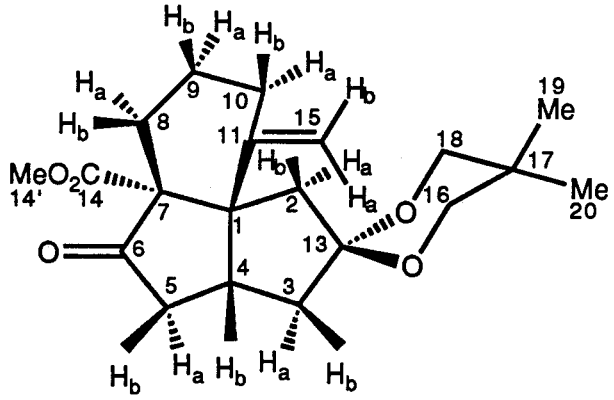


Figure 4. The 400 MHz COSY spectrum of the keto ester ketal **171**.

Table 2: The 400 MHz COSY Data for the Keto Ester Ketal **171**.



171

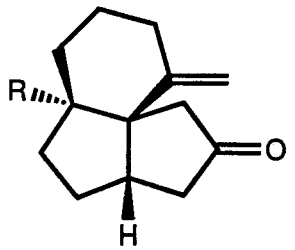
Position (H-x)	Signal δ ppm (multiplicity;[a] J; number of H)	COSY Correlations (H-x)
2a	1.88 (d; 16.0; 1H)	2b
2b	2.95 (br d; 16.0; 1H)	2a; 4b (W-coupling); 15a[b]
3a	1.96 (distorted dd; 14.0, 6.0; 1H)	3b; 4b
3b	2.10 (distorted d; 14.0; 1H)	3a; 4b[b]
4b	2.76-2.84 (m; 1H)	3a; 3b[b]; 5b; 5a; 2b (W-coupling)
5a or 5b	2.54 (distorted dd; 19.5, 9.0; 1H)	5b or 5a; 4b
5b or 5a	2.69 (distorted dd; 19.5, 9.0; 1H)	5a or 5b; 4b
8a or 8b	1.54-1.71 (m; 2H)	8b or 8a; 9b and 9a
8b or 8a	2.15-2.21 (m; 1H)	8a or 8b; 9a and 9b; 10a or 10b (W-coupling)
9a or 9b	1.72-1.80 (m; 1H)	9b or 9a; 8b or 8a; 10a and 10b
9b or 9a	1.54-1.71 (m; 2H)	9a or 9b; 8b or 8a; 10a and 10b
10a and 10b	2.26-2.39 (m; 2H)	9a and 9b; 8b or 8a (W-coupling); 15a and 15b
14'	3.74 (s; 3H)	- -
15a	5.07 (s; 1H)	15b; 10a or 10b[b]; 2b[b]
15b	5.01 (d; 1.0; 1H)	15a; 10a or 10b

Table 2: continued.

16 and 18	3.40-3.57 (m; 4H)	20 or 19 (W-coupling)
19 or 20	0.91 (s; 3H)	- -
20 or 19	1.01 (s; 3H)	16 or 18 (W-coupling)

a. The signals labelled s, d and dd may incorporate unresolved fine couplings.
b. Small couplings observed.

The synthesis of **171** represented the fulfillment of one of the goals of the project, that is, the synthesis of an enone with a tetrasubstituted double bond and its utilization in the methylene-cyclohexane annulation sequence. It remained only to carry out various functional group manipulations to arrive at the projected intermediate **72** on which to perform a ring contraction to assemble the correct tricyclic carbon framework of the natural product.

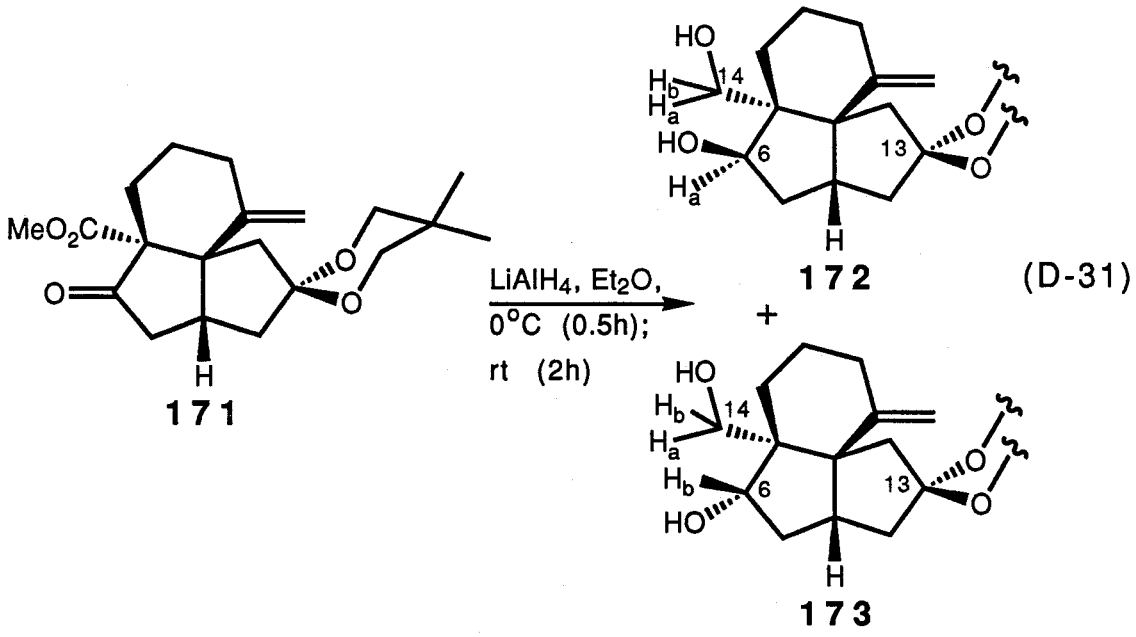


72

2.3.2.3. Preparation of a Substrate (Intermediate **72**) for Ring Contraction.

In order to prepare the desired ketone substrate **72** for the planned ring contraction sequence, it was necessary to deoxygenate the keto group (and perhaps the methoxycarbonyl group) in **171** and to convert the ketal group into a keto function.

A double deoxygenation of the keto and ester functions to give the corresponding methylene and methyl groups was attempted first. Consequently, the keto and methoxycarbonyl groups of the keto ester ketal **171** were reduced with lithium aluminum hydride in diethyl ether to give a mixture of the epimeric diols **172** and **173** (ratio varied from ~5:3 to >4:<1 **172**:**173**, ^{1}H nmr spectral analysis) in 80-95% yield (equation D-31). In the ^{1}H nmr spectrum (300 MHz, $CDCl_3$) of a sample containing both **172** and **173**, the signals for their respective epimeric carbinol hydrogens were displayed at δ 4.57 (distorted td, J = ~8, ~4 Hz, H-6a) and at 3.91-3.97 (m, H-6b), which were converted to a triplet (J = ~8 Hz) and a less complex multiplet upon the addition of D_2O. In the mixture, the signals for the $C\underline{H}_2OH$ hydrogens appeared at δ 3.57-3.63 and 3.76-3.90 (m, m, 2H total).



(D-31)

The major epimer (**172**), which could be separated from the minor epimer by recrystallization of the mixture from 4:1 and then

from 7:1 petroleum ether-diethyl ether, exhibited m.p. 117-118°C. An ir spectrum of **172** (solution in chloroform, polystyrene reference) showed absorptions due to the hydroxyl group at 3630, the ketal group at 1125, and the olefin function at 1640 cm^{-1}. In a ^1H nmr spectrum (300 MHz, $CDCl_3$) of the major epimer (**172**), the signals for the methylene hydrogens of the hydroxymethyl group appeared at δ 3.79 (dd, J = ~11, ~5 Hz, H-14b) and at 3.61 (br dd, J = ~11, ~5 Hz, H-14a), which were converted, respectively, to a doublet (J = ~11 Hz) and a broad doublet (J = ~11 Hz) upon the addition of D_2O.* Further confirmation of the identity of diol **172** was obtained from the mass spectra. Thus, in the high resolution mass spectrum, the molecular ion peak was found at 322.2136, which corresponds to the molecular formula, $C_{19}H_{30}O_4$, while in the low resolution mass spectrum, peaks corresponding to the loss of one and two molecules of water (M^+-18 and M^+-36, respectively) were observed.

It was of interest to determine the stereochemistry at the 6-position of the diol **172**. *A priori*, one would have trouble predicting the stereochemical outcome of the reduction process, since both faces of the keto function in **171** are sterically hindered. In key nOe difference experiments (400 MHz, summarized in structure **172'**) to determine the stereochemistry of **172**, irradiation of the signal at 4.57 (H-6a) led to an enhancement of the signal at 3.61 (H-14a), while irradiation of the signal at 3.61 (H-14a) led to enhancements of the signals at 3.79 (H-14b) and 4.57 (H-6a). Thus, it seemed

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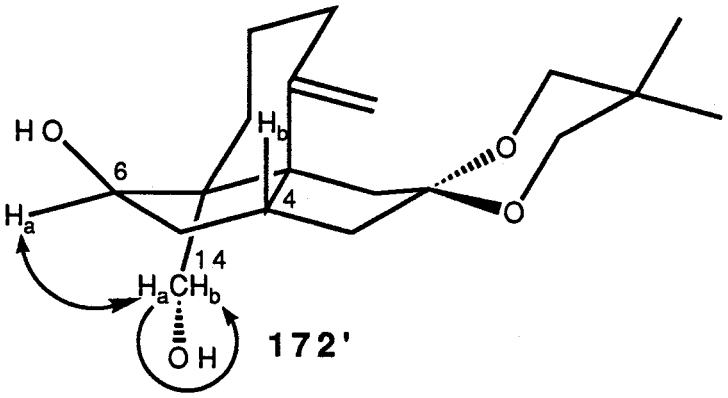
* Signals due to the other hydrogens appeared in the ^1H nmr spectrum at δ 0.91 (s, 3H), 1.01 (s, 3H), 1.32-1.61 (m, 2H), 1.66-1.95 (m, 5H), 1.99-2.13 (m, 4H), 2.26-2.40 (m, 3H), 2.71-2.79 (m, 1H), 3.42 (s, 2H), 3.44-3.56 (m, 2H), 4.82 and 4.85 (s, s, 2H total).

reasonable to conclude that H-6a was *cis* to the hydroxymethyl group and that the stereochemistry at C-6 of the major product **172** was as assigned.



172'

Various attempts to carry out the double deoxygenation reaction of both hydroxyl functions of **172** and **173** *via* derivatives of the diols were unsuccessful. Krishnamurthy and Brown have reported a super hydride (lithium triethylborohydride) deoxygenation procedure[98] utilizing the *p*-toluenesulfonate derivatives of alcohols. Attempts to convert the diol mixture to the corresponding bissulfonates by reaction with *p*-toluenesulfonyl chloride (*p*-TsCl, 3 equiv or 2.2 equiv) in the presence of a base (4-(*N*,*N*-dimethylamino)pyridine (DMAP), 3.5 equiv or KH, 3 equiv) in a suitable solvent (dichloromethane or THF) were unsuccessful when an unstable mixture of the mono- (mainly the primary sulfonate) and bissulfonates, unreacted diol and other uncharacterized materials was produced. The sterically hindered nature of the secondary alcohol was also implicated when the reaction of an acetonitrile solution of the diol **172** with phenoxythiocarbonyl chloride (PTC-Cl,

2.3 equiv) in the presence of DMAP (4.2 equiv) generated a complex mixture of products. The failure to form the bis-*O*-phenoxythiocarbonyl derivative of the diol **172** in a reasonable yield thwarted plans to employ the Robins radical deoxygenation reaction with tri-*n*-butyltin hydride.[99]

Sterically hindered alcohols have been converted into their *N,N,N',N'*-tetramethylphosphorodiamidate derivatives by a procedure developed by Liu and coworkers.[100] Thus, the bisalkoxide prepared from the diol **172** by its reaction with *n*-butyllithium was treated with *N,N*-dimethylphosphoramidic dichloride (**174**) followed by dimethylamine (equation D-32). A mixture of products resulted in which the cyclic *N,N*-dimethylphosphoramidate **175** predominated. The structure of **175** was deduced from its ^{1}H nmr spectrum wherein the signals for the olefinic hydrogens at δ 4.85 and 4.88 (s, 1H each), the methyl groups on the nitrogen at 2.76 (d, 6H, J = ~10 Hz, overlapped with a multiplet, 1H, at 2.69-2.9) and the tertiary methyl groups at 0.94 and 0.97 (s, s, 6H total) were in a 2:7:6 ratio.* The attempted double deoxygenation (lithium metal/ methylamine/ 0°C) of **175** failed,[12] but the results indicated (^{1}H nmr spectral analysis on the crude mixture) that the derivatized secondary hydroxyl function had been deoxygenated in preference to the primary hydroxyl group to generate a compound formulated as **176**.

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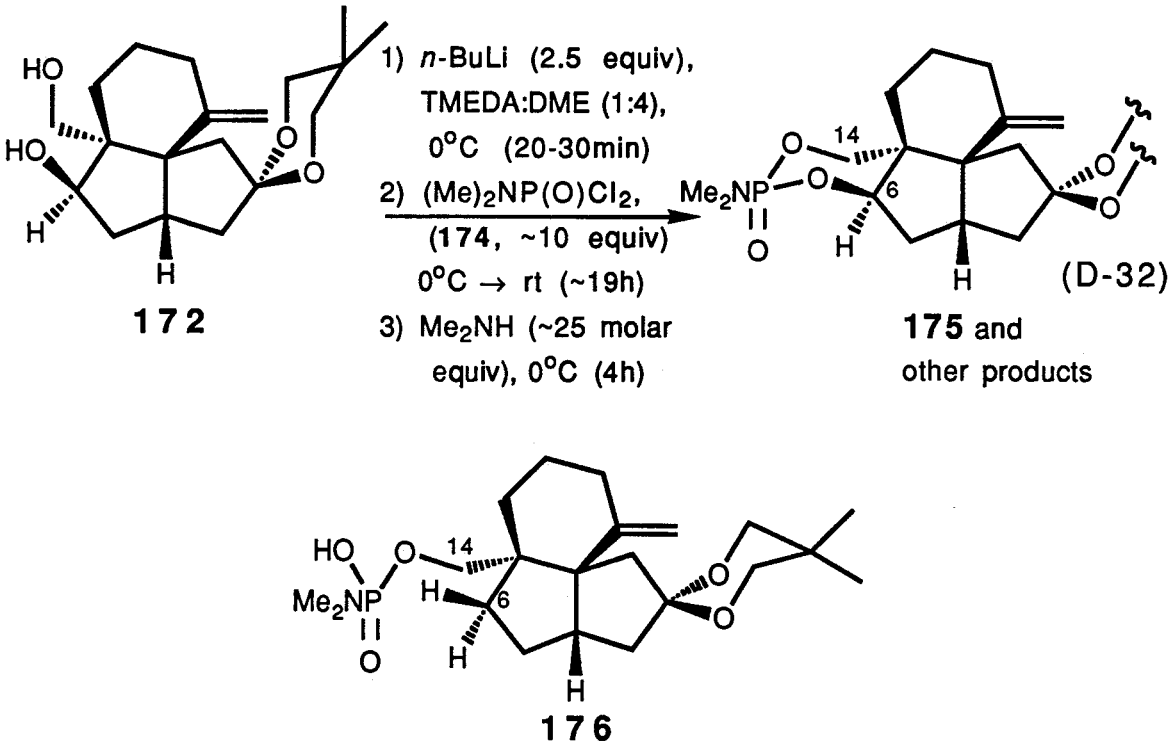
* Other hydrogen signals were also observed: the methine hydrogen (H-6a) at δ 5.09 (br t, 1H, J = ~9Hz); the methylene hydrogens (2H-14) at 4.36 (br d, 1H, J = ~10 Hz), and 4.15 (dd, 1H, J = ~10, ~22 Hz); the ketal methylene hydrogens as singlets at 3.52 and 3.42 (2H each); the rest of the aliphatic hydrogens (12H) as multiplets at 1.4-2.4.

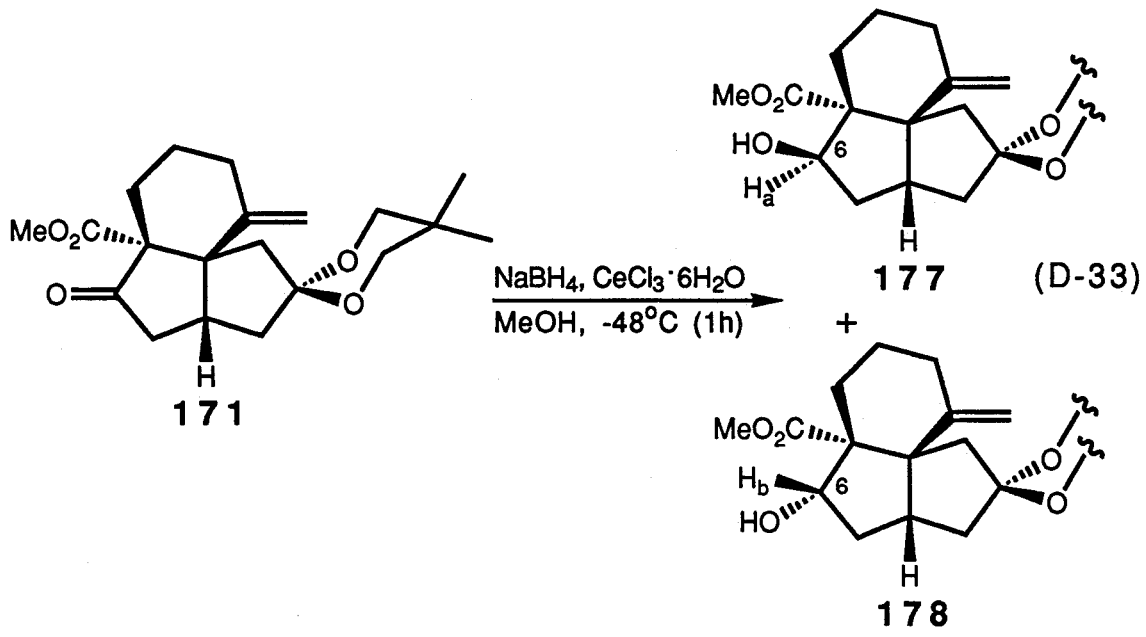


172 **175** and other products

176

It was apparent that a sequential deoxygenation of the keto and ester functions would be preferable as the reactivities of the primary and secondary hydroxyl groups were significantly different. Consequently, it was decided to postpone the deoxygenation of the methoxycarbonyl group until the end of the synthesis and to deoxygenate it together with another methoxycarbonyl which would be present at that stage. Thus, the keto function in **171** was reduced selectively with sodium borohydride in methanol (with a small amount of ethyl acetate to solubilize the keto ester ketal **171**). An ~2-3:1 mixture of the epimeric alcohols **177** and **178** was produced, which proved to be difficult to separate by chromatography on silica gel or by fractional recrystallization. For subsequent reactions it was desirable to have exclusively the major epimer (**177**) present (*vide infra*), so a variety of reducing agents

were tested to see if the ratio of epimers could be improved in favour of the major epimer. Reduction procedures attempted included: zinc borohydride in diethyl ether, which is known to reduce via chelation;[101] L-selectride in THF, which is expected to approach from the less hindered face of the carbonyl;[102] and sodium borohydride with varying amounts of cerium trichloride hexahydrate at various temperatures in methanol (Luche's reagent).[103] Reductions using Luche's reagent were the most consistent in terms of selectivity and yield. Therefore, treatment of a methanolic solution of **171** with sodium borohydride (1.3 equiv) in the presence cerium trichloride hexahydrate (0.53 equiv) at -48°C (equation D-33) led to the production of a mixture of the epimers **177** and **178** in ~98% yield. The ratio of epimers (**177** to **178**) in the crude mixture of alcohol esters using Luche's reagent was usually ~5:1 with a ratio as good as ~12:1 obtained upon occasion depending on small variations in the reaction conditions. (The ratios were based on the relative integration area for the signals due to H-6a versus H-6b in the ^{1}H nmr spectrum). Recrystallization of the mixture from ethyl acetate-hexane generally improved the ratio slightly.



The ir spectrum of an ~12:1 mixture of **177** and **178** displayed a strong absorption at 3511 cm^{-1} indicative of the presence of the alcohol function, while a very strong band at 1726 cm^{-1} was characteristic of the ester carbonyl group. In the ^1H nmr spectrum of the mixture, the signal due to the methoxycarbonyl group of both epimers appeared at δ 3.68 (s, 3H). The carbinol hydrogen (H-6a) adjacent to the hydroxyl group of **177** resonated as a triplet of doublets (J = 9.0, 2.0 Hz) at δ 4.69 which simplified to a triplet (J = 9.0 Hz) upon the addition of D_2O. On the other hand, H-6b of the epimer **178** appeared as a multiplet at δ 4.11-4.14, which simplified somewhat upon the addition of D_2O. The elemental analysis and high resolution mass spectral analysis (performed on the mixture of **177** and **178**) provided results consistent with the molecular formula, $C_{20}H_{30}O_5$.

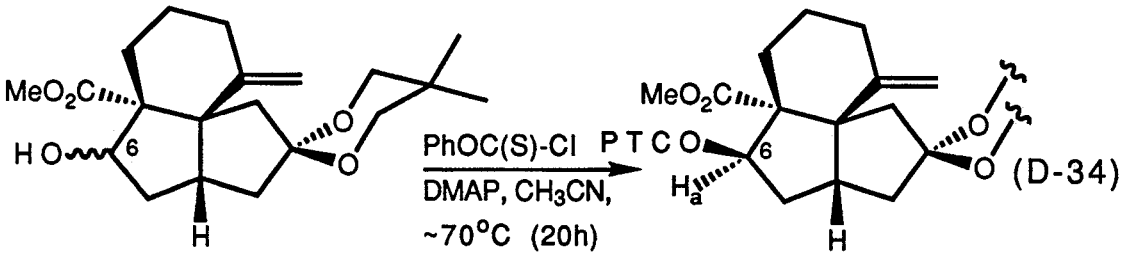
The stereochemistry at the 6-position was not determined for either the alcohol ester **177** or the alcohol ester **178**. However,

assuming that the relative chemical shifts and the signal multiplicities of the hydrogen at the 6-position of the diol epimers **172** and **173** (*vide supra*, p. 83) and those of the alcohol esters **177** and **178** are comparable, then the relative stereochemistries of the alcohol esters **177** and **178** may be assigned. Thus, the resonance of the 6-hydrogen of the major diol epimer **172** was downfield from that of the 6-hydrogen in the minor epimer **173** and the signals appeared as a distorted triplet of doublets (J = ~8, ~4 Hz) and a multiplet, respectively. Similarly, the chemical shift of 6-hydrogen of the major alcohol ester epimer (**177**) appeared downfield from that of the minor epimer **178** and the signals were a triplet of doublets (J = 9.0, 2.0 Hz) and a multiplet, respectively. Thus, it seemed reasonable that compound **177** had the same configuration at the 6-position as did the diol **172**. Further evidence for the depicted stereochemistry came from the fact that the epimer **177** was the major product in reductions using zinc borohydride, a reagent which tends to give products from reduction *via* chelation.[101] In the case of keto ester ketal **171**, reduction *via* chelation with the ester function would be expected to give preferentially an alcohol possessing the configuration found at the 6-position of the compound **177**.

The deoxygenation of the secondary alcohol function in the alcohol esters **177** and **178** was performed using the radical deoxygenation of the corresponding *O*-phenoxythiocarbonyl derivative (PTC derivative) prepared *via* a modification of the procedure developed by Robins and coworkers.[99] The typical procedures utilized by Robins and coworkers to convert secondary

alcohol groups into their PTC derivatives were to stir the alcohol with phenoxythiocarbonyl chloride (PTC-Cl) either in the presence of pyridine (3-4 equiv) in dichloromethane (2 hours) or, for more hindered alcohols, in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 2 equiv) in acetonitrile at room temperature (16 hours). In the most sluggish case they reported, 6-9 equivalents of DMAP were required. The PTC derivatives were then deoxygenated using tri-*n*-butyltin hydride in the presence of a free radical initiator in warm toluene (75°C or at reflux, 3 hours).

The conditions utilized for the preparation of the PTC derivatives of alcohol esters **177** and **178** were more drastic than the most severe case reported by Robins and coworkers.[99] Thus, a solution of a mixture of **177** and **178** (ratio ~5:1) in acetonitrile was converted into a mixture of the corresponding PTC derivatives by treatment of the former material with PTC-Cl (1.5 equiv) in the presence of DMAP (8 equiv) at ~70°C for 20 hours (equation D-34). The major epimer **179** was obtained in 76% yield, while the minor epimer **180**, which was difficult to separate from an impurity, was not characterized nor used in further reactions. It was due to the difficulty in purifying the minor epimer that the effort was made to obtain a good stereoselectivity in the reduction of the keto ester ketal **171** to the alcohol esters **177** and **178**.

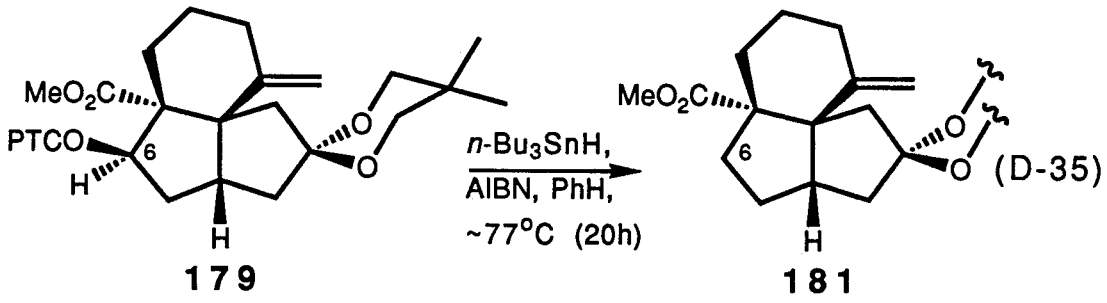


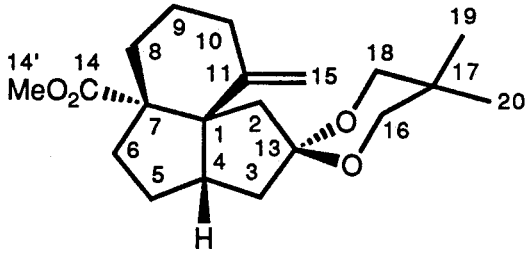
177 and **178**

179 and small amount of epimer (**180**)

The ir spectrum of the phenyl thionocarbonate **179** displayed absorptions due to the carbonyl group at 1736 cm^{-1}, the exocyclic methylene group at 1639 and 888 and a monosubstituted aromatic ring at 774 and 690 cm^{-1}. In the ^1H nmr spectrum, the signal for the methoxycarbonyl group appeared as a singlet at δ 3.70 (3H), the signal for H-6a was a triplet at 6.08 (J = 8.5 Hz, 1H), and the aromatic hydrogens gave rise to multiplets at 7.09-7.12 (2H), 7.25-7.30 (1H) and 7.38-7.43 (2H). The elemental analysis and high resolution mass spectral data were in accord with a molecular formula of $C_{27}H_{34}O_6S$.

The PTC derivative **179** was deoxygenated according to a modification of the procedure reported by Robins and coworkers. Thus, a solution of **179** in benzene (instead of toluene) was treated with tri-*n*-butyltin hydride (2.5 equiv) and the radical initiator, 2,2'-azobisisobutyronitrile (AIBN, 0.18 equiv), and was heated under an argon atmosphere at ~77°C for 20 hours (equation D-35). The purified deoxygenated product **181** was obtained in 72% yield.



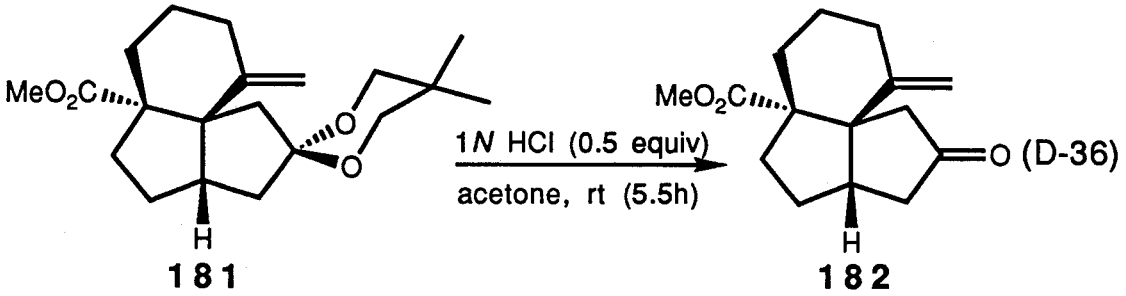


181

Recrystallized **181** (m.p. 87.5-89.5°C) showed the expected absorptions in the ir spectrum for the ester carbonyl at 1719, for the ketal C-O at 1116 and for the exocyclic methylene group at 1638 and 892 cm^{-1}. The ^{1}H nmr spectrum, as expected, still showed the presence of signals for the tertiary methyl groups as singlets at δ 0.95 and 0.97 (3H, each), the methoxycarbonyl function as a singlet at 3.63 (3H) and the olefinic hydrogens as singlets at 4.87 and 4.92 (1H each). The ^{13}C nmr displayed the required 20 signals, including one for the ester carbonyl carbon (C-14) at δ 176.3, the quaternary olefinic carbon (C-11) at 149.1 and the olefinic methylene ($\underline{C}H_2$-15) at 109.8. From an APT experiment, it was possible to assign the tertiary methyl groups to the signals at δ 22.3 and 22.4 ($\underline{C}H_3$-19 and $\underline{C}H_3$-20), the methyl of the methoxycarbonyl group to the signal at 51.2 ($\underline{C}H_3$-14'), and the methine ($\underline{C}$H-4) to the signal at 45.0. The results from the high resolution mass spectrum (found M^{+}=334.2141)

and the elemental analysis were consistent with a molecular formula $C_{20}H_{30}O_4$, thus further confirming that the *O*-phenoxythiocarbonyl group had been replaced with a hydrogen. In the low resolution mass spectrum the molecular ion and a fragment due to the loss of the methoxycarbonyl group (M^+-59) were among the peaks observed.

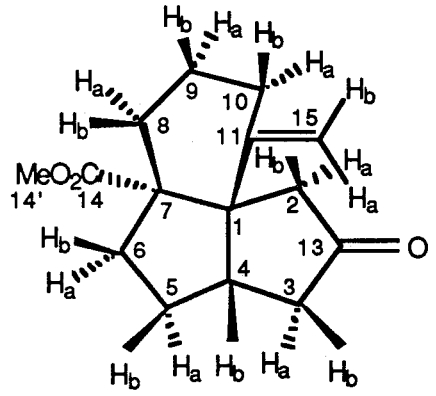
The keto ester substrate for the ring contraction reaction sequence was prepared by deprotection of the ketal function in the ketal ester **181**. A procedure similar to the one reported by Moss and Piers[38,85] was utilized. Thus, an acetone solution of the keto ketal **181** was treated with 1*N* hydrochloric acid (0.5 equiv) at room temperature for 5.5 hours (equation D-36). After an appropriate workup and purification, the keto ester **182** was obtained in ~85% yield (equation D-36).



181 **182**

The ^1H nmr and ^{13}C nmr spectra confirmed that the ketal group of **181** had been removed. Thus, the signals for the tertiary methyl groups and the ketal methylene groups were not seen in the ^1H nmr spectrum and the rest of the signals were consistent with the structure of **182**. Similarly, in the ^{13}C nmr spectrum the ketal carbon signals were replaced by a ketone carbonyl carbon signal (C-

13) at δ 219.2 and the expected 19 other carbon signals required by the structure of **182** were present. Thus, the ester carbonyl carbon signal (C-14) resonated at δ 175.7, the olefinic methylene carbon signal ($\underline{C}H_2$-15) was at 109.8 and the quaternary olefinic carbon resonance (C-11) appeared at 148.4. Based on a ^{13}C nmr APT experiment, signals at δ 42.1 and 51.6 could be assigned to $\underline{C}$H-4 and $\underline{C}H_3$-14', respectively. Additional confirmation of the molecular formula, $C_{15}H_{20}O_3$, was provided by the low and high resolution mass spectra as well as an elemental analysis.



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Further details of the molecular structure were obtained from the one and two dimensional ^1H nmr spectra and from decoupling experiments. Thus, in the one dimensional ^1H nmr spectrum (see figure 5), the signal due to the bridgehead methine (H-4b) was readily assigned to the multiplet at δ 2.84-2.92 (1H), the signal for the methoxycarbonyl group (Me-14') appeared at 3.64 (s, 3H), and the signals for the olefinic hydrogens were at 4.65 and 4.87 (s, 1H each, H-15a and H-15b, respectively). In decoupling experiments, irradiation of the signal at δ 2.88 (H-4b, the center of the multiplet)

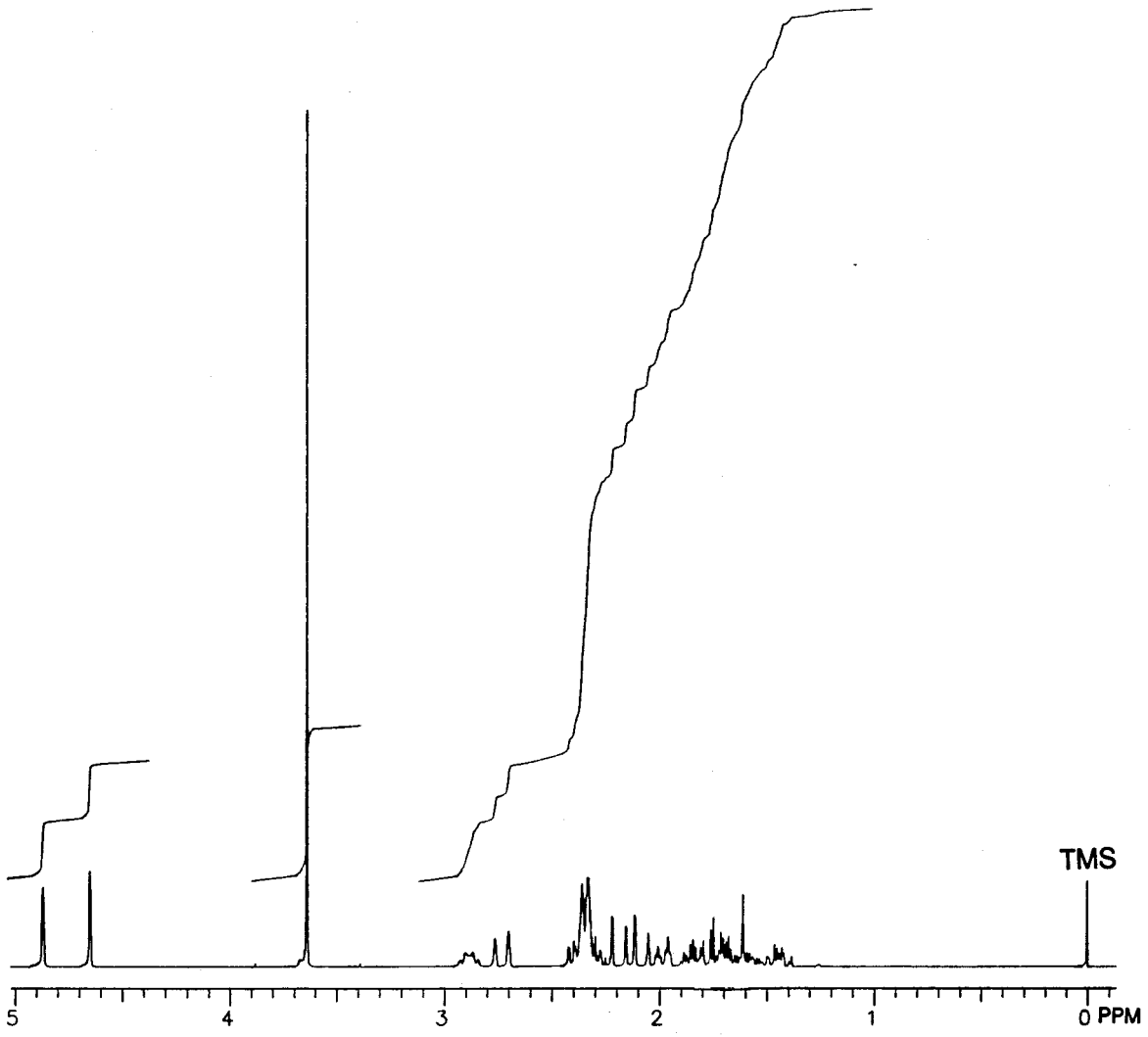


Figure 5. The 300 MHz ^{1}H nmr spectrum of the keto ester **182**.

simplified the doublet of doublets at 2.73 (J = 19.0, 1.0 Hz, 1H) to a doublet (J = 19 Hz), sharpened the multiplet at 2.25-2.42 (5H) and simplified the multiplet at 1.38-1.50 (1H). Irradiation of the signal at δ 2.73 simplified the doublet of doublets at 2.08 (J = 19.0, 1.0 Hz, 1H) to a doublet (J = 19 Hz) and the doublet of doublets at 2.19 (J = 19.0, 0.5 Hz, 1H) to a broad singlet. Irradiation of the doublet of doublets at δ 2.08 sharpened the two doublets of doublets at 2.19 and 2.73 and simplified the multiplet at 2.25-2.42. It was clear,

therefore, that the signals at δ 2.73 and 2.19 were due to geminal hydrogens. However, neither signal showed a large enough coupling to H-4b to be due to hydrogens at the 3-position, hence the signals at δ 2.73 and 2.19 were caused by hydrogens at the 2-position (H-2b and H-2a, respectively). The signal at δ 2.08 also did not show coupling to H-4b, but it and the one due to H-4b were coupled to part of the multiplet (5H) at 2.25-2.42. Consequently, the assumption that vicinal *cis* couplings between hydrogens α- to a keto function and the angular hydrogen are larger than the corresponding *trans* couplings[93] (see also p. 69) led to the assignment of the signal due to H-3a to δ 2.08 and the signal due to H-3b to the multiplet at 2.25-2.42.

The two dimensional ^{1}H-^{1}H COSY nmr spectrum (400 MHz) confirmed the above assignments and made it possible to assign tentatively most of the other hydrogen signals (see figure 6 and Table 3). As in the case of the COSY spectrum of the keto ester ketal **171**, the signals for the bridgehead methine (H-4b) and the olefinic hydrogens (H-15a and H-15b) of **182** provided key entries into the two spin systems of the five-membered rings and of the six-membered ring, respectively. Thus, the signal assigned to H-4b at δ 2.84-2.92 showed correlations to the signals corresponding to H-2b (at 2.73, long range coupling), H-3b and H-5b (both part of the multiplet at 2.25-2.42) and H-5a (at 1.38-1.50). In turn, the signal at δ 1.38-1.50 (H-5a) showed other correlations to the signals at 1.84 (br tt, 1H, J = 12.5, 3.5 Hz) and at 2.25-2.42 (m, 5H). Therefore, of the five hydrogens giving rise to the multiplet at 2.25-2.42, three were assignable to H-3b, H-5b, and H-6a or H-6b. The signals for

the olefinic hydrogens at δ 4.65 (H-15a) and at 4.87 (H-15b) also showed correlations to the multiplet at 2.25-2.42, so H-10a and/or H-10b were part of the multiplet. The remaining signals, at δ 1.52-1.65 (1H), 1.67-1.73 (1H), 1.78 (1H) and 1.98 (1H), could be assigned to the hydrogens of the six-membered ring, but specific assignments were not made. The partial assignments are listed in Table 3.

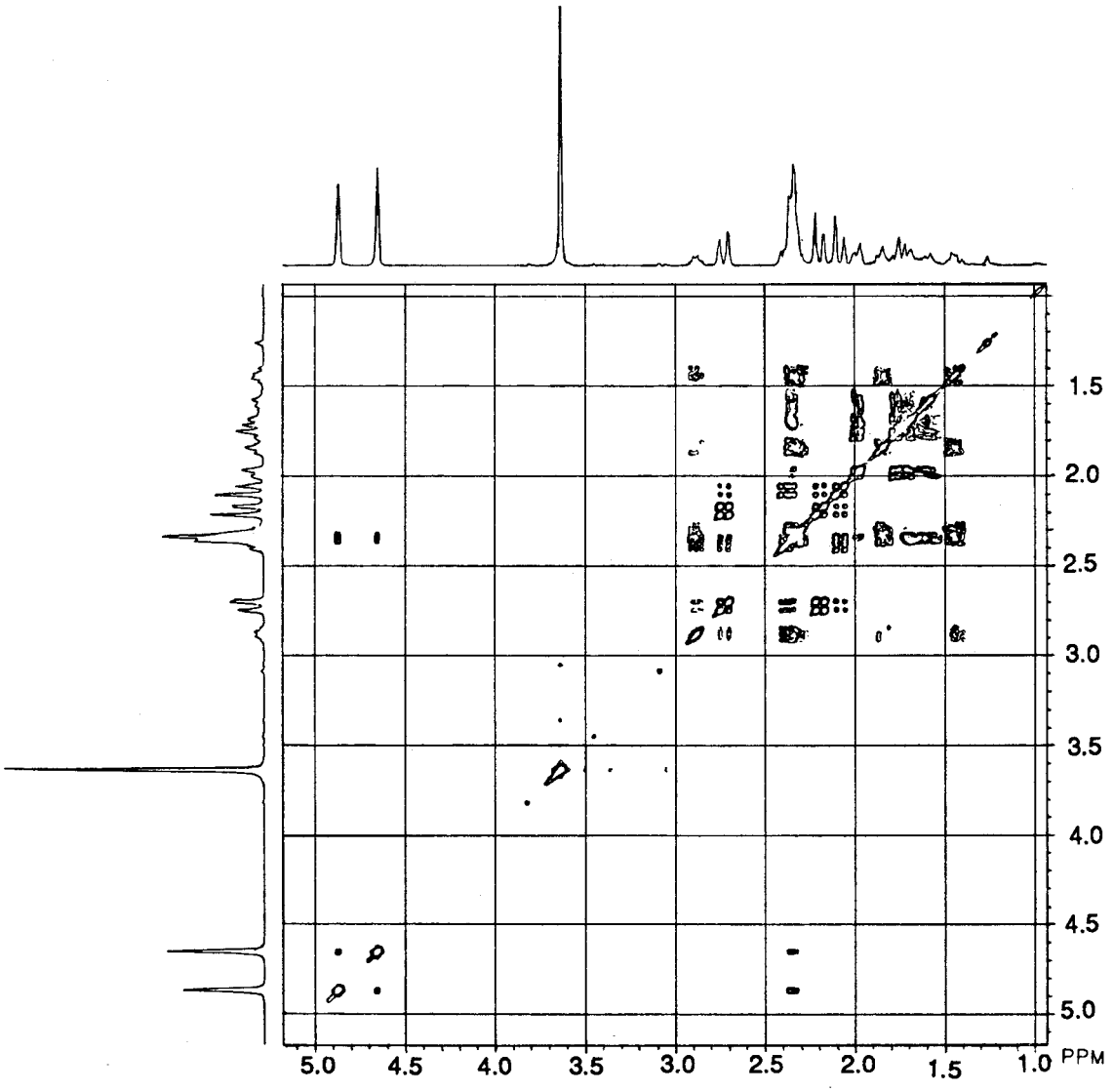
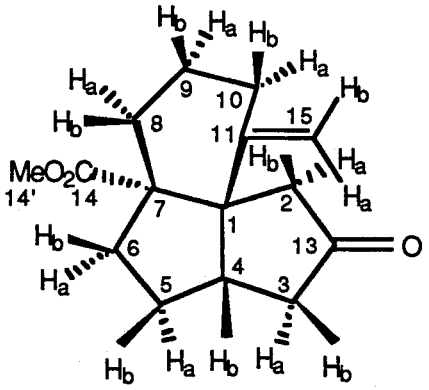


Figure 6. The 400 MHz COSY spectrum of the keto ester **182**.

Table 3: The 400 MHz COSY Data for the Keto Ester **182**.



182

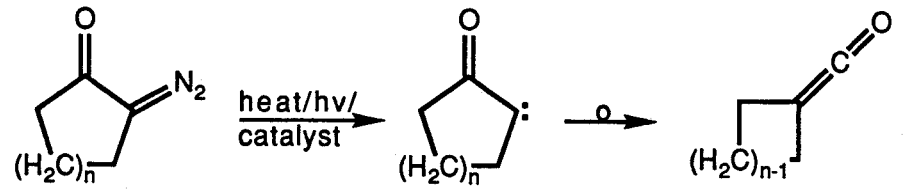
Position (H-x)	Signal δ ppm (multiplicity;[a] J; number of H)	COSY Correlations (H-x)
2a	2.19 (dd; 19.0, 0.5; 1H)	2b; 3a (W-coupling)
2b	2.73 (dd; 19.0, 1.0; 1H)	2a; 3b (W-coupling)[b]; 3a (W-coupling); 4b (W-coupling)
3a	2.08 (dd; 19.0, 1.0; 1H)	3b[b]; 2a (W-coupling); 2b (W-coupling)
3b	2.25-2.42 (m; 5H)	**c**
4b	2.84-2.92 (m; 1H)	2b (W-coupling); 3b[b]; 5a; 5b[b]
5a	1.38-1.50 (m; 1H)	5b[b]; 4b; 6a; 6b[b]
5b	2.25-2.42 (m; 5H)	**c**
6a or 6b	1.84 (br tt; 12.5, 3.5; 1H)	6b or 6a[b]; 5a; 5b[b]
6b or 6a	2.25-2.42 (m; 5H)	**c**
d	**e**	**f**
10a and/or 10b	2.25-2.42 (m; 5H)	**c**
14'	3.64 (s; 3H)	- -
15a	4.65 (s; 1H)	15b; 10a and/or 10b[b]
15b	4.87 (s; 1H)	15a; 10a and/or 10b[b]

a. The signals labelled s, d, dd, may incorporated unresolved fine couplings.
b. The hydrogen is part of the signal at δ 2.25-2.42 (m, 5H).
c. The signal at δ 2.25-2.42 (m, 5H; 3b, 5b, 6b or 6a, 10a and/or 10b) showed correlations to 2b, 3a, 4b, 5a, 6a or 6b, as well as to the signals at δ 1.52-1.65, 1.67-1.73 and 1.98.
d. The signals for 8a, 8b, 9a and 9b were not specifically assigned.
e. Signals were observed at 1.52-1.65 (m, 1H), 1.67-1.73 (m, 1H), 1.78 (distorted dd, 1H, J = 13.5, 3.5 Hz) and 1.98 (dm, 1H, J = 13.5 Hz).
f. The correlations were not determined.

The synthesis of the keto ester **182** meant it was possible to study the one-carbon ring contraction of the functionalized five-membered ring. Application of such a ring contraction to **182** would generate a carbon framework with ring sizes corresponding to those in the target natural product.

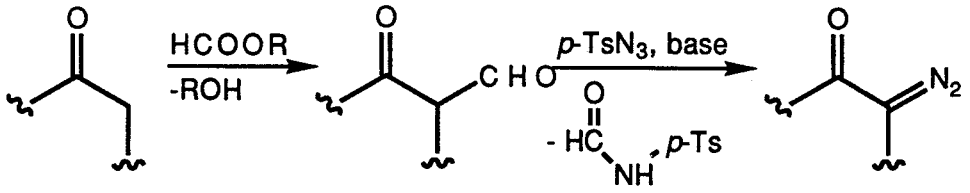
2.3.2.4. Ring Contraction to Give a 4-5-6 Tricyclic Carbon Skeleton.

There are many different procedures available for performing one-carbon ring contractions.[104] One common method employed is the Wolff rearrangement of cyclic α-diazo ketones **183** (equation D-37).[105] The reaction can be performed thermally, photochemically or catalytically. Generally, the mechanism for the photochemical process is thought to involve the formation of a singlet carbene **184** *via* the loss of a molecule of nitrogen in a first order rate process. The group α- to the carbonyl group migrates with its electron pair to the carbene site and a ketene **185** is generated. If a nucleophile such as water, an alcohol, ammonia or an amine is present, it can add to the ketene to produce the corresponding acid, ester or primary or secondary amide.



183 **184** **185** (D-37)

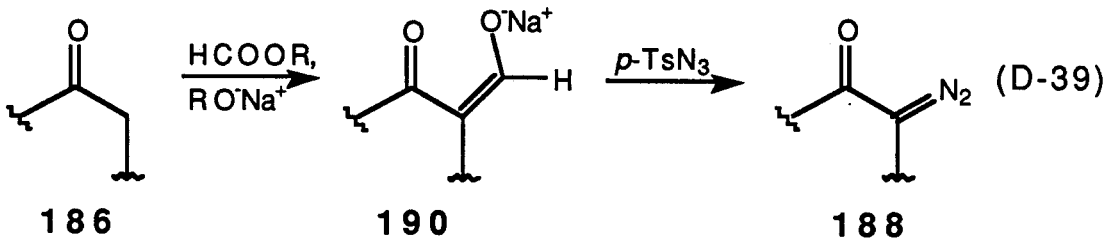
A variety of procedures exist for the preparation of the desired α-diazo carbonyl compounds, but one of the most widely used methods is the "deformylation diazo group transfer".[106] In this procedure, a second activating group, usually a formyl group, is introduced α- to the carbonyl group of a ketone (general formula, **186**) to give **187**. During the introduction of the diazo group from a diazo transfer reagent (for example, *p*-toluenesulfonyl azide, *p*-TsN_3[107]) to give an α-diazo ketone **188**, the formyl group is cleaved to form an amide, **189** (equation D-38).



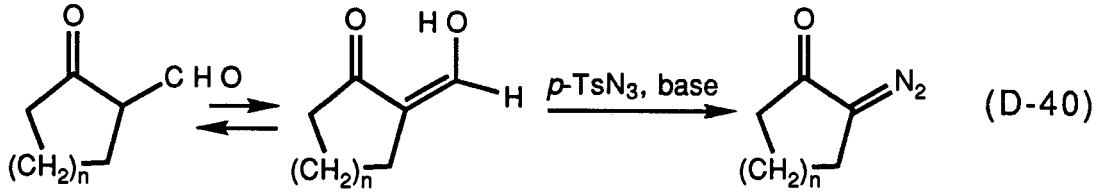
186 **187** **189** **188** (D-38)

Two main procedures have been developed to perform the diazo group transfer reaction.[108] In one method, the sodium salt **190** resulting from the Claisen condensation of a carbonyl compound **186** with alkyl formate/sodium alkoxide is treated with *p*-toluene-sulfonyl azide (*p*-TsN_3) to give the α-diazo ketone **188** (equation D-39). In the second method, which is more commonly utilized for cycloalkanones, the tautomeric mixture of **191** and **192** is allowed

to react with *p*-TsN_3 in the presence of an organic base to generate **183** (equation D-40).



186 **190** **188**

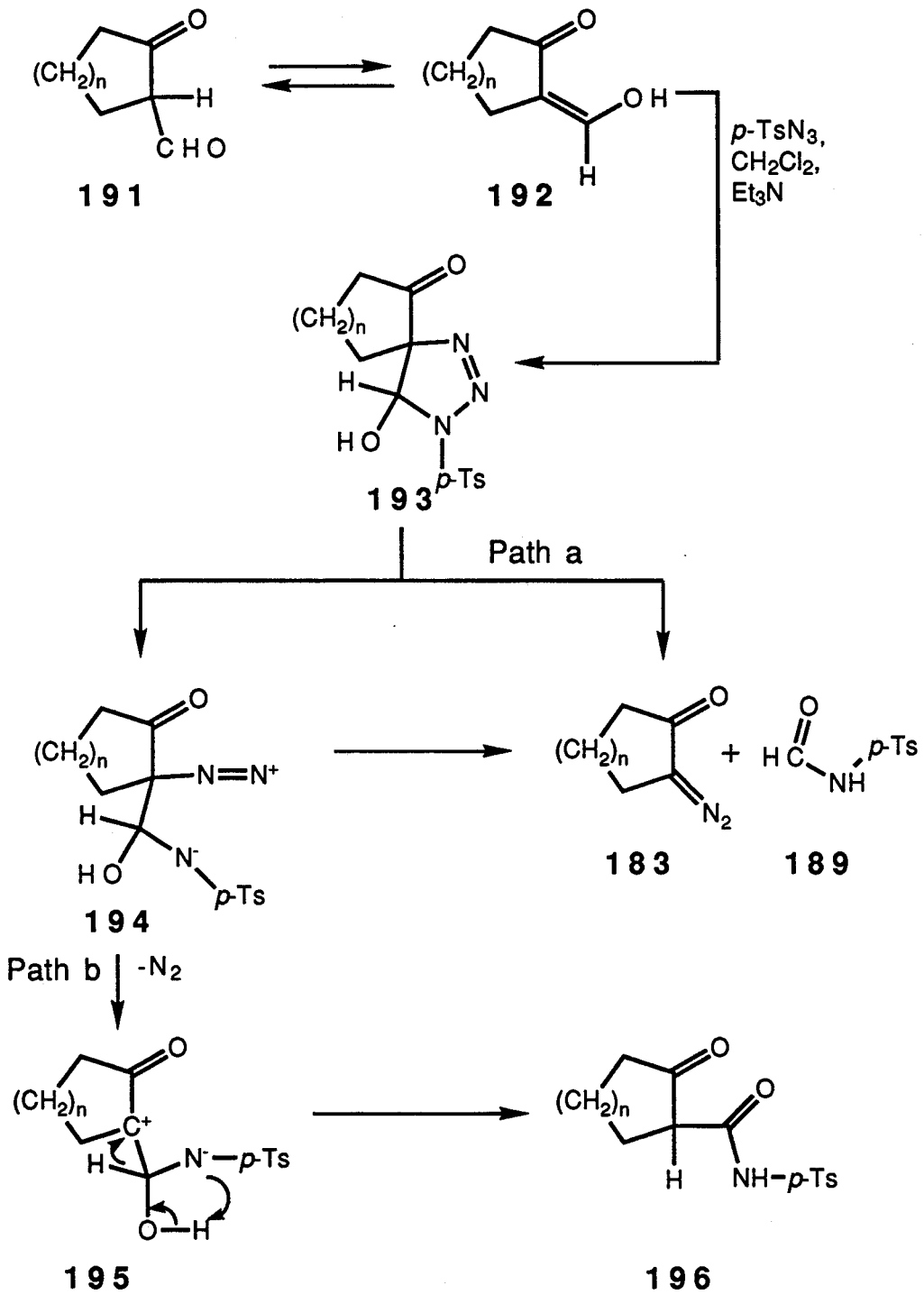


191 **192** **183**

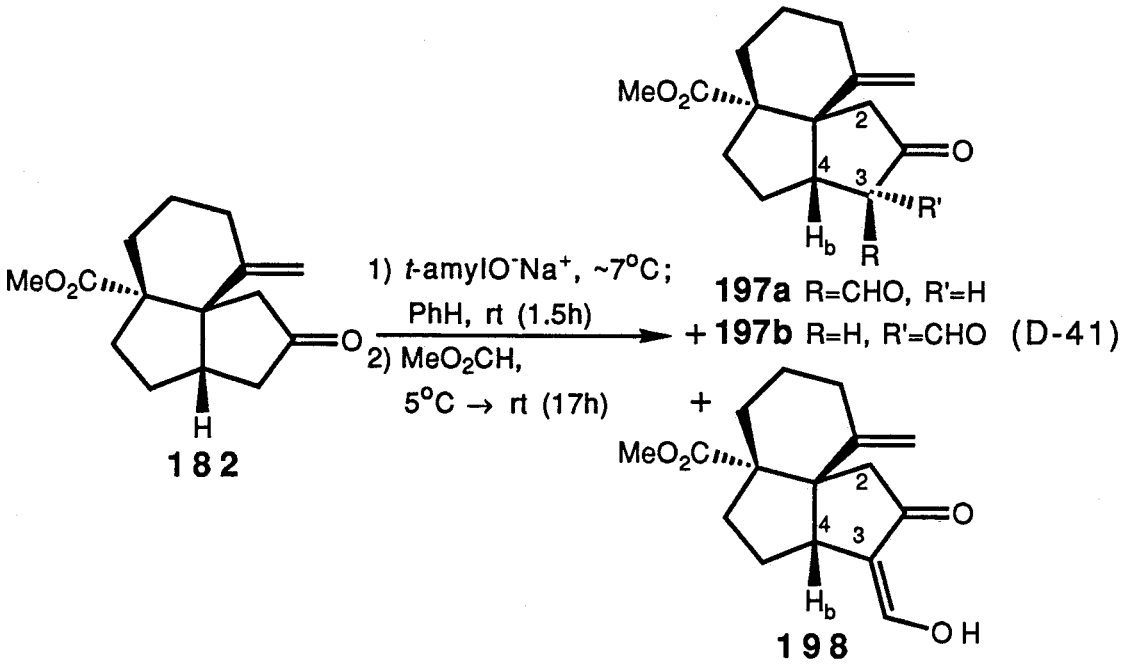
Diazo group transfer reagents other than *p*-TsN_3 have been used (for example, *p*-carboxybenzenesulfonyl azide[109], 2,4,6-triisopropylbenzenesulfonyl azide[110] and methanesulfonyl azide[111]), but the use of *p*-TsN_3 has been most widespread. The diazo transfer process may be described as the attack of the anion of the formylated carbonyl compound on a diazo transfer reagent consisting of N_2^+ attached to a leaving group.[109] The formyl group is transferred to the sulfonyl leaving group to give a sulfonamide (i.e., **189**) while the diazo group is transferred to the carbonyl compound to give the α-diazo carbonyl compound (**188** or **183**). For α-formyl cycloalkanones **191** or their hydroxymethylene tautomers **192**, diazo group transfer likely goes *via* the cyclic triazoline **193** (Scheme D-11).[112] Decomposition of the triazoline **193** can occur by two different pathways depending on the ring size.[106,112] The α-

diazo cycloalkanone **183** and *N*-(*p*-toluenesulfonyl)formamide **189**, products of the desired decomposition, are formed mainly by path a and are the only products observed for 5-, 7-, and 8-membered rings. It is also possible that the α-diazo cycloalkanone **183** may be formed by the sequence **193** → **194** → **183**. On the other hand, the formation of the *p*-toluenesulfonyl-2-oxo-cycloalkylcarbonamide **196** *via* path b occurs to a certain extent for 6-, 9-, 10-, 11-, and 12-membered rings. Thus, loss of dinitrogen from the intermediate **194** is followed by a rearrangement of the intermediate **195** to produce the amide **196**.

Application of the deformylation diazo group transfer process to the keto ester **182** in order to prepare an α-diazo cycloalkanone for the Wolff ring contraction required the synthesis of the formylated ketone **197**. A variety of attempts to perform the formylation (KH/ ethyl formate/ THF; NaH/ ethyl formate/ THF; NaH/ ethyl formate/ diethyl ether;[113] NaH/ methyl formate/ diethyl ether;[114] NaOMe/ methyl formate/ diethyl ether; KH/ methyl formate/ THF), resulted either in the formation of the product in low yields or in the recovery of the starting ketone **182**. In the end, treatment of a benzene solution of the keto ester **182** with sodium *t*-amyloxide[115] (4 equiv) at room temperature, followed by the addition of methyl formate (8 equiv) (equation D-41) led to the quantitative formation of the keto aldehydes **197a** and **197b** and the enol tautomer **198** (ratio ~1:traces:8.5). The products **197** and **198** were not stable to purification by chromatography. Hence the mixture was characterized with traces of impurities present.


(CH2)n
H
CHO
191
OH
192
p-TsN3,
CH2Cl2,
Et3N
N
N
HO
p-Ts
193
Path a
N≡N+
N-
p-Ts
194
183
189
Path b
-N2
C+
N-—p-Ts
O—H
195
NH—p-Ts
196

Scheme D-11



An ir spectrum of the mixture of **197** and **198** indicated the presence of the ester carbonyl, and the enolized β-keto aldehyde group with absorptions at 1725, and 1699, 1609 (broad) cm^{-1}, respectively.[61] Based on the ^1H nmr spectrum of the formylated mixture, the formylation of **182** occurred at the sterically less hindered 3-position rather than at the 2-position and gave mainly the enol **198**, as evidenced by the change in the chemical shift for H-4b (δ 2.84-2.92 in **182** and 3.20-3.23 in **198**) and the presence in the spectrum of **198** of a signal at δ 7.08 (s, 1H) for the olefinic hydrogen of hydroxymethylene function. The signal for the aldehyde hydrogen of the major aldehyde epimer **197a** (stereochemistry based on steric considerations) was at δ 9.52 (s), while the presence of traces of **197b** were indicated by a singlet at 9.83. In the low resolution mass spectrum, the molecular ion was found at 276 and fragments corresponding to the loss of CO (M^+-28), MeOH (M^+-32) and

CO_2Me (M^+-59) were present; the latter fragment was the base peak. In the high resolution mass spectrum, the mass found for the molecular ion of **197/198** (M^+=276.1363) was consistent with the expected formula, $C_{16}H_{20}O_4$.

Initially, the α-diazo ketone **199** was prepared from the formylated keto/enol esters **197/198** using p-TsN_3* in dichloromethane with triethylamine as the base.[116] Unfortunately, it proved impossible to separate unreacted p-TsN_3 from the diazo ketone, a problem which has been noted before.[111] Despite the presence of the unreacted p-TsN_3, the α-diazo ketone **199** was subjected to the photochemical Wolff rearrangement in methanol.[113,116b] The reaction proceeded, albeit in very poor yields (<25% of the ring contracted product was obtained from the photolysis), and an uncharacterized aromatic by-product proved difficult to remove. The expected by-product, the amide **189** (see equation D-38 or Scheme D-11), was obtained which indicated that the diazo transfer was indeed occurring.

Taber and coworkers found that the use of methanesulfonyl azide (MsN_3) was advantageous[111] due to the fact that unreacted MsN_3 can be separated from the α-diazo carbonyl compound by washing an organic solution of the diazo compound with aqueous 10% sodium hydroxide solution. Consequently, MsN_3 was prepared according to Danheiser's modification[117a] of Boyer's procedure.[117b] The diazo group transfer reaction was then performed by treating a dichloromethane solution of **197** and **198** with MsN_3 in the presence

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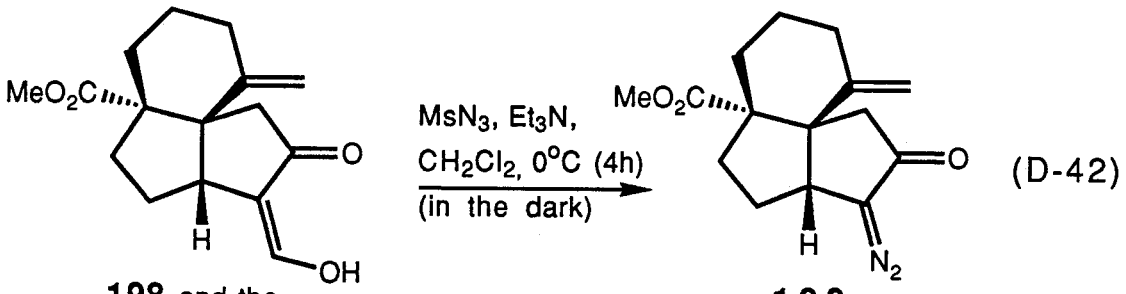
* CAUTION: All sulfonyl azide compounds are potentially explosive and must be handled with due care.

of triethylamine at 0°C (equation D-42).[118] The product, α-diazo ketone **199**, was light-sensitive so the reaction mixture was protected from light and the subsequent manipulations were executed in a dimly lit room. Partial removal of some impurities by an aqueous base/dichloromethane extraction was followed by a rapid chromatographic separation (silica gel) of **199** from more polar material. Also, removal of the triethylamine (rotary evaporator) from the diazo ketone **199** was important since even traces of triethylamine led to the formation of by-products in the photolysis reaction. An ir spectrum of **199** displayed the diazo group stretch at 2082 and the α-diazo carbonyl stretch at 1674 cm^{-1}.[61] Absorptions due to the exocyclic methylene were at 1636 and 898 cm^{-1}.



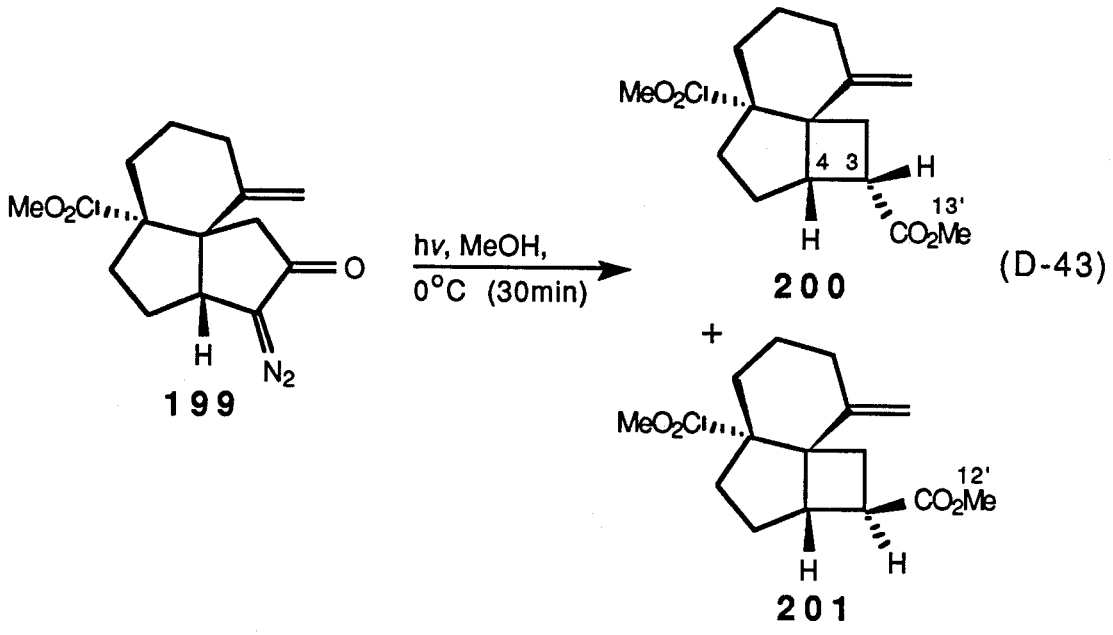
198 and the keto aldehydes **197**

199

(D-42)

Due to its instability, the α-diazo ketone **199** was used as quickly as possible after its preparation for the photochemical ring contraction to prepare the diesters **200** and **201**. Thus, **199** was dissolved in deoxygenated distilled methanol in a quartz photolysis tube and the tube was closed under an argon atmosphere. Generally, the photolysis reaction, using a medium pressure Hanovia mercury

lamp (450 Watt) with a Corex filter,[119] was complete in 30 minutes at 0°C (equation D-43). An ~1.6:1 mixture of the diester epimers **200** and **201** was obtained in a 40.5% overall yield from the keto ester **182**.



(D-43)

Usually, protonation of the ketene intermediate occurs from the less sterically hindered face of the ketene.[120] From an examination of molecular models, the major epimer formed in the Wolff rearrangement of the diazo ketone **199** in the presence of methanol was expected to be epimer **200**.

The mixture of epimers obtained was hard to separate and only a small amount of the major epimer **200** was obtained uncontaminated with the minor epimer **201**. However, the elemental analysis and high resolution mass spectral data for the mixture provided results consistent with the molecular formula, $C_{16}H_{22}O_4$. In the ^1H nmr spectrum, several signals readily distinguished the two epimers.

For example, a doublet of doublets resonated at δ1.78 (J = 13.0, 8.0 Hz) in the major epimer **200**, and at 1.69 (J = 13.5, 7.0 Hz) in the minor epimer **201**. In addition, the signals for the epimeric methoxycarbonyl groups appeared as singlets (3H each) at δ3.68 (Me-13') and 3.67 (Me-12'), respectively, while a triplet of doublets resonated at 2.71 (J = 9.0, 3.0 Hz) for **200** and a doublet of doublets of doublets was at δ2.77 (J = 14.0, 5.0, 2.5 Hz) for the minor epimer.

The major diester epimer (**200**) was characterized more fully by one and two dimensional nmr experiments (^{13}C and ^{1}H) in order to assign reasonably all of the signals for the carbons and the hydrogens and to determine the relative stereochemistry at C-3. The broad band decoupled and APT ^{13}C nmr spectra, as well as a ^{1}H-^{13}C HETCOR were obtained. Signals for only 15 of the 16 carbon atoms were displayed in the one dimensional ^{13}C nmr spectra as the signals for two methylenes resonated at the same frequency. From the HETCOR ^{1}H-^{13}C correlations (see figure 7 and Table 4), assignments for the methines, the methoxycarbonyls and the geminal pairs of hydrogens were obtained. Thus, for example, the carbon signals for the two methines at δ 36.2 (C<u>H</u>-3) and 46.8 (C<u>H</u>-4) correlated to the hydrogen signals at δ3.18 (dt, 1H) and 2.71 (br td, 1H), respectively. Also, the carbon signal at δ 32.7 correlated to four signals for hydrogens at δ1.41-1.52, 1.89, 1.95-2.07 and 2.33, which indicated that two methylene carbons resonated at the same position. Other correlations between the carbon and hydrogen signals permitted the determination of the rest of the geminal pairs of hydrogens, but the assignments to specific positions were dependent on the COSY correlation results.

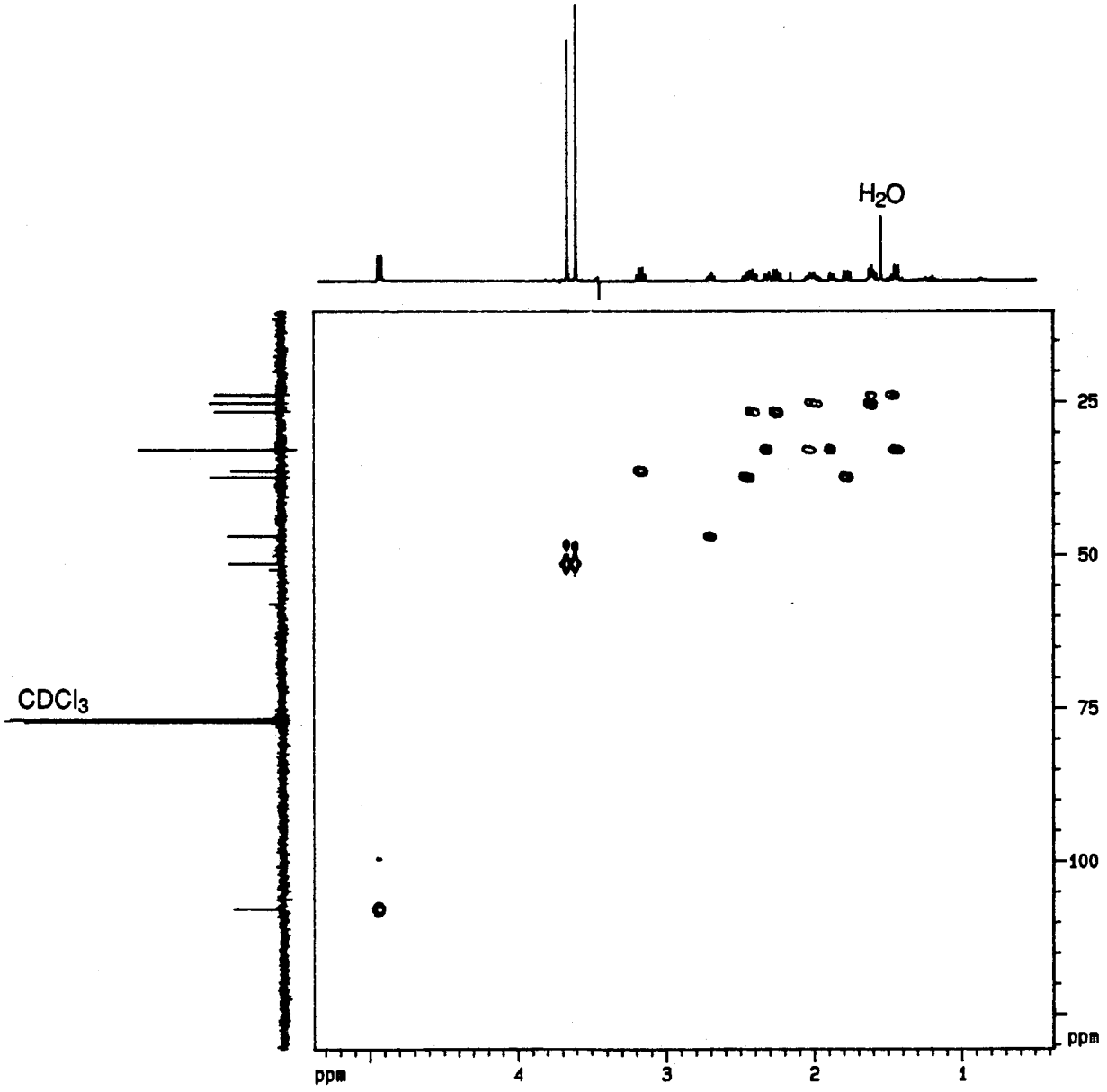
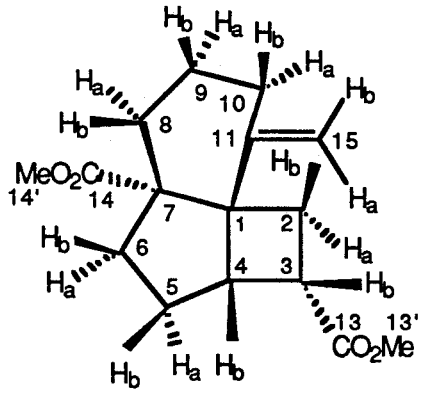


Figure 7. The 125 MHz HETCOR spectrum of the diester **200**.

Table 4: The 125 MHz HETCOR Data for the Diester **200**.



200

Position (C-x)	^{13}C (125 MHz) δ ppm	^{1}H (500 MHz) δ ppm (H-x)
1	52.4[a]	- -
2	26.6	2.26 (2a); 2.39-2.44 (2b)
3	36.2	3.18 (3b)
4	46.8	2.71 (4b)
5	25.2	1.58-1.65 (5a); 1.95-2.07 (5b)
6	37.2	2.43-2.50 (6a); 1.78 (6b)
7	57.9[a]	- -
8	23.8	1.41-1.52 (8a or 8b); 1.58-1.65 (8b or 8a)
9	32.7	1.89 (9a or 9b); 1.41-1.52 (9b or 9a)
10	32.7	1.95-2.07 (10a or 10b); 2.33 (10 b or 10a)
11	147.9	- -
13 and 14	174.0, 175.5	- -
13' and 14'	51.37, 51.40	3.68 (13'); 3.62 (14')
15	107.7	4.93 (15a); 4.96 (15b)

a. Signals may be interchanged.

^{1}H nmr decoupling and nOe experiments (500 and 400 MHz, respectively) were performed on a solution of the diester **200** in order to determine the (a) identities of the hydrogen signals for hydrogens on the four-membered ring and (b) the relative configuration at C-3 (see figure 8 for the normal ^{1}H nmr spectrum). Thus, in decoupling experiments, irradiation of the signal at δ 3.18

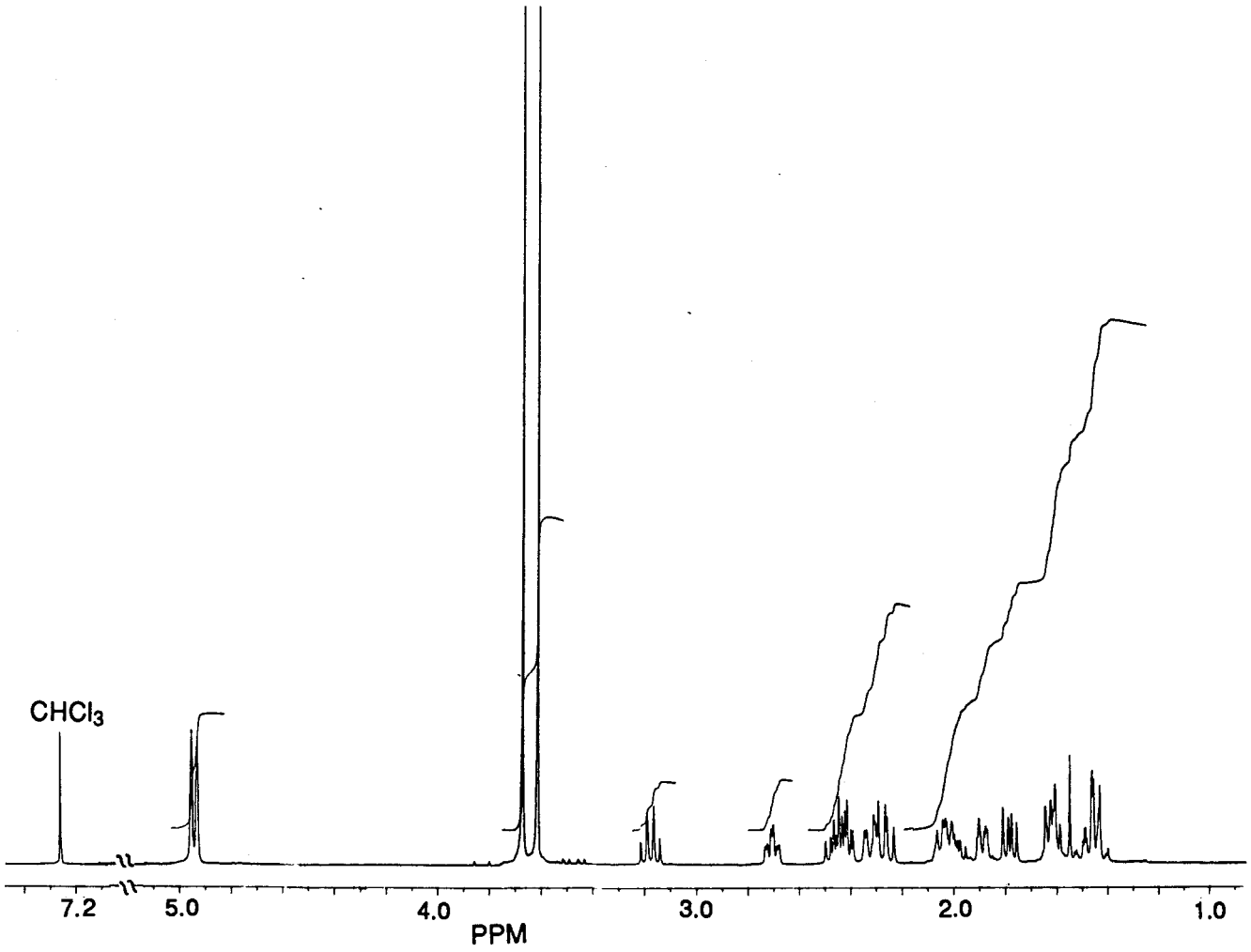
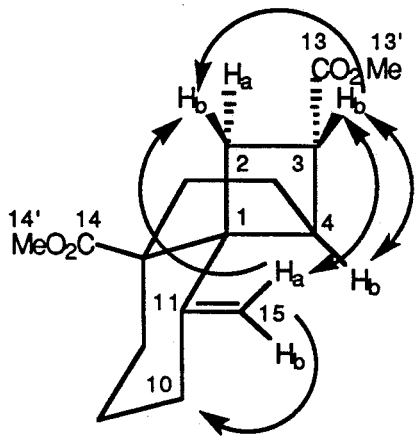


Figure 8. The 400 MHz ^{1}H nmr spectrum of the diester **200**.

(H-3b) simplified the broad triplet of doublets at 2.71 (H-4b) to a distorted doublet of multiplets (J = 9 Hz), simplified the doublet of doublets at 2.26 (H-2a) to a doublet (J = 13 Hz) and simplified the multiplet at 2.39-2.44 (H-2b). Irradiation of the signal at δ 2.71 (H-4b) simplified the multiplets at 1.95-2.07 (H-5b and one other hydrogen) and at 2.39-2.44 (H-2b) and caused the doublet of triplets

at 3.18 (H-3b) to collapse to a doublet of doublets (J = ~9, ~10 Hz). Irradiation of the signal at δ 2.26 (H-2a) simplified the multiplet at 2.39-2.44 (H-2b) and caused the doublet of triplets at 3.18 (H-3b) to collapse to a distorted triplet (J = 9 Hz). The above assignments of the signals for hydrogens on the four-membered ring were further confirmed by nOe difference experiments (summarized in structure **202'**). Thus, irradiation of the signal at δ 2.71 (H-4b) led to enhancement of the signal at 3.18 (H-3b), while irradiation of the signal at 3.18 (H-3b) led to enhancement of the signals at 2.39-2.44 (H-2b), 2.71 (H-4b) and 4.93 (H-15a). Irradiation at δ 4.95 (between H-15a and H-15b) led to enhancements of the signals at 2.33 (H-10b or H-10a), 2.39-2.44 (H-2b) and 3.18 (H-3b). From the nOe results, it was apparent that H-2b, H-3b and H-4b were on the same side of the four-membered ring and that H-3b and H-2b were spatially close to the olefinic H-15a hydrogen. Therefore, the six-membered ring was syn to the bridgehead methine (H-4b) as is found in the natural product and the methoxycarbonyl group on the four-membered ring had the configuration shown in **200**.



200'

The identification of other signals in the ^1H nmr spectrum was facilitated by combining the results summarized above with those from the COSY and HETCOR spectra. For example, in the COSY spectrum (see figure 9), the signal for H-4b (δ 2.71) showed correlations to the signals at δ 2.39-2.44 (H-2b), 3.18 (H-3b) and 1.95-2.07 (2H). In the foregoing discussion, the identities of the hydrogen signals at δ 2.39-2.44 and 3.18 had been established from decoupling and nOe experiments. Consequently, one of the hydrogens resonating at δ 1.95-2.07 was H-5b. From the HETCOR results, the hydrogens geminal to those at δ 1.95-2.07 (m, H-5b and H-x) resonated at 1.58-1.65 (m, 2H) and 2.33 (1H). The signal at δ 2.33 could be assigned to a hydrogen at the 10-position (H-10b or H-10a) based on the nOe results. Thus, the signal for H-5a appeared as part of the multiplet at δ 1.58-1.65 and the other hydrogen at 1.95-2.07 was H-10a or H-10b. A similar combination of the various nmr results led to the further assignment of the remaining carbon and hydrogen signals to the positions listed in Tables 4 and 5.

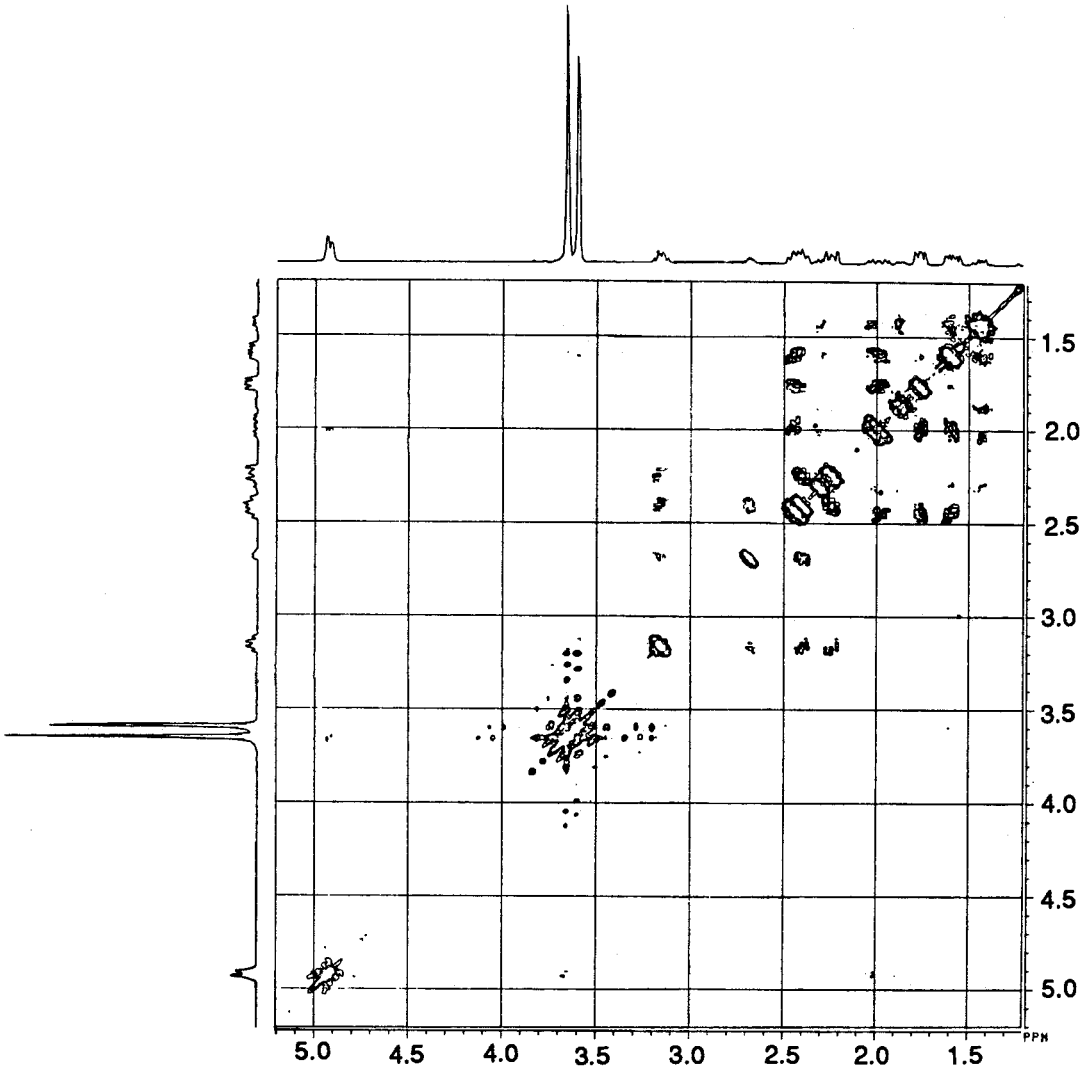
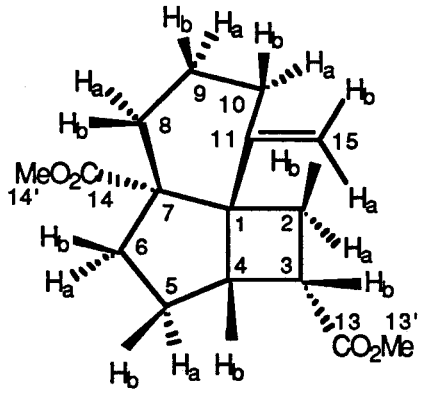


Figure 9. The 400 MHz COSY spectrum of the diester **200**.

Table 5: The 400 MHz COSY Data for the Diester **200**.



200

Position (H-x)	Signal δ ppm (multiplicity;[a] J; number of H)	COSY Correlations (H-x)
2a	2.26 (dd; 13.5, 10.5; 1H)	2b; 3b
2b	2.39-2.44 (m; 1H)	2a; 3b; 4b
3b	3.18 (dt; 10.5, 9.5; 1H)	2a; 2b; 4b
4b	2.71 (br td; 9.0, 3.5; 1H)	2b; 3b; 5b
5a	1.58-1.65 (m; 2H)	5b; 6a
5b	1.95-2.07 (m; 2H)	5a; 4b; 6a; 6b
6a	2.43-2.50 (m; 1H)	6b; 5a; 5b
6b	1.78 (dd; 13.0, 8.0)	6a; 5b
8a or 8b	1.41-1.52 (m; 2H)	[b]
8b or 8a	1.58-1.65 (m; 2H)	8a or 8b; 9a and 9b[c]; 10b or 10a (W-coupling)
9a or 9b	1.89 (dm; 10.5; 1H)	9b or 9a[c]; 8b or 8a; 10b or 10a
9b or 9a	1.41-1.52 (m; 2H)	[b]
10a or 10b	1.95-2.07 (m; 2H)	10b or 10a; 9b or 9a
10b or 10a	2.33 (dm; 13.5; 1H)	10a or 10b; 8b or 8a (W-coupling); 9a and 9b
13'	3.68 (s; 3H)	- -
14'	3.62 (s; 3H)	- -
15a	4.93 (s; 1H)	15b
15b	4.96 (s, 1H)	15a

a. The signals labelled s, d, dd may incorporate unresolved fine couplings.
b. Assignment of correlations is uncertain due to overlapped signals. The signal at δ 1.41-1.52 (m, 2H) showed correlations to 8b or 8a, 9a or 9b, and 10a and 10b.
c. The signal for 9b or 9a is at the same position as the one for 8a or 8b. Thus, the correlations of 8b or 8a to 9b or 9a, and *vice versa*, are impossible to determine from the data.

2.3.2.5. Preparation of (±)-β-Panasinsene (**31**) *via* the Diacetate **213**.

The successful generation of the diesters **200** and **201** *via* the Wolff rearrangement reaction set the stage for the performance of the final functional group manipulations to complete the synthesis of (±)-β-panasinsene (**31**). Thus, the introduction of a methyl group at the 3-position of the diester mixture (**200** and **201**) followed by a double deoxygenation of the methoxycarbonyl functions would provide the natural product.

The methylated diesters **202** and **203** were prepared by treating a cold (-78°C) THF solution of a mixture of the diesters **200** and **201** (ratio ~1.6:1) first with a THF solution of lithium diisopropylamide to generate an anion at the 3-position, then with hexamethylphosphoramide* (HMPA, 1.6 equiv) and finally, with excess methyl iodide. After an appropriate workup, an ~18:1 mixture (^{1}H nmr analysis) of the diester epimers **202** and **203** was isolated in 65% yield (equation D-44). The two epimers could not easily be separated at this stage so were characterized as the mixture.

The elemental analysis and the low and high resolution mass spectroscopy performed on the diester mixture (**202** and **203**) provided results consistent with the molecular formula, $C_{17}H_{24}O_4$. Details of the structure of **202** were obtained from an ir spectrum, ^{13}C nmr spectra and one and two dimensional ^{1}H nmr experiments.

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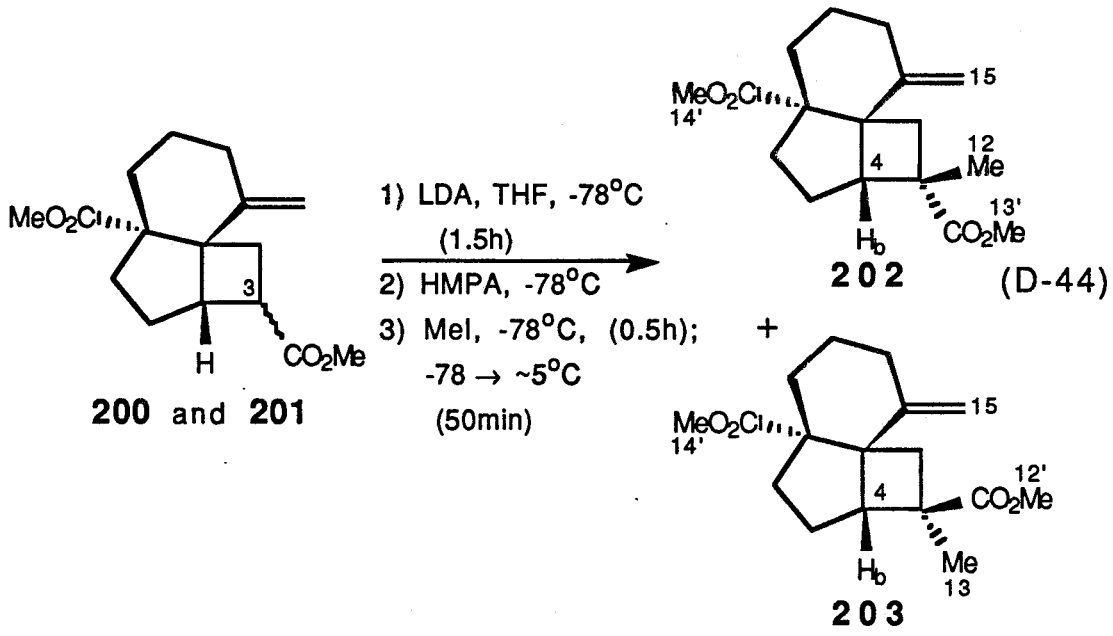
* CAUTION: HMPA is known to be a potent carcinogen.



Thus, in the ir spectrum of the mixture of **202** and **203**, the absorption for the ester carbonyl stretch was displayed at 1729 cm^{-1}, while the exocyclic olefinic function gave rise to absorptions at 1642 and 887 cm^{-1}. The broad band decoupled ^{13}C nmr spectrum of the 18:1 mixture of **202** and **203** displayed the expected 17 carbons for **202** and baseline signals (i.e., hardly distinguishable from the noise) for **203**. From an APT experiment, the signal at δ 25.3 was assigned to the methyl group ($\underline{C}H_3$-12), while the signal at 53.6 was assigned to the methine ($\underline{C}H$-4). The methyl groups of the methoxycarbonyl functions resonated at δ 51.4 and 51.5 ($\underline{C}H_3$-13' and $\underline{C}H_3$-14'). In the ^1H nmr spectrum (see figure 10), the signal for the newly installed methyl group of the major epimer (**202**) appeared as a singlet at δ 1.42, while that of the minor epimer **203** was at 1.18. The signals for the two methoxycarbonyl groups of **202** were singlets at δ 3.61 (Me-14') and at 3.69 (Me-13'), while the two

olefinic hydrogens appeared as singlets at δ 4.98 (H-15a) and 5.00 (H-15b).

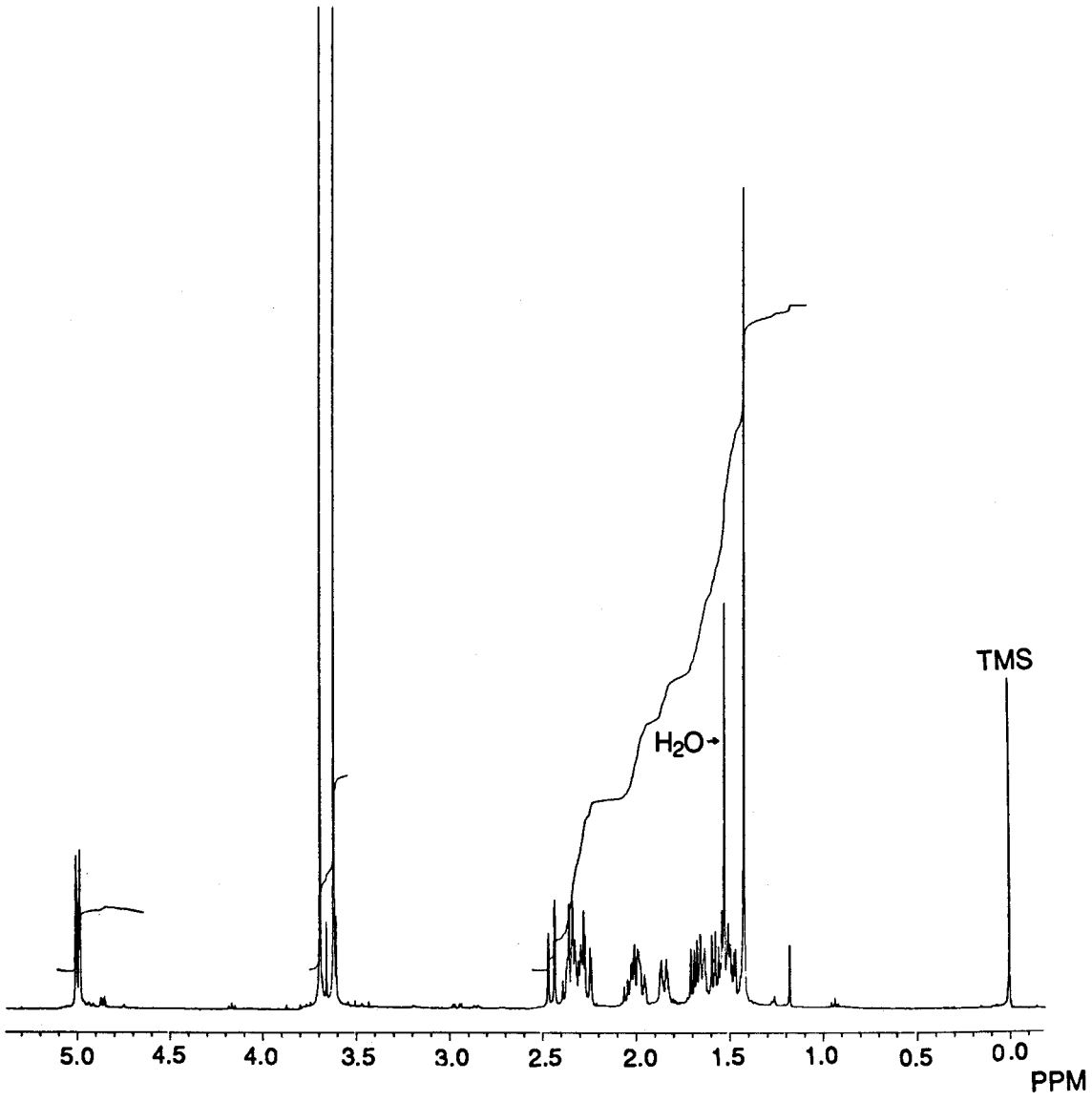
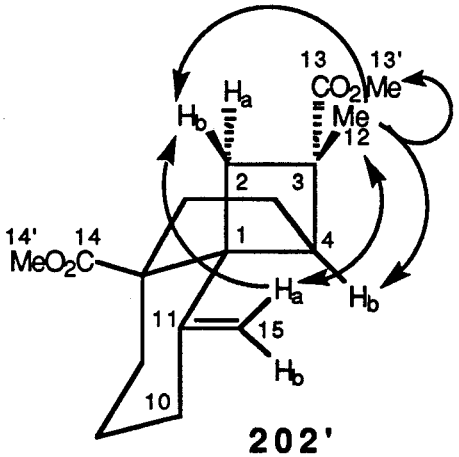


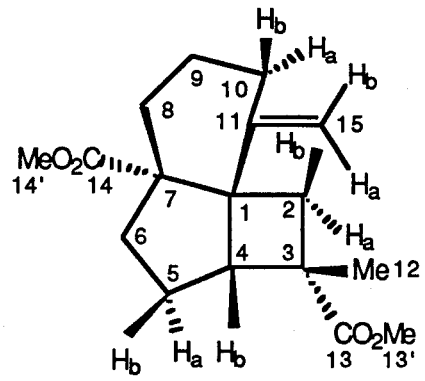
Figure 10. The 400 MHz ^{1}H nmr spectrum of the diester **202**.



202'

In order to determine the relative configuration at C-3, nOe difference experiments (summarized above in structure **202'**) were performed on the mixture of **202** and **203**. Thus, irradiation of the signal at δ 1.42 (Me-12) led to enhancement of the signals at 2.26, ~2.35, 3.69 (Me-13') and 4.98 (H-15a). Due to unavoidable irradiation of part of the multiplet at δ 1.46-1.59, the signals at 1.85 and 1.95-2.06 (H-10a or H-10b) also showed enhancements. Irradiation of the signal at δ 4.98 (H-15a) led to enhancements of the signals at 1.42 (Me-12) and at 2.26. From these results it was apparent that the methyl group (Me-12) in the major epimer was in close proximity to an olefinic hydrogen (H-15a) and, therefore, had the relative configuration depicted for **202**. The configuration is that expected if the methyl group had approached from the less sterically hindered face of the anion obtained by deprotonation at the 3-position of the diesters **200** and **201**. Further evidence that the structure was correct was obtained once the identities of the hydrogens resonating at δ 2.26 and 2.35 were determined. In **202**, H-2b and H-4b are *cis* to the methyl group (Me-12) and H-2b is in close

proximity to the olefinic hydrogen (H-15a). Consequently, the nOe results were consistent with the assignment of the signal at δ 2.26 (dd, 1H, J = 14.0, 3.0 Hz) to H-2b and the signal at ~2.35 (part of a 3H-multiplet at 2.28-2.39) to H-4b.



202

Confirmation of the assignments for H-2b and H-4b was obtained from decoupling and/or COSY experiments. Thus, in a decoupling experiment, irradiation of the doublet at δ 2.45 (J = 14.0 Hz, H-2a) led to the collapse of the doublet of doublets at 2.26 (H-2b) to a distorted triplet (J = 3.0 Hz) indicating that the signals at 2.26 and 2.45 were due to geminal hydrogens (J = 14.0 Hz). In a COSY experiment (see figure 11), the signals for (a) the methyl group (Me-12) at δ 1.42 and (b) the olefinic hydrogens (H-15a and H-15b) at δ 4.98 and 5.00 provided key entries, *via* couplings unresolved in the one dimensional spectrum, into the spin systems of the interrelated four and five-membered rings and the six-membered ring, respectively. Thus, the signal at δ 1.42 (Me-12) showed a correlation (W-coupling) to only the signal at 2.45 (H-2a), while the signal at 2.45 (H-2a) showed a further correlation to the signal at

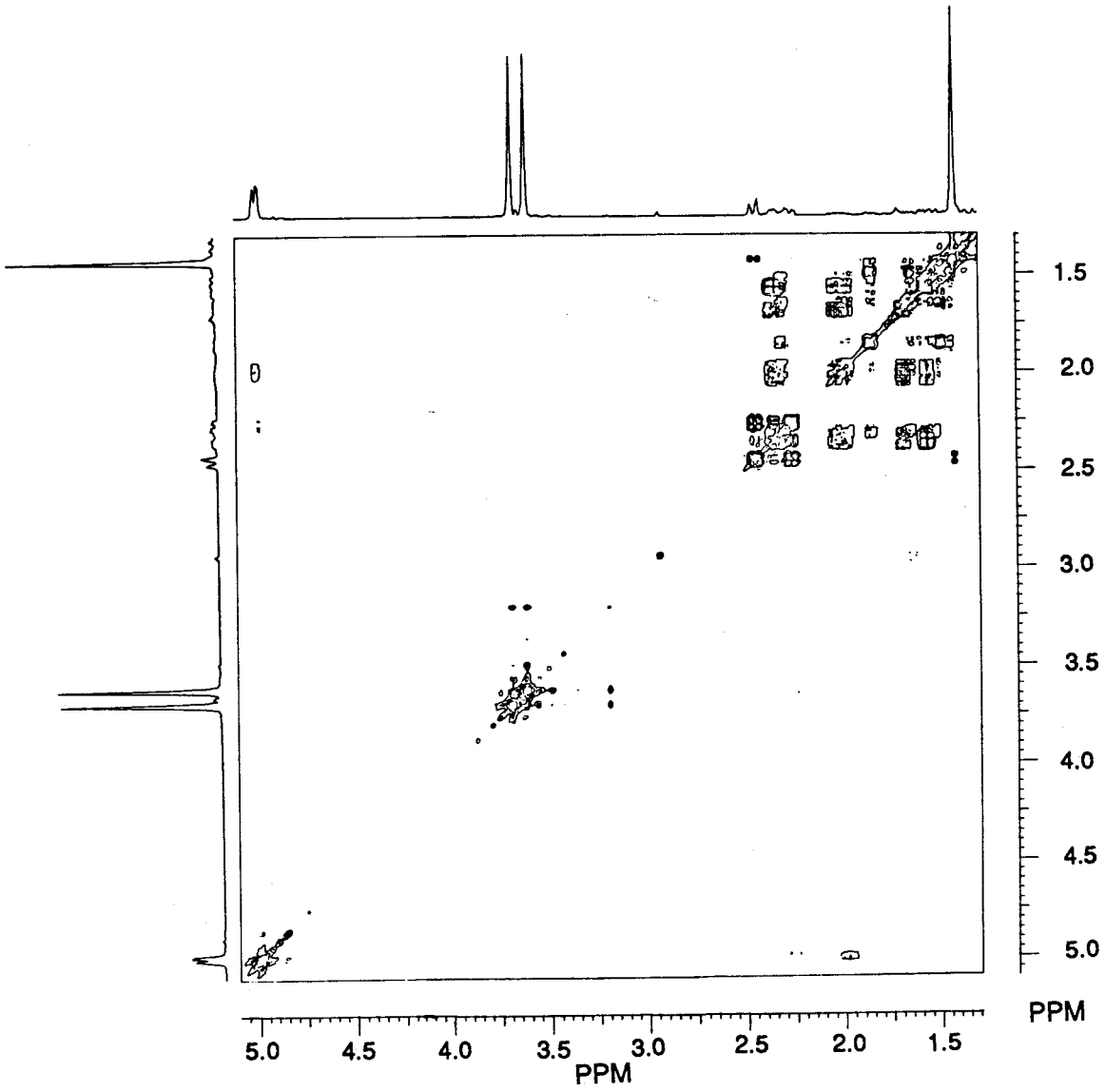
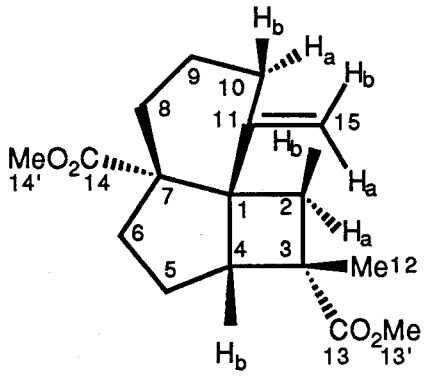


Figure 11. The 400 MHz COSY spectrum of the diester **202**.

2.26 (H-2b). In turn, the signal at δ 2.26 (H-2b) showed other correlations to the signals at 2.28-3.39 (H-4b and two other hydrogens) and extremely small (long range) correlations to the signal at 4.98 (H-15a). The correlations shown by the signal at δ 2.28-2.39 were too complex to further assign with certainty. Thus, the correlations due to the signals for the olefinic hydrogens (H-15a and H-15b) were examined. Apart from the correlation of the signal

at δ 4.98 (H-15a) with the one at 2.26 (H-2b), both olefinic hydrogens showed correlations to the multiplet at 1.95-2.06 (H-10a or H-10b and another H). Further tracing of the spin systems was not performed, but the COSY results, presented above and summarized in Table 6, are consistent with the nOe and decoupling results and confirm that the structure of the major epimer **202** is as assigned.

Table 6: The 400 MHz COSY Data for the Diester **202**.



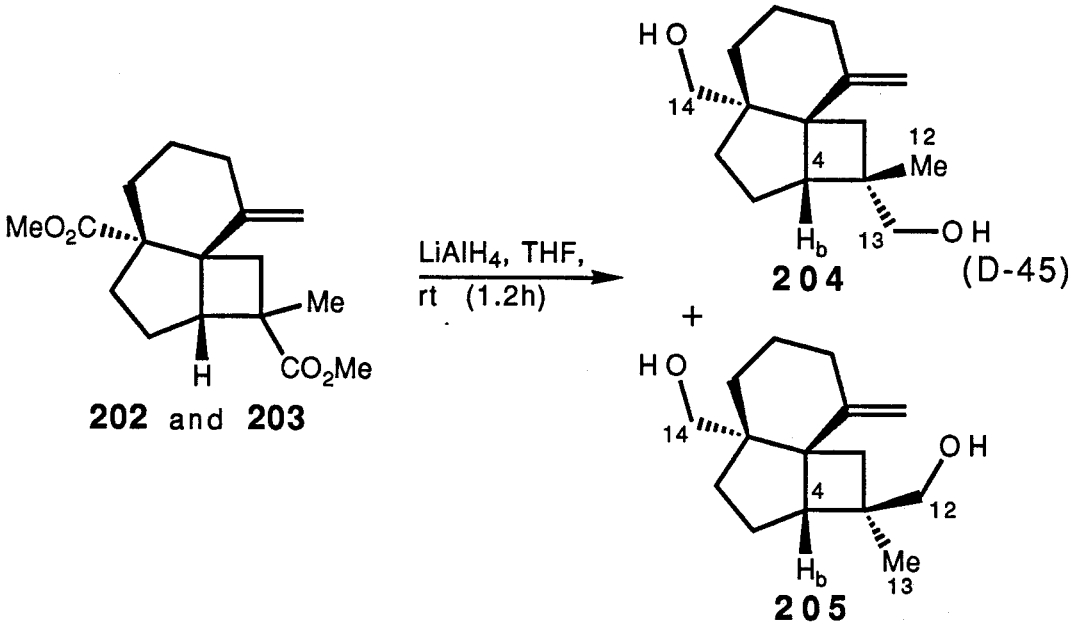
202

Position (H-x)	Signal δ ppm (multiplicity;[a] J; number of H)	COSY Correlations (H-x)
2a	2.45 (d; 14.0; 1H)	2b; 12 (W-coupling)
2b	2.26 (dd; 14.0, 3.0; 1H)	2a; 4b; 15a (long range coupling)
4b	2.28-2.39 (m; 3H)	2b; [b]
c	**c**	**d**
10a or 10b	1.95-2.06 (m; 2H)	15a; 15b; [b]
12	1.42 (s; 3H)	2a (W-coupling)
13'	3.69 (s; 3H)	- -
14'	3.61 (s; 3H)	- -
15a	4.98 (s; 1H)	15b; 2b (long range coupling); 10a or 10b
15b	5.00 (s; 1H)	15a; 10a or 10b

a. The signals labelled s, d, dd may incorporate unresolved fine couplings.
b. Other correlations also were observed.

Table 6: footnotes continued.
c. The positions of H-x (x=5a, 5b, 6a, 6b, 8a, 8b, 9a, 9b and 10b or 10a) are uncertain.
d. The correlations were not determined.

A THF solution of the mixture of the diesters **202** and **203** (ratio ~18:1) was transformed into the corresponding mixture of the diols **204** and **205** by reduction with lithium aluminum hydride (equation D-45). After an appropriate workup and purification, the major epimer **204** was obtained in 88% yield, while only traces of the minor epimer **205** were isolated.



Recrystallization of the major epimer **204** gave colorless needles with m.p. 139-139.5°C (sealed tube). Due to low solubility in other solvents, the nmr spectra of **204** were obtained in acetone-d_6. In the ^{1}H nmr spectrum (400 MHz) of the diol **204**, the signal for the methyl group (Me-12) appeared as a singlet (3H) at δ 1.11. The signals for the two hydroxyl hydrogens were triplets (1H, each) at δ 3.20 (J = 5.5 Hz) and at 3.32 (J = 5.0 Hz), both of which disappeared

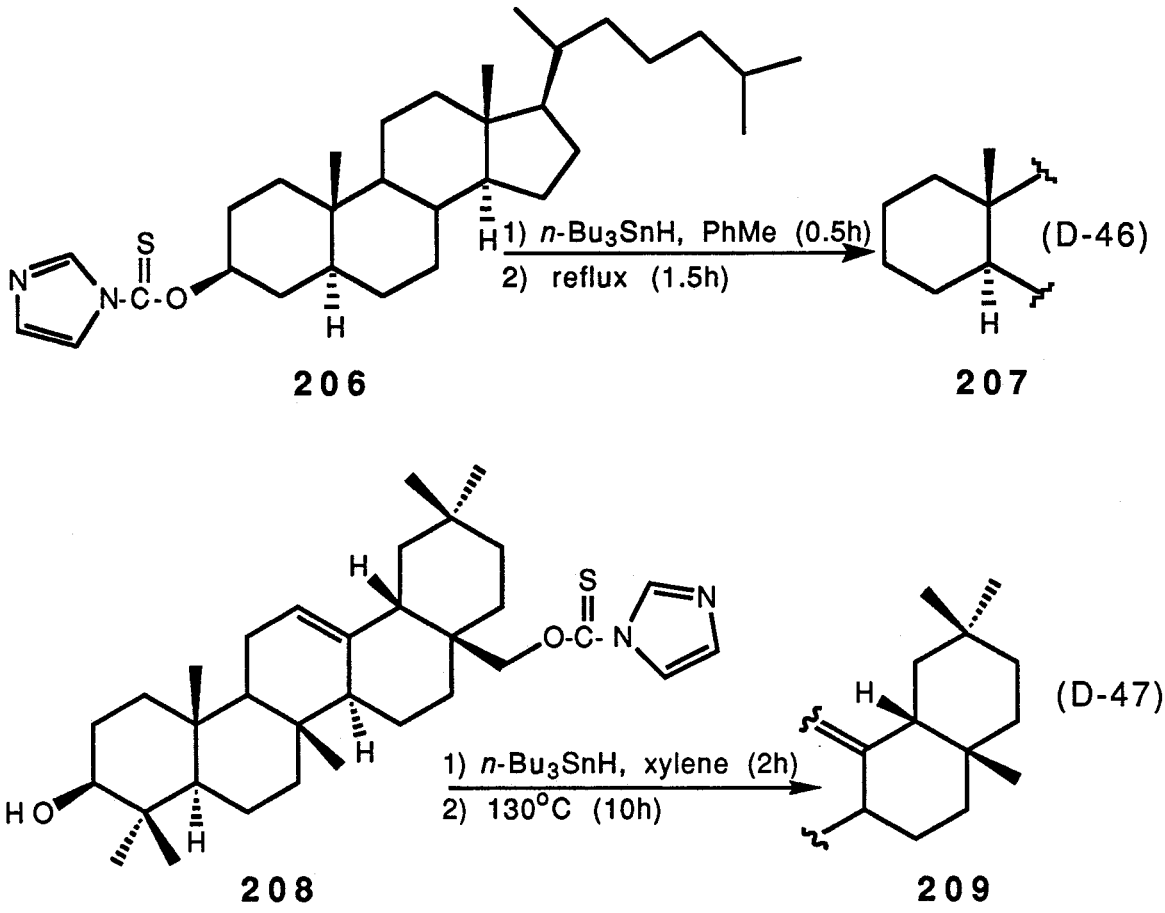
upon the addition of D_2O. The signals for the $C\underline{H}_2OH$ hydrogens were displayed at δ 3.23-3.30 (m, 2H), 3.40 (dd, 1H, J = 10.5, 5.5 Hz) and 3.46 (dd, 1H, J = 10.5, 5.0 Hz); upon the addition of D_2O, the multiplet was simplified and the two doublets of doublets gave rise to doublets (J = 10.5 Hz). The ^{13}C nmr spectrum of **204** displayed the expected 15 signals required for $C_{15}H_{24}O_2$. The elemental analysis and high resolution mass spectral data (found M^+=236.1780) were also consistent with the molecular formula. In the low resolution mass spectrum, the peak due to the molecular ion was very weak (0.4%) and peaks were found which corresponded to the loss of one and two molecules of water (M^+-18 and M^+-36, respectively). The ir spectrum of **204** indicated the presence of the hydroxyl groups by an absorption at 3312 cm^{-1}.

A small amount of the minor epimer **205** was isolated for characterization purposes. Thus, in the ^1H nmr spectrum of **205**, the signal for the methyl group (Me-13) appeared at δ 0.93 (s, 3H). The signal for one hydroxyl group was displayed as a triplet at δ 3.20 (J = 5.5 Hz) and disappeared upon the addition of D_2O, while the other hydroxyl hydrogen and both of the $C\underline{H}_2OH$ signals were part of a multiplet at δ 3.30-3.49 (5H). The addition of D_2O simplified the multiplet at δ 3.30-3.49 to give four distorted doublets at 3.26 (br d, J = 11.0 Hz), 3.31 (J = 10.5 Hz), 3.35 (J = 11.0 Hz) and at 3.43 (J = 10.5 Hz). The exact mass of the molecular ion in the high resolution mass spectrum (M^+= 236.1777) was consistent with the expected molecular formula of **205**.

Several factors were considered when choosing which method to use for the double deoxygenation of the diol **204**. In the first place,

both of the primary hydroxyl groups in **204** are neopentyl in nature and, therefore, the carbinol carbon atoms are very hindered. Thus, S_N2-type reactions, which are susceptible to steric effects,[121] were not deemed feasible for use in the performance of the deoxygenation.[122] On the other hand, radical reactions[122,123] (unlike S_N2 processes) are not as susceptible to steric effects. In addition, the radical reactions occur under neutral conditions,[122] so acid or base sensitive groups are compatible with the conditions utilized for the reactions. One problem in applying radical reactions to the deoxygenation of primary alcohols reflects the decreased stability of primary radicals in comparison with secondary radicals. Thus, the reaction conditions used are generally more drastic for the deoxygenation of primary alcohols than for the same reaction of secondary alcohols.[122,124] For example, deoxygenation of the secondary monothiocarbonylimidazolide **206** using tri-*n*-butyltin hydride to give 5α-cholestane (**207**) took 1.5 hours in refluxing toluene.[125] In contrast, deoxygenation of the primary monothiocarbonylimidazolide **208** with the same reagent to give β-amyrin **209** took 10 hours at 130°C in xylene[124] (equations D-46 and D-47, respectively).

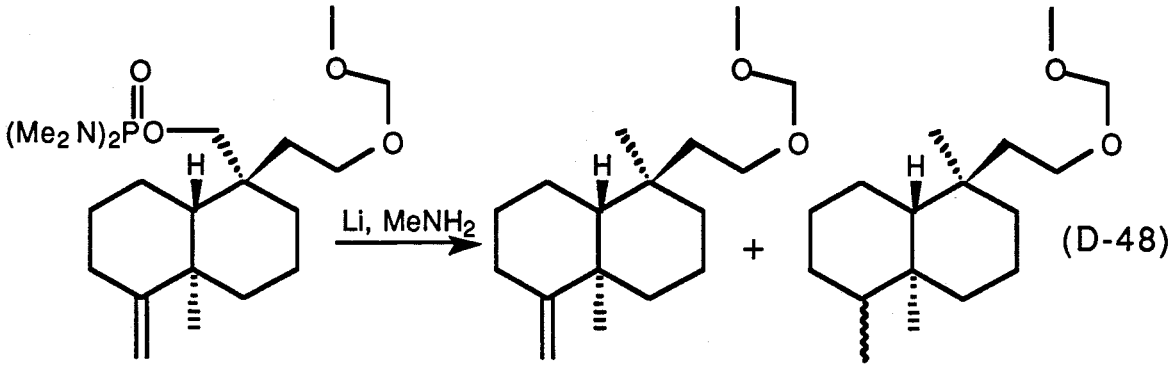
The possible application of a radical-based deoxygenation to the double deoxygenation of a derivative of the diol **204** led to the consideration of how to separate the hydrocarbon product, β-panasinsene, from the solvent and by-products of the reaction. Ideally, solvents, reagents and by-products with low boiling points (<60°C), or that were water soluble, or formed filterable solids were



deemed to be most suitable. Due to known problems in separating the product from reagents and by-products, triorganotin hydride[126] reductions or the more recent variations using silanes (triethylsilane,[127] tris(trimethylsilyl)silane,[128] or diphenylsilane[129]) were not attempted.

Reductions using dissolving metals, such as those employed in Ireland's deoxygenation of phosphodiamidates,[129] were expected to be feasible, but problematic due to the possible over-reduction of the olefinic functional group to give the saturated deoxygenated product. Thus, for example, Wai and Piers found that the sterically hindered primary alcohol **210** could be deoxygenated *via* its

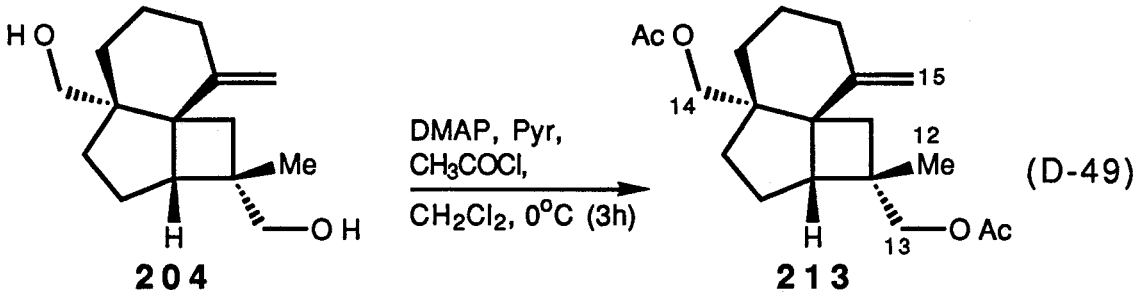
phosphorodiamidate derivative to give **211**,[12,131] but the reaction was somewhat capricious and varying amounts of the over-reduced saturated product **212** also were formed if conditions were not carefully controlled (equation D-48).[132]



210 **211** **212**

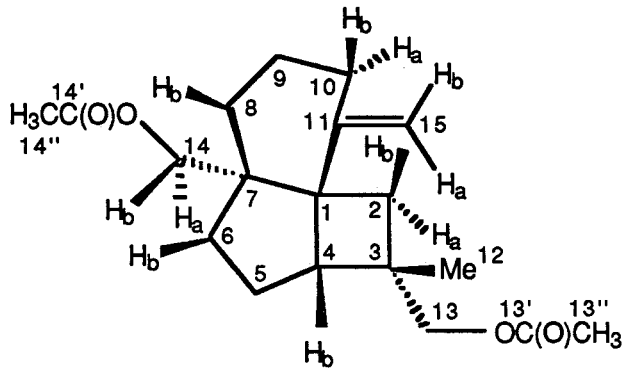
Pete[133] and coworkers reported that the photolysis of acetates in HMPA/water works well for acetate derivatives of primary and secondary alcohols, while Collins and Munasinghe[134] found that the reaction could also be successfully applied to the diacetates or tripivaloates derived from diols and triols, respectively. The deoxygenated product may be recovered by adding water to the reaction solvent and performing extractions with an organic solvent.

In order to attempt Pete's procedure, the diacetate **213** was prepared. Thus, a cold (0°C) dichloromethane solution of the diol **204**, containing DMAP (~1.1 equiv) and pyridine (9 equiv), was treated with acetyl chloride (6 equiv) (equation D-49). After an appropriate workup and purification, the diacetate **213** was obtained in 85% yield.



(D-49)

In the ir spectrum of the diacetate **213**, the presence of a carbonyl absorption at 1742 cm^{-1} indicated that the replacement of the hydroxyl functions by acetate groups had occurred. The expected absorptions for the exocyclic methylene were displayed at 1636 and 889 cm^{-1}. In the ^1H nmr spectrum (see figure 12), the signals for the three methyl groups appeared at δ 1.15 (Me-12), 2.02 and 2.05 (Me-13" and Me-14"), while the signals for the methylene hydrogens of the acetoxymethyl functions were found at 3.79 (dd, 1H, J = 11.0, 1.0 Hz, H-14a), 3.86 and 3.89 (AB pair of d, 2H, J = 11.0 Hz, 2H-13) and 4.03 (d, 1H, J = 11.0 Hz, H-14b). The origin of the unexpected small coupling in the signal for H-14a (J = 1.0 Hz) was explained upon examination of a COSY spectrum of **213** (see figure 13) which showed a correlation (W-coupling) between the signals at δ 3.79 (H-14a) and at 1.29-1.39 (m, 1H, H-8b or H-6b). From the shape of the



213

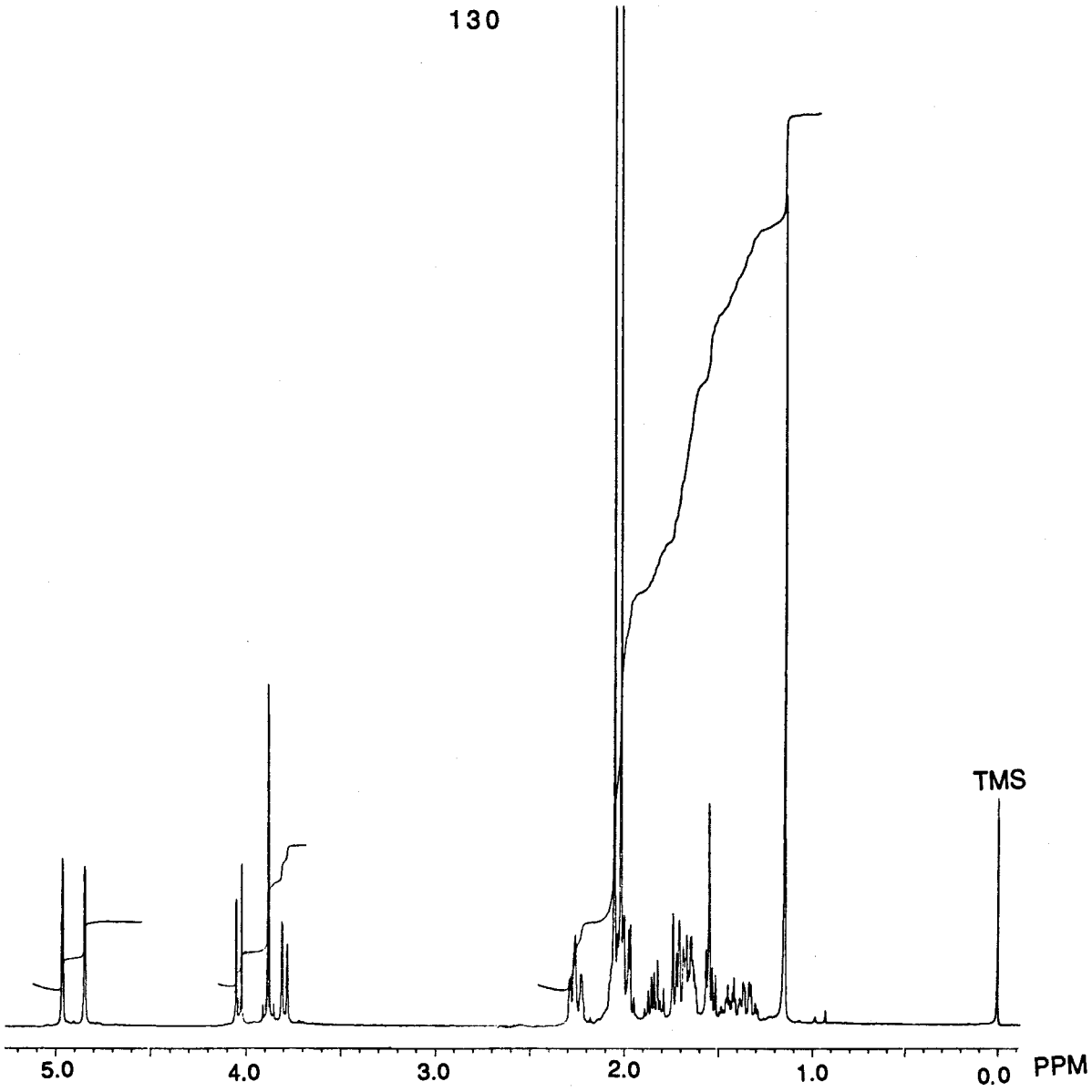


Figure 12. The 400 MHz ^{1}H nmr spectrum of the diacetate **213**.

signal at δ 1.29-1.39 (m) in the normal ^{1}H nmr spectrum, it was more likely that the signal was due to H-8b rather than to H-6b. Other assignments of hydrogen signals were possible based on the results of the COSY experiment. The resonance due to the methyl group (Me-12) provided an entry into the spin system of the four-membered ring, while the signals due to an olefinic hydrogen (H-15b) and H-14a provided the needed access into the spin system of the six-membered ring. Thus, the signal at δ 1.15 (Me-12) showed a

correlation (W-coupling) to the signal at 1.72 (d, J = 13.0 Hz, H-2a). In turn, the signal at δ 1.72 (H-2a) showed a correlation to the signal at 1.98 (dd, J = 13.0, 3.0 Hz, part of a 9H multiplet at 1.94-2.07). Due to the complexity of the correlation pattern of the signal at δ 1.94-2.07, the correlations due to the signals for olefinic hydrogens H-15a and H-15b at 4.84 and 4.96, respectively, were then examined. However, apart from correlations to each other, both showed correlations to the multiplet at δ 1.94-2.07 (9H) indicating that the signals for one or both of the allylic hydrogens (H-10a and/or H-10b) were part of the multiplet. Finally, the signal at δ 3.79 (H-14a) gave rise to a correlation to the signal at 1.29-1.39 (m, 1H, H-8b). The signal at δ 1.29-1.39 (H-8b) also showed correlations to the signals at 1.43 (br qt, 1H, J = 13.0, 3.0 Hz) and 1.62-1.72 (m, 3H). Due to the presence in the ^{1}H nmr spectrum of several complex multiplets, other assignments of signals were not feasible.

To confirm the assignments of the various hydrogen signals given above (and in Table 7), a NOESY[97] (two dimensional nOe) spectrum of **213** was obtained. The NOESY correlations are summarized in Table 8. For example, the signal at δ 1.72 (H-2a) showed nOe enhancements to signals at 1.98 (H-2b), 3.79 (H-14a) and 3.86 and 3.89 (2H-13), while the signal at 1.98 (H-2b) showed enhancements to the signals at 1.15 (Me-12), 1.72 (H-2a) and 4.84 (H-15a). The signal for the acetoxymethyl group at δ 3.86 and 3.89 (AB pair of d, 2H-13) showed enhancements to the signals at 1.72 (H-2a) and 1.15 (Me-12). The signal for one of the hydrogens of the other acetoxymethyl group H-14a (at δ 3.79) displayed enhancements to the signals at 4.03 (H-14b) and at 1.72 (H-2a). It thus appeared,

that the depicted structure for the diacetate **213** was correct and that the assignments of the hydrogen signals were reasonable.

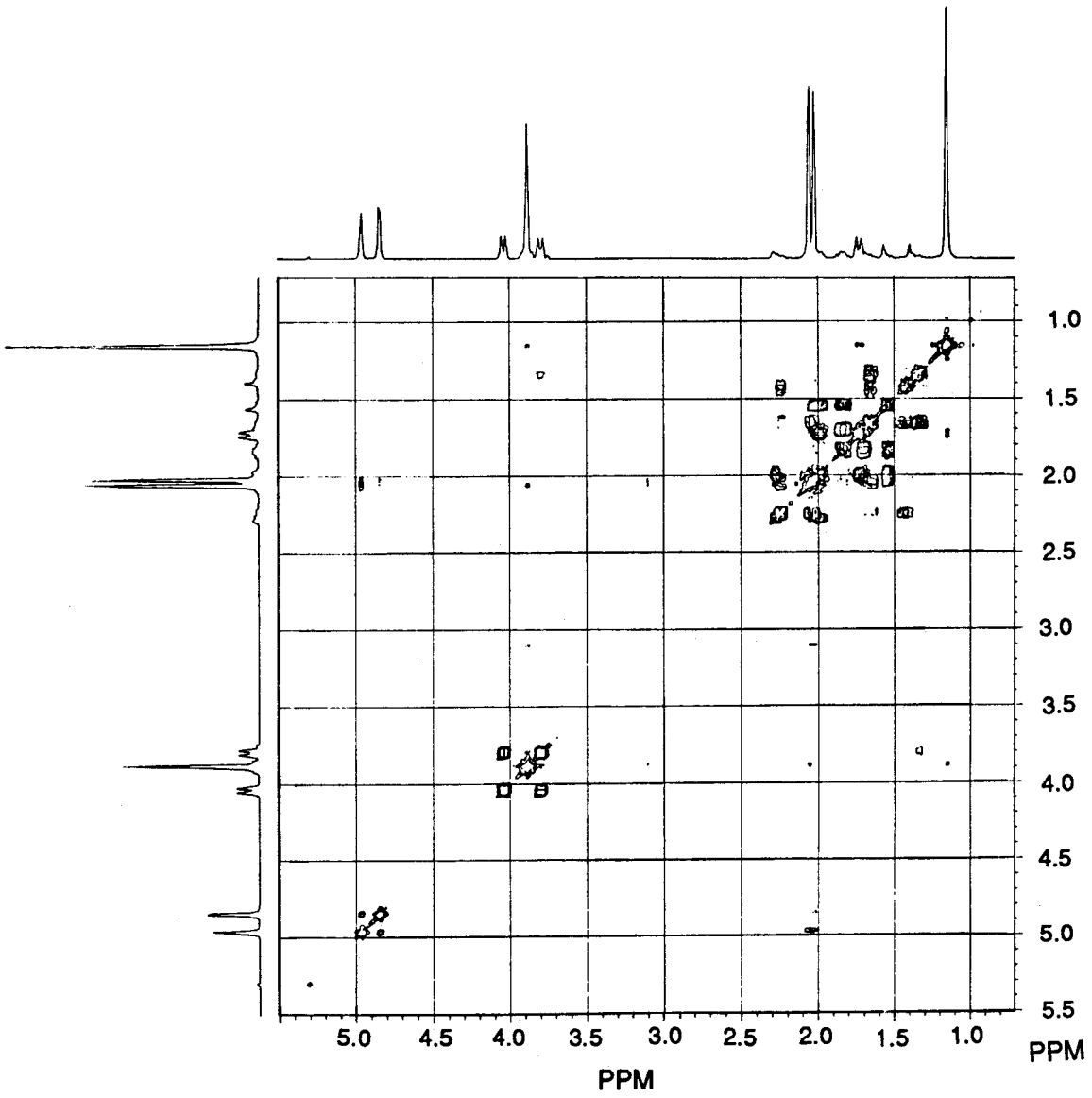
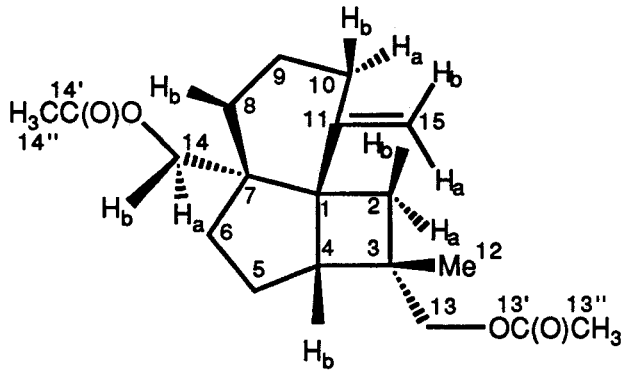


Figure 13. The 400 MHz COSY spectrum of the diacetate **213**.

Table 7: The 400 MHz COSY Data for the Diacetate **213**.

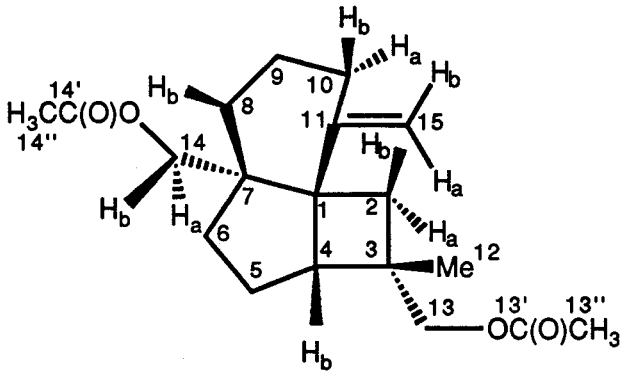


213

Position[a] (H-x)	Signal δ ppm (multiplicity;[b] *J*; number of H)	COSY Correlations (H-x)
2a 2b[c]	1.72 (d; 13.0; 1H) 1.98 (dd; 13.0, 3.0; 1H)	2b;[c] 12 (W-coupling) [d]
8b 10a or 10b[c]	1.29-1.39 (m; 1H) 1.94-2.07 (m; 9H)	14a (W-coupling)[e] 15a[d]
12 13 13" and 14" 14a 14b 15a 15b	1.15 (s; 3H) 3.86 and 3.89 (AB pair of d; 11.0; 2H) 2.02 (s, 3H); 2.05 (s; 3H) 3.79 (dd; 11.0, 1.0; 1H) 4.03 (d; 11.0; 1H) 4.84 (s; 1H) 4.96 (s; 1H)	2a (W-coupling); 13 (W-coupling) 12 (W-coupling); [f] - - 14b; 8b (W-coupling) 14a 15b 15a; 10a or 10b[c]

a The assignments of the hydrogens H-x (x= 4b, 5a, 5b, 6a, 6b, 8a, 9a, 9b, and 10b or 10a) were not feasible.
b The signals labelled s, d or dd may also incorporate unresolved fine couplings.
c The hydrogen is part of the signal at δ 1.94-2.07 (m, 9H; 2b, 10a or 10b, Me-13", Me-14" and 1 other H).
d The signal at δ 1.94-2.07 showed correlations to: 1.72 (d, 2a), 2.27 (br dd, 1H), 1.62-1.72 (m, 3H), 1.54 (dd, 1H), 1.43 (qt, 1H), 2.21-2.27 (m, 1H), 1.15 (s, Me-12), 3.86 and 3.89 (AB pair of d, 2H-13), 4.84 (s, 15a) and 4.96 (s, 15b).
e The signal also showed correlations to 1.43 (br qt, 1H) and 1.67-1.72 (m, 3H).
f There is also a correlation to δ 1.94-2.07 (m, 9H).

Table 8: The 400 MHz NOESY Data for the Diacetate **213**.



213

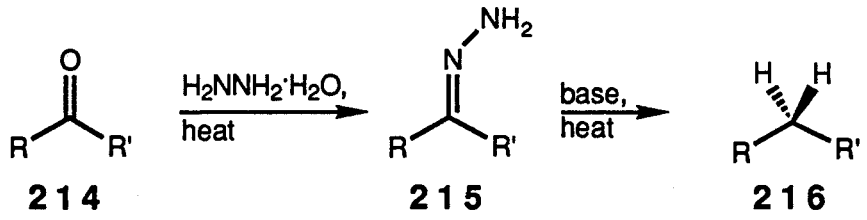
Position (H-x)	Signal δ ppm (multiplicity; J; number of H)	NOESY Correlations (H-x)
2a	1.72 (d; 13.0; 1H)	2b; 13; 14a
2b	1.98 (dd; 13.0, 3.5; 1H)	2a; 12; 15a
12	1.15 (s; 3H)	2b; 13; 15a
13	3.86 and 3.89 (AB pair of d; 11.0; 2H)	2a; 12
14a	3.79 (dd; 11.0, 1.0; 1H)	14b; 2a
14b	4.03 (d; 11.0; 1H)	14a
15a	4.84 (s; 1H)	15b; 2b; 12
15b	4.96 (s; 1H)	15a

The preparation of the diacetate **213** set the stage for the crucial double deoxygenation reaction to prepare the natural product, (±)-β-panasinsene (**31**) *via* Pete's procedure.[133] Thus, solutions of the diacetate **213** in HMPA-H_2O (~95:5) were photolyzed using either a single low pressure mercury lamp (emission at 253.7 nm) or a Rayonet reactor (16 such lamps) until no more starting material was detected (~7-9 hours). Dilution of the reaction mixture with water, followed by an extraction with pentane and removal of the solvent led to the isolation of low yields of (±)-β-panasinsene (**31**), which was usually contaminated by a small amount of a compound with very similar properties. The impurity could be removed by

chromatography of the mixture on silica gel impregnated with silver nitrate (1.25 g $AgNO_3$/ 5.00 g of 70-230 mesh silica gel),[131] but the yields of the target compound were too low (<10%) to make the procedure feasible. After several unsuccessful attempts to improve the results, a different approach to the double deoxygenation of the diol **204** was undertaken.

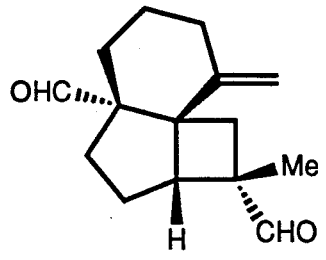
2.3.2.6. Preparation of (±)-β-Panasinsene (**31**) *via* a Wolff-Kishner Reduction.

There are various methods known for the reduction of aldehyde or keto groups to the corresponding methylene groups, but the two most common methods are the Clemmensen and Wolff-Kishner reductions.[135] The Clemmensen reduction uses zinc amalgam and aqueous, or in some cases gaseous, HCl. β-Panasinsene (**31**) is known to rearrange in acid to give neoclovene **56** (*vide supra*, Introduction),[13] so the Clemmensen reduction would not be useful in this case. The Wolff-Kishner reduction, in contrast, involves conversion of an aldehyde or ketone of general structure **214** to the hydrazone **215** and heating the hydrazone with base to give the deoxygenated product **216** (equation D-50). In a one pot procedure, the aldehyde or ketone may be heated with hydrazine hydrate and a base to produce the deoxygenated product.



214 **215** **216** (D-50)

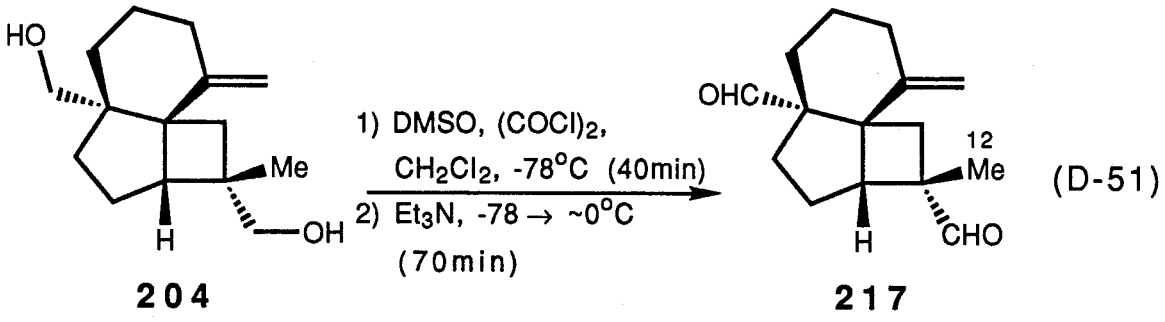
Recently, Roberge[136] found that the use of anhydrous hydrazine* as a cosolvent, rather than just as a reagent,[137] to form the hydrazone improved the yields of the reaction. Thus, heating a solution of the ketone in an ~1:2 mixture of anhydrous hydrazine-diethylene glycol at ~130-140°C generated the hydrazone. Removal of the excess hydrazine by a reduced pressure distillation, followed by reaction of the hydrazone with potassium hydroxide at 200-210°C, led to the formation of the deoxygenated product. Yields were reduced and reaction times were increased if the excess hydrazine was not removed before the base was added. The product could be isolated by the addition of water to the cooled reaction mixture followed by extractions with an organic solvent. The procedure seemed suitable for the deoxygenation of the dialdehyde **217**, presumed to be available from the diol **204**.



217

* Anhydrous hydrazine is explosive in the presence of oxidizing agents (including air) and must be handled with great care.

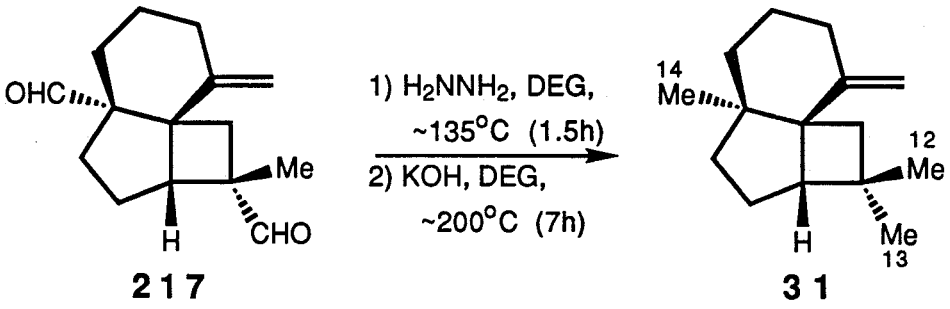
The dialdehyde **217** was prepared from the diol **204** *via* a Swern oxidation.[138] Thus, the diol **204**, in a mixture of dichloromethane and dimethyl sulfoxide (DMSO), was allowed to react with a mixture of DMSO and oxalyl chloride. Treatment of the mixture with triethylamine, followed by an appropriate workup and a rapid filtration of a solution of the product through a silica gel column, led to the isolation of the dialdehyde **217** in 98% yield (equation D-51). The product thus obtained was pure enough to be characterized.



204 **217** (D-51)

The ir spectrum of the dialdehyde **217** showed the expected absorptions for the aldehyde functions at 2723 (w) and at 1718 (vs) cm^{-1}, while the absorptions for the exocyclic methylene were displayed at 1638 and 894 cm^{-1}. In the ^1H nmr spectrum, the signal for the methyl group (Me-12) appeared at δ 1.36 (s, 3H), while the signals for the aldehyde hydrogens were at 9.50 (s, 1H) and 9.65 (s, 1H). In the low resolution mass spectrum, the molecular ion (1.9%) and fragments corresponding to the loss of one and two formyl groups (M^+-29 and M^+-58, respectively) were observed. The exact mass of 232.1459, found for the molecular ion of **217** in the high resolution mass spectrum, was consistent with the formula, $C_{15}H_{20}O_2$.

The dialdehyde **217** was then submitted to the Wolff-Kishner deoxygenation procedure using the modifications developed by Roberge.[136] Thus, a solution of the dialdehyde **217** in diethylene glycol and anhydrous hydrazine (5:3 diethylene glycol-hydrazine) was heated at ~135°C for 1.5 hours under an argon atmosphere. After removal of excess hydrazine and addition of base (potassium hydroxide), the mixture was heated at ~200°C for 7.5 hours. Cooling, followed by an aqueous workup, led to the isolation of crude (±)-β-panasinsene (**31**) in ~76% yield (equation D-52). A reduced pressure distillation of this material resulted in a 46% yield of the synthetic natural product **31** in >97% purity (glc analysis).



217 **31** (D-52)

The purified synthetic (±)-β-panasinsene (**31**) displayed spectral characteristics similar to those reported in the literature. Unfortunately, all our attempts to obtain samples of natural[13,16] or synthetic[30,31] β-panasinsene or the appropriate spectra for comparison purposes were unavailing. There is no doubt, however, that (±)-β-panasinsene (**31**) was the compound synthesized *via* the reaction sequence described in this thesis. This contention is borne out by a comparison of the data obtained for the newly synthesized (±)-β-panasinsene (**31**) with the data reported in the literature[13]

(see Table 9), and by an examination of the other spectral data that were obtained for the synthetic natural product.

Table 9. A Comparison of the Spectral Data for Authentic and Synthetic β-Panasinsene (**31**).

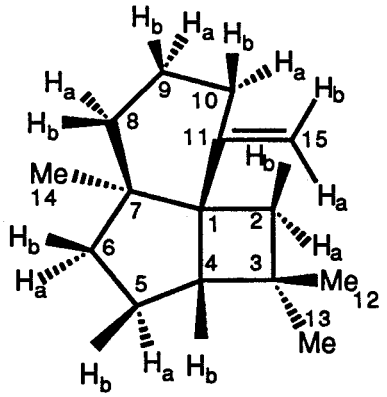
Type of Data	Authentic (-)-β-Panasinsene[a]	Synthetic (±)-β-Panasinsene[b]
Infrared (cm^{-1})	3080, 1620, 1365, 1360, 1260, 1080, 930, and 885	3088, 1636, 1377, 1365, 1269, and 885
^1H nmr[c] δ ppm (multiplicity; *J*; number of H; H-x)	0.74 (s; 3H) 0.86 (s; 3H) 1.08 (s; 3H) 4.78 (d; *J* = 2 Hz; 1H) 4.84 (d; *J* = 2 Hz; 1H)	0.75 (s; 3H; Me-14) 0.86 (s, 3H; Me-13) 1.07 (s, 3H; Me-12) 4.80 (d; *J* = 1.5 Hz; 1H; H-15a) 4.91 (dd; *J* = 1.5, 1.5 Hz; 1H; H-15b)
Low Resolution Mass Spectrum Peak (% relative intensity)	204 (M^+) 189, 175, 161 (base peak), 146, 133, 122, 109, and 107	204 (M^+, 29%) 189 (23), 175 (14), 162 (16), 161 (100), 147 (19), 133 (44), 122 (46), 119 (23), 107 (47), 105 (40), 91 (38)

a. From reference 13. No other data were reported.
b. From this thesis.
c. The spectrum of authentic **31** was recorded on a JEOL-JNM-C-60 60 MHz spectrometer (solvent not identified).[13] The spectrum of synthetic **31** was recorded on a Bruker WH 400 MHz spectrometer in $CDCl_3$.

The data for the authentic and synthetic β-panasinsene (**31**) as compiled in Table 9 are similar, but a few differences may be noted. Firstly, according to the ir spectral data, the synthetic sample did not display significant absorptions at 1080 or 930 cm^{-1} as were reported for the natural product and the absorption due to the exocyclic methylene (C=C stretch) occurred at different positions (1620 and 1636 cm^{-1}). The reasons for the difference are uncertain.

Secondly, from the ^{1}H nmr spectral data, the signal for one of the olefinic methylene hydrogens differs significantly with regard to both position and multiplicity (at δ 4.84 (d) *versus* at 4.91 (dd)). The discrepancies in the nmr results may be mainly due to the different instruments used (60 MHz *versus* 400 MHz). Also, the solvent used in the literature was not identified. Finally, the low resolution mass spectral patterns differ particularly with regard to the peak at 146 (literature) or at 147 (synthetic). The disagreement may be due to a typographical error in the literature. Other mass spectral differences probably are unimportant as no contradiction is involved. The discrepancies between the literature data and the data from the synthetic β-panasinsene as summarized in Table 9 are minor in comparison with the similarities and thus, it may be concluded that **31** was synthesized.

Further confirmation of the identity of the synthetic (±)-β-panasinsene (**31**) was procured in the form of a high resolution mass spectrum, ^{13}C nmr spectra (broad band and APT), as well as several one and two dimensional nmr spectra (nOe, HETCOR and COSY). A molecular formula of $C_{15}H_{24}$, as expected for β-panasinsene, was indicated by the presence of a molecular ion with an exact mass of 204.1875 in the high resolution mass spectrum of **31**. The number of carbons was also implied by the presence of 15 carbon signals in the broad band decoupled ^{13}C nmr spectrum (see figure 14). Based on the chemical shifts of the signals, those at δ 108.3 and 152.3 could be assigned to the olefinic methylene ($\underline{C}H_2$-15) and to the quaternary olefinic carbon ($\underline{C}$-11), respectively. According to a ^{13}C nmr APT experiment, four signals (at δ 52.60, 18.2, 24.85 and 30.64) were due



31

to either methine or methyl carbons. The signal at δ 52.60 was clearly due to the methine, CH-4, while the other three signals corresponded to the signals of the three methyl groups in **31**.

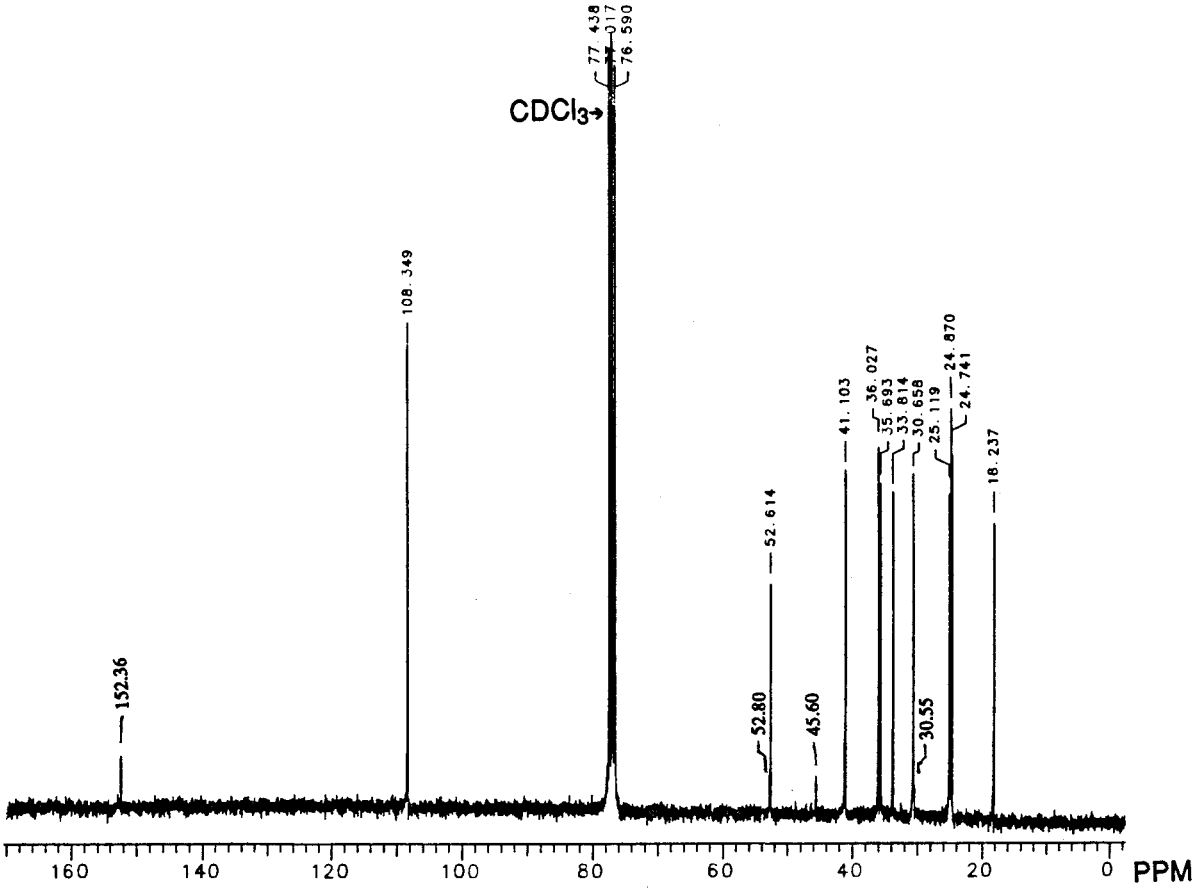


Figure 14. The 75 MHz broad band decoupled ^{13}C nmr spectrum of synthetic (±)-β-panasinsene (**31**).

The ^1H nmr spectrum (see figure 15) of our synthetic **31**, in addition to the signals mentioned in Table 9, showed signals for another 13 hydrogens, of which only two signals overlapped in an indistinguishable manner (δ 1.35-1.41, m, 2H). In order to identify the methine (H-4b) and the pairs of geminal hydrogens in the ^1H nmr spectrum, a HETCOR experiment was performed and yielded the

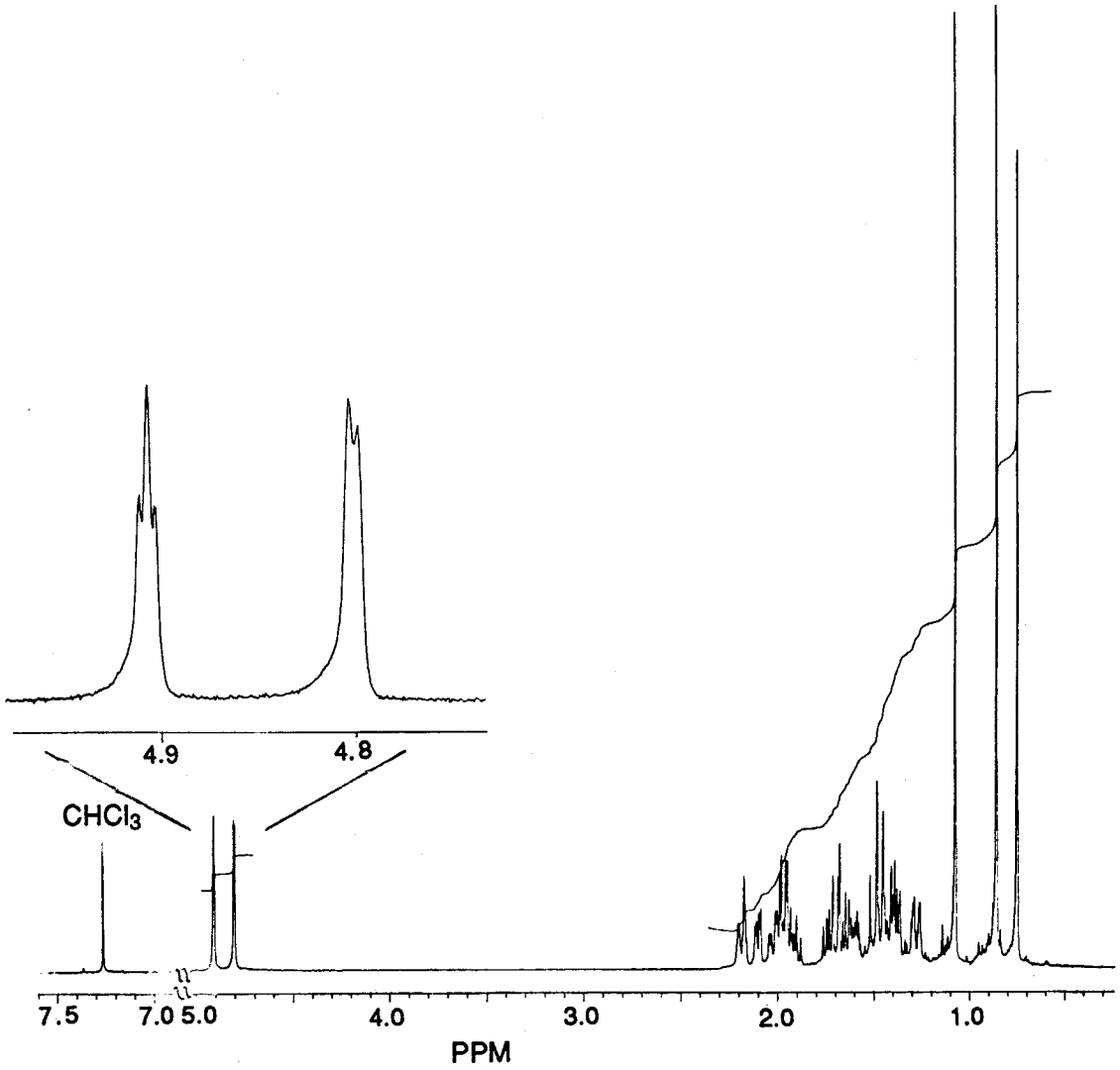


Figure 15. The 400 MHz ^1H nmr spectrum of synthetic (±)-β-panasinsene (**31**).

results summarized in Table 10 (see also figure 16). For example, the methine carbon signal (CH-4) at δ 52.60 correlated with the hydrogen signal at 2.10 (br dd, 1H, J = 8.5, 3.0 Hz, H-4b), while a carbon signal at 35.7 correlated with two hydrogen signals at 1.46 (d, 1H, J = 12.5 Hz, H-2a) and at 1.96 (dd, 1H, J = 12.5, 3.0 Hz, H-2b), thus indicating that the pair of hydrogens was geminal.

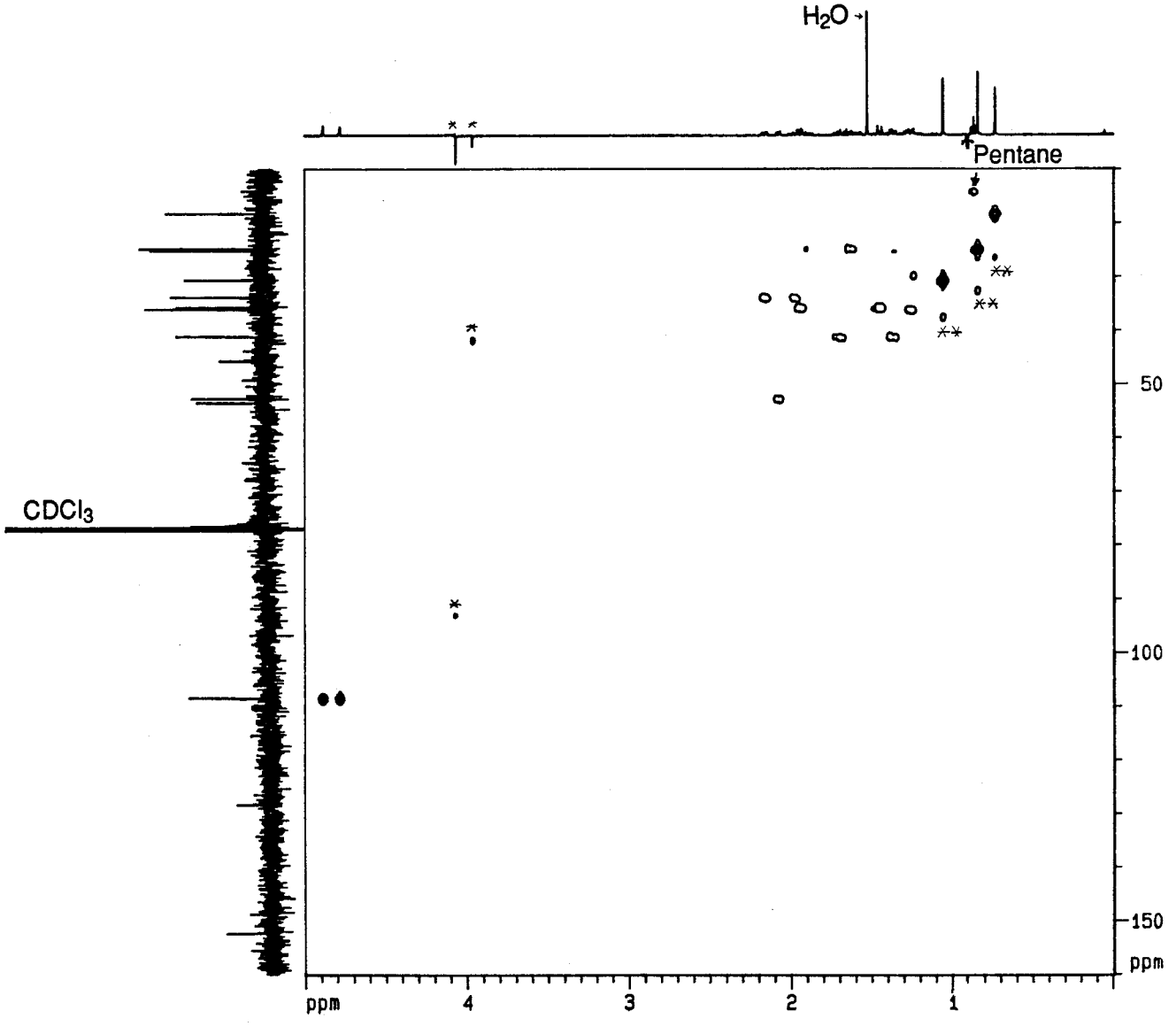
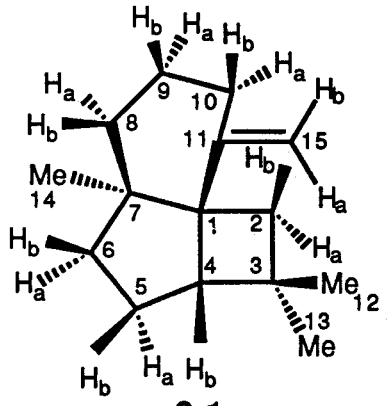


Figure 16. The 125 MHz HETCOR spectrum of synthetic (±)-β-panasinsene (**31**). (* Folded peaks. ** T1 noise).

Table 10: The 125 MHz HETCOR Data for Synthetic (±)-β-Panasinsene (**31**).



31

Position (C-x)	^{13}C (125 MHz)	^{1}H (500 MHz) δ (H-x)
1	52.77	- -
2	35.7	1.46 (2a); 1.96 (2b)
3	45.6[a]	- -
4	52.60	2.10 (4b)
5	24.72	1.63-1.68 (5a); 1.87-1.97 (5b)
6	41.1	1.73 (6a); 1.35-1.41 (6b)
7	30.53[a]	- -
8	36.0	1.27 (8a); 1.42-1.48 (8b)
9	25.10	1.35-1.41 (9a or 9b); 1.57-1.63 (9b or 9a)
10	33.8	2.00 (10a or 10b); 2.18 (10b or 10a)
11	152.3	- -
12	30.64	1.07 (3H-12)
13	24.85	0.86 (3H-13)
14	18.2	0.75 (3H-14)
15	108.3	4.80 (15a); 4.91 (15b)

a Signals may be interchanged.

The precise assignments of the positions of the geminal pairs of hydrogens and the methyl groups were made based on the COSY correlations observed for the signals (see figure 17 and Table 11). Entry into the spin systems was afforded by the signal for the methine at δ 2.10 (H-4b) and the signal for olefinic hydrogen at 4.91

(H-15b). Thus, the signal at δ 2.10 (br dd, 1H, J = 8.5, 3.0 Hz, H-4b) showed correlations to the signals at 1.96 (dd, 1H, J = 12.5, 3.0 Hz, H-2b, W-coupling) and at 1.87-1.97 (m, 1H, H-5b). The signal at δ 1.46 (1H) for the hydrogen geminal to the one at 1.96 (1H) showed a correlation to the methyl group at 1.07 (Me-12), while neither the signal at 1.87-1.97 (H-5b) nor the one due to the geminal hydrogen (at 1.63-1.68) did so. Thus, the former pair of signals (i.e., at δ 1.46 and 1.96) was assigned to the 2-position and the latter pair (i.e., at δ 1.63-1.68 and 1.87-1.97) was assigned to the 5-position. The signals arising from the hydrogens at the 6-position were then identified by determining with which other signals the signals due to H-5a and H-5b showed correlations. Based on the nOe results described below and from consideration of molecular models, the a- and b-hydrogens on carbons 5 and 6 were assigned as listed in Table 11. Similarly, the spin system of the six-membered ring was entered by way of an olefinic hydrogen at δ 4.91 (dd, 1H, J = 1.5, 1.5 Hz, H-15b). The methyl groups were assigned based on the fact that the signals at δ 1.07 and 0.86 (Me-12 and Me-13, respectively) showed W-coupling to each other, while the signals at 1.07 and 0.75 (Me-12 and Me-14, respectively) showed W-coupling to the signals for two ring hydrogens at 1.42-1.48 (a multiplet overlapping the doublet at 1.46). The W-coupling between the signals at δ 1.07 (Me-12) and at 0.86 (Me-13) meant that the two signals were due to the geminal methyl groups and thus, that the signals at δ 1.07 and 0.75 correlated, respectively, to the signals at 1.46 (d, H-2a) and at 1.42-1.48 (m, H-8b).

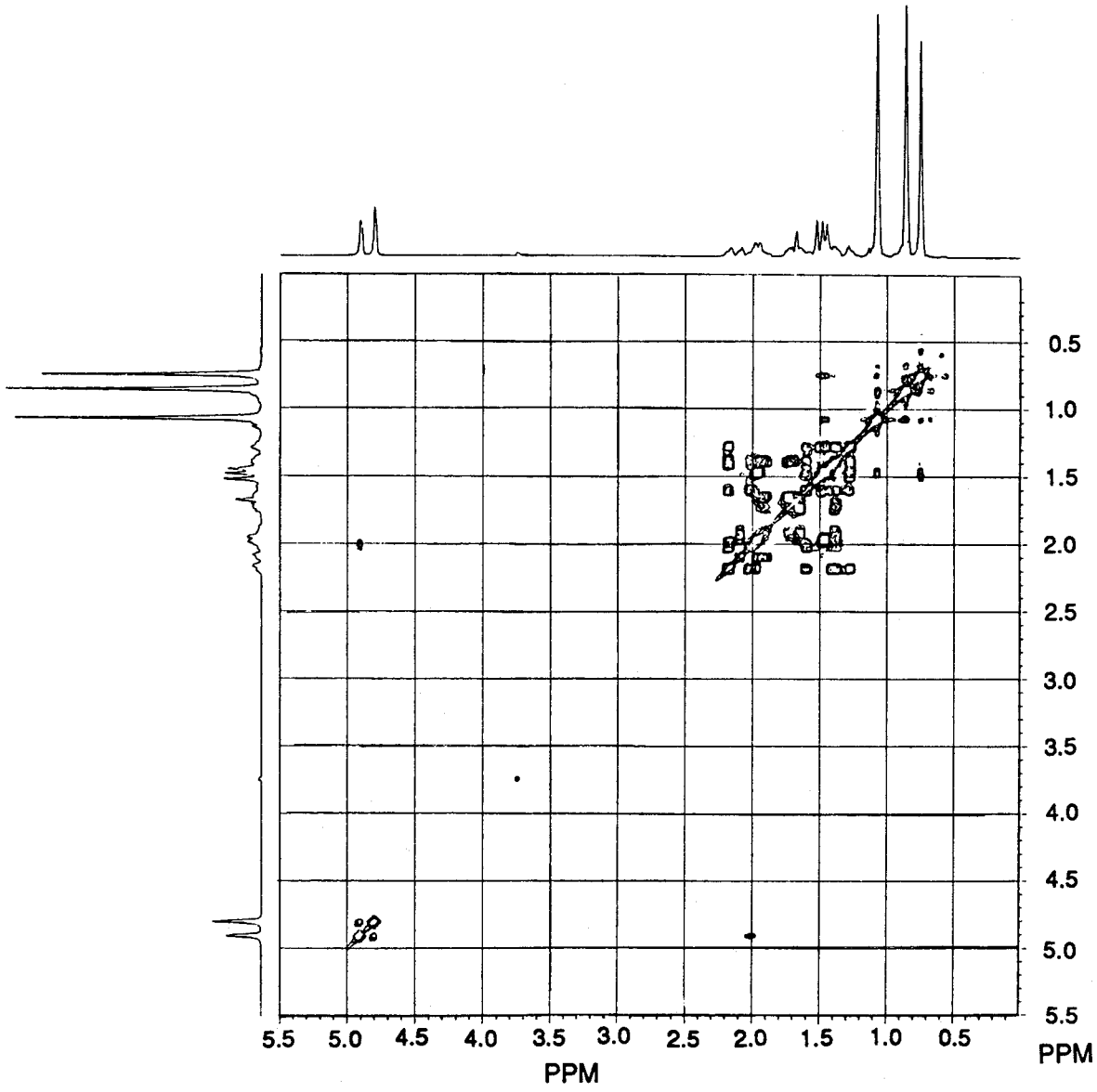
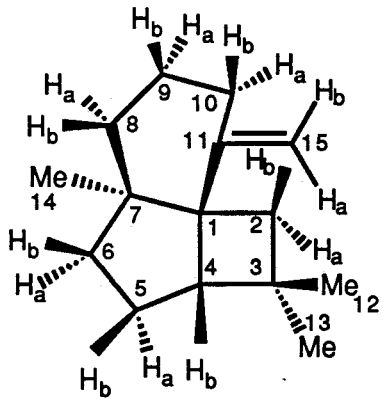


Figure 17. The 400 MHz COSY spectrum of synthetic (±)-β-panasinsene (**31**).

Table 11: The 400 MHz COSY Data for Synthetic (±)-β-Panasinsene (**31**).

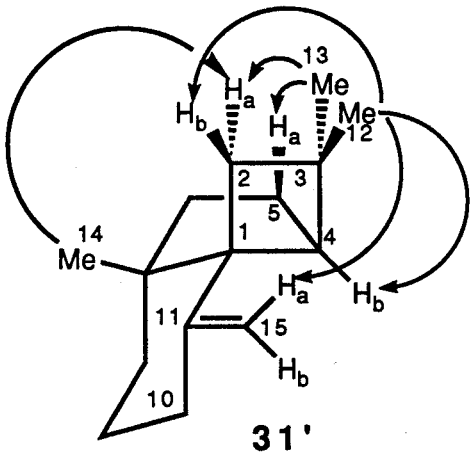


31

Position (H-x)	Signal δ ppm (multiplicity;[a] J; number of H)	COSY Correlations (H-x)
2a	1.46 (d; 12.5; 1H)	2b; 12 (W-coupling)
2b	1.96 (dd; 12.5, 3.0; 1H)	2a; 4b
4b	2.10 (br dd; 8.5, 3.0; 1H)	2b; 5b
5a	1.63-1.68 (m; 1H)	5b; 6a
5b	1.87-1.97 (m; 1H)	5a; 4b; 6b; 6a[b]
6a	1.73 (dd; 12.0, 7.0; 1H)	6b; 5a; 5b[b]
6b	1.35-1.41 (m; 2H)	6a; 5b
8a	1.27 (dm; 12.5; 1H)	8b; 9a and 9b; 10a or 10b (W-coupling)
8b	1.42-1.48 (m; 1H)	8a; 9b or 9a; 14 (W-coupling)
9a or 9b	1.35-1.41 (m; 2H)	9b or 9a; 8a; 10a and 10b
9b or 9a	1.57-1.63 (m; 1H)	9a or 9b; 8a; 8b; 10a and 10b
10a or 10b	2.00 (br td; 12.5, 4.0; 1H)	10b or 10a; 9b and 9a; 15b
10b or 10a	2.18 (dm; 12.5; 1H)	10a or 10b; 9a and 9b; 8a (W-coupling)
12	1.07 (s; 3H)	2a (W-coupling); 13 (W-coupling)
13	0.86 (s; 3H)	12 (W-coupling)
14	0.75 (s; 3H)	8b (W-coupling)
15a	4.80 (d; 1.5; 1H)	15b
15b	4.91 (dd; 1.5, 1.5; 1H)	15a; 10a or 10b

a Signals labelled s, d, or dd may also incorporate unresolved fine couplings.
b Small correlations observed.

In nOe difference experiments (summarized in structure **31'**), irradiation of the singlet at δ 1.07 (Me-12) led to enhancement of the signals at 1.96 (H-2b), 2.10 (H-4b) and 4.80 (H-15a), while irradiation of the singlet at δ 0.86 (Me-13) led to enhancements of the signals at 1.46 (d, H-2a) and 1.63-1.68 (m, H-5a). Irradiation of the singlet at δ 0.75 (Me-14) led to enhancement of the doublet at 1.46 (H-2a). Thus, the assignments for the methyl groups were consistent with the other nmr data.

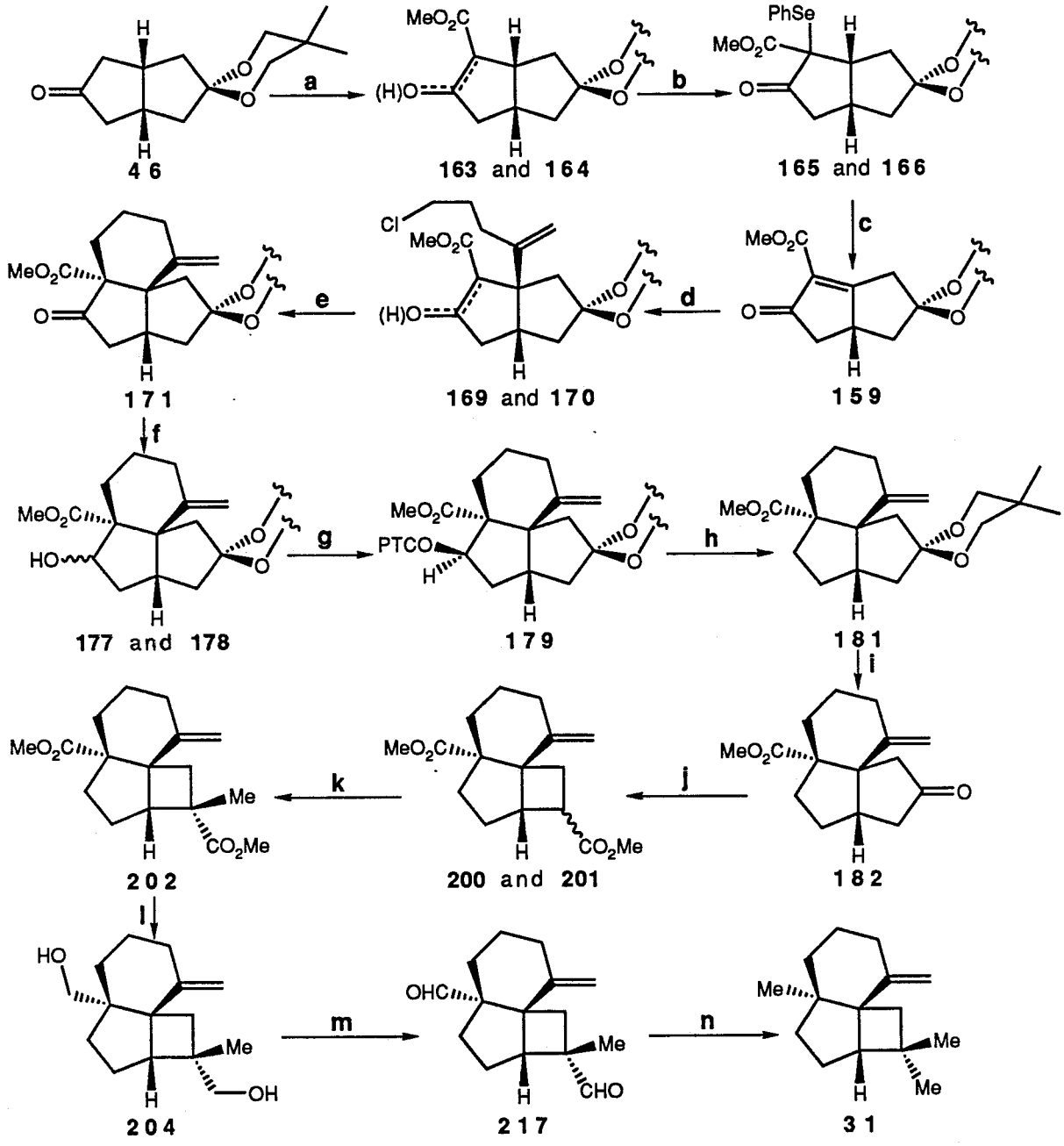


31'

The results outlined above for the synthetic (±)-β-panasinsene (**31**) provide further information about the spectroscopic properties of the natural product and confirm the identity of the synthetic material.

III. CONCLUSION

The work summarized above and outlined in Scheme D-12, constitutes a successful total synthesis of (±)-β-panasinsene (**31**) in fourteen steps from the keto ketal **46**. While the approach to the synthesis of (±)-β-panasinsene (**31**) *via* the Pauson-Khand cyclization reaction was unsuccessful, the Weiss-Cook condensation provided a viable alternative for the synthesis of an enone (**159**) with a tetrasubstituted double bond. The key methylenecyclohexane annulation sequence previously developed in our laboratories was successfully applied to the enone **159** and efficiently provided the tricyclic keto ester ketal **171** which has the desired relative stereochemistry at the three chiral centers. Functional group manipulations followed by a Wolff rearrangement provided intermediates **200** and **201** with the required tricyclic carbon skeleton. Further reactions, including the double deoxygenation of the sterically hindered aldehyde functions in the dialdehyde **217**, generated synthetic (±)-β-panasinsene **31**. The previously unreported ^{13}C, HETCOR, COSY and nOe data were obtained for **31** as a part of this research and provide a more complete picture of the spectroscopic characteristics of the natural product.



Scheme D-12

a. KH, THF, ~60°C; dimethyl carbonate, ~60°C (~93%), **b**. KH, THF, rt; PhSeCl, 0°C (86%), **c**. H_2O_2, CH_2Cl_2, 0°C; rt (~quant.), **d**. 5-chloro-1-pentenyl-2-magnesium bromide, $CuBr{\cdot}SMe_2$, THF, -78°C (~94%), **e**. Cs_2CO_3, CH_3CN, ~60°C (64%), **f**. $NaBH_4$, $CeCl_3{\cdot}6H_2O$, MeOH, -48°C (98%), **g**. PTC-Cl, DMAP, CH_3CN, ~70°C (76%), **h**. *n*-Bu_3SnH, AIBN, PhH, ~77°C, (74%), **i**. 1 *N* HCl (aq), acetone, rt (85%), **j**. i) *t*-amylONa, PhH, ~7°C; rt; MeO_2CH, 5°C to rt (~quant.); ii) MsN_3, Et_3N, CH_2Cl_2, 0°C (in the dark); iii) h*v*, MeOH, 0°C (40.5%), **k**. LDA, THF, -78°C; HMPA, -78°C; MeI, -78°C to ~5°C (65%), **l**. $LiAlH_4$, THF, rt (88%), **m**. DMSO, oxalyl chloride, CH_2Cl_2, -78°C; Et_3N, -78°C to 0°C (98%), **n**. H_2NNH_2, DEG,~135°C; KOH, ~200°C (46%).

IV. EXPERIMENTAL

4.1. General.

Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on either a Varian XL-300 or a Bruker WH-400 nmr spectrometer using deuterochloroform as the solvent and tetramethylsilane (TMS) or the proton of the residual chloroform (δ 7.26) as the internal standard, unless otherwise noted. Signal positions are given in parts per million (δ) from TMS. Coupling constants (J) are given in Hertz (Hz). The multiplicity, number of protons, coupling constant(s), and assignments (when known) are given in parentheses. Abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Carbon nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Varian XL-300 nmr spectrometer at 75.3 MHz, or on a Bruker AM-400 spectrometer at 100 MHz, or on a Bruker AMX-500 spectrometer at 125.8 MHz using deuterochloroform as the solvent, unless otherwise noted. Signal positions are given in parts per million (δ) relative to the chloroform signal at δ 77.0.[61] Signal multiplicities were determined by the Attached Proton Test (APT) experiment.

Two dimensional spectra were recorded on the Bruker WH-400 nmr spectrometer (COSY, NOESY), or a Varian XL-300 spectrometer (HETCOR) using a dual probe or a Bruker AMX-500 nmr spectrometer (HETCOR) employing an inverse detection probe. References were as

indicated above or, in some cases, residual chloroform at δ 7.24 was used for the ^1H reference and a correction factor (x + 0.02 ppm) was applied to the data.

Infrared (ir) spectra were recorded on a Perkin-Elmer 1710 Fourier Transform Spectrophotometer with internal calibration. Abbreviations used are: s, strong; v, very; w, weak.

Low resolution mass spectra (LRMS) were recorded on a Kratos MS80RFA spectrometer. High resolution mass spectra (HRMS) were recorded on a Kratos/AEI MS 50 spectrometer.

Elemental analyses were performed on a CARLO ERBA CHN elemental analyzer, Model 1106, or a Schöniger's Oxygen Flask (analysis of sulfur).

Melting points (uncorrected) were measured on a Fisher-Johns melting point apparatus, unless otherwise noted. Distillation temperatures (uncorrected) are indicated as air-bath temperatures of Kugelrohr distillations, unless otherwise noted.

Gas-liquid chromatography (glc) was performed on either a Hewlett-Packard model 5880A or 5890 capillary gas chromatograph, each having a flame ionization detector and a fused silica column, either ~20 m x 0.21 mm coated with cross-linked SE-54 (former instrument) or ~25 m x 0.20 mm coated with 5% phenyl-methyl silicone (latter instrument).

Thin layer chromatography (tlc) was performed on commercially available aluminum backed silica gel plates (E. Merck, type 5554). Visualization was accomplished using ultraviolet light, a 5% solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v), or a solution of phosphomolybdic acid in ethanol (20%, w/v).

Conventional column and flash[139] chromatography were done on 230-400 mesh silica gel (E. Merck, Silica Gel 60).

Unless otherwise stated, all reactions were performed under an atmosphere of dry argon using dry solvents in flame dried glassware. Liquid reagents or solutions of compounds were added *via* syringe, unless otherwise noted.

Cold temperatures were maintained by use of the following baths: 5-10°C, water/(ice); 0°C, ice/water; -20°C and -48°C, aqueous calcium chloride/CO_2 (27.0 g calcium chloride/ 100 mL water; 46 g calcium chloride/ 100 mL water, respectively); -78°C, acetone/CO_2. Temperatures were measured in degrees Celsius.

Solvents and Reagents

Solvents and reagents were dried and purified using standard procedures.[140]

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. Benzene, dichloromethane and dimethyl sulfoxide were distilled from calcium hydride. Petroleum ether refers to a hydrocarbon mixture with b.p. ~30-45°C (from the distillation of a commercially available mixture with b.p. 30-60°C).

Diisopropylamine, triethylamine, hexamethylphosphoramide, pyridine and acetonitrile were distilled from calcium hydride. Anhydrous hydrazine (explosive in the presence of oxidizing agents) was prepared by refluxing hydrazine hydrate over an equal weight of sodium hydroxide pellets for 2 h and distilling under a flow of

argon.[141] Methanesulfonyl azide (MsN_3, potentially explosive) was prepared from distilled methanesulfonyl chloride (distilled from PCl_5) and sodium azide, according to the Danheiser *et al.*[117a] modification of the procedure of Boyer *et al.*,[117b] and was used without distillation.

A 0.78 M benzene solution of sodium *t*-amyloxide was prepared according to the procedure of Conia[142] and was standardized using aqueous hydrochloric acid in ethanol (phenolphthalein indicator). Solutions of methyllithium in diethyl ether and *n*-butyllithium in hexanes were obtained from Aldrich Chemical Co., Inc. and were standardized using the procedure of Kofron and Baclawski.[143] An ~0.32 M tetrahydrofuran solution of lithium diisopropylamide was prepared by the reaction of diisopropylamine (1.1 equiv) and *n*-butyllithium (1 equiv) in THF at -78°C (~45 min). The solution was not standardized, and was warmed to 0°C immediately prior to use.

Methanol and *t*-amyl alcohol were distilled from magnesium. Diethylene glycol was distilled from sodium.

Oxalyl chloride was distilled before use. Acetyl chloride was distilled from PCl_5. Dimethyl carbonate was dried over 4Å molecular sieves and was distilled before use. Methyl formate was distilled from phosphorus pentoxide. Iodomethane was passed through a short column of flame dried basic alumina before use.

Copper (I) bromide-dimethyl sulfide complex was prepared by the method described by Wuts.[144] Magnesium bromide-etherate was prepared by the reaction of magnesium metal with 1,2-dibromoethane in diethyl ether, followed by the removal of the

diethyl ether under reduced pressure (~0.2 Torr) at room temperature.

5-Chloro-2-trimethylstannyl-1-pentene (**5**) was prepared according to a previously reported modification[10b] of the original procedure.[5] Thus, the reaction mixture was stirred at -78°C for ~6.5-7 hours, instead of at -63°C for 12 hours and no methanol was added during the reaction. The purified product exhibited the expected ^{1}H nmr spectrum.

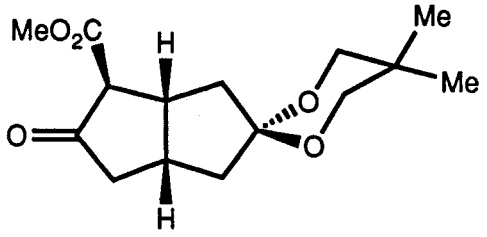
The keto ketal **46** was prepared according to the procedure described by Moss[38,85] except that the purification of the product was modified. Thus, a mixture of the keto ketal **46**, diketal **153** and diketone **43** (glc ratio ~57:28:13, 18.5 g, adsorbed on 36 g of Celite) obtained by the reaction of the diketone **43** with 2,2-dimethyl-1,3-propanediol (**152**), was subjected to flash chromatography on silica gel (400 g, elution with 2:1 diethyl ether-petroleum ether to elute the diketal **153**; elution with 9:1 diethyl ether-ethyl acetate to elute the keto ketal **46**; and elution with ethyl acetate to elute the diketone **43**). The appropriate fractions were combined to yield 7.5 g of the keto ketal **46** as a white solid, m.p. 46.5-47.5°C (lit. m.p. 48°C)[85] which was spectroscopically (^{1}H nmr) identical with the material reported by Moss. The combined recovery of the diketal **153** and the diketone **43** was 8.1 g.

Distilled solvents were deoxygenated by bubbling argon through the stirred solvent for at least 1 h.

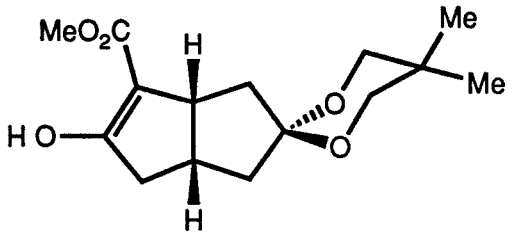
All other reagents were commercially available and were used without further purification.

4.2. Experimental Procedures for the Synthesis of (±)-β-Panasinsene (31) *via* the Weiss-Cook Condensation Approach.

Preparation of the Bicyclic Keto Ester Ketals **163** and **164**.



163



164

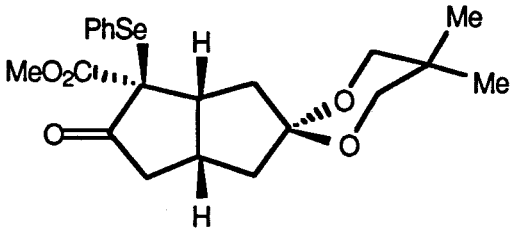
A stirred suspension of potassium hydride (0.945 g, 23.6 mmol, 2.6 equiv, freed from mineral oil by washing with three 5 mL portions of dry THF) in 43 mL of dry THF, under an argon atmosphere, was warmed briefly to ~50°C. The mixture was allowed to cool to room temperature and a solution of the keto ketal **46** (2.002 g, 8.93 mmol) in 2 mL of dry THF was added, with three rinses of dry THF (8 mL total). The mixture was heated at ~60°C for 2 h. To the resultant orange-tan suspension was added quickly dry dimethyl carbonate (2.1 mL, 2.2 g, 25 mmol, 2.8 equiv). After the dark-colored mixture had been heated at ~60°C for a further 1.5 h, it was cooled to 0°C (ice bath). The vigorously stirred reaction mixture was treated with a mixture consisting of 100 mL of saturated aqueous ammonium chloride (pH 5), 100 mL of ice, and 100 mL of chloroform. The aqueous layer was acidified (1 *N* hydrochloric acid) to pH 6-7 and the phases were separated. The

aqueous phase was extracted with two 50 mL portions of chloroform. The combined chloroform extracts were washed with brine, dried (anhydrous sodium sulfate), filtered, and concentrated to give the keto ester **163** and the ester enol tautomer **164** (2.352 g, 93%; ratio ~1.5:1, ^{1}H nmr analysis) as an orange oil* which solidified slowly to an off-white waxy solid. This material was used without further purification in the next reaction.

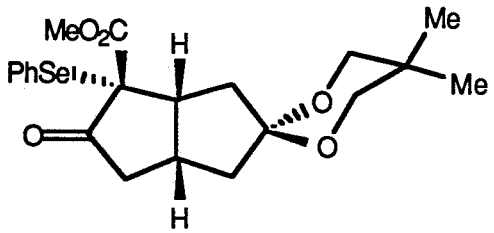
The crude material, which consisted of a mixture of **163** and **164** exhibited ir (neat): 1756 (m), 1729 (s), 1661 (s), 1621 (m), 1281 (s), 1202 (s), 1113 (vs) cm^{-1}; ^{1}H nmr (300 MHz): δ 0.946, 0.952 (s, s, tertiary Me of **163**), 0.93, 0.98 (s, s, tertiary Me of **164**) (combined tertiary Me, 6H), 1.59-1.74 (m, 1H), 1.79-1.86, 2.03 (m, dm (J = 8.0 Hz), 1H total), 2.20-2.42 (m, 3H), 2.54-2.81, 2.86-2.99, 3.12-3.32 (m, m, m, 4H total), 3.43-3.50 (m, 4H, both ketal -C$\underline{H}_2$- groups), 3.73, 3.75 (s, s, 3H total, $CO_2\underline{Me}$, **163** and **164**, respectively), 10.35 (br s, 0.1H, enol O$\underline{H}$); MS *m/z* (% rel. int.): 282 (M^+, 41), 250 (12), 226 (10), 223 (44), 213 (17), 181 (22), 167 (37), 165 (49), 164 (53), 154 (36), 153 (27), 128 (47), 121 (27), 69 (100). *Exact Mass* calcd. for $C_{15}H_{22}O_5$: 282.1467; found: 282.1459.

* In some runs, the oil was deep red. In these cases, the crude product was dissolved in diethyl ether and the resultant solution was filtered rapidly through a short column of silica gel (~3X by weight, elution with diethyl ether).

Preparation of the Keto Ester Selenides **165** and **166**.



165



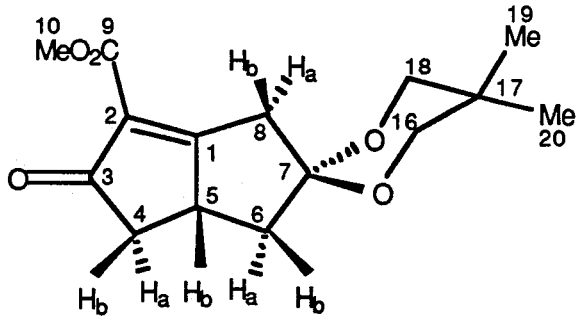
166

To a stirred suspension of potassium hydride (0.455 g, 1.3 mmol, 1.3 equiv, freed from mineral oil by washing with three 3 mL portions of dry THF) in 35 mL of dry THF, under an argon atmosphere, was added, over a period of 10 min, a solution of the mixture of the keto esters **163** and **164** (ratio ~1.5:1, 2.403 g, 8.51 mmol) in 5 mL of dry THF, with two rinses of dry THF (10 mL total). After the mixture had been stirred for 40 min at room temperature, the brown suspension was cooled in an ice bath and a solution of benzeneselenenyl chloride (2.20 g, 11.5 mmol, 1.35 equiv) in 2 mL of dry THF, with several rinses of dry THF (11 mL total), was added quickly. The orange reaction mixture was stirred at 0°C for 20 min and then was pipetted carefully (over a period of 10 min) into a vigorously stirred mixture consisting of ice (15 mL), saturated aqueous sodium bicarbonate (25 mL), and a 1:1 pentane-diethyl ether mixture (50 mL). The organic layer was separated and the aqueous phase was extracted twice with 1:1 pentane-diethyl ether (75 mL total). The combined organic extracts were washed with brine (50 mL), dried (anhydrous sodium sulfate), filtered and concentrated to yield an orange oil (4.098 g, >100%). Unreacted

benzeneselenenyl chloride was separated from the crude product by flash chromatography on silica gel (211 g, elution with 2:1 petroleum ether-ethyl acetate). A normally unseparated mixture (ratio ~4:1, ^{1}H nmr analysis) of the epimeric selenides **165** and **166** (3.185 g, 86%) was obtained as an orange oil. The mixture was used for the next reaction without further purification. An ~5:1 epimeric mixture of the isomers exhibited ir (neat): 1752 (vs), 1730 (vs), 1120 (vs), 744 (w), 692 (w), 669 (w) cm^{-1}; ^{1}H nmr (300 MHz): δ 0.89 (s, 3H, tertiary Me, **165**), 0.92 (s, tertiary Me, **166**), 0.97 (s, 3H, tertiary Me, **165**), 0.99 (s, tertiary Me, **166**), 1.54-1.62 (m, 2H), 1.90-2.03 (m, 2H), 2.23-2.34 (m, 3H), 2.44 (dd, 1H, J = 14.5, 7.0 Hz), 2.83-3.01 (m, 3H), 3.39 (s, 2H, ketal -C$\underline{H}_2$-), 3.45 (s, ~2H, ketal -C$\underline{H}_2$-, partially burying a m, **166**), 3.51 (s, $CO_2\underline{Me}$, **166**), 3.71 (s, 3H, $CO_2\underline{Me}$, **165**), 7.29-7.36 (m, ~3H, aromatic C$\underline{H}$), 7.53-7.57 (m, 2H, aromatic C$\underline{H}$, **165**), 7.63-7.65 (m, aromatic C$\underline{H}$, **166**).

The minor, undesired isomer (**166**), was less polar and small amounts could sometimes be isolated pure using the chromatographic procedure described above (*vide supra*). The minor isomer **166**, exhibited ir (neat): 1751 (vs), 1728 (vs), 1117 (vs), 742 (s), 693 (m) cm^{-1}; ^{1}H nmr (300 MHz): δ 0.92 (s, 3H, tertiary Me), 0.99 (s, 3H, tertiary), 1.90-2.03 (m, 2H), 2.24-2.31 (m, 2H), 2.41 (dd,1H, J = 14.0, 9.0 Hz), 2.60-2.78 (m, 2H), 3.29-3.46 (m, 5H, both ketal -C$\underline{H}_2$- groups and a bridgehead C$\underline{H}$), 3.51 (s, 3H, $CO_2\underline{Me}$), 7.29-7.38 (m, 3H, aromatic C$\underline{H}$), 7.63-7.65 (m, 2H, aromatic C$\underline{H}$). *Exact Mass* calcd. for $C_{21}H_{26}O_5{}^{80}Se$: 438.0946; found: 438.0940.

Preparation of the Enone Ester **159**.

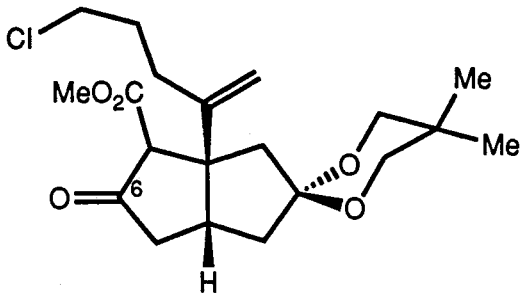


159

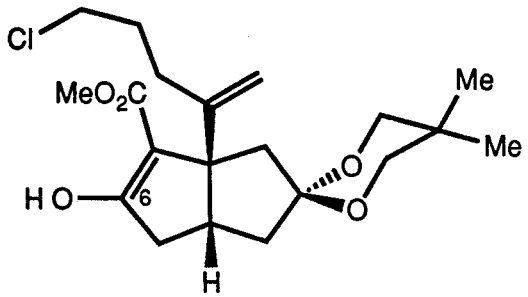
To a cold (0°C) stirred solution of the mixture of keto ester selenides **165** and **166** (ratio ~5:1, 2.437 g, 5.57 mmol) in 20 mL of distilled dichloromethane was added, over a period of 7 min, an aqueous hydrogen peroxide solution (2.4 mL of a 15% solution, 11.7 mmol, 2.1 equiv). After the mixture had been stirred for 10 min at 0°C and for ~20 min at room temperature, 10 mL of water was added and the phases were separated. The dichloromethane layer was washed with water (10 mL). Then each aqueous phase was extracted with dichloromethane (two 2 mL portions). All the dichloromethane layers were combined, dried (anhydrous sodium sulfate), filtered and concentrated to yield a yellow-orange oil containing a solid. The crude product was diluted with diethyl ether (6 mL) and the mixture was filtered through Celite (elution with diethyl ether) to remove any benzeneselenenic acid. The eluate was concentrated to yield the enone ester **159** (1.589 g, >100%, due to small amounts of impurities, including some aromatic products) as an orange oil which was not further purified. The crude product exhibited ir (neat): 1750 (vs), 1719 (vs), 1653 (w), 1274 (m), 1149

(w), 1112 (s) cm^{-1}; ^1H nmr (300 MHz): δ 0.94 (s, 3H, tertiary Me), 1.09 (s, 3H, tertiary Me), 1.48 (t, 1H, J = 12.5 Hz, H-6a), 2.25 (dd, 1H, J = 18.0, 4.0 Hz, H-4a), 2.70 (ddd, 1H, J = 12.5, 8.0, 1.0 Hz, H-6b), 2.79 (dd, 1H, J = 18.0, 6.5 Hz, H-4b), 3.14-3.26 (m, 1H, H-5b), 3.30 (br s, 2H, H-8a and H-8b), 3.45-3.60 (m, 4H, both ketal -$C\underline{H_2}$- groups), 3.85 (s, 3H, $CO_2\underline{Me}$). Some minor signals due to impurities were also present. In ^1H nmr decoupling experiments (400 MHz), irradiation of the signal at δ 1.48 (H-6b) simplified the ddd at 2.70 (H-6a) to a br d (J = 8.0 Hz); irradiation of the signal at δ 2.25 (H-4a) simplified the dd at 2.79 (H-4b) to a br d (J = 6.5 Hz); and irradiation of the multiplet at δ 3.14-3.26 (H-5b) simplified the t at 1.48 (H-6b) to a d (J = 12.5 Hz), the dd at 2.25 (H-4a) to a d (J = 18.0 Hz), the ddd at 2.70 (H-6a) to a br d (J = 12.5 Hz), and the dd at 2.79 (H-4b) to a d (J = 18.0 Hz); MS *m/z* (% rel. int.): 280 (M^+, 36), 248 (13), 194 (12), 180 (21), 163 (40), 162 (26), 135 (23), 134 (27), 121 (20), 69 (100). *Exact Mass* calcd. for $C_{15}H_{20}O_5$: 280.1311; found: 280.1311.

Preparation of the Keto/Enol Ester Chlorides **169/170.**



169



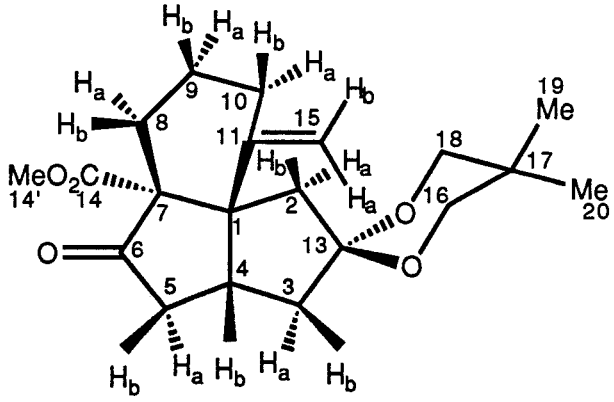
170

To a cold (-78°C) stirred solution of 5-chloro-2-trimethylstannyl-1-pentene **5** (2.585 g, 9.67 mmol, 1.37 equiv) in 60 mL of dry THF, under an argon atmosphere, was added a solution of methyl-lithium in diethyl ether (1.55 M, 7.20 mL, 11.2 mmol, 1.59 equiv). After the solution had been stirred for 20 min at -78°C, anhydrous magnesium bromide etherate (2.886 g, 11.2 mmol, 1.59 equiv) was added in one portion. The white suspension was stirred for 20 min at -78°C and then copper bromide-dimethyl sulfide complex (0.366 g, 1.78 mmol, 0.25 equiv) was added in one portion. The pale yellow suspension was stirred for 20 min at -78°C and then a solution of the ester enone **159** (1.98 g, 7.04 mmol) in 3 mL of dry THF, with three rinses of dry THF (9 mL total), was added over 5 min. The orange suspension was stirred for 25 min at -78°C, and then was treated with saturated aqueous ammonium chloride solution (pH ~6, 90 mL) and diethyl ether (90 mL). The cooling bath was removed and after the mixture had been stirred for 10 min at room temperature, the phases were separated. The aqueous phase was extracted with three 60 mL portions of diethyl ether. The combined organic extracts were washed with brine (90 mL), dried (anhydrous magnesium sulfate), filtered and concentrated to yield a green-brown oil which was quickly filtered through a short silica gel column (4.8 g, elution with diethyl ether). Concentration of the eluate yielded the keto/enol ester chlorides **169/170** (2.568 g, 94%) as a brown oil which was not further purified, but was used directly in the next reaction.

The crude keto/enol ester chlorides **169/170** (which existed mainly as the enol tautomer, **170**) exhibited ir (neat): 1754 (w),

1722 (w), 1657 (vs), 1619 (s), 1258 (s), 1218 (s), 1116 (vs), 806 (w) cm^{-1}; ^1H nmr (300 MHz): δ 0.90 (s, 3H, tertiary Me), 1.02 (s, 3H, tertiary Me), 1.70 (dd, 1H, J = 12.5, 8.5 Hz), 1.88-2.04 (m, 2H), 2.07-2.43 (m, 6H), 2.51 (dd, 1H, J = 14.5, 1.5 Hz), 2.74 (dd, 1H, J = 18.0, 8.0 Hz), 3.42-3.62 (m, 6H, -C$\underline{H}_2$Cl and both ketal -C$\underline{H}_2$- groups), 3.74 (s, 3H, $CO_2\underline{Me}$), 4.74 (s, 1H, C=C$\underline{H}_2$), 4.82 (s, 1H, C=C$\underline{H}_2$), 10.79 (br s, 1H, enol O$\underline{H}$). Some minor signals due to impurities were also present. MS *m/z* (% rel. int.): 384 (M^+, 3), 352 (7), 324 (3), 317 (4), 307 (5), 281 (5), 266 (11), 249 (11), 203 (18), 161 (15), 154 (17), 141 (16), 135 (16), 129 (32), 128 (100), 121 (17). *Exact Mass* calcd. for $C_{20}H_{29}O_5{}^{35}Cl$: 384.1704; found: 384.1704.

Preparation of the Tricyclic Keto Ester Ketal **171**.



171

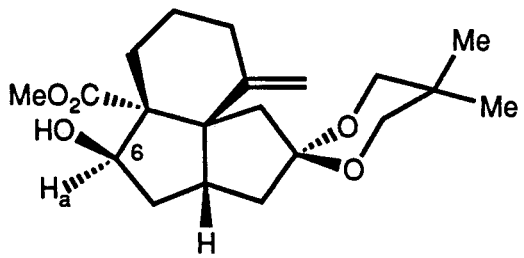
To a stirred solution of the keto/enol ester chlorides **169**/**170** (1.351 g, 3.51 mmol) in 21 mL of freshly distilled acetonitrile, under an argon atmosphere, was added, in one portion, cesium carbonate (5.685 g, 17.4 mmol, 5.0 equiv). The suspension was

heated at 58-61°C for 20 h. The color changed from dark red-orange to light brown by the end of the reaction. After the mixture had been cooled to room temperature, cold water (45 mL) and diethyl ether (40 mL) were added. The deep red aqueous layer was separated, was extracted with diethyl ether (40 mL), was acidified to pH ~8 with hydrochloric acid (1 *N*, ~20 mL) and then was extracted with three 40 mL portions of diethyl ether. The combined ethereal extracts were washed with brine (two 50 mL portions), dried (anhydrous magnesium sulfate), filtered and concentrated to yield the crude tricyclic keto ester ketal **171** (1.133 g, 93%) as a red-brown oily solid. The crude product (dissolved in 4:1 petroleum ether-ethyl acetate (~8 mL) and dichloromethane (1.5 mL)) was purified by flash chromatography on silica gel (135 g, elution with 4:1 petroleum ether-ethyl acetate). Concentration of the appropriate fractions yielded colorless crystals (0.846 g, 69%) of 97% purity (GLC analysis) which were then recrystallized (three crops) from hot ethyl acetate and cold petroleum ether (initial ratio ~1:3, additional petroleum ether added twice at 15 min intervals in portions ~double the ethyl acetate volume) to yield colorless crystals (0.787 g, 64.3%). The crystalline material thus obtained exhibited m.p. 127.5-128.5°C; ir (KBr): 3088 (vw), 1745 (vs), 1723 (vs), 1637 (w), 1115 (vs), 921 (m), 893 (w) cm^{-1}; ^1H nmr (300 MHz): δ 0.91 (s, 3H, Me-19 or Me-20), 1.01 (s, 3H, Me-20 or Me-19), 1.54-1.71 (m, 2H, H-8a or H-8b and H-9b or H-9a), 1.72-1.80 (m, 1H, H-9a or H-9b), 1.88 (d, 1H, J = 16.0 Hz, H-2a), 1.96 (distorted dd, 1H, J = 14.0, 6.0 Hz, H-3a), 2.10 (distorted d, 1H, J = 14.0 Hz, H-3b), 2.15-2.21 (m, 1H, H-8b or H-8a), 2.26-2.39 (m, 2H, H-10a and H-10b),

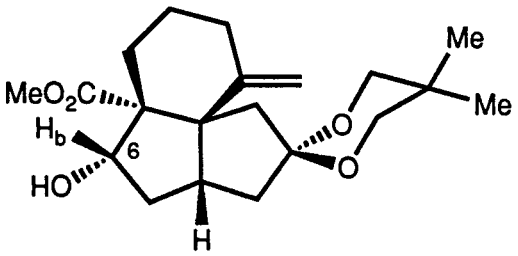
2.54 (distorted dd, 1H, J = 19.5, 9.0 Hz, H-5a or H-5b), 2.69 (distorted dd, 1H, J = 19.5, 9.0 Hz, H-5b or H-5a), 2.76-2.84 (m, 1H, H-4b), 2.95 (br d, 1H, J = 16.0 Hz, H-2b), 3.40-3.57 (m, 4H, 2H-16 and 2H-18), 3.74 (s, 3H, Me-14'), 5.01 (d, 1H, J = 1.0 Hz, H-15b), 5.07 (s, 1H, H-15a); ^{13}C nmr (75 MHz): δ 22.23 ($\underline{C}H_3$-19 or $\underline{C}H_3$-20), 22.32 ($\underline{C}H_3$-20 or $\underline{C}H_3$-19), 23.8 ($\underline{C}H_2$-9), 30.0 ($\underline{C}$-17), 30.6 ($\underline{C}H_2$-8), 32.4 ($\underline{C}H_2$-10), 38.65 ($\underline{C}$H-4), 38.74 ($\underline{C}H_2$-3), 39.9 ($\underline{C}H_2$-5), 42.8 ($\underline{C}H_2$-2), 52.1 ($\underline{C}H_3$-14'), 58.2 ($\underline{C}$-1 or $\underline{C}$-7), 68.0 ($\underline{C}$-7 or $\underline{C}$-1), 71.8 ($\underline{C}H_2$-16 or $\underline{C}H_2$-18), 72.4 ($\underline{C}H_2$-18 or $\underline{C}H_2$-16), 109.0 ($\underline{C}$-13), 112.7 ($\underline{C}H_2$-15), 145.1 ($\underline{C}$-11), 170.5 ($\underline{C}$-14), 211.8 ($\underline{C}$-6); MS *m/z* (% rel. int.): 348 (M^+, 14), 317 (4), 289 (4), 280 (15), 279 (59), 247 (8), 231 (9), 203 (11), 193 (26), 165 (22), 161 (25), 155 (22), 129 (61), 128 (100), 105 (40). *Exact Mass* calcd. for $C_{20}H_{28}O_5$: 348.1936; found: 348.1929. *Anal.* calcd. for $C_{20}H_{28}O_5$: C 68.94, H 8.10; found: C 69.01, H 8.15.

For the HETCOR and COSY data, see Tables 1 and 2, pp. 78 and 81, respectively.

Preparation of the Alcohol Ester Ketals **177** and **178**.



177

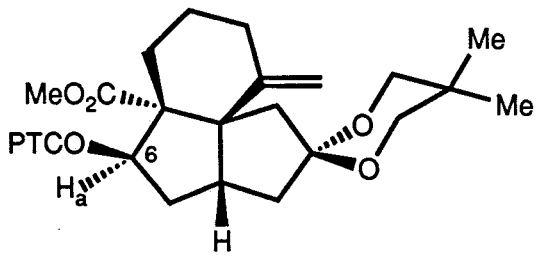


178

To a stirred solution of the keto ester ketal **171** (152.5 mg, 0.438 mmol) in 8.8 mL of reagent grade methanol, under an argon atmosphere, was added cerium trichloride hexahydrate (82.1 mg, 0.232 mmol, 0.53 equiv). When the solution became homogeneous (~1 min), it was cooled to -48°C and stirred for 4 min. Solid sodium borohydride (21.2 mg, 0.560 mmol, 1.3 molar equiv) was added in one portion to the now white suspension. The mixture bubbled vigorously and then cleared somewhat. After the mixture had been stirred for 1 h at ~-48°C, the cooling bath was removed and, 2 min later, ~1 *N* hydrochloric acid (370 μL, 0.37 mmol, ~1.2 equiv) was added, followed 1 min later by 10 mL of cold water and 10 mL of pentane. The mixture was stirred at 0°C for 5 min, then a further 10 mL of pentane was added and the phases were separated. The aqueous phase was extracted three times with pentane. The combined pentane extracts were concentrated to yield a mixture of a white solid and an oil, which was dissolved in pentane (~30 mL). The solution was dried (anhydrous magnesium sulfate), filtered and concentrated to yield the epimeric alcohols **177** and **178** (150.9 mg, 98%; ratio 5.5:1, ^{1}H nmr analysis) as a white solid. The alcohols could be recrystallized from an ~1:2 mixture of ethyl acetate-hexane to yield colorless needles which exhibited m.p. 105-107°C (ratio of epimers ~8:1, ^{1}H nmr analysis). A 12:1 mixture of epimers (^{1}H nmr analysis) exhibited m.p. 105-106.5°C. The ratio of epimers in the unrecrystallized mixture varied from ~4.5:1 to ~12:1 (^{1}H nmr analysis) depending on the scale of the reaction and slight changes in reaction conditions.

A 12:1 mixture of alcohols **177** and **178** exhibited ir (KBr): 3511 (s), 3087 (w), 1726 (vs), 1636 (m), 1240 (s), 1193 (s), 1124 (vs), 1101 (vs), 886 (s) cm^{-1}; ^1H nmr (400 MHz): δ 0.90 (s, ~3H, tertiary Me), 0.99 (s, ~3H, tertiary Me), 1.47-1.63 (m, 2H), 1.66-1.74 (m, 2H, includes 1.70 (d, J = 16.0 Hz)), 1.79 (dd, 1H, J = 13.5, 7.5 Hz), 1.87-2.00 (m, 3H), 2.14 (d, 1H, J = 13.5 Hz), 2.20-2.31 (m, 1H), 2.35-2.42 (m, 2H, includes 2.35 (d, J = 2.0 Hz, O<u>H</u> of **177**, exchanged with D_2O)), 2.45-2.51 (m, 1H), 2.65 (d, 1H, J = 16.0 Hz), 3.42-3.54 (m, 4H, both ketal -C<u>H</u>$_2$- groups), 3.68 (s, ~3H, CO_2<u>Me</u>), 4.69 (td, 1H, J = 9.0, 2.0 Hz, H-6a, simplified to a t (J = 9.0 Hz) upon D_2O exchange), 4.85 (d, 1H, J = 1.0 Hz, C=C<u>H</u>$_2$), 4.88 (br s, ~1H, C=C<u>H</u>$_2$, both epimers). Signals due to the minor epimer, **178**, appeared at: 0.92 (s, tertiary Me),0.98 (s, tertiary Me), 4.11-4.14 (m, H-6b, simplified upon D_2O exchange), 5.00 (br s, C=C<u>H</u>$_2$); MS *m/z* (% rel. int.) 350 (M^+, 17), 280 (5), 279 (7), 264 (10), 194 (15), 187 (26), 161 (16), 145 (18), 135 (22), 129 (70), 128 (100), 107 (16), 105 (24). *Exact Mass* calcd. for $C_{20}H_{30}O_5$: 350.2093; found: 350.2087. *Anal.* calcd. for $C_{20}H_{30}O_5$: C 68.85, H 8.63; found: C 68.64, H 8.64.

<u>Preparation of the Phenyl Thionocarbonate **179**.</u>

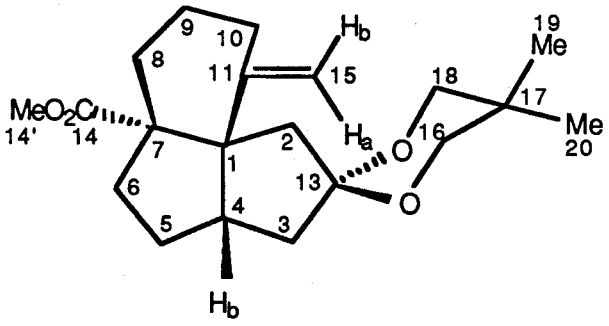


179

To a stirred solution of the mixture of the alcohols **178** and **179** (ratio ~5:1, 295.8 mg, 0.844 mmol) in 7.7 mL of dry, freshly distilled acetonitrile, under an argon atmosphere, was added 4-(*N,N*-dimethylamino)pyridine (DMAP, 830.5 mg, 6.80 mmol, 8 equiv). The solution was cooled to ~10°C (cold water bath) and phenoxythiocarbonyl chloride (180 μL, 225 mg, 1.27 mmol, 1.5 equiv) was added. Within 1 min a precipitate formed and, after a period of 8 min, the cooling bath was removed and the mixture was heated at 67-72°C for 20 h. The reaction mixture was cooled and the solvent was removed under reduced pressure to yield a tan solid. This material was suspended in water (25 mL) and the resultant mixture was extracted with ethyl acetate (50 mL, then three 25 mL portions). The combined ethyl acetate extracts were washed, successively, with 1 *N* hydrochloric acid (30 mL, 20 mL, rapidly), water (30 mL), saturated aqueous sodium bicarbonate (30 mL) and brine (two 30 mL portions). The organic phase was dried (anhydrous sodium sulfate) and concentrated to yield the crude phenyl thionocarbonate **179** as an oil (463.4 mg, > 100% due to the presence of impurities). The crude product was dissolved in a minimum volume of dichloromethane and purified by flash chromatography on silica gel (84 g, elution with 9:1 petroleum ether-ethyl acetate). The appropriate fractions were combined and concentrated to yield the pure phenyl thionocarbonate **179** (310.7 mg, 76%) as one epimer. The purified product thus obtained could be recrystallized from a minimum volume of hot ethyl acetate and cold petroleum ether to give colorless plates which exhibited m.p. 151-152.5°C; ir (KBr): 3091 (w), 3066 (w), 1736 (s), 1639 (w) 1594 (w),

1395 (m), 1296 (vs), 1236 (vs), 1169 (s), 1124 (s), 1106 (s), 888 (m), 774 (m), 690 (m) cm^{-1}; ^1H nmr (300 MHz): δ 0.95 (s, 3H, tertiary Me), 0.97 (s, 3H, tertiary Me), 1.69-1.74 (m, 3H), 1.82-1.88 (m, 2H), 1.95-2.06 (m, 2H), 2.12 (d, 1H, J = 13.5 Hz), 2.24-2.55 (m, 3H), 2.60-2.68 (m, 2H), 3.40-3.49 (m, 2H, ketal -C$\underline{H}_2$-), 3.53 (br s, 2H, ketal -C$\underline{H}_2$-), 3.70 (s, 3H, $CO_2\underline{Me}$), 4.93 (br s, 2H, C=C$\underline{H}_2$), 6.08 (t, 1H, J = 8.5 Hz, H-6a), 7.09-7.12 (m, 2H, aromatic C$\underline{H}$), 7.25-7.30 (m, 1H, aromatic C$\underline{H}$), 7.38-7.43 (m, 2H, aromatic C$\underline{H}$); MS *m/z* (% rel. int.): 486 (M^+, 0.9), 333 (25), 273 (11), 247 (28), 187 (53), 159 (22), 145 (29), 129 (43), 128 (100), 117 (11), 105 (10). *Exact Mass* calcd. for $C_{27}H_{34}O_6S$: 486.2076; found: 486.2082. *Anal.* calcd. for $C_{27}H_{34}O_6S$: C 66.66, H 7.06, S 6.59; found: C 66.56, H 7.10, S 6.54.

Preparation of the Ester Ketal **181.**



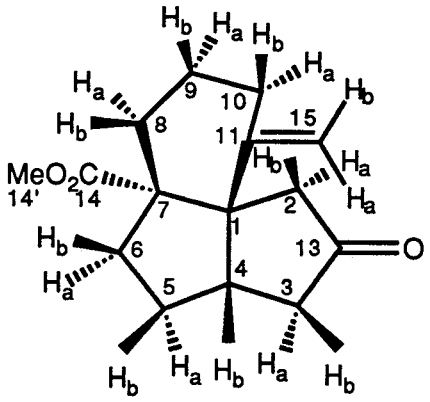
181

To a stirred solution of the phenyl thionocarbonate **179** (117.0 mg, 0.240 mmol) in 2.4 mL of dry, degassed benzene, under an argon atmosphere, was added tri-*n*-butyltin hydride (160 µL, 173 mg, 0.595 mmol, 2.5 equiv) and recrystallized 2,2'-azobisisobutyro-

nitrile (AIBN, 5.9 mg, 43 μmol, 0.18 equiv). After argon had been passed over the surface of the reaction mixture for 10 min, the solution was heated at 75-79°C for 20 h. The reaction mixture was cooled and the solvent was removed under reduced pressure to yield an oil which was purified by flash chromatography on silica gel (44 g, elution with 10:1 petroleum ether-ethyl acetate). The appropriate fractions were combined and concentrated to yield the slightly impure ester ketal **181** (74.4 mg, 92%). The pure ester ketal **181** (58.0 mg, 72%) was obtained by combining and concentrating the appropriate fractions after further flash chromatography on silica gel (17.9 g, elution with 10:1 petroleum ether-ethyl acetate; 5.5 g, elution with 15:1 petroleum ether-ethyl acetate). The product could be recrystallized from hot hexane to give colorless plates, which exhibited m.p. 87.5-89.5°C; ir (KBr): 1719 (vs), 1638 (w), 1203 (m), 1179 (s), 1163 (s), 1116 (s), 892 (m) cm^{-1}; ^1H nmr (300 MHz): δ 0.95 (s, 3H, tertiary Me), 0.97 (s, 3H, tertiary Me), 1.53-1.73 (m, 5H), 1.78 (d, 1H, J = 15.5 Hz), 1.82-2.09 (m, 4H), 2.23-2.40 (m, 3H), 2.50-2.58 (m, 1H), 2.68 (d, 1H, J = 15.5 Hz), 3.41-3.52 (m, 4H, both ketal -C$\underline{H}_2$- groups), 3.63 (s, 3H, $CO_2\underline{Me}$), 4.87 (s, 1H, C=C$\underline{H}_2$), 4.92 (s, 1H, C=C$\underline{H}_2$); ^{13}C nmr (75 MHz): δ 22.3 ($\underline{C}H_3$-19 or $\underline{C}H_3$-20), 22.4 ($\underline{C}H_3$-20 or $\underline{C}H_3$-19), 23.4 ($\underline{C}H_2$), 26.6 ($\underline{C}H_2$), 29.9 ($\underline{C}$-17), 32.8 ($\underline{C}H_2$), 33.8 ($\underline{C}H_2$), 34.7 ($\underline{C}H_2$), 39.7 ($\underline{C}$), 43.8 ($\underline{C}$), 45.0 ($\underline{C}$H-4), 51.2 ($\underline{C}H_3$-14'), 59.2 ($\underline{C}$-1 or $\underline{C}$-7), 60.0 ($\underline{C}$-7 or $\underline{C}$-1), 71.7 ($\underline{C}H_2$-16 or $\underline{C}H_2$-18), 72.4 ($\underline{C}H_2$-18 or $\underline{C}H_2$-16), 109.8 ($\underline{C}H_2$-15), 110.0 ($\underline{C}$-13), 149.1 ($\underline{C}$-11), 176.3 ($\underline{C}$-14); MS *m/z* (% rel. int.): 334 (M^+, 10), 275 (12), 189 (12), 145 (14), 131 (14), 129 (40), 128 (100), 117 (15), 105 (28). *Exact Mass* calcd. for $C_{20}H_{30}O_4$: 334.2144;

found: 334.2141. *Anal.* calcd. for $C_{20}H_{30}O_4$: C 71.82, H 9.04; found: C 72.11, H 9.19.

Preparation of the Keto Ester **182.**



182

To a stirred solution of the ketal ester **181** (29.5 mg, 88.4 μmol) in 2.5 mL of reagent grade acetone was added 1 *N* hydrochloric acid (44 μL, 44 μmol, 0.5 equiv). The solution was stirred at room temperature for 5.5 h and then was added to 5 mL of water. The aqueous suspension was extracted with four 5 mL portions of diethyl ether. The combined ether phases were washed with water (5 mL), brine (5 mL), dried (anhydrous magnesium sulfate), and concentrated to yield the crude keto ester **182** as a colorless oil (22.4 mg, >100% due to the presence of impurities). The crude product was purified by flash chromatography on silica gel (5.5 g, elution with 3:1 petroleum ether-ethyl acetate) and the appropriate fractions were combined to yield a colorless oil which was distilled (115-120°C/0.3 Torr) to provide the pure keto ester

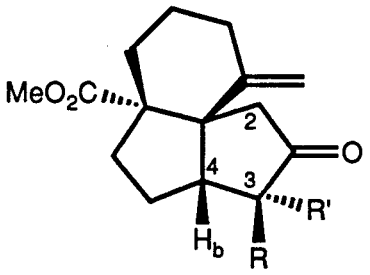
182 (18.6 mg, 84.7%) as a colorless oil. The oil could be recrystallized from pentane to yield colorless needles which exhibited m.p. 43-43.5°C; ir (KBr): 3080 (m), 1729 (vs), 1633 (m), 1236 (vs), 1157 (vs), 903 (s), 890 (m) cm^{-1}; ^1H nmr (300 MHz): δ 1.38-1.50 (m, 1H, H-5a), 1.52-1.65 (m, 1H), 1.67-1.73 (m, 1H), 1.78 (distorted dd, 1H, J = 13.5, 3.5 Hz) overlapped with 1.84 (br tt, 1H, J = 12.5, 3.5 Hz, H-6a or H-6b), 1.98 (dm, 1H, J = 13.5 Hz), 2.08 (dd, 1H, J = 19.0, 1.0 Hz, H-3a), 2.19 (dd, 1H, J = 19.0, 0.5 Hz, H-2a), 2.25-2.42 (m, 5H, H-3b, H-5b, H-6b or H-6a, H-10a and/or H-10b), 2.73 (dd, 1H, J = 19.0, 1.0 Hz, H-2b), 2.84-2.92 (m, 1H, H-4b), 3.64 (s, 3H, Me-14'), 4.65 (s, 1H, H-15a), 4.87 (s, 1H, H-15b). In ^1H nmr decoupling experiments (400 MHz), irradiation of the dd at δ 2.08 (H-3a) sharpened the two dd at 2.19 (H-2a) and 2.73 (H-2b), and simplified the m at 2.25-2.42 (H-3b); irradiation of the dd at δ 2.19 (H-2a) simplified the dd at 2.73 (H-2b) to a br d (J = 1 Hz) and sharpened the dd at 2.08 (H-3a), the m at 2.25-2.42 (H-3b) and the m at 2.84-2.92 (H-4b); irradiation of the dd at δ 2.73 (H-2b) simplified the dd at 2.08 (H-3a) to a d (J = 19 Hz) and the dd at 2.19 (H-2a) to a br s, and sharpened the two multiplets at 2.25-2.42 (H-3b) and 2.84-2.92 (H-4b); and irradiation at δ 2.88 (the center of the m at 2.84-2.92 (H-4b)), simplified the dd at 2.73 (H-2b) to a d (J = 19 Hz), sharpened the m at 2.25-2.42 (H-3b and H-5b) and simplified the m at 1.38-1.50 (H-5a). ^{13}C nmr (75 MHz): δ 23.6 ($\underline{C}H_2$), 28.5 ($\underline{C}H_2$), 32.4 ($\underline{C}H_2$), 33.5 ($\underline{C}H_2$), 35.1 ($\underline{C}H_2$), 42.1 ($\underline{C}$H-4), 43.0 ($\underline{C}H_2$), 45.9 ($\underline{C}H_2$), 51.6 ($\underline{C}H_3$-14'), 57.3 ($\underline{C}$-1 or $\underline{C}$-7), 58.0 ($\underline{C}$-7 or $\underline{C}$-1), 109.8 ($\underline{C}H_2$-15), 148.4 ($\underline{C}$-11), 175.7 ($\underline{C}$-14), 219.2 ($\underline{C}$-13); MS *m/z* (% rel. int.): 248 (M^+, 34), 220 (11), 216 (21), 191 (34), 190 (17),

189 (100), 188 (76), 180 (30), 161 (32), 147 (39), 145 (29), 133 (26), 131 (88), 130 (51), 119 (43), 117 (28), 107 (28), 105 (60). *Exact Mass* calcd. for $C_{15}H_{20}O_3$: 248.1412; found: 248.1416. *Anal.* calcd. for $C_{15}H_{20}O_3$: C 72.55, H 8.12; found: C 72.62, H 8.15.

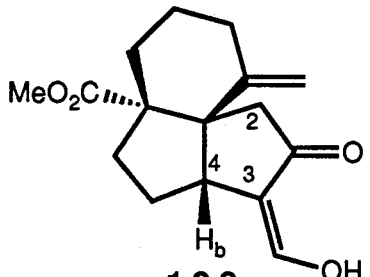
For the COSY data, see Table 3, p. 99.

Preparation of the Diesters **200** and **201.**

a) Preparation of the formylated keto esters **197** and **198**



197a R=CHO, R'=H
197b R=H, R'=CHO

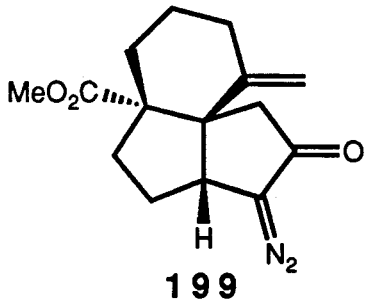


198

To a cold (5-10°C) stirred solution of the keto ester **182** (160.5 mg, 0.646 mmol) in 2.1 mL of dry benzene, under an argon atmosphere, was added, dropwise, a benzene solution of sodium *t*-amyloxide (0.78 M, 3.3 mL, 2.58 mmol, 4 equiv). After a period of 6 min the cooling bath was removed, and the solution was stirred at room temperature for 1.5 h. The mixture was recooled to 5-10°C and freshly distilled methyl formate (330 µL, 311 mg, 5.17 mmol, 8 equiv) was added quickly and the reaction mixture was stirred for a further 17 h at 5°C to rt. The solvent was removed under reduced

pressure to yield a reddish-orange oil which was dissolved in aqueous sodium hydroxide (10 mL of a 0.25 *N* solution). The solution was extracted with 2 portions of dichloromethane. The basic aqueous phase was acidified with 1 *N* hydrochloric acid (~4 mL) and the resultant mixture was extracted with dichloromethane (10 mL, four 5 mL portions). The combined dichloromethane solutions were washed with brine (8 mL), dried (anhydrous magnesium sulfate), and concentrated to yield an isomeric mixture of the formylated keto esters **197** and **198** (185.7 mg, >100% due to the presence of minor impurities; ratio 1:~8.5, ^{1}H nmr analysis) as a yellow oil. The mixture was not purified further, but was used directly in the next reaction. The crude formylated keto esters **197** and **198** exhibited ir (neat): 1725 (vs), 1699 (s), 1609 (s, broad), 1227 (s), 1202 (s), 1157 (vs), 1084 (m), 893 (w), 800 (w) cm^{-1}; ^{1}H nmr (400 MHz): δ 1.48-1.77 (m, 5H), 1.78-1.89 (m, 1H), 1.90-1.95 (m, 1H), 2.23-2.42 (m, 5H), 2.48 (d, 1H, J = 18.5 Hz), 2.77 (d, 1H, J = 18.5 Hz), 3.20-3.23 (m, bridgehead proton), 3.63 (s, 3H, $CO_2\underline{Me}$), 4.64 (distorted d, 1H, J = ~1.5 Hz, C=C$\underline{H}_2$), 4.84 (d, 1H, J = 1.5 Hz, C=C$\underline{H}_2$), 7.08 (s, 1H, C=C$\underline{H}$OH). Signals due to the major aldehyde isomer (**197a**) appeared at δ 1.98-2.04 (m), 3.68 (s, $CO_2\underline{Me}$), 4.49 and 4.78 (d, d, J = ~1.5 Hz, C=C$\underline{H}_2$), 9.52 and 9.83 (s, s, C$\underline{H}$O, **197a** and **197b**, respectively); MS *m/z* (% rel. int.): 276 (M^+, 46), 248 (12), 244 (10), 217 (100), 216 (59), 208 (30), 189 (33), 188 (36), 187 (34), 173 (36), 147 (33), 145 (38), 131 (43), 129 (30), 117 (31), 115 (30), 105 (46). *Exact Mass* calcd. for $C_{16}H_{20}O_4$: 276.1361; found: 276.1363.

b) Preparation of the α-diazoketone **199**.



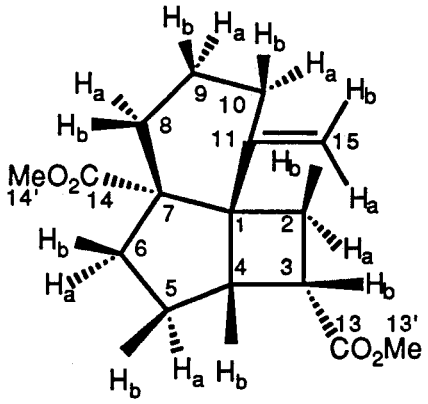
199

To a stirred solution of the crude formylated keto ester mixture **197** and **198** (ratio 1:~8.5, 71.3 mg, 0.258 mmol) in 1.9 mL of dry dichloromethane at 0°C, under an argon atmosphere, was added methanesulfonyl azide* (MsN_3, 29 μL, 40.6 mg, 0.335 mmol). After 3 min, freshly distilled dry triethylamine (54 μL, 39 mg, 0.387 mmol) was added. The reaction mixture was fully protected from light and stirred at 0°C for 4 h. The following experimental manipulations were performed in a dimly lit room. The reaction mixture was treated with 40 drops of water and 40 drops of 6% aqueous potassium hydroxide and then was stirred for 5 min. Distilled dichloromethane (4 mL) was added and the phases were separated. The aqueous phase was extracted with 4 more portions of dichloromethane. The combined organic phases were washed with a small amount of brine, dried (anhydrous magnesium sulfate) and concentrated. The resultant off-white solid and yellow oil were dissolved in a small volume of 1:1 pentane-diethyl ether and the resulting suspension was filtered quickly through a short column of silica gel (0.4 g, elution with 1:1 pentane-diethyl ether). The eluate

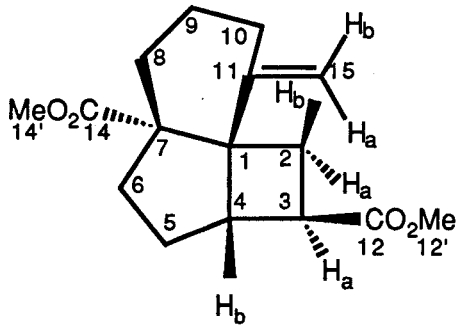
* CAUTION: All sulfonyl azides are potentially explosive.

was concentrated* to yield the α-diazo ketone **199** (44.5 mg, 62%) as a yellow oil which exhibited ir (neat): 2082 (vs), 1727 (s), 1674 (s), 1636 (w), 1352 (m), 1247 (m), 1157 (m), 898 (w) cm^{-1}. This material was not stable and, therefore, was used immediately in the next reaction.

c) Preparation of the diesters **200** and **201**.



200



201

The crude α-diazo ketone **199** was dissolved in 10.4 mL of deoxygenated, distilled methanol (~0.025 M solution, based on 71.3 mg, 0.258 mmol of formylated keto esters **197** and **198**) in a quartz photolysis tube (dimensions: 8 cm X 1.5 cm). After argon had been passed over the solution for 10 min, the vessel was closed with a glass stopper and placed as close as possible to a medium pressure Hanovia mercury lamp (450 watt, Corex filter in a water-cooled quartz jacket). The reaction mixture was photolyzed at 0°C (the

* If all the triethylamine was not removed from the product at this stage, the yield of the diester mixture from the photolysis reaction was reduced due to side reactions.

lamp and reaction vessel were immersed in a cooling bath) for 30 min. In order to follow the progress of the reaction by TLC or ir spectroscopy, the reaction vessel could be opened under a stream of argon and a small aliquot removed. After the solvent had been removed, a mixture of the ring contracted diesters **200** and **201** (36.5 mg, 51%) was obtained as a colorless oil (ratio ~1.6:1, glc analysis). The crude product was purified by flash chromatography on silica gel (5.5 g, elution with 8:1 hexanes-ethyl acetate). The appropriate fractions were combined to yield the less polar major diester epimer **200** (5.6 mg) as a solid and a mixture of the diesters **200** and **201** (23.5 mg) as a colorless oil (29.1 mg total, 40.5%, from the keto ester **182**). The diester **200** could be recrystallized from pentane to yield colorless prisms which exhibited m.p. 39.5-40°C; ir (KBr): 3101 (w), 1728 (vs), 1640 (w), 1439 (s), 1244 (s), 1199 (s), 1156 (s), 883 (m) cm^{-1}; ^1H nmr (400 MHz): δ 1.41-1.52 (m, 2H, H-8a or H-8b and H-9b or H-9a), 1.58-1.65 (m, 2H, H-5a and H-8b or H-8a), 1.78 (dd, 1H, J = 13.0, 8.0 Hz, H-6b), 1.89 (dm, 1H, J = 10.5 Hz, H-9a or H-9b), 1.95-2.07 (m, 2H, H-5b and H-10a or H-10b), 2.26 (dd, 1H, J = 13.5, 10.5 Hz, H-2a), 2.33 (dm, 1H, J = 13.5 Hz, H-10b or H-10a), 2.39-2.44 (m, 1H, H-2b), 2.43-2.50 (m, 1H, H-6a), 2.71 (br td, 1H, J = 9.0, 3.5 Hz, H-4b), 3.18 (dt, 1H, J = 10.5, 9.5 Hz, H-3b), 3.62 (s, 3H, Me-14'), 3.68 (s, 3H, Me-13'), 4.93 (s, 1H, H-15a), 4.96 (s, 1H, H-15b); ^{13}C nmr (75 MHz): δ 23.8 ($\underline{C}H_2$-8), 25.2 ($\underline{C}H_2$-5), 26.6 ($\underline{C}H_2$-2), 32.7 ($\underline{C}H_2$-9 and $\underline{C}H_2$-10), 36.2 ($\underline{C}H$-3), 37.2 ($\underline{C}H_2$-6), 46.8 ($\underline{C}H$-4), 51.37 ($\underline{C}H_3$-13' or $\underline{C}H_3$-14'), 51.40 ($\underline{C}H_3$-14' or $\underline{C}H_3$-13'), 52.4 ($\underline{C}$-1 or $\underline{C}$-7), 57.9 ($\underline{C}$-7 or $\underline{C}$-1), 107.7 ($\underline{C}H_2$-15), 147.9 ($\underline{C}$-11), 174.0 ($\underline{C}$-13 or $\underline{C}$-14), 175.5 ($\underline{C}$-14 or $\underline{C}$-13). In nOe difference nmr

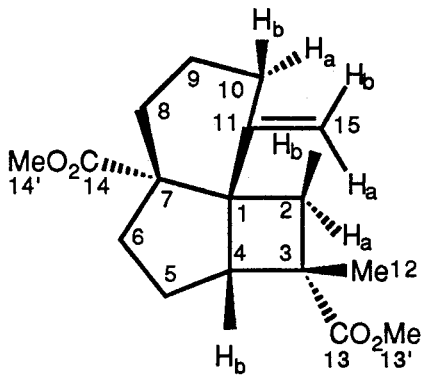
experiments (400 MHz), irradiation at δ 2.71 (H-4b) led to enhancement at 3.18 (H-3b); irradiation at 3.18 (H-3b) led to enhancements at 2.39-2.44 (H-2b), 2.71 (H-4b) and 4.93 (H-15a); irradiation at 4.95 (H-15a/H-15b) led to enhancement at 2.33 (H-10b or H-10a), 2.39-2.44 (H-2b) and 3.18 (H-3b). In ^{1}H nmr decoupling experiments (500 MHz), irradiation of the dt at δ 3.18 (H-3b) simplified the td at 2.71 (H-4b) to a distorted dm (J = 9 Hz), simplified the m at 2.39-2.44 (H-2b) and simplified the dd at 2.26 (H-2a) to a d (J = 13 Hz); irradiation of the td at 2.71 (H-4b) simplified the dt at 3.18 (H-3b) to a dd (J = ~9, ~10 Hz) and simplified the mutiplets at 2.39-2.44 (H-2b) and at 1.95-2.07 (H-5b and another H); and irradiation of the dd at 2.26 (H-2a) simplified the m at 2.39-2.44 (H-2b) and simplified the dt at 3.18 (H-3b) to a distorted t (J = 9 Hz). MS *m/z* (% rel. int.): 278 (M^+, 1.8), 247 (19), 246 (100), 219 (34), 218 (58), 187 (39), 186 (35), 165 (36), 160 (28), 159 (77), 158 (24), 145 (24), 133 (54), 132 (22), 131 (26), 119 (21), 117 (33), 107 (20), 105 (29). *Exact Mass* calcd. for $C_{16}H_{22}O_4$: 278.1518; found: 278.1527.

The ~1.6:1 mixture of epimers **200** and **201** (colorless oil) exhibited ir (neat): 1732 (vs), 1639 (w), 1435 (m), 1241 (m), 1200 (m), 1180 (m), 1157 (m), 889 (w) cm^{-1}; ^{1}H nmr (400 MHz): δ 1.40-1.65 (m, ~4H), 1.69 and 1.78 (dd, dd, 1H total, J = 13.5, 7.0 Hz; J = 13.0, 8.0 Hz, **201** and **200**, respectively), the latter dd overlapped with 1.81-2.08 (m, 2H), which overlapped with 2.06-2.16 (m, <1H, **201**), 2.23-2.35 (m, 2H), 2.39-2.53 (m, 2H), 2.71 and 2.77 (td, ddd, 1H total, J = 9.0, 3.5 Hz; J = 14.0, 5.0, 2.5 Hz, **200** and **201**, respectively), 3.18 (dt, <1H, J = 10.5, 9.5 Hz, **200**), 3.62 (s, 3H, Me-

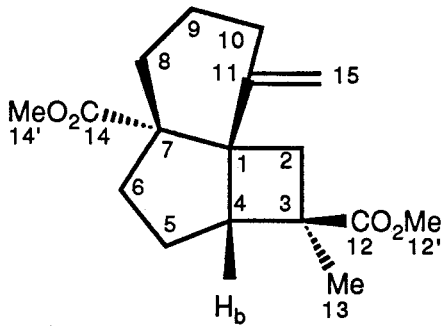
14'), 3.67 and 3.68 (s, s, 3H total, epimeric $CO_2\underline{Me}$, **201** (Me-12') and **200** (Me-13'), respectively), 4.92-4.96 (m, 2H, C=C$\underline{H_2}$). MS *m/z* (% rel. int.): 278 (M^+, 3.2), 247 (23), 246 (100), 219 (27), 218 (39), 187 (44), 186 (48), 165 (26), 160 (25), 159 (63), 145 (21), 133 (53), 131 (24), 119 (22), 117 (27), 107 (22), 105 (29). *Exact Mass* calcd. for $C_{16}H_{22}O_4$: 278.1518; found: 278.1524. *Anal.* calcd. for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 69.30, H 8.03.

For the HETCOR and COSY data, see Tables 4 and 5, pp. 111 and 116, respectively.

Preparation of the Diesters **202** and **203**.



202



203

To a cold (-78°C), stirred solution of lithium diisopropylamide (0.33 M, 630 µL, 208 µmol, 4.0 equiv) in dry THF, under an argon atmosphere, was added (via a cannula) a solution of the mixture of diesters **200** and **201** (ratio 2:1, 14.1 mg, 50.7 µmol) dissolved in

200 μL of dry THF and rinsed in with three portions of dry THF (~300 μL total). After the solution had been stirred at -78°C for 1.5 h, hexamethylphosphoramide* (HMPA, 14 μL, 14.4 mg, 80.5 μmol, 1.6 equiv) was added and the solution was stirred for 12 min. Freshly dried iodomethane (48 μL, 109 mg, 771 μmol, 15 equiv) was then added quickly and the reaction mixture was stirred for a further 30 min at -78°C. The reaction mixture was warmed to ~5°C over a period of 50 min and then was treated with saturated aqueous ammonium chloride and dilute aqueous sodium thiosulfate (just enough to decolorize the solution). The mixture was extracted with diethyl ether (4 portions). The combined ethereal extracts were washed with 2 portions of brine, dried (anhydrous magnesium sulfate) and concentrated. The resultant yellow oil was dissolved in a small amount of diethyl ether and the solution was filtered through a short column of silica gel (~0.4 g, elution with diethyl ether). The colorless eluate was concentrated to yield 12.9 mg (87%) of a mixture of the crude diesters **202** and **203** (12.9 mg, 87%; ratio ~18:1, ^{1}H nmr analysis), which was purified by chromatography on silica gel (0.9 g, elution with 15:1 hexanes-ethyl acetate; repeated 2-3 times until the material obtained consisted only of a mixture of the two diesters **202** and **203**). The appropriate fractions were combined to yield 9.6 mg (65%) of a mixture of the pure diesters **202** and **203** (9.6 mg, 65%; ratio ~18:1, ^{1}H nmr analysis) as a colorless oil. The mixture of diesters **202** and **203** exhibited ir (neat): 1729 (vs), 1642 (w), 1456 (w), 1240 (m),

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* CAUTION: HMPA is known to be a potent carcinogen.

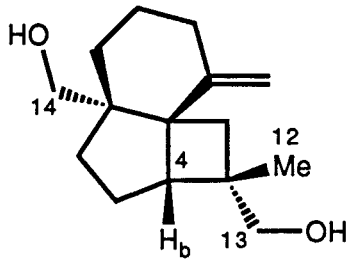
1146 (s), 887 (w) cm^{-1}; ^1H nmr (400 MHz): δ 1.42 (s, 3H, Me-12), 1.46-1.59 (m, 3H), 1.63-1.68 (m, 1H), overlapped with 1.68 (dd, 1H, J = 13.0, 7.5 Hz), 1.85 (dm, 1H, J = 11.0 Hz), 1.95-2.06 (m, 2H, H-10a or H-10b and another H), 2.26 (dd, 1H, J = 14.0, 3.0 Hz, H-2b), 2.28-2.39 (m, 3H, H-4b and 2H), 2.45 (d, 1H, J = 14.0 Hz, H-2a), 3.61 (s, 3H, Me-14'), 3.69 (s, 3H, Me-13'), 4.98 (s, 1H, H-15a), 5.00 (s, 1H, H-15b). Signals due to the minor isomer (**203**) appeared at δ 1.18 (s, Me-13), 3.60 (s, $CO_2\underline{Me}$), 3.66 (s, $CO_2\underline{Me}$), 4.85 (s, C=C$\underline{H}_2$), 4.87 (s, C=C$\underline{H}_2$). In ^1H nmr decoupling experiments (400 MHz), irradiation of the signal at δ 1.85 (dm, 1H, J = 11.0 Hz) led to simplification of the multiplets at 1.46-1.59 (3H) and 2.28-2.39 (H-4b and 2H); irradiation of the m at δ 2.00 (H-10a and H-10b) led to simplification of a d in the signal at 1.46-1.59 (m, 4H), the collapse of the dd at 1.68 to a distorted d (J = 13.0 Hz) and simplification of the m at 2.28-2.39 (H-4b, and 2H); and irradiation of the signal at δ 2.45 (H-2a) simplified the dd at 2.26 (H-2b) to a distorted t (J = 3.0 Hz). In nOe difference experiments (400 MHz), irradiation of the singlet at δ 1.42* ppm (Me-12) led to enhancement of the signals at 1.85, 1.95-2.06 (H-10a and H-10b), 2.26 (H-2b), ~2.35 (H-4b), 3.69 (Me-13'), and 4.98 (H-15a); and irradiation of the signal at δ 4.98 (H-15a) led to enhancement of the signals at 2.26 (H-2b) and 1.42 (Me-12); ^{13}C nmr (75 MHz): δ 24.7 ($\underline{C}H_2$), 25.3 ($\underline{C}H_3$-12), 26.3 ($\underline{C}H_2$), 32.1 ($\underline{C}H_2$), 33.1 ($\underline{C}H_2$), 33.3 ($\underline{C}H_2$), 36.1 ($\underline{C}H_2$), 42.0 (C), 49.9 (C), 51.4 ($\underline{C}H_3$-13', or $\underline{C}H_3$-14'), 51.5 ($\underline{C}H_3$-14', or $\underline{C}H_3$-13'), 53.6 ($\underline{C}$H-4), 58.2 (C), 109.2 ($\underline{C}H_2$-15), 149.8 ($\underline{C}$-11), 175.6 ($\underline{C}$-13 or $\underline{C}$-14), 176.2 ($\underline{C}$-14 or $\underline{C}$-13);

* Unavoidable irradiation of part of the multiplet at 1.46-1.59 also occurred as the signals were too close.

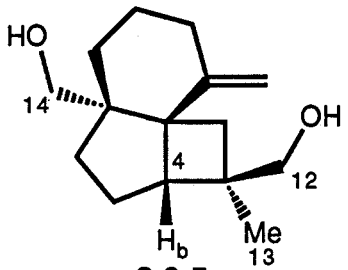
MS *m/z* (% rel. int.): 292 (M^+, 2.4), 261 (25), 260 (100), 233 (22), 232 (42), 201 (34), 200 (55), 173 (87), 172 (30), 145 (51), 133 (47), 131 (45), 117 (36), 107 (32), 105 (52). *Exact Mass* calcd. for $C_{17}H_{24}O_4$: 292.1674; found: 292.1675. *Anal.* calcd. for $C_{17}H_{24}O_4$: C 69.84, H 8.27; found: C 69.58, H 8.51.

For the COSY data, see Table 6, p. 123.

Preparation of the Diols **204** and **205**.



204



205

A solution of a mixture of the diesters **202** and **203** (ratio ~18:1, 41.8 mg, 0.143 mmol) in 400 µL of dry THF was added *via* a cannula (with four 200 µL rinses of THF), over a period of 15 min, to a cold (0°C) stirred solution of lithium aluminum hydride (12.7 mg, 0.335 mmol, ~2 molar equiv) in 800 µL of dry THF, under an argon atmosphere. The cooling bath was removed and the mixture was stirred at room temperature for 1.2 hours. Then sodium sulfate decahydrate was added cautiously to react with the excess lithium aluminum hydride. The mixture was stirred for a few minutes before it was filtered through a short column of Florisil (~0.28 g, elution with THF and small amounts of diethyl ether). The solvent

was removed under reduced pressure to give the crude product (35 mg, >100% due to the presence of impurities) which was purified by flash chromatography on silica gel (6 g, elution with diethyl ether). The sample was loaded on the column by dissolving it in a mixture of acetone (~250 μL) and hot ethyl acetate (~800 μL). The appropriate fractions were combined and concentrated to yield the pure diol **204** (29.9 mg, 88%, major epimer) as a solid.

The diol **204** could be recrystallized from ethyl acetate-pentane to yield colorless needles which exhibited m.p. 139-139.5°C (sealed tube; **204** sublimed at 137°C on a Fisher-Johns melting point apparatus); ir (KBr): 3312 (vs), 1635 (m), 1401 (s), 1039 (s), 1024 (s), 885 (m) cm^{-1}; ^1H nmr (400 MHz, acetone-d_6, external TMS): δ 1.11 (s, 3H, Me-12), 1.24 (tdd, 1H, J = 13.5, 4.5, 1.0 Hz), 1.40 (qt, 1H, J = 13.0, 3.5 Hz), 1.49-1.63 (m, 2H), 1.66 (d, 1H, J = 12.5 Hz), 1.79-2.00 (m, 5H), 2.08 (br td, 1H, J = 13.0, 4.5 Hz, partially buried under the acetone peak), 2.16-2.22 (m, 2H), 3.20 (t, 1H, J = 5.5 Hz, O<u>H</u>, exchanged with D_2O*), 3.23-3.30 (m, 2H, C<u>H</u>$_2$OH, simplified upon D_2O exchange), 3.32 (t, 1H, J = 5.0 Hz, O<u>H</u>, exchanged with D_2O), 3.40 (dd, 1H, J = 10.5, 5.5 Hz, C<u>H</u>$_2$OH, simplified to a d (J = 10.5 Hz) upon D_2O exchange), 3.46 (dd, 1H, J = 10.5, 5.0 Hz, C<u>H</u>$_2$OH, simplified to a d (J = 10.5 Hz) upon D_2O exchange), 4.81 (d, 1H, J = 1.5 Hz, C=C<u>H</u>$_2$), 4.89 (distorted dd, 1H, J = 1.5, 1.5 Hz, C=C<u>H</u>$_2$); ^{13}C nmr (125 MHz, acetone-d_6): δ 25.1, 25.58, 25.62, 30.0 (buried in the acetone Me), 31.0, 34.3, 36.5 (C), 38.1, 51.9 (C), 52.4 (C), 52.6, 63.3 (<u>C</u>H$_2$OH-13 or <u>C</u>H$_2$OH-14), 67.7 (<u>C</u>H$_2$OH-14 or <u>C</u>H$_2$OH-13), 108.6 (<u>C</u>H$_2$-15), 153.7 (<u>C</u>-11); MS *m/z*

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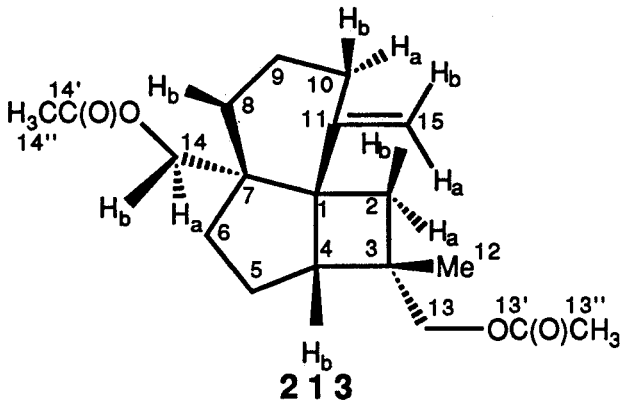
* The addition of D_2O caused the chemical shifts of non-exchanged hydrogens to change.

(% rel. int.): 236 (M^+, 0.4), 218 (4.8), 206 (8.6), 205 (36), 200 (3.2), 187 (60), 147 (78), 146 (52), 145 (46), 133 (45), 131 (40), 109 (42), 105 (69), 91 (100). *Exact Mass* calcd. for $C_{15}H_{24}O_2$: 236.1776; found: 236.1780; *Anal.* calcd. for $C_{15}H_{24}O_2$: C 76.23, H 10.23; found: C 76.25, H 10.24.

A very small amount of the minor (less polar) epimer **205** (an oil), which was isolated from repeated flash chromatography of the combined impure fractions from several reactions using the procedure described above, exhibited ir (neat): 3305 (s), 1635 (m), 1448 (m), 1053 (s), 1030 (s), 1000 (m), 887 (m) cm^{-1}; ^1H nmr (400 MHz, acetone-d_6): δ 0.93 (s, 3H, Me-13), 1.27-1.31 (m, 1H), 1.41 (qt, 1H, J = 13.0, 4.0 Hz), 1.52-1.64 (m, 3H), 1.72 (dd, 1H, J = 13.5, 7.0 Hz), 1.80-2.24 (m, ~7H, includes acetone peak), 3.20 (t, 1H, J = 5.5 Hz, O<u>H</u>, exchanged with D_2O), 3.30-3.49 (m, 5H, simplifies upon D_2O exchange to give four distorted d at 3.26 (br d, J = 11.0 Hz), 3.31 (J = 10.5 Hz), 3.35 (J = 11.0 Hz) and 3.43 (J = 10.5 Hz)), 4.79 (d, 1H, J = 1.5 Hz, C=C<u>H</u>$_2$), 4.87 (distorted dd, 1H, J = 1.5, 1.5 Hz, C=C<u>H</u>$_2$); MS *m/z* (% rel. int.): 236 (M^+, 2.3), 218 (3.6), 206 (13), 205 (69), 200 (1.7), 187 (54), 159 (28), 147 (68), 146 (36), 145 (43), 133 (32), 131 (37), 123 (25), 119 (27), 117 (27), 109 (31), 107 (23), 105 (61), 91 (100). *Exact Mass* calcd. for $C_{15}H_{24}O_2$: 236.1776; found: 236.1777.

Preparation of the Diacetate **213**.



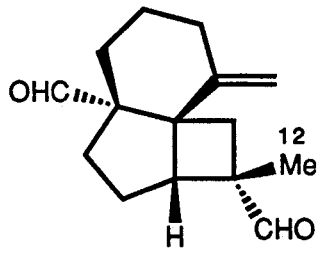
213

To a cold (0°C), stirred solution of the diol **204** (5.3 mg, 22 μmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, ~3 mg, ~25 μmol, ~1.1 equiv) in 800 μL of dry dichloromethane, under an argon atmosphere, was added dry pyridine (16.5 μL, 16.1 mg, 0.20 mmol, 9 equiv) followed 5 min later by freshly distilled acetyl chloride (9.6 μL, 10.6 mg, 0.14 mmol, 6 equiv). The mixture was stirred at 0°C for 3 h and then diethyl ether (8 mL) and 0.15 *N* hydrochloric acid (1.3 mL) were added. The aqueous phase was extracted with two portions of diethyl ether. The combined ethereal phases were washed with water (1.5 mL), saturated sodium bicarbonate (1.5 mL), and brine (two ~1.5 mL portions) and then were dried (anhydrous magnesium sulfate) and concentrated to yield the crude diacetate **213** (7.4 mg, >100% due to small amounts of impurities) as an oil. The crude diacetate **213** was purified by chromatography on silica gel (0.9 g, elution with 1:1 pentane-diethyl ether). The appropriate fractions were combined and concentrated to yield the diacetate **213** (6.1 mg, 85%) as a colorless oil which exhibited ir (neat): 1742 (vs), 1636

(w), 1238 (vs), 1034 (m), 889 (w) cm^{-1}; ^1H nmr (400 MHz): δ 1.15 (s, 3H, Me-12), 1.29-1.39 (m, 1H), 1.43 (br qt, 1H, J = 13.0, 3.5 Hz), 1.54 (dd, 1H, J = 12.5, 7.5 Hz, partially buried under water), 1.62-1.72 (m, 3H), 1.72 (d, 1H, J = 13.0 Hz, H-2a), 1.83 (dt, 1H, J = 7.0, 12.5 Hz), 1.94-2.07 (m, 9H, which includes: 1.94-2.07 (m, 2H; H-10a or H-10b and H-x), 1.98 (dd, 1H, J = 13.0, 3.0 Hz, H-2b), 2.02 (s, 3H, Me-13" or Me-14"), 2.05 (s, 3H, Me-14" or Me-13")), 2.21-2.27 (m, 1H), overlapped with 2.27 (br dd, 1H, J = 9.0, 3.0 Hz), 3.79 (dd, 1H, J = 11.0, 1.0 Hz, H-14a), 3.86 and 3.89 (AB pair of d, 2H, J = 11.0 Hz, 2H-13), 4.03 (d, 1H, J = 11.0 Hz, H-14b), 4.84 (s, 1H, H-15a), 4.96 (s, 1H, H-15b); ^{13}C nmr (125 MHz): δ 20.88, 20.92, 24.56, 24.67, 25.2, 30.3, 30.7, 33.3, 33.7 (C), 37.1, 49.1 (C), 51.3, 51.9 (C), 66.0 ($\underline{C}H_2$-13 or $\underline{C}H_2$-14), 69.1($\underline{C}H_2$-14 or $\underline{C}H_2$-13), 109.4 ($\underline{C}H_2$-15), 150.8 (C-11), 171.2 (C-13' or C-14'), 171.3 (C-14' or C-13'); MS *m/z* (% rel. int.): 320 (M^+, 9.7), 260 (4.8), 247 (4.6), 201 (11), 200 (47), 187 (92), 185 (34), 172 (60), 159 (43), 157 (23), 146 (52), 145 (52), 133 (28), 131 (47), 120 (54), 119 (27), 117 (31), 105 (72), 91 (100). *Exact Mass* calcd. for $C_{19}H_{28}O_4$: 320.1988; found: 320.1994. *Anal.* calcd. for $C_{19}H_{28}O_4$: C 71.22, H 8.81; found: C 71.48, H 8.82.

For the COSY and NOESY data, see Tables 7 and 8, pp. 133 and 134, respectively.

Preparation of the Dialdehyde **217**.

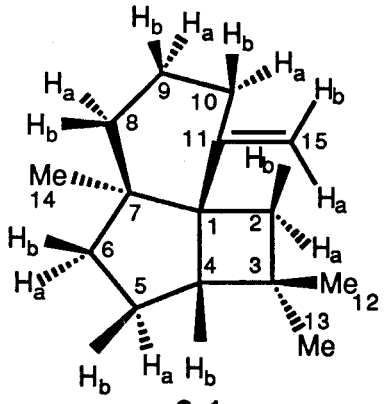


217

To a cold (-78°C), stirred solution of dry dimethyl sulfoxide (DMSO, 54 μL, 0.76 mmol) in 300 μL of dry dichloromethane, under an argon atmosphere, was added freshly distilled oxalyl chloride (34 μL, 49 mg, 0.39 mmol). After the mixture had been stirred for 30 min, a solution of the diol **204** (10.0 mg, 42 μmol) in 40 μL of dry DMSO and 500 μL of dry dichloromethane was added via a cannula and rinsed in with dry dichloromethane (700 μL total). The reaction mixture was stirred for 40 min at -78°C and then dry triethylamine (240 μL, 174 mg, 1.72 mmol) was added and the mixture was warmed to ~0°C over a period of 70 min. Water (~3 mL) was added and the product was extracted with dichloromethane (5 mL, four 3 mL portions). The combined organic phases were dried (anhydrous magnesium sulfate) and concentrated to give a mixture of an oil and a white solid. The crude product was suspended in diethyl ether and the mixture was filtered through a short silica gel column (~0.2 g, elution with diethyl ether) to remove the solid. The eluate was concentrated to yield the dialdehyde **217** (9.6 mg, 98%) as a colorless oil which was not further purified. The dialdehyde **217** thus obtained exhibited ir (neat): 3091 (w), 2723 (w), 1718 (vs),

1638 (w), 1459 (w), 894 (w) cm^{-1}; ^1H nmr (400 MHz): δ 1.26-1.49 (m, 6H, includes 1.36 (s, 3H, Me-12)), 1.71-1.76 (m, 2H), 1.90-2.10 (m, 4H), 2.24 (td, 1H, J = 13.0, 7.5 Hz), 2.34 (dq, 1H, J = 13.0, 2.0 Hz), 2.51 (dd, 1H, J = 8.5, 3.0 Hz), 2.67 (d, 1H, J = 13.5 Hz), 5.01 (s, 1H, C=C$\underline{H}_2$), 5.05 (s, 1H, C=C$\underline{H}_2$), 9.50 (s, 1H, C$\underline{H}$O), 9.65 (s, 1H, C$\underline{H}$O); MS *m/z* (% rel. int.): 232 (M^+, 1.9), 214 (1.4), 204 (13), 203 (23), 175 (23), 147 (34), 145 (23), 135 (25), 134 (25), 133 (62), 131 (28), 119 (32), 117 (24), 107 (28), 105 (56), 91 (100). *Exact Mass* calcd. for $C_{15}H_{20}O_2$: 232.1463; found: 232.1459.

Preparation of (±)-β-Panasinsene (**31**).



31

The crude dialdehyde **217** (9.6 mg, 41 μmol), was dissolved in a mixture of 250 μL of dry diethylene glycol and 150 μL of anhydrous hydrazine (151 mg, 4.73 mmol). Argon was passed over the mixture for ~5 min and then the mixture was heated, under an argon atmosphere, at 133-138°C for 1.5 h. The reaction mixture was cooled to room temperature and then most of the water and excess hydrazine

were removed via distillation (~65°C, ~15 Torr) over a period of 20 min. Crushed potassium hydroxide pellets (48 mg, 0.85 mmol) were added and the mixture was heated under an argon atmosphere at ~190-210°C for 7.5 h. After the reaction mixture had been cooled to room temperature, ~250 μL of water was added and the product was extracted with pentane (~3 mL total). The combined pentane extracts were dried (anhydrous magnesium sulfate) and most of the solvent was removed via distillation at atmospheric pressure. The residue was then filtered through a short column of silica gel (~0.2 g, elution with pentane) to remove polar impurities. Most of the pentane was removed from the eluate by distillation (atmospheric pressure) through a short Vigreux column and the last traces of solvent were removed by a Kugelrohr distillation (heated up to 80°C) to yield crude (±)-β-panasinsene (**31**) (~6.4 mg, ~76%). The product was then distilled (80-90°C, 100 Torr) to yield pure (±)-β-panasinsene (**31**) (3.9 mg, 46%) as a colorless oil. The distilled (±)-β-panasinsene (**31**) exhibited ir (neat): 3088 (w), 1636 (m), 1377 (m), 1365 (w), 1269 (w), 885 (s) cm^{-1}; ^1H nmr (400 MHz): δ 0.75 (s, 3H, Me-14), 0.86 (s, 3H, Me-13), 1.07 (s, 3H, Me-12), 1.27 (dm, 1H, J = 12.5 Hz, H-8a), 1.35-1.41 (m, 2H, H-6b and H-9a or H-9b), 1.46 (d, 1H, J = 12.5 Hz, H-2a), overlapped with 1.42-1.48 (m, 1H, H-8b), 1.57-1.63 (m, 1H, H-9b or H-9a), 1.63-1.68 (m, 1H, H-5a), 1.73 (dd, 1H, J = 12.0, 7.0, H-6a), 1.87-1.97 (m, 1H, H-5b), overlapped with 1.96 (dd, 1H, J = 12.5, 3.0 Hz, H-2b), 2.00 (br td, 1H, J = 12.5, 4.0 Hz, H-10a or H-10b), 2.10 (br dd, 1H, J = 8.5, 3.0 Hz, H-4b), 2.18 (dm, 1H, J = 12.5 Hz, H-10b or H-10a), 4.80 (d, 1H, J = 1.5 Hz, H-15a), 4.91 (dd, 1H, J = 1.5, 1.5 Hz, H-15b); ^{13}C nmr (75 MHz): δ 18.2 ($\underline{C}H_3$-14),

24.72 ($\underline{C}H_2$-5), 24.85 ($\underline{C}H_3$-13), 25.10 ($\underline{C}H_2$-9), 30.53 ($\underline{C}$-7 or $\underline{C}$-3), 30.64 ($\underline{C}H_3$-12), 33.8 ($\underline{C}H_2$-10), 35.7 ($\underline{C}H_2$-2), 36.0 ($\underline{C}H_2$-8), 41.1 ($\underline{C}H_2$-6), 45.6 ($\underline{C}$-3 or $\underline{C}$-7), 52.60 ($\underline{C}$H-4), 52.77 ($\underline{C}$-1), 108.3 ($\underline{C}H_2$-15), 152.3 ($\underline{C}$-11); In nOe difference experiments (400 MHz), irradiation of the signal at δ 0.75 (s, Me-14) led to enhancement of the signal at 1.46 (d, H-2a); irradiation of the signal at 0.86 (s, Me-13) led to enhancement of the signals at 1.46 (d, H-2a), and at 1.63-1.68 (m, H-5a); and irradiation of the signal at 1.07 (s, Me-12) led to enhancement of the signals at 1.96 (dd, H-2b), 2.10 (br dd, H-4b) and at 4.80 (d, H-15a). MS *m/z* (% rel. int.): 204 (M^+, 29), 189 (23), 175 (14), 162 (16), 161 (100), 147 (19), 133 (44), 122 (46), 119 (23), 107 (47), 105 (40), 91 (38). *Exact Mass* calcd. for $C_{15}H_{24}$: 204.1878; found: 204.1875.

For the HETCOR and COSY data, see Tables 10 and 11, pp. 144 and 147, respectively.

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