CARBOCYCLE CONSTRUCTION IN TERPENOID SYNTHESIS. THE TOTAL SYNTHESES OF (±)-SARCODONIN G AND (±)-1-EPI-9-NORPRESILPHIPERFOLAN-9-ONE.

by

MICHAEL W. GILBERT

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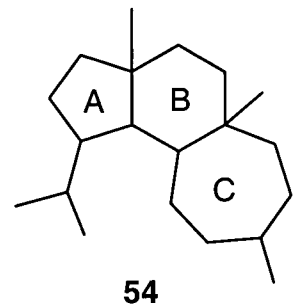
ABSTRACT

Carbocycle construction represents a significant challenge in synthetic studies geared towards terpenoid natural products. A step-wise annulation approach to the construction of the diterpenoid framework of the cyathanes (**54**) was investigated, ultimately leading to the first reported total synthesis of (±)-sarcodonin G (**36**). The sesquiterpenoid carbon skeleton of the presilphiperfolanes (**270**) was assembled *via* a tandem cyclization strategy, affording the known ketone, (±)-1-epi-9-norpresilphiperfolan-9-one (**306**).

The construction of the cyathane 5-6-7 fused tricyclic framework commenced with 3-methyl-2-cyclohexen-1-one **38**, representing the B-ring. The annulation sequences for A and C-rings utilized the bifunctional reagents **39** and **44**, respectively. With the help of these reagents, the 5-6-6 fused tricycle **155** was quickly assembled from **38**. Intermediate **155** was further elaborated, including a key SmI_2-mediated ring expansion, to afford the 5-6-7 fused tricycle **159**, which displays the complete cyathane framework. The target structure, (±)-sarcodonin G (**36**), was obtained in several steps from **159**. In addition, an advanced intermediate in the synthesis of **36** was transformed into substance **269**, a likely synthetic precursor of the corresponding keto triol natural product, (±)-cyathin A_4 (**37**).

Assembly of the presilphiperfolane 5-5-6 fused tricyclic carbon skeleton **270** was approached *via* a tandem cyclization strategy involving free-radical reactions. The key intermediates of this synthetic study, xanthates **367**, were readily prepared from enone **49** in several steps. Bu_3SnH-mediated free-radical reaction of **367** yielded a mixture of

cyclization products, alkenes **368**, whose frameworks include the carbon skeleton of the natural product presilphiperfolan-9-ol (**53**). Alkenes **368** were subjected to oxidative cleavage conditions, affording the known ketone (±)-1-epi-9-norpresilphiperfolan-9-one (**306**).



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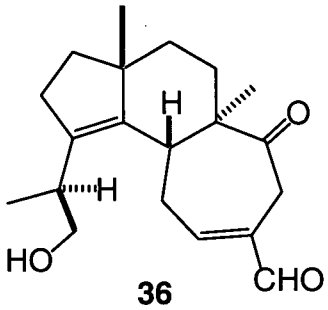

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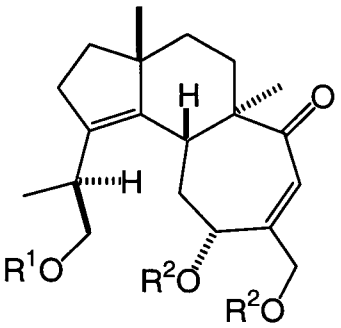
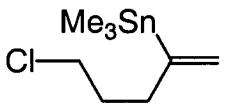


37 R^1, R^2 = H
269 R^1 = PMB, R^2 = PNB



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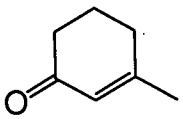

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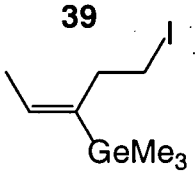

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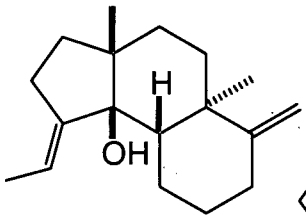

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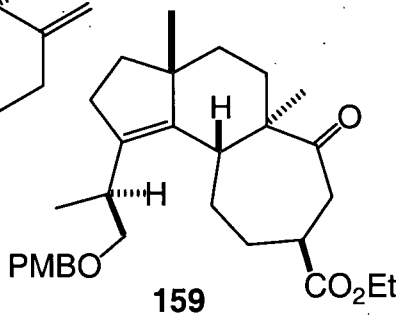

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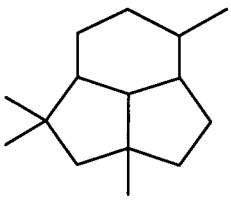

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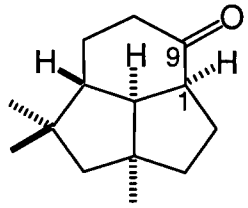

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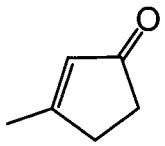

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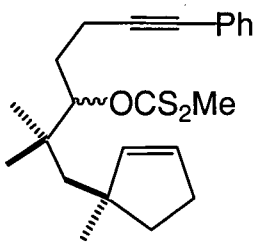

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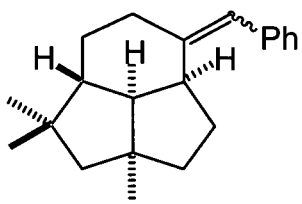

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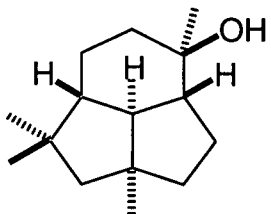

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α	-	below the plane of the ring or 1,2 relative position
Ac	-	acetyl
AIBN	-	azobisisobutyronitrile
anal.	-	analysis
APT	-	attached proton test
ax	-	axial
β	-	above the plane of a ring or 1,3-relative position
9-BBN	-	9-borabicyclo[3.3.0]nonane
Bn	-	benzyl
bp	-	boiling point
br	-	broad
Bu	-	butyl
Bz	-	benzoyl
calcd	-	calculated
cm	-	centimeter
COSY	-	(^{1}H-^{1}H)-homonulcear correlation spectroscopy
18-cr-6	-	18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane)
CSA	-	camphorsulfonic acid
C–x	-	carbon number x
d	-	doublet
δ	-	chemical shift in parts per million from tetramethylsilane
Δ	-	heat
DBN	-	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	-	1,8-diazabicylco[5.4.0]undec-7-ene
DDQ	-	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	-	diethyl azodicarboxylate
DIBALH	-	diisobutylaluminum hydride
DIEA	-	diisopropylethylamine
DMAP	-	4-dimethylaminopyridine
DMSO	-	dimethyl sulfoxide
DNA	-	deoxyribonucleic acid
E	-	entgegen (configuration)
ed.	-	edition
ED., Eds.	-	editor, editiors
ED_{50}	-	effective dose
epi	-	epimeric
eq	-	equatorial
equiv.	-	equivalent(s)
Et	-	ethyl
g	-	gram
glc	-	gas-liquid chromatography
h	-	hour(s)
HMBC	-	(^{1}H-^{13}C) heteronuclear multiple bond coherence
HMPA	-	hexamethylphosphoramide

HMQC	-	(^{1}H-^{13}C) heteronuclear multiple quantum coherence
HPLC	-	high performance liquid chromatography
HRMS	-	high resolution mass spectroscopy
H–x	-	hydrogen number x
Hz	-	hertz
i	-	iso
IC_{50}	-	inhibitory concentration (for 50% of a biological sample)
i-PrDMS	-	*iso*-propyldimethylsilyl
IR	-	infrared
J	-	coupling constant in hertz
KDA	-	potassium diisopropylamide
KHMDS	-	potassium 1,1,1,3,3,3,-hexamethyldisilazide
LAH	-	lithium aluminum hydride
LDA	-	lithium diisopropylamide
LiHMDS	-	lithium 1,1,1,3,3,3-hexamethyldisilazide
m	-	multiplet
m	-	meta
M	-	molar
*m*CPBA	-	*meta*-chloroperoxybenzoic acid
Me	-	methyl
mg	-	milligram(s)
µg	-	microgram(s)
MHz	-	megahertz
min	-	minute(s)
mL	-	milliliter(s)
µL	-	microliter(s)
mm	-	millimeter(s)
µm	-	micrometer(s)
mmol	-	millimole(s)
mol.	-	molecular
mp	-	melting point
Ms	-	methanesulfonyl
n	-	normal
NBS	-	*N*-bromosuccinimide
NIS	-	*N*-iodosuccinimide
NMR	-	nuclear magnetic resonance
NOE	-	nuclear Overhauser enhancement
p	-	page
p	-	para
PCC	-	pyridinium chlorochromate
pH	-	$-\log_{10}[H^+]$
Ph	-	phenyl
PMB	-	*para*-methoxybenzyl
PNB	-	*para*-nitrobenzoyl
PP	-	pyrophosphate
ppm	-	parts per million

PPTS	-	pyridinium *p*-toluenesulfonate
Pr	-	propyl
pyr	-	pyridine
q	-	quartet
R	-	rectus (configuration)
s	-	singlet
S	-	sinister (configuration)
sec	-	secondary
t	-	triplet
t	-	tertiary
TBAF	-	tetrabutylammonium fluoride
TBDPS	-	*tert*-butyldiphenylsilyl
TBS	-	*tert*-butlydimethylsilyl
tert	-	tertiary
Tf	-	trifluoromethanesulfonyl
TFA	-	trifluoroacetic acid
THF	-	tetrahydrofuran
tlc	-	thin layer chromatography
TMS	-	trimethylsilyl
TPAP	-	tertrapropylammonium perruthenate
Ts	-	*para*-toluenesulfonyl
uv	-	ultraviolet
-ve	-	negative
v/v	-	volume to volume ratio
w/v	-	weight to volume ratio
•	-	coordination or complex
±	-	racemic

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Firstly, I would like to thank Dr. Edward Piers, my supervisor and mentor, for continued guidance throughout my stay at UBC. For giving me the opportunity to join his research group and for teaching me the science of organic synthesis, I am forever grateful.

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This thesis is dedicated to my parents, whose support and encouragement continuously fuel my ambitions.

Finally, I wish to thank Sara for being her wonderful self and making everything worthwhile.

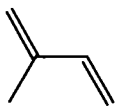
I. INTRODUCTION

1.1. General

As we enter the 21st century, synthetic organic chemistry is at center stage of scientific and technological discovery. Since its conception nearly two centuries ago, this discipline of chemistry has played in increasingly important role in biological and medicinal research. As an example, the ability to synthesize organic compounds represents the foundation of pharmaceutical drug-discovery programs, which have lead to numerous biomedical breakthroughs. The evolution of synthetic chemistry has been possible, in large, because of technological advances in the fields of chemical separation and identification. With a growing library of proven synthetic methods and an upward number of commercially available reagents, synthetic chemistry allows for increasingly short and efficient preparations of target structures.

There are numerous motives that might entice a chemist in choosing to synthesize a target structure from commercially available materials, a study known as total synthesis. The target structures are often naturally occurring compounds or families of structurally related compounds that have limited availability from natural sources. In some cases, these natural compounds have demonstrated potentially important biological activity and total synthesis can provide additional quantities of material for further biological and chemical evaluation. Total synthesis also provides a testing ground for novel methods of bond construction. The limitations of a novel reaction developed in simple models systems are often revealed in complex total syntheses. To be sure, total synthesis represents an exciting yet challenging study through which one can learn the many facets of chemistry.

Terpenoid natural products, which have attracted significant attention from synthetic chemists, display a seemingly unlimited complexity with regard to construction of carbon skeleta, the backbones of the structures. Biosynthetically evolving from 5-carbon building blocks (C_5) generally represented by isoprene (**1**), terpenoids are classified as either mono-(C_{10}), sesqui-(C_{15}), di-(C_{20}), sester-(C_{25}) or triterpenoids (C_{30}). Through isotope-labeling experiments and NMR studies on the resulting metabolites, chemists have uncovered many of nature's strategies for the transformation of simple chains of isoprene units into complex carbocyclic terpenoids. These biosynthetic pathways often involve a combination of enzyme-catalyzed cyclizations, rearrangements and alkyl shifts. The elaborate architecture displayed in structure **2**, representing the carbon skeleta of the recently discovered salvadione triterpenoids,[1] nicely illustrates the complexity of carbocycle construction in terpenoid chemistry. Several of the different tactics employed by synthetic chemists in terpenoid construction, including biomimetic, tandem and step-wise annulation approaches, shall be outlined.



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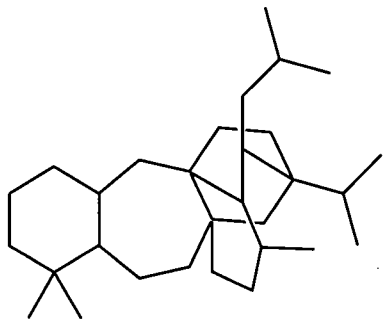
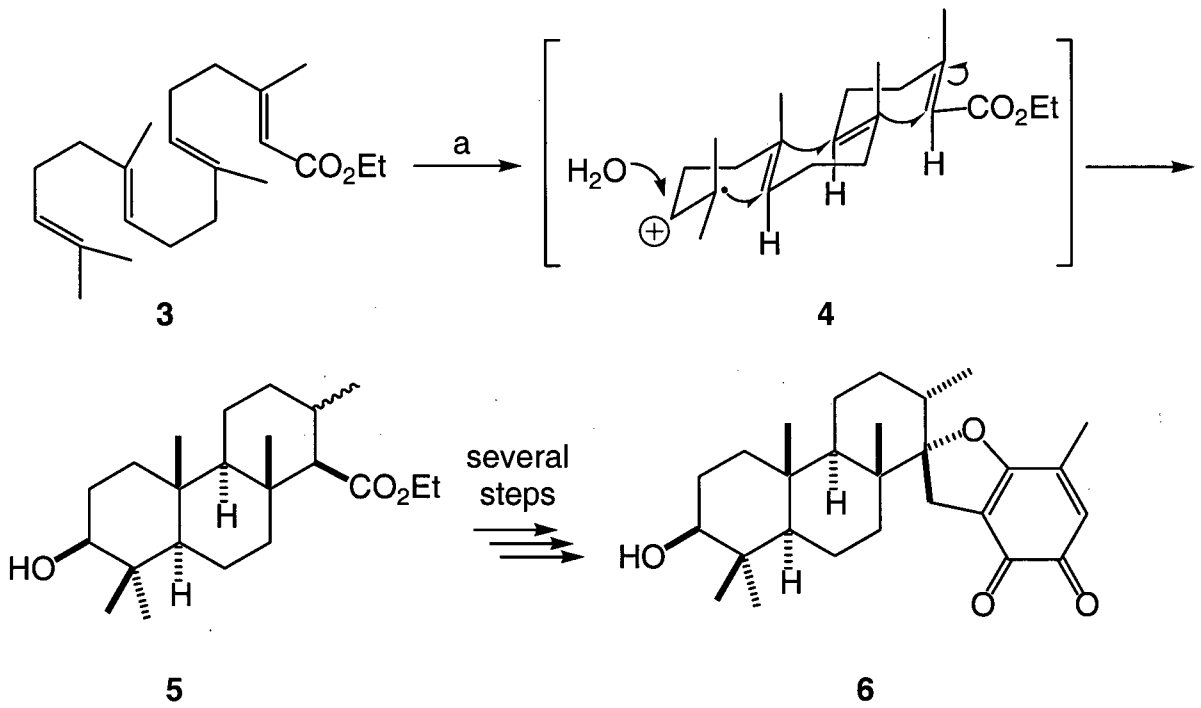


2

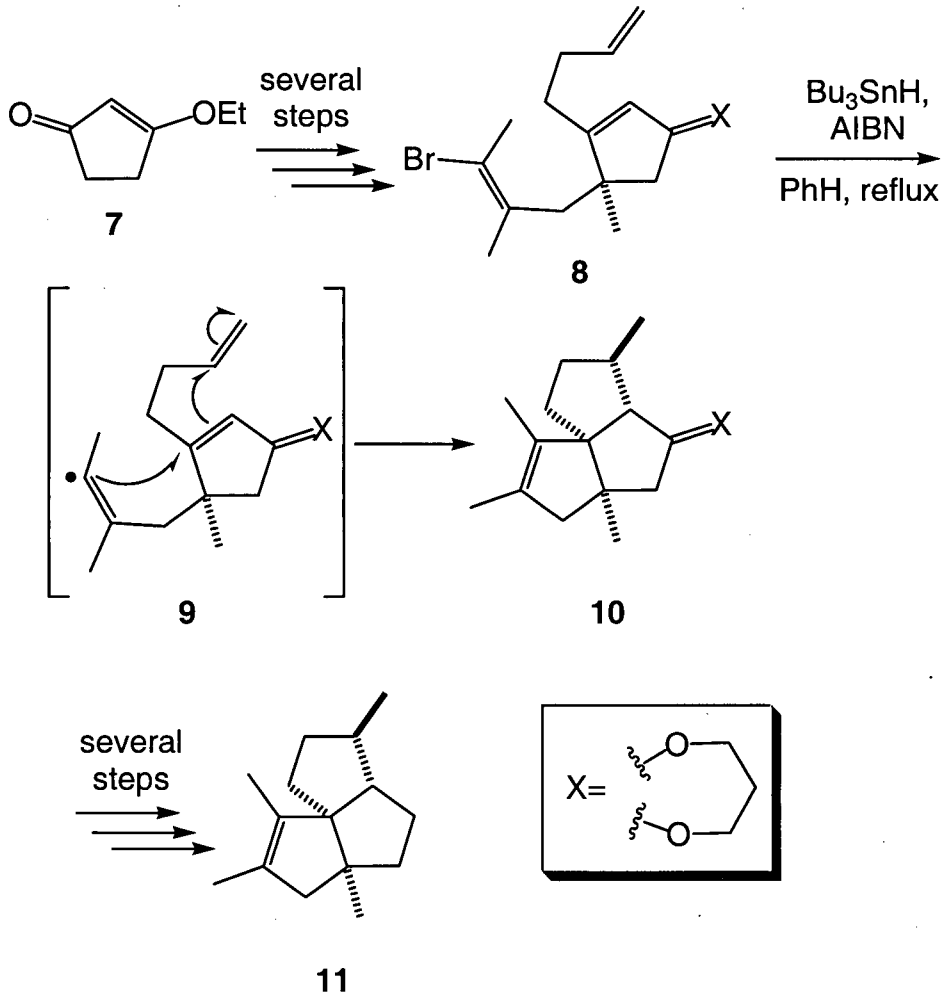
A biomimetic synthetic strategy is one in which the key reactions are based on the proposed biogenesis of the target structure. For example, according to the Stork-Eschenmoser hypothesis,[2,3] certain polyunsaturated molecules with *trans* C=C double bonds should cyclize in a stereospecific manner to furnish polycyclic systems with *trans,anti,trans* stereochemistry at the ring fusions. Recently, Demuth and coworkers reported[4] a biomimetic cascade cyclization of a polyalkene, which led to a total synthesis of (±)-stypoldione (**6**) (Scheme 1). A photo-induced electron transfer (PET) reaction triggered cyclization of polyalkene **3**, yielding a mixture of *trans-anti-trans* 6-6-6 fused tricyclic substances **5**. The natural product, (±)-stypoldione (**6**), was ultimately obtained in 11 steps from **5**.



Reagents: hv, poly(oxy-1,2-ethanediyloxycarbonyl-1,4-phenylenecarbonyl), 1,4-dicyano-2,3,5,6-tetramethylbenzene, biphenyl, MeCN, H_2O.

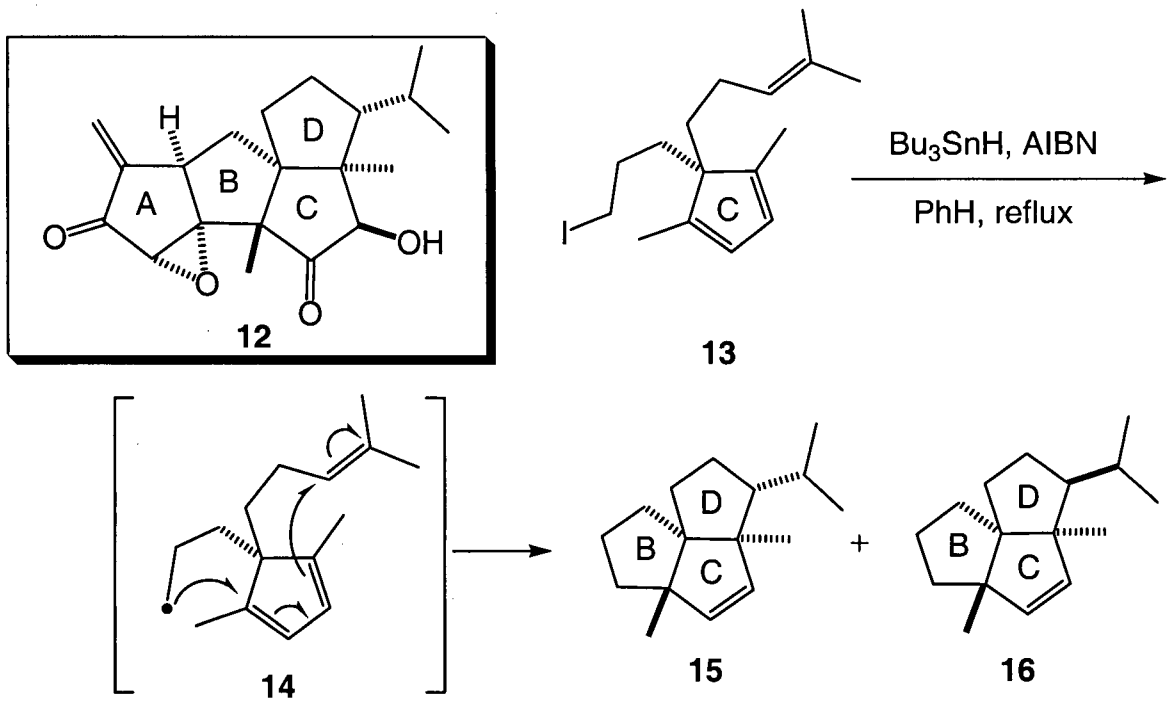
Scheme 1

Many types of reactions, including pericyclic, radical, cationic and anionic processes, have been incorporated in cascade or tandem sequences for the construction of carbocycles.[5] For instance, a radical-based tandem cyclization was employed in the synthesis of triquinane silphiperfolene (**11**), as reported by Curran and coworkers (Scheme 2).[6] The key intermediate of the study, bromide **8**, was prepared in several steps from enone **7**. Treatment of **8** with Bu_3SnH and AIBN gave tricycle **10** *via* the radical intermediate **9**. Transformation of **10** into the target structure **11** was accomplished in few steps.



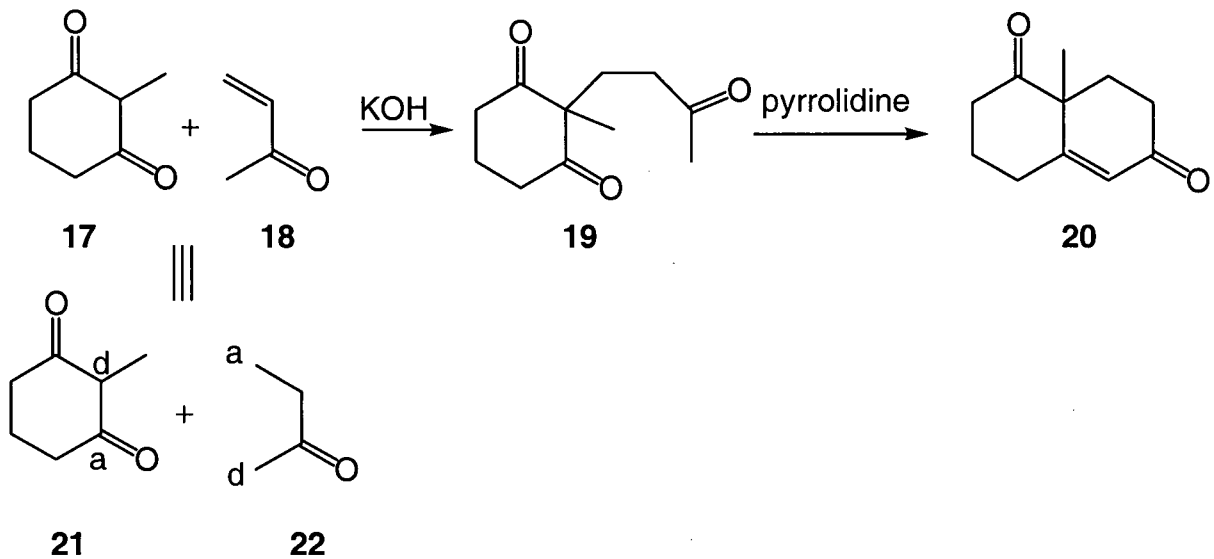
Scheme 2

Although the combination of several bond-forming steps in one tandem sequence certainly appeals, the difficult task of controlling the selectivity in each step must also be considered. As an example, Curran and coworkers reported[7] unexpected stereoselectivity difficulties in their investigation of a tandem cyclization approach to (±)-crinipellin A (**12**) (Scheme 3). In a model study directed towards the synthesis of the B-C-D ring system of **12**, Bu_3SnH-mediated tandem free radical cyclization of iodide **13** afforded a 1:5 mixture of **15** and **16**. Although this remarkable reaction showed the desired *cis* geometry at both ring fusions, the tandem approach was not carried through to the target structure **12**, because the major isomer (**16**) displayed the isopropyl appendage in the unnatural β-configuration.



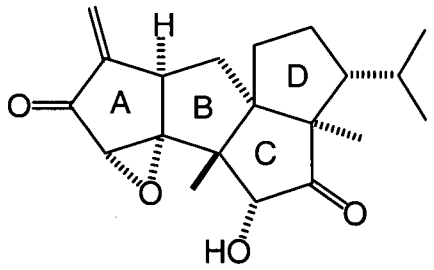
Scheme 3

An attractive approach to the construction of carbocycles involves the use of bifunctional reagents in stepwise annulation sequences.[8] An annulation sequence is a ring-forming process in which two molecular fragments are united with the formation of two new bonds.[9] The reactive sites leading to the newly formed bonds can be described as either acceptor (a) or donor (d) sites.[10] Upon analysis of the potential reactive sites of a substrate, one may envisage the annulation synthon that displays the desired corresponding acceptor or donor reactive sites. This relationship is illustrated in the reported[11] synthesis of the Wieland-Miescher ketone[12] **20** *via* the well-known Robinson annulation[13] (Scheme 4). Under base-mediated conditions, diketone **17** undergoes a Michael addition with methyl vinyl ketone (**18**) to give adduct **19**. Treatment of **19** with pyrrolidine results in an intramolecular aldol condensation, yielding the Wieland-Miescher ketone (**20**). Therefore, methyl vinyl ketone (**18**), the synthetic equivalent of the 2-butanone a^4,d^1-synthon **22**, represents an excellent annulation reagent for diketone **17**, corresponding to donor-acceptor synthon **21**.



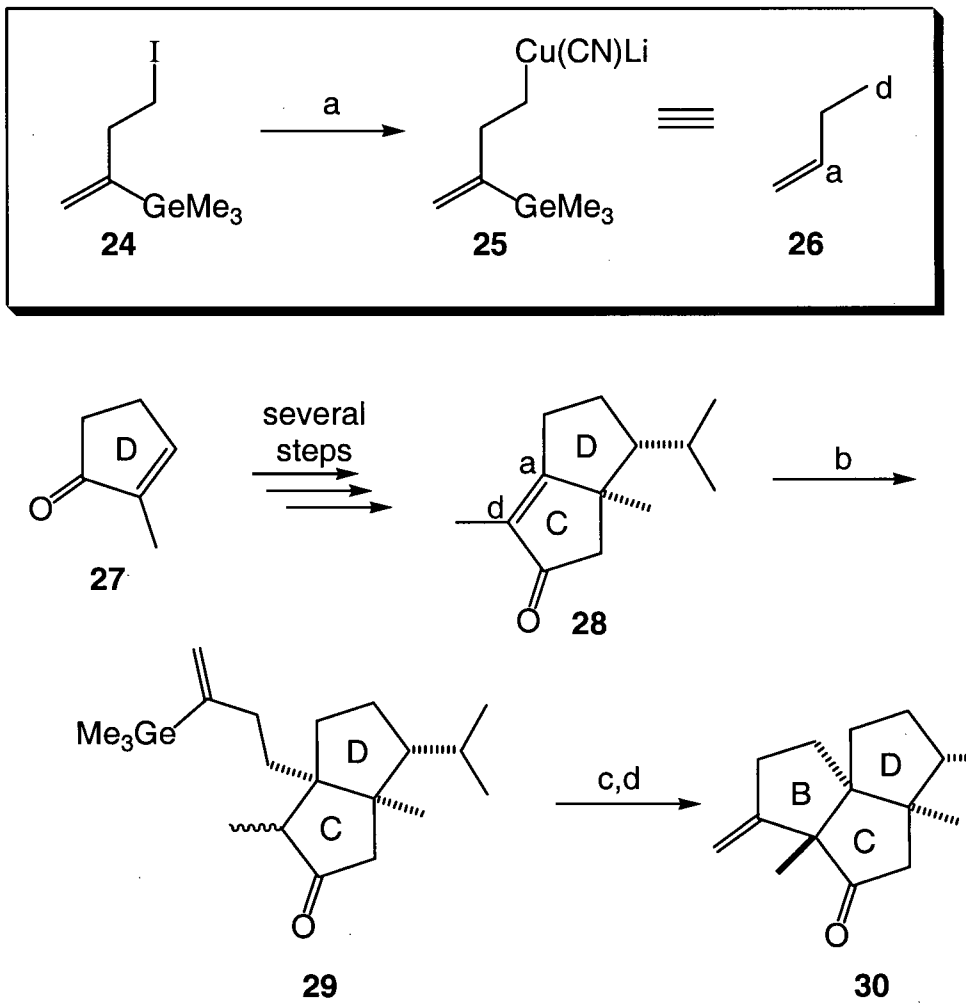
Scheme 4

Recently, one of the areas of study in the Piers group has been the development of novel bifunctional reagents and their application in annulation sequences. For example, the first total synthesis of (±)-crinipellin B (**23**)[14,15] employed novel bifunctional reagents in the annulation sequences leading to the A- and B-rings, as outlined in Schemes 5 and 6.



23

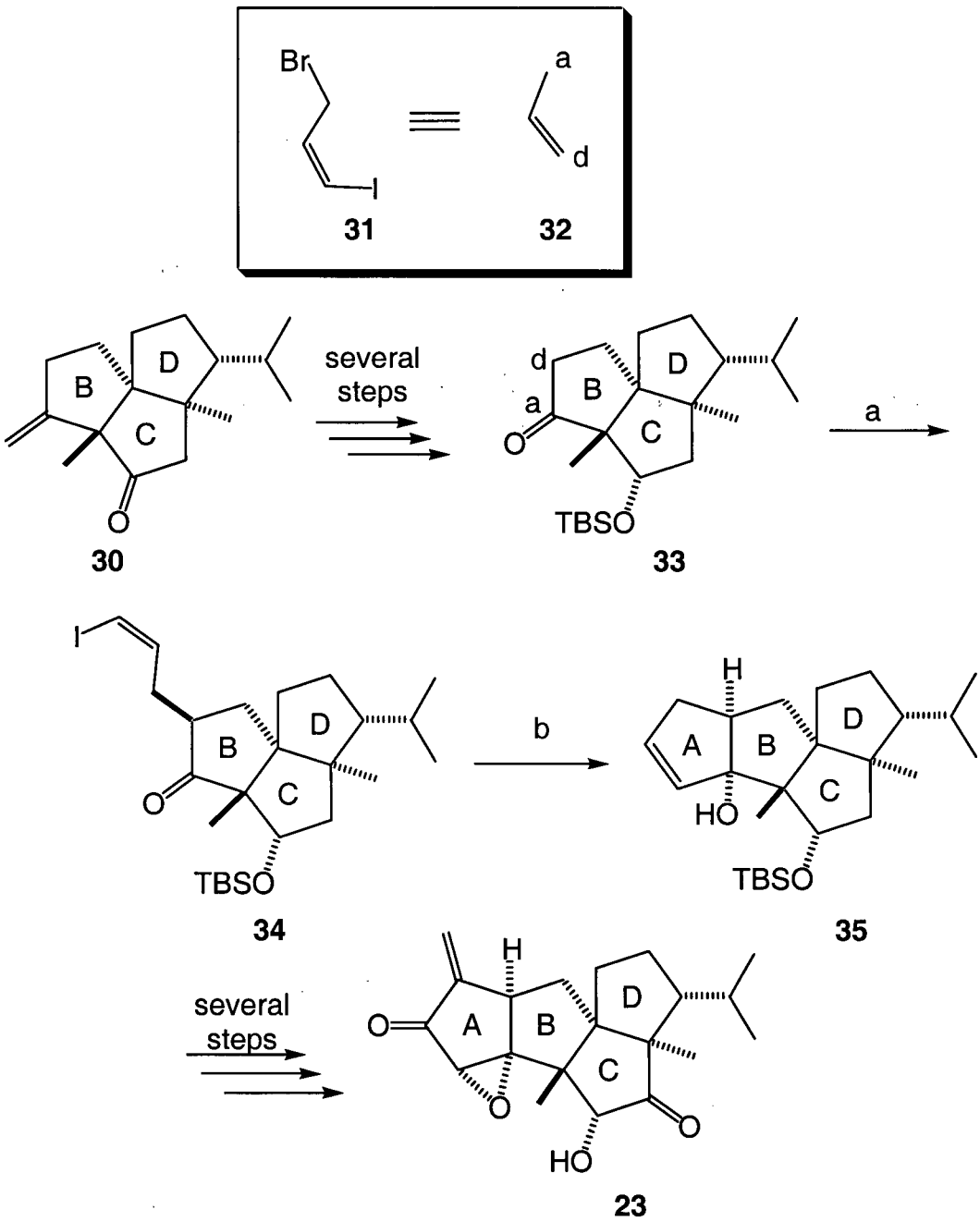
The bifunctional reagent **24**, which is readily transformed into cuprate **25**, the synthetic equivalent of the 1-butene a^2,d^4-synthon **26**, was employed in the preparation of the B-ring (Scheme 5). The synthesis commenced with 2-methyl-2-cyclopentenone (**27**), which was transformed in several steps into the 5,5-fused bicyclic compound **28**, representing the C-D ring system. The annulation sequence began with a conjugate addition of a cuprate **25** to enone **28**, affording adduct **29**. Treatment of **29** with iodine provided the corresponding alkenyl iodide. Slow addition of *t*-BuOK/*t*-BuOH to solution of this alkenyl iodide and $(Ph_3P)_4Pd$ in THF resulted in the triquinane product **30**.



Reagents: a) *t*-BuLi, THF; CuCN; b) **25**, TMSBr, THF; NH_4Cl, NH_4OH, H_2O; c) I_2, CH_2Cl_2; d) $(Ph_3P)_4Pd$, *t*-BuOK, *t*-BuOH-THF.

Scheme 5

The annulation sequence leading to the A-ring employed bifunctional reagent **31**, the synthetic equivalent of the 1-propene a^3,d^1-synthon **32** (scheme 6). The conversion of triquinane **30** into ketone **33** was accomplished in a few steps. Alkylation of the enolate derived from **33** with reagent **31** yielded adduct **34**, as the major product. Treatment of **34** with butyllithium resulted in a cyclization, affording the tetracyclic alcohol **35**. The target structure, (±)-crinipellin B (**23**), was ultimately obtained from **35** in 10 steps.

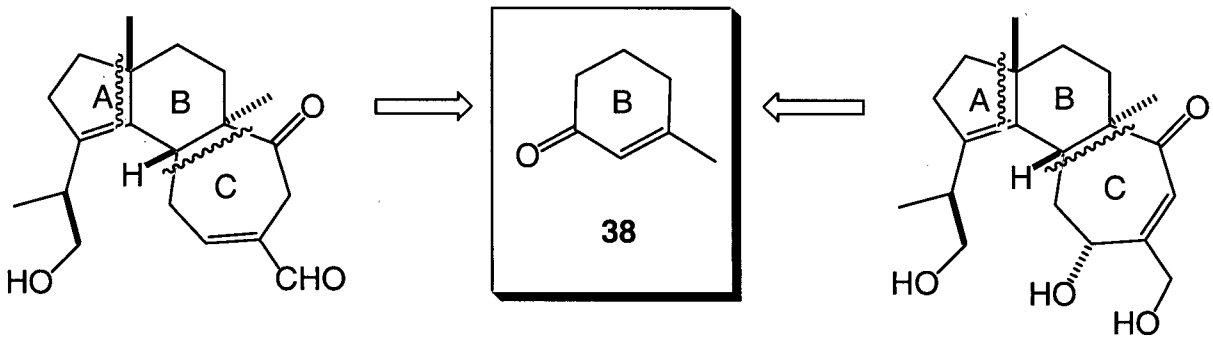


Reagents: a) LDA, THF; **31**; b) BuLi, THF; $NaHCO_3$, H_2O.

Scheme 6

1.2. Proposal

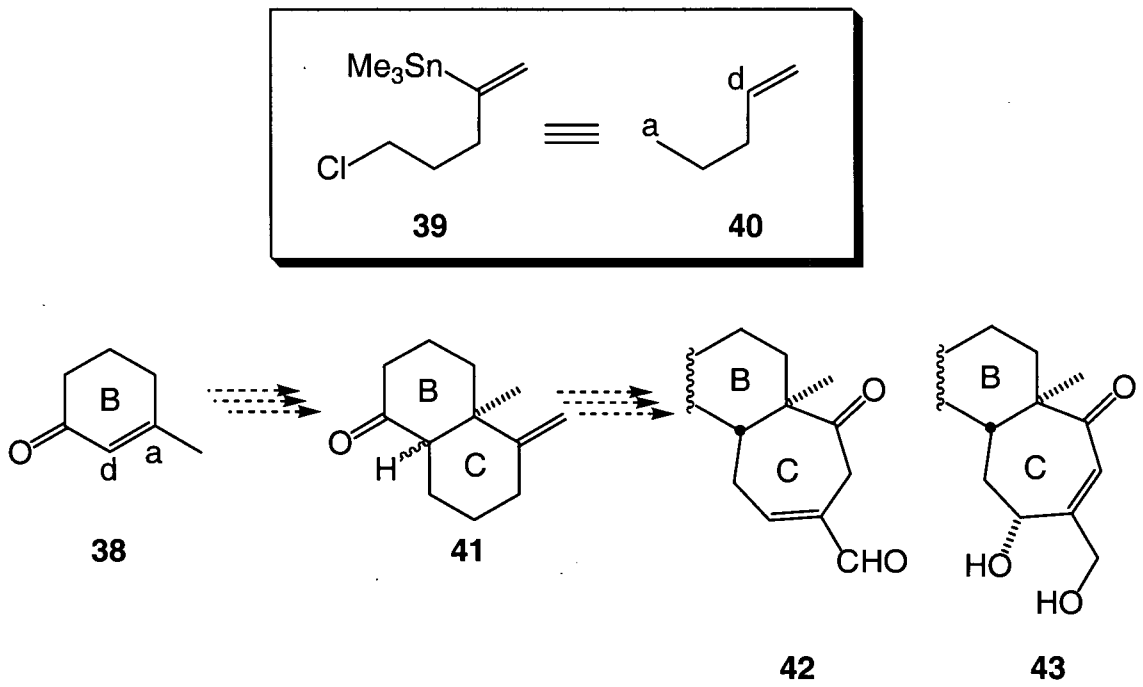
In the first part of the research program described in this thesis, it was planned to employ a sequential annulation strategy to the assembly of 5-6-7 fused ring systems. It was anticipated that the carbon framework of the structurally-related diterpenoids, sarcodonin G (**36**) and cyathin A_4 (**37**),[16,17] would be accessible from commercially available 3-methyl-2-cyclohexen-1-one (**38**), which would ultimately serve as the B-ring of these two natural products (Scheme 7).



36 **37**

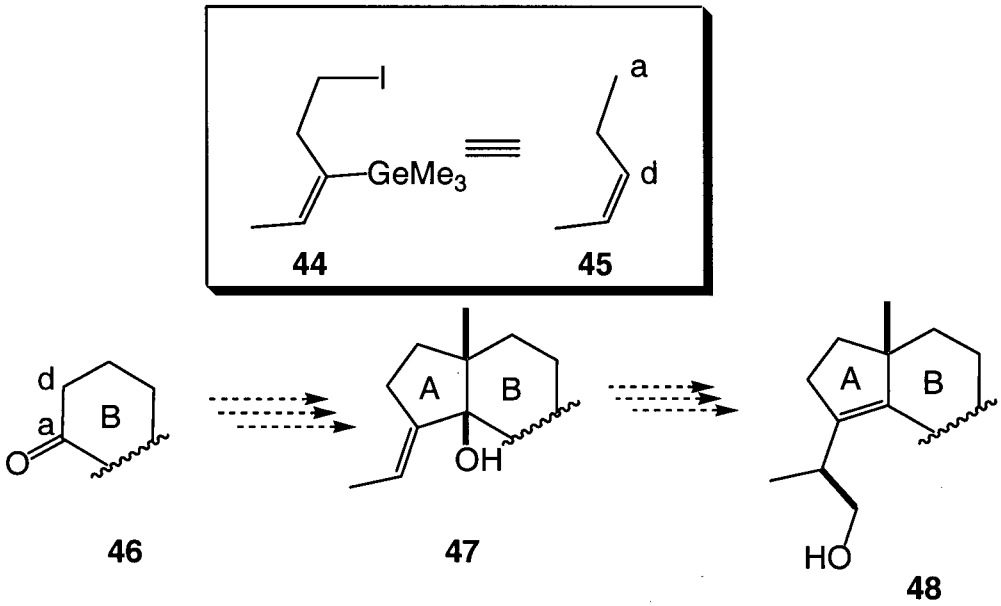
Scheme 7

The annulation sequence leading to construction of the C-ring was anticipated to involve bifunctional reagent **39**, representing the 1-pentene a^5,d^2-synthon **40** (Scheme 8). The preparation of the 6-6 fused bicycles **41**, utilizing enone **38** and reagent **39**, was previously reported by our group.[18] The 6-membered C-ring in **41** was thought to be a suitable precursor to the 7-membered C-rings illustrated in partial structures **42** and **43**, representing sarcodonin G (**36**) and cyathin A_4 (**37**), respectively.



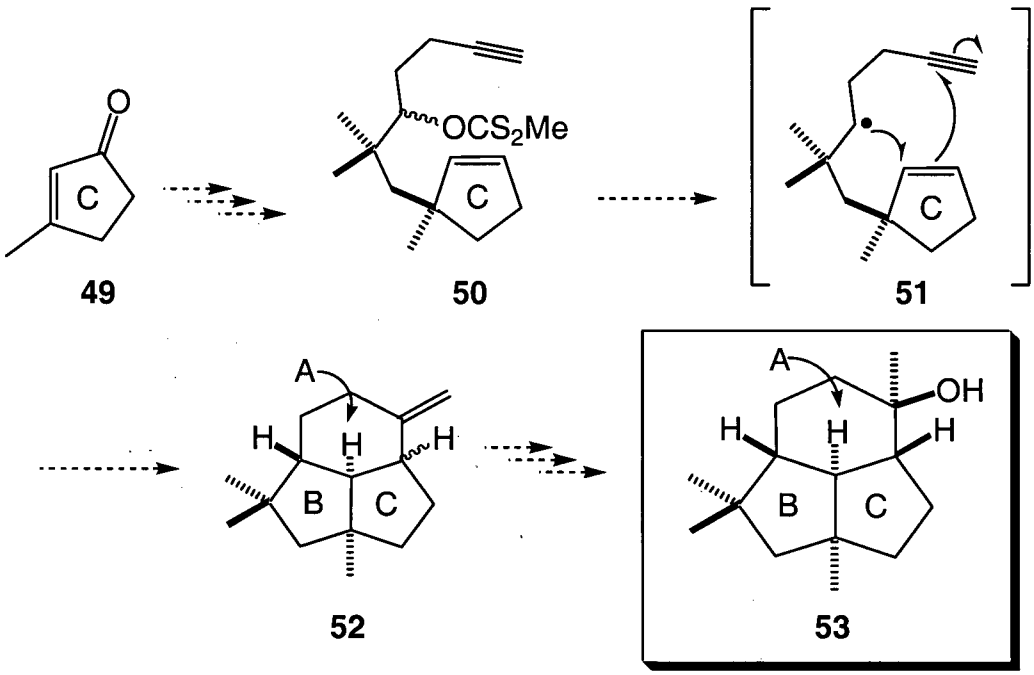
Scheme 8

The A-ring construction was anticipated to result from an annulation sequence employing the (*Z*)-2-pentene a^5,d^3-synthon **45**, which translates to bifunctional reagent **44** (Scheme 9). A representation of the sequence, starting with partial structure **46**, is illustrated. The annulation sequence, which includes a methylation step, was anticipated to give alcohol **47**. Partial structure **48**, representing the A- and B-rings of both target compounds **42** and **43**, was expected to be available from **47** *via* a Still-Mitra rearrangement protocol.[19]



Scheme 9

The second part of the research study described herein revolves around the possible use of a proposed tandem cyclization strategy, envisaged for the construction of the 5-5-6 fused framework of (±)-presilphiperfolan-9-ol (**53**) (Scheme 10).[20] It was hoped that the key cyclization precursors, intermediates **50**, would be available in a few steps from enone **49**, which would become the C-ring of target **53**. Tandem formation of the A- and B-rings was anticipated to involve a radical-mediated cyclization of **50** *via* the intermediate **51**. The β-isomer of the proposed cyclization products **52**, which display a 5-5-6 fused ring system, is a known[20] precursor of (±)-presilphiperfolan-9-ol (**53**).



Scheme 10

II. RESULTS AND DISCUSSION

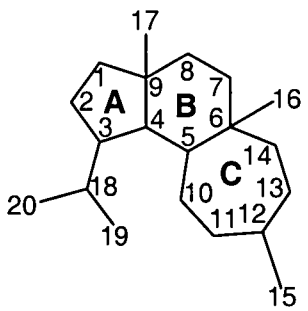
2.1. Studies Towards Cyathane Diterpenoid Synthesis

2.1.1. Background

2.1.1.1. Cyathane History and Biogenesis

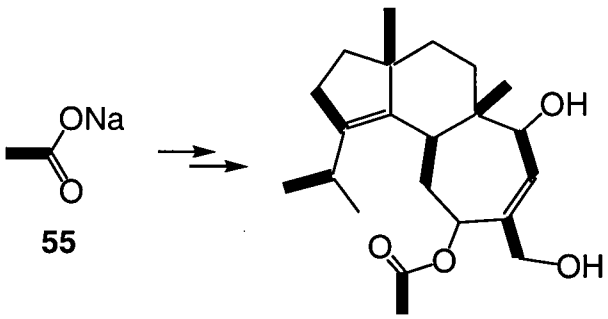
The history of the cyathane family of diterpenoids begins in 1966 with Brodie's discovery[21] of the bird's nest fungus *Cyathus helenae* in the Canadian Rockies. In a chance observation, cultures of *C. helenae* were shown[22] to inhibit the growth of bacteria. Starting in the early 1970s, Ayer and co-workers characterized[23] numerous biologically active cyathane components from several *Cyathus* fungi. To date, over forty different cyathanes have been isolated and characterized.

Using bioassay guided fractionation methods, Ayer and coworkers isolated several C_{20} compounds from the cyathin extracts. Each of these novel diterpenoids was named cyathin and was classified according to its molecular formula. The cyathin name includes a letter that denotes the degree of unsaturation (A for 30 hydrogens, B for 28 hydrogens and C for 26 hydrogens) and a subscript number that indicates the number of oxygen atoms. A trivial numbering scheme was assigned to the novel 5-6-7 fused tricyclic core (**54**) of the cyathanes.



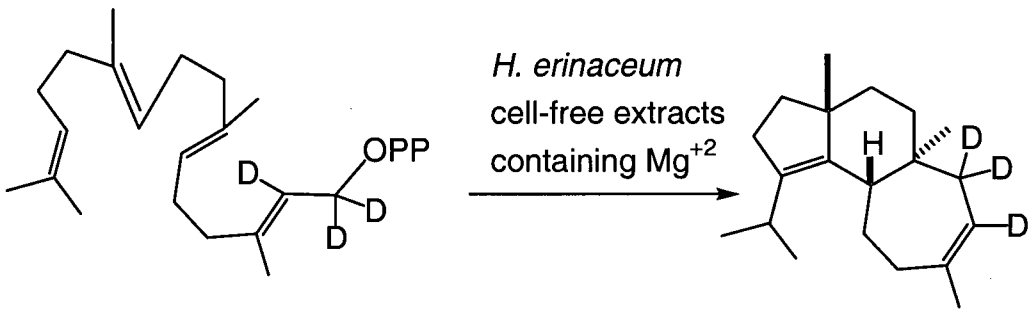
54

In 1979, Ayer and coworkers reported their investigations into cyathane biogenesis through labeling experiments.[24] Since the biosynthetic pathway was presumed to involve acetate incorporation into geranylgeranyl pyrophosphate, [1,2-$^{13}C_2$]-labeled acetate (**55**) was fed to *Cyathus earlei* and the labeling pattern of the resulting 11-*O*-acetylcyathatriol product (**56**) was determined by ^{13}C NMR analysis (eq 1).



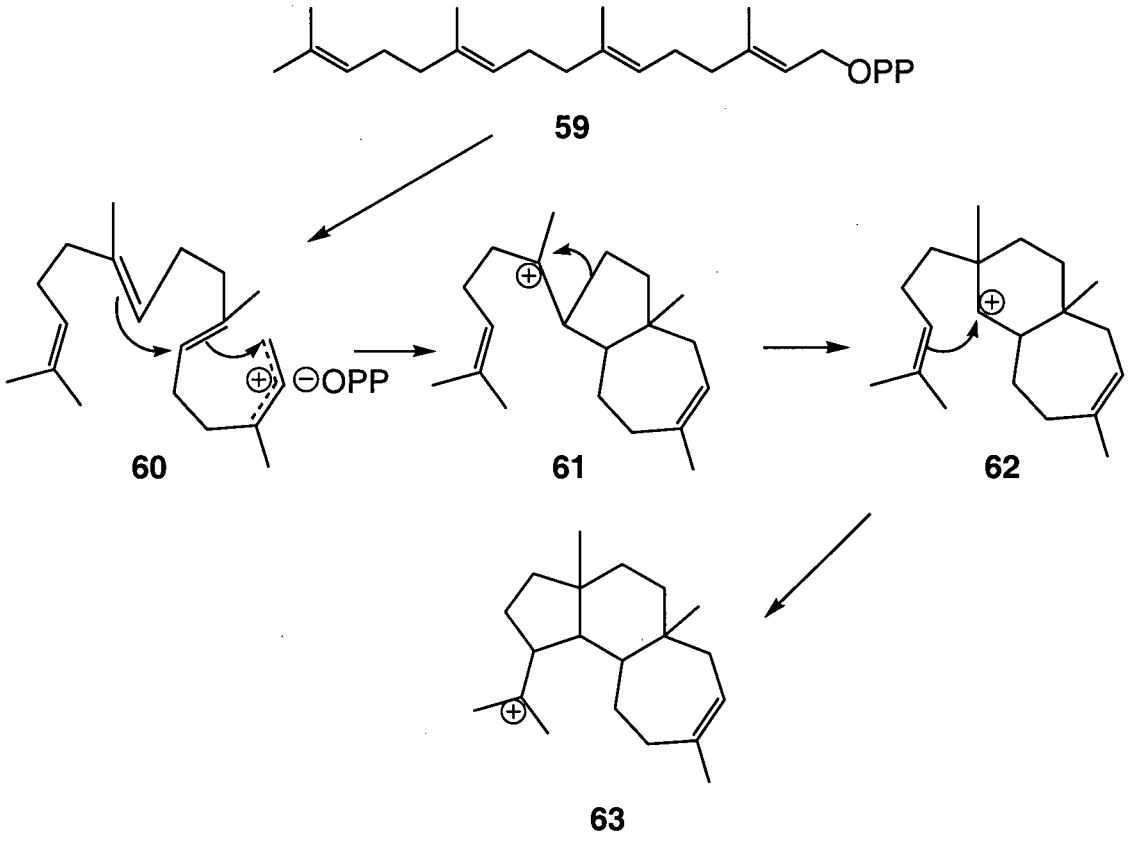
55 **56** (1)

Recently, Sassa and coworkers reported[25] a study of the fungal diterpene cyclase, cyathadiene synthase. Treatment of a cell-free extract of *Hericum erinaceum* with deuterated all-trans-geranylgeranyl diphosphate (**57**) for 2 h at 30 °C provided the deuterated cyatha-3,12-diene **58** in 30% yield (eq 2).



57 **58** (2)

Both Ayer's and Sassa's results (*vide supra*) support the biosynthetic pathway postulated[24] by Ayer in 1979 (Scheme 11).

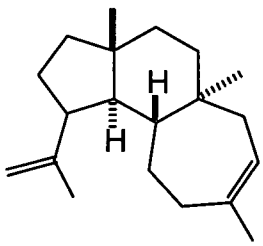


Scheme 11

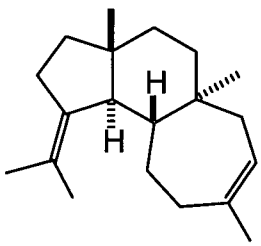
The first steps of the postulated biosynthetic pathway involve tandem cationic ring closures of all-trans-geranylgeranyl diphosphate (**59**) to form the hydroazulene-like cation (**61**), which undergoes a Wagner-Meerwein migration to provide a 6-7 fused bicyclic intermediate (**62**). Cyclization of the isopropylidene moiety onto the bicyclic core of **62** provides the 5-6-7 fused tricyclic cation **63**, which displays the cyathin skeletal core.

2.1.1.2. Hydrocarbon Cyathanes

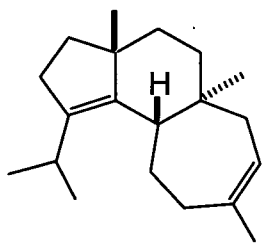
Several cyathadiene hydrocarbons, postulated[25] progenitors of the oxygenated cyathanes, have recently been isolated. In 1993, Cassidy reported[26] the isolation of cyatha-12,18-diene (**64**) from a non-polar fraction of *Higginsia sp* extract. In 2001, Sassa and coworkers isolated[25] cyatha-3(18),12-diene (**65**) and cyatha-3,12-diene (**66**) from the erinacine-producing basodiomycete *Hericium erinaceum.*



64



65



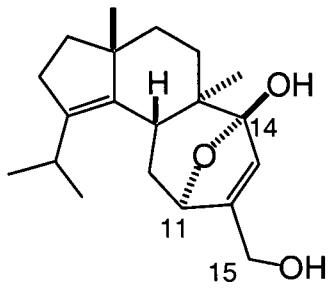
66

The isolation of hydrocarbons **64-66** suggests that intermediate **63** in Ayer's proposed pathway (*vide supra*) can follow different sequences of elimination and/or hydride shifts prior to oxidation.[25]

2.1.1.3. Oxygenated Cyathanes

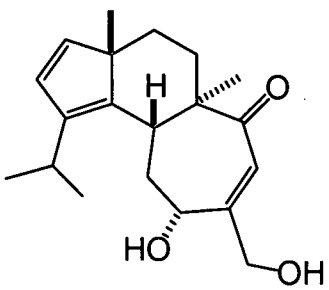
Nature's elaboration of the cyathane core includes, primarily, oxidation at allylic positions. Oxygenation on the three cyathin rings as well as on the methyl and isopropyl appendages has been noted. Certain oxygenation patterns introduce, from a synthetic viewpoint, considerable structural complexity to the cyathin structures. The diverse oxygenation patterns of several structurally elucidated cyathanes are discussed below.

The most common sites of oxygenation on the cyathin core are the carbons of the C-ring and its methyl appendage, C–15. Cyathin A_3 (**67**), the first cyathane to yield to structural elucidation,[27] exhibits oxygen functions at C–11, 14 and 15.

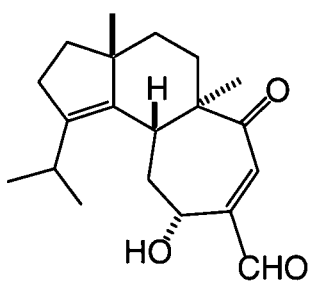


67

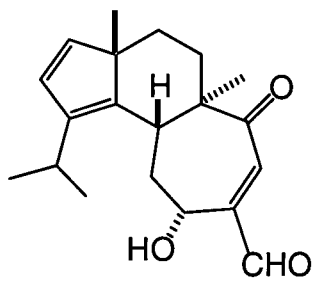
In their study of *Cyathus helenae* extracts, Ayer and coworkers reported several cyathanes that display an oxidation pattern similar to that of cyathin A_3. The structures of allocyathin B_3 (**68**), cyathin B_3 (**69**), and cyathin C_3 (**70**) were elucidated through chemical correlations with cyathin A_3 (**67**).[27,28]



68

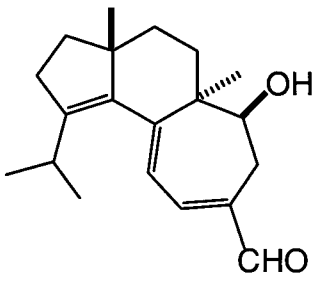


69

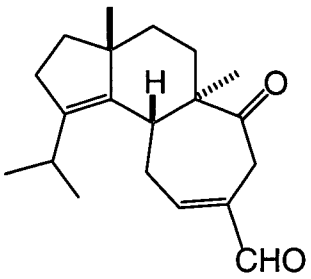


70

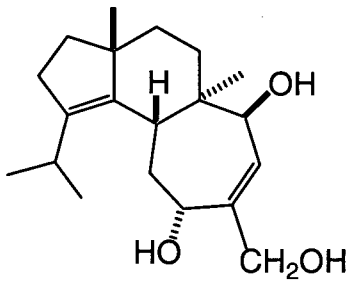
Extracts of the tropical species of bird's nest fungus *Cyathus earlei* yielded several acetylated cyathin-type compounds as well as three new cyathanes: allocyathin B_2 (**71**), cyathin B_2 (**72**) and cyathatriol (**73**).[29]



71

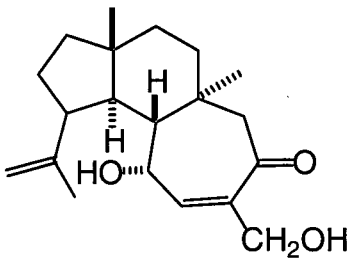


72

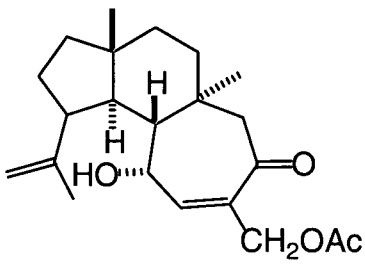


73

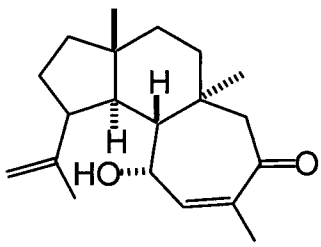
In 1985, Cassidy and co-workers isolated[30] cyathanes **74-76** from the extracts of the marine sponge *Higginsia sp.* The structure of cyathane **74**, which includes oxygen functions at C–10, 13 and 15, was verified by X-ray crystallographic analysis.



74

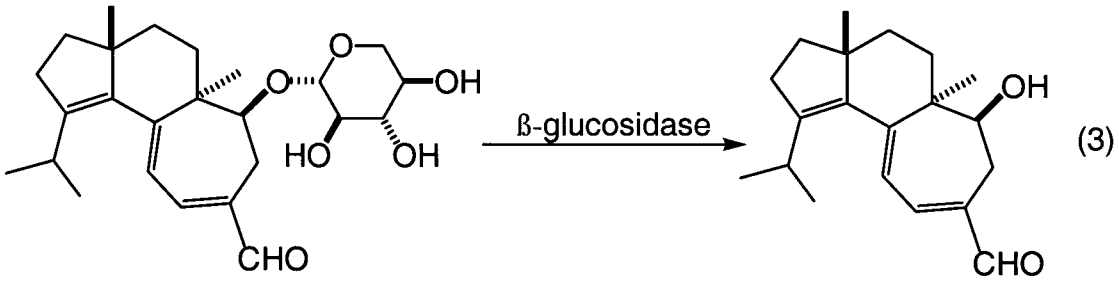


75



76

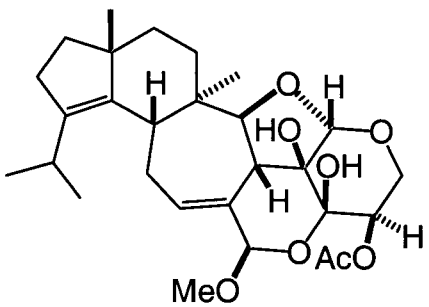
The erinacines, which are glycosylated cyathanes, were isolated from the mycelia of the fungus *Herimicium erinaceum.*[31-34] The xylose moiety of erinacine A (**77**) was cleaved[31] using a β-glucosidase and the resulting aglycone product was identified as allocyathin B_2 (**71**) (eq 3).[29]



(3)

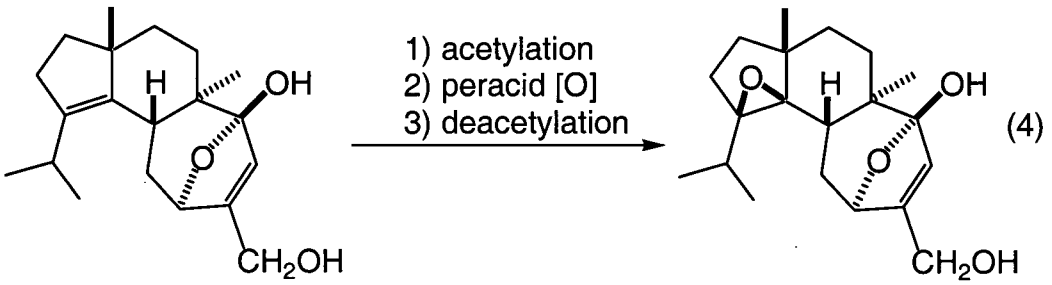
77 **71**

Hecht and coworkers reported three novel diterpenoids, named straitins, from the fungus *Cyathus striatus*.[35] The structure of straitin A (**78**) displays a cyathin core that is triple-linked to a pentose carbohydrate.



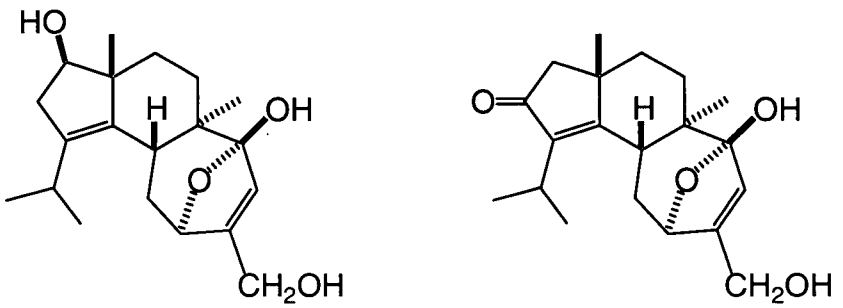
78

A number of cyathanes exhibit extensive oxygenation on the A-, B- and/or C-rings. The structure[17] of neoallocyathin A_4 (**79**), which displays an epoxide function in the A ring, was confirmed through chemical correlations with cyathin A_3 (**67**) (eq 4).



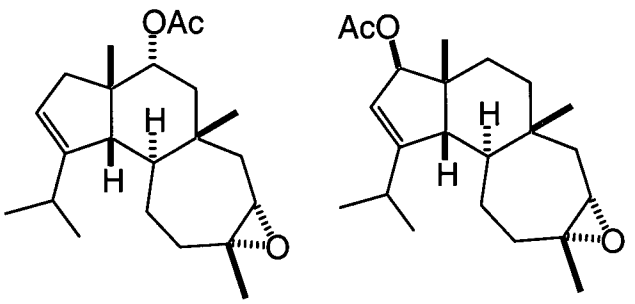
67 **79**

Oxygenation on both the A- and C-rings was noted in cyafrins A_4 (**80**) and B_4 (**81**), which were isolated[36] from the extracts of *Cyathus africanas,* a fungus collected in Tanzania.



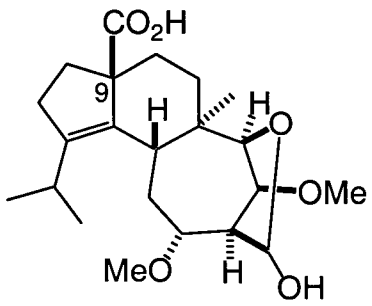
80 **81**

Cyathanes **82** and **83**, isolated[37] from the marine sponge *Myrekioderma styx,* have oxygenation patterns that include an epoxide on the C-ring.

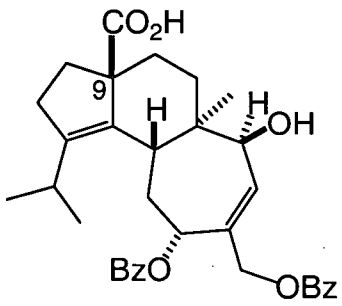


82 **83**

A novel group of cyathanes, named scabronines, were isolated[38-40] from the fruiting bodies of the mushroom *Sarcodon scabrosus*. As in all scabronines, scabronines A (**84**), B (**85**) and C (**86**) display an acid function at the C–9 angular carbon.



84



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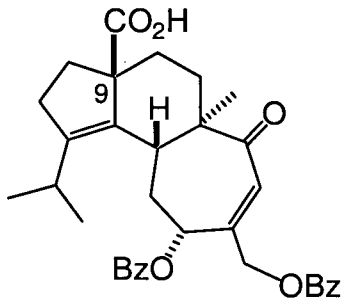
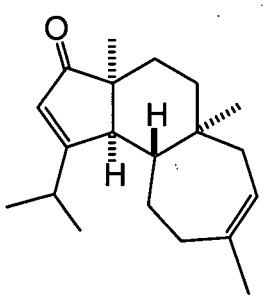
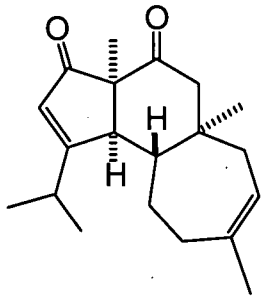


86

Few members of the cyathane family display an oxygenation pattern that excludes the C-ring. Cyanthiwigins A (**87**) and C (**88**), which display oxygenation on the A- and/or B-rings, were isolated by Green and coworkers from the extracts of *Apipolasis reiswigi*.[41]

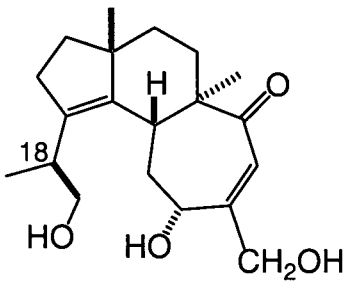


87

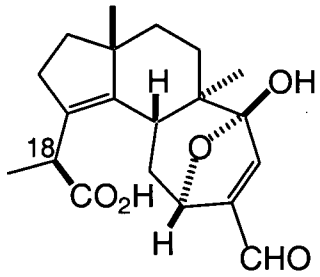


88

Oxygenation of the isopropyl group attached to C–3 is a rare feature in the cyathane family. In 1978, Ayer and coworkers reported[17] the isolation of cyathins A_4 (**37**) and C_5 (**89**), which display oxygenation of the C–3 isopropyl group.[42]

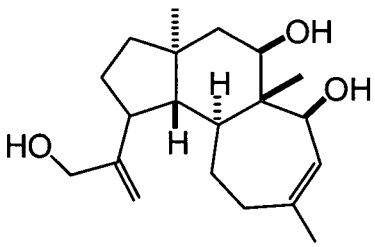


37



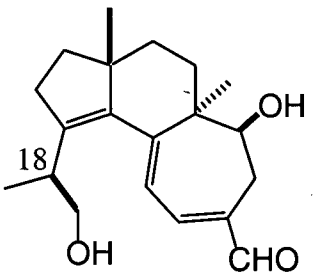
89

Onychiol B (**90**), isolated[43] from the rhizome of the fern *Onchium japonicum,* displays oxygenation on the B- and C-rings and on the isopropenyl group attached at A–3.

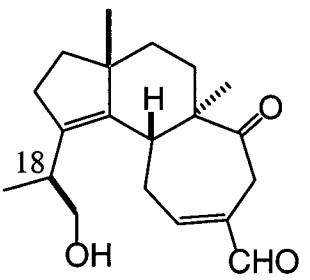


90

In 1989, Shibata and coworkers reported[16] the isolation of eight novel cyathane-type diterpenoids from the fruiting bodies of *Sarcodon scabrosus*: sarcodonins A-H. Of these eight sarcodonins, only A (**91**) and G (**36**), which display oxygenation on the isopropyl moiety, yielded to structural elucidation. The absolute stereochemistry of sarcodonin G (**36**) was determined by X-ray crystallographic analysis of its *p*-bromobenzoate derivative.



91



36

2.1.1.4. Biological Activity of the Cyathanes

Members of the cyathane family have been shown to exhibit diverse biological activities. The cyathin complexes of the *Cyathus* fungi *C. helenae, C. earli and C. striatus* exhibit[17,23,29] pronounced antibacterial and antifungal activities. The cyathanes isolated from *Myrmekioderma styx* exhibit[37] moderate cytotoxic activity against the P388 leukemia cell line and the A549 human lung tumor cell line, with IC_{50}'s as low as 5.6 and 4.0 μg/mL, respectively. The cyanthiwigin cyathanes exhibit[41] cytotoxic activity against P388 leukemia cells, with IC_{50}'s as low as 2.5 μg/mL. The straitin cyathane-xylosides were shown to have leishmanicidal activity.[44]

Saito and coworkers recently reported[45] that certain erinacines[31-34,46] behave as potent kappa opioid receptor agonists. Activation of membrane-bound opioid receptors (μ, δ and κ), which are located throughout the nervous system,[47] can induce various physiological effects including antinociception and neurotransmitter release.[48] Morphine, an opioid drug used in the clinical management of pain, acts on the μ receptor and causes untoward side effects such as tolerance, dependence and respiratory depression. Stein and coworkers have reported[49] that activation of the κ receptor induces hyperalgesia in a

rat model of inflammation. It is postulated that the application of erinacines as selective κ receptor agonists may produce the desired antinociceptive activity without the adverse side effects observed with μ receptor agonists.

Certain members of the erinacine[31-33] and scabronine[38-40,50] cyathanes exhibit the ability to stimulate the biosynthesis of nerve growth factor (NGF) *in vitro*. NGFs play an important role in the early development of the embryonic central nervous system as well as in the phenotypic maintenance and cell regulation of neurons in adults. The role of NGFs in a novel mode of treatment for neurodegenerative disorders is currently under investigation.[51] However, the inability[52] of NGFs to penetrate the blood brain barrier (BBB) has limited their clinical application to the direct infusion into the cerebral spinal fluid.[53] The inconvenience of this medical implementation initiated a search for low-molecular-weight NGF inducers, such as the erinacines and scabronines, which can penetrate the BBB.

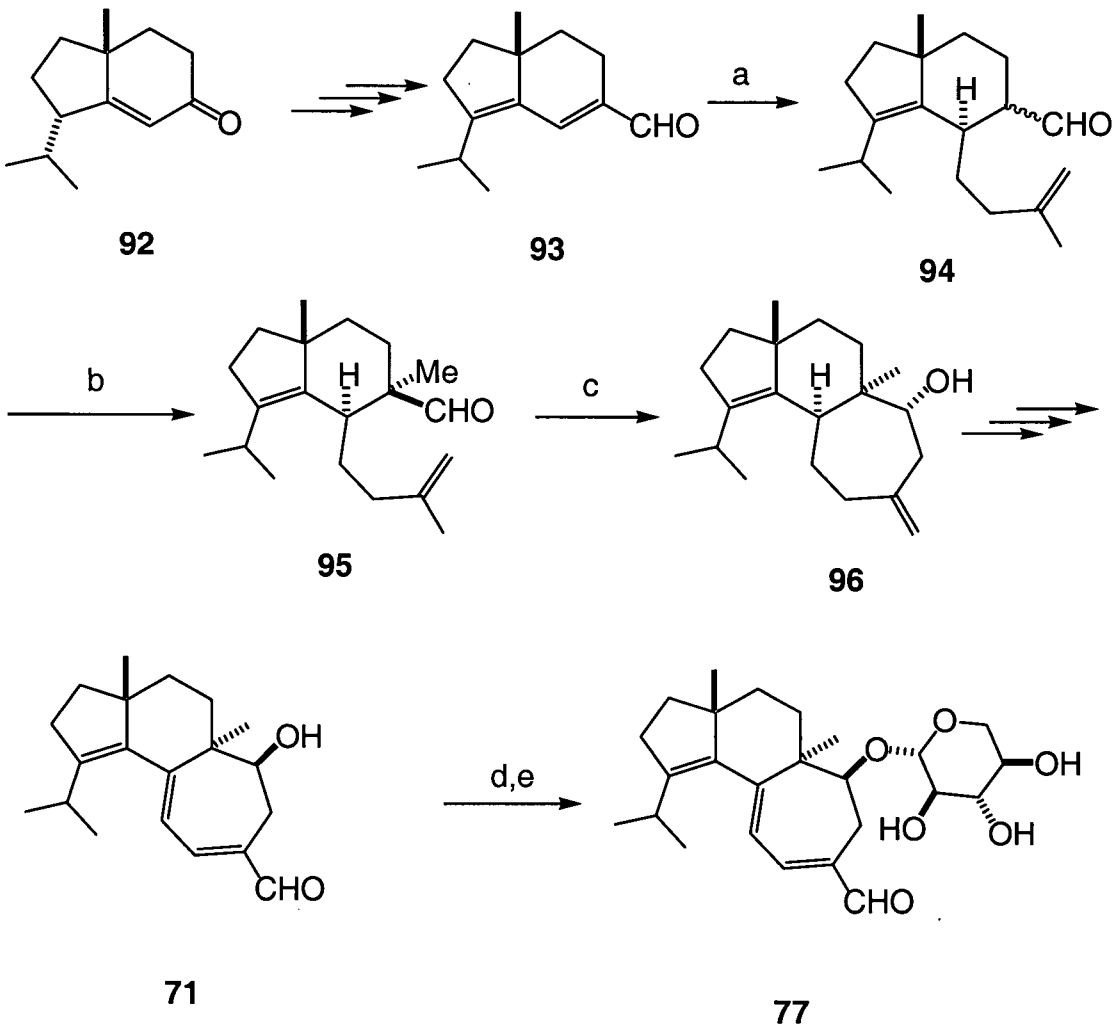
2.1.2. Previous Studies in Cyathane Synthesis

The diverse biological activities and structural novelty displayed by the cyathanes have made them attractive targets for total synthesis.[54] From a synthetic viewpoint, the diverse oxygenation patterns, the *anti* 1,4 angular methyls and the 5-6-7 fused tricyclic core represent significant challenges. As an illustration of the diverse approaches to the construction of the cyathane framework, the outlines of the studies described in this section focus primarily on key ring-forming steps.

2.1.2.1. Total Syntheses of Cyathanes

Although the first structural elucidation of a cyathane appeared in the literature in the early 1970s,[23] the first account of a cyathane total synthesis, reported by Snider and coworkers,[55,56] was not published until 1996. Their synthetic sequence leading to (±)-allocyathin B_2 (**71**) and (+)-erinacine A (**77**) relied on an intramolecular carbonyl ene reaction as a key step (Scheme 12). The synthesis commenced with the known 5-6 fused bicyclic ketone **92**, which was converted to aldehyde **93** in four steps. TMS-accelerated copper(I)-catalyzed conjugate addition of isopentenylmagnesium bromide to **93** provided a mixture of epimeric aldehydes **94**. Methylation of **94** afforded aldehyde **95**. Treatment of **95** with Me_2AlCl resulted in an intramolecular carbonyl ene reaction, furnishing alcohol **96**, which displayed the complete cyathane skeleton. This material was transformed into (!)-allocyathin B_2 (**71**) in ten chemical operations. Glycosylation of racemic **71** with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide provided a 1:1 mixture of

(+)-erinacine A triacetate and its diastereomer. Deacetylation of the former with potassium carbonate in methanol afforded (+)-erinacine A (**77**).

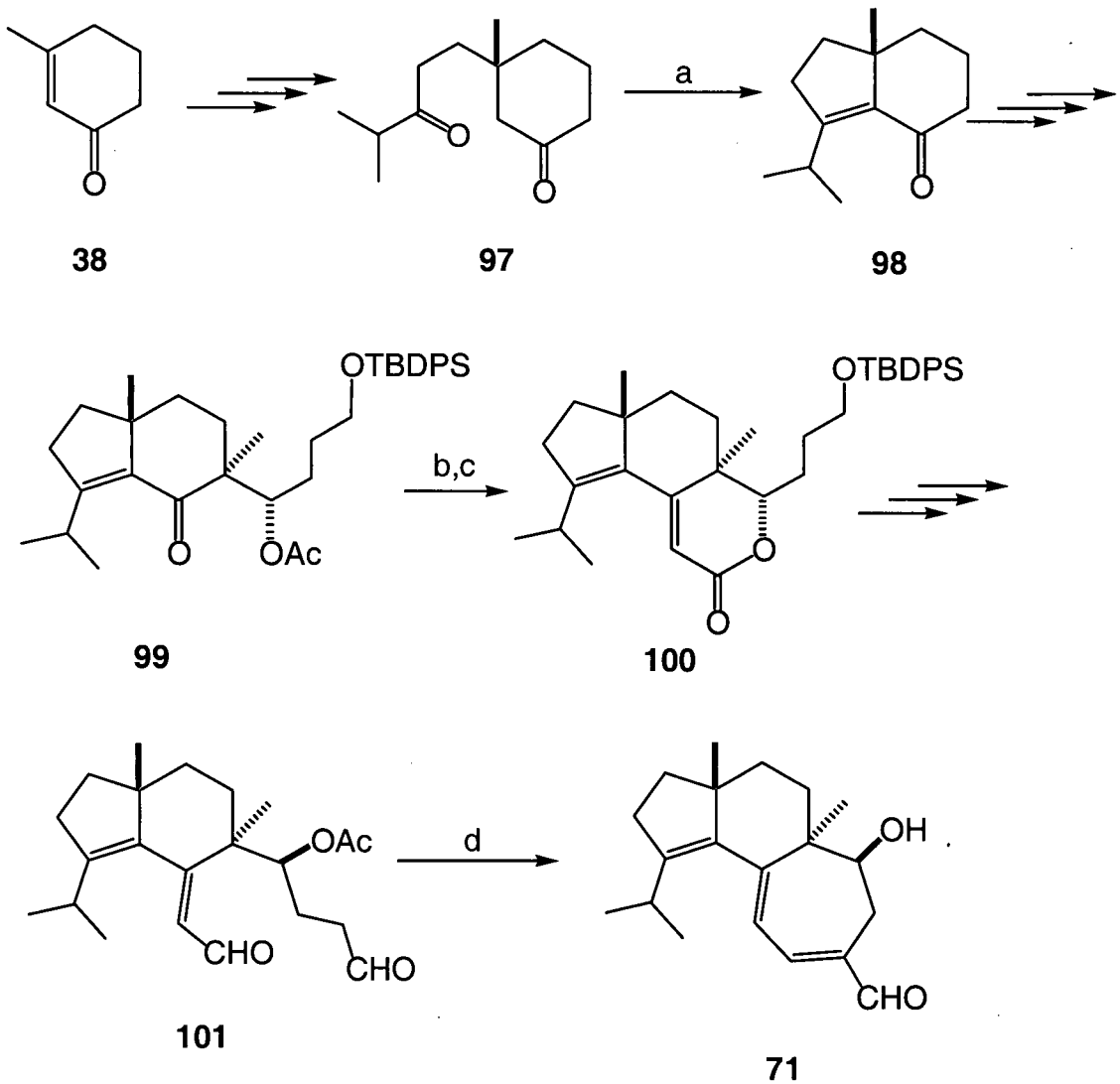


Reagents: a) $H_2C{=}C(CH_3)CH_2CH_2MgBr$, CuBr·DMS, TMSCl, HMPA; b) *t*-BuOK, MeI; c) Me_2AlCl; d) 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide, $Hg(CN)_2$, $HgCl_2$; e) K_2CO_3, MeOH.

Scheme 12

In 1998, Tori and coworkers reported[57] the second total synthesis of (!)-allocyathin B_2 (**71**), which involved three key aldol condensation reactions (Scheme 13). Dione **97**, precursor for the first aldol condensation, was prepared in five steps from 3-

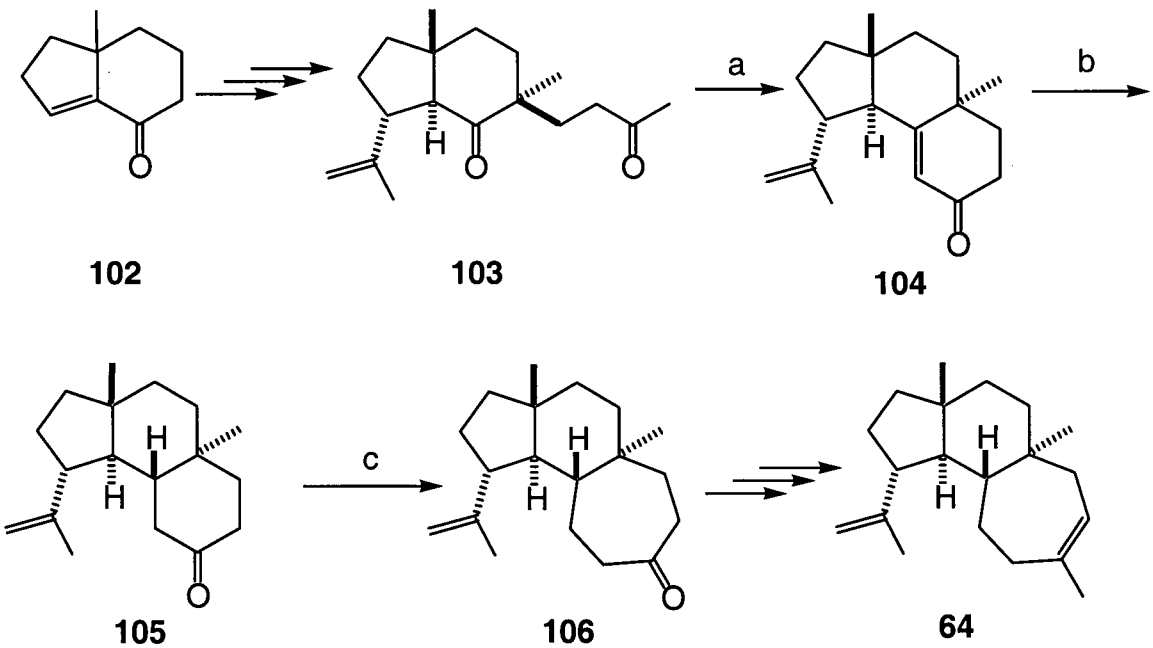
methyl-2-cyclohexen-1-one (**38**). Intramolecular condensation of **97** provided the fused hydrindenone system **98**, which was transformed into compound **99** in four chemical operations. Base-mediated intramolecular cyclization of **99**, followed by dehydration of the resultant tertiary alcohol using $SOCl_2$, furnished the α,β-unsaturated lactone **100**. Conversion of **100** to dialdehyde **101** was accomplished in five steps. Aldol condensation of **101**, with concomitant acetate hydrolysis, provided (±)-allocyathin B_2 (**71**).



Reagents: a) 5% aq. KOH, MeOH, ⇝; b) LiHMDS; c) $SOCl_2$, pyr; d) KOH, MeOH.

Scheme 13

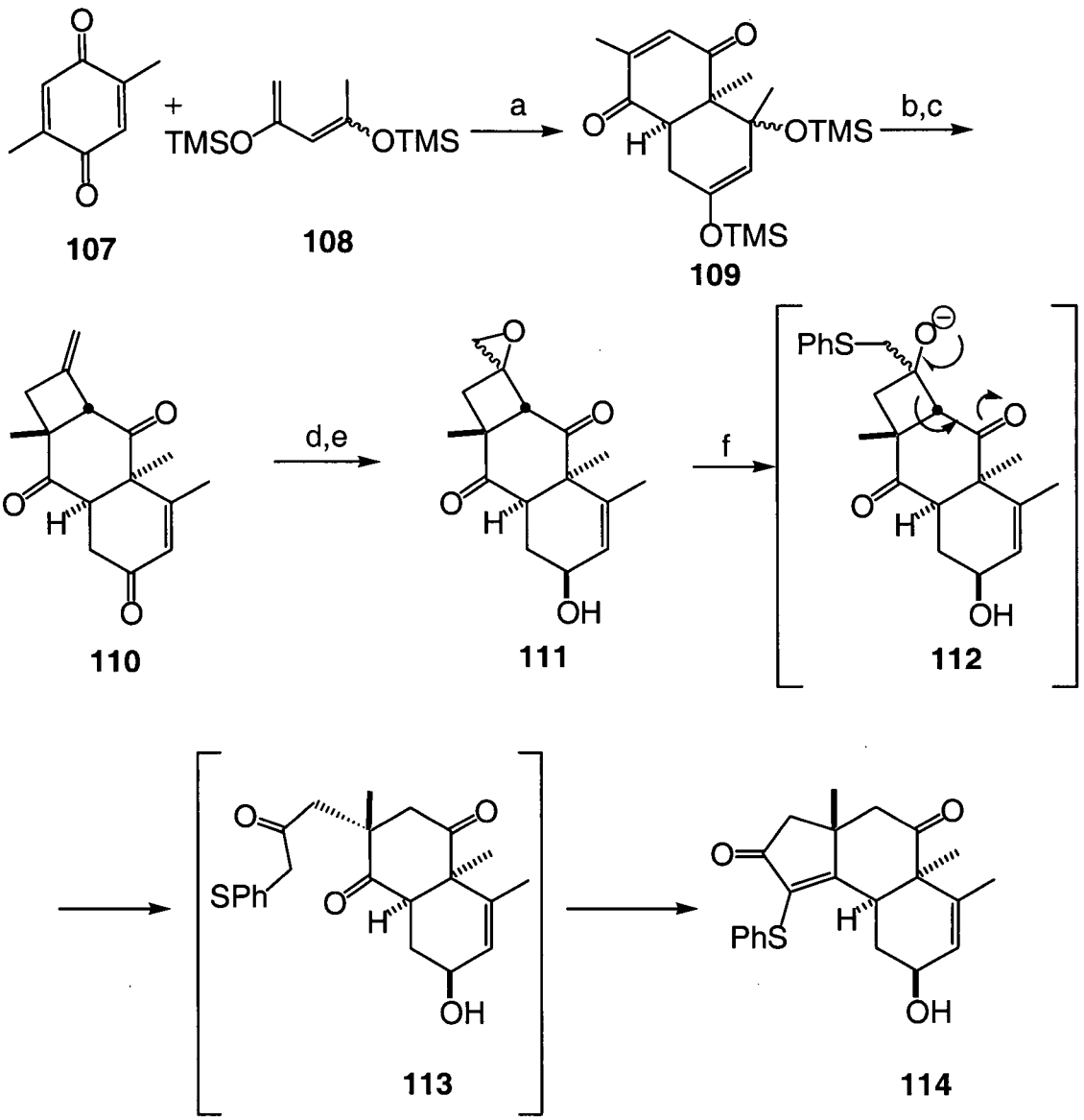
Taking advantage of an advanced intermediate in a synthetic study of verrucosane natural products,[58] Piers and Boulet developed a synthesis[59] of (!)-cyatha-12,18-diene (**64**) (Scheme 14). The sequence commenced with the known bicyclic enone **102**, which was transformed into dione **103** in six steps. Base-mediated intramolecular aldol condensation of **103** afforded tricyclic enone **104**. Metal-ammonia reduction of **104** provided ketone **105**, which displayed the requisite *trans* stereochemistry at the ring fusion. The branching point in a divergent synthetic plan, compound **105** was also employed in the total syntheses of several verrucosane natural products.[58] Lewis-acid catalyzed homologation of **105**, followed by decarboxylation of the resultant β-keto ester, provided the 5-6-7 fused tricyclic ketone **106**. Final conversion of **106** to (!)-cyatha-12,18-diene (**64**) was accomplished in two steps.



Reagents: a) NaOMe, ⬬; b) Li, NH_3, *t*-BuOH; solid NH_4Cl; c) BF_3·OEt, N_2CHCO_2Et; DMSO, NaCl, ⬬.

Scheme 14

Recently, Ward and coworkers completed the total synthesis of allocyathin B_3 (**68**), a synthetic endeavor that began while Ward was a student in Ayer's group.[60-62] The first part of the synthesis, reported by Ayer and coworkers,[60] relied on two key cycloaddition reactions (Scheme 15). Diels-Alder reaction between benzoquinone **107** and dienes **108**, gave the *cis*-fused bicycle **109**. Photochemical [2+2] cycloaddition of **109** with allene, followed hydrolysis of the silyl enol ether function, afforded tricycle **110** as the major isomer. Epoxidation of the exocyclic double bond, followed by 1,2 reduction of the enone, furnished a mixture of epoxides **111**. Treatment of **111** with benzenethiol and potassium hydroxide caused a sequence of reactions, commencing with a nucleophilic ring-opening of the epoxide to give intermediate **112**. Fragmentation of **112**, followed by intramolecular aldol condensation of the resultant triketone **113,** ultimately provided tricycle **114**.

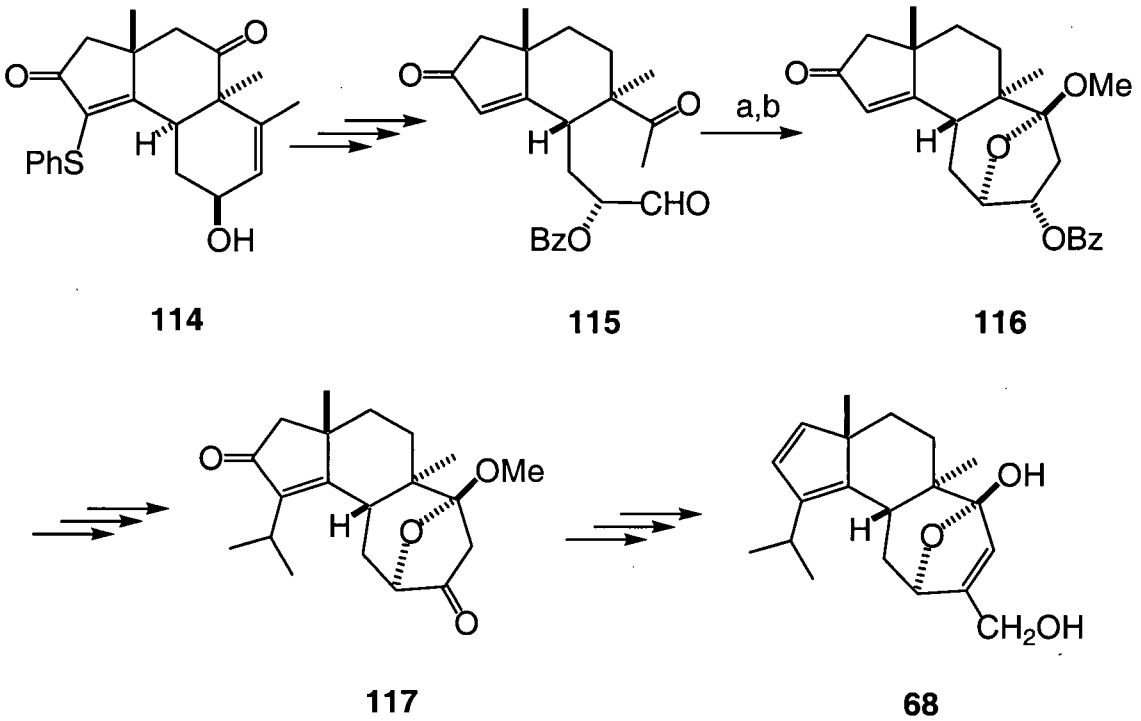


Reagents: a) xylene, ⌁; b) allene, hν; c) Rexyn 101 acidic ion exchange resin; d) *m*-CPBA; e) 9-BBN; f) PhSH, 5% aq. KOH, ⌁.

Scheme 15

Transformation of Ayer's advanced intermediate **114** (*vide supra*) to (±)-allocyathin B_3 (**68**) was completed by Ward and coworkers.[61,62] Conversion of **114** to keto aldehyde **115** required ten chemical operations (Scheme 16). Acid-promoted aldol cyclization of **115** proceeded with a concomitant intramolecular benzoyl transfer. The

resultant hemiketal was methylated, providing 5-6-7 fused tricycle **116**. The task of affixing an isopropyl moiety at C–3 (cyathane numbering) of **116** was accomplished in eight steps, affording intermediate **117**. (±) Allocyathin B_3 (**68**) was obtained from **117** in three steps.



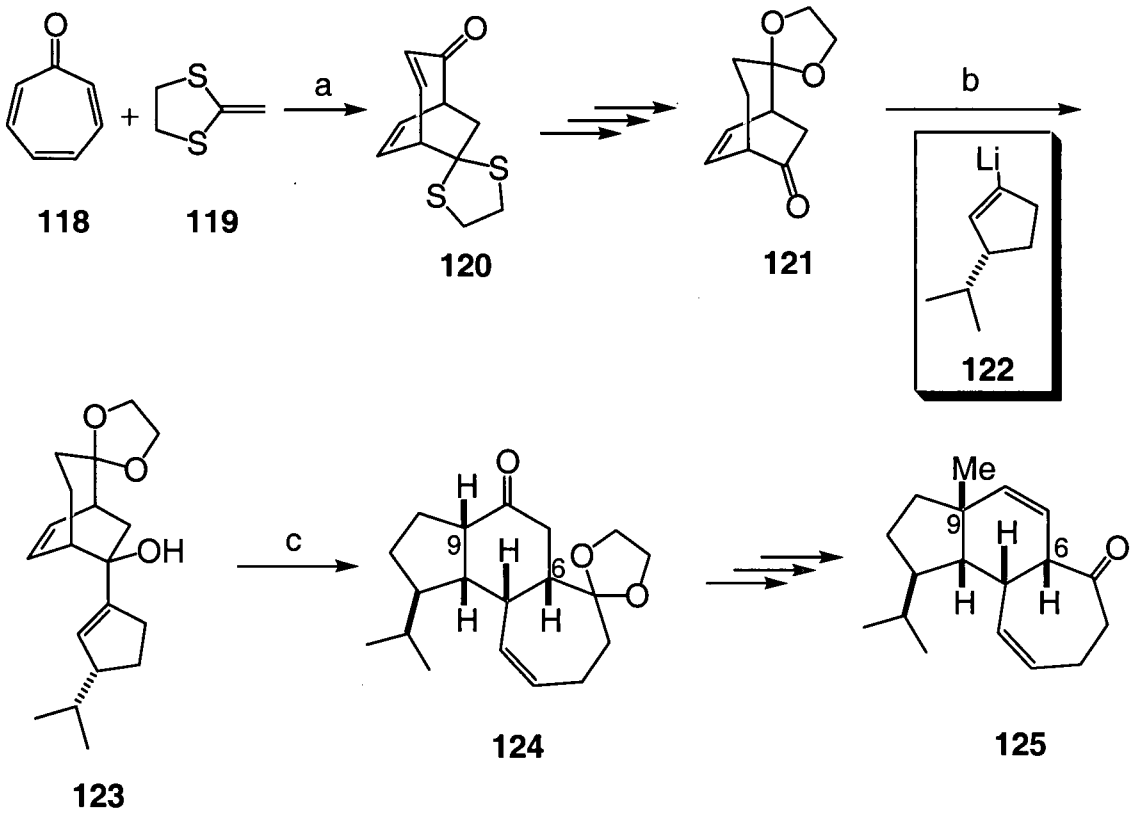
Reagents: a) *p*-TsOH; b) MeI, Ag_2O.

Scheme 16

2.1.2.2. Approaches to the Cyathanes

In addition to the total synthesis publications, there have been numerous reports that describe novel methods of constructing the cyathane skeletal core. In 1994, Dahnke and Paquette reported[63] a synthetic approach to the cyathane core *via* an anionic oxy-Cope rearrangement. An inverse demand Diels-Alder reaction between tropone (**118**) and

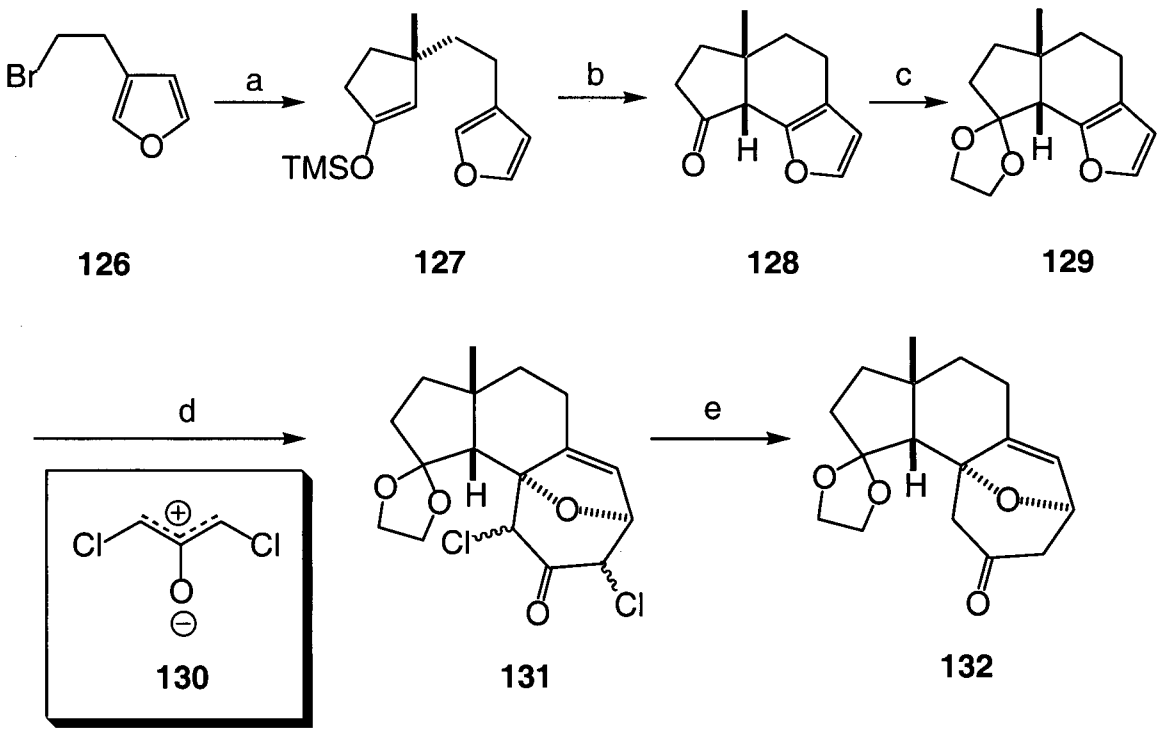
2-methylidene-1,3-dithiolane (**119**) provided bicyclo[3.2.2]nonane **120** (Scheme 17). Several steps, which included a resolution of enantiomers, afforded the levorotatory enantiomer of ketone **121** from intermediate **120**. Treatment of (–)-**121** with the enantiopure organolithium reagent **122** provided the rearrangement precursor **123**. Oxyanion accelerated Cope rearrangement of **123** furnished the 5-6-7 fused tricycle **124**. Compound **124** was transformed into ketone **125** in six steps, which included a methylation at C–9 from the β-face. Unfortunately, the requisite installation of a methyl group at C–6, which must occur from the α-face, proved difficult and this synthetic approach to cyathanes was ultimately abandoned.



Reagents: a) Et_3N, ☚; b) **122**; c) KH, 18-cr-6, ☚.

Scheme 17

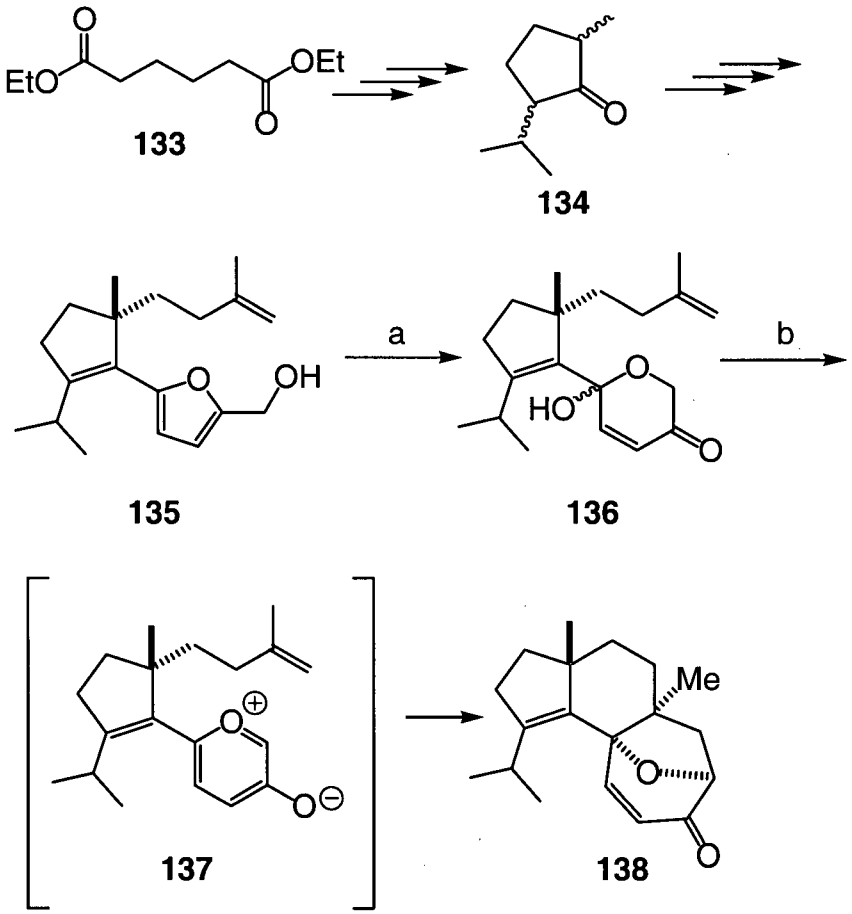
In 1999, Wright and coworkers disclosed a novel approach to the cyathane core that relied on sequential oxidative coupling and [4+3] cycloaddition steps.[64] The sequence began with a TMSCl-accelerated copper(I)-catalyzed addition of the Grignard reagent derived from bromide **126** to 3-methyl-2-cyclopenten-1-one (Scheme 18). Exposure of the resultant adduct **127** to a carbon anode promoted an oxidative coupling reaction, yielding the tricyclic product **128**. Ketone **128** was converted to its cyclic ketal derivative **129**. Treatment of **129** with oxyallyl cation **130**, which was generated *in-situ* from trichloroacetone, resulted in a [4+3] cycloaddition. The cycloaddition products **131** were dechlorinated with a zinc–copper couple to afford compound **132**, which displayed a 5-6-7 fused carbon skeleton present in cyathanes.



Reagents: a) Mg; CuI, TMSCl; 3-methyl-2-cyclopenten-1-one; b) carbon anode, $LiClO_4$, 2,6-lutidine; c) p-TsOH, $HO(CH_2)_2OH$, $CH(OEt)_3$; d) 1,1,3-trichloroacetone, $NaOCH_2CF_3$; e) Zn-Cu couple, NH_4Cl .

Scheme 18

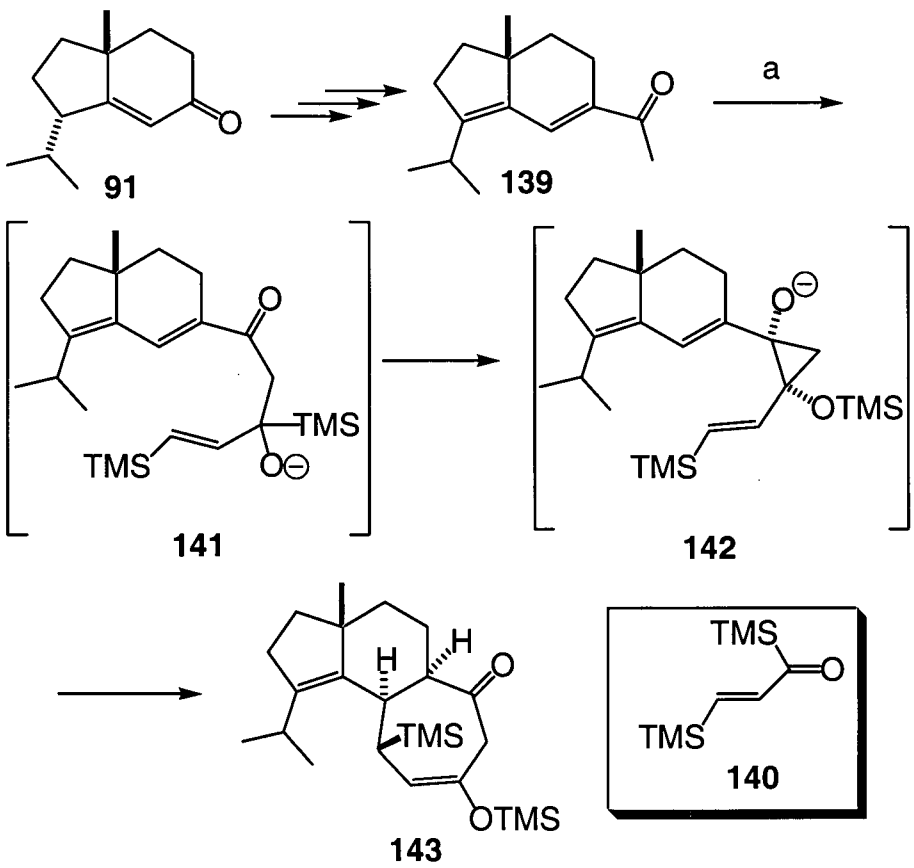
Magnus and Shen reported[65] a synthetic approach to the cyathane core that relied on a key [5+2] annulation reaction (Scheme 19). The sequence commenced with diethyl adipate (**133**), which was converted to the mixture of ketones **134**. Transformation of **134** to alcohol **135** was accomplished in four steps. Irradiation of **135** in the presence of O_2 resulted in an oxidative rearrangement, affording the unstable pyranone **136**. Treatment of **136** with TFA generated the corresponding pyrylium ylide **137**, which underwent an intramolecular [5+2] cycloaddition to give the 5-6-7 fused tricycle **138**.



Reagents: a) O_2, rose bengal, hν; DMS; b) TFA.

Scheme 19

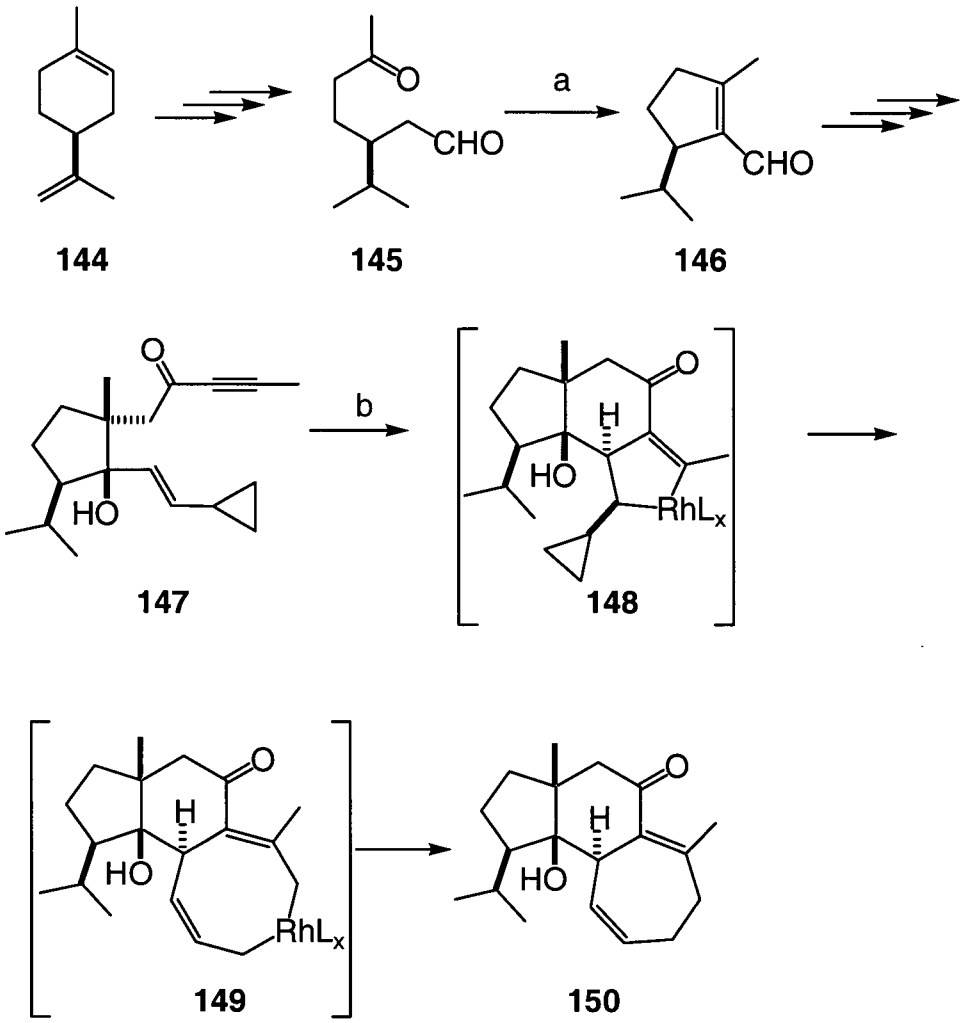
Takeda and coworkers reported a rapid assembly of the cyathane tricyclic core *via* a Brook rearrangement-mediated [3+4] annulation (Scheme 20).[66] Dienone **139**, precursor of the key annulation, was obtained in two chemical operations from the known enone **91**, which was also employed in Snider's cyathane studies (see Scheme 12, *vide supra*). Addition of the enolate of **139** to a solution of the acryloylsilane **140** resulted in a [3+4] annulation *via* intermediates **141** and **142**. 1,2-Adduct **141** underwent a Brook rearrangement to afford the divinylcyclopropane intermediate **142**. A homo-Cope rearrangement of **142** afforded compound **143**, which displayed the 5-6-7 fused tricyclic cyathane ring system.



Reagents: a) LDA, **140**.

Scheme 20

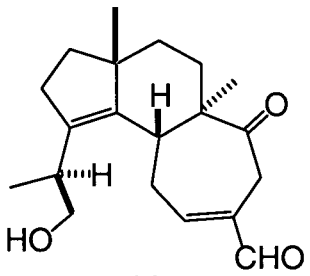
In 2001, Wender and coworkers reported an asymmetric approach to the cyathane core *via* a transition metal-catalyzed [5+2] cycloaddition.[67] (*S*)-(–)-Limonene (**144**) was converted to keto aldehyde **145** in two steps (Scheme 21). An intramolecular aldol condensation of **145** provided enal **146**. Transformation of **146** to **147** required ten chemical operations. Treatment of **147** with $[Rh(CO)_2Cl]_2$ caused the key intramolecular [5+2] cycloaddition. The proposed pathway of this cycloaddition involved an initial complexation of the alkyne and vinylcyclopropane moieties of **147** with the Rh-catalyst. Upon oxidative addition, this complex provided intermediate **148**. Strain-driven cleavage of the cyclopropane ring in **148** led to intermediate **149**. Reductive elimination of **149** provided the cycloaddition product **150**, which displays the cyathane 5-6-7 fused tricyclic ring-system.



Reagents: a) piperidine, AcOH, ☚; b) 5 mol % $[Rh(CO)_2Cl]_2$, ☚.

Scheme 21

In a synthetic study directed towards (±)-sarcodonin G (**36**), Piers and Cook prepared the 5-6-6 fused tricycle **151** *via* sequential ring closure and Still-Mitra [2,3] sigmatropic rearrangement reactions.[68,69]



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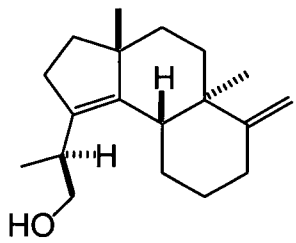
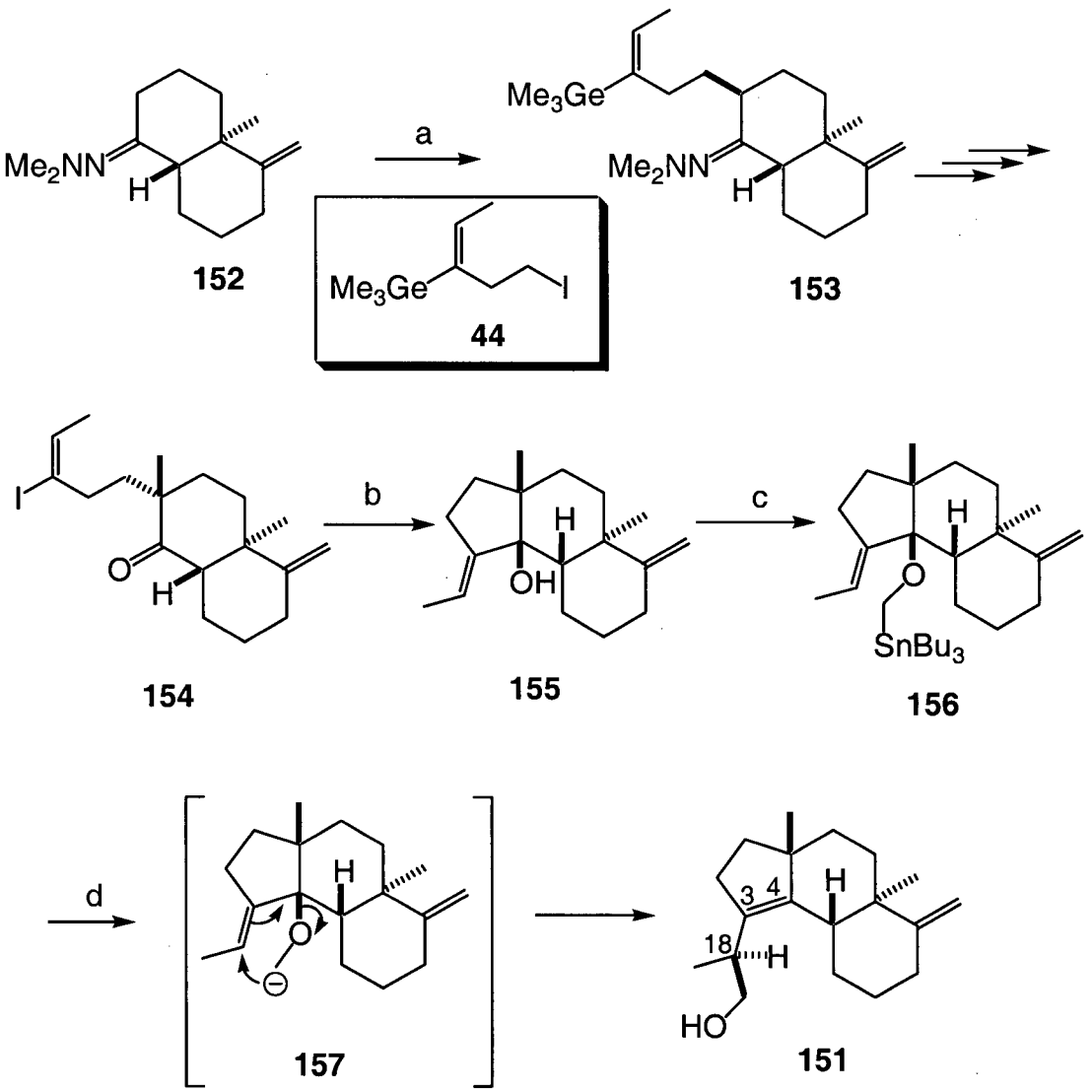


151

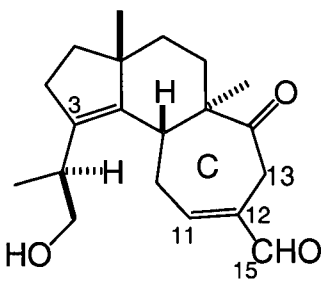
The synthesis of **151** commenced with an alkylation of the anion derived from *trans*-fused bicyclic dimethylhydrazone **152** with iodide **44,** affording adduct **153** (Scheme 22). Conversion of **153** to keto alkenyl iodide **154** was accomplished in four steps. A stereoselective BuLi-mediated anionic cyclization of **154** yielded the 5-6-6 fused tricyclic carbinol **155**. Conversion of **155** to the corresponding (tributylstannyl)methyl ether derivative **156**, followed by BuLi-mediated transmetallation, provided carbanion intermediate **157**. A [2,3]-sigmatropic rearrangement of **157** afforded alcohol **151,** which displayed the desired C–3,4 double bond and possessed the correct relative configuration of the stereogenic center at C–18 (cyathane numbering).



Reagents: a) KDA, HMPA; **44**; b) BuLi; c) KH, 18-cr-6; Bu_3SnCH_2I d) BuLi.

Scheme 22

The work described in this thesis involves synthetic studies directed towards the diterpenoids sarcodonin G (**36**) and cyathin A_4 (**37**). Both compounds display the cyathane 5-6-7 fused ring system with identical relative configurations at the ring-fusion centers. In addition, both compounds are among the few cyathanes that display a hydroxyl function on the isopropyl side chain at C–3 (see Section 2.1.1.3., *vide supra*). The structural differences between sarcodonin G (**36**) and cyathin A_4 (**37**) are restricted to the C-ring and its one-carbon appendage. Although both compounds display a ketone function at C–10, sarcodonin G (**36**) displays an aldehyde function at C–15 whereas cyathin A_4 (**37**) displays hydroxyl functions at C–11 and C–15. In addition, sarcodonin G (**36**) displays a C–11,12 double bond as opposed to the C–12,13 double bond exhibited by cyathin A_4 (**37**). These similarities and differences of structures **36** and **37** lend themselves to a centralized and divergent synthetic approach that addresses the oxygenation and unsaturation pattern of the C-ring in the later stages of the syntheses.*



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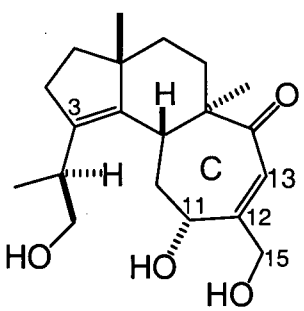


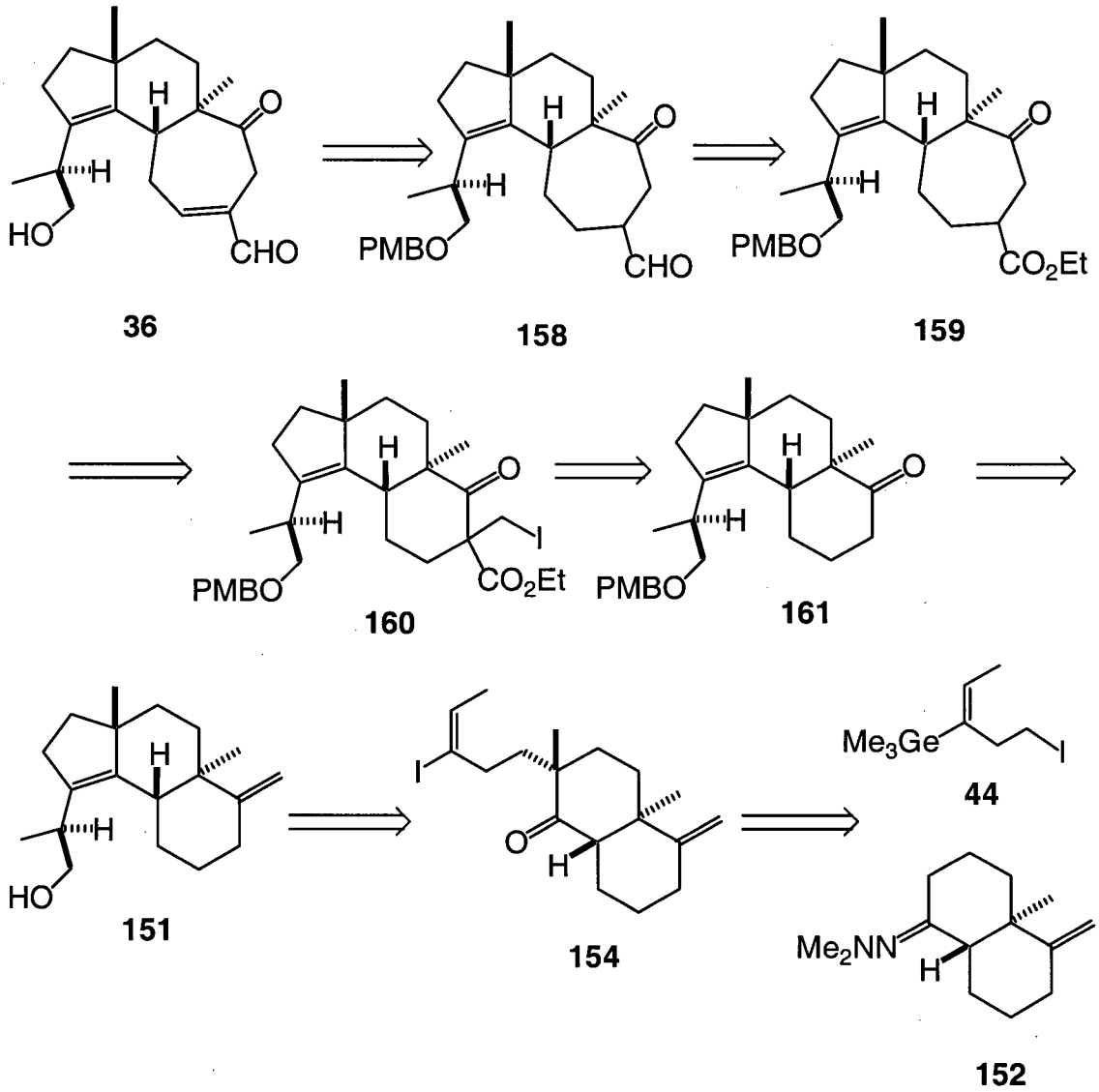
37

* In the text of this thesis, Ayer's cyathane numbering system is used in most descriptions of cyathane-type natural products and a systematic IUPAC-based numbering system is used to describe the synthetic intermediates and the final products. The experimental section of this thesis contains IUPAC names for the synthetic intermediates and the final products.

2.1.3. Total Synthesis of (!)-Sarcodonin G

2.1.3.1. Retrosynthetic Analysis

Our proposed synthetic plan for the construction of the cyathane natural product sarcodonin G (**36**) is outlined in Scheme 23. The target compound **36** can presumably be derived from keto aldehyde **158** *via* a selenenylation/oxidation/elimination sequence to introduce a double bond in the seven-membered ring, followed by a cleavage of the PMB ether to generate the alcohol function. Reduction of keto ester **159,** followed by Dess–Martin oxidation of the resultant diol, should provide the corresponding keto aldehyde **158**. In theory, the 5-6-7 fused tricyclic keto ester **159** can be obtained from the 5-6-6 fused tricycle **160** *via* a radical-based ring-expansion reaction. A sequence of ethoxy carbonylation and iodomethylation steps should provide the ring-expansion precursor **160** from ketone **161**. Ketone **161** should be available from alcohol **160** through a protection of the hydroxyl function as a PMB ether and an oxidative cleavage of the exocyclic double bond. On the basis of previous work in our laboratories (see Section 2.1.2.2 , *vide supra*),[68,69] alcohol **160** was expected to be accessible from the bicyclic dimethylhydrazone **161** and the bifunctional reagent **44** *via* keto alkenyl iodide **154**. Conversion of **154** to **151** would involve sequential BuLi-mediated cyclization and Still–Mitra [2,3]-sigmatropic rearrangement reactions.

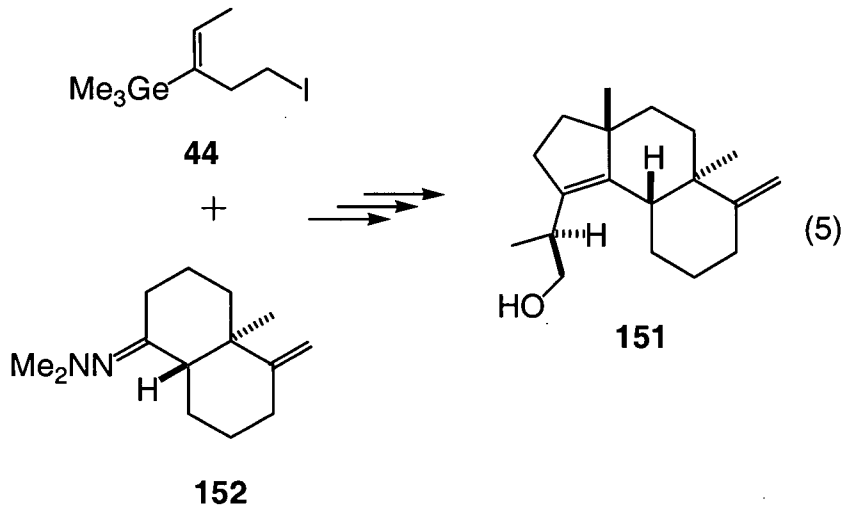


Scheme 23

2.1.3.2. Preparation of 5-6-6 Fused Tricycle 101

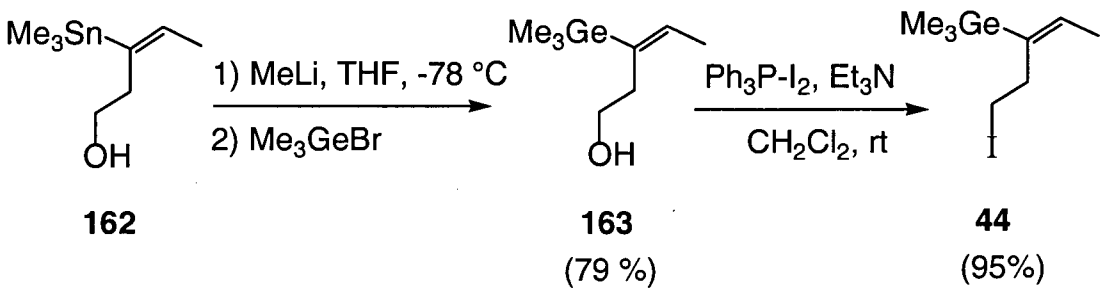
As described in Section 2.1.2.2 (Scheme 22, *vide supra*), previous work in our laboratories by K. L. Cook provided a synthetic route to the 5-6-6 fused tricyclic alcohol **151** from the bifunctional reagent **44** and *trans*-fused bicyclic dimethylhydrazone **152** (eq 5).[69] Since our study involved transformation of the advanced intermediate **151** into the

target compound sarcodonin G (*vide supra*), we embarked on a large-scale preparation of **151** and investigated several possible improvements to the previous synthesis.



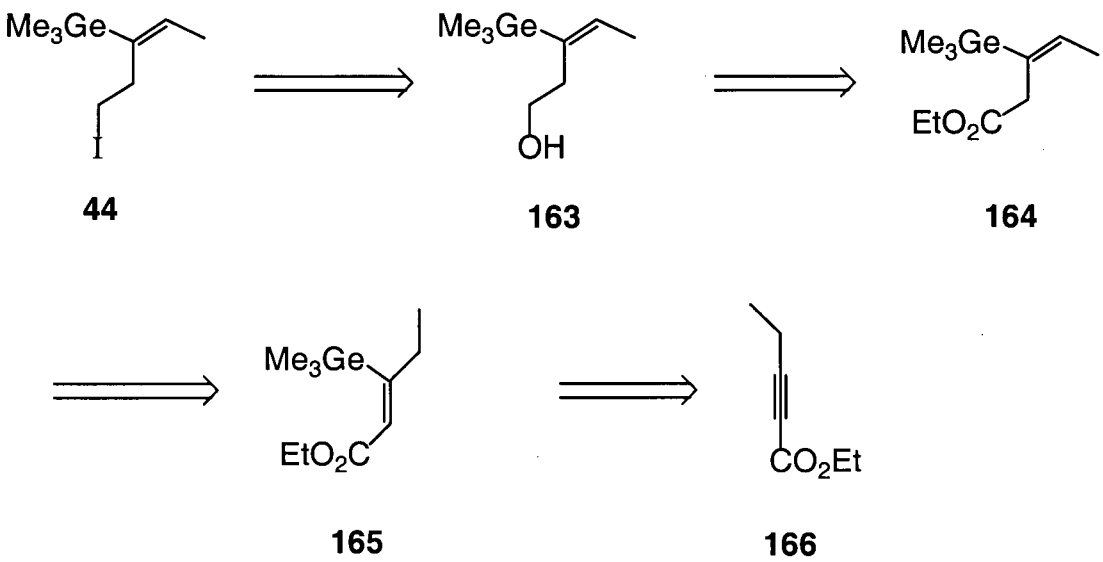
2.1.3.2.1. Preparation of Bifunctional Reagent 44

In Cook's study, the synthesis of iodide **44** (Scheme 24) commenced with the known alcohol **162**, which was readily obtained in three steps from commercially available materials.[70] Transmetallation of **162** with MeLi, followed by addition of Me_3GeBr, provided the corresponding germane **163**. Treatment of **163** with Ph_3P–I_2 and Et_3N furnished **44** in high yield.



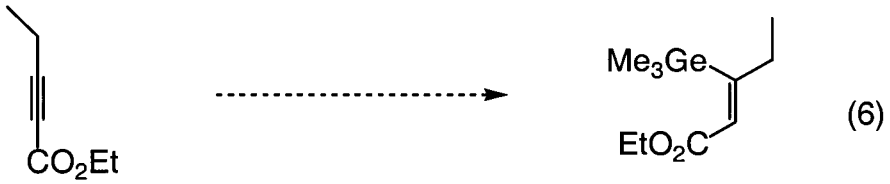
Scheme 24

An alternative synthesis of **44**, which would circumvent the tin-germanium exchange step (*vide supra*), is outlined in Scheme 25. Presumably, alcohol **163**, a known precursor to iodide **44**, could be obtained from a reduction of ester **164**. On the basis of previous studies by our group, it was thought that a stereospecific deconjugation of the ethyl (*Z*)-2-pentenoate **165** would provide ethyl (*E*)-3-pentenoate **164**. Compound **165** should to be available from ethyl 2-pentynoate (**166**) *via* a germylcuprate conjugate addition reaction also developed in our laboratories.



Scheme 25

The first step of our proposed synthesis of **44** involved the preparation of ethyl (*Z*)-3-trimethylgermyl-2-pentenoate (**165**) from the commercially available ethyl 2-pentynoate (**166**) (eq 6).



166 **165** (6)

The preparation of ethyl 3-trimethylgermyl-2-butenoates *via* conjugate addition of (trimethylgermyl)copper(I) reagents **167-170** to ethyl 2-butynoates has recently been reported[71] by Piers and Lemieux.

$Me_3GeCuMe_2S$ **167**

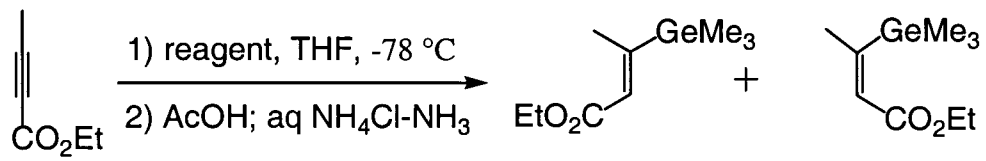
$Me_3GeCu(CN)Li$ **168**

$(Me_3Ge)_2CuLi$ **169**

$Me_3Ge(Me)Cu(CN)Li_2$ **170**

Treatment of alkynic ester **171** with germylcopper(I) reagents **167-170** was shown to afford the *E*- and *Z*-alkenylgermane isomers, **172** and **173** (**Table 1**). Conjugate addition of reagents **167** and **168** to alkynic ester **171** afforded the *E*-isomer **172** in high yields (entries 1-2, **Table 1**). A mixture of **172** and its geometric isomer **173** were obtained employing cuprate reagent **169** (entry 3, **Table 1**). Of particular interest to our study, conjugate addition of **170** favored formation of the Z-isomer **173** over the *E*-isomer **172** in a 3.9:1 ratio (entry 4, **Table 1**).

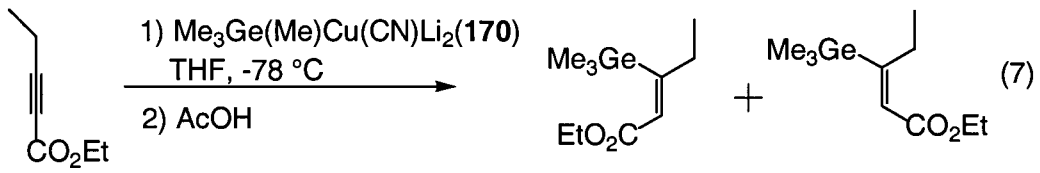
Table 1. Addition of Germylcopper(I) Reagents (**167-170**) to Ethyl 2-Butynoate (**171**).



171 **172** **173**

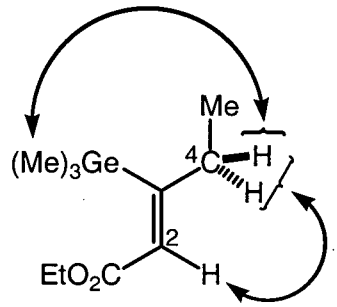
Entry	Reagent	**172**:**173** Ratio	Yield (%)
1	$Me_3GeCuMe_2S$ **167**	>99:1	81
2	$Me_3GeCu(CN)Li$ **168**	>99:1	90
3	$(Me_3Ge)_2CuLi$ **169**	1.7:1	90
4	$Me_3Ge(Me)Cu(CN)Li_2$ **170**	1:3.9	86

On the basis of the stereoselectivity displayed by the reaction summarized in entry 4 (**Table 1**), the conjugate addition of germylcuprate reagent $Me_3Ge(Me)Cu(CN)Li_2$ (**170**) was applied to the preparation of ethyl (*Z*)-3-trimethylgermyl-2-pentenoate (**165**). Ethyl 2-pentynoate (**166**) was added to a cold (–78 °C) solution of **170**, and the resultant mixture was treated with AcOH (eq 7). Upon aqueous work-up and purification of the resulting material by flash chromatography, ethyl (*Z*)-3-trimethylgermyl-2-pentenoate (**165**) and the corresponding *E*-isomer, **174**, were obtained in 71% and 20% yields, respectively.



166 **165** (71%) **174** (20%)

The structure of **165** was confirmed by spectrometric analysis. The IR spectrum of **165** exhibited an ester carbonyl stretch at 1718 cm^{-1}. The ^1H NMR spectrum of **165** displayed singlets at δ 0.29 (9H) and 6.21 (1H) attributed to the Me_3Ge– moiety and the olefinic proton, respectively. The ^{13}C NMR resonances for the olefin carbons and the ester carbonyl carbon were observed at δ 126.6 and 166.8, and at δ 171.4, respectively.

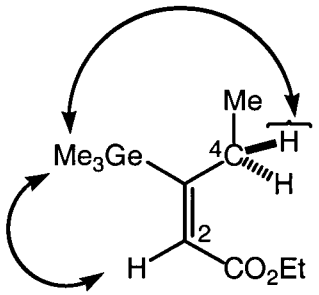


165

^1H NMR NOED experiments were performed to establish the geometry of the alkene function in **165**. Thus, irradiation at δ 2.30, a quartet attributed to the allylic methylene protons (H–4), caused enhancement of the signals at δ 6.21 and at δ 0.29, assigned to the olefinic proton (H–2) and the Me_3Ge– protons, respectively. When the signal at δ 0.29 (Me_3Ge–) was irradiated, enhancement of the quartet at δ 2.30 (H–4) was observed. Irradiation of the signal at δ 6.21 (H–2) also caused the quartet at δ 2.30 (H–4) to be enhanced. These experiments, along with the spectral data presented above are consistent with the structural assignment for ethyl (*Z*)-3-trimethylgermyl-2-pentenoate (**165**).

Spectrometric analysis of the *E*-isomer **174** supported its assigned structure. The ester carbonyl stretch of **174** was observed at 1718 cm^{-1} in its IR spectrum. The ^1H NMR

signals for the Me_3Ge– moiety and olefinic proton in **174** were displayed at δ 0.23 and 5.89, respectively. The ^{13}C NMR spectrum of **174** displayed resonances at δ 124.5 and 164.9, and at δ 171.3, representing the olefin and carbonyl carbons, respectively.

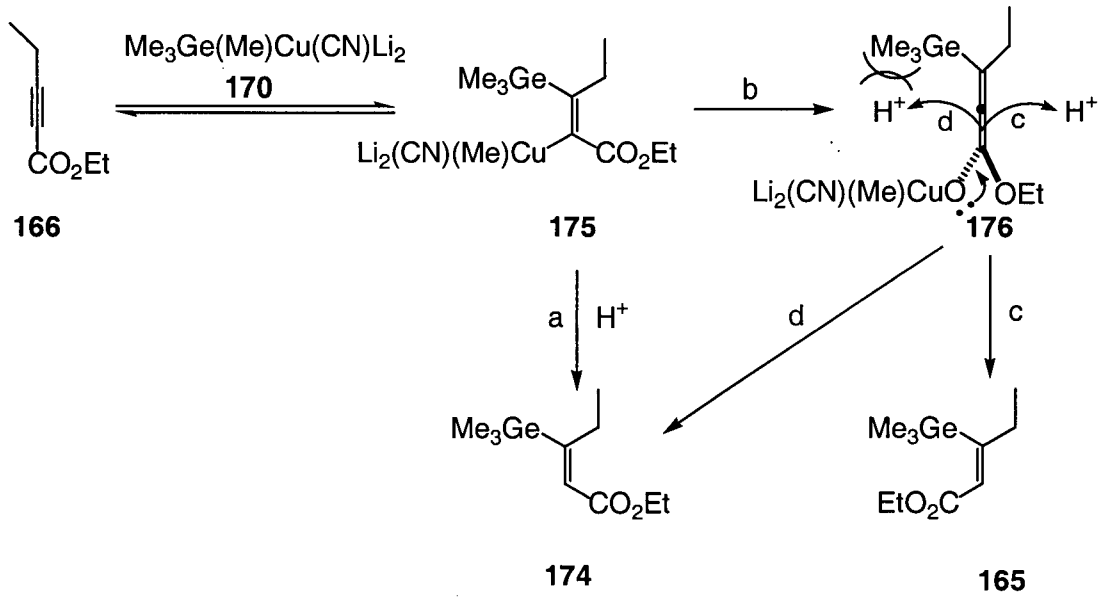


174

The geometry of the alkene function in **174** was established by ^1H NMR NOED experiments. Irradiation at δ 2.73, a quartet attributed to the allylic methylene protons (H–4), caused enhancement of the singlet at δ 0.23, assigned to the protons of the Me_3Ge– group. Irradiation of the olefinic proton (H–2) signal at δ 5.89 caused enhancement of the singlet at δ 0.23 (Me_3Ge–). When the signal at δ 0.29 (Me_3Ge–) was irradiated, the signals at δ 2.73 (H–4) and 5.89 (H–2) were enhanced. These experiments confirm the *E* configuration of the alkene function in **174**.

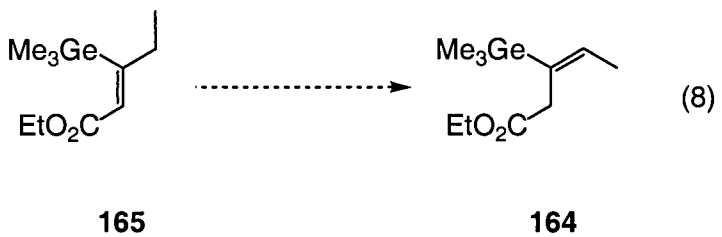
The formation of **165** and **174** can be rationalized by the possible pathway[71] depicted in Scheme 26. A reversible *cis* addition of cuprate **170** to ethyl 2-pentynoate (**166**) provides the alkenyl copper immediate **175**. Although direct protonation of **175** would produce the *E*-isomer **174** (path a), it appears that the majority of **175** isomerizes to the allenoate species **176** (path b). Protonation of allenoate **176** would occur predominantly from the side opposite to of the bulky Me_3Ge– moiety (path c), providing

primarily the *Z*-isomer **165**. Protonation of allenoate **176** from the same side as the Me_3Ge– moiety (path d) would provide *E*-isomer **174**.



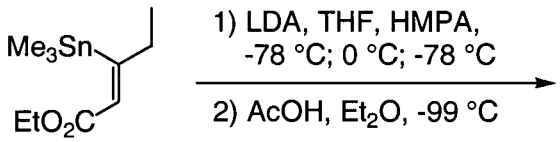
Scheme 26

With the ethyl (*Z*)-2-pentenoate **165** in hand, the next step involved a stereospecific deconjugation to provide ethyl (*E*)-3-pentenoate **164** (eq 8).

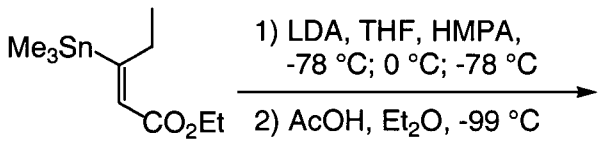


165 **164**

In 1990, Piers and Gavai reported[70] a study on the stereospecific deconjugations of ethyl 3-trimethylstannyl-2-pentenoates. For example, addition of (*Z*)-2-pentenoate **177** to a solution of LDA, followed by an inverse addition of the resultant enolate to a solution of AcOH, provided (*E*)-3-alkenoate **178** (eq 9). In a similar fashion, (*E*)-2-alkenoate **179** was transformed, completely stereoselectively, into the corresponding (*Z*)-3-alkenoate **180** (eq 10).

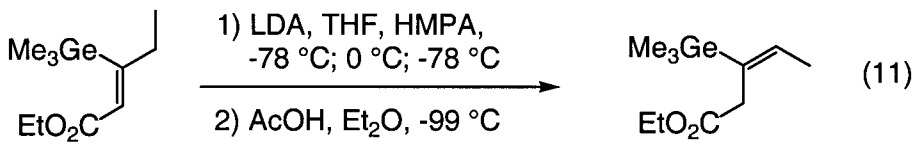


177 **178** (87%) (9)



179 **180** (82%) (10)

It was expected that the application of this deconjugation reaction (*vide supra*) to ethyl (*Z*)-3-trimethylgermyl-2-pentenoate **165** would provide the corresponding ethyl (*E*)-3-pentenoate **164**. Thus, a solution of **165** in THF was added to a solution of LDA and HMPA in THF (eq 11). Subsequent inverse addition of the resultant enolate solution to a cold (–98 °C) solution of AcOH in Et_2O provided, upon work-up, a 91% yield of the desired ethyl (*E*)-3-pentenoate **164**.

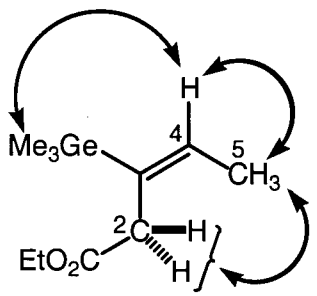


(11)

165

164
(91%)

Standard spectroscopic methods were used to confirm the structure of trimethylgermyl alkenoate **164**. A carbonyl absorption at 1737 cm^{-1} in the IR spectrum of **164** was characteristic of an aliphatic ester. The ^{1}H NMR spectrum of **164** displayed a singlet (2H) at δ 3.16, attributed to the allylic methylene α to the ester function. The signals corresponding to the alkenyl methyl and proton moieties were observed at δ 1.69 (doublet, J = 6.7 Hz) and δ 5.87 (quartet, J = 6.7 Hz), respectively. The ^{13}C NMR spectrum displayed resonances at δ 135.5 and 135.7, assigned to the olefinic carbons. The ^{13}C signal for the ester carbonyl carbon was observed at δ 171.8.

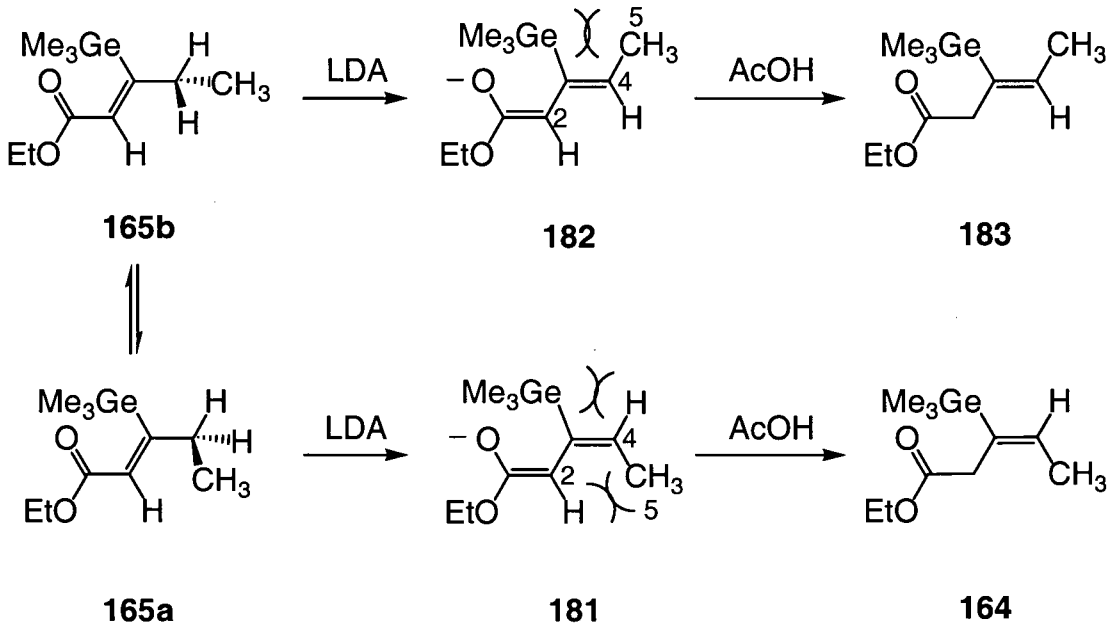


164

The geometry of the alkene function in **164** was confirmed by ^{1}H NMR NOED experiments. Irradiation at δ 1.69, attributed to the methyl protons (H–5), caused enhancement of resonances at δ 5.87 and 3.16, assigned to the olefinic proton (H–4) and

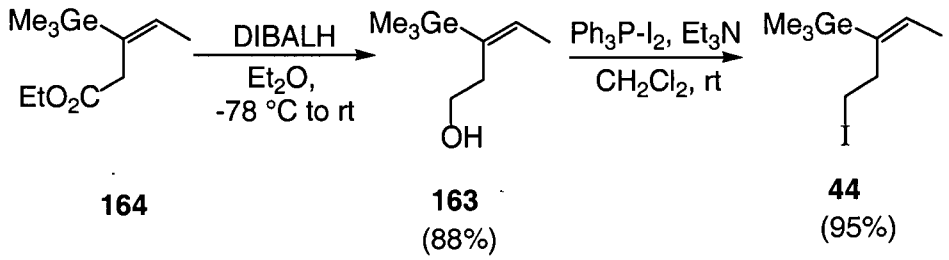
methylene protons (H–2), respectively. When the olefinic proton (H–4) signal at δ 5.87 was irradiated, the signals at δ 1.15 (Me_3Ge–) and 1.69 (H–5) were enhanced. These experiments, along with the spectral data presented above are consistent with the structural assignment for ethyl (*E*)-3-trimethylgermyl-3-pentenoate (**164**).

The stereoselective formation of **164** from **165** may be qualitatively rationalized[70] as shown in Scheme 27. The relative transition states for the kinetically controlled deprotonation of two ground state conformations, **165a** and **165b,** leading to the respective extended enolates **181** and **182**, were considered. The transition state leading to the extended enolate **182** would be highly destabilized by the developing $A^{1,2}$ strain (between CH_3–5 and the Me_3Ge–group). On the other hand, the transition state leading to the extended enolate **181** would be destabilized by the relatively smaller steric repulsions due to $A^{1,2}$ strain (H–4 and Me_3Ge–) and $A^{1,3}$ strain (CH_3–5 and H–2). In addition, if the transition state leading to the extended enolate **181** contains some allylic anion-type character it may experience stabilization from the fact that the **181** contains a *cis* alkyl group.[72] Strong evidence provided by experimental and theoretical studies suggests that allylic anions systems containing *cis* alkyl groups are more stable than those possessing *trans* alkyl moieties.[73] Hence, for this reason and for steric reasons, the deprotonation step would be expected to favor the formation of the allylic anion **181**, which affords the *E*-alkenoate **164**, upon protonation.



Scheme 27

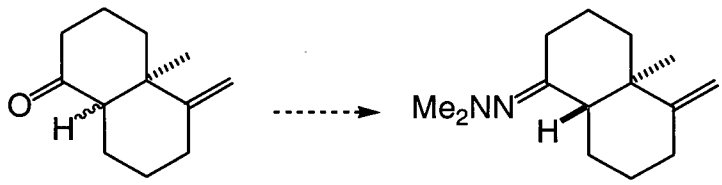
The final steps in the synthesis of bifunctional reagent **44** from ester **164** were straightforward (Scheme 28). DIBALH reduction of ester **164** provided alcohol **163** in 88% yield. As demonstrated by Cook (see Scheme 24 earlier), addition of **163** and Et_3N to a solution of Ph_3P–I_2 in CH_2Cl_2 provided the corresponding iodide **44** in high yield. All spectral data derived from compounds **163** and **44** were identical to those reported[69] by Cook.



Scheme 28

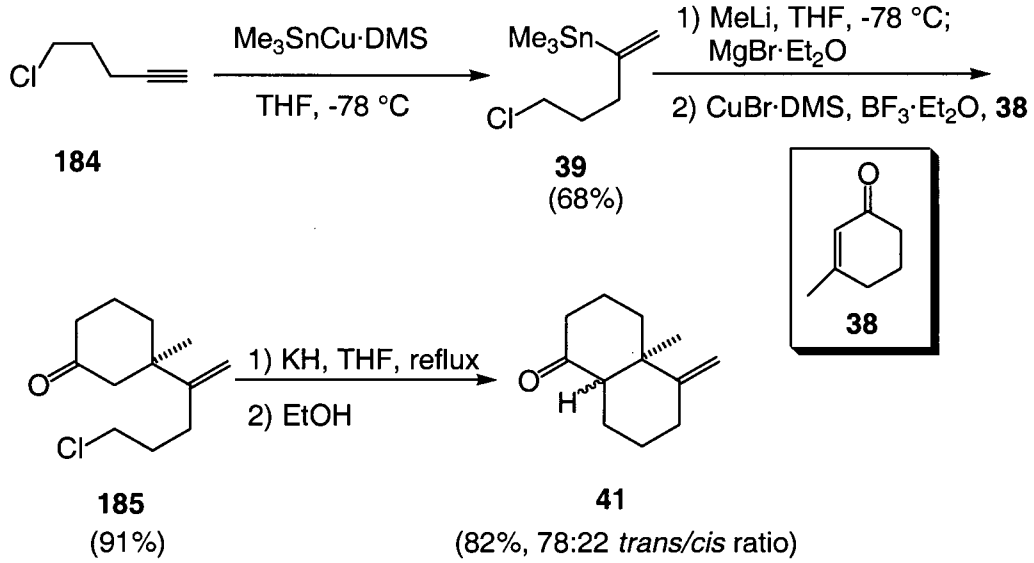
2.1.3.2.2. Preparation of *cis*-Fused Bicyclic Dimethylhydrazone 102

With the desired electrophile **44** in hand, preparation of the *trans*-fused bicyclic dimethylhydrazone **152** from the ketones **41** was investigated (eq 12).



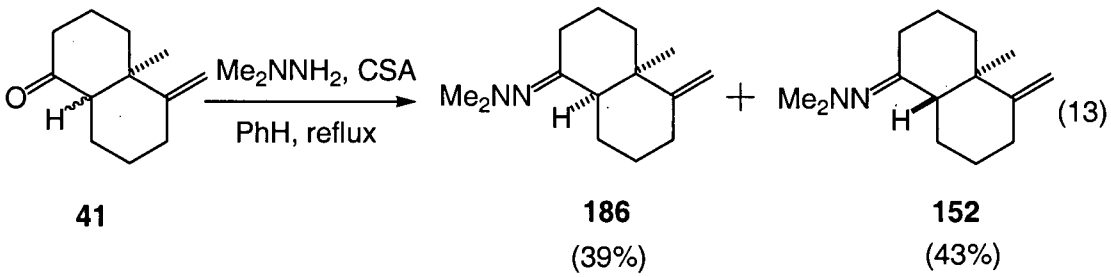
41 **152** (12)

The known bicyclic ketones **41** were prepared following a 3-step procedure developed in our laboratories.[18] Commercially available 5-chloro-1-pentyne (**184**) was added to a solution of $Me_3SnCu{\cdot}DMS$ complex, providing, upon work-up, the bifunctional reagent **39** (Scheme 29). A copper-catalyzed conjugate addition of the Grignard reagent derived from **39** to 3-methyl-2-cyclohexen-1-one (**38**) afforded the cyclic keto chloride **185**. KH-mediated cyclization of the keto chloride **185**, followed by an ethoxide-mediated epimerization reaction, yielded a 78:22 mixture of the *trans*- and *cis*- fused bicyclic ketones **41**.

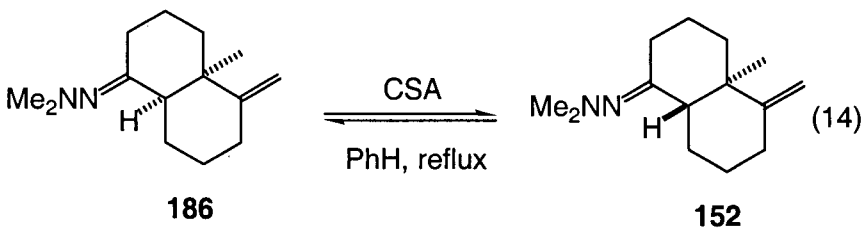


Scheme 29

As described in Cook's study,[69] the conversion of ketones **41** into the corresponding hydrazone derivatives was accomplished by treatment of a benzene solution of the former with dimethylhydrazine and a catalytic amount of CSA (eq 13). The resultant mixture was refluxed for 72 h with azeotropic removal of water. Upon solvent removal and purification of the resultant material by flash chromatography, the *cis*- and *trans*-fused bicyclic dimethylhydrazones, **186** and **152**, were obtained in 39% and 43% yields, respectively.



In the previous study, the *trans*-fused isomer **152** was carried through to the next step but the undesired *cis*-fused isomer **186** was abandoned. For our large-scale synthesis, a method of recycling the large quantities of the *cis*-fused **186** was sought. Although **186** did not appear to isomerize under standard base-mediated conditions (NaOMe/MeOH or *t*-BuOK/*t*-BuOH), acid-mediated isomerization conditions (CSA, benzene) yielded significant amounts of the desired *trans*-fused isomer **152** (eq 14). Thus, a catalytic amount of CSA was added to a benzene solution of the **186** and the resultant mixture was refluxed for 48 h. Upon work-up and purification of the resulting material by flash chromatography, **186** and **152** were obtained in nearly a 1:1 ratio. The *cis*-fused isomer **186** was recycled twice through the epimerization step, yielding additional **152** for a total overall yield of 71% from the mixture of ketones **41**.

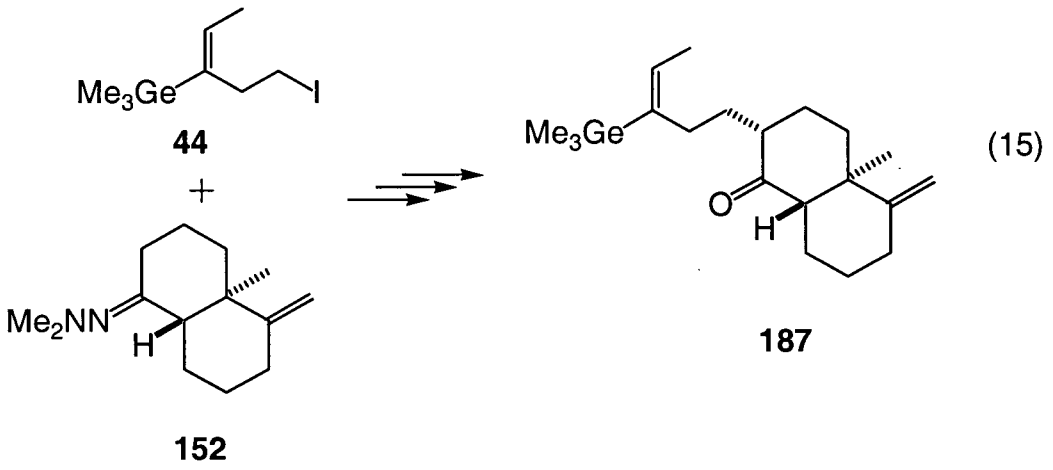


186 **152**

1:1 ratio of **186:152**

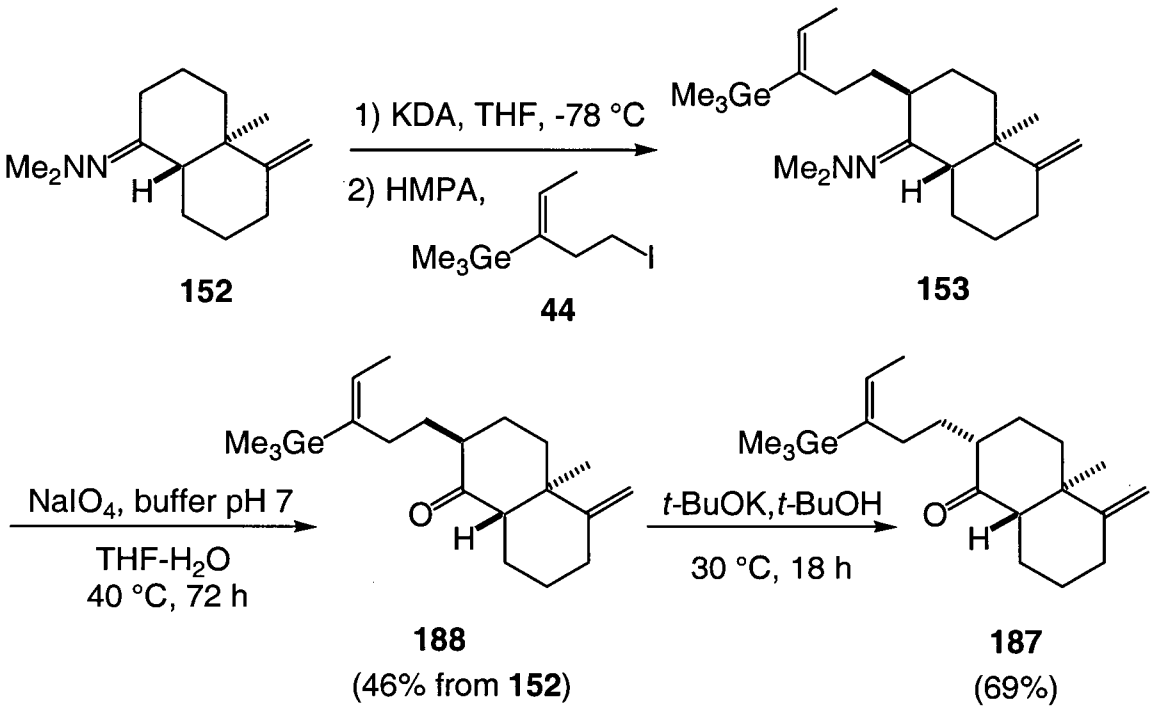
2.1.3.2.3. Preparation of Ketone 187

With building blocks **152** and **44** in hand, the synthetic sequence leading to ketone **187** was investigated (eq 15).



(15)

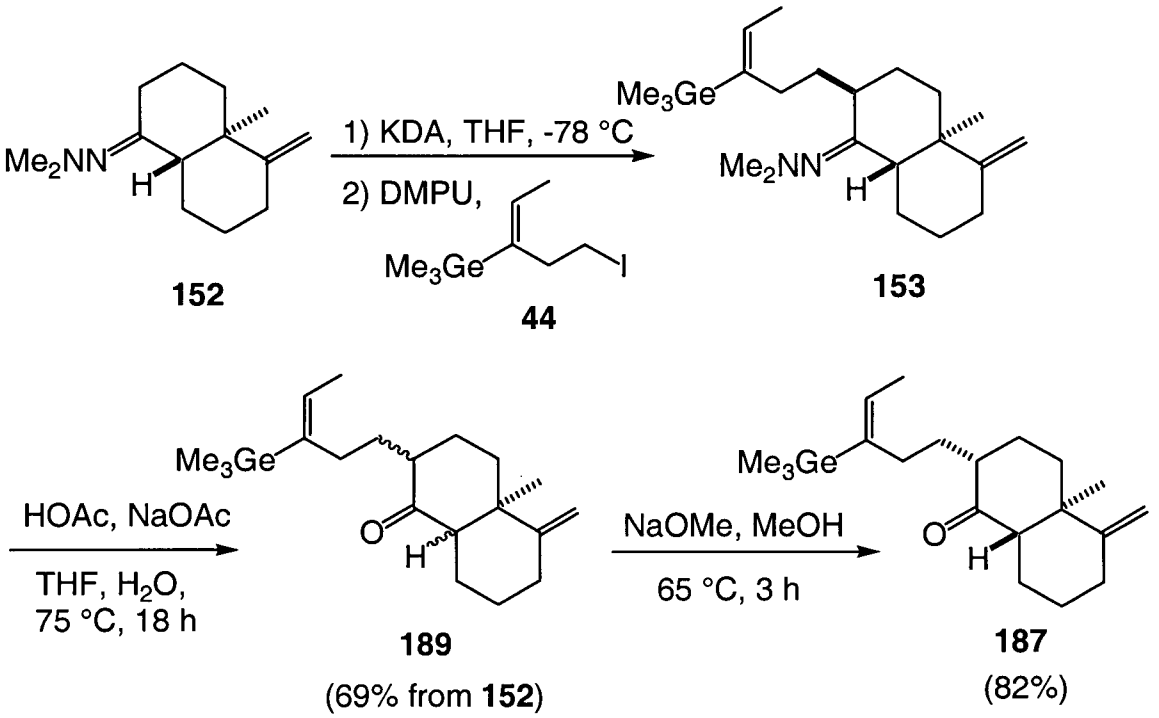
Cook's preparation[69] of **187** from **152** and **44** is outlined in Scheme 30. Deprotonation of the *trans*-fused hydrazone **152** with KDA, followed by addition of HMPA and iodide **44** to the resulting enolate solution, afforded adduct **153** after work-up. The crude **153** was taken up in a buffered aqueous THF mixture and the latter was treated with sodium periodate. The resultant mixture was heated to 40 °C and stirred for 72 h, affording ketone **188** in 46% yield. Isomerization of **188** was accomplished by treatment of this material with *t*-BuOK/*t*-BuOH, thus providing a 69% yield of isomer **187**. The overall yield from **152** to **187** was 32% and the reaction times for the last two steps totaled 90 h.



Scheme 30

The optimized experimental procedures employed for our large-scale conversion of **152** to **187** are outlined in Scheme 31. Alkylation of the potassium enolate derived from **152** with iodide **44** was accomplished in the presence of DMPU, a less-toxic alternative to carcinogenic HMPA. The crude hydrazone **153** was subjected to hydrolysis with NaOAc/AcOH in aqueous THF, affording a mixture of isomeric ketones **189** in 69% yield from **152**. A 3 h isomerization of **189** in NaOMe/MeOH afforded a 66% yield of ketone **187** and 22% of three other diastereomers. The mixture of undesired ketone isomers was resubmitted to the same isomerization reaction to yield an additional quantity of **187** for a total overall yield of 82% from **189**. In comparison with the previous synthesis (*vide supra*), the total overall yield from **152** to **187** had been

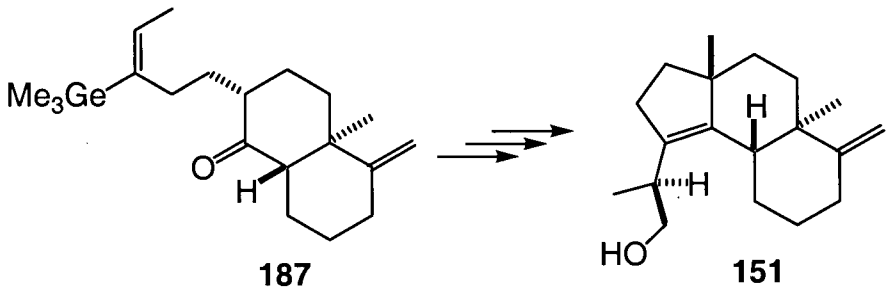
increased from 32% to 57% and the total reaction times of the latter two steps had decreased from 90 h to 24 h. All spectral data derived from **187** were identical with those of the corresponding data reported[69] by Cook.



Scheme 31

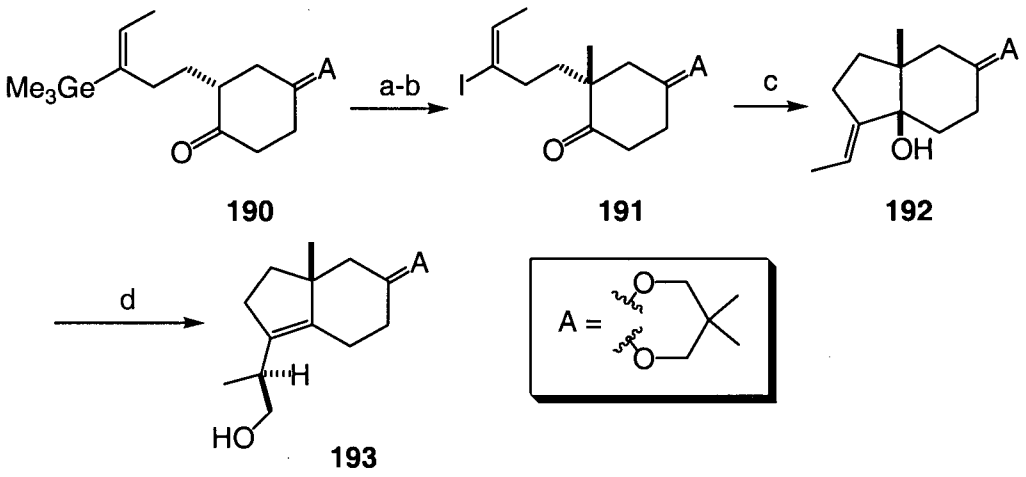
2.1.3.2.4. Preparation of Alcohol 151

With ketone **187** in hand, the sequence of reactions leading from this substance to alcohol **151** was investigated (eq 16).



(16)

In 1996, Piers and Cook reported[68] an annulation method that relied on sequential BuLi-mediated ring closure and Still–Mitra [2,3]-sigmatropic rearrangement[19] reactions. For example, methylation of **190**, followed by iododegermylation, gave keto alkenyl iodide **191** (Scheme 32). Treatment of **191** with BuLi resulted in an anionic ring closure, affording the *cis*-fused alcohol **192**. Conversion of **192** to its tributylstannylmethyl ether derivative, followed by a Still–Mitra [2,3]-sigmatropic rearrangement, provided alcohol **193**.

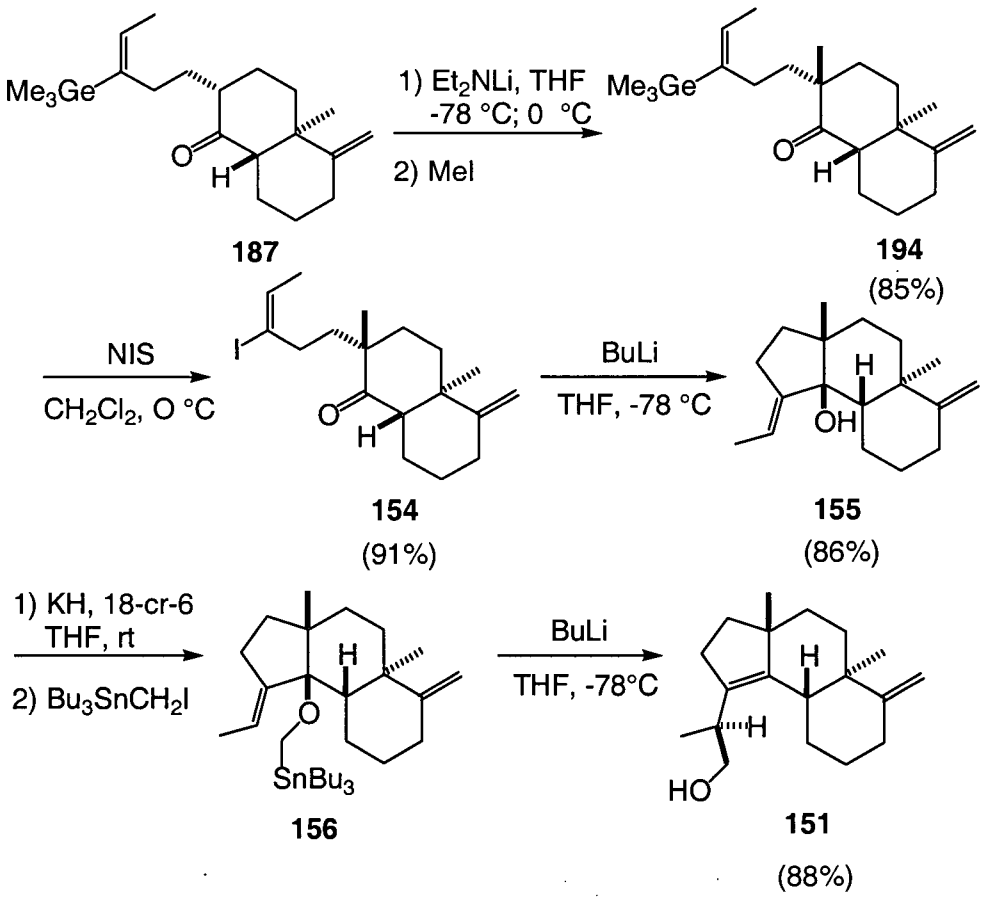


Reagents: a) *t*-BuOK, THF, HMPA; MeI; b) I_2, CH_2Cl_2; c) BuLi, THF; d) KH, 18-cr-6; Bu_3SnCH_2I; BuLi.

Scheme 32

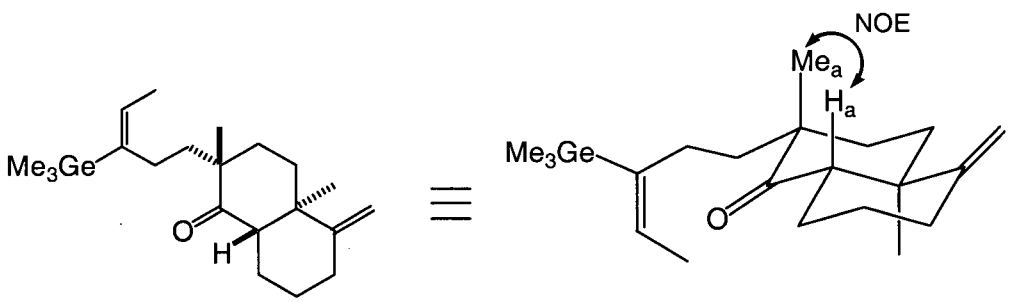
This novel annulation sequence (*vide supra*) was successfully applied to the conversion of **187** to **151**, as reported in Cook's previous study. The experimental procedures developed[69] by Cook were also employed in our large-scale preparation of **151** (Scheme 33). Methylation of **187** furnished **194** in 85% yield. The reaction involving iododegermylation of **194** with NIS in CH_2Cl_2 was stopped after 1 h, affording the corresponding alkenyl iodide **154** in 91% yield. In Cook's study, the NIS-mediated

iododegermylation process was stopped after 15 min, affording **154** in only 69% yield. A BuLi-mediated anionic ring-closure of keto alkenyl iodide **154** provided alcohol **155** in 86% yield. Treatment of **156**, the tributylstannylmethyl ether derivative of alcohol **155**, with BuLi resulted in the required [2,3]-sigmatropic rearrangement, affording alcohol **151** in 88% yield from **155**. All spectral data derived from the **194**, **154**, **155** and **151** were identical with those reported[69] by Cook.



Scheme 33

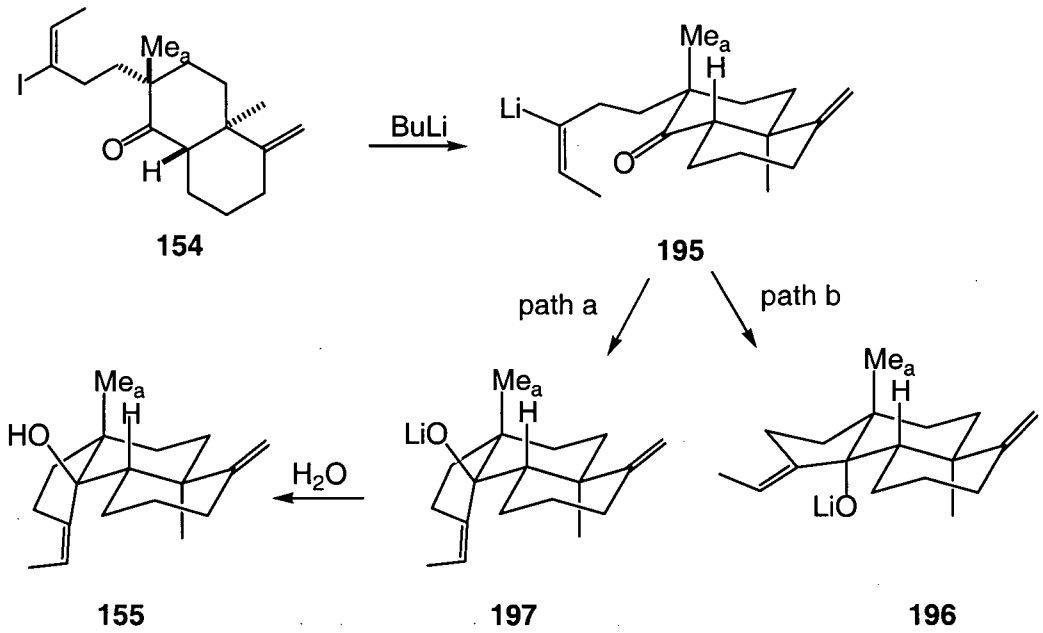
Many stereochemical aspects of the sequence of transformations leading from **187** to **151** have been discussed elsewhere.[68,69] However, several key features noted[69] by Cook that support the assigned relative configurations of intermediates **194**, **155** and **151**, are certainly worth outlining. The successful stereoselective axial methylation of **187** was confirmed by ^{1}H NMR NOED experiments performed on compound **194**. In the ^{1}H NMR spectrum of **194,** the newly introduced methyl group (Me_a) and the angular proton (H_a) gave rise to signals at δ 1.17 and 2.44, respectively. In NOED experiments, irradiations at δ 1.17 and 2.24 resulted in a mutual enhancement of these two resonances, thus establishing the *cis* relationship between the newly introduced methyl moiety (Me_a) and the angular proton (H_a).



194

The BuLi-mediated cyclization of iodide **154** was completely stereoselective, affording the *cis*-fused tricycle **155,** exclusively (Scheme 34). The *cis* configuration of the ring-fusion of **155** was not unambiguously determined. However, on the basis of previously reported studies[68] and molecular modeling, the presence of the angular methyl Me_a in **195**, the intermediate derived from **154**, was expected to result in the exclusive

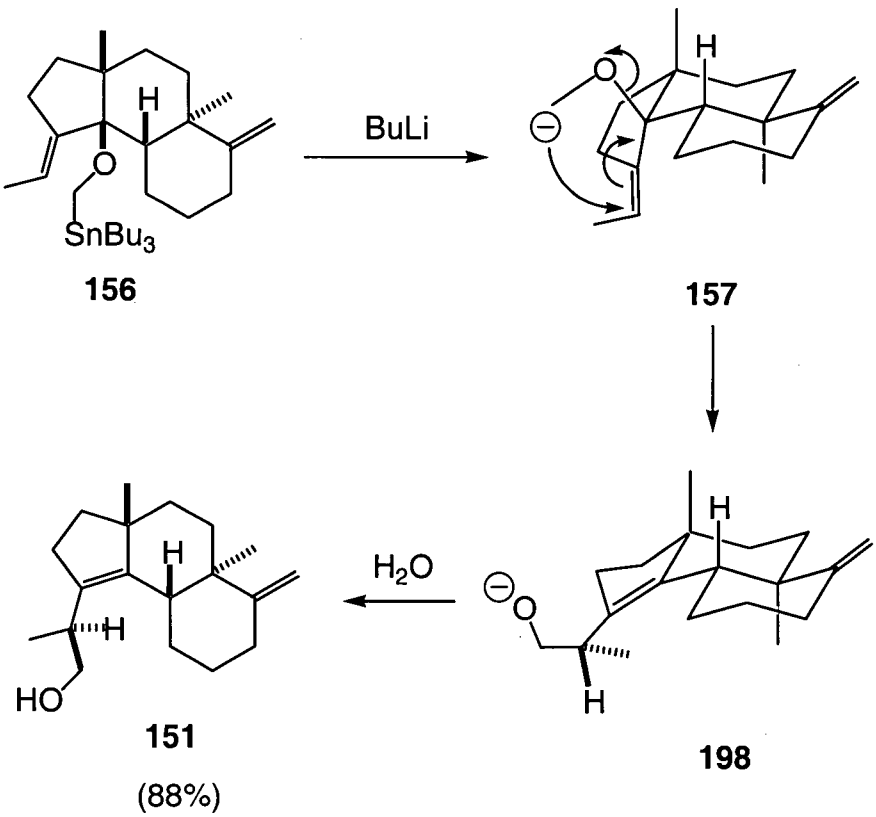
formation of a *cis*-fused cyclization product **197**. The molecular conformation of the transition state necessary for the cyclization of the alkenyllithium intermediate **195** leading to *cis*-fused alcohol **197** (path a) would appear to be considerably less strained than that leading to the corresponding *trans*-fused alcohol **196** (path b). The molecular conformation of the transition state leading to the *trans*-fused alcohol **196** would likely experience significant angle strain in the forming five membered ring in addition to the steric strain involving gauche interaction between the angular methyl Me_a and the incoming alkenyllithium moiety.



Scheme 34

The stereospecific nature of the Still–Mitra [2,3]-rearrangement, which provided alcohol **151** from tributylstannylmethyl ether **156**, has been well established (Scheme 35).[19,74] Transmetallation of tributylstannylmethyl ether **156** with BuLi afforded the

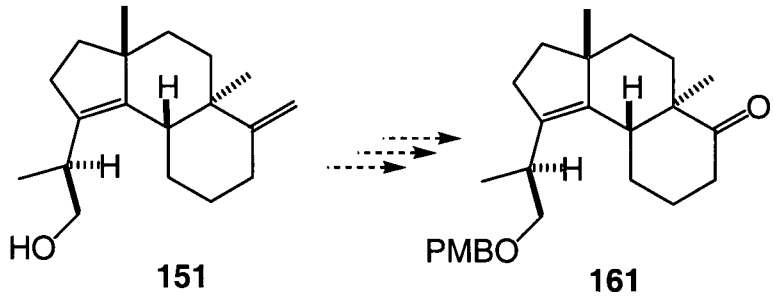
carbanion intermediate **157**. The rearrangement process would take place in a suprafacial manner, affording alkoxide **198**. Thus, the relative configuration of alcohol **151**, obtained upon aqueous work-up of **198** could be assigned with confidence.



Scheme 35

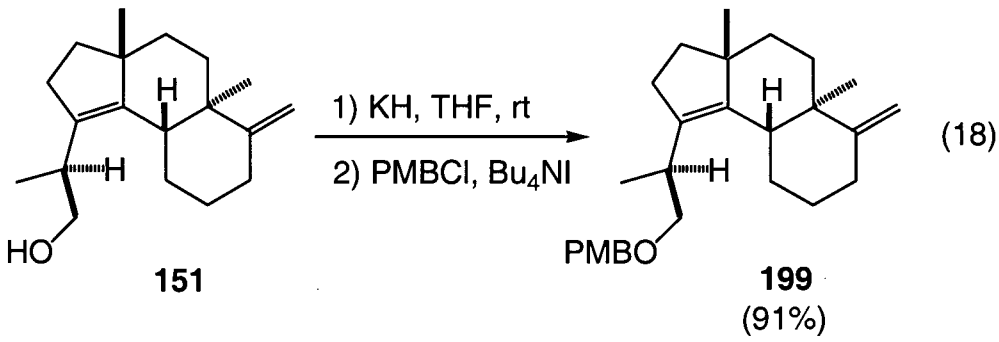
2.1.3.3. Preparation of Ketone 112

Having completed a large-scale preparation of alcohol **151**, which represents the most advanced intermediate in Cook's study,[69] the preparation of ketone **161** was investigated (eq 17).



(17)

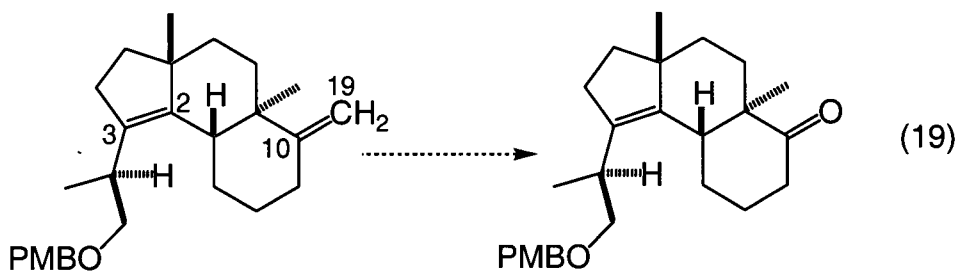
The first step was envisaged to be the protection of the hydroxyl moiety in **151** by converting this material into the corresponding *p*-methoxybenzyl ether **199** (eq 18). The *p*-methoxybenzyl (PMB) protecting group was chosen for its resistance to acidic and basic conditions. When required, the PMB group can be readily removed under mild neutral conditions with DDQ at room temperature.[75] Thus, the alkoxide derivative of alcohol **151,** which was generated *via* a deprotonation of **151** by KH in THF, was treated with *p*-methoxybenzyl chloride and a catalytic amount of $Bu_4N^+I^-$. The $Bu_4N^+I^-$ caused a Finkelstein-type *in situ* conversion of the PMBCl into the more reactive electrophile, *p*-methoxybenzyl iodide. Standard work-up and purification of the resultant material by flash chromatography provided the *p*-methoxybenzyl ether **199** in 91% yield.



151 **199** (91%) (18)

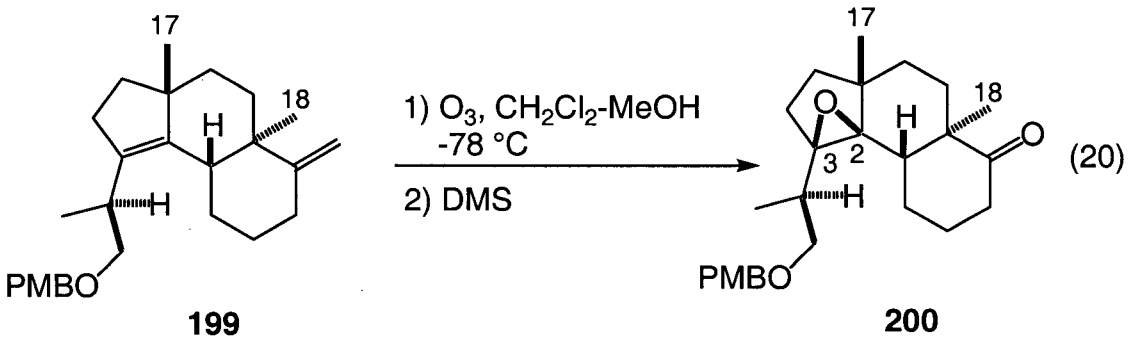
The successful formation of ether **199** was supported by ^{1}H NMR spectroscopic analysis of the product. The ^{1}H NMR spectrum of **199** displayed a 3-proton singlet at δ 3.78, representing the methoxy moiety of the PMB protecting group. In addition, two doublets were observed at δ 6.86 (2H, J = 8.9 Hz) and δ 7.23 (2H, J = 8.9 Hz), representing the aromatic protons of the *para*-substituted benzyl group.

With the ether diene **199** in hand, the next task was the chemoselective oxidative cleavage of the C–10(19) exocyclic double bond to form ketone **161** (eq 19). However, it was found (*vide infra*) that this chemoselective oxidation was difficult to achieve owing to the small difference in reactivity between the C–10(19) exocyclic double bond and the C–2 endocyclic double bond.



199 **161** (19)

Ozonolysis was the first method investigated to achieve the required chemoselective oxidative cleavage. Following a standard ozonolysis procedure, a gaseous flow of ozone in O_2 was passed through a cold solution of diene **199** in $MeOH/CH_2Cl_2$ for 10 min, at which point the solution turned light blue, indicating the presence of excess ozone in the mixture (eq 20). Reductive work-up with dimethyl sulfide was followed by removal of the volatiles under reduced pressure. Purification of the resultant material by flash chromatography provided a major product, which was tentatively assigned structure **200**.

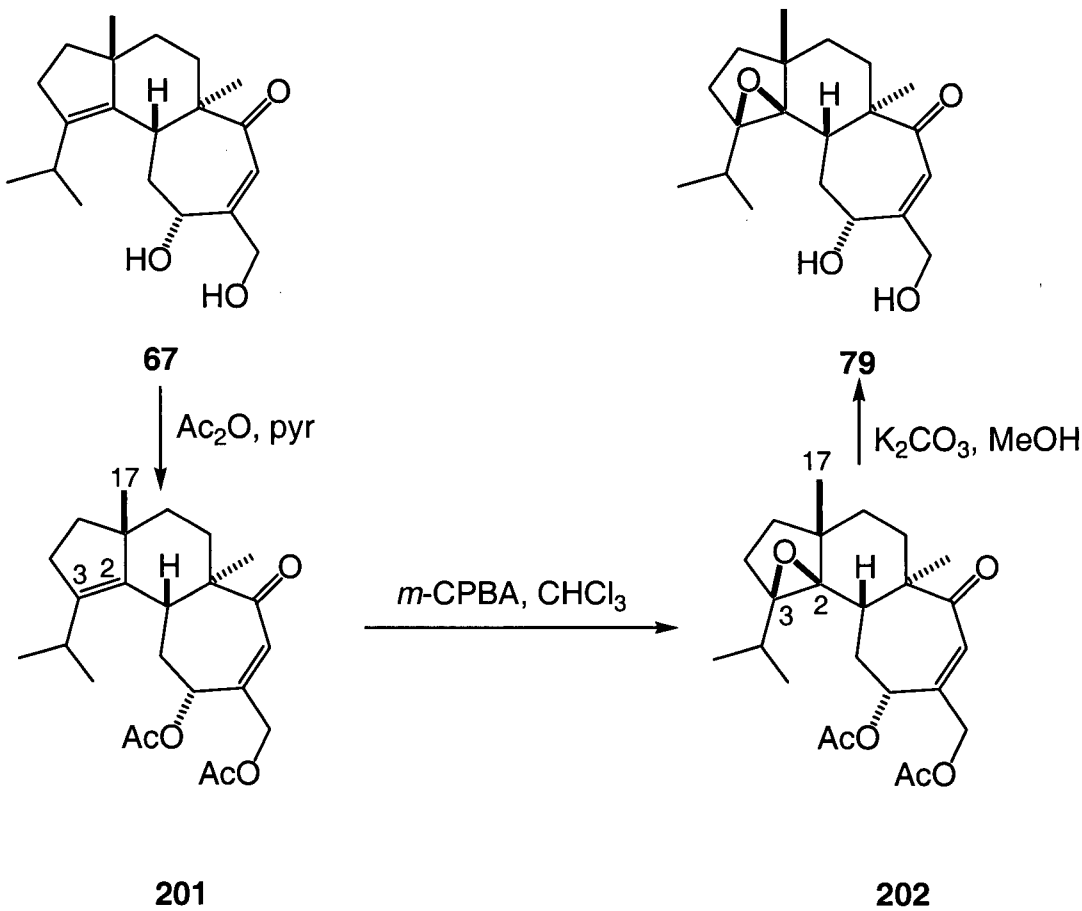


199 **200** (20)

The assigned structure of compound **200** was supported by spectrometric analysis. A molecular mass peak at 412 in the mass spectrum of **200** confirmed its $C_{26}H_{36}O_4$ chemical formula. The ^1H NMR spectrum of **200** displayed 3-proton singlets at δ 1.24 and 0.86, attributed to the H–17 and H–18 angular methyl protons, respectively. Previously, the ^1H NMR signal for the corresponding H–17 and H–18 angular methyl protons in diene **200** had been noted at δ 1.01 and 0.92, respectively. The apparent deshielding of the H–17 angular methyl protons in **200** relative to those of **199** was attributed to the newly introduced β-face epoxide function at C–2,3 in **200**. This rationale

for the proposed structure of **200** was based on an analogous argument by Ayer and coworkers (*vide infra*).

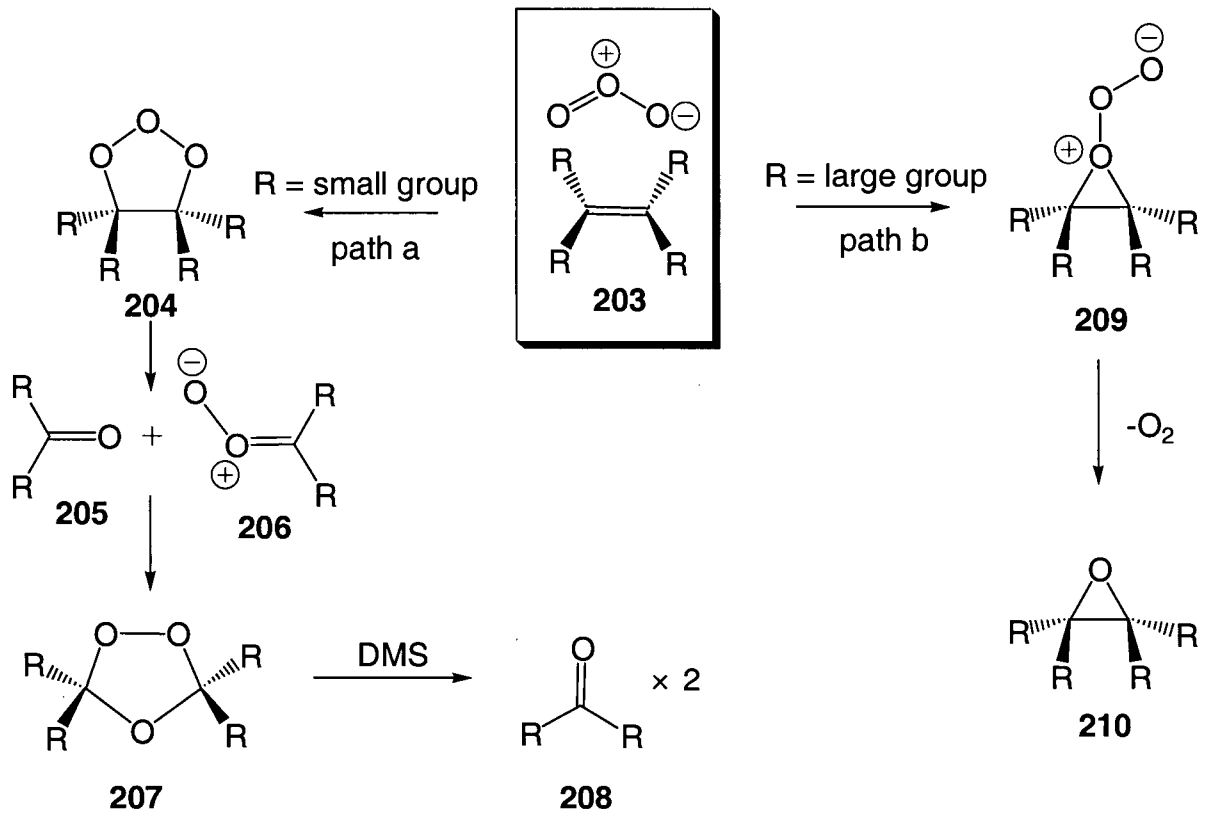
A similar β-face selective epoxidation was noted by Ayer and coworkers in their reported structural elucidation studies on neoallocyathin A_4 (**79**) involving spectroscopic correlations with a derivative of cyathin A_3 (**67**) (see Section 2.1.1.3., *vide supra*).[17] Compound **201**, a diacetyl derivative of cyathin A_3 (**67**), was treated with *m*-CPBA to afford the β-epoxide **202** (Scheme 36). Treatment of a methanol solution of **202** with potassium carbonate gave neoallocyathin A_4 (**79**), which was spectroscopically identical with the corresponding natural product.



Scheme 36

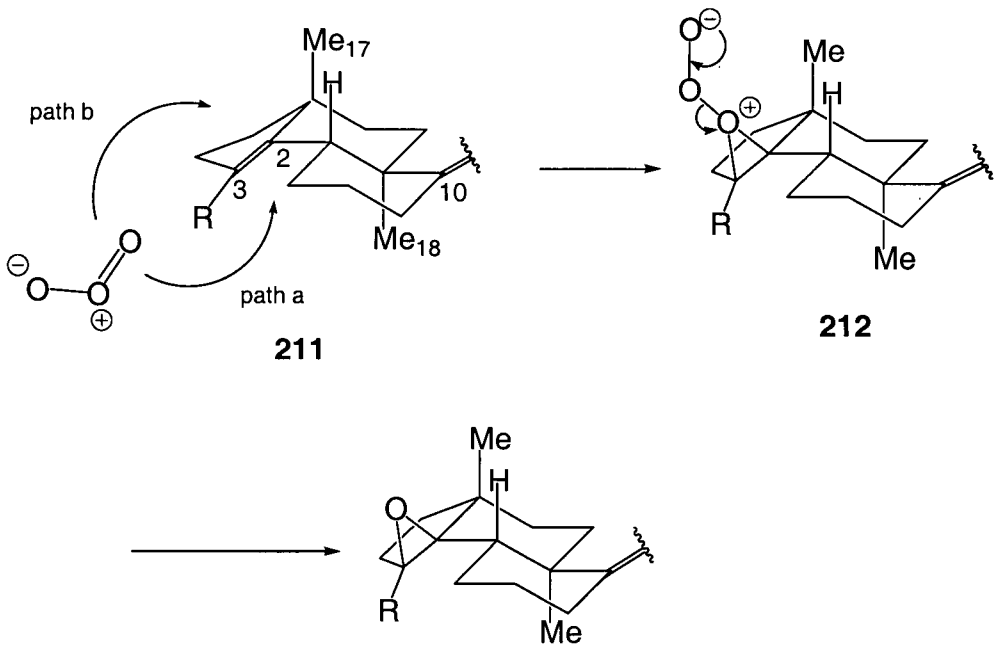
The rationale used to assign the structure of **200** in our study (*vide supra*) was based on the following evidence presented by Ayer and coworkers. The ^{1}H NMR signal attributed to the H–17 angular methyl protons of **202** was noted at δ 1.28. The ^{1}H NMR signal for the corresponding H–17 methyl protons in **201** had previously been noted at δ 1.07. The downfield shift of the H–17 signal for **202** relative to that of the H–17 signal for **201** was attributed to significant deshielding by the newly introduced C–2,3 β-epoxide in **202**.

Although the epoxidation of **201** upon treatment with *m*-CPBA, as reported by Ayer and coworkers, was certainly expected, the epoxidation of **200** by ozonolysis, as noted in our study (*vide supra*), was not anticipated. A brief review of the literature provided some insight into this undesired ozonolysis side-reaction. The proposed mechanism for the ozonolysis reaction of non-hindered olefins (path a) involves three steps (Scheme 37).[76] The first step is an electrophilic cycloaddition of ozone to the alkene (see **203** → **204**, Scheme 37). Cleavage of the resultant ozonide **204** provides carbonyl **205** and carbonyl oxide zwitterion **206**, which recombine to afford the cyclic ozonide **207**. Reductive work-up of **207** with dimethyl sulfide provides two carbonyl compounds, **208**. On the other hand, it has been shown that some hindered alkenes appear to be too sterically encumbered to allow for an electrophilic cycloaddition with ozone.[77] Alternatively, upon treatment with ozone, a hindered alkene (**203**) may form the peroxyepoxide intermediate **209** (path b). Loss of one molecule of dioxygen from **209** provides epoxide **210**.[78]



Scheme 37

In our study, the observed formation of a β-face epoxide upon ozonolysis of **199**, represented by partial structure **211**, may be rationalized with the help of Scheme 38. Only partial structures are illustrated because the state of the alkene at C–10, which is ultimately cleaved in this step, is not known at the time of the epoxidation. On the basis of molecular models, an approach by ozone to the α-face of C–2 double-bond in **211** (path a) would experience more steric interference, including 1,3-diaxial interaction with Me–18, than would the corresponding β-face approach (path b). Loss of dioxygen by the resulting peroxyepoxide **212** would afford intermediate **213**, displaying a β-configuration of the epoxide moiety.

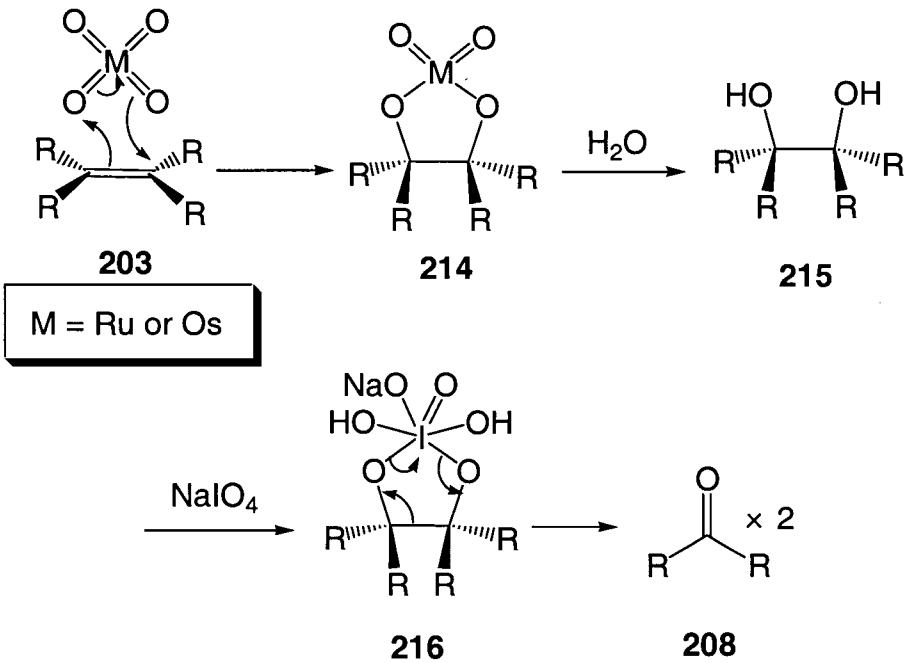


Scheme 38

In an attempt to prevent epoxide formation, the ozonolysis was repeated in the presence of Sudan Red 7B,[79] a dye that allows detection of low ozone concentrations. Despite careful observation and short reaction times, the epoxidation could not be prevented and the desired reaction could not be accomplished. Therefore, the ozonolysis approach to preparing **161** from **199** was abandoned and alternative methods for the chemoselective oxidative cleavage were investigated.

Certain transition metal-based oxidants have been shown to effect the cleavage of C–C double bonds *via* the pathway illustrated in Scheme 39.[80] Treatment of an alkene (**203**) with ruthenium tetroxide or osmium tetroxide generates intermediate **214** *via* a stereospecific *syn*-addition. Vicinal diol **215**, derived from **214**, can be oxidatively

cleaved by treatment with a periodate reagent. The proposed mechanism of this transformation involves cleavage of the cyclic adduct **216** to afford carbonyl compounds **208**.

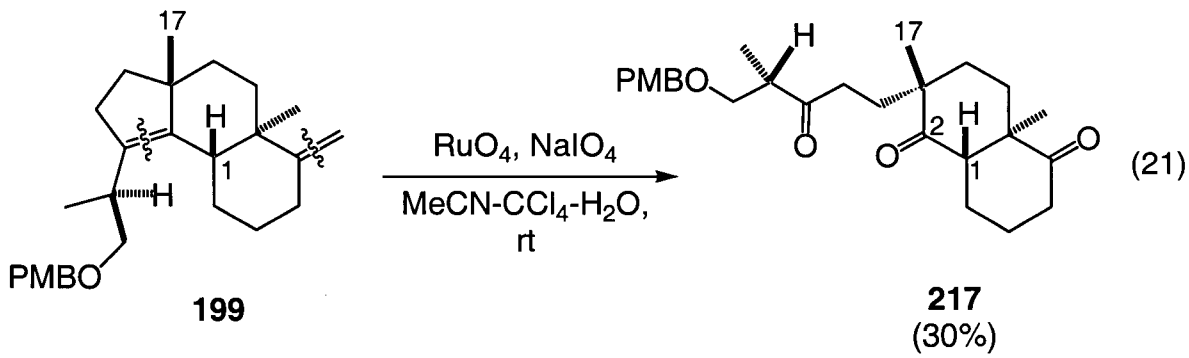


203 **214** **215** **216** **208**

Scheme 39

Ruthenium tetroxide is a toxic, volatile oxidant that is generally prepared by *in situ* oxidation of RuO_2 by a stoichiometric amount of periodate. The periodate reagent therefore serves the dual purpose of re-oxidizing the catalyst and cleaving the diol intermediate. Thus, in the presence of two equivalents of periodate and a catalytic amount of ruthenium dioxide, an olefin can undergo complete oxidative cleavage. Using modified conditions described by Sharpless and coworkers,[81] a solution of the diene **199** in a 1:1:1.5 mixture of acetonitrile, carbon tetrachloride and water was treated with a catalytic amount of ruthenium dioxide and two equivalents of sodium periodate (eq 21).

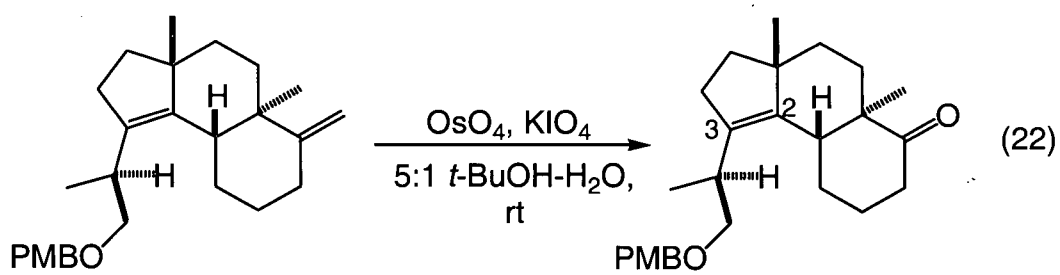
Work-up and purification of the resultant material by flash chromatography provided one major product and 50% of recovered starting material (**199**). On the basis of spectroscopic analysis, the major product was tentatively assigned structure **217**, derived from the oxidative cleavage of both double bonds in diene **199**. A molecular mass peak at 428 in the mass spectrum of **217** confirmed its $C_{26}H_{36}O_5$ chemical formula. The ^1H NMR spectrum of **217** displayed signals at δ 1.15 and 2.65, attributed to H–17 and H–1, respectively. The corresponding ^1H NMR signals for the H–17 and H–1 in diene **199** were previously noted at δ 1.01 and 1.99, respectively. The downfield shifts noted for the signals of the H–17 and H–1 of **217** relative to those of diene **199** may be partially attributed to deshielding by the newly introduced carbonyl at C–2 in **217**.



199 **217** (30%) (21)

Considering the lack of chemoselectivity displayed by ruthenium tetroxide, the less reactive osmium tetroxide oxidant was investigated. Like ruthenium tetroxide, osmium tetroxide is a toxic, volatile oxidant and is generally used in catalytic amounts with *in-situ* re-oxidation. Gratifyingly, treatment of diene **199** with a catalytic amount of osmium tetroxide and several equivalents of sodium periodate afforded the desired ketone **161** as the main product. However, the reaction was quite sluggish and, despite long reaction times (12-24 h) and increased reaction temperatures (from 20 °C to 50 °C),

the yields were disappointingly low (30-40%). Addition of sodium bicarbonate and replacement of the sodium periodate co-oxidant with potassium periodate slightly improved the observed yields.[56] The optimal reaction conditions involved the addition of potassium periodate and sodium bicarbonate to a solution of diene **199** in 5:1 *t*-BuOH–H_2O (eq 22). A catalytic amount of osmium tetroxide was added and the resultant brown mixture was stirred for 72 h. Standard work-up and purification of the resultant material by flash chromatography provided the ketone **161** in 65% yield.

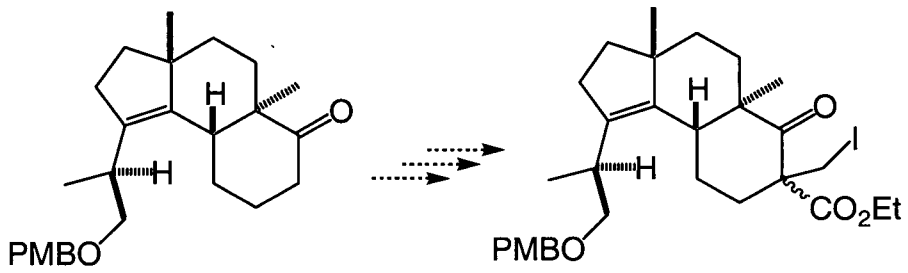


199 **161** (65%) (22)

Spectroscopic analysis of product **161** confirmed that the required chemoselective oxidative cleavage of the exocyclic double bond in **199** had been achieved. The IR spectrum of the ketone **161** showed a sharp absorption band at 1703 cm^{-1}, characteristic of an aliphatic ketone function. The ^{13}C NMR spectrum of ketone **161** displayed a carbonyl carbon signal at δ 216.3. Olefinic ^{13}C NMR resonances were observed at δ 137.7 and 138.2, confirming the integrity of the C–2 double bond in **161**.

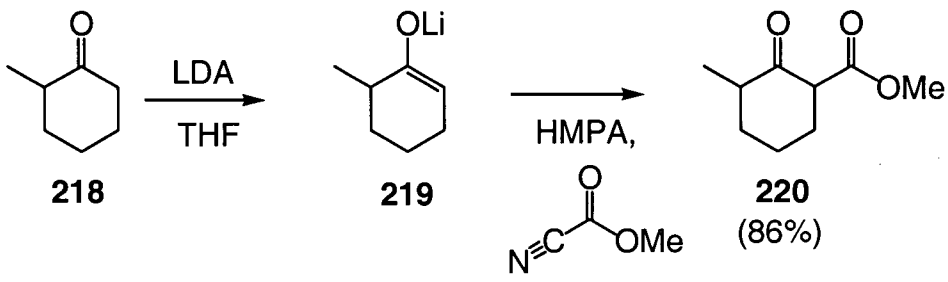
2.1.3.4. Preparation of Iodides 160

With ketone **161** in hand, the preparation of iodides **160** *via* sequential ethoxy carbonylation and halomethylation steps was investigated (eq 23).



161 **160** (23)

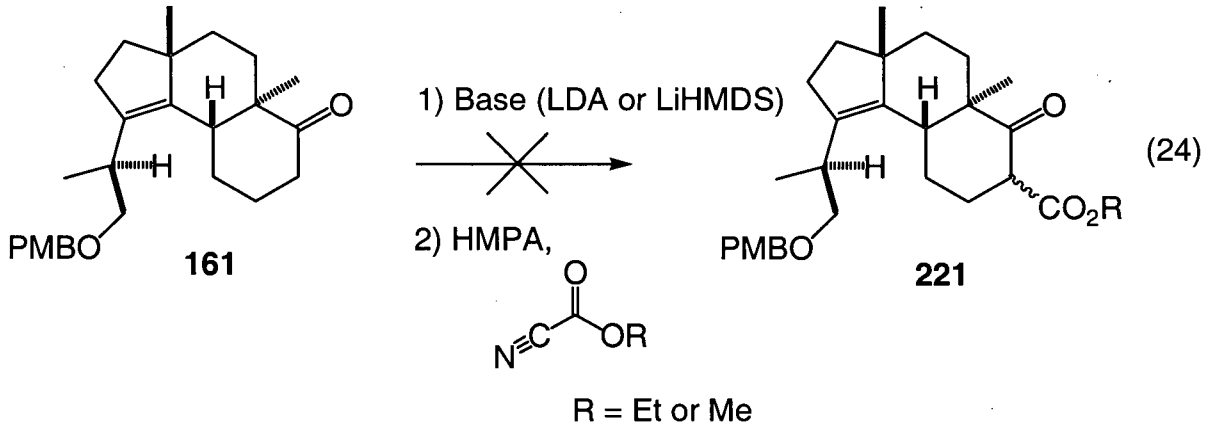
In 1983, Mander and coworkers reported an efficient method for effecting the alkoxycarbonylation of ketones with high *C*–selectivity (Scheme 40).[82] Their method was based on the reaction of lithium enolates with alkyl cyanoformate reagents. For example, deprotonation of 2-methylcyclohexanone **218** with LDA generated the corresponding lithium enolate **219**, which, when treated with methyl cyanoformate in the presence of HMPA, afforded the β-keto ester **220**.



218 **219** **220** (86%)

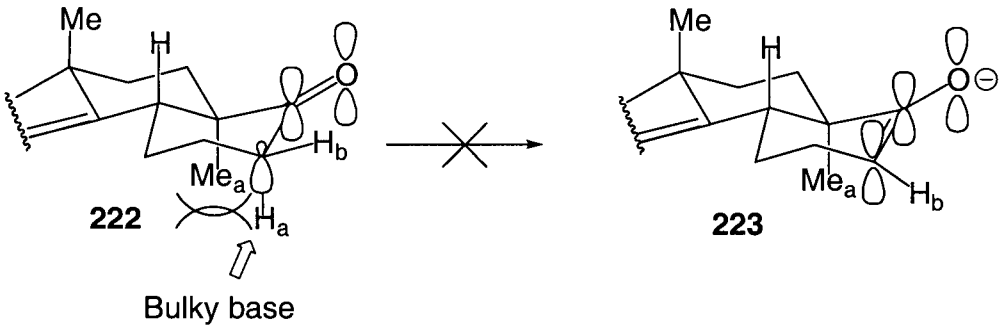
Scheme 40

The alkoxycarbonylation of ketone **161** following Mander's procedure was attempted several times with either LDA or LiHMDS as the base and either methyl or ethyl cyanoformate as the acylating reagent (eq 24). To our disappointment, the desired keto ester **221** was not produced and nearly quantitative recovery of starting material was noted in most attempts.



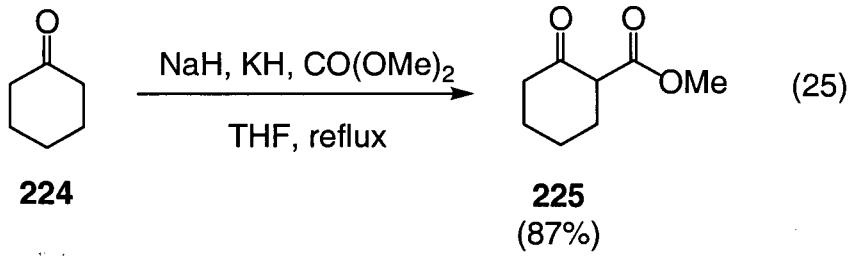
(24)

To determine whether or not the generation of the enolate of **161** had occurred, the ketone was again treated with base (LDA or LiHMDS) and the resulting solutions were treated with TMSCl. However, the corresponding enol silyl ether was not detected and, in each case, starting material was completely recovered. A rationale for the apparent difficulty in generating the requisite ketone enolate of **161** was based on steric and stereoelectronic effects (Scheme 41). In accordance with Corey's proposal,[83] the axial proton H_a in **222**, a partial structure representing ketone **161**, should be more readily abstracted than H_b, the equatorial proton, for stereoelectronic reasons. However, on the basis of possible steric interaction between the incoming base and the angular methyl group (Me_a), the transition state energy for the deprotonation of **222** with a bulky base (LDA or LiHMDS) leading to enolate **223** was expected to be relatively high.



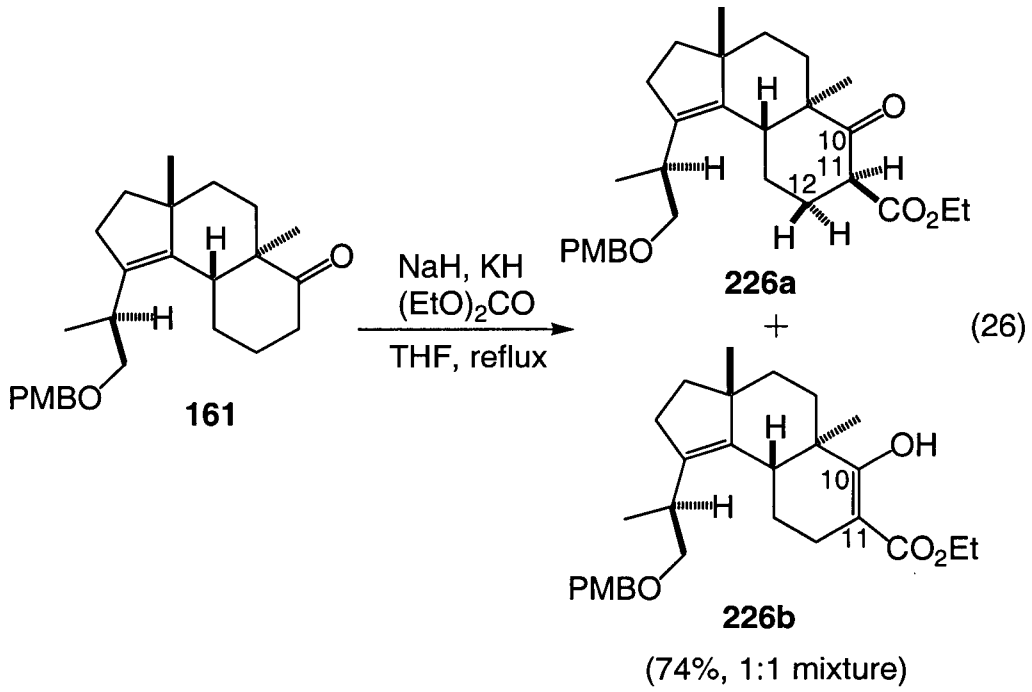
Scheme 41

In 1990, Weiler and coworkers reported an efficient method of generating β-keto esters, which employed the relatively small bases NaH and KH.[84] For example, a solution of ketone **224** and dimethyl carbonate in THF was refluxed in the presence of several equivalents of sodium hydride and 0.1 equivalent of potassium hydride (eq 25). Upon work-up, the desired β-keto ester **225** was obtained in 87% yield.



(25)

A diethyl carbonate version of Weiler's procedure[84] was applied to our synthesis. A mixture of ketone **161** and diethyl carbonate in THF was refluxed with sodium hydride and a catalytic amount of potassium hydride (eq 26). Upon work-up and purification of the resultant material by flash chromatography, product **226** was obtained in 74 % yield as a 1:1 tautomeric mixture of enol ester **226a** and keto ester **226b**.

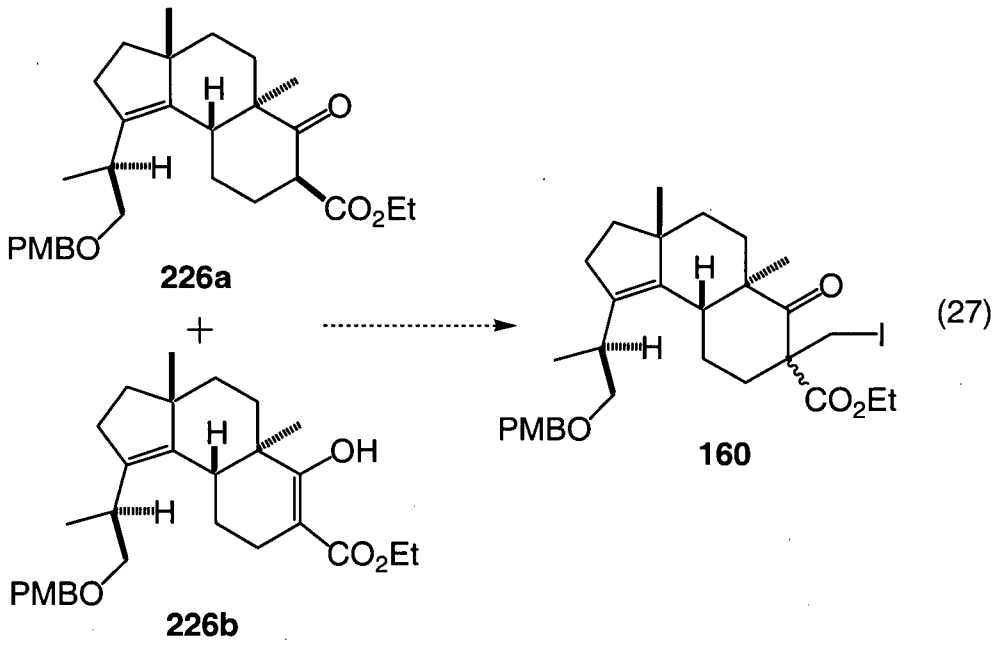


(74%, 1:1 mixture)

The structures of **226a** and **226b** were confirmed by spectroscopic methods. The IR spectrum of the mixture of tautomers **226** displayed an absorption at 1649 cm^{-1}, attributed to the ester carbonyl stretch of the enol ester **226b**. In addition, absorptions at 1709 and 1743 cm^{-1}, derived from the ketone and ester carbonyls of the keto ester **226a**, were also observed. The ^1H NMR spectrum of the mixture of tautomers **226** displayed overlapping triplets (3H) at δ 1.29 and overlapping quartets (2H) at δ 4.19, attributed to the methyl and methylene protons of the ethoxyl moieties. A doublet of doublets (1H, J = 5.5, 13.5 Hz) at δ 3.68 was assigned to the H–11 proton of the α-keto ester tautomer **226a**. The larger of the two coupling constants, 13.5 Hz, was attributed to the trans diaxial relationship between H–11 and the β-face H–12 proton. A singlet (1H) at δ 12.4 was attributed to the hydroxyl proton of the enol ester tautomer **226b**. The assigned 1:1 ratio of **226a** and **226b** was supported by an observed 1:1 integral ratio for the signals at δ 3.68 and 12.4, attributed to H–11 in **226a** and the hydroxyl proton in **226b**,

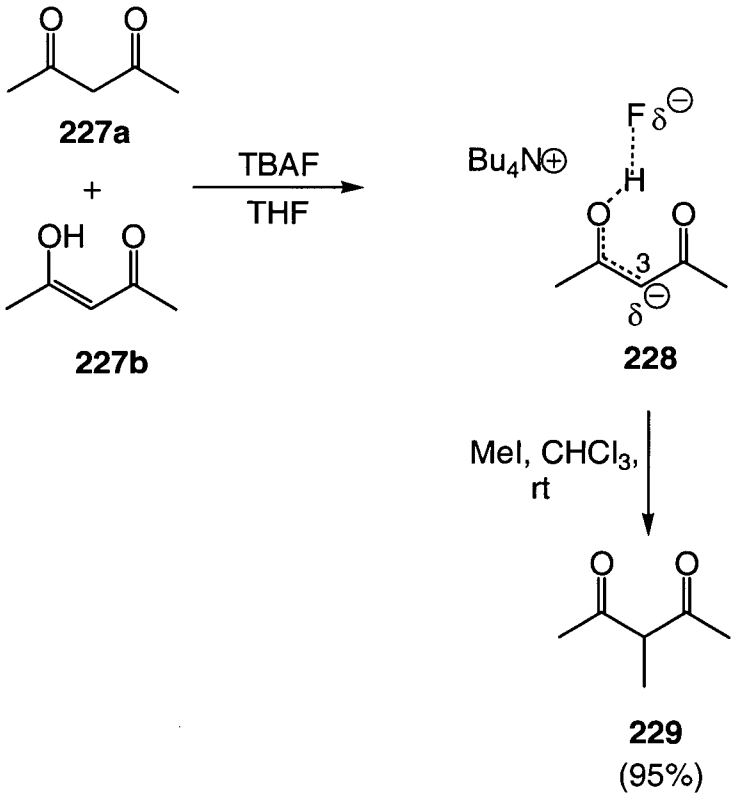
respectively. The ^{13}C NMR resonances of the alkenic enol carbons in **226b** appeared at δ 170.6 (C–10) and 94.8 (C–11), respectively. The ester carbonyl carbons in **226a** and **226b** were displayed at δ 178.2and 173.5, respectively.

The next transformation, an iodomethylation reaction, was to be carried out on the mixture of tautomers, **226a** and **226b**, to give iodides **160** (eq 27).



A literature search revealed a protocol by Clark and Miller for the selective *C*–alkylation of β-dicarbonyl compounds through the intermediacy of tetrabutylammonium fluoride salt complexes (Scheme 42).[85] Treatment of a mixture of **227a** and **227b** with tetrabutylammonium fluoride (TBAF) in THF afforded the monosolvate **228**. On the basis of several NMR studies on **228**, the authors ruled out a proton transfer to the fluoride anion. They proposed that hydrogen-bonding between the fluoride anion and the

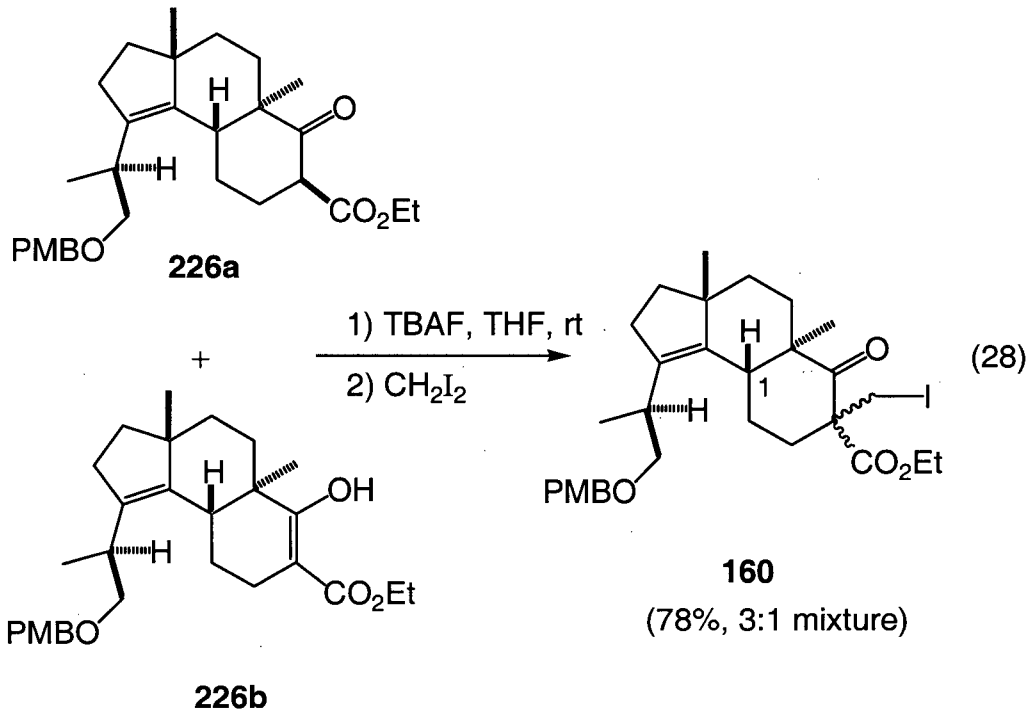
enolic hydroxyl proton results in a delocalization of the charge on the fluoride ion into the enol π-system. This delocalization appears to reduce the amount of enolic double bond character and increase the carbanion character at C–3. Treatment of **228** with iodomethane resulted in a highly *C*–selective alkylation, affording **229** in nearly quantitative yield.



Scheme 42

It was hoped that the high degree of *C*–selectivity noted in the aforementioned alkylation of a TBAF monosolvate with iodomethane could be reproduced in our study with diiodomethane as the electrophile. Thus, a solution of a 1:1 mixture of enol ester and keto ester tautomers **226** in THF was treated with a solution TBAF in THF. The

resultant solution of the corresponding monosolvate was treated with ten equivalents of diiodomethane, providing a 3:1 mixture of the epimeric iodides **160** after work-up (eq 28).

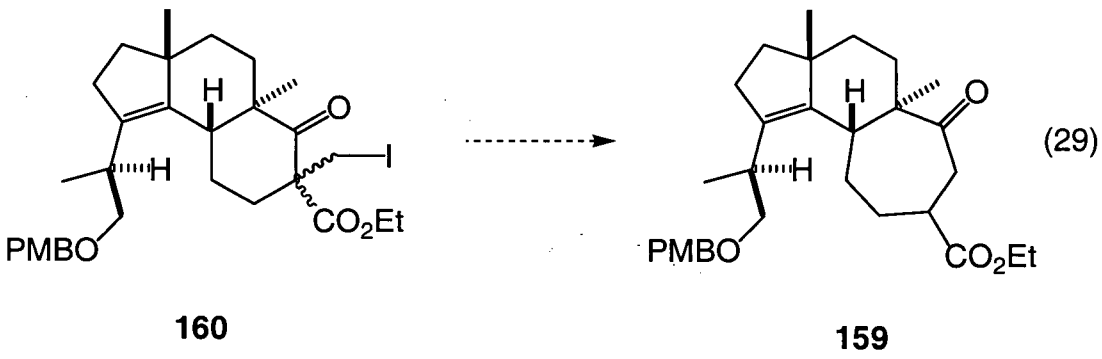


The structures of the epimeric iodides **160** were confirmed by spectroscopic methods. The IR spectrum of the mixture of iodides **160** exhibited the ketone and ester carbonyl stretching bands at 1708 and 1735 cm^{-1}, respectively. The ^1H NMR spectrum of the mixture of iodides **160** displayed overlapping multiplets (2H) between δ 4.36-4.45 attributed to the protons of the iodomethyl moieties. The assigned 3:1 ratio of the **160** isomers was supported by a 3:1 integral ratio of two ^1H NMR signals observed at δ 2.67 and δ 2.77, representing the angular ring-fusion protons (H–1) of the major and minor isomers, respectively. Since the mixture of isomers **160** was to be employed in the ensuing ring-expansion reaction, the respective relative configurations of the major and

minor isomers were not determined. The ^{13}C NMR spectrum of **160** displayed resonances at δ 169.3 and 210, assigned to the major isomer's ester and ketone carbonyl carbons, respectively. The ^{13}C NMR resonances for the ester and ketone carbonyl carbons of the minor isomer were observed at δ 168.4 and 208.6, respectively.

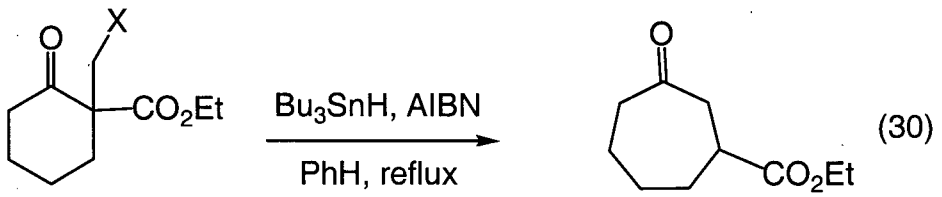
2.1.3.5. Preparation of Keto Ester 159

The next step in the synthesis of sarcodonin G involved a ring expansion of the α-halomethyl β-keto esters **160** to form the homologated γ-keto ester **159** (eq 29).



160 **159** (29)

Concurrent studies by the research group of Dowd and that of Beckwith resulted in the discovery of a novel radical-mediated ring expansion of α-halomethyl β-keto esters. Dowd and coworkers reported studies on the Bu_3SnH-mediated ring expansion of α-bromomethyl β-keto esters to the corresponding γ-ketoester.[86,87] As an example, treatment of bromide **230** with Bu_3SnH and a catalytic amount of AIBN in refluxing benzene afforded γ-keto ester **231** in a good yield (eq 30). Beckwith and coworkers reported an analogous ring expansion of iodide **232**, affording γ-keto ester **231**, also in good yield (eq 30).[88]

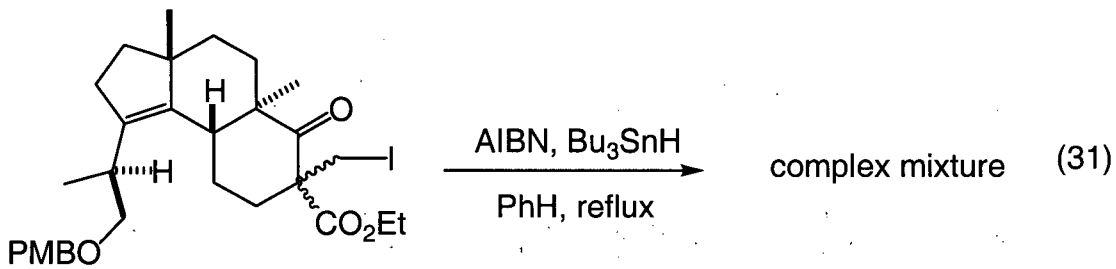


(30)

230 (X = Br) **231** 73%

232 (X = I) **231** 76%

To our disappointment, attempts to effect Bu_3SnH-mediated ring expansion reactions of iodides **160**, following Dowd's procedure,[87] resulted in complex mixtures of unidentified products. (eq 31). Despite variations in the concentration of the iodides and addition time of the reagents, the desired ring-expansion product was not detected.

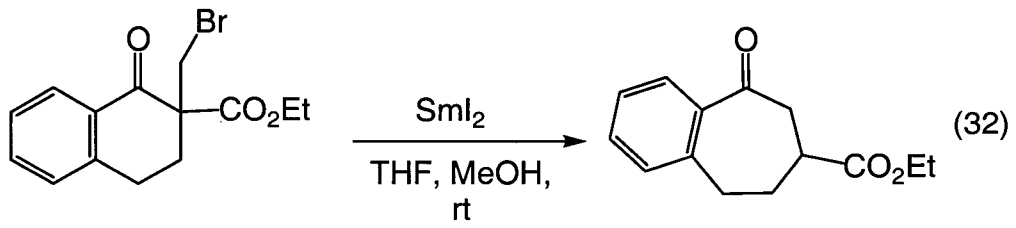


(31)

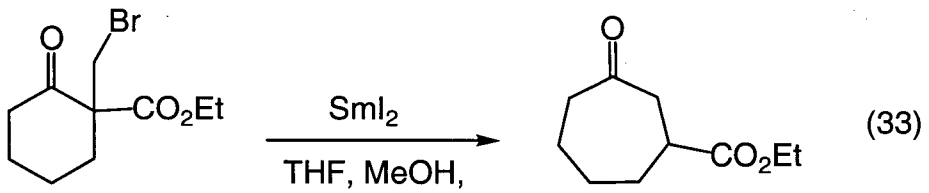
160

Recently, Hasegawa and coworkers reported an analogous SmI_2-mediated ring-expansion reaction to produce homologated γ-keto esters.[89] For example, treatment of aromatic α-bromomethyl β-keto ester **233** with 2 equiv of SmI_2 provided the ring-expansion product **234** (eq 32). However, addition of SmI_2 to a solution of the aliphatic

α-bromomethyl β-keto ester **230**, a substrate used in Dowd's study (*vide supra*),[87] provided the ring-expansion product **231** in relatively modest yield (eq 33).

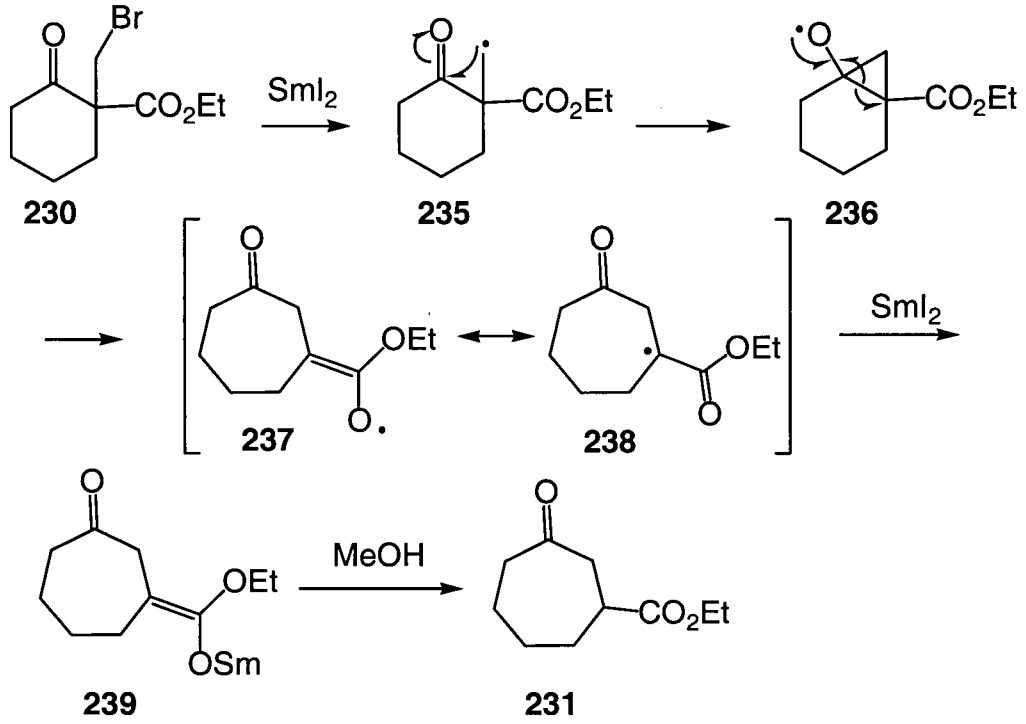


233 **234** (65%) (32)



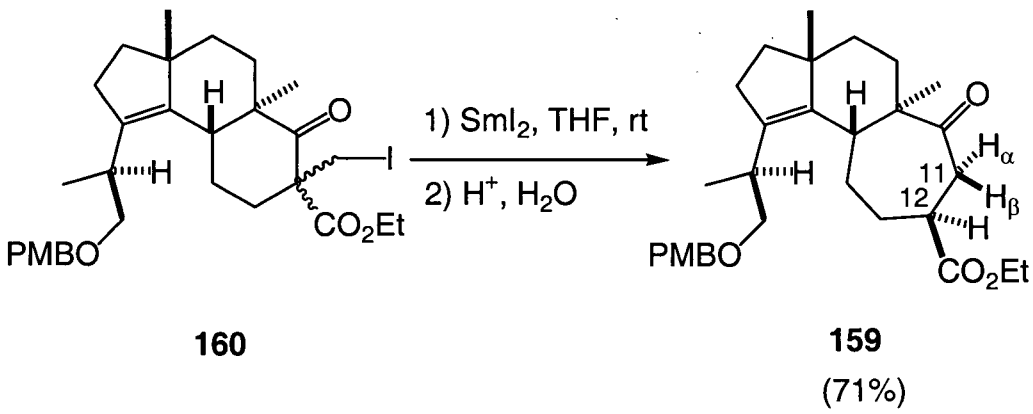
230 **231** (44%) (33)

The proposed mechanism of the SmI_2-mediated ring expansion of α-bromomethyl β-keto ester **230**, which is similar to that proposed for the analogous Bu_3SnH-mediated reactions, is depicted in Scheme 43.[89] The first step involves single electron transfer from SmI_2 to **230**, providing the carbon radical **235**. Attack of the resultant primary radical on to the ketone carbonyl function yields a cyclopropyloxy radical intermediate **236**. Fragmentation of **236**, which involves cleavage of the ring fusion bond, provides the seven-membered carbocycle **237**. The resonance-stabilized radical **237** undergoes a one-electron transfer from a second equivalent of SmI_2, to yield the samarium enolate **239**. In the presence of methanol or water, the samarium enolate is protonated to generate γ-keto ester **231**.



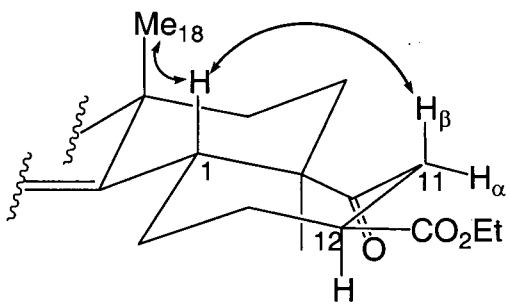
Scheme 43

Hasegawa's SmI_2-mediated ring-expansion protocol[89] was applied to the mixture of iodides **160**. A solution of the 3:1 mixture of epimeric iodides **160** in THF was treated with SmI_2 (eq 34). Aqueous acidic work-up and purification of the resultant material by flash chromatography afforded the ring-expansion product, γ-keto ester **159**, as a single isomer in 71% yield.



(34)

Evidence for the successful ring expansion of **160** was obtained by analysis of the ^{1}H and ^{13}C NMR spectra derived of the γ-keto ester **159**. The ^{1}H NMR spectrum of **159** displayed a doublet of doublets (1H, J = 9.5 and 14 Hz) at δ 3.05 attributed to H–11$_{\beta}$. The ^{1}H signals for H–11$_{\alpha}$ and H–12 were attributed to overlapping signals observed between δ 2.77-2.84. The ^{13}C NMR spectrum of **159** exhibited resonances at δ 39.3 and 38.7, assigned to C–11 and C–12, respectively. HMQC correlations were noted between the H–11 and H–12 signals and the corresponding C–11 and C–12 signals. The ^{13}C NMR spectrum of **159** also displayed resonances at δ 174.5 and 215.0, representing the ester and ketone carbonyl carbons, respectively.



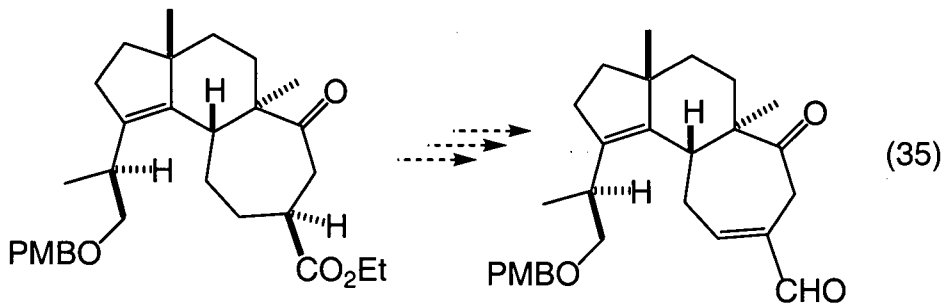
159

The proposed β-orientation of the ethoxycarbonyl moiety in **159** was supported by ^{1}H NMR NOED experiments on **159**. Irradiation at δ 2.65, a multiplet (1H) attributed the angular proton H–1, caused enhancement of a singlet at δ 1.06 assigned to H–18 and the doublet of doublets at δ 3.05 (J = 9.5, 14.4 Hz) assigned to H–11$_{\beta}$. The larger (14.5 Hz) of the coupling constants for the doublet of doublets at δ 3.05 was attributed to the geminal coupling between H–11$_{\beta}$ and H–11$_{\alpha}$ whereas the smaller coupling (9.5 Hz) was

attributed to the coupling between H–11_β and H–12. The magnitude of the latter coupling suggests that H–11_β and H–12 have a trans diaxial-type relationship, which supports the proposed equatorial orientation of the ethoxycarbonyl group in **159**. Although the configuration at C–12 in **159** was clearly established, the reasons for the stereoselective α-face protonation, exclusively affording intermediate **159,** were not evident to us.

2.1.3.6. Preparation of Keto Aldehyde 240

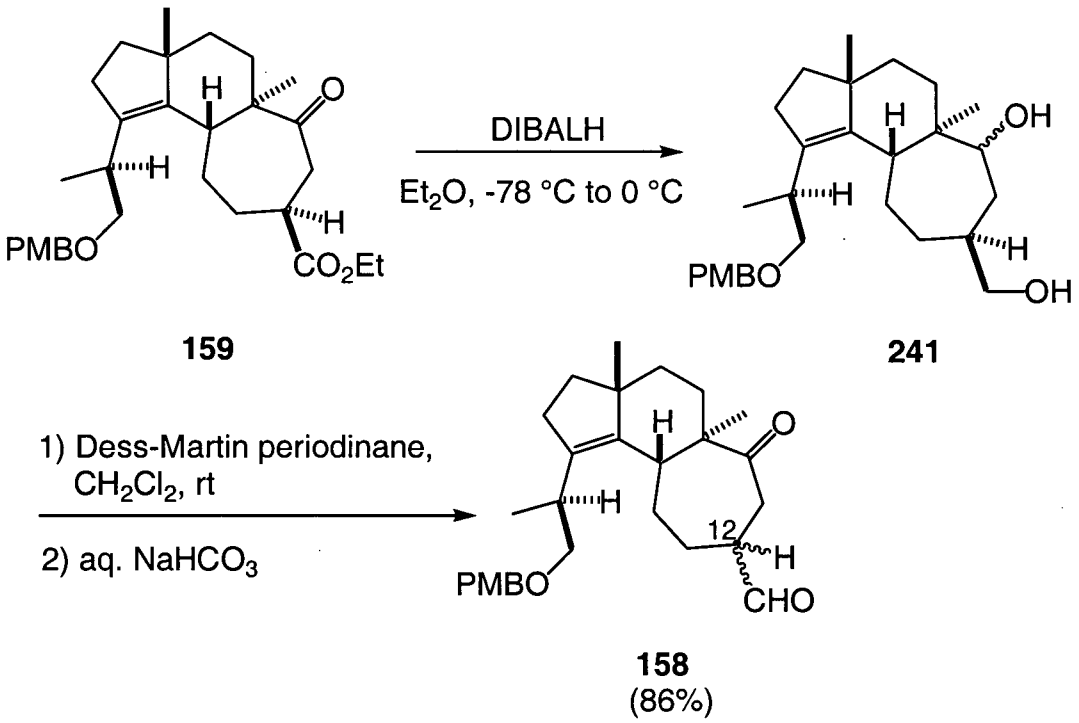
With the ring-expansion step completed, the transformation of keto ester **159** into keto aldehyde **240** was investigated (eq 35).



159 **240** (35)

The first step of this transformation was envisioned to be conversion of keto ester **159** to the corresponding keto aldehyde **158** (Scheme 44). Following a standard procedure, a solution of keto ester **159** in Et_2O was treated with several equivalents of DIBALH. A suitable work-up procedure provided the mixture of diols **241**. The crude

diols **241** were taken up in CH_2Cl_2 and treated with Dess-Martin's periodinane reagent.[90] After standard work-up and purification of the resultant material by flash chromatography, a 1:1 mixture of epimeric keto aldehydes **158** was obtained in 86% yield. Since the ratio of epimers varied with the duration of the work-up procedure, the C–12 epimerization of the highly enolizable aldehydes **158** presumably occurred during the aqueous $NaHCO_3$ wash.

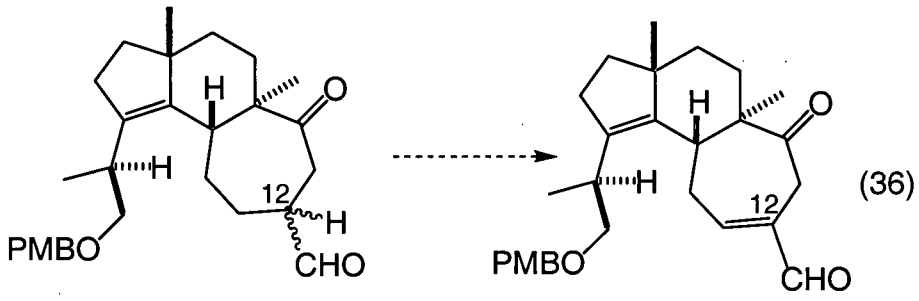


Scheme 44

Evidence for the structure, and a measure of the ratio of the epimeric keto aldehydes **158**, was obtained by standard spectroscopic methods. The IR spectrum of the mixture of keto aldehydes **158** exhibited ketone and aldehyde carbonyl stretching bands at 1726 and 1697 cm^{-1}, respectively. The ^1H NMR spectrum of **158** displayed a pair of doublets at δ 9.60 and 9.63, attributed to the aldehydic proton signals. A 1:1 integral

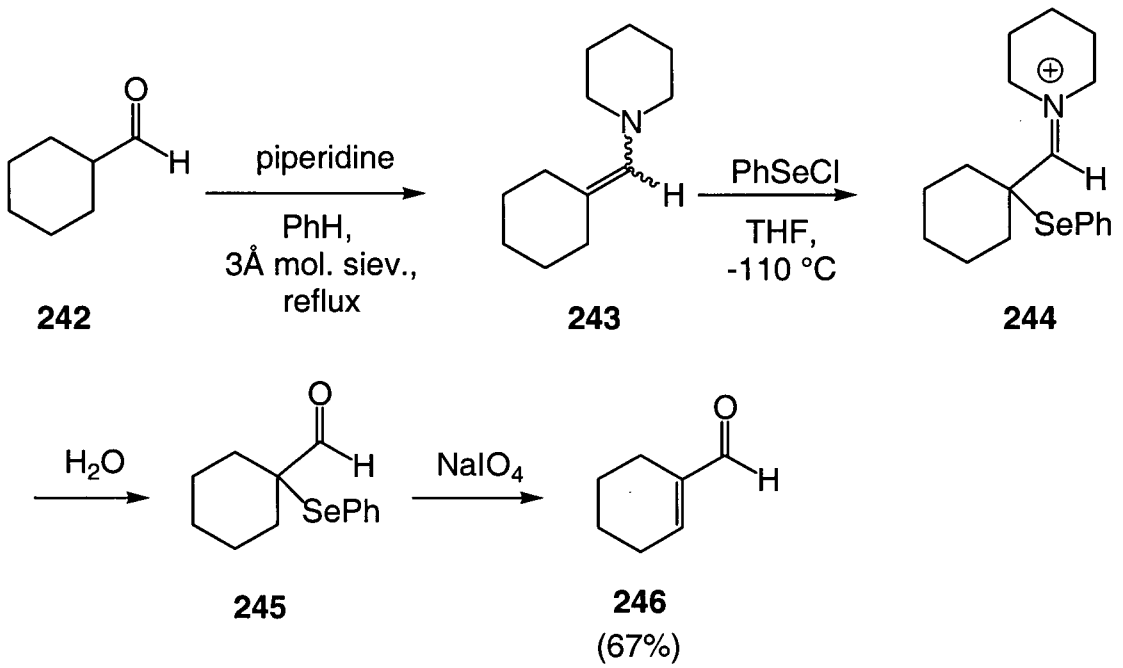
ratio was observed for these aldehydic proton signals, indicating a 1:1 mixture of aldehydes. The ^{13}C NMR spectrum displayed resonances at δ 201.0 and 201.5, representing the aldehydic carbonyl carbons. The ^{13}C NMR resonances of the ketonic carbonyl carbons appeared at δ 214.9 and 215.8.

The next step in the synthesis of sarcodonin G involved the introduction of a double bond in the seven-membered ring at C–12 in **158** to give **240** (eq 36).



158 **240** (36)

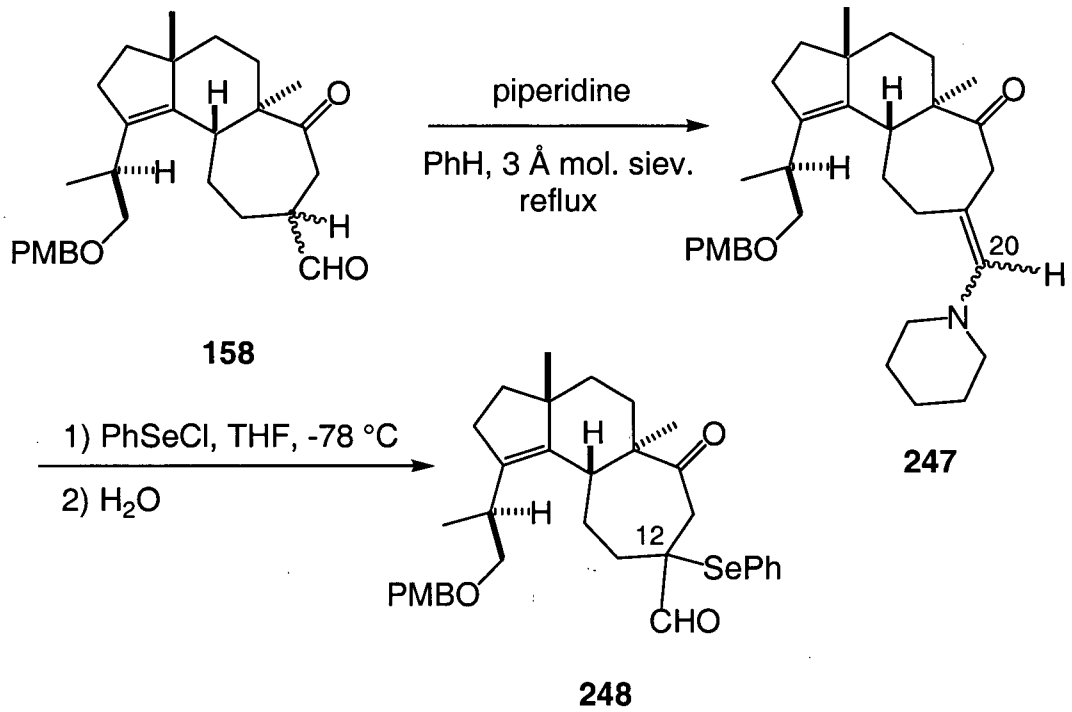
Williams and coworkers have reported a mild method of preparing α,β-unsaturated aldehydes from the corresponding aldehydes *via* enamine derivatives.[91] For example, conversion of aldehyde **242** to the corresponding enamine **243** was accomplished by heating a mixture of **242** and piperidine in benzene with removal of water with 3Å molecular sieves (Scheme 45). Treatment of the enamine derivative **243** with phenylselenenyl chloride provided the intermediate **244**, which afforded the corresponding α-phenylselenoaldehyde **245** after aqueous work-up. A periodate oxidation of **245** generated the corresponding selenoxide intermediate, which underwent a *syn*-elimination reaction to give the desired α,β-unsaturated aldehyde **246**.



Scheme 45

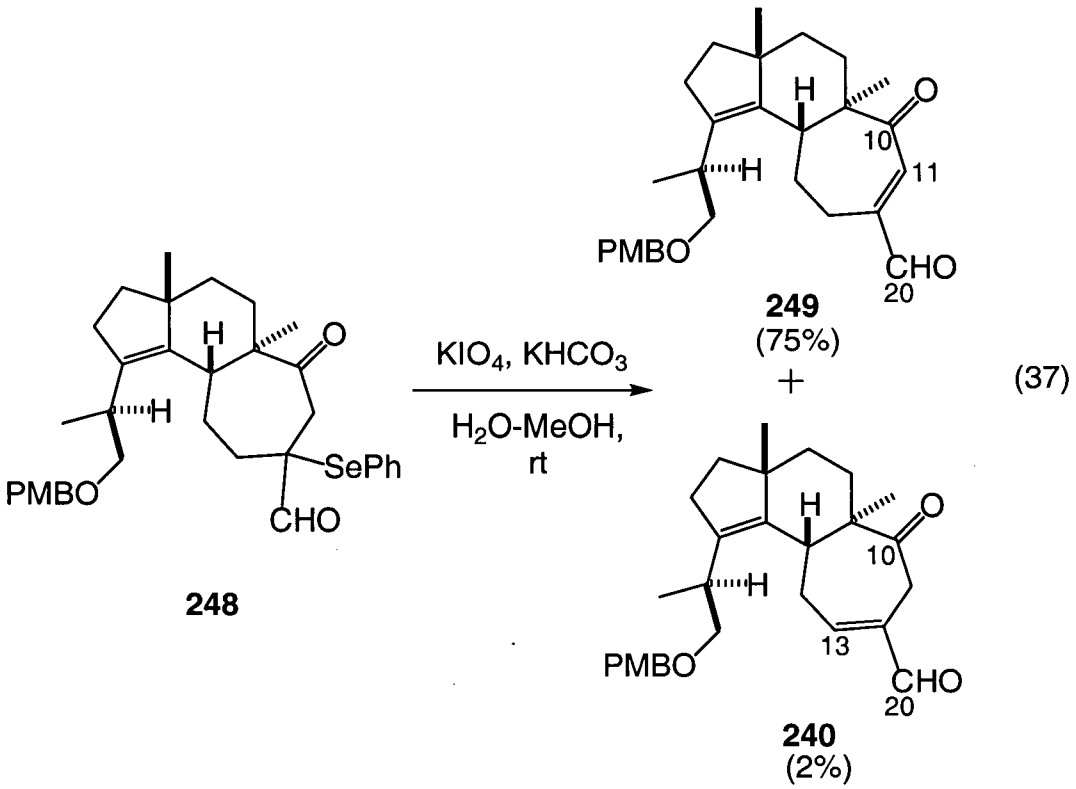
It was hoped that William's mild oxidation protocol (*vide supra*) could be successfully applied to the mixture of aldehydes **158**. On the basis of previous studies by Clinton and coworkers,[92] the enamine formation step was expected to be chemoselective for the aldehyde function over that involving the ketone function in **158**. Thus, aldehydes **158** were converted into the corresponding piperidine enamines **247** by treatment of the former with 5 equivalents of piperidine in refluxing benzene over 3Å molecular sieves (Scheme 46). After removal of the solvent and excess piperidine, the resultant crude material was analyzed by ^{1}H NMR spectroscopy, which confirmed the successful formation of enamines **247**. The ^{1}H NMR spectrum of **247** displayed two singlets at δ 5.32 and 5.43, representing the olefinic enamine protons (H–20). Overlapping multiplets displayed between δ 1.4–1.6 and between δ 2.5-2.7 were attributed to the methylene protons of the piperidine rings. The crude enamines **247** were taken up in

THF and the solution was treated with freshly recrystallized phenylselenenyl chloride. After aqueous work-up, the resultant solution was concentrated and the α-phenylselenoaldehyde **248** was analyzed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of crude **248** displayed an aldehydic proton signal at δ 9.19. Several multiplets between δ 7.2 and 7.7 were also observed, attributed to the aromatic protons of a phenylselenide moiety. The relative configuration at C–12 was not determined.



Scheme 46

The crude α-phenylselenoaldehyde **248** was taken up MeOH and the solution was treated with solid KIO_4 and aqueous $KHCO_3$ (eq 37). Aqueous work-up and purification of the resultant material by flash chromatography afforded two isomeric α,β-unsaturated aldehydes, **249** and **240,** in 75% and 2 % yields, respectively

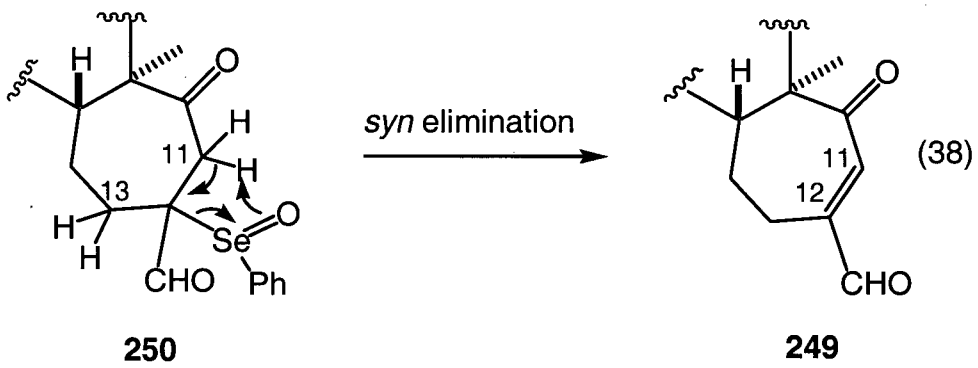


(37)

The structure of **249** was confirmed by spectrometric analysis. The IR spectrum of **249** exhibited a broad band at 1697 cm^{-1}, representing the carbonyl stretches of the conjugated ketone and aldehyde functions. The ^{1}H NMR spectrum of **249** displayed a 1-proton singlet at δ 9.56 (1H), attributed to the aldehydic H–20 proton. The ^{1}H NMR signal for the olefinic C–11 proton in **249** was observed a singlet at δ 6.63 (1H). The lack of H-H coupling displayed by this olefinic signal supported the proposed C–11 position of the double bond in **249**. The ^{13}C NMR resonances of the two alkene functions in **249** appeared at δ 136.9, 139.6, 144.2 and 146.1. The ^{13}C NMR resonances of the aldehydic (C–20) and ketonic (C–10) carbonyl carbons appeared at δ 194.7 and 209.6, respectively

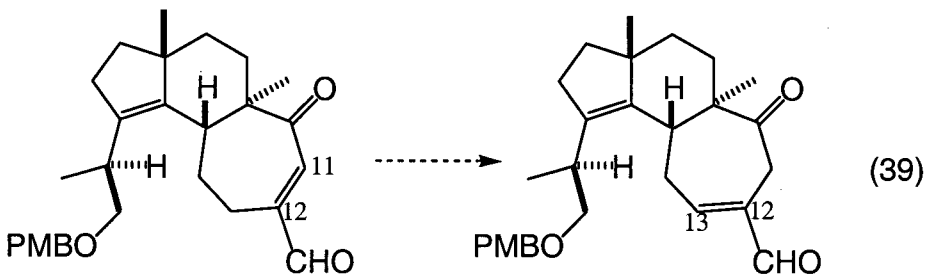
The structure of the minor product, aldehyde **240**, was also confirmed by spectrometric analysis. The ketone and aldehyde functions in **240** were represented by carbonyl stretches in IR spectrum at 1704 and 1688 cm^{-1}, respectively. The ketone stretch at 1704 cm^{-1} is characteristic of an aliphatic ketone, supporting the C–12 position of the double bond in **240**. The ^1H NMR signals for H–13 and H–20 for **240** were observed as a multiplet at δ 6.63–6.68 and a singlet at δ 9.33, respectively. The multiplicity of the olefinic H–13 signal, attributed to coupling with the adjacent H–14 protons, supports the C–12 positioning of the double bond. The ^1H NMR signals for the geminal H–11 protons were observed as a pair of doublets (J = 14 Hz) at δ 3.46 and 3.72. The ^{13}C NMR resonances of the two alkene functions in **240** appeared at δ 135.7, 137.0, 137.9 and 153.7. The ^{13}C NMR resonances at δ 192.3 and 210.6 were attributed to the aldehydic and ketonic carbonyl carbons, respectively.

The ratio of the two products **249** and **240** derived from the selenoxide elimination reaction can be rationalized by comparison of the relative acidities of the H–11 and H–13 protons of selenoxide **250** (eq 38). The H–11 protons in **250**, which are α to a carbonyl group, are much more acidic than the H–13 protons since the former experience favorable overlap of the C–H sigma bonds with the π-bonds of the adjacent carbonyl function. Thus, the irreversible *syn*-elimination of the selenoxide moiety should favor the removal of the more acidic proton, H–11, affording primarily α,β-unsaturated ketone **249**.



250 **249** (38)

Since the C-ring alkene function in the target structure, sarcodonin G, is positioned at C–12, the next task at hand involved an isomerization of **249**, which displays a C–11 double bond, to afford **240**, which displays the requisite C–12 double bond (eq 39).

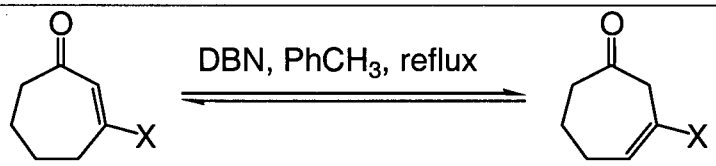


249 **240** (39)

In 1984, Mease and Hirsch reported a study on the syntheses and base-catalyzed isomerizations of medium-ring cycloalkenones.[93] The effect of C–3 substituents on the base-catalyzed equilibration ratio of carbocycles **251** and **252** was investigated (**Table 2**). In the unsubstituted case, the product composition of the thermodynamically controlled isomerization of **251** or **252** significantly favored the 2-cycloheptenone isomer **251** (entry

1, **Table 2**). On the other hand, the isomerization of compounds with electron-withdrawing substituents at C–3 favored the 3-cycloheptenone isomer **252** (entries 2-4, **Table 2**). The authors' explanation for the substituent effect was based on the premise that the 3-cycloheptenone isomers **252** were more effectively conjugated with less conformational demands on the ring system than the corresponding 2-cycloheptenone isomers **251**.

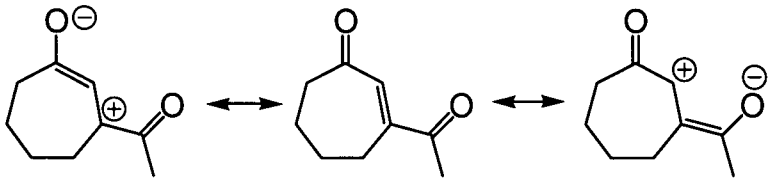
Table 2. Isomerization of C–3 Substituted Cycloheptenones **251** and **252**.



251 **252**

Entry	Substituent (X)	Composition % of **251**	Composition % of **252**
1	H	76.8	23.2
2	CO_2CH_3	16.8	83.2
3	CN	15.1	84.9
4	$COCH_3$	20.7	79.3

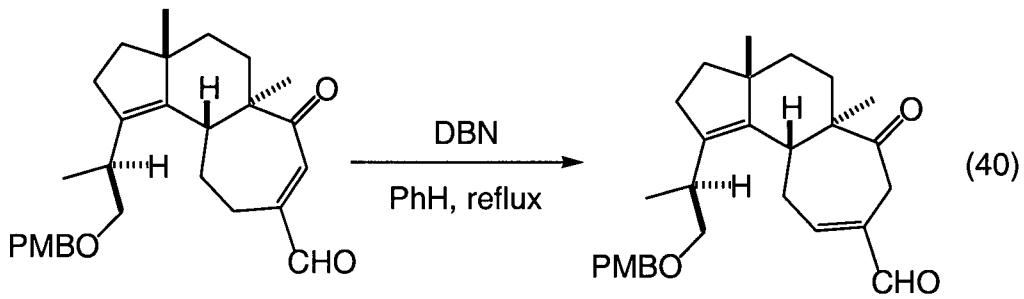
The authors also suggested that the double bonds in the 2-cycloheptenone isomers **251** with electron-withdrawing substituents experience destabilization due to similar electronic interactions at both ends of the double bond (entries 2-4, **Table 2**). As an example, the contributing resonances structures available to 2-cycloheptenone **251** with an electron-withdrawing acyl substituent (entry 4, **Table 2**) place positives charges at opposite ends of the double bond (Scheme 47).



251 (entry 4, **Table 2**)

Scheme 47

On the basis of findings by Mease and Hirsch (*vide supra*), it was expected that **249** could be isomerized under thermodynamically controlled equilibrating conditions to **240**. Thus, a benzene solution of **249** containing 2 equivalent of DBN was refluxed for 12 h (eq 40). After removal of solvent and purification of the resultant material by flash chromatography, the desired isomer **240** was isolated in nearly quantitative yield (96%).



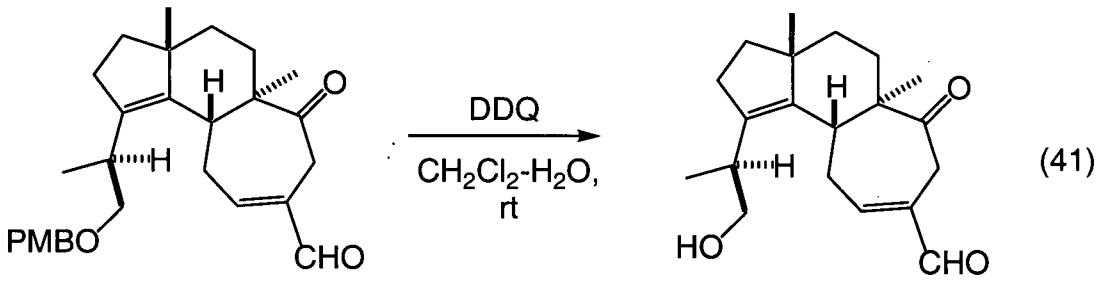
(40)

249

240
(96%)

2.1.3.7. Preparation of (±)-Sarcodonin G (36)

The preparation of (±)-sarcodonin G (**36**) from **240** involved removal of the PMB protecting group (eq 41). Following optimized conditions reported by Oikawa,[75] a solution of keto aldehyde **240** in aqueous CH_2Cl_2 was treated with DDQ. After a standard work-up procedure and purification of the resultant material by flash chromatography, (±)-sarcodonin G (**36**) was isolated in 92% yield.[94]



240 **36** (92%) (41)

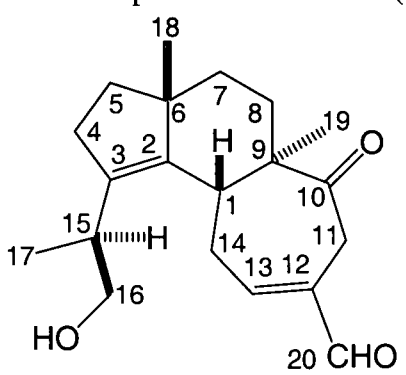
The synthetic (±)-sarcodonin G (**36**) exhibited spectral data in full accordance with those reported[16] for the isolated natural product, (–)-sarcodonin G.[95] The IR, MS, ^{1}H NMR and ^{13}C NMR spectra of the synthetic material and isolated material are compared in **Tables 3**, **4** and **5**. The ^{1}H NMR spectrum derived from synthetic (±)-sarcodonin G (**36**) is displayed in Fig. 1.

Table 3. Comparison of IR and MS Spectral Data for Synthetic (±)-Sarcodonin G (**36**) with those Reported[16] for Natural (–)-Sarcodonin G (**36**).

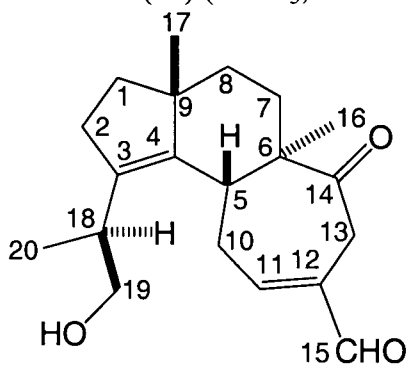
Data	Synthetic (±)-Sarcodonin G (**36**)	Natural (–)-Sarcodonin G (**36**)
IR[a] (cm^{-1})	3445	3400
	1703	1705
	1640	1640
	1450	1450
	1376	1380
MS[b] (m/z)	316.2038 (DCI+)	316 (EIMS)

[a] The IR spectra were recorded using KBr pellets.
[b] Exact mass calcd for $C_{20}H_{28}O$: 316.2039.

Table 4. Comparison of ^{1}H NMR Data for Synthetic (±)-Sarcodonin G (**36**) ($CDCl_3$, 400 MHz) with those Reported[16] for Natural (–)-Sarcodonin G (**36**) ($CDCl_3$, 250 MHz).



36 showing IUPAC-based numbering



36 showing cyathane numbering

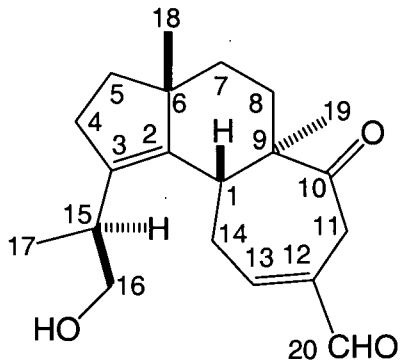
^{1}H NMR ($CDCl_3$, 400 MHz) Signals Displayed[a] by Synthetic (±)-Sarcodonin G (**36**) δ ppm (Multiplicity, *J* (Hz))	^{1}H Assignment[b] H–x	Reported ^{1}H NMR ($CDCl_3$, 250 MHz) Signals Displayed by Natural (–)-Sarcodonin G (**36**) δ ppm (Multiplicity, *J* (Hz))	Cyathane Numbering[c]
0.97 (d, 6.9)	H–17	0.96 (d, 7.3)	H–20
1.03 (s)	H–19	1.01 (s)	H–16
1.14 (s)	H–18	1.12 (s)	H–17
1.24–1.30 (m)		1.24 (dt, 3.9, 13.2)	
1.46 (s)		part of m at 1.59	
1.49–1.55 (m)		part of m at 1.59	
1.58–1.70 (m)		part of m at 1.59	
1.95 (dt, 5, 13.4)		1.94 (dt, 5.3, 13.3)	
2.21–2.40 (m)		2.31 (m)	
2.69–2.80 (m)		2.74 (m)	
2.98–3.08 (m)	H–15	3.02 (sextet, 7.3)	H–18
3.10–3.20 (m)		3.16 (dd, 13.4, 6.4)	
3.36 (br d, 12.6)		3.34 (d, 12)	
3.41–3.51 (m)		3.42 (d, 13.9), 3.45 (d, 7.3)	
3.71–3.75 (m)		3.72 (br d, 13.6)	
6.70–6.73 (m)	H–13	6.71 (m)	H–11
9.35 (s)	H–20	9.31(s)	H–15

[a] The difference between observed and reported δ is likely due to different $CDCl_3$ reference assignments.

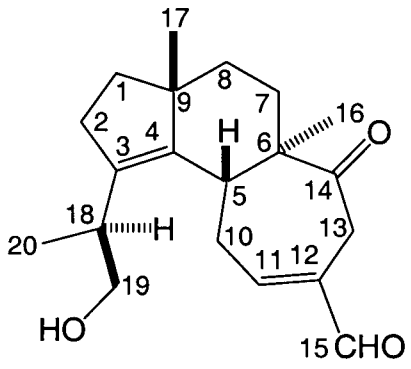
[b] Systematic IUPAC-based numbering system.

[c] Ayer's cyathane numbering system.[23]

Table 5. Comparison of ^{13}C NMR Data for Synthetic (±)-Sarcodonin G (**36**) ($CDCl_3$, 100.6 MHz) with those Reported[16] for Natural (–)-Sarcodonin G (**36**) ($CDCl_3$, 62.5 MHz).



36 showing IUPAC-based numbering



36 showing cyathane numbering

^{13}C NMR ($CDCl_3$, 100.6 MHz) Signals Displayed by Synthetic (±)-Sarcodonin G (**36**) δ ppm	^{13}C Assignment[a] C–x	Reported ^{13}C NMR ($CDCl_3$, 62.5 MHz) Signals Displayed by Natural (–)-Sarcodonin G (**36**) δ ppm	Cyathane Numbering[b]
12.7	C–19	12.7	C–16
15.6	C–17	15.6	C–20
24.8	C–19	24.8	C–17
28.6		28.6	
32.1		32.1	
32.7		32.7	
34.1		34.1	
35.2		35.2	
35.5		35.5	
37.7		37.7	
39.7		39.5	
49.8		49.8	
55.3		55.3	
65.8	C–16	65.8	C–19
135.9 (two signals superimposed)		135.8, 135.9	
141.3		141.2	
153.2	C–13	153.5	C–11
192.2	C–20	192.4	C–15
210.3	C–10	210.6	C–14

[a] Systematic IUPAC-based numbering system.
[b] Ayer's cyathane numbering system.[23]

(±)-Sarcodonin G (**36**)

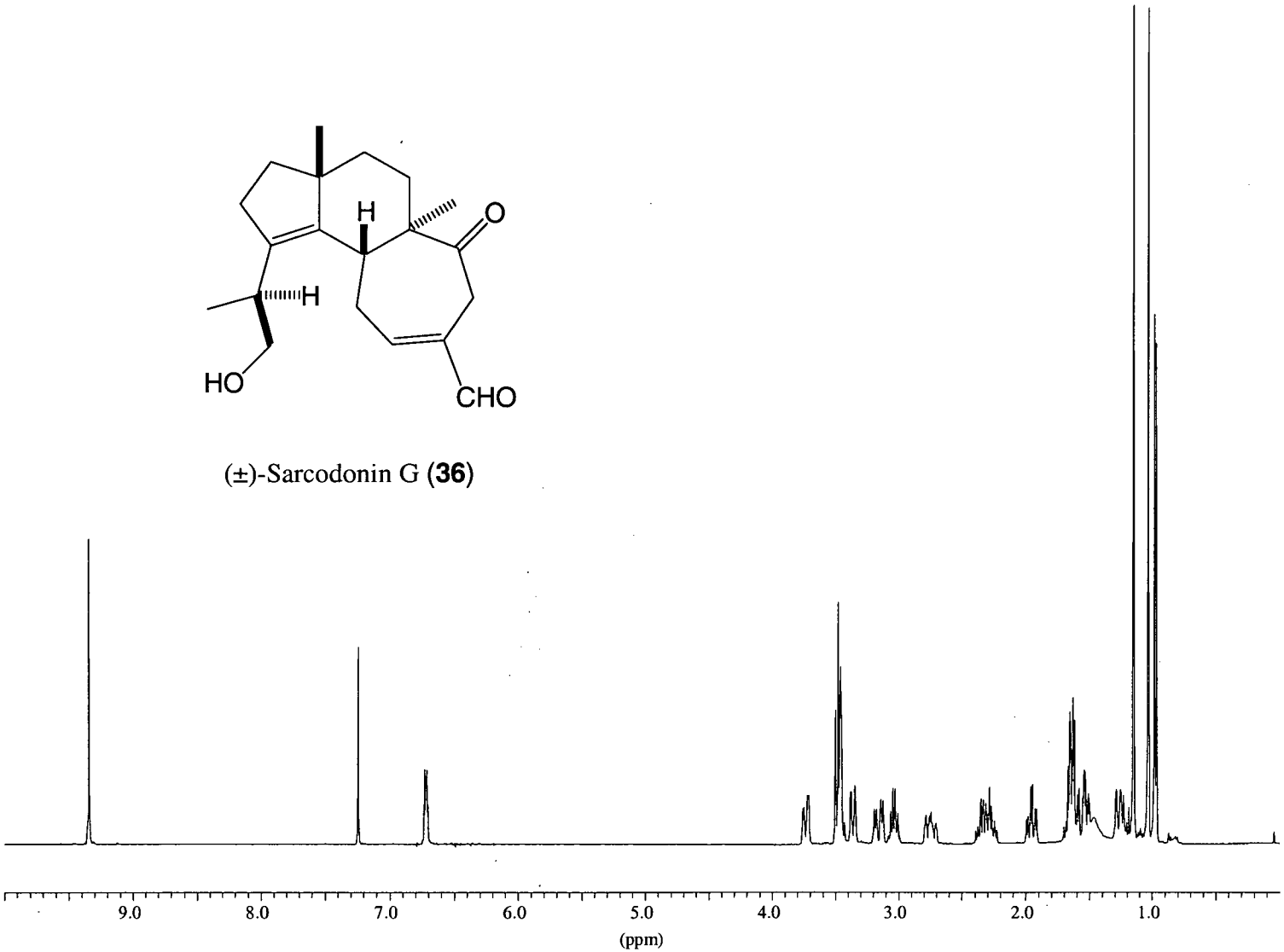
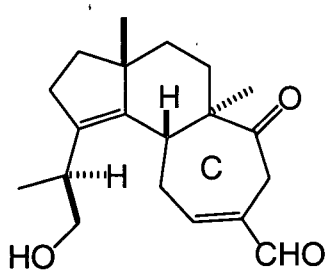


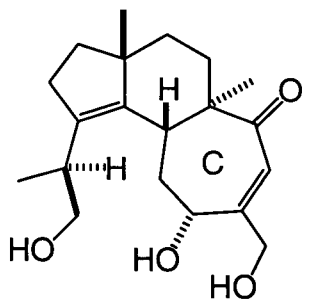
Figure 1. ^{1}H NMR spectrum of Synthetic (±)-Sarcodonin G (**36**) ($CDCl_3$, 400 MHz)

2.1.4. Studies Towards the Synthesis of (±)-Cyathin A_4

After the completion of total synthesis of (±)-sarcodonin G (**36**), the synthesis of the structurally related cyathane diterpenoid (±)-cyathin A_4 (**37**)[17] was attempted. Our synthetic approach to sarcodonin G (**36**), which addressed the construction of oxygenation and unsaturation pattern of the C-ring in the later stages of the route, was expected to provide an advanced branching point from which cyathin A_4 (**37**) could be derived.



36

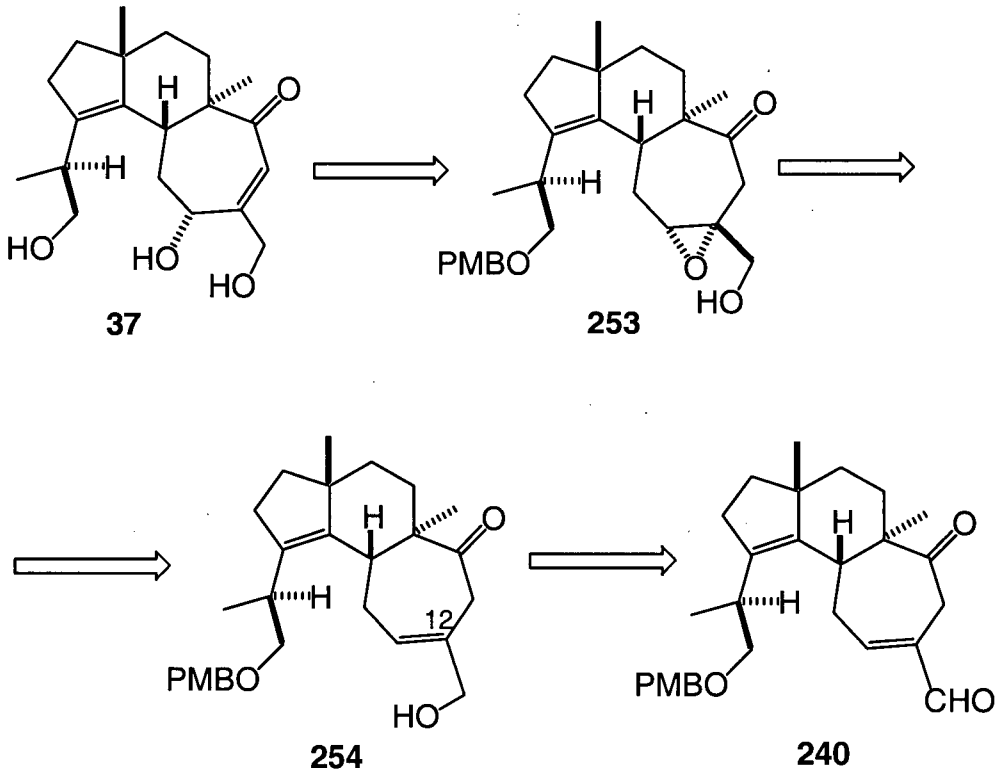


37

2.1.4.1. Retrosynthetic Analysis

Our proposed synthetic plan for the construction of cyathin A_4 (**37**) is outlined in Scheme 48. The target structure **37** should be available from compound **253** *via* ring opening of the epoxide function to give the corresponding allylic alcohol and cleavage of the PMB ether to generate the hydroxyl function. A chemo- and stereoselective epoxidation of C–12 double bond in **254** should provide epoxide **253**. Finally, compound

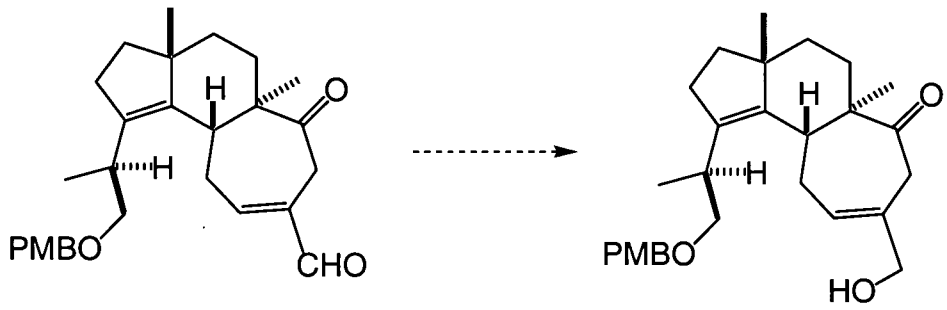
253 should be available *via* a chemoselective reduction of aldehyde **240**, an advanced intermediate available from our previously described total synthesis of sarcodonin G (see Section 2.1.3. *vide supra*).



Scheme 48

2.1.4.2. Preparation of Keto Alcohol 254

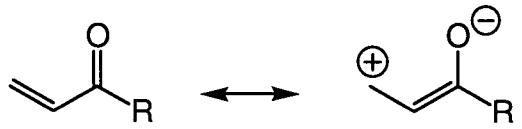
The first step in our proposed synthesis of cyathin A_4 involved a chemoselective reductive transformation of keto aldehyde **240** to give keto alcohol **254** (eq 42). This chemoselective reduction proved difficult to achieve owing to a small difference in reactivity between the aldehyde and ketone carbonyl functions (*vide infra*).



240 **254** (42)

Both steric and stereoelectronic effects are important factors that may contribute to the relative reactivity of saturated and unsaturated carbonyl functions towards a hydride source (reducing agent).[96] For steric reasons, carbonyls with one alkyl substituent (aldehydes) should be more readily reduced than those with two alkyl substituents (ketones). The steric bulk of a ketone's two alkyl substituents significantly restricts the approach of the nucleophile to the carbonyl and increases the energy of the transition state leading from a trigonal intermediate to the tetrahedral product. For stereoelectronic reasons, the carbonyl function of an α,β-unsaturated aldehyde or ketone function is significantly less electrophilic than that of the corresponding substance lacking the alkene function. The decreased electrophilicity of the former may be partially attributed to a

decrease in carbonyl double-bond character as illustrated by contributing resonance structures **255** (Scheme 49).

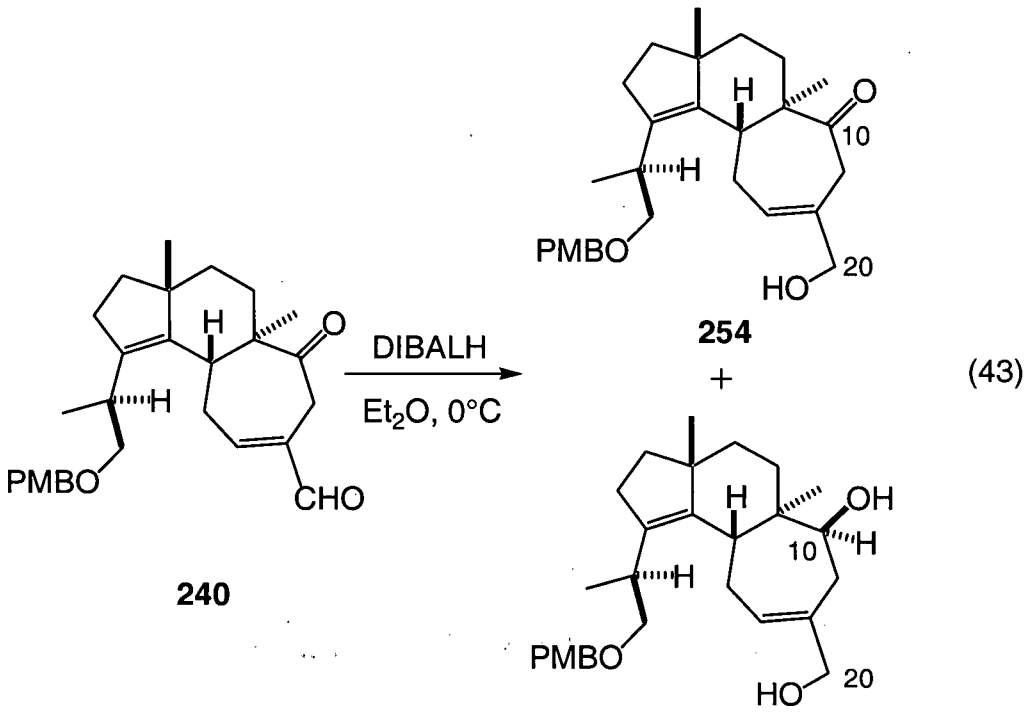


255

Scheme 49

On balance, the relative transition state energies involved in the reduction of the ketone function and unsaturated aldehyde function of compound **240** might be expected to be energetically similar, since the former is disfavored for steric reasons whereas the later is disfavored for stereoelectronic reasons.

Diisobutylaluminum hydride (DIBALH) was the first reducing agent investigated for the chemoselective reduction of **240**. Treatment of a cold (–78 °C) Et_2O solution of keto aldehyde **240** with one equivalent of DIBALH simply resulted in the complete recovery of starting material. Consequently, the DIBALH reduction of **240** was repeated in Et_2O at 0 °C, which provided a 46% yield of keto alcohol **254** and diol **256** in a 1:4 ratio, along with 40% recovered starting material (eq 43). The three compounds were easily separated by silica gel flash chromatography.

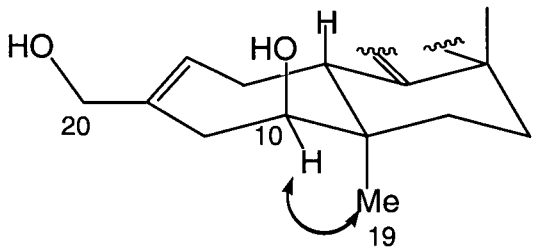


(43)

(46%, 1:4 ratio of **254**:**256**)

Evidence for the successful chemoselective reduction of keto aldehyde **240** to provide keto alcohol **254** was obtained by spectroscopic methods. The IR spectrum of **254** exhibited a broad signal at 3435 cm^{-1}, attributed to the OH stretching vibration. An absorption band observed at 1701 cm^{-1} in the IR spectrum of **254** was characteristic of a saturated ketone. The ^{1}H NMR spectrum of **254** displayed a multiplet (2H) between δ 3.95–4.08 assigned to the H–20 methylene protons. The ^{13}C NMR spectrum of **254** displayed resonances at δ 68.8 and 211.3, attributed to the C–20 methylene and the C–10 ketone carbons, respectively.

The structure of diol product **256** was also confirmed by spectroscopic analysis. The IR spectrum of **256** displayed a broad absorption at 3368 cm^{-1}, representing the OH stretch. The ^1H NMR signal for H–10 proton in **256** was observed at δ 3.42. A multiplet between δ 3.92–3.99 in the ^1H NMR spectrum was assigned to the H–20 protons. The ^{13}C NMR resonance for the C–10 carbon in **256** was displayed at δ 75.3.

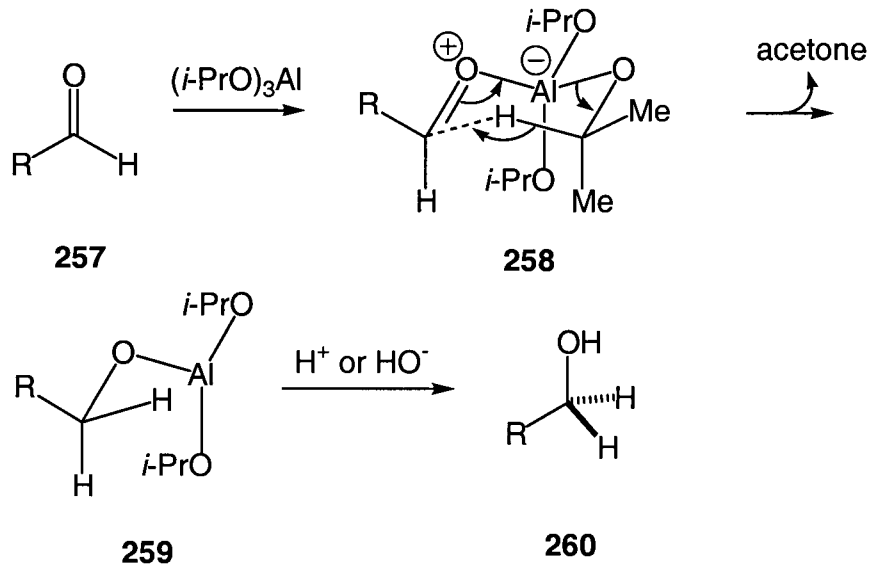


256

The relative configuration of the C–10 hydroxyl moiety was confirmed by ^1H NMR NOED experiments on **256**. Irradiation of the H–10 signal, displayed at δ 3.42 in the ^1H NMR of **256**, caused enhancement of a singlet at δ 0.89, attributed to the H–19 methyl protons. A reciprocal enhancement of the H–10 signal was observed upon irradiation of the H–19 signal. These results support the β-configuration of the C–10 hydroxyl moiety in **256**.

On the basis of the low chemoselectivity displayed by the DIBALH reduction of **240**, an alternative reduction method was investigated. The Meerwein–Ponndorf–Verley (MPV) reduction with aluminum isopropoxide has been shown to reduce unsaturated aldehydes to the corresponding allylic alcohols.[97] The proposed mechanistic pathway of the aluminum isopropoxide MPV reduction is outlined in Scheme 50.[98] Treatment of an aldehyde (**257**) with aluminum isopropoxide generates the cyclic coordination complex

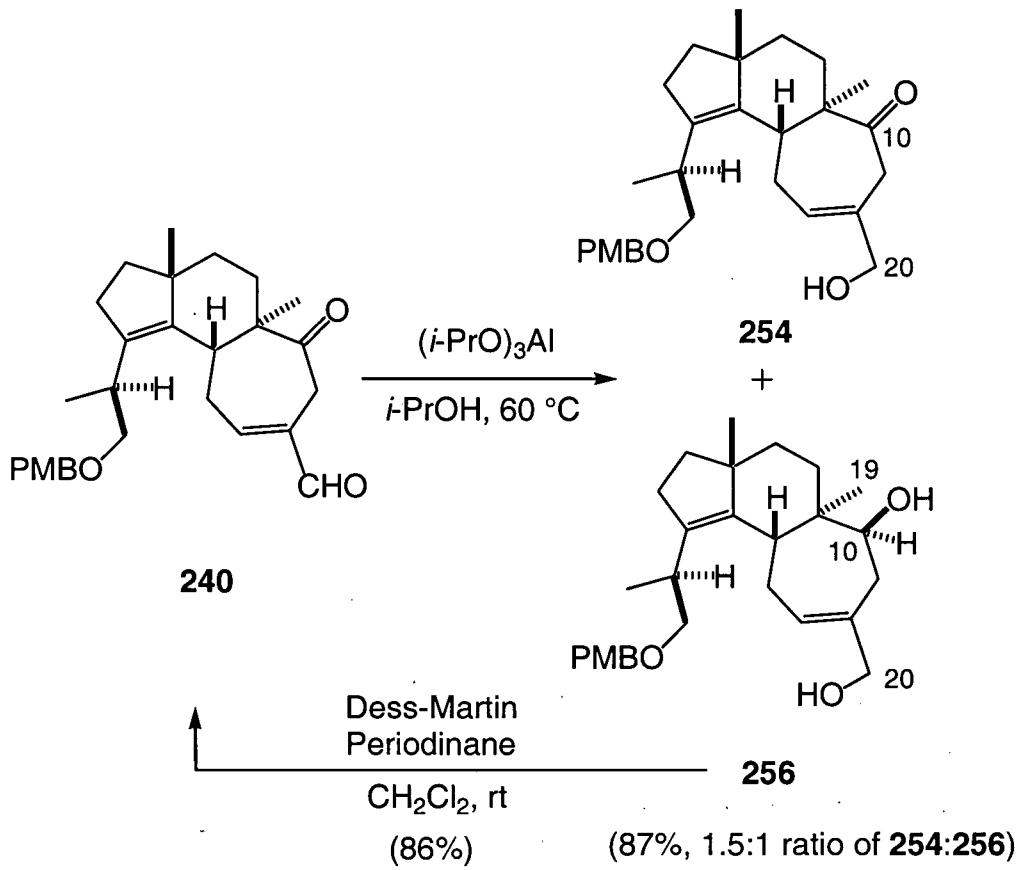
258, which undergoes intramolecular hydride transfer to afford the mixed alkoxide **259** and one equivalent of acetone. Hydrolysis of the mixed alkoxide **259** under acidic or basic conditions affords the corresponding alcohol **260**.



Scheme 50

It was hoped that an aluminum isopropoxide-mediated MPV reduction of keto aldehyde **240** would be chemoselective for the aldehyde function. A solution of the keto aldehyde **240** in a 1:1 mixture of benzene and *i*-proponal was treated with one equivalent of aluminum isopropoxide and the resultant mixture was heated to reflux. Work-up and purification of the resultant material by flash chromatography provided a 1:2 ratio of keto alcohol **254** and diol **256** as well as 40% recovered starting material. Gratifyingly, an MPV reduction of **240** performed in 100% *i*-propanol at 60 °C afforded an 87% yield of **254** and **256** with an improved ratio of 1.5:1 in favor of the desired keto alcohol **254** (Scheme 51). The undesired diol **256** was subsequently oxidized with Dess–Martin periodinane reagent[90] in 86% yield and the resultant keto aldehyde **240** recycled through

the MPV reduction. After one cycle, the desired alcohol **254** was obtained in 70% yield from keto aldehyde **240**.

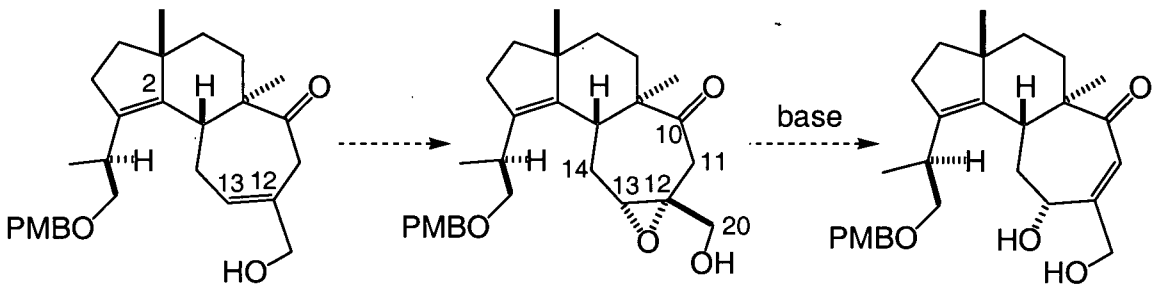


Scheme 51

2.1.4.3. Attempted Preparation of Diol 261

With the keto alcohol **254** in hand, the preparation of diol **261** *via* the epoxide intermediate **253** was investigated (Scheme 52). The first transformation would require an epoxidation method that was (a) chemoselective for the C–12 double bond over the C–

2 double bond in **254**, and (b) stereoselective for the α-face of the C–12 double bond. It was anticipated that the hydroxymethyl appendage at C–12, through coordination with a suitable reagent, might help chemoselectively direct the C–12 alkene epoxidation. Based on molecular models, an approach to the α-face of the C–12 alkene appeared slightly less sterically hindered. Thus, it was hoped that an epoxidation of **254** would favour formation of the α-epoxide **253**. The next step would involve a ring opening of the epoxide function *via* a base-mediated deprotonation α to the C–10 ketone function, with subsequent β-elimination of the epoxide oxygen anion. Work-up should then afford diol **261**.

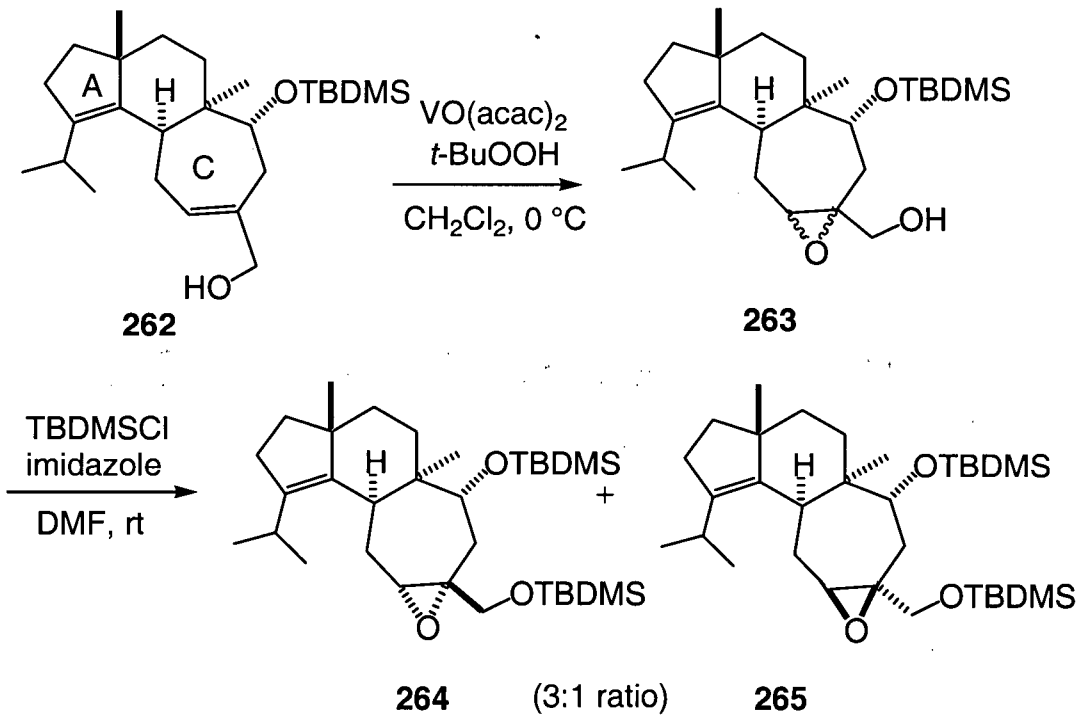


254 **253** **261**

Scheme 52

An epoxidation similar to that required for our synthesis (*vide supra*) was previously noted by Snider and co-workers in their synthetic studies directed towards the diterpenoid allocyathin B_2 (see Section 2.1.2.1., *vide supra*).[56] Their account of several abandoned synthetic routes included the selective epoxidation of intermediate **262** (Scheme 53). Treatment of **262** with *t*-BuOOH and a catalytic amount of $VO(acac)_2$

resulted in a hydroxyl-directed epoxidation of the C-ring double bond, providing a mixture of epoxides **263**. This material, which was too acid-sensitive for purification by silica gel chromatography, was treated with TBDMSCl to afford the corresponding silyl ether epoxides **264** and **265** in a 3:1 ratio. Evidently, the epoxidation step (**262** to **263**) was threefold stereoselective for the α-face of the C-ring double bond in **262**.



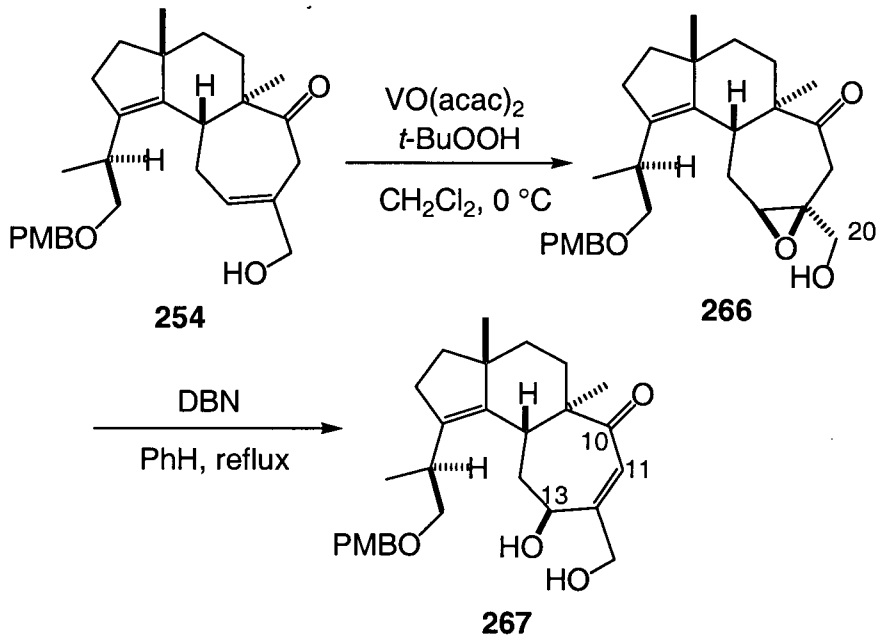
262 **263**

264 (3:1 ratio) **265**

Scheme 53

It was hoped that a $VO(acac)_2$/*t*-BuOOH hydroxyl-directed epoxidation of our intermediate **254** would display both the chemo- (ring C double bond vs ring A double bond) and stereoselectivity (α- vs β-face) reported by Snider and coworkers (*vide supra*). Thus, a cool (0 °C) solution of alkene **254** and *t*-BuOOH in CH_2Cl_2 was treated with a catalytic amount of $VO(acac)_2$ (Scheme 54).[99] The resultant mixture was stirred for 2 h at

0 °C. Work-up, followed by attempted purification of a portion of the resultant material by flash chromatography on silica gel, led to product decomposition. ^{1}H NMR spectral analysis of the remaining crude material revealed the presence of only one major product, which was subsequently shown to possess structure **264**, the product of a α-face epoxidation of **254**. Successful reaction of the C–12 alkene in **264** was supported by of the ^{1}H NMR spectroscopic analysis of the product **266**. The ^{1}H NMR spectrum derived from the latter did not display signals in the olefinic region (δ 5-7). Further evidence supporting the epoxidation was obtained upon analysis of the H–20 methylene signal, observed as a multiplet between δ 4.8–4.9 in the ^{1}H NMR spectrum of **266**. The corresponding signal for the H–20 protons in the ^{1}H NMR spectrum of the starting material **254** had been noted at δ 3.9–4.1. The downfield shift of the signal for the H–20 protons in **266**, relative to that for the H–20 protons in **254**, was attributed to the newly introduced epoxide function in **266**. Evidence supporting the assigned β-configuration of the epoxide in **266** was later obtained through chemical transformations and spectroscopic correlations (*vide infra*). Without further purification, a benzene solution of crude **266** was treated with DBN, resulting in a ring opening of the epoxide function. Upon solvent removal under reduced pressure and purification of the resulting material by flash chromatography, the allylic alcohol **267** was obtained in 65% yield from **254**.

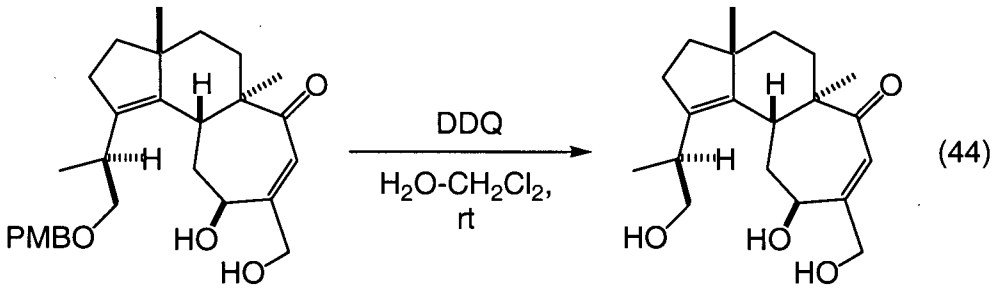


254 **266** **267**

(65% from **203**)

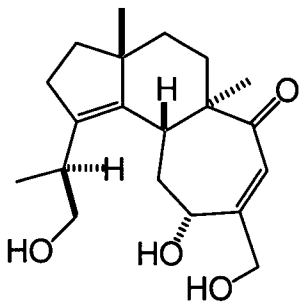
Scheme 54

The constitutional structure of **267** was supported by spectroscopic analysis. The IR spectrum of **267** exhibited a broad absorption at 3402 cm^{-1} and a carbonyl stretch at 1665 cm^{-1}, attributed to the hydroxyl and ketone functions, respectively. The ^1H NMR spectrum of **267** displayed a singlet (1H) at δ 5.96, representing the H–11 olefinic proton. The ^{13}C NMR resonance for the C–10 ketone carbon in **267** was observed at δ 210.1. ^1H NMR NOED experiments preformed on **267,** in hopes of confirming the relative configuration of the C–13 hydroxyl moiety, were not conclusive. Nevertheless, on the basis of spectroscopic analysis of a derivative of **267** (*vide infra*), the C–13 hydroxyl moiety was assigned a β-configuration. The PMB protecting group in **267** was removed by treatment of a solution of this material in aqueous CH_2Cl_2 with DDQ. Standard work-up and purification of the resultant material by flash chromatography provided triol **268**, the C–13 epimer of the target structure, cyathin A_4 (eq 44).



267 **268** (64%) (44)

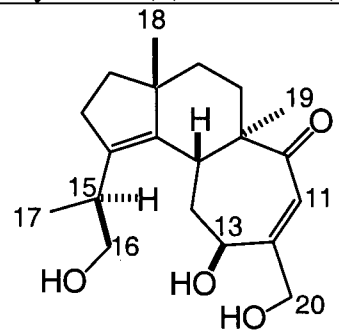
The successful removal of the PMB group in **267** was supported by ^{1}H NMR analysis of the product, triol **268**. The lack of signals in the aromatic region of the ^{1}H NMR spectrum of **268** showed that the PMB group was no longer present. The signals in the ^{1}H NMR spectrum derived from triol **268** (**Table 6**) and those reported[16] for its C–13 epimer, cyathin A_4 (**37**), were compared. The notable differences in the chemical shifts of corresponding protons in **268** and **37** were attributed to the C–13 epimeric relationship of the two substances.



37

Reported ^{1}H NMR ($CDCl_3$, 100 MHz)
Signals δ (Multiplicity, *J* (Hz)):
5.98 (m)
4.40 (m)
4.21 (m)
3.38 (d,6)
0.93 (s)
0.96 (s)

Table 6. ^{1}H NMR Data for Synthetic (±)-Triol **268** ($CDCl_3$, 400 MHz).



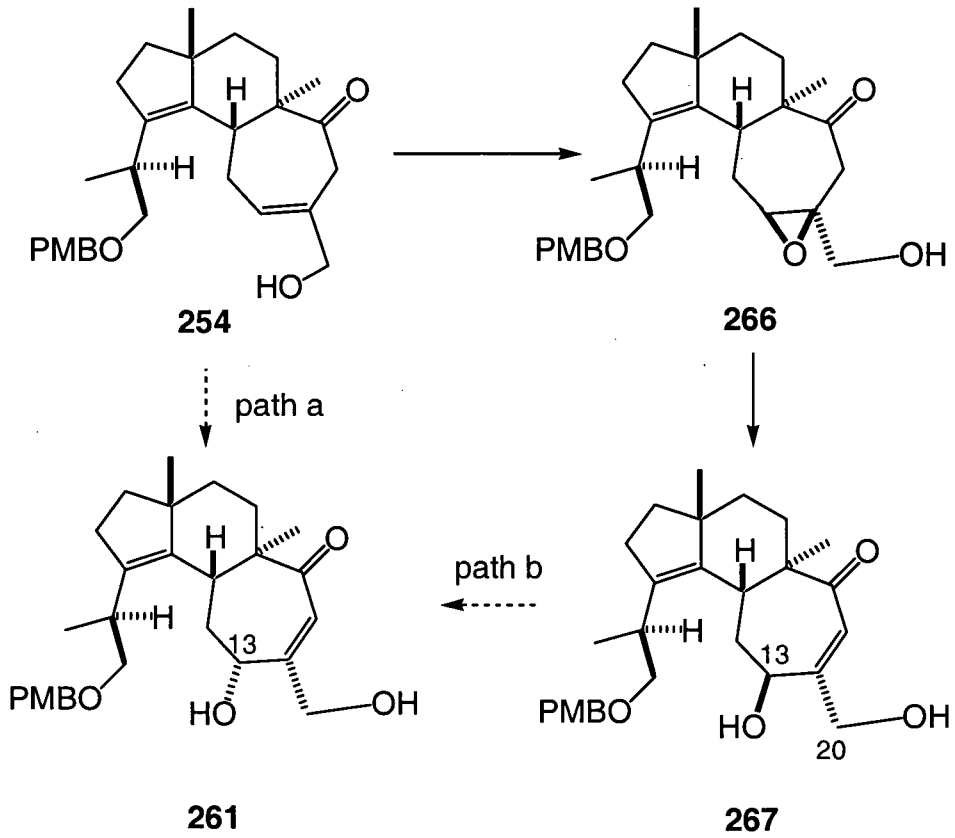
268

^{1}H assignment[a] H–x	^{1}H NMR ($CDCl_3$, 400 MHz) Signals Displayed by Triol **268** δ (Multiplicity, *J* (Hz))
H–17	0.96 (d, 6.7)
H–19	1.04 (s)
H–18	1.12 (s)
	1.43–1.51 (m)
	1.53–1.69 (m)
	1.81 (dt, 4.9, 13.4)
	1.97–2.07 (m)
	2.19–2.37 (m)
	2.63–2.70 (m)
	3.07–3.15 (m)
H–16	3.25–3.31 (m)
	3.37–3.52 (m)
H–20	4.24–4.42 (m)
H–13	4.55–4.59 (m)
H–11	6.00 (s)

[a] Systematic IUPAC-based numbering system.

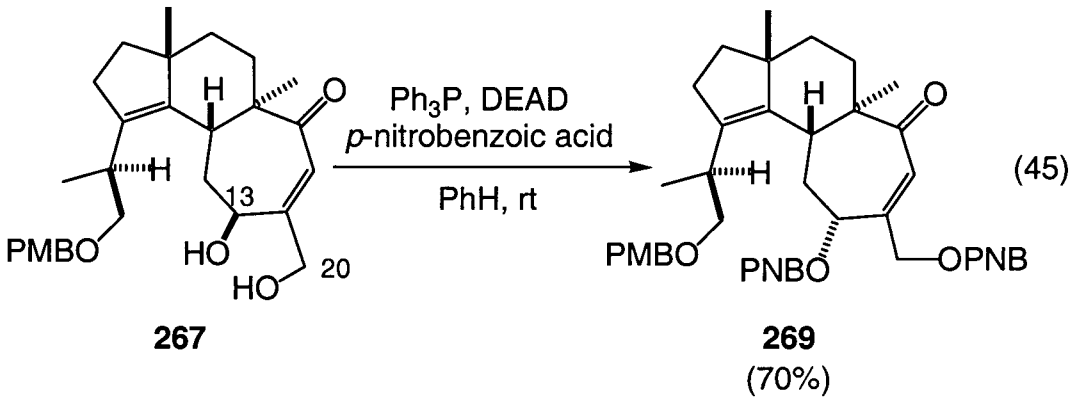
Evidently, epoxidation of **254** proceeded with high β-face stereoselectivity to give epoxide **266**, which ultimately afforded **267** (Scheme 55). However, the main contributing factors responsible for this undesired selectivity are not fully understood. With only limited amounts of intermediate **254** available, the search for an α-face stereoselective epoxidation method to afford **261** from **254** (path a) *via* an α-epoxide was not pursued. As an alternative, the preparation of **261** was approached *via* a Mitsunobu[100]

inversion of the C–13 hydroxyl group in **267** (path b). To minimize the steps required for this transformation, the primary hydroxyl function at C–20 was not protected from the Mitsunobu reaction.



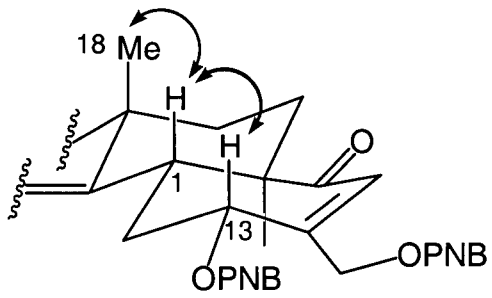
Scheme 55

Following optimized procedures developed by Martin and Dodge,[101] a solution of the diol **267** in benzene was treated with Ph_3P and *p*-nitrobenzoic acid. Diethyl azodicarboxylate (DEAD) was slowly added and the mixture was stirred for 18 h at room temperature. The solvent was removed and the resulting material was purified by flash chromatography to give the desired diester **269** in 70% yield.



267 **269** (70%) (45)

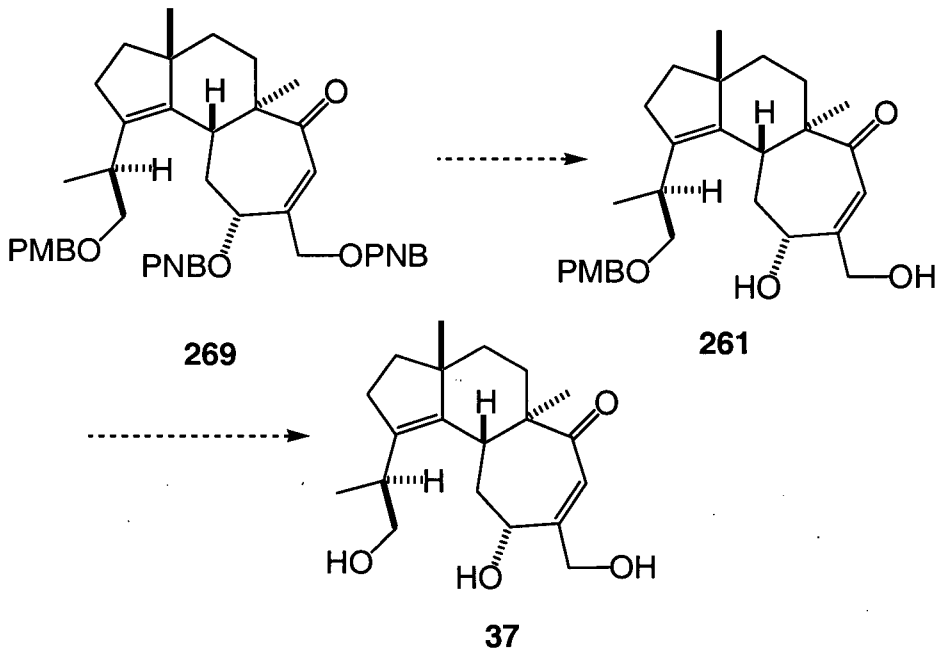
The assigned structure of diester **269** was supported by standard spectrometric analysis. The IR spectrum of **269** exhibited absorptions at 1729 and 1688 cm^{-1}, representing the ester and ketone carbonyl stretches, respectively. Sharp absorptions were also observed at 1530 and 1270 cm^{-1}, characteristic of aromatic nitro groups. The ^1H NMR spectrum of **269** displayed doublets at δ 8.06 (2H, J = 8.2 Hz) and δ 8.16 (2H, J = 8.6 Hz) and a multiplet (4H) between δ 8.20–8.29, attributed to the aromatic protons of the *para*-substituted nitrobenzoate esters. A multiplet (1H) observed between δ 5.70–5.78 in the ^1H NMR spectrum of **269** was attributed to the allylic proton on C–13. Unfortunately, the $C_{44}H_{44}N_2O_{11}$ molecular formula of **269** could not be confirmed by mass spectroscopic analysis. Although the mass spectra of **269** were obtained by DCI+ with isobutene and NH_3 and by LSMIS with thioglycerol and $CHCl_3$ matrix, a parent ion representing a structure with $C_{44}H_{44}N_2O_{11}$ molecular formula was not detected. The inability to detect the requisite parent molecular ion for **269** was attributed to the labile nature of the *p*-nitrobenzoate ester moieties under ionization conditions.



269

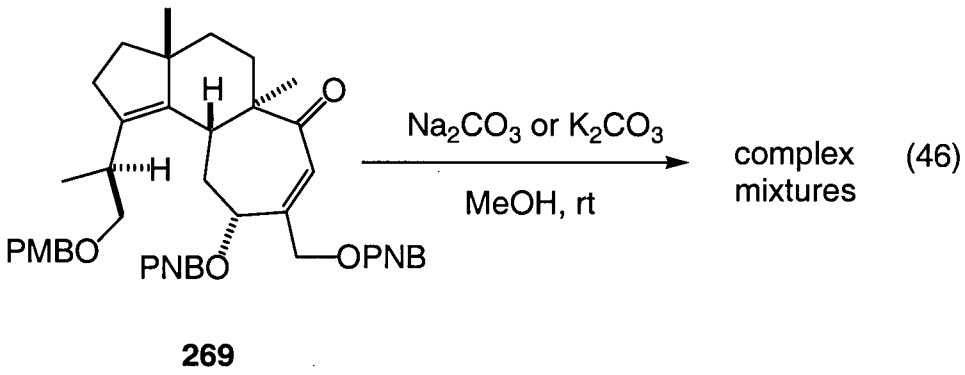
The assigned relative configuration of the *p*-nitrobenzoyl moiety at C–13 in **269** was supported by ^{1}H NMR NOE difference experiments. Irradiation of the signal at δ 2.95 in the ^{1}H NMR of **269**, a broad doublet attributed to the angular proton H–1, caused enhancement of a singlet at δ 1.08 and a multiplet between δ 5.70–5.78, assigned to H–18 and H–13, respectively. Irradiation of the H–18 and H–13 signals both caused enhancement of the H–1 signal. These results support the assigned α relative configuration of the *p*-nitrobenzoyl moiety at C–13 in **269**.

The target structure, cyathin A_4 (**37**), was expected to be available from **269** *via* saponification of the two PNB esters in **269** and subsequent removal of the PMB group (Scheme 56).



Scheme 56

With only limited amounts of substance **269** in hand, the first step, a saponification reaction, was attempted. To our disappointment, treatment of a MeOH solution of diester **269** with K_2CO_3 afforded, upon work-up, a complex mixture of unidentified products (eq 46). The saponification step was also attempted with Na_2CO_3 in MeOH but these conditions also led to a complex mixture of products.



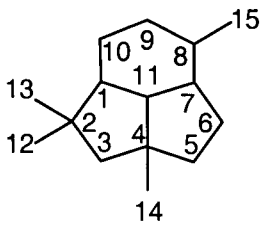
269

Unfortunately, limitations in available advanced materials prevented further investigations into the preparation of diol **261**. On the basis of time restraints, a scale-up preparation of these advanced intermediates was not pursued and our synthetic study geared towards the natural product cyathin A_4 (**37**) was abandoned.

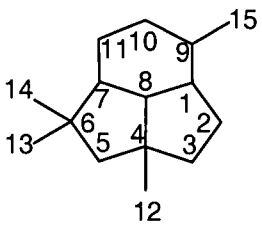
2.2. Studies Towards Presilphiperfolane Sesquiterpenoid Synthesis

2.2.1. Background: Presilphiperfolane Isolation, Biogenesis and Biological Activity

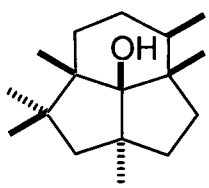
The presilphiperfolane family of sesquiterpenoids share the common carbon skeleton **270**, which displays an unusual tricyclo[5.3.1.$0^{4,11}$]undecane framework. The IUPAC-based numbering and presilphiperfolane natural product numbering schemes are illustrated in **270** and **271**, respectively.* In 1981, Bohlmann and coworkers reported the first structural elucidation of a member of the presilphiperfolane family, presilphiperfoan-8-ol (**272**), from the California coastal succulent *Eriophyllum staechadifolium*.[102] In 1996, the research group of Weyerstahl and that of Marco concurrently reported the isolation of presilphiperfolan-9-ol (**53**) from *Artemisia laciniata* and from *Artemisia chamaemelifolia*, respectively.[20,103]



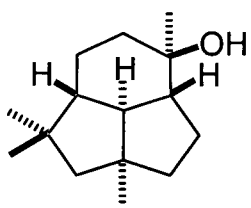
270



271



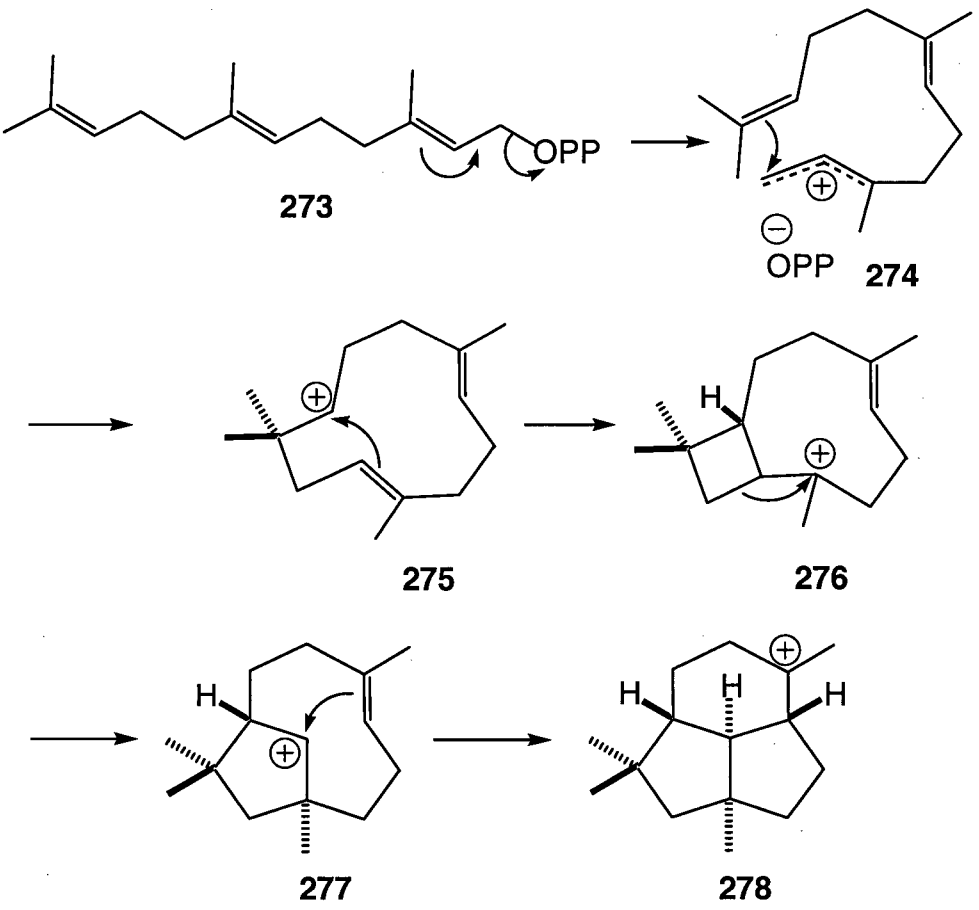
272



53

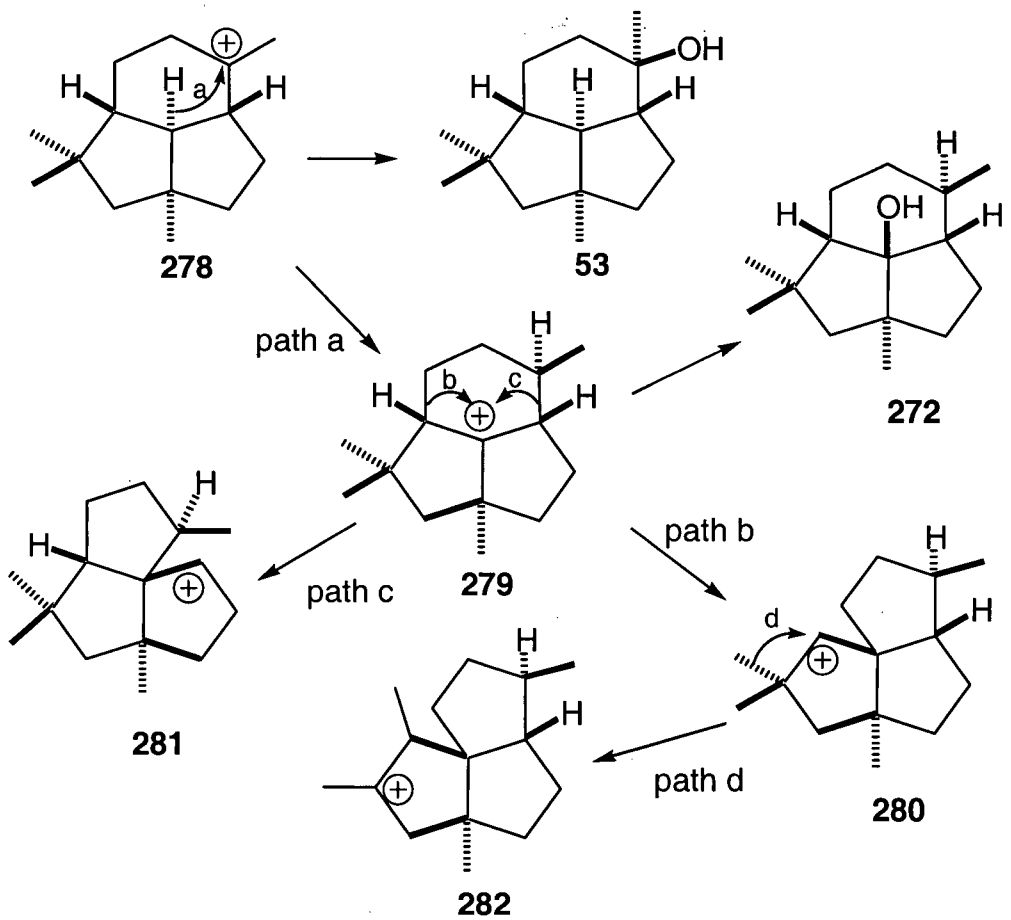
* In the text of this thesis, the presilphiperfolane numbering system **271** is used in most descriptions of presilphiperfolane-related natural products and the IUPAC-based numbering system **270** is used to describe the synthetic intermediates. The experimental section of this thesis contains IUPAC names for the synthetic intermediates.

Bohlmann and coworkers have proposed a biogenetic pathway for the formation of presilphiperfolane natural products from (*E,E*)-farnesyl diphosphate (**273**) (Schemes 57 and 58).[104] Sequential cationic cyclizations of salt **274** provide the caryophyllen-8-yl cation **276** *via* 11-membered macrocycle intermediate **275** (Scheme 57). Cyclobutylcarbinyl ring expansion of **276** generates a cyclopentyl cation with a bridging (*E*)-3-hexenyl chain, **277**. Cationic cyclization of **277** affords the tricyclo[5.3.1.$0^{4,11}$]undecyl cation **278**, which displays the presilphiperfolane skeleton.



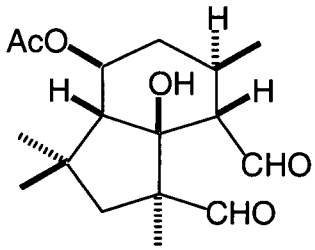
Scheme 57

The natural product presilphiperfolan-9-ol (**53**) presumably arises directly from cation **278** *via* an oxygenation step (Scheme 58). On the other hand, a 1,3-hydride shift in **278** generates cation **279** (path a), the precursor for presilphiperfolan-8-ol (**2**). The biogenetic pathway leading to the presilphiperfolanes is common to several structurally related families of sesquiterpenes, including the silphiperfolanes, the silphinanes and the camaroonanes.[102,104,105] The proposed biogenetic pathways to these families share the advanced intermediate **279**. 1,2-Alkyl shifts involving cation **279** gives the cameroonane (**280**) (path b) or silphinane (**281**) (path c) skeletons. A 1,2-methyl shift in the cameroonane cation **280** affords the silphiperfolane skeleton (**282**) (path d).

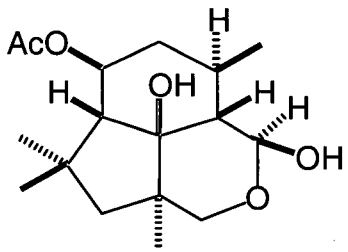


Scheme 58

Although several members of the presilphiperfolane and related families of sesquiterpenoids exhibit pleasant odiferous qualities, only a select few display pharmaceutically applicable biological activities. As an example, two sesquiterpenoids isolated from *Botrytis cinerea,* botrydial (**283**) and dihydoxybotrydial (**284**), demonstrate phytotoxic and antibiotic properties.[106]

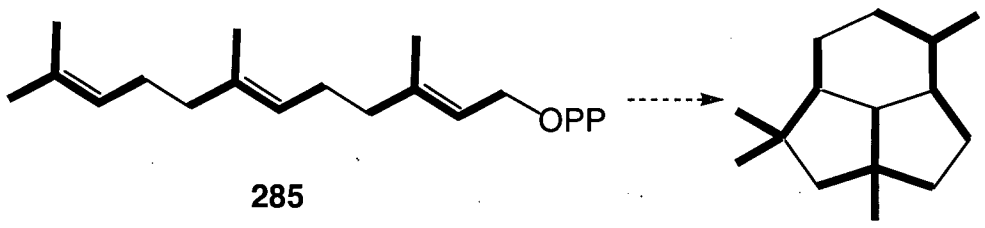


283



284

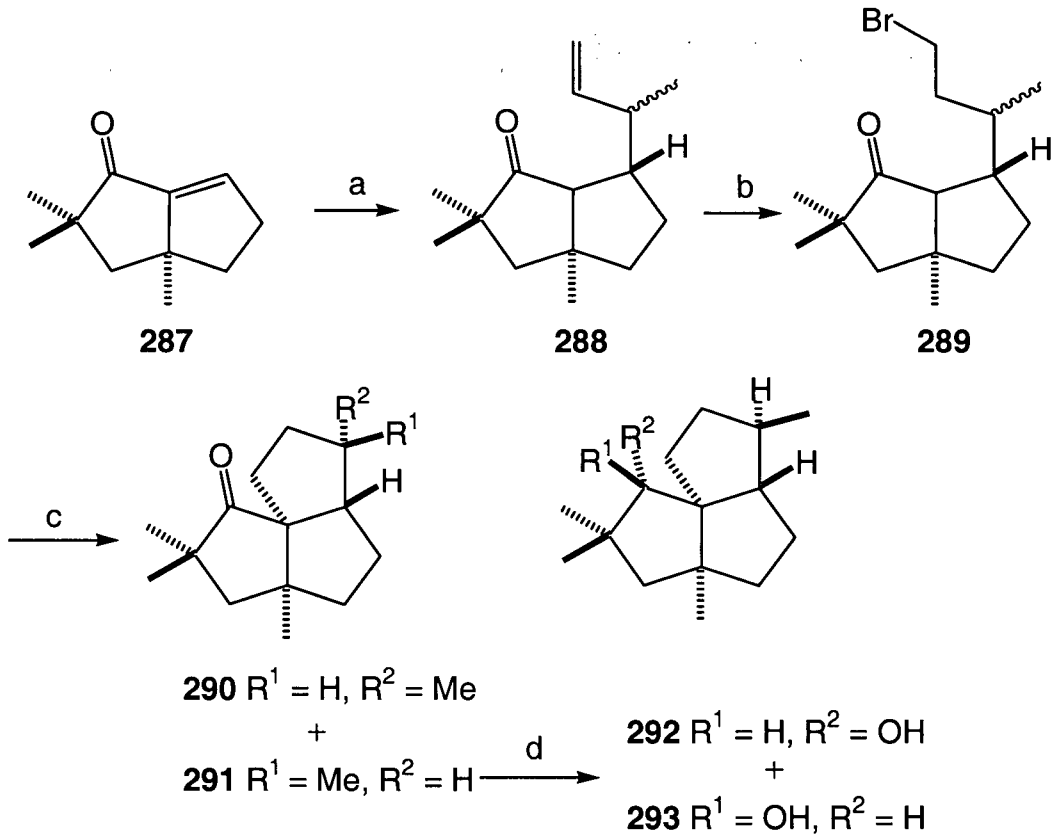
Studies[107-109] by Hanson and coworkers on the metabolites **283** and **284** support the biosynthetic pathway proposed by Bohlmann and coworkers (*vide supra*). The fungus *Botrytis cinerea* was fed [1-^{13}C]- and [2-^{13}C]-acetate as well as [4,5-$^{13}C_2$]-mevalonate, and the labeling patterns of the resulting metabolites were investigated. The pattern of incorporation of three isoprene units, highlighted in **285**, into the carbon framework of **286** was rationalized *via* a sequence of cationic cyclizations in agreement with those proposed by Bohlmann (eq 47). Coates and coworkers have also reported several studies on the presilphiperfolanes biogenesis. [110-113]



285 **286** (47)

2.2.2. Previous Syntheses

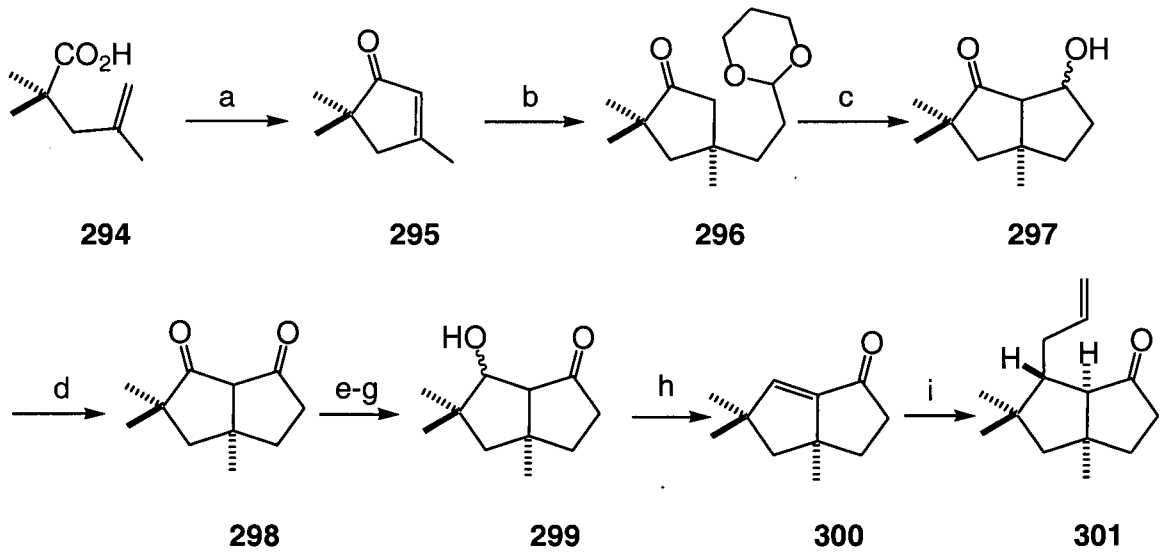
In 2000, Coates and coworkers reported[114] the first total synthesis of (±)-cameroonan-7-ol[105] (**293**) from the known[115,116] bicyclic enone **287**. The key step in this synthesis involved an intramolecular alkylation reaction (Scheme 59). Enone **287** was subjected to a Sakurai reaction[117] with (Z)-2-buten-1-yltrimethylsilane and $TiCl_4$, affording a 2:1 mixture of epimers **288**. A photochemical free radical hydrobromination of this mixture yielded the corresponding bromides **289**. Base-mediated cyclization of these bromides afforded two cyclic ketones, **290** and **291**. The desired isomer, ketone **291**, was reduced with $LiAlH_4$, yielding the target structure (±)-cameroonan-7-ol **293** and its epimer, **292,** in a 1.4:1 ratio.



Reagents: a) (Z)-2-buten-1-yltrimethylsilane, $TiCl_4$; b) HBr, hυ; c) *t*-BuOK; d) $LiAlH_4$.

Scheme 59

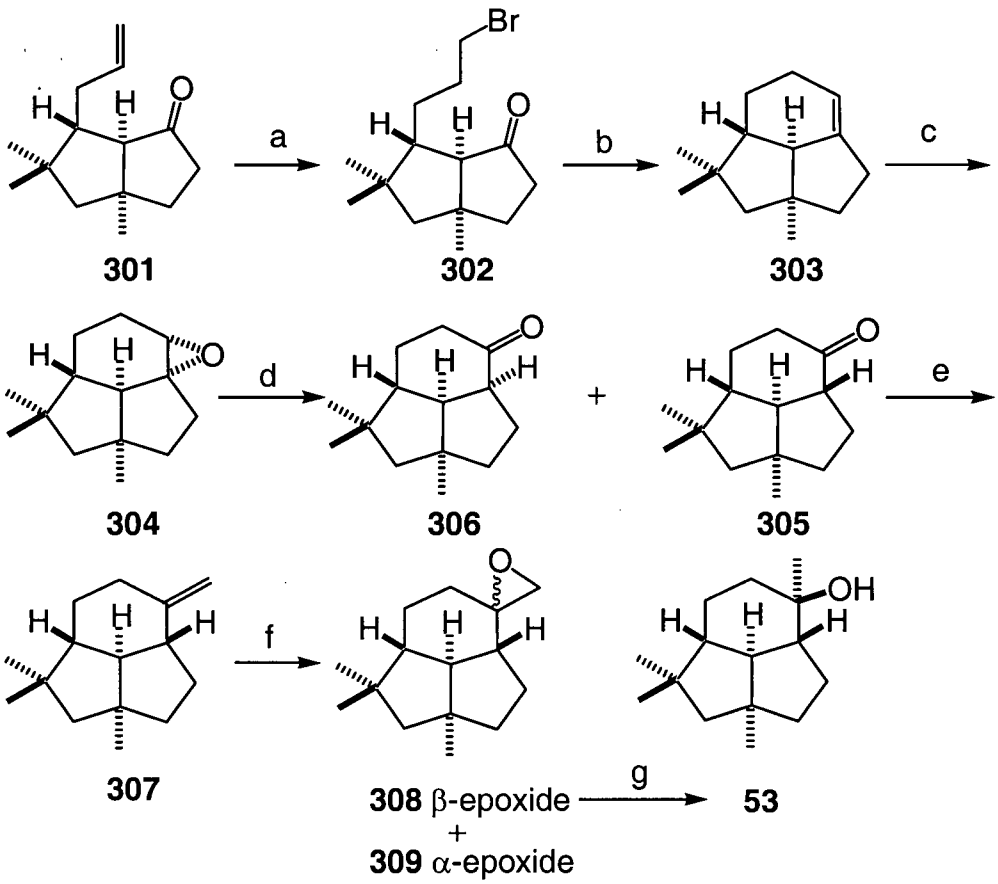
In 1996, Weyerstahl and coworkers reported the first total synthesis of (±)-presilphiperfolan-9-ol (**53**) (Schemes 60 and 61). The 16-step synthesis of (±)-**53** commenced with the conversion of the pentenoic acid **294** to the corresponding acid chloride, which was subsequently treated with $AlCl_3$ to afford the cyclopentenone **295** (Scheme 60). Copper(I)-catalyzed conjugate addition of the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane to enone **295** provided ketone **296** in good yield. Acid hydrolysis of **296**, followed by an aldol cyclization of the resultant keto aldehyde, gave a mixture of hydroxy ketones **297**. Jones oxidation of this mixture provided diketone **298**, which was transformed to hydroxy ketone **299** in three steps. Conversion of **299** to the corresponding mesylates, followed by a DBU-mediated elimination reaction, gave enone **300**. $TiCl_4$-mediated Sakurai conjugate allylation of enone **300** with allyltrimethylsilane provided ketone **301**.



Reagents: a) $(COCl)_2$; $AlCl_3$; b) 2-[(1,3)-dioxan-2-yl]-1-ethylmagnesium bromide, CuI, TMEDA, TMSCl; c) acetone, HCl; d) CrO_3, H_2SO_4, H_2O; e) $(CH_2OH)_2$, $HC(OMe)_3$, TsOH; f) $LiAlH_4$; g) dil. HCl; h) MsCl, Et_3N; DBU; i) allyltrimethylsilane, $TiCl_4$.

Scheme 60

The final synthetic steps leading to (±)-presilphiperfolan-9-ol (**53**) are illustrated in Scheme 61. Benzoyl peroxide-mediated addition of HBr to enone **301** afforded bromide **302**. The Wittig salt derived from bromide **302** was treated with base, resulting in a cyclization that gave the tricyclic alkene **303**. A stereoselective α-epoxidation of **303**, followed by a $ZnBr_2$-mediated rearrangement of the resultant epoxide **304**, afforded norpresilphiperfolan-9-one **305** and its epimer **306**. Treatment of **305** with Lombardo's reagent ($CH_2Br_2/Zn/TiCl_4$) provided the corresponding alkene **307**, which was oxidized with mCPBA to give epoxides **308** and **309** in a 3:2 ratio. $LiAlH_4$ reduction of epoxide **308** yielded the target structure, (±)-presilphiperfolan-9-ol (**53**).

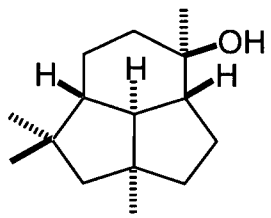


Reagents: a) HBr, Bz_2O_2;b) Ph_3P; NaHMDS; c) mCPBA; d) $ZnBr_2$; e) Zn, CH_2Br_2, $TiCl_4$; f) mCPBA; g) $LiAlH_4$.

Scheme 61

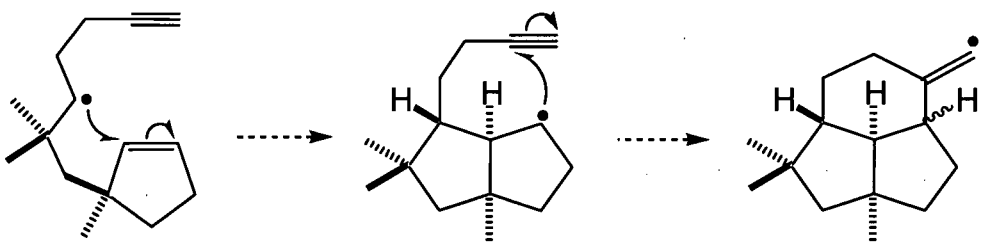
2.2.3. Studies Towards a Formal Synthesis of (±)-Presilphiperfolan-9-ol

Our synthetic studies directed towards the formal synthesis of (±)-presilphiperfolan-9-ol (**53**) relied on a proposed radical-mediated tandem cyclization[118] sequence in the construction of the tricyclo[5.3.1.$0^{4,11}$]undecane carbon framework (*vide infra*).



53

Our proposed tandem cyclization sequence commences with the secondary radical **51**. The first reaction is a 5-*exo* cyclization of the 5-hexenyl-type radical **51**, which was anticipated to result in the *cis*-fused 5-5 bicyclic radical **310** (Scheme 62). The 6-heptynyl-type radical **310** was expected to cyclize in a 6-*exo* fashion, generating the *cis*-fused bridge in **311**. A more detailed analysis of the proposed transition states for the tandem cyclizations and the expected relative configurations for the ring-fusion centers will follow.

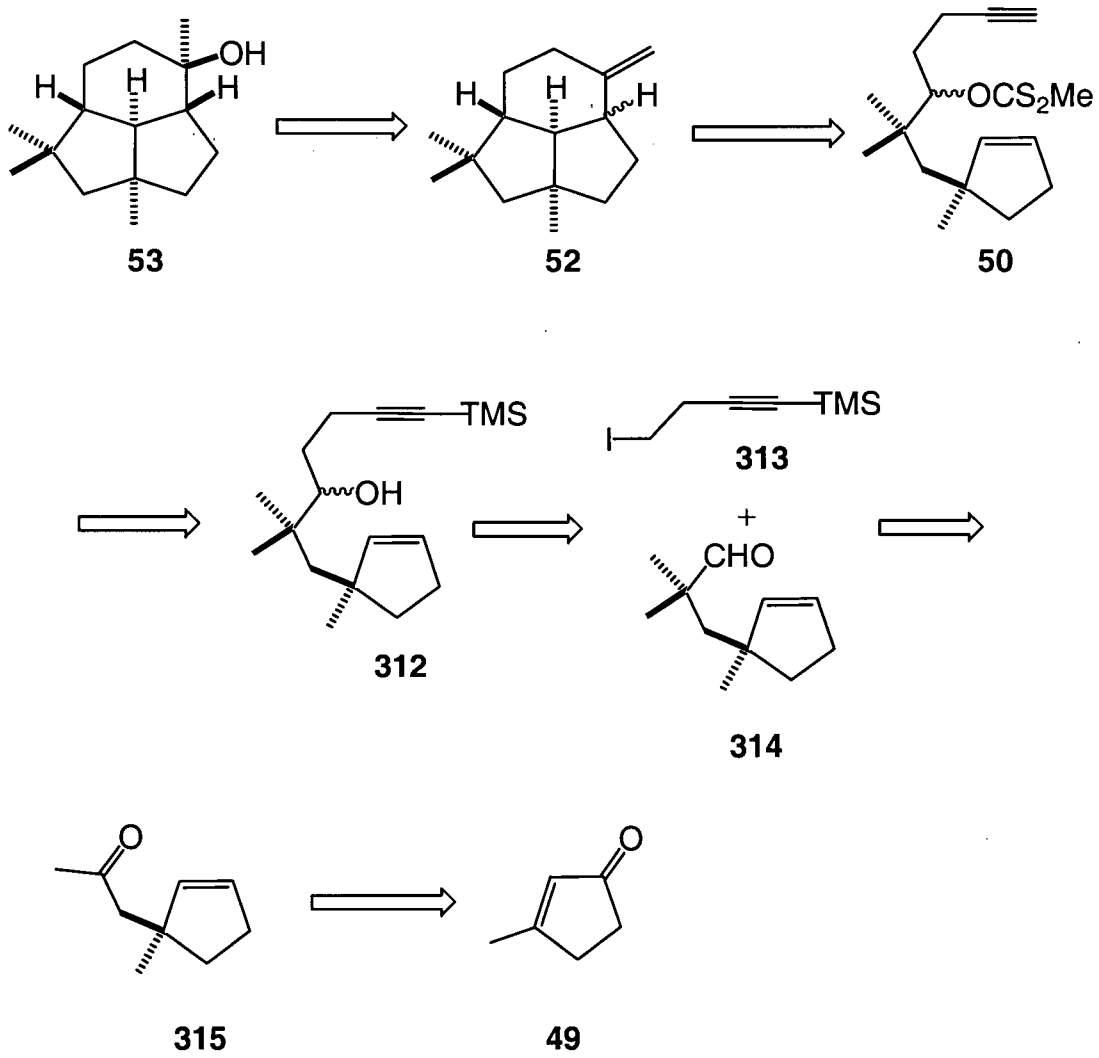


51 **310** **311**

Scheme 62

2.2.3.1. Retrosynthetic Analysis

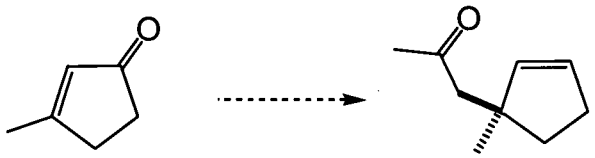
Our retrosynthetic plan for the formal synthesis of (±)-presilphiperfolan-9ol (**53**) is outlined in Scheme 63. The target compound **53** is readily available from the β-isomer of alkenes **52**, as reported by Weyerstahl and coworkers (see Section 2.2.2., *vide supra*).[20] Treatment of xanthates **50** with Bu_3SnH and AIBN should provide the corresponding secondary alkyl radical, the first intermediate in our proposed radical-mediated tandem cyclization leading to alkenes **52** (*vide supra*). The cyclization precursors, xanthates **50,** should be readily derived from alcohols **312**. 1,2-Addition of the alkyllithium species derived from the known[119] iodide **313** to aldehyde **314** was not expected to be stereoselective and should afford a mixture of alcohols **312**. A sequence of chain homologation and α-methylation steps should provide aldehyde **314** from ketone **315**. Finally, ketone **315** should be available from enone **49** *via* a sequence of steps that include a Carroll [3,3] rearrangement.[120]



Scheme 63

2.2.3.2. Preparation of Ketone 315

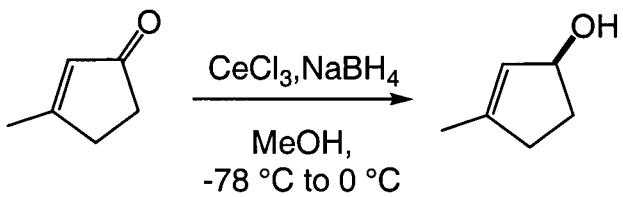
The first synthetic sequence in our study involved the preparation of ketone **315** from 3-methyl-2-cyclopenten-1-one (**49**) (eq 48).



(48)

49 **315**

A racemic mixture of the known[121-125] alcohol **316** was prepared from commercially available enone **49** by selective 1,2-reduction with $CeCl_3$ and $NaBH_4$ (eq 49).[126] Alcohol **316**, obtained in 81% yield upon purification by flash chromatography, was analyzed by standard spectrometric methods. All spectral data derived from **316** were identical to those reported in the literature.[125]

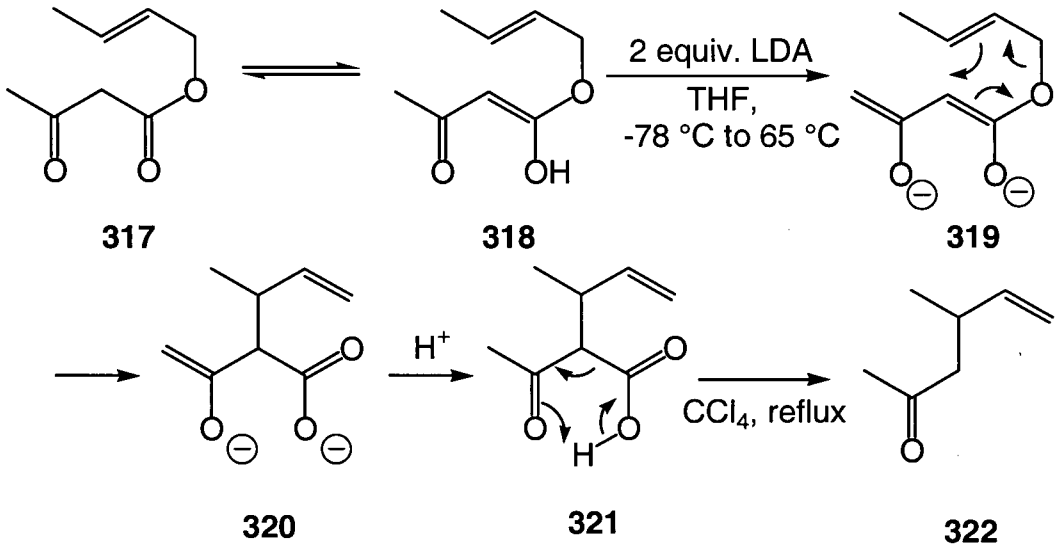


(49)

49 **316**
(81%)

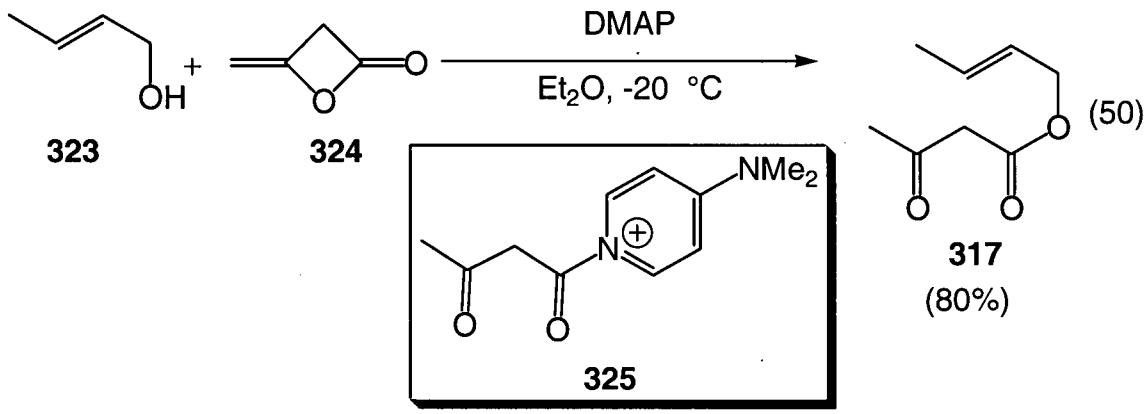
In 1984, Wilson and coworkers reported[127] a dianionic version of the well-known Carroll rearrangement[120] of allylic β-keto esters. A THF solution of allylic β-keto ester

317 and its tautomer **318** was treated with two equivalents of LDA (Scheme 64). The resultant solution of dianion **319** was heated to 65 °C, generating, after a suitable work-up procedure, the [3,3] rearrangement product, β-keto acid **321**. Heating a solution of **321** in CCl_4 resulted in a decarboxylation, affording alkenone **322**.

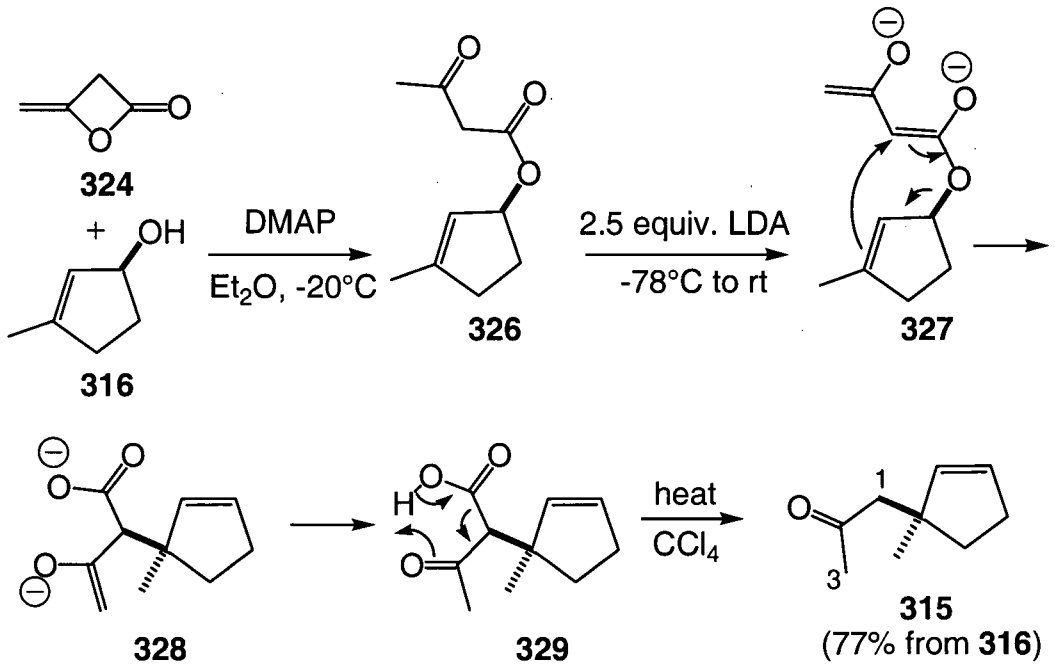


Scheme 64

Wilson and coworkers also developed[127] an efficient preparation of the allylic β-keto ester **317** from the corresponding allylic alcohol **323** (eq 50). Treatment of a cold (–20 °C) solution of **323** in Et_2O with diketene (**324**), followed by the addition of a catalytic amount of DMAP, provided the corresponding allylic β-keto ester **317** in good yield. The active acylating reagent, compound **325**, is formed *in-situ* by reaction of DMAP and diketene (**324**), followed by protonation.



The sequence developed by Wilson and coworkers for the preparation of allylic esters and their subsequent Carroll rearrangement was applied to alcohol **316** (Scheme 65). An ethereal solution of **316** and diketene (**324**) was treated with a catalytic amount of DMAP and the resultant allylic ester **326** was subsequently treated 2.5 equiv. of LDA. Dianion **327** underwent a [3,3] sigmatropic rearrangement to dianion **328**, providing keto acid **329** after work-up. A solution of the crude keto acid **329** in CCl_4 was refluxed, affording the desired ketone **315**.

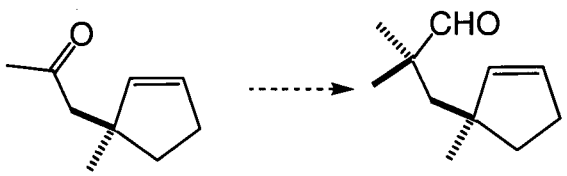


Scheme 65

The structure of ketone **315** was supported by standard spectrometric analysis. The IR spectrum of **315** displayed a sharp absorption at 1718 cm^{-1}, characteristic of an aliphatic ketone. The ^1H NMR spectrum of **315** exhibited a 3-proton singlet at δ 2.11 and a 2-proton singlet at δ 2.49, attributed to the H–3 and H–1, respectively. The ^1H NMR spectrum of **315** also exhibited overlapping multiplets between δ 5.61–5.68, attributed to the olefinic protons. The ^{13}C NMR resonances for the carbonyl and olefinic carbons of **315** were observed at δ 208.3 and at δ 129.1 and 139.0, respectively.

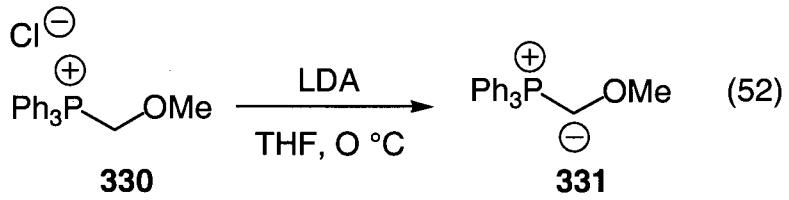
2.2.3.3. Preparation of Aldehyde 314

With ketone **315** in hand, the preparation of **314** *via* a sequence of chain-homologation and methylation steps was investigated (eq 51).



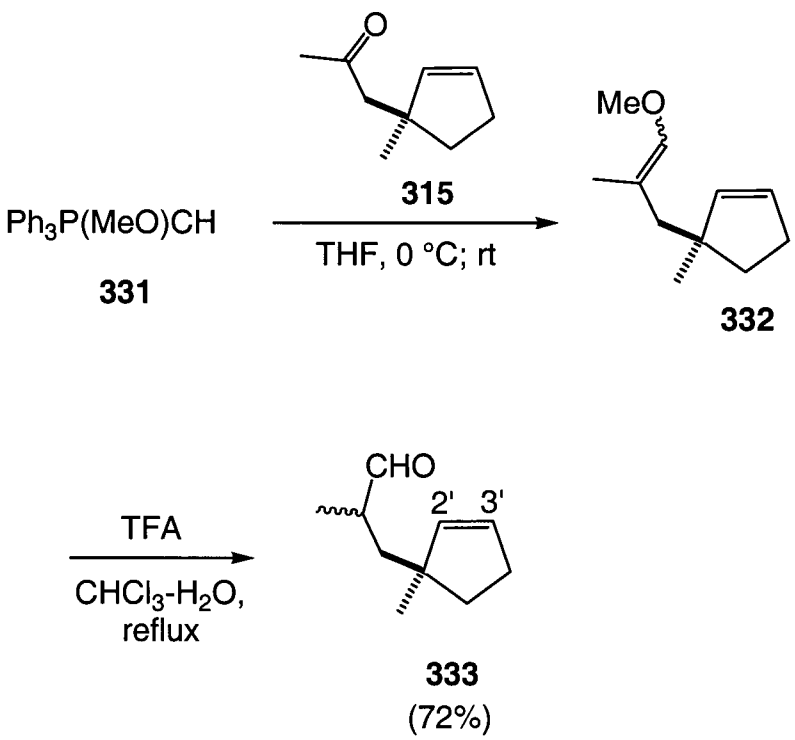
315 **314** (51)

The first transformation of this sequence was attempted with the modified Wittig reagent **331**,[128] which was prepared by treatment of a cold (0 °C) solution of **330** in THF with LDA (eq 52).



(52)

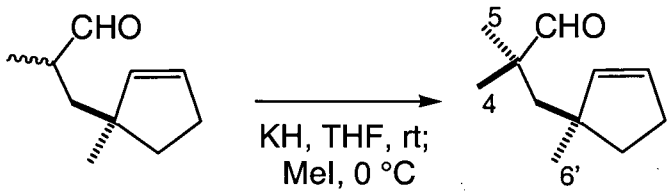
A cold (0 °C) solution of **331** was treated with ketone **315**, was stirred for 1 h at 0 °C and then was allowed to warm to room temperature (Scheme 66). After aqueous work-up, the resultant crude mixture of enol ethers **332** was subjected to hydrolysis conditions (TFA in refluxing aqueous $CHCl_3$), affording a 1:1 mixture of aldehydes **333**, in 72% yield.



Scheme 66

Evidence for the successful carbonyl homologation of ketone **315** was obtained by spectroscopic analysis of aldehydes **333**. The IR spectrum of **333** displayed an absorption at 1735 cm^{-1}, characteristic of aldehydic carbonyls. The ^1H NMR spectral signals of the aldehydic protons in **333** were observed as doublets at δ 9.51 (J = 2.9 Hz) and 9.53 (J = 2.7 Hz). Resonances at δ 205.2 and 205.3 in the ^{13}C NMR spectrum of **333** were attributed to the aldehydic carbons. The ^{13}C NMR resonances for the C–2' and C–3' olefinic carbons in **333** were observed at δ 139.2 and 139.5 and at δ 129.4 and 129.9, respectively.

With aldehydes **333** in hand, the preparation of the corresponding α,α-dimethyl aldehyde **314** was straightforward (eq 53). Aldehydes **333** were added to a THF solution of potassium hydride and the resultant enolate solution was treated with methyl iodide at 0 °C.[129] Work-up and purification of the resulting material by flash chromatography provided the desired aldehyde **314** in 90% yield.

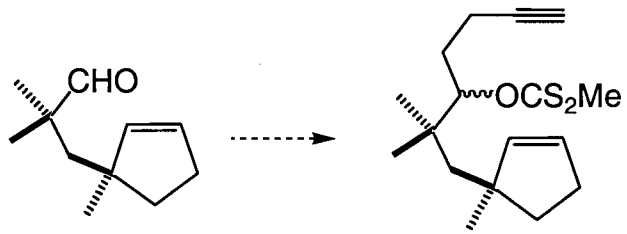


333 **314** (90%) (53)

The successful α-methylation of **333** was supported by ^1H NMR spectroscopic analysis of the product **314**. The ^1H NMR spectrum derived from **314** exhibited 3-proton singlets at δ 1.01 and 1.04 attributed to the H–4 and H–5 methyl protons. The ^1H NMR spectral resonance for the aldehydic proton in **333** was observed as a 1-proton singlet at δ 9.44.

2.2.3.4. Preparation of the Tandem Cyclization Precursors, Xanthates 50

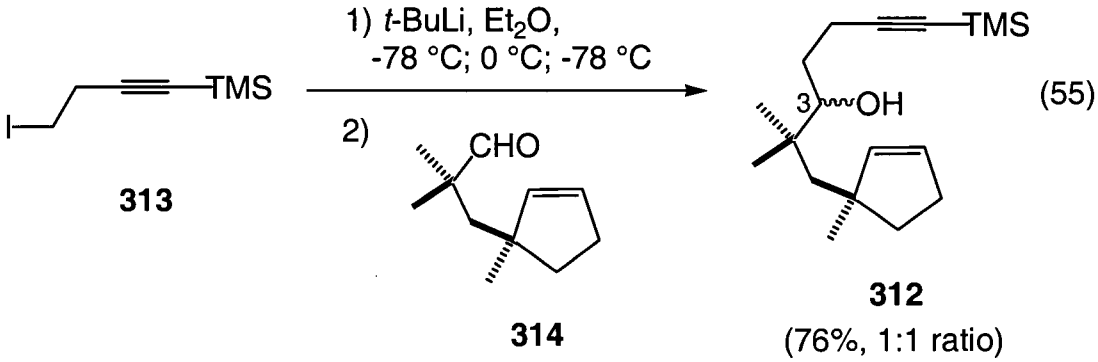
Xanthates **50**, the tandem cyclization precursors, were readily prepared in three steps from aldehyde **314** (*vide infra*) (eq 54).



(54)

314 **50**

Following a protocol developed[130] by Negishi and coworkers, a cold (–78 °C) Et_2O solution of the known[119] iodide **313** was treated with 2.5 equiv. of *t*-BuLi and the resulting mixture was warmed to 0 °C, generating the corresponding alkyllithium species (eq 55). Upon cooling to –78 °C, the solution of the alkyllithium was treated with aldehyde **314**, affording, after a work-up step, a 1:1 mixture of alcohols **312**.



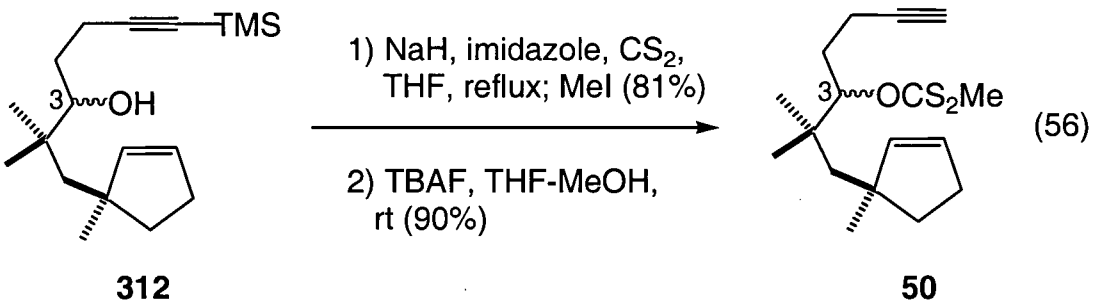
(55)

313 **314** **312**
(76%, 1:1 ratio)

The 1:1 mixture alcohols **312**, inseparable by silica gel flash chromatography, was analyzed by NMR spectroscopy. The ^1H NMR spectrum of **312** displayed overlapping 1-

proton multiplets between δ 3.3–3.45, attributed to H–3. The C–3 carbons gave rise to resonances at δ 78.4 and 79.2 in the ^{13}C NMR spectrum of **312**.

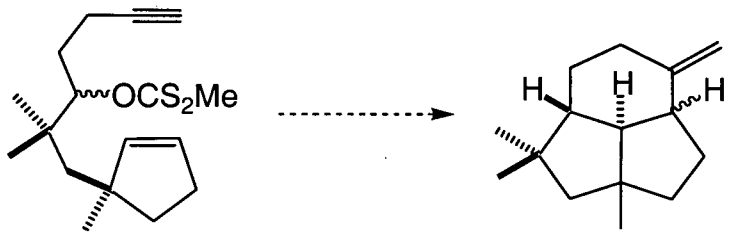
The preparation of xanthates **50** from alcohols **312** was straightforward. A solution of alcohols **312** in THF was added to a THF solution of NaH and the resultant mixture was treated with imidazole and carbon disulfide (eq 56). The resultant solution of dithiocarboxylate anions was treated with methyl iodide, affording the corresponding xanthates. The TMS function on the alkyne moiety was removed by treatment a THF–MeOH solution of the latter material with TBAF, affording the desilylation products **50**. The structures of **50** were confirmed by ^{1}H NMR spectroscopic analysis. The ^{1}H NMR spectrum of xanthates **50** displayed two 3-proton singlets at δ 2.55 and 2.57, representing the methyls in the xanthates moieties. The H–3 protons in xanthates **50** were observed as overlapping multiplets between δ 5.79–5.85, characteristic of secondary xanthates.



312 **50** (56)

2.2.3.5. Tandem Free-radical Cyclization

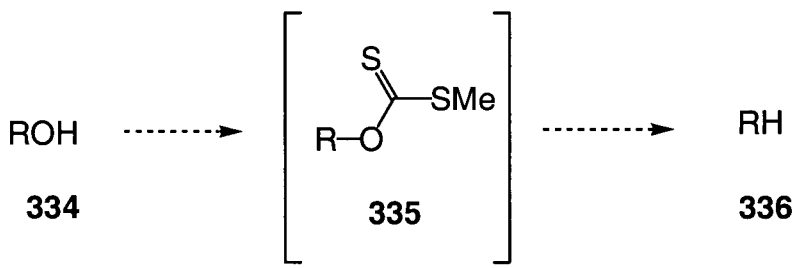
With xanthates **50** in hand, attention was turned to the proposed tandem radical-mediated cyclization (eq 57).



(57)

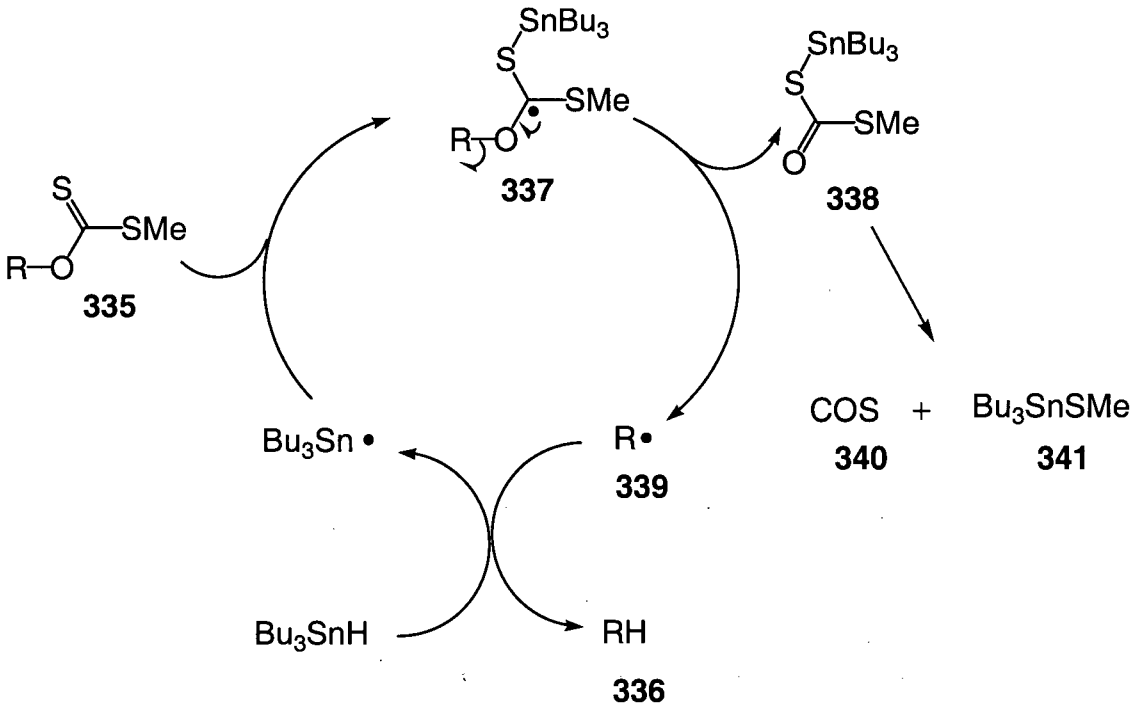
50 **52**

The xanthate functional group has traditionally served as convenient derivative for the Barton–McCombie deoxygenation of alcohols (Scheme 67). In 1975, Barton and McCombie reported[131] that xanthates (**335**), readily derived from the corresponding alcohols (**334**), generate the reduced products (**336**) *via* Bu_3SnH-mediated processes that proceed by way of radical intermediates.



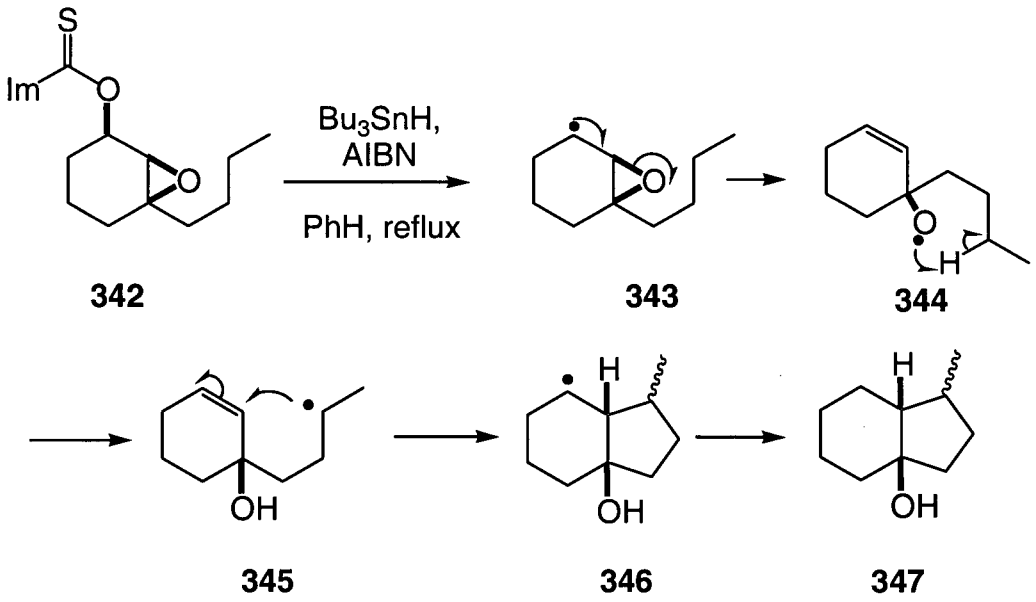
Scheme 67

The proposed mechanistic pathway[131,132] for the Barton–McCombie radical-mediated reduction of xanthates is illustrated in Scheme 68. The stannyl radical, which displays a high affinity for sulfur, attacks the thiocarbonyl group in xanthate **335**, generating radical adduct **337**. A β-scission of the carbon–oxygen bond in **337** provides the alkyl radical **339** and the co-product **338**, which is unstable with respect to elimination of carbon oxysufide **340**. Abstraction by the alkyl radical **339** of a hydrogen atom from Bu_3SnH generates the desired alkane **336** and regenerates the stannyl radical, which results in propagation of the chain reaction.



Scheme 68

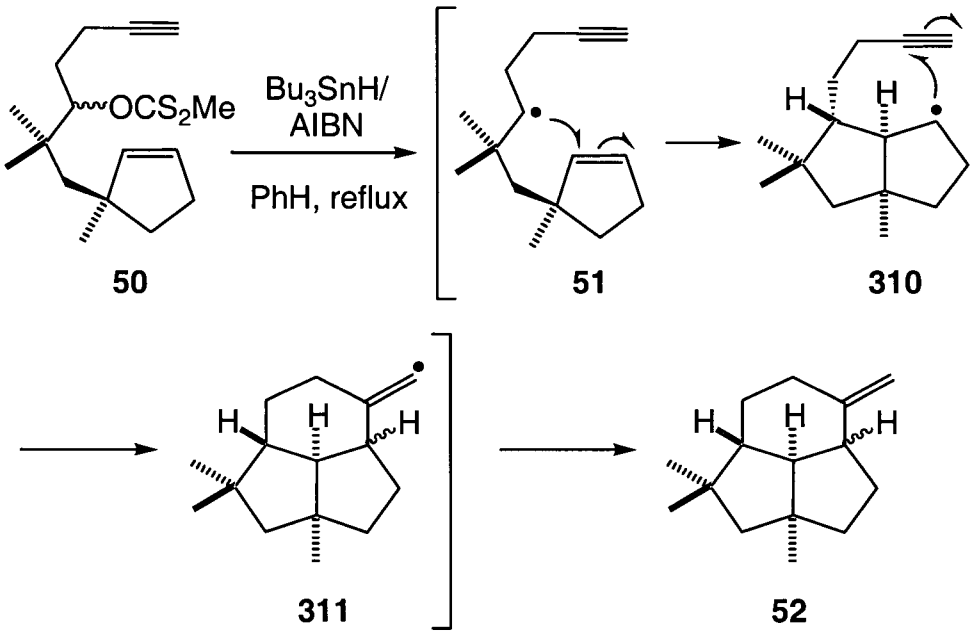
The radical intermediate obtained from treatment of xanthate-type derivatives with Bu_3SnH/AIBN have also been used for reactions other than direct reduction by hydrogen atom abstraction.[133,134] For example, in 1990, Rawal and coworkers reported[135] the preparation of carbocyclic systems from xanthates *via* radical-induced epoxide fragmentation (Scheme 69). Xanthate **342** was converted to the corresponding radical **343**, which fragmented to the oxy-radical **344**. Intramolecular hydrogen abstraction converted **344** into the radical **345**. A 5-*exo* cyclization of the 5-hexenyl radical **345** generated a mixture of the *cis*-fused bicyclic intermediates **346**, which yielded **347** upon hydrogen atom abstraction.



Scheme 69

The proposed tandem reactions of the radical intermediate **51**, obtained by the Barton–McCombie-type reaction of xanthates **50**, are outlined in Scheme 70. In

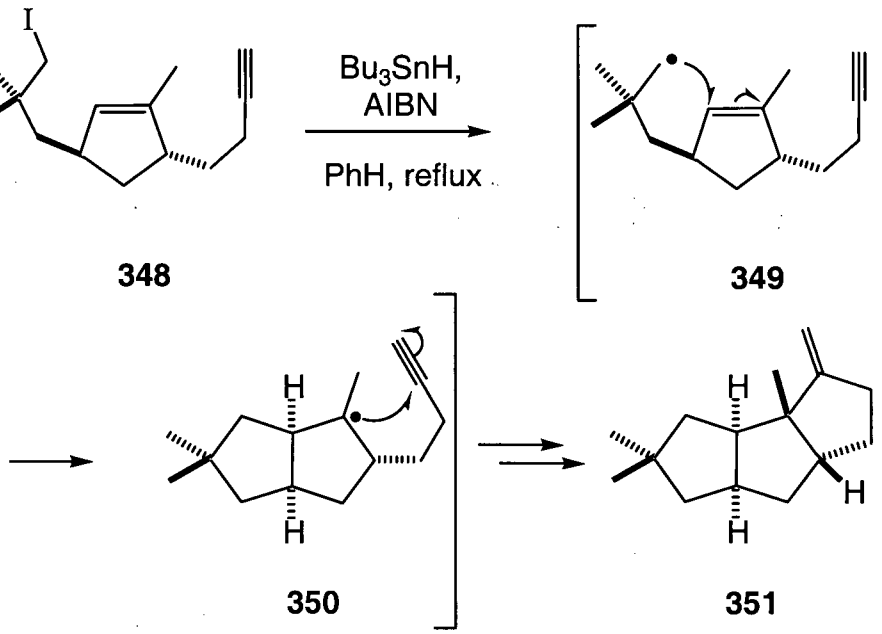
accordance with guidelines[136] developed for the stereochemical predictions of radical-mediated cyclizations, a 5-*exo* cyclization of the 5-hexenyl-type radical in **51** was anticipated to form the *cis*-fused 5-5 bicyclic intermediate **310**. The second reaction, a 6-*exo*-type cyclization of the 6-heptynyl-type radical in **310**, was expected to result in a six-membered ring, as displayed in **311**. Finally, hydrogen abstraction by **311** would afford the tricycles **52**.



Scheme 70

The first cyclization reaction in the proposed sequence (*vide supra*) is analogous to that of a tandem sequence developed by Curran and coworkers for the total synthesis of (±)-hirsutene (**351**) (Scheme 71).[137] Thus, treatment of iodide **348** with Bu_3SnH and AIBN generated the corresponding 5-hexenyl-type radical **349**, which underwent a 5-*exo*

cyclization to give the *cis*-fused 5-5 bicyclic intermediate **350**. A 5-*exo* cyclization of the 5-hexynyl-type radical **350**, followed by hydrogen abstraction, afforded (±)-hirsutene (**351**).

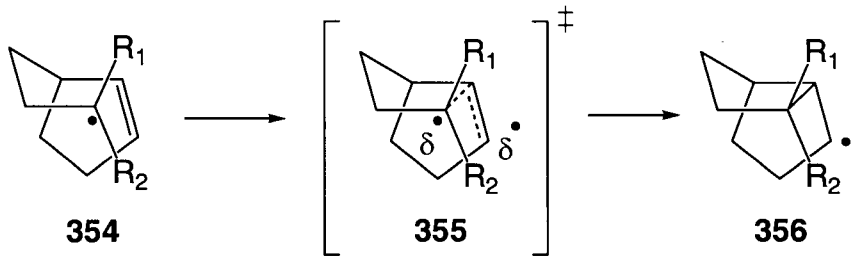


Scheme 71

Predictions and rationalizations of stereoselectivity[136] in 5-*exo* hexenyl cyclization are generally based on the Beckwith–Houk transition state model.[138-141] In brief, the Beckwith–Houk model involves a combination of the proposed transition structure for bimolecular radical additions to alkenes and the principles of conformational analysis, which support the postulated chair- and boat-like transition state structures, **352** and **353**, for the cyclization of acyclic substrates.

352 **353**

Radical cyclizations resulting in the formation of a 5-5- or smaller fused ring-systems favour chair-like transition-structures and usually form *cis*- rather than *trans*-fused products.[136] The first step of our proposed tandem sequence, represented by the cyclization of **354** to **356** in Scheme 72, was anticipated to involve a transition state resembling **355** in which R_1 = H and R_2 = tethered acetylene or vice versa.

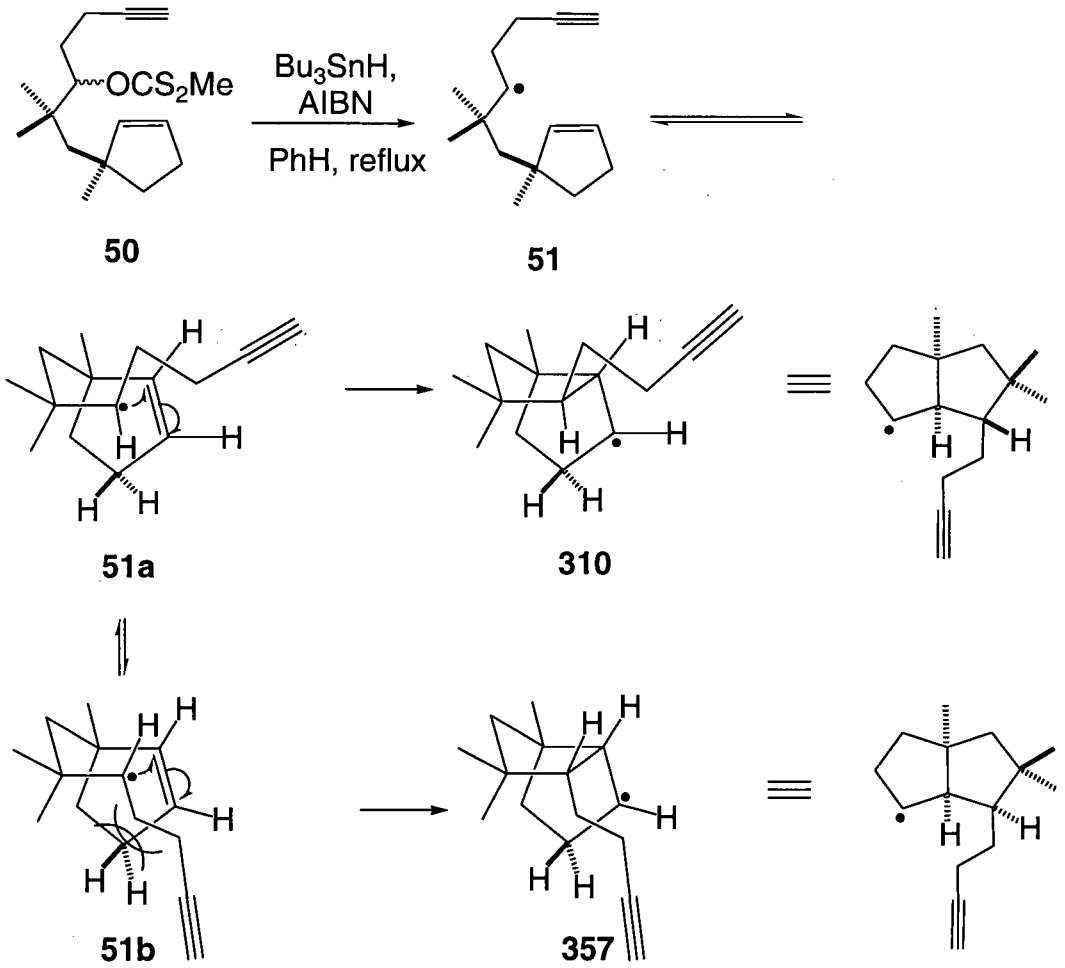


354 **355** **356**

Scheme 72

Upon treatment with Bu_3SnH/AIBN, the mixture of xanthates **50** was expected to form the secondary radical intermediate **51** (Scheme 73). On the basis of molecular modeling and conformational analysis, the preferred transition state for the cyclization of **51** was expected to resemble structures **51a** or **51b**, leading to the diastereomeric intermediates, **310** and **357**, respectively. The main difference between **51a** and **51b** is the orientation of the substituents on the radical-bearing carbon. In **51a**, the smaller substituent (hydrogen) is positioned over the cyclopentenyl ring. Conversely, in **51b**, the larger substituent lies over the ring. On the basis of the possible steric interactions between the larger substituent and the ring-protons in **51b**, the transition state for the

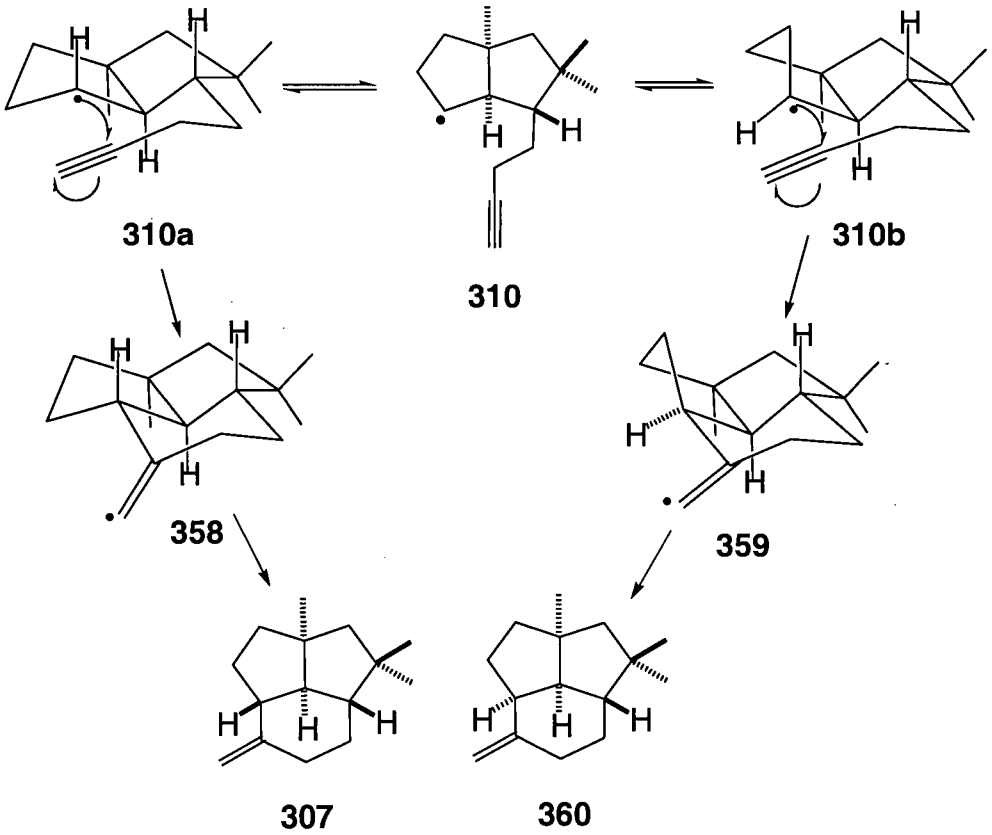
cyclization of **51** was anticipated to favour a geometry resembling **51a**, leading to radical **310**.



Scheme 73

For the second step of the proposed tandem sequence, a 6-*exo* cyclization of 6-heptynyl radical **310**, the transition structures leading from **310a** and **310b** to give intermediates **358** and **359**, respectively, were considered (Scheme 74). Conformational analysis and molecular modeling studies of these transition structures suggested that a

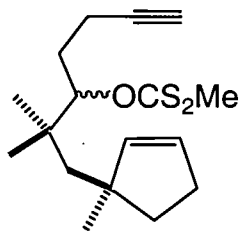
mixture of isomers, favouring **360** *via* **359**, might be obtained. The most notable difference between the two proposed transition structures was the closer structural proximity of the tethered acetylene to the radical center afforded by the transition structure leading from **310b** to **359** compared to that afforded by the transition structure leading from **310a** to **358**.



Scheme 74

In the event, slow syringe-addition of Bu_3SnH and a catalytic amount of AIBN to a refluxing solution of xanthates **50** in benzene afforded neither tandem cyclization product **307** nor **360** (eq 58). Upon removal of the solvent, a mixture of tin-containing products, representing less than 5% mass balance with respect to xanthates **50**, was

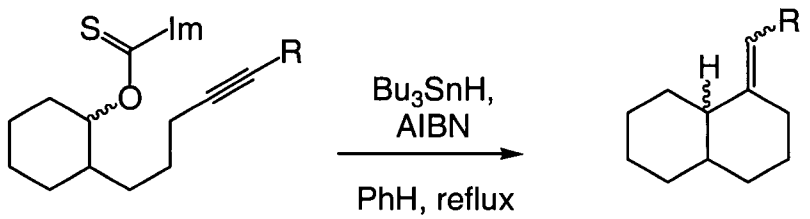
obtained. Presumably, the products were volatile and consequently, under the work-up conditions, were lost to the atmosphere.



(58)

50

The literature pertaining to radical chemistry was reviewed for possible methods of improving our cyclization reaction. Specifically, alterations to our cyclization substrate that might reduce product loss by evaporation were sought. In 1984, Clive and coworkers reported[142] that the radical cyclization of phenylacetylene **361** provided the corresponding cyclic product **362** in a yield higher than that obtained from the corresponding cyclization of the non-phenyl derivative **363** to **364** (eq 59).



(59)

361 R = Ph

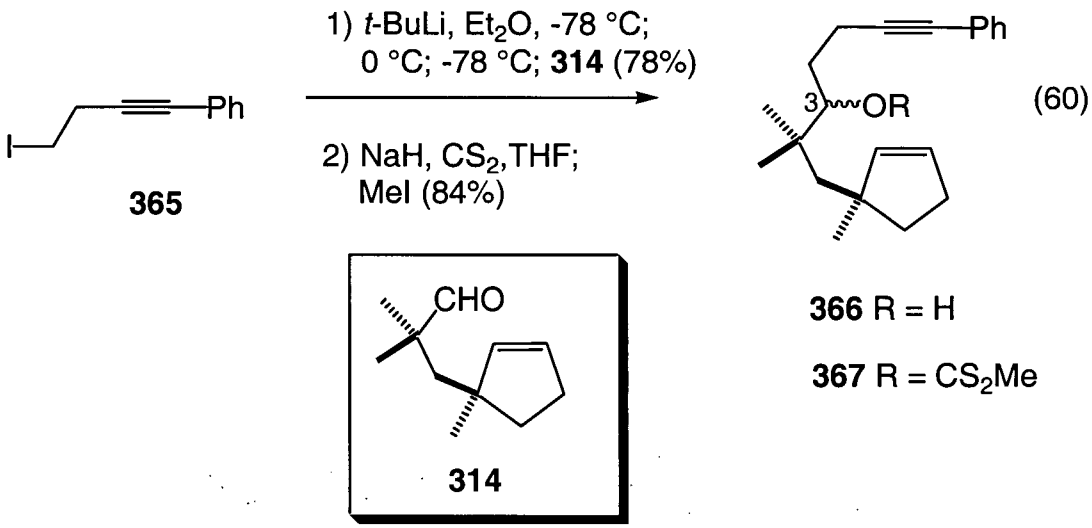
362 R = Ph (79%)

363 R = H

364 R = H (24%)

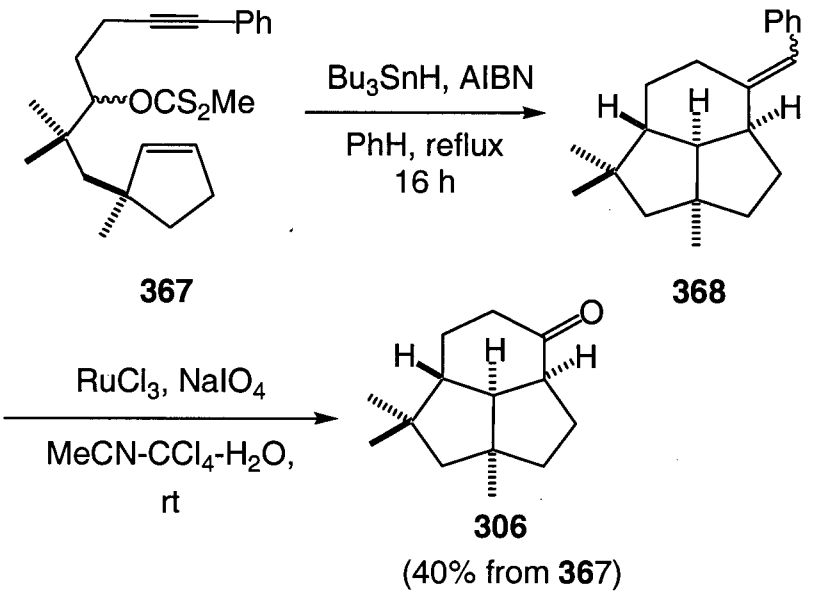
It was expected that phenyl derivatives of our acetylenic substrates would provide less volatile products upon cyclization. Thus, the phenyl-substituted substrates were

prepared following the procedures described earlier for xanthates **50**. The known[143] iodide **365** was treated with 2.1 equiv. of *t*-BuLi and the resultant solution of the required alkyllithium species was treated with aldehyde **314** (eq 60). The alcohol adducts **366**, obtained in 78% yield, were then transformed into the corresponding xanthates **367**. Xanthates **367** were purified by flash chromatography on silica gel and analyzed by standard spectroscopic methods. The ^{1}H NMR spectrum of **367** displayed multiplets between δ 7.20–7.42, representing the aromatic protons of the phenyl ring. Overlapping doublets at δ 5.91 in the ^{1}H NMR of **367** were attributed to H–3, the proton on the carbon bearing the xanthate moiety.



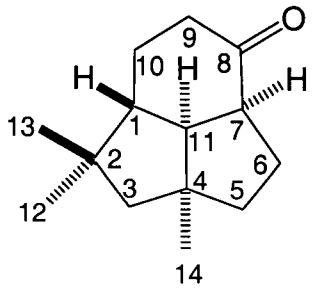
With xanthates **367** in hand, the proposed tandem cyclization reaction to generate the presilphiperfolane skeleton was further investigated. Treatment of a benzene solution of xanthates **367** with Bu_3SnH and AIBN (slow syringe addition over 18 h) provided a mixture of non-polar compounds, which were inseparable by silica gel flash chromatography (Scheme 75). On the basis of spectroscopic analysis (*vide infra*), the two

main components of this mixture were tentatively assigned structures **368**. The ^{1}H NMR spectrum of the mixture displayed two overlapping signals at δ 6.35, attributed to respective olefinic protons in **368**. The ^{13}C NMR spectrum of the mixture displayed four olefinic signals between δ 125 and 126, representing the carbons of the double bonds in **368**. The known ketone **306**, reported as 1-epi-9-norpresilphiperfolan-9-one,[20] was readily obtained from the mixture of cyclization products **368** upon subjection of the latter to an oxidative cleavage protocol developed[81] by Sharpless and coworkers. Treatment of a solution of **368** in MeCN–CCl_4–H_2O with $NaIO_4$ and $RuCl_3$ afforded ketone **306**, obtained in 40% overall yield from **367**. The assigned structure of ketone **306** was supported by comparison of its derived spectral data with those previously reported by Weyerstahl and coworkers for 1-epi-9-norpresilphiperfolan-9-one. Comparisons of the ^{1}H and ^{13}C NMR data are included in **Tables 7** and **8**, respectively.

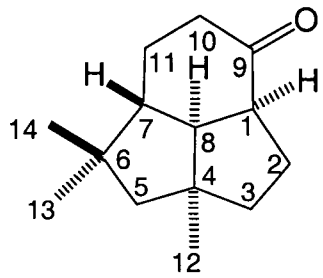


Scheme 75

Table 7. Comparison of selected (assigned) ^{1}H NMR ($CDCl_3$, 400 MHz) Data for Ketone **306** with those Reported[20] for (±)-1-Epi-9-norpresilphiperfolan-9-one (**306**).



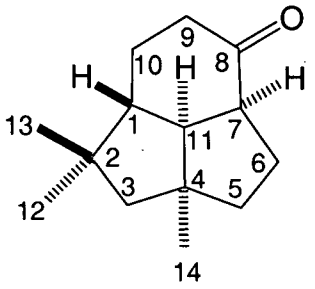
306 showing IUPAC-based numbering



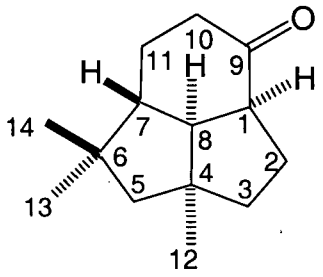
306 showing presilphiperfolane numbering

Assignment H–x (**306**)	^{1}H NMR δ ppm (Multiplicity, *J* (Hz))	Presilphiper-folane Numbering H–x	Literature ^{1}H NMR Assignments δ ppm (Multiplicity, *J* (Hz))
H–1	1.40 (ddd, 4, 12.5, 13)	H–7	1.39 (ddd, 4, 12.5, 13)
H–11	2.19 (dd, 7, 12.5)	H–8	2.18 (dd, 7,12.5)
H–12	0.88 (s) or 1.01 (s)	H–13	0.88 (s) or 1.01 (s)
H–13	0.88 (s) or 1.01 (s)	H–14	0.88 (s) or 1.01 (s)
H–14	1.07 (s)	H–12	1.07 (s)

Table 8. Comparison of the ^{13}C NMR ($CDCl_3$, 100.6 MHz) Data for Ketone **306** and those Reported[20] for (±)-1-Epi-9-norpresilphiperfolan-9-one (**306**).



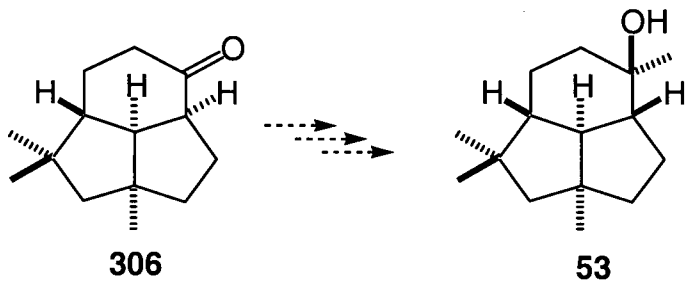
306 showing IUPAC-based numbering



306 showing presilphiperfolane numbering

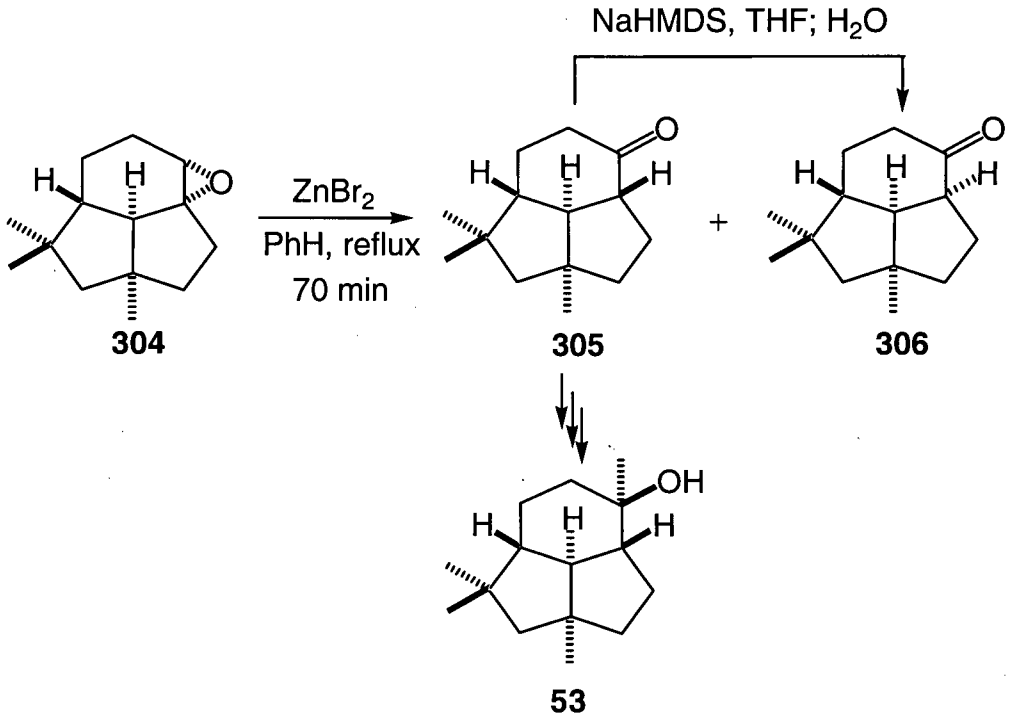
Assignment C–x (**306**)	^{13}C NMR δ ppm (Multiplicity, *J* (Hz))	Presilphiperfolane Numbering C–x (**306**)	Literature ^{13}C NMR Assignments δ ppm (Multiplicity, *J* (Hz))
C–1	50.9	C–7	50.9
C–2	40.6	C–6	40.6
C–3	58.0	C–5	58.0
C–4	47.5	C–4	47.5
C–5	41.9	C–3	41.9
C–6	28.2	C–2	28.2
C–7	52.7	C–1	52.6
C–8	216.2	C–9	216.2
C–9	38.3	C–10	38.3
C–10	21.8	C–11	21.8
C–11	59.1	C–8	59.1
C–12	22.7	C–13	22.7
C–13	28.9 or 29.0	C–14	29.0
C–14	28.9 or 29.0	C–12	29.0

The transformation of ketone **306** into the target structure (±)-presilphiperfolan-9-ol (**53**) was briefly investigated (eq 61).



306 **53** (61)

The prospect of transforming ketone **306** into its C–1 epimer **305**, an advanced intermediate in Weyerstahl and coworkers' total synthesis of presilphiperfolan-9-ol (**53**), was considered. In the study by Weyerstahl and coworkers (see Section 2.2.2 *vide supra*), ketones **305** and **306** were obtained upon treatment of a benzene solution of epoxide **304** with $ZnBr_2$ (Scheme 76). If the reaction was stopped after 40 min, ketone **305** was obtained exclusively. However, prolonged reaction times (70 min) resulted in the formation of **305** and **306** in a 3:1 ratio. The same isomers, **305** and **306,** were obtained in a 1:7 ratio upon equilibration of **305** with 0.9 equiv. of NaHMDS.



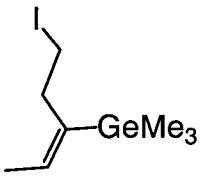
Scheme 76

Although the desired isomer **305** was less favoured under thermodynamically controlled epimerizing conditions (*vide supra*), ketone **306** was nevertheless subjected to base-mediated isomerization conditions (0.9 equiv. LDA /THF, *t*-BuOK/*t*-BuOH or NaOMe/MeOH) in hopes of obtaining a minor portion of **305**. Disappointingly, in each case, **306** was completely recovered.

On the basis of time-restraints, our proposed formal synthesis of presilphiperfolan-9-ol (**53**) *via* direct conversion of ketone **305** to ketone **306** was abandoned. Although an alternate method of preparing the target structure **53** from ketone **306** likely exists, a more concise approach to the presilphiperfolane core, displaying all the correct ring-fusion configurations, was desired. Thus, further investigation into the possibility of effectively controlling the stereoselectivity of the tandem cyclization reaction are necessary.

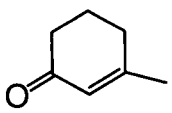
III. CONCLUSIONS

The work described in the first part of this thesis illustrates a successful application of annulation sequences developed in our laboratories to the construction of the 5-6-7 fused ring system of the cyathanes. The synthetic studies commenced with 3-methyl-2-cyclohexen-1-one (**38**), which eventually became the B-ring of the cyathane carbon skeleton (Scheme 77). An annulation sequence with bifunctional reagent alkenylstannane **39** was employed in the construction of the C-ring. In turn, the A-ring annulation was achieved with alkenylgermane **44**. As a result of the step-wise annulation strategy used in this synthesis, several advanced functionalized intermediates, which display the complete cyathane 5-6-7 fused tricyclic framework **54**, were made readily available.



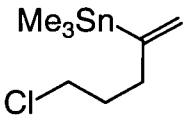
44

Ring A annulation reagent



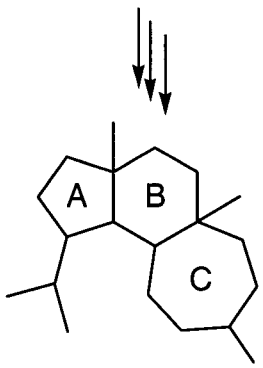
38

Ring B substrate



39

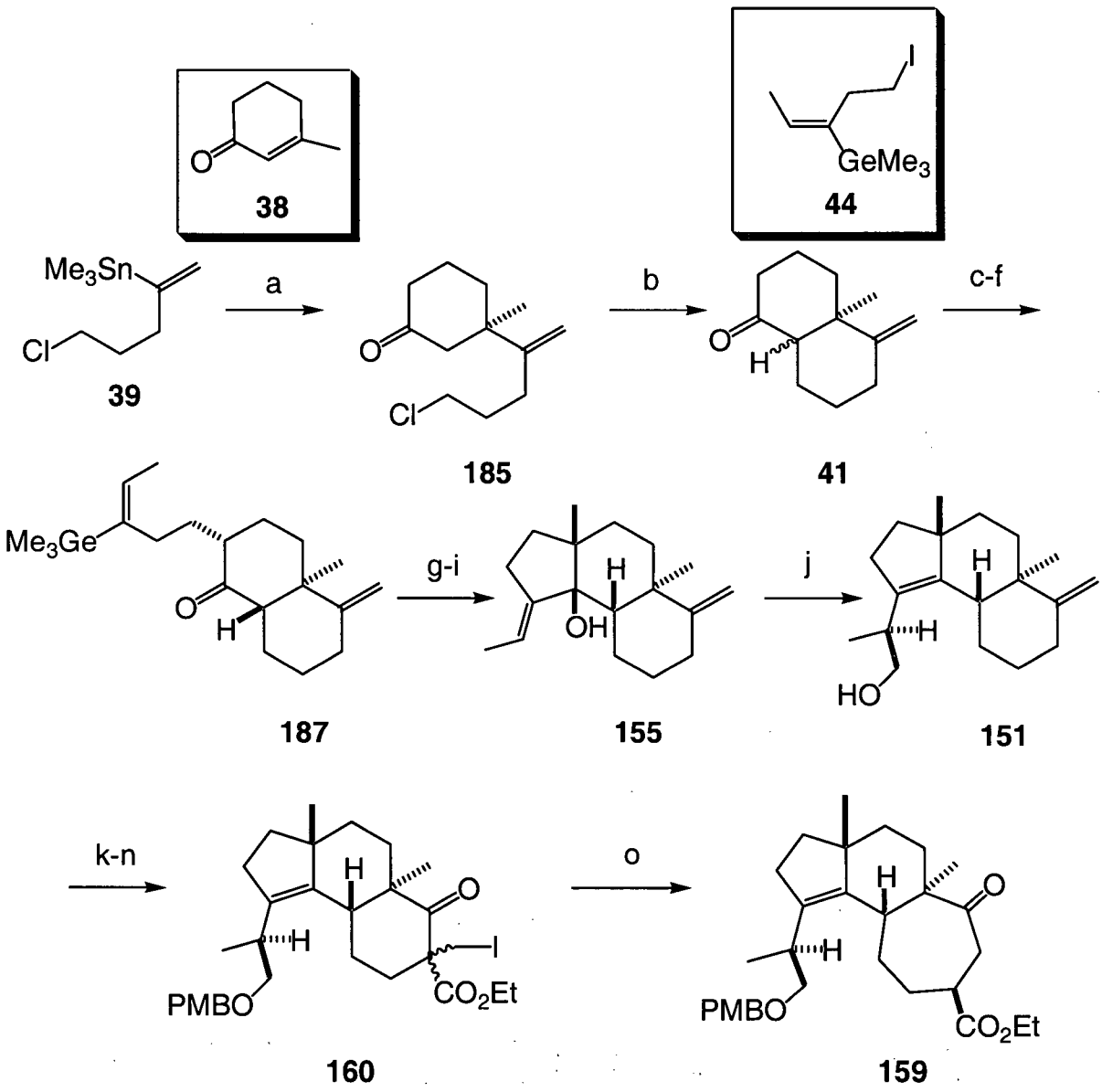
Ring C annulation reagent



54

Scheme 77

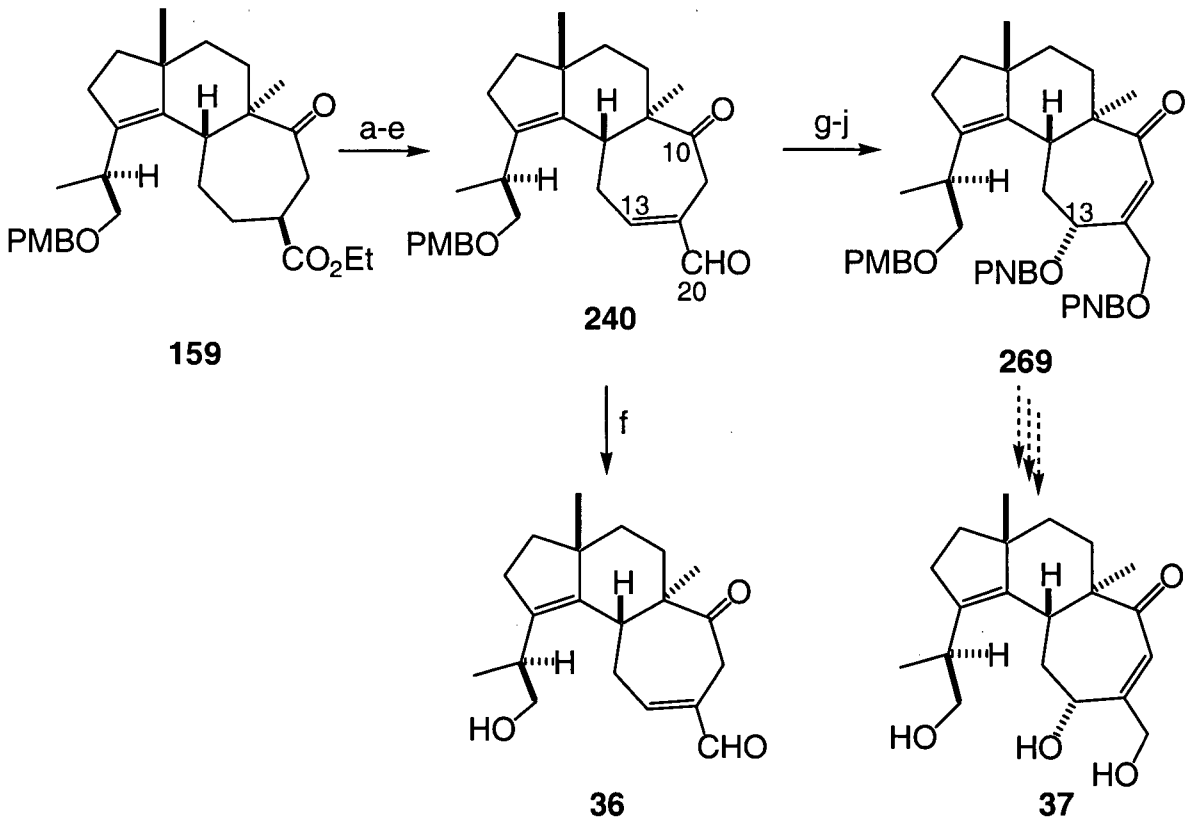
A summary of the cyathane synthetic studies, including key intermediate structures, is outlined in Schemes 78 and 79. The synthesis commenced with a copper(I)-catalyzed conjugate addition of the Grignard reagent derived from **39** to enone **38**, affording adduct **185** (Scheme 78). Base-mediated cyclization of **185** gave the known bicyclic enones **41**,[18] which represent the B-C ring system of the cyathane core. The subsequent A-ring annulation sequence employed bifunctional reagent **44** in the transformation of **41** to ketone **187**, which ultimately afforded the tricyclic alcohol **155**. Subjection of **155** to the Still-Mitra protocol yielded carbinol **151**.[69] With the A-ring and its hydroxyl isopropyl appendage in place, attention was turned to elaboration of the C-ring. Substance **151** was converted to iodides **160**, which were subjected to a SmI_2-mediated ring expansion reaction. The resulting product, keto ester **159**, displayed the complete 5-6-7 fused cyathane framework.



Reagents: a) MeLi, THF, -78 °C; $MgBr{\cdot}Et_2O$; CuBr·DMS, $BF_3{\cdot}Et_2O$, **38**; b) KH, THF, reflux; EtOH; c) Me_2NNH_2, CSA, PhH, reflux; d) KDA, DMPU, THF, -78 °C; **44**; e) AcOH, NaOAc, THF, H_2O, 75 °C; f) KOMe, MeOH, 65 °C; g) Et_2NLi, THF, -78 °C; 0 °C; MeI; h) NIS, CH_2Cl_2, 0 °C; i) BuLi, THF, -78 °C; j) KH, 18-cr-6, THF, rt; Bu_3SnCH_2I; BuLi, -78 °C; k) KH, THF, rt; PMBCl, Bu_4NI; l) OsO_4, KIO_4, *t*-BuOH, $NaHCO_3$, H_2O, rt; m) KH, NaH, $(EtO)_2CO$, THF, 65 °C; aq. HCl; n) TBAF, THF; CH_2I_2; o) SmI_2, THF, rt.

Scheme 78

Efforts to transform the advanced intermediate **159** into natural product target structures are summarized in Scheme 79. Keto aldehyde **240** was obtained from **159** in five steps. Removal of the PMB protecting group in **240** represented the final step in the first reported[94] total synthesis of (±)-sarcodonin G (**36**).[16] Synthetic studies towards a second cyathane target, (±)-cyathin A_4 (**37**),[17] afforded the advanced intermediate **269** in four steps from **240**. On the basis of limited amounts of advanced materials, the final deprotection steps involved in the conversion of **269** to the target structure, (±)-cyathin A_4 (**37**), were not completed.



Reagents: a) DIBALH, Et_2O; b) Dess-Martin periodinane, CH_2Cl_2; c) piperidine, 3Å mol. sieves, PhH, reflux; PhSeCl, THF, -78 °C; H_2O; d) KIO_4, THF, MeOH, H_2O, rt; 3) DBN, PhH, reflux; f) DDQ, CH_2Cl_2-H_2O; g) Al(*i*-PrO)$_3$, *i*-PrOH, 60 °C; h) VO(acac)$_2$, *t*-BuOOH, CH_2Cl_2, 0 °C; i) DBN, PhH, reflux; j) PPh_3, *p*-nitrobenzoic acid, DEAD, PhH.

Scheme 79

As illustrated by this concise 22-step total synthesis of (±)-sarcodonin G (**36**) from the known ketones **41**, our step-wise annulation strategy provides an efficient approach to the cyathane carbon skeleton. In addition, the specific sequence of transformations and the high stereoselectivity of the reactions allowed for excellent control of the relative configuration of all stereogenic centers. Indeed, the *anti* configuration of the 1,4 angular methyl groups, which was a problematic issue in several previously reported approaches to the cyathanes (see section 2.1.2., *vide supra*), was well established at an early point in the synthesis. The hydroxyl isopropyl side chain at C–3, which displays an *S* configuration at C–18, represents a rare structural complexity with regards to cyathane synthetic studies that had yet to be challenged. In our synthesis, the task of fashioning this side chain was successfully accomplished with complete stereoselectivity *via* a sequence of steps, culminating with a Still-Mitra rearrangement[19] reaction of the *cis*-fused cyclization product **155**. Of note, the use of a SmI_2-mediated ring-expansion reaction to prepare a 5-6-7 tricycle from a 5-6-6 tricycle, was the first reported application of this free-radical reaction, developed by Hasegawa and coworkers,[89] in natural product synthesis.

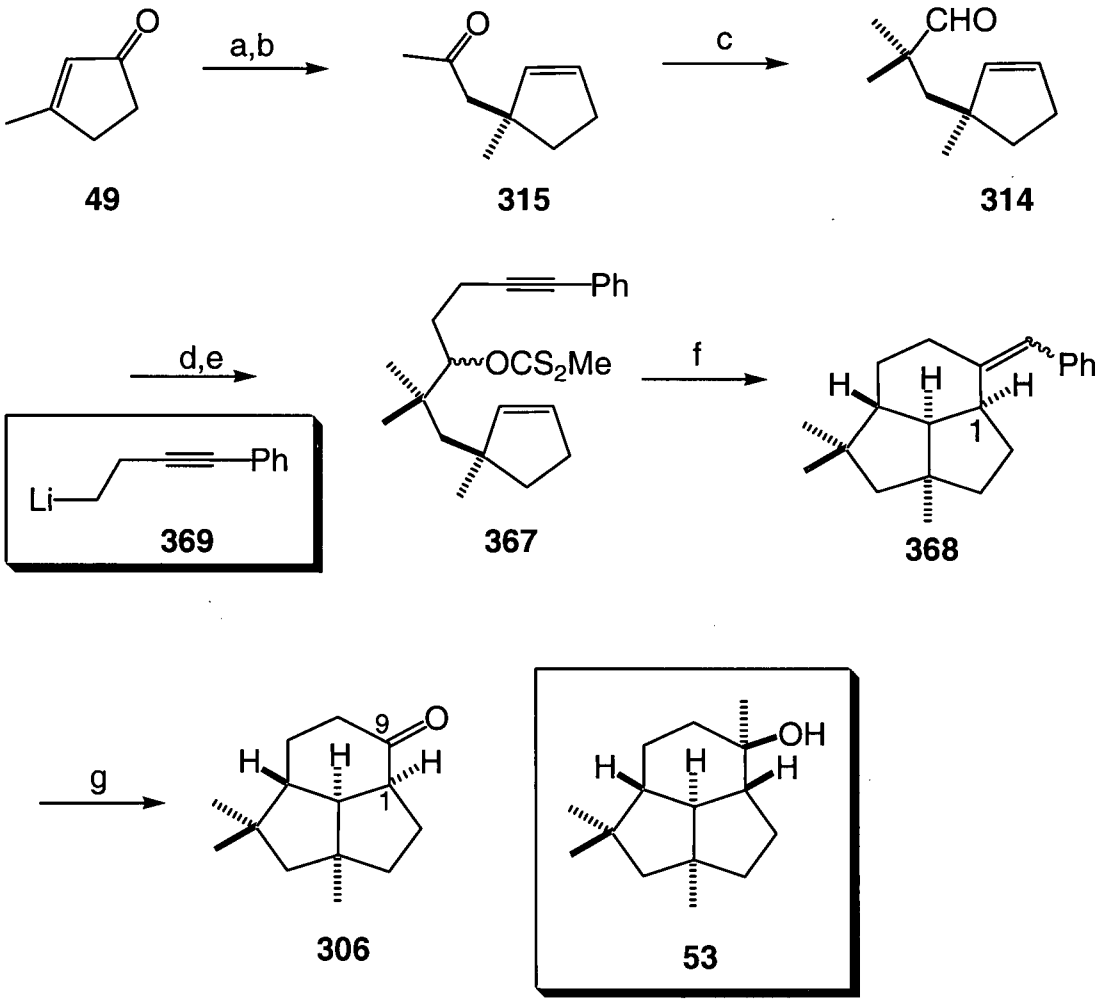
The difficulties encountered in our attempt to prepare (±)-cyathin A_4 (**37**) from advanced intermediate **240** illustrate the synthetic complexity associated with elaboration of highly functionalized ring-systems. While the selective reduction of the aldehyde function at C–20 over the ketone function at C–10 in **240** was eventually accomplished, the subsequent introduction of an α-face hydroxyl moiety at C–13 represented a serious challenge. In our studies, an intermediate with a β-face hydroxyl moiety at C–13 was obtained and, following a Mitsunobu-type inversion protocol, this substance was

transformed into compound **269**, which displays the desired configuration at C–13. Although **269** should provide access to the target structure, ±-**37** upon removal of the PMB and PNB moieties, further investigations into a more direct method of introducing the α-face C–13 hydroxyl moiety are warranted.

In the second part of this thesis, a tandem radical cyclization was proposed for the assembly of 5-5-6 fused carbocycles. The synthetic study commenced with the commercially available 3-methyl-2-cyclopenten-1-one (**49**), which was converted to ketone **315** in several steps, including a Carroll [3,3] rearrangement reaction (Scheme 80). Subsequent transformation of ketone **315** into aldehyde **314** proved straightforward. A Negishi-type reaction of lithio species **369** with aldehyde **314** afforded a mixture of alcohols, which was converted into the corresponding mixture of xanthates **367**. Bu_3SnH-mediated tandem cyclization of xanthates **367** yielded a mixture of alkenes **368**, which display the 5-5-6 fused tricyclic ring system of the presilphiperfolane framework. Subjection of **368** to oxidative cleavage conditions afforded the known[20] ketone (±)-1-epi-9-norpresilphiperfolan-9-one (**306**).

A formal synthesis of the target structure, (±)-presilphiperfolan-9-ol (**53**), from cyclization products **368** *via* ketone **306** was not realized. To obtain **53**, the unnatural configuration at C-1, exhibited in **368** and **306,** needed to be corrected. Although a substance with the desired relative configuration at C-1 might eventually be obtained in several steps from **306**, an alternate strategy that would reverse the undesired stereoselectivity in the second of the tandem cyclizations, which afforded **368**, would be ideal. The inherently difficult nature of either of these tasks represents a drawback of our tandem reaction strategy to presilphiperfolane natural product synthesis. Nevertheless, in

the course of this synthetic study, a concise approach to 5-5-6 fused tricyclic ring systems was developed, illustrating the power of tandem free radical cyclizations in carbocycle construction.



Reagents: a) $NaBH_4$, $CeCl_3$, MeOH; b) diketene, DMAP, Et_2O, -20 °C; LDA, -78 °C to rt; CCl_4, reflux; c) $Ph_3P(OMe)CHLi$; THF; 0 °C to rt; TFA, H_2O-$CHCl_3$, reflux; d) **369**, Et_2O, -78 °C; e) NaH, imidazole, CS_2, THF, reflux; MeI, rt; f) AIBN, Bu_3SnH, PhH, reflux; g) $RuCl_3$, $NaIO_4$, MeCN-CCl_4-H_2O.

Scheme 80

IV. EXPERIMENTAL

4.1. General

4.1.1. Data Acquisition and Presentation

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker models WH-400 (400 MHz), AM-400 (400 MHz), AV-300 (300 MHz), AV-400 (400 MHz) or AMX-500 (500 MHz) spectrometers using deuteriochloroform ($CDCl_3$) as a solvent. Signal positions (δ) are given in parts per million (ppm) from tetramethylsilane and were measured relative to that of chloroform ($CHCl_3$) (δ 7.24 ppm). The multiplicity, number of protons and coupling constants are indicated in parentheses following the chemical shift. In some cases, when mixtures of compounds are present, ratios of integration are given. The abbreviations used in describing multiplicity are: s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, br-broad. Coupling constants (*J* values) are given in Hertz (Hz).

Carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained on Bruker models AV-300 (75.5 Hz), AM-400 (100.6 MHz), AV-400 (100.6 MHz), and AMX-500 (125.8 MHz) spectrometers or a Varian model XL-300 (75.5 MHz) spectrometer using $CDCl_3$ as the solvent. Signal positions (δ) are given in parts per million (ppm) from tetramethylsilane and were measured relative to the signal of $CDCl_3$ (δ 77.0 ppm). In some cases, the proton and carbon assignments were supported by two-dimensional (^{1}H, ^{13}C)-heteronuclear multiple quantum coherence experiments (HMQC) which were carried out on the Bruker AV-400 and AMX-500 spectrometers.

Infrared (IR) spectra were recorded on a Perkin-Elmer model 1710 Fourier transform spectrophotometer with internal calibration on liquid films (sodium chloride plates) or solid pellets (infrared grade potassium bromide). Only selected characteristic absorptions are listed for each compound.

Low and high resolution mass spectra were recorded on a Kratos Concept II HQ or on a Kratos MS 80 mass spectrometer by the UBC MS laboratory. High resolution mass spectra were measured using electron impact ionization (EI) or desorption chemical ionization (DCI) using CH_4 or NH_3. (M^+) and $(M–Me)^+$ ions were detected and analyzed by EI. $(M+NH_4)^+$, $(M+H)^+$ and (M^+) ions were detected and analyzed by DCI. Unless otherwise noted, the molecular ion (M^+) masses are given.

Elemental analysis were performed on a Carlo Erba CHN model 1106 or on a Fisons EA model 1108 elemental analyzer by the Microanalytical Laboratory at UBC.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon using glassware that had been oven-dried (~140 °C) and/or flame dried. Glass syringes, stainless steel needles and Teflon® cannulae used to handle anhydrous solvents and reagents were oven-dried (~140 °C), cooled in a dessicator and flushed with argon prior to use. Plastic syringes were flushed with argon prior to use. Microsyringes were stored in a dessicator and were flushed with argon prior to use.

Cold temperatures were maintained using the following baths: 0 °C, ice–water; –10 °C and –20 °C, aqueous calcium chloride–dry ice (17 g, 27 g of $CaCl_2$/100 mL of H_2O respectively); –78 °C, acetone–dry ice; –98 °C, methanol–dry ice.

Thin layer chromatography (TLC) was performed using commercial aluminum backed silica gel 60 F 254 plates (E. Merck, type 5554, thickness 0.2 mm). Visualization of the chromatograms was accomplished using ultraviolet light (254 nm) followed by heating of the TLC plate after staining with one of the following solutions: (a) vanillin in a sulfuric acid–ethanol mixture (6% vanillin w/v, 4% sulfuric acid v/v, 10% water v/v in EtOH), (b) phosphomolybdic acid in ethanol (20% phosphomolybdic acid w/v, Aldrich), (c) anisaldehyde in a sulfuric acid–ethanol mixture (5% anisaldehyde v/v and 5% sulfuric acid v/v in EtOH). Flash column chromatography was performed using 230–400 mesh silica gel (E, Merck, Silica Gel 60 or Silicycle, Silica Gel).

Gas liquid chromatography (GLC) was performed on Hewlett-Packard models 5880A or 5890 capillary gas chromatographs, both equipped with flame ionization detectors and fused silica columns. The former instrument contained a 25 m × 0.21 mm column, while the latter chromatograph utilized a 25 m × 0.20 mm column. Both were coated with HP-5 (crosslinked 5% phenylmethyl silicone).

4.1.2. Solvents and Reagents

All solvents and reagents were purified, dried and/or distilled using standard procedures. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone, while benzene (C_6H_6) and dichloromethane (CH_2Cl_2) were distilled from calcium hydride, all under an atmosphere of dry argon. Magnesium was added to methanol and, after the mixture had been refluxed, the methanol was distilled from the resulting solution of magnesium methoxide. Solvents were distilled immediately prior to use.

Diisopropylamine, diethylamine, triethylamine, hexamethylphosphoramide (HMPA) and dimethyltetrahydropyrimidinone (DMPU) were distilled from calcium hydride. The reagents were stored in Sure Seal™ (Aldrich Chemical Co. Inc.) bottles over 3Å molecular sieves under an atmosphere of argon.

Before use, methyl iodide and deuteriochloroform ($CDCl_3$) were passed through a short column of basic alumina activity I, which had been over-dried (~140 °C), and then cooled in a dessicator prior to use.

Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 35–60 °C.

Solutions of diisobutylaluminum hydride (DIBALH) in hexanes and *t*-butyllithium (*t*-BuLi) in pentane were purchased from Aldrich Chemical Co. Inc. Solutions of methyllithium (MeLi) in diethyl ether and *n*-butyllithium (*n*-BuLi) in hexanes were obtained from Aldrich Chemical Co. Inc. and Acros, and were standardized using diphenylacetic acid as a primary standard using the procedure of Kofron and Baclawski.[144]

Potassium hydride (KH) was obtained as a 35% suspension in mineral oil and sodium hydride (NaH) as a 60% dispersion in mineral oil from Aldrich Chemical Co. Inc., and were rinsed free of oil with solvent under a stream of argon prior to use.

Iodine was sublimed and was stored no longer than three months.

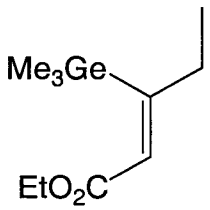
Aqueous ammonium chloride–ammonia (NH_4Cl–NH_3) (pH 8) was prepared by the addition of ~50 mL of concentrated aqueous ammonia (28–30%) to 950 mL of a saturated aqueous ammonium chloride (NH_4Cl) solution.

Lithium diisopropylamide (LDA) was prepared by the addition of a solution of *n*-butyllithium in hexanes to a solution of diisopropylamine (1.1 equiv.) in dry tetrahydrofuran at –78 °C. The resulting solution was warmed to 0 °C, stirred for 15 min, and cooled back to –78 °C prior to use.

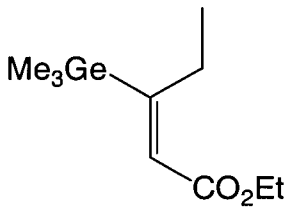
Argon was dried by bubbling it through concentrated sulfuric acid (H_2SO_4) and then passing it through a drying tube packed with potassium hydroxide (KOH) and Drierite®.

4.2. Total Synthesis of the Cyathane Diterpenoid (±)-Sarcodonin G

Preparation of Ethyl (Z)-3-Trimethylgermyl-2-pentenoate (165)



165



174

To stirred cold (–10 °C) dry THF (50 mL) was added cold (0 °C) Me_3GeH (14.1 g, 0.119 mol) *via* a cannula. A solution of *t*-BuLi (1.7 M in pentane, 87.5 mL, 0.149 mol) was added *via* a syringe over 5 min. The resulting yellow solution was stirred at –10 °C for 5 min to afford a colourless solution. A solution of MeLi (1.4 M in Et_2O, 106.0 mL, 0.149 mol) was added and the resulting mixture was transferred *via* a cannula to a cold (–78 °C) stirred suspension of CuCN (13.3 g, 0.149 mol) in dry THF (20 mL). The resulting suspension was stirred a –78 °C for 1 h to afford a colourless solution. A solution of ethyl 2-pentynoate (10.0 g, 0.079 mol) in THF (5 mL) was added *via* a cannula and the reaction mixture was stirred at –78 °C for 45 min. AcOH (12.4 g, 0.206 mol) was added *via* a syringe. The resulting heterogeneous mixture was stirred for 5 min and then poured into stirred aqueous NH_4Cl–NH_3 (pH 8, 500 mL). Et_2O (500 mL) was added and the mixture was opened to the atmosphere and then stirred vigorously until the aqueous layer was deep blue. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic extracts were washed with H_2O (2 × 200 mL) and

brine (2 × 200 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude oil was subjected to flash chromatography (600 g of silica gel, 40:1 petroleum ether–Et_2O) to afford two fractions, which were concentrated under reduced pressure. The first fraction to be eluted afforded 13.7 g (71%) of ethyl (*Z*)-3-trimethylgermyl-2-pentenoate (**165**) as a colourless oil. The second fraction afforded 3.91 g (20%) of ethyl (*E*)-3-trimethylgermyl-2-pentenoate (**174**) as a colourless oil.

Ethyl (*Z*)-3-trimethylgermyl-2-pentenoate (**165**) exhibited the following spectral data:

IR (neat): 2968, 1718, 1607 cm^{-1}.

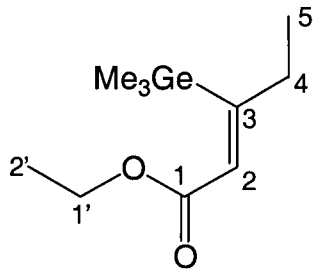
^1H NMR ($CDCl_3$, 400 MHz) δ: 0.29 (s, 9H), 0.99 (t, 3H, J = 7.3 Hz), 1.24 (t, 3H, J = 7.0 Hz), 2.30 (q, 2H, J = 7.3 Hz), 4.12 (q, 2H, J = 7.0 Hz), 6.21 (s, 1H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: –0.4, 13.5, 14.2, 31.9, 59.9, 126.6, 166.8, 171.4.

Exact mass calcd for $C_{10}H_{21}O_2{}^{74}Ge$ $(M+H)^+$: 247.0753. Found: 247.0762.

Anal. calcd for $C_{10}H_{20}O_2Ge$: C 49.05, H 8.23. Found: C 48.84, H 8.10.

Table 9. ^{1}H NMR ($CDCl_3$, 400 MHz) Data for Ethyl (*Z*)-3-Trimethylgermyl-2-pentenoate (**165**): NOED Experiment.

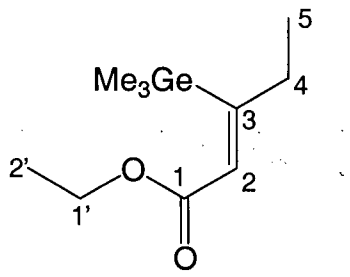


165

Assignments H–x	^{1}H NMR δ ppm (Multiplicity, *J* (Hz))	Observed NOEs
H–2[a]	6.21 (s)	H–4, H–5
H–4[a]	2.30 (q, 7.3)	H–5, H–2, –$GeMe_3$
H–5	0.99 (t, 7.3)	
H–1'[a]	4.12 (q, 7.0)	H–2'
H–2'	1.24 (t, 7.0)	
–$GeMe_3$[a]	0.29 (s)	H–4

[a] Irradiation of this signal generated the corresponding NOEs in the right hand column

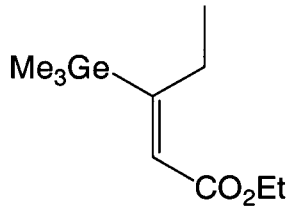
Table 10. ^{13}C NMR ($CDCl_3$, 100.6 MHz) and ^{1}H NMR ($CDCl_3$, 400 MHz) Data for Ethyl (*Z*)-3-Trimethylgermyl-2-pentenoate (**165**): HMQC Experiment.



165

Assignments C–x	^{13}C NMR δ ppm	APT	HMQC ^{1}H NMR Correlations (δ ppm)
C–1	166.8 or 171.4	**C** or CH_2	
C–2	126.6	**CH** or CH_3	H–2 (6.21)
C–3	166.8 or 171.4	**C** or CH_2	
C–4	31.9	C or **CH_2**	H–4 (2.30)
C–5	13.5	CH or **CH_3**	H–5 (0.99)
C–1'	59.9	C or **CH_2**	H–1' (4.12)
C–2'	14.2	CH or **CH_3**	H–2' (1.24)
–$GeMe_3$	–0.4	CH or **CH_3**	–$GeMe_3$ (0.29)

Ethyl (*E*)-3-trimethylgermyl-2-pentenoate (**174**) exhibited the following spectral data:



174

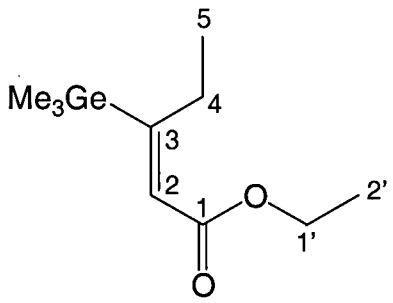
IR (neat): 2975, 1718, 1608 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ: 0.23 (s, 9H), 1.00 (t, 3H, J = 7.5 Hz), 1.24 (t, 3H, J = 7.2 Hz), 2.73 (q, 2H, J = 7.5 Hz), 4.11 (q, 2H, J = 7.2 Hz), 5.89 (s, 1H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: –2.1, 13.8, 14.2, 25.4, 59.5, 124.5, 164.9, 171.3.

Exact mass calcd for $C_{10}H_{21}O_2{}^{74}Ge$ $(M+H)^+$: 247.0753. Found: 247.0758.

Table 11. ^{1}H NMR ($CDCl_3$, 400 MHz) Data for Ethyl (*E*)-3-Trimethylgermyl-2-pentenoate (**174**): NOED Experiment.

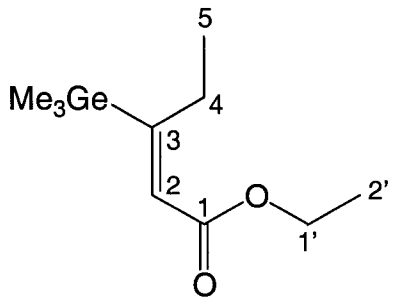


174

Assignments H–x	^{1}H NMR δ ppm (Multiplicity, *J* (Hz))	Observed NOEs
H–2[a]	5.89 (s)	–$GeMe_3$
H–4[a]	2.73 (q, 7.5)	H–5, –$GeMe_3$
H–5	1.00 (t, 7.5)	
H–1'[a]	4.11 (q, 7.2)	H–2'
H–2'	1.24 (t, 7.2)	
–$GeMe_3$[a]	0.23 (s)	H–2, H–4, H–5

[a] Irradiation of this signal generated the corresponding NOEs in the right hand column

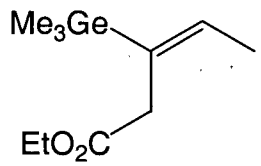
Table 12. ^{13}C NMR ($CDCl_3$, 100.6 MHz) and ^{1}H NMR ($CDCl_3$, 400 MHz) Data for Ethyl (*Z*)-3-Trimethylgermyl-2-pentenoate (**174**): HMQC Experiment.



174

Assignments C–x	^{13}C NMR δ ppm	APT	HMQC ^{1}H NMR Correlations (δ ppm)
C–1	164.9 or 171.3	**C** or CH_2	
C–2	124.5	**CH** or CH_3	H–2 (5.89)
C–3	164.9 or 171.3	**C** or CH_2	
C–4	25.4	C or **CH_2**	H–4 (2.73)
C–5	13.8	CH or **CH_3**	H–5 (1.00)
C–1'	59.5	C or **CH_2**	H–1' (4.11)
C–2'	14.2	CH or **CH_3**	H–2' (1.24)
–$GeMe_3$	–2.1	CH or **CH_3**	–$GeMe_3$ (0.23)

Preparation of Ethyl (*E*)-3-Trimethylgermyl-3-pentenoate (164)



164

To a cold (–78 °C), stirred solution of LDA (130 mmol) in dry THF (500 mL) was added HMPA (23.3 g, 130 mmol). The mixture was stirred for 30 min and a solution of ethyl (*Z*)-3-trimethylgermyl-2-pentenoate (**165**) (13.0 g, 53.1 mmol) in dry THF (50 mL) was added *via* a cannula. The resulting mixture was stirred for 30 min at –78 °C, warmed to 0 °C for 1 h and then recooled to –78 °C for 15 min. The mixture was transferred, *via* a cannula, to a cold (–98 °C) stirred solution of acetic acid (31.9 g, 0.531 mol) in dry Et_2O (500 mL). The mixture was allowed to warm to room temperature and saturated aqueous $NaHCO_3$ (500 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 500 mL). The combined organic extracts were washed with brine (300 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the resulting material was purified by flash chromatography (500 g of silica gel, 20:1 petroleum ether–Et_2O) to yield 11.8 g (91%) of ethyl (*E*)-3-trimethylgermyl-3-pentenoate (**164**) as a colourless oil.

IR (neat): 2976, 1737, 1626 cm^{-1}.

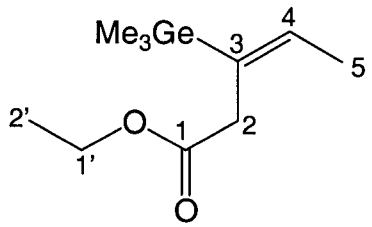
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (s, 9H), 1.21 (t, 3H, J = 7.2 Hz), 1.69 (d, 3H, J = 6.7 Hz), 3.16 (s, 2H), 4.07 (q, 2H, J = 7.2 Hz), 5.87 (q, 1H, J = 6.7 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: –2.0, 14.1, 14.4, 35.3, 60.4, 135.5, 135.7, 171.8.

Exact mass calcd for $C_{10}H_{21}O_2{}^{74}Ge$ $(M+H)^+$: 247.0753. Found: 247.0764.

Anal. calcd for $C_{10}H_{20}O_2GeI$: C 49.05, H 8.23. Found: C 49.15, H 8.23.

Table 13. ^{1}H NMR ($CDCl_3$, 400 MHz) Data for Ethyl (*E*)-3-Trimethylgermyl-3-pentenoate (**164**): NOED Experiment.

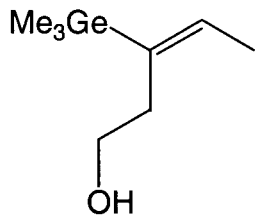


164

Assignments H–x	^{1}H NMR δ ppm (Multiplicity, J (Hz))	Observed NOEs
H–2[a]	3.16 (s)	H–5, –$GeMe_3$
H–4[a]	5.87 (q, 6.7)	H–5, –$GeMe_3$
H–5[a]	1.69 (d, 6.7)	H–2, H–4
H–1'	4.07 (q, 7.2)	
H–2'	1.21 (t, 7.2)	
–$GeMe_3$[a]	1.15 (s)	H–2, H–4

[a] Irradiation of this signal generated the corresponding NOEs in the right hand column

Preparation of (*E*)-3-Trimethylgermyl-3-penten-1-ol (163)



163

To a cold (–78 °C), stirred solution of ethyl (*E*)-3-trimethylgermyl-3-pentenoate (**164**) (8.0 g, 32.7 mmol) in dry Et_2O (300 mL) was added a solution of DIBALH (1.0 M in hexanes, 82.5 mL, 82.5 mmol). The resulting mixture was stirred at –78 °C for 1 h, warmed to 0 °C and then stirred for an additional h. Aqueous NH_4Cl–NH_3 (pH 8, 8 mL) was added, and the resulting white slurry was warmed to room temperature and was then stirred for 1 h. Solid anhydrous $MgSO_4$ (2.0 g) was added and the mixture was stirred for 1 h. The slurry was filtered through a column of Florisil® (50 g) and the column was washed with Et_2O (3 × 200 mL). The solvent of the combined eluates was removed under reduced pressure and the resulting material was purified by flash chromatography (400 g of silica gel, 8:1 pentane–Et_2O) to give 5.85 g (88%) of (*E*)-trimethylgermyl-3-penten-1-ol (**163**) as a colourless oil.

IR (neat): 3331, 1622, 1235, 1043, 824, 754, 597, 570 cm^{-1}.

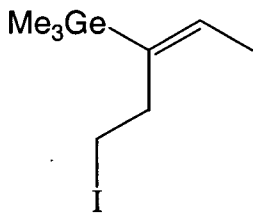
^1H NMR ($CDCl_3$, 400 MHz) δ: 0.17 (s, 9H), 1.28 (t, 1H, J = 6.0 Hz), 1.72 (d, 3H, J = 6.6 Hz), 2.51 (t, 2H, J = 7.0 Hz), 3.58 (td, 2H, J = 7.0, 6.0 Hz), 5.88 (q, 1H, J = 6.6 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: –1.7, 14.4, 33.4, 61.7, 135.1, 138.9.

Exact mass calcd for $C_7H_{15}{}^{74}GeO$ (M^+–Me): 189.0335. Found: 189.0336.

Anal. calcd for $C_8H_{18}GeO$: C 47.38, H 8.95. Found: C 47.57, H 9.12.

Preparation of (*E*)-5-Iodo-3-trimethylgermyl-2-pentene (44)



44

I_2 (6.20 g, 24.4 mmol) was added to a solution of Ph_3P (6.41 g, 24.4 mmol) in dry CH_2Cl_2 (200 mL) and the mixture was stirred for 20 min. (*E*)-3-Trimethylgermyl-3-penten-1-ol (**163**) (4.13 g, 20.4 mmol) and dry Et_3N (3.4 mL, 24 mmol) were added as a solution in dry CH_2Cl_2 (20 mL) and the resulting mixture was stirred for 18 h. Most of the solvent was removed under reduced pressure and the residual material was diluted with pentane (100 mL). The mixture was filtered through a sintered glass funnel (8 cm diameter) containing Florisil® (10 cm deep) on top of a thin layer of Celite®. The column was flushed with pentane (600 mL). The solvent of the combined eluates was removed under

reduced pressure. The residual material was purified by distillation (48–54 °C / 0.3 Torr) to give 6.02 g (95%) of (*E*)-5-iodo-3-trimethylgermyl-2-pentene (**44**) as a colourless oil. IR (neat): 1619, 1236, 1168, 823, 756, 597, 567 cm^{-1}.

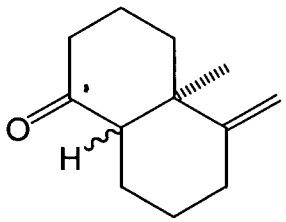
^1H NMR ($CDCl_3$, 400 MHz) δ: 0.18 (s, 9H), 1.67 (d, 3H, J = 6.7 Hz), 2.78 (t, 2H, J = 8.5 Hz), 3.02 (t, 2H, J = 8.5 Hz), 5.82 (q, 1H, J = 6.7 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: –1.8, 3.9, 14.4, 35.2, 134.5, 142.2.

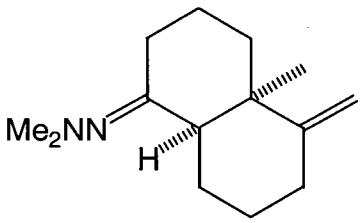
Exact mass calcd for $C_7H_{14}{}^{74}GeI$ (M^+–Me): 298.9352. Found: 298.9359.

Anal. calcd for $C_8H_{17}GeI$: C 30.73, H 5.48. Found: C 30.86, H 5.74.

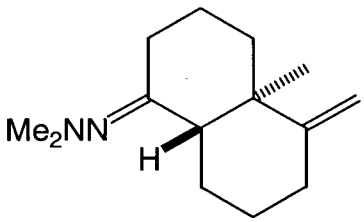
Preparation of (1*S,6*R**)-6-Methyl-7-methylidenebicyclo[4.4.0]decan-2-one Dimethylhydrazone (152)**



41



186



152

1,1-Dimethylhydrazine (7.50 g, 123 mmol) was added to a stirred solution of the bicyclic ketone **41**[18] (3.5:1 mixture of the *trans*- and *cis*-fused isomers, 10.9 g, 61.6 mmol) in dry benzene (300 mL). A catalytic amount of 10-camphorsulfonic acid (1.1 g, 4.7 mmol) was added and the mixture was refluxed for 72 h employing a Dean-Stark trap. The excess 1,1-dimethylhydrazine and most of the solvent were removed by distillation under Ar (90 °C). The remaining material was diluted with Et_2O (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) was added. The resulting layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (600 g of silica gel, 5:1 pentane–Et_2O) to yield 5.82 g (42.9%) of the *trans*-fused bicyclic hydrazone **152** and 5.32 g (39.2%) of the *cis*-fused bicyclic hydrazone **186** as colourless oils.

Isomerization of (1*R,6*R**)-6-Methyl-7-methylidenebicyclo[4.4.0]decan-2-one Dimethylhydrazone (186)**

1,1-Dimethylhydrazine (3.0 g, 50 mmol) was added to a stirred solution of the *cis*-fused bicyclic hydrazone **186** (5.32 g, 24.1 mmol) in dry benzene (100 mL). A catalytic amount of 10-camphorsulfonic acid (50 mg, 0.2 mmol) was added and the mixture was refluxed for 48 h employing a Dean-Stark trap. The excess 1,1-dimethylhydrazine and most of the solvent were removed by distillation under Ar (90 °C). The remaining material was diluted with Et_2O (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) was added. The resulting layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (300 g of silica gel, 5:1 pentane–Et_2O) to yield 2.55 g (48.3%) of the *trans*-fused bicyclic hydrazone **152** and 2.45 g (46.3%) of the *cis*-fused hydrazone **186**. The *cis*-fused bicyclic hydrazone **186** was recycled twice though the epimerization step to yield a total of 9.61 g (71%) of the *trans*-fused bicyclic hydrazone **152** from 10.9 g of the mixture of ketones **41** (*vide supra*).

The *trans*-fused bicyclic hydrazone **152** exhibited the following spectral data:

IR (neat): 1638, 1446, 1373, 1022, 965, 894 cm^{-1}.

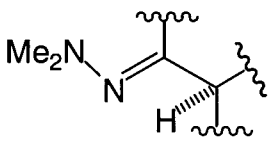
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88 (s, 3H), 1.22–1.26 (m, 1H), 1.54–1.79 (m, 6H), 1.79–1.89 (m, 2H), 1.95 (dd, 1H, J = 11.7, 3.7 Hz), 2.09–2.16 (m, 1H), 2.25–2.35 (m, 1H), 2.4 (s, 6H), 3.26–3.32 (m, 1H), 4.63–4.68 (m, 2H).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 18.1, 22.1, 23.1, 27.4, 28.5, 32.6, 36.5, 43.1, 47.8, 52.5 (two signals superimposed), 105.3, 157.1, 169.5.

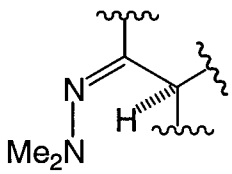
Exact mass calcd for $C_{14}H_{24}N_2$: 220.1940. Found: 220.1940.

Anal. calcd for $C_{14}H_{24}N_2$: C 76.31, H 10.98, N 12.71. Found: C 76.16, H 10.86, N 12.72.

The *cis*-fused bicyclic hydrazone **186** exists as a mixture of isomers with respect to the configuration of the imine double bond.



major



minor

The mixture of *cis*-fused bicyclic hydrazone **186** isomers exhibited the following spectral data:

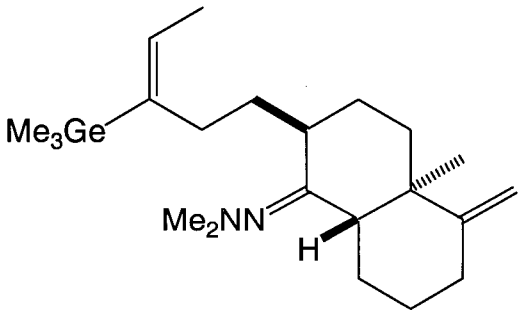
IR (neat): 1635, 1446, 1374, 1021, 967, 892 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.06 (minor) and 1.08 (major) (s, s, 3H total), 1.2–2.5 (m, 12H), 2.36 (minor) and 2.41 (major) (s, s, 6H total), 3.07–3.17 (major) and 3.19–3.26 (minor) (m, m, 1H total), 4.66–4.73 (m, 2H).

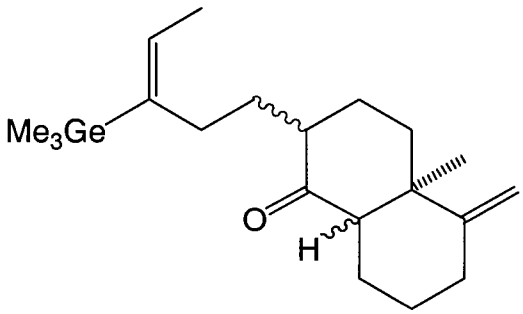
^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 21.6, 22.7, 23.4, 23.7, 27.2, 27.3, 27.4, 28.7, 31.1, 31.5, 31.7, 32.8, 40.7, 41.0, 45.5, 47.4, 47.7 (two signals superimposed), 52.8 (two signals superimposed), 107.2, 155.1, 155.4, 172.0, 174.4 (three signals are not accounted for).

Exact mass calcd for $C_{14}H_{24}N_2$: 220.1940. Found: 220.1935.

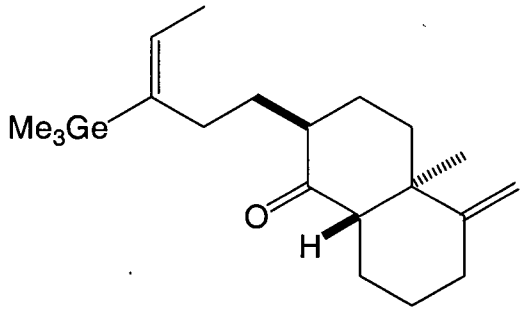
Preparation of (1*S,3*R**,6*R**)-6-Methyl-7-methylidene-3-[(3*E*)-3-trimethylgermyl-3-pentenyl]bicyclo[4.4.0]decan-2-one (188)**



153



189



188

To a stirred solution of *t*-BuOK (5.00 g, 44.6 mmol) in dry THF (150 mL) was added dry *i*-Pr_2NH (4.52 g, 44.6 mmol). The mixture was cooled to –78 °C. A solution of BuLi (1.6 M in hexanes, 27.9 mL, 44.6 mmol) was added and the mixture was stirred for 30 min. The *trans*-fused hydrazone **152** (4.93 g, 22.3 mmol) was added as a solution in dry THF (10 mL) and the mixture was stirred at –78 °C for 1 h. Dry DMPU (5.72 g, 44.6 mmol) and a solution of freshly distilled (*E*)-5-iodo-3-trimethylgermyl-2-pentene (**44**) (10.5 g, 33.5 mmol) in dry THF (10 mL) were sequentially added and the mixture was stirred at –78 °C for 1.5 h. Aqueous NH_4Cl–NH_3 (pH 8, 200 mL) was added and the mixture was allowed to warm to room temperature. Et_2O (200 mL) was added and the

resulting layers were separated. The aqueous layer was extracted with Et_2O (3 × 200 mL), and the combined organic layers were washed with brine (200 mL). The solvent was removed under reduced pressure and the resulting crude hydrazone **153** was taken up in THF (30 mL). H_2O (7 mL) and solid NaOAc∃3H_2O (13.8 g, 0.101 mol) were added and the mixture was stirred for 5 min. AcOH (43.0 g, 0.716 mol) was added and the mixture was heated to 75 °C for 18 h. The mixture was cooled to room temperature and saturated aqueous $NaHCO_3$ (60 mL) was added. Solid $NaHCO_3$ was added until the solution was alkaline to litmus paper. Et_2O (150 mL) was added to the mixture and the resulting layers were separated. The aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine (150 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the resulting material was purified by flash chromatography (600 g of silica gel, 40:1 pentane–Et_2O) to afford 5.60 g (69.0%) of a mixture of ketones **189,** of which ketone **188** was the major isomer.

For characterization, pure ketone **188** was obtained by flash chromatography (50:1 pentane–Et_2O) of a small amount of the mixture of ketones **189**.

Ketone **188** exhibited the following spectral data:

IR (neat): 1709, 1639, 1628, 1448, 1376, 1234, 952 cm^{-1}.

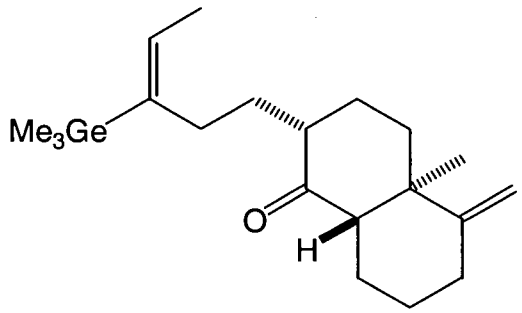
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.13 (s, 9H), 0.91 (s, 3H), 1.18–1.30 (m, 1H), 1.43–1.56 (m, 1H), 1.56–1.69 (m, includes 3-proton doublet at δ 1.62, J = 6.6 Hz, 7H total), 1.82–1.89 (m, 2H), 1.91–2.00 m, 1H), 2.01–2.08 (m, 2H), 2.10–2.40 (m, 5H), 4.65–4.72 (m, 2H), 5.67 (q, 1H, J = 6.6 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: –1.7, 13.9, 18.8, 20.9, 26.6 (two signals superimposed), 28.2, 31.4, 32.0, 32.2, 44.9, 50.0, 54.1, 105.8, 132.2, 142.4, 155.7, 215.3.

Exact mass calcd for $C_{20}H_{34}{}^{74}GeO$: 364.1822. Found: 364.1818.

Anal. calcd for $C_{20}H_{34}GeO$: C 66.16, H 9.44. Found C 66.35, H 9.55.

Preparation of (1*S,3*S**,*6R**)-6-Methyl-7-methylidene-3-[(3*E*)-3-trimethylgermyl-3-pentenyl]bicyclo[4.4.0]decan-2-one (187)**



187

To a stirred solution of NaOMe (7.83 g, 145 mmol) in dry MeOH (300 mL) was added a solution of the mixture of ketones **189** (17.4 g, 48.0 mmol) in dry MeOH (100 mL). The mixture was heated to 65 °C for 3 h and then cooled to room temperature. H_2O (300 mL) and Et_2O (500 mL) were added, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 300 mL). The combined organic layers were washed with brine (200 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the resulting material was purified by flash chromatography (1 kg of silica gel, 40:1 pentane–Et_2O) to yield 11.5 g (66.2%) of ketone **187** as well as 3.9 g (22.4%) of a mixture of three other diastereomers. This mixture of isomers was resubmitted to the same isomerization reaction to yield an additional 2.71 g of **187** for a total overall yield of 14.21 g (82%).

IR (neat): 1713, 1638, 1623, 1447, 1376, 1234, 1098, 940, 895, 823, 754 cm^{-1}.

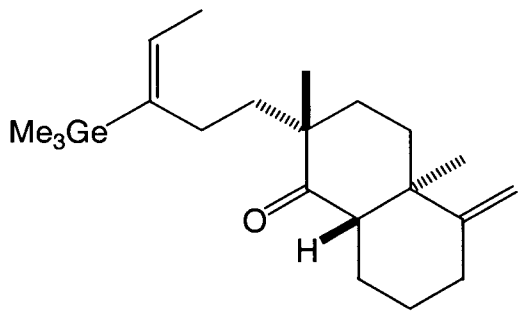
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.15 (s, 9H), 0.86 (s, 3H), 1.05–1.17 (m, 1H), 1.17–1.31 (m, 2H), 1.53–1.69 (m, includes 3-proton doublet at δ 1.66, J = 6.6 Hz, 5H total), 1.74–1.89 (m, 3H), 1.90–2.00 (m, 1H), 2.10–2.32 (m, 7H), 4.69 (m, 2H), 5.68 (q, 1H, J = 6.6 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: –1.7, 14.0, 18.9, 21.0, 26.6, 27.7, 29.0, 30.0, 32.2, 36.0, 45.4, 49.7, 58.3, 105.6, 131.9, 143.3, 155.8, 212.7.

Exact mass calcd for $C_{19}H_{31}{}^{74}GeO$ (M^+–Me): 349.1587. Found: 349.1590.

Anal. calcd for $C_{20}H_{34}GeO$: C 66.66, H 9.44. Found: C 66.25, H 9.38.

Preparation of (1*S,3*S**,6*R**)-3,6-Dimethyl-7-methylidene-3-[(3*E*)-3-trimethylgermyl-3-pentenyl]bicyclo[4.4.0]decan-2-one (194)**



194

To a cold (–78 °C), stirred solution of dry Et_2NH (4.35 g, 59.5 mmol) in dry THF (100 mL) was added a solution of BuLi (1.6 M in hexanes, 30.2 mL, 48.3 mmol). The mixture was warmed to 0 °C for 30 min and cooled to –78 °C. A solution of ketone **187** (13.5 g, 37.2 mmol) in dry THF (20 mL) was added and the resulting mixture was warmed to 0 °C and stirred for 1 h. MeI (107 g, 750 mmol) was added and the mixture was warmed to room temperature. The mixture was stirred for 1.5 h and aqueous NH_4Cl–NH_3 (pH 8, 100 mL) was added. The resulting layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude material was purified by flash chromatography (500 g of silica gel, 50:1 pentane–Et_2O) to give 11.86 g (84.7%) of ketone **194** as a colourless oil.

IR (neat): 1704, 1637, 1623, 1457, 1379, 1234, 1118, 896, 824, 754, 597, 569 cm^{-1}.

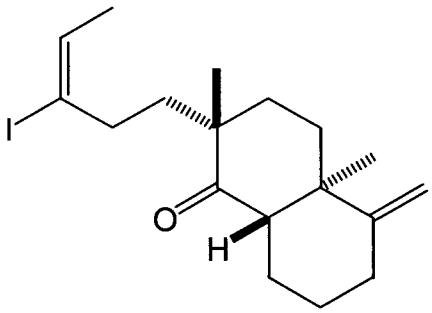
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.17 (s, 9H), 0.86 (s, 3H), 1.17 (s, 3H), 1.18–1.31 (m, 1H), 1.31–1.48 (m, 2H), 1.48–1.61 (m, 1H), 1.63–1.79 (m, includes 3-proton doublet at δ 1.70, J = 6.6 Hz, 6H total), 1.83–1.96 (m, 2H), 2.04–2.33 (m, 5H), 2.44 (dd, 1H, J = 11.9, 3.5 Hz), 4.68–4.74 (m, 2H), 5.67 (q, 1H, J = 6.6 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: –1.7, 14.0, 18.7, 21.2, 24.1 (two signals superimposed), 26.7, 32.1, 32.2, 33.4, 38.0, 44.6, 46.8, 53.7, 105.7, 131.6, 143.5, 155.9, 215.6.

Exact mass calcd for $C_{21}H_{36}{}^{74}GeO$: 378.1978. Found: 378.1986.

Anal. calcd for $C_{21}H_{36}GeO$: C 66.89, H 9.62. Found: C 66.63, H 9.69.

Preparation of (1*S,3*S**,6*R**)-3-[(3*E*)-3-Iodo-3-pentenyl]-3,6-dimethyl-7-methylidenebicyclo[4.4.0]decan-2-one (154)**



154

To a cold (0 °C), stirred solution of ketone **194** (11.4 g, 30.5 mmol) in dry CH_2Cl_2 (250 mL) was added solid *N*-iodosuccinimide (8.24 g, 36.6 mmol) in one portion and the mixture was stirred for 1 h. This solution was then poured into a cold (0 °C) mixture of aqueous $Na_2S_2O_3$ (1.0 M, 100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The biphasic mixture was stirred for 0.5 h and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the remaining crude material was purified by flash chromatography (500 g of silica gel, 40:1 pentane–Et_2O) to give 10.55 g (91%) of the iodide **154** as a colourless oil.

IR (neat): 1703, 1637, 1448, 1380, 895 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ: 0.85 (s, 3H), 1.17 (s, 3H), 1.17–1.30 (m, 1H), 1.48–1.76 (m, includes 3-proton doublet at δ 1.67, J = 7.0 Hz, 9H total), 1.81–1.91 (m, 2 H), 2.04–

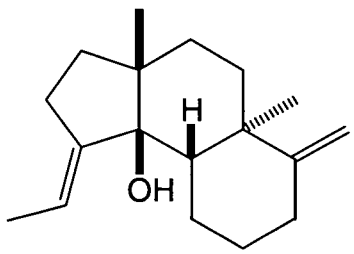
2.17 (m, 2H), 2.21–2.32 (m, 1H), 2.35–2.51 (m, 3H), 4.67–4.73 (m, 2H), 6.18 (q, 1H, J = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 16.2, 18.7, 21.2, 24.1, 26.6, 32.0, 32.1, 33.6, 33.8, 37.6, 44.8, 46.4, 53.7, 103.0, 105.8, 135.5, 155.7, 215.5.

Exact mass calcd for $C_{18}H_{27}IO$: 386.1107. Found: 386.1101.

Anal. calcd for $C_{18}H_{27}IO$: C 55.96, H 7.04. Found: C 56.09, H 7.01.

Preparation of (1*S,2*R**,3*E*,6*S**,9*R**)-3-Ethylidene-6,9-dimethyl-10-methylidene-tricyclo[7.4.0.0^{2,6}]tridecan-2-ol (155)**



155

To a cold (–78 °C), stirred solution of iodide **154** (10.4 g, 26.9 mmol) in dry THF (200 mL) was added a solution of BuLi (1.6 M in hexanes, 25.3 mL, 40.4 mmol) *via* syringe. After the mixture had been stirred for 40 min, H_2O (100 mL) and Et_2O (100 mL) were added. The biphasic mixture was allowed to warm to room temperature over 0.5 h and the layers were separated. The aqueous layer was extracted with the Et_2O (3 × 100 mL) and the combined organic layers were washed with brine (100 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude oil was purified by flash chromatography (500 g of silica gel, 20:1 pentane–Et_2O) to give 5.99 g (86%) of the alcohol **155** as a colourless oil.

IR (neat): 3478, 1660, 1635, 1448, 1375, 1034, 1000, 986, 949, 909, 891, 864, 819 cm^{-1}.

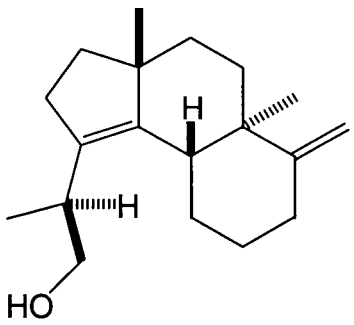
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.92 (s, 3H), 1.01 (s, 3H), 1.17 (s, 1H, exchanges with D_2O), 1.15–1.31 (m, 2H), 1.31–1.42 (m, 2H), 1.52–1.78 (m, 4H), 1.59 (d, 3H, J = 6.7

Hz), 1.81–1.95 (m, 2H), 2.07–2.18 (m, 2H), 2.27–2.40 (m, 3H), 4.56–4.58 (m, 2H), 5.88 (q, 1H, J = 6.7 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 15.2, 19.3, 19.8, 22.6, 26.0, 29.3, 30.7, 32.4, 33.4, 36.4, 41.1, 47.0, 50.4, 81.5, 104.3, 121.5, 149.7, 158.9.

Exact mass calcd for $C_{18}H_{28}O$: 260.2140. Found: 260.2144.

Preparation of (1*S,6*S**,9*R**)-3-[(*S**)-2-Hydroxy-1-methylethyl]-6,9-dimethyl-10-methylidenetricyclo[7.4.0.0^{2,6}]tridec-2-ene (151)**



151

To a stirred suspension of KH (3.98 g, 34.7 mmol) in dry THF (80 mL) was added a solution of alcohol **155** (4.52 g, 17.4 mmol) in dry THF (40 mL). The mixture was stirred for 1 h and a solution of 18-cr-6 ether (9.17 g, 34.7 mmol) in THF (40 mL) was added. After the mixture had been stirred 0.5 h, a solution of Bu_3SnCH_2I (18.71 g, 43.4 mmol) in THF (40 mL) was added *via* a cannula. The resulting thick white slurry was stirred for 1 h at room temperature and then was cooled to –78 °C. A solution of BuLi (1.6 M in hexanes, 48.8 mL, 78.1 mmol) was added, and the mixture was allowed to warm to room temperature over 30 min. H_2O (120 mL) and Et_2O (120 mL) were added, and the resulting layers were separated. The aqueous layer was extracted with Et_2O (3 × 120 mL), and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residual material was purified by flash chromatography (200 g of silica gel, 7:1 pentane–Et_2O) to yield 4.10 g (86%) of the alcohol **151** as a colourless oil.

IR (neat): 3388, 1633, 1455, 1373, 1032, 894, 788 cm^{-1}.

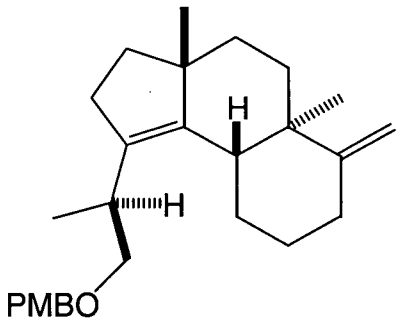
^1H NMR ($CDCl_3$, 400 MHz) δ: 0.92 (s, 3H), 0.96 (d, 3H, J = 6.8 Hz), 1.03 (s, 3H), 1.16–1.31 (m, 2H), 1.48–1.59 (m, 4H), 1.59–1.68 (m, 1H), 1.75–1.91 (m, 3H), 1.91–1.99 (m, 1H), 2.10–2.36 (m, 5H), 3.18–3.29 (m, 1H), 3.38–3.45 (m, 2H), 4.64–4.68 (m, 2H).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 16.1, 18.4, 24.7, 27.8, 28.5, 28.6, 33.1, 34.0, 34.8, 37.1, 38.8, 42.1, 46.6, 49.3, 66.0, 105.6, 134.5, 144.0, 157.6.

Exact mass calcd for $C_{19}H_{30}O$: 274.2297. Found: 274.2289.

Anal. calcd for $C_{19}H_{30}O$: C 83.15 H 11.02. Found: C 82.76 H 11.33.

Preparation of (1*S,6*S**,9*R**)-3-[(*S**)-2-(4-Methoxyphenyl)methoxy-1-methylethyl]-6,9-dimethyl-10-methylidenetricyclo[7.4.0.0^{2,6}]tridec-2-ene (199)**



199

To a stirred suspension of KH (354 mg, 8.81 mmol) in dry THF (40 mL) was added a solution of alcohol **151** (1.72 g, 6.28 mmol) in dry THF (40 mL) *via* a cannula. After the mixture had been stirred for 1 h, 4-methoxybenzyl chloride (1.38 g, 8.81 mmol) and solid Bu_4NI (465 mg, 1.26 mmol) were sequentially added. The mixture was stirred overnight at room temperature. H_2O (60 mL) and Et_2O (60 mL) were added and the resulting layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (50 g of silica gel, 25:1 pentane–Et_2O) to yield 2.25 g (91%) of ether **199** as a colourless oil.

IR (neat): 2933, 2857, 1631, 1613, 1513, 1247 cm^{-1}.

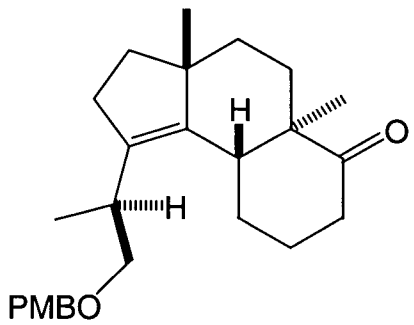
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.92 (s, 3H), 1.00 (d, 3H, J = 6.4 Hz), 1.01 (s, 3H), 1.41–1.68 (m, 6H), 1.75–1.92 (m, 3H), 1.95–2.03 (m, 1H), 2.12–2.40 (m, 5H), 3.22–3.40 (m, 3H), 3.78 (s, 3H), 4.38–4.46 (m, 2H), 4.62–4.70 (m, 2H), 6.86 (d, 2H, J = 8.9 Hz), 7.23 (d, 2H, J = 8.9 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 17.1, 18.5, 24.0, 27.2, 28.6, 29.4, 32.5, 33.2, 34.2, 37.5, 39.3, 41.9, 46.7, 48.8, 55.2, 72.5, 74.2, 105.3, 113.7 (two signals superimposed), 129.0 (two signals superimposed), 131.0, 136.0, 140.1, 157.9, 159.1.

Exact mass calcd for $C_{27}H_{39}O_2$ $(M+H)^+$: 395.2950. Found: 395.2952.

Anal. calcd for $C_{27}H_{38}O_2$: C 82.12, H 9.71. Found C 82.12, H 9.74.

Preparation of (1*R,6*R**,9*R**)-3-[(*S**)-2-(4-Methoxyphenyl)methoxy-1-methylethyl]-6,9-dimethyltricyclo[7.4.0.0^{2,6}]tridec-2-en-10-one (161)**



161

To a stirred solution of alkene **199** (2.10 g, 5.32 mmol) in 5:1 *t*-BuOH–H_2O (120 mL) at room temperature were added KIO_4 (7.34 g, 31.9 mmol) and $NaHCO_3$ (4.47 g, 53.2 mmol). A catalytic amount of OsO_4 (25 mg, 0.01 mmol) was added and the resulting brown mixture was stirred for 72 h. Et_2O (100 mL) and H_2O (100 mL) were added and the resulting layers were separated. The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic layers were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (100 g of silica gel, 20:1 toluene–Et_2O) to yield 1.37 g (64.9%) of ketone **161** as a colourless oil.

IR (neat): 2938, 2860, 1703, 1613, 1514, 1248 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.99 (s, 3H), 1.02 (d, 3H, J = 7.3 Hz), 1.03 (s, 3H), 1.35–1.66 (m, 5H), 1.76 (dt, 1H, J = 4.3, 14.3 Hz), 1.96–2.30 (m, 7H), 2.42–2.49 (m, 1H), 2.60

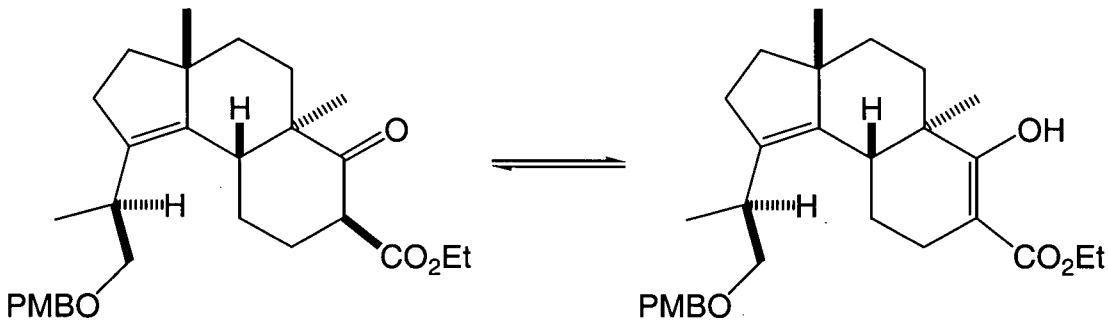
(dt, 1H, J = 6.1, 14.3 Hz), 3.20–3.35 (m, 3H), 3.78 (s, 3H), 4.35–4.45 (m, 2H), 6.84 (d, 2H, J = 8.9 Hz), 7.20 (d, 2H, J = 8.9 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 17.1, 17.2, 23.9, 25.8, 26.7, 29.4, 29.9, 32.6, 36.6, 37.8, 39.1, 46.7, 48.5, 50.9, 55.5, 72.6, 74.0, 113.7 (two signals superimposed), 129.0 (two signals superimposed), 130.8, 137.7, 138.2, 159.1, 216.3.

Exact mass calcd for $C_{26}H_{40}O_3N$ $(M+NH_4)^+$: 414.3008. Found 414.2997.

Anal. calcd for $C_{26}H_{36}O_3$: C 78.75, H 9.15. Found C 78.63, H 9.19.

Preparation of a 1:1 Mixture of (1*R,6*R**,9*R**,11*S**)-3-[(*S**)-2-(4-Methoxyphenyl)-methoxy-1-methylethyl]-6,9-dimethyl-10-oxotricyclo[7.4.0.0^{2,6}]trideca-2-ene-11-carboxylic Acid Ethyl Ester (226a) and (1*R**,6*R**,9*R**)-3-[(*S**)-2-(4-Methoxyphenyl)-methoxy-1-methylethyl]-6,9-dimethyl-10-hydroxytricyclo[7.4.0.0^{2,6}]trideca-2,10-diene-11-carboxylic Acid Ethyl Ester (226b)**



226a **226b**

To a stirred suspension of NaH (132 mg, 5.50 mmol) in dry THF (40 mL) was added a solution of ketone **161** (725 mg, 1.83 mmol) in dry THF (10 mL). $(EtO)_2CO$ (425 mg, 3.6 mmol) was added *via* syringe and the mixture was heated to reflux for 20 min. A catalytic amount of KH (5 mg, 0.13 mmol) was added and the mixture was refluxed for a further 18 h. The solution was cooled to room temperature and dilute aqueous HCl (0.5 M, 30 mL) was added. Et_2O (50 mL) was added and the resulting layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (25 g of silica gel, 10:1 pentane–Et_2O) to yield 625 mg (74%) of a mixture of keto ester **226a** and enol ester **226b** as a colourless oil.

IR (neat): 2937, 2859, 1743, 1709, 1649, 1613, 1514, 1245 cm^{-1}.

A solution of 1:1 mixture of keto ester **226a** and enol ester **226b** in $CDCl_3$ exhibited the following NMR data:

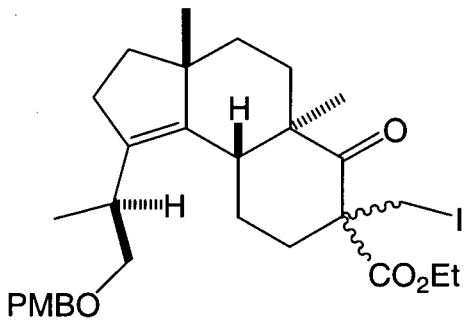
^1H NMR ($CDCl_3$, 400 MHz) δ: 0.95–1.1 (m), 1.23–1.32 (m), 1.35–1.96 (m), 2.00–2.40 (m), 2.52 (bd, J = 12 Hz), 3.13–3.36 (m), 3.68 (dd, J = 5.5, 13.5 Hz), 3.78 (s), 4.12–4.26 (m), 4.35–4.45 (m), 6.82–6.88 (m), 7.18–7.25 (m), 12.4 (s).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 14.2, 14.3, 16.8, 16.9, 17.1, 18.0, 22.6, 23.3, 23.8, 24.1, 24.7, 29.2, 29.4, 29.5, 29.8, 31.7, 32.3, 32.7, 36.4, 37.0, 39.1, 39.3, 41.5, 43.1, 46.8, 48.3, 48.4, 51.2, 53.1, 55.2, 60.2, 60.9, 72.5, 72.6, 73.8, 74.0, 94.8, 113.7 (four signals superimposed), 128.9 (four signals superimposed), 131.0 (two signals superimposed), 136.3, 137.6, 138.3, 139.2, 159.1, 170.6, 173.5, 178.2 (three signals not accounted for).

Exact mass calcd for $C_{29}H_{41}O_5$ $(M+H)^+$: 469.2954. Found: 469.2950.

Anal. calcd for $C_{29}H_{40}O_5$: C 74.33, H 8.60. Found: C 74.19, H 8.60.

Preparation of a 3:1 Mixture of (1*R,6*R**,9*R**)-11-(Iodomethyl)-3-[(*S**)-2-(4-methoxy-phenyl)methoxy-1-methylethyl]-6,9-dimethyl-10-oxotricyclo[7.4.0.0^{2,6}]-tridec-2-ene-11-carboxylic Acid Ethyl Esters (160)**



160

To a stirred solution of a mixture of keto ester **226a** and enol ester **226b** (139 mg, 0.297 mmol) in dry THF (40 mL) was added a solution of TBAF (1.0 M in THF, 0.6 ml, 0.6 mmol). The mixture was stirred for 1 h and neat CH_2I_2 (800 mg, 3.0 mmol) was added. After the mixture had been stirred for an additional 1 h, Et_2O (30 mL) and saturated aqueous $NaHCO_3$ (30 mL) were added. The resulting layers were separated and the aqueous layer was washed with Et_2O (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, concentrated and purified by flash chromatography (5 g of silica gel, 5:1 petroleum ether–Et_2O) to yield 141 mg (78.0%) of a 3:1 mixture of diasteriomeric iodides **160** as a colourless oil.

The relative configurations of the isomers were not determined. The 3:1 mixture of diasteriomeric iodides **160** exhibited the following spectral data:

IR (neat): 2937, 2859, 1735, 1708, 1614, 1514 cm^{-1}.

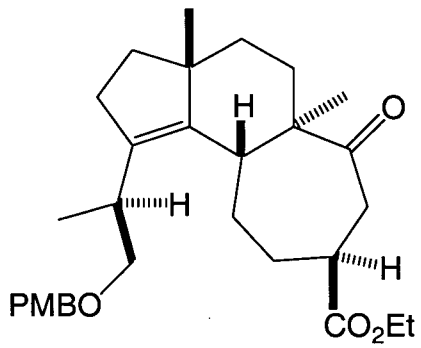
^1H NMR ($CDCl_3$, 400 MHz) (signals assigned to major isomer) δ: 0.94 (s, 3H), 0.98 (s, 3H), 0.99 (d, 3H, J = 5.5 Hz), 1.27 (t, 3H, J = 7.0 Hz), 1.35–2.55 (m, 12H), 2.67 (br d, 1H, J = 12.8 Hz), 3.13–3.35 (m, 3H), 3.52 (m, 2H), 3.79 (s, 3H), 4.20 (dq, 2H, J = 2.1, 7.0 Hz), 4.36–4.45 (m, 2H), 6.86 (d, 2H, J = 8.6 Hz), 7.22 (d, 2H, J = 8.6 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) (signals assigned to major isomer) δ: 9.5, 14.0, 17.0, 17.1, 20.7, 23.6, 29.4, 29.8, 32.0, 32.6, 36.1, 39.2, 40.3, 48.1, 49.6, 55.2, 57.9, 62.0, 72.5, 73.8, 113.6 (two signals superimposed), 129.0 (two signals superimposed), 130.8, 137.8, 137.9, 159.0, 169.3, 210.

Exact mass calcd for fragment $C_{22}H_{32}O_4I$ $(M–MeOPhCH_2)^+$: 487.1346. Found: 487.1337

Exact mass calcd for fragment C_8H_9O $(MeOPhCH_2^+)$: 121.0653. Found: 121.0654

Preparation of (1*R,6*R**,9*R**,12*S**)-3-[(*S**)-2-(4-Methoxyphenyl)methoxy-1-methyl-ethyl]-6,9-dimethyl-10-oxotricyclo[7.5.0.0^{2,6}]tetradec-2-ene-12-carboxylic Acid Ethyl Ester (159)**



159

To a stirred solution of a 3:1 mixture of iodides **160** (161 mg, 0.265 mmol) in dry THF (30 mL) was added a solution of SmI_2 (0.1 M in THF, 7.9 mL, 0.79 mmol). The resulting mixture was stirred for 1 h at room temperature. Dilute aqueous HCl (0.5 M, 40 mL) and Et_2O (40 mL) were added and the resulting layers were separated. The aqueous layer was extracted with Et_2O (3 × 40 mL) and the combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (5 g of silica gel, 40:1 petroleum ether–Et_2O) to yield 91 mg (71%) of keto ester **159** as a colourless oil.

IR (neat): 2933, 2859, 1733, 1698, 1514, 1248 cm^{-1}.

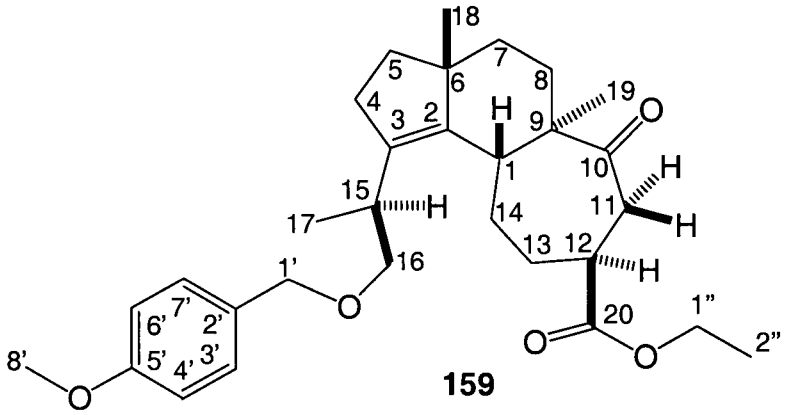
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.97 (d, 3H, J = 6.8 Hz), 1.00 (s, 3H), 1.07 (s, 3H), 1.18–1.23 (m, 1H), 1.24 (t, 3H, J = 7.1 Hz), 1.40–1.72 (m, 5H), 1.81 (dt, 1H, J = 5.2, 13.3 Hz), 1.85–2.30 (m, 5H), 2.65 (br d, 1H, J = 11.2 Hz), 2.77–2.84 (m, 2H), 3.05 (dd, 1H, J = 9.5, 14.4 Hz), 3.10–3.20 (m, 1H), 3.23–3.34 (m, 2H), 3.78 (s, 3H), 4.08–4.15 (m, 2H), 4.36–4.44 (m, 2H), 6.85 (d, 2H, J = 8.6 Hz), 7.21 (d, 2H, J = 8.6 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 14.1, 14.6, 16.6, 24.2, 26.6, 29.2, 29.9, 33.0, 33.1, 36.0, 38.3, 38.7, 39.3, 43.3, 49.0, 53.6, 55.2 60.8, 72.5, 73.8, 113.7 (two signals superimposed), 128.9 (two signals superimposed), 130.8, 136.6, 139.4, 159.0, 174.5, 215.0.

Exact mass calcd for $C_{30}H_{43}O_5$ $(M+H)^+$: 483.3110. Found: 483.3114.

Anal. calcd for $C_{30}H_{42}O_5$: C 74.66, H 8.77. Found: C 74.77, H 8.99.

Table 14. ^{1}H NMR ($CDCl_3$, 400 MHz) Data for Keto Ester **159**: NOED Experiment.

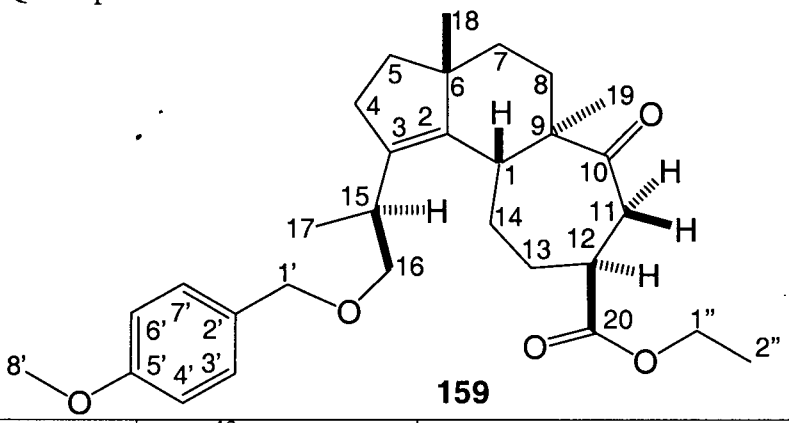


159

Assignments H–x	^{1}H NMR δ ppm (Multiplicity, *J* (Hz))	Observed NOEs
H–1[a]	2.65 (br d, 11.2)	H–18, H–11(β)
H–4	part of m at 1.85–2.30, part of m at 1.40–1.72	
H–5	part of m at 1.40–1.72	
H–7	part of m at 1.40–1.72,	
H–8	1.81 (dt, 5.2, 13.3), 1.18–1.23 (m)	
H–11(α)	part of m at 2.77–2.84	
H–11(β)	3.05 (dd, 9.5,14.4)	
H–12	part of m at 2.77–2.84	
H–13	part of m at 1.85–2.30	
H–14	part of m at 1.85–2.30	
H–15	3.10–3.20 (m)	
H–16	3.23–3.34 (m)	
H–17	0.97 (d, 6.8)	
H–18[a]	1.07 (s)	H–1
H–19[a]	1.00 (s)	H–11(α)
H–1'	4.08–4.15 (m)	
H–3', H–7'	7.21 (d, 8.6)	
H–4', H–6'	6.85 (d, 8.6)	
H–8'	3.78 (s)	
H–1"	4.36–4.44 (m)	
H–2"	1.24 (t, 7.1)	

[a] Irradiation of this signal generated the corresponding NOEs in the right hand column

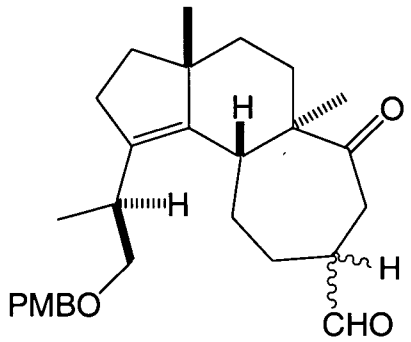
Table 15. ^{13}C NMR ($CDCl_3$, 100.6 MHz) and ^{1}H NMR ($CDCl_3$, 400 MHz) Data for Keto Ester **159**: HMQC Experiment.



159

Assignments C–x	^{13}C NMR δ ppm	Observed HMQC Correlations (δ ppm)
C–1	43.3	H–1 (2.65)
C–2	139.4	
C–3	136.6	
C–4	29.2	H–4 (part of m at 1.40–1.72, part of m at 1.85–2.30)
C–5	38.3	H–5 (part of m at 1.40–1.72)
C–6	49.0	
C–7	36.0	H–7(part of m at 1.40–1.72)
C–8	33.1	H–8 (1.81, part of m at 1.18–1.23)
C–9	53.6	
C–10	215.0	
C–11	39.3	H–11 (part of m at 2.77–2.84, 3.05)
C–12	38.7	H–12 (part of m at 2.77–2.84)
C–13	29.9	H–13 (part of m at 1.85–2.30)
C–14	26.6	H–14 (part of m at 1.85–2.30)
C–15	33.0	H–15 (3.10–3.20)
C–16	73.8	H–16 (3.24–3.34)
C–17	16.6	H–17 (0.97)
C–18	24.2	H–18 (1.07)
C–19	14.6	H–19 (1.00)
C–20	174.5	
C–1'	60.8	H–1' (4.08–4.15)
C–2'	130.8	
C–3', C–7'	128.9	H–3', H–7' (7.21)
C–4', C–6'	113.7	H–4', H–6' (6.85)
C–5'	159.0	
C–8'	55.2	H–8' (3.78)
C–1"	72.5	H–1" (4.36–4.44)
C–2"	14.1	H–2" (1.24)

Preparation of a 1:1 Mixture of (1*R,6*R**,9*R**)-3-[(*S**)-2-(4-Methoxyphenyl)-methoxy-1-methylethyl]-6,9-dimethyl-10-oxotricyclo[7.5.0.0^{2,6}]tetra-dec-2-ene-12-carboxaldehydes (158)**



158

To a cold (0 °C) stirred solution of keto ester **159** (181 mg, 0.374 mmol) in dry Et_2O (20 mL) was added a solution of DIBALH (1.0 M in hexanes, 1.8 mL, 1.80 mmol) and the resulting mixture was stirred for 1 h. After this time, the mixture was warmed to room temperature and was stirred for an additional 1 h. Saturated aqueous NH_4Cl–NH_3 (pH 8, 180 *u*L) was added and the mixture was stirred for 1 h. Anhydrous $MgSO_4$ (100 g) was added and the mixture was stirred for 1 h. EtOH (2 mL) was added and the mixture was stirred for 1 h. The mixture was filtered through a sintered glass funnel (4 cm diameter) containing Florisil® (4 cm depth) on top of a thin layer of Celite®. The column was washed with 20:1 EtOH–Et_2O (50 mL). The solvent of the combined eluates was removed under reduced pressure to give a crude mixture of the diols.

The crude mixture of diols was taken up in dry CH_2Cl_2 (5 mL) and the solution was added to a solution of Dess-Martin's periodinane reagent (510 mg, 1.2 mmol) in dry CH_2Cl_2 (30 mL). After the mixture had been stirred for 1 h, saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous $Na_2S_2O_3$ (100 mL) were added. The biphasic mixture

was stirred for 1 h and the layers were then separated. The aqueous portion was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (10 g of silica gel, 2:1 petroleum ether–Et_2O) to give 141 mg (86%) of a 1:1 mixture of epimeric keto aldehydes **158** as a colourless oil.

The 1:1 mixture of epimeric keto aldehydes **158** exhibited the following spectral data:

IR (neat): 2932, 2857, 1726, 1697, 1514, 1248, 1089 cm^{-1}.

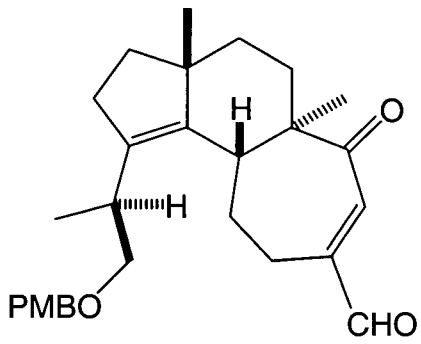
^1H NMR ($CDCl_3$, 400 MHz) δ: 0.96 and 0.99 (s, s, ratio 1:1, 3H), 0.96–1.00 (m, 3H), 1.08 and 1.10 (s, s, ratio 1:1, 3H), 1.14–1.24 (m, 2H), 1.42–1.92 (m, 6H), 2.05–2.46 (m, 5H), 2.53–2.79 (m, 2H), 2.88–3.15 (m, 2H), 3.23–3.35 (m, 2H), 3.78 (s, 3H), 4.35–4.44 (m, 2H), 6.82–6.87 (m, 2H), 7.18–7.23 (m, 2H), 9.60 and 9.63 (s, s, ratio 1:1, 1H).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 14.0, 14.3, 16.3, 16.7, 24.1, 24.4, 25.9, 26.7, 27.4, 29.0, 29.1, 29.2, 32.7, 33.0, 33.1, 35.7, 35.8, 36.0, 37.5, 43.0, 43.1, 45.1, 48.9, 49.2, 49.3, 53.4, 54.5, 55.2, 72.5, 73.7, 73.8, 113.6 (two signals superimposed), 113.7 (two signals superimposed), 128.8 (two signals superimposed), 128.9 (two signals superimposed), 130.7, 130.8, 135.9, 137.0, 138.7, 139.7, 159.0, 201.0, 201.5, 214.9, 215.8 (six signals not accounted for).

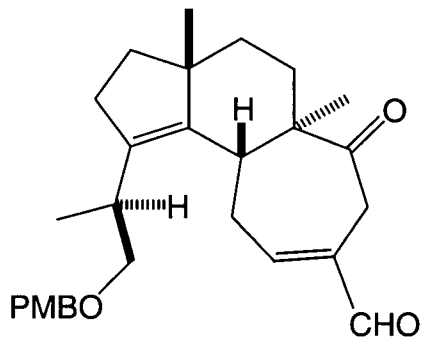
Exact mass calcd for $C_{28}H_{42}O_4N$ $(M+NH_4)^+$: 456.3114. Found: 456.3122.

Anal. calcd for $C_{28}H_{38}O_4$: C 76.68, H 8.73. Found: C 77.00, H 8.81.

Preparation of (1*R,6*R**,9*R**)-3-[(*S**)-2-(4-Methoxyphenyl)methoxy-1-methylethyl]-6,9-dimethyl-10-oxotricyclo[7.5.0.0^{2,6}]tetradeca-2,11-diene-12-carboxaldehyde (249)**



249



240

To a stirred solution of a 1:1 mixture of keto aldehydes **158** (106 mg, 0.242 mmol) in dry benzene (12 mL) over 3Å mol sieves was added piperidine (103 mg, 1.21 mmol). The mixture was heated to reflux for 3 h and cooled to room temperature. The solvent and excess piperidine were removed under reduced pressure and the remaining material was taken up in dry THF (12 mL). The mixture was cooled to –78 °C and solid PhSeCl (232 mg, 1.21 mmol) was added. After the mixture had been stirred for 5 min, Et_2O (15 mL) and H_2O (15 mL) were added. The biphasic mixture was warmed to room temperature and stirred for 3 h. The phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were concentrated and taken up in MeOH (10 mL). Saturated aqueous $KHCO_3$ (2 mL) and solid KIO_4 (557 mg, 2.42 mmol) were sequentially added, and the mixture was stirred for 20 min. Et_2O (20 mL) and H_2O (20 mL) were added, and the resulting layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine

(20 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (5 g of silica gel, 4:1 petroleum ether–Et_2O) to yield 79.5 mg (75.2%) of the α,β-unsaturated ketone **249** and 2.4 mg (2.3%) of the β,γ-unsaturated ketone **240** as colourless oils

α,β-Unsaturated ketone **249** exhibited the following spectral data:

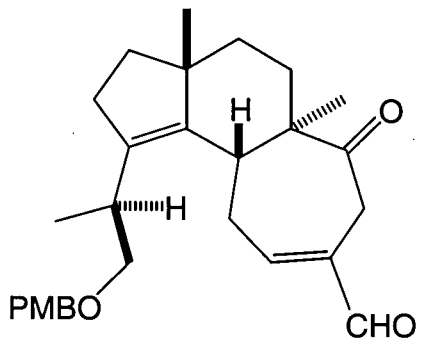
IR (neat): 2932, 2152, 1697, 1514, 1248 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ: 0.99 (d, 3H, J = 6.7 Hz), 1.03 (s, 3H), 1.10 (s, 3H), 1.22–1.64 (m, 5H), 1.83–1.97 (m, 2H), 2.23–2.43 (m, 4H), 2.59 (dt, 1H, J = 18.6, 4.3 Hz), 2.67 (br d, 1H, J = 9.7 Hz), 3.02–3.13 (m, 1H), 3.24–3.36 (m, 2H), 3.80 (s, 3H), 4.34–4.45 (m, 2H), 6.63 (m), 6.86 (d, 2H, J = 8.6 Hz), 7.21 (d, 2H, J = 8.6 Hz), 9.56 (s, 1H).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 15.9, 16.5, 24.2, 25.2, 26.6, 29.2, 33.1, 33.2, 35.5, 37.6, 43.0, 49.4, 55.0, 55.3, 72.6, 73.7, 113.7 (two signals superimposed), 128.9 (two signals superimposed), 130.7, 136.9, 139.6, 144.2, 146.1, 159.1, 194.7, 209.6.

Exact mass calcd for $C_{28}H_{40}O_4N$ $(M+NH_4)^+$: 454.29575. Found: 454.29515

Preparation of (1*R,6*R**,9*R**)-3-[(*S**)-2-(4-Methoxyphenyl)methoxy-1-methylethyl]-6,9-dimethyl-10-oxotricyclo[7.5.0.0^{2,6}]tetradeca-2,12-diene-12-carboxaldehyde (240)**



240

To a stirred solution of ketone **249** (51.6 mg, 0.118 mmol) in dry benzene (5 mL) was added DBN (29.3 mg, 0.236 mmol). The mixture was heated to reflux for 12 h and cooled to room temperature. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (2 g of silica gel, 3:1 petroleum ether–Et_2O) to yield 49 mg (95.8%) of ketone **240** as a colourless oil.

IR (neat): 2931, 2854, 1704, 1688, 1513, 1248 cm^{-1}.

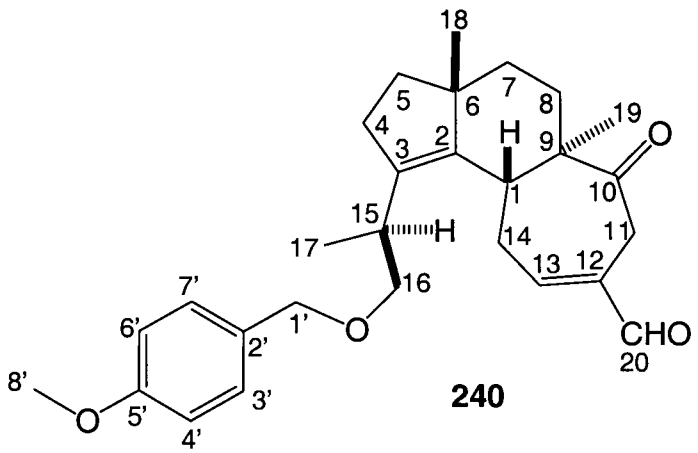
^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.99 (d, 3H, J = 6.7 Hz), 1.02 (s, 3H), 1.13 (s, 3H), 1.20–1.30 (m, 1H), 1.50–1.70 (m, 4H), 1.94 (dt, 1H, J = 5.3, 13.1 Hz), 2.15–2.25 (m, 2H), 2.66–2.75 (m, 1H), 3.05–3.10 (m, 1H), 3.14 (dd, 1H, J = 6.4, 19.8 Hz), 3.25–3.35 (m, 3H), 3.46 (d, 1H, J = 14.0 Hz), 3.72 (br d, 1H, J = 14.0 Hz), 3.78 (s, 3H), 4.35–4.46 (m, 2H), 6.63–6.68 (m, 1H), 6.85 (d, 2H, J = 8.6 Hz), 7.20 (d, 2H, J = 8.6 Hz), 9.33 (s, 1H).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 12.8, 16.4, 24.2, 29.1, 31.7, 32.9, 33.3, 34.1, 35.9, 38.1, 39.6, 49.4, 55.0, 55.3, 72.7, 73.6, 113.7 (two signals superimposed), 128.9 (two signals superimposed), 130.7, 135.7, 137.0, 137.9, 153.7, 159.2, 192.3, 210.6.

Exact mass calcd for $C_{28}H_{40}O_4N$ $(M+NH_4)^+$: 454.29575. Found: 454.29541.

Anal. calcd for $C_{28}H_{36}O_4$: C 77.03, H 8.31. Found: C 77.03, H 8.36.

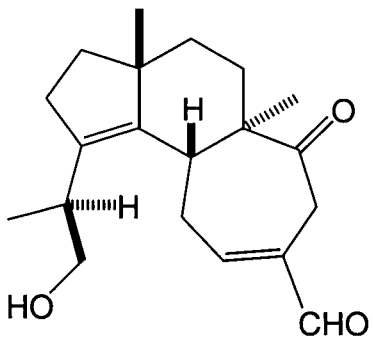
Table 16. ^{13}C NMR ($CDCl_3$, 100.6 MHz) and ^{1}H NMR ($CDCl_3$, 400 MHz) Data for Ketone **240**: HMQC Experiment.



240

Assignments C–x	^{13}C NMR δ ppm	Observed HMQC Correlations (δ ppm)
C–1	39.6	H–1 (part of m at 3.25–3.35)
C–2	135.7	
C–3	137.0	
C–4	29.1	H–4 (2.15–2.25)
C–5	35.9	H–1 (part of m at 1.50–1.70)
C–6	49.4	
C–7	38.1	H–7 (part of m at 1.50–1.70)
C–8	32.9	H–8 (1.94, 1.20–1.30)
C–9	55.0	
C–10	210.6	
C–11	34.1	H–11 (3.46, 3.72)
C–12	137.9	
C–13	153.7	H–13 (6.63–6.68)
C–14	31.7	H–14 (2.65–2.75, 3.14)
C–15	33.3	H–15 (3.05–3.10)
C–16	73.6	H–16 (part of m at 3.25–3.35)
C–17	16.4	H–17 (0.99)
C–18	24.2	H–18 (1.13)
C–19	12.8	H–19 (1.02)
C–20	192.3	H–20 (9.33)
C–1'	72.7	H–1' (4.35–4.46)
C–2'	130.7	
C–3', C–7'	128.9	H–3', H–7' (7.20)
C–4', C–6'	113.7	H–4', H–6' (6.85)
C–5'	159.2	
C–8'	55.3	H–8' (3.78)

Preparation of (1*R,6*R**,9*R**)-3-[(*S**)-2-Hydroxy-1-methylethyl]-6,9-dimethyl-10-oxotricyclo[7.5.0.0^{2,6}]tetradeca-2,12-diene-12-carbaldehyde [(±)-Sarcodonin G] (36)**



36

To a stirred solution of ketone **240** (6.2 mg, 0.014 mmol) in a biphasic mixture of 20:1 CH_2Cl_2–H_2O (5.25 mL) was added DDQ (4.8 mg, 0.021 mmol). The mixture was stirred at room temperature for 0.5 h and H_2O (5 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residual material was purified by flash chromatography (1 g of silica gel, 1:1 petroleum ether–Et_2O) to yield 4.1 mg (92%) of (±)-sarcodonin G (**36**) as an amorphous solid.

IR (KBr): 3445, 1703, 1640, 1450, 1376 cm^{-1}.

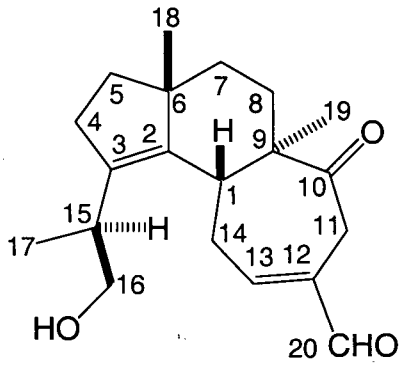
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.97 (d, 3H, J = 6.9 Hz), 1.03 (s, 3H), 1.14 (s, 3H), 1.24–1.30 (m, 1H), 1.46 (s, 1H), 1.49–1.55 (m, 1H), 1.58–1.70 (m, 2H), 1.95 (dt, 1H, J = 5.0,

13.4 Hz), 2.21–2.40 (m, 3H), 2.69–2.80 (m, 1H), 2.98–3.08 (m, 1H), 3.10–3.20 (m, 1H), 3.36 (br d, 1H, J = 12.6 Hz), 3.41–3.51 (m, 3H), 3.71–3.75 (m, 1H), 6.70–6.73 (m, 1H), 9.35 (s, 1H).

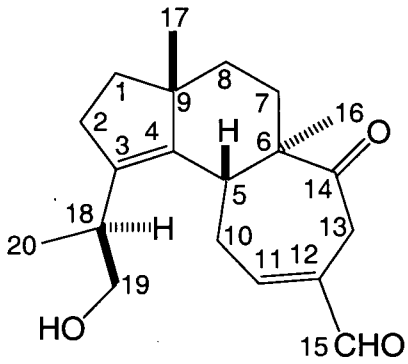
^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 12.7, 15.6, 24.8, 28.6, 32.1, 32.7, 34.1, 35.2, 35.5, 37.7, 39.7, 49.8, 55.3, 65.8, 135.9 (two signals superimposed), 141.3, 153.2, 192.2, 210.3.

Exact mass calcd for $C_{20}H_{28}O$: 316.2039. Found: 316.2038.

Table 17. Comparison of ^{1}H NMR Data for Synthetic (1*R**,6*R**,9*R**)-3-[(*S**)-2-Hydroxy-1-methylethyl]-6,9-dimethyl-10-oxotricyclo[7.5.0.0^{2,6}]tetradeca-2,12-diene-12-carbox-aldehyde [(±)-Sarcodonin G] (**36**) ($CDCl_3$, 400 MHz) with those Reported[16] for Natural (–)-Sarcodonin G (**36**) ($CDCl_3$, 250 MHz).



36 showing IUPAC-based numbering

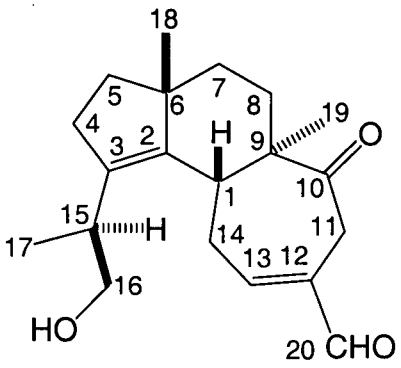


36 showing IUPAC-based numbering

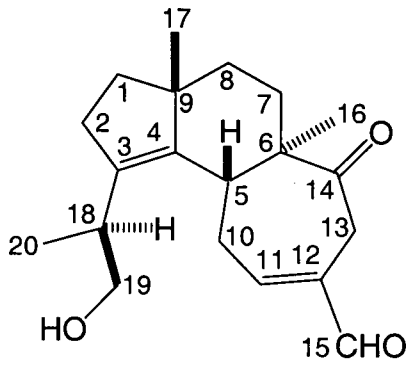
^{1}H NMR ($CDCl_3$, 400 MHz) Signals Displayed[a] by Synthetic (±)-Sarcodonin G (**36**) δ ppm (Multiplicity, *J* (Hz))	^{1}H Assignment H–x	Reported ^{1}H NMR ($CDCl_3$, 250 MHz) Signals Displayed by Natural (–)-Sarcodonin G (**36**) δ ppm (Multiplicity, *J* (Hz))	Cyathane Numbering
0.97 (d, 6.9)	H–17	0.96 (d, 7.3)	H–20
1.03 (s)	H–19	1.01 (s)	H–16
1.14 (s)	H–18	1.12 (s)	H–17
1.24–1.30 (m)		1.24 (dt, 3.9, 13.2)	
1.46 (s)		part of m at 1.59	
1.49–1.55 (m)		part of m at 1.59	
1.58–1.70 (m)		part of m at 1.59	
1.95 (dt, 5, 13.4)		1.94 (dt, 5.3, 13.3)	
2.21–2.40 (m)		2.31 (m)	
2.69–2.80 (m)		2.74 (m)	
2.98–3.08 (m)	H–15	3.02 (sextet, 7.3)	H–18
3.10–3.20 (m)		3.16 (dd, 13.4, 6.4)	
3.36 (br d, 12.6)		3.34 (d, 12)	
3.41–3.51 (m)		3.42 (d, 13.9), 3.45 (d, 7.3)	
3.71–3.75 (m)		3.72 (br d, 13.6))	
6.70–6.73 (m)	H–13	6.71 (m)	H–11
9.35 (s)	H–20	9.31	H–15

[a] The difference between observed and reported δ is likely due to the $CDCl_3$ reference.

Table 18. Comparison of ^{13}C NMR Data for Synthetic (1*R**,6*R**,9*R**)-3-[(*S**)-2-Hydroxy-1-methylethyl]-6,9-dimethyl-10-oxotricyclo[7.5.0.0^{2,6}]tetradeca-2,12-diene-12-carboxaldehyde [(±)-Sarcodonin G] (**36**) ($CDCl_3$, 400 MHz) with those Reported[16] for Natural (–)-Sarcodonin G (**36**) ($CDCl_3$, 62.5 MHz).



36 showing IUPAC-based numbering

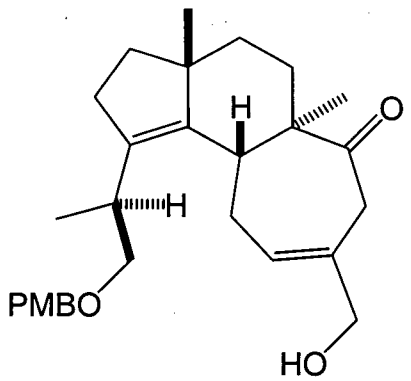


36 showing IUPAC-based numbering

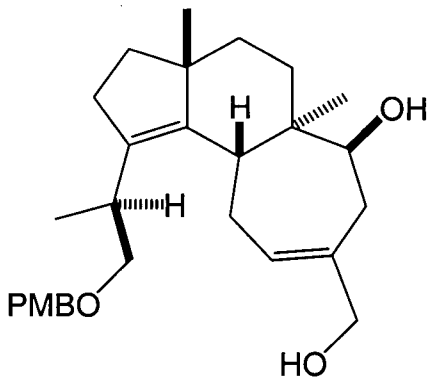
^{13}C NMR ($CDCl_3$, 100.6 MHz) Signals Displayed by Synthetic (±)-Sarcodonin G (**36**) δ ppm	^{13}C assignment C–x	Reported ^{13}C NMR ($CDCl_3$, 62.5 MHz) Signals Displayed by Natural (–)-Sarcodonin G (**36**) δ ppm	Cyathane Numbering
12.7	C–19	12.7	C–16
15.6	C–15	15.6	C–20
24.8	C–18	24.8	C–17
28.6		28.6	
32.1		32.1	
32.7		32.7	
34.1		34.1	
35.2		35.2	
35.5		35.5	
37.7		37.7	
39.7		39.5	
49.8		49.8	
55.3		55.3	
65.8	C–16	65.8	C–19
135.9 (two signals superimposed)		135.8, 135.9	
141.3		141.2	
153.2	C–13	153.5	C–11
192.2	C–20	192.4	C–15
210.3	C–10	210.6	C–14

4.3. Synthetic Studies Directed Towards Cyathane Diterpenoid (±)-Cyathin A_4

Preparation of (1*R,6*R**,9*R**)-12-Hydroxymethyl-3-[(1*S**)-2-(4-methoxyphenyl)-meth-oxy-1-methylethyl]-6,9-dimethyltricyclo[7.5.0.$0^{2,6}$]tetradeca-2,12-dien-10-one (254)**



254



256

To a stirred solution of keto aldehyde **240** (200 mg, 0.458 mmol) in *i*-PrOH (10 mL) was added $(i\text{-PrO})_3Al$ (140 mg, 0.687 mmol). The mixture was heated to 60 °C for 8 h and cooled to room temperature. Et_2O (10 mL) and aqueous NH_4Cl–NH_3 (pH 8, 0.1 mL) were added and the resulting slurry was stirred for 18 h. $MgSO_4$ (100 mg) was added and the mixture was stirred for 1 h. The slurry was filtered through a column of Florisil® (1 g) and the column was washed with a mixture of 1:1 Et_2O–EtOH (10 mL). The solvent of the eluate was removed under reduced pressure and the resulting material was purified by flash chromatography (5 g of silica gel, 9:1 Et_2O–petroleum ether) to give 110 mg (55%) of keto alcohol **254** and 65 mg (32%) of diol **256** as colourless oils.

The diol **256** (65 mg, 0.147 mmol) was taken up in dry CH_2Cl_2 (2 mL) and the solution was added to a solution of Dess-Martin's periodinane reagent (250 mg, 0.6 mmol) in dry CH_2Cl_2 (15 mL). After the mixture had been stirred for 1 h, saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous $Na_2S_2O_3$ (50 mL) were added. The biphasic mixture was stirred for 1 h and the layers were separated. The aqueous portion was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (5 g of silica gel, 3:1 petroleum ether–Et_2O) to give 55 mg (86%) of keto aldehyde **240** as a colourless oil. Keto aldehyde **240** was resubmitted to the reduction reaction to yield an additional 31 mg of keto alcohol **254** for a total overall yield of 141 mg (70%).

Keto alcohol **254** exhibited the following spectral data:

IR (neat): 3436, 2932, 2855, 1702, 1613, 1513 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ: 0.99 (d, 3H, J = 6.7 Hz), 1.03 (s, 3H), 1.12 (s, 3H), 1.45–1.65 (m, 6H), 1.91 (dt, 1H, J = 5.0, 12.8 Hz), 2.10–2.35 (m, 2H), 2.45–2.53 (m, 1H), 2.68–2.82 (m, 2H), 3.06–3.15 (m, 1H), 3.21–3.36 (m, 3H), 3.79 (s, 3H), 3.92 (br d, 1H, J = 12.8 Hz), 3.95–4.08 (m, 2H), 4.32–4.49 (m, 2H), 5.60–5.69 (m, 1H), 6.85 (d, 2H, J = 8.6 Hz), 7.21 (d, 2H, J = 8.6 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 12.9, 16.5, 24.3, 29.2, 30.0, 32.8, 33.0, 36.1, 38.2, 39.3, 40.3, 49.3, 54.6, 55.3, 68.8, 72.5, 73.8, 113.7 (two signals superimposed), 126.6, 128.8 (two signals superimposed), 130.8, 131.7, 136.5, 138.5, 159.0, 211.3.

Exact mass calcd for $C_{28}H_{39}O_4$ $(M+H)^+$: 439.28482. Found: 439.28435.

Diol **256** exhibited the following spectral data:

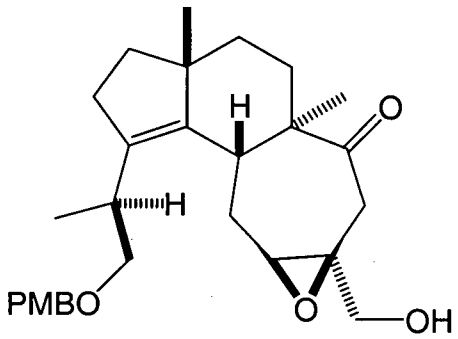
IR (neat): 3368, 2931, 2860, 1613, 1514 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.89 (s, 3H), 0.99 (d, 3H, J = 6.8 Hz), 1.05 (s, 3H), 1.32–1.58 (m, 8H), 1.72–1.90 (m, 2H), 2.02–2.16 (m, 2H), 2.21–2.64 (m, 3H), 3.03–3.13 (m, 1H), 3.24–3.38 (m, 2H), 3.43 (d, 1H, J = 8.1 Hz), 3.79 (s, 3H), 3.92–3.99 (m, 2H), 4.38–4.47 (m, 2H), 5.85 (d, 1H, J = 7.0 Hz), 6.85 (d, 2H, J = 8.7 Hz), 7.21 (d, 2H, J = 8.7 Hz).

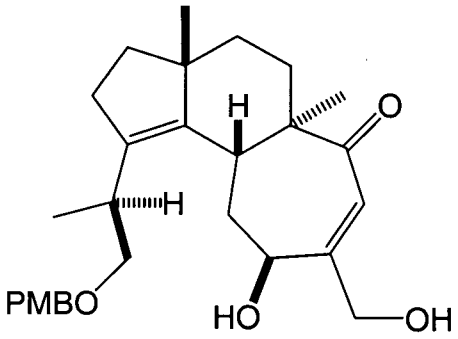
^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 16.3, 17.1, 24.5, 28.2, 29.1, 30.3, 31.8, 33.1, 35.8, 37.6, 39.0, 45.2, 49.8, 55.2, 68.4, 72.4, 74.0, 75.3, 113.7 (two signals superimposed), 128.9 (two signals superimposed), 130.0, 130.9, 134.5, 137.6, 142.0, 159.0.

Exact mass calcd for $C_{28}H_{44}O_4N$ $(M+NH_4)^+$: 458.32703. Found: 458.32817.

Preparation of (1*R,6*R**,9*R**,13*S**)-13-Hydroxy-12-hydroxymethyl-3-[(*S**)-2-(4-methoxyphenyl)methoxy-1-methylethyl]-6,9-dimethyltricyclo[7.5.0.0^{2,6}]tetradeca-2,11-dien-10-one (267)**



266



267

To a cool (0 °C), stirred solution of keto alcohol **256** (110 mg, 0.250 mmol) in dry CH_2Cl_2 (6 mL) was added *t*-BuO_2H (70% in water, 51 uL, 0.375 mmol) *via* syringe. $VO(acac)_2$ (7 mg, 0.026 mmol) was added and the mixture was stirred for 2 h. The solution was poured into a cold (0 °C) mixture of aqueous $Na_2S_2O_3$ (1.0 M, 3 mL) and saturated aqueous $NaHCO_3$ (3 mL) and the mixture was stirred for 0.5 h. The resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residual material, crude keto epoxide **266**, was taken up in dry benzene (10 mL). DBN (62 mg, 0.50 mmol) was added and the mixture was heated to reflux for 6 h. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude oil was

purified by flash chromatography (5 g of silica gel, 50:1 Et_2O–petroleum ether) to yield 74 mg (65%) of keto diol **267** as a colourless oil.

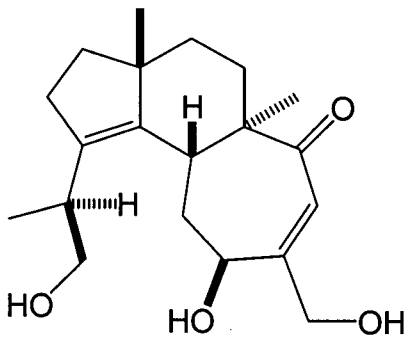
IR (neat): 3402, 2932, 1665, 1514 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ: 0.98 (d, 3H, J = 6.8 Hz), 1.03 (s, 3H), 1.09 (s, 3H), 1.20–1.32 (m, 1H), 1.42–1.67 (m, 5H), 1.78 (dt, 1H, J = 4.9, 13.0 Hz), 1.98–2.09 (m, 1H), 2.13–2.34 (m, 3H), 2.42–2.57 (m, 1H), 3.09–3.20 (m, 2H), 3.32 (d, 2H, J = 7.9 Hz), 3.79 (s, 3H), 4.16–4.45 (m, 5H), 5.96 (s, 1H), 6.86 (d, 2H, J = 8.6 Hz), 7.21 (d, 2H, J = 8.6 Hz).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 14.8, 16.5, 24.1, 39.0, 33.0, 33.9, 34.6, 36.0, 36.9, 38.1, 49.4, 55.1, 65.7, 65.8, 70.5, 72.8, 73.9, 113.8 (2 signals superimposed), 124.9, 129.3 (2 signals superimposed), 130.4, 135.6, 140.3, 150.4, 159.3, 210.1.

Exact mass calcd for $C_{28}H_{38}O_5$: 454.27191. Found: 454.27163.

Preparation of (1*R,6*R**,9*R**,13*S**)-13-Hydroxy-12-hydroxymethyl-3-[(*S**)-2-hydroxy-1-methylethyl]-6,9-dimethyltricyclo[7.5.0.0^{2,6}]tetradeca-2,11-dien-10-one (268)**



268

To a stirred solution of keto diol **267** (11 mg, 0.024 mmol) in a biphasic mixture of 20:1 CH_2Cl_2–H_2O (10.5 mL) was added DDQ (11 mg, 0.048 mmol). The mixture was stirred at room temperature for 1 h and H_2O (10 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residual material purified by flash chromatography (1 g of silica gel, 10:1 Et_2O–MeOH) to yield 5.4 mg (64%) of keto triol **268** as an amorphous solid.

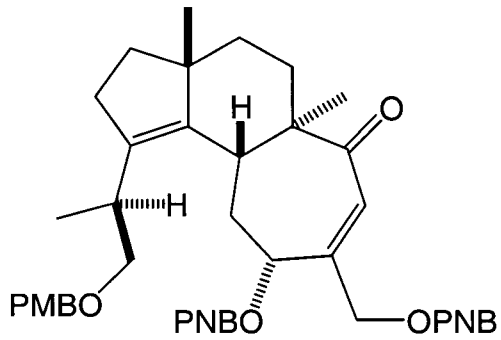
IR: not obtained

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.96 (d, 3H, J = 6.7 Hz), 1.04 (s, 3H), 1.12 (s, 3H), 1.20–1.34 (m, 2H), 1.43–1.51 (m, 1H), 1.53–1.69 (m, 4H), 1.81 (dt, 1H, J = 4.9, 13.4 Hz), 1.97–2.07 (m, 1H), 2.19–2.37 (m, 2H), 2.63–2.70 (m, 1H), 3.07–3.15 (m, 1H), 3.25–3.31 (m, 1H), 3.37–3.52 (m, 3H), 4.24–4.42 (m, 2H), 4.55–4.59 (m, 1H), 6.00 (s, 1H).

^{13}C NMR: not obtained

Exact mass calcd for $C_{20}H_{30}O_4$: 334.21442. Found: 334.21369.

Preparation of (1*R,6*R**,9*R**,13*R**)-3-[(*S**)-2-(4-Methoxyphenyl)methoxy-1-methyl-ethyl]-6,9-dimethyl-13-(4-nitro-benzoyl)oxy-12-(4-nitro-benzoyl)oxymethyltricyclo-[7.5.0.0^{2,6}]tetradeca-2,11-dien-10-one (269)**



269

To a stirred solution of keto diol **267** (20 mg, 0.044 mmol) in dry benzene (2 mL) were added PPh_3 (57 mg, 0.217 mmol) and *p*-nitrobenzoic acid (33 mg, 0.193 mmol). Neat DEAD (38 mg, 0.217 mmol) was added *via* syringe and the mixture was stirred for 18 h at room temperature. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (1 g of silica gel, 1:1 Et_2O–petroleum ether) to give 23 mg (70%) of the keto diester **269** as an amorphous solid.

IR (neat): 2920, 2850, 1729, 1688, 1608, 1529 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.98 (d, 3H, J = 6.7 Hz), 1.08 (s, 3H), 1.21 (s, 3H), 1.34–1.80 (m, 6H), 2.16–2.38 (m, 3H), 2.81–2.87 (m, 1H), 2.93–2.98 (m, 1H), 3.03–3.10 (m, 1H), 3.22–3.35 (m, 2H), 3.75 (s, 3H), 4.31–4.38 (m, 2H), 5.02 (s, 2H), 5.70–5.78 (m,

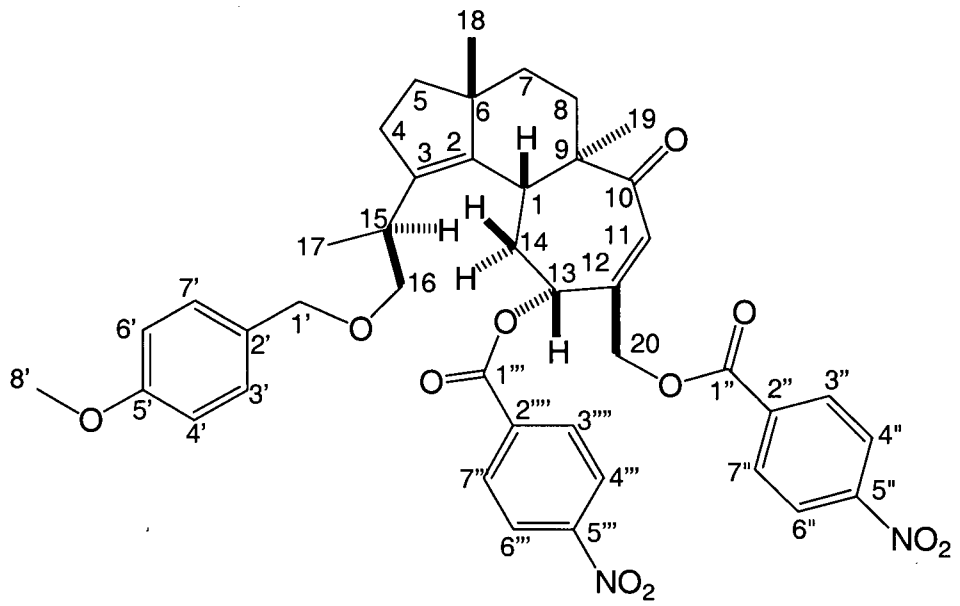
1H), 6.31 (s, 1H), 6.77 (d, 2H, J = 8.6 Hz), 7.12 (d, 2H, J = 8.6 Hz), 8.06 (d, 2H, J = 8.2 Hz), 8.16 (d, 2H, J = 8.6 Hz), 8.20–8.29 (m, 4H).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 14.5, 16.7, 24.0, 29.5, 31.9, 33.4, 34.7, 36.2, 38.2, 39.2, 49.3, 54.1, 55.2, 66.0, 72.6, 73.2, 73.9, 113.7, 123.6, 123.7, 128.7, 128.9, 130.7, 130.8, 130.9, 134.7, 134.8, 137.3, 138.0, 141.7, 150.8 (2 signals superimposed), 159.1, 163.8, 164.0, 208.6.

Exact mass calcd for $C_{42}H_{44}N_2O_{11}$: 752.2945. Parent ion was not detected.

Melting point: amorphous material displayed a broad melting point range: 40–60 °C.

Table 19. ^{1}H NMR ($CDCl_3$, 400 MHz) Data for Diester **269**: NOED Experiment.



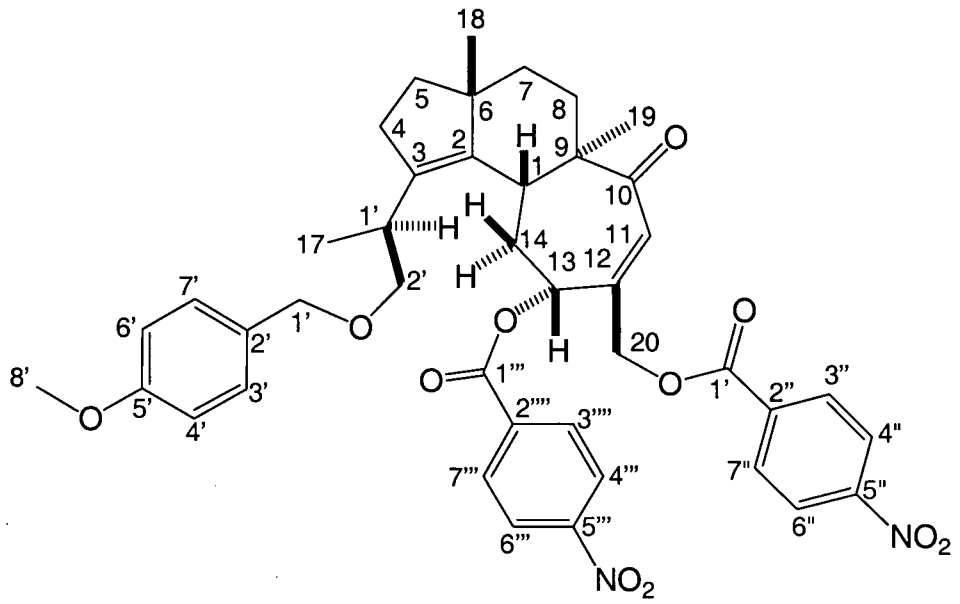
269

Assignments H–x	^{1}H NMR δ ppm (Multiplicity, *J* (Hz))	Observed NOEs
H–1[a]	2.93–2.98 (m)	H–13, H–18
H–4	part of m at 2.16–2.38	
H–5	part of m at 1.34–1.80	
H–7	part of m at 1.34–1.80	
H–8	part of m at 1.34–1.80	
H–11[a]	6.31 (s)	H–20
H–13[a]	5.70–5.78 (m)	H–1, H–14(β), H–20
H–14(α)	part of m at 2.16–2.38	
H–14(β)[a]	2.81–2.87 (m)	H–14(α), H–1, H–15
H–15[a]	3.30–3.10 (m)	H–14, H–16, H–17
H–16[a]	3.22–3.35 (m)	H–15, H–17
H–17[a]	0.98 (d, 6.7)	H–15, H–16
H–18[a]	1.08 (s)	H–1

H–19	1.21 (s)	
H–20[a]	5.02 (s)	H–11
H–1'	4.31–4.38	
H–3', H–7'	7.12 (d, 8.6)	
H–4', H–6'	6.77 (d, 8.6)	
H–8'	3.75 (s)	
H–3", H–7"	8.06 (d, 8.2) or 8.16 (d, 8.6)	
H–4", H–6"	part of m at 8.20–8.29	
H–3"', H–7"'	8.06 (d, 8.2) or 8.16 (d, 8.6)	
H–4"', H–6"'	part of m at 8.20–8.29	

[a] Irradiation of this signal generated the corresponding NOEs in the right hand column

Table 20. ^{13}C NMR ($CDCl_3$, 100.6 MHz) and ^{1}H NMR ($CDCl_3$, 400 MHz) Data for Diester **269**: HMQC Experiment.



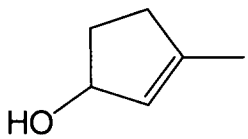
269

Assignments C–x	^{13}C NMR δ ppm	Observed HMQC Correlations (δ ppm)
C–1	39.2	H–1 (2.93–2.98)
C–2	138.0	
C–3	137.3	
C–4	29.5	H–4 (part of m at 2.16–2.38)
C–5	36.2	H–5 (part of m at 1.34–1.80)
C–6	49.3	
C–7	38.2	H–7 (part of m at 1.34–1.80)
C–8	34.7	H–8 (part of m at 1.34–1.80)
C–9	54.1	
C–10	208.6	
C–11	128.9	H–11 (6.31)
C–12	141.7	
C–13	73.2	H–13 (5.70–5.78)

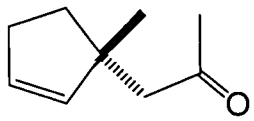
C–14	31.9	H–14 (2.81–2.87, part of m at 2.16–2.38)
C–15	33.4	H–15 (3.30–3.10)
C–16	73.9	H–16 (3.22–3.35)
C–17	16.7	H–17 (0.98)
C–18	24.0	H–18 (1.08)
C–19	14.5	H–19 (1.21)
C–20	66.0	H–20 (5.02)
C–1'	72.6	H–1' (4.31–4.38)
C–2'	130.7	
C–3', C–7'	128.7	H–3', H–7' (7.12)
C–4', C–6'	113.7	H–4', H–6' (6.77)
C–5'	159.1	
C–8'	55.2	H–8' (3.75)
C–1"	163.8 or164.0	
C–2"	134.7 or 134.8	
C–3", C–7"	130.8 or 130.9	H–3", H–7" (8.06 or 8.16)
C–4", C–6"	123.6 or 123.7	H–4", H–6" (part of m at 8.20–8.29)
C–5"	150.8	
C–1"'	163.8 or164.0	
C–2"'	134.7 or 134.8	
C–3"', C–7"'	130.8 or 130.9	H–3"', H–7"' (8.06 or 8.16)
C–4"', C–6"'	123.6 or 123.7	H–4"', H–6"' (part of m at 8.20–8.29)
C–5"'	150.8	

4.4. Synthetic Studies Directed Towards the (±)-Presilphiperfolan-9-ol

Preparation of 1-(1-Methyl-cyclopent-2-enyl)-propan-2-one (315)



316



315

To a cold (–20 °C), stirred solution of (±)-3-methylcyclopent-2-en-1-ol (**316**) (16.51 g, 0.168 mol) in dry Et_2O (250 mL) was added a solution of diketene (16.99 g, 0.202 mol) in dry Et_2O (25 mL) *via* cannula. A catalytic amount of DMAP (204 mg, 1.68 mmol) was added and the resulting yellow mixture was stirred for 1 h. The mixture was warmed to room temperature, stirred for 18 h and cooled to –78 °C. A cold (–78 °C) solution of LDA (0.73 M in THF, 575 mL, 0.420 mmol) was added over 15 min *via* cannula and the resulting mixture was stirred for 1 h. The mixture was warmed to 0 °C for 30 min and then to room temperature for 5 h. The mixture was extracted with aqueous NaOH (2N, 3 × 150 mL). The combined aqueous extracts were acidified by dropwise addition of concentrated HCl and back-extracted with Et_2O (3 × 300 mL). The combined ethereal extracts were washed with brine (100 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the remaining material was taken up CCl_4 (50 mL). The mixture was heated to reflux for 12 h and cooled to room temperature. Most of the solvent was removed under reduced pressure and the residual

material was purified by flash chromatography (150 g of silica gel, 10:1 pentane–Et_2O) to give 17.8 g (77%) of the ketone **315** as a clear colourless oil.

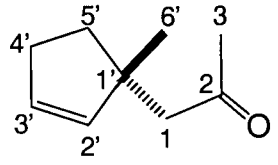
IR (neat): 3050, 2952, 1718, 1452, 1358 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ: 1.12 (s, 3H), 1.63–1.74 (m, 1H), 1.78–1.87 (m, 1H), 2.11 (s, 3H), 2.26–2.37 (m, 2H), 2.49 (s, 2H), 5.61–5.68 (m, 2H).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 26.2, 31.2, 31.7, 37.2, 47.2, 54.0, 129.1, 139.0, 208.3.

Exact mass calcd for $C_9H_{14}O$: 138.10446. Found: 138.10502.

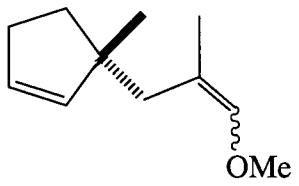
Table 21. ^{13}C NMR ($CDCl_3$, 100.6 MHz) and ^{1}H NMR ($CDCl_3$, 400 MHz) Data for 1-(1-Methyl-cyclopent-2-enyl)-propan-2-one (**315**): HMQC Experiment.



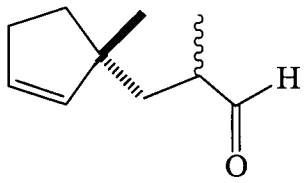
315

Assignments C–x	^{13}C NMR δ ppm	HMQC ^{1}H NMR Correlations (δ ppm)
C–1	54.0	H–1 (2.49)
C–2	208.3	
C–3	31.7	H–3 (2.11)
C–1'	47.2	
C–2'	139.0	H–2' (part of m at 5.61–5.68)
C–3'	129.1	H–3' (part of m at 5.61–5.68)
C–4'	31.2	H–4' (2.26–2.37)
C–5'	37.2	H–5' (1.63–1.74, 1.78–1.87)
C–6'	26.2	H–6' (1.12)

Preparation of a 1:1 Mixture of 2-Methyl-3-(1-methyl-cyclopent-2-enyl)-propion-aldehydes (333)



332



333

To a cool (0 °C), stirred solution of (methoxymethyl)triphenylphosphonium chloride (84.3 g, 0.246 mol) in dry THF (1 L) was added a cold (–78 °C) solution of LDA (0.33 M in THF, 943 mL, 0.312 mol) *via* cannula. The resulting purple solution was stirred for 1 h. A cool (0 °C) solution of ketone **315** (17.0 g, 0.123 mol) in dry THF (100 mL) was added *via* cannula and the mixture was stirred for 1 h. The mixture was warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (300 mL) was added and resulting layers were separated. The aqueous layer was extracted with Et_2O (3 × 300 mL). Most of the solvent of the combined organic layers was removed under reduced pressure and the residual material, a crude mixture of enol ethers **332**, was taken up in $CHCl_3$ (200 mL). TFA (10 mL) and H_2O (10 mL) were added and the resulting mixture was heated to reflux for 18 h. The solution was cooled to room temperature and H_2O (200ml) was added. The resulting layers were separated and the organic layer was washed with aqueous NaOH (2N, 2 × 100 mL). The organic layer was then washed with brine (200 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (500 g of silica

gel, 2:1 petroleum ether–CH_2Cl_2) to yield a 13.4 g (72%) of a 1:1 mixture of epimeric aldehydes **333** as clear colourless oils.

The 1:1 mixture of epimeric aldehydes **333** exhibited the following spectral data:

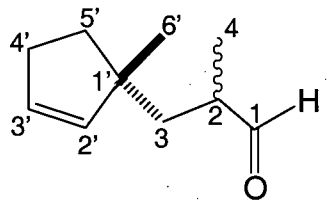
IR (neat): 2952, 1735, 1457 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ: 1.02 and 1.03 (s, s, ratio 1:1, 3H), 1.04 and 1.05 (d, J = 7.1 Hz, d, J = 7.1 Hz, ratio 1:1, 3H), 1.25 and 1.32 (dd, J = 4.8, 14.2 Hz, dd, J = 3.9, 14.3 Hz, ratio 1:1, 1H), 1.53–1.72 (m, 2H), 1.87–1.99 (m, 1H), 2.22–2.41 (m, 3H), 5.37–5.44 (m, 1H), 5.56–5.63 (m, 1H), 9.51 and 9.53 (d, J = 2.9 Hz, d, J = 2.7 Hz, ratio 1:1, 1H).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 15.9, 16.2, 27.1, 27.6, 31.7, 31.9, 36.8, 37.0, 42.2, 42.9, 43.6, 43.7, 48.4 (two signals superimposed), 129.4, 129.9, 139.2, 139.5, 205.2, 205.3.

Exact mass calcd for $C_{10}H_{16}O$: 152.12012. Found: 152.12068.

Table 22. ^{13}C NMR ($CDCl_3$, 100.6 MHz) and ^{1}H NMR ($CDCl_3$, 400 MHz) Data for the 1:1 Mixture of 2-Methyl-3-(1-methyl-cyclopent-2-enyl)-propionaldehydes (**333**): HMQC Experiment.

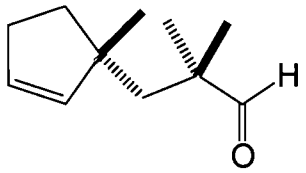


333

Assignment C–x	^{13}C NMR[a] δ ppm	HMQC ^{1}H NMR Correlations[a] δ ppm (Multiplicity, *J* (Hz))
C–1	205.2, 205.3	H–1 (9.51, 9.53)
C–2	31.7, 31.9	H–2 (part of m at 2.22–2.41)
C–3	36.8, 37.0	H–3 (1.53–1.72)
C–4	15.9, 16.2	H–4 (1.04, 1.05)
C–1'	48.4	
C–2'	139.2, 139.5	H–2' (5.37–5.44)
C–3'	129.4, 129.9	H–3' (5.56–5.63)
C–4'	43.6, 43.7	H–4' (part of m at 2.22–2.41)
C–5'	42.2, 42.9	H–5' (1.25, 1.32, 1.87–1.99)
C–6'	27.1, 27.6	H–6' (1.02, 1.03)

[a] The respective signals of both isomers of **333** are noted.

Preparation of 2,2-Dimethyl-3-(1-methyl-cyclopent-2-enyl)-propionaldehyde (314)



314

To a stirred suspension of KH (3.81 g, 0.095 mol) in dry THF (500 mL) was added a solution of a 1:1 mixture of epimeric aldehydes **333** (13.0 g, 0.086 mol) in dry THF (50 mL). The resulting yellow mixture was stirred at room temperature for 1 h and cooled to 0 °C. Neat MeI (13.5 g, 0.095 mol) was added and the mixture was stirred for 1 h. The resulting slurry was slowly poured into a stirred mixture of 1:1 Et_2O–H_2O (0.5 L). The resulting layers were separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (300 g of silica gel, 15:1 pentane–Et_2O) to yield 12.8 g (90%) of aldehyde **314** as a clear colourless oil.

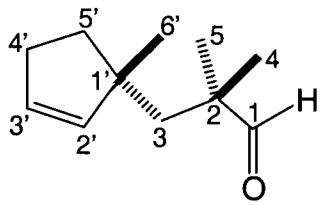
IR (neat): 3050, 2956, 1727, 1456 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ: 0.93 (s, 3H), 1.01 (s, 3H), 1.04 (s, 3H), 1.50–1.83 (m, 4H), 2.20–2.30 (m, 2H), 5.45–5.49 (m, 2H), 5.53–5.58 (m, 1H), 9.44 (s, 1H).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 22.9, 23.7, 27.7, 31.3, 39.1, 46.6, 48.4, 49.3, 128.9, 140.4, 206.6.

Exact mass calcd for $C_{11}H_{18}O$: 166.13577. Found 166.13591.

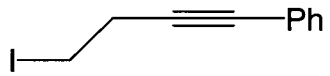
Table 23. ^{13}C NMR ($CDCl_3$, 100.6 MHz) and ^{1}H NMR ($CDCl_3$, 400 MHz) Data for 2,2-Dimethyl-3-(1-methyl-cyclopent-2-enyl)-propionaldehyde (**314**): HMQC Experiment.



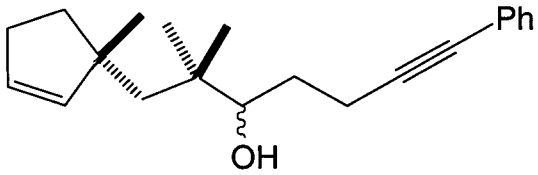
314

Assignment C–x	^{13}C NMR δ ppm	HMQC ^{1}H NMR Correlations δ ppm (Multiplicity, *J* (Hz))
C–1	206.6	H–1 (9.44)
C–2	46.6	
C–3	49.3	H–3 (part of m at 1.50–1.83)
C–4	22.9	H–4 (1.04)
C–5	23.7	H–5 (1.01)
C–1'	48.4	
C–2'	140.4	H–2' (5.45–5.49)
C–3'	128.9	H–3' (5.53–5.58)
C–4'	31.3	H–4' (2.20–2.30)
C–5'	39.1	H–5' (part of m at 1.50–1.83)
C–6'	27.7	H–6' (0.93)

Preparation of a 1:1 Mixture of 2,2-Dimethyl-1-(1-methyl-cyclopent-2-enyl)-7-phenyl-hept-6-yn-3-ols (366)



369



366

To a cold (–78 °C), stirred solution of iodide **369**[81] (1.71 g, 6.69 mmol) in dry Et_2O (40 mL) was added a solution of *t*-BuLi (1.7 M in pentane, 8.26 mL, 14.05 mmol) *via* syringe over 2 minutes. The mixture was stirred for 1 h, warmed to 0 °C for 15 min and then recooled to –78 °C for 30 min. A solution of aldehyde **314** (1.0 g, 6.02 mmol) in dry Et_2O (10 mL) was added *via* cannula and the mixture was stirred for 30 min. H_2O (25 mL) was added and the mixture was warmed to room temperature. The resulting layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residual material was purified by flash chromatography (40 g of silica gel, 5:1 petroleum ether–Et_2O) to give 1.40 g (78%) of a 1:1 mixture of alcohols **366** as a clear colourless oil.

The 1:1 mixture of alcohols **366** exhibited the following spectral data:

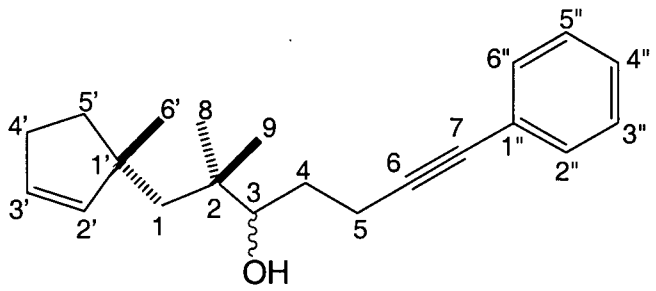
IR (neat): 3500, 3030, 2952, 2230, 1490 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.96 and 0.98 (s, s, ratio 1:1, 3H), 0.99 (s, 3H), 1.11 and 1.12 (s, s, ratio 1:1, 3H), 1.32–1.89 (m, 7H), 2.27–2.35 (m, 2H), 2.46–2.65 (m, 2H), 3.42–3.51 (m, 1H), 5.51–5.59 (m, 1H), 5.60–5.72 (m, 1H), 7.22–7.29 (m, 3H), 7.35–7.39 (m, 2H).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 17.1 (two signals superimposed), 24.6, 24.7, 24.8 (two signals superimposed), 28.9, 29.0, 30.2, 30.3, 31.2, 31.4, 38.9 (two signals superimposed), 39.5, 40.3, 48.1 (two signals superimposed), 48.7, 48.9, 78.6, 79.3, 81.1 (two signals superimposed), 90.0, 90.1, 123.8, 123.9, 127.6, 128.2, 128.3 (four signals superimposed), 131.5 (two signals superimposed), 141.3, 141.7.

Exact mass calcd for $C_{21}H_{28}O$: 296.21402. Found 296.21390.

Table 24. ^{13}C NMR ($CDCl_3$, 100.6 MHz) and ^{1}H NMR ($CDCl_3$, 400 MHz) Data for a 1:1 Mixture of 2,2-Dimethyl-1-(1-methyl-cyclopent-2-enyl)-7-phenyl-hept-6-yn-3-ol (**366**): HMQC Experiment.

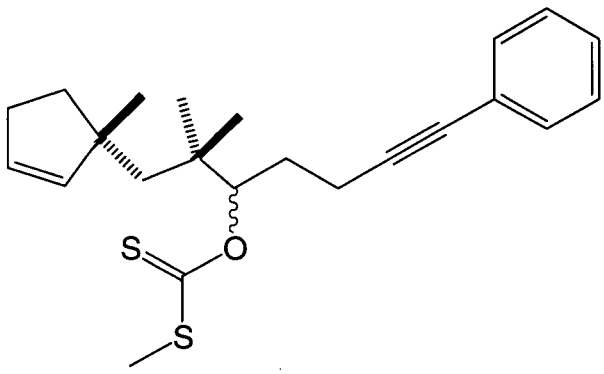


366

Assignment C–x	^{13}C NMR [a] δ ppm	HMQC ^{1}H NMR Correlations [a] δ ppm (Multiplicity, *J* (Hz))
C–1	48.1	H–1 (part of m at 1.32–1.89)
C–2	38.9	
C–3	78.6, 79.3	H–3 (3.42–3.51)
C–4	30.2, 30.3	H–4 (part of m at 1.32–1.89)
C–5	17.1	H–5 (2.46–2.65)
C–6	90.0, 90.1	
C–7	81.0	
C–8	24.6, 24.7	H–8 (0.96, 0.98)
C–9	24.8	H–9 (0.99)
C–1'	39.5, 40.3	
C–2'	141.3, 141.7	H–2' (5.60–5.72)
C–3'	127.6, 128.2	H–3' (5.51–5.59)
C–4'	31.2, 31.4	H–4' (2.27–2.35)
C–5'	48.7, 48.9	H–5' (part of m at 1.32–1.89)
C–6'	28.9, 29.0	H–6' (1.11, 1.12)
C–1"	123.8, 123.9	
C–2", C–6"	131.5	H–2", H–6" (7.35–7.39)
C–3", C–5"	128.3	H–3", H–5" (part of m at 7.22–7.29)
C–4"	128.3	H–4" (part of m at 7.22–7.29)

[a] The respective signals for both isomers of the 1:1 mixture of **366** were noted.

Preparation of a 1:1 Mixture of Dithiocarbonic Acid *O*-{1-[1,1-Dimethyl-cylopent-2-enyl]-5-phenyl-pent-4-ynyl} Ester *S*-Methyl Esters (367)



367

To a stirred suspension of NaH (49 mg, 2.04 mmol) in dry THF (40 mL) was added a solution of a 1:1 mixture of alcohols **366** (291 mg, 1.021 mmol) in dry THF (1 mL). Carbon disulfide (233 mg, 3.06 mmol) was added *via* syringe followed by a catalytic amount of imidazole (3.5 mg, 0.05 mmol). The mixture was heated to reflux for 3 h and then cooled to room temperature. MeI (724 mg, 5.11 mmol) was added and the mixture was stirred for 30 min. H_2O (20 mL) and Et_2O (20 mL) were added and the biphasic mixture was stirred for 10 min. The resulting layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residual material was purified by flash chromatography (20 g of silica gel, 20:1 petroleum ether–Et_2O) to give 332 mg (84%) of a 1:1 mixture of xanthates **367** as a clear red oil.

The 1:1 mixture of xanthates **367** exhibited the following spectral data:

IR (neat): 3050, 2221, 1715, 1598, 1490, 1230, 1050 cm^{-1}.

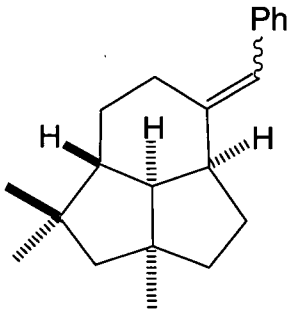
^1H NMR ($CDCl_3$, 300 MHz) δ: 1.02 (s, 3H), 1.05 (s, 3H), 1.11 and 1.12 (s, s, ratio 1:1, 3H), 1.45–1.69 (m, 3H), 1.94–2.15 (m, 3H), 2.24–2.36 (m, 2H), 2.37–2.46 (m, 2H), 2.54 (s, 3H), 5.52–5.58 (m, 1H), 5.61–5.68 (m, 1H), 5.91 (br d, J = 10 Hz, 1H), 7.20–7.30 (m, 3H), 7.32–7.42 (m, 2H).

^{13}C NMR ($CDCl_3$, 75.2 MHz) δ: 16.8, 18.9, 24.7, 24.8, 25.1, 28.7, 28.2, 29.7, 31.3, 39.5, 40.1, 48.6, 48.7, 48.9, 80.9, 89.5, 90.4, 123.8, 127.6, 128.0, 128.2, 131.6, 141.2, 141.3. Most of the ^{13}C signals of the respective xanthate isomers **367** were superimposed on each other.

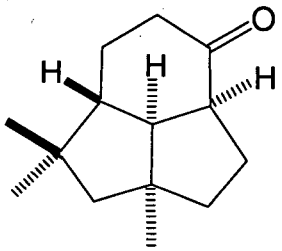
Exact mass calcd for $C_{23}H_{31}OS_2$ $(M+H)^+$: 387.18163. Found 387.18155.

Anal. calcd for $C_{23}H_{30}OS_2$: C 71.45, H 7.81. Found: C 71.38, H 7.81.

Preparation of (1*S,4*R**,7*R**,11*R**)-2,2,4-Trimethyltricyclo[5,3,1,$0^{4,11}$]undecan-8-one (306)**



368



306

To a stirred, refluxing solution of a 1:1 mixture of xanthates **367** (100 mg, 0.258 mmol) in dry, degassed benzene (3 mL) were added solutions of Bu_3SnH (0.31 M in benzene, 1 mL, 0.31 mmol) and AIBN (0.061 M in benzene, 1 mL, 0.061 mmol) *via* syringes on a double barrel syringe pump over 16 hrs. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residual material, a mixture of olefins **368** (ratio not determined), was taken up in a 1:1:1.5 mixture of MeCN–CCl_4–H_2O (3.5 mL). $NaIO_4$ (150 mg, 0.69 mmol) and a catalytic amount of $RuCl_3$ (2 mg, 0.01 mmol) were added and the resulting black mixture was stirred at room temperature for 2 h. CH_2Cl_2 (2 mL) was added and the mixture was stirred for 10 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with brine (2 mL) and dried over anhydrous $MgSO_4$. Most of the solvent was removed under reduced pressure and the residual material was diluted

with Et_2O (5 mL). The mixture was filtered through a short column of Celite® and the column was flushed with Et_2O (5 mL). The solvent of the combined eluates was removed under reduced pressure and the crude oil was purified by flash chromatography (1 g of silica gel, 9:1 petroleum ether–Et_2O) to give 21.3 mg (40%) of the ketone **306** as a clear colourless oil.

Ketone **306** exhibited the following spectral data:

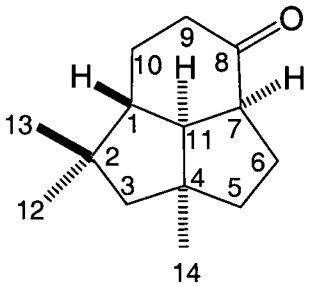
IR (neat): 2950, 1719 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ: 0.88 (s, 3H), 1.01 (s, 3H), 1.07 (s, 3H), 1.40 (ddd, 1H, J = 4, 12.5, 13 Hz), 1.45–1.69 (m, 5H), 1.72–1.84 (m, 1H), 1.95–2.05 (m, 2H), 2.19 (dd, 1H, J = 7, 12.5 Hz), 2.25–2.53 (m, 2H), 2.71–2.86 (m, 1H).

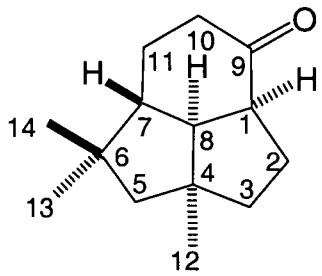
^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 21.8, 22.7, 28.2, 28.9, 29.0, 38.3, 40.6, 41.9, 47.5, 50.9, 52.7, 58.0, 59.1, 216.2

Exact mass calcd for $C_{14}H_{22}O$: 206.16707. Found 206.16727.

Table 25. Comparison of the ^{1}H NMR ($CDCl_3$, 400 MHz) Data for (1R*,4R*,7S*,8R*)-4,6,6-Trimethyltricyclo[5.3.1.$0^{4,11}$]undecan-9-one (**306**) with those Reported[20] for (±)-1-Epi-9-norpresilphiperfolan-9-one (**306**).



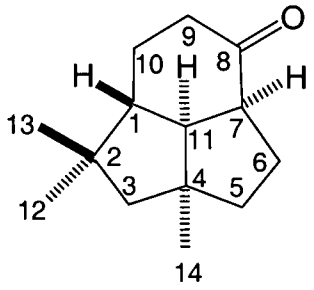
306 showing IUPAC-based numbering



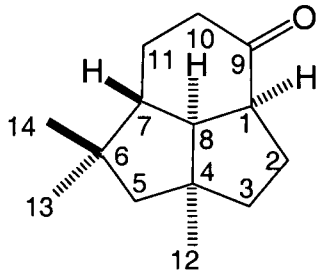
306 showing presilphiperfolane numbering

Assignment H–x (**306**)	^{1}H NMR δ ppm (Multiplicity, *J* (Hz))	Presilphiperfolane Numbering H–x (**306**)	Literature ^{1}H NMR Assignments δ ppm (Multiplicity, *J* (Hz))
H–1	1.40 (ddd, 4, 12.5, 13)	H–7	1.39 (ddd, 4, 12.5, 13)
H–3	part of m at 1.45–1.69	H–5	1.58 and 1.68 (AB, 13)
H–5	part of m at 1.45–1.69	H–3	1.52 (m) and 1.65 (m)
H–6	1.95–2.05 (m)	H–2	2.01 (m)
H–7	2.71–2.86 (m)	H–1	2.81 (ddd, 9, 8, 7)
H–9	2.25–2.53 (m)	H–10	2.31 and 2.47 (AB, 16)
H–10	part of m at 1.45–1.69 and 1.72–1.84 (m)	H–11	1.55 (m) and 1.78 (m)
H–11	2.19 (dd, 7, 12.5)	H–8	2.18 (dd, 7.12.5)
H–12	0.88 (s) or 1.01 (s)	H–13	0.88 (s) or 1.01 (s)
H–13	0.88 (s) or 1.01 (s)	H–14	0.88 (s) or 1.01 (s)
H–14	1.07 (s)	H–12	1.07 (s)

Table 26. Comparison of the ^{13}C NMR ($CDCl_3$, 100.6 MHz) Data for (1R*,4R*,7S*,8R*)-4,6,6-Trimethyltricyclo[5.3.1.$0^{4,11}$]undecan-9-one (**306**) and those Reported[20] for (±)-1-Epi-9-norpresilphiperfolan-9-one (**306**).



306 showing IUPAC-based numbering



306 showing presilphiperfolane numbering

Assignment C–x (**306**)	^{13}C NMR δ ppm (Multiplicity, *J* (Hz))	Presilphiperfolane Numbering C–x (**306**)	Literature ^{13}C NMR Assignments δ ppm (Multiplicity, *J* (Hz))
C–1	50.9	C–7	50.9
C–2	40.6	C–6	40.6
C–3	58.0	C–5	58.0
C–4	47.5	C–4	47.5
C–5	41.9	C–3	41.9
C–6	28.2	C–2	28.2
C–7	52.7	C–1	52.6
C–8	216.2	C–9	216.2
C–9	38.3	C–10	38.3
C–10	21.8	C–11	21.8
C–11	59.1	C–8	59.1
C–12	22.7	C–13	22.7
C–13	28.9 or 29.0	C–14	29.0
C–14	28.9 or 29.0	C–12	29.0

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