COPPER(I)-MEDIATED INTRAMOLECULAR CONJUGATE ADDITIONS. TOTAL SYNTHESES OF (±)-1-DESOXYHYPNOPHILIN AND (±)-6,7-EPOXY-4(15)-HIRSUTEN-5-OL

by

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ABSTRACT

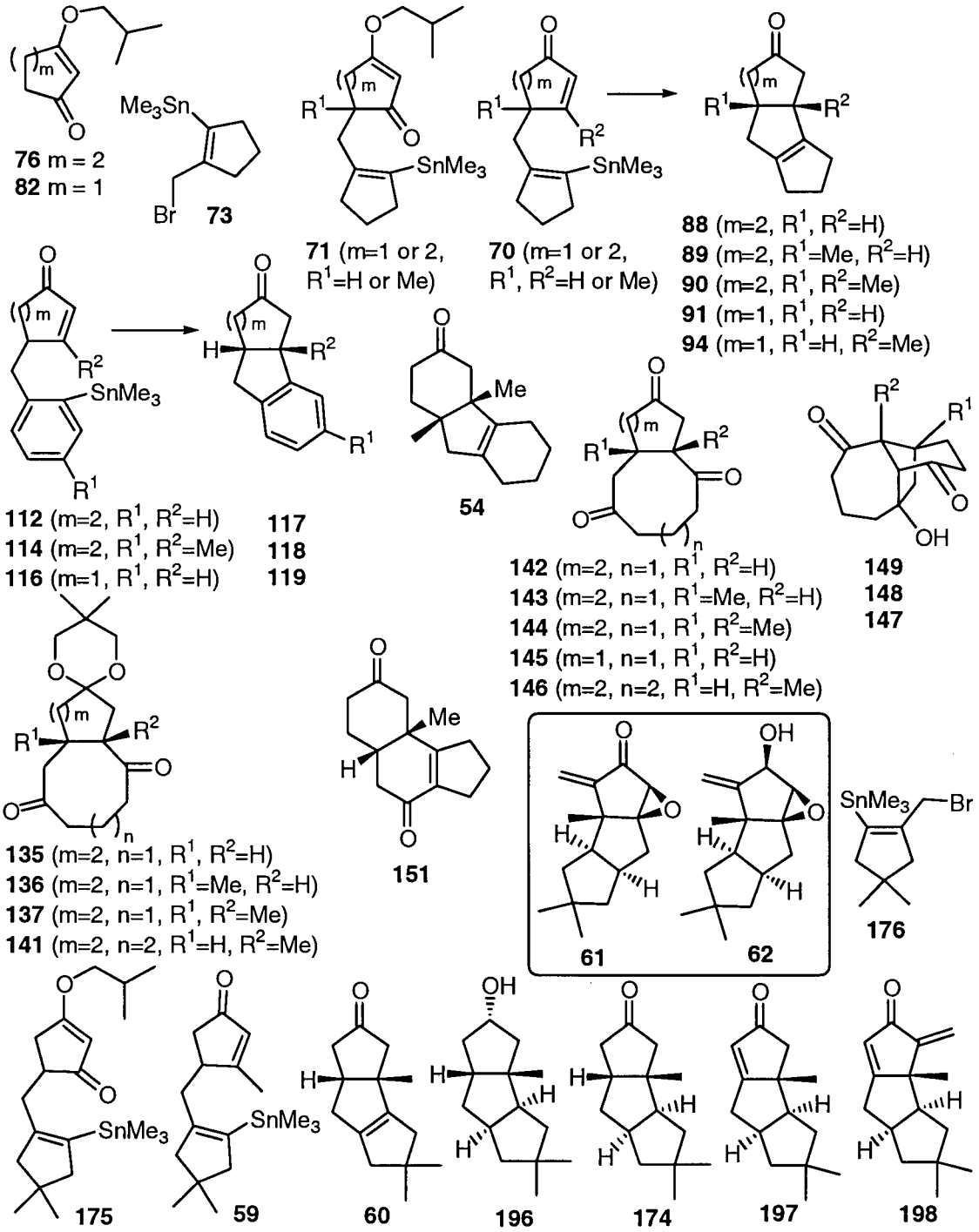
The use of Cu(I)-mediated intramolecular conjugate addition reactions of alkenyltrimethylstannane functions to α,β-unsaturated ketones to afford novel, functionalized tricyclic ketones **88-91**, and **94** was investigated. Vinylogous esters of general structure **71** were prepared by alkylation of the vinylogous esters **76** (m=2) or **82** (m=1) with the allylic bromide **73** and MeI (for **71** where R^1=Me). Compounds **71** were readily transformed via either reduction or Grignard addition, followed by hydrolysis and dehydration of the resultant products, into enones of general structure **70**. Treatment of compounds **70** with CuCN in DMSO provided tricyclic ketones **88-91** and **94**.

The analogous Cu(I)-mediated cyclization of aryltrimethylstannanes was also studied. Upon treatment with CuCN in DMSO, enones **112**, **114**, and **116** underwent cyclization to provide functionalized, tricyclic ketones **117-119**, containing an aromatic ring.

Further synthetic transformations involving olefinic ketones **88-91** and **54** were investigated. The oxidative cleavage of the tetrasubstituted double bond of **88-91** and **54** provided triones **142-146**. Similar transformation of the olefinic ketals prepared from **88-90** and **54** generated the ketal diones **135**, **136**, **137** and **141**, respectively. Interestingly, treatment of the triones **142**, **143** and **144** with a catalytic amount of *p*-toluenesulfonic acid in refluxing THF afforded products of the aldol condensation reaction (**149**, **148** and **147**, respectively). Under similar reaction conditions triketone **146** generated compound **151**.

The Cu(I)-mediated intramolecular conjugate addition reaction of alkenyltrimethylstannane functions to enones was used in a key step of the total syntheses of the triquinane natural products, (±)-1-deoxyhypnophilin **61** and the related alcohol (±)-**62**. Vinylogous ester **175** was obtained by alkylation of **82** with the allylic bromide **176**. Compound **59** was prepared by treatment of the vinylogous ester **175** with methylmagnesium bromide, followed by treatment of the resultant material with *p*-toluenesulfonic acid. Conversion of **59** into the tricyclic ketone **60** was accomplished by treatment of the former substance with CuCN in DMSO in a sealed reaction vessel. The ketone function of **60** was reduced to the α alcohol, which was used in the hydroxy-directed hydrogenation of the alkenic function to form the alcohol **196**. The alcohol

function of **196** was oxidized to provide ketone **174**. Compound **174** was converted to the enone **197**. Introduction of the α methylidene function gave the dienone **198**. Monoepoxidation of the internal olefinic function of **198** afforded the natural product (±)-1-desoxyhypnophilin (**61**). Subsequent reduction of the ketone function of (±)-**61** provided (±)-**62**.



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α	-	below the plane of a ring or 1,2-relative position
Ac	-	acetyl
anal.	-	analysis
APT	-	attached proton test
Ar	-	aryl
atm	-	atmosphere
β	-	above the plane of a ring or 1,3-relative position
Bn	-	benzyl
b.p.	-	boiling point
br	-	broad
Bu	-	butyl
Bz	-	benzoyl
°C	-	degrees Celsius
calcd	-	calculated
cat.	-	catalytic
cm	-	centimetre
COD	-	cyclooctadiene
COSY	-	(^{1}H-^{1}H) - homonuclear correlation spectroscopy
Cp	-	cyclopentadienyl
C-x	-	carbon number x
Cy	-	cyclohexyl
d	-	doublet
δ	-	chemical shift in parts per million from tetramethylsilane
DBU	-	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	-	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	-	diisobutylaluminum hydride
DMF	-	*N*,*N*-dimethylformamide
DMG	-	directed metalation group

DMS	-	dimethyl sulfide
DMSO	-	dimethyl sulfoxide
DoM	-	directed orthometalation
E^+	-	electrophile
Ed., Eds.	-	editor, editors
e.g.	-	*exempli gratia* (for example)
eq	-	equation
equiv.	-	equivalent(s)
Et	-	ethyl
Et_2O	-	diethyl ether = ether
g	-	gram
γ	-	1,4-relative position
gem	-	geminal
GLC	-	gas-liquid chromatography
h	-	hour(s)
HMBC	-	heteronuclear multiple bond coherence
HMDS	-	1,1,1,3,3,3-hexamethyldisilazane
HMPA	-	hexamethylphosphoramide
HMQC	-	heteronuclear multiple quantum coherence
hν	-	light
HRMS	-	high resolution mass spectrometry
H-x	-	hydrogen number x
Hz	-	hertz
i	-	iso
IR	-	infrared
J	-	coupling constant in hertz
$^nJ_{Sn-H}$	-	n bond coupling for tin and proton nuclei (in hertz)
KHMDS	-	potassium 1,1,1,3,3,3-hexamethyldisilazide
L	-	ligand
LDA	-	lithium diisopropylamide
LHMDS	-	lithium 1,1,1,3,3,3-hexamethyldisilazide

LTMP	-	lithium 2,2,6,6-tetramethylpiperidide
m	-	multiplet
m	-	*meta*
m-CPBA	-	*meta*-chloroperbenzoic acid
Me	-	methyl
MIC	-	minimal inhibitory concentration
min	-	minute(s)
mg	-	milligram(s)
mL	-	millilitre(s)
μg	-	microgram(s)
μL	-	microlitre(s)
mmol	-	millimole(s)
m.p.	-	melting point
MS	-	mass spectrometry
n	-	normal
NMR	-	nuclear magnetic resonance
NOE	-	nuclear Overhauser effect
p	-	page
p	-	*para*
PCC	-	pyridinium chlorochromate
pH	-	$-\log_{10}[H^+]$
Ph	-	phenyl
pp	-	pages
ppm	-	parts per million
Pr	-	propyl
pyr	-	pyridine
q	-	quartet
rt	-	room temperature
s	-	singlet
t	-	triplet
t	-	tertiary

TBAF	-	tetrabutylammonium fluoride
TBS	-	*tert*-butyldimethylsilyl
Tf	-	trifluoromethanesulfonyl, triflyl
THF	-	tetrahydrofuran
TLC	-	thin layer chromatography
™	-	trade mark
TMS	-	trimethylsilyl
TMEDA	-	*N,N,N',N'*-tetramethylethylenediamine
p-Ts	-	*para*-toluenesulfonyl, tosyl
p-TsOH	-	*para*-toluenesulfonic acid
-ve	-	negative
v/v	-	volume-to-volume ratio
•	-	coordination complex
±	-	racemic

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I. INTRODUCTION

1.1 General introduction

Synthetic organic chemistry is a sub-discipline of chemistry which deals with the construction of carbon based molecules. Since the serendipitous preparation of urea, the first synthetic organic substance, from ammonium isocynate by Wohler in 1828,[1] synthetic organic chemistry has grown and continues to grow in complexity as chemists strive to improve transformations and create increasingly more intricate structures.

It is generally accepted that synthetic organic chemists engage in two areas of academic research. Development of new methods of bond construction, improvement of the efficiency and selectivity of existing reactions, and the study of their limitations and extensions are the main goals of *methodological studies*. In the process, many novel compounds are prepared in order to assess the scope of the reaction studied. While the structure of these products is of secondary interest to the method of preparation, the diversity of compounds may serve to illustrate the generality and applicability of the method. It is usually hoped that besides shedding light on the effectiveness of the transformation, the reaction will be added to the array of methods available to organic chemists and will prove useful in a *total synthesis*, a second area of research conducted by synthetic organic chemists. The goal of any total synthesis is the preparation of a compound, often a naturally occurring substance, via a series of synthetic steps. The choice of the target can be dictated by various motives. Sometimes the compound is known to possess biological activity of interest but is only available in small amounts from natural sources. Another rationale behind a total synthesis may be the desire to unambiguously assign the structure of the isolated compound, since, usually, every transformation used in the synthetic sequence will have a predictable outcome. While the above two reasons are often used in justifying the efforts towards a synthetic target, it is also possible to conduct total synthesis solely for the intellectual and practical exercise resulting from the challenge presented by the target chosen. Whatever the reason, the total synthesis becomes a testing ground for the synthetic methods developed in

methodological studies, often proving to be one of its hardest examples. The total synthesis is additionally tied to methodological studies by the fact that, frequently, it requires an improvement in methodology or a development of a new process to accomplish the transformation. Hence, both the methodological studies and total synthesis, although they have different goals, in many instances become connected.

The field of synthetic organic chemistry is a rigorous, logical as well as highly creative science. Methodological studies, by necessity, involve a systematic approach to a problem centering on the design of test systems and the consideration of various factors affecting reactivity (e.g. amount of catalyst used, choice of solvents or reaction temperatures). The first challenge facing an organic synthetic chemist engaged in the total synthesis involves the planning of a rational synthetic scheme. *Retrosynthetic* analysis, first developed in 1960s and described by 1991 Nobel laureate E.J. Corey,[2] is a strategy for converting a target molecule into simpler structures via a series of *transforms*. A transform is an operation that simplifies the molecular complexity (breaking of bonds) or changes functional groups present and is a reverse of a synthetic reaction. This rigorous and logical approach allows the simplification of a complex target molecule into structures that are easily accessible and/or commercially available. However, in spite of a thorough analysis prior to embarking on a total synthesis project, many problems may be encountered along the way, necessitating modifications and refinements in the original plan. The unexpected twists and complications become part of the challenge and learning process, deepening the current knowledge of synthesis and molecular systems.

The advancements made in organic chemistry, both in synthetic methods and total synthesis,[3-7] would not be possible without concurrent developments in other fields. The development of chromatographic techniques allows for the rapid purification of organic compounds, as well as separation and isolation of complex mixtures of compounds. Structure determination has been greatly facilitated by spectroscopic techniques such as mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, infrared (IR) spectroscopy and X-ray crystallographic diffraction methods. Computers have made possible theoretical modeling of systems, including energy calculations and predictions of molecular conformations, as well as facile manipulation of data. Computational

chemistry has recently combined the use of computer technology with that of organic and bioorganic chemistry in the application to the structure-based drug design. A newly developed branch of synthetic chemistry is the area of combinatorial chemistry, where large libraries of compounds can be synthesized, identified and tested for biological activity due to increased automation and emergence of "robotic synthesis".

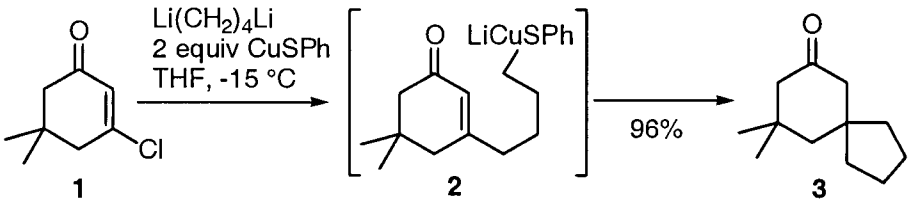
While profiting from these and other advances, organic synthetic chemistry has also had an enormous impact on other fields of science and technology. Materials science and engineering have seen the advent of polymers and their extensive use in many diverse areas from electronics to contact lenses. Synthesis of drugs and their analogues have also affected the fields of pharmaceutical and medical sciences and the pharmaceutical industry. The preparation of organic molecules has allowed the probing of functions of numerous biological systems broadening the knowledge in the areas of biochemistry, molecular biology and pharmacology. As we enter the 21st century, the field of organic chemistry, especially synthesis, is far from becoming stale and outdated. It remains in the center of technological advancement, and promises to remain an interesting and stimulating field of research.

1.2 Background: Intramolecular conjugate additions of nonstabilized carbanions

Conjugate addition reactions involving the addition of nucleophiles to activated carbon-carbon π bonds, have long been known to organic chemists as powerful synthetic processes for the construction of carbon-carbon bonds.[8] The oldest and most widely used version of this type of reaction involves the conjugate addition of *stabilized* carbanions (e.g. malonate anion, ketone enolates) to Michael acceptors.[9] The discovery of organocopper(I) reagents have initiated the use of *nonstabilized* carbanionic functions (organometallic reagents such as alkyllithiums, organozincates, organocopper) in conjugate additions[10,11] and in recent years the *intermolecular* version of this reaction has been used extensively.

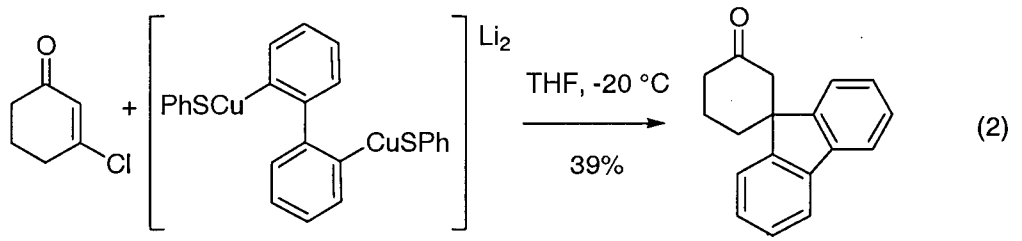
The development of the *intramolecular* conjugate additions has also been pursued as a method of ring construction. However, even though the *intramolecular* conjugate addition of *stabilized* carbanionic centers has been widely used,[12-15] the corresponding addition of *nonstabilized* carbanions is still relatively scarce. The difficulty of forming highly reactive *nonstabilized* nucleophilic species in the presence of an activated π system is the main limitation of this reaction. The examples reported in the literature of the *intramolecular* conjugate additions encompass mainly the organometallic mediated Michael addition of *primary* alkyl functions, while the addition of unsaturated (alkenyl) functions remains largely unexplored.

Among successful applications of intramolecular conjugate additions is the method of Wender and Eck[16] involving the use of organobis(cuprates) for spiroannulation (eq 1). In this transformation, the bifunctional reagent adds to the β-chloro enone **1**, generating a nonstabilized primary alkyl organocopper intermediate **2**, which undergoes intramolecular conjugate addition to the enone function forming the spiro product **3**.



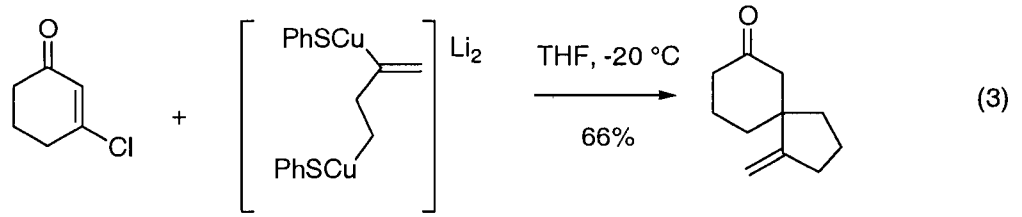
(1)

Wender and White[17] also reported the preparation and use of aryl- and alkenyl-alkyl bifunctional organocopper reagents such as **5** and **7** (eq 2 and 3). The yields of the spiro products **6** and **8** were lower (39% and 66% respectively) than with the primary alkyl bis(cuprate) employed in the previous study. It should be noted, that although in case of reagent **7** (eq 3) the order of the addition of the reagent functionalities (alkenylcuprate *versus* alkylcuprate function) is uncertain, formation of product **6** (eq 2) indicates that an aryl function undergoes intramolecular conjugate addition, albeit in a low yield.



(2)

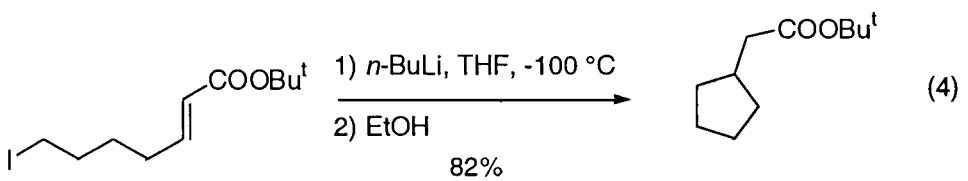
4 **5** **6**



(3)

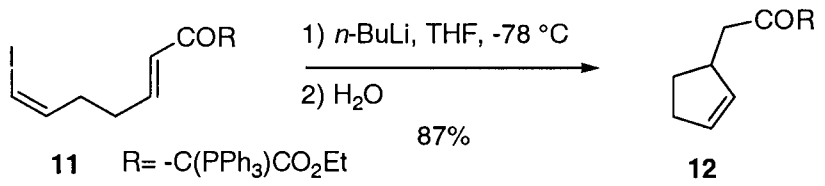
4 **7** **8**

Cooke and coworkers have developed the lithium-halogen exchange-initiated intramolecular conjugate addition reaction to unsaturated esters. Both the addition of primary alkyl[18] and alkenyl[19] functions to Michael acceptors were investigated in separate studies (eq 4 and 5). In each of these reactions, an organolithium species, generated by treatment of the iodide (**9** or **11**) with *n*-butyllithium at low temperature, adds to a Michael acceptor. In each case, the enolate species formed from the 1,4 addition is quenched by a proton source and produces the cyclized product (**10** or **12**) in very good yield.



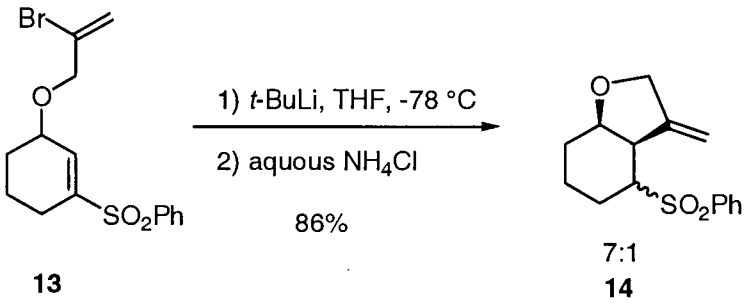
(4)

9 **10**



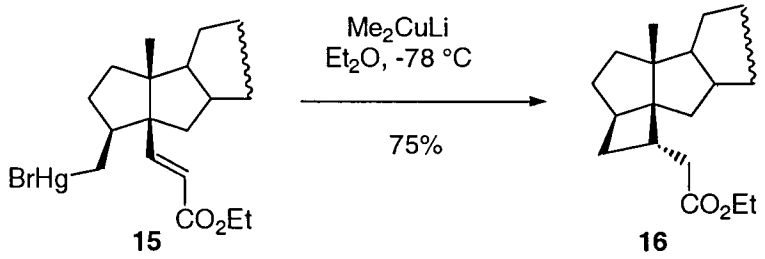
(5)

A similar approach was applied by Lee and Fuchs[20] in the synthesis of *cis*-fused bicyclic ethers. Treatment of the alkenyl bromide precursor **13** with 1.1 equivalents of *t*-butyllithium produced the cyclized product **14** (7:1 ratio of diastereomers) via the intramolecular 1,4-addition of the alkenyllithium species to an activated double bond (eq 6).



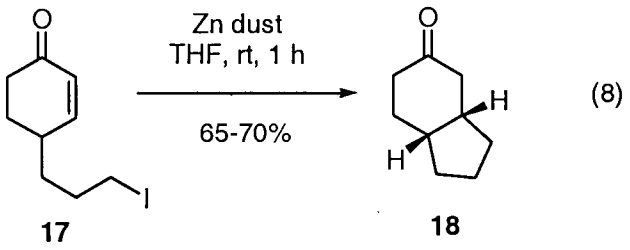
13 **14** (6)

Kocovsky and Srogl[21] have recently reported an example of a formation of a four-membered ring by intramolecular conjugate addition of an organocopper(I) species, generated from an organomercury compound **15**, to an unsaturated ester moiety (eq 7).

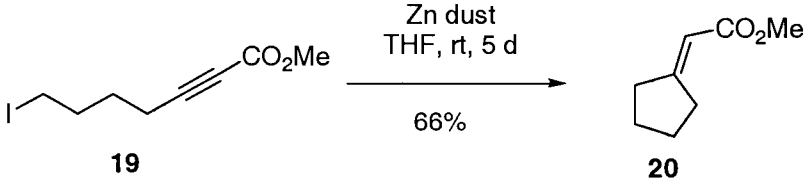


15 **16** (7)

Danheiser *et al.* [22] investigated the application of the organozinc compounds in achieving intramolecular conjugate addition with nonstabilized carbanion derivatives (eq 8 and 9). The primary iodide function of compounds **17** and **19**, for example, upon treatment with 1.1 to 4.0 equivalents of zinc dust, is thought to generate an organozinc iodide species, which undergoes 1,4 addition to the Michael acceptor. Both five- and six-membered rings can be formed using this method.



17 18 (8)

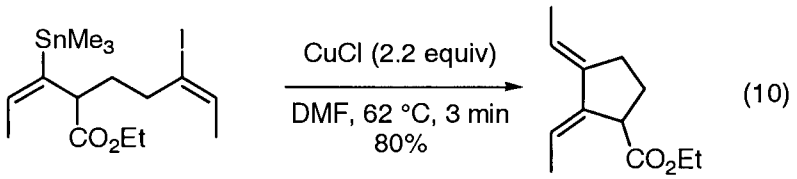


19 20 (9)

The mechanistic studies indicate that an organozinc iodide species, formed by oxidative addition of zinc metal to the iodide, cyclizes to form a zinc enolate which is quenched in a work-up step to generate the product.

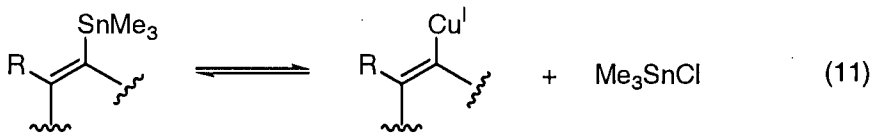
1.3 Background: Copper(I)-mediated intramolecular conjugate additions of alkenylstannane functions

One of the focuses of research in our laboratories in recent years has been copper(I) salt-mediated intramolecular conjugate additions of alkenylstannane functions to Micheal acceptors. This direction of research was initiated by the discovery by T. Wong[23,24] that treatment of a substrate such as **21** (eq 10) with copper(I) chloride affords an intramolecular cross-coupling of the alkenyltrimethylstannane and alkenyl halide functions in an efficient and stereospecific manner (eq 10). This transformation, although resembling the well known Stille coupling,[25-29] proceeds without a Pd(0) catalyst and, in some cases, is faster and cleaner than the corresponding Stille process.[23]



21 **22** (10)

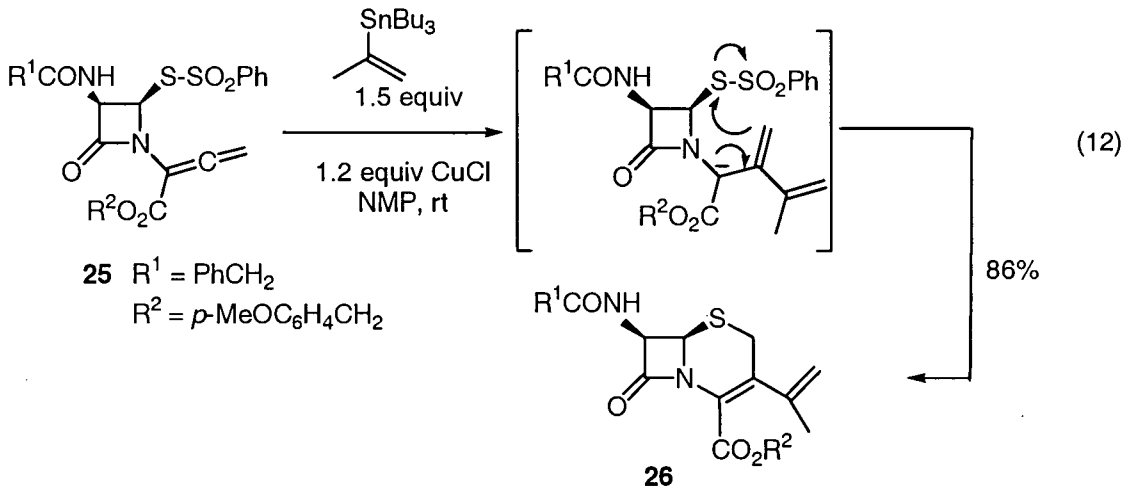
Further experiments[24] have demonstated that at least two equivalents of copper(I) chloride are required for the coupling to proceed expediently and efficiently. With one equivalent, the reaction did not go to completion, while 1.5 equivalents produced good yields, but in many cases extended reaction times were required. Mechanistic studies have indicated that the coupling process is initiated by the transmetalation between the alkenylstannane function and the copper(I) salt, generating an intermediate alkenylcopper(I) species and trimethylstannyl chloride (eq 11). While transmetalation of alkenic stannanes by organocopper reagents to form organocuprates had been reported,[30] a process of transmetalation with an inorganic copper(I) salt had not been previously observed.



23 **24** (11)

Convincing evidence for this mechanistic proposal was presented in a study by Liebeskind and coworkers,[31] who monitored by ^{119}Sn NMR spectroscopy the reaction of an alkenyltributylstannane and phenyltributylstannane with 1 equivalent of copper(I) iodide in a polar, aprotic solvent (NMP, DMF). The consumption of the alkenylstannane was observed with the formation of tributylstannyl iodide in the process. It was proposed that the second product of the reaction is likely to be the alkenylcopper(I) species. Further investigation by Liebeskind and Allred[32] into the copper(I) salt-mediated cross-coupling of organostannanes with organic iodides showed that the addition of a tributylstannyl halide hindered the progress of the reaction indicating that the transmetalation of the stannane function by copper halide is a reversible process. This observation explains the need for the use of 2 equivalents of CuCl in Wong's work in order to drive the coupling process to completion.

A report by Tanaka *et al.*[33] described the use of copper(I) chloride promoted *intermolecular* conjugate addition of alkenylstannane compounds to allenecarboxylates as part of the synthesis of cephalosporins (eq 12).



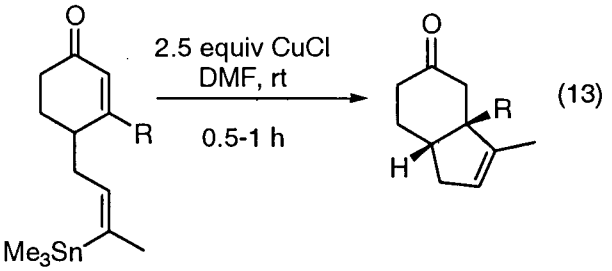
25 $R^1 = PhCH_2$
$R^2 = p\text{-}MeOC_6H_4CH_2$

26

(12)

These observations provided the impetus for the study, in our laboratories, of copper(I)-mediated *intramolecular* conjugate additions of alkenyltrimethylstannane functions to Michael acceptors. The bulk of the work to date has concentrated on the conjugate additions of alkenyltrimethylstannane functions to α,β-unsaturated ketones and α,β-alkynic esters.

Recent investigations by McEachern and Burns[34-36] into the copper(I)-mediated intramolecular Michael additions of alkenyltrimethylstannanes to α,β-unsaturated ketones demonstrated that treatment of substrates **27-30** with 2.5 equivalents of copper(I) chloride in dry DMF at room temperature resulted in the formation of the *cis*-fused bicyclo[4.3.0]nonenone derivatives **31-34**. The process was rapid and efficient with substrates **27** and **28**. However, sterically more bulky groups at the β-position of the enone (substrates **29** and **30**) resulted in a lower yields of the cyclized products (**33** and **34**) and formation of substantial amounts of uncyclized chloro- and protio-destannylated by-products (i.e. **29** and **30** where the Me_3Sn- group was replaced by -Cl or -H).[35]



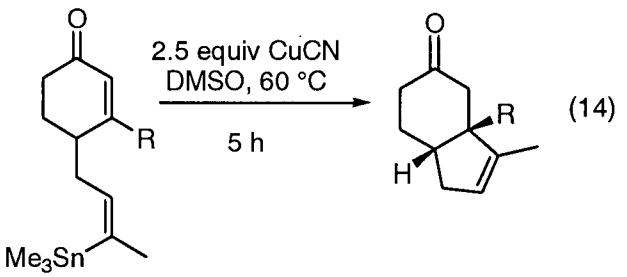
(13)

27 R = H
28 R = Me
29 R = Et
30 R = *i*-Pr

31 96%
32 82%
33 48%
34 15%

The use of 2.5 equivalents of CuCl was required for the conversion of **27** into **31** to proceed to completion in a minimum amount of time. With 1.0 equivalent of copper(I) chloride, the conversion was sluggish (18 h), while the use of a catalytic amount of CuCl (0.1 equivalents) required 48 h and temperature of 60 °C for the reaction to reach completion.

Further investigations showed that treatment of substrates **28-30** with 2.5 equivalents of CuCN in DMSO at 60 °C produced results superior to those derived from the use of CuCl. Although, the CuCN-mediated reactions generally require longer reaction times and elevated temperatures to reach completion within a reasonable time periods, substantially better yields (compared to the CuCl-mediated reactions) were obtained with substrates containing more bulky R groups (R = Et, *i*-Pr, **29** and **30**) (eq 14).[35]

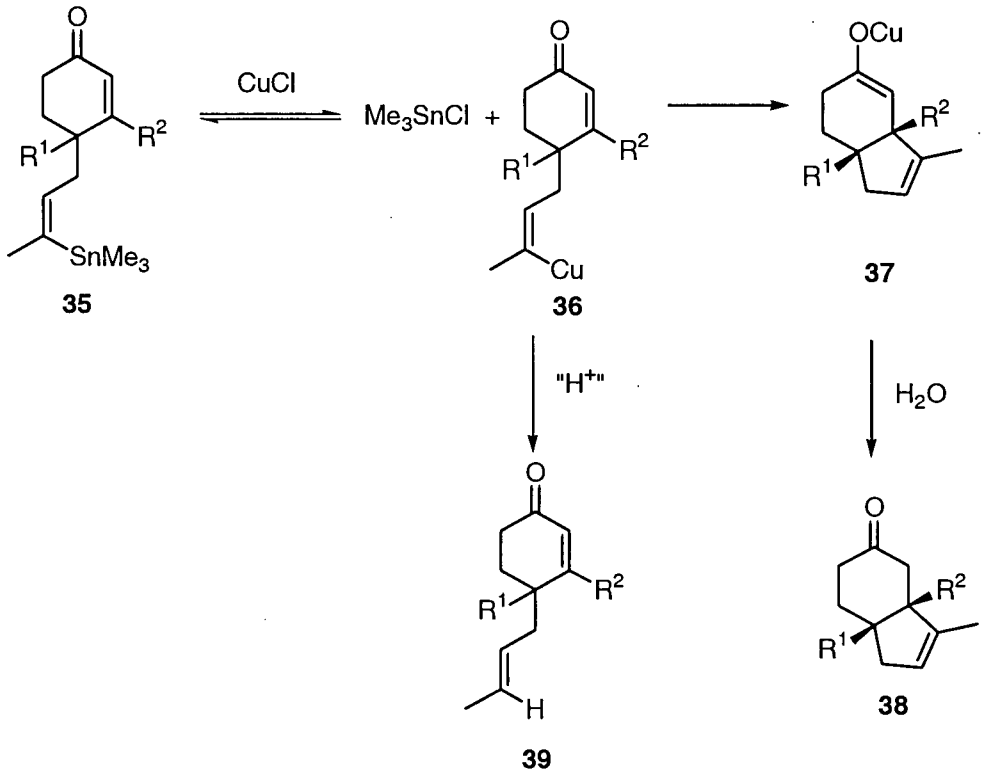


(14)

27 R = H
28 R = Me
29 R = Et
30 R = *i*-Pr

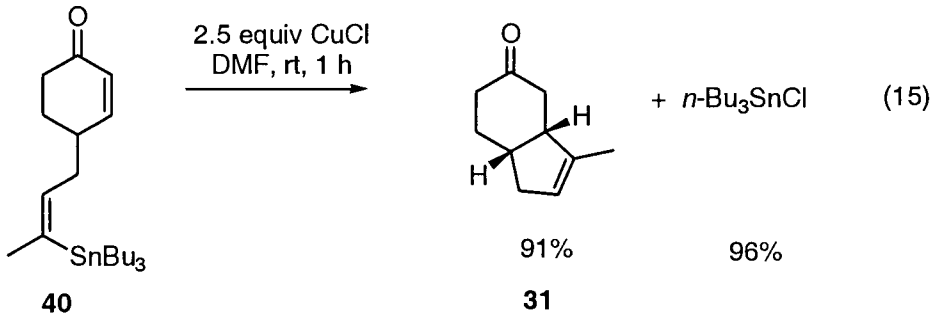
31 94%
32 92%
33 91%
34 73%

A possible mechanistic pathway has been proposed for the copper(I) chloride-mediated intramolecular conjugate additions (Scheme 1) and it is believed that a similar mechanism occurs when CuCN is used in place of CuCl.[35] The initial step is proposed to be a reversible transmetalation between the alkenyltrimethylstannane fuction of **35** and copper(I) chloride that generates trimethylstannyl chloride and the alkenylcopper(I) intermediate **36**. The alkenylcopper(I) function of the intermediate **36** then adds in a 1,4 fashion to the α,β-unsaturated ketone moiety to generate the copper(I) enolate **37**, which, upon work-up, forms the cyclized product **38**. The intermediate alkenylcopper(I) species **36** may also react with a proton source ("H^+") prior to cyclization, thus generating the protiodestannylated, uncyclized product **39**. The predominant pathway would be determined by the relative rates of the two processes.



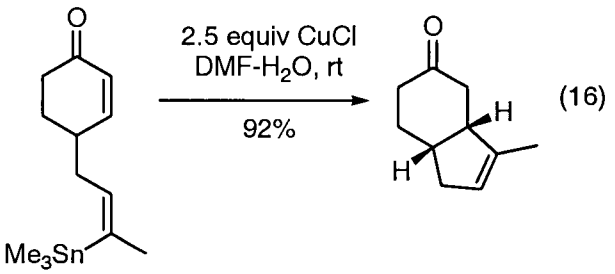
Scheme 1

Several experiments were carried out to support this mechanistic proposal.[35] First, the amount of trialkylstannyl chloride produced in the cyclization reaction was quantified. Since Me_3SnCl reacts rapidly with water, a substrate containing a Bu_3Sn function (**40**, eq 15) was studied. In this case, 0.96 equivalents of *n*-Bu_3SnCl was isolated, supporting the prediction that 1 equivalent of trialkylstannyl chloride should be produced per equivalent of the starting material consumed (eq 15).

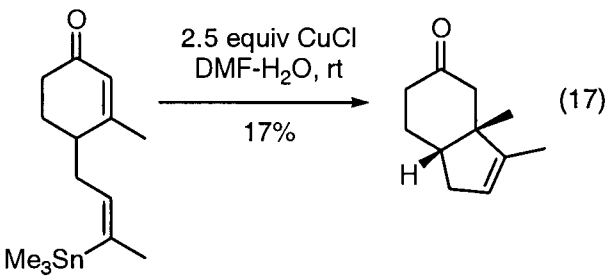


Moreover, it was determined that the addition of *n*-Bu_3SnCl to the reaction mixture prior to the CuCl, inhibits the conjugate addition. This observation is in agreement with the results of previous experiments reported by Liebeskind.[31]

Another aspect of the proposed mechanism is that a proton source is necessary for the formation of the protiodestannylated compound **39** (see Scheme 1). It was suggested that even though DMF and DMSO were dried prior to use,[37] the extreme hygroscopicity of these solvents makes it possible that small amounts of moisture could be present. The cyclization reaction was repeated with substrates **27** and **28** in the presence of water (10:1 DMF-H_2O). The yield of product **31** was not greatly affected; however, cyclized product **32** was obtained in only 17% yield and was accompanied by a large amount (63%) of protiodestannylated material.[35]



27 **31** (16)

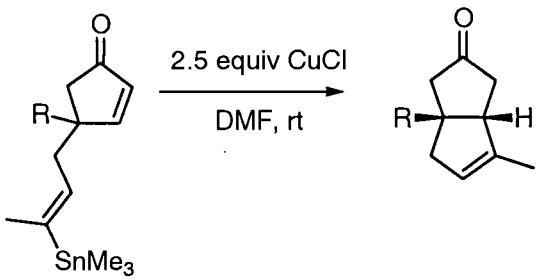


28 **32** (17)

It was suggested that the intramolecular conjugate addition step with hindered substrates is relatively slow, allowing the protonation of the intermediate alkenylcopper(I) species by water to occur in preference.

Up to this point, most of the work involving the intramolecular copper(I)-mediated conjugate additions to enones had been limited to substrates in which the enone was incorporated into a 6-membered ring. The only exceptions involved the

preparation of the bicyclo[3.3.0]oct-6-en-3-ones **43** and **44** by P.A. Burns, as shown in eq 18.[34]

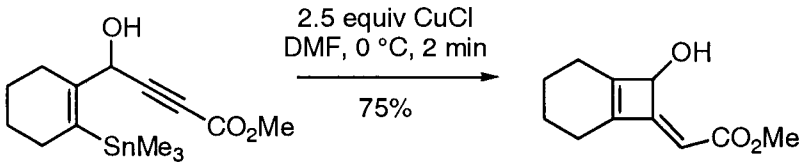


(18)

41 R = H
42 R = Me

43 76%
44 77%

The methodology was also extended to include intramolecular copper(I) chloride-mediated conjugate additions of alkenyltrimethylstannane and aryltrimethylstannane function to the triple bonds of α,β-alkynic esters.[38,39] To date, various functionalized cyclobutane derivatives (e.g. **45** → **46**, eq 16) were prepared via this method in good to excellent yields.

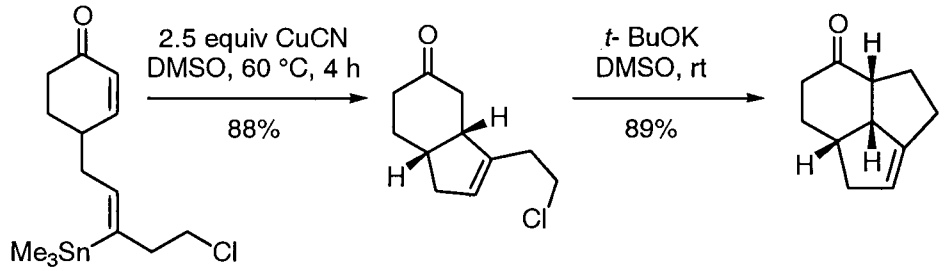


(19)

45 **46**

1.4 Proposals

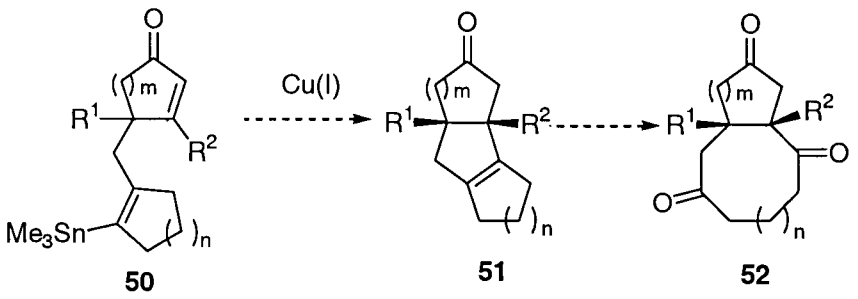
The development of the intramolecular copper(I)-mediated conjugate addition methodology opened doors to many extensions, which could allow a facile preparation of fused, functionalized carbocycles. This has already been demonstrated by the synthesis of tricyclic compounds (e.g. **49**, Scheme 2) by base-promoted intramolecular alkylations of substrates (e.g. **48**) that had been produced by the intramolecular copper(I)-mediated conjugate additions of alkenyltrimethylstannane functions to enone Michael acceptors (e.g. **47**).[40]



47 **48** **49**

Scheme 2

Variations in the structure of the group containing the alkenylstannane function, as well as changes in the size of the ring containing the enone function, would theoretically allow the preparation of a variety of functionalized compounds with interesting carbon skeletons. In particular, it was envisaged that precursors such as **50** would generate, upon treatment with a copper(I) salt, tricyclic compounds of general structure **51**. The tetrasubstituted double bond of compounds **51** could then serve as a handle in further synthetic transformations. For instance, oxidative cleavage of the alkene would generate functionalized bicycles **52** in which a relatively small ring (5- or 6-membered, m = 1 or 2) is fused to a medium sized ring (8- or 9-membered, n = 1 or 2) (Scheme 3).

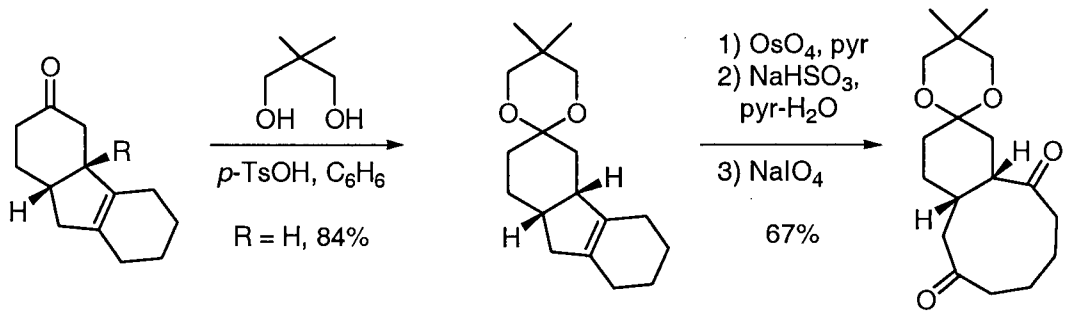


50 **51** **52**

Scheme 3

Preparation of such ring systems is of interest because many natural products contain as part of their structure medium-sized rings (especially 8-membered)[41] fused to 5- or 6-membered carbon rings. Many synthetic efforts have in the past been directed towards the synthesis of such ring systems.[42]

It has been shown by preliminary studies by D. J. Wallace[43] that tricyclic systems of general structure **51** can be prepared in good yields. Attempts were made to oxidatively cleave the double bond of compound **55** with the use of osmium tetroxide to form the functionalized bicyclo[7.4.0]dodecane compound **56** (Scheme 4). However, use of this reagent proved to be problematic since the oxidative cleavage was successful only when a stoichiometric amount of OsO_4 was used. Furthermore, the reaction gave poor results when attempted directly on the olefinic ketone **53** and it was found necessary to convert the carbonyl function into a ketal (**53** → **55**) prior to oxidation (Scheme 4). It was also found that efforts to effect cleavage of more substituted substrates (e.g. **54** or the corresponding ketal) failed as well.



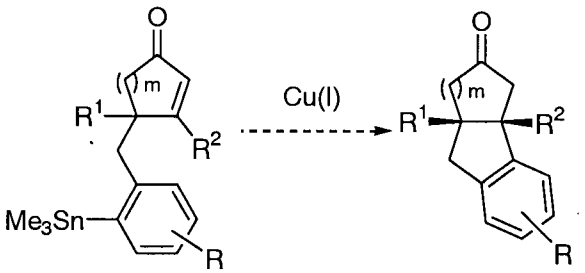
53 R = H
54 R = Me

55 **56**

Scheme 4

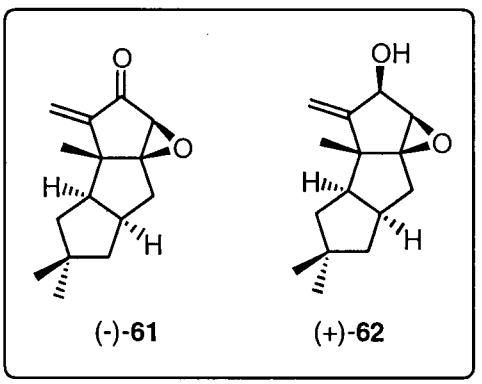
Tricyclic ketones of general structure **58**, containing an *aromatic* ring, could theoretically be prepared via copper(I)-mediated intramolecular conjugate additions of

substrates such as **57** (eq 20), transformations analogous to that depicted in Scheme 3. The cyclization precursors of general structure **57** would contain an *aryl*trimethylstannane function, which in theory could also be functionalized (various R groups), thus providing a route to more elaborate carbon frameworks. A short investigation of this process was going to be attempted as an extension of the Cu(I)-mediated cyclization method.



57 **58** (20)

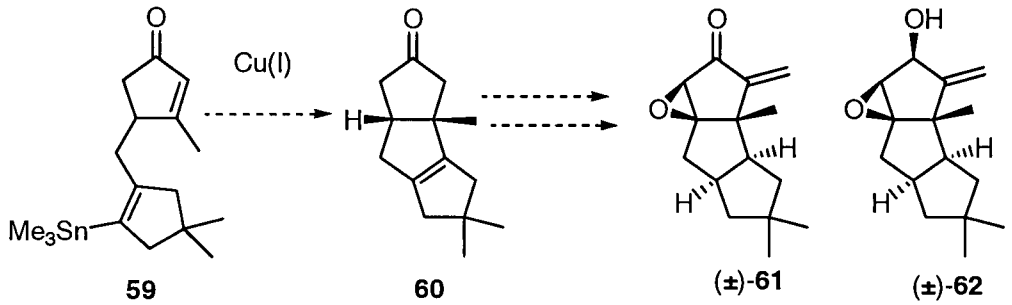
In addition to explorations into extensions to the conjugate addition method (Scheme 3, eq 20), it was proposed to apply the methodology to a total synthesis of a natural product. The target molecules chosen, (±)-1-desoxyhypnophilin **61** and the corresponding alcohol (±)-**62**,[44] have a linear triquinane skeleton similar to compound **51** (Scheme 3, m, n = 1).



(-)-**61** (+)-**62**

The key step of the synthesis was envisaged to be a copper(I)-mediated intramolecular conjugate addition reaction involving the key intermediate **59**, as shown in

Scheme 5.* The resultant product **60** was envisaged to be a suitable precursor for the synthesis of (±)- **61** and (±)- **62**.



Scheme 5

(-)-1-Desoxyhypnophilin (**61**) and its corresponding alcohol (+)-**62** are new fungal metabolites isolated from *Lentinus crinitus* widespread in Eastern Africa.[44] They belong to a class of sesquiterpenoids with a hirsutane skeleton **63**.[45] The hirsutane class of compounds possess a triquinane, tricyclo[6.3.0.$0^{2,6}$]undecane, framework with the *cis-anti-cis* fusion. Members of this family include hirsutene **64**, hypnophilin **65**, hirsutic acid-C **66**, complicatic acid **67** and coriolin **68**.

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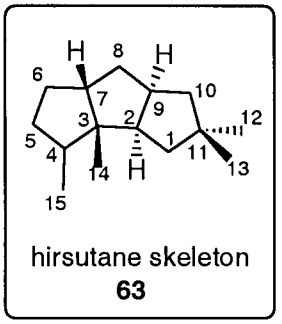
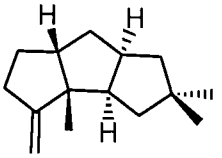
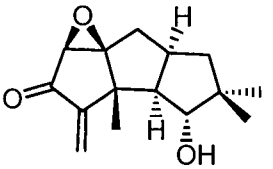
* The numbering system normally employed for hirsutane sesquiterpenoids is used in naming of compounds **61** and **62** in the text of the thesis. The experimental section of this thesis contains IUPAC names of both **61** and **62** as well as IUPAC names of all of the synthetic intermediates. It should be noted that throughout this thesis the structures of the synthetic *racemic* compounds **61** and **62** are drawn as the enantiomers of the isolated compounds (-)-**61** and (+)-**62**. This was done in order to keep the representation of the Cu(I)-mediated cyclization products (such as **60**, see Scheme 5) in agreement with the convention established in the methodology part of this work.



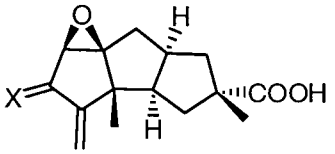
hirsutane skeleton
63



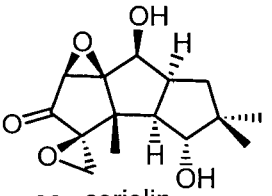
hirsutene
64



hypnophilin
65



66 X = H, OH; hirsutic acid-C
67 X = O, complicatic acid



68 coriolin

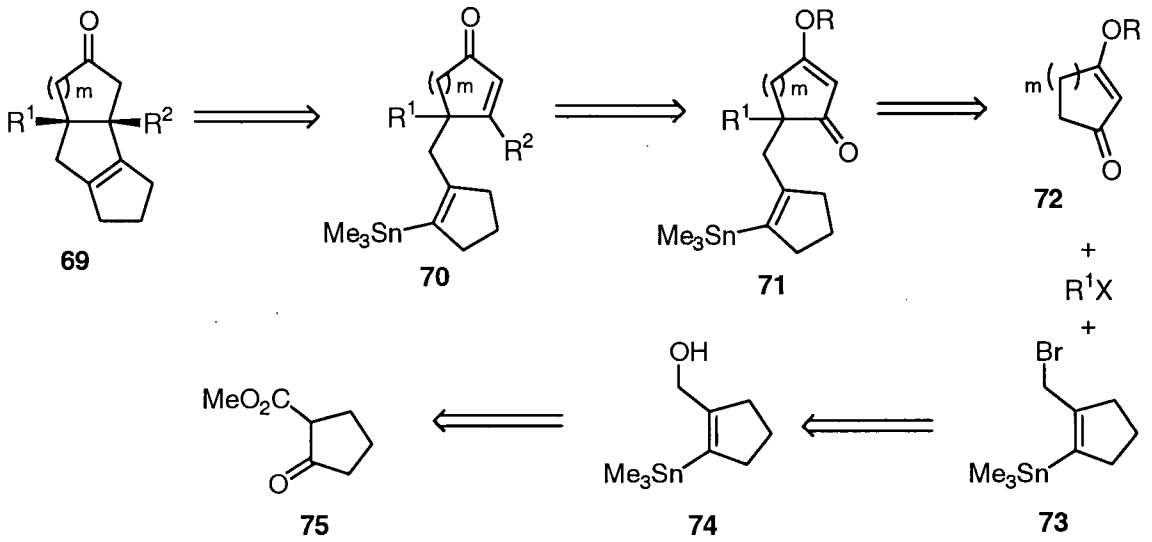
The hirsutane-type sesquiterpenoids have attracted and continue to attract the interest of synthetic chemists due to their biological activities and extensive functionalization. Over the years, special interest has been directed towards the synthesis of the highly oxygenated substances coriolin (**68**)[45,46] and hypnophilin (**65**).[45] Especially in the 1980s and 1990s, the hirsutanes have been a testing ground for new cyclopentane annulation methods. Discussion of these syntheses is beyond the scope of this thesis, and the reader is directed to a recent review on the polyquinane synthesis[45] for more information. Selected approaches are briefly outlined in the discussion section of this thesis.

II. RESULTS AND DISCUSSION

2.1 Copper(I) cyanide-mediated intramolecluar conjugate additions of alkenyltrimethylstannanes to α,β-unsaturated ketones.

2.1.1 Preparation of the cyclization precursors

In order to investigate the use of the Cu(I)-mediated intramolecular conjugate additions in the synthesis of tricyclic ketones of general structure **69**, it was necessary to prepare 4-substituted cyclopent-2-en-1-ones **70** (m = 1) and cyclohex-2-en-1-ones **70** (m = 2). A possible route to the synthesis of the required cyclohexenone and cyclopentenone systems was envisaged to involve an adaptation of the method developed by Stork[47,48] for the synthesis of 4-alkylcyclohex-2-en-1-ones (Scheme 6). Enones of general structure **70** could be obtained from the vinylogous esters **71** by treatment of the latter compounds with DIBAL-H or Grignard reagents (R^2MgBr) and subsequent treatment of the resultant products with aqueous acid. The vinylogous esters **71** should be attainable by sequential alkylations of **72** with the allylic bromide **73** and an alkyl halide (R^1X). The five-membered ring allylic bromide **73** has been previously prepared in our laboratories from the allylic alcohol **74**, which in turn is accessible from the commercially available β-keto ester **75**.[39,49,50]



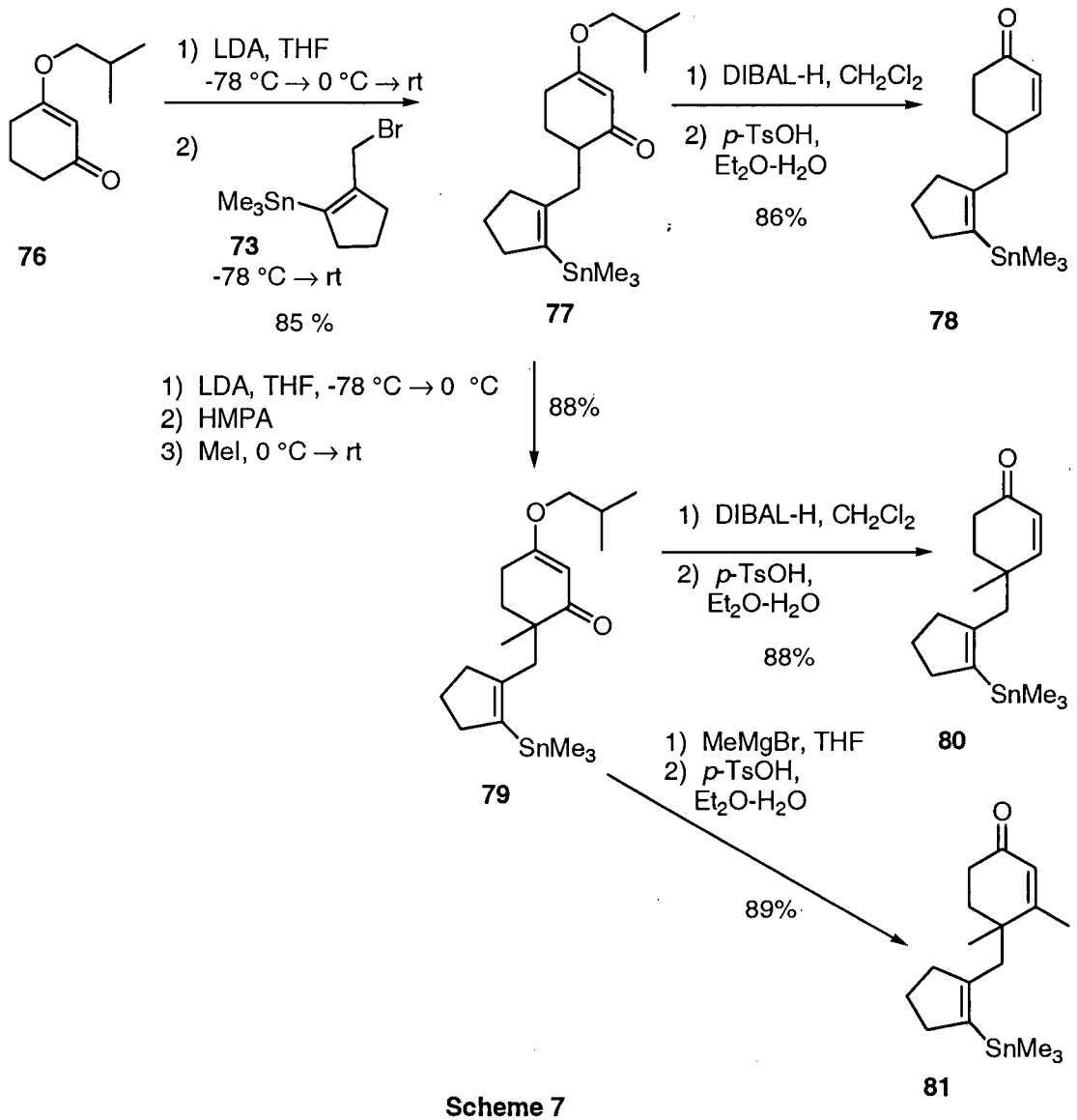
Scheme 6

Since previous work in this area in our laboratories had shown that Stork's method is viable to prepare 4-substituted cyclohex-2-en-1-ones, it was decided to first synthesize the substituted cyclohex-2-en-1-ones **70**, where m = 2 and R^1 and R^2 were either H or Me.

Alkylation of the enol ether **76**[51] was accomplished by treatment of a cold solution of **76** in THF with LDA, followed by the addition of the bromide **73** (see Scheme 7). The solution was allowed to warm to room temperature and, after aqueous work-up and flash chromatography of the crude product on silica gel, the vinylogous ester **77** was obtained in 85% yield. The structure of the alkylated product **77** was confirmed by spectroscopic methods. The ^{1}H NMR spectrum displayed a 6-proton doublet at δ 0.94 (J = 6.5 Hz), characteristic of the methyl groups of the isobutyl unit. A one-proton singlet at δ 5.30 was indicative of the alkenyl proton of the vinylogous ester moiety. The characteristic 9-proton singlet at δ 0.10 confirmed the presence of the Me_3Sn group. This signal was accompanied by small satellite doublets with an average coupling constant of 53 Hz ($^2J_{Sn\text{-}H}$), which result from the two bond coupling of the methyl protons to NMR active ^{117}Sn and ^{119}Sn isotopes.[52] The ^{13}C NMR spectrum of **77** showed the Me_3Sn carbon signal at δ -9.2. Resonances at δ 102.3, 138.3, 151.1 and 177.1 can be assigned to alkenyl carbons and a ketone carbonyl signal was present at δ 200.8. The ^{1}H NMR and ^{13}C NMR spectra also contained all other expected signals. The IR spectrum of compound **77** exhibited an absorption band at 1659 cm^{-1}, characteristic of

the carbonyl stretching frequency of a six-membered ring enone, and at 1610 cm^{-1}, which typically results from an alkene stretching absorption. Finally, the high resolution mass spectral determination confirmed the molecular mass of the vinylogous ester **77**.

Conversion of compound **77** into the enone **78** was achieved by treatment of the former substance with DIBAL-H, followed by acid-catalyzed hydrolysis and dehydration (*p*-TsOH, H_2O, Et_2O) of the resulting alcohol (Scheme 7).[47,48,53] Work-up and purification of the resulting crude oil by flash chromatography on silica gel afforded the desired enone **78** in 86% yield. Spectroscopic data confirmed the structure of the product. The two signals for the alkenyl protons of the enone function appeared at δ 5.96 for the α proton and at δ 6.78 for the β proton and showed mutual coupling of 10.0 Hz. The ^{13}C NMR spectrum showed the resonance at δ 199.8, typical of the carbonyl resonance of a six-membered ring enone. Four alkenic carbon signals were also visible, two of which had negative phase in the APT experiment (δ 129.0 and δ 154.4) and therefore could be assigned to the α and β carbons of the enone **78**, respectively.



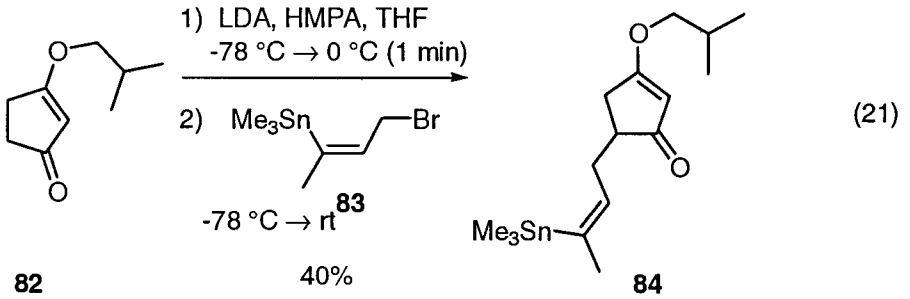
Scheme 7

Methylation of the vinylogous ester **77** by sequential treatment with LDA and methyl iodide in the presence of HMPA, gave compound **79** in 88% yield. The additional 3-proton singlet in the ^{1}H NMR spectrum of **79** at δ 1.06 confirmed the incorporation of the methyl group. Subjection of this material to reduction by DIBAL-H, followed by treatment of the resultant alcohol with aqueous acid (*p*-TsOH), afforded the enone **80** in 88% yield. In the ^{1}H NMR spectrum of **80**, two signals for the alkenyl protons of the enone function appeared at δ 5.84 for the α proton and at δ 6.78 for the β proton and showed mutual coupling of 10.0 Hz. The ^{13}C NMR spectrum showed the carbonyl resonance at δ 199.5. Four alkenic carbon signals were also visible, two of

which had negative phase in the APT experiment (δ 127.1 and δ 159.7, CH) and therefore could be assigned to the α and β carbons of the enone, respectively.

Alternatively, treatment of the vinylogous ester **79** with MeMgBr, followed by acid-catalyzed dehydration-hydrolysis of the resultant tertiary alcohol with *p*-TsOH resulted in the formation of the enone **81** in 89% yield. The ^{1}H NMR spectrum of **81** showed, in addition to the 9-proton singlet for the methyls of the Me_3Sn group at δ 0.14, two other 3-proton singlets at δ 1.17 and 1.94 attributed to the methyl groups at the β and γ positions. The ^{13}C NMR spectrum displayed a resonance at δ 199.2 characteristic of a cyclohexenone carbonyl. Two alkenic carbon signals of the enone function were visible at δ 127.2 (CH) and 168.8 (C).

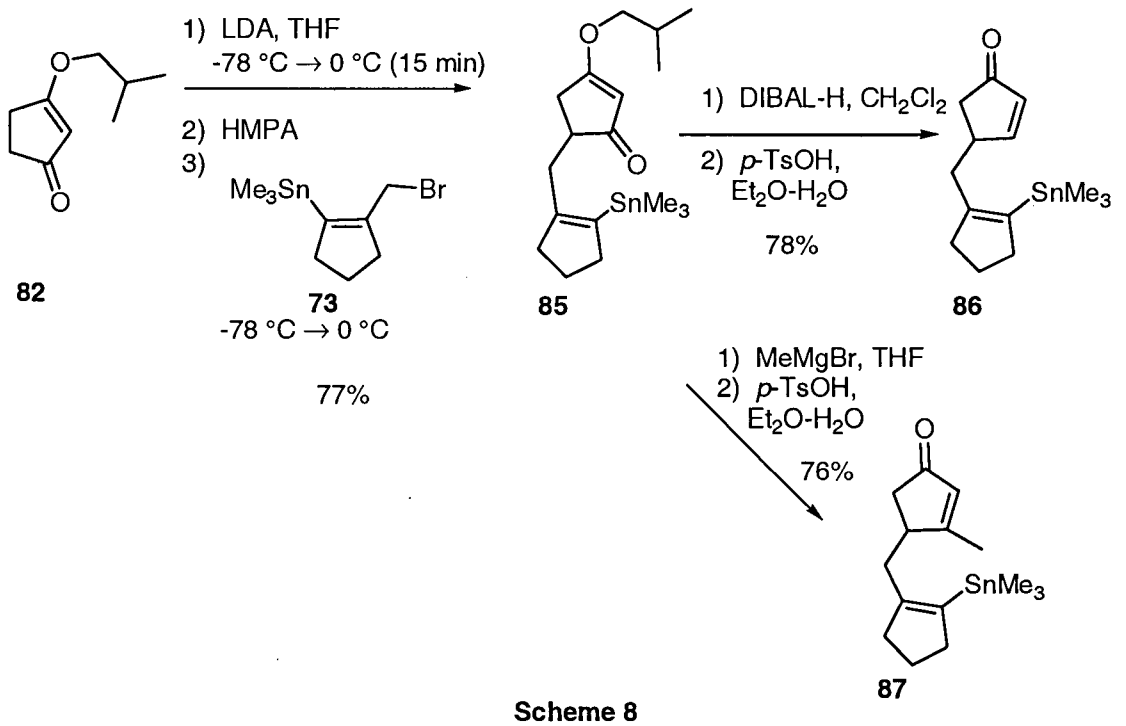
Suitable reaction conditions for the formation of the enolate anion of the vinylogous ester **82** have been reported[36,54] for the preparation of the 4-substituted cyclopentenone derivative **84** (eq 21). The vinylogous ester **82** was treated with LDA in THF in the presence of HMPA at -78 °C for 20 min, and the solution was then warmed briefly to 0 °C. The allylic bromide **83** was added at -78 °C and the solution was warmed to room temperature to afford, after work-up and purification of the crude product, the alkylated product **84** in 40% yield. It was noted that, in the absence of HMPA, the reaction proceeded poorly and if the enolate solution was not warmed to 0 °C prior to the addition of the electrophile, the yield decreased substantially.



(21)

When the above conditions were employed for the alkylation of **82** with the allylic bromide **73**, the yield of the alkylated product **85** was only ~ 20% (Scheme 8). Several optimization experiments revealed that the best yield was obtained when the

vinylogous ester **82** was treated with LDA in THF at -78 °C for 30 min and then the mixture was then allowed to warm to 0 °C for 15 min. Over the 15 min of warming, the solution slowly turned from pale yellow to dark orange in colour. The reaction mixture was subsequently recooled to -78 °C, and HMPA and a solution of the bromide **73** in THF were added sequentially. The solution was then warmed to 0 °C. Under these reaction conditions, the isolated yield of the alkylated compound **85**, after work-up and purification, was 77%. The structure of **85** was confirmed by spectroscopic methods. The ^{1}H NMR spectrum showed the presence of the Me_3Sn moiety, evident by the 9-proton singlet at δ 0.09. The spectrum also displayed a 6-proton doublet at δ 0.96, due to the methyl groups of the isobutyl ($(\underline{CH_3})_2$-CH-CH_2), as well as a doublet at δ 3.70 due to methylene protons adjacent to the oxygen (-O$\underline{CH_2}$-CH).



Scheme 8

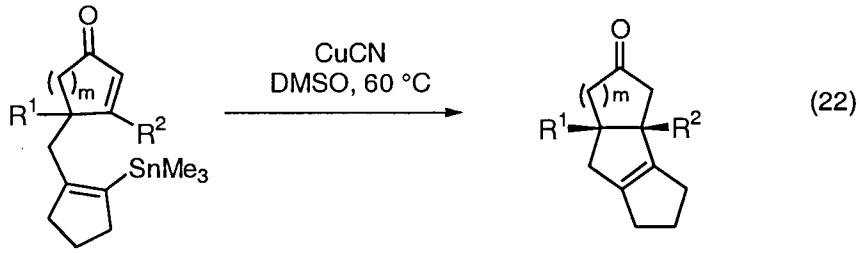
Subjection of compound **85** to reduction by DIBAL-H, followed by acid-catalyzed hydrolysis and dehydration of the resultant product, afforded the enone **86** in 78% yield (Scheme 8). The IR spectrum of compound **86** exhibited a carbonyl stretching band at 1717 cm^{-1} and an alkene stretch at 1612 cm^{-1}, characteristic of a five-membered ring enone moiety. In the ^{1}H NMR spectum of **86** the two signals for the alkenyl protons

of the enone function appeared at δ 6.12 for the α proton and at δ 7.56 for the β proton and showed mutual coupling of 6.0 Hz. The ^{13}C NMR spectrum showed the carbonyl carbon resonance at δ 209.6. Four alkenic carbon signals were also visible, two of which had negative phase in the APT experiment (δ 133.6 and δ 168.2), and therefore could be assigned to α and β carbons of the enone, respectively.

Reaction of the vinylogous ester **85** with MeMgBr, followed by treatment of the acquired product with *p*-TsOH, converted compound **85** into the enone **87** in 76% yield. The successful incorporation of the methyl group was confirmed by the ^{1}H NMR spectrum, which displayed a 3-proton singlet at δ 2.09. In addition only a single 1-proton signal at δ 5.87 attributed to the alkenyl proton was observed. All other spectroscopic data were also consistent with the assigned structure. The molecular mass was confirmed by high resolution mass spectral analysis on the molecular ion.

2.1.2 Copper(I) cyanide-mediated cyclizations

The enones **78**, **80**, and **81** underwent rapid and efficient conversion to the corresponding *cis*-tricyclo[6.4.0.$0^{2,6}$]dodec-2(6)-en-11-ones **88-90** (eq 22, Table 1, entries 1-3) upon treatment with 2.5 equivalents of copper(I) cyanide in DMSO at 60 °C at a substrate concentration of 0.05 M. Slightly longer times were necessary for the reaction to reach completion when a methyl group was present at the β position of the enone function of the starting material (substrate **81**; compare entries 1-3, Table 1).



(22)

78, 80, 81, 86 **88-91**

Table 1. Copper(I) cyanide-mediated intramolecular conjugate additions of enones **78**, **80**, **81** and **86** (eq 22)[a]

Entry	Substrate	m	R^1	R^2	Equiv CuCN	Time (h)	Product	Yield (%)
1	**78**	2	H	H	2.5	4	**88**	94
2	**80**	2	Me	H	2.5	4	**89**	91
3	**81**	2	Me	Me	2.5	6	**90**	87
4	**86**	1	H	H	5.0	17	**91**	80[b]

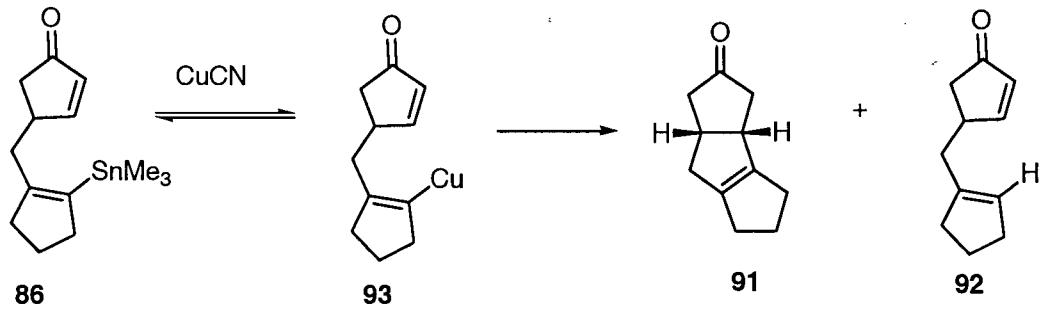
[a]All reactions were carried out at 60 °C using commercial CuCN.
[b]~6% of uncyclized, protiodestannylated material was also isolated (MS, ^{1}H NMR).

Ketones **88-90** were obtained in excellent yields (87-94%) after aqueous workup and purification of the crude products by flash chromatography on silica gel, followed by Kugelrohr distillation of the resultant oils under reduced pressure (0.1-0.2 torr). Evidence for the formation of compounds **88**, **89** and **90** was provided by the IR and NMR spectra of these materials. For instance, the IR spectrum of the tricyclic compound **90** exhibited a carbonyl stretching absorption at 1715 cm^{-1}, typical of a cyclohexanone

carbonyl function. The ^{1}H NMR spectrum of **90** showed two 3-proton singlets at δ 0.98 and 1.15 due to the angular methyl groups, as well as two multiplets in the aliphatic region between δ 1.76 and 2.39, corresponding to a total of 14 protons, in agreement with the assigned structure. In the ^{13}C NMR spectrum, a signal for the carbonyl carbon was seen at δ 214.0, while the two alkene carbon signals appeared at δ 141.9 and 151.2. Additionally, the molecular mass was confirmed by high resolution mass spectroscopic analysis on the molecular ion. The *cis* fusion of the formed ring system was not proven spectroscopically on the tricyclic compounds, but was assigned by analogy to previous work.[34] The structures of compounds **88** and **89**[43] were confirmed in a similar manner.

Intramolecular cyclization of the enone **86** (Table 1, entry 4) required the use of 5.0 equivalents of CuCN and an increase of the reaction time to 17 h for the conversion to proceed in 80% yield. When 2.5 equivalents of CuCN were used, the reaction was sluggish and only a 55% yield of the cyclized product **91** was obtained after a reaction time of 17 h. The major side product (^{1}H NMR and MS analysis) was the protiodestannylated, uncyclized material **92** (see Scheme 9). The increased difficulty of the cyclization onto a preexisting five-membered ring enone, as opposed to the six-membered ring enone, is most likely due to the fact that **91**, a linearly fused triquinane, is considerably more strained than the tricycles **88-90**. Consequently, the transition state leading to **91** would be expected to be higher in energy than those producing **88-90**.

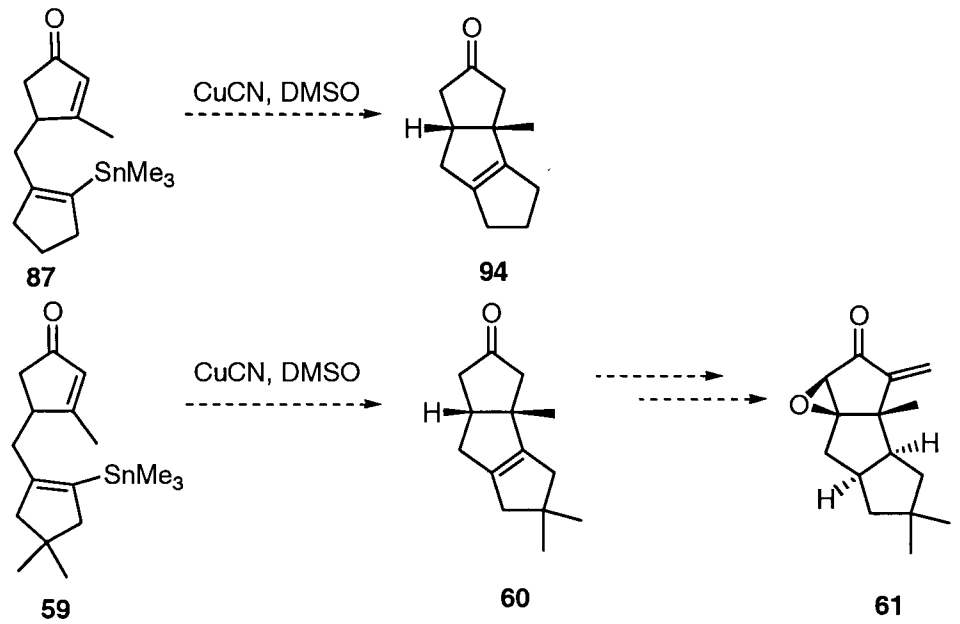
The need for the use of 5.0 equivalents of CuCN in the reaction of **86** may be explained by invoking the proposed reaction pathway (Scheme 9). The additional CuCN shifts the initial equilibrium of the tin-copper transmetalation step and generates more of the alkenylcopper(I) species **93**. This, in turn, facilitates the ring closure step and thus increases the yield of **91**. In addition, CuCN, a weak Lewis acid,[35] may facilitate the conjugate addition reaction by coordinating with the ketone functionality and activating the enone function towards Michael addition. The use of excess of CuCN salt would be expected to assist in this process.



86 **93** **91** **92**

Scheme 9

The intramolecular conjugate addition reaction of the enone **87** was of particular interest in this study. Compound **87** was chosen as a model system for the planned total synthesis of the triquinane natural product, (±)-1-desoxyhypnophilin (**61**) (Scheme 10). The only difference between the structure of **94** (model compound) and **59** (intermediate for the synthesis of **61**) is the presence of a *gem*-dimethyl group on the alkenylstannane ring of **59**. The method developed for the intramolecular conjugate addition of the model system **87** was thus related to the planned key step of the synthesis (**59** → **61**, Scheme 10) and, therefore, the primary objective of these initial studies was to achieve the most efficient conversion of **87** into **94**. As was already noted, the cyclization onto a pre-existing five-membered ring enone presented some challenges in the case of substrate **86**. In addition, the steric and electronic effects due to the presence of the methyl group at the β position of the enone were expected to have a deleterious effect on the intramolecular conjugate addition of the enone **87**.



Scheme 10

Treatment of the enone **87** with 2.5 equivalents of CuCN at 0.05 M concentration of the substrate in DMSO at 60 °C resulted in a very slow reaction as determined by the GLC analyses of aliquots of the reaction mixture (see Table 2 below, entry 1). After 18 h, the crude reaction mixture contained the starting material **87** (~62%), the priotiodestannylated material **95** (~28%), and a small amount of the desired cyclized product **94** (~10%). After work-up and separation of the mixture by flash column chromatography on silica gel, the cyclized product **94** was obtained in approximately 5% yield. In addition, the destannylated material **95** was isolated in 21% yield and 50% of the starting material **87** remaining unreacted.

The structures of the products were confirmed by spectroscopic methods. The IR spectrum of the tricyclic compound **94** exhibited a carbonyl stretching band at 1742 cm^{-1}, typical of a five-membered ring ketone. Evidence for the formation of **94** was further provided by the ^1H NMR spectrum, which showed a 3-proton singlet at δ 1.19 due to the methyl group, as well as the expected signals in the aliphatic region (δ 1.88-2.85) corresponding to the remaining 13 protons. In the ^{13}C NMR spectrum the carbonyl carbon resonance was visible at δ 219.9, while two alkene carbon signals appeared at δ 143.3 and 151.1. Additionally, the molecular mass of compound **94** was confirmed by high resolution mass spectroscopic analysis on the molecular ion (HRMS calcd for

$C_{12}H_{16}O$: 176.1201; found: 176.1197). The structure of the protiodestannylated material **95** was confirmed similarly. The IR carbonyl stretching absorption appeared at 1713 cm^{-1}, typical of a cyclopentenone functionality. The ^1H NMR spectrum of **95** indicated the presence of two alkenic protons, with resonances at δ 5.38 and 5.88. The latter signal was a triplet with a coupling constant of 1.0 Hz, and therefore could be assigned to the proton resulting from protiodestannylation. The ^{13}C NMR resonance of the carbonyl and the alkene conjugated with the carbonyl function remained essentially unchanged in comparison to the starting material **87**, and appeared at δ 208.9, and at δ 130.8 and δ 181.3 respectively. Two other alkenic carbon signals were also visible at δ 126.2 and 141.7. The high resolution mass spectrum of **95** indicated the molecular mass in agreement with that calculated for $C_{12}H_{16}O$ (calcd: 176.1201; found: 176.1206).

Various reaction conditions were investigated for the conversion of **87** into **94** (eq 23). The results are summarized in Table 2. The numbers reported in Table 2 do not refer to the isolated yields, but rather to the relative ratios of **87**, **94** and **95** in the crude reaction mixture, as determined by the GLC analyses.

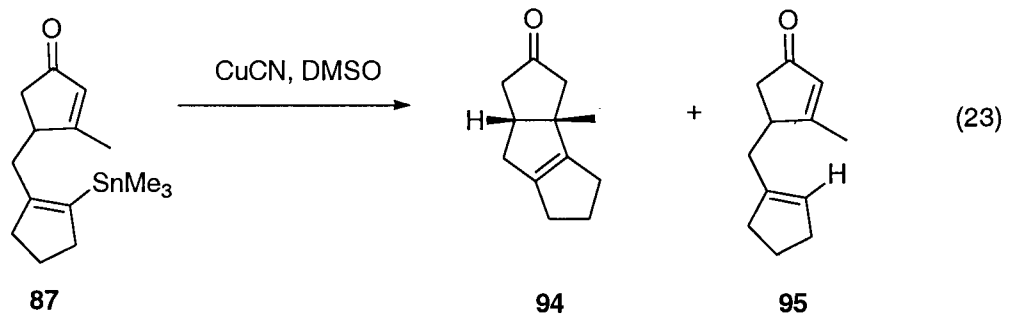


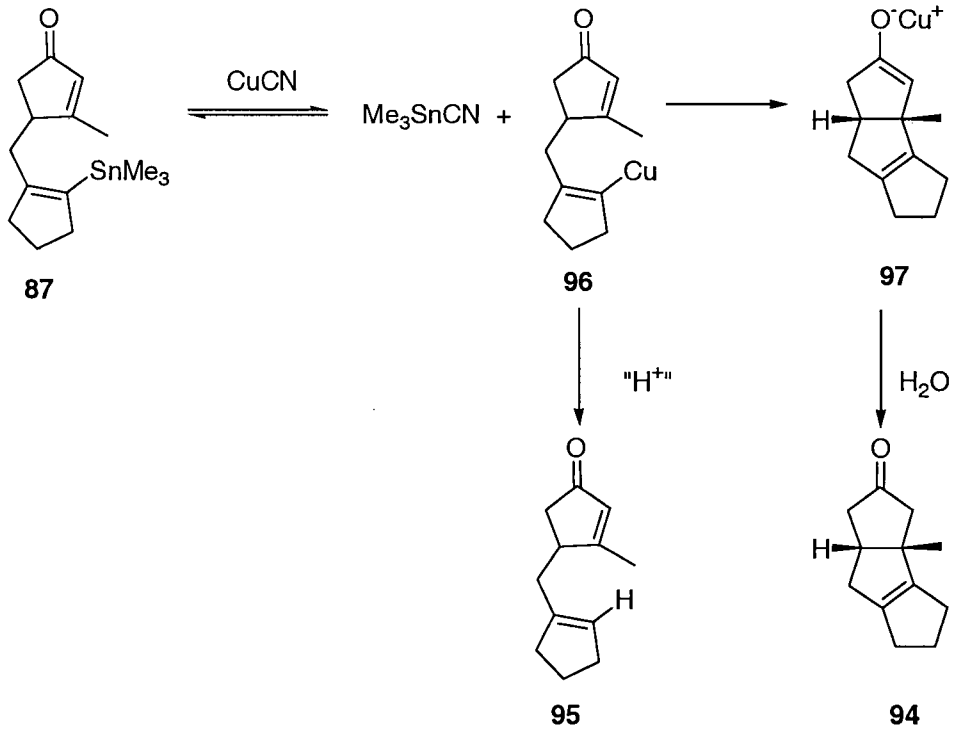
Table 2. Copper(I) cyanide mediated conjugate additions of enone **87**.[a]

Entry	Equiv CuCN	Temp. (°C)	Time (h)	Ratio in crude reaction mixture (GLC) **87**	**94**	**95**
1	2.5	60	18	62	10	28
2	5	60	18	39	16	45
3	10	60	18	12	10	78
4	10	90	3	32	39	29
			18	0	39	61
5	20	90	3	14	46	40
			18	0	46	54
6	40	90	3	1	46	53
			18	0	44	56

[a] An aliquot of the reaction mixture was withdrawn via a capillary and was subjected to a mini work-up (saturated NH_4Cl pH 8, Et_2O). Small amount of the organic phase was injected onto a GLC column.

An increase in the amount of CuCN from 2.5 to 5 to 10 equivalents (Table 2, entries 1-3) resulted in the increased consumption of the starting material **87** over a period of 18 h (62% versus 39% versus 12% of **87** remaining), with a concomitant increase in the formation of the protiodestannylated material **95** (28% versus 45% versus 78%). Surprisingly, the formation of the cyclized product **94** (~10-16%) was not significantly affected by the increase in the amount of CuCN employed. When the proposed reaction pathway for the conversion of **87** into **94** and **95** is considered (Scheme 11), it seems plausible that the additional CuCN would affect the transmetalation equilibrium. Thus, more of the stannane **87** would be converted to the alkenylcopper(I) intermediate **96**. However, under the reaction conditions used here the yield of the

cyclized material **94** remains essentially unchanged, suggesting that rather than undergoing the conjugate addition reaction, the majority of the alkenylcopper(I) species **96** reacts with a proton source to generate **95**. The protonation of **96** to form **95** may occur as a result of moisture in the reaction mixture or upon work-up with aqueous NH_4Cl-NH_3.



Scheme 11

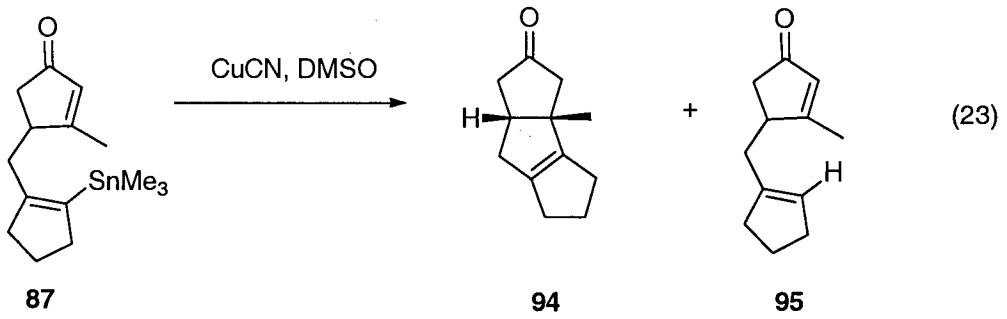
Increasing the temperature of the reaction mixture from 60 °C to 90 °C affected the rate and yield of the conversion of the starting material **87** into the cyclized product **94**. When 10 equivalents of CuCN were used, all of **87** was consumed at 90 °C after 18 h (Table 2, entry 4) and the amount of the cyclized product **94** was significantly greater (39%), compared to the reaction performed at 60 °C (10% of **94** after 18 h, entry 3). Clearly, an increase in temperature causes an increase in the rate of cyclization and hence facilitates formation of the tricyclic product **94**.

The amount of the cyclized product **94** formed was not significantly affected by further increase in the amount of copper(I) cyanide from 10 to 20 to 40 equivalents (~39-46%, entries 4-6). In addition, once all of the stannane **87** was essentially consumed

(entry 6) after 3 h, the extension of the reaction time to 18 h did not cause further increase in the yield of the cyclized product **94** (~44-46%). The presumed protonation of the alkenylcopper(I) species **96** to generate **95** would prevent further increase in the amount of the cyclized product **94**.

Previous work[35] has indicated that in cases where the cyclization is particularly difficult due to steric and/or electronic effects, protiodestannylation is the predominant reaction. Several alternative sources of the proton have been discussed.[35] However, as yet this issue remains unresolved. It was postulated[35] that, most likely, the protiodestannylated material results from the reaction of the alkenylcopper(I) intermediate with water that is either present in the reaction mixture (wet solvent) or seeps through the septum during the reaction. DMSO is notorious for being an extremely hygroscopic solvent, and it is very difficult (if not impossible) to obtain this solvent in anhydrous form. Hence the possibility of trace amounts of water being present in the solvent, despite drying[37] and storing of the solvent under inert atmosphere over molecular sieves, is a valid concern. It was suggested[35] that even though the reactions were performed under an inert atmosphere of argon, which was passed over KOH pellets and Drierite™, the atmosphere, too, could potentially contain traces of water. In the present work, according to the above argument, an approximate amount of water that would be needed to destannylate 50% of the starting material **87** would require a concentration of 0.05% H_2O in DMSO (v/v). That is, for 0.3 mmol of **87** in 6 ml of DMSO, 0.15 mmol or approximately 3 μl of H_2O would result in 50% destannylation.

In a search for reaction conditions under which the amount of protiodestannylated product would be decreased, some reactions were performed in a sealed ampoule with a large excess (~50 equivalents) of CuCN in DMSO at 60 °C.[35] Thus, in a fashion analogous to that used in previous work, several reactions with substrate **87** were carried out in a "sealed-vessel" in an effort to exclude a possible external "influx" of moisture (Table 3).



87 94 95 (23)

Table 3. Copper(I) cyanide-mediated conjugate additions of enone **87** in a sealed ampoule.[a]

Entry	Equiv. CuCN	Temp. (°C)	Ratio in crude reaction mixture (GLC) **87**	**94**	**95**
1	10	60	77	12	10
2	10	90	42	42	16
3	20	90	13	57	30
4	40	90	0	67	29
5	50	90	0	83	11

[a]All reactions were performed in a flame-dried Kimble™, glass ampoule sealed with an oxygen torch. The reaction vessels were heated in an oil bath at 90 °C for 18 h.

A comparison of entry 1 (Table 3) with entry 3 (Table 2), and entry 2 (Table 3) with entry 4 (Table 2), employing the same amount of CuCN (10 equivalents) and temperature (60 or 90 °C), revealed that the amount of the cyclized product **95** was essentially unchanged (~10% at 60 °C and ~40% at 90 °C) regardless of whether the reaction was performed in a septa sealed flask or in a sealed ampoule. However, when the reaction was carried out in a sealed ampoule, relatively large amounts (77% at 60 °C and 42% at 90 °C, Table 3, entries 1 and 2) of the alkenylstannane **87** remained unreacted after 18 h. In contrast, when the reaction was performed in a non-sealed flask after 18 h, 12% of **87** at 60 °C and 0% of **87** at 90 °C remained in the crude reaction mixture (Table 2, entries 3 and 4). This observation suggests that when the reaction is not performed under sealed conditions, there is a driving force present which pushes the transmetalation equilibrium (**87** + CuCN $\rightleftharpoons$ Me_3SnCN + **96**) (Scheme 11) towards the formation of the alkenylcopper(I) species **96**. Apparently, this phenomenon does not occur when the

reaction is carried out in a sealed reaction vessel. A possible explanation, invoking the argument discussed previously, could be that there is, in fact, a way for moisture to seep into the reaction mixture that is not sealed in an ampoule. The alkenylcopper(I) intermediate **96** could react with H_2O, thus shifting the transmetalation equilibrium (**87** → **96**). Water originating from wet DMSO may contribute to the protiodestannylation, but is not the only factor in this process. If this were the case, the same amount of protiodestannylated product would be expected to form under both sealed and non-sealed reaction conditions.

Another potential source of proton, which was not investigated, but cannot be discounted, is the presence of -OH groups on the surface of the glass reaction vessels. The contact surface area of the DMSO solution in the glass reaction flask or the sealed ampoule was not controlled and the glassware was not silated prior to use.

The addition of a large excess of CuCN resulted in a significant increase in the amount of the cyclized product **94** formed (Table 3, entries 4 and 5). The use of 50 equivalents of CuCN in DMSO (90 °C) in a sealed glass ampoule gave the highest amount of the desired cyclized material **94** (entry 5). The isolated yield of **94**, however, was somewhat lower than that expected on the basis of the GLC analyses. Thus, in a number of experiment carried out under conditions as summarized in entry 5, Table 3, the isolated yields of **94** were in the range of 50-59% after work-up and column chromatography of the crude material on silica gel. The protiodestannylated material **95** was obtained in yields of 10-14%. Some polar, unidentified material was not eluted from the silica columns.

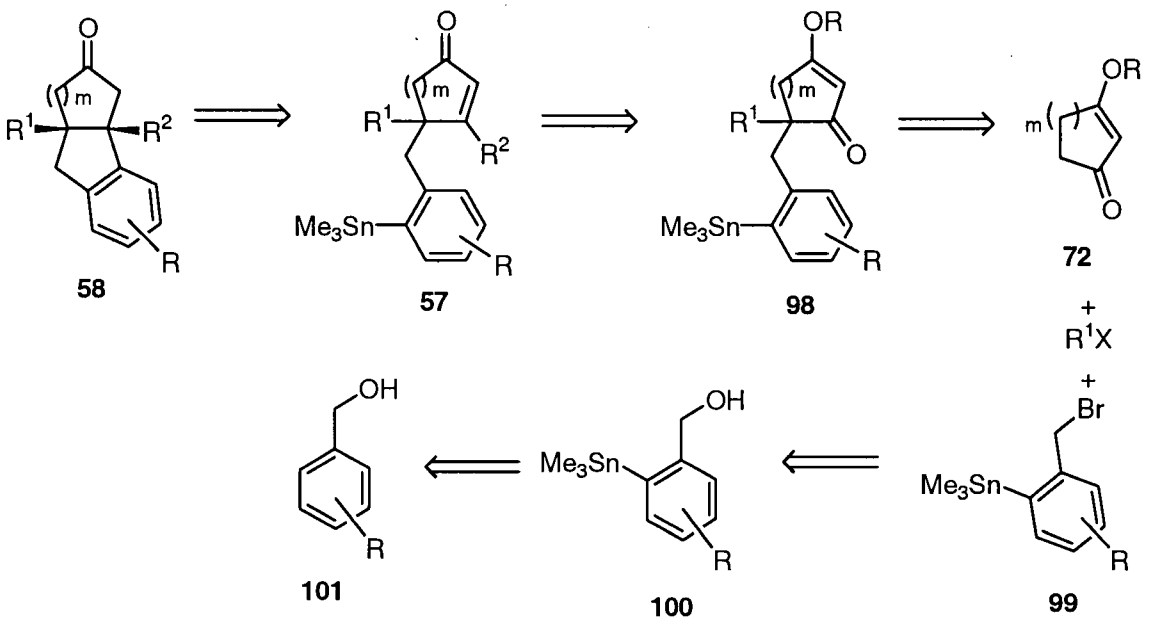
The goal of this study was to find conditions for the transformation of **87** into **94** that would provide a good yield of the product. These conditions would be applied subsequently in a key step of the projected total synthesis of (±)-1-desoxyhypnophilin (**61**). Even though the use of a large excess of CuCN in DMSO was necessary, the yield of the cyclized product **94**, although not excellent, was acceptable. It should be noted that several reactions were attempted in which CuCl was used in the place of CuCN, but these proved to be highly unsatisfactory. For example, when 50 equivalents of CuCl in a sealed ampoule were used, ~66% of the material produced was the protiodestannylated

product **95**, while only ~6% of the cyclized material **94** was formed. Several other unidentified products (possibly chloro-destannylated material or the product of a oxidative coupling reaction) were also produced.

2.2 Copper(I) cyanide-mediated intramolecular conjugate additions of aryltrimethylstannanes to enones

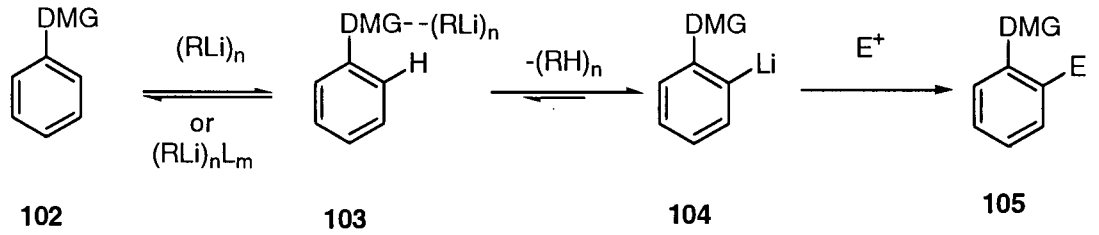
2.2.1 Preparation of cyclization precursors

To test the viability of the CuCN-mediated cyclizations of arylstannanes and to complement the studies carried out by J. G. K. Yee[55] on the intramolecular conjugate additions of aryltrimethylstannanes to *α,β-alkynic ester* functions, it was of interest to study the analogous conjugate additions of aryltrimethylstannanes to α,β-unsaturated ketones. It was envisaged that tricyclic ketones of general structure **58** could be obtained by CuCN-mediated intramolecular conjugate additions involving substrates such as **57** (see the retrosynthetic scheme in Scheme 12). Enones of general structure **57** could be obtained from the vinylogous esters **98**, by treatment of the latter materials with DIBAL-H or Grignard reagents (R^2MgBr), and subsequent dehydration-hydrolysis of the resulting alcohols with aqueous acid. The vinylogous esters **98** should be attainable by sequential alkylations of **72** with the aryl bromides **99** and alkyl halides (R^1X). The required bromides **99** could be obtained by bromination of the corresponding alcohols **100**. The trimethylstannyl group could be introduced via directed orthometalation[56] of the commercially available alcohols **101**.



Scheme 12

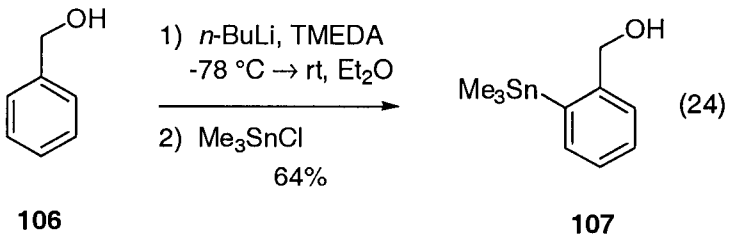
Generally, the directed orthometalation (DoM) reaction involves the deprotonation of an aromatic compound (general structure **102**) at the site *ortho* to the directed metalation group (DMG). The base employed is normally an alkyllithium, RLi. The *ortho*-lithium species **104** formed can then be treated with an electrophile (E^+) yielding a 1,2-disubstituted aromatic product **105** (Scheme 13).[56]



Scheme 13

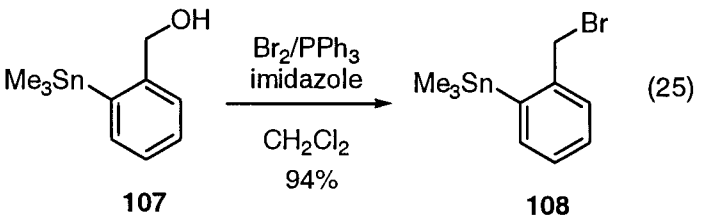
The use of a coordinating solvent (e.g. THF) and the addition of a bidentate ligand (L) such as *N,N,N',N'*-tetramethylethyldiamine (TMEDA) to the reaction mixture increases the basicity of the alkyllithium reagent by breaking down the alkyllithium aggregates and forming monomers and dimers in solution.[56] Although the CH_2O^- is a weak directed metalation group, it has shown promising synthetic utility.[57]

The first step in the preparation of 2-trimethylstannylbenzyl bromide was a directed orthometalation reaction[56] of benzyl alcohol (**106**). Benzyl alcohol (**106**) was treated with 2 equivalents of *n*-BuLi in TMEDA and Et_2O, and the resulting dianionic species was allowed to react with trimethylstannyl chloride (eq 24). The spectral properties of the derived product **107** were in agreement with those previously reported.[57]



106 **107**

2-Trimethylstannylbenzyl alcohol **107** was converted to the bromide **108** using a standard bromination procedure (eq 25).[50] Thus, alcohol **107** was treated with bromotriphenylphosphonium bromide (formed from bromine and triphenylphosphine *in situ*)[58,59] in the presence of imidazole to afford, in 94% yield, 2-trimethylstannylbenzyl bromide (**108**). The ^1H NMR spectrum of **108** displayed a 9-proton singlet at δ 0.39 with a small satellite doublet ($^2J_{Sn\text{-}H}$ = 54.0 Hz) due to the Me_3Sn group. The benzylic protons (-C<u>H</u>$_2$Br) appeared as a singlet at δ 4.51, and four aromatic proton signals were visible at δ 7.24 (1H), 7.30 (1H) and 7.38-7.54 (2H).



107 **108**

4-Methyl-2-trimethylstannylbenzyl alcohol* (**109**) was converted to the bromide **110** in 81% yield in a similar manner (eq 26). The structure of **110** was confirmed on the basis of spectral evidence in a fashion analogous to that employed in the case of **108**.

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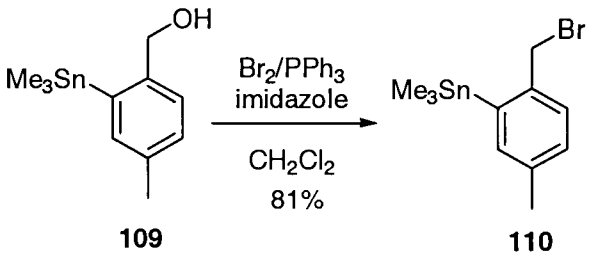
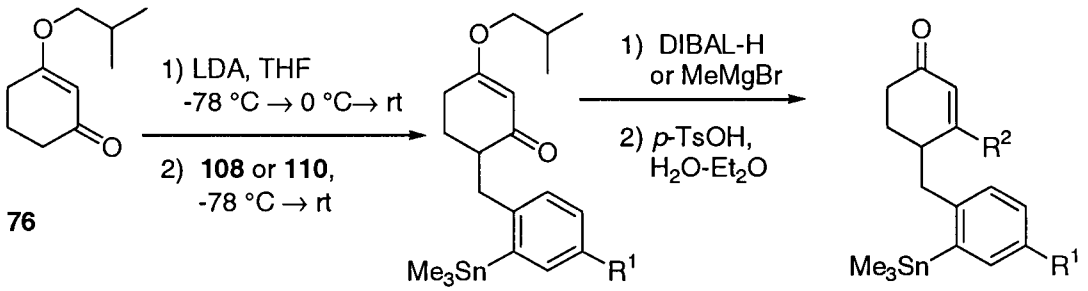
* This compound was prepared by J. G. K. Yee.



109 110 (26)

Alkylation of the vinylogous ester **76** with the alkylating agent **108** proceeded in excellent yield (97%) (Scheme 14). The successful incorporation of the benzylic moiety was confirmed by spectroscopic analysis of the product **111**. Four aromatic proton signals were visible in the ^{1}H NMR spectrum of **111** at δ 6.92-7.22 (2H), 7.22-7.30 (1H) and 7.42-7.48 (1H). A 9-proton singlet due to the Me_3Sn group appeared at δ 0.31. The two 3-proton doublets for the methyl groups of the isobutyl unit appeared at δ 0.97 and 0.98. The alkenic proton of the enone functionality was visible at δ 5.34.



76

111 R^1 = H 97%
113 R^1 = Me 96%

112 R^1, R^2 = H 82%
114 R^1, R^2 = Me 86%

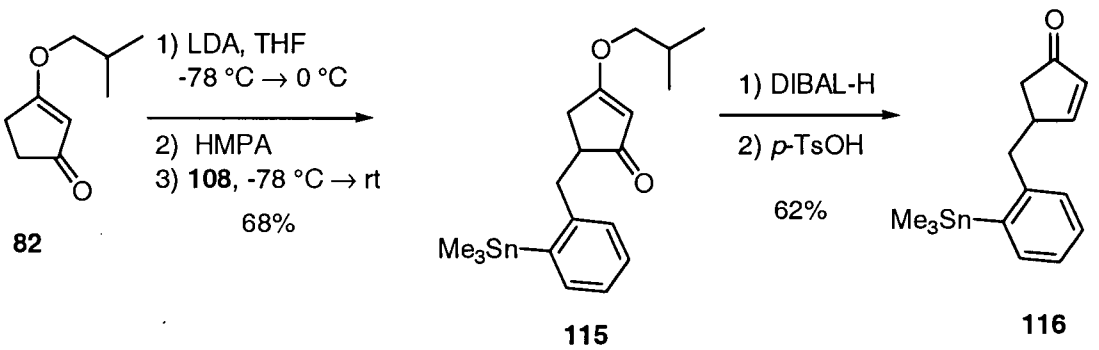
Scheme 14

The vinylogous ester **111** was converted into the enone **112** in 82% overall yield by reduction of the ketone function with DIBAL-H and acid-catalyzed dehydration-hydrolysis of the resultant alkenyl-ether alcohol (Scheme 14). In the ^{1}H NMR spectrum of **112** the alkenic proton signals of the enone function appeared at δ 5.98 and 6.78 and displayed a mutual coupling of 10.0 Hz.

Alkylation of the vinylogous ester **76** with the bromide **110** provided compound **113** in 96% yield. 1,2-Addition of the methylmagnesium bromide to the ketone function of **113**, followed by acid-catalyzed dehydration-hydrolysis of the resultant alcohol, provided the enone **114** (86%) (Scheme 14). The ^{1}H NMR spectrum of the enone **114**

showed one alkenic signal at δ 5.87, two 3-proton methyl singlets at δ 1.88 and 2.31, as well as three aromatic proton signals at δ 7.07-7.12 (2 H) and 7.12-7.32 (1H).

The vinylogous ester **115** was also readily prepared via an alkylation reaction (Scheme 15). Thus, treatment of **82** with LDA in THF, followed by the sequential addition of HMPA and the bromide **108** gave, upon work-up and purification of the crude material on silica gel, the compound **115** in 68% yield. The ^{1}H NMR spectral signals of compound **115** could be assigned to particular protons based on their chemical shifts and coupling constants. Thus, the methyl groups of the isobutyl unit appeared as a 6-proton doublet at δ 0.96 (J = 6.5 Hz), with the methylene doublet (-OC<u>H</u>$_2$-) at δ 3.72 (J = 6.5 Hz) and a methine (-CH-) multiplet at δ 1.97-2.09. The Me_3Sn singlet appeared at δ 0.30. There were four aromatic signals visible at δ 7.13-7.25 (3H) and 7.38-7.45 (1H). The methylene protons α to the enol ether function are diastereotopic and appeared as doublet of doublets (dd) at δ 2.30 and 2.57. The geminal coupling for these protons was 18.0 Hz, while additional coupling to the methine (CH) signal at δ 2.75-2.83 exhibited coupling constants of 2.0 and 7.0 Hz, respectively. The benzylic methylene protons (Ar-C<u>H</u>$_2$-) are also diastereotopic and appeared at δ 2.47 and 3.35. The geminal coupling constant was 14.0 Hz, while the vicinal couplings to the adjacent methine proton at δ 2.75-2.83 showed coupling constants of 11.5 and 4.0 Hz, respectively.



82 **115** **116**

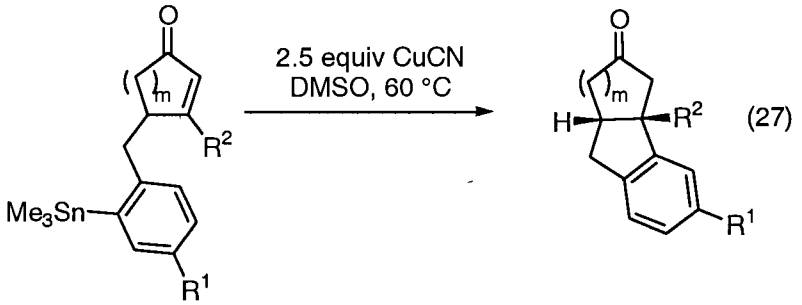
Scheme 15

Reduction of ketone **115** with DIBAL-H, followed by treatment of the acquired alcohol with aqueous acid, gave the enone **116** in 62% yield. The ^{1}H NMR spectrum of the enone **116** showed the methyl signal of Me_3Sn group as a singlet at δ 0.29, with a

satellite doublet (average coupling constant of 53 Hz ($^2J_{Sn-H}$)). There were 4 aromatic proton signals visible at δ 7.18-7.23 (m, 2H), 7.23-7.33 (m, 1H) and 7.45 (br d, 1H). The alkenic proton α to the carbonyl of the enone appeared at δ 6.19 as a doublet with coupling (J = 5.5 Hz) to the β proton at δ 7.57. The latter signal showed additional coupling (J = 2.0 Hz) to the methine (-CH-) (δ 3.18-3.27, m, 1H). The methylene signals α to the C=O appeared at δ 2.09 and 2.52 and showed geminal coupling (J =19.0 Hz), as well as additional coupling (J = 2.0 and 6.5 Hz respectively) to the adjacent methine proton (-CH-) (δ 3.18-3.27, m, 1H). The two diastereotopic benzylic protons at δ 2.77 and 2.84 displayed a geminal coupling constant of 14.0 Hz, and both additionally coupled to the methine proton at δ 3.18-3.27 (J = 8.0 Hz for both). Other spectral data (^{13}C NMR, IR, HRMS) were also found to be in agreement with the assigned structure.

2.2.2 Copper(I) cyanide-mediated cyclizations of aryltrimethylstannanes to enones

Upon treatment with 2.5 equivalents of copper(I) cyanide in DMSO at 60 °C, the stannanes **112**, **114** and **116** underwent intramolecular conjugate addition reactions in good to excellent yields (eq 27; Table 4).



112 m = 2, R^1, R^2 = H — **117**
114 m = 2, R^1, R^2 = Me — **118**
116 m = 1, R^1, R^2 = H — **119**

Table 4. Copper(I) cyanide-mediated conjugate additions of aryltrimethylstannanes **112**, **114**, and **116**.[a]

Entry	Substrate	Time (h)	Product	Yield (%)
1	**112**	2	**117**	87
2	**114**	29	**118**	66[b]
3	**116**	2	**119**	75

[a]All reactions were carried out using 2.5 equivalents of CuCN. [b] A small amount of protiodestannylated material was also obtained (^{1}H NMR, MS).

The CuCN-mediated cyclization of enone **112** proceeded (Table 4, entry 1) rapidly and efficiently to give the cyclized product **117** in 87% yield. The IR spectrum of the cyclized ketone **117** exhibited a ketone carbonyl stretching absorption at 1720 cm^{-1}. In the ^{1}H NMR spectrum a 4-proton multiplet in the aromatic region (δ 7.11-7.22) was visible, as well as signals due to the 10 aliphatic protons (δ 1.70-3.64). In the ^{13}C NMR spectrum the carbonyl carbon resonance appeared at δ 212.5, and the aromatic carbon signals resonated at δ 123.7, 124.9, 126.7, 127.0 (all CH, -ve phase in the APT) and at δ 142.2 and 145.0 (both C).

The conjugate addition of the substrate containing a methyl group in the β position of the enone, **114**, proceeded quite slowly (Table 4, entry 2). After a reaction time of 2 h, a substantial amount (approximately 60%) of starting material **114** was present in the reaction mixture as determined by the GLC analysis. The progress of the reaction was monitored for 29 h. Upon work-up and purification of the crude material by flash column chromatography, the cyclized product **118** was obtained in 66% yield. A small amount of protiodestannylated material was also isolated (GLC-MS, ^{1}H NMR). This material was not fully characterized, but the ^{1}H NMR spectrum showed four aromatic proton signals (δ 7.00-7.11) and an alkenic proton at δ 5.87. The ^{1}H NMR spectrum of the cyclized product **118** displayed two 3-proton methyl singlets at δ 1.28 and 2.29. Three aromatic signals were also visible at δ 6.88 (1H), 6.96 (1H) and 7.08 (1H). Other signals appeared between δ 1.82 and 3.17. The ^{13}C NMR spectrum of compound **118** showed a carbonyl resonance at δ 212.2, and a total of six aromatic carbon signals at δ 122.7, 124.6, 127.8 (all CH, -ve phase in APT) and 136.5, 137.9 and 150.4 (all C).

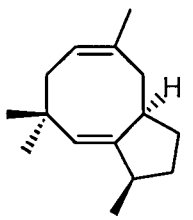
The intramolecular conjugate addition reaction involving the substrate **116** (entry 3) took place in a short amount of time and produced a very good yield of compound **119** (75%). In this experiment, 2.5 equivalents of CuCN were used. The spectral data for *cis*-6, 7-benzobicyclo[3.3.0]octan-3-one have been reported previously in the literature[60] and compound **119** displayed identical spectral data.

These examples of the intramolecular conjugate additions of aryltrimethylstannane functions to α,β-unsaturated ketones demonstrate that they proceed in a manner analogous to the additions of the alkenyltrimethylstannanes. Cyclizations involving both six- and five-membered ring enones were investigated.

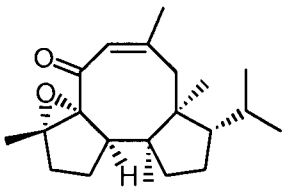
2.3. Preparation of functionalized, *cis*-fused bicyclo[6.3.0]undecanes, bicyclo[6.4.0]dodecanes, and bicyclo[7.4.0]tridecanes

2.3.1 Introductory remarks

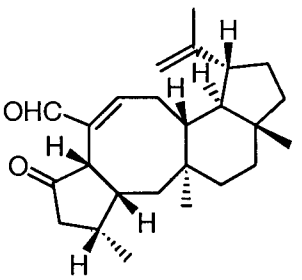
In recent years, there has been a profusion of synthetic efforts directed towards the construction of carbocyclic systems in which small (usually 5- or 6- membered) rings are fused to medium-sized rings. Particularly, synthetic approaches to systems containing eight-membered carbocycles[41,61] have been explored intensively. This interest has been stimulated by the discovery of cyclooctanoid fragments in many, structurally diverse terpenoid natural products such as precapnelladiene (**120**), 7,8-epoxy-4-basement-6-one (**121**) and variecolin (**122**), to name just a few.



Precapnelladiene (**120**)

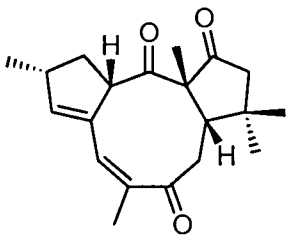


7,8-Epoxy-4-basement-6-one (**121**)

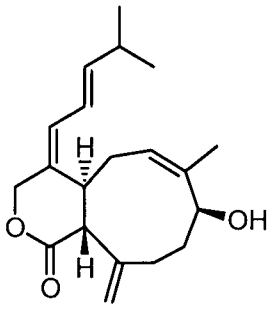


Variecolin (**122**)

While over 100 natural products containing an eight-membered ring are now known, nine-membered ring terpenes are not as common. Very recently, a synthetic approach to the functionalized cyclononane-containing substance, jatrophatrione (**123**), an unusual antileukemic diterpene, has been reported.[62,63] Reports on the isolation of several new xenicane-type[64] diterpenes (e.g florlide H (**124**)), possessing substituted cyclononane ring systems, have also been published.[65]



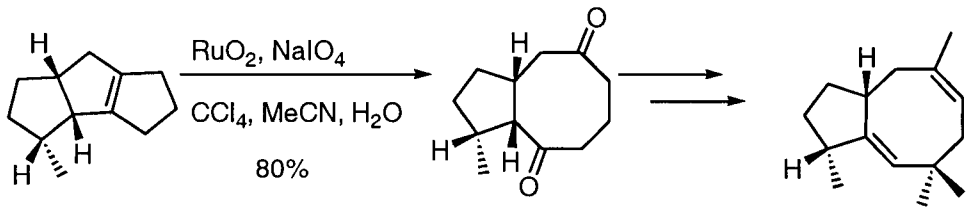
Jatrophatrione (**123**)



Florlide H (**124**)

Efforts towards the assembly of cyclooctanoid systems have provided a wide array of synthetic strategies,[41] which include the direct formation of the eight-membered rings via cycloaddition reactions, sigmatropic rearrangements, cyclizations, and coupling processes, as well as indirect formation via ring expansions, fragmentations, rearrangements and oxidative/reductive protocols. Since discussion of these methods is beyond the scope of this thesis, the reader is referred to an excellent recent review by Mehta and Singh that summarizes methods that have been used for the construction of cyclooctanoid systems and that discusses the application of these methods to the synthesis of natural products.[41]

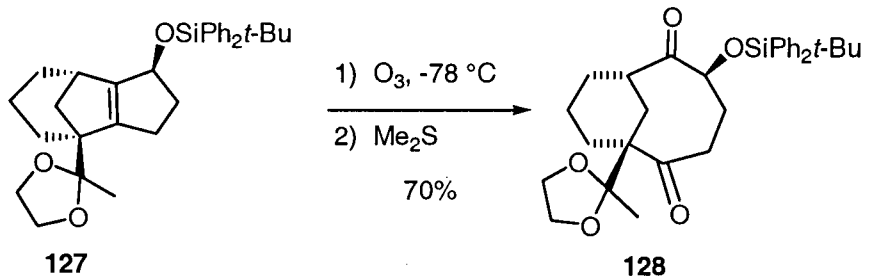
Oxidative cleavage of the tetrasubstituted double bond of bicyclo[3.3.0]oct-1(5)-ene or bicyclo[4.2.0]oct-1(6)-ene moieties has been previously employed in the synthesis of 8-membered rings. An early example of this method by Mehta and coworkers,[66] applies the ruthenium tetroxide promoted oxidative cleavage of a double bond of the triquinane **125** to provide the bicyclic dione **126**, an intermediate in the total synthesis of (±)-precapnelladiene (**120**) (Scheme 16).[67]



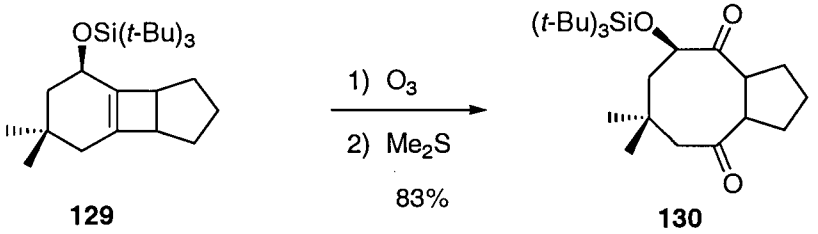
125 **126** (±)-Precapnelladiene (**120**)

Scheme 16

Another example of generating 8-membered rings by oxidative cleavage of a double bond involves the formation of **128** from **127** as reported by Little and coworkers.[68] This transformation, achieved with ozone, played a key role in the synthesis of taxol analogues (eq 28). Galatsis demonstrated the use of the same method[69] in the preparation of functionalized 1,4-cyclooctadione ring systems. For example, the substrate **129**, containing a tetrasubstituted double bond as part of a 6-4 ring system, was converted efficiently into **130** (eq 29).

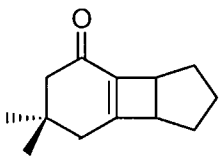


127 **128** (28)

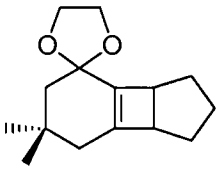


129 **130** (29)

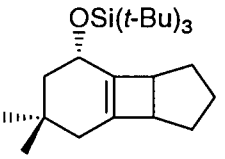
Remarkably, in the latter report, the alkene function of ketone **129a** or ketal **129b** (shown below) could not be cleanly cleaved by ozone and both compounds had to be converted to **129** in order for the reaction to succeed. Additionally, the configuration of the -OTBS group also had a significant bearing on the yield of the oxidative cleavage. The yield of the cyclooctadione resulting from the treatment of **129c** with ozone was found to be 57%, considerably lower than the yield obtained with the use of substrate **129**.



129a



129b

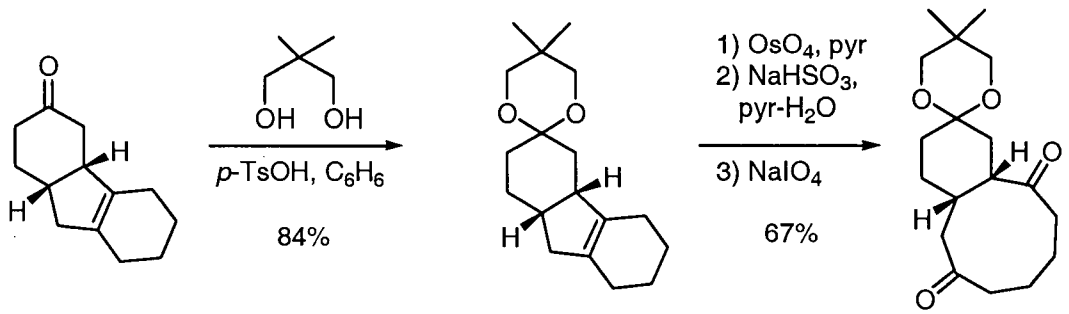


129c

These observations indicate that, although the method may be generally effective, structural intricacies of the starting material in the proximity of the olefinic bond affect the success of its ozonolysis.

2.3.2 Preparation of ketals

Preliminary work[43] (see Section 1.4 earlier) into the oxidative cleavage of the tetrasubstituted alkenic function of the ketone **53** with OsO_4 showed that this reaction was unsuccessful. On the other hand, sequential treatment of the corresponding ketal **55** with OsO_4 and $NaHSO_3$, followed by reaction of the resultant diol with $NaIO_4$, gave the ketal dione **56** in 67% yield (Scheme 17).

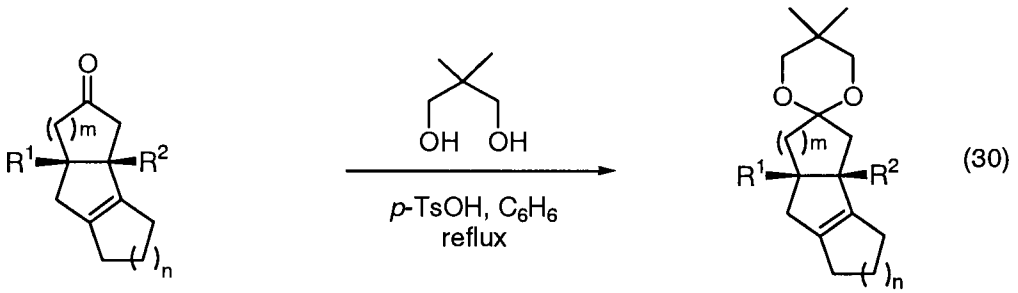


53 **55** **56**

Scheme 17

For this reason, attempts to effect oxiditive cleavage of the olefinic ketals prepared from **88-90** and **54*** were investigated first (eq 30). In any case, masking the ketone functions of compounds **88-90** and **54** prior to oxidative cleavage would provide a useful way of differentiating synthetically between the newly generated carbonyl functions and one present in the precursors.

Solutions of the ketones **88-90** and **54** in benzene containing 2,2-dimethyl-1,3-propanediol and a catalytic amount of *p*-toluenesulfonic acid were refluxed with azeotropic removal of water (eq 30). The crude products, upon purification by column chromatography on silica gel, followed by a bulb-to-bulb distillation of the acquired liquids, afforded the ketal olefins **131-134** in very good to excellent yields (78-90%).



(30)

88 m = 2, n = 1, R_1, R_2 = H
89 m = 2, n = 1, R_1 = Me, R_2 = H
90 m = 2, n = 1, R_1, R_2 = Me
54 m = 2, n = 2, R_1 = H, R_2 = Me

131 82%
132 78%
133 83%
134 90%

Spectral data provided evidence for the successful formation of the desired ketals **131-134**. The IR spectrum of **131** showed a strong absorption due to the C-O-C of the ketal function at 1105 cm^{-1}. Compounds **132**, **133** and **134** showed analogous IR bands at 1113, 1115, and 1113 cm^{-1}, respectively. The ^1H NMR spectrum of **131** showed signals characteristic of the 2,2-dimethylpropylene ketal function - two 3-proton singlets at δ 0.93 and 0.94 due to the methyl groups and a 4-proton multiplet at δ 3.40-3.51 due to the methylene protons. The corresponding signals of **132** were visible at δ 0.93 (3H), 0.94 (3H), and at δ 3.41-3.53 (4H). The ^1H NMR spectrum of ketal **133** showed four 3-proton singlets at δ 0.84, 0.88, 0.96 and 0.99, as well as four distinct signals for each of the methylene protons of the ketal at δ 3.35, 3.41, 3.48 and 3.51. Each of these signals

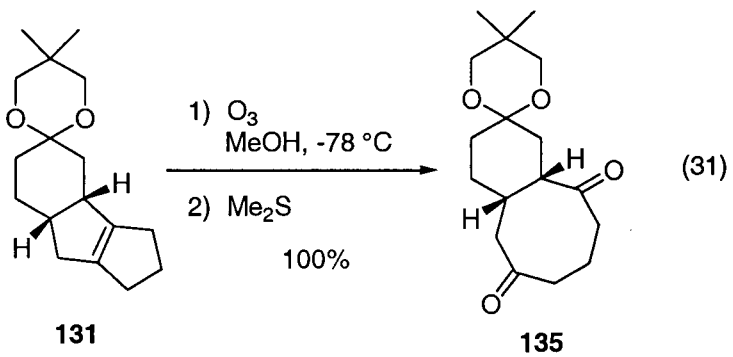
---

* Compound **54** was prepared by D. J. Wallace.[43]

displayed a geminal coupling of 11.0 Hz. The ketal **134** showed three 3-proton singlets at δ 0.90, 1.00 and 1.05 due to the methyl groups, as well as a 2-proton multiplet at δ 3.35-3.43 and two doublets (J = 16.0 Hz) at δ 3.49 (1H) and 3.52 (1H), due to the four methylene protons of the ketal unit. In addition, ^{13}C NMR spectra and HRMS of ketals **131-134** were in agreement with the assigned structures.

2.3.3 Oxidative cleavage of the tetrasubstituted double bond

The ozonolysis reaction is generally a very useful transformation, and thus is widely taught in introductory organic chemistry courses. In a typical procedure, a solution of the ketal **131** in cold methanol was treated with ozone until the reaction mixture turned pale blue in colour, indicating that the presence of excess of ozone in the mixture. Reductive work-up with dimethyl sulfide, removal of volatiles and purification of the crude compound by flash column chromatography on silica gel provided the ketal dione **135** as a colourless solid in quantitative yield (eq 31).

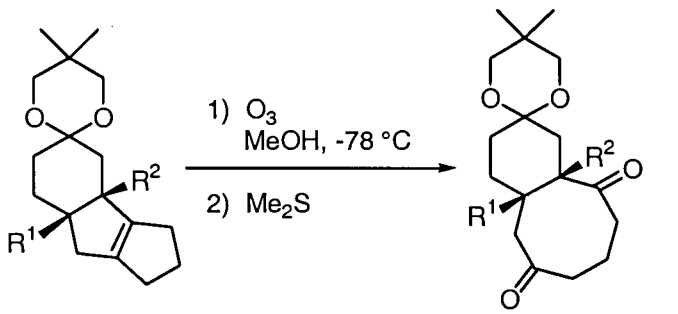


131 **135** (31)

The structure of the product **135** was confirmed using spectroscopic techniques. The ^{13}C NMR spectrum provided convincing evidence for the oxidative cleavage, since two carbon signals, characteristic of carbonyl carbon resonances, were visible at δ 211.6 and 212.3. The strong absorption at 1694 cm^{-1} in the IR spectrum of **135** additionally confirmed the formation of the carbonyl groups. The ^{1}H NMR spectrum displayed signals that could be assigned to the 2,2-dimethylpropylene ketal group: two 3 proton

singlets of the methyls at δ 0.84 and 0.96, as well as four distinct 1-proton signals at δ 3.34, 3.40, 3.42 and 3.60 due to the methylene protons. Each pair of methylene protons is diastereotopic and showed a geminal coupling constant of 11.5 Hz. In addition, the high resolution mass measurement on the peak corresponding to the molecular ion confirmed the molecular mass of **135**.

In spite of the initial successful ozonolysis of the double bond of the ketal **131**, much lower yields were obtained from the substrates **132** and **133**. When compound **132** was treated with ozone, the corresponding ketal dione **136** was isolated in only 63% yield. The yield decreased to 37% in the case of substrate **133**. In this reaction, the process yielded a complex mixture of unidentified compounds, as indicated by TLC analyses. Only compound **137** was isolated.

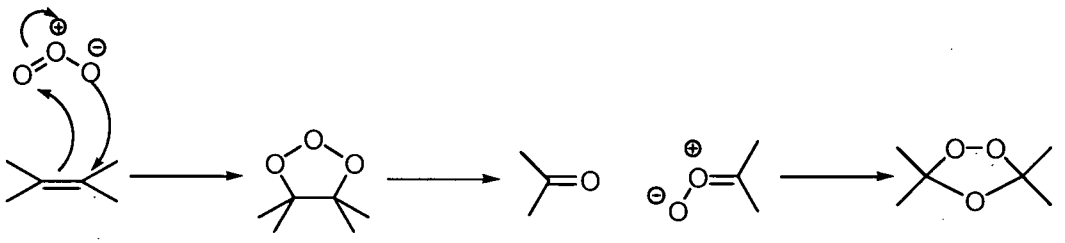


(32)

132 R^1 = Me, R^2 = H
133 R^1, R^2 = Me

136 63%
137 37%

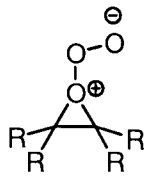
A possible explanation for the poor yields obtained from ozonolysis of compounds **132** and **133** can be suggested. The generally accepted mechanism of ozonolysis, proposed by R. Criegee, involves a three-step pathway (Scheme 18).[70] In the first step, an electrophilic 1,3-dipolar cycloaddition of ozone to the carbon-carbon double bond forms a primary ozonide **138**. The primary ozonide decomposes into a carbonyl compound and zwitterionic carbonyl oxide. In the third step, the two species recombine to give an ozonide **139**.



138 139

Scheme 18

In a reductive work-up step, the ozonide **139** is reduced by, for example, dimethyl sulfide, to generate two carbonyl functions and dimethyl sulfoxide as a by-product. However, it has been suggested[71] that when an olefin is sterically hindered, the structure of the primary ozonide is different from **138** and is more likely to be a peroxyepoxide **140**.



140

The peroxyepoxide species **140**, upon decomposition, may form epoxides as the reaction products as well as other products of partial cleavage.[71,72] Such products have been known to form from hindered alkenes.[72]

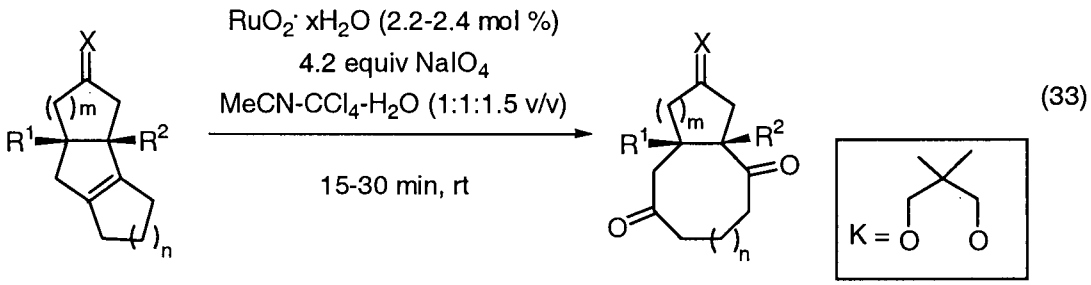
The alkene function of **133** is sterically more hindered than that of **131**, due to the fact that R^1 and R^2 are both methyl groups. Hence, it could be expected that other products would be formed during the ozonolysis and/or reductive work-up step. In the case of compound **132** (R^1 = Me) the double bond is also somewhat more hindered than that present in **131**, and therefore, a lower yield of product **136** might be anticipated.

Since the oxidative cleavage of tricyclic substrates such as **132** and **133** by ozone was not generally applicable other methods were explored. The choice of ruthenium tetroxide as an oxidizing agent was suggested by work of Mehta (*vide supra*, Scheme 16).[66] Ruthenium tetroxide is a more powerful oxidant than osmium tetroxide and, in

addition, is also known to cleave carbon-carbon double bonds that are resistant to ozonolysis.[73]

Ruthenium tetroxide is a toxic, highly volatile (b.p. 40 °C) yellow compound, which tends to explode in the solid state.[74] For these reasons, the reagent is usually used in catalytic amounts and is prepared by *in situ* oxidation of RuO_2 or $RuCl_3$ by a stoichiometric oxidant such as sodium periodate. The reaction is typically done in a heterogenous solvent system of water and carbon tetrachloride. RuO_2 is a black solid that is insoluble in water and most other solvents and, as a result, remains at the interface of the two-phase system. When the RuO_2 comes in contact with the oxidant (e.g. $NaIO_4$) that is dissolved in the water, it is oxidized to RuO_4. RuO_4 is only moderately soluble in water, but is very soluble in carbon tetrachloride and therefore dissolves in the organic layer of the two-phase solvent system.[73] A modification of this procedure by Sharpless and coworkers [75] includes the addition of acetonitrile as a co-solvent, which presumably prevents the loss of activity of the ruthenium catalyst in cases where carboxylic acids are present or generated. This method is now a generally accepted procedure for ruthenium tetroxide catalyzed oxidative cleavage of alkenes.

The Sharpless protocol was used to effect the oxidative cleavage of the olefinic ketals **132-134** and the olefinic ketones **88-91** and **54**. Treatment of each of these substrates with a catalytic amount of RuO_2 and 4.2 equivalents of $NaIO_4$ in a 1:1:1.5 (v/v) mixture of acetonitrile, carbon tetrachloride and water at room temperature, resulted, in each case, in the cleavage of the tetrasubstituted alkenic function in very good to excellent yields (79-95%) (eq 33, Table 5). The reactions were fast and were typically completed (TLC analysis) in 15 to 30 minutes at room temperature.



(33)

Table 5. Ruthenium tetroxide catalyzed cleavage of the alkenes **132-134, 88-91** and **54**.

Entry	Substrate	X	m	n	R^1	R^2	Product	Yield (%)
1	**132**	K	2	1	Me	H	**136**	95
2	**133**	K	2	1	Me	Me	**137**	83
3	**134**	K	2	2	H	Me	**141**	81
4	**88**	O	2	1	H	H	**142**	95
5	**89**	O	2	1	Me	H	**143**	94
6	**90**	O	2	1	Me	Me	**144**	91
7	**91**	O	1	1	H	H	**145**	79
8	**54**	O	2	2	H	Me	**146**	87

The evidence for the successful formation of compounds **136**, **137**, **141-146** was provided by spectroscopic analyses. The ^{13}C NMR spectrum of the ketal dione **136** showed two carbonyl carbon resonances at δ 212.0 and 212.5. The ketal diones **137** and **141** displayed analogous carbon signals at δ 211.7 and 215.1 for **137** and at δ 215.1 and 217.2 for **141**. In the IR spectrum of **136**, the C-O-C stretching frequency due to the ketal function appeared at 1103 cm^{-1}, while the carbonyl streching band appeared at 1685 cm^{-1}. The corresponding absorptions for **137** were visible at 1107 and 1688 cm^{-1}, and for **141** at 1104 and 1693 cm^{-1}.

The structures of the triketones **142-146** were similarly confirmed by spectral data. The ^{13}C NMR spectrum of compound **142** displayed three carbonyl carbon signals at δ 208.5, 211.2 and 211.8. The corresponding carbonyl signals were visible at δ 207.5, 210.6 and 214.3 for **143**, at δ 207.5, 210.9, and 215.9 for **144**, δ 211.5, 213.3 and 214.3

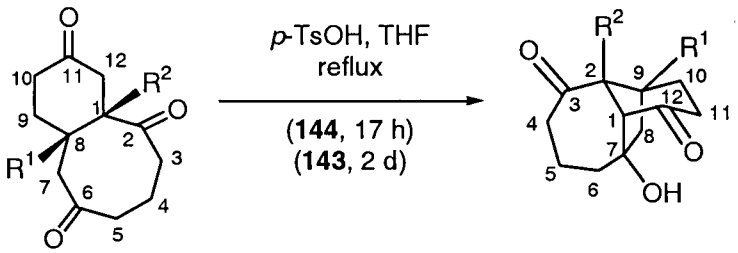
for **145,** and at δ 210.9, 212.9 and 216.3 for **146**. In the IR spectrum of the triketone **142** a wide carbonyl band was present at 1693 cm^{-1}. The triketones **143** and **144** displayed similar absorptions at 1698 cm^{-1}. The trione **145** displayed two distinct carbonyl stretching bands in the IR spectrum at 1762 cm^{-1} and at 1697 cm^{-1}, characteristic of the carbonyl of a five-membered ring and a larger (6-8 CH_2 units) ring respectively.[76] The trione **146** also displayed two carbonyl absorption bands at 1705 and 1697 cm^{-1}.

Clearly, the RuO_4-catalyzed oxidation method provided an efficient and rapid method for the oxidative cleavage of the alkenic function of the substrates listed in Table 5. Functionalized, *cis*-fused bicyclo[6.3.0]undecane, bicyclo[6.4.0]dodecane and bicyclo[7.4.0]tridecane systems were prepared via this method from the corresponding tricyclic olefinic precursors **132-134**, **88-91** and **54**.

2.4. Aldol condensation reactions of the triones 142-146.

Further synthetic manipulations using the novel bicyclic triketones **142-146** were envisaged. In particular, a possibility of generating structurally more complex products via acid-catalyzed aldol condensations of these substrates was pursued.

When each of the compounds **144** and **143** was treated with a catalytic amount of *p*-toluenesulfonic acid in refluxing THF, the corresponding aldol condensation products **147** and **148** were obtained in isolated yields of 97% and 94%, respectively (eq 34).



144 R^1, R^2 = Me
143 R^1 = Me, R^2 = H

147 97%
148 94%

(34)

The IR spectra of the products **147** and **148** showed strong, broad absorptions at 3406 cm^{-1} and 3382 cm^{-1}, respectively, indicating the presence of a hydroxyl group. The carbonyl stretching absorption was visible at 1701 cm^{-1} for **147** and at 1716 cm^{-1} for **148**. In addition, for each of these products, only two carbonyl signals were visible in the ^{13}C NMR spectrum at δ 211.1 and 214.6 for the **147** and at δ 209.9 and 210.7 for **148**. The ^{13}C NMR spectra also displayed a carbon signal at δ 79.3 for **147** and at δ 82.6 for **148**, again suggesting the presence of a hydroxyl group. These observations indicated the formation of aldol condensation products when substrates **144** and **143** were treated with acid.

Analyses of molecular models of various possible aldol condensation products derived from **144** and **143**, each involving the closing of a five-membered ring, indicated that structures **147** and **148**, respectively, would show the least amount of strain, and

should be thermodynamically favoured. X-ray crystallographic studies* confirmed that the aldol condensation between C-12 and C-6 of **144** and **143** occurred, and that the products formed were, in fact, **147** and **148** (Figure 1 and 2).

The assignments of the ^{1}H NMR and ^{13}C NMR signals of the product **147** were accomplished using two dimensional NMR techniques: ^{1}H-^{1}H correlation spectroscopy (COSY), ^{13}C-^{1}H one bond and long range correlation experiments (HMQC and HMBC). The results of these experiments are summarized in the experimental section of this thesis.

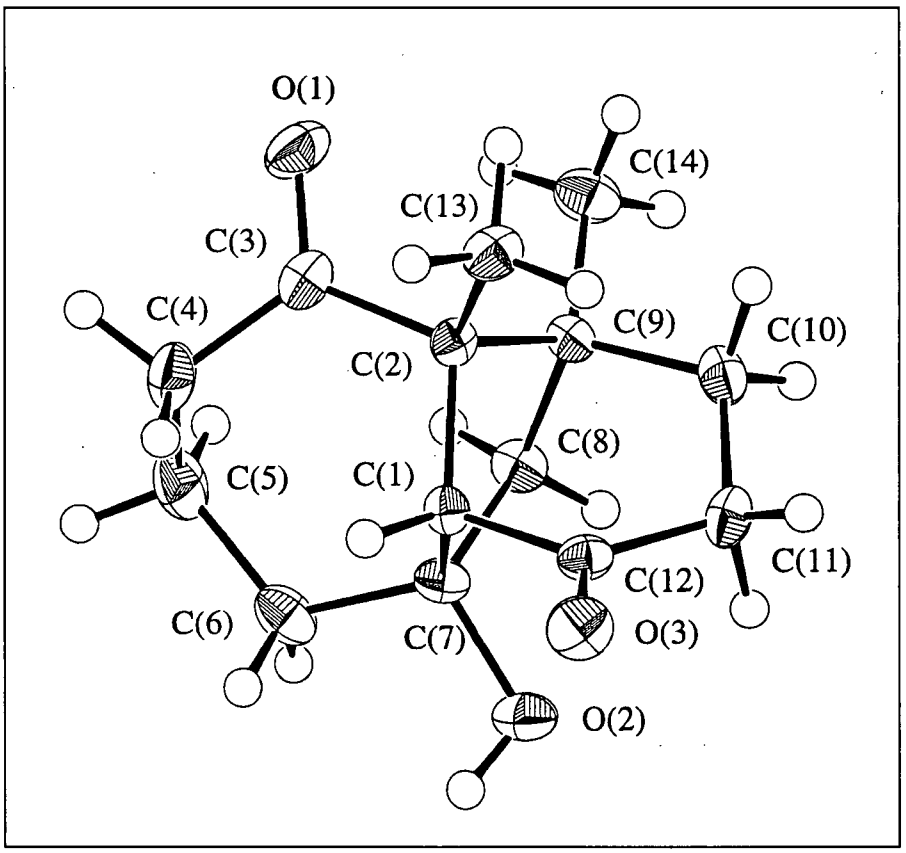


Figure 1. X-ray crystal structure of **147** (50% probability thermal ellipsoids are shown for the non-hydrogen atoms).

* X-ray crystallographic analyses were performed by S. J. Rettig (deceased October 27, 1998) of the UBC X-ray Crystal Structure Laboratory.

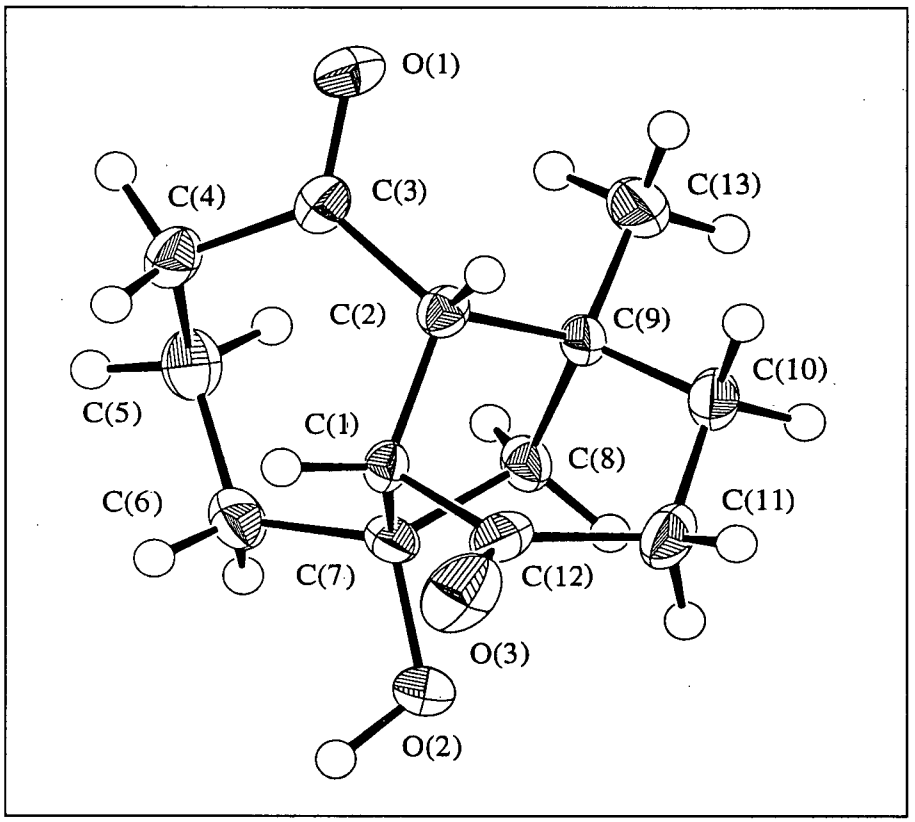
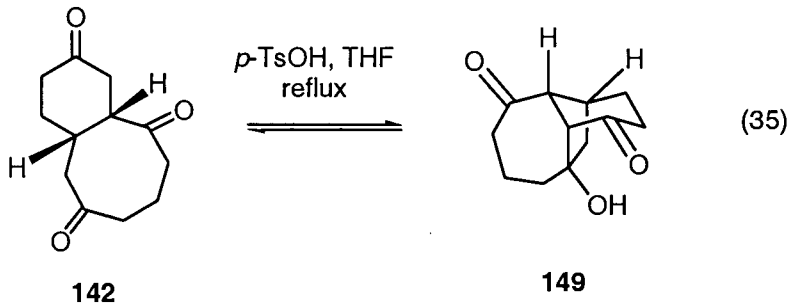


Figure 2. X-ray crystal structure of **148** (50% probability thermal ellipsoids are shown for the non-hydrogen atoms).

The presence of the methyl groups in the R^1 and R^2 positions of **144** and **143** seems to influence the thermodynamically controlled equilibrium of the reaction. Treatment of the triketone **142**, where R^1 and R^2 are both H, with a catalytic amount of *p*-TsOH in refluxing THF, resulted in formation of approximately 1:1 mixture of the triketone **142** and the aldol product **149** (eq 35). After 3 days of refluxing conditions, no further change in the ratio of the starting material and product was observed.

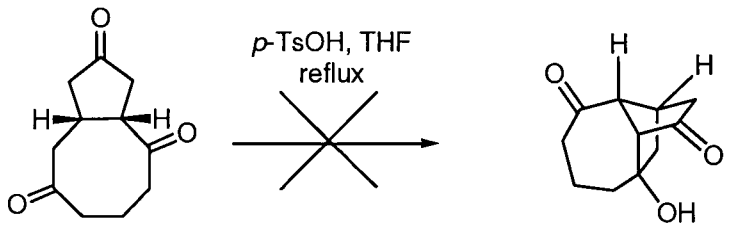


142 149 (35)

The aldol product **149** was isolated as a white solid in 46% yield, and its structure was determined by comparison of its spectral data to those of compounds **147** and **148**. The IR spectrum of **149** showed a broad absorption band at 3436 cm^{-1} as well as absorption arising from the carbonyl stretching at 1698 cm^{-1}. The ^{13}C NMR spectrum displayed two carbonyl carbon signals at δ 210.2 and 213.5 as well as a signal at δ 82.0, due to a carbon bonded to a hydroxyl group. The ^{1}H NMR spectrum displayed all signals corresponding to the expected number of protons. In addition, the HRMS measurement on the molecular ion confirmed the molecular mass of **149**.

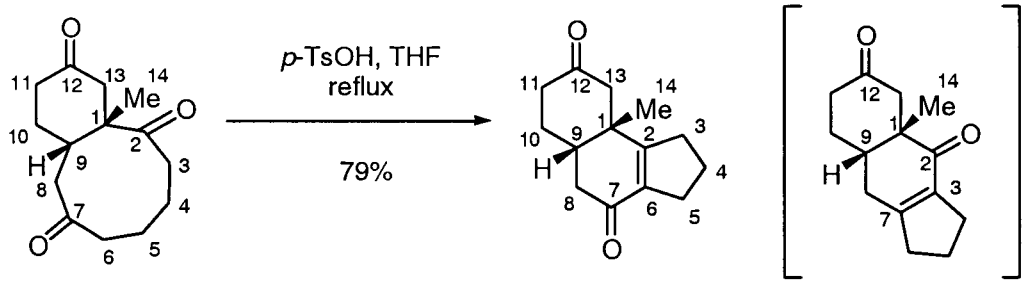
The recovered starting material **142** was isolated in 52% yield. The spectral properties (^{1}H NMR, ^{13}C NMR) and the melting point (m.p. 128-130 °C) of recovered **142** were compared to those of the original material **142** (m.p. 129-131 °C). The comparison demonstrated that isomerization of the tertiary centre α to the C=O, which could potentially generate a 6-8 ring system with a *trans* fusion, did not occur.

An analogous acid-catalyzed aldol condensation reaction was not observed when the triketone **145** was treated with *p*-TsOH in refluxing THF. The unreacted starting material **145** was isolated from the reaction mixture in quantitative yield (eq 36). An aldol condensation of the 5-8 membered ring system analogous to that observed for the 6-8 ring systems (*vide supra*) would generate the tricyclic ring system **150**. Compound **150** would undoubtedly be more strained than **149**, the aldol product derived from **142**, which possesses a 6-8 carbon framework.



145 150 (36)

An acid-catalyzed aldol reaction was also performed on the triketone **146**, which possesses a 6-9 bicyclic fused ring system. Thus, treatment of this material with *p*-TsOH in refuxing THF provided a single product in 79% yield. However, in contrast to the products **147-149**, the IR spectrum of this product did not show the hydroxyl stretching absorption, but displayed absorption bands at 1713 and 1664 cm^{-1}, the latter suggesting the presence of an alkene function. In addition, the ^{13}C NMR spectrum showed two signals at δ 136.4 and 168.1, consistent with the presence of an alkene function, and two carbonyl carbon signals at δ 209.5 and 195.8. This data, along with mass spectral data, indicated that the aldol condensation had been followed by elimination of water to form an α,β-unsaturated ketone (eq 37).



146 151 152 (37)

The two possible products **151** and **152**, both resulting from the formation of a 6-5 system from the nine-membered ring, could be formed by condensation between carbons 6 and 2 in **146** (**151**) or carbons 3 and 7 (**152**). Since the product obtained was a viscous oil, X-ray crystallography could not be used directly to determine its structure. To distinguish between the two possible products, an HMBC (heteronuclear multiple bond correlation) experiment was performed in conjunction with an HMQC (heteronuclear multiple quantum coherence) experiment. It was expected that only compound **152**

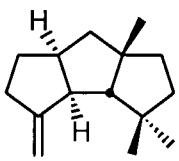
would show a long range (two and three bond) correlation (HMBC) between the carbon of the C-2 carbonyl and the protons of the methyl group (Me-14). On the other hand, compound **151** would show a correlation between a carbon of the alkenic function (i.e. C-2) and the methyl group (Me-14). In fact, the multiple bond correlation between the alkene signal at δ 168.1 (C-2) and the methyl group protons (δ 1.26) (H-14) was observed. Such a correlation would be impossible in the case of **152**. Therefore, the identity of the aldol product as **151** had been established.

In summary, it was shown in this brief study that intramolecular aldol condensations involving substances **142-144** and **146** readily produce products that possess novel carbon skeletons. Thus, the substances **142-144**, upon treatment with *p*-TsOH in THF provided the functionalized tricyclo[5.5.0.$0^{2,9}$]dodecanes **147-149**. On the other hand, the triketone **146**, when treated under similar conditions, generated the functionalized tricyclo[7.4.0.$0^{2,6}$]tridecane **151**.

2.5 Total synthesis of (±)-1-desoxyhypnophilin (61) and (±)-6,7-epoxy-4(15)-hirsuten-5-ol (62)

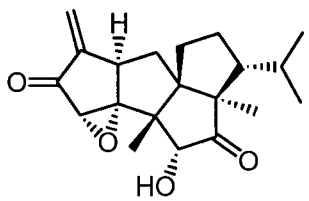
2.5.1 Triquinane Natural Products: Background

Among the most popular synthetic targets in the 1980s and 1990s were the polyquinane natural products. During the 1970s and 1980s many members of this general class of compounds, including sesqui- (C_{15}), di- (C_{20}) and sester- (C_{25}) terpenoids, were isolated from various terrestrial and marine organisms. Indeed, reports regarding the structure elucidation of novel polyquinane natural products isolated from previously unexplored sources continue to appear periodically in the literature.[77-79] The wide interest devoted to this class of natural products has been in part due to their potent biological activity; many members have been found to possess antitumor, antibacterial, or antiviral properties.[45] The numerous reported syntheses of polyquinane natural products, fueled by the interest in their unique structures, provided a testing ground for new cyclopentane annulation methodologies.[45,80] In our laboratories, exploration of the use of bifunctional reagents in 5-membered ring annulations culminated in the synthesis of the linear triquinane (±)-9(12)-capnellane (**153**),[81] as well as the first synthesis of a tetraquinane natural product, (±)-crinipellin B (**154**).[82]



(±)-9(12)-capnellane

153

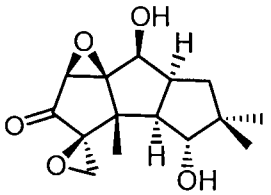


(±)-crinipellin B

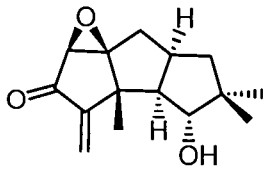
154

One of the most prevalent polyquinane synthetic targets has been the sesquiterpene coriolin (**68**), a metabolite of *Coriolus consors* with interesting antibiotic and antitumor properties.[83] This highly oxygenated hirsutane-type compound was the objective of over 20 different total and formal syntheses since 1980, with the most recent

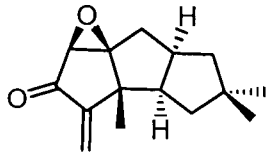
approaches having been reported in 1999.[84,85] A related substance, hypnophilin (**65**),[86] isolated from *Pleurotellus hypnophilus*, has also been a popular target. Hypnophilin (**65**) displays activity toward gram-positive and gram-negative bacteria, fungi, yeast and cancer cells.[87]



coriolin
68



hypnophilin
65

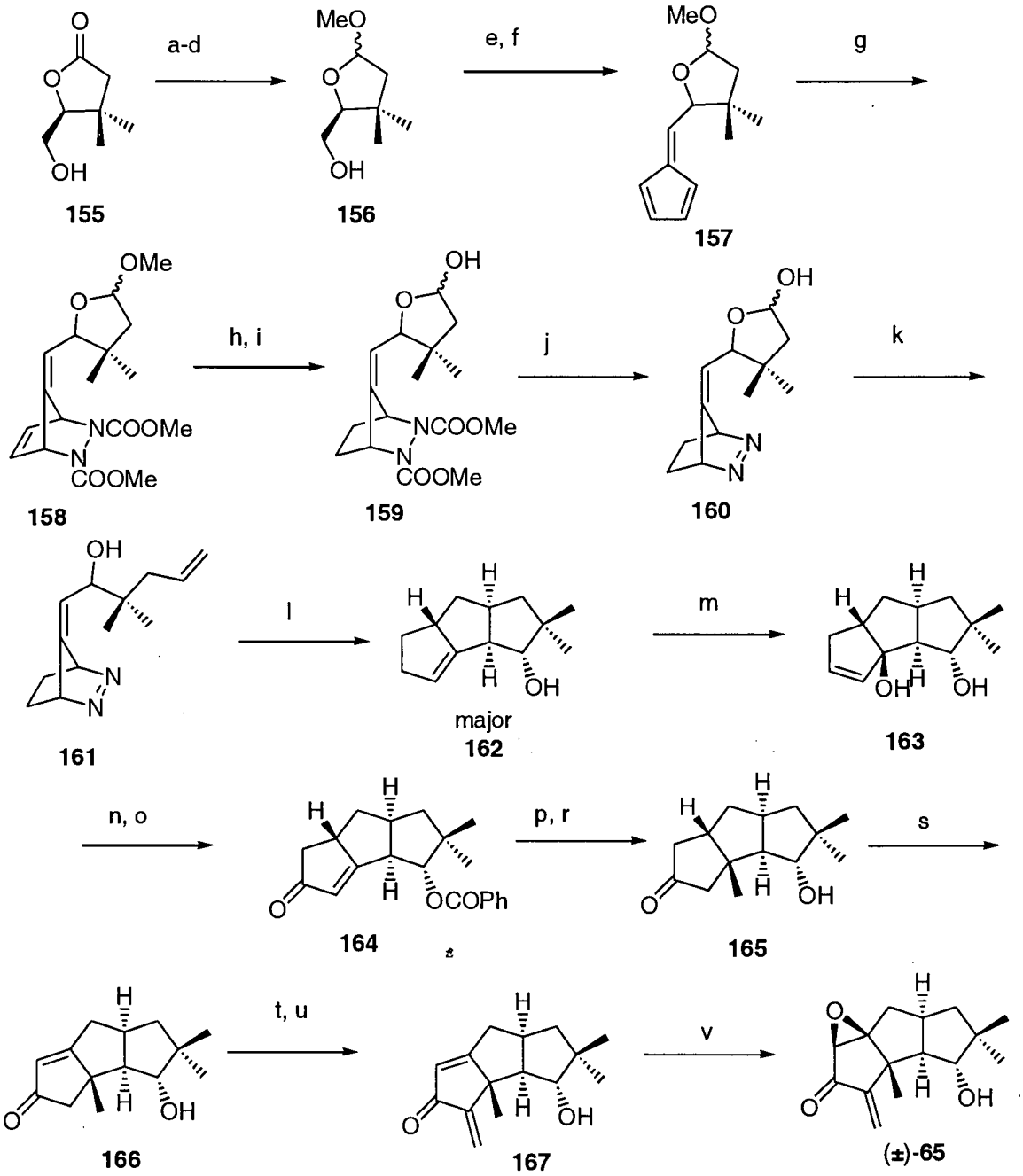


1-desoxyhypnophilin
61

As an illustration of the various synthetic innovations in the assembly of the triquinane framework, some approaches to their formation are worth outlining. Since numerous methods have been developed, those discussed in this section will involve the synthesis of hypnophilin (**65**), which is particularly relevant due to its structural similarity to the chosen target compound of this study, 1-desoxyhypnophilin (**61**).

The key step in the first reported total synthesis of (±)-hypnophilin by Little and coworkers[87] was the construction of the triquinane framework of **162** via an intramolecular 1,3-diyl trapping reaction (Scheme 19). The precursor for this reaction was prepared from the furanone **155**. The primary alcohol group of this compound was first protected as a benzyl ether. This protection step was followed by reduction of the lactone function to provide a diastereomeric mixture of lactols. Conversion of the lactol moiety into the corresponding methyl acetal, followed by removal of the benzyl protecting group, afforded **156**. Swern oxidation of the alcohol **156** provided an aldehyde which was treated under previously developed conditions[88] with cyclopentadiene to form the fulvene **157**. A Diels-Alder reaction of **157** and dimethylazodicarboxylate provided the dicarbamate **158**. The internal double bond of **158** was selectively hydrogenated with diimide and the acetal function was converted to the lactol **159** by treatment with acetic acid. The dicarbamate **159** was saponified and the resulting hydrazine was oxidized with potassium ferric cyanide to provide the diazene **160**. Reaction of the masked aldehyde with methylenetriphenylphosphorane provided compound **161**. The diazene **161** was

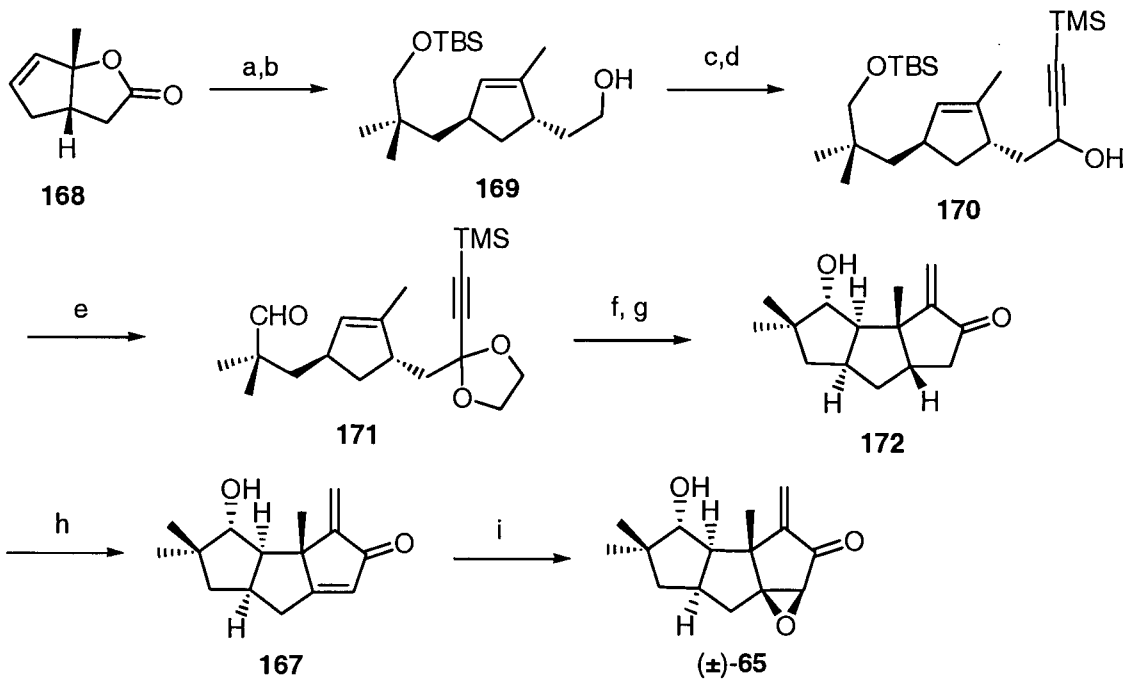
converted via a 1,3-diyl trapping reaction to the triquinane **162** in excellent yield (90%). The diradical intermediate of this reaction was generated by photolysis of the diazaene **161** at low temperature. Four other minor products were obtained in the 1,3-diyl trapping reaction. However, when the reaction temperature was maintained at -60 °C the ratio of the major compound **162** to the combined minor products was 30:1. Having formed the triquinane skeleton, elaboration of this advanced intermediate **162** into the final product **65** required only a few steps. Thus, treatment of **162** with *meta*-chloroperoxybenzoic acid (*m*-CPBA), followed by heating the resultant epoxide with LDA led to the formation of diol **163**. The primary alcohol function was protected as a benzoate ester and oxidation of the free allylic alcohol using PCC afforded the enone **164**. The angular methyl group was installed by the treatment of **164** with a cuprate reagent. The benzoyl protecting group was then removed to yield **165**. The ketone **165** was treated with a bulky base, lithium tetramethylpiperidide, to afford a mixture of the silyl enol ethers in a ration of 6:1. The mixture of the enol ethers was subjected to the Saegusa[89] conditions to introduce the enone function of **166**. The yield of the desired product was quite low (30%), although, based on the recovered ketone **165**, it was reported to be 93%. The α methylidene was formed in a three-step procedure. Compound **165** was treated with LDA and the resultant enolate was reacted with formaldehyde gas to generate a mixture of diastereomeric alcohols. Treatment of this mixture with tosyl chloride and a subsequent elimination reaction promoted by 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) afforded the dienone **167**. Monoepoxidation of the strained internal olefin gave (±)-hypnophilin (**65**) in 50% isolated yield along with some recovered starting material (30%).



Reagents: a) $C_6H_5CH_2Br$, Ag_2O; 76%; b) DIBAL-H; 97 %; c) MeOH, H^+;
d) H_2, PdOH; 94 %; e) $(COCl)_2$, DMSO, Et_3N; f) AcOH, pyrrolidine, cyclopentadiene;
55 %; g) MeOOC-N=N-COOMe; 90 %; h) KOOC-N=N-COOK, AcOH; 96 %;
i) aq. AcOH, heat; 95 %; j) KOH; $K_3Fe(CN)_6$; 86 %; k) $CH_2=PPh_3$; 67 %;
l) hv, -60 °C; 90 %; m) *m*-CPBA; LDA, heat; 54 %; n) BzCl; 85%; o) PCC; 89 %;
p) $Me_2Cu(CN)Li_2$, BF_3 Et_2O; 93 %; r) KOH; 99 %; s) LTMP, TMSCl; Et_3N;
$Pd(AcO)_2$, MeCN; 31 %; t) LDA; CH_2O; 85 %; u) *p*-TsCl, pyr;DBU; 80 %;
v) H_2O_2, Na_2CO_3; 50 %.

Scheme 19

A more concise approach to (±)-hypnophilin (**65**), involving an application of the tandem samarium diiodide-mediated radical cyclization, was developed by Curran and coworkers (Scheme 20).[90] Lactone **168** was treated with the cuprate reagent derived from 1-bromo-3-[(*t*-butyldimethylsilyl)oxy]-2,2-dimethylpropane. Reduction of the resultant carboxylic acid function with lithium aluminum hydride generated the alcohol **169**. Oxidation of this alcohol, followed by the addition of lithium trimethylsilylacetylide to the resultant aldehyde provided **170**. Oxidation of the secondary alcohol of **170** gave the ketone which was converted to the corresponding ketal **171**. At this stage the key samarium diiode-mediated tandem radical cyclization was performed. Treatment of **171** with SmI_2 in the presence of HMPA generated the triquinane framework in one step. Hydrolysis of the ketal function of the cyclized product resulted in the formation of **172** in 58% yield over the two steps. The dienone **167** was formed by treatment of **172** with excess LDA and TBSCl in THF/DMPU followed by the addition of DDQ in 2,6-lutidine. Compound **167** was treated with H_2O_2 to generate the final product (±)-hypnophilin (**65**) in 53% yield in a protocol similar to that used by Little.[87]



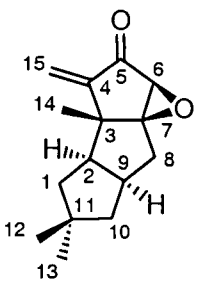
Reagents: a) $BrCH_2C(Me)_2CH_2OTBS$, Li, CuBr; b) $LiAlH_4$; 94 %; c) PCC; d) Li-C≡C-TMS; 98 %; e) PCC; H^+, $(CH_2OH)_2$; TBAF; PCC; 72 %; f) SmI_2; g) H^+; 58 % h) LDA; TBSCl; DDQ, 2,6-lutidine; 72 %; i) H_2O_2, K_2CO_3; 53 %.

Scheme 20

The syntheses of (±)-hypnophilin ((±)-**65**) outlined above, which represent just two of the numerous approaches to triquinane natural products,[45,80] provided a proving ground for novel synthetic methods (i.e. a 1,3-diyl trapping reaction and a samarium diiodide tandem radical cyclization approach). The most recent approaches tend to focus on the concise formation of the triquinane skeleton[91-93] of both natural and non-natural compounds and continue to provide illustration of the synthetic power of novel methods.

2.5.2 Isolation of (-)-1-desoxyhypnophilin (**61**) and (+)-6,7-epoxy-4(15)-hirsuten-5-ol (**62**)

(-)-1-Desoxyhypnophilin (**61**) and (+)-6,7-epoxy-4(15)-hirsuten-5-ol (**62**),* previously unknown substances, were isolated in 1994 from *Lentinus crinitus*, a fungus collected in Ethiopia from dead wood.[44] These two metabolites were isolated along with the known (-)-hypnophilin (**65**) and the corresponding diol (**173**). The antimicrobial activity of the new compounds **61** and **62** against several test organisms was determined by a serial dilution assay and the minimal inhibitory concentration (MIC) was reported. Compound **61** contains an α-methylidenecyclopentanone moiety, a functional group that is often associated with strong antibiotic activity in natural products. Therefore, it is not surprising that alcohol **62** showed reduced antimicrobial activity in comparison to (-)-1-desoxyhypnophilin (**61**). For instance, the MIC of compound **61** against *Bacillus cereus* was 2-5 μg/mL and against *Staphylococcus aureus* 10-25 μg/mL while the reported MIC of the alcohol **62**, in both cases, was greater than 100 μg/mL.[44]



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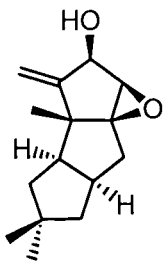

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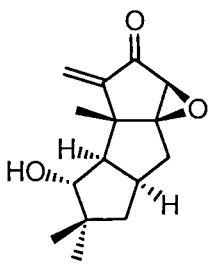
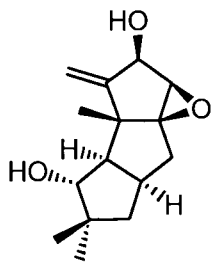


65



173

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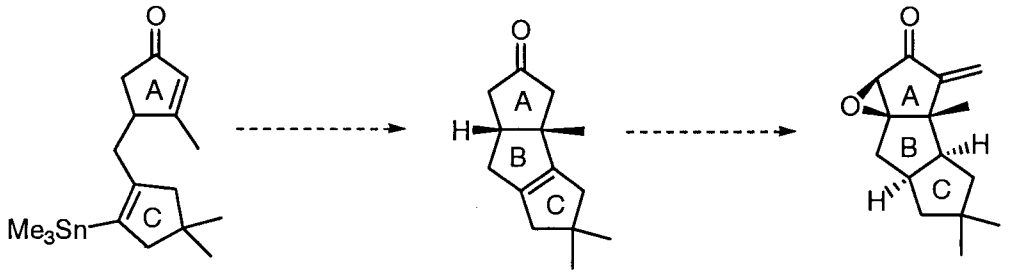
* The numbering system normally employed for hirsutane sesquiterpenoids is used in naming of compounds **61** and **62** in the text of the discussion. The experimental section of this thesis contains IUPAC names of both **61** and **62** as well as IUPAC names of all of the synthetic intermediates. It should be noted that throughout this thesis the structures of the synthetic *racemic* compounds **61** and **62** are drawn as the enantiomers of the isolated compounds (-)-**61** and (+)-**62**. This was done in order to keep the representation of the Cu(I)-mediated cyclization products (such as **60**, see Scheme 21 on the next page) in agreement with the convention established in the methodology part of this work.

2.5.3 Retrosynthetic plan for the synthesis of (±)-1-desoxyhypnophilin (**61**) and (±)-6,7-epoxy-4(15)-hirsuten-5-ol (**62**)

The proposed synthetic plan for the construction of the natural products (±)-**61** and (±)-**62** involved formation of the triquinane skeleton by use of the CuCN mediated conjugate addition method (Scheme 21) discussed in greater depth earlier (see Section 2.1.2).

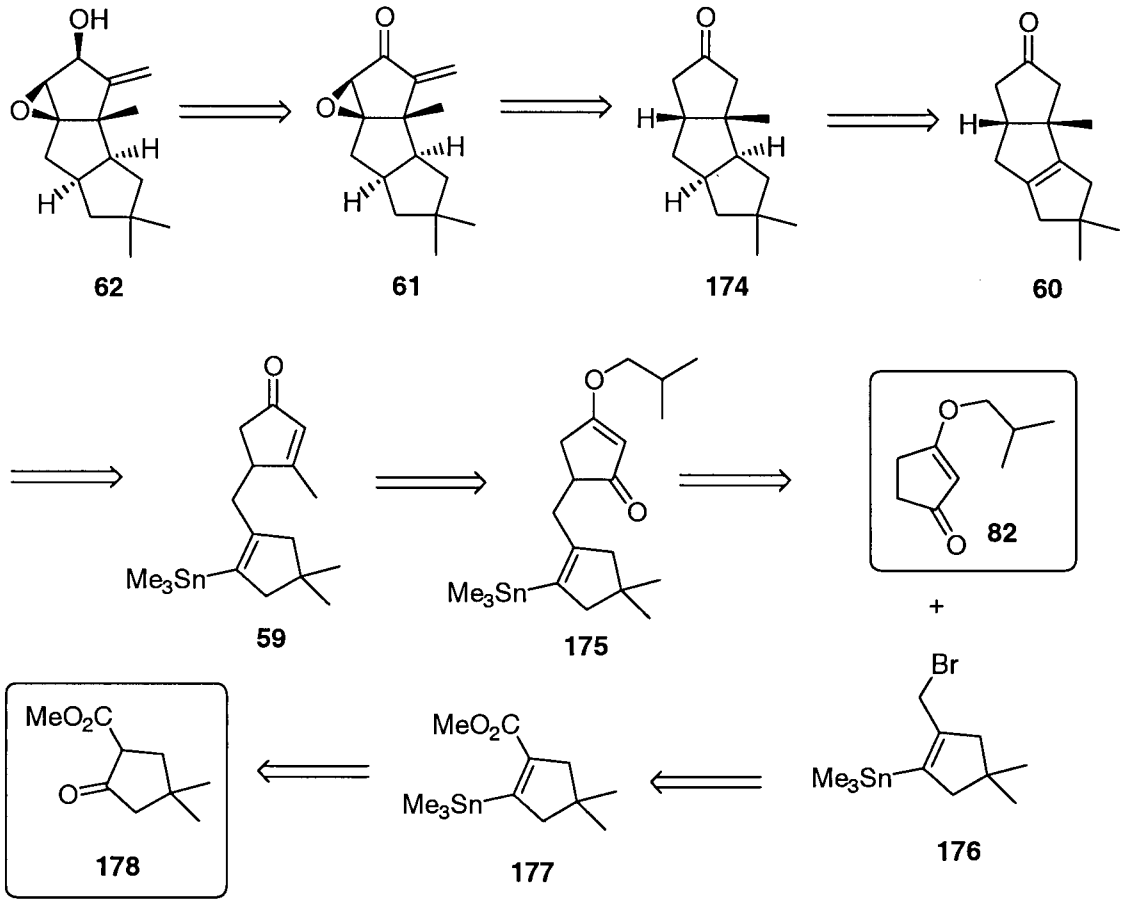


59 **60** **61**

Scheme 21

It is clear that the synthesis of the natural product (±)-**62** from (±)-1-desoxyhypnophilin **61** would involve a one step reduction process (Scheme 22) analogous to that reported for the synthesis of hirsutic acid C.[94] It was anticipated that the epoxide and α methylidene functionalities present in **61** could be introduced into the tricyclic ketone **174**. Based on literature precedence in the synthesis of hypnophilin,[87] the introduction of the exocyclic methylene unit was planned to precede the epoxidation step. In theory, though, the steps could be reversed in the protocol employed in the synthesis of crinipellin B.[82] It was conceived that the triquinane skeleton of **174** could be readily generated from the tricyclic compound **60** by stereoselective reduction of the tetrasubstituted double bond. It was envisaged that access to the ketone **60** could be gained via the CuCN-mediated cyclization of the intermediate **59**. Presumably, the enone **59** could be prepared by treatment of the vinylogous ester **175** with methylmagnesium bromide, followed by acid hydrolysis of the resultant product. It was anticipated that **175** could be generated by alkylation of the vinylogous ester **82** with the bromide **176** via a procedure analogous to the method developed earlier (Section 2.1.1). Preparation of the bromide **176** from the ester **177** was expected to proceed without complications.[50]

Preparation of the alkenylstannane **177** from the the known β-keto ester **178**[95] was also predicted to be facile.

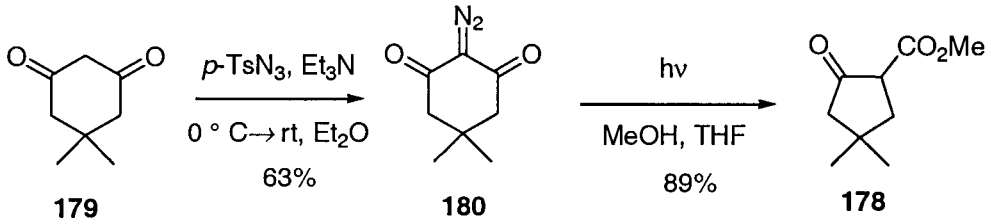


Scheme 22

2.5.4 Synthesis of (±)-1-desoxyhypnophilin ((±)-**61**)

*2.5.4.1 Preparation of the bromide **176***

Synthesis of the required methyl 4,4-dimethyl-2-oxocyclopentanecarboxylate (**178**) was accomplished by following a literature procedure (Scheme 23).[95,96]



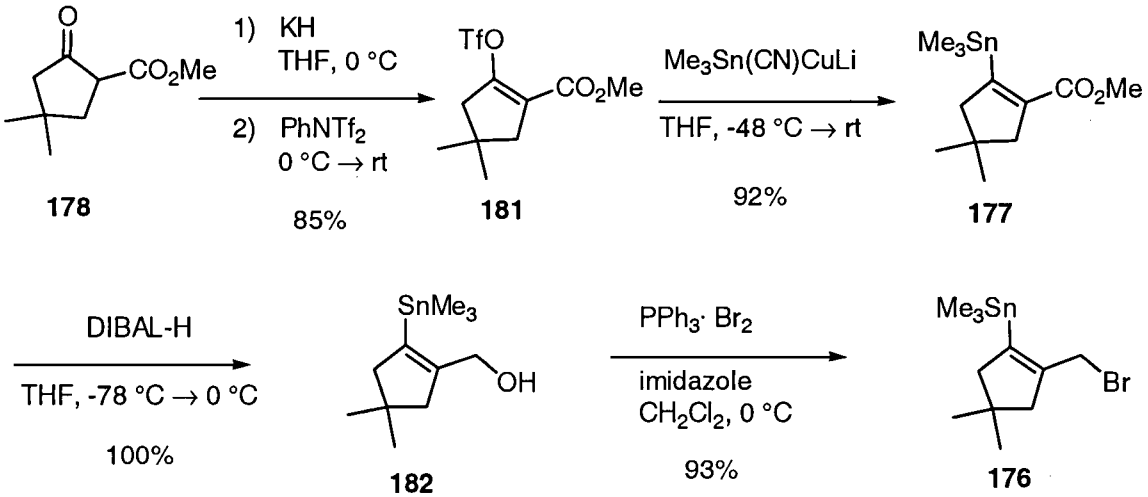
Scheme 23

Thus, treatment of commercially available dimedone (**179**) with triethylamine and *p*-toluenesulfonyl azide provided, after work-up and successive recrystallizations from ethanol at -25 °C, 2-diazodimedone (**180**) as yellowish needles in 63% yield.[96] The appearance of the product, its melting point, as well as the IR and ^{1}H NMR spectroscopic data were in full agreement with the reported values.[96,97] The ^{1}H NMR spectrum of the product displayed a 6-proton singlet at δ 1.10 due to the *gem*-dimethyl group and a 4-proton singlet at δ 2.43 due to the methylene protons. The IR spectrum showed a band at 2146 cm^{-1}, characteristic of a diazo stretching frequency.

2-Diazodimedone (**180**) was transformed into the β–keto ester (**178**) by a photolytic Wolff rearrangement followed by trapping of the resultant ketene intermediate with methanol. A solution of 2-diazodimedone in THF and methanol was irradiated until the reaction was complete as judged by TLC analysis. Removal of the solvent, followed by distillation of the resulting material, provided compound **178** as a clear oil in 89% yield. The preparation of **178** was conveniently carried out on a large scale, since the purifications of both compounds **180** and **178** required no tedious chromatographic separations. Since the published ^{1}H NMR spectral data for **178** were recorded on a 60 MHz instrument,[95] updated spectral data is provided in the experimental section of this thesis. The ^{1}H NMR spectrum displayed two 3-proton singlets at δ 1.04 and δ 1.21 for

the *gem*-dimethyl group and a 3-proton singlet for the methyl ester at δ 3.72. The methine (CH) signal appeared as a doublet of doublets at δ 3.37, which exhibited coupling to the two adjacent diastereotopic methylene protons with coupling constants of 9.0 and 11.0 Hz. The corresponding methylene proton signals appeared at δ 2.12 (1H, dd, J = 9.0 and 13.0 Hz) and as part of the signal at δ 2.17-2.20. The latter signal was overlapping with a broad 2-proton singlet (δ 2.19) due to the methylene protons adjacent to the ketone.

The next step in the synthesis of (±)-1-desoxyhypnophilin was the conversion of the β–keto ester **178** into the bromide **176**. The preparation of a similar bromide (**73**) was previously accomplished in the methodological part of this work and an analogous procedure was followed for the preparation of **176** (Scheme 24).

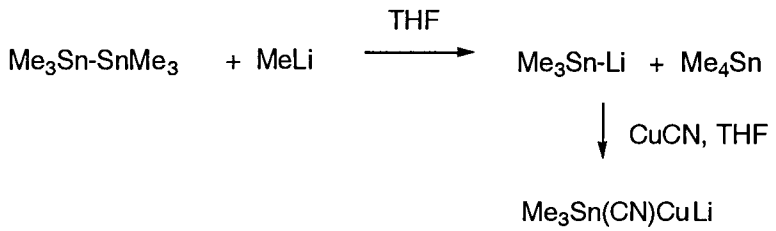


Scheme 24

A cool (0 °C) solution of the β-keto ester **178** in THF was treated with potassium hydride and the resulting enolate was triflated on oxygen by addition of solid *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$) to the reaction mixture. Upon completion of the reaction Et_2O was added to dilute the mixture and the solids were removed by filtration of the mixture through a silica/Celite plug. Concentration of the filtrate and purification of the crude material by chromatography on silica gel afforded the triflate

181 in 85% yield. The structure of the product **181** was confirmed by spectroscopic methods. The ^{1}H NMR spectrum displayed a 6-proton singlet due to the *gem*-dimethyl group at δ 1.15. The methyl ester signal was visible at δ 3.76. The signals for the two pairs of methylene protons appeared as triplets at δ 2.47 (2H) and δ 2.54 (2H) and exhibited small mutual coupling with a coupling constant of 2.5 Hz. The successful incorporation of the triflate function was confirmed by the ^{13}C NMR spectrum, which showed a quartet due to the -CF_3 group at δ 118.3 ($J_{C\text{-}F}$ = 319 Hz).

The triflate **181** was converted to the stannane **177** by use of the cyanocuprate reagent $Me_3Sn(CN)CuLi$.[98] The cuprate was generated by the addition of 1 equivalent of MeLi to hexamethylditin in THF at -48 °C, followed by the addition of 1 equivalent of solid copper cyanide (Scheme 25).



Scheme 25

Phenylthiocopper(I) has also been used in place of CuCN; however commercial CuSPh often provided unreliable yields of the stannane **177**. The use of commercially available CuCN in the preparation of the cuprate reagent gave consistently high (> 90%) yields of **177**.

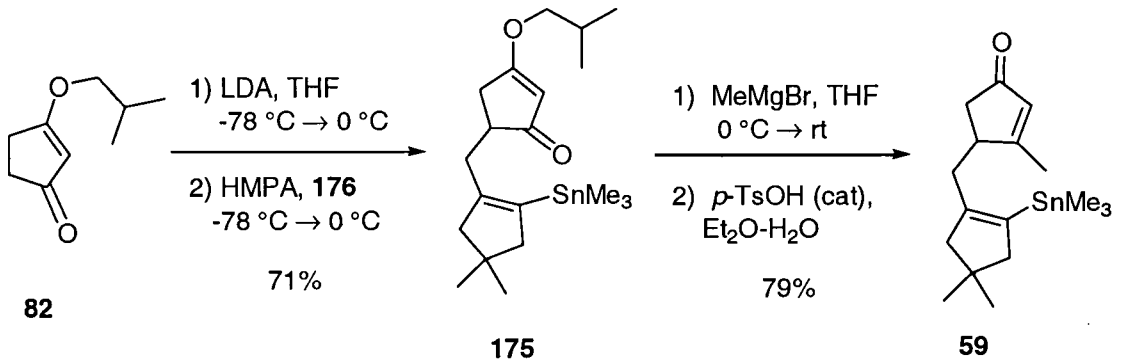
The successful conversion of the triflate **181** into the stannane **177** was confirmed by both ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **177** displayed a 9-proton singlet with a satellite peaks ($^2J_{Sn\text{-}H}$ = 55.0 Hz) at δ 0.14, characteristic of the Me_3Sn moiety. A 6-proton singlet due to the *gem*-dimethyl group was also visible at δ 1.06. The methyl ester singlet appeared at δ 3.69. The signals for the two pairs of methylene protons were displayed at δ 2.40 (2H) and δ 2.45 (2H). In the ^{13}C NMR spectrum a peak at δ -8.6 confirmed the presence of the Me_3Sn group and the spectrum showed the expected number of carbon signals.

A solution of the ester **177** in THF was treated with 2.5 equivalents of DIBAL-H. After work-up and purification of the crude material by column chromatography on silica gel, the alcohol **182** was obtained as a colourless oil in quantitative yield. The IR spectrum of the product **182** showed a broad absorption band at 3343 cm^{-1}due to the hydroxyl group. The ^1H NMR spectrum showed a 9-proton singlet at δ 0.11 due to the Me_3Sn group. A broad -OH signal at δ 1.30 and a 2-proton doublet at δ 4.12 due to the hydroxymethyl group were also visible.

The alcohol **182** was converted to the corresponding bromide using triphenylphosphine and bromine in the presence of imidazole. When the reaction was complete, pentane was added to the reaction mixture. The mixture was then filtered through a cake of silica gel/Celite in order to remove a majority of the precipitated triphenylphosphine oxide. It was found that the yields of the bromide **176** improved by about 10% if the residue left in the flask following the filtration was treated with aqueous sodium bicarbonate solution (10%). The aqueous mixture was extracted with pentane and the pentane solution was filtered as above. Concentration of the combined filtrates provided bromide **176** in 93% yield. Spectroscopic data confirmed the conversion of the alcohol **182** into the primary bromide **176**. Thus, the ^1H NMR spectrum showed a 9-proton signal at δ 0.18 attributed to the Me_3Sn moiety, a 6-proton singlet at δ 1.06, two 2-proton signals at δ 2.25 and δ 2.32 as well as a 2-proton singlet at δ 4.02 due to the bromomethyl group. The high resolution mass spectral analysis on the (M^+-CH_3) fragment confirmed its molecular mass (HRMS calcd for $C_{10}H_{18}{}^{120}Sn^{79}Br$: 336.9614; found: 336.9620).

2.5.4.2 Synthesis of the cyclization precursor (59)

With the bromide **176** in hand, the preparation of the cyclization precursor, the enone **59**, could be accomplished. A procedure very similar to that employed previously (see Section 2.1.1) for the alkylation of 3-isobutoxycyclopent-2-en-1-one (**82**) was adopted (Scheme 26).



82 **175** **59**

Scheme 26

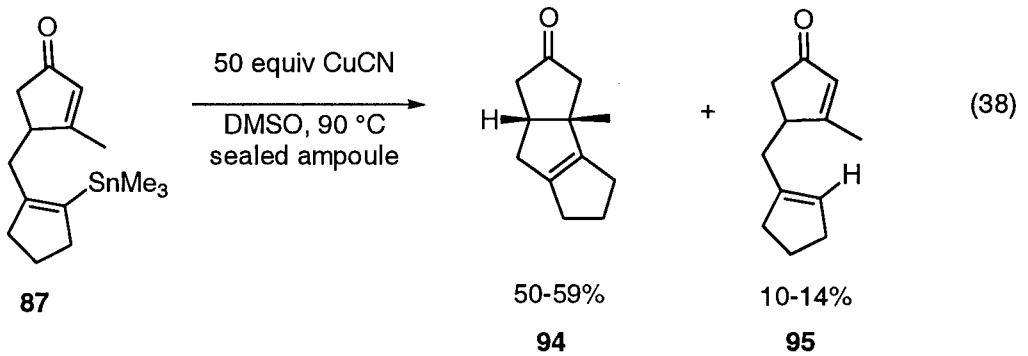
A solution of the vinylogous ester **82** in THF was treated with LDA at -78 °C. This mixture was warmed for 15 min to 0 °C, after which time the clear solution became orange in colour. Once the solution had been recooled to -78 °C, HMPA and a solution of the bromide **176** in THF were added. After aqueous work-up and purification of the crude material by column chromatography on silica gel and bulb-to-bulb distillation (220-230 °C at 0.6 torr), the alkylated product **175** was obtained in 71% yield as a viscous oil which solidified upon standing (m.p. 35-36 °C). The structure of **175** was confirmed by the usual spectroscopic methods. The ^{1}H NMR spectrum of **175** showed the presence of the Me_3Sn moiety, as evidenced by the 9-proton singlet at δ 0.08. The *gem*-dimethyl group appeared as two 3-proton singlets at δ 1.00 and δ 1.02. The spectrum also displayed a 6-proton doublet at δ 0.96, due to the methyl groups of the isobutyl unit ($(\underline{CH_3})_2$-CH-CH_2-), as well as a doublet at δ 3.70 due to the methylene protons adjacent to the oxygen (-O$\underline{CH_2}$-CH-). The signal due to the alkenyl proton of the vinylogous ester moiety was visible at δ 5.18. The remaining protons were displayed as multiplets between δ 2.02-2.31 (7H) and δ 2.56-2.62 (3H). The ^{13}C NMR spectrum of

175 showed the expected number of carbon signals. In addition, the high resolution mass spectral analysis on the peak corresponding to the molecular ion provided confirmation of the molecular mass of **175** (HRMS calcd for $C_{20}H_{34}O_2{}^{120}Sn$: 426.1581; found 426.1575).

Reaction of the vinylogous ester **175** with MeMgBr, followed by treatment of the acquired material with *p*-TsOH in wet Et_2O, converted compound **175** into the enone **59**. Standard work-up, purification of the crude product by column chromatography, and bulb-to-bulb distillation of the acquired liquid under reduced pressure (125-130 °C at 1.5 torr) gave **59** in 79% yield. This viscous oil solidified upon standing (m.p. 31-32 °C). The successful incorporation of the methyl group was confirmed by the ^1H NMR spectrum, which displayed an additional 3-proton singlet at δ 2.09. The remaining two methyl groups were visible at δ 1.02 and δ 1.05. In addition, a 1-proton singlet at δ 5.87, attributed to the alkenyl proton, was observed. All other spectroscopic data were also consistent with the assigned structure. The molecular mass was confirmed by high resolution mass spectral analysis on the (M^+-CH_3) peak (HRMS calcd for $C_{16}H_{25}O^{120}Sn$: 353.0927; found: 353.0931).

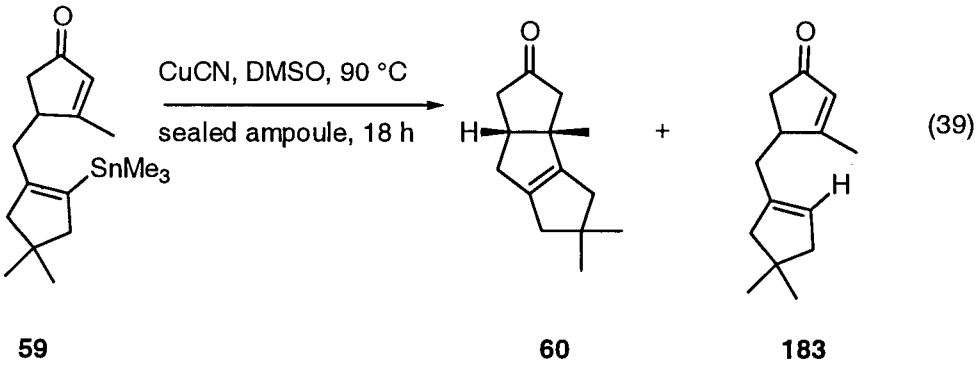
*2.5.4.3 CuCN-mediated intramolecular conjugate addition to generate the triquinane **60***

The conditions that gave the highest yield of the cyclized product **94** from the model system **87**, involved the use of 50 equivalents of CuCN in DMSO in a sealed ampoule with the concentration of substrate **87** at 0.05 M (see Section 2.1.2 and eq 38 below).



87 50-59% **94** 10-14% **95** (38)

These reaction conditions, when applied to the cyclization of **59** (eq 39, Table 6, entry 1) provided yields of the cyclized product **60** (57%) and protiodestannylated, uncyclized material **183** (14%) similar to those of **94** and **95** obtained with **87**. However, the use of such a large excess of CuCN was thought to be impractical in the synthesis of large amounts of the required intermediate **60**. In order to optimize the reaction conditions, several reactions were attempted in which both the amount of CuCN and the volume of DMSO were decreased concomitantly. In this manner, the concentration of CuCN was maintained at 2.7 M for all of the reactions, while the concentration of the stannane **59** was varied (Table 6).



(39)

59 **60** **183**

Table 6. CuCN-mediated cyclization of **59** with various amounts of CuCN in DMSO (maintained at 2.7 M).

Entry	Equiv of CuCN (at 2.7 M)	Concentration of **59** (M)	Yield of **60** (%)	Yield of **183** (%)
1	50	0.05	57	14
2	25	0.10	52	15
3	17	0.15	59	11
4	**10**	**0.27**	**59**	**14**
5	5	0.5	45	14[a]
6	2.5	1	33	10[b]

[a] Approximately 6% of **59** was isolated. [b] Approximately 20% of **59** was isolated.

Decreasing the amount of CuCN from 50 to 10 equivalents (Table 6, entries 1-4) resulted in essentially unchanged yields of the cyclized product **60** and the protiodestannylated product **183**. Further decreases in the amount of CuCN to 5 and 2.5 equivalents resulted in a decrease in the yield of the cyclized product **60** and incomplete consumption of the stananne **59**. When 5 equivalents of CuCN were used, 45% of the cyclized material **60** was accompanied by about 6% of the unreacted starting material **59** (entry 5). Considerably worse results were obtained when 2.5 equivalents of CuCN were used (entry 6). The optimal reaction conditions involved the use of 10 equivalents of CuCN (Table 6, entry 4) with the concentration of the starting material **59** at 0.27 M. These reaction conditions were used to prepare sufficient quantities of the cyclized tricyclic ketone **60** for the total synthesis of (±)-1-desoxyhypnophilin.

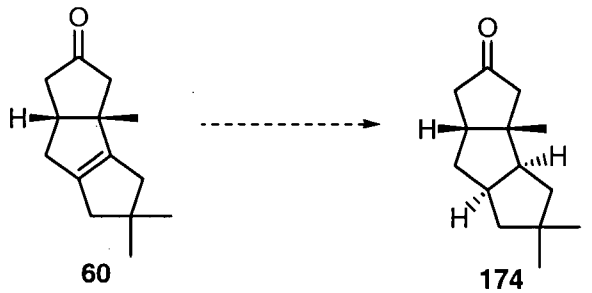
The structures of both compounds **60** and **183** were confirmed by spectroscopic methods. The IR spectrum of the tricyclic compound **60** exhibited a carbonyl stretching band at 1746 cm^{-1}, characteristic of an isolated cyclopentyl ketone. Further evidence for the formation of **60** was provided by the ^{1}H NMR spectrum, which showed three 3-proton singlets at δ 1.05, 1.08 and 1.15 due to the methyl groups. In addition, the expected number of signals in the aliphatic region (δ 1.79-2.79), corresponding to the remaining 11 protons, was observed. In the ^{13}C NMR spectrum the carbonyl carbon resonance was visible at δ 219.7, while the two alkene carbon signals appeared at δ 141.0 and 149.0. Additionally, the molecular mass of compound **60** was confirmed by high resolution mass spectroscopic analysis on the molecular ion (HRMS calcd for $C_{14}H_{20}O$: 204.1514; found: 204.1519).

The structure of the protiodestannylated material **183** was confirmed in a similar manner. The IR carbonyl stretching frequency appeared at 1714 cm^{-1}, typical of a conjugated cyclopentenone functionality. The ^{1}H NMR spectrum of **183** indicated the presence of two alkenic protons, with resonances at δ 5.21 and δ 5.82. The latter signal was a triplet with a coupling constant of 1.5 Hz, and therefore could be assigned to the β-proton, a result of protiodestannylation. The ^{13}C NMR resonances of the carbonyl and the alkene function conjugated with the carbonyl function appeared at δ 208.7, and at δ 130.7 (CH) and δ 181.2 respectively. Two other alkenic carbon signals were also visible at δ 124.9 (CH) and 140.2. The high resolution mass spectrum of **183** indicated

the molecular mass in agreement with that calculated for $C_{14}H_{20}O$ (calcd: 204.1514; found: 204.1517).

*2.5.4.4 Reduction of the double bond to form the cis-anti-cis triquinane **174**.*

With the tricyclic ketone **60** in hand, the reduction of the tetrasubstituted double bond to form the *cis-anti-cis* fused triquinane skeleton of 1-desoxyhypnophilin (**61**) was the next task (eq 40).



(40)

Conformational analysis of compound **60** indicates that hydrogenation of the double bond might not be stereoselective for production of the desired *cis-anti-cis* product. The the A-B *cis*-fused ring system could result in steric hindrance to the α face of the molecule. On the other hand, the presence of the angular methyl group could provide some steric hindrance to the β face of the compound (Figure 3).

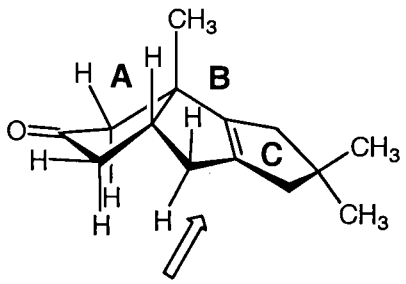
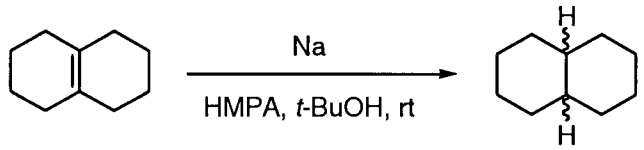


Figure 3. Reduction from the α face of **60** is needed to form the *cis-anti-cis* triquinane.

However, since the linear *cis-anti-cis* triquinane would be expected to be thermodynamically more stable than the corresponding *cis-syn-cis* triquinane, the initial plan involved a dissolving metal reduction of the olefin with the ketone functionality

protected. It seemed plausible that such a reduction protocol would favour the thermodynamically more stable product.

The reduction of unactivated alkenes using a solution of sodium metal in HMPA in the presence of *t*-butanol has been reported to give nearly thermodynamic product distributions (when more than one product could be formed). Such a distribution arises through equilibration of the organosodium or carbanionic intermediates.[99] This method was successfully applied[99] to the reduction of the tetrasubstituted double bond of a 9(10)-octalin system **184** (eq 41). A mixture of *trans* and *cis*-fused decalin **185** was obtained in a 30:1 ratio.



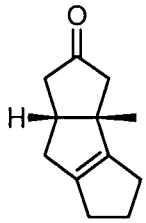
184 **185**

trans 91%
cis 3%

(41)

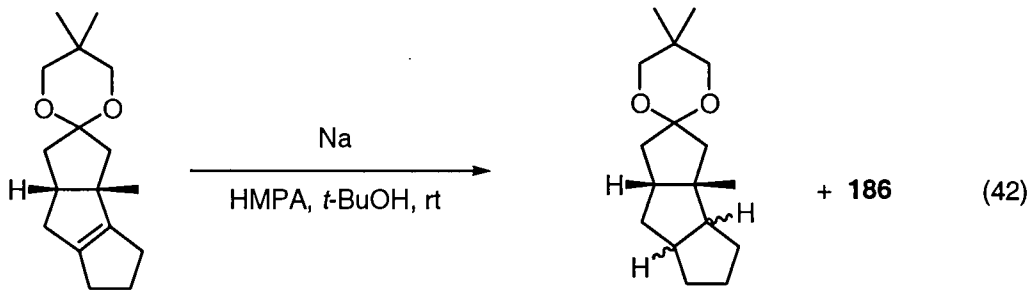
It was hoped that the application of this method to the reduction of the olefinic bond of **60** would provide the thermodynamically more stable *cis-anti-cis* triquinane.

The transformation was first attempted on a model system that had been prepared during the course of methodological studies. The ketone **94** and its derivatives were used in these preliminary investigations.



94

Several attempts to reduce the olefinic function of the model compound **186**, with sodium-HMPA-*t*-butanol resulted in the recovery of some of the starting material **186** and the formation of two reduction products **187** (GLC-MS) in a ratio of ~2:1 (eq 42). These products could not be separated by flash column chromatography on silica gel.

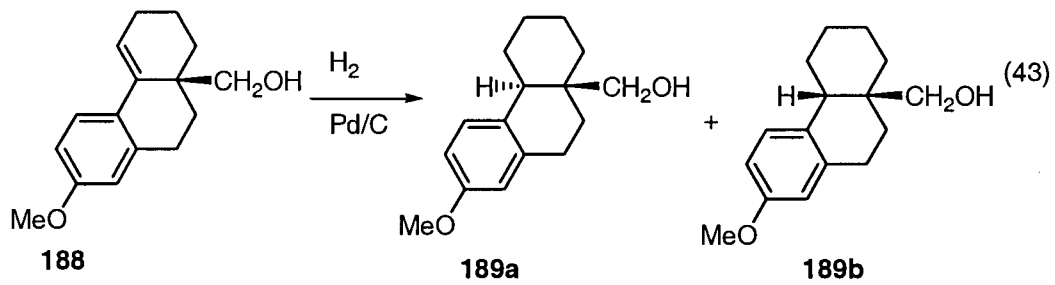


186

187
2:1 ~75%

This lack of stereoselectivity was disappointing and the difficulties associated with separation of the products caused this approach to be abandoned and other alternatives to be explored.

A previous report[100] had indicated that the presence of a hydroxymethyl group (-CH_2OH) (e.g. **188**, eq 43) afforded some degree of stereochemical control in heterogenous catalytic hydrogenations performed in non-polar solvents. For example, hydrogenation of compound **188** over a catalytic amount of palladium on carbon generated a mixture of products **189a** and **189b**. When the reaction was performed in ethanol the ratio of **189a** to **189b** was 94:6. However, when the hydrogenation was carried out in hexanes, a 39:61 ratio of **189a** to **189b** was obtained.



188

189a

189b

in EtOH	94	:	6
in hexanes	39	:	61

Presumably, this effect arises from "anchoring" of the hydroxyl group of the molecule to the surface of the catalyst. It is believed that this property, termed *haptophilicity*, affects the stereochemical outcome of the hydrogenation process. When the reaction is carried out in ethanol, the solvent eliminates this "anchoring" effect.

On the basis of conformational analysis of a molecular model (Dreiding) of compound **94**, it was expected that reduction of the carbonyl group would take place stereoselectively from the less hindered β face of the molecule. It was hoped that the α alcohol, thus generated, could then be used to induce stereoselectivity in the catalytic hydrogenation of the olefin from the desired α face (Figure 4).

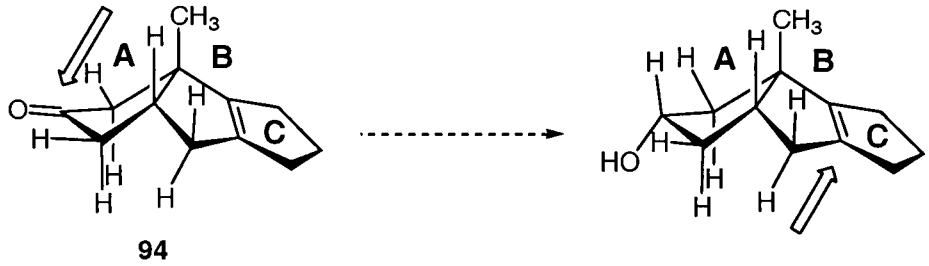
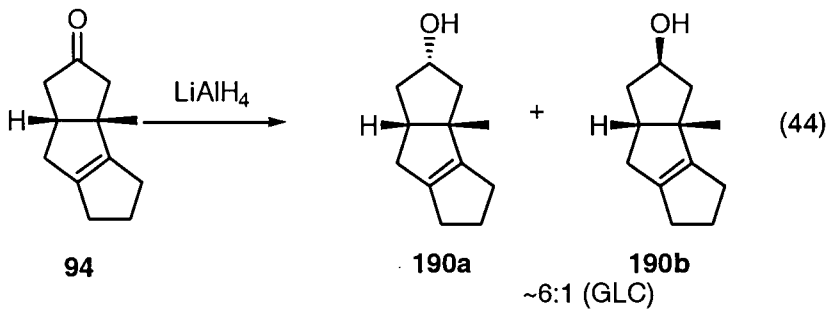


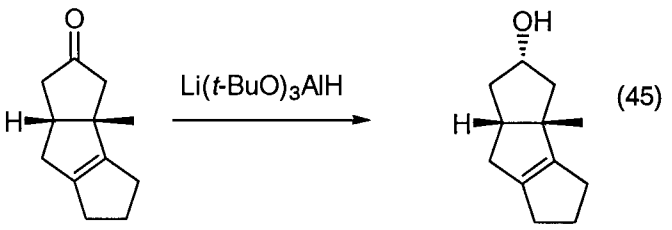
Figure 4. Expected reduction of **94** to the alcohol and hydroxy directing effect in olefin hydrogenation.

Treatment of the model system **94** with $LiAlH_4$ provided a 6:1 mixture (by GLC analysis) of alcohols **190a** and **190b**, which were inseparable by chromatography on silica gel (eq 44).



It was hoped that by employing a bulky hydride reducing reagent the stereoselectivity of the reaction could be improved. Thus, the ketone function of **94** was reduced using lithium tri-*tert*-butoxyaluminohydride to provide a *single* alcohol in excellent yield (>95%) corresponding to the major compound obtained in reduction with $LiAlH_4$ (eq 45). The relative configuration of the alcohol was expected to be as shown in structural formula **190a** (eq 45) based on conformational analysis of a Dreiding molecular model of the starting material **94**. However, the configuration of the hydroxyl group could not be unambiguously assigned on the basis of NOE experiments. The stereochemistry of **94**

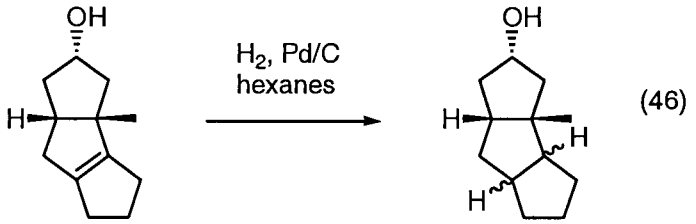
was later assigned based on the X-ray crystallographic studies employing substrate **196** (*vide infra*), an intermediate in the synthesis of 1-desoxyhypnophilin (**61**).



(45)

94 **190a** single isomer

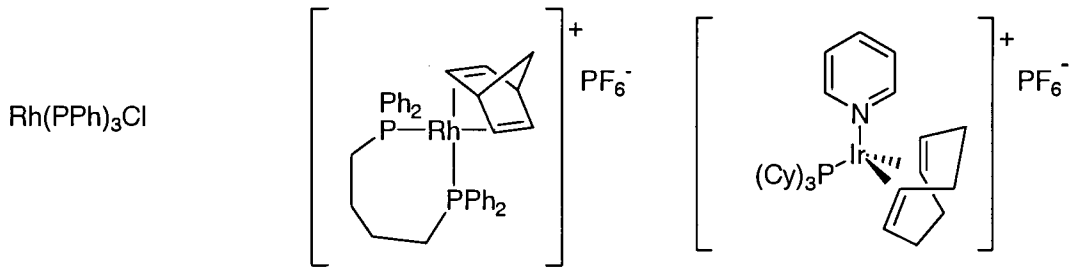
Hydrogenation of **190a** over palladium on carbon in hexanes provided a mixture of two products **191** that were found to be inseparable by column chromatography (eq 46). The ratio of the products was determined by GLC analysis to be 4:6. Since the two products could not be successfully separated, the identity of the major and minor products was not determined. Thus, for the purpose of the total synthesis of (±)-1-desoxyhyphophilin, the hydroxy-directed *heterogenous* hydrogenation conditions attempted here were ill suited for the generation of the *cis-anti-cis* triquinane.



(46)

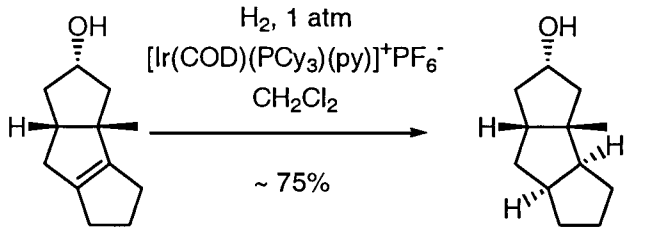
190a **191** ~4:6 (GLC)

The directing effect in hydrogenations, especially with a hydroxyl moiety, have also been explored in hydrogenation with *homogenous* catalysts.[101] The most effective catalysts used in these hydrogenations include Wilkinson's rhodium catalyst **192,**[102] the cationic rhodium complex **193** (Brown catalyst)[103] and iridium complex **194** (Crabtree catalyst)[104]. It has been found that the polar hydroxyl group coordinates to the metal centre of the catalyst, thereby directing the addition of hydrogen to the proximal face of the olefinic function.[101,105]



192 **193** **194**

Hydrogenation of the alcohol **190a** using the Crabtree catalyst (**194**) resulted in the formation of a *single* product **191a** in very good isolated yield (~75%) (eq 47). This was a very encouraging result, as the product was expected to have the required stereochemistry (proved in later X-ray crystallographic studies (*vide infra*)).



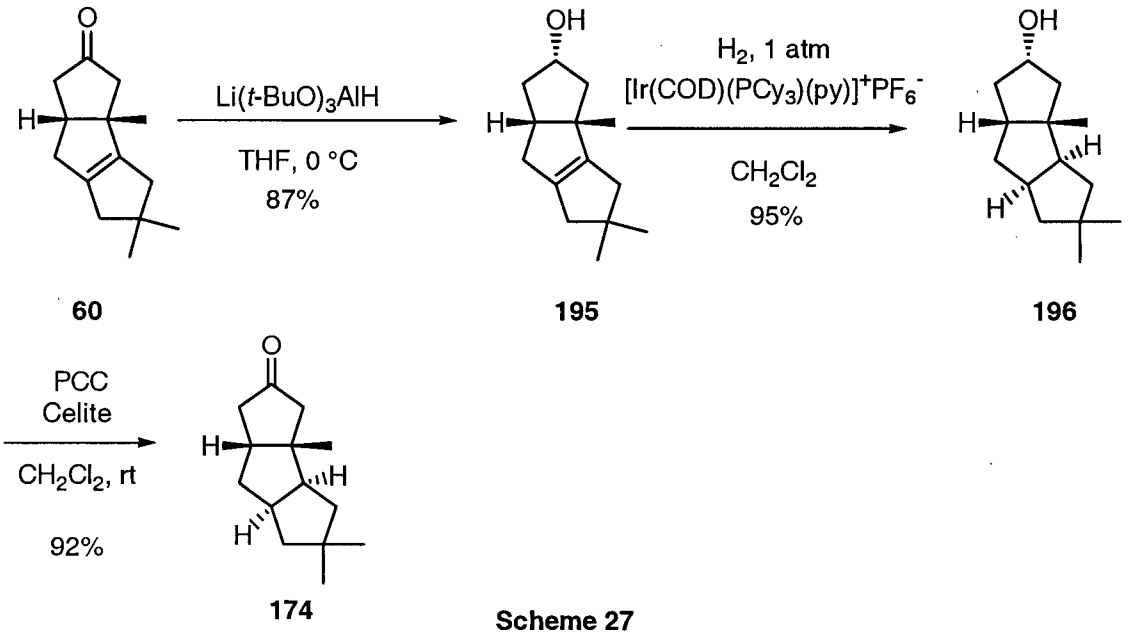
(47)

190a

1 diastereomer

191a

Having accomplished the highly stereoselective reduction of the model alkene **190a** to (presumably) yield the product with a *cis-anti-cis* configuration, this approach was applied to the synthesis of the natural product 1-desoxyhypnophin. Thus, a solution of ketone **60** in THF at 0 °C was treated with lithium tri-*tert*-butoxyaluminohydride to provide, after work-up and purification of the crude material by column chromatography and bulb-to-bulb distillation under reduced pressure (98-100 °C at 0.4 torr), the alcohol **195** in 87% yield (Scheme 27). The IR spectrum of this compound showed a hydroxyl stretching absorption at 3290 cm^{-1}. A broad 1-proton multiplet at δ 4.18 in the ^1H NMR spectrum was attributed to the carbinol proton. The relative configuration at the carbinol centre was not determined at this stage, but was revealed after the following step of the synthesis. Hydrogenation of **195** under 1 atm of dry hydrogen gas in the presence of the Crabtree catalyst **194**,[104] followed by removal of the catalyst and purification of the crude material, provided the alcohol **196** in 95% yield.



Scheme 27

The alcohol **196** proved to be a crystalline solid and recrystallization of a small amount of the material from hexanes afforded a sample suitable for X-ray crystallographic analysis.* This analysis established unequivocally the relative configuration of the hydroxyl group and confirmed the expected formation of the *cis-anti-cis* triquinane skeleton of both **196** and the earlier model system **191a**. The assignment of the ^{1}H NMR signals of **196** was accomplished by the analysis of the COSY spectrum, summarized in the experimental section.

* X-ray crystallographic analysis was performed by S. J. Rettig (deceased October 27, 1998) of the UBC X-ray Crystal Structure Laboratory.

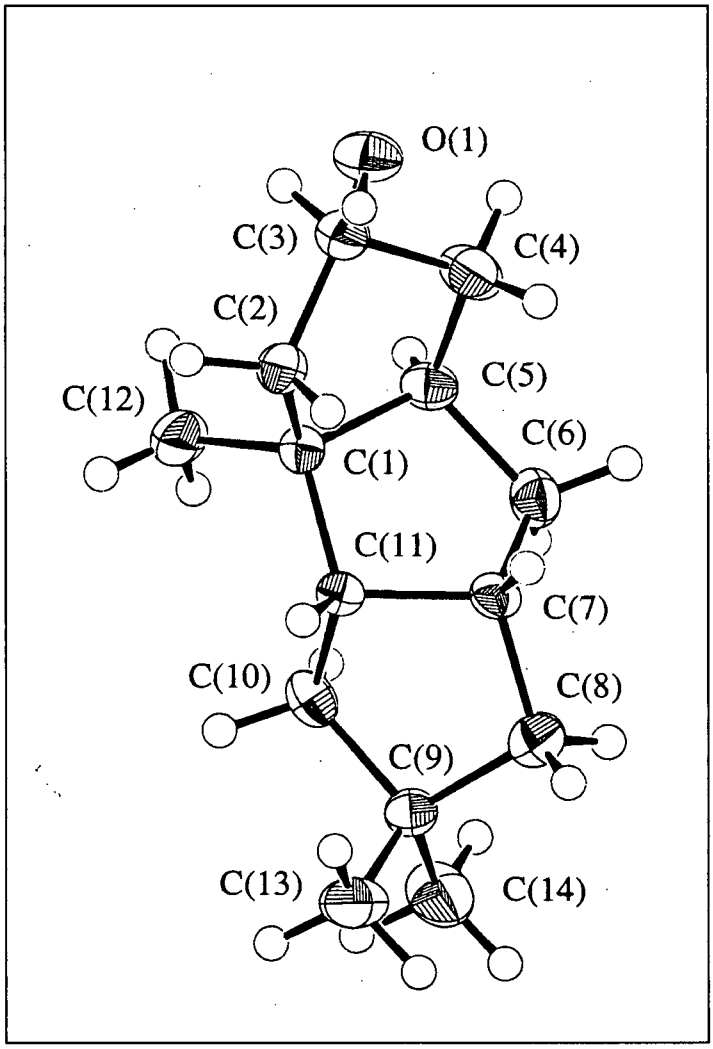
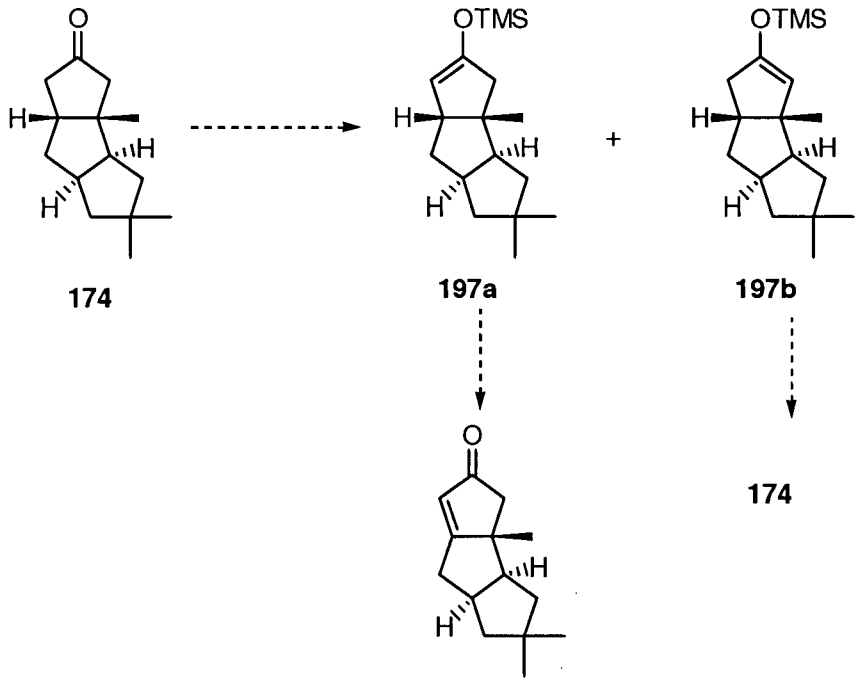


Figure 5. X-ray crystal structure of **196** (50% probability thermal ellipsoids are shown for the non-hydrogen atoms).

The alcohol **196** was treated with pyridinium chlorochromate (PCC) to afford, after work-up, purification of the crude material by column chromatography on silica gel, and bulb-to-bulb distillation under reduced pressure (99-102 °C at 0.4 torr), the ketone **174** in 92% yield (Scheme 27). The presence of the ketone function was confirmed by the presence of a carbonyl stretching absorption band at 1746 cm^{-1} in the IR spectrum of **174**, as well as a carbonyl carbon signal in the ^{13}C NMR spectrum at δ 220.6.

2.5.4.5 Completion of the syntheses of (±)-1-desoxyhypnophilin and (±)-6,7-epoxy-4(15)-hirsuten-5-ol

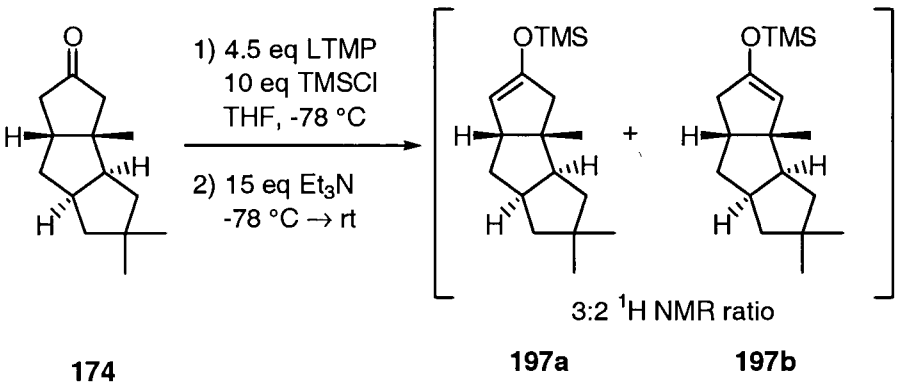
The next task in the synthesis of 1-desoxyhypnophilin was the introduction of a carbon-carbon double bond to form the enone **197**. Many methods for accomplishing this type of transformation have been reported in the literature.[106,107] The Saegusa protocol[89] for the formation of the enone function was adopted owing to its successful application in the preparation of a structurally related compound in the synthesis of hypnophilin (**65**) by Little.[87] The first step in this method is the generation of a silyl enol ether. In the case of ketone **174**, it was expected that the generation of the silyl enol ether would be chemoselective and would favour the formation of **197a** over **197b** (Scheme 28) due to the presence of the angular methyl group. Treatment of this mixture with palladium diacetate[89] was expected to generate the enone **197** *directly* from **197a**. The starting material **174** would be recovered from **197b** after work-up and separation from the enone **197** by chromatography on silica gel.



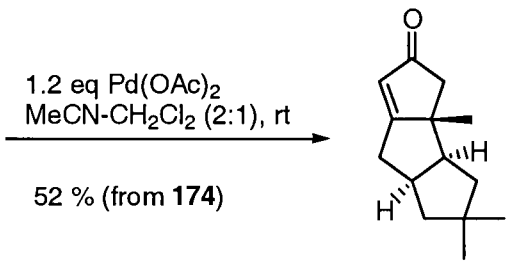
174 **197a** **197b** **174** **197**

Scheme 28

Treatment of a cold (-78 °C) solution of the ketone **174** in THF with lithium tetramethylpiperide[87] in the presence of chlorotrimethylsilane, followed by the addition of triethylamine (Scheme 29) provided a mixture of the silyl enol ethers **197a** and **197b**. Since trimethylsilyl ethers are known to be acid and water labile, the work-up step had to be carried out quickly to minimize hydrolysis. The crude material was placed under reduced pressure (vacuum pump) to remove traces of solvent and remaining amines. The ^{1}H NMR spectrum of the crude material showed two olefinic signals at δ 4.48 (broad unresolved d, J = 2.0 Hz) and 4.45 (s). Based on their appearance, the former signal can be assigned to the olefinic proton of **197a**, while the latter can be attributed to **197b**. The ratio of **197a** to **197b** in the mixture was determined to be 3:2 by the integration of the two olefinic signals.



174 **197a** **197b**

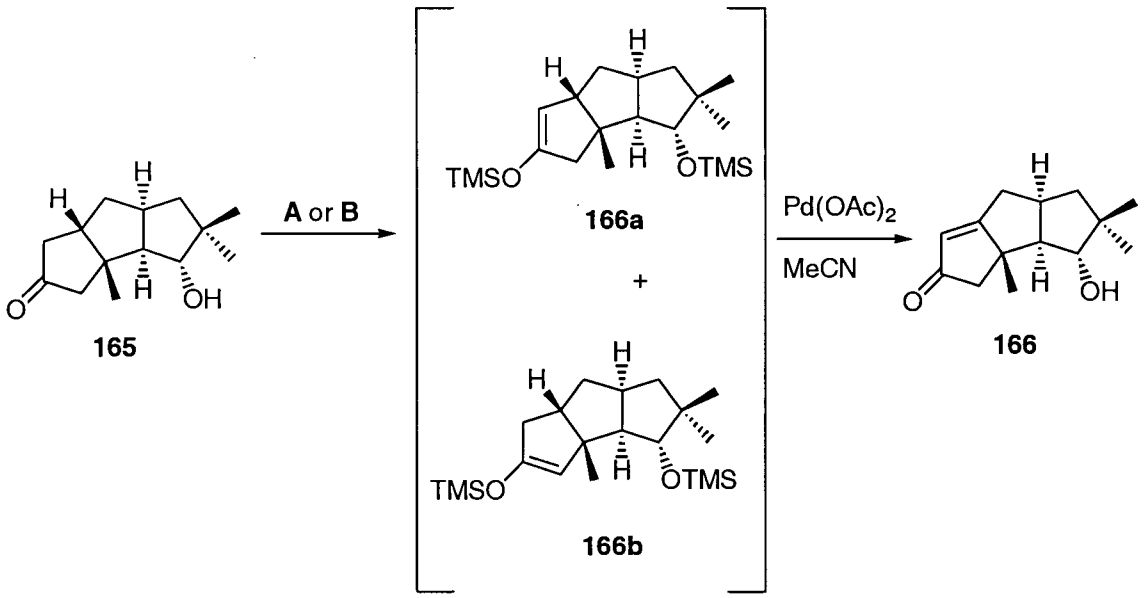


197

Scheme 29

The poor chemoselectivity of the formation of the silyl enol ethers was disappointing. Little[87] reported that sequential treatment of substrate **165** with lithium tetramethylpiperidide and trimethylsilyl chloride afforded the enol ethers **166a** and **166b** in a 6:1 ratio (Scheme 30). On the other hand, when LDA was used as the base **166a** and **166b** were obtained in a ratio of 3:2. In our work with the ketone **174**, the use of LDA

provided a 1:1 ratio of the two silyl ethers **197a** and **197b**. As was noted above, use of LTMP as the base gave **197a** and **197b** in a 3:2 ratio. Clearly, for reasons that are not evident, the chemoselectivities reported by Little for the conversion **165** → **166a** + **166b** were consistently higher than those observed in our studies with substrate **174**.



A: LDA, THF, -78 °C; TMSCl **166a:166b** 3:2
B: LTMP, THF, TMSCl, -78 °C; NEt_3 **166a:166b** 6:1

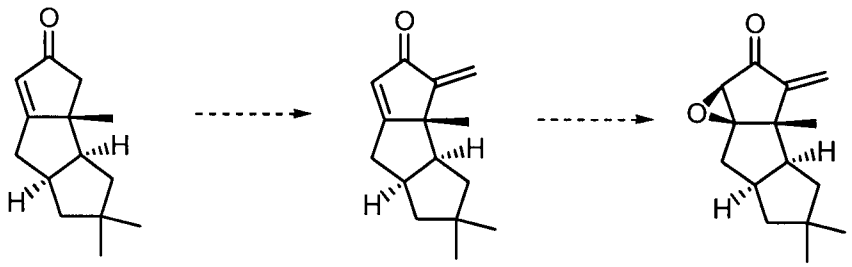
Scheme 30

The silyl enol ethers **197a** and **197b** were dissolved in a 2:1 mixture of acetonitrile and methylene chloride (Scheme 29 above). The use of CH_2Cl_2 as a co-solvent was necessary, because the mixture of **197a** and **197b** was only sparingly soluble in acetonitrile. Palladium acetate was added to this solution and the reaction mixture was stirred at room temperature for 12 h. After work-up and separation of the acquired materials by flash column chromatography on silica gel, the enone **197** was obtained in 52% isolated yield, along with 35% of the recovered ketone **174**. Thus, the yield based on recovered starting material was 87%.

Evidence for the successful formation of the enone **197** was obtained by analysis of the ^1H and ^{13}C NMR spectra. In the ^{13}C NMR spectrum the carbonyl carbon signal appeared at δ 210.8, while the two olefinic carbons gave rise to signals at δ 122.0 (-ve

APT, CH) and δ 195.8. The signal due to the olefinic proton was visible at δ 5.65 in the ^{1}H NMR spectrum. Other ^{1}H NMR signals have been assigned based on the COSY spectrum of **197** and are reported in the experimental section.

It was decided to install the α methylidene function prior to the introduction of the epoxide oxygen (Scheme 31). There are several examples reported in the literature where, in systems related in structure to **198**, the epoxidation of the more strained, internal alkene function proceeds at a faster rate than epoxidation of the exocyclic olefin.[87,90]

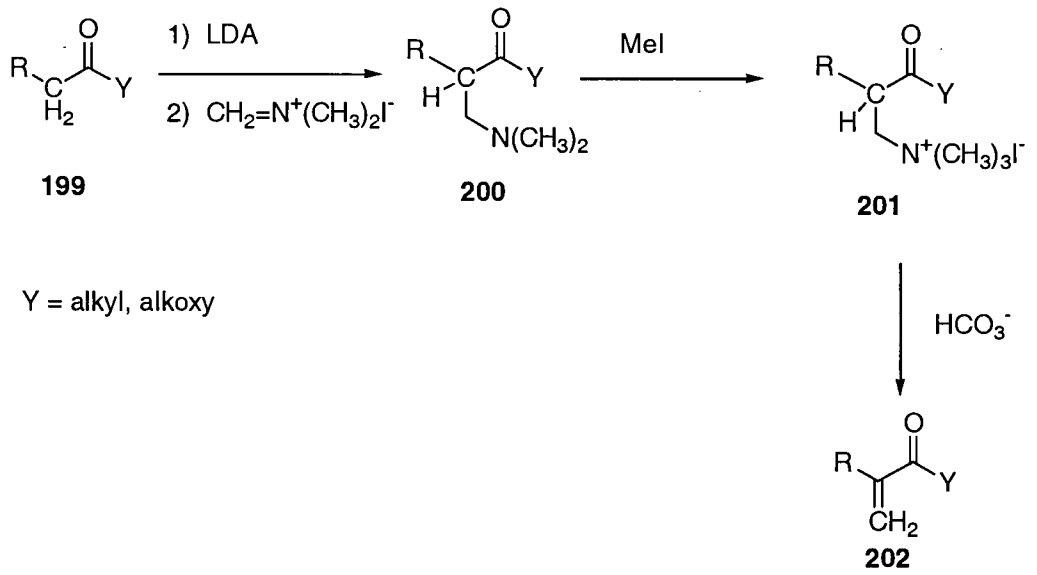


197 **198** **61**

Scheme 31

Several methods for the introduction of the α methylidene function have been reported in the literature and some of these have been applied to the synthesis of biologically active compounds containing α methylidene ketone or lactone units.[108,109]

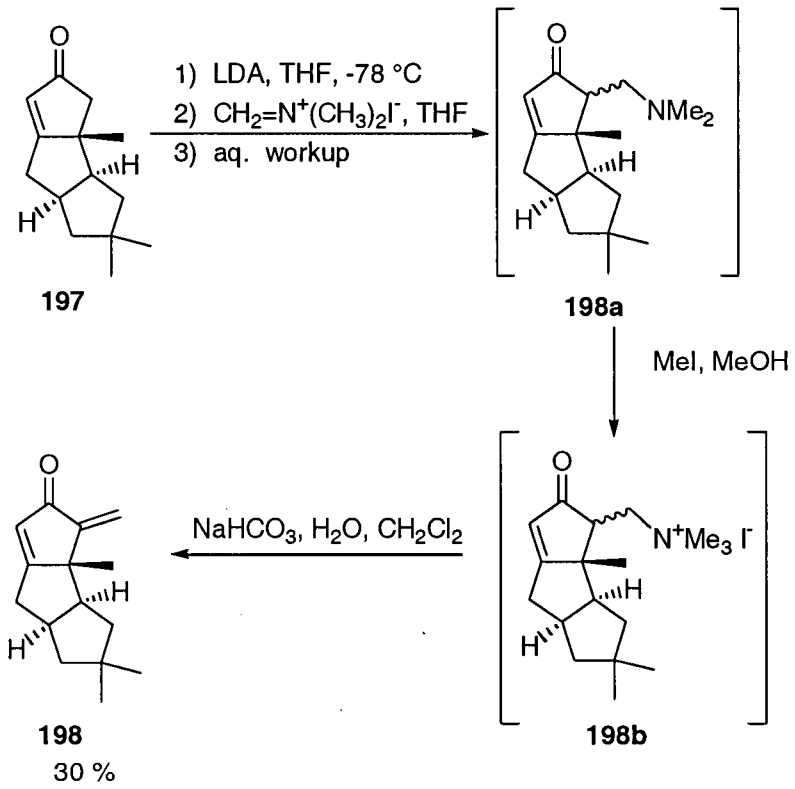
One of the approaches involves the generation of an enolate anion and its subsequent reaction with Eschenmoser's salt (dimethyl(methylene)ammonium iodide)[110] (Scheme 32). Typically, the resulting Mannich intermediate **200** is converted to an ammonium salt **201**. Base promoted elimination of the ammonium salt generates the methylidene compound **202** (Scheme 32).[109,111]



199 **200** **201** **202**

Scheme 32

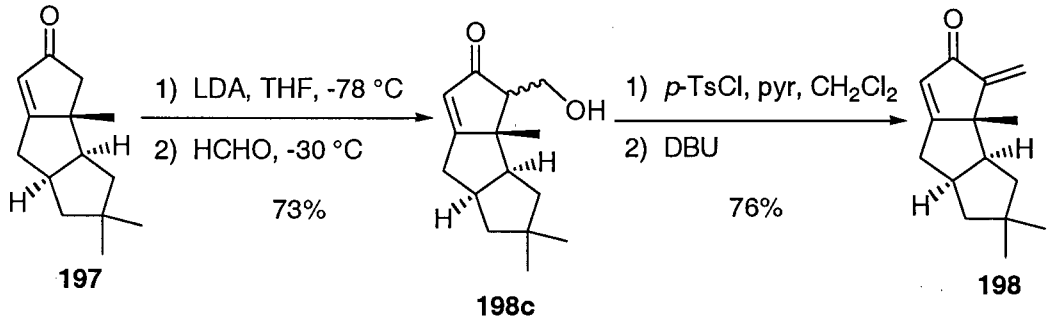
A solution (-78 °C) of the enone **197** was treated with LDA, followed by the addition of the Eschenmoser salt as a suspension in THF (Scheme 33). The crude amine **198a** was obtained upon aqueous work-up of the reaction mixture. The successful formation of the amine was supported by the ^{1}H NMR spectrum of the crude product, which displayed a signal at δ 5.60 ppm (broad signal) consistent with the presence of a methylene group attached to a tertiary nitrogen atom. A small amount of the elimination product **198** was also present in the crude material. The crude **198a** was dissolved in methanol and treated with methyl iodide. Further treatment of the resultant crude material with aqueous sodium bicarbonate in CH_2Cl_2 afforded, after work-up and purification of the crude product by chromatography on silica gel, the dienone **198** in 30% yield. It was thought that the low yield and poor mass balance in this reaction was a result from incomplete elimination of the quaternary ammonium salt **198b** and its possible loss during aqueous work-up or chromatography. Several attempts to improve the yield of this reaction were made, but unfortunately they proved to be unsuccessful. Therefore, another method to generate **198** more efficiently was investigated.



Scheme 33

The dienone **198** was prepared in good yield from **197** by a three-step procedure (Scheme 34).[87] A cold (-78 °C) solution of the enone **197** in THF was treated with LDA. Formaldehyde gas that had been passed through a short column of drying reagent, was bubbled through the resulting solution. After work-up and chromatography of the crude material on silica gel, a mixture of diastereomeric alcohols (**198c**) (ratio ~1:5) was obtained in 73% yield. The mixture of the alcohols **198c** was treated with *p*-toluenesulfonyl chloride and pyridine in CH_2Cl_2 and the mixture was stirred for 4 days.[87] The resultant tosylate mixture was treated with DBU to promote the elimination of the elements of *p*-toluenesulfonic acid. The dienone **198** was obtained in 76% yield upon work-up and column chromatography of the crude product on silica gel. Spectral data provided information to support the formation of the dienone **198**. The ^1H NMR spectrum displayed three olefinic proton signals at δ 5.11, 5.85 and 5.86 consistent with the structure of **198**. In addition, the high resolution mass spectral analysis on the

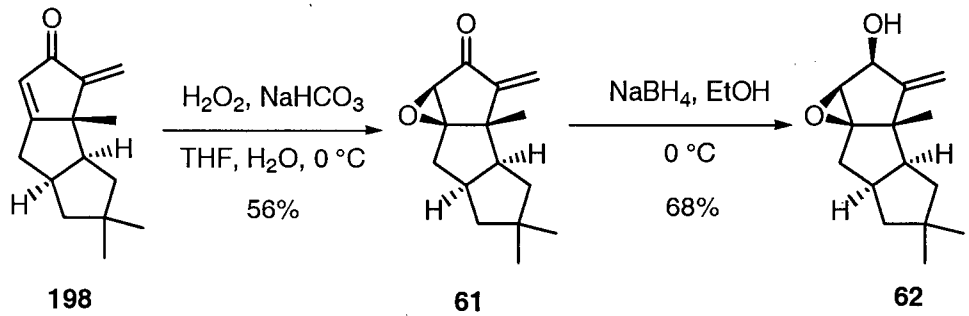
molecular ion was in agreement with that expected for $C_{15}H_{20}O$ (calc. 216.1514; found 216.1518).



Scheme 34

The final step in the total synthesis of (±)-1-desoxyhypnophilin was the monoepoxidation of the more strained, internal olefinic function (Scheme 35).[87,112] It was necessary to closely monitored the reaction by TLC in order to prevent the formation of the bis-epoxide product. Thus, treatment of solution of the dienone **198** in cold (0 °C) THF and water with hydrogen peroxide provided, after work-up and chromatography of the crude material on iatrobeads, (±)-1-desoxyhypnophilin (**61**) in 56% isolated yield. A small amount of unreacted dienone **198** was also isolated.

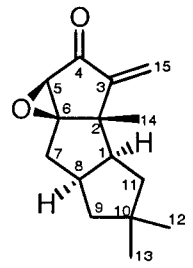
The synthetic (±)-1-desoxyhypnophilin exhibited spectral data in full accordance with those reported for the isolated natural product, (-)-1-desoxyhypnophilin.[44] Comparison of the ^1H NMR and ^{13}C NMR spectra for the synthetic material with that of the isolated natural product is presented in Tables 7 and 8. Additionally, the ^1H NMR spectrum of (±)-**61** is presented in Figure 6.



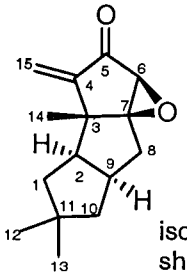
Scheme 35

(±)-1-Desoxyhypnophilin was converted to the alcohol **62** by reduction of the ketone function with sodium borohydride in ethanol at 0 °C.[94] After aqueous work-up and chromatography of the crude material on iatrobeads, the alcohol **62** was obtained in 68% yield. Signals presumed to arise from the presence of trace amounts of the other epimer of the alcohol were visible in the ^{1}H NMR spectrum of the crude mixture. This compound was not isolated by chromatography due to the small scale of the reaction. The spectral data derived from **62** agreed well with those reported for the isolated natural product and are presented in the Tables 9 and 10 below. The ^{1}H NMR spectrum of (±)-**62** is shown in Figure 7.

Table 7. Comparison of ^{1}H NMR data for synthetic (±)-1-desoxyhypnophillin **61** with those reported for natural (-)-1-desoxyhypnophilin[44] (400 MHz, $CDCl_3$).



(±)-**61**

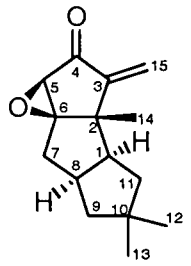


isolated (-)-1-desoxyhypnophilin showing hirsutane numbering

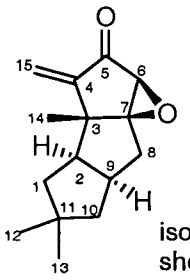
^{1}H assignment H-x	δ,[a] multiplicity, *J* (Hz)	Hirsutane numbering of H	Lit. ^{1}H assignments δ, multiplicity, *J* (Hz)
H-1	2.37 ddd *J* = 9.0, 9.0, 11.5	H-2	2.40 dt *J* = 12, 9
H-5	3.41 s	H-6	3.44 s
H-7	1.97 d *J* = 9.0	H-8	2.00 d *J* = 9
H-8	2.65-2.75 m	H-9	2.73 ddtd *J* = 8, 12, 9, 12
H-9	1.77 ddd *J* = 1.5, 8.0, 12.0	H-10	1.80 ddd *J* = 1, 8, 12
H-9'	1.14 m	H-10'	1.17 dd *J* = 12, 12
H-11	part of 1.43-1.58 m	H-1	1.54 dd *J* = 9, 13
H-11'	part of 1.43-1.58 m	H-1'	1.48 ddd *J* = 1, 9, 13
H-12	0.90 s	H-12	0.92 s
H-13	1.10 s	H-13	1.12 s
H-14	1.14 s	H-14	1.16 s
H-15	5.24 s	H-15'	5.27 s
H-15'	6.03 s	H-15	6.05 s

[a] The difference between observed and reported δ of ~0.03 ppm is likely due to the $CDCl_3$ reference.(δ 7.24 in this work)

Table 8. Comparison of ^{13}C NMR data for synthetic (±)-1-desoxyhypnophillin **61** (100.6 MHz, $CDCl_3$) with those reported for natural (-)-1-desoxyhypnophilin[44] (75.5 MHz, $CDCl_3$).



(±)-**61**



isolated (-)-1-desoxyhypnophilin showing hirsutane numbering

^{13}C assignments C-x	δ (ppm) observed	Hirsutane numbering C-x	Lit. ^{13}C signals and DEPT-135 data[a]
C-1	49.9	C-2	49.8 +
C-2	46.5	C-3	46.5 0
C-3	153.4	C-4	153.4 0
C-4	198.1	C-5	198.1 0
C-5	61.1	C-6	61.1 +
C-6	76.6	C-7	76.6 0
C-7	30.1	C-8	30.1 -
C-8	39.2	C-9	39.2 +
C-9	49.5	C-10	49.5 -
C-10	42.5	C-11	42.5 0
C-11	40.1	C-1	40.1 -
C-12	17.5	C-12	17.5 +
C-13	28.9	C-13	28.9 +
C-14	27.3	C-14	27.3 +
C-15	119.9	C-15	119.9 -

[a] Amplitude of signals in DEPT-135 spectrum (CH_3 or CH = +, CH_2 = -, C = 0)

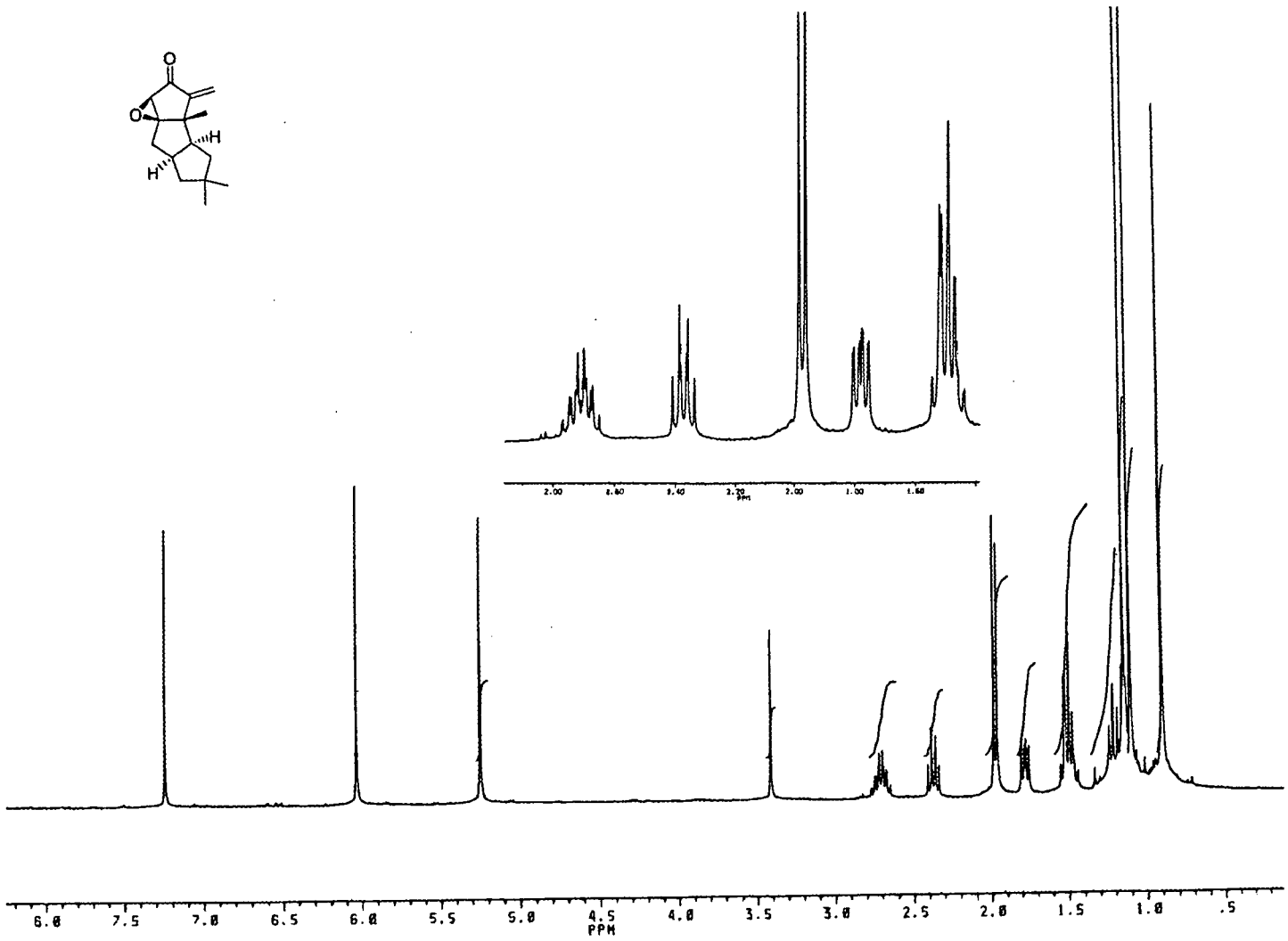
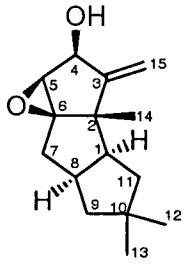
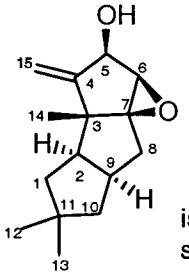


Figure 6. ^{1}H NMR spectrum of synthetic (±)-1-desoxyhypnophillin (**61**) (400 MHz, $CDCl_3$).

Table 9. Comparison of ^{1}H NMR data for synthetic (1*S**, 2*S**, 4*S**, 5*S**, 6*R**, 8*S**)-5,6-epoxy-3-methylidene-2,10,10-trimethyltricyclo[6.3.0.0^{2,6}]undecan-4-ol) [(±)-6,7-epoxy-4(15)-hirsuten-5-ol (**62**)] with those reported for natural (+)-6,7-epoxy-4(15)-hirsuten-5-ol[44] (400 MHz, $CDCl_3$).



(±)-**62**

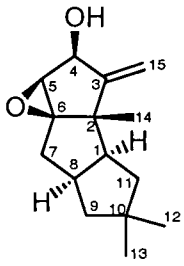


isolated (+)-**62**
showing hirsutane numbering

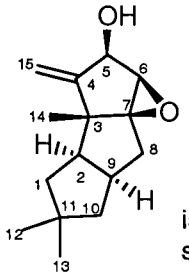
^{1}H assignment	δ, multiplicity, *J* (Hz)	Hirsutane numbering of H	Lit. ^{1}H assignments δ, multiplicity, *J* (Hz)
H-1	2.27 dt *J* = 11.0, 9.0	H-2	2.27 dt *J* = 11, 9
H-4	4.59 dddd *J* =2.0, 2.0, 2.0, 11.0	H-5	4.59 dddd *J* = 2, 2, 2, 10.8
H-5	3.45 d *J* = 2.0	H-6	3.45 d *J* = 5[a]
H-7	1.84 d *J* = 8.5	H-8	1.84 d *J* = 8.5
H-8	2.55-2.70 m	H-9	2.65 ddtd *J* = 7.5, 11, 8.5, 11
H-9	1.06-1.14 m	H-10'	1.10 dd *J* = 11, 12
H-9'	1.72 dd *J* = 7.5, 12.0	H-10	1.72 dd *J* = 7.5, 12.0
H-11	1.41 d *J* = 9.0	H-1	1.42 d *J* = 9
H-12	0.89 s	H-12	0.89 s
H-13	1.07 s	H-13	1.07 s
H-14	1.01 s	H-14	1.01 s
H-15	4.96 d *J* = 2.0	H-15'	4.96 d *J* = 2
H-15'	5.23 d *J* = 2.0	H-15	5.23 d *J* = 2
OH	1.63 d *J* = 11.0	OH	not reported

[a]This coupling constant is a mistake since the corresponding coupling to H-4 is reported to have a coupling constant of 2 Hz.

Table 10. Comparison of ^{13}C NMR data for synthetic (1*S**, 2*S**, 4*S**, 5*S**, 6*R**, 8*S**)-5,6-epoxy-3-methylidene-2,10,10-trimethyltricyclo[6.3.0.0^{2,6}]undecan-4-ol) [(±)-6,7-epoxy-4(15)-hirsuten-5-ol (**62**)] (100.6 MHz, $CDCl_3$) with those reported for natural (+)-6,7-epoxy-4(15)-hirsuten-5-ol[44] (75.5 MHz, $CDCl_3$)



(±)-**62**



isolated (+)-**62**
showing hirsutane numbering

^{13}C assignments C-x	δ (ppm) observed	Hirsutane numbering C-x	^{13}C signals and DEPT-135 data[a]
C-1	48.7	C-2	48.7 +
C-2	48.7	C-3	48.7 0
C-3	159.3	C-4	159.3 0
C-4	74.2	C-5	74.2 +
C-5	63.6	C-6	63.6 +
C-6	75.4	C-7	75.4 0
C-7	30.3	C-8	30.3 -
C-8	39.1	C-9	39.1 +
C-9	49.6	C-10	49.6 -
C-10	42.4	C-11	42.4 0
C-11	39.8	C-1	39.8 -
C-12	17.1	C-12	17.1 +
C-13	28.9	C-13	28.9 +
C-14	27.4	C-14	27.4 +
C-15	111.3	C-15	111.3 -

[a] Amplitude of signals in DEPT-135 spectrum (CH_3 or CH = +, CH_2 = -, C = 0)

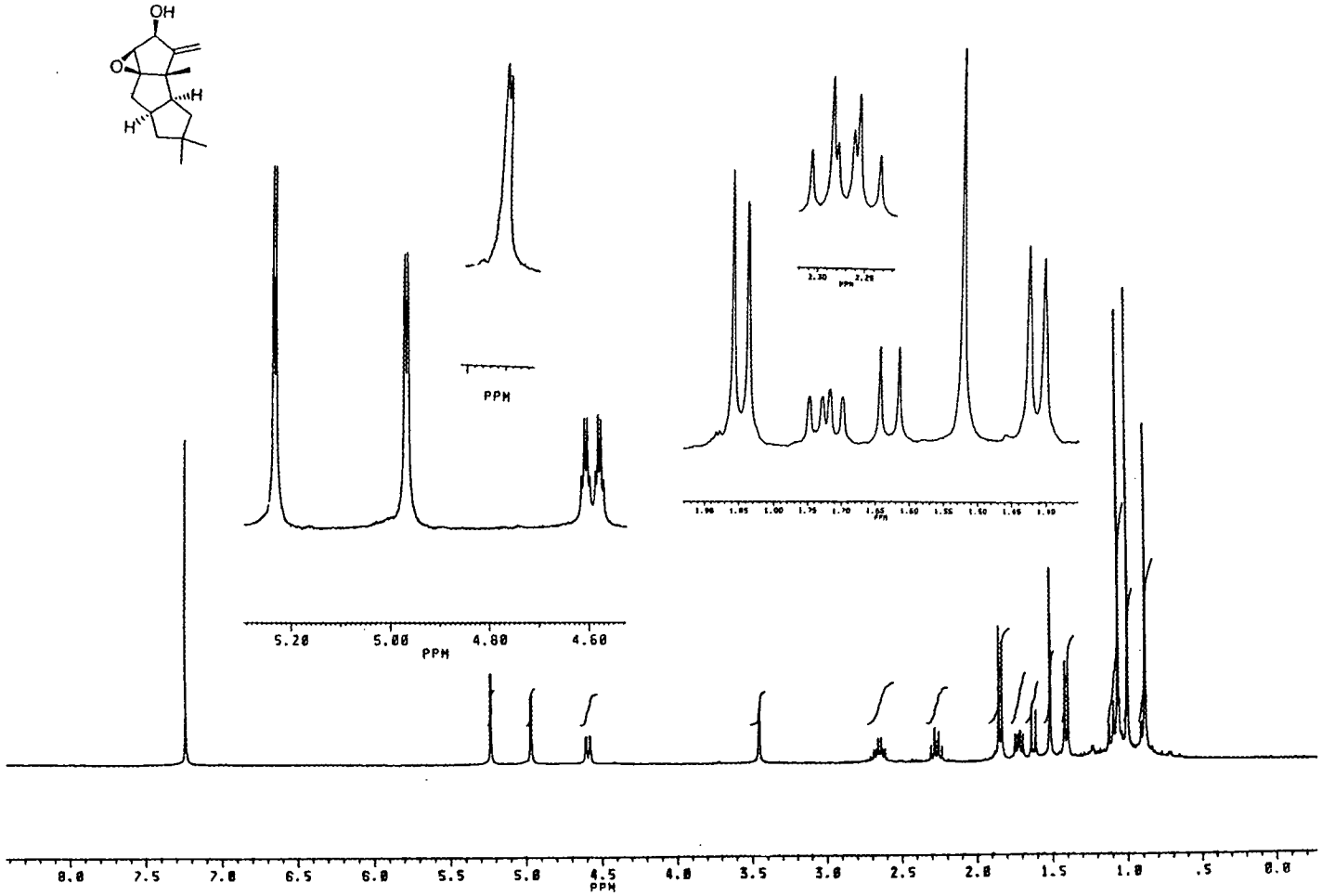
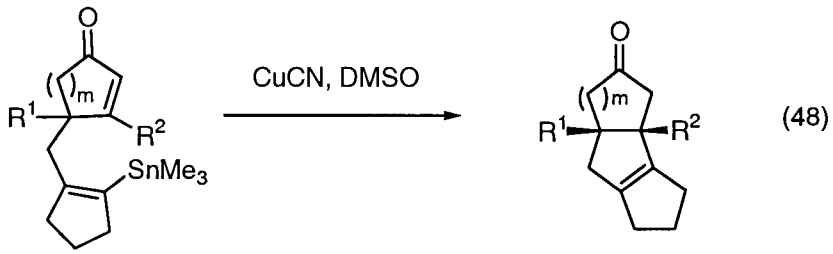


Figure 7. ^{1}H NMR spectrum of synthetic (±)-6,7-epoxy-4(15)-hirsuten-5-ol (**62**) (400 MHz, $CDCl_3$).

III. CONCLUSIONS

3.1 CuCN-mediated intramolecular conjugate additions of alkenyltrimethylstannanes to enones

The Cu(I)-mediated intramolecular conjugate addition reaction of alkenyltrimethylstannane functions to enones was applied to the synthesis of functionalized tricyclic ketones **88-91** and **94** (eq 48).

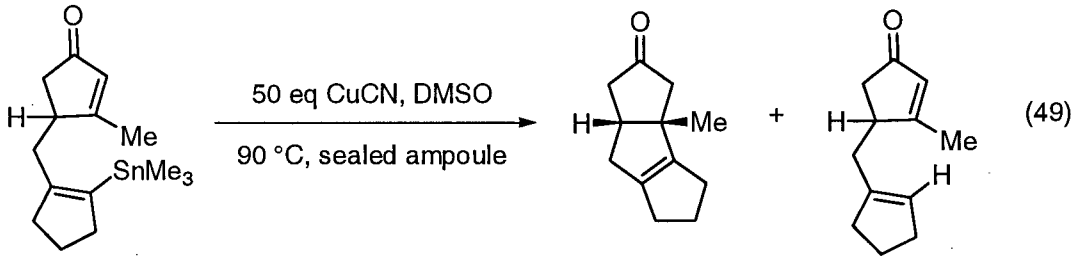


(48)

78 m = 2, R^1, R^2 = H
80 m = 2, R^1 = Me, R^2 = H
81 m = 2, R^1, R^2 = Me
86 m = 1, R^1, R^2 = H
87 m = 1, R^1 = H, R^2 = Me

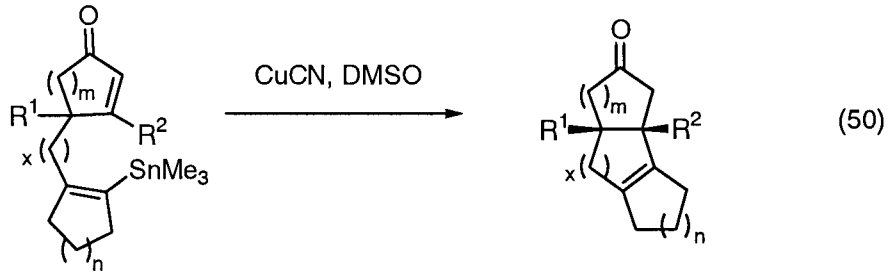
88 94%
89 91%
90 87%
91 80%
94 59%

Compounds **78**, **80**, and **81**, which contain a 6-membered enone (m = 2), underwent rapid and efficient conversion to the corresponding *cis*-tricyclo[6.4.0.$0^{2,6}$]dodec-2(6)-en-11-ones **88-90**. These conversions employed 2.5 equivalents of copper(I) cyanide in DMSO at 60 °C with the substrate concentration of 0.05 M. The intramolecular 1,4-addition onto the *five*-membered ring enone (m = 1) of compound **86** proved to be more difficult and required the use of 5.0 equivalents of CuCN in DMSO at 60 °C. Additional difficulties arose during attempts to effect the intramolecular cyclization of **87**, which in addition to the 5-membered ring (m = 1) also contained a methyl group in the β position of the enone. The major product of the reaction under typical conditions was the uncyclized, protiodestannylated material **95** (see eq 49). The conditions for this reaction were modified such that **87** was reliably converted to the tricyclic ketone **94** in yields ranging from 50-59% (eq 49). In this case, the protocol required a large excess (~50 equivalents) of CuCN in DMSO at 90 °C in a sealed reaction vessel.



87 **94** **95** (49)

The method developed in this study allowed the preparation of tricyclic ketones **88-90**, **94** in good to excellent yields. An extension to this work may be envisaged (eq 50) in which the cyclization precursors of general structure **203** contain larger rings (m, n > 2) resulting in the generation of a large variety of tricycles **204** (eq 50). To date, only the closure of a five membered ring (x = 1) was investigated. In theory, however, it may be possible to effect the closure of a six-membered ring (x = 2, eq 50), thereby, opening doors for the preparation of additional carbon-based structures via the CuCN-mediated intramolecular conjugate addition of alkenyltrimethylstannane functions to α,β-unsaturated ketones.

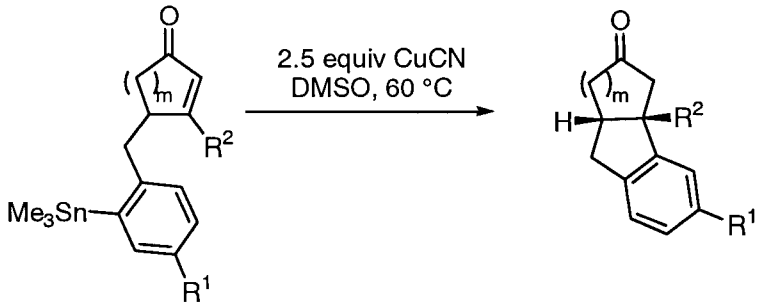


203 **204** (50)

One of the applications of this method is the rapid assembly of the linear triquinane carbon skeletons. In the later part of this thesis, the use of the CuCN-mediated intramolecular conjugate addition reaction was demonstrated in the key step of a total synthesis of the triquinane natural products, (±)-1-desoxyhypnophilin (**61**) and the corresponding alcohol (±)-**62**.

3.2 CuCN-mediated intramolecular conjugate additions of aryltrimethylstannanes to enones

*Aryl*trimethylstannane functions were also demonstrated to undergo analogous CuCN-mediated intramolecular conjugate additions to α, β-unsaturated ketones. This study work showed that substrates **112**, **114** and **116**undergo cyclizations to generate ketones containing an aromatic ring (**117-119**) in good to excellent yields (66-87%) (eq 51).



(51)

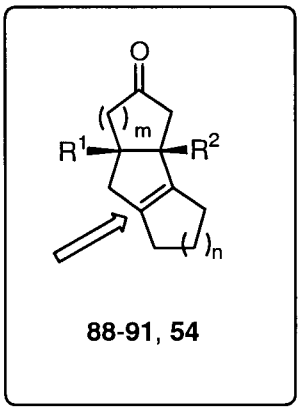
112 m = 2, R^1, R^2 = H
114 m = 2, R^1, R^2 = Me
116 m = 1, R^1, R^2 = H

117 87%
118 66%
119 75%

These examples indicate that the Cu(I)-mediated intramolecular conjugate addition reaction is a viable method of preparation for tricyclic ketones such as **117-119**. An obvious extension of this work is the use of the method in the synthesis of compounds containing various substituents on the aromatic ring.

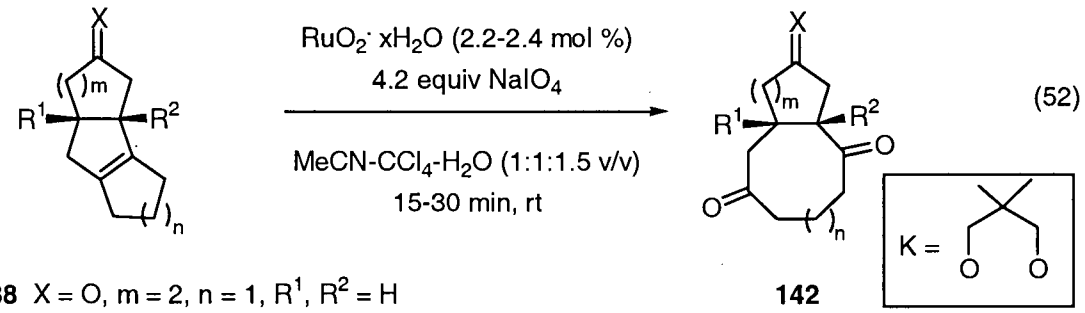
3.3 Preparation of novel carbocyclic structures derived from the products of CuCN-mediated conjugate addition reaction of alkenyltrimethylstannanes to enones

The tetrasubstituted double bond contained in the triketones **88-91** and **54** prepared via Cu(I)-mediated intramolecular conjugate additions proved useful as a handle for further synthetic manipulations. In particular, its use in the preparation of medium sized ring systems (8- or 9-membered) fused to 5- or 6-membered rings was explored.



88-91, 54

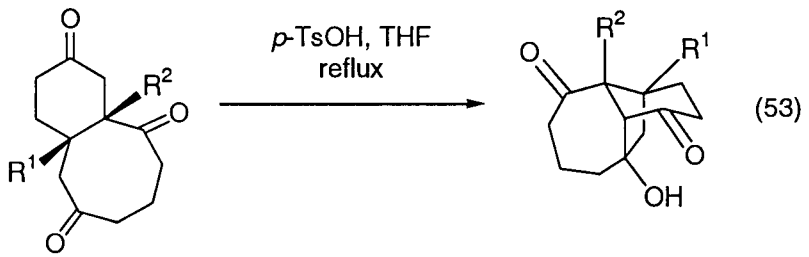
Ruthenium tetroxide catalyzed oxidative cleavage of the alkenic function of **132-134**, **88-91** and **54** cleanly and efficiently, provided functionalized, *cis*-fused bicyclo[6.3.0]undecane (**145**), bicyclo[6.4.0]dodecane (**136-144**) and bicyclo[7.4.0]tridecane systems (**146**) in excellent yields (79-94%) (eq 52).



(52)

88 X = O, m = 2, n = 1, R^1, R^2 = H	**142**
89 X = O, m = 2, n = 1, R^1 = Me, R^2 = H	**143**
90 X = O, m = 2, n = 1, R^1 = Me, R^2 = Me	**144**
91 X = O, m = 1, n = 1, R^1, R^2 = H	**145**
54 X = O, m = 2, n = 2, R^1 = H, R^2 = Me	**146**
132 X = K, m = 2, n = 1, R^1 = Me, R^2 = H	**136**
133 X = K, m = 2, n = 1, R^1 = Me, R^2 = Me	**137**
134 X = K, m = 2, n = 2, R^1 = H, R^2 = Me	**141**

The bicyclic carbon skeleton of triketones **142-146** and the presence of multiple ketone functionalities prompted investigations into the acid-catalyzed intramolecular aldol condesations of these substances. It was found that compounds **144** and **143** upon treatment with *p*-TsOH in refluxing THF provided products **147** and **148**, respectively, in excellent yields. In an analogous manner, product **149** was obtained from **142**, albeit in a lower yield (eq 53).

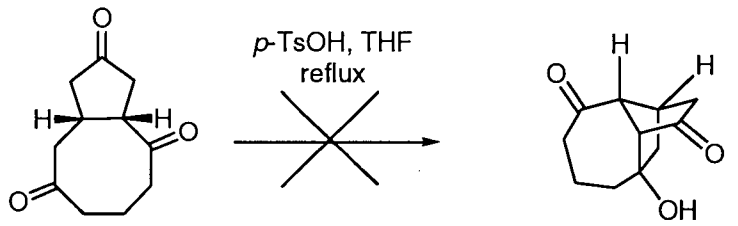


(53)

144 R^1, R^2 = Me	**147** 97%
143 R^1 = Me, R^2 = H	**148** 94%
142 R^1, R^2 = H	**149** 46%

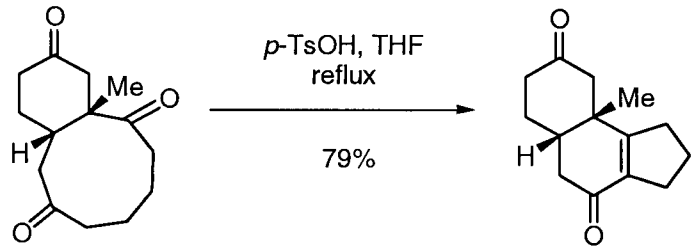
The interesting feature of this reaction from the synthetic point of view is the generation of products **147-149** which possess highly functionalized tricyclo[5.5.0.$0^{2,9}$]dodecane skeleton. This complex carbon framework was easily generated from the corresponding bicyclic triketones.

This process, however, was not general in the application to the synthesis of tricycles related to **147-149** from substrates containing 6-9 (**146**) or 5-8 (**145**) ring systems. Treatment of **145** with *p*-TsOH in refluxing THF did not generate a new product and only the starting material was isolated.



145 **150** (54)

On the other hand, intramolecular aldol condensation within the nine-membered ring of substrate **146**, followed by elimination of water, provided product **151** in a very good yield.

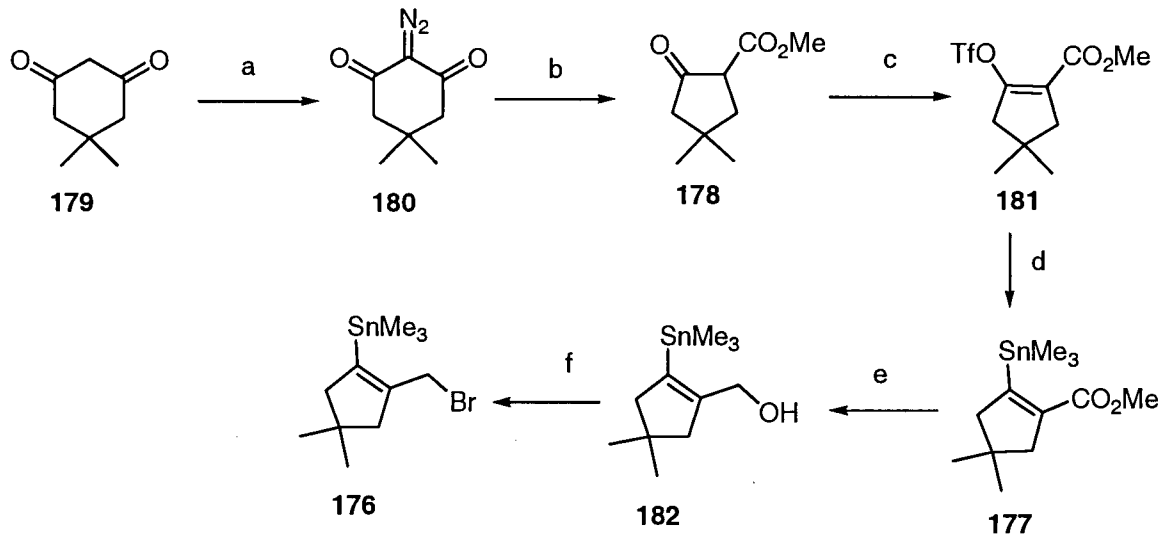


146 **151** (55)

3.4 Application of CuCN-mediated intramolecular conjugate addition of alkenyltrimethylstannes to enones in the total synthesis of (±)-1-desoxyhypnophilin (61) and (±)-6,7-epoxy-4(15)-hirsuten-5-ol (62)

The total synthesis of a natural product is often an ultimate test for a developed synthetic method (see Section 1.1). The usefulness of the Cu(I)-mediated intramolecular conjugate addition of alkenyltrimethylstannane functions to α, β-unsaturated ketones was demonstrated in the key step of the first total synthesis of (±)-1-deoxyhypnophilin **61** and the related alcohol **62**,[44] both of which are linear triquinane natural products.

The preparation of the bromide **176** was accomplished in 41% overall yield via six highly efficient steps, starting from commercially available dimedone **179**. A summary of synthesis is outlined in Scheme 36.



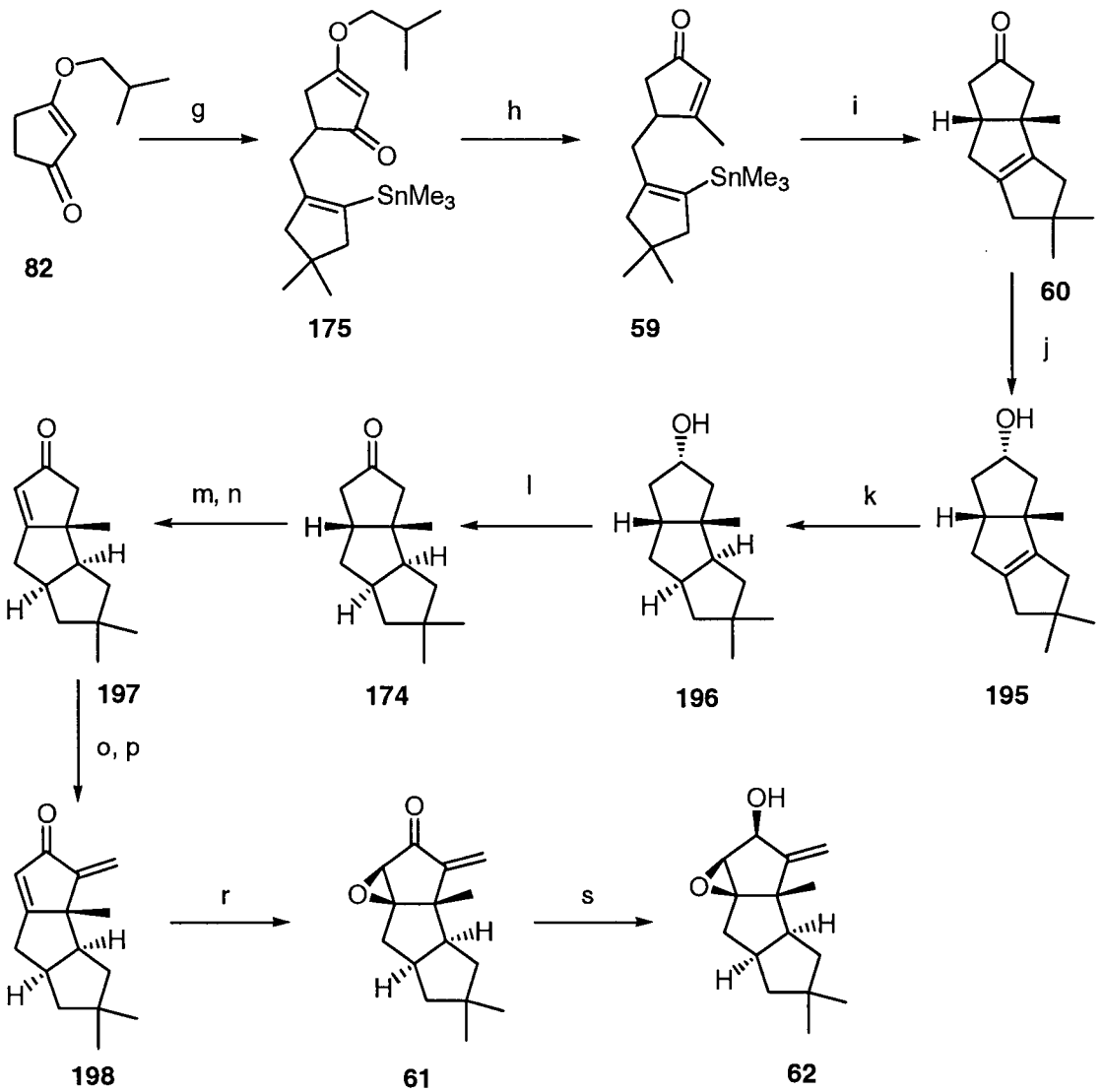
Reagents: a) *p*-TsN_3, Et_3N, 0 ° C→ rt, Et_2O, 63%; b) hv, MeOH, THF, 89%; c) KH, THF, 0 °C; $PhNTf_2$, 0 °C → rt, 85%; d) $Me_3Sn(CN)CuLi$,THF, -48 °C → rt, 92%; e) DIBAL-H,THF, -78 °C → 0 °C, 100%; f) $PPh_3 \cdot Br_2$, imidazole, CH_2Cl_2, 0 °C, 93%

Scheme 36

The bromide **176** was used in the alkylation of the vinyligous ester **82** to provide **175** (Scheme 37). This intermediate was transformed into the enone **59** by sequential treatment with MeMgBr and *p*-TsOH. The enone **59** was used in the key transformation involving the construction of the middle (B) ring of the triquinane skeleton via the

CuCN-mediated intramolecular conjugate addition of the alkenyltrimethylstannane function (ring C) to the enone (ring A). The reaction conditions developed in the methodology studies were further optimized to provide the tricyclic ketone **60** in 59% yield. The conditions employed involved the use of 10 equivalents of CuCN in DMSO at 90 °C in a sealed ampoule with the concentration of the substrate **59** of 0.27 M. Reduction of the tetrasubstituted alkenic function to generate a *cis-anti-cis* triquinane skeleton was accomplished via a three-step procedure. Reduction of the carbonyl function of **60** with a bulky hydride reagent provided **195** in excellent yield. Application of a hydroxyl-directed hydrogenation, with the use of the Crabtree catalyst,[104] provided alcohol **196**. The ketone **174** was obtained by oxidation of **196** with PCC, while the enone **197** was formed from **174** by Seagusa method.[89] Introduction of the α methylidene unit provided the dienone **198**. Subsequent epoxidation of the more strained, internal alkene function provided (±)-1-desoxyhypnophilin (**61**). Finally, reduction of the ketone function generated the alcohol **62**.

The syntheses of (±)-1-desoxyhypnophilin (**61**) and (±)-6,7-epoxy-4(15)-hirstunen-5-ol (**62**) were relatively concise and efficient in comparison with other approaches used in the preparation of a structurally related substance (±)-hypnophilin (**65**) (see Section 2.5.1). The overall yield of (±)-1-desoxyhypnophilin (**61**) over 17 steps was ~2%. (±)-6,7-Epoxy-4(15)-hirsuten-5-ol (**62**) was prepared in ~1.4% overall yield in 18 steps. A summary of the synthesis is outlined in Scheme 37. This synthesis demonstrated that the use of Cu(I)-mediated cyclization in the construction of the triquinane framework is an efficient route for the preparation of natural products (±)-1-desoxyhypnophilin (**61**) and (±)-6,7-epoxy-4(15)-hirstunen-5-ol (**62**).



Reagents: g) LDA, THF, -78 °C → 0 °C; HMPA, **176**, -78 °C → 0 °C, 71%; h) MeMgBr, THF, 0 °C → rt, *p*- TsOH (cat),Et_2O-H_2O, 79%; i) CuCN, DMSO, 90 °C, sealed ampoule, 59%; j) Li(*t*-BuO)$_3$AlH, THF, 0 °C, 87%; k) H_2, 1 atm, [Ir(COD)(PCy$_3$)(py)]$^+PF_6^-$, CH_2Cl_2, 95%; l) PCC, Celite, CH_2Cl_2, rt, 92%, m) LiTMP, TMSCl,THF, 0 °C; Et_3N, -78 °C → rt, n) $Pd(OAc)_2$, MeCN-CH_2Cl_2 (2:1), rt, 52% from **174**, o) LDA, THF, -78 °C; HCHO, -30 °C, 73%, p) TsCl, pyr, CH_2Cl_2; DBU, 76%, r) H_2O_2, $NaHCO_3$,THF, H_2O, 0 °C, 56%; s) $NaBH_4$, EtOH, 0 °C, 68%.

Scheme 37

3.5 General

The work described in this thesis combines two areas of academic research typically carried out by a synthetic organic chemist: methodological studies and the total synthesis of a natural product (see Section 1.1). Extensions to a new Cu(I)-mediated intramolecular conjugate addition method and its application to the synthesis of novel carbocyclic compounds were the major goals of this study. The methodology proved useful in the preparation of structurally diverse carbocyclic substances, some of which could potentially find use as lead compounds in pharmaceutical research or as intermediates in the synthesis of other natural and non-natural products.

The applicability of the Cu(I)-based method was demonstrated in work leading to to the assembly of a triquinane skeleton of the intermediate **60** in the total synthesis of (±)-1-desoxyhypnophilin (**61**) and (±)-6,7-epoxy-4(15)-hirstunen-5-ol (**62**) (see previous page). It was found that the conditions previously employed in cyclizations of systems related in structure to that of **60** had to be adjusted in order to effect the transformation (**59** $\rightarrow$ **60**) effectively. Thus, this total synthesis provided an impetus for further development and increased of the scope of the CuCN-mediated intramolecular conjugate addition reaction of alkenyltrimethylstannanes to α,β-unsaturated ketone functions.

IV. EXPERIMENTAL SECTION

4.1 General

4.1.1 Data Acquisition and Presentation

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker model WH-400 (400 MHz) or AMX-500 (500 MHz) spectrometers using deuteriochloroform ($CDCl_3$) as the solvent. Signal positions (δ) are given in parts per million (ppm) from tetramethylsilane and were measured relative to that of chloroform (δ 7.24). The multiplicity, number of protons, coupling constants and assignments (where possible) are indicated in parentheses following the chemical shift. The abbreviations used in describing multiplicity are: s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, br-broad. When a hydrogen was observed to be coupled with the same coupling constants to two, three, four or five other hydrogens which are chemically and magnetically nonequivalent, the designation dd, ddd, dddd and ddddd is used, instead of t, q, quintet or sextet. Coupling constants (J values) are given in Hertz (Hz) and are reported to the nearest 0.5 Hz. The tin-proton coupling constants (J_{Sn-H}) are reported as an average of the ^{117}Sn and ^{119}Sn values. In some cases, the proton assignments were supported by two-dimensional (^{1}H-^{1}H) homonuclear correlation spectroscopy (COSY), which was carried out using the WH-400 spectrometer. In the ^{1}H NMR spectra, H-x and H-x' have been used to designate hydrogens on the same carbon, with H-x' being the hydrogen at lower field.

Carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained on a Bruker models AC-200E (50.3 MHz), AM-400 (100.6 MHz) and AMX-500 (125.8 MHz) spectrometers or a Varian model XL-300 (75.5 MHz) spectrometer using deuteriochloroform ($CDCl_3$) as the solvent. Signal positions are given in parts per million (ppm) from tetramethylsilane and were measured relative to the signal of

deuteriochloroform (δ 77.0). Attached proton tests (APTs), used to differentiate methyl and methine (negative phase signals) from methylene and quaternary carbons (positive phase signals), were recorded on the Varian XL-300 spectrometer. Where APT data is given, signals with negative phases are indicated in brackets (-ve) following the ^{13}C NMR chemical shift. In some cases, the proton and carbon assignments were supported by two-dimensional (^{1}H, ^{13}C)-heteronuclear multiple quantum coherence experiments (HMQC) and heteronuclear multiple bond correlation (HMBC) experiments, which were carried out on the Bruker AMX-500 spectrometer.

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. The molecular ion (M^+) masses are given unless otherwise noted. For some compounds containing the trimethylstannyl (Me_3Sn) group, the high resolution mass spectrometry molecular mass determinations were based on the (M^+-Me) peak. Unless otherwise noted, all high resolution mass spectra were measured using electron impact ionization (EI). All compounds subjected to high resolution mass measurements were homogeneous by GLC and/or TLC analyses.

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

X-ray crystallographic analyses were performed on a Rigaku/ADSC CCD area detector with graphite monochromated Mo-Kα radiation by the UBC X-ray Crystallography Laboratory.

Melting points (m.p.) were measured on a Fisher-Johns melting point apparatus and are uncorrected. Distillation temperatures, which refer to air bath temperatures of the bulb-to bulb (Kugelrorh) distillations, are uncorrected.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon using glassware that had been flame- or oven-dried (~140 °C). Glass syringes, stainless steel needles, and Teflon® cannulae for handling anhydrous solvents and reagents were oven dried, 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, -30 °C, -48 °C, aqueous calcium chloride-dry ice (17 g, 35 g, 47 g of $CaCl_2$/100 ml of H_2O respectively); -78 °C, acetone-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) and/or iodine (iodine which has been preabsorbed onto unbound silica gel), 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).

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).

Concentration, evaporation or removal of the solvent under reduced pressure refers to solvent removal using a Büchi rotary evaporator at ~15 torr (water aspirator).

4.1.2 Solvents and reagents

All solvents and reagents were purified, dried and/or distilled using standard procedures.[113] Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone, while benzene (C_6H_6), dichloromethane (CH_2Cl_2), acetonitrile and pyridine 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, triethylamine and hexamethylphosphoroamide (HMPA) were distilled from calcium hydride. Dimethyl sulfoxide (DMSO) was dried sequentially over activated 3 Å molecular sieves.[37] These reagents were stored in Sure Seal™ (Aldrich Chemical Co. Inc.) bottles over 3 Å molecular sieves under an atmosphere of argon.

Before use, methyl iodide and deuteriochloroform were passed through a short column of basic alumina activity I, which had been dried in an oven (~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.

Copper(I) cyanide, palladium acetate, *p*-toluenesulfonyl chloride were purchased from Aldrich Chemical Co. Inc, and were used without further purification.

Hexamethylditin was obtained from Organometallics Inc., was stored under an atmosphere of argon in a glove box, and was used without prior purification.

Solutions of diisobutylaluminum hydride (DIBAL-H) in hexanes and methylmagnesium bromide in diethyl ether were purchased from Aldrich Chemical Co. Inc. Solutions of methyllithium in diethyl ether and *n*-butyllithium 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.[114]

Potassium hydride was obtained as a 35 weight% suspension in mineral oil and sodium hydride 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.

All other reagents were commercially available and were used with further purification.

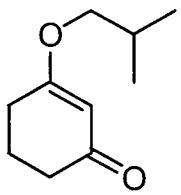
Aqueous ammonium chloride-ammonia (NH_4Cl-NH_3) (pH 8) was prepared by the addition of ~50 mL of concentrated aqueous ammonia (28-30%) to 950 mL of a saturated aqueous ammonium chloride solution.

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

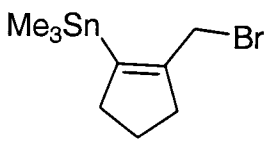
4.2 Copper cyanide mediated intramolecular conjugate additions of alkenyltrimethylstannanes and aryltrimethylstannanes to enones

4.2.1 Preparation of the alkenyltrimethylstannane precursors

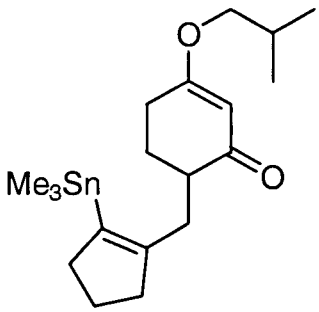
Preparation of 6-[(2-trimethylstannylcyclopent-1-en-1-yl)methyl]-3-isobutoxycyclohex-2-en-1-one (77)[43]



76



73



77

To a cold (-78 °C), stirred solution of LDA (23.0 mmol) in dry THF (110 mL) was added a solution of 3-isobutoxycyclohex-2-en-1-one (**76**)[47] (3.87g, 23.0 mmol) in dry THF (60 mL). The solution was warmed to 0 °C and was stirred for 30 min and then at room temperature for 1.5 h. The mixture was subsequently cooled to -78 °C and a solution of the bromide **73**[50] (4.96 g, 15.3 mmol) in dry THF (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 2 h. Water (100 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was purified by flash column chromatography (400 g of silica gel, 1:4 Et_2O-petroleum ether) to yield 5.37 g (85%) of alkylated product **77** as a viscous colourless oil which solidified upon standing (m.p. 39-40 °C).

IR (film): 1659, 1610 cm^{-1}.

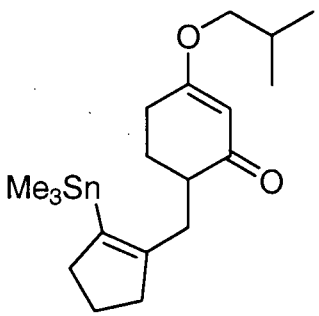
^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.10 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn\text{-}H}$ = 53.0 Hz, 0.94 (d, 6H, J = 6.5 Hz, -(C$\underline{H}_3$)$_2$), 1.48-1.54 (m, 1H), 1.70-2.40 (m, 13H), 2.74-2.75 (m, 1H) , 3.56 (d, 2H, J = 6.5 Hz, -OC$\underline{H}_2$-CH), 5.30 (s, 1H, =C$\underline{H}$).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -9.2 (-ve), 19.1 (2C, -ve), 24.3, 26.0, 27.7 (-ve), 28.4, 33.1, 35.8, 39.4, 43.6 (-ve), 74.7, 102.3 (-ve), 138.3, 151.1, 177.1, 200.8.

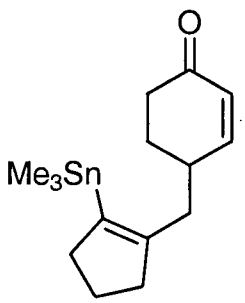
HRMS calcd for $C_{19}H_{32}O_2{}^{120}Sn$: 412.1424; found: 412.1419.

Anal. calcd for $C_{19}H_{32}O_2Sn$: C 55.50, H 7.84; found: C 55.24, H 7.98.

*Preparation of 4-[(2-trimethylstannylcyclopent-1-en-1-yl)methyl]cyclohex-2-en-1-one (**78**)*[43]



77



78

To a cool (0 °C), stirred solution of the ketone **77** (1.47 g, 3.57 mmol) in dry CH_2Cl_2 (40 mL) was added a solution of DIBAL-H (4.70 mL, 1.0 M solution in hexanes, 4.70 mmol) via a plastic syringe. The mixture was stirred at 0 °C for 2 h, after which time a saturated aqueous solution of Rochelle's salt (40 mL) was added. The resulting mixture was warmed to room temperature and stirred, open to air, for 30 min. The layers

were separated and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude material was dissolved in Et_2O (40 mL) containing ~6 drops of H_2O and the mixture was treated with a catalytic amount of *p*-toluenesulfonic acid (~50 mg). The reaction mixture, open to air, was stirred for 1 h at room temperature. It was diluted with H_2O (40 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 40 mL) and the combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (70 g of silica gel, 1:4 Et_2O-petroleum ether) to provide 1.03 g (86%) of the enone **78** as a colourless oil.

IR (neat): 1680, 1614, 1387, 768 cm^{-1}.

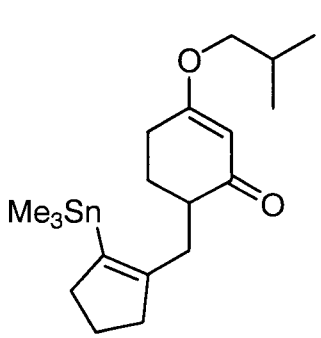
^1H NMR (400 MHz, $CDCl_3$) δ: 0.11 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53.0 Hz), 1.50-1.62 (m, 1H), 1.78-1.90 (m, 2H), 2.00-2.10 (m, 1H), 2.20-2.61 (m, 9H), 5.96 (dd, 1H, *J* = 2.0, 10.0 Hz), 6.78 (ddd, 1H, *J* = 1.5, 2.0, 10.0 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -9.2 (-ve), 24.4, 29.1, 34.8 (-ve), 36.1, 37.1, 38.4, 39.5, 129.0 (-ve), 139.6, 149.8, 154.4 (-ve), 199.8.

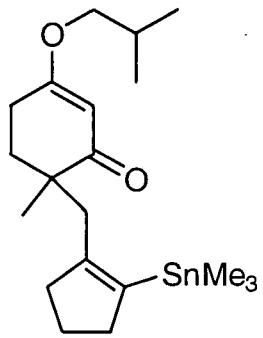
HRMS calcd for $C_{15}H_{24}O^{120}Sn$: 340.0849; found: 340.0847.

Anal. calcd for $C_{15}H_{24}OSn$: C 53.14, H 7.13; found: C 53.36, H 6.98.

*Preparation of 6-methyl-6-[(2-trimethylstannylcyclopent-1-en-1-yl)methyl]-3-isobutoxycyclohex-2-en-1-one (**79**)* [43]



77



79

To a cold (-78 °C), stirred solution of LDA (3.10 mmol) in dry THF (20 mL) was added a solution of the ketone **77** (1.16 g, 2.81 mmol) in dry THF (10 mL). The mixture was warmed to 0 °C and stirred for 1 h. HMPA (0.98 mL, 5.62 mmol) was added and the reaction mixture was stirred for an additional 1 h. The mixture was then cooled to -78 °C and an excess of freshly distilled methyl iodide (~2.6 mL, 42 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 1 h. Water (30 mL) was added and the resulting mixture was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with H_2O (2 x 30 mL), aqueous $CuSO_4$ (10%, 30 mL), brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was purified by flash column chromatography (100 g of silica gel, 1:4 Et_2O-petroleum ether) to yield 1.05 g (88%) of alkylated product **79** as a colourless oil, which solidified upon standing (m.p. 39-41 °C).

IR (neat): 1652, 1611, 1375, 1200, 770 cm^{-1}.

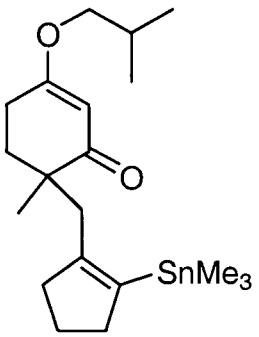
^1H NMR (400 MHz, $CDCl_3$) δ: 0.12 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn\text{-}H}$ = 53.0 Hz), 0.94 (d, 6H, J = 6.5 Hz, -($C\underline{H}_3$)$_2$), 1.06 (s, 3H, -$C\underline{H}_3$), 1.51-1.60 (m, 1H), 1.70-1.88 (m, 3H), 1.95-2.12 (m, 2H), 2.13-2.24 (m, 2H), 2.30-2.40 (m, 3H), 2.41-2.51 (m, 1H), 2.80 (br d, 1H, J = 14.0 Hz), 3.55 (d, 2H, J = 6.5 Hz, -O$C\underline{H}_2$-CH), 5.24 (s, 1H, =C$\underline{H}$).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -9.1 (-ve), 19.1 (2C, -ve), 24.1 (-ve), 24.8, 26.0, 27.7 (-ve), 31.6, 37.5, 39.0, 41.2, 43.1, 74.6, 101.4 (-ve), 139.9, 150.6, 175.7, 203.3.

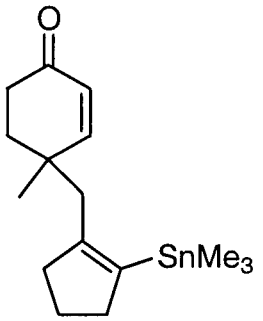
HRMS calcd for $C_{20}H_{34}O_2{}^{120}Sn$: 426.1581; found: 426.1584.

Anal. calcd for $C_{20}H_{34}O_2Sn$: C 56.50, H 8.06; found: C 56.87, H 7.87.

*Preparation of 4-methyl-4-[2-trimethylstannylcyclopent-1-en-1-yl)methyl]-cyclohex-2-en-1-one (**80**)* [43]



79



80

To a cool (0 °C), stirred solution of the ketone **79** (1.16 g, 2.74 mmol) in dry CH_2Cl_2 (35 mL) was added a solution of DIBAL-H (4.10 mL, 1.0 M solution in hexanes, 4.10 mmol) via a plastic syringe. The mixture was stirred at 0 °C for 2 h, after which time a saturated aqueous solution of Rochelle's salt (35 mL) was added. The resulting mixture was warmed to room temperature and stirred, open to air, for 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude material was dissolved in Et_2O (35 mL) containing ~6 drops of H_2O and the mixture was treated with a catalytic amount of *p*-toluenesulfonic acid (~50 mg). The solution, open to air, was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O (40 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 40 mL)

and the combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the resulting crude oil by flash column chromatography (70 g of silica gel, 1:4 Et_2O-petroleum ether) and subsequent bulb-to-bulb distillation (178-182 °C/0.2 torr) of the acquired liquid provided 849 mg (88%) of the enone **80** as a colourless oil.

IR (neat): 1684, 1606, 1389, 1222, 768 cm^{-1}.

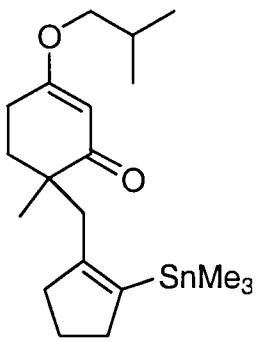
^1H NMR (400 MHz, $CDCl_3$) δ: 0.13 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.0 Hz), 1.13 (s, 3H, -C<u>H</u>$_3$), 1.65-1.74 (m, 1H), 1.74-1.85 (m, 2H), 1.93-2.03 (m, 1H), 2.17-2.53 (m, 8H), 5.84 (d, 1H, J = 10.0 Hz), 6.78 (d, 1H, J = 10.0 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -9.0 (-ve), 25.0, 25.9 (-ve), 34.0, 34.2, 36.3, 38.3, 39.2, 45.5, 127.1 (-ve), 141.6, 149.5, 159.7 (-ve), 199.5.

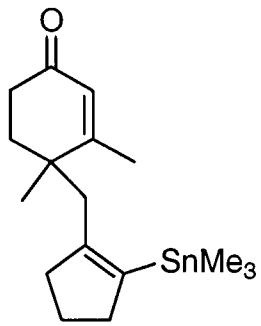
HRMS calcd for $C_{16}H_{26}O^{120}Sn$: 354.1006; found: 354.0997.

Anal. calcd for $C_{16}H_{26}OSn$: C 54.43, H 7.42; found: C 54.65, H 7.52.

*Preparation of 3,4-dimethyl-4-[(2-trimethylstannylcyclopent-1-en-1-yl)methyl]cyclohex-2-en-1-one (**81**)*



79



81

To a cool (0 °C), stirred solution of the ketone **79** (1.11 g, 2.60 mmol) in dry THF (30 mL) was added a solution of MeMgBr (2.60 mL, 3.0 M solution in Et_2O, 7.80 mmol) via a syringe. The mixture was warmed to room temperature and was stirred for 17 hours. Water (30 mL) was added slowly and the resulting mixture was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude material was dissolved in Et_2O (30 mL) containing ~6 drops of H_2O and the mixture was treated with a catalytic amount of *p*-toluenesulfonic acid (~50 mg). The reaction mixture, open to air, was stirred for 2 h at room temperature. It was diluted with H_2O (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 30 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (50 g of silica gel, 1:4 Et_2O-petroleum ether) to provide 854 mg (89%) of the enone **81** as a viscous colourless oil, which solidified upon standing (m.p. 44-46 °C).

IR (neat): 1669, 1606, 1184, 769 cm^{-1}.

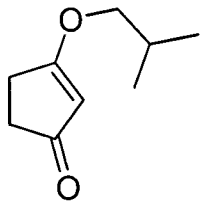
^1H NMR (400 MHz, $CDCl_3$) δ: 0.14 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn\text{-}H}$ = 53.0 Hz), 1.17 (s, 3H, -C$\underline{H}_3$), 1.60-1.70 (m, 1H), 1.72-1.83 (m, 2H), 1.94 (s, 3H, -C$\underline{H}_3$), 1.94-2.02 (m, 1H), 2.20-2.54 (m, 8H), 5.79 (s, 1H, =C$\underline{H}$).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -9.0 (-ve), 20.6 (-ve), 24.9, 25.8 (-ve), 34.3, 34.3, 37.2, 38.9, 39.0, 42.6, 127.2 (-ve), 141.5, 149.7, 168.8, 199.2.

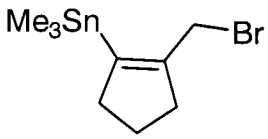
HRMS calcd for $C_{17}H_{28}O^{120}Sn$: 368.1162; found: 368.1169.

Anal. calcd for $C_{17}H_{28}OSn$: C 55.62, H 7.69; found: C 55.86, H 7.65.

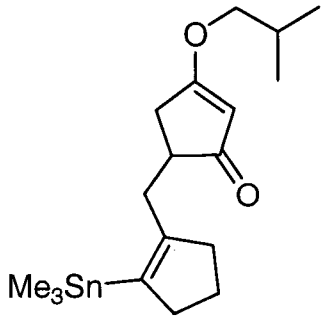
Preparation of 5-[(2-trimethylstannylcyclopent-1-en-1-yl)methyl]-3-isobutoxycyclopent-2-en-1-one (85)



82



73



85

To a cold (-78 °C), stirred solution of LDA (7.48 mmol) in dry THF (38 mL) was added a solution of 3-isobutoxycyclopent-2-en-1-one (**82**)[115] (1.15 g, 7.48 mmol) in dry THF (38 mL). The mixture was stirred at -78 °C for 30 min and then was warmed to 0 °C for 15 min. It was subsequently cooled back to -78 °C and HMPA (1.75 mL, 9.98 mmol) was added, followed by a solution of the bromide **73** (1.63 g, 4.99 mmol) in dry THF (10 mL). The reaction mixture was warmed to 0 °C and stirred for 1 h. Water (50 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with H_2O (2 x 50 mL), aqueous $CuSO_4$ (10%, 50 mL), brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was purified by flash column chromatography (77 g of silica gel, 2:3 Et_2O-petroleum ether) to yield 1.53 g (77%) of alkylated product **85** as a colourless oil.

IR: 1697, 1600, 1470, 1351, 1173, 996 cm^{-1}.

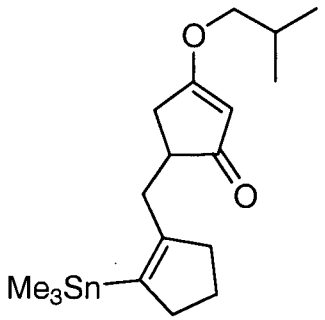
^1H NMR (400 MHz, $CDCl_3$) δ: 0.09 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn\text{-}H}$ = 53.5 Hz), 0.96 (d, 6H, J = 6.5 Hz, -CH($C\underline{H}_3$)$_2$), 1.72-1.85 (br m, 2H), 2.00-2.15 (m, 2H), 2.19-2.33 (m, 3H), 2.35-2.43 (m, 2H), 2.53-2.65 (m, 2H), 2.70 (br d, 1H, J = 14.5 Hz), 3.70 (d, 2H, J = 6.5 Hz, -OC$\underline{H}_2$CH), 5.18 (s, 1H, =C$\underline{H}$).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -9.4 (-ve), 18.9 (2C, -ve), 24.3, 27.8 (-ve), 33.8, 35.2, 35.8, 39.3, 43.8 (-ve), 77.9, 103.2 (-ve), 138.7, 150.9, 189.0, 207.8.

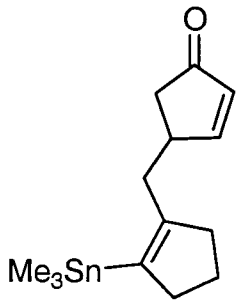
HRMS calcd for $C_{18}H_{30}O_2{}^{120}Sn$: 398.1268; found: 398.1262.

Anal. calcd for $C_{18}H_{30}O_2Sn$: C 54.44, H 7.61; found: C 54.70, H 7.55.

Preparation of 4-[(2-trimethylstannylcyclopent-1-en-1-yl)methyl]cyclopent-2-en-1-one (86)



85



86

To a cool (0 °C), stirred solution of the ketone **85** (1.44 g, 3.63 mmol) in dry CH_2Cl_2 (35 mL) was added a solution of DIBAL-H (4.35 mL, 1.0 M solution in hexanes, 4.35 mmol) via a plastic syringe. The mixture was stirred at 0 °C for 2 hours, after which time a saturated aqueous solution of Rochelle's salt (35 mL) was added. The resulting mixture was warmed to room temperature and stirred, open to air, for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 35 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude material was dissolved in Et_2O (35 mL) containing ~6 drops of H_2O and the mixture was treated with a catalytic amount of *p*-toluenesulfonic acid (~50 mg). The solution, open to air, was stirred for 1 h at room temperature. The mixture was then diluted with H_2O (35 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 35 mL) and the combined

organic extracts were washed with brine (35 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the resulting crude oil by flash column chromatography (50 g of silica gel, 1:4 Et_2O-petroleum ether) and subsequent bulb-to-bulb distillation (170-175 °C/0.5 torr) of the acquired material provided 0.922 g (78%) of the enone **86** as a colourless oil.

IR (neat): 1718, 1612, 1184, 771 cm^{-1}.

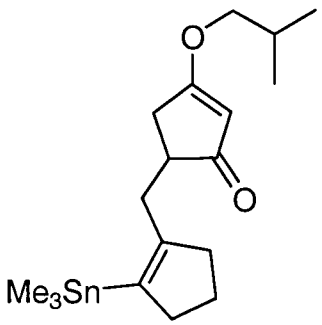
^1H NMR (400 MHz, $CDCl_3$) δ: 0.09 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.5 Hz), 1.78-1.90 (m, 2H), 1.98 (dd, 1H, J = 2.0, 19.0 Hz), 2.21-2.43 (m, 6H), 2.46 (dd, 1H, J = 6.5, 19.0 Hz), 3.05-3.12 (m, 1H), 6.12 (dd, 1H, J = 2.0, 6.0 Hz), 7.56 (dd, 1H, J = 2.0, 6.0 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -9.3 (-ve), 24.4, 36.2, 38.5, 39.3, 40.1 (-ve), 40.6, 133.6 (-ve), 139.2, 150.1, 168.2 (-ve), 209.6.

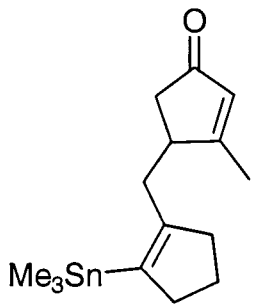
HRMS calcd for $C_{14}H_{22}O^{120}Sn$: 326.0693; found: 326.0700.

Anal. calcd for $C_{14}H_{22}OSn$: C 51.73, H 6.82; found: C 51.65, H 7.00.

Preparation of 4-[(2-trimethylstannylcyclopent-1-en-1-yl)methyl]-3-methylcyclopent-2-en-1-one (87)



85



87

To a cool (0 °C), stirred solution of the ketone **85** (1.38 g, 3.47 mmol) in dry THF (35 mL) was added a solution of MeMgBr (4.62 mL, 3.0 M solution in Et_2O, 13.9 mmol) via a syringe. The solution was warmed to room temperature and was stirred for 17 h. Water (35 mL) was added slowly and the resulting mixture was extracted with Et_2O (3 x 35 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude material was dissolved in Et_2O (35 mL) containing ~6 drops of H_2O and the mixture was treated with a catalytic amount of *p*-toluenesulfonic acid (~50 mg). The reaction mixture, open to air, was stirred for 4 h at room temperature. The mixture was diluted with H_2O (35 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 35 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude oil by flash column chromatography (106 g of silica gel, 2:3 Et_2O-petroleum ether) and subsequent bulb-to-bulb distillation (172-180 °C/0.2 torr) of the acquired material provided 888 mg (76%) of the enone **87** as a colourless oil.

IR (neat): 1695, 1610, 1446, 766 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.10 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.5 Hz), 1.82 (tt, 2H, *J* = 7.5, 7.5 Hz), 2.01-2.13 (m, 2H; s, 3H, -C<u>H</u>$_3$, (δ 2.09)), 2.25-2.33 (m, 2H), 2.33-2.45 (m, 3H), 2.60 (br dd, 1H, *J* = 5.0, 13.5 Hz), 2.91 (br m, 1H), 5.87 (t, 1H, *J* = 1.5 Hz).

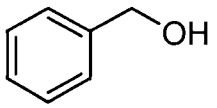
^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -9.3 (-ve), 17.5, 24.3 (-ve), 36.0, 37.0, 39.3, 41.2, 43.0 (-ve), 130.6 (-ve), 139.3, 150.5, 181.4, 208.6.

HRMS calcd for $C_{15}H_{24}O^{120}Sn$: 340.0849; found: 340.0843.

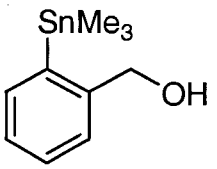
Anal. calcd for $C_{15}H_{24}OSn$: C 53.14, H 7.13; found: C 53.22, H 7.26.

4.2.2 Preparation of the aryltrimethylstannane precursors

*Preparation of 2-trimethylstannylbenzyl alcohol (**107**)*



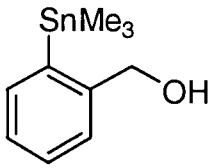
106



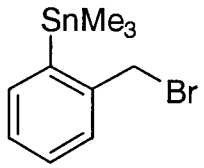
107

To a cold (-78 °C), stirred solution of TMEDA (7.39 mL, 50.0 mml) in dry Et_2O (200 mL) was added *n*-BuLi (30.1 mL, 1.60 M in hexanes, 48.2 mmol) via a syringe and stirring was continued for 5 min. Commercially available benzyl alcohol (2.11 mL, 20.4 mmol) was added neat via a syringe and the mixture was warmed to room temperature. After 3 h, the solution turned a dark red colour. The mixture was cooled to -78 °C and trimethyltin chloride (6.00 g, 30.2 mmol) was added in one solid portion. The reaction mixture was warmed to room temperature and stirred for 2 h. Water (200 mL) was added and the mixture was extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with H_2O (200 mL), brine (200 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (200 g of silica gel, 1:4 Et_2O-petroleum ether) to yield 3.50 g (64%) of the alcohol **107** as a colourless oil. This oil exhibited spectral properties (^1H NMR) identical with those previously reported.[57]

*Preparation of 2-trimethylstannylbenzyl bromide (**108**)*



107



108

To a cool (0 °C), stirred solution of triphenylphosphine (8.48 g, 32.3 mmol) in dry CH_2Cl_2 (130 mL) was added bromine (~1.7 mL) via a syringe, until a yellow colour persisted. A small amount of PPh_3 (~50 mg) was added until the colour disappeared. The mixture was stirred at 0 °C for 15 min, during which time a white precipitate formed. Solid imidazole (2.37 g, 34.8 mmol) was added and the white precipitate disappeared. The mixture was stirred for 15 min before addition of a solution of the alcohol **107** (3.50 g, 12.9 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred for 30 min. Most of the solvent was removed under reduced pressure until the volume remaining was approximately 30 mL. Pentane (200 mL) was added. The mixture (containing a precipitate) was filtered through a cake of silica gel (~50 g) and Celite® (~50 g) and the cake was eluted with pentane. To the residue left in the flask was added aqueous $NaHCO_3$ (10%, 100 mL) and the aqueous layer was extracted with pentane (2 x 100 mL). The combined organic extracts were filtered through the same cake of silica gel and Celite® (*vide supra*) and the cake was eluted with ~1 L of pentane. Concentration of the combined filtrate under reduced pressure afforded 4.05 g (94%) of the bromide **108** as a colourless oil.

IR (neat): 1471, 1220, 764, 609, 529 cm^{-1}.

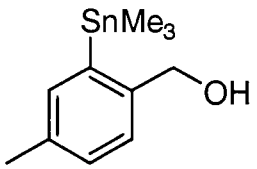
^1H NMR (400 MHz, $CDCl_3$) δ: 0.39 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.0 Hz), 4.51 (s, 2H, J = 6.0 Hz, -C<u>H</u>$_2$Br), 7.24 (dt, 1H, J = 1.5, 7.5 Hz), 7.30 (dt, 1H, J = 1.5, 7.5 Hz), 7.38-7.54 (m, 2H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ: -7.8, 36.9, 127.8, 129.0, 129.9, 136.8, 143.5, 144.5.

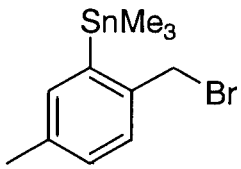
HRMS calcd for $C_9H_{12}{}^{79}Br\,{}^{120}Sn$ (M^+-Me): 318.9144; found: 318.9144.

Anal. calcd for $C_{10}H_{15}BrSn$: C 35.98, H 4.53; found: C 36.28, H 4.49.

*Preparation of 4-methyl-2-trimethylstannylbenzyl bromide (**110**)*



109



110

To a cool (0 °C), stirred solution of triphenylphosphine (5.06 g, 19.3 mmol) in dry CH_2Cl_2 (70 mL) was added bromine (~1 mL) via a syringe, until a yellow colour persisted. A small amount of PPh_3 (~50 mg) was added until the colour disappeared. The mixture was stirred at 0 °C for 15 min, during which time a white precipitate formed. Solid imidazole (1.40 g, 20.8 mmol) was added and the white precipitate disappeared. The mixture was stirred for 15 min before addition of a solution of the alcohol **109*** (2.20 g, 7.72 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred for 30 min. Most of the solvent was removed under reduced pressure until the volume remaining was approximately 15 mL. Pentane (100 mL) was added. The mixture (containing a precipitate) was filtered through a cake of silica gel (~20 g) and Celite® (~20 g) and the cake was eluted with pentane. Concentration of the combined filtrate under reduced pressure afforded 2.19 g (81%) of the bromide **110** as a colourless oil.

IR (neat): 1594, 1443, 1480, 1210 cm^{-1}.

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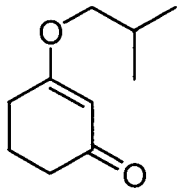
* This compound was prepared by J. G. K. Yee.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.32 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 50.0 Hz), 2.31 (s, 3H, -C<u>H</u>$_3$), 4.50 (s, 2H, -C<u>H</u>$_2$Br), 7.05-7.10 (m, 1H), 7.20-7.45 (m, 2H).

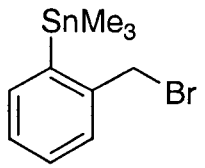
^{13}C NMR (50.3 MHz, $CDCl_3$) δ: -7.9, 21.2, 37.0, 128.9, 129.7 (2C), 137.5, 141.5, 143.2.
HRMS calcd for $C_{10}H_{14}{}^{79}Br^{120}Sn$ (M^+-Me): 322.9301; found: 322.9301.

Anal. calcd for $C_{11}H_{17}BrSn$: C 37.98, H 4.93; found: C 38.13, H 4.89.

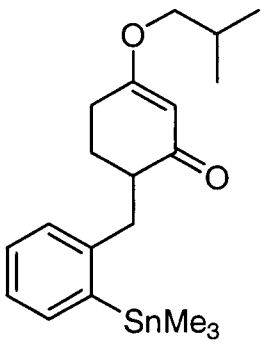
*Preparation of 6-(2-trimethylstannylbenzyl)-3-isobutoxycyclohex-2-en-1-one (**111**)*



76



108



111

To a cold (-78 °C), stirred solution of LDA (3.03 mmol) in dry THF (20 mL) was added a solution of 3-isobutoxycyclohex-2-en-1-one (**76**) (509 mg, 3.03 mmol) in dry THF (20 mL). The solution was warmed to 0 °C and stirred for 30 min and then at room temperature for 1.5 h. The mixture was subsequently cooled to -78 °C and a solution of the bromide **108** (506 mg, 1.514 mmol) in dry THF (10 mL) was added. The reaction mixture was warmed to room temperature and stirred for 2 h. Water (40 mL) was added and the mixture was extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with H_2O (40 mL), brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was purified by flash column chromatography (40 g of silica gel, 1:4 Et_2O-petroleum ether) to yield 618 mg (97%) of alkylated product **111** as a viscous colourless oil.

IR (neat): 1651, 1615, 1384, 1240, 992, 770 cm^{-1}.

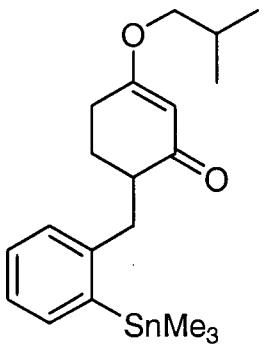
^1H NMR (400 MHz, $CDCl_3$) δ: 0.31 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.0 Hz), 0.97 (d, 3H, J = 6.5 Hz), 0.98 (d, 3H, J = 6.5 Hz), 1.53-1.66 (m, 1H), 1.88-1.93 (m, 1H), 1.93-2.04 (m, 1H), 2.30-2.45 (m, 3H), 3.50-3.60 (m, 4H), 5.34 (s, 1H, =C<u>H</u>), 6.92-7.22 (m, 2H), 7.22-7.30 (m, 1H), 7.42-7.48 (m, 1H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ: -7.2, 19.1 (2C), 26.0, 27.7, 28.6, 38.3, 47.2, 74.8, 102.2, 125.6, 128.4, 129.0, 136.5, 142.5, 146.9, 177.0, 199.8.

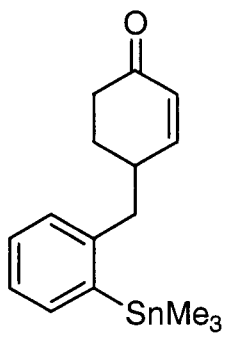
HRMS calcd for $C_{20}H_{30}O_2{}^{120}Sn$: 422.1268; found: 422.1271.

Anal. calcd for $C_{20}H_{30}O_2Sn$: C 57.04, H 7.18; found: C 56.89, H 7.09.

*Preparation of 4-(2-trimethylstannylbenzyl)cyclohex-2-en-1-one (**112**)*



111



112

To a cool (0 °C), stirred solution of the ketone **111** (278 mg, 0.659 mmol) in dry CH_2Cl_2 (15 mL) was added a solution of DIBAL-H (0.99 mL, 1.0 M solution in hexanes, 0.99 mmol) via a plastic syringe. The mixture was stirred at 0 °C for 2 h, after which time a saturated aqueous solution of Rochelle's salt (15 mL) was added. The resulting

mixture was warmed to room temperature and stirred, open to air, for 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with H_2O (15 mL), brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude material was dissolved in Et_2O (15 mL) containing ~3 drops of H_2O and the mixture was treated with a catalytic amount of *p*-toluenesulfonic acid (~10 mg). The reaction mixture, open to air, was stirred for 2 h at room temperature. It was diluted with H_2O (15 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 15 mL) and the combined organic extracts were washed with brine (15mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (20 g of silica gel, 1:4 Et_2O-petroleum ether) to afford 189 mg (82%) of the enone **112** as a colourless oil.

IR (neat): 1682, 1250, 773 cm^{-1}.

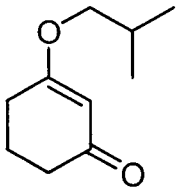
^1H NMR (400 MHz, $CDCl_3$) δ: 0.31 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.0 Hz), 1.69-1.80 (m, 1H), 2.04-2.14 (m, 1H), 2.33 (ddd, 1H, *J* = 5.0, 12.5, 17.0 Hz), 2.51 (ddd, 1H, *J* = 5.0, 5.0, 17.0 Hz), 2.65-2.74 (m, 1H), 2.74-2.82 (m, 2H), 5.98 (dd, 1H, *J* = 2.0, 10.0 Hz, =C<u>H</u>), 6.78 (d, 1H, *J* = 10.0 Hz, =C<u>H</u>), 7.16-7.32 (m, 3H), 7.42-7.48 (m, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -7.8 (-ve), 29.0, 36.9, 38.2 (-ve), 43.6, 126.1 (-ve), 128.7 (-ve), 128.8 (-ve), 129.3 (-ve), 136.7 (-ve), 142.5, 145.4, 153.4 (-ve), 199.5.

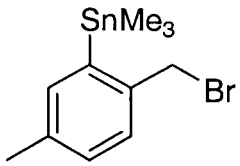
HRMS calcd for $C_{15}H_{19}O^{120}Sn$ (M^+-Me): 335.0458; found: 335.0457.

Anal. calcd for $C_{16}H_{22}OSn$: C 55.06, H 6.35; found: C 55.22, H 6.42.

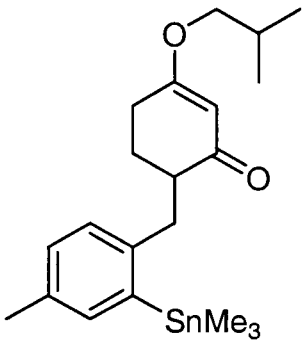
*Preparation of 6-(4-methyl-2-trimethylstannylbenzyl)-3-isobutoxycyclohex-2-en-1-one (**113**)*



76



110



113

To a cold (-78 °C), stirred solution of LDA (2.75 mmol) in dry THF (20 mL) was added a solution of 3-isobutoxycyclohex-2-en-1-one (**76**) (463 mg, 2.75 mmol) in dry THF (20 mL). The solution was warmed to 0 °C and stirrred for 30 min and then at room temperature for 1.5 h. The mixture was subsequently cooled to -78 °C and a solution of the bromide **110** (479 mg, 1.38 mmol) in dry THF (10 mL) was added. The reaction mixture was warmed to room temperature and stirred for 2 h. Water (40 mL) was added and the mixture was extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with H_2O (40 mL), brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was purified by flash column chromatography (40 g of silica gel, 1:4 Et_2O-petroleum ether) to yield 572 mg (96%) of alkylated product **113** as a viscous colourless oil.

IR (neat): 1664, 1615, 1467, 1183, 991, 761 cm^{-1}.

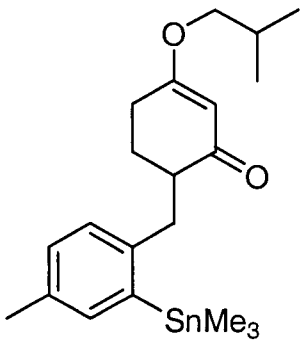
^1H NMR (400 MHz, $CDCl_3$) δ: 0.29 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.0 Hz), 0.97 (d, 3H, J = 6.5 Hz), 0.98 (d, 3H, J = 6.5 Hz), 1.55-1.66 (m, 1H), 1.88-1.96 (m, 1H), 1.96-2.05 (m, 1H), 2.30 (s, 3H, -C<u>H</u>$_3$), 2.30-2.43 (m, 3H), 3.45-3.65 (m, 4H), 5.34 (s, 1H, =C<u>H</u>), 7.00-7.15 (m, 2H), 7.22-7.30 (m, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -7.9(-ve), 19.0 (2C, -ve), 20.9 (-ve), 25.9, 27.7 (-ve), 28.5, 37.7, 47.2 (-ve), 74.7, 102.2 (-ve), 128.8 (-ve), 129.1 (-ve), 134.8, 137.2 (-ve), 142.3, 143.7, 177.0, 199.9.

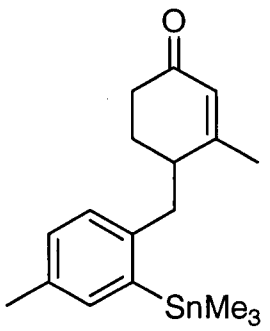
HRMS calcd for $C_{21}H_{32}O_2{}^{120}Sn$: 436.1424; found: 436.1419.

Anal. calcd for $C_{21}H_{32}O_2Sn$: C 57.96, H 7.41; found: C 57.81, H 7.54.

*Preparation of 3-methyl-4-(4-methyl-2-trimethylstannylbenzyl)cyclohex-2-en-1-one (**114**)*



113



114

To a cool (0 °C), stirred solution of the ketone **113** (236 mg, 0.541 mmol) in dry THF (25 mL) was added a solution of MeMgBr (0.72 mL, 3.0 M solution in Et_2O, 2.2 mmol) via a syringe. The mixture was warmed to room temperature and was stirred for 17 hours. Water (25 mL) was added slowly and the resulting mixture was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude material was dissolved in Et_2O (25 mL) containing ~5 drops of H_2O and the mixture was treated with a catalytic amount of *p*-toluenesulfonic acid (~10 mg). The reaction mixture, open to air, was stirred for 4 h at room temperature. It was diluted with H_2O (25 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 25 mL) and the combined organic extracts were washed with H_2O (25 mL), brine (25 mL), dried

($MgSO_4$), and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (40 g of silica gel, 1:4 Et_2O-petroleum ether) to provide 175 mg (86%) of the enone **114** as a viscous, colourless oil.

IR (neat): 1670, 1623, 1478, 1377, 1250, 769 cm^{-1}.

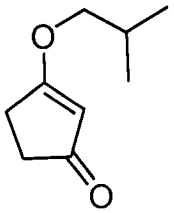
^1H NMR (400 MHz, $CDCl_3$) δ: 0.31 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 52.5 Hz), 1.70-1.81 (m, 1H), 1.81-2.00 (m, 1H; s, 3H, -C<u>H</u>$_3$, (δ 1.88)), 2.20-2.38 (m, 1H; s, 3H, -C<u>H</u>$_3$, (δ 2.31)), 2.45 (ddd, 1H, J = 4.5, 11.0, 16.0 Hz), 2.55-2.68 (m, 2H), 3.08 (dd, 1H, J = 4.5, 13.0 Hz), 5.87 (s, 1H, =C<u>H</u>), 7.07-7.12 (m, 2H), 7.12-7.32 (m, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -7.7 (-ve), 21.0 (-ve), 23.6 (-ve), 26.8, 34.0, 39.9, 40.9 (-ve), 127.2 (-ve), 128.5 (-ve), 129.4 (-ve), 135.3, 137.4 (-ve), 141.9, 142.7, 165.3, 199.2.

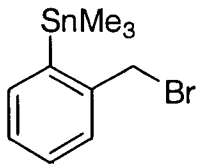
HRMS calcd for $C_{18}H_{26}O^{120}Sn$: 378.1006; found: 378.0994.

Anal. calcd for $C_{18}H_{26}OSn$: C 57.33, H 6.95; found: C 57.54, H 6.96.

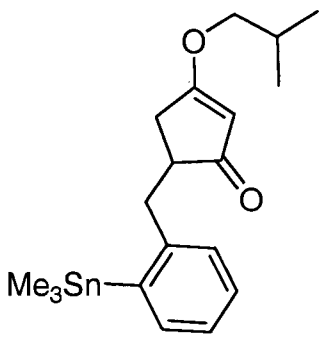
*Preparation of 5-(2-trimethylstannylbenzyl)-3-isobutoxycyclopent-2-en-1-one (**115**)*



82



108



115

To a cold (-78 °C), stirred solution of LDA (2.64 mmol) in dry THF (20 mL) was added a solution of 3-isobutoxycyclopent-2-en-1-one (**82**) (408 mg, 2.64 mmol) in dry THF (20 mL). The mixture was stirred at -78 °C for 30 min and at 0 °C for 15 min. It was subsequently cooled back to -78 °C and HMPA (0.466 mL, 2.64 mmol) was added, followed by a solution of the bromide **108** (441 mg, 1.32 mmol) in dry THF (10 mL). The reaction mixture was warmed to 0 °C and stirred for 1 h. Water (50 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with H_2O (2 x 50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was purified by flash column chromatography (30 g of silica gel, 2:3 Et_2O-petroleum ether) to yield 367 mg (68%) of alkylated product **115** as a colourless oil.

IR: 1696, 1594, 1470, 1351, 1173, 995 cm^{-1}.

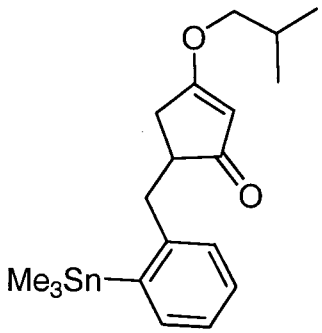
^1H NMR (400 MHz, $CDCl_3$) δ: 0.30 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn\text{-}H}$ = 53.0 Hz), 0.96 (d, 6H, J = 6.5 Hz, -CH($C\underline{H}_3$)$_2$), 1.97-2.09 (m, 1H, -$CH_2C\underline{H}(CH_3)_2$), 2.30 (dd, 1H, J = 2.0, 18.0 Hz), 2.47 (dd, 1H, J = 11.5, 14.0 Hz), 2.57 (dd, 1H, J = 7.0, 18.0 Hz), 2.75-2.83 (m, 1H), 3.35 (dd, 1H, J = 4.0, 14.0 Hz), 3.72 (d, 2H, J = 6.5 Hz, -O$C\underline{H}_2$CH), 5.25 (s, 1H, =C$\underline{H}$), 7.13-7.25 (m, 3H), 7.38-7.45 (m, 1H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ: -8.1, 18.9 (2C), 27.3, 34.3, 40.0, 46.6, 78.0, 103.6, 125.8, 127.9, 128.7, 136.3, 142.5, 146.3, 189.0, 206.8.

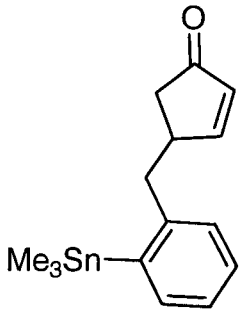
HRMS calcd for $C_{19}H_{28}O_2{}^{120}Sn$: 408.1111; found: 408.1104.

Anal. calcd for $C_{19}H_{28}O_2Sn$: C 56.05, H 6.93; found: C 56.19, H 7.00.

*Preparation of 4-(2-trimethylstannylbenzyl)-cyclopent-2-en-1-one (**116**)*



115



116

To a cool (0 °C), stirred solution of the ketone **115** (335 mg, 0.823 mmol) in dry CH_2Cl_2 (20 mL) was added a solution of DIBAL-H (1.24 mL, 1.0 M solution in hexanes, 1.24 mmol) via a plastic syringe. The mixture was stirred at 0 °C for 2 h, after which time a saturated aqueous solution of Rochelle's salt (20 mL) was added. The resultant mixture was warmed to room temperature and stirred, open to air, for 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude material was dissolved in Et_2O (20 mL) containing ~3 drops of H_2O and the mixture was treated with a catalytic amount of *p*-toluenesulfonic acid (~10 mg). The reaction mixture, open to air, was stirred for 2 h at room temperature. It was diluted with H_2O (20 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (16 g of silica gel, 2:3 Et_2O-petroleum ether) to afford 172 mg (62%) of the enone **116** as a colourless oil.

IR (neat): 1718, 1182, 770 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.29 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.0 Hz), 2.09 (dd, 1H, J = 2.0, 19.0 Hz, one of -CHC<u>H</u>$_2$-C(O)), 2.52 (dd, 1H, J = 6.5, 19.0 Hz, one of

-CHC<u>H</u>$_2$-C(O)), 2.77 (dd, 1H, J = 8.0, 14.0 Hz, one of Ar-C<u>H</u>$_2$-CH-), 2.84 (dd, 1H, J = 8.0, 14.0 Hz, one of Ar-C<u>H</u>$_2$-CH-), 3.18-3.27 (m, 1H, -C<u>H</u>-), 6.19 (d, 1H, J = 5.5 Hz, =C<u>H</u>), 7.18-7.23 (m, 2H), 7.23-7.33 (m, 1H), 7.45 (br d, 1H, J = 8.0 Hz), 7.57 (dd, 1H, J = 2.0, 5.5 Hz, =C<u>H</u>).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -7.9 (-ve), 40.9, 43.1 (-ve), 43.7, 126.1 (-ve), 128.4 (-ve), 128.8 (-ve), 134.1(-ve), 136.7 (-ve), 142.3, 145.5, 167.3 (-ve), 209.1.

HRMS calcd for $C_{14}H_{17}O^{120}Sn$ (M^+-Me): 321.0301; found: 321.0303.

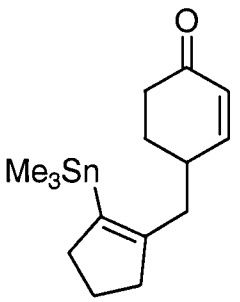
Anal. calcd for $C_{15}H_{20}OSn$: C 53.78, H 6.02; found: C 54.13, H 6.11.

4.2.3 CuCN mediated cyclizations

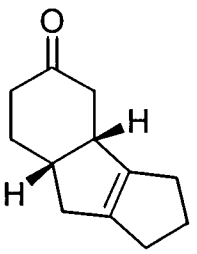
General Procedure 1. Copper(I) cyanide mediated cyclizations

A solution of the appropriate enone (1 equiv) in dry DMSO (~20 mL/mmol of the enone) was transferred via a cannula to a flask containing CuCN (2.5 equiv) under an atmosphere of argon. The stirred mixture was heated at 60 °C for 3-6 h and then was allowed to cool to room temperature. Saturated aqueous NH_4Cl-NH_3 (pH 8, ~20 mL/mmol of the enone) and Et_2O (~20 mL/mmol of the enone) were added and the resulting mixture was stirred, open to air, until the aqueous layer became deep blue (~30 min). The layers were separated and the aqueous layer was extracted with Et_2O (2 x ~20 mL/mmol of the enone). The combined organic extracts were washed with H_2O (2 x ~20 mL/mmol of the enone), brine (~20 mL/mmol of the enone), were dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude material was achieved by flash column chromatography on silica gel.

Preparation of cis-*tricyclo[6.4.0.0^{2,6}]dodec-2(6)-en-11-one (88)*[43]



78



88

Following general procedure 1, a mixture of the enone **78** (950 mg, 2.80 mmol) and CuCN (627 mg, 7.00 mmol) in dry DMSO (55 mL) was heated at 60 °C for 4 h. Purification of the crude material by flash column chromatography (50 g of silica gel, 1:4

Et_2O-petroleum ether) and subsequent bulb-to-bulb distillation (76-80 °C/0.1 torr) of the acquired material provided 464 mg (94%) of the ketone **88** as a colourless oil.

IR (neat): 1717, 1419 cm^{-1}.

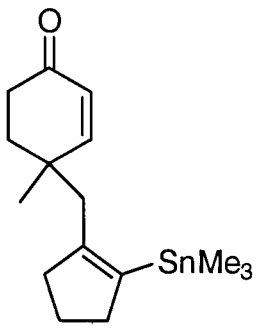
^1H NMR (400 MHz, $CDCl_3$) δ: 1.70-1.82 (m, 1H), 1.90-2.30 (m, 11H), 2.45-2.59 (m, 2H), 2.88-3.01 (m, 2H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 27.1, 27.4, 27.6, 29.1, 35.9, 37.0, 39.4 (-ve), 40.2 (-ve), 41.3, 144.9, 147.3, 214.2

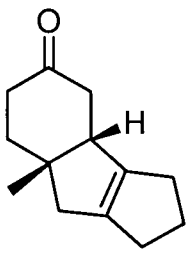
HRMS calcd for $C_{12}H_{16}O$: 176.1201; found: 176.1198.

Anal. calcd for $C_{12}H_{16}O$: C 81.77, H 9.15; found: C 81.65, H 9.23.

*Preparation of cis-8-methyltricyclo[6.4.0.0^{2,6}]dodec-2(6)-en-11-one (**89**)*[43]



80



89

Following general procedure 1, a mixture of the enone **80** (789 mg, 2.23 mmol) and CuCN (512 mg, 5.72 mmol) in dry DMSO (45 mL) was heated at 60 °C for 4 h. Purification of the crude material by flash column chromatography (40 g of silica gel, 1:4 Et_2O-petroleum ether) and subsequent bulb-to-bulb distillation (102-110°C/0.1 torr) of the acquired material provided 364 mg (85%) of the ketone **89** as a colourless oil.

IR (neat): 1717, 1446 cm^{-1}.

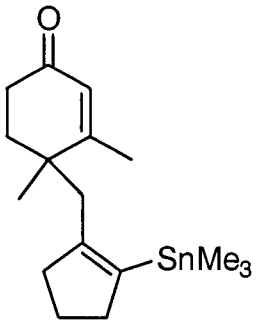
^1H NMR (400 MHz, $CDCl_3$) δ: 1.23 (s, 3H, -$C\underline{H}_3$), 1.76-1.83 (m, 2H), 1.97-2.30 (m, 11H), 2.48-2.59 (m, 2H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 27.3, 27.5, 29.4, 30.0 (-ve), 35.1, 35.9, 41.1, 44.3, 45.8, 47.9 (-ve), 144.0, 146.6, 214.3.

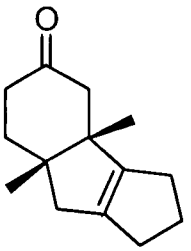
HRMS calcd for $C_{13}H_{18}O$: 190.1358; found: 190.1355.

Anal. calcd for $C_{13}H_{18}O$: C 82.06, H 9.53; found: C 81.90, H 9.49.

*Preparation of cis-1,8-dimethyltricyclo[6.4.0.0^{2,6}]dodec-2(6)-en-11-one (**90**)*



81



90

Following general procedure 1, a mixture of the enone **81** (482 mg, 1.31 mmol) and CuCN (294 mg, 3.28 mmol) in dry DMSO (26 mL) was heated at 60 °C for 6 h. Purification of the crude material by flash column chromatography (18 g of silica gel, 1:4 Et_2O-petroleum ether) and subsequent bulb-to-bulb distillation (118-120 °C/0.2 torr) of the acquired material provided 240 mg (88%) of the ketone **90** as a colourless viscous oil, which solidified upon standing (m.p. 27-29 °C).

IR (neat): 1715, 1446 cm^{-1}.

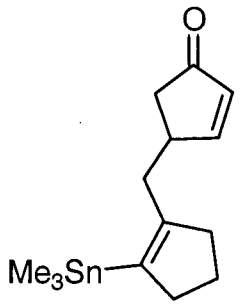
^1H NMR (400 MHz, $CDCl_3$) δ: 0.98 (s, 3H, -C<u>H</u>$_3$), 1.15 (s, 3H, -C<u>H</u>$_3$), 1.76-1.81 (m, 2H), 1.97-2.39 (m, 12H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7 (-ve) , 25.2 (-ve), 25.6, 27.0, 29.4, 36.3, 37.2, 44.1, 47.4, 48.1, 48.7, 141.9, 151.2, 214.0.

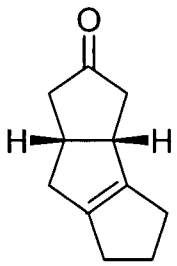
HRMS calcd for $C_{14}H_{20}O$: 204.1514; found: 204.1510.

Anal. calcd for $C_{14}H_{20}O$: C 82.30, H 9.87; found: C 82.46, H 9.85.

*Preparation of cis-tricyclo[6.3.0.0^{2,6}]undec-1(8)-en-4-one (**91**)*



86



91

To a stirred solution of the enone **86** (164 mg, 0.505 mmol) in dry DMSO (9.3 ml), under an atmosphere of argon, was added CuCN (227 mg, 2.53 mmol). The reaction mixture was heated at 60 °C for 17 h. Saturated aqueous NH_4Cl-NH_3 solution (pH 8, 10 mL) and Et_2O (10 mL) were added and the mixture was stirred, open to air, until the aqueous layer turned deep blue. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with H_2O (2 x 10 mL), brine (10 mL), were dried ($MgSO_4$), and concentrated under reduced pressure.

Purification of the crude material by flash column chromatography (31 g of silica gel, 1:4 Et_2O-petroleum ether) and subsequent bulb-to-bulb distillation (84-88 °C/0.3 torr) of the acquired material provided 65 mg (80%) of the ketone **91** as a colourless oil.

IR (neat): 1740, 1402, 1255, 1160 cm^{-1}.

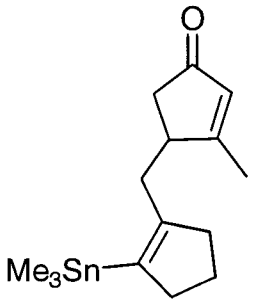
^1H NMR (400 MHz, $CDCl_3$) δ: 2.10-2.23 (m, 9H), 2.10 (ddd, 1H, J = 1.5, 9.5, 19.0 Hz), 2.46-2.60 (m, 2H), 3.14-3.28 (m, 2H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 27.5, 28.0, 29.4, 37.0, 40.6, 42.6 (-ve), 43.1 (-ve), 45.5, 145.4, 147.4, 220.5.

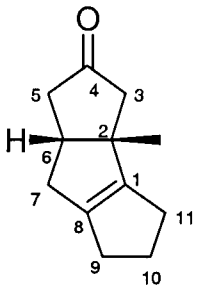
HRMS calcd for $C_{11}H_{14}O$: 162.1045; found: 162.1042.

Anal. calcd for $C_{11}H_{14}O$: C 81.44, H 8.70; found: C 81.32, H 8.85.

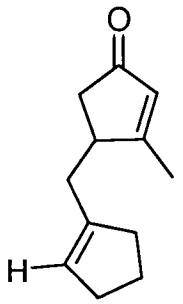
*Preparation of cis-2-methyltricyclo[6.3.0.0^{2,6}]undec-1(8)-en-4-one (**94**)*



87



94



95

To a flame dried, 20 mL glass, sealable ampoule equipped with a magnetic stir bar, under an atmosphere of argon, was added the enone **87** (335 g, 0.986 mmol), dry DMSO (17 mL), and solid CuCN (4.35 g, 48.6 mmol). The ampoule was flushed with a stream of argon gas and sealed using a natural gas-oxygen torch. The mixture was heated to 90 °C using an oil bath and was stirred at this temperature for 17 h. The ampoule was opened and the brown reaction mixture was poured into an aqueous solution of NH_4Cl-NH_3 (pH 8, 50 mL) and the resulting mixture was diluted with Et_2O (50 mL). The mixture was stirred vigorously, open to air, until the aqueous phase became blue. The mixture, which contained a purple precipitate that remained insoluble at the interface of the two layers, was filtered through a sintered glass funnel. The solid in the funnel was rinsed with a solution of aqueous NH_4Cl-NH_3 (pH 8, ~50 mL) and Et_2O (~50 mL). The phases of the combined filtrate were separated and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with H_2O (100 mL), brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (28 g of silica gel, 1:4 Et_2O-petroleum ether) to yield 96 mg (55%) of the ketone **94** along with 24 mg (14%) of protiodestannylated material **95**, both as colourless oils.

Characterization data for *cis*-2-methyltricyclo[6.3.0.0^{2,6}]undec-1(8)-en-4-one (**94**):

IR (neat): 1742, 1401, 1160 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (s, 3H, -C<u>H</u>$_3$), 1.88 (br d, 1H, J = 16.0 Hz), 1.95-2.23 (m, 8H), 2.35 (dd, 1H, J = 1.5, 19.0 Hz), 2.53-2.61 (m, 1H), 2.65 (ddd, 1 H, J = 1.5, 10.0, 19.0 Hz), 2.75-2.85 (m, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 25.2, 25.7, 27.8, 29.6, 36.0, 46.7, 48.2, 49.2, 50.8 (-ve), 143.3, 151.1, 219.9.

HRMS calcd for $C_{12}H_{16}O$: 176.1201; found: 176.1197.

Anal. calcd for $C_{12}H_{16}O$: C 81.77, H 9.15; found: C 81.65, H 9.13.

Characterization data for the protiodestannylated material **95**:

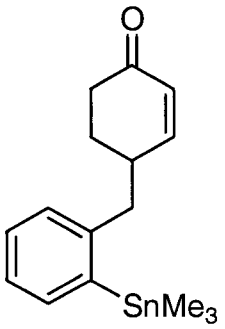
IR (neat): 1713, 1615, 1444, 1182 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.84 (tt, 2H, J = 7.5, 7.5 Hz), 1.98 (dd, 1H, J = 10.5, 14.0 Hz), 2.09 (s, 3H, -C<u>H</u>$_3$), 2.13-2.32 (m, 5H), 2.45-2.55 (m, 2H), 2.91 (br m, 1H), 5.38 (s, 1H, =C<u>H</u>C=O), 5.88 (t, 1H, J = 1.0 Hz, =C<u>H</u>-CH_2-).

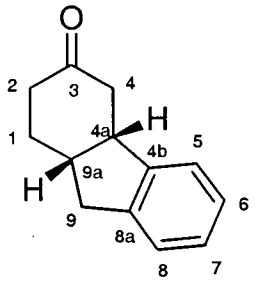
^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 17.4, 23.5, 32.4, 34.6, 35.2, 42.0, 42.9, 126.2, 130.8, 141.7, 181.3, 208.9.

HRMS calcd for $C_{12}H_{16}O$: 176.1201; found: 176.1206.

*Preparation of cis-1, 2, 4, 4a, 9, 9a-hexahydro-3H-fluorene-3-one (**117**)*



112



117

Following general procedure 1, a mixture of the enone **112** (78 mg, 0.22 mmol) and CuCN (50 mg, 0.56 mmol) in dry DMSO (4 mL) was heated at 60 °C for 2 h. The crude material was purified by flash column chromatography (4 g of silica gel, 1:4 Et_2O-petroleum ether) to provide 36 mg (87%) of the ketone **117** as a colourless oil.

IR (neat): 1720, 1457, 1257, 745 cm^{-1}.

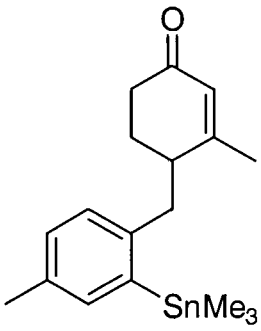
^1H NMR (400 MHz, $CDCl_3$) δ: 1.70-1.81 (m, 1H), 1.97-2.09 (m, 1H), 2.23-2.30 (m, 2H), 2.62 (dd, 1H, J = 7.5, 15.0 Hz), 2.70-2.82 (m, 3H), 3.16-3.27 (m, 1H), 3.64 (ddd, 1H, J = 7.5, 7.5, 7.5 Hz), 7.11-7.22 (m, 4H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 27.6, 36.8 (-ve), 38.4, 38.4, 42.5, 43.8 (-ve), 123.7 (-ve), 124.9 (-ve), 126.7 (-ve), 127.0 (-ve), 142.2, 145.0, 212.5.

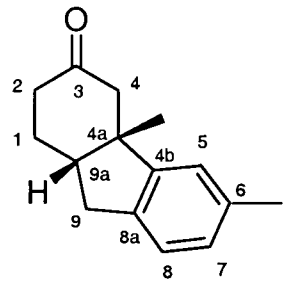
HRMS calcd for $C_{13}H_{14}O$: 186.1045; found: 186.1048.

Anal. calcd for $C_{13}H_{14}O$: C 83.83, H 7.58; found: C 83.65, H 7.35.

*Preparation of cis-4a, 6-dimethyl-1, 2, 4, 4a, 9, 9a-hexahydro-3H-fluorene-3-one (**118**)*



114



118

Following general procedure 1, a mixture of the enone **114** (80 mg, 0.21 mmol) in dry DMSO (4 mL) and CuCN (47 mg, 0.53 mmol) was heated at 60 °C for 29 h. The progress of the reaction was monitored by GLC analysis. The crude material was purified by flash column chromatography (4 g of silica gel, 1:4 Et_2O-petroleum ether) to provide 30 mg (66%) of the ketone **118** as a colourless oil, as well as 5 mg of protiodestannylated material that was not fully characterized. The ^1H NMR spectrum of the latter material showed the presence of 4 aromatic protons (δ 7.00-7.11, m) and an alkenic proton (δ 5.87, s, 1H), as well as lack of the -$SnMe_3$ group.

IR (neat): 1714, 1452, 1229, 810 cm^{-1}.

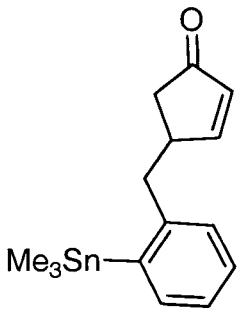
^1H NMR (400 MHz, $CDCl_3$) δ: 1.28 (s, 3H, -$C\underline{H}_3$), 1.82-1.92 (m, 1H), 2.02-2.13 (m, 1H), 2.20-2.36 (m, 3H; s, 3H, -$C\underline{H}_3$, (δ 2.29)), 2.42 (dd, 1H, J = 1.0, 14.5 Hz), 2.60 (d, 1H, J = 14.5 Hz), 2.75 (dd, 1H, J = 6.0, 16.0 Hz), 3.17 (dd, 1H, J = 8.0, 16.0 Hz), 6.88 (s, 1H), 6.96 (d, 1H, J = 7.5 Hz), 7.08 (d, 1H, J = 7.5 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.3 (-ve), 27.3, 28.2 (-ve), 36.1, 37.3, 45.1 (-ve), 49.3, 50.5, 122.7 (-ve), 124.6 (-ve), 127.8 (-ve), 136.5, 137.9, 150.4, 212.2.

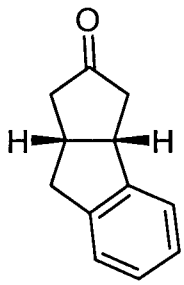
HRMS calcd for $C_{15}H_{18}O$: 214.1358; found: 214.1363.

Anal. calcd for $C_{15}H_{18}O$: C 84.06, H 8.46; found: C 84.21, H 8.41.

*Preparation of cis-6, 7-benzobicyclo[3.3.0]octan-3-one (**119**)*



116



119

Following general procedure 1, a mixture of the enone **116** (101 mg, 0.30 mmol) and CuCN (65 mg, 0.72 mmol) in dry DMSO (6 mL) was heated at 60 °C for 2 h. The crude material was purified by flash column chromatography (10 g of silica gel, 1:4 Et_2O-petroleum ether) to provide 39 mg (75%) of the ketone **119** as a colourless oil. This compound has been reported in the literature.[60]

IR (neat): 1738, 1399, 1154, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.95 (dd, 1H, J = 8.0, 19.0 Hz), 2.46-2.60 (m, 2H), 2.69 (ddd, 1H, J = 1.5, 9.0, 19.0 Hz), 2.80 (d, 1H, J = 16.0 Hz), 3.11-3.30 (m, 2H), 3.83-3.92 (m, 1H), 7.14-7.24 (m, 4H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 38.4, 39.4 (-ve), 43.5, 43.8, 46.0 (-ve), 124.6 (-ve), 125.4 (-ve), 127.0 (-ve), 127.2 (-ve), 142.3, 144.9, 219.3.

HRMS calcd for $C_{12}H_{12}O$: 172.0888; found: 172.0889.

Anal. calcd for $C_{12}H_{12}O$: C 83.69, H 7.02; found: C 83.90, H 6.97.

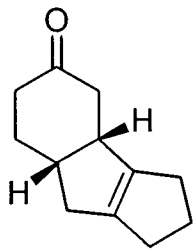
4.3 Oxidative cleavage of tricyclic ketals and ketones to form functionalized *cis*-fused bicyclo[6.3.0]undecane, bicyclo[6.4.0]dodecanes and bicyclo[7.4.0]tridecanes

4.3.1 Preparation of ketals from ketones.

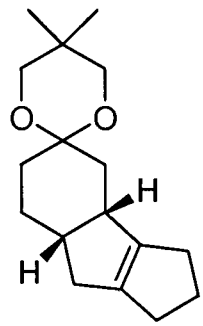
General Procedure 2. Conversion of ketones into ketals.

To a solution of the appropriate tricyclic ketone (1 equiv) in dry benzene (0.1 M solution) was added 2,2-dimethyl-1,3-propanediol (2.5 equiv) and a catalytic amount of *p*-toluenesulfonic acid. The mixture was heated at reflux under an atmosphere of argon with the use of a Dean-Stark trap for 17 h and then was cooled to room temperature. Water (~10 mL/mmol of ketone) was added and the mixture was extracted with Et_2O (3 x ~10 mL/mmol of ketone). The combined organic extracts were washed with H_2O (~10 mL/mmol of ketone) and brine (~30 mL/mmol of ketone), were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel.

*Preparation of cis-5', 5'-dimethylspiro[(tricyclo[6.4.0.0^{2,6}]dodec-2(6)-ene)-11, 2'-(1', 3'-dioxane)] (**131**)*



88



131

Following general procedure 2, the ketal **131** was prepared by heating at reflux a solution of the ketone **88** (175 mg, 0.991 mmol), 2,2-dimethyl-1,3-propanediol (258 mg, 2.48 mmol) and a catalytic amount of *p*-toluenesulfonic acid (~10 mg) in benzene (10 mL). Purification of the crude material by flash column chromatography (20 g of silica gel, 1:50 Et_2O-petroleum ether) and subsequent bulb-to-bulb distillation (85-90 °C/0.1 torr) of the acquired material provided 212 mg (82%) of the ketal **131** as a colourless oil.

IR (neat): 1362, 1105, 1018 cm^{-1}.

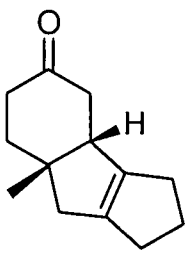
^1H NMR (400 MHz, $CDCl_3$) δ: 0.93 (s, 3H, -C<u>H</u>$_3$), 0.94 (s, 3H, -C<u>H</u>$_3$), 1.15-1.23 (m, 1H), 1.50-1.78 (m, 3H), 1.82-1.97 (m, 2H), 2.01-2.20 (m, 8H), 2.44-2.53 (m, 1H), 2.54-2.65 (m, 1H), 3.40-3.51 (m, 4H, -C<u>H</u>$_2$-O-).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7 (2C, -ve), 24.8, 27.6, 27.8, 29.6, 29.6, 30.1, 33.6, 33.7, 38.6 (-ve), 42.2 (-ve), 70.1, 70.1, 98.4, 144.0, 149.7.

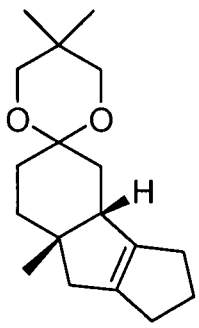
HRMS calcd for $C_{17}H_{26}O_2$: 262.1933; found: 262.1928.

Anal. calcd for $C_{17}H_{26}O_2$: C 77.82., H 9.99; found: C 78.02, H 9.96.

Preparation of cis-5', 5'-dimethylspiro[(8-methyltricyclo[6.4.0.0^{2,6}]dodec-2(6)-ene)-11, 2'-(1', 3'-dioxane)] ***(132)***



89



132

Following general procedure 2, the ketal **132** was prepared by heating at reflux a solution of the ketone **89** (307 mg, 1.60 mmol), 2,2-dimethyl-1,3-propanediol (419 mg, 4.03 mmol) and a catalytic amount of *p*-toluenesulfonic acid (~15 mg) in benzene (16 mL). Purification of the crude material by flash column chromatography (40 g of silica gel, 1:50 Et_2O-petroleum ether) and subsequent bulb-to-bulb distillation (112-118 °C/0.1 torr) of the acquired material provided 347 mg (78%) of the ketal **132** as a colourless oil.

IR (neat): 1360, 1113, 987 cm^{-1}.

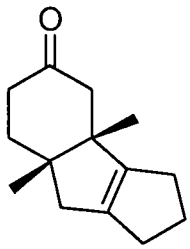
^1H NMR (400 MHz, $CDCl_3$) δ: 0.93 (s, 3H, -C<u>H</u>$_3$), 0.94 (s, 3H, -C<u>H</u>$_3$), 1.06 (s, 3H, -C<u>H</u>$_3$), 1.38-1.49 (m, 2H), 1.57-1.73 (m, 2H), 1.75-1.85 (m, 2H), 1.99-2.22 (m, 9H), 3.41-3.53 (m, 4H, -C<u>H</u>$_2$-O-).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.6 (-ve), 22.7 (-ve), 27.5, 28.2, 28.6 (-ve), 29.3, 29.8, 30.2, 32.7, 33.6, 42.4, 46.1, 46.3 (-ve), 70.2, 70.2, 98.3, 142.2, 148.8.

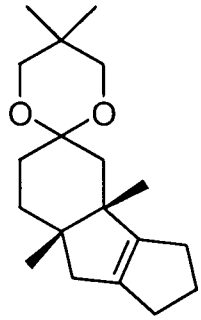
HRMS calcd for $C_{18}H_{28}O_2$: 276.2089; found: 276.2083.

Anal. calcd for $C_{18}H_{28}O_2$: C 78.21, H 10.21; found: C 78.01, H 10.19.

*Preparation of cis-5', 5'-dimethylspiro[(1, 8-dimethyltricyclo[6.4.0.0^{2,6}]dodec-2(6)-ene)-11, 2'-(1',3'-dioxane)] (**133**)*



90



133

Following general procedure 2, the ketal **133** was prepared by heating at reflux a solution of the ketone **90** (422 mg, 2.06 mmol), 2,2-dimethyl-1,3-propanediol (540 mg, 5.16 mmol) and a catalytic amount of *p*-toluenesulfonic acid (~20 mg) in benzene (20 mL). Purification of the crude material by flash column chromatography (45 g of silica gel, 1:50 Et_2O-petroleum ether) and subsequent bulb-to-bulb distillation (139-145 °C/0.1 torr) of the acquired material provided 495 mg (83%) of the ketal **133** as a colourless oil.

IR (neat): 1356, 1115, 987 cm^{-1}.

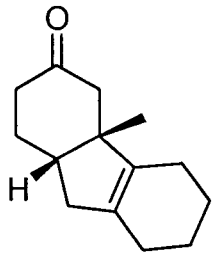
^1H NMR (400 MHz, $CDCl_3$) δ: 0.84 (s, 3H, -C<u>H</u>$_3$), 0.88 (s, 3H, -C<u>H</u>$_3$), 0.96 (s, 3H, -C<u>H</u>$_3$), 0.99 (s, 3H, -C<u>H</u>$_3$), 1.28-1.35 (m, 1H), 1.49 (d, 1H, J = 15.0 Hz), 1.52-1.60 (m, 1H), 1.67-1.75 (m, 1H), 1.78-1.98 (m, 4H), 2.00-2.20 (m, 6H), 3.35 (dd, 1H, J = 1.0, 11.0 Hz, one of -C<u>H</u>$_2$-O-), 3.41 (d, 1H, J = 1.0, 11.0 Hz, one of -C<u>H</u>$_2$-O-), 3.48 (d, 1H, J = 11.0 Hz, one of -C<u>H</u>$_2$-O-), 3.51 (d, 1H, J = 11.0 Hz, one of -C<u>H</u>$_2$-O-).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.9 (-ve), 22.5 (-ve), 22.6 (-ve), 22.6 (-ve), 26.6, 27.2, 30.0 (2C), 30.2, 33.6, 38.0, 42.3, 46.0, 48.3, 70.1, 70.3, 98.0, 139.5, 153.4.

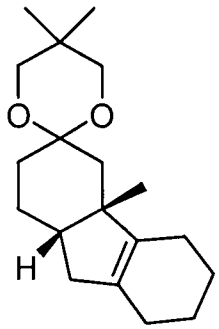
HRMS calcd for $C_{19}H_{30}O_2$: 290.2246; found: 290.2244.

Anal. calcd for $C_{19}H_{30}O_2$: C 78.57, H 10.41; found: C 78.64, H 10.54.

*Preparation of cis-5', 5'-dimethylspiro[(1-methyltricyclo[7.4.0.0^{2,7}]tridec-2(7)-ene)-12, 2'-(1', 3'-dioxane)] (**134**)*



54



134

Following general procedure 2, the ketal **134** was prepared by heating at reflux a solution of the ketone **54**[43] (225 mg, 1.10 mmol), 2,2-dimethyl-1,3-propanediol (286 mg, 2.75 mmol) and a catalytic amount of *p*-toluenesulfonic acid (~10 mg) in benzene (11 mL). Purification of the crude material by flash column chromatography (20 g of silica gel, 1:19 Et_2O-petroleum ether) and subsequent bulb-to-bulb distillation of the acquired material (105-110 °C/0.1 torr) provided 288 mg (90%) of the ketal **134** as a colourless oil.

IR (neat): 1363, 1113, 988 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.80-0.90 (m, 1H), 0.90 (s, 3H, -C<u>H</u>$_3$), 1.00 (s, 3H, -C<u>H</u>$_3$), 1.05 (s, 3H, -C<u>H</u>$_3$), 1.30 (d, 1H, *J* = 14.0 Hz), 1.44-1.95 (m, 13H), 1.95-2.15 (m, 2H), 3.35-3.43 (m, 2H, -C<u>H</u>$_2$-O-), 3.49 (d, 1H, *J* = 16.0 Hz, one of -C<u>H</u>$_2$-O-), 3.52 (d, 1H, *J* = 16.0 Hz, one of -C<u>H</u>$_2$-O-).

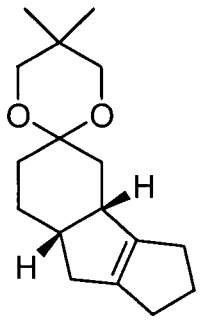
^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.7, 22.6 (-ve), 22.8 (-ve), 22.9, 23.1, 23.2, 24.6 (-ve), 25.9, 30.1, 30.2, 37.6, 38.6, 43.7 (-ve), 47.4, 69.9, 70.0, 98.1, 131.1, 143.2.

HRMS calcd for $C_{19}H_{30}O_2$: 290.2246; found: 290.2243.

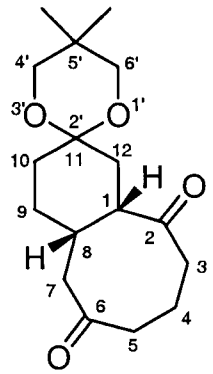
Anal. calcd for $C_{19}H_{30}O_2$: C 78.57, H 10.41; found: C 78.59, H 10.37.

4.3.2 Preparation of ketal diones via oxidative cleavage

*Preparation of cis-5', 5'-dimethylspiro[(bicyclo[6.4.0]dodecane-2, 6-dione)-11, 2'-(1', 3'-dioxane)] (**135**)*



131



135

Into a cold (-78 °C), stirred solution of the ketal **131** (88.5 mg, 0.337 mmol) in methanol (6 mL) was passed ozone in a stream of oxygen gas for approximately 10 min. The reaction mixture turned a pale blue colour, indicating the presence of excess ozone in the mixture. An excess of dimethyl sulfide (~1 mL) was added. The reaction flask innlet was covered with a septum, and the reaction mixture was warmed to room temperature and stirred for 2 h. The volatiles were removed under reduced pressure and the remaining crude solid was purified by flash column chromatography (8 g of silica gel, Et_2O) to provide 100.0 mg (100%) of the ketal dione **135** as a colourless solid (m.p. 162-163 °C).

IR (KBr): 1694, 1448, 1170, 1094 cm^{-1}.

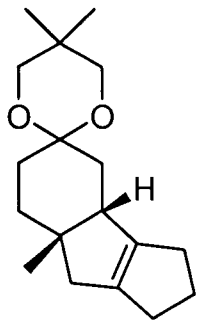
^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84 (s, 3H, -C<u>H</u>$_3$), 0.96 (s, 3H, -C<u>H</u>$_3$), 1.32-1.47 (m, 2H), 1.58 (dm, 1H, *J* for d = 13.0 Hz), 1.89-2.06 (m, 4H), 2.12 (dd, 1H, *J* = 2.5, 15.0 Hz), 2.20-2.28 (m, 2H), 2.44 (ddd, 1H, *J* = 2.5, 2.5, 15.0 Hz), 2.62-2.86 (m, 4H), 3.21 (br d, 1H, *J* = 13.0 Hz, -C<u>H</u>-C(O)), 3.34 (dd, 1H, *J* = 1.0, 11.5 Hz, one of -C<u>H</u>$_2$-O-), 3.40 (d, 1H, *J* = 11.5 Hz, one of -C<u>H</u>$_2$-O-), 3.42 (dd, 1H, *J* = 1.0, 11.5 Hz, one of -C<u>H</u>$_2$-O-), 3.60 (d, 1H, *J* = 11.5 Hz, one of -C<u>H</u>$_2$-O-).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.4 (-ve), 22.8 (-ve), 25.3, 25.4, 28.6 (-ve), 28.7, 28.8, 30.1, 39.5, 39.9, 45.6, 51.2 (-ve), 69.8, 69.9, 97.4, 211.6, 212.3.

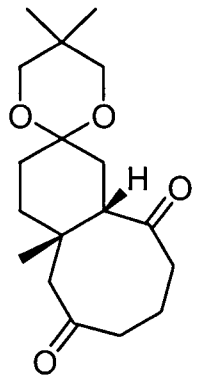
HRMS calcd for $C_{17}H_{26}O_4$: 294.1831; found: 294.1830.

Anal. calcd for $C_{17}H_{26}O_4$: C 69.34, H 8.92; found: C 69.32, H 8.77.

*Preparation of cis-5', 5'-dimethylspiro[(8-methylbicyclo[6.4.0]dodecane-2, 6-dione)-11, 2'-(1', 3'-dioxane)] (**136**)*



132



136

To a heterogeneous mixture of the ketal alkene **132** (91.0 mg, 0.329 mmol) in CH_3CN (1.5 mL), CCl_4 (1.5 mL) and water (2.3 mL) was added sodium periodate (296 mg, 1.38 mmol) and a catalytic amount of $RuO_2 \cdot xH_2O$ (1.2 mg, 0.0077 mmol based on x = 1). The mixture, open to the atmosphere, was stirred vigorously for 15 min at room temperature.

Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with H_2O (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residual material was filtered through a Pasteur pipette containing flash silica gel and the pipette was eluted with Et_2O. The eluate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (5 g of silica gel, Et_2O) to afford 96.3 mg (95%) of the ketal dione **136** as a colourless solid (m.p. 148-151 °C).

IR (KBr): 1685, 1455,1373, 1103 cm^{-1}.

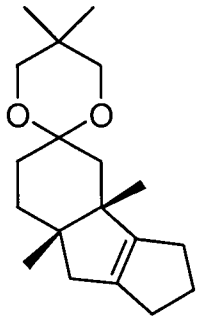
^1H NMR (400 MHz, $CDCl_3$) δ: 0.90 (s, 3H, -C<u>H</u>$_3$), 0.99 (s, 3H, -C<u>H</u>$_3$), 1.04 (s, 3H, -C<u>H</u>$_3$), 1.36 (ddd, 1H, J = 3.5, 3.5, 13.0 Hz), 1.43-1.64 (m, 2H), 1.75 (d, 1H, J = 12.0 Hz, H-7), 1.91-2.01 (m, 1H), 2.14-2.25 (m, 3H), 2.25-2.40 (m, 3H), 2.44 (dd, 1H, J = 3.5, 14.0 Hz), 2.53 (dd, 1H, J = 9.0, 12.5 Hz), 2.86 (ddd, 1H, J = 3.5, 7.0, 13.0 Hz), 3.35-3.45 (m, 3H, one of -C<u>H</u>$_2$-C(O) and -C<u>H</u>$_2$-O-), 3.48 (dd, 1H, J = 1.0, 11.5 Hz, one of -C<u>H</u>$_2$-O-), 3.59 (d, 1H, J = 11.5 Hz, one of -C<u>H</u>$_2$-O-).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.5 (-ve), 22.7 (-ve), 23.0, 27.0 (-ve), 27.2, 30.2, 32.6, 37.2, 40.1, 41.4, 44.4, 46.1, 55.3 (-ve), 69.9, 70.3, 96.9, 212.0, 212.5.

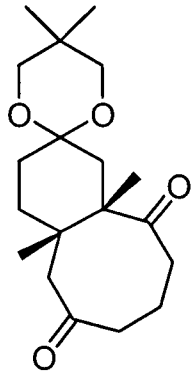
HRMS calcd for $C_{18}H_{28}O_4$: 308.1988; found: 308.1981.

Anal. calcd for $C_{18}H_{28}O_4$: C 70.10, H 9.15; found: C 70.09, H 9.10.

*Preparation of cis-5', 5'-dimethylspiro[(1, 8-dimethylbicyclo[6.4.0]dodecane-2, 6-dione)-11, 2'-(1', 3'-dioxane)] (**137**)*



133



137

To a heterogeneous mixture of the ketal alkene **133** (101.9 mg, 0.3508 mmol) in CH_3CN (1.6 mL), CCl_4 (1.6 mL) and water (2.4 mL) was added sodium periodate (312.5 mg, 1.462 mmol) and a catalytic amount of $RuO_2 \cdot xH_2O$ (1.5 mg, 0.0097 mmol based on x = 1). The mixture, open to the atmosphere, was stirred vigorously for 15 min at room temperature. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with H_2O (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residual material was filtered through a Pasteur pipette containing flash silica gel and the pipette was eluted with Et_2O. The eluate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (5 g of silica gel, Et_2O) to afford 94.1 mg (83%) of the ketal dione **137** as a colourless solid (m.p. 161-163 °C).

IR (KBr): 1688, 1471,1375, 1203, 1107 cm^{-1}.

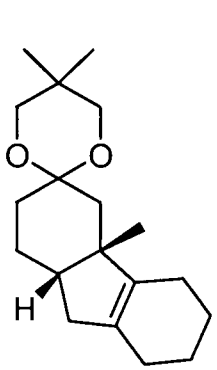
^1H NMR (400 MHz, $CDCl_3$) δ: 0.93 (s, 3H, -C<u>H</u>$_3$), 0.98 (s, 3H, -C<u>H</u>$_3$), 1.04 (s, 3H, -C<u>H</u>$_3$), 1.17-1.20 (m, 1H; s, 3H, -C<u>H</u>$_3$, (δ 1.19)), 1.57 (ddd, 1H, J = 4.0, 4.0, 14.0 Hz), 1.70 (d, 1H, J = 12.0 Hz), 1.84 (ddd, 1H, J = 4.0, 4.0, 14.0 Hz), 2.01-2.12 (m, 2H), 2.18-2.28 (m, 1H), 2.28-2.46 (m, 5H), 3.01-3.07 (m, 1H), 3.40-3.46 (m, 3H), 3.51 (d, 1H, J = 11.5 Hz), 3.57 (d, 1H, J = 11.5 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 20.4 (-ve), 22.6 (-ve), 22.7 (-ve, 2C), 22.8, 29.0, 30.1, 36.5, 36.6, 39.7, 39.9, 43.7, 47.3, 53.0, 69.9, 70.3, 97.3, 211.7, 215.1.

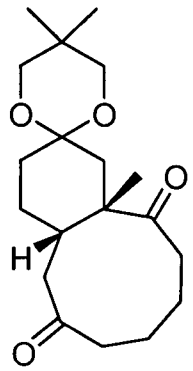
HRMS calcd for $C_{19}H_{30}O_4$: 322.2144; found: 322.2140.

Anal. calcd for $C_{19}H_{30}O_4$: C 70.77, H 9.38; found: C 70.93, H 9.42.

*Preparation of cis-5', 5'-dimethylspiro[(1-methylbicyclo[7.4.0]tridecane-2,7-dione)-12, 2'-(1', 3'-dioxane)] (**141**)*



134



141

To a heterogeneous mixture of the ketal-alkene **134** (70.0 mg, 0.241 mmol) in CH_3CN (1.2 mL), CCl_4 (1.2 mL) and water (1.8 mL) was added sodium periodate (216 mg, 1.01 mmol) and a catalytic amount of $RuO_2 \cdot xH_2O$ (0.9 mg, 0.0058 mmol based on x = 1). The mixture, open to the atmosphere, was stirred vigorously for 1 h at room temperature. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with H_2O (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residual material was filtered through a Pasteur pipette containing flash silica gel and the pipette was eluted with Et_2O. The eluate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (5 g of silica gel, 1:1 Et_2O-petroleum ether) to afford 62.6 mg (81%) of the ketal dione **141** as a colourless solid (m.p. 159-160 °C).

IR (KBr): 1693, 1441, 1104 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.82 (s, 3H, -C<u>H</u>$_3$), 1.00 (s, 3H, -C<u>H</u>$_3$), 1.20-1.25 (m, 1H; s, 3H, -C<u>H</u>$_3$, (δ 1.22)), 1.40-1.55 (m, 1H), 1.58 (dm, 1H, *J* for d = 14.0 Hz), 1.69 (d, 1H, *J* = 15.0 Hz), 1.76-1.85 (m, 3H), 1.95 (dm, 1H, *J* for d = 14.0 Hz), 2.11-2.28 (m, 4H), 2.28-2.42 (m, 3H), 2.44-2.52 (m, 1H), 2.60 (dd, 1H, *J* = 8.0, 14.0 Hz), 3.34 (dd, 1H, *J* = 2.0, 11.5 Hz, one of -C<u>H</u>$_2$-O), 3.40 (dd, 1H, *J* = 2.0, 11.5 Hz, one of -C<u>H</u>$_2$-O), 3.47 (d, 1H, *J* = 11.5 Hz, one of -C<u>H</u>$_2$-O), 3.69 (d, 1H, *J* = 11.5 Hz, one of -C<u>H</u>$_2$-O).
^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.9 (-ve), 22.0, 22.4 (-ve), 22.9 (-ve), 24.6, 27.2, 30.0, 30.9, 33.8, 40.9 (-ve), 43.5, 43.8, 51.9, 69.9 (2C), 70.0, 97.7, 215.1, 217.2.

HRMS calcd for $C_{19}H_{30}O_4$: 322.2144; found: 322.2139.

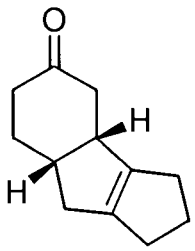
Anal. calcd for $C_{19}H_{30}O_4$: C 70.77, H 9.38; found: C 70.88, H 9.38.

4.3.3 Preparation of triketones via oxidative cleavage

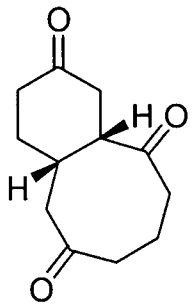
General Procedure 3: Ruthenium tetroxide catalyzed oxidation[75] of alkenes to form diones

To a heterogeneous mixture of the appropriate alkene (1 equiv) in acetonitrile, carbon tetrachloride and water (in 1:1:1.5 v/v ratio) was added sodium periodate (~4.2 equiv) and a catalytic amount of ruthenium dioxide x-hydrate (~2-3 mol%, based on ruthenium dioxide *mono*hydrate, x = 1). The mixture, open to the atmosphere, was stirred vigorously for 15 min at room temperature. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with H_2O (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residual material was filtered through a Pasteur pipette containing flash silica gel and the pipette was eluted with a 1:1 mixture of CH_2Cl_2-Et_2O. The combined eluate was concentrated under reduced pressure and the crude material was purified by flash column chromatography on silica gel.

*Preparation of cis-bicyclo[6.4.0]dodecane-2,6,11-trione (**142**)*



88



142

Following general procedure 3, the alkene **88** was converted into the trione **142** with the following amounts of solvents and reagents: alkene **88** (176.5 mg, 1.001 mmol), $NaIO_4$ (898 mg, 4.20 mmol), $RuO_2 \cdot xH_2O$ (3.7 mg, 0.024 mmol based on x = 1), CH_3CN (5 mL), CCl_4 (5 mL) and H_2O (7.5 mL). The crude solid was purified by flash column chromatography (15 g of silica gel, 1:1 CH_2Cl_2-Et_2O) to afford, upon removal of solvent, 197.5 mg (95%) of the trione **142** as a colourless solid (m.p. 129-131 °C).

IR (KBr): 1693, 1466, 1341, 1159 cm^{-1}.

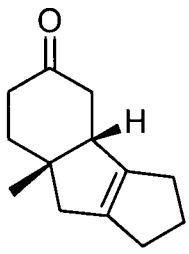
^1H NMR (400 MHz, $CDCl_3$) δ: 1.85-2.22 (m, 4H), 2.24-2.49 (m, 6H), 2.50-2.62 (m, 2H), 2.68-2.78 (m, 2H), 2.90-2.99 (m, 1H), 3.25 (ddd, 1H, *J* = 4.5, 4.5, 7.0 Hz, C<u>H</u>-C(O)-).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 23.1, 29.5, 32.4 (-ve), 38.1, 39.4, 42.3, 42.8, 44.6, 50.9 (-ve), 208.5, 211.2, 211.8.

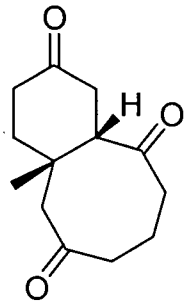
HRMS calcd for $C_{12}H_{16}O_3$: 208.1099; found: 208.1102.

Anal. calcd for $C_{12}H_{16}O_3$: C 69.21, H 7.74; found: C 69.19, H 7.76.

*Preparation of cis-8-methylbicyclo[6.4.0]dodecane-2,6,11-trione (**143**)*



89



143

Following general procedure 3, the alkene **89** was converted into the trione **143** with the following amounts of solvents and reagents: alkene **89** (144.8 mg, 0.7609 mmol), $NaIO_4$ (683 mg, 3.20 mmol), $RuO_2 \cdot xH_2O$ (2.8 mg, 0.018 mmol based on x = 1), CH_3CN (3.5 mL), CCl_4 (3.5 mL) and H_2O (5.3 mL). The crude solid was purified by flash column chromatography (14 g of silica gel, 1:1 CH_2Cl_2-Et_2O) to afford, upon removal of solvent, 159.6 mg (94%) of the trione **143** as a colourless solid (m.p. 118-119 °C).
IR (KBr): 1698, 1369, 1252, 1150 cm^{-1}.

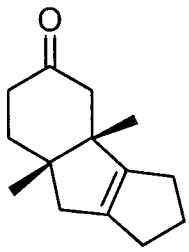
^1H NMR (400 MHz, $CDCl_3$) δ: 1.37 (s, 3H,-$C\underline{H}_3$), 1.52 (ddt, 1H, J = 13.5, 6.0, 2.0 Hz), 2.05-2.16 (m, 3H), 2.24-2.60 (m, 10 H), 3.18 (br d, 1H, J = 8.0 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 20.9, 25.3 (-ve), 32.8, 36.2, 36.6, 39.0, 45.1, 45.8, 51.2, 52.8 (-ve), 207.5, 210.6, 214.3.

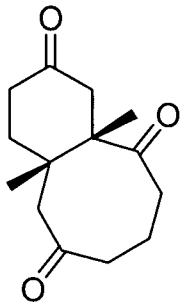
HRMS calcd for $C_{13}H_{18}O_3$: 222.1256; found: 222.1259.

Anal. calcd for $C_{13}H_{18}O_3$: C 70.24, H 8.16; found: C 70.10, H 8.06.

*Preparation of cis-1,8-dimethylbicyclo[6.4.0]dodecane-2,6,11-trione (**144**)*



90



144

Following general procedure 3, the alkene **90** was converted into the trione **144** with the following amounts of solvents and reagents: alkene **90** (63.8 mg, 0.312 mmol), $NaIO_4$

(280 mg, 1.31 mmol), $RuO_2 \cdot xH_2O$ (1.4 mg, 0.018 mmol based on x = 1), CH_3CN (1..5 mL), CCl_4 (1.5 mL) and H_2O (2.3 mL). The crude solid was purified by flash column chromatography (4.5 g of silica gel, 1:1 CH_2Cl_2-Et_2O) to afford, upon removal of solvent, 67.5 mg (91%) of the trione **144** as a colourless solid (m.p. 154-156 °C).

IR (KBr): 1698, 1321, 1143 cm^{-1}.

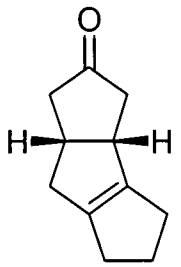
^1H NMR (400 MHz, $CDCl_3$) δ: 1.23 (s, 3H, -C<u>H</u>$_3$), 1.44 (s, 3H, -C<u>H</u>$_3$), 1.62 (ddd, 1H, J = 3.0, 6.0, 14.5 Hz), 1.95-2.20 (m, 4H), 2.20-2.47 (m, 6H), 2.48-2.58 (m, 1H), 2.98-3.06 (m, 2H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 20.8 (-ve), 23.3, 23.9 (-ve), 33.6, 36.8, 39.4, 40.3, 45.0, 48.5, 48.8, 56.1, 207.5, 210.9, 215.9.

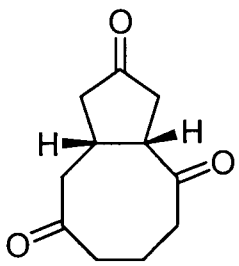
HRMS calcd for $C_{14}H_{20}O_3$: 236.1413; found: 236.1415.

Anal. calcd for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found: C 70.95, H 8.47.

*Preparation of cis-bicyclo[6.3.0]undecane-2,6,10-trione (**145**)*



91



145

Following general procedure 3, the alkene **91** was converted into the trione **145** with the following amounts of solvents and reagents: alkene **91** (25.1 mg, 0.155 mmol), $NaIO_4$

(139 mg, 0.650 mmol), $RuO_2 \cdot xH_2O$ (0.5 mg, 0.003 mmol based on x = 1), CH_3CN (0.7 mL), CCl_4 (0.7 mL) and H_2O (1 mL). The crude solid was purified by flash column chromatography (4 g of silica gel, 1:1 CH_2Cl_2-Et_2O) to afford, upon removal of solvent, 23.7 mg (79%) of the trione **145** as a colourless solid (m.p. 132-133 °C).

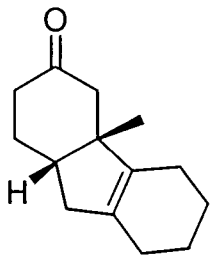
IR (KBr): 1762, 1697, 1444, 1326, 1158 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$) δ: 2.11-2.26 (m, 4H), 2.35-2.59 (m, 6H), 2.59-2.75 (m, 2H), 3.02-3.13 (m, 1H), 3.48-3.56 (m, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 22.9, 37.1 (-ve), 40.1, 42.3, 43.7, 43.7, 43.9, 49.0 (-ve), 211.5, 213.3, 214.3.

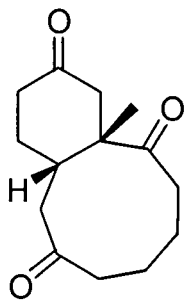
HRMS calcd for $C_{11}H_{14}O_3$: 194.0943; found: 194.0946.

Anal. calcd for $C_{11}H_{14}O_3$: C 68.02, H 7.27; found: C 67.98, H 7.10.

*Preparation of cis-1-methylbicyclo[7.4.0]tridecane-2,7,12-trione (**146**)*



54



146

Following general procedure 3, the alkene **54**[43] was converted into the trione **146** with the following amounts of solvents and reagents: alkene **54** (79.3 mg, 0.388 mmol), $NaIO_4$

(348 mg, 1.63 mmol), $RuO_2 \cdot xH_2O$ (1.5 mg, 0.0097 mmol based on x = 1), CH_3CN (1.9 mL), CCl_4 (1.9 mL) and H_2O (2.9 mL). The crude solid was purified by flash column chromatography (6 g of silica gel, 1:1 CH_2Cl_2-Et_2O) to afford, upon removal of solvent, 80.1 mg (87%) of the trione **146** as a colourless solid (m.p. 136-138 °C).

IR (KBr): 1705, 1697, 1418, 1332, 1162, 1030 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.13 (s, 3H, $C\underline{H}_3$), 1.52-1.61 (m, 1H), 1.82-1.91 (m, 2H), 1.98-2.30 (m, 9H), 2.38-2.55 (m, 3H), 2.83 (dd, 1H, J = 8.5, 13.5 Hz), 2.90 (d, 1H, J = 15.0 Hz).

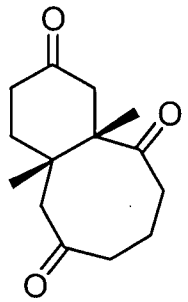
^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.8, 22.8 (-ve), 25.2, 30.5, 34.6, 36.8, 40.3 (-ve), 43.3, 44.4, 45.0, 55.3, 210.9, 212.9, 216.3.

HRMS calcd for $C_{14}H_{20}O_3$: 236.1413; found: 236.1421.

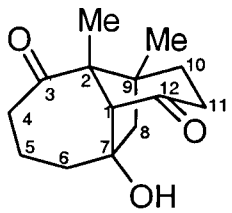
Anal. calcd for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found: C 71.09, H 8.55.

4.4. Aldol Condensations

*Preparation of 2,9-dimethyltricyclo[5.5.0.0^{2,9}]dodecane-3,12-dion-1-ol (**147**)*



144



147

To a solution of the triketone **144** (12.2 mg, 0.052 mmol) in dry THF (2 mL) was added a catalytic amount of *p*-toluenesulfonic acid (~0.5 mg). The mixture was stirred under reflux for 17 h and then was allowed to cool to room temperature. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (1 g of silica gel, 1:1 Et_2O-EtOAc) to afford 11.8 mg (97%) of the dione alcohol **147** as a white solid. A small amount of the solid was recrystallized from Et_2O (m.p. 132-133 °C) and the acquired material was subjected to X-ray crystallographic analysis (see Appendix).

IR (KBr): 3406, 1701, 1234, 1035 cm^{-1}.

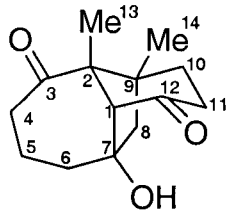
^1H NMR (400 MHz, $CDCl_3$) δ: 0.92 (s, 3H, -C<u>H</u>$_3$), 1.01 (s, 3H, -C<u>H</u>$_3$), 1.54-1.67 (m, 2H, H-5, H-10), 1.70-1.80 (br signal, 1H, -O<u>H</u>), 1.82-2.00 (m, 6H, H-5', H-6, H-6', H-8, H-8', H-10'), 2.29-2.39 (m, 2H, H-4, H-11), 2.60-2.70 (m, 1H, H-4'), 2.90 (ddd, 1H, J = 10.5, 10.5, 18.0 Hz, H-11'), 2.95 (s, 1H, H-1).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 17.3 (-ve), 20.7, 22.7 (-ve), 34.8, 35.7, 41.7, 42.6, 45.8, 47.7, 59.5, 70.7 (-ve), 79.3, 211.1, 214.6.

HRMS calcd for $C_{14}H_{20}O_3$: 236.1413; found: 236.1415.

Anal. calcd for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found: C 70.78, H 8.60.

Table 11. ^1H NMR (400 MHz, $CDCl_3$) data for the dione alcohol **147**: COSY Experiment.

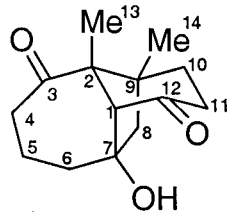


147

Assignment H-x	^1H NMR δ (multiplicity, *J* (Hz))	COSY Correlations[a]
H-1	2.95 (s)	
H-4	part of m at 2.29-2.39	H-4', H-5
H-4'	2.60-2.70 (m)	H-4, H-5
H-5	part of m at 1.54-1.67	
H-5', H-6, H-6', H-8, H-8', H-10'	part of m at 1.82-2.00	
H-10	part of m at 1.54-1.67	H-11, H-11'
H-11	part of m at 2.29-2.39	H-10, H-11'
H-11'	2.90 (ddd, *J* = 10.5, 10.5, 18.0)	H-10, H-11
OH	1.70-1.80 (br signal)	
Me-13, Me-14	0.92, 1.01	

[a] Only those correlations which can be assigned unambiguously are reported.

Table 12. ^{13}C (125.8 MHz, $CDCl_3$) and ^{1}H NMR (500 MHz) data for the dione alcohol **147**: HMQC and HMBC Experiments

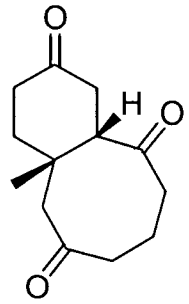


147

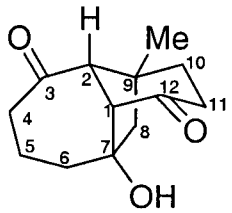
Assignment C-x	^{13}C NMR δ ppm	APT	HMQC ^{1}H NMR Correlations (δ ppm)	HMBC ^{1}H NMR Correlations (δ ppm)[a]
C-13	17.3	CH or **CH_3**	Me-13 (0.92)	
C-5	20.7	C or **CH_2**	H-5 (part of m at 1.54-1.67), H-5' (~1.9 ppm) (part of m at 1.82-2.00)	
C-14	22.7	CH or **CH_3**	Me-14 (1.01)	
C-10	34.8	C or **CH_2**	H-10 (part of m at 1.54-1.67), H-10' (~1.85 ppm) (part of m at 1.82-2.00)	
C-11	35.7	C or **CH_2**	H-11 (part of m at 2.29-2.39), H-11' (2.90)	
C-4	41.7	C or **CH_2**	H-4 (part of m at 2.29-2.39), H-4' (2.60-2.70)	
C-6	42.6	C or **CH_2**	H-6, H-6' (part of m at 1.82-2.00)	
C-9	45.8	**C** or CH_2		
C-8	47.7	C or **CH_2**	H-8, H-8' (part of m at 1.82-2.00)	Me-14 (1.01)
C-2	59.5	**C** or CH_2		
C-1	70.7	**CH** or CH_3	H-1 (2.95)	Me-13 (0.92)
C-7	79.3	**C** or CH_2		
C-12	211.1	**C** or CH_2		H-1 (2.95), H-11 (part of m at 2.29-2.39), H-11' (2.90)
C-3	214.6	**C** or CH_2		Me-13 (0.92), H-1 (2.95), H-4 (part of m at 2.29-2.39), H-4' (2.60-2.70)

[a]Only relevant correlations are reported

*Preparation of 9-methyltricyclo[5.5.0.0^{2,9}]dodecane-3,12-dion-1-ol (**148**)*



143



148

To a solution of the triketone **143** (31.4 mg, 0.141 mmol) in dry THF (5 mL) was added a catalytic amount of *p*-toluenesulfonic acid (~0.5 mg). The mixture was stirred under reflux for 48 h and then was allowed to cool to room temperature. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (3 g of silica gel, 1:1 Et_2O-EtOAc) to afford 29.4 mg (94%) of the dione alcohol **148** as a white solid. A small amount of the solid was recrystallized from Et_2O (m.p. 142-143 °C) and the acquired material was submitted for X-ray crystallographic analysis (see Appendix).

IR (KBr): 3382, 1716, 1690, 1207, 1061 cm^{-1}.

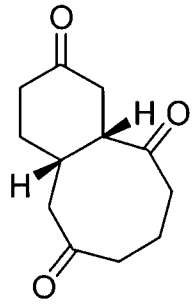
^1H NMR (400 MHz, $CDCl_3$) δ: 1.11 (s, 3H, -C<u>H</u>$_3$), 1.55-2.50 (m, 9H), 2.35 (s, 1H), 2.37-2.56 (m, 3H), 2.86 (ddd, 1H, J = 9.5, 12.0, 17.5 Hz), 2.95 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 19.5, 23.6(-ve), 36.2, 41.0, 42.7, 43.5, 45.5, 46.2, 62.6 (-ve), 65.7(-ve), 82.6, 209.9, 210.7.

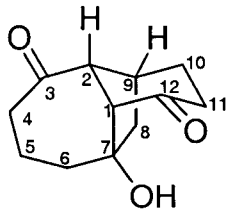
HRMS calcd for $C_{13}H_{18}O_3$: 222.1256; found: 222.1253.

Anal. calcd for $C_{13}H_{18}O_3$: C 70.24, H 8.16; found: C 70.15, H 8.02.

*Preparation of tricyclo[5.5.0.0^{2,9}]dodecane-3,12-dion-1-ol (**149**)*



142



149

To a solution of the triketone **142** (36.8 mg, 0.177 mmol) in dry THF (5 mL) was added a catalytic amount of *p*-toluenesulfonic acid (~0.5 mg). The mixture was stirred under reflux for 3 days until no further progress was observed by TLC analysis. The reaction mixture was allowed to cool to room temperature. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography (3 g of silica gel, 1:1 Et_2O-EtOAc) to afford 17.0 mg (46%) of the dione alcohol **149** as a white solid (m.p. 124-126 °C). A significant amount of starting material (19.3 mg (52%)), which displayed properties (m.p. 128-130 °C; ^1H, ^{13}C NMR) identical with those of **142**, was also isolated.

IR (KBr): 3436, 1698, 1244, 1201, 1147, 1061 cm^{-1}.

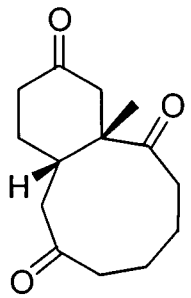
^1H NMR (400 MHz, $CDCl_3$) δ: 1.50-1.65 (m, 1H), 1.70 (d, 1H, *J* = 15.0 Hz), 1.82-2.06 (m, 5H), 2.18 (dd, 1H, *J* = 7.5, 15.0 Hz), 2.22 (br signal, 1H), 2.31-2.44 (m, 2H), 2.46 (s, 1H), 2.62 (ddd, 1H, *J* = 2.5, 13.0, 13.0 Hz), 2.71-2.74 (m, 1H), 2.81 (ddd, 1H, *J* = 9.5, 12.0, 17.5 Hz), 3.00 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.5, 31.5, 35.7, 37.9, 41.7 (2C, one -ve), 42.9, 58.9 (-ve), 65.1(-ve), 82.0, 210.2, 213.5.

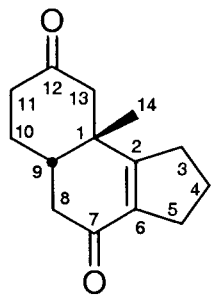
HRMS calcd for $C_{12}H_{16}O_3$: 208.1099; found: 208.1108.

Anal. calcd for $C_{12}H_{16}O_3$: C 69.21, H 7.74; found: C 69.15, H 7.70.

*Preparation of cis-1-methyltricyclo[7.4.0.0^{2,6}]tridec-2(6)-ene-7,12-dione (**151**)*



146



151

To a solution of the triketone **146** (17.2 mg, 0.0728 mmol) in dry THF (2.5 mL) was under reflux for 22 h and then was allowed to cool to room temperature. Water (10 mL) added a catalytic amount of *p*-toluenesulfonic acid (~0.5 mg). The mixture was stirred was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (5 g of silica gel, 7:3 Et_2O-petroleum ether) to afford 13.6 mg (79%) of compound **151** as a colourless oil, as well as 2 mg of unreacted starting material.

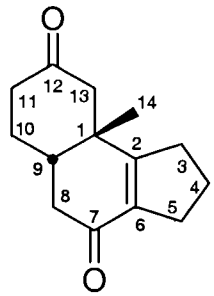
IR (film): 1713, 1664, 1387, 1240 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.26 (s, 3H, -C<u>H</u>$_3$), 1.75-1.89 (m, 3H, H-4, H-4', H-10), 2.02-2.10 (m, 1H, H-10'), 2.26-2.38 (m, 4H, H-9, H-13, H-11, H-11'), 2.45-2.59 (m, 6H, H-8, H-5, H-5', H-3, H-3', H-13'), 2.66 (dd, 1H, J = 4.5, 17.0 Hz, H-8').

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.5, 26.1(-ve), 28.7, 29.4, 33.3, 39.0, 40.4, 41.3, 42.5 (-ve), 49.5, 136.4, 168.1, 195.8, 209.5.

HRMS calcd for $C_{14}H_{18}O_2$: 218.1307; found: 218.1313.

Table 13. Selected ^{13}C (125.8 MHz, $CDCl_3$) and ^1H NMR (500 MHz) data for the dione **151**: HMQC and HMBC Experiments



151

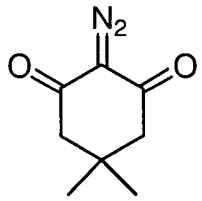
Assignment C-x	^{13}C NMR δ ppm	APT	HMQC ^1H NMR Correlations (δ ppm)	HMBC ^1H NMR Correlations[a] (δ ppm)
C-4	21.5	C or **CH_2**	H-4, H-4' (part of m at 1.75-1.89)	
C-14	26.1	CH or **CH_3**	Me-14 (1.26)	
C-10	28.8	C or **CH_2**	H-10 (part of m at 1.75-1.89), H-10' (2.02-2.10)	H-8' (2.66)
C-3 or C-5	29.4	C or **CH_2**	H-3, H-3' or H-5, H-5' (part of m at 2.45-2.59)	H-4, H-4' (part of m at 1.75-1.89)
C-5 or C-3	33.3	C or **CH_2**	H-3, H-3' or H-5, H-5' (part of m at 2.45-2.59)	H-4, H-4' (part of m at 1.75-1.89)
C-11	39.0	C or **CH_2**	H-11, H-11' (part of m at 2.26-2.38)	H-10 (part of m at 1.75-1.89), H-10' (2.02-2.10)
C-8	40.4	C or **CH_2**	H-8 (part of m at 2.45-2.59) H-8' (2.66)	H-10 (part of m at 1.75-1.89), H-10' (2.02-2.10)
C-9	41.4	**CH** or CH_3	H-9 (part of m at 2.26-2.38)	Me-14 (1.26), H-10 (part of m at 1.75-1.89), H-8' (2.66)

C-1	42.5	**C** or CH_2		Me-14 (1.26), H-10 (part of m at 1.75-1.89), H-10' (2.02-2.10), H-8' (2.66)
C-13	49.5	C or **CH_2**	H-13 (part of m at 2.26-2.38), H-13' (part of m at 2.45-2.59)	Me-14 (1.26)
C-6	136.4	**C** or CH_2		H-4, H-4' (part of m at 1.75-1.89)
C-2	168.1	**C** or CH_2		Me-14 (1.26), H -4, H-4' (part of m at 1.75-1.89)
C-7	195.8	**C** or CH_2		H-8' (2.66)
C-12	209.5	**C** or CH_2		H-10 (part of m at 1.75-1.89), H-10' (2.02-2.10)

[a] Only those correlations which can be assigned unambiguously are reported.

4.5. Synthesis of (±)-1-desoxyhypnophilin (61) and (±)-6,7-epoxy-4(15)-hirsuten-5-ol (62)

*Preparation of 2-diazo-5,5-dimethyl-1,3-cyclohexanedione (**180**)*[95,96]



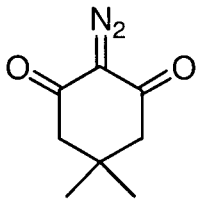
180

To a cool (0 °C), stirred suspension of dimedone (19.0 g, 0.136 mol) and *p*-toluenesulfonyl azide (26.8 g, 0.136 mol) (prepared from *p*-toluenesulfonyl chloride and sodium azide) in dry Et_2O (500 mL) was added triethylamine (37.9 mL, 0.272 mol). The mixture was stirred for 10 min at 0 °C and was warmed to room temperature for 45 min. Aqueous $NaHCO_3$ (10%, 250 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 250 mL) and the combined organic extracts were washed with H_2O (2 x 500 mL), brine (500 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude material was recrystallized three times from ethanol at -25 °C (freezer) to provide 14.2 g (63%) of slightly yellow needle-like crystals. Diazodimedone (**180**) displayed melting point, IR and ^1H NMR properties as reported in the literature[96] (m.p. 106-108 °C, lit. m.p. 106-108 °C).

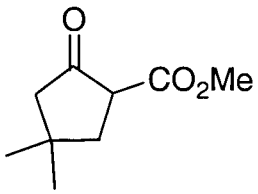
IR (KBr): 2146, 1636, 1309 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.10 (s, 6H, 2 x $C\underline{H}_3$), 2.43 (s, 4H, 2 x $C\underline{H}_2$)

*Preparation of methyl 4,4-dimethyl-2-oxocyclopentanecarboxylate (**178**)*[95,96]



180



178

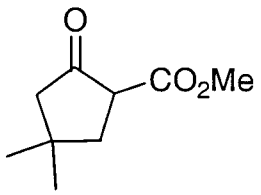
Following the literature procedure, a 1 L, three-necked, pyrex vessel equipped with a stirring bar, a 450 W mercury lamp (water cooled, pyrex filter) in the center, and a gas outlet, was charged with diazodimedone (**180**) (12.1 g, 73.0 mmol), dry THF (800 mL) and dry MeOH (20 mL). The mixture was purged with nitrogen gas and was irradiated. The progress of the reaction was monitored by TLC. After 3 hours, the solvent was removed under reduced pressure and the residual material was purified by bulb-to-bulb distillation (92-100 °C/1.0 torr) to yield 10.95 g (89%) of the β-keto ester **178** as a colourless oil. This material (**178**) displayed IR and ^{1}H NMR similar to those reported previously in the literature.[95] The updated spectral data is presented below.

IR (neat): 1756, 1729, 1650, 1437, 1311, 1120, 1043 cm^{-1}.

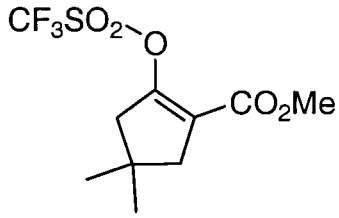
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.04 (s, 3H, -C<u>H</u>$_3$), 1.21 (s, 3H, -C<u>H</u>$_3$), 2.12 (dd, 1H, J = 9.0, 13.0 Hz, one of -C<u>H</u>$_2$-CH), 2.17-2.20 (m + s (δ 2.19), 3H, C-C<u>H</u>$_2$-C(O) + one of -C<u>H</u>$_2$-CH), 3.37 (dd, 1H, J = 9.0, 11.0 Hz, -CH$_2$-C<u>H</u>), 3.72 (s, 3H, -CO$_2$C<u>H</u>$_3$).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 27.6, 28.9, 34.5, 40.7, 52.5, 53.0, 54.2, 169.9, 203.1.

*Preparation of methyl 4,4-dimethyl-2-trifluoromethanesulfonyloxycyclopent-1-enecarboxylate (**181**)*



178



181

To a cool (0 °C), stirred suspension of KH (2.73 g of 35 wt% dispersion in mineral oil, washed twice with dry THF (20 mL) and dried under vacuum, 23.8 mmol) in dry THF (150 mL), was added a solution of methyl 4,4-dimethyl-2-oxocyclopentanecarboxylate (**178**) (3.36 g, 19.8 mmol) in dry THF (50 mL). The mixture was stirred for 30 min. Solid *N*-phenyltrifluoromethanesulfonimide (8.50 g, 23.8 mmol) was added and the reaction mixture was stirred for 30 min at 0 °C and at room temperature for 90 min. The reaction mixture was diluted with Et_2O (200 mL) and filtered through a cake of silica gel (~40 g) and Celite® (~40 g). The cake was eluted thoroughly with Et_2O and the combined filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (200 g of silica gel, 1:9 Et_2O-petroleum ether) to afford, after concentration of appropriate fractions, 5.99 g (85%) of the triflate **181** as a colourless oil.

IR (neat): 1729, 1671, 1429, 1347, 1213, 1142 cm^{-1}.

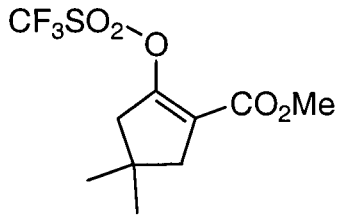
^1H NMR (400 MHz, $CDCl_3$) δ: 1.15 (s, 6H, 2 x -C$\underline{H}_3$), 2.47 (t, 2H, J = 2.5 Hz), 2.54 (t, 2H, J = 2.5 Hz), 3.76 (s, 3H, -$CO_2C\underline{H}_3$).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 29.3 (-ve, 2C), 35.2, 43.8, 47.1, 51.8 (-ve), 118.3 (q, J = 319 Hz, -$\underline{C}F_3$), 121.8, 151.9, 162.7.

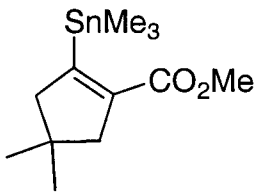
HRMS calcd for $C_{10}H_{13}O_5SF_3$: 302.0436; found: 302.0436.

Anal. calcd for $C_{10}H_{13}O_5SF_3$: C 39.73, H 4.34; found: C 39.67, H 4.28.

*Preparation of methyl 4,4-dimethyl-2-trimethylstannylcyclopent-1-enecarboxylate (**177**)*



181



177

To a cold (-48 °C), stirred solution of hexamethylditin (7.28 g, 22.2 mmol) in dry THF (200 mL) was added MeLi (1.60 M solution in Et_2O, 14 mL, 22.2 mmol). The mixture was stirred for 30 min. Solid CuCN (1.99 g, 22.2 mmol) was added and the mixture was stirred for 30 min. A solution of the triflate **181** (4.96 g, 16.4 mmol) in dry THF (20 mL) was added dropwise and the mixture was stirred at -48 °C for 1 h and at 0 °C for 1 h. Aqueous NH_4Cl-NH_3 (pH 8, 150 mL) was added, the mixture was opened to air, and then was stirred vigorously until the aqueous layer turned deep blue. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with H_2O (2 x 200 mL), brine (200 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was purified by flash column chromatography (200 g of silica gel, 1:99 then 1:19 Et_2O-petroleum ether) to yield 4.79 g (92%) of the stannane **177** as a colourless oil.

IR (neat): 1704, 1671, 1591, 1314, 1245 cm^{-1}.

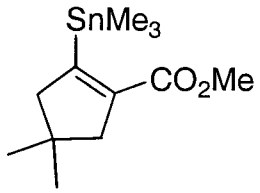
^1H NMR (400 MHz, $CDCl_3$) δ: 0.14 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 55.0 Hz), 1.06 (s, 6H, 2 x -C<u>H</u>$_3$), 2.40 (m, 2H), 2.45 (m, 2H), 3.69 (s, 3H, -CO_2C<u>H</u>$_3$).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ: -8.6, 29.5 (2C), 39.7, 48.3, 51.2, 55.9, 142.0, 165.8, 166.7.

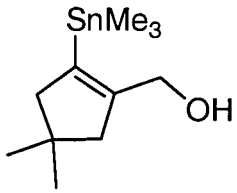
HRMS calcd for $C_{11}H_{19}O_2{}^{120}Sn$ (M^+-Me): 303.0407; found: 303.0406.

Anal. calcd for $C_{12}H_{22}O_2Sn$: C 45.46, H 6.99; found: C 45.61, H 7.18.

*Preparation of (4,4-dimethyl-2-trimethylstannylcyclopent-1-en-1-yl)methanol (**182**)*



177



182

To a cold (-78 °C), stirred solution of the ester **177** (4.53 g, 14.3 mmol) in dry THF (100 mL) was added DIBAL-H (1.0 M solution in hexanes, 36 mL, 36 mmol) via a syringe. The reaction mixture was stirred for 1 h at -78 °C and was warmed to 0 °C for 1 h. The mixture was treated with aqueous NH_4Cl-NH_3 (pH 8, 10 mL) and then was stirred for 30 min until a white, gelatinous precipitate formed. $MgSO_4$ (1 g) was added to the mixture and stirring was continued for 45 min. The mixture was diluted with Et_2O (100 mL) and filtered through a cake of silica gel (~20 g) and Celite® (~20 g). The cake was eluted with Et_2O (~1 L). The combined filtrate was concentrated under reduced pressure and the resulting material was purified by flash column chromatography (100 g of silica gel, 1:4 Et_2O-petroleum ether) to yield 4.13 g (100%) of the alcohol **182** as a colourless oil.

IR (neat): 3343, 1619, 1363, 769 cm^{-1}.

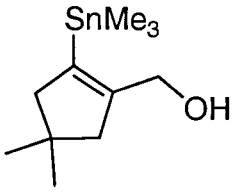
^1H NMR (400 MHz, $CDCl_3$) δ: 0.11 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.0 Hz), 1.05 (s, 6H, 2 x -C<u>H</u>$_3$), 1.30 (br s, 1H), 2.24 (br signal, 4H), 4.12 (d, 2H, J = 5.5 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -8.9, 29.7 (2C), 39.2, 49.9, 54.7, 63.5, 138.8, 150.7.

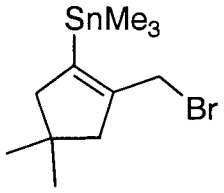
HRMS calcd for $C_{10}H_{19}O^{120}Sn$ (M^+-Me): 275.0458; found: 275.0460.

Anal. calcd for $C_{11}H_{22}OSn$: C 45.71, H 7.67; found: C 45.81, H 7.84.

*Preparation of 1-bromomethyl-4,4-dimethyl-2-trimethylstannylcyclopentene (**176**)*



182



176

To a cool (0 °C), stirred solution of triphenylphosphine (8.94 g, 34.1 mmol) in dry CH_2Cl_2 (140 mL) was added bromine (~1.8 mL) via a syringe, until a yellow colour persisted. A small amount of PPh_3 (~50 mg) was added until the solution became clear. The mixture was stirred at 0 °C for 15 min, during which time a white precipitate formed. Solid imidazole (2.50 g, 36.7 mmol) was added and the white precipitate disappeared. The mixture was stirred for 15 min before addition of a solution of the alcohol **182** (3.94 g, 13.6 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixure was stirred for 30 min. Most of the solvent was removed under reduced pressure until the volume remaining was approximately 30 mL. Pentane (200 mL) was added. The mixture (containing a precipitate) was filtered through a cake of silica gel (~50 g) and Celite® (~50 g). To the residue left in the flask was added aqueous $NaHCO_3$ (10%, 100 mL) and the aqueous layer was extracted with pentane (2 x 100 mL). The combined organic extracts were filtered through the same cake of silica gel and Celite® (*vide supra*) and the cake was eluted with ~1 L of pentane. Concentration of the combined filtrate under reduced pressure afforded 4.46 g (93%) of the bromide **176**, as a colourless liquid. This compound proved to be volatile and a successful elemental analysis was not obtained.

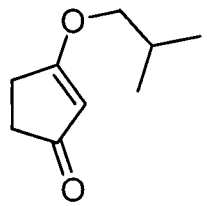
IR (neat): 1465, 1364, 1200, 771 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.18 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.0 Hz), 1.06 (s, 6H, -2 x -C<u>H</u>$_3$), 2.25 (s, 2H), 2.32 (s, 2H), 4.02 (s, 2H, -C<u>H</u>$_2$Br).

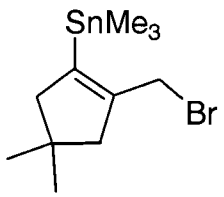
^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -9.6 (-ve), 29.4 (-ve, 2C), 34.1, 39.7, 50.1, 55.2 (-ve), 145.7, 147.8.

HRMS calcd for $C_{10}H_{18}{}^{120}Sn^{79}Br$ (M^+-Me): 336.9614; found: 336.9620.

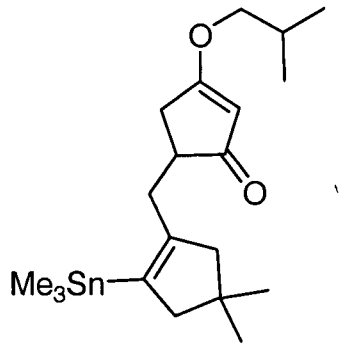
*Preparation of 5-[(4,4-dimethyl-2-trimethylstannylcyclopent-1-en-1-yl)methyl]-3-isobutoxycyclopent-2-en-1-one (**175**)*



82



176



175

To a cold (-78 °C), stirred solution of LDA (18.4 mmol) in dry THF (100 mL) was added a solution of 3-isobutoxycyclopent-2-en-1-one (**82**)[115] (2.84 g, 18.4 mmol) in dry THF (100 mL). The mixture was stirred at -78 °C for 30 min and at 0 °C for 15 min. It was subsequently cooled back to -78 °C and HMPA (2.54 mL, 14.6 mmol) was added, followed by a solution of the bromide **176** (4.32 g, 12.3 mmol) in dry THF (20 mL). The reaction mixture was warmed to 0 °C and stirred for 1 h. Water (200 mL) was added and the mixture was extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with H_2O (2 x 100 mL), aqueous $CuSO_4$ (10%, 100 mL), brine (200 mL), dried

($MgSO_4$), and concentrated under reduced pressure. The crude material was purified by flash column chromatography (300 g of silica gel, 1:1 Et_2O-petroleum ether) to yield 3.97 g (76%) of alkylated product **175**. Bulb-to-bulb distillation (220-230 °C/0.6 torr) of this material gave 3.70 g (71%) of colourless viscous oil which solidified upon standing (m.p. 35-36 °C).

IR (KBr): 1688, 1592, 1352, 997 cm^{-1}.

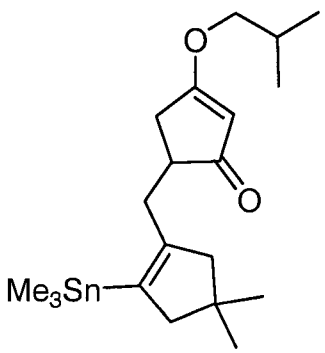
^1H NMR (400 MHz, $CDCl_3$) δ: 0.08 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53.0 Hz), 0.96 (d, 6H, J = 7.0 Hz, -CH(C<u>H</u>$_3$)$_2$), 1.00 (s, 3H, -CH_3), 1.02 (s, 3H, -CH_3), 2.02-2.31 (m, 7 H), 2.56-2.62 (m, 3H), 3.70 (d, 2H, J = 6.5 Hz, -OC<u>H</u>$_2$CH), 5.18 (s, 1H, =C<u>H</u>).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -9.4 (-ve), 18.9 (-ve, 2C), 27.8 (-ve), 29.4 (-ve), 29.7 (-ve), 33.6, 35.3, 39.4, 43.6 (-ve), 50.9, 54.3, 77.4, 103.3, 138.0, 149.8, 189.0, 207.9.

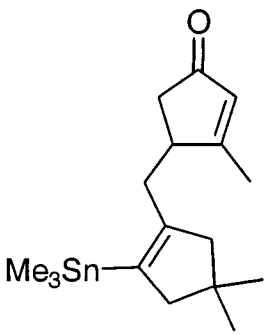
HRMS calcd for $C_{20}H_{34}O_2{}^{120}Sn$: 426.1581; found: 426.1575.

Anal. calcd for $C_{20}H_{34}O_2Sn$: C 56.50, H 8.06; found: C 56.67, H 7.94.

*Preparation of 4-[(4,4-dimethyl-2-trimethylstannylcyclopent-1-en-1-yl)methyl]-3-methylcyclopent-2-en-1-one (**59**)*



175



59

To a cool (0 °C), stirred solution of the ketone **175** (3.31 g, 7.79 mmol) in dry THF (100 mL) was added a solution of MeMgBr (10.4 mL, 3.0 M solution in Et_2O, 31 mmol). The mixture was warmed to room temperature and was stirred for 4 hours. Water (100 mL) was added slowly and the resultant mixture was diluted with Et_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude material was dissolved in Et_2O (100 mL) containing ~10 drops of H_2O and the mixture was treated with a catalytic amount of *p*-toluenesulfonic acid (~100 mg). The reaction mixture, open to air, was stirred for 4 h at room temperature. It was diluted with H_2O (100 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (100 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (150 g of silica gel, 1:4 Et_2O-petroleum ether) and subsequent bulb-to-bulb distillation (125-130 °C/1.5 torr) to provide 2.25 g (79%) of a viscous oil which solidified upon standing (m.p. 31-32 °C).

IR (KBr): 1687, 1620, 1441, 1308, 766 cm^{-1}.

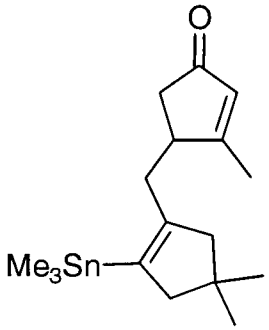
^1H NMR (400 MHz, $CDCl_3$) δ: 0.09 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.5 Hz), 1.02 (s, 3H, -C<u>H</u>$_3$), 1.05 (s, 3H, -C<u>H</u>$_3$), 1.97 (dd, 1H, *J* = 10.5, 13.5 Hz), 2.09 (s, 3H, C=C(C<u>H</u>$_3$)-), 2.12-2.17 (m, 3H), 2.17-2.25 (m, 2H), 2.41 (dd, 1H, *J* = 6.5, 19.0 Hz), 2.56 (m, 1H), 2.88 (br m, 1H), 5.87 (s, 1H, =C<u>H</u>).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -9.3 (-ve), 17.5 (-ve), 29.5 (-ve), 29.7 (-ve), 37.2, 39.4, 41.1, 43.0 (-ve), 51.3, 54.3, 130.7 (-ve), 138.6, 149.4, 181.3, 208.6.

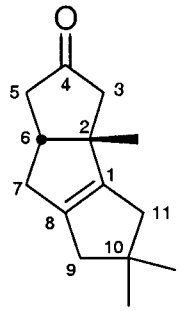
HRMS calcd for $C_{16}H_{25}O^{120}Sn$ (M^+-Me): 353.0927; found: 353.0931.

Anal. calcd for $C_{17}H_{28}OSn$: C 55.62, H 7.69; found: C 55.84, H 7.72.

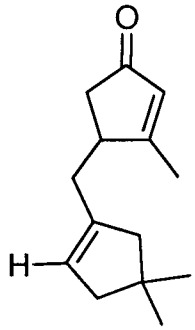
Preparation of (2S, 6R*)-2,10,10-trimethyltricyclo[6.3.0.0^{2,6}]undec-1(8)-en-4-one (**60**)*



59



60



183

To a flame dried, 20 mL glass, sealable ampoule equipped with a magnetic stir bar, under an atmosphere of argon, was added the enone **59** (1.75 g, 4.78 mmol), dry DMSO (18 mL), and solid CuCN (4.28 g, 47.8 mmol). The ampoule was flushed with a stream of argon gas and sealed using a natural gas-oxygen torch. The mixture was heated to 90 °C using an oil bath. After about 15 min, all of the CuCN dissolved to form a homogenous, slightly yellow, clear, viscous solution. The mixture was stirred for 17 hours at 90 °C. The ampoule was opened and the brown reaction mixture was poured into an aqueous solution of NH_4Cl-NH_3 (pH 8, 100 mL) and the resultant mixture was diluted with Et_2O (100 mL). The mixture was stirred vigorously open to air until the aqueous phase became blue. The mixture, which contained a purple precipitate that remained insoluble at the interface of the two layers, was filtered through a sintered glass funnel. The solid in the funnel was rinsed with aqueous NH_4Cl-NH_3 (pH 8, ~50 mL) and Et_2O (~50 mL). The phases of the combined filtrate were separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with H_2O (300 mL), brine (2 x 300 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (100 g of silica gel, 1:4 Et_2O-petroleum ether) to yield 580 mg (59%) of the ketone **60** along with 137 mg (14%) of protiodestannylated material **183**, both as colourless oils.

Characterization data for (2*S**, 6*R**)-2,10,10-trimethyltricyclo[6.3.0.$0^{2,6}$]undec-1(8)-en-4-one (**60**):

IR (neat): 1746, 1402, 1363, 1164 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.05 (s, 3H, -C<u>H</u>$_3$), 1.08 (s, 3H, -C<u>H</u>$_3$), 1.15 (s, 3H, -C<u>H</u>$_3$), 1.79-2.00 (m, 5H), 2.05 (m, 2H), 2.29 (dd, 1H, J = 1.5, 18.5 Hz), 2.50-2.59 (m, 1H), 2.63 (ddd, 1H, J = 1.5, 10.0, 18.5 Hz), 2.70-2.79 (m, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 25.1 (-ve), 30.4 (-ve), 30.5 (-ve), 36.4, 41.4, 44.3, 45.2, 46.6, 48.1, 49.4, 50.0 (-ve), 141.0, 149.0, 219.7.

HRMS calcd for $C_{14}H_{20}O$: 204.1514; found: 204.1519.

Anal. calcd for $C_{14}H_{20}O$: C 82.30, H 9.87; found: C 82.36, H 9.87.

Characterization data for the protiodestannylated material **183**:

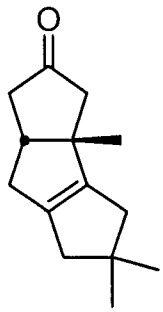
IR (neat): 1714, 1620, 1437, 1186 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.98 (s, 3H, -C<u>H</u>$_3$), 1.00 (s, 3H, -C<u>H</u>$_3$), 1.88 (dd, 1H, J = 11.0, 14.5 Hz), 1.92-2.11 (m, 5H; s, 3H, -C<u>H</u>$_3$, (δ 2.05)), 2.37-2.47 (m, 2H), 2.81-2.89 (br m, 1H), 5.21 (br s, 1H), 5.82 (t, 1H, J = 1.5 Hz).

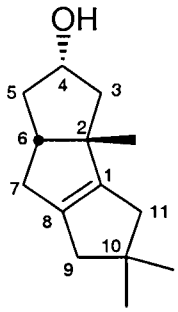
^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 17.3 (-ve), 29.7 (-ve), 29.8 (-ve), 34.8, 38.5, 41.7, 42.7 (-ve), 47.4, 50.1, 124.9 (-ve), 130.7 (-ve), 140.2, 181.2, 208.7.

HRMS calcd for $C_{14}H_{20}O$: 204.1514; found: 204.1517.

Preparation of (2S, 4S*, 6R*)-2,10,10-trimethyltricyclo[6.3.0.0^{2,6}]undec-1(8)-en-4-ol (**195**)*



60



195

To a cool (0 °C), stirred solution of the ketone **60** (322 mg, 1.57 mmol) in dry THF (30 mL) was added a solution of Li(*t*-BuO)$_3$AlH in THF (2.36 mL, 1.0 M, 2.36 mmol) via a syringe. The mixture was stirred at 0 °C for 1 h. A saturated aqueous solution of Rochelle's salt (30 mL) was added, and the mixture was diluted with Et_2O (30 mL) and then was stirred open to air for 30 min. The layers were separated and the aqueous phase was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with H_2O (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by flash column chromatography (20 g of silica gel, 1:4 Et_2O-petroleum ether) and by bulb-to-bulb distillation (98-100 °C/0.4 torr) to provide 282 mg (87%) of the alcohol **195** as a colourless viscous oil, which solidified upon standing (m.p. 44-46 °C).

IR (KBr): 3290, 1463, 1445, 1360, 1343, 1065 cm^{-1}.

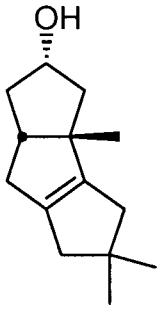
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (s, 3H, -C<u>H</u>$_3$), 1.08 (s, 3H, -C<u>H</u>$_3$), 1.10 (s, 3H, -C<u>H</u>$_3$), 1.48-1.59 (m, 2H), 1.69 (ddd, 1H, *J* = 1.5, 4.5, 13.0 Hz), 1.84 (br s, 1H), 1.88-2.00 (m, 5H), 2.18-2.26 (m, 1H), 2.45-2.55 (m, 2H), 4.18 (br m, 1H, -C<u>H</u>(OH)).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 25.9 (-ve), 30.6 (-ve), 30.7 (-ve), 37.3, 41.7, 44.2, 44.9, 45.3, 45.5, 52.3, 52.4 (-ve), 75.6 (-ve), 140.0, 151.8.

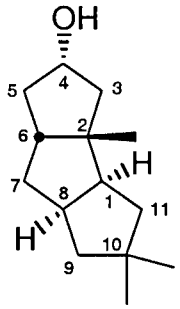
HRMS calcd for $C_{14}H_{22}O$: 206.1671; found: 206.1677.

Anal. calcd for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.78, H 10.89.

Preparation of (1S, 2S*, 4S*, 6R*, 8R*)-2,10,10-trimethyltricyclo[6.3.0.0^{2,6}]undecan-4-ol (**196**)*



195



196

To a solution of the alcohol **195** (276 mg, 1.34 mmol) in dry CH_2Cl_2 (13 mL) at room temperature was added (1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate (Crabtree catalyst)[104] (115 mg, 0.142 mmol). The reaction flask was evacuated and refilled three times with hydrogen gas. The reaction mixture was stirred for 17 h under an atmosphere of hydrogen (1 atm). The solvent was removed under reduced pressure and Et_2O (15 mL) was added to the residual solid. The mixture was stirred for 1 h. The mixture was filtered through a cake of silica gel (~5 g) and Celite® (~5 g) and the collected material was washed with Et_2O (~100 mL). The filtrate was concentrated under reduced pressure. The crude material was purified by flash column chromatography (20 g of silica gel, 2:3 Et_2O-petroleum ether) to afford 264 mg (95%) of the alcohol **196** as a white solid (m.p. 67-69 °C). A small amount of the solid

was recrystallized from hexanes and the acquired material (m.p. 69-71 °C) was subjected to X-ray crystallographic analysis (see Appendix).

IR (KBr): 3246, 1461, 1074 cm^{-1}.

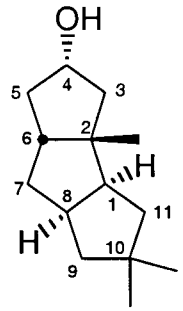
^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (s, 3H, -C<u>H</u>$_3$), 0.91 (s, 3H, -C<u>H</u>$_3$), 1.02 (s, 3H, -C<u>H</u>$_3$), 1.09 (dd, 1H, *J* = 6.5, 13.0 Hz, H-9), 1.14-1.25 (m, 1H, H-11), 1.25-1.40 (m, 2H, H-5, H-11'), 1.42-1.60 (m, 3H, H-3, H-7, H-9'), 1.61-1.72 (m, 2H, H-7', -O<u>H</u>), 1.88 (dd, 1H, *J* = 7.0, 12.5 Hz, H-3'), 1.93-2.00 (m, 1H, H-6), 2.20 (dddd, 1H, *J* = 0.5, 7.5, 7.5, 13.0 Hz, H-5'), 2.37 (ddd, 1H, *J* = 7.5, 7.5, 12.0 Hz, H-1), 2.64-2.74 (m, 1H, H-8), 4.21-4.36 (m, 1H, H-4).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 24.0 (-ve), 28.3 (-ve), 30.4 (-ve), 40.8, 40.8, 41.9, 42.1 (-ve), 43.4, 47.8, 48.5 (-ve), 50.9, 51.4, 54.8 (-ve), 73.4 (-ve).

HRMS calcd for $C_{14}H_{24}O$: 208.1827; found: 208.1825.

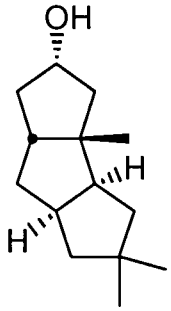
Anal. calcd for $C_{14}H_{24}O$: C 80.71, H 11.61; found: C 80.79, H 11.68.

Table 14. ^{1}H NMR (400 MHz, $CDCl_3$) data for the alcohol **196**: COSY Experiment.

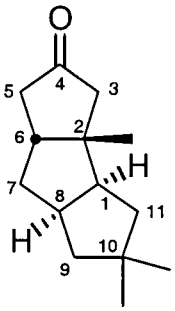


Assignment H-x	^{1}H NMR δ (multiplicity, *J* (Hz))	COSY Correlations
H-1	2.37 (ddd, *J* = 7.5, 7.5, 12.0)	H-8, H-11, H-11'
H-3	part of m at 1.42-1.60	H-3', H-4
H-3'	1.88 (dd, *J* = 7.0, 12.5)	H-3, H-4
H-4	4.21-4.36 (m)	H-3, H-3', H-5, H-5'
H-5	part of m at 1.25-1.40	H-4, H-5', H-6
H-5'	2.20 (dddd, *J* = 0.5, 7.5, 7.5, 13.0)	H-4, H-5, H-6
H-6	1.93-2.00 (m)	H-5, H-5', H-7, H-7'
H-7	part of m at 1.42-1.60	H-6, H-7', H-8
H-7'	part of m at 1.61-1.72	H-6, H-7, H-8
H-8	2.64-2.74 (m)	H-1, H-7, H-7', H-9, H-9'
H-9	1.09 (dd, *J* = 6.5, 13.0)	H-8, H-9'
H-9'	part of m at 1.42-1.60	H-8, H-9'
H-11	1.14-1.25 (m)	H-1, H-11'
H-11'	part of m at 1.25-1.40	H-1, H-11
OH	part of m at 1.61-1.72	
Me-12, Me-13, Me-14	0.88, 0.91, 1.02	

Preparation of (1S, 2S*, 6R*, 8R*)-2,10,10-trimethyltricyclo[6.3.0.0^{2,6}]undecan-4-one (**174**)*



196



174

To a stirred solution of the alcohol **196** (817 mg, 3.92 mol) in dry CH_2Cl_2 (50 mL) at room temperature was added oven-dried Celite® (1.69 g) and PCC (1.69 g, 7.84 mmol). The dark brown mixture was stirred at room temperature for 3 h. Dry Et_2O (150 mL) was added and the mixture was stirred for 1 h at room temperature. The mixture was filtered through a column of Florisil® (~60 g) and the column was eluted with Et_2O (~1.5 L). The filtrate was concentrated under reduced pressure. Purification of the crude material by flash column chromatography (50 g of silica gel, 1:4 Et_2O-petroleum ether), followed by bulb-to-bulb distillation (99-102 °C/0.4 torr) of the acquired liquid, provided 756 mg (93%) of the ketone **174** as a colourless oil.

IR (neat): 1746, 1461, 1407, 1366, 1170, 1133 cm^{-1}.

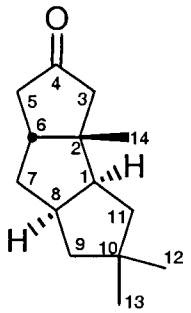
^1H NMR (500 MHz, $CDCl_3$) δ: 0.86 (s, 3H, -C$\underline{H}_3$), 0.97-1.01(m, 1H, H-9; s, 3H, -C$\underline{H}_3$ (δ 0.99)), 1.02 (s, 3H, -C$\underline{H}_3$), 1.18 (br dd, 1H, *J* = 11.5, 12.0 Hz, H-11), 1.38 (ddd, 1H, *J* = 2.5, 8.0, 12.0 Hz, H-11'), 1.46-1.58 (m, 1H, H-7), 1.65 (ddd, 1H, *J* = 2.0, 8.0, 14.0 Hz, H-7'), 1.72 (ddd, 1H, *J* = 2.5, 9.0, 12.5 Hz, H-9'), 1.98 (br d, 1H, *J* = 18.5 Hz, H-3), 2.05-2.12 (m, 1H, H-5; d, 1H, *J* = 18.5 Hz, H-3', (δ 2.09)), 2.30-2.40 (m, 2H, H-5', H-6), 2.53 (ddd, 1H, *J* = 8.0, 9.0, 11.5 Hz, H-1), 2.65-2.75 (m, 1H, H-8).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.2 (-ve), 26.1 (-ve), 29.0 (-ve), 39.7, 40.9, 41.3 (-ve), 43.0, 43.5, 44.6 (-ve), 49.0, 49.6, 51.5, 52.9 (-ve), 220.6.

HRMS calcd for $C_{14}H_{22}O$: 206.1671; found: 206.1674.

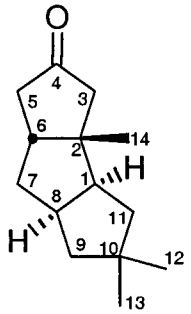
Anal. calcd for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.70, H 10.63.

Table 15. ^1H NMR (400 MHz, $CDCl_3$) data for the ketone **174**: COSY Experiment.



Assignment H-x	^1H NMR δ (multiplicity, *J* (Hz))	COSY Correlations
H-1	2.53 (ddd, *J* = 8.0, 9.0, 11.5)	H-8, H-11, H-11'
H-3	1.98 (br d, *J* = 18.5) (d of AB quartet)	H-3', H-5'
H-3'	2.09 (br d, *J* = 18.5) (d of AB quartet)	H-3, H-5'
H-5	2.05-2.12 (m)	H-5', H-6, H-7
H-5'	part of m at 2.30-2.40	H-3, H-3', H-5
H-6	part of m at 2.30-2.40	H-5, H-5', H-7, H-7'
H-7	1.46-1.58 (m)	H-5, H-6, H-7', H-8
H-7'	1.65 (ddd, *J* = 2.0, 8.0, 14.0)	H-6, H-7, H-8
H-8	2.65-2.75 (m)	H-1, H-7, H-7', H-9, H-9'
H-9	0.97-1.01 (signal under Me peak at 0.99)	H-8, H-9'
H-9'	1.72 (ddd, *J* = 2.5, 9.0, 12.5)	H-8, H-9
H-11	1.18 (br dd, *J* = 11.5, 12.0)	H-1, H-11'
H-11'	1.38 (ddd, *J* = 2.5, 8.0, 12.0)	H-1, H-11
Me-12, Me-13, Me-14	0.86, 0.99, 1.02	

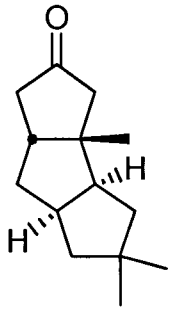
Table 16. ^{13}C (125.8 MHz, $CDCl_3$) and ^{1}H NMR (500 MHz) data for the ketone **174**: HMQC Experiment



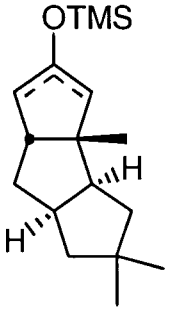
174

Assignment C-x	^{13}C NMR δ ppm	APT	HMQC ^{1}H NMR Correlations (δ ppm)
Me	22.2	CH or **CH_3**	Me (0.99)
Me	26.1	CH or **CH_3**	Me (0.86)
Me	29.0	CH or **CH_3**	Me (1.02)
C-7	39.7	C or **CH_2**	H-7 (1.46-1.58), H-7' (1.65)
C-10	40.9	**C** or CH_2	
C-8	41.3	**CH** or CH_3	H-8 (2.65-2.75)
C-5	43.0	C or **CH_2**	H-5 (2.05-2.12), H-5' (part of m at 2.30-2.40)
C-11	43.5	C or **CH_2**	H-11 (1.18), H-11' (1.38)
C-6	44.6	**CH** or CH_3	H-6 (part of m at 2.30-2.40)
C-2	49.0	**C** or CH_2	
C-9	49.6	C or **CH_2**	H-9 (0.97-1.01), H-9' (1.72)
C-3	51.5	C or **CH_2**	H-3 (1.98), H-3' (2.05-2.12)
C-1	52.9	**CH** or CH_3	H-1 (2.53)
C-4	220.6	**C** or CH_2	

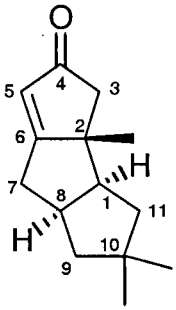
Preparation of (1S, 2R*, 8S*)-2,10,10-trimethyltricyclo[6.3.0.0^{2,6}]undec-5-en-4-one (197)*



174



197a/b



197

Following a procedure reported by Little,[87] to a cold (-78 °C), stirred solution of lithium tetramethylpiperidide (from tetramethylpiperidine (1.23 mL, 7.26 mmol) and *n*-BuLi (4.09 mL, 1.6 M in hexane, 6.54 mmol)) in dry THF (10 mL), was added, with a gas-tight syringe, freshly distilled chlorotrimethylsilane (1.84 mL, 14.5 mmol). A solution of the ketone **174** (300 mg, 1.45 mmol) in dry THF (10 mL) was added. After about 5 minutes, triethylamine (3.04 mL, 21.8 mmol) was added via a syringe. The reaction mixture was warmed slowly to room temperature over a period of 1 h. Et_2O (100 mL) and water (20 mL) were added and the layers were separated. The organic layer was washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude material was placed under reduced pressure (vacuum pump) for about 4 hours to remove remaining amines and traces of solvent. The crude mixture contained a 3:2 mixture of silyl enol ethers, which was determined by the ^1H NMR integration of olefinic signals at δ 4.48 (br unresolved d, J = 2.0 Hz) and 4.45 ppm (s). Based on the appearance of the olefinic signal, the major product (δ 4.48) is the desired silyl enol ether, formed by abstraction of the less hindered proton.

The crude mixture of silyl enol ethers **197a/b** was dissolved in a mixture of acetonitrile (12 mL) and CH_2Cl_2 (6 mL). Palladium acetate (Aldrich, 99.9%, 391 mg, 1.74 mmol) was added to this solution and the mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure and Et_2O (50 ml) was added to the residual

material. The mixture was filtered through a column of silica gel (~30 g), and the products were eluted with Et_2O. The combined eluate was concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (50 g of silica gel, 1:4 Et_2O-petroleum ether) to yield 155 mg (52%) of the enone **197** as a colourless oil, as well as 120 mg of the ketone **174**. The overall yield of **197**, based on the recovered **174**, was 87%.

IR (neat): 1713, 1636, 1466, 1367, 1242, 1189, 844 cm^{-1}.

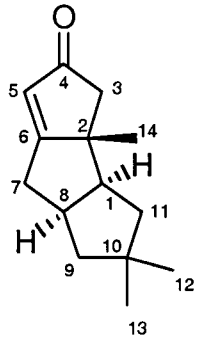
^1H NMR (400 MHz, $CDCl_3$) δ: 0.93 (s, 3H, -C$\underline{H}_3$), 1.06 (s, 3H, -C$\underline{H}_3$), 1.08 (s, 3H, -C$\underline{H}_3$), 1.19 (dd, 1H, *J* = 11.0, 12.0 Hz, H-9), 1.42 (dd, 1H, *J* = 9.0, 13.0 Hz, H-11), 1.49 (ddd, 1H, *J* = 1.5, 9.0, 13.0 Hz, H-11'), 1.76 (ddd, 1H, *J* = 1.5, 7.0, 12.0 Hz, H-9'), 2.17-2.31 (m, 3H, H-3, H-7, H-7'), 2.36 (ddd, 1H, *J* = 9.0, 9.0, 11.0 Hz, H-1), 2.70-2.83 (m, 2H, H-3', H-8), 5.65 (d, 1H, *J* = 2.0 Hz, H-5).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 24.6 (-ve), 27.4 (-ve), 29.0 (-ve), 32.9, 40.2, 43.8, 44.4 (-ve), 49.2, 49.5, 50.5 (-ve), 52.7, 122.0 (-ve), 195.8, 210.8.

HRMS calcd for $C_{14}H_{20}O$: 204.1514; found: 204.1519.

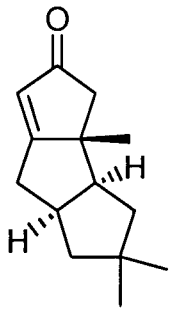
Anal. calcd for $C_{14}H_{20}O$: C 82.30, H 9.87; found: C 82.15, H 9.89.

Table 17. ^{1}H NMR (400 MHz, $CDCl_3$) data for the enone **197**: COSY Experiment.

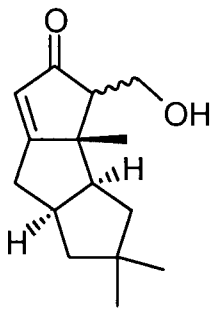


Assignment H-x	^{1}H NMR δ (multiplicity, *J* (Hz))	COSY Correlations
H-1	2.36 (ddd, 1H, *J* = 9.0, 9.0, 11.0)	H-8, H-11, H-11'
H-3	part of m at 2.17-2.31	H-5, H-3'
H-3'	part of m at 2.70-2.83	H-3
H-5	5.65 (d, 1H, *J* = 2.0).	H-3 and/or H-7 or H-7'
H-7, H-7'	part of m at 2.17-2.31	H-8, long range to H-9 and H-9'
H-8	part of m at 2.70-2.83	H-1, H-7, H-7', H-9, H-9'
H-9	1.19 (dd, 1H, *J* = 11.0, 12.0)	H-8, H-9', long range to H-7 or H-7'
H-9'	1.76 (ddd, 1H, *J* = 1.5, 7.0, 12.0)	H-8, H-9, long range to H-7 or H-7'
H-11	1.42 (dd, 1H, *J* = 9.0, 13.0)	H-1, H-11'
H-11'	1.49 (ddd, 1H, *J* = 1.5, 9.0, 13.0)	H-1, H-11
Me-12, Me-13, Me-14	0.93, 1.06, 1.08	

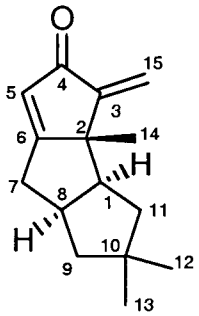
Preparation of (1S, 2S*, 8S*)-3-methylidene-2,10,10-trimethyltricyclo[6.3.0.0 ^{2,6}]undec-5-en-4-one (**198**)*



197



198c



198

To a cold (-78 °C), stirred solution of LDA (0.308 mmol) in dry THF (2 mL) was added, dropwise via a syringe, a solution of the enone **197** (31.5 mg, 0.154 mmol) in dry THF (2 mL). After 15 minutes, the mixture was warmed to -30 °C, and formaldehyde gas (formed from paraformaldehyde) was passed into the stirred reaction mixture in a stream of argon gas for 5 minutes. Saturated aqueous NH_4Cl (5 mL) was added, followed by Et_2O (10 mL), and the mixture was warmed to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was purified by flash column chromatography (15 g of silica gel, 1:1 Et_2O-petroleum ether) to provide 26.2 mg (73%) of a mixture of the alcohols **198c** as a colourless oil. The ratio of diastereomers, determined from the ^1H NMR integration of olefinic signals, was 1:4.6.

The mixture of the alcohols **198c** and tosyl chloride (70 mg) was dissolved in dry CH_2Cl_2 (1 mL) and pyridine (0.070 mL). The reaction mixture was stirred at room temperature for 4 days. DBU (0.140 mL) was added and the mixture was stirred for additional 2 h. Brine (10 mL) and water (10 mL) were added and the aqueous layer was extracted with Et_2O (4 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified

immediately by flash column chromatography (15 g of silica gel, 1:4 Et_2O-petroleum ether) to yield 18.5 mg (76%) of the dienone **198** as a colourless oil.

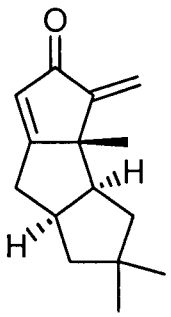
IR (neat): 1702, 1623, 1462, 1368, 1259, 1153 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.93 (s, 3H, -C<u>H</u>$_3$), 1.11 (s, 3H, -C<u>H</u>$_3$), 1.14 (s, 3H, -C<u>H</u>$_3$), 1.23 (br dd, 1H, J = 11.0, 12.0 Hz, H-9), 1.51-1.60 (m, 2H, H-11), 1.78 (dd, 1H, J = 9.0, 12.0 Hz, H-9'), 2.20-2.31 (m, 1H, H-7), 2.39 (ddd, 1H, J = 9.0, 9.0, 11.0 Hz, H-1), 2.70-2.81 (m, 2H, H-8, H-7'), 5.11 (s, 1H, H-15), 5.85 (s, 1H, H-15'), 5.86 (d, 1H, J = 1.5 Hz, H-5).

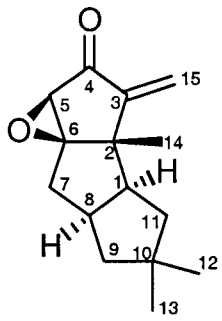
^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 23.5 (-ve), 27.4 (-ve), 29.0 (-ve), 32.7, 40.3, 44.1, 44.9 (-ve), 48.2 (-ve), 49.7, 51.8, 112.8, 123.1 (-ve), 154.3 (-ve), 189.8, 197.8.

HRMS calcd for $C_{15}H_{20}O$: 216.1514; found: 216.1518.

Preparation of (1S, 2S*, 5R*, 6R*, 8S*)-5,6-epoxy-3-methylidene-2,10,10-trimethyl-tricyclo[6.3.0.0^{2,6}]undecan-4-one [(±)-1-Desoxyhypnophilin] (**61**)*



198



61

To a mixture of the dienone (**198**) (10 mg, 0.046 mmol), sodium bicarbonate (50 mg), water (1 mL) and THF (1 mL) at 0 °C was added a 30% solution of aqueous hydrogen peroxide (0.10 mL). The mixture was stirred for 8 h at 0 °C, and the progress of the

reaction was monitored by TLC. Et_2O (20 mL) and saturated aqueous NH_4Cl (10 mL) were added. The layers were separated and the organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was immediately purified by flash column chromatography on iatrobeads (5 g of iatrobeads, 1:5 Et_2O-petroleum ether), to yield 6 mg (56%) of (±)-1-desoxyhypnophilin (**61**) as a clear oil, along with 2 mg of unreacted starting material. The comparison of the spectral data of the synthetic and isolated natural product[44] is presented in Tables 18 and 19. Since the numbering system used in naming the synthetic intermediates and (±)-1-desoxyhypnophilin (**61**) is different from that generally employed for the hirsutane family of sesquiterpenoids, both are shown in Tables 18 and 19 for comparison of spectral data of synthetic and natural (±)-1-desoxyhypnophilin.

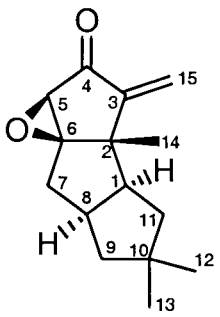
IR (neat): 1730, 1642, 1466, 1367, 1259, 1124 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.90 (s, 3H, -C<u>H</u>$_3$, H-12), 1.10 (s, 3H, -C<u>H</u>$_3$, H-13), 1.12-1.15 (m, 1H, H-9'; s, 3H, -C<u>H</u>$_3$, H-14 (δ 1.14)), 1.43-1.58 (m, 2H, H-11, H-11'), 1.77 (ddd, 1H, J = 1.5, 8.0, 12.0 Hz, H-9), 1.97 (d, 2H, J = 9.0 Hz, H-7), 2.37 (ddd, 1H, J = 9.0, 9.0, 11.5 Hz, H-1), 2.65-2.75 (m, 1H, H-8), 3.41 (s, 1H, H-5), 5.42 (s, 1H, H-15), 6.03 (s, 1H, H-15').

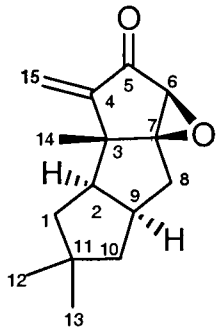
^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 17.5, 27.3, 28.9, 30.1, 39.2, 40.1, 42.5, 46.5, 49.5, 49.9, 61.1, 76.6, 119.9, 153.4, 198.1.

HRMS calcd for $C_{15}H_{20}O_2$: 232.1463; found: 232.1459.

Table 18. Comparison of ^{13}C NMR data for synthetic (±)-1-desoxyhypnophillin **61** (100.6 MHz, $CDCl_3$) with those reported for natural (-)-1-desoxyhypnophilin[44] (75.5 MHz, $CDCl_3$).



(±)-**61**

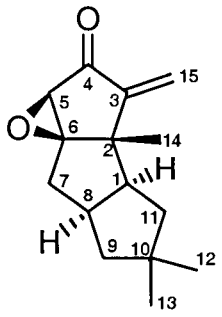


Hirsutane numbering (-)-**61**

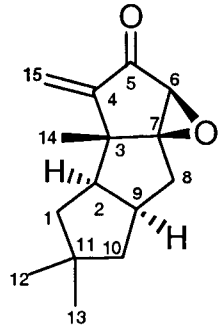
^{13}C assignments C-x	δ (ppm)	Hirsutane numbering C-x	Lit. ^{13}C signals and DEPT-135 data[a]
C-1	49.9	C-2	49.8 +
C-2	46.5	C-3	46.5 0
C-3	153.4	C-4	153.4 0
C-4	198.1	C-5	198.1 0
C-5	61.1	C-6	61.1 +
C-6	76.6	C-7	76.6 0
C-7	30.1	C-8	30.1 -
C-8	39.2	C-9	39.2 +
C-9	49.5	C-10	49.5 -
C-10	42.5	C-11	42.5 0
C-11	40.1	C-1	40.1 -
C-12	17.5	C-12	17.5 +
C-13	28.9	C-13	28.9 +
C-14	27.3	C-14	27.3 +
C-15	119.9	C-15	119.9 -

[a] Amplitude of signals in DEPT-135 spectrum (CH_3 or CH = +, CH_2 = -, C = 0)

Table 19. Comparison of ^{1}H NMR data for synthetic (±)-1-desoxyhypnophillin **61** with those reported for natural (-)-1-desoxyhypnophilin[44] (400 MHz, $CDCl_3$).



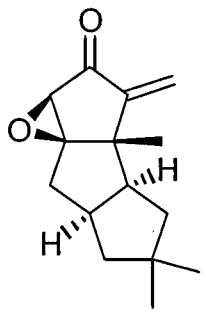
(±)-**61**



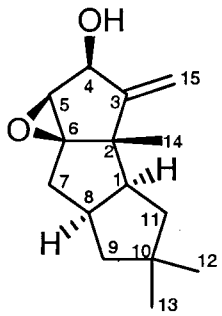
Hirsutane numbering (-)-**61**

^{1}H assignment H-x	δ, multiplicity, *J* (Hz)	Hirsutane numbering of H	Lit. ^{1}H assignments δ, multiplicity, *J* (Hz)
H-1	2.37 ddd *J* = 9.0, 9.0, 11.5	H-2	2.40 dt *J* = 12, 9
H-5	3.41 s	H-6	3.44 s
H-7	1.97 d *J* = 9.0	H-8	2.00 d *J* = 9
H-8	2.65-2.75 m	H-9	2.73 ddtd *J* = 8, 12, 9, 12
H-9	1.77 ddd *J* = 1.5, 8.0, 12.0	H-10	1.80 ddd *J* = 1, 8, 12
H-9'	1.14 m	H-10'	1.17 dd *J* = 12, 12
H-11	part of 1.43-1.58 m	H-1	1.54 dd *J* = 9, 13
H-11'	part of 1.43-1.58 m	H-1'	1.48 ddd *J* = 1, 9, 13
H-12	0.90 s	H-12	0.92 s
H-13	1.10 s	H-13	1.12 s
H-14	1.14 s	H-14	1.16 s
H-15	5.24 s	H-15'	5.27 s
H-15'	6.03 s	H-15	6.05 s

Preparation of (1S, 2S*, 4S*, 5S*, 6R*, 8S*)-5,6-epoxy-3-methylidene-2,10,10-trimethyltricyclo[6.3.0.0^{2,6}]undecan-4-ol) [(±)-6,7-epoxy-4(15)-hirsuten-5-ol] (**62**)* [44]



61



62

To a cool (0°C), stirred mixture of (±)-1-desoxyhypnophilin (**61**) (3.7 mg, 0.016 mmol) in absolute ethanol (0.5 mL) was added sodium borohydride (0.9 mg, 0.023 mmol) and the reaction mixture was stirred for 15 min. Water (10 mL) was added, and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was immediately purified by flash column chromatography on iatrobeads (1 g of iatrobeads, 1:2 Et_2O-petroleum ether), to afford 2.5 mg (68%) of the alcohol **62** as a colourless oil.

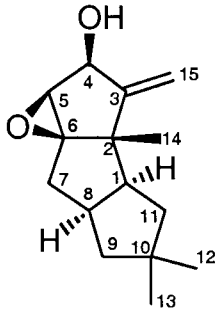
IR (film): 3436, 1465, 1107, 1066, 886 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.89 (s, 3H, -C<u>H</u>$_3$, H-12), 1.01 (s, 3H, -C<u>H</u>$_3$, H-14), 1.07 (s, 3H, -C<u>H</u>$_3$, H-13), 1.06-1.14 (m, 1H, H-9), 1.41 (d, 2H, *J* = 9.0 Hz, H-11), 1.63 (d, 1H, *J* = 11.0 Hz, -O<u>H</u>), 1.72 (dd, 1H, *J* = 8.0, 12.0 Hz, H-9'), 1.84 (d, 2H, *J* = 8.5 Hz, H-7), 2.27 (dt, 1H, *J* = 11.0, 9.0 Hz, H-1), 2.55-2.70 (m, 1H, H-8), 3.45 (d, 1H, *J* = 2.0 Hz, H-5), 4.59 (dddd, 1H, *J* = 2.0, 2.0, 2.0, 11.0 Hz, H-4), 4.96 (d, 1H, *J* = 2.0 Hz, H-15), 5.23 (d, 1H, *J* = 2.0 Hz, H-15').

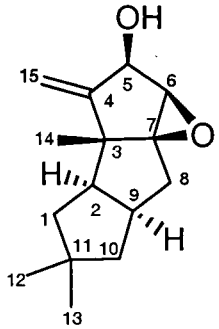
^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 17.1, 27.4, 28.9, 30.3, 39.1, 39.8, 42.4, 48.7, 48.7, 49.6, 63.6, 74.2, 75.4, 111.3, 159.3.

HRMS calcd for $C_{15}H_{22}O_2$: 234.1620; found: 234.1620.

Table 20. Comparison of ^{13}C NMR data for synthetic (1*S**, 2*S**, 4*S**, 5*S**, 6*R**, 8*S**)-5,6-epoxy-3-methylidene-2,10,10-trimethyltricyclo[6.3.0.$0^{2,6}$]undecan-4-ol [(±)-6,7-epoxy-4(15)-hirsuten-5-ol] (**62**) (100.6 MHz, $CDCl_3$) with those reported for natural (+)-6,7-epoxy-4(15)-hirsuten-5-ol[44] (75.5 MHz, $CDCl_3$)



(±)-**62**

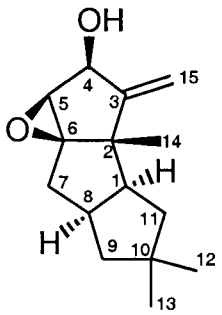


Hirsutane numbering (+)-**62**

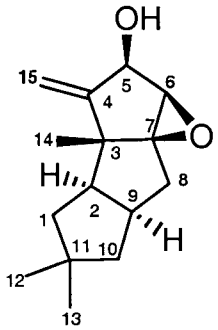
^{13}C assignments C-x	δ (ppm)	Hirsutane numbering C-x	^{13}C signals and DEPT-135 data[a]
C-1	48.7	C-2	48.7 +
C-2	48.7	C-3	48.7 0
C-3	159.3	C-4	159.3 0
C-4	74.2	C-5	74.2 +
C-5	63.6	C-6	63.6 +
C-6	75.4	C-7	75.4 0
C-7	30.3	C-8	30.3 -
C-8	39.1	C-9	39.1 +
C-9	49.6	C-10	49.6 -
C-10	42.4	C-11	42.4 0
C-11	39.8	C-1	39.8 -
C-12	17.1	C-12	17.1 +
C-13	28.9	C-13	28.9 +
C-14	27.4	C-14	27.4 +
C-15	111.3	C-15	111.3 -

[a] Amplitude of signals in DEPT-135 spectrum (CH_3 or CH = +, CH_2 = -, C = 0)

Table 21. Comparison of ^{1}H NMR data for synthetic (1*S**, 2*S**, 4*S**, 5*S**, 6*R**, 8*S**)-5,6-epoxy-3-methylidene-2,10,10-trimethyltricyclo[6.3.0.0^{2,6}]undecan-4-ol) [(±)-6,7-epoxy-4(15)-hirsuten-5-ol] (**62**) with those reported for natural (+)-6,7-epoxy-4(15)-hirsuten-5-ol[44] (400 MHz, $CDCl_3$).



(±)-**62**

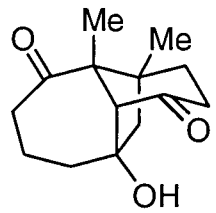


Hirsutane numbering (+)-**62**

^{1}H assignment	δ, multiplicity, *J* (Hz)	Hirsutane numbering of H	Lit. ^{1}H assignments δ, multiplicity, *J* (Hz)
H-1	2.27 dt *J* = 11.0, 9.0	H-2	2.27 dt *J* = 11, 9
H-4	4.59 dddd *J* =2.0, 2.0, 2.0, 11.0	H-5	4.59 dddd *J* = 2, 2, 2, 10.8
H-5	3.45 d *J* = 2.0	H-6	3.45 d *J* = 5
H-7	1.84 d *J* = 8.5	H-8	1.84 d *J* = 8.5
H-8	2.55-2.70 m	H-9	2.65 ddtd *J* = 7.5, 11, 8.5, 11
H-9	1.06-1.14 m	H-10'	1.10 dd *J* = 11, 12
H-9'	1.72 dd *J* = 7.5, 12.0	H-10	1.72 dd *J* = 7.5, 12.0
H-11	1.41 d *J* = 9.0	H-1	1.42 d *J* = 9
H-12	0.89 s	H-12	0.89 s
H-13	1.07 s	H-13	1.07 s
H-14	1.01 s	H-14	1.01 s
H-15	4.96 d *J* = 2.0	H-15'	4.96 d *J* = 2
H-15'	5.23 d *J* = 2.0	H-15	5.23 d *J* = 2
OH	1.63 d *J* = 11.0	OH	not reported

APPENDIX

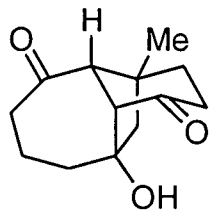
X-ray crystalllographic data for the dione alcohol 147.



147

Formula	$C_{14}H_{20}O_3$
Crystal System	Monocyclic
Space Group	$P2_1/n$ (#14)
Lattice Parameters	a (Å) = 6.9319 (10)
	b (Å) = 16.678 (4)
	c (Å) = 10.9304 (6)
	β (°)= 101.4844 (14)
	V ($Å^3$) =1238.4 (3)
Z value	4
Number of reflections used in refinement	3034
R	0.090
R_w	0.089

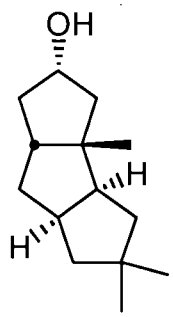
X-ray crystalllographic data for the dione alcohol 148.



148

Formula	$C_{13}H_{18}O_3$
Crystal System	
Space Group	$P2_1/n$ (#14)
Lattice Parameters	a (Å) = 6.9319 (10)
	b (Å) = 16.678 (4)
	c (Å) = 10.9304 (6)
	β (°)= 101.4844 (14)
	V (Å^3) =1238.4 (3)
Z value	4
Number of reflections used in refinement	3034
R	0.090
R_w	0.089

X-ray crystalllographic data for the alcohol 196.



196

Formula	$C_{14}H_{24}O$
Crystal System	Monocyclic
Space Group	C2/c (#15)
Lattice Parameters	a (Å) = 20.437 (3)
	b (Å) = 14.387 (3)
	c (Å) = 9.7108 (3)
	β (°)= 92.9752 (7)
	V ($Å^3$) =2557.8 (5)
Z value	4
Number of reflections used in refinement	3244
R	0.053
R_w	0.087

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