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List of Abbreviations

Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	azobis(isobutyro)nitrile
Anal. Calcd	elemental analysis calculated
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
cat.	catalytic
CI	chemical ionization
CSA	camphorsulfonic acid
d	day
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DNA	deoxyribonucleic acid
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
E_a	energy of activation
EI	electron impact
equiv.	equivalents
Et	ethyl
Ether	diethyl ether
GC	gas chromatography
h	hour
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrum
Ipc	isopinocampheyl
i-Pr	isopropyl

IR	infra red
KHMDS	potassium hexamethyldisilylamide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilylamide
LTMP	lithium tetramethylpiperidine
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
min	minute
MOM	methoxymethyl
ms	molecular sieves
Ms	methanesulfonyl
NMR	nuclear magnetic resonance
Nuc	nucleophile
Ox.	oxidation
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Phth	phthaloyl
PG	protecting group
Piv	pivaloyl
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PTSA	*p*-toluenesulfonic acid
Py	pyridine
RT	room temperature
salen	*N,N'*-Bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexane-diamino
s.m.	starting material
TBAF	tetrabutylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TES	triethylsilyl
TESOTf	triethylsilyl trifluoromethanesulfonate

Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

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Abstract

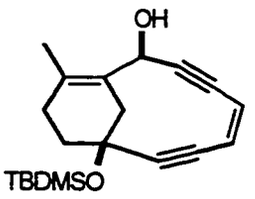
The enediyne antibiotics have generated widespread interest due to their novel mechanism of DNA cleavage and the synthetic challenge these structures represent. Similarly, considerable effort is being devoted to the study of the structurally complex and potent antitumour agent, Taxol®. This thesis describes the preparation of a new family of compounds, the "taxamycins", which contain important features from both types of natural products. The synthesis and functionalization of the 10-, 11- and 12-membered, bicyclic ring taxamycin adducts **290**, **270** and **240a** respectively, are described.

The construction of several models was first examined using the enediyne synthon **176**. The building block **177** was prepared by two successive Pd(0)-based couplings followed by selective removal of the trimethylsilyl group. The lithiated derivative of **177** was condensed onto several carbonyl-containing precursors (**182**, **204** and **212**) to synthesize 10- and 11-membered bicyclic enediyne systems but, in each case, final ring closure could not be effected under various reaction conditions.

Thus, attention was directed towards the Taxol® A ring analogue **245**, prepared efficiently in 5 steps from the commercially available 2,3-dimethyl-2-butene (overall yield of 22%). Enediyne **177** was condensed stereoselectively onto precursor **245** and elaborated to iodoaldehyde **239**. The final cyclization to the taxamycin-12 model **240a** was achieved stereoselectively by intramolecular Cr(II)-Ni(II) mediated Nozaki-Kishi condensation of **239** in variable yield (7-60%). The Bergman cycloaromatization of **240a** provided the tricyclic, taxane nucleus in low yield.

A similar approach, using the A ring compound **263**, was employed in the preparation of the taxamycin-11 adduct **270**. The Nozaki-Kishi coupling of iodoaldehyde **269** afforded **270** in low to modest yield (7-37%). Intramolecular acetylide condensation of aldehyde **271** also effected ring closure in low yield (15-25%).

The preparation of the 10-membered ring model **290** completed the taxamycin series. The *gem* dimethyl group was omitted in this model to obtain higher yields of cyclization compared to the preceding examples. Preparation of taxamycin-10 **290** was accomplished by addition and subsequent elaboration of synthon **177** to precursor **283**. The final ring closure was effected stereoselectively by intramolecular Cr(II)-mediated Nozaki-Kishi coupling or by intramolecular anionic cyclization in good yields (60-76%). Further derivatization of **291** by SeO_2 allylic oxidation was successful and allowed for the attachment of the Taxotere® side chain. The resolution of the racemic taxamycin-10 adduct was accomplished by introduction of this enantiomerically enriched side chain and provided derivatives **300a** and **300b**. Currently, the biological activity of these and related enantiomeric adducts is being investigated. Preliminary attempts to induce Bergman cycloaromatization of taxamycin-10 were also examined, *via* introduction of different triggering devices at the C-8 hydroxyl position.



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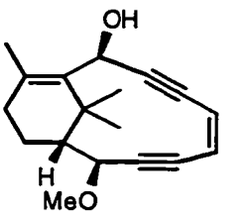
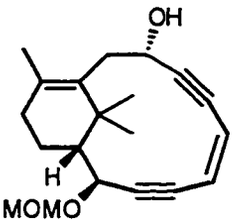
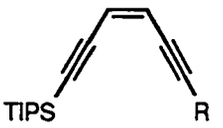


270



240a



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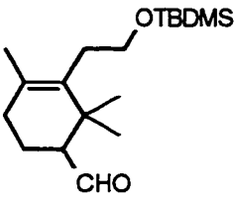
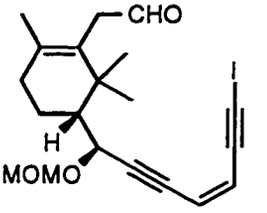
177 R = H



245



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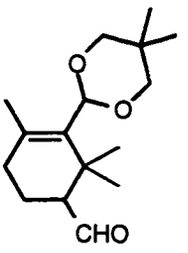
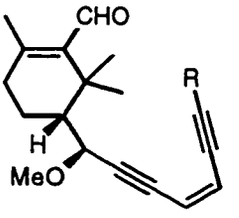
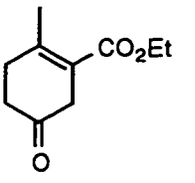


263



269 R = I
271 R = H



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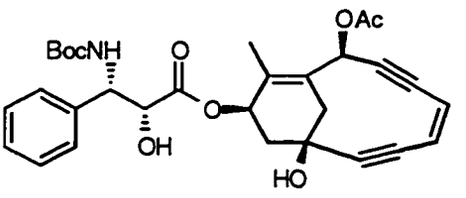
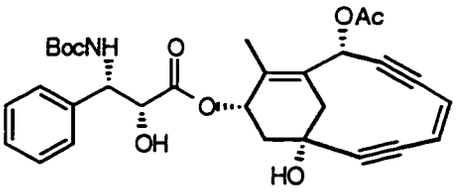


300a

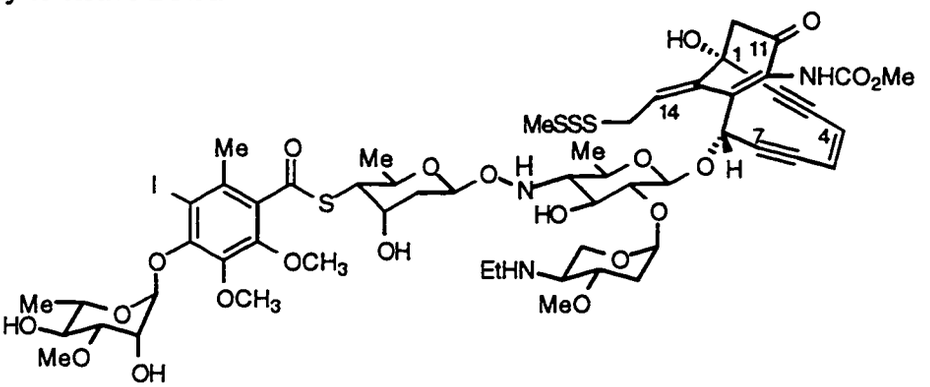


300b

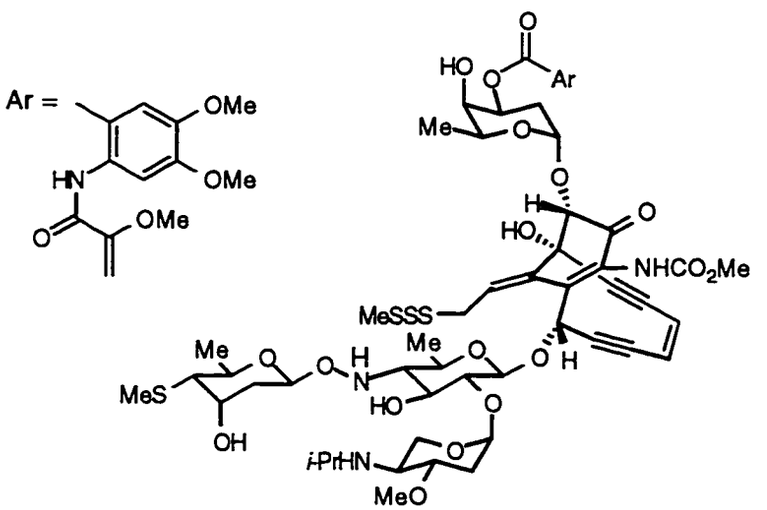
1 Introduction

1.1 The Enediyne Antibiotics

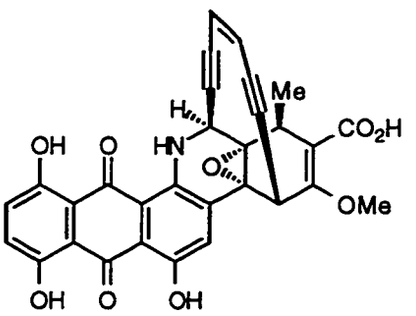
The enediyne class of antibiotics, as represented by calicheamicin γ_1^I **1**, esperamicin A_1 **2**, dynemicin A **3** and neocarzinostatin chromophore **4**, comprise some of the most potent, naturally occurring, antitumour agents actually known (Figure **1**). These compounds display *in vitro* and *in vivo* activity against a number of tumour systems at ng/mL levels (IC_{50}'s).[1] The biological activity of this family of compounds stems from their ability to cleave DNA.



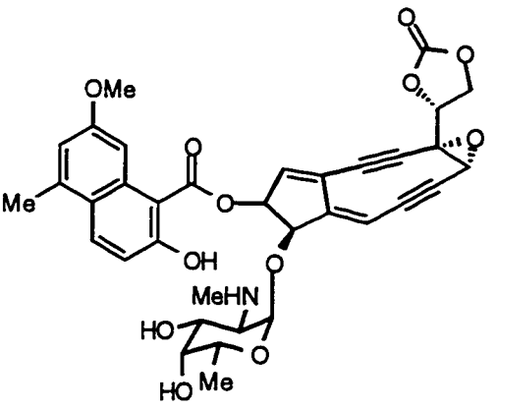
Calicheamicin γ_1^I **1**



Esperamicin A_1 **2**



Dynemicin A **3**



Neocarzinostatin chromophore **4**

Figure 1. Enediyne Antibiotics

The impressive DNA cleaving properties of the enediynes is accounted for by the complex and unique molecular architecture of these molecules. For the most part, these compounds are equipped with three functional domains. One domain acts as a "delivery system" guiding the molecule to its target, DNA. A second domain is responsible for producing the reactive fragments that damage DNA. The ability to generate highly reactive sp^2 carbon centered radicals upon suitable activation is common to all members of the enediyne family.[2] The final portion of these compounds serves as a triggering device. Upon suitable activation, this triggering device initiates a cascade of reactions that leads to the generation of the damaging radicals.[2]

The combination of the enediynes' novel molecular structures, potent biological activities and interesting mode of action, has elicited research investigations in many disciplines of science including the areas of chemistry, biology and medicine. In particular, these compounds have generated intense interest in the synthetic community. Organic chemists have studied these molecules and synthesized them in order to mimic their unique structures and to design new biologically active agents. These synthetic efforts have ultimately led to a greater understanding of the mechanism of action of these fascinating

molecules. The chemistry of calicheamicin and esperamicin will be discussed here in detail.

1.2 Calicheamicin and Esperamicin

1.2.1 Structure and Activity

In the mid 1980's, calicheamicin **1** and esperamicin **2** became the first recognized members of the enediyne antibiotics.[3,4] Both of these molecules were isolated from the fermentation extracts of soil bacteria. The calicheamicins are produced by the fermentation of *Micromonsporo echinospora* ssp. *calichensis*, a bacteria isolated from soil collected in Texas.[5] The esperamicins, on the other hand, were discovered as metabolites of a strain of *Actinomadura verrucosospora* isolated from a soil sample collected at Pto Esperanza, Misiones, Argentina.[6]

Despite the different origins of these molecules, they are structurally very similar. Both possess three common features: 1) the 3-ene-1,5-diyne (or enediyne) unit which bridges a conformationally rigid six-membered ring, forming a bicyclo[7.3.1]tridecane framework, 2) an allylic trisulfide moiety of *E* geometry, and 3) an enone system in which the double bond occupies the bridgehead position, C-9 to C-10. These common aglycon portions of calicheamicin and esperamicin are the crucial elements in the mode of action of the two antibiotics (Scheme **1**).[1,2]

Calicheamicin and esperamicin are further characterized by the same amino sugars, thio sugar, glycosidic N-O linkage and aromatic ring in the sugar component. There is, however, a difference in substitution adjacent to the keto group of the enediyne chromophore, the substitution of the aromatic groups and the arrangement of sugar units attached to the bicyclic core. An aryltetrasaccharide is branched at the C-8 position of calicheamicin whereas in esperamicin there is a trisaccharide at C-8 and an arylmonosaccharide at C-12. Both molecules cleave DNA by the same mechanism

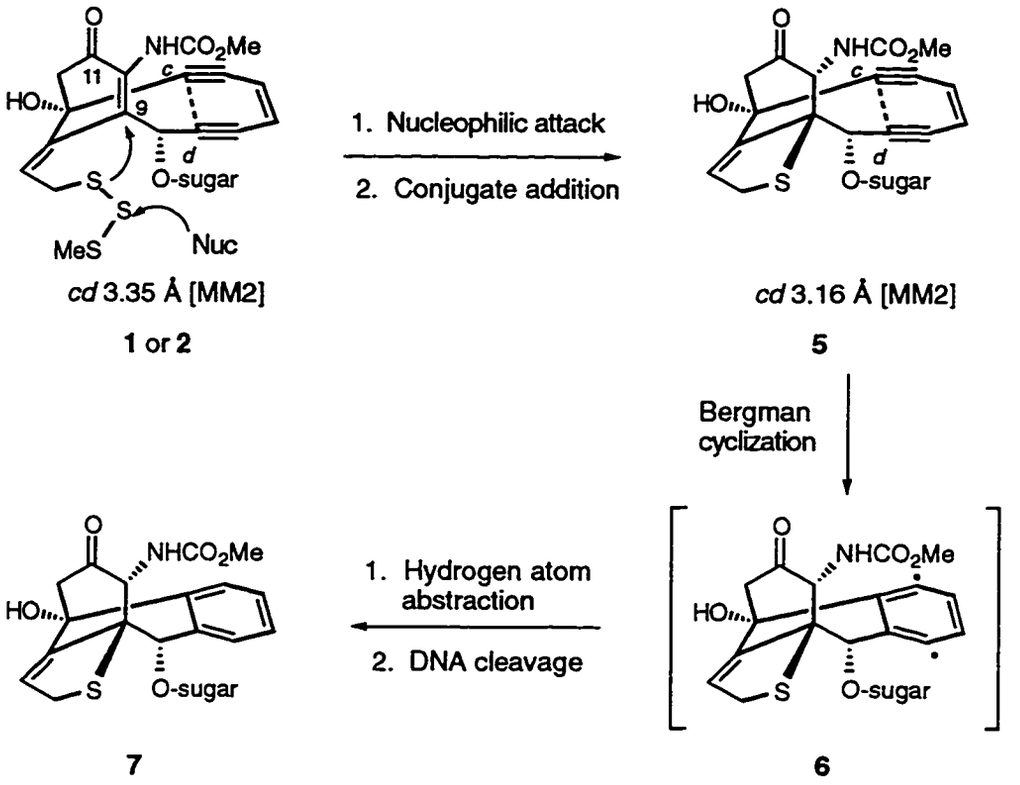
although these differences in structure lead to a different DNA sequence cutting specificity.[1]

The similarities between the esperamicins and the calicheamicins also extend over biological activity and mode of action. Both natural products exhibit powerful activity against murine tumours such P338 and L1210 leukemias and solid neoplasms such as B-16 melanoma at injected doses in the μg/kg range.[3-5] The extraordinary potency of these compounds arises from their ability to damage DNA by making sequence specific single and double strand cuts.[7]

1.2.2 Mode of Action of Calicheamicin and Esperamicin

The detailed series of events which lead to DNA cleavage can be described as follows (Scheme 1). Initially, it is understood that the carbohydrate fragments assist in the binding of the enediyne agents to the minor groove of double stranded, helical DNA.[8] In the case of calicheamicin, the molecule binds to DNA specifically at TCCT sites by orientation of the oligosaccharide tail towards the 3'-end of DNA fragments.[9] A nucleophile then attacks the central sulfur atom of the trisulfide group, resulting in the formation of a thiolate anion.[3,10] One possible candidate for such a nucleophile is believed to be the peptide glutathione, which is the most prevalent thiol in mammalian cells.[11] Recent studies suggest that it may react with calicheamicin bound to DNA to trigger the sequence of events leading to DNA damage. After this bioreduction process, the thiolate is perfectly positioned, due to the geometry of the 13,14-exocyclic double bond, to attack the α,β-unsaturated ketone intramolecularly at C-9 in a Michael fashion to afford compound **5**. This addition converts the C-9 sp^2 carbon atom to an sp^3 carbon and hence, alters the conformation of the cyclohexanone ring of the tricyclic enediyne core. As a result, the distance between the *c* and *d* carbon atoms in calicheamicin and esperamicin is significantly shortened from 3.35 Å (MM2) to 3.16 Å (MM2), resulting in the formation of the highly strained intermediate **5**.[12] This structural modification unlocks the destructive potential of

the enediyne molecule. The strain in **5** is relieved by a Bergman cycloaromatization of the enediyne moiety. This reaction leads to the generation of the highly reactive 1,4-phenylene diradical intermediate **6**, which abstracts hydrogen atoms from the DNA backbone and results in single and double stranded DNA cleavage and ultimately cell death.[9,13]

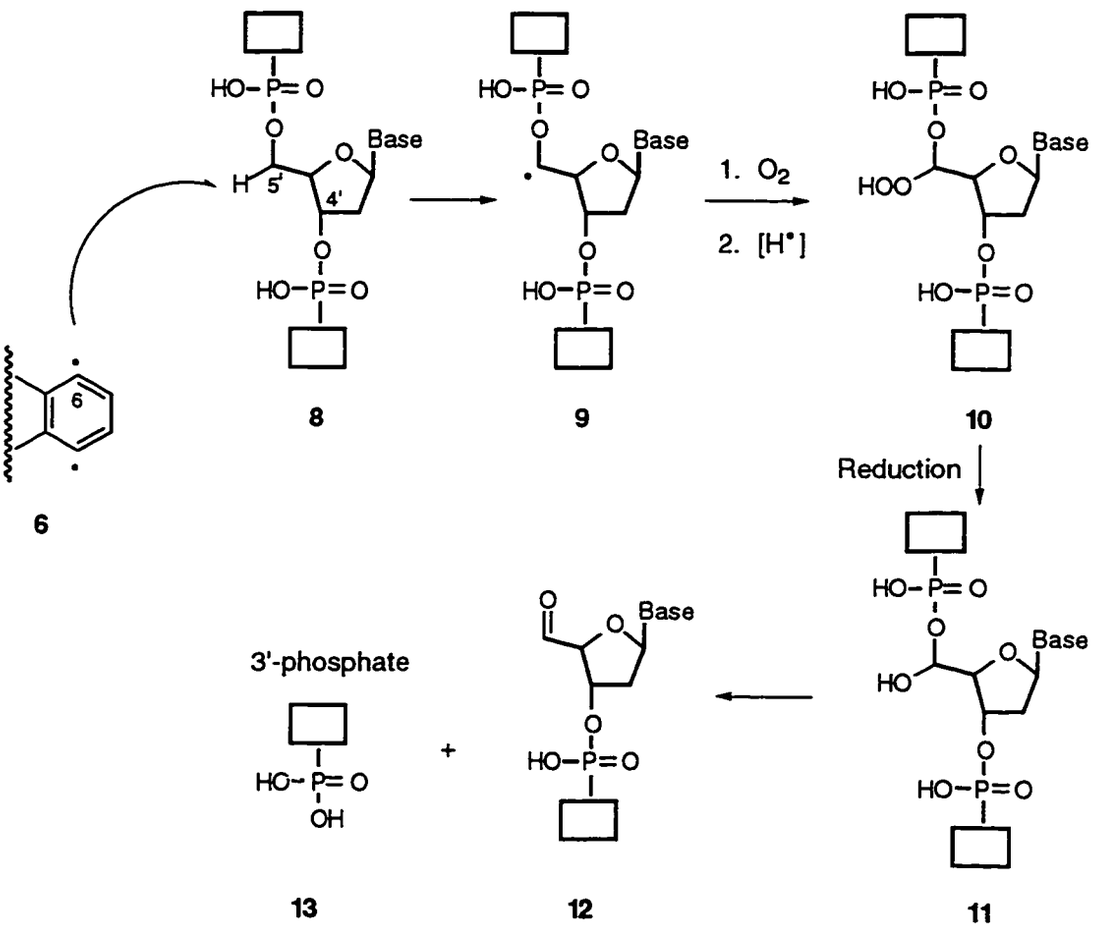


Scheme **1**. Mode of Action of Calicheamicin and Esperamicin

1.2.3 Mechanism of DNA Cleavage

The use of several 5' and 3',5'-labelled restriction fragments in the presence of thiol cofactors have shown that calicheamicin **1** exhibits a very high specificity for attack at the 5'C of a 5'-TCCT sequence and three nucleotides towards the 3'-side of the 3'-AGGA sequence on the opposing DNA strand.[7] This asymmetric cleavage pattern indicates interaction of the calicheamicin benzenoid diradical intermediate **6** within the minor groove of DNA.

The generation of the radical at the C-6 position of calicheamicin or esperamicin is involved in the abstraction of the prochiral 5'-hydrogen from the sugar moiety of cytidine in the 5'-TCCT strand (Scheme **2**).[7,9,13] The resultant radical **9** then reacts with molecular oxygen forming a peroxy radical which is reduced to **10**. Further reduction generates a hemiacetal **11** which hydrolyzes to the 5'-aldehyde **12** and the 3'-phosphate fragment **13**. The second radical at C-3 attacks the C-4' position of the DNA sugar backbone, three nucleotides further towards the 3'-side on the opposing DNA strand.[7b,14] The second DNA strand is cleaved by a similar mechanism.[15]

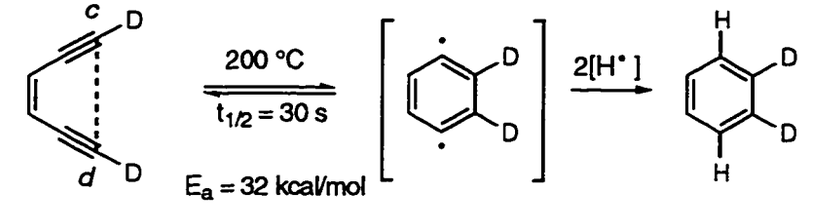


Scheme **2**. DNA Strand Cleavage by C5' Hydrogen Atom Abstraction

1.3 The Bergman Cyclization

1.3.1 Discovery

In the early 1970's, before the discovery of the enediyne antibiotics, Bergman and coworkers showed that thermolysis (~200 °C) of the parent acyclic *cis*-3-hexene-1,5-diyne **14** in hydrocarbon solvent produced benzene (Scheme **3**).[16] They showed that this process involves the rearrangement of **14** to the reactive 1,4-didehydrobenzene intermediate **15**. Furthermore, they calculated an activation energy (E_a) of 32 kcal/mol for this cycloaromatization.[17] The aromatic compound **16** is produced from the intermediate diradical **15** in the presence of a suitable hydrogen atom source.

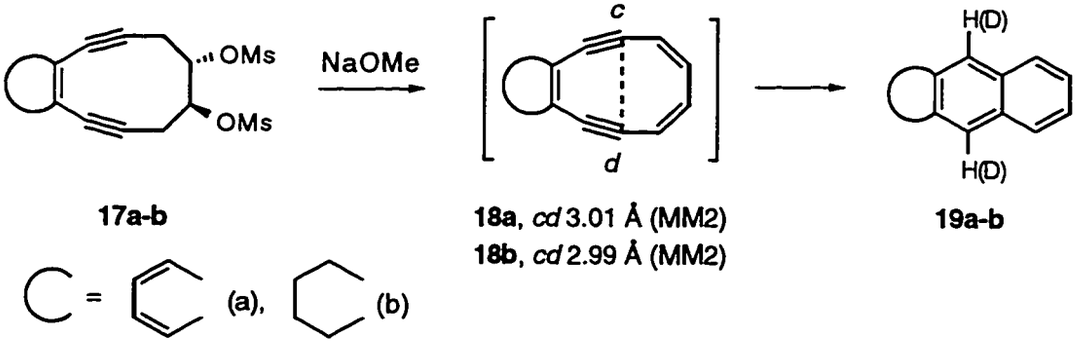


14 **15** **16**

cd 4.12 Å (MM2)

Scheme **3**. The Bergman Cyclization

This work followed the study of Masamune *et al.* who observed the conversion of the two cyclic enediynes **17a-b** into the benzenoid annulene systems **19a-b** (Scheme **4**).[18]

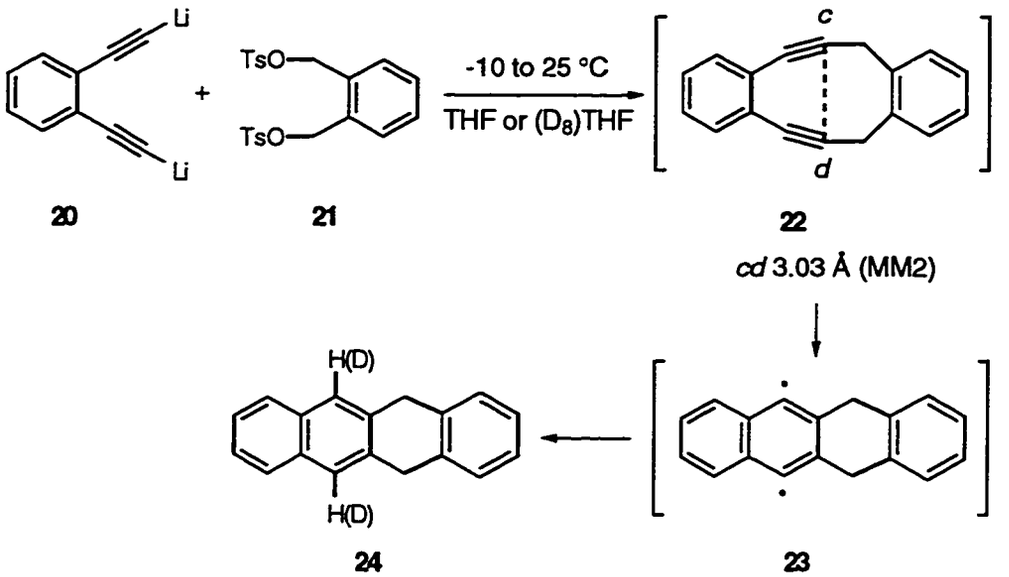


17a-b **18a**, *cd* 3.01 Å (MM2) **19a-b**

18b, *cd* 2.99 Å (MM2)

Scheme **4**. Observations by Masamune *et al.*

Subsequently to Masamune, Wong and Sondheimer also discovered the cyclization of an *in situ* generated strained cyclic enediyne **22** and postulated the involvement of a diradical intermediate.[19] These results represent two examples of the cycloaromatization process, now referred to as the Bergman cyclization.



Sheme **5**. Bergman Cyclization Studies by Wong and Sondheimer

1.3.2 Factors Controlling Bergman Cyclization

Unlike acyclic enediyne **14**, which required high temperatures to undergo Bergman cyclization, the naturally occurring enediyne antibiotics are able to initiate spontaneous cycloaromatization at ambient temperatures of 20-37 °C with an energy of activation of 21-24 kcal/mol.[20,21] The interatomic *cd* distance and torsional strain are the two important factors controlling the cycloaromatization. By incorporating the enediyne moiety within a bicyclic framework, the interatomic *cd* distance between the two acetylenic carbons is reduced and the bond angles of the acetylenic component are distorted. The distance between carbons *c* and *d* is shortened from 4.17 Å in acyclic **14** to 3.35 Å in calicheamicin **1**. The bond angles of the acetylenes are also distorted from linearity, measuring approximately 165°.[12] Furthermore, appropriate "triggering" of the enediyne antibiotics is required before they undergo Bergman cyclization at physiological temperatures. In the

case of calicheamicin and esperamicin, the bridgehead double bond at C-9 and C-10 locks the conformation of the molecule and prevents cycloaromatization until appropriate activation. Intramolecular thiol addition, converting the sp^2 centre at C-9 to an sp^3 one, not only reduces the *cd* distance but lowers the barrier to activation by increasing the strain energy of intermediate **5**. This strain in the Michael addition product **5** is relieved by Bergman cyclization (Scheme **1**). In order to understand the factors governing the cycloaromatization rate, simplified enediyne models have been prepared and their Bergman cyclization studied *in vitro*.

Nicolaou *et al.* have synthesized a series of monocyclic enediynes **25a-g** to determine the influence of ring size on the Bergman cyclization rate.[12,22] It was found that, as a general rule, the distance between the remote acetylenic carbons provides a useful guide for determining the ease of cyclization (Figure **2**). This distance gives an approximate measure of the degree of p-orbital overlap leading to bond formation during Bergman cyclization. For example, the 10-membered enediyne **25a** (n=2) with a *cd* distance (r_{cd}) of 3.25 Å cyclizes smoothly at 37 °C in the presence of the hydrogen donor, 1,4-cyclohexadiene, to give the tetralin **27**.[12] Compounds **28-30** whose r_{cd} = 2.99-3.03 Å, also undergo cycloaromatization below room temperature.[18,19] On the other hand, much higher temperatures are required to induce the 11-membered (150-170 °C) and 12-membered (210-230 °C) monocycles **25b** and **25c** to react.[12,22] The *cd* distance for these systems, as calculated from molecular mechanics calculations (MM2 force field) and X-ray crystallographic data, is greater than 3.60 Å . By comparing his results to the calculated distances in calicheamicin **1** (3.35 Å) and the Michael adduct **5** (3.16 Å), Nicolaou provided further agreement that the threshold to spontaneous Bergman cyclization at ambient temperature lies between 3.20 and 3.31 Å. In these simple, unsubstituted monocyclic enediynes, the *cd* distance provides a useful guide for determining the ease of cyclization. This analysis is insufficient for more complicated systems, however, since it does not include the contribution of strain energy.

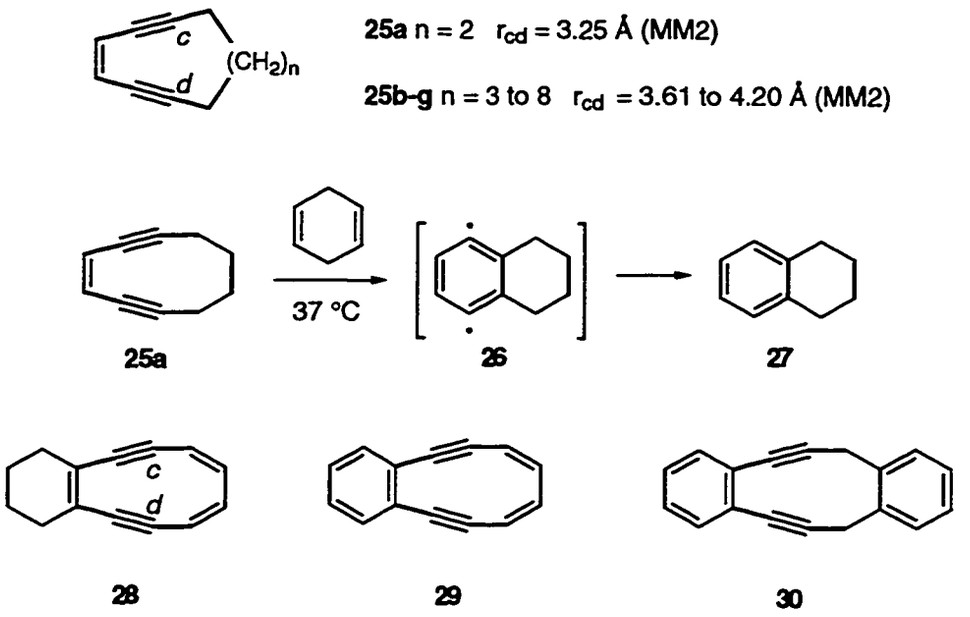
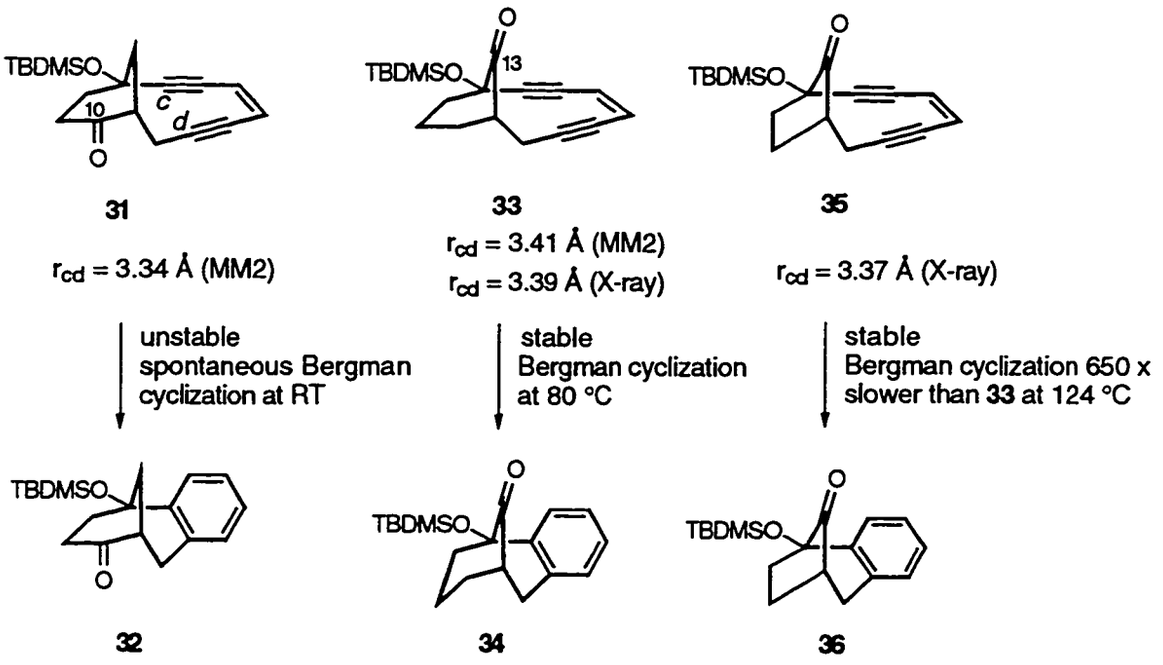


Figure 2. Nicolaou's Study of Simple Enediynes

The overall change in strain energy from enediyne to cycloaromatized adduct is another factor which has been proposed to account for the cyclization rates of 10-membered cyclic enediynes. Magnus and Snyder suggested that, although the distance between acetylenic carbons provides a qualitative guide to the ease of cyclization, it is the differential strain energy in the ground state and transition state which describes more accurately ring closure in more complex bicyclic systems.[23,24] They proposed that it is the release of strain in going from the ground state enediyne to the aromatized product *via* the intermediate 1,4-phenylene diradical which is the dominant factor contributing to the ease of cyclization.

The results of Snyder's mechanistic calculations were confirmed experimentally by Magnus *et al.* who synthesized the enediynes **31**, **33** and **35** and studied the difference in cycloaromatization rates (Scheme **6**).[24,25] The calculated r_{cd} of enediynes **31** and **33** are 3.34 Å and 3.41 Å (MM2) respectively. Despite this small difference in r_{cd}, enediyne **31** is unstable and cycloaromatizes spontaneously to **32** at room temperature, whereas the

isomer **33** is stable up to a temperature of 80 °C whereupon it cycloaromatizes to **34**. Furthermore, the five-membered ring analogue **35** undergoes Bergman reaction 650 times slower than **33** even though its X-ray r_{cd} distance of 3.37 Å is shorter than that of **33** (r_{cd}=3.39 Å). This difference in reactivity can be explained by the conformational difference between the two analogues. The boat conformation of cyclohexane **33** becomes a chair after cycloaromatization and provides a drop in strain energy of approximately 6 kcal as it moves to the diradical transition state.[24,25b] The five-membered ring analogue, on the other hand, has no comparable driving force. In this example, the distance between the bonding acetylenic carbon atoms in the ground state cannot account for the difference in the cycloaromatization rates. Instead, the ease of cyclization for more complicated bicyclic systems is better explained by the transition state strain release model proposed by Snyder.

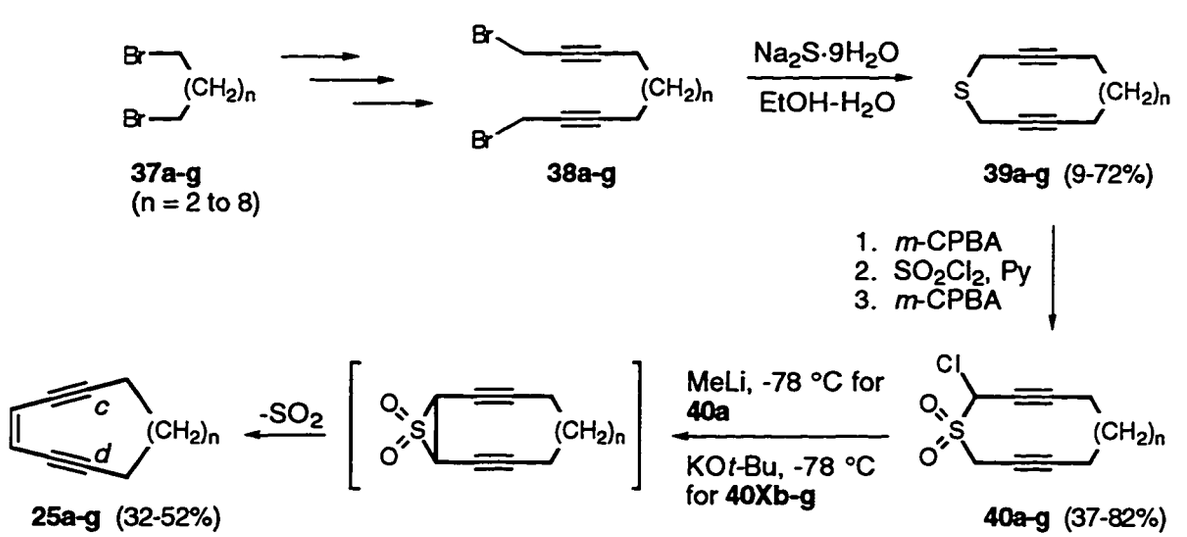


Scheme 6. Magnus' Cycloaromatization Rate Studies

1.4 Synthesis of Enediyne Systems

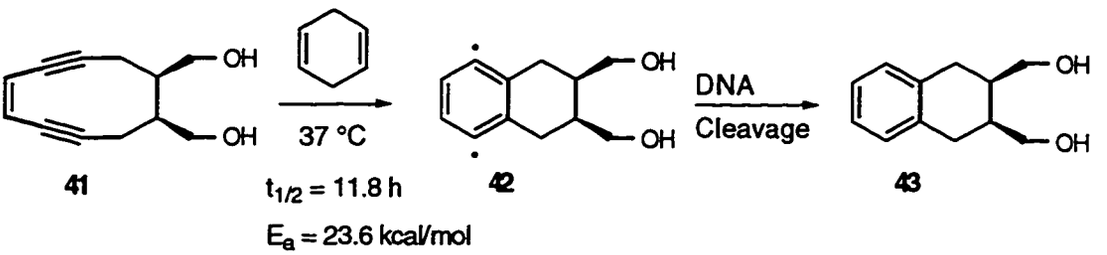
1.4.1 Monocyclic Enediynes

The discovery of the enediyne antibiotics has inspired the design of simplified mono and bicyclic enediynes, not only to evaluate the factors governing the Bergman cyclization, but also to probe and mimic the chemical and biological actions of these drugs in an attempt to uncover new DNA cleaving agents. As mentioned earlier, Nicolaou *et al.* synthesized a series of monocyclic enediynes **25a-g**, using the Ramberg-Bäcklund reaction as the key step to form the enediyne moiety within these ring systems (Scheme 7).[12,22] The dibromides **38a-g** were reacted with sodium sulfide under high dilution conditions to furnish the cyclic sulfides **39a-g** in varying yields. These sulfides were then oxidized to the corresponding sulfoxides, monochlorinated using sulfuryl chloride and further oxidized to the corresponding chlorosulfones. Treatment of these compounds **40a-g** with methyllithium or potassium *t*-butoxide gave the desired enediynes in 32-52% isolated yields.



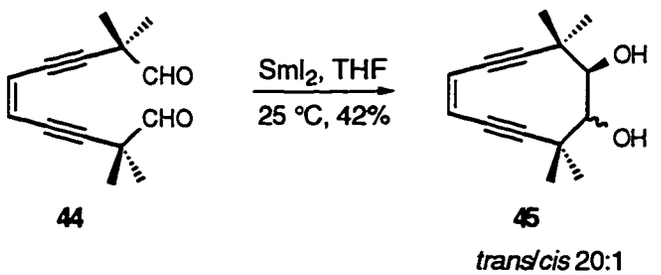
Scheme 7. Nicolaou's Rämberg-Backlund Approach to Monocyclic Enediyne Synthesis

This Ramberg-Bäcklund approach was used to construct enediyne **41**, which was found to cyclize and cleave double-stranded DNA at 37 °C and 0.5 mM concentration (Scheme **8**).[22] These results showed that simple cyclic enediynes could be used in the absence of a "delivery" or "triggering" system to cleave DNA and be useful biologically.



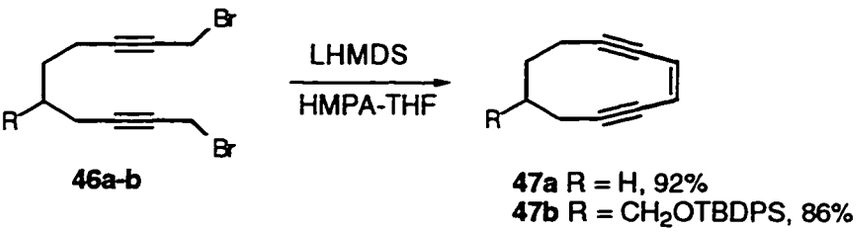
Scheme **8**. Bergman Cyclization of the DNA-Cleaving Enediyne **41**

A similar 10-membered enediyne diol **45** was constructed using an intramolecular pinacol coupling of the corresponding dialdehyde **44** (Scheme **9**).[26] This compound cut DNA at 5 mM concentration in pH 8.5 buffer at 50 °C.



Scheme **9**. SmI_2 Promoted Ring Closure

A more recent route to these simple monocyclic enediyne systems by Jones and Huber involved an intramolecular carbenoid coupling of *bis*-prop-2-ynylic halides (Scheme **10**).[27] This single-step coupling reaction represents a significant improvement over the conventional multistep Ramberg-Bäcklund approach since yields of up to 92% are obtained.

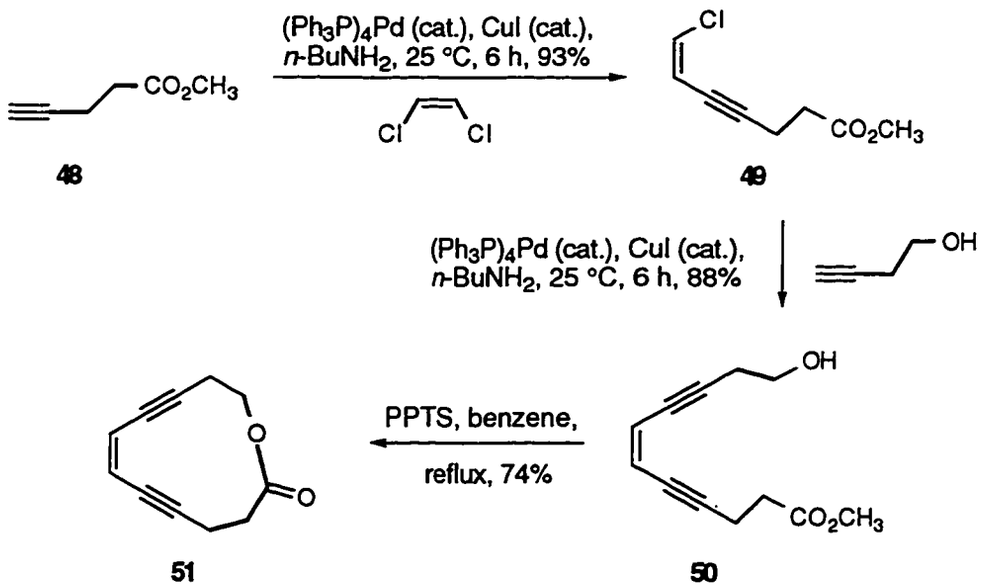


46a-b

47a R = H, 92%
47b R = $CH_2OTBDPS$, 86%

Scheme **10**. Jones' Intramolecular Carbenoid Coupling Protocol

Palladium(0)-based coupling reactions have played an important role in the construction of the enediyne system. These methods allow for the rapid assembly of the 3-ene-1,5-diyne motif under operationally simple, mild and high yielding conditions using a wide variety of olefin and acetylene precursors.[20,28] Even before the discovery of calicheamicin and esperamicin, Linstrumelle showed that the 12-membered enediyne lactone **51** could be rapidly assembled by coupling of*cis*-dichloroethylene with two different acetylenic units, followed by an acid catalyzed macrolactonization (Scheme **11**).[29]

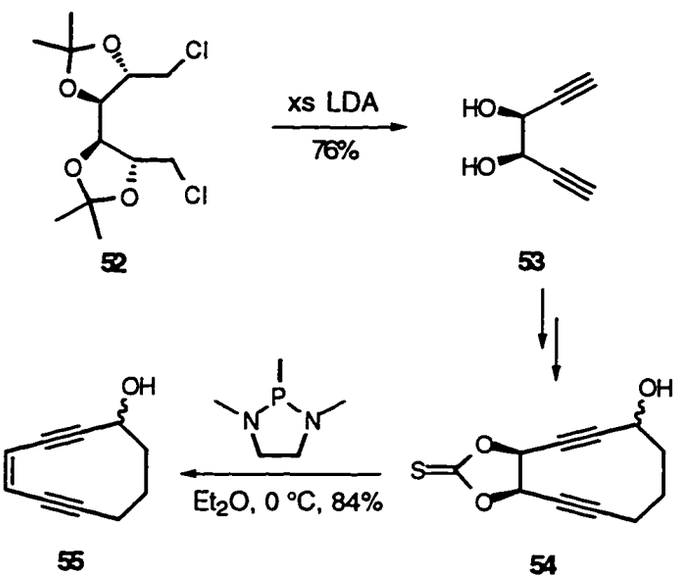


48 **49** **51** **50**

Scheme **11**. Pd(0)-based Coupling in the Synthesis of Monocyclic Enediyne **51**

Semmelhack has devised a method for the introduction of the central double bond of the enediyne system.[30] His procedure is based upon the Corey-Winter reaction of

thiocarbonates such as **54**, and allows for the mild and efficient introduction of the ene unit at a late stage of the synthesis (Scheme **12**). The two acetylenic functions in **53** were elaborated by the reaction of the chlorohydrin **52** with excess LDA.

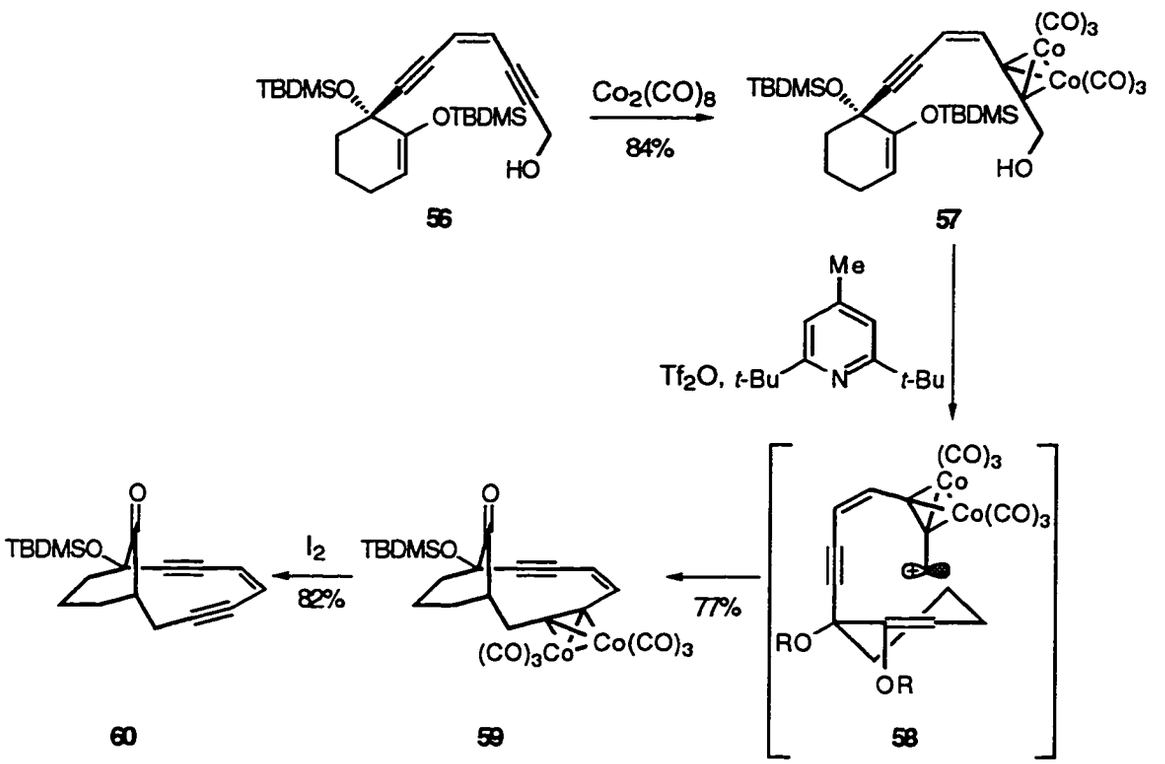


Scheme **12**. Semmelhack's Use of the Corey-Winter Elimination in the Synthesis of Monocyclic Enediynes

1.4.2 Bicyclic Enediyne Systems

A reoccurring problem in the synthesis of the enediyne core of the antitumour antibiotics is the formation of the crucial C-C bond which completes assembly of the strained enediyne bridge. An early approach to this problem was carried out by Magnus and coworkers (Scheme **13**).[25,31] They used a cyclization of an enol ether onto a propargylic cation equivalent as an entry into the bicyclo[7.3.1]tridecane enediyne system. Treatment of compound **56** with $Co_2(CO)_8$ in heptane resulted in complexation of the less sterically hindered acetylene. Subsequent treatment of this dicobalt hexacarbonyl adduct with Lewis acid, generated a carbocation intermediate **58**, which is ideally aligned with respect to the π-system of the enol ether to promote adjacent bond formation. Initial formation of the $\eta^2Co_2(CO)_6$ metallocycles, bends the normally linear sp-hybridized acetylene from 180° to approximately 145° and thus brings the two reacting centres close in

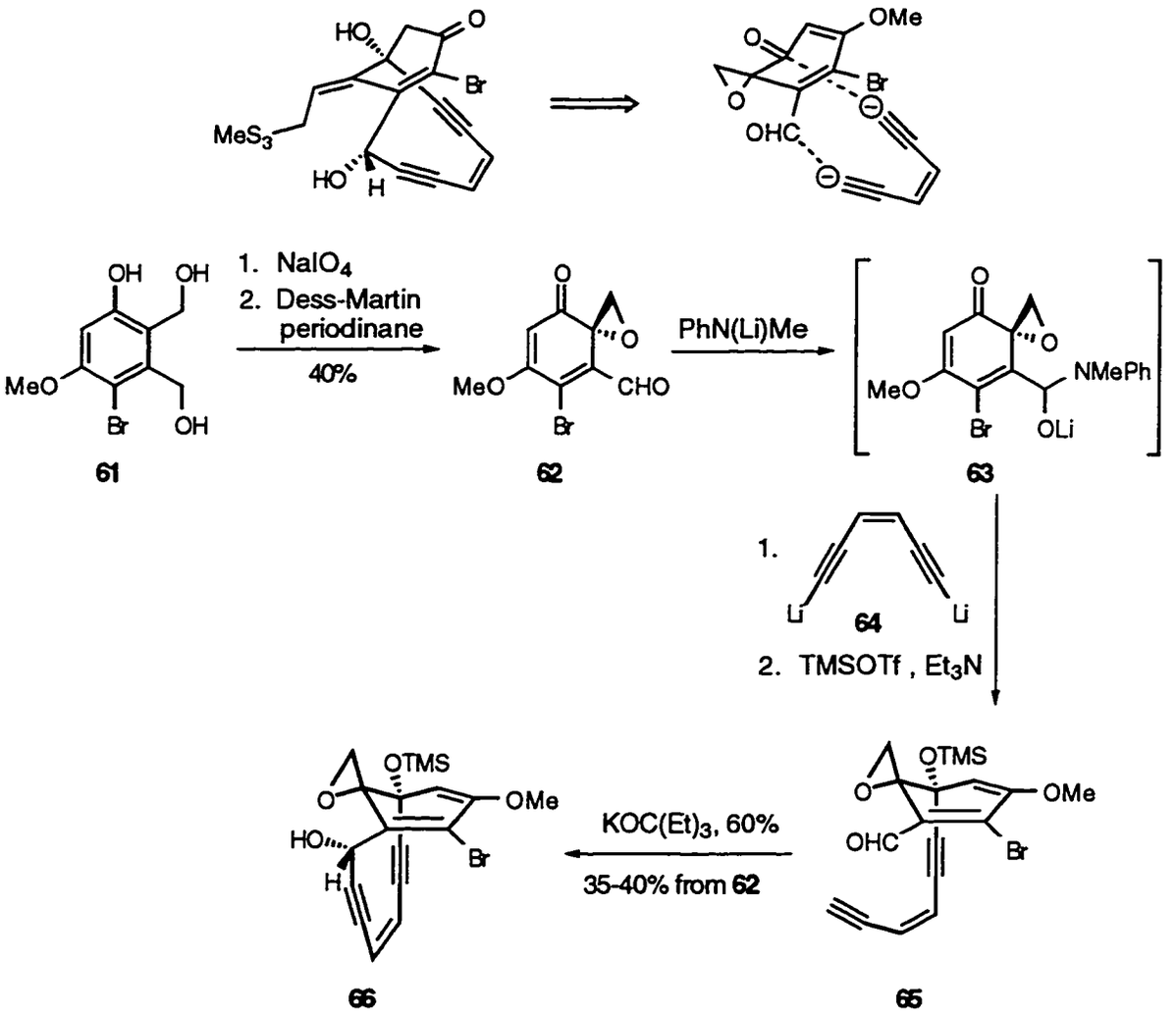
proximity. This Nicholas type reaction, using triflic anhydride in the presence of 2,6-di-*t*-butyl-4-methylpyridine, effected cyclization and afforded **59** in 77% yield.[25b] In addition to facilitating ring closure, the dicobalt hexacarbonyl complexation protected the product **59** and prevented it from undergoing spontaneous Bergman cycloaromatization.



Scheme **13**. Synthesis of a Calicheamicin/Esperamicin Related Model by Magnus *et al.*

A more conventional approach to the construction of the bicyclo[7.3.1] ring system has been the use of acetylide anion cyclizations. In the first total synthesis of the aglycone portion of (±)-calicheamicin, Danishefsky *et al.* envisaged the condensation of a preformed enediyne dianion across the two carbonyl centres of a fully functionalized six-membered ring, creating the enediyne bridge in one step (Scheme **14**).[32] In practice, however, it was found that a two step procedure provided the most favourable results for the enediyne ring annulation. This procedure involved initial regioselective addition of the enediyne dianion to the ketone functionality by using an *in situ* protection of the aldehyde functionality according to the protocol of Comins.[33] Treatment of **62** with lithium N-methylanilide

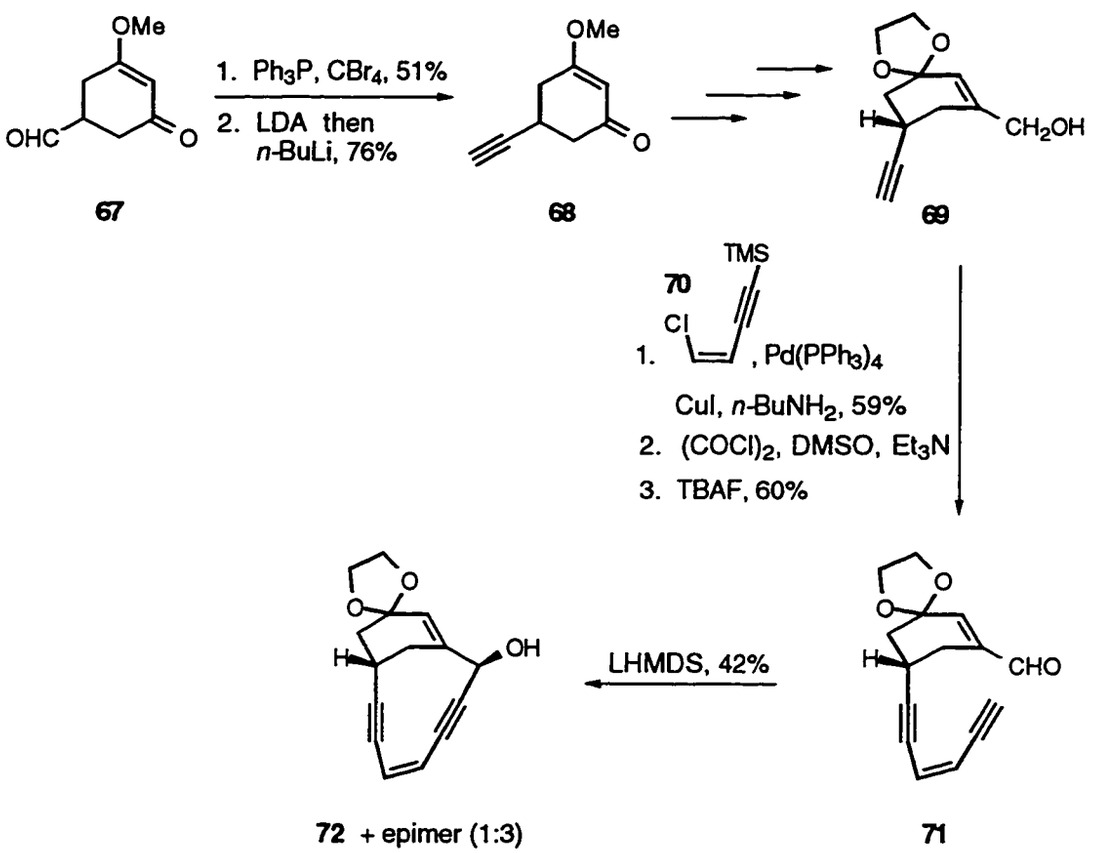
resulted in protection of the aldehyde as its lithio α-aminoalkoxide adduct **63** which allowed for addition of dilithioenediyne **64** to only the ketone centre. The major isomer **65** was obtained by addition of the enediyne nucleophile to the face of the ketone *syn* to the epoxide oxygen. Subsequent deprotonation of the acetylene moiety and stereoselective anionic cyclization gave the strained enediyne intermediate **66** with the correct C-8 stereochemistry in 60% yield. The correct configuration of this propargylic alcohol resulted from addition of the acetylide to the preferred *s-trans* rotamer of the enal.



Scheme 14. Danishefsky's Synthesis of Calicheamicinone **66**

Kende *et al.* incorporated a similar intramolecular anionic cyclization approach in the synthesis of the bicyclo[7.3.1]tridecane compound **72** (Scheme **15**).[34] The aldehyde

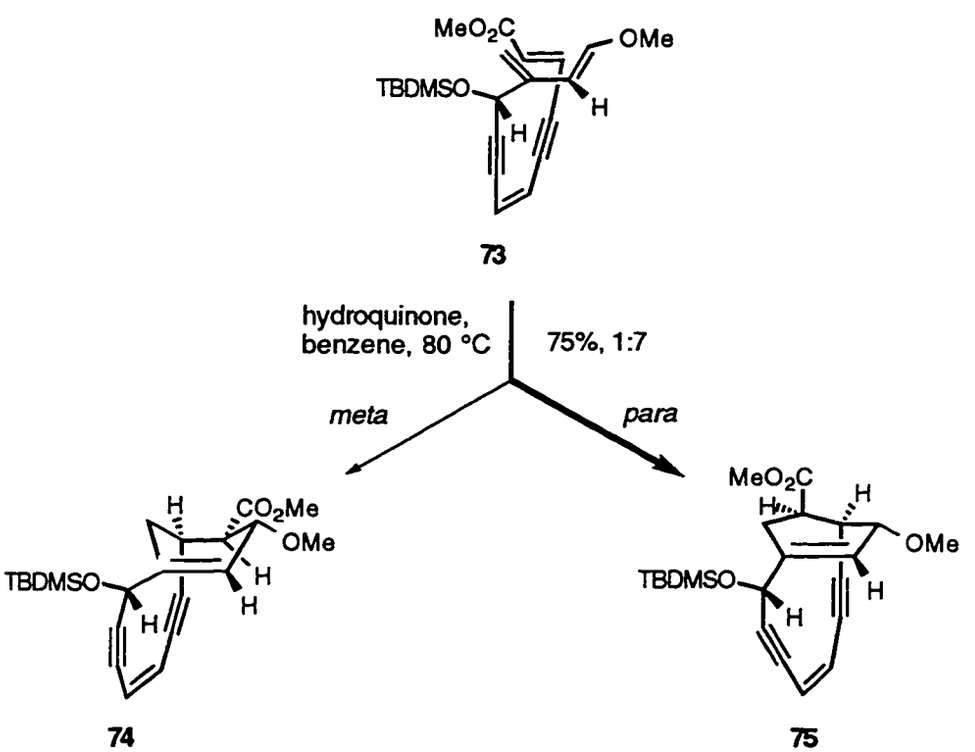
function in **67** was converted to the ethynyl substituent according to the Corey-Fuchs procedure[35], and the keto group was elaborated into the α,β-unsaturated aldehyde system **71**. The remaining carbon atoms of the enediyne unit were attached using a Castro-Stephens coupling[36] with the chloroenyne **70** and deprotonation of the acetylene of **71** with LHMDS effected cyclization to produce **72** along with its C-8 epimer (1:3 mixture) in a 42% yield (based upon 30% recovered starting material).



Scheme **15**. Kende's Synthesis of the Calicheamicin/Esperamicin Related Model **72**

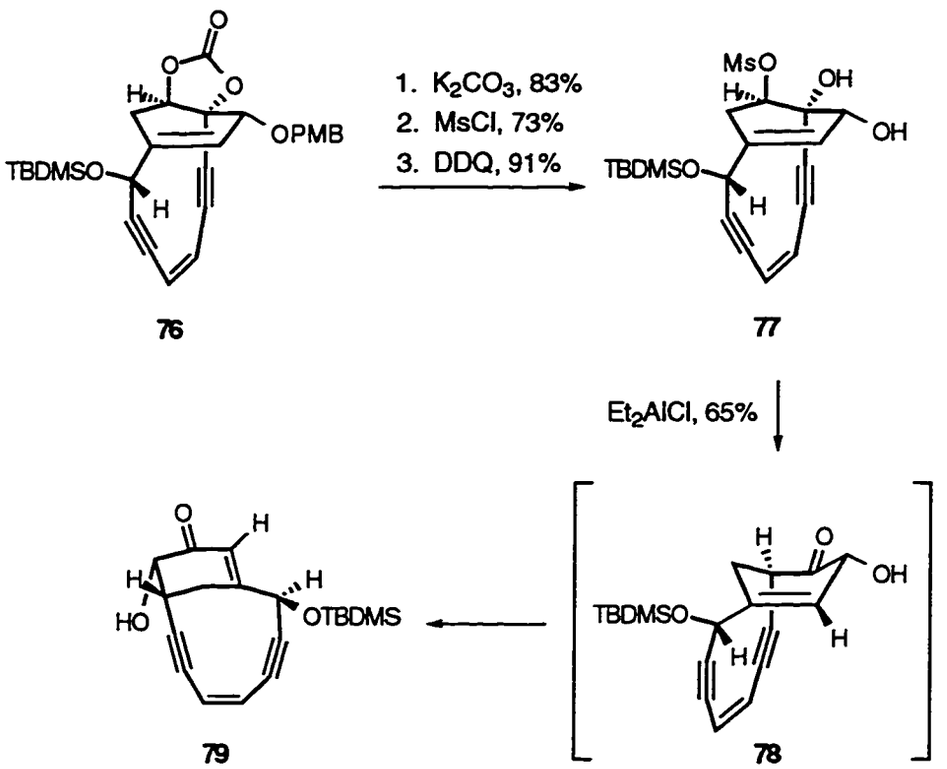
Schreiber's approach to the synthesis of the calicheamicin aglycone is conceptually different to those already discussed. His strategy involved an intramolecular Diels-Alder reaction to construct the bicyclic ring system in a single transformation.[37] Instead of annulation of the enediyne bridge onto a cylohexane-like precursor, Schreiber used the

enediyne moiety as a rigid chain to connect the diene and dienophile components. The bridgehead double bond is created during the Diels-Alder step and renders the cycloadduct thermally stable towards cycloaromatization (Scheme **16**). The precursor **73** which was constructed through a series of Pd(0) coupling steps was predicted to give the desired *meta* product **74** *via* a geometry imposed *exo* transition state. Unfortunately, heating in benzene selectively afforded the *para* adduct **75** (*para* with respect to the points of attachment of the enediyne bridge to the cyclohexene ring).



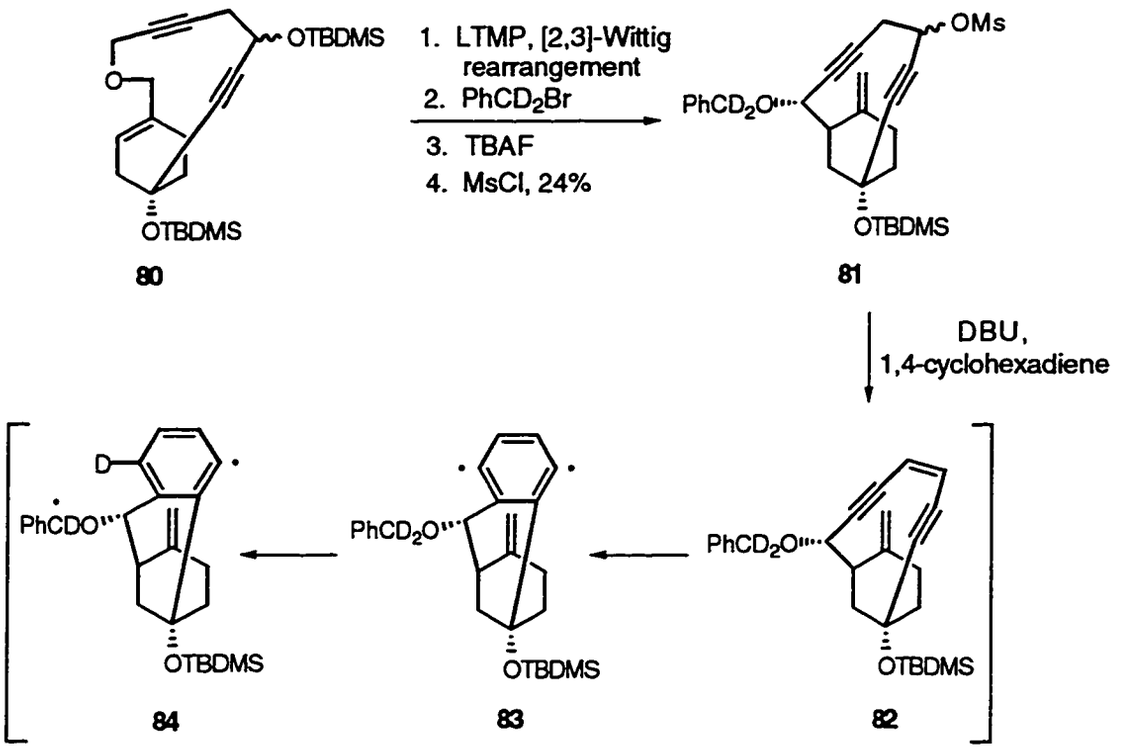
Scheme **16**. Schreiber's Intramolecular Diels-Alder Approach to the Calicheamicin/Esperamicin Model **75**

Schreiber corrected this outcome by converting another cycloadduct **76** to the mesylate **77** which then underwent an efficient Lewis acid promoted pinacol type rearrangement, giving the desired esperamicin ring skeleton **79** (Scheme **17**).[37c,38] This transformation was believed to proceed *via* the acyloin isomer **78**.



Scheme 17. Completion of the Synthesis by a Pinacol Type Rearrangement

In an imaginative approach to the strained, bicyclic core structures of calicheamicin and esperamicin, Grierson *et al.* envisaged the ring contraction of a larger, less strained system (Scheme **18**).[39] They prepared the 13-membered macrocyclic ether **80** and found that upon treatment with LTMP, compound **80** underwent [2,3]-Wittig rearrangement to provide the desired ring contracted product **81**. As anticipated by the calculated r_{cd} distance (3.20 Å, MMX), the *in situ* generated enediyne **82** cycloaromatized to the intermediate phenylene diradical **83** which then underwent 1,5-hydrogen translocation to give the diradical **84**.



Scheme **18**. Grierson's [2,3]-Wittig Approach to the Enediyne Core

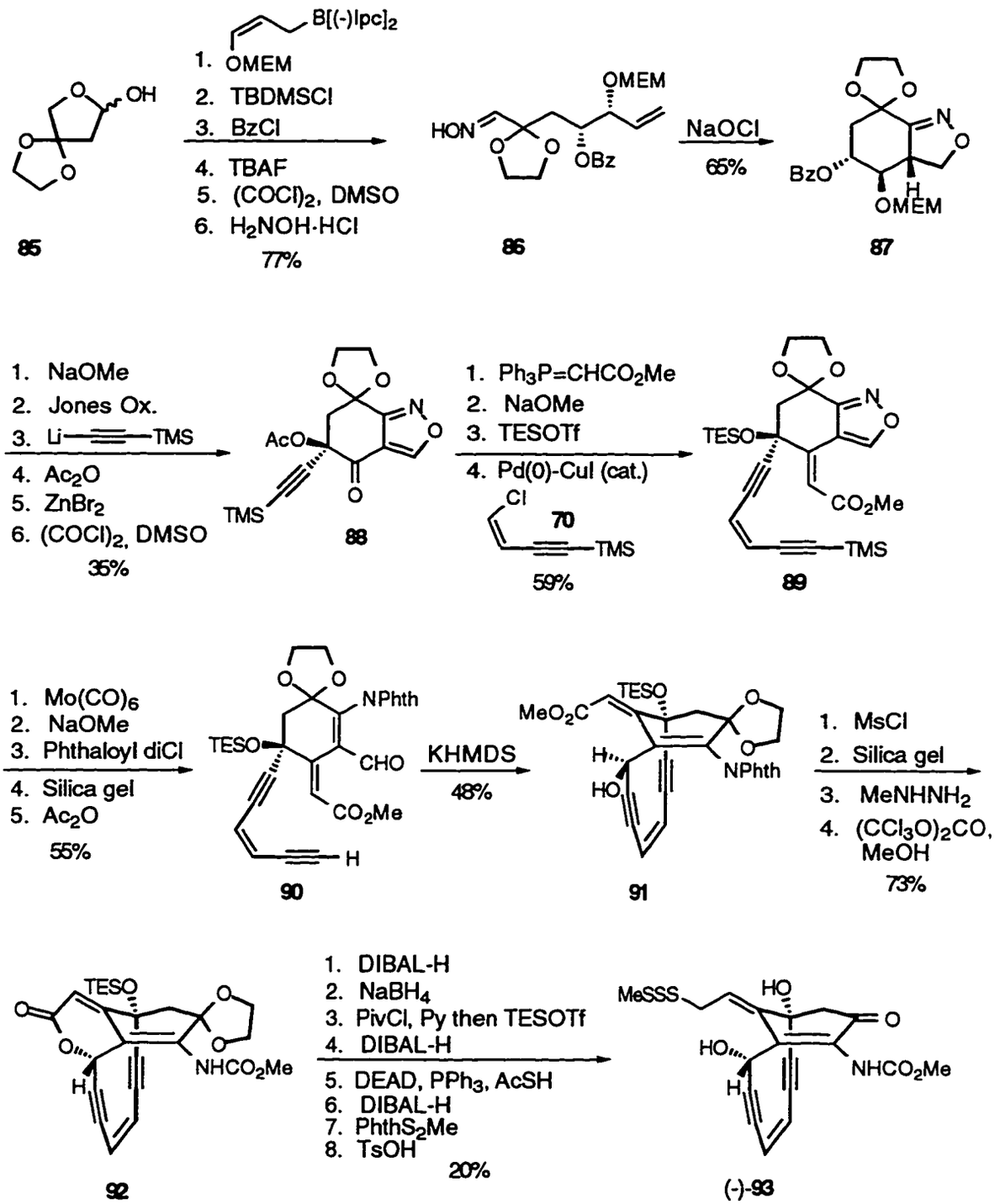
These examples represent only a fraction of the research efforts directed towards construction of both the natural enediyne antibiotics, calicheamicin and esperamicin, and novel enediyne analogues. Furthermore, only the key transformations and cyclization steps have been presented. The amount of work published in this area is, however, extensive.[20,21] For example, several total syntheses of calicheamicin have been reported, including Nicolaou's enantioselective route to both aglycon and glycon domains of calicheamicin γ_1^I.[40]

1.4.3 Enantioselective Total Synthesis of Calicheamicinone

Nicolaou's total asymmetric synthesis of calicheamicin γ_1^I represents an incredible accomplishment in the field of synthetic organic chemistry.[40h-j] This work involved development of strategies for the construction of the rigid bicyclic aglycon and the

oligosaccharide domain of the molecule. In the final stages, the two regions were coupled in a convergent manner. Only the synthesis of the core aglycon (-)-calicheamicinone will be highlighted here (Scheme **19**).[40i]

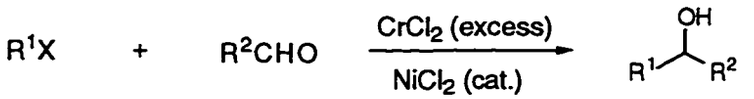
The addition of Brown's chiral allylborane reagent to the tetronic acid derivative **85** was used in the beginning of the synthesis to establish asymmetry. Further manipulation provided **86** in 77% yield (95% ee). Oxime **86** was oxidized to the corresponding nitrile oxide to afford **87** *via* an intramolecular [2+3] cycloaddition. This step enabled Nicolaou and coworkers to capture the urethane nitrogen and the C-8 hydroxy bearing centre of calicheamicin in a latent form within the newly formed dihydroisoxazole ring. Subsequent transformations including a stereoselective acetylide addition provided the keto-isoxazole **88**. The two precursor carbons to the allylic trisulfide were introduced by a Horner-Emmons reaction, giving **89** as a single geometrical isomer. A Pd(0)-catalyzed coupling with chloroenyne **70** introduced the enediyne moiety and reductive cleavage of the isoxazole ring with molybdenum hexacarbonyl then gave the vinylogous formamide which was protected as the corresponding phthalimide **90**. Ring closure of precursor **90** with KHMDS in toluene at -90 °C afforded a 9:1 mixture of alcohol **91** and lactone **92** in a combined yield of 48%. Alcohol **91** possessing the incorrect stereochemistry at C-8 was converted to its mesylate and treated with silica gel to afford the lactone **92**. Removal of the phthalimide with methylhydrazine gave the corresponding enamine which was converted to methyl carbamate **92** by treatment with triphosgene/pyridine followed by methanol. Reductive opening of the lactone and installation of the trisulfide moiety was then carried out following the chemistry developed by Danishefsky and Magnus.[40c,d,41] Finally, the ethylene ketal and the two silyl ethers were deprotected in one step with TsOH in aqueous THF, thus completing the first asymmetric synthesis of (-)-calicheamicinone **93**.



Scheme 19. Nicoloaou's Enantioselective Synthesis of (-)-Calicheamicinone

1.4.4 Intramolecular Nozaki-Kishi Reaction

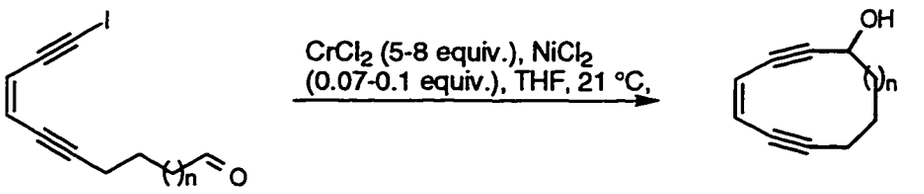
One particularly useful coupling strategy for the synthesis of enediyne systems has involved the use of chromium(II) chloride. This chromium(II)-based method was originally developed by Nozaki and Kishi for the intermolecular coupling of allylic, alkenyl or propargyl halides or triflates with aldehydes (Scheme **20**).[42,43] It involves treating the respective substrate with excess chromium(II) in either THF or DMF in the presence of catalytic amounts of nickel(II). The reducing power of chromium(II) salts is not as strong as with metals such as Li, Mg and Zn. As a result, this transformation is highly chemoselective and can be applied to a wide array of multifunctional substrates. Consequently, the Nozaki-Kishi reaction is a powerful method for C-C bond formation, especially in cases where conventional organometallic reagents are difficult to apply.



R^1 = allyl, alkenyl, propargyl, aryl
X = I, Br, OTf

Scheme **20**. Nozaki-Kishi Intermolecular Coupling Reaction

An intramolecular version of this coupling reaction has subsequently been used to effect the final key ring closure in a number of strained enediyne systems. Beau and Crevisy, for example, have used this coupling strategy to construct simple monocyclic 10- and 11-membered ring enediynes bearing a propargyl hydroxyl group (Scheme **21**).[44] The addition of iodinated aldehydes **94a-b** to a suspension of $CrCl_2$-$NiCl_2$ in THF produced the enediynes **95a-b** in 34% and 76% yield respectively.

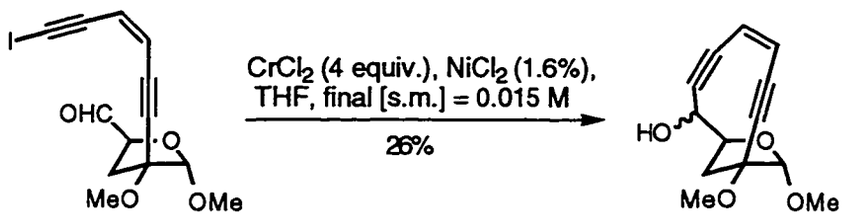


94a n = 1
94b n = 2

95a n = 1, 34%
95b n = 2, 76%

Scheme **21**. Beau's Construction of Monocyclic Enediynes

The highly strained oxabicyclo[7.2.1]enediyne **97** was also prepared using similar conditions.[45]

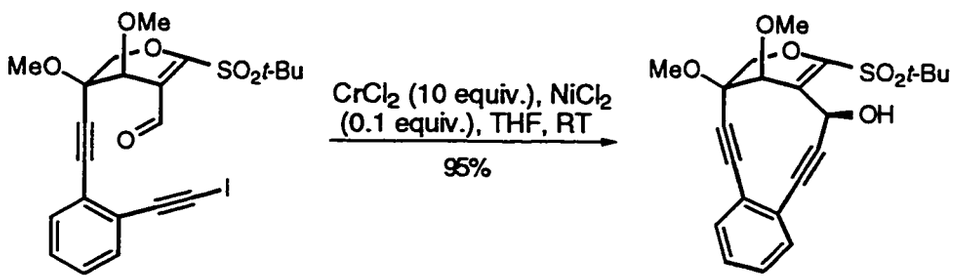


96 **97**

Scheme **22**. Nozaki-Kishi Coupling of the Strained Oxabicyclic System **97**

In these two examples, attempts at cyclization by intramolecular acetylide anion addition using LHMDS as a base proved unsuccessful, illustrating the effectiveness of this method when dealing with enolizable aldehydes.

Recent synthetic efforts towards more complex model enediyne systems have also relied on the chromium(II)-mediated cyclization as the key C-C bond forming step.[46] For example, Beau and coworkers have generated the novel [7.3.1] bicyclic model **99** as a single isomer in 95% yield (Scheme **23**).[47] The high efficiency and stereospecificity observed in this particular case underscores the power of this coupling reaction for the synthesis of strained ring systems.



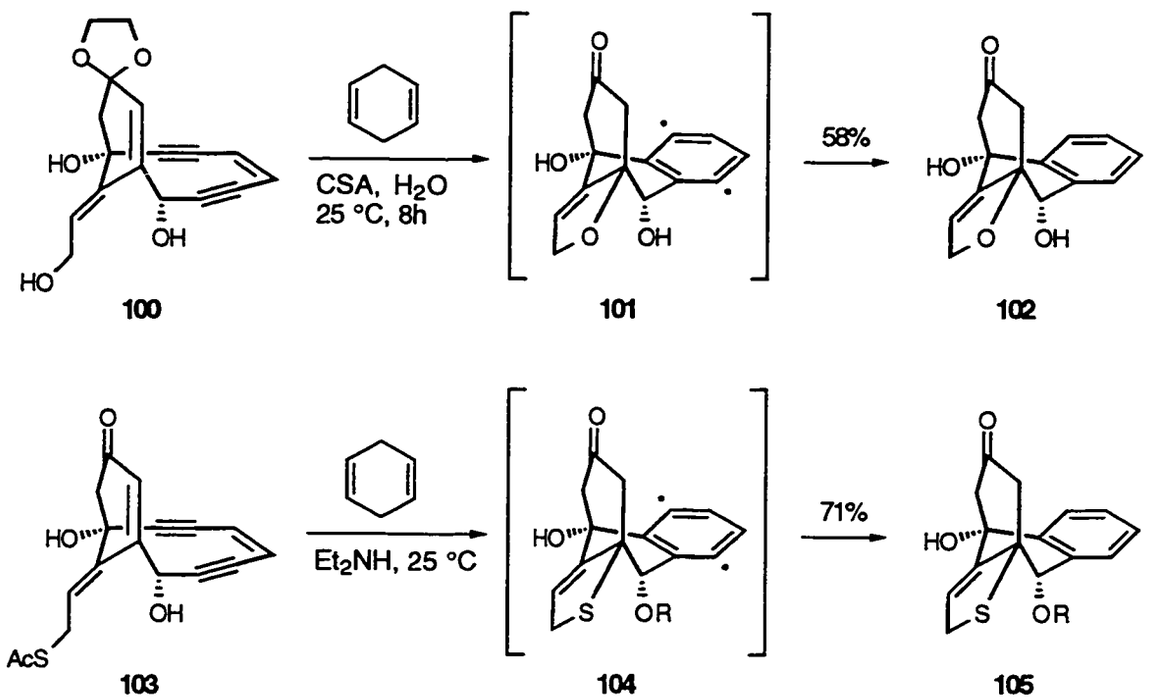
98 99

Scheme 23. Intramolecular Nozaki-Kishi Coupling of Enediyne Model 98

1.5 Activation of Model Enediyne Systems

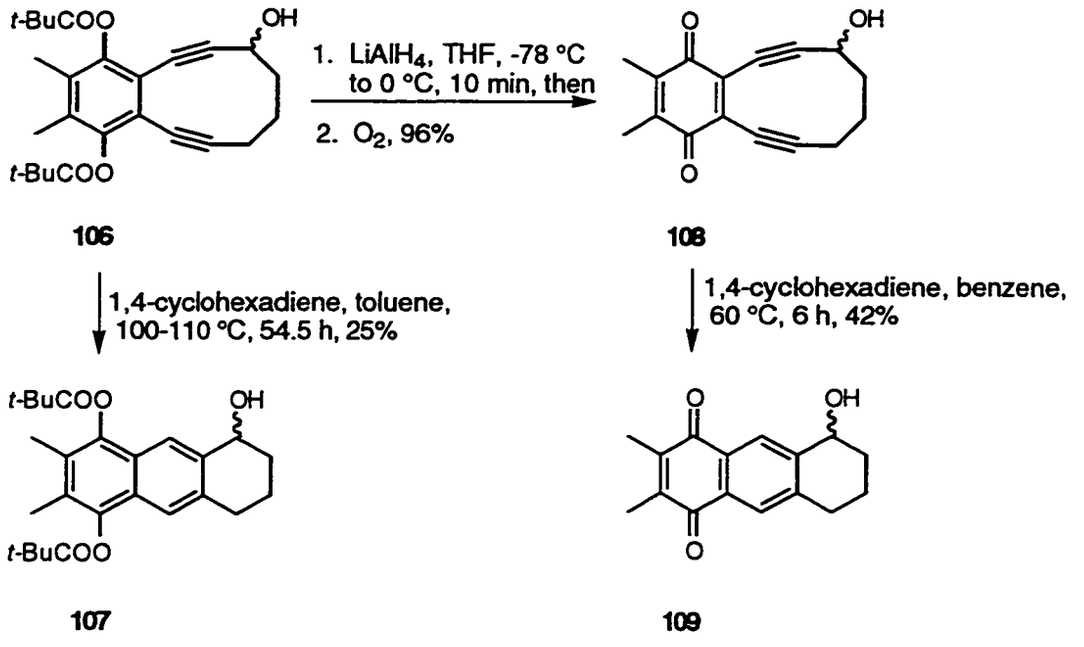
In addition to the synthesis of complex enediyne systems, there has been a great deal of effort directed towards both understanding and mimicking the mode of action of the naturally occurring enediyne antibiotics. The goal of these studies is to develop synthetic analogues for biological evaluation and to elaborate new conjugates for cell targeting.

Simulation of the calicheamicin/esperamicin cascade has been developed by Danishefsky and coworkers with a variety of compounds including analogues **100** and **103** (Scheme **24**).[48] This experimental modeling involved triggering the cycloaromatization reactions by intramolecular Michael addition. Treatment of compound **100** with camphorsulfonic acid in the presence of 1,4-cyclohexadiene gave a 58% yield of dihydrofuran **102**, presumably *via in situ* Michael addition by the proximal allyl alcohol. Similar treatment of enone thioacetate **103** with diethylamine gave dihydrothiophene **105** in 71% yield, again *via* intramolecular 1,4-thiolate addition to the double bond.[48a]



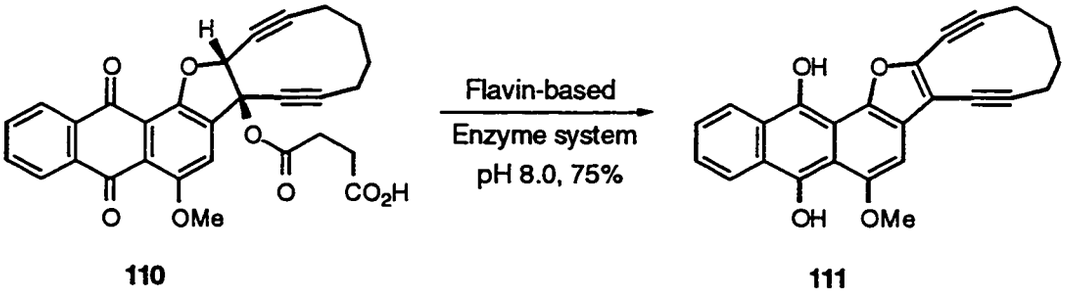
Scheme **24**. Cycloaromatization of Enediyne Analogues **100** and **103**

Nicolaou *et al.* have designed a different type of activation system in which the Bergman cyclization is controlled by a hydroquinone⇔quinone redox process (Scheme **25**).[49] It was anticipated that hydroquinone **106**, with its enediyne double bond incorporated in the aromatic ring, should be more stable towards cycloaromatization than the corresponding quinone **108**.[49,50] This postulate was verified by the measurement of the half-lives and the study of the DNA cleaving capabilities of these two compounds. The quinone **108** had a $t_{1/2}$ of 2.6 h at 55 °C and showed significant DNA damaging properties at a concentration of 0.5 μM, whereas hydroquinone **106** had a $t_{1/2}$ of 74 h at 110 °C and exhibited no DNA cleaving activity.



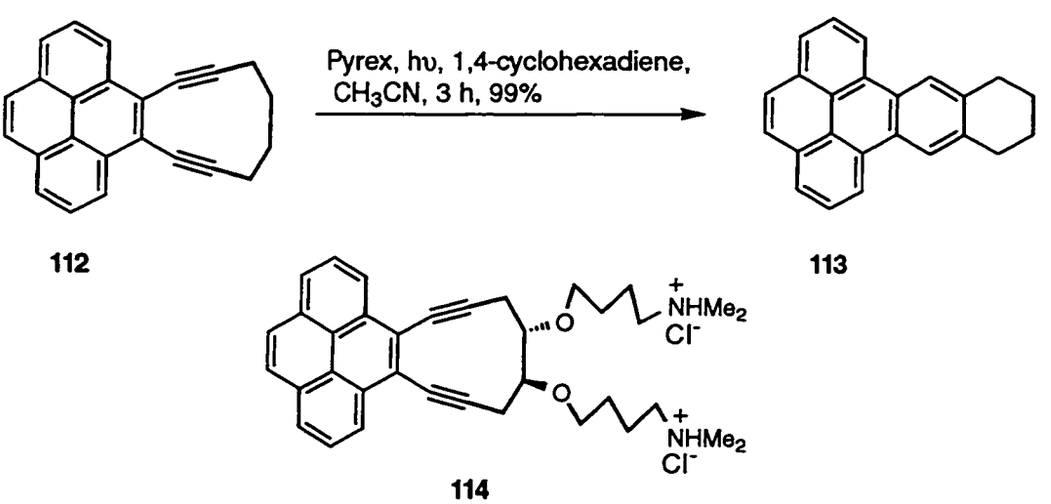
Scheme **25**. Control of Bergman Cyclization Through a Redox Process

A potentially powerful triggering device developed by Myers and Dragovich also involved activating an enediyne system through a redox process (Scheme **26**).[51] In this approach, they were able to generate the central double bond *in situ* from a stable hexa-1,5-diyne. Enzyme-mediated reduction of the anthraquinone **110** at pH 8.0 led to the elimination of succinic acid to give enediyne **111** which then slowly underwent the Bergman cyclization at 37 °C ($t_{1/2}$ = 2 days).



Scheme **26**. Enzyme-Mediated Activation of an Enediyne System

Recently, a novel class of enediyne compounds developed by Funk *et al.* has shown promise as a potential chemotherapeutic agent (Scheme **27**).[52] It was envisaged that *ortho*-dialkynylarenes such as **112** would intercalate into DNA and would be susceptible to photochemical, as opposed to thermal cycloaromatization, due to the planar nature of the π systems. In this manner, the binding and photoactive domains are consolidated within one functional domain. Indeed, the dialkylarene **112** underwent cycloaromatization upon irradiation in the presence of 1,4-cyclohexadiene. Furthermore, the water soluble dialkylpyrene **114** gave rise to single-strand DNA breaks at 20 μM concentration upon irradiation with a 450 W light source.



Scheme **27**. Photochemical Cycloaromatization of *ortho*-Dialkynylpyrene

The most extensive study of designed enediynes with potent and selective antitumour activity has been carried out by Nicolaou *et al.*[53] These relatively simple enediyne systems were developed to mimic the naturally occuring enediyne antibiotics, in particular dynemicin A (Figure **3**). They were equipped with locking and triggering devices which allowed for both *in vitro* and *in vivo* activation by chemical or biological

means. Furthermore, they were provided with tethering devices to attach ligands to aid in delivery to DNA and deactivators to modulate the reactivity of the enediyne system.

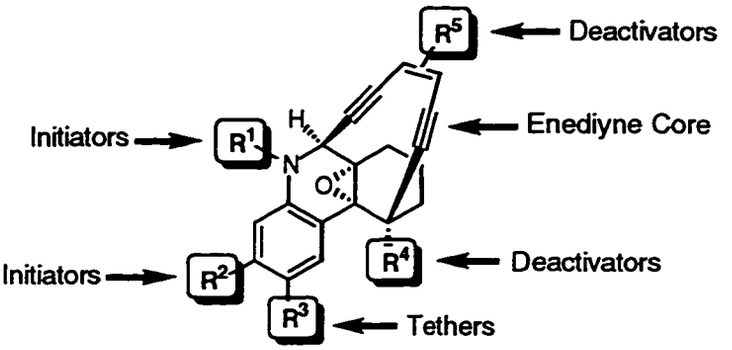
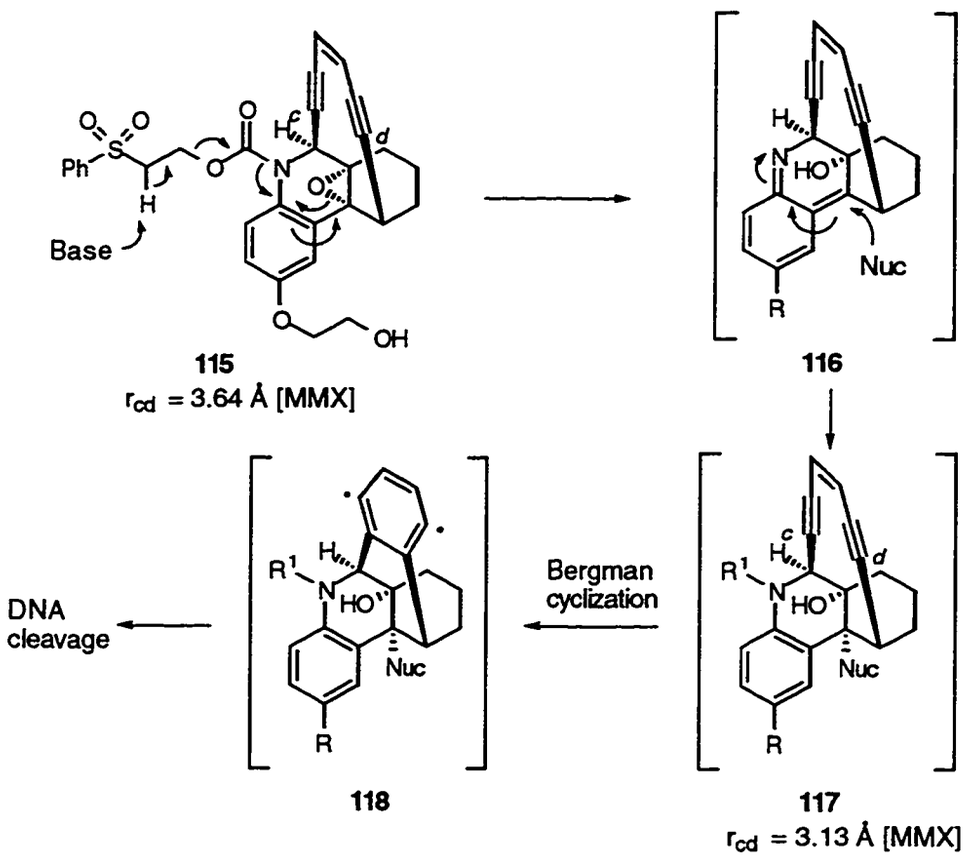


Figure 3. Nicolaou's Designed Enediynes

The phenylsulfone **115** represents one of the designed enediynes constructed and tested for biological activity. This compound exhibited noticeable DNA cleaving activity at pH values greater than 7.0 and displayed cytotoxicities against a variety of different cancer cell lines at concentrations as low as 10^{-14} M. The mode of action of this impressive analogue presumably involves β-elimination of the phenylsulfone ethylene carbamate moiety under mild basic conditions, and opening of the epoxide to form the reactive species **116** (Scheme **28**). Nucleophilic attack gives *cis*-opened intermediate **117** which leads to a shortening of the inner acetylenic *cd* distance based on molecular mechanics calculations. The *cd* distance in the locked epoxide sytem **115** is shortened considerably from 3.64 Å to 3.13Å in the *cis*-opened product **117**, an event which allows the Bergman cyclization to proceed spontaneously at ambient temperature. The formation of the benzenoid diradical **118** leads to DNA cleavage and subsequent cell death.



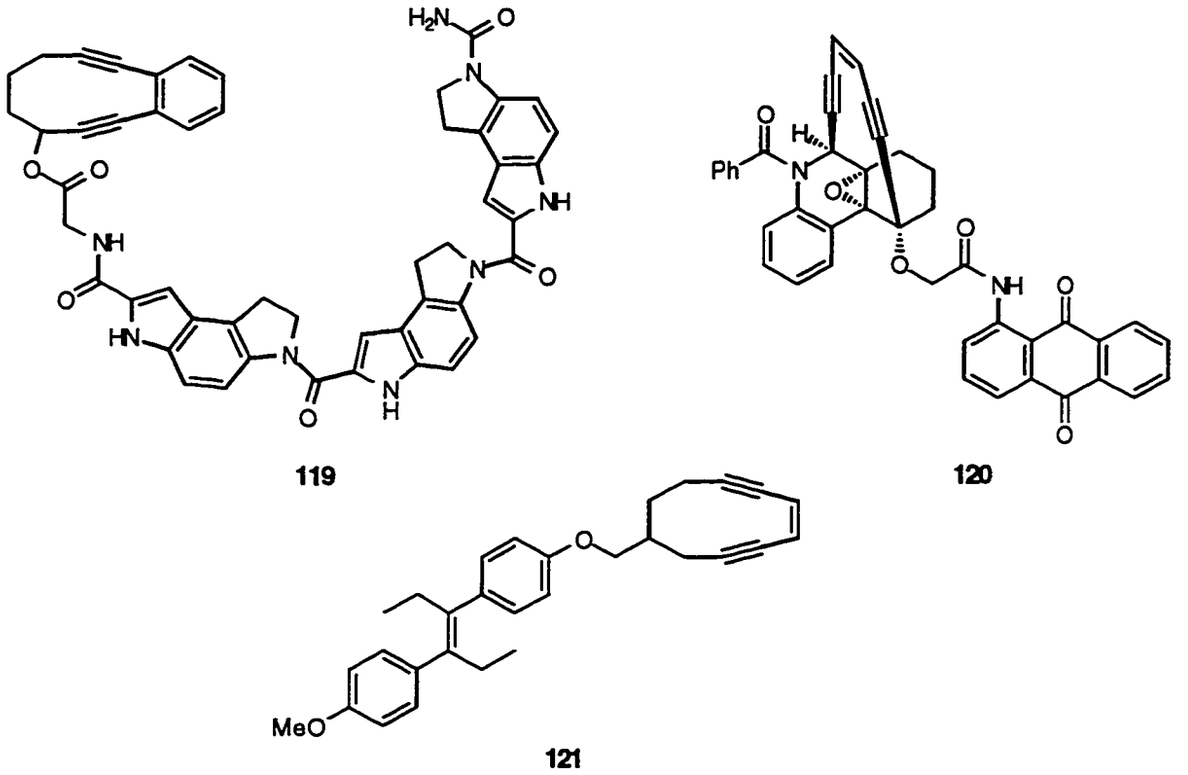
Scheme **28**. Postulated Mechanism of Action of Designed Enediyne **115**

The results obtained from these studies have helped in understanding the mechanism of action of the enediynes. They have also allowed for further developments in the area of drug design, to create new leads for cancer chemotherapy.

1.6 Hybrid Enediyne Compounds

Already a number of conjugated enediynes have been designed with the aim of generating new potential antitumour drugs (Figure **4**). These "hybrids" have been constructed in order to attach delivery systems to improve the DNA affinity and selectivity. Boger, for example, has attached a simple 10-membered ring enediyne to the minor groove DNA binding agent, $CDPI_3$, to give the corresponding conjugate **119**.[54] Similarly, Nicolaou has linked the intercalating anthraquinone moiety to one of his synthetic enediyne

systems to create **120**.[2] Jones and coworkers have coupled a bioactive cyclic enediyne with a phenolic estrogen mimic in order to encourage selective accumulation of the drug in estrogen responsive tumours by facilitating transport into these cells.[55] The enediyne conjugate **121** was found to cause significant DNA strand scission at 10^{-3} M and has demonstrated cytotoxicity against the estrogen receptor rich human breast cancer cell line.



119 **120**

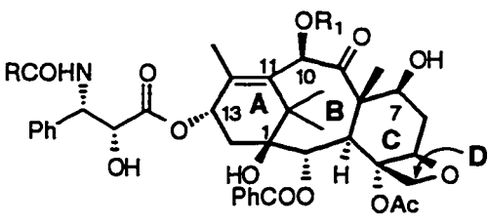
121

Figure 4. Hybrid Enediyne Systems

1.7 The Taxane Anticancer Agents

1.7.1 Structure and Activity

Taxol® **122** and Taxotere® **123** are two antitumour drugs completely unrelated to the enediyne antibiotics (Figure 5). These drugs have shown great promise as antineoplastic agents and are currently being used to treat both breast and ovarian cancer.[56]



122 Taxol®, R = Ph, R_1 = Ac
123 Taxotere®, R = *t*-BuO, R_1 = H

Figure 5. Taxane Anticancer Agents

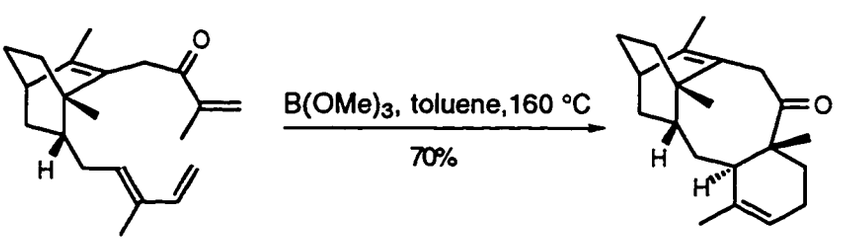
The mode of action of the taxane drugs is different in that it does not cleave DNA as in the case of the enediyne compounds. Instead, Taxol® and Taxotere® function by binding to and interfering with the microtubules, an important intracellular component required for the normal regulation of the cell cycle.[56b,57-58] The microtubules are in a dynamic equilibrium with tubulin dimers, their basic protein subunits. The modification of this equilibrium can disrupt cell mitosis and result in cell death. Classical antimicrotubal agents such as colchicine and podophyllotoxin are known to function by inhibiting the assembly of microtubules.[59] Taxol® and Taxotere®, on the other hand, promote assembly and act as a type of "molecular glue". The action of these drugs causes the microtubules to polymerize and bundle irreversibly, resulting in cell death.

Taxol® (paclitaxel) is a natural product isolated from the bark of the Pacific yew *Taxus brevifolia.* Unfortunately, it has become impractical to rely on the yew tree as the sole source of Taxol® due to the low concentrations present.[60] A semisynthetic approach to the analogue Taxotere® has however been developed to meet the growing demands for this drug.[61] Taxotere® is different from Taxol® in that it possesses an N-*t*-butoxycarbonyl group in the side chain (C-13) and a hydroxy group at the C-10 position. These structural changes give Taxotere® greater water solubility and higher cytotoxicity than Taxol®.[56b,61] Numerous taxane analogues have also been prepared in an attempt to uncover new compounds with even more potent activity and fewer side effects than Taxol®.[62]

The synthesis of Taxol® and Taxol® analogues has proven to be difficult due to the unusual structural features that this molecule possesses. This diterpene consists of a highly oxygenated tricyclic[9.3.1.$0^{3,8}$]pentadecene ring system. Other structural characteristics include the A ring bridgehead double bond, an unusual oxetane D ring and the eight-membered B ring which possesses a *gem* dimethyl group projecting into its centre. These features contribute to a sterically congested and highly strained molecule and make its synthesis particularly challenging. There are currently over 30 research groups engaged in the synthesis of Taxol® and Taxol® analogues and, to date, only three groups have completed its total synthesis.[63] Due to the incredible volume of work published in this area, only a fraction of the work reported will be highlighted here. Furthermore, only the key steps towards construction of the ABC taxane framework will be presented.

1.7.2 Synthetic Approaches to the Taxane Skeleton

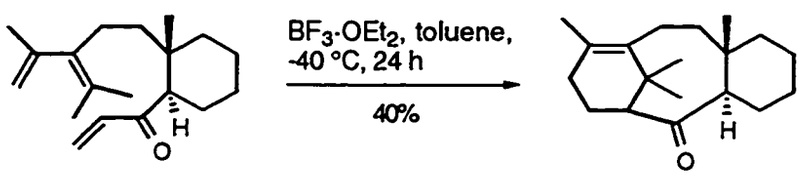
A popular route to the taxane skeleton has involved using an intramolecular Diels-Alder cycloaddition. One of the earliest attempts was carried out by Sakan and Craven who constructed the rigid bicyclo[2.2.2]octene precursor **124** (Scheme **29**).[64] This bicyclic framework was required to hold the diene and dienophile in close proximity to achieve proper alignment for cycloaddition to occur.



124 **125**

Scheme **29**. Sakan's Diels-Alder Approach to Taxane Skeleton

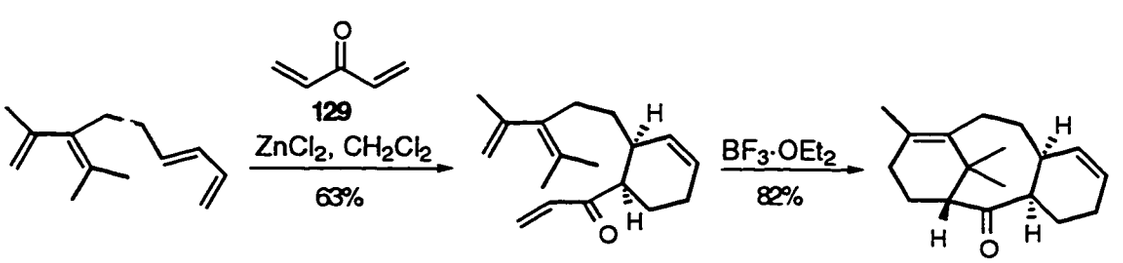
Similarly, Shea and Jenkins have independently generated the tricyclic taxane nucleus, with the bridgehead A ring double bond in place, by applying another intramolecular version of the Diels-Alder reaction. In their approach, a preformed C ring precursor **126** was used as the cyclization precursor (Scheme **30**).[65]



126 **127**

Scheme **30**. Jenkins' Diels-Alder Approach to Taxane Skeleton

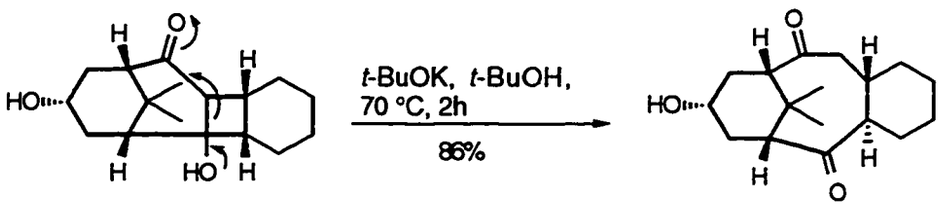
Winkler has taken this concept one step further and has used a tandem Diels-Alder sequence to generate the taxane nucleus in a highly stereoselective, two-step synthesis, starting from the readily available acyclic precursors **128** and **129** (Scheme **31**).[66]



128 **130** **131**

Scheme **31**. Winkler's Tandem Diels-Alder Strategy

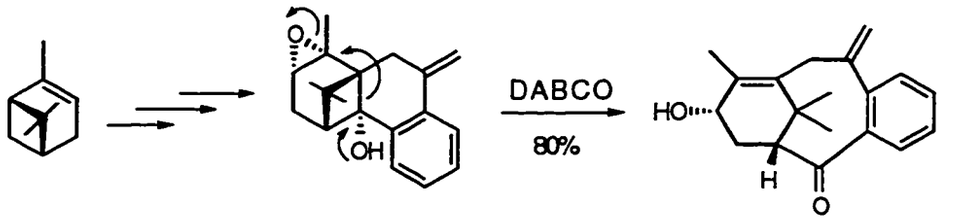
An approach based on a retroaldol type fragmentation and oxidative ring expansion has been used by Blechert *et al.* in the synthesis of a number of taxoids (Scheme **32**).[67] Substrate **132**, derived from an intermolecular [2+2] photocycloaddition reaction, afforded the tricyclic model **133** in good yield after treatment with base.



132 133

Scheme 32. Blechert's Construction of the Taxane Nucleus by Retroaldol Cleavage

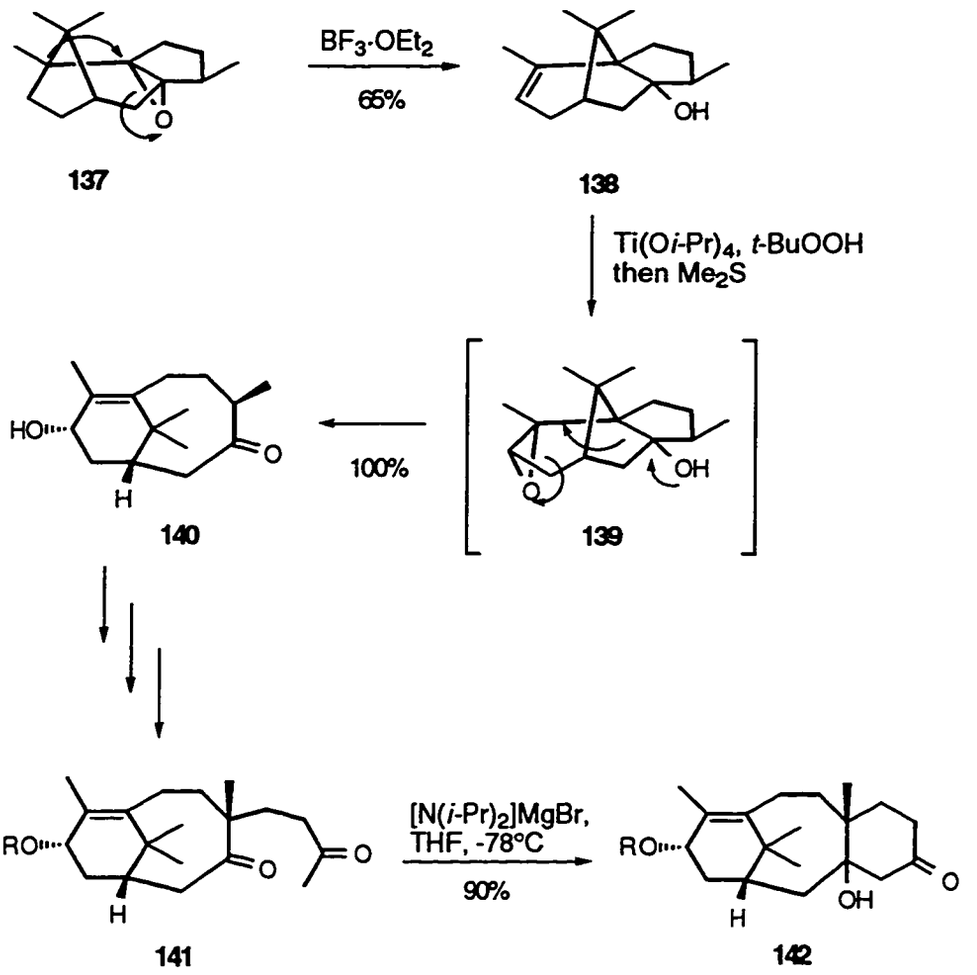
Another elegant base-induced fragmentation approach to the taxane skeleton has been reported by Wender (Scheme 33).[68] Treatment of hydroxyepoxide **135** with base induced ring expansion to give the desired tricycle in a 80% yield. An attractive feature of this strategy is that it used the cheap and readily available (+)-pinene **134** as a starting material.



134 135 136

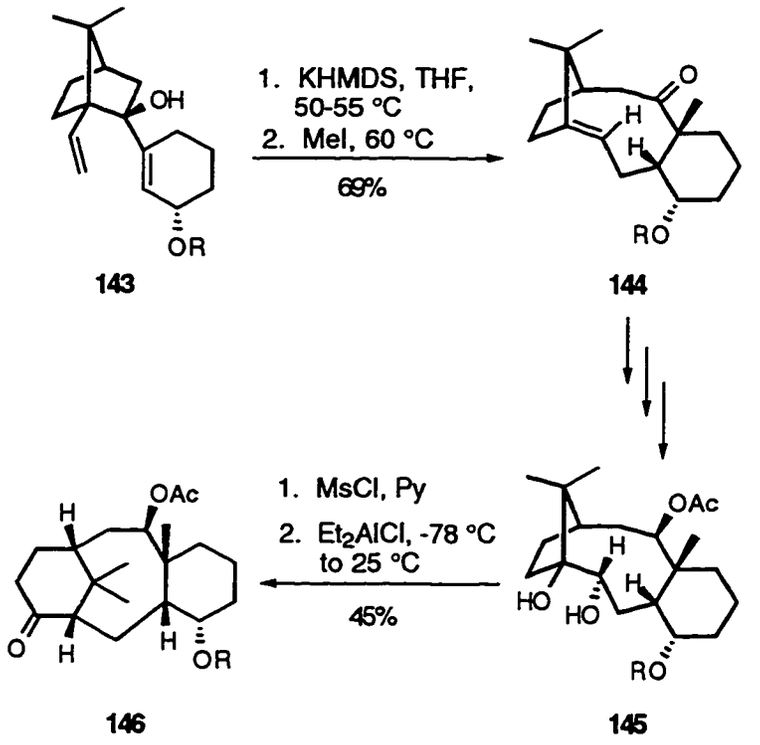
Scheme 33. Wender's Fragmentation Route to the Taxane Tricycle

Holton and coworkers laboratory have completed the total synthesis of Taxol® using the hydroxyepoxide fragmentation of (+)-β-patchoulene oxide as a key step.[63a,b] In the study of an early model system **142**, the commercially available and optically active (-)-β-patchoulene oxide **137** was treated with Lewis acid and the resulting hydroxy alkene **138** was epoxidized to give **140** (Scheme 34).[69] An intramolecular aldol condensation of **141** then provided the ABC ring system.



Scheme 34. Holton's Fragmentation Approach to the Taxane Skeleton

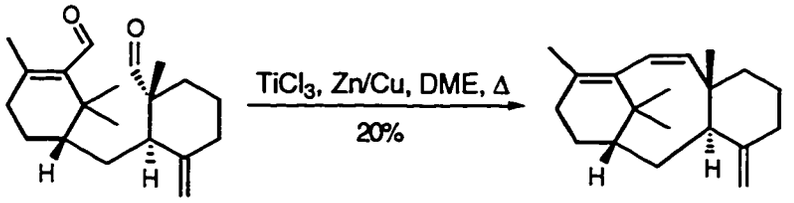
Paquette has reported an anionic oxy-Cope rearrangement route to the taxol nucleus (Scheme 35).[70] Treatment of **143** with base gave the rearrangement product **144** which was further elaborated to **145**. Pinacol type rearrangement of **145** afforded the tricyclic framework.



143 144 146 145

Scheme 35. Paquette's Oxy-Cope Rearrangement Approach to Taxol® Skeleton

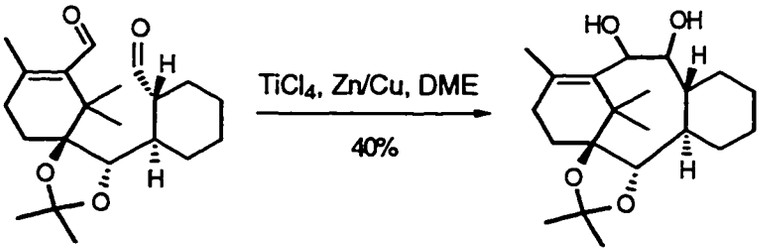
Several approaches towards taxoids have relied on a McMurry type intramolecular, reductive pinacol coupling reaction (Scheme 36). Kende, for example, has used this reaction as the key step in forming the eight-membered B ring from the dialdehyde **147**.[71]



147 148

Scheme 36. Kende's Approach to the Taxane Skeleton by Intramolecular McMurry Cyclization

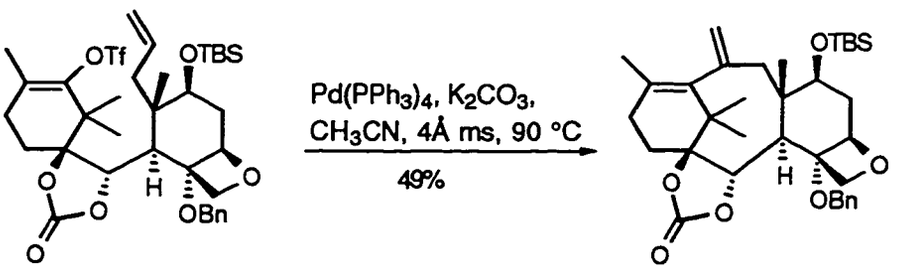
The Nicolaou group has also applied this intramolecular coupling strategy to their syntheses of Taxol® and Taxol® analogues (Scheme 37).[63c,72] Intramolecular pinacol type coupling within **149** gave the diol **150**.



149 150

Scheme 37. Nicolaou's Use of an Intramolecular Pinacol Coupling

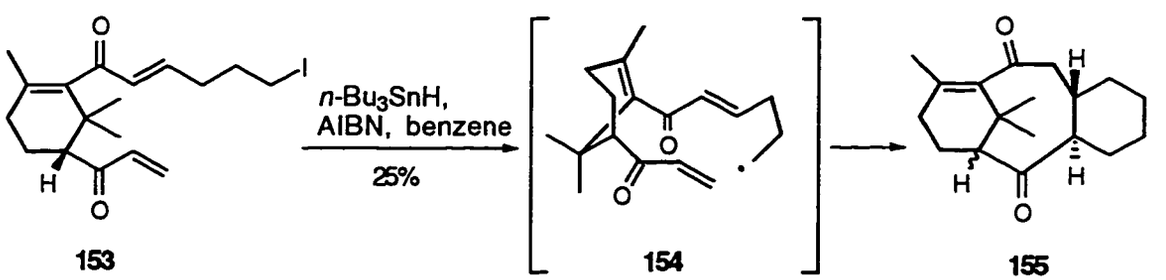
In Danishefsky's total synthesis of Taxol®, an intramolecular Heck ring closure was employed to form the B ring late in the synthesis (Scheme 38).[63d]



151 152

Scheme 38. Danishefsky's Intramolecular Heck Ring Closure towards Synthesis of Taxol®

Pattenden's radical-based approach using a simple cyclic iodoalkane has also proved successful in preparing the ABC ring skeleton (Scheme 39).[73]

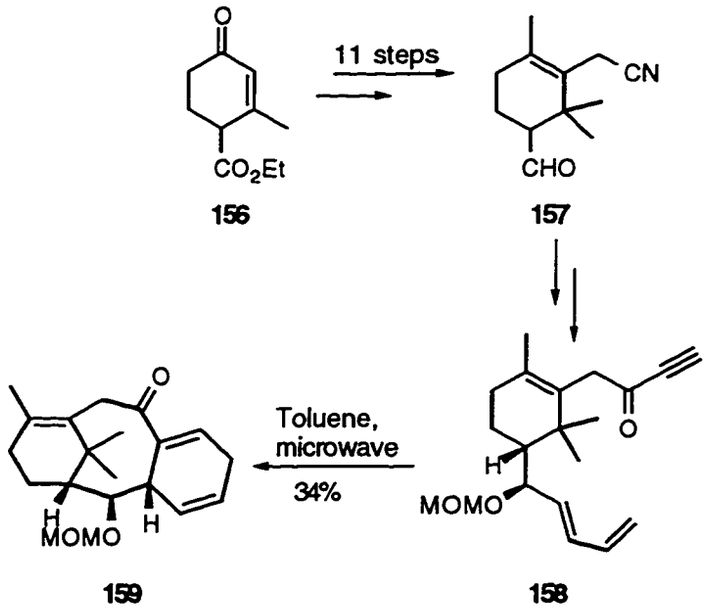


153 154 155

Scheme 39. Pattenden's Tandem Radical-Based Intramolecular Ring Closure

These examples represent a few of the routes used towards the construction of the taxane tricyclic framework. The Fallis laboratory has similarly been interested in developing strategies towards the synthesis of this structurally complex system.

A popular approach to the synthesis of Taxol® has been to use an intramolecular Diels-Alder reaction as the key ring forming step.[64-66] Fallis and coworkers have successfully employed this strategy to assemble simultaneously the B and C rings of the tricyclic framework (Scheme **40**).[74] The microwave assisted intramolecular cycloaddition of precursor **158** provided the cyclized adduct **159** in a 34% yield. The success of this approach relied on attaching the diene and dienophile components to the cyclohexene intermediate **157**, which was prepared in an 11 step sequence from commercially available Hagemann's ester **156**. Aldehyde **157** served as an important A ring building block en route to the desired taxane nucleus.



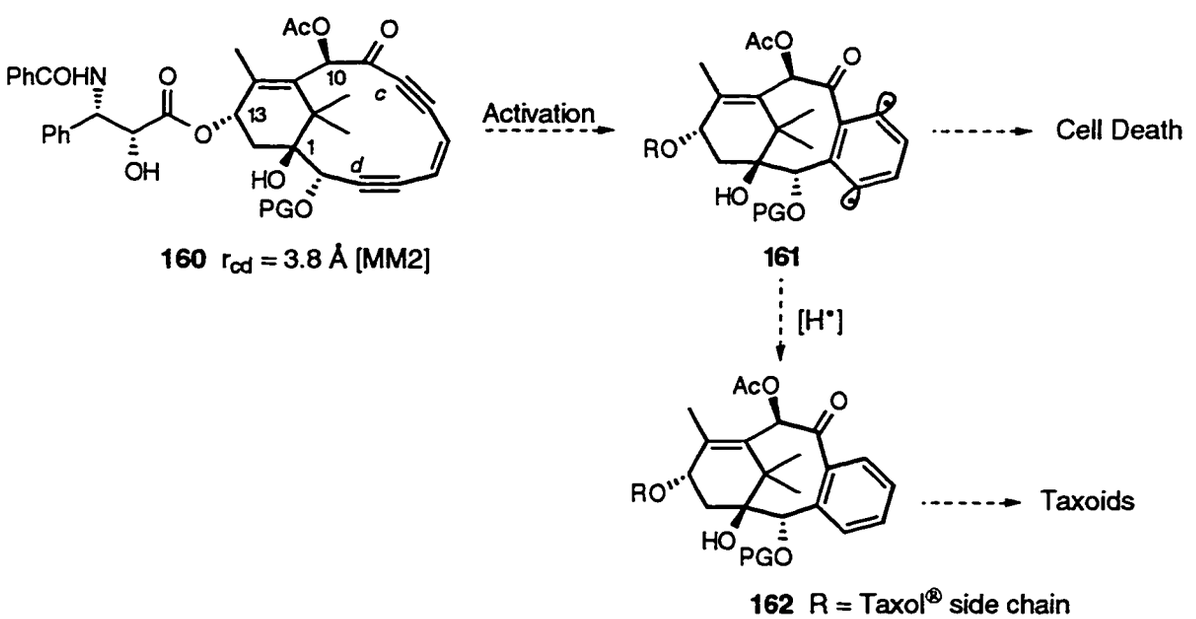
Scheme **40**. Fallis' Intramolecular Diels-Alder Route to Taxane Nucleus

The interest in Taxol® synthesis, combined with the growing popularity of enediyne chemistry, gave rise to a new approach to construction of the taxane nucleus by means of a Bergman cycloaromatization.

1.8 Research Objectives

1.8.1 A Novel Approach to the Taxane Nucleus

Initially, the goal of this study was to combine the important structural features of Taxol®, such as its A ring components, with aspects of enediyne chemistry in a novel, synthetic approach to the 6-8-6, tricyclic taxane skeleton (Scheme **41**). The Bergman cycloaromatization of a 12-membered, bicyclic enediyne compound would lead to an aromatic version of this ring system, as illustrated by the conversion of **160** to **162**. The construction of **160** was envisaged by attaching the enediyne unit to an A ring building block such as **157**.



Scheme **41**. Enediyne Chemistry as a Route to the Taxoids

The preparation of this particular system appeared worthwhile since aromatic taxanes such as **162** have been prepared and used in studies towards the total synthesis of Taxol®.[68,75] Furthermore, similar aromatic C ring taxanes have recently displayed some interesting biological activity.[62h]

1.8.2 The Taxamycins: A New Family of Enediyne Compounds

In addition to serving as a potential route to the taxoids, bicyclic enediyne systems of this type might also provide new lead compounds with interesting activity. With the appropriate functionality in place, it was anticipated that these compounds might associate with tubulin inside the cell. For example, it has been shown that the C-13 Taxol® side chain may be attached to modified nuclei with retention of respectable tubulin activity.[62h,67b,76] In addition, if equipped with an appropriate cycloaromatization trigger, these systems should aromatize and result in DNA or related damage in a manner similar to the mode of action exhibited by the naturally occurring enediyne antibiotics. These compounds are therefore doubly "armed" or activated towards the destruction of cancer cells.

Consequently, a new family of potential, biologically active agents was conceived. These compounds incorporate structural features from both Taxol® and the enediyne antibiotics and, as a result, are labeled "taxamycins" (Figure **6**).[77] The structure **160** is representative of this new family of hybrid molecules, but many variations are possible depending on ring size and substitution pattern. Each member is characterized by a number, where the number represents the size of the largest ring containing the enediyne unit. Structure **160**, for example, represents the parent taxamycin-12 ring system, which would provide the taxane skeleton upon cycloaromatization.

The taxamycins would be used to examine the factors responsible for Bergman cyclization, including the effects of ring size. They would also allow for the investigation of different triggering processes, with the aim of developing a system which could be activated under relatively mild, physiological conditions.

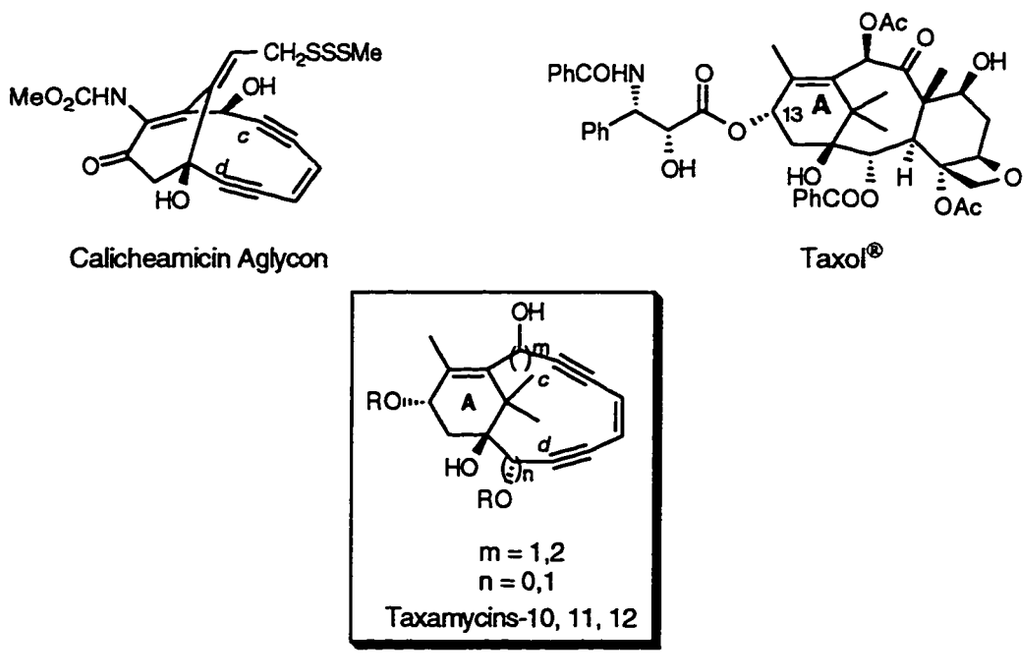


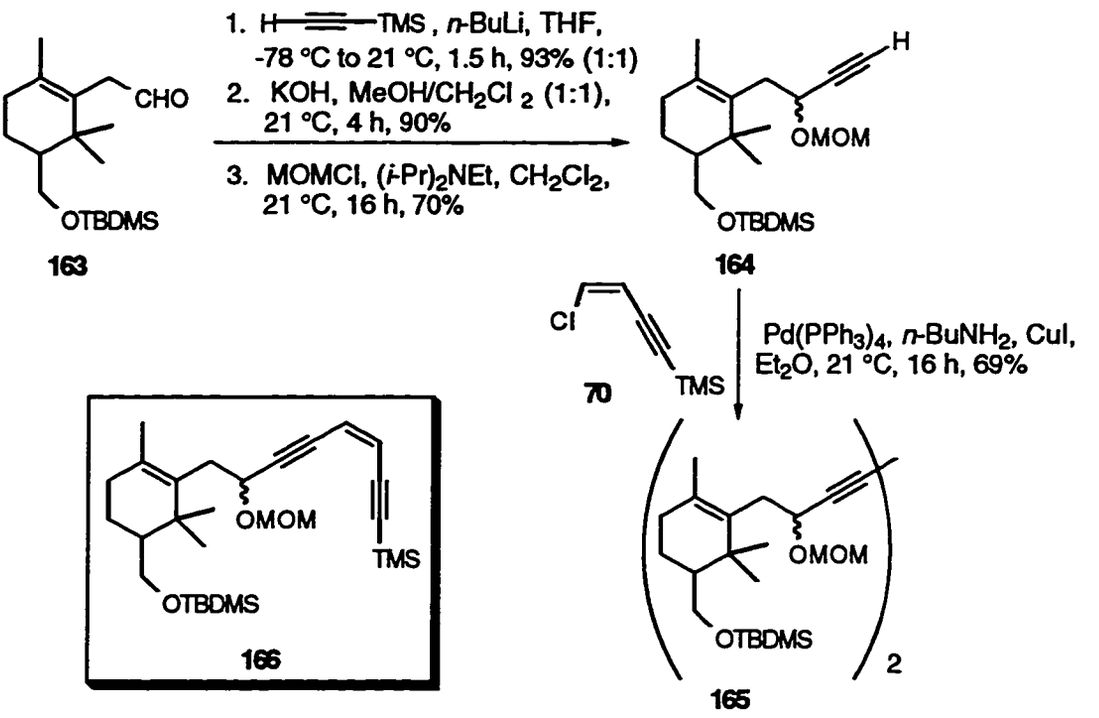
Figure 6. The Taxamycins: A New Family of Enediyne Compounds

In order to generate these taxamycin model systems, a practical method of incorporating the enediyne unit onto the A ring molecules was required. Hence, a versatile enediyne building block which could be used to construct different enediyne systems was developed. This enediyne synthon was coupled to different "platform" building blocks using various bond construction strategies in order to synthesize some novel bicyclic enediyne compounds in a rapid and convergent approach.

2 Synthetic Approaches to Enediyne Models

2.1 Construction of an Enediyne Synthon

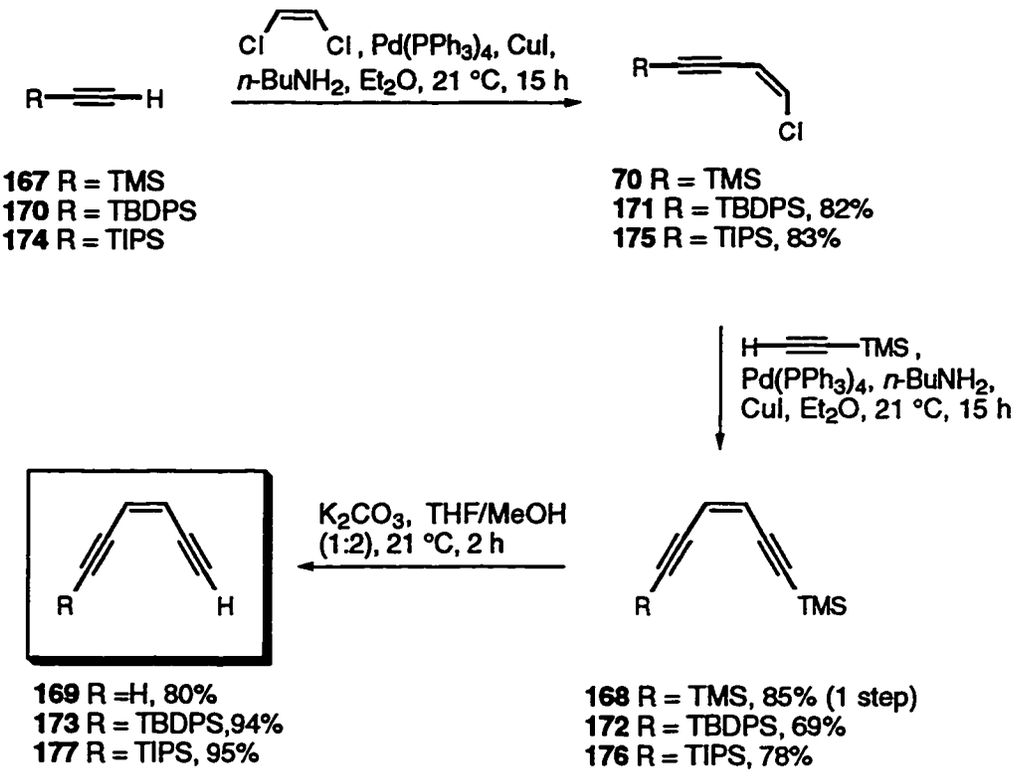
Initial efforts by Dr. Yee-Fung Lu to incorporate the enediyne moiety onto a model A ring aldehyde involved using the classical stepwise approach which has been employed by others to construct similar systems.[34,40i,46b,53c,d,78] This sequence involves adding lithium acetylide to a carbonyl group and building up the enediyne unit using the Pd(0)-catalyzed chemistry developed by Sonogishira.[29,79] In this initial study, lithium (trimethylsilyl)acetylide was condensed with the aldehyde **163** to afford the corresponding alcohol as a 1:1 mixture of diastereomers (Scheme **42**).[74b] The trimethylsilyl group was removed with potassium hydroxide at room temperature and the secondary alcohol protected as its methoxymethyl ether to provide alkyne **164** in good yield. Unfortunately, the Pd(0)-CuI mediated coupling with chloro (*Z*)-enyne **70** failed to give the desired enediyne **166** and instead afforded dimer **165** in 69% yield. Attempts to first attach *cis*-1,2-dichloroethylene to **164**, again resulted mainly in dimerization. This result was surprising since identical conditions (concentration, solvent, reaction temperature *etc.*) have been used in other systems to successfully effect coupling with enyne **70**.[34,53c,d]



Scheme **42**. Early Attempted Stepwise Incorporation of Enediyne Unit

In order to circumvent this problem, a versatile, preconstructed enediyne building block which could be used in the preparation of various systems was desired. The construction of such an enediyne synthon relied on two successive Pd(0)-based coupling steps (Scheme **43**). This Pd(0)-catalyzed method has had a major impact in the area of enediyne chemistry and has been used extensively to assemble the enediyne motif under operationally simple, mild and high yielding conditions.[20,80] Danishefsky and coworkers initially made use of this sequence to generate the parent compound **169** where R = H.[32a] The dilithio derivative of **169** was used to insert the enediyne chromophore into their calicheamicin/esperamicin model as described in section **1.4.2.**[32b] However, this reagent is volatile, difficult to handle and cannot be stored for long periods of time, even at low temperature. It was therefore expected that an enediyne unit with two different protecting groups could be prepared by changing the nature of the R groups on the acetylenic ends.

The selective removal of one of these groups would result in a more stable enediyne building block which would be easier to handle.



Scheme **43**. Construction of Enediyne Synthons

Initial attempts to incorporate two different elements at the terminal acetylenic positions, such as silicon and tin, were disappointing and the coupling of *cis*-1,2-dichloroethylene to tributyltin acetylene[81] with catalytic $Pd(PPh_3)_4$ and CuI resulted only in decomposition of starting material.[82] Enediyne compounds **172** and **176**, possessing two different silyl protecting groups, were then examined as potential synthons. The *t*-butyldiphenylsilyl derivative **172** was initially elaborated in good overall yield (53%), although the starting (*t*-butyldiphenylsilyl)acetylene **170** is not commercially available and had to be prepared from lithium acetylide and *t*-butyldiphenylsilyl chloride. As a result, this sequence proved longer and lower yielding than in the subsequent triisopropylsilyl case. Furthermore, silica gel chromatography could not remove silicon impurities from the

t-butyldiphenylsilyl enediyne **173** after removal of the trimethylsilyl group. These difficulties led to the preparation of the triisopropylsilyl derivative **177**.

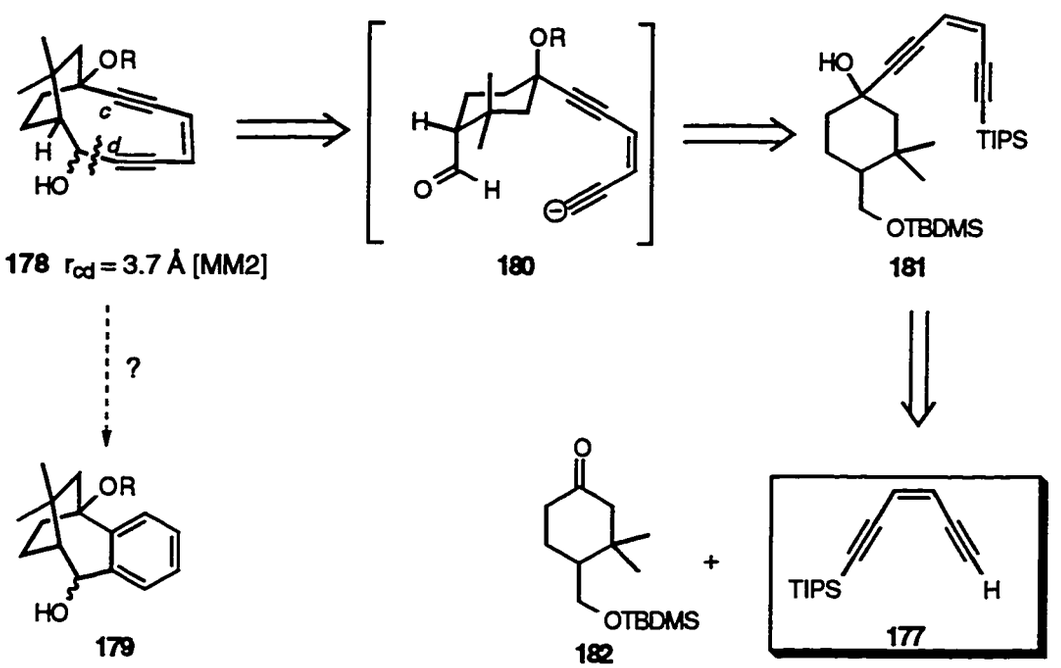
The triisopropylsilyl protected enediyne **177** proved to be the ideal synthon. The starting (triisopropylsilyl)acetylene reagent was purchased from Aldrich and repetitive Pd(0)-CuI based coupling, first with *cis*-1,2-dichloroethylene and then with (trimethylsilyl)acetylene, afforded rapidly the (Z)-1-triisopropylsilyl-6-trimethylsilyl-3-hexene-1,5-diyne **176** in a 65% yield for the two steps. The steric bulk of the triisopropylsilyl protecting group allowed for the selective removal of the trimethylsilyl group using K_2CO_3 in MeOH/THF (2:1). This result was based on the fact that the rates of base-induced cleavage of silylalkynes depend upon the relative steric bulk of the groups involved [relative rates: Et_3Si (1), Ph_3Si (12), $EtMe_2Si$ (49), Me_3Si (277)].[83] The release of the trimethylsilyl group from **176** afforded the desired enediyne building block **177** in 95% yield. The monoprotected enediyne **177** has a relatively long shelf life and can be stored in the fridge for several weeks without need for further purification.

2.2 Synthesis of Enediyne Model Systems

2.2.1 Enediyne Model for Approach to Taxane Framework

The addition of the enediyne synthon **177** to various carbonyl-containing precursors was performed in order to examine the feasibility and generality of **177** as a building block (Scheme **44**). This plan would provide bicyclic enediyne systems such as **178** in a rapid and convergent manner. Compound **178** was chosen as an inital target since the ketone **182** could be prepared in four expeditious steps from cheap and commercially available Hagemann's ester. The model **178** possesses a *gem* dimethyl group, a structural feature present in Taxol®. Furthermore, the interacetylenic *cd* distance within **178** was calculated to be 3.7 Å by molecular mechanic calculations.[84] This value is similar to the r_{cd} of 3.8 Å that has been calculated for the 12-membered taxamycin-12

derivative **160** which leads to the taxane nucleus (Scheme **41**).[84] Consequently, the feasibility of using the Bergman cycloaromatization towards construction of the taxane framework could be examined by generating a bicyclic compound of this nature.

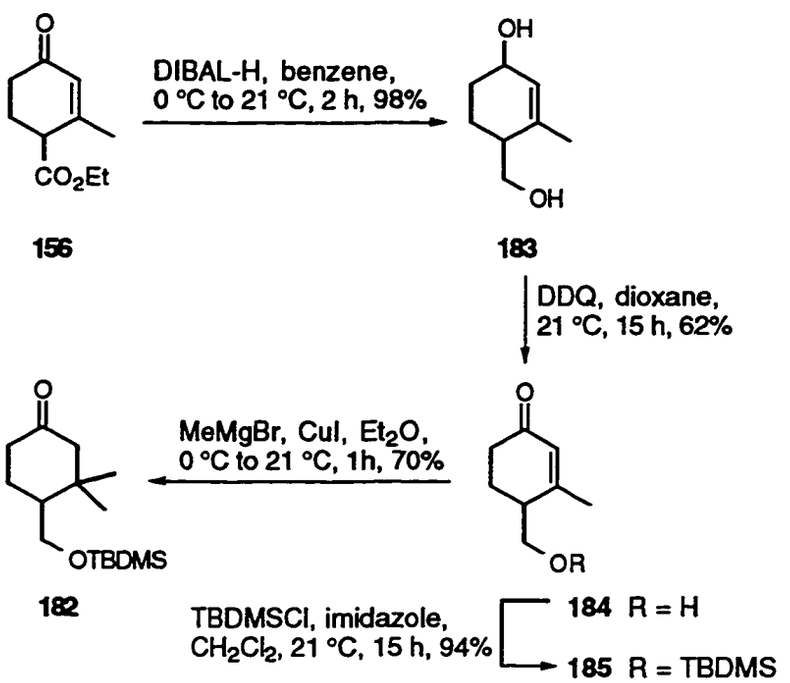


Scheme **44**. Retrosynthetic Analysis of Bicyclic Enediyne Model **178**

The bicyclic enediyne system **178**, complete with the required *gem* dimethyl group, could be constructed in a convergent manner by adding the enediyne synthon **177** to the cyclohexanone building block **182**. Manipulation of the protecting groups and subsequent intramolecular cyclization of precursor **181** would then afford the desired bicyclic ring sytem **178**. Initially, an intramolecular anionic condensation was selected to effect the final ring closure.

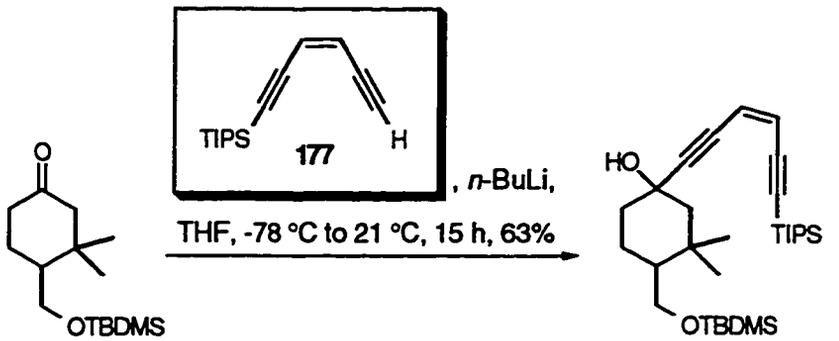
The precursor **182** was easily prepared in four steps from the commercially available Hagemann's ester **156** (Scheme **45**). Prior studies had provided the diol **183** on a multi-gram scale by reduction of **156** with 3 equivalents of DIBAL-H.[74] Subsequent chemoselective oxidation of the allylic alcohol **183** with DDQ afforded enone **184** in 62%

yield and protection of the remaining primary alcohol with *t*-butyldimethylsilyl chloride gave the corresponding protected derivative **185**. Treatment of enone with the organocopper reagent derived from MeMgBr and CuI then produced the desired 1,4-addition product **182** in a 70% yield.



Scheme **45**. Preparation of the Building Block **182**

The lithiated derivative of the synthon **177** was condensed with the cyclohexanone building block **182** to provide adduct **181** as a single diastereomer in 63% yield. It was initially expected that removal of the proton α to the carbonyl of **182** by the enediyne acetylide may prove to be problematic and result in low yields. This problem has been remedied by the generation of the organocerium(III) species from the corresponding organolithium reagent.[85] Organocerium(III) reagents are, in general, less basic and more nucleophilic than organolithium or organomagnesium reagents. In this case, however, the addition of anhydrous $CeCl_3$ to lithiated **177** did not improve the yield of this condensation reaction.



182 **181**

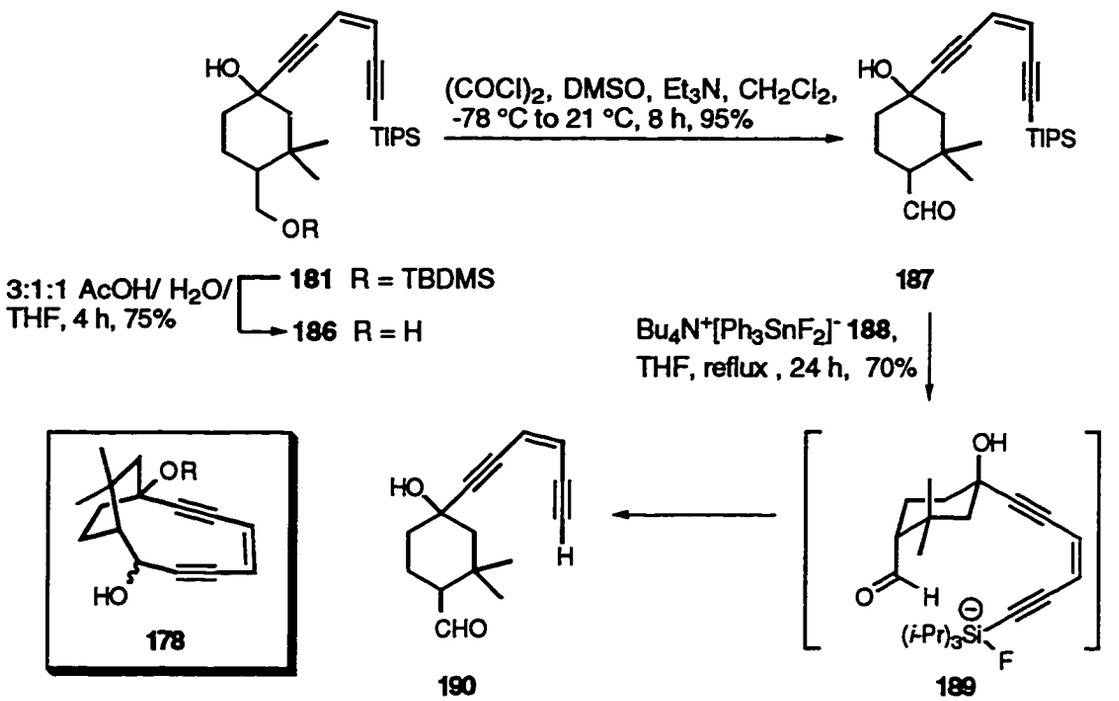
Scheme **46**. Addition of Enediyne Synthon to Building Block **182**

2.2.2 Attempts to Effect Final Ring Closure

Initial attempts to synthesize the bicyclic system **178** involved an anhydrous fluoride-mediated cyclization of enediyne adduct **187** with tetrabutylammonium difluorophenylstannate **188** (Scheme **47**). Unlike other fluorinating agents such as TBAF, this hypervalent tin complex is not hydrated nor hygroscopic. It was prepared by treating triphenyltin fluoride with TBAF according to Gingras' procedure.[86]

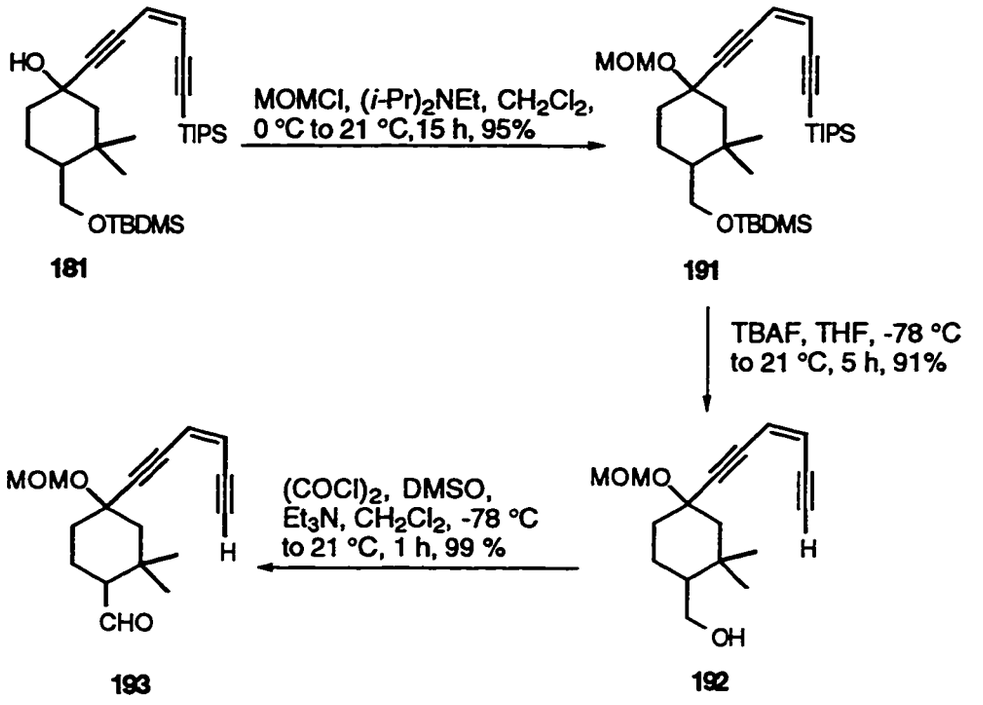
Selective removal of the *t*-butyldimethylsilyl ether in a mixture of acetic acid, H_2O and THF (3:1:1) afforded the diol **186**. Subsequent Swern oxidation[87] of **186** gave the desired cyclization precursor **187** in 95% yield. Unfortunately, treatment of this aldehyde

with Gingras' tetrabutylammonium difluorophenylstannate **188** in THF under reflux resulted only in triisopropylsilyl deprotection and no cyclized adduct **178** was observed.



Scheme **47**. Attempted Anhydrous Fluoride-Mediated Cyclization of **187**

The enediyne addition product **181** was also elaborated in three steps to the protected aldehyde **193** to attempt a different method of intramolecular acetylide condensation (Scheme **48**). The tertiary alcohol was protected as its methoxymethyl ether **191** on treatment with chloromethyl methyl ether and *N,N*-diisopropylethylamine in a 95% yield. Removal of both silyl protecting groups with excess TBAF furnished alcohol **192**, which was then oxidized under Swern conditions to give aldehyde **193** in quantitative yield.



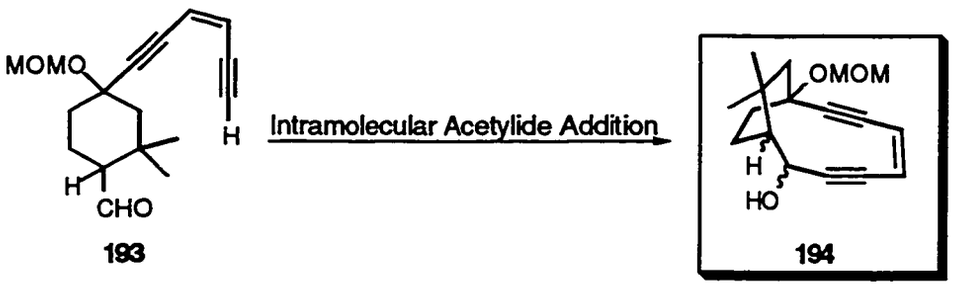
181 191 193 192

Scheme 48. Elaboration to Cyclization Precursor 193

Enediyne **193** possessed the appropriate functionality for intramolecular anionic cyclization. It was anticipated that the use of a bulky base would result in the selective deprotonation of the less hindered acetylenic proton of the enediyne appendage and not the aldehyde α-proton. Typically, the pk_a of a proton attached to simple acetylenes ($pk_a \approx 20$-25) is greater than that of a proton α to an aldehyde ($pk_a \approx 16$-18).[88] In this case, however, the acidity of the acetylenic proton of enediyne precursor **193** should be increased substantially by conjugation with the remaining enyne portion of the enediyne moiety. Furthermore, the presence of the neighbouring *gem* dimethyl group should hinder abstraction of the proton α to the aldehyde. Therefore, acetylene deprotonation was expected to take place more rapidly than enolization of the aldehyde. Intramolecular addition of this acetylide to the aldehyde functionality of **193** would effect the crucial C-C bond formation. Intramolecular condensations of this nature have been applied in a number of other systems to achieve final ring closure.[32b,c,34,40i,54,89] Tius, for example, has used

the bulky base, LHMDS, to deprotonate an acetylene in the presence of an enolizable unsaturated aldehyde, to cyclize a 14-membered cembranoid.[90]

A slight excess (1.2 equivalents) of KHMDS was added dropwise to a solution of aldehyde **193** in THF in the presence of $CeCl_3$. A dilute solution of **193** (0.02 M) was used to prevent intermolecular coupling but only starting material was recovered under these conditions. Treatment of aldehyde **193** with LDA in the presence of a variety of Lewis acids such as $ZnCl_2$ and $BF_3{\cdot}OEt_2$ also resulted in recovery of starting material (Scheme **49**). An attempt to increase the nucleophilicity of the acetylide by adding HMPA before treatment with LDA, had no effect on the reaction. The enediyne **193** was also treated with excess KHMDS (3 equivalents) and no reaction was detected at -78 °C. Considerable decomposition of starting material was, however, observed when the reaction was allowed to warm to room temperature.



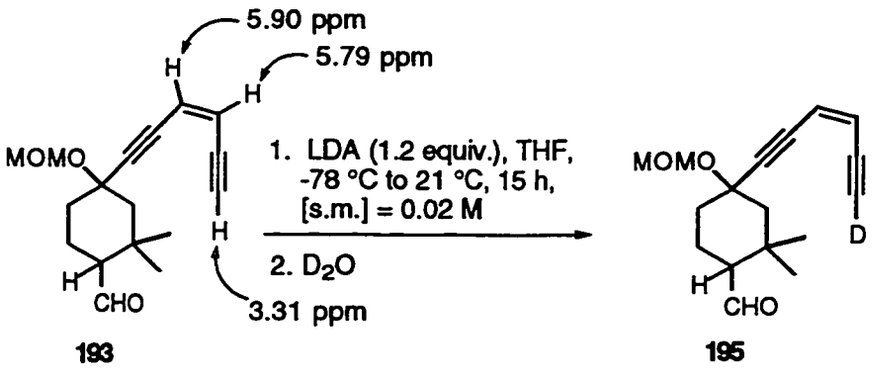
1. KHMDS (1.2 equiv.), $CeCl_3$ (3 equiv.),THF, -78 °C to 21 °C, 15 h, [s.m.] = 0.02 M
2. LDA (1.2 equiv.), $ZnCl_2$ (3 equiv.), THF, -78 °C to 21 °C, 15 h, [s.m.] = 0.02 M
3. LDA (1.2 equiv.), $BF_3{\cdot}OEt_2$ (3 equiv.), THF, -78 °C to 21 °C, 15 h, [s.m.] = 0.02 M (addition of HMPA had no effect)

} no reaction, starting material was recovered

Scheme **49**. Approach to Cyclization by Intramolecular Acetylide Addition

A D_2O quench experiment was performed in order to determine if the enediyne acetylenic proton was, in fact, being removed under these basic conditions (Scheme **50**). Aldehyde **193** was again treated with a slight excess of LDA in THF at -78 °C and allowed

to stir overnight. It was discovered, upon quenching with D_2O, that deuterium had indeed been incorporated at the terminal acetylenic position. The ^1H NMR spectrum of the resultant crude product lacked the signal at 3.31 ppm corresponding to the acetylenic proton of **193**. Furthermore, the splittings of the signals found at 5.79 and 5.90 ppm in the ^1H NMR spectrum of **193**, due to coupling of the vinylic protons with the acetylenic proton, were not observed in the ^1H NMR spectrum of the D_2O quenched reaction. The remaining signals in both ^1H spectra were identical, including the ^1H signals corresponding to the protons at the α-position with respect to the aldehyde group. These results indicate that deuterium incorporation had occurred at the terminal acetylenic position and not α to the carbonyl.



Scheme **50**. Deuterium Quench Experiment of Enediyne **193**

Several reasons might explain the inability of the acetylide anion to cyclize onto the carbonyl group of **193**. Steric effects or the reversible formation of the acetylide from the desired, cyclized alkoxide adduct are two rationales which could account for the recovery of starting material. Another explanation might be that the lithium acetylide of the enediyne **193** was poorly aligned for intramolecular attack. An examination of the stereochemistry of adduct **181**, initially formed from attack of the enediyne nucleophile onto cyclohexanone **182**, supports this supposition (Figure 7).

A single diastereomer was detected from the addition of enediyne **196** to **182** upon inspection of the ^1H NMR spectrum of the crude product. Furthermore, only one set of

peaks corresponding to one diastereomer were found in both the ^{1}H and the ^{13}C NMR spectra after purification of alcohol **181**. However, the relative stereochemistry, between the newly formed hydroxyl group and the *t*-butyldimethylsilyloxymethyl group at the C-1 and C-4 positions respectively was not elucidated. Hence, the stereochemical outcome was predicted by examining the trajectory of approach of the lithium enediyne acetylide nucleophile to the carbonyl of cyclohexanone **182**. It has been observed that small nucleophiles such as acetylide anions prefer to approach the carbonyl group of cyclohexanones from the axial direction.[91] In this case, however, the enediyne nucleophile **196** is much larger than simple lithium acetylide. Furthermore, the presence of the *gem* dimethyl group at the C-3 position would bring about non-bonding interactions when the enediyne nucleophile approaches from the axial direction.[92] These factors would block axial attack (path **A**) and favour equatorial attack (path **B**) (Figure 7). Based on this rationalization, the relative stereochemistry between the enediyne moiety at C-1 and the *t*-butyldimethylsilyloxymethyl group at C-4 was tentatively assigned as being *anti* (**181b**).

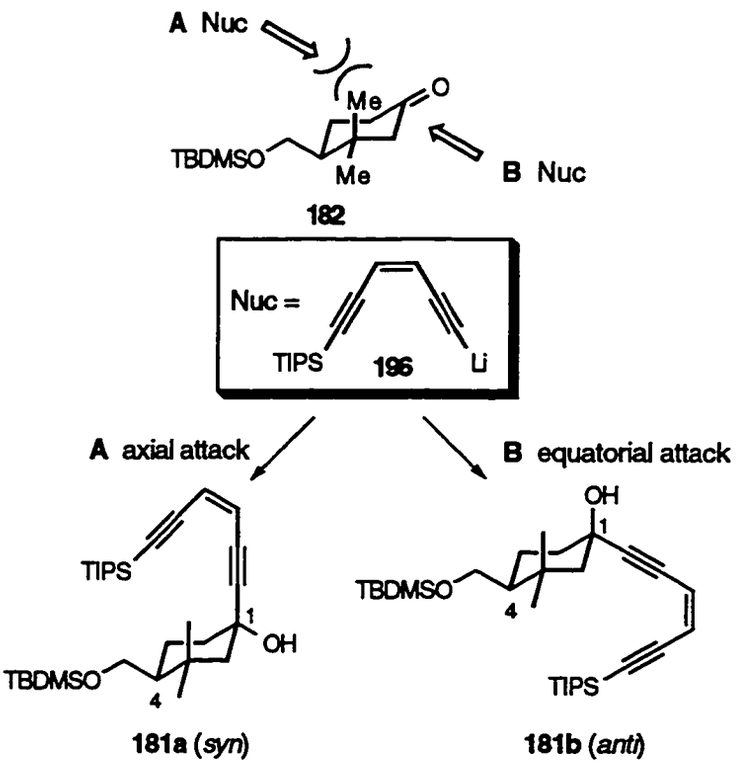
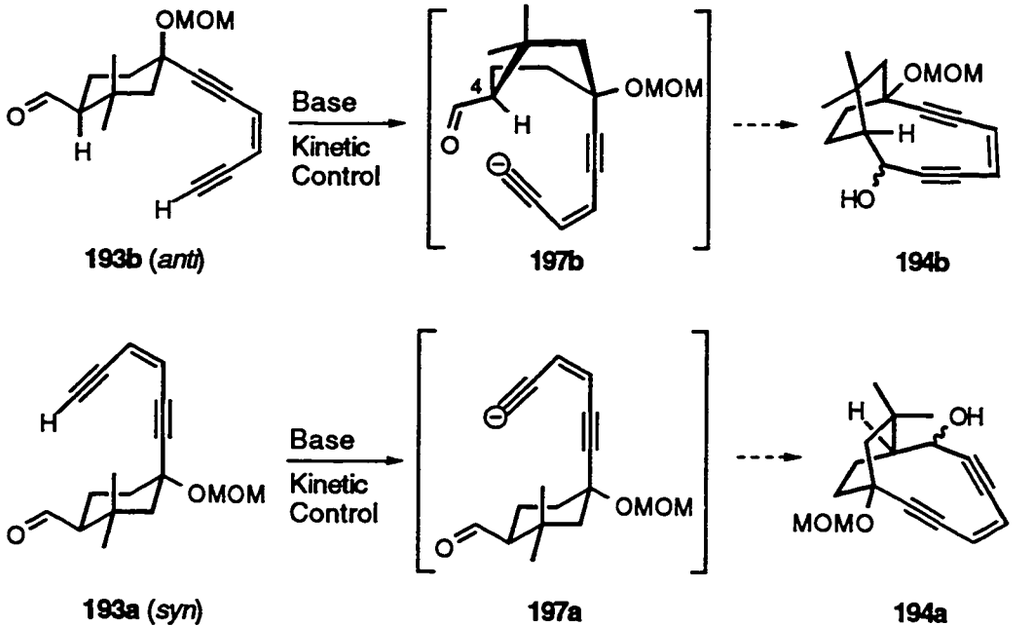


Figure 7. Trajectories of Approach of Enediyne Nucleophile to **182**

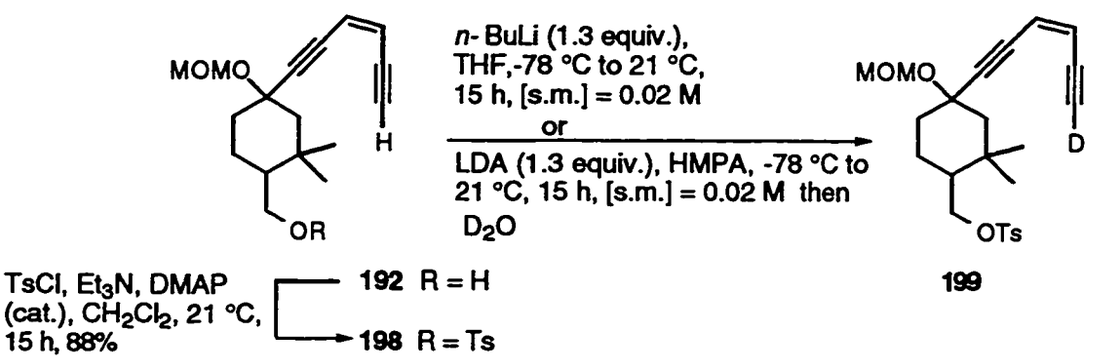
A conformational analysis of the *anti* diastereomer **193b**, synthesized from **181b**, shows that the acetylide is poorly aligned for intramolecular condensation (Scheme **51**). The *anti* diastereomer **193b** must interconvert to the boat conformation **197b** in order for the enediyne acetylide to approach the carbonyl at C-4. Furthermore, Darling molecular models indicate that intramolecular addition within **193b** would generate the strained, bicyclic enediyne **194b**. By comparison, the acetylide within the *syn* isomer **193a**, produced from axial attack of the enediyne synthon **196** onto **182**, would be better aligned for intramolecular attack and would produce the less strained system **194a**. The complete recovery of starting material from these cyclization attempts, therefore, reinforces the hypothesis that the adduct **181** has the *anti* configuration and that there was too much strain needed to be overcome to form the bicyclic system **194**.



Scheme **51**. Intramolecular Acetylide Addition in Diastereomers **193a** and **193b**

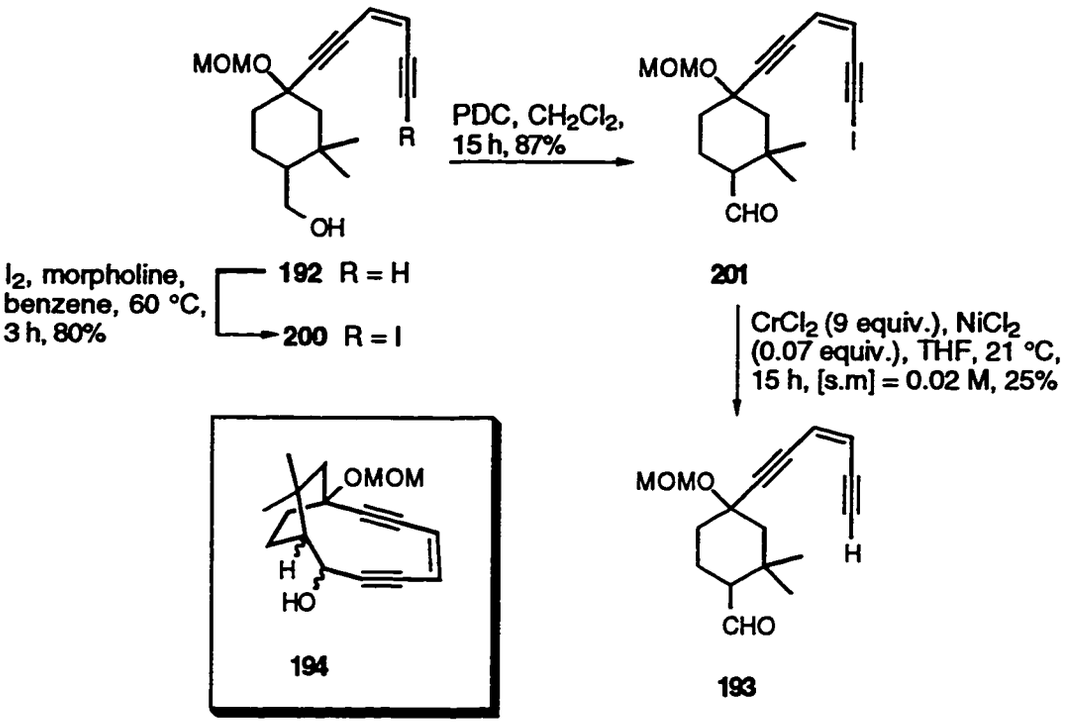
An alternative approach to cyclization *via* an intramolecular S_N2 displacement was also attempted (Scheme **52**). Alcohol **192** was converted to tosylate **198** with *p*-toluenesulfonyl chloride, triethylamine and a catalytic amount of DMAP in CH_2Cl_2.

Treatment of **198** with either *n*-BuLi or LDA/HMPA in THF under dilute conditons, from -78 °C to room temperature, did not afford any cyclized adduct. In both instances, the crude reaction mixtures were quenched with D_2O and analyzed by ^1H NMR spectroscopy. Disappearance of the acetylenic proton signal confirmed that deprotonation had occurred, but that the resultant acetylide was unable to effect the intramolecular displacement.



Scheme **52**. Approach to Ring Closure by Intramolecular S_N2 Displacement

Not to be discouraged by these results, the discovery of a different coupling strategy, which could be applied to this particular model, appeared promising (Scheme **53**). Intramolecular versions of the $CrCl_2$-mediated coupling reaction, originally developed by Nozaki and Kishi[42], have been used to effect ring closure of similarly strained enediyne systems.[44-47,49] The alcohol **192** was elaborated to iodoalkyne **200** in a yield of 80% by heating in benzene to 60 °C in the presence of iodine and morpholine. Oxidation of the resultant alcohol with PDC in CH_2Cl_2 provided the aldehyde **201** in a yield of 87%. Attempted ring closure was performed by slowly adding a solution of **201** in THF to a suspension of excess $CrCl_2$ and catalytic $NiCl_2$ in THF according to the procedure described by Maier *et al.* in their synthesis of the strained oxabicyclo enediyne system **97**.[45] These conditions failed to furnish the desired adduct, and instead yielded a small amount of reduced acetylene **193** (25%) along with considerable decomposition.



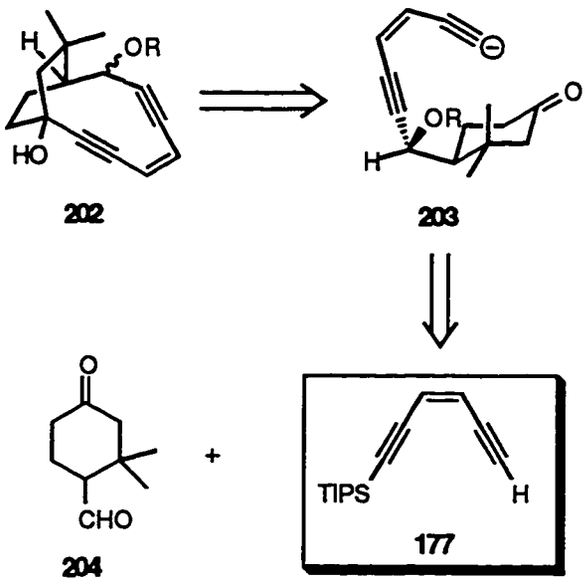
Scheme 53. Cyclization Approach by Intramolecular Nozaki-Kishi Coupling

The failure to cyclize precursors **198** and **201**, *via* either an intramolecular S_N2 displacement or Nozaki-Kishi condensation, can be explained by the same arguments as for the intramolecular acetylide cyclization attempt of **193**. In all three cases, the relative stereochemistry of the starting precursor appears to be unsuitable for intramolecular attack.

2.2.3 Alternative Route to Intramolecular Cyclization

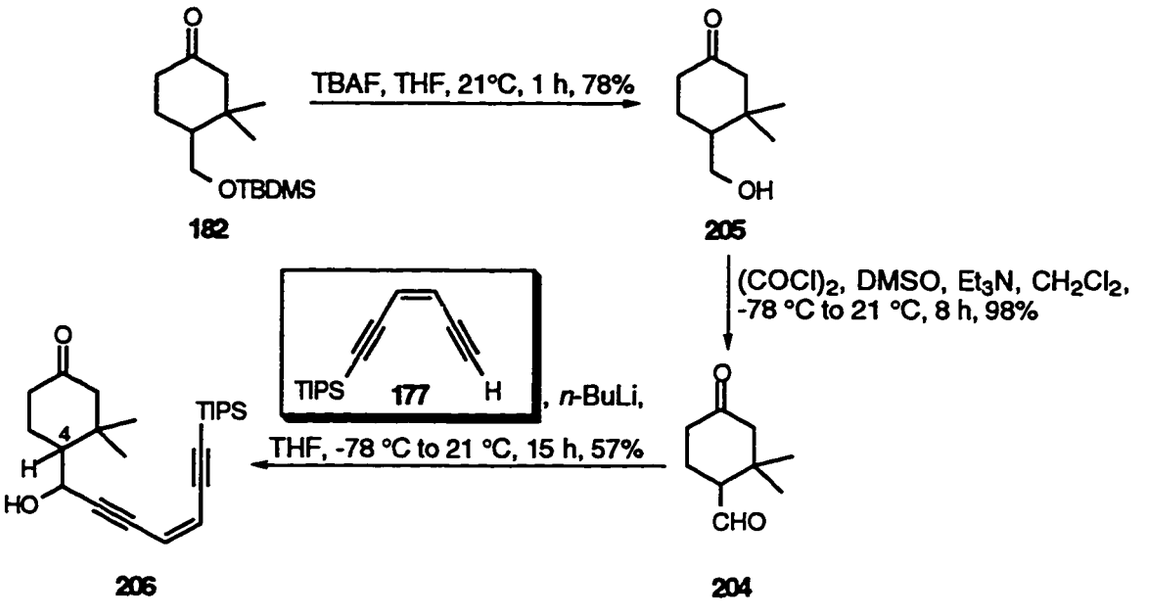
In the preceeding cyclization attempts, it appears that the enediyne acetylide is poorly aligned for intramolecular attack onto the carbonyl and *p*-toluenesulfonyloxymethyl groups of **193**, **198** and **201**. Consequently, a different approach to the construction of the target system was examined using the same starting building blocks (Scheme **54**). In this case, the enediyne synthon would be first condensed onto the formyl group at the C-4 position of the cyclohexanone precursor **204**. The final C-C bond formation would be then accomplished by intramolecular addition onto the ketone functionality of the

cyclohexanone ring. It was anticipated that this sequence of events would allow for better alignment of the enediyne acetylide anion with respect to the carbonyl of the cyclohexanone precursor.



Scheme 54. Alternative Approach to Cyclization Using Building Blocks **177** and **204**

The precursor **204** required for this approach was easily prepared from the cyclohexanone **182** (Scheme 55). Removal of the *t*-butyldimethylsilyl protecting group with TBAF and Swern oxidation of the resultant alcohol gave the desired aldehyde **204** in an overall yield of 76% yield. The chemoselective addition of the lithiated derivative of enediyne **177** to the dicarbonyl compound **204** provided adduct **206** as a single diastereomer in 57% yield. The relative stereochemistry between the proton at the C-4 position and the adjacent hydroxyl group was not determined. However, the stereochemical outcome of this nucleophilic addition can be predicted by examining the Felkin-Anh model[93] of this system (Figure 8).



Scheme 55. Construction of Cyclization Precursor **206**

The Newman projection of aldehyde **204** (conformers **A** and **B**) reveals that attack will proceed on conformer **A** rather than on conformer **B** in which the cyclohexanone ring hinders the approach of the nucleophile **196** to the aldehyde functionality (path **c** and **d**). In conformer **A**, attack on the *Si* face is favoured (path **b**) since the *Re* face is sterically hindered by the neighbouring *gem* dimethyl group (path **a**). Consequently, the major isomer was expected to be the *syn* adduct **206a**.

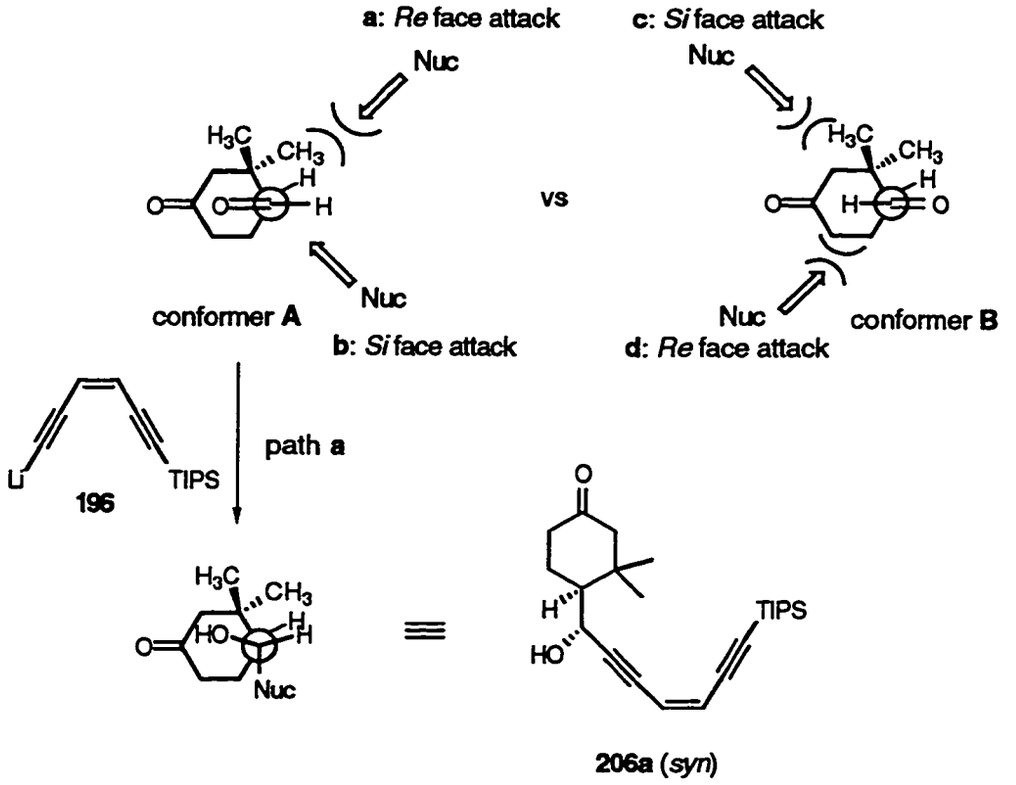
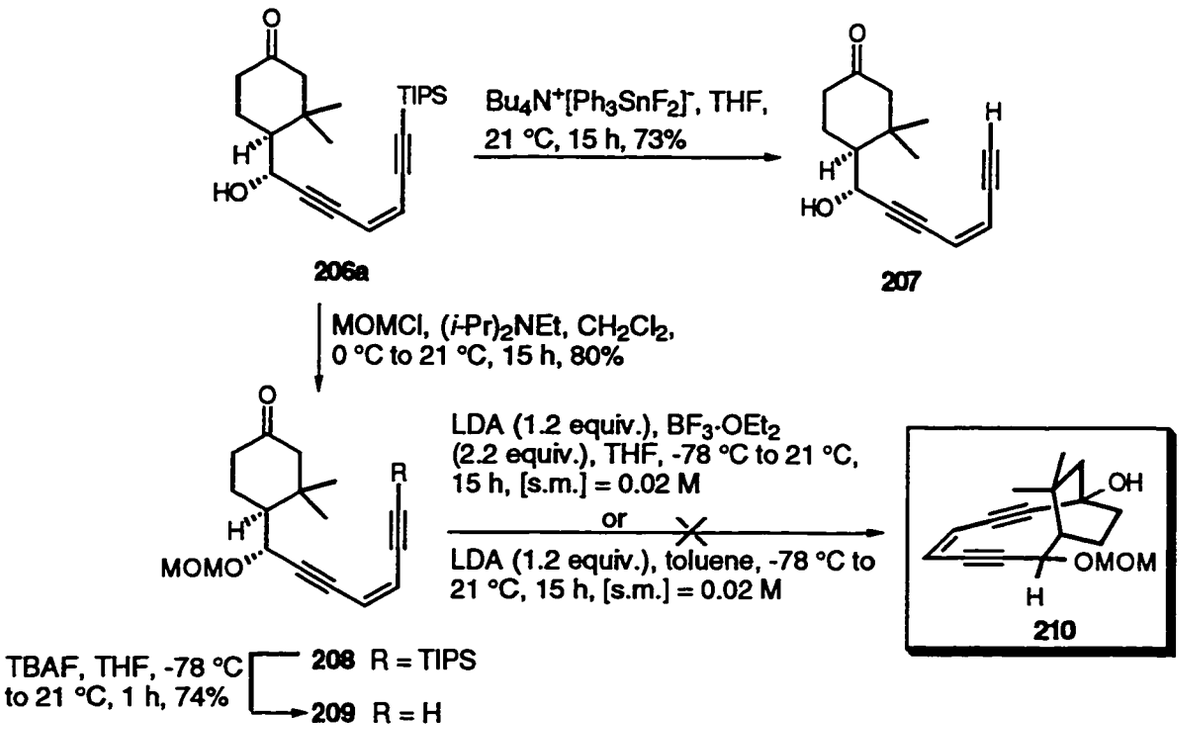


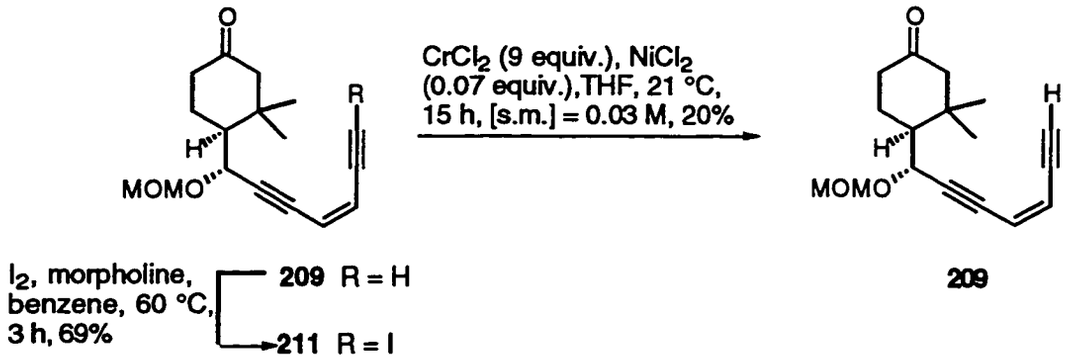
Figure 8. Felkin-Anh Model of Trajectory of Approach of Enediyne Nucleophile

The intramolecular cyclization of **206a** was initially investigated using Gingras' anhydrous fluorinating agent.[86] However, treatment of alcohol **206a** with tetrabutylammonium difluorophenylstannate resulted only in removal of the triisopropylsilyl protecting group as before (Scheme **56**). Alcohol **206a** was therefore elaborated to cyclization precursor **209** in two steps by protection of the alcohol as its methoxymethyl ether and removal of the silyl group with TBAF. Unfortunately, this new strategy also proved unsuccessful. The treatment of the resultant ketone with LDA under dilute conditions (0.02 M) in the presence of $BF_3 \cdot OEt_2$ or $ZnCl_2$ only yielded recovered starting material.



Scheme 56. Attempted Intramolecular Acetylide Addition of **209**

The enediyne **209** was also converted to iodide **211** in an attempt to perform an intramolecular Nozaki-Kishi coupling (Scheme **57**). Treatment of **209** with iodine and morpholine in benzene at 60 °C gave iodinated ketone **211** in 69% yield. Iodide **211** was subjected to $CrCl_2$-$NiCl_2$ mediated conditions and afforded only the reduced acetylene **209** with no observed cyclization. This result was not entirely unexpected since the Nozaki-Kishi reaction is used primarily for the chemoselective addition of vinyl and alkynyl iodides to aldehydes and not ketones.[42c,d,43a]

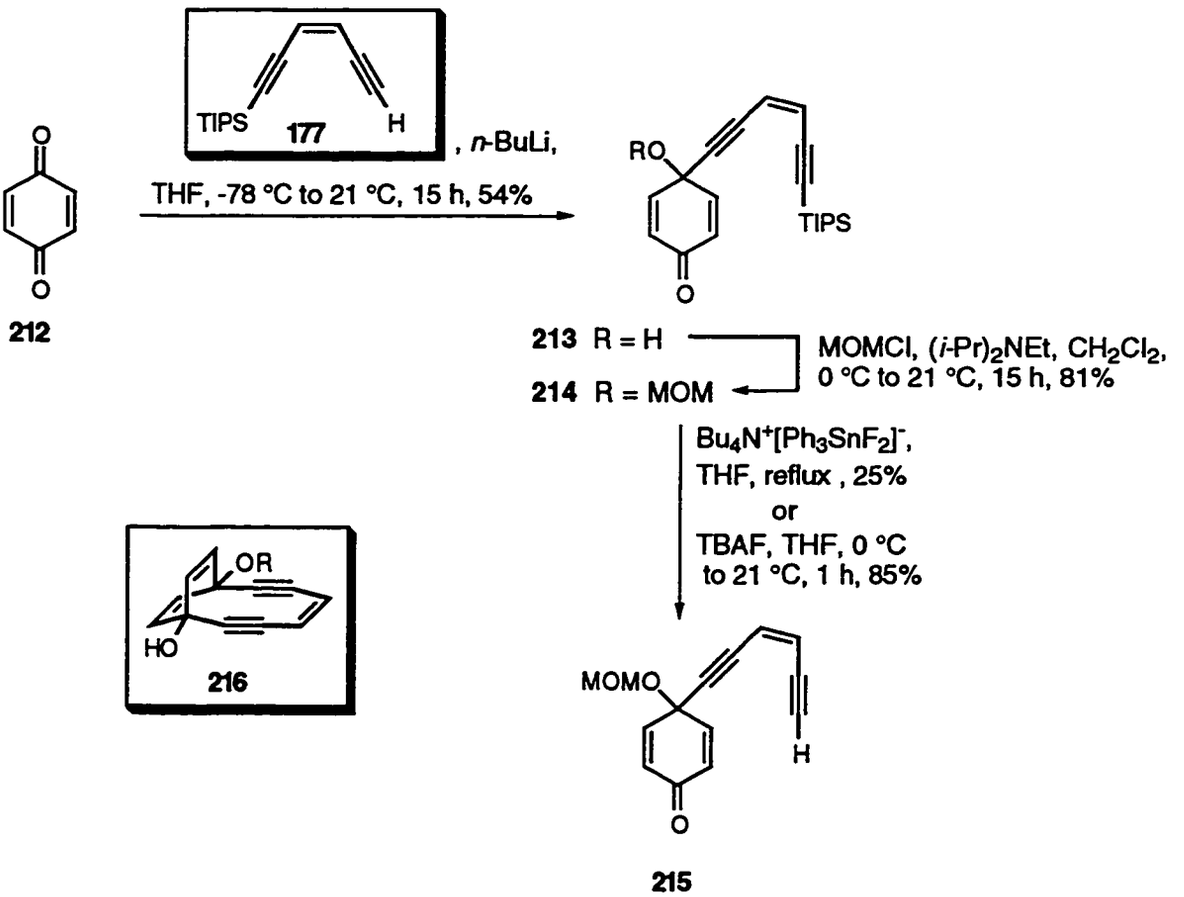


Scheme 57. Attempted Intramolecular Nozaki-Kishi Coupling of Iodide **211**

2.2.4 A New Enediyne Model

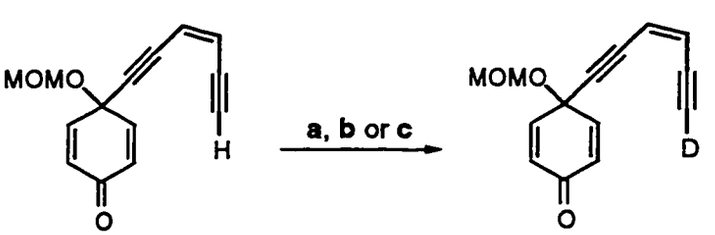
The inability to cyclize this particular system led to the examination of another model bicyclic enediyne **216** (Scheme **58**). The 1,4-benzoquinone **212** was chosen as the starting building block since the feasibilty of final ring closure could be investigated in a minimum number of synthetic steps. Furthermore, this particular precursor lacks the *gem* dimethyl group which may have contributed to the difficulties in generating the earlier enediyne model **178**.

Addition of the lithiated enediyne synthon **177** to 1,4-benzoquinone provided the adduct **213** in 54% yield, which was subsequently protected as its methoxymethyl ether **214**. Attempted cyclization of **214** with Gingras' difluorophenylstannate reagent in THF at reflux gave exclusive removal of the triisopropylsilyl group. This conversion was also performed with TBAF to give the cyclization precursor **215** in a 85% yield.



Scheme **58**. Elaboration of 1,4-Benzoquinone to Enediyne **215**

Efforts to cyclize enediyne **215** *via* acetylide additon were carried out by treating **215**, under dilute conditions, with several different bases such as KH, *n*-BuLi and LDA in the presence of Lewis acids, such as Et_2AlCl and $BF_3{\cdot}OEt_2$ (Scheme **59**). In each instance, only starting material was recovered from the reaction. In one case, the reaction was quenched with D_2O after stirring **215** with LDA for 15 hours. Both the ^1H and ^2D NMR spectra of the crude product from this reaction showed incorporation of deuterium at the acetylenic position. The broad singlet at 3.38 ppm in the ^1H NMR of **215**, which integrates for the acetylenic proton and the three methyl protons of the methoxymethyl protecting group, diminished in intensity for the D_2O quenched reaction product **217**. The ^2D NMR spectrum of the crude product of this reaction revealed a single broad signal at 3.4 ppm, confirming that deuterium had been incorporated at the terminal acetylenic position. The enediyne acetylide was, therefore, generated but was not adding to the quinone carbonyl. This result suggests that the enediyne bridge is too rigid to allow for intramolecular addition and formation of the strained 10-membered ring bicyclic enediyne **216**.



215 **217**

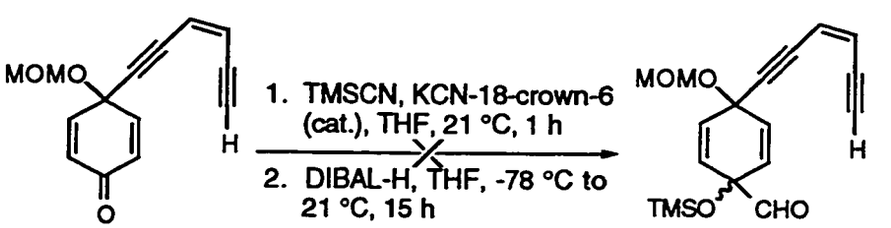
a: KH, $CeCl_3$, THF, 0 °C to 21 °C, 8 h, [s.m.] = 0.01 M then D_2O

b: *n*-BuLi (1.2 equiv.), Et_2AlCl (3 equiv.), THF, -78 °C to reflux, 8 h, [s.m.] = 0.01 M then D_2O

c: LDA, $BF_3{\cdot}OEt_2$ (3 equiv.), THF, -78 °C to 21 °C, 15 h, [s.m.] = 0.01 M then D_2O

Scheme **59**. Attempted Base-Induced Cyclization of Precursor **215**

The inability to cyclize **215** led to an idea which would hopefully make intramolecular addition more facile. It was envisaged that the carbonyl of quinone **215** could be extended by one carbon in order to decrease the bond forming distance between the two reacting centers (Scheme **60**).[94] A solution of enediyne **215** and trimethylsilylcyanide in CH_2Cl_2 was stirred with a catalytic amount of potassium cyanide-18-crown-6 complex for 1 hour. A new, less polar product was observed by TLC, however, attempts to characterize this compound by removal of the solvent *in vacuo*, only led to recovered starting material. Attempts to reduce the presumably unstable cyanohydrin to aldehyde **218** by the *in situ* addition of DIBAL-H at -78 °C also proved unsuccessful.



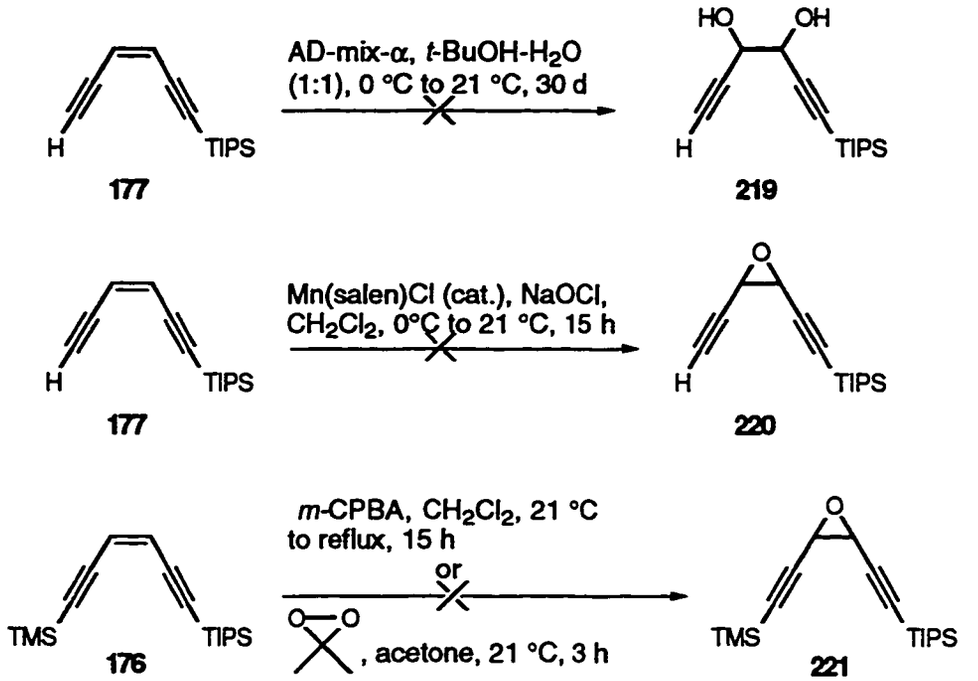
215 **218**

Scheme **60**. Attempted One-Carbon Homologation of Enediyne **215**

2.2.5 Reactivity of the Enediyne Moiety

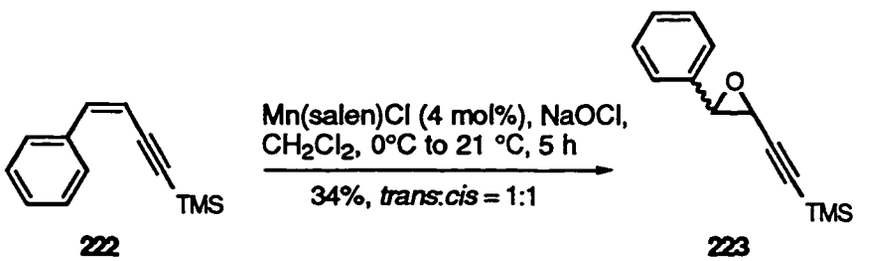
The strain of the bicyclic enediyne system **216** appears to inhibit the formation of the crucial C-C bond which would complete assembly of the enediyne bridge. This strain is, in part, created by the structural rigidity imposed by the double bond of the enediyne moiety. Consequently, selective modifications of the alkene moiety of compounds **177** and **176** were examined. The enediyne building block **177** was exposed to the dihydroxylation conditions developed by Sharpless[95] to examine the reactivity of the double bond (Scheme **61**). The treatment of **177** with Sharpless' AD-mix-α reagent in *t*-butyl alcohol and water resulted only in complete recovery of starting material even after stirring the mixture for 30 days. Enediyne **177** was also treated with Jacobsen's

(salen)Mn(III) catalyst in the presence of sodium hypochlorite (bleach) in an attempt to epoxidize the double bond.[96] Enediyne **176** was treated with epoxidizing agents such as *m*-CPBA and dimethyldioxirane[97] but, in each instance, only starting material was recovered from the reaction.



Scheme **61**. Attempted Oxidations of Enediyne Synthons **177** and **176**

The stability of this double bond is surprising, especially since Jacobsen's epoxidation process has been used to epoxidize structurally similar *cis*-enynes such as **222**.[96]

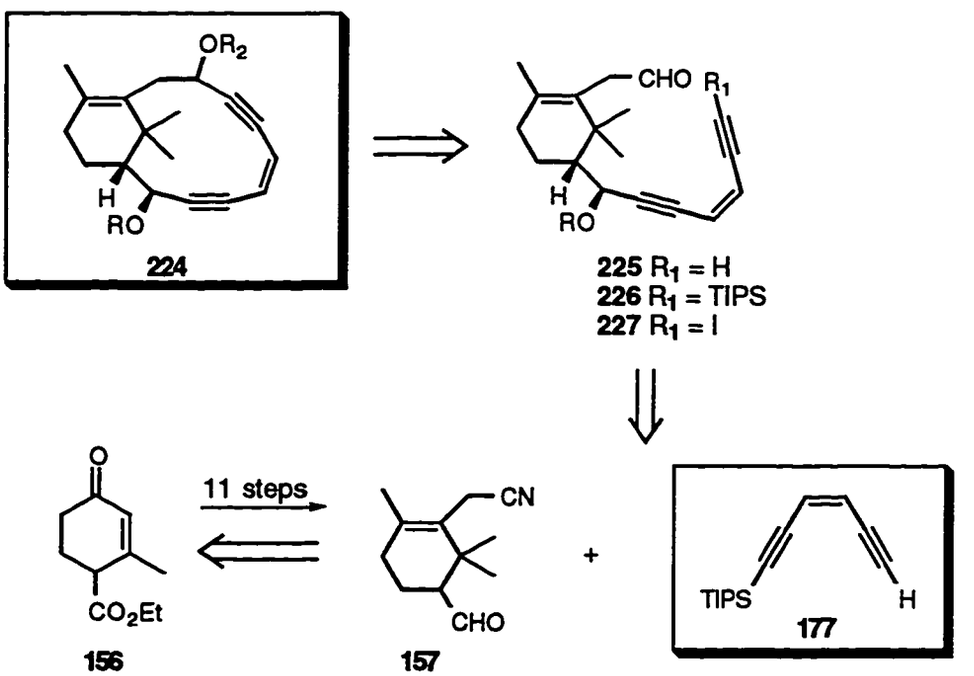


Scheme **62**. Jacobsen's Epoxidation of *cis*-Enyne **222**

3 Construction of a Taxamycin-12 Model

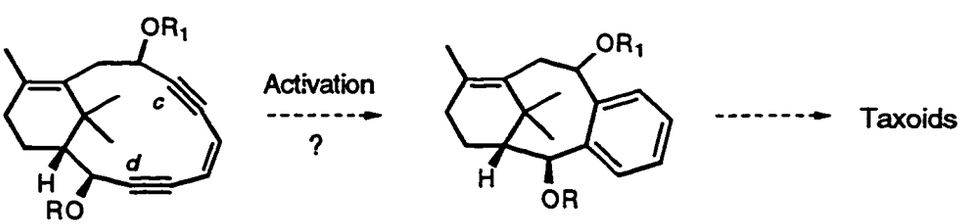
3.1 Design of Taxamycin-12

As work towards the construction of the enediyne model compounds was being carried out, initial efforts were also being undertaken to assemble a 12-membered, bicyclic enediyne system. The synthesis of a "taxamycin-12" enediyne was initially envisaged by combining the Taxol® A ring building block **157** with the enediyne synthon **177**, in a manner similar to that used for the model compounds (Scheme **63**). This strategy would lead to the preparation of intermediates **225** to **227**, possessing different functional groups at the acetylenic position. Hence, different bond construction strategies could be examined to provide access to the desired, bicyclic ring system **224**. Intramolecular acetylide condensation, anhydrous fluoride-mediated cyclization and Nozaki-Kishi type coupling are a few of the different approaches which could be employed to effect final ring closure.



Scheme 63. Retrosynthetic Analysis of Taxamycin-12 Model

The taxamycin-12 compound, **224**, was initially designed as a potential intermediate in the construction of the taxane framework. The Bergman cyclization of **224** would afford the desired tricyclic nucleus. Unlike the r_{cd} of calicheamicin and esperamicin, which lies between 3.16 and 3.35 Å, the *cd* distance between the two acetylenic carbons of **224** was calculated to be approximately 3.8 Å by molecular modeling calculations.[84] As a result, it was anticipated that forcing conditions would be required to induce cycloaromatization. These conditions would be evaluated with the aim of designing an activation process which would shorten the *cd* distance and facilitate the Bergman cyclization. The development of a "trigger", which could be used to generate the benzenoid diradical under mild, ambient temperatures, would hopefully provide a model enediyne which would exhibit biological activity in a manner similar to that displayed by the naturally occurring enediyne antibiotics.



224 **228**

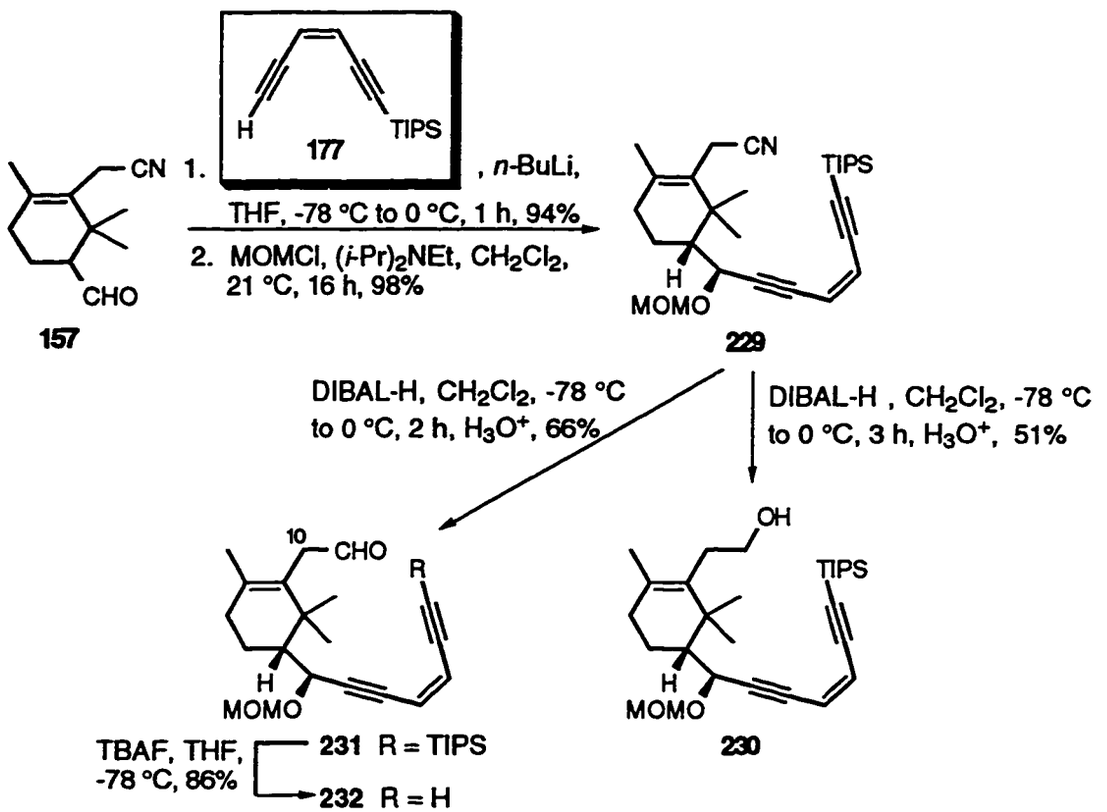
r_{cd} = 3.8 Å (MM2)

Scheme 64. Construction of Taxane Nucleus by Cycloaromatization of Taxamycin-12

3.2 Initial Studies Towards Synthesis of Taxamycin-12

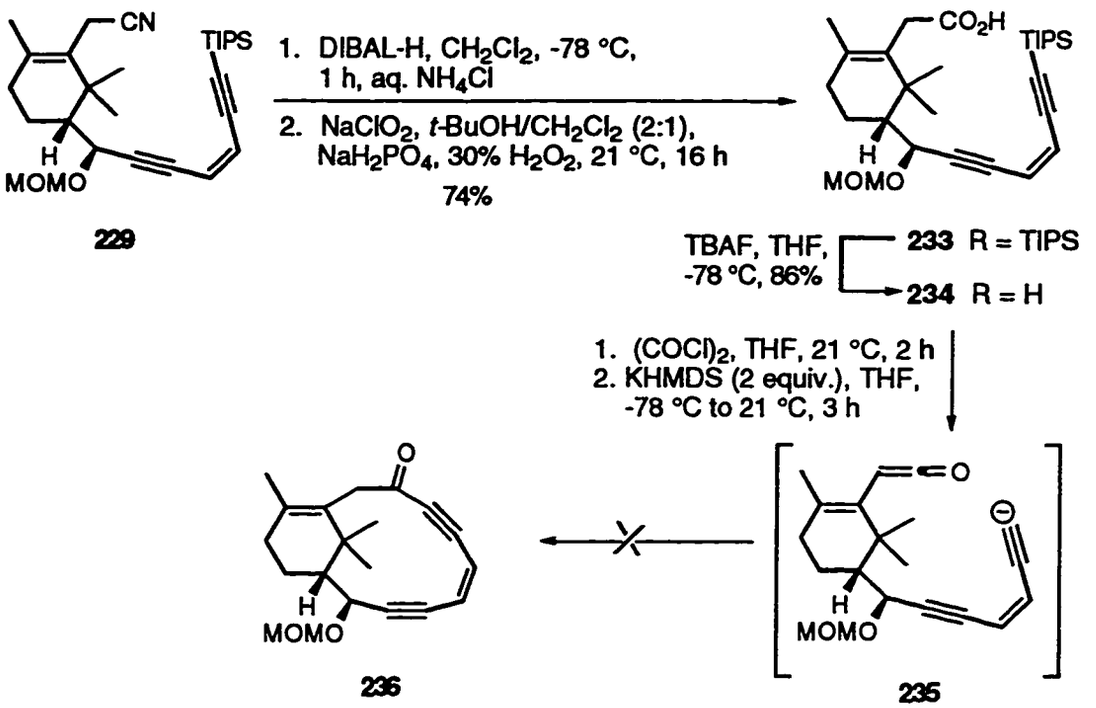
Preliminary studies by Dr. Yee-Fung Lu towards a taxamycin-12 model enediyne were initiated with the Taxol® A ring cyclohexene building block **157** used in the Diels-Alder approach to the taxane framework (Scheme **65**).[74,77] The lithiated acetylide derived from the enediyne synthon **177** was condensed with the cyanoaldehyde **157** to afford a 4:1 mixture of alcohol diastereomers in a 94% yield (78% isolated yield of major isomer).

The secondary alcohol of the major diasteromer was protected as its methoxymethyl ether **229** and the nitrile function was reduced with excess DIBAL-H to alcohol **230**. This reduction could also be terminated at the aldehyde stage to generate **231** directly. The fluoride-induced desilylation-condensation of **231** with several anhydrous fluoride sources proved unsuccessful. The use of cesium fluoride and Gingras' tetrabutylammonium difluorotriphenylstannate reagent, for example, resulted only in cleavage of the triisopropylsilyl group. The removal of this silyl protecting group with TBAF in THF also gave the acetylene **232** in 86% yield. Aldehyde **232** was used to examine ring closure *via* an intramolecular anionic condensation. However, treatment of **232** with $Sn(OTf)_2$ and 1,8-*bis*(dimethylamino)naphthalene did not effect the desired transformation.[98] The use of acetylide cyclizations has been a popular method of forming this type of bicyclic ring system.[54,89] In this case, however, the ring size is larger (12-membered) than in any of the reported examples. Furthermore, the C-10 hydrogens (Taxol® numbering system) of **232** are both allylic and adjacent to the aldehyde so their acidity was expected to be higher than that of the acetylenic proton. Due to these complications, further attempts at cyclization by this approach were not investigated .



Scheme **65**. Elaboration of A Ring Building Block to Precursors **230** and **232**

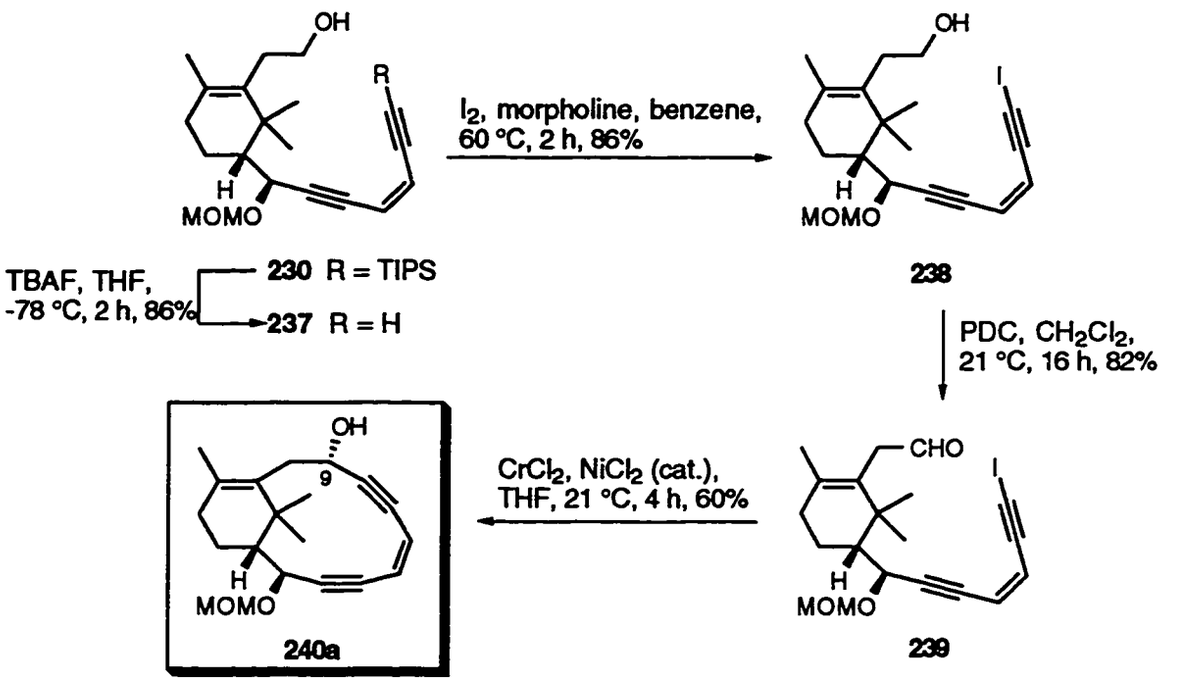
In order to overcome these problems, a new approach to ring closure was envisioned. The nitrile **229** was converted to the carboxylic acid **233** by DIBAL-H reduction to the aldehyde followed by sodium chlorite-hydrogen peroxide oxidation (Scheme **66**).[99] Removal of the triisopropylsilyl group was effected with TBAF and treatment of acid **234** with oxalyl chloride afforded the corresponding acid chloride. Intramolecular cyclization of this precursor using various reagents such as Pd(0)[100], $AlCl_3$[101] or base proved unsuccessful. In the latter case, it was expected that the ketene intermediate **235** would be formed upon treatment of the acid chloride with two equivalents of base and that this flattening of the reaction components would encourage addition. Unfortunately, attempts using this intermediate acid chloride only resulted in decomposition of starting material.



Scheme **66**. Attempted Cyclization *via* Ketene Intermediate **235**

The inability to cyclize the taxamycin-12 precursors by the methods described above led to the recourse of the $CrCl_2$-mediated, intramolecular Nozaki-Kishi coupling reaction.[42] At the time, several groups had employed this reaction to effect the ring closure of some strained enediyne systems.[49] Beau and coworkers, for example, had applied these conditions to produce 10- and 11-membered monocyclic enediynes in modest to good yields.[44] Thus, the alcohol **230** was elaborated to precursor **239** in an aim to cyclize **239** by this procedure (Scheme **67**). The desilylation of **230** was effected with TBAF in THF and the resultant alkyne **237** was converted to the iodoacetylene **238** on treatment with iodine and morpholine in 86% yield. The primary alcohol was oxidized to the aldehyde **239** with pyridinium dichromate. The final C-C bond closure was finally effected with excess $CrCl_2$ and catalytic $NiCl_2$ to provide the desired bicyclo[9.3.1]pentadecadienediyne system **240a** as a single diastereomer in 60% isolated yield. The formation of cyclized adduct was supported by the appearance of a triplet at 5.11 ppm in the ^1H NMR spectrum of **240a** (see Appendix A). This signal corresponds to the methine H_9 proton at the newly

formed hydroxyl centre. This effective intramolecular coupling reaction proved to be the only procedure for cyclization of this 12-membered system, of all the conditions examined. The stereochemical outcome of the condensation will be discussed later.



Scheme 67. Synthesis of Taxamycin-12 Model by Intramolecular Nozaki-Kishi Coupling

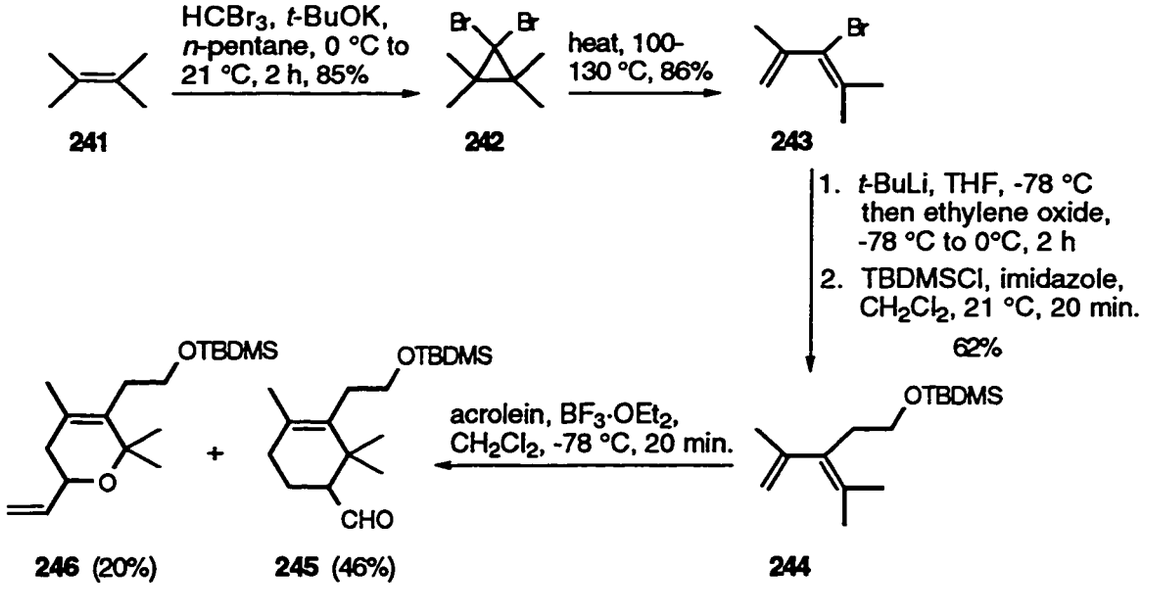
In this initial study, the final key cyclization reaction was carried out on a 60 mg scale. Furthermore, a total of 20 steps was required to reach the iodoaldehyde precursor **239**, starting from the commercially available Hagemann's ester. Due to the time and effort needed to arrive to this point, the scale up to produce more of the 12-membered bicyclic enediyne for subsequent studies proved impractical.

3.3 Improved Route to Taxamycin-12

3.3.1 Construction of A Ring Building Block

Studies in the Fallis laboratory towards the synthesis of Taxol® and Taxol® analogues have recently led to the development of an efficient and high yielding route to

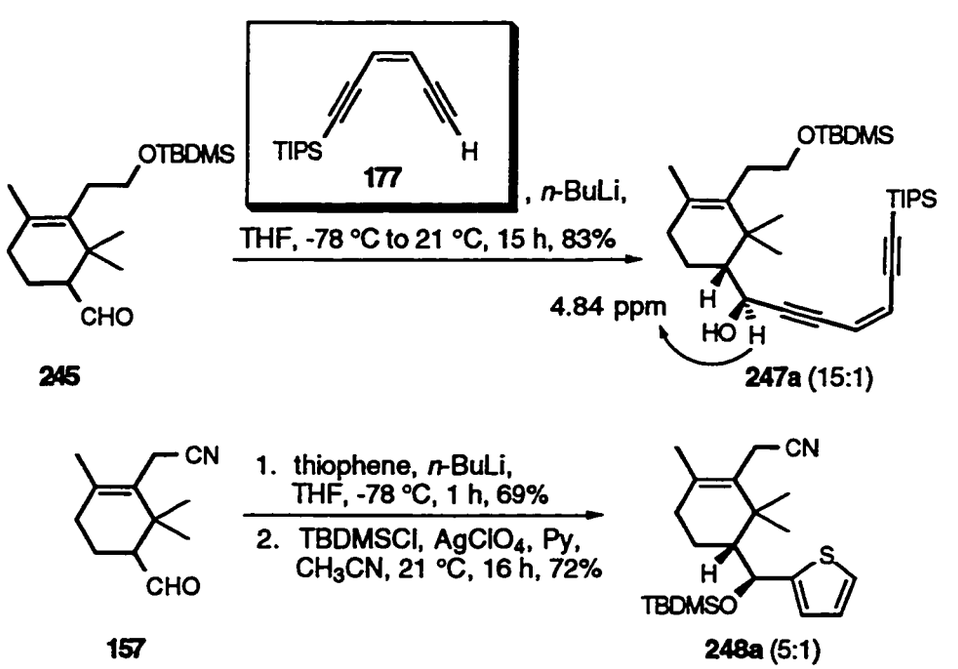
various A ring precursors.[102] These building blocks have subsequently been used towards the construction of different taxamycin systems. The route to these compounds is much shorter and more efficient than the 11 step sequence developed from Hagemann's ester in the earlier approach. The A ring cyclohexene **245** was prepared in 5 steps using the commercially available 2,3-dimethyl-2-butene **241** as starting material (Scheme **68**). This alkene was first reacted with dibromocarbene generated from bromoform and potassium *t*-butoxide in pentane to give the dibromocyclopropane **242** in 85% yield as a white crystalline compound.[103] Dehydrobromination of this solid gave the bromodiene **243** in 86% yield as a clear liquid. Halogen-lithium exchange with *t*-BuLi and trapping of the lithio species with ethylene oxide, afforded a chain-extended diene alcohol which was protected as its *t*-butyldimethylsilyl ether **244** in a yield of 62% for the two steps. The Diels-Alder cycloaddition of this diene with acrolein at -78 °C provided the desired Taxol® A ring building block **245** in 46% yield, along with some of the hetero Diels-Alder product **246** as a side product.



Scheme **68**. Construction of A Ring Building Block **245**

3.3.2 Elaboration to Cyclization Precursor

The A ring precursor **245** was condensed with the enediyne building block **177** to construct the taxamycin-12 model in a convergent approach (Scheme **69**). The addition of a solution of the A ring **245** in THF to the lithiated enediyne synthon provided the adduct **247** as a 15:1 mixture of diastereomers in 83% yield. The diastereomeric ratio was determined by integration of the methine signals at the newly formed hydroxyl center in the ^1H NMR spectrum of the crude reaction mixture. The methine proton of the major diastereomer **247a** at the C-1 position of the endiyne chain appears as a doublet at 4.84 ppm, whereas the corresponding proton of the minor isomer is seen as a broad singlet at 4.70 ppm. The diastereomers were separated and purified by silica gel chromatography. The relative stereochemistry was based on the X-ray analysis of a related crystalline addition product **248a**, obtained by condensation of 2-lithiothiophene with aldehyde **157**, followed by silylation with *t*-butyldimethylsilyl chloride.[74] Alcohol **247a** was assigned the same relative stereochemistry by analogy and comparison of spectral data. The major isomer **247a** was used for subsequent experiments.



Scheme **69**. Determination of Relative Stereochemistry of Enediyne Addition Product **247a**

The relative stereochemistry of this addition can also be predicted by examining the Felkin-Anh model of the approach of the lithiated enediyne nucleophile (Figure 9). Attack of this lithio species from the less sterically hindered *Re* face of conformer **A** results in the formation of diastereomer **247a**, possessing the same relative stereochemistry as that predicted from the X-ray analysis of the thiophene adduct **248a**. Attack of conformer **B** is unfavoured because of steric interactions between the nucleophile **196** and the cyclohexene ring **245**.

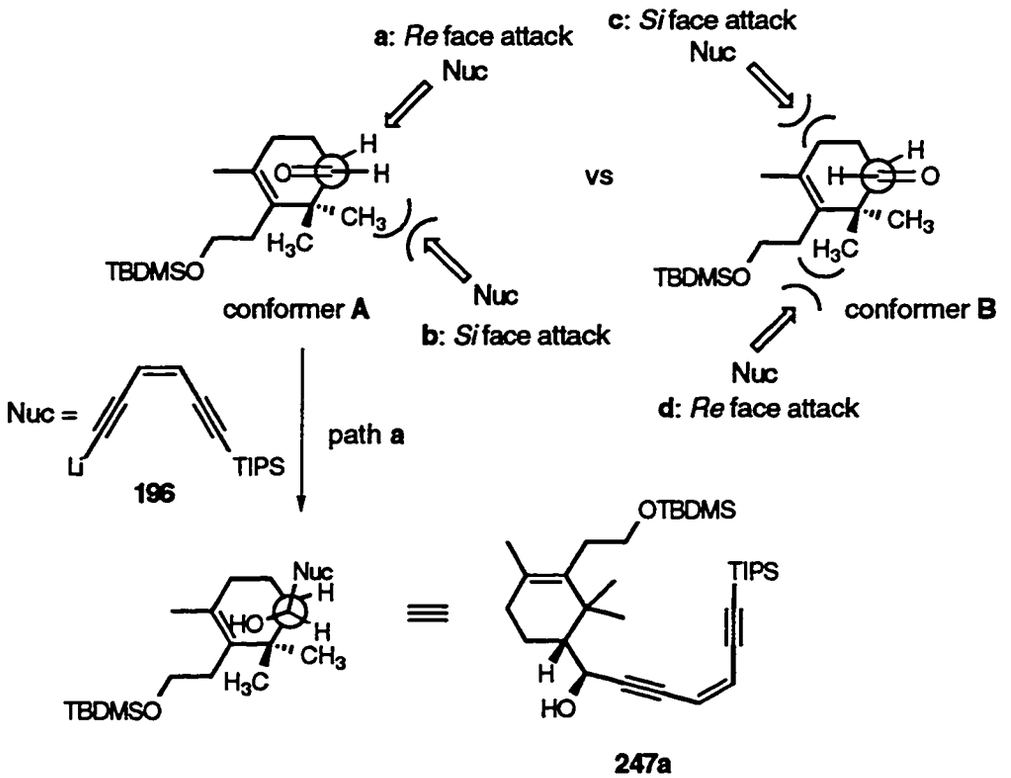
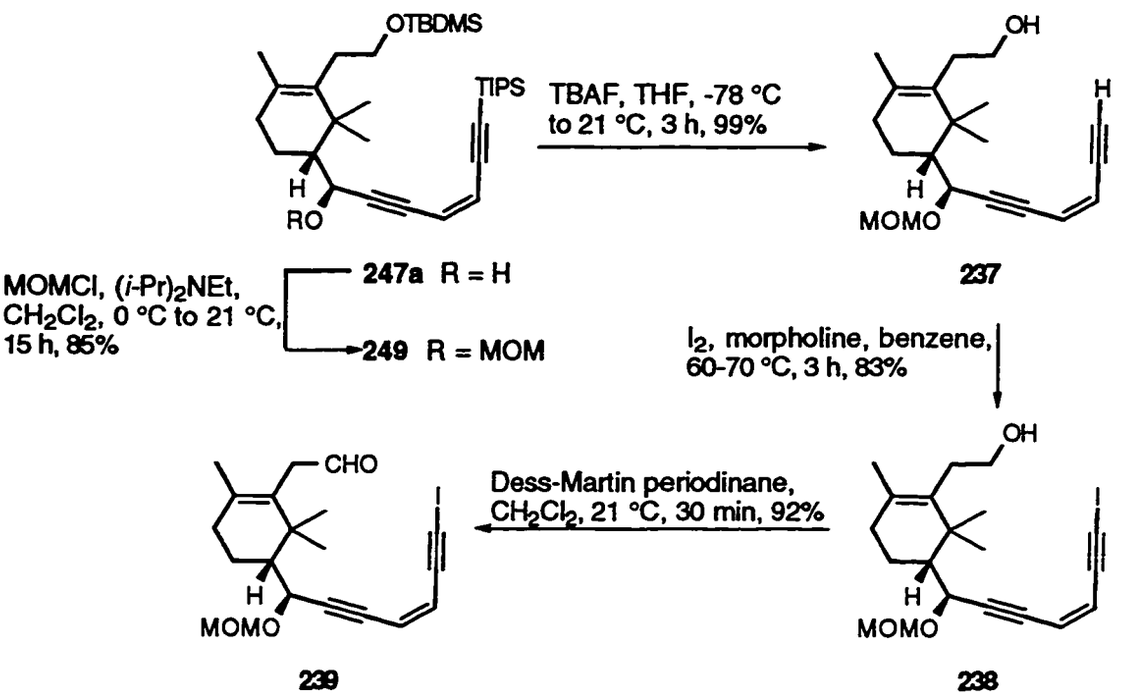


Figure 9. Felkin-Anh Model of Addition of Lithiated Enediyne to **245**

Elaboration of adduct **247a** to a cyclization precursor was straightforward. The secondary alcohol was protected as its methoxymethyl ether in 85% yield and both silyl protecting groups were removed with excess TBAF in THF to afford alcohol **237** in quantitative yield. Treatment of **237** with iodine and morpholine at 60-70 °C gave the iodoacetylene **238** in 83% yield. Oxidation of the primary alcohol with Dess-Martin periodinane[104] cleanly provided the desired cyclization substrate **239** in 93% yield. This

iodoaldehyde is unstable in solution or as an oil stored in the freezer and had to be used almost immediately after silica gel purification.



Scheme **70**. Elaboration of Compound **247a** to Cyclization Precursor **239**

3.3.3 Ring Closure by Intramolecular Nozaki-Kishi Coupling

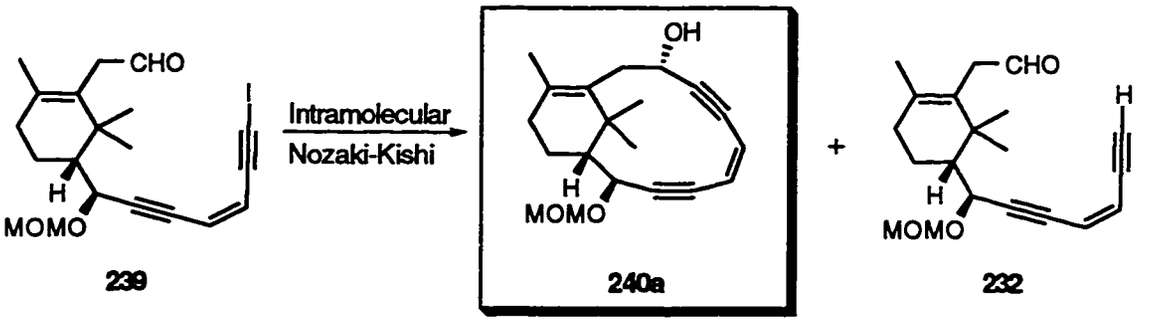
The iodoaldehyde **239** was subjected to the $NiCl_2$-catalyzed, $CrCl_2$-mediated Nozaki-Kishi coupling condition used in the initial sequence to the taxamycin-12 system (Table 1). When the reaction was carried out under identical conditions (concentration, quantities of reagents, solvent, *etc.*), only a 10% yield of cyclized material was obtained along with a 13% yield of reduced acetylene **232** (entry 2). A low concentration of starting material was employed to discourage intermolecular coupling and dimerization. In order to assess the role of solvent in this transformation, the reaction was carried out in DMF, the solvent typically used in intermolecular couplings (entry 3).[42,43] Complete decomposition of starting material was observed under these conditions. This result agrees with those obtained by Isobe *et al.* who found that the intramolecular cyclization of a similar enediyne

system proceeded only in THF.[105] The use of other solvents such as DMF, DMSO, Et_2O, dioxane and toluene gave no reaction.

The intramolecular coupling of taxamycin-12 was repeated many times but the original 60% yield which was obtained in the first trial could not be reproduced. In the following trials, it appeared that the yields of cyclized adduct depended on the quality and source of $CrCl_2$. The first reaction was carried out using anhydrous $CrCl_2$ obtained directly from Aldrich® without further purification. Subsequent attempts with this same source of $CrCl_2$ resulted in lower yields of isolated adduct (entries 2 and 4). The $CrCl_2$ was dried azeotropically using a Dean-Stark apparatus in an attempt to remove any traces of moisture. This procedure initially improved the yields of the desired adduct, however, the yields of subsequent attempts were again variable (entries 5, 6 and 7). The $CrCl_2$(THF) complex, prepared and kindly donated by Dr. Gambarotta (University of Ottawa), also provided respectable yet irreproducible yields of **240a** (entries 8, 9 and 10). This reagent was prepared from Cr pellets, HCl gas and THF and was stored under under nitrogen to prevent exposure to air and moisture.[106] It is known that $CrCl_2$ is very hygroscopic and decomposes rapidly in the presence of even traces of moisture.[43] However, variable results were obtained even when every precaution was taken to ensure that the $CrCl_2$ was not exposed to air or moisture. These measures involved thoroughly drying all glassware and handling the reagent and equipment in a nitrogen glove bag. Attempts to generate $CrCl_2$ *in situ* from $CrCl_3$ and LAH[42a] in the presence of a catalytic amount of $NiCl_2$ resulted only in low yields (5-10%) of cyclized material.

Due to the unpredictable nature of this reaction, a reliable set of reaction conditions was not developed. The amount of $NiCl_2$ was varied but no firm conclusions regarding its role in the coupling were drawn. Typically, only a catalytic amount of $NiCl_2$ is required to effect coupling. In the first trial, 0.7 equivalents were used to effect the 60% yield of cyclized product **240a**. The use of less $NiCl_2$ (0.08 equiv.) gave lower yields of cyclized adduct although these yields may be attributed to decomposition of the $CrCl_2$ (entries 7 and

9). Interestingly, a respectable 40% yield of **240a** was obtained when excess $NiCl_2$ (1.6 equiv.) was employed (entry 8) . This observation agrees with the results obtained by Brüchner *et al.* who discovered that the usual conditions employing catalytic amounts of $NiCl_2$ gave mediocre yields of their desired cyclization product.[107] Instead, a more respectable 53% yield was obtained when $NiCl_2$ was employed stoichiometrically.



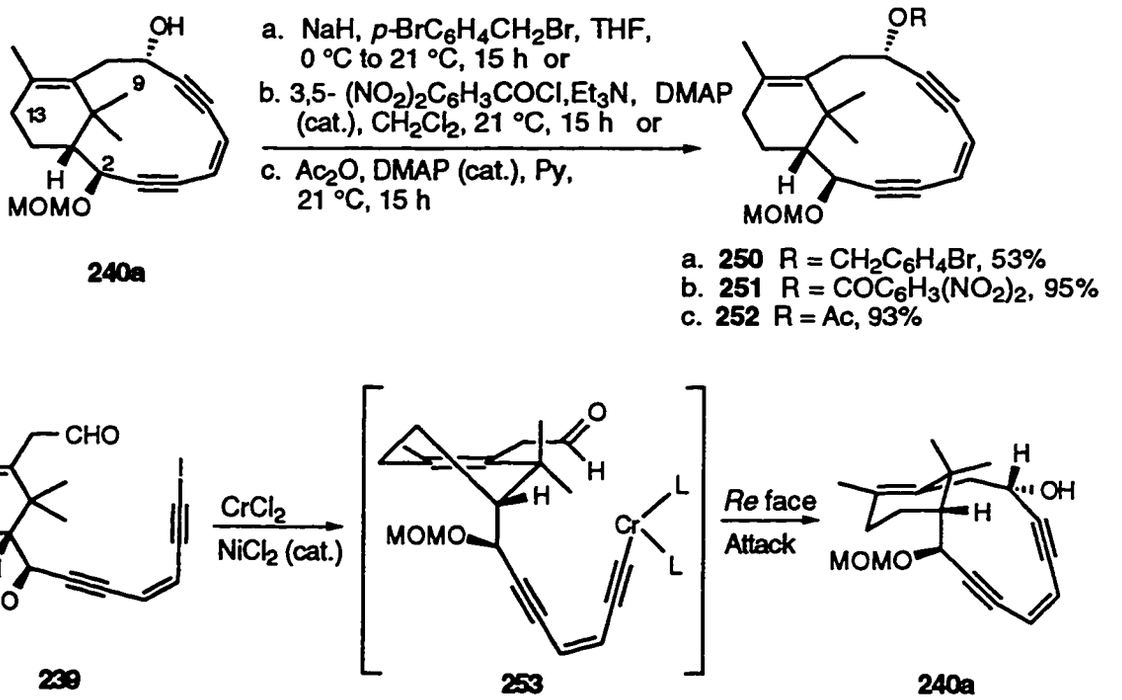
239 **240a** **232**

entry	final [**239**] (M)	solvent	equiv. of $CrCl_2$	source of $CrCl_2$	equiv. of $NiCl_2$	%cyclized	%reduced
1	0.007	THF	9.0	Aldrich	0.7	60%	-
2	0.006	THF	9.0	Aldrich	0.7	10%	13%
3	0.006	DMF	9.0	Aldrich	0.7	-	(decomp.)
4	0.015	THF	9.0	Aldrich	0.7	7%	34%
5	0.007	THF	9.0	Aldrich (dried in toluene)	0.7	45%	5%
6	0.010	THF	9.0	Aldrich (dried in toluene)	0.7	25%	26%
7	0.007	THF	9.0	Aldrich (dried in toluene)	0.08	22%	5%
8	0.014	THF	6.0	$CrCl_2$(THF) (Dr. Gambarotta)	1.6	40%	5%
9	0.017	THF	5.0	$CrCl_2$(THF) (Dr. Gambarotta)	0.08	24%	20%
10	0.016	THF	2.5	$CrCl_2$(THF) (Dr. Gambarotta)	1.0	30% (10:1)	5%

Table 1. Conditions for Intramolecular Nozaki-Kishi Coupling to Taxamycin-12 **240a**

In all of the experiments but one, only one diastereomer was isolated. A minor isomer was also isolated when the reaction was performed on a large scale (>1.5 g) and proceeded in modest yield (>25%) (entry 10). The diastereomeric ratio was calculated to be 10:1 by inspection of the crude ^1H NMR and by purification of the two isomers by chromatography.

The stereochemical outcome of this reaction was based on examination of Darling molecular models. The *p*-bromobenzyl ether derivative **250** and the 3,5-dinitrobenzoyl ester **251** were both prepared, although, in each case, attempts to provide crystals suitable for X-ray analysis proved unsuccessful. The *anti* relative stereochemistry between the methoxymethyl ether group at C-2 and the hydroxy group at C-9 was, therefore, tentatively assigned by examining molecular models, which suggest a preferential *Re* face attack of the aldehyde function in the chromium acetylide species **253**. This particular conformer **253** appears to be the least sterically encumbered.



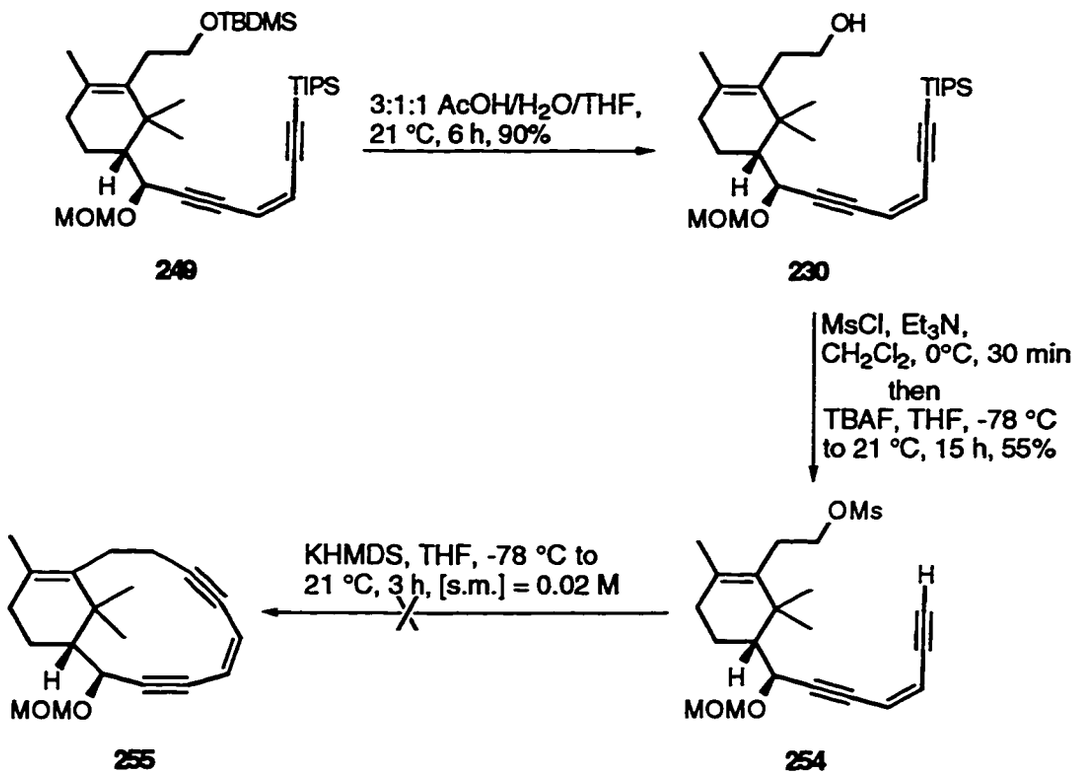
Scheme 71. Determination of Stereochemistry of Taxamycin-12 **240a**

3.3.4 Other Attempts at Cyclization

Other reaction conditions were employed in an attempt to improve the reliability of the intramolecular cyclization process. The iodoaldehyde **239** was treated with SmI_2 and HMPA but only a small amount of reduced acetylenic compound **232** was recovered from the reaction along with considerable decomposition. This SmI_2-mediated coupling appeared promising since it has been employed in the coupling of iodoalkynes and aldehydes to give propargyl alcohols.[108]

Mori *et al.* have also developed an intramolecular cyclization process which couples vinyl halides with aldehydes or ketones.[109] This method involves the generation of the stannyl anion, [Bu_3Sn^-], from $Bu_3SnSiMe_3$ and CsF. Halogen-metal exchange between this species and a vinyl halide produces a vinyl anion which then cyclizes onto an internal carbonyl group. Unfortunately, only decomposition was observed when these reaction conditions were applied to iodoaldehyde **239**.

The irreproducibility and unpredictability of the Nozaki-Kishi reaction proved frustrating and prevented the large scale preparation of the taxamycin-12 enediyne **240a**. Consequently, further elaboration of this compound could not be adequately carried out. This chromium-mediated reaction was, however, the only method found which could effect the desired transformation. A different approach involving an intramolecular S_N2 displacement was also attempted (Scheme **72**). The *t*-butyldimethylsilyl protecting group of compound **249** was selectively removed by stirring in a mixture of AcOH/H_2O/THF (3:1:1) to afford alcohol **230** in a 90% yield. This alcohol was converted to the mesylate **254** with methanesulfonyl chloride and triethylamine and the triisopropylsilyl group was removed with TBAF under the standard conditions. Deprotonation of the terminal acetylene was effected with KHMDS under dilute conditions at low temperature. However, formation of the desired, bicyclic enediyne **255** was not detected. The inability to generate this 12-membered system by any other method underscores the utility of the Nozaki-Kishi coupling in the construction of strained enediyne systems.



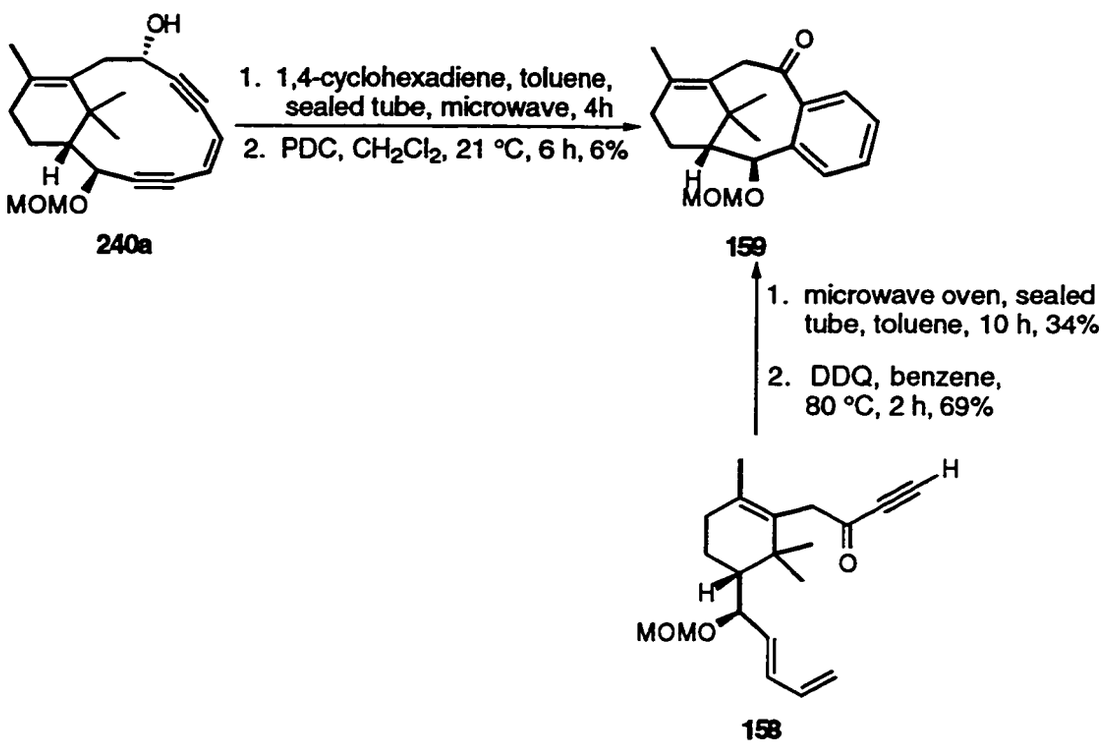
Scheme 72. Attempted Approach to Taxamycin-12 *Via* Intramolecular S_N2 Displacement

3.4 Studies of Taxamycin-12

3.4.1 Bergman Cyclization of Taxamycin-12

The conditions required for Bergman cycloaromatization of the taxamycin-12 **240a** were examined by Dr. Yee-Fung Lu to ascertain the potential for entry into the aromatic taxane nucleus **159** (Scheme **73**).[77] Thus, compound **240a** was heated for 4 hours with excess 1,4-cyclohexadiene in a sealed tube in a microwave oven to produce a complex mixture of products. In order to identify the presence of the expected cycloaromatized product, this crude mixture was treated with PDC, conditions which would yield the known ketone **159**. This ketone **159** was independently synthesized in the laboratory by a different approach involving a Diels-Alder reaction as the key step.[74] In this latter case, cycloaddition of the diene-dienophile compound **158**, followed by aromatization with

DDQ, afforded the taxane nucleus **159** in a yield of 24% for the two steps. The ^1H NMR spectrum of this ketone **159** was compared to the spectrum of the crude mixture obtained by heating and oxidation of **240a**. This comparison allowed for the identification of the desired product **159** from the attempted Bergman cyclization reaction. However, the yield of isolated product **159** was as low as 5-10%, suggesting that the Bergman cyclization of such a system is not a viable synthetic route to the aromatic taxanes at present.

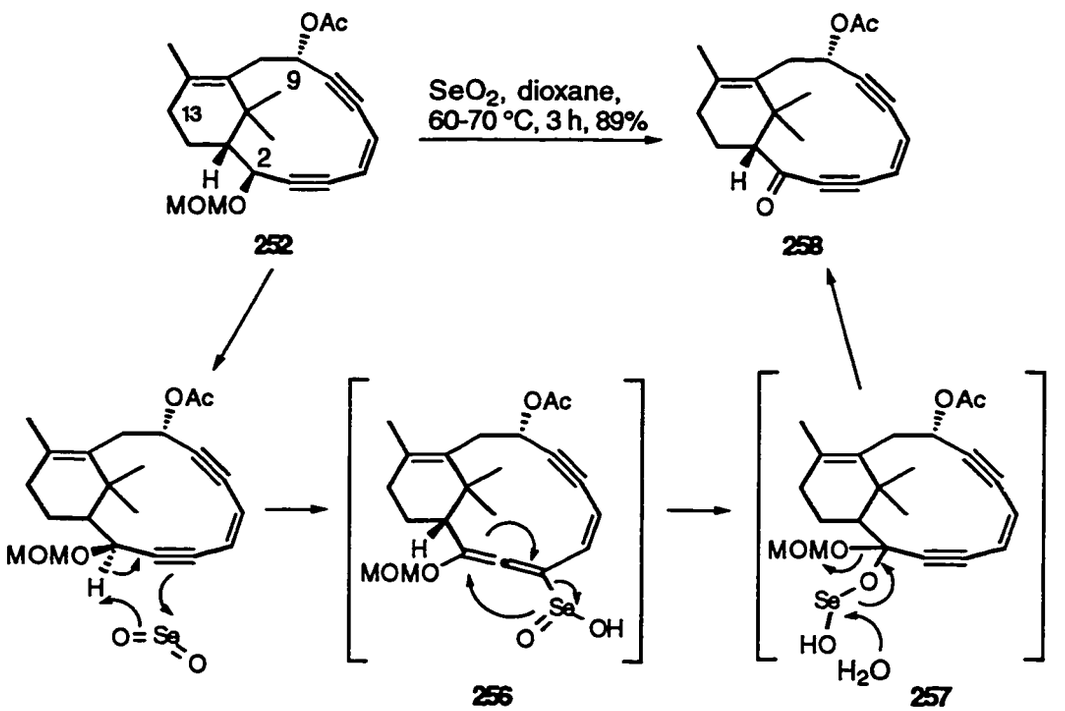


Scheme 73. Approach to Aromatic Taxane Nucleus *Via* Cycloaromatization of **240a**

3.4.2 Allylic Oxidation of Taxamycin-12

Further functionalization of the taxamycin-12 **252** was undertaken in order that the Taxol® side chain could be attached as originally planned. The enediyne **252** was subjected to a variety of oxidizing conditions in an attempt to oxidize the allylic C-13 position. The use of oxidants such as CrO_3 or PCC resulted only in recovery of starting material. The treatment of **252** with SeO_2 in dioxane at 60-70 °C afforded exclusively the ketone **258** in 89% yield.[110] A possible mechanism for this unusual oxidation process at

the C-2 position is depicted in scheme **74**.[111] It was envisaged that the pericyclic reaction of **252** with SeO_2 would generate the allene intermediate **256** in a process similar to the ene reaction. Next, a sigmatropic-type rearrangement would reintroduce the triple bond to give the hemiketal species **257** which would be then hydrolyzed to ketone **258** upon aqueous workup. The double bond of the A ring is presumably blocked by the enediyne bridge on one face and by the sterically demanding *gem* dimethyl group on the other. Consequently, SeO_2 is only able to approach the allylic C-2 position to afford oxidized product **258**.



Scheme 74. Oxidation of the C-2 Position by Treatment with SeO_2

3.5 The *cd* Distances in Taxamycin Analogues

Molecular mechanic calculations revealed that the *cd* distance in **240a** is approximately 3.8 Å, which is significantly larger than the r_{cd} separation of 3.2-3.3 Å required for spontaneous Bergman cyclization. According to calculations, isomerization of

the double bond away from the bridgehead, as in **259**, would result in a shortening of the r_{cd} by 0.3 Å (Figure **10**)[84] The *cd* separation is also reduced to 3.7 Å and 3.5 Å in the 10- and 11-membered taxamycin analogues, **260** and **261** respectively. These calculations suggest that synthetic modifications to this family could yield bicyclic enediynes that cycloaromatize more readily. These studies would hopefully lead to a triggering process which could be used to initiate Bergman cyclization under mild, ambient reaction conditions.

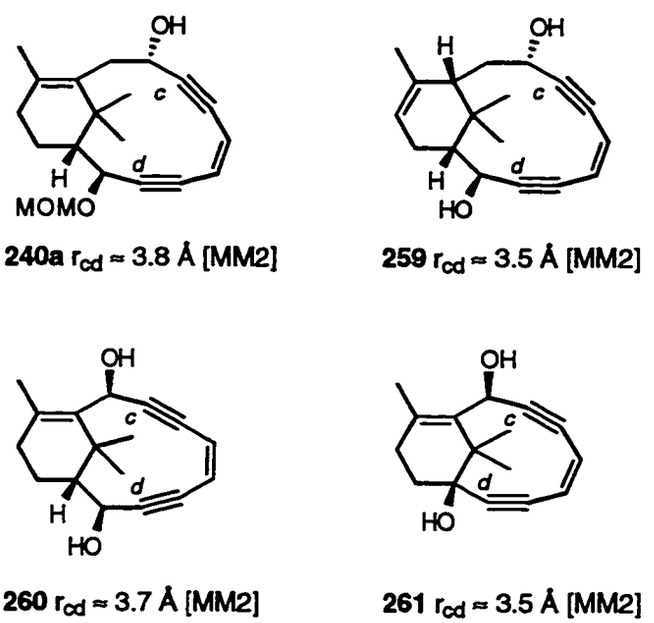


Figure **10.** Interatomic *cd* Separations in Various Taxamycin Analogues

4 Construction of Taxamycin-11 Model

4.1 Design of Taxamycin-11

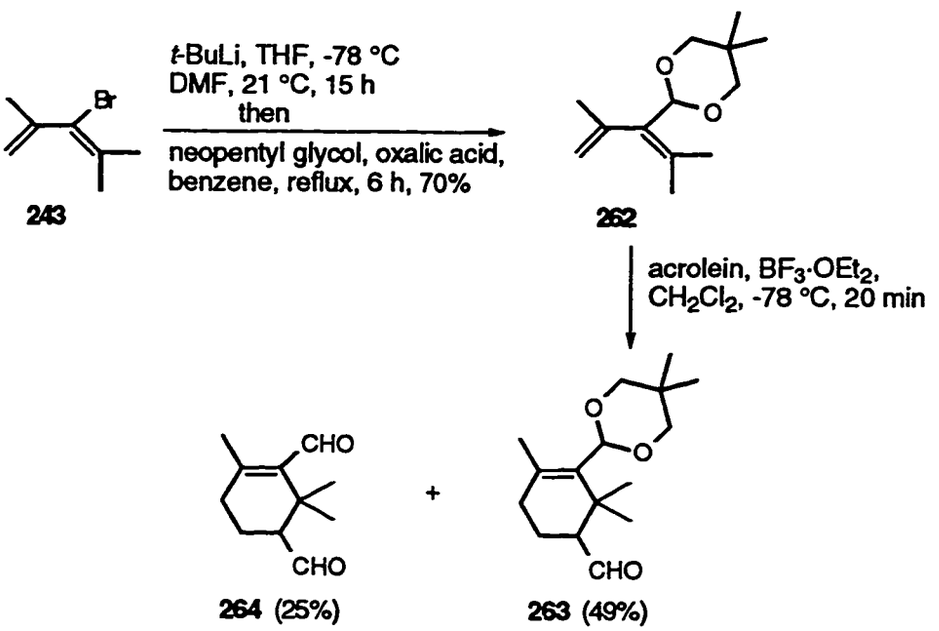
It was expected that other members of the taxamycin family could be assembled by applying the same sequence of steps used in the construction of the taxamycin-12 model. The generality and practicality of employing the enediyne synthon **177** as a building block could again be evaluated. An 11-membered bicyclic enediyne was thus designed by condensing the enediyne fragment **177** to a modified Taxol® A ring building block. It was anticipated from MM2 calculations that the intermolecular *cd* distance in the taxamycin-11 homologue would be shortened, yielding a cyclic compound that would cycloaromatize more readily than in the 12-membered case. The construction of this 11-membered model would add to the taxamycin family and, hopefully, lead to a suitably functionalized compound which might exhibit biological activity.

4.2 Synthesis of Taxamycin-11

4.2.1 Construction of Taxol® A ring Analogue

An A ring analogue similar to the one used in the taxamycin-12 case was elaborated by modification of two of the steps used previously.[102] The preparation of this precursor was accomplished in 3 steps from the bromodiene **243** (Scheme **75**). This compound was synthesized from 2,3-dimethyl-2-butene **241** as described earlier. The treatment of diene **243** with *t*-BuLi followed by DMF afforded the 3-formyl-pentadiene which was immediately protected as its 2,2-dimethylpropylene acetal **262** in a yield of 70% for the two steps. Diels-Alder reaction of the protected diene **262** with acrolein in the presence of $BF_3{\cdot}OEt_2$ at -78 °C for 20 min gave the desired cycloadduct **263** in 49% yield along with appreciable amounts of the deprotected dialdehyde **264** (25%). Attempts to improve the

yields of cycloaddition and minimize the rate of acetal deprotection with the use of other Lewis acids such as Et_2AlCl and $ZnCl_2$ proved unsuccessful.



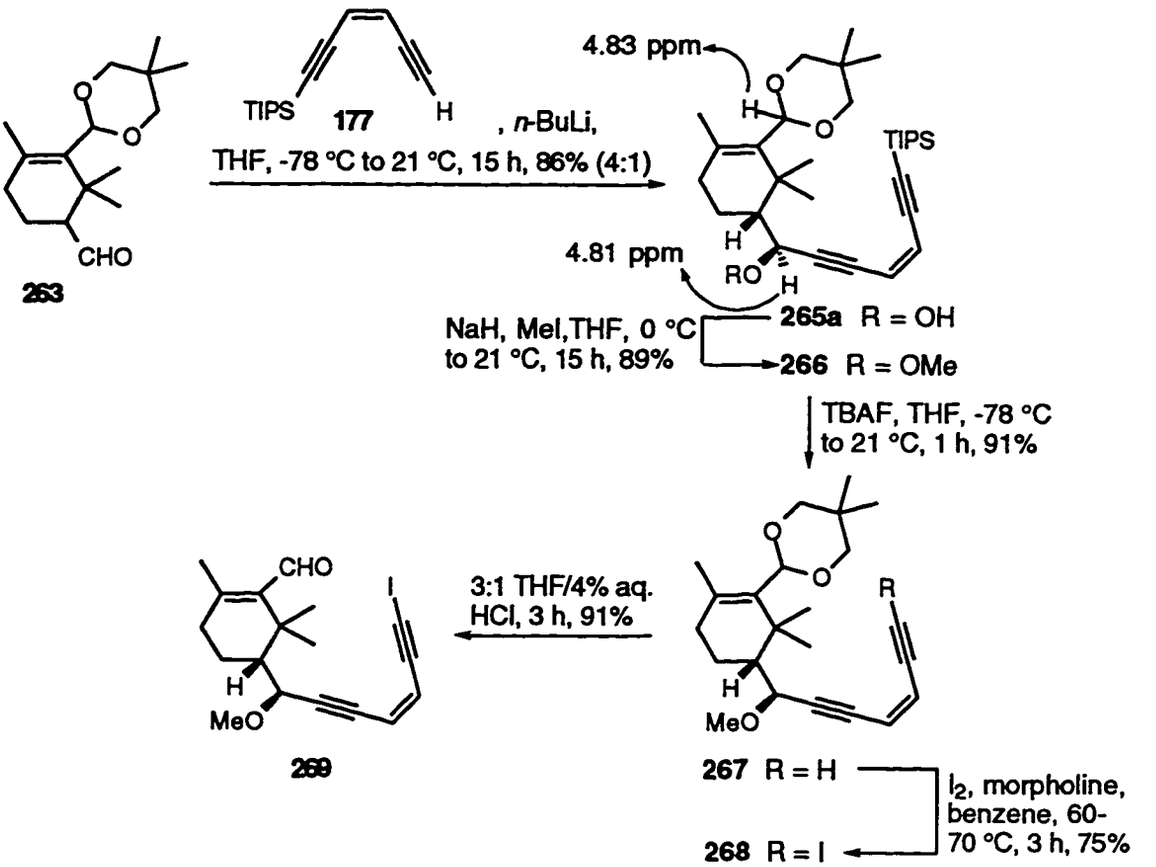
Scheme **75**. Construction of A Ring Building Block **263**

4.2.2 Elaboration to Cyclization Precursor

A taxamycin-11 model compound was constructed with the A ring building block **263** by the same approach as that used in the construction of the 12-membered compound **240a**. It was expected that the Nozaki-Kishi coupling reaction would effect final ring closure in this case, despite the problems encountered with the 12-membered system. Furthermore, it was anticipated that taxamycin-11 could be also constructed *via* an intramolecular acetylide condensation. This type of reaction has been used extensively by other research groups to cyclize unsaturated aldehydes.[54,89] Kende, Danishefsky and Nicolaou, for example, have all used this approach to assemble strained bicyclic enediyne systems of this nature.[32b,c,34,40i]

Addition of a solution of aldehyde **263** to the lithiated triisopropylsilyl protected enediyne **177** afforded a 4:1 mixture of diastereomeric alcohols in a combined yield of

86% (Scheme **76**). This ratio was determined by integration of the methine signals found in the ^{1}H NMR spectrum of the crude reaction mixture. The diastereomers were separated and purified by silica gel chromatography. In the major diastereomer **265a**, the proton next to the enediyne triple bond at the newly formed hydroxyl center appears as a singlet at 4.81 ppm next to the methine acetal signal at 4.83 ppm. The corresponding proton of the minor isomer appears as a broad singlet at 4.69 ppm. The relative stereochemistry of the major diastereomeric adduct was based on the X-ray analysis of the related derivative **248a** as before (Scheme **69**). This major isomer was protected as its methyl ether **266** in 89% yield by treating alcohol **265a** with NaH at 0 °C and trapping the resultant alkoxide with iodomethane. The methoxymethyl protecting group was not used in this case since treatment of **265a** with chloromethyl methyl ether and *N,N*-diisopropylethylamine resulted in some removal of the 2,2-dimethylpropylene acetal group and lower yields of desired product. Cleavage of the triisopropylsilyl group was performed with TBAF in THF and afforded **267** in 91% yield. The iodoacetylene **268** was produced in a yield of 75% by treatment of **267** with iodine and morpholine in benzene at 60-70 °C. The iodide was introduced at this stage since attempts to incorporate it after hydrolysis of the acetal function resulted only in decomposition of starting material. The 2,2-dimethylpropylene acetal was removed under dilute acidic conditions by stirring **268** in a 3:1 mixture of THF and 4% aqueous HCl for 3 hours, to afford the desired cyclization precursor **269** in a 91% yield.

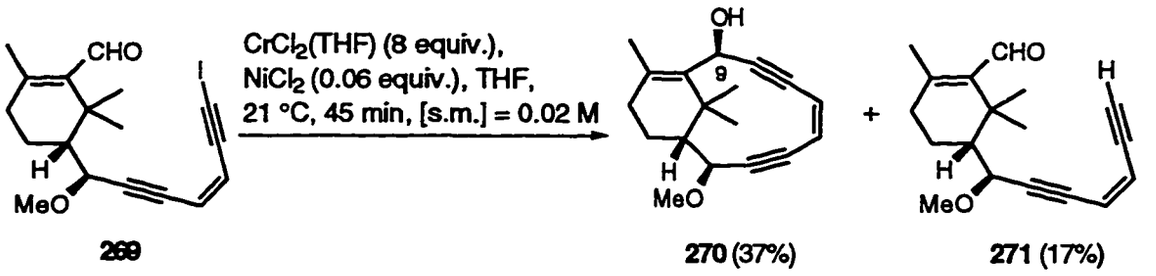


Scheme **76**. Elaboration of A Ring Analogue **263** to Cyclization Precursor **269**

4.2.3 Intramolecular Nozaki-Kishi Coupling

The Nozaki-Kishi coupling of the iodoaldehyde **269** was undertaken using the same conditions as those which successfully provided the taxamycin-12 compound **240a** (Scheme **77**). Treatment of **269** with excess $CrCl_2$ and catalytic $NiCl_2$ provided the cyclized adduct **270** as a single diastereomer in variable yield (7-37%). The appearance of a broad singlet at 5.75 ppm, which corresponds to H_9 of **270**, supported the formation of the desired bicyclic system. The two dimensional HMQC (heteronuclear correlation) NMR spectrum of **270** confirmed that this proton is attached to the newly formed hydroxyl C_9 carbon found at 63.5 ppm. Again, the yields of cyclization appeared to depend on the quality and source of $CrCl_2$ used. The best results were achieved with the $CrCl_2$(THF) complex donated by Dr. Gambarotta. The treatment of aldehyde **269** in THF under dilute

conditions (0.02 M) with excess $CrCl_2$(THF) (8 equiv.) in the presence of catalytic $NiCl_2$ (0.06 equiv.) afforded the taxamycin-11 **270** in a yield of 37%, along with reduced acetylene **271** in a yield of 17%.



269 **270** (37%) **271** (17%)

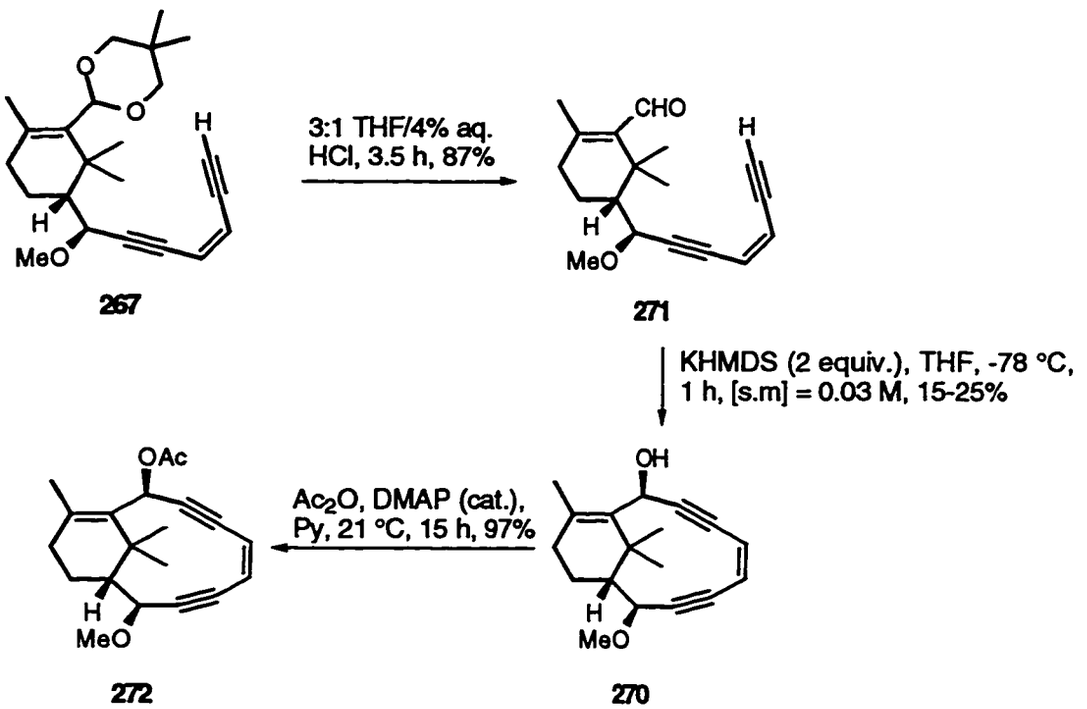
Scheme 77. Preparation of Taxamycin-11 by Nozaki-Kishi Coupling

However, treatment of **269** under the same conditions using an anhydrous source of $CrCl_2$ supplied by Aldrich® gave **270** in a low yield of 7%. The efficiency of this key step being unsatisfactory, other methods at ring closure were examined in order to develop a more reliable and higher yielding route to **270**.

4.2.4 Intramolecular Acetylide Cyclization

It was expected that formation of the final C-C bond which completes assembly of the bicyclic ring system would also be achieved by intramolecular acetylide cyclization (Scheme **78**). The precursor required for this cyclization was prepared from adduct **267** by removal of the 2,2-dimethylpropylene acetal with a 3:1 solution of THF and 4% aqueous HCl. Treatment of the resultant unsaturated aldehyde **271** with two equivalents of KHMDS at -78 °C for 1 hour afforded the cyclized adduct in a yield of 15-25%. These reaction conditions were developed by Grierson *et al.* in an efficient, stereoselective synthesis of a 10-membered bicyclic enediyne.[89c] Formation of the desired cyclized product was confirmed by conversion of alcohol **270** to acetate **272** with Ac_2O, pyridine and catalytic amount of DMAP. Attempts to improve the yields of this intramolecular condensation process with the use of trapping agents such as MeI, $(EtO)_2POCl$ and

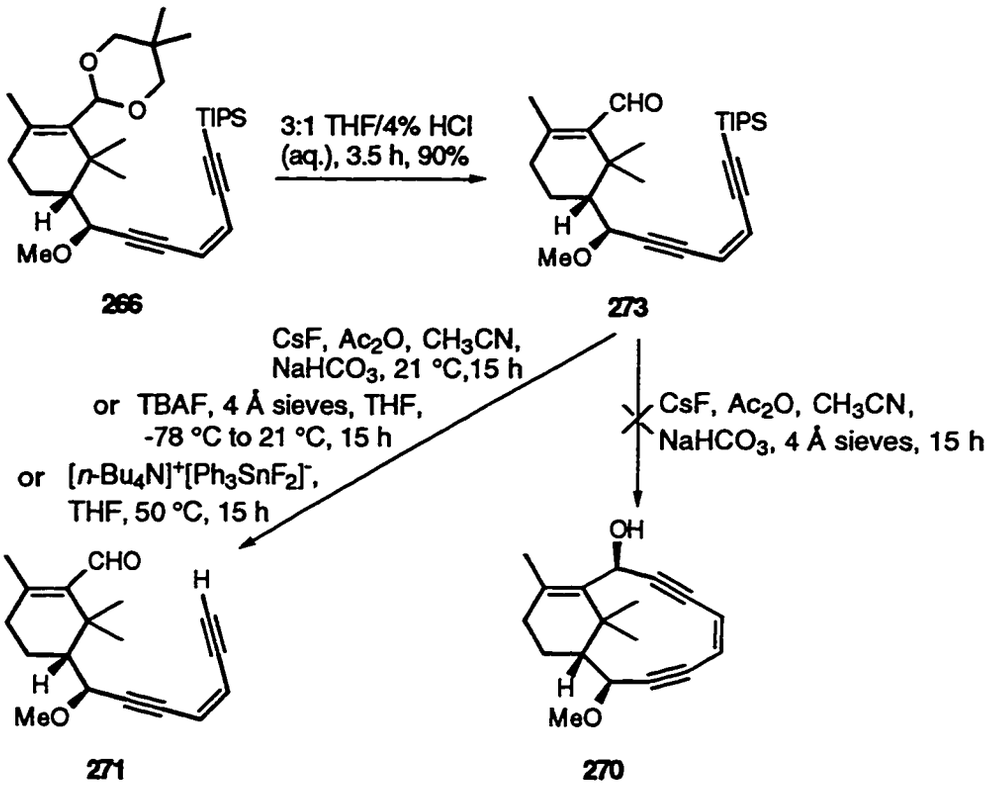
$PhN(SO_2CF_3)_2$ proved unsuccessful. The stereoselectivity of this reaction will be discussed later.



Scheme 78. Preparation of Taxamycin-11 by Intramolecular Acetylide Cyclization

Another approach to cyclization was examined using Wender's fluoride-induced, desilylative condensation procedure.[112] This method was used to construct a series of strained, 10-membered dynemicin analogues by the intramolecular addition of a trimethylsilyl protected acetylene to an aldehyde. This approach was appealing since it avoided the additional desilylation step and the use of strong base required to generate the acetylide. Consequently, the aldehyde **273** was prepared by removing the 2,2-dimethylpropylene acetal group of **266** with dilute HCl in 87% yield. Treatment of the silyl protected enediyne **273** with $NaHCO_3$, Ac_2O and CsF in CH_3CN containing 4 Å molecular sieves gave only recovered starting material. Only cleavage of the triisopropylsilyl group, to give enediyne **271**, was observed when the molecular sieves were omitted from the mixture. Other sources of anhydrous fluoride such as Gingras'

tetrabutylammonium difluorophenylstannate reagent and TBAF, dried over molecular sieves, also only effected triisopropylsilyl group removal.

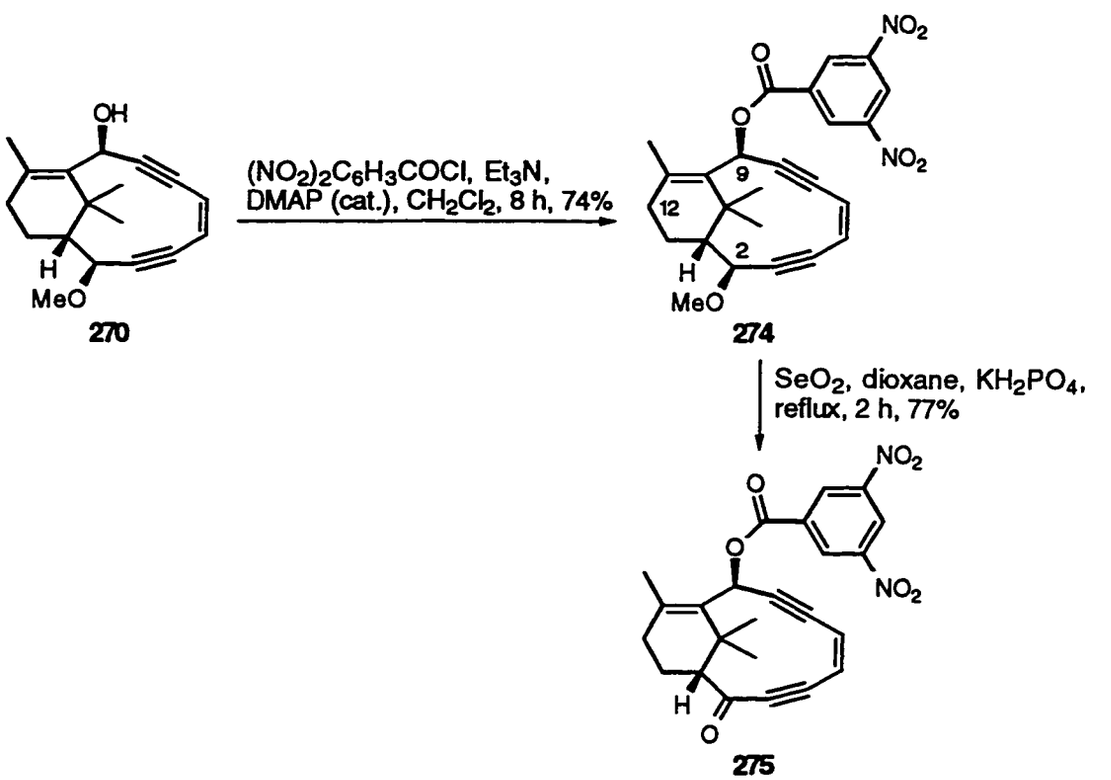


Scheme 79. Attempted Ring Closure by Wender's Anhydrous Fluoride Method

4.2.5 Functionalization of Taxamycin-11

A single diastereomeric adduct was detected and isolated from both the Nozaki-Kishi coupling reaction and the intramolecular acetylide cyclization step. The 3,5-dinitrobenzoyl derivative **274** was prepared from this alcohol in an attempt to determine the stereochemistry at the newly formed center. Treatment of **270** with 3,5-dinitrobenzoyl chloride, Et_3N and catalytic DMAP gave the corresponding benzoyl ester **274** as a white solid in 74% yield. However, crystals suitable for X-ray analysis could not be obtained. Subsequently, enediyne **274** was treated with SeO_2 in an attempt to oxidize the allylic C-12 position. Allylic oxidation of a similar taxamycin-10 system had been performed in the mean time using these same conditions, and oxidation of the resultant allylic alcohol

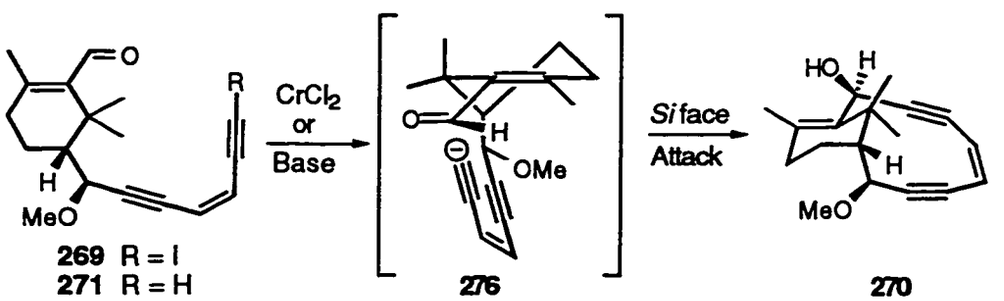
afforded a crystalline ketone **301** (Scheme **87**). In this 11-membered case, however, treatment of **274** with excess SeO_2 in dioxane at reflux for 15 hours gave exclusive oxidation at the C-2 position to afford the ketone **275** in a yield of 77%. A similar result was found in the attempted allylic oxidation of the taxamycin-12 model. In these two enediyne systems, the approach of SeO_2 was presumably blocked by the *gem* dimethyl group on one face of the A ring double bond and by the enediyne bridge on the other. As a result, the methyl ether at C-2 was susceptible to oxidation *via* the mechanism proposed earlier in scheme **74**. Surprisingly, only the allylic proton at the C-2 position was affected. The doubly allylic proton at the C-9 position remained intact.



Scheme **80**. Attempts to Prepare X-ray Suitable Crystals from **270**

The stereochemical outcome of the $CrCl_2$-mediated and base-induced intramolecular cyclizations was based on Darling molecular models which suggest a preference for *Si* face attack of the preferred *s-trans* conformer of the α,β-unsaturated aldehydes **269** or **271** (Scheme **81**). Addition of the enediyne acetylide onto this face would give adduct **270**,

where the newly formed hydroxyl group at C-9 and methyl ether at C-2 bear a *syn* relationship. Stereoselective anionic cyclizations of this nature onto α,β-unsaturated aldehydes have been described previously in other systems.[32b,40d] A similar stereochemical outcome was also discovered in the synthesis of a taxamycin-10 model (Scheme **87**). In this particualr system, the X-ray analysis of the resultant cyclized adduct showed that attack of the enediyne nucleophile occurred from the *Si* face of the *s-trans* conformer.



269 R = I
271 R = H

276 **270**

Scheme **81**. Intramolecular Approach of Enediyne Acetylide to *s-trans* Aldehyde

4.3 Summary of Cyclization Methods

In both the taxamycin-11 and -12 model systems, variable results were obtained when performing the final key cyclization step. The only method which could successfully effect ring closure for the 12-membered enediyne **240a** proved to be the Nozaki-Kishi coupling reaction. However, this cyclization reaction was unreliable, and respectable yields of adduct could not be successfully reproduced in repeated experiments. Similar results were observed for the synthesis of taxamycin-11 **270**. It was initially believed that the sensitivity and instability of the $CrCl_2$ reagent used in these reactions were responsible for these observations. However, in forming the taxamycin-11 **270**, low yields of cyclized material were also obtained *via* the intramolecular acetylide cyclization approach. Consequently, a combination of factors appeared to be inhibiting the formation of these two bicycles. The strain inherent in forming both 11- and 12-membered rings was one problem

which needed to be addressed. The *gem* dimethyl group which projects into the center of these two molecules also seemed to hinder the cyclization of these two systems. By examining molecular models, it appeared that the enediyne acetylide could approach the aldehyde function in both cases without severe interactions with the *gem* dimethyl group. Experimental work, however, proved contrary. Hence, the combined difficulties including the sterics of the systems being investigated, the size of the rings being formed and the sensitivity of the reagents being used, all contributed to low yields of cyclized adduct.

Unfortunately, gram quantities of either desired bicyclic enediyne system could not be prepared due to the unreliability of the final key cyclization step. Consequently, further studies and derivatization of these molecules could not be carried out. A new system was therefore developed in order to examine the Bergman cycloaromatization and to develop conditions to initiate or "trigger" this process.

5 Studies of a Taxamycin-10 Model

5.1 Design of Taxamycin-10

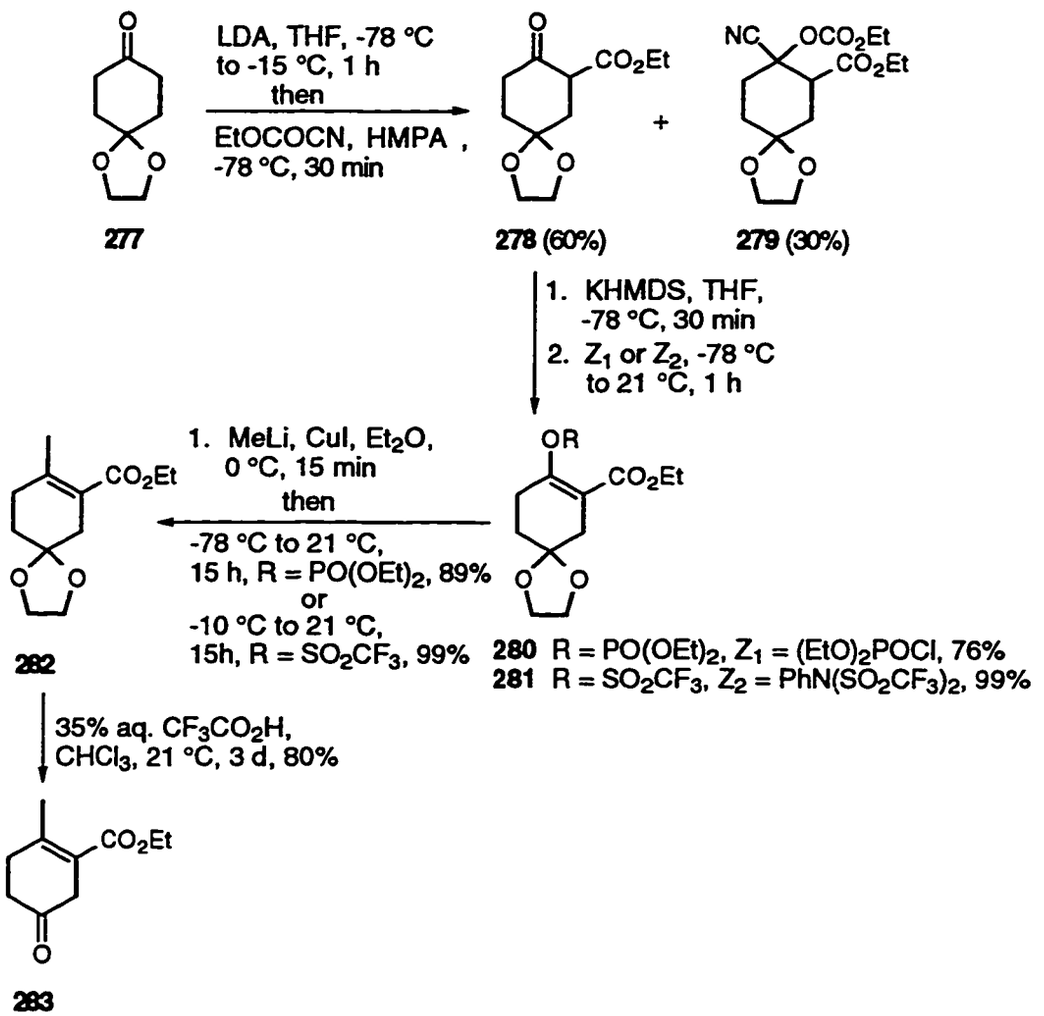
A 10-membered enediyne model was developed in order to complete the taxamycin series. The interacetylenic *cd* distance in this system was calculated to be approximately 3.5 Å, which would enable the Bergman cyclization to proceed under milder conditions than those required in the taxamycin-12 case.[84] In order to optimize the conditions for construction of the bicyclic system, the sterically demanding *gem* dimethyl group, present in both the 11- and 12-membered examples, was omitted in this case. It was expected that the removal of this group would facilitate the final ring closure process and enable gram scale quantities of the desired taxamycin-10 model to be prepared. With appreciable amounts of cyclized adduct in hand, several different approaches to cycloaromatization could be examined. Furthermore, Darling molecular models showed that the absence of the *gem* dimethyl group should not have a significant effect on the conformation of taxamycin-10. The importance of this group in the structure-activity relationship of taxoid compounds has, however, not yet been established.

The other key structural features of the taxamycins were preserved in the 10-membered ring model. The vinyl methyl group of the A ring cyclohexenone was retained since it was expected to act as a "handle" to allow for further functionalization of the bicyclic system once formed. The presence of the A ring brideghead double bond was also required in order to lock the enediyne moiety in place and prevent spontaneous cycloaromatization. Therefore, the isolation of an intact enediyne model could be used to develop a triggering system which would initiate Bergman cyclization once activated.

5.2 Synthesis of Taxamycin-10

5.2.1 Construction of the A Ring Building Block

The construction of the six-membered ring precursor for the taxamycin-10 homologue was expeditiously assembled in 4 steps (Scheme **82**). The commercially available *mono*-ethylene ketal of 1,4-cyclohexanedione, **277**, was used as the starting material. Treatment of this ketone with LDA resulted in the formation of the corresponding enolate which was trapped with ethyl cyanoformate[113] in the presence of HMPA, according to Mander's procedure[114], to generate the β-ketoester **278** in 60% yield. An appreciable amount of the cyano compound **279** was also produced under these conditions. Treatment of ester **278** with KHMDS followed by $(EtO)_2POCl$ provided the phosphate ester derivative **280** in 76% yield.[115] The enolate derived from deprotonation of **278** with KHMDS was also trapped with $PhN(SO_2CF_3)_2$ to give the corresponding triflate **281** in quantitative yield. Introduction of the vinyl methyl group was accomplished by treating phosphate **280** or triflate **281** with Me_2CuLi in ether.[115,116] The ethylene ketal was selectively removed by stirring **282** in a 35% aqueous solution of CF_3COOH for 3 days to provide the cyclohexenone precursor **283** in 80% yield.[117] This building block lacked the *gem* dimethyl group present in the other systems but possessed the two carbonyl functions which would allow for insertion of the enediyne synthon.

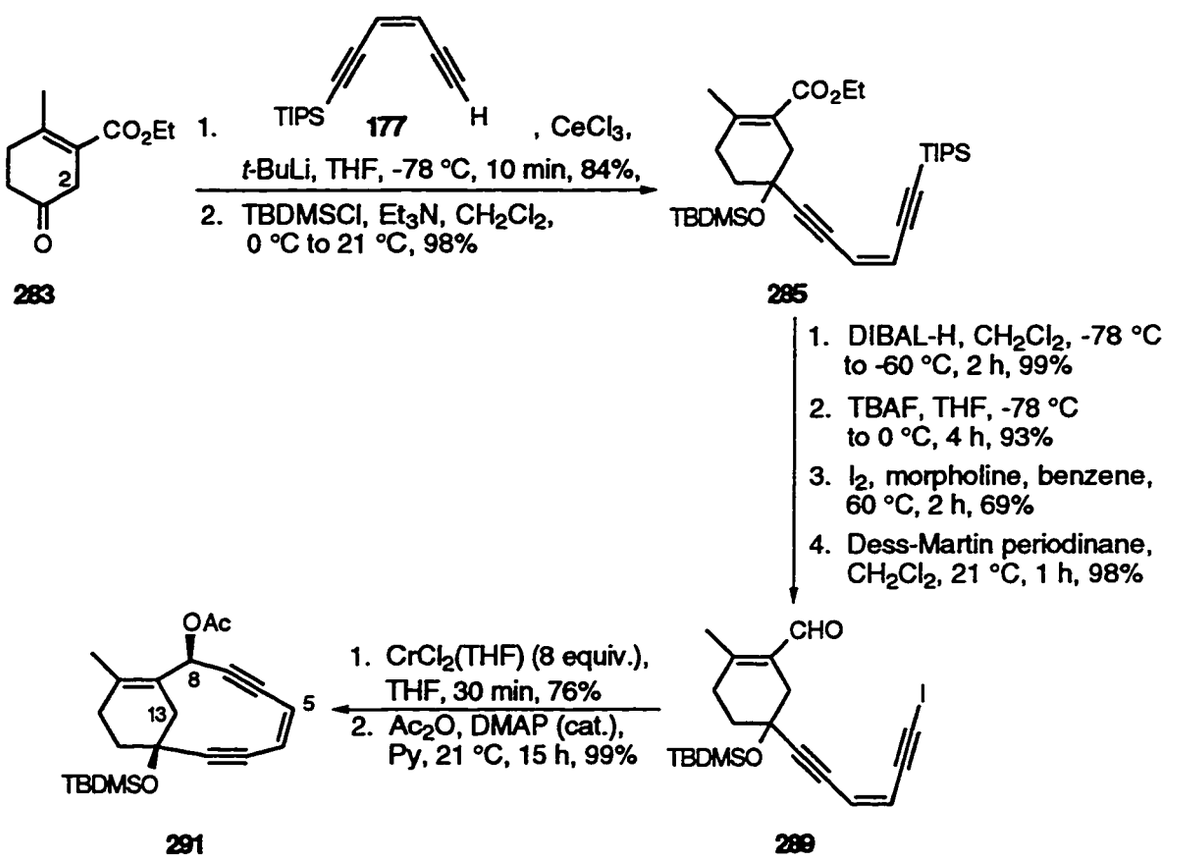


Scheme 82. Construction of A Ring Building Block Lacking the *Gem* Dimethyl Group

5.2.2 Assembly of Cyclization Precursor

The cyclohexenone building block **283** was combined with the enediyne synthon **177** to elaborate the desired taxamycin-10 compound **291** (Scheme 83). This work was carried out in association with Dr. Sandrine Py in order to prepare gram quantites of the desired taxamycin-10 system. The ketone **283** was first condensed with the cerium acetylide of enediyne **177** to afford the corresponding alcohol in 84% yield. The cerium species was employed in this case to encourage nucleophilic addition and to prevent deprotonation of the acidic protons at C-2, which are both allylic and adjacent to the carbonyl. The resultant alcohol was protected as its *t*-butyldimethylsilyl ether **285** in

excellent yield. Manipulation of the remaining functional groups was carried out to generate the desired cyclization precursor **289** in good yield. The ester function was reduced to the alcohol with DIBAL-H at low temperature and the triisopropylsilyl group was removed with TBAF. The resultant acetylene was converted to the corresponding iodoacetylene derivative with iodine and morpholine and oxidized with Dess-Martin periodinane to provide iodoaldehyde **289** in an overall yield of 62% for the 4 steps. This expedient sequence allowed for the multi-gram preparation of the cyclization substrate **289**.



Scheme 83. Synthesis of Taxamycin-10 Lacking the *Gem* Dimethyl Group

5.2.3 Intramolecular Nozaki-Kishi Coupling

Contrary to the 11- and 12-membered examples, the intramolecular Nozaki-Kishi coupling of this 10-membered enediyne precursor **289** proceeded smoothly and in good yields using an excess of $CrCl_2$. The best results were obtained using the freshly prepared

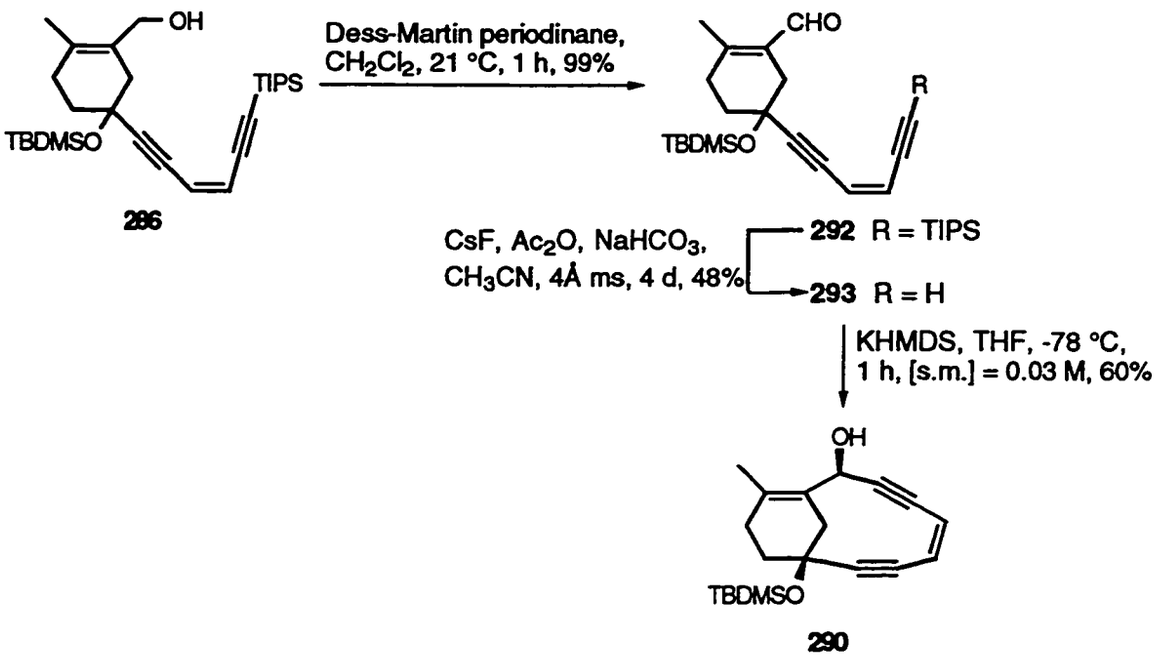
$CrCl_2$(THF) complex and provided adduct **290** in 76% yield. A doublet at 6.26 ppm in the ^1H NMR spectrum of **291** supported formation of cyclized product. This signal corresponds to the proton at C_8 which exhibits a small $^5J_{HH}$ coupling of 1.6 Hz with the vinyl enediyne proton at C_5. Furthermore, one of the protons at C_{13} is shifted downfield by 0.4 ppm upon formation of the strained bicyclic system. This proton appears as a doublet of doublets at 2.99 ppm (see Appendix A). Reproducible yields of cyclization in the 60-70% range were also acquired using commercially available, anhydrous $CrCl_2$. These results suggest that the *gem* dimethyl group present in both **240a** and **270** was, in fact, responsible for the problems associated with cyclization of these systems. This group apparently increases the strain energy needed to be overcome for formation of both the 11 and 12-membered bicyclic ring systems. This rationale accounts for the low yields of final ring closure of these two enediynes.

It is interesting to note that a catalytic amount of $NiCl_2$ was not required to effect cyclization in the 10-membered ring example. A similar result was discovered by Isobe *et al.* in their synthesis of a similar, cyclic enediyne compound.[105] This observation is contrary to many cases, where the reaction will only proceed by the addition of a catalytic amount of Ni(II).[42,43] The role of Ni(II) in the mechanism of this Nozaki-Kishi coupling reaction remains unclear.

5.2.4 Intramolecular Acetylide Cyclization

The formation of the final C-C formation was also examined using an intramolecular acetylide addition (Scheme **84**). Alcohol **286** was oxidized with Dess-Martin periodinane to afford aldehyde **292** in quantitative yield. Wender's anhydrous fluoride-mediated cyclization procedure[112], using CsF, Ac_2O in CH_3CN, was attempted but these conditions gave only triisopropylsilyl group removal. However, the resultant acetylene **293** was treated with KHMDS at -78 °C to provide the taxamycin-10 adduct **290** in a yield of 60%. The efficiency of this process demonstrates the feasibilty of this

approach and strengthens the hypothesis that the steric effects imposed by the *gem* dimethyl group of taxamycin-11 and -12 affected the yields of ring closure in those systems.



Scheme 84. Construction of Taxamycin-10 *via* Intramolecular Acetylide Cyclization

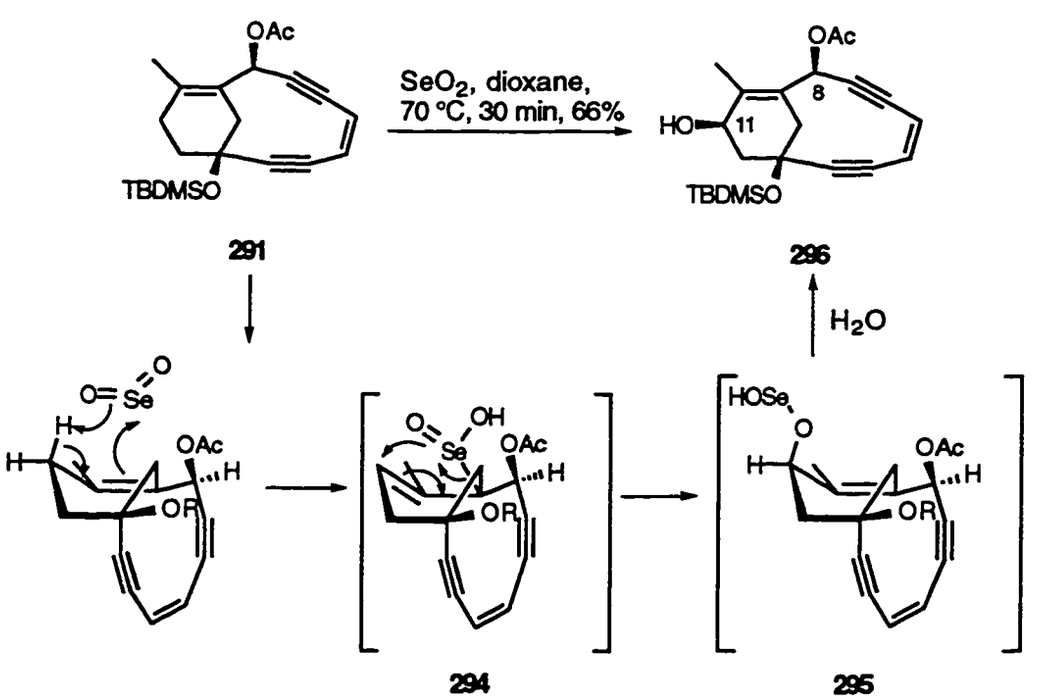
A single diasteromer was formed in both coupling reactions. The X-ray analysis of the oxidized adduct **301** reveals a *syn* relationship between the *O-t*-butyldimethylsilyl group and the newly formed hydroxyl function (Scheme **87**). This stereochemical outcome can be explained by acetylide attack onto the *Si* face of the preferred *s-trans* conformer of the α,β-unsaturated aldehydes **289** or **293** by analogy with the taxamycin-11 system.

This reliable and efficient route allowed for the preparation of a multi-gram quantity of the taxamycin-10 bicyclic ring system. Consequently, further derivatization of this molecule was carried out Dr. Sandrine Py. The design of unique triggering mechanisms was also developed in an attempt to initiate the Bergman cyclization of this particular system.

5.3 Derivatization of Taxamycin-10

5.3.1 Allylic Oxidation

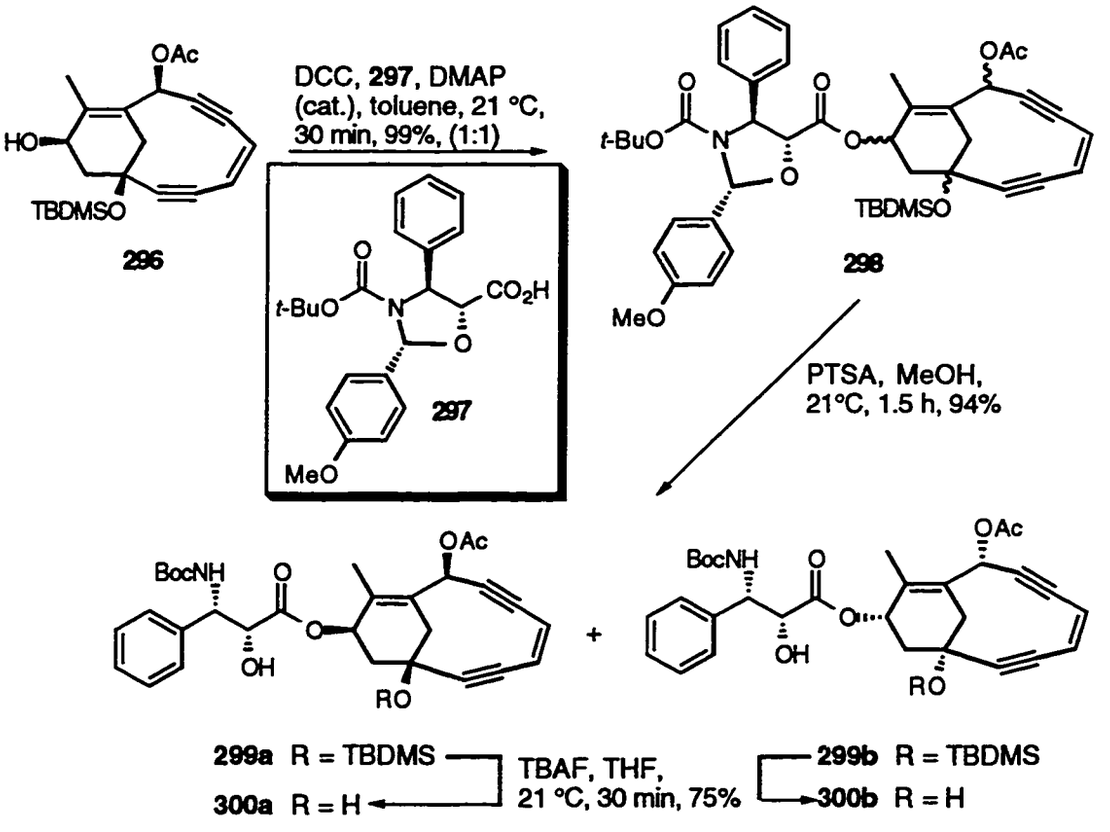
Further functionalization of **291** by allylic oxidation was examined (Scheme **85**). Treatment of enediyne **291** with SeO_2 in dioxane at 70 °C afforded the allylic alcohol **296** as a single diastereomer in a yield of 66%. The H_{11} proton at the newly formed hydroxyl position appears as a signal at 4.01 ppm in the ^1H NMR spectrum. No product resulting from oxidation of the vinylic methyl position was isolated. The relative stereochemistry of this alcohol was tentatively assigned as *syn* with respect to the *O*-*t*-butyldimethylsilyl ether group at C-1 and the *O*-acetate group at C-8 by comparison with the SeO_2 allylic oxidation of related models.[31b,118] The absence of the *gem* dimethyl group in this system allowed oxidation to take place from the top face of the cyclohexene ring. The enediyne bridge presumably inhibited approach of the SeO_2 reagent from the bottom side, resulting in the exclusive formation of the *syn* alcohol **296**.



Scheme 85. Allylic Oxidation of Taxamycin-10 with SeO_2

5.3.2 Attachment of Taxotere® Side Chain

The allylic oxidation of **291** enabled taxamycin-10 to be derivatized with a protected form of the Taxotere® side chain (Scheme **86**). The coupling of **296** with the enantiomerically enriched Taxotere® side chain, protected as its oxazolidine[119] provided adduct **298** as a 1:1 mixture of diastereomers in quantitative yield.[120] The diastereomers were separated and isolated upon opening of the oxazolidine ring with tosic acid. This cleavage process thus successfully effected the resolution of the racemic taxamycin-10 adduct **296**. The silyl protecting group of each diastereomer was removed with TBAF to furnish enediynes **300a** and **300b**, both possessing the unprotected Taxotere® side chain.[121]



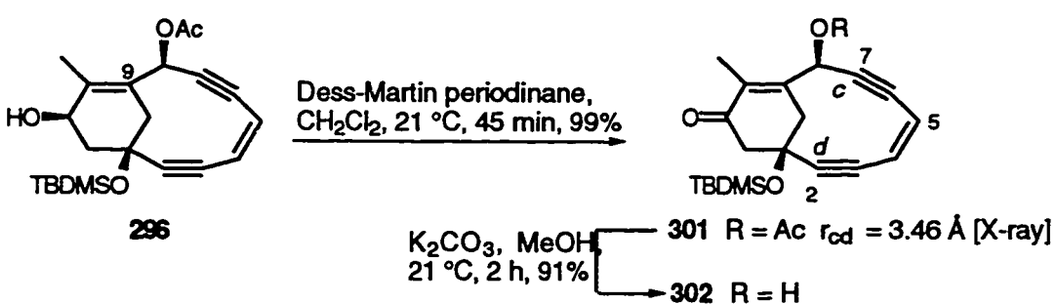
Scheme **86**. Attachment of Taxotere® Side Chain toTaxamycin-10

The taxamycin-10 compounds **300a** and **300b** along with intermediates **298** and **299** were submitted for biological testing, even though an effective trigger for Bergman cycloaromatization had yet to be installed. The cell toxicity of these compounds was investigated using the HT-29 and SK-MEL-28 human cancer cell lines.[122] Taxol® was used as a standard. It was initially hoped that the presence of the Taxotere® side chain in these adducts would allow for transport into the cells and binding to tubulin. Unfortunately, no cell toxicity was exhibited by any of the adducts up to drug concentrations as high as 10^{-4} M. Close to 90% of the HT-29 cancer cells survived upon treatment with 10^{-9} M **300a** whereas, by comparison, only 10% of the cells remained after treatment with 10^{-9} M Taxol®. These results suggest that the taxamycin-10 derivatives do not exhibit antimitotic activity and that their binding to tubulin is not effective enough to cause cell death according to the mechanism displayed by the taxane anticancer drugs. However, further studies were carried out to develop a "trigger" that would allow these compounds to cycloaromatize and be cytotoxic *via* a mechanism similar to the one exhibited by the natural enediyne antibiotics.

5.4 Attempts to Activate Bergman Cyclization

Several triggering systems have been designed by other research groups in order to make stable enediyne compounds biologically active.[48-51] In a similar manner, alcohol **296** was also used to develop some novel methods for initiating the Bergman cycloaromatization of this 10-membered bicyclic enediyne. The alcohol **296** was first oxidized with Dess-Martin periodinane to afford the enone **301** in quantitative yield as a crystalline solid (Scheme **87**). The *syn* relative stereochemistry between the two protected alcohol functions was confirmed from the X-ray analysis of this derivative. The distance between the *c* and *d* acetylenic carbons of **301** was also elucidated from its X-ray structure (Figure **11** in Appendix B). This distance was measured to be 3.46 Å which compares well with the 3.52 Å calculated from molecular modeling.[84] This distance lies outside the

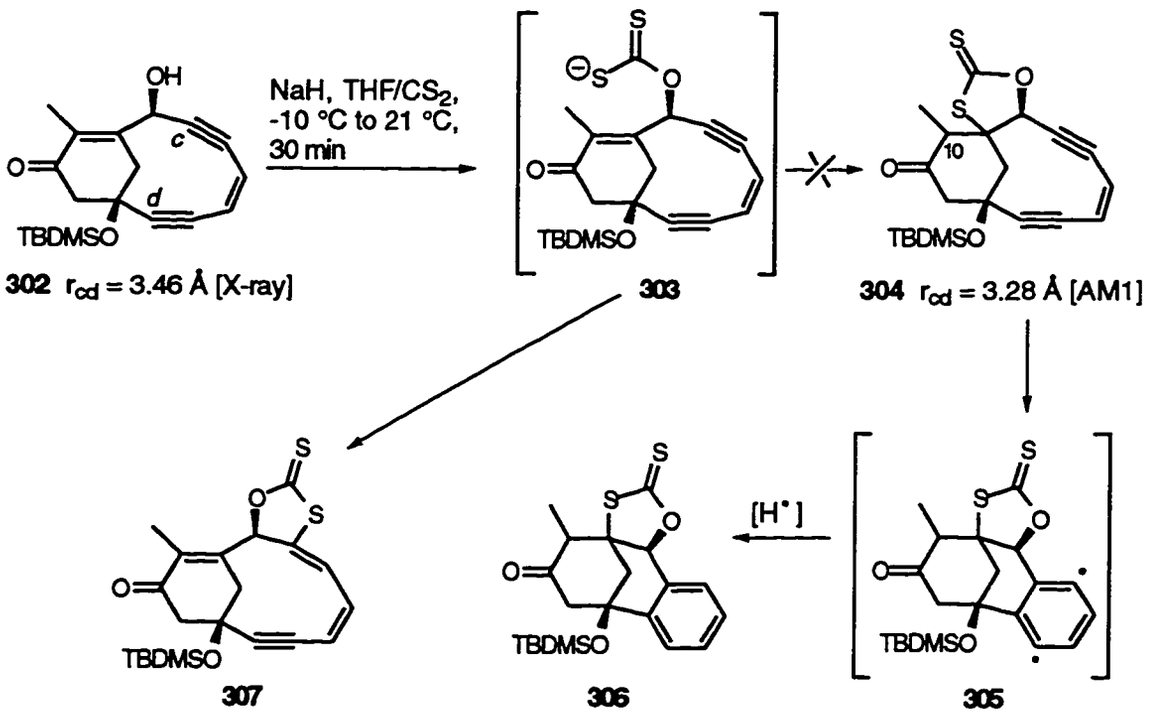
range of 3.2 to 3.3 Å which is required for spontaneous cycloaromatization.[22] Furthermore, the bridgehead A ring double bond of taxamycin-10 locks the enediyne moiety in place and prevents Bergman cyclization at ambient temperature. The cycloaromatization is disfavoured since it would generate a highly strained aromatic product containing an anti-Bredt bridgehead double bond. However, molecular modeling calculations reveal that conversion of the C-9 carbon from sp^2 to sp^3 hybridization results in a shortening of the *cd* distance to 3.3 Å. Therefore, different methods of effecting this transformation were examined in order to develop reaction conditions which could reduce the *cd* distance and initiate cycloaromatization. Interestingly, containment of the enediyne unit within the bicyclic framework of **301** distorts the normally linear acetylenic bond angles by approximately 12°. The bond angles about C_2, C_3, C_6 and C_7 measure 167.5°, 170.4°, 167.7° and 164.6° respectively. On the other hand, the bond angles about the C_4 and C_5 trigonal sp^2-hybridized carbons measure 119.5° and 118.8° (Figure **11**).



Scheme **87**. Oxidation of Alcohol **296** to the X-ray Derivative **301**

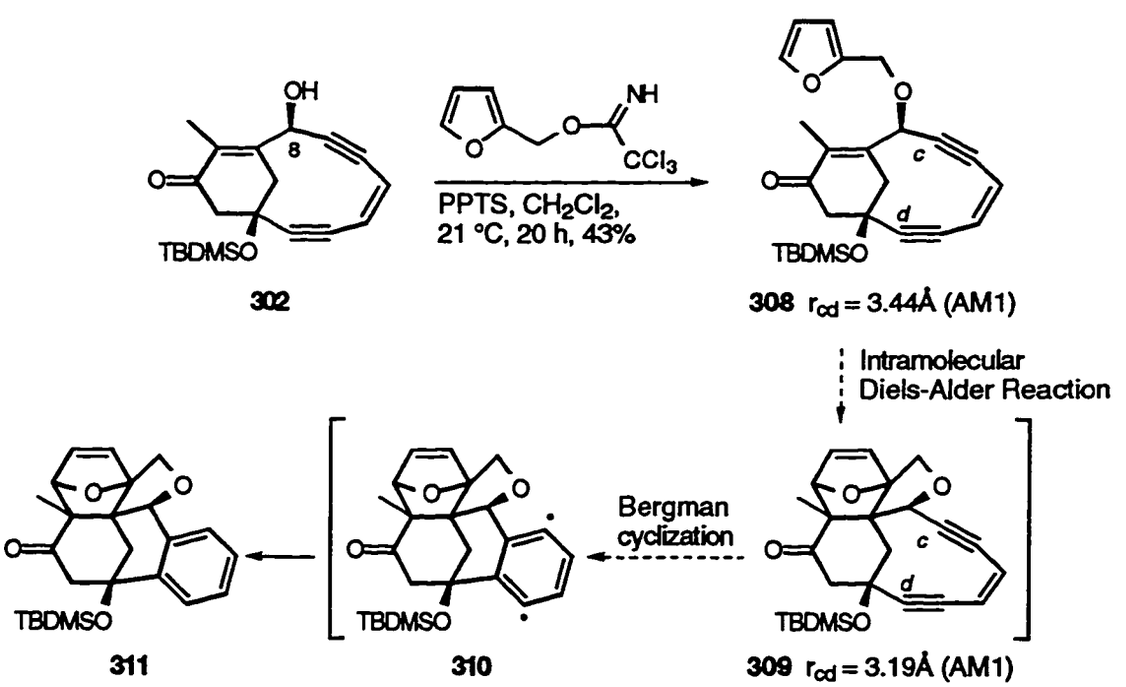
The oxidation of alcohol **296** was performed in order to activate the A ring bridgehead double bond to nucleophilic attack. Initially, it was expected that Michael addition to **301** with some external nucleophile could be accomplished. This reduction would result in a change of the hybridization at C-9 from sp^2 to sp^3 and lead to cycloaromatization. The 1,4-addition to **301** using methoxythiophenol as a nucleophile was, however, not observed. A similar result was obtained by Danishefsky and coworkers.[48a] They found that the Michael reaction of their calicheamicin model with standard nucleophiles such as thiolate, cyanide and cuprate could not be effected.

Consequently, an intramolecular approach to nucleophilic addition was examined. The acetate group in taxamycin-10 was removed with K_2CO_3 to provide alcohol **302** in 91% yield. The alcohol function served as a handle to introduce tethers and other reactive components which could potentially be used as triggering devices. Alcohol **302** was treated with NaH in CS_2 (Scheme **88**). It was anticipated that the resultant alkoxide would add to CS_2 to generate the xanthate intermediate **303** which would then add to the adjacent enone double bond. This Michael addition would result in a decrease in the *cd* distance, similar to the mechanism displayed by calicheamicin and esperamicin, and would initiate Bergman cyclization to provide, ultimately, the aromatic tetracyclic compound **306**. The expected conjugate addition was not observed, and instead, the intermediate xanthate **303** added to the neighbouring acetylenic bond to give **307**. A similar, intramolecular thiolate addition to an acetylene has been observed by Magnus *et al.* during their construction of the trisulfide functionality of calicheamicin.[31b,123]



Scheme **88**. Attempted Activation of Bergman Cyclization by Intramolecular Thiolate Addition

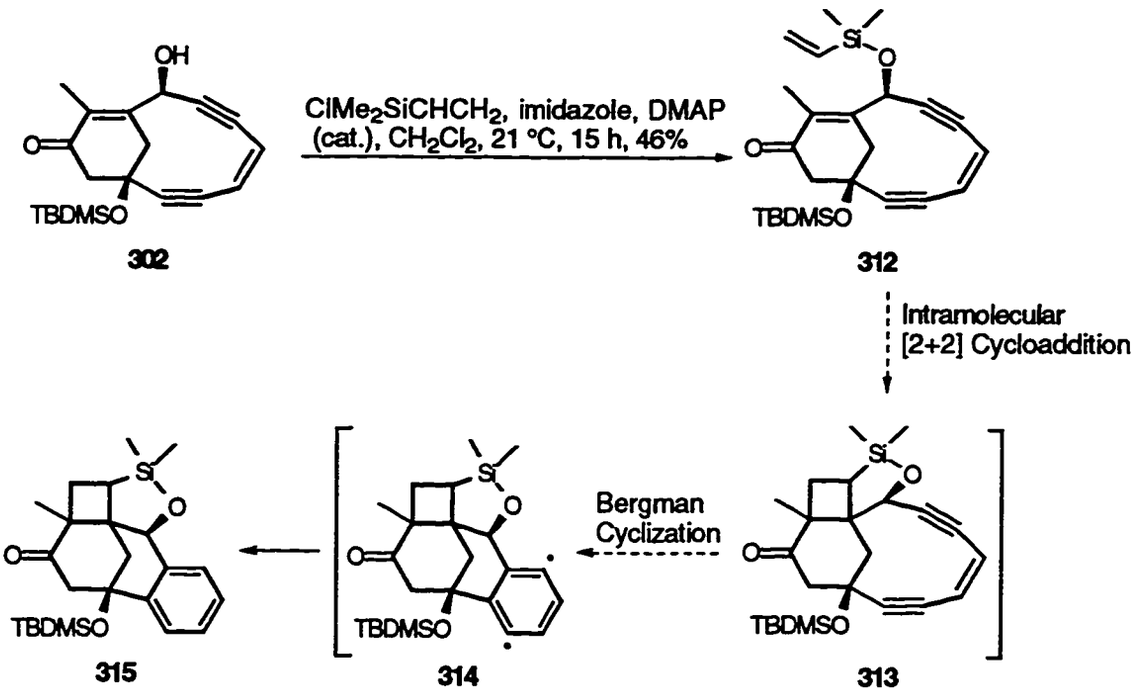
Other strategies have been devised to induce the cycloaromatization of taxamycin-10 due to the resistance of the bridgehead double bond to Michael addition. One plan involved the attachment of a diene containing tether to the C-8 position of **302** to attempt an intramolecular Diels-Alder reaction with the A ring double bond (Scheme **89**). Thus, alcohol **302** was coupled to furfuryl trichloroacetimidate.[124] Molecular modeling calculations show that, upon intramolecular cycloaddition of the precursor **308** to the adduct **309**, the *cd* bond distance is shortened from 3.44 Å to 3.19 Å.[84] This cycloaddition should thus induce Bergman cyclization. Initial attempts to conduct the Diels-Alder reaction in the presence of $BF_3{\cdot}OEt_2$ and excess 1,4-cyclohexadiene in CH_2Cl_2 have not, however, led to the desired cycloadduct.



Scheme **89**. Attempt to Activate Bergman Cyclization by Intramolecular Diels-Alder Reaction

In a similar fashion, it was anticipated that Bergman cycloaromatization of **302** could be initiated by an intramolecular, photoactivated [2+2] cycloaddition. Preliminary investigation involved generating adduct **312** by treating the alcohol **302** with chlorodimethylvinylsilane (Scheme **90**).[125] The [2+2] cycloaddition of **312** would afford the tetracyclic species **313** whose calculated interacetylenic *cd* distance of 3.25 Å should be

short enough to initiate the Bergman cyclization. Initial attempts at inducing the cycloaddition by photochemical means have, however, proved unsuccessful.



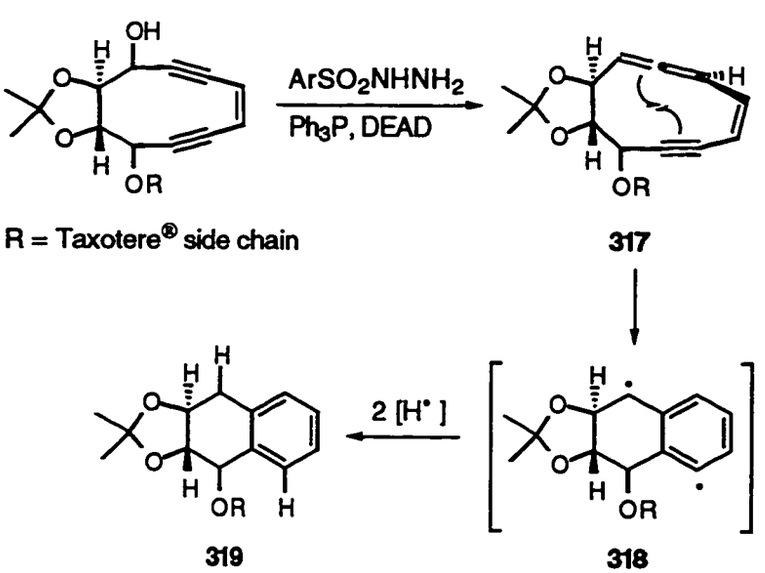
Scheme 90. Attempt to Activate Bergman Cyclization by Intramolecular [2+2] Cycloaddition

5.5 Summary and Future Work

The preparation of strained, 10-, 11- and 12-membered bicyclic compounds, containing structural features from both the taxoids and the enediyne antibiotics, has led to the development of a new family of molecules referred to as the "taxamycins". The $CrCl_2$-mediated, intramolecular Nozaki-Kishi coupling reaction was successfully used in all three systems to achieve final ring closure. An intramolecular acetylide addition approach was also used to effect formation of the taxamycin-10 and-11 models. The yields of cyclization obtained in the 11- and 12-membered ring examples were fair to low, making the synthesis of these two compounds on a large scale difficult. These unreliable results appear to be a result of a combination of factors, including the size and strain of the rings being formed and the sensitivity of the reagents being used. Although the anhydrous $CrCl_2$ employed in

the intramolecular Nozaki-Kishi reaction successfully afforded the desired compounds, its sensitivity to even traces of moisture often gave irreproducible results. The presence of the sterically demanding *gem* dimethyl group in both the taxamycin-11 and-12 models also appeared to be an important factor in effecting final ring closure. Its omission in the 10-membered ring model was accompanied by an efficient and high yielding cyclization process. Consequently, taxamycin-10 was prepared on a multi-gram scale, allowing for further functionalization and derivatization of this molecule. These studies included attachment of the Taxotere® side chain. The Bergman cycloaromatization of taxamycin-12 was also examined as a potential route to the taxane framework and provided the desired tricyclic nucleus, albeit in low yield. Preliminary attempts to elicit the Bergman cyclization of taxamycin-10, *via* an intramolecular Diels-Alder or [2+2] cycloaddition, were also examined and these studies form the basis of future work.

Another strategy to develop a "trigger" for cycloaromatization involves the synthesis of a 10-membered ring model based on a *trans*-isopropylidene system (Scheme **91**). It is anticipated that cleavage of the acetal in **316** will result in facile Bergman cyclization. Furthermore, the presence of the propargylic alcohol moiety will allow for the study of allene cyclizations.[126]



316 R = Taxotere® side chain

317

319

318

Scheme **91**. Study of an Allene Cyclization from Isopropylidene Enediyne **316**

6 Experimental Section

6.1 General Procedures

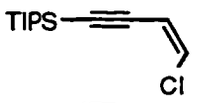
Melting points were determined in capillary tubes with a Thomas-Hoover Unit-Melt apparatus and are uncorrected. Infrared (IR) spectra were obtained either as neat films, or as a thin film of a dichloromethane solution of the compound on sodium chloride discs. All IR spectra were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR) and the data are reported in reciprocal centimeters (cm^{-1}). Proton magnetic resonance spectra (^1H NMR) were measured at 200 MHz with a Varian Gemini spectrometer, at 300 MHz with a Varian XL-300 spectrometer or at 500 MHz with a Bruker AMX500 spectrometer in deuterochloroform unless otherwise stated. Carbon magnetic resonance spectra (^{13}C NMR) were measured at 50 MHz (Varian Gemini), at 75 MHz (Varian XL-300) or at 125 MHz (Bruker). The residual signal was used as an internal lock; $CDCl_3$, ^1H: δ 7.24 ppm; ^{13}C: δ 77.0 ppm. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (δ scale). The multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad), coupling constants (Hz) and number of protons are indicated in parentheses. Mass spectra (MS) were determined on a V.G. micromass 7070 HS instrument using an ionization energy of 70 eV. Gas chromatograph - mass spectral (GC-MS) analyses were determined on a Hewlett-Packard 5890 Series II gas chromatograph - 5971A Mass Selective Detector equipped with a 12.5 m capillary column (0.2 mm i.d.) coated with cross-linked dimethylsilicone (0.33 μm). Elemental analyses were performed at M-H-W Laboratories, Phoenix, Arizona, USA or were performed in house. The purity of all title compounds was judged to be >95% as determined by a combination of GC-MS, ^1H NMR and ^{13}C NMR analyses.

Unless otherwise stated, all non-aqueous reactions were performed under an atmosphere of dry nitrogen in flame-dried glassware equipped with a magnetic stir bar and

a rubber septum. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Reactions were monitored by analytical thin layer chromatography (TLC) using commercial aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E.Merck). The TLC spots were viewed under ultraviolet light and by heating the TLC plate after treatment with either a 5% solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v), or a *p*-anisaldehyde staining solution (80 mL 95% ethanol, 2.9 mL sulfuric acid, 0.86 mL acetic acid, 2.1 mL *p*-anisaldehyde). Product purification by conventional and flash column chromatography was performed using E. Merck Silica Gel 60 (70-230 or 230-400 mesh). Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvents with a Büchi rotatory evaporator connected to a water aspirator. Trace solvents were removed on a vacuum pump. All compounds were stored at -15 °C in vials flushed with nitrogen.

Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30-60 °C. Anhydrous diethyl ether (ether) anhydrous tetrahydrofuran (THF) were freshly distilled from benzophenone/sodium. Dry benzene, toluene, dimethylformamide (DMF), dichloromethane (CH_2Cl_2), triethylamine, diisopropylamine, diisopropylethylamine and hexamethylphosphoramide (HMPA) were distilled from calcium hydride. Dioxane was distilled from $LiAlH_4$ and stored over Linde type 4 Å molecular sieves. All commercial starting materials were purchased from Aldrich Chemical Company unless otherwise stated.

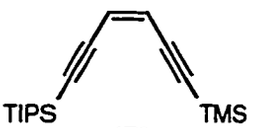
Preparation of (*Z*)-1-chloro-4-triisopropylsilyl-1-buten-3-yne (175)



175

Copper(I) iodide (61 mg, 0.30 mmol) was added to a stirred mixture of (triisopropyl)acetylene (1.98 g, 10.8 mmol), 1,2-*cis*-dichloroethylene (1.63 mL, 21.0 mmol), tetrakis(triphenylphosphine)palladium(0) (376 mg, 0.30 mmol), and *n*-butyl amine (2.10 mL, 21.6 mmol) in ether (50 mL). The reaction was stirred for 15 hours at room temperature, filtered through a plug of Celite and washed thoroughly with ether. The resultant solution was concentrated and purified by chromatography (petroleum ether) to yield 2.17 g (83%) of the enyne **175** as a yellow oil; IR (neat, cm^{-1}) 2945, 2154, 1463, 882; ^1H NMR (200 MHz, $CDCl_3$) δ 6.37 (d, J = 7.4 Hz, 1H), 5.88 (d, J = 7.4 Hz, 1H), 1.08 (s, 18H), 1.06 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 129.2, 112.3, 100.7, 100.1, 18.6, 11.2; HRMS calcd for $C_{13}H_{23}SiCl$ (M^+): 242.1257. Found: 242.1285.

Preparation of (*Z*)-1-triisopropylsilyl-6-trimethylsilyl-3-hexene-1,5-diyne (176)



176

Copper(I) iodide (46 mg, 0.24 mmol) was added to a stirred mixture of the chloride **175** (1.96 g, 8.07 mmol), (trimethylsilyl)acetylene (2.27 mL, 16.1 mmol), *n*-butyl amine (1.60 mL, 16.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (280 mg, 0.24 mmol) in ether (50 mL). The reaction was stirred for 15 hours at room temperature, filtered

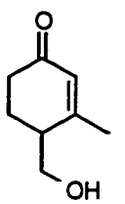
through a plug of Celite and washed thoroughly with ether. The resultant solution was concentrated and purified by chromatography (petroleum ether) to yield 1.91 g (78%) of the enediyne **176** as a brown, yellow oil; IR (neat, cm^{-1}) 2948, 2153, 2121, 1250, 1069; ^1H NMR (200 MHz, $CDCl_3$) δ 5.83 (s, 2H), 1.10-1.04 (br s, 21H), 0.17 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 120.4, 120.0, 103.8, 102.9, 101.9, 99.8, 18.7, 11.2, 0.22; HRMS calcd for $C_{18}H_{32}Si_2$ (M^+): 304.2042. Found: 304.2032; Anal. calcd for $C_{18}H_{32}Si_2$: C, 70.97; H, 10.59. Found: C, 70.48; H, 10.79.

Preparation of (*Z*)-1-triisopropylsilyl-3-hexene-1,5-diyne (177)

177

Potassium carbonate (0.11 g, 0.80 mmol) was added to a solution of the enediyne **176** (217 mg, 0.713 mmol) in THF/methanol (1:2, 10 mL) and the resultant mixture was stirred at room temperature for 2 hours. The solvent was then removed *in vacuo* and water (50 mL) and ether (50 mL) were added to the residue. The aqueous phase was extracted with ether (2 x 50 mL) and the combined ether extracts were washed with brine (1 x 50 mL), dried, filtered and concentrated. Purification of the crude oil by chromatography (petroleum ether) afforded 157 mg (95%) of the enediyne **177** as a brown, green oil; IR (neat, cm^{-1}) 3303, 2945, 2149, 1463, 1049; ^1H NMR (200 MHz, $CDCl_3$) δ 5.93 (dd, J_1 = 11.0 Hz, J_2 = 0.8 Hz, 1H), 5.79 (dd, J_1 = 11.0 Hz, J_2 = 2.2 Hz, 1H), 3.29 (dd, J_1 = 2.2 Hz, J_2 = 0.8 Hz, 1H), 1.10-1.04 (br s, 21H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 121.9, 119.3, 103.3, 100.1, 84.8, 80.8, 18.6, 11.2; HRMS calcd for $C_{12}H_{17}Si$ ($M^+ - C_3H_7$): 189.1099. Found: 189.1100.

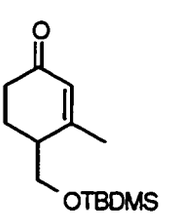
Preparation of 4-hydroxymethyl-3-methyl-2-cyclohexenone (184)



184

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (11.3 g, 49.8 mmol) was added in one portion to a solution of the diol **183** (6.42 g, 45.2 mmol) in 1,4-dioxane (100 mL) and the resultant mixture was stirred for 15 hours in a 250 mL flask covered in aluminum foil. The mixture was then passed through a plug of neutral alumina using a 50% solution of ethyl acetate/petroleum ether (200 mL). The filtrate was concentrated and purified by chromatography (50% ethyl acetate/petroleum ether) to afford 3.90 g (62%) of the oxidized product **184** as a clear oil; IR (neat, cm^{-1}) 3300, 1665, 1630, 1462, 1244, 1081; ^1H NMR (200 MHz, $CDCl_3$) δ 5.92 (s, 1H), 3.79 (m, 2H), 3.48 (br s, 1H), 2.53-2.33 (m, 2H), 2.30-2.11 (m, 1H), 2.09-1.99 (m, 2H), 1.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.5, 162.1, 128.5, 70.0, 42.1, 34.2, 24.9, 22.7; Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.60. Found: C, 67.91; H, 8.70.

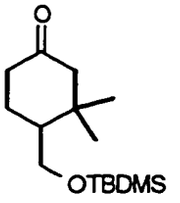
Preparation of 4-*tert*-butyldimethylsilyloxymethyl-3-methyl-2-cyclohexenone (185)



185

Imidazole (4.02 g, 59.0 mmol) and *tert*-butyldimethylsilylchloride (4.59 g, 30.5 mmol) were added sequentially to a solution of the alcohol **184** (3.90 g, 27.9 mmol) in CH_2Cl_2 (100 mL) at room temperature and the resultant mixture was stirred for 15 hours. A saturated solution of aqueous ammonium chloride (30 mL) was then added to the reaction and the mixture was poured into a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were washed with brine (1 x 30 mL), dried, filtered and concentrated. Purification of the residual oil by chromatography (25% ether/petroleum ether) yielded 6.68 g (94%) of the protected product **185** as a colourless oil; IR (neat, cm^{-1}) 2930, 1675, 1632, 1463, 1249, 1090; ^1H NMR (200 MHz, $CDCl_3$) δ 5.87 (s, 1H), 3.72 (d, J = 5.5 Hz, 2H), 2.39 (m, 3H), 2.02 (m, 2H), 1.97 (s, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.4, 162.5, 128.1, 63.3, 42.7, 34.3, 25.8, 25.5, 22.7, 17.8, –5.3; HRMS calcd for $C_{10}H_{17}O_2Si$ ($M^+ - C_4H_9$): 197.1013. Found: 197.1013; Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.08; H, 10.30. Found: C, 65.91; H, 9.51.

Preparation of 4-*tert*-butyldimethylsilyloxymethyl-3,3-dimethylcyclohexanone (182)

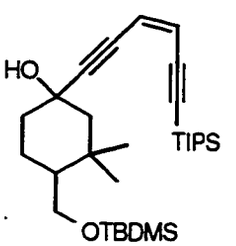


182

A solution of 3.0 M methylmagnesium bromide in ether (13.1mL, 0.039 mmol) was added to a suspension of copper(I) iodide (0.510 g, 2.78 mmol) in ether (100 mL) at 0 °C and the resultant slurry was stirred at 0 °C for 15 minutes. A solution of the enone **185** (6.68 g, 0.26 mmol) in ether (50 mL) was added dropwise. The reaction was

warmed to room temperature and stirred for one hour. The mixture was poured into a separatory funnel containing ether (100 mL) and a saturated aqueous solution of ammonium chloride (100 mL). The aqueous layer was extracted with ether (3 x 50 mL) and the combined organic layers were washed with brine (1 x 100 mL), dried, filtered and concentrated. Purification of the residual oil by chromatography (25% ether/petroleum ether) afforded 4.96g (70%) of ketone **182** as a clear oil; IR (neat, cm^{-1}) 2914, 1713, 1465, 1252, 1093; ^1H NMR (200 MHz, $CDCl_3$) δ 3.80 (dd, J_1 = 9.8 Hz, J_2 = 3.3 Hz, 1H), 3.42 (dd, J_1 = 9.8 Hz, J_2 = 7.3 Hz, 1H), 2.31-1.99 (m, 5H), 1.78-1.53 (m, 2H), 1.02 (s, 3H), 0.84 (s, 9H), 0.78 (s, 3H), 0.00 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.9, 63.3, 56.1, 47.2, 40.4, 37.4, 29.9, 25.9, 25.8, 21.8, 18.2, –5.5; HRMS calcd for $C_{11}H_{21}O_2Si$ (M^+ - C_4H_9): 213.1311. Found: 213.1327; Anal. calcd for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18. Found: C, 66.98; H, 11.24.

Preparation of 4-*tert*-butyldimethylsilyloxymethyl-1-hydroxy-3,3-dimethyl-1-[(*Z*)-triisopropylsilyl-3-hexene-1,5-diynyl]cyclohexane (181)

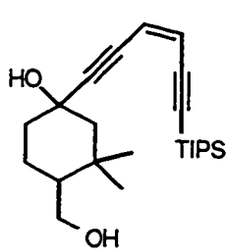


181

A 2.5 M solution of *n*-butyllithium in hexanes (2.8 mL, 7.0 mmol) was added dropwise to a solution of the enediyne **177** (1.80 g, 7.76 mmol) in THF (50 mL) at -78 °C. The solution was stirred at -78 °C for 30 minutes and became dark brown in colour. A solution of the ketone **182** (1.40 g, 5.19 mmol) in THF (10 mL) was added dropwise. The reaction was warmed to room temperature and stirred 15 hours. The

mixture was then poured into a separatory funnel containing ether (100 mL) and water (100 mL). The aqueous layer was extracted with ether (3 x 70 mL) and the combined organic layers were washed with brine (1 x 70 mL), dried, filtered and concentrated. Purification of the crude residual oil by chromatography (5% ether/petroleum ether) afforded 1.64 g (63%) of the addition product **181** as a yellow oil; IR (neat, cm^{-1}) 3428, 2912, 2142, 1678, 1464, 1089; ^1H NMR (200 MHz, $CDCl_3$) δ 5.81 (s, 2H), 3.76 (dd, J_1 = 9.9 Hz, J_2 = 4.0 Hz, 1H), 3.30 (dd, J_1 = 9.9 Hz, J_2 = 8.4 Hz, 1H), 2.08-1.92 (m, 1H), 1.80-1.40 (m, 6H), 1.35-1.21 (m, 1H), 1.12-1.06 (br s, 21H), 0.95 (s, 3H), 0.94 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 119.7, 119.3, 103.7, 102.4, 99.1, 79.6, 68.0, 63.8, 52.5, 48.2, 38.7, 32.7, 31.4, 25.9, 22.8, 20.9, 18.7, 18.3, 11.2, –5.3; MS (CI) 486 (M^+ - H_2O, 4%), 485 (MH^+ - H_2O, 9%), 385 (MH^+ - H_2O - C_4H_9 - C_3H_7, 23%); HRMS calcd for $C_{27}H_{47}O_2Si_2$ (M^+ - C_3H_7): 459.3117. Found: 459.3125; Anal. calcd for $C_{30}H_{54}O_2Si_2$: C, 71.65; H, 10.82. Found: C, 71.59; H, 10.38.

Preparation of 1-hydroxy-4-hydroxymethyl-3,3-dimethyl-1-[(*Z*)-triisopropylsilyl-3-hexene-1,5-diynyl]cyclohexane (186)

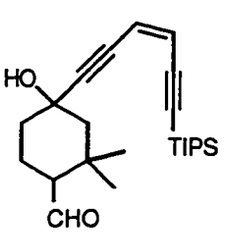


186

Alcohol **181** (265 mg, 0.534 mmol) was stirred in a mixture of acetic acid, water and THF (3:1:1, 10 mL) at room temperature for 4 hours. The mixture was quenched with saturated aqueous sodium bicarbonate to a neutral pH 7 and poured into a separatory funnel containing ether (70 mL) and a saturated aqueous solution of sodium bicarbonate (70 mL).

The aqueous layer was extracted with ether (2 x 70 mL) and the combined organic layers were washed with brine (3 x 70 mL), dried, filtered and concentrated. Purification of the resultant oil by chromatography (40% ethyl acetate/petroleum ether) afforded 157 mg (75%) of the alcohol **186** as a clear oil; IR (neat, cm^{-1}) 3361, 3295, 2943, 2140, 1684, 1022; ^1H NMR (200 MHz, $CDCl_3$) δ 5.80 (s, 2H), 3.82 (dd, J_1 = 10.4 Hz, J_2 = 3.7 Hz, 1H), 3.33 (dd, J_1 = 10.4 Hz, J_2 = 9.0 Hz, 1H), 2.07-1.95 (m, 1H), 1.88-1.51 (m, 7H), 1.36-1.20 (m, 1H), 1.10-1.04 (br s, 21H), 0.95 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 119.6, 119.4, 103.6, 102.3, 99.2, 79.6, 67.8, 63.7, 52.3, 48.3, 38.5, 32.7, 31.3, 22.8, 20.9, 18.7, 11.2; MS(CI) 389 (MH^+, 6%), 388 (M^+, 2%), 371 (MH^+ - H_2O, 100%), 345 (M^+ - C_3H_7, 10%); HRMS calcd for $C_{24}H_{38}OSi$ (M^+ - H_2O): 370.2694. Found: 370.2690.

Preparation of 4-formyl-1-hydroxy-3,3-dimethyl-1-[(*Z*)-triisopropylsilyl-3-hexene-1,5-diynyl]cyclohexane (187)

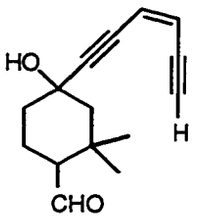


187

Dimethyl sulfoxide (50 μL, 0.7 mmol) was added to a solution of oxalyl chloride (54 μL, 0.6 mmol) in CH_2Cl_2 (5 mL) at -78 °C and the mixture was stirred for 30 minutes. A solution of the alcohol **186** (97 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) and triethylamine (245 μL, 1.8 mmol) were added sequentially to the reaction. The resultant mixture was warmed to room temperature and stirred for 8 hours. The mixture was then poured into a separatory funnel containing CH_2Cl_2 (15 mL) and water (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with

aqueous 10% HCl (1 x 15 mL), saturated aqueous sodium bicarbonate (1 x 15 mL) and brine (1 x 15 mL) respectively and then dried, filtered and concentrated. Purification of the crude oil by chromatography (25% ethyl acetate/petroleum ether) afforded 92 mg (95%) of the aldehyde **187** as a clear oil; IR (neat, cm^{-1}) 3424, 2912, 2727, 2142, 1715, 1574, 1007; ^1H NMR (200 MHz, $CDCl_3$) δ 9.80 (d, J = 1.9 Hz, 1H), 5.82 (s, 2H), 2.18-1.90 (m, 2H), 1.86-1.60 (m, 6H), 1.14 (s, 3H), 1.12 (s, 3H), 1.10-1.06 (br s, 21H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.2, 119.9, 119.5, 103.5, 101.4, 99.5, 80.1, 67.3, 58.0, 51.8, 37.7, 33.4, 31.4, 23.5, 18.7, 18.0, 11.2; MS(CI) 387 (MH^+, 29%), 386 (M^+, 27%), 385 (M^+ - H, 100%), 369 (MH^+ - H_2O, 12%), 343 (M^+ - C_3H_7, 23%); HRMS calcd for $C_{21}H_{31}O_2Si$ (M^+ - C_3H_7): 343.2095. Found: 343.2080.

Preparation of 4-formyl-1-[(*Z*)-3-hexene-1,5-diynyl]-1-hydroxy-3,3-dimethylcyclohexane (190)

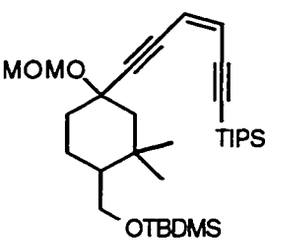


190

Tetrabutylammonium difluorotriphenylstannate (208 mg, 0.325 mmol) was added to a solution of **187** (98 mg, 0.25 mmol) in THF (5 mL) at reflux and the reaction was stirred for 24 hours. The mixture was then passed through a short column of silica using CH_2Cl_2 as an eluant. Purification of the resultant oil by chromatography (10% ethyl acetate/petroleum ether) afforded 40 mg (70%) of the aldehyde **190** as a clear oil; IR (neat, cm^{-1}) 3405, 3285, 2928, 2731, 2092, 1719, 1451, 1037; ^1H NMR (500 MHz, $CDCl_3$) δ 9.84 (d, J = 2.2 Hz, 1H), 5.99 (d, J = 10.9 Hz, 1H), 5.76 (dd, J_1 = 10.9 Hz, J_2 = 2.4Hz,

1H), 3.34 (dd, J_1 = 2.4 Hz, J_2 = 0.8Hz, 1H), 2.43-2.36 (m, 1H), 2.31-2.12 (m, 4H), 2.03-1.98 (m, 1H), 1.78-1.69 (m, 1H), 1.55 (br s, 1H), 1.25 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 121.6, 117.7, 98.3, 85.1, 84.8, 80.8, 67.3, 55.3, 43.3, 34.9, 29.1, 28.5, 24.0, 19.2; MS(CI) 231 (MH^+, 33%), 230 (M^+, 80%), 229 (M^+ - H, 100%), 213 (MH^+ - H_2O, 57%), 212 (M^+, H_2O, 33%), 201 (M^+ - CHO, 27%).

Preparation of 4-*tert*-butyldimethylsilyloxymethyl-1-methyloxymethoxy-3,3-dimethyl-1-[(*Z*)-triisopropylsilyl-3-hexene-1,5-diynyl]cyclohexane (191)

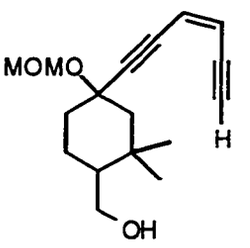


191

Chloromethyl methyl ether (0.50 mL, 6.5 mmol) was added to a cold (0 °C) solution of the alcohol **181** (640 mg, 1.3 mmol) and diisopropylethylamine (1.25 mL, 7.2 mmol) in CH_2Cl_2 (10 mL). The reaction was warmed to room temperature and stirred for 15 hours. The mixture was poured into a separatory funnel containing ether (70 mL) and water (70 mL). The aqueous phase was extracted with ether (3 x 70 mL) and the combined organic extracts were washed with aqueous 10% HCl (1 x 70 mL), saturated sodium bicarbonate (1 x 70 mL) and brine (1 x 70 mL) respectively and then dried, filtered and concentrated. Purification of the crude oil by chromatography (10% ethyl acetate/petroleum ether) yielded 656 mg (95%) of the compound **191** as a clear oil; IR (neat, cm^{-1}) 2913, 2141, 1463, 1055; ^1H NMR (200 MHz, $CDCl_3$) δ 5.81 (s, 2H), 5.00 (d, J = 6.6 Hz, 1H), 4.69 (d, J = 6.6 Hz, 1H), 3.76 (dd, J_1 = 9.9 Hz, J_2 = 4.0 Hz, 1H), 3.39 (s, 3H),

3.32 (dd, J_1 = 9.9 Hz, J_2 = 8.6 Hz, 1H), 2.27-2.12 (m, 1H), 1.87-1.22 (m, 6H), 1.10-1.06 (br s, 21H), 0.95 (s, 3H), 0.93 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 119.5, 103.6, 99.6, 99.3, 93.3, 81.8, 73.9, 63.8, 56.3, 51.4, 48.2, 36.9, 32.8, 31.5, 25.9, 22.8, 21.1, 18.7, 18.3, 11.2, –5.3; MS (CI) 516 (MH^+ - OCH_3, 27%), 485 (M^+ - OCH_3 - CH_3 - CH_3, 100%); Anal. calcd for $C_{32}H_{58}O_3Si_2$: C, 70.27; H, 10.69. Found: C, 70.56; H, 10.28.

Preparation of 1-[(*Z*)-3-hexene-1,5-diynyl]-4-hydroxymethyl-3,3-dimethyl-1-methyloxymethoxycyclohexane (192)

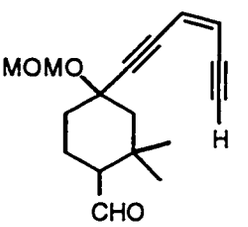


192

A 1 M solution of tetrabutylammonium fluoride (1.30 mL, 1.30 mmol) was added to a solution of **191** (287 mg, 0.526 mmol) in THF (10 mL) at -78 °C. The reaction was warmed to room temperature and stirred for 5 hours. The mixture was then poured into a separatory funnel containing a saturated aqueous solution of ammonium chloride (50 mL) and ether (50 mL). The aqueous phase was extracted with ether (3 x 50 mL) and the combined organic layers were washed with brine (1 x 50 mL), dried, filtered and concentrated. Purification of the resultant oil by chromatography (40% ethyl acetate/petroleum ether) afforded 132 mg (91%) of the alcohol **192** as a clear oil; IR (neat, cm^{-1}) 3360, 3295, 2918, 2093, 1575, 1022; ^1H NMR (200 MHz, $CDCl_3$) δ 5.89 (dd, J_1 = 10.9 Hz, J_2 = 0.8 Hz, 1H), 5.75 (dd, J_1 = 10.9 Hz, J_2 = 2.2 Hz, 1H), 5.05 (d, J = 6.6 Hz, 1H), 4.72 (d, J = 6.6 Hz, 1H), 3.83 (dd, J_1 = 10.4 Hz, J_2 = 3.7 Hz, 1H), 3.40 (s,

3H), 3.34 (m, 1H), 3.30 (dd, J_1 = 2.2 Hz, J_2 = 0.8 Hz, 1H), 2.30-2.14 (m, 1H), 2.00-1.88 (br s, 1H), 1.87-1.44 (m, 5H), 1.42-1.21 (m, 1H), 0.98 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 121.2, 118.6, 99.6, 93.3, 84.6, 81.6, 80.6, 73.8, 63.5, 56.4, 51.0, 48.2, 36.6, 32.8, 31.3, 23.0, 21.0; HRMS calcd for $C_{15}H_{19}O_2$ (M^+ - CH_2OCH_3): 231.1386. Found: 231.1393. MS (CI) 277 (MH^+, 1%), 246 (MH^+ - OCH_3, 35%).

Preparation of 4-formyl-1-[(*Z*)-3-hexene-1,5-diynyl]-3,3-dimethyl-1-methyloxymethoxycyclohexane (193)

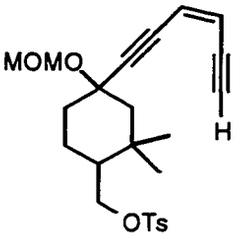


193

Dimethyl sulfoxide (150 μL, 2.1 mmol) was added to a solution of oxalyl chloride (160 μL, 1.8 mmol) in CH_2Cl_2 (5 mL) at -78 °C and the mixture was stirred for 30 minutes. A solution of the alcohol **192** (200 mg, 0.72 mmol) in CH_2Cl_2 (10 mL) and triethylamine (730 μL, 5.4 mmol) were added sequentially to the reaction. The resultant mixture was warmed to room temperature and stirred for 3 hours. The mixture was then poured into a separatory funnel containing CH_2Cl_2 (30 mL) and water (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with aqueous 10% HCl (1 x 25 mL), saturated aqueous sodium bicarbonate (1 x 25 mL) and brine (1 x 25 mL) respectively and then dried, filtered and concentrated. Purification of the crude oil by chromatography (25% ethyl acetate/petroleum ether) afforded 199 mg (99%) of the aldehyde **193** as a clear oil; IR (neat, cm^{-1}) 3408, 2944, 2866, 2102, 1719, 1463, 1025; ^1H NMR (200 MHz, $CDCl_3$) δ 9.83 (d, J = 2.0 Hz, 1H), 5.90 (dd, J_1 = 11.0 Hz, J_2 = 0.7 Hz, 1H), 5.79 (dd, J_1 = 11.0 Hz, J_2 = 2.2 Hz, 1H),

5.09 (d, J = 6.9 Hz, 1H), 4.74 (d, J = 6.9 Hz, 1H), 3.42 (s, 3H), 3.31 (dd, J_1 = 2.2 Hz, J_2 = 0.7 Hz, 1H), 2.32-2.21 (m, 1H), 2.12-1.80 (m, 4H), 1.74-1.63 (m, 2H), 1.17 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 121.0, 119.0, 100.9, 93.5, 84.8, 82.2, 80.7, 73.4, 57.8, 50.8, 47.3, 35.9, 33.5, 31.3, 23.9, 18.1; MS(CI) 273 (M^+ - H, 2%), 259 (M^+ - CHO, 3%), 213 (M^+ - C_6H_3, 100%).

Preparation of 1-[(*Z*)-3-hexene-1,5-diynyl]-3,3-dimethyl-1-methyloxymethoxy-4-*p*-toluenesulfonyloxymethylcyclohexane (198)

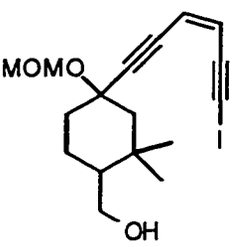


198

p-Toluenesulfonyl chloride (68 mg, 0.36 mmol) was added to a solution of the alcohol **192** (50 mg, 0.18 mmol), triethylamine (100 μL, 0.72 mmol) and 4-dimethylaminopyridine (5 mg, 0.04 mmol) in CH_2Cl_2 (5 mL) at room temperature and the resultant mixture was stirred for 15 hours. The mixture was poured into a separatory funnel containing CH_2Cl_2 (15 mL) and water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic extracts were washed with aqueous 10% HCl (1 x 15 mL), saturated sodium bicarbonate (1 x 15 mL) and brine (1 x 15 mL) respectively and then dried, filtered and concentrated. Purification of the crude oil by chromatography (20% ethyl acetate/petroleum ether) yielded 69 mg (88%) of the tosylate **198** as a clear, yellow oil; IR (neat, cm^{-1}) 3281, 2924, 2094, 1718, 1598, 1170; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 5.87 (dd, J_1 = 10.8 Hz, J_2 = 0.7 Hz, 1H), 5.77 (dd, J_1 = 10.8 Hz, J_2 = 2.4 Hz, 1H), 5.02 (d, J = 6.6

Hz, 1H), 4.69 (d, J = 6.6 Hz, 1H), 4.18 (dd, J_1 = 9.5 Hz, J_2 = 3.8 Hz, 1H), 3.76 (t, J = 9.5 Hz, 1H), 3.36 (s, 3H), 3.29 (dd, J_1 = 2.4 Hz, J_2 = 0.7 Hz, 1H), 2.43 (s, 3H), 2.20-2.08 (m, 1H), 1.80 (dd, J_1 = 14.6 Hz, J_2 = 2.5 Hz, 1H), 1.70-1.42 (m, 5H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 133.0, 129.8, 127.8, 121.0, 118.9, 99.1, 93.4, 84.7, 81.9, 80.4, 73.5, 71.6, 56.4, 50.8, 44.9, 36.3, 32.7, 31.1, 22.8, 21.6, 20.9; MS(CI) 400 (MH^+ - OCH_3, 1%), 369 (M^+ - OCH_2OCH_3, 10%).

Preparation of 4-hydroxymethyl-1-[(Z)-6-iodo-3-hexene-1,5-diynyl]-3,3-dimethyl-1-methyloxymethoxycyclohexane (200)

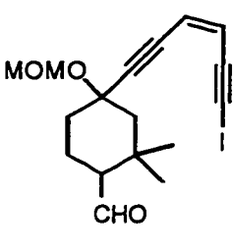


200

Morpholine (284 μL, 3.26 mmol) and iodine (305 mg, 1.20 mmol) were sequentially added to a solution of the acetylene **192** (150 mg, 0.54 mmol) in benzene (25 mL) and the reaction was warmed to 60 °C for 3 hours. The mixture was then cooled to room temperature and poured into a separatory funnel containing ether (50 mL) and a 10% aqueous sodium thiosulfate solution (50 mL). The aqueous layer was extracted with ether (3 x 50 mL) and the combined organic layers were washed with 10% aqueous sodium thiosulfate (1 x 50 mL) and brine (1 x 50 mL) and then dried, filtered and concentrated. Purification of the resultant oil by chromatography (25-40% ethyl acetate/petroleum ether) afforded 165 mg (80%) of the iodoacetylene **200** as a yellow oil; IR (neat, cm^{-1}) 3398, 2925, 2153, 1457, 1028; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.88 (d, J = 10.7 Hz, 1H), 5.76 (d, J = 10.7 Hz, 1H), 5.02 (d, J = 6.6 Hz, 1H), 4.73 (d, J = 6.6 Hz, 1H), 3.82 (dd, J_1 =

10.4 Hz, J_2 = 3.7 Hz, 1H), 3.40 (s, 3H), 3.34 (dd, J_1 = 10.4 Hz, J_2 = 8.7 Hz, 1H), 2.26-2.13 (m, 1H), 1.86-1.18 (m, 7H), 0.99 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 121.8, 119.8, 99.9, 93.4, 91.7, 81.8, 73.8, 63.6, 56.4, 51.1, 48.1, 36.7, 32.9, 31.3, 23.1, 21.1, 14.7; HRMS calcd for $C_{15}H_{18}O_2I$ (M^+ - CH_2OCH_3): 357.0352. Found: 357.0329.

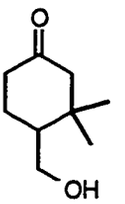
Preparation of 4-formyl-1-[(*Z*)-6-iodo-3-hexene-1,5-diynyl]-3,3-dimethyl-1-methyloxymethoxycyclohexane (201)



201

Pyridinium dichromate (115 mg, 0.30 mmol) was added to a solution of the alcohol **200** (76 mg, 0.19 mmol) in CH_2Cl_2 (15 mL) and the reaction was stirred for 15 hours. The mixture was then filtered through a plug of Celite, washing thoroughly with ether. The resultant solution was concentrated and purified by chromatography (40% ethyl acetate/petroleum ether) to afford 66 mg (87%) of the title compound **201** as a yellow oil; IR (neat, cm^{-1}) 2928, 2740, 2154, 1716, 1455, 1025; ^1H NMR (200 MHz, $CDCl_3$) δ 9.81 (d, J = 2.2 Hz, 1H), 5.90 (d, J = 10.8 Hz, 1H), 5.77 (d, J = 10.8 Hz, 1H), 5.04 (d, J = 6.9 Hz, 1H), 4.73 (d, J = 6.9 Hz, 1H), 3.40 (s, 3H), 2.30-2.18 (m, 1H), 2.12-1.60 (m, 6H), 1.16 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.3, 121.6, 120.1, 99.0, 93.5, 91.7, 82.2, 73.4, 57.8, 56.5, 50.9, 35.9, 33.5, 31.3, 24.0, 18.3, 14.9; Anal. calcd for $C_{17}H_{21}O_3I$: C, 51.01; H, 5.29. Found: C, 51.49; H, 5.48.

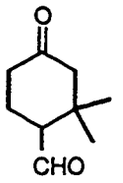
Preparation of 4-hydroxymethyl-3,3-dimethyl-cyclohexanone (205)



205

A 1 M solution of tetrabutylammonium fluoride (7.50 mL, 7.50 mmol) was added to a solution of **182** (1.35 g, 5.00 mmol) in THF (50 mL) at room temperature and the reaction was stirred for one hour. The mixture was then poured into a separatory funnel containing a saturated aqueous solution of ammonium chloride (50 mL) and ether (50 mL). The aqueous phase was extracted with ether (3 x 50 mL) and the combined organic layers were washed with brine (1 x 50 mL), dried, filtered and concentrated. Purification of the resultant oil by chromatography (50% ethyl acetate/petroleum ether) afforded 608 mg (78%) of the alcohol **205** as a clear liquid; IR (neat, cm^{-1}) 3393, 2916, 1704, 1467, 1082; ^1H NMR (200 MHz, $CDCl_3$) δ 3.83 (dd, J_1 = 10.4 Hz, J_2 = 3.7 Hz, 1H), 3.34 (dd, J_1 = 10.4 Hz, J_2 = 8.6 Hz, 1H), 3.01 (br s, 1H), 2.35-2.09 (m, 4H), 1.96 (dd, J_1 = 13.6 Hz, J_2 = 1.5 Hz, 1H), 1.79-1.62 (m, 1H), 1.60-1.43 (m, 1H), 0.99 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 212.4, 62.5, 55.9, 47.2, 40.2, 37.4, 29.7, 25.7, 21.4; HRMS calcd for $C_9H_{16}O_2$ (M^+): 156.1151. Found: 156.1162.

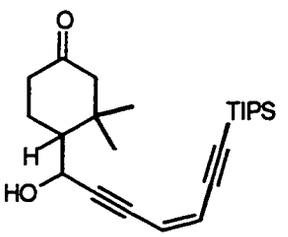
Preparation of 4-formyl-3,3-dimethyl-cyclohexanone (204)



204

Dimethyl sulfoxide (0.71 mL, 10 mmol) was added to a solution of oxalyl chloride (0.68 mL, 7.8 mmol) in CH_2Cl_2 (50 mL) at -78 °C and the mixture was stirred for 30 minutes. A solution of the alcohol **205** (545 mg, 3.5 mmol) in CH_2Cl_2 (10 mL) and triethylamine (3.4 mL, 25 mmol) were then added sequentially to the reaction. The resultant mixture was warmed to room temperature and stirred for 8 hours. The mixture was poured into a separatory funnel containing CH_2Cl_2 (50 mL) and water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with aqueous 10% HCl (1 x 50 mL), saturated aqueous sodium bicarbonate (1 x 50 mL) and brine (1 x 50 mL) respectively and then dried, filtered and concentrated. Purification of the crude oil by chromatography (25% ethyl acetate/petroleum ether) afforded 527 mg (98%) of the aldehyde **204** as a clear liquid; IR (neat, cm^{-1}) 2916, 2736, 1713, 1462, 1075; ^1H NMR (200 MHz, $CDCl_3$) δ 9.86 (d, J = 1.9 Hz, 1H), 2.57-2.48 (m, 1 H), 2.46-2.17 (m, 4H), 2.10-1.96 (m, 2H), 1.19 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.6, 203.5, 56.6, 55.1, 39.0, 37.8, 29.5, 22.7, 22.2; Anal. calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.32; H, 9.55.

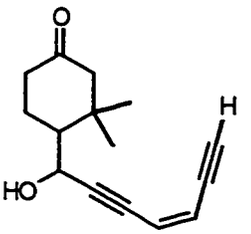
Preparation of 4-[(*Z*)-1-hydroxy-7-triisopropylsilyl-4-heptene-2,6-diynyl]-3,3-dimethyl-cyclohexanone (206)



206

A 1.6 M solution of *n*-butyllithium in hexanes (3.6 mL, 5.8 mmol) was added dropwise to a solution of the enediyne **177** (1.40 g, 6.03 mmol) in THF (50 mL) at -78 °C. The solution was stirred at -78 °C for 30 minutes and became dark brown in colour. A solution of the aldehyde **204** (0.75 g, 4.87 mmol) in THF (10 mL) was added dropwise. The reaction was warmed to room temperature and stirred for 15 hours. The mixture was then poured into a separatory funnel containing ether (100 mL) and water (100 mL). The aqueous layer was extracted with ether (3 x 70 mL) and the combined organic layers were washed with brine (1 x 70 mL), dried, filtered and concentrated. Purification of the crude residual oil by chromatography (10-40% ethyl acetate/petroleum ether) afforded 1.07 g (57%) of the addition product **206** as a yellow oil; IR (neat, cm^{-1}) 3434, 3051, 2948, 2140, 1709, 1464, 1020; ^1H NMR (200 MHz, $CDCl_3$) δ 5.83 (br s, 2H), 4.97 (br s, 1H), 2.55-2.41 (m, 1H), 2.38-1.98 (m, 6H), 1.82-1.72 (m, 1H), 1.09-1.04 (br s, 24H), 0.97 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.7, 120.3, 119.2, 103.6, 99.9, 98.0, 82.6, 62.8, 56.2, 50.3, 40.6, 38.0, 30.0, 23.3, 22.3, 18.7, 11.2; HRMS calcd for $C_{21}H_{31}O_2Si$ ($M^+ - C_3H_7$): 343.2095. Found: 343.2079; Anal. calcd for $C_{24}H_{38}O_2Si$: C, 74.55; H, 9.91. Found: C, 74.52; H, 9.92.

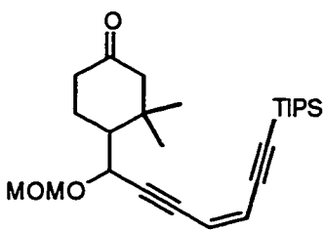
Preparation of 4-[(*Z*)-4-hepten-1-ol-2,6-diynyl]-3,3-dimethyl-cyclohexanone (207)



207

Tetrabutylammonium difluorotriphenylstannate (50 mg, 0.08 mmol) was added to a solution of **206** (25 mg, 0.07 mmol) in THF (5 mL) at room temperature and the reaction was stirred for 15 hours. The mixture was then passed through a short column of silica using CH_2Cl_2 as an eluant. Purification of the resultant oil by chromatography (50% ethyl acetate/petroleum ether) afforded 11 mg (73%) of the compound **207** as a yellow oil; IR (neat, cm^{-1}) 3374, 3049, 2925, 2093, 1701, 1575, 1072; ^1H NMR (200 MHz, $CDCl_3$) δ 5.92 (ddd, J_1 = 11.0 Hz, J_2 = 2.0 Hz, J_3 = 1.0 Hz, 1H), 5.80 (dd, J_1 = 11.0 Hz, J_2 = 2.3 Hz, 1H), 4.98 (t, J = 2.0 Hz, 1H), 3.32 (dd, J_1 = 2.3 Hz, J_2 = 1.0 Hz, 1H), 2.57-2.42 (m, 1H), 2.38-2.00 (m, 6H), 1.86-1.79 (m, 1H), 1.10 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.9, 120.9, 119.2, 98.5, 84.8, 81.9, 80.6, 62.6, 56.2, 50.3, 40.5, 38.0, 30.0, 23.2, 22.3; MS (CI) 231 (MH^+, 100%), 213 ($MH^+ - H_2O$, 66%).

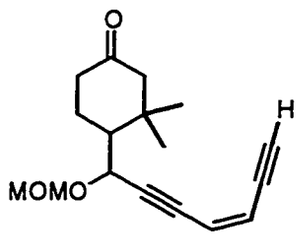
Preparation of 3,3-dimethyl-4-[(*Z*)-1-methyloxymethoxy-7-triisopropylsilyl-4-heptene-2,6-diynyl]cyclohexanone (208)



208

Chloromethyl methyl ether (1.08 mL, 14.2 mmol) was added to a cold (0 °C) solution of the alcohol **206** (610 mg, 1.6 mmol) and diisopropylethylamine (3.02 mL, 17.3 mmol) in CH_2Cl_2 (10 mL). The reaction was then warmed to room temperature and stirred for 15 hours. The mixture was poured into a separatory funnel containing ether (70 mL) and water (70 mL). The aqueous phase was extracted with ether (3 x 70 mL) and the combined organic extracts were washed with aqueous 10% HCl (1 x 70 mL), saturated sodium bicarbonate (1 x 70 mL) and brine (1 x 70 mL) respectively and then dried, filtered and concentrated. Purification of the crude oil by chromatography (10% ethyl acetate/petroleum ether) yielded 544 mg (80%) of the compound **208** as a clear oil; IR (neat, cm^{-1}) 3051, 2916, 2140, 1712, 1573, 1070; ^1H NMR (200 MHz, $CDCl_3$) δ 5.87 (s, 2H), 4.99 (d, J = 6.8 Hz, 1H), 4.98 (s, 1H), 4.53 (d, J = 6.8 Hz, 1H), 3.40 (s, 3H), 2.58-2.43 (m, 1H), 2.37-2.10 (m, 5H), 1.93-1.85 (m, 1H), 1.12-1.07 (br s, 24H), 1.05 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.9, 120.0, 119.1, 103.5, 99.7, 95.5, 94.5, 83.5, 66.4, 56.6, 56.0, 49.4, 40.5, 37.8, 29.8, 23.6, 22.9, 18.6, 11.2; HRMS calcd for $C_{23}H_{35}O_3Si$ (M^+ - C_3H_7): 387.2308. Found: 387.2365; Anal. calcd for $C_{26}H_{42}O_3Si$: C, 72.51; H, 9.83. Found: C, 72.65; H, 10.13.

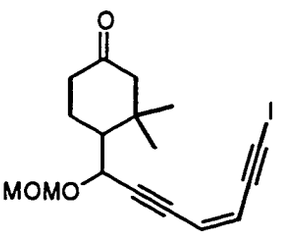
Preparation of 3,3-dimethyl-4-[(*Z*)-1-methyloxymethoxy-4-heptene-2,6-diynyl]cyclohexanone (209)



209

A 1 M solution of tetrabutylammonium fluoride (0.45 mL, 0.45 mmol) was added to a solution of **208** (159 mg, 0.370 mmol) in THF (10 mL) at -78 °C. The reaction was warmed to room temperature and stirred for one hour. The mixture was then poured into a separatory funnel containing a saturated aqueous solution of ammonium chloride (50 mL) and ether (50 mL). The aqueous phase was extracted with ether (3 x 50 mL) and the combined organic layers were washed with brine (1 x 50 mL), dried, filtered and concentrated. Purification of the resultant oil by chromatography (20% ethyl acetate/petroleum ether) afforded 75 mg (74%) of the ketone **209** as a white solid; mp 58-59 °C; IR (neat, cm^{-1}) 3267, 3050, 2927, 2250, 2093, 1708, 1574, 1077; ^1H NMR (200 MHz, $CDCl_3$) δ 5.91 (ddd, J_1 = 11.0 Hz, J_2 = 2.2 Hz, J_3 = 1.0 Hz, 1H), 5.80 (dd, J_1 = 11.0 Hz, J_2 = 2.1 Hz, 1H), 5.02 (d, J = 6.8 Hz, 1H), 4.93 (br s, 1H), 4.54 (d, J = 6.8 Hz, 1H), 3.38 (s, 3H), 3.30 (dd, J_1 = 2.1 Hz, J_2 = 1.0 Hz, 1H), 2.56-2.42 (m, 1H), 2.34-2.16 (m, 5H), 1.92-1.83 (m, 1H), 1.10 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 120.9, 119.3, 95.8, 94.5, 84.7, 83.1, 80.6, 66.4, 56.6, 56.1, 49.6, 40.5, 37.8, 30.0, 23.5, 23.0; MS (CI) 275 (MH^+, 6%), 245 ($MH^+ - CH_3 - CH_3$, 100%), 213 ($MH^+ - OCH_3 - CH_3 - CH_3$, 100%); Anal. calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.04; H, 7.79.

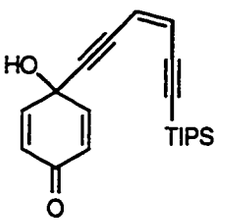
Preparation of 4-[(*Z*)-7-iodo-1-methyloxymethoxy-4-heptene-2,6-diynyl]-3,3-dimethyl-cyclohexanone (211)



211

Morpholine (80 μL, 0.92 mmol) and iodine (80 mg, 0.32 mmol) were sequentially added to a solution of the acetylene **209** (38 mg, 0.14 mmol) in benzene (15 mL) and the reaction was warmed to 60 °C for 3 hours. The mixture was then cooled to room temperature and poured into a separatory funnel containing ether (15 mL) and a 10% aqueous sodium thiosulfate solution (15 mL). The aqueous layer was extracted with ether (3 x 15 mL) and the combined organic layers were washed with 10% aqueous sodium thiosulfate (1 x 15 mL) and brine (1 x 15 mL) and then dried, filtered and concentrated. Purification of the resultant oil by chromatography (25% ethyl acetate/petroleum ether) afforded 38 mg (69%) of the iodoacetylene **211** as a yellow oil; IR (neat, cm^{-1}) 2919, 2250, 2154, 1704, 1174; ^1H NMR (200 MHz, $CDCl_3$) δ 5.95 (d, J_1 = 10.8 Hz, 1H), 5.80 (dd, J_1 = 10.8 Hz, J_2 = 1.7 Hz, 1H), 5.01 (d, J = 6.8 Hz, 1H), 4.95 (br s, 1H), 4.58 (d, J = 6.8 Hz, 1H), 3.40 (s, 3H), 2.61-2.47 (m, 1H), 2.44-2.08 (m, 5H), 1.96-1.88 (m, 1H), 1.12 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 121.4, 120.4, 95.9, 94.6, 91.7, 83.2, 66.5, 56.7, 56.1, 49.7, 40.8, 37.9, 30.0, 23.5, 23.0, 14.7; MS (CI) 401 (MH^+, 2%), 371 (MH^+ - CH_3 - CH_3, 100%); Anal. calcd for $C_{17}H_{21}O_3I$: C, 51.01; H, 5.29. Found: C, 51.47; H, 5.16.

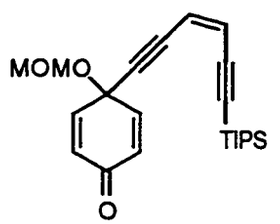
Preparation of 4-hydroxy-4-[(*Z*)-triisopropylsilyl-3-hexene-1,5-diynyl]-2,5-cyclohexadienone (213)



213

A 1.4 M solution of *n*-butyllithium in hexanes (3.80 mL, 5.320 mmol) was added dropwise to a solution of the enediyne **177** (1.26 g, 5.43 mmol) in THF (50 mL) at -78 °C. The solution was stirred at -78 °C for 30 minutes and became dark brown in colour. A solution of the 1,4-benzoquinone (560 mg, 5.17 mmol) in THF (10 mL) was added dropwise and the mixture became dark blue. The reaction was warmed to room temperature and stirred 15 hours. The mixture was then poured into a separatory funnel containing ether (100 mL) and water (100 mL). The aqueous layer was extracted with ether (3 x 70 mL) and the combined organic layers were washed with brine (1 x 70 mL), dried, filtered and concentrated. Purification of the crude residual oil by chromatography (5-10% ethyl acetate/petroleum ether) afforded 0.946 g (54%) of the addition product **213** as a yellow oil; IR (neat, cm^{-1}) 3363, 3053, 2944, 2866, 2163, 1672, 1463, 1032; ^1H NMR (200 MHz, $CDCl_3$) δ 6.85 (d, J = 10.2 Hz, 2H), 6.13 (d, J = 10.2 Hz, 2H), 5.93 (d, J = 11.1 Hz, 1H), 5.80 (d, J = 11.1 Hz, 1H), 3.22-3.17 (br s, 1H), 1.08-1.03 (br s, 21H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 184.8, 146.5, 126.9, 122.1, 118.0, 103.0, 101.2, 92.0, 83.3, 62.6, 18.6, 11.1; MS (CI) 341 (MH^+, 62%), 323 ($MH^+ - H_2O$, 46%), 297 ($M^+ - C_3H_7$, 48%). HRMS calcd for $C_{18}H_{21}O_2Si$ ($M^+ - C_3H_7$): 297.1312. Found: 297.1283; Anal. calcd for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29. Found: C, 73.99; H, 7.99.

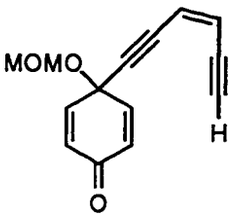
Preparation of 4-methyloxymethoxy-4-[(*Z*)-triisopropylsilyl-3-hexene-1,5-diynyl]-2,5-cyclohexadienone (214)



214

Chloromethyl methyl ether (0.95 mL, 12.5 mmol) was added to a cold (0 °C) solution of the alcohol **213** (300 mg, 0.88 mmol), *N,N*-diisopropylethylamine (2.42 mL, 13.9 mmol) and 4-dimethylaminopyridine (10 mg, 0.082 mmol) in CH_2Cl_2 (10 mL). The reaction was warmed to room temperature and stirred for 15 hours. The mixture was then poured into a separatory funnel containing ether (70 mL) and water (70 mL). The aqueous phase was extracted with ether (3 x 70 mL) and the combined organic extracts were washed with aqueous 10% HCl (1 x 70 mL), saturated sodium bicarbonate (1 x 70 mL) and brine (1 x 70 mL) respectively and then dried, filtered and concentrated. Purification of the crude oil by chromatography (20% ethyl acetate/petroleum ether) yielded 276 mg (81%) of the compound **214** as a yellow oil; IR (neat, cm^{-1}) 2912, 2142, 1685, 1386, 1033; ^1H NMR (200 MHz, $CDCl_3$) δ 6.90 (d, J = 10.1 Hz, 2H), 6.19 (d, J = 10.1 Hz, 2H), 5.95 (d, J = 11.1 Hz, 1H), 5.82 (d, J = 11.1 Hz, 1H), 4.90 (s, 2H), 3.36 (s, 3H), 1.09-1.03 (br s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 145.4, 127.7, 122.3, 117.9, 103.0, 101.4, 93.1, 89.3, 85.3, 68.2, 55.8, 18.6, 11.2; MS (CI) 385 (MH^+, 12%), 353 (M^+ - OCH_3, 56%), 341 (MH^+ - C_3H_7, 100%). HRMS calcd for $C_{20}H_{25}O_3Si$ (M^+ - C_3H_7): 341.1574. Found: 341.1586.

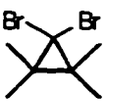
Preparation of 4-[(*Z*)-3-hexene-1,5-diynyl]-4-methyloxymethoxy-2,5-cyclohexadienone (215)



215

A 1 M solution of tetrabutylammonium fluoride (0.66mL, 0.66 mmol) was added to a solution of **214** (210 mg, 0.547 mmol) in THF (10 mL) at 0 °C. The reaction was stirred for 30 minutes and then warmed to room temperature. The mixture was poured into a separatory funnel containing a saturated aqueous solution of ammonium chloride (50 mL) and ether (50 mL). The aqueous phase was extracted with ether (3 x 50 mL) and the combined organic layers were washed with brine (1 x 50 mL), dried, filtered and concentrated. Purification of the resultant oil by chromatography (25% ethyl acetate/petroleum ether) afforded 106 mg (85%) of the compound **215** as a yellow oil; IR (neat, cm^{-1}) 3273, 2929, 2094, 1678, 1153; ^1H NMR (200 MHz, $CDCl_3$) δ 6.94 (d, J = 10.1 Hz, 2H), 6.22 (d, J = 10.1 Hz, 2H), 5.91 (s, 2H), 4.98 (s, 2H), 3.38 (br s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 184.7, 145.4, 127.7, 121.4, 119.8, 93.2, 89.7, 85.0, 86.0, 80.1, 68.2, 55.8; HRMS calcd for $C_{13}H_9O_2$ (M^+ - OCH_3): 197.0603. Found: 197.0586.

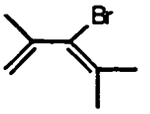
Preparation of 1,1-dibromo-2,2,3,3-tetramethylcyclopropane (242)



242

Bromoform (23.4 mL, 0.268 mol) was added dropwise over a period of one hour to a cold (0 °C), stirred suspension of 2,3-dimethyl-2-butene (16.5 mL, 0.138 mol) and potassium *tert*-butoxide (28.0 g, 0.25 mol) in *n*-pentane (125 mL). The resultant slurry was stirred at room temperature for 2 hours and then recooled to 0 °C. Water (100 mL) was added and the mixture poured into a separatory funnel. The aqueous layer was extracted with *n*-pentane (2 x 50 mL) and the combined organic extracts were washed with brine (2 x 50 mL), dried ($MgSO_4$), filtered and concentrated. The resultant white solid was dissolved in methanol (75 mL) and cooled to 0 °C. The white crystals produced were filtered, washed with cold (0 °C) methanol (20 mL) and dried by suction filtration. The filtrate was concentrated and the resultant white solid was again recrystallized with methanol (25 mL) at 0 °C to afford another crop of crystals. This sequence was repeated a third time to yield a total of 30.0 g (85%) of the dibromocyclopropane **242** as white crystals; mp 79-80 °C (77-78 °C)[103]; IR (CH_2Cl_2, cm^{-1}) 2907, 1457, 793; ^1H NMR (200 MHz, $CDCl_3$) δ 1.19 (s, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 58.9, 29.7, 21.7; MS (CI) 256 (M^+, 1%), 254 (M^+, 1%), 176 (MH^+ - Br, 41%), 174 (MH^+ - Br, 43%); Anal. calcd for $C_7H_{12}Br_2$: C, 32.85; H, 4.73. Found: C, 32.80; H, 4.60.

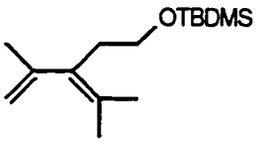
Preparation of 3-bromo-2,4-dimethyl-1,3-pentadiene (243)



243

The solid dibromocyclopropane **242** (21.0 g, 0.082 mol) was heated using a propane torch. The resultant colourless liquid was then quickly distilled using a Vigreux column and condenser and by rapid heating with a propane torch. The distillate was collected between 100 and 130 °C and redistilled using the same set-up to afford 12.4 g (86%) of the diene **243** as a colourless liquid which was stored over sodium hydroxide pellets; IR (neat, cm^{-1}) 2929, 1626, 1443, 1092; ^1H NMR (200 MHz, $CDCl_3$) δ 5.02 (m, 1H), 4.89 (m, 1H), 1.88 (s, 3H), 1.87 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.1, 131.0, 120.2, 116.5, 24.4, 21.8, 21.7; MS (CI) 177 (M^+, 100%), 175 (M^+, 100%); Anal. calcd for $C_7H_{11}Br$: C, 48.03; H, 6.33. Found: C, 47.53; H, 6.54.

Preparation of 3-(2-*tert*-butyldimethylsilyloxyethyl)-2,4-dimethyl-1,3-pentadiene (244)

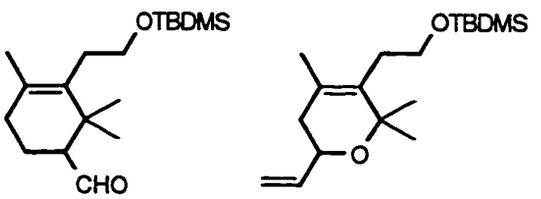


244

A 1.58 M solution of *tert*-butyllithium in pentane (46.0 mL, 72.7 mmol) was added dropwise to a stirred solution of the bromopentadiene **243** (5.77 g, 33.0 mmol) in THF (100 mL) at -78 °C and the resultant mixture was allowed to stir at -78 °C for 15 minutes. Liquid ethylene oxide (13 mL, 0.3 mol) at -78 °C was then added *via* cannula and the

mixture was allowed to stir for 1 hour at -78 °C and for another hour.at 0 °C. The reaction was warmed to room temperature and stirred for 30 minutes. The mixture was quenched with water (100 mL)and poured into a separatory funnel. The aqueous layer was extracted with ether (3 x 100 mL) and the combined organic extracts were washed with brine (2 x 100 mL), dried, filtered and concentrated. The resultant residual oil was purified by chromatography (25% ether/petroleum ether) to yield a colourless liquid. Imidazole (3.24 g, 47.6 mmol) and *tert*-butyldimethylsilylchloride (5.50 g, 36.5 mmol) were added sequentially to a solution of this colourless liquid (3.6 g) in CH_2Cl_2 (100 mL) at room temperature and the resultant mixture was stirred for 20 minutes. A saturated solution of aqueous sodium bicarbonate (30 mL) was then added to the reaction and the mixture poured into a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were washed with brine (1 x 30 mL), dried, filtered and concentrated. Purification of the crude product by chromatography (petroleum ether) yielded 5.20 g (total yield of 62% for the two steps) of the protected pentadiene **244** as a colourless liquid; IR (neat, cm^{-1}) 2918, 1631, 1457, 1096; ^1H NMR (200 MHz, $CDCl_3$) δ 4.89 (m, 1H), 4.51 (br d, J = 2.7 Hz, 1H), 3.54 (dd, J_1 = 8.1 Hz, J_2 = 7.7 Hz, 2H), 2.32 (t, J = 8.1 Hz, 2H), 1.74 (s, 3H), 1.67 (s, 3H), 1.64 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.6, 132.8, 127.2, 113.1, 61.8, 34.8, 26.0, 22.6, 21.7, 19.8, 18.3, –5.2; HRMS calcd for $C_{11}H_{21}OSi$ (M^+ - C_4H_9): 197.1363. Found: 197.1347.

Preparation of 1-(2-*tert*-butyldimethylsilyloxyethyl)-5-formyl-2,6,6-trimethyl-1-cyclohexene (245) and 3-(2-*tert*-butyldimethylsilyloxyethyl)-2,2,4-trimethyl-6-vinyl-5,6-dihydro-2*H*-pyran (246)

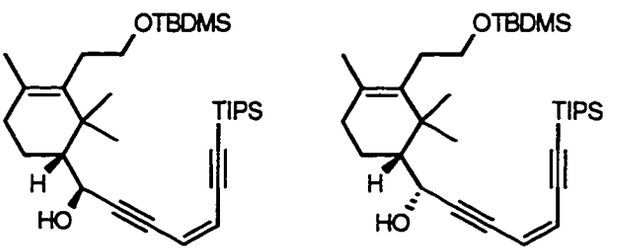


245 **246**

Boron trifluoride diethyl etherate (2.75 mL, 22.4 mmol) was added dropwise over a period of 30 minutes to a stirred solution of the diene **244** (5.00 g, 19.7 mmol) and acrolein (8.0 mL, 120 mmol) in CH_2Cl_2 (120 mL) at -78 °C and the resultant mixture was stirred for 20 minutes at this temperature. The reaction was quenched at -78 °C with a saturated solution of sodium bicarbonate (50 mL) and stirred vigorously as it was allowed to warm to room temperature. The mixture was then poured into a separatory funnel and the aqueous layer extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with brine (2 x 50 mL), dried, filtered and concentrated. Purification of the crude roduct by chromatography (10% ether/petroleum ether) afforded 2.78 g (46%) of aldehyde **245** and 1.22 g (20%) of ether **246** both as a colourless oil. Aldehyde **245**: IR (neat, cm^{-1}) 2944, 2858, 2726, 1722, 1467, 1089; ^1H NMR (200 MHz, $CDCl_3$) δ 9.81 (d, J = 3.1 Hz, 1H), 3.55 (t, J = 8.0 Hz, 2H), 2.30 (br t, J = 8.0 Hz, 2H), 2.14 (dt, J_1 = 10.0 Hz, J_2 = 3.4 Hz, 1H), 1.99-1.96 (m, 2H), 1.82-1.69 (m, 2H), 1.64 (s, 3H), 1.18 (s, 3H), 1.03 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.4, 132.7, 129.4, 62.8, 57.6, 36.9, 32.1, 30.6, 27.7, 26.0, 23.5, 20.2, 19.7, 18.4, –5.2; HRMS calcd for $C_{18}H_{34}O_2Si$ (M^+ - C_4H_9): 253.1625. Found: 253.1604; Anal. calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04. Found: C, 69.01; H, 11.22. Pyran **246**: IR (neat, cm^{-1}) 2920, 1467, 1092; ^1H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddd, J_1 = 17.4 Hz, J_2 =

10.4 Hz, J_3 = 5.6 Hz, 1H), 5.22 (dt, J_1 = 17.4 Hz, J_2 = 1.4 Hz, 1H), 5.09 (dt, J_1 = 10.4 Hz, J_2 = 1.4 Hz, 1H), 4.09 (m, 1H), 3.55 (m, 2H), 2.23 (t, J = 8.5 Hz, 2H), 2.08 (ddd, J_1 = 16.6 Hz, J_2 = 10.9 Hz, J_3 = 1.1 Hz, 1H), 1.78 (dd, J_1 = 16.6Hz, J_2 = 3.2 Hz, 1H), 1.66 (s, 3H), 1.27 (s, 6H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.4, 132.2, 126.5, 115.1, 76.0, 68.9, 62.4, 37.2, 32.9, 28.5, 26.0, 25.0, 19.6, 18.4, –5.2; HRMS calcd for $C_{17}H_{31}O_2Si$ (M^+ - CH_3): 295.2095. Found: 295.2073.

Preparation of (5*R)-1-(2-*tert*-butyldimethylsilyloxyethyl)-5-[(1*S**)-(*Z*)-1-hydroxy-7-triisopropylsilyl-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (247a) and (5*R**)-1-(2-*tert*-butyldimethylsilyloxyethyl)-5-[(1*R**)-(*Z*)-1-hydroxy-7-triisopropylsilyl-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (247b)**

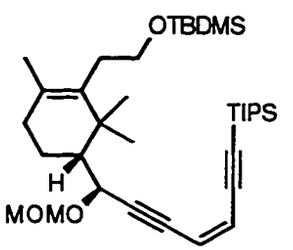


247a **247b**

A 2.5 M solution of *n*-butyllithium in hexanes (7.2 mL, 18 mmol) was added dropwise to a solution of the enediyne **177** (5.20 g, 22.4 mmol) in THF (200 mL) at -78 °C. The solution was stirred at -78 °C for 30 minutes and became dark brown in colour. A solution of the aldehyde **245** (3.50 g, 11.3 mmol) in THF (50 mL) was then added dropwise. The reaction was warmed to room temperature and stirred for 15 hours. The mixture was poured into a separatory funnel containing ether (100 mL) and water (100 mL). The aqueous layer was extracted with ether (3 x 100 mL) and the combined organic layers were washed with brine (1 x 100 mL), dried, filtered and concentrated. Purification

of the crude residual oil by chromatography (5-10% ether/petroleum ether) afforded 4.31 g (78%) of the addition product **247a** and 0.32 g (5.2%) of the diastereomer **247b** both as yellow oils. Compound **247a**: IR (neat, cm^{-1}) 3444, 2914, 2142, 1677, 1573, 1082; ^1H NMR (200 MHz, $CDCl_3$) δ 5.83 (s, 2H), 4.84 (d, *J* = 5.2 Hz, 1H), 3.52 (t, *J* = 7.9 Hz, 2H), 2.28 (t, *J* = 7.9 Hz, 2H), 2.01-1.98 (m, 2H), 1.93-1.80 (m, 1H), 1.78-1.63 (m, 3H), 1.62 (s, 3H), 1.07-1.03 (br s, 24H), 1.01 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 133.4, 129.5, 119.8, 103.7, 99.4, 99.2, 81.8, 63.5, 63.0, 51.1, 37.9, 32.5, 32.1, 27.6, 26.0, 23.1, 20.3, 19.0, 18.7, 18.4, 11.2, –5.1; MS (CI) 543 (MH^+, 10%), 525 ($MH^+ - H_2O$, 28%), 499 ($M^+ - C_3H_7$), 485 ($M^+ - C_4H_9$); HRMS calcd for $C_{30}H_{51}O_2Si_2$ ($M^+ - C_3H_7$): 499.3430. Found: 499.3444; Anal. calcd for $C_{33}H_{58}O_2Si_2$: C, 73.00; H, 10.77. Found: C, 72.45; H, 10.87. Compound **247b**: IR (neat, cm^{-1}) 3388, 2916, 2141, 1577, 1073; ^1H NMR (200 MHz, $CDCl_3$) δ 5.81 (s, 2H), 4.70 (br s, 1H), 3.52 (t, *J* = 8.5 Hz, 2H), 2.27 (br t, *J* = 8.5 Hz, 2H), 2.07-1.82 (m, 5H), 1.61 (s, 3H), 1.62-1.58 (m, 1H), 1.10-1.05 (br s, 21H), 1.09 (s, 3H), 1.02 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 133.1, 129.3, 119.7, 119.4, 103.7, 99.4, 97.8, 83.9, 64.0, 63.0, 51.3, 37.4, 32.5, 32.1, 27.1, 26.0, 22.6, 20.6, 20.4, 18.6, 17.7, 11.2, –5.1; HRMS calcd for $C_{29}H_{49}O_2Si_2$ ($M^+ - C_4H_9$): 485.3273. Found: 485.3249.

Preparation of (5*R)-1-(2-*tert*-butyldimethylsilyloxyethyl)-2,6,6-trimethyl-5-[(1*S**)-(*Z*)-1-methyloxymethoxy-7-triisopropylsilyl-4-heptene-2,6-diynyl]-1-cyclohexene (249)**

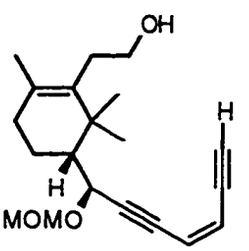


249

Chloromethyl methyl ether (4.20 mL, 55.3 mmol) was added to a cold (0 °C) solution of the alcohol **247a** (4.31 g, 7.95 mmol) and diisopropylethylamine (15.2 mL, 87.3 mmol) in CH_2Cl_2 (70 mL). The reaction was warmed to room temperature and stirred for 15 hours. The mixture was poured into a separatory funnel containing ether (100 mL) and water (100 mL). The aqueous phase was extracted with ether (3 x 100 mL) and the combined organic extracts were washed with aqueous 10% HCl (1 x 100 mL), saturated sodium bicarbonate (1 x 100 mL) and brine (1 x 100 mL) respectively and then dried, filtered and concentrated. Purification of the crude oil by chromatography (15% ether/petroleum ether) yielded 3.96 g (85%) of the compound **249** as a yellow oil; IR (neat, cm^{-1}) 2913, 2141, 1575, 1087; ^1H NMR (200 MHz, $CDCl_3$) δ 5.82 (s, 2H), 4.95 (d, J = 6.7 Hz, 1H), 4.73 (br s, 1H), 4.52 (d, J = 6.7 Hz, 1H), 3.52 (t, J = 8.8 Hz, 2H), 3.36 (s, 3H), 2.34-2.21 (m, 2H), 1.99-1.82 (m, 2H), 1.64-1.57 (m, 2H), 1.61 (s, 3H), 1.09 (s, 3H), 1.06 (s, 19H), 1.03 (s, 3H), 0.98 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 133.4, 129.1, 119.6, 119.3, 103.7, 99.2, 97.2, 94.7, 82.6, 66.8, 63.0, 56.5, 51.0, 38.1, 32.7, 27.2, 26.0, 22.8, 22.6, 20.3, 20.0, 18.6, 18.4, 11.2, –5.2; MS (CI) 587 (MH^+, 4%), 556 (MH^+ - OCH_3, 22%), 525 (M^+ - OCH_2OCH_3,

85%); HRMS calcd for $C_{33}H_{57}O_2Si_2$ (M^+ - CH_2OCH_3): 541.3900. Found: 541.3892; Anal. calcd for $C_{35}H_{62}O_3Si_2$: C, 71.61; H, 10.65. Found: C, 71.32; H, 10.24.

Preparation of (5*R)-1-(2-hydroxyethyl)-2,6,6-trimethyl-5-[(1*S**)-(*Z*)-1-methyloxymethoxy-4-heptene-2,6-diynyl]-1-cyclohexene (237)**

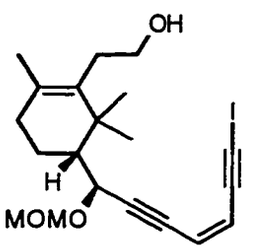


237

A 1 M solution of tetrabutylammonium fluoride (17.3 mL, 17.3 mmol) was added to a solution of **249** (4.33 g, 7.39 mmol) in THF (150 mL) at -78 °C. The reaction was warmed to room temperature and stirred for 3 hours. The mixture was then poured into a separatory funnel containing a saturated aqueous solution of ammonium chloride (100 mL) and ether (100 mL). The aqueous phase was extracted with ether (3 x 100 mL) and the combined organic layers were washed with brine (1 x 100 mL), dried, filtered and concentrated. Purification of the resultant oil by chromatography (30% petroleum ether/ether) afforded 2.31 g (99%) of the alcohol **237** as a yellow oil; IR (neat, cm^{-1}) 3339, 3160, 3040, 2920, 2850, 2094, 1575, 1030; ^1H NMR (200 MHz, $CDCl_3$) δ 5.90 (br d, J = 11.0 Hz, 1H), 5.77 (dd, J_1 = 11.0 Hz, J_2 = 2.2 Hz, 1H), 5.01 (d, J = 6.8 Hz, 1H), 4.73 (br s, 1H), 4.55 (d, J = 6.8 Hz, 1H), 3.57 (t, J = 8.1 Hz, 2H), 3.38 (s, 3H), 3.29 (dd, J_1 = 2.2 Hz, J_2 = 0.7 Hz, 1H), 2.32 (br t, J = 8.1 Hz, 2H), 2.08-1.85 (m, 3H), 1.79-1.52 (m, 3H), 1.62 (s, 3H), 1.11 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 132.9, 129.7, 121.3, 118.7, 97.3, 94.7, 84.5, 82.4, 80.7, 67.0, 62.5, 56.6,

50.9, 38.1, 32.6, 32.2, 27.4, 22.9, 20.3, 20.1; MS (CI) 317 (MH^+, 1%); HRMS calcd for $C_{18}H_{23}O_2$ (M^+ - CH_2OCH_3): 271.1699. Found: 271.1661.

Preparation of (5*R)-1-(2-hydroxyethyl)-5-[(1*S**)-(*Z*)-7-iodo-1-methyloxymethoxy-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (238)**

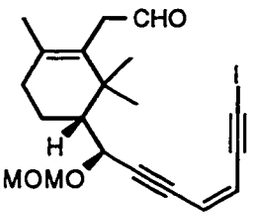


238

Morpholine (3.85 mL, 44.2 mmol) and iodine (4.13 g, 16.3 mmol) were sequentially added to a solution of the acetylene **237** (2.33 g, 7.37 mmol) in benzene (120 mL) and the reaction was warmed to 60-70 °C for 3 hours. The mixture was cooled to room temperature and poured into a separatory funnel containing ether (100 mL) and a 10% aqueous sodium thiosulfate solution (100 mL). The aqueous layer was extracted with ether (3 x 100 mL) and the combined organic layers were washed with 10% aqueous sodium thiosulfate (1 x 100 mL) and brine (1 x 100 mL) and then dried, filtered and concentrated. Purification of the resultant oil by chromatography (30% petroleum ether/ether) afforded 2.70 g (83%) of the iodoacetylene **238** as a yellow oil; IR (neat, cm^{-1}) 3373, 2920, 2154, 1457, 1110; ^1H NMR (200 MHz, $CDCl_3$) δ 5.90 (d, J = 10.8 Hz, 1H), 5.78 (dd, J_1 = 10.8 Hz, J_2 = 2.0 Hz, 1H), 4.99 (d, J = 6.8 Hz, 1H), 4.73 (br s, 1H), 4.58 (d, J = 6.8 Hz, 1H), 3.58 (t, J = 8.1 Hz, 2H), 3.39 (s, 3H), 2.33 (br t, J = 8.1 Hz, 2H), 2.06-1.89 (m, 3H), 1.77-1.60 (m, 3H), 1.63 (s, 3H), 1.13 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (50

MHz, $CDCl_3$) δ 132.8, 129.8, 121.7, 119.7, 97.4, 94.7, 91.7, 82.5, 67.0, 62.5, 56.6, 50.9, 38.2, 32.7, 32.2, 27.5, 22.8, 20.4, 20.2, 14.5; MS (CI) 411 (M^+ - OCH_3, 19%).

Preparation of (5*R)-1-formylmethyl-5-[(1*S**)-(*Z*)-7-iodo-1-methyloxymethoxy-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (239)**

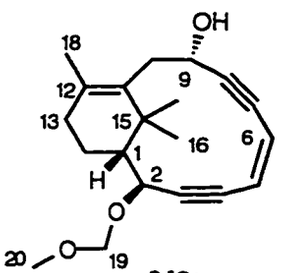


239

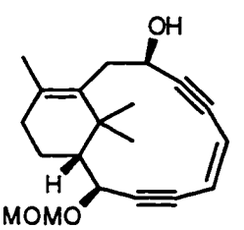
Dess-Martin periodinane (3.17 g, 7.47 mmol) was added in one portion to a solution of the alcohol **238** (2.20 g, 4.98 mmol) in CH_2Cl_2 (75 mL) and the resultant mixture was stirred for 30 minutes at room temperature. Ether (300 mL), a saturated aqueous solution of sodium thiosulfate (100 mL) and a saturated aqueous solution of sodium bicarbonate (100 mL) were added and the mixture was stirred for about 30 minutes until it became clear. The solution was poured into a separatory funnel and the aqueous layer was extracted with ether (3 x 200 mL). The combined organic extracts were washed with a 20% aqueous solution of sodium thiosulfate (1 x 200 mL), a saturated solution of sodium bicarbonate (1 x 200 mL) and brine (1 x 200 mL) and then dried, filtered and concentrated. Purification of the residual oil by chromatography (40% ether/petroleum ether) afforded 2.01 g (92%) of the iodoaldehyde **239** as a yellow oil; IR (neat, cm^{-1}) 3030, 2920, 2819, 2725, 2154, 1717, 1095; ^1H NMR (200 MHz, $CDCl_3$) δ 9.42 (t, J = 2.2 Hz, 1H), 5.90 (d, J = 10.8 Hz, 1H), 5.78 (dd, J_1 = 10.8 Hz, J_2 = 1.6 Hz, 1H), 4.99 (d, J = 6.8 Hz, 1H), 4.73 (t, J = 1.6 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 3.38 (s, 3H), 3.07 (br s, 2H), 2.20-1.55 (m, 5H), 1.56 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H); ^{13}C NMR

(50 MHz, $CDCl_3$) δ 201.2, 132.6, 128.8, 121.7, 119.8, 97.1, 94.7, 91.7, 82.7, 66.9, 56.6, 50.7, 43.8, 38.1, 32.9, 27.1, 22.2, 20.3, 20.2, 14.5; MS (CI) 441 (MH^+, 1%), 395 ($M^+ - CH_2OCH_3$, 15%), 379 ($M^+ - OCH_2CH_3$, 100%); HRMS calcd for $C_{18}H_{20}O_2I$ ($M^+ - CH_2OCH_3$): 395.0467. Found: 395.0501.

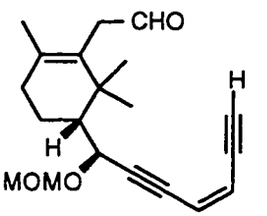
Preparation of (1*R,2*S**,9*S**)-(*Z*)-9-hydroxy-12,15,15-trimethyl-2-methyloxymethoxy-bicyclo[9.3.1]pentadeca-5,11-diene-3,7-diyne (240a), (1*R**,2*S**,9*R**)-(*Z*)-9-hydroxy-12,15,15-trimethyl-2-methyloxymethoxy-bicyclo[9.3.1]pentadeca-5,11-diene-3,7-diyne (240b) and (5*R**)-1-formylmethyl-2,6,6-trimethyl-5-[(1*S**)-(*Z*)-1-methyloxymethoxy-4-heptene-2,6-diynyl]-1-cyclohexene (232)**



240a



240b



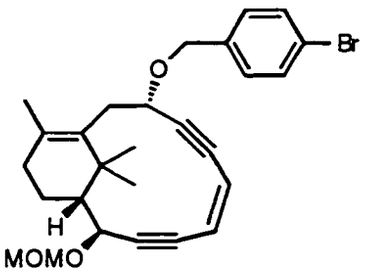
232

(Tetrahydrofuran)chromium(II) chloride (2.70 g, 10.1 mmol) and nickel(II) chloride (0.53 g, 4.08 mmol) were introduced into a flame-dried flask using a nitrogen glove bag and were stirred in THF (150 mL) for 30 minutes under an argon atmosphere at room temperature . An argon-purged solution of the iodoaldehyde **239** (1.80 g, 4.09 mmol) in THF (100 mL) was then added *via* cannula and the initially grey suspension turned brown. The mixture was stirred for 45 minutes and poured into a separatory funnel containing a saturated solution of ammonium chloride (50 mL) and ether (100 mL). The aqueous phase was extracted with ether (3 x 100 mL) and the combined organic layers were washed with brine (1 x 100 mL), dried, filtered and concentrated. Purification of the

crude product by chromatography (25-40% ether/petroleum ether) afforded 347 mg (27%) of the compound **240a**, 40 mg (3%) of the diastereomer **240b** and 60 mg (5%) of the reduced aldehyde **232**, all as colourless oils. Compound **240a**: IR (neat, cm^{-1}) 3400, 2929, 2196, 1699, 1660, 1030; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (s, 2H, H_5 and H_6), 5.11 (t, J = 8.8 Hz, 1H, H_9), 4.89 (d, J = 6.8 Hz, 1H, H_{19}), 4.60 (br s, 1H, H_2), 4.51 (d, J = 6.8 Hz, 1H, H_{19}), 3.35 (s, 3H, H_{20}), 2.63-2.55 (m, 2H, H_{10}), 2.45 (ddd, J_1 = 18.0 Hz, J_2 = 13.1 Hz, J = 6.1 Hz, 1H, H_{13}), 2.09-2.02 (m, 1H, H_{14}), 1.99 (br s, 1H, O<u>H</u>), 1.90 (m, 1H, H_1), 1.76 (dd, J_1 = 18.0 Hz, J_2 = 6.1 Hz, 1H, H_{13}), 1.65 (s, 3H, H_{18}), 1.61-1.56 (m, 1H, H_{14}), 1.30 (s, 3H, H_{16}), 1.11 (s, 3H, H_{17}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.5, 131.2 (C_{11} and C_{12}), 121.3, 120.7 (C_5 and C_6), 98.5, 95.4, 93.4, 84.9, 82.9 (C_3, C_4, C_{19}, C_7 and C_8), 70.3 (C_2), 63.5 (C_9), 55.5 (C_{20}), 49.1 (C_1), 37.2 (C_{10}), 36.8 (C_{15}), 32.1 (C_{17}), 29.4 (C_{13}), 25.2 (C_{16}), 25.1 (C_{14}), 20.9 (C_{18}); HRMS calcd for $C_{18}H_{21}O_2$ (M^+ - CH_2OCH_3): 269.1542. Found: 269.1541. Diastereomer **240b**: (neat, cm^{-1}) 3380, 2945, 2192, 1717, 1658, 1084; ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (d, J = 10.3 Hz, 1H), 5.72 (d, J = 10.3 Hz, 1H), 4.96 (t, J = 9.0 Hz, 1H), 4.94 (d, J = 6.7 Hz, 1H), 4.74 (d, J = 4.6 Hz, 1H), 4.60 (d, J = 6.7 Hz, 1H), 3.36 (s, 3H), 2.63-2.60 (m, 1H), 2.58-2.53 (m, 2H), 2.15 (m, 1H), 1.92 (m, 1H), 1.86-1.74 (m, 2H), 1.64 (s, 3H), 1.54 (br s, 1H), 1.14 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.4, 129.6, 120.6, 119.3, 98.0, 97.0, 93.9, 85.1, 83.6, 65.7, 63.6, 55.6, 48.7, 36.6, 36.0, 31.9, 29.4, 25.0, 21.0, 18.7; HRMS calcd for $C_{18}H_{21}O_2$ (M^+ - CH_2OCH_3): 269.1542. Found: 269.1516. Aldehyde **232**: IR (neat, cm^{-1}) 3336, 2930, 2353, 1719, 1034; ^1H NMR (200 MHz, $CDCl_3$) δ 9.50 (t, J = 2.2 Hz, 1H), 5.91 (ddd, J_1 = 10.9 Hz, J_2 = 1.7 Hz, J_3 = 0.7 Hz, 1H), 5.79 (dd, J_1 = 10.9 Hz, J_2 = 2.2 Hz, 1H), 5.02 (d, J = 6.8 Hz, 1H), 4.74 (t, J = 1.7 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 3.39 (s, 3H), 3.29 (dd, J_1 = 2.2 Hz, J_2 = 0.7 Hz, 1H), 3.09 (br s, 2H), 2.12-1.92 (m, 3H), 1.81-1.60 (m, 2H), 1.56 (s, 3H), 1.07 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 132.7, 128.9, 121.3, 118.9, 97.0, 94.7, 84.6, 82.6, 80.7, 66.9, 56.7, 50.8,

43.8, 38.1, 32.8, 27.1, 22.3, 20.4, 20.2; MS (CI) 315 (MH^+, 1%), 314 (M^+, 1%), 283 (M^+ - OCH_3, 8%), 253 (M^+ - OCH_2CH_3, 100%); HRMS calcd for $C_{18}H_{21}O$ (M^+ - OCH_2OCH_3): 253.1593. Found: 253.1601.

Preparation of (1*R,2*S**,9*S**)-(*Z*)-9-(4-bromobenzyl)-12,15,15-trimethyl-2-methyloxymethoxy-bicyclo[9.3.1]pentadeca-5,11-diene-3,7-diyne (250)**

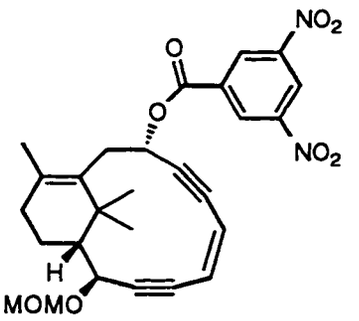


250

A suspension of sodium hydride in THF was prepared by washing a 60% dispersion of sodium hydride in mineral oil (15 mg, 0.38 mmol) with ether (3 x 1 mL), drying it under a stream of nitrogen and adding dry THF (2 mL). A solution of the alcohol **240a** (35 mg, 0.11 mmol) in THF (2 mL) was added dropwise to this stirred suspension at 0 °C. The reaction was warmed to room temperature, stirred for 30 minutes and recooled to 0 °C. The 4-Bromobenzylbromide (47 mg, 0.19 mmol) was added in one portion to this mixture and the resultant suspension was warmed to room temperature and stirred for 15 hours. The mixture was then poured into a separatory funnel containing ether (10 mL) and a saturated aqueous solution of ammonium chloride (10 mL). The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic layers were washed with brine (1 x 10 mL), dried, filtered and concentrated. Purification of the crude product by chromatography (15-20% ether/petroleum ether) afforded 29 mg (53%) of the benzylated product **250** as a white solid; IR (CH_2Cl_2, cm^{-1}) 2914, 2248, 1596, 1055; ^1H NMR (200 MHz, $CDCl_3$) δ 7.46 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 5.81 (s, 2H), 4.90

(d, J = 6.8 Hz, 1H), 4.80 (t, J = 8.7 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H), 4.60 (br s, 1H), 4.50 (d, J = 6.8 Hz, 1H), 4.45 (d, J = 11.6 Hz, 1H), 3.36 (s, 3H), 2.77-2.37 (m, 3H), 2.18-1.95 (m, 1H), 1.93-1.85 (br s, 1H), 1.82-1.71 (m, 1H), 1.64 (s, 3H), 1.72-1.48 (m, 1H), 1.25 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.0, 132.6, 131.5, 130.7, 129.5, 121.5, 121.3, 120.7, 96.4, 95.4, 93.2, 86.6, 82.8, 70.5, 70.2, 70.1, 55.5, 49.0, 36.7, 34.4, 32.0, 29.3, 25.2, 25.1, 20.9; MS (EI) 454 (M^+ - OCH_3, 0.6%), 452 (M^+ - OCH_3, 0.6%), 423 (M^+ - OCH_2OCH_3, 0.7%), 421 (M^+ - OCH_2OCH_3, 0.7%).

Preparation of (1*R,2*S**,9*S**)-(*Z*)-9-(3,5-dinitrobenzoyl)-12,15,15-trimethyl-2-methyloxymethoxy-bicyclo[9.3.1]pentadeca-5,11-diene-3,7-diyne (251)**

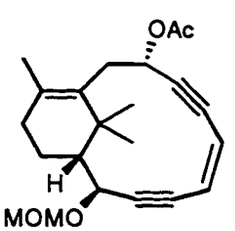


251

3,5-Dinitrobenzoylchloride (120 mg, 0.52 mmol) was added to a solution of the alcohol **240a** (65 mg, 0.21 mmol), triethylamine (145 μL, 1.04 mmol) and 4-dimethylaminopyridine (5 mg, 0.04 mmol) in CH_2Cl_2 (5 mL) at room temperature and the resultant mixture was stirred for 15 hours. The mixture was poured into a separatory funnel containing CH_2Cl_2 (15 mL) and water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic extracts were washed with aqueous 10% HCl (1 x 15 mL), saturated sodium bicarbonate (1 x 15 mL) and brine (1 x 15 mL)

respectively and then dried, filtered and concentrated. Purification of the crude product by chromatography (25% ether/petroleum ether) yielded 100 mg (95%) of the benzoyl ester **251** as a yellow solid; IR (neat, cm^{-1}) 3055, 2949, 1734, 1628, 1031; ^1H NMR (200 MHz, $CDCl_3$) δ 9.23 (t, J = 2.1 Hz, 1H), 9.18 (d, J = 2.1 Hz, 2H), 6.33 (t, J = 9.2 Hz, 1H), 5.88 (dd, J_1 = 10.3 Hz, J_2 = 2.2 Hz, 1H), 5.80 (d, J = 10.3 Hz, 1H), 4.91 (d, J = 6.8 Hz, 1H), 4.63 (t, J = 2.2 Hz, 1H), 4.53 (d, J = 6.8 Hz, 1H), 3.37 (s, 3H), 2.81 (t, J = 9.2 Hz, 2H), 2.61-2.40 (m, 1H), 2.18-1.92 (m, 2H), 1.90-1.73 (m, 1H), 1.73 (s, 3H), 1.68-1.54 (m, 1H), 1.42 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 148.6, 133.9, 133.6, 129.8, 129.6, 122.6, 121.8, 120.5, 95.9, 93.3, 93.1, 87.4, 82.7, 70.0, 68.1, 55.6, 48.9, 36.8, 33.3, 32.0, 29.4, 25.4, 24.9, 21.0; MS(CI) 478 (MH^+ - OCH_3, 9%), 463 (M^+ - CH_2OCH_3, 6%), 447 (M^+ - OCH_2OCH_3, 34%).

Preparation of (1*R**,2*S**,9*S**)-(*Z*)-9-acetoxy-12,15,15-trimethyl-2-methyloxymethoxy-bicyclo[9.3.1]pentadeca-5,11-diene-3,7-diyne (252)

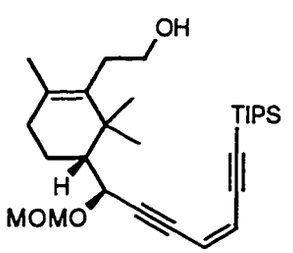


252

Acetic anhydride (171 μL, 1.81 mmol) and a catalytic amount of 4-dimethylaminopyridine (5 mg, 0.04 mmol) were added to a solution of the alcohol **240a** (114 mg, 0.36 mmol) in pyridine (5 mL) and the reaction was stirred for 15 hours at room temperature. The mixture was then poured into a separatory funnel containing CH_2Cl_2 (20 mL) and a saturated solution of sodium bicarbonate (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with brine (1 x 20 mL), dried, filtered and concentrated. Purification of the crude product by

chromatography (25% ether/petroleum ether) afforded 120 mg (93%) of the title compound **252** as a colourless oil; IR (neat, cm^{-1}) 3054, 2943, 2894, 1740, 1559, 1027; ^1H NMR (200 MHz, $CDCl_3$) δ 6.00 (t, J = 9.0 Hz, 1H), 5.77 (s, 2H), 4.87 (d, J = 6.8 Hz, 1H), 4.58 (br s, 1H), 4.49 (d, J = 6.8 Hz, 1H), 3.33 (s, 3H), 2.59 (d, J = 9.0 Hz, 2H), 2.56-2.34 (m, 1H), 2.07 (s, 3H), 2.10-1.89 (m, 2H), 1.80-1.58 (m, 2H), 1.63 (s, 3H), 1.34 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.9, 133.1, 130.4, 121.0, 120.9, 95.5, 94.6, 93.2, 85.8, 82.7, 70.0, 65.2, 55.5, 48.9, 36.7, 33.4, 32.0, 29.3, 25.1, 24.9, 21.0, 20.8; HRMS calcd for $C_{20}H_{23}O_3$ (M^+ - CH_2OCH_3): 311.1648. Found: 311.1631.

Preparation of (5*R)-1-(2-hydroxyethyl)-2,6,6-trimethyl-5-[(1*S**)-(*Z*)-1-methyloxymethoxy-7-triisopropylsilyl-4-heptene-2,6-diynyl]-1-cyclohexene (230)**

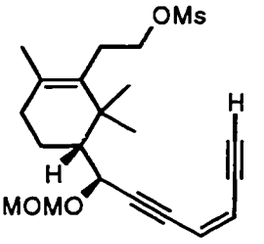


230

The addition product **249** (154 mg, 0.263 mmol) was stirred in a mixture of acetic acid, water and THF (3:1:1, 5 mL) at room temperature for 4 hours. The mixture was quenched with saturated aqueous sodium bicarbonate to a neutral pH 7 and poured into a separatory funnel containing ether (40 mL) and a saturated aqueous solution of sodium bicarbonate (40 mL). The aqueous layer was extracted with ether (2 x 40 mL) and the combined organic layers were washed with brine (3 x 40 mL), dried, filtered and concentrated. Purification of the resultant oil by chromatography (40% ether/petroleum ether) afforded 108 mg (87%) of the alcohol **230** as a clear oil; IR (neat, cm^{-1}) 3348,

2913, 2141, 1461, 1028; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.81 (br s, 2H), 4.94 (d, J = 6.6 Hz, 1H), 4.77 (br s, 1H), 4.52 (d, J = 6.6 Hz, 1H), 3.58 (br t, J = 8.0 Hz, 2H), 3.36 (s, 3H), 2.32 (br t, J = 8.0 Hz, 2H), 2.10-1.86 (m, 3H), 1.67-1.43 (m, 3H), 1.62 (s, 3H), 1.09 (s, 3H), 1.06 (s, 21H), 1.00 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 132.8, 129.6, 119.5, 119.4, 103.6, 99.3, 97.0, 94.7, 82.7, 66.9, 62.4, 56.5, 50.8, 38.1, 32.6, 32.2, 27.3, 22.9, 20.3, 19.9, 18.6, 11.2; MS(CI) 473 (MH^+, 4%), 472 (M^+, 6%), 441 (M^+ - OCH_3, 10%), 427 (M^+ - CH_2OCH_3, 12%), 411 (M^+ - OCH_2OCH_3, 100%); HRMS calcd for $C_{29}H_{48}O_3Si$ (M^+): 472.3373. Found: 472.3426.

Preparation of (5*R)-1-(2-hydroxyethyl)-2,6,6-trimethyl-5-[(1*S**)-(*Z*)-1-methyloxymethoxy-4-heptene-2,6-diynyl]-1-cyclohexene (254)**

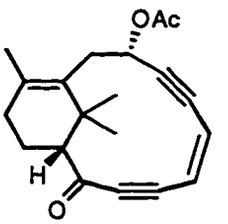


254

Methanesulfonyl chloride (15 μL, 0.20 mmol) was added to a solution of **230** (77 mg, 0.16 mmol) and triethylamine (100 μL, 0.72 mmol) in CH_2Cl_2 (5 mL) at room temperature and the resultant mixture was stirred for 15 hours. The mixture was poured into a separatory funnel containing CH_2Cl_2 (15 mL) and water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic extracts were washed with aqueous 10% HCl (1 x 15 mL), saturated sodium bicarbonate (1 x 15 mL) and brine (1 x 15 mL) respectively and then dried, filtered and concentrated. A 1 M solution of tetrabutylammonium fluoride (200 μL, 0.2 mmol) was then added to a solution of this crude product in THF (5 mL) at -78 °C. The reaction was warmed to room

temperature and stirred for 3 hours. The mixture was poured into a separatory funnel containing a saturated aqueous solution of ammonium chloride (15 mL) and ether (15 mL). The aqueous phase was extracted with ether (3 x 15 mL) and the combined organic layers were washed with brine (1 x 15 mL), dried, filtered and concentrated. Purification of the crude oil by chromatography (40% ether/petroleum ether) yielded 35 mg (55% for the two steps) of the mesylate **254** as a yellow oil; IR (neat, cm^{-1}) 3280, 2922, 2095, 1574, 1032; ^1H NMR (200 MHz, $CDCl_3$) δ 5.91 (ddd, J_1 = 11.0 Hz, J_2 = 1.7 Hz, J_3 = 0.8 Hz, 1H), 5.79 (dd, J_1 = 11.0 Hz, J_2 = 2.3 Hz, 1H), 5.02 (d, J = 6.7 Hz, 1H), 4.73 (br s, 1H), 4.58 (d, J = 6.7 Hz, 1H), 4.12 (t, J = 9.2 Hz, 2H), 3.39 (s, 3H), 3.30 (dd, J_1 = 2.3 Hz, J_2 = 0.8 Hz, 1H), 2.98 (s, 3H), 2.52 (br t, J = 9.0 Hz, 2H), 2.08-1.80 (m, 3H), 1.75-1.52 (m, 2H), 1.67 (s, 3H), 1.12 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 131.6, 131.1, 121.3, 118.8, 97.0, 94.6, 84.6, 82.5, 80.7, 68.9, 66.7, 56.6, 50.8, 38.1, 37.6, 32.6, 28.7, 27.3, 22.6, 20.7, 20.0; MS(CI) 363 (MH^+ - OCH_3, 1%), 333 (M^+ - OCH_2OCH_3, 10%); HRMS calcd for $C_{19}H_{25}O_4S$ (M^+ - CH_2OCH_3): 349.1473. Found: 349.1476.

Preparation of (1*R**,9*S**)-(*Z*)-9-acetoxy-12,15,15-trimethyl-2-oxo-bicyclo[9.3.1]pentadeca-5,11-diene-3,7-diyne (258)

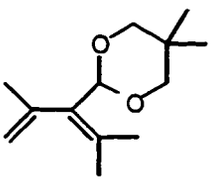


258

Selenium(IV) oxide (15 mg, 0.14 mmol) was added to a solution of the cyclized product **252** (40 mg, 0.11 mmol) in 1,4-dioxane (7 mL) and the resultant mixture was heated to 60-70 °C for 3 hours. The reaction was cooled to room temperature and poured

into a separatory funnel containing ether (15 mL) and a saturated aqueous solution of sodium bicarbonate (15 mL). The aqueous phase was extracted with ether (3 x 15 mL) and the combined organic layers were washed with brine (2 x 15 mL), dried, filtered and concentrated. Purification of the crude product by chromatography (25% ether/petroleum ether) yielded 31 mg (89%) of the oxidized product **258** as a colourless oil; IR (neat, cm^{-1}) 3060, 2931, 2179, 1740, 1643, 1552, 1019; ^1H NMR (200 MHz, $CDCl_3$) δ 6.02 (d, J = 10.4 Hz, 1H), 5.94 (t, J = 9.0 Hz, 1H), 5.93 (d, J = 10.4 Hz, 1H), 2.68-2.59 (m, 3H), 2.10 (s, 3H), 2.02-1.63 (m, 4H), 1.71 (s, 3H), 1.23 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.6, 169.9, 134.1, 128.8, 124.9, 119.1, 97.0, 95.6, 87.6, 85.5, 64.8, 61.8, 35.8, 32.0, 30.9, 28.8, 24.9, 21.3, 21.0, 20.9; HRMS calcd for $C_{20}H_{22}O_2$ (M^+): 310.1570. Found: 310.1556.

Preparation of 3-formyl-2,4-dimethyl-1,3-pentadiene (2,2-dimethylpropylene) acetal (262)

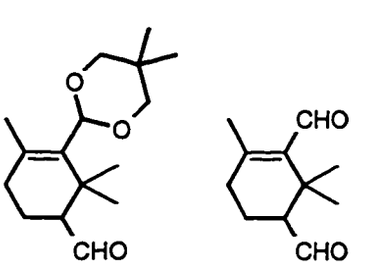


262

A 1.58 M solution of *tert*-butyllithium (13.7 mL, 21.6 mmol) in pentane was added dropwise to a solution of the diene **243** (1.73 g, 9.89 mmol) in THF (30 mL) at -78 °C and the mixture was stirred at -78 °C for 30 minutes. *N,N*-Dimethylformamide (2.3 mL, 29.7 mmol) was then added dropwise. The reaction was warmed to room temperature and stirred for 15 hours. The mixture was poured into a separatory funnel containing ether (100 mL) and a saturated aqueous solution of ammonium chloride (100 mL). The aqueous layer was extracted with ether (3 x 70 mL) and the combined organic layers were washed

with brine (1 x 70 mL), dried, filtered and concentrated. A mixture of the resultant colourless oil, 2,2-dimethyl-1,3-propanediol (3.12 g, 30.0 mmol) and oxalic acid (225 mg, 1.79 mmol) in benzene (50 mL) was then refluxed using a Dean and Stark apparatus for 5.5 hours. The reaction was cooled to room temperature, diluted with petroleum ether (100 mL) and poured into a separatory funnel. The organic phase was washed with a saturated aqueous solution of sodium bicarbonate (3 x 40 mL), dried and concentrated. Purification of the crude residual oil by chromatography (5% ethyl acetate/petroleum ether) afforded 1.45 g (70%) of the protected diene **262** as a colourless liquid; IR (neat, cm^{-1}) 2908, 1635, 1098; ^1H NMR (200 MHz, $CDCl_3$) δ 5.15 (s, 1H), 5.03 (m, 1H), 4.63 (m, 1H), 3.65 (d, J = 11.2 Hz, 2H), 3.45 (d, J = 11.2 Hz, 2H), 1.88 (s, 3H), 1.76 (s, 3H), 1.68 (s, 3H), 1.18 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.5, 134.7, 132.9, 114.8, 100.8, 77.7, 30.0, 23.9, 23.2, 22.1, 21.9, 19.8; HRMS calcd for $C_{13}H_{22}O_2$ (M^+): 210.1621. Found: 210.1632.

Preparation of 1,5-diformyl-2,6,6-trimethyl-1-cyclohexene 1-mono(2,2-dimethylpropylene) acetal (263) and 1,5-diformyl-2,6,6-trimethyl-1-cyclohexene (264)

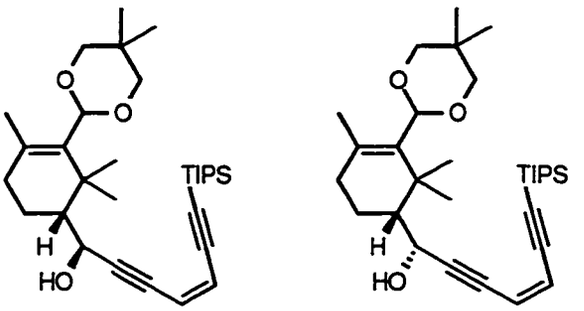


263 **264**

Boron trifluoride diethyl etherate (1.6 mL, 13 mmol) was added dropwise over a period of 30 minutes to a stirred solution of the diene **262** (2.60 g, 12.4 mmol) and acrolein (4.9 mL, 73 mmol) in CH_2Cl_2 (60 mL) at -78 °C and the resultant mixture was

stirred for 20 minutes at this temperature. The reaction was then quenched at -78 °C with a saturated solution of sodium bicarbonate (30 mL) and stirred vigorously as it was allowed to warm to room temperature. The mixture was poured into a separatory funnel and the aqueous layer extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with brine (2 x 50 mL), dried, filtered and concentrated. Purification of the crude roduct by chromatography (10% ether/petroleum ether) afforded 1.60 g (49%) of aldehyde **263** as white crystals and 0.56 g (25%) of dialdehyde **264** as a clolourless liquid. Compound **263:** mp 63-66°C; IR (neat, cm^{-1}) 2914, 2868, 2833, 1719, 1090; ^1H NMR (200 MHz, $CDCl_3$) δ 9.83 (d, J = 2.9 Hz, 1H), 4.88 (s, 1H), 3.70 (d, J = 11.2 Hz, 2H), 3.47 (d, J = 11.2 Hz, 2H), 2.20-2.03 (m, 3H), 1.97 (s, 3H), 1.78-1.58 (m, 2H), 1.27 (s, 3H), 1.26 (s, 3H), 1.10 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.9, 135.6, 134.0, 101.4, 78.6, 78.5, 57.5, 36.1, 31.7, 30.2, 27.2, 24.0, 23.4, 22.1, 20.7, 19.4; HRMS calcd for $C_{16}H_{26}O_3$ (M^+): 266.1883. Found: 266.1874. Compound **264**: IR (neat, cm^{-1}) 2916, 2759, 1720, 1671, 1118; ^1H NMR (200 MHz, $CDCl_3$) δ 10.08 (s, 1H), 9.85 (d, J = 2.2 Hz, 1H), 2.31-2.12 (m, 2H), 2.08 (s, 3H), 1.91-1.62 (m, 3H), 1.43 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.9, 191.5, 155.9, 139.5, 57.7, 35.5, 33.6, 27.1, 22.7, 19.2, 18.4; MS(EI) 180 (M^+, 12%), 165 (M^+ - CH_3, 27%), 152 (M^+ - CHO, 27%); HRMS calcd for $C_{11}H_{16}O_2$ (M^+): 180.1150. Found: 180.1142.

Preparation of (5*R)-1-formyl-5-[(1*S**)-(*Z*)-1-hydroxy-7-triisopropylsilyl-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (2,2-dimethylpropylene) acetal (265a) and (5*R**)-1-formyl-5-[(1*R**)-(*Z*)-1-hydroxy-7-triisopropylsilyl-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (2,2-dimethylpropylene) acetal (265b)**

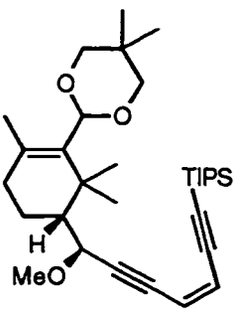


265a **265b**

A 2.5 M solution of *n*-butyllithium in hexanes (3.3 mL, 8.3 mmol) was added dropwise to a solution of the enediyne **177** (2.13 g, 9.18 mmol) in THF (80 mL) at -78 °C. The solution was stirred at -78 °C for 30 minutes and became dark brown in colour. A solution of the aldehyde **263** (1.55 g, 5.83 mmol) in THF (10 mL) was then added dropwise. The reaction was warmed to room temperature and stirred for 15 hours. The mixture was poured into a separatory funnel containing ether (100 mL) and water (100 mL). The aqueous layer was extracted with ether (3 x 70 mL) and the combined organic layers were washed with brine (1 x 70 mL), dried, filtered and concentrated. Purification of the crude residual oil by chromatography (10-20% ether/petroleum ether) afforded 2.00 g (67%) of the addition product **265a** and 0.49 g (17%) of the diastereomer **265b** both as yellow oils. Compound **265a**: IR (neat, cm^{-1}) 3434, 2910, 2141, 1666, 1575, 1107; ^1H NMR (200 MHz, $CDCl_3$) δ 5.83 (s, 2H), 4.83 (s, 1H), 4.81 (s, 1H), 3.70 (d, *J* = 11.1 Hz, 2H), 3.47 (d, *J* = 11.1 Hz, 2H), 2.13-2.05 (m, 2H), 1.99 (s, 3H), 1.88-1.78 (m, 1H), 1.75-1.57 (m, 3H), 1.26 (s, 3H), 1.18 (s, 3H), 1.12-1.03 (br s, 24H), 0.73 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.5, 119.7, 103.7, 102.0, 99.5, 99.0, 82.1, 78.6, 63.0, 51.3, 37.1, 33.3, 30.1, 27.0, 24.1, 22.9, 22.2, 20.9, 19.0, 18.6, 11.2; MS (CI) 499 (MH^+, 3%), 481 ($MH^+ - H_2O$, 8%); HRMS calcd for $C_{31}H_{50}O_3Si$ (M^+): 498.3531. Found: 498.3510. Compound **265b**: IR (neat, cm^{-1}) 3430, 2909, 2140, 1668, 1575, 1089; ^1H NMR (200 MHz, $CDCl_3$) δ 5.82 (s, 2H), 4.80 (s, 1H), 4.69 (br s, 1H), 3.69 (d, J = 11.2 Hz, 2H), 3.47 (d, J = 11.0 Hz, 2H), 2.04-1.95 (m, 1H), 2.00 (s, 3H), 1.89-1.79 (m, 2H), 1.69-1.44 (m, 3H), 1.26 (s, 3H), 1.17 (s, 3H), 1.14-1.03 (br s, 21H), 1.01 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.5, 119.9, 119.5, 103.6, 101.9, 99.5, 97.7, 84.0, 78.5, 64.1, 51.2, 36.6, 33.2, 30.1, 26.6, 24.1, 22.3, 22.1, 20.9, 20.8, 18.6, 11.2; HRMS calcd for $C_{31}H_{50}O_3Si$ (M^+): 498.3531. Found: 498.3519.

Preparation of (5*R)-1-formyl-5-[(1*S**)-(*Z*)-1-methoxy-7-triisopropylsilyl-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (2,2-dimethylpropylene) acetal (266)**

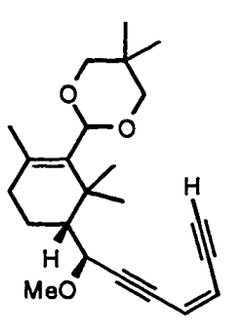


266

A suspension of sodium hydride in THF was prepared by washing a 60% dispersion of sodium hydride in mineral oil (0.287 g, 7.2 mmol) with ether (3 x 10 mL), drying it under a stream of nitrogen and adding dry THF (40 mL). A solution of the alcohol **265a** (1.49 g, 2.99 mmol) in THF (40 mL) was added dropwise to this stirred

suspension at 0 °C. The reaction was warmed to room temperature, stirred for 30 minutes and recooled to 0 °C. Iodomethane (0.93 mL, 14.9 mmol) was added dropwise to this mixture and the resultant suspension was warmed to room temperature and stirred for 15 hours. The mixture was then poured into a separatory funnel containing ether (100 mL) and a saturated aqueous solution of ammonium chloride (100 mL). The aqueous layer was extracted with ether (3 x 70 mL) and the combined organic layers were washed with brine (1 x 70 mL), dried, filtered and concentrated. Purification of the crude residual oil by chromatography (5-10% ethyl acetate/petroleum ether) afforded 1.36 g (89%) of the methylated product **266** as a colourless oil; IR (neat, cm^{-1}) 2910, 2142, 1670, 1095; ^1H NMR (200 MHz, $CDCl_3$) δ 5.84 (s, 2H), 4.80 (s, 1H), 4.22 (s, 1H), 3.70 (d, J = 11.2 Hz, 2H), 3.47 (d, J = 10.9 Hz, 2H), 3.33 (s, 3H), 2.04-1.99 (br s, 4H), 1.82-1.79 (m, 1H), 1.59-1.55 (m, 3H), 1.27 (s, 3H), 1.11 (s, 3H), 1.09-1.05 (br s, 21H), 0.97 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.6, 134.5, 119.9, 119.5, 103.7, 102.1, 99.3, 97.3, 82.7, 78.63, 78.58, 72.1, 56.7, 51.0, 37.2, 33.7, 30.1, 26.8, 24.1, 22.5, 22.2, 20.9, 19.6, 18.6, 11.2; MS (CI) 513 (MH^+, 13%), 481 ($M^+ - CH_3O$, 56%); HRMS calcd for $C_{32}H_{52}O_3Si$ (M^+): 512.3688. Found: 512.3702.

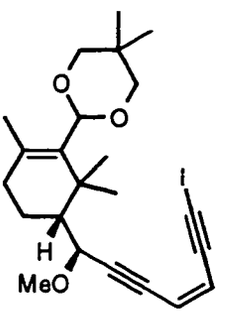
Preparation of (5*R)-1-formyl-5-[(1*S**)-(*Z*)-1-methoxy-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (2,2-dimethylpropylene) acetal (267)**



267

A 1 M solution of tetrabutylammonium fluoride (0.68 mL, 0.68 mmol) was added to a solution of **266** (289 mg, 0.564 mmol) in THF (20 mL) at -78 °C. The reaction was warmed to room temperature and stirred for one hour. The mixture was then poured into a separatory funnel containing a saturated aqueous solution of ammonium chloride (50 mL) and ether (50 mL). The aqueous phase was extracted with ether (3 x 50 mL) and the combined organic layers were washed with brine (1 x 50 mL), dried, filtered and concentrated. Purification of the resultant oil by chromatography (2-5% ethyl acetate/petroleum ether) afforded 183 mg (91%) of the acetylene **267** as a yellow oil; IR (neat, cm^{-1}) 3272, 2909, 2093, 1670, 1463, 1093; ^1H NMR (200 MHz, $CDCl_3$) δ 5.92 (ddd, J_1 = 10.9 Hz, J_2 = 1.6 Hz, J_3 = 0.8 Hz, 1H), 5.77 (dd, J_1 = 10.9 Hz, J_2 = 2.2 Hz, 1H), 4.81 (s, 1H), 4.25 (s, 1H), 3.69 (d, J = 11.2 Hz, 2H), 3.48 (d, J = 11.3 Hz, 1H), 3.47 (d, J = 11.2 Hz, 1H), 3.36 (s, 3H), 3.19 (dd, J_1 = 2.2 Hz, J_2 = 0.8 Hz, 1H), 2.03-1.99 (br s, 4H), 1.88-1.78 (m, 1H), 1.70-1.56 (m, 3H), 1.26 (s, 3H), 1.13 (s, 3H), 0.98 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.6 134.5, 121.5, 118.6, 102.0, 97.7, 84.5, 82.2, 80.7, 78.6, 78.5, 72.0, 56.6, 51.3, 37.3, 33.7, 30.1, 26.8, 24.1, 22.5, 22.2, 20.9, 19.6; MS (CI) 357 (MH^+, 73%), 325 (M^+ - OCH_3, 100%); HRMS calcd for $C_{22}H_{29}O_2$ (M^+ - OCH_3): 325.2169. Found: 325.2131; Anal. calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.29; H, 9.25.

Preparation of (5*R)-1-formyl-5-[(1*S**)-(*Z*)-7-iodo-1-methoxy-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (2,2-dimethylpropylene) acetal (268)**

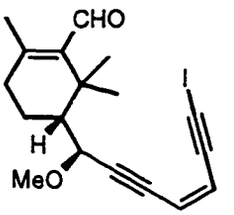


268

Morpholine (326 μL, 3.74 mmol) and iodine (321 mg, 1.26 mmol) were sequentially added to a solution of the acetylene **267** (200 mg, 0.56 mmol) in benzene (40 mL) and the reaction was warmed to 60-70 °C for 3 hours. The mixture was cooled to room temperature and poured into a separatory funnel containing ether (50 mL) and a 10% aqueous sodium thiosulfate solution (50 mL). The aqueous layer was extracted with ether (3 x 50 mL) and the combined organic layers were washed with 10% aqueous sodium thiosulfate (1 x 50 mL) and brine (1 x 50 mL) and then dried, filtered and concentrated. Purification of the resultant oil by chromatography (10% ether/petroleum ether) afforded 203 mg (75%) of the iodoacetylene **268** as a yellow oil; IR (neat, cm^{-1}) 2903, 2720, 2155, 1664, 1102; ^1H NMR (200 MHz, $CDCl_3$) δ 5.89 (d, J = 10.8 Hz, 1H), 5.79 (dd, J_1 = 10.8 Hz, J_2 = 1.5 Hz, 1H), 4.79 (s, 1H), 4.24 (s, 1H), 3.68 (d, J = 11.0 Hz, 2H), 3.46 (d, J = 11.1 Hz, 2H), 3.35 (s, 3H), 2.05-2.01 (m, 1H), 1.98 (s, 3H), 1.86-1.78 (m, 1H), 1.75-1.55 (m, 3H), 1.25 (s, 3H), 1.13 (s, 3H), 0.98 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.6, 134.4, 121.8, 119.6, 102.0, 97.6, 91.6, 82.4, 78.54, 78.48, 72.0, 56.6, 51.1, 37.2, 33.8, 30.1, 26.9, 24.0, 22.4, 22.1, 20.9, 19.7, 14.6; MS (CI)

483 (MH^+, 6%), 451 (M^+ - OCH_3, 47%); Anal. calcd for $C_{23}H_{31}O_3I$: C, 57.27; H, 6.48. Found: C, 56.78; H, 6.54.

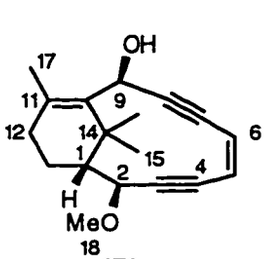
Preparation of (5*R)-1-formyl-5-[(1*S**)-(*Z*)-7-iodo-1-methoxy-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (269)**



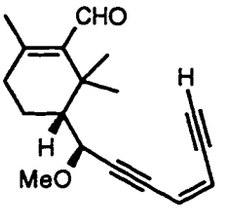
269

The iodoacetylene **268** (120 mg, 0.25 mmol) was stirred in a mixture of THF and 4% aqueous hydrochloric acid (3:1, 12 mL) for 3 hours. The reaction was quenched with a saturated solution of sodium bicarbonate (25 mL), stirred for 1 hour and poured into a separatory funnel containing ether (25 mL). The aqueous layer was extracted with ether (2 x 25 mL) and the combined ether extracts were washed with water (3 x 25 mL), dried, filtered and concentrated. Purification of the resultant oil by chromatography (20% ether/petroleum ether) afforded 90 mg (91%) of the unsaturated aldehyde **269** as a colourless oil; IR (neat, cm^{-1}) 2925, 2820, 2154, 1664, 1100; ^1H NMR (200 MHz, $CDCl_3$) δ 10.07 (s, 1H), 5.93 (d, J = 10.7 Hz, 1H), 5.81 (dd, J_1 = 10.7 Hz, J_2 = 1.5 Hz, 1H), 4.33 (s, 1H), 3.36 (s, 3H), 2.31-2.27 (m, 2H), 2.08 (s, 3H), 1.99-1.88 (m, 1H), 1.82-1.64 (m, 2H), 1.32 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 192.4, 156.4, 140.3, 121.9, 119.9, 97.5, 91.7, 82.4, 71.6, 56.8, 51.6, 36.5, 35.8, 27.1, 21.9, 19.5, 19.1, 14.3; MS (CI) 396 (M^+, 49%), 381 (M^+ - CH_3, 12), 365 (M^+ - OCH_3, 100%).

Preparation of (1*R,2*S**,9*R**)-(*Z*)-9-hydroxy-2-methoxy-11,14,14-trimethyl-bicyclo[8.3.1]tetradeca-5,10-diene-3,7-diyne (270) and (5*R**)-1-formyl-5-[(1*S**)-(*Z*)-1-methoxy-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (271)**



270



271

Intramolecular Nozaki-Kishi Coupling

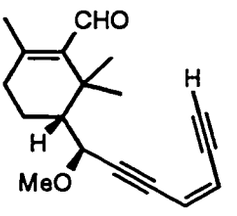
(Tetrahydrofuran)chromium(II) chloride (887 mg, 3.32 mmol) and nickel(II) chloride (5 mg, 0.04 mmol) were introduced into a flame-dried flask using a nitrogen glove bag and were stirred in THF (12 mL) for 30 minutes under an argon atmosphere at room temperature . An argon-purged solution of the iodoaldehyde **239** (159 mg, 0.40 mmol) in THF (6 mL) was then added *via* cannula and the initially grey suspension turned brown. The mixture was stirred for 45 minutes and poured into a separatory funnel containing a saturated solution of ammonium chloride (15 mL) and ether (25 mL). The aqueous phase was extracted with ether (3 x 25 mL) and the combined organic layers were washed with brine (1 x 25 mL), dried, filtered and concentrated. Purification of the crude product by chromatography (10-25% ether/petroleum ether) afforded 40 mg (37%) of the cyclized compound **270** and 18 mg (17%) of the reduced aldehyde **271** both as colourless oils; IR (neat, cm^{-1}) 3416, 3052, 2913, 2825, 2189, 1675, 1086; ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (ddd, J_1 = 9.3 Hz, J_2 = 1.7 Hz, J_3 = 0.3 Hz, 1H, H_6), 5.75 (br s, 1H, H_9), 5.73 (ddd, J_1 = 9.3 Hz, J_2 = 1.7 Hz, J_3 = 0.6 Hz, 1H, H_5), 3.97 (t, J = 1.7 Hz, 1H, H_2), 3.36 (s, 3H, H_{18}), 2.15-2.08 (m, 1H, H_{12}), 1.98 (m, 1H, H_{13}), 1.77 (m, 1H, H_1), 1.77 (s,

3H, H_{17}), 1.66 (s, 3H, H_{15}), 1.57 (m, 2H, H_{12} and O<u>H</u>), 1.26 (s, 3H, H_{16}), 1.23 (m, 1H, H_{13}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 128.9 (C_{10} and C_{11}), 123.9, 120.8 (C_5 and C_6), 100.5, 95.9, 86.1, 85.2 (C_3, C_4, C_7 and C_8), 76.2 (C_9), 63.5 (C_2), 56.4 (C_{18}), 52.6 (C_1), 36.4 (C_{14}), 34.9 (C_{16}), 29.7 (C_{13}), 25.8 (C_{17}), 25.0 (C_{12}), 19.7 (C_{15}); MS(CI) 271 (MH^+, 7%), 270 (M^+, 7%), 253 ($MH^+ - H_2O$, 44%), 239 ($M^+ - OCH_3$, 16%), 223 ($MH^+ - H_2O - OCH_3$, 97%); HRMS calcd for $C_{18}H_{22}O_2$ (M^+): 270.1621. Found: 270.1572.

Intramolecular Acetylide Addition

A 0.5M solution of potassium bis(trimethylsilyl)amide in toluene (1.50 mL, 0.75 mmol) was added dropwise to a solution of the aldehyde **271** (125 mg, 0.46 mmol) in THF (10 mL) at -78 °C. The mixture turned dark brown in colour and was stirred at -78 °C for 1.5 hours. The reaction was quenched with a saturated solution of ammonium chloride (10 mL) and poured into a separatory funnel containing ether (25 mL) and water (15 mL). The aqueous layer was extracted with ether (3 x 25 mL) and the combined organic layers were washed with brine (2 x 25 mL), dried, filtered and concentrated. Purification of the crude product by chromatography (20-40% ether/petroleum ether) afforded 19 mg (15%) of the cyclized product **270** as a colourless oil.

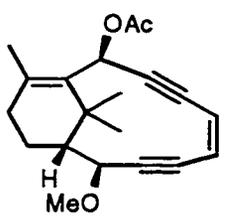
Preparation of (5*R)-1-formyl-5-[(1*S**)-(*Z*)-1-methoxy-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (271)**



271

The acetylene **267** (190 mg, 0.53 mmol) was stirred in a mixture of THF and 4% aqueous hydrochloric acid (3:1, 12 mL) for 3.5 hours. The reaction was quenched with a saturated solution of sodium bicarbonate (40 mL), stirred for 1 hour and poured into a separatory funnel containing ether (40 mL). The aqueous layer was extracted with ether (2 x 40 mL) and the combined ether extracts were washed with water (3 x 40 mL), dried, filtered and concentrated. Purification of the resultant oil by chromatography (20% ether/petroleum ether) afforded 125 mg (87%) of the unsaturated aldehyde **271** as a colourless oil; IR (neat, cm^{-1}) 3285, 3052, 2929, 2822, 2095, 1670, 1100; ^1H NMR (200 MHz, $CDCl_3$) δ 10.07 (s, 1H), 5.93 (ddd, J_1 = 10.9 Hz, J_2 = 2.4 Hz, J_3 = 0.8 Hz, 1H), 5.79 (dd, J_1 = 10.9 Hz, J_2 = 2.2 Hz, 1H), 4.32 (s, 1H), 3.35 (s, 3H), 3.30 (dd, J_1 = 2.2 Hz, J_2 = 0.8 Hz, 1H), 2.29-2.23 (m, 2H), 2.07 (s, 3H), 1.98-1.88 (m, 1H), 1.72-1.62 (m, 2H), 1.31 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 192.3, 156.4, 140.3, 121.3, 118.8, 97.4, 84.5, 82.2, 80.7, 71.5, 56.7, 51.6, 36.5, 35.7, 27.1, 21.8, 19.5, 19.0; MS (CI) 271 (MH^+, 7%), 255 ($M^+ - CH_3$, 29%), 239 ($M^+ - OCH_3$, 40%).

Preparation of (1*R**,2*S**,9*R**)-(*Z*)-9-acetoxy-2-methoxy-11,14,14-trimethyl-bicyclo[8.3.1]tetradeca-5,10-diene-3,7-diyne (272)

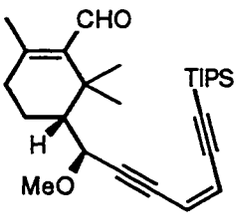


272

Acetic anhydride (350 μL, 3.7 mmol) and a catalytic amount of 4-dimethylaminopyridine (5 mg, 0.04 mmol) were added to a solution of the alcohol **270** (39 mg, 0.15 mmol) in pyridine (3 mL) and the reaction was stirred for 15 hours at room temperature. The mixture was then poured into a separatory funnel containing CH_2Cl_2 (15

mL) and a saturated solution of sodium bicarbonate (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine (1 x 15 mL), dried, filtered and concentrated. Purification of the crude product by chromatography (20% ether/petroleum ether) afforded 44 mg (97%) of the title compound **272** as a colourless oil; IR (neat, cm^{-1}) 3050, 2931, 2824, 2198, 1742, 1545, 1091; ^1H NMR (200 MHz, $CDCl_3$) δ 6.59 (s, 1H), 5.94 (dd, J_1 = 9.8 Hz, J_2 = 0.8 Hz, 1H), 5.73 (dd, J_1 = 9.8 Hz, J_2 = 0.8 Hz, 1H), 3.96 (br s, 1H), 3.35 (s, 3H), 2.10 (s, 3H), 2.07-1.98 (m, 3H), 1.75 (s, 3H), 1.72 (s, 3H), 1.63-1.56 (m, 2H), 1.13 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.8, 133.2, 131.3, 124.4, 120.7, 97.1, 96.0, 86.2, 77.4, 76.0, 64.2, 56.4, 52.3, 36.3, 34.5, 29.6, 25.7, 24.8, 21.3, 19.8; MS(CI) 313 (MH^+ - CH_3CO, 49%), 253 (MH^+ - CH_3COOH, 100%).

Preparation of (5*R)-1-formyl-5-[(1*S**)-(*Z*)-1-methoxy-7-triisopropylsilyl-4-heptene-2,6-diynyl]-2,6,6-trimethyl-1-cyclohexene (273)**

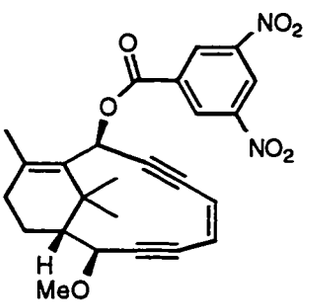


273

The enediyne **266** (67 mg, 0.13 mmol) was stirred in a mixture of THF and 4% aqueous hydrochloric acid (3:1, 8 mL) for 3.5 hours. The reaction was quenched with a saturated solution of sodium bicarbonate (15 mL), stirred for 1 hour and poured into a separatory funnel containing ether (15 mL). The aqueous layer was extracted with ether (2 x 15 mL) and the combined ether extracts were washed with water (3 x 15 mL), dried, filtered and concentrated. Purification of the resultant oil by chromatography (20% ether/petroleum ether) afforded 50 mg (90%) of the unsaturated aldehyde **273** as a

colourless oil; IR (neat, cm^{-1}) 2917, 2142, 1673, 1611, 1125; ^1H NMR (200 MHz, $CDCl_3$) δ 10.07 (s, 1H), 5.85 (s, 2H), 4.31 (s, 1H), 3.32 (s, 3H), 2.26 (m, 2H), 2.07 (s, 3H), 1.95-1.58 (m, 3H), 1.28 (s, 3H), 1.15 (s, 3H), 1.11-1.05 (br s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 156.3, 140.4, 119.7, 103.7, 99.5, 97.1, 82.6, 71.5, 56.7, 51.5, 36.5, 35.6, 27.0, 21.9, 19.4, 18.9, 18.6, 11.2; MS (CI) 427 (MH^+, 26%), 395 (M^+ - OCH_3, 100%), 383 (M^+ - C_3H_7, 75%); HRMS calcd for $C_{27}H_{42}O_2Si$ (M^+): 426.2956. Found: 426.2968.

Preparation of (1*R,2*S**,9*R**)-(*Z*)-9-(3,5-dinitrobenzoyl)-11,14,14-trimethyl-2-methoxy-bicyclo[8.3.1]tetradeca-5,10-diene-3,7-diyne (274)**

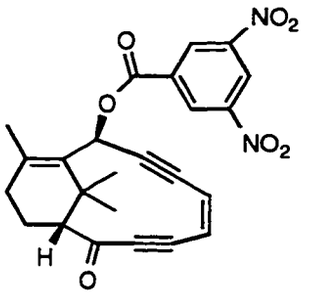


274

3,5-Dinitrobenzoylchloride (65 mg, 0.28 mmol) was added to a solution of the alcohol **270** (31 mg, 0.11 mmol), triethylamine (83 μL, 1.04 mmol) and 4-dimethylaminopyridine (5 mg, 0.04 mmol) in CH_2Cl_2 (5 mL) at room temperature and the resultant mixture was stirred for 15 hours. The mixture was poured into a separatory funnel containing CH_2Cl_2 (15 mL) and water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic extracts were washed with aqueous 10% HCl (1 x 15 mL), saturated sodium bicarbonate (1 x 15 mL) and brine (1 x 15 mL) respectively and then dried, filtered and concentrated. Purification of the crude product by chromatography (25% ether/petroleum ether) yielded 40 mg (74%) of the benzoyl ester **274** as a white solid; IR (neat, cm^{-1}) 3112, 3025, 2945, 2170, 1738, 1625, 1100; ^1H

NMR (200 MHz, $CDCl_3$) δ 9.24 (t, J = 2.1 Hz, 1H), 9.20 (d, J = 2.1 Hz, 2H), 6.94 (s, 1H), 6.02 (dd, J_1 = 9.8 Hz, J_2 = 0.7 Hz, 1H), 5.79 (dd, J_1 = 9.8 Hz, J_2 = 0.8 Hz, 1H), 3.97 (br s, 1H), 3.38 (s, 3H), 2.10 (br s, 3H), 1.85 (br s, 6H), 1.70-1.44 (m, 2H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 148.6, 134.0, 133.6, 131.5, 129.5, 127.2, 124.2, 120.8, 97.3, 96.0, 86.3, 78.1, 76.0, 64.0, 56.4, 52.4, 36.3, 34.8, 29.6, 25.8, 25.0, 19.8; MS(CI) 478 (MH^+, 15%).

Preparation of (1*R,2*S**,9*R**)-(*Z*)-9-(3,5-dinitrobenzoyl)-11,14,14-trimethyl-2-oxo-bicyclo[8.3.1]tetradeca-5,10-diene-3,7-diyne (275)**

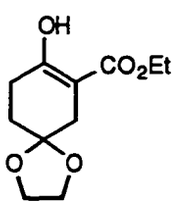


275

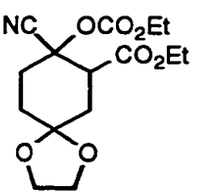
Selenium(IV) oxide (20 mg, 0.18 mmol) was added to a mixture of the cyclized product **274** (38 mg, 0.082 mmol) and potassium dihydrogen phosphate (50 mg, 0.36 mmol) in 1,4-dioxane (3 mL) and the resultant mixture was stirred at reflux for 2 hours. The reaction was then cooled to room temperature and poured into a separatory funnel containing ether (15 mL) and a saturated aqueous solution of sodium bicarbonate (15 mL). The aqueous phase was extracted with ether (3 x 15 mL) and the combined organic layers were washed with brine (2 x 15 mL), dried, filtered and concentrated. Purification of the crude product by chromatography (25% ether/petroleum ether) yielded 30 mg (77%) of the oxidized product **275** as a yellow oil; IR (neat, cm^{-1}) 3102, 3020, 2932, 2174, 1735, 1635, 1546, 1459, 1346, 1266, 1158, 1111; ^1H NMR (500 MHz, $CDCl_3$) δ 9.25 (t, J = 2.1 Hz, 1H), 9.20 (d, J = 2.1 Hz, 2H), 7.05 (s, 1H), 6.14 (dd, J_1 = 9.7 Hz, J_2 = 0.7 Hz,

2.26-2.18 (m, 1H), 2.15-2.06 (m, 1H), 2.01-1.96 (m, 1H), 1.93 (s, 3H), 1.91 (s, 3H), 1.23 (m, 1H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 161.7, 148.9, 133.9, 133.3, 131.4, 129.4, 127.0, 124.0, 122.8, 97.6, 94.8, 89.7, 87.1, 67.2, 61.7, 34.9, 33.7, 29.7, 26.8, 24.4, 20.1; MS (CI) 449 (MH^+, 50%).

Preparation of 3-ethoxycarbonyl-4-hydroxy-3-cyclohexenone ethylene ketal (278) and 4-cyano-3-ethoxycarbonyl-4-ethoxycarbonyloxy-cyclohexanone ethylene ketal (279)



278

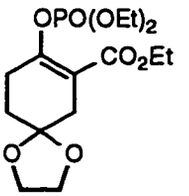


279

A 1.3 M solution of *n*-butyllithium in hexane (30 mL, 39 mmol) was added to a solution of *N,N*-diisopropylamine (5.6 mL, 40 mmol) in THF (50 mL) at -20 °C and stirred for 30 minutes. The temperature was lowered to -78 °C and a solution of 1,4-cyclohexanedione *mono*-ethylene ketal (5.17 g, 33 mmol) in THF (25 mL) added. The reaction was stirred at -15 °C for 1hour and recooled to -78 °C. HMPA (6.1 mL, 35 mmol) and ethyl cyanoformate (4 mL, 40 mmol) were then added sequentially. The resultant mixture was stirred at -78 °C for 30 minutes and poured into cold water (200 mL). The aqueous layer was extracted with ether (3 x 200 mL) and the combined organic layers were washed with brine (3 x 100 mL), dried, filtered and concentrated. Purification of the crude product by chromatography (20% petroleum ether/ethyl acetate) yielded 4.49 g (60%) of compound **278** and 9.82 g (30%) of compound **279** as yellow oils. Recrystallization from methanol and ethyl acetate afforded both **278** and **279** respectively, as white crystals. Compound **278** (a mixture of enol and ketone tautomers in solution): m.p. 49-50 °C; IR

(CH_2Cl_2, cm^{-1}) 2966, 1741, 1720, 1656, 1617, 1061; ^1H NMR (200 MHz, $CDCl_3$) δ 4.13 (q, J = 7.1 Hz, 2H), 3.97 (m, 4H), 2.47 (t, J = 7.0 Hz, 2H), 2.44 (s, 2H), 1.80 (t, J = 7.0 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.6, 172.0, 170.9, 107.1, 95.2, 64.7, 64.5, 61.1, 60.3, 53.8, 38.0, 36.4, 34.3, 32.6, 30.2, 27.8, 14.1, 14.0; MS(EI) 228 (M^+, 15%); HRMS calcd for $C_{11}H_{16}O_5$ (M^+): 228.0998. Found: 228.0990; Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.87; H, 7.07. Found: C, 57.80; H, 6.96. Compound **279**: m.p. 92-94 °C; IR (CH_2Cl_2, cm^{-1}) 2973, 2894, 2237, 1748; ^1H NMR (500 MHz, $CDCl_3$) δ 4.18 (s, 4H), 3.91 (m, 4H), 3.17 (dd, J_1 = 11.7 Hz, J_2 = 4.2 Hz, 1H), 2.78 (dt, J_1 = 13.1 Hz, J_2 = 4.2 Hz, 1H), 2.12-1.75 (m, 5H), 1.26 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 152.0, 115.4, 105.8, 74.4, 65.0, 64.9, 64.6, 61.4, 47.9, 34.6, 31.7, 31.1, 14.1, 14.0; MS(CI) 328 (MH^+, 74%); HRMS calcd. for $C_{15}H_{21}O_7N$ (M^+): 327.1318. Found: 327.1330; Anal. Calcd for $C_{15}H_{21}O_7N$: C, 55.05; H, 6.42; N, 4.28. Found: C, 54.87; H, 6.33; N, 4.25.

Preparation of 3-ethoxycarbonyl-4-(diethoxyphosphoryl)oxy-3-cyclohexenone ethylene ketal (280)

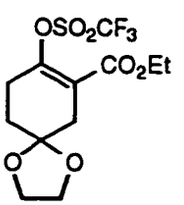


280

A solution of the keto-ester **278** (470 mg, 2.06 mmol) in THF (20 mL) was added to a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (5 mL, 2.5 mmol) and THF (20 mL) at -78 °C and the resultant mixture was stirred for 30 minutes at this temperature. Diethyl chlorophosphate (0.45 mL, 3.1 mmol) was added and the reaction was allowed to warm to room temperature. After 1 hour of stirring, the solvents were

removed *in vacuo*. Purification of the resultant crude product by chromatography (20% ethyl acetate/petroleum ether) yielded 750 mg (70%) of the title compound **280** as a colourless liquid; IR (neat, cm^{-1}) 2966, 1714, 1658, 1041; ^1H NMR (200 MHz, $CDCl_3$) δ 4.25-4.13 (m, 6H), 3.93 (m, 4H), 2.68 (br t, J = 7 Hz, 2H), 2.52 (br s, 2H), 1.84 (t, J = 6.7 Hz, 2H), 1.31-1.21 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 152.5, 112.7, 106.3, 65.5, 65.4, 64.5, 64.4, 60.3, 35.1, 30.5, 27.8, 16.0, 15.9, 14.0; MS(CI) 365 (MH^+, 38%), 319 (MH^+ - OCH_2CH_3, 38%).

Preparation of 3-ethoxycarbonyl-4-(trifluoromethanesulfonyl)oxy-3-cyclohexenone ethylene ketal (281)

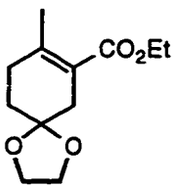


281

A solution of the keto-ester **278** (754 mg, 3.3 mmol) in THF (20 mL) was added to a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (8 mL, 4 mmol) and THF (30 mL) at -78 °C and the resultant mixture was stirred for 30 minutes at this temperature. *N*-Phenyltrifluoromethanesulfonimide (1.3 g, 3.64 mmol) in THF (15 mL) was added and the reaction mixture was allowed to warm to room temperature. After 1 hour of stirring, the solvents were removed *in vacuo*. Purification of the resultant crude product by flash chromatography (13% ethyl acetate/petroleum ether) yielded 1.178 g (99%) of the title compound **281** as a colourless liquid; IR (neat, cm^{-1}) 2978, 2896, 1709, 1600, 1100; ^1H NMR (200 MHz, $CDCl_3$) δ 4.25 (q, J = 7.0 Hz, 2H), 3.97 (m, 4H), 2.65 (br s, 2H), 2.61 (t, J = 7.0 Hz, 2H), 1.88 (t, J = 7.0 Hz, 2H), 1.30 (t, J = 7.0 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 150.9, 133.7, 120.6, 105.7, 64.8, 61.9, 35.8, 30.8, 27.5, 13.9; MS(CI) 361 (MH^+, 59%).

Preparation of 3-ethoxycarbonyl-4-methyl-3-cyclohexenone ethylene ketal (282)



282

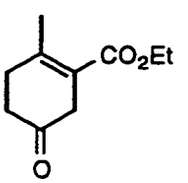
From 280

Copper(I) iodide (762 mg, 4.0 mmol), ether (40 mL), and a 1.4 M solution of methyllithium in ether (2.9 mL, 4.1 mmol) were combined sequentially at 0 °C. The mixture was stirred for 15 minutes and cooled to -78 °C. A solution of the enol phosphate **280** (293 mg, 0.80 mmol) in ether (12 mL) was added dropwise to the mixture. The reaction was stirred for 1 hour at -78 °C, warmed to room temperature and stirred for 15 hours. The mixture was poured into a separatory funnel containing a saturated, aqueous solution of ammonium chloride (20 mL) and the aqueous phase was extracted with ether (3 x 20 mL). The combined organic layers were dried, filtered and concentrated. Purification of the crude product by chromatography (20% ethyl acetate/petroleum ether) afforded 129 mg (89%) of compound **282** as a colourless oil. Compound **282**: IR (neat, cm^{-1}) 2931, 1710, 1643, 1237; ^1H NMR (200 MHz, $CDCl_3$) δ 4.09 (q, J = 7.1 Hz, 2H), 3.92 (m, 4H), 2.45 (br s, 2H), 2.31 (br t, J = 6.6 Hz, 2H), 2.00 (s, 3H), 1.67 (t, J = 6.6 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.8, 146.6, 121.8, 107.7, 64.6, 60.1, 36.3, 33.3, 30.8, 21.5, 14.4; MS(EI) 226 (M^+, 12%), 197 (M^+ - CH_2CH_3, 2%); HRMS calcd for $C_{12}H_{18}O_4$ (M^+): 226.1205. Found: 226.1194.

Second method: from 281

A solution of dimethylcuprate was prepared by adding a 1.4 M solution of methyllithium in ether (2.4 mL, 3.3 mmol) to a stirred slurry of CuI (638 mg, 3.3 mmol) in THF (10 mL) at -10 °C. A solution of enol trifluoromethanesulfonate **281** (240 mg, 0.97 mmol) in THF (10 mL) was added dropwise to the mixture at -10 °C. The reaction was warmed to room temperature and stirred for 15 hours. The mixture was then diluted with hexane (50 mL), filtered through a pad of Fluorisil and concentrated. Purification of the residue by chromatography (15% ethyl acetate/petroleum ether) provided 217 mg (99%) of compound **282** as a colourless oil.

Preparation of 3-ethoxycarbonyl-4-methyl-3-cyclohexenone (283)

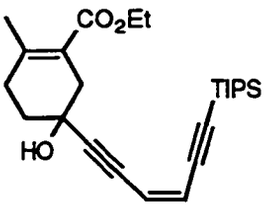


283

A 35% aqueous solution of trifluoroacetic acid (60.mL) was added to a solution of ethylene ketal **282** (2.17 g, 9.6 mmol) in chloroform (100 mL) and the reaction was stirred at room temperature for three days. The mixture was poured into a separatory funnel and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed sequentially with a saturated solution of sodium bicarbonate (1 x 100 mL) and brine (1 x 100 mL) and then dried, filtered and concentrated. Purification of the crude product by chromatography (15% ethyl acetate/petroleum ether) afforded 1.40 g (80%) of the title compound **283** as a yellow oil; IR (neat, cm^{-1}) 2938, 1712, 1644, 1065; ^1H NMR (200 MHz, $CDCl_3$) δ 4.12 (q, J = 7.1 Hz, 2H), 3.07 (br s, 2H), 2.50-2.30 (m, 4H), 2.11 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.0, 166.5, 147.6,

121.3, 60.2, 40.2, 37.3, 33.0, 21.4, 14.1; MS(EI) 182 (M^+, 29%), 153 (M^+ - CH_2CH_3, 9%); HRMS calcd for $C_{10}H_{14}O_3$ (M^+): 182.0943. Found: 182.0931.

Preparation of 3-ethoxycarbonyl-4-methyl-1-[(*Z*)-6-triisopropylsilyl-3-hexene-1,5-diynyl]-3-cyclohexen-1-ol (284)

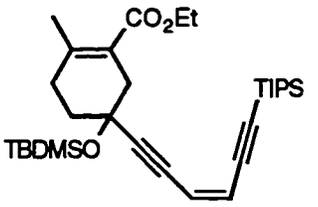


284

Cerium(III) chloride heptahydrate (11.78 g, 31.5 mmol) was dried slowly under vacuum from 60 to 100 °C over the course of several hours. The temperature was raised to 140 °C and drying was continued for 2 hours. The white powder was then allowed to cool to room temperature under argon and dry THF (150 mL) was added. The resultant white supension was stirred for 1 hour. The mixture was cooled to -78 °C and 2.5 M *tert*-butyllithium was added until the persistance of an orange colour. A 2.5 M solution of *tert*-butyllithium was added to the enediyne **177** (3.51 g, 15.1 mmol) in THF (20 mL) at -78 °C and the resultant mixture stirred for 30 minutes. This separate mixture was then added to the suspension of cerium(III) chloride *via* cannula at -78 °C and stirred for 30 minutes at this temperature. A solution of the ketone **283** (2.302 g, 12.6 mmol) in dry THF (20 mL) was added dropwise to the suspension and the mixture was stirred for 10 minutes at -78 °C. The mixture was diluted with ether (75 mL) and saturated aqueous ammonium chloride (25 mL) at -78 °C and warmed to room temperature. The mixture was poured into a separatory funnel, the phases separated and the aqueous layer extracted with ether (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried, filtered and concentrated. Purification of the residual oil by flash chromatography (15% ethyl acetate/petroleum ether) afforded 4.38 g (84%) of the alcohol **284** as a yellow oil; IR (neat,

cm^{-1}) 3430, 2943, 2865, 2142, 1703, 1642, 1247; ^1H NMR (200 MHz, $CDCl_3$) δ 5.81 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.74 (br d, J = 18.1 Hz, 1H), 2.60 (br d, J = 18.1 Hz, 1H), 2.29 (m, 3H), 2.03 (s, 3H), 1.87 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.06 (s, 21H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.3, 147.2, 120.9, 120.5, 120.0, 104.2, 100.7, 100.0, 81.3, 66.7, 60.6, 40.7, 35.2, 32.2, 22.1, 19.3, 14.9, 11.8; MS(CI) 397 (MH^+ - H_2O, 83%); MS(EI) 371 (M^+ - C_3H_7, 19%); HRMS calcd for $C_{22}H_{31}O_3Si$ (M^+ - C_3H_7): 371.2043. Found: 371.2031.

Preparation of 1-*tert*-butyldimethylsilyloxy-3-ethoxycarbonyl-4-methyl-1-[(*Z*)-6-triisopropylsilyl-3-hexene-1,5-diynyl]-3-cyclohexene (285)

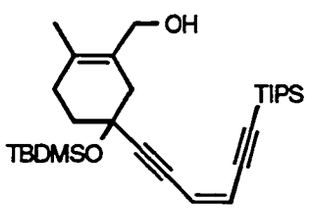


285

Triethylamine (0.9 mL, 6.5 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.9 mL, 3.9 mmol) were added sequentially to a solution of the alcohol **284** (1.312 g, 3.19 mmol) in CH_2Cl_2 (30 mL) at 0 °C and the reaction was stirred for 15 hours at room temperature. A saturated aqueous solution of sodium bicarbonate (10 mL) was added to the mixture which was then poured into a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with brine (30 mL), dried, filtered and concentrated. Purification of the residual oil by flash chromatography (10% ethyl acetate/petroleum ether) afforded 1.639 g (98%) of the silyl ether **285** as a yellow oil; IR (neat, cm^{-1}) 2944, 2863, 2143, 1711, 1643, 1243; ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (s, 2H), 4.15 (q, J = 7.1 Hz, 2H), 2.68 (br d, J = 18.1 Hz, 1H), 2.67 (br d, J = 18.1 Hz, 1H), 2.27 (m, 2H), 2.01 (s, 3H), 1.87 (m, 1H), 1.80 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.07 (s, 21H), 0.80 (s, 9H), 0.14 (s,

3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 146.3, 120.6, 119.5, 119.3, 103.6, 100.9, 99.3, 81.4, 67.0, 59.8, 41.0, 36.0, 31.6, 25.7, 21.4, 18.7, 18.0, 14.3, 11.2, -3.0; MS(EI) 499 (M^+ - CH_2CH_3, 13%), 471 (M^+ - C_4H_9, 100%); HRMS calcd for $C_{27}H_{43}O_3Si_2$ (M^+ - C_4H_9): 471.2751. Found: 471.2716.

Preparation of 1-*tert*-butyldimethylsilyloxy-3-hydroxymethyl-4-methyl-1-[(*Z*)-6-triisopropylsilyl-3-hexene-1,5-diynyl]-3-cyclohexene (286)

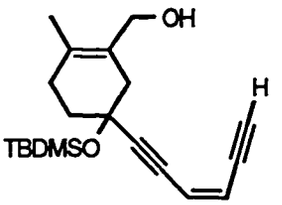


286

A 1 M solution of diisobutylaluminum hydride in toluene (10 mL, 10.0 mmol) was added to a solution of the ester **285** (1.591 g, 3.27 mmol) in CH_2Cl_2 (30 mL) at -78 °C. The solution was stirred for 2 hours between -78 °C and -60 °C and was then poured into a separatory funnel containing a saturated solution of ammonium chloride (20 mL), a 10% aqueous solution of H_2SO_4 (20 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed sequentially with a saturated aqueous solution of sodium bicarbonate (1 x 50 mL) and brine (1 x 50 mL), dried, filtered and concentrated. Purification of the residual oil by flash chromatography (15% ethyl acetate/petroleum ether) afforded 1.450 g (99%) of the primary alcohol **286** as a yellow oil; IR (neat, cm^{-1}) 3340, 2910, 2142, 1680, 1086; ^1H NMR (200 MHz, $CDCl_3$) δ 5.81 (s, 2H), 4.04 (br s, 2H), 2.53 (br d, J = 18.1 Hz, 1H), 2.37 (br d, J = 18.1 Hz, 1H), 2.10 (m, 2H), 1.82 (t, J = 6 Hz, 2H), 1.67 (s, 3H), 1.08 (s, 22H), 0.81 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 130.8, 126.6, 120.0, 119.9, 104.2, 102.0, 99.8, 81.7, 68.5, 63.5, 43.5, 37.1, 30.5, 26.3, 19.3, 18.8, 18.6, 11.8, -2.4; MS(EI) 486 (M^+, 2%), 443 (M^+ - C_3H_7, 3%), 429 (M^+ - C_4H_9, 14%); HRMS calcd for

$C_{29}H_{50}O_2Si_2$ (M^+): 486.3351. Found: 486.3334. Anal. Calcd for $C_{29}H_{50}O_2Si_2$: C, 71.60; H, 10.29. Found: C, 71.55; H, 10.30.

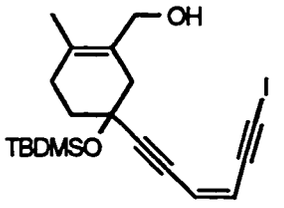
Preparation of 1-*tert*-butyldimethylsilyloxy-1-[(*Z*)-3-hexene-1,5-diynyl]-3-hydroxymethyl-4-methyl-3-cyclohexene (287)



287

A 1 M solution of tetrabutylammonium fluoride in THF (1.31 mL, 1.31 mmol) was added to a solution of compound **286** (580 mg, 1.19 mmol) in THF (30 mL) at -78 °C. The solution was stirred for 2 hours at -78 °C and at 0 °C for an additional 90 minutes. The mixture was poured into a separatory funnel containing a saturated solution of ammonium chloride (20 mL) and ether (50 mL). The aqueous phase was extracted with ether (3 x 50 mL) and the combined organic layers were washed with brine (1 x 50 mL), dried, filtered and concentrated. Purification of the residual oil by flash chromatography (10% ethyl acetate/petroleum ether) afforded 365 mg (93%) of the title compound **287** as an orange oil; IR (cm^{-1}) 3352, 3295, 3030, 2902, 2155, 1675, 1080; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (dd, J_1 = 11.0 Hz, J_2 = 0.8 Hz, 1H), 5.74 (dd, J_1 = 11.0 Hz, J_2 = 2.3 Hz, 1H), 4.09 (d, J = 11.5 Hz, 1H), 4.01 (d, J = 11.5 Hz, 1H), 3.24 (dd, J_1 = 2.3 Hz, J_2 = 0.8 Hz, 1H), 2.56 (br d, J = 17.0 Hz, 1H), 2.39 (br d, J = 17.0 Hz, 1H), 2.25-2.11 (m, 2H), 1.92-1.77 (m, 2H), 1.68 (s, 3H), 1.15 (br s, 1H), 0.83 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.3, 126.2, 121.4, 118.1, 101.6, 84.3, 80.9, 80.8, 68.3, 62.8, 43.2, 36.9, 30.5, 25.7, 18.2, 18.0, -2.9; MS(EI) 330 (M^+, 2%), 273 (M^+ - C_4H_9, 14%); HRMS calcd for $C_{20}H_{30}O_2Si$ (M^+): 330.2016. Found: 330.2053.

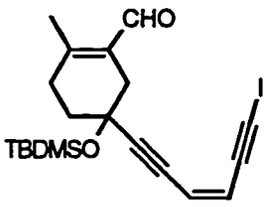
Preparation of 1-*tert*-butyldimethylsilyloxy-3-hydroxymethyl-1-[(*Z*)-6-iodo-3-hexene-1,5-diynyl]-4-methyl-3-cyclohexene (288)



288

Morpholine (9.38 mL, 107.3 mmol) and iodine (10 g, 39.4 mmol) were added sequentially to a solution of the acetylene **287** (5.90 g, 17.9 mmol) in benzene (400 mL). The reaction mixture was heated and stirred at 55 °C for 2 hours. The reaction was cooled to room temperature and a saturated aqueous sodium thiosulfate solution (100 mL) was added to the mixture. The aqueous phase was extracted with ether (3 x 200 mL) and the combined organic layers were washed with brine (1 x 100 mL), dried, filtered and concentrated. Purification of the residual oil by flash chromatography (1% ethyl acetate/petroleum ether) afforded 5.55 g (69%) of the title compound **288** as a brown oil; IR (neat, cm^{-1}) 3349, 3091, 2908, 2154, 1676, 1577, 1095; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (d, J = 10.8 Hz, 1H), 5.76 (d, J = 10.8 Hz, 1H), 4.09 (d, J = 11.7 Hz, 1H), 4.06 (d, J = 11.7 Hz, 1H), 2.56 (br d, J = 16.7 Hz, 1H), 2.40 (br d, J = 16.7 Hz, 1H), 2.28-2.10 (m, 2H), 1.95-1.80 (m, 2H), 1.71 (s, 3H), 1.16 (br s, 1H), 0.83 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.3, 126.1, 121.7, 119.1, 101.7, 91.8, 80.9, 68.2, 62.9, 43.2, 36.9, 30.4, 25.7, 18.4, 18.0, 14.2, -2.9; MS(EI) 456 (M^+, 1%), 399 (M^+ - C_4H_9, 8%); HRMS calcd for $C_{20}H_{29}O_2SiI$ (M^+): 456.0983. Found: 456.0980.

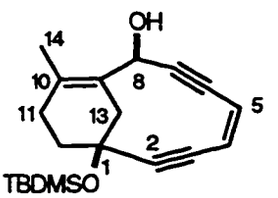
Preparation of 1-*tert*-butyldimethylsilyloxy-3-formyl-1-[(*Z*)-6-iodo-3-hexene-1,5-diynyl]-4-methyl-3-cyclohexene (289)



289

Dess-Martin periodinane (10.3 g, 24.4 mmol) was added in one portion to a solution of the alcohol **288** (5.55 g, 12.2 mmol) in CH_2Cl_2 (100 mL) and the reaction mixture was stirred for 1 hour at room temperature. Ether (500 mL), a saturated aqueous solution of sodium thiosulfate (100 mL) and a saturated aqueous solution of sodium bicarbonate (100 mL) were then added sequentially to the mixture. The solution was stirred for 30-40 minutes until it became clear and then poured into a separatory funnel. The aqueous layer was extracted with ether (3 x 500 mL) and the combined organic extracts were washed with brine (1 x 200 mL), dried, filtered and concentrated. Purification of the residual oil by flash chromatography (10% ethyl acetate/petroleum ether) afforded 5.43 g (98%) of the iodoaldehyde **289** as a yellow oil; IR (cm^{-1}) 3042, 2915, 2830, 2152, 1670, 1572, 1090; ^1H NMR (200 MHz, $CDCl_3$) δ 10.09 (s, 1H), 5.89 (d, J = 10.9 Hz, 1H), 5.75 (d, J = 10.9 Hz, 1H), 2.65 (br d, J = 16.9 Hz, 1H), 2.56 (br d, J = 16.9 Hz, 1H), 2.44 (t, J = 6.0 Hz, 2H), 2.16 (s, 3H), 1.88 (t, J = 6.6 Hz, 2H), 0.81 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.1, 155.9, 131.0, 122.0, 120.1, 101.3, 92.1, 82.1, 67.8, 38.3, 36.7, 33.2, 26.3, 18.6, 18.5, 15.2, -2.4; MS(CI) 455 (MH^+, 11%); MS(EI) 397 (M^+- C_4H_9, 34%); HRMS calcd. for $C_{16}H_{18}O_2SiI$ (M^+-C_4H_9): 397.0121. Found: 397.0141.

Preparation of (1*R,8*R**)-(*Z*)-1-*tert*-butyldimethylsilyloxy-8-hydroxy-10-methyl-bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne (290)**



290

Intramolecular Nozaki-Kishi Coupling

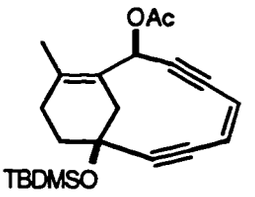
Chromium(II) chloride (2.80 g, 22.8 mmol) was introduced into a flame-dried flask using a nitrogen glove bag and was stirred in THF (120 mL) for 30 minutes under an argon atmosphere at room temperature . A solution of the iodoaldehyde **289** (1.29 g, 2.83 mmol) in THF (50 mL) was then added *via* cannula and the initially grey suspension turned brown. The mixture was stirred for 20 minutes and poured into a separatory funnel containing a saturated solution of ammonium chloride (50 mL) and ether (100 mL). The aqueous phase was extracted with ether (3 x 100 mL) and the combined organic layers were washed with brine (1 x 100 mL), dried, filtered and concentrated. Purification of the crude product by chromatography (10% ethyl acetate/petroleum ether) afforded 659 mg (71%) of the compound **290** as a colourless oil. Compound **290**: IR (neat, cm^{-1}) 3350, 2942, 2196, 1665, 1656, 1100; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (d, J = 9.5 Hz, 1H, H_4), 5.70 (dd, J_1 = 9.5 Hz, J_2 = 1.5 Hz, 1H, H_5), 5.51 (d, J_1 = 1.5 Hz, 1H, H_8), 3.04 (dd, J_1 = 14.5 Hz, J_2 = 2.5 Hz, 1H, H_{13}), 2.31 (dq, J_1 = 14.5 Hz, J_2 = 1.9 Hz, 1H, H_{13}), 2.25 (dd, J_1 = 18.1 Hz, J_2 = 7.5 Hz, 1H, H_{11}), 2.08 (m, 1H, H_{11}), 1.96-1.88 (m, 2H, H_{12}), 1.83-1.77 (m, 1H, H_{12}), 1.65 (d, J = 1.9 Hz, 3H, H_{14}), 0.87 (s, 9H, $SiC(C\underline{H}_3)_3$), 0.18 (s, 3H, $Si(C\underline{H}_3)_2$), 0.17 (s, 3H, $Si(C\underline{H}_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.5, 127.6 (C_9 and C_{10}), 124.8, 122.5 (C_4 and C_5), 104.2, 100.5, 84.8, 84.4 (C_2, C_3, C_6 and C_7), 70.7 (C_1), 64.0 (C_8), 44.4 (C_{13}), 35.8 (C_{12}), 31.8 (C_{11}), 25.8

(SiC($\underline{C}H_3)_3$), 18.1 (C_{14}), 18.0 (Si$\underline{C}(CH_3)_3$), -2.9 (Si($\underline{C}H_3)_2$); MS(CI) 329 (MH^+, 16%), 311 ($MH^+ - H_2O$, 100%); MS(EI) 328 (M^+, 5%), 271 ($M^+ - C_4H_9$, 30%); HRMS calcd. for $C_{20}H_{28}O_2Si$ (M^+): 328.1859. Found: 328.1861.

Intramolecular Acetylide Addition

A 0.5M solution of potassium bis(trimethylsilyl)amide in toluene (0.69 mL, 0.35 mmol) was added dropwise to a solution of the aldehyde **293** (67 mg, 0.20 mmol) in THF (5 mL) at -78 °C. The mixture turned dark brown in colour and was stirred at -78 °C for 30 minutes. The reaction was quenched with a saturated solution of ammonium chloride (10 mL) and poured into a separatory funnel containing ether (15 mL) and water (15 mL). The aqueous layer was extracted with ether (3 x 15 mL) and the combined organic layers were washed with brine (2 x 15 mL), dried, filtered and concentrated. Purification of the crude product by chromatography (10% ethyl acetate/petroleum ether) afforded 40 mg (60%) of the cyclized product **290** as a colourless oil.

Preparation of (1*R,8*R**)-(*Z*)-8-acetyloxy-1-*tert*-butyldimethylsilyloxy-10-methyl-bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne (291)**

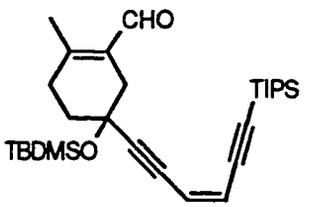


291

Acetic anhydride (6.5 mL, 68.9 mmol) and a catalytic amount of 4-dimethylaminopyridine (50 mg, 0.42 mmol) were added to a solution of the alcohol **290** (3.84 g, 11.7 mmol) in pyridine (60 mL). The reaction was stirred for 15 hours at room temperature, diluted with CH_2Cl_2 (100 mL) and a saturated aqueous solution of sodium bicarbonate (50 mL) and poured into a separatory funnel. The aqueous layer was extracted

with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were washed with brine (1 x 50 mL), dried, filtered and concentrated. Purification of the crude product by flash chromatography (10% ethyl acetate/petroleum ether) afforded 4.29 g (99%) of the title compound **291** as a colourless oil; IR (neat, cm^{-1}) 3021, 2940, 2195, 1738, 1670, 1110; ^1H NMR (500 MHz, $CDCl_3$) δ 6.26 (d, J = 1.6 Hz, 1H), 5.84 (d, J = 9.5 Hz, 1H), 5.71 (dd, J_1 = 9.5 Hz, J_2 = 1.6 Hz, 1H), 2.99 (dd, J_1 = 14.6 Hz, J_2 = 2.6 Hz, 1H), 2.26 (m, 1H), 2.10 (m, 2H), 2.09 (s, 3H), 1.93 (m, 1H), 1.79 (m, 1H), 1.71 (d, J = 1.7 Hz, 3H), 0.86 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 129.6, 127.3, 125.5, 122.4, 104.3, 97.1, 85.8, 84.8, 70.5, 66.3, 44.9, 35.7, 31.7. 25.7, 20.9, 18.3, 17.9, -2.9; MS(EI) 370 (M^+, 1%), 313 (M^+- C_4H_9, 16%); MS(CI) 371 (MH^+, 4%), 311 (MH^+ - CH_3CO_2H, 100%).

Preparation of 1-*tert*-butyldimethylsilyloxy-3-formyl-1-[(*Z*)-6-triisopropylsilyl-3-hexene-1,5-diynyl]-4-methyl-3-cyclohexene (292)

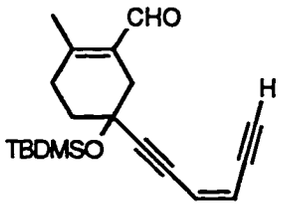


292

Dess-Martin periodinane (163 mg, 0.38 mmol) was added in one portion to a solution of the alcohol **286** (121 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) and the reaction mixture was stirred for 1 hour at room temperature. Ether (10 mL), a saturated aqueous solution of sodium thiosulfate (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL) were then added sequentially to the mixture. The solution was stirred for 30-40 minutes until it became clear and then poured into a separatory funnel. The aqueous layer was extracted with ether (3 x 15 mL) and the combined organic extracts were washed with brine (1 x 15 mL), dried, filtered and concentrated. Purification of the

residual oil by flash chromatography (10% ethyl acetate/petroleum ether) afforded 119 mg (99%) of the aldehyde **292** as a colourless oil. Aldehyde **292**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.02 (s, 1H), 5.83 (s, 2H), 2.69 (br d, J = 16.7 Hz, 1H), 2.58 (br d, J = 16.7 Hz, 1H), 2.42 (br t, J = 7 Hz, 2H), 2.13 (s, 3H), 1.88 (t, J = 6.6 Hz, 2H), 1.08 (s, 21H), 0.81 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H).

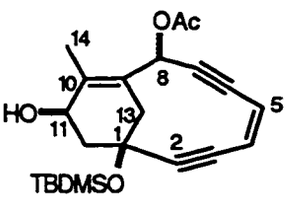
Preparation of 1-*tert*-butyldimethylsilyloxy-3-formyl-1-[(*Z*)-3-hexene-1,5-diynyl]-4-methyl-3-cyclohexene (293)



293

Anhydrous cesium fluoride (37 mg, 0.25 mmol) was added to a mixture of aldehyde **292** (108 mg, 0.22 mmol), acetic anhydride (41 μL, 0.44 mmol), sodium bicarbonate (18 mg, 0.22 mmol) and 4Å molecular sieves in acetonitrile (3 mL) at room temperature. The reaction was stirred for 4 days and then filtered through Celite and concentrated. Purification of the crude oil by chromatography (10% ethyl acetate/petroleum ether) afforded 88 mg (48%) of deprotected acetylene **293** as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (s, 1H), 5.87 (dd, J_1 = 11.0 Hz, J_2 = 0.9 Hz, 1H), 5.76 (dd, J_1 = 11.0 Hz, J_2 = 2.4 Hz, 1H), 3.26 (dd, J_1 = 2.4 Hz, J_2 = 0.9 Hz, 1H), 2.65 (br d, J = 16.7 Hz, 1H), 2.48 (br d, J = 16.7 Hz, 1H), 2.47 (br t, J = 7 Hz, 2H), 2.13 (s, 3H), 1.88 (t, J = 6.7 Hz, 2H), 0.81 (s, 9H), 0.18 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 155.4, 128.3, 121.0, 118.6, 84.8, 84.4, 81.4, 80.7, 67.1, 37.7, 36.1, 32.5, 25.7, 18.0, 17.9, –3.0.

Preparation of (1*R,8*R**,11*R**)-(*Z*)-8-acetyloxy-1-*tert*-butyldimethylsilyloxy-10-methyl-11-hydroxy-bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne (296)**



296

Selenium(IV) oxide (144 mg, 1.3 mmol) was added in one portion to a solution of compound **291** (422 mg, 1.14 mmol) in 1,4-dioxane (10 mL). The reaction was heated to 70 °C and stirred for 30 minutes. A saturated aqueous solution of sodium bicarbonate (10 mL) was added and the mixture poured into a separatory funnel. The aqueous layer was extracted with ether (3 x 20 mL) and the combined organic extracts were washed with brine (1 x 20 mL), dried, filtered and concentrated. Purification of the residual oil by flash chromatography (20% ethyl acetate/petroleum ether) afforded 290 mg (66%) of the allylic alcohol **296** as a colourless oil; IR (neat, cm^{-1}) 3423, 3055, 2945, 1739, 1024; ^1H NMR (500 MHz, $CDCl_3$) δ 6.24 (s, 1H, H_8), 5.85 (d, J = 9.5 Hz, 1H, H_4), 5.73 (br d, J = 9.5 Hz, 1H, H_5), 4.01 (ddd, J_1 = 9.4 Hz, J_2 = 8.0 Hz, J_3 = 2.5 Hz, 1H, H_{11}), 2.95 (dd, J_1 = 14.7 Hz, J_2 = 3.0 Hz, 1H, H_{13}), 2.48 (m, 1H, H_{12}), 2.35 (dt, J_1 = 14.7 Hz, J_2 = 2.0 Hz, 1H, H_{13}), 2.09 (s, 3H, $COCH_3$), 1.82 (d, J = 2.0 Hz, 3H, H_{14}), 1.77 (dd, J_1 = 12.5 Hz, J_2 = 9.4 Hz, 1H, H_{12}), 1.34 (br s, 1H, OH), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.17 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 ($COCH_3$), 130.5, 130.1 (C_9 and C_{10}), 125.5, 122.6 (C_4 and C_5), 102.9, 96.5, 86.0, 84.8 (C_2, C_3, C_6 and C_7), 72.0 (C_{11}), 70.9 (C_1), 66.4 (C_8), 46.1, 45.2 (C_{12} and C_{13}), 25.7 ($SiC(CH_3)_3$), 20.8 ($COCH_3$), 17.9 ($SiC(CH_3)_3$), 14.6 (C_{14}), -2.9 ($Si(CH_3)_2$); MS(CI) 387 (MH^+, 2%), 369 ($MH^+ - H_2O$, 56%); MS(EI) 326 ($M^+ - CH_3CO_2H$, 9%); HRMS calcd. for $C_{20}H_{26}O_2Si$ ($M^+ - CH_3CO_2H$): 326.1703. Found: 326.1964.

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Claims to Original Research

1. The versatile triisopropylsilyl protected enediyne synthon **177** was prepared and used as a building block to synthesize a series of bicyclic enediyne compounds in a convergent approach.[1]

2. Enediyne **177** was condensed stereoselectively onto the Taxol® A ring analogue **245**. Susequent elaboration and eventual ring closure by intramolecular Nozaki-Kishi coupling afforded the novel 12-membered bicyclic enediyne **240a**.[1] The Bergman cycloaromatization of taxamycin-12 **240a** produced the aromatic taxane nucleus in low yield.

3. A similar synthetic sequence was used to prepare the 10- and 11-membered ring taxamycin adducts **290** and **270**. Intramolecular acetylide condensation also effected cyclization of these two systems.

4. The 10-membered ring adduct **296** was coupled to the Taxotere® side chain to afford the enantiomerically enriched taxamycin derivatives **300a** and **300b**. The biological activity of these and related compounds is currently being evaluated.

5. Treatment of the taxamycin-11 and 12 compounds, **274** and **252**, with SeO_2 in dioxane at 70 °C afforded the unusual oxidation products **275** and **258** respectively.

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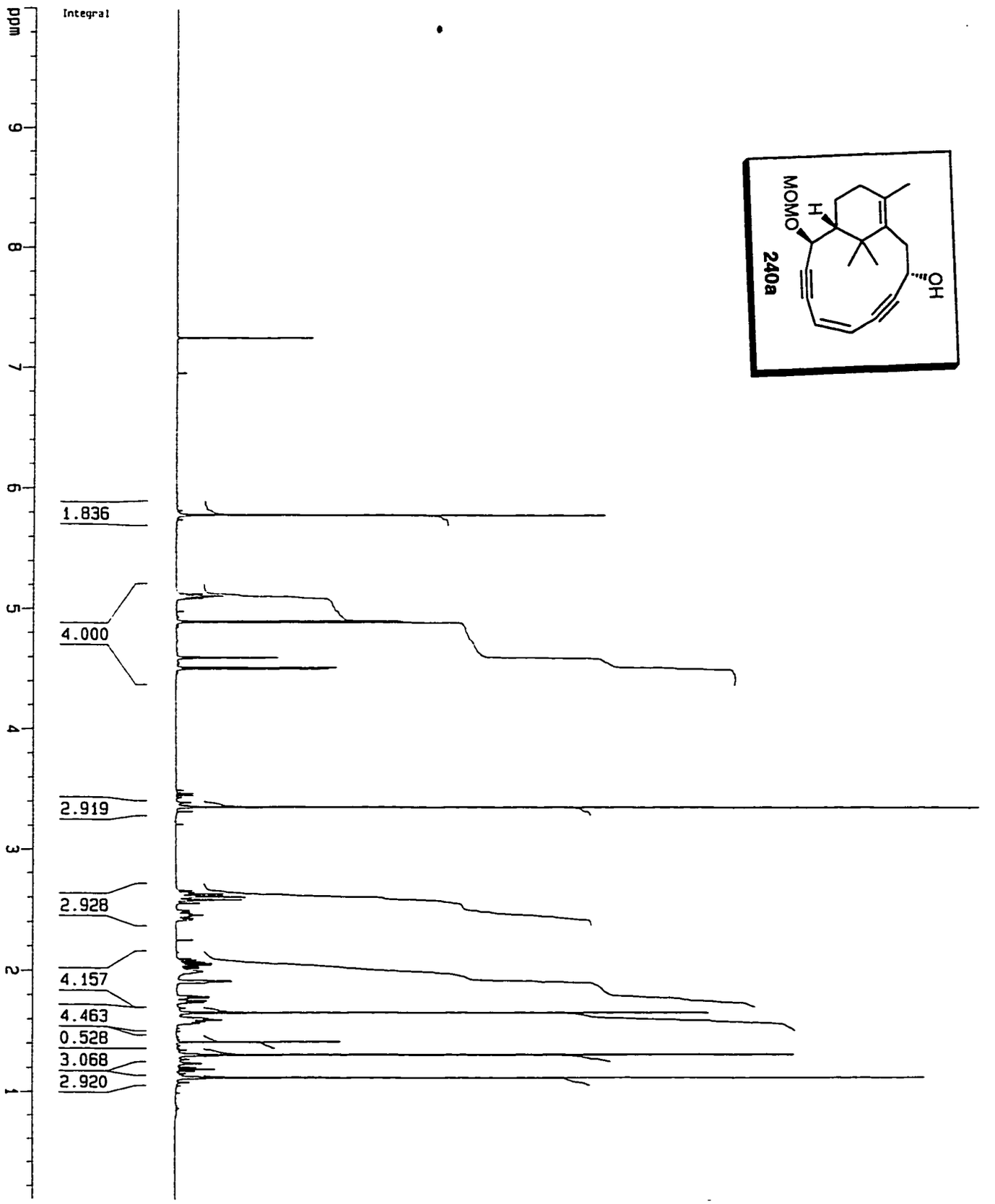
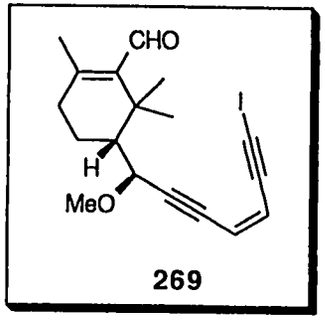
Appendix A: Selected Spectra

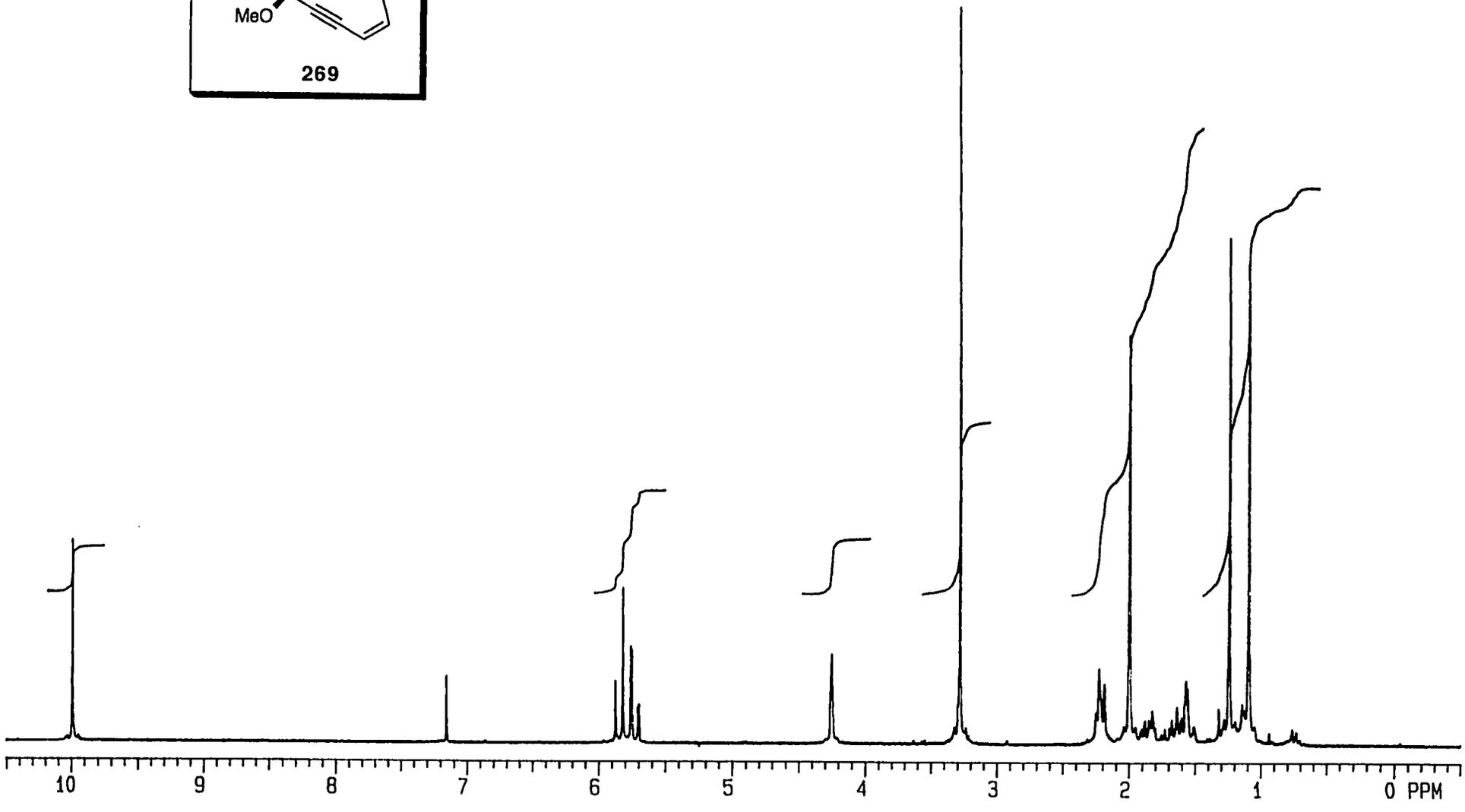
MOMO
H
CHO
239

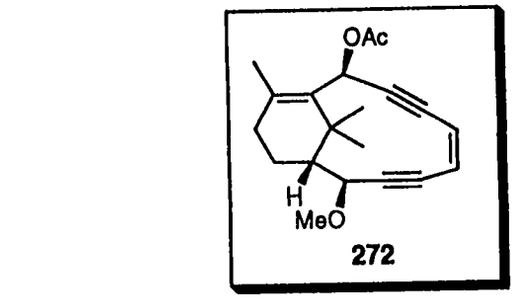
10
9
8
7
6
5
4
3
2
1
0
PPM


ppm
Integral
9
8
7
6
5
4
3
2
1
1.836
4.000
2.919
2.928
4.157
4.463
0.528
3.068
2.920
MOMO
H
OH
240a

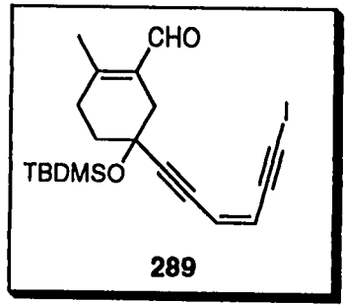


269





272



289

Integral
ppm
8
7
6
5
4
3
2
1
0
2.92
1.00
11.57
0.49
9.82
6.15
TBDMSO
OAc
291

Appendix B: X-ray Crystallographical Data of the Taxamycin-10 Derivative 301

Space Group and Cell Dimensions Triclinic, P -1
a 10.4105(13) b 10.7191(17) c 11.1667(11)
alpha 100.688(12) beta 106.298(10) gamma 108.042(14)
Volume 1085.39(24)A**3

Empirical formula : O4 C22 H28 Si

Cell dimensions were obtained from 30 reflections with 2Theta angle
in the range 100.00 - 130.00 degrees.

Crystal dimensions : 0.20 X 0.20 X 0.20 mm

FW = 384.54 Z = 2 F(000) = 413.62

Dcalc 1.177Mg.m-3, mu 0.96mm-1, lambda 1.54056A, 2Theta(max) 130.0

The intensity data were collected on a Nonius diffractometer,
using the theta/2theta scan mode.
The h,k,l ranges used during structure solution and refinement are :--
Hmin,max -12 11; Kmin,max 0 12; Lmin,max -13 12
No. of reflections measured 5422
No. of unique reflections 3715
No. of reflections with Inet > 2.5sigma(Inet) 3194
Merging R-value on intensities 0.018
No correction was made for absorption

The last least squares cycle was calculated with
55 atoms, 357 parameters and 3194 out of 3715 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is 0.000100

The residuals are as follows :--
For significant reflections, RF 0.040, Rw 0.052 GoF 3.19
For all reflections, RF 0.047, Rw 0.053.
where RF = Sum(Fo-Fc)/Sum(Fo),
Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]
The maximum shift/sigma ratio was 0.156.

In the last D-map, the deepest hole was -0.160e/A**3,
and the highest peak 0.260e/A**3.

Secondary ext. coeff. 0.4606microns sigma 0.0300

The following references are relevant to the NRCVAX System.

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Gabe, E.J., Le Page, Y., Charland,.J.-P., Lee, F.L. and White, P.S.
(1989) J. Appl. Cryst., 22, 384-387.

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Johnson, C.K., (1976) ORTEP - A Fortran Thermal Ellipsoid Plot Program, Technical Report ORNL-5138, Oak Ridge

4. Pluto Plotting :
S. Motherwell, University Chemical Laboratory, Cambridge, 1978

5. Missing Symmetry Treatment by MISSYM :
Le Page, Y., (1988) J. Appl. Cryst., 21, 983-984.

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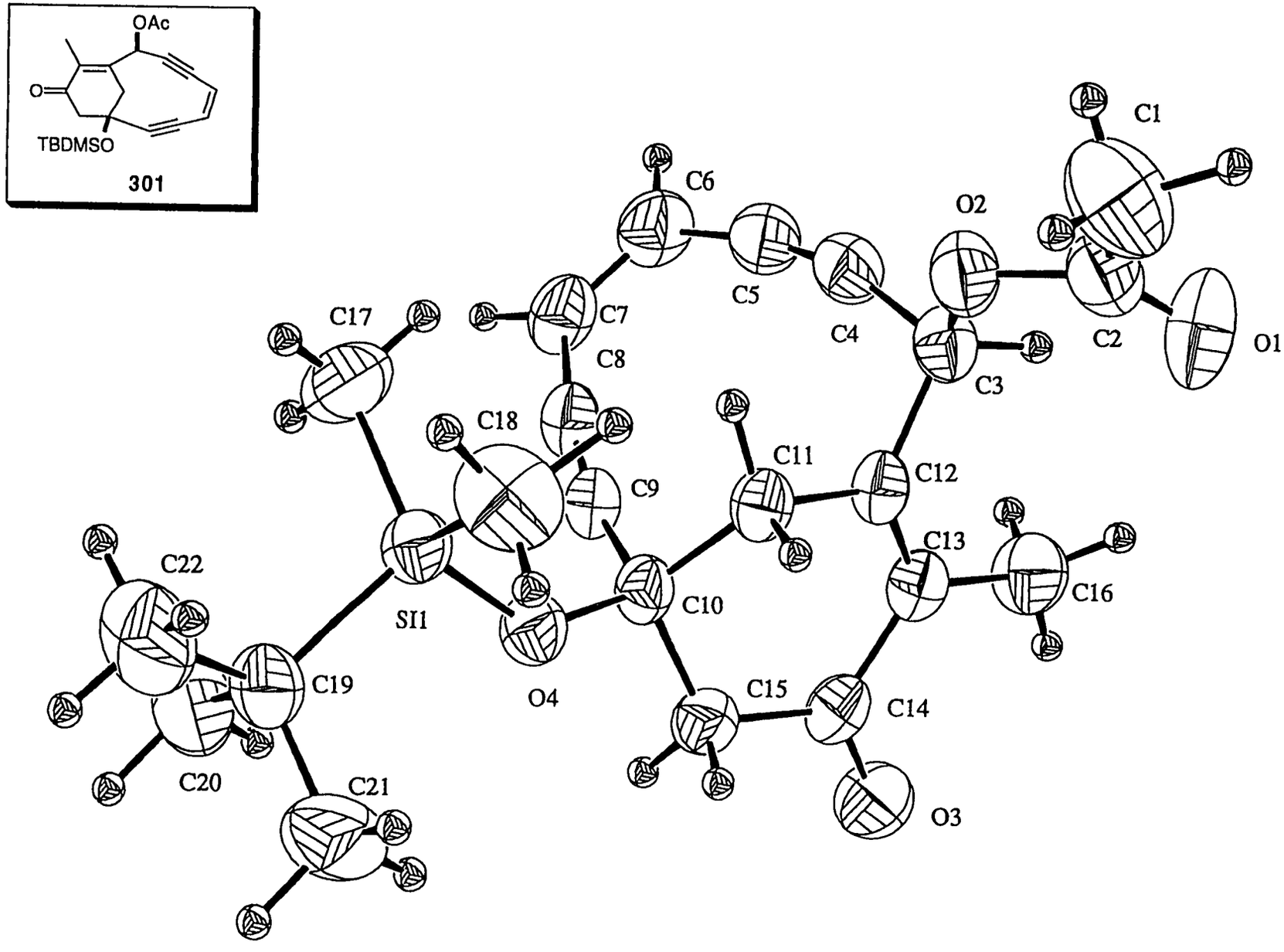

Figure 11. X-ray Structure of the Taxamycin-10 Derivative **301**

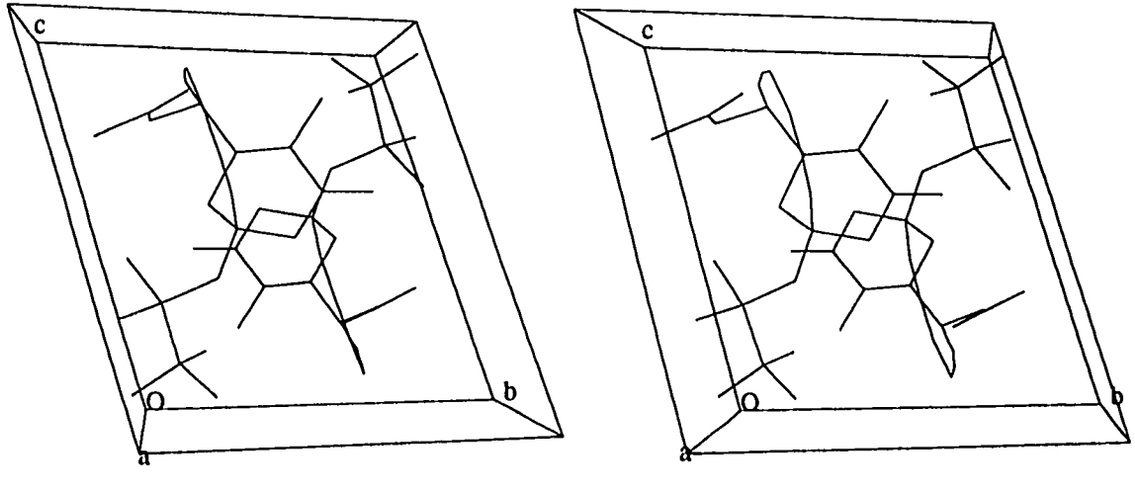
c
O
b
a
c
O
b
a

Table of Atomic Parameters x,y,z and Biso.
E.S.Ds. refer to the last digit printed.

	x	y	z	Biso
SI1	0.45864(6)	0.13812(5)	0.29973(5)	3.679(23)
O1	1.21066(15)	0.35512(18)	0.79207(18)	6.92 (10)
O2	0.97195(13)	0.24915(13)	0.73175(13)	4.55 (7)
O3	0.94203(16)	0.73752(14)	0.57158(15)	5.51 (8)
O4	0.57251(13)	0.29934(12)	0.36183(11)	3.88 (6)
C1	1.0995 (3)	0.1118 (3)	0.6868 (3)	7.12 (17)
C2	1.10507(22)	0.25127(23)	0.74362(19)	4.66 (11)
C3	0.96457(18)	0.38139(19)	0.77671(18)	3.89 (9)
C4	0.85667(21)	0.36648(21)	0.83943(18)	4.42 (10)
C5	0.76111(22)	0.37487(22)	0.87503(18)	4.60 (11)
C6	0.63403(23)	0.38694(24)	0.89032(20)	5.19 (12)
C7	0.53860(21)	0.40109(22)	0.79193(20)	4.73 (11)
C8	0.56576(18)	0.40412(19)	0.67362(17)	3.85 (9)
C9	0.60505(17)	0.40178(18)	0.58317(17)	3.49 (8)
C10	0.67543(17)	0.38615(17)	0.48604(15)	3.26 (8)
C11	0.79039(17)	0.32896(17)	0.54190(16)	3.37 (8)
C12	0.91248(17)	0.43417(18)	0.66286(16)	3.31 (8)
C13	0.96298(18)	0.56839(18)	0.67499(17)	3.53 (8)
C14	0.89143(19)	0.61888(18)	0.57158(17)	3.65 (8)
C15	0.75094(19)	0.52166(19)	0.46390(17)	3.81 (9)
C16	1.08619(23)	0.67694(21)	0.79182(20)	5.17 (11)
C17	0.3624 (3)	0.08304(25)	0.40902(22)	6.07 (13)
C18	0.5603 (3)	0.02831(25)	0.26812(25)	6.41 (15)
C19	0.32995(21)	0.13559(20)	0.14246(18)	4.63 (10)
C20	0.2351 (3)	0.2131 (3)	0.1689 (3)	6.53 (14)
C21	0.4163 (3)	0.2053 (3)	0.06601(22)	6.87 (16)
C22	0.2330 (3)	-0.0131 (3)	0.05983(24)	7.81 (16)
H1A	1.062 (3)	0.049 (3)	0.721 (3)	13.8 (10)
H1B	1.041 (5)	0.072 (5)	0.610 (4)	19.6 (15)
H1C	1.202 (3)	0.111 (3)	0.724 (3)	11.1 (8)
H3	1.0606 (17)	0.4429 (16)	0.8381 (15)	3.4 (4)
H6	0.6259 (24)	0.3892 (24)	0.9770 (22)	8.0 (6)
H7	0.4441 (22)	0.4126 (21)	0.7919 (20)	6.4 (5)
H11A	0.7521 (18)	0.2458 (17)	0.5688 (17)	4.2 (4)
H11B	0.8304 (20)	0.3085 (18)	0.4789 (18)	5.1 (5)
H15A	0.6881 (19)	0.5793 (19)	0.4444 (17)	5.0 (4)
H15B	0.7729 (20)	0.4956 (19)	0.3854 (18)	4.9 (4)
H16A	1.061 (3)	0.683 (3)	0.8637 (24)	9.0 (7)
H16B	1.116 (3)	0.758 (3)	0.7812 (25)	9.1 (7)
H16C	1.1755 (24)	0.6538 (24)	0.8246 (22)	8.3 (6)
H17A	0.307 (3)	-0.0065 (24)	0.3684 (24)	8.3 (7)
H17B	0.431 (3)	0.086 (3)	0.489 (3)	10.1 (8)
H17C	0.296 (3)	0.132 (3)	0.4100 (25)	9.7 (7)
H18A	0.502 (3)	-0.0643 (24)	0.2440 (24)	8.9 (7)
H18B	0.5935 (25)	0.0471 (24)	0.2024 (22)	8.2 (6)
H18C	0.650 (3)	0.043 (3)	0.360 (3)	11.4 (8)
H20A	0.162 (3)	0.208 (3)	0.071 (3)	10.2 (8)
H20B	0.292 (3)	0.311 (3)	0.2136 (24)	9.0 (7)
H20C	0.181 (3)	0.1696 (24)	0.2179 (23)	8.4 (7)
H21A	0.4822 (25)	0.3189 (23)	0.1234 (22)	7.7 (6)

H21B	0.483	(3)	0.155	(3)	0.051	(3)	10.2	(8)
H21C	0.3496	(25)	0.2081	(24)	-0.0200	(23)	8.1	(6)
H22A	0.161	(3)	-0.008	(3)	-0.0145	(25)	9.5	(7)
H22B	0.170	(3)	-0.051	(3)	0.113	(3)	9.0	(7)
H22C	0.290	(4)	-0.075	(4)	0.036	(3)	14.5	(11)

Biso is the Mean of the Principal Axes of the Thermal Ellipsoid

Table of u(i,j) or U values *100.
E.S.Ds. refer to the last digit printed

	u11(U)	u22	u33	u12	u13	u23
SI1	4.69(3)	4.10(3)	3.95(3)	0.870(22)	1.098(21)	0.578(20)
O1	4.59(8)	9.60(13)	10.94(13)	2.26 (8)	2.99 (9)	0.93 (10)
O2	4.13(7)	5.23(8)	7.25(9)	1.89 (6)	1.24 (6)	1.51 (7)
O3	6.58(9)	4.70(8)	7.69(10)	0.53 (7)	1.45 (8)	2.04 (7)
O4	4.27(7)	5.05(7)	3.62(6)	0.52 (6)	0.65 (5)	0.60 (5)
C1	9.80(19)	8.94(19)	9.28(19)	6.21 (16)	2.55 (16)	1.81 (15)
C2	5.37(11)	7.74(15)	5.43(11)	3.37 (11)	1.95 (9)	2.38 (10)
C3	3.83(9)	4.96(11)	5.00(10)	1.41 (8)	0.83 (8)	0.93 (8)
C4	5.39(11)	6.64(13)	4.50(10)	2.23 (10)	1.29 (9)	1.92 (9)
C5	5.67(11)	7.11(14)	4.64(10)	2.15 (10)	1.88 (9)	2.09 (10)
C6	6.49(13)	8.33(16)	5.29(11)	2.26 (12)	3.27 (10)	2.09 (11)
C7	4.93(11)	6.94(13)	5.86(12)	1.68 (10)	2.90 (10)	0.96 (10)
C8	3.53(9)	5.50(11)	5.04(10)	1.47 (8)	1.48 (8)	0.85 (8)
C9	3.22(8)	4.64(10)	4.64(10)	1.16 (7)	1.10 (7)	0.79 (8)
C10	3.43(8)	4.31(10)	3.57(8)	0.82 (7)	0.93 (7)	0.43 (7)
C11	3.76(9)	4.15(9)	4.27(9)	1.21 (7)	1.38 (7)	0.51 (7)
C12	3.16(8)	4.63(10)	4.36(9)	1.32 (7)	1.39 (7)	0.64 (7)
C13	3.64(9)	4.59(10)	4.42(9)	1.01 (8)	1.48 (7)	0.60 (8)
C14	4.36(9)	3.97(10)	4.99(10)	0.92 (8)	2.04 (8)	0.74 (8)
C15	4.56(10)	4.69(11)	4.59(10)	1.10 (8)	1.46 (8)	1.39 (8)
C16	5.81(12)	5.09(12)	5.74(12)	0.27 (10)	0.68 (10)	0.22 (10)
C17	7.88(16)	6.81(15)	6.51(14)	0.22 (12)	2.68 (12)	2.20 (11)
C18	9.56(18)	6.79(16)	7.97(16)	4.03 (14)	2.76 (14)	1.23 (13)
C19	5.64(12)	4.94(11)	4.44(10)	0.68 (9)	0.39 (9)	0.17 (9)
C20	6.65(15)	7.83(17)	8.53(17)	2.65 (13)	0.84 (13)	1.61 (13)
C21	10.16(20)	10.02(20)	4.98(13)	2.67 (16)	2.42 (13)	2.70 (13)
C22	10.21(20)	6.29(16)	6.80(16)	0.42 (14)	-1.36 (14)	-0.76 (12)

Anisotropic Temperature Factors are of the form
Temp=-2*Pi*Pi*(h*h*u11*astar*astar+---+2*h*k*u12*astar*bstar+---)

Table of Atomic Bond Distances in Angstroms

SI1-O4	1.6424(13)	C14-C15	1.5083(24)
SI1-C17	1.8518(24)	C15-H15A	1.038(19)
SI1-C18	1.8594(24)	C15-H15B	0.980(18)
SI1-C19	1.8759(21)	C16-H16A	0.908(25)
O1-C2	1.194(3)	C16-H16B	0.87(3)
O2-C2	1.3472(23)	C16-H16C	1.023(23)
O2-C3	1.4464(22)	C17-H17A	0.898(23)
O3-C14	1.2165(23)	C17-H17B	0.97(3)
O4-C10	1.4168(18)	C17-H17C	0.99(3)
C1-C2	1.488(3)	C18-H18A	0.929(24)
C1-H1A	0.87(3)	C18-H18B	0.923(23)
C1-H1B	0.83(4)	C18-H18C	1.13(3)
C1-H1C	1.03(3)	C19-C20	1.528(3)
C3-C4	1.466(3)	C19-C21	1.532(3)
C3-C12	1.517(3)	C19-C22	1.532(3)
C3-H3	0.972(15)	C20-H20A	1.12(3)
C4-C5	1.192(3)	C20-H20B	0.981(24)
C5-C6	1.422(3)	C20-H20C	0.971(24)
C6-C7	1.327(3)	C21-H21A	1.145(22)
C6-H6	0.992(23)	C21-H21B	1.03(3)
C7-C8	1.430(3)	C21-H21C	1.027(24)
C7-H7	1.028(21)	C22-H22A	0.97(3)
C8-C9	1.1904(25)	C22-H22B	1.04(3)
C9-C10	1.4819(23)	C22-H22C	1.07(3)
C10-C11	1.5409(25)		
C10-C15	1.524(3)		
C11-C12	1.5150(22)		
C11-H11A	0.995(18)		
C11-H11B	0.938(18)		
C12-C13	1.336(3)		
C13-C14	1.476(3)		
C13-C16	1.5081(25)		

Table of Atomic Bond Angles in Degrees

O4-SI1-C17	111.91(8)	C13-C16-H16C	115.1(12)
O4-SI1-C18	108.77(10)	H16A-C16-H16B	109.7(23)
O4-SI1-C19	103.41(8)	H16A-C16-H16C	99.4(21)
C17-SI1-C18	110.43(13)	H16B-C16-H16C	106.9(22)
C17-SI1-C19	111.25(11)	SI1-C17-H17A	104.6(15)
C18-SI1-C19	110.86(10)	SI1-C17-H17B	109.5(16)
C2-O2-C3	115.69(14)	SI1-C17-H17C	107.4(16)
SI1-O4-C10	136.60(12)	H17A-C17-H17B	105.3(23)
C2-C1-H1A	115.3(22)	H17A-C17-H17C	107.6(21)
C2-C1-H1B	114(3)	H17B-C17-H17C	121.2(21)
C2-C1-H1C	108.6(15)	SI1-C18-H18A	111.2(15)
H1A-C1-H1B	96(4)	SI1-C18-H18B	108.8(15)
H1A-C1-H1C	93(3)	SI1-C18-H18C	111.3(14)
H1B-C1-H1C	125(3)	H18A-C18-H18B	109.9(21)
O1-C2-O2	122.07(19)	H18A-C18-H18C	103.2(22)
O1-C2-C1	126.49(20)	H18B-C18-H18C	112.5(21)
O2-C2-C1	111.42(19)	SI1-C19-C20	110.72(14)
O2-C3-C4	109.41(16)	SI1-C19-C21	109.38(15)
O2-C3-C12	111.03(14)	SI1-C19-C22	109.90(17)
O2-C3-H3	107.0(9)	C20-C19-C21	108.48(21)
C4-C3-C12	105.84(15)	C20-C19-C22	109.23(19)
C4-C3-H3	111.2(9)	C21-C19-C22	109.09(19)
C12-C3-H3	112.4(10)	C19-C20-H20A	106.8(13)
C3-C4-C5	164.62(22)	C19-C20-H20B	112.2(14)
C4-C5-C6	167.73(22)	C19-C20-H20C	108.7(14)
C5-C6-C7	118.84(18)	H20A-C20-H20B	104.9(21)
C5-C6-H6	116.7(14)	H20A-C20-H20C	112.1(20)
C7-C6-H6	124.4(14)	H20B-C20-H20C	112.1(20)
C6-C7-C8	119.51(17)	C19-C21-H21A	109.6(12)
C6-C7-H7	126.0(12)	C19-C21-H21B	108.6(16)
C8-C7-H7	114.5(12)	C19-C21-H21C	111.8(14)
C7-C8-C9	170.43(20)	H21A-C21-H21B	111.0(19)
C8-C9-C10	167.48(19)	H21A-C21-H21C	103.7(18)
O4-C10-C9	111.21(13)	H21B-C21-H21C	112.1(20)
O4-C10-C11	112.41(13)	C19-C22-H22A	106.0(14)
O4-C10-C15	105.57(14)	C19-C22-H22B	104.9(13)
C9-C10-C11	106.18(14)	C19-C22-H22C	114.6(18)
C9-C10-C15	113.11(14)	H22A-C22-H22B	101.6(21)
C11-C10-C15	108.46(14)	H22A-C22-H22C	115.5(24)
C10-C11-C12	111.15(13)	H22B-C22-H22C	112.9(25)
C10-C11-H11A	113.8(10)		
C10-C11-H11B	108.7(12)		
C12-C11-H11A	105.9(10)		
C12-C11-H11B	107.7(11)		
H11A-C11-H11B	109.5(15)		
C3-C12-C11	116.31(15)		
C3-C12-C13	120.87(15)		
C11-C12-C13	122.51(17)		
C12-C13-C14	119.38(15)		
C12-C13-C16	124.66(18)		
C14-C13-C16	115.89(16)		

O3-C14-C13	121.71(16)
O3-C14-C15	118.95(18)
C13-C14-C15	119.33(16)
C10-C15-C14	116.18(16)
C10-C15-H15A	115.0(10)
C10-C15-H15B	105.1(11)
C14-C15-H15A	105.9(10)
C14-C15-H15B	107.5(11)
H15A-C15-H15B	106.6(15)
C13-C16-H16A	110.2(16)
C13-C16-H16B	114.4(17)

Torsion angles

C17	SI1	O4	C10	42.65(14)	C18	SI1	O4	C10	-79.63(16)
C19	SI1	O4	C10	162.49(17)	O4	SI1	C17	H17A	-177.0(20)
O4	SI1	C17	H17B	-64.6(21)	O4	SI1	C17	H17C	68.8(20)
C18	SI1	C17	H17A	-55.7(20)	C18	SI1	C17	H17B	56.8(21)
C18	SI1	C17	H17C	-169.8(20)	C19	SI1	C17	H17A	67.9(20)
C19	SI1	C17	H17B	-179.7(21)	C19	SI1	C17	H17C	-46.3(20)
O4	SI1	C18	H18A	172.0(20)	O4	SI1	C18	H18B	-66.9(19)
O4	SI1	C18	H18C	57.6(20)	C17	SI1	C18	H18A	48.8(20)
C17	SI1	C18	H18B	169.9(19)	C17	SI1	C18	H18C	-65.6(20)
C19	SI1	C18	H18A	-75.0(20)	C19	SI1	C18	H18B	46.1(19)
C19	SI1	C18	H18C	170.6(20)	O4	SI1	C19	C20	-69.69(18)
O4	SI1	C19	C21	49.80(16)	O4	SI1	C19	C22	169.55(24)
C17	SI1	C19	C20	50.60(18)	C17	SI1	C19	C21	170.09(24)
C17	SI1	C19	C22	-70.17(19)	C18	SI1	C19	C20	173.89(24)
C18	SI1	C19	C21	-66.61(19)	C18	SI1	C19	C22	53.13(19)
C3	O2	C2	O1	2.35(15)	C3	O2	C2	C1	-176.3(3)
C2	O2	C3	C4	-142.7(3)	C2	O2	C3	C12	100.81(23)
C2	O2	C3	H3	-22.1(12)	SI1	O4	C10	C9	-62.35(14)
SI1	O4	C10	C11	56.55(12)	SI1	O4	C10	C15	174.62(21)
H1A	C1	C2	O1	123. (3)	H1A	C1	C2	O2	-59. (3)
H1B	C1	C2	O1	-126. (4)	H1B	C1	C2	O2	52. (4)
H1C	C1	C2	O1	19.9(20)	H1C	C1	C2	O2	-161.5(21)
C2	C1	H1A	H1B	121. (4)	C2	C1	H1A	H1C	-112. (3)
H1B	C1	H1A	H1B	0. (5)	H1B	C1	H1A	H1C	126. (6)
H1C	C1	H1A	H1B	-126. (5)	H1C	C1	H1A	H1C	0. (3)
C2	C1	H1B	H1A	-122. (5)	H1A	C1	H1B	H1A	0. (4)
H1C	C1	H1B	H1A	99. (5)	C2	C1	H1C	H1A	118. (3)
H1A	C1	H1C	H1A	0. (3)	H1B	C1	H1C	H1A	-100. (5)
O2	C3	C4	C5	-139.1(3)	C12	C3	C4	C5	-19.38(17)
H3	C3	C4	C5	102.9(13)	O2	C3	C12	C11	40.87(14)
O2	C3	C12	C13	-145.4(3)	C4	C3	C12	C11	-77.77(20)
C4	C3	C12	C13	95.98(24)	H3	C3	C12	C11	160.7(13)
H3	C3	C12	C13	-25.6(12)	C3	C4	C5	C6	34.31(17)
C4	C5	C6	C7	-0.88(17)	C4	C5	C6	H6	-177.7(18)
C5	C6	C7	C8	-0.12(14)	C5	C6	C7	H7	-178.8(16)
H6	C6	C7	C8	176.4(18)	H6	C6	C7	H7	-2.2(23)
C6	C7	C8	C9	7.53(17)	H7	C7	C8	C9	-173.7(16)
C7	C8	C9	C10	9.07(14)	C8	C9	C10	O4	120.9(3)
C8	C9	C10	C11	-1.71(14)	C8	C9	C10	C15	-120.5(3)
O4	C10	C11	C12	170.4(3)	O4	C10	C11	H11A	-70.2(13)
O4	C10	C11	H11B	52.1(15)	C9	C10	C11	C12	-67.78(18)
C9	C10	C11	H11A	51.6(13)	C9	C10	C11	H11B	173.9(15)
C15	C10	C11	C12	54.06(16)	C15	C10	C11	H11A	173.4(13)
C15	C10	C11	H11B	-64.3(15)	O4	C10	C15	C14	-164.2(3)
O4	C10	C15	H15A	71.2(13)	O4	C10	C15	H15B	-45.6(14)
C9	C10	C15	C14	73.96(19)	C9	C10	C15	H15A	-50.6(13)
C9	C10	C15	H15B	-167.4(15)	C11	C10	C15	C14	-43.54(15)
C11	C10	C15	H15A	-168.1(13)	C11	C10	C15	H15B	75.1(14)
C10	C11	C12	C3	136.44(25)	C10	C11	C12	C13	-37.19(15)

H11A	C11	C12	C3	12.4(13)
H11B	C11	C12	C3	-104.6(15)
C3	C12	C13	C14	-168.8(3)
C11	C12	C13	C14	4.51(12)
C12	C13	C14	O3	-172.4(3)
C16	C13	C14	O3	10.46(14)
C12	C13	C16	H16A	-65.0(21)
C12	C13	C16	H16C	46.3(17)
C14	C13	C16	H16B	-12.2(22)
O3	C14	C15	C10	-166.1(3)
O3	C14	C15	H15B	76.6(14)
C13	C14	C15	H15A	142.2(13)
C13	C16	H16A	H16B	-127. (3)
H16B	C16	H16A	H16B	0. (3)
H16C	C16	H16A	H16B	112. (3)
C13	C16	H16B	H16A	124. (3)
H16A	C16	H16B	H16A	0. (3)
H16C	C16	H16B	H16A	-107. (3)
C13	C16	H16C	H16A	-117.6(24)
H16A	C16	H16C	H16A	0. (3)
H16B	C16	H16C	H16A	114. (4)
SI1	C17	H17A	H17B	115.4(23)
H17B	C17	H17A	H17B	0. (3)
H17C	C17	H17A	H17B	-131. (4)
SI1	C17	H17B	H17A	-112.0(24)
H17C	C17	H17B	H17A	122. (4)
H17A	C17	H17C	H17A	0.0(25)
SI1	C18	H18A	H18B	120.5(22)
H18C	C18	H18A	H18B	-120. (3)
H18A	C18	H18B	H18A	0.0(24)
SI1	C19	C20	H20A	179.3(18)
SI1	C19	C20	H20C	-59.6(19)
C21	C19	C20	H20B	-55.1(19)
C22	C19	C20	H20A	-59.5(18)
C22	C19	C20	H20C	61.6(19)
SI1	C19	C21	H21B	57.2(20)
C20	C19	C21	H21A	56.6(15)
C20	C19	C21	H21C	-57.8(17)
C22	C19	C21	H21B	-63.1(20)
SI1	C19	C22	H22A	173.0(20)
SI1	C19	C22	H22C	-58.3(24)
C20	C19	C22	H22B	-55.6(19)
C21	C19	C22	H22A	-67.1(20)
C21	C19	C22	H22C	61.6(24)
H1C	H1A	H1B	C1	-38. (3)
H1B	H1A	H1C	C1	33. (3)
C16	H16A	H16B	H16C	-45.6(24)
H16C	H16A	H16B	H16C	0.0(16)
C16	H16A	H16C	H16B	36.0(22)
H16B	H16A	H16C	H16B	0.0(18)
C16	H16B	H16C	H16A	-40.8(24)
H16A	H16B	H16C	H16A	0.0(18)
H17C	H17A	H17B	C17	-30.2(20)
H17B	H17A	H17C	C17	30.8(20)

H11A	C11	C12	C13	-161.2(13)
H11B	C11	C12	C13	81.7(15)
C3	C12	C13	C16	8.03(14)
C11	C12	C13	C16	-178.6(3)
C12	C13	C14	C15	8.39(13)
C16	C13	C14	C15	-168.7(3)
C12	C13	C16	H16B	170.8(22)
C14	C13	C16	H16A	111.9(21)
C14	C13	C16	H16C	-136.7(17)
O3	C14	C15	H15A	-37.0(13)
C13	C14	C15	C10	13.13(12)
C13	C14	C15	H15B	-104.2(14)
C13	C16	H16A	H16C	121. (3)
H16B	C16	H16A	H16C	-112. (4)
H16C	C16	H16A	H16C	0.0(21)
C13	C16	H16B	H16C	-129. (3)
H16A	C16	H16B	H16C	107. (4)
H16C	C16	H16B	H16C	0.0(21)
C13	C16	H16C	H16B	128.3(24)
H16A	C16	H16C	H16B	-114. (4)
H16B	C16	H16C	H16B	0. (3)
SI1	C17	H17A	H17C	-114.0(22)
H17B	C17	H17A	H17C	131. (4)
H17C	C17	H17A	H17C	0.0(25)
H17A	C17	H17B	H17A	0. (3)
SI1	C17	H17C	H17A	112.2(23)
H17B	C17	H17C	H17A	-121. (4)
H18B	C18	H18A	H18B	0.0(23)
SI1	C18	H18B	H18A	-121.9(22)
H18C	C18	H18B	H18A	114. (3)
SI1	C19	C20	H20B	65.0(19)
C21	C19	C20	H20A	59.3(18)
C21	C19	C20	H20C	-179.6(19)
C22	C19	C20	H20B	-173.9(19)
SI1	C19	C21	H21A	-64.3(15)
SI1	C19	C21	H21C	-178.6(18)
C20	C19	C21	H21B	178.0(20)
C22	C19	C21	H21A	175.5(15)
C22	C19	C21	H21C	61.1(17)
SI1	C19	C22	H22B	66.0(19)
C20	C19	C22	H22A	51.4(19)
C20	C19	C22	H22C	-180.0(25)
C21	C19	C22	H22B	-174.0(19)
C1	H1A	H1B	C1	0.0(4)
C1	H1A	H1C	C1	0.0(6)
C16	H16A	H16B	C16	0.0(3)
H16C	H16A	H16B	C16	46. (3)
C16	H16A	H16C	C16	0.0(4)
H16B	H16A	H16C	C16	-36.0(20)
C16	H16B	H16C	C16	0.0(5)
H16A	H16B	H16C	C16	40.8(21)
C17	H17A	H17B	C17	0.0(3)
C17	H17A	H17C	C17	0.0(4)
C18	H18A	H18B	C18	0.0(3)

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
-12, 2, 1				6	6	6	450*	0	38	39	118	8	53	58	84
3	7	6	287*	7	17	16	118	1	38	37	85	9	59	59	80
4	2	5	1249*	8	11	15	161	2	71	68	78	10	9	7	214*
5	10	6	142	-11, 3, 1				3	4	8	685*	-10, 3, 1			
-12, 3, 1				-1	8	17	625*	4	22	24	105	-3	39	36	112
2	42	41	101	0	16	12	155	5	18	20	97	-2	39	39	122
3	21	24	141	1	5	7	580*	6	20	19	84	-1	62	61	124
4	36	36	102	2	15	20	192	-11, 8, 1				0	66	68	123
5	23	26	131	3	23	23	106	0	14	15	167	1	43	42	93
6	32	34	71	4	8	3	368*	1	33	33	84	2	82	85	87
-12, 4, 1				5	29	32	97	2	2	1	1308*	3	2	3	1570*
2	11	16	338*	6	17	16	122	3	52	49	74	4	81	83	88
3	7	2	432*	7	16	19	129	4	10	11	176	5	6	10	513*
4	11	5	178	8	69	68	72	-10, 0, 1				6	58	58	89
5	6	3	498*	-11, 4, 1				1	10	11	354*	7	62	66	87
-12, 5, 1				-2	2	3	1793*	2	85	83	85	8	13	19	172
2	4	6	726*	-1	39	33	109	3	28	27	105	9	15	13	106
3	29	29	111	0	2	4	1755*	4	2	2	1349*	10	21	20	92
4	7	4	444*	1	2	2	1542*	5	69	69	88	-10, 4, 1			
5	34	37	106	2	29	33	102	6	61	65	88	-4	29	29	102
-12, 6, 1				3	97	95	82	7	16	16	171	-3	12	16	339*
2	36	36	102	4	31	30	102	8	25	24	97	-2	73	74	117
3	9	12	348*	5	45	44	85	9	17	17	120	-1	59	59	120
-11, 0, 1				6	32	30	91	10	18	18	88	0	26	25	160
1	19	19	100	7	48	48	78	-10, 1, 1				1	77	75	88
2	94	92	72	8	81	83	69	-2	35	33	114	2	71	69	90
3	77	74	76	-11, 5, 1				-1	44	45	116	3	11	15	201
4	15	16	156	-2	28	28	111	0	55	59	124	4	22	20	123
5	23	23	95	-1	45	43	109	1	96	97	86	5	2	6	1643*
6	30	26	86	0	57	57	110	2	20	22	125	6	13	13	296*
7	16	18	139	1	72	68	80	3	54	56	91	7	5	8	715*
8	37	35	74	2	2	7	1448*	4	33	31	105	8	2	3	1581*
-11, 1, 1				3	11	7	238*	5	48	45	97	9	29	29	86
0	46	48	103	4	26	26	103	6	12	18	286*	-10, 5, 1			
1	54	51	76	5	21	19	110	7	44	43	90	-4	4	12	1003*
2	3	8	1030*	6	12	8	180	8	2	0	1365*	-3	18	18	169
3	17	19	113	7	15	13	130	9	45	46	82	-2	43	44	120
4	50	49	83	-11, 6, 1				10	30	32	86	-1	91	93	120
5	83	81	79	-2	37	35	106	-10, 2, 1				0	2	9	2068*
6	56	59	81	-1	6	4	550*	-3	11	8	168	1	30	31	105
7	7	3	372*	0	2	9	2145*	-2	30	29	131	2	34	32	98
8	26	27	85	1	27	25	99	-1	40	44	123	3	66	62	90
-11, 2, 1				2	6	2	468*	0	23	22	164	4	2	3	1388*
-1	7	10	382*	3	29	28	93	1	48	46	90	5	70	71	87
0	2	10	2007*	4	55	52	81	2	44	45	94	6	48	47	88
1	31	34	95	5	7	0	357*	3	40	35	94	7	2	5	1547*
2	78	76	80	6	49	51	78	4	2	0	1675*	8	15	15	142
3	21	21	108	7	63	66	70	5	45	45	93	9	2	4	1214*
4	88	88	81	-11, 7, 1				6	6	5	482*	-10, 6, 1			
5	46	46	85	-1	2	3	1701*	7	9	10	272*	-4	46	49	102

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
-10, 6, 1				2	33	30	106	-1	104	103	122	-1	24	27	144
-3	36	38	122	3	90	90	88	0	56	59	134	0	74	77	125
-2	26	27	146	4	56	54	92	1	73	76	88	1	11	15	345*
-1	82	89	118	5	74	76	89	2	110	105	86	2	87	86	88
0	9	8	260*	6	52	51	93	3	54	54	90	3	51	49	91
1	81	82	87	7	37	35	97	4	34	39	109	4	74	72	90
2	43	41	93	8	12	12	193	5	132	134	86	5	66	63	90
3	37	37	101	9	29	30	99	6	113	112	88	6	2	1	1439*
4	106	105	86	10	20	17	110	7	2	0	1627*	7	55	54	87
5	77	77	85	11	52	55	74	8	115	118	86	8	2	8	1697*
6	32	30	94	-9, 1, 1				9	43	46	90	9	48	49	75
7	44	42	83	-4	39	43	111	10	20	22	106	-9, 7, 1			
8	46	45	76	-3	59	58	116	-9, 4, 1				-5	59	59	106
-10, 7, 1				-2	48	48	125	-5	40	36	109	-4	12	11	226
-3	33	29	120	-1	27	28	158	-4	31	27	138	-3	7	11	758*
-2	31	33	134	0	26	21	150	-3	46	49	125	-2	28	33	155
-1	30	31	133	1	72	70	89	-2	36	39	138	-1	28	27	156
0	10	4	429*	2	89	87	88	-1	106	106	125	0	104	104	124
1	20	19	118	3	111	111	87	0	106	106	122	1	12	15	266*
2	44	44	91	4	12	12	211	1	12	3	206	2	136	138	87
3	22	22	112	5	11	8	288*	2	7	8	566*	3	70	66	93
4	18	17	128	6	14	17	196	3	4	11	888*	4	25	23	111
5	12	10	238*	7	98	93	88	4	41	39	97	5	8	6	378*
6	30	28	90	8	60	60	90	5	146	147	87	6	43	41	89
7	17	18	101	9	27	22	103	6	117	116	88	7	34	35	92
-10, 8, 1				10	20	17	103	7	65	66	88	8	15	14	107
-3	9	8	173	11	28	30	84	8	122	125	84	-9, 8, 1			
-2	37	40	117	-9, 2, 1				9	13	14	133	-5	48	50	105
-1	20	18	144	-5	30	29	107	10	49	51	74	-4	16	18	165
0	60	61	116	-4	47	51	116	-9, 5, 1				-3	85	92	114
1	24	23	106	-3	91	93	117	-5	2	5	1894*	-2	78	85	120
2	4	9	785*	-2	42	44	130	-4	16	15	166	-1	53	56	128
3	8	1	304*	-1	178	175	122	-3	47	40	127	0	67	72	125
4	7	1	337*	0	16	10	184	-2	5	2	724*	1	28	26	110
5	31	31	86	1	72	71	90	-1	23	22	158	2	30	29	99
6	38	39	76	2	32	31	103	0	10	7	506*	3	26	25	106
-10, 9, 1				3	54	50	92	1	80	75	88	4	46	39	91
-2	20	14	125	4	45	48	93	2	54	58	91	5	80	77	82
-1	29	20	122	5	56	55	93	3	73	74	88	6	20	21	104
0	2	3	2346*	6	11	3	209	4	69	71	89	7	40	38	76
1	22	23	104	7	10	8	248*	5	74	70	89	-9, 9, 1			
2	18	15	109	8	11	8	302*	6	10	10	382*	-4	37	34	112
3	52	49	75	9	12	19	282*	7	48	46	90	-3	3	11	1580*
4	2	6	1313*	10	67	69	80	8	9	2	229*	-2	20	21	167
-10, 10, 1				11	36	39	78	9	44	44	79	-1	30	27	157
0	26	25	118	-9, 3, 1				-9, 6, 1				0	29	31	136
1	45	37	72	-5	21	21	128	-5	82	83	106	1	31	31	94
2	24	25	84	-4	36	35	126	-4	62	60	117	2	16	16	129
-9, 0, 1				-3	50	50	125	-3	4	3	1128*	3	9	11	387*
1	130	125	87	-2	40	42	135	-2	46	50	130	4	5	3	493*

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
-9, 9, 1				-2	157	155	122	9	29	32	104	4	39	43	96
5	7	6	352*	-1	8	12	616*	10	15	17	117	5	31	31	106
6	16	16	96	0	49	53	127	-8, 5, 1				6	29	31	104
-9, 10, 1				1	26	25	108	-7	34	38	108	7	11	1	228*
-3	35	27	108	2	55	50	84	-6	30	28	131	8	25	25	92
-2	16	16	188	3	119	112	80	-5	60	62	124	-8, 8, 1			
-1	28	26	123	4	2	1	1499*	-4	60	58	122	-6	3	0	1257*
0	51	45	112	5	152	151	82	-3	21	24	165	-5	8	11	595*
1	33	29	90	6	139	142	85	-2	23	28	183	-4	6	8	832*
2	28	29	91	7	57	59	92	-1	12	13	378*	-3	11	5	358*
3	53	51	76	8	19	13	126	0	109	100	119	-2	19	14	184
4	48	48	73	9	55	56	90	1	24	25	103	-1	24	25	164
-9, 11, 1				10	28	23	98	2	136	137	83	0	13	15	443*
0	41	37	101	11	24	27	96	3	65	62	87	1	93	92	89
-8, 0, 1				-8, 3, 1				4	160	154	84	2	28	29	112
1	74	77	87	-6	56	56	109	5	103	108	87	3	42	43	100
2	113	109	84	-5	24	28	153	6	36	39	107	4	66	61	89
3	165	163	83	-4	19	13	166	7	44	44	95	5	57	53	88
4	96	87	84	-3	110	109	123	8	60	63	88	6	18	20	152
5	109	105	84	-2	125	127	121	9	36	40	93	7	62	60	78
6	4	7	769*	-1	13	3	382*	10	6	1	405*	-8, 9, 1			
7	25	25	106	0	10	14	472*	-8, 6, 1				-6	56	47	101
8	28	31	111	1	147	152	81	-7	17	15	149	-5	38	34	111
9	23	18	118	2	45	46	88	-6	16	11	148	-4	60	53	117
10	18	21	121	3	47	54	89	-5	45	45	131	-3	10	11	579*
11	35	31	86	4	21	20	129	-4	34	35	146	-2	77	69	123
-8, 1, 1				5	131	132	83	-3	10	14	576*	-1	52	57	128
-6	44	42	100	6	46	46	97	-2	80	85	126	0	105	104	122
-5	28	27	135	7	27	32	115	-1	98	96	122	1	55	53	92
-4	17	19	238	8	94	91	89	0	16	9	182	2	80	78	88
-3	57	56	128	9	15	16	173	1	119	118	85	3	45	41	93
-2	112	112	122	10	17	15	120	2	168	165	85	4	14	11	162
-1	4	1	1117*	11	52	50	75	3	81	80	87	5	29	27	93
0	132	131	119	-8, 4, 1				4	58	56	89	6	34	33	81
1	11	9	197	-7	24	24	118	5	150	148	87	-8, 10, 1			
2	105	105	81	-6	47	47	115	6	136	136	87	-5	39	34	107
3	61	64	83	-5	23	22	148	7	52	51	91	-4	49	43	111
4	16	15	165	-4	22	24	167	8	33	29	91	-3	9	5	448*
5	26	24	115	-3	12	4	252*	9	2	1	1301*	-2	55	46	117
6	41	40	95	-2	12	21	575*	-8, 7, 1				-1	21	18	161
7	216	217	86	-1	113	113	119	-6	76	83	110	0	26	27	162
8	37	34	101	0	24	22	153	-5	13	13	211	1	10	4	221*
9	111	111	87	1	66	69	84	-4	84	88	123	2	30	29	92
10	29	28	101	2	83	77	82	-3	2	14	2706*	3	28	27	94
11	7	9	287*	3	98	98	82	-2	8	3	472*	4	40	38	82
-8, 2, 1				4	229	230	82	-1	64	63	130	5	27	27	84
-6	31	36	118	5	51	49	93	0	8	9	628*	-8, 11, 1			
-5	126	123	112	6	39	41	95	1	83	87	88	-3	2	1	2197*
-4	56	54	125	7	6	4	540*	2	51	50	97	-2	21	23	152
-3	31	31	148	8	2	9	1548*	3	33	33	102	-1	18	13	161

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
-8, 11, 1				3	5	2	558*	11	9	11	216*	0	111	114	118
0	11	10	446*	4	86	88	76	-7, 5, 1				1	18	17	120
1	68	62	76	5	86	87	79	-8	16	15	159	2	77	72	86
2	26	23	85	6	45	50	89	-7	13	14	193	3	28	23	115
3	14	14	98	7	82	81	86	-6	33	31	139	4	146	143	86
-7, 0, 1				8	159	160	87	-5	51	50	131	5	31	33	105
1	182	184	76	9	20	22	157	-4	2	6	2131*	6	57	54	93
2	129	119	76	10	59	61	90	-3	38	39	133	7	40	41	98
3	92	91	77	11	22	18	105	-2	105	106	116	8	42	44	87
4	106	103	77	12	34	34	77	-1	31	26	133	9	42	42	75
5	11	15	283*	-7, 3, 1				0	78	81	112	-7, 8, 1			
6	20	17	113	-7	73	72	116	1	109	114	78	-7	32	36	126
7	54	54	89	-6	76	78	121	2	138	141	77	-6	53	54	121
8	2	5	1435*	-5	8	14	629*	3	119	116	78	-5	63	69	124
9	106	100	89	-4	29	25	149	4	43	44	88	-4	34	33	141
10	27	26	105	-3	123	120	119	5	113	116	83	-3	98	102	125
11	59	61	84	-2	151	153	114	6	77	77	88	-2	13	12	237
12	19	21	102	-1	143	139	109	7	64	68	91	-1	124	127	123
-7, 1, 1				0	60	61	108	8	101	104	88	0	79	80	123
-7	35	37	117	1	120	115	73	9	26	29	108	1	40	41	94
-6	77	75	116	2	119	111	73	10	12	12	233	2	63	60	91
-5	22	21	138	3	185	190	73	-7, 6, 1				3	38	40	96
-4	26	25	157	4	176	170	75	-8	30	30	114	4	34	34	99
-3	24	22	156	5	142	138	78	-7	54	52	113	5	20	17	128
-2	2	0	2153*	6	245	239	81	-6	2	11	2214*	6	8	2	333*
-1	2	7	2175*	7	66	70	88	-5	94	96	125	7	94	90	80
0	42	39	116	8	10	2	237*	-4	53	52	133	8	50	51	73
1	23	24	92	9	27	23	114	-3	58	56	125	-7, 9, 1			
2	36	36	80	10	56	58	86	-2	167	171	118	-7	19	23	122
3	79	76	74	11	46	45	81	-1	27	31	150	-6	38	28	118
4	99	91	75	-7, 4, 1				0	144	148	114	-5	4	13	1563*
5	126	124	77	-8	39	36	102	1	17	12	142	-4	32	27	138
6	79	83	82	-7	9	9	449*	2	12	8	273*	-3	65	54	128
7	51	46	90	-6	23	18	161	3	100	103	83	-2	53	46	130
8	102	99	88	-5	36	36	129	4	95	94	85	-1	58	58	127
9	2	4	1470*	-4	116	115	122	5	64	64	89	0	46	52	131
10	86	88	86	-3	191	193	118	6	66	66	91	1	41	45	98
11	23	27	112	-2	9	12	636*	7	81	81	90	2	32	30	102
12	61	60	76	-1	140	146	109	8	65	63	89	3	71	67	89
-7, 2, 1				0	8	5	429*	9	16	15	107	4	34	33	99
-7	24	27	160	1	14	12	136	10	27	31	83	5	50	45	85
-6	12	6	312*	2	10	14	257*	-7, 7, 1				6	27	26	98
-5	18	18	168	3	2	1	1439*	-8	2	7	1963*	7	31	32	81
-4	176	173	122	4	43	43	82	-7	39	42	124	-7, 10, 1			
-3	172	170	118	5	146	146	81	-6	37	40	139	-6	37	31	113
-2	73	72	116	6	83	83	86	-5	39	44	140	-5	37	34	119
-1	2	9	2075*	7	175	176	87	-4	23	20	155	-4	25	19	160
0	83	86	106	8	79	84	90	-3	56	57	124	-3	34	27	130
1	131	124	73	9	45	40	92	-2	150	154	121	-2	67	58	124
2	15	17	131	10	8	8	364*	-1	71	73	125	-1	11	8	324*

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
-7, 10, 1				7	125	119	80	-9	19	20	128	-2	198	206	111
0	84	85	121	8	5	4	656*	-8	30	29	135	-1	72	70	110
1	130	123	84	9	56	57	91	-7	2	8	2367*	0	72	83	109
2	50	48	87	10	91	93	90	-6	11	18	452*	1	96	97	76
3	17	16	116	11	71	69	87	-5	38	35	134	2	41	42	86
4	17	13	144	12	66	71	79	-4	90	85	117	3	93	93	79
5	42	40	79	-6, 2, 1				-3	210	218	109	4	17	17	128
-7, 11, 1				-8	67	70	108	-2	85	85	105	5	70	71	87
-5	6	10	664*	-7	61	53	123	-1	312	317	99	6	86	84	88
-4	40	36	114	-6	91	88	122	0	69	69	98	7	111	112	89
-3	46	41	116	-5	151	147	121	1	345	342	67	8	87	87	88
-2	2	2	2291*	-4	134	141	116	2	257	247	67	9	5	7	591*
-1	100	90	111	-3	148	150	110	3	27	29	89	10	9	13	241*
0	68	62	118	-2	176	173	103	4	4	5	695*	-6, 7, 1			
1	7	2	363*	-1	85	89	99	5	37	35	87	-8	28	34	121
2	14	14	161	0	106	107	94	6	121	126	81	-7	66	67	123
3	8	11	228*	1	66	66	66	7	146	145	85	-6	104	113	122
-7, 12, 1				2	254	260	64	8	17	17	187	-5	2	1	2402*
-2	16	12	138	3	131	129	65	9	25	25	106	-4	66	63	126
-1	14	9	139	4	8	3	340*	10	41	42	92	-3	58	53	122
0	21	18	123	5	149	145	71	11	22	20	88	-2	71	75	119
-6, 0, 1				6	241	242	75	-6, 5, 1				-1	44	46	124
1	119	116	68	7	48	46	87	-9	36	35	106	0	59	58	119
2	34	31	78	8	73	76	86	-8	64	62	118	1	82	78	83
3	23	25	83	9	2	5	1578*	-7	37	38	136	2	70	72	85
4	38	33	75	10	29	27	104	-6	103	105	123	3	2	4	1278*
5	78	74	73	11	43	43	92	-5	73	72	127	4	6	4	598*
6	9	8	349*	12	7	17	370*	-4	24	29	166	5	60	61	91
7	93	95	80	-6, 3, 1				-3	79	81	116	6	10	2	213*
8	29	31	105	-8	2	7	2214*	-2	59	66	115	7	43	46	94
9	39	37	99	-7	2	9	2274*	-1	192	193	103	8	2	1	1551*
10	47	47	94	-6	102	101	124	0	125	133	102	9	18	17	95
11	52	54	91	-5	124	125	121	1	142	140	71	-6, 8, 1			
12	31	29	89	-4	52	49	123	2	144	138	72	-8	47	47	108
-6, 1, 1				-3	33	36	121	3	43	43	78	-7	2	8	2312*
-8	2	1	1974*	-2	57	50	108	4	80	80	78	-6	35	41	146
-7	25	26	138	-1	77	77	98	5	84	88	82	-5	60	63	127
-6	53	53	133	0	39	40	99	6	14	10	208	-4	17	19	166
-5	108	105	123	1	104	99	65	7	39	44	98	-3	14	12	243
-4	49	48	131	2	59	57	68	8	19	18	159	-2	24	21	148
-3	42	44	121	3	93	99	67	9	31	32	96	-1	19	19	184
-2	7	5	534*	4	226	220	69	10	38	38	86	0	8	1	476*
-1	65	61	103	5	79	81	75	-6, 6, 1				1	45	44	91
0	15	15	148	6	20	18	145	-9	42	40	102	2	19	14	141
1	30	29	73	7	140	141	83	-8	12	17	344*	3	22	23	121
2	136	132	64	8	48	47	92	-7	20	12	153	4	13	12	221
3	65	64	67	9	42	43	94	-6	54	58	131	5	50	45	91
4	367	355	67	10	55	55	90	-5	40	40	136	6	81	80	87
5	251	251	70	11	62	63	82	-4	34	35	142	7	139	139	80
6	315	302	74	-6, 4, 1				-3	36	35	126	8	8	12	348*

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	-6, 9, 1				-5, 0, 1			4	398	381	62	9	2	2	1763*
-8	2	3	2092*	1	285	266	59	5	378	365	66	10	8	1	337*
-7	22	21	149	2	94	88	58	6	98	98	72	11	85	87	76
-6	14	18	385*	3	183	177	59	7	72	74	80		-5, 5, 1		
-5	80	77	125	4	164	159	61	8	107	109	84	-10	2	5	2076*
-4	60	62	130	5	156	146	65	9	73	77	89	-9	28	31	137
-3	53	51	131	6	176	172	70	10	68	71	91	-8	18	17	186
-2	157	160	124	7	72	78	77	11	46	46	88	-7	16	21	401*
-1	10	9	259*	8	2	2	1665*	12	50	51	78	-6	114	111	121
0	114	113	124	9	96	99	87		-5, 3, 1			-5	118	115	116
1	18	15	177	10	35	40	101	-9	70	68	110	-4	89	90	110
2	36	37	101	11	61	62	89	-8	53	50	123	-3	125	142	104
3	84	81	88	12	61	64	84	-7	72	70	132	-2	62	64	101
4	18	22	131		-5, 1, 1			-6	48	42	135	-1	151	157	94
5	79	79	85	-9	2	4	2094*	-5	237	236	113	0	11	5	157
6	60	61	84	-8	95	96	115	-4	182	192	106	1	62	60	67
7	50	49	75	-7	17	14	198	-3	64	60	100	2	52	55	70
	-6, 10, 1			-6	118	115	121	-2	200	203	91	3	56	55	71
-7	49	41	110	-5	147	148	117	-1	44	53	89	4	66	72	75
-6	12	6	337*	-4	105	107	110	0	190	189	82	5	17	22	110
-5	24	19	151	-3	79	80	103	1	191	193	58	6	60	64	85
-4	24	22	162	-2	75	75	94	2	24	18	70	7	15	13	143
-3	28	23	156	-1	71	70	88	3	375	364	60	8	46	46	95
-2	20	18	175	0	54	52	86	4	184	172	64	9	86	88	88
-1	10	18	539*	1	43	42	60	5	70	72	71	10	24	28	99
0	57	58	129	2	246	227	56	6	103	107	75		-5, 6, 1		
1	39	33	98	3	16	7	91	7	26	27	100	-9	8	5	418*
2	17	17	121	4	112	108	61	8	36	30	95	-8	60	58	125
3	28	26	102	5	70	69	66	9	54	54	94	-7	56	54	129
4	15	11	139	6	90	88	71	10	28	27	103	-6	39	41	144
5	25	24	95	7	88	94	77	11	25	26	108	-5	76	74	120
	-6, 11, 1			8	52	52	86		-5, 4, 1			-4	97	102	115
-6	2	1	2023*	9	129	132	87	-9	30	29	122	-3	186	183	107
-5	20	17	138	10	24	23	110	-8	20	26	165	-2	160	158	104
-4	29	22	131	11	65	64	90	-7	22	17	167	-1	93	91	101
-3	43	35	124	12	26	30	95	-6	26	23	155	0	41	47	105
-2	2	1	2329*		-5, 2, 1			-5	63	59	116	1	29	25	80
-1	62	55	117	-9	2	4	2148*	-4	144	146	106	2	54	57	75
0	9	7	479*	-8	32	29	128	-3	89	88	100	3	25	29	94
1	36	34	91	-7	9	3	559*	-2	167	175	93	4	32	29	90
2	47	44	80	-6	116	115	122	-1	34	43	101	5	57	56	88
3	36	32	80	-5	182	174	115	0	86	86	87	6	44	45	94
4	84	83	70	-4	145	142	107	1	12	7	132	7	108	108	89
	-6, 12, 1			-3	177	173	99	2	227	235	62	8	70	69	88
-4	20	15	125	-2	198	197	91	3	123	124	64	9	36	34	92
-3	6	9	645*	-1	192	198	85	4	136	143	68	10	48	49	75
-2	8	3	379*	0	63	65	83	5	12	6	163		-5, 7, 1		
-1	39	35	111	1	257	254	56	6	124	127	79	-9	60	60	111
0	53	48	107	2	206	205	56	7	11	4	210	-8	12	13	300*
1	6	0	324*	3	83	81	59	8	20	19	126	-7	86	91	125

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	-5, 7, 1			5	47	47	90	11	59	59	91		-4, 3, 1		
-6	35	32	145	6	12	8	138	12	20	19	111	-10	24	25	138
-5	2	2	2108*	7	34	33	81		-4, 1, 1			-9	26	25	169
-4	48	50	128		-5, 10, 1			-10	40	39	103	-8	14	17	361*
-3	82	82	115	-8	6	6	581*	-9	65	63	114	-7	26	24	155
-2	50	56	114	-7	7	1	644*	-8	34	32	152	-6	104	95	114
-1	64	65	112	-6	40	39	135	-7	101	99	124	-5	60	59	109
0	64	69	111	-5	2	3	1939*	-6	49	44	129	-4	31	26	103
1	57	51	80	-4	13	10	337*	-5	33	31	122	-3	93	92	88
2	58	56	83	-3	80	73	128	-4	25	28	121	-2	93	83	82
3	74	72	82	-2	130	136	126	-3	2	4	1918*	-1	137	137	76
4	82	80	86	-1	57	59	130	-2	83	91	82	0	45	53	78
5	53	54	92	0	24	26	178	-1	83	79	76	1	442	426	52
6	60	65	92	1	44	44	93	0	53	49	73	2	101	100	53
7	76	77	89	2	36	32	103	1	252	254	48	3	109	110	56
8	2	1	1477*	3	67	68	87	2	390	372	68	4	152	143	60
9	34	36	84	4	86	82	83	3	214	196	51	5	126	128	66
	-5, 8, 1			5	3	6	762*	4	688	644	262	6	29	30	84
-9	51	52	107		-5, 11, 1			5	255	254	60	7	73	73	81
-8	41	42	125	-7	35	33	111	6	39	42	71	8	23	24	116
-7	28	33	135	-6	8	11	476*	7	24	19	89	9	5	3	832*
-6	14	6	201	-5	38	34	118	8	42	35	87	10	57	57	92
-5	53	57	129	-4	72	65	122	9	109	109	86	11	2	4	1669*
-4	46	47	136	-3	90	78	119	10	91	91	89		-4, 4, 1		
-3	49	50	124	-2	15	16	203	11	26	24	107	-10	47	46	116
-2	55	52	125	-1	61	61	122	12	50	48	81	-9	20	10	161
-1	70	70	118	0	18	17	172		-4, 2, 1			-8	46	41	132
0	73	76	118	1	16	13	124	-10	32	33	112	-7	50	42	131
1	124	125	83	2	21	17	104	-9	14	8	181	-6	95	97	115
2	83	79	86	3	15	13	126	-8	66	62	128	-5	8	12	536*
3	31	22	101	4	10	13	289*	-7	123	122	123	-4	174	171	97
4	57	57	92		-5, 12, 1			-6	44	38	132	-3	6	12	511*
5	25	25	112	-5	28	25	114	-5	114	118	106	-2	543	548	398
6	50	51	91	-4	10	7	305*	-4	15	14	131	-1	523	516	81
7	10	9	289*	-3	28	20	117	-3	258	247	87	0	338	311	78
8	38	39	77	-2	2	1	2138*	-2	41	44	86	1	148	140	55
	-5, 9, 1			-1	12	12	311*	-1	312	310	74	2	136	133	57
-8	46	52	112	0	6	9	496*	0	159	156	70	3	17	12	78
-7	5	8	1067*	1	46	44	76	1	70	72	50	4	18	12	87
-6	43	44	132		-4, 0, 1			2	198	187	50	5	67	66	73
-5	3	17	1765*	1	118	109	50	3	150	141	53	6	158	157	77
-4	26	28	148	2	325	303	50	4	287	275	57	7	145	143	83
-3	43	44	143	3	37	38	56	5	3	15	679*	8	34	34	104
-2	70	73	125	4	94	85	55	6	24	27	86	9	111	110	89
-1	129	132	122	5	176	166	60	7	213	215	76	10	48	51	89
0	64	59	127	6	199	195	65	8	164	164	82	11	79	81	76
1	35	33	103	7	172	166	72	9	15	13	154		-4, 5, 1		
2	23	25	117	8	66	62	81	10	47	46	96	-10	72	67	109
3	21	18	161	9	104	103	85	11	64	64	86	-9	55	52	124
4	72	71	90	10	54	53	93	12	7	8	310*	-8	75	75	126

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
-4, 5, 1				-2	8	3	457*	-4, 10, 1				-9	36	32	150
-7	58	55	129	-1	17	9	143	-8	24	26	138	-8	106	109	124
-6	95	99	118	0	21	21	143	-7	29	29	130	-7	209	210	119
-5	36	43	130	1	20	25	103	-6	12	0	305*	-6	40	37	124
-4	32	36	111	2	19	16	105	-5	36	33	132	-5	9	7	389*
-3	222	227	94	3	194	193	80	-4	2	9	2454*	-4	234	244	88
-2	221	224	89	4	60	64	88	-3	51	52	132	-3	97	102	79
-1	46	40	93	5	144	142	87	-2	19	17	170	-2	219	216	70
0	167	166	85	6	9	3	357*	-1	94	98	126	-1	207	193	63
1	32	33	69	7	29	31	104	0	50	48	129	0	107	106	59
2	317	307	63	8	37	35	91	1	17	18	174	1	496	476	193
3	89	93	67	9	12	13	142	2	60	57	91	2	464	460	200
4	215	211	71	-4, 8, 1				3	70	68	88	3	243	218	46
5	80	80	78	-10	13	7	146	4	31	28	90	4	202	190	51
6	98	98	83	-9	11	7	289*	5	9	5	268*	5	6	3	303*
7	26	26	106	-8	4	7	946*	-4, 11, 1				6	195	188	64
8	24	24	119	-7	2	3	2175*	-7	55	45	106	7	50	51	76
9	63	62	89	-6	98	97	126	-6	11	9	203	8	34	38	91
10	49	51	82	-5	11	10	458*	-5	18	18	207	9	63	64	90
-4, 6, 1				-4	118	116	119	-4	38	36	131	10	80	82	90
-10	4	8	891*	-3	36	36	136	-3	32	31	142	11	67	68	89
-9	11	11	407*	-2	197	202	116	-2	33	38	141	12	11	9	176
-8	49	49	130	-1	84	78	116	-1	40	43	137	-3, 2, 1			
-7	127	127	122	0	100	100	115	0	2	4	2348*	-11	57	55	97
-6	64	72	122	1	43	40	91	1	84	80	83	-10	78	78	116
-5	76	77	115	2	64	66	86	2	78	78	80	-9	5	5	1066*
-4	46	47	116	3	27	30	106	3	22	19	93	-8	12	0	238*
-3	181	182	101	4	120	118	88	-4, 12, 1				-7	243	237	116
-2	2	2	2187*	5	70	74	91	-5	34	28	111	-6	130	134	108
-1	112	108	95	6	36	35	96	-4	19	16	151	-5	123	124	97
0	70	79	96	7	83	84	81	-3	19	15	147	-4	19	19	126
1	31	26	74	8	2	6	1293*	-2	2	0	2170*	-3	356	349	77
2	21	27	96	-4, 9, 1				-1	8	11	507*	-2	50	54	73
3	34	34	86	-9	44	37	109	0	32	31	126	-1	388	389	299
4	73	78	80	-8	33	33	135	1	18	21	102	0	610	596	288
5	85	84	83	-7	15	18	269	-3, 0, 1				1	198	193	42
6	8	2	382*	-6	30	28	127	1	92	85	42	2	499	499	211
7	88	90	90	-5	72	76	128	2	90	82	43	3	14	21	70
8	82	83	87	-4	43	45	136	3	134	129	46	4	114	111	54
9	20	18	106	-3	105	111	123	4	111	114	51	5	140	135	60
10	53	55	71	-2	105	104	123	5	143	145	57	6	93	97	68
-4, 7, 1				-1	41	42	130	6	191	205	63	7	105	106	76
-10	47	46	107	0	41	41	128	7	115	112	71	8	204	210	82
-9	109	110	120	1	25	23	115	8	131	127	78	9	46	45	95
-8	34	39	140	2	102	102	89	9	150	154	85	10	45	45	97
-7	13	20	481*	3	69	67	90	10	67	70	92	11	7	12	383*
-6	12	14	486*	4	24	27	110	11	38	36	96	12	30	29	82
-5	49	53	132	5	11	12	236*	12	10	2	216*	-3, 3, 1			
-4	104	111	113	6	43	40	82	-3, 1, 1				-11	15	13	157
-3	77	80	112	7	31	31	76	-10	8	1	407*	-10	41	35	126

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
-3, 3, 1				-8	100	96	123	-2	97	104	104	-8	47	46	115
-9	2	10	2360*	-7	87	93	122	-1	73	75	104	-7	5	18	1109*
-8	52	44	130	-6	134	138	110	0	100	100	104	-6	33	35	141
-7	110	115	117	-5	113	126	102	1	156	148	74	-5	101	100	125
-6	41	38	114	-4	123	124	95	2	9	1	259*	-4	74	77	131
-5	196	195	96	-3	80	80	90	3	142	140	80	-3	12	8	379*
-4	185	190	87	-2	59	59	87	4	12	9	158	-2	9	13	474*
-3	198	200	78	-1	172	165	81	5	26	23	124	-1	17	14	190
-2	162	167	72	0	17	15	130	6	42	44	96	0	22	23	163
-1	288	288	67	1	181	169	58	7	41	40	91	1	42	41	94
0	190	182	65	2	67	73	63	8	13	14	237	2	14	10	175
1	400	398	218	3	50	53	70	-3, 8, 1				3	17	17	116
2	12	9	97	4	70	73	72	-10	3	8	1099*	4	14	9	150
3	251	246	53	5	16	13	109	-9	41	41	135	5	27	26	84
4	188	191	58	6	59	64	86	-8	2	1	2248*	-3, 11, 1			
5	158	162	65	7	88	87	90	-7	24	20	156	-8	2	5	1835*
6	99	97	72	8	32	32	112	-6	33	35	140	-7	11	12	377*
7	33	36	94	9	67	65	87	-5	62	63	123	-6	38	36	125
8	39	36	99	10	16	16	123	-4	126	136	118	-5	42	48	134
9	117	116	89	-3, 6, 1				-3	113	117	115	-4	96	92	122
10	151	153	86	-11	28	26	120	-2	139	142	113	-3	15	12	210
11	34	35	89	-10	65	64	123	-1	120	119	113	-2	21	20	161
-3, 4, 1				-9	13	10	338*	0	12	9	206	-1	2	4	2191*
-11	15	10	163	-8	75	69	131	1	142	136	82	0	2	2	2092*
-10	10	11	447*	-7	65	66	124	2	39	34	96	1	2	8	1430*
-9	56	54	128	-6	22	16	160	3	124	122	87	2	14	11	156
-8	47	44	129	-5	52	55	111	4	16	14	131	3	63	61	88
-7	139	140	117	-4	108	108	102	5	59	58	91	-3, 12, 1			
-6	43	36	113	-3	10	15	369*	6	43	45	92	-6	34	33	110
-5	43	35	106	-2	73	78	94	7	2	2	1463*	-5	49	47	109
-4	16	17	114	-1	217	223	92	-3, 9, 1				-4	2	4	1756*
-3	32	35	91	0	330	328	91	-10	11	13	294*	-3	2	6	1992*
-2	79	86	78	1	49	52	70	-9	24	24	135	-2	7	11	527*
-1	158	160	73	2	323	312	69	-8	32	28	132	-1	16	14	158
0	157	155	72	3	72	66	76	-7	44	44	130	0	30	29	119
1	537	538	246	4	125	127	78	-6	41	41	146	1	41	37	82
2	54	49	56	5	74	74	84	-5	21	22	186	-2, 0, 1			
3	114	105	59	6	17	14	155	-4	220	230	125	1	557	535	162
4	67	68	66	7	157	153	88	-3	195	201	122	2	1042	961	186
5	84	97	72	8	91	88	87	-2	5	8	1109*	3	834	790	204
6	9	14	323*	9	46	45	82	-1	25	23	152	4	7	0	202*
7	114	114	84	-3, 7, 1				0	45	48	131	5	141	141	55
8	183	184	88	-10	69	69	114	1	2	2	1723*	6	47	46	66
9	108	111	88	-9	38	35	127	2	120	117	89	7	93	89	71
10	2	5	1417*	-8	26	24	154	3	8	6	375*	8	162	154	78
11	2	2	1300*	-7	82	85	125	4	67	64	89	9	130	134	86
-3, 5, 1				-6	86	96	123	5	19	24	114	10	25	24	114
-11	34	36	112	-5	156	158	114	6	9	4	236*	11	82	82	88
-10	9	14	604*	-4	95	105	110	-3, 10, 1				12	40	38	84
-9	45	44	144	-3	75	77	108	-9	2	6	2005*	-2, 1, 1			

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	-2, 1, l			-11	32	34	122	-8	127	126	122	-3	39	34	114
-11	63	57	103	-10	11	5	201	-7	2	3	2148*	-2	147	152	102
-10	29	24	133	-9	25	21	171	-6	104	109	106	-1	131	129	101
-9	34	30	149	-8	57	58	124	-5	26	22	125	0	100	104	104
-8	68	68	124	-7	116	115	111	-4	66	61	90	1	177	177	74
-7	195	191	112	-6	87	84	100	-3	216	229	84	2	197	193	78
-6	178	179	101	-5	123	118	89	-2	171	179	81	3	185	176	81
-5	159	149	90	-4	134	126	80	-1	352	361	79	4	20	19	128
-4	162	171	79	-3	368	373	72	0	153	146	80	5	127	126	88
-3	300	298	69	-2	251	270	65	1	228	220	58	6	137	132	88
-2	261	266	60	-1	157	148	60	2	123	115	61	7	4	2	792*
-1	264	266	52	0	23	21	72	3	300	289	66	8	14	11	144
0	144	142	47	1	12	12	69	4	130	127	72		-2, 8, l		
1	775	736	167	2	204	203	47	5	21	20	100	-11	18	18	146
2	576	578	179	3	148	146	52	6	120	118	84	-10	23	24	143
3	458	442	202	4	52	47	61	7	103	103	88	-9	25	24	160
4	30	31	53	5	79	84	66	8	26	24	108	-8	2	0	2113*
5	64	68	58	6	8	10	239*	9	17	12	141	-7	58	56	131
6	87	88	65	7	33	31	95	10	19	19	117	-6	148	153	123
7	76	77	74	8	27	26	109		-2, 6, l			-5	66	65	124
8	52	53	85	9	68	71	91	-11	48	48	114	-4	267	276	116
9	37	38	96	10	16	17	136	-10	106	107	120	-3	33	35	139
10	23	22	118	11	13	17	164	-9	6	2	802*	-2	116	116	113
11	24	26	112		-2, 4, l			-8	11	11	337*	-1	30	24	125
12	17	14	139	-11	6	5	571*	-7	27	35	149	0	131	131	114
	-2, 2, l			-10	132	127	121	-6	37	39	125	1	192	188	82
-11	55	54	111	-9	70	68	126	-5	112	117	104	2	47	47	92
-10	31	34	146	-8	87	80	120	-4	10	3	177	3	61	61	91
-9	46	41	134	-7	11	11	409*	-3	8	12	431*	4	114	111	88
-8	51	47	130	-6	79	79	103	-2	186	187	90	5	93	93	88
-7	23	27	136	-5	2	8	1911*	-1	99	100	91	6	20	18	107
-6	171	165	99	-4	318	307	84	0	119	114	91	7	38	36	93
-5	121	120	88	-3	11	16	139	1	117	112	67		-2, 9, l		
-4	165	170	78	-2	134	133	72	2	167	171	69	-10	6	4	564*
-3	171	182	69	-1	29	28	80	3	27	27	84	-9	37	37	125
-2	728	733	296	0	20	27	88	4	22	18	101	-8	51	53	125
-1	172	179	54	1	131	119	50	5	45	41	90	-7	30	29	143
0	626	633	250	2	188	180	53	6	13	18	226	-6	84	85	131
1	334	340	175	3	13	8	93	7	92	93	89	-5	17	17	207
2	74	72	41	4	168	176	64	8	2	0	1629*	-4	2	3	2712*
3	129	124	47	5	47	46	76	9	40	42	84	-3	7	7	717*
4	34	38	59	6	144	146	78		-2, 7, l			-2	29	25	148
5	35	37	65	7	17	13	171	-11	33	33	117	-1	71	69	125
6	181	190	68	8	197	197	88	-10	15	10	173	0	72	66	126
7	86	89	77	9	118	114	88	-9	2	1	2116*	1	81	79	91
8	45	42	91	10	42	41	86	-8	2	7	2430*	2	58	56	94
9	126	126	89		-2, 5, l			-7	101	101	123	3	2	1	1339*
10	45	44	99	-11	47	49	116	-6	37	40	132	4	29	29	114
11	26	29	103	-10	22	24	164	-5	5	7	878*	5	42	40	92
	-2, 3, l			-9	66	65	128	-4	58	58	112	6	19	23	112

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
-2, 10, 1				-11	33	30	116	-12	33	27	110	-11	86	81	117
-9	43	41	110	-10	125	125	122	-11	53	45	122	-10	25	27	157
-8	25	26	142	-9	83	81	125	-10	34	31	135	-9	73	66	127
-7	30	33	141	-8	46	46	124	-9	20	9	167	-8	105	103	121
-6	12	11	211	-7	52	60	111	-8	166	162	116	-7	134	134	111
-5	99	104	127	-6	57	53	98	-7	31	40	123	-6	60	65	104
-4	12	5	333*	-5	33	31	89	-6	123	127	94	-5	10	1	174
-3	39	41	154	-4	278	274	72	-5	32	32	99	-4	100	102	88
-2	36	38	137	-3	175	181	61	-4	267	260	74	-3	103	102	83
-1	83	85	129	-2	66	59	53	-3	312	322	68	-2	30	31	88
0	96	95	128	-1	216	226	194	-2	15	5	89	-1	259	257	78
1	6	5	519*	0	356	355	170	-1	76	79	58	0	5	3	540*
2	34	30	95	1	607	592	140	0	15	3	83	1	22	11	73
3	3	2	933*	2	84	77	35	1	241	251	43	2	164	172	64
4	59	55	79	3	227	219	42	2	132	131	48	3	23	19	83
-2, 11, 1				4	254	254	50	3	224	230	53	4	58	59	77
-8	11	7	175	5	225	216	58	4	28	29	67	5	18	19	145
-7	48	49	123	6	73	72	67	5	94	86	68	6	136	138	86
-6	9	10	521*	7	17	17	142	6	162	164	75	7	68	62	91
-5	39	41	131	8	50	48	88	7	161	167	82	8	3	6	1178*
-4	2	5	2336*	9	37	37	98	8	98	100	89	9	40	37	82
-3	31	27	151	10	127	128	87	9	16	12	163	-1, 6, 1			
-2	65	68	126	11	43	44	88	10	39	41	91	-12	35	34	104
-1	94	98	122	12	32	33	78	11	2	4	1283*	-11	47	50	117
0	2	10	2020*	-1, 2, 1				-1, 4, 1				-10	57	57	127
1	7	8	381*	-12	4	4	878*	-12	2	2	1966*	-9	52	56	132
2	47	44	91	-11	66	64	116	-11	38	36	132	-8	18	13	174
3	42	39	101	-10	83	83	125	-10	124	127	123	-7	126	127	115
-2, 12, 1				-9	178	174	123	-9	11	4	261*	-6	43	42	121
-6	42	44	103	-8	72	69	119	-8	29	29	148	-5	128	133	102
-5	10	6	258*	-7	61	59	107	-7	134	132	107	-4	9	9	361*
-4	41	39	110	-6	328	321	93	-6	255	261	98	-3	39	44	102
-3	5	1	626*	-5	220	221	82	-5	107	110	89	-2	114	121	91
-2	14	14	141	-4	775	757	349	-4	14	21	126	-1	260	256	90
-1	22	25	112	-3	114	116	63	-3	234	243	74	0	296	279	92
0	2	1	2118*	-2	457	467	256	-2	29	24	76	1	120	117	69
-1, 0, 1				-1	412	438	230	-1	138	148	68	2	282	280	72
1	317	302	119	0	435	467	224	0	152	158	68	3	118	111	77
2	33	32	35	1	618	626	172	1	182	186	51	4	74	73	84
3	371	364	56	2	31	30	45	2	248	227	55	5	265	263	85
4	171	175	47	3	96	93	47	3	92	95	61	6	15	9	162
5	77	79	56	4	87	83	55	4	76	67	67	7	97	97	87
6	207	195	63	5	205	207	62	5	109	107	74	8	30	28	89
7	19	13	95	6	212	209	70	6	96	97	81	9	69	70	71
8	111	111	80	7	37	34	86	7	111	111	87	-1, 7, 1			
9	15	12	186	8	76	75	86	8	52	53	92	-11	13	12	182
10	24	20	125	9	155	156	88	9	16	15	155	-10	49	45	127
11	35	33	101	10	86	82	88	10	54	56	80	-9	52	61	134
12	38	38	83	11	6	6	433*	-1, 5, 1				-8	83	77	127
-1, 1, 1				-1, 3, 1				-12	68	63	103	-7	110	117	122

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
-1, 7, 1				3	68	62	90	-12	49	47	105	-12	7	4	505*
-6	2	2	2496*	4	60	56	88	-11	24	25	140	-11	43	45	134
-5	16	13	177	5	5	1	498*	-10	2	6	2417*	-10	96	95	125
-4	24	18	139	-1, 10, 1				-9	230	226	121	-9	70	67	126
-3	203	215	104	-9	2	10	2260*	-8	34	36	127	-8	235	232	111
-2	255	258	102	-8	27	25	147	-7	222	221	101	-7	186	187	101
-1	29	36	121	-7	48	47	126	-6	79	77	90	-6	277	262	91
0	129	136	105	-6	92	91	125	-5	238	243	78	-5	412	409	82
1	49	47	82	-5	105	103	125	-4	114	110	67	-4	153	155	72
2	48	53	85	-4	38	33	142	-3	796	802	281	-3	578	595	312
3	30	30	95	-3	17	18	199	-2	267	265	46	-2	191	207	60
4	16	16	211	-2	31	31	139	-1	280	292	171	-1	271	280	58
5	2	7	1566*	-1	46	48	134	0	503	529	118	0	412	418	59
6	2	9	1469*	0	65	62	124	1	375	390	143	1	256	242	45
7	30	28	93	1	97	88	86	2	150	144	38	2	181	187	50
8	21	23	102	2	65	62	88	3	55	52	46	3	30	13	63
-1, 8, 1				3	14	12	125	4	42	44	55	4	125	123	63
-11	6	6	640*	4	26	22	119	5	29	35	68	5	89	87	72
-10	57	57	118	-1, 11, 1				6	109	107	69	6	64	63	81
-9	10	18	568*	-8	42	41	114	7	44	41	82	7	92	88	85
-8	13	11	220	-7	48	50	117	8	75	75	86	8	35	35	99
-7	61	60	125	-6	22	23	202	9	68	68	92	9	34	35	95
-6	63	67	127	-5	12	14	357*	10	49	51	91	10	8	0	266*
-5	152	156	119	-4	2	13	2313*	11	16	17	144	0, 4, 1			
-4	58	57	120	-3	3	14	1598*	0, 2, 1				-12	71	68	108
-3	13	9	380*	-2	42	39	128	-12	30	28	124	-11	103	97	119
-2	34	35	136	-1	26	28	153	-11	10	4	380*	-10	90	88	125
-1	66	66	117	0	72	72	118	-10	77	73	127	-9	43	41	130
0	70	71	122	1	48	46	94	-9	25	23	155	-8	31	26	128
1	69	65	88	2	19	17	153	-8	28	36	135	-7	155	154	105
2	68	69	89	-1, 12, 1				-7	11	1	172	-6	66	68	97
3	80	77	90	-5	41	38	108	-6	34	43	100	-5	24	22	109
4	55	57	93	-4	41	38	113	-5	121	115	78	-4	12	6	136
5	40	36	97	-3	8	1	306*	-4	151	145	69	-3	204	210	73
6	76	76	81	-2	13	8	253	-3	158	163	60	-2	37	31	75
7	2	2	1198*	-1	7	5	368*	-2	493	504	249	-1	122	131	70
-1, 9, 1				0, 0, 1				-1	706	714	234	0	403	411	51
-10	45	42	108	1	473	470	114	0	195	197	34	1	82	85	54
-9	38	34	126	2	583	584	162	1	758	778	190	2	334	323	58
-8	32	31	130	3	96	100	42	2	104	100	44	3	71	64	65
-7	93	93	126	4	14	24	70	3	143	135	50	4	152	152	70
-6	140	144	125	5	104	99	58	4	21	16	71	5	105	103	78
-5	67	67	130	6	9	2	263*	5	43	44	69	6	202	200	83
-4	82	81	127	7	80	83	75	6	196	186	73	7	9	5	337*
-3	172	173	122	8	123	127	82	7	69	64	83	8	90	87	87
-2	33	31	134	9	38	38	100	8	80	80	88	9	56	56	83
-1	184	189	123	10	12	9	219	9	85	85	89	10	97	93	69
0	99	100	124	11	50	45	84	10	22	25	108	0, 5, 1			
1	46	48	102	12	20	18	91	11	61	63	73	-12	62	64	107
2	45	45	95	0, 1, 1				0, 3, 1				-11	81	83	123

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	0, 5, 1			-5	166	173	111	-9	15	16	161	0	432	436	150
-10	33	36	158	-4	57	62	112	-8	14	19	407*	1	381	401	170
-9	31	30	149	-3	72	73	107	-7	63	60	121	2	235	241	42
-8	66	68	121	-2	35	37	114	-6	26	29	151	3	363	366	49
-7	73	73	112	-1	90	94	107	-5	10	15	503*	4	260	249	56
-6	77	79	102	0	111	111	77	-4	8	0	571*	5	97	99	65
-5	58	58	95	1	223	219	79	-3	97	101	125	6	89	85	73
-4	195	203	87	2	152	151	83	-2	126	127	125	7	162	158	81
-3	69	69	84	3	312	307	86	-1	71	65	126	8	145	146	87
-2	82	84	81	4	71	68	91	0	13	11	274*	9	58	57	92
-1	92	94	82	5	56	54	91	1	66	66	86	10	26	25	105
0	172	180	59	6	2	9	1449*	2	18	12	135	11	27	22	85
1	269	271	62	7	73	70	91	3	42	41	104		1, 2, 1		
2	69	73	67		0, 8, 1				0, 11, 1			-12	32	32	123
3	179	178	71	-11	3	0	1074*	-8	32	30	107	-11	32	33	137
4	152	157	78	-10	2	4	2476*	-7	24	21	142	-10	57	53	131
5	15	21	179	-9	14	9	214	-6	24	22	148	-9	188	185	118
6	95	95	88	-8	12	8	384*	-5	51	51	118	-8	162	160	109
7	2	3	1464*	-7	176	181	124	-4	11	12	303*	-7	343	332	98
8	15	17	161	-6	171	171	122	-3	50	44	126	-6	427	422	87
9	6	8	459*	-5	55	55	126	-2	40	32	118	-5	90	78	77
	0, 6, 1			-4	91	91	118	-1	17	19	301	-4	70	77	69
-12	61	60	105	-3	74	76	120	0	62	56	100	-3	266	261	60
-11	13	10	348*	-2	135	135	116	1	12	16	211	-2	376	395	258
-10	63	62	129	-1	41	40	132		1, 0, 1			-1	272	286	53
-9	6	1	745*	0	184	183	85	0	32	30	26	0	919	921	198
-8	39	41	132	1	49	48	94	1	411	420	146	1	545	547	205
-7	12	12	361*	2	24	23	118	2	382	383	179	2	52	57	50
-6	93	102	110	3	16	18	184	3	668	671	220	3	312	293	55
-5	83	86	103	4	36	31	94	4	117	123	53	4	44	38	66
-4	17	18	114	5	57	58	100	5	220	216	61	5	135	128	70
-3	43	48	100	6	35	37	110	6	59	58	71	6	189	187	77
-2	20	16	115		0, 9, 1			7	12	13	172	7	21	22	118
-1	125	120	93	-10	14	19	193	8	77	82	86	8	38	37	97
0	113	104	68	-9	85	83	118	9	119	117	88	9	103	99	87
1	353	343	71	-8	10	6	487*	10	132	131	85	10	9	10	291*
2	48	47	83	-7	24	22	154	11	42	41	82		1, 3, 1		
3	97	96	81	-6	30	27	142		1, 1, 1			-12	40	35	116
4	82	82	86	-5	32	31	145	-12	10	13	368*	-11	88	85	122
5	96	97	88	-4	50	51	136	-11	49	47	132	-10	43	44	147
6	21	17	116	-3	32	33	144	-10	10	16	608*	-9	44	40	131
7	18	13	127	-2	103	105	125	-9	2	11	2443*	-8	141	150	110
8	5	8	476*	-1	54	55	130	-8	83	83	111	-7	11	6	390*
	0, 7, 1			0	29	30	105	-7	106	101	99	-6	74	67	92
-11	20	22	163	1	23	22	121	-6	204	206	86	-5	58	61	84
-10	47	47	138	2	24	23	114	-5	94	90	76	-4	150	150	73
-9	18	23	213	3	47	46	103	-4	618	593	312	-3	29	24	74
-8	58	56	131	4	29	30	103	-3	233	229	56	-2	44	41	67
-7	50	55	130	5	9	10	230*	-2	611	604	231	-1	213	211	63
-6	140	142	116		0, 10, 1			-1	525	510	204	0	314	317	47

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	1, 3, 1			3	85	82	78	-9	53	56	125	-2	32	35	176
1	296	281	50	4	107	111	82	-8	81	78	125	-1	22	21	200
2	16	9	79	5	42	41	92	-7	66	70	129		2, 0, 1		
3	321	304	61	6	68	64	92	-6	96	98	125	0	360	355	163
4	35	37	75	7	52	52	88	-5	101	96	121	1	24	22	47
5	160	153	76	8	13	14	152	-4	66	69	123	2	392	388	62
6	10	1	314*		1, 6, 1			-3	69	66	124	3	425	408	51
7	78	76	88	-12	12	13	339*	-2	85	91	122	4	169	184	58
8	9	19	407*	-11	9	5	412*	-1	2	7	2693*	5	69	49	67
9	41	41	89	-10	30	28	145	0	55	51	93	6	58	59	77
10	34	31	75	-9	2	15	2688*	1	35	34	102	7	11	7	193
	1, 4, 1			-8	70	73	124	2	18	14	178	8	25	22	115
-12	72	68	111	-7	42	42	124	3	108	106	88	9	68	65	89
-11	17	21	250	-6	66	69	112	4	33	37	96	10	90	87	81
-10	17	20	216	-5	82	77	104	5	69	72	97	11	16	18	130
-9	104	101	122	-4	128	132	101		1, 9, 1				2, 1, 1		
-8	73	72	118	-3	213	213	98	-10	14	21	347*	-12	46	46	123
-7	207	214	103	-2	61	56	98	-9	49	47	124	-11	70	68	125
-6	120	112	95	-1	108	109	99	-8	42	42	130	-10	53	51	129
-5	58	59	88	0	17	4	102	-7	26	24	150	-9	157	158	118
-4	181	173	80	1	8	6	396*	-6	111	110	126	-8	78	80	111
-3	147	150	76	2	164	160	80	-5	29	26	159	-7	115	120	98
-2	161	159	74	3	145	146	84	-4	79	84	131	-6	56	51	88
-1	326	319	74	4	132	133	87	-3	151	151	124	-5	171	162	76
0	425	417	55	5	35	37	105	-2	26	30	171	-4	244	221	67
1	142	135	58	6	84	85	86	-1	86	88	129	-3	107	102	60
2	178	175	63	7	43	45	85	0	8	4	373*	-2	134	132	55
3	140	136	69		1, 7, 1			1	143	138	88	-1	71	61	54
4	17	11	133	-12	10	6	173	2	2	2	1617*	0	87	90	40
5	213	210	81	-11	47	45	118	3	75	71	105	1	154	150	43
6	66	64	89	-10	69	71	122	4	24	21	143	2	76	78	50
7	46	50	92	-9	40	37	140		1, 10, 1			3	303	284	55
8	31	28	99	-8	26	24	170	-9	11	12	348*	4	151	144	63
9	4	0	552*	-7	2	5	2458*	-8	70	66	114	5	226	231	70
	1, 5, 1			-6	80	89	119	-7	11	10	354*	6	42	34	84
-12	48	46	113	-5	118	117	114	-6	65	65	122	7	120	124	84
-11	21	16	151	-4	62	65	116	-5	2	3	2074*	8	5	4	656*
-10	51	50	130	-3	159	166	109	-4	2	2	2472*	9	2	6	1683*
-9	100	100	124	-2	132	130	109	-3	2	1	2038*	10	33	30	90
-8	2	3	2267*	-1	35	35	122	-2	74	73	125		2, 2, 1		
-7	148	144	109	0	95	90	81	-1	48	44	124	-13	22	19	127
-6	9	6	175	1	50	48	89	0	29	28	113	-12	31	32	144
-5	95	96	95	2	47	40	94	1	10	12	337*	-11	35	35	140
-4	25	16	106	3	138	128	89	2	33	28	111	-10	65	68	126
-3	363	362	86	4	72	73	90		1, 11, 1			-9	62	62	123
-2	196	191	85	5	26	25	99	-7	2	8	1937*	-8	41	39	117
-1	242	234	86	6	12	13	139	-6	9	0	304*	-7	129	122	99
0	31	37	70		1, 8, 1			-5	17	21	293	-6	58	50	90
1	184	180	67	-11	11	10	356*	-4	16	16	254	-5	173	164	78
2	121	119	71	-10	8	13	549*	-3	40	43	167	-4	230	218	71

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	2, 2, 1			-2	58	58	83	4	8	9	456*	-2	81	77	128
-3	506	506	308	-1	323	319	82	5	21	24	131	-1	51	52	130
-2	73	79	62	0	15	9	125	6	21	20	128	0	9	7	255*
-1	31	32	67	1	303	297	64	7	33	34	112	1	23	25	129
0	195	193	46	2	129	126	69		2, 7, 1			2	2	8	1487*
1	172	163	49	3	245	231	74	-12	7	4	412*	3	25	27	142
2	31	30	60	4	13	9	183	-11	34	30	123		2, 10, 1		
3	303	291	61	5	116	112	85	-10	16	13	187	-9	33	32	113
4	352	345	68	6	59	65	90	-9	112	107	125	-8	2	2	1975*
5	118	112	76	7	21	24	111	-8	190	192	124	-7	22	19	159
6	62	58	87	8	59	60	80	-7	44	45	136	-6	11	3	302*
7	12	13	276*		2, 5, 1			-6	131	136	120	-5	35	42	130
8	29	25	111	-12	2	1	2052*	-5	2	3	2198*	-4	42	37	133
9	87	86	82	-11	38	38	132	-4	9	7	561*	-3	103	101	119
10	40	42	74	-10	11	12	425*	-3	2	8	2148*	-2	17	13	170
	2, 3, 1			-9	96	98	125	-2	78	82	117	-1	30	22	121
-13	23	21	118	-8	16	17	216	-1	77	78	119	0	18	16	159
-12	12	4	328*	-7	74	81	115	0	268	266	85	1	35	36	136
-11	55	52	128	-6	39	38	113	1	189	188	87		2, 11, 1		
-10	171	173	124	-5	90	98	100	2	15	13	183	-6	44	43	147
-9	10	14	490*	-4	84	85	96	3	12	16	302*	-5	35	32	174
-8	270	269	110	-3	86	82	93	4	13	14	235	-4	15	17	261
-7	39	42	108	-2	76	85	94	5	73	72	81	-3	38	35	163
-6	296	300	91	-1	160	167	94	6	25	27	126		3, 0, 1		
-5	287	281	83	0	132	130	69		2, 8, 1			0	84	81	44
-4	84	93	78	1	37	37	78	-11	9	5	300*	1	292	284	47
-3	150	147	72	2	40	42	85	-10	26	28	142	2	463	455	73
-2	80	79	71	3	47	45	89	-9	71	69	123	3	106	109	59
-1	111	112	71	4	97	95	87	-8	52	46	127	4	41	42	69
0	139	144	53	5	27	24	107	-7	54	49	132	5	69	63	74
1	272	269	57	6	46	45	90	-6	13	17	416*	6	40	42	87
2	29	22	72	7	50	51	87	-5	22	16	152	7	95	87	85
3	13	13	147	8	11	14	124	-4	71	71	124	8	69	67	90
4	254	239	74		2, 6, 1			-3	69	69	126	9	111	110	83
5	147	145	80	-12	21	19	142	-2	99	100	125	10	61	58	74
6	166	162	86	-11	36	34	129	-1	13	3	211		3, 1, 1		
7	43	50	95	-10	2	1	2335*	0	43	49	98	-13	38	39	107
8	18	8	143	-9	22	21	173	1	28	27	100	-12	7	9	532*
9	2	2	1419*	-8	75	82	126	2	88	82	88	-11	53	56	130
	2, 4, 1			-7	178	184	117	3	24	25	100	-10	108	104	125
-12	70	70	116	-6	84	82	113	4	61	61	102	-9	79	75	122
-11	31	33	141	-5	30	21	130		2, 9, 1			-8	132	128	109
-10	21	18	209	-4	105	104	107	-10	38	36	114	-7	207	205	98
-9	30	38	155	-3	155	165	103	-9	63	62	115	-6	146	142	89
-8	115	113	114	-2	140	139	104	-8	23	23	150	-5	343	328	80
-7	61	64	110	-1	24	26	136	-7	54	53	123	-4	439	405	73
-6	97	92	97	0	259	249	77	-6	18	22	204	-3	181	178	67
-5	21	21	110	1	205	196	80	-5	89	91	126	-2	97	104	65
-4	68	64	86	2	93	98	87	-4	12	15	487*	-1	184	195	64
-3	278	283	82	3	45	43	95	-3	52	49	130	0	14	15	69

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	3, 1, 1			2	99	96	69	7	14	13	101	-1	24	23	170
1	404	396	52	3	96	88	75		3, 6, 1			0	12	9	257*
2	350	326	56	4	202	198	80	-12	34	30	116	1	43	43	106
3	222	228	63	5	54	54	91	-11	42	40	128	2	45	43	122
4	17	15	100	6	87	85	88	-10	46	49	132	3	32	27	108
5	345	328	76	7	2	1	1523*	-9	2	6	2423*		3, 9, 1		
6	67	68	85	8	36	29	83	-8	9	14	565*	-10	47	44	101
7	83	85	89		3, 4, 1			-7	69	78	125	-9	50	46	115
8	51	47	89	-13	26	19	120	-6	8	8	552*	-8	2	0	2188*
9	21	20	118	-12	45	42	119	-5	24	25	132	-7	34	32	129
	3, 2, 1			-11	37	39	136	-4	124	128	112	-6	34	37	150
-13	7	7	445*	-10	11	7	345*	-3	150	149	111	-5	51	57	131
-12	58	58	117	-9	20	18	169	-2	75	77	114	-4	20	21	160
-11	17	20	205	-8	85	89	119	-1	18	20	185	-3	2	4	2185*
-10	2	5	1935*	-7	3	4	1357*	0	93	93	84	-2	64	61	123
-9	111	107	118	-6	62	52	105	1	116	115	86	-1	27	29	229
-8	12	10	392*	-5	66	61	98	2	125	120	87	0	92	88	103
-7	73	78	103	-4	66	60	95	3	87	84	90	1	93	95	101
-6	92	94	92	-3	325	319	90	4	42	41	92		3, 10, 1		
-5	160	153	83	-2	251	253	89	5	10	12	212*	-8	27	31	121
-4	304	296	77	-1	154	148	91	6	55	54	94	-7	2	7	1845*
-3	5	12	480*	0	87	89	68		3, 7, 1			-6	6	4	565*
-2	222	217	71	1	181	176	71	-11	40	40	124	-5	42	44	173
-1	38	44	77	2	243	229	76	-10	17	10	170	-4	57	57	141
0	422	393	53	3	29	29	101	-9	40	40	140	-3	10	14	393*
1	15	18	85	4	123	122	85	-8	38	36	134	-2	34	35	167
2	308	292	62	5	58	60	90	-7	59	61	131	-1	43	45	171
3	286	283	68	6	42	40	92	-6	110	102	123		4, 0, 1		
4	95	92	75	7	43	43	86	-5	52	51	128	0	44	53	54
5	96	101	82	8	30	33	96	-4	35	39	133	1	12	9	116
6	66	68	89		3, 5, 1			-3	144	148	120	2	30	22	67
7	92	95	88	-12	47	49	114	-2	30	26	143	3	59	53	69
8	100	91	84	-11	2	6	2178*	-1	45	41	131	4	211	210	73
9	49	49	77	-10	121	118	125	0	34	29	99	5	39	27	88
	3, 3, 1			-9	104	96	124	1	87	78	89	6	60	60	88
-13	51	48	99	-8	74	78	124	2	62	68	93	7	85	87	88
-12	10	16	406*	-7	68	63	119	3	2	12	1629*	8	14	13	286*
-11	78	75	126	-6	177	175	108	4	81	81	100	9	58	55	80
-10	75	73	127	-5	299	295	104	5	38	36	119		4, 1, 1		
-9	49	54	134	-4	173	175	101		3, 8, 1			-13	44	42	108
-8	19	15	177	-3	143	149	100	-11	20	21	134	-12	10	7	368*
-7	64	60	107	-2	212	217	100	-10	40	39	127	-11	32	30	145
-6	2	7	1843*	-1	2	9	1805*	-9	13	14	202	-10	77	82	127
-5	149	149	89	0	89	86	76	-8	63	64	128	-9	69	66	123
-4	90	88	85	1	228	224	79	-7	40	37	142	-8	27	19	134
-3	24	24	93	2	140	145	83	-6	31	36	138	-7	14	5	163
-2	159	152	79	3	72	76	88	-5	50	57	134	-6	112	113	94
-1	116	116	81	4	9	5	263*	-4	87	92	129	-5	266	257	85
0	6	11	195*	5	112	109	87	-3	35	33	140	-4	134	138	80
1	46	41	67	6	11	6	239*	-2	32	31	141	-3	113	106	77

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	4, 1, 1			0	59	64	70	-12	28	30	125	-8	8	10	401*
-2	85	82	75	1	158	144	71	-11	18	10	142	-7	28	31	128
-1	126	120	76	2	211	206	76	-10	87	84	121	-6	19	18	175
0	21	18	67	3	95	90	82	-9	93	87	126	-5	87	84	119
1	300	281	60	4	149	154	85	-8	32	31	154	-4	55	56	121
2	194	192	65	5	25	30	111	-7	100	95	124	-3	22	23	243
3	39	43	75	6	13	10	222	-6	30	34	160	-2	28	31	226
4	155	161	77	7	59	56	81	-5	30	34	141	-1	50	48	147
5	49	47	91		4, 4, 1			-4	115	120	119	0	57	62	114
6	45	39	93	-12	47	41	112	-3	32	33	153		4, 10, 1		
7	2	3	1574*	-11	23	23	156	-2	226	223	118	-5	6	13	632*
8	100	91	81	-10	49	41	129	-1	152	156	120	-4	10	14	399*
9	61	59	72	-9	3	2	1584*	0	70	69	90		5, 0, 1		
	4, 2, 1			-8	7	1	637*	1	38	38	98	0	99	92	61
-13	2	8	1605*	-7	121	124	113	2	33	32	101	1	164	159	64
-12	69	68	118	-6	157	159	108	3	62	65	92	2	126	115	69
-11	83	79	127	-5	151	146	103	4	37	34	88	3	128	117	75
-10	3	13	1719*	-4	21	25	131	5	52	57	100	4	182	174	80
-9	42	29	124	-3	172	172	99		4, 7, 1			5	27	23	99
-8	174	178	112	-2	43	37	111	-11	93	92	108	6	20	19	128
-7	126	127	105	-1	46	45	107	-10	42	45	121	7	88	83	86
-6	22	21	113	0	6	6	336*	-9	61	62	125	8	2	2	1530*
-5	16	18	126	1	20	6	114	-8	112	110	124		5, 1, 1		
-4	13	18	144	2	149	152	82	-7	33	28	146	-12	30	30	134
-3	26	27	97	3	48	48	93	-6	8	12	714*	-11	11	2	364*
-2	109	112	82	4	71	65	89	-5	12	14	412*	-10	177	180	125
-1	19	26	107	5	27	23	104	-4	75	80	127	-9	34	35	135
0	129	123	62	6	53	52	85	-3	90	90	127	-8	161	156	116
1	161	158	65	7	2	7	1249*	-2	12	1	204	-7	104	94	108
2	23	21	87		4, 5, 1			-1	18	15	259	-6	13	21	344*
3	325	309	76	-12	25	22	122	0	25	21	106	-5	46	41	96
4	39	34	93	-11	2	1	2477*	1	34	29	99	-4	218	213	89
5	121	124	86	-10	2	3	1997*	2	24	24	118	-3	48	47	91
6	52	52	91	-9	2	5	2287*	3	2	1	1429*	-2	16	22	110
7	34	30	96	-8	31	39	137		4, 8, 1			-1	104	100	88
8	39	37	85	-7	79	77	119	-10	57	53	107	0	76	85	66
	4, 3, 1			-6	40	36	124	-9	32	32	124	1	122	123	69
-13	26	28	118	-5	85	88	114	-8	2	3	1927*	2	8	7	343*
-12	18	14	184	-4	109	113	111	-7	24	25	154	3	41	36	86
-11	25	23	172	-3	132	144	109	-6	2	4	2144*	4	107	105	84
-10	37	37	142	-2	35	29	128	-5	31	27	142	5	96	98	87
-9	65	71	127	-1	108	108	113	-4	53	46	131	6	50	50	92
-8	120	116	115	0	129	125	82	-3	82	76	125	7	89	87	82
-7	87	80	111	1	115	115	85	-2	17	19	309	8	25	25	90
-6	68	66	103	2	16	18	175	-1	10	7	529*		5, 2, 1		
-5	27	28	111	3	19	18	138	0	6	6	349*	-13	17	19	129
-4	389	371	92	4	18	18	115	1	2	2	1232*	-12	71	73	117
-3	125	122	90	5	37	32	88	2	31	33	125	-11	2	11	2464*
-2	115	104	90	6	14	12	178		4, 9, 1			-10	45	43	130
-1	160	161	92		4, 6, 1			-9	26	25	120	-9	55	60	127

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	5, 2, 1			-1	136	133	113	-6	69	75	129	2	102	99	82
-8	25	24	152	0	143	136	82	-5	12	17	418*	3	55	51	88
-7	70	70	111	1	32	25	103	-4	36	33	138	4	35	33	100
-6	59	56	106	2	38	39	96	-3	30	34	145	5	52	50	90
-5	65	67	100	3	54	54	92	-2	48	46	126	6	33	34	91
-4	105	96	96	4	49	54	95	-1	57	59	125	7	72	70	71
-3	132	134	93	5	40	39	85	0	18	25	124		6, 2, 1		
-2	217	210	93	6	8	1	252*	1	95	98	99	-12	27	24	121
-1	83	81	96		5, 5, 1			2	119	124	95	-11	2	2	2213*
0	130	128	70	-12	33	30	113		5, 8, 1			-10	74	73	130
1	24	27	101	-11	21	19	147	-9	24	24	141	-9	107	104	125
2	110	107	79	-10	105	102	121	-8	14	16	224	-8	30	33	150
3	163	163	82	-9	32	31	140	-7	76	76	115	-7	75	74	118
4	19	24	129	-8	144	145	125	-6	30	29	126	-6	197	193	112
5	37	33	97	-7	120	116	124	-5	64	65	123	-5	91	86	110
6	100	92	84	-6	41	41	134	-4	9	10	486*	-4	9	8	391*
7	3	9	1013*	-5	116	117	118	-3	74	74	120	-3	97	98	106
	5, 3, 1			-4	6	4	738*	-2	57	57	118	-2	139	135	105
-12	18	19	169	-3	118	120	119	-1	97	97	147	-1	12	16	315*
-11	38	34	140	-2	165	172	119	0	25	23	135	0	113	110	79
-10	5	9	1026*	-1	229	231	120		5, 9, 1			1	13	20	300*
-9	146	145	125	0	64	69	89	-7	10	5	176	2	197	194	85
-8	103	95	121	1	76	81	90	-6	26	26	178	3	73	76	88
-7	21	18	165	2	92	97	89	-5	2	0	1924*	4	2	3	1564*
-6	28	20	133	3	55	55	88	-4	19	27	256	5	9	8	251*
-5	148	154	104	4	50	50	82	-3	34	36	167	6	47	45	78
-4	151	156	101	5	33	30	82		6, 0, 1				6, 3, 1		
-3	20	15	118		5, 6, 1			0	228	224	70	-12	44	46	117
-2	42	44	105	-11	32	29	115	1	64	63	76	-11	56	51	117
-1	146	154	104	-10	31	30	140	2	48	46	82	-10	34	32	140
0	85	83	77	-9	2	3	2512*	3	169	164	82	-9	9	1	474*
1	131	137	80	-8	32	23	142	4	96	97	86	-8	57	60	128
2	41	41	90	-7	13	11	398*	5	95	88	88	-7	116	105	120
3	38	44	98	-6	45	39	129	6	11	2	176	-6	140	133	117
4	7	13	477*	-5	52	53	131	7	75	73	79	-5	58	54	118
5	21	24	136	-4	138	141	123		6, 1, 1			-4	109	105	114
6	37	37	89	-3	32	28	142	-12	44	46	123	-3	37	40	125
7	5	0	389*	-2	46	46	129	-11	31	33	138	-2	30	30	138
	5, 4, 1			-1	130	131	124	-10	21	19	186	-1	132	134	115
-12	30	29	122	0	62	59	92	-9	79	84	126	0	26	27	107
-11	67	63	122	1	19	23	122	-8	9	1	501*	1	182	184	85
-10	11	12	465*	2	68	64	85	-7	145	143	115	2	175	175	87
-9	51	50	135	3	55	51	104	-6	54	47	115	3	64	65	88
-8	85	90	126	4	16	16	154	-5	135	141	103	4	51	51	89
-7	105	112	120		5, 7, 1			-4	74	76	101	5	22	17	96
-6	92	90	117	-11	29	24	109	-3	84	85	99		6, 4, 1		
-5	103	108	112	-10	41	40	115	-2	8	11	424*	-12	11	9	339*
-4	104	101	110	-9	106	99	116	-1	167	163	101	-11	14	14	192
-3	218	209	109	-8	57	52	123	0	168	165	74	-10	35	36	130
-2	35	36	122	-7	41	43	135	1	17	16	103	-9	10	13	482*

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
6, 4, 1				-6	46	46	128	-6	26	29	153	-8	56	55	124
-8	85	82	126	-5	20	25	304	-5	18	22	193	-7	76	72	123
-7	8	12	596*	-4	43	44	124	-4	33	31	142	-6	67	70	127
-6	17	18	172	-3	19	23	171	-3	82	74	117	-5	106	109	123
-5	54	52	123	-2	62	59	135	-2	71	70	118	-4	96	95	125
-4	31	37	136	-1	36	32	162	-1	37	37	140	-3	89	86	122
-3	38	42	136	0	33	39	128	0	84	86	87	-2	13	12	344*
-2	14	11	411*	6, 8, 1				1	82	81	88	-1	43	44	124
-1	77	82	128	-8	4	1	762*	2	20	12	115	0	49	54	88
0	78	77	89	-7	45	46	111	3	16	12	144	1	49	49	90
1	46	44	93	-6	53	52	147	4	40	42	87	2	83	85	88
2	37	34	96	-5	2	3	2247*	5	67	69	72	7, 6, 1			
3	84	86	84	-4	15	17	184	7, 3, 1				-10	46	45	107
4	42	43	82	-3	10	2	292*	-12	55	56	102	-9	41	39	123
6, 5, 1				-2	15	11	241	-11	2	10	1914*	-8	33	29	118
-11	69	69	111	7, 0, 1				-10	9	9	468*	-7	19	20	259
-10	33	28	130	0	65	61	82	-9	2	2	2406*	-6	13	19	417*
-9	49	51	125	1	170	170	82	-8	24	16	216	-5	10	9	396*
-8	95	90	125	2	9	1	402*	-7	116	117	125	-4	40	41	126
-7	117	109	125	3	239	238	86	-6	119	115	122	-3	84	83	117
-6	18	11	166	4	67	66	89	-5	118	120	121	-2	18	19	177
-5	60	59	129	5	42	39	90	-4	75	76	122	-1	55	54	149
-4	122	126	124	6	60	61	78	-3	82	88	123	0	74	77	99
-3	125	122	124	7, 1, 1				-2	141	143	121	7, 7, 1			
-2	13	11	223	-12	20	20	133	-1	82	82	126	-8	29	27	137
-1	56	53	129	-11	73	74	121	0	88	85	89	-7	71	72	105
0	90	89	88	-10	33	33	134	1	13	14	240	-6	57	56	111
1	2	3	1597*	-9	8	6	565*	2	4	0	776*	-5	13	15	282*
2	16	14	138	-8	69	64	124	3	9	5	287*	-4	2	12	2153*
3	35	36	91	-7	97	92	121	4	22	25	99	-3	22	23	207
6, 6, 1				-6	153	142	116	7, 4, 1				-2	34	33	146
-11	11	7	319*	-5	28	31	146	-11	41	36	114	8, 0, 1			
-10	60	57	113	-4	249	242	111	-10	12	15	370*	0	78	75	87
-9	106	107	117	-3	28	31	131	-9	123	115	120	1	44	43	92
-8	49	48	134	-2	80	79	113	-8	2	1	1908*	2	24	22	110
-7	9	6	520*	-1	66	64	118	-7	38	32	147	3	10	3	268*
-6	15	11	179	0	23	20	107	-6	35	32	141	4	26	25	96
-5	23	31	170	1	49	46	90	-5	9	12	543*	5	6	11	474*
-4	85	89	125	2	48	49	91	-4	118	122	126	8, 1, 1			
-3	27	29	152	3	96	98	88	-3	136	134	124	-11	54	50	117
-2	64	62	127	4	23	25	101	-2	68	72	125	-10	24	21	151
-1	87	87	123	5	31	31	91	-1	42	41	140	-9	23	21	197
0	28	24	116	6	21	22	93	0	26	27	115	-8	70	71	125
1	51	48	92	7, 2, 1				1	16	18	179	-7	10	0	433*
2	21	29	164	-12	8	14	486*	2	20	21	118	-6	79	77	125
6, 7, 1				-11	8	4	467*	3	32	34	83	-5	30	33	149
-10	2	6	1902*	-10	49	43	129	7, 5, 1				-4	7	3	679*
-9	23	21	126	-9	14	9	374*	-11	30	31	117	-3	81	81	124
-8	43	38	117	-8	13	5	235	-10	13	16	318*	-2	104	101	124
-7	2	1	2264*	-7	124	125	121	-9	24	21	140	-1	149	151	121

Columns are 10Fo 10Fc 1000Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
8, 1, 1				-6	25	28	154	0	17	16	159	-5	5	7	643*
0	87	90	88	-5	15	8	177	1	60	58	85	-4	2	0	1581*
1	91	91	88	-4	72	76	124	2	28	28	89	10, 0, 1			
2	106	106	86	-3	46	40	131	3	30	34	80	0	48	48	84
3	38	39	95	-2	73	71	123	9, 2, 1				1	18	18	116
4	32	32	86	-1	10	17	563*	-10	19	19	168	2	10	3	154
8, 2, 1				0	33	33	95	-9	26	26	151	10, 1, 1			
-11	25	25	140	1	33	28	81	-8	11	14	497*	-9	32	33	118
-10	30	29	134	8, 5, 1				-7	11	0	324*	-8	2	1	2163*
-9	64	65	128	-9	16	15	271	-6	7	6	766*	-7	51	53	120
-8	56	48	128	-8	89	88	111	-5	37	38	141	-6	94	89	116
-7	14	7	232	-7	31	32	129	-4	41	38	136	-5	71	66	121
-6	40	40	149	-6	94	96	117	-3	12	0	398*	-4	22	22	144
-5	171	165	122	-5	10	5	388*	-2	108	111	120	-3	34	32	131
-4	58	59	128	-4	29	26	138	-1	36	37	138	-2	69	69	118
-3	146	145	123	-3	49	47	114	0	35	36	93	-1	62	63	115
-2	23	23	158	-2	19	24	146	1	42	44	82	0	14	15	146
-1	121	121	123	-1	46	51	135	2	25	27	84	1	27	26	81
0	117	111	87	0	23	27	109	9, 3, 1				10, 2, 1			
1	2	6	1478*	8, 6, 1				-10	20	22	113	-9	36	33	110
2	12	9	188	-8	42	41	130	-9	65	58	110	-8	77	74	104
3	35	36	84	-7	2	11	2296*	-8	44	45	120	-7	39	35	122
4	30	32	78	-6	60	63	112	-7	111	106	115	-6	25	24	133
8, 3, 1				-5	22	23	137	-6	10	14	494*	-5	8	3	432*
-11	64	64	103	-4	31	29	107	-5	134	132	118	-4	27	28	138
-10	74	68	111	-3	25	25	168	-4	91	92	120	-3	84	84	112
-9	77	74	118	9, 0, 1				-3	50	52	126	-2	58	61	112
-8	47	43	133	0	136	134	86	-2	56	55	116	-1	50	50	103
-7	132	128	123	1	147	145	84	-1	64	66	113	10, 3, 1			
-6	9	4	456*	2	65	66	84	0	25	29	86	-8	42	43	99
-5	11	5	431*	3	63	62	77	1	3	4	676*	-7	26	25	130
-4	54	53	129	4	5	4	261*	9, 4, 1				-6	7	5	489*
-3	69	68	130	9, 1, 1				-9	27	27	114	-5	8	4	391*
-2	32	36	147	-11	2	4	1786*	-8	8	10	541*	-4	16	15	218
-1	112	116	124	-10	24	19	122	-7	27	29	135	-3	22	23	135
0	15	10	170	-9	58	54	119	-6	58	60	117	-2	28	29	180
1	34	37	91	-8	98	88	121	-5	40	42	120	11, 1, 1			
2	23	25	100	-7	86	86	124	-4	35	36	123	-7	37	41	104
3	51	49	70	-6	144	140	124	-3	25	26	134	-6	33	32	112
8, 4, 1				-5	2	6	2289*	-2	37	34	113	-5	25	26	121
-10	7	0	464*	-4	71	67	126	-1	10	19	350*	-4	68	69	103
-9	32	32	129	-3	12	8	237*	9, 5, 1				-3	70	70	103
-8	46	41	123	-2	139	138	123	-7	5	8	539*	-2	22	22	130
-7	88	88	124	-1	92	90	125	-6	8	4	165*				