CENTENARY LECTURE. Bridgehead Unsaturation in Compounds of Nature: A Proper Forum for Unleashing the Potential of Organic Synthesis

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1 Introduction

The group of compounds known as bridgehead olefins have held a unique position in the development of organic chemistry. In 1913, Bredt formulated a rule pointing out that reactions requiring the introduction of a bridgehead double bond would be directed to an alternative site or not operate at all.[1] This phenomenon exists in strained systems because the *p*-orbitals at the bridgehead carbon and vicinal trigonal centre are far from coparallel and exhibit no π-like character. The generalization no longer applies when the interconnective rings become sufficiently large.[2] The fact that (1)[3] and (2)[4] are isolable alkenes has established the criterion of ring size as a reliable indicator of kinetic stability.[5] Both (1) and (2) possess a level of strain energy comparable to that of the known *trans*-cyclooctene. Reduction of the number of atoms to the *trans*-cycloheptene level and below results in the transient existence of these substances.[6]

(1)   (2)

The fascinating structural environment offered by bridgehead olefins has not escaped the attention of Nature, which has chosen to produce a limited number of compounds of this class

for assumedly specific purposes in widely differing biochemical contexts. These developments have in turn aroused our interest in developing *de novo* synthetic routes to representative examples. Our goal has been to uncover with modern synthetic methods successful strategies that would provide alternatives to what Nature has so admirably perfected by enzymatic means. Regrettably, space limitations force us to deal provincially with research undertaken uniquely in these laboratories.

2 [3,3] Sigmatropy. Its Advantages and Consequences

One structural unit inextricably associated with [3,3] sigmatropy is the 1,5-diene (3). The success of conventional Cope rearrangements such as (3a)→(4a) rests on the greater thermodynamic stability of the product. The oxy-Cope variant is less reversible because the initially formed enol tautomerizes to the carbonyl derivative.[8] Enormous rate accelerations materialize under anionic conditions because the immediate product is a resonance-stabilized enolate anion.[7]

(3a, X = H)   (4a, X = H)
(b, X = OH)   (b, X = OH)
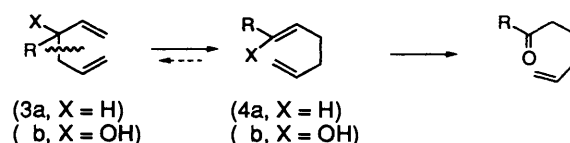
Application of the latter process to complex natural product synthesis holds many advantages. For example, the starting alcohols are amenable to preparation *via* a convergent coupling scheme [note wiggly line in (3)] that can be highly diastereoselective.[8] Also relevant is the regiospecificity with which the enolate anion (4; X = O⁻) is formed. Equally attractive is the very appreciable asymmetric transmission that arises because of adoption of a highly ordered transition state. While chair-like features are frequently adopted, boat alternatives are also energetically accessible if structurally imposed by the substrate. The conversion of (5) into (6) (chair arrangement)[9] and of (7) into (8) (boat topography)[10] is illustrative of these issues, which must be fully appreciated in each specific example as they dictate stereochemistry and double bond geometry concurrently. Note that (6) and (8) are bridgehead olefins. The facility with which this carbonyl regenerative scheme[11a] [the immediate precursors of (5) and (7) are norbornanones] can be applied to the rapid construction of elaborate unsaturated systems of this type is highlighted below.

On occasion, isomerization of the first-formed enolate anion occurs. This erosion of regiocontrol often can be attenuated to a non-troublesome level by the careful modulation of conditions. Less amenable to control are those secondary intramolecular reactions which the enolate may enter into because of the close proximity of a second reactive centre.[12] Two examples of the tandem pairing of the oxy-Cope rearrangement with a second chemical event are illustrated below.[13,14]

We shall also demonstrate herein that the venerable Claisen rearrangement,[15] a hetero variant of the Cope process, can also serve admirably well as a tool for constructing complex bridgehead olefinic natural products.[11b]

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Professor Paquette has been a visiting professor at numerous universities in the U.S. as well as in France and Germany. He has served in an advisory capacity on the Chemistry Division Advisory Committee of the National Science Foundation and the Medicinal Chemistry B Study Section of the National Institutes of Health. Currently, he is a member of the editorial boards of many journals, and is editor-in-chief of Organic Reactions.
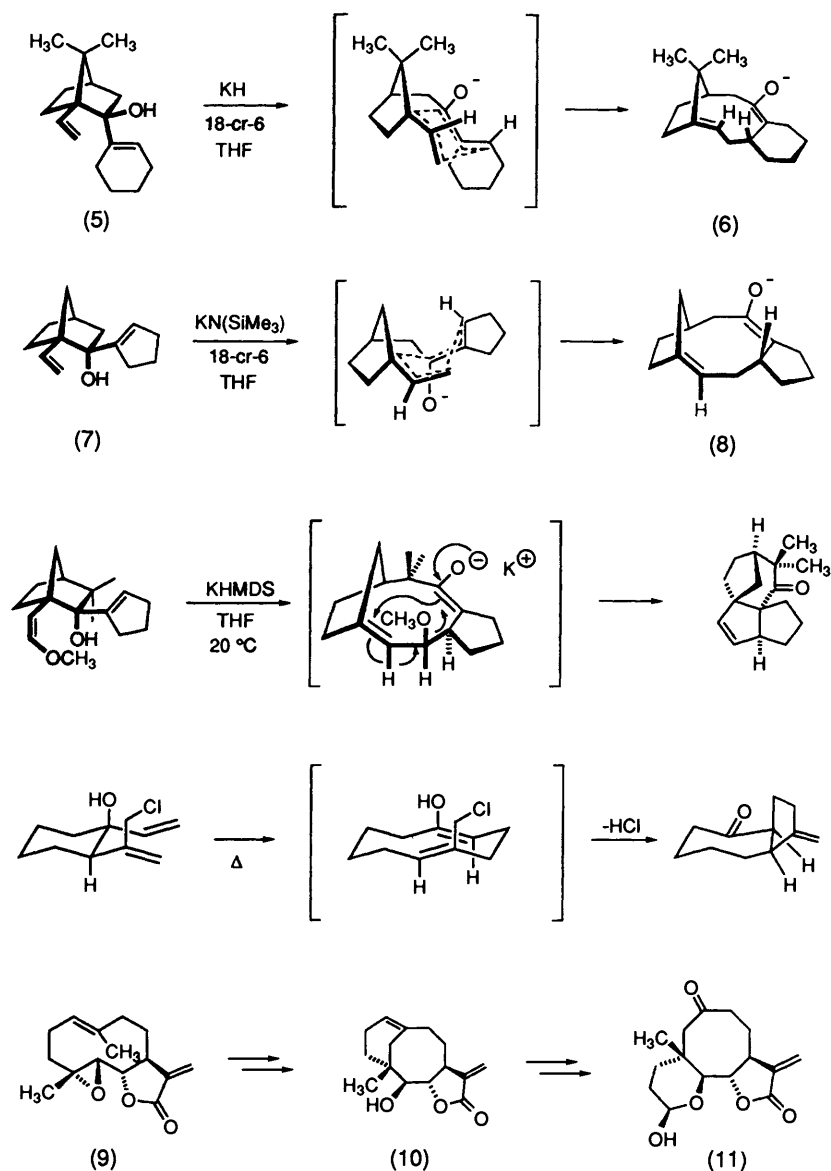
He has been honoured by the ACS on several occasions. He was the holder of a Guggenheim fellowship during the 1976–77 academic year, elected to the National Academy of Sciences in 1984, and named a Senior Humboldt fellow in 1989 and a Japanese Society for the Promotion of Science awardee in 1991.

KH
18-cr-6
THF

(5)

(6)

KN(SiMe₃)
18-cr-6
THF

(7)

(8)

KHMDS
THF
20 °C

-HCl

Δ

(9)

(10)

(11)

3 Biogenetic-like Synthesis of Vulgarolide

Vulgarolide (11) is a unique isoprenoid whose highly rearranged framework consists of two oxygenated rings serially fused across positions 3—6 of a cyclooctanone core.[16a] Biosynthetically, (11) is believed to arise from parthenolide (9) via (10), which suffers oxidative cleavage of its bridgehead double bond.[16b] Our projected end game was to utilize a close relative of (10) as a target of opportunity for accessing vulgarolide in enantioselective fashion.
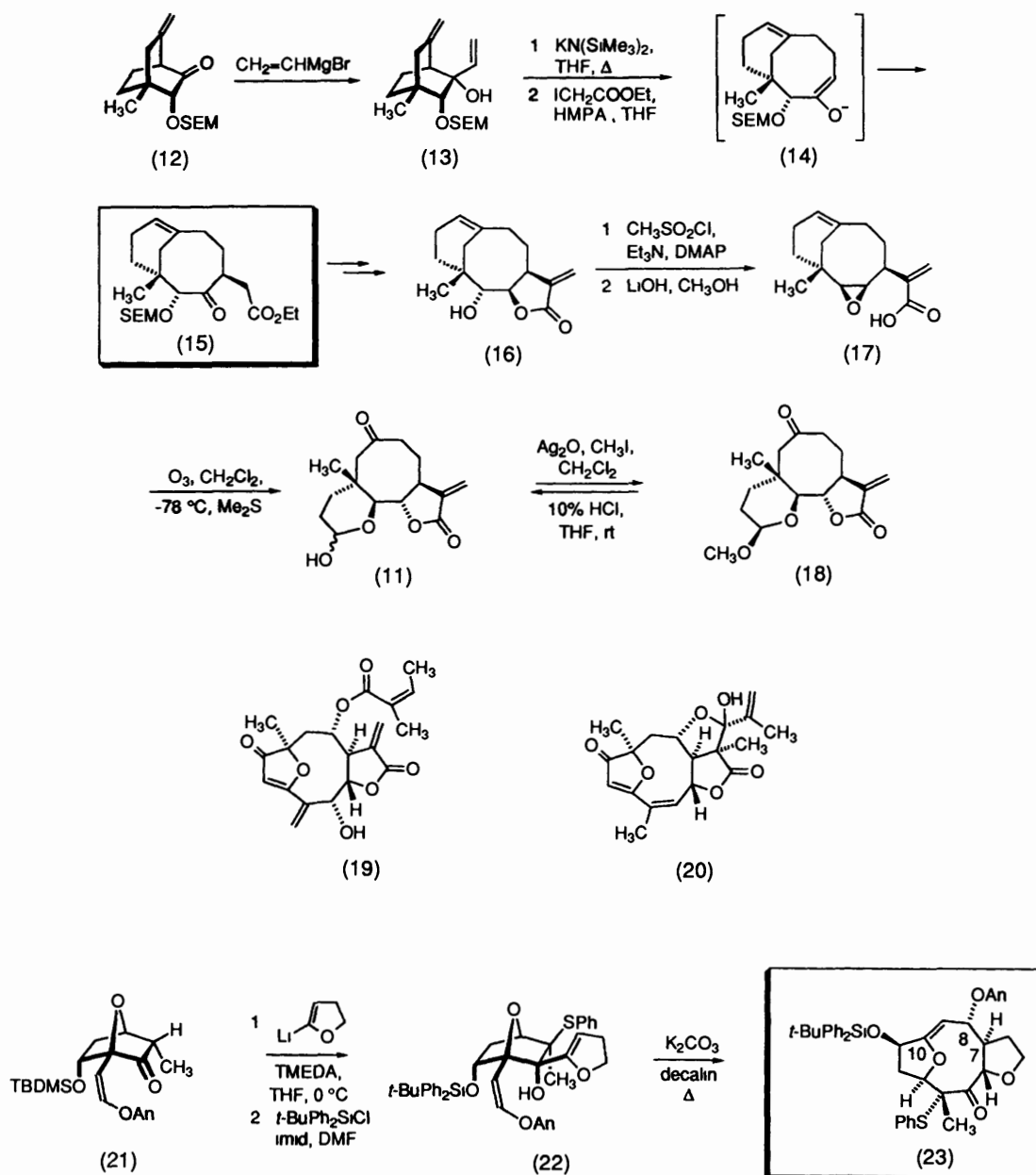
The acquisition of enantiomerically enriched (11) rests on the readiness with which bicyclo[2.2.2]octanone (12) can be resolved by means of Johnson's sulfoximine technology and the adoption of an exo trajectory during the 1,2-addition of vinyl-magnesium bromide to its carbonyl group. In a key manoeuvre, charge-accelerated sigmatropy within (13) proceeds via a chair-like transition state to generate enolate anion (14), whose in situ alkylation with ethyl iodoacetate delivers (15) (78%).[17] Once the subsequent conversion into (16) had been accomplished, the pre-planned element of our strategy, viz., initially to set the configurations of both CH—O stereogenic centres opposite to the corresponding ones in (11), is made apparent. Activation of the hydroxyl group in (16) in advance of lactone hydrolysis produces oxirane (17) with inversion of configuration at one of these centres. The ensuing regioselective ozonolysis of (17) triggers a spectacular cascade reaction that leads directly via a

second stereo-inversion step to vulgarolide and its epimer in a 1:1 ratio. Upon methylation, both of these lactols are transformed into O-methylvulgarolide (18), from which (11) can be regenerated by means of mild acid hydrolysis.[17]

4 Furanoheliangolide Construction

The ubiquitous class of biologically active 6,9-epoxycyclo-deca[b]furan sesquiterpenes share in common the structural feature of an oxygen atom directly linked to a bridgehead double bond.[18] Isocentratherin (19) and eremantholide C (20) are representative examples, for which synthetic precedent is scarce.[19]

Our own approach to the synthesis of these furanoheliango-lides has been to construct by means of furan-based Diels–Alder chemistry the heavily functionalized 7-oxanorbornanone (21). This β,γ-unsaturated ketone was considered to hold the prospect of accommodating all of the diverse levels of unsaturation ultimately demanded by the target compounds. Condensation of (21) with 4,5-dihydro-2-furanyllithium, a prototypical syn-thon for the lactone subunit, proceeds smoothly from the exo direction to deliver (22) after reprotection of the secondary hydroxyl. Fabrication of the desired polycyclic backbone was accomplished by heating (22) in decalin containing a small amount of potassium carbonate to guard against the adventi-

tious generation of acid which would hydrolyse the enol ether As expected, an *exo*-boat transition state was adhered to [compare (7)], thereby setting the proper stereochemical relationship at C-7 and C-8 in (23) Molecular mechanics calculations had indicated that the *trans*-fused B/C ring arrangement is thermodynamically advantaged This bias appears genuine as (23) is not prone to epimerization
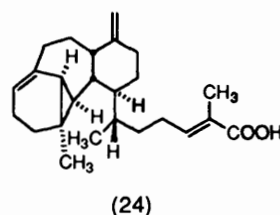
Thus, the facial selectivity of the 1,2 vinyl anion addition and the topological selectivity of the sigmatropic rearrangement are notably well coordinated for our intended purposes It remains to involve a nucleophile more highly oxygenated than the parent dihydrofuran, to introduce an angular methyl group at C-10, and to implement thermal sulfoxide extrusion in the proper context These studies are underway
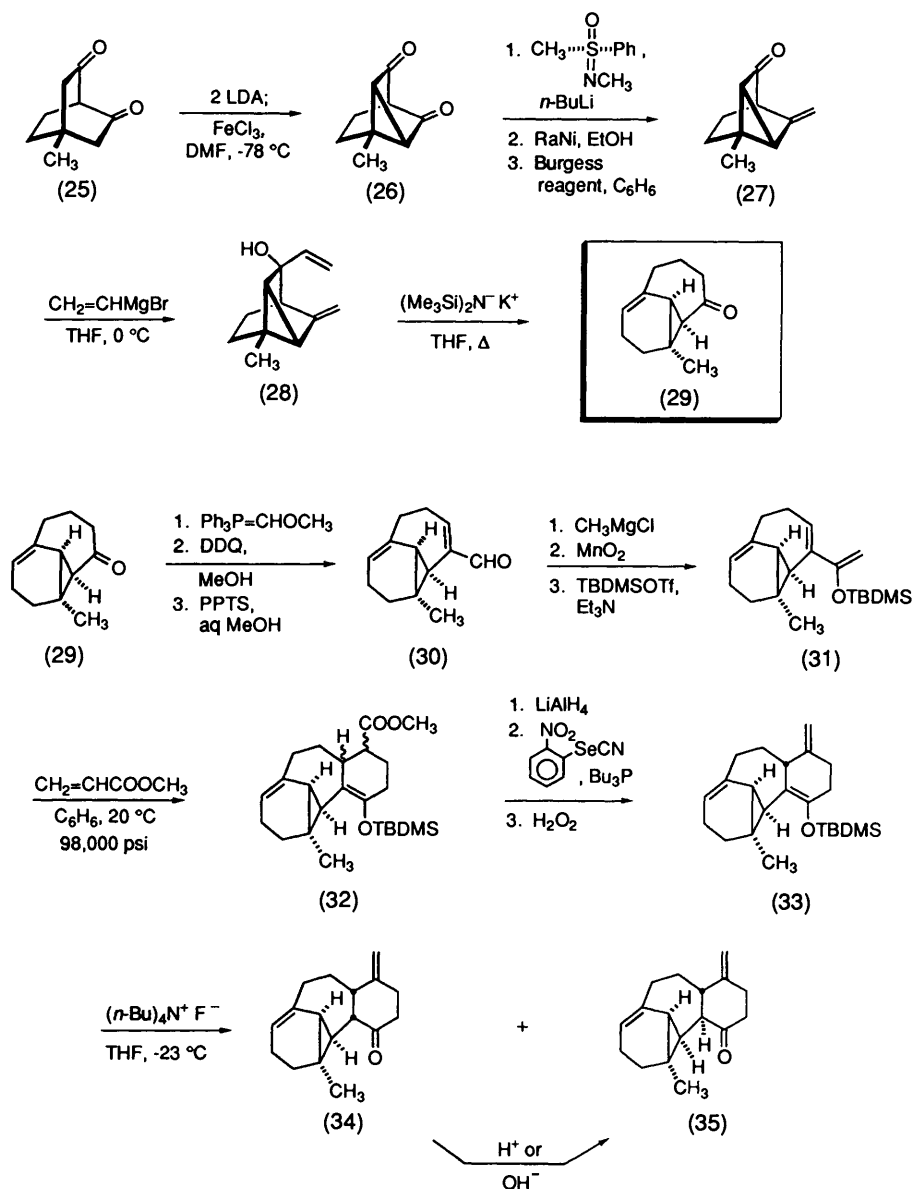
5 A Designed Approach to Cerorubenic Acid-III

Entomologists in Japan have convincingly established the existence of an especially high specificity between the encyrtid wasp *Anicetus beneficus* and the scale insect *Ceroplastes rubens* The latter, which serves as the host in this parasitic relationship,

controls the normal mating and feeding traits of the wasp by secreting five most unusual sesterterpenes These kairomones bring about recognition behaviour by contact chemoreception A principal component of the secretion is cerorubenic acid-III (24), the first natural substance recognized to possess a framework of this type [21]

A provocative feature of (24) is the vinylcyclopropane subunit so positioned in the ABC network that the double bond occupies a bridgehead site Notwithstanding its intricacy, this 'western' portion of cerorubenic acid-III can be rapidly elaborated by means of oxy-Cope technology Intramolecular oxidative coupling of the dienolate of (25) leads to (26), which can be

(25)   →   2 LDA;   FeCl₃,   DMF, -78 °C   →   (26)

1. CH₃····S̈····Ph , NCH₃   n-BuLi
2. RaNi, EtOH
3. Burgess reagent, C₆H₆   →   (27)

CH₂=CHMgBr   THF, 0 °C   →   (28)

(Me₃Si)₂N⁻ K⁺   THF, Δ   →   (29)

(29)

1. Ph₃P=CHOCH₃
2. DDQ, MeOH
3. PPTS, aq MeOH   →   (30)

1. CH₃MgCl
2. MnO₂
3. TBDMSOTf, Et₃N   →   (31)

CH₂=CHCOOCH₃   C₆H₆, 20 °C   98,000 psi   →   (32)

1. LiAlH₄
2. NO₂ —SeCN , Bu₃P
3. H₂O₂   →   (33)

(n-Bu)₄N⁺ F⁻   THF, -23 °C   →   (34)   +   (35)

H⁺ or OH⁻

concurrently desymmetrized and resolved to deliver both antipodes of (27).[22] The addition of vinylmagnesium bromide to (27) proceeds in highly stereoselective fashion to position the unsaturated centres proximal to each other as in (28). [3,3] Sigmatropic isomerization is thereby made possible as illustrated by the conversion into (29) upon heating with potassium hexamethyldisilazide in tetrahydrofuran. This ketone has all three stereogenic centres properly established and is also equipped with the requisite bridgehead unsaturation.

We have studied several tactics for annealing ring D to this very accessible tricyclic intermediate. The first approach begins with the homologation of (29) to α,β-unsaturated aldehyde (30) from which the dienyl enol ether (31) is crafted.[22a] Diels–Alder cycloaddition of methyl acrylate to (31) under high pressure conditions proceeds to give an 8:2 stereoisomeric mixture of esters (32), reductive elimination in which provides access predominantly to (33). When desilylation of (33) had established trans-fused ketone (35) to have much greater thermodynamic stability than the desired cis isomer (24), it became clear that no enolizable group could be positioned immediately adjacent to ring C if trans stereochemistry is to be preserved.
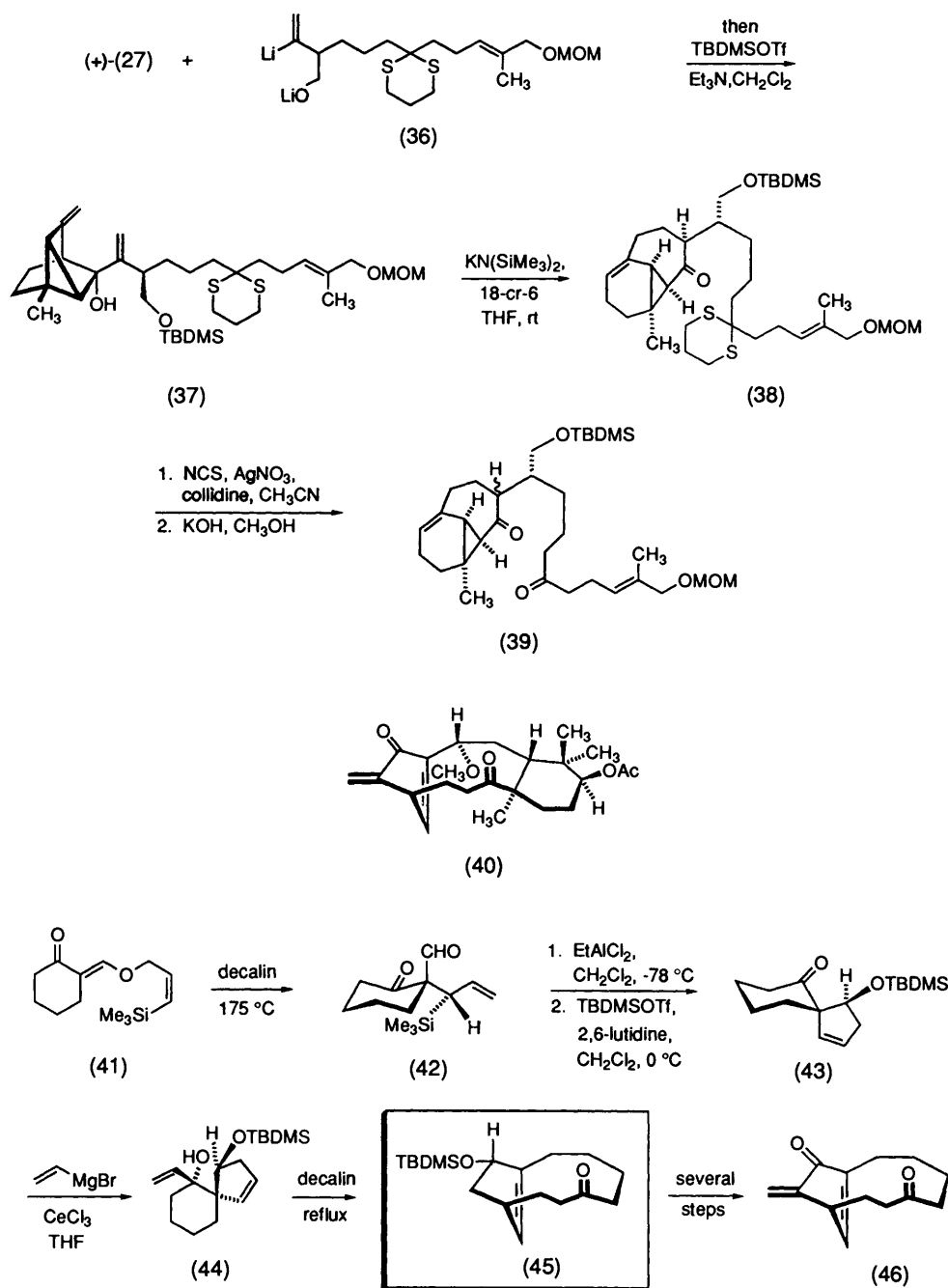
Next to be probed was the possibility of realizing ring D formation by means of extraannular Robinson annulation.[22b] To this end, the dilithio species (36) was condensed with (27) to give two allylic alcohols which are diastereomeric at the carbon

bearing the CH₂OH substituent (only one is shown). These adducts could be separated after O-silylation and were therefore taken separately through the oxy-Cope rearrangement and dithiane hydrolysis steps. We were pleased to find that the mechanistic events associated with the conversion of (37) into (38) are not altered as a consequence of ponderal effects brought on by the significantly larger sidechain involved in the migration. However, we have been singularly unable to bring about ring closure in (39) and its epimer. Although the presence of the vinylcyclopropane moiety precludes the use of acidic catalysts, adequate precedent exists for base-promoted variants of this pivotal cyclization.

Since an attempt to accomplish ring D cyclization by a more conventional intraannular Robinson approach also failed,[22c] an alternative strategy needs to be developed for proper fusion of the 'eastern' sector of cerorubenic acid-III onto (29). An assault on the proper resolution of these issues has been mounted.

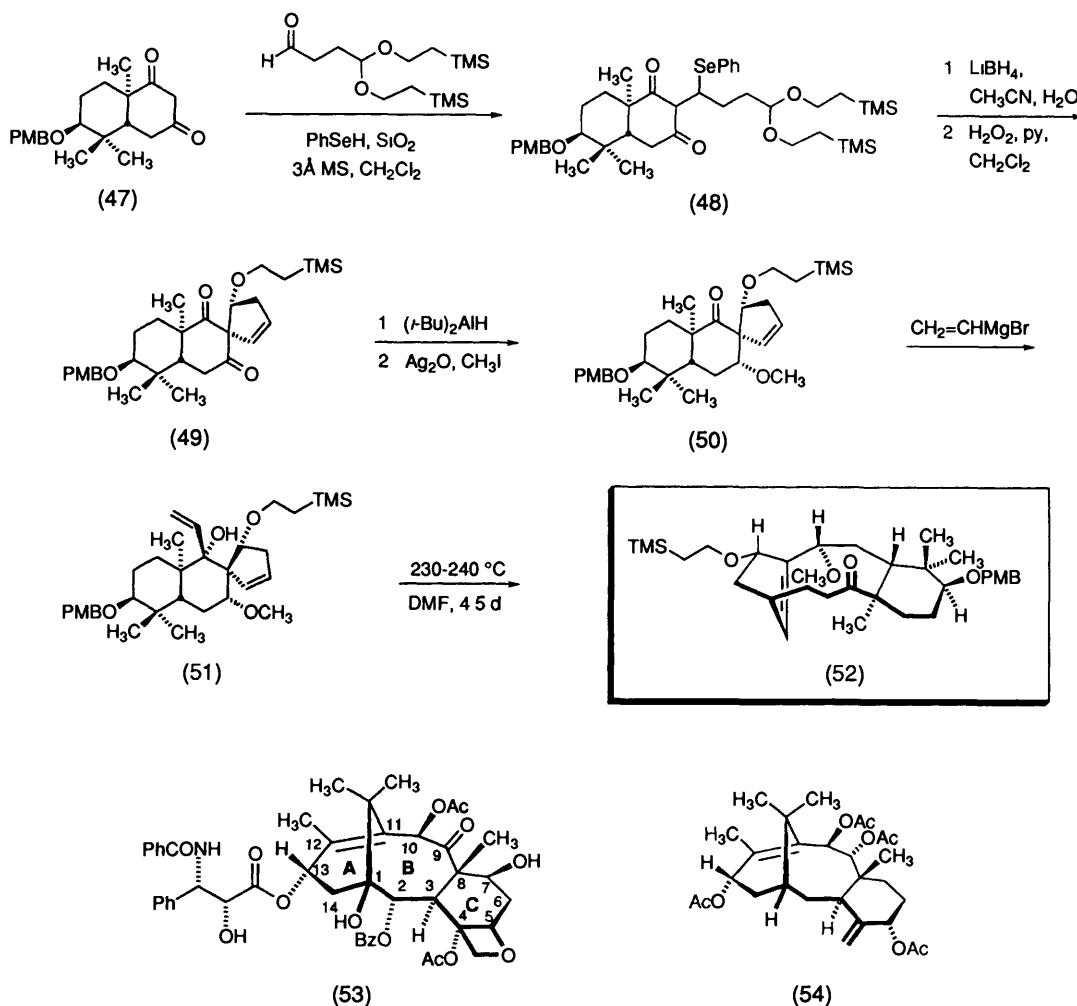## 6 Elaboration of the Cytotoxic 8,9-Seco-ent-kaurene Diterpenes

O-Methylshikoccin (40) and several closely related diterpenes have been identified as cytotoxic 8,9-seco-ent-kaurenes having an intracyclic double bond positioned at a bridgehead site.[23] The decision was made to explore initially via a model study the

(+)-(27) +

(36)

then
TBDMSOTf
─────────
Et₃N,CH₂Cl₂

(37)

KN(SiMe₃)₂,
18-cr-6
THF, rt

(38)

1. NCS, AgNO₃,
   collidine, CH₃CN
─────────
2. KOH, CH₃OH

(39)

(40)

(41)

decalin
─────────
175 °C

(42)

1. EtAlCl₂,
   CH₂Cl₂, -78 °C
─────────
2. TBDMSOTf,
   2,6-lutidine,
   CH₂Cl₂, 0 °C

(43)

MgBr
─────────
CeCl₃
THF

(44)

decalin
─────────
reflux

(45)

several
─────────
steps

(46)

possibility of preparing the pivotal A/B subunit of this generic class in a concise, stereocontrolled manner. Central to our thinking was the realization that the targeted bicyclo[7.2.1]dodec-1(12)-ene-6,11-dione core is related to spirocycle (44) via an oxy-Cope rearrangement.[24] In order to arrive at this precursor, 2-(hydroxymethylene)cyclohexanone was dehydratively coupled with (Z)-3-(trimethylsilyl)-2-propen-1-ol to give (41). Claisen rearrangement of this intermediate adheres strictly to a chair transition state geometry and furnishes exclusively the aldehyde (42). In turn, ethylaluminium dichloride promotes the intramolecular cyclization of (42) and conveniently delivers (43). Product stererochemistry in this instance stems from adoption by the Lewis acid complex of that antiperiplanar arrangement where aluminium coordination to oxygen operates from the less sterically encumbered direction anti to the R group of the aldehyde. Following 1,2-addition to (43) of the cerium reagent derived from vinylmagnesium bromide, the stage was set for the [3,3] sigmatropic event. Owing to the base sensitivity of (44), the

rearrangement is routinely performed in refluxing decalin. Such thermal activation results in efficient (92%) transformation into (45), which is subsequently transformed in routine fashion into (46).

As matters have turned out, the impressively concise series of manoeuvres leading to (43) could not be adapted to more conformationally rigidified trans-fused decalins. An alternative route was soon developed that took advantage of a tailored method for trapping the highly reactive Knoevenagel products formed between cyclohexane-1,3-diones such as (47) and aliphatic aldehydes.[25] The protocol involves simple stirring of a three-component mixture consisting of each reactant and thiophenol or phenylselenol in dichloromethane containing suspended silica gel. In this way, the highly reactive 2-alkylidene-1,3-dione is intercepted to give a stable Michael adduct such as (48). When a monoprotected succinaldehyde is involved, the important option exists for generation of a spirocyclic centre via intramolecular capture of an oxonium ion formed under Lewis acid

(47) → PhSeH, SiO2, 3Å MS, CH2Cl2 → (48)

1 LiBH4, CH3CN, H2O
2 H2O2, py, CH2Cl2

(49) → 1 (i-Bu)2AlH 2 Ag2O, CH3I → (50) → CH2=CHMgBr

(51) → 230–240 °C, DMF, 4 5 d → (52)

(53)

(54)

catalysis Subsequently, selenoxide elimination can be implemented to introduce the needed β,γ-unsaturation as in (49)

Following stereocontrolled introduction of the requisite methoxyl group, (50) is condensed with vinylmagnesium bromide to set the stage for uncatalysed oxy-Cope rearrangement, which is accomplished in 83% yield by heating (51) at 230—240 °C in dimethylformamide for 4 5 days Although (52) is currently our most advanced intermediate, its structural relationship to O-methylshikoccin (40) is unmistakable Efforts to realize the final linkup are under active investigation

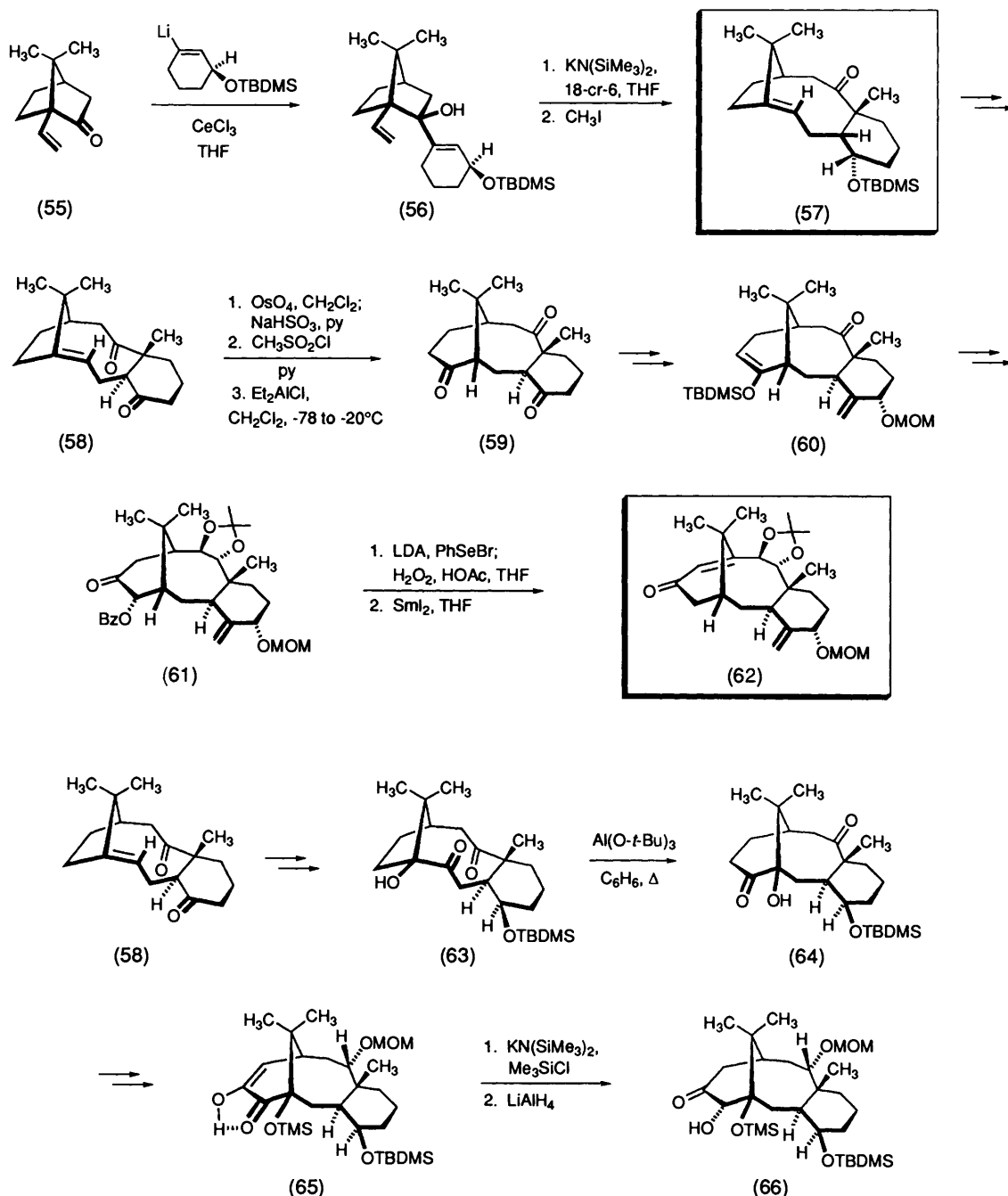## 7 Dual Synthesis of Taxusin and Taxol from Common Bridgehead Olefin Intermediates

The taxane diterpenes have been accorded an enormous level of synthetic attention in recent years, chiefly as a direct result of the remarkable effectiveness of taxol (53)[27a] in the treatment of ovarian cancer The taxane family may be formally divided into two sub-classes The first, which includes taxol, contains a bridgehead hydroxyl substituent Other members represented by taxusin (54)[27b] are not oxidized at C-1 One of our goals has been to devise a synthetic approach to both structural types starting from (+)-(1R)-camphor, an inexpensive precursor of the proper absolute configuration, that would involve bridgehead olefin intermediates capable of allowing bridge migration with total control of the C-1 oxidation level [28]

It has proven entirely feasible to produce ketones such as (57) via anionic oxy-Cope rearrangement of (56),[29a] to effect cis- → trans equilibration across the B/C ring fusion as in (58),[29b] and to engage the gem-dimethyl substituted bridge exclusively in a pinacol-like Wagner–Meerwein process to generate triketone

(59)[29c] The triad of carbonyl groups in (59) are easily differentiated,[29d] thereby allowing the conversion into (60) to proceed without event[29e] No logistical problems have been encountered in effecting proper carbonyl transposition within (60) to afford (61) and in carrying out regioselective introduction of the double bond as in (62)[29e] Only the C-12 methyl requires introduction and this need is being attended to

Bridgehead hydroxylation has been realized with equivalent satisfaction via an a-hydroxy ketone rearrangement, e g, (63)→(64)[29f] Oxygenation studies have unveiled the possibility of advancing (64) to (66) via (65)[29g] The plan is to complete ring A construction along lines comparable to those being worked out in the taxusin effort

With these accomplishments behind us, attention has been directed to the stereocontrolled introduction of the various additional oxygenated centres present in taxol These goals have been successfully realized in the following manner Since the pivotal oxy-Cope rearrangement operates stereospecifically, the geometry of the vinyl ether double bond in (67) is directly translated with complete configurational fidelity into the a-stereoisomeric product (68)[29h] Further, ketone (55) has proven amenable to efficient conversion into both (69) and its bridgehead enol ether analogue These additional oxido centres do not at all inhibit the oxy-Cope rearrangements, thereby allowing the 10-hydroxy substitution pattern of taxol to be quickly established either singly as in (71), or in tandem with C-2 functionality to give (73)[29i] The task presently before us is to merge the most relevant observations into a feasible route to the taxanes, with a continuing view to shortening the number of steps wherever possible With significant brevity might come a practical de novo synthesis of taxol
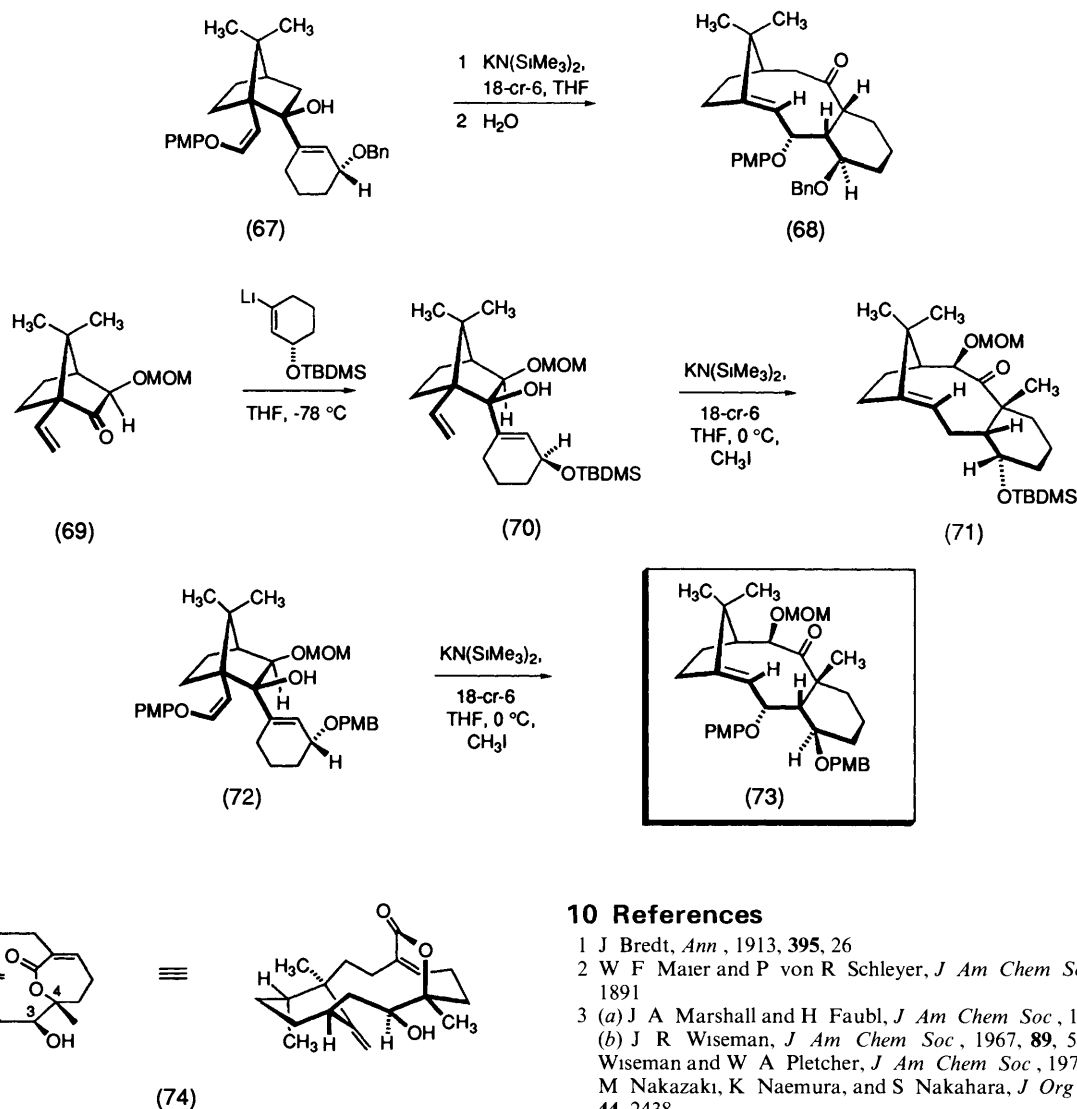
H3C CH3

Li

H
OTBDMS

CeCl3
THF

H3C CH3

OH

H
OTBDMS

(55)   **(56)**

1. KN(SiMe3)2,
   18-cr-6, THF
2. CH3I

H3C CH3

O
CH3

H

H

OTBDMS

(57)

H3C CH3

CH3

H

O

H

O

(58)

1. OsO4, CH2Cl2;
   NaHSO3, py
2. CH3SO2Cl
   py
3. Et2AlCl,
   CH2Cl2, -78 to -20°C

H3C CH3

O
CH3

O   H   H

O

(59)

H3C CH3

O
CH3

TBDMSO   H   H

OMOM

(60)

H3C CH3 O
O
CH3

O

BzO   H   H

OMOM

(61)

1. LDA, PhSeBr;
   H2O2, HOAc, THF
2. SmI2, THF

H3C CH3 O
O
CH3

O

H   H

OMOM

(62)

H3C CH3

CH3

H

O

H

O

(58)

H3C CH3

CH3

O
O

HO

H

H

OTBDMS

(63)

Al(O-t-Bu)3
C6H6, Δ

H3C CH3

O
CH3

O   OH   H

H   OTBDMS

(64)

H3C CH3

H   OMOM
CH3

O

H···O   OTMS   H

H   OTBDMS

(65)

1. KN(SiMe3)2,
   Me3SiCl
2. LiAlH4

H3C CH3

H   OMOM
CH3

O

HO   OTMS   H

H   OTBDMS

(66)

8 Enantioselective Synthesis of (+)-Cleomeolide

The unusual structural features of cleomeolide (74) include a nine-membered carbon chain cis-linked to a methylenecyclohexane subunit and a seven-membered lactone containing a double bond positioned at a bridgehead site.[30] In this instance, the key construction elements differ from those described above in that the unsaturated centre of interest is introduced via an intramolecular Wadsworth–Emmons cyclization. While the consequences of this process are replete with its own nuances, attention is focused on the particular steric demands associated with the western sector of (74). Several preliminary probe experiments clearly revealed to us that introduction of the exo-methylene group at C-15 could not be accomplished from a ketonic precursor after the flanking sidechains had been set in place.

The means devised for accomplishing proper molecular assembly in this highly congested sector ultimately relied on the serviceability of two Claisen rearrangements in tandem.[31] Once optically pure Wieland–Miescher ketone has been selectively

transformed into (75), the protected hydroxy ester (76) was generated by sequential O-methylation of the extended enolate, cleavage with m-chloroperbenzoic acid, and controlled reduction of the aldehyde functionality thereby produced. Arrival at this intermediate guaranteed the carbon–carbon connectivity in question, as reflected in the thermal activation of allyl vinyl ether (77). Although the [3,3] sigmatropic rearrangement proved intrinsically to be highly efficient, conformational biases introduced by the other cyclohexyl substituents cause (78) to be less prevalent than its axial epimer (ratio 1:2.7). This drawback is offset by the finding that both stereoisomers of (79) converge smoothly to the identical aldehyde (80) during Claisen rearrangement.

Activation of the position α to the cyano function requires temporary protection of the aldehyde. Once (81) was in hand, its exposure to potassium carbonate and 18-crown-6 in toluene proved most efficacious in effecting macrocyclization exclusively to (82). Note that both functionalized sidechains in (82) are directed equatorially as expected. This is not so in cleomeolide,

(67) → (68)

1 KN(SiMe₃)₂, 18-cr-6, THF
2 H₂O

(69) (70) (71)

Li / OTBDMS, THF, -78 °C

KN(SiMe₃)₂, 18-cr-6, THF, 0 °C, CH₃I

(72) → (73)

KN(SiMe₃)₂, 18-cr-6, THF, 0 °C, CH₃I

(74)

and a substantial conformational change therefore had to be dealt with in appropriate tactical fashion It was soon determined by MM2 calculations that positioning an oxirane ring on the sterically more hindered inner surface of the trisubstituted double bond in (83) would be met by conformational realignment in the intended direction The targeted diastereofacial epoxidation was achieved with silver(I) oxide and iodine in aqueous dioxane That the methyl ester of (84) does adopt the geometry akin to that of cleomeolide was deduced by means of NOE measurements Furthermore, acid-catalysed cyclization of (84) was met with spontaneous lactonization to give (74) This process is, in fact, reversible The close similarity of the high field ¹H NMR spectra of cleomeolide and its penultimate precursor is construed as added evidence for common adoption by both systems of related global energy conformational minima
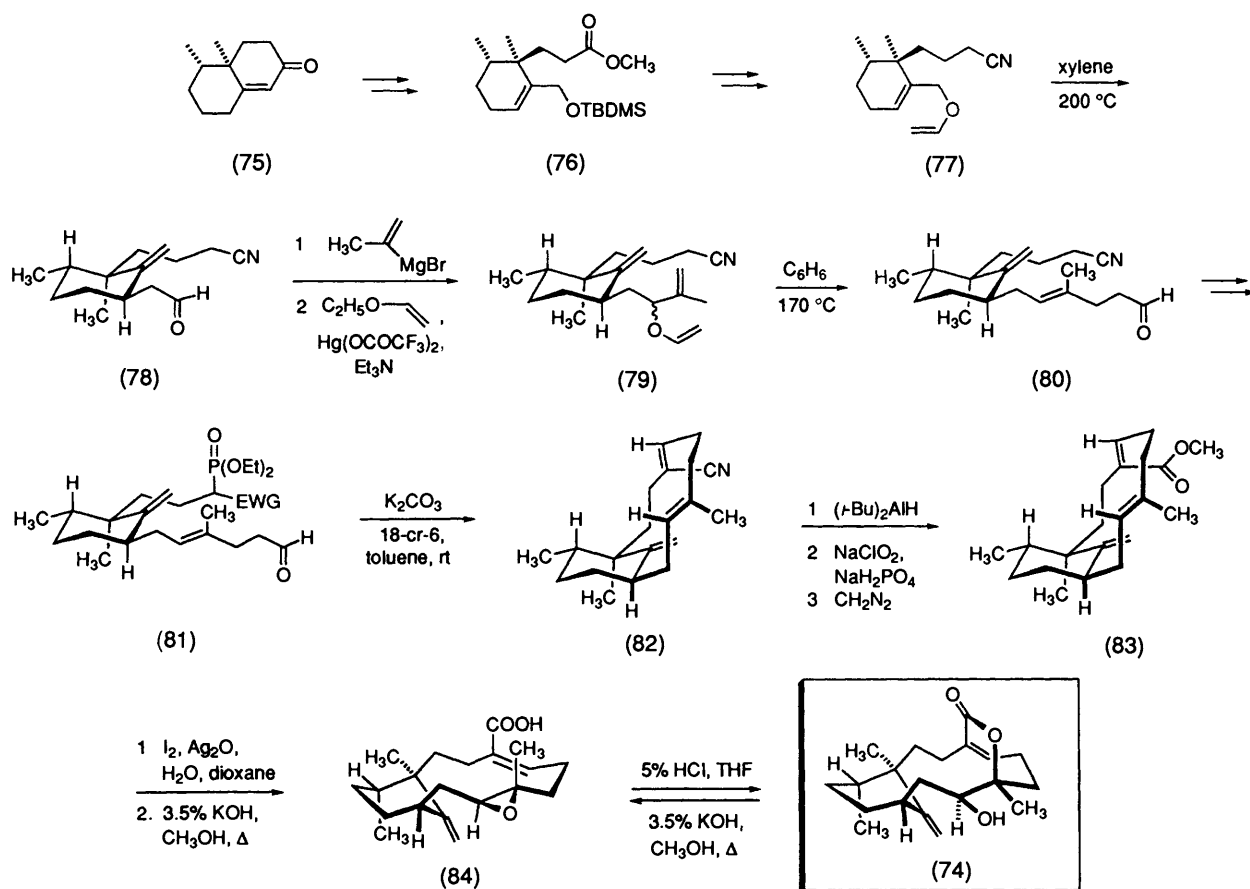
9 Conclusion

These studies demonstrate that enantioselective routes to natural products containing bridgehead unsaturation can be reliably based on the designed application of [3,3] sigmatropy The feasibility of such tactics provides the basis for their future adoption in a myriad of contexts that fall well outside the limited arena under discussion here It is now clear that the exceptional stereocontrol generally available has the potential to be utilized in tandem with other recognized transformations to achieve the rapid scaffolding of complex structure Synthetic efficiency will thereby be well served

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(75) (76) (77)

xylene
200 °C

(78)

1 H₃C MgBr
2 C₂H₅O , Hg(OCOCF₃)₂, Et₃N

(79)

C₆H₆
170 °C

(80)

(81)

K₂CO₃
18-cr-6,
toluene, rt

(82)

1 (ƒ-Bu)₂AlH
2 NaClO₂, NaH₂PO₄
3 CH₂N₂

(83)

1 I₂, Ag₂O,
H₂O, dioxane
2. 3.5% KOH,
CH₃OH, Δ

(84)

5% HCl, THF
3.5% KOH,
CH₃OH, Δ

(74)

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