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Bridgehead intermediates in organic synthesis: two direct syntheses of racemic lycopodine

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BRIDGEHEAD INTERMEDIATES IN ORGANIC SYNTHESIS: TWO DIRECT SYNTHESES OF RACEMIC LYCOPODINE

Iowa State University PH.D. 1985

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Bridgehead intermediates in organic synthesis: Two direct syntheses of racemic lycopodine

by

Yung-Son Hon

A Dissertation Submitted to the
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DOCTOR OF PHILOSOPHY

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For the Major Department

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For the Graduate College

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Ames, Iowa

1985

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GENERAL INTRODUCTION

"The chemists are a strange class of mortals, impelled by an almost insane impulse to seek their pleasure among smoke and vapor, soot and flame, poisons and poverty; yet among all these evils I seem to live so sweetly that may I die if I would change places with the Persian King."

Johann Becher

New reactions, reagents and methodologies are pursued by the synthetic organic chemist. This thesis will deal with the development of the bridgehead bond formation methodology. Racemic lycopodine was synthesized by way of this new methodology.

PART I. BRIDGEHEAD INTERMEDIATES IN ORGANIC SYNTHESIS

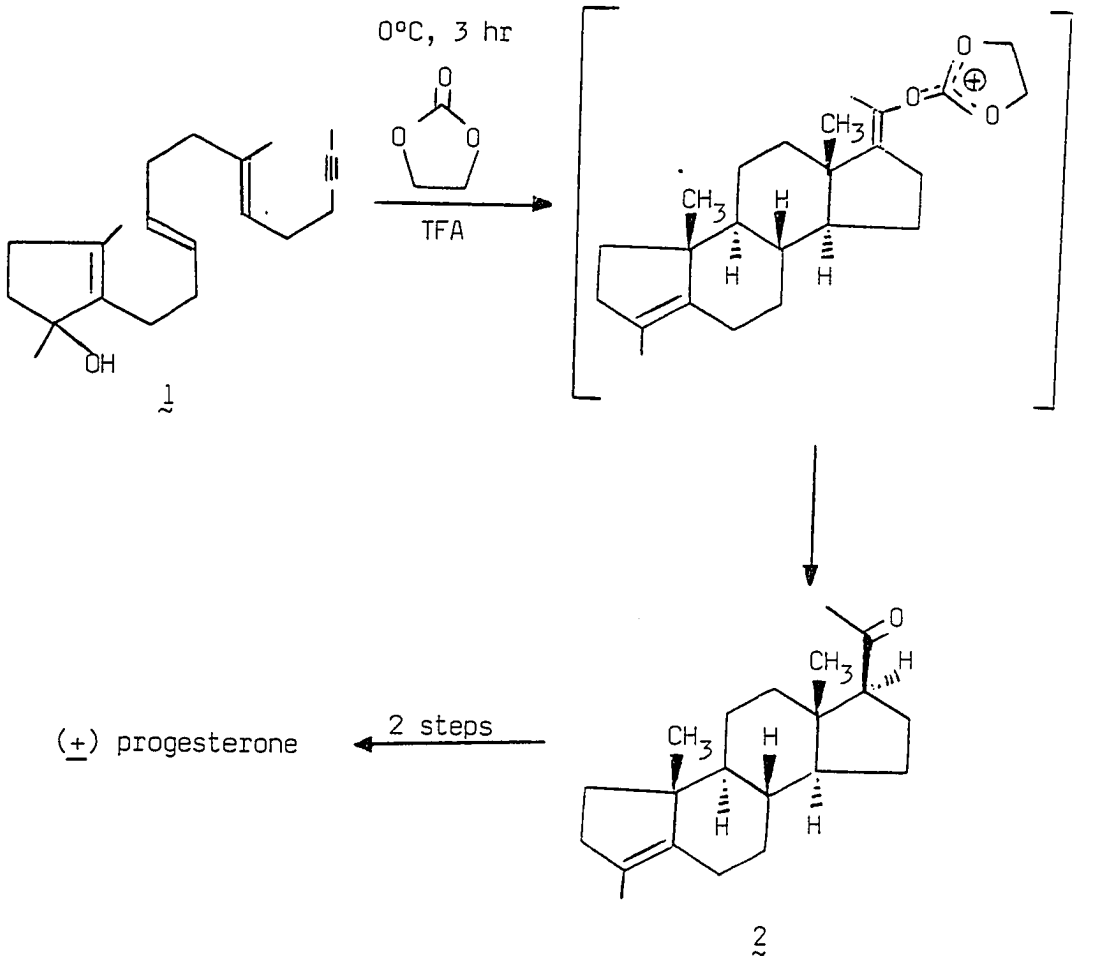
INTRODUCTION

Bridgehead Carbocation Chemistry

A carbocation can be a useful intermediate in organic synthesis only when the product derived from it is predictable and when the predictable product is the desired one. However, molecular rearrangement, non-regiospecific β-elimination and nonstereoselective nucleophilic attack on the planar carbocationic center yield complicated mixtures. Many organic chemists are looking for ways to solve those problems.

Professors W. S. Johnson and Van Tamelen have achieved the biogenetic type carbocationic polyene cyclizations (1,2). They used suitable initiators and terminators to effect the intramolecular cyclization. Acetal, allylic alcohol and epoxide moieties are effective initiators for the polyene cyclizations. Methylacetylenic end groups are particularly useful terminators since they lead to five-membered rings. The trienynol 1 was treated with trifluoroacetic acid (TFA) and ethylene carbonate. Basic workup provided the tetracyclic product 2 stereoselectively (3).

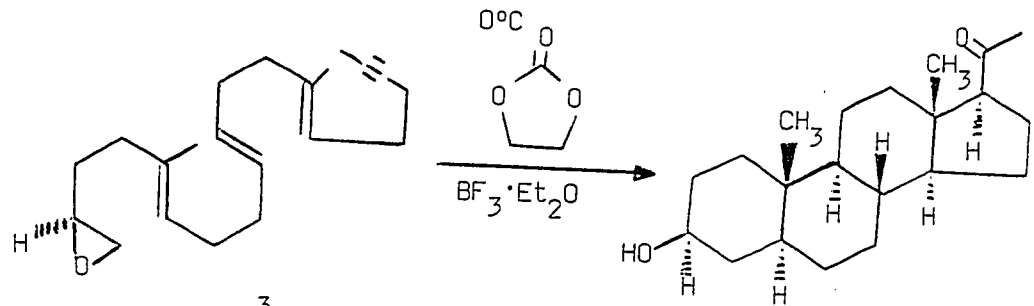
Carbocationic cyclization via polyolefinic epoxides has been extensively studied by Dr. Van Tamelen. Treatment of monosubstituted epoxide 3 with boron trifluoride etherate and ethylene carbonate



1

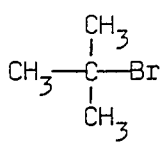
2

yielded (±)-allopregnanolone 4 in 2% yield (4). Although the yield is very low, it should be noted that the cyclization process achieves generation not only of four new rings but also seven new asymmetric centers.

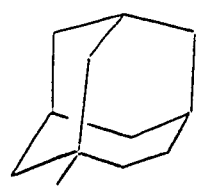


3 4

While many synthetic chemists have studied the application of aliphatic and alicyclic carbocations, the area of bridgehead carbocations has been studied primarily by physical organic chemists (5). The rate of solvolysis usually reflects the stability of the carbocations for a series of related compounds (6). The following relative solvolytic reactivity data were measured in 80% ethanol at 25°C, except 1-bromo-



1.0



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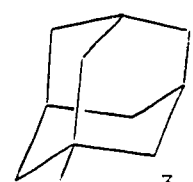
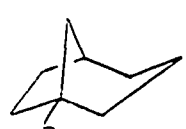
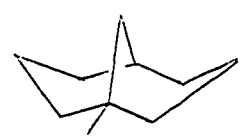


10^{-3}

10^{-6}



10^{-6}



10^{-6}

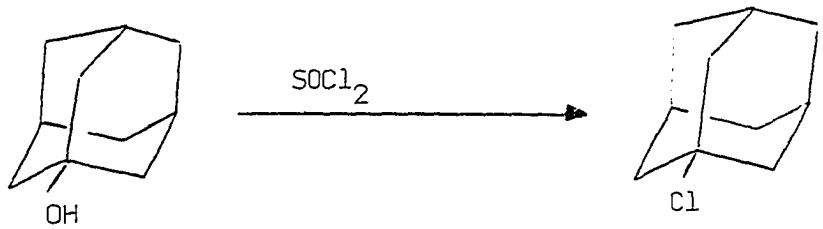
10^{-13}

bicyclo[3.2.1]octane which was measured in 70% dioxane at 132°C. The bicyclo[2.2.2]octane, bicyclo[3.2.1]- and bicyclo[3.3.1]nonane bridgehead bromide solvolyze about 1 million times more slowly than

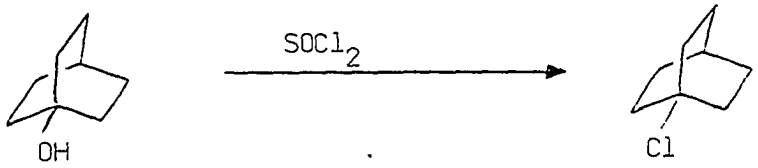
tert-butyl bromide. In bridged molecules such as bicyclo[2.2.1]heptane one may recognize two kinds of strain which tend to hinder the formation of a bridgehead carbocation, out-of-plane strain and in-plane strain. The out-of-plane strain prevents the carbocation from becoming planar and the in-plane strain distorts the valence angles in a plane. The smaller the bicyclic skeleton, the more difficult it is for bridgehead carbocation formation.

In small- to medium-sized ring systems the bridgehead carbocations do not undergo hydride shifts, despite their relative instability compared to the analogous acyclic systems. The reaction of alcohols with thionyl chloride has been shown to proceed via an ion pair intermediate and the net result is front side substitution of chloride for hydroxide. Treatment of bicyclo[2.2.2]octyl-, bicyclo[3.2.1]nonyl- or adamantyl bridgehead alcohols with thionyl chloride provided the corresponding unrearranged bridgehead chlorides (Eqs. 1-3) (7,8). However, reaction of apocamphanol with thionyl chloride yielded only the chlorosulfite ester; further decomposition to the chloride is prohibited by the instability of the bridgehead carbocation (Eq. 4).

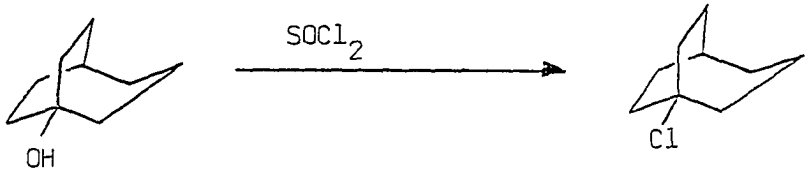
The primary carbocations of bridgehead neopentyl systems are extremely unstable. Under solvolytic conditions they rearrange to form bridgehead carbocations which are trapped by the nucleophiles without further rearrangement (Eqs. 5 and 6) (8,9).


SOCl2
OH
Cl

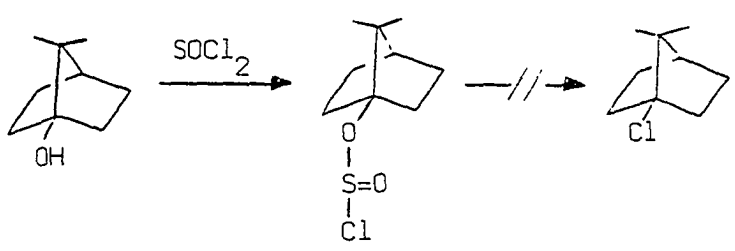
(1)


SOCl2
OH
Cl

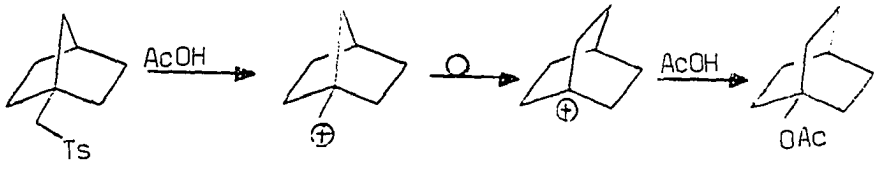
(2)


SOCl2
OH
Cl

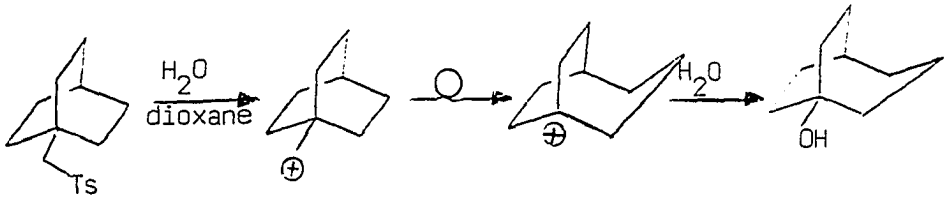
(3)


SOCl2
OH
O
S=O
Cl
Cl

(4)

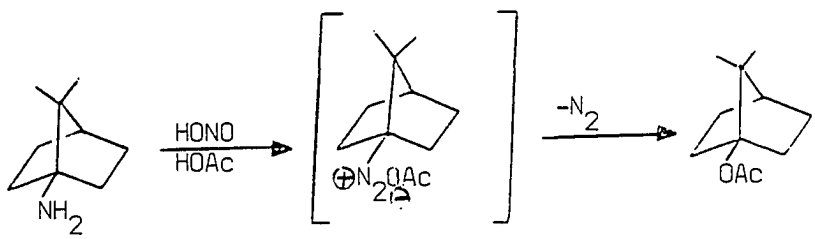

AcOH
Ts
AcOH
OAc

(5)


H2O
dioxane
Ts
H2O
OH

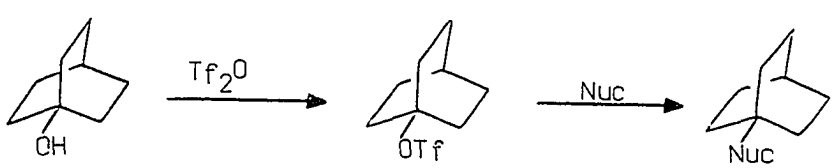
(6)

There are many ways to generate and to trap bridgehead carbocations. The deamination of bridgehead amines proceeds with considerable facility. For example, even apocamphyl amine reacts smoothly with either nitrous acid or nitrosyl chloride (10). The acidic conditions required for the formation of diazonium salt intermediates usually exclude the use of acid sensitive nucleophiles. Furthermore, chloride or acetate ions present in the reaction can also react with the bridgehead carbocation to form the undesired bridgehead chloride or acetate (Eq. 7).



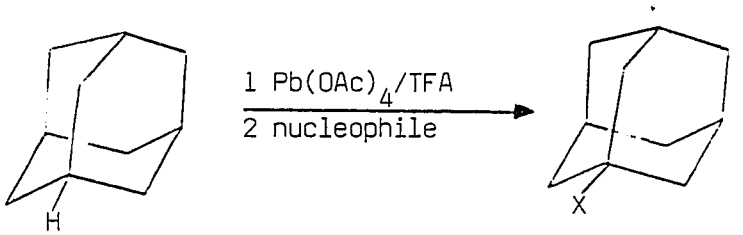
(7)

The bridgehead alcohols react with trifluoromethanesulfonic anhydride (Triflic anhydride) to generate the bridgehead triflates in situ and the nucleophiles are added to trap the bridgehead carbocations (Eq. 8) (11). The triflate leaving group has been shown to be $10^{4.8}$ times more reactive than the p-toluenesulfonate (tosylate) (12).



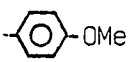
(8)

Drs. Jones and Mellor were able to obtain bridgehead trifluoroacetates in high yield by treatment of bridged hydrocarbons with lead tetraacetate and trifluoroacetic acid (TFA) (13). Furthermore, the bridgehead trifluoroacetate which they generated in situ was reacted with nucleophiles leading to the respective products in "one pot", as shown in eqs. 9 and 10 (14). The bridgehead carbocation intermediates are involved in both the oxidation and solvolysis steps.



(9)

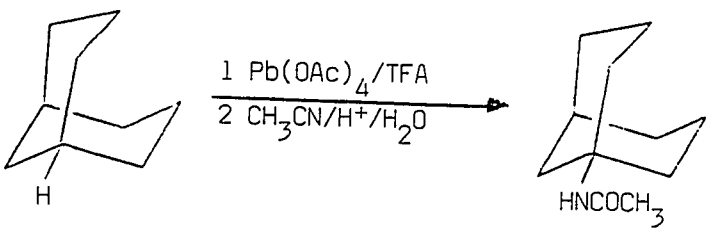
X = $NHCOCH_3$ 85%



84%

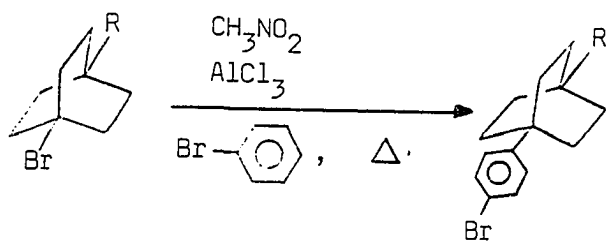
—S—Bu 97%

—CH(CO2Et)—$COCH_3$ 87%



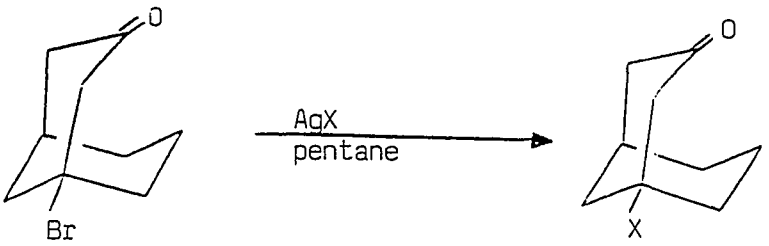
(10)

Lewis acids such as aluminum chloride are able to coordinate to bridgehead halides to form bridgehead carbocation intermediates. For example, 1-bromo-4-alkylbicyclo[2.2.2]octanes were used in novel Friedel-Crafts alkylation reactions with bromobenzene to yield 1-alkyl-4-(4-bromophenyl)bicyclo[2.2.2]octanes (Eq. 11) (15).



(11)

Taking advantage of the low solubility product of the silver halide (1.1×10^{-10} for AgCl, 4×10^{-13} for AgBr and 1×10^{-16} for AgI), the bridgehead carbocations can be formed by treatment of bridgehead halides with silver salts. In order to put synthetically useful functional groups at the bridgehead, a nonnucleophilic counter-ion of the silver salt is required. Fluoride, acetate and nitrate are too nucleophilic to be used (Eq. 12) (16). Another significant feature is that substitution reactions proceed with retention of configuration because of the constraints imposed by the bicyclic system. The absence of hydride shifts, substitution with retention of configuration, high reactivity and easy formation make bridgehead carbocations attractive intermediates for organic synthesis.



(12)

X = F 83%

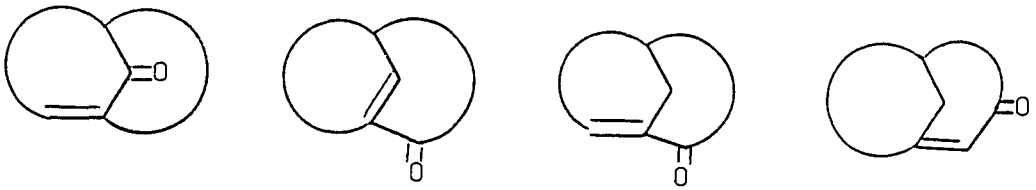
X = OAc 84%

X = ONO_2 96%

Bridgehead Enone Chemistry

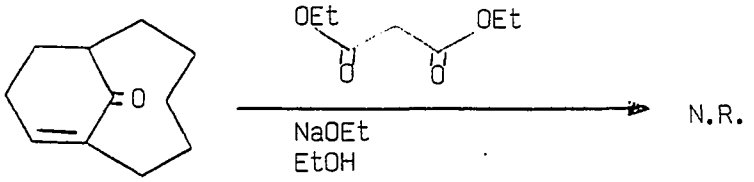
Strain can be introduced in a molecule by distorting one or more bonds from their "normal" bond length or bond angles. A substantial effort has been directed towards the generation and study of strained molecules (17). Bridgehead enones represent a class of strained organic molecules that have been extensively studied for about two decades.

The many examples of compounds that contain a conjugated bridgehead enone can be categorized into four types (5 - 8). Geometric constraints render the coplanarity of the enone unit in structures 5 and 6 extremely difficult. As a result, conjugation is inhibited.



5 6 7 8

The analogous enone 5a fails to react with malonic ester under Michael addition conditions (18,19). On the other hand, the enone groups in 7 and 8 can achieve some degree of coplanarity without introduction of a substantial degree of additional strain. The principal distortion

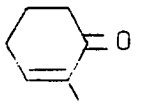
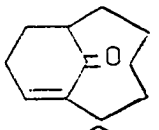
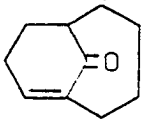
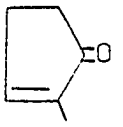
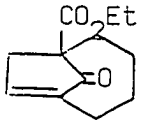
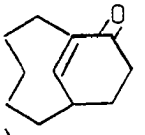
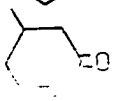
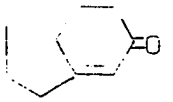
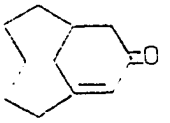


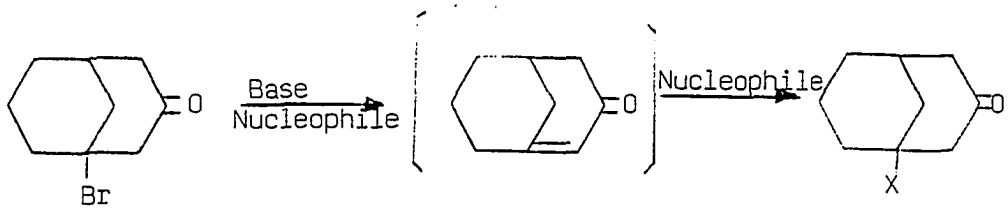
5a

arises from twisting the double bond which results in a geometry that normally would only be expected for the photochemically excited state or the radical ion (20). The distortion should be more favorable in species where the first antibonding orbitals of the enone system (with a node between C_α and C_β) is populated rather than in the ground state of the enone. More specifically, one might expect the energy separating the enone ground state and the lowest electronically excited state to be lowered by this distortion. From Table I, it is apparent that the $\pi \longrightarrow \pi^*$ absorption shifts to lower energy as the enone systems become increasingly distorted. The ring distortion effect can also be explained by IR and NMR data (Table I).

The chemical and physical properties of bicyclo[n.3.1]enone systems have been extensively studied by House and coworkers (21). Reaction of 1-bromobicyclo[3.3.1]nonan-3-one with base yielded the bridgehead enone 9 which was rapidly trapped by a number of nucleophiles (Eq. 13) (21a). In the absence of competing nucleophiles, the

Table I. Spectral data of the bridgehead enones (*measured UV in CH_3CN)

Entry	Compound	$\nu_{CO}^{CCl_4}(cm^{-1})$	$\lambda_{max}^{EtOH}(nm)$	[ε]	=CH (δ) (NMR)
1		1675	235	9400	6.68
2		1680, 1702	238	5630	6.16
3		1710	238	3000	5.9
4		1711	226	8550	7.23
5		1715, 1740	241	3908	6.76
6		1675	254	7500	6.85
7		1670	232*	13800	5.86
8		1680, 1667	250*	5070	5.53
9		1673	240*	14800	5.70

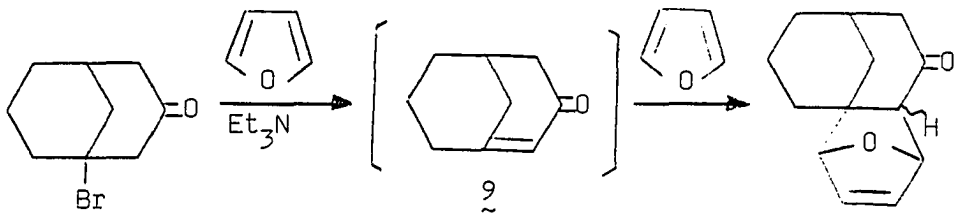


9

(13)

X =	PhS	89%
	PhSe	87%
	Me_2N	92%

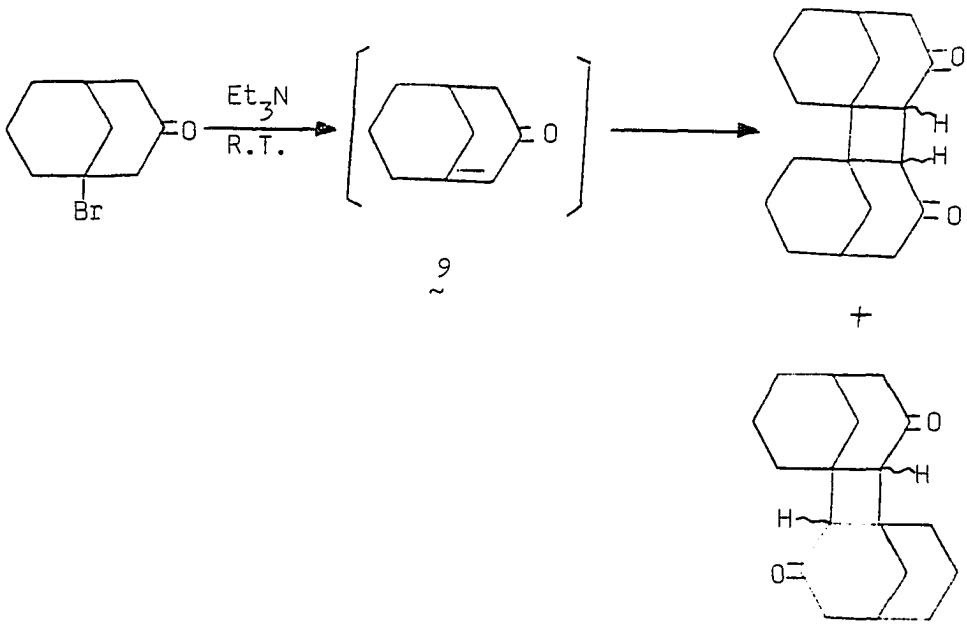
enone 9 will form a Diels-Alder adduct 10 with furan (Eq. 14) (21b). If neither nucleophiles nor furan are in the reaction mixture, the



9

(14)

dimers of the enone 9 will be formed (Eq. 15) (21b).

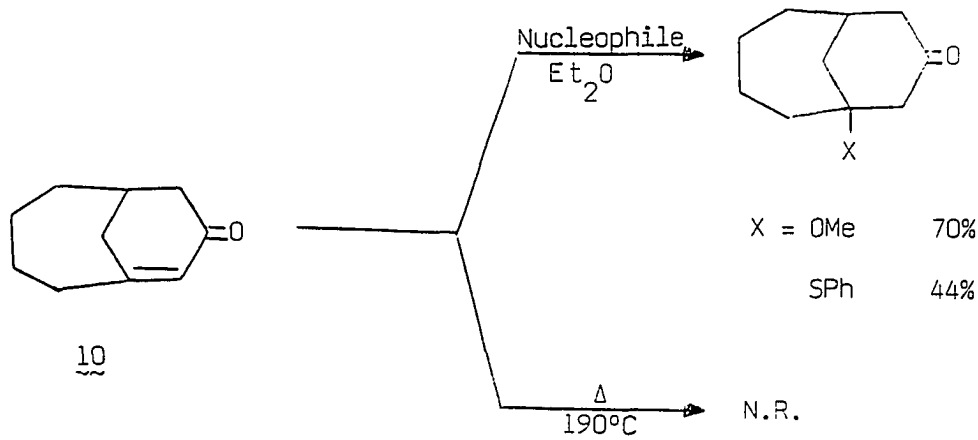


9

+

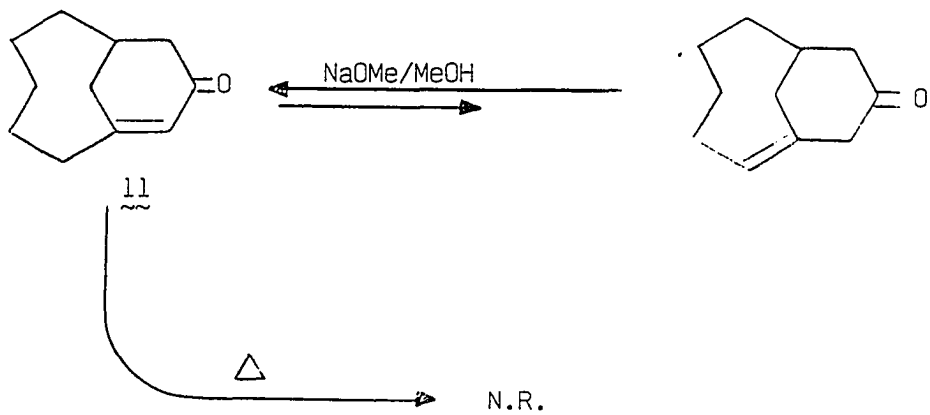
(15)

Bridgehead enone 10 is a stable compound in the absence of nucleophiles and it has shown no tendency to undergo thermal dimerization (21d). However, it is a relatively reactive acceptor for the conjugate addition of nucleophiles (Eq. 16) (21d).



(16)

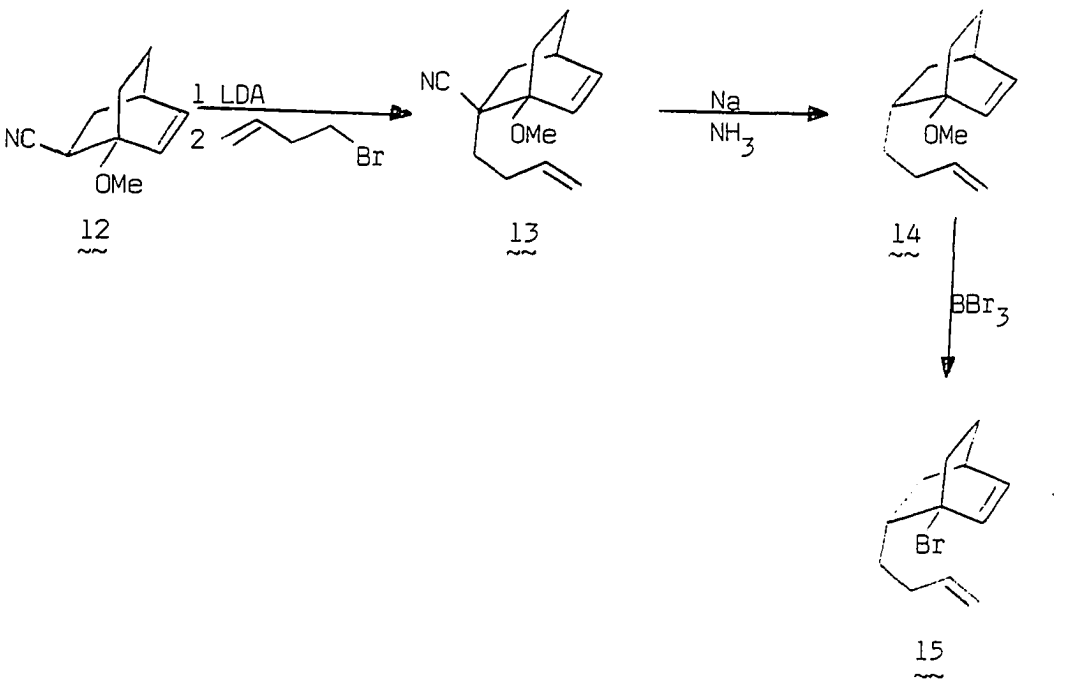
The enone system 11 is a rather stable compound which shows less tendency to undergo conjugate addition by nucleophiles. It does not dimerize (Eq. 17) (21e). Although the bridgehead enone 9 is too reactive to be isolated, it can be prepared in situ. Its synthetic applications have not been studied.



(17)

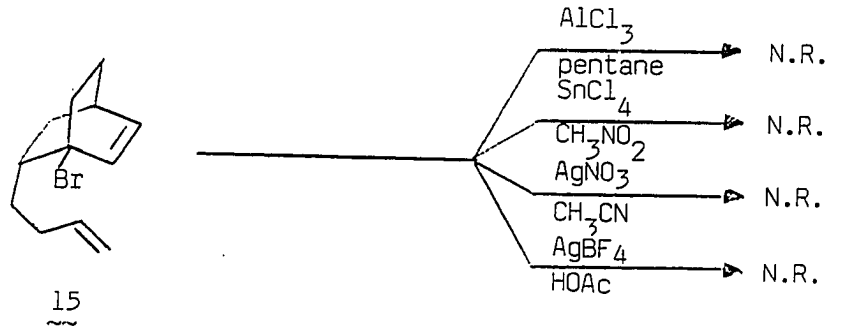
RESULTS AND DISCUSSION

In order to study the chemistry of the bicyclo[2.2.2]octane bridgehead carbocations, the commercially available 1-methoxybicyclo-[2.2.2]oct-5-ene-2-carbonitrile 12 was chosen as starting material. This compound is readily alkylated with 4-bromo-1-butene using



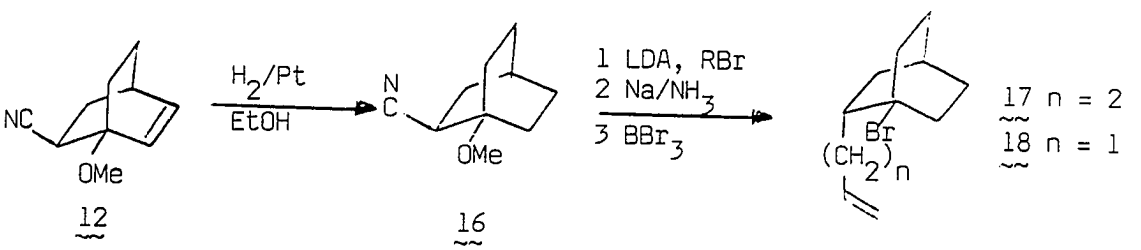
12 13 14 15

lithiumdiisopropylamide (LDA) as base. It is then decyanated using sodium in liquid ammonia to produce 14 which can be converted into 1-bromo-6-(3-butenyl)bicyclo[2.2.2]oct-2-ene 15 with boron tribromide in methylene chloride at -78°C (22). Neither Lewis acids nor silver salts were effective in forming the bridgehead carbocation (Eq. 18). The difficult bridgehead carbocation formation can be ascribed to the inductive effect and enhanced ring strain of the alkene. In order to



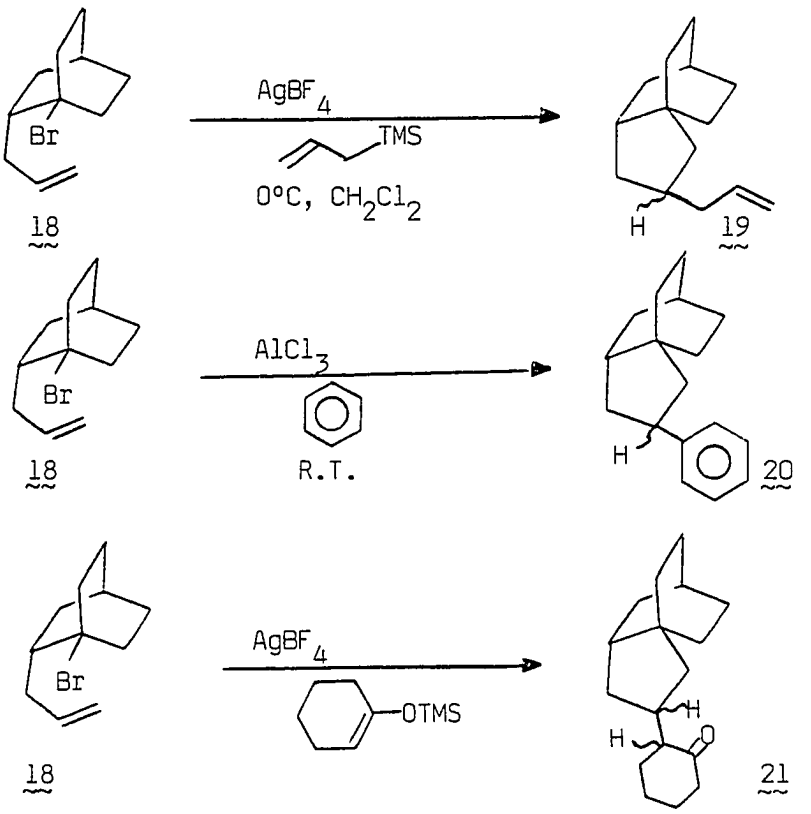
15 (18)

diminish these effects, compound 12 was converted to 16 by catalytic hydrogenation. LDA mediated alkylation, reductive decyanation and



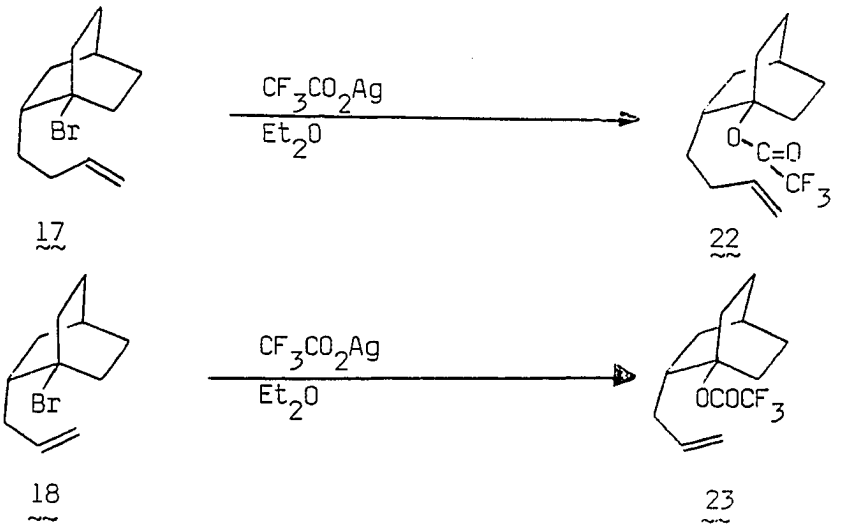
12 16 17 n = 2, 18 n = 1

bromide formation produced the bridgehead bromides 17 and 18, respectively. We are able to generate the bridgehead carbocation from 17 by treatment with either aluminum chloride in the presence of allyltrimethylsilane or silver tetrafluoroborate in trifluoroacetic acid. Unfortunately, the products were very nonpolar and hard to characterize. In contrast, one can trap the bridgehead carbocation derived from compound 18 with allyltrimethylsilane, benzene or an enol silyl ether to form compounds 19, 20 and 21 respectively as mixtures of diastereomers. However, if silver trifluoroacetate was



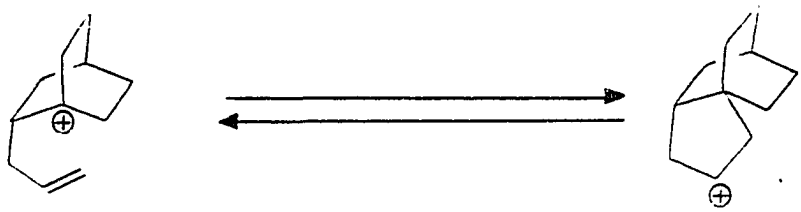
18 19 18 20 18 21

used, one could only isolate the bridgehead trifluoroacetates 22 and 23. The cyclopentyl cation might be in equilibrium with the bridgehead

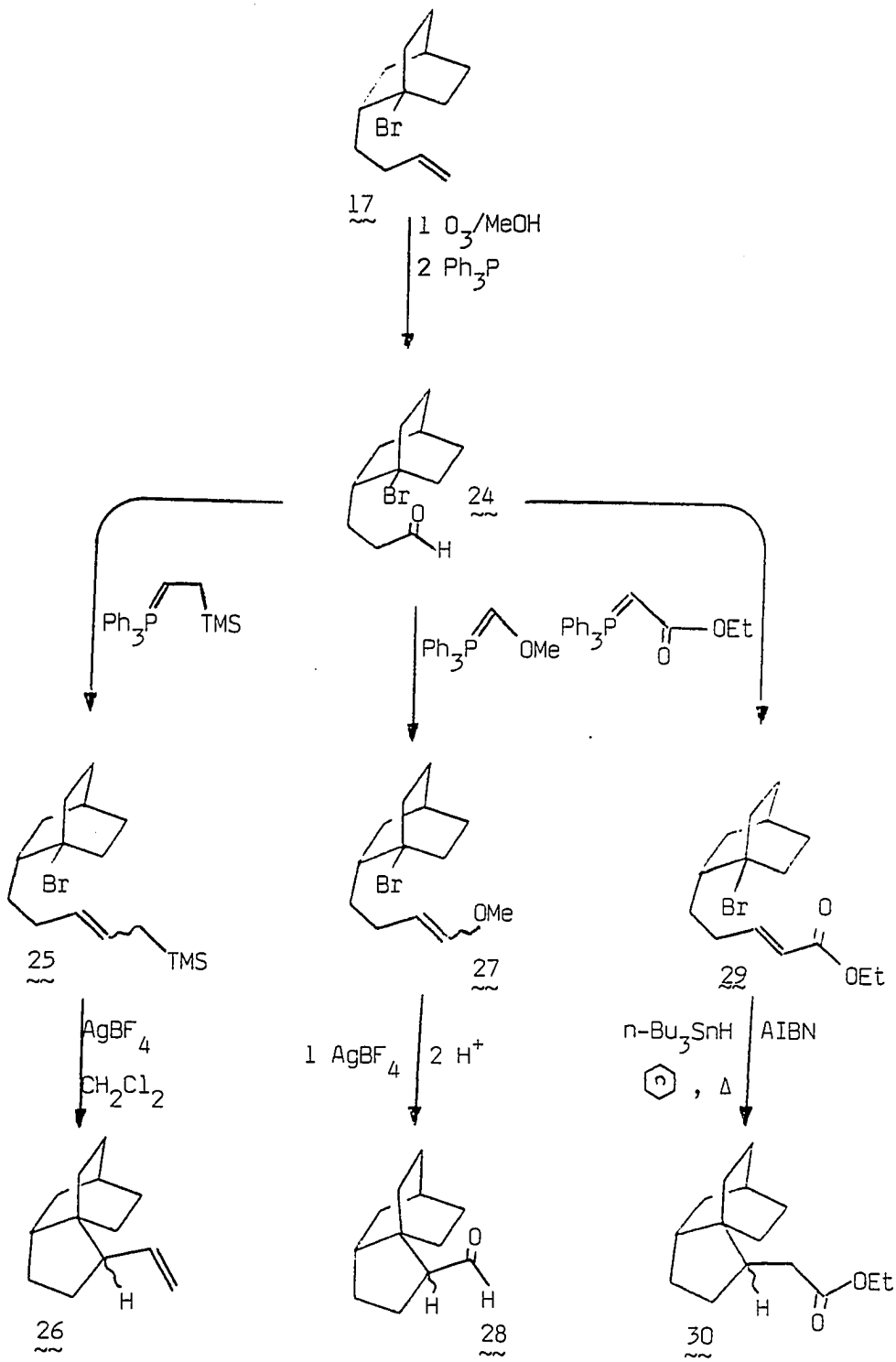


17 22 18 23

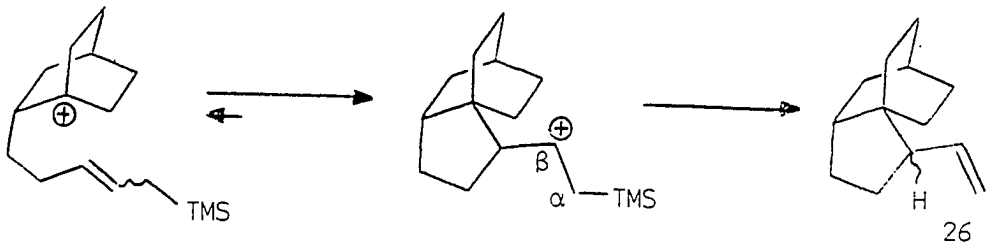
carbocation and the site of attack is determined by the size of the nucleophile and the nucleophilicity of the counterion of the silver salt.



Although bromide 17 did not afford any synthetically useful results, it did serve as a key intermediate in the preparation of compounds 25, 27 and 29. Bromide 17 was reacted with ozone followed by reductive workup of the ozonide with excess triphenylphosphine to provide aldehyde 24. This aldehyde was unstable and was immediately converted into allylic silane 25 using the Seyferth methodology (23). Aldehyde 24 was also converted into enol ether 27 and unsaturated ester 29. Reaction of 25 in methylene chloride with silver tetrafluoroborate gave the tricyclic alkene 26 in 75% yield. Likewise, the enol ether 27 afforded aldehyde 28 in 80% yield. Compounds 26 and 28 were produced as mixtures of diastereomers. The β-effect of the silyl substituent in 25 is the driving force for the cyclization, because the silyl substituent strongly favors carbocation development at the β-carbon atom. The resonance effect of the methoxyl group in 27 is the driving force for its cyclization. The bridgehead carbocation generated from compound 29 did not give any useful product. Therefore, we used compound 29 to examine the bridgehead radical chemistry. In contrast to the bridgehead carbocation situation, bridgehead radicals are reported to be only ten times more reactive than their acyclic counterparts. The 5-hexenyl radical cyclizations

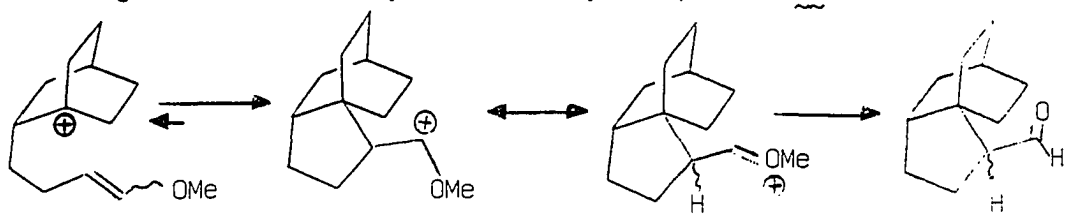

Br
17
1 O3/MeOH
2 Ph3P
Br
O
H
24
Ph3P
TMS
Ph3P
OMe
Ph3P
O
OEt
Br
TMS
25
Br
OMe
27
Br
O
OEt
29
AgBF4
CH2Cl2
1 AgBF4
2 H+
n-Bu3SnH
AIBN
, Δ
H
26
O
H
H
28
OEt
O
H
30

are usually facile and have been extensively studied (24). The 5-hexenyl subunit exists in bromide 29. It was subjected to tributyltin hydride



26

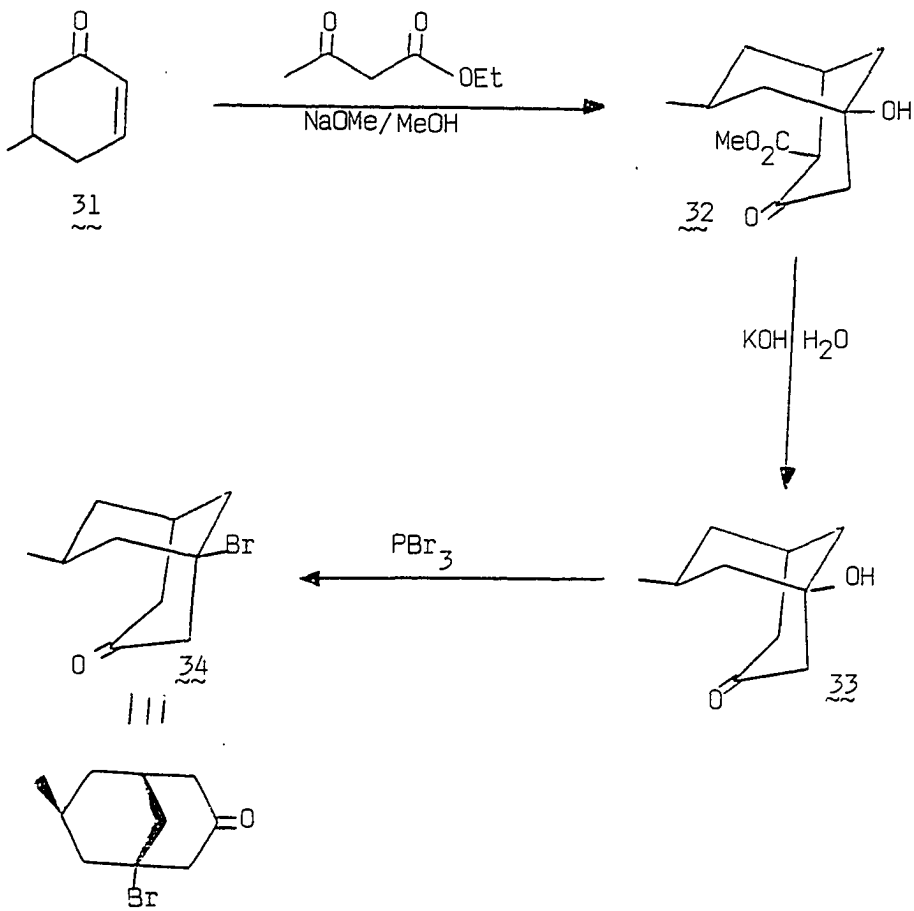
and a catalytic amount of 2,2'-azobis(2-methylpropionitrile) (AIBN) in boiling benzene. A 50% yield of tricyclic product 30 was obtained.



28

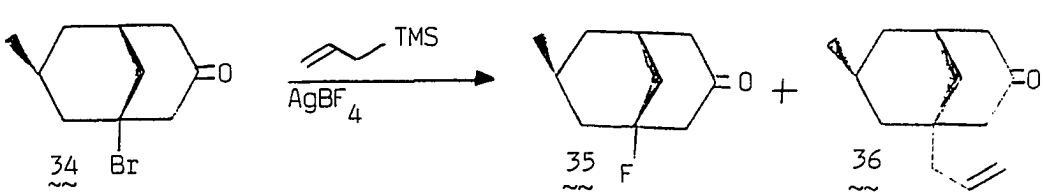
Only one other example of an intramolecular bridgehead radical cyclization has been reported. This example involved an oxabicyclo-[3.2.1]octane ring system and resulted in the total synthesis of agarofuran (25).

The preparation of the bicyclo[3.3.1]nonane system was accomplished by literature methods (16). The bridgehead alcohol 32 was formed when 5-methyl-2-cyclohexen-1-one 31, ethyl acetoacetate and one equivalent of sodium methoxide in methanol were heated under reflux for three days. In the same pot, without isolation, the reaction mixture was treated with aqueous potassium hydroxide to give bridgehead alcohol 33. The reaction of 33 with phosphorus tribromide gave bromoketone 34.



31 32 33 34

As before, the bromo ketone was treated with silver tetrafluoroborate in the presence of allyltrimethylsilane. Two products, 35 and 36, were obtained in a ratio of 7:3.



34 35 36

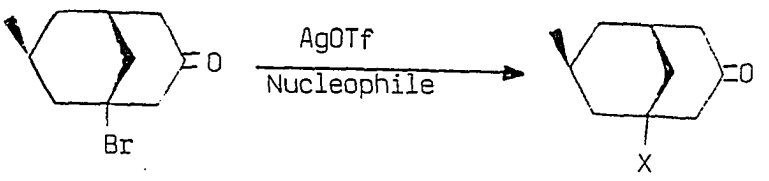
35:36 = 7:3

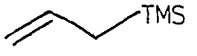
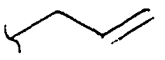
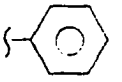
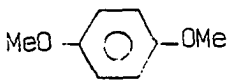
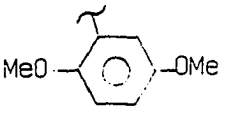
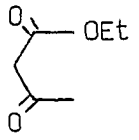
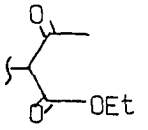
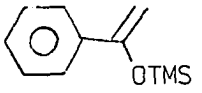
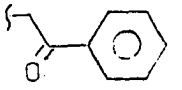
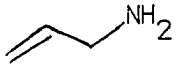
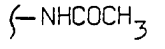
and 36, were formed in a ratio of seven to three. Unfortunately, the major product was the bridgehead fluoride. In order to decrease the nucleophilicity of the counterion of the silver salt, silver trifluoromethanesulfonate (silver triflate) was used, because the triflate is a very poor nucleophile.

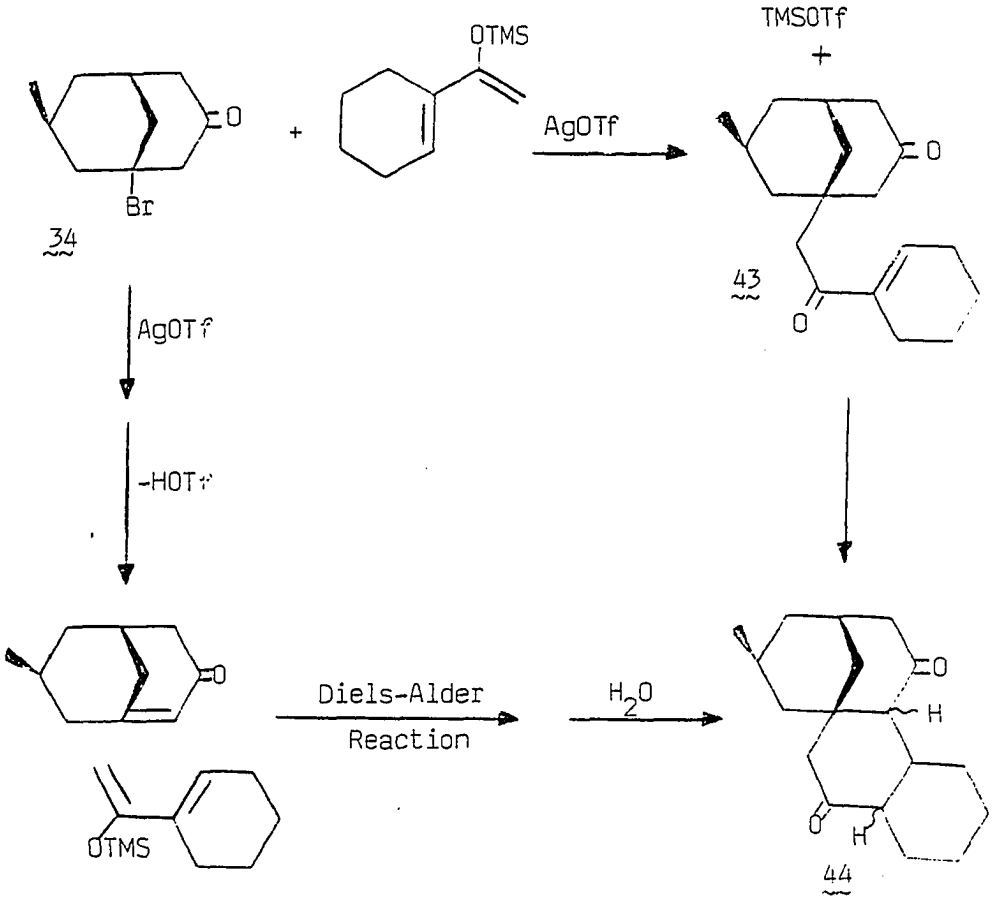
The methylene chloride solution of bromo ketone 34 and allyltrimethylsilane was treated with silver triflate at room temperature. It produced only compound 36 in high yield. Following the same procedure, benzene, 1,4-dimethoxybenzene, ethyl acetoacetate, enol silyl ethers, acetonitrile and allylamine all afforded excellent yields of products 36 - 42, respectively. A slight experimental variation was developed in the case of the allylamine and acetonitrile. The bridgehead triflate was first generated and then either the amine or acetonitrile was added.

The reaction of 34 with the enol silyl ether of acetyl cyclohexene provided the tetracyclic diketone 44. Presumably this results from the reaction of the enol silyl ether with the bridgehead carbocation, followed by an intramolecular Michael addition catalyzed by the trimethylsilyl triflate formed in the initial step. However, a Diels-Alder reaction with the bridgehead enone (derived by initial loss of triflic acid) cannot presently be ruled out (21e).

When ethyl vinyl ether and the enol acetate of acetophenone were used as nucleophiles, O-alkylation products 45 and 46 were formed in high yield. The reason is not clear. One possible

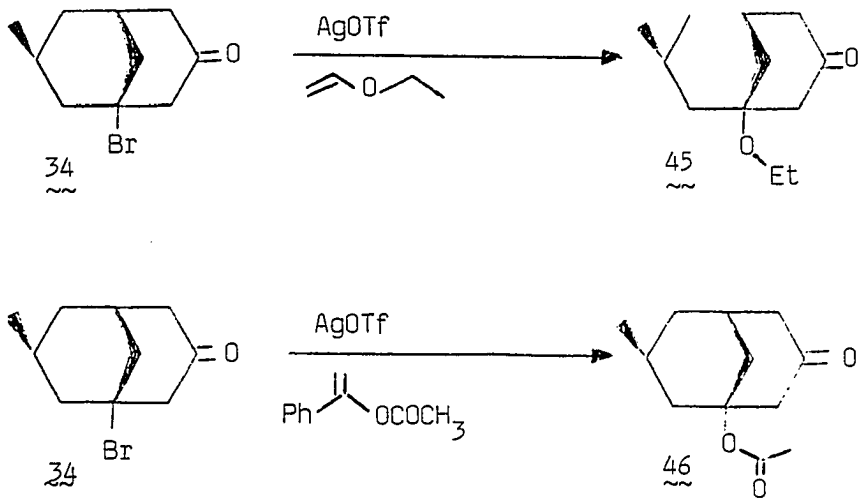


Nucleophile	X	Compound	% Yield
		36	66
		37	52
		38	100
		39	52
		40	57
		41	81
CH_3CN		42	86

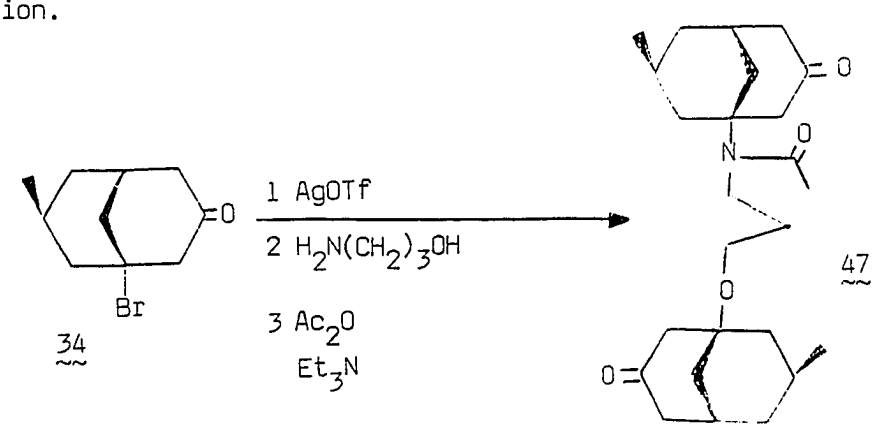


explanation is that the hard oxygen atom prefers to attack the hard bridgehead carbocation.

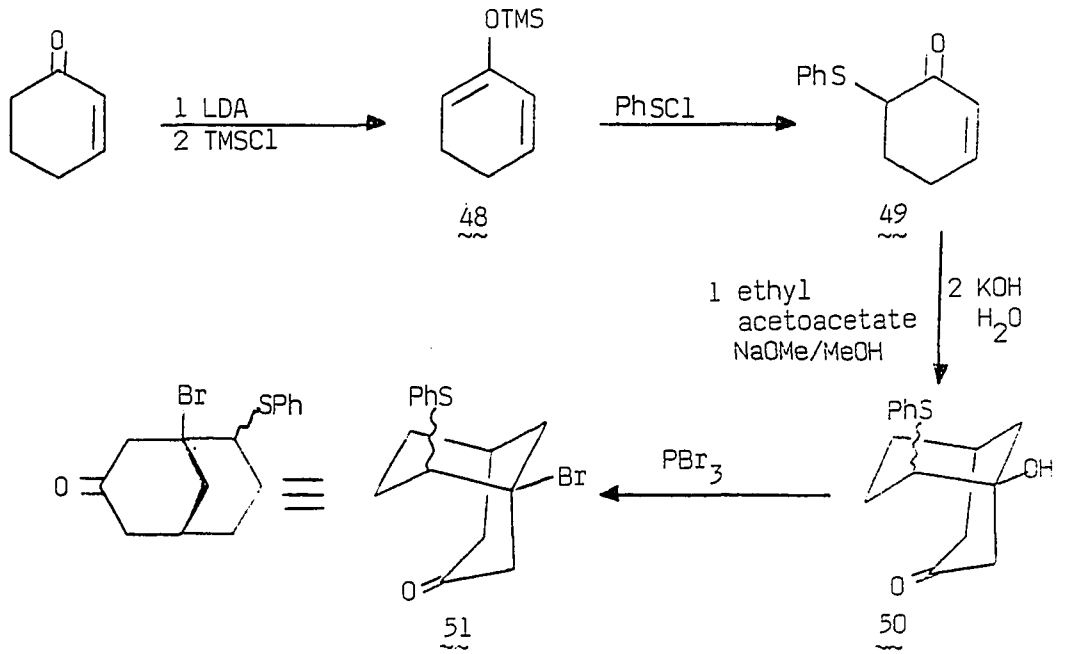
The reaction of the bridgehead carbocations with a dinucleophilic molecule was also examined. In this case 3-amino-1-propanol was used as nucleophile. The product initially formed by trapping of the bridgehead carbocation was treated with acetic anhydride and triethylamine to yield compound 47. The molecular ion peak in the mass spectrum is 417 which is convincing evidence for the proposed structure.



Both the hydroxyl group and amino group exhibit the same nucleophilicity probably because of the extremely high reactivity of the bridgehead carbocation.

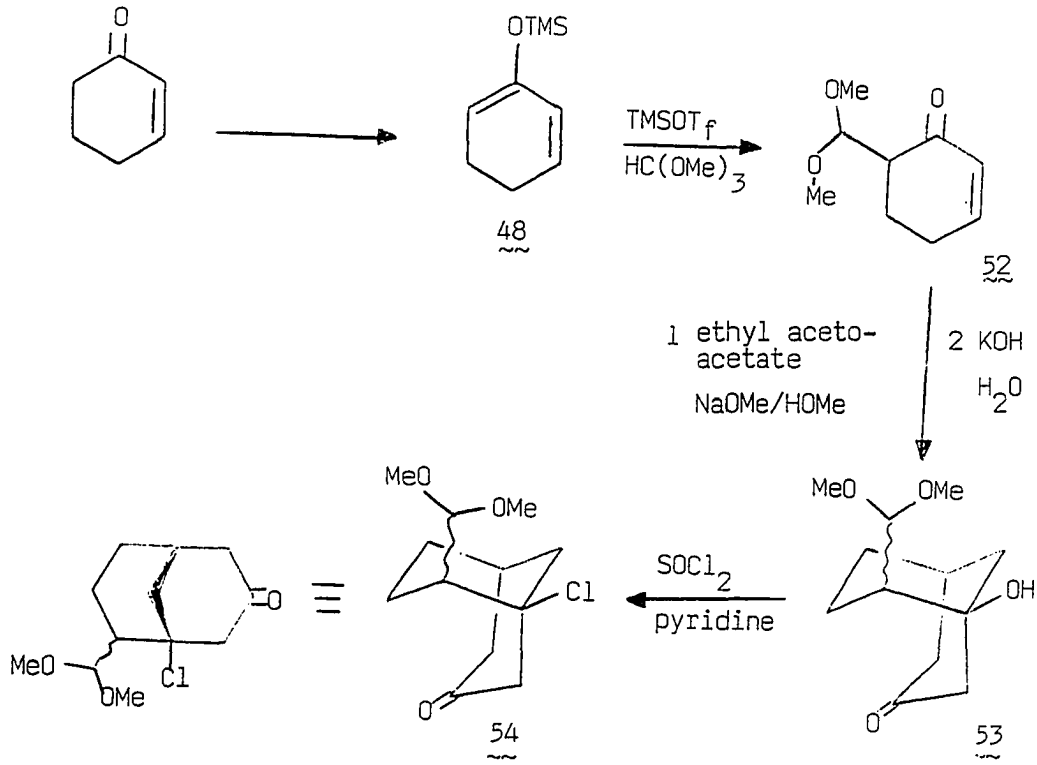


8-Substituted-1-bromobicyclo[3.3.1]nonan-3-ones were required for future research. Treatment of the enol silyl ether of 2-cyclohexen-1-one (48) with benzenesulfenyl chloride yielded compound 49 (26). Compound 49, ethyl acetoacetate and one equivalent sodium methoxide were refluxed in methanol solution for one day. Decarbo-

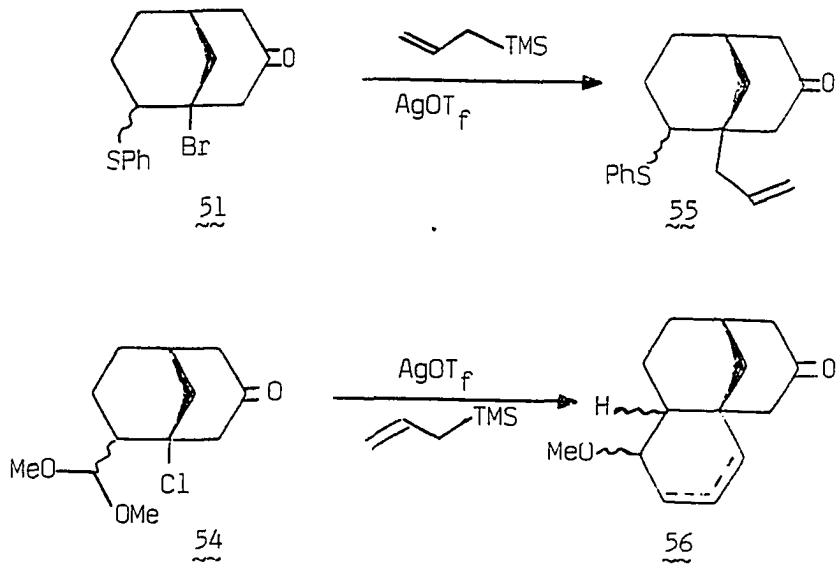


methoxylation provided a diastereomeric mixture of bridgehead alcohols 50. Bridgehead bromide 51 was formed by treatment of 50 with phosphorus tribromide. Likewise, the enol silyl ether of 2-cyclohexen-1-one was reacted with trimethyl orthoformate with trimethylsilyl triflate as catalyst to yield compound 52. The bridgehead alcohol 53 formation can be achieved following the same reaction sequence and conditions as described above. Treatment of bridgehead alcohol 53 with thionyl chloride and pyridine provided the bridgehead chloride 54 in high yield, as a mixture of diastereomers.

The bridgehead carbocation of 51 can be trapped by allyltrimethylsilane to yield compound 55. The bridgehead carbocation of 54 can also be trapped by allyltrimethylsilane. However, the product was tricyclic

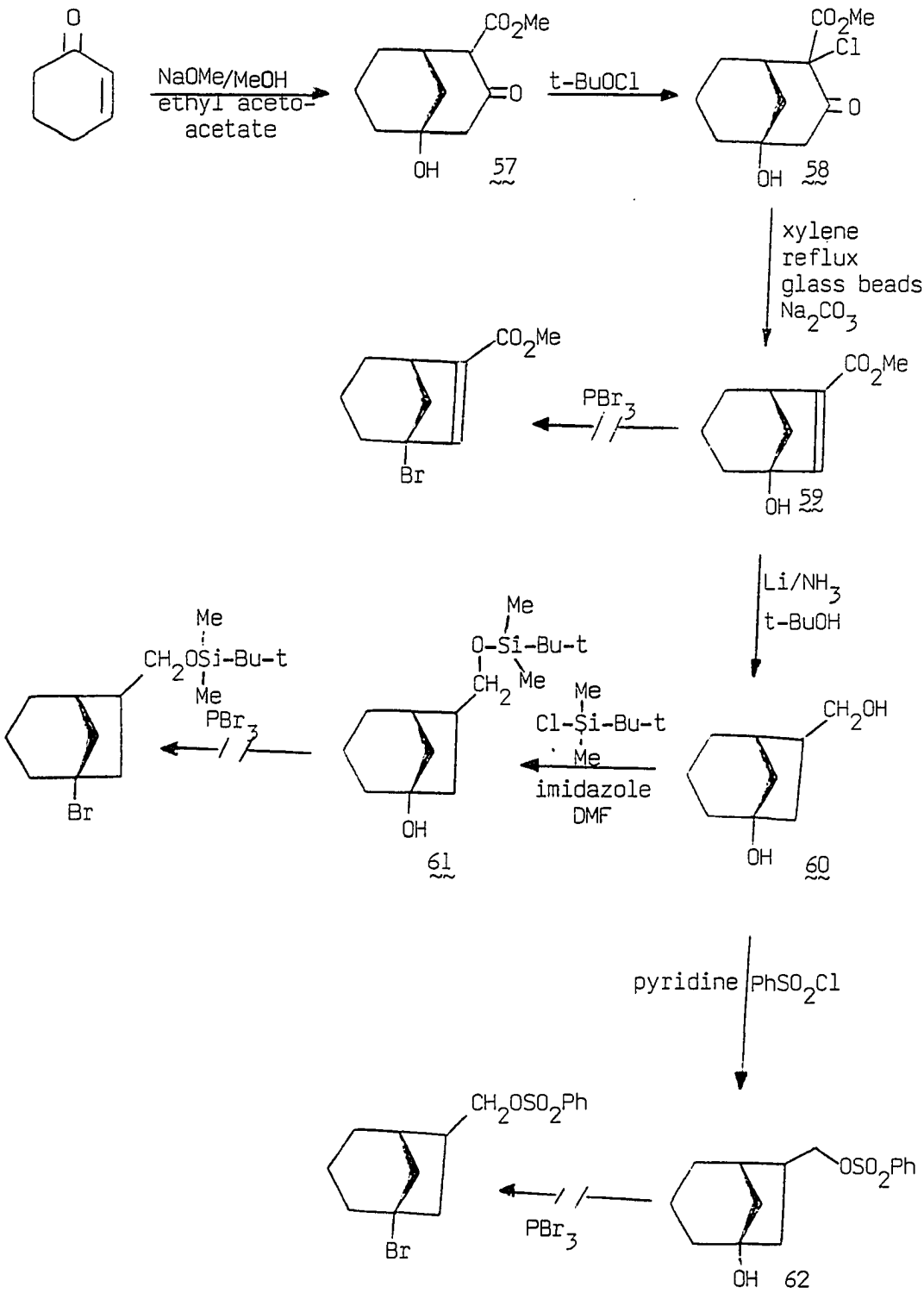


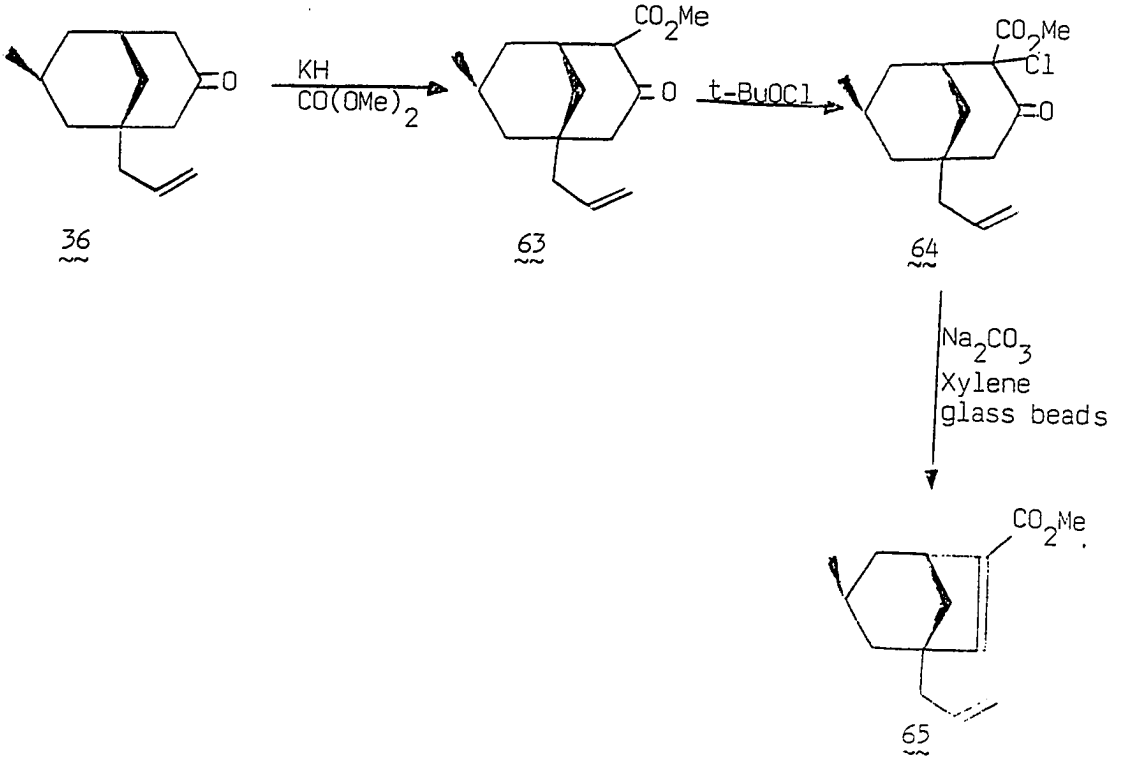
compound 56. Presumably, the trimethylsilyl triflate generated in the reaction catalyzed the unexpected ring formation.



In order to generate a key intermediate for the construction of both bicyclo[3.3.1]nonane and bicyclo[3.2.1]octane ring systems, the ring contraction of compound 57 was investigated.

Keto ester 57 was prepared by following the literature method as described previously (16). Treatment of 57 with tert-butyl hypochlorite provided chloro compound 58, which was then converted to compound 59 by reaction with sodium carbonate and glass beads in refluxing xylene (28). We were unable to form the bridgehead bromide by treatment of bridgehead alcohol 59 with phosphorus tribromide. The alkene was then reduced by a metal/ammonia reduction to form diol 60. Mono protection of the primary alcohol either with tert-butyldimethylsilyl chloride or with benzenesulfonyl chloride provided compounds 61 and 62. Unfortunately, we were unable to convert either compound to the bridgehead bromide. The problems with bridgehead bromide formation in the bicyclo[3.2.1]octane system led us to change tactics. Compound 36 was chosen as the starting material of the model system study. Treatment of 35 with potassium hydride and ethyl carbonate yielded the only regioisomer 63. Utilizing the sequence described above, the bridgehead compound 65 can be made in high yield. The regioselectivity of the carbomethoxylation is due to the steric effect of the allyl group.

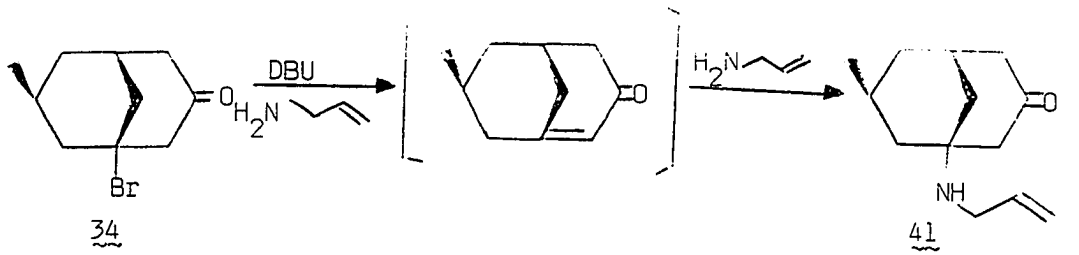

NaOMe/MeOH
ethyl aceto-
acetate
t-BuOCl
xylene
reflux
glass beads
Na_2CO_3
PBr_3
Li/NH_3
t-BuOH
imidazole
DMF
pyridine
$PhSO_2Cl$
57
58
59
60
61
62



36 63 64 65

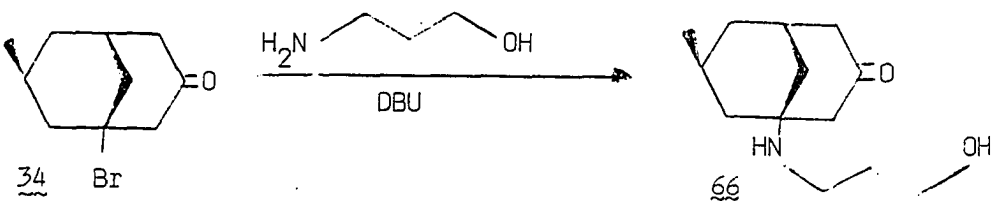
The bridgehead enone chemistry of the bicyclo[3.3.1]nonane system was also examined in order to compare with the results from our bridgehead carbocation chemistry.

Compound 33 was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and allylamine to give the bridgehead amine 41 in high yield.

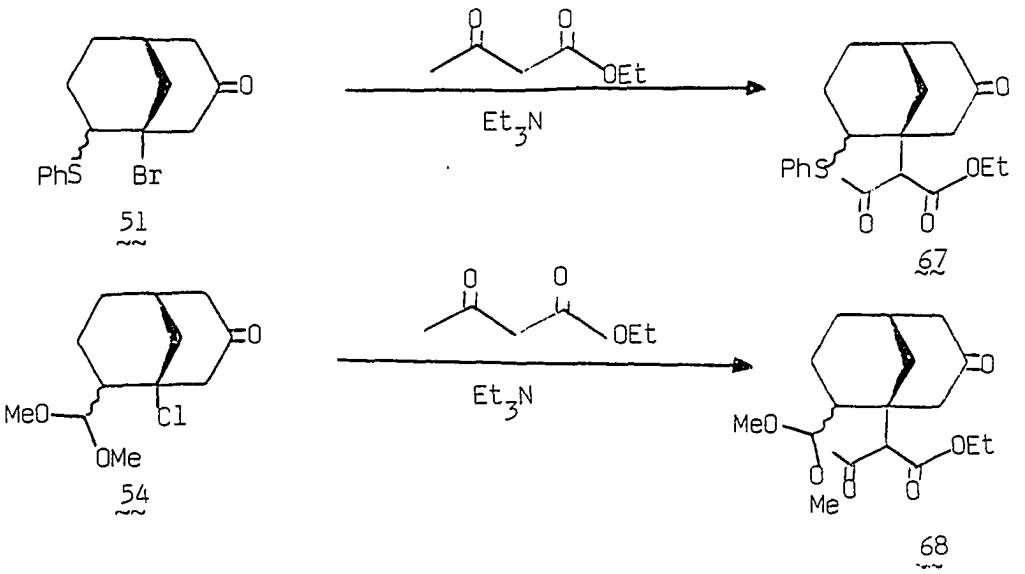


34 41

The bridgehead enone was only trapped by the amino group of 3-amino-1-propanol to form compound 66. This result cannot be achieved by bridge-



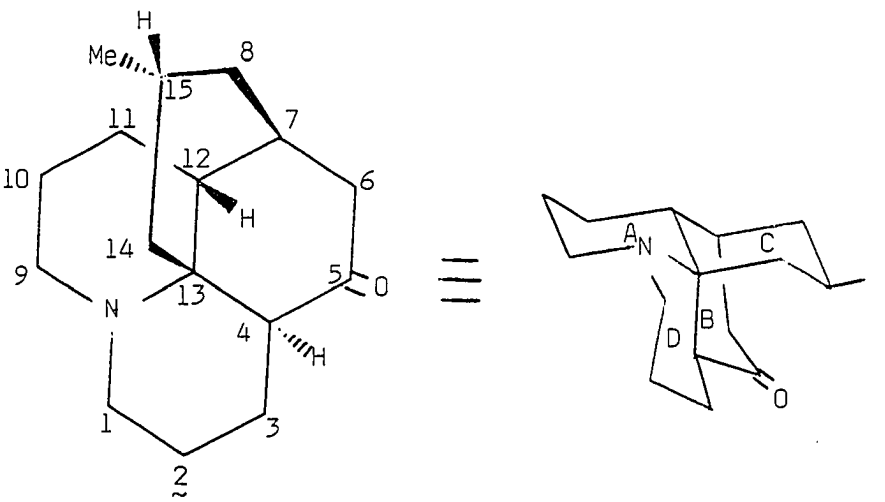
head carbocation trapping methodology. Compounds 67 and 68 can also be made in a similar manner.



PART II. TOTAL SYNTHESIS OF (±) LYCOPODINE

INTRODUCTION

The lycopodium alkaloids are a family of about 100 biogenetically related compounds elaborated by the genus Lycopodium (club mosses) (29). Lycopodine 69 is the first known, most abundant, and most widely distributed member in the family (30). The structure of lycopodine was established in 1960 (31), and confirmed by X-ray analysis in 1974 (32).



69 69

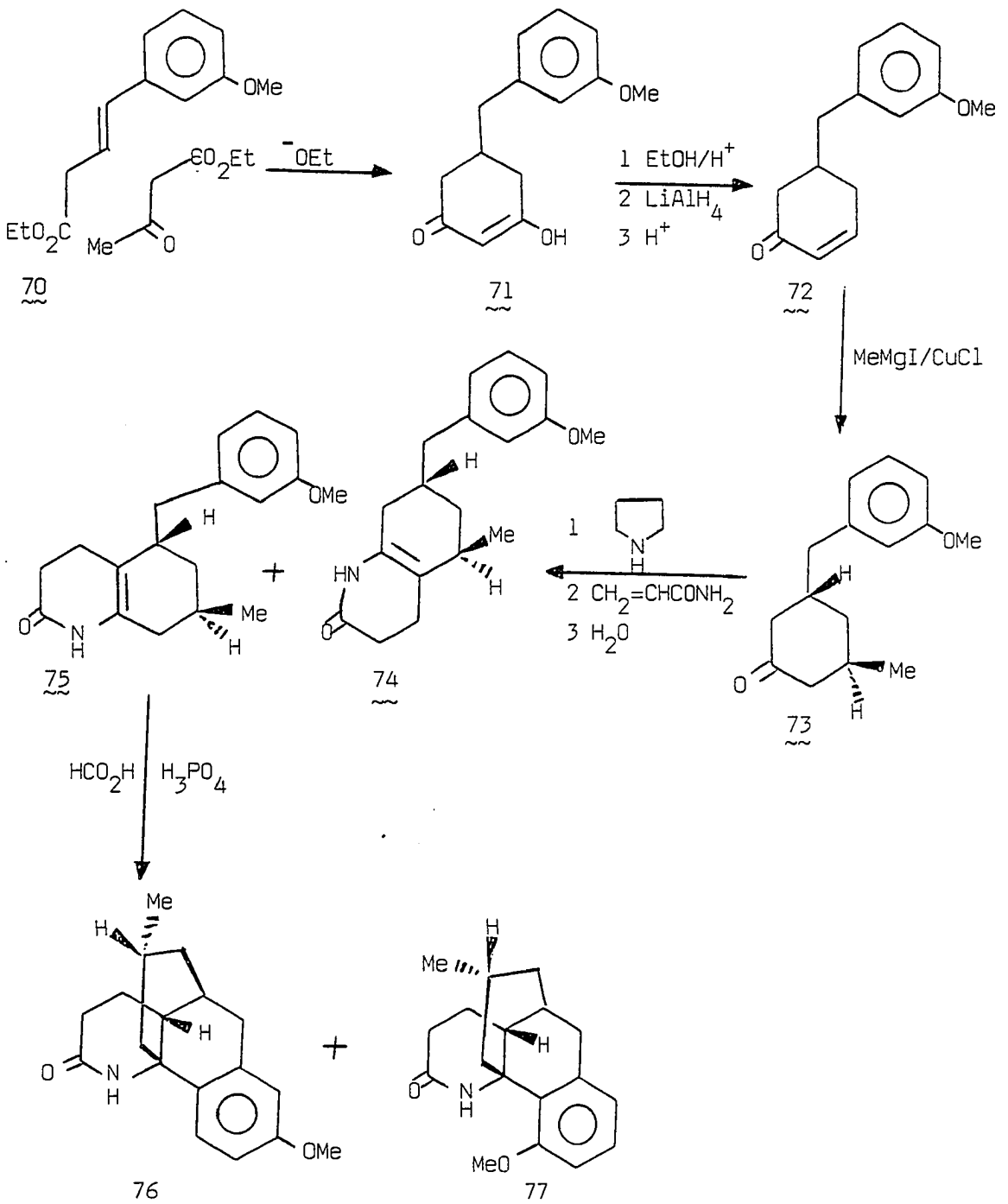
A number of synthetic groups have chosen lycopodine as a target molecule. There are five successful syntheses which have been done by Stork and coworkers (33), Ayer and coworkers (34), Heathcock and coworkers (35), Wenkert and Broka (36), and Schumann and coworkers (37). The unnatural 12-epilycopodine was synthesized by Wiesner and co-workers (38). Several other interesting approaches were either unsuccessful or were not pursued to completion (39). The routes of those successful syntheses are strikingly different from one another.

The synthesis done by Professor Stork's group is shown in Scheme I (33). Reaction of ethyl acrylate with triphenylphosphine and m-methoxybenzaldehyde gave compound 70. Compound 70 reacted with ethyl acetoacetate and sodium ethoxide followed by hydrolysis and decarboxylation to give the cyclohexanedione 71. The monoenol ethyl ether of 71 was reduced with lithium aluminum hydride followed by acidic workup to produce the unsaturated ketone 72. Methyl magnesium iodide with a catalytic amount of cuprous chloride attacked the unsaturated ketone 72 stereoselectively to yield saturated ketone 73. In order to maintain the continuous overlap of orbitals, the attack of the methyl copper reagent on the unsaturated ketone must take place from an axial orientation (40). The enamine of 73 was alkylated with acrylamide to give a mixture of 74 and 75 which were separable. Compound 75 was used to complete the synthesis. On treatment with acid, 75 gave two products 76 and 77 in a ratio of 2:1. Lithium aluminum hydride reduction and then Birch reduction of 76 gave the expected product 78. Treatment of 78 with a strong base gave the conjugated diene in which the other double bond had migrated. The diene was then acylated to give 79. The less substituted and more nucleophilic alkene in 79 was selectively cleaved by ozone to give 80. Compound 80 could be oxidized with selenium dioxide and hydrogen peroxide to give Baeyer-Villiger product 81. Methanolysis of 81 gave the corresponding keto-ester, and zinc reduction removed the trichloroethoxycarbonyl group.

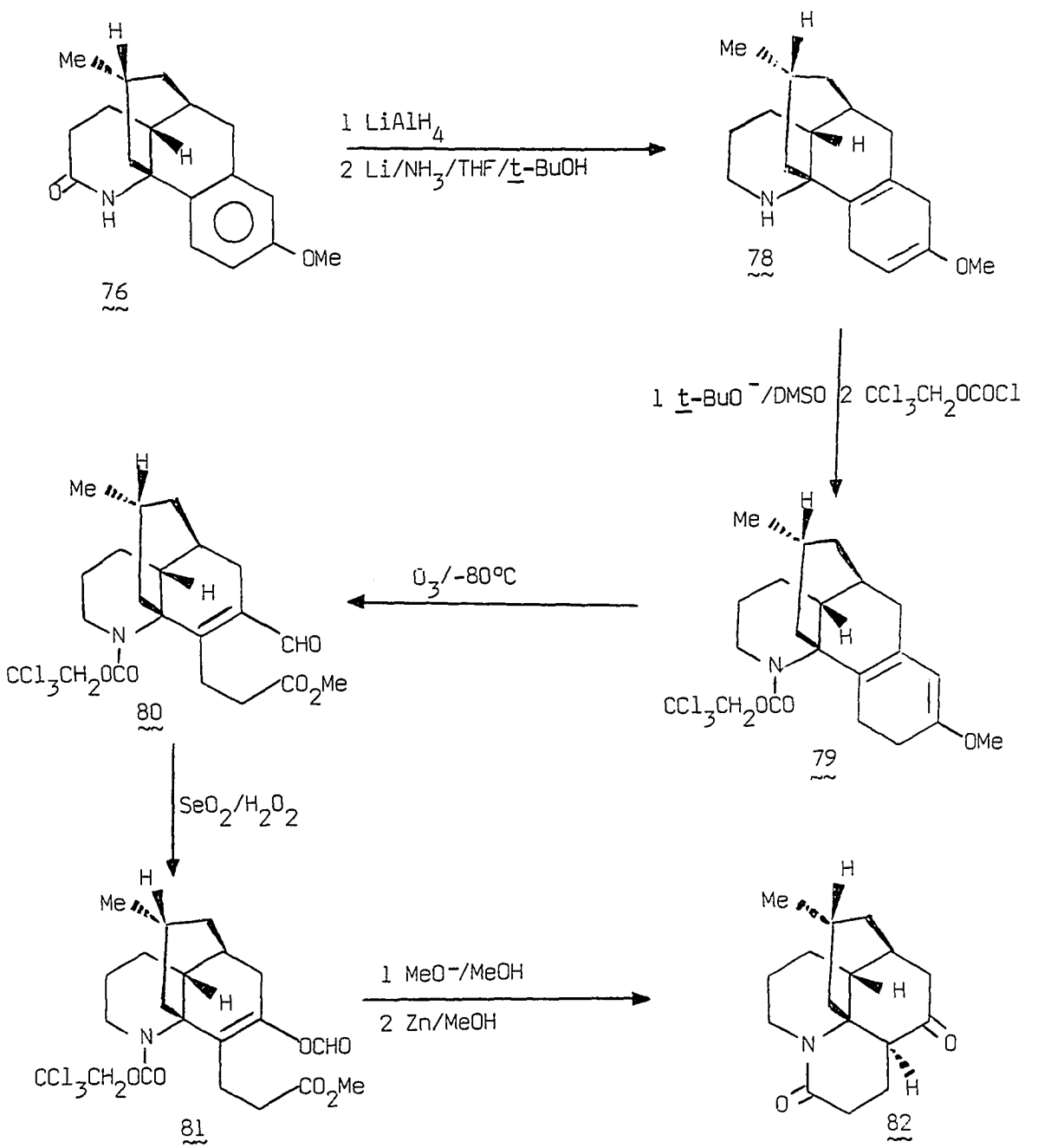
The amino ester cyclized spontaneously to give the ketolactam 82. Lithium aluminum hydride reduction followed by reoxidation of the alcohol gave racemic lycopodine 69.

The starting material for Ayer and coworkers synthesis was thalline 83 (Scheme II) (34). The reaction of thalline with 1-bromo-3-chloropropane gave 9-methoxyjulolidine 84. Reduction of 84 with lithium-ammonia-tert-butanol yielded the unstable dihydro derivative which was transformed immediately to the ketal immonium perchlorate 85. The immonium salt 85 was treated in tetrahydrofuran with the Grignard reagent prepared from 1-chloro-2-methyl-3-methoxypropane followed by acid hydrolysis of the ketal group to give cis,cis-hexahydrojulolidine 86. The epimerization was achieved by a series of reactions: bromination, dehydrobromination and lithium-ammonia reduction to give a diastereomeric mixture of 87 and 88 which are inseparable. The corresponding alcohols 89 and 90, prepared by treatment of the mixture of 87 and 88 with boron tribromide in methylene chloride are easily separable on an alumina column. The ratio of 89 to 90 is 2:3, in which the desired compound 89 is the minor component. Compound 89 was therefore acetylated (acetic anhydride and pyridine) and oxidized (potassium permanganate in acetone) to the lactam 91. Hydrolysis of 91 with 2% potassium hydroxide in methanol gave the lactam alcohol 92. Treatment of 92 with methanesulfonyl chloride in pyridine gave the mesylate which was treated with potassium tert-butoxide in refluxing tert-butyl alcohol. The major product was lactam 93. Lactam 93 was reduced with lithium

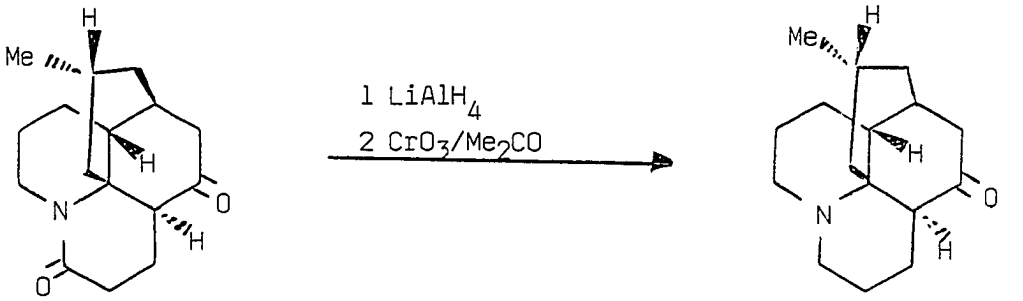
Scheme I


OMe
CO_2Et
^-OEt
EtO_2C
Me
O
70
OH
71
1 EtOH/H^+
2 $LiAlH_4$
3 H^+
72
MeMgI/CuCl
73
1
2 CH_2=CHCONH$_2$
3 H_2O
74
75
HCO_2H
H_3PO_4
76
77
MeO

Scheme I (continued)

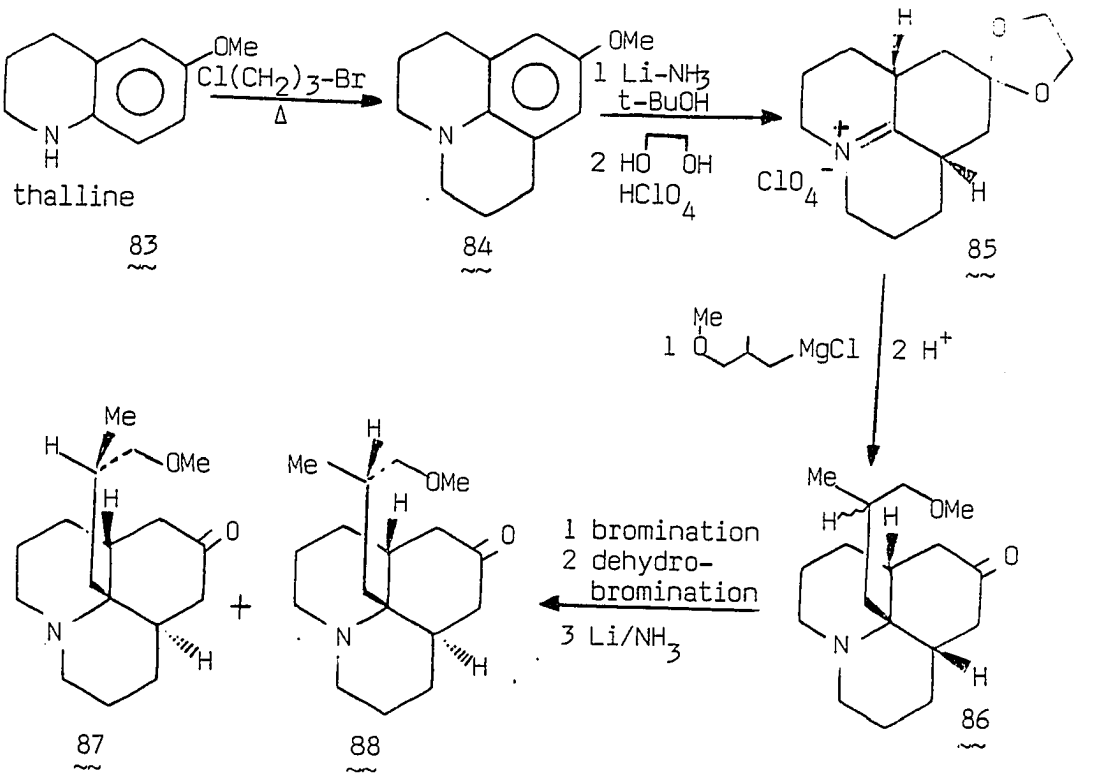


Scheme I (continued)



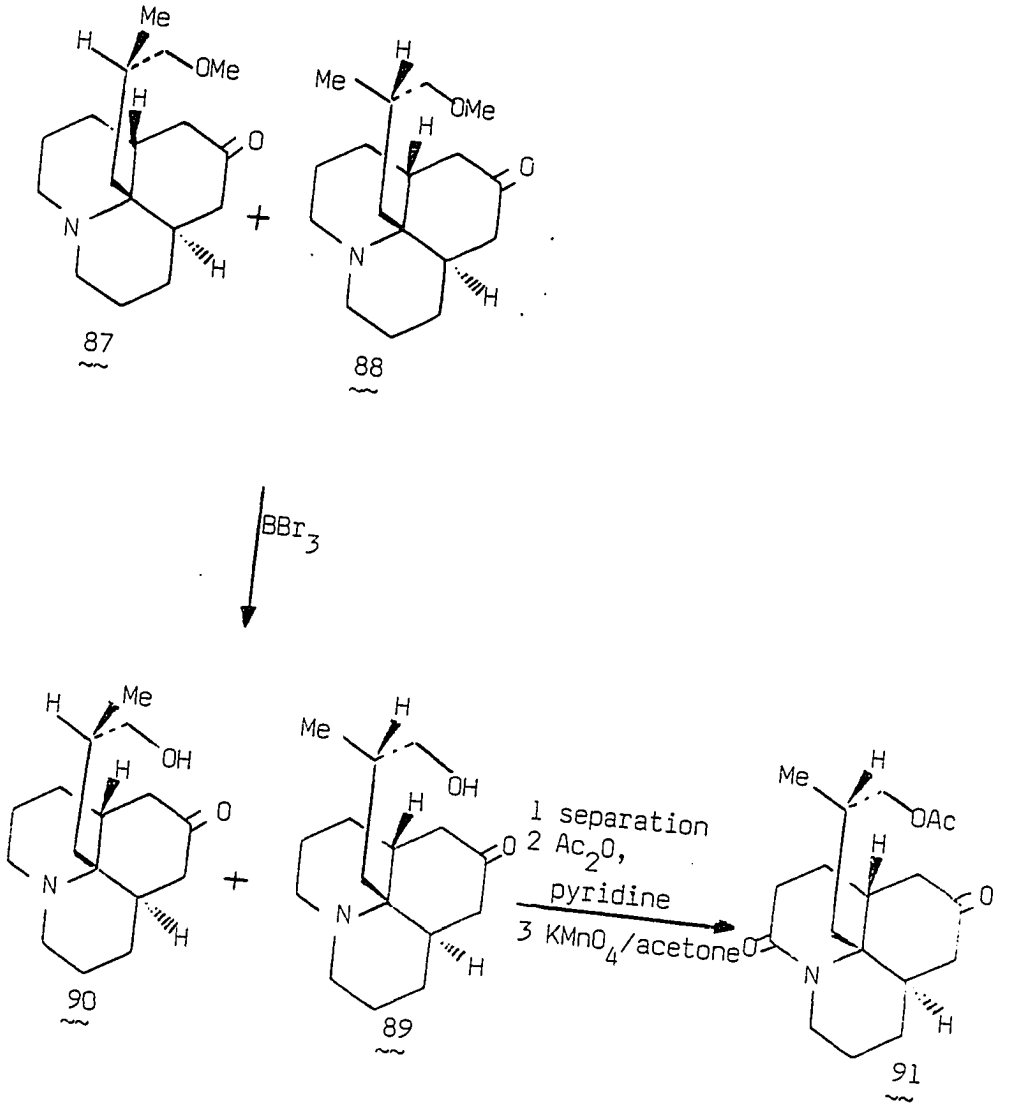
82 69

Scheme II

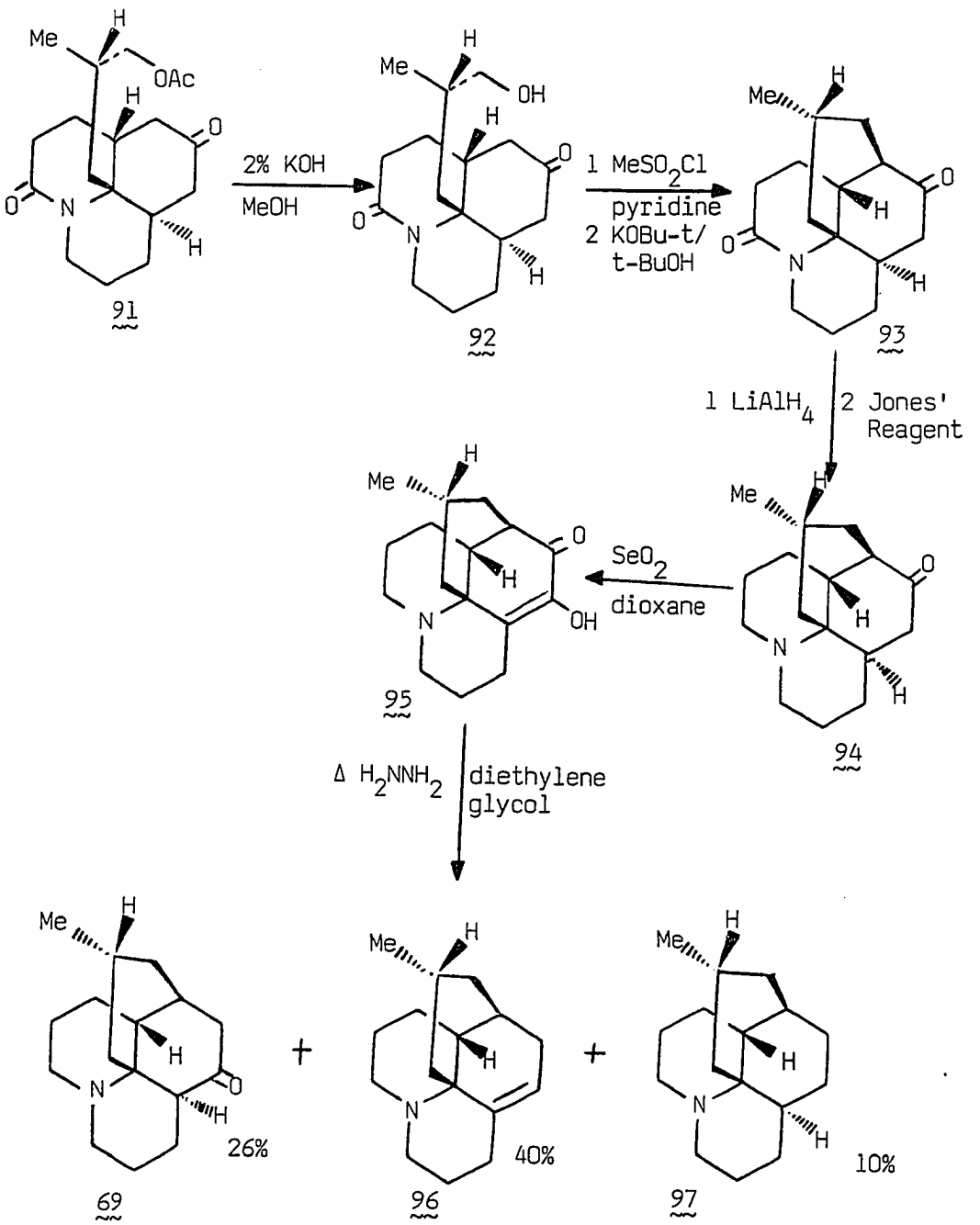


83 84 85 86 87 88

Scheme II (continued)

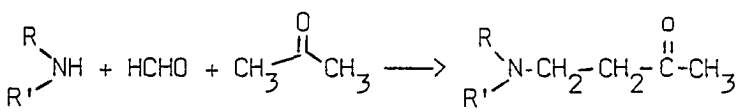


Scheme II (continued)



aluminum hydride, followed by oxidation with Jones' reagent to provide the ketone 94. Oxidation of 94 with selenium dioxide in aqueous dioxane provided the known diosphenol 95. The diosphenol 95 was heated to 155°C for 1 hr with hydrazine hydrate in diethylene glycol. The product, separated on alumina, contained only 26% lycopodine. The A, B and D rings of lycopodine were formed in the first two steps. Most of the effort in this synthesis was directed toward formation of the C ring.

The third synthesis of lycopodine was elegantly done in Professor Heathcock's group (35). The A, B and C rings were formed in one step by an intramolecular Mannich reaction. Reaction of active methylene compounds with formaldehyde and ammonia or primary or secondary amines to give β-amino carbonyl compounds is called the Mannich reaction (41) and is shown in equation 18. There are two approaches to make lycopodine

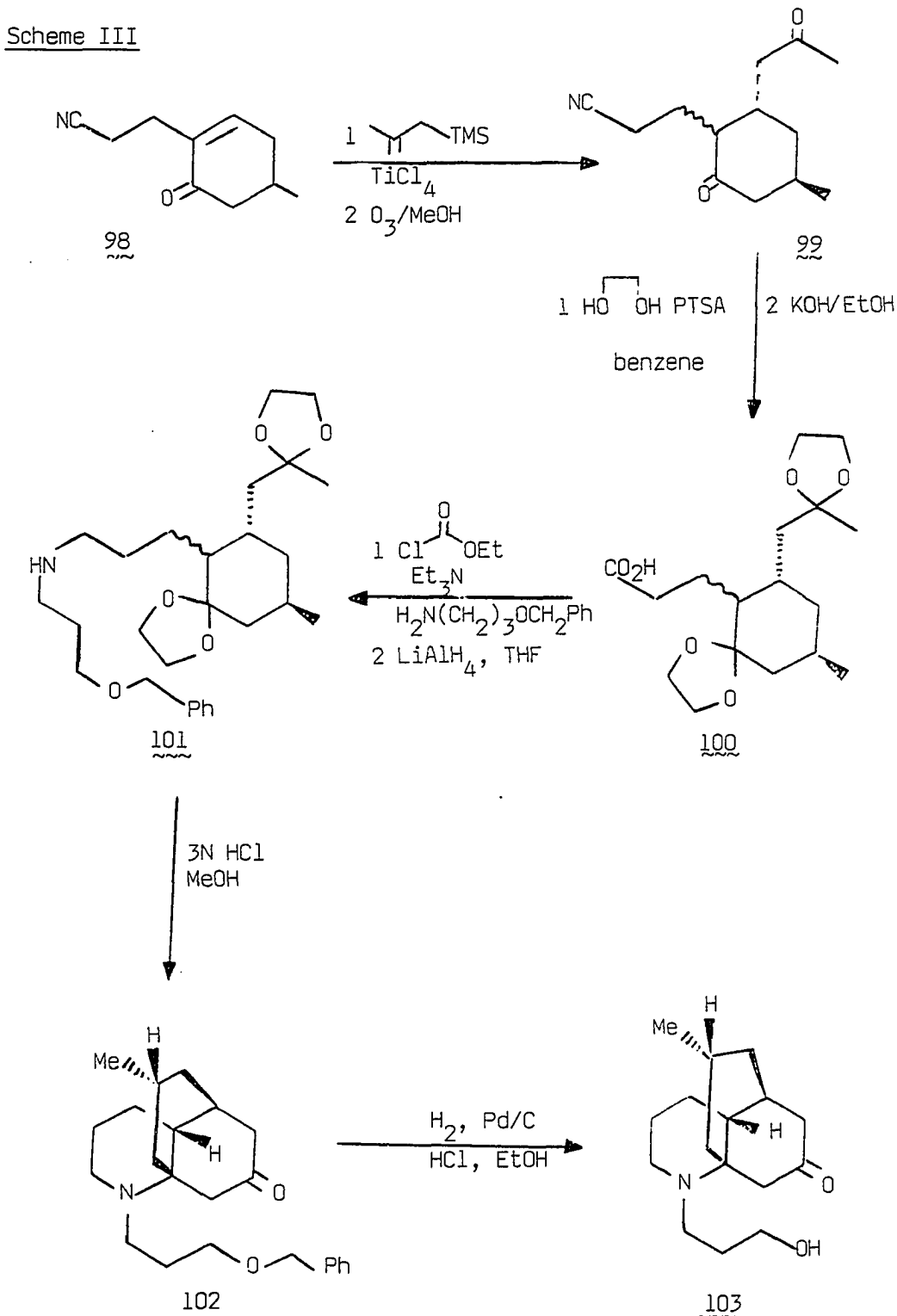


(18)

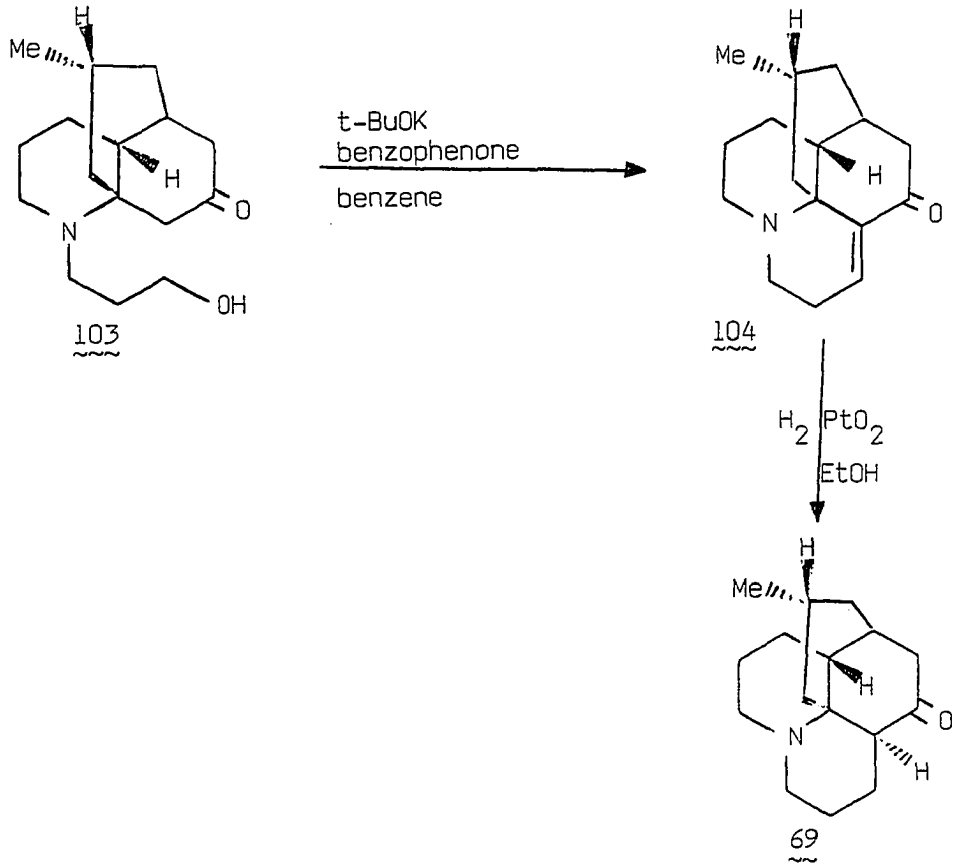
using the same methodology.

Path A is shown in Scheme III. Lewis acid catalyzed Michael addition of methallyltrimethylsilane to 98, termed the Sakurai reaction (42), afforded a highly stereoselective addition with respect to the C-5 methyl group. The ozonolysis of this adduct gave 99. Ketalization of dione 99 followed by alkaline hydrolysis of the nitrile moiety provided acid 100 which was transformed, via the intermediate amide, into amine 101. Treatment of 101 with methanolic HCl resulted in a smooth Mannich cyclization, giving a single amino ketone 102. It

Scheme III


NC
O
98
1 TMS
TiCl4
2 O3/MeOH
NC
O
O
99
1 HO OH PTSA
benzene
2 KOH/EtOH
O O
CO2H
O
O
100
1 Cl OEt
Et3N
H2N(CH2)3OCH2Ph
2 LiAlH4, THF
O O
HN
O
O
O
Ph
101
3N HCl
MeOH
H
Me
H
N
O
O
Ph
102
H2, Pd/C
HCl, EtOH
H
Me
H
N
O
OH
103

Scheme III (continued)



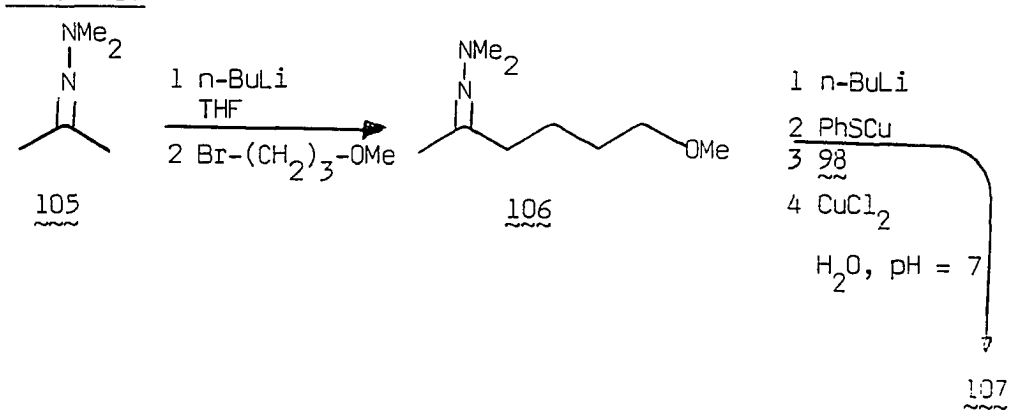
took 14 days to complete the cyclization. Hydrogenolysis of benzyl ether 102 provided the crystalline alcohol 103. Treatment of hydroxy ketone 103 with potassium tert-butoxide and benzophenone in refluxing benzene provided (±)-dehydrolycopodine 104, which was smoothly hydrogenated to obtain (±) lycopodine 69.

The pathway B is shorter and more convergent, but afforded a lower yield (Scheme IV). Hydrazone 106 was prepared by alkylating the N,N-dimethylhydrazone of acetone 105 with 1-methoxy-3-bromopropane. The mixed cuprate reagent was formed from the lithium anion of 106 and cuprous thiophenoxide (43).

As expected, the conjugate addition proceeded smoothly, affording adduct 107. Diketone 107 was smoothly diketalized to diketal 108, which was reduced to the amino diketal 109. This undergoes the Mannich reaction, providing aminoketone 110, which is converted into (±) lycopodine by treatment with HBr in glacial acetic acid followed by neutralization with base.

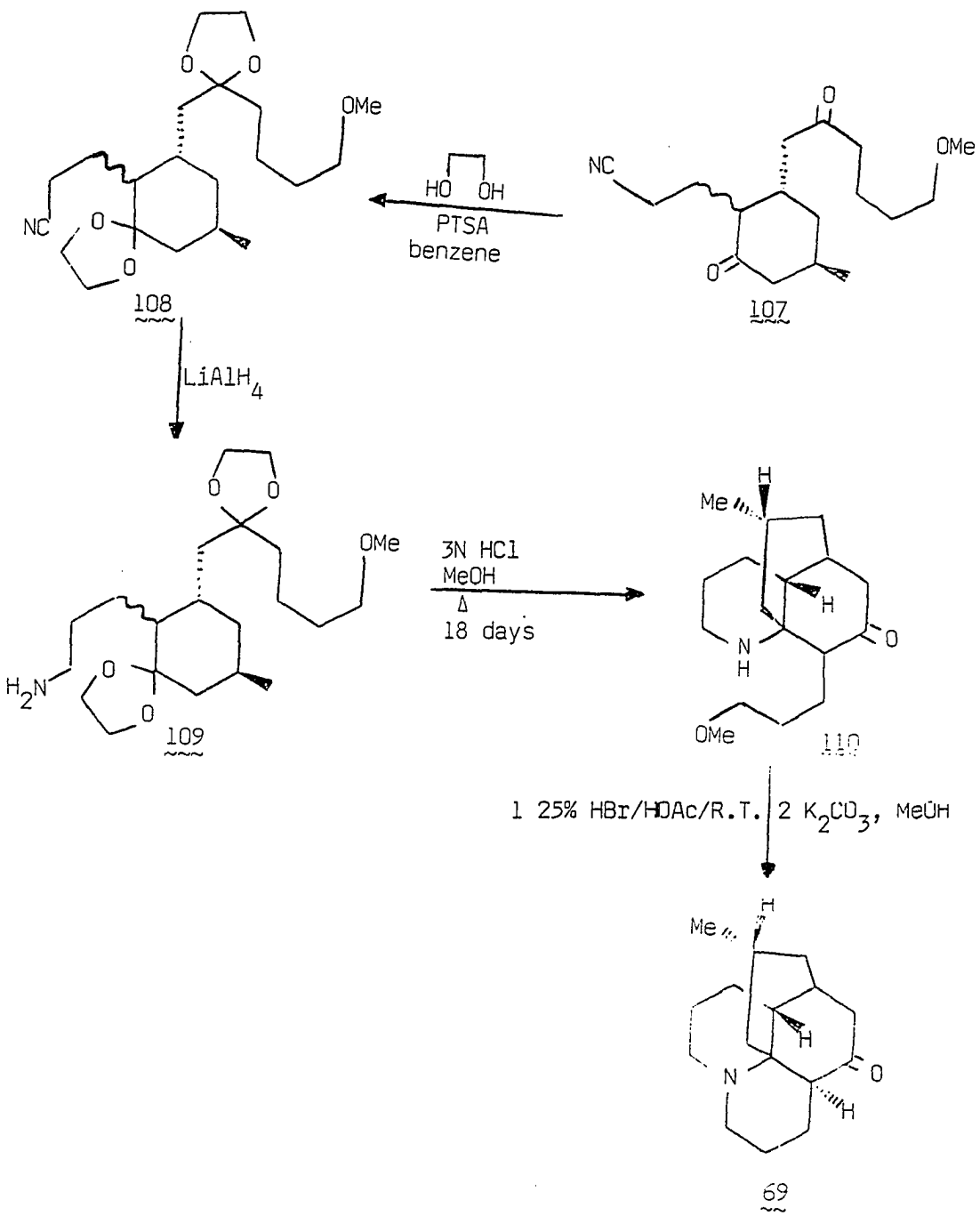
In 1984, Wenkert and Broka were able to synthesize lycopodine by a completely different route (Scheme V) (36). Reduction of dimethyl quinolinate 111 yielded the hexahydro compound 112. Alkylation with the ethylene ketal of 6-bromo-2-hexanone and base afforded 113 (44). Treatment of 113 with m-chloroperbenzoic acid surprisingly led to compound 114. Ketal 114 was treated with acid. Base-catalyzed cyclization then led to ester 116 (45). Treatment of ester 116 with methanolic hydrogen chloride produced 117. Reduction of ester 117

Scheme IV

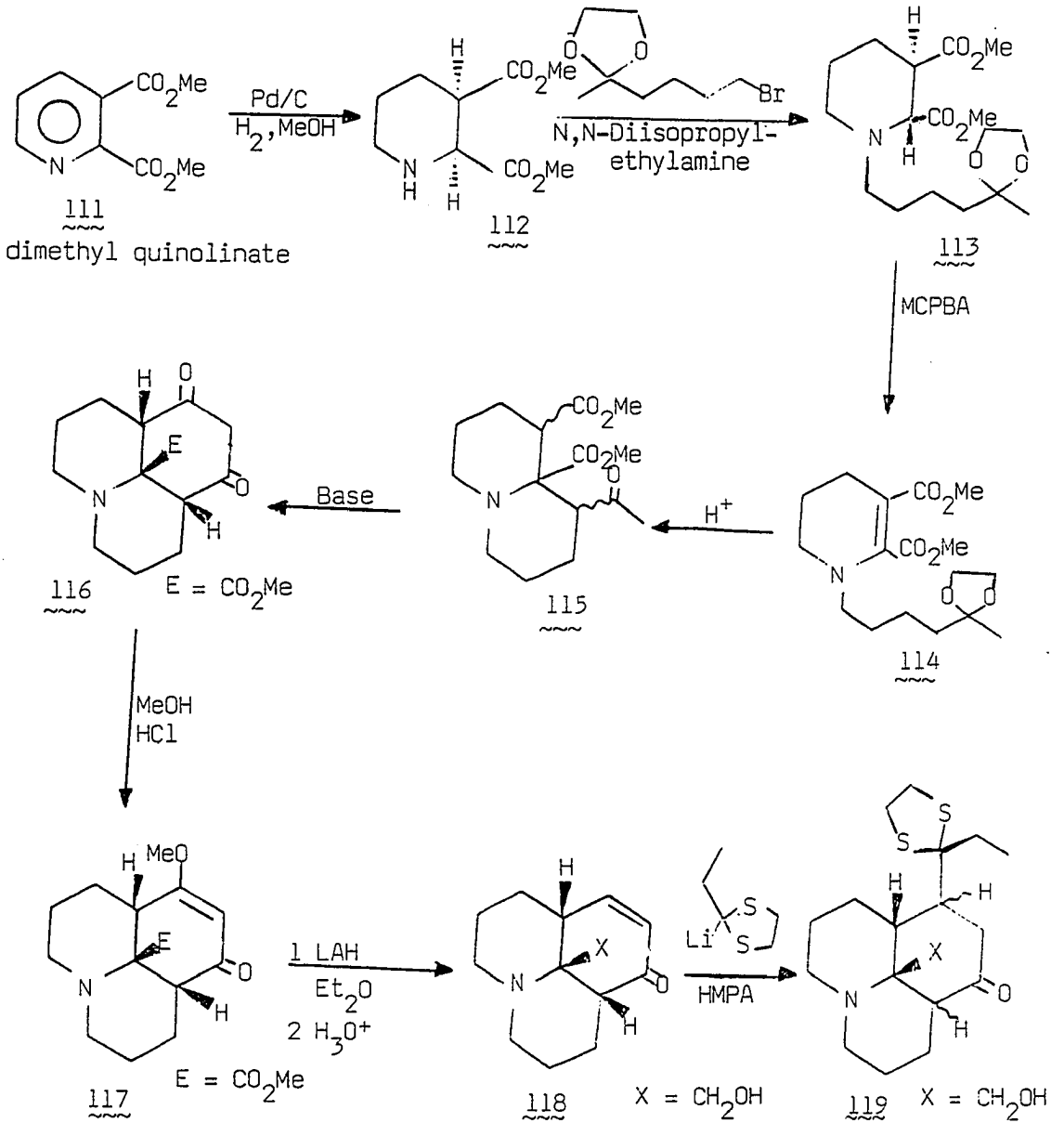


105 106 107

Scheme IV (continued)



Scheme V



111 dimethyl quinolinate

112

113

114

115

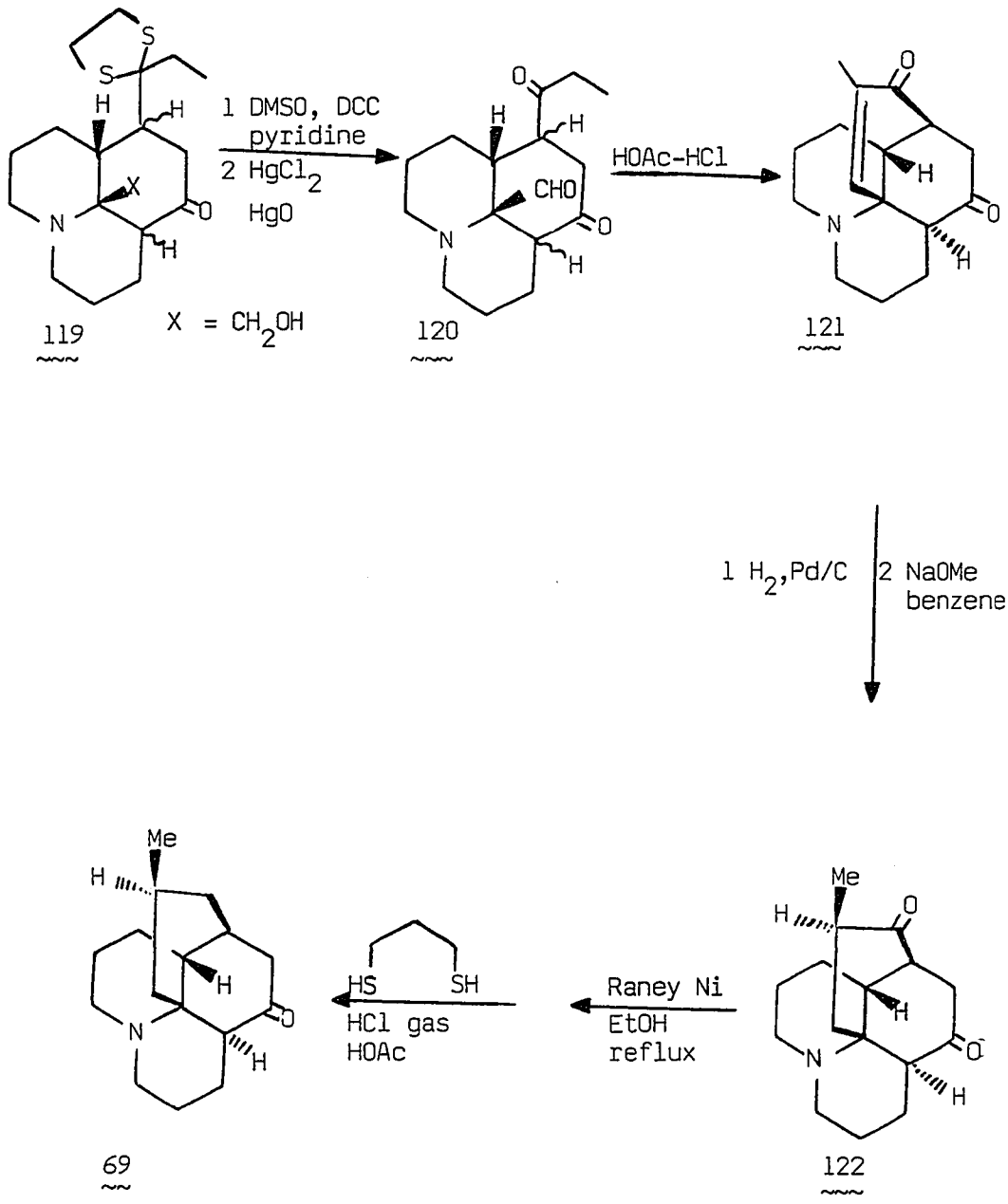
116

117

118

119

Scheme V (continued)



with lithium aluminum hydride in diethyl ether, followed by exposure of the crude product to aqueous acid, produced alcohol 118. Interaction of 118 in tetrahydrofuran solution with 3 equivalents of 2-ethyl-2-lithio-1,3-dithiane and 6 equivalents of hexamethylphosphoric triamide at -78°C yielded 119. Pfitzner-Moffatt oxidation of 119 followed by hydrolysis afforded 120 (46). Acid-induced cyclization of 120 furnished diketone 121. Hydrogenation of enone 121 followed by epimerization with base yielded diketone 122. Conversion of 122 into the thioketal and reduction of the thioketal gave (±) lycopodine 69.

Schumann and coworkers reported a successful total synthesis of lycopodine from 2-cyanoethyl-5-methyl-1,3-cyclohexadione 123 in 6 steps (Scheme VI) (37). Ketone 123 was treated with lithium aluminum hydride. Oxidation with pyridinium dichromate yielded imine 125. The stereoselective 1,3-annulation reaction of imine 125 with acetone dicarboxylic acid provided the tricyclic ketone 126. Ketone 126 reacted with 3-bromo-1-propanol to yield keto alcohol 103 which is identical to Heathcock's intermediate. Two more steps will afford the target molecule.

A comparison of the syntheses is shown in Table II. The order of the ring formation, the number of steps and the overall yield are quite different.

Encouraged by the results of our bridgehead carbocation chemistry described in Part I, lycopodine was chosen as a target to test the utility of the bridgehead bond formation methodology.

Scheme VI

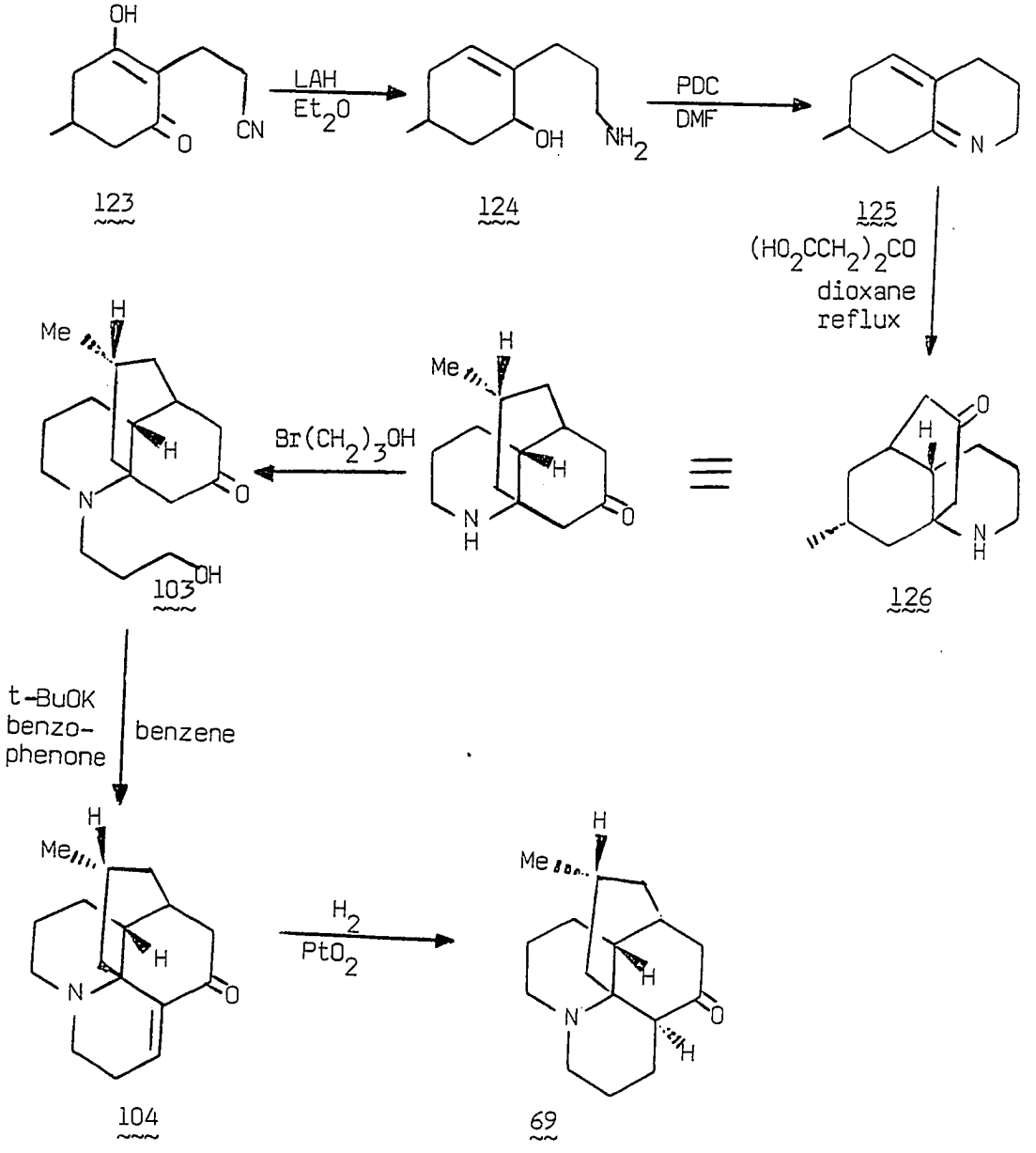
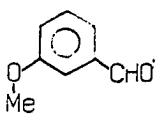
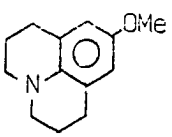
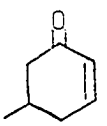
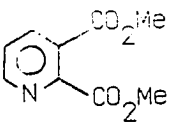
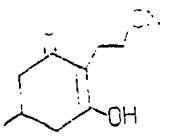

OH
CN
O
LAH
Et_2O
OH
NH_2
PDC
DMF
N
123
124
125
$(HO_2CCH_2)_2CO$
dioxane
reflux
Me
H
N
O
OH
103
$Br(CH_2)_3OH$
126
t-BuOK
benzo-
phenone
benzene
104
H_2
PtO_2
69

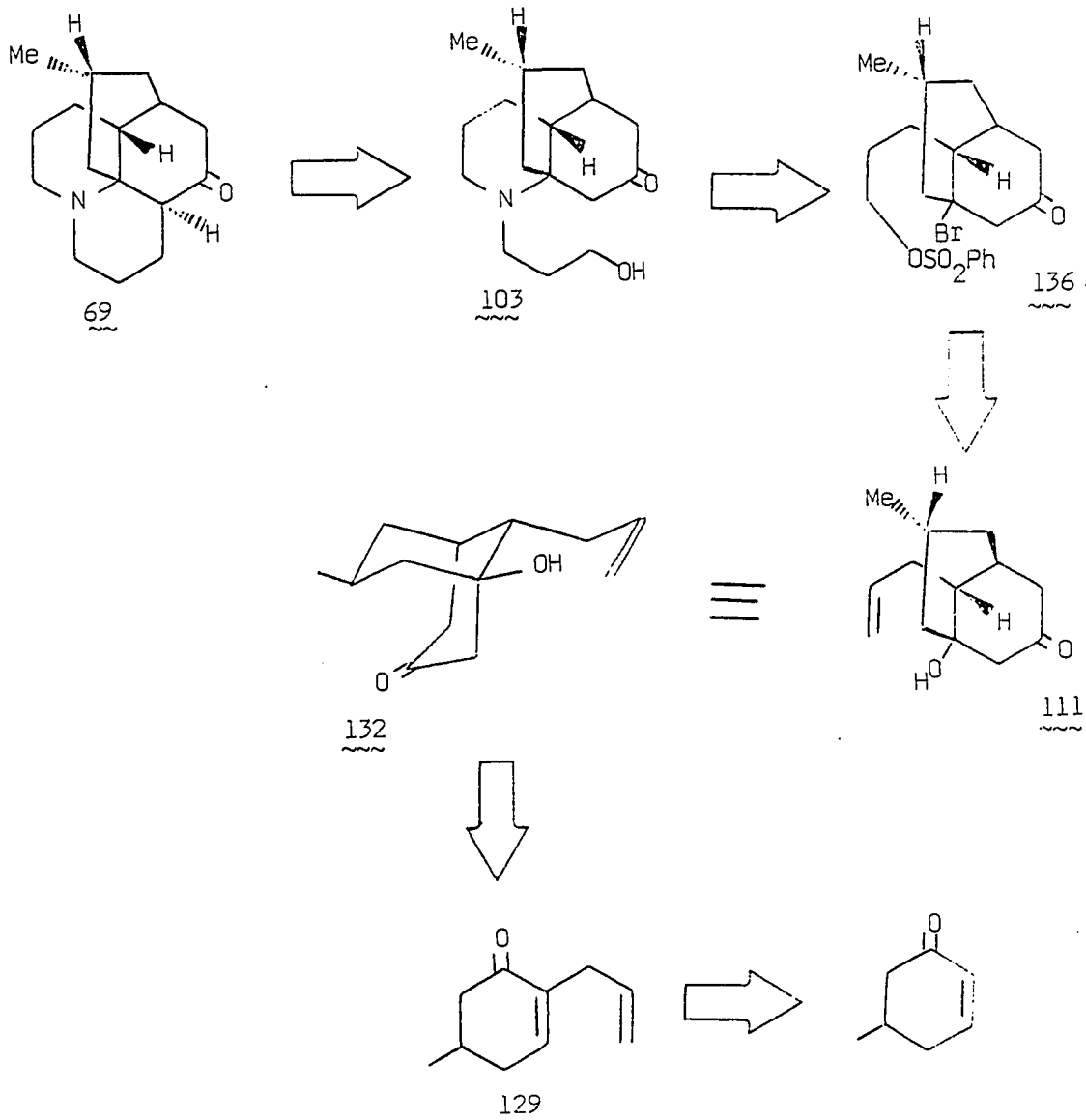
Table II. A comparison of five total syntheses

	Stork's route	Ayer's route	Heathcock's route	Wenkert's route	Schumann's route
The order of ring formation	B⟶A ↓ D⟵C	AB⟶D ↓ C	B⟶A ↓ D⟵C	A⟶D ↓ C⟵B	C⟶A ↓ D⟵B
The number of steps to the lycopodine	17	17	13	15	6
Starting material					
Overall yield if available	1.1%	0.06%	16.6%	<0.65%	10.5%

RESULTS AND DISCUSSION

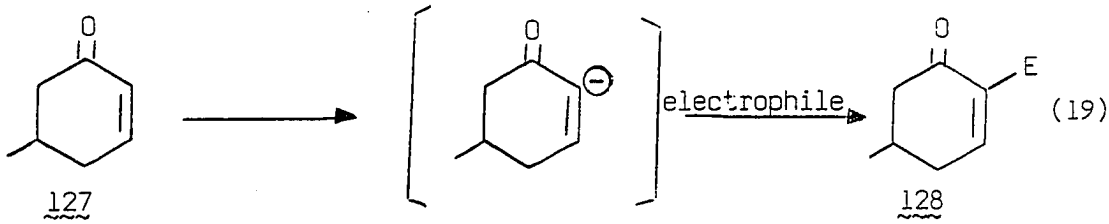
The retrosynthetic analysis of our approach to (±)-lycopodine is shown in Scheme VII. Two challenges are present in this design. Firstly, the diequatorial orientation of the methyl and allyl substituents

Scheme VII



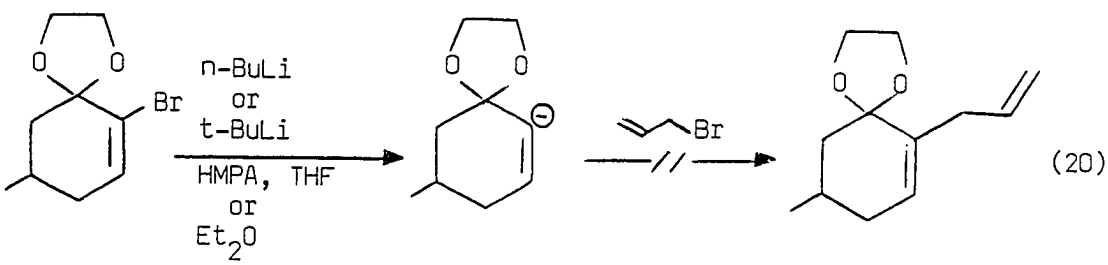
in bicyclic system 132 is required. Secondly, the bridgehead carbocation generated from 136 must be trapped selectively to form the desired carbon-nitrogen bond.

The most direct route to introducing a substituent at the α-position of an α,β-unsaturated cyclohexenone is the generation of the corresponding α-ketovinyl anion followed by trapping with an appropriate



(19)

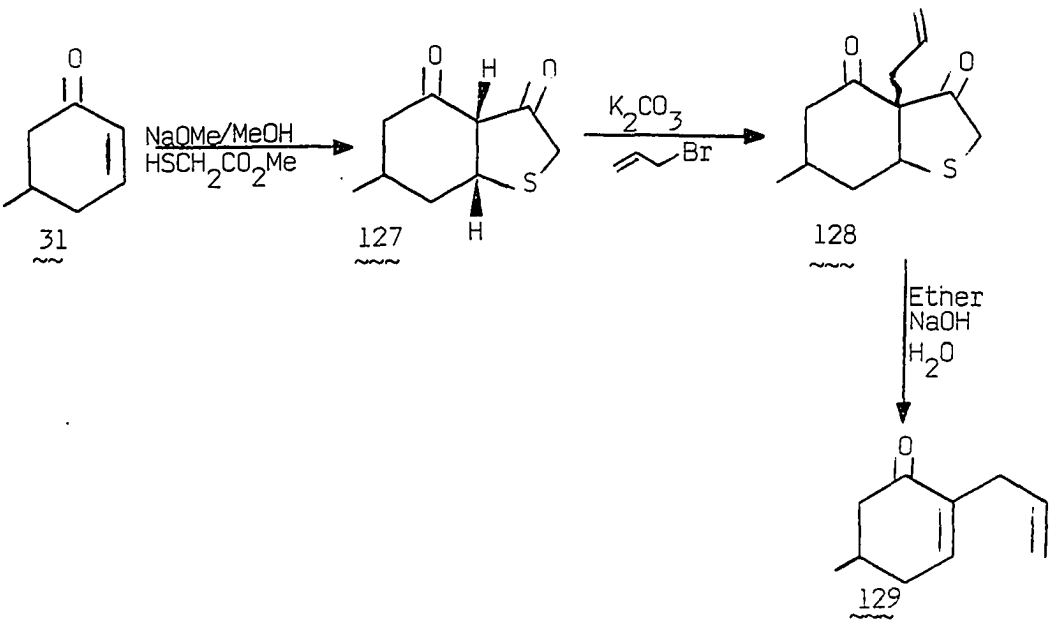
electrophile (Eq. 19). The metallation of an α-bromo ketal followed by addition of allyl bromide did not provide the desired compound (Eq. 20) (47). However, the same type of transformation can be achieved



(20)

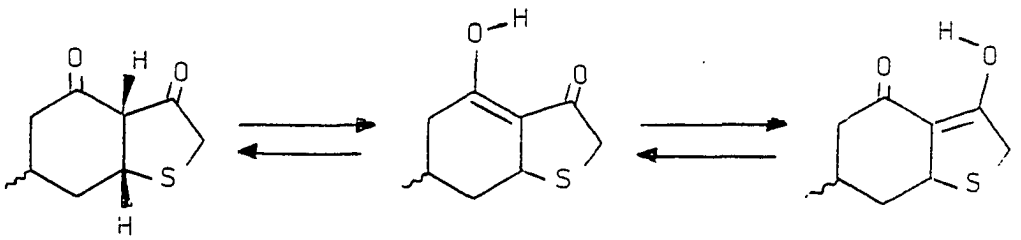
by an alternative route (48).

To a mixture of ethyl 2-mercaptoacetate and sodium methoxide in methanol was added 5-methyl-2-cyclohexen-1-one 31 to provide the bicyclic compound 127. Spectroscopic data indicated that the diketone 127 is highly enolized and is best represented as the equilibrium



31 127 128 129

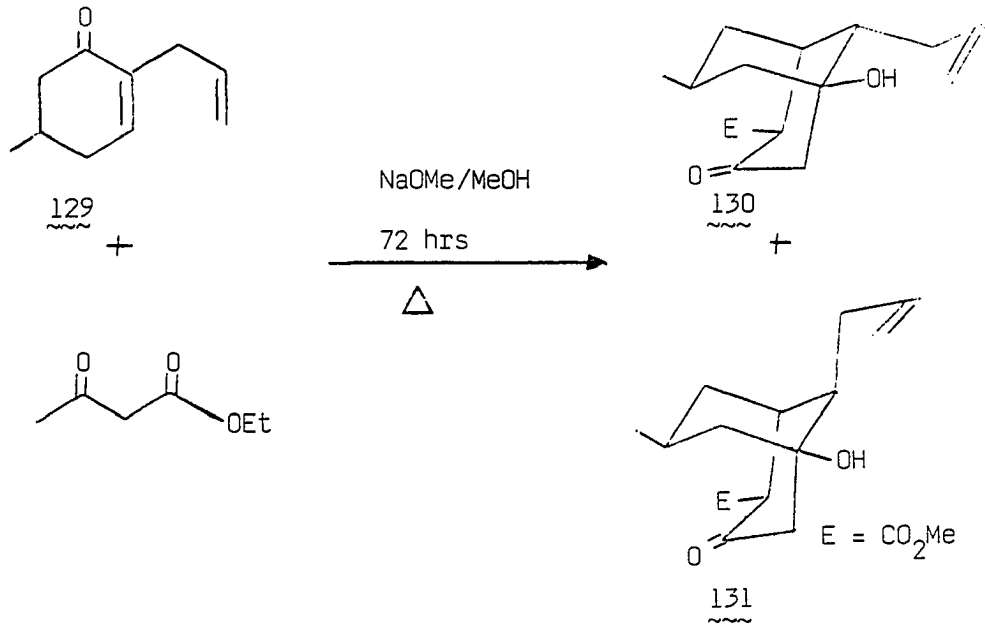
mixture of ketone-enol tautomers as shown (49). Treatment of 127 with potassium carbonate in the presence of allyl bromide yielded the



127a 127b 127c

diketone 128. Treatment of an ether solution of 128 with aqueous sodium hydroxide solution gave the desired compound 129 which is formed via a retro-Dieckmann-Michael reaction. Even though the overall yield is only 30%, compound 129 can be made in large quantities by using readily available and cheap materials.

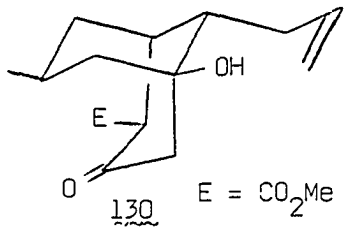
To a mixture of ethyl acetoacetate and one equivalent of sodium methoxide in methanol solution was added compound 129. The solution was refluxed for 72 hours to give bicyclic compounds 130 and 131. The reaction proceeded very slowly, probably due to the steric hindrance



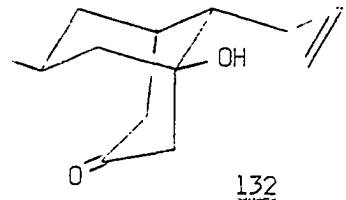
of the allyl group which could interfere with the intramolecular aldol condensation step. The incompleteness of the reaction (64% conversion) can also be ascribed to interference of the allyl group.

Since compounds 130 and 131 are not cleanly separated by column chromatography, they were decarbomethoxylated to the corresponding compounds 132 and 133 with refluxing aqueous potassium hydroxide solution. Compounds 132 and 133 could be separated by column chromatography. The gas chromatographic integration showed that the ratio of these two

diastereomers was 19:1. The R_f is 0.45 for the major compound and 0.35 for the minor compound on thin layer chromatography using the mixed solvent system of 1:3 ethyl acetate:hexane.



130 E = CO_2Me

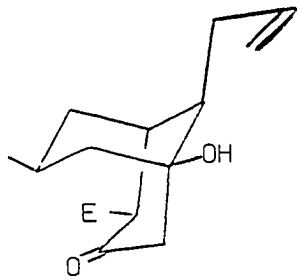


132

+

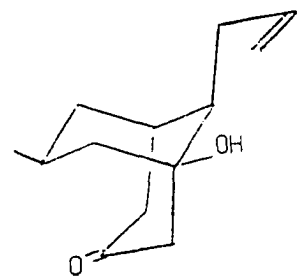
KOH
MeOH
H_2O

+



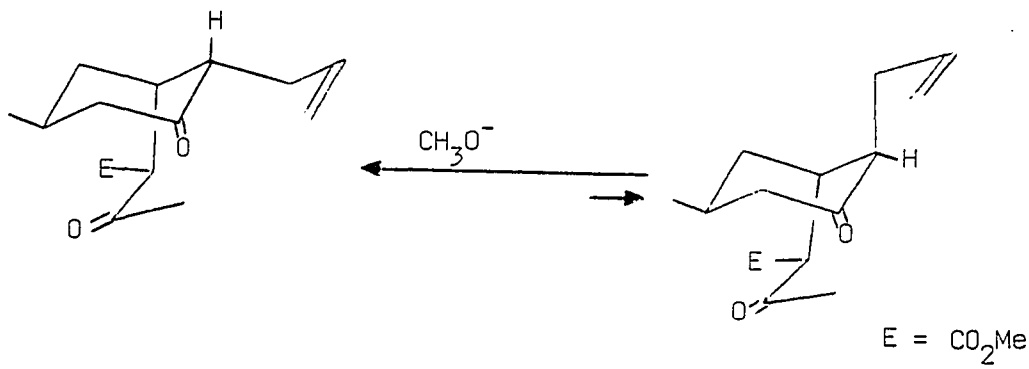
E = CO_2Me

131



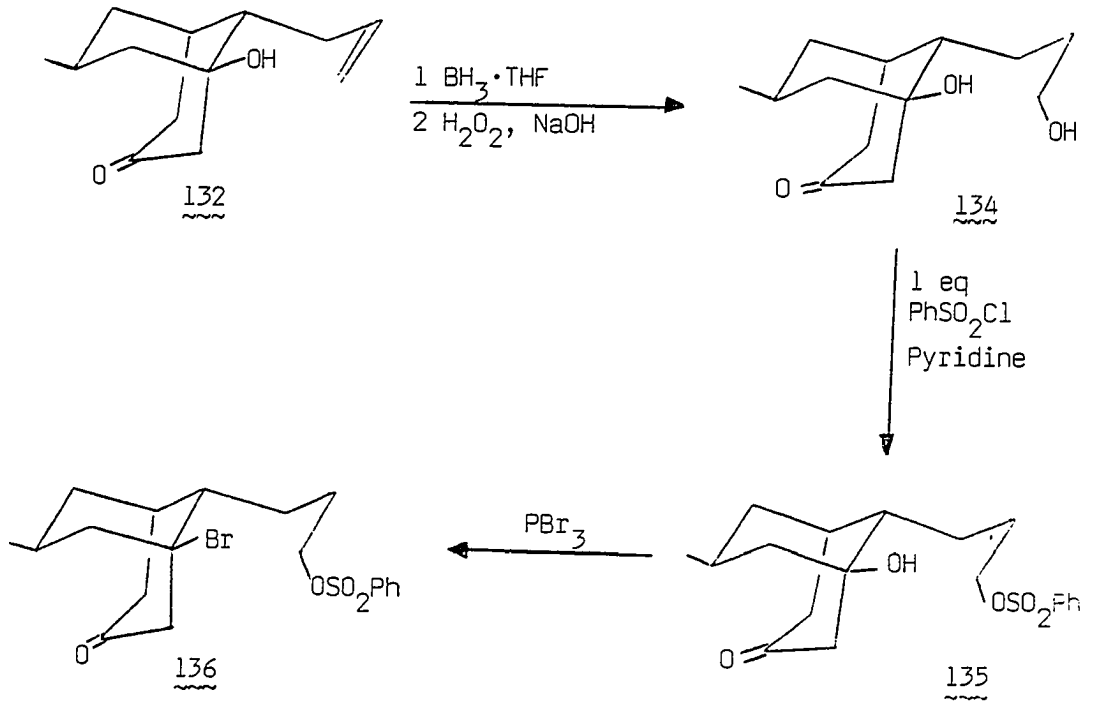
133

The diequatorial isomer 132 should be the major product because the stereogenic center generated by the Michael addition can be epimerized. In principle, the diequatorial intermediate should



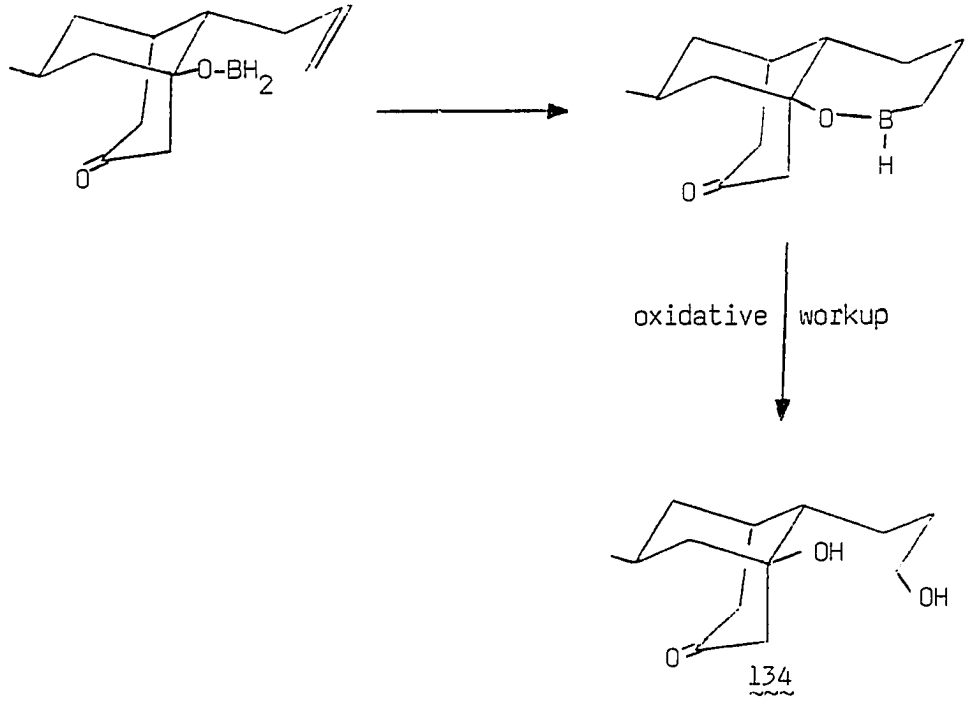
be more favorable than the axial-equatorial isomer under equilibrium conditions. However, we were unable to prove our assumption based on spectroscopic data. Therefore; we temporarily assumed the major product was the desired one.

Treatment of allyl compound 132 with borane-tetrahydrofuran complex followed by oxidative workup yielded the diol 134. The chemoselectivity of the hydroboration is probably controlled by the bridgehead hydroxyl group. The borane may have reacted first with the alcohol followed by an intramolecular hydroboration on the double bond. Treatment of 134 with one equivalent of benzenesulfonyl chloride in the presence of pyridine provided monosulfonate 135. The bridgehead alcohol 135 could be converted to the bridgehead bromide 136 by treatment with



phosphorus tribromide. The overall yield from 132 to 136 is 48%.

Now, the stage is set for the crucial reaction.



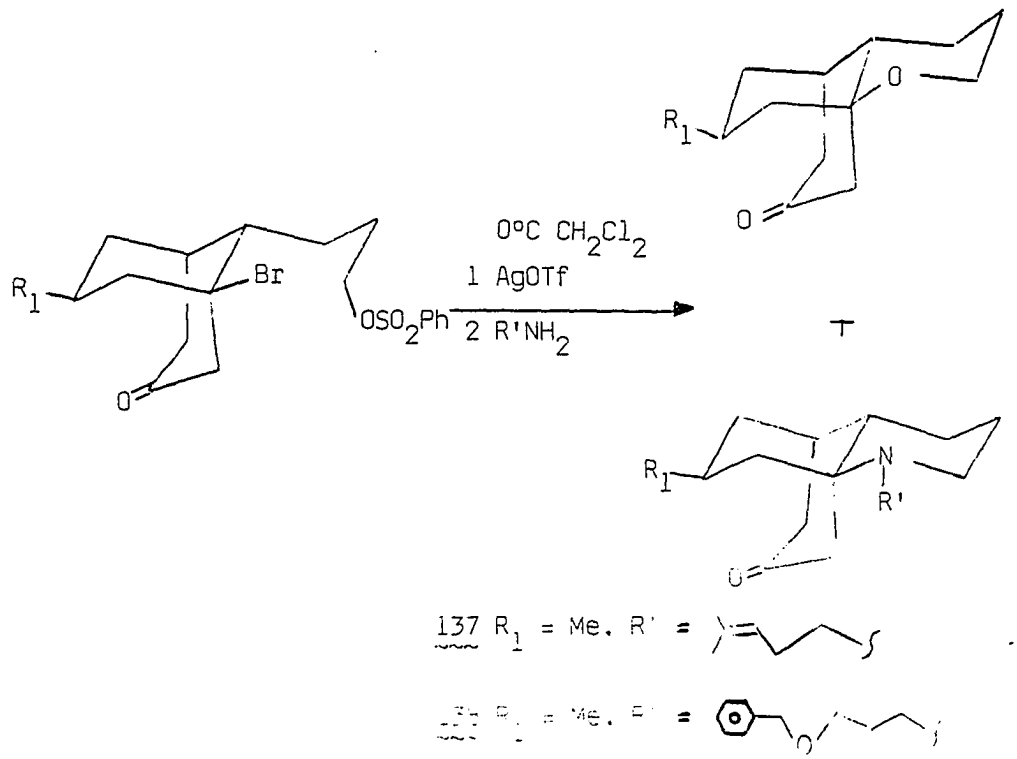
In order to prevent silver-amine complex formation, the amine could only be added after the bridgehead triflate formation. However, the intramolecular O-alkylation competes with intermolecular N-alkylation in this reaction. Table III indicates a special procedure we found to get predominantly the N-alkylation product. Bridgehead triflate formation is a very fast process. If the amine was added in large excess immediately after the addition of the silver triflate, the intermolecular N-alkylation product is almost the sole product.

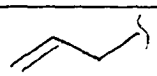
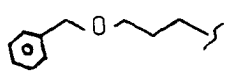
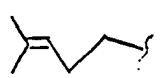
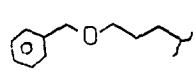
Hydrogenolysis of benzyl ether 138 provided the crystalline alcohol 103. The melting point, NMR, IR and UV spectral data are all identical to those reported by Heathcock and coworkers (35). The UV spectrum of 103 contains an absorption at 220 nm which has been noticed in lycopodine and other lycopodium alkaloids, but not in 12-epilycopodine (50). Therefore, we have now confirmed that compound 132 is not only the major component but also the desired product.

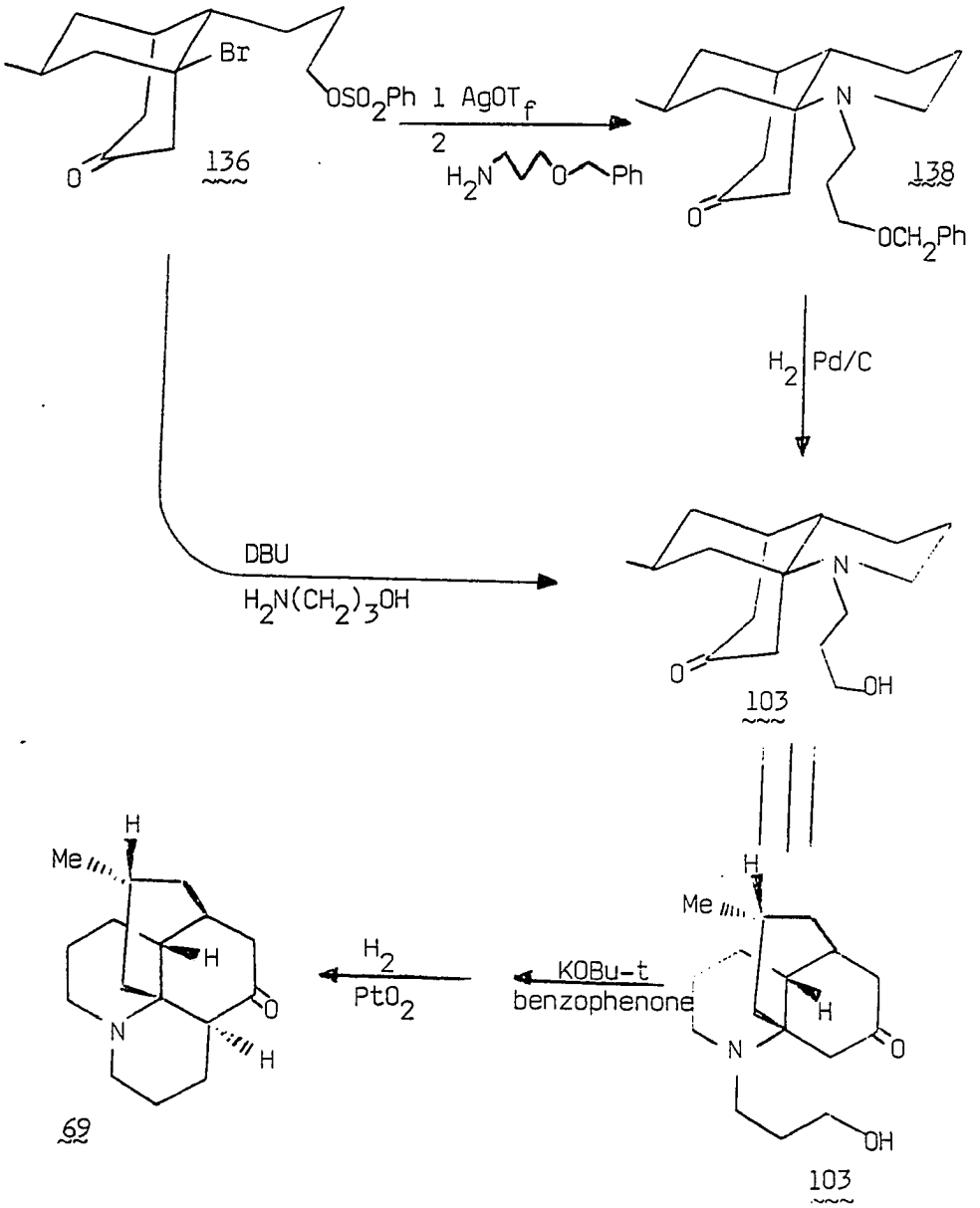
We also investigated the possibility of trapping the bridgehead enone by 3-amino-1-propanol. Treatment of compound 136 with DBU followed by trapping with 3-amino-1-propanol gave compound 103 as the sole product in quantitative yield. This alternative way shortens the synthesis by one step.

Treatment of hydroxy ketone 103 with potassium tert-butoxide and benzophenone in refluxing benzene provided (±)-dehydrolycopodine 104, which was smoothly hydrogenated to obtain (±)-lycopodine 69.

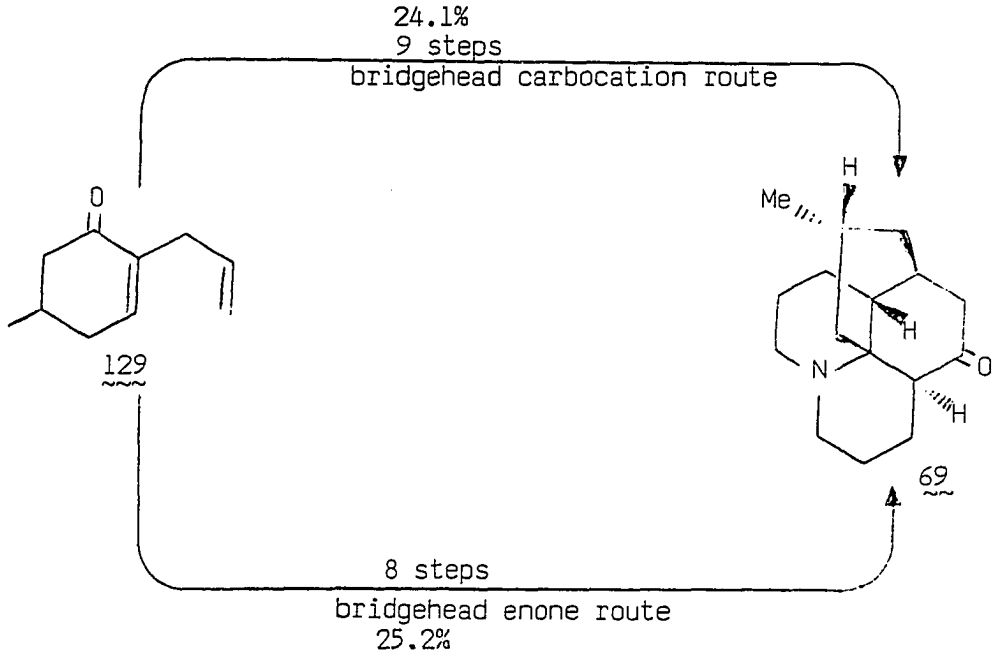
Table III. Competition of the intramolecular O- and intermolecular N-alkylation



R_1	R'	Time to add amine after addition of $AgOT_f$	The number of the eq. of amine used	O-alkylation:N-alkylation
H		10 min	1.2 eq	1:3
H		1 min	1.5 eq	major:trace
Me		0.5 min	5 eq	1:9
Me		immediately	5 eq	trace:major



Our racemic lycopodine has a C-13 NMR spectrum identical to that reported in the literature (51). The overall yield starting from compound 129 is about 25%. To our knowledge, this is the first time



a bridgehead enone has been used in natural product synthesis. It is only the second time that bridgehead carbocations have been utilized in a natural product synthesis.

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to usage. Methylene chloride was distilled from phosphorus pentoxide. Benzene was distilled from lithium aluminum hydride. N,N-Dimethylformamide (DMF) was dried over 4Å molecular sieves. Acetonitrile was distilled from calcium hydride. All reactions were conducted under a nitrogen atmosphere, and all extracts were dried over anhydrous sodium sulfate. Apparatus for experiments requiring anhydrous conditions was flame-dried under a stream of nitrogen or was dried in an oven at 150°C for 12 hours. Flash chromatography was performed on Kieselgel 60, mesh 230-400. Column chromatography was performed on Grace silica gel, grade 62, mesh 60-200. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or Acculab 2 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (single), d (doublet), t (triplet), and m (multiplet); addition of br indicates a broadened pattern. Carbon-13 NMR spectra were determined on a JOEL

FX-90Q or Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). Ultraviolet spectra were obtained on a Perkin-Elmer 320 UV-Vis spectrophotometer. High resolution mass spectra were recorded on a AEI-MS 902 high resolution mass spectrometer. Low resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Elemental analyses were determined by Galbraith Laboratories, Inc.

4-(1-Bromo-2-bicyclo[2.2.2]oct-5-enyl)-1-butene 15

To a solution of 6.65 mmol of lithium diisopropylamide (LDA) in 10 mL of tetrahydrofuran (THF) at -78°C was added 943 mg of compound 12 (5.78 mmol) in 5 mL of THF over 5 min. The reaction was stirred at -78°C for 1 h. The 4-bromo-1-butene (0.82 mL, 8.1 mmol) was then added and the reaction was stirred at -78°C for 30 min and then allowed to warm to room temperature. The reaction was partitioned twice between water and methylene chloride. The organic layer was dried and concentrated. The crude alkylated product was obtained in approximately 90% yield and was taken on to the next step without purification.

To a solution of sodium (302 mg, 13.13 mmol) in 25 mL of liquid ammonia was added the alkylated nitrile (285 mg, 1.31 mmol) in 1 mL of THF. The solution was stirred at -33°C for 1 h. Solid ammonium chloride was then carefully added to quench the excess sodium. After the blue color of the solution disappeared, the ammonia was then

allowed to evaporate, water was added and the aqueous layer was extracted with ether. The organic layer was dried and concentrated. The crude decyanated product was sufficiently pure to be taken on to the next step.

To a solution of the decyanated product (841 mg, 4.4 mmol) in 20 mL of methylene chloride at -78°C was added dropwise a 1 M solution of borontribromide in hexane (5.4 mL, 5.4 mmol). The solution was stirred at -78°C for 50 min. Aqueous sodium bicarbonate solution was then added. The aqueous layer was extracted twice with ether, dried and concentrated to afford the crude product. The product was purified by passage through a silica gel column using hexane as the eluent. The overall yield of this sequential transformation is 56%. NMR ($CDCl_3$) δ 1.1-2.8 (m, 12 H), 4.8-6.7 (m, 5 H); IR ($CDCl_3$) 3050, 3080, 2940, 2860, 1645, 1445, 985, 900, 735 cm^{-1}. MS (m/e) 78, 91, 105, 119, 133, 160, 161, 241, 320 (M^+), 322 (M^+).

1-Methoxybicyclo[2.2.2]octane-2-carbonitrile 16

To a suspension of 10% platinum on carbon in 10 mL of ethanol under a hydrogen atmosphere was added 1-methoxybicyclo[2.2.2]oct-5-ene-2-carbonitrile 12 (2.12 g, 12.95 mmol) in 20 mL of ethanol. The suspension was filtered through Celite and concentrated to provide the crude product. It was chromatographed on silica gel using 1:10 ethyl acetate:hexane to provide 1.95 g (91% yield) of pure product. NMR ($CDCl_3$) δ 1.0-3.1 (m, 12 H), 3.25 (s, 3 H); IR (film) 2950, 2870, 2830, 2240, 1455, 1110 cm^{-1}.

4-(1-Bromo-2-bicyclo[2.2.2]octyl)-1-butene 17

Using the procedure developed for compound 15, compound 16 can be converted to compound 17 in 42% yield. NMR ($CDCl_3$) δ 1.1-2.45 (m, 16 H), 4.75-6.25 (m, 3 H); C-13 NMR ($CDCl_3$) δ 23.86, 28.85, 29.01, 31.17, 32.75, 34.21, 35.78, 39.90, 43.47, 72.40, 114.60, 138.60; IR (film) 3090, 2950, 2870, 1640, 1450, 1310, 1260, 975, 910 cm^{-1}. High resolution mass spectrum for $C_{12}H_{19}Br$ requires 242.06701, measured 242.06760.

3-(1-Bromo-2-bicyclo[2.2.2]octyl)-1-propene 18

Using the procedure developed for compound 15, compound 16 can be converted to compound 18 in 35% yield. NMR ($CDCl_3$) δ 1.1-2.45 (m, 14 H), 4.75-6.25 (m, 3 H); C-13 NMR ($CDCl_3$) δ 23.81, 28.85, 29.01, 32.75, 35.13, 39.46, 39.90, 43.58, 71.81, 116.07, 136.92; IR ($CDCl_3$) 3070, 2920, 2860, 1640, 1450, 900 cm^{-1}. High resolution mass spectrum for $C_{11}H_{17}Br$ requires 228.05182, measured 228.05136.

General procedure for intermolecular bridgehead carbocation trapping reactions

To a suspension of silver salt (1.1 equivalents) in methylene chloride was added the mixture of the corresponding bromide and nucleophile in methylene chloride at 0°C. The suspension was stirred at 0°C for 1 h. The reaction was partitioned between aqueous sodium chloride and methylene chloride. The organic layer was dried and concentrated to afford the crude product. Silica gel column chromatography was used to purify the product.

General procedure for intramolecular bridgehead carbocation trapping reactions

To a solution of the bromide (0.5 M in methylene chloride at 0°C) was added a 10% excess of the requisite silver salt. The suspension was stirred for 1 h. The reaction was partitioned between aqueous sodium chloride and methylene chloride. The organic layer was then dried, concentrated and purified by passage through silica gel.

3-Allyltricyclo[5.2.2.$0^{1,5}$]undecane 19

Using the general procedure, compound 18 (102.4 mg, 0.45 mmol) was converted to compound 19 with 56 mg of allyltrimethylsilane (0.49 mmol) and 96 mg of silver triflate (0.49 mmol) at 0°C. The reaction yield was 51%. NMR ($CDCl_3$) δ 1.08-2.50 (m, 19 H), 4.90-6.56 (m, 3 H); IR (CH_2Cl_2) 3080, 2960, 2880, 1650, 1460, 1275, 923, 750, 710 cm^{-1}. MS (m/e) 67, 79, 81, 93, 107, 121, 133, 149, 161, 162, 190 (M^+). High resolution mass spectrum for $C_{14}H_{22}$ requires 190.17215, measured 190.1717.

3-Phenyltricyclo[5.2.2.$0^{1,5}$]undecane 20

To a solution of 155 mg compound 18 (0.68 mmol) in 6 mL of benzene was added 100 mg of aluminum chloride (0.74 mmol) at room temperature. The solution was stirred at room temperature overnight. The solution was partitioned between aqueous sodium bicarbonate and methylene chloride. The organic layer was dried and concentrated. The crude product was chromatographed using hexane as eluent to afford 77 mg of product. (50% yield) NMR ($CDCl_3$) δ 0.9-2.8 (m, 17 H), 7.00-7.50 (m, 5 H); IR (CH_2Cl_2)

3030, 3015, 2920, 2850, 1605, 1490, 1450, 1375, 1265, 910, 740 cm^{-1}. MS (m/e) 55, 67, 77, 91, 105, 115, 129, 141, 155, 169, 183, 197, 211, 226 (M^+). High resolution mass spectrum for $C_{17}H_{22}$ requires 226.17215, measured 226.1723.

2-(3-Tricyclo[5.2.2.$0^{1,5}$]undecyl)cyclohexanone 21

Using the general procedure, compound 18 (112 mg, 0.49 mmol) was converted to compound 21 with 1-trimethylsilyloxycyclohexene (87.4 mg, 0.51 mmol) and silver triflate (105 mg, 0.54 mmol) at 0°C. The reaction yield was 56%. NMR ($CDCl_3$) δ 1.1-2.7 (m, 26 H); IR (film) 3060, 2930, 2860, 1700, 1675, 1610, 1440, 1260, 1120, 720 cm^{-1}. MS (m/e) 58, 67, 79, 91, 98, 107, 121, 135, 149, 164, 178, 192, 210, 231, 246, 260 (M^+).

2-Allyl-1-trifluoroacetoxybicyclo[2.2.2]octane 22

To a solution of compound 17 (180 mg, 0.74 mmol) in 2 mL of ethyl ether was added silver trifluoroacetate (172 mg, 0.78 mmol) at 0°C under nitrogen. The reaction solution was stirred at 0°C for 1 h. The reaction was partitioned between aqueous sodium chloride and ether. The organic layer was dried and concentrated to afford the crude product. The crude product was purified by silica gel column eluted with 5:1 hexane:ethyl acetate to afford 156 mg of the product. (76% yield) NMR ($CDCl_3$) δ 0.9-2.5 (m, 16 H), 4.8-6.2 (m, 3 H); IR ($CDCl_3$) 2940, 2880, 1775, 1375, 1220, 1160, 900, 720 cm^{-1}.

4-(1-Trifluoroacetoxy-2-bicyclo[2.2.2]octyl)-1-butene 23

Using the procedure developed for 22, compound 18 (72 mg, 0.31 mmol) was converted to compound 23. The crude product was chromatographed on silica gel using hexane to yield 61 mg (75%) of 23. NMR ($CDCl_3$) δ 1.1-2.6 (m, 14 H), 4.8-6.1 (m, 3 H); IR (film) 3070, 2930, 2870, 1770, 1650, 1450, 1360, 1200, 1150, 1000, 900 cm^{-1}.

3-(1-Bromo-2-bicyclo[2.2.2]octyl)propanal 24

Through a solution of compound 17 (2.31 g, 9.51 mmol) in 15 mL of methylene chloride at -78°C was passed ozone until the solution turned blue. The solution was flushed with nitrogen to remove the excess ozone. Triphenylphosphine (2.62 g, 10 mmol) was then added and the solution was allowed to warm to room temperature. A 35% yield of aldehyde 24 was obtained. NMR ($CDCl_3$) δ 1.22-2.65 (m, 16 H), 9.84 (t, J = 1 Hz, 1 H); IR (film) 2920, 2865, 1720, 1450, 900, 725 cm^{-1}.

5-(1-Bromo-2-bicyclo[2.2.2]octyl)-1-trimethylsilyl-2-pentene 25

To a suspension of methyltriphenylphosphonium bromide (0.74 g, 2.07 mmol) in 4 mL of THF at 0°C under nitrogen was added n-butyllithium (1.1 mL of a 2.1 M solution in hexane, 2.29 mmol) dropwise. The mixture was warmed to room temperature and stirred for 1 h, recooled to 0°C, and iodomethyltrimethylsilane (0.44 g, 2.07 mmol) was added. The mixture was again allowed to warm slowly to room temperature to precipitate the new phosphonium salt. After 1 h, the reaction mixture was treated with a second equivalent of n-butyllithium (1.1 mL of a

2.1 M solution in hexane, 2.29 mmol) at -78°C. The mixture was allowed to warm slowly to room temperature and stirred for a further 1.5 h to give the dark red solution of the ylide. Compound 24 (0.45 g, 1.83 mmol) in 1 mL of THF was then added dropwise over 15 min to the ylide solution at -78°C under nitrogen. After 30 min, the mixture was allowed to warm slowly to room temperature, stirred under nitrogen for a further 16 h, quenched by pouring into saturated ammonium chloride solution (10 mL) and extracted with ether. The organic layer was dried and concentrated. The crude product was purified by silica gel column chromatography using 1:20 ethyl acetate:hexane to provide 0.42 g (72% yield) of pure product. NMR ($CDCl_3$) δ 0.14 (s, 9 H), 1.27-2.50 (m, 18 H), 5.24-5.58 (m, 2 H).

2-Ethenyltricyclo[5.2.2.$0^{1,5}$]undecane 26

Using the general procedure, compound 25 (95 mg, 0.29 mmol) was converted to 26 with silver tetrafluoroborate (62 mg, 0.32 mmol) in 2 mL of methylene chloride in 50% yield. NMR ($CDCl_3$) δ 1.05-2.40 (m, 17 H), 4.85-6.00 (m, 3 H). MS (m/e) 53, 67, 79, 93, 105, 119, 133, 147, 161, 176 (M^+).

4-(1-Bromo-2-bicyclo[2.2.2]octyl)-1-methoxy-1-butene 27

The ylide was formed by the reaction of LDA (2.72 mmol) with methoxymethyltriphenylphosphonium chloride (0.932 g, 2.72 mmol) in 9 mL of toluene at 0°C for 5 min. To this solution was added a solution of compound 24 (0.222 g, 0.91 mmol) in 8 mL of toluene. The resulting

solution was stirred in an ice bath for 1 h. The reaction was partitioned twice between ether and water. The organic layer was dried and concentrated. The product was a 60:40 mixture of stereoisomeric enol ethers. NMR ($CDCl_3$) δ 1.18-2.50 (m, 16 H), 3.52 and 3.60 (s, 3 H), 5.92 (d, J = 6 Hz, 0.6 H), 6.35 (d, J = 13 Hz, 0.4 H); IR (film) 3060, 2940, 2870, 1650, 1435, 1260, 1205, 1105, 925, 730, 690 cm^{-1}.

2-Formyltricyclo[5.2.2.$0^{1,5}$]undecane 28

Using the general procedure, compound 27 (124 mg, 0.45 mmol) was converted to 28 with silver tetrafluoroborate (106 mg, 0.55 mmol) in 2 mL of methylene chloride followed by acidic workup. (61% yield) NMR ($CDCl_3$) δ 1.10-2.10 (m, 16 H), 2.45 (bs, 1 H), 9.78 (d, J = 1 Hz, 1 H); MS (m/e) 55, 59, 67, 72, 79, 85, 94, 97, 107, 111, 121, 125, 131, 135, 149, 160, 178 (M^+).

Ethyl 5-(1-bromo-2-bicyclo[2.2.2]octyl)-2-pentenonate 29

A solution of aldehyde 24 (0.367 g, 1.50 mmol) and carboethoxymethylenetriphenylphosphorane (0.55 g, 1.57 mmol) in 10 mL of methylene chloride was heated to reflux for 10 h. The solution was concentrated and then diluted with hexanes. The suspension was filtered through Celite. The filtrate was concentrated and then purified by silica gel column chromatography using 1:5 ethyl acetate:hexane to provide 0.36 g of 29 (77% yield). NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H), 1.22-2.55 (m, 16 H), 4.20 (q, J = 7 Hz, 2 H), 5.82 (d, J = 15 Hz, 1 H), 6.68-7.30 (m, 1 H); IR (film) 2940, 2870, 1720, 1650, 1455, 1260, 970 cm^{-1}.

Ethyl 2-(2-tricyclo[5.2.2.$0^{1,5}$]undecyl)acetate 30

A solution of the bromide 29 (195 mg, 0.62 mmol), tributyltin hydride (0.18 mL, 0.68 mmol) and AIBN (15 mg, 0.09 mmol) in benzene (0.1 M with respect to the bromide) was heated at 80°C for 8 h. The solution was concentrated and ethyl ether was added. Aqueous potassium fluoride was added and the mixture was stirred for 30 min. The ethyl ether extract was dried and concentrated. The crude product was chromatographed on silica gel using 10:1 hexane:ethyl acetate to afford the pure product. (72% yield) NMR ($CDCl_3$) δ 1.05-2.05 (m, 20 H), 2.25-2.35 (m, 2 H), 4.10-4.20 (q, J = 7 H, 2 H); IR ($CDCl_3$) 2920, 2850, 1715, 1450, 1255, 1150, 900, 720 cm^{-1}. MS (m/e) 55, 67, 79, 91, 119, 133, 149, 162, 195, 236 (M^+). High resolution mass spectrum for $C_{15}H_{24}O_2$ requires 236.17764, measured 236.1779.

1-Hydroxy-4-carbomethoxy-7-methylbicyclo[3.3.1]nonan-3-one 32

To the freshly prepared 2 M sodium methoxide in 400 mL of methanol (210 mmol) was added ethyl acetoacetate (32.5 g, 249 mmol) and 5-methyl-2-cyclohexen-1-one (22.88 g, 208 mmol). The resulting solution was heated under reflux for 72 h. The mixture was cooled to room temperature. The methanol was then evaporated. The resulting oil product was neutralized by 3N HCl to pH = 6 and then extracted with methylene chloride. The organic layer was dried and concentrated. Flash column chromatography using 1:4 ethyl acetate:hexane yielded 39.95 g (85% yield) of 31 as an oil. NMR ($CDCl_3$) δ 0.9 (d, J = 6 Hz,

3 H), 1.2-3.3 (m, 14 H), 3.7 (s, 3 H). IR ($CDCl_3$) 3400, 2940, 2860, 1730, 1710, 1650, 1620, 1440, 1380, 1350, 1280, 1225, 1090, 900, 720 cm^{-1}.

1-Hydroxy-7-methylbicyclo[3.3.1]nonan-3-one 33

To a solution of compound 31 (22.6 g, 100 mmol) in 100 mL of methanol was added 6.16 g (110 mmol) of potassium hydroxide in 40 mL of water. The mixture was then refluxed for 12 h. The mixture was cooled to room temperature and the solvent was evaporated. The residual aqueous solution was extracted twice with methylene chloride. The organic layer was dried and concentrated to afford an oily compound. Flash column chromatography using 1:2 ethyl acetate:hexane yielded 15.46 g (92% yield) of compound 32 as a white solid. (m.p. = 66-68°C) NMR ($CDCl_3$) δ 0.88 (d, J = 6 Hz, 3 H), 1.1-2.6 (m, 15 H). IR ($CDCl_3$) 3400, 2910, 1690, 1320, 1210, 1090, 1020, 890, 710 cm^{-1}. High resolution mass spectrum for $C_{10}H_{16}O_2$ requires 168.11503, measured 168.1155.

1-Bromo-7-methylbicyclo[3.3.1]nonan-3-one 34

To a solution of compound 32 (183 mg, 1.09 mmol) in 2 mL of dry ethyl ether was added phosphorus tribromide (298 mg, 1.1 mmol) in 2 mL of ethyl ether dropwise at room temperature. The mixture was stirred at room temperature for 6 h. The mixture was poured into ice and then extracted with methylene chloride. The organic layer was dried and concentrated. Flash column chromatography using 1:6 ethyl acetate:hexane yielded 206 mg (82% yield) of 33 as a white solid. (m.p. = 56-57°C) NMR ($CDCl_3$) δ 0.88 (d, J = 6 Hz, 3 H), 1.2-2.6 (m, 10 H), 3.1 (q,

J = 12 Hz, 2 H); C-13 NMR ($CDCl_3$) δ 22.04, 2803, 32.00, 39.02, 43.35, 45.59, 52.93, 58.53, 62.36, 207.64. IR ($CDCl_3$) 2970, 2960, 1715, 1460, 1410, 1340, 1310, 1220, 1120, 1100, 950, 930, 740 cm^{-1}. High resolution mass spectrum for $C_{10}H_{15}OBr$ requires 230.03063, measured 230.03027.

1-Allyl-7-methylbicyclo[3.3.1]nonan-3-one 36

Using the general procedure, compound 34 (163 mg, 0.71 mmol) was converted to compound 36 with silver triflate (190 mg, 0.74 mmol) and allyltrimethylsilane (242 mg, 2.11 mmol) in methylene chloride. The product is an oil (89% yield). NMR ($CDCl_3$) δ 0.82 (d, J = 6 Hz, 3 H), 0.9-2.6 (m, 12 H), 5.0-5.9 (m, 3 H); C-13 NMR ($CDCl_3$) δ 22.79, 25.18, 30.98, 37.40, 37.91, 40.76, 46.73, 48.54, 51.98, 118.08, 133.43, 212.30. IR (film) 3040, 2900, 1700, 1450, 1435, 1400, 1340, 1260, 1225, 905, 720 cm^{-1}. High resolution mass spectrum for $C_{13}H_{20}O$ requires 192.15142, measured 192.15148.

1-Phenyl-7-methylbicyclo[3.3.1]nonan-3-one 37

Using the general procedure, compound 34 (162 mg, 0.70 mmol) was converted to compound 37 with silver triflate (189 mg, 0.74 mmole) in 2 mL of methylene chloride and 2 mL of benzene in 52% yield. The purified product is a white solid. (m.p. = 107-108°C) NMR ($CDCl_3$) δ 0.87 (d, J = 6 Hz, 3 H), 1.1-2.9 (m, 12 H), 7.3 (s, 5 H); C-13 NMR ($CDCl_3$) δ 22.81, 25.61, 31.08, 37.56, 40.44, 40.99, 46.60, 48.62, 53.62, 124.60, 126.27, 128.50, 149.30, 211.49. IR ($CDCl_3$) 3050,

2920, 1695, 1260, 900, 720 cm^{-1}. High resolution mass spectrum for $C_{16}H_{20}O$ requires 228.15142, measured 228.15100. Elemental analysis calculated for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 83.93; H, 8.78.

1-(2,5-Dimethoxyphenyl)-7-methylbicyclo[3.3.1]nonan-3-one 38

Using the general procedure, compound 34 (189 mg, 0.82 mmol) was converted to compound 38 with silver triflate (231 mg, 0.90 mmol) and 1,4-dimethoxybenzene (340 mg, 2.5 mmol) in 2 mL of methylene chloride. The product was isolated in quantitative yield as a white solid. (m.p. = 87-88°C) NMR ($CDCl_3$) δ 0.90 (d, J = 6 Hz, 3 H), 1.1-3.1 (m, 12 H), 3.80 (s, 3 H), 3.87 (s, 3 H), 6.6-6.85 (m, 3 H); C-13 NMR ($CDCl_3$) δ 22.82, 25.22, 31.03, 37.43, 37.97, 40.81, 46.76, 48.59, 52.03, 118.12, 133.46, 212.37. IR (CCl_4) 3000, 2960, 2910, 1700, 1580, 1480, 1460, 1410, 1220, 900 cm^{-1}. High resolution mass spectrum for $C_{18}H_{24}O_3$ requires 288.17255, measured 288.17217. Elemental analysis calculated for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.30; H, 8.44.

Ethyl 2-(7-methyl-3-ketobicyclo[3.3.1]nonyl)acetoacetate 39

Using the general procedure, compound 34 (161.5 mg, 0.70 mmol) was converted to compound 39 with silver tetrafluoroborate and ethyl acetoacetate (182 mg, 1.4 mmol) in 5 mL of methylene chloride. The product was isolated as a mixture of diastereomers in 52% yield as a colorless oil. NMR ($CDCl_3$) δ 0.83 (d, 6.3 Hz, 3 H), 0.9-2.9 (m, 18 H), 3.4 (d, 1 H), 4.2 (m, 2 H). IR ($CDCl_3$) 2960, 2920, 1740, 1700, 1450,

1350, 1300, 1220, 1170, 1140, 1015, 900, 720 cm^{-1}. High resolution mass spectrum for $C_{16}H_{24}O_4$ requires 280.16747, measured 280.1669.

1-(7-Methyl-3-ketobicyclo[3.3.1]nonyl)acetophenone 40

Using the general procedure, compound 34 (197 mg, 0.85 mmol) was converted to compound 40 with silver triflate and the enol silyl ether of acetophenone (490 mg, 2.55 mmol) in 3 mL of methylene chloride. The product was isolated in 57% yield as a white solid. (m.p. = 89-90°C) NMR ($CDCl_3$) δ 0.83 (d, 6 Hz, 3 H), 1.0-2.6 (m, 12 H), 2.9 (q, J = 11 Hz, 2 H), 7.5 (m, 3 H), 7.9 (d, J = 7 Hz, 2 H), C-13 NMR ($CDCl_3$) δ 22.75, 25.10, 30.86, 37.72, 37.98, 40.56, 46.66, 47.52, 50.13, 51.93, 128.14, 128.65, 133.03, 138.55, 198.87, 211.59. IR ($CDCl_3$) 2900, 1685, 1445, 1340, 1225, 1200, 980, 900, 720 cm^{-1}. High resolution mass spectrum for $C_{18}H_{22}O_3$ requires 270.16198, measured 270.16154. Elemental analysis calculated for $C_{18}H_{22}O_3$: C, 79.96; H, 8.20. Found C, 79.76; H, 8.22.

1-Allylamino-7-methylbicyclo[3.3.1]nonan-3-one 41

Bridgehead carbocation route: To the flask containing silver triflate (218 mg, 0.85 mmol) was added compound 34 (178 mg, 0.77 mmol) in 2 mL of methylene chloride at 0°C. Two minutes later, 1 mL of allylamine was added and the mixture was stirred at 0°C for 1 h. The solution was added to aqueous sodium chloride solution and extracted with methylene chloride. The organic layer was dried and concentrated. It was chromatographed on silica gel using 5:95 methanol:chloroform to provide 129 mg (81% yield) of oily compound. NMR ($CDCl_3$) δ 0.86

(d, J = 6 Hz, 3 H), 1.05-2.55 (m, 12 H), 3.25 (d, J = 6 Hz, 2 H), 5.07-5.31 (m, 2 H), 5.85-6.00 (m, 1 H); C-13 NMR ($CDCl_3$) δ 22.58, 25.72, 30.48, 38.77, 40.44, 43.97, 46.42, 47.21, 52.94, 54.87, 115.35, 137.52, 211.27. IR (film) 3300, 3080, 2920, 1700, 1450, 1400, 1340, 1230, 1110, 990, 910 cm^{-1}. High resolution mass spectrum for $C_{13}H_{21}NO$ requires 207.16232, measured 207.1620.

Bridgehead enone route: To a solution of 163.2 mg of compound 34 (0.71 mmol) and 0.1 mL of allylamine (1.33 mmol) in 1 mL of THF was added a solution of 0.12 ml of DBU (1.8-diazabicyclo[5.4.0]undec-7-ene) in 1 mL of THF dropwise at -78°C. The solution was warmed slowly to room temperature and then stirred for 4 h. The solution was diluted with water and extracted with methylene chloride. The organic layer was dried and concentrated. The crude product was chromatographed using 95:5 chloroform:methanol to afford 125 mg of compound 41 as a brown oil. (85% yield)

N-(7-Methyl-3-ketobicyclo[3.3.1]nonyl)acetamide 42

Using the procedure developed for compound 41, compound 34 (142.2 mg, 0.62 mmol) was converted to compound 42 with silver triflate (166 mg, 0.65 mmol) in 4 mL of methylene chloride and then 1 mL of acetonitrile at 0°C. The product was isolated in 86% yield as a white solid. (m.p. = 113-114°C) NMR ($CDCl_3$) δ 0.87 (d, J = 5.7 Hz, 3 H), 1.1-2.8 (m, 10 H), 1.94 (s, 3 H), 3.34 (d, J = 16 Hz, 2 H), 5.36 (br, 1 H); C-13 NMR δ 22.38, 24.42, 25.26, 30.08, 36.97, 40.21, 46.20, 47.14, 51.08,

55.18, 169.46, 210.94. IR (film) 3320, 3060, 2920, 1700, 1650, 1530, 1370, 1340, 1310, 1260, 1230, 1140, 700 cm^{-1}. Elemental analysis calculated for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15. Found: C, 68.65; H, 8.94.

15-Methylbicyclo[11.3.1.$0^{1.10}$.$0^{4.9}$]heptadecan-3,11-dione 44

Using the procedure developed for compound 41, compound 34 (181 mg, 0.78 mmol) was converted to compound 44 with silver triflate (221 mg, 0.86 mmol) in 4 mL of methylene chloride and then the enol silyl ether of 1-acetyl-1-cyclohexene (459 mg, 2.34 mmol). The product was isolated as a diastereomeric mixture in 61% yield as a white solid. NMR ($CDCl_3$) δ 0.80 (d, J = 5.4 Hz, 3 H), 0.8-2.8 (m, 23 H); C-13 NMR ($CDCl_3$) δ 20.15, 21.77, 21.87, 22.50, 23.90, 24.73, 25.40, 25.53, 25.58, 26.27, 26.69, 27.01, 27.27, 28.21, 28.53, 29.99, 32.23, 37.66, 40.57, 40.67, 42.42, 45.00, 45.10, 47.70, 48.00, 49.24, 53.41, 54.59, 55.80, 60.06, 210.63, 210.94, 211.26, 213.72. IR (film) 2920, 2870, 1710, 1690, 1440, 1340, 1210, 800 cm^{-1}. Elemental analysis calculated for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.54; H, 9.50.

1-Ethoxy-7-methylbicyclo[3.3.1]nonan-3-one 45

Using the general procedure, compound 34 (160 mg, 0.69 mmol) was converted to compound 45 with silver triflate (196 mg, 0.76 mmol) in the presence of ethyl vinyl ether (0.2 mL, 2.1 mmol) in 2 mL of methylene chloride. The product was isolated in 52% yield. NMR ($CDCl_3$) δ 0.90 (d, J = 6 Hz, 3 H), 1.0-2.8 (m, 15 H), 3.5 (q, J = 6 Hz, 2 H). MS (m/e) 55, 67, 83, 93, 111, 139, 196 (M^+).

1-Acetoxy-7-methylbicyclo[3.3.1]nonan-3-one 46

Using the general procedure, compound 34 (145.2 mg, 0.63 mmol) was converted to compound 46 with silver triflate (178 mg, 0.69 mmol) in 4 ml of methylene chloride and then 1-acetoxystyrene (306 mg, 1.89 mmol). The product was isolated in quantitative yield. NMR ($CDCl_3$) δ 0.85 (d, J = 6 Hz, 3 H), 2.0 (s, 3 H), 1.1-2.7 (m, 10 H), 2.95 (s, 2 H). MS (m/e) 210 (M^+).

N-Acety-N,O-bis-(7-methyl-3-keto-1-bicyclo[3.3.1]nonyl)-3-amino-1-propanol 47

To a solution of 412 mg of compound 34 (1.78 mmol) in 3 mL of methylene chloride was added silver triflate at 0°C under nitrogen. The 3-amino-1-propanol (201 mg, 2.67 mmol) was added 1 min later. The resulting solution was stirred at 0°C for 1 h. The reaction mixture was diluted with aqueous sodium chloride solution and extracted with methylene chloride. The organic layer was dried and concentrated to afford 424 mg of crude product. Without purification, the crude product was taken on to the next step.

To the solution of the crude product (424 mg) was added 0.31 mL of triethylamine (2.26 mmol) and 0.18 mL of acetic anhydride (1.88 mmol) at 0°C. The solution was warmed slowly to room temperature and then stirred overnight. The solution was poured into ice water and extracted with methylene chloride. The organic layer was dried and concentrated. The crude product was chromatographed using ethyl acetate to afford compound 47. NMR ($CDCl_3$) δ 0.9 (d, J = 5 Hz, 6 H), 2.28 (s, 3 H),

1.1-3.7 (m, 28 H), 4.15 (m, 2 H); IR (CH_2Cl_2): 3070, 2970, 2940, 1710, 1640, 1420, 1270, 1110, 740 cm^{-1}. MS (m/e) 100, 116, 151, 192, 210, 224, 266, 374, 417 (M^+).

Preparation of benzenesulfenyl chloride

To a solution of N-chlorosuccinimide (67 g, 500 mmol) in 300 mL of benzene was added benzenethiol (41 mL, 400 mmol) dropwise at 0°C. After the solution was stirred at room temperature overnight, it was filtered through Celite to remove the succinimide. The filtrate was concentrated in vacuo. The pure product was collected at 45-50°C as a red liquid by vacuum distillation (4 torr) in 67% yield, (ref. 52, 49°C/4 mm Hg).

6-Benzenesulfenyl-2-cyclohexen-1-one 49

To a solution of 2-trimethylsilyloxy-1,3-cyclohexadiene (38.8 g, 231 mmol) in 200 mL of methylene chloride was added the solution of benzenesulfenyl chloride (33.4 g, 231 mmol) in 60 mL of methylene chloride dropwise at -60°C. The solution was then warmed to room temperature and stirred 2 more h. The mixture was concentrated and chromatographed using 1:5 ethyl acetate:hexane to yield 46.62 g of product as a brown oil. (99% yield) NMR ($CDCl_3$) δ 2.0-2.6 (m, 4 H), 3.8 (t, J = 5.5 Hz, 1 H), 5.8-6.2 (m, 2 H), 6.8-7.5 (m, 5 H). IR (film) 3050, 2930, 1680, 1590, 1485, 1440, 1390, 1250, 1220, 1125, 1030, 835, 745 cm^{-1}.

1-Hydroxy-8-benzenesulfenylbicyclo[3.3.1]nonan-3-one 50

Using the procedures developed for compounds 31 and 32, compound 49 (5.07 g, 24.9 mmol) was converted to compound 50 with ethyl acetoacetate (3.56 g, 27.3 mmol) and sodium methoxide (27.3 mmol) in 300 mL of methanol, followed by treatment with aqueous potassium hydroxide (1.4 g, 24.9 mmol). The crude product was chromatographed using 3:1 hexane:ethyl acetate to yield 3.52 g of compound 50 as a diastereomeric mixture. (54% yield) NMR ($CDCl_3$) δ 1.1-3.5 (m, 12 H), 7.1-7.6 (m, 5 H); IR ($CDCl_3$) 3450, 2940, 1710, 1470, 1450, 1410, 1370, 1325, 1220, 1090, 900, 720 cm^{-1}.

1-Bromo-8-benzenesulfenylbicyclo[3.3.1]nonan-3-one 51

Using the procedure developed for compound 33, compound 50 (46.3 g, 176.8 mmol) was converted to compound 51 with phosphorus tribromide (18.3 mL, 194.5 mmol) in 250 mL of ethyl ether. The crude product was chromatographed using 4:1 hexane:ethyl acetate to afford 38.90 g of pure product. (68% yield) NMR ($CDCl_3$) δ 0.9-3.7 (m, 12 H), 7.1-7.6 (m, 5 H); IR ($CDCl_3$) 2940, 2860, 1710, 1660, 1480, 1460, 1445, 1410, 1210, 1100, 1010, 900, 720 cm^{-1}. High resolution mass spectrum for $C_{15}H_{17}SOBr$ requires 324.01835, measured 324.01853.

6-(1,1-Dimethoxymethyl)-2-cyclohexen-1-one 52

To a solution of 2-trimethylsilyloxy-1,3-cyclohexadiene (9.71 g, 57.8 mmol) and trimethyl orthoformate (6.75 g, 63.5 mmol) in 180 mL of methylene chloride was added a solution of trimethylsilyl triflate

(0.6 mL, 2.89 mmol) in 20 mL of methylene chloride dropwise at -78°C. After 6.5 h stirring at -78°C, the solution was diluted with aqueous sodium hydroxide solution and was warmed to room temperature. Two layers were separated. The aqueous layer was extracted with methylene chloride. The combined methylene chloride fractions were dried and concentrated. The pure product was isolated at 85-90°C (1-2 mm Hg) by vacuum distillation in 63% yield.

1-Hydroxy-8-(1.1-dimethoxymethyl)bicyclo[3.3.1]nonan-3-one 53

Using the procedures developed for compounds 31 and 32, compound 52 (20.76 g, 122 mmol) was converted to compound 53 with ethyl acetoacetate (17.48 g, 134 mmol) and sodium methoxide (134 mmol) in 300 mL of methanol followed by treatment with aqueous potassium hydroxide (2.76 g, 49.3 mmol). The crude product was purified by column chromatography using 4:1 hexane:ethyl acetate to afford 10.2 g of compound 53 as a yellow oil in 37% yield. NMR ($CDCl_3$) δ 1.0-2.8 (m, 12 H), 3.3 (s, 3 H), 3.4 (s, 3 H), 4.2 (d, J = 8 Hz, 0.5 H), 4.4 (d, J = 8 Hz, 0.5 H); IR ($CDCl_3$) 3450, 3060, 2940, 2870, 1710, 1460, 1410, 1340, 1220, 1140, 1090, 1040, 910, 720 cm^{-1}.

1-Chloro-8-(1,1-dimethoxymethyl)-bicyclo[3.3.1]nonan-3-one 54

To a solution of compound 53 (10.2 g, 44.7 mmol) and pyridine (4.4 ml, 53.68 mmol) in 110 mL of benzene was added a solution of thionyl chloride (3.6 mL, 49.2 mmol) in 20 mL of benzene dropwise at 0°C. Two h later, the solution was poured into ice water and extracted with methylene chloride. The organic layer was dried and concentrated.

The crude product was purified by column chromatography using 5:1 hexane:ethyl acetate to afford 7.25 g of compound 54 as a diastereomeric mixture. (66% yield) The less polar diastereomer NMR ($CDCl_3$) δ 1.2-3.0 (m, 12 H), 3.41 (s, 3 H), 3.50 (s, 3 H), 4.78 (d, J = 2.1 Hz, 1 H); IR ($CDCl_3$) 3050, 2920, 1710, 1450, 1400, 1260, 1210, 1115, 1065, 950, 720 cm^{-1}. The more polar diastereomer NMR ($CDCl_3$) δ 1.2-2.6 (m, 12 H), 3.43 (s, 3 H), 3.49 (s, 3 H), 4.70 (bs, 1 H). IR (CH_2Cl_2) 3060, 2920, 2840, 1710, 1452, 1405, 1260, 1215, 1150, 1010, 1070, 1050, 960, 730 cm^{-1}. High resolution mass spectrum for $C_{11}H_{16}O_2Cl_2$ requires 215.08389, measured 215.08383.

1-Allyl-8-benzenesulfenylbicyclo[3.3.1]nonan-3-one 55

Using the general procedure, compound 51 (126 mg, 0.39 mmol) was converted to compound 55 with silver triflate (110 mg, 0.43 mmol) and allyltrimethylsilane (134 mg, 1.17 mmol) in 1.5 mL of methylene chloride. The crude product was chromatographed using 5:1 hexane:ethyl acetate to afford 66 mg of compound 55. (59% yield) NMR ($CDCl_3$) δ 1.1-3.9 (m, 14 H), 4.6-6.2 (m, 3 H), 7.2-7.7 (m, 5 H); IR ($CDCl_3$) 3070, 2920, 1700, 1560, 1460, 1425, 1405, 1215, 1075, 975, 900, 715 cm^{-1}. MS (m/e) 55, 67, 79, 91, 107, 119, 135, 150, 159, 157, 177, 186, 286 (M^+).

5-Methoxytricyclo[7.3.1.$0^{1,6}$]trideca-3(4)-ene-11-one 56

Using the general procedure, compound 54 (60 mg, 0.24 mmol) was converted to compound 56 with silver triflate (69 mg, 0.27 mmol) and allyltrimethylsilane (84 mg, 0.73 mmol) in 1 mL of methylene chloride.

The crude product was chromatographed using 3:1 hexane:ethyl acetate to afford 32 mg of compound 56. (61% yield) NMR ($CDCl_3$) δ 1.0-2.6 (m, 17 H), 3.3 (m, 3 H), 4.98-5.8 (m, 2 H); IR (film) 3020, 2920, 1710, 1450, 1420, 1350, 1220, 1100, 900, 700 cm^{-1}. MS (m/e) 55, 71, 79, 91, 105, 131, 145, 160, 188, 205, 220 (M^+).

1-Hydroxy-4-carbomethoxybicyclo[3.3.1]nonan-3-one 57

Using the procedure developed for compound 31, 1-cyclohexen-2-one (3.71 g, 38.6 mmol) was converted to compound 57 with ethyl acetoacetate (6.02 g, 46.27 mmol) and 2 M sodium methoxide in methanol solution (42.4 mmol). The product was isolated in 87% yield. NMR ($CDCl_3$) δ 1.1-3.3 (m, 12 H), 3.75 (s, 3 H); IR ($CDCl_3$) 3400, 2940, 2860, 1735, 1710, 1650, 1620, 1440, 1415, 1380, 1350, 1305, 1280, 1220, 1090, 1040, 980, 940, 900, 810, 720 cm^{-1}.

1-Hydroxy-4-carbomethoxy-4-chlorobicyclo[3.3.1]nonan-3-one 58

To a solution of compound 57 (205 mg, 0.97 mmol) in 1 mL of methanol was added tert-butyl hypochlorite (116 mg, 1.06 mmol) in 1 mL of methanol at -15°C under nitrogen. The mixture was then cooled in the refrigerator overnight and then stirred at room temperature for 4 h. The mixture was then concentrated to afford 179 mg of crude product. (75% yield) It was taken on to the next step without purification. NMR ($CDCl_3$) δ 1.2-3.7 (m, 11 H), 3.85 (s, 3 H); IR ($CDCl_3$) 3400, 2950, 2880, 1750, 1720, 1460, 1430, 1405, 1350, 1310, 1270, 1090, 1050, 1030, 900, 730 cm^{-1}.

1-Hydroxy-3-carbomethoxybicyclo[3.2.1]oct-2-ene 59

To a solution of compound 58 (246 mg, 0.97 mmol) in 5 mL of xylene was added glass beads (0.5 g) and sodium carbonate (106 mg, 1.02 mmol). The mixture was heated to reflux for 12 h. The mixture was filtered through Celite and then concentrated to afford an oily product. It was chromatographed using 1:3 ethyl acetate:hexane to afford 143 mg of product. (81% yield) NMR ($CDCl_3$) δ 1.1-3.2 (m, 9 H), 3.72 (s, 3 H), 6.6 (s, 1 H); IR (film) 3440, 3060, 2960, 2880, 1740, 1710, 1610, 1445, 1280, 1200, 1140, 1070, 880, 735 cm^{-1}. MS (m/e) 55, 67, 81, 95, 108, 123, 140, 153, 167, 182 (M^+).

1-Hydroxy-3-hydroxymethylenebicyclo[3.2.1]octane 60

To the liquid ammonia (35 mL) was added a solution of compound 59 (235 mg, 1.29 mmol) and tert-butyl alcohol (478 mg, 6.45 mmol) in 3 mL of THF. To the resulting solution was added lithium (70 mg, 10 mmol) piece by piece. The solution was stirred at -33°C for 2 h and then the ammonia was allowed to evaporate. The crude mixture was neutralized by 3N HCl and extracted with methylene chloride. The organic layer was dried and concentrated. It was chromatographed using ethyl acetate to yield 82 mg of product. (41% yield) NMR ($CDCl_3$) δ 1.0-2.8 (m, 12 H), 3.7 (d, J = 8 Hz, 2 H); IR ($CDCl_3$) 3400, 2960, 2880, 1440, 1330, 1260, 1090, 1020, 810, 720 cm^{-1}.

1-Hydroxy-3-tert-butyldimethylsilyloxymethylenebicyclo[3.2.1]octane 61

To a solution of compound 60 (266 mg, 1.71 mmol) in 3 mL of N,N-dimethyl formamide (DMF) was added t-butyldimethylsilyl chloride (271 mg,

1.80 mmol) and imidazole (175 mg, 2.6 mmol) at room temperature. The solution was stirred overnight. To the solution was added 50 mL pentane. The pentane layer was washed with water several times. The pentane layer was dried and concentrated. It was chromatographed using 1:5 ethyl acetate:hexane to yield 337 mg of product. (73% yield) NMR ($CDCl_3$) δ 0.1 (s, 6 H), 0.9 (s, 9 H), 1.2-2.5 (m, 12 H), 3.6 (d, J = 7 Hz, 2 H); IR (CH_2Cl_2) 3340, 2940, 2850, 1470, 1460, 1370, 1250, 1105, 1080, 830, 770, 740 cm^{-1}.

1-Hydroxy-3-benzenesulfonatomethylenebicyclo[3.2.1]octane 62

To a solution of compound 60 (79 mg, 0.51 mmol) in 5 mL of benzene was added pyridine (0.05 mL, 0.61 mmol) and benzenesulfonyl chloride (95 mg, 0.53 mmol) at 0°C. The solution was warmed slowly to room temperature and then stirred for 5 h. The mixture was added to water and extracted with methylene chloride. The organic layer was dried and concentrated. It was chromatographed using ethyl acetate to yield 94 mg of product. (62% yield) NMR ($CDCl_3$) δ 1.1-2.7 (m, 12 H), 4.1 (d, J = 8 Hz, 2 H), 7.4-8.1 (m, 5 H); IR (film) 3400, 3050, 2940, 2860, 1440, 1355, 1260, 1180, 1165, 1090, 950, 820 cm^{-1}. MS (m/e) 55, 67, 77, 82, 95, 110, 123, 138, 159, 253, 296 (M^+).

1-Allyl-4-carbomethoxy-7-methylbicyclo[3.3.1]nonan-3-one 63

To a flask containing potassium hydride (1.73 mmol) was added a mixture of compound 35 (144 mg, 0.75 mmol) and 2.5 mL of dimethyl carbonate at room temperature under nitrogen. The mixture was stirred at room temperature overnight. The mixture was poured into cold

aqueous ammonium chloride solution and extracted with methylene chloride. The organic layer was dried and concentrated. It was chromatographed using 10:1 hexane:ethyl acetate to yield 152 mg of product (81% yield). NMR ($CDCl_3$) δ 0.84 (d, J = 6.3 Hz, 3 H), 0.9-2.9 (m, 13 H), 3.75 (s, 3 H), 5.1 (m, 2 H), 5.8 (m, 1 H); IR ($CDCl_3$) 3060, 2940, 2900, 2840, 1740, 1700, 1640, 1600, 1430, 1370, 1345, 1285, 1265, 1200, 1145, 1100, 1070, 1020, 980, 900, 800, 720 cm^{-1}.

1-Allyl-4-carbomethoxy-4-chloro-7-methylbicyclo[3.3.1]nonan-3-one 64

Using the procedure developed for compound 58, compound 63 (394 mg, 1.58 mmol) was converted to compound 64 with tert-butyl hypochlorite (188 mg, 1.73 mmol) in 4 mL of methanol. The concentrated crude product was chromatographed using 7:1 hexane:ethyl acetate to afford 324 mg of compound 64 as a diastereomeric mixture. (72% yield) NMR ($CDCl_3$) δ 0.82 (m, 3 H), 0.9-3.6 (m, 12 H), 3.9 (s, 3 H), 5.1 (m, 2 H), 5.8 (m, 1 H); IR (film) 2900, 1705, 1430, 1230, 900 cm^{-1}.

1-Allyl-3-carbomethoxy-7-methylbicyclo[3.2.1]octa-2-ene 65

Using the procedure developed for compound 59, compound 64 (324 mg, 1.14 mmol) was converted to compound 65 with sodium carbonate (176 mg, 1.66 mmol) and glass beads (0.81 g) in 5 mL of xylene. The crude product was chromatographed using 7:1 hexane:ethyl acetate to afford 197 mg of product. (79% yield) NMR ($CDCl_3$) δ 0.90 (d, J = 6 Hz, 3 H), 1.1-3.0 (m, 10 H), 3.72 (s, 3 HY, 5.05 (m, 2 H), 5.8 (m, 1 H), 6.6 (s, 1 H); C-13 NMR ($CDCl_3$) δ 21.65, 26.47, 33.04, 39.02, 40.19, 42.47, 48.77, 49.55, 51.24, 117.25, 134.55, 137.47, 147.81, 165.31; IR ($CDCl_3$):

3070, 2950, 2020, 1710, 1640, 1610, 1455, 1435, 1310, 1260, 1225, 1195, 1080, 910, 780 cm^{-1}. High resolution mass spectrum for $C_{14}H_{20}O_2$ requires 220.14633, measured 220.1469.

1-(N-(3-Hydroxypropyl)amino)-7-methylbicyclo[3.3.1]nonan-3-one 66

To a solution of 177 mg of compound 33 (0.77 mmol) and 231 mg 3-amino-1-propanol (3.08 mmol) in 1 mL of THF was added a solution of 128.4 mg DBU (0.84 mmol) in 1 mL of THF at -78°C under nitrogen. The solution was warmed slowly to room temperature. The solution was diluted with water and extracted with methylene chloride. The organic layer was dried and concentrated to yield 173 mg of compound 66 which was very pure. (quantitative yield) NMR ($CDCl_3$) δ 0.9 (d, J = 5 Hz, 3 H), 1.1-2.7 (m, 14 H), 2.8 (t, J = 6 Hz, 2 H), 3.8 (t, J = 7 Hz, 2 H); C-13 NMR ($CDCl_3$) δ 22.43, 25.49, 30.17, 31.93, 38.37, 40.12, 40.51, 46.24, 46.69, 52.28, 54.89, 63.53, 211.22; IR ($CDCl_3$) 3270, 2920, 1700, 1650, 1630, 1460, 1345, 1230, 1115, 1070, 900 cm^{-1}. High resolution mass spectrum for $C_{13}H_{23}NO_2$ requires 225.1729, measured 225.1733.

Ethyl 2-(8-benzenesulfenyl-3-keto-1-bicyclo[3.3.1]nonyl)acetoacetate 67

To a mixture of compound 51 (348 mg, 1.07 mmol) and ethyl acetoacetate (1.82 g, 14.0 mmol) was added triethylamine (0.33 ml, 2.38 mmol) at room temperature. After stirring for 2 h, the mixture was diluted with water and extracted with methylene chloride. The organic layer was dried and concentrated. The excess ethyl acetoacetate was removed by Kugelrohr vacuum distillation at 55°C (1-2 torr). The

crude product was then chromatographed using 3:1 hexane:ethyl acetate to afford 368 mg of compound 67 as a diastereomeric mixture. (92% yield) NMR ($CDCl_3$) δ 7.25 (bs, 5 H); IR (film) 3025, 2920, 1730, 1690, 1575, 1470, 1430, 1350, 1220, 1175, 1090, 1015, 740, 680 cm^{-1}. MS (m/e) 91, 135, 177, 200, 223, 329, 374 (M^+).

Ethyl 2-(8-dimethoxymethyl -3-keto-1-bicyclo[3.3.1]nonyl)acetoacetate 68

Using the procedure developed for compound 67, compound 54 (622 mg, 2.52 mmol) was converted to compound 68 with 4.30 g of ethyl acetoacetate (33.1 mmol) and 0.8 mL of triethylamine (5.63 mmol). After chromatography, the product was isolated in 89% yield as a diastereomeric mixture. IR ($CDCl_3$) 2920, 1725, 1690, 1640, 1610, 1550, 1535, 1515, 1500, 1450, 1350, 1120, 940, 720 cm^{-1}. MS (m/e) 75, 179, 211, 266, 276, 308, 340 (M^+).

6-Methyl 2,3a,5,6,7,7a-pentahydro-3H,4H-benzothiophene-3,4-dione 127

To 33 mL of a 1.5 M sodium methoxide in methanol solution (50.2 mmol) was added 5.0 mL of ethyl 2-mercaptoacetate (45.7 mmol) dropwise at 0°C. To the resulting solution was then added a solution of 5.02 g 5-methyl-2-cyclohexen-1-one (45.7 mmol) in 60 mL of methanol. The solution was refluxed overnight. After removal of the solvent, the brown residue was acidified by 3N hydrogen chloride and extracted with methylene chloride. The organic layer was dried and concentrated. The crude product was chromatographed using 5:1 hexane:ethyl acetate to afford 5.71 g of product. (68% yield) NMR ($CDCl_3$) δ 1.1 (d, J = 6 Hz,

3 H), 3.25 and 3.62 (q, J = 16 Hz, 2 H), 4.1 (m, 1 H), 12 (b, 1 H); IR (film) 2970, 2940, 2880, 1750, 1720, 1660, 1600, 1460, 1395, 1345, 1275, 1230, 1140, 890, 800 cm^{-1}.

2-Allyl-5-methyl-2-cyclohexen-1-one 129

To a mixture of 96.23 g of compound 127 (523 mmol) in 500 mL of acetone was added 109 g of potassium carbonate (785 mmol) and 95 g of allyl bromide (785 mmol). The resulting solution was refluxed overnight. The inorganic salts were separated by filtration through sintered glass. The filtrate was concentrated and was taken on to the next step without further purification.

To the concentrated crude product was added 500 mL of ethyl ether and then 200 mL of a 5 M aqueous sodium hydroxide solution at room temperature. After stirring for 5 h, the solution was separated. The aqueous layer was extracted with ethyl ether. The combined organic layers were dried and concentrated. The product was purified by vacuum distillion to afford 44.07 g of product at 50-60°C (1-2 torr). (56% yield) NMR ($CDCl_3$) δ 1.0 (d, J = 5 Hz, 3 H), 1.5-3.1 (m, 7 H), 4.7-6.2 (m, 3 H), 6.6 (m, 1 H); IR (CH_2Cl_2) 3075, 2975, 2920, 2820, 1705, 1670, 1635, 1450, 1425, 1370, 1230, 990, 905 cm^{-1}. High resolution mass spectrum for $C_{10}H_{14}O$ requires 150.14447, measured 150.1044.

9-Allyl-3-carbomethoxy-1-hydroxy-7-methylbicyclo[3.3.1]nonan-3-one 130 and 131

To the freshly prepared 2 M sodium methoxide in 400 mL of methanol (221 mmol) was added ethyl acetoacetate (28.7 g, 221 mmol) and compound

129 (30.1 g, 200 mmol). The resulting solution was heated under reflux for 84 h. The mixture was cooled to room temperature and then the methanol was removed. The concentrated mixture was neutralized by 3N HCl to pH = 6 and then extracted with methylene chloride. The organic layer was dried and concentrated. Flash column chromatography using 1:5 ethyl acetate:hexane afforded 10.33 g of recovered compound 129 and 28.6 g of a mixture of compounds 130 and 131. (84% net yield, 64% conversion) NMR ($CDCl_3$) δ 0.9 (d, J = 6 Hz, 3 H), 1.1-3.3 (m, 12 H), 3.75 (s, 3 H), 4.7-6.2 (m, 3 H); IR ($CDCl_3$) 3450, 3080, 2960, 2922, 2865, 1700, 1650, 1620, 1440, 1422, 1360, 1275, 1210, 1090, 1040, 900, 810, 730 cm^{-1}.

9-Allyl-1-hydroxy-7-methylbicyclo[3.3.1]nonan-3-one 132

To a solution of compounds 130 and 131 (27.16 g, 102.1 mmol) in 100 mL of methanol was added 100 mL of 1.1 M aqueous potassium hydroxide (110 mmol). The solution was refluxed for 12 h. The methanol in the solution was removed in vacuo. The organic compound was extracted with methylene chloride. The organic layer was dried and concentrated. The crude product was chromatographed using 1:3 ethyl acetate:hexane to afford 19.70 g (94.7 mmol) of compound 132 and 1.02 g of compound 133 (4.90 mmol) in 98% yield. For compound 132, NMR ($CDCl_3$) δ 0.90 (d, J = 6 Hz, 3 H), 1.1-2.8 (m, 13 H), 4.8-6.2 (m, 3 H); C-13 NMR ($CDCl_3$) δ 22.04, 26.60, 30.95, 32.13, 40.84, 41.49, 46.37, 50.72, 51.18, 72.64, 116.34, 136.95, 211.15; IR ($CDCl_3$) 3440, 3090, 2960, 2930, 2880, 1700, 1645, 1460, 1410, 1310, 1230, 1110, 1035, 1000, 910, 730 cm^{-1}. High resolution mass spectrum for $C_{13}H_{20}O_2$ requires 208.14633,

measured 208.1466. Elemental analysis calculated for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.63; H, 9.62.

1-Hydroxy-9-(3-hydroxypropyl)-7-methylbicyclo[3.3.1]nonan-3-one 134

To a solution of compound 132 (2020 mg, 9.7 mmol) in 15 mL of THF was added 9.7 mL of 1 M Borane-THF complex (9.7 mmol) dropwise at 0°C. After 1.5 h, 14.6 mL of 1 M aqueous sodium hydroxide was carefully added and then 7.3 mL of 30% hydrogen peroxide at 0°C. The solution was then refluxed for 1.5 h until all of the white precipitate disappeared. The solution was cooled down and extracted with ethyl ether. The organic layer was dried and concentrated to afford 2459 mg of crude product. Without purification, compound 134 was taken on to the next step. NMR ($CDCl_3$) δ 0.9 (d, J = 6 Hz, 3 H), 1.1-3.3 (m, 17 H), 3.65 (m, 2 H); IR (film) 3360, 2930, 2880, 1710, 1460, 1410, 1380, 1320, 1250, 1110, 1055, 945, 900, 735 cm^{-1}.

9-(3-Benzenesulfonyloxypropyl)-1-hydroxy-7-methylbicyclo[3.3.1]nonan-3-one 135

To a mixture of crude product 134 (2459 mg) in 20 mL of methylene chloride was added 1.1 mL of pyridine (14.1 mmol) and 1.3 mL of benzenesulfonyl chloride (10.9 mmol) at 0°C. The solution was then stirred at room temperature overnight. The solution was poured into water and extracted with methylene chloride. The organic layer was dried and concentrated to afford 3590 mg of crude product. Without purification, it was taken on to the next step.

9-(3-Benzenesulfonyloxypropyl)-1-bromo-7-methylbicyclo[3.3.1]nonan-3-one 136

To a mixture of crude product 136 (3590 mg) in 20 mL of ethyl ether was added phosphorus tribromide (1.01 mL, 10.8 mmol) dropwise at 0°C. The solution was warmed slowly to room temperature. After 2.5 h at room temperature, the solution was poured into ice water and extracted with methylene chloride. The organic layer was dried and concentrated. The crude product was chromatographed using 5:1 hexane:ethyl acetate to afford 1.58 g of compound 136 as a brown oil. (38% overall yield from compound 132) NMR ($CDCl_3$) δ 0.88 (d, J = 6 Hz, 3 H), 1.1-2.6 (m, 13 H), 2.9 (s, 2 H), 4.15 (bt, J = 5 Hz, 2 H), 7.3-8.0 (m, 5 H); C-13 NMR ($CDCl_3$) δ 21.52, 25.95, 27.18, 27.90, 33.03, 40.58, 41.29, 48.19, 53.97, 55.34, 69.65, 70.36, 75.63, 77.06, 78.49, 127.72, 129.21, 133.70, 136.17, 207.19; IR (film) 3080, 2940, 2880, 1715, 1455, 1420, 1365, 1315, 1275, 1220, 1190, 1115, 1100, 1020, 1000, 940, 820, 760, 735 cm^{-1}. High resolution mass spectrum for $C_{19}H_{25}O_4BrS$-Br requires 349.1474, measured 349.1476.

(4aRS, 5SR, 8aSR, 10RS)-10-Methyl-1-[3-(phenylmethoxy)propyl]-hexahydro-1H-5,8a-propanoquinolin-7(8H)-one 138

To a solution of compound 136 (194 mg, 0.45 mmol) in 1 mL of methylene chloride was added silver triflate (128 mg, 0.50 mmol), followed by 3-benzyloxy-1-propylamine (373 mg, 2.26 mmol) in 0.5 mL of methylene chloride at 0°C immediately. After 1 h at 0°C, the solution was diluted with brine and extracted with methylene chloride. The

organic layer was dried and concentrated. The crude product was chromatographed using 95:5 chloroform:methanol to afford 153 mg of compound 138. (96% yield) NMR ($CDCl_3$) δ 0.85 (d, J = 6 Hz, 3 H), 1.1-3.2 (m, 21 H), 3.5 (t, J = 6 Hz, 2 H), 4.45 (s, 2 H), 7.3 (s, 5 H); C-13 NMR ($CDCl_3$) δ 22.57, 25.43, 25.69, 29.13, 35.77, 39.28, 41.81, 42.27, 43.51, 44.74, 47.21, 59.05, 68.15, 72.70, 75.65, 77.00, 78.49, 127.33, 128.11, 138.45, 212.84; IR (film) 3070, 2940, 2870, 1700, 1455, 1270, 1105, 910, 730 cm^{-1}. MS (m/e) 91, 162, 192, 206, 220, 249, 264, 298, 312, 340, 355 (M^+). High resolution mass spectrum for $C_{23}H_{33}NO_2$ requires 355.2511, measured 355.2510.

(4aRS, 5SR, 8aSR, 10RS)-(3-Hydroxypropyl)-10-methylhexahydro-1H-5,9a-propanoquinolin-7(8H)-one (103)

To a solution of compound 138 (413 mg, 1.16 mmol) in 8 mL of absolute ethanol was added 1 mL of aqueous 3N hydrogen chloride solution. At this point 40 mg of 10% palladium on charcoal was added, and the mixture was stirred under hydrogen (1 atm) for 2.5 h. After filtration of the catalyst and removal of the solvent, the residue was diluted with aqueous sodium bicarbonate solution to pH = 8. The precipitate was extracted with methylene chloride. The organic layer was dried with potassium carbonate and concentrated. The crude product was chromatographed using 5:95 methanol:chloroform to afford 295 mg of compound 103 (96% yield) as a tan crystal . (m.p. = 86-87°C) NMR ($CDCl_3$) δ 0.93 (d, J = 5 Hz, 3 H), 1.1-3.5 (m, 21 H), 3.6-3.9 (m, 2 H), 5.4 (bs, 1 H); IR (film) 3320, 2900, 1700, 1460, 1410, 1335, 1310,

1220, 1170, 1110, 1060, 980, 725 cm^{-1}. MS (m/e) 55, 111, 149, 208, 220, 250, 265 (M^+).

(4aRS, 5SR, 8aSR, 10RS)-(3-Hydroxypropyl)-10-methylhexahydro-1H-5,8a-propanoquinolin-7(8H)-one (103) via bridgehead enone route

To a mixture of 254 mg of compound 136 (0.59 mmol) and 222 mg of 3-amino-1-propanol (2.95 mmol) in 3 mL of THF was added a mixture of 99 mg DBU (0.65 mmol) in 1 mL of THF at -78°C. The solution was warmed slowly to room temperature. The solution was diluted with water and extracted with methylene chloride. The organic layer was dried and concentrated to afford 172 mg of product 103. It was chromatographed using 5:95 methanol:chloroform to afford 156 mg of purified compound 103 (quantitative yield).

(±)-3,4-Dehydrolycopodine 104

To a mixture of 2530 mg of benzophenone (13.9 mmol) and 467 mg of potassium tert-butoxide (4.2 mmol) in 14 mL of dry benzene under nitrogen was added a solution of 368 mg (1.39 mmol) of compound 103 in 5 mL of dry benzene. The resulting mixture was heated at reflux for 2 h. After cooling to room temperature, the solution was diluted with 3N HCl to pH = 3 and extracted with ether. The aqueous layer was made basic (pH = 11) with aqueous 6N sodium hydroxide solution and extracted with methylene chloride. The organic layer was dried with potassium carbonate and concentrated. The crude product was chromatographed using 5:95 methanol:chloroform to afford 245 mg of product as a

yellow-brown solid in 72% yield. (m.p. = 104-105°C) NMR ($CDCl_3$) δ 0.88 (d, J = 5 Hz, 3 H), 1.1-3.9 (m, 19 H), 7.0 (bt, 1 H); C-13 NMR ($CDCl_3$) δ 21.13, 22.50, 25.62, 25.88, 26.86, 34.08, 41.23, 42.40, 43.12, 43.83, 48.12, 49.75, 58.01, 135.59, 138.19, 199.51; IR (CH_2Cl_2) 3025, 2920, 1680, 1610, 1460, 1425, 1245, 1215, 1115, 1010, 905, 750 cm^{-1}. MS (m/e) 55, 77, 91, 160, 188, 245 (M^+).

(±)Lycopodine 69

To a solution of 331 mg (1.35 mmol) of compound 104 in 13 mL of methanol was added 13 mg of platinum (IV) oxide, and the resulting mixture was stirred under 1 atm of hydrogen for 15 h. The catalyst was removed by filtration and the solvent was evaporated to obtain 326 mg of crude product as a yellow solid. Sublimation of this solid (100°C, 0.001 torr) afforded 291 mg (87% yield) of (±)lycopodine as white needles. (m.p. = 127-129°C) NMR ($CDCl_3$) δ 0.85 (d, J = 6 Hz, 3 H), 1.2-2.7 (m, 17 H), 2.9 (dd, J = 7 Hz and 3 Hz, 1 H), 3.12 (td, J = 12 Hz and 3 Hz, 2 H), 3.35 (td, J = 15 Hz and 3 Hz, 2 H); C-13 NMR ($CDCl_3$) δ 18.73, 19.46, 22.77, 25.11, 25.20, 26.08, 36.67, 42.43, 42.71, 42.82, 43.18, 44.93, 46.55, 47.14, 59.65, 77.63, 77.06, 77.48, 213.27; IR (CCl_4) 2920, 2800, 1700, 1450, 1350, 1310, 1215, 1110, 1090, 970, 900 cm^{-1}.

CONCLUSIONS

The bridgehead bond formation methodology has been proven to be an effective approach for lycopodine synthesis. The bridgehead carbocation and bridgehead enone routes were found to be useful for bridgehead-carbon and bridgehead-nitrogen bond formation. The ring contraction from bicyclo[3.3.1]nonanes to bicyclo[3.2.1]octanes could be a useful reaction to expand this methodology to synthesize natural products with the bicyclo[3.2.1]octane moiety.

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