Organic Synthesis Using Bridgehead Carbocations and Bridgehead Enones

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Contents

I. Introduction 1591
II. Previous Synthetic Contributions 1591
III. Bridgehead Carbocations 1592
A. Preliminary Studies on Bridgehead Carbocations 1592
B. A Case Study: Synthesis of Lycopodine 1594
C. A Case Study: An Approach to Colchicine 1594
IV. Bridgehead Enones 1595
A. Preliminary Studies on Bridgehead Enones 1595
B. A Case Study: Synthesis of a Taxane Subunit 1596
C. A Case Study: Synthesis of Diterpene Alkaloid Subunits 1597
V. Summary 1597
VI. References 1597

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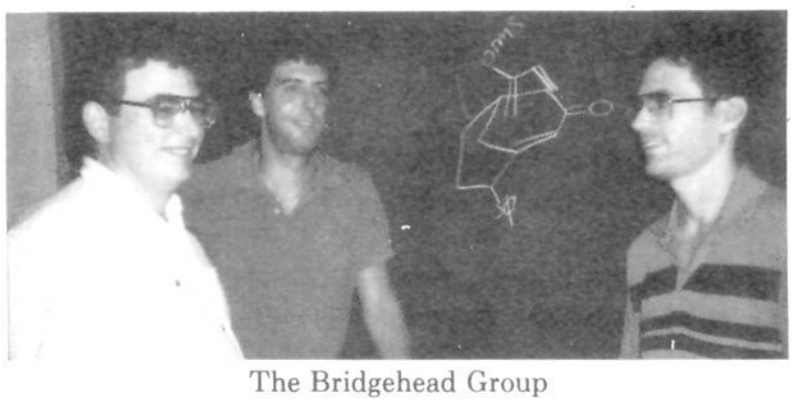

The Bridgehead Group

Steve Laramay (left) received his B.A. from the State University of New York at Potsdam in 1985. He will receive his Ph.D. from Iowa State University in 1990. Spiros Liras (middle) received his B.S. from St. Ambrose University in 1985. He will receive his Ph.D. from Iowa State University in 1989. Jeff Hanson (right) received his B.A. from DePau in 1986. He is currently a graduate student at Iowa State University.

I. Introduction

The development of new pathways by which organic molecules can be stereoselectively constructed remains an important direction for organic chemistry. The palladium-mediated cyclizations of Trost,[1] Stille,[2] Hegedus,[3] Larock,[4] Negishi,[5] and Overman[6] and the radical cyclization reactions of Keck,[7] Stork,[8] Hart,[9] Curran,[10] Barton,[11] and Beckwith[12] represent important new strategies. A comparatively unstudied strategy is the formation of bicyclic or tricyclic systems via reactive bridgehead intermediates.

There has long been active interest in bridgehead intermediates in the physical organic community. Classic studies by Vogel,[13] Schleyer,[14] and Warner[15] served to elucidate structural information about different bridgehead carbocations. Much of this data is collected in an excellent review by Fort.[16] Important investigations by Wiseman,[17] Dauben,[18] and Marshall[19] provided valuable information on the preparation and stability of bridgehead alkenes. Recently, a comprehensive review by Warner has appeared.[20] In contrast, the synthetic applications of bridgehead intermediates have been marked by only a few concerted studies.

In this article the contributions of earlier investigators are summarized first, followed by our preliminary studies and then by our applications of bridgehead methodology to natural product synthesis.

II. Previous Synthetic Contributions

House and co-workers contributed a classic study of substituent effects on bridgehead enone stability.[21] Their results laid the ground work for most of the later applications. They prepared both bicyclo[3.3.1]nonen-3-ones and bicyclo[3.2.1]octen-3-ones, usually by base-promoted halide eliminations. While the unsubstituted bicyclo[3.3.1]nonen-3-one dimerized readily at subambient temperatures, the α-phenyl enone was much more stable; however, it reacted readily with water, methanol, oxygen, and butadiene. The latter

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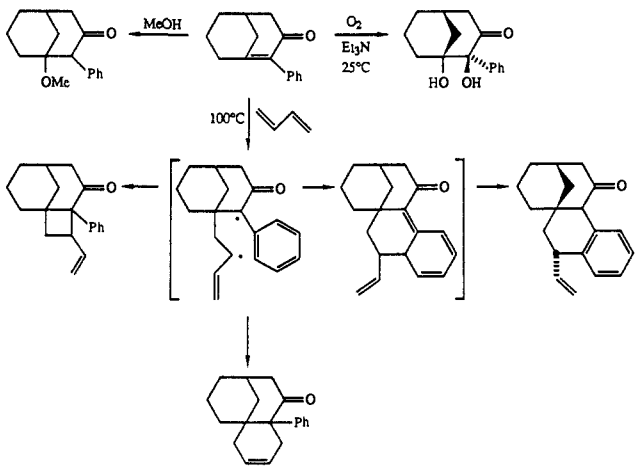
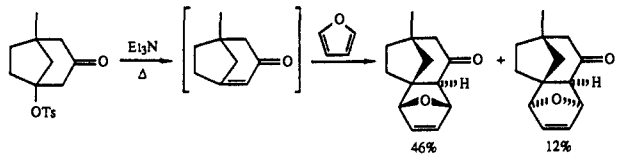
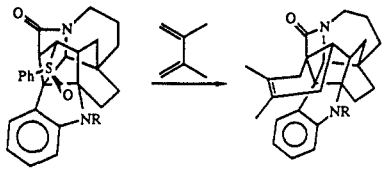
reaction produced three products via a diradical intermediate.



In the bicyclo[3.2.1]octen-3-one series, the enone was produced by elimination of a β-keto tosylate. House was able to trap this reactive enone with both methanol and furan. A more highly functionalized bridgehead enone was prepared by the intramolecular cyclization of a ketophosphonate. This work also provided a tetracyclic intermediate for the synthesis of the gibberellins.

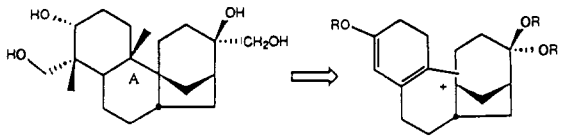


Magnus utilized a bridgehead enone in his creative synthesis of the kopsane alkaloids.[22] The enone was generated by a sulfoxide elimination. Magnus trapped the reactive bridgehead enone with 2,3-dimethylbutadiene. To the best of our knowledge, this represents the first use of a bridgehead enone in natural product synthesis.

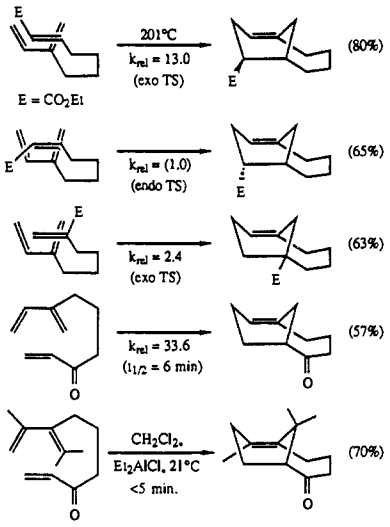


Shea and co-workers prepared bridgehead alkenes by an innovative intramolecular Diels–Alder reaction.[23] These reactions were accelerated by a suitably electron-withdrawing group and were highly regio- and stereoselective. The product derived from an exo transition state was obtained. The reactions could be conducted either as gas-phase pyrolyses or as solution-phase pyrolyses. Temperatures between 200 and 400 °C were required for the thermally induced reactions when the dienophile contained an electron-withdrawing group. Shea also generated bridgehead alkenes via Lewis acid mediated cycloadditions at ambient temperature. Some of the bridgehead alkenes produced by the Lewis acid catalyzed reaction represent attractive intermediates for the synthesis of taxanes. Shea recently synthesized enol lactones wherein the double

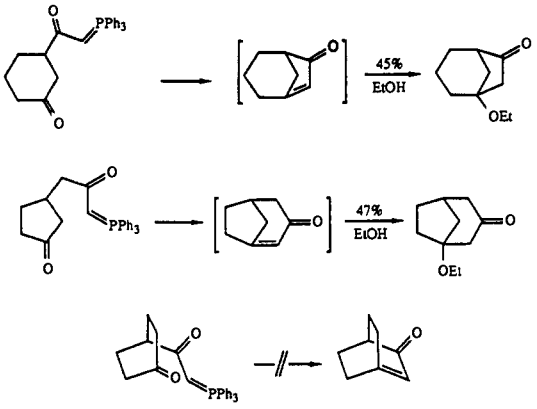
SCHEME I



bond of the enol lactone was a bridgehead alkene in an oxabicyclo[4.3.1]decene system.



Bestmann used an intramolecular Wittig reaction to produce bridgehead enones.[24] This strategy was successful for certain bicyclo[3.3.1]nonenones, bicyclo[3.2.1]octenones, and bicyclo[4.3.1]decenones. However, all attempts to generate a bicyclo[2.2.2]octenone by this strategy failed, undoubtedly due to the strain inherent in this system.

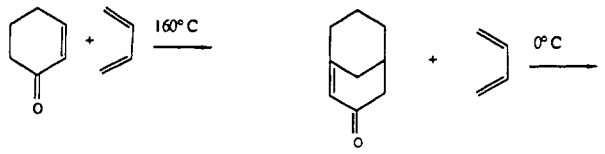


III. Bridgehead Carbocations

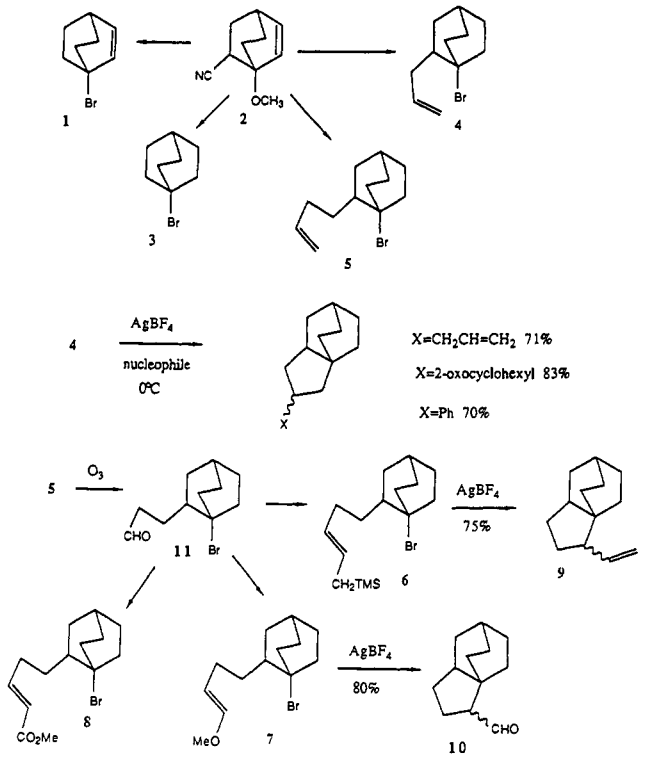
A. Preliminary Studies on Bridgehead Carbocations

Our initial interest in bridgehead reactivity was prompted by a retrosynthetic analysis of aphidicolin, a novel anticancer and antiviral agent, wherein disconnection via bond A led to an extremely direct and interesting pathway (Scheme I). Interestingly, dissection at a bridgehead carbon atom in a variety of molecules led to novel pathways. In order to actually construct molecules via a bridgehead pathway, many fundamental questions remained to be answered. We then embarked on a study of bridgehead reactivity from a synthetic perspective.

SCHEME II



SCHEME III



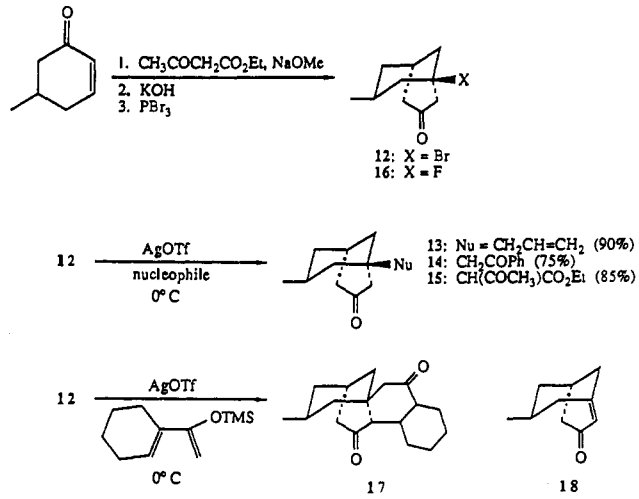
Before any synthetic studies are discussed, it is worthwhile to compare bridgehead intermediates with their nonbridgehead counterparts. Carbocations are important intermediates for synthesis; however, the use of carbocation-based methodologies is often complicated by undesired rearrangements and by mixtures of stereoisomers produced from the planar carbocation. Bridgehead carbocations offer attractive advantages. In bicyclic systems such as bicyclo[2.2.2]octanes and bicyclo[3.3.1]nonanes, the bridgehead carbocation does not suffer hydride shifts. Indeed, there are some examples in which Friedel–Crafts reactions have been conducted on bridgehead halides. Additionally, the large energy difference between the bridgehead carbocation and the analogous acyclic carbocation provides a strong driving force for bond formation. Moreover, there is no stereochemical ambiguity with regard to the newly created quaternary center, since attack from only one face is enforced by the structure of the bicyclic system. Bridgehead enones also enjoy these three advantages over simple cyclic and acyclic enones. Bridgehead enones are readily prepared by the dehydrohalogenation of the β-halo ketones. By way of comparison, uncatalyzed Diels–Alder reactions with cyclohexenone are typically conducted around 160 °C, while the bridgehead enone derived from 1-bromobicyclo[3.3.1]nonan-3-one reacts with dienes at 0 °C (Scheme II).

The first system that we examined[25] was the readily available 1-bromobicyclo[2.2.2]octene 1. It was generated from commercially available 1-methoxybicyclo-

TABLE I. Reaction of Bromides 3 and 12 with Various Nucleophiles

bromide	nucleophile	% yield
3	benzene	90
3	1,3-$(OMe)_2C_6H_4$	74
3	PhC(OTMS)=CH_2	65
3	CH_2=$CHCH_2SiMe_3$	85
12	CH_2=$CHCH_2SiMe_3$	90
12	PhC(OTMS)=CH_2	75
12	CH_2=$CHCH_2NH_2$	99
12	1,4-$(OMe)_2C_6H_4$	99
12	1-((trimethylsilyl)oxy)cyclohex-1-ene	75

SCHEME IV

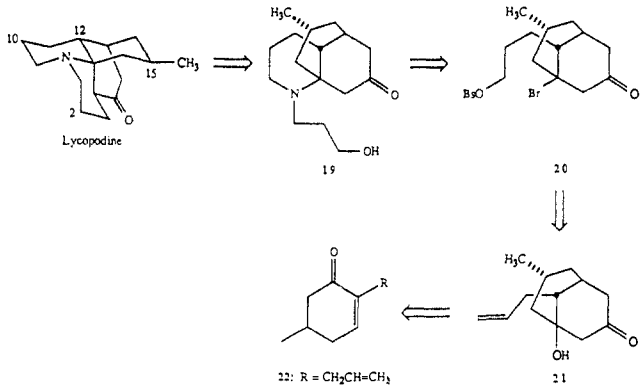


[2.2.2]octenecarbonitrile 2 by reductive decyanation followed by treatment with BBr_3 (Scheme III). Surprisingly, this bridgehead bromide did not react with silver trifluoroacetate or silver triflate at 0 °C. It did not react with silver acetate in boiling acetic acid! It is possible that silver ion complexation with the olefin in 1 destabilized cation formation. However, recent theoretical calculations indicate that even an uncomplexed olefin can, in the proper orientation, destabilize carbocation formation by approximately 20 kcal/mol.[26] Fortunately, the saturated analogue 3 reacted rapidly with silver trifluoroacetate in methylene chloride at 0 °C. The carbocation derived from 3 reacted with a variety of representative nucleophiles. The results are depicted in Table I.

Intramolecular cyclizations were also examined. The starting materials were prepared from 2 by straightforward synthetic reactions. The allyl-substituted compound 4 reacted with silver tetrafluoroborate in the presence of trapping agents such as allyltrimethylsilane, benzene, and the enol silyl ether of cyclohexanone. The sequence of carbocation generation, intramolecular cyclization, and intermolecular trapping proceeded in overall yields of 70–83%. The trapping agent could also be part of the alkene, as evidenced by the reactions employing 6 and 7. Unsaturated ester 8 did not afford an adduct, presumably because the alkene was not sufficiently nucleophilic to react with the carbocation.

The reactions of 1-bromobicyclo[3.3.1]nonan-3-one were next investigated. The keto alcohol was a known compound that had been prepared by a Michael/aldol protocol using cyclohexenone and ethyl acetoacetate.[27] The bromide 12 was readily prepared by treatment of the keto alcohol with PBr_3 (Scheme IV). Bromide 12 reacted with silver tetrafluoroborate and allyltri-

SCHEME V



methylsilane to afford the expected olefinic ketone **13** plus the fluoro ketone **16** in almost equal amounts. This undesirable byproduct was easily avoided by reacting **12** with silver triflate and allyltrimethylsilane, providing ketone **13** in 90% yield. Similarly, a variety of other nucleophiles reacted with **12** to generate useful products. The reactions are shown in Table I. Interestingly, amines could be used as nucleophiles if the amine was added after the silver triflate was allowed to react with **12**. The reaction of **12** with the enol silyl ether of acetylcyclohexene afforded the tetracyclic compound **17** (Scheme IV). While **17** could have been produced via trapping of the bridgehead carbocation followed by an intramolecular Michael addition, it could also have arisen from an intermolecular Diels–Alder reaction with bridgehead enone **18**. The possibility that some of the product may be formed via the bridgehead enone pathway cannot be ruled out, particularly since the in situ generated enone **18** actually reacts rapidly with the enol silyl ether of acetylcyclohexene.

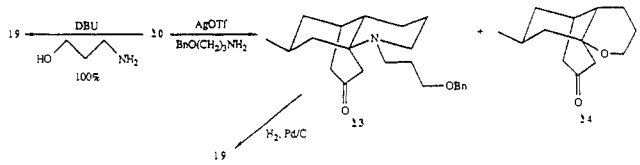
B. A Case Study: Synthesis of Lycopodine

With these results in hand, the alkaloid lycopodine was chosen as our first synthetic objective.[28] Lycopodine, produced by the genus *Lycopodium*, is the prototype of a family of alkaloids that now contains over 100 members. Lycopodine had already been synthesized by several researchers. The pioneering synthetic work was done by Stork[29] and by Ayer.[30] Their research culminated in total synthesis in 1968. Heathcock[31] and co-workers achieved an elegant total synthesis in 1982. Schumann[32] and co-workers also reported a clever synthesis of lycopodine from a bicyclic imine in 1982. Finally, Wenkert and Broka[33] published an interesting total synthesis in 1984.

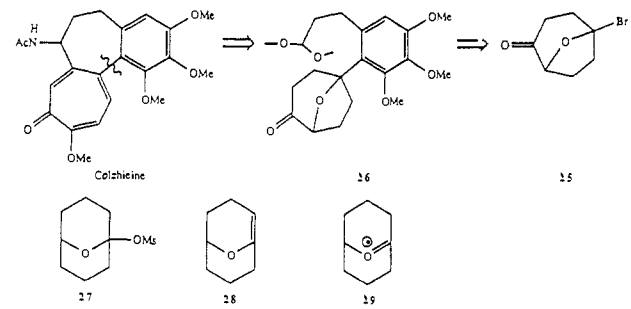
The retrosynthetic analysis of our route to lycopodine is shown in Scheme V. Keto alcohol **19**, an advanced intermediate in the Heathcock synthesis, will be produced from ketone **20**, which in turn will be produced from bicyclic ketone **21**. Bicyclic ketone **21** will be generated from enone **22** by the method of Saito.[34] Ketone **22** is readily available from 5-methylcyclohexenone by the method of Baraldi.[35]

Hydroxy ketone **21** was produced by the reaction of **22** with ethyl acetoacetate in boiling methanol containing sodium methoxide. The crude product was decarbalkoxylated using aqueous KOH, to afford a mixture of two isomeric products in a 20:1 ratio. Since the allyl group was expected to epimerize to the equatorial position before the intramolecular aldol condensation, the major product was assigned structure **21**. The reaction of **21** with borane–THF was highly chemoselective, affording a dihydroxy ketone. Selective benzenesulfonylation of the primary alcohol over the tertiary alcohol worked well. Benzenesulfonylation not only activated the alcohol for displacement but also rendered the oxygen atom much less nucleophilic. *This point was crucial to the success of our plan, since a carbocation was later to be generated only five carbon atoms away.* The reaction of the tertiary alcohol with phosphorus tribromide provided bromo ketone **20**.

SCHEME VI



SCHEME VII



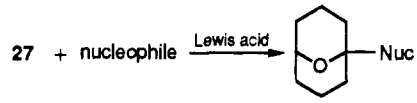
The conversion of **20** into **19** was accomplished by two different bridgehead intermediates. The transformations are shown in Scheme VI. The bridgehead carbocation pathway was initiated by reacting **20** with silver triflate to generate the bridgehead triflate. The amine must be added after triflate formation in order to prevent formation of a silver–amine complex. Under optimal conditions, the yield of **23** was 96% with only a trace of ether **24**. The benzyl ether was cleaved by hydrogenation to afford alcohol **19**.

The bridgehead enone pathway, inspired by House's classic studies, involved the reaction of **20** with 3-amino-1-propanol and DBU. This reaction produced alcohol **19** in quantitative yield. Ketone **19** was converted into racemic lycopodine in two steps using Heathcock's procedures. Our racemic lycopodine has a ^{13}C spectrum that is identical with that reported in the literature. Our total synthesis was effected in only nine steps and in 25% yield from ketone **22**. The basic route is now being modified to allow the synthesis of more complex *Lycopodium* alkaloids.

C. A Case Study: An Approach to Colchicine

In addition to the construction of compounds that contain bridgehead subunits, the bridgehead pathway will also be useful for the synthesis of key bridged intermediates which may then be taken on to fused or spirocyclic ring systems. One application of this strategy is to the synthesis of colchicine. Colchicine exerts biologically significant effects on microtubule assembly. It has been synthesized by several researchers, most recently by Evans[36] and by Boger.[37] Banwell[38] has demonstrated that simple tropolones also exhibit colchicine-like effects on microtubules.

TABLE II



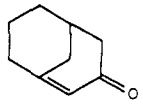
Lewis acid	nucleophile	T, °C	% yield
$TiCl_4$	$1,3\text{-}(OMe)_2C_6H_4$	0	45
$BF_3{\cdot}Et_2O$	$1,3\text{-}(OMe)_2C_6H_4$	0	25
$TiCl_4$	$1,3\text{-}(OMe)_2C_6H_4$	−78	73
$TiCl_4$	toluene	−78	60
$TiCl_4$	$1,4\text{-}(OMe)_2C_6H_4$	−78	61
$TiCl_4$	$3,4,5\text{-}(OMe)_3C_6H_2CHO$	−78	
$TiCl_4$	$3,4,5\text{-}(OMe)_3C_6H_2CH_2CH_2CO_2Me$	−78	55

Our retrosynthetic analysis, which is illustrated in Scheme VII, has ether **26** as a key synthetic intermediate. This bridged ether might arise from ether **25** via a bridgehead carbocation reaction with an electron-rich aromatic ring. Before this route could be undertaken, the chemistry of **25** needed to be investigated.[39] Wiseman[40] had prepared the analogous ether **27** for his synthesis of bridgehead alkene **28**. He noted that **27** was a stable compound, probably because the oxonium ion **29** was destabilized by ring strain. We found that **27** reacted with 1,4-dimethoxybenzene at subambient temperatures in the presence of titanium tetrachloride. The results of our studies with **27** and various nucleophiles and Lewis acids are collated in Table II. Importantly, even highly substituted benzene rings participate in this reaction.

IV. Bridgehead Enones

A. Preliminary Studies on Bridgehead Enones

Although bridgehead alkenes in small-ring bicyclic systems are reactive, the corresponding bridgehead enones are so reactive that even isolation at low temperatures is not feasible. House and Trahanovsky[41] have demonstrated that bridgehead enone **30** when

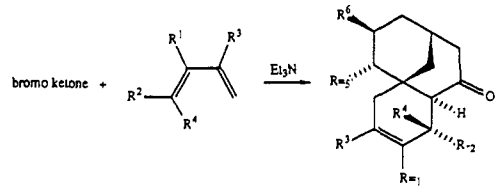


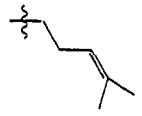
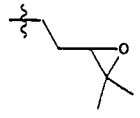
30

generated by a retro-Diels–Alder reaction using flash vacuum pyrolysis can be detected in solution at −78 °C. At higher temperatures, **30** dimerizes rapidly to a mixture of stereoisomers. Enone **30** also reacts rapidly with molecular oxygen. Calculations using Allinger's MM2 program indicate that the double bond in the bridgehead enone is twisted from planarity by approximately 25°. This deformation greatly enhances the inherent electrophilicity of the enone subunit. Good nucleophiles such as alcohols and amines add rapidly at subambient temperatures. The Diels–Alder reaction, another fundamental reaction of enones, also proceeds well in the bridgehead series. This reaction had been briefly examined by House and by Magnus. We were the first to determine the regiochemistry and stereochemistry of the cycloaddition with unsymmetrical dienes.[42]

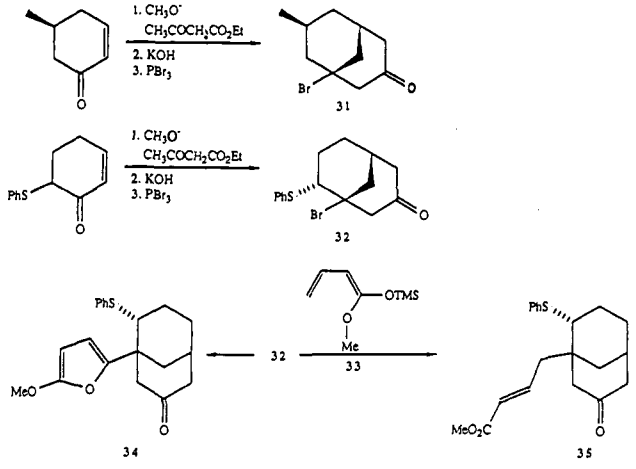
A study of the scope and limitations of this reaction began with bromo ketones **31** and **32**. They were prepared as previously described. The bridgehead enones were formed in situ by reaction at 0 °C with triethylamine in the presence of 2 equiv of the diene. The

TABLE III



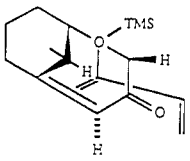
ketone	R1	R2	R3	R4	% yield
32		$(CH_2)_4$	OTMS	H	97
31		$(CH_2)_4$	OTMS	H	52
32	H	H_3CO	OTMS	H	98
32	H	OAc	H	H	63
32	H	H	H	H	41
31	H	OAc	H	H	55
32	H	CH_3	OTMS	CH_3	46
32	H		OTMS	CH_3	46
32	H		OTMS	CH_3	81

SCHEME VIII



results of our study are depicted in Table III. The facile addition of 1,1,3-trisubstituted dienes at 0 °C is very unusual. Unexpectedly, only a *single stereoisomer* was obtained. This reaction profile was also observed with 1,3-disubstituted dienes. In each case only the exo adduct was obtained. The determination of exo stereochemistry in the 1,3-disubstituted diene cases was based on the magnitude of the vicinal coupling constant for the methines α and β to the ketone. With the trisubstituted diene adducts, we had to apply 2D NMR COSY and NOESY techniques. While the assignments are admittedly less certain, the products also appear to be exo adducts. With two very reactive dienes we obtained addition products rather than Diels–Alder adducts (Scheme VIII). The reaction of the bridgehead enone derived from **32** with methoxyfuran and diene **33** produced ketones **34** and **35**, respectively.

The reaction of bridgehead enones with dienes could proceed via a polarized transition state or even an ionic one. Because of the twist in the enone unit and certain nonbonded interactions (see structure A) between the diene and axial hydrogens, secondary orbital overlap is unlikely to play a role in determining the exo/endo



A

selectivity. In order to probe the possible ionic nature of the transition state, diene **36** was prepared. *The regiochemistry of Diels–Alder reactions of diene **36**[43] with simple cyclic ketones is known to be controlled by the methyl substituent at C-1.* We reasoned that the (trimethylsilyl)oxy substituent at C-2 might direct the regiochemistry if the transition state was polarized. The reaction of diene **36** with the bridgehead enone derived from **32** afforded only adduct **37** (Scheme IX). Enone formation by the method of Saegusa[44] generated enone **38**. The olefinic pattern in **38** was an AB quartet of doublets. Decoupling experiments further established the structure of **38**. Clearly, the (trimethylsilyl)oxy substituent controlled the regiochemistry of addition. We next prepared diene **39** with the rationale that an ionic transition state could lead to the opening of the cyclopropane ring via a cyclopropyl carbinyl carbocation. Although the yield of adduct **40** was modest, no products due to cyclopropane opening were observed.

The use of the Diels–Alder adducts for the synthesis of terpene anticancer agents is in progress.[45] Adduct **41** reacts efficiently with palladium acetate and benzoquinone to afford enone **42**. Unfortunately, enone **42** does not react with Me_2CuLi, heterocuprates, or higher order cuprates. As shown in Scheme X, it does react with trimethylaluminum and trimethylsilyl cyanide to afford nitrile **43**. The stereochemistry of **43** is based on the structure of **44**.

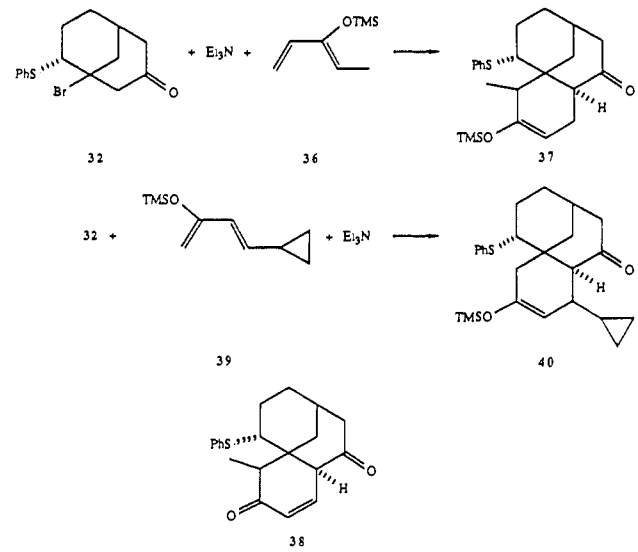
Bridgehead enones also react effectively with cuprates.[46] This reaction permits the introduction of a simple alkyl group into a bridgehead position. The crucial part of this transformation is the base that must be used to make the bridgehead enone. Scheme XI shows our results with a variety of cuprates.

B. A Case Study: Synthesis of a Taxane Subunit

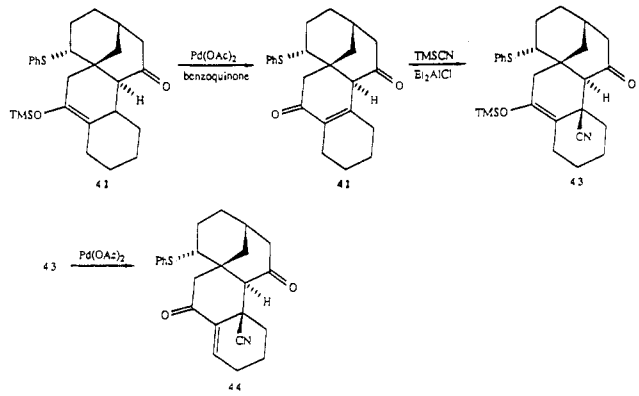
Because of their high reactivity, bridgehead enones also react with electron-rich alkenes.[47] The product of this reaction, a cyclobutyl ketone, is extremely sensitive to acid. We examined a range of electron-rich alkenes, including ethyl vinyl ether, vinyl acetate, the pyrrolidine enamine of cyclohexanone (**46**), 1-((trimethylsilyl)oxy)-1-ethoxyethylene (**47**), the TBS enol silyl ether of acetaldehyde, and 1,1-dimethoxyethylene (**48**). Both the enamine and vinyl acetate afforded complex mixtures of products. Ethyl vinyl ether and the enol silyl ether or acetaldehyde did not react. Unexpectedly, the reaction of **47** with the bridgehead enone provided ether **49**. The reaction of **48** with the bridgehead enone at 0 °C afforded cyclobutane **50** in almost quantitative yield. On silica gel chromatography, cyclobutane **50** was quantitatively cleaved to form methyl ester **51** (Scheme XII).

The fragmentation of **50** to give **52** was next examined. This reaction is significant in that the bicyclo[5.3.1]undecene moiety is a significant subunit in the

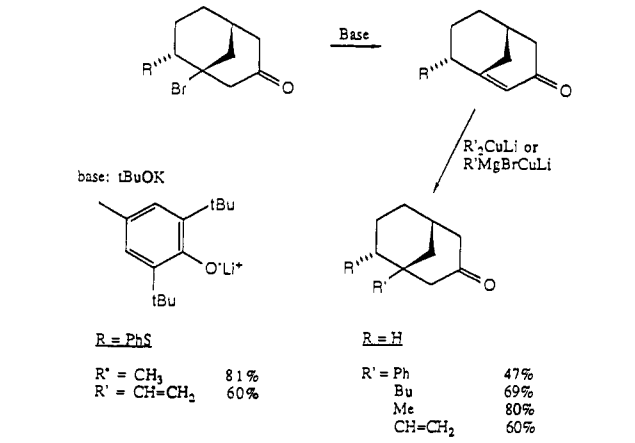
SCHEME IX



SCHEME X

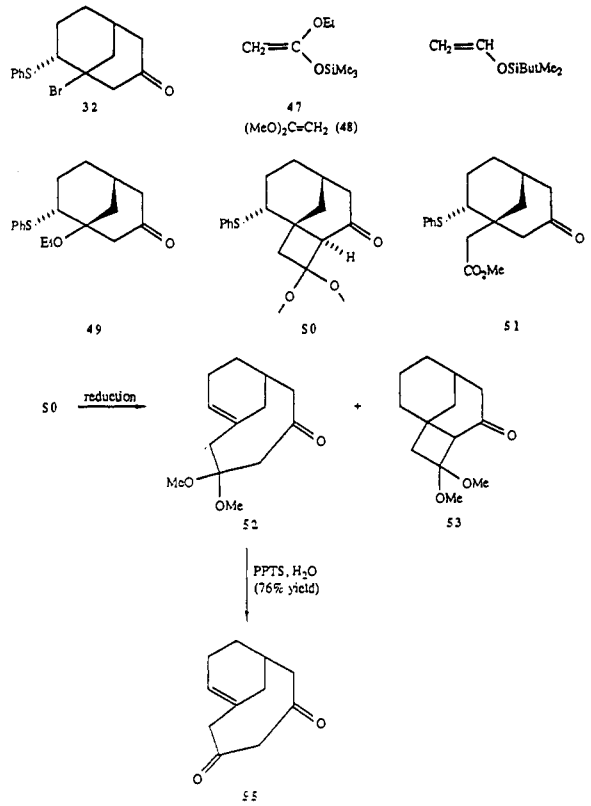


SCHEME XI



taxane family of terpenes. Several reaction conditions were examined to determine the optimal conditions for the fragmentation. While most of these conditions produced some ketone **52**, the major product was ketone **53**. For example, Li–$C_{10}H_8$ produced only ketone **53** in 73% yield. Our best conditions for the fragmentation reaction involved the use of lithium in liquid ammonia. Ketone **52** was generated in 51% isolated yield with only a 10% yield of **53**. Interestingly, the bridgehead alkene in **52** is not affected by the reduction conditions. The strain introduced by the cyclobutane ring is a necessary requirement for fragmentation. If a cyclohexene ring is present instead of a cyclobutane (com-

SCHEME XII



pound 54), fission of the C–S bond occurs, but fragmentation does not occur.

The hydrolysis of 52 with pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone afforded diketone 55. This diketone is not enolic, nor does it appear to be very acidic. This is in stark contrast to the behavior of 1,3-diketones in six- and seven-membered rings. Molecular models indicate that the two carbonyls are at an angle of approximately 80°. A model of 55 as an enolic diketone is extremely strained, perhaps explaining the low kinetic acidity of 55. Only complex mixtures have resulted from attempted alkylation with MeI.

C. A Case Study: Synthesis of Diterpene Alkaloid Subunits

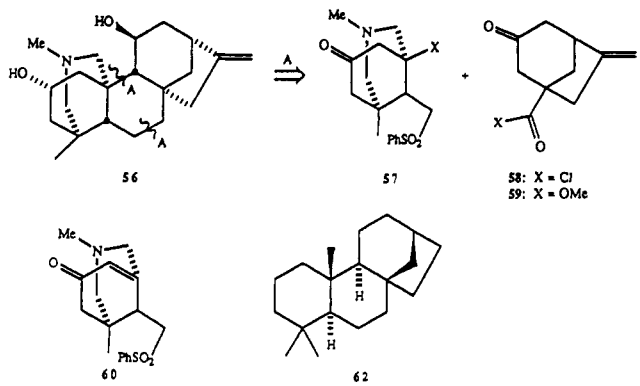
The extension of the bridgehead pathway to more complex natural products is also under way. A disconnection that simplifies the synthesis of diterpene alkaloid 56 is illustrated in Scheme XIII. The retrosynthetic analysis could proceed by either of two bridgehead disconnections. The azabicyclo[3.3.1]nonanone 57 (X = CO_2Me) has already been constructed. The bicyclo[3.2.1]octane unit 58 can be derived from the known keto ester 59.[48] We expect to connect units 57 and 58 via the reactive bridgehead enone 60.

Bicyclic building blocks 57 and 58 are common subunits in several terpene and alkaloid structures such as 61 and 62. Our long-term goal is to assemble these complex compounds from performed chiral nonracemic bicyclic units.

V. Summary

Bridgehead connectivity has the potential for achieving flexible and convergent synthetic pathways. Now that a broad picture of bridgehead reactivity exists, increased applications in organic synthesis can be anticipated.

SCHEME XIII



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