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Expansion to Seven-Membered Rings

Eric J. Kantorowski and Mark J. Kurth*

Department of Chemistry, One Shields Avenue, University of California, Davis, CA 95616, USA

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1. Introduction

The impetus for developing methods for the construction of seven-membered rings derives from the common occurrence of these frameworks in biologically active natural products. It is well known that few straight-chain cyclization methods are successful and then usually only in low yields. The more accessible smaller rings (three through six) are common starting points in medium-ring forming methods.

This review provides an account of synthetic methods designed to prepare seven-membered rings from pre-existing smaller rings (three, four, five, and six) or bicyclic systems. Seven-membered carbocycles, azacycles, thiacycles and variants thereof (e.g. diazapines, azathiapins, etc.) are covered in this review. Oxacycles are included only if a second heteroatom (N or S) is included in the ring. Seven-membered oxacycles will not be covered, as a recent review on the preparation of these systems has been recently compiled by Hoberg.[1] Although the focus is on seven-membered rings, it should be noted that many of the reviewed works contain norlogues and homologues, and the reader should not dismiss the possibility that a more comprehensive study was performed. We direct the reader to other reviews or monographs for a more general review on ring expansions.[2–4] Additionally, reviews focusing on carbon insertion reactions,[5,6] nitrogen insertion reactions,[7–11] medium-ring azacycles,[12,13] medium-ring thiacycles,[14] radical-based expansion,[15] and rearrangements and electrocyclic reactions[16–20] are available.

Keywords: expansion; medium-ring carbocycles; medium-ring heterocycles; rearrangements; seven-membered rings.

* Corresponding author. Tel.: +530-752-8192; fax: +530-752-8995; e-mail: mjkurth@ucdavis.edu

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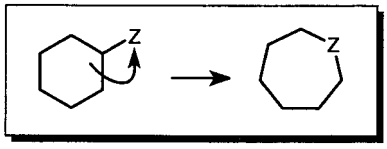
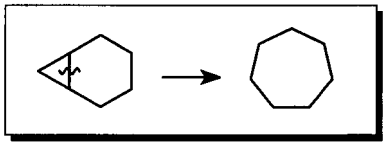
Our aim is to review a wide variety of methods that access seven-membered rings. Approaches that are highly inconvenient, require highly specialized or expensive equipment or would be of limited use to the synthetic organic chemist have been omitted. Our review covers the literature inclusive of 1998, with attention focused mainly on readily accessible literary journals. In a number of cases the reported yields may be low, but it is anticipated that when viewed in full, improvement to previous methods may be realized.

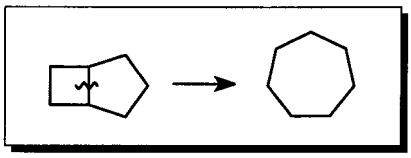
There are four main approaches to realizing ring expansion (Schemes 1–4). These are displayed generically with the ring-containing carbon and/or heteroatoms. The first is based on the use of group Z, which is pendant to a preexisting ring (Scheme 1). This group possesses a charge (either full or latent) or has carbene character. These features allow Z to be incorporated into the ring either via a migratory shift or insertion. Z may also be part of a bicyclic system wherein ring expansion is realized at the expense of the adjoining ring that undergoes ring-contraction. The other approaches take advantage of strain associated with three- or four-membered rings (Schemes 2 and 3). Heterolysis or homolysis of the shared bond, promoted by functional groups adorning the ring, of either a [4.1.0] or [3.2.0] bicyclic ring system leads to the seven-membered ring. The strained ring may not necessarily be present in the starting substrate, but may be a pivotal intermediate that guides the ensuing reaction towards ring expansion. Finally, electrocyclic reactions may be employed that allow for preparation of seven-membered rings (Scheme 4).



Scheme 1.



Scheme 2.



Scheme 3.

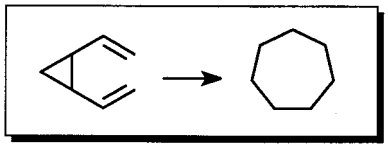
2. Migration- and Insertion-based Ring Expansions

2.1. Incorporation of carbon

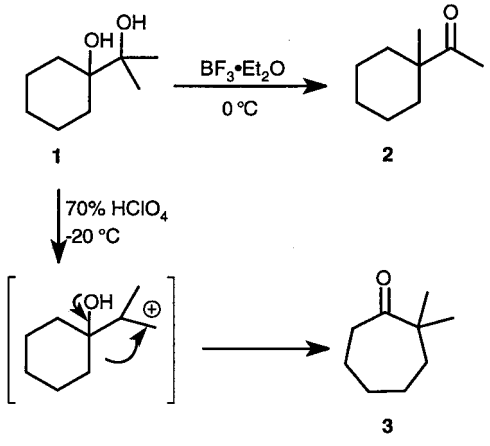
2.1.1. Pinacol-type. The most common strategy for ring expansion is to incorporate a group that will serve as a latent carbocation adjacent to a preexisting ring. Upon generation of the carbocation (or development of the incipient carbocation) a 1,2-alkyl migration from the ring is encouraged. Indeed, pinacol and pinacol-type rearrangements constitute a significant body of expansion technology. The developing strain energy associated with seven-membered rings is certainly a factor in the moderate yields commonly encountered.

Corey has demonstrated the utility of a pinacol rearrangement for the preparation of 2,2-dimethylcycloheptanone.[21] The course of the rearrangement of vicinal diol **1** is dependent on the choice of reagent employed (Scheme 5). When boron trifluoride etherate is used, methyl migration occurs, leading to **2**. Alternatively, treating **1** with perchloric acid furnishes the ring-expanded product **3** in 81% yield.

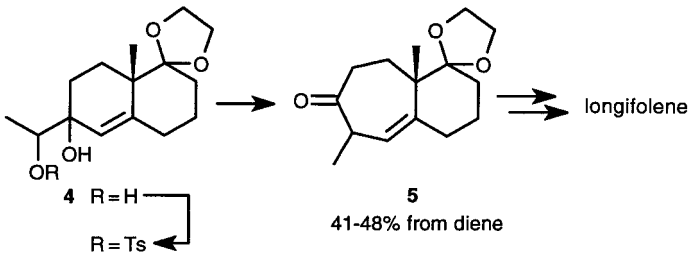
A classic expansion to a seven-membered carbocycle was demonstrated by Corey in his synthesis of longifolene.[22,23] The requisite diol **4** was prepared from dihydroxylation of the corresponding 1,3-diene, which was then selectively tosylated (Scheme 6). Treatment with $CaCO_3$ and $LiClO_4$ in THF induced pinacol rearrangement, providing the desired β,γ-unsaturated cycloheptanone **5** (41–48% yield from the diene). As expected, the vinyl fragment migrated preferentially over the alkyl substituent.



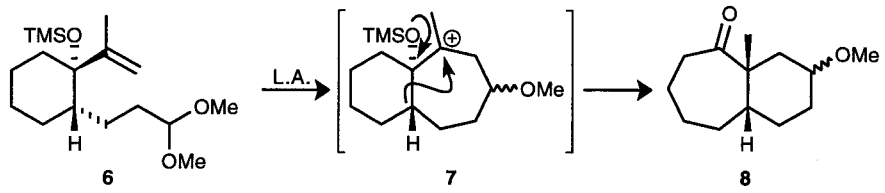
Scheme 4.



Scheme 5.



Scheme 6.

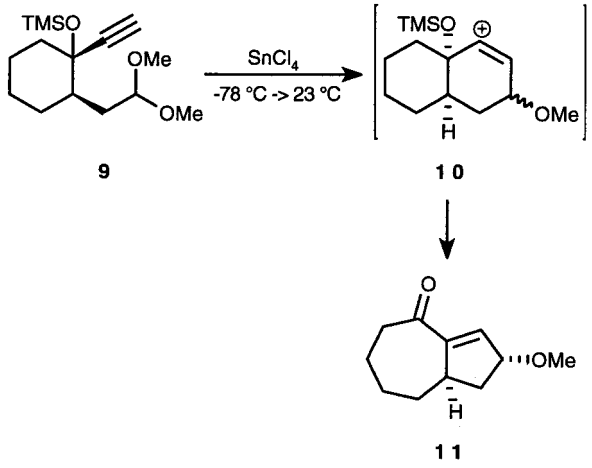


Scheme 7.

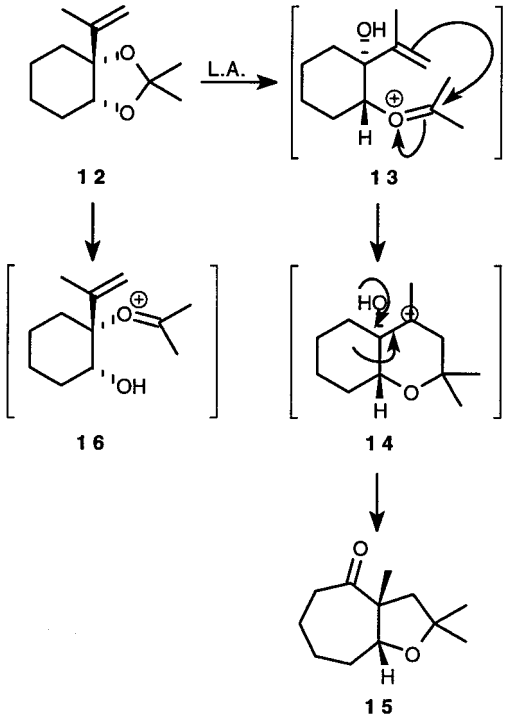
Overman has devised a route to medium-sized rings based on a Prins-pinacol rearrangement.[24,25] The sequence begins with an unsaturated acetal **6**, which is readily accessible in three steps from cyclohexanone (Scheme 7). Exposure of this material to a Lewis acid results in a Prins cyclization intermediate **7**, which is immediately subject to a pinacol rearrangement, affording cycloheptanone **8** in 73–82% yield. Stereochemistry at the ring juncture is consistently *cis* for a variety of examples. One limitation of this process is that the alkene must be more nucleophilic than a terminal vinyl group for the initial cyclization to proceed.

The aforementioned strategy is amenable to replacement of the alkene with an alkyne, which leads to ring-expanded enones.[26] Treatment of acetal **9** with 1.2 equiv. of $SnCl_4$ instigates the sequence wherein cationic cyclization provides the bicyclic intermediate **10** (Scheme 8). Subsequent pinacol rearrangement leads to the ring-expanded enone **11** in 68% yield as a 6:1 ratio of diastereomers (major stereoisomer shown). The same cycloheptanone product is isolated when starting from the diastereomer of **9**, but in 48% yield and as a 1:1 ratio of diastereomers.

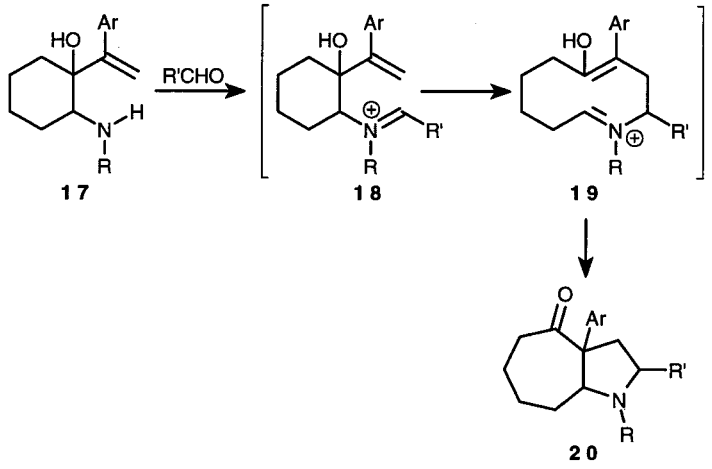
Overman has also shown that a Prins-pinacol sequence can be applied to the preparation of cycloheptatetrahydrofurans.[27]



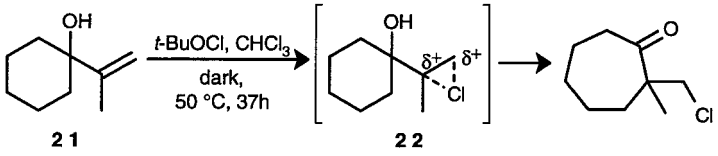
Scheme 8.



Scheme 9.



Scheme 10.



Scheme 11.

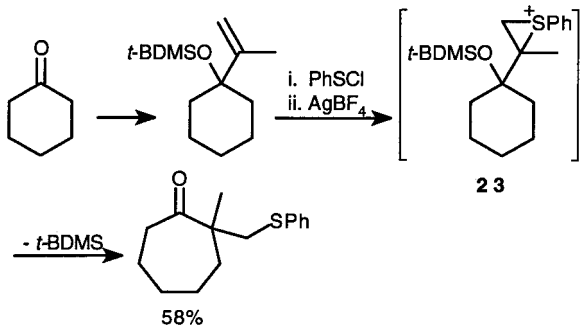
The ring expansion of acetal **12**, which can be readily prepared from the corresponding 1,2-diol, is representative (Scheme 9). Exposure to Lewis acid ($BF_3{\cdot}Et_2O$, $TiCl_4$, $EtAlCl_2$, or $MgBr_2$) generates oxonium ion **13**, which promotes cyclization to **14**. The ensuing pinacol rearrangement provides the *cis*-fused cycloheptatetrahydrofuran **15** in 94% yield. The fact that oxonium ion **13** forms preferentially over **16** is pivotal to the success of this expansion. Furthermore, although electron-donating substituents on the alkene promote the cyclization step, their presence may also encourage allyl cation formation by loss of the tertiary alcohol. Yields were typically in the range of 53–94%, with excellent control of stereochemistry observed for each case.

A similar sequence may be mapped onto aminocyclohexanols such as **17** (Scheme 10).[28–30] Condensation of **17** with an aldehyde leads to the intermediate iminium ion **18**. A 2-azonia[3,3]sigmatropic rearrangement follows, providing intermediate enol **19**. This system engages in an intramolecular Mannich condensation, forming cycloheptanone **20**. A variant of the initial condensation reaction utilizes a cyanomethyl group on nitrogen to serve as a formaldehyde iminium ion progenitor.[30]

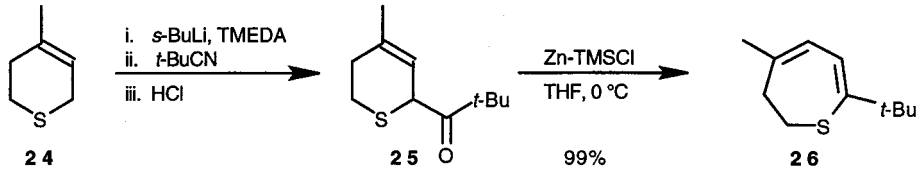
Johnson disguised a latent carbocation in the form of an alkene adjacent to a cycloalkanol, with the intention of promoting ring expansion.[31] Thus treating cyclohexanone with 2-propenyl Grignard led to the required allylic alcohol **21**, which was subsequently treated with *t*-butyl hypochlorite (Scheme 11). The intermediate chloronium ion **22** induces a 1,2-alkyl migration, affording 2-chloromethyl-2-methyl cycloheptanone in 38% yield. Use of Br_2 or Cl_2 led to complex mixtures. As an alternative, the analogous epoxide was prepared and treated with a Lewis acid to afford 2-hydroxymethyl-2-methylcycloheptanone in 15% (BF_3 etherate) or 33% yield (alumina).[32]

Kim has employed a similar strategy for the one-carbon ring expansion of 1-alkenylcycloalkanols.[33] The *tert*-butyldimethylsilyl group was selected as the protecting group for the alcohol (Scheme 12). The expansion is triggered by the intermediate episulfonium ion **23** derived from treatment of the alkene with PhSCl. Subsequent treatment with $AgBF_4$ provides the α-(1-phenylthioalkyl)cycloheptanone in 58% yield. Interestingly, when the alcohol is protected as the TMS ether, no expansion is observed. Furthermore, for unsymmetrical ketones, the more substituted component migrates preferentially.

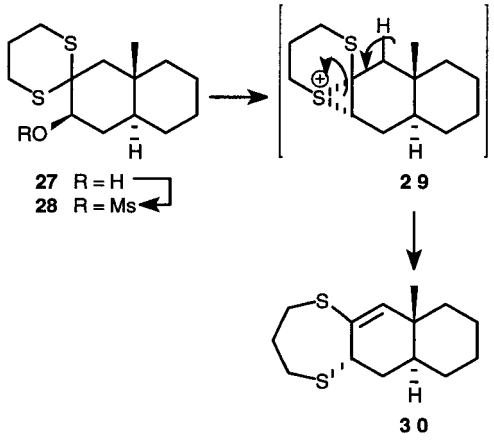
Murata has also designed a ring-expansion method for the preparation of 2,3-dihydrothiepin **26** (Scheme 13).[34] The requisite ketone **25** was readily prepared from dihydrothiopyran **24** by treatment with *sec*-butyllithium followed by introduction of *tert*-BuCN and hydrolysis. Application of



Scheme 12.



Scheme 13.



Scheme 14.

Zn–TMSCl led to successful ring expansion, providing **26** in 99% yield.

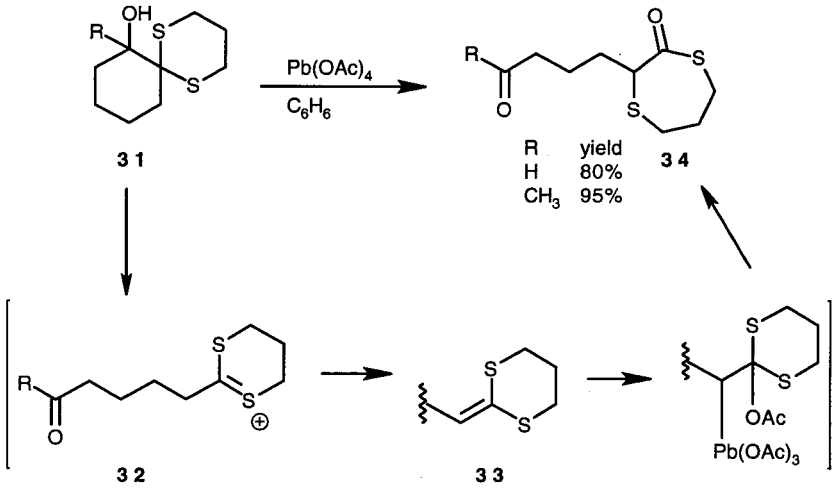
Marshall unexpectedly formed a seven-membered dithiacycle, while attempting to deoxygenate alcohol **27** (Scheme 14).[35] It was anticipated that conversion to mesylate **28** would prepare for reduction to methylene. However, this approach was thwarted by anchimeric displacement of mesylate by the proximal thioacetal. The resulting ion **29**, upon deprotonation, is converted to ring-expanded compound **30** in nearly quantitative yield.

A one-carbon ring expansion to dithiepanone **34** from thioacetal **31** was reported by Trost.[36] Here, lead tetraacetate (2.6 equiv.) facilitates cleavage of the cyclohexanol ring, presumably leading to intermediate **32** (Scheme 15). Isomerization to **33**, addition of lead tetraacetate across the olefin, and rearrangement accounts for the observed product.

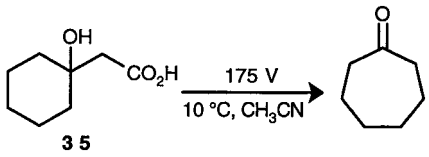
Corey has shown that aniodic oxidation of β-hydroxycarboxylic acids promotes 1,2-alkyl shifts which can result in ring expansion.[37] Hence, exposing 2-(cyclohexan-1-ol)acetic acid (**35**) to aniodic oxidation in acetonitrile provides cycloheptanone in 45–53% yield (Scheme 16).

2.1.2. Sulfur and selenium as leaving groups. Thioacetals have also been employed in ring expansion to seven-membered rings requiring a cyclohexanone derivative to begin the sequence. Thus, addition of the lithium anion of bis(phenylthio)methane to cyclohexanone produces β-hydroxythioacetal **36**. Exposing this compound to copper (I) triflate and diisopropylethylamine in benzene causes a pinacol-type rearrangement, resulting in formation of 2-phenylthiocycloheptanone (**37**) in 58% yield (Scheme 17).[38] Temperatures greater than 56°C led to increased amounts of 1-formyl-1-phenylthiocyclohexane (**38**). As an alternative to the Lewis acid conditions, it was found that *sec*-butyllithium (2 equiv.) also effected the transformation (55% yield).[39] The dianion that is formed in this case exhibits carbenoid behavior wherein departure of a thiolate group is formally an α-elimination, which explains the observed alkyl migration. The lower temperature employed for the rearrangement (0°C) and the ability to forego the use of the air and moisture sensitive copper salt extends the scope of this process.

Ranu has demonstrated that *N*-chlorosuccinimide (NCS) may be used to promote the one-carbon ring expansion of cyclic α-hydroxydithiane derivatives.[40] The reaction is

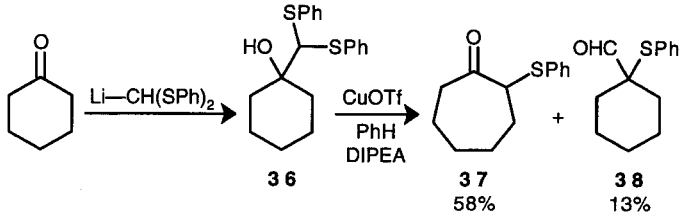


Scheme 15.

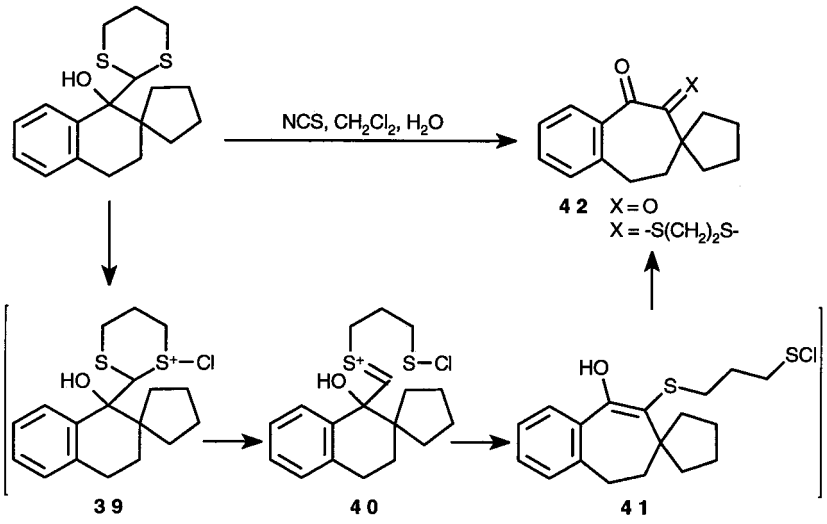


Scheme 16.

(2 equiv.) and heating the mixture to 75°C for 4 h. The bicyclo[3.2.1]octan-3-one derivative **43** is obtained in 61% yield. When cyclohexanone was subjected to this method, thio ester **44** was isolated after the rearrangement step, with no evidence of the anticipated cycloheptanone product (Scheme 20). Hindered or readily enolized ketones tend to participate in proton transfer when treated with



Scheme 17.



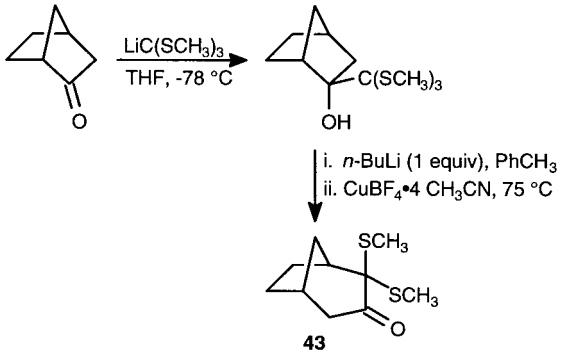
Scheme 18.

presumed to be initiated by attack of sulfur on NCS, generating intermediate **39** (Scheme 18). Anchimerically assisted heterolysis of the thioacetal provides **40**, which undergoes rearrangement to the ring-expanded enol **41**. Attack of the enol on the pendant electrophilic sulfur reforms the thioacetal, affording **42** in 75% yield. The thioacetal group remains intact unless water is present, in which case the 1,2-diketone is isolated in 70% yield. The process is amenable to modifications of the aromatic ring or substituents on the cyclic alcohol, with yields ranging between 60–92% yield. However, the reaction requires that the carbinol carbon be flanked by a quaternary center and a fused aromatic ring. If these criteria are not met, the reaction proceeds to provide the corresponding α-hydroxyaldehyde analogous to that observed in the aforementioned scheme.

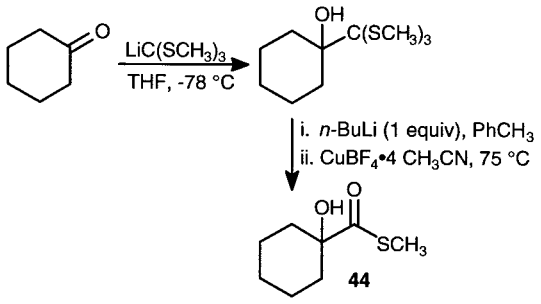
A slight variant of the thioacetal approach utilizes tris(methylthio)methyllithium.[41,42] Addition of this reagent to norcamphor proceeded in 95% yield (Scheme 19). The ring expansion could be effected by generating the alkoxide with *n*-butyllithium (toluene, −78°C) then adding $CuBF_4$

tris(methylthio)methyllithium, which limits their availability for this process.

Two notable variants have been developed from the aforementioned thioacetal approach. Trost has modified the method by beginning the sequence with the lithium anion



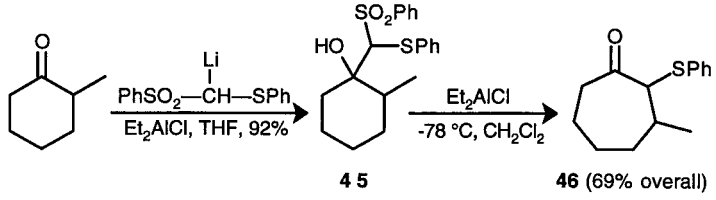
Scheme 19.



Scheme 20.

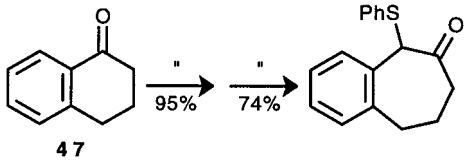
carbon ring expansion of α-tetralone (**47**) was also realized by this method (Scheme 22). The more substituted group migrates preferentially in this process, but exceptions are noted. In a related approach, attempts to use the lithium anion of methoxymethyl phenyl sulfone on camphor failed to produce any ring-expansion product.

The second variant of the thioacetal operation utilizes a seleno analogue that has been explored by Krief.[44–47] The selenoacetal **48**, available from the corresponding ketone, can be converted into α-selenoalkyllithium **49** by treatment with *sec*-butyllithium (Scheme 23). Addition of this reagent

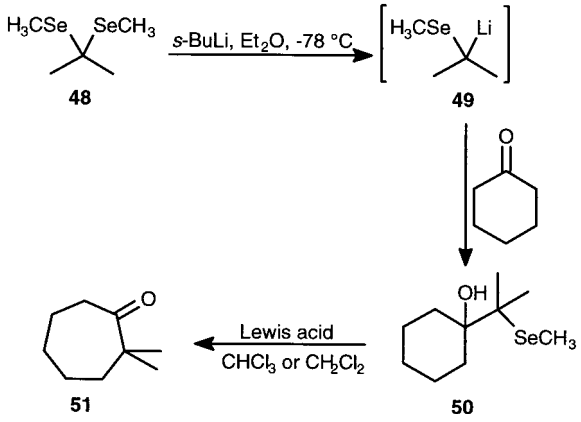


Scheme 21.

of phenylsulfonylphenylthiomethane (Scheme 21).[43] This anion adds smoothly to ketones, typically in >90% yield, provided that an excess of diethylaluminum chloride is also present. The replacement of one of the phenylthio groups with the phenylsulfone offers some distinct advantages. In the presence of Lewis acids, the sulfone functions as a leaving group with the liberated species (benzenesulfinate) possessing low nucleophilicity. Additionally, the ease of generating anions adjacent to the sulfone group and the mild conditions required for their ionization make for an improved method. Rearrangement of **45** occurs when treated with diethylaluminum chloride in methylene chloride at −78°C, affording cycloheptanone **46** in 69% overall yield from the starting cyclohexanone. The one-



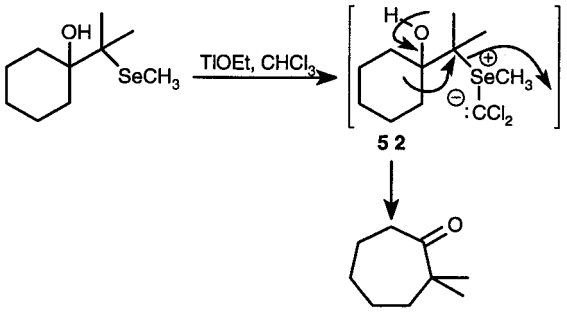
Scheme 22.



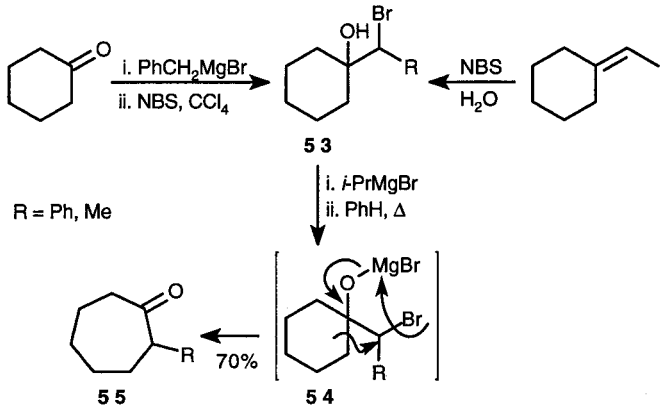
Scheme 23.

to carbonyl compounds affords the corresponding β-hydroxyselenide **50** in moderate to good yields (70–85%). Activation of the selenium center with a variety of reagents can effect rearrangement leading to the ring-expanded ketone **51**. The three most effective conditions found are: (i) thallous ethoxide, $CHCl_3$; (ii) phase transfer with KOH, benzyl triethyl ammonium chloride, CH_2Cl_2; or (iii) silver tetrafluoroborate on alumina, CH_2Cl_2. Halogenated solvents appear to be critical for the rearrangement.

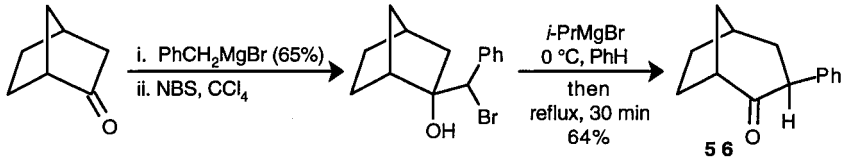
The first set of conditions generates dichlorocarbene, which attacks selenium to produce **52** (Scheme 24). Rearrangement of **52** provides the expanded ketone as well as $CH_3SeCHCl_2$, corroborating the carbene mechanism. Further evidence for this mechanism is found in the isolation of a dichlorocyclopropane derivative in a control reaction with TlOEt, $CHCl_3$, and an olefin. Switching to phase transfer conditions greatly enhances the rate of the rearrangement, but also produces varying amounts of an allylic alcohol derived from loss of the selenyl moiety. Generally, for the first two conditions listed, migration of the more substituted residue is favored (approximately 4:1).[46] For cyclic enones it is observed that the alkyl group migrates preferentially over the vinyl residue.[48] When a substrate possesses a double bond elsewhere in its framework, undesired dichlorocyclopropane formation may also occur. The silver



Scheme 24.



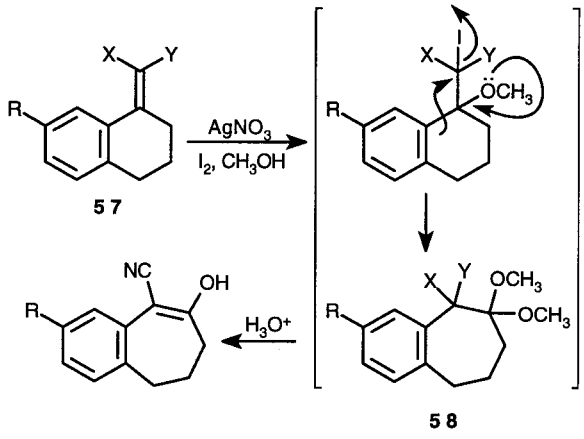
Scheme 25.



Scheme 26.

tetrafluoroborate conditions, although effective at promoting the rearrangement, exhibit reduced regioselectivity for unsymmetrical ketones, with occasional instances of reversal of the trend.

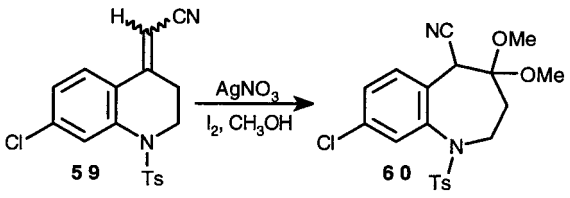
The net result of this method is a formal α-insertion of a ketone into a second carbonyl compound. Indeed, it is essential that two alkyl groups be attached to the carbon bearing the selenium. Although this is a limitation of the method, it complements the previously discussed thioacetal technology. Additionally, no epoxide formation was noted in these cases, although increasing amounts of olefin byproducts are observed when an acidic medium is employed. Yields of expanded adducts are highly structure-dependent and range from 50 to 100%.



Scheme 27.

R	X	Y	Yield (%)
H	H	CN	25
H	H	H	80
H	Me	CN	57
OMe	H	H	72
OMe	H	Me	83

2.1.3. Halogen, nitro, and thallium as leaving groups. The rearrangement of magnesium salts of halohydrins has been used by Sisti to prepare seven-membered rings in fair to good yield.[49–53] Addition of benzyl magnesium bromide to cyclohexanone followed by benzylic bromination (NBS, CCl_4) leads to the requisite halohydrin **53** (Scheme 25). Treatment with *i*-PrMgBr generates the magnesio alkoxide **54**, which, upon heating in benzene, undergoes smooth pinacol-like rearrangement to the expanded 2-phenylcycloheptanone (**55**). Presumably, electrophilic attack of the proximal magnesium on the halide facilitates the rearrangement. Little or no epoxide formation was noted. Yields for this expansion process are consistently between 57–70%. Only select cases of unsymmetrical ketones display regioselectivity. Sisti has also shown the method to be applicable to bicyclic systems.[51–53] 2-Norbornanone enters the sequence by initially forming the adduct derived from exo attack by the Grignard reagent (Scheme 26). Bromination and subsequent deprotonation affords, in this particular case, a single rearrangement product identified as **56**.



Scheme 28.

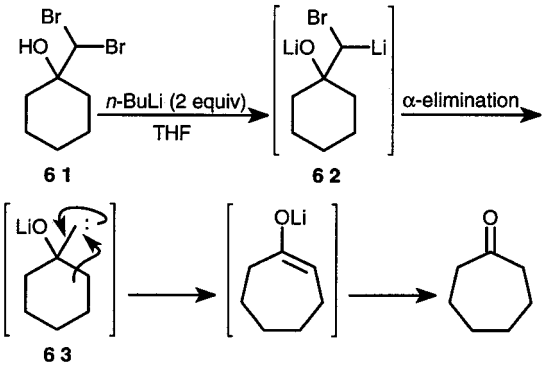
Ring expansion of α-tetralones and related systems can be realized via a Wittig–Prévost sequence[54] (Scheme 27). Proctor has prepared several exocyclic alkenes (**57**) from a variety of α-tetralone derivatives that were subsequently treated with Prévost reaction conditions ($AgNO_3$, I_2, CH_3OH). The seven-membered adduct is obtained as the acetal (**58**) that was hydrolyzed to the corresponding ketone (obtained as the enol when Y=CN). The yields (25–83%) for these expansions are highly dependent on the substituents present. The same sequence was applied to heterocyclic ketone **59**, providing acetal **60** in 60% yield (Scheme 28).

Yamamoto has offered a ring-expansion method wherein cyclohexanone is first treated with Br_2CHLi (generated in situ from CH_2Br_2 and Cy_2NLi).[55] The derived dibromo alcohol **61** (Scheme 29) is then treated with *n*-BuLi (2 equiv.), generating β-oxido carbenoid **62**, which undergoes α-elimination to provide β-oxido carbene **63**. The ensuing insertion reaction provides the ring-expanded compound via the corresponding enolate. The success of this process is due in part to the more facile lithium–halogen exchange, compared with the alternative lithium–hydrogen exchange event.

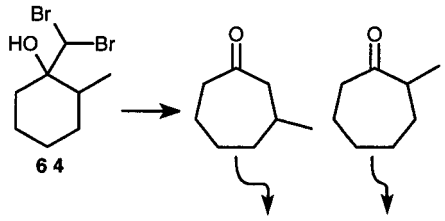
Further studies revealed a distinct bias in the case of unsymmetrical ketones.[56] Specifically, 2-methylcyclohexanone was reacted with Br_2CHLi, providing *cis* dibromoalcohol **64** (Scheme 30). Subsequent treatment with *n*-BuLi (2 equiv.) provided mixtures of 2- and 3-methylcycloheptanone. In all cases it was observed that the carbene preferred to react with the more substituted side. It is evident in that the choice of temperature and, more importantly, solvent can markedly affect the observed regioselectivity.

The outcome of the ring expansion is somewhat altered in the case of the dichloro analogue **65** (Scheme 31).[57,58] Here, lithium–hydrogen exchange dominates providing the dichloride intermediate **66**. α-Elimination of LiCl leads to a chlorocarbene which rearranges and, after workup, provides 2-chlorocycloheptanone in 41% yield. In this vein, attempts have been made to utilize a carbene-based expansion of adamantyl systems, but dimers and decomposition derivatives comprised the isolated products.[59,60]

The nitro group can also serve as a leaving group as has been demonstrated by Kim.[61] The dianion of (phenylthio)nitromethane can be readily prepared with *n*-butyllithium (2 equiv.) in THF at −80°C and adds smoothly to ketones.



Scheme 29.

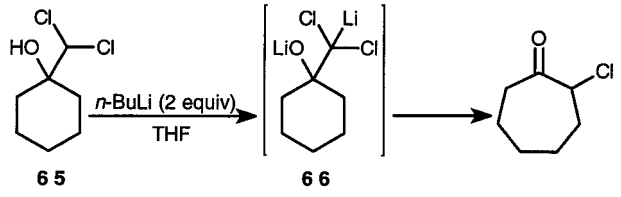


Scheme 30.

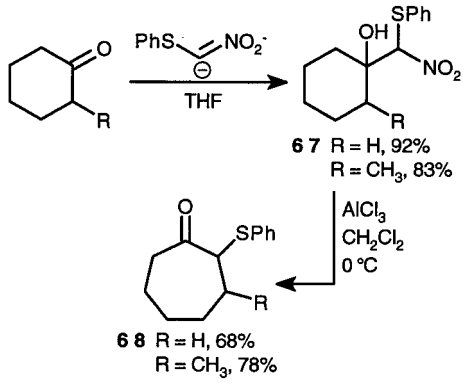
T (°C)	Solvent			Yield (%)
−78	THF	98	2	29
−95	THF	99	1	51
−45	Et_2O	86	14	61
−78	Et_2O	95	5	82
−95	Et_2O	97	3	86
−78	Hexane	66	34	71
−95	Hexane	65	35	68

When cyclohexanone is treated with this reagent, the cyclohexyl alcohol **67** is realized in 92% yield (Scheme 32). It was found that mixing **67** with aluminum chloride in methylene chloride at 0°C effected ring expansion to α-phenylthiocycloheptanone in 68% yield. When 2-methylcyclohexanone is employed in the same sequence, the ring-expansion product **68** is isolated in 78% yield as a 98:2 ratio of isomers with the favored one shown. Hence, as with similar expansion protocols, the more substituted α-carbon migrates preferentially.

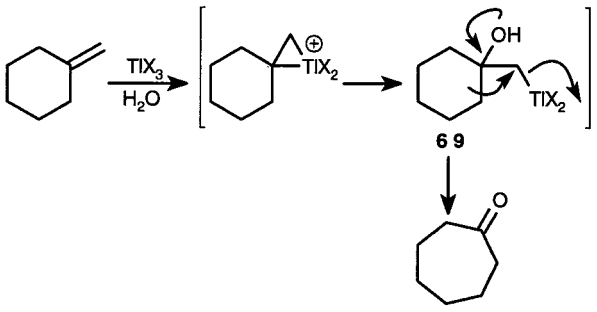
Halpern has demonstrated the capability of an oxythallation reaction to effect ring expansion of methylenecycloalkanes.[62] Hence, treatment of methylenecyclohexane with thallium (III) perchlorate results in cyclohexanol **69** (Scheme 33). The ability of Tl^+ to act as a leaving group



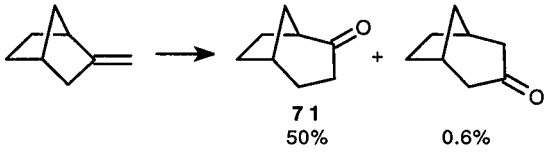
Scheme 31.



Scheme 32.



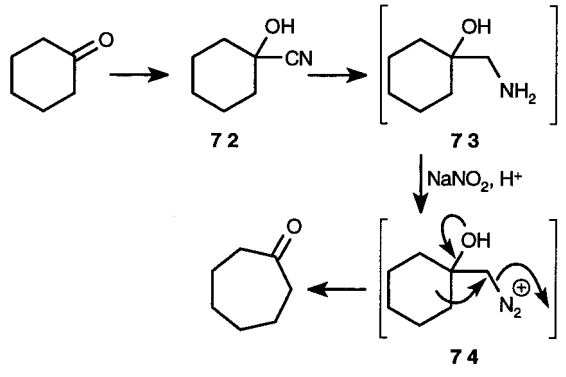
Scheme 33.



Scheme 34.

facilitates ring expansion to cycloheptanone. The occurrence of 1,2-diol **70** in significant yield is a drawback to this approach, although the combined yields of these two products are consistently quantitative. Furthermore, the aqueous conditions would prove unsuitable for larger organic compounds. Schleyer has applied this approach to 2-methyleneadamantane and 2-methylenenorbornane.[63] The former system provides the ring-expanded product in 15–20%, the corresponding 1,2-diol in 50–55%, and 2-adamantanecarboxaldehyde, which is trapped as the acetal with the aforementioned diol, in 18–20% yield. The norbonyl system provides slightly more satisfying results, with 50% yield of one of the possible isomers (**71**) being realized (Scheme 34). Interestingly, no diol was obtained in this case.

2.1.4. Nitrogen as leaving group. The Tiffeneau–Demjanov reaction has been employed on numerous occasions to effect a one-carbon homologation. A review has been prepared by Smith and Baer.[5] The three-step process begins with conversion of cyclohexanone to its cyanohydrin (**72**) (Scheme 35). Cyanohydrin formation can be poor yielding in certain cases, due to an equilibrium in favor of the carbonyl. The cyano group is then reduced to β-aminoalcohol **73**, typically via lithium aluminum hydride or hydrogenation over platinum. Subsequent treatment with



Scheme 35.

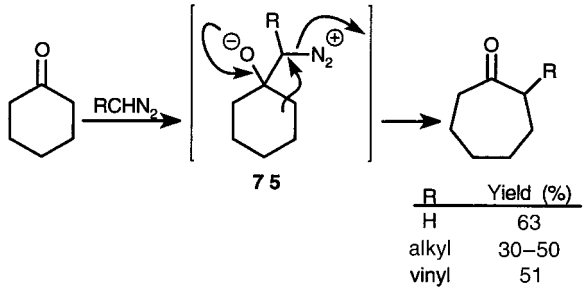
sodium nitrite under acidic conditions provides intermediate diazo alcohol **74**. A pinacol-type rearrangement ensues, releasing nitrogen and providing the ring-expanded ketone.

Epoxide formation can be a common side product for the Tiffeneau–Demjanov reaction and arises from displacement of nitrogen by the adjacent alcohol. Hexahydroazepinone derivatives can also be prepared through this sequence, however, ring expansion is accompanied by *N*-nitrosation.[64] The amine may be restored by treatment with Cu_2Cl_2 in acetic acid. The Tiffeneau–Demjanov expansion can be applied to bridged system as well, wherein 4-homoadamantanone is accessible from adamantanone in 48% yield (over the three steps).[65,66]

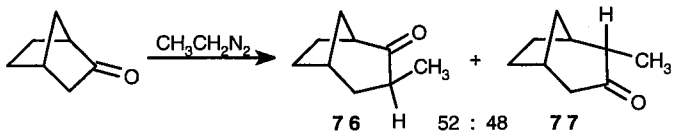
Diazoalkanes have been used for the homologation of ketones with varying degrees of success and a review has been prepared by Gutsche.[6] The reaction between cyclohexanone and diazomethane is shown in Scheme 36. The event proceeds in the presence of a Lewis acid by nucleophilic attack of diazomethane on the carbonyl group providing **75** followed by pinacol-type displacement of nitrogen. The diazoalkane employed is usually structurally simple (e.g. R=H, CH_3 etc.), but is not limited to alkyl. A useful variant is diazopropene (R=CH_2=CH–) which provides, in addition to one-carbon homologation, a β,γ-unsaturated ketone.[67]

Diazoalkanes have proven useful for homologation of a variety of substrates. Thiepanones may be prepared by treating thiacyclohexanones with a diazoalkane.[68,69] Azacycloheptanes are produced by reacting tetrahydropyridinium salts with diazomethane.[70,71] When norcamphor is treated with diazoethane, a mixture of two isomers (**76** and **77**) is isolated in 59% combined yield (Scheme 37).[72] The action of diazomethane on adamantanone produces 4-homoadamantanone in 85% yield.[73] The action of diazomethane on benzene derivatives affords the corresponding 1,3,5-cycloheptatriene adduct.[74]

The diazoalkane approach can suffer from multiple homologation (indiscriminate attack of the diazoalkane on the carbonyl functionalities present) and epoxide formation. Additionally, the substitution pattern on the cyclohexanone ring can dramatically affect the proportion of these potential products. In the case of α,β-unsaturated cyclohexenones, the olefin migrates preferentially providing β,γ-unsaturated cycloheptenones.[75] Although occasionally sluggish, ring expansion with diazoalkanes can be greatly accelerated, with improved yields, if carried out with an alcoholic



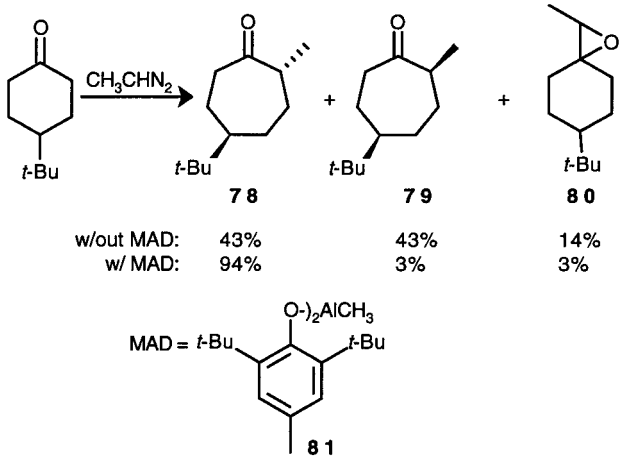
Scheme 36.



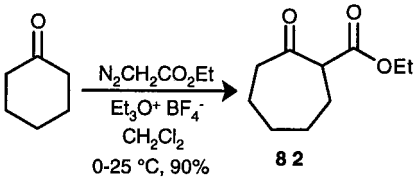
Scheme 37.

cosolvent.[76,77] Several groups have demonstrated that greater control of the reaction may be realized when alternative Lewis acids are employed or when the diazoalkane is substituted with additional functional groups.[67,78,79] For example, Yamamoto reported that 4-*tert*-butylcyclohexanone and diazoethane, when treated with methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (**81**), provides a 93:3:3 mixture of the *trans*:*cis*:oxirane (**78**:**79**:**80**) isomers in 87% combined yield, with no evidence of higher homologues (Scheme 38).

A widely employed one-carbon ring expansion of cycloalkanones was reported by Mock and Hartman.[80,81] Typically, the cyclohexanone and ethyl diazoacetate are treated with triethyloxonium fluoroborate in CH_2Cl_2 between 0–25°C (Scheme 39). The resulting β-ketoester **82** is produced in high yields (83–90%) and without contamination from higher homologues or epoxides. The product is conveniently poised for decarboxylation to provide the simple ketone if desired. Symmetrical ketones are ideal candidates for this methodology.[82] The observed regioselectivity for unsymmetrical ketones is not high, with the less substituted α-carbon preferentially migrating.[83] Replacement of triethyloxonium fluoroborate with $SbCl_5$ allows the effective reaction temperature to be lowered to −78°C. Alternate diazo compounds were investigated in an effort to improve on the process with only CF_3CHN_2



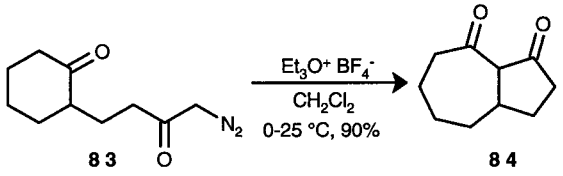
Scheme 38.



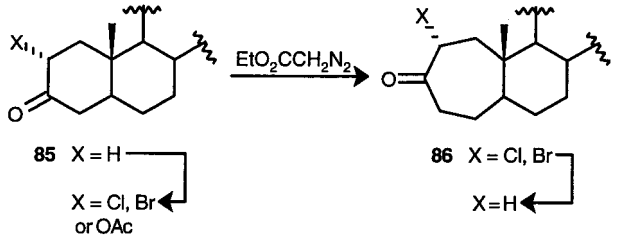
Scheme 39.

offering promise (85% yield). A Hammett treatment was also performed in these studies to elucidate more information regarding the mechanism.[84] A particularly productive variant on this methodology comes in the form of an intramolecular version which allows for ring expansion concomitant with annelation (**83→84**) (Scheme 40).[80] As an alternative to non-neutral or elevated temperatures for decarboxylation, benzyl or allyl diazoacetate may be used as hydrogenolysis or dissolving metal reduction lead to removal of the ester.[85]

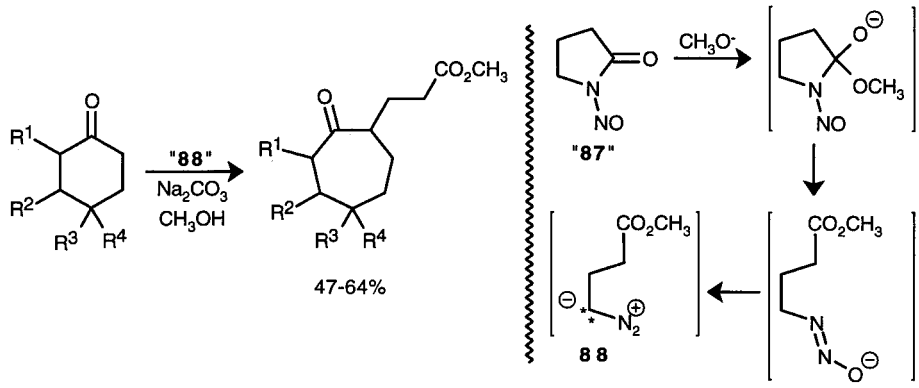
The low regioselectivity encountered in the preceding methodology was partially bypassed by first preparing the corresponding α-haloketone or α-acetoxyketone.[86] Here, Dave and Warnhoff exploited the one anomaly noted by Mock and Hartman wherein 2-chlorocyclohexanone provided a 98:2 ratio of the ring expansion product with the non-halogenated alkyl group migrating. This discrimination was demonstrated by halogenation of a 3-ketosteroid (**85**) at C_2 followed by application of ethyl diazoacetate which led to regioselective homologation, producing **86** (Scheme 41). The halide was then removed by treatment with zinc in acetic acid. It was anticipated that the α-acetoxy group would reverse this selectivity and thereby offer a complementary strategy. Ultimately, it was found that the acetoxy group has an effect which parallels the halo analogue (i.e. the unsubstituted alkyl group migrates preferentially). It was concluded that the halogen's influence stems from a steric and electronic effect whereas for the acetoxy group it is only a steric manifestation. A related study on preparation of homo-A ring steroids relied on use of diazomethane or Tiffeneau–Demjanov methodology,[87] but regioselectivity was less than 3:1.



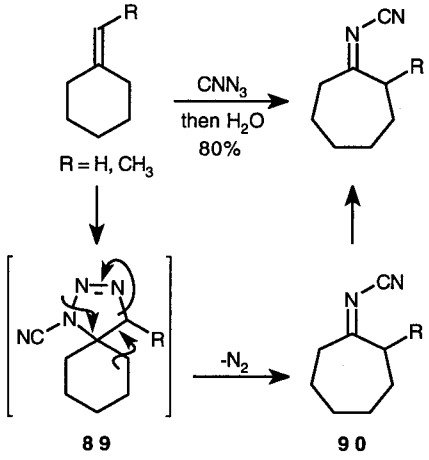
Scheme 40.



Scheme 41.



Scheme 42.



Scheme 43.

A route to 2-substituted cycloheptanones was developed by Gutsche in which *N*-nitrosolactams were employed as ring-enlarging reagents.[88] Treating *N*-nitrosobutyrolactam (**87**) with methoxide allowed for in situ generation of the corresponding γ-diazoester (**88**) (Scheme 42). The homologation proceeds in 47–64% yield with substitution around the ketone and the *N*-nitrosolactam being possible.

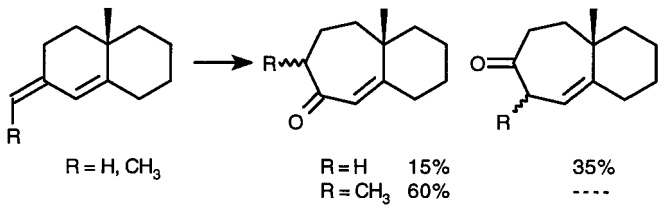
McMurry employed cyanogen azide (CNN_3) for the one-carbon ring expansion of methylenecyclohexane derivatives.[89] In the presence of this reagent, methylenecyclohexane and ethylidenecyclohexane both yield the expected cycloheptane derivative in 80% yield (Scheme 43). Presumably, the starting olefin is subject to a 1,3-dipolar cycloaddition reaction that provides cyanotriazoline **89**. Rearrangement accompanied by loss of nitrogen leads to imine **90**, which is then hydrolyzed to the ketone. Studies on the bicyclic system shown in Scheme 44 revealed a preference for migration of the vinyl moiety. Interestingly, when this sequence is performed on the ethylidene derivative, alkyl migration dominates.

Murata has reported a synthesis of a thiepin derivative via a one-carbon ring-expansion event.[90] Thiepins are commonly unstable making their preparation difficult. Their decomposition can be prevented or slowed when bulky substituents are included on the ring. Thiopyran **91** is first oxidized with trityl tetrafluoroborate to produce thiopyrylium salt **92** (Scheme 45). Treatment with ethyl lithiodiazoacetate led to ester **93** in 90% yield. Thiepin **94** was then constructed in 99% yield via the catalytic action of π-allylpalladium dimer (5 mol%) on **93** in chloroform at 0°C.

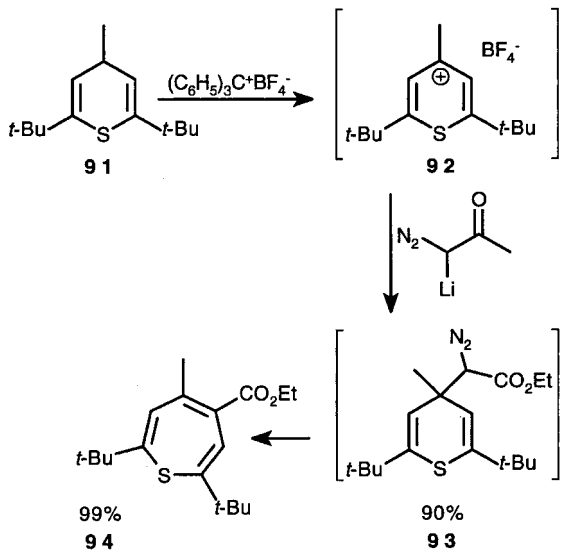
2.2. Incorporation of nitrogen

2.2.1. Nitrogen as leaving group. The Schmidt reaction has proven to be a valuable method of inserting nitrogen adjacent to carbonyl groups.[9,91] Application of this method to cyclohexanone and its derivatives allows for an entry into seven-membered lactams. In the prototypical case, cyclohexanone is treated with hydrazoic acid (and sulfuric acid or a Lewis acid catalyst) initially yielding hydroxy azide **95** (Scheme 46). Departure of water leads to **96**, which is poised for carbon-to-nitrogen alkyl migration with simultaneous loss of N_2. The resultant electrophilic carbon in **97** is then captured by water, ultimately leading to the ring-expansion lactam **98**.

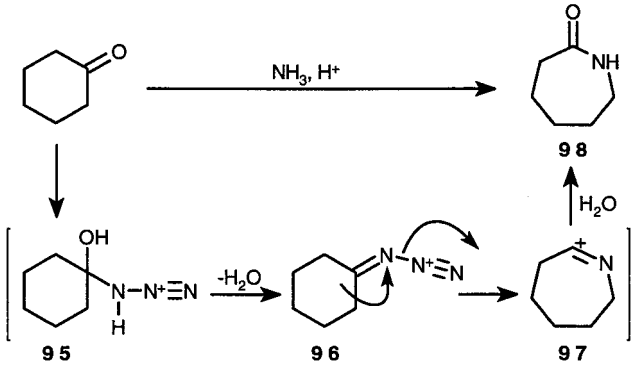
The regioselectivity observed in the Schmidt reaction is rooted in the migratory aptitudes of the groups attached to the carbonyl group. It is generally observed that for acyclic or monocyclic ketones the more electron donating substituent attached to the carbonyl will preferentially migrate.[92] Additionally, aryl groups will migrate preferentially over alkyl groups. Bicyclic ketones will oftentimes



Scheme 44.



Scheme 45.



Scheme 46.

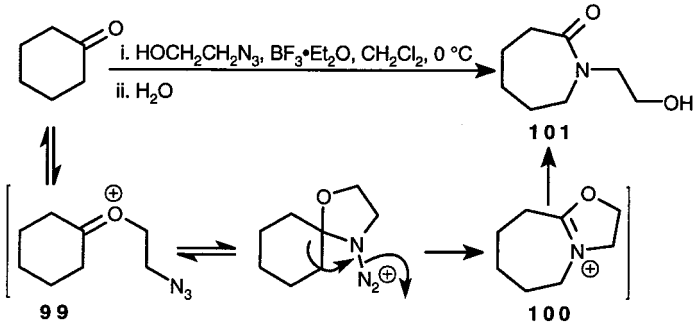
show a reversal of this trend. A review of nitrogen insertion reactions pertaining to bicyclic ketones has been prepared by Krow.[10] Finally, when more than one ketone is present, a degree of chemoselectivity may be exercised. In general, the relative rates of reactivity follow the order of: dialkyl ketones>alkyl aryl ketones>diaryl ketones.

The Boyer reaction represents a clever intramolecular version of the Schmidt reaction for insertion of nitrogen. Aubé has compiled a report on ring expansion employing this method.[93] Hydrazoic acid is abandoned in favor of a 1,2- or 1,3-hydroxy azide. Thus, when cyclohexanone and 2-azidoethanol are mixed in the presence of a Lewis acid, oxonium ion **99** is formed via the corresponding hemiketal (Scheme 47). Intramolecular attack and rearrangement involving the azide moiety leads to iminium ether **100**. Quenching the reaction with sodium bicarbonate affords the *N*-substituted lactam **101** in 98% yield. It is also possible to intercept the iminium ether **100** with a variety of nucleophiles, thereby broadening the versatility of this method.[94]

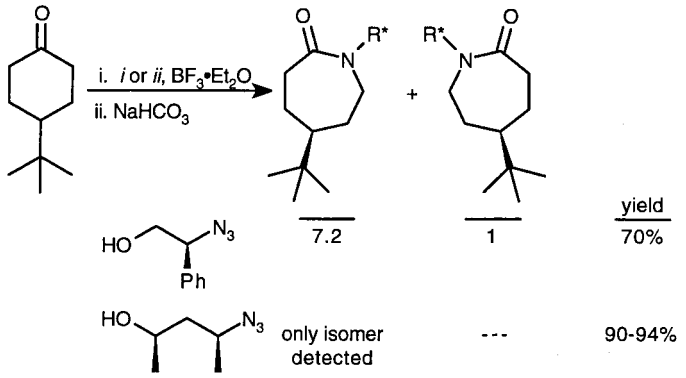
In the case of unsymmetrical ketones, the Boyer reaction displays modest or reversed selectivity, depending on the substituent. Aubé has shown that 2-alkylcycloalkanones exhibit only a slight preference for migration of the more substituted group (1:1.3 for the case of 2-methylcyclopentanone). Alternatively, 2-methoxy substituted ketones provide the product derived from migration of the methylene group. This result is opposite of that obtained for the Schmidt reaction. When a chiral hydroxy azide is chosen for the sequence, it is possible to obtain high diastereoselectivity in the alkyl migration step[95] (Scheme 48).

Along the theme of nitrogen insertion via a tethered azide, Schultz has described a ring expansion in which the azide residue is attached via a thioether (Scheme 49).[96,97] The classification of this reaction as an intramolecular Schmidt reaction (Boyer reaction) was dismissed, as heating **102** in the presence of a catalytic amount of hydrochloric acid resulted in decomposition. Furthermore, when mixed at ambient temperature in benzene and concentrated sulfuric acid, the carbon bearing the azide was converted into the corresponding aldehyde. This pointed to the possibility of [3+2] cycloadduct **103** being the pivotal intermediate along the reaction course rather than the Boyer intermediate **104**. In the event (refluxing xylene), it is supposed that acyl migration to nitrogen with departure of nitrogen leads to the ring-expanded **106**. Alternatively, acyl migration to the β-carbon (carbonyl numbering) would account for the formation of **105**. These two isomers were obtained in a 1:1 ratio in 85% yield. Separation followed by desulfurization with nickel boride provided the *N*-ethyl lactam **107**.

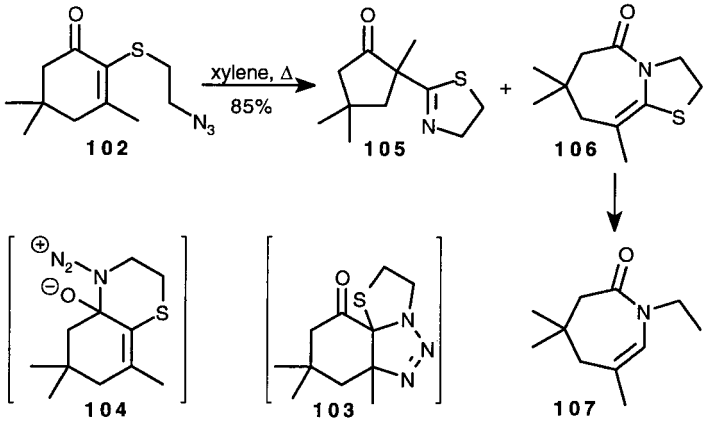
The bifurcated reaction path in the previous scheme leading to ring-expansion and ring-contraction products **106** and **105** is not applicable when the enone is part of a fused ring system. Hence, heating **108** produces unsaturated lactam **109** in 70% yield (Scheme 50). It is thought that intramolecular 1,3-dipolar cycloaddition of the azide with



Scheme 47.



Scheme 48.

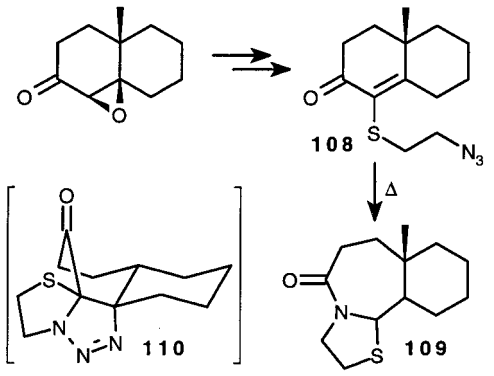


Scheme 49.

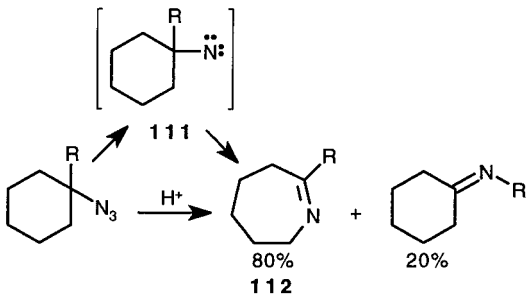
the olefin occurs on the α face resulting in the thermodynamically more favorable *trans*-fused intermediate (**110**). When the same conditions were applied to an A ring enone of a steroid derivative, the corresponding A-aza-A-homosteroid was formed in 64% overall yield (calculated from its α,β-epoxy intermediate).

The pyrolysis and photolysis of cycloalkyl azides constitutes a useful venue of creating ring-expanded products that are accompanied by nitrogen atom insertion (Scheme 51). Nitrogen is first liberated from the azide providing a free nitrene intermediate (**111**). Next, alkyl migration to nitrogen occurs, affording imine **112** in 80% yield. Acid catalysis may be applied to the process, but these conditions can potentially hydrolyze the imine. The mechanism parallels the Curtius rearrangement,[11] although evidence for a free alkyl nitrene intermediate such as **111** exists.

Aryl azides are also candidates for nitrogen insertion into the ring.[98–105] Indeed, this approach is a mainstay for preparation of unsaturated azepines such as **113** (Scheme 52). The expansion can be accompanied by nucleophilic attack to generate substituted derivatives.[106–108] Nitrene insertion is well-behaved and usually proceeds efficiently, providing good to excellent yields in most cases. The nitrene intermediate has also been generated from the nitro group.[109]



Scheme 50.

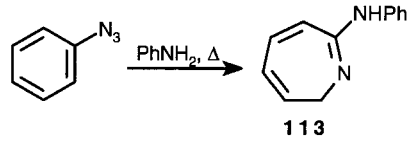


Scheme 51.

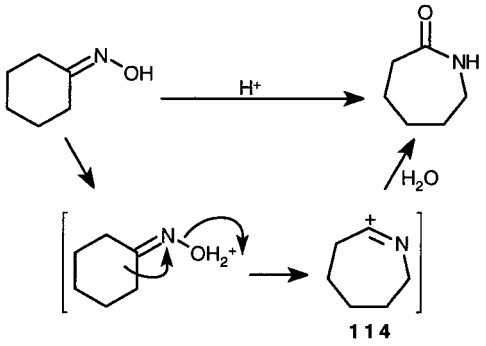
2.2.2. –OR as leaving group. The Beckmann rearrangement constitutes another approach to inserting nitrogen adjacent to a carbonyl group. The reaction has been reviewed by Gawley.[7] The oxime is first prepared by condensation of the carbonyl compound with hydroxylamine. A mixture of oxime stereoisomers is possible, but unsymmetrical ketones will favor the isomer which is less sterically encumbered. Activation of the hydroxyl group by a variety of reagents (e.g. PCl_5, $SOCl_2$, acid, HMPA, etc.) triggers the rearrangement (Scheme 53). Alkyl migration (usually with the more substituted one prevailing) occurs with concomitant displacement of the activated hydroxyl group providing stabilized carbocation **114**. Mixtures are common. Generally, the group anti to the hydroxyl is the one that migrates although this is not always the case. Isomerization of the oxime can precede migration giving the impression that the group located syn was the participant in the rearrangement. When the substrate is an α-tetralone derivative, aryl over alkyl migration is common but not guaranteed, leading to 1-benzazepinones. The reagent chosen to activate the hydroxyl group can also affect the outcome of the regioselectivity. Toda has reported the preparation of optically active oximes and their subsequent conversion to optically active ϵ-caprolactams in 80% ee.[110,111] The remainder of the mechanism is comparable to the Schmidt reaction discussed above. The rearrangement may also be carried out directly on the starting ketone with H_2NOSO_3H in formic acid.[112]

Hoffman has shown that equipping nitrogen with an efficient leaving group allows for the possibility of carbon-to-nitrogen rearrangements.[113–115] In the case of amine **115**, this leads to an overall transformation to azacycloheptane **118** (Scheme 54). Thus, treating the starting primary amine with *p*-nitrobenzenesulfonyl peroxide provides the readily ionized nosylate **116**. Once dissolved in methanol or chloroform the iminium salt **117** is rapidly produced presumably via a concerted mechanism. After neutralization, the azacycle is obtained in 83% yield. A similar process is observed when cyclohexanols are treated with HN_3 and sulfuric acid.[116] Rearrangement of a norbonyl derivative has also been demonstrated (Scheme 55).[117] In many cases, it is found that the parent amine is a common byproduct that requires that homolytic loss of the leaving group or a triplet nitrenium ion be invoked.

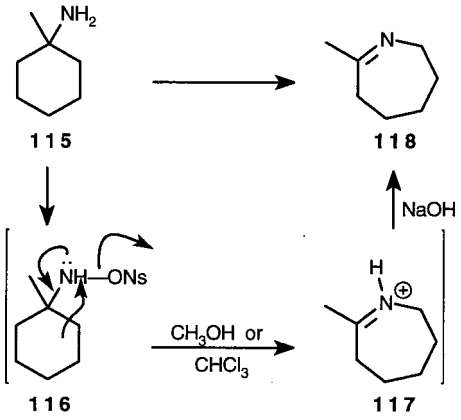
Yamamoto has shown that hydroxylamine carbonates (**119**) rearrange to azacycloheptanes (**120**) on treatment with trialkylaluminum in methylene chloride (Scheme 56).[118] One of the alkyl residues on the aluminum reagent is transferred to the 2-position of the expanded ring. It was demonstrated that the method is amenable to incorporating a chiral benzyl derivative which allows for a diastereoselective expansion process.



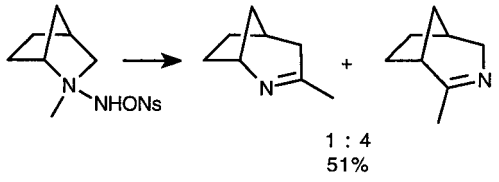
Scheme 52.



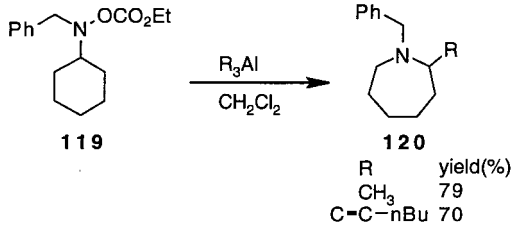
Scheme 53.



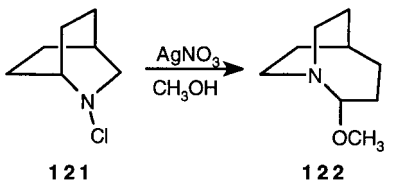
Scheme 54.



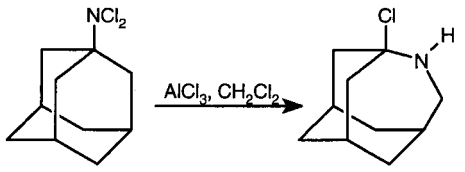
Scheme 55.



Scheme 56.

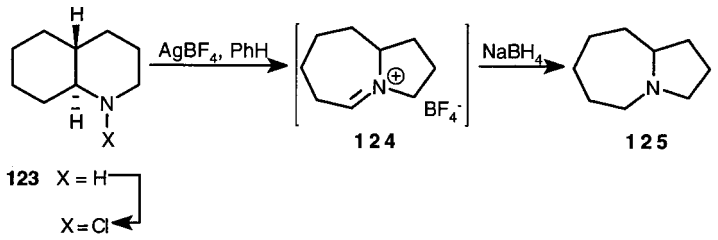


Scheme 57.



Scheme 58.

derivatives it has been shown that the group which migrates is consistently *trans* to the nitrogen lone pair. Hence, the stereochemistry of the imine and direction from which the oxygen atom is delivered in the preparation of the oxaziridine will ultimately decide the stereochemical outcome in the subsequent rearrangement step. A commonly employed tactic is to condense the cyclohexanone substrate with (*R*)- or (*S*)-α-methylbenzylamine followed by a chiral oxidizing agent to obtain high diastereoselection of a particular

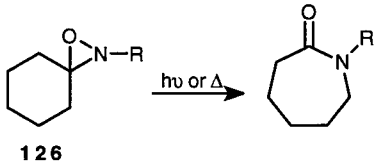


Scheme 59.

2.2.3. Halogen as leaving group. Treatment of *N*-chloramines with Lewis acids has been a commonly employed method of realizing electrophilic nitrogen species. Alkyl migration to nitrogen is then possible, allowing for ring expansion of appropriate substrates.[119–121] For example, Gassman has demonstrated the ability of 2-chloro-2-azabicyclo[2.2.2]octane (**121**), under the influence of silver nitrate, to rearrange to provide seven-membered azacycle **122** (Scheme 57).[119] A similar rearrangement has been performed on an adamantyl system wherein $AlCl_3$ was chosen as the Lewis acid (Scheme 58).[121] Kovacic has also shown that exo-2-chloronorbornane reacts with trichloramine–aluminum chloride to provide 2-azabicyclo[3.2.1]octane in 88% yield.[122]

Schell has employed a silver ion-promoted rearrangement of *N*-chloramines to effect ring expansion of bicyclic tertiary amines.[123] The secondary amine **123** is first chlorinated and then treated with silver tetrafluoroborate (Scheme 59). The anticipated nitrenium ion intermediate could not be trapped (by using anisole as solvent) possibly implicating that σ-bond participation assists with the loss of chlorine. It was found that the resultant immonium ion **124** could be isolated and characterized by NMR. This species is readily reduced by sodium borohydride, affording the rearranged product **125** in >90% yield. The possibility of an intermediate nitrogen radical cation is also posited.

2.2.4. Rearrangements. Seven-membered lactams may be prepared by the thermal or photochemical rearrangement of oxaziridines (Scheme 60).[124–126] The requisite three-membered heterocycle (**126**) is typically prepared from oxidation of the corresponding imine. In unsymmetrical



Scheme 60.

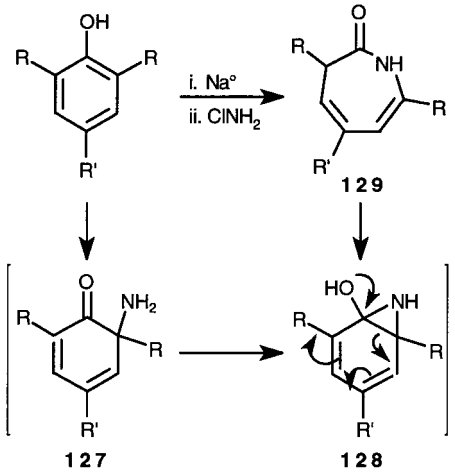
isomer. In this way, control over the regiochemical outcome can be realized. Furthermore, the auxiliary benzyl group may be discarded via hydrogenolysis.

Paquette has provided a method of preparing 1,3-dihydro-2*H*-azepin-2-ones from phenol derivatives.[127–129] The corresponding phenoxide anion is generated and subsequently treated with chloramine (Scheme 61). Nucleophilic attack on chloramine by the ambident phenoxide nucleophile presumably occurs at carbon generating **127**. The resulting α-aminoketone is converted to hydroxyaziridine **128**, which, under the reaction conditions (90–150°C), rearranges to afford **129** in 50–55% yield. Similar rearrangements have been described.[130–133]

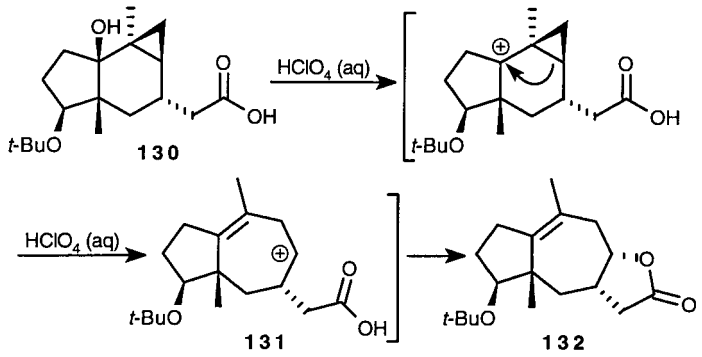
3. Bicyclo[4.1.0]Heptyl-based Ring-Expansions

3.1. Heterolysis of bicyclo[4.1.0]heptyl derivatives

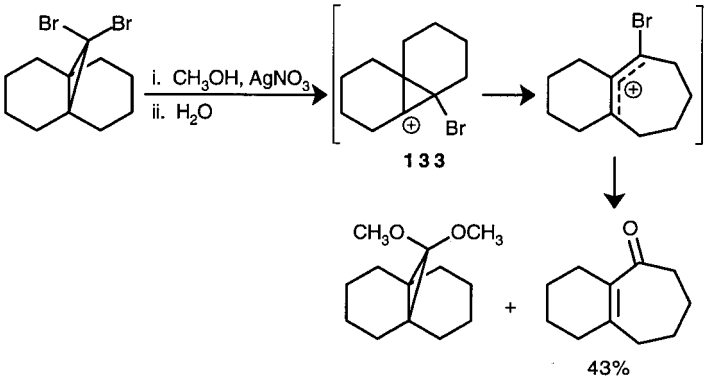
A key step in Marshall's stereoselective synthesis of the pseudoguaianolide confertin involves a rearrangement of a cyclopropylcarbinyl cation.[134] Hence, treatment of **130** with



Scheme 61.



Scheme 62.

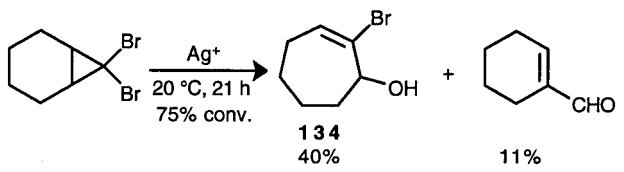


Scheme 63.

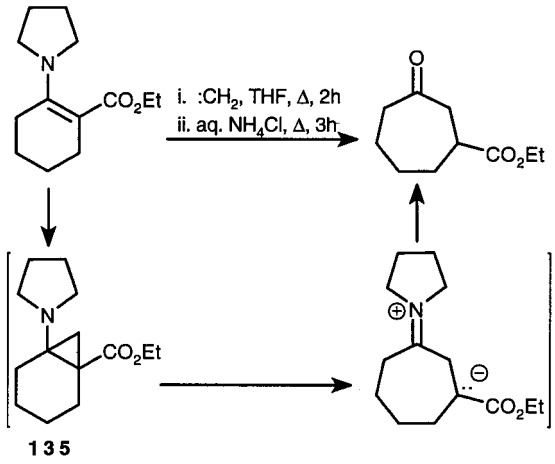
perchloric acid generates the corresponding tertiary carbocation adjacent to the strained three-membered ring (Scheme 62). A ring expansion event follows resulting in formation of homoallyl cation **131** which is immediately trapped by the pendant carboxylic acid group. Lactone **132** is obtained in greater than 80% yield en route to the natural product.

Silver-promoted Wagner–Meerwein shifts of 1,1-dihalocyclopropanes have been commonly used for ring expansions.[135,136] Electrophilic attack of silver on the halide generates an intermediate carbocation (**133**) which undergoes rapid rearrangement (Scheme 63 and 64). The ring expanded product is typically functionalized as the 2-halocyclohept-2-en-1-ol (e.g. **134**). Yields range from approximately 40–60% depending on substitution around the bicyclo[4.1.0]heptyl system. Banwell has applied a version of this method to the synthesis of the colchicine framework.[137] McMurray has applied this process to the preparation of the cycloheptyl ring in longifolene in quantitative conversion.[138]

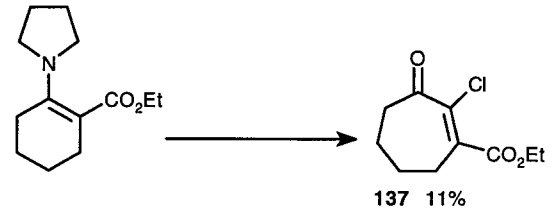
Pandit has shown that the reaction between carbene or



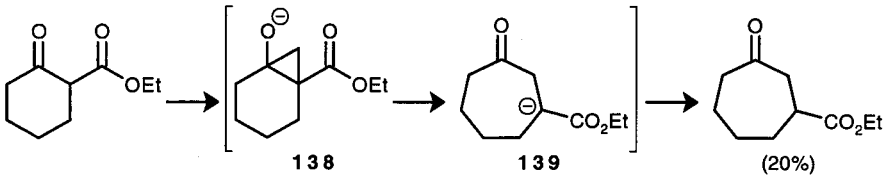
Scheme 64.



Scheme 65.



Scheme 66.



Scheme 67.

dichlorocarbene with the enamine derivative of β-ketoesters provides a one-carbon ring expansion.[139] Addition of carbene to the olefin yields an intermediate cyclopropane (**135**) wherein the shared σ-bond is poised for heterolysis (Scheme 65). The amine and ester cooperatively open the strained ring generating the seven-membered carbocycle. Treatment with aqueous ammonium chloride provides γ-ketoester **136** in 17% yield. The reaction follows a similar course when dichlorocarbene is employed. After addition and heterolysis, the expected α,α-dichloroketone is formed, which subsequently loses chloride to provide cycloheptenone **137** in similarly poor yield (Scheme 66).

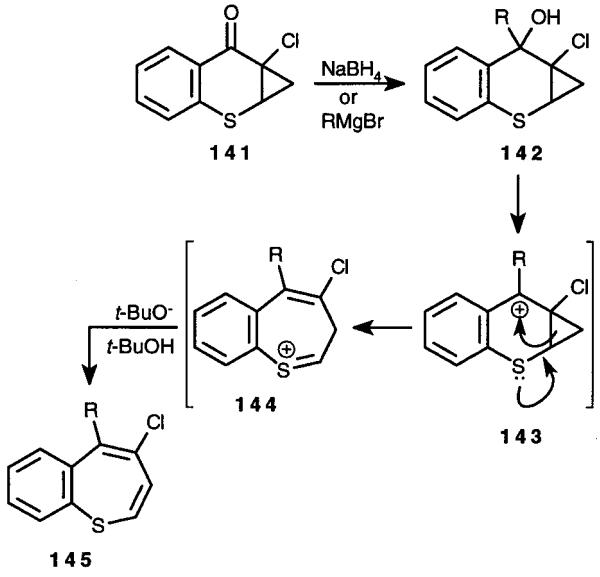
Zercher has shown that β-ketoesters can directly undergo chain extension through the use of diethylzinc and methylene iodide.[140] It is suspected that an intermediate cyclopropyl alcohol species (**138**) is formed, possibly through the enol or enolate form of the dicarbonyl compound, which fragments to the corresponding zinc enolate of the ester (**139**) (Scheme 67). The net result is methylene insertion between the carbonyl functionalities nearest to the ketone. As in the preceding example, the yields are low for this approach, despite that acyclic analogues usually proceed in good yield. In the case of 1,3-dicyclohexanone, a second equivalent of the carbenoid species rapidly adds to the resultant enolate generating the cyclopropyl alcohol (**140**) in 25% yield (Scheme 68).

Traynelis and MacDowell have demonstrated a method for preparing 5-aryl and 5-alkyl derivatives of 1-benzothiepins.[141,142] Grignard (R=aryl, alkyl) or sodium borohydride addition to ketone **141** provides benzylic alcohol **142** in 82% or greater yield (Scheme 69). Treatment with HCl leads to cyclopropylcarbinyl cation **143** which undergoes sulfur-assisted ring opening to intermediate **144**. Upon quenching with *tert*-butoxide, the 5-substituted benzothiepin **145** is isolated in 35–82% yield. When the bromo analogue is employed, lower yields are observed for both the addition and expansion steps.

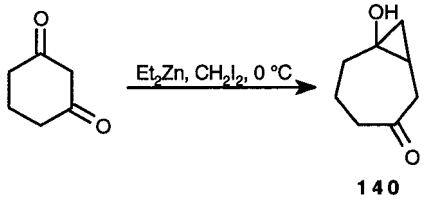
3.2. Homolysis of bicyclo[4.1.0]heptyl derivatives

The bicyclo[4.1.0]heptane system (**146**) is a valuable framework from which to access seven-membered rings. A radical center vicinal to the strained cyclopropyl ring allows for rearrangement to the corresponding homoallyl radical (Scheme 70). Stereoelectronic effects govern the direction of this fragmentation, however. When the radical center is located on the adjoining cyclohexyl ring (e.g. **147**), then fragmentation is, with rare exceptions, primarily along the exo bond providing intermediate **148**. Overlap of the radical center in **147** with the shared bond of the bicyclo system is minimal, resulting in only trace amounts of the ring-expanded intermediate **149** to be accessed.[143]

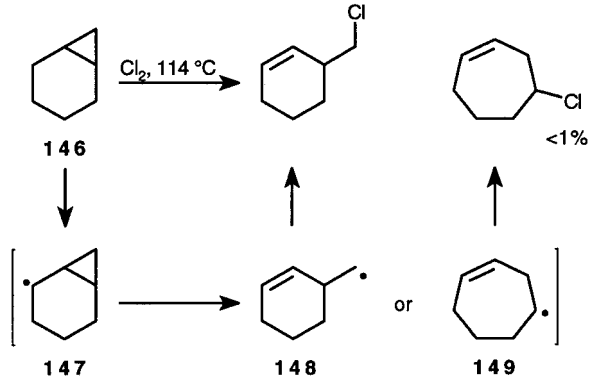
One exceptional example is provided by Motherwell and Rzepa.[144] Here, reaction of carbon tetrachloride with **150** (along with initiator) afforded high yield of cycloheptadiene



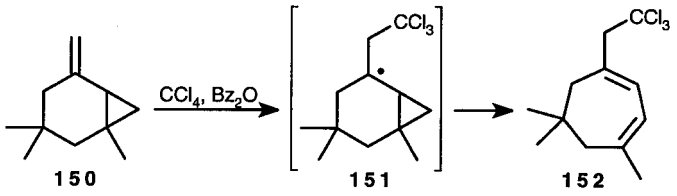
Scheme 69.



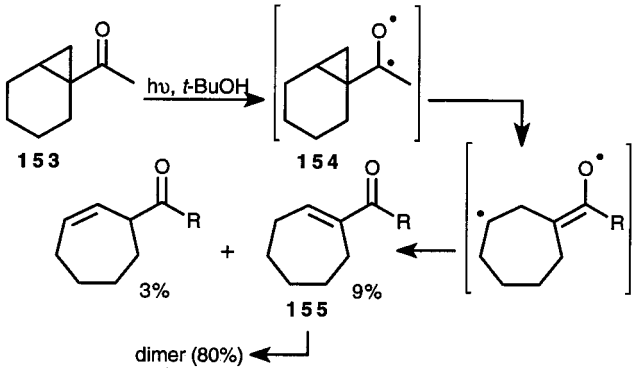
Scheme 68.



Scheme 70.



Scheme 71.



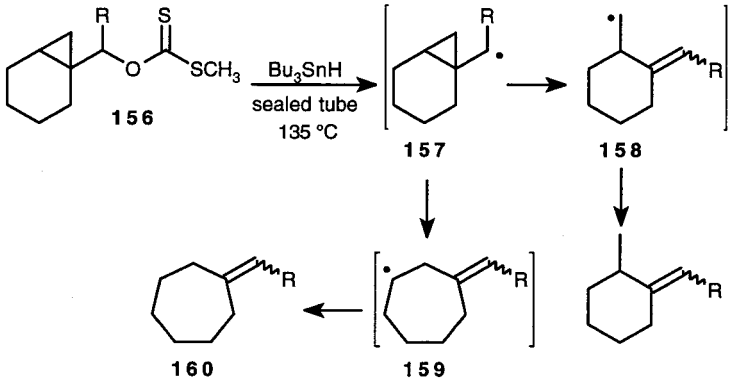
Scheme 72.

152 (Scheme 71). Trichloromethyl radical first adds to the alkene generating intermediate radical **151**. Fragmentation to the exo or endo radical (cf. **148** or **149**, respectively) proceeds kinetically in favor of the former. However, owing to the slow reaction between carbon tetrachloride and carbon-centered radicals, the initially formed fragmentation intermediate has time to revert allowing the thermodynamically more stable intermediate to prevail. Ultimately, the ring-expanded product overcomes the non-expansion product by 2:1.

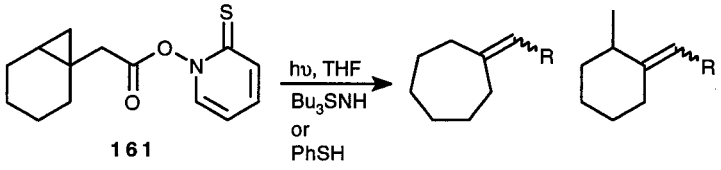
A revealing insight into the stereoelectronic nuances of cyclopropylcarbinyl radicals was provided by Dauben.[145] Irradiation of α,β-cyclopropylketone **153** generates intermediate **154**, which possesses a radical center pendant to the bicyclic system as opposed to being part of the cyclohexyl ring (e.g. **147**) (Scheme 72). The singly occupied molecular orbital on carbon is freely rotating and permits overlap with either of the cyclopropyl bonds. The increased opportunity for ring expansion is possible for this reason and results in efficient conversion to 1-acetylcycloheptene. As a consequence of the reaction conditions, however, **155** is isolated primarily as a dimer.

Kurth has provided a radical-mediated method to seven-membered rings. The xanthate ester **156** (R=H), prepared from the corresponding cyclopropyl alcohol, is heated with Bu_3SnH in benzene (sealed tube, 135°C), inducing homolysis (Scheme 73).[146] The resulting cyclopropylcarbinyl radical **157** rapidly rearranges to the homoallyl radicals **158** and **159**, providing the ring expansion product **160** and non-expansion product in >95:5 ratio. In the case of secondary radical **157** ($R=C_6H_{11}$), ring expansion is favored over non-expansion by 3:1. The substitution and hybridization around the cyclohexyl ring can also have dramatic effects on the direction of the rearrangement. Indeed, when an aromatic ring was fused onto the cyclohexyl moiety, only the non-expansion product was observed.

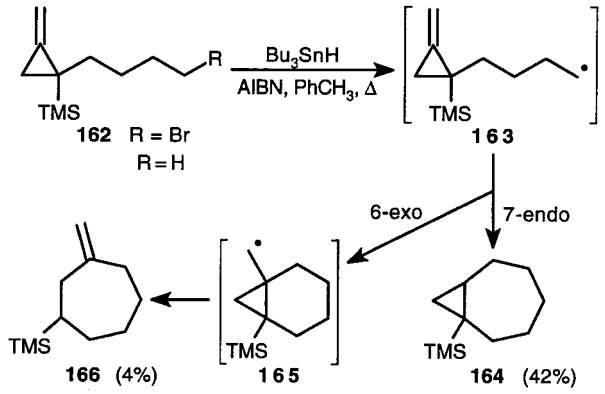
A kinetic analysis of the prototypical system by Kurth and



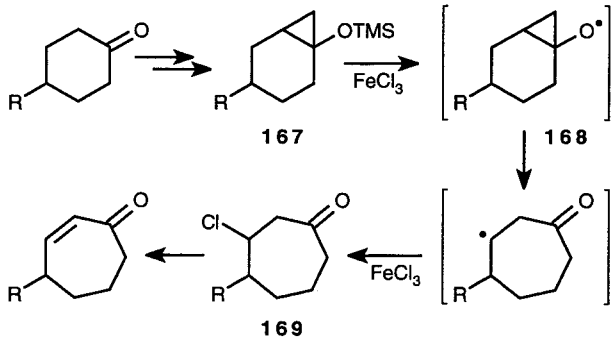
Scheme 73.



Scheme 74.



Scheme 75.



Scheme 76.

R	Yield (%)
H	84
CH_3	97
t-Bu	70

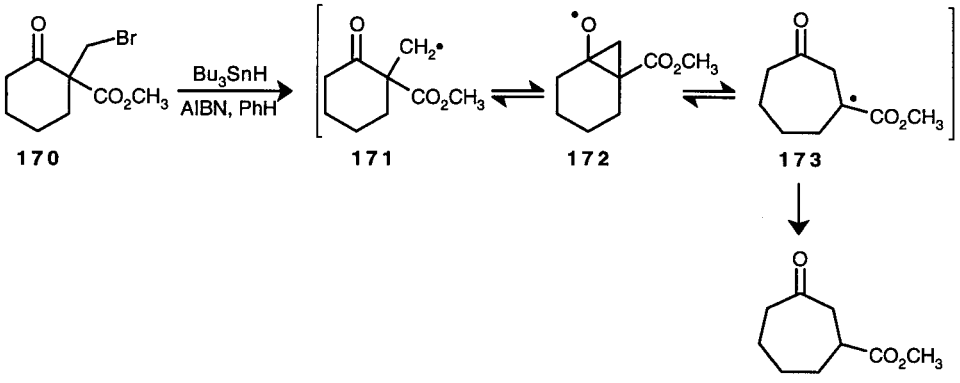
Fink was possible when Barton's PTOC ester was utilized.[147] This derivative (**161**) allowed for generation of radical **157** at lower temperatures thereby permitting a detailed study of the fragmentation processes (Scheme 74). It was found that the ring-expanded product forms 3.6 times faster at 298 K than the non-expansion product. Hence, production of seven-membered ring may be preferentially increased under kinetic conditions (low temperatures, high concentration of reducing agent).

Kilburn has used methylenecyclopropyl butyl radicals to construct cycloheptane rings.[148] Treating bromide **162** (R=Br) with tri-*n*-butylstannane (syringe pump addition) in toluene generates primary radical **163** which has three fates (Scheme 75). First, direct reduction of the radical is possible, and provides **162** (R=H) in 13% yield. The other two observed products are a result of cyclization of **163** onto the olefin either in a 7-*endo-trig* or 6-*exo-trig* fashion. The former process, which may be directed to a degree by the TMS group, leads to bicyclo[5.1.0]octane **164** in 42% yield. The only true ring-expansion event that takes place in this reaction is the one that proceeds via 6-*exo* attack. The resulting 1-bicyclo[4.1.0]heptanylmethyl radical intermediate **165** is subject to homolytic fragmentation along the shared bond ultimately affording **166** in 4% yield.

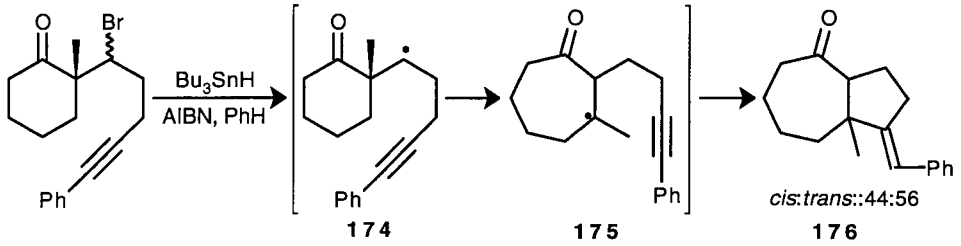
Saegusa has shown that 1-silyloxybicyclo[4.1.0]heptanes can be converted to their corresponding 2-cycloheptenones by treatment with $FeCl_3$.[149] The initial oxidation of **167** leads to alkoxy radical intermediate **168** which can fragment along the shared bond of the bicyclo[4.1.0]heptane system (Scheme 76). The resultant ring-expanded radical is then chlorinated to form 3-chlorocycloheptanone (**169**) in 93% yield. After treatment with NaOAc in refluxing methanol the unsaturated ketone is obtained in 84% yield.

Dowd and Beckwith have developed a method of ring expansion using 2-halomethylcycloalkanones.[150–153] The halide derivative **170** can be readily prepared from alkylation of the β-ketoester under basic conditions, with the corresponding dihalomethane (Scheme 77). Treatment of this compound with Bu_3SnH results in primary radical **171** which presumably attacks the neighboring ketone, producing cyclopropyloxy radical intermediate **172**. This strained species fragments producing tertiary radical **173** which undoubtedly receives additional resonance stabilization from the adjacent carbonyl of the ester. Reduction with stannane delivers the carbocycle.

This approach has also been applied in tropinone preparation[154] and for benzannelated cycloheptanes.[155] An electroreductive version of this process has also been demonstrated.[156] An analogous approach employing



Scheme 77.



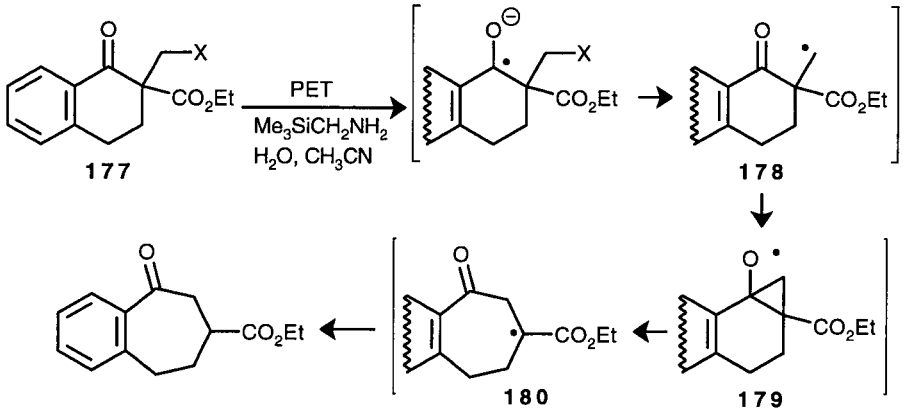
Scheme 78.

vitamin B_{12} and organocobalt complexes has been reported.[157,158] Heterocyclic analogues of **170** have also been successfully subjected to this process.[159,160] However, in these cases it is necessary to generate the radical from the corresponding phenylseleno derivative rather than the halide.

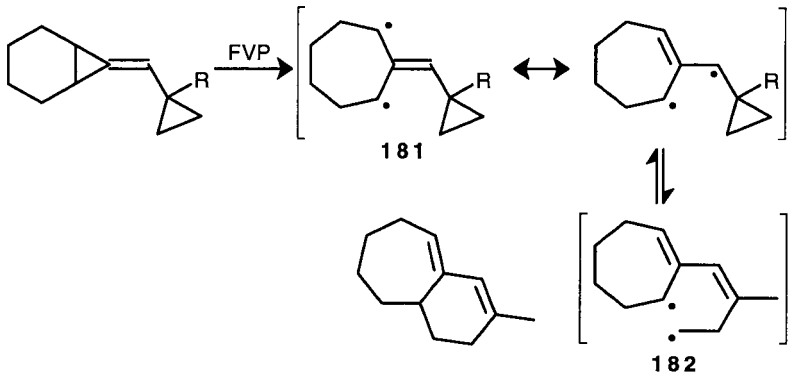
Boger showcased this methodology in a tandem ring expansion–cyclization event (Scheme 78).[161] The secondary radical (**174**) generated with Bu_3SnH (AIBN, benzene) participates in the addition–fragmentation pathway discussed above. The resulting cycloheptyl radical (**175**) is immediately trapped intramolecularly by the tethered alkyne. Reduction of the resulting vinyl radical provides **176** as a 44:56 mixture of *cis:trans* isomers.

Recently, Hasegawa has shown that photoinduced electron transfer (PET) reactions of 2-halomethyl benzocyclic ketones leads to one-carbon ring expansion.[162] Irradiation of ethyl 2-bromomethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**177**) in the presence of an amine generates a radical anion which undergoes intramolecular electron transfer to provide methyl radical **178** (Scheme 79). This radical equilibrates, via cyclopropyloxy radical **179**, to ring expanded species **180** which is subject to reduction or dimerization. Yields ranged from 50–73% for the desired product, 12–24% for the dimer, and starting material was converted in 61–76%.

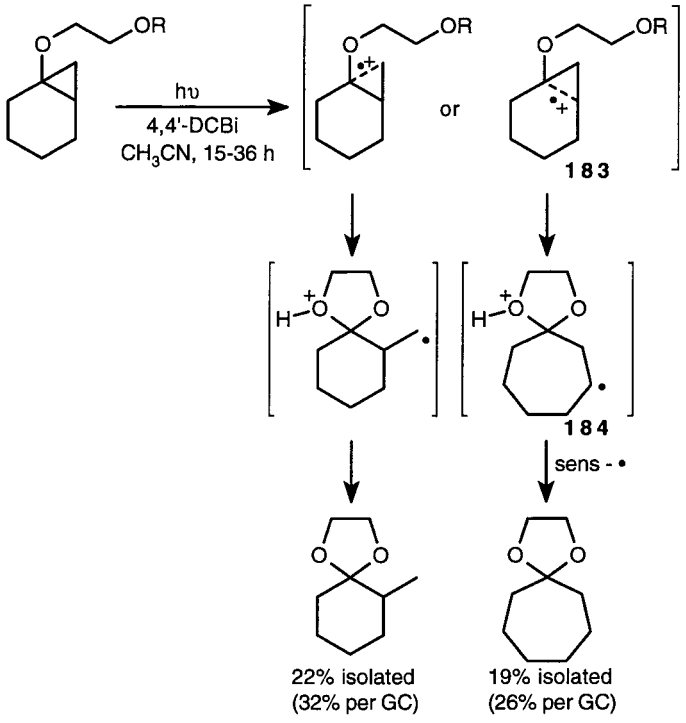
A double ring expansion mediated by flash vacuum pyrolysis (470–560°C at 0.01 Torr) employed by Cohen and co-workers led to the bicyclo[5.4.0]undecane framework.[163] Initial homolysis of the shared bond of the fused bicyclic system leads to trimethylenemethane diradical **181** providing



Scheme 79.



Scheme 80.



Scheme 81.

the cycloheptyl core (Scheme 80). The latent cyclopropylcarbinyl radical then fragments to homoallylic radical **182** and, in the case of the *Z* isomer, closes to a six-membered ring. Substitution around the pendant cyclopropane ring (e.g. R=EtO, PhS) led to bicyclic enones or thienyldienes in 58–68% yield. Other variants provided unsaturated ketones in 53–89% yield.

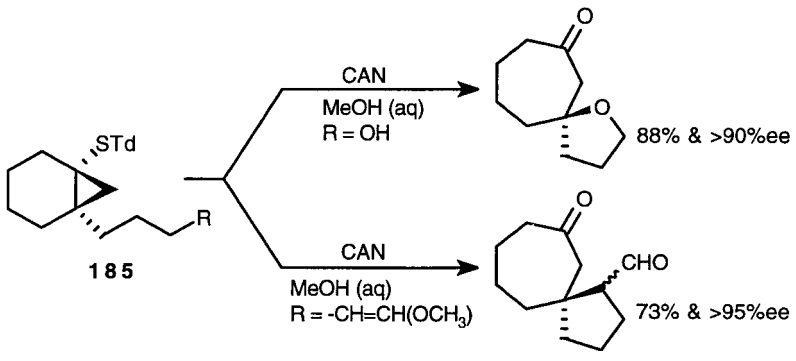
The Gassman group took advantage of the low oxidation potential of cyclopropyl ethers ($E^{ox}_{1/2}$>2.2 V) to promote ring expansion.[164] The process is promoted by the presence of a sensitizer such as 4,4′-dicyanobiphenyl (4,4′-DCBi) and light. The ensuing single electron transfer (SET) reaction leads to radical cation **183** (Scheme 81). Intramolecular trapping by the alcohol produces intermediate **184**, which ultimately leads to the seven-membered carbocycle.

Iwata has utilized single electron transfer (SET) oxidation of chiral cyclopropyl sulfides to effect expansion to seven-membered rings.[165] Treating sulfide **185** with ceric ammonium nitrate (CAN) in aqueous methanol leads to selective cleavage of the shared bond of the cyclopropane ring (Scheme 82). Cyclization to the corresponding spiro derivative follows if a heteroatom or electron-rich olefin are pendant to the cycloheptyl moiety. In the absence of such functional groups, methanol or water capture the latent charge. The fragmentation is apparently concomitant with approach of the nucleophilic group as a high degree of chirality is preserved. Additional investigation confirmed that nucleophilic attack occurs opposite of the cyclopropyl group leading to inversion.

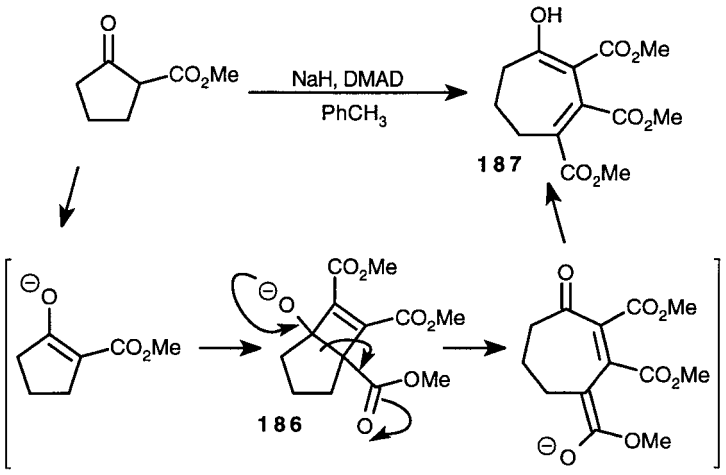
4. Bicyclo[3.2.0]Heptyl-based Ring-Expansions

4.1. Heterolysis of bicyclo[3.2.0]heptyl derivatives

A two-carbon ring expansion of carbocyclic β-ketoesters involving an acetylenic ester has been described by Proctor.[166] Treatment of 2-carbomethoxycyclopentanone



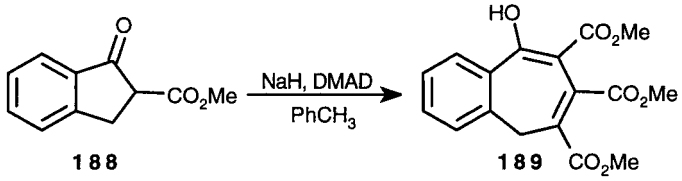
Scheme 82.



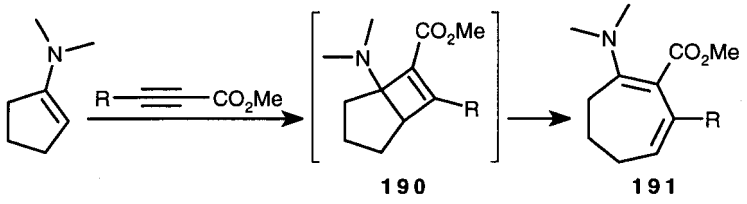
Scheme 83.

with NaH and dimethyl acetylenedicarboxylate (DMAD) yields intermediate cyclobutene **186** which presumably forms in a two-step Michael addition–aldol sequence (Scheme 83). Relief of ring strain is realized by a retro-aldol reaction fragmenting the shared bond of the bicyclo system providing the well-functionalized seven-membered carbocycle **187** in 50% yield. The corresponding benzo-cyclopentanone (**188**) similarly participated in ring expansion when treated with NaH and DMAD, affording **189** in 60% yield (Scheme 84).

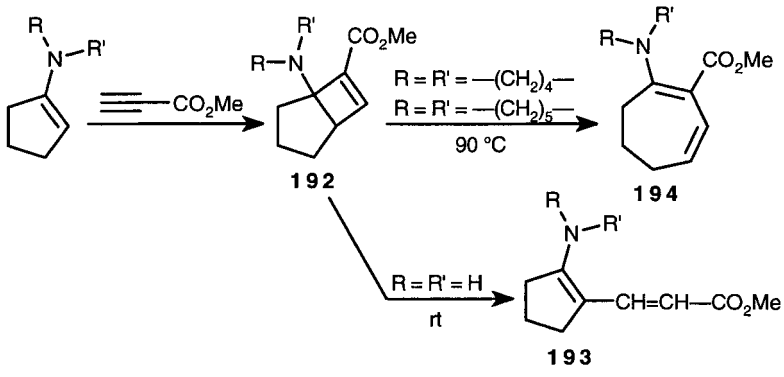
A two-carbon ring expansion of cyclic enamines and acetylenic esters has also been reported. The enamine derived from cyclopentanone and a secondary amine undergoes cycloaddition with dimethyl acetylenedicarboxylate (DMAD, R=CO_2CH_3), affording intermediate cyclobutene



Scheme 84.



Scheme 85.

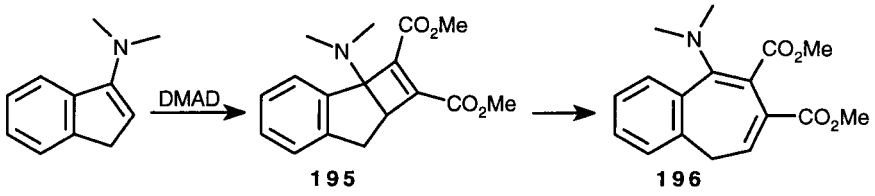


Scheme 86.

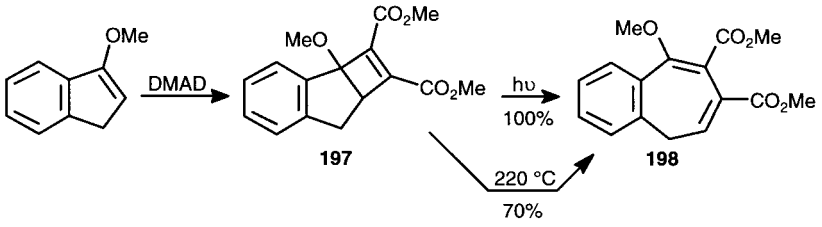
190 (Scheme 85). This cycloadduct rearranges providing the unsaturated cycloheptyl compound **191** in 71% yield.[167,168] It has also been shown that reacting the same enamine with an alkyl propiolate (R=H) at temperatures less than 35°C leads to isolation of cyclobutene **192** (Scheme 86).[169,170] Treating **192** with AcOH yields the Michael-type addition product **193**. Alternatively, heating the starting enamine and unsaturated ester for 15 min provides the expected ring-expansion product **194** in 36% yield. The ring-expansion reaction of fulvenes with DMAD have also been reported.[171] The advantages associated with this method are the neutral conditions employed and a simple workup wherein only removal of the solvent is necessary.

Doyle has explored variations of the aforementioned strategy by examining the reaction between dimethyl acetylenedicarboxylate and the analogous indenyl system.[172] Hence, when 1-dimethylaminoindene and DMAD were combined in benzene at −15°C, it was found that the cyclobutene adduct (**195**) is isolated in quantitative yield (Scheme 87). When performed at reflux, seven-membered carbocycle **196** is obtained in 90% yield. In a similar vein, the reaction between 1-methoxyindene and DMAD yielded the corresponding cyclobutene (**197**) in 73% after refluxing in toluene for 5 h[173] (Scheme 88). In order to effect ring expansion, it proved necessary to heat the reaction to 220°C, which afforded **198** in 70% yield. In contrast, irradiation of the cyclobutene compound at room temperature provided **198** in quantitative yield. These results are in agreement with what is predicted by the Woodward–Hoffman rules of electrocyclic reactions in that the rearrangement is thermally forbidden but photochemically allowed. The ease with which the analogous aminocyclobutenes rearrange is ascribed to the possible development of a polarized bond (the shared σ-bond) in the transition state and the enhanced ability of the amino group to stabilize this feature compared with the methoxy group.

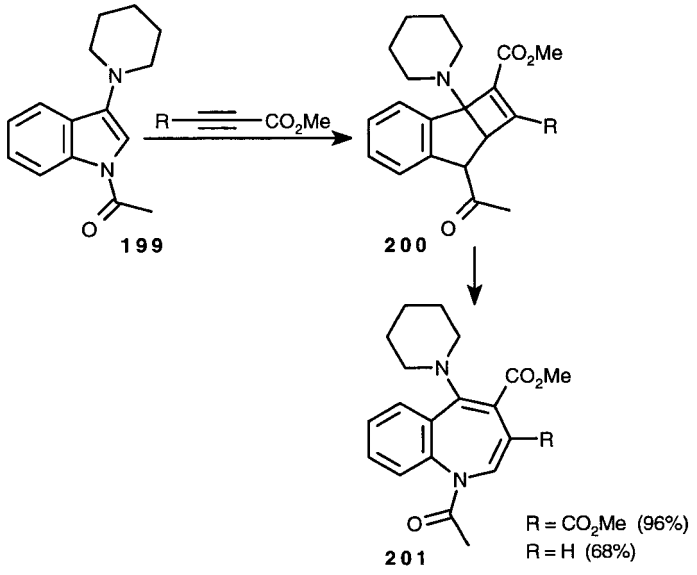
The azepine framework can be constructed from enamine derivatives and electrophilic acetylene compounds. For



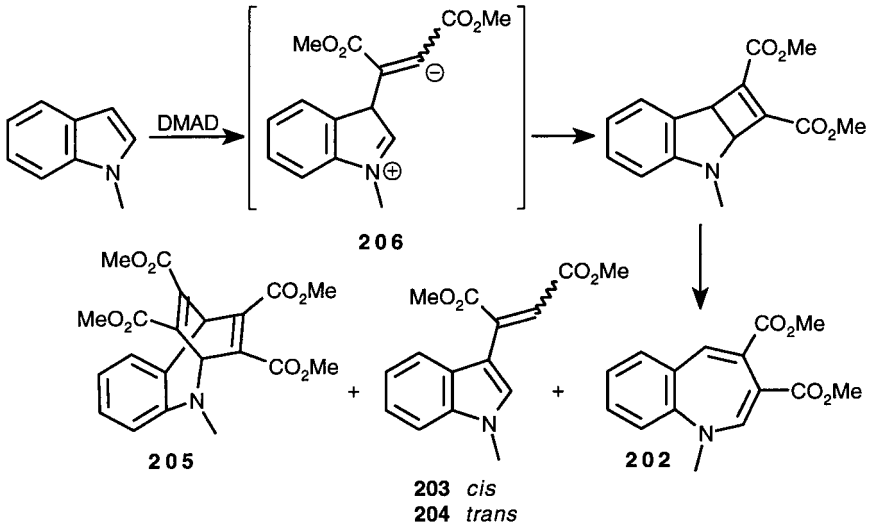
Scheme 87.



Scheme 88.



Scheme 89.



Scheme 90.

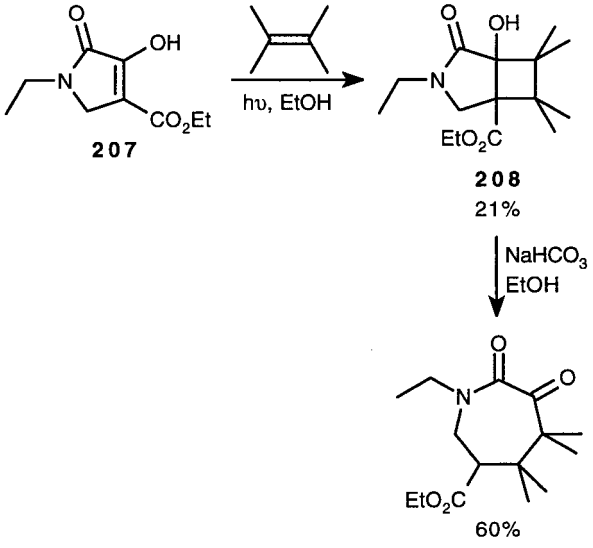
example, when 1-acetyl-3-piperidinoindole (**199**) and dimethyl acetylenedicarboxylate are allowed to react in refluxing dioxane for one day, the 1:1 adduct **201** is isolated in 96% yield[174] (Scheme 89). Cyclobutene **200** (R=CO_2CH_3) is implicated in this two-carbon ring-expansion process, although not isolated in this case. Cyclobutene **200** (R=H), however, was isolated when methyl propiolate was employed as the electrophile. The ring-expansion product is formed in 68% yield after refluxing for 11 days in dioxane. In both cases, the substitution around the periphery of the seven-membered ring can be exploited for further chemical transformations. Yamazaki reported that azepines can be accessed by the reaction between DMAD and ketene-S,N-acetals.[175] Reinhoudt has shown that synthesis of dihydrothiepines can be accomplished in a similar fashion by employing enamine derivatives of tetrahydrothiophen-3-ones.[176]

Less activated indoles can also be converted to azepines when treated with electrophilic alkynes.[177] 1-Methylindole and dimethyl acetylenedicarboxylate, after six days in refluxing acetonitrile, give a mixture of azepine **202**, maleate **203**, fumarate **204**, and minor amounts of the 1:2 adduct **205** (Scheme 90). Evidence of a non-concerted process to form the cyclobutene is to be found in the isolation of the 1,4-addition products **203** and **204**. This is further supported by the large solvent effect observed in similar cases and the high yields of these compounds when a protic solvent is employed, which allows for rapid quenching of intermediate **206**.[178,169]

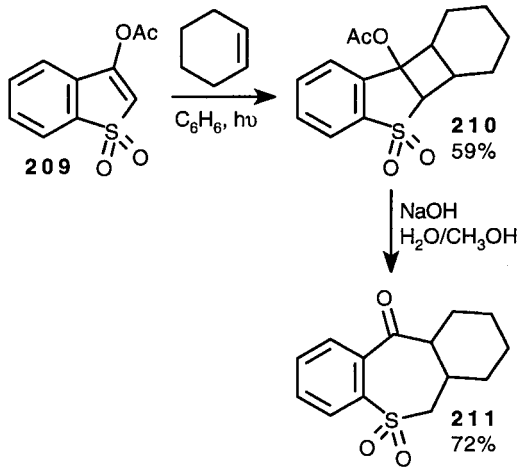
The advantage of strained cyclobutene rings in ring-expansion methodology is evident as demonstrated in the previous examples. The analogous saturated bicyclo[3.2.0]-heptane framework also has proven valuable as a platform from which to generate cycloheptyl derivatives. These synthetic intermediates may be obtained from photochemical [2+2] cycloaddition reactions and, with proper functionality equipped on the periphery of the cycloadduct, may experience fragmentation to form the desired expansion product. A compilation of the synthetic applications of [2+2] cycloadditions has been prepared by Baldwin.[179]

Reid has reported that the enol form of β-ketoesters can serve as a template for a two-carbon ring expansion involving a photocycloaddition–retroaldol sequence.[180] When enol **207** and 2,3-dimethylbut-2-ene are irradiated in ethanol, the cyclobutane adduct **208** is formed in 21% yield (Scheme 91). This compound undergoes reverse aldol when treated with 0.1% sodium bicarbonate in ethanol, affording the ring-expanded product in 60% yield. The same sequence was performed with cyclohexene with comparable results. In each case, the photodimer of **207** accounted for a portion of the product mixture.

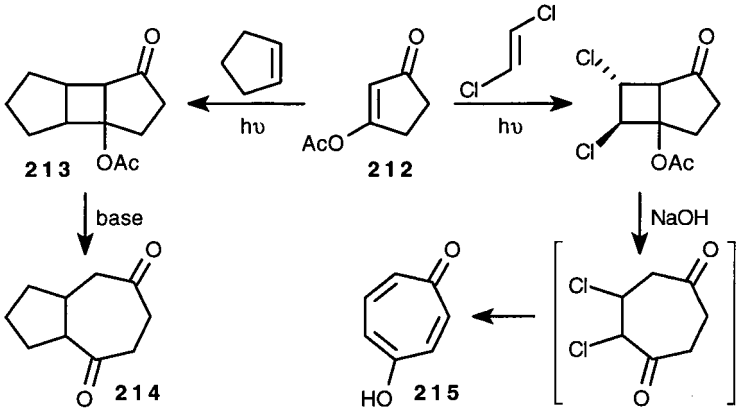
The success of the photocycloaddition–retroaldol sequence relies on the ability of the carbonyl group to stabilize the developing anion during the heterolysis of the shared bond of the bicyclo[3.2.1]heptyl system. Other functional groups which possess this ability are then candidates for this ring-expansion process. Indeed, Reid has shown that judicious incorporation of the sulfone group may serve to this end.[181] Photocycloaddition of cyclohexene onto α,β-unsaturated



Scheme 91.



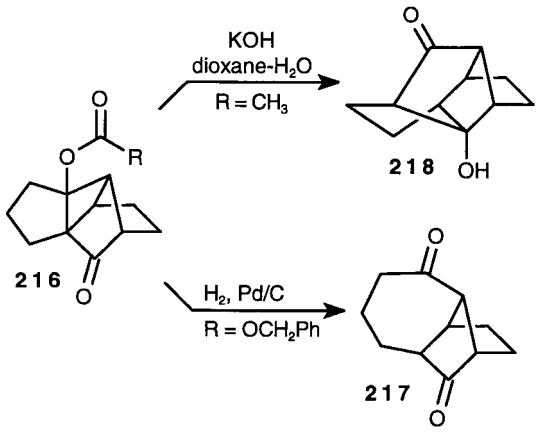
Scheme 92.



Scheme 93.

sulfone **209** affords **210** in 59% yield (Scheme 92). A significant amount (33%) of the dimer of **209** was also isolated. The action of sodium hydroxide (in aqueous methanol) brought about the formation of the 1,1-dioxothiepin **211** in 72% yield. The same sequence was also successful with cyclopentene.

The de Mayo reaction incorporates a photocycloaddition–retroaldol sequence resulting in a two-carbon homologation.[16,182–185] Irradiation of the enol acetate of 1,3-cyclopentadione (**212**) and cyclopentene in cyclohexane produces β-acetoxy ketone **213**[182] (Scheme 93). Treatment with base induces a retroaldol reaction which is driven by relief of cyclobutane ring strain, affording **214** (no yield given). When 1,2-dichloroethylene is employed and the cycloadduct (a mixture of three stereoisomers) is treated with sodium hydroxide, tropolone **215** is obtained in 45% yield. Oppolzer's synthesis of longifolene[186] included an intramolecular [2+2] photocycloaddition, leading to **216** (R=CH_3) (Scheme 94). Upon treatment with KOH (4% in dioxane–water), the desired retroaldol event occurred but was accompanied by adventitious aldol reaction between the enolate of **217** and the norbornanone moiety, producing **218**. The problem was circumvented by preparing benzyl carbonate **216** (R=OBn) and employing hydrogenolysis conditions to trigger the ring expansion. In this way, cycloheptanone **217** was isolated in 83% yield and converted to longifolene in five additional steps.

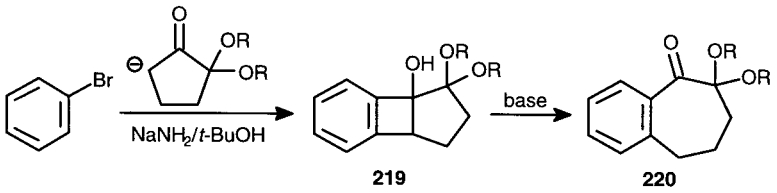


Scheme 94.

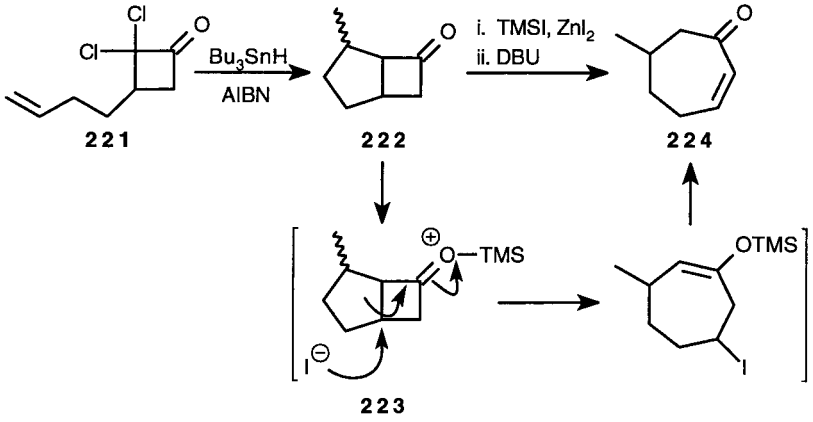
A route to benzocycloheptanones has been developed by Caubère.[187–189] The enolate of a cyclopentanone derivative is reacted with benzyne to afford cyclobutanol **219** in 75% yield (Scheme 95). It was found that the reaction proceeds best when benzyne is generated from bromobenzene using the complex base $NaNH_2$-Bu-*t*-ONa. Further treatment of the strained alcohol with base leads to isolation of benzocycloheptanone **220**. Yields range from 37% to quantitative, depending on the substitution on the aromatic and aliphatic rings.

Dowd has introduced a facile route to cycloheptenones from substituted cyclobutanones.[190] A [2+2] cycloaddition between a 1,5-diene and dichloroketene begins the sequence providing cyclobutanone **221** in 85% yield (Scheme 96). Treatment of **221** with tributylstannane initiates a 5-exo-trig cyclization onto the pendant olefin. A second equivalent of tributylstannane is included to remove the remaining chlorine. The resulting bicyclo[3.2.0]heptyl derivative (**222**) is treated with TMSI and ZnI_2 to effect ring expansion via intermediate **223**. Dehydrohalogenation with DBU affords cycloheptenone **224** in 90% yield. Bicyclic examples were also reported with similar efficiency.

Synthetic efforts aimed at preparation of unsaturated cycloheptyl derivatives have included heterolysis of



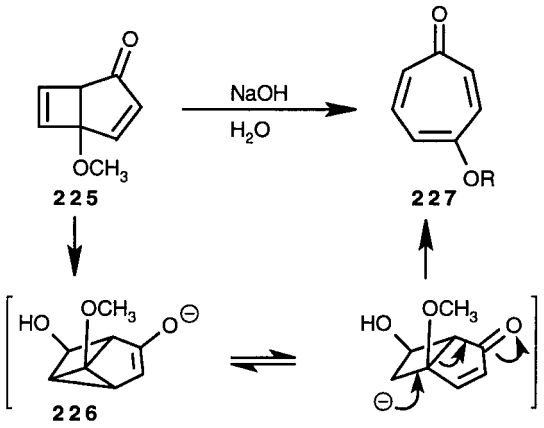
Scheme 95.



Scheme 96.

bicyclo[3.2.0]heptyl derivatives.[191–193] For example, treatment of **225** with hydroxide initiates ring expansion to provide **227** (Scheme 97). Hydroxide adds to the cyclobutene ring, generating intermediate **226**, which ultimately fragments to provide **227**. Similarly, 1,3,5-cycloheptatriene can be prepared by treatment of **228** with acetic acid and Na_2HPO_4 (Scheme 98).

Kurihara, while investigating radical-mediated preparation of azaspirolactones, discovered an alternate process that led to a two-carbon ring expansion of pyrrolidine-2-ethanol derivatives.[194] When **229** is treated with phenyl chlorothionoformate with DMAP in acetonitrile, the thionocarbonate derivative **230** (X=O, Ar=C_6H_5) is obtained in 62% yield (Scheme 99). Heating this compound in acetonitrile prompts intramolecular attack by nitrogen, resulting in



Scheme 97.

departure of COS from the thionocarbonate moiety. The newly formed azetidinium ion **231** then reacts with phenoxide to provide the ring-expanded product **232** in 55% yield. As **231** is an ambident electrophile, the formation of pyrrolidine **233** is also observed (16% yield). Other thionocarbonate derivatives (i.e. Ar=C_6H_5S–, 2-C_5NH_4S–) proved less satisfying in production of **232**. It is also worth noting that the carbonate analogue of **230** failed to react even after 18 h in refluxing toluene.

The aforementioned report also included tetrahydrothiophene-2-ethanol as one of the substrates.[194] The thionocarbonate **234** (X=O, prepared in 74% yield) required higher temperatures for the reaction to proceed and was heated in *o*-dichlorobenzene (Scheme 100). A mixture of products was obtained that contained the expected thiepane **235**, tetrahydrothiophene **236**, and a significant amount of a rearranged product identified as thiolcarbonate **237**. When the dithionocarbonate (X=S) was subjected to the same conditions, only the COS elimination product was obtained in 74% yield.

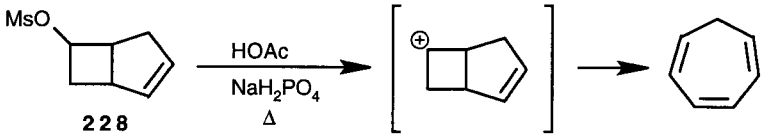
4.2. Homolysis of bicyclo[3.2.0]heptyl derivatives

Dowd has subjected cyclobutanones containing a haloalkyl side-chain to free radical-mediated ring expansion.[195–198] The initial four-membered ring (**238**) is conveniently prepared from a [2+2] cycloaddition employing a ketene. The halide is subjected to homolysis (Bu_3SnH, AIBN), which results in ring closure of the pendant radical onto the ketone providing cyclobutyloxy radical intermediate **239** (Scheme 101). This species fragments preferentially along the internal bond of the new bicycle, affording, after reduction, ring-expanded product **240**. Yields of

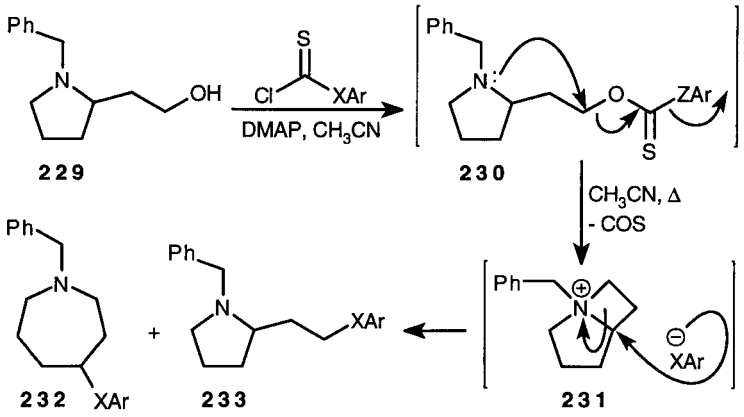
cycloheptanones for similar systems range from 55–100%. It should be noted that the endo isomers do not lead to ring expansion as the initial ring closure is dissuaded by steric effects.

Ziegler has demonstrated that a similar event occurs for a related cyclobutylcarbinyl radical.[199] When thionocarbonate **241** was subjected to radical deoxygenation conditions (tri-*n*-butylstannyl radical), primary radical **242** was unexpectedly formed in preference to the alternate secondary radical (Scheme 102). Cyclobutylcarbinyl radical **242** experiences fragmentation along the internal bond to provide tertiary radical **243**. Subsequent reduction of **243** is indiscriminant, resulting in a 1:1 mixture of methylenecycloheptane **244** (yield not provided).

Crimmins has shown that generation of a radical endo to the bicyclo[3.2.0]heptyl ring system can lead to ring expansion.[200] Hence, treatment of iodo compound **245** with tributylstannane produces secondary radical **246** (Scheme 103). Fragmentation of the cyclobutane ring occurs predominantly along the shared bond leading to intermediate radical **247**, which, after reduction, provides cycloheptene **248** in 80% yield (R=H) or 75% yield ($R=CH_3$). These examples are unusual as *exo* fragmentation is typically the observed pathway. Indeed, replacement of

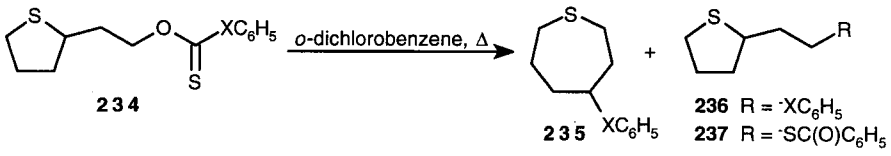


Scheme 98.

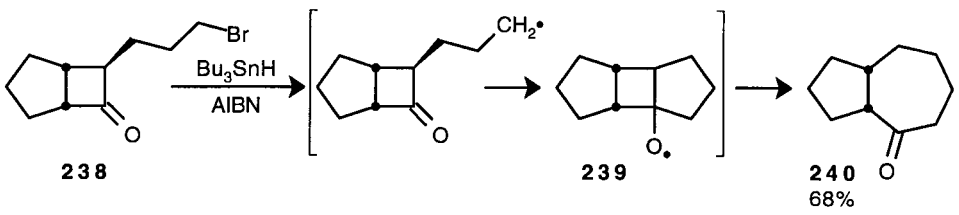


Scheme 99.

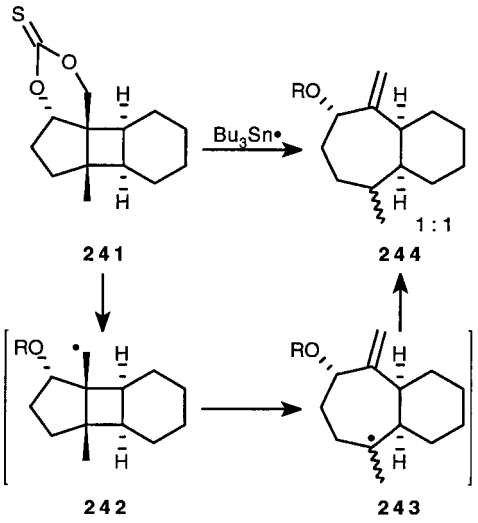
OC_6H_5	55%	16%
SC_6H_5	30%	59%
S-2-py	22%	34%



Scheme 100.



Scheme 101.



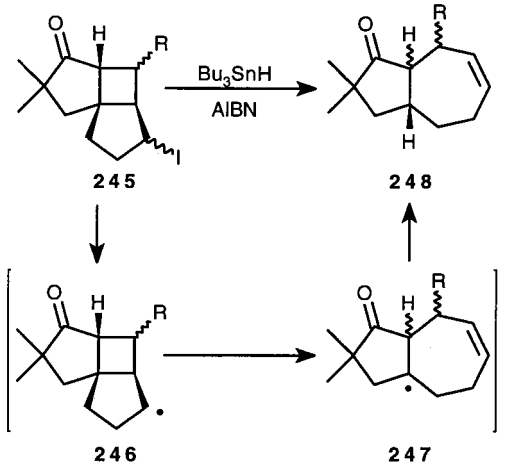
Scheme 102.

the hydrogen α to the ketone by $-CH_3$ or $-CO_2CH_3$ leads to products derived from the *exo* fragmentation pathway.

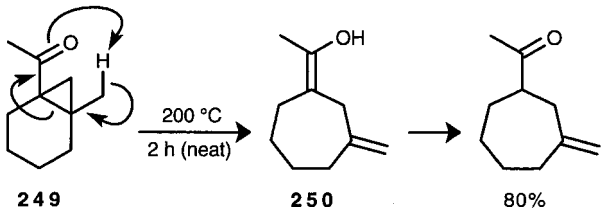
5. Electrocyclic Ring-Expansions

A wide variety of ring-expansion processes that rely on electrocyclic events have been described. Wong has prepared a thorough review of cyclopropane derivatives and their use in organic synthesis with a section focusing on Cope rearrangements that provide seven-membered rings.[19] An extensive review on the use of pericyclic reactions for construction of seven-membered heterocycles has recently been prepared by Hassenrück and Martin.[17] We refer the reader to these authors' compilations rather than duplicate their work.

An electrocyclic ring expansion was observed by Monti in the case of α-cyclopropylketones at elevated temperatures.[201] This process requires a γ-hydrogen be available on the cyclopropyl side of the ketone. When heated at 200°C (neat, 2 h) 1-acetyl-2-methylbicyclo[4.1.0]heptane (**249**) rearranges, via intermediate enol **250**, to afford



Scheme 103.

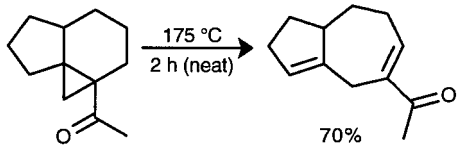


Scheme 104.

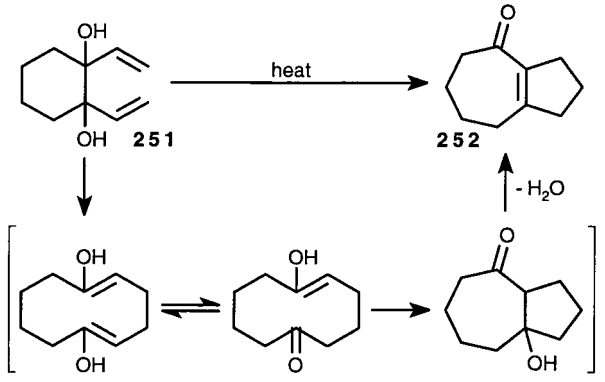
1-acetyl-3-methylenecycloheptane in 80% yield (Scheme 104). This approach was applied to preparation of the hydroazulene skeleton in 70% yield (Scheme 105).

Conia and Marvell have independently found that heating 1,2-divinyl-1,2-cyclohexanediol (**251**) (either *cis* or *trans*) will result in a net ring expansion providing cycloheptenone **252** (Scheme 106).[202,203] The initial Cope rearrangement generates the corresponding ten-membered ring functionalized with two enol moieties. Tautomerization of one of the enols poises the system for an aldol reaction, which, after dehydration, provides the seven-membered enone. Examination of the individual rearrangements of the *cis* and *trans* isomers shows the former to be 1.10 times faster. Additionally, under milder conditions, it is possible to isolate the β-hydroxyketone in good yield. Heating the *trans* diol results in a single isomer, whereas the *cis* diol leads to a 2.5:1 mixture of the β-hydroxyketone isomers. The specific isomers could not be identified, as these compounds readily dehydrate. Conia also described the expansion of (−)-camphoquinone by first preparing the 1,2-divinyl-1,2-bornanediol (**253**).[161] Heating **253** to 220°C resulted in a 2:1 mixture of the expected isomers (assignment not determined) (Scheme 107).

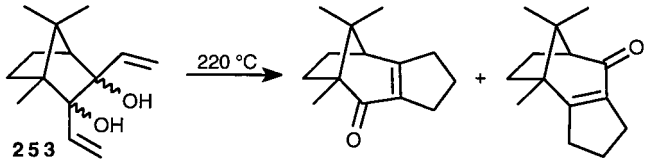
The Cope rearrangement of 1,2-divinylcyclopropanes allows direct access to seven-membered rings. Both the



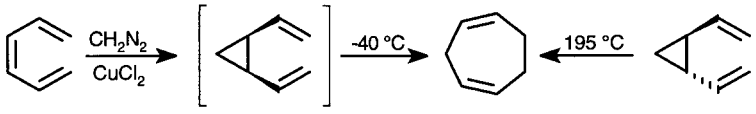
Scheme 105.



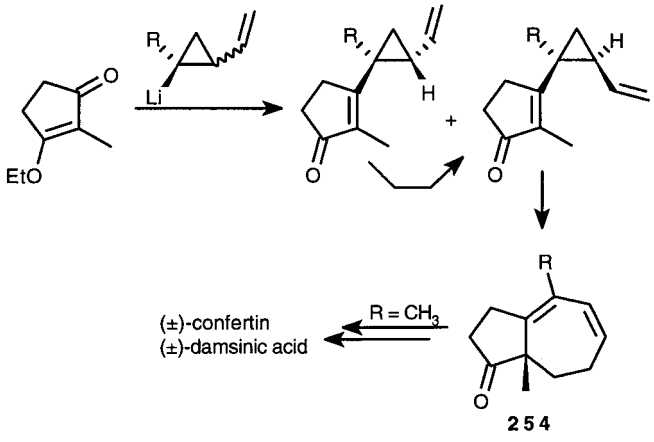
Scheme 106.



Scheme 107.



Scheme 108.

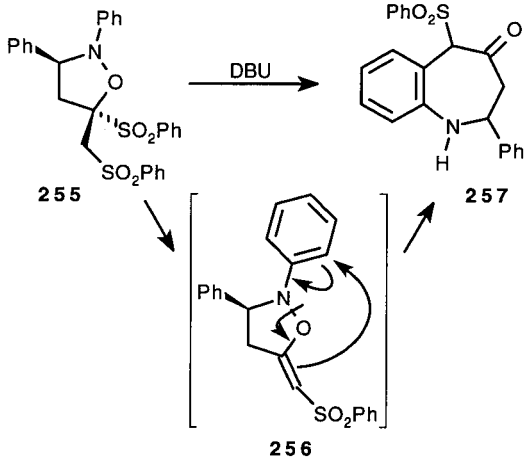


Scheme 109.

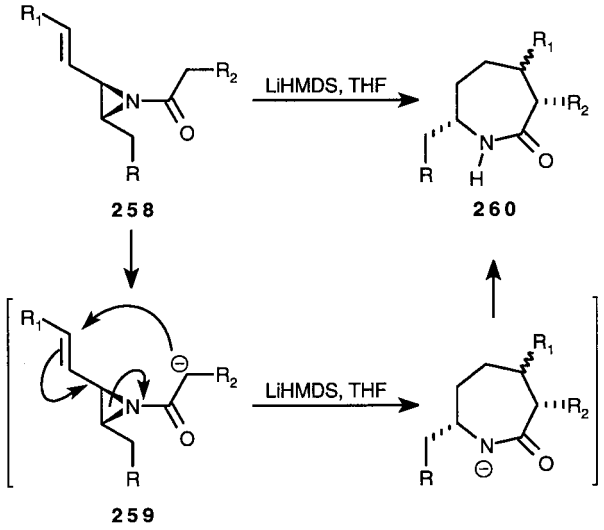
trans and *cis* isomers are candidates for the rearrangement with the latter occurring at significantly lower temperatures (Scheme 108).[204,205] This process has been applied on numerous occasions to construct the perhydrophenanthrene core.[206–209] Wender has demonstrated the utility of this reaction by accomplishing total syntheses of (±)-damsinic acid and (±)-confertin.[209] Addition of 1-lithio-2-vinylcyclopropane to 3-ethoxy-2-methylcyclopentenone led to the corresponding 1,2-divinylcyclopropane (Scheme 109). Heating this mixture led to formation of cycloheptadiene **254**. Although the *cis*-1,2-divinylcyclopropane will more readily undergo the rearrangement, it was suspected that the *trans* isomer can thermally epimerize to the *cis* form. The natural products could be synthesized from **254** (R=CH_3). This example is representative, although there is an extensive list of similar uses of this transformation that has been compiled by Wong.[19] Azepin-2-ones may similarly be prepared by the rearrangement of cyclopropanes containing a vinyl and isocyanate group that are *cis* to each other.[210] Likewise, 4,5-dihydrothiepin and 4,5-dihydro[1*H*]azepine can be prepared via Cope rearrangement of *cis*-1,2-divinylthiirane and *cis*-1,2-divinylaziridine, respectively.[211–212]

Padwa has shown an approach to the preparation of benzazepin-4-one **257** via a hetero-Cope rearrangement.[213] Isoxazolidine **255** is readily prepared by a [3+2] cycloaddition from the corresponding nitrone (Scheme 110). Treatment of **255** with DBU leads to **256**, which undergoes the pivotal hetero-Cope process, ultimately affording the ring-expanded product **257** as a 1:2 mixture of *cis* and *trans* stereoisomers.

Somfai has utilized an aza-[3,3]-Claisen rearrangement to effect the preparation of seven-membered lactams.[214] A variety of *N*-acetyl vinylaziridines (**258**) were treated with LiHMDS to generate the corresponding enolate **259** (Scheme 111). This intermediate rearranges on warming (−78°C to ambient temperature) to provide, after workup,



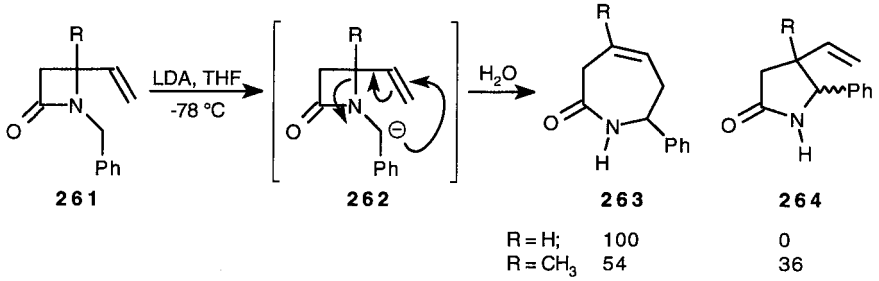
Scheme 110.



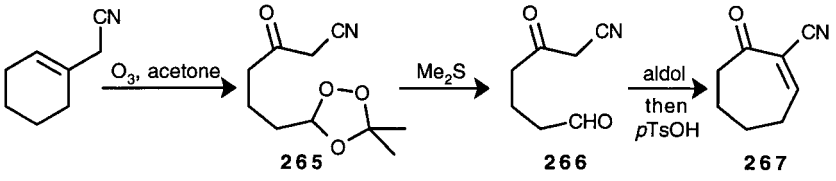
Scheme 111.

tetrahydroazepin-2-one **260**. The stereochemistry of the alkene is retained throughout the rearrangement. Yields typically ranged from 73–85% from the starting aziridine (two steps).

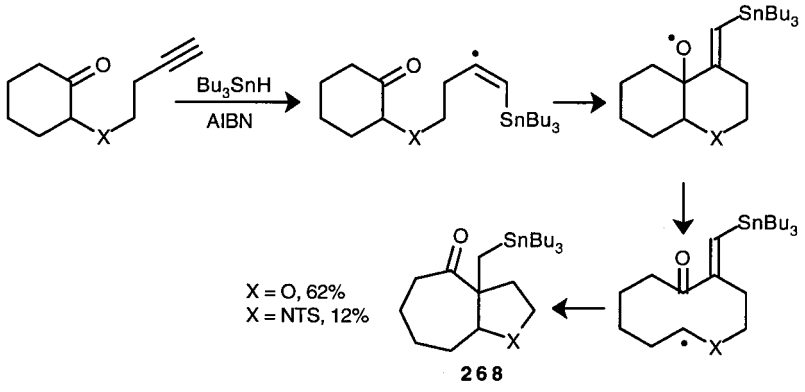
Durst has reported a base-promoted ring expansion of 1-benzyl-2-azetidinones.[215] When azetidinone **261** is treated with LDA in THF, the benzyl carbanion **262** is formed in preference to the enolate (Scheme 112). This anion smoothly participates in a [2,3] sigmatropic rearrangement, which, upon quenching, results in quantitative isolation of lactam **263**. When the 4-methyl analogue (R=CH_3) is subjected to the same conditions, the yield is significantly lower. Additionally, the appearance of the five-membered lactam **264** is also observed. It is presumed that formation of this side product is a result of fragmentation of the benzylic anion into a radical–radical anion intermediate that recombines to form **264**. Replacement of the vinyl group with a phenyl substituent failed to provide any of the desired ring-expansion product, providing only the five-membered ring analogous to **264**.



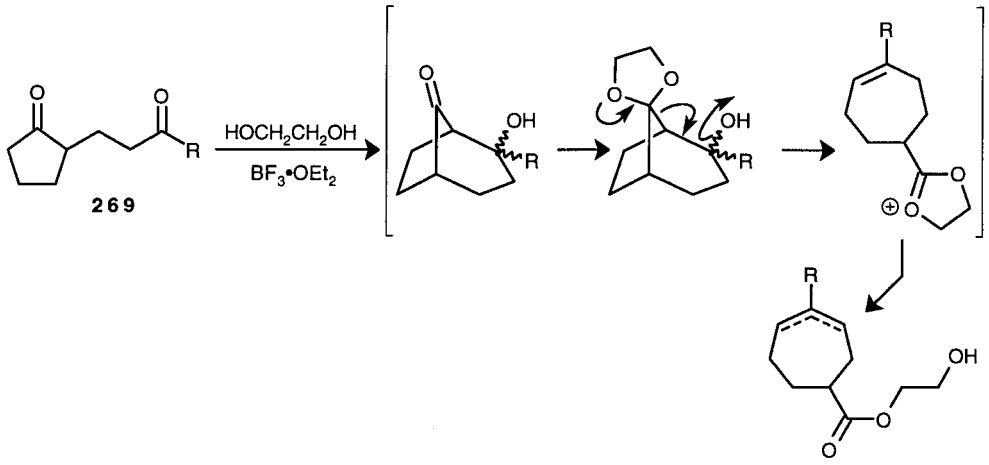
Scheme 112.



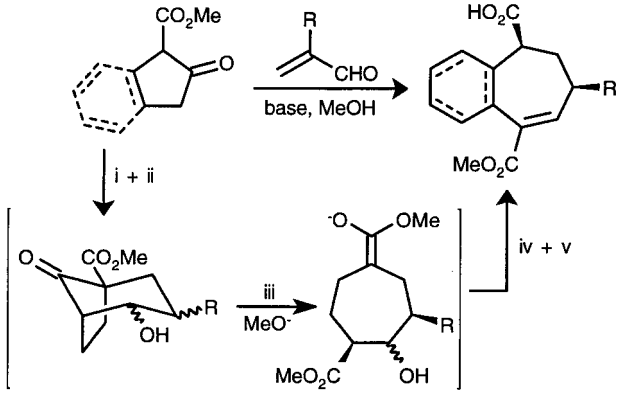
Scheme 113.



Scheme 114.



Scheme 115.



Scheme 116.

6. Miscellaneous

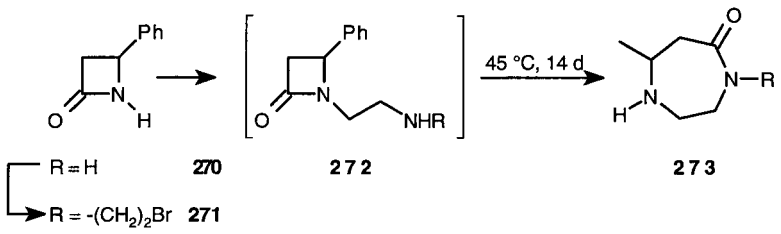
Fleming and co-workers found a route to 2-cyanocycloheptenone based on ozonolysis of 1-cyanomethylcyclohexene (Scheme 113).[216] Addition of dimethyl sulfide to the intermediate ozonide (**265**) produces β-ketonitrile **266**, which readily tautomerizes and participates in an intramolecular aldol reaction with the aldehyde. The resulting β-hydroxy ketone rapidly dehydrates on exposure to acid to afford ring-expanded product **267**. The use of acetone as a solvent was crucial in minimizing polymer formation and improved the yield from 13–58%.

Nishida has shown a fascinating sequence in the preparation of bicyclic systems (Scheme 114).[217] Addition of $Bu_3Sn^{\cdot}$ to the alkyne begins a ring closure-ring expansion-ring closure process resulting in the corresponding seven–five ring system (**268**). The tetrahydrofuran-fused derivative is produced in 62% yield and the tetrahydropyrrolidine-fused compound in 12% yield.

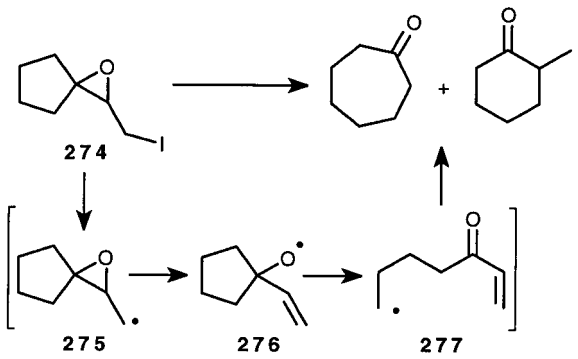
An interesting conversion of cyclopentanones to cycloheptenes was reported by Sakai and co-workers.[218] Here a 2-(3-oxoalkyl)cyclopentanone (**269**) is treated with BF_3-etherate and ethylene glycol (Scheme 115). A sequence of aldol condensation, ethylene glycol acetal formation, and cyclopentane fragmentation explains the observed formation of seven-membered rings. Yields ranged from 36–98%. Increased substitution at R correlated with higher yields (R=Ph>*i*-Pr>Et>Me). This methodology was successfully applied to the synthesis of (±)-bulnesol.

A base-induced domino reaction producing highly functionalized cycloheptenes was introduced by Rodriguez.[219] Mixing a Dieckmann ester and α,β-unsaturated aldehyde under basic conditions (Scheme 116) leads to a five-step sequence involving: (i) Michael addition; (ii) intramolecular aldol condensation; (iii) retro-Dieckmann; (iv) dehydration; and (v) saponification. Aldehydes used included R=Me, Et, Ph, $-C{\equiv}CSiMe_3$, $(CH_2)_2OBn$, $(CH_2)_2COOMe$. Yields ranged from 62–98%.

Crombie has prepared seven-membered azalactams via transamidation of β-lactams.[220] The readily prepared 4-phenylazetidin-2-one (**270**) is first alkylated with 1,2-dibromoethane under phase-transfer conditions to provide **271** (Scheme 117). Treatment of this halide with ammonia



Scheme 117.



Scheme 118.

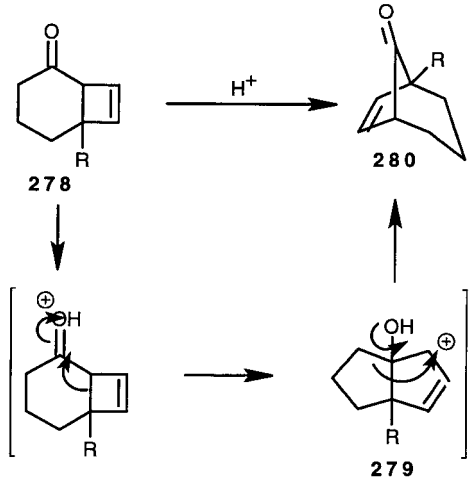
or ethylamine leads to intermediate **272**, which undergoes intramolecular transamidation to afford the ring-expanded azalactam **273** in 70% (R=H) or 88% (R=Et) yield.

Galatsis has employed iodospiroepoxides to effect a net two-carbon ring expansion.[221] Hence, when **274** is treated with tributylstannane in the presence of AIBN primary radical **275** is initially formed (Scheme 118). Ring-opening of the epoxide ensues leading to alkoxy radical **276**, which fragments to provide radical **277**. Competitive *endo* versus *exo* cyclization of this radical onto the olefin results in a 9% yield of cycloheptanone and 20% yield of 2-methylcyclohexanone.

Cargill and Matsumoto have investigated acid-catalyzed rearrangements of bicyclo[4.2.0]oct-7-en-2-ones (**278**) that provide bicyclic products such as **280**.[222–225] The skeletal rearrangement begins with 1,2-alkyl migration of the shared bond in the bicyclo system to the activated carbonyl. The resulting allylic carbocation (**279**) undergoes a second rearrangement that yields **280**. An account on related rearrangements has been prepared (Scheme 119).[20]

7. Conclusion

Numerous approaches exist and a multitude of refinements have been made on the four main approaches to realizing ring expansions seven-membered rings (Schemes 1–4).



Scheme 119.

That said, ring expansion to seven-membered rings is not always a straightforward undertaking. Indeed, the success of realizing seven-membered carbo- and heterocycles is highly dependent on the nature of the substrate as well as on the techniques employed. Ionic, radical, and electron-deficient (e.g. carbene, nitrene) methods have all shown varying degrees of success.

Acknowledgements

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Biographical Sketch

Eric J. Kantorowski was born in Downey, California in 1970. He received his B.Sc. in Chemistry at California State University, Fullerton in 1993, where he worked with Assistant Professor Steven A. Hardinger. He earned his Ph.D. in Chemistry at the University of California, Davis in 1998, under the direction of Professor Mark J. Kurth. His graduate years spanned the areas of organic synthesis, methodology, polymer-supported synthesis, and kinetics. He then augmented his field of research to include the area of marine natural products and carried out post-doctoral studies with Professor Tadeusz F. Molinski at UC Davis. In 1999, he joined the research group of Professor D. John Faulkner at the Scripps Institution of Oceanography, where he is currently a post-doctoral researcher involved with isolation, structural elucidation, and synthesis of marine natural products.

Mark J. Kurth was born in Iowa in 1953. He received his B.A. degree in 1976 from the University of Northern Iowa, where he worked with Professor James G. MacMillan. He earned his Ph.D. degree at the University of Minnesota (1980), where he worked with Professor Thomas R. Hoye on the total synthesis of brominated marine natural products such as aplysistatin. After a post-doctoral study with Professor Wolfgang Oppolzer at the University of Geneva (1980–1981) developing chiral auxiliaries for the Diels–Alder reaction, he joined the chemistry faculty at the University of California, Davis. His current research activities span natural products total synthesis, synthetic methods development, solid-phase organic synthesis and combinatorial chemistry, and polymer synthesis and characterization.