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ONE CARBON RING EXPANSIONS OF BRIDGED BICYCLIC KETONES

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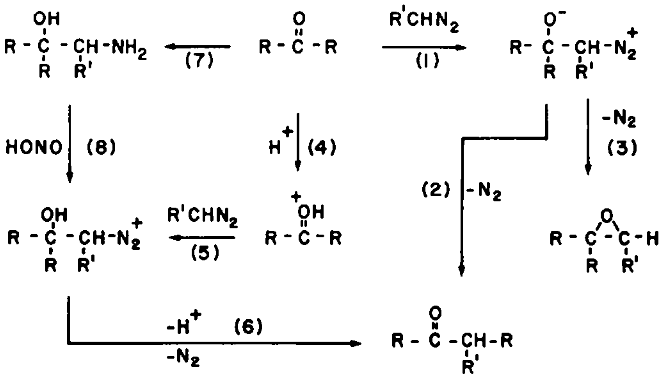
CONTENTS

INTRODUCTION

There are numerous situations where the lower homologue of a desired structure is more readily available or is needed for some other purpose, such as control of stereochemistry. In these cases the synthetic chemist must resort to chain extension or ring expansion methodology to add the requisite carbon atom. Although innumerable procedures for ring expansions can be envisaged, this review is limited to discussions of one carbon insertion procedures of bridged bicyclic and polycyclic ketones. The carbonyl groups are integral to the skeletal framework and not merely acyl substituents. The focus of the discussion is the ring enlargement of ketones with diazoalkanes[1-3] or by the mechanistically similar Tiffeneau-Demjanov reaction.[4] Other pinacol-type rearrangements and a variety of ring expansions, in which addition to the carbonyl functionality is a key step at some stage of the procedure, have been included where appropriate.[*,5] Leading references to some recent alternative one-carbon ring expansion methodologies are included where appropriae or are provided at the conclusion of this review.

The discussion to follow presumes the generally accepted mechanism for diazoalkane insertion reactions with ketones shown in Scheme 1.[1,2a,6] Addition of the diazoalkane to the ketone carbonyl to form a diazonium betaine (Step 1) is usually rate determining and creates a tetrahedral intermediate I.



Scheme 1. A general mechanism for diazoalkane reactions with ketones to form carbon insertion products.

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[*] Utilizing the systematic nomenclature of Gutsche and Redmore,[1] this review is primarily concerned with reactions from district 3, CRER, MLOC with some overlap of districts 2 and 4. CRER = Carbocyclic Ring Expansion Reactions (a city) and MLOC = Magnificent Land of Organic Chemistry.

Subsequently (Step 2), carbon bond migration occurs as nitrogen is lost in the step leading to product ketone. Epoxide formation (Step 3) is a frequent side reaction. The initial addition of diazoalkane to the carbonyl carbon can be catalyzed by a variety of Lewis acids (Steps 4 and 5). The intermediate I—H$^+$ also can rearrange to product ketone with loss of nitrogen (Step 6). Since the hydroxyl of I—H$^+$ is less nucleophilic than the alkoxide of I, competitive epoxide formation from I—H$^+$ is dramatically reduced. Intermediate I—H$^+$ is also generated in the Tiffeneau–Demjanov reaction[4] by treatment of a 1,2-aminoalcohol with nitrous acid (Step 8). The requisite 1,2-aminoalcohols (R′ = H) are available from ketones by a variety of methods.

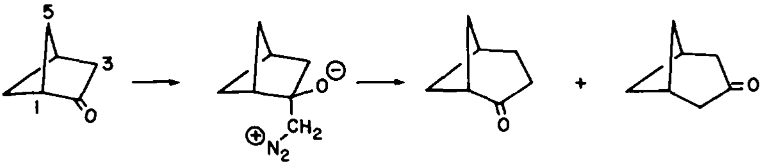
Of major interest for this review are reactivities of substrates and the regioselectivity of carbon insertion with various nonsymmetrically substituted bridge bicyclic ketones. Unsymmetrical ketones often yield mixtures of carbon insertion products and control of regioselectivity is a problem. We will attempt to identify those reagents, catalysts, and reaction conditions which best satisfy the reactivity and selectivity requirements of synthesis. A further goal of the present survey is to stimulate development of new reagents and methodology for carbon insertion reactions.

The classification scheme used in this review follows that of similar surveys of nitrogen[7] and oxygen[8] insertions of bridged bicyclic ketones in which the substrate ketone is identified in the major headings. For polycyclic ketones, the ring system is considered to be the bridged bicyclanone with the smallest sum for the three bridging units, and the ring system is arbitrarily numbered as this bicyclic ketone would be numbered. The abbreviation DAM will refer to diazomethane; Diazald is N-methyl-N-nitroso-*p*-toluenesulfonamide.

I. BICYCLO[2.1.1]HEXANONES

(A) 2-*Oxo-isomers*

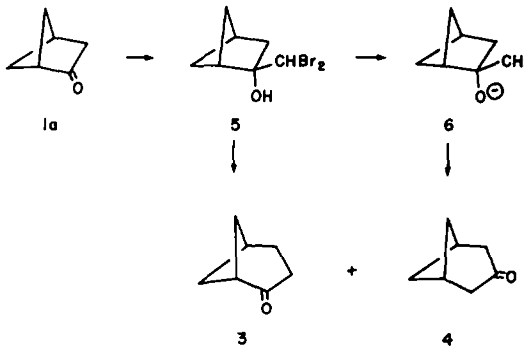
Diazomethane ring expansion of bicyclo[2.1.1]hexan-2-ones **1**, synthesized by photoirradiation of acyclic precursors, has been found by Gibson[9] to be a convenient method for the synthesis of bicyclo[3.1.1]heptan-2-ones **3**, which are not easily obtained by a direct photochemical route. Although **1** could be reacted with a 2-fold excess of diazomethane generated *in situ* from N-nitroso-N-methylurethane, the procedure was sluggish. Starting material remained after overnight to four days reaction times, material balances were poor, and yields were in the 26–60% range. The regiochemical preference for methylene migrated ketones **3** over bridgehead migrated ketones **4** (5–7 : 1) was attributed by Gibson to a weakening of the 2,3 bond in the diazonium ion intermediate **2** caused by eclipsing of substituents. Notable in these reactions is the failure to observe expoxide formation from **2**; this has been attributed to the preference for relief of ring strain by carbon migration. The absence of further ring expansion in the presence of excess DAM is surprising in view of the greater reactivity of cyclohexanone over cyclopentanone and of bicyclo[3.2.1]octanone **15** over norcamphor **14** [Section IIA1(a)]; nevertheless, the bicyclo[3.1.1]-heptanone systems **3** and **4** were unreactive.

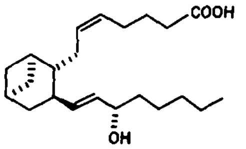


1 2 3 4

(a) Parent; (b) 3-Me; (c) 1-Me; (d) 5-Me (mixture)

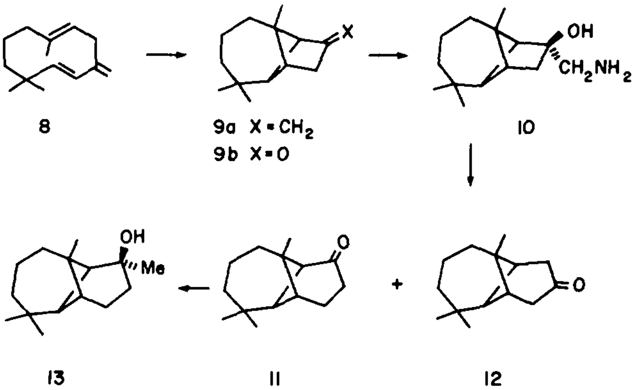
In an alternative approach to ring expansion of ketone 1a Nicolaou *et al.*[10] have used the Yamamota[11] procedure for rearrangement of β-oxidocarbenoids [Section IIB3]. Ketone 1a was reacted with dibromomethyllithium, formed *in situ* from methylene bromide and lithium dicyclohexylamide in tetrahydrofuran. The resultant adduct 5 and n-butyllithium afforded carbenoid **6**, which rearranged in 75% yield to a 6 : 1 mixture of **3** and **4**. Subsequently, bicyclo[3.1.1]heptan-2-one **3** was converted efficiently to the carbocyclic thromboxane A_2 (CTA_2) skeleton **7** and its hydroxy epimer. CTA_2 was reported to exhibit interesting and potent biological properties.





7

The cyclodeca-1,5-diene **8** has been photocyclized to the cross cycloadduct **9a** as part of the synthetic approach of Miyashita and Yoshikoshi[12] to longipinanol **13** and its dehydration products longipinenes. Attempts to ring expand olefin **9a** with lead tetraacetate or by solvolytic rearrangement of a derived *diol* monotosylate failed. Olefin cleavage of **9a** with osmium tetroxide followed by periodic acid afforded ketone **9b**, which either barely reacted with DAM, even using boron trifluoride catalysis, or led to a complex mixture with aluminum chloride catalysis. Ketone **9b** could be converted to aminoalcohol **10** by sequential reactions with dimethylsulfonium methylide, then sodium azide followed by catalytic hydrogenation. Tiffeneau–Demjanov ring expansion of the aminoalcohol **10** provided in quantitative yield a 90 : 6 ratio of ketones **11** and **12**. Stereoselective addition of methyllithium to ketone **11** afforded longipinanol **13**.

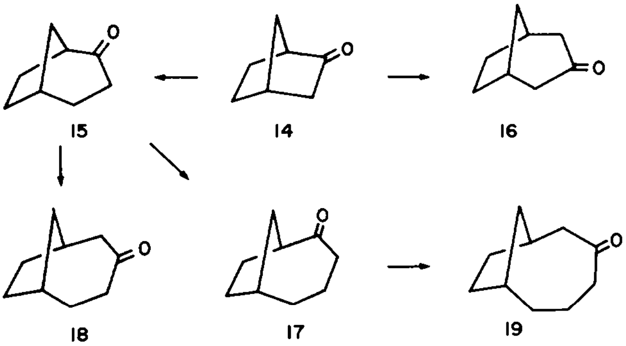


II. BICYCLO[2.2.1]HEPTANONES

(A) 2-*Oxo-isomers*

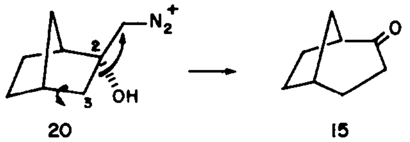
1. *Parent*

(a) *Major methylene migration.* Bly *et al.*[13] observed no reaction between norcamphor **14** and excess ethereal DAM containing 10% methanol, even after 6 days. However, **14** reacts with DAM formed *in situ* from N-nitroso-N-methylurethane or from Diazald and base in aqueous alcoholic solvents to form the ketones **15–19** (yields unspecified) in ratios dependent upon the quantity of DAM utilized.[14–16] On the basis of competitive experiments using 0.1 equivalents of DAM Pietra *et al.*[14] found a reactivity order: cyclohexanone ~ **15** > cyclopentanone ~ **14** > **17** > **18** > **16**, and methylene migration to give **15** was found to be about twice as fast as bridgehead migration to give **16**[14–18]. The reactivity order is not determined by the strain of the bicyclic system. Bicycloalkanones with the carbonyl adjacent to the bridgehead display "normal" reactivity of the corresponding cycloalkanone while reduced reactivity is observed as the carbonyl group is further removed from the bridgehead: for example, ketone **16** requires BF_3 catalysis to react appreciably

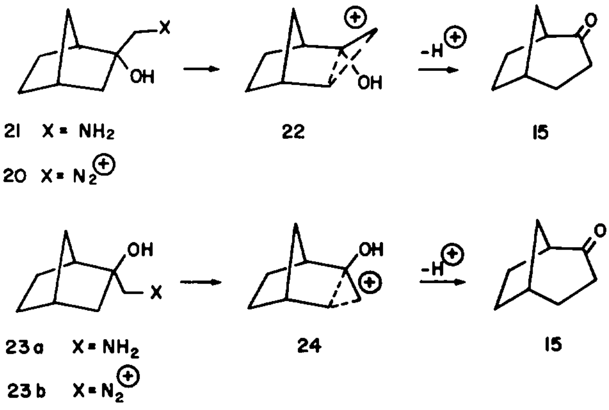


with DAM.[14] The failure to observe oxirane products, important for DAM reactions with unstrained and open-chain ketones, is apparently the result of an increase in the rate of C—C bond migration as a consequence of release of ring strain.

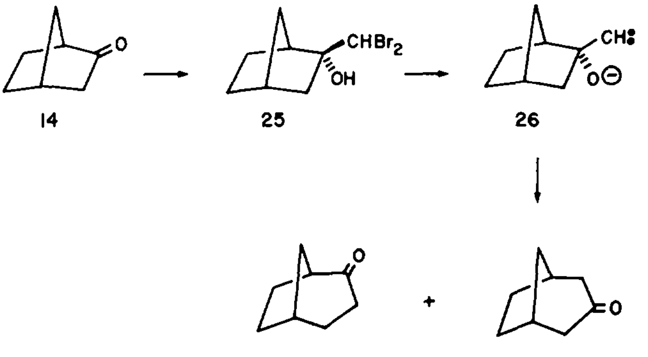
Migratory aptitudes favoring methylene migration to give **15** from norbornanone **14** have been attributed to relief of the bond eclipsing forces between the C2–C3 bond,[14,18] a factor first discussed by Sauers and Beisler.[14b] Preference for boat-like or chair-like transition states in the rearrangement of intermediate **20** do not appear to be of significance, since C3 methylene migration to give ketone **15** involves a boat-like transition state. McKinney *et al.*[15] preferred to rationalize the predominance of methylene migration from **20** by a least motion argument; C3 migration, proceeding by rotation about the C3–C4 bond to give **15**, involves motion of relatively few atoms in the molecule compared to the motions for bridgehead migration to **16**.[19]



McKinney *et al.*[15] have reported the Tiffeneau–Demjanov reaction of 2-*exo*-aminomethyl-2-*endo*-hydroxynorbornane **21** to give **15** and **16** in 86% combined yield with a 62:38 preference for methylene migrated product **15** over bridgehead migrated product **16**. The isomeric 2-*endo*-aminomethyl-2-*exo*-hydroxynorbornane **23a** afforded the same products with a 91:9 preference for **15** over **16**. Pietra *et al.*[17] observed qualitatively similar 71:29 and 95:5 ratios of **15** to **16** from **21** and **23a**, respectively. In the *endo* series factors favoring methylene migration are reinforced by loss of nitrogen from **23b** via a conformationally favorable chair-like transition-state **24**. In the *exo* series the loss of nitrogen from **20** involves a boat-like transition-state **22** for methylene migration; thus, more bridgehead migration is observed in the *exo* series.



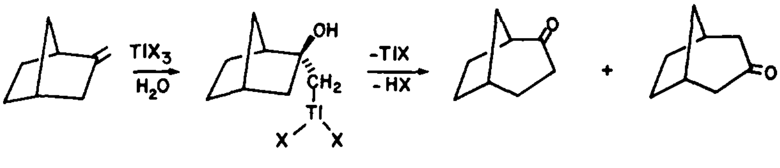
Norbornanone **14** has also been ring expanded by Ward and Murray[20] using the Yamamoto procedure[11] in 77% overall yield to provide a 1.8 : 1 mixture of ketones **15** and **16**. The preference for methylene over bridgehead migration of β-oxidocarbenoid **26** can be explaind by the conformational energy factors discussed above for rearrangement of **20**.



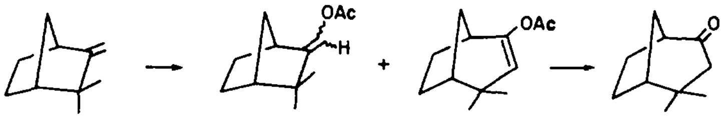
14 25 26

15 16

A highly regioselective synthesis of **15** has been based upon oxidative rearrangement of **27**, the *exo*-methylene derivative of **14**, which could be prepared by a Wittig reaction. Schleyer *et al.*[21] have obtained mainly ketone **15** (50%) with a trace (0.6%) of ketone **16** upon treatment of **27** with thallium(III)perchlorate in aqueous 1,2-dimethoxyethane. Rearrangement of **27** to **15** is believed to occur from a 2-*endo*-carbinyl-2-*exo*-hydroxynorbornyl species **28**, formally formed by *exo* attack of water upon a 2-alkylnorbornyl cation equivalent. Wolinsky[22a] has reported a related oxidative rearrangement of camphene **29** to a mixture of enol acetates **30** and **31**. Hydrolysis of the mixture, then selective formation of 32-semicarbazone followed by its hydrolysis provided 4,4-dimethylbicyclo[3.2.1]octan-2-one **32** in 30% yield[22b] [cf. Section IIA1b].

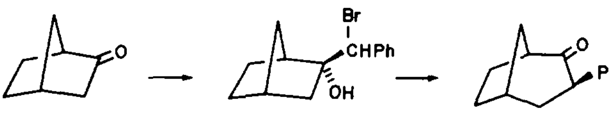


27 28 15 16



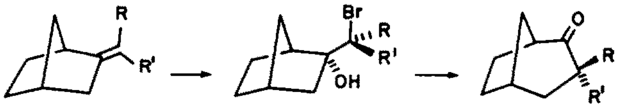
29 30 31 32

An alternative regioselective route to a 3-substituted bicyclo[3.2.1]octan-2-one **34** has been reported by Sisti,[23] who has studied the thermal rearrangement of magnesium salts of halohydrins. Norcamphor **14** was reacted with benzylmagnesium chloride (*exo* attack) and the resulting adduct was brominated using N-bromosuccinimide to give **33**. The magnesium salt of **33**, formed from **29** using isopropyl magnesium bromide, was rearranged in refluxing benzene to give ketone **34** in 42% overall yield. The torsional factor, in which C2–C3 eclipsing interactions are relieved, favors methylene migration, but the exclusive regiochemistry of migration is surprising.



14 33 34

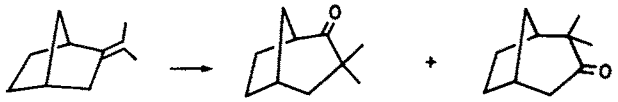
Sisti *et al.*[23,24] have also carried out a variation of the above procedure for bromohydrin formation in which an alkylidene derivative **35** of norbornanone **14** was reacted with aqueous N-bromosuccinimide. Bromine adds to the *exo* face of the olefin **35** and the hydroxyl group adds to the *endo* face to give **36**. Thermal rearrangement of the magnesium salts of **36** afforded from **36a** and **36b** the ketones **37a** (65%, stereochemistry not proven)[23a] and **37b** (13%, extensive decomposition upon pyrolysis).[24]



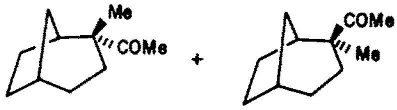
35 36 37

(a) R = Me, R' = H
(b) R = R' = Me

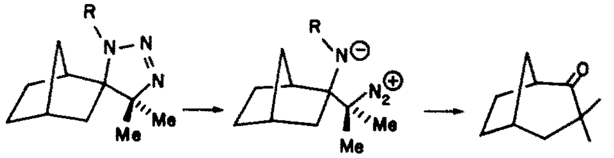
McManus *et al.*[25] have described another regioselective alternative to the ring expansions of *exo*-alkylidene derivatives of norbornanone **14** described above. After heating of 2-isopropylidenebicyclo[2.2.1]heptane **35b** with *p*-nitrophenylsulfonylazide (PNBSA) for 16 days in benzene at 90^{c} (sealed tube) and resultant hydrolysis these workers obtained a mixture of **37b** (37%),



35b 37b 38



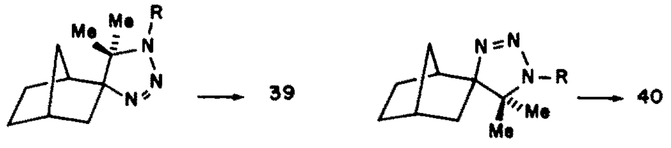
39 40



41 42 37b

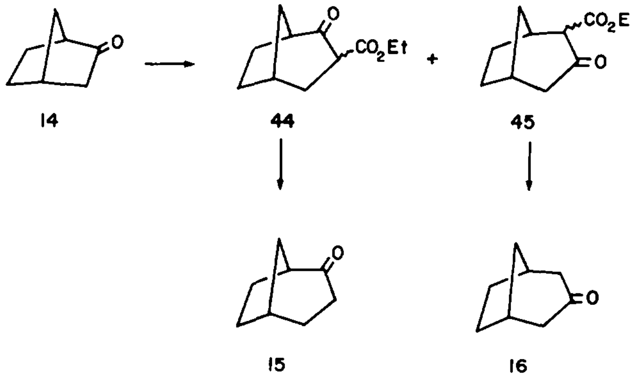
R = p-NO$_2$ Ph-SO$_2$

38 (2%, not isolated), **39** (4%), and **40** (16%) based upon GLC analysis. The major product **37b** arises by ring expansion of **42** with methylene migration. Intermediate **42**, derived from the sterically more hindred cycloadduct **41**, is formally the *endo* addition product from reaction of 2-diazopropane with norcamphor-N-*p*-nitrobenzene-sulfonylimine. Preferential formation of **37b** is analogous to the preference for methylene migration in the ring enlargements of **23b** and **28** (*vide supra*), in which the carbinyl carbon is also *endo*. The ketones **39** and **40** arise via methyl migration from adducts **43a** and **43b**, formed respectively by *endo* and *exo* attack of PNBSA on olefin **35b**.



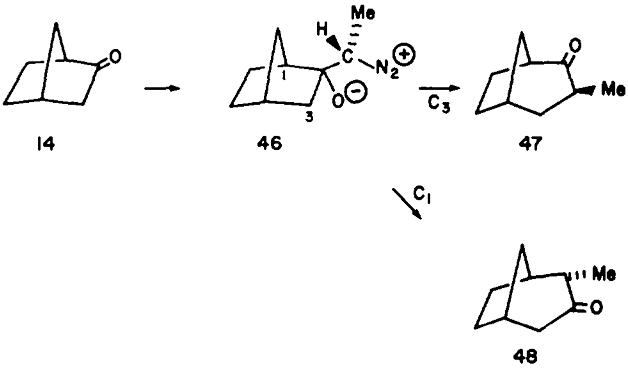
43a 43b R = p-NO$_2$Ph SO$_2$-

Reactions of substituted diazoalkanes with norboranone **14** are a source of α-substituted bicyclo[3.2.1]octan-2(3)ones. Ethyldiazoacetate, with triethyloxonium tetrafluoroborate (3 eq) as catalyst,[26] reacted with **14** to afford a mixture of **44** and **45**, which upon hydrolysis gave primarily

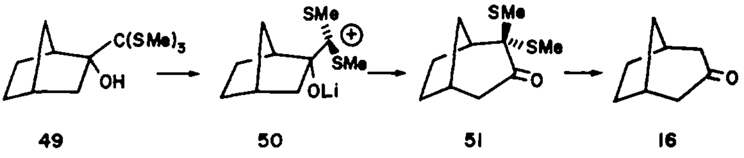


(86%) methylene migrated ketone **15** in 92% yield. The same reaction with antimony pentafluoride (0.5 eq) as catalyst led to nearly equal amounts (51 : 49) of **15** and **16** in 79% combined yield.[27] No rationale was given for the effect of catalyst upon the regiochemistry of carbon migration. Multiple ring expansion and epoxide formation were not problems using the ethyldiazoacetate method.

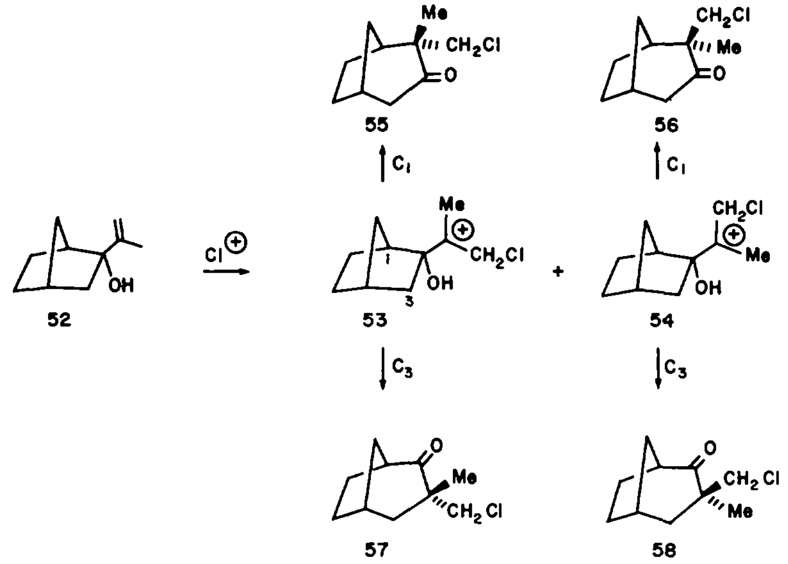
Diazoethane (DAE) in methanol afforded a nearly equal mixture of methylene and bridgehead migrated ketones **47** and **48** from norbornanone **14**; however, only the more stable α-methyl isomers were isolated.[28] The product selectivity was explained on the basis of rate limiting addition of DAE to the *exo*-face of ketone **14** to give intermediate **46** in which the methyl group is oriented away from the carbon skeletal framework.[29] Only the stereochemistries observed in **47** and **48** arise from either methylene or bridgehead migration from the product determining intermediate **46**.

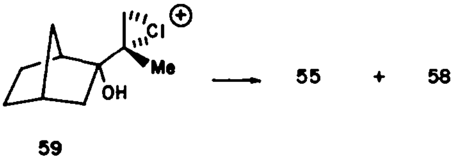


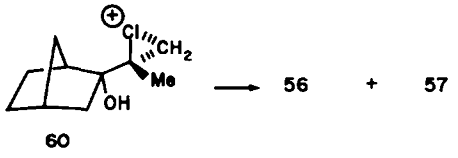
(b) *Major bridgehead migration.* Recently, Knapp *et al.*[30] have reported a ring expansion of norbornanone **14**, which provides product derived solely by bridgehead migration. The *exo*-tris(methylthio)methyllithium adduct **49**, obtained from norbornanone **14**, was treated with tetrakis (acetonitrile)copper(I) perchlorate (or tetrafluoroborate) (2 eq) for 1–4 hr at 75° to afford 61% yield of the 3-ketoisomer **51** formed by migration of the more highly substituded bridgehead carbon. Zinc/acetic acid reduction of **51** provided bicyclo[3.2.1]octan-3-one **16** (no yield given) with less than 0.5% of the 2-keto isomer **15**. Preferential bridgehead migration was attributed to formation of a highly stabilized cation (or developing cation **50**), followed by a transition-state leading to **51** in which the migrating bridgehead carbon assumes substantial charge. Steric and conformational effects were discounted, since the appropriate orbital alignments are possible for both bridgehead and methylene bond migrations [Sections IIB3, VA3].



Preferential bridgehead migration has also been noted by Johnson and Herr[31] in the ring enlargement of *exo*-2-isopropenyl norbornan-2-ol **52** with t-butyl hypochlorite. A mixture of ketones in the ratios **55** (23%), **56** (41%), **57** (11%), and **58** (25%) was formed in unspecified yield. The 64 : 36 preference for methine over methylene migration was rationalized by assuming a nonconcerted mechanism involving intermediate carbocations **53** and **54**. It was felt that electronic considerations would favor *bridgehead* migration to such charged sites. However, methylene migration is favored for ring expansions of norbornan-2-one **14** with DAM or by the Tiffeneau–Damjanov method (IIA1a). Both of these methods have high carbocation character at the migration terminus. Electronic considerations might favor migration of the more electron-rich bridgehead carbon to a carbon center with a poor leaving group as found in the bridged chloronium ions **59** and **60**. It was suggested that the *exo*/*endo* ratios **55**/**56** and **57**/**58** are related to the conformational preference for the isopropenyl group of **52**. Following formation of **53** and **54**, alkyl migration was presumed to occur prior to rotational equilibration of these cations.[31] Formation and rearrangement of the stereoisomeric chloronium ions **59** and **60** also leads to the isomers **55**–**58**, but does not require that rotation about an exocyclic single bond be slow relative to rearrangement.

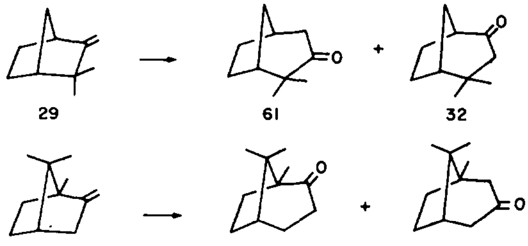






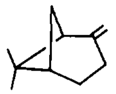
2. *Functional derivatives*

Camphene **29** and a mixture of palladium chloride, cupric chloride, oxygen and aqueous isopropanol afforded a 3 : 1 mixture of tertiary bridgehead migrated ketone **61** and quaternary carbon migrated ketone **32** in unspecified yield, and methylenecamphor **62** afforded in a poor 20% yield a 3 : 1 mixture of **63** and **64** in which secondary methylene carbon migration was favored over quaternary bridgehead migration. [See also Section IIA1a, conversion of **29** to **32**.] Ring expansion was not observed with either β-pinene **65** [Section IIIA] or methylenenorbornane **27** under similar reaction conditions; only bis-π-allylpalladium chloride dimers were isolated.[32]



29 61 32

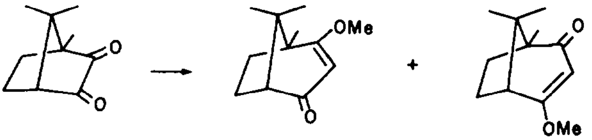
62 63 64



65

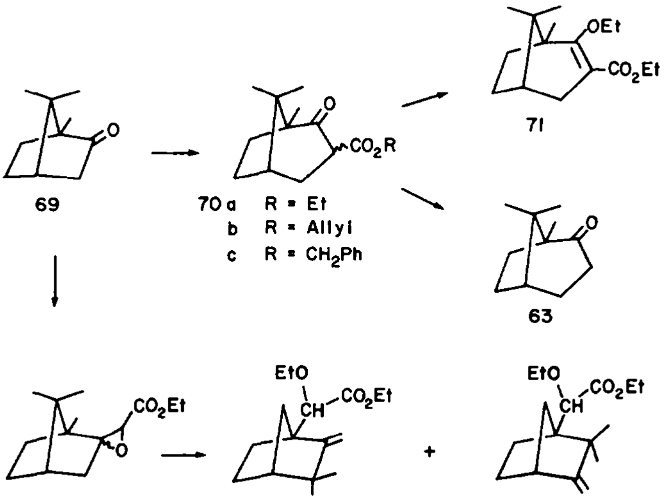
27

Camphorquinone **66** reacts with DAM to afford a mixture of β-methoxyketones **67** and **68**. These arise by methylation of the enolates of a 1,3-diketone formed from acyl migration of the DAM addition product of **66**.[33]



66 67 68

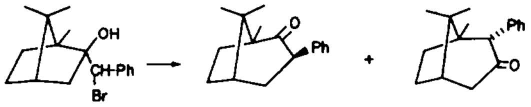
Liu *et al.*,[34a] upon reaction of camphor **69** with ethyldiazoacetate (EDA) in ether containing excess boron trifluoride etherate for 63 hr, obtained 24% of the enol ether **71** in addition to 63% of a pair of olefins **73** and **74**. The epoxide **72** was postulated as an intermediate, which could provide the olefinic products upon acid catalyzed rearrangement (and O-alkylation). Baldwin and Landmesser[35] found that enol ether information, as observed in the conversion of **70a**, to **71**, was suppressed when freshly distilled boron trifluoride etherate was utilized as catalyst for the conversion of **69** to ketoesters **70b** and **70c** with allyl or benzyl diazoacetates. Sodium/ammonia or hydrogen/palladium on carbon reductions converted **70b** and **70c** to the methylene migrated camphor homologue **63** in 60% and 70% overall yields, respectively. Reportedly, only the methylene migrated ketone **63** was formed.



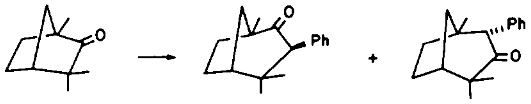
69 70 71 63 72 73 74

Sisti and Rusch[36] observed both methylene and bridgehead migrations in the thermal rearrangement of the magnesium salt of bromohydrin **75**, synthesized from camphor **69** (Section IIA1a).

Methylene migrated ketone **76** (51%) was favored over bridgehead migrated ketone **77** (23%); the phenyl group was assumed to occupy the most stable orientation in each case. Similarly, Sisti *et al.*[37] converted fenchone **78** to a mixture of ketones **79** (42%) and **80** (6%) and camphenilone **81** to ketone **82** (68%, phenyl stereochemistry assumed) by the three-step procedure of benzylmagnesium chloride, N-bromosuccinimide/benzoyl peroxide, isopropylmagnesium bromide/heat.



75 76 77

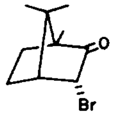


78 79 80

81 82

Dave and Warnhoff[38] have developed a method for regioselective homologation of unhindered unsymmetrical steroidal ketones. The procedure involves reaction of α-haloketones with ethyldiazoacetate catalyzed by boron trifluoride etherate, which is followed by zinc dust reduction and hydrolytic decarbethoxylation. The electron-withdrawing power of the halogen prevents migration of the attached carbon. Attempts to extend this procedure to ring expansion of 3-*exo*-bromonorcamphor **83** or 3-*endo*-bromocamphor **84** failed to provide ring expansion products. Sealed tube reactions with **83** at elevated temperatures gave less than 5% of uncharacterized homologation products; more powerful Lewis acid catalysts, diazoacetonitrile or DAM/boron trifluoride etherate were similarly ineffective, while DAM/methanol gave mixtures from multiple homologation.

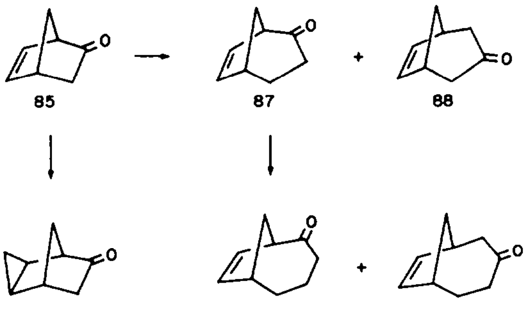
83



84

3. *Dehydroderivatives*

(a) *Major methylene migration.* Bly *et al.*[13] obtained cyclopropyl ketone **86**, but not product of insertion alpha to the carbonyl, when dehydronorcamphor **85** was reacted with DAM in ether containing 10% methanol. However, McKinney and Patel[15] found that dehydronorcamphor **85** and DAM, generated *in situ* in pure methanol, afforded a mixture of insertion products in ratios dependent upon the quantity of DAM utilized. With nearly 0.8 equivalents of DAM the bridgehead migrated product **88**, although obtained in only 16.5% yield, was the major carbon insertion product. With 3.3 equivalents of DAM, both bridgehead migrated products **88** (42%) and **90** (23%)

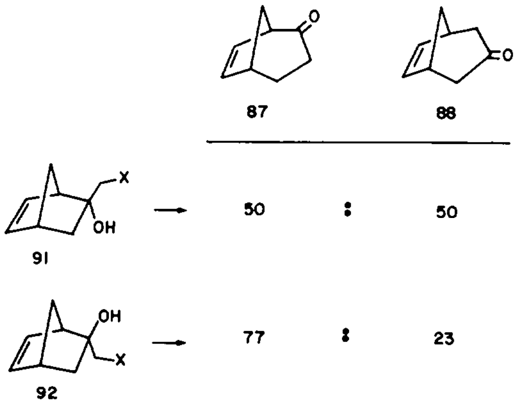


85 87 88

86 89 90

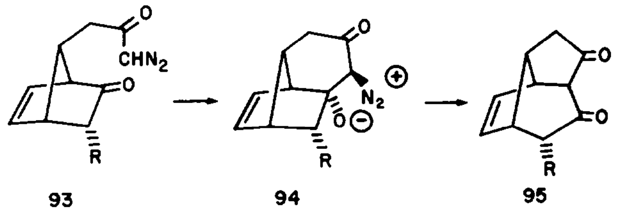
predominated over **87** (5%) and **88** (6%). The migratory preference in the reaction of **85** is bridgehead = methylene; however, the methylene product **87** reacts further with DAM to give **89** and **90**. Similarly, **89** reacts further with DAM to give higher substitution products (not shown). The result is that the less reactive **88** and **90** are the predominant lower molecular weight structures in the final product mixture.

To confirm the similar preference for bridgehead or methylene migration from DAM reactions with **85**, Bly *et al.*[13] have shown that the Tiffeneau–Demjanov reaction of 2-*exo*-aminomethyl-2-*endo*-hydroxynorbornene **91a**, which provides the same diazonium ion **91b** expected from *exo*-addition of DAM to **85** in protic solvents, gives equal amounts of **87** and **88**. By contrast, the 2-*endo*-aminomethyl-*exo*-2-hydroxynorbornenone **92a** affords mainly **87**. The rationale is that rearrangement of the diazonium ion **92b** through a chair-like transition-state to give **87** is preferred over the alternative boat-like transition-state to give **88**[39] [cf. the rearrangement of **20**, Section IIA1 (a)].



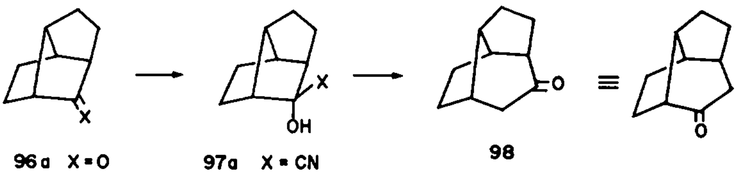
(a) $X = NH_2$, (b) $X = N_2^{\oplus}$

(b) *Major bridgehead migration.* Mander and Wilshire[40] have looked at some of the few intramolecular diazoalkane ring expansion reactions in the conversions of **93** to **95**. The products **95** are derived from bridgehead migration of **94**; the alternative intermediate leading to methylene migration would require the diazonium group to adopt a less favored axial orientation.



4. *Bridged tricycles and polycycles*

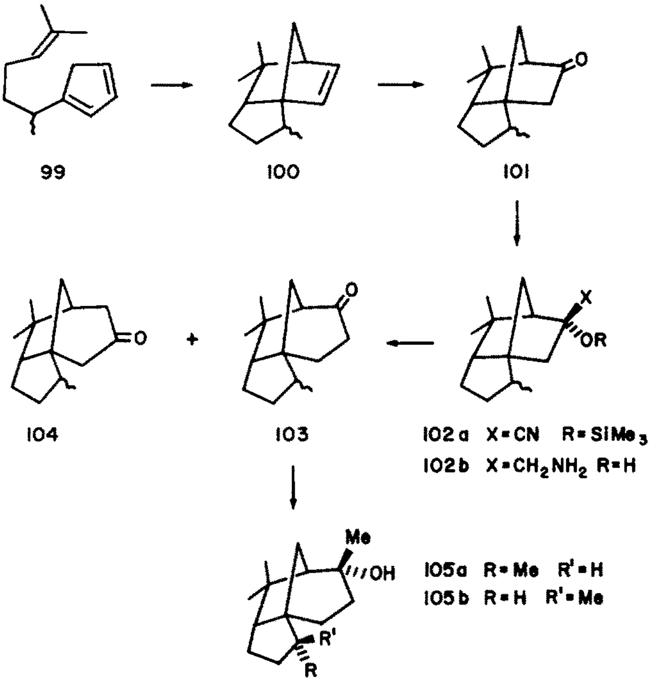
Nickon *et al.*[41] have converted brexan-2-one **96a** to homobrexan-2-one **98** in 98.5% yield by the Tiffeneau–Demjanov procedure. The requisite aminoalcohol **97b** (*endo* OH = *exo* OH) was formed by reduction of the cyanohydrin prepared by the trimethylsilyl cyanide method of Evans *et al.*[42] An alternative route to **98** (46%) was to react 2-methylenebrexane **96b** with cyanogen azide[43] and to follow with a hydrolytic workup of the resultant ring enlarged N-cyanoimine (cf. the rearrangement of **41**, Section IIA1a). Migration of either bridgehead upon nitrous acid treatment of **97b** affords the same ketone **98**. (See also Section IVB3.)



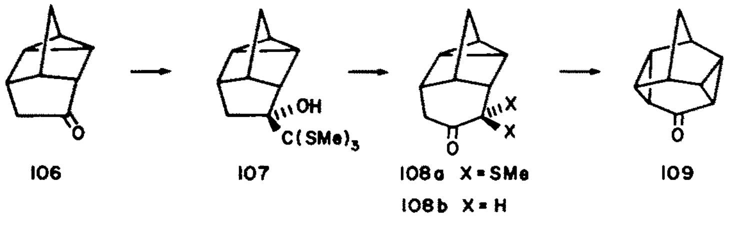
96a $X = O$ **97a** $X = CN$

96b $X = CH_2$ **97b** $X = CH_2NH_2$

A total synthesis of racemic cedrol **105a**, in which intramolecular cycloaddition of **99** to give **100** and ring expansion of a derived ketone **101** were key steps, has been described by Breitholle and Fallis.[44] Ketones **101**, a mixture of methyl epimers, were inert to DAM, even under Lewis acid catalyzed conditions. However, the cyanohydrin **102a**, prepared by the procedure of Evans *et al.*[42] could be reduced to the aminoalcohols **102b** and subsequently ring expanded by the Tiffeneau–Demjanov procedure to afford ketones **103** and **104** in 73% overall yield from ketones **101**. Variable amounts (15–25%) of the minor positional isomer **104** were obtained. Addition of methyllithium to the *exo* face of the major ketones **103** afforded the methyl epimers cedrol **105a** and epicedrol **105b**.



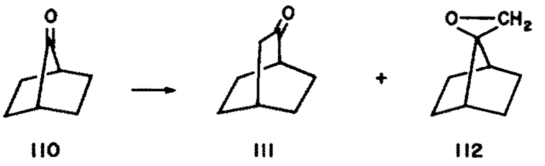
Israel and Murray[45] have applied the procedure of Knapp *et al.*[30] to effect regioselective bridgehead migration in the ring expansion of δ-cyclan-8-one **106**. Upon treatment of the lithium salt of the tris(methylthio)methyl adduct **107** with tetrakis(acetonitrile)copper(I) perchlorate, ketone **108a** was obtained in 71% yield. Reduction of **108a** with zinc in acetic acid provided ketone **108b**, which upon further modification provided 4,5,9,10-tetradehydroadamantan-2-one **109**.



(B) 7-*Oxo-isomer*

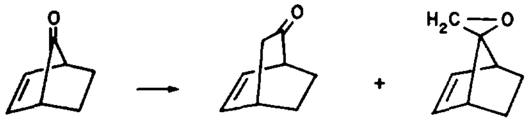
1. *Parent*

Reaction of 7-norbornanone **110** with 1.5 equivalents of ethereal DAM in 10% methanol for one day afforded bicyclo[2.2.2]octanone **111** in 73% yield. Bly *et al.*[13] found less than 2% of epoxide **112** was formed in this reaction and no higher homologues of **111** were identified.



2. *Dehydroderivatives*

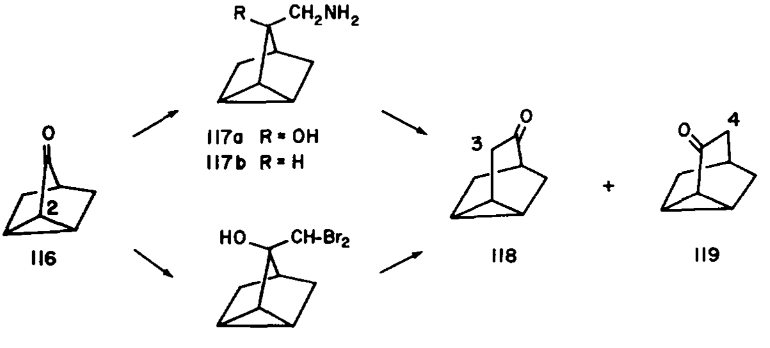
Bly *et al.*[13] obtained bicyclo[2.2.2]octenone **114** (44%) and the epoxide **115** (34%) upon reaction of 7-norbornenone **113** overnight at 25° with ethereal DAM containing 10% methanol. Under the rection conditions 7-norbornenone **113** is four times more reactive than 7-norbornanone **110** and much more reactive than 2-norbornanone **14**.



113 114 115

3. *Bridged tricycles and polycycles*

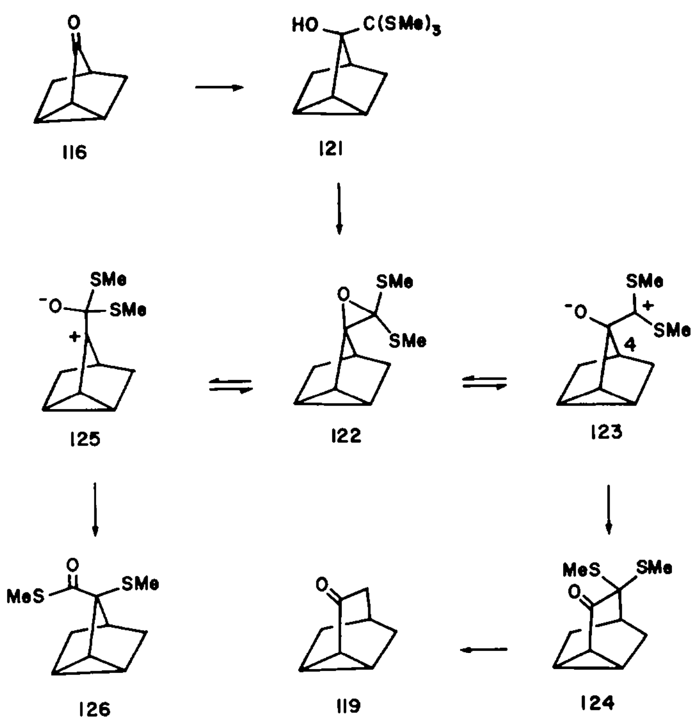
The first one-carbon ring expansion of nortricyclanone **116** was carried out using the Tiffeneau–Demjanov procedure on intermediate **117a**. Lumb and Witham[46] isolated 83% of tricyclo-[2.2.2.0^{2,6}]octan-8-one **118** and 9% of tricyclo[2.2.2.0^{2,6}]octan-7-one **119**. These same workers found that ethereal DAM and **116** with boron trifluoride catalyst afforded 30% of a ketone with the GC retention time of **118**; however, the yield was not reproducible and **116** was frequently recovered unchanged. Later, Sauers *et al.*,[47] found that DAM generated *in situ* from Diazald in aqueous ethanol at 5° converted **116** to methylene migrated ketone **118** in 42% isolated yield. Less than 1% of the isomeric ketone **119** was observed. Preferential cyclopropyl carbon migration in the Demjanov rearrangement of **117b** has also been noted by Sauers and Beisler.[48]



In a more efficient approach to ring expansion of nortricyclanone **116**, Ward and Murray[20] utilized the Yamamoto procedure[11] in which the dibromomethyllithium adduct **120** was reacted with butyllithium [Section IA]. An 85:15 mixture of **118** and **119**, in which migration of the C2 cyclopropyl carbon was favored, was obtained in 49% overall yield for two steps from **116**.

Cyclopropyl C2 migration is not always favored in ring expansions of cyclopropyl ketones, as Israel and Murray[49] have discovered when the ring enlargement procedure of Knapp *et al.*[30] [Section IIA1b] was used on tricyclanone **116**. Sequential treatment of the tris(methylthio)methyl adduct **121** formed from **116** with butyllithium, then tetrakis(acetonitrile)copper(I) perchlorate and heating at 78° provided a mixture of 72% 4,4-bis(methylthio)tricyclo[3.2.1.0^{2,7}]octan-3-one **124** and 27% S-methyl-3-(methylthio)tricyclo[2.2.1.0^{2,6}]heptane-3-carbothioate **126**. Formation of **126** provides strong evidence for epoxide **122** as an intermediate in the ring expansion process. Opening of epoxide **122** to **125** and migration of a thiomethyl group provides **126**. The alternative mode of epoxide ring opening from **122** to **123** and migration of C4 provides **124**. Why only C4 migrates is not known. Reductive desulfurization with Raney nickel converted **124** to tricyclo[3.2.1.0^{2,7}]octan-3-one **119**.

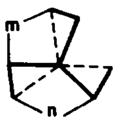
Nakazaki *et al.*[50] have utilized ring expansion methodology in their synthetic approaches to analogs of D_3-twisted bicyclo[2.2.2]octane **127**. Tricyclic, tetracyclic, and pentacyclic cage-shaped hydrocarbons are provided by successive bridging of C2–C8, C3–C6, and C5–C7 with polymethylene units. Nakazaki has coined the generic names [m]-, [m,n]-, and [m,n,p]-triblattane for these hydrocarbons **128–130**, in which m, n, and p are the number of methylenes in each diagonal bridge connecting the bicyclo[2.2.2]octane skeleton. Attempts by Nakazaki *et al.*[51] to ring enlarge dinoradamantan-2-one **131** to 4-twist-brendanone **113** with DAM under various, but not described,



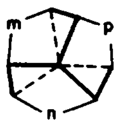
conditions were unsuccessful; however, it was possible to successfully bring about the ring expansion of **131** to **132**, a [1]-triblattane precursor, using the Demjanov procedure.[51] Sosnowski and Murray[52] have also prepared **132** in 27% yield using the Tiffeneau–Demjanov procedure; ketone **131** was reacted with trimethylsilylcyanide followed by lithium aluminum hydride and nitrous acid.

127

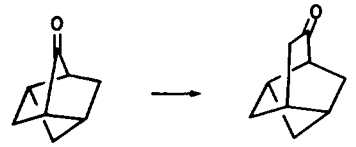
128



129

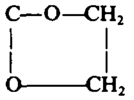


130



As part of their study of the chiroptical properties of tetracyclic triblattanes, the Nakazaki group[50] prepared several [m.0]- and [m.1]-triblattanes by DAM ring enlargement followed by Wolff–Kishner reduction of the derived ketones. Tetracyclo$[4.3.0.0^{2,5}.0^{3,8}]$nonan-9-one **133a**, or [1.0]-triblattan-9-one, and ethereal DAM (10 eq) after six days at 0° afforded upon reduction a 4:6 mixture of [2.0]- and [1.0]-triblattanes **134** in unspecified yields. Ketone **133a** with ethereal DAM (4 eq) and boron trifluoride etherate (1 eq) after 1 hr at 0° followed by reduction led to isolation of [2.0]-, [3.0]-, [4.0]-triblattanes **134a**. The [1.1]-triblattane **133b** did not react with DAM in the absence of catalyst. However, ethereal DAM (15 eq) and boron trifluoride etherate (1 eq) after 30 min at 0° followed by reduction afforded isolable quantities of [m.1]-triblattanes **134b** where m = 2–7. Yields were found to be dependent upon both temperature and the quantity of DAM utilized.[50]

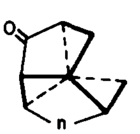
Table I. Carbon insertion reactions of triblattanones **135**. Ethereal DAM 0°C

	Ketone structure		Conditions		Product structure			Yield	
	m	n	DAM (eq)	Time (da)	Ketone	q[(a)]		(%)	Ref.
135a	CH_2	bond	$5^{(b)}$	0.04	**136a**	CH_2	(44)		53a, b
					136b	$(CH_2)_2$	(13)		
					136c	$(CH_2)_3$	(25)		
					136d	$(CH_2)_4$	$(11)^{(c)}$		
135b	$(CH_2)_2$	bond	$5^{(b)}$	0.04	**137a**	CH_2	(11)		53b
					137b	$(CH_2)_2$	(6)		
					137c	$(CH_2)_3$	(39)		
					137d	$(CH_2)_4$	(13)		
					137e	$(CH_2)_5$	(18)		
			5.5	0.5	**137a**	CH_2		73	53b
135c		bond	5.8	1.0	**138a**	CH_2		85	53b
			12	11	**138b**	$(CH_2)_2^{(d)}$		20	53a
135d	$(CH_2)_3$	bond	$3^{(b)}$	0.5	**139a**	CH_2	(52)		53a
					139b	$(CH_2)_2$	(25)		
					139c	$(CH_2)_3$	(18)		
135e	CH_2	CH_2	excess	1.0	**140a**	CH_2		98	53c
				3.0	**140a**	CH_2	(81)		
					140b	$(CH_2)_2$	(19)		
				8.0	**140a**	CH_2	(65)		
					140b	$(CH_2)_2$	(35)		
			$5^{(b)}$	1.0	**140a–d**	CH_2 to $(CH_2)_4^{(e)}$			
			$10^{(b)}$	1.0	**140b–e**	$(CH_2)_2$ to $(CH_2)_5^{(e)}$			
135f	CH_2	C=O	3	1.0	**141**	CH_2		40	55
			14	1.0	**142**	$CH_2^{(f)}$		40	55
135g	$(CH_2)_2$	C=O	22	2.0	**143a**	CH_2		61	55
			50	7.0	**143b**	$(CH_2)_2^{(g)}$		8	55
			$—^{(h)}$	—	**144**	(CH_2)		68	56
135h	$(CH_2)_2$	$CHOAc^{(i)}$	5–6	7.0	**145**	CH_2		71–74	53d
135i	$(CH_2)_2$	$(CH_2)_2$	$excess^{(j)}$		**146**	CH_2		0	55

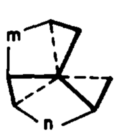
(a) The position of the carbonyl group in **136–146** was not determined where regioisomers could be formed. The numbers in brackets represent product ratios for the hydrocarbons formed following Wolff–Kishner reduction of the ketones. Yields are also for the hydrocarbons. (b) Boron trifluoride etherate (1.0 eq). (c) Additional higher homologs were not characterized. (d) **138a** was also formed in unspecified yield. (e) Ratios of products are given in the reference. (f) A second CH_2 insertion into the n-bridge occurred. (g) A mixture of **143a** and **143b**, ratio unspecified, was formed. (h) See ref. 11, Yamamoto ring enlargement. (i) The syn/anti isomers were reacted separately. Reactions were run at 5°. (j) Conditions were not reported.

The Nakazaki group[53] has also studied ring expansion of [m.n.1]-triblattanones **135**, considered for our purposes as bridged 7-oxobicyclo[2.2.1]heptanones, as part of their efforts to study the chiroptical properties of the pentacyclic triblattanes **130**.[53–55] Some of their results are shown in Table I. The hydrocarbons formed from a number of such bridged ketones, for example, **137a** (C_2-6,8-dehydrotwistane), **140a** or **141** (C_3-bismethanotwistane), **143a** or **145** (C_2-methanoditwistane), and **147** (D_3-tritwistane), have unusual symmetry.[55] In no case, where selectivity is possible, was there a determination of the regiochemistry of carbon insertion with DAM into either compounds **135** or the products **136–146**.

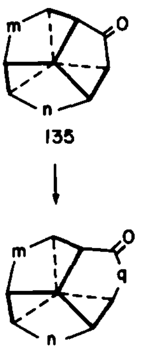
Notable in Table I is the catalytic effect of boron trifluoride etherate on the DAM insertion. Nakazaki *et al.*[53c] were able to prepare mixtures of higher homologs **137d** and **137e** (p = 5 and 6) of [p.1.1]-triblattanes **130** in reasonable quantities from D_3-trishomocubanone **135e** (m = n = CH_2) using excess DAM and boron trifluoride etherate; without catalyst mainly one carbon insertion to **137a** was observed. Also of interest in Table I are the preparations from **135g** and **135h** of D_3-tritwistane **127**, a prototype of the "twist" diamond structure in which the 6-membered rings are twist boats. DAM will insert only into one bridge of the diketone **135g**, despite use of large excesses of DAM and extended reaction times.[55] In order to introduce the third two-carbon bridge into a [2.2.1]-triblattanone **135**, Nakazaki *et al.*[53b] first converted **135i** to the nitrile **149** with tosylmethyl isocyanide/potassium t-butoxide. Next, **149** was reduced to the amine **150**, which was ring expanded



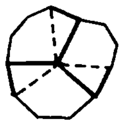
133a n = bond
b n = CH_2



134a n = bond
b n = CH_2

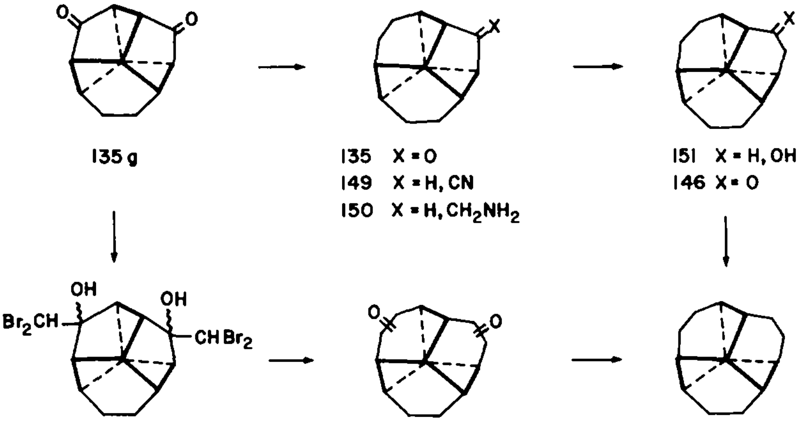


136 - 146 (unspecified carbonyl regioisomer)



147

to **151** using the Demjanov procedure. Alcohol **151** was oxidized to ketone **146** and Wolff–Kishner reduction afforded tritwistane **147**.



135g

135 X = O
149 X = H, CN
150 X = H, CH_2NH_2

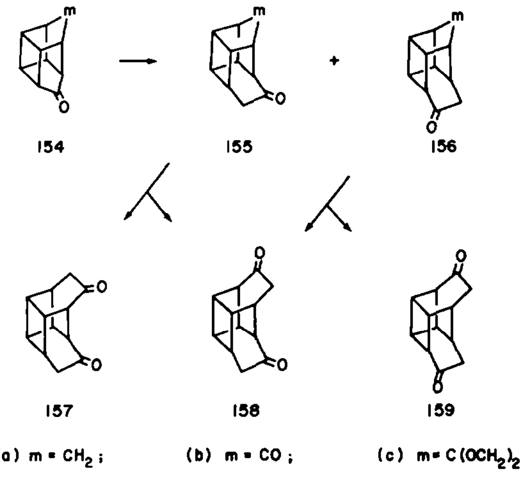
151 X = H, OH
146 X = O

152 **153** **147**

In an alternative approach to tritwistane **147**, which overcame the failure of DAM to insert into both bridges of **135g**, Hirao and Yonemitsu[56] used the Yamamoto[11] procedure for rearrangement of beta-oxido carbenoids. In this procedure dibromomethyllithium, formed *in situ* by reaction of methylene bromide and lithium dicyclohexylamide in tetrahydrofuran at −100°, was added to each of the carbonyl groups of **135g**. Reaction of the intermediate bis-dibromomethylalcohol **152** with n-butyllithium in tetrahydrofuran at −78° afforded ring expanded diketone **153** in 64% overall yield. Wolff–Kishner reduction of **153** afforded tritwistane **147**.

The results of studies by Hirao, Yonemitsu *et al.*[57,58] concerning the formation of ketones **157**–**159** by reaction of bridged pentacyclic ketones **154** with ethereal DAM are shown in Table II. It

Table II. Carbon insertion reaction of bishomocubanones **154** and derivatives **155b**, **156b**.[a]



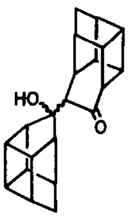
Structure		Conditions					
Entry	m	(Equiv.)	Time (hr)	Products	Ratio	Yield (%)	Ref.
154a	CH$_2$	3	3	**155a/156a**	1.5	45	56
154b	CO	1.2	2	**155b/156b**	1.5	39	58a
154c	C—O—CH$_2$ O——CH$_2$	—		**155c/156c**[b]	—	—	58a
155b	CO	excess	5	**157/158**	1.06	—	58a
156b	CO	excess	5	**159/158**	1.26	—	58a

(a) Ethereal DAM, 0–5°.
(b) **155b** and **156b** were formed upon hydrolysis. Experimental details were not given.

was found that no more than one carbon was inserted adjacent to the carbonyl(s) of **154** with or without methanol catalysis. The greater reactivity of the 5-membered rings of **154** than the 6-membered rings of **157–159** is a reversal for these caged structures of the normal DAM reactivity order, cyclohexanone > cyclopentanone. (Note Section IIA1a.) It was suggested that the homologous 7-membered ketones must have quite large strain due to inclusion in the cage systems of a bicyclo[2.2.0] hexane moiety; thus insertion could be expected to stop at the 6-membered ketone stage. This argument implies reversibility in the addition of DAM to the 6-membered ring carbonyl. It is also possible that addition of DAM to the 5-membered ring carbonyl is considerably more facile. Only a slight regiochemical preference for **155a,b** over **156a,b** was observed in the carbon insertion reactions with the substrates **154a,b** shown in Table II.

The unusual aldol dimers **160/161**, **164**, **167**, and **170** accompanied the normal products of one carbon ring expansion (Table III) when excess ethereal DAM was reacted with the strained caged ketones **154a**, **162** (1,4-bishomocubanone), **165** (homocubanone), and **168**. Hirao, Yonemitsu *et al.*[58] have shown that the aldol products are not the result of mixed aldol condensations between product and starting ketones, but arise because of uniqueness of the strained cage molecules. A mechanistic rationale for dimer formation is shown in Scheme 2.

Although strain increases the electrophilicity of the carbonyl group in each of the cage sructures in Table III, strain decreases the likelihood of rearrangement of intermediate I (path c) and also the propensity for epoxide formation (path a). An alternative process (path b), which involves a proton shift to oxygen and regeneration of diazoalkane intermediate II, becomes competitive. The diazoalkane II attacks a second molecule of substrate to then generate the aldol dimer. In mechanistic studies using **162** and DAM in 15:1 ether/methanol solvent, formation of dimer **164** could be suppressed. The betaine intermediate I is trapped upon protonation by external methanol (path d) to generate intermediate III before internal proton exchange to intermediate II (path b) can occur. Intermediate III rearranges to afford carbon insertion product **163**. The importance of strain in



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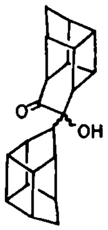

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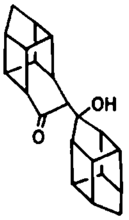
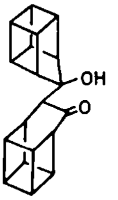
161



164



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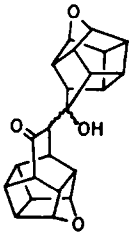
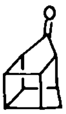
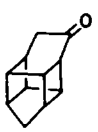
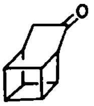
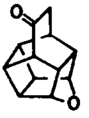
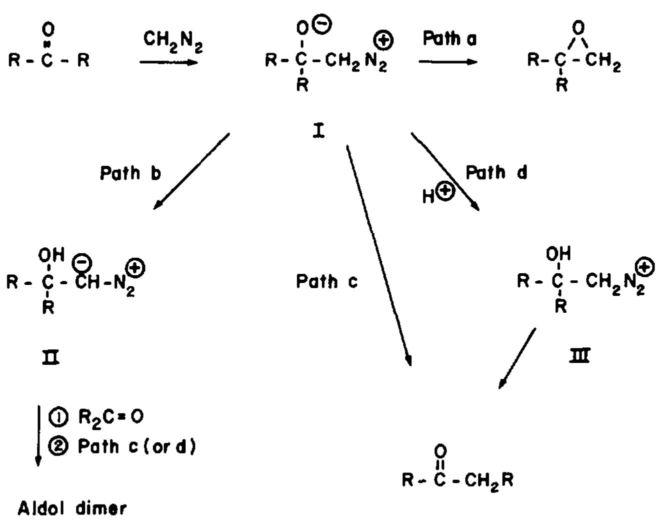


170

Table III. Ethereal DAM reactions with selected cage substrates (5°C). (58)

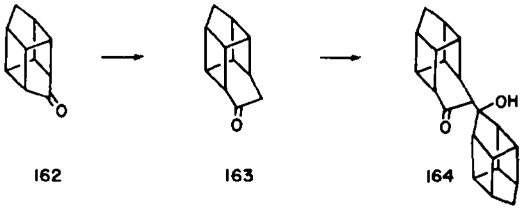
Substrate	Time (hr)	Product Ketone (%)	Aldol Dimer (%)
154a 	24	155a + 156a (47)	160 + 161 (43)
162 	16 20(a)	 (37) (70) 163	164 (32) 164 (4)
165 	22	 166 (55)	167 (28)
168 	96 (b)	 169 (36)	170 (35)

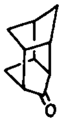
(a) Ether/MeOH, 15 : 1 ; (b) THF/Ether, 15 : 1, 25°.



Scheme 2. Reaction Pathways from DAM—Carbonyl Adducts.

dimer formation is shown by the failure of **171**[58a] to afford dimer upon reaction with DAM under the same conditions as used for the substrates in Table III; actual products or yields from reaction of **171** with DAM were not reported.

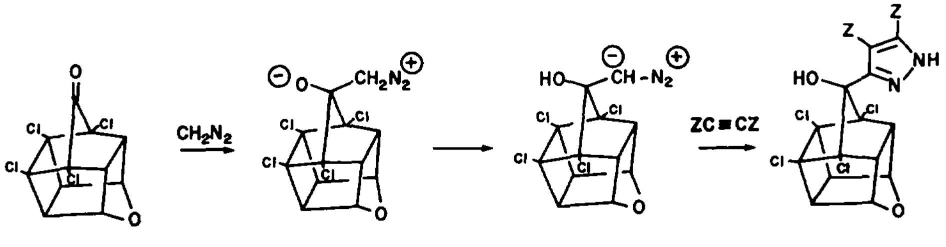




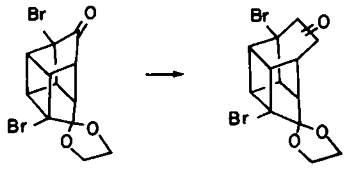
171

4. *Functionalized polycycles*

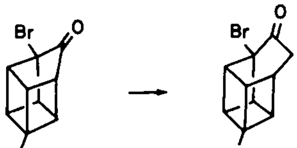
The cage structure **172** could be converted to the unusual heterocycles **175** (hydroxyl epimers) following reaction with excess DAM in ether for 24 hr at 0–5° to give the addend **173**. The chlorine atoms retard rearrangement of intermediate **173** to give either carbon insertion or epoxide products. Intermediate **173** can rearrange by proton exchange to give **174**, but dimer formation via intermediate **174** is also retarded by the chlorine atoms.[59] It was possible for **174** to be trapped with dimethylacetylenedicarboxylate to form the heterocycles **175**.[58]



Homocubanones **176** and **178** have been converted by van Seters *et al.*[60] to functionalized basketanes by cage expansion. The polycycle **176** with ethereal DAM at 0° for 3 days afforded a one carbon ring expansion product **177** of undetermined regiochemistry. The related ring contracted ketones **178** with excess ethereal DAM at 0° for 3 days afforded solely the products **179** (45–50% yields) following migration of the bridgehead away from bromine.[59] Addition of boron trifluoride etherate or methanol had no effect upon either rates or product compositions.



176 177



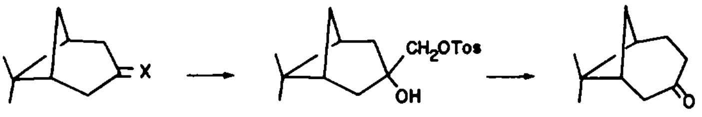
178 179

(a) R = CO_2Me; (b) R = Br; (c) R = Me

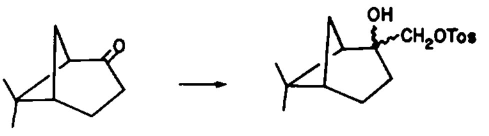
III. BICYCLO[3.1.1]HEPTANONES

(A) 2-(3)-*Oxo-isomers*

Using the Corey procedure[61] for pinacolic rearrangements, Tubiana and Waegell[62] prepared 7,7-dimethylbicyclo[4.1.1]octan-3-one **182** from the monotosylated diol **181**. The methylene derivative **180b**, formed from isonopinone **180a**, was treated sequentially with osmium tetroxide, toluenesulfonyl chloride/lithium chlorate (cat.) to give **182** in 18% overall yield from **180b**. The same procedure failed to afford ring expansion product when applied to the monotosylate **184** prepared from nopinone **183**. DAM generated *in situ* from N-methyl-N-nitrosourethane in methanol also failed to ring enlarge **183** or the related structures **3** or **4**[9] (Section IA).



180 a X = O
180 b X = CH_2
181
182

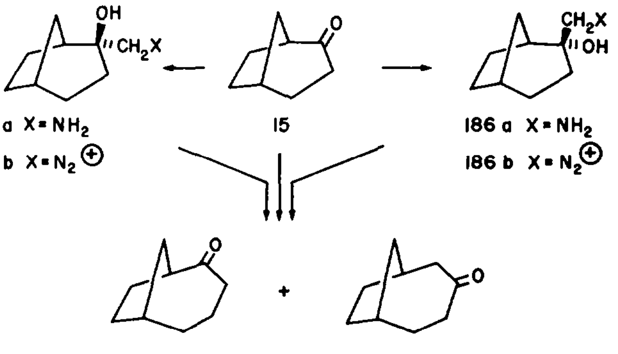


183 184

IV. BICYCLO[3.2.1]OCTANONES

(A) 2-*Oxo-isomers*

In competitive experiments utilizing DAM (0.1 or 0.06 equivs) in ether/methanol[14,17] bicyclo[3.2.1]octan-2-one **15** afforded methylene migrated product **17** twice as readily as bridgehead migrated product **18**. Pietra *et al.*,[17] in their study of the relationship between leaving group configuration and the regiochemistry of bond migration for the Tiffeneau–Demjanov reactions of 3-*endo*-aminomethyl-3-*exo*-hydroxy-bicyclo[3.2.1]octane **185a** and 3-*exo*-aminomethyl-3-*endo*-hydroxy-bicyclo[3.2.1]octane **186a**, found a 52:48 ratio of **17**:**18** from the diazonium ion **185b** and a 90:10 ratio of **17**:**18** from diazonium ion **186b**.[63] These workers concluded that the product distribution from the DAM reaction more closely resembles that from rearrangement of diazonium ion **185b**, formed by equatorial attack of DAM on **15**; however, it appears that DAM addition to **15** is not highly stereoselective.



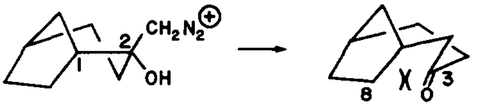
185 a $X = NH_2$
185 b $X = N_2^{\oplus}$

15

186 a $X = NH_2$
186 b $X = N_2^{\oplus}$

17 + 18

To explain the regioselectivity observed in rearrangement of **186b** to give mainly **17**, Pietra *et al.*[17] postulated that during the migration of the C1–C2 bond interactions arise between the developing C–8 and C–3 atoms of the product **18**. Migration of the C2–C3 bond of **186b** does not involve any strong steric compression. The small excess of methylene migration from **185b**, in which a slight preference for migration of tertiary carbon was expected,[28] was not rationalized.

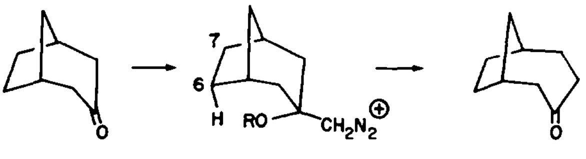


186b 18

(B) 3-*Oxo-isomers*

1. *Parent*

Boron trifluoride etherate catalysis was needed to facilitate reaction of bicyclo[3.2.1]octan-3-one **16** with DAM.[14] The lack of reactivity of **16** toward DAM has been attributed to repulsive interactions between the oxygen atom and the two *endo* hydrogens at C—6 and C—7 in the transition-state for rearrangement of intermediate **187**. However, the lack of reactivity is more likely due to difficulty in formation of **187**, since Hartman[63] has carried out the Tiffeneau–Demjanov ring expansion of **188** to give **18** in 60% yield. (Note ref. 64.)



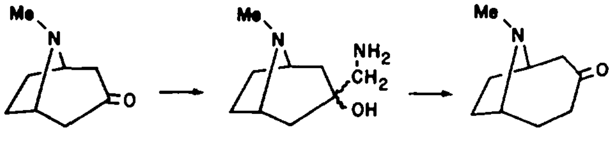
16

187 $R = \overset{\ominus}{B}F_3$
188 $R = H$

18

2. *Heterocyclic analogs*

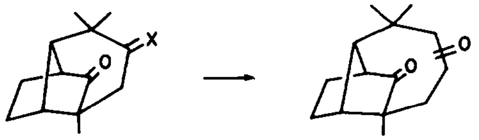
Cope *et al.*[65] have ring enlarged the 3-aminomethyl-3-hydroxy derivative **190**, formed from N-methyltropinone **189**, using nitrous acid in acetic acid. Homotropinone **191** was formed in 57% yield.



189 190 191

3. *Bridged tricycles and polycycles*

As part of a synthetic approach to longifolene, McMurray and Isser[43c] needed to expand the large ring of the tricyclic diketone **192a** by one carbon atom. No reaction of **192a** with a large excess of DAM was observed, even with aluminum chloride catalyst. When reaction of the *exo*-methylene derivative **192b** with cyanogen azide (10 eq) at 60° for 2 days gave only 10% yield of a mixture of ketones **193**, an alternative ring expansion method, based upon reaction of dibromocarbene with the endocyclic olefin **192b** derived from **192a**, was utilized in the route to longifolene.

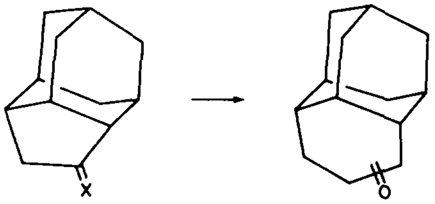


192a X=O 193

192b X=CH$_2$

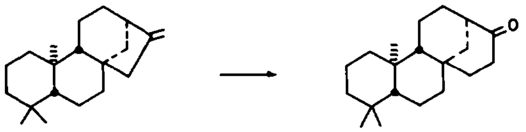
(C) 6-*Oxo-isomers*

The cage ketone **194** was converted by Schleyer *et al.*[21] to its *exo*-methylene derivative **195**, which was ring expanded with aqueous thallium perchlorate to a mixture of ketones **196** of undetermined ratio in 49% yield. Some α-hydroxyketone was obtained from further oxidation of **196** (Section IVD). Similarly, thallium nitrate was utilized by Fujita and Ochiari[66] to ring expand the tetracyclic diterpene **197**. Methylene migrated ketone **198** was isolated in 33% yield as the only ring expanded product.



194 X=O 196

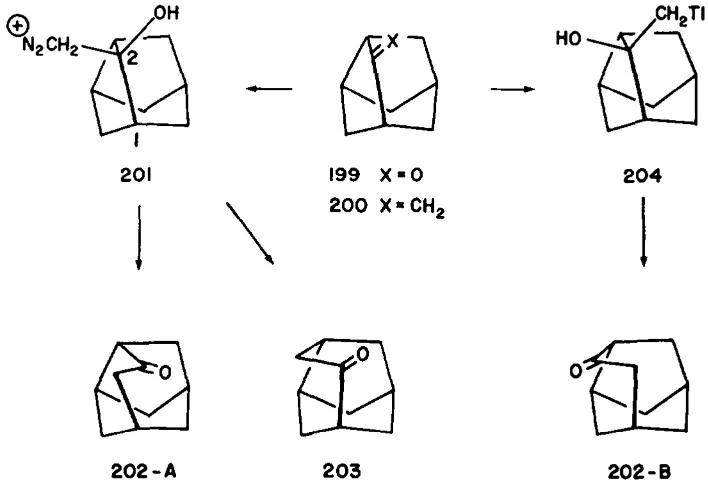
195 X=CH$_2$



197 198

(D) 8-*Oxo-isomers*

Schleyer *et al.*[67] have developed regioselective syntheses of 4- and 5-protoadamantanones **202** and **203** from 2-noradamantanone **199**. DAM in methanol–water attacks **199** from the less hindered *exo* face to form **201**, which provides solely **178** in 90–96% yield. Force field calculations on protoadamantane indicate that the conformation of protoadamantane similar to **202-A** is about 6 kcal/mole higher in energy than the conformation of protoadamantane resembling **203**. Conformer **202-A** is formed by migration of the C1–C2 bond in intermediate **201**, while conformer **203** is formed by migration of the C2–C3 bond of **201**. In order to form solely the 4-keto isomer **202**, Schleyer *et* *al.*[67] utilized an alternative ring enlargement route. Ketone **199** was converted to the *exo*-methylene derivative **200**. This olefin was reacted with aqueous thallium perchlorate to afford intermediate **204**. Since attack of water at C2 occurs from the less hindered *exo* face of **200**, the hydroxyl group in **204** is epimeric with that of intermediate **201**, obtained in the DAM reaction with **199**. Migration of the C1–C2 bond of **204** is now favored because conformer **202-B** is not unduly strained as is **202-A**.

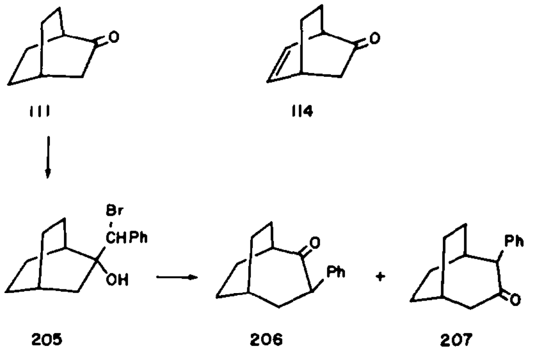


V. BICYCLO[2.2.2]OCTANONES

(A) 2-*Oxo-isomers*

1. *Parent*

No ring enlarged products have been identified from DAM reaction with bicyclo[2.2.2]octanone **111**, although Bly *et al.*[13] have prepared **111** by ring enlargement of 7-norbornanone **110** using DAM (1.5 eq) and there was gas chromatographic evidence for other components in the reaction mixture (Section IIB1). Bicyclo[2.2.2]octanone **111** has been ring expanded by Sisti and Rusch[36] via thermal rearrangement of the magnesium salt of halohydrin **205**, formed from **111** (Section IIA1a). Reaction of **205** with isopropylmagnesium bromide and thermolysis of the resulting salt in refluxing benzene afforded **206** (43%) and **207** (20%). Preferential migration of the C2–C3 bond to form **206** was attributed to relief of torsional eclipsing strain or, in the alternative, to least motion arguments[68] (Section IIA1a). (Note also ref. 19.)

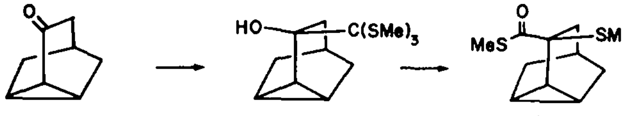


2. *Dehydroderivatives*

Bly *et al.*[13] did not isolate higher carbon insertion products from ring enlargement of bicyclo[2.2.2]octenone **114** obtained upon reaction of norbornen-7-one **113** with DAM (1.5 eq) (Section IIB2). (Note also ref. 19.)

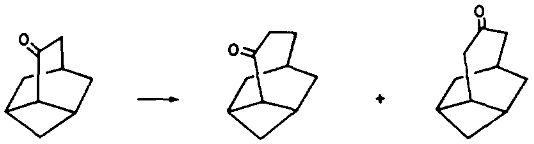
3. *Bridged tricycles and polycycles*

Ring expansion of 3-homonortricyclanone **119** was attempted by Israel and Murray[49] using the Knapp procedure[30] [Sections IIA1b and IIB3]. S-methyl 3-(methylthio)tricyclo[3.2.1.0^{2,7}]octane-3-carbothioate **209** was obtained in 68% yield as the only isolable product from intermediate **208**.



119 208 209

Sosnowski and Murray[52] have carried out the Tiffeneau–Demjanov ring expansion of the 6,7-methylene-bridged bicyclo[2.2.2]octan-2-one **210** and have found a 3:1 preference for methylene migration to give **211** rather than bridgehead migration to give **212**. The total yield of **211** and **212** following sequential reaction of **210** with trimethylsilylcyanide, lithium aluminum hydride, and nitrous acid was only 20%.



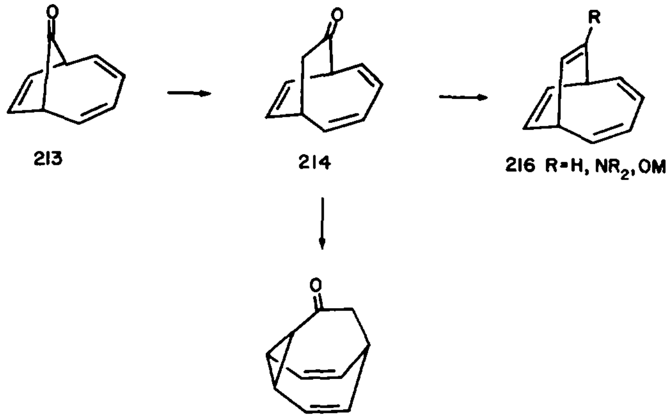
210 211 212

The two-carbon bridges of a number of cage structures **155a**, **156a**, **157–158**, **163**, **166**, **169**, **177**, and **179** have been found by Hirao and Yonemitsu[57,58] or by van Seters *et al.*[60] to be resistant to further ring enlargement using DAM (Sections IIB3, Tables II and III; IIB4.) However, the Nakazaki group[53a–c] has expanded the twisted bicyclo[2.2.2]octanones **136a–140a** and **143a**, as described in Table I (Section IIb3), to form bicyclo[3.2.2]nonanone systems **136b–140b** and **143b** as part of more complex polycycles. Since the target molecules were the corresponding hydrocarbons, the regiochemistry of the carbonyl groups for the carbon insertion products was not determined in those cases in which symmetry did not negate the question of migratory aptitude. As noted in Table I, ring expansion of these ring systems is aided by boron trifluoride catalysis or by using a large excess of DAM and long reaction times.

VI. BICYCLO[4.2.1]NONANONES

(A) 9-*Oxo-isomers*

Bicyclo[4.2.1]nona-2,4,8-trien-7-one **213** was converted by Press and Shechter[69] to bicyclo-[4.2.2]deca-2,4,9-trien-7-one **214** utilizing DAM (LiCl catalyst) in methanol/ether. Diverse aspects of the chemistry of **214** were described; for example, **214** was rearranged to the fluctional structure bullvalone **215** upon irradiation in acetone through Vycor optics, and **214** was converted to bicyclo-[4.2.2]deca-2,4,7,9-tetraene and various 7-substituted analogs **216**.

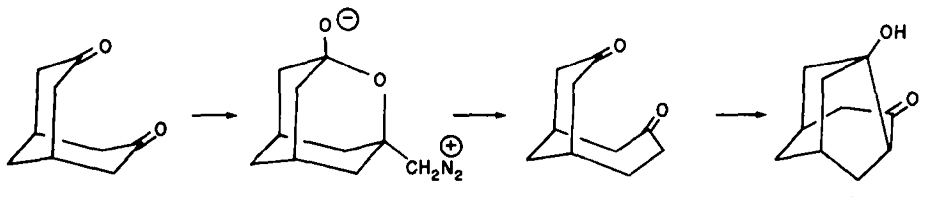


215

VII. BICYCLO[3.3.1]NONANONES

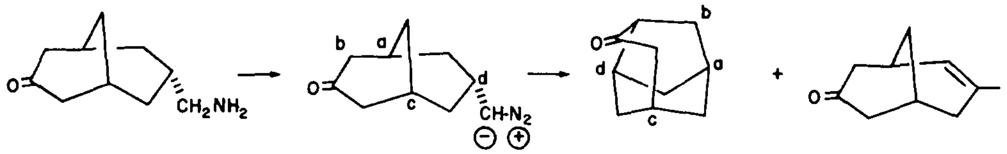
(A) 3-*Oxo-isomers*

Bicyclo[3.3.1]nonan-3,7-dione **217** was reacted with DAM to afford quantitatively **219**, the product of single carbon insertion. Oxaadamantane **218** postulated by Momose *et al.*[70] to be an intermediate in this selective transformation. Diketone **219**, upon intramolecular aldol condensation, afforded the tricyclodecanol **220**.



217 218 219 220

Diazotization of *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one **221** using 1 : 1 isoamyl nitrite/acetic acid in aprotic benzene medium afforded principally 4-protoadamantane **202** (67%) in addition to olefin **223** (20%). One mechanism for formation of **202** proposed by Liu and Koviac[71] involves the intramolecular insertion of a diazoalkane upon the carbonyl group of **222**.

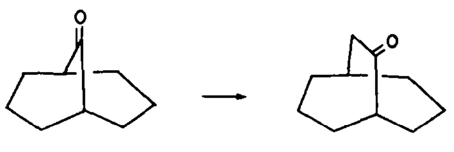


221 222 202 223

(B) 9-*Oxo-isomers*

1. *Parent*

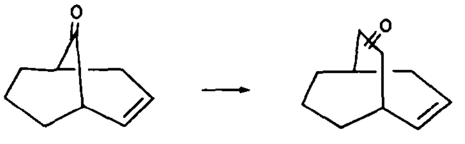
Leonard *et al.*[72] have converted bicyclo[3.3.1]nonan-9-one **224** to bicyclo[3.2.2]decan-9-one **225** (60% yield) with methanolic DAM (2 eq), generated *in situ* from Diazald and potassium hydroxide. No further ring enlargement of **225** with DAM was found. (Section XIA1 for further chemistry of **225**.)



224 225

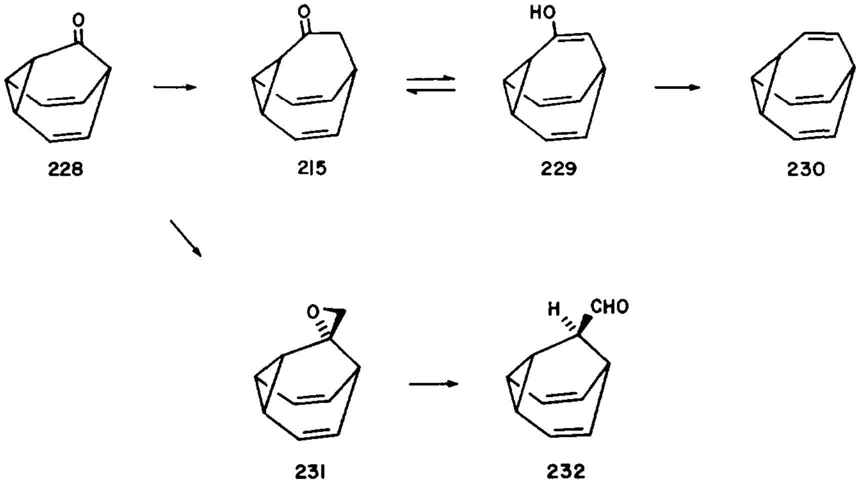
2. *Dehydroderivatives*

Bicyclo[3.3.1]non-2-en-9-one **226** and methanolic DAM in strongly basic solution afforded a mixture of ring expanded ketones **227** (60% yield).[72] (Section VIB1; see XIA2 for further chemistry of **227**.)



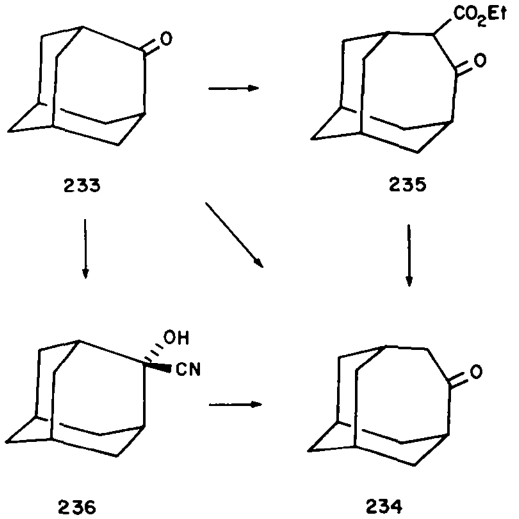
226 227

Doering *et al.*[73] in 1967, as part of their ring expansion route from barbaralone **228**, through bullvalone **215**, to bullvalene **230**, reacted **228** with ethereal DAM containing methanol for 18 hr at 0° to obtain **215** (25%) and an aldehyde **232** (24%). The latter aldehyde is presumably an artifact of the epoxide **231**, formed from **228** and DAM. Since all ten hydrogens of **215** exchange deuterium in dilute alkaline deuterium oxide, **215** must be in equilibrium with its enol (or enolate) isomer **229**, which is capable of undergoing the bullvalene rearrangement.



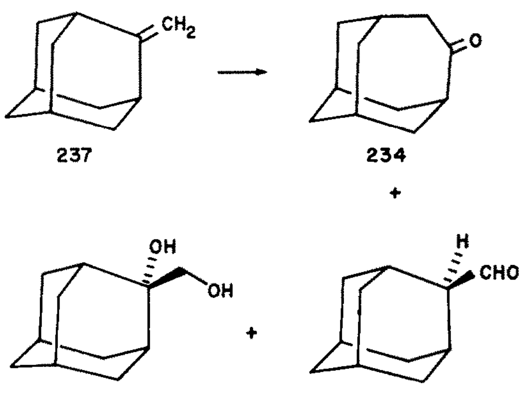
3. *Bridged tricycles and polycycles*

Adamantanone **233** has been converted to homoadamantanone **234** with ethereal DAM (8–10 eq) using boron trifluoride catalysis.[74] *In situ* generation of DAM in the absence of Lewis acid from Diazald using aqueous methanolic potassium hydroxide avoided formation of undesirable side products derived from cationic rearrangements and provided **234** from **233** in 87–92% yield.[74,75]



Ethyldiazoacetate (1.7 eq) was inserted into adamantanone **233** to provide 3-carbethoxy-2-oxo-tricyclo[4.3.1.1^{4,8}]undecane **235**. Using triethyloxonium fluoroborate (3 eq) catalyst for 4 hr at 24°, Mock and Hartman[27] obtained homoadamantanone **234** from **235** by hydrolysis. Although there was incomplete conversion of **233** to **235** under the chosen reaction conditions, no oxirane was formed and only a single carbon insertion occurred. Adamantanone **233** was also converted to homoadamantanone **234** (90% yield) using the Tiffeneau–Demjanov route. Synthesis of the requisite cyanohydrin **236** with hydrogen cyanide did not present difficulty.[76]

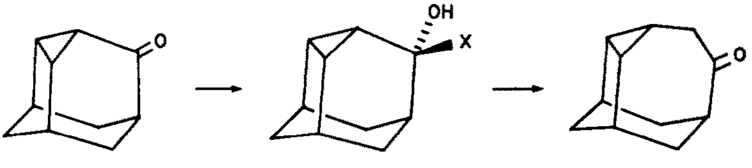
Aqueous thallium perchlorate in 1,2-dimethoxyethane converted the *exo*-methylene derivative **237**, prepared from **233** by a Wittig reaction, to homoadamantanone **234** in only 15–20% yield. The other major products from this reaction were 1,2-diol **238** (50%) and an acetal (18–20%) formed from diol **238** and aldehyde **239**.[21] (See also Sections IIA1a and IVD.) The increase in ring strain in going from **237** to **234** hinders the expansion by this route.



237 234

238 239

Preferential migration of the carbon bonded to cyclopropyl has been observed by Murray and Ford[77] in the Tiffeneau–Demjanov rearrangement of **241b** to afford 2,11-dehydro-5-homoadamantanone **242** (70%) (Section IIB3). The requisite **241b** was prepared from 8,9-dehydro-2-adamantanone **240** using the trimethylsilylcyanide procedure of Evans *et al.*[42]



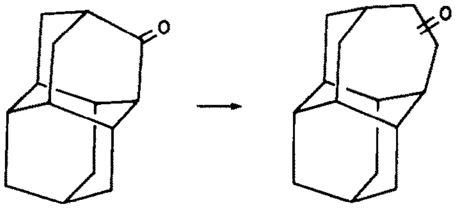
240

241 a X = CN

241 b X = CH_2NH_2

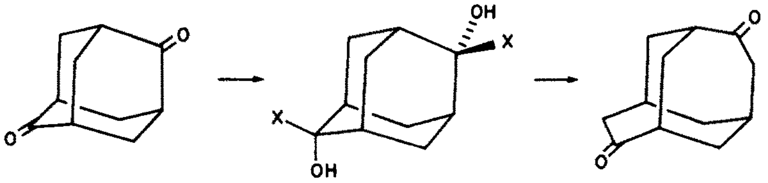
242

Diamantanone **243** has been reacted by Schleyer *et al.*[78] with DAM, generated *in situ* from Diazald in aqueous methanolic potassium hydroxide. A 1 : 1 mixture of homodiamantanones **244** (96%) was formed.



243 244

Gerlach[79] synthesized tricyclo[4.4.1.1^{3,8}]dodecan-4,9-dione **247**, a 1,5-bishomoadamantane derivative, from 2,6-adamantanedione **245**. The dicyanohydrin **246a**, prepared from **245** using diethyl aluminum cyanide in toluene, an earlier alternative to the procedure of Evans *et al.*,[42] was reduced with lithium aluminum hydride to form aminoalcohol **246b** (85%). Treatment of **246b** with nitrous acid afforded **247** (65%). Skare and Majerski[80] carried out the transformation **245** to **247** much more simply and in 80% yield using methanolic DAM.



245

246 a X = CN

246 b X = CH_2NH_2

247

VIII. BICYCLO[3.2.2]NONANONES

(A) 2(3)-*Oxo-isomers*

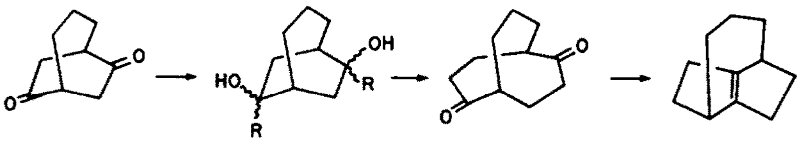
1. *Bridged tricycles and polycycles*

The bicyclo[3.2.2]nonan-2(3)-one structure is found in the polycycles **136b**, **137b**, **139b**, and **140b**, which have been ring expanded by Nakazaki *et al.*[53a–c] using DAM in ether as described in Table I (Section IIB3).

(B) 6-*Oxo-isomers*

1. *Functionalized derivatives*

Borden, Clardy *et al.*[81] have prepared the torsionally strained tricyclo-[3.3.3.0^{2,6}]undec-2(6)-ene **251**, a *trans*-cycloheptene derivative, by a sequence which began with the available bicyclo-[3.2.2]nona-6,8-dione **248**. DAM failed to react with diketone **248**, but the bis-aminomethyl alcohol **249b** could be formed by bis-addition of isocyanomethyllithium to give **249a** and subsequent hydrolysis. Nitrous acid treatment of **249b** afforded **250** in 87% yield. Diketone **250** was converted to olefin **251** by transannular pinacolic ring closure, thiocarbonate formation of the resultant diol, and thermolysis of the thiocarbonate. Olefin **251** was not isolated, but was trapped as is diphenylbenzofuran cycloadduct or, following intermolecular dimerization, as a mixture of an ene dimer in equilibrium with a 1,3-proton shift isomer.



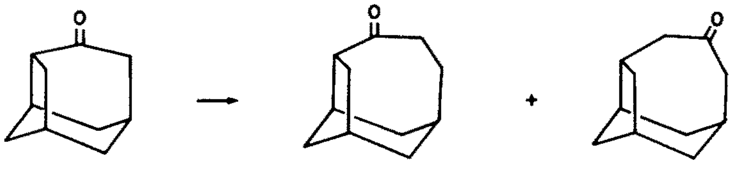
248

249 a R = CH_2NC
249 b R = CH_2NH_2

250

251

Sosnowski and Murray[52] have ring expanded 4-protoadamantanone **202** by treatment with trimethylsilylcyanide followed by lithium aluminum hydride and then nitrous acid. The Tiffeneau–Demjanov procedure gave a 4 : 1 mixture of methylene migrated ketone **252** and bridgehead migrated ketone **253** in 50% overall yield.



202

252

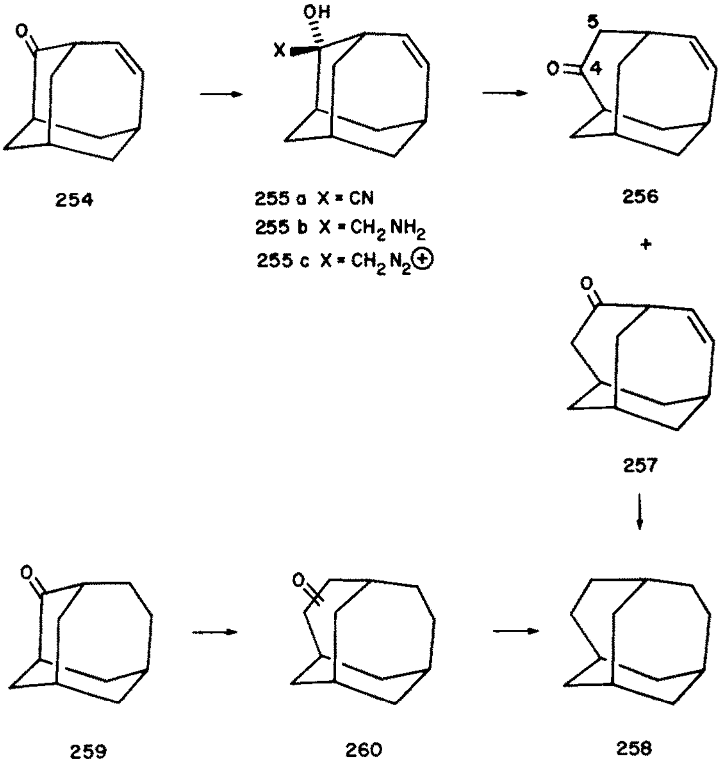
253

IX. BICYCLO[4.3.1]DECANONES

(A) 10-*Oxo-isomers*

Polley and Murray[82] prepared 1,3-bishomoadamantane **258** by a Tiffeneau–Demjanov ring expansion route beginning with homoadamant-4-en-2-one **254**. The cyanohydrin **255a**, formed from **254**,[42] was reduced to aminoalcohol **255b**. The configuration assigned to **255b** was based upon the assumption that the stereochemistry of cyanohydrin formation would mirror the known stereochemistry of sodium borohydride reduction of **254**. Nitrous acid rearrangement of **255b** afforded **256** (90%) and **257** (10%), which could be converted by standard reductive pathways to **258**. The preferred reaction pathway from **255c** of a 1,2-shift of the allylic carbon to afford **256** was attributed to lower conformational strain in the migration of C3 relative to C1; the argument parallels that made by Schleyer *et al.*[67] for the transformation of **201** to **203** (Section IVD). Saturated homoadamantanone **259** was similarly rearranged to an inseparable mixture of ketones **260** (70%

yield), highly enriched in the 4-ketoisomer. These ketones **260** also were converted to 1,3-bishomoadamantane **258** by standard methods.



254

255 a X = CN
255 b X = CH_2NH_2
255 c X = $CH_2N_2^{\oplus}$

256
+
257

259 260 258

X. BICYCLO[4.2.2]DECANONES

(A) 2(3)-*Oxo-isomers*

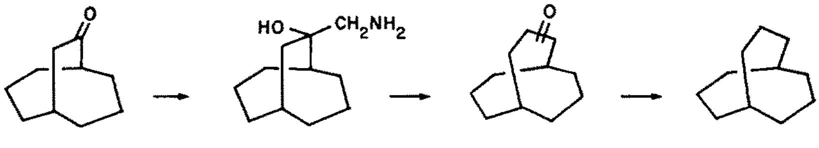
Bicyclo[4.2.2]decan-2-(3)-one **136c**, **137c**, and **140c** have been ring expanded using DAM in ether as described in Table I[53a–c] (Section IIB3).

XI. BICYCLO[3.3.2]DECANONES

(A) 9-*Oxo-isomers*

1. *Parent*

Leonard *et al.*[72] did not observe reaction of bicyclo[3.3.2]nonan-9-one **225** with DAM in methanol, even in the presence of boron trifluoride etherate. However, they were able to ring expand aminoalcohol **261** using the Tiffeneau–Demjanov procedure to afford a 2 : 1 mixture of 2- and 3-oxo isomers **262** (yield not reported). After failure to **225** to react with hydrocyanic acid, nitromethane, or the Corey epoxidation reagents, synthesis of aminoalcohol **261** was achieved finally through a

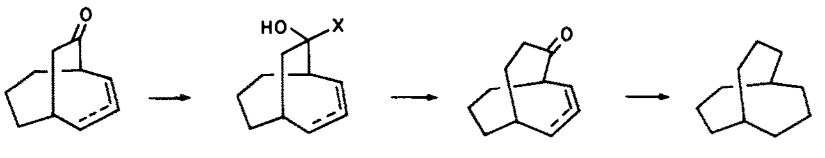


225 261 262 263

sequence from **225** of Wittig methylenation, epoxidation, sodium azide/boric acid in DMF ring cleavage, and catalytic hydrogenation. Wolff–Kishner reduction of **262** afforded bicyclo[3.3.3]-undecane (manxane) **263**, a C_{3h} hydrocarbon which undergoes degenerate ring inversions.

2. *Dehydroderivatives*

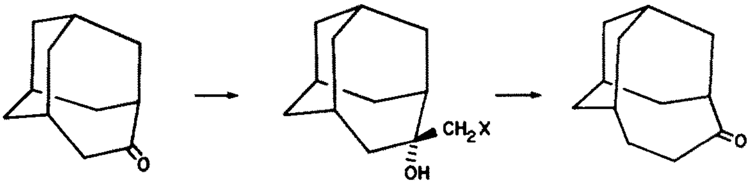
Manxane **263** also has been prepared by Parker *et al.*[83] via a Tiffeneau–Demjanov ring enlargement from a mixture of bicyclo[3.3.2]dec-2-en-9(10)-ones **227** (Section XIA1). Addition of hydrogen cyanide to **227** gave **264a** in a moderate 40% yield. Acetylation of **264a** followed by lithium aluminum hydride reduction and reaction of **264b** with nitrous acid afforded a 1 : 1 mixture of methylene-migrated ketones **265** (yield not reported), which were converted to manxane **263**.



227 264 a X = CN 264 b X = CH_2NH_2 265 263

3. *Bridged tricycles and polycycles*

Homoadamantanone **234**, upon conversion to 4-aminomethyl-4-hydroxyhomoadamantane **266a** and subsequent treatment with nitrous acid, has been ring expanded by Sasaki *et al.*[84] to 1,1-bishomoadamantan-4-one **267** (64%) accompanied by 5-methylhomoadamantan-4-one **268** (9%). No more than 3% of the isomeric 1,1-bishomoadamantan-5-one **269**, the result of bridgehead migration, could have been formed in this reaction. The mechanism for formation of α-methylketone **268** from diazonium ion **266b** has been suggested to involve either a protonated cyclopropane intermediate or a 1,3-hydride shift followed by methyl migration. The preference for methylene migration from **266b** to afford **267** has been attributed to a conformational effect, which probably refers to relief of eclipsing strain during methylene migration (Sections IA and IIA1). The ring system **267** has also been synthesized by a Wagner–Meerwein route.[84]



234 266 a X = NH_2 266 b X = N_2 ⊕ 267

+

269 268

XII. BICYCLO[5.2.2]UNDECANONES

(A) 2(3)(4)-*Oxo-isomers*

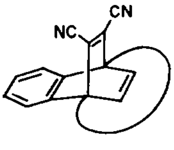
Structures **137d** and **140d** have been ring expanded to their next highest homologs as described in Table I[53b–c] (Section IIB3).

XIII. BICYCLO[8.2.2]TETRADECANONES

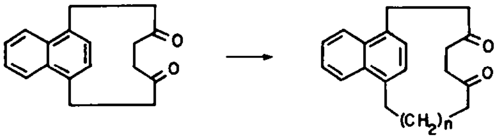
(A) 4-*Oxo-isomers*

Wiberg *et al.*,[85] as part of an effort to prepare carbon atoms distorted toward square planar or pyramidal geometries, endeavored to synthesize the paddlane **270**. The planned route to **270**, a molecule with four nonzero bridges between a pair of bridgehead atoms, was by cycloaddition of

[9](1,4)naphthalenophane **273a** with dicyanoacetylene. In the route to **273a**, the diketone **271** was reacted with ethereal DAM (28 eq) in chloroform/ethanol for 15 days to provide a 26 : 63 : 11 mixture of **271**, **272a**, and **272b**, identified by molecular mass measurements. The regiochemistry of carbon insertion was not determined in any case. Wolff–Kishner reduction of the mixture and gas chromatographic separation provided **273a** in less than 10% yield. Unfortunately, **273a** reacted only on the unsubstituted ring with dicyanoacetylene to give **274**.

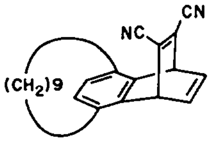


270

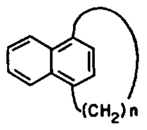


271

272 a n = 1
272 b n = 2



274



273 a n = 9
273 b n = 10

CONCLUSIONS

A number of generalities have emerged from this survey. DAM ring expansions of bridge bicyclic ketones have been found to be facilitated by Lewis acid catalysts, which at the same time further suppress the minimal amount of oxirane formation observed with strained ring systems. Bridged bicyclanones having a carbonyl group adjacent to a bridgehead are generally more reactive than otherwise, but the preference is for methylene rather than bridgehead migration. The regiochemistry of carbon migration is largely dependent upon conformational, rather than electronic factors. Relief of eclipsing interactions, preference for chair-like over boat-like transition-states, and least motion arguments have been suggested to be the dominating factors which account for the general methylene migratory aptitude. Either over-reaction, for some reactive systems, or lack of reactivity with DAM can be occasional problems. Single carbon insertions have been found to be possible under aprotic reaction conditions without Lewis acid catalysis, or when using α-substituted diazoalkanes, or occasionally because the ketone products are unreactive. For less reactive systems large excesses of DAM and Lewis acid catalysts have often led to successful methylene insertion.

A number of alternatives to DAM ring insertions have been developed which overcome the reactivity problems of DAM. Dibromomethyllithium addition to a ketone followed by rearrangement of the resultant dibromomethyl alcohol with n-butyllithium via a β-oxidocarbenoid has been successful.[11] The Tiffeneau–Demjanov reaction also inserts a single carbon atom and synthesis of the requisite aminomethyl alcohols has succeeded with numerous carbonyl compounds which have failed to react with DAM; trimethylsilylcyanide[42] and isocyanomethyllithium[81] as aminomethyl equivalents have been especially useful advances in this area. Stereoisomeric aminomethyl alcohols have been found to give different ratios of regioisomeric ketones upon Tiffeneau–Demjanov ring expansion. Thus, by separation of isomers of derivatized cyanohydrins a measure of regioselection is available; certainly greater regioselectivity is possible than that found in DAM reactions which attack both faces of the carbonyl group. However, the Tiffeneau–Demjanov reaction has not been found to be a solution to the regioselectivity problem, since the transition-state for reaction, discounting solvent or catalyst effects, mirrors that of a stereochemically analogous DAM ring enlargement.

There are several alternative ring expansion methods which often give highly regioselective carbon insertions. Oxidative rearrangements of exo-methylene derivatives with thallium(III) salts[21,66,67] allows formation of a β-hydroxycarbinyl cation equivalent, which is epimeric with that formed by addition of DAM to a ketone. In several cases in which the regiochemistry of carbon insertion was strongly a function of hydroxyl stereochemistry, regioselective formation of ring expanded ketones was observed. The thallium(III) oxidations appear to be useful for ring expansion of 5-membered rings, but are less favorable when applied to 6-membered rings where yields are limited by side reactions.[21]

Thermal decomposition of the adducts of *exo*-methylene compounds with *p*-nitrophenylsulfonyl azide,[25] or of the anions of bromohydrins,[23] has resulted in ring expansions involving totally regioselective methylene migrations in several, but not all, cases. The same conformational factors, which favor methylene migration in DAM and Tiffeneau–Demjanov ring enlargements, also are dominant in these alternative methods.

Given the nearly uniform preference for methylene migration of the above described carbon insertion methods, regioselective formation of a bridgehead migrated ketone upon reaction of the *exo*-tris(thiomethyl)methyl addition product of norbornan-2-one **49** with tetrakis(acetonitrile)-copper perchlorate is significant.[30] Unfortunately, the method so far has not been successful for ring expansion of bridged 6-membered ring ketones, which lack angle strain and torsional strain needed to drive this ring expansion reaction.[30a,49] Also notable is the preference for bridgehead migration in an intramoleculear diazoalkane ring expansion to give **95**. (See also ref. 19.)

Trimethylsilyldiazomethene has recently been reported as a thermally stable and safe substitute for DAM.[86] Ketones undergo homologation in the presence of boron trifluoride etherate in yields generally superior to DAM and the carbon is inserted selectively from the less hindered side of the ketone. The method has not been applied to bridged bicyclic ketones, but its selectivity appears promising. Ring enlargement procedures which might be applied to bridged bicyclic ketones include: metal catalyzed decompositions of lithiodiazoacetate adducts,[87] lithium/diiodomethane homologations,[88] and silver tetrafluoroborate or thallium ethoxide in chloroform catalyzed reaction of β-hydroxyselenides having two alkyl groups on the selenium bearing carbon.[89] Ring expansions which have been applied to cyclobutanones and which might be applied to strained bicyclic ketones include: lithium halide catalyzed rearrangements of the epoxides of *exo*-methylene derivatives,[90] silver fluoroborate catalyzed rearrangements of chlorohydrins derived from *exo*-methylene derivatives,[89c] treatment of 1-methylsulfinyl-1-(methylthio)alkylcycloalkanols with acid,[91] and rearrangement of the oxyanions of 1-(phenylselenoxy)alkylcycloalkanols.[92] A novel one-carbon ring enlarged cyclopropanation or β-vinylation reaction of cyclic β-ketoesters or β-ketosulfones has been described.[93] Some recent one-carbon ring expansions, based upon formation and opening of cyclopropanes, utilize enolsilanes[19] or allyl alcohols.[94]

It is unfortunate that this review could not touch upon all the possible one-carbon ring expansion methods available for bridged bicyclic systems, not to mention the multitude of two-carbon and multi-carbon insertion methods now available. The population explosion predicted by Gutsche and Redmore[1] truly has occurred.

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