Strained Bridgehead Cage Alcohols and Derivatives

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Contents

I. Introduction

Rigid alicyclic compounds provide ideal systems for investigating interactions between nonbonded atoms and for studying stereochemical and mechanistic aspects of organic reactions. They often serve as models to provide insight into complex chemical phenomena in various areas of chemistry. An intriguing part of alicyclic chemistry has been, and still is, the synthesis and study of highly strained polycyclic ring systems. The discovery of the intramolecular photochemical [$\pi^2 + \pi^2$]-cycloaddition reaction as a powerful and convenient tool for the synthesis of highly strained cyclobutane-containing polycycles, about 3 decades ago,[1] constitutes the beginning of a new era in organic alicyclic chemistry. Most of these photochemical reactions lead to space-enclosing molecules that have since been denoted as "cage" compounds.[2] Examples that are considered as the classical reactions in this area are the norbornadiene–quadricyclene conversion[1] (eq 1) and the photoisomerization of the cyclopentadiene–quinone Diels–Alder adduct to the pentacyclic dione[3] (eq 2) (Scheme 1).

Strained polycyclic cage compounds appeal to the imagination of many chemists because of their special structural features, especially the deformation of the ideal carbon–carbon bond angle, the inherent ring strain, their novel and distinctive architecture, and their synthetic challenge. Some typical examples of such structures are depicted in Figure 1, together with their relative strain energies.[4-6]

The synthesis of the cubane system by Eaton and Cole,[7] who elegantly merged known synthetic methodology for the construction of this intriguing cage structure, constitutes a landmark in the chemistry of strained cage systems. In spite of an early theoretical calculation of its strain energy that seemed to preclude its existence at room temperature,[8] cubane appeared to be surprisingly thermally stable, decomposing only above 200 °C. This remarkable observation undoubtedly contributed to the formulation of the orbital symmetry rules[9] that later satisfactorily rationalized the exceptional stability of cubane and the like. Encouraged by the successful synthesis of cubane and its congeners (Figure 1) and excited by the possibility of unexpected and unusual behavior of highly strained

Antonius J. H. Klunder was born in 1945 in Enschede, The Netherlands. He received his M.Sc. degree from the University of Groningen in 1968 on a synthetic study of five-membered heterocycles annelated to bicyclic systems in the laboratory of Prof. H. Wijnberg. He moved to Nijmegen, where he earned the Ph.D. degree from the University of Nijmegen in 1973 on research undertaken with Prof. B. Zwanenburg on the synthesis and properties of highly strained cage compounds such as cubane and homocubanes. In 1975, he did postdoctoral work on the rearrangement of [4.3]spirooctadienes with Dr. R. D. Miller at the IBM Research Center at San Jose, CA. He returned to Nijmegen, where he joined the group of Prof. B. Zwanenburg. He was appointed to lecturer in 1975 and to "Universitair Hoofddocent" (Associate Professor) in 1984. His main research interest is currently directed on the utilization of polycyclic structures for the synthesis of interesting natural and unnatural compounds. Enzymes and flash vacuum thermolysis play an important role therein.

Binne Zwanenburg was born in 1934 in Lippenhuizen, The Netherlands. He received his M.Sc. and Doctor's degrees from the University of Groningen (The Netherlands) in 1959 and 1962, respectively, on a kinetic study of acetylenic ethers under the supervision of Profs. J. F. Arens and W. Drenth. He did postdoctoral work with Prof. R. A. Raphael at the University of Glasgow (Scotland) on the Favorskii rearrangement (1963) and with Prof. N. J. Leonard at the University of Illinois (Urbana–Champaign, IL) on azirine chemistry (1964–1965). He joined the research group of Prof. J. Strating in 1961 and studied the synthesis of sulfines and the mechanism of reaction of diazo sulfones. He was appointed Assistant Professor at the University of Groningen in 1963 and Associate Professor in 1965. He accepted his present position as Professor of Organic Chemistry at the University of Nijmegen in 1971. His current research interests are organic sulfur chemistry, functionalized epoxides, strained polycyclic systems, organoboron compounds, organic enzyme chemistry, flash vacuum thermolysis, asymmetric synthesis, and natural product synthesis.

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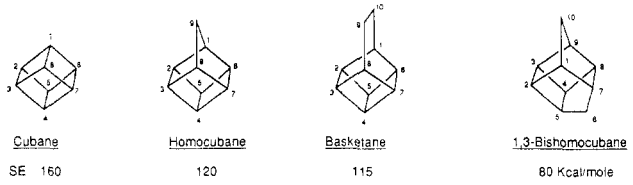

Figure 1.

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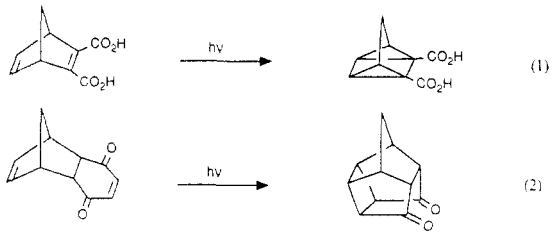

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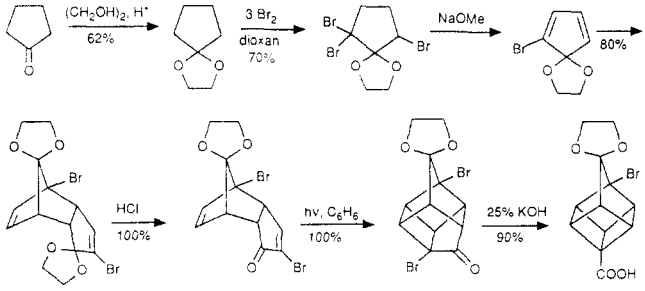

cage compounds, several research groups entered this field.[10] The result of all these activities is a valuable contribution to both synthetic and physical organic chemistry.[11]

In this review attention will be primarily focused on the synthesis and properties of strained cage alcohols and their derivatives in which the oxygen-containing functionality is positioned at a bridgehead position.[12] Due to the capacity of oxygen to interact electronically with the electron-deficient cage moiety, such functionalities can initiate *nonconcerted* cage degradation, fragmentation, or reorganization processes. The unusual but enlightening behavior of this class of bridgehead functionalized cage compounds justifies a treatise. Since aspects of this chemistry have already been reviewed in part,[13,14] we will emphasize particularly the cubane-type cage alcohols and further discuss all related chemistry.

II. Preparation of Strained Cage Alcohols and Their Derivatives

The synthesis of a wide variety of bridgehead substituted cage alcohols is accomplished by utilizing the general methodology for the construction of cage molecules.[2] The key step in the synthesis of bridgehead substituted cage compounds of the cubane type is the intramolecular $[\pi^2 + \pi^2]$ photocyclization of an appropriate tricyclic diene. In subsequent steps further modification of the cage is then accomplished either by ring contraction or by ring expansion. In many cases the bridgehead functionality must be adjusted. An obvious but essential step in the sequence is the preparation of a suitable photoprecursor. A typical sequence for the synthesis of a cage compound is depicted in Scheme 2. The photoprecursor is obtained by Diels–

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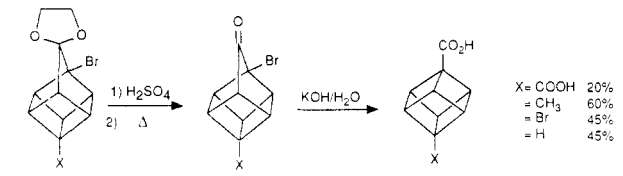

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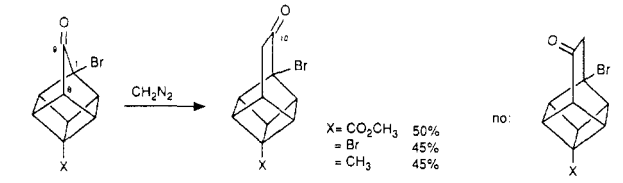

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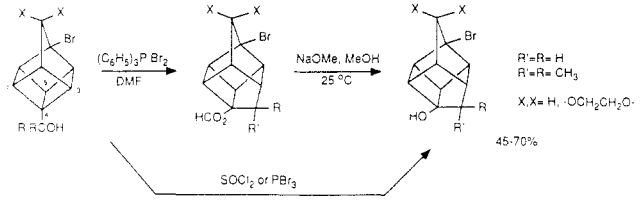

Alder dimerization of bromocyclopentadienone acetal followed by a selective hydrolysis of one of the acetal groups. The 1,3-bishomocubane system obtained upon irradiation is subjected to a Favorskii-type cage contraction reaction. Further contraction can be accomplished by the same type of reaction, as shown in Scheme 3. The synthesis of cubane derivatives,[15] as depicted in Schemes 2 and 3, is actually an improved modification[16] of Eaton and Cole's original cubane synthesis.[7]

A cage expansion reaction of a homocubanone leading to the basketane system[17] is shown in Scheme 4. This particular expansion reaction is a regiospecific process giving the 10-ketone exclusively. Migration of the more electron rich C_8–C_9 bond is favored over the migration of the C_1–C_9 bond, in full accordance with the accepted mechanism for this conversion.

Another useful cage expansion reaction (Scheme 5) is the regiospecific cationic rearrangement of homocubyl carbinols, which, if the reaction conditions are chosen appropriately, may lead directly to bridgehead oxygen substituted 1,3-bishomocubanes in good yields.[18] The driving force in this regiospecific rearrangement is the relief of about 40 kcal/mol ring strain. Force field calculations[5] reveal that migration of the C_3–C_4 bond (or the equivalent C_4–C_7 bond) releases more strain energy than migration of the central C_4–C_5 bond, which would have led to a 1,4-bishomocubane.

The synthesis of strained bridgehead alcohols or their derivatives is no sinecure as direct nucleophilic replacement of an appropriate bridgehead functionality such as halogen by a hydroxylic or other oxygen-containing functionality is generally not a real synthetic possibility.[12] Therefore, indirect approaches need to be considered. Furthermore, it should be noted that the eventual position of the bridgehead alcohol function in the cage system is primarily determined by the substitution pattern present in the photoprecursor. Hence, when one designs a particular bridgehead-substituted cage alcohol, all aspects of cage *and* functional group transformations should be considered and be embodied

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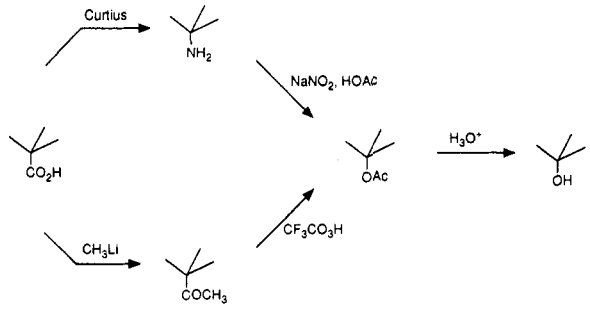

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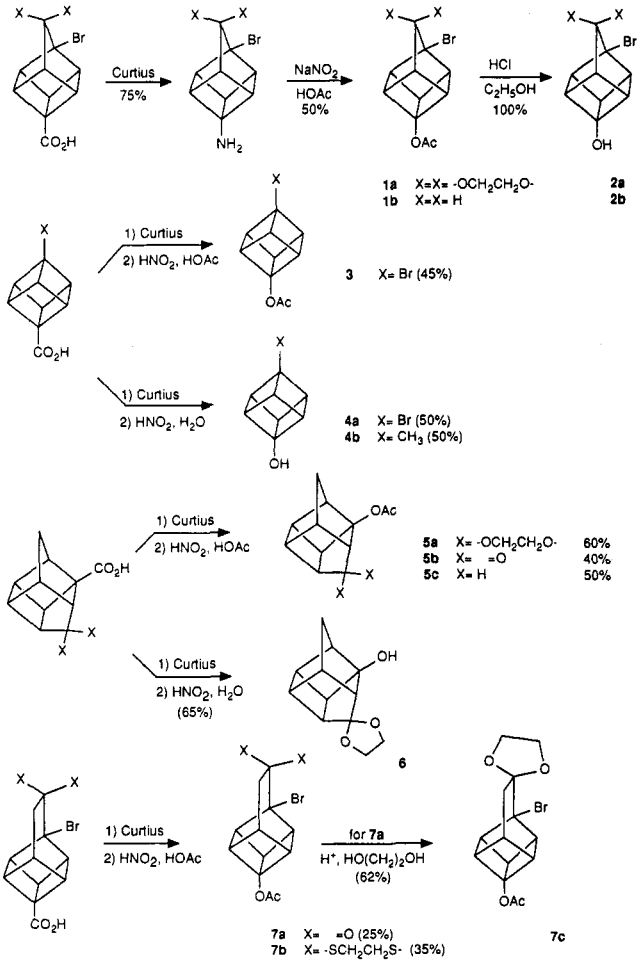

in the structural features of the photoprecursor.

In the cubane series, the introduction of a bridgehead oxygen function (alcohol, ester, or ether) is directly related to the synthetic route used for the generation of the cage moiety. Using an appropriate substituted tricyclodecadienone as the initial photoprecursor and applying the Favorskii reaction for cage contraction (Schemes 2 and 3), one can chemically transform the resulting bridgehead carboxylic acid into either a bridgehead amine by a Curtius[15,17] or Schmidt[19,20] rearrangement or a bridgehead acetoxy compound by a Baeyer–Villager oxidation of the corresponding methyl ketone with trifluoroperacetic acid[6,15,21] (Scheme 6). Subsequent deamination of the amine in either water or acetic acid leads to the alcohol[15] or the acetate,[6,15,17] respectively. Careful ethanolysis of the acetates under acidic conditions has been used to prepare the corresponding bridgehead alcohols.[15] A variety of cubane-type alcohols and acetates have been synthesized by the

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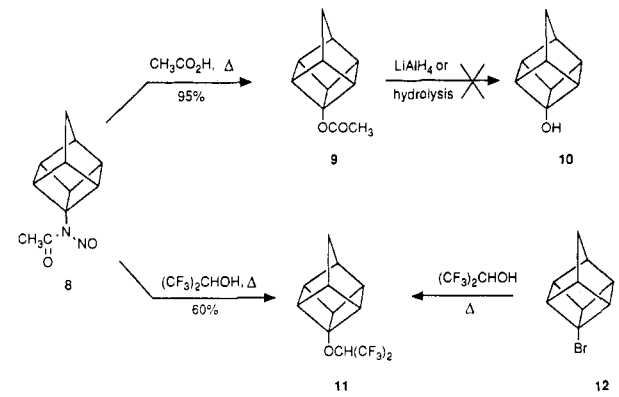

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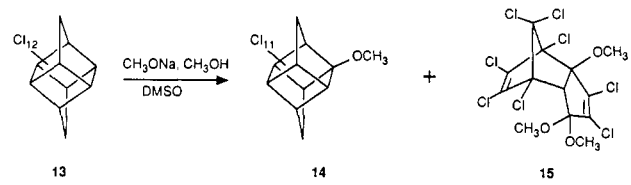

deamination approach[6,15,17,22] (Scheme 7). Initial attempts to prepare the homocubyl bridgehead alcohols from the corresponding acetates by base-catalyzed alcoholysis led to no success due to rapid cage-opening reactions[15] (see section III.2). Although the homocubyl alcohols **2a,b** could be obtained by acid-catalyzed ethanolysis of **1a,b**, their isolation is hampered by rapid decomposition on isolation.[15] Recent attempts to prepare the parent homocubanol **10** from its acetate **9** by either $LiAlH_4$ reduction or hydrolysis failed completely[21] (Scheme 8). Only cage-opened products were obtained. Basketane bridgehead acetates **7** behave similarly. It is interesting to note that the most strained alcohols viz., cubyl alcohols **4**, are considerably more thermally stable than the less strained homocubanols **2** and the corresponding basketanols[15] (Scheme 7). The presence of a carbonyl function positioned β to the bridgehead acetate group in the 1,3-bishomocubane system as in **5b** completely blocks the formation of the corresponding alcohol.[22] In contrast, the ethylene ketal protected acetate **5a** afforded alcohol **6** in high yield, even under basic conditions.

In their efforts to establish the existence of a 4-homocubyl carbenium ion, Rüchardt et al. observed the formation of the corresponding bridgehead homocubyl acetate **9** as the main product during the thermolysis of bridgehead nitroso acetamide **8** in acetic acid[21] (Scheme 8). The hexafluoropropyl ether **11** was formed when this reaction was carried out in hexafluoropropanol. This ether **11** was also formed when 4-bromohomocubane (**12**) was refluxed in hexafluoropropanol at 120 °C for more than 4 days, seemingly by a direct nucleophilic displacement of the bridgehead bromide atom. Strikingly, 1-bromonorbornane does not react at all under identical conditions, showing that the ionization of 4-bromohomocubane is more facile.[21]

Another example of an apparent nucleophilic displacement of a bridgehead halogen atom has been reported for perchloro-1,4-bishomocubane (**13**) in the reaction with NaOMe in DMSO[23] (Scheme 9). The bridgehead methoxy ether **14** was isolated in 15% yield in addition to the main product **15**.

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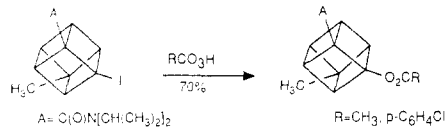

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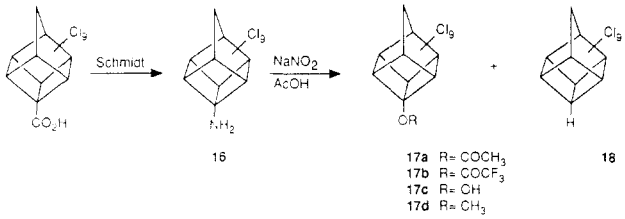

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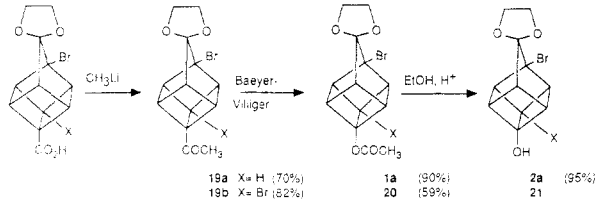

A synthetically more useful method for direct displacement of bridgehead substituents in strained polycycles is the oxidative deiodination of alkyl iodides. Eaton and Cunkle[24] recently demonstrated that cubyl acetates can be obtained in good yields from the corresponding cubyl iodides by oxidation with peracetic acid in acetic acid (Scheme 10). This displacement of iodine is suggested to proceed via a hypervalent iodine substituent, which is an exceptional nucleofuge and therefore allows conversion of otherwise solvolytically very stable bridgehead iodides.

Whereas the deaminative transformation of a bridgehead amine into an alcohol or acetate works well for a variety of relatively modestly substituted cage compounds (Scheme 7), no bridgehead acetate **17a** was obtained when perchlorohomocubyl amine **16** was subjected to diazotation in acetic acid[19,20,25] (Scheme 11). Instead a complex mixture was obtained in which **18** appeared to be the major product. Whereas the deamination products described in Scheme 7 are typical for an ionic process, the formation of **18** agrees well with a radical deamination pathway.[20,25] Acetate **17a** could be obtained in a rather poor yield (14%) by adding 70% perchloric acid to the acetic acid. In contrast, the deamination of **16** in trifluoroacetic acid gives trifluoroacetate **17b** as the sole product in excellent yield (82%). Although this appears to be the product from an ionic reaction, it is likely that a bridgehead radical, which undergoes some kind of electron-transfer reaction, is the initial intermediate since both hydrogen abstraction and fluorine abstraction are now rather unfavorable. Trifluoroacetate **17b** is readily hydrolyzed to the bridgehead alcohol **17c**, which is unstable in water and decomposes to a complex mixture of unidentifiable products. Alcohol **17c** can, however, be converted to methyl ether **17d** with diazomethane and to acetate **17a** with acetyl chloride[20] in good yields.

The Baeyer–Villiger approach was successfully applied to the synthesis of homocubyl acetates **1a**[15] and **20**[6] (Scheme 12). With trifluoroperacetic acid, the methyl ketones **19** were regioselectively converted into

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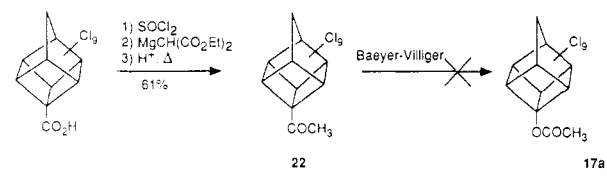

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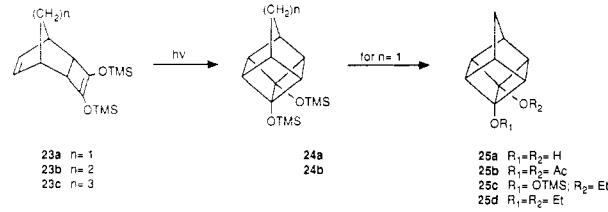

the corresponding homocubyl acetates **1a** and **20** in good overall yields.[6,15] Whereas acetate **1a** has been transformed[15] into the corresponding alcohol **2a**, no attempts to prepare the corresponding 5-bromo alcohol **21** are reported.[6]

Again the perchlorohomocubane analogue reacted differently. Under a variety of conditions, methyl ketone **22** failed to undergo a Baeyer–Villiger reaction to give acetate **17a**[20] (Scheme 13). Both the failure of this reaction and the results of the deamination of amine **16** indicate that in this perchlorohomocubyl cage system the formation of an "electron-deficient" bridgehead intermediate is unfavorable as it is strongly destabilized by the electron-withdrawing effect of the nine chlorine atoms.[15,19,20,25]

A most direct and convenient access to bridgehead cage alcohols and their derivatives would be the utilization of photoprecursors that already contain the alcohol group or a suitable oxygen functionality at the desired position. Miller and Dolce[26,27] were the first to use this approach for the synthesis of 4,5-dihydroxyhomocubane (**25a**) (Scheme 14). Irradiation of 3,4-bis(trimethylsiloxy)tricyclononene (**23a**) in cyclohexane resulted in the rapid and efficient formation (85% yield) of 4,5-bis(trimethylsiloxy)homocubane (**24a**). Surprisingly, **24a** was not formed when the irradiation of **23a** was carried out in acetone as the solvent. Attempts to extend the scope of this reaction to the homologous derivatives **23b** and **23c** met with limited success. Irradiation of **23b** led only to a minor amount (5%) of the desired cage compound **24b** together with large amounts of polymeric material. Under identical conditions irradiation of **23c** resulted in the rapid consumption of starting material but failed to give any isolable products. The failure of **23b** and **23c** to undergo efficient cycloaddition in contrast to **23a** may result from a combination of the progressively increasing distance between the reactive centers in the higher homologues coupled with the greater reactivity of the more strained norbornene double bond in **23a**.[26-28] 4,5-Dihydroxyhomocubane (**25a**) was obtained as a white solid in 80% yield by treatment of **24a** with dry methanol at room temperature.[26] The diol was readily soluble in polar solvents such as acetone, methanol, pyridine, and DMSO without decomposition. However, in an attempt to record an IR spectrum of **25a** in a KBr pellet, a weak carbonyl absorption appeared at 1770 cm^{-1}, implying partial decomposition during pressing. The bis(trimethylsilyl) ether **24a** could be

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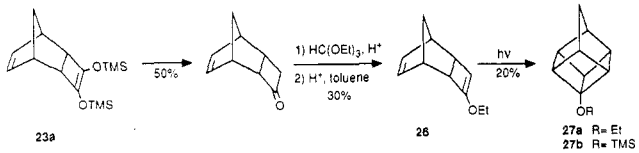

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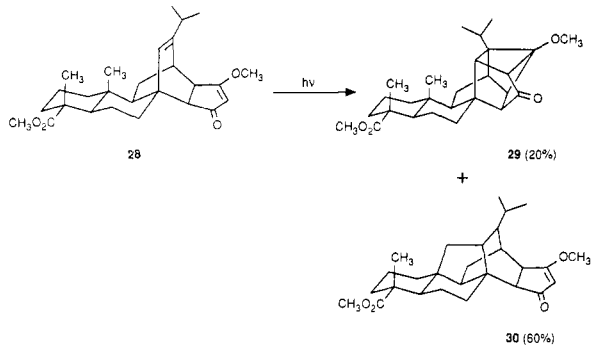


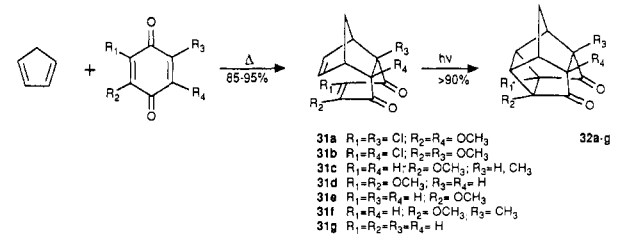
regenerated by treating **25a** with trimethylsilyl chloride and pyridine at room temperature. In a similar manner, the diacetate **25b** was obtained from **25a** with acetyl chloride. Interestingly, **25b** could also be produced in high yield directly from **24a** upon treatment with acetyl chloride and boron trifluoride etherate. The mixed ether **25c** can be prepared by reacting **24a** with MeLi at −15 °C followed by the addition of triethyloxonium tetrafluoroborate in dichloromethane.[29] Finally, the bis-ethoxy ether **25d** has been prepared starting from **24a**; however, no experimental details were reported.[30]

By essentially the same synthetic scheme, 4-ethoxyhomocubane (**27a**) was prepared from **26**[31] (Scheme 15). However, whereas the photocyclization of **23a** to form the corresponding cage compound **24a** is an excellent reaction,[26,27] irradiation of **26** in hexane led only to 20% conversion after 17 h with the predominant formation of polymeric products.[31] Sensitization (acetone) conditions did not improve this result. The desired homocubyl ether **27a** was isolated only after preparative gas chromatography. Curiously, the successful synthesis of an analogue of **27a**, viz., the 4-silyloxy ether **27b**, is only referred to in this paper[31] as being a generous gift by Dr. Miller. No experimental details are provided in this nor in one of Miller's reports.

An interesting bridgehead oxygen substituted cage structure has been reported by Herz et al.,[32,33] who studied the photolysis of enol ether **28** (Scheme 16). Cage ether **29** is formed in 20% yield together with **30** (60%), in which the enol ether moiety is retained. It was found that this photochemical formation of **29** is a reversible process, whereas the formation of **30**, which is the result of an intramolecular H transfer, is irreversible.[34] Consequently, on prolonged irradiation hardly any cage product **29** remains left. This photochemical behavior appeared to be restricted to enol ether **28**. No such H-transfer products were observed for the β-methyl- and phenyl-substituted cyclopentenone analogues of **28**.[34]

On their route to linearly fused tricyclopentenoids, Mehta et al.[35,36] synthesized bridgehead methoxy substituted pentacycloundecanediones **32a,b,c,e,f** by photocyclization of the Diels–Alder adducts **31**, which are readily prepared from the corresponding methoxybenzoquinones and cyclopentadiene (Scheme 17).

SCHEME 17



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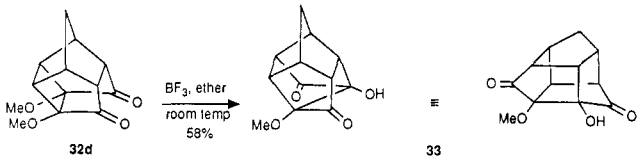

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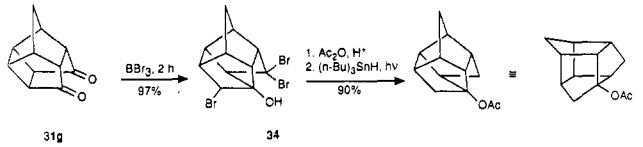

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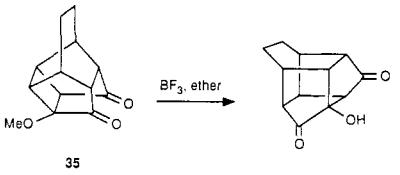

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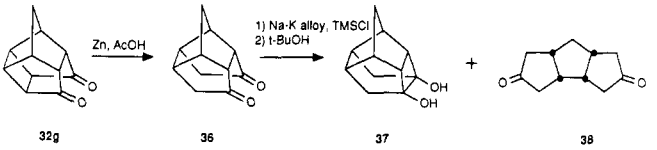

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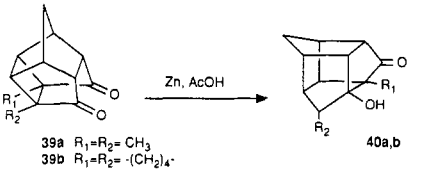
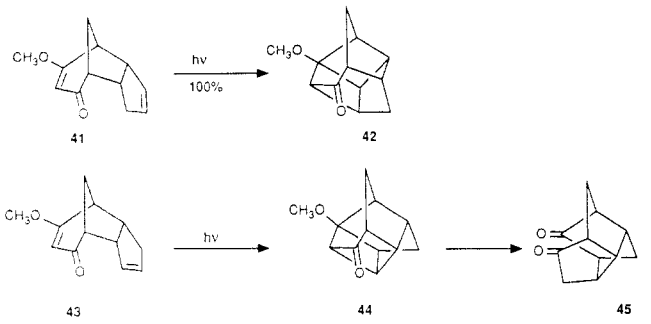


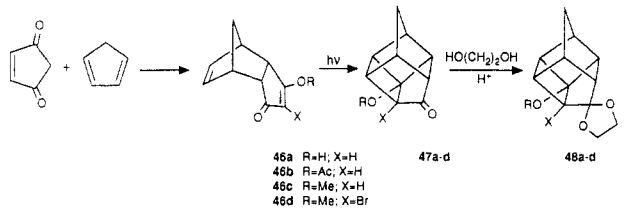
Analogously, Kanematsu et al.[37] prepared the dimethoxy analogue **32d** from **31d**. No attempts to convert ethers **32** into the corresponding alcohols were reported. Treatment of **32d** with $BF_3 \cdot Et_2O$ produced the rearranged cage alcohol **33**[38] (Scheme 18). With BBr_3 as the Lewis acid and the parent compound **32g**, concomitant rearrangement and bromination are observed,[39] producing bridgehead alcohol **34** (Scheme 19). Acylation followed by reductive removal of the bromine affords the corresponding parent bridgehead trishomocubyl acetate in almost quantitative yield. Similarly, the bridgehead methoxy substituted dione **35**, which was prepared from 1,3-cyclohexadiene and methoxybenzoquinone, readily rearranged to a homologue of trishomocubyl alcohol by treatment with $BF_3 \cdot Et_2O$ at room temperature[36] (Scheme 20).

A bridgehead diol was obtained as the minor product upon reaction of tetracyclic dione **36** with Na–K alloy

SCHEME 23



SCHEME 24

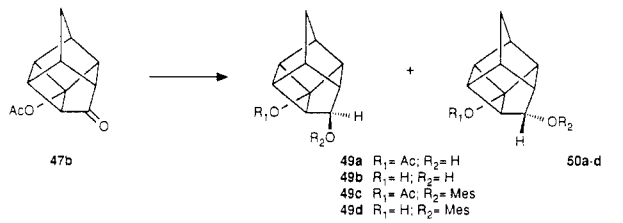


in the presence of trimethylchlorosilane and subsequent quenching with *tert*-butyl alcohol[40] (Scheme 21). A mixture of cage diol **37** and the unfolded tricyclic dione **38** (1:8) was formed in 40% total yield in this reductive conversion. In essentially the same manner alcohols **40a,b** were obtained from diones **39a,b**, respectively, by Zn/HOAc reduction[40] (Scheme 22).

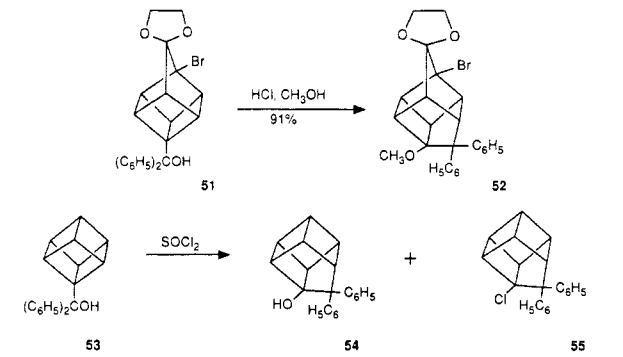
A further example of a direct formation of a bridgehead-substituted polycyclic ether is the photolysis of tricyclic β-methoxy enone **41** in benzene[41,42] (Scheme 23). The trishomocubane cage compound **42** was formed in quantitative yield. In the same manner, enone **43** gave the unstable cage compound **44**, which decomposed to tetracyclic diketone **45** on standing in a refrigerator. Since cage precursors having H or Me in place of the OMe in **43** lead to stable cage structures, the instability of **44** is apparently related to the presence of an ether function positioned β to the strained ketone function.

A direct and efficient route to bridgehead oxygen functionalized 1,3-bishomocubanes **47** was realized by utilizing the Diels–Alder adduct of cyclopentadiene and cyclopentene-1,3-dione (Scheme 24).[6,22,43,44] Unexpectedly, irradiation of enol **46a** in benzene, acetone, or MeOH did not lead to any photocyclization product; however, the corresponding enol acetate **46b** and enol ether **46c** smoothly produced the cage compounds **47b** and **47c**, respectively, in quantitative yields. In a similar way, 5-bromo-4-methoxy-1,3-bishomocubanone (**47d**) was obtained from enol bromide **46d**.[6,44] However, due to its sensitivity toward acids, **47d** was only obtained as such when the photocyclization was carried out in toluene containing some ammonia. Ketalization of **47b,c** smoothly led to **48b,c** in yields over 90%.[22,43] Attempts to prepare 1,3-bishomocubyl alcohols **47** by careful acidic or basic alcoholysis of the corresponding acetates failed due to rapid cage-opening reactions. As cage ketals **48** are less prone to undergo such cage-opening reactions, here the corresponding bridgehead alcohol can be obtained by alcoholysis. Reduction of the bridged ketone function in **47b** with $LiAlH(t\text{-}OBu)_3$ gave a 3.5:1 mixture of the bridged alcohols **49a** and **50a** in a total yield of 80%[22,45] (Scheme 25). Base-catalyzed alcoholysis of **49a** and **50a** led to the corresponding diols

SCHEME 25



SCHEME 26



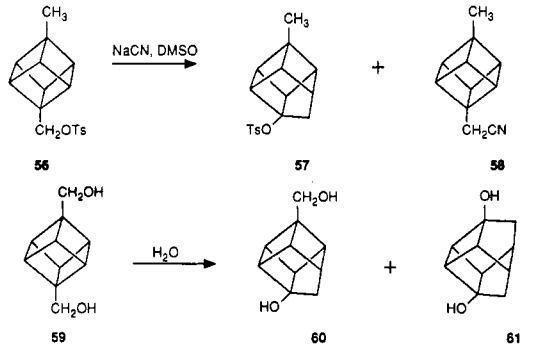
49b and **50b**.[46] In the same way, mesylate **50c** could be converted into alcohol **50d**. However, **49c** led to rapid cage opening with the concomitant expulsion of the mesylate group, and consequently no alcohol **49d** could be isolated.[22,45]

Another approach to bridgehead polycyclic alcohols is based on a skeletal reorganization of an appropriately substituted cage compound. Two such reorganization processes are of importance here, viz., the cationic cage expansion reaction of bridgehead carbinols[18] and the metal-catalyzed isomerization of strained polycycles.[47]

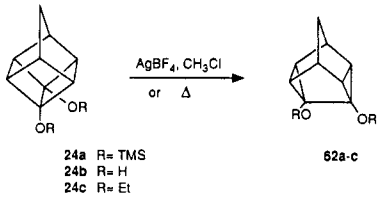
The regiospecific cage expansion of homocubyl carbinols has already been put forward here as a method to prepare the 1,3-bishomocubane cage system[18] (Scheme 5). By careful selection of reagents and reaction conditions, good yields of the corresponding bridgehead alcohols could be obtained.[18,48] In some cases the formation of the alcohols is accompanied by the corresponding bridgehead halogen compounds.[18,48] Unexpectedly, diphenylcarbinol **51** behaves differently. Upon treatment with either aqueous HCl or $SOCl_2$, no bridgehead bishomocubyl alcohol is formed, but instead a high-melting solid is obtained to which no structure has been assigned yet.[18] In contrast, bridgehead homocubyl alcohol **54** together with some chloride **55** was readily obtained from cubyldiphenylcarbinol (**53**) upon treatment with $SOCl_2$ under the same conditions[48] (Scheme 26). Surprisingly, by replacing aqueous hydrochloric acid by methanolic hydrochloric acid, diphenylcarbinol **51** now underwent the desired Wagner–Meerwein rearrangement leading exclusively to the bridgehead methoxy ether **52**.[48] No satisfactory explanation has been tendered to explain either this solvent effect or the deviating behavior of **51** as compared with its cubyl analogue **53**.

In our efforts[49] to accomplish nucleophilic substitution of cubylmethyl tosylate **56** with NaCN in DMSO, the bridgehead homocubyl tosylate **57** was isolated in 15% yield, together with the desired nitrile **58** (80% yield) (Scheme 27). Despite considerable efforts it was impossible to prevent the formation of **57**. An analogous ring expansion reaction was observed by Farrell

SCHEME 27



SCHEME 28

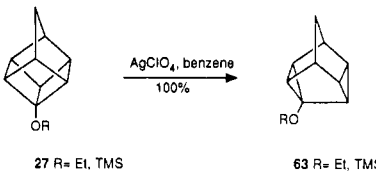


et al.[50] when they attempted the preparation of cubylbiscarbinol (**59**) by reduction of cubane-1,4-dicarboxylic acid with $LiAlH_4$. Under the applied conditions, a facile isomerization of **59** to a mixture of bridgehead homocubyl and 1,3-bishomocubyl alcohols **60** and **61** is observed (Scheme 27). No isolation or characterization of these latter compounds was reported. These spontaneous cage expansion reactions are probably due to the high strain present in the cubane skeleton.

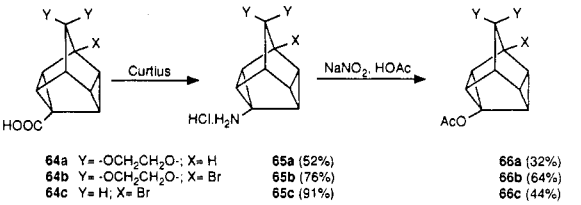
The silver ion catalyzed transformation of homocubanes is an effective method to prepare bridgehead oxygen substituted homocuneanes.[47] This is most strikingly demonstrated by Miller and Dolce,[26] who realized an effective rearrangement of homocubyl 4,5-bissilyl ether **24a** to the homocuneane analogue **62a** by treatment with a catalytic amount of silver tetrafluoroborate in chloroform (Scheme 28). Curiously, this homocuneane derivative was also produced by heating **24a** in the absence of solvent to 245 °C. This facile thermal rearrangement of **24a** to **62a** is unexpected in light of the reported stability of homocubane derivatives and is suggested to be associated with its substitution pattern. The corresponding homocuneane diol **62b** has been prepared from **62a** in 80% yield by just stirring it in dry methanol at room temperature for 3–4 h.[26,51] Interestingly, the intermediacy of **62b** is postulated in the $Pb(OAc)_4$ oxidation of 4,5-dihydroxyhomocubane (**24b**).[30] Attempts to prove this hypothesis by using the corresponding homocubyl diethyl ether **24c** instead of the diol in the Pb^{IV} oxidation reaction to prevent subsequent oxidation failed as no rearranged isomer **62c** could be detected.[30]

In order to probe the effect of bridgehead substituents on the rate of Ag^+-catalyzed homocubyl rearrangements, Paquette et al.[31] studied a series of 4- and 4,5-substituted homocubane derivatives, including the 4-(silyloxy)- and 4-ethoxyhomocubanes **27** and the 4,5-bisethers **24a** and **25d**. In all cases, the corresponding homocuneanes (also alternatively named norsnoutanes) **62** and **63** were obtained in excellent yields upon treatment with silver perchlorate in benzene (Schemes 28 and 29).

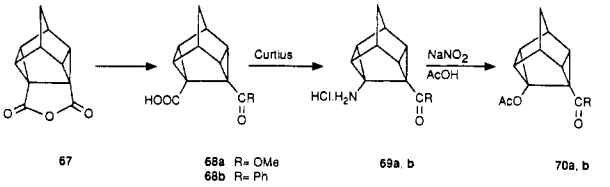
SCHEME 29



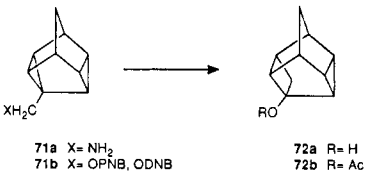
SCHEME 30



SCHEME 31



SCHEME 32

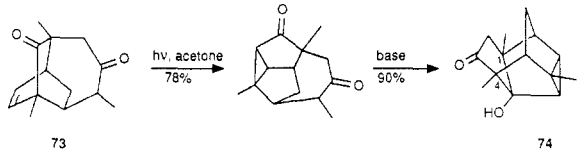


Starting from homocuneanecarboxylic acids **64**, an effective synthesis of homocuneyl acetates **66** could be realized by using the aforementioned (see Scheme 6) deamination procedure[52] (Scheme 30). Attempts to prepare the corresponding homocuneyl alcohols by direct deamination of amines **65** in water, metal hydride reduction, or acid-catalyzed transesterification of acetates **66** failed. In all cases mixtures of cage-opened products were formed.[52]

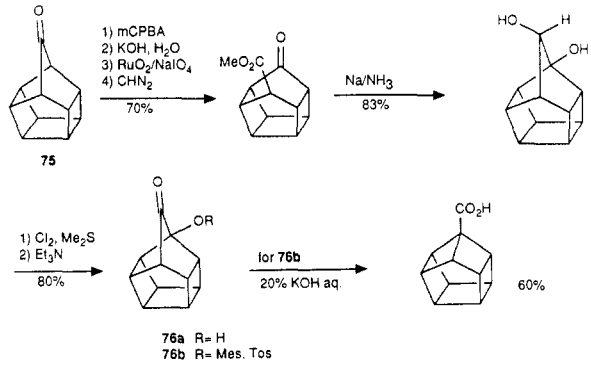
5-Functionalized homocuneyl acetates **70** have been prepared from homocuneanedicarboxylic anhydride (**67**) as the starting material[53] (Scheme 31). This anhydride allowed the selective introduction of a carbomethoxy or benzoyl function at the 5-position in the homocuneane system. Conversion of the 4-carboxylic acid group in **68** into the desired bridgehead acetate function could be realized by again applying the deamination procedure. However, this approach worked only satisfactorily for the 5-benzoyl-substituted homocuneane **68b**. Acetate **70b** was obtained in 35% overall yield. With the ester-substituted homocuneyl compound **69a** problems were encountered in the deamination reaction. A complex mixture was obtained from which acetate **70a** could be isolated in 20% yield. No attempts were made to prepare the corresponding alcohols.

Bridgehead-substituted bishomocuneyl alcohol **72a** and its acetate **72b** have been prepared by deamination of homocuneane methylamine **71a** in acetic acid and hydrolysis of nitrobenzoic esters **71b**, respectively[54] (Scheme 32). These ring expansion reactions, which are examples of the cyclopropylcarbinyl/cyclobutyl cation rearrangement, proceeded with good efficiency (yields ranging from 60 to 80%).

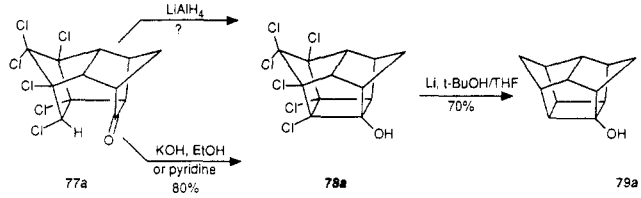
SCHEME 33



SCHEME 34



SCHEME 35

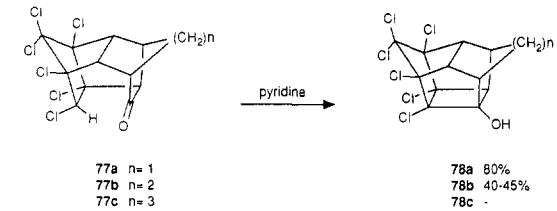


Bridgehead-substituted trishomocuneyl alcohol **74** has been obtained by an oxa-di-π-methane rearrangement of tricyclic diketone **73** initiated by sensitized irradiation, followed by base-induced intramolecular condensation[55] (Scheme 33). Due to severe steric crowding of the OH functionality by the methyl groups at C_1 and C_4, acylation of this alcohol could only be achieved by using Steglich's reagent.

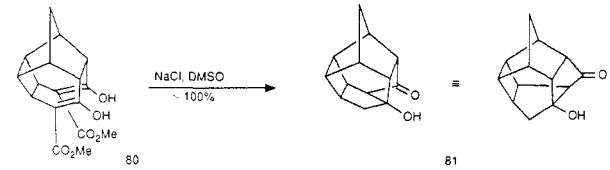
The hexacyclic pentaprismane cage system can be considered the cage homologue of the pentacyclic cubane in which the cage skeleton has been extended with an extra cyclobutane ring face. Both compounds are members of the prismane family.[56] The synthesis of pentaprismane, which has recently been accomplished by starting from the Diels–Alder adduct of benzoquinone and 1,1-dimethoxytetrachlorocyclopentadiene, is again based on the general concepts discussed above, viz., intramolecular photocyclization and subsequent cage transformation. In their route to pentaprismane, Eaton et al.[56] prepared α-hydroxyhomopentaprismanone (**76a**) through a bridgehead hydroxylation of homopentaprismanone (**75**) involving an intramolecular ring opening/ring closure procedure (Scheme 34). Conversion of this bridgehead alcohol into a mesylate or tosylate then allowed the Favorskii-type cage contraction of homopentaprismanone into pentaprismanecarboxylic acid.[56] No bridgehead alcohols of this latter cage system have been described.

Bridgehead-substituted bishomopentaprismane alcohols **78a** and **79a**, also known as birdcage alcohols, were the first cage alcohols ever reported in literature (Schemes 35 and 36). As early as 1960, Soloway et al.[57] claimed the formation of hexachloro birdcage alcohol **78a** during the $LiAlH_4$ reduction of half-cage ketone **77a**. This ring-closure reaction is explained as a "transannular enolization" reaction in which the reducing agent acts as both a Lewis acid and proton abstractor. Winstein et al.,[58] who were unable to repeat this conversion of **77a** into **78a**, realized the synthesis of **78a** by accomplishing the base-catalyzed homoenolization of **77a** with alcoholic sodium hydroxide or pyridine. In this way, crystalline birdcage alcohol **78a** was isolated in 80% yield (Scheme 35). The formation of **78a** not only indicates that the starting ketone has a favorable geometry to form the birdcage skeleton but it also shows that there cannot be a large difference in steric energy between reactant and product. In contrast to cubane-type systems, the birdcage framework can be obtained without utilizing an intramolecular photocyclization step, demonstrating that less strain is involved in the cage-closure reaction.[59,60] Dechlorination of alcohol **78a** was performed in 70% yield by the lithium *tert*-butyl alcohol–tetrahydrofuran procedure practically without any disturbing homoketonization of the product birdcage alcohol **79a**.[58,60] Whereas the base-induced homoenolization of half-cage ketone **77a** works well for the synthesis of bridgehead alcohol **78a**, extension of the right-hand one-carbon wing of the half-cage to a two- or three-carbon bridge as in **77b** and **77c** adversely affects the formation of the corresponding bridgehead alcohols[61] (Scheme 36). Under the conditions that afforded **78a** in 80% yield, its homologue, homo-birdcage alcohol **78b**, could be isolated in only 40–45% yield after 5 days, while none of the bishomobirdcage alcohol **78c** was detected even after prolonged reaction times. Structural considerations indicate a substantial increase in strain in going from reactant to product when the one-carbon wing is expanded by one or two carbon atoms, with the apparent consequence that cage formation is more difficult.

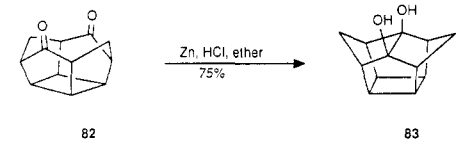
SCHEME 36



SCHEME 37



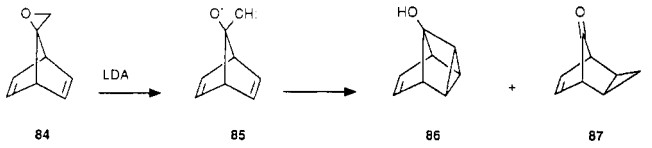
SCHEME 38



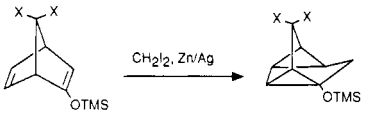
Another example of a relatively unstrained cage alcohol has recently been described by Marchand et al.,[62] who observed the smooth and high-yield formation of **81** by initial decarbomethoxylation of **80** followed by spontaneous intramolecular aldol condensation of the intermediate diketone (Scheme 37).

On their route to [4]peristylane, birdcage diol **83** was obtained in 75% yield by Paquette et al.[63] from the

SCHEME 39



SCHEME 40



pinacolization of dione **82** with zinc in ether saturated with hydrogen chloride (Scheme 38).

A bishomoprismane alcohol **86** was synthesized by Klumpp et al.[64] by initiating an α-elimination of bicyclic epoxide **84** by deprotonation with lithium diisopropylamide in ether at −60 °C for 110 h (Scheme 39). A mixture of starting epoxide **84**, alcohol **86**, and its homoketonization product **87** was obtained from which the alcohol was isolated by preparative gas chromatography. Its formation was explained by invoking oxy carbene **85** as an intermediate.

Stothers et al.[65] prepared a series of 8-substituted 2-trimethylsilyl ethers of homoquadricyclenes (bishomotriprismanes) **89** by Simmons–Smith cyclopropanation of the norbornene trimethylsilyl enol ethers **88** in order to study their base-induced homoketonization (Scheme 40). No conversion of these silyl ethers into the corresponding alcohols is reported.

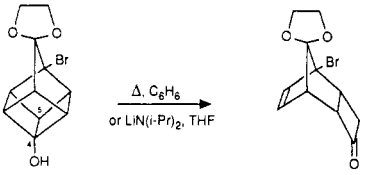
In employing the available methodology for the synthesis of strained, bridgehead-substituted cage alcohols, esters, and ethers, one usually needs to carefully consider the order of events in the synthetic sequence. It is advisable to plan the transformation of a bridgehead substituent, e.g., the carboxyl function to the alcohol or their esters as the last step, in view of the usually high reactivity of these bridgehead substrates under various conditions.

III. Chemical Properties

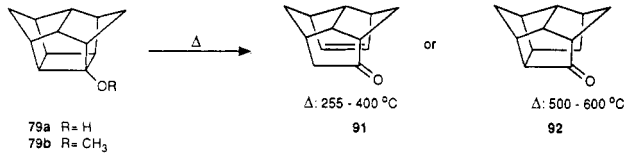
1. Thermal Reactions

With few exceptions no systematic studies have been carried out on the thermolysis of strained bridgehead-substituted cage alcohols or their derivatives. In most cases no serious synthetic problems with respect to thermal instability as a result of cage strain are encountered during the isolation of these compounds. Exceptions are the homocubanols[15,21] and basketanols[17] (Scheme 7). Whereas the homocubanols are reasonably thermally stable in the pure state, their isolation as such requires much skill as minor contaminants initiate rapid thermal decomposition.[15] Basketanols as such cannot be obtained on alcoholysis of the corresponding bridgehead acetates, neither under mild acidic nor under neutral conditions.[17] In both cases cage-opened decomposition products are obtained. Curiously, the much more strained cubane alcohols can readily be obtained under identical experimental conditions[15] (Scheme 7).

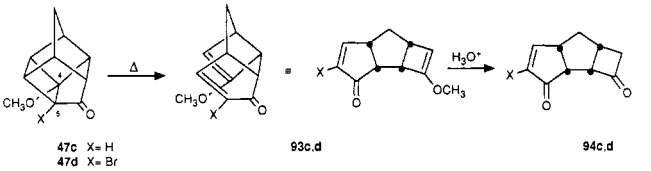
SCHEME 41



SCHEME 42



SCHEME 43



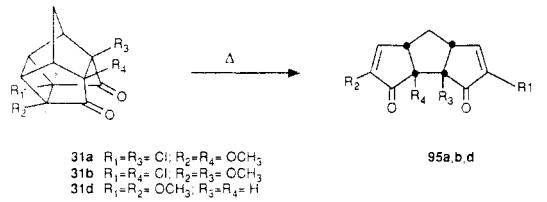
Heating 4-homocubanol **2a** in benzene brings about a two-bond cleavage reaction to give tricyclic ketone **90** in nearly quantitative yield[66,67] (Scheme 41). No products arising from initial scission of the central C_4–C_5 bond in the homocubane cage system have been detected. A similar cage-opening reaction was observed for birdcage alcohol **79a**[68] when it was subjected to thermolysis (Scheme 42). The thermal behavior of **79a** was studied over heated quartz chips using a pyrolytic gas chromatograph unit. Between 255 and 400 °C a clean cage-opening reaction to enone **91** takes place. At temperatures between 500 and 600 °C another ketone, viz., **92**, is formed. Above 700 °C complete decomposition is observed.

Whereas thermal reorganization of **79a** takes place more readily than that of the unsubstituted birdcage itself, methoxy derivative **79b** does not isomerize below 450 °C and decomposes completely above 500 °C.[68] No explanation is given for the greater stability of **79b** as compared with its alcohol **79a**. Thermal reorganizations of cyclobutanols have been accounted for by the initial formation of 1-hydroxy 1,4-diradicals, possibly followed by further bond cleavage or hydrogen migration.[69] Both the thermal reorganization of homocubanol **2a** and that of birdcage alcohol **79a** are in agreement with this proposed mechanism. In both cases the thermal cage fragmentation appeared to be completely regiospecific in the direction of the least strained ketone.[5]

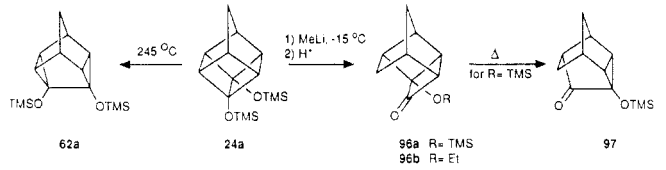
Methoxy-substituted 1,3-bishomocubanones **47c,d** gave a smooth thermal cycloreversion[6] that was most efficiently carried out by using the technique of flash vacuum thermolysis (400 °C/0.35 Torr) (Scheme 43). The initially formed tricyclic enol ethers **93** gave upon hydrolysis the syn doubly annelated cyclopentanes **94**. This thermal cage cleavage probably also proceeds by a radical pathway, involving the initial formation of a 1-methoxy 1,4-diradical by cleavage of the central C_4–C_5 bond, followed by further bond scission.[6]

In their search for a simple and general route to triquinanes, Mehta et al.[35,36] studied the thermal fragmentation of a series of pentacycloundecanediones **31** (Scheme 44). Most of the diones studied furnished

SCHEME 44



SCHEME 45



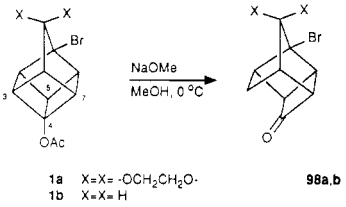
tricyclopentenoids **95** in good to excellent yields on thermolysis either under flash (450–560 °C/1 Torr) or static conditions (reflux in diphenyl ether). The groups of both Mehta[35] and Kanematsu and Osawa[37] found that substituents on the cyclobutane ring do have a significant influence on the relative ease of this thermal fragmentation. Particularly, electron-donating substituents such as bridgehead methoxy groups at C_1 or C_7 as in **31a,b,d** considerably accelerate the cage-opening reaction; e.g., **31d** undergoes ring cleavage already around 100 °C in ethanol,[37] whereas the parent cage compound **31g** ($R_1 = R_2 = R_3 = R_4 = H$) is only opened at temperatures as high as 560 °C in the gas phase.[35,37] A captodative stabilization of the intermediate C_1,C_7 diradical by the electron-releasing methoxy group and the electron-withdrawing carbonyl function has been suggested.[36-38]

Heating bis(trimethylsiloxy)homocubane (**24a**) to 245 °C for 2 h in the absence of a solvent afforded the corresponding cuneane **62a** (Scheme 28).[26] A related rearrangement is observed for bridgehead-substituted half-cage trimethylsilyl ether **96a** (prepared from **24a** upon reaction with MeLi at −15 °C), which in CCl_4 at both 25 and 77 °C affords **97** (Scheme 45).[29] The facile transformation of **96a** to **97** is unusual, since it involves not only a skeletal rearrangement but also an oxygen-to-oxygen migration of the trimethylsilyl group. The special role of the trimethylsilyl group in this rearrangement has been established by comparing its thermal behavior with that of the substrate having a simple alkyl group instead of the silyl group. Heating ethyl ether **96b** at 110 °C in tetrachloroethylene did not cause any rearrangement. Moreover, it survived GLC collection at 160 °C. It is suggested that the enhanced reactivity of **96a** may be caused by the interaction of the nonbonding electrons of the carbonyl group with the adjacent silicon atom which increases the electrophilicity of the carbonyl carbon atom and hence promotes ring contraction in this strained system.[29] The role of silicon in the thermal rearrangement of **24a** to homocuneane **62a** has not been established.

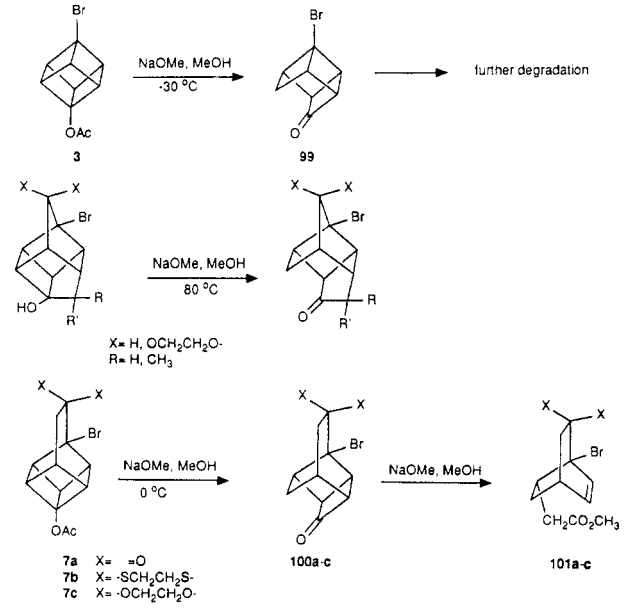
2. Base-Induced Cage-Opening Reactions

In attempts to prepare homocubane bridgehead alcohols **2** (Scheme 7) by a base-catalyzed alcoholysis of the corresponding acetates **1**, Klunder and Zwanenburg observed[70,71] an exclusive one-bond cleavage reaction (Scheme 46). It was found that the seco-cage ketones **98** are the result of a regiospecific scission of the C_3–C_4 (or the equivalent C_4–C_7) bond. Cleavage of the central C_4–C_5 bond does not occur. Analogous cage-opening reactions were encountered for the bridgehead cubyl,[71] 1,3-bishomocubyl,[71] and basketyl alcohols[72] (or acetates) as depicted in Scheme 47. In the case of cubyl acetate **3** the secocubanone **99** could not be isolated, but its formation was deduced from the degradation products. The half-cage ketones **100** derived from the corresponding basketane bridgehead acetates **7** could only be isolated by using short reaction times.[72] Prolonged base treatment induced further breakdown to the bicyclooctene esters **101**. It is noteworthy that such an extended degradation was not observed in the case of secohomocubanones **98**. However, when homocubanol **2a** was treated with base under aprotic conditions, viz., $LiN(i\text{-}Pr)_2$ in THF at room temperature, a rapid two-bond cleavage cage opening of **2a** to tricyclic butanone **90** was observed.[71] The product of this reaction is the same as observed for the thermal fragmentation of **2a** (Scheme 41).

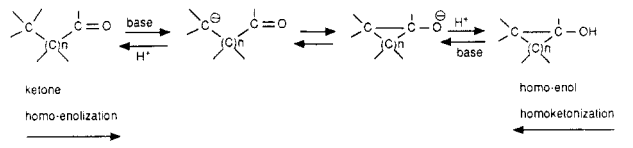
SCHEME 46



SCHEME 47



SCHEME 48



The one-bond cleavage reactions of bridgehead cage alcohols shown in Schemes 46 and 47 can, in general terms, be formulated as homoketonizations (Scheme 48).[14] The cyclanol constrained in the polycyclic structure is actually a homoenol.

The regiochemistry of the one-bond opening reactions of these cubane-type bridgehead alcohols (or acetates)

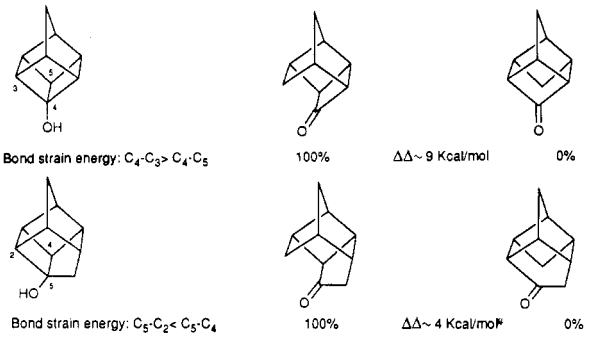


Figure 2.

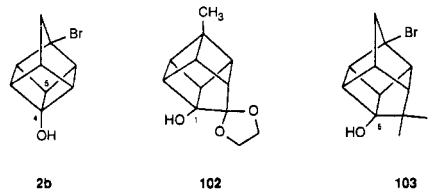


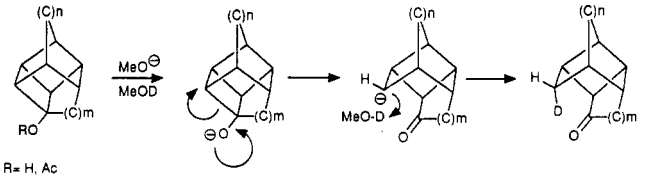
Figure 3.

is primarily governed by relief of cage strain, resulting in the exclusive formation of the thermodynamically most stable half-cage ketones. This is demonstrated by the enthalpy data[5] for the conceivable half-cage ketones from homocuban-4-ol and 1,3-bishomocuban-5-ol, respectively, given in Figure 2. An alternative explanation for the regiospecificity of the cage-opening reaction would be that one of the bonds of the original cage compound is significantly more strained than the others, already in the ground state, and therefore reacts preferentially. Calculations revealed[5] that in the homocubane system the bond strain energy of the C_4–C_3 bond is indeed higher than that of the C_4–C_5 bond, but that the reverse is true in the 1,3-bishomocubane system in which the central C_4–C_5 bond appears to be somewhat more strained than the C_5–C_2 bond (Figure 2). Hence, this explanation seems inconsistent with the experimental findings. Consequently, these homoketonization reactions can probably be best understood by assuming that the product-developing stage is located rather late along the reaction coordinate and are accordingly influenced strongly by the thermodynamic stability of the product.[5]

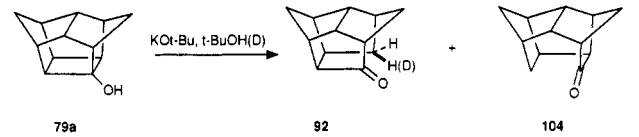
The reactivity of the cubane-type alcohols (or acetates) in this homoketonization process grosso modo parallels the total cage strain energy: cubane > basketane ~ homocubane > 1,3-bishomocubane.[4,5,15,71,72] The basketane system is anomalous since basketyl acetate homoketonizes much faster than the more strained homocubyl acetate.[72] This increased reactivity is probably attributable to the outbending effect of the ethylene bridge, which increases the strain around the C_4 and C_5 atoms in basketane relative to homocubane. The structural features of homocubane and basketane derivatives, determined by X-ray diffraction analyses,[73] show clearly that the C–C bonds around C_4 and C_5 in basketane are in fact somewhat compressed compared with those in the homocubane system.

This phenomenon is also nicely demonstrated by the difference in reactivity of the 4- and 1-homocubanols **2b** and **102**, respectively (Figure 3). The 4-substituted compound reacts smoothly[71] (Scheme 46), whereas the 1-hydroxy derivative does not homoketonize at all,[72] even during prolonged treatment with sodium methoxide in methanol at 100 °C. However, the 1,3-bishomocubanol **103**, which has about 40 kcal/mol less strain energy, readily undergoes a cage-opening reaction[71] at 80 °C (Scheme 47). The extra methylene group present in this latter system when compared with the 1-homocubanol **2b** apparently causes extra compression around C_5 and, accordingly, is more reactive.

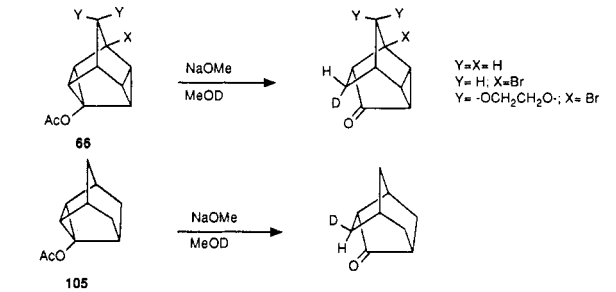
SCHEME 49



SCHEME 50



SCHEME 51

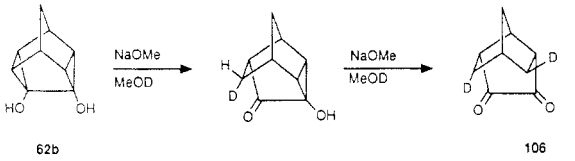


An interesting aspect of the homoketonization reactions of the cubane-type bridgehead cage alcohols and their esters is that they invariably take place with complete retention of configuration[70–72] (Scheme 49). This stereochemical course of the cage-opening reactions could readily be established by means of deuterium-labeling experiments using NaOMe in MeOD. Similar stereospecific reactions, i.e., with retention of configuration, were observed for other types of strained polycyclic alcohols.[14] This stereochemical behavior seems to be typical for polycyclic bridgehead alcohols in which the bridgehead is flanked by four- and/or five-membered rings, with no exceptions as yet.[14]

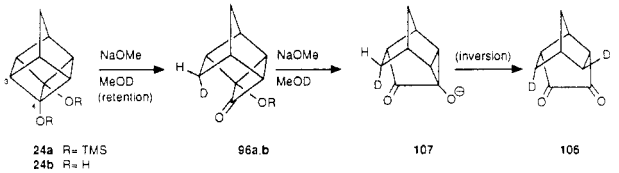
The regio- and stereospecific cage-opening reaction observed for birdcage alcohol **79a** falls into the same category[60,68,74,75] (Scheme 50). Due to its less strained nature **79a** homoketonizes only when heated for 48 h at 100 °C to give the thermodynamically more stable[5] half-cage ketone **92** as the predominant product with only a small amount (4%) of isomeric ketone **104**.[60,68,74,75] Deuterium-labeling studies showed that the opening of **79a** to **92** proceeded with 95 ± 3% retention of configuration in *tert*-butyl alcohol-*d* as the reaction medium.[75]

Base-induced ring-opening reactions of cyclopropanols constrained in polycyclic structures show a stereochemical behavior that strongly depends on the nature of the polycyclic structure.[14] This is most strikingly demonstrated by the difference in stereochemistry of the cyclopropanol opening of the homocuneyl acetates **66**[52] and triaxyl acetate **105**[76] (Scheme 51). The observation of exclusive retention for **66** and

SCHEME 52



SCHEME 53

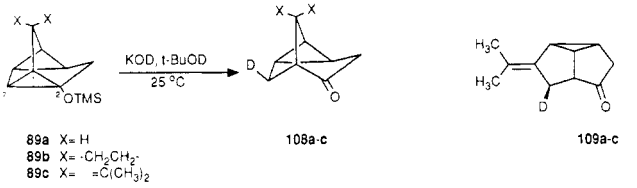


inversion for **105** can only be attributed to the difference in total strain energy of the two structures. The extra three-membered rings present in homocuneane when compared with triaxane is responsible for a considerably higher strain energy in homocuneane as is evidenced by inspection of molecular models.[52] Another elegant demonstration of the influence of strain on the stereochemistry of the cyclopropanol opening has been reported by Miller and Dolce[51] (Scheme 52). The homocuneanediol **62b** undergoes a double homoketonization reaction, the first of which proceeds with retention and the second one with inversion of configuration. This is in full accordance with the established behavior of the highly strained homocuneane and the considerably less strained triaxane, respectively.

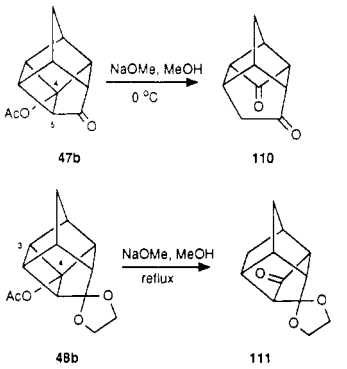
An interesting bishomoketonization process has been reported by Miller and Dolce for 4,5-dihydroxyhomocubane (**24b**) and its bis(trimethylsilyl) ether (**24a**).[77] With NaOMe in MeOH at room temperature both compounds rapidly react to afford diketone **106** (D = H) in 50–60% yield as the only isolable product (Scheme 53). Deuterium-labeling experiments show this information of **106** to be a stereospecific process in which two deuterons are incorporated, one into an exo position and one into an endo position. A mechanism that rationalizes the stereospecific formation of **106** is depicted in Scheme 53. The suggested intermediate half-cage ketone **96a** (D = H) could be obtained[29] from **24a** in nearly quantitative yield by careful treatment with MeLi at −15 °C (cf. Scheme 45). As mentioned earlier (Scheme 45), compound **96a** readily undergoes a thermal rearrangement, even at ambient temperature, to give cyclopropyl trimethyl ether **97**. Subsequent base-induced homoketonization then produces, via anion **107**, diketone **106**. The direction of the first bond cleavage, viz., that of the C_4–C_3 bond, as well as its stereochemistry (endo protonation implying retention of configuration) is consistent with the observed behavior of homocubanols **2** and their congeners.[70–72] The second homoketonization reaction, i.e., the conversion of **107** into **106**, fully conforms to the behavior of a cyclopropanol[13,14] incorporated in a moderately strained polycyclic system, viz., formation of the least strained diketone with inversion of configuration (exo protonation; cf. Scheme 51).

A high degree (>90%) of inversion is observed in the base-induced homoketonization of homoquadricyclene trimethylsilyl ethers **89** despite the presence of two cyclopropane rings in this cage structure[65] (Scheme 54). In all cases the cyclopropanol ring opening follows a unique course but its regiochemistry depends on the

SCHEME 54



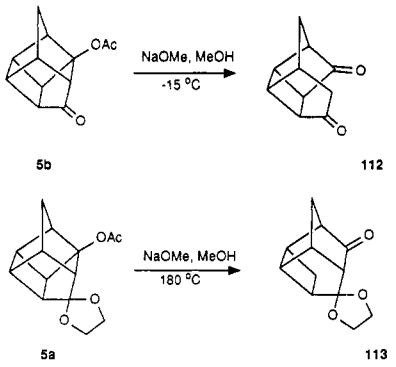
SCHEME 55



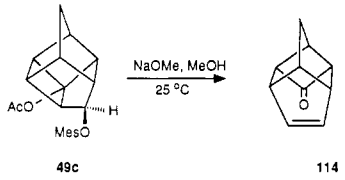
bridge substitution. Whereas for **89a** and **89b** the thermodynamically most stable ketones **108** are formed by scission of the C_2–C_7 bond, isopropylidene analogue **89c** affords exclusively tricyclic ketone **109** as a result of cleavage of the C_1–C_2 bond which leads to an allylic carbanionic intermediate. This finding shows that increasing the stability of the incipient carbanion formed upon cleavage of the cyclopropoxide ring can alter the regiochemical course of the reaction.

This phenomenon of directing the regiochemistry of homoketomization by attachment of a carbanion stabilizing group at a nucleofugal carbon has been extensively studied for bridgehead-substituted homocubyl,[6,44] 1,3-bishomocubyl,[22,43] and homocuneyl[53] alcohols and acetates. The homoketonization reactions of bridgehead cage alcohols can, in principle, be viewed as nucleophilic eliminative ring fissions in which a carbon–oxygen double bond is formed by elimination of a carbon leaving group.[13,22] The occurrence of unactivated carbon leaving groups in acyclic systems is rare; in alicyclic compounds, particularly in small-ring systems, an increasing number of examples have been reported.[13] For highly strained molecules, the release of strain energy during the bond fission process apparently compensates for the high activation energy required for the expulsion of a nonactivated nucleofugal carbon. As discussed so far, the regiochemistry of the base-induced cage-opening reaction of highly strained bridgehead polycyclanols is primarily determined by the thermodynamic stability of the conceivable half-cage structures.[5] Electronic factors do not play a role since for none of the three possible bond cleavages is the developing carbanion particularly stabilized. Therefore, the intriguing question has been posed[6,22,53] whether it would be possible to alter the regiochemistry of the homoketonization process in such highly strained cages as homocubanes and 1,3-bishomocubanes by simple stabilization of one of the possible carbanionic intermediates with the eventual consequence that a thermodynamically less favorable seco-cage framework is obtained. For this purpose, the homoketonization of 1,3-bishomocubyl acetates **47b** and **48b** has been studied[22,43] (Scheme 55).

SCHEME 56



SCHEME 57

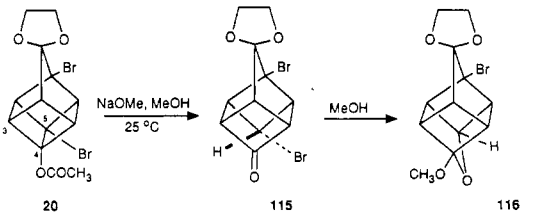


Mild treatment of ketone acetate **47b** with sodium methoxide in methanol at 0 °C gave an almost instantaneous cage-opening reaction to furnish the C_4–C_5 cleavage product **110** in quantitative yield. The acetal acetate **48b**, which is structurally similar to **47b** except that the carbonyl function is protected, underwent base-induced homoketonization only in refluxing methanol to produce the C_3–C_4 cleavage product **111** (Scheme 55). In both cases the cage-opening reactions proceed with retention of configuration. The observed difference in reactivity between **47b** and **48b** and the difference in regiochemistry of their base-induced homoketonization reactions clearly demonstrate the influence of the cage substituent. The regiospecific formation of the C_3–C_4 cleavage product from the acetal acetate **48b** conforms entirely to the general pattern observed for the nonactivated nucleophilic eliminative ring fission of strained cage bridgehead acetates.[5] MM2 calculations[78] show that of the three possible cage-opened structures, **111** is the thermodynamically most stable half-cage ketone, whereas **110** appeared to be the most strained. The formation of this "contra thermodynamic product" shows convincingly that the conjugative stabilization of the nucleofugal carbanion is sufficient to overrule the aforementioned thermodynamic control within the 1,3-bishomocubane cage system.

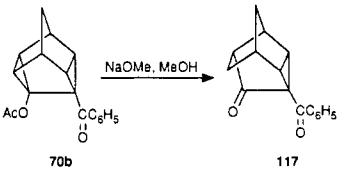
In a similar way it was shown[22] that bridgehead β-ketalized acetate **5a** homoketonizes only at 180 °C to afford the thermodynamically most stable half-cage ketone **113** in quantitative yield (Scheme 56). In contrast, the β-keto acetate **5b** is a highly reactive substrate that already at −15 °C rapidly reacts with NaOMe in MeOH to give a complex mixture of cage-opened products probably via the intermediacy of diketone **112**.

A contrathermodynamic cage-opening reaction can also be enforced by a 1,3-through-cage *elimination* reaction in a bridgehead 1,3-bishomocubyl acetate (or alcohol) appropriately substituted with a leaving group at the β-position with respect to the acetate (or alcohol).[22,45] Treatment of anti-mesylate **49c** with sodium methoxide in methanol at room temperature for 1 h

SCHEME 58



SCHEME 59

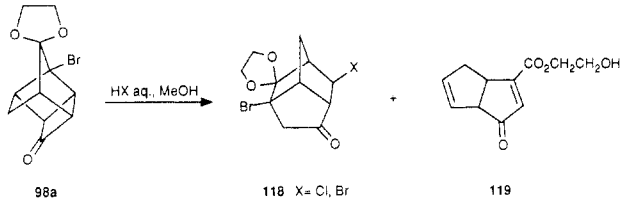


gave the interesting olefinic ketone **114** in an excellent yield (Scheme 57). It is noteworthy that the syn-mesylate acetate **50c** does not show any cage cleavage at all during treatment with sodium methoxide in methanol. There is only conversion to the corresponding syn-mesylate alcohol **50b** (cf. Scheme 25). This difference in behavior of the syn and anti compound strongly suggests that the 1,3-through-cage elimination process is subject to a strict stereoelectronic control, resembling a Grob-type elimination reaction with the leaving group and the bond to be cleaved in a trans-antiparallel orientation.[22]

In the more strained homocubane system the difference in thermodynamic stability between the two possible seco-cage ketones arising from the homoketonization of 4-homocubanol amounts to ca. 9 kcal/mol[5] (Figure 2). Hence, in comparison with the 1,3-bishomocubane system discussed hitherto, it may be much more difficult to overrule the thermodynamic control of the cage cleavage reaction[6,44] by means of an appropriate substituent placed at C_5 in the 4-acetoxy- or 4-hydroxyhomocubane **2**. Attempts to prepare 5-acetyl- or 5-benzoylhomocubyl 4-acetates for this purpose failed.[6] Therefore, 5-bromohomocubyl 4-acetate **20** was considered as a candidate for C_4–C_5 bond cleavage reaction[6] (Scheme 58). Homoketonization of **20** with sodium methoxide in methanol at room temperature turned out to be a fast reaction to give acetal **116**. The formation of this acetal clearly demonstrates that the bromine substituent has the ability to direct the base-induced homoketonization in a contrathermodynamic fashion.[6] The bromo ketone **115** formed initially by cleavage of the C_4–C_5 bond subsequently reacts with methanol from the exo side, giving a hemiacetal that will intramolecularly displace the bromine at C_5 and result in the acetal **116**. In this reaction there was no indication whatsoever of fission of the alternative C_4–C_3 (or equivalent C_4–C_7) bond.[6] The directive effect exerted by the relatively poorly carbanion-stabilizing bromine substituent illustrates the subtle balance between thermodynamic and electronic parameters determining the regiochemistry of the base-induced bond cleavage reaction in strained polycyclanols.

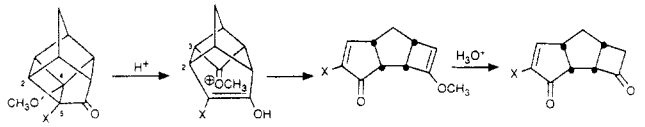
This feature is also demonstrated by an attempt[53] to divert the ring-opening reaction of 4-substituted homocuneyl bridgehead acetates **66** by means of an anion-stabilizing substituent at the alternative nucleofugal carbon C_5 as in **70**. It was found, however, that in 5-benzoylhomocuneyl 4-acetate (**70b**), the direction of

SCHEME 60



98a 118 X= Cl, Br 119

SCHEME 61



47c X= H
47d X= Br 120c,d 93c,d 94c,d

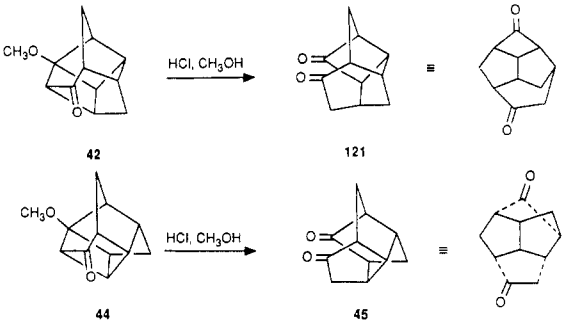
the bond cleavage is not affected by the carbonyl-containing β-function at C_5 and only the thermodynamically most favorable ketone **117** is formed[53] (Scheme 59). Apparently, the thermodynamic control cannot be overridden in this case.

3. Acid-Induced Cage-Opening Reactions

In contrast to the relatively large number of reports concerning the reactivity of strained bridgehead cage alcohols, acetates, and ethers in alkaline media, only little information is available on their behavior toward acidic reagents. This is probably due to the fact that the bridgehead oxygen substituted polycycles are generally relatively stable toward acids. In many cases bridgehead cage acetates can undergo acid-catalyzed alcoholysis to form the corresponding alcohols without disturbing the cage structure. Notable exceptions are the 4-homocubyl,[15,19-21] 4-basketyl,[17] and homocuneyl[52] acetates (Scheme 7). Although the 4-homocubanols **2** can be obtained by careful acid-catalyzed ethanolysis, they are very sensitive to acid.[15] In an independent experiment it was shown[66,67] that homocubanol **2a** slowly undergoes a two-bond cleavage reaction to form **90** when treated with aqueous hydrochloric acid in methanol (cf. Scheme 41). An acceptable pathway for this cage opening would involve the intermediacy of secohomocubanone **98a** produced by an initially formed proton–homocubane σ-complex.[67] However, when this supposed intermediate **98a** was treated with acid (HCl or HBr) under the same conditions, no **90** was formed at all. Instead a mixture of tricyclic ketone **118** and bicyclic enone **119** was produced as a result of a deep-seated cyclopropylcarbinyl/cyclobutyl cation rearrangement[67,79] (Scheme 60). So far, no satisfactory explanation for the acid-catalyzed cage opening of **2a** has been reported.

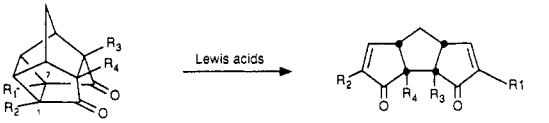
An extremely facile regiospecific acid-catalyzed cage opening is observed for bridgehead methoxy substituted 1,3-bishomocubanones **47c,d**.[6,44] Even with a trace of acid the exclusive formation of tricyclic enone **94** is observed (Scheme 61). In essence, the initial step of this acid-catalyzed nucleophilic ring fission closely resembles the base-induced homoketonization of acetate **47b**[22,43] (Scheme 55). However, after the cleavage of the central C_4–C_5 bond to form the enol **120**, a subsequent C_2–C_3 bond fission occurs to compensate for the positive charge of this rather strained oxonium intermediate. Rapid hydrolysis of the vinyl ether **93** thus formed then leads to the observed product.[6] As mentioned earlier, the vinyl ethers **93** have been obtained by thermal cycloreversion of **47c,d**[6,44] (Scheme 43).

SCHEME 62



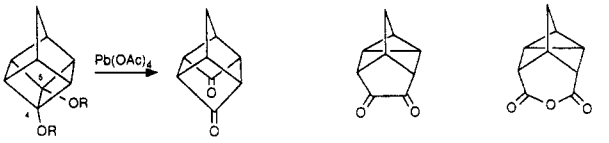
42 121 44 45

SCHEME 63



31c R_1=R_4= H; R_2= OCH_3; R_3= H
31d R_1=R_2= OCH_3; R_3=R_4= H
31f R_1=R_4= H; R_2= OCH_3; R_3= CH_3 95c,d,f

SCHEME 64



25a R= H
25d R= Et 122 123 124

A related acid-catalyzed cage opening has been observed for β-methoxytrishomocubanones **42** and **44** (Scheme 62). With hydrochloric acid in methanol a fast rearrangement to the tetracycles **121** and **45**, respectively, is observed.[42]

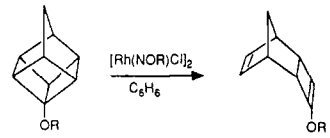
Evidently, a combination of strain and electronic factors is responsible for these fast cage-opening reactions. The electron-releasing ability of the methoxy group and the favorably positioned β-ketone function facilitate this process considerably. Masking the ketone function, e.g., by an ethylene ketal group, completely blocks this cage-opening reaction.[6]

An acid-catalyzed cage-opening reaction has also been reported[36,38] for the "push–pull" methoxy-substituted Cookson cage ketones **31c,d,f** (Scheme 63). With a variety of Lewis acids a quantitative conversion into tricyclopentenones **95c,d,f** is observed. As for methoxy-substituted 1,3-bishomocubanones **47**, this conversion of **31** to **95** can also be realized thermolytically[35,37] (Scheme 44).

4. Miscellaneous

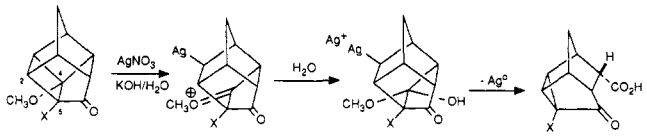
The highly strained tetracyclo[4.3.0.$0^{3,9}$.$0^{4,7}$]nonanedione **122** could be prepared in 50–60% yield by oxidative cleavage of the central C_4–C_5 bond in homocubane-4,5-diol (**25a**) with $Pb(OAc)_4$ in acetone[30] (Scheme 64). Interestingly, this oxidation shows a peculiar solvent dependency. In benzene, dione **122** is a minor product and two additional products are isolated, viz., α-diketone **123** and anhydride **124**. The anhydride is apparently produced from **123** by further oxidation with $Pb(OAc)_4$, since the use of 2 mol of this

SCHEME 65



27 R= Et, TMS

SCHEME 66



47c X= H
47d X= Br

125c,d

126c,d

oxidant raised the yield of **124** to 60%. It has been suggested that the oxidation of diol **25a** to dione **123** is preceded by rearrangement to homocuneane-4,5-diol (**62b**) (cf. Scheme 45). Consistently, **62b** is rapidly transformed into a mixture of **123** and **124**. The suggested lead-catalyzed conversion of the homocubyl skeleton of **25a** to the homocuneanediol **62b** is reminiscent of similar transformations induced by transition metals.[47] In hopes of observing this skeletal rearrangement without subsequent oxidation, diether **25d** was also treated with $Pb(OAc)_4$ in benzene. However, **25d** was recovered in 50–60% yield without the formation of any 4,5-diethoxyhomocuneane.

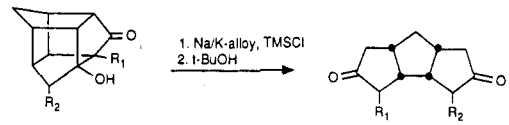
Bridgehead 4-substituted homocubyl ethers **27** underwent a considerably slower[31] rhodium-catalyzed cycloreversion to tricyclononadiene than the parent homocubane or 4-alkylhomocubane (Scheme 65). This has been attributed to the absence of carbocation character in the rate-determining transition state of this two-bond cleavage reaction.[80] The reverse is true for the Ag(I)-catalyzed homocubane/homocuneane rearrangements[31] (Schemes 28 and 29).

The effect of a bridgehead methoxy group on the chemical reactivity of strained polycyclic compounds toward transition metals is most strikingly demonstrated by the Ag^+-catalyzed rearrangement of 4-methoxy-1,3-bishomocubanes **47c,d**[6,44] (Scheme 66). In an attempt to promote the Favorskii rearrangement of **47d**, $AgNO_3$ was added to a suspension of **47d** in 20% aqueous KOH. The desired homocubanecarboxylic acid was not formed, however, but instead an almost quantitative conversion of **47d** to the keto carboxylic acid **126d** was observed. This peculiar transformation appeared to be dependent on the presence of an electron-releasing oxygen substituent at C_4 in **47** as no such rearrangement is observed when such a function is absent.[6] The presence of bromine is not essential as **47c** also smoothly undergoes this transformation to give **126c**. The mechanistic rationale, which involves oxonium intermediate **125**, is depicted in Scheme 66.

The β-keto cage alcohols **40a,b** could be reductively cleaved with Na–K alloy to give tricyclopentenoids **127a,b**[40] (Scheme 67). These reductions are mechanistically related to metal reductions of 1,4-dicarbonyl systems.

In their studies of band parameters of OH-stretching vibrations of tertiary alcohols, Lutz and van der Maas[81] included cubyl alcohols **4a,b**. The data of the strained cubyl alcohols proved to be clearly different from those of the normal saturated tertiary alcohols. This different

SCHEME 67



40a $R_1=R_2=CH_3$
40b $R_1=R_2=-(CH_2)_4-$

127a,b

vibrational behavior is related to an increase ionic character and a decreased shielding of the OH. Compared with phenols the saturated tertiary alcohols are less sensitive to intermolecular interactions whereas the cubyl alcohols behave more or less like the phenols.[81]

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