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CONTROL OF CAGE OPENING REACTIONS IN THE 1,3-BISHOMOCUBANE AND HOMOCUBANE SYSTEMS

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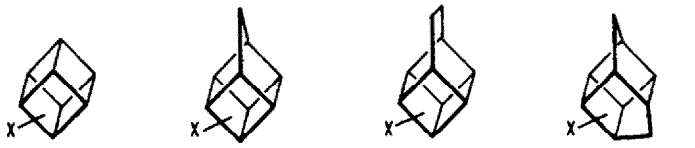
Abstract—The synthesis and base-induced cage opening of 5-functionalized homocubyl alcohols **22** (R is some protective group) is described. In a first approach, the synthesis of **22** has been attempted starting from tricyclic enol **14** and involving the Favorskii cage contraction of 1,3-bishomocubanones **24**. Unexpectedly, 4-methoxypentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-ones **24b** and **29** undergo a facile acid-catalyzed cage fragmentation to give tricyclo[5.3.0.0^{2,5}]decene diones **28a** and **b**, respectively. The Favorskii cage contraction of **24** to homocubane carboxylic acid **25c** has been accomplished for the MEM-protected **24c**, albeit in low yield. With silver cations under basic conditions, **24b** and **c** undergo an unusual oxidative cage fission reaction leading to tetracyclo[4.3.0.0^{2,4}.0^{3,8}]nonan-5-one 7-carboxylic acids **40** and **41**. An efficient route to 4-bromohomocubyl acetate **48** has finally been accomplished starting from 4,5-dibromo-1,3-bishomocubanone **43**. Base-induced homoketonization of **48** is essentially directed by the 5-bromine atom and a regiospecific cleavage of the central C_4—C_5 bond is observed, producing, in a stereospecific manner, 10-oxapentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane **51**.

In 1964, the first synthesis of cubane **1** (X = H) was reported by Eaton and Cole,[1] who elegantly merged known methodology for the construction of this intriguing cage structure. In spite of an early theoretical calculation of its strain energy that seemed to preclude its existence at room temperature,[2] cubane appeared to be thermally surprisingly stable, decomposing only at 200°. This remarkable observation undoubtedly contributed to the formulation of the orbital symmetry rules[3] that later satisfactorily explained its exceptional stability. Encouraged by the successful synthesis of cubane and its homologues, and excited by the possibility of unexpected and unusual behaviour of these highly strained cage compounds, several research groups entered this field. The result of all these activities is a valuable contribution both to synthetic and physical organic chemistry.[4]

Background information

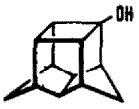
When we began our research in this area in 1968, we were particularly interested in the synthesis of cubane and related cage structures functionalized at bridgehead positions in order to establish the relationship between their chemical reactivity and their cage strain energy. The principal structures which have been and still are the subject of our studies, are depicted below, together with their relative strain energies as obtained by force field calculations.[5]



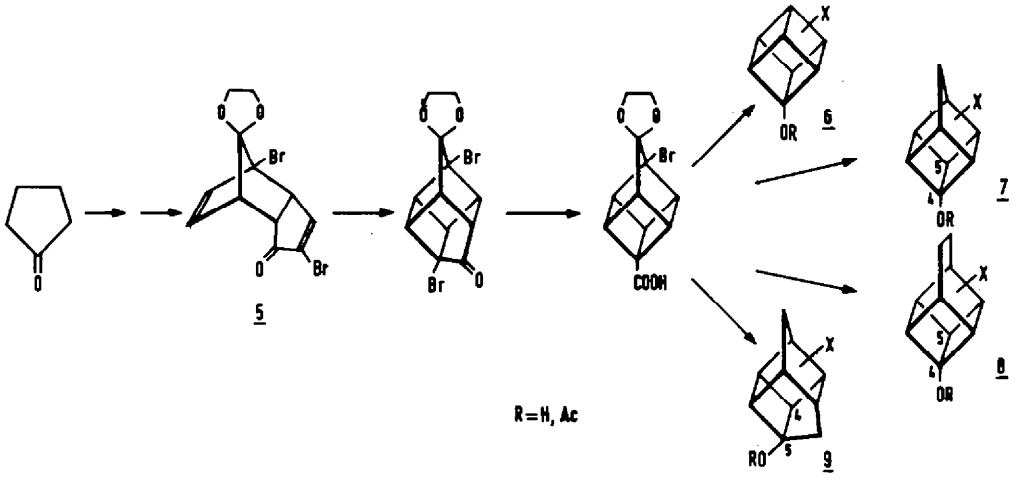
1 Cubane SE ~ 169 | **2** Homocubane 125 | **3** Basketane 124 | **4** 1,3-Bishomocubane 85 Kcal/mole

The observed thermal stability of these polycyclic hydrocarbons (X = H) and their calculated strain energies seem paradoxical. However, this thermal stability is merely caused by the inability of the cage molecule to undergo bond reorganization in a *concerted* manner in the ground state.[3] When there is the possibility of reorganization via a *non-concerted* process, a fast cage degradation or fragmentation reaction may take place, even at low temperatures. Based on the reasoning, we chose to synthesize bridgehead cage alcohols **1**–**4**(X = OH). The hydroxyl function is capable of interacting electronically with the electron deficient cage moiety and can initiate such a *non-concerted* process.† The synthesis of a broad variety of bridgehead substituted cage alcohols was accomplished utilizing the general methodology for cage construction.[8] The key step in this methodology is the intramolecular [$\pi^2+\pi^2$] photocyclization of an appropriate tricyclodecadienone (photoprecursor). Further structural modification of the cage is then

† Formally, these bridgehead alcohols can be regarded as homoenols. Their simplest member is cyclopropanol which has been extensively studied by DePuy.[6] Birdcage alcohol **53** constitutes the first bridgehead substituted cage alcohol which was synthesized and studied.[7]



53



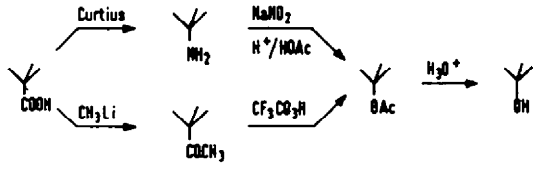
Scheme 1.

accomplished either by cage contraction or by cage expansion, provided that prerequisite functionalities have been introduced at the proper positions. In our hands, dibromotricyclodecadienone ethylene ketal **5** turned out to be a most rewarding photoprecursor as it is readily available from cyclopentanone in large quantities[1,9] and allows the synthesis of all the desired bridgehead cage alcohols or acetates[10] as portrayed in Scheme 1.

With the exception of bishomocubanol **9**, the introduction of a bridgehead oxygen function (OH or OAc) was most efficiently realized in the final stage of the reaction sequence by chemical transformation of a bridgehead carboxylic acid group involving either deamination of a bridgehead amine or Baeyer–Villiger oxidation of a methyl ketone (Scheme 2).

Acidic hydrolysis of the acetates under carefully controlled conditions afforded the corresponding bridgehead cubyl, homocubyl and 1,3-bishomocubyl alcohols **6**, **7** and **9**, respectively. Surprisingly however, whereas the highly strained cubyl alcohols were isolated in excellent yields and exhibited a relatively high thermal stability, the considerably less strained homocubyl alcohol **7** appeared to be thermally very labile which thwarted its isolation. Even more pronounced, the basketane alcohol **8** could not be obtained as yet. These experimental observations indicate that there is no direct correlation between the thermal stability and total strain energy of the respective polycyclic alcohols.

Attempts to obtain the bridgehead alcohols **6**–**8** by base-catalyzed alcoholysis of the corresponding acetates failed completely. Instead, a base-catalyzed cage opening reaction was observed that leads to seco-cage ketones **11** in high yields[11] (Scheme 3). This process that can be formulated as a homoketonization



Scheme 2.

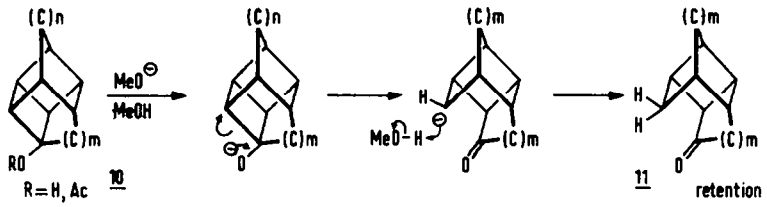
reaction, appeared to be completely stereo- and regiospecific.

In the homocubane, basketane as well as in the 1,3-bishomocubane system, this cage opening proceeds with complete *retention* of configuration. This stereochemical outcome is typical for polycyclic bridgehead alcohols in which the bridgehead is being flanked by 4- and/or 5-membered rings. No exception to this rule has been observed as yet.[12] These stereochemical results can be best understood by assuming the initial formation of a carbanionic species that is not stabilized by homoconjugative interaction with the developing carbonyl function due to strain effects (SE_1 process).[13] As a consequence rapid protonation will occur from the polar *endo* side.

The regiochemistry of bond cleavage in the bridgehead acetates **10** (R = Ac) is primarily governed by relief of cage strain, resulting in the *exclusive* formation of the thermodynamically most stable half cage ketones **11**. As shown by force field calculations,[5b] this certainly does not imply the involvement of the most strained C—C bond.

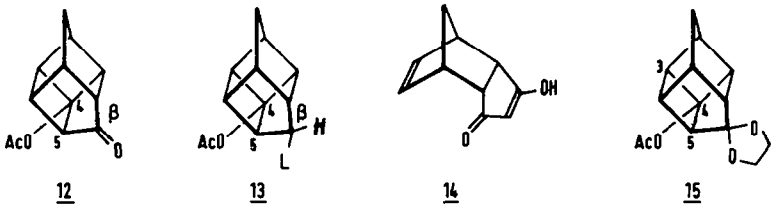
The reactivity of the polycyclic alcohols or acetates **10** in this homoketonization process *grosso modo* parallels the total cage strain energy: cubane > basketane > homocubane > 1,3-bishomocubane. However, again the basketane analogue behaves somewhat exceptionally as basketyl acetate **8** homoketonizes much more rapidly than homocubyl acetate **7**, despite its somewhat lower cage strain energy. This increased reactivity reflects the effect of the expanded ethylene bridge which increases the constraint around the C_4 and C_5 atoms in the basketane system relative to that in the homocubane analogue. As already noticed for the thermal stability of the cage alcohols **10** (R = H), local strain features seem to be of more importance than total cage strain energy in determining the chemical reactivity of these cage alcohols.

In the examples discussed so far, the regiochemistry of the base-induced homoketonization of bridgehead alcohols is determined solely by thermodynamic parameters. Electronic factors do not play a significant role here, since in none of the three conceivable C—C bond cleavages is the developing carbanion particularly stabilized. Therefore, we were intrigued by the



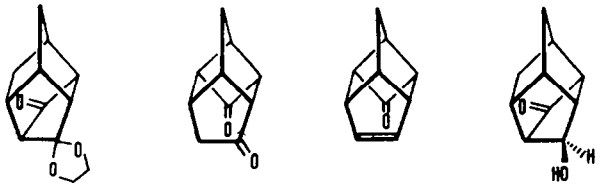
Scheme 3.

possibility of directing the regiochemistry of this cage opening by stabilization of one of the possible carbanionic intermediates, which eventually could lead to a thermodynamically less stable seco-cage framework. For this purpose, we selected bridgehead substituted 1,3-bishomocubyl acetates **12** and **13**, containing either a carbanion stabilizing carbonyl group or an efficient leaving group L at the position β to the bridgehead acetate function.[14]



12 **13** **14** **15**

The synthesis of **12** and **13** starts from tricyclic enol **14**, which is actually the Diels–Alder adduct of cyclopentadiene and cyclopentene-1,3-dione. As the enol acetate of **14** is quantitatively converted into 1,3-bishomocubanone acetate **12**, we have a very efficient route to this bridgehead cage acetate at hand. Homoketonization of ketal acetate **15**, which could only be accomplished with NaOMe in refluxing MeOH, conformed entirely to the general pattern, i.e. producing the thermodynamically most stable half cage ketone **16** among the three conceivable structures.



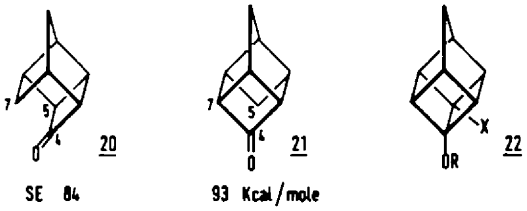
16 **17** **18** **19**

In contrast, keto acetate **12** underwent an extremely fast cage opening affording regiospecifically diketone **17** in quantitative yield. The observed regiochemistry, as well as the relative rate of formation of **17** as compared with that of **16**, clearly demonstrates the effect of conjugative carbon-leaving group stabilization of a C=O function in this eliminative ring fission process. The alternative way to enforce the homoketonization to proceed in such a "contra thermodynamic" direction, namely via a heterolytic fragmentation with the concomitant expulsion of nucleofuge L, was studied for mesylate **13** (L = OMes). Under relatively mild conditions, the *anti*-mesylate afforded the interesting keto-olefin **18** in quantitative yield. This 1,3-through cage elimination process appeared to be critically dependent on structural features, indicating a subtle balance between the thermodynamic stabilities of the conceivable ring opened products and eliminative carbanionic stabilization. Thus, under identical conditions, the *syn*-mesylate does not show any cage opening pointing to stringent stereo-electronic control of this process. Replacement of the mesylate group by an alcohol function in the proper *anti*-position completely blocks this elimination reaction, even at higher temperatures. Instead, the exclusive formation of the thermodynamically most favourable ketone **19** was observed. Evidently, in the 1,3-bishomocubane system, a "contra thermodynamic" C_4—C_5 bond cleavage can be realized, provided that stabilization of the intermediate C_5-carbanionic species, by either direct conjugation or an eliminative process, is sufficiently large. Force field calculations reveal that the difference in thermodynamic stability of **16** and **17** is at least 7 kcal mol^{-1},[15] implying at least this decrease in activation energy for C_4—C_5 bond cleavage.

The present challenge

In the more strained homocubane system, the difference in thermodynamic stability between seco-cage ketones **20** (C_4—C_7 cleavage) and **21** (C_4—C_5 cleavage) is even more pronounced and amounts to at least 9 kcal mol^{-1}.[5] Therefore, in comparison with the hitherto discussed 1,3-bishomocubane case, product formation in the base-induced homoketonization of 5-functionalized homocubyl alcohols **22** (X is some carbanion stabilizing group) may be more dependent on the balance between the relative thermodynamic stabilities of the conceivable seco-cage structures **20** and **21** and the stabilities of their respective carbanionic intermediates. Challenged by this hypothesis, we sought to synthesize 5-functionalized homocubyl

alcohols or acetates **22** and study their base-induced homoketonization. The results of this study are reported in this paper.



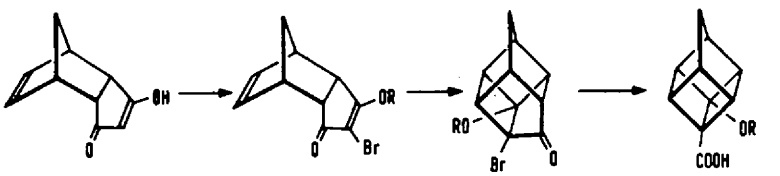
An attractive and direct route to these substrates **22** would start from tricyclic enol **23a** as the photoprecursor and involve the Favorskii ring contraction of bromobishomocubanone **24** to carboxylic acid **25** (Scheme 4). The alkaline conditions needed for this latter cage contraction reaction necessitates the use of a base stable protective group R, which eventually can be removed under mild acidic conditions.

The synthesis of the required bromoenol **23a** could readily be achieved by bromination of enol ether **14** in acetic acid.[16] As in the case of enol ether **14**, direct irradiation of **23a** in MeOH failed to give the desired photoproduct **24a**. Therefore, protection of the OH function was attempted at the stage of enol **23a**. Among the various possibilities, we considered the t-butyldimethylsilyl group most attractive for the set purposes. Unfortunately, despite extensive efforts utilizing several conditions, e.g. DMF/DMAP/Et_3N, CH_2Cl_2/DMAP/Et_3N, or DMF/imidazole, the formation of silyl enol ethers **23** (R = TBDMS, TMS) from **23a** could not be accomplished. This failure is probably due to efficient steric shielding of the enol function by both the adjacent bromine atom and the norbornene moiety which does not allow the incoming bulky silyl group to take the required position for substitution.

However, methylation of **23a** was realized through its sodium salt, using dimethyl sulfate in refluxing MeOH. Again the steric effect of the vicinal bromine atom is seen in the relatively low conversion of 60% in this substitution reaction. Methylation of enolether **14**, under identical conditions, proceeded quantitatively. The mixture of enolether **23b** and starting enol **23a** could readily be separated by crystallization from toluene. Attempts to mask the enol as an acetal type enolether were only partly successful. The formation of the 1-ethoxyethyl enolether by reaction of **23a** with ethyl vinylether and TosOH under standard conditions failed. In contrast, (2-methoxy)ethoxymethylether (MEM-ether) **23c** was obtained in high yield from **23a** upon treatment with MEM-chloride and Et_3N. At a later stage of our study, we also needed access to enolacetate **23d** and enolmesylate **23e**. These enolesters were readily prepared by the reaction of **23a** with Ac_2O/DMAP and mesylchloride/Et_3N, respectively.

First unexpected result

The synthesis of the 1,3-bishomocubanone system by photocyclization of tricyclodecadienones **23** appeared to be less obvious than anticipated. Irradiation of methyl enolether **23b** in benzene or toluene under the usual conditions did not result in the isolation of bishomocubanone **24b**. Instead, a mixture of cage opened products was obtained. Careful analysis of this photoreaction using GLC and ^{1}H-NMR spectroscopy unambiguously established the initial formation of the anticipated cage ketone **24b**, which, however, slowly rearranged under the conditions applied. The isolated mixture contained, besides some **24b** (20% of the mixture), one major component (60–70% of the mixture). The formation of this product could be completely suppressed by performing the photocyclization of **23b** in toluene containing some ammonia. Under these conditions bishomocubanone **24b** was obtained as a slightly yellow oil in 73% yield, that on storage at $-18°$ appeared to be indefinitely stable. Its suspected acid sensitivity was confirmed by its instantaneous rearrangement upon treatment with HCl(g) in toluene. The spectral features of this rearranged product immediately suggested the occurrence of a deep seated cage opening process. The IR, ^{1}H-NMR, ^{13}C-NMR and UV spectra revealed the presence of a cyclopentenone moiety, whereas the IR and ^{13}C-NMR spectra also indicated the occurrence of a cyclobutanone ring (see experimental section for details). This information, together with mechanistic considerations, allowed the assignment of structure **28a** for this cage degradation product. An X-ray diffraction analysis[17] unambiguously established the all-*cis* structure of this tricyclodecene dione **28a** (Fig. 1). A rational for its formation is depicted in Scheme 5. As this process is acid catalyzed, protonation of the carbonyl function is assumed to initiate scission of the central C_4—C_5 bond to form a relatively stable oxonium ion with release of a considerable amount of strain energy. In non-nucleophilic solvents such as benzene and toluene, this relatively strained cation **26** can be further stabilized by a subsequent C_2—C_3 bond cleavage leading to tricyclic enolether **27** (X = Br).



14

23 a. R=H
b. R=CH$_3$
c. R=MEM
d. R=Ac
e. R=Mes

24 a. R=H
b. R=CH$_3$
c. R=MEM
d. R=Ac
e. R=Mes

25 b. R=CH$_3$
c. R=MEM

Scheme 4.

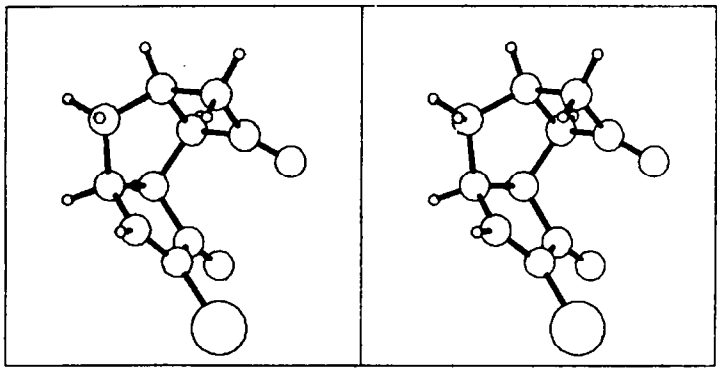
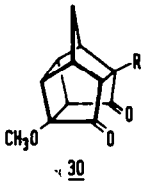


Fig. 1. Stereoview of compound **28a**.

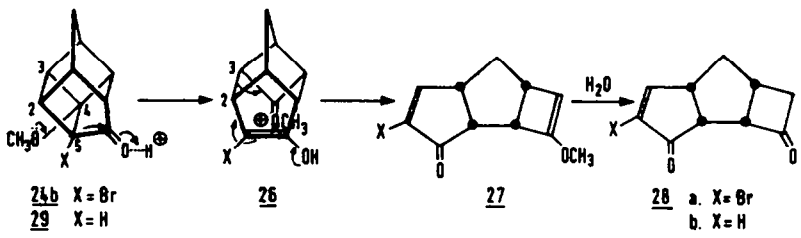
These cyclobutane enolethers are prone to undergo rapid hydrolysis, and accordingly, it is not surprising to find that under the conditions of photocyclization, only its hydrolysis product **28a** is isolated. The intermediacy of **27** (X = Br) could be proven by performing the acid-catalyzed rearrangement of **24b** in $CDCl_3$/HCl(g) in an NMR tube. In a very slow reaction, the characteristic vinylether proton and OCH_3 protons appeared at the expected positions, namely at δ 4.52 and 3.40 ppm, respectively. As implied by the proposed mechanism, the 5-bromo substituent in **24b** considerably accelerates this cage opening process. Photocyclization of the bromine lacking methyl enolether of **14** in toluene under standard conditions afforded 1,3-bishomocubanone **29** in quantitative yield without any formation of its ring opened product **28b**. The addition of some acid slowly converted **29** into tricyclic diketone **28b**. In contrast, the presence of an electron-releasing substituent at the C_4-position in **24** is essential. The 4-acetoxy- and the 4-mesylate-1,3-bishomocubanone **24d** and **e**, and even the MEM-ether **24c**, obtained by irradiation of the corresponding tricyclodecadienones **23**, did not show this acid-catalyzed cage opening reaction.

The first step in this *regiospecific* cage opening process of **24b** and **29** essentially constitutes an acid-catalyzed nucleophilic ring fission which is closely related to the base-induced homoketonization of 5-acetoxy-1,3-bishomocubanone **12** in methanol. A rather strained oxonium intermediate **26** is formed here, that in benzene or toluene cannot be neutralized by the simple extraction of a bridgehead proton. Instead, a subsequent C_2—C_3 bond scission is enforced to compensate for the positive charge. As this bond cleavage also releases a considerable amount of strain energy, we assume this reaction to be very fast. The observed dependency of this two-step cage degradation process on the electron-releasing ability of the 4-oxygen substituent confirms that the formation of the oxonium intermediate is indeed the rate-determining step. The complete unfolding of a bridgehead methoxy-substituted 1,3-bishomocubanone is a new and appealing example in which strain features of the cage skeleton, together with electronic factors as imposed by the attached functional groups, delicately determine ultimate chemical behaviour. Another example of such an acid-catalyzed cage opening reaction was recently described by Mehta *et al.*,[18] for the "push–pull" methoxy-substituted Cookson's cage ketones **30**.



30

Interestingly, the cycloreversion of methoxy-substituted 1,3-bishomocubanone **24b** could also be accomplished very efficiently using the flash vacuum thermolysis technique.[19] At 400°/3.5 × 10^{-1} Torr both **24b** and **29** were smoothly converted into enolethers **27**. This thermal reorganization can be best accounted for by a radical pathway, involving the initial formation of a 1-methoxy-1,4-radical by regioselective cleavage of the C_4—C_5 bond followed by further bond scission.[20] The formation of such a 1,4-diradical is particularly favoured in terms of Viehe's concept of capto-dative



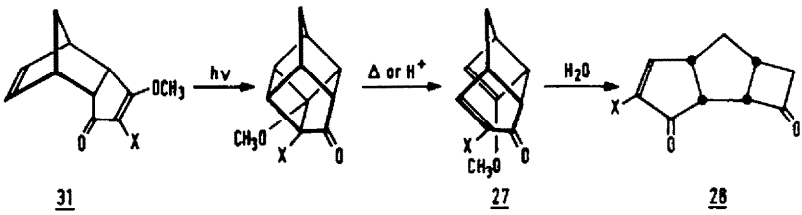
24b X = Br
29 X = H

26

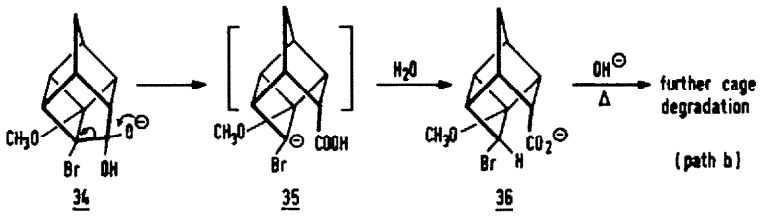
27

28 a. X = Br
b. X = H

Scheme 5.



Scheme 6.

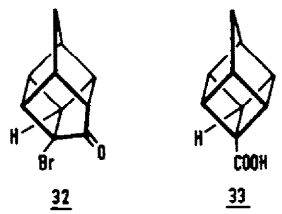


Scheme 7.

stabilization.†[21] The ultimate formation of the all-*cis*-tricyclo[5.3.0.0^{2,5}]decane system **28** can actually be formulated as a two-step methathesis reaction starting from **31** (Scheme 6). Further elaboration of this tricyclic system for the synthesis of cyclopentanoids is currently under investigation.

The second unexpected result

After having accomplished the synthesis of 4-oxygen-substituted 1,3-bishomocubanones **24**, we attempted the Favorskii cage contraction to obtain the corresponding homocubane carboxylic acids **25** (Scheme 4). We started off with methoxy bromoketone **24b**, that was treated with 30% KOH in water under the usual conditions. Most unexpectedly, this Favorskii reaction failed completely. No carboxylic acid **25b** or any other identifiable material could be obtained from this reaction. Variation of the reaction conditions and the applied base system did not alter this result. The failure must be attributed to the presence of the bridgehead methoxy group as the corresponding bromoketone **32**, which lacks this function, smoothly contracts to homocubane carboxylic acid **33**.[24]



As there is no reason to believe that the methoxy group itself would not survive the strong basic conditions used, we suggest that its dramatic effect on the course of the Favorskii reaction is of electronic origin. An explanation is depicted in Scheme 7. The first step in this process is the addition of the hydroxide anion to the strained carbonyl function of **24b** leading to hydrate **34** that can undergo either a concerted semi-benzilic acid type cage contraction to the desired carboxylic acid **25b** (path a), or an eliminative nucleophilic ring fission to form carbanion **35** (path b). Electronic stabilization of this latter carbanion by the adjacent electron-withdrawing methoxy group could now favour path b over path a. Subsequent protonation of **35** would then lead to seco-cage structure **36**, that under the severe alkaline conditions may undergo further degradation to water-soluble material. This suggestion of a strong regio-electronic effect of the OCH_3 function is firmly supported by a report by McDonald and Curi,[25] who studied the Favorskii reaction of a β-methoxy substituted bicyclo-[2.2.1]heptanone. As the mesylate function is even more electron attracting, an increased lability of the bridgehead-substituted methylsulfonate **24e** is anticipated. This appeared to be true. In refluxing 15% KOH aq complete degradation of **24e** was observed within 15 min. In contrast, a more successful result was obtained with MEM-ether **24c**. Whereas in aqueous medium only decomposition was observed, the use of NaOH in xylene afforded the desired homocubane carboxylic acid **25c** as an oil in low yield. This MEM-protected bridgehead homocubanol turned out to be extremely difficult to purify.

In despair, we tried to promote the Favorskii cage contraction of **24b**, by enhancing the leaving ability of the α-bromine atom through Ag^+ catalysis.[26] Although silver is well known for its ability to isomerize strained polycyclic structures such as homocubanes and cubanes,[27] the occurrence of only one report on an Ag^+-catalyzed cycloreversion of a 1,3-bishomocubane was encouraging.[28] Thus, to a suspension of bromoketone **24b** in 20% KOH aq, an excess of $AgNO_3$ was added and the reaction mixture stirred for 4 h at 60°. The almost immediate formation of a silver mirror manifestly revealed the occurrence of an oxidative reaction, making a straightforward Ag^+ assisted Favorskii cage contraction of **24b** very unlikely. Indeed,

† Such a capto-dative stabilization involving methoxy-substituted Cookson's cage ketones has recently been reported by the research groups of Mehta *et al.*,[22] and Kanematsu and co-workers.[23]

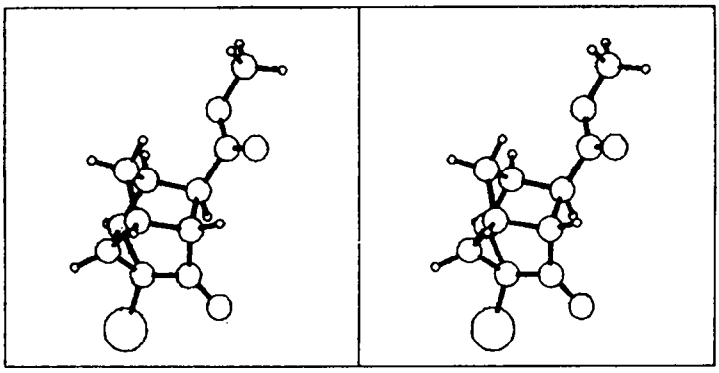
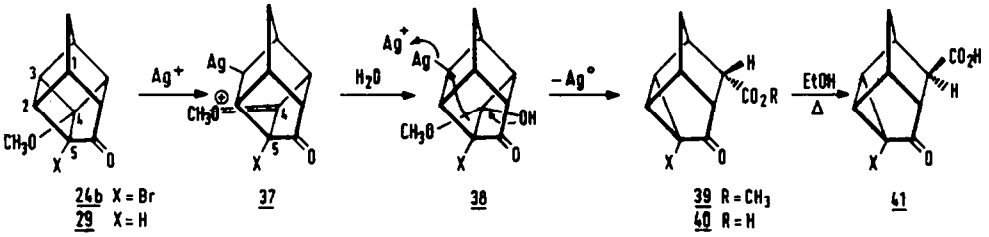


Fig. 2. Stereoview of methyl ester of compound **41**.



24b X = Br
29 X = H

37

38

39 R = CH_3
40 R = H

41

Scheme 8.

a single crystalline carboxylic acid was isolated in 85% yield, which according to its spectral data was certainly not the desired homocubane carboxylic acid **25b**. Repeated crystallization from toluene afforded a pure sample with m.p. 127.5–129°. However, using ethanol as solvent for the crystallization caused a remarkable increase in melting point (m.p. 220–221°) indicating a rearrangement reaction under these conditions. Both the IR and NMR spectra showed only minor changes suggesting epimerization of the carboxylic acid function. The complexity of the ^{1}H-NMR spectra did not allow a definite assignment of the structures of these carboxylic acids. However, an X-ray analysis of the methyl ester of the epimerized carboxylic acid unequivocally ascertained its structure as the methyl ester of **41**.[29] A stereopicture is shown in Fig. 2.

An explanation for the high yield formation of this tetracyclic structure from 1,3-bishomocubanone **24b** is given in Scheme 8. As known from the extensive work on the Ag^+-catalyzed valence isomerization of cubane and homocubane derivatives,[27] the first step in this cage opening of a 1,3-bishomocubane derivative most certainly involves electrophilic interaction of the Ag^+ cation with one of the σ-bonds of the cage, followed by C—C bond cleavage and formation of a cationic intermediate. Here, cleavage of the C_3—C_4 bond is particularly favoured as, first, it involves the most strained σ-bond in this cage structure.† Secondly, it leads to the thermodynamically most stable half cage intermediate **37** (X = Br). Thirdly, it allows an attractive accommodation of the positive charge as an oxonium ion. Based on similar transformation in the cubane and homocubane systems, stabilization of such a cationic intermediate would normally involve subsequent scission of the C_2—C_5 bond and expulsion of the Ag^+ cation affording the formal cycloreversion product **31**.[28] However, under the conditions applied, no formation of tricyclodecadienone **31** or its hydrolysis product was established. The lifetime of oxoniumion **37** is apparently long enough to permit efficient trapping by H_2O/OH^- to form hemiacetal **38**. This interception of a silver-substituted cation by an external nucleophile is very unusual and has, to our knowledge, no precedent in the area of cage chemistry. Hemiacetal **38** is now suited to undergo a formal retro-Claisen condensation reaction by scission of the C_4—C_5 bond, immediately followed by a cyclopropanation reaction with elimination of Ag^0 (in structure **38** shown in a concerted manner), leading to tetracyclic ester **39** (X = Br). Saponification of the ester function then gives carboxylic acid **40**, that in refluxing ethanol slowly epimerizes to **41** (X = Br). This Ag^+-induced cage opening is also observed for MEM-ether **24c**. The presence of a masked bridgehead alcohol function at the C_4 position appeared to be crucial as the parent 1,3-bishomocubanone does not undergo such an electrophilic cage opening reaction. Finally, we proved that the bridgehead bromine at C_5 is not essential for this cage opening reaction as methoxy ketone **29**, lacking this atom, is also smoothly transformed into tetracyclic carboxylic acid **41** (X = H) under these conditions.

In conclusion, the presence of a bridgehead oxygen containing substituent at the β-position to the ketone function in the 1,3-bishomocubanone system considerably affects its chemical reactivity both under acidic and basic conditions. As a consequence, the

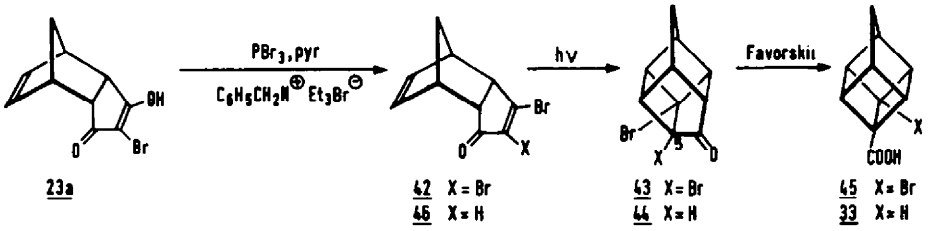
† The C_3—C_4 bond essentially constitutes the central bond of a bicyclo[2.2.0]hexane moiety constrained in a 1,3-bishomocubane cage skeleton.

Favorskii cage contraction, which thus far has always been a reliable method for the contraction of a 1,3-bishomocubanone to the homocubane system[30] cannot be applied here for the synthesis of 4-oxygen-substituted homocubane 4-carboxylic acids. Although the above experiments did not provide the desired results, this study has been rewarded by the discovery of efficient routes to the multi-functionalized tricyclo-[5.3.0.0^{2,5}]decane and tetracyclo[4.3.0.0^{2,4}.0^{3,8}]nonane systems.

Reward

The strategy for the synthesis of substrate **22** was hitherto based on the introduction of the OR substituent in the primary stage of the sequence, followed by a conversion of the COOH group into a suitable anion stabilizing function. The reluctance of the oxygen-substituted 1,3-bishomocubanones **24** to undergo a Favorskii cage contraction to **25** necessitated adaption of our strategy to **22**. We chose to reverse the principal synthetic steps, that is, to introduce first an anion stabilizing function and in a later stage the required oxygen substituent by a functional group transformation. An attractive starting material for this approach seems to be 4,5-dibromobishomocubanone **43**, where the 5-bromo substituent is predestined to serve as an anion stabilizing group. The Favorskii cage contraction to 5-bromohomocubane carboxylic acid **45** may be hampered by a competitive cage opening of the Haller–Bauer type (Scheme 7) favoured by the electronegative Br at C_5. On the other hand, the reported successful contraction of a tetrachlorobishomocubanone to a homocubane carboxylic acid is encouraging.[24] For the synthetic plan outlined above the bicyclic dibromide **42** is needed as the photoprecursor (Scheme 9). An obvious route to **42** seems to start from bromoenol **23a** and involve subsequent replacement of the enolic hydroxyl function by bromine.

Initial attempts to achieve this transformation in the usual way with PBr_3 in $HCCl_3$[31] were disappointing. At room temperature, no reaction was observed at all, due to the poor solubility of enolbromide **23a** in this medium, whereas under reflux intractable mixtures were formed which contained only a minor amount of the desired product **42**. Under the latter conditions, enolbromide **23a** rapidly dissolved indicating the successful formation of the corresponding enol phosphate ester. However, subsequent replacement of this phosphate ester function by bromide, which involves a Michael type addition–elimination process, is apparently very slow under these conditions, causing considerable decomposition. We reasoned that this sluggish addition reaction could be due to a rather low concentration of bromide ions. Indeed, the addition of pyridine[32] significantly increased the yield of **42**. An excellent transformation of enolbromide **23a** into **42** was finally achieved by adding an excess of benzyltriethylammonium bromide as the bromide source. This dibromide appeared to be a rather labile compound, that after purification was immediately to be used for the photocyclization to **43**. Irradiation of **42** was performed in toluene in the usual way. The first experiment afforded the desired cage compound **43** in quantitative yield in a clean reaction. However, when this preparation was repeated on a larger scale and with a different batch of **42**, the yield dropped considerably and tarry by-products were formed. By careful chromatography, a new cage compound could be isolated in low yield to which, on the basis of its spectral properties, structure **44** was assigned. As this bishomocubanone differs only from **43** in its substitution at C_5, speculation on its formation circles around some radical process involving reductive removal of this C_5-bromine. Obviously, such a radical reduction requires a H-donor. To test this hypothesis, we performed the irradiation of **42** in benzene instead of in toluene. Indeed, a much cleaner reaction was observed now in favour of the desired **43**. However, even now some reduction product **44** was still present. No such product was found when the starting dibromide **42** had been carefully purified by repeated crystallization from ethanol. This finding indicated that some impurity present in the starting material could be responsible for the initiation of the radical reduction of **43**. In our first experiment we used a batch of **42** which was obtained from **23a** without using benzyltriethylammonium bromide. We suspected this reagent to be the radical initiator. Hence, the irradiation of **42** was repeated in benzene to which a minor amount of the ammonium bromide was added. Under these conditions, the formation of **44** was indeed almost completely favoured to the expense of **43**. The absence of any tricyclic enon **46** in this reaction makes photoreduction of the photoprecursor **42** and the formation of **44** therefrom unlikely. This remarkable effect of the benzyltriethylammonium bromide can be understood by assuming its triplet sensitization by triplet excited dibromobishomocubanone **43** or its photoprecursor **42**. Fragmentation of this excited species leads among other things to the formation of benzylradicals, which regioselectively abstracts the 5-bromine from **43** and forms the corresponding C_5-bridgehead radical. Propagation of this radical process is realized by subsequent hydrogen abstraction from either the ammonium salt or the solvent.



Scheme 9.

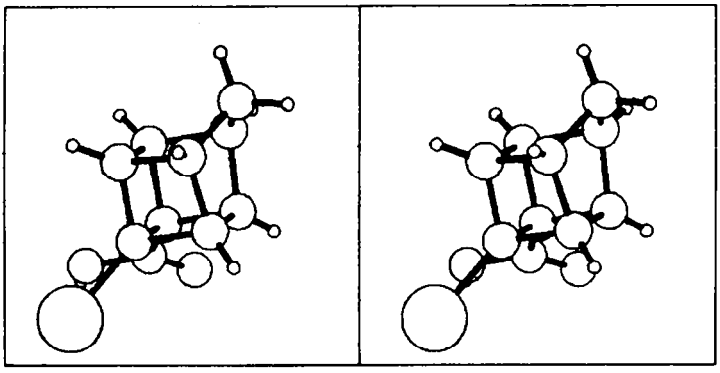
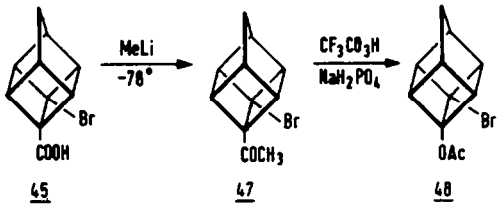


Fig. 3. Stereoview of compound **45**.



Scheme 10.

With a reproducible synthesis of dibromobishomocubanone **43** at hand, its cage contraction was undertaken. Much to our delight, the 5-bromo substrate **43** underwent a smooth Favorskii rearrangement when treated with 35% KOH aq at 100° for 1.5 h. 4-Bromohomocubane carboxylic acid **45** was isolated in a quite satisfactory yield of 67%. Recrystallization from ethanol afforded **45** as a nice crystalline material which allowed verification by X-ray analysis (Fig. 3).†

The next step, the conversion of the carboxylic function into a bridgehead oxygen substituent, was performed by the sequence outlined in Scheme 10.

Methyl ketone **47** was obtained in 80% yield by reacting acid **45** with MeLi at −78°. Under these conditions, the competing formation of the corresponding tertiary carbinol could almost completely be avoided. Subsequent Baeyer–Villiger oxidation with trifluoroperacetic acid afforded the desired bridgehead acetate **48** contaminated with a minor amount of the corresponding trifluoroacetate. As both acetates appeared to be rather labile compounds, no separation was attempted.

Homoketonization of **48** was carried out under the usual conditions with NaOMe in MeOH. At room temperature complete conversion was observed within 1 h. An oily product was obtained which according to TLC and capillary GLC consisted of a single product that was only slightly contaminated. A pure sample was obtained by flash chromatography on silica, although at the cost of considerable losses. The mass spectrum revealed the absence of bromine. Chemical ionization established the molecular mass to be 164.0837, which corresponds with the elemental composition $C_{10}H_{12}O_2$. The IR spectrum lacked the anticipated C=O function but instead indicated the presence of an OCH_3 group (2840 cm^{-1}). The ^{1}H-NMR spectrum confirmed the presence of such an OCH_3 group at δ 3.53 A singlet signal at δ 1.61 for the bridge methylene protons and a complex multiplet for six protons between δ 2.4–2.9 ppm suggested a symmetrical cage structure. Finally, the observed low field resonance for one proton at δ 4.45–4.6 ppm made structure **51** a very likely candidate for the homoketonization product (Scheme 11). Unambiguous proof for the correctness of this assignment was provided by the ^{13}C-NMR spectrum which showed the required eight resonances at the correct positions and with the right multiplicities.

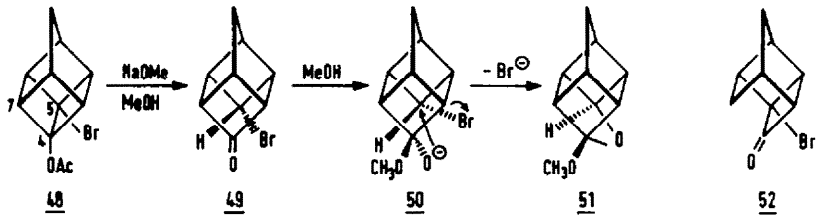
This formation of acetal **51** firmly establishes the ability of bromine to direct the base-induced homoketonization process in the homocubane system. Methanolysis of the acetoxy function initiates cage opening by scission of the central C_4—C_5 bond and leads regio- and stereoselectively to half cage ketone **49**.

Due to ring strain this ketone is still very reactive.[33] Addition of methanol to the C_4-ketone function from the accessible *exo*-side produces a hemiacetal **50**, that readily reacts intramolecularly at the C_5-centre with expulsion of the ideally situated bromine atom. This intramolecular substitution proves the anticipated *exo*-configuration of the bromine substituent and establishes the homoketonization of **48** to proceed with retention of configuration.

This rewarding directive effect of the relatively poor carbanion stabilizing bromine is illustrative of the subtle balance between thermodynamic and electronic parameters that determines the regiochemistry of the base-induced nucleophilic cage opening reactions. It proves, at least in this homocubane case, the initial formation of an anionic species in which considerable negative charge is localized at the carbon leaving group. This finding strongly favours an SE_1-type substitution process.[34]

From the extended analysis of the minor by-products of this homoketonization of **48**, no indication whatsoever for the formation of the thermodynamically more favoured half cage ketone **52** was found. Hence, this homoketonization of **48** is a regiospecific process and does not constitute a "borderline case" in which also some cleavage of the C_4—C_7 bond has occurred. Having accomplished the first homoketoniz-

† J. M. M. Smits and P. T. Beurskens, Department of Crystallography, University of Nijmegen (1985).



Scheme 11.

ation of a 4-homocubyl acetate which proceeds in a "contra thermodynamic" fashion, we are particularly anxious to find such a borderline case, as this would set a reference point for electronic interference of a functional group in these cage opening processes. Work to this end is currently underway in our laboratory.

Concluding remarks

We have shown that appropriate functionalization of bridgehead-substituted 1,3-bishomocubyl and homocubyl acetates drastically affects the regiochemistry of their base-induced homoketonization. The introduction of a carbanion stabilizing group such as a carbonyl function and even a bromine substituent, or a good leaving group such as a mesylate function, regiospecifically directs this cage fission process. In these cases electronic stabilization leads to a decrease of the transition state energy for C_4—C_5 cleavage to such an extent that product formation is no longer determined by the relative thermodynamic stabilities of the conceivable cage opened products.

From a synthetic point of view, the possibility of directing the regiochemistry of the homoketonization process in strained cage compounds is particularly attractive as it allows the synthesis of different polycyclic structures from one single bridgehead substituted acetate or alcohol by a simple modification of its substitution pattern. Usually, such a variation in substitution pattern is most conveniently achieved at the stage of the photoprecursor. However, in some cases modification can also be readily accomplished by group transformation on the cage structure. This latter approach is nicely illustrated by the formation of seco-cage ketones **16–18** from bishomocubanone acetate **12** as the common starting material. The great potential of tricyclic enol **14** as the common precursor for functionalized 1,3-bishomocubanes as well as for homocubanes is demonstrated in this paper. Being readily available from cyclopentadiene in appreciable quantities, this enol contains all the structural features to allow the desired functionalization. As the subsequent photocyclization is close to quantitative, a short, convenient and cheap synthesis of functionalized 1,3-bishomocubanones and in essence also of homocubanes has now become available. In this and other papers, we have shown that these complex high energetic cage structures are liable to stereo- and regio-controlled bond cleavages allowing access to a variety of interesting polycyclic ring systems, which may be put to good use both in natural product synthesis and mechanistic studies.

EXPERIMENTAL

IR spectra were taken on a Perkin–Elmer 257 grating spectrometer. NMR spectra were recorded on a Varian EM-390, Bruker WH-90 or Bruker WP-60 using TMS as internal standard. Mass spectra were recorded on a VG 7070E spectrometer. All m.ps are uncorrected. Elemental analyses were carried out in the Microanalytical Department of the University of Nijmegen.

5-*Hydroxytricyclo*[5.2.1.$0^{2,6}$]*deca*-4,8-*dien*-3-*one* (**14**). This was prepared in 82% yield as described by DePuy and Zaweski.[35]

4-*Bromo*-5-*hydroxytricyclo*[5.2.1.$0^{2,6}$]*deca*-4,8-*dien*-3-*one* (**23a**). This was prepared in 82% yield as described by Oda and co-workers.[16]

4-*Bromo*-5-*methoxytricyclo*[5.2.1.$0^{2,6}$]*deca*-4,8-*dien*-3-*one* (**23b**). Bromo enolether **23a** was added to a fresh soln of NaOMe in MeOH (1 M, 25 ml) to which, under reflux, Me_2SO_4 (4.7 g, 37 mmol) was added dropwise during 30 min. After refluxing for another 30 min, excess Me_2SO_4 and the solvent were removed *in vacuo* and the residue CH_2Cl_2 extracted. This organic phase was washed with 5% $NaHCO_3$ aq and water, and dried ($MgSO_4$). Solvent was removed to give **23b** (3.13 g, 57%) as an oil which slowly solidified. Recovery of the starting **23a** was realized by acidifying the $NaHCO_3$ aq increasing the effective yield of **23b** to ~90%. Recrystallization from toluene gave an analytical pure sample, m.p. 118.5–119°.

IR ν_{max} (KBr) 1690 (C=O), 1590 (C=C) cm^{-1}; UV λ 263.5 nm (EtOH, ε 13,000); ^{1}H-NMR ($CDCl_3$) δ 1.79 and 1.59 (ABq, J = 8.6 Hz, 2H, H_{10}, $H_{10'}$), 2.97–3.47 (m, 4H, H_1, H_2, H_6, H_7), 4.11 (s, 1H, OMe), 5.85 (d of d, J_{H_8,H_9} ~ 6 Hz, J ~ 3 Hz, 1H, H_8 or H_9), 6.03 (d of d, J_{H_8,H_9} ~ 6 Hz, J ~ 3 Hz, 1H, H_8 or H_9); ^{13}C-NMR ($CDCl_3$) δ 40.44, 43.49, 51.51, [illegible], 57.99, 99.99 (C_4), 131.0 (C_8 or C_9), 134.3 (C_8 or C_9), 184.2 (C_5), 197.8 (C_3); *m/e* 254/256 (M^+, 1 Br), 188/190 (100%, 1 Br, —C_5H_6). (Found: C, 51.75; H, 4.28. Calc for $C_{11}H_{11}O_2Br$: C, 51.79; H, 4.35%.)

4-*Bromo*-5-([2-*methoxy*-]*ethoxy*-)*methoxytricyclo*[5.2.1.$0^{2,6}$]*deca*-4,8-*dien*-3-*one* (**23c**). To a suspension of **23a** (2.43 g, 10 mmol) in dry CH_2Cl_2 (100 ml) was added dropwise MEM-chloride (1.71 ml, 15 mmol) and Et_3N (2.1 ml, 15 mmol). After stirring overnight at room temp, this mixture was thoroughly washed with 0.1 N HCl aq and dried ($MgSO_4$). Solvent was removed to yield **23c** (3.04 g, 92%) as a yellow oil. Pure **23c** was obtained by column chromatography over silica gel (EtOAc).

IR ν 1700 (C=O), 1595 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.70 (ABq, J = 7.5 Hz, 2H, H_{10}, $H_{10'}$), 2.96–3.35 (m, 3H), 3.35–3.70 (m, 3H), 3.38 (s, 3H, OMe), 3.80–3.98 (m, 2H), 5.50 (s, 2H, —OCH_2O—), 5.92 (d of d, J_{H_8,H_9} ~ 6 Hz, J ~ 3 Hz, 1H, H_8 or H_9), 6.07 (d of d, J_{H_8,H_9} ~ 6 Hz, J ~ 3 Hz, 1H, H_8 or H_9).

5-*Acetoxy*-4-*bromotricyclo*[5.2.1.$0^{2,6}$]*deca*-4,8-*dien*-3-*one* (**23d**). A suspension of **23a** (3.05 g, 13 mmol) and a catalytic amount of DMAP in Ac_2O (25 ml) was stirred at room temp until a clear soln was obtained. Removal of Ac_2O and AcOH under *vacuo* afforded an oil which was dissolved in CH_2Cl_2 (100 ml), washed with 1% $NaHCO_3$ aq, treated with charcoal and dried ($MgSO_4$). Removal of the solvent gave **23d** as an oil (3.6 g, 100%) which slowly solidified, m.p. 60–62.5°.

IR ν_{max} (KBr) 1775 (C=O, acetate), 1705 (C=O), 1615 (C=C) cm^{-1}; UV λ 252 nm (EtOH, ε 8100); ^{1}H-NMR ($CDCl_3$) δ 1.70 (ABq, J = 9 Hz, 2H, H_{10}, $H_{10'}$), 2.30 (s, 3H, CH_3CO_2—), 3.00–3.20 (m, 2H), 3.20–3.37 (m, 1H), 3.78 (d of d, J_{H_2,H_6} ~ 6 Hz, J_{H_2,H_1} ~ 3 Hz, H_2), 5.98 (m, 2H, H_8, H_9); ^{13}C-NMR ($CDCl_3$) δ 20.8 (CH_3—CO_2—), 43.7, 44.1, 45.8, 49.9, 51.4 (C_{10}), 110.7 (C_4), 132.3 (C_8 or C_9), 133.5 (C_8 or C_9), 165.1 (C=O, acetate), 177.8 (C_5), 198.5 (C_3); *m/e* 282.284 (M^+, 1 Br).

(Found: C, 50.81; H, 3.86. Calc for $C_{12}H_{11}BrO_3$: C, 50.91; H, 3.92%.)

4 - *Bromo* - 5 - *methanesulfonyltricyclo*[5.2.1.0^{2,6}]*deca* - 4,8 - *dien* - 3 - *one* (**23e**). To a stirred suspension of **23a** (2.41 g, 10 mmol) in toluene (100 ml) was added mesylchloride (0.85 ml, 11 mmol) followed by dropwise addition of Et_3N (2.1 ml, 15 mmol). After stirring for 45 min at room temp, the mixture was filtered and the solvent removed. The oily residue was dissolved in CH_2Cl_2 (100 ml), washed with water and dried ($MgSO_4$). Concentration of the solvent gave **23e** (2.9 g, 91%) as a yellow solid, which was recrystallized from EtOH, m.p. 110–113.5°.

IR ν_{max} (KBr) 1715 (C=O), 1610 (C=C), 1375 and 1170 (—OSO_2—) cm^{-1}; UV λ 274.5 nm (EtOH, ε 8200); ^{1}H-NMR ($CDCl_3$) δ 1.70 (ABq, J = 8 Hz, H_{10}, $H_{10'}$), 3.00–3.45 (m, 3H), 3.33 (s, 3H, CH_3SO_2O—), 3.77 (d of d, $J_{H_2,H_6} \sim 6$ Hz, $J_{H_2,H_1} \sim 4$ Hz, H_2), 6.00 (s, 2H, H_8, H_9); ^{13}C-NMR ($CDCl_3$) δ 39.9, 44.2, 44.4, 46.3, 50.9, 51.4, 111.5 (C_4), 132.9 (C_8 or C_9), 133.7 (C_8 or C_9), 175.8 (C_5), 197.7 (C_3); *m/e* 318–320 (M^+, 1 Br). (Found: C, 41.14; H, 3.50. Calc for $C_{11}H_{11}BrO_4S$: C, 41.39; H, 3.47%.)

9 - *Bromotricyclo*[5.3.0.0^{2,5}]*dec* - 8 - *en* - 3,10 - *dione* (**28a**). A soln of **23b** (1.05 g) in toluene (130 ml) was irradiated with a 150 W Hanovia immersion lamp (Pyrex filter). No special precautions were taken to remove all traces of acid. The course of the reaction was followed by GLC (SE 30–5%, 220°). After completion of the reaction, the soln was concentrated. After standing at room temp for several days, all of the produced **24b** was converted in **28a**. Medium pressure chromatography (Merck silica gel 60H, CH_2Cl_2) afforded **28a** (60%) as an oil. An analytical pure sample was obtained by crystallization from EtOH, m.p. 148.5–149.5°.

IR ν_{max} (KBr) 1770 (C=O, cyclobutanone), 1715 (C=O), 1580 (C=C) cm^{-1}; UV λ 244.5 (EtOH, ε 5000), 198.5 (ε 2400); ^{1}H-NMR ($CDCl_3$) δ 2.0 (d of t, J = 14.4 Hz, 1H), 2.22–2.90 (m, 2H), 2.88–3.48 (m, 3H), 3.50–4.13 (m, 2H), 7.69 (d, J = 2.3 Hz, H_8); ^{13}C-NMR ($CDCl_3$) δ 33.6, 36.4 (C_6), 51.0, 53.3, 53.9 (C_4), 66.7, 124.2 (C_9), 162.8 (C_8), 198.5 (C_{10}), 206.4 (C_3); *m/e* 239.981 (M^+, 1 Br). (Found: C, 49.85; H, 3.73. Calc for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76%.)

9 - *Bromo* - 3 - *methoxytricyclo*[5.3.0.0^{2,5}]*deca* - 3,8 - *dien* - 10 - *one* (**27**) (X = Br). Bromoketone **23b** (68 mg) was subjected to flash vacuum thermolysis[19] (400°, 3.5×10^{-2} Torr, 20 cm quartz tube) and the product trapped at −78°. After warming to room temp, the trap was rinsed with CH_2Cl_2. Removal of the solvent gave **27** (75%) together with ketone **28a** (25%). ^{1}H-NMR ($CDCl_3$) δ 3.40 (s, 3H, OMe), 4.52 (s, 1H, H_4), 7.60 (d, $J_{H_7,H_8} \sim 2.4$ Hz, H_8). The other signals coincided with those of **28a**. Hydrolysis of **27** led to quantitative formation of **28a**.

5 - *Bromo* - 4 - *methoxypentacyclo*[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]*decan* - 6 - *one* (**24b**). All glassware was rinsed with ammonia and dried at 110°. A soln of **23b** (1.0 g) in toluene (130 ml) to which some ammonia (g) was introduced, was irradiated as described before. After completion of the reaction, solvent was removed, the residue washed with 10% KOH aq (30 ml) and extracted with CH_2Cl_2 (3 × 25 ml). After drying ($K_2CO_3/MgSO_4$) and removal of the solvent, **24b** was isolated as a yellowish oil (73%). Bulb-to-bulb distillation (100°, 8×10^{-2} mmHg) afforded a pure sample.

IR ν 1760 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.82 (ABq, J ~ 14 Hz, 2H, H_{10}, $H_{10'}$), 2.33–2.53 (m, 1H), 2.83–3.07 (m, 2H), 3.23 (s, 3H, OMe), 3.07–3.66 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ 40.1, 42.6, 42.9, 43.1, 46.6, 48.1, 49.9, 51.7, 60.0 (C_5), 76.0 (C_4), 208 (C_5); *m/e* 254.128; calc for $C_{11}H_{11}O_2Br$: 254.1303.

5 - *Bromo* - 4 - ([2 - *methoxy* -]*ethoxy* -)*methoxypentacyclo*[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]*dec* - 6 - *one* (**24c**). MEM-ether **24c** was obtained as an oil starting from **23c** using essentially the same procedure as described for **24b**. Purification by bulb-to-bulb distillation (150–200°, 10^{-1} Torr) is possible, however, with considerable losses.

IR ν 1770 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.80 (s, 2H, H_{10}, $H_{10'}$), 2.45 (m, 1H), 2.97 (m, 2H), 3.33 (s, 3H, OCH_3), 3.08–3.87 (m, 7H), 4.88 (ABq, J ~ 8 Hz, —OCH_2—, diastereotopic protons).

4 - *Acetoxy* - 5 - *bromopentacyclo*[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]*decan* - 6 - *one* (**24d**). A soln of **23d** (2.0 g) in toluene (130 ml) was irradiated for 4.5 h (Hannovia 150 W). Solvent was removed and the residue purified by bulb-to-bulb distillation (150°, 10^{-1} Torr). Acetate **24d** (1.21 g, 61%) was obtained as an oil which slowly solidified. Recrystallization from ether gave a pure sample, m.p. 83–85.5°.

IR (KBr) ν_{max} 1790 and 1770 (split C=O, cage), 1735 ($OCOCH_3$) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.77 (ABq, J = 12 Hz, 2H, H_{10}, $H_{10'}$), 2.02 (s, 3H, $OCOCH_3$), 2.52 (m, 1H), 2.78–3.68 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 20.2 (CH_3CO_2—), 40.4, 41.8, 42.6, 44.7, 48.3, 48.9, 50.1, 60.4 (C_4 or C_5), 74.3 (C_4 or C_5), 168.3 (C=O, acetate), 204.8 (C_6); *m/e* 282/284 (M^+, 1 Br). (Found: C, 51.04; H, 3.94. Calc for $C_{12}H_{11}BrO_3$: C, 50.91; H, 3.92%.)

5 - *Bromo* - 4 - *methanesulfonylpentacyclo*[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}] - *decan* - 6 - *one* (**24e**). Mesylate **24e** was obtained as an oil from **23e** using essentially the same procedure as described for **24d**. No purification was attempted.

IR (KBr) ν_{max} 1785 and 1770 (split C=O, cage) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.82 (ABq, J ~ 14 Hz, 2H, 2H, H_{10}, $H_{10'}$), 2.55 (m, 1H), 2.85–3.27 (m, 2H), 3.12 (s, 3H, —SO_2CH_3), 3.27–3.55 (m, 1H), 3.55–3.92 (m, 2H).

5 - *Methoxytricyclo*[5.2.1.0^{2,6}]*deca* - 4,8 - *dien* - 3 - *one*. Methylation of **14** was carried out in essentially the same way as described for the synthesis of **23b**. The methyl enol-ether was obtained as an oil (100%) which slowly solidified. Recrystallization from toluene gave an analytical pure sample, m.p. 74–75.5°.

IR (KBr) ν_{max} 1680 (C=O), 1582 (C=C) cm^{-1}; UV λ 241 nm (EtOH, ε 6100); ^{1}H-NMR ($CDCl_3$) δ 1.63 (ABq, J ~ 9.0 Hz, 2H, H_{10}, $H_{10'}$), 2.8–3.27 (m, 4H), 3.70 (s, 3H, OCH_3), 5.05 (s, 1H, H_4), 5.83 (d of d, $J_{H_8,H_9} \sim 6$ Hz, J ~ 3 Hz, H_8 or H_9), 6.00 (d of d, $J_{H_8,H_9} \sim 6$ Hz, J ~ 3 Hz, H_8 or H_9); ^{13}C-NMR ($CDCl_3$) δ 43.2, 43.6, 46.0, 50.9, 51.8 (C_{10}), 58.1, 106.5 (C_4), 131.7 (C_8 or C_9), 133.6 (C_8 or C_9), 190.4 (C_5), 205.5 (C_3); *m/e* 176 (M^+), 66 ($C_5H_6^+$). (Found: C, 74.74; H, 6.82. Calc for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86%.)

4 - *Methoxypentacyclo*[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]*decan* - 6 - *one* (**29**). Methoxyketone **29** was obtained as an oil (83%) from the methyl enolether of **14** using essentially the same procedure as described for **24b**.

IR ν 1760 (C=O, cage), 1700, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.72 (ABq, J ~ 13 Hz, 2H, $H_{10'}$, H_{10}), 2.17–2.43 (m, 1H), 2.43–2.68 (m, 1H), 2.68–2.95 (m, 2H), 2.95–3.18 (m, 2H), 3.24 (s, 3H, OMe), 3.25–3.70 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 31.9, 40.7, 41.7, 42.2, 45.2, 46.9, 49.6, 51.4 (C_{10}), 52.0, 77.1 (C_4), 215.9 (C_6); *m/e* 176.082; calc for $C_{11}H_{12}O_2$: 176.0837.

Tricyclo[5.3.0.0^{2,5}]*dec* - 8 - *en* - 3,10 - *dione* (**28b**). Dione **28b** was obtained as oil starting from **29** (0.5 g) using essentially the same procedure as described for **28a**. Medium pressure chromatography (Merck silica gel 60H, CH_2Cl_2–EtOAc (9:1)) afforded **28b** (45%) as an oil which slowly solidified. Recrystallization from EtOH afforded an analytically pure sample, m.p. 68–71°.

IR (KBr) ν_{max} 1765 (cyclobutanone), 1692 (C=O), 1580 (C=C) cm^{-1}; UV λ 220.5 nm (EtOH, ε 7100); ^{1}H-NMR ($CDCl_3$) δ 2.01 (d, 1H, H_6 (*endo*)), 2.23–2.88 (m, 2H), 2.88–3.55 (m, 3H), 3.55–4.03 (m, 2H), 5.93 (d of d, $J_{H_7,H_9} \sim 2.4$ Hz, $J_{H_9,H_8} \sim 2.4$ Hz, 1H, H_9), 7.65 (d of d, $J_{H_8,H_9} \sim 5.5$ Hz, $J_{H_8,H_7} \sim 2.6$ Hz, 1H, H_8); *m/e* 162 (M^+). (Found: C, 73.95; H, 6.30. Calc for $C_{10}H_{10}O_2$: C, 74.06; H, 6.22%.)

5 - ([2 - *Methoxy* -]*ethoxy* -)*methoxypentacyclo* - [4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]*nonane* 4-*carboxylic acid* (**25c**). To a soln of MEM-ether **24c** (1.02 g, 3.10 mmol) in dry toluene (40 ml) was added dry KOH (6 g). This mixture was treated under reflux for 90 min (Dean–Stark separation). Solvent was removed under *vacuo* and the residue dissolved in water (100 ml). The water layer was washed with CH_2Cl_2, acidified with HCl aq to pH ~ 5 and again CH_2Cl_2 extracted. The organic phase was washed with water and dried ($MgSO_4$). Removal of the solvent yielded **25c** as a light yellow oil (28%).

IR ν 3600–2500 (broad OH, carboxylic acid), 1700 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.73 (s, 2H, H_9, $H_{9'}$), 3.1–3.8 (m, 10H), 3.28 (s, 3H, OCH_3), 4.87 (s, 2H, —OCH_2O—), 8.7 (broad s, —COOH). This acid (230 mg) was purified as its methylester which was obtained by treatment of **25c** with CH_2N_2 in ether. Preparative TLC (Merck Al_2O_3 150 F_{254} (Typ T), 1.5 mm,

20 × 20 cm), applying ether, saturated by treatment with NH_3 (g), as the eluents, afforded a pure sample.

IR ν 1725 (C=O, ester); ^{1}H-NMR ($CDCl_3$) δ 1.72 (s, 2H, H_9, $H_{9'}$), 3.2–3.9 (m, 10H), 3.37 (s, 3H, OMe, MEM-group), 3.65 (s, 3H, OMe), 4.82 (s, 2H, —OCH_2O—); ^{13}C-NMR ($CDCl_3$) δ 40.8, 41.0, 41.6 (OCH_3), 44.9 (C_4), 49.4 (OMe), 50.8, 57.8, 58.6, 67.3 (—OCH_2CH_2O—), 71.4, 83.1 (C_3), 92.3 (OCH_2O), 171.0 (C=O); *m/e* 281.1394; calc for $C_{15}H_{21}O_5$: 281.1389 (determined by CI).

4 - *Bromotetracyclo*[4.3.0.0^{2,4}.0^{3,8}]*nonan* - 5 - *one* 7 - endo - *carboxylic acid* (**40**) (X = Br). To a stirred suspension of methyl ether **24b** (1.069 g, 4.19 mmol) in 20% KOH aq (25 ml) was added a soln of $AgNO_3$ (2 g, 11.8 mmol) in water (10 ml). The mixture was kept at 60° for 4.5 h. After cooling, the mixture was filtered, diluted with water (100 ml), washed with CH_2Cl_2 and carefully acidified with 4 N HCl aq to pH ~ 5. The water phase was extracted with CH_2Cl_2 (4 × 50 ml) and dried ($MgSO_4$). Removal of the solvent gave **40** as a white solid (654 mg, 61%). Recrystallization from toluene gave an analytical pure sample, m.p. 127.5–129°.

IR (KBr) ν 3500–3000 (—OH, carboxylic acid), 1745 (C=O), 1705 (weak) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.92 (ABq, $J_{H_9,H_{9'}}$ ~ 10 Hz, 2H), 2.12–2.35 (m, 1H), 2.50–3.13 (m, 5H), 4.76 (broad s, 1H, OH); *m/e* 256/258 (M^+, 1 Br), 77 ($C_6H_5^+$). (Found: C, 47.18; H, 3.53. Calc for $C_{10}H_9BrO_3$: C, 46.72; H, 3.53%.)

Methyl 4 - *bromotetracyclo*[4.3.0.0^{2,4}.0^{3,8}]*nonan* - 5 - *one* 7 - endo - *carboxylate* (**39**) (X = Br). This was prepared from **40** (0.13 g) by treatment with diazomethane in CH_2Cl_2. Removal of the solvent yielded **39** as an oil which was purified by medium pressure LC (Merck silica gel 60H, H_2CCl_2–EtOAc (9:1)). Crystallization from ether afforded analytically pure ester **39**, m.p. 82–83.5°.

IR (KBr) ν_{max} 1730 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.86 (ABq, J ~ 10 Hz, 2H, H_9, $H_{9'}$), 2.50–3.05 (m, 6H), 3.63 (s, 3H, OCH_3); ^{13}C-NMR ($CDCl_3$) δ 39.0, 40.2, 43.3, 43.9, 45.3, 47.3, 52.2, 57.5, 171.0 (COO—), 204 (C_5); *m/e* 270/272 (M^+, 1 Br). (Found: C, 49.00; H, 4.14. Calc for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09%.)

4 - *Bromotetracyclo*[4.3.0.0^{2,4}.0^{3,8}]*nonan* - 5 - *one* 7 - exo - *carboxylic acid* (**41**) (X = Br). *Endo*-carboxylic acid **40** is dissolved in refluxing EtOH. Evaporation of the solvent afforded **41** in quantitative yield, m.p. 220–221°.

IR (KBr) ν_{max} 3100–2500 (—OH, carboxylic acid), 1745 (C=O), 1705 (—COO—) cm^{-1}; ^{1}H-NMR (CD_3COCD_3) δ 1.79 (ABq, $J_{H_9,H_{9'}}$ ~ 10 Hz, 2H, H_9, $H_{9'}$), 2.00–2.12 (m, 1H), 2.55–3.13 (m, 5H). Methyl ester of **41** was obtained by treatment of a soln of **41** in CH_2Cl_2 with diazomethane. Recrystallization from EtOH gave an analytical pure sample, m.p. 99.8–100.2°.

IR (KBr) ν_{max} 1730 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.77 (ABq, 2H, H_9, $H_{9'}$), 2.5–3.1 (m, 6H), 3.63 (s, 3H, OCH_3); ^{13}C-NMR ($CDCl_3$) δ 38.6, 40.0, 42.8, 43.0, 44.1, 45.8, 52.1, 56.5, 170.5 (CO_2—), 203.6 (C=O); *m/e* 270.272 (M^+, 1 Br). (Found: C, 48.85; H, 4.10. Calc for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09%.)

Methyl tetracyclo[4.3.0.0^{2,4}.0^{3,8}]*nonan* - 5 - *one* 7 - endo - *carboxylate* (**39**) (X = H). Methyl ester **39** (X = H) was obtained as an oil in ~50% yield starting from **29** using essentially the same method as described for the preparation of **39** (X = Br). Crystallization from ether gave an analytically pure sample, m.p. 39–42° (lit.[36] 44–45°).

IR (KBr) ν_{max} 1730 (broad C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.66 (one half of AB quartet, $J_{H_9,H_{9'}}$ ~ 9 Hz, 1H, H_9 or $H_{9'}$), 2.04 (one half of AB quartet, $J_{H_9,H_{9'}}$ ~ 9 Hz, 1H, H_9 or $H_{9'}$), 1.96–3.00 (m, 7H), 3.65 (s, 3H, OCH_3); ^{13}C-NMR ($CDCl_3$) δ 33.4, 37.5, 37.6, 39.8, 45.7, 48.5 (C_9), 51.9, 57.6, 171.6 (C=O, ester), 210.5 (C_5); *m/e* 192 (M^+). (Found: C, 68.59; H, 6.26. Calc for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29%.)

4,5 - *Dibromotricyclo*[5.2.1.0^{2,6}]*deca* - 4,8 - *dien* - 3 - *one* (**42**). To a soln of **23a** (5 g, 0.021 mol) and pyridine (15 drops) in $CHCl_3$ (150 ml), was added freshly distilled PBr_3 (6 ml, 0.062 mol). This mixture was heated under reflux until a clear soln was obtained. After benzyltriethylammonium bromide (6.0 g, 0.22 mol) was added, the mixture was refluxed for another 0.5 h. After cooling down to 0°, pyridine (4 ml) was added to the mixture. After being stirred for 10 min, the mixture was poured onto crushed ice, vigorously stirred for 1 h and the organic phase separated. The water phase was extracted with $CHCl_3$ and the combined organic layers washed with water and filtered over silica gel. Concentration of this soln afforded **42** as a yellow solid (70–75%) which slowly decomposed at room temp. Recrystallization from EtOH afforded pure dibromide **42**, m.p. 120–120.5°.

IR (KBr) ν_{max} 1705 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.72 (ABq, $J_{H_{10},H_{10'}}$ ~ 8 Hz, 2H, H_{10}, $H_{10'}$), 3.05–3.38 (m, 3H), 3.58 (d of d, J = 4.05 Hz, J = 1.8 Hz, 1H), 5.87–6.08 (m, 2H, C_8, C_9); *m/e* 302 (M^+, 2 Br). (Found: C, 39.16; H, 2.56. Calc for $C_{10}H_8Br_2O$: C, 39.51; H, 2.65%.)

4,5 - *Dibromopentacyclo*[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]*decan* - 6 - *one* (**43**). A soln of *pure* **42** (2.5 g, 8.2 mmol) in benzene was irradiated for 10 h (Hannovia medium pressure 150 W, Pyrex filter). After filtering the soln over silica gel, solvent was removed to give **43** (2.4 g, 95%) as an oil which slowly solidified. Recrystallization from hexane gave pure material, m.p. 109–110°.

IR (KBr) ν_{max} 1770 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.83 (d, J = 1.5 Hz, 2H), 2.53–2.68 (m, 1H), 3.14–3.67 (m, 5H); *m/e* 302 (M^+, 2 Br). (Found: C, 39.73; H, 2.64. Calc for $C_{10}H_8Br_2O$: C, 39.51; H, 2.65%.)

4 - *Bromopentacyclo*[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]*decan* - 6 - *one* (**44**). A soln of crude **42** in toluene was irradiated for 16 h (Hannovia medium pressure 150 W, Pyrex filter). The brown soln was filtered over silica gel. Removal of the solvent gave a dark oil which contained mainly **43** and **44**. Separation was achieved by flash chromatography (silica gel, hexane–ether (4:1)). Ketone **44** was isolated as an oil.

IR (KBr) ν_{max} 1780, 1760 (split C=O); ^{1}H-NMR ($CDCl_3$) δ 1.63–1.76 (m, 2H, H_{10}, $H_{10'}$), 2.52–2.40 (m, 1H), 2.73 (d, J ~ 5.9 Hz, 1H), 2.67–3.60 (m, 5H); *m/e* 223.9837; calc for $C_{10}H_9BrO$: 223.9840.

5 - *Bromopentacyclo*[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]*nonane* 4 - *carboxylic acid* (**45**). A suspension of **43** (3.0 g, 9.9 mmol) in 30% KOH aq was heated at 100–110° for 1.5 h. After cooling, the dark soln was extracted with ether and acidified with 30% HCl aq: the obtained suspension was extracted with ether and the organic phase dried ($MgSO_4$). Concentration of the soln afforded **45** (1.6 g, 67%) as a yellow solid, which was recrystallized from EtOH, m.p. 194.5°.

IR (KBr) ν_{max} 1685 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.75 (s, 2H, H_9, $H_{9'}$), 3.27–3.77 (m, 6H), 10.4 (s, broad, 1H, OH); *m/e* 239 (M^+ − H, 1 Br). (Found: C, 49.84; H, 3.73. Calc for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76%.)

4 - *Acetyl* - 5 - *bromopentacyclo*[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]*nonane* (**47**). To a stirred soln of **45** (0.96 g, 3.98 mmol) in ether (50 ml) at −78°, was added MeLi (1.55 M in ether, 7 ml, 10.9 mmol). After stirring for 0.5 h at −78°, the soln was slowly warmed up to 0°, stirred for another 3 h and poured onto crushed ice. The organic phase was separated and the water layer extracted with ether (2 ×). The organic layers were dried ($MgSO_4$) and concentrated to give ketone **47** (0.777 g, 82%) as a yellow oil. Crystallization from ether–hexane (1:5) at low temperature gave a crystalline sample, which melted at room temp.

IR (KBr) ν_{max} 1685 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.77 (s, 2H, H_9, $H_{9'}$), 2.12 (s, 3H, CH_3CO), 3.23–3.75 (m, 6H); *m/e* 222.9762 ($M^+ - CH_3$); calc for $C_{10}H_8BrO$: 222.9759. (Found: C, 55.22; H, 4.51. Calc for $C_{11}H_{11}BrO$: C, 55.25; H, 4.64%.)

4 - *Acetoxy* - 5 - *bromopentacyclo*[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}] - *nonane* (**48**). A soln of trifluoroperacetic acid was prepared by mixing trifluoroacetic anhydride (3.4 ml) with 98% H_2O_2 (0.5 ml) and CH_2Cl_2 (6.6 ml). The resulting peracid soln was added dropwise to a stirred soln of **47** (0.16 g, 0.71 mmol), anhyd Na_2HPO_4 (3.4 g) and CH_2Cl_2 (20 ml). The mixture was stirred and refluxed for 15 h, filtered and the inorganic salts washed thoroughly with CH_2Cl_2. The organic soln was dried ($MgSO_4$) and the solvent evaporated to give **48** (0.107 g, 59%), containing some trifluoroacetate as indicated by an additional carbonyl band at 1780 cm^{-1}.

IR (KBr) ν_{max} 1740 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.77 (s, 2H, H_9, $H_{9'}$), 2.08 (s, 3H, CH_3CO_2), 3.23–3.53 (m, 4H), 3.53–3.78 (m, 2H); *m/e* 211.9844 ($M^+ - CH_2{=}C{=}O$); calc for C_9H_9BrO: 211.9837.

1-*Methoxy*-10-*oxapentacyclo*[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]*decane* (**51**). NaOMe (0.8 g, 15 mmol) was added to a stirred soln of **48** (1.0 g, 3.9 mmol) in MeOH (20 ml). After stirring at room temp for 1 h, NH_4Cl (0.18 g, 15 mmol) was added and MeOH removed *in vacuo* and the residue extracted with absolute ether. The oily residue which mainly contained **51** was purified by flash chromatography over silica gel (hexane–ether (4:6)) to give pure **51** (0.24 g, 37%) as an oil.

IR ν 2840 (OCH_3) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.61 (s, 2H, H_5, $H_{5'}$), 2.91–2.42 (m, 6H), 3.53 (s, 3H, OCH_3), 4.44–4.61 (m, 1H, H_6); ^{13}C-NMR δ 36.6 (d, J_{CH} ~ 147.04 Hz), 37.9 (d, J_{CH} ~ 149.26 Hz), 41.1 (t, J_{CH} ~ 129.84 Hz, C_5), 46.6 (d, J_{CH} ~ 154.25 Hz), 48.3 (d, J_{CH} ~ 153.81 Hz), 53.5 (q, J_{CH} ~ 143.16 Hz, OCH_3), 72.2 (d, J_{CH} ~ 166.46 Hz, C_9), 112.4 (s, C_1); *m/e* 164.0837 (M^+); calc for $C_{10}H_{12}O_2$: 164.0837.

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