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NUCLEOPHILIC ELIMINATIVE RING FISSION OF BRIDGEHEAD SUBSTITUTED 1,3-BISHOMOCUBYL ACETATES

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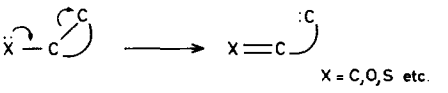
Abstract—The base induced cage fission of three different types of functionalized bridgehead substituted 1,3-bishomocubyl acetates, *viz* **A**, **B** and **C** is described. The synthesis of two 6-functionalized 1,3-bishomocubyl 4-acetates (type **A**), *viz* 4-acetoxypentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one **5** and its ethylene acetal **6** has been accomplished starting from the readily available Diels–Alder adduct **4**. The synthesis of three 1,3-bishomocubyl 8-acetates (type **B**), *viz* 8-acetoxypentacyclo[5.3.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one **15**, its ethylene acetal **16** and the parent acetate **20** has been carried out starting from the cyclopentadiene-benzoquinone adduct **7**. Base induced homoketonization of **6**, **16** and **20** leads regio- and stereospecifically to the thermodynamically favored half cage ketones **22**, **28** and **31**, respectively. In contrast, the cage opening of the β-ketoacetates **5** and **15** is essentially directed by the β-ketone function. In the case of **5**, regiospecific cleavage of the central C_4—C_5 bond is observed producing in a stereospecific manner diketone **25** in quantitative yield. Under similar conditions, acetate **15** gives a complex mixture of cage opened products arising from further fragmentation of the initially formed diketone **34**. Deuterium labeling experiments reveal an *anti*-Bredt behavior of half cage ketones **28** and **31**. The synthesis of a bridgehead acetate of type **C** has been accomplished by stereoselective reduction of ketone acetate **5** with LiAlH(t-OBu)$_3$ followed by mesylation. A mixture of epimers **36a** and **36b** (ratio 1 : 4) is obtained from which the predominant *anti*-epimer **36b** could be isolated. An X-ray analysis established its structure. Base induced cage fission of **36b** leads regiospecifically to tetracyclo[5.3.0.0^{2,5}.0^{4,8}]decenone **37**. In contrast the *syn*-epimer **36a**, under similar conditions, only affords the bridgehead alcohol **38**.

Nucleophilic eliminative ring fission in which a C=C or a C=O double bond is formed by elimination of a C-leaving group (Scheme 1) requires either ring strain or substantial leaving-group stabilization or both.[1]



Scheme 1.

In acyclic systems the occurrence of unactivated C-leaving groups in simple base promoted alkene or carbonyl forming elimination reactions is hardly known, however, an increasing number of examples of such eliminative ring fissions in alicyclic compounds, particularly in small ring systems, becomes available.[1] The release of ring strain during this process clearly compensates for the high activation energy required for the expulsion of a non-activated C-leaving group.

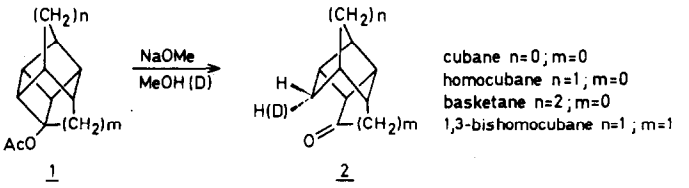
An illustrative example of such a nucleophilic eliminative process is encountered in the base induced homoketonization of bridgehead substituted cage acetates such as **1** (Scheme 2). Under mild conditions, these acetates undergo a regio- and stereospecific C—C bond cleavage leading to seco-cage systems **2**.[2]

We and others[2,3] demonstrated that the stereochemical outcome, i.e. proton uptake with exclusive retention of configuration, and the regiochemical course, i.e. exclusive formation of the thermodynamically most stable half-cage ketone, of this cage opening is primarily determined by the strain features of these polycyclic structures. Electronic factors do not play a role here since in none of the three conceivable C—C bond cleavages the developing carbanion is particularly stabilized. We thought it pertinent to investigate such an electronic effect of C-leaving group stabilization both on the regio- and stereochemistry of this cage fission process. We were particularly interested to learn whether a conjugative stabilization of one of the possible carbanionic intermediates would be sufficient to overrule the aforementioned strain factors, leading to a thermodynamically less stable seco-cage framework.

Bridgehead substituted acetates (or alcohols) of type **A** and **B**, which contain a carbanion-stabilizing carbonyl group at the position β to the bridgehead acetate function are suitable structures for this purpose. Cleavage of the central C_4—C_5 bond in **A** or the C_8—C_7 bond in **B** will lead to a carbanionic intermediate which is considerably stabilized by the β-carbonyl function. On the other hand, scission of the two alternative C—C bonds will produce carbanionic species of relatively high energy. Masking the β-carbonyl group in **A** and **B** with an ethylene acetal function will dispose of this electronic effect and none of the three conceivable C—C bond cleavages will lead to a particularly stabilized carbanion.‖

§ On leave from Bharathidasan University, Tiruchirapalli, India.

‖ On a suggestion of a referee a quantitative assessment using molecular mechanics (MM2) calculations of the conceivable seco-structures was performed. The predictive value of these calculations depends strongly on the polycyclic substrate. The results are described in the accompanying paper.[4] We thank Professor E. Ōsawa for his cooperation by performing the computational analysis.

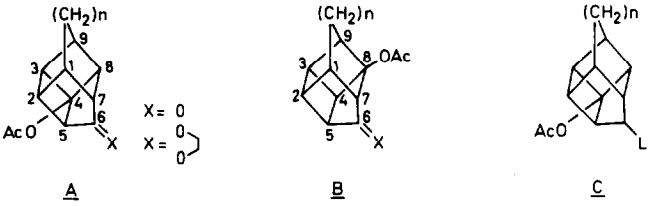


1 2

Scheme 2.

Alternatively, a "contra-thermodynamic" cage fission may also be enforced by a 1,3-through-cage elimination reaction in an appropriately β-functionalized bridgehead cage acetate or alcohol such as **C** (L = leaving group). In this case the relative stereochemical position of the leaving group may play a decisive role in the regiochemistry of this Grob-type elimination.

In this paper the synthesis of substrates of the type **A**, **B** and **C** (n = 1), and their base induced homoketonization are reported.[5]



A B C

The 1,3-bishomocubane cage system is readily accessible from *endo*-tricyclo[5.2.1.$0^{2,6}$]decadienones applying a $(2\pi + 2\pi)$ intramolecular photocyclization.

Retrosynthetically, 1,3-bishomocubyl alcohol **A** (n = 1) is derived from tricyclodecadienone **4**, which is actually the Diels–Alder adduct of cyclopentadiene and cyclopenten-1,3-dione **3**[6] (Scheme 3). Tricyclic dione **4** is completely enolic and it probably possesses the *endo*-configuration.

Unexpectedly, irradiation of enol **4** in benzene, acetone or MeOH did not lead to any photocyclization product. However, its enol acetate smoothly produced 1,3-bishomocubyl acetate **5** in almost quantitative yield on irradiation in MeOH. Purification of **5** met with difficulties due to its instability toward both acidic and basic reagents. Surprisingly, acetalization of **5** with ethylene glycol using TosOH as the catalyst smoothly gave **6** in high yield (87%). This acetal is much more stable than ketone acetate **5** and can readily be purified.

Our route to 1,3-bishomocubyl acetate of type **B** starts off with tricyclodecenone ester **9** which is prepared from the benzoquinone cyclopentadiene adduct **7** (Scheme 4).

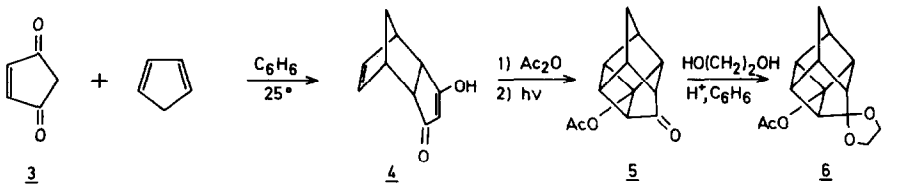
Following the original procedure of Herz *et al.*,[7] ester **9** was only obtained in low yields (20–30%), which was mainly due to a very slow conversion of epoxide **8** in the Favorskii ring contraction reaction. We optimized the experimental conditions and the isolated yield of cyclopentenone **9** could be raised to 65%. The ester **9** appeared to be rather labile, therefore it was immediately transformed into the corresponding 1,3-bishomocubyl ester **10** by irradiation in toluene (yield 90%). Acetalization of **10** afforded **11** in *ca* 80% yield. Both esters **10** and **11** were hydrolysed to give the respective carboxylic acids **12** and **13**. The parent 1,3-bishomocubane carboxylic acid **14** could be obtained in 70% yield from **10** by a Wolff–Kishner reduction. Starting from acids **12**, **13** and **14**, the corresponding bridgehead acetates **15**, **16** and **20** were prepared.

The most direct approach to these substrates involves the photo-oxidation of the carboxylic acids with lead tetra-acetate in acetic acid in the presence of $Cu(OAc)_2$ and KOAc.[8] However, applying this procedure for the oxidation of **12** did not yield any of the desired acetate **15** (Scheme 5). Under the same conditions acetal carboxylic acid **13** afforded a mixture of the desired acetate **16** and 1,3-bishomocubanone ethylene ketal **17**. Unfortunately, acetate **16** only constituted about 10% of the mixture.

A more circuitous but reliable approach to these strained bridgehead acetates involves the deamination of the corresponding bridgehead amines in acetic acid.[9] Employing this method, acetal carboxylic acid **13** was converted into acetate **16** in a satisfactory overall yield of 60% (Scheme 6).

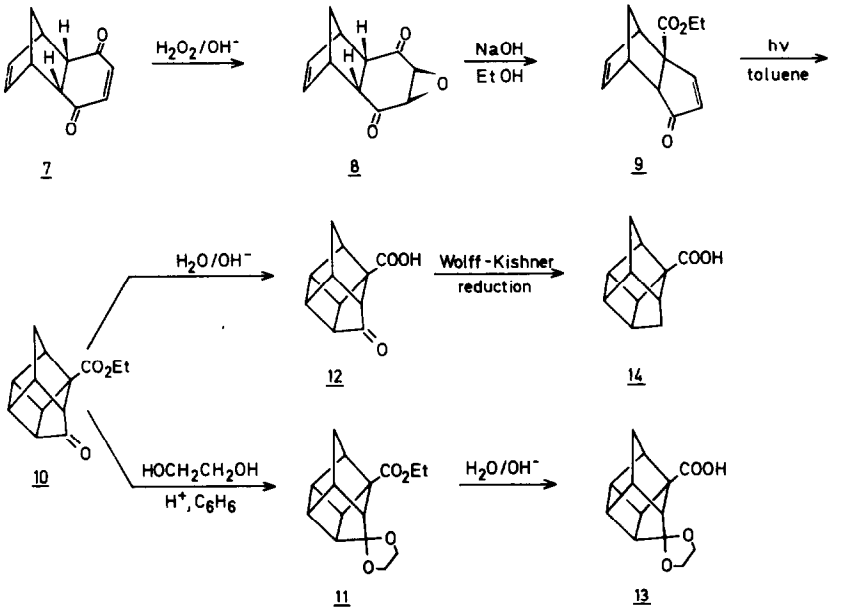
Deamination of amine **18** with $NaNO_2$ in diluted aq. HOAc (10% solution) at 0° gave predominantly alcohol **19** along with some acetate **16**.

Acid **14** was transformed into acetate **20** following

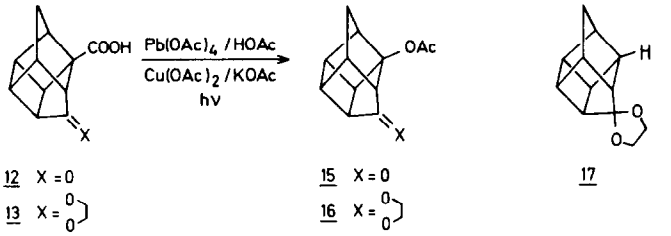


3 4 5 6

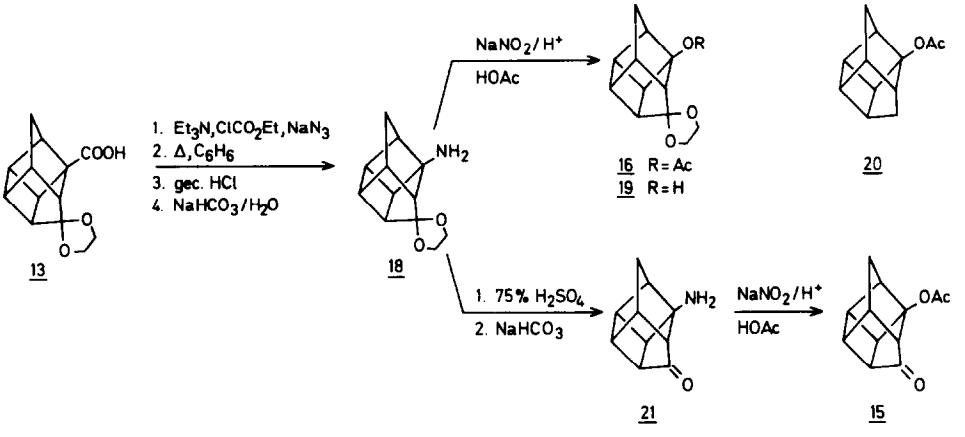
Scheme 3.



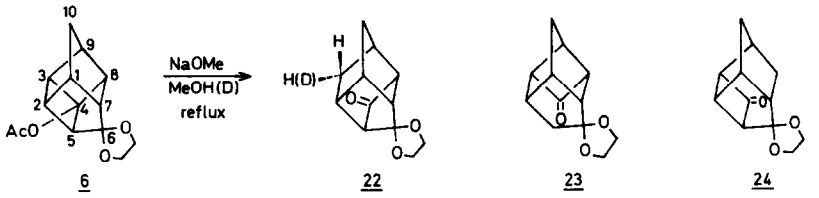
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

the same route. For the preparation of ketone acetate **15** first the ethylene ketal function in **18** was removed with 75% H_2SO_4 aq. Subsequent deamination of **21** in HOAc gave acetate **15** in 44% overall yield. This acetate **15** and the amine **21** are thermally rather labile compounds.

The cage opening of ketal acetate **6** with NaOMe in refluxing MeOH for 7 hr gave a single crystalline ketone in almost quantitative yield. On the basis of spectral evidence structure **22** was assigned (Scheme 7). At room temperature only methanolysis of **6** to the corresponding bridgehead alcohol was observed. The IR spectrum of **22** shows a C=O stretching frequency at 1750 cm^{-1}, typical for a cyclopentanone constrained in a polycyclic system. The ^{1}H-NMR spectrum of **22** in $CDCl_3$ displays a rather complicated pattern which could be unravelled by applying the NMR-shift reagent $Eu(fod)_3$ combined with spin–spin decoupling. The observed $\Delta\delta$ and spin multiplicities for the various protons strongly suggested **22**. However, the alternative structures **23** and **24** which can be envisaged by fission of the central C_4—C_5 bond and C_4—C_8 bond in **6**, respectively, could not definitely be ruled out. Unambiguous proof for structure **22** was provided by the ^{13}C-NMR spectrum which among others shows a ^{13}C=O resonance at δ 213.6, which confirmed the presence of a cyclopentanone ring. A cyclobutanone ^{13}C=O function such as is present in **23** and **24** is expected to absorb around δ 199 in the ^{13}C-NMR[10] (*cf.* the ^{13}C-NMR spectra of **25** and **37**, *vide infra*).

The regiospecific formation of **22** in this homoketonization reaction conforms entirely to the general pattern observed for the non-activated nucleophilic eliminative ring fission of these strained cage acetate derivatives, i.e. producing the thermodynamically most stable half cage ketone among the three conceivable structures.[11] The formation of **22** is also a stereospecific process as established with D-labeling, which, in accordance with earlier observations in these strained cage systems, occurs with retention of configuration at the leaving C atom.[12]

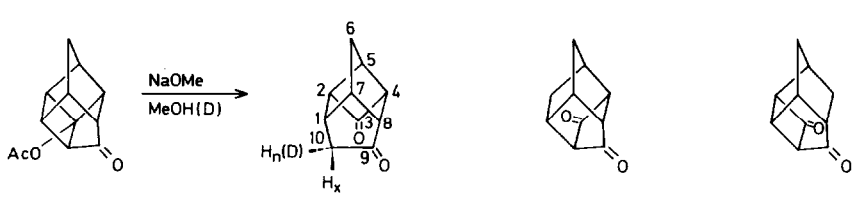
Ketone acetate **5** appeared to be considerably more reactive toward NaOMe in MeOH than **6**. At 0° **5** disappeared instantaneously to give, after the usual work-up, a single crystalline compound in quantitative yield. The IR spectrum showed two distinct carbonyl absorptions at 1745 and 1765 cm^{-1}, suggesting the presence of a cyclobutanone and cyclopentanone ring system, respectively. In agreement herewith the ^{13}C-NMR spectrum showed among the expected ten C-resonances, the typical four and five membered ring ^{13}C=O absorptions at δ 214.0 and 198.5, respectively. The ^{1}H-NMR spectrum, although complex, could be partly unravelled. It showed a singlet for two protons at δ 2.10 and a narrow multiplet for two protons at δ 2.40. These resonances were attributed to methylene bridge protons and a pair of geminal protons adjacent to a C=O function, respectively. A complex multiplet was observed for the remaining protons between δ 2.7 and 3.4. On the basis of these spectral data, half cage ketone **26**, which is one of the possible cage opened products could be definitely ruled out as this structure does not contain a cyclobutanone ring (Scheme 8). However, an unequivocal differentiation between **25** and its isomer **27** could not yet be made.

Conclusive structural information on the diketone was deduced from deuterium labeling experiments. Upon treatment of this homoketonization product with NaOMe in MeOD, a slow H/D exchange reaction was observed which was complete after 4 days. The ^{1}H-NMR spectrum (complete disappearance of the two proton signal at δ 2.40) established the incorporation of two deuterions. This H/D exchange reaction can only be reconciled with structure **25** as only this compound contains an enolizable carbonyl function which allows base induced exchange of two geminal α-protons.

Interestingly, the H/D exchange rate of these protons H_x and H_n is quite different. Whereas exchange of the first proton is complete within one day, the second one needs 4 days. The methylene protons H_x and H_n which coincide in the ^{1}H-NMR spectrum can be readily resolved by means of $Eu(Fod)_3$. One of these protons exhibits a large $\Delta\delta$ and shows a sharp doublet as part of an AB-pattern (J = 18 Hz). The other one has a smaller $\Delta\delta$ and absorbs as a doublet of doublets (J_1 = 18 Hz, J_2 = 6 Hz). A molecular model indicates a dihedral angle of 90° between H_n and the bridgehead proton at C_1. According to the Karplus equation, a coupling constant of *ca* 0 Hz would be expected. For its diastereotopic partner H_x, a coupling of *ca* 6 Hz would be predicted. The doublet with no observable vicinal coupling first disappears on deuteration and therefore is attributed to H_n.

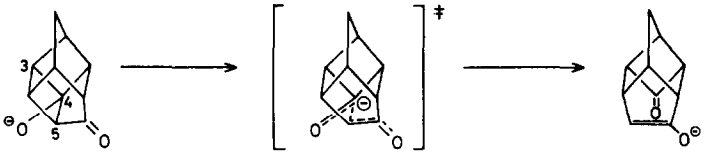
This faster exchange of the H_n proton cannot be explained by steric control because deprotonation and subsequent deuterium uptake will occur most rapidly from the relatively unhindered outerface of **25** and cause the *exo*-proton to be exchanged more rapidly than the inside proton H_n. Stereoelectronic control is also unlikely as the orientation of protons H_x and H_n with respect to the adjacent π-orbital of the carbonyl function is hardly different.[13] Most likely, the inside proton H_n is considerably more acidic than H_x owing to the proximity of the cyclobutanone C=O function, which serves as an internal base and as a consequence facilitates the exchange of H_n.[4]

Consistently, homoketonization of **5** with NaOMe in MeOD furnished a monodeuterated ketone **25** which appeared to be identical with the monodeuterated ketone obtained in the aforementioned H/D exchange



5 25 26 27

Scheme 8.

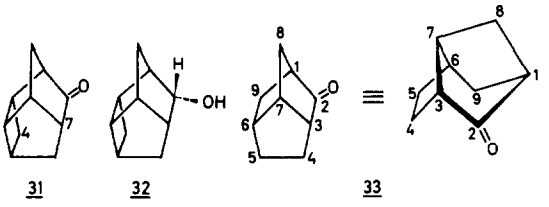


Scheme 9.

reaction. Hence, this cage opening of **5** proceeds again with complete retention of configuration in spite of the conjugative stabilization of the intermediate carbanionic species.

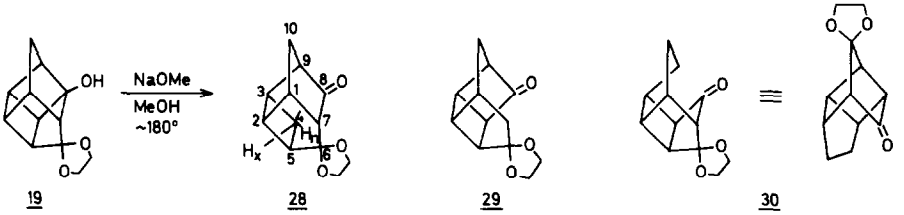
The relative rate of formation of **25** in the homoketonization of **5** as compared with that of **6**, clearly demonstrates the conjugative carbon-leaving group stabilization effect of a C=O function in this eliminative ring fission process in the 1,3-bishomocubane cage system (Scheme 9). Evidently, the decrease in activation energy for the cleavage of the central C_4—C_5 bond, which is the ultimate result of stabilization of a C_5-carbanionic species, is sufficient to completely override the thermodynamic control which is, as shown by the homoketonization of **6**, in favor of C_4—C_3 bond scission.

In the 1,3-bishomocubyl acetates of type **B** viz **15**, **16** and **20**, the acetate function is connected to a bridgehead position which actually is the junction of one 4-membered ring and two 5-membered rings. In the acetates **5** and **6**, the acetate group occupies a bridgehead position which is formed by two cyclobutane rings and one cyclopentane ring. For this reason, one would expect[11] a higher reactivity for the latter acetates toward base than for those of type **B**. This anticipation turned out to be correct. Treating ketal acetate **16** with NaOMe in MeOH at temperatures up to 160° in an autoclave did not result in a cage opening reaction but instead produced alcohol **19** in almost quantitative yield. Homoketonization of this alcohol could only be accomplished at 180° for 5 hr. Then a single ketone was obtained in 90% yield to which the structure **28** was assigned (Scheme 10). The IR spectrum shows a cyclopentanone C=O absorption at 1740 cm^{-1}, definitely excluding isomer **29** which contains a cyclobutanone ring. In the ^{1}H-NMR spectrum ($CDCl_3$) the methylene bridge protons at C_{10} appear as a clear cut two proton AB-system at δ 1.7 ($J_{H_{10},H_{10'}}$ = 11 Hz) with no significant additional coupling. This makes structure **30** unlikely as here significant coupling between the two pairs of adjacent methylene protons is expected. The base induced cage fission of acetate **20** at 180° led regiospecifically to ketone **31**. Unambiguous proof for the correctness of structures **28** and **31** was provided by the X-ray analysis of *endo*-alcohol **32**.[14] This alcohol was produced stereospecifically from ketone **31** by reduction with $NaBH_4$.[15]



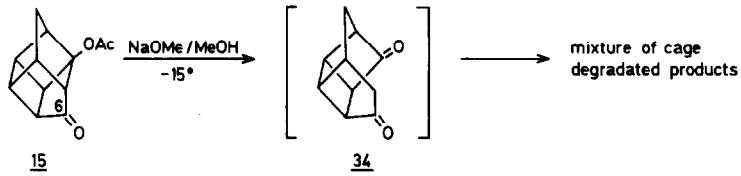
31 **32** **33**

Careful analysis of the Lanthanide-shifted ^{1}H-NMR spectra of both **28** and **31** led to an almost complete assignment of the protons including H_{4n} and H_{4x}. Based on this NMR-interpretation, D labeling experiments, using NaOMe in CH_3OD, showed that the base induced homoketonization of **16** and **20** proceeds again with complete retention of configuration. Besides the introduction of an *endo*-deuteron at C_4 in **28**, both the ^{1}H-NMR and the mass spectrum revealed the unexpected introduction of a second deuteron. This latter deuterium atom appeared to be present at the C_7-bridgehead position. Exclusive exchange of this proton could be accomplished by treating non-deuterated ketone **28** with NaOMe in MeOD at 100° for 20 hr. A similar exchange reaction was also observed for ketone **31**. This anti-Bredt behavior of ketones **28** and **31** is quite remarkable as these polycyclic systems are still considerably strained and enolization of the carbonyl function involving H_7 seems not very favorable. Based on reported failures of Bredt's rule, Wiseman has proposed that the strain in bridgehead alkenes is closely related to the strain of the corresponding *trans*-cycloalkene.[17] Such a *transoid* cycloalkene is a consequence of the bridgehead double bond being *endo*-cyclic to two rings. This bridgehead double bond will be more stable when it is oriented *trans* in the larger ring. Nickon[18] has shown that this hypothesis satisfactorily explains the fast H/D exchange at C_3 in the tricyclic brendan-2-one **33**. In **33** the 2,3-double bond which results from enolization is *transoid* in the 7-membered ring as the cyclohexanone is



19 **28** **29** **30**

Scheme 10.



15 34

Scheme 11.

a locked boat. This rigid configuration allows H/D exchange at C_3 with NaOMe in MeOD at temperatures as low as room temperature. Ketones **28** and **31** are structurally similar to brendan-2-one and can actually be constructed from **33** by connecting the C_5 and C_9 carbon atoms with a methylene unit. Although the extra cyclobutane ring in **28** and **31** considerably increases the rigidity as compared with **33**, molecular models show that the geometry around C_3 hardly changes. Consequently, Nickon's explanation for the fast H/D exchange of H_3 in **33** can also be adopted for the H/D exchange in **28** and **31**. The effect of the additional cyclobutane ring is seen in the higher temperatures needed to achieve an effective H/D exchange in **28** and **31**.[11]

The occurrence of a β-carbonyl function at C_6 as in acetate **15** impressively enhanced the sensitivity toward the base induced cage fission of this **B**-type bridgehead 1,3-homocubyl acetate. At temperatures as low as $-15°$ the keto-acetate **15** reacted rapidly with NaOMe in MeOH. In contrast to the aforementioned cases no single product was formed but instead a mixture of several cage opened products. Unfortunately, attempts to separate these compounds by chromatographic methods did not meet with much success. However, the influence of the β-carbonyl function is clearly demonstrated by the enormous rate enhancement of this base induced cage fission process which strongly suggests bond cleavage leading to half cage dione **34**. Because of the large constraint in this tetracyclic dione, which still contains a bicyclo[2.2.0]hexane ring system, subsequent fragmentation will take place readily (Scheme 11).

After having established the role of a β-carbonyl function on the regiochemistry of the base induced eliminative ring fission in bridgehead substituted 1,3-bishomocubyl acetates, we turned our attention to the effect of a leaving group L at the β-position relative to the acetate function (substrate type **C**). In this case, a heterolytic fragmentation may take place with the formation of a carbonyl fragment and an olefinic bond both being constrained in a rigid polycyclic structure with the concomitant expulsion of nucleofuge L. This Grob-type elimination reaction may be subject to stringent stereoelectronic control. The nature of the leaving group L may also be of crucial importance.[19]

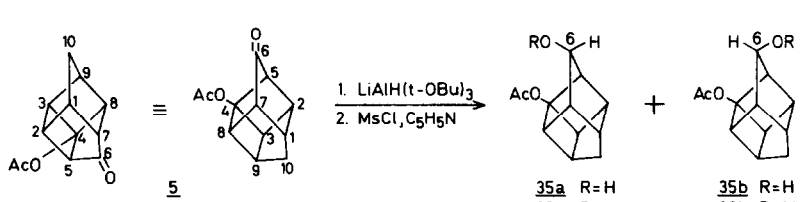
1,3-Bishomocubyl acetates of type **C** with a variety of leaving groups L are essentially accessible from ketone acetate **5**. Selective reduction of the 6-ketone function in **5** could be accomplished with either $NaBH_4$ in MeOH or LiAlH $(t\text{-OBu})_3$ in ether at room temperature. In either case the sensitive acetate function was retained in the molecule and a 4 : 1 mixture of epimeric alcohols **35** was formed in total yields of 60 and 80%, respectively (Scheme 12).

In the ^{1}H-NMR spectrum of this mixture of **35**, the epimeric protons H_6 appeared as two distinct, somewhat broadened singlets at δ 4.15 and 4.4 ppm, thus allowing a simple and accurate determination of the epimer-ratio. Attempts to separate these epimers **35** by chromatographic methods failed. However, the mesylates **36** which were obtained by treatment with mesylchloride in pyridine, could partly be separated by repeated crystallization from MeOH. This procedure afforded the predominant epimer analytically pure. The ^{1}H-NMR spectrum of this isomer did not allow a definite assignment of the stereochemistry around C_6. On merely steric grounds one would expect that in the reduction of **5**, the formation of **35a** should be favored over **35b** as the attack of the hydride donating reagent from one face of the molecule is seriously hindered by the acetate function. Alternatively, initial complexation of the reducing reagent with the acetate function can be envisaged consequently leading to a stereoselective preference for the anti-isomer **35b**.[20] Definite proof of the structure was provided by an X-ray analysis of the predominant mesylate. Fractional coordinates are listed in Table 1.

Bond lengths and angles are shown in Table 2. A projection of the molecular structure is given in Fig. 1.

The stereoview in Fig. 2 clearly shows that the predominant mesylate possesses the antistructure **36b** thus pointing to an anchimeric effect of the acetate function during the hydride reduction of the ketone moiety in **5**.

A noteworthy feature of the molecule structure of **36b** is the long C_2—C_3 bond [1.605(9) Å]. Both the X-ray diffraction study of homocubane and the electron



5

Scheme 12.

Table 1. Fractional coordinates with estimated standard deviations in parentheses

Atom	x	y	z	Ueq* 100	Atom	x	y	z	Ueq* 100
S1	−0.4602(3)	0.3526(1)	0.1200(1)	3.8	C2	−0.2520(9)	0.2121(4)	0.0011(4)	4.2
O1	−0.3615(7)	0.2615(3)	0.1634(3)	4.1	C1	−0.2218(9)	0.1270(4)	0.2943(4)	4.2
O2	−0.6793(8)	0.3268(4)	0.0930(3)	5.8	C10	−0·0759(9)	0.0547(5)	0.3416(5)	6.0
O3	−0.4330(9)	0.4311(3)	0.1760(3)	5.8	C9	0.1008(9)	0.1264(4)	0.3716(5)	5.3
O4	0.2361(7)	0.3476(3)	0.3531(3)	4.5	C3	−0.0248(9)	0.2100(5)	0.4116(5)	4.8
O5	0.0200(9)	0.4317(4)	0.4416(4)	7.5	C11	−0.2882(9)	0.3701(5)	0.0269(5)	5.8
C6	−0.1459(9)	0.2716(4)	0.2081(4)	4.0	C12	0.1935(9)	0.4211(5)	0.4036(5)	5.2
C7	−0.0568(9)	0.1708(4)	0.2288(4)	4.1	C13	0.3923(9)	0.4865(5)	0.4080(5)	5.9
C8	0.1422(9)	0.1896(4)	0.2896(4)	4.5					
C4	0.0649(9)	0.2795(4)	0.3412(4)	4.5					
C5	−0.1693(9)	0.3018(4)	0.3034(4)	4.1					

diffraction study of basketene show similar long bond lengths for the related C—C bonds viz. 1.60 Å for the C_2—C_3 bond in homocubane[21] and 1.609 Å for the C_2—C_3 bond in basketene.[22] As the parent 1,3-bishomocubane skeleton has a C_2-axis of symmetry one would expect the C_4—C_8 bond to have a similar length. However, in **36b** this bond has about the normal length of 1.569(9) Å. This suggests an effect of substitution on the actual geometry of the 1,3-bishomocubyl skeleton.[23]

Table 2. Bond lengths (Å) and bond angles (degrees) with estimated standard deviations in parentheses

Atoms	Distance	Atoms	Distance
S1-O1	1.567(4)	C8-C9	1.563(9)
S1-O2	1.413(5)	C4-C5	1.539(8)
S1-O3	1.415(5)	C3-C4	1.556(9)
S1-C11	1.772(7)	C2-C5	1.575(9)
O1-C6	1.459(8)	C1-C2	1.533(8)
O4-C4	1.413(7)	C2-C3	1.605(9)
O4-C12	1.323(8)	C1-C10	1.525(9)
O5-C12	1.194(9)	C9-C10	1.532(9)
C6-C7	1.557(8)	C3-C9	1.529(9)
C5-C6	1.528(8)	C12-C13	1.503(9)
C7-C8	1.528(9)		
C1-C7	1.534(9)	C—H distances are in the	
C4-C8	1.569(9)	range 1.00–1.13 Å	

Atoms	Angle	Atoms	Angle
O1-S1-C2	104.8(3)	C5-C4-O4	124.0(5)
O1-S1-O3	110.4(3)	O4-C4-C3	126.1(5)
O2-S1-O3	119.1(3)	C6-C5-C4	102.7(5)
O2-S1-C11	109.4(3)	C6-C5-C2	106.4(4)
O1-S1-C11	103.9(3)	C4-C5-C2	85.9(4)
O3-S1-C11	108.2(3)	C5-C2-C1	107.2(5)
C6-O1-S1	116.5(3)	C5-C2-C3	91.4(5)
C4-O4-C12	118.4(5)	C1-C2-C3	102.4(5)
O1-C6-C7	107.7(4)	C7-C1-C10	102.7(5)
O1-C6-C5	113.3(5)	C2-C1-C10	107.9(5)
C7-C6-C5	95.3(4)	C7-C1-C2	98.8(4)
C6-C7-C8	103.1(4)	C1-C10-C9	94.9(5)
C6-C7-C1	106.7(5)	C10-C9-C8	104.3(6)
C8-C7-C1	99.5(5)	C10-C9-C3	107.5(6)
C7-C8-C4	102.9(5)	C8-C9-C3	87.4(5)
C7-C8-C9	105.6(5)	C4-C3-C9	92.7(5)
C4-C8-C9	90.9(5)	C4-C3-C2	84.3(5)
C8-C4-C5	104.0(5)	C2-C3-C9	102.0(5)
C8-C4-C3	86.2(4)	O4-C12-O5	123.4(6)
C8-C4-O4	114.2(5)	O4-C12-C13	111.2(6)
C5-C4-C3	94.7(5)	O5-C12-C13	125.4(6)

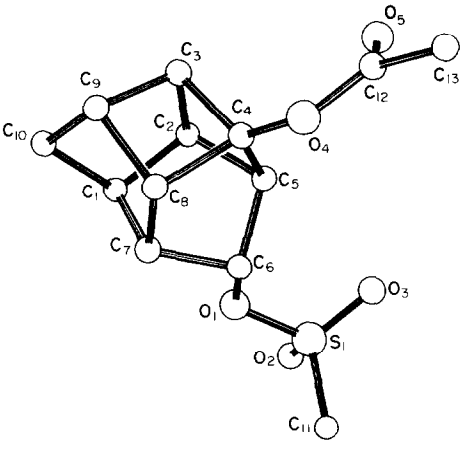


Fig. 1. Atomic numbering scheme.

When the mixture of *syn*- and *anti*-mesylate **36a, b** (ratio 1 : 4) was treated with NaOMe in MeOH for 1 hr at room temperature a colorless oil was isolated which did not contain any of the original mesylates. A mixture of two products was obtained which could readily be separated by flash chromatography on silica gel. Elution with petroleum ether–ethyl acetate (5 : 1) afforded a single oily compound which slowly solidified on standing. Based on its spectral characteristics structure **37** was assigned to this very volatile compound (Scheme 13).

Further elution with ethyl acetate furnished an oily

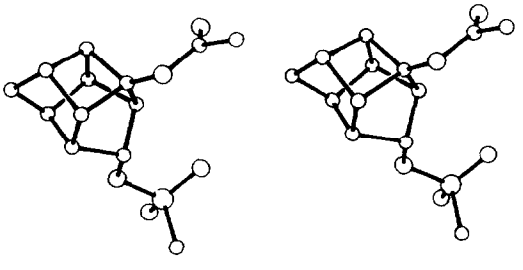
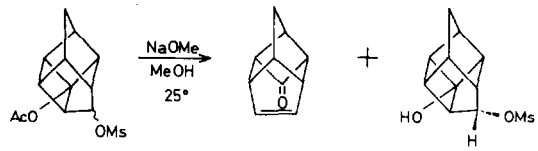


Fig. 2. Stereoscopic view of the molecule.

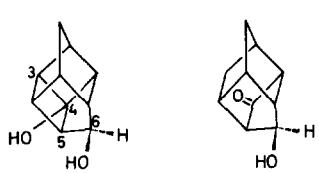


36a,b 37 38

Scheme 13.

compound which was *syn*-mesylate alcohol **38**. This *syn*-configuration of **38** was proven by conversion of **38** into the acetate **36a** with Ac_2O in the presence of a catalytic amount of DMAP. No *anti*-acetate **36b** could be detected. Independent treatment of alcohol **38** with NaOMe in MeOH for extended reaction times did not afford any cage fission products, proving that at room temperature the Grob-type elimination reaction is completely blocked here. In contrast, treatment of *anti*-mesylate acetate **36b** with NaOMe in MeOH at room temperature gave an almost instantaneous reaction leading exclusively to alkene ketone **37**. Evidently, the 1,3-through-cage elimination process is subject to stringent stereoelectric control and proceeds in a concerted manner.

The leaving ability of the β-substituent also plays an essential role in the effectiveness of this through-cage elimination reaction. When *anti*-alcohol acetate **35b** was treated with NaOMe in MeOH at reflux temperature no expulsion of the C_6 OH-function was observed as indicated by the absence of an alkene resonance in the ^{1}H-NMR spectrum. Instead, both the IR and ^{1}H-NMR spectrum of the reaction mixture indicated the presence of bridgehead alcohol **39** and the homoketonization product **40**.

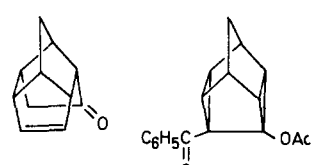


39 40

Poor leaving groups such as OH and OR (R = alkyl) are not able to lower the transition state energy for central C_4—C_5 cleavage to such an extent that this mode of cage fission competes with the homoketonization process in these 1,3-bishomocubyl acetates involving C_4—C_3 bond scission.

Alkene ketone **37** appeared to be extremely volatile. Therefore, considerable losses had to be accepted during the isolation. Its highly symmetrical structure is nicely demonstrated both by the ^{1}H-NMR and ^{13}C-NMR spectra. The ^{1}H-NMR spectrum ($CDCl_3$) shows a relatively simple resonance pattern. Both the olefinic protons and bridge protons appear as a singlet at δ 6.20 and 1.95, respectively. The remaining six cage protons are observed as a rather narrow multiplet between δ 2.7 and 3.3. The ^{13}C-NMR spectrum ($CDCl_3$) shows the anticipated seven carbon signals among which the ^{13}C=O as a singlet at δ 199.5 and the olefinic carbon atoms as a doublet at δ 137.8. Both the position of the ^{13}C=O absorption in the ^{13}C-NMR spectrum and the relatively high C=O absorption in the IR spectrum at 1760 cm^{-1} proves the presence of a cyclobutane ring. Interestingly, the UV spectrum of **37** showed a maximum at λ 204 nm (n-hexane, ε 3200) which may be indicative of an orbital–orbital interaction between the carbonyl-π-system and the olefinic double bond which, in this rigid structure, are forced close together. Such a high-wavelength absorption is not observed for the closely related but less rigid tetracycloundecenone **41**.[24] Experiments to chemically prove such an orbital–orbital interaction in **37** are currently underway in our laboratory.

In conclusion, we showed that appropriate substitution at the β-position to the bridgehead acetate or alcohol function in the 1,3-bishomocubane system can completely change the regiochemistry of the base induced homoketonization reaction of these compounds. The introduction of a carbanion stabilizing carbonyl function or a good leaving-group such as a mesylate function in the proper stereochemical position, regiospecifically directs this cage fission process. Evidently, in these cases the formation of a high energetic carbanionic species somewhere on the reaction coordinate can be avoided, resulting in a decrease of transition state energy for C_4—C_5 cleavage in **5** and in **36b**, and for C_8—C_7 cleavage in **15** to such an extent that product formation is no longer governed by the relative thermodynamic stabilities of the conceivable cage opened products.[11] In general, the ultimate product formation in a base induced homoketonization reaction of strained bridgehead alcohols or acetates will depend on a subtle balance between the relative thermodynamic stabilities of the conceivable cage fission products and the stability of the corresponding intermediates leading to these products. This phenomenon is exemplified by the homoketonization of β-benzoyl substituted homocuneane acetate **42**. Here, the base induced cage-opening is not effected by the β-carbonyl function and product formation is solely determined by the relative thermodynamic stabilities.[25] Also the dependency of product formation on the leaving ability of the β-functionality in the through-cage elimination reaction shows the delicacy of this energy balance.



41 42

From a synthetic point of view, this possibility of directing the regiochemistry of the homoketonization process in strained cage compounds is attractive as it allows the synthesis of different polycyclic structures from one single bridgehead substituted acetate or alcohol by a simple modification of the β-functionality. This is illustrated by the formation of **22**, **25** and **37** starting from ketone acetate **5** as the common starting material.

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 Varian SM-1B spectrometer. All m.ps are uncorrected. Elemental analyses were carried out in the micro analytical department of the University of Nijmegen.

5 - *Hydroxytricyclo*[5.2.1.$0^{2,6}$]*deca* - 4,8 - *dien* - 3 - *one* (**4**) was prepared in 87% yield as described by Depuy and Zaweski.[6]

4 - *Acetoxypentacyclo*[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]*decan*-6-*one* (**5**). A suspension of **4** (0.51 g, 3 mmol) in Ac_2O (3 ml) was stirred at room temp until a clear soln was obtained (after *ca* 24 hr). Removal of Ac_2O and acetic acid *in vacuo* afforded 5-*acetoxytricyclo*[5.2.1.$0^{2,6}$]*deca*-4,8-*dien*-3-*one* (0.66 g, 100%) as a white solid. Recrystallization from hexane gave a pure sample, m.p. 87–88.5°; IR ν_{max}^{KBr} 1780 (C=O, ester), 1685, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.6 (q, 2H, H_{10}, $H_{10'}$), 2.2 (s, 3H, CH_3CO), 2.8–3.4 (m, 4H, $H_1H_2H_6H_7$), 5.9 (s, 1H, H_4), 5.9 (m, 2H, H_8, H_9); *m/e* 204 (M^+). (Found: C, 70.24, H, 5.89; Calc for $C_{12}H_{12}O_3$: C, 70.58, H, 5.92%.) A soln of this acetate (0.185 g, 0.9 mmol) in MeOH (20 ml) was irradiated with a 700-W Hanovia immersion lamp (Pyrex filter). The course of the reaction was followed by GLC (SE 30–5%, 180°). After 7 hr, the solution was concentrated to give a semisolid residue which was crystallized from MeOH to give **5** as a white crystalline solid (m.p. 45–80°) which as was shown by GLC and NMR appeared to be pure enough for further transformations. Repeated crystallization from MeOH did hardly improve its quality. IR ν_{max}^{KBr} 1770 (C=O), 1740 (C=O, ester) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.7 (d, 2H, H_{10}, $H_{10'}$), 2.0 (s, 3H, CH_3CO), 2.2–3.7 (m, 7H); *m/e* 204 (M^+). (Found: C. 69.48; H, 6.31; Calc for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92%.)

4 - *Acetoxypentacyclo*[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]*decan* - 6 - *one ethylene acetal* **6**. A mixture of **5** (4.42 g, 22 mmol), toluene-*p*-sulfonic acid (100 mg), ethylene glycol (1.41 g, 23 mmol) and benzene (250 ml) was refluxed for *ca* 20 hr. Water that was formed in this reaction was removed with molecular sieves (soxhlet). The course of the reaction was followed by GLC (UCW, 150°). After the reaction was complete, the cooled soln was washed with NaOH aq (8%) and water, and dried ($MgSO_4$). The solvent was removed to give **6** as a crystalline solid (87%), which was recrystallized from hexane, m.p. 67–68°. IR ν_{max}^{KBr} 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5 (AB quartet, 2H, H_{10}, $H_{10'}$), 2.05 (s, 3H, CH_3CO), 2.1–3.3 (m, 7H, cage protons), 3.9 (m, 4H, ethylene, acetal protons); ^{13}C-NMR ($CDCl_3$) δ 21.2, 35.6, 39.2, 39.6, 43.0, 48.1, 48.4, 49.3, 51.2, 64.8 (2C), 79.5, 121.8 (O—C—O), 170 (O—C=O); *m/e* 248 (M^+). (Found: C, 67.87; H, 6.64; Calc for $C_{14}H_{16}O_3$: C, 67.73; H, 6.50%.)

Ethyl 5 - *oxo* - *tricyclo*[5.2.1.$0^{2,6}$]*deca* - 3,8 - *diene* 2 - *carboxylate* **9**. To a suspension of tricyclic epoxide 8[7] (40 g, 0.21 mol) in EtOH (250 ml) was added sat NaOH aq in EtOH (16 ml). This mixture was stirred at 40° under N_2. The course of the reaction was followed with GLC (SE-30, 180°). After 90 min, an additional amount of base (*ca* 5–10 ml) was added and the mixture stirred for another 20 min. This procedure was repeated until most of starting epoxide **8** had disappeared. Water was added and the dark mixture extracted with ether. The organic phase was washed with water, treated with charcoal and dried ($MgSO_4$). Removal of the solvent gave **9** as a dark-colored oil (65%) which, however, was pure enough for further transformations. Both the IR and ^{1}H-NMR spectrum were identical with those published by Herz *et al.*[7]

Ethyl pentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]*decan* - 6 - *one* 8 - *carboxylate* **10** was prepared by irradiation of crude **9** as described by Herz *et al.*[7]

Pentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]*decan* - 6 - *one* - 8 - *carboxylic acid* **12**. A suspension of **10** in 10% KOH aq (100 ml) was stirred for 2 hr at room temp. The mixture was neutralized and ether extracted. The water layer was acidified with 4 N HCl aq and $CHCl_3$ extracted. The organic phase was washed with water, treated with coal and dried ($MgSO_4$). Concentration of the solvent gave **12** (7.2 g, 64%) as an oil. IR ν_{max}^{NaCl} 1760, 1730, 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.8 (ABq, 2H, H_{10}, $H_{10'}$), 2.5–3.5 (m, 7H, cage protons), 10.6 (s, 1H, OH); *m/e* 190 (M^+). The crude carboxylic acid was sufficiently pure for further transformation.

Pentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]*deca*-6-*one ethylene acetal* 8-*carboxylic acid* **13**. A mixture of **10** (13.5 g, 0.062 mol), toluene-*p*-sulfonic acid (50 mg), ethylene glycol (4.2 g, 0.069 mol) in benzene (100 ml) was refluxed for 3 hr (Dean–Stark separation). Solvent was removed and the formed **11** was stirred in 10% KOH aq for 2 hr at 80°. The pH of this mixture was then lowered to 10 by the careful addition of conc HCl aq and the soln was ether extracted. The water layer was acidified with 4 N HCl (pH 2) and $CHCl_3$ extracted. The organic phase was treated with charcoal and dried ($MgSO_4$). Solvent was removed yielding **13** as a white crystalline solid (9.5 g, 65%). Recrystallization from MeOH/H_2O gave an analytically pure sample, m.p. 123–125°. IR ν_{max}^{KBr} 1690 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.6 (ABq, 2H, H_{10}, $H_{10'}$), 2.4–3.2 (m, 7H, cage protons), 3.9 (m, 4H, ethylene ketal protons), 9.9 (s, 1H, OH); *m/e* 234 (M^+). (Found: C, 66.13; H, 6.11; Calc for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02%.)

Pentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]*decane* 8-*carboxylic acid* (**14**). A soln of **12** (40 g, 0.183 mol) in hydrazine hydrate (400 ml, 100%) was refluxed for 5 hr. After cooling, diethylene glycol (400 ml) and KOH (57 g, 1.02 mol) were added. The apparatus was arranged for distillation and the mixture was slowly heated in an oil bath to 220°. This temp was maintained for 3 hr. The mixtures were allowed to cool, poured into water and ether extracted. This organic phase was treated with coal and dried ($MgSO_4$). Solvent was removed to yield **14** (22.5 g, 70%) as a white crystalline solid. A pure sample was obtained by crystallization from MeOH/H_2O, m.p. 90–92°. IR ν_{max}^{KBr} 3400 (OH), 1690 (COOH) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.2–1.9 (complex AB pattern, 4H, H_6, $H_{6'}$, H_{10}, $H_{10'}$), 2.4–3.1 (m, 7H, cage protons), 11 (s, 1H, OH); *m/e* 176 (M^+). (Found: C, 75.15; H, 7.02; Calc for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86%.)

8-*Acetoxypentacyclo*[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]*decan*-6-*one ethylene acetal* **16**. To a stirred ice-cooled soln of **13** (7 g, 30 mmol) in a mixture of acetone (50 ml) and water (4 ml) was added dropwise Et_3N (3.6 g, 35.6 mmol) in acetone (50 ml). After the addition, a soln of ethylchloroformate (4.12 g, 38 mmol) in acetone (11 ml) was added dropwise during 45 min, the mixture stirred for 30 min at 0°, followed by the addition of a soln of NaN_3 (2.9 g, 44.6 mol) in water (8 ml). After being stirred for 2 hr at 0°, the mixture was poured onto crushed ice and extracted with toluene. The toluene phase was dried ($MgSO_4$), filtered and heated under reflux for 1 hr. The solvent was removed *in vacuo* affording the corresponding isocyanate as an oil. IR $\nu_{N=C=O}$ 2550 cm^{-1}. The crude isocyanate was dissolved in THF (50 ml), conc HCl (12 ml) was added and the mixture refluxed for 30 min. The THF was removed *in vacuo*, the residue diluted with distilled water and ether extracted. The water layer was evaporated to dryness giving *pentacyclo*[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]*decan* - 6 - *one ethylene acetal* 8 - *amino hydrochloride* (6.1 g, 84%). This crude amine hydrochloride was transformed into the corresponding free amine **18** by dissolving it (2 g, 8.3 mmol) in H_2O (20 ml) and adding sat $NaHCO_3$ aq (16 ml). This mixture was extracted with $CHCl_3$, the organic phase washed with water and dried ($MgSO_4$). Removal of the solvent *in vacuo* at room temp yielded **18** (1.7 g, 100%) as a rather unstable semi-solid, which by capillary GLC-analysis (crosslinked methyl silicone, 25 m) was shown to be a single compound. IR ν_{max}^{NaCl} 3350 (NH_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.6 (ABq, 2H, H_{10}, $H_{10'}$), 1.85 (s, 3H, NH_2 and one cage proton), 2.4–2.9 (m, 6H, cage protons), 3.9 (m, 4H, ethylene acetal protons); *m/e* 205.1101; Calc for $C_{12}H_{15}NO_2$: 205.1103. $NaNO_2$ (3.5 g, 50 mmol) was added in small portions during 1 hr to a soln of **18** (1.5 g, 7.3 mmol) in AcOH (20 ml). After stirring at room temp for 3 hr, the soln was neutralized with $NaHCO_3$ aq. The mixture was $CHCl_3$ extracted, the chloroform phase washed with water, treated with coal and dried ($MgSO_4$). Solvent was removed to give **16** (1.46 g, 70%) as an oil. A pure sample could be obtained by chromatography over silica gel ($CHCl_3$). IR ν_{max}^{NaCl} 1730 ($OOCCH_3$) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.75 (ABq, 2H, H_{10}, $H_{10'}$), 2.0 (s, 3H, CH_3COO), 2.3–3.2 (m, 7H, cage protons), 3.9 (m, 4H, ethylene acetal protons); *m/e* 248.1029. Calc for $C_{14}H_{16}O_4$: 248.1049.

8 - *Acetoxy - pentacyclo*[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]*decan - 6 - one* **15**. Amine **18** (1.25 mmol) was dissolved in 75% H_2SO_4 (5 ml) and stirred at room temp for 41 hr. Then the solution was poured into sat $NaHCO_3$ aq and $CHCl_3$ extracted. The $CHCl_3$ phase was washed with water, treated with charcoal and dried ($MgSO_4$). Careful removal of the solvent gave **21** as an oil which by capillary GLC analysis (crosslinked methyl silicone, 25 m) was shown to be a single compound. IR ν_{max}^{NaCl} 3350 (NH_2), 1760 (C=O), 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.3–3.3 (complex multiplet); *m/e* 177.0782; Calc for $C_{10}H_{11}NO_2$: 177.0790. Acetate **15** was obtained by deamination of **21** using the same procedure as described for the preparation of **16**. It was isolated in 44% yield as a rather unstable oil which according to capillary-GLC (crosslinked methyl silicone, 25 m) consists of a single compound. IR ν_{max}^{NaCl} 1760(C=O), 1730($OCOCH_3$) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.9 (ABq, 2H, H_{10}, $H_{10'}$), 2.0 (s, 3H, $OCOCH_3$), 2.3–3.3 (m, 7H, cage protons); ^{13}C-NMR ($CDCl_3$) δ 19.6, 36.3, 37.0, 38.7, 40.7, 40.9 (2C), 48.7, 54.0, 57.3, 168.7 ($OCOCH_3$), 213.0 (C=O); *m/e* 204.0791; Calc for $C_{12}H_{12}O_3$: 204.0786.

8-*Acetoxypentacyclo*[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]*decane* (**20**). Acetate **20** was obtained as an oil in 50% yield starting from **14** using essentially the same procedure as described for the synthesis of **16**. IR ν_{max}^{NaCl} 1730 ($OCOCH_3$) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4 (s, 2H, methylene protons), 1.6 (ABq, 2H, methylene protons), 2.2–3.0 (m, 7H, cage protons); *m/e*: 190.0967; Calc for $C_{12}H_{14}O_2$: 190.0994.

Tetracyclo[5.2.1.0^{2,6}.0^{4,9}]*decan - 3,5 - dione* 3 - *ethylene acetal* (**22**). NaOMe (0.51 g, 9.4 mmol) was added to a stirred soln of **6** (0.85 g, 3.4 mmol) in MeOH (25 ml). After refluxing for 7 hr, MeOH was removed *in vacuo*, the residue diluted with water and $CHCl_3$ extracted. The $CHCl_3$ layer was dried ($MgSO_4$) and the solvent evaporated to give ketone **22** (0.62 g, 87%). Recrystallization from cyclohexane gave a pure sample, m.p. 54–57°; IR ν_{max}^{KBr} 1750 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.3–1.9 (ABq, 2H, H_{10}, $H_{10'}$), 1.4–1.6 (d, 2H, H_{8n}, H_{8x}), 2.2–3.0 (m, 6H, cage protons), 3.9–4.1 (m, 4H, ethylene acetal protons); ^{13}C-NMR δ 35.2 (t), 35.5 (d), 39.6 (t), 41.6 (d), 41.8 (d), 51.2 (d), 54.5 (d), 58.9 (d), 64.8 (t), 114.3 (s, —O^{13}CO—), 213.6 (s, C=O, cyclopentanone); *m/e* 206 (M$^+$). (Found: C, 69.9; H, 6.9; Calc for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84%.) 8 - Endo - *deuterio - tetracyclo*[5.2.1.0^{2,6}.0^{4,9}]*decan - 3,5 - dione - 3 - ethylene acetal* was prepared as described above using MeOD instead of MeOH; ^{1}H-NMR ($CDCl_3$) δ 1.1–1.8 (ABq and m, 3H, H_{10}, $H_{10'}$ and H_{8x}), 2.0–3.0 (m, 6H, cage protons), 3.83 (m, 4H, ethylene acetal protons.

Tetracyclo[5.3.0.0^{2,5}.0^{4,8}]*decan*-3,9-*dione* (**25**). NaOMe (0.386 g, 7.1 mmol) was added to a stirred soln of **5** (1 g, 6 mmol) in MeOH (35 ml). After stirring at room temp for 20 min, MeOH was removed *in vacuo*, the residue diluted with H_2O and $CHCl_3$ extracted. The $CHCl_3$ layer was dried ($MgSO_4$) and the solvent evaporated to give **25** as a white crystalline material. Crystallization from hexane gave an analytically pure sample, m.p. 159–161° (closed capillary). IR ν_{max}^{KBr} 1765 (C=O, cyclobutanone), 1745 (C=O, cyclopentanone) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.1 (s, 2H, H_6, $H_{6'}$), 2.4 (s, 2H, H_{10x}, H_{10n}), 2.7–3.4 (m, 6H, cage protons); ^{13}C-NMR ($CDCl_3$) δ 36.7 (d), 36.8 (t), 42.8 (t), 44.4 (d), 47.0 (d), 60.0 (d), 62.5 (d), 63.0 (d), 198.5 (s), 214.0 (s); *m/e* 162 (M$^+$). (Found: C, 74.07; H, 6.32. Calc for $C_{10}H_{10}O_2$: C, 74.06; H, 6.22%.) 10 - Endo - *deuteriotetracyclo*[5.3.0.0^{2,5}.0^{4,8}]*decan*-3,9-*dione* was prepared as described above using MeOD instead of MeOH; ^{1}H-NMR ($CDCl_3$) δ 2.1 (s, 2H, H_6, $H_{6'}$), 2.4 (s, 1H, H_{10x}), 2.7–3.3 (m, 6H, cage protons). 10,10 - Endo, exo - *dideuteriotetracyclo*[5.3.0.0^{2,5}.0^{4,8}]*decan - 3,9 - dione*. A mixture of **25** (0.15 g) and NaOMe (0.13 g, 2.4 mmol) in MeOH (5 ml) was stirred at room temp for 4 days. Solvent was removed *in vacuo*, the residue diluted with H_2O and ether extracted. The ether layer was dried ($MgSO_4$) and concentrated to give the dideuterated dione (0.015 g, 10%) as a single product. Most likely, the low yield is due to formation of the hydrate of the dideuterated dione, which is very soluble in water. No attempts were made to optimize the yield. ^{1}H-NMR ($CDCl_3$) δ 2.1 (s, 2H, H_6, $H_{6'}$), 2.7–3.3 (m, 6H, cage protons).

Tetracyclo[5.3.0.0^{2,5}.0^{3,9}]*decan - 6,8 - dione* 6 - *ethylene acetal* (**28**). A soln of **19** (0.32 g, 1.29 mmol) and NaOMe (0.5 g, 9.3 mmol) in MeOH (5 ml) was heated for 5 hr in an autoclave at 170–180°. MeOH was removed *in vacuo*, the residue diluted with H_2O and chloroform extracted. The chloroform phase was washed, treated with charcoal and dried ($MgSO_4$). Evaporation of the solvent gave **28** as an oil (94%), which was purified by chromatography over silica gel ($CHCl_3$). IR ν_{max}^{NaCl} 1740 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5 (d, J ~ 14 Hz, 1H, H_{4n}), 1.7 (ABq, 2H, H_{10}, $H_{10'}$), 2.2–2.8 (m, 5H, cage protons and H_x), 2.85–3.3 (m, 2H, cage protons), 3.9 (m, 4H, ethylene acetal protons); *m/e*: 206.0914; Calc for $C_{12}H_{14}O_3$: 206.0943. 4 - Endo, 7 - *dideuteriotetracyclo*[5.3.0.0^{2,5}.0^{3,9}]*decan* - 6,8 - *dione* 6 - *ethylene acetal* was prepared as described above using MeOD instead of MeOH. ^{1}H-NMR ($CDCl_3$) δ 1.7 (ABq, 2H, H_{10}, $H_{10'}$), 2.2–2.75 (m, 4H), 2.8–3.3 (m, 2H), 3.9 (m, 4H, ethylene acetal protons); *m/e*: 208.1083; Calc for $C_{12}H_{12}D_2O_3$: 208.1099.

Tetracyclo[5.3.0.0^{2,5}.0^{3,9}]*decan*-8-*one* (**31**) was obtained in 80% yield by homoketonization of **20** using the same procedure as described above for the formation of **28**. An analytically pure sample was obtained by TLC on silica gel ($CHCl_3$); m.p. 189–191°. IR ν_{max}^{KBr} 1740 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.1 (d, J ~ 12 Hz, 1H, H_{4n}), 1.4–2.0 (complex AB pattern, 4H, H_6, $H_{6'}$, H_{10}, $H_{10'}$), 2.3–2.85 (m, 6H, cage protons and H_{4x}), 3.1 (m, 1H, cage proton); *m/e* 148 (M$^+$). (Found: C, 81.03; H, 8.05; Calc for $C_{10}H_{12}O$: C, 81.04; H, 8.16%.) 4 - Endo, 7 - *dideuteriotetracyclo*[5.3.0.0^{2,5}.0^{3,9}]*decan* - 8 *one* was prepared as described above using MeOD instead of MeOH. NMR ($CDCl_3$) δ 1.45–2.0 (m, 4H), 2.2–2.9 (m, 5H), 3.1 (m, 1H); *m/e*: 150.1039; Calc for $C_{10}H_{10}D_2O$: 150.1045.

Endo-8-*hydroxytetracyclo*[5.3.0.0^{2,5}.0^{3,9}]*decane* (**32**). To ice-cooled soln of **31** (1.9 g, 12.8 mmol) in MeOH (32 ml) was added gradually $NaBH_4$ (3.8 g, 100 mmol). After stirring for 45 min, the solvent was removed *in vacuo*, the residue treated with NH_4Cl aq and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried ($MgSO_4$) and concentrated to give crude **32** (1.8 g, 95%). Recrystallization from EtOH gave an analytically pure sample, m.p. 224–225°; IR ν_{max}^{KBr} 3300 (OH) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0–3.0 (m, 13H), 3.3 (br d, 1H, CHOH); *m/e* 150 (M$^+$). (Found: C, 79.74; H, 9.53; Calc for $C_{10}H_{14}O$: C, 79.96; H, 9.39%.)

4 - *Acetoxypentacyclo*[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]*decan* - 6 - *ol* (**35a**, **b**). A soln of **5** (0.1 g, 0.49 mmol) in ether (5 ml) was added to a suspension of $LiAlH(t\text{-}OBu)_3$ (0.3 g, 12 mmol) in ether (50 ml). After stirring at room temp for 30 min dil HCl aq was added until a clear soln was obtained. The ether phase was washed with H_2O, dried ($MgSO_4$) and conc to give **35** (**35a** : **35b**/1 : 4) as a colorless oil (78%). IR ν_{max}^{NaCl} 3400 (OH), 1740 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.6 (ABq, 2H, H_{10}, $H_{10'}$), 2.0 (s, 3H, CH_3COO); 2.1–3.3 (m, 7H, cage protons), 3.6 (s, 1H, OH), 4.15 (s, 0.2H, H_6 in **36a**); 4.4 (s, 0.8H, H_6 in **36b**).

4 - *Acetoxy - 6 - (methylsulfonyl)pentacyclo*[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]*decane* (**36a**, **b**). To an ice-cold soln of the epimeric mixture of alcohols **35** (1.4 g, 6.8 mmol) and mesylchloride (0.91 g, 8 mmol) was added $N(Et)_3$ (1.1 g, 10.8 mmol). The mixture was allowed to warm up to room temp and stirred for another 30 min. After filtration, the solvent was removed and the residue extracted with ether. The ether phase was washed with dil HCl aq, $NaHCO_3$ aq and water and subsequently dried ($MgSO_4$). Concentration of the soln gave a 1:4 mixture of **36a** and **36b** (1.7 g, 87%) as an oil which slowly solidified at −20°. IR ν_{max}^{KBr} 1740 (C=O), 1360, 1170 (OSO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.6 (ABq, 2H, H_{10}, $H_{10'}$), 2.0 (s, 3H, CH_3COO), 2.95 (s, 0.6H, CH_3SO_2O in **36a**), 3.0 (s, 2.4H, CH_3OSO in **36b**), 2.4–3.3 (m, 7H, cage protons), 4.95 (s, 0.2H, H_6 in **36a**), 5.2 (s, 0.8H, s, H_6 in **36b**). Fractional recrystallization of the mixture of **36a** and **36b** from MeOH gave **36b** analytically pure, m.p. 92–93°. ^{1}H-NMR ($CDCl_3$) δ 1.6 (ABq, 2H, H_{10}, $H_{10'}$), 2.0 (s, 3H, CH_3COO), 3.0 (s, 3H, CH_3SO_2O), 2.4–3.3 (m, 7H, cage protons), 5.2 (s, 1H, H_6). (Found: C, 54.92; H, 5.65; Calc for $C_{13}H_{16}O_5S$: C, 54.92; H, 5.67%.)

Tetracyclo[5.3.0.0^{2,5}.0^{4,8}]*dec* 9 - *en* - 3 - *one* (**37**). A soln of

NaOMe (6.55 mol) in MeOH (68 ml) was added dropwise to a soln of **36a** and **36b** (1 : 4) (5.15 g, 0.018 mol). After stirring at room temp for 30 min, MeOH was removed *in vacuo* at room temp until a concentrated turbid soln was obtained. This residue was dissolved in ether and the ether phase washed with HCl aq (3%). The water phase was extracted ether, the combined ether layers dried ($MgSO_4$) and concentrated to give a yellow oil. Flash column chromatography [silica 60H, petroleum ether 40–60°–EtOAc (5 : 1)] gave **37** (1.94 g, 73%) as an oil which slowly solidified on standing. Recrystallization from hexane gave an analytical pure sample, m.p. 129–130° (sealed twice). IR ν_{max}^{KBr} 3060 (C=CH), 1760 (C=O), 1575, 1450, 1330, 1250 cm^{-1}; UV λ 204 nm (n-hexane, ε 3200); λ 206 nm (ethanol, ε 2000); ^{1}H-NMR ($CDCl_3$) δ 1.95 (2H, s, H_6, $H_{6'}$), 2.7–3.3 (6H, m, cage protons), 6.2 (2H, s, H_9, H_{10}); ^{13}C-NMR ($CDCl_3$) δ 199.5 (s, C=O), 137.8 (d, olefinic carbons), 65.1 (d), 61.2 (d), 53.5 (d), 43.5 (d), 36.8 (t, C_{10}); *m/e*: 146.0706; Calc for $C_{10}H_{10}O$: 146.0732.

Further elution (EtOAc) afforded **38** (1.3 g, 27%). A soln of **38** (1.3 g, 5.73 mmol) in Ac_2O (10 ml) to which a catalytic amount of N,N-dimethyl aminopyridine (DMAP) was added, was stirred for 14 hr at room temp. Ac_2O was removed *in vacuo* to give an oil which was dissolved in $CHCl_3$. This soln was washed with 0.1 N HCl aq, sat $NaHCO_3$ aq and water. After drying ($MgSO_4$), solvent was removed to give **36a** (1.19 g, 73%) as an oil and was solidified in the freezer. Recrystallization from MeOH gave a pure sample, m.p. 96–97°; IR ν_{max}^{KBr} 1730 (C=O), 1350, 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5 (ABq, 2H, H_{10}, $H_{10'}$), 2.0 (s, 3H, CH_3COO), 2.9 (s, 3H, CH_3SO_2O), 3.4–2.3 (m, 7H, cage protons) 4.9 (1H, s, H_6). (Found: C, 54.88; H, 5.69; Calc for $C_{18}H_{16}O_5S$: C, 54.92; H, 5.67%.)

X-ray diffraction

Crystal data. $C_{13}H_{15}O_5S$. Mol. wt = 284.33, a = 5.939(3), b = 14.181(3), c = 15.323(3) Å; V = 1290.5 Å, Z = 4. Space group $P2_12_12_1$ from systematic absences; μ(CuKα) = 22.2 cm^{-1}; D_c = 1.376 g cm^{-3}; F(OOO) = 564.

Crystal characteristics. Crystals for X-ray diffraction work were obtained by recrystallization from MeOH, which yielded long transparent needles. A piece of 0.3 × 0.3 × 0.4 mm, cut from a larger crystal was used for data collection. All crystallographic measurements were done on a Nonius CAD4 diffractometer, employing CuHx radiation.

Intensity measurements, structure determination, refinement. The intensity data of all reflections with $2\theta < 132°$ and $H \geqslant 0$ were measured. Data in the other hemisphere were collected partially because crystal decomposition prevented measurement of all the data. After correction for the decomposition and averaging of the symmetry equivalent reflections, 1332 unique reflections resulted, of which 1297 were "observed" [$I > 3\sigma(I)$]. Lorentz and polarization corrections were applied, but no absorption correction. The data were reduced to [F_{obs}] values. The structure was solved with MULTAN. Block-diagonal least-squares refinement with isotropic thermal parameters in the initial stages of the refinement and full-matrix least-squares refinement with anisotropic thermal parameters in the final stages converged at an R-value of 0.075. After calculation of the H-atoms, continued full-matrix least-squares refinement with fixed H-parameters resulted in a final R-value of 0.069. In the final stages of the refinement a weighting scheme $w = (\sigma^2 + 0.0008\ Fo^2)^{-1}$ was used. Calculations were carried out with a local version of the NRC crystal structure system[26] and XRAY76.[27]

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