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DIRECTIVE EFFECT OF β-FUNCTIONALIZATION ON THE REGIOCHEMISTRY OF THE BASE INDUCED HOMOKETONIZATION OF BRIDGEHEAD SUBSTITUTED 1,3-BISHOMOCUBANE ACETATES

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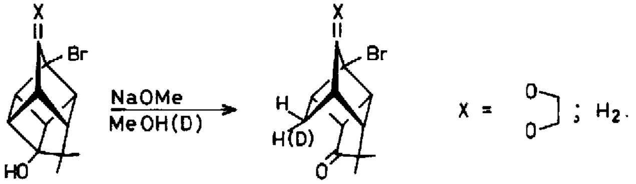
Summary: Base induced homoketonization of bridgehead acetate 6 leads to the thermodynamically favored half cage skeleton 7, whereas cage opening of 5 is directed by the β-ketofunction to give cleavage of the central C_5-C_6 bond producing half cage diketone 10.

Bridgehead substituted 1,3-bishomocubanols[1] 1 are reactive substrates which under basic conditions give rise to a regio- and stereospecific homoketonization reaction (Scheme 1). The regiochemistry of these cage opening reactions is primarily governed by the relief of cage strain, resulting in the exclusive formation of the thermodynamically most stable half cage ketones 2. The first step in the homoketonization process involves formation of a carbanionic species. In the examples shown, product formation is determined solely by thermodynamic factors since in none of the three conceivable C-C bond cleavages the developing carbanion is particularly stabilized. Recently, Osawa *et al*[2] confirmed by means of force field calculations that the skeleton of the half cage ketone formed is indeed the thermodynamically favored one.

Scheme 1

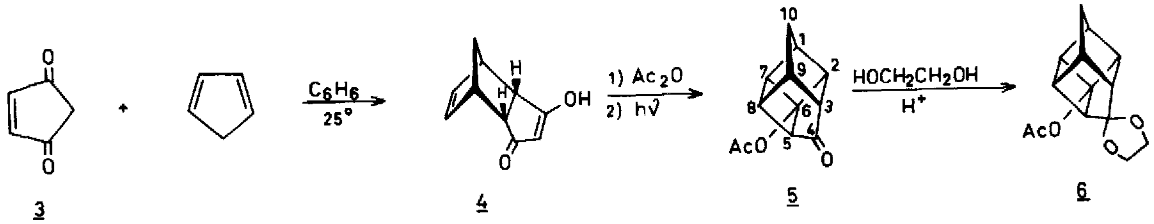


1 2

The objective of the present work is to investigate whether a stabilization of the formal carbanion has a directive effect on the regiochemistry of the homoketonization process, ultimately leading to a thermodynamically less stable half cage framework. For this purpose we studied the base induced cage opening of the 1,3-bishomocubane acetates 5 and 6 (Scheme 2). In structure 5, scission of the central C_6-C_5 bond gives a carbanionic intermediate which is considerably stabilized by the carbonyl function at C_4. On the other hand, cleavage of the C_6-C_7 or C_6-C_2 bond will lead to a carbanionic species of relatively high energy. In structure 6 none of the three conceivable C-C bond cleavages will lead to a particular stabilized carbanion.

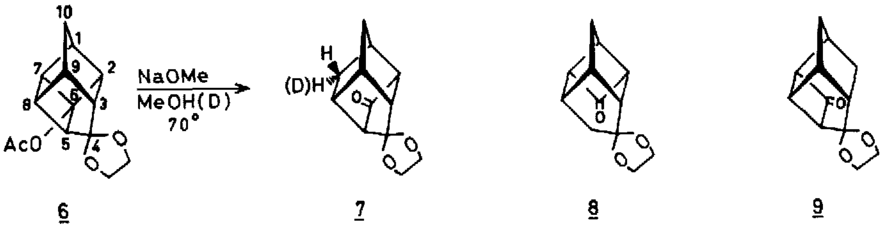
1,3-Bishomocubane acetate 5 could be conveniently synthesized by a new route starting from cyclopentene-3,5-dione 3[3] as outlined in Scheme 2 (overall yield 85%). For the photochemical cyclization of 4, conversion into its enol acetate turned out to be essential. Ketalization of 5 smoothly gave ketal 6 in a yield of 87%.

Scheme 2



Homoketonization of ketal acetate 6 could be accomplished by treatment with NaOMe in refluxing methanol for 7 hrs. After work-up, an oil was isolated in high yield, which slowly solidified on standing. Both spectral and analytical data revealed the presence of a single ketone to which structure 7 was assigned (Scheme 3). The IR spectrum showed a carbonyl absorption at 1750 cm^{-1} which is indicative of a cyclopentanone ring constrained in a polycyclic system. The ^1H-NMR spectrum, although very complex, could be unravelled by using shift reagents in combination with decoupling techniques. This strongly suggested the formation of ketone 7. However, the alternative structures 8 and 9, which arise by scission of the central C_6-C_5 bond and C_6-C_2 bond in 6, respectively, could not be definitely excluded. Unambiguous proof for structure 7 was provided by the ^{13}C-NMR spectrum, which among others displayed a ^{13}C=O resonance at δ 213.6 ppm, confirming the presence of a cyclopentanone ring[4]. On this basis structures 8 and 9 can be rejected as these ketones contain only a cyclobutanone ring.

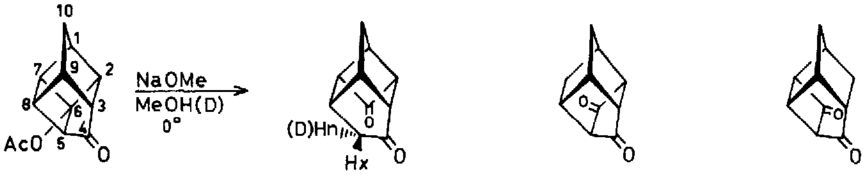
Scheme 3



Hence, base induced homoketonization of 6 is a regiospecific process proceeding by exclusive cleavage of the C_6-C_7 bond. Inspection of molecular models suggests structure 7 to be more relaxed than the half cages 8 and 9. The C_6-C_7 bond, being the central bond of a bicyclo[2.2.0]hexane ring system, is more strained than the C_6-C_2 and C_6-C_5 bonds. Accordingly, this homoketonization of ketal acetate 6 leads as expected to the thermodynamically most stable half cage ketone 7. The stereochemistry of this homoketonization process was established by treating 6 with NaOMe in MeOD. This labeling experiment convincingly showed that this process is stereospecific and proceeds with retention of configuration.

Strikingly, keto acetate 5 was extremely sensitive towards base. Treatment with NaOMe in MeOH at 0° gave an almost instantaneous reaction leading to a crystalline product (m.p. 159-161°) in almost quantitative yield. On the basis of both spectral data and deuterium labeling experiments structure 10 was assigned to this compound (Scheme 4). The IR spectrum displayed two carbonyl absorptions at 1765 and 1745 cm^{-1} indicative of a four and a five membered ring ketone. The ^{1}H-NMR spectrum ($CDCl_3$) showed three distinct sets of resonances *viz.* a singlet for two protons at δ 2.10 which was attributed to the methylene bridge protons at C_{10}, a narrow multiplet at δ 2.40 for the *exo-* and *endo-*proton at C_5 and a complex multiplet between δ 2.7 and δ 3.4 ppm for the remaining cage protons. The ^{13}C-NMR spectrum ($CDCl_3$) exhibited ten distinct ^{13}C resonances of which the signals at δ 198.5 and δ 214.0 are typical for $^{13}C=O$ functions constrained in a four and five membered ring[4], respectively. These spectral data definitely rule out the alternative structure 11 as this structure does not contain a cyclobutanone ring. However, they do not allow an unequivocal differentation between 10 and its isomer 12. Conclusive evidence for structure 10 was obtained from deuterium labeling experiments. Upon treatment of the half cage ketone with NaOMe in MeOD at room temperature, a slow H/D exchange reaction was observed which was complete after 4 days. Both the ^{1}H-NMR and mass spectra showed the incorporation of two deuterium atoms. This H/D exchange reaction can only be reconciled with structure 10 as only this structure contains an enolizable carbonyl function which allows

Scheme 4



5 10 11 12

the introduction of two deuterium atoms. In the isomeric half cage ketones 11 and 12 enolization is entirely precluded in conformity with Bredt's rule[5].

The stereochemistry of the homoketonization of 5 proceeded with complete retention of configuration (exclusive formation of *endo*-monodeuterated 10 upon treatment with NaOMe in MeOD for 10 minutes at 0°). This process is not disturbed by concurrent exchange of the *exo*-proton as this reaction was found to be much slower.

The divergency in product formation observed for the base induced homoketonization of 1,3-bishomocubane acetates 5 and 6 convincingly demonstrates that this cage opening can indeed be directed by β-functionalization, even to the extent that thermodynamic control is overridden. It should be noted that the cage opening of 5 represents the first example of a base induced homo ketonization in a bishomocubane system in which cleavage of the central C_5-C_6 bond is accomplished.

REFERENCES AND NOTES

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5. In principle, homoenolization in 11 and 12 may lead to H/D exchange in these structures[6]. However, no such exchange was observed when half cage ketone 7 was treated with NaOMe in MeOD under the same conditions.
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