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A DECISIVE ELECTRONIC EFFECT OF A BRIDGEHEAD METHOXY SUBSTITUENT ON THE ELECTROPHILIC CAGE OPENING OF 1,3-BISHOMOCUBANONES

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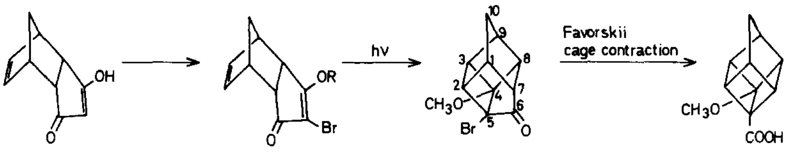
Abstract: 4-Methoxypentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]decan-6-ones 4 and 9 undergo an acid catalyzed cage fragmentation to give tricyclodecenediones 6 and 10, respectively. With silver cations under basic conditions, an unusual oxidative cage fission reaction is observed leading to tetracyclo[4.3.0.$0^{2,4}$$0^{3,8}$]nonan-5-one 7-carboxylic acids.

Recently, we showed that in the 1,3-bishomocubane system, the regiochemistry of the homoketonization is highly dependent on the relative stability of the conceivable carbanionic intermediates and consequently can be directed by the introduction of an appropriate β-functionality such as a ketone function[1]. In order to extend these studies to the more strained homocubane skeleton, we needed an expedient route to 4,5-difunctionalized homocubanes which would allow the ultimate introduction of an alcohol function at one of these bridgehead positions. An attractive and direct approach would be a Favorskii ring contraction of 5-bromo-4-methoxy-1,3-bishomocubanone 4 to 5-methoxyhomocubane carboxylic acid 5 (scheme I). However, as will be reported in this communication, this cage ketone 4 undergoes unforseen cage opening reactions due to electronic participation of the bridgehead methoxy group.

Scheme I

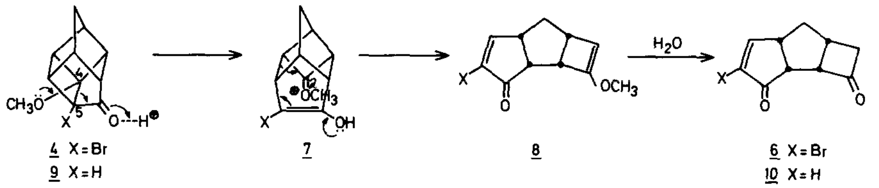


1 2 R=H 3 R=CH3 4 5

For the synthesis of 4, we started off with readily available *endo*-tricyclodecenone 1[2] which on bromination in acetic acid produces enolbromide 2 in 65% yield[3]. The corresponding methyl enolether 3 was obtained in high yield by treating 2 with $CH_3(SO_4)_2$ in methanol. Unexpectedly, initial attempts to obtain 4 by irradiation of 3 in benzene or toluene (pyrex) did not lead to any bishomocubanone. After removal of the solvent and subsequent purification of the solid residue by chromatography on silica, a crystalline compound was obtained (m.p. 148.5-149.5°) in 60% yield to which, based on spectral and analytical data, tricyclic structure 6 was assigned. By carefully monotoring the photochemical conversion of 3 using NMR and GLC, it was established that the anticipated intramolecular [π2 + π2] cycloaddition indeed had taken place. However, under the conditions used, the initially formed 1,3-bishomocubanone 4 slowly rearranged to the tricyclodecadienone 8, which rapidly reacted with moisture from the air to form 6. This rearrangement appeared to be catalyzed by minor traces of acid on the glass wall or in the solvent as it could be completely blocked by performing the irradiation in toluene containing some ammonia. In this manner, bromoketone 4 was obtained quantitatively as a yellow oil that could be purified by bulb to bulb destillation at 100 °C ($8x10^{-2}$torr), however, with considerable decomposition. Treatment of this analytically pure bromoketone 4 with HCl(g) in toluene gave an instantaneous rearrangement to tricyclodecenedione 6.

The spectral data of dione 6 (m/e 239.981, $C_{10}H_9BrO_2$; 198 ($M-CH_2=C=O$); IR νmax (KBr) 1770 (C=O, cyclobutanone), 1715 and 1580 (enone absorptions) cm^{-1} ; UV (EtOH) λmax 244.5 (ε5000), 198.5 (ε 2400) nm; ^{1}HNMR ($CDCl_3$) δ7.69 (1H, d, J = 2.34 Hz), 4.13-3.50 (2H, m), 3.48-2.88 (3H, m), 2.90-2.22 (2H, m), 2.08 and 1.93 (1H, d of t, J = 14.4 Hz); ^{13}CNMR ($CDCl_3$) δ206.4 (C=O cyclobutanone), 198.5 (C=O, cyclopentenone), 162.8, 124.2, 53.9, 36.4, 66.7, 53.3, 51.0, 33.6 ppm) were in full accord with the proposed structure. An X-ray diffraction analysis unambiguously established the all-*cis* structure of this tricyclodecenedione 6[4]. The formation of 6 from 4 can be rationalized as depicted in scheme II.

Scheme II



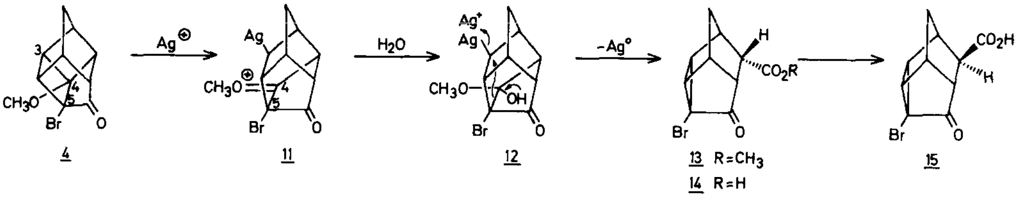
Protonation of the carbonyl function initiates scission of the central C_4-C_5 bond and the concomitant formation of an oxonium ion. In non-nucleophilic solvents such as toluene this cation 7 can be stabilized by subsequent C_2-C_3 cleavage leading to tricyclic enolether 8. Under the experimental conditions used, this enolether reacts rapidly with traces of water to form the isolated diketone 6. The occurrence of 8 could be proven by performing the acid catalyzed cage opening of 4 in $CDCl_3$/HCl(g) in an NMR-tube. The ^{1}HNMR-spectrum showed the characteristic vinylether proton absorption at δ4.52 and a methoxy group at δ3.40 ppm of 8 together with the resonances of the diketone 6. In this mechanism, the presence of the bromo-substituent may have an important accelerating effect on the cage opening but it need not to be. The bromine lacking substrate, 4-methoxy-1,3-bishomocubanone 9, which was obtained in excellent yield from the methyl enolether of 1 by irradiation in toluene, appeared to be more stable than its α-bromo analogue. However, on standing at room temperature in toluene for several weeks it also rearranged to tricyclodecenedione 10. In contrast, the presence of a electron-releasing substituent at the 4-position turned out to be essential. Replacement of the methoxy group by an acetate, a mesylate, or even an (2-methoxy)ethoxy methyl (MEM) ether function completely suppressed this acid-catalyzed cage-opening reaction[5].

The driving force of this regiospecific cage opening reaction of methoxy substituted homocubanones 4 and 9 is the push pull effect during the cleavage of the C_4-C_5 bond which is flanked on one end by an electron releasing bridgehead methoxy-group and on the other end by an electronwithdrawing carbonyl function[6].

Having prepared methoxy-bromoketone 4, attempts were made to perform a Favorskii contraction to obtain 5. Under a variety of basic conditions only a total degradation of the cage skeleton was observed. It is noteworthy that the bromoketone lacking the bridgehead methoxy group smoothly contracts to homocubane carboxylic acid using 30% KOH aq. under reflux[10]. The weakening effect of the methoxy group is not yet understood. The Favorskii cage contraction could be realized for the MEM-ether analogue of 4. The corresponding homocubane carboxylic acid was obtained in 25% yield.

Attempts were made to promote the cage contraction by enhancing the leaving ability of the α-bromo substituent by Ag cation assistance[11]. To this end, an excess of $AgNO_3$ was added to a suspension of bromoketone 4 in 20% KOH aq. and the mixture heated at 60 °C for 4 hrs. The formation of a silver-mirror was observed. A single crystalline carboxylic acid (m.p. 127.5-129 °C, yield 85%) was isolated that after repeated crystallization from ethanol rearranged to an isomeric carboxylic acid (m.p. 220-221 °C). Based on spectral data of both[12] and an X-ray analysis of the methyl ester of the latter acid[13], structures 14 and 15 were assigned to these acids. A rationale for the high yield formation of these tetracyclic ketone carboxylic acids is depicted in scheme III.

Scheme III



Firstly, attack of the silver cation initiates a regiospecific C_3-C_4 bond cleavage leading to oxoniumion 11. The lifetime of this cation is apparently long enough to permit trapping by H_2O/OH^- to form hemi-acetal 12. Subsequent migration of the C_4-C_5 bond then leads to 13 under the concomitant expulsion of Ag^0. Saponification of the ester function then produces 14, which in refluxing ethanol slowly epimerizes to 15[14]. This Ag^+-induced reaction is also observed for 9. Although, there is ample evidence on the Ag^+-catalyzed isomerization of strained cage systems[15], this reaction presents to our knowledge the first example of an Ag^+-induced cage opening in which the intermediate carbocation is intercepted by an external nucleophile, causing a deviation of the normal reaction pattern. The expected product[16], *viz.* tricyclodecenone 3, could not be detected in the reaction mixture.

In conclusion, the presence of an electron-donating methoxy substituent at the C_4-bridgehead position in 1,3-bishomocubanones decisively governs the course of the cage-opening reactions, induced either by a proton acid or by silver cations. The facile formation of tricyclodecenone 6 has prospects for its use as a building block in natural product synthesis[17].

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5. The synthesis of these compounds will be reported in due course.
6. Interestingly, this cage opening can also be accomplished thermally, using the flash vacuum pyrolysis technique[7]. At 400 °C/3.5×10^{-2}torr, both **4** and **9** were smoothly converted into the cyclobutyl enolethers **8**[8]. This thermal reorganization can be best accounted for by a radical pathway involving the initial formation of a 1-methoxy-1,4-radical by a regioselective cleavage of the C_4-C_5 bond, followed by further bond scission[9].
7. For a recent review on this technique see: R.F.C. Brown, 'Pyrolytic methods in Organic Chemistry', Academic Press, New York, N.Y. (1980).
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12. Spectral data of **14**: IR νmax (KBr): 3500-3000 (OH), 1745 (C=O), 1705 (C=O) cm^{-1}; ^{1}HNMR($CDCl_3$) δ4.76 (1H, s, OH), 3.13-2.50 (5H, m), 2.35-2.12 (1H, m), 2.01 and 1.83 (2H, AB quartet, J = 10 Hz); m/e 256/258 (M^+, 1 Br), and of **15**: IR νmax (KBr) 3100-2500 (OH), 1745 (C=O), 1705 (C=O) cm^{-1}; ^{1}HNMR (d_6-acetone) δ3.13-2.55 (5H, m), 2.12-2.00 (1H), 1.87 and 1.72 (2H, AB quartet, J = 10 Hz).
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14. Ester **13** not necessarily needs to be an intermediate in this process. Acid **14** may also be directly formed from the hydrolysis product of **12**, which is the corresponding C_4-hydrate.
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