Pergamon

*Tetrahedron Letters*, Vol. 38, No. 2, pp. 295-298, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02296-4

# Synthesis of Bridged Cyclooctane Derivatives *via* Alkoxy Radical Fragmentation

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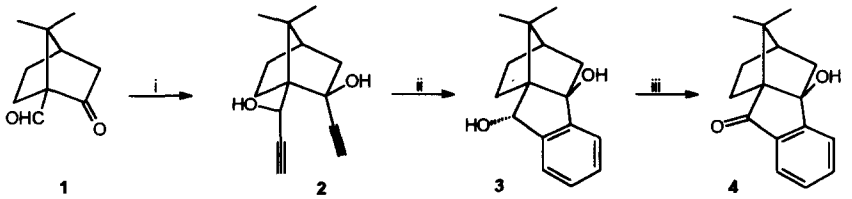
*Abstract:* β-Fragmentation of an alkoxy radical generated from ketol 4 under the conditions of hypohalite reaction afforded functionalized bridged cyclooctane derivatives 5 and 7 in excellent yields. Copyright © 1996 Published by Elsevier Science Ltd

Efficient methods for the direct synthesis of cyclooctane derivatives are rare, due to the inherent reluctance of these systems towards ring closure. In natural product synthesis, additional structural features of a target molecule often make this synthetic task even more difficult. A good example is provided by the taxane class diterpenes, whose retrosynthetic analysis faces the problem of the efficient construction of the densely functionalized bridged 8-membered ring; convergent synthetic approaches to this class of compounds, relying on direct 8-membered ring formation, showed this to be a limiting, low yielding step.[1] Alternatively, fragmentation of fused bicyclic systems is a well established route to medium rings. Cyclohexane ring enlargements *via* the fragmentation of the corresponding cyclobutane adducts were reported by several groups;[2] however, the fragmentation of bicyclo[3,3,0]octanols does not seem to have been fully exploted, given the plethora of synthetic methods for the construction of the corresponding [3,3,0]bicycles (*via* cyclopentane ring closure), and for their fragmentation, as well. The rare examples of related approaches have shown that this strategy indeed offers an efficient entry into bridged cyclic 8-membered frameworks.[3] We endeavoured to examine the feasibility of the cyclization/fragmentation route, using the alkoxy radical fragmentation as a crucial step in the formation of a polycyclic skeleton containing a functionalized, bridged cyclooctane unit.

The fragmentation precursor 4 was prepared as displayed in *Scheme 1*. Lithium acetylide addition (excess LiCCH, THF, -78°C)[4] to the ketoaldehyde 1,[5] afforded the diyne 2 in 87% yield, as a single diastereoisomer.[6] Cyclotrimerization of 2 with acetylene in the presence of a catalytic amount of Wilkinson's catalyst (excess acetylene, 8 mol% $(Ph_3P)_3RhCl$, EtOH, 0°C to r.t., 3h)[7] provided the tetracyclic diol 3 (75% after recrystallization), which was further oxidized to the ketol 4 (PCC, $CH_2Cl_2$, r.t., 30 min.; 94%).

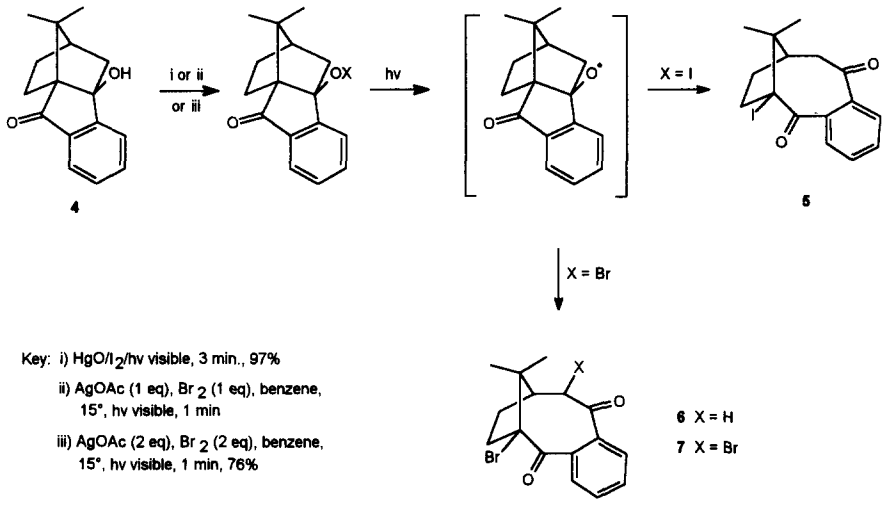



1 2 3 4

Key: i) Li-acetylide/THF, -78°C, 87% ii) acetylene/EtOH/$(Ph_3P)_3PhCl$ 8 mol%, 0°-r.t., 75%
iii) PCC/$CH_2Cl_2$, r.t., 94%

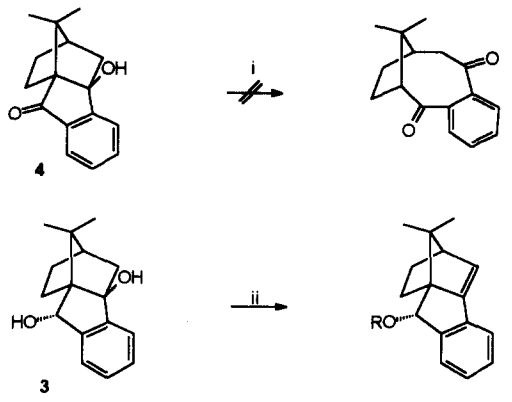
*Scheme 1*

Initial attempts to perform the alkoxy radical fragmentation of 4 with the direct introduction of oxygen functionality onto the bridgehead carbon atom failed: ketol 4 proved unreactive towards lead tetraacetate under forcing conditions (3 mol eq LTA, benzene, reflux, 18[h]), while it's reaction with CAN gave a mixture of products. However, when submitted to the conditions of hypoiodite reaction (yellow HgO, $I_2$, benzene, xenofot sun lamp, 15°C, 3 min.), 4 smoothly rearranged to the tricyclic iodo derivative 5 which was isolated in 97% yield (*Scheme 2*).[8] Surprisingly, the hypobromite reaction, under the similar conditions (AgOAc 1eq, $Br_2$ 1eq, benzene, 15°C, xenofot lamp irrad., 1 min), afforded a mixture of two compounds which were identified as mono- and dibromo derivatives 6 and 7, along with one minor unidentified product. Apparently, the fragmentation step is followed by a second bromination reaction, whose mechanism, so far, remained unclear. However, when two equivalents of AgOAc/$Br_2$ reagent were used under the same reaction conditions, a clean reaction afforded the dibromo derivative 7 as the sole product, in 76% isolated yield (single diastereoisomer).[8]




*Scheme 2*

The high regioselectivity of the fragmentation reaction is noteworthy. Alkoxy radical fragmentations of bicyclic systems have occasionally been used in syntheses of medium and large rings;[9] yet however, studies of several groups have shown that these reactions often proceed with unpredictable regioselectivity, the lateral fragmentation giving rise to the less stable carbon centered radical even when the scission of the central bond is thermodynamically strongly favoured.[10] Our results show that substantial strain release, associated with the desired rearrangement, provides sufficient driving force for a regioselective ring enlargement. It is worth mentioning that a similar transformation could not be accomplished under the ionic conditions: treatment of 4 with base ($KO^tBu$, THF, 18-K-6 or $KO^tBu$, DMSO) failed to induce the retroaldol reaction, while attempted Grob fragmentation of the diol 3 (TsCl, Pyr or MsCl, Pyr) gave the unsaturated alcohol 8 or the corresponding mesylate 9 as the major reaction products (*Scheme 3*).




Key: i) a) KO$^t$Bu/THF/18-K-6, or b) KO$^t$Bu/DMSO
ii) a) TsCl/Pyr/$CH_2Cl_2$, 40°C, or b) MsCl/Pyr, 5°C

*Scheme 3*

To summarize, from the readily available ketoaldehyde 1, tricyclic bridged functionalized cyclooctane derivatives 5 and 7 were obtained by a cyclization/fragmentation sequence, in four steps, in 60% (47% respectively) overall yield, in the latter case with the unexpected (but synthetically useful) introduction of an additional functionality. Investigations oriented towards the application of this strategy on more elaborated systems are underway.

***Acknowledgements:*** A part of this work was done at the Institut de Chimie des Substances Naturelles, CNRS, Gif sur Yvette, France. The author is grateful to Dr Samir Zard for his interest in this work, and to Dr Jean-Francois Gallard who performed HMQC and HMBC NMR experiments.

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(*Received in UK* 22 *October* 1996; *revised* 20 *November* 1996; *accepted* 22 *November* 1996)