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Intramolecular 4 + 3 Cycloadditions. The Synthesis of Cyclooctanoids

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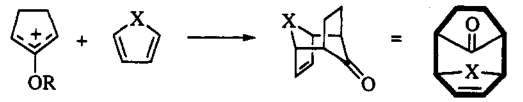
Summary: The synthesis of fused cyclooctanoids from the products of intramolecular 4 + 3 cycloaddition of cyclic oxyallylic and alkoxyallylic cations is described.

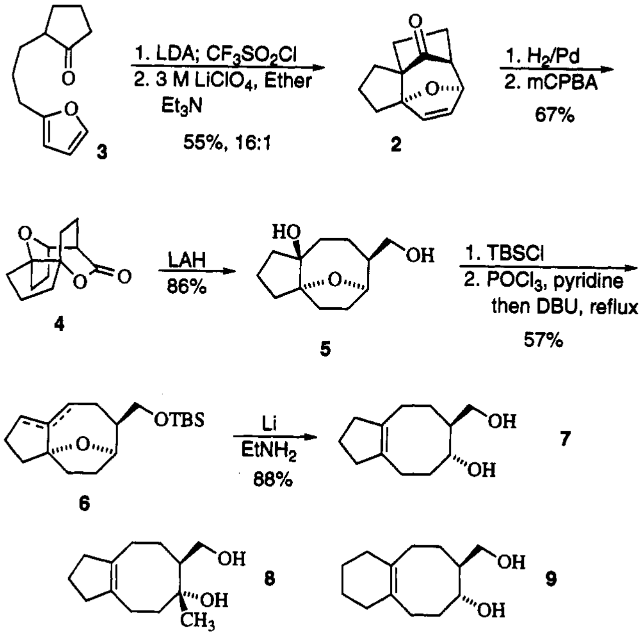
The synthesis of cyclooctanoids has been of major significance for some time and continues to attract the attention of synthetic organic chemists.[1] Among the methodologies which stand out in this area are those which use a cycloaddition approach to construct the eight-membered ring. The nickel-catalyzed 4 + 4 cycloaddition of butadienes to produce fused cyclooctadienes represents a particularly powerful approach.[2] Related photochemical cyclizations of dienes, pyridones, and pyrones have also been reported.[3–5] Our work with intramolecular 4 + 3 cycloadditions led us to consider an approach equivalent to a 4 + 4 cycloaddition process in which a five-membered cyclic allylic cation would react with a diene to give an eight-membered ring (eq 1).[6–8] In this report we document the successful realization of this concept.

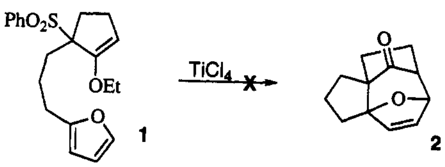


(1)

We originally set out to apply our alkoxyallylic sulfone methodology to the cycloaddition of cyclic substrates but quickly discovered that all attempts at cyclizing 1 failed (eq 2). We then turned to the methodology introduced by Föhlisch and found that cyclization occurred readily and stereoselectively.[9] Thus, chlorination of 3 followed by stirring in 3 M $LiClO_4$ in ether in the presence of triethylamine gave 2 in 55% overall yield in a 16:1 ratio of stereoisomers.[10] The structure of the major isomer shown in Scheme 1 was established by X-ray analysis of the hydrogenation product of 2.[11] A number of attempts to remove the bridging oxygen and carbonyl groups were unsuccessful or led to rearranged products.[7e] We eventually pursued the route shown in Scheme 1. Thus, hydrogenation of 2 followed by Baeyer–Villiger oxidation gave lactone 4 in 67% yield. Lithium aluminum hydride reduction proceeded in 86% yield to give diol 5. The first bridge had been broken. Protection of the primary alcohol and $POCl_3$-mediated elimination gave a 1.68:1 mixture (GC) of alkenes 6 as an inseparable mixture in 57% yield. Finally, treatment with excess lithium in ethylamine both

Scheme 1





(2)

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(11) MW = 192.26; space group: $P21/n$; $a = 15.1850(20)$ Å, $b = 7.5735(6)$ Å, $c = 8.8187(12)$ Å, $\beta = 106.024(6)°$; $V = 974.78(20)$ Å^3; $Z = 4$; $D_{calc} = 1.310$; radiation = Cu Kα ($l = 1.5418$ Å); $\mu = 0.66$ mm^{-1}; $F(000) = 416$; temperature = 23/−1o; final $R = 0.045$ for 1391 reflections with $I > 2s(I)$.

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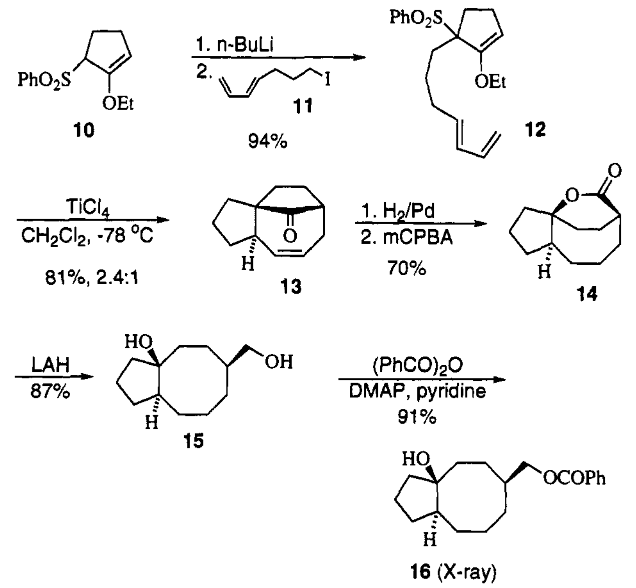
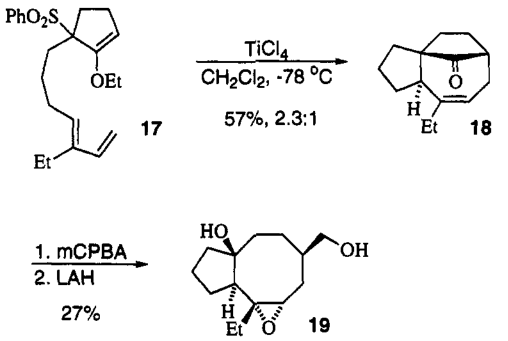
Scheme 2



Scheme 3



cleaved the allylic ether and resulted in deprotection to give the diol 7 in 88% yield.[12]

We have prepared the 5,8 fused ring system 8 and the 6,8 fused system 9 by a similar route.[13] The stereochemistry of the former is assigned on the basis of analogy to 2 and that of the latter has not yet been rigorously determined.

Not convinced that the alkoxyallylic sulfone approach to 4 + 3 cycloadditions in cyclic systems should be abandoned and interested in using simple butadienes to trap allylic cation intermediates, we prepared a precursor which we thought would be better suited to exposure to the strong Lewis acids typically used in that procedure.[7a] Thus, 10 was treated with n-BuLi and dienyl iodide 11 to give 12 in 94% yield.[14] Treatment of this compound with TiCl$_4$ in CH$_2$Cl$_2$ at −78 °C gave a 2.4:1 stereoisomeric mixture of cycloadducts in 81% yield. The major isomer 13 shown in Scheme 2 was hydrogenated and converted to lactone 14 in 70% overall yield. Reduction afforded the diol 15 in 87% yield. Selective benzoylation afforded 16, whose structure was established by X-ray crystallography.[15]

Similarly, 17 gave 18 in 57% yield as a 2.3:1 mixture of isomers upon treatment with TiCl$_4$. Combined Baeyer–Villiger and epoxidation reactions followed by reduction gave the fused five–eight compound 19. This sequence illustrates that the double bonds of 4 + 3 cycloadducts need not be reduced to successfully generate eight-membered rings.

In summary, we have developed two routes for the intramolecular 4 + 3 cycloaddition of cyclic allylic cations. The adducts can be converted in a straightforward fashion to fused eight-membered ring systems. Issues of internal and relative stereocontrol and applications of this methodology are under study and will be reported in due course.[16]

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Supplementary Material Available: Experimental procedures and ^{1}H and ^{13}C NMR data of 2–5, 7–9, and 12–19 (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information. The author has deposited atomic coordinates for structures dihydro-2 and 16 with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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[12] (a) Sakai, K.; Ohtsuka, T.; Misumi, S.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1981**, 335. (b) Wender, P. A.; Dreyer, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 5805.

[13] Compound 8 was obtained in 18% and compound 9 in 11% overall yield using the sequence of reactions shown in Scheme 1. It should be noted that high stereoselectivity was observed in the formation of the 4 + 3 cycloadducts leading to these cyclooctanoids.

[14] Funk, R. L.; Bolton, G. L.; Brummond, K. M.; Ellestad, K. E.; Stallman, J. B. *J. Am. Chem. Soc.* **1993**, *115*, 7023.

[15] MW = 302.41; space group: $P21/n$; a = 8.465(5) Å, b = 10.44490(20) Å, c = 18.797(9) Å, β = 90.500(20)°; V = 1660.8(13) Å^3; Z = 4; D_{calc} = 1.209; radiation = Mo Kα (l = 0.709 30 Å); μ = 0.07-mm^{-1}; $F(000)$ = 656; temperature = 23/−1o; final R = 0.039 for 1881 reflections with $I > 2s(I)$.

[16] All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR data and IR spectral data as well as satisfactory combustion analysis or exact mass data.