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A New General Method for the Construction of Angular Triquinanes from 4-Allylcyclobutenones. Rearrangement of Linear Triquinanes to the Angular Isomers

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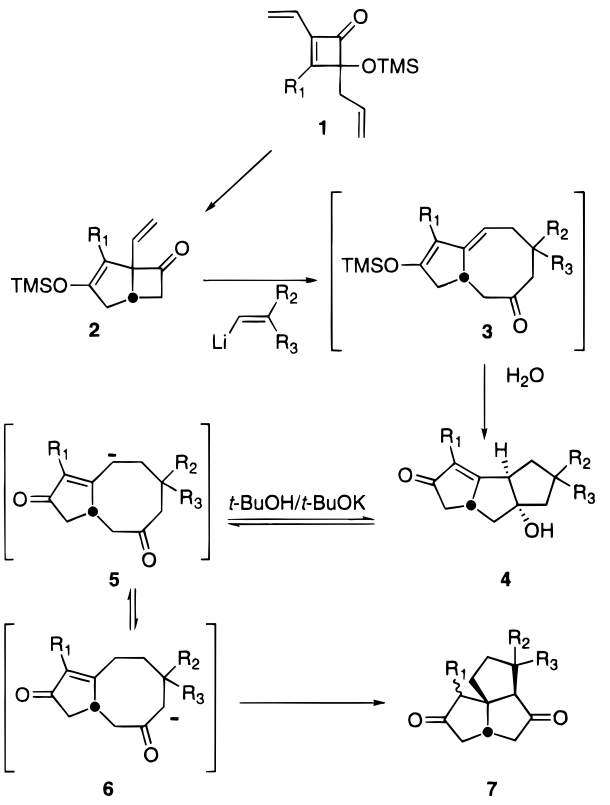
Previously we described the synthesis and rearrangement of 4-allylcyclobutenones **1** to bicyclo[3.2.0]heptenones **2** and their subsequent conversions to the linear triquinanes **4**, a transformation involving a tandem oxy-Cope ring expansion to **3** followed by transannular ring closure upon aqueous workup (Scheme 1).[1] We now report a general method for the regiospecific synthesis of angular triquinanes **7** via a novel retro-aldol rearrangement of the corresponding linear isomers **4**. This rearrangement is envisaged to involve formation and equilibration of the enolates **5** and **6** followed by an intramolecular Michael Addition of the enolate ion in **6** to the enone moiety.

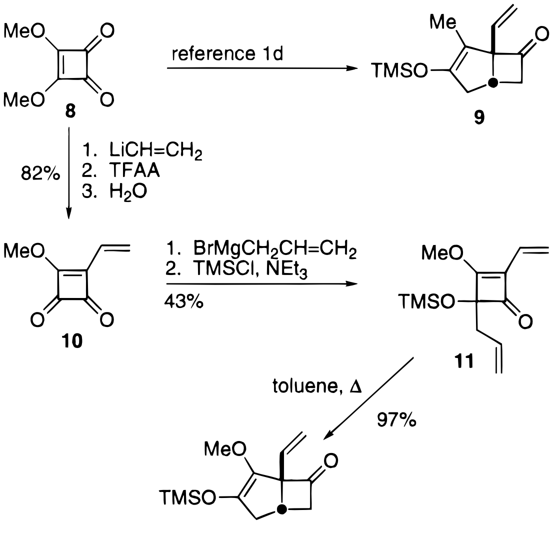
The required bicycloheptenone precursors **9** and **12** are readily available from dimethylsquarate **8**.[2−4] The synthesis of the former was previously reported (40%),[1d] and, in a modification of that synthesis, the latter was prepared as outlined in Scheme 2. Specifically, treatment of **8** with vinyllithium followed by TFAA-assisted hydrolysis of the β-hydroxy enol ether moiety in the initially formed adduct gave 3-ethenyl-4-methoxycyclobutenedione **10** in 82% isolated yield.[5] Treatment of **10** with allylmagnesium bromide[1a] followed by trimethylsilyl chloride provided **11** in 43% yield. A modest reduction in yield was due to the tendency of **10** to undergo competing 1,6-addition of allylmagnesium bromide.[6] Thermolysis of **11** (toluene, 110 °C) then gave **12** in excellent yield (97%).

Preparation of the new linear triquinanes **13** and **14** (Scheme 3) is analogous to the previously noted tandem oxy-Cope ring expansion/transannular ring closure method employed for the synthesis of **15**−**17** from **9**.[1c,d] That is, bicyclo[3.2.0]heptanone **12** was treated with vinyllithium in THF at −78 °C, and the oxy-Cope rearrangement was induced by warming to room temperature. The resulting bicyclo[6.3.0]undecadienone was desilylated upon aqueous workup, and the resulting enolate underwent transannular ring closure to give **13** (66%). When the reaction was quenched with methyl iodide prior to the aqueous workup, the enolate formed in the oxy-Cope reactions was trapped from the convex face, and this ultimately resulted in the formation of the linear triquinane **14** (57%).

Scheme 1



Scheme 2



Treatment of the triquinanes **13**−**17** with potassium *tert*-butoxide in warm *tert*-butyl alcohol caused their remarkable rearrangement to the angular isomers **18**−**22**, respectively (Scheme 4). The structure assignments of these products are based upon their characteristic spectral properties as well as a single crystal X-ray structure of the major diasteriomer of **22**. The ^{13}C NMR spectra of all angular triquinanes displayed two downfield carbonyls (δ, 213−221) and no alkene carbon unsaturation.

Several additional points merit further discussion. The enhanced diastereoselection observed in the formation of **22** is believed to result from an unfavorable nonbonding interaction that occurs between the angular methyl group and a C-1 methyl on the α-face. The fact that this

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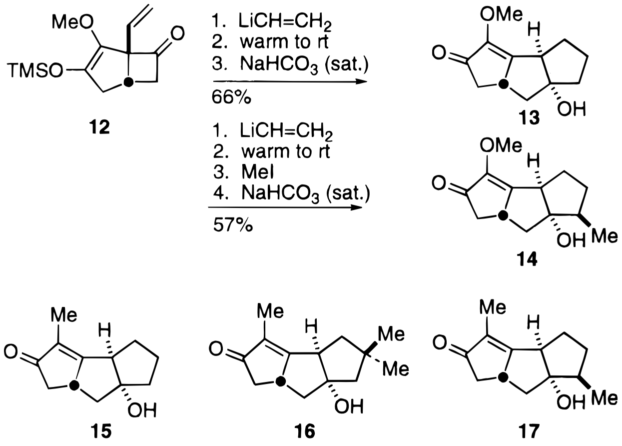
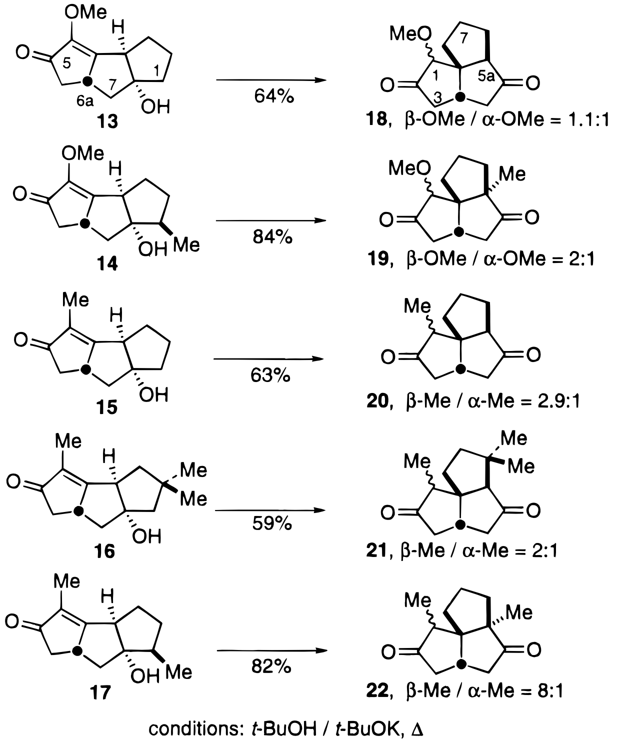
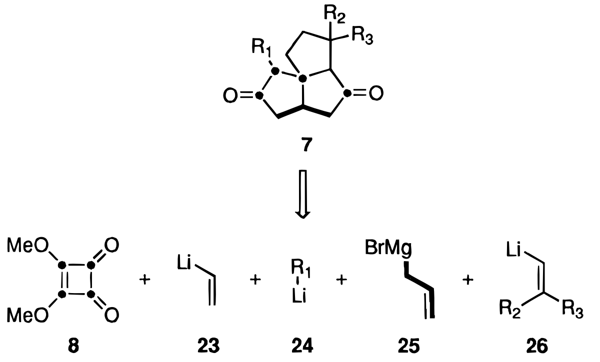
Scheme 3



Scheme 4



Scheme 5



diastereoselectivity is significantly reduced in **20** and **21** is consistent with this hypothesis. A similar trend is obvious upon comparison of the diastereoselectivity for the formation of **18** and **19**. While it is presently unclear what factors influence the relatively efficient rearrangement of **14** and **17**, one explanation could be the elimination of an unfavorable steric interaction between the C-1 methyl and the C-7 and C-6a hydrogens upon fragmentation.

In conclusion we note that a number of synthetic methods for the construction of the triquinane framework have appeared in recent years.[7,8] While many of these are amenable to the regiospecific synthesis of either angular or linear triquinanes,[9] reports of the direct interconversion of such isomers are rare.[10] The method outlined here documents a general approach for the regiospecific synthesis of functionalized angularly-fused triquinanes from their linear counterparts and further illustrates the rich synthetic potential of cyclobutenone derivatives as a route to highly condensed ring systems.[2] In this regard it is noted that the generalized triquinane **7** translates to simple starting materials that can be efficiently employed, i.e., dimethylsquarate **8** and the organometallic reagents **23**–**26** (Scheme 5). We are currently investigating applications of this methodology as key steps in the total synthesis of several angularly-fused triquinane natural products.

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Supporting Information Available: Procedures and characterization data (5 pages).

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