stantially correct.

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Direct Formation of a Tricyclic Cycloheptanone-Containing System by Enolate Condensation with a Cyclopropanone Derivative

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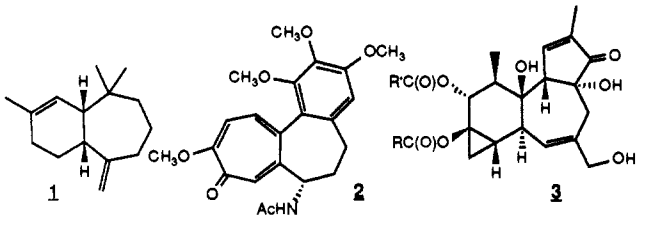
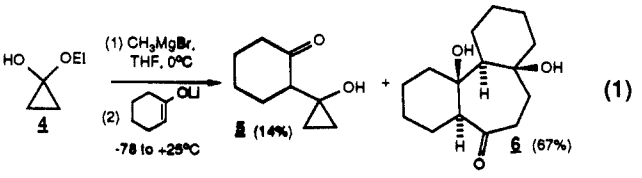
Seven-membered carbocycles occur among many classes of natural products. Most commonly, the seven-membered ring is bound to at least one additional ring of another size. Especially well-known examples are the guaianes and pseudoguaianes,[1] but other cases include the himachalenes (e.g., α-himachalene, **1**),[2] colchicine (**2**),[3] and the phorbol esters (e.g., **3**).[4] Because of the importance of these compounds, many methods have been devised for the construction of cycloheptane derivatives.[5] However, we now report the very direct formation of a tricyclic cycloheptanone-containing system in a one-pot reaction sequence, which is based upon the condensation of an enolate with a cyclopropanone derivative and which apparently employs the homoenolate reactivity of a cyclopropanoxide intermediate.[6]



Reaction of the readily available cyclopropanone ethyl hemiacetal (**4**)[7] with methylmagnesium bromide followed by the addition of lithium cyclohexenolate affords a mixture of products composed of the formal cyclopropanone adduct **5** in 14% yield and, much more interestingly, the tricyclic product **6** in 67% yield (eq 1). A small amount (3%) of starting material **4** is recovered,



(1)

but other components, present in trace quantities in the reaction mixture, have not been identified.

Determination of the structure of product **6** was initially difficult, even with the use of 300-MHz ^{1}H NMR and europium shift reagent studies. However, the ^{1}H NMR spectrum obtained at 600 MHz is sufficiently resolved to permit assignment of the indicated structure.[8] Subsequent single-crystal X-ray diffraction studies (Figure 1) confirm this assignment.[9]

In order to probe the pathway by which **6** is formed, we have done a number of further experiments, the most important of which are summarized here. When the simple adduct **5** is isolated from the original reaction mixture, purified, and then subjected to further reaction with methylmagnesium bromide and lithium cyclohexenolate, tricyclic **6** is obtained in 80% yield (eq 2). Silylation of adduct **5** to give **7** followed by reaction with lithium cyclohexenolate permits isolation of the further adducts **8**–**10** (eq

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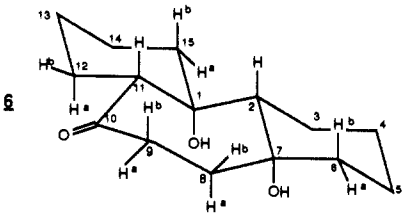
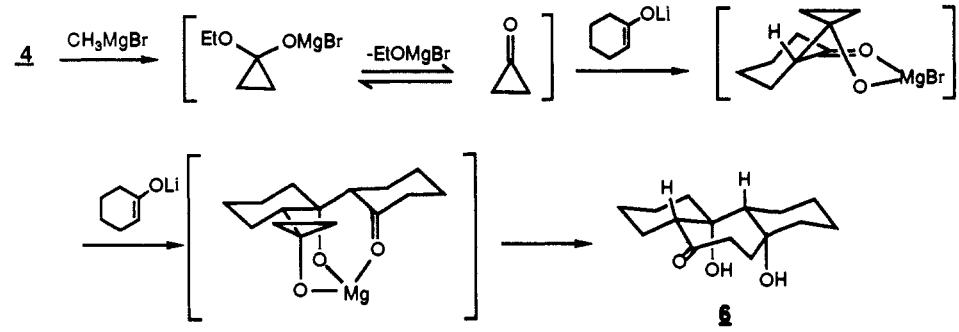
(8) The 600-MHz ^{1}H NMR spectrum of **6** ($CDCl_3$; after exchange with



D_2O) was obtained at Carnegie-Mellon University: δ 2.92 (dd, J = 12.7, 4.3 Hz, H_{11}), 2.75 (ddd, J = 15.8, 12.3, 6.0 Hz, H_{9b}), 2.41 (ddd, J = 15.9, 5.9, 2.6 Hz, H_{9a}), 2.25 (br d, J = 13.4 Hz, H_{12a}), 2.14 (ddd, J = 15.2, 12.4, 6.0 Hz, H_{8a}), 2.02 (dq, J = 13.9, 3.7 Hz, H_{12b}), 1.89 (br d, J = 13.4 Hz, H_{6b}) 1.83 (ddd, J = 14.9, 6.0, 2.6 Hz, H_{8b}), 1.80 (br d, J = 13.4 Hz, H_{6a}), 1.74 (br d, J = 13.0 Hz, H_{15b}), 1.45–1.64 (m, 8H, CH_2), 1.35 (dd, J = 12.2, 3.4 Hz, H_2), 1.07–1.24 (m, 3 H, CH_2).
(9) Compound **6** crystallized in the monoclinic space group $P2_1$ with a = 5.808 (2) Å, b = 9.036 (4) Å, c = 12.839 (3) Å, and β = 97.68 (2)°. The structure was solved with Multan (189 reflections with a minimum E of 1.54 and 1404 relationships), using 1518 unique reflections with $F_o^2 > 2.0\sigma(F_o^2)$ ($2\theta \leq 48.3°$) measured on an Enraf-Nonius CAD4 diffractometer using Mo Kα radiation. Refinement with anisotropic temperature factors and calculated hydrogen atom positions led to R = 0.038 and R_w = 0.059. Complete details of this structure determination will be reported in our full paper on the cycloheptanone annulation.
(10) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

0002-7863/86/1508-8313$01.50/0

Scheme I



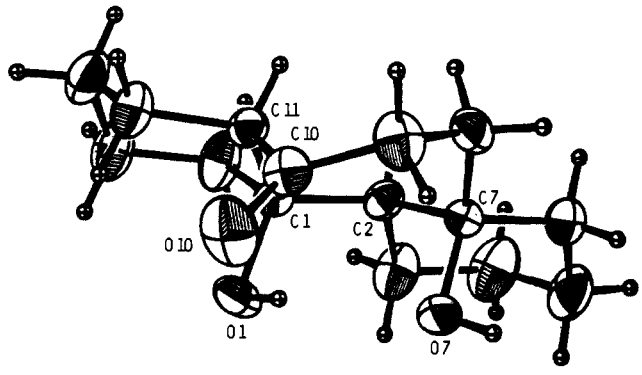
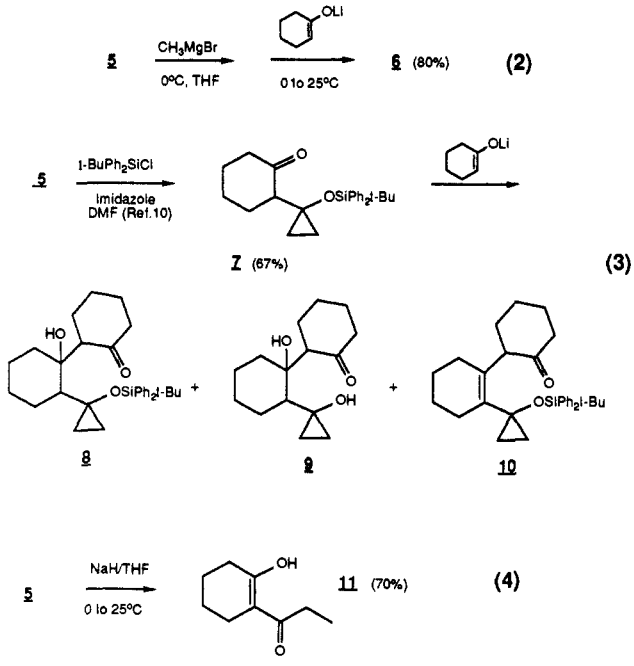


Figure 1.

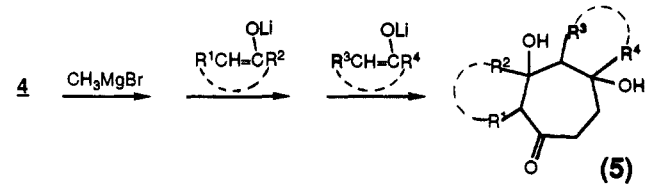
3), although we have yet to find suitable conditions for conversion of **8** or **9** into **6**. The homoenolate reactivity of these systems is



clearly demonstrated by the cleavage of adduct **5** to give the ethyl ketone **11** (eq 4). Reaction of the silyl ether **7** with tetra-*n*-butylammonium fluoride also gives ketone **11**.

Based upon the above observations, we propose the pathway shown in Scheme I for formation of tricyclic product **6**. Magnesium chelation apparently plays a key role in that when control experiments of the types described above are done in the absence of magnesium species, formation of **6** is greatly diminished or even fails completely. Note that the conformations that we have chosen for the intermediates account for the overall stereochemistry of the reaction sequence.

In conclusion, we have discovered a pathway for the very direct construction of complex cycloheptanone-containing systems. The utility of this reaction sequence is potentially very great if two different enolates, either of which may be generated from cyclic or acyclic ketones, can be used sequentially (eq 5). Our further efforts are being directed toward this generalization of the annulation procedure.[12]



Acknowledgment. We thank Dr. Charles Eigenbrot of the University of Notre Dame X-Ray Diffraction Facility and Dr. T. K. Mishra of the Carnegie-Mellon NMR Laboratory for their most valuable assistance in obtaining structural data, Professor Frank W. Fowler (State University of New York at Stony Brook), Dr. Anthony S. Serianni (University of Notre Dame), and Joseph Snyder for their very helpful discussions, and the National Science Foundation (CHE8219466) and University of Notre Dame for providing generous financial support of this work. Structures were drawn by using the ChemDraw Program, developed by Stewart Rubenstein. P.H. also thanks Professor Björn Åkermark and the Royal Institute of Technology (Stockholm, Sweden) for providing a Visting Scientist position (1986).

(11) Reference deleted in press.

(12) A detailed procedure is given for the preparation of **6**. A solution of cyclopropanone ethyl hemiacetal (**4**, 2.10 g, 20.6 mmol) in THF (20 mL) was added to methylmagnesium bromide (2.50 M solution in THF, 8.2 mL, 21 mmol) in THF (40 mL) with an addition funnel over a 20-min period at 0 °C under nitrogen.[13] After the reaction mixture was stirred for 1 h at 0 °C, a solution of lithium cyclohexenolate [prepared by addition of *n*-butyllithium (1.50 M solution in hexane, 13.7 mL, 21 mmol) to diisopropylamine (2.08 g, 20.6 mmol) in THF (40 mL) at −78 °C, followed by warming to 0 °C for 30 min, recooling to −78 °C, addition of cyclohexanone (2.02 g, 20.6 mmol), and warming to 0 °C over 15 min] was added with a cannula over a 30-min period. The reaction mixture was then warmed to 25 °C over 15 min and stirred for 1 h. Ether (150 mL) and saturated aqueous NH_4Cl (40 mL) were added, the layers were separated, and the organic phase was washed with water (40 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual yellow oil was chromatographed on silica gel (1:1 ether/hexane) to give 0.045 g (3%) of **4** (R_f 0.80), 0.45 g (14%) of **5** (R_f 0.41), and 1.75 g (67%) of **6** (R_f 0.14) as a colorless solid: mp 187–188 °C; IR (CCl_4) 3450, 2960, 2870, 1700, 1460, 1380, 1100 cm^{-1}.

(13) Brown, H. C.; Rao, C. G. *J. Org. Chem.* **1978**, *43*, 3602.