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Communications

Rearrangements of Bridgehead Bromides. A Direct Synthesis of *epi*-Modhephene

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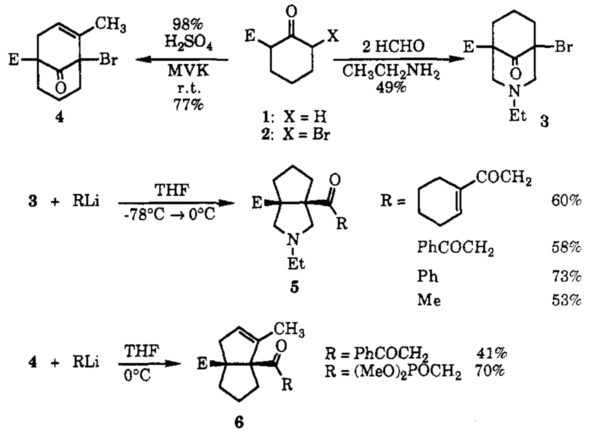
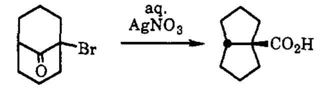
Summary: The reaction of nucleophiles with bridgehead bromides **3** and **4** affords rearrangement products resulting from addition of the nucleophile to the carbonyl group followed by ring contraction. This rearrangement has been employed in a direct synthesis of *epi*-modhephene.

Several researchers, most notably Wiesner,[1] Masamune,[2] Nagata,[3] and Fukumoto[4] have reported clever syntheses of diterpene alkaloids. Our approach required the preparation of an AB ring system that would be converted into the diterpene skeleton via bridgehead radical chemistry. The synthesis of the requisite bicyclic intermediate commenced with the bromination of readily available keto ester **1** to afford bromide **2**. The most direct path from bromide **2** to amine **3** was via a Mannich condensation with ethylamine and formaldehyde. Although displacement of the bromide by the amine seemed a likely complication, the double Mannich condensation actually proceeded very smoothly to generate **3** in 49% isolated yield along with 40% recovered starting material.

Scheme I



On the basis of extensive literature precedent in the radical addition area, the intramolecular interception of the bridgehead radical appeared to offer the best chance for a high-yield connection of **3** with an alkene.[5] Toward this goal, amine **3** was added to a THF solution of the lithium enolate of 1-acetylcyclohexene at −78 °C (Scheme I). The solution was then allowed to warm to 0 °C. The expected product was the hydroxy ketone. Surprisingly, the only product isolated was the novel diketone **5**. The resonances at 94.99 and 180.13 ppm (corresponding to the β-diketone unit) in the ^{13}C NMR spectrum strongly supported the structural assignment. This product presumably arose from enolate addition to the ketone followed by ring contraction of the resulting tertiary alkoxide to a 3-azabicyclo[3.3.0]octane system. There is little precedent of this nucleophilic addition/ring contraction sequence in bridged ring systems. The rearrangement of the bromo ketone shown below employed aqueous silver nitrate.[6]



When **3** was treated with phenyllithium, methyllithium, or the lithium enolate of acetophenone, rearrangement products were also observed.

For determination of whether the rearrangement would occur in the all-carbon framework, keto ester **4** was prepared. The reaction of bromo ketone **2** and MVK in

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(1) Wiesner, K. *Tetrahedron* **1985**, *41*, 485–497.

(2) Masamune, S. *J. Am. Chem. Soc.* **1964**, *86*, 291.

(3) Nagata, W.; Sugasawa, T.; Narisada, M.; Wakabayashi, T.; Hayase, Y. *J. Am. Chem. Soc.* **1963**, *85*, 2342.

(4) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164.

(5) Curran, D. P. *Synthesis* **1988**, *417*, 489.

(6) Warnhoff, E. W.; Wong, C. M.; Tai, W. T. *J. Am. Chem. Soc.* **1968**, *90*, 514.

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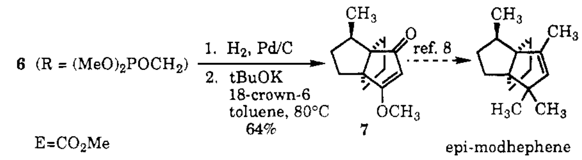
Scheme II



concentrated sulfuric acid at 0 °C generated a diketone from a Michael addition reaction. This diketone could be cyclized to 4 in 77% yield by treatment with concentrated sulfuric acid at ambient temperature.[7] The reaction of 4 with the lithium enolate of acetophenone (−78 °C to 0 °C) furnished diketone 6 in 41% yield. The reaction of 4 with $(MeO)_2POCH_2Li$ afforded keto phosphonate 6 in 70% yield. The reaction of 4 with MeMgBr in ether at 0 °C produced the unrearranged tertiary alcohol as a mixture of stereoisomers.

The bicyclic compound 6 contains two of the three rings of modhephene, a novel terpene (Scheme II). Unexpectedly, catalytic hydrogenation of 6 produced one isomer by reduction from the more hindered endo face. Cyclization with potassium *tert*-butoxide and 18-crown-6 at 80 °C in toluene afforded 7, an intermediate in the Mundy syntheses of *epi*-modhephene,[8] in 64% yield. Since 7 was converted by Mundy into *epi*-modhephene, this represents a formal synthesis of *epi*-modhephene. Compound 7 is available from 2 in 34% overall yield.

This rearrangement reaction is compatible with a variety of functional groups. The synthesis of an advanced intermediate in the Mundy synthesis of *epi*-modhephene confirms the structural assignments of the rearrangement products.[9] The research described herein opens up a new pathway by which bicyclo[3.3.0]octanes and their 3-aza counterparts can be constructed.

Registry No. (±)-1, 98263-13-9; 2, 30132-23-1; (±)-3, 128164-63-6; (±)-4, 128164-64-7; (±)-5 (R = (1-cyclohexenylcarbonyl)methyl), 128164-65-8; (±)-5 (R = $PhCOCH_2$), 128164-66-9; (±)-5 (R = Ph), 128164-67-0; (±)-5 (R = Me), 128164-68-1; (±)-6 (R = $PhCOCH_2$), 128164-69-2; (±)-6 (R = $(MeO)_2P(O)CH_2$, 128164-70-5; (±)-7, 127419-76-5; $PhCOCH_2Li$, 55905-98-1; PhLi, 591-51-5; MeLi, 917-54-4; $(MeO)_2P(O)CH_2Li$, 34939-91-8; 1-acetylcyclohexene lithium enolate, 128164-71-6; (±)-*epi*-modhephene, 76739-65-6.

Supplementary Material Available: Experimental procedure for 4 and spectral data for 5 and 6 (2 pages). Ordering information is given on any current masthead page.

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[7] For a related procedure, see: Heathcock, C. H.; Ellis, J. E.; McMurry, J. E.; Coppolino, A. *Tetrahedron Lett.* **1971**, 4995.

[8] For comparison with authentic spectra, see: Mundy, B. P.; Wilkening, D.; Lipkowitz, K. B. *J. Org. Chem.* **1985**, *50*, 5727.

[9] Jasperse, C. P.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 5601–5608. Explanation of this unusual reduction reaction will be provided in the full paper. Reduction of 6 with $[Ir(COD)(PCy_3)py]PF_6$ and H_2 followed by cyclization (KH, PhH) and alkylative transposition (MeLi, HCl) afforded Curran's intermediate.

High Diastereofacial Differentiation in Osmium Tetraoxide Catalyzed Dihydroxylation of Acyclic Bis-allylic Compounds

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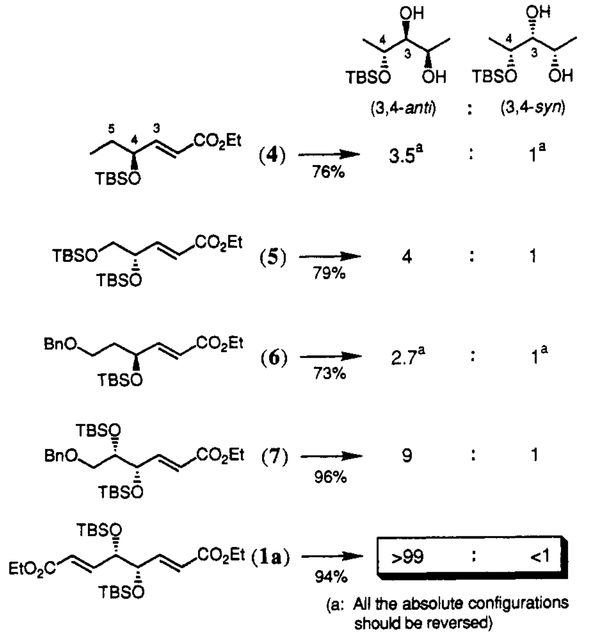
Summary: Bis-allylic compounds such as diethyl (4*S*,5*S*)-4,5-bis((*tert*-butyldimethylsilyl)oxy)-2,6-octadienedioate (**1a**) exhibit very high diastereoselection in osmium tetraoxide catalyzed dihydroxylation; a particular ground-state conformation is proposed to be responsible.

Osmium tetraoxide catalyzed oxidations of carbon–carbon double bonds have proven to be very useful for introducing vicinal dihydroxyl groups onto 1,2-disubstituted olefins bearing an allylic oxygen stereocenter in a stereochemically predictable manner.[1] Kishi has proposed a useful empirical model based on a reactant-like eclipsed transition state.[1d] However, the diastereomeric excesses observed in these processes vary considerably from sub-

Scheme I



(a: All the absolute configurations should be reversed)

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[1] (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943–3946. (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947–3950. (c) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951–3954. (d) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247–2255. (e) Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass. L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458–2459. (f) Johnson, C. R.; Barbachyn, M. R. *Ibid.* **1984**, *106*, 2459–2461. (g) Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C.; Munari, S. D. *Tetrahedron Lett.* **1985**, *26*, 5459–5462. (h) Solladié, G.; Fréchou, C.; Demailly, G. *Ibid.* **1986**, *27*, 2867–2870. (i) Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094–1096. (j) Solladié, G.; Hutt, J.; Fréchou, C. *Ibid.* **1987**, *28*, 61–64. (k) Annunziata, R.; Cinquini, M.; Cozzi, F. *Ibid.* **1987**, *28*, 3139–3142. (l) Fleming, I.; Sarker, A. K.; Thomas, A. P. *J. Chem. Soc., Chem. Commun.* **1987**, 157–159. (m) DeNinno, M. P.; Danishefsky, S. J.; Schulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 3925–3929. (n) Vedejs, E.; Dent, W. H. III *J. Am. Chem. Soc.* **1989**, *111*, 6861–6862. (o) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 1698–1700. (p) for a review, see: Nakajima, M.; Tomioka, K.; Koga, K. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 878–888.

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