70 eV) m/e 198.1517 (198.1494 calcd for $C_{11}H_{19}NO_2$ + H).

***rel*-(2*R*,6*S*,α*S*)-6-Cyano-6-methyl-α-(1-methylethyl)-tetrahydro-2*H*-pyran-2-methanol (17b).** A solution of ketone **2** (0.34 mg, 0.2 mmol) in 2 mL of CH_2Cl_2 was stirred and cooled at −78 °C as TMSCN (0.08 mL, 0.6 mmol) and BF_3·OEt_2 (0.06 mL, 0.5 mmol) were added. The temperature was maintained at −78 °C for ca. 8 h and then slowly warmed to −19 °C (in a cold room) over 40 h. Ether and saturated $NaHCO_3$ were added, and the crude product was isolated by the standard method. ^1H NMR spectrum of the isolate indicated that <5% of cis diastereomer **17a** was present in the crude product. Trans diastereomer **17b** was isolated in 87% yield (34 mg, 0.17 mmol) using RC (3.5:1 and then 1:1 pentane–ether, pretreated plate with 7% triethylamine in 3.5:1 pentane–ether): ^1H NMR[16] (500 MHz, $CDCl_3$) δ 3.63 (1 H, ddd, $J_{H\text{-}H\alpha}$ = 8.5 Hz, J = 10, 7.5 Hz, H-2), 3.46 (1 H, dd, $J_{H\text{-}H_2}$ = 8.5 Hz, $J_{H\text{-}Hb}$ = 3 Hz, H-α), 2.1 (2 H, m, H-3(α), H-5(α)), 2.08 (1 H, d of sep (partially buried under 2.1 δ), J = 2.5, 1.5 Hz, H-β), 1.94 (1 H, app dd, J = 8, 8 Hz, H-5(β)), 1.69 (1 H, m, H-4(β)), 1.6 (1 H, br s, OH), 1.53 (3 H, s), 1.49–1.38 (2 H, m, H-4(α) and H-3(β)), 1.07 (3 H, d, J = 7 Hz), 0.88 (3 H, d, J = 7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.8, 83.08, 73.27, 71.37, 39.79, 28.83, 26.99, 19.65, 17.32, 14.86; IR (neat) 3450 (br), 2963, 2234 (w), 1083, 1071, 1045 cm^{-1}; MS (EI, 70 eV) m/e 125 (M − C_4H_9O, 14.73), 96 (82), 82 (70.53), 68 (C_3H_6CN, 100); MS (CI, 70 eV) m/e 198 (MH^+, 3.40), 171 (MH − HCN, 100); HRMS (CI, 70 eV) m/e 198.1515 (198.1495 calcd for $C_{11}H_{19}NO_2$ + H).

***rel*-(2*R*,7*R*,α*S*)-7-Methyl-α-(1-methylethyl)oxepane-2-methanol (19).** Triphenylsilane (420 mg, 1.6 mmol) in 0.9 mL of CH_2Cl_2 was added to ketone **3** (37 mg, 0.2 mmol) at 20 °C. The solution was cooled to −45 °C, and BF_3·OEt_2 (0.11 mL, 0.89 mmol) was added dropwise. After being stirred for 1.5 h at −45 °C and for 6 h at −25 °C, the solution was warmed to 20 °C and stirred for 14 h. Ether and saturated $NaHCO_3$ were added, and the crude product was isolated following the standard workup procedure. Less than 5% of the minor diastereomer was present in the crude sample as indicated by the ^1H NMR spectrum. Purified oxepane **19** was isolated in an 81% yield (30 mg, 16 mmol) after RC (19:1 pentane–ether): ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (1 H, m, H-7), 3.45 (1 H, m, H-2), 3.31 (1 H, t, J = 6 Hz, H-α), 2.01 (1 H, br s, OH), 1.79 (1 H, sep, J = 6.6 hz, H-β), 1.78–1.4 (8 H, m, ring H), 1.16 (3 H, d, J = 7.8 Hz, H-α), 0.95 (3 H, d, J = 6.9 Hz), 0.89 (3 H, d, J = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 79.74, 79.41, 76.75, 37.93, 29.78, 29.18, 25.71, 24.51, 22.88, 19.22, 17.52; IR (neat) 3462 (br), 2928, 1101, 1002 cm^{-1}; MS (EI, 70 eV) m/e 143 (M − C_3H_7, 120), 113 (M − C_4H_9O, 51.56), 95 (100); MS (CI, 70 eV) m/e 187 (MH^+, 3.90), 169 (MH − H_2O, 5.41), 117 (MH − C_4H_6O, 100); HRMS (CI, 70 eV) m/e 187.1697 (187.1698 calcd for $C_{11}H_{22}O_2$ + H).

***rel*-(1*R*,6*S*,8*S*)-6-Methyl-8-(1-methylethyl)-7,9-dioxabicyclo[4.2.1]nonane (18).** Ketone **3** (37 mg, 0.2 mmol) in 1 mL of CH_2Cl_2 was cooled in a −40 °C bath, and BF_3·OEt_2 (0.05 mL, 0.4 mmol) was added. After being stirred for 1 h, the reaction mixture was warmed to 0 °C over 2 h and then quenched using saturated $NaHCO_3$. Following the standard workup procedure, ketal **18** was isolated in a 70% yield (26 mg, 14 mmol): ^1H NMR (300 MHz, $CDCl_3$) δ 4.23 (1 H, app t, J = 4.8 Hz, H-1), 3.48 (1 H, dd, J = 10.5, 4.5 Hz, H-8), 1.9–1.51 (9 H, m), 1.36 (3 H, s), 1.05 (3 H, d, J = 6.6 Hz), 0.83 (3 H, d, J = 6.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 110.2, 84.26, 77.36, 38.83, 29.93, 27.63, 27.02, 24.23, 24.00, 20.55, 19.03; IR (neat) 2928, 1469, 1449, 1151, 1053 cm^{-1}; MS (EI, 70 eV) m/e 184 (M^+, 1.15), 142 (M − C_3H_6, 55.17), 127 (60.73), 100 (75.19), 85 (100); MS (CI, 70 eV) m/e 185 (MH^+, 100), 167 (MH − H_2O, 2.97), 117 (82.42); HRMS (EI, 70 eV) m/e 184.1474 (184.1463 calcd for $C_{11}H_{22}O_2$).

***rel*-(2*R*,5*S*,α*S*)-5-Cyclohexoxy-α-(1-methylethyl)tetrahydrofuran-2-methanol (22a).** BF_3·OEt_2 (0.03 mL, 0.22 mmol) was added dropwise to epoxy ester **4** (48 mg, 0.2 mmol) in 2.5 mL of CH_2Cl_2 at −78 °C. After 5 min, 0.44 mL of a freshly prepared 0.5 M solution of $LiAlH_4$ in THF (0.22 mmol) was added over 5 min and the reaction mixture was stirred for 3 h at −78 °C. The reaction was warmed to 20 °C over 14 h, and the product was isolated using the standard workup procedure. Following RC (10:1 hexanes–ether pretreated with 1% triethylamine), 33 mg of cis acetal **22a** was isolated (81%, 39 mg, 0.18 mmol) with a small amount of the other diastereomer. Diastereomeric ratio (15:1 cis:trans) was determined by GC. Data for **22a**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.23 (1 H, d, J = 3.5 Hz, H-5), 4.31 (1 H, d of t, J = 7.8, 2.5 Hz, H-2), 3.56 (1 H, m, (cyclohexyl)CHOR), 3.47 (1 H, d, J = 8.5 Hz), 3.15 (1 H, br s, OH), 2.15–1.1 (15 H, m), 1.04 (3 H, d, J = 7 Hz), 0.88 (3 H, d, J = 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.8, 82.41, 76.65, 75.84, 33.70, 33.47, 31.97, 30.61, 25.45, 24.15, 24.01, 21.14, 19.50, 18.81; IR (neat) 3490, 2940, 2860, 1470, 1455, 1090, 1040, 1000 cm^{-1}; MS (EI, 70 eV) m/e 169 (M − C_4H_9O, 6.36), 143 (M − $C_6H_{11}O$, 6.93), 99 ($C_6H_{11}O$, 9.82), 87 ($C_5H_{11}O$, 100), 55 (44.64); MS (CI, 70 eV) m/e 143 (M − $C_6H_{11}O$, 100); MS (CI, negative ion, 70 eV) m/e 242 (M^+, 7.97), 241 (M − 1, 63.14), 141 (100); HRMS (EI, 70 eV) m/e 169.1223 (169.1228 calc for $C_{14}H_{26}O_3$ − C_4H_9O). Spectral data for minor diastereomer **22b**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (1 H, dd, J = 6.1, 1.8 Hz, H-5), 4.19 (1 H, app sex, J = 1.8 Hz, H-2), 3.53 (1 H, m, (cyclohexyl)CHOR), 3.47 (1 H, dd, J = 9, 3 Hz, H-α), 2.02–1.07 (16 H, m), 1.02 (3 H, d, J = 6.6 Hz), 0.90 (3 H, d, J = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.7, 78.51, 74.85, 33.89, 32.83, 31.94, 30.57, 25.61, 24.40, 24.24, 22.21, 19.14, 18.66; IR ($CHCl_3$) 3500, 2940, 1470, 1455, 1090, 1025, 990 cm^{-1}; MS (EI, 70 eV) m/e 169 (M − C_4H_9O, 11.43), 143 (M − $C_6H_{11}O$, 17.88), 87 ($C_5H_{11}O$, 84.62), 57 (100); MS (CI, 70 eV) m/e 243 (M + 1, 0.01), 143 (M − $C_6H_{11}O$, 100); MS (CI, negative ion, 70 eV) m/e 242 (MH^+, 0.84), 2.41 (M − 1, 6.10), 218 (100); HRMS (EI, 70 eV) m/e 169.1232 (169.1228 calcd for $C_{14}H_{28}O_3$ − C_4H_9O).

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Supplementary Material Available: Experimental procedures for the synthesis of compounds 1–4 along with the ^1H and ^{13}C NMR spectra for all new compounds and DNOE data and 2-D homonuclear decoupling spectra (74 pages). Ordering information is given on any current masthead page.

Reactions of Bridgehead Halides. A Synthesis of Modhephene, Isomodhephene, and *epi*-Modhephene

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A synthesis of modhephene has been achieved, the key feature of which is the use of a novel nucleophilic addition/rearrangement reaction to develop the carbon framework. Stereochemical control of the stereogenic center bearing the methyl group was accomplished by variation of the hydrogenation conditions. As a byproduct of this work, we have clarified structural assignments of intermediates from previous syntheses.

The discovery of the novel sesquiterpene modhephene (1) has led to a renewed interest in the synthesis of propellanes. Total syntheses of this naturally occurring hydrocarbon have been recorded by a number of researchers.[1]

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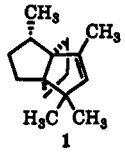
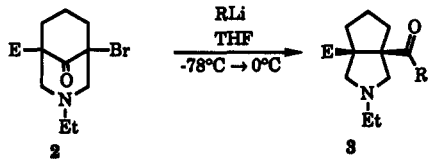


1

We recently discovered a novel rearrangement in the course of our studies on the generation and reactions of bridgehead radicals.[2] This rearrangement, which is depicted below, transforms the readily available azabicyclo[3.3.1]nonane skeleton 2 into an azabicyclo[3.3.0]octane skeleton of general structure 3, a bicyclic ring system for which very few synthetic routes have been reported. The

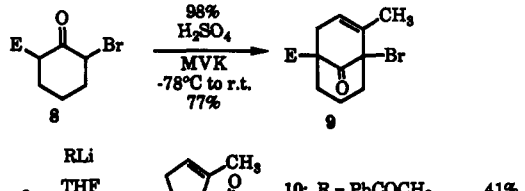


2 3

rearrangement is reasonably general in that alkyllithium reagents, enolate anions, and phosphonate anions all react with ketone 2 to generate 3–6. Interestingly, Grignard reagents afforded only the unrearranged alcohol. The results are collated in Table I.

In view of the successful rearrangements of 2, we decided to examine the chemistry of bicyclo[3.3.1]nonenone 9, a potential precursor to 1. This compound was prepared by the reaction of keto ester 8 with methyl vinyl ketone (MVK) in the presence of concentrated sulfuric acid.[3] The reaction conditions were very critical. The optimal conditions involved the slow dropwise addition of sulfuric acid to a mixture of 8 and MVK at −78 °C. If the reaction was conducted at higher temperatures or if the addition of sulfuric acid was too fast, dark polymeric byproducts were formed. These unusual conditions were dictated because the use of solvents such as benzene, methylene chloride, or acetonitrile led only to recovered 8.

With gram quantities of 9 in hand, the nucleophilic addition/ring contraction sequence was studied. The reaction of 9 with the anions of acetophenone and dimethyl methylphosphonate led to esters 10 and 11 in 41% and 70% yields, respectively.



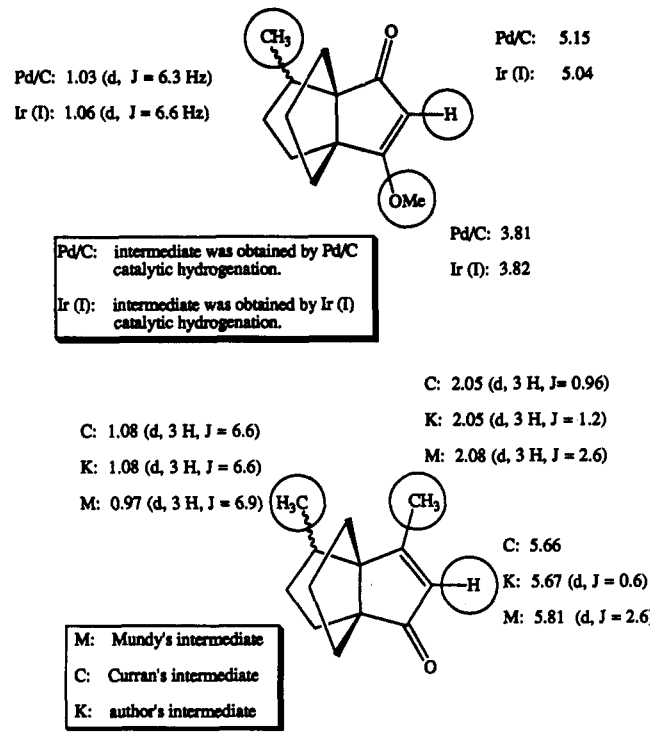
8 9

10: R = $PhCOCH_2$ 41%
11: R = $(MeO)_2POCH_2$ 70%

E=CO_2Me

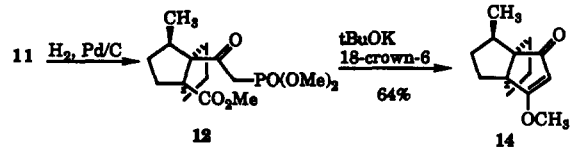
Catalytic Hydrogenation Route to *epi*-Modhephene. Ester 11 contains two of the three rings of modhephene. We subjected ester 11 to catalytic hydogenation with hydrogen and Pd/C. A single stereoisomer was obtained which we *initially* assigned to be isomer 13 derived from catalytic hydrogenation from the exo face of the bicyclo[3.3.0]octane system. Cyclization of the resulting keto

Chart I. Comparison of NMR Chemical Shifts of Key Compounds



phosphonate had little literature precedent. Although we actually expected to obtain a diketo phosphonate, we were delighted to isolate the vinylogous ester. Based on NMR and IR data, the vinylogous ester which we had obtained was identical by 300-MHz NMR and IR to the compound produced by Mundy.[4] We appeared to have achieved a formal synthesis of 1.

However, a paper by Curran and co-workers appeared shortly after we had obtained the vinylogous ester described above.[1] They case doubt on the structure of the penultimate intermediate in the Mundy synthesis. Our claim of a synthesis of modhephene via the Mundy intermediate became uncertain. We felt that if a structural misassignment had been made, it most likely had occurred in the assignment of either the stereochemistry of the hydrogenation product or the regiochemistry of the phosphonate cyclization product. The possibility that the hydrogenation reaction had produced isomer 12 could more readily be tested. Although the production of 12 necessitated a hydrogenation from the crowded endo face of the bicyclo[3.3.0]octane system, approach from the exo face was hindered by both the ester and keto phosphonate groups at the bridgehead carbons. *As subsequent discussion will clarify, the actual structures of the Pd/C hydrogenation product and the vinylogous ester are 12 and 14, respectively.*

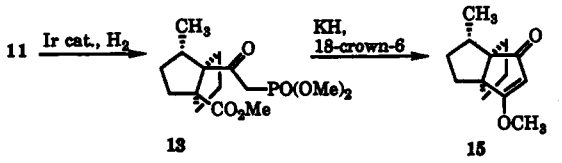


12 14

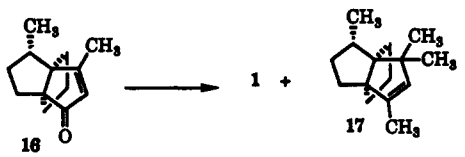
Iridium Catalyst Route to Modhephene and Isomodhephene. Recently, both Stork[5] and Crabtree[6] re-

(1) For a general discussion of propellane chemistry, see: Ginsburg, D. *Propellanes, Structure and Reactions*; Verlag Chemie: Weinheim, 1975. Synthesis: Jasperse, C. P.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 5601 and references therein.
(2) Kraus, G. A.; Shi, J. *J. Org. Chem.* **1990**, *55*, 5423.
(3) For a related procedure, see: Heathcock, C. H.; Ellis, J. E.; McMurry, J. E.; Coppolino, A. *Tetrahedron Lett.* **1971**, 4995. The solvent used in the sulfuric acid reaction was methylene chloride.
(4) Mundy, B. P.; Wilkening, D.; Lipkowitz, K. B. *J. Org. Chem.* **1985**, *50*, 5727.
(5) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072.
(6) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.

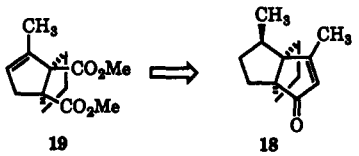
ported the use of an iridium catalyst for directed hydrogenation of alkenes. Since they demonstrated that carbonyl groups exerted a strong directing effect, we employed this catalyst for the hydrogenation of keto phosphonate 11. The iridium-mediated reduction afforded 13 which



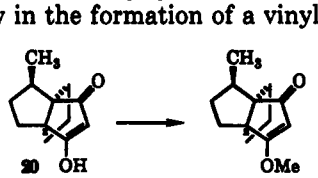
was different from 12. Cyclization with KH (tBuOK afforded much lower yields in this case) in boiling benzene afforded a vinylogous ester 15 whose 300-MHz NMR spectrum was quite different from that of 14. Reaction of 15 with methyllithium in hot THF followed by hydrolysis of the alcohol with sulfuric acid produced 16. The 300-MHz NMR spectrum of ketone 16 was identical with the 300-MHz NMR spectrum provided by Curran. This comparison established the structure of the iridium-mediated reduction product which we had tentatively assigned as 13 and also established the structure of the vinylogous ester as 15. Since Curran has converted 16 into a mixture of 1 and isomodhephene 17, the preparation of 16 constitutes a formal synthesis of 1.



Structural Assignments in Previous Modhephene Syntheses. The major clue to resolving the stereochemical misassignments was found in a footnote in Curran's paper, which mentions a reversal of proton NMR assignments for some compounds in the modhephene series and the *epi*-modhephene series in a full paper by Smith and co-workers detailing their clever synthesis of modhephene.[7] Unfortunately, the structural assignment for the key Mundy intermediate 18 was based on a proton NMR comparison with one of these inadvertently misassigned compounds.



Interestingly, the stereogenic center bearing the methyl group in the Mundy synthesis had been introduced by catalytic hydrogenation of diester 19 using Pd/C as the catalyst. Additionally, it is now clear why diketone 20, an intermediate in the Mundy synthesis, afforded such high regioselectivity in the formation of a vinylogous ester.



Conclusions

Our synthesis represents a direct synthetic application of a novel nucleophilic addition/rearrangement sequence of bicyclic bridgehead bromides. We have also shown that either isomer can be obtained by the appropriate choice of hydrogenation conditions. Additionally, this approach has helped to clarify unresolved stereochemical assignments from prior modhephene syntheses.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes–ethyl acetate solvent mixtures for TLC and chromatography. The purity of all title compounds was determined to be >90% by proton NMR and/or elemental analysis.

Ethyl 5-Bromo-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate (2). To a solution of ethyl 3-bromo-2-oxocyclohexanecarboxylate (4.98 g, 20 mmol) in 120 mL of MeOH at 25 °C was added formaldehyde (37% in H_2O, 3.24 g, 40 mmol) and ethylamine (70% in H_2O, 1.29 g, 20 mmol). The solution was stirred at 25 °C for 48 h. The methanol was removed in vacuo and the product was taken up in CH_2Cl_2. The solvent was removed in vacuo. The residue was purified by silica gel (sg) chromatography using 15:1 H:EA to afford 3.12 g (49% yield) of ester 2. The starting ester (1.1 g) was also recovered. The product was a colorless oil with R_f = 0.28 in 15:1 H:EA.

2: NMR ($CDCl_3$) δ 4.232 (q, J = 7.2, 2 H), 3.602 (dd, J = 2.4, 10.8, 1 H), 3.253 (dd, J = 2.4, 11.4, 1 H), 3.144 (m, 2 H), 3.033 (dd, J = 2.1, 11.7, 1 H), 2.952 (dd, J = 2.1, 11.1, 1 H), 2.700 (m, 1 H), 2.570 (m, 1 H), 2.448 (q, J = 7.2, 2 H), 2.560 (m, 1 H), 1.600 (m, 1 H), 1.299 (t, J = 7.2, 3 H), 1.117 (t, J = 7.2, 3 H); IR (film) 2976, 2935, 2814, 1730, 1454, 1258, 700 cm^{-1}; MS m/e 319, 317, 302, 300, 274, 272, 238, 220, 192, 164, 125, 108; HRMS m/e for $C_{13}H_{20}O_3NBr$ calcd. 317.06266, measured 317.06197; ^{13}C NMR ($CDCl_3$) δ 201.984, 169.704, 69.738, 68.697, 61.428, 61.097, 59.835, 50.450, 46.278, 36.270, 22.783, 14.032, 12.488.

General Procedure for the Nucleophilic Addition/Ring Contraction Reaction. To a solution of ketone 2 (1.0 equiv) in THF (0.1 M) at −7.8 °C was added the anion (1.1 equiv). The solution was stirred at −78 °C for 10 min and then allowed to slowly warm to 0 °C over 1 h. Acetic acid in THF was added at 0 °C to quench the reaction. Water was added, and the aqueous layer was then extracted twice with ether. The combined organic layers were dried and concentrated in vacuo. The residue was purified by sg chromatography with H:EA.

3: NMR ($CDCl_3$) δ 15.489 (s, 1 H), 6.862 (s, 1 H), 5.866 (s, 1 H), 3.972 (m, 2 H), 3.154 (d, J = 9.0, 1 H), 2.854 (d, J = 9.0, 1 H), 2.627 (dd, J = 9.0, .21, 2 H), 2.485 (m, 2 H), 2.223 (m, 6 H), 1.843 (m, 4 H), 1.630 (m, 4 H), 1.116 (t, J = 6.6, 3 H), 1.091 (t, J = 6.6, 3 H); IR (film) 3383, 2935, 2802, 1730, 1641, 1585, 1448, 1277, 1209, 1040 cm^{-1}; MS m/e 361, 344, 316, 288, 270, 252, 209, 194, 164, 136, 127, 109, 91, 71, 58; HRMS m/e for $C_{21}H_{31}O_4N$ calcd 361.22531, measured 361.22518; ^{13}C NMR ($CDCl_3$) δ 201.343, 180.126, 175.003, 135.525, 132.955, 92.986, 66.388, 65.114, 64.351, 63.112, 60.432, 49.343, 39.070, 39.155, 25.822, 25.284, 23.450, 22.019, 21.476, 13.631; TLC (1:1 H:EA) R_f = 0.60. Anal. Calcd: C, 69.78; H, 8.64. Found: C, 69.32: H, 8.81.

4: NMR ($CDCl_3$) δ 16.002 (s, 1 H), 7.938 (d, J = 7.2, 2 H), 7.450 (m, 3 H), 6.404 (s, 1 H), 3.960 (m, 2 H), 3.238 (d, J = 9.3, 1 H), 2.937 (d, J = 9.0, 1 H), 2.647 (t, J = 9.6, 2 H), 2.536–2.223 (m, 4 H), 1.882 (m, 4 H), 1.113 (t, J = 6.6, 3 H), 1.092 (t, J = 6.6, 3 H); IR (film) 2968, 2874, 2804, 1730, 1610, 1574, 1454, 1279, 768, 694 cm^{-1}; MS m/e 357, 340, 312, 284, 252, 210, 164, 136, 105, 71, 58; HRMS m/e for $C_{21}H_{27}O_4N$ calcd 357.19401, measured 357.19454; ^{13}C NMR ($CDCl_3$) δ 201.348, 180.528, 175.128, 134.616, 131.955, 128.552, 126.743, 94.178, 66.382, 65.255, 64.380, 63.496, 49.466, 39.207, 37.060, 25.396, 13.768, 13.728; ^{13}C apt 201.432, 180.583, 175.223, 134.654, 66.400, 63.515; TLC (1:1 H:EA) R_f = 0.38. Anal. Calcd: C, 70.56; H, 7.61. Found: C, 70.44; H, 7.59.

5: NMR ($CDCl_3$) δ 7.708 (m, 2 H), 7.432 (m, 3 H), 4.069 (q, J = 7.2, 2 H), 3.173 (d, J = 9.0, 1 H), 2.900 (s, 2 H), 2.823 (d, J = 9.3, 1 H), 2.472 (m, 2 H), 2.318 (m, 2 H), 2.171 (m, 1 H), 1.936 (m, 3 H), 1.192 (t, J = 7.2, 3 H), 1.075 (t, J = 7.2, 3 H); IR (film) 2970, 2874, 2806, 1732, 1678, 1600, 1271, 717, 698 cm^{-1}; MS m/e 315, 298, 272, 242, 226, 210, 188, 156, 136, 105, 77, 71, 58; HRMS m/e for $C_{19}H_{25}O_3N$ calcd 315.18344, measured 315.18377; ^{13}C NMR ($CDCl_3$) δ 203.850, 175.646, 137.583, 131.635, 127.987, 127.863, 68.788, 65.321, 63.847, 62.947, 60.143, 49.535, 40.095, 38.173, 25.577, 13.919, 13.551; TLC (1:1 H:EA) R_f = 0.38.

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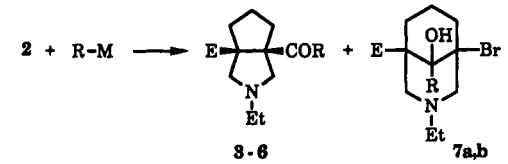
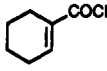
Table I. Organometallic Additions to Keto Ester 2



3-6 7a,b

RM	% yield		compd
	60	0	3
$PhCOCH_2Li$	58	0	4
PhLi	73	0	5
MeLi	53	0	6
MeMgBr	0	85	7a
CH_2=$CHCH_2MgBr$	0	92	7b

6: NMR ($CDCl_3$) δ 4.075 (q, J = 7.2, 2 H), 3.025 (d, J = 9.3, 1 H), 2.790 (d, J = 9.0, 1 H), 2.663 (d, J = 8.4, 2 H), 2.450 (m, 2 H), 2.236–2.167 (m, 2 H), 2.134 (d, J = 0.6, 3 H), 1.821 (m, 4 H), 1.212 (t, J = 6.9, 3 H), 1.079 (t, J = 7.5, 3 H); IR (film) 2968, 2874, 2804, 1730, 1705, 1448, 1229, 1028, 932 cm^{-1}; MS m/e 253, 236, 210, 180, 164, 136, 123, 108, 80, 71, 58; HRMS m/e for $C_{14}H_{23}O_3N$ calcd 253.16779, measured 253.16716; ^{13}C NMR ($CDCl_3$) δ 209.029, 175.305, 69.483, 64.438, 64.003, 62.405, 60.564, 49.387, 39.036, 37.328, 27.267, 25.163, 13.813, 13.548; TLC (1:1 H:EA) R_f = 0.26.

10: NMR ($CDCl_3$) δ 15.906 (1 H, s), 7.804 (2 H, d, J = 7.5), 7.555 (3 H, m), 6.065 (1 H, s), 5.572 (1 H, s), 3.979 (2 H, m), 3.438 (1 H, m), 2.311 (3 H, m), 1.849 (4 H, m), 1.567 (3 H, s), 1.093 (3 H, t, J = 6.9); MS m/e 340, 294, 266, 220, 194, 147, 121, 105, 91, 77, 65; HRMS m/e for $C_{21}H_{24}O_4$ calcd 340.16746, measured 340.16722; ^{13}C NMR ($CDCl_3$) δ 200.265, 179.924, 175.972, 139.505, 134.478, 131.892, 128.500, 127.292, 126.719, 94.733, 76.704, 63.080, 60.647, 43.100, 42.662, 30.302, 24.488, 13.699, 13.204.

Methyl 5-Bromo-4-methyl-9-oxobicyclo[3.3.1]non-3-enecarboxylate (9). Ester 8 (4.70 g, 20 mmol) and methyl vinyl ketone (2.1 g, 30 mmol) were cooled to −78 °C. To this swirled mixture was added slowly dropwise 98% H_2SO_4 (5 mL). The stirred mixture was allowed to slowly warm to 0 °C. The mixture was then stirred at 25 °C for 36 h. The mixture was carefully poured into 200 mL of cold saturated $NaHCO_3$. The aqueous layer was extracted with ether three times. The combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel using 10:1 H:EA to afford 1.98 g (35% yield) of ester 9. This clear liquid had an R_f of 0.38 in 5:1 H:EA.

9: NMR ($CDCl_3$) δ 5.748 (1 H, m), 3.784 (3 H, s), 3.350 (1 H, m), 2.619–2.262 (4 H, m), 2.06–1.89 (5 H, m), 1.716 (1 H, m); IR (film) 2953, 2870, 1744, 1730, 1448, 1435, 1269, 1252, 1130, 1040, 733, 690 cm^{-1}; MS m/e 288, 286, 254, 256, 207, 175, 147, 119, 105, 91, 77, 65; HRMS m/e for $C_{12}H_{15}O_3Br$ calcd 288.01854, measured 288.01790; ^{13}C NMR ($CDCl_3$) δ 199.575, 170.747, 133.794, 123.598, 75.050, 58.238, 52.194, 43.263, 37.582, 21.704, 20.544; TLC (5:1 H:EA) R_f = 0.38.

Methyl 4-Methyl-5-((dimethylphosphono)acetyl)bicyclo-[3.3.0]oct-3-enecarboxylate (11). To a solution of dimethyl methylphosphonate (0.423 g, 3.4 mmol) in 5 mL of THF at −78 °C was added n-BuLi (1.36 mL, 3.4 mmol). The solution became a white suspension that was stirred for 15 min. The bromo ketone 9 (0.750 g, 2.62 mmol) in 10 mL of THF was added dropwise. The solution was stirred for 15 min at −78 °C and then allowed to slowly warm to 25 °C over 1 h. The solution was then cooled to −78 °C and quenched with 15 mL of 2 N HCl. The aqueous layer was extracted four times with 30 mL of ether. The combined extracts were dried and concentrated in vacuo. The residue was purified by sg chromatography using 15:15:1 H:EA:EtOH to afford 0.365 g (49% yield) of ester 11. The ester was a colorless oil with R_f 0.24 in 15:15:1 H:EA:EtOH.

11: NMR ($CDCl_3$) δ 5.610 (1 H, s), 3.790 (3 H, d, J = 11.4), 3.767 (3 H, d, J = 11.4), 3.670 (3 H, s), 3.189 (1 H, m), 3.902 (1 H, m), 2.814 (1 H, m), 2.637 (1 H, m), 2.233 (2 H, m), 1.905–1.458 (7 H, m); IR (film) 2959, 2872, 1726, 1655, 1439, 1385, 1250, 1032, 804 cm^{-1}; MS m/e 330, 298, 270, 179, 151, 119, 109, 91, 79, 65; HRMS m/e for $C_{15}H_{23}O_6P$ calcd 330.12323, measured 330.12270; ^{13}C NMR ($CDCl_3$) δ 201.554, 201.471, 176.126, 139.091, 128.021, 79.978, 79.908, 62.477, 52.795, 52.708, 52.447, 52.373, 52.070, 42.900, 42.635, 37.506, 35.646, 30.001, 23.860, 13.036; TLC (15:15:1 H:EA:EtOH) R_f = 0.24. Anal. Calcd: C, 54.54; H, 7.02. Found: C, 53.81; H, 7.28.

4-Methoxy-8-methyltricyclo[3.3.3.0]undec-3-en-2-one (14). To a suspension of 10% Pd/C (0.010 g) in 6 mL of MeOH under an atmosphere of hydrogen was added ester 11 (0.170 g, 0.59 mmol) in 1 mL of MeOH. The suspension was stirred at ambient temperature for 72 h. The suspension was then filtered through Celite with MeOH. (Do not let catalyst become dry!) The methanol solution was concentrated in vacuo. The residue was purified by chromatography on 3:3:1 H:EA:EtOH to afford 0.175 g (100% yield) of 12.

Compound 12 (0.080 g, 0.28 mmol) and potassium *tert*-butoxide (0.078 g, 0.70 mmol) and a crystal of 18-crown-6 were heated at 80 °C in 5 mL of toluene for 15 h. The solution was then cooled to 0 °C, water was added, and the aqueous layer was extracted twice with ether. The combined organic layers were dried and concentrated in vacuo. The residue was purified by sg chromatography using 5:5:1 H:EA:EtOH to afford 0.023 g (30% yield) of compound 14.

14: NMR ($CDCl_3$) δ 5.150 (1 H, s), 3.812 (3 H, s), 2.1–1.25 (11 H, m), 1.031 (3 H, d, J = 6.6); IR (film) 2957, 2876, 1715, 1603, 1458, 1353, 1228, 1141, 830 cm^{-1}; MS m/e 206, 178, 165, 152, 137, 124, 105, 91, 77, 65; HRMS m/e for $C_{13}H_{18}O_2$ calcd. 206.13068, measured 206.13042; TLC (5:1 H:EA) R_f = 0.21.

4-Methoxy-8-methyltricyclo[3.3.3.0]undec-3-en-2-one (15). A solution of ester 11 (0.150 g, 0.45 mmol) and [Ir(COD)-(PCy_3)(py)]PF_6 (0.020 g, 0.025 mmol) in 3 mL of CH_2Cl_2 was charged with an atmosphere of hydrogen. The solution was stirred for 15 h at 25 °C. The solvent was removed in vacuo and ether was added. The suspension was passed through a sg column with 5:5:1 H:EA:EtOH. The crude product had been quantitatively converted into the bicyclo[3.3.0]octane as evidenced by proton NMR. The crude product (0.060 g, 0.18 mmol) was dissolved in 5 mL of benzene. To this solution was added 18-crown-6 (5 mg) and KH (1.8 mg, 0.42 mmol). The solution was heated to reflux for 6 h. The solution was cooled, washed with water, and concentrated in vacuo. The residue was purified by sg chromatography using 5:1 H:EA to elute the product and 5:5:1 H:EA:EtOH to elute the starting material (0.025 g). Chromatography gave 0.020 g (33% yield) of ketone 15.

15: NMR ($CDCl_3$) δ 5.041 (1 H, s), 3.815 (3 H, s), 2.2–1.25 (11 H, m), 1.066 (3 H, d, J = 6.6); IR (film) 2974, 2865, 1687, 1355, 1232, 1119, 830, 724 cm^{-1}; MS m/e 206, 178, 163, 152, 124, 105, 91, 77, 65; HRMS m/e for $C_{13}H_{18}O_2$ calcd 206.13068, measured 206.13061; TLC (5:1 H:EA) R_f = 0.21.

4,6-Dimethyltricyclo[3.3.3.0]undec-3-en-3-one (16). To a solution of enone 15 (0.005 g, 0.024 mmol) in 1.5 mL of THF at 25 °C was added MeLi (0.12 mL, 0.15 mmol). The solution was heated to 60 °C for 6 h. The solution was cooled to 25 °C, and 1 mL of 2 N HCl was added. The reaction mixture was stirred for 30 min. The aqueous layer was extracted twice with ether. The combined organic layers were dried and concentrated in vacuo. The residue was purified by sg chromatography using 5:1 H:EA to afford 0.003 g (65% yield) of enone 16. The product was a colorless oil with R_f 0.38 in 5:1 H:EA.

16: NMR ($CDCl_3$) δ 5.666 (1 H, d, J = 0.6 Hz), 2.057 (3 H, d, J = 1.2), 1.90–1.18 (11 H, m), 1.084 (3 H, d, J = 6.6); GC–IR 2958, 2878, 1724, 1618, 1459, 1382, 1316, 1268, 1128, 865 cm^{-1}; MS m/e 190, 175, 162, 148, 133, 120, 105, 91, 77, 65; HRMS m/e for $C_{13}H_{18}O$ calcd 190.13577, measured 190.13553; TLC (5:1 H:EA) R_f = 0.38.

Acknowledgment. We thank the National Institutes of Health (Grant GM 33604) and the American Cyanamid Company for generous financial support.

Registry No. (±)-1, 76739-64-5; (±)-2, 128164-63-6; (±)-3, 128164-65-8; (±)-4, 128164-66-9; (±)-5, 128164-67-0; (±)-6, 128164-68-1; (±)-7, 133627-57-3; (±)-7a, 133627-64-2; 8 (R = CO_2Me), 57001-08-8; 8 (R = CO_2Et), 30132-23-1; (±)-9, 133627-58-4; (±)-10, 128164-69-2; (±)-11, 133627-59-5; (±)-12, 133627-60-8; (±)-13, 133627-61-9; (±)-14, 133696-79-4; (±)-15, 133696-80-7; (±)-16, 127419-76-5; (±)-17, 127354-01-2; (±)-18, 133696-81-8;

(±)-19, 133627-62-0; (±)-20, 133627-63-1; $PhCOCH_2Li$, 55905-98-1; PhLi, 591-51-5; MeLI, 917-54-4; MeMgBr, 75-16-1; CH_2=CHCH_2MgBr, 1730-25-2; 1-acetylcyclohexene lithium enolate, 128164-71-6; (±)-*epi*-modhephene, 76739-65-6.

Supplementary Material Available: ^{1}H NMR spectra of compounds for which elemental analyses are not reported (8 pages). Ordering information is given on any current masthead page.

Concerning the Diastereofacial Selectivity of the Aldol Reactions of α-Methyl Chiral Aldehydes and Lithium and Boron Propionate Enolates

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The diastereofacial selectivity of the aldol reactions of α-methyl chiral aldehydes and propionate and ethyl ketone derived lithium and boron enolates is analyzed from the perspective of a transition state model suggested by Evans in 1982. The dominant stereocontrol element in these reactions, as in the mechanistically related reactions of crotylmetal reagents and α-substituted chiral aldehydes (refs 6, 7a), appears to be the minimization of gauche pentane interactions in the competing transition states. Transition structure **35** is viewed as the lowest energy structure in the "anti-Felkin" selective aldol reactions of *Z*(O)-enolates as long as the steric requirements of R are greater than that of the α-Me group. Transition state **36** is similarly the lowest energy structure available in the aldol reactions of *E*(O)-enolates (Felkin selective). The model also reconciles data involving the aldol reactions of Ph(Me)CHCHO (**1a**) and R_2C=CHCH(Me)CHO (**1b**, **1c**) that preferentially provide the 2,3-syn-3,4-syn ("Felkin") diastereomers **3**: the Ph or vinyl substituents are viewed as the smaller of the two α-substituents (Me > Ph or vinyl) since they expose a sterically undemanding, flat surface to the incoming nucleophile in the lowest energy transition structures **39** (for **1a**) and **41** (for **1b**, **1c**).

The aldol reaction has proven to be a very powerful method for the stereocontrolled synthesis of acyclic molecules.[1] The relationship between enolate geometry and product stereostructure (i.e., simple diastereoselection) is well established, and several classes of highly enantioselective chiral enolates have been developed for use in double asymmetric reactions.[2-4] Numerous applications of aldol technology in the synthesis of stereochemically complex natural products have since appeared.[1d] In spite of the attention devoted to this process, the factors that determine aldehyde diastereofacial selectivity in reactions of achiral enolates and chiral aldehydes are less well understood.[1,5] Diastereofacial selectivity is usually rationalized by invoking either the Felkin–Anh or the Cram chelate transition-state models.[1] As has been noted by several investigators, however, the Felkin–Anh paradigm fails to adequately rationalize the results of many aldol reactions involving *Z*(O)-enolates.[1,6a,b] Moreover, the Felkin–Anh model fails to predict the major product obtained in the mechanistically related reactions of (*Z*)-crotylboronates and α-methyl branched chiral aldehydes.[6a,b] Hoffmann stated in his initial paper that "molecular models show that the anti-Cram transition state is less hindered in the case of [the (*Z*)-crotylboronate], and the Cram transition state less hindered in the case of [the (*E*)-crotylboronate]".[6a] Evans provided transition structures for these reactions in his 1982 review of the aldol reaction and suggested that the anti-Felkin behavior of the (*Z*)-crotylboronates was the consequence of destabilizing gauche pentane interactions in the usually favored Felkin–Anh transition state.[1b] This model has been further developed and expanded by Hoffmann and Roush on the basis of a large body of data concerning the reactions of

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