6, CH_3), 2.05 (s, 3, CH_3), 0.98 (t, 6, CH_3); IR (neat) 2960, 2920, 2870, 2810, 1740, 1595, 1460, 1370, 1320, 1295, 1235, 1170, 1060, 830, 690 cm^{-1}.

1-(Dimethylamino)-2-acetoxy-3-(3,5-dimethylphenoxy)-propane: NMR ($CDCl_3$) δ 6.6 (br, 3), 5.28 (m, 1, CHOAc), 4.15 (m, 2, CH_2O), 2.56 (d, 2, CH_2N), 2.28 (s, 12, four CH_3 groups), 2.06 (s, 3, CH_3); IR (neat) 2970, 2940, 2920, 2860, 2820, 2770, 1740, 1610, 1590, 1505, 1455, 1370, 1295, 1235, 1170, 1155, 1070, 1050, 1035, 830 cm^{-1}.

1-(Diethylamino)-2-acetoxy-3-(3,4-dimethylphenoxy)-propane: NMR ($CDCl_3$) δ 7.6–6.55 (m, 3), 5.20 (m, 1, CHOAc), 4.15 (2, AB part of ABX, CH_2O), 2.85–2.3 (m, 6, CH_2N), 2.30 (s, 3, CH_3), 2.26 (s, 3, CH_3), 2.05 (s, 3, CH_3), 1.01 (t, 6, CH_3); IR (neat) 2960, 2920, 2870, 2800, 1740, 1610, 1500, 1450, 1370, 1235, 1205, 1165, 1050, 810 cm^{-1}.

1-(Diethylamino)-2-acetoxy-3-(4-methoxyphenoxy)-propane: NMR ($CDCl_3$) δ 6.9 (s, 4, Ar), 5.20 (m, 1, CHOAc), 4.15 (2, AB part of ABX, CH_2O), 3.80 (s, 3, CH_3O), 2.8–2.3 (m, 6, CH_2N), 2.05 (s, 3, CH_3), 1.03 (t, 6, CH_3); IR (neat) 2960, 2930, 2870, 2830, 1740, 1510, 1460, 1370, 1230, 1040, 820, 750 cm^{-1}.

1-(Diethylamino)-2-acetoxy-3-(4-chlorophenoxy)propane: NMR ($CDCl_3$) δ 7.3–6.7 (m, 4), 5.20 (m, 1, CHOAc), 4.15 (2, AB part of ABX, CH_2O), 2.7–2.25 (m, 6, CH_2N), 2.05 (s, 3, CH_3), 1.03 (t, 6, CH_3); IR (neat) 2960, 2920, 2870, 2800, 1740, 1600, 1490, 1450, 1370, 1230, 1060, 1040, 820 cm^{-1}.

1-(Benzylmethylamino)-2-acetoxy-3-phenoxypropane: NMR ($CDCl_3$) δ 7.5–6.8 (m, 10, aromatic), 5.37 (m, 1, CHOAc), 4.15 (m, 2, CH_2O), 3.55 (br s, 2, $PhCH_2$), 2.65 (d, 2, CH_2N), 2.28 (s, 3, CH_3N), 2.03 (s, 3, CH_3); IR (neat) 3050, 3020, 2940, 2840, 2780, 1735, 1595, 1585, 1490, 1450, 1365, 1230, 1170, 1070, 1045, 1020, 970, 750 cm^{-1}.

1-(Benzylmethylamino)-2-acetoxy-3-[4-(2-methoxyethyl)phenoxy]propane: NMR ($CDCl_3$) 7.6–6.8 (m, 9), 5.36 (m, 1, CHOAc), 4.15 (m, 2, CH_2), 3.58 (s, 2, $PhCH_2$), 3.5 (concealed t, 2, CH_2), 3.35 (s, 3, CH_3O), 3.0–2.5 (m, 4, CH_2N, CH_2 in CH_2CH_2), 2.23 (s, 3, CH_3N), 2.05 (s, 3, CH_3); IR (neat) 3080, 3050, 3020, 2970, 2920, 2860, 2840, 2820, 1740, 1620, 1580, 1510, 1450, 1330, 1230, 1115, 1045, 970, 740, 700 cm^{-1}.

1-(Isopropylbenzylamino)-2-acetoxy-3-phenoxypropane: NMR ($CDCl_3$) δ 7.5–6.7 (m, 10), 5.15 (m, 1, CHOAc), 4.0 (m, 2, CH_2), 3.63 (br s, 2, $PhCH_2$), 3.3–2.5 (m, 3, CHN, CH_2N), 2.00 (s, 3, CH_3), 0.99 (d, 6, CH_3); IR (neat) 3050, 3020, 2960, 2920, 2870, 2830, 1735, 1595, 1585, 1490, 1455, 1365, 1230, 1270, 1050, 1030, 965, 750 cm^{-1}.

Hydrolysis of 1-(Isopropylbenzylamino)-2-acetoxy-3-phenoxypropane. The amino acetate (266 mg, 0.78 mmol) was dissolved in 3 mL of 5 M KOH–CH_3OH and refluxed for 30 min. After cooling, the mixture was neutralized (pH ~5) with 2 M HCl, and the methanol was removed under vacuum. The mixture was made alkaline (pH ~11) with 2 M NaOH and extracted with ether (3 × 10 mL). The organic phase was washed with brine and dried over K_2CO_3. Evaporation of the ether gave 228 mg (98%) of 1-(isopropylbenzylamino)-3-phenoxypropan-2-ol: NMR ($CDCl_3$) δ 7.4–6.7 (m, 10, aromatic), 3.9 (br s and m, 3, CH_2O, CHO), 3.6 (AB q, 2, only two strong lines visible, $PhCH_2$), 2.93 (m, 1, CH), 2.57 (m, 2, CH_2N), 1.06, 1.00 (2 d, 6, CH_3); IR (neat) 3420, 2960, 1595, 1495, 1245 cm^{-1}.

The following amino alcohols were obtained in quantitative yields (95–100%) by the same hydrolysis procedure.

1-(Benzylmethylamino)-3-phenoxypropan-2-ol: NMR ($CDCl_3$) δ 7.5-6.6 (m, 10, aromatic), 4.0 (m, 1, CHO), 3.96 (br s, 2, CH_2O), 3.6 (AB q, 2, only two strong lines visible, $PhCH_2$), 3.33 (br, 1, OH), 2.60–2.55 (2, AB part of ABX, CH_2N), 2.26 (s, 3, CH_3N); IR (neat) 3420, 2930, 1595, 1585, 1450, 1240, 1040 cm^{-1}.

1-(Benzylmethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol: NMR ($CDCl_3$) δ 7.4–6.5 (m, 9, aromatic), 4.2–3.8 (concealed m, 1, CHO), 3.90 (br s, 2, CH_2O), 3.55 (concealed t, 2, CH_2), 3.6 (AB q, 2, only two strong lines visible, $PhCH_2$), 3.35 (s, 3, CH_3O), 2.73 (t, 3, CH_2), 2.50 (d, 2, CH_2N), 2.20 (s, 3, CH_3); IR (neat) 3440, 2920, 1610, 1510, 1245, 1115 cm^{-1}.

Debenzylation of 1-(Benzylmethylamino)-3-(aryloxy)-propan-2-ols. The amino alcohol (0.4 mmol) and palladium on carbon (50 mg, 10% Pd) in ethanol (2 mL) were stirred under hydrogen (1 atm) for 15 h. The results are given in Table II. **3a**: NMR ($CDCl_3$) δ 7.47–6.73 (m, 5, aromatic), 4.2–3.8 (concealed m, 1, CHO), 3.97 (br s, 2, CH_2O), 3.07–2.30 (br m, 6, CH_2N, CH_3, NH).

3b: NMR ($CDCl_3$) δ 7.20–6.60 (q, 4, aromatic), 4.0–3.8 (br m, 3, CH_2O, CHO) 3.5 (t, 2, CH_2), 3.33 (s, 3, CH_3O), 3.13 (br s, 1, OH), 2.70 (concealed m, 7, CH_2, CH_2N, CH_3N). **3c**: NMR ($CDCl_3$) δ 7.4–6.6 (m, 5, aromatic), 4.2–3.8 (concealed m, 1, CHO), 3.96 (br s, 2, CH_2O), 3.2–2.4 (m, 4, CH_2N, CHN, OH), 1.06 (d, 6, CH_3).

3c from Direct Oxyamination with Isopropylamine. Procedure B was used. After reduction with KBH_4 and removal of palladium black, the organic layer was concentrated in vacuo. The remaining residue was dissolved in 10 mL of 5 M KOH–CH_3OH, refluxed for 30 min, and then neutralized with 2 M HCl. The methanol was removed in vacuo and ether (20 mL) and 1 M HCl (10 mL) was added to the residue. The aqueous phase was separated and the organic layer was extracted with 1 M HCl (3 × 10 mL). The combined aqueous phases were washed with ether (10 mL) made alkaline and extracted with ether (4 × 10 mL). Drying (K_2CO_3) and evaporation of the ether gave 0.105 g (50%) of white crystals, mp 91–93 °C (cyclohexane).

1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol. The same procedure was used (5 mmol scale). The crude product was purified by preparative TLC to give 0.62 g (46%) of a yellow oil which gave white crystals from cyclohexane/pentane: mp 45–47 °C; NMR ($CDCl_3$) δ 7.2–6.7 (q, 4, aromatic), 3.96 (m, 3, CH_2O, CHO), 3.56 (t, 2, CH_2), 3.35 (s, 3, CH_3O), 2.82 (m, 5, CH_2, CH_2N, CHN), 1.09 (d, 6, CH_3).

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Registry No. **1** (Ar = 4-MeC_6H_4), 23431-48-3; **1** (Ar = 3-MeC_6H_4, 1758-10-7; **1** (Ar = 2-MeC_6H_4), 936-72-1; **1** (Ar = 3,5-diMeC_6H_3), 20531-93-5; **1** (Ar = 3,4-diMeC_6H_3), 51788-72-8; **1** (Ar = 4-$MeOC_6H_4$), 13391-35-0; **1** (Ar = 4-ClC_6H_4), 13997-70-1; **1** (Ar = C_6H_5), 1746-13-0; **1** (Ar = 4-$MeOCH_2CH_2C_6H_4$), 80448-05-1; **2** (Ar = 4-MeC_6H_4; R′ = R″ = Et), 80448-06-2; **2** (Ar = 3-MeC_6H_4; R′ = R″ = Et), 80448-07-3; **2** (Ar = 2-MeC_6H_4; R′ = R″ = Et), 80448-08-4; **2** (Ar = 2-MeC_6H_4; R′ = R″ = Me), 80448-09-5; **2** (Ar = 3,5-diMeC_6H_3; R′ = R″ = Et), 80448-10-8; **2** (Ar = 3,5-diMeC_6H_3; R′ = R″ = Me), 80448-11-9; **2** (Ar = 3,4-diMeC_6H_3; R′ = R″ = Et), 80448-12-0; **2** (Ar = 4-$MeOC_6H_4$; R′ = R″ = Et), 80448-13-1; **2** (Ar = 4-ClC_6H_4; R′ = R″ = Et), 41965-58-6; **2** (Ar = C_6H_5; R′ = R″ = Et), 38302-63-5; **2** (Ar = C_6H_5; R′ = R″ = Me), 73687-90-8; **2** (Ar = C_6H_5; R′ = Me; R″ = CH_2Ph), 80448-14-2; **2** (Ar = C_6H_5; R′ = *i*-Pr; R″ = CH_2Ph), 80448-15-3; **2** (Ar = 4-$MeOCH_2CH_2C_6H_4$; R′ = Me; R″ = CH_2Ph), 80448-16-4; **3a**, 39631-73-7; **3b**, 80448-17-5; **3c**, 7695-63-8; **3** (Ar = C_6H_5; R′ = H; R″ = *t*-Bu), 64980-40-1; **3** (Ar = 4-$MeOCH_2CH_2C_6H_4$; R′ = H; R″ = *i*-Pr), 51384-51-1; **3** (Ar = C_6H_5; R′ = Me; R″ = CH_2Ph), 80448-18-6;)3 (Ar = 4-$MeOCH_2CH_2C_6H_4$; R′ = Me; R″ = CH_2Ph), 80448-19-7; **3** (Ar = C_6H_5; R′ = *i*-Pr; R″ = CH_2Ph), 22820-39-9; diethylamine, 109-89-7; dimethylamine, 124-40-3; benzylmethylamine, 103-67-3; benzylisopropylamine, 102-97-6; isopropylamine, 75-31-0; *tert*-butylamine, 75-64-9.

High-Yield Synthesis of 1-Isopropyl-7-methylbicyclo[4.3.0]non-6-ene by a Cationic Olefin Cyclization-Rearrangement Process[1]

William W. Epstein,* James R. Grua, and Donald Gregonis

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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Cationic olefin cyclizations have been extensively studied,[2] and the results indicate a wide variety in both yields and complexity of the products formed. We have found a related and somewhat unusual cyclization where the

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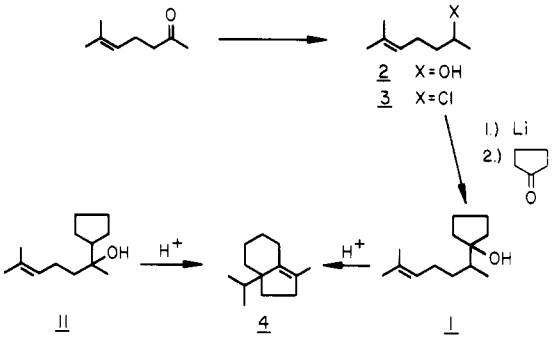
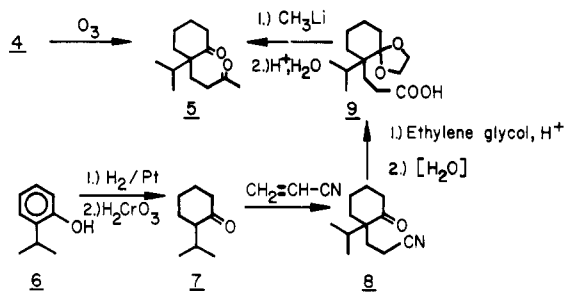
(2) For reviews of this general area, see: Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. Johnson. W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9. VanTamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152. Harding, K. E. *Bioorg. Chem.* **1973**, *2*, 248. Goldsmith, D. *Fortschr. Chem. Org. Naturst.* **1971**, *29*, 363. VanTamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111. Johnson, W. S. *Ibid.* **1968**, *1*, 1. Johnson, W. S. *Trans. N. Y. Acad. Sci.* **1967**, *29*, 1001.

0022-3263/82/1947-1128$01.25/0

Scheme I



Scheme II



product is formed in very high yield (greater than 95%).

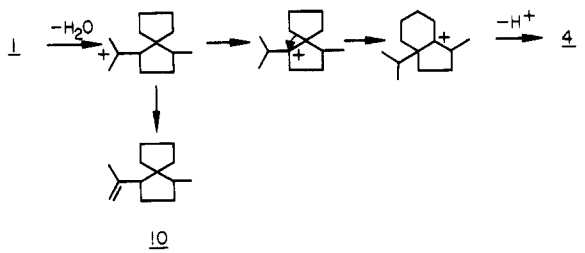
As part of a biosynthesis study we had occasion to prepare 2-methyl-6-(1-hydroxycyclopentyl)-2-heptene (1). In this paper we report the results of the acid cyclization of 1 to give 1-isopropyl-7-methylbicyclo[4.3.0]non-6-ene (4).

The straightforward synthesis of 1 (Scheme I) started with the previously reported[3] reduction of 2-methyl-2-hepten-6-one to 2 followed by conversion to the known chloride 3. The literature preparation[3] of 3 involved the triphenylphosphine/carbon tetrachloride approach. We accomplished the same conversion in comparable yields by a variation of the $SOCl_2$ in pyridine method.[4] The normal technique requires equimolar amounts of alcohol and $SOCl_2$ with a slight molar excess of pyridine. When 2 was treated under these conditions, 3 was formed in low yield along with dark polymeric material. Reaction of only 0.5 equiv of $SOCl_2$ with 1 equiv of 2 followed by isolation of the sulfite ester and reaction of a second 0.5 equiv of $SOCl_2$ led easily to 3. The lithium reagent of 3 was added to cyclopentanone to form 1 in modest yield.

A variety of conditions and acids were studied to induce cyclization, but trifluoroacetic acid was favored because of its tendency to promote olefinic participation.[5] The optimal conditions utilized a sevenfold molar excess of trifluoroacetic acid at ice-bath temperature for 10 min to give product in greater than 95% isolated yield. Formic and perchloric acids were also satisfactory but with reduced yields while boron trifluoride etherate gave predominantly elimination products, and acetic acid gave no reaction.

A consideration of the analytical and spectral data (IR, ^1H NMR, and ^{13}C NMR) suggested that the cyclization product had structure 4 which was confirmed by the synthesis of ozone-degradation product 5 (Scheme II). Reduction of 2-isopropylphenol (6) with H_2/Pt followed by

Scheme III



Jones oxidation gave known[6] 2-isopropylcyclohexanone (7). Michael addition of acrylonitrile to 7 in the presence of potassium *tert*-butoxide yielded 8.[7] The carbonyl of 8 was protected as its ethylene glycol ketal prior to base hydrolysis of the nitrile to give 9. Reaction of 9 with methyllithium followed by deblocking yielded 5 identical in all respects with the ozonization product from 4.

The cyclization–rearrangement can be postulated to occur as indicated in Scheme III where acid dehydration gives rise to a tertiary carbocation. Participation and/or cyclization would give a spiro cation. There is ample precedence for this type of ring closure,[8] and it is perhaps surprising that the reaction did not stop here. A small amount of material (less than 1%) was isolated whose IR (890 cm^{-1}) was consistent with the formation of 10. A 1,2 hydride shift, ring enlargement, and a proton loss would lead to 4. It is of interest to note that 11 also forms 4 in high yield where an initial 1,2 hydride shift or deprotonation–reprotonation must occur prior to participation of the trisubstituted olefin.[9]

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Ether was distilled from sodium/benzophenone prior to use. Hexane was distilled and stored over sodium wire. Pyridine was distilled from NaOH pellets and stored over 4-Å molecular sieves. Boiling points and melting points are reported uncorrected. Infrared (IR) spectra were recorded on Bechman IR 5A or Perkin-Elmer Model 298 spectrophotometers. Ultraviolet (UV) spectra were determined with a Cary Model 15 ultraviolet spectrophotometer. ^1H NMR spectra were determined on the following spectrometers: Varian A-60, Varian EM-360, or Varian EM-390. ^{13}C NMR spectra were measured with a Varian FT-80 spectrometer. Gas–liquid partition chromatography (GLC) was done on a Varian-Aerograph Model A-90P or Model 1200 using Carbowax 20M on Chromosorb W columns; chromatography on silica gel was performed with Merck 254 thin-layer (TLC) plates or 1.5 × 100 cm columns packed with Merck silica gel 60 (230–400 mesh ASTM). Elemental analyses were performed by MHW Laboratories, Chemalytics, or Galbraith Laboratories.

2-Methyl-6-hydroxy-2-heptene (2). Compound 2 was synthesized from 2-methyl-2-hepten-6-one (Chemical Samples Co.) by the $LiAlH_4$ reduction method of Fetizon et al.:[3] 90% yield; bp 77 °C (15 mm) [Lit.[10] bp 78–79 °C (14 mm Hg)]; IR (neat) 3380 cm^{-1}; ^1H NMR (CCl_4) δ 1.18 (d, 3 H, J = 6 Hz), 1.60 (s, 3 H), 1.64 (s, 3 H), 3.65 (m, 1 H), 4.27 (s, 1 H), 5.10 (d, 1 H, J = 7 Hz).

2-Methyl-6-chloro-2-heptene (3). Into a 2000-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer

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and dropping funnel were added 95 g (0.742 mol) of 2-methyl-6-hydroxy-2-heptene (2), 62 mL of pyridine, and 1200 mL of anhydrous ether. The solution was cooled to −20 °C, and 28.5 mL (47.3 g, 0.398 mol) of $SOCl_2$ (freshly distilled from triphenylphosphite) in 100 mL of anhydrous ether was slowly added with stirring. The solution was stirred for 15 min and filtered to remove pyridinium hydrochloride, and the filtrate was poured into 750 mL of vigorously stirred saturated sodium bicarbonate. The organic portion was separated and the aqueous layer washed three times with 100-mL portions of ether. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude sulfite ester in a 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, dropping funnel, and gas outlet tube was heated to 60 °C, and 31.0 mL (51.5 g, 0.432 mol) of $SOCl_2$ was slowly added with stirring. The solution was stirred for 1 h at 60 °C until gas evolution ceased, and 350 mL of saturated sodium bicarbonate was added. The mixture was shaken, the organic layer separated, and the aqueous layer washed three times with 50-mL portions of ether. The organic phases were combined, dried over anhydrous potassium carbonate, filtered, andd concentrated in vacuo to give an oil which was distilled to yield 72.7 g (67% from alcohol) of **3**: bp 81–84 °C (45 mmHg); IR (neat) 1070, 822, 668 cm^{-1}; ^1H NMR (CCl_4) δ 1.3–1.7 (m, 2 H), 1.47 (d, 3 H), 1.60 (s, 3 H), 1.65 (s, 3 H), 2.13 (m, 2 H), 3.92 (m, 1 H), 5.03 (t, 1 H).

2-Methyl-6-(1-hydroxycyclopentyl)-2-heptene (1). To a 500-mL, three-necked, round-bottomed flask equipped with a high-speed stirrer and an argon bleed were added 100 mL of anhydrous ether and 3.0 g (0.44 mol, 5% Na alloy) of lithium sand. The mixture was stirred for 10 min at room temperature and cooled to −40 °C, and 23 mL (20 g, 0.14 mol) of **3** was added over 1 h. The reaction mixture was stirred 10 min and cooled to −70 °C, and 7 mL (6.6 g, 0.08 mol) of cyclopentanone in 20 mL of anhydrous ether was added. The solution was stirred 30 min, 80 mL of saturated NH_4Cl was added, and the mixture was allowed to warm to room temperature. The aqueous phase was extracted with three 50-mL portions of ether, and the organic phases were combined and dried ($MgSO_4$). The solvent was removed in vacuo and the remaining oil distilled to give 12.0 mL (11.3 g, 41%) of **1**: bp 125–129 °C (10 mmHg); IR (neat) 3410, 1452, 1380, 980, 832 cm^{-1}; ^1H NMR (CCl_4) δ 0.97 (d, 3 H), 1.2–2.6 (m, 13 H), 1.60 (s, 3 H), 1.65 (s, 3 H), 5.05 (t, 1 H); ^{13}C NMR (C_6D_6) δ 14.70, 17.71, 24.29, 24.35, 25.83, 26.81, 32.55, 38.48, 38.68, 42.51, 85.21, 125.53, 130.87. Anal. Calcd for $C_{13}H_{24}O$: C, 79.51; H, 12.24. Found: C, 79.79; H, 12.06.

1-Isopropyl-7-methylbicyclo[4.3.0]non-6-ene (4). To a 3-mL vial equipped with a magnetic stirrer in an ice bath was added 2 mL (2.96 g, 26 mmol) of trifluoroacetic acid (Aldrich). The vial was removed from the bath and 690 mg (3.52 mmol) of **1** added dropwise with vigorous stirring. TLC (hexane) indicated no starting material (R_f 0.15) and one major spot of R_f 0.74 after 10 min. The two-phase reaction mixture was transferred to a separatory funnel with 10 mL of pentane, and saturated $NaHCO_3$ solution was added until CO_2 evolution ceased. The aqueous phase was extracted with one 10-mL portion of pentane, and the combined organic phases were washed with saturated NaCl solution. The solvent was removed to give 627 mg of almost colorless oil which was chromatographed with hexane as the eluent to give 600 mg (95.6%) of a colorless oil: IR (neat) 2980, 2910, 1383, 1363 cm^{-1}; ^1H NMR (CCl_4) δ 0.69 (d, 3 H, J = 6 Hz), 0.84 (d, 3 H, J = 6 Hz), 1.1–2.5 (m, 13 H), 1.59 (s, 3 H); ^{13}C NMR (CD_2Cl_2) δ 13.28 (q), 17.17 (q), 17.34 (d), 22.39 (q), 22.39 (t), 23.78 (t), 28.01 (t), 28.54 (s), 30.46 (t), 37.33 (t), 38.98 (t), 127.10 (s), 139.41 (s). Anal. Calcd for $C_{13}H_{22}$: C, 87.65; H, 12.35. Found: C, 87.91; H, 12.42. In other runs **4** was distilled; bp 105–107 °C (20 mmHg).

2-Isopropyl-2-(3-oxobutyl)cyclohexanone (5). A solution of 90 mg (0.50 mmol) of **4** and 36 μL of pyridine in 2.7 mL of dichloromethane was cooled to −78 °C and treated with O_3 until a definite blue color developed (3 min). Zinc dust (200 mg) and glacial acetic acid (200 μL were added, and the stirred solution was allowed to warm to room temperature (1 h). Chromatography on silica gel (25 × 125 mm; ethyl acetate/hexane, 1:3) yielded 46 mg (44%) of an oil (>95% pure by TLC; ethyl acetate/hexane, 1:3; R_f 0.2): IR (neat) 1720, 1700 cm^{-1}; ^1H NMR (CCl_4) δ 0.71 (d, 3 H, J = 7 Hz), 0.84 (d, 3 H, J = 7 Hz), 1.5–2.0 (m, 9 H), 2.05 (s, 3 H), 2.1–2.6 (m, 4 H). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.43; H, 10.48. Found: C, 74.25; H, 10.61.

2-Isopropylcyclohexanone (7). Freshly distilled [142 °C (90 mmHg)] 2-isopropylphenol [Aldrich; 70 mL (0.52 mol) in 70 mL of glacial acetic acid] was catalytically (PtO_2) hydrogenated by using a Parr apparatus. Acetic acid was removed in vacuo and the crude product was diluted with 100 mL of ether and washed with 50 mL of 5% NaOH solution and twice with 50-mL portions of H_2O. The ether solution was combined with 100 mL of acetone, and 500 mL of 0.66 M chromic acid solution was added slowly. The reaction mixture was stirred for 12 h and worked up in the standard fashion. The brownish oil was distilled to give 50 mL (45.5 g, 0.32 mol, 61% yield) of **7**: bp 90–98 (30 mmHg) [lit.[11] bp 83 °C (17 mmHg)]; IR (neat) 1708, 1386, 1370 cm^{-1}; ^1H NMR (CCl_4) δ 0.92 (d, 6 H, J = 6 Hz), 1.2–1.4 (m, 10 H).

2-Isopropyl-2-(2-cyanoethyl)cyclohexanone (8). To a solution of 600 mg of K in dry *tert*-butyl alcohol in a 250 mL three-necked flask equipped with a mechanical stirrer and a N_2 bleed was added 27.2 mL (25.1 g, 0.179 mol) of **7** in one portion followed by 10 mL (8.1 g, 0.153 mol) of acrylonitrile dropwise at such a rate as to keep the temperature in the flask from rising above 30 °C. The mixture was stirred for 4 h, 100 mL of 2 N H_2SO_4 was added, and the mixture was extracted with two 50-mL portions of ether. The organic phases were combined, washed with saturated $NaHCO_3$, and dried ($MgSO_4$). The solvent was removed in vacuo and the oil distilled to give 10.2 mL (10.3 g, 35%) of 90% pure **8**, bp 127 °C (0.5 mmHg). The analytical sample was prepared by GLC (6-ft Carbowax 20M column): IR (neat) 2260, 1710 cm^{-1}, ^1H NMR (CCl_4) δ 0.69 (d, 3 H, J = 7 Hz), 0.87 (d, 3 H, J = 7 Hz), 1.2–2.5 (m, 13 H); ^{13}C NMR (C_6D_6) δ 12.31 (t), 16.16 (t), 16.39 (t), 19.59 (t), 26.38 (t), 26.62 (t), 29.26 (d), 31.23 (t), 38.87 (t), 53.89 (s), 120.34 (s), 212.32 (s). Anal. Calcd for $C_{12}H_{19}ON$: C, 74.55; H, 9.91; N, 7.28. Found: C, 74.24; H, 10.04; N, 7.58.

2-Isopropyl-2-(2-cyanoethyl)cyclohexanone Ethylene Ketal. A solution of 7 g (6.9 mL) of **8**, 0.6 g of *p*-toluenesulfonic acid, and 30 mL of ethylene glycol in 150 mL of benzene in a 250-mL flask equipped with a Dean–Stark trap was refluxed for 3 days. The benzene layer was washed with saturated $NaHCO_3$ and dried and the solvent removed in vacuo to give 96% yield of ketal based on consumed ketone; bp 140 °C (0.5 mmHg). The analytical sample was purified by GLC (6-ft Carbowax 20M column) and the remainder used in the next step: IR (neat) 2260 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (d, 3 H, J = 7 Hz), 1.00 (d, 3 H, J = Hz), 1.2–2.6 (m, 13 H), 3.88 (brs, 4 H); ^{13}C NMR (C_6D_6) δ 13.58, 18.49, 18.79, 20.21, 23.43, 25.90, 29.58, 30.07, 30.48, 44.54, 62.87,64.46, 114.43, 120.86. Anal. Calcd for $C_{14}H_{23}O_2N$: C, 70.83; H, 9.77; N, 5.93. Found: C, 71.00; H, 9.77; N, 6.06.

2-Isopropyl-2-(2-carboxyethyl)cyclohexanone Ethylene Ketal (9). A solution of 2.75 g (11.6 mmol) of the ethylene ketal of **8** in a mixture of 5 mL of MeOH, 2 mL of H_2O, and 1.0 g of NaOH was refluxed 48 h (TLC, 1:1 ethyl acetate/hexane, R_f 0.35). The reaction mixture was neutralized with saturated NH_4Cl solution and continuously extracted with ether for 48 h. The combined ether phases were concentrated in vacuo, and the solid residue was chromatographed on silica gel (ethyl acetate/hexane, 1:3) to give 2.91 g (98%) of **9** which could be recrystallized from petroleum ether (bp 30–60 °C): mp 90 °C; IR (KBr) 1710 cm^{-1}; ^1H NMR (CCl_4) δ 0.89 (d, 3 H, J = 7 Hz), 0.99 (d, 3 H, J = 7 Hz), 1.2–2.6 (m, 13 H), 11.81 (s, 1 H). Anal. Calcd for $C_{14}C_{24}O_4$: C, 65.63; H, 9.43. Found: C, 65.46; H, 9.41.

2-Isopropyl-2-(3-oxobutyl)cyclohexanone (5). To a solution of 1.3 g (5.0 mmol) of **9** in 15 mL of dry ether maintained at 0 °C and under a N_2 atmosphere was added 5.5 mL of a 2.0 M solution of CH_3Li in hexane (11.0 mmol). The stirred solution was allowed to warm to room temperature (1 h), slowly poured into 20% HCl and ice, and stirred vigorously for 2 h. The aqueous mixture was extracted with ether (3 × 25 mL). The combined organic phases were washed with 30 mL of saturated $NaHCO_3$ and saturated NaCl solution (3 × 30 mL). Medium-pressure liquid chromatography of the concentrated organic phase (ethyl acetate/hexane, 1:6) afforded 725 mg (69%) of **5** identical with the material obtained from ozonolysis of **4** (IR, ^1H NMR, GLC retention time).

(11) VaVon, G.; Conia, J. C. R. *Hebd. Seances Acad. Sci.* **1946**, *223*, 245.

2-Methyl-6-hydroxy-6-cyclopentyl-2-heptene (11). To a mixture of 2.0 g (288 mmol) of Li sand (5% Na) and 100 mL of dry hexane in a three-necked, 250-mL flask fitted with a mechanical stirrer and maintained under a He atmosphere was added 13.9 mL (19.4 g, 130 mmol) of cyclopentyl bromide (Aldrich). After 10% of the bromide had been added, the mixture was brought to reflux. The mixture became cloudly, developed a purple color, and was refluxed 1 h after the addition was complete. The mixture was cooled to −70 °C, 19.4 mL (16.4g, 130 mmol) of 2-methyl-2-hepten-6-one added, and the solution stirred an additional 2 h. The reaction mixture was acidified with 80 mL of saturated NH_4Cl and extracted three times with 50-mL portions of ether, the combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. The resulting oil was distilled to give 6.0 g (6.2 mL, 30%) of 11: bp 108–111 °C (6 mmHg); IR (neat) 3480 cm^{-1}; ^1H NMR (CCl_4) δ 1.17 (s, 3 H), 1.4–2.4 (m, 13 H), 1.6 (brs, 6 H), 2.75 (s, 1 H), 5.48 (brt, 1 H, J = 7 Hz). Anal. Calcd for $C_{13}H_{24}O$: C, 79.51; H, 12.24. Found: C, 79.79; H, 12.06.

1-Isopropyl-7-methylbicyclo[4.3.0]non-6-ene (4) from 11. By use of a procedure similar to the previous preparation of 4, 6.8 g (3.8 mmol) of 11 was converted into 4.5 g (73%) of distilled 4, bp 105–107 °C (20 mmHg).

Registry No. 1, 80447-64-9; 2, 1569-60-4; 3, 80325-37-7; 4, 80447-65-0; 5, 80461-60-5; 6, 88-69-7; 7, 1004-77-9; 8, 80447-66-1; 8 ketal, 80447-67-2; 9, 80447-68-3; 10, 80447-69-4; 11, 80447-70-7.

Addition of Lithio-α-thiophenyl Nitriles to Aldehydes and Ketones†

David Morgans, Jr.,* and Gregg B. Feigelson[1]

Department of Chemistry, University of California, Santa Cruz, California 95064

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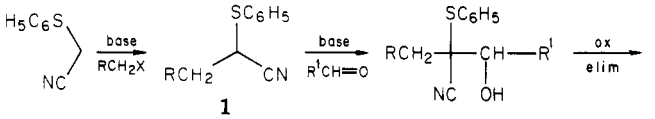
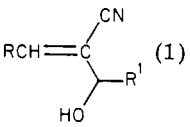
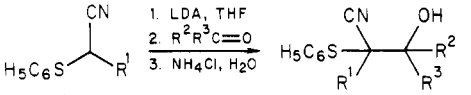
In connection with a natural product synthesis currently under investigation in our laboratories, we required a method for the construction of α′-hydroxy-α,β-unsaturated nitriles based on the scheme shown in eq 1.





Literature precedent[2] indicated that the initial alkylation would proceed without problem; however, the outcome of the second carbon–carbon bond-forming step was not secure. Our cause for concern was based on the lack of precedent for such reactions (1 → 2) and reinforced by recent reports[3] concerning reactions of this type with α-thiophenyl esters and lactones. In particular, one report[3a] mentioned problems in obtaining good yields from lithio-α-thiophenyl esters and aldehydes. These workers conveniently solved this problem by using a $ZnCl_2$ additive, which presumably perturbs the equilibrium (unfavorable for M = Li) shown in eq 2 to the product side by chelation[4] of the 1,2-adduct 4. Given the apparent geometrical constraints in such a chelated intermediate, the utility of this device for the case at hand was not clear should the addition equilibrium (eq 3) be found unfavorable.

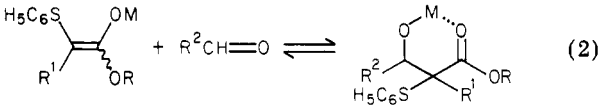
Table I. 1,2-Addition Reactions with Aldehydes and Ketones[a]

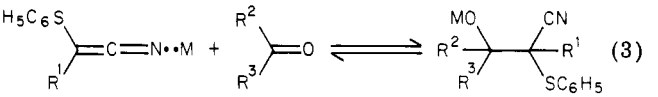


5 6

entry	R^1	R^2	R^3	product yield, %
1	CH_3 (5a)	H	$CH(CH_3)_2$	(6a) 89
2	CH_3 (5a)	H	C_6H_5	(6b) 90
3	CH_3 (5a)		$-(CH_2)_5-$	(6c) 90[b]
4	n-C_4H_9 (5b)	H	$CH(CH_3)_2$	(6d) 90
5	n-C_4H_9 (5b)	H	C_6H_5	(6e) 80
6	n-C_4H_9 (5b)		$-(CH_2)_5-$	(6f) 62[c]
7	n-C_4H_9 (5b)		$-(CH_2)_4-$	(6g) 67[d]
8	i-C_4H_9 (5c)	H	$CH(CH_3)_2$	(6h) 53
9	i-C_4H_9 (5c)	H	C_6H_5	(6i) 54
10	i-C_4H_9 (5c)		$-(CH_2)_5-$	(6j) 0
11	CH_2=$CHCH_2$ (5d)	H	$CH(CH_3)_2$	(6k) 72
12	n-C_4H_9 (5b)	H	CH_2=$C(CH_3)$	(6l) 44

[a] All yields refer to chromatographically purified products. Satisfactory combustion analysis was obtained for representative samples from experiments 3, 6, and 8. All substances were obtained as colorless oils unless otherwise noted. Routine characterization included TLC, ^1H NMR, IR, and EI MS. [b] Mp 72–74 °C. [c] Mp 90–91 °C. [d] Mp 53–56 °C.





In practice, the anticipated problems were encountered in initial experiments. Reaction of the anion of α-(phenylthio)propionitrile (**5a**) from lithium diisopropylamide in THF) with isobutyraldehyde at −70 °C for 30 min afforded only a 30% yield of the desired product. Longer reaction times or elevated temperatures offered no improvement. Eventually, it was found that immediate quenching of the reaction mixture (within 15 s of addition of the carbonyl electrophile) dramatically increased the yield for the case above.[5] This procedure was found to be generally applicable to a variety of 1,2 adducts (Table I). Furthermore, reaction of these lithionitriles with α,β-unsaturated carbonyl electrophiles revealed a curious and potentially useful propensity for the exclusive formation of 1,4 adducts (Table II) in almost all of the cases studied.

In general, the 1,2-addition products are formed in good yields with aldehydes and ketones. The representative

† Dedicated to Professor Gilbert Stork on the occasion of his 60th birthday.

(1) Undergraduate Research Associate (1980–1981).

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(3) (a) T. R. Hoye and M. J. Kurth, *J. Org. Chem.*, **45**, 3549 (1980; (b) B. M. Trost and H. C. Arndt, *Ibid.*, **38**, 3140 (1973); (c) N. Kumeda, J. Nobami, and M. Kinoshita, *Tetrahedron Lett.*, 3523 (1980).

(4) The utility of this modification was first described by House and co-workers: H. O. House: D. S. Cummrine: A. Y. Teranishi, H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).

(5) The advantage of short reaction times in aldol reactions with aldehydes and ketone enolates was described in early studies by House and co-workers. See ref 4.

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