α-Keto-γ-valerolactone (14): 68%; mp 71–73 °C (lit.[5] mp 70–73 °C); IR ($CHCl_3$) 3500, 3300, 1760, 1400, 1320 cm^{-1}; NMR ($CDCl_3$) δ 6.65 (bs, 1 H), 6.27 (d, 1 H), 5.08 (m, 1 H), 3.0 (m), 2.25 (m), 1.42 (d, 3 H); MS *m/e* 114 (M^+), 69, 57, 44.

Anal. Calcd for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.19; H, 4.98.

α-Keto-γ-phenyl-γ-butyrolactone (15): 66%; IR ($CHCl_3$) 3500, 3350, 1765, 1500 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (bs, 5 H), 6.29 (d, 1 H), 5.82 (d, 1 H); DNP derivative, mp 115–117 °C.

Anal. Calcd for $C_{16}H_{12}N_4O_6$: C, 53.94; H, 3.39; N, 15.72. Found: C, 54.28; H, 3.60; N, 15.96.

α-Keto Lactone 16: 86%; mp 98–101 °C (lit.[3] mp 99–110 °C); IR ($CHCl_3$) 3500, 3300, 1750 cm^{-1}; NMR ($CDCl_3$) δ 6.55 (bs, 1 H), 4.58 (m, 1 H), 3.00 (m, 2 H), 2.6–1.0 (m, 6 H); MS *m/e* 154 (M^+), 110, 97, 80, 79.

α-Keto Lactone 17: 72%; mp 93–96 °C: IR ($CHCl_3$) 3500, 3300, 1750, 1690, 1600 cm^{-1}; NMR ($CDCl_3$) δ 6.55 (d, 1 H), 6.08 (m, 1 H), 5.87 (dd, 1 H), 2.71–1.4 (m, 4 H).

Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 62.80; H, 5.04.

α-Keto-δ-valerolactone (18): 72%; IR ($CHCl_3$) 3450, 1765–1700 cm^{-1}; NMR ($CDCl_3$) δ 5.95 (t, 1 H), 5.75 (bs, 1 H), 4.60 (t, 2 H), 4.45 (t, 2 H), 2.87 (t, 2 H), 2.50 (m, 2 H); MS *m/e* 114 (M^+), 69, 57, 56, 41.

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Registry No.—**1**, 96-48-0; **2**, 108-29-2; **3**, 1008-76-0; **4**, 27345-71-7; **5**, 34896-02-1; **6**, 542-28-9; **7**, 34009-40-0; **8**, 62527-57-5; **9**, 66516-03-8; **10**, 66516-02-7; **11**, 66516-01-6; **12**, 66516-00-5; **13**, 25409-36-3; **13** DNP, 3777-94-4; **14**, 21053-73-6; **15**, 19252-20-1; **15** DNP, 66515-98-8; **16**, 66515-99-9; **17**, 66516-05-0; **18**, 66516-04-9; tris(dimethylamino)-methane, 5762-56-1; dimethylformamide, 68-12-2; dimethylcarbamyl chloride, 79-44-7.

References and Notes

(1) H. H. Wasserman and J. L. Ives, *J. Am. Chem. Soc.*, **98**, 7868 (1976).
(2) K. H. Meyer, *Justus Liebigs Ann. Chem.*, **398**, 49 (1913).
(3) P. A. Plattner and L. M. Jamplosky, *Helv. Chim. Acta*, **26**, 687 (1943).
(4) H. Schintz and M. Hinder, *Helv. Chim. Acta*, **30**, 1349 (1947).
(5) C. H. Wermuth, *Bull. Soc. Chim. Fr.*, 1435 (1966), and references cited therein.
(6) H. Bredereck, F. Effenberger, and T. Brendle, *Angew. Chem., Int. Ed. Engl.*, **5**, 132 (1966); H. Weingarten and N. K. Edelman, *J. Org. Chem.*, **32**, 3293 (1967); H. Bredereck, F. Effenberger, T. Brendle, and H. Muffler, *Chem. Ber.*, **101**, 1885 (1968).
(7) S. F. Martin and D. R. Moore, *Tetrahedron Lett.*, 4459 (1976).
(8) For recent reviews on the synthesis of α-methylene lactones, see R. B. Gammill, C. A. Wilson, and T. A. Bryson, *Synthetic Commun.*, **5**, 245 (1975), and P. Grieco, *Synthesis*, 67 (1975).
(9) For example, see A. Maercker, *Org. React.*, **14**, 270 (1965); G. Wittig and U. Schollkopf, "Organic Synthesis", Collect. Vol. 5, Wiley, New York, N.Y., 1973, p 751; R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963); H. O. House and G. H. Rasmusson, *ibid.*, **26**, 4728 (1961).

An Efficient Route to Intermediates for the Synthesis of 11-Deoxyprostaglandins

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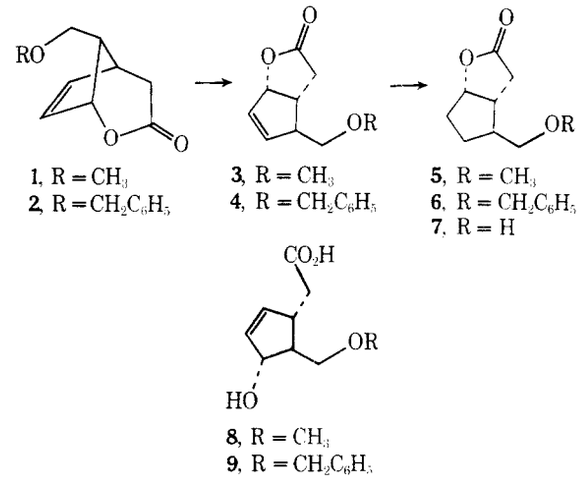
The benzyloxy bicyclic lactone **2** is an important starting material for the preparation of the unsaturated lactone **4**, an intermediate for the synthesis of A prostaglandins[1] and the lactone alcohol **7**. The latter is a key intermediate for the synthesis of pharmacologically interesting 11-deoxyprostaglandins.[2] Since the existing route from the bicyclic lactone **2** to **4** and thence to **7** involves several steps,[3–5] we have developed a simple one-step transformation of **2** to **4** involving a cationic rearrangement cyclization sequence. Compound **4** can be transformed into **7** in two additional steps, thus providing a convenient approach to 11-deoxyprostaglandins. A corresponding sequence from **1**, the methyl ether analogue of **2**, to **7** has also been developed.



1, R = CH_3
2, R = $CH_2C_6H_5$
3, R = CH_3
4, R = $CH_2C_6H_5$
5, R = CH_3
6, R = $CH_2C_6H_5$
7, R = H
8, R = CH_3
9, R = $CH_2C_6H_5$

Treatment of the lactone methyl ether **1** or the benzyl ether **2** with concentrated sulfuric acid in an aprotic solvent at room temperature for 12 h smoothly afforded in ca. 90% yield the rearranged lactones **3** and **4**. The rearrangement was effected in similar yields with *p*-toluenesulfonic acid or boron trifluoride etherate as catalysts. Alternatively, the optically active lactones **3** and **4** were obtained directly from the resolved intermediates **8** and **9** by treatment with concentrated H_2SO_4 as described above. Catalytic hydrogenation of **3** over 5% Rh/alumina gave the saturated ether **5**, which was demethylated using BBr_3 to furnish the desired alcohol **7** in 77% overall yield. However, catalytic hydrogenation and debenzylation of the benzyl ether **4** to provide **7** in 90% overall yield were best effected sequentially over 5% Rh/alumina[4] (to give **6**) followed by 5% Pd/C in ethyl acetate. Contrary to an earlier report, there was no evidence of hydrogenolysis of the allylic hydroxyl group in **4**.[3,6]

The three-step sequence of **2** to **7** or alternatively **9** to **7** (if optically active material is desired) constitutes the preferred route for intermediates for the preparation of 11-deoxyprostaglandins.

Experimental Section[7]

Preparation of Methyl Ether Lactone 3. A solution of 5.26 g (15 mmol) of the lactone **1** in 30 mL of Et_2O was treated with 0.3 mL of concentrated H_2SO_4, and the mixture was stirred under a nitrogen atmosphere overnight at room temperature. The reaction mixture was neutralized (pH 8) with saturated sodium bicarbonate solution, the Et_2O layer was separated, and the aqueous layer was further extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to a crude oil weighing 2.4 g (95% yield). The product was purified by chromatography on silica gel (Baker) using CH_2Cl_2 followed by CH_2Cl_2/EtOAc (9:1) as eluent to furnish **3**: 2.2 g (87% yield); mp 50–51 °C; IR ($CHCl_3$) 1779 cm^{-1}; NMR ($CDCl_3$) δ 2.0–3.1 (4 H, m), 3.25 (3 H, s, $-OCH_3$), 3.2–3.4 (2 H, m, $-CH_2O$), 5.45 (1 H, m, –CHOCO), and 5.94 (2 H, m, olefinic); TLC R_f 0.5 (EtOAc).

Reduction of the Methyl Ether Lactone 3 to 5. A solution of 1.8 g (10.7 mmol) of unsaturated lactone methyl ether **3** in 20 mL of THF and 0.2 g of 5% rhodium on alumina was hydrogenated at 25 °C and atmospheric pressure until absorption ceased (15 min). The reaction mixture was filtered through Celite and evaporated to yield an oil weighing 1.8 g (100% yield). The oil was chromatographed on silica gel (Baker) eluting with CH_2Cl_2 followed by CH_2Cl_2/EtOAc (4:1) to afford **5** as a colorless oil: 1.76 g (96.0% yield); IR 1779 cm^{-1}; NMR ($CDCl_3$) δ 1.2–3.0 (8 H, m), 3.35 (2 H, d, J = 6 Hz, $-CH_2O-$), 3.38 (3 H, s, $-OCH_3$), and 5.00 (1 H, br, –CHOCO); TLC R_f 0.25 (3:1 C_6H_6/EtOAc).

Preparation of Benzyl Ether Lactone 4. Following the procedure described for the preparation of **3**, the lactone **2** or the corresponding hydroxy acid (+)-**9** was converted to **4** (91% yield), a pale yellow oil, identical in all respects with a sample prepared by the method of Corey and Snider.[4] Optically active material had $[\alpha]^{27}_D$ +214° (*c* 1.0, $CHCl_3$).

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Reduction of the Benzyl Ether Lactone 4 to 6. Following the procedure described for the preparation of **5**, the double bond in benzyl ether **4** was selectively reduced over 5% Pd/C to furnish the saturated benzyl ether **6** in 97% yield: bp 150–155 °C (0.5 mm); IR ($CHCl_3$) 1776 cm^{-1}; NMR ($CDCl_3$) δ 3.4 (2 H, d, J = 6 Hz, $-CH_2O-$), 4.54 (2 H, br, $-OCH_2Ph$), 4.9 (1 H, m, –CHOCO), and 7.3 (5 H, s, C_6H_5); TLC R_f 0.55 (1:1 C_6H_6/ether).

Preparation of Lactone Alcohol 7: (a) From the Methyl Ether 5. A solution of 0.17 g (1 mmol) of lactone methyl ether **5** in 5 mL of CH_2Cl_2 was stirred at −78 °C under a nitrogen atmosphere. To this solution was added 0.5 mL (5.5 mmol) of BBr_3, and the resulting white slurry was brought rapidly to 0 °C. After completion of the reaction (5.5 h), 2 mL of ether was added dropwise and the mixture was stirred for 5 min and then added to a stirred slurry of 2.3 g of $NaHCO_3$ in 12 mL of saturated sodium potassium tartrate solution. The organic layer was separated and the water layer extracted with CH_2Cl_2. The combined organic extracts were washed with saturated sodium potassium tartrate and dried (Na_2SO_4). The crude product, weighing 154 mg, was purified by chromatography on silica gel (Baker) eluting with CH_2Cl_2 followed by CH_2Cl_2/EtOAc (9:1). Evaporation of the combined fractions gave pure **7** (121 mg, 77% yield): bp 135–138 °C (0.1 mm); IR ($CHCl_3$) 1770 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.3–2.9 (8 H, m), 3.05 (1 H, s, OH), 3.60 (2 H, d, J = 6 Hz, $-CH_2O-$), and 5.00 (1 H, br, –CHOCO); TLC R_f 0.3 (EtOAc). Optically active material had $[\alpha]^{27}D$ −26.1° (*c* 1, $CHCl_3$).

(b) From the Benzyl Ether 6. A 52-g amount of the benzyl ether **6**, dissolved in 400 mL of EtOAc containing 0.5 mL of concentrated HCl, was hydrogenated over 10% Pd/C (4 g) at room temperature and pressure. After hydrogen absorption had ceased (1 h), workup followed by distillation gave 33 g of **7** (98% yield), identical in all respects with the material prepared above.

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Registry No.—**1**, 52578-42-4; **2**, 50889-56-0; **3**, 39673-26-2; **4**, 35761-79-6; **5**, 66748-93-4; **6**, 54382-69-3; **7**, 43119-34-2; (+)-**9**, 41787-51-3.

References and Notes

(1) E. J. Corey and P. A. Grieco, *Tetrahedron Lett.*, 107 (1972).
(2) For a detailed review of the chemistry and biology of 11-deoxyprostaglandins, see J. S. Bindra and R. Bindra, "Prostaglandin Synthesis", Academic Press, New York, N.Y., 1977, Chapter 20.
(3) P. Crabbé and A. Guzmán, *Tetrahedron Lett.*, 115 (1972).
(4) E. J. Corey and B. B. Snider, *J. Org. Chem.*, **39**, 256 (1974).
(5) S. Ranganathan, D. Ranganathan, and R. Iyengar, *Tetrahedron*, **32**, 961 (1976).
(6) P. Crabbé, A. Cervantes, and A. Guzmán, *Tetrahedron Lett.*, 1123 (1972).
(7) Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian A-60 and T-60 spectrometers with Me_4Si as an internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrometer.

The *E* Isomer of Acetophenone Iminoxy, an Overlooked Radical

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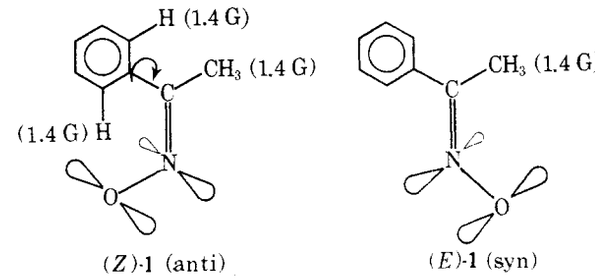
The acetophenone iminoxy radical has been observed by ESR spectroscopy during oxidation of acetophenone oxime in a number of studies: in a flow system[1] with ceric salts, in static systems with lead tetraacetate in benzene[2,3] or methylene chloride,[4,5a] and by other methods.[5b]

It is a transient radical which rapidly disappears after its generation at ambient temperatures, giving rise to diamagnetic products[3] and secondary radicals of the nitroxide type as noted by several authors. The latter radicals are readily distinguished from the iminoxy radical by their lower nitrogen hyperfine splitting constants (hfsc): a_N(iminoxy) ≃ 31 G; a_N(nitroxide) ≤ 16 G.

In these studies only one iminoxy radical was detected, and



(*Z*)-1 (anti) (*E*)-1 (syn)

it was established by Gilbert and Norman[5a] to be the *Z* isomer [(*Z*)-1] in which a characteristic 1.4 G coupling with both ortho hydrogens is present due to interaction of the rapidly rotating phenyl group with the unpaired electron which is contained in a σ-type orbital.[6a] This orbital is derived from an oxygen p orbital and the nitrogen nonbonding sp^2 orbital which are in the C=N–O plane. The spin density in iminoxy radicals is almost evenly distributed over nitrogen and oxygen. The C=N–O angle has been calculated to be 139°, and thus it is larger than in the parent oxime.[6b] It is rather surprising that for the iminoxy radical only the *Z* form has been found so far, while for the oxime the *E* form strongly predominates (≃95% in the equilibrium mixture; the isolation of the *Z* isomer has only recently been accomplished[7,8,9]). Apparently, in **1** the *E* → *Z* isomerization is a very rapid process and (*Z*)-1 is the thermodynamically more stable isomer.

Z/*E* isomerization in iminoxy radicals leading to an equilibrated mixture of two radicals with separate ESR signals has been observed frequently.[10] The same situation exists in a number of para- or meta-substituted acetophenone iminoxy radicals.[11,12] It therefore seemed desirable to confirm the previous assignment of the ESR signal of the acetophenone iminoxy radical to exclusively (*Z*)-1 with the aid of the compounds perdeuterated either in the methyl or phenyl group.

Experimental Section

(*E*)-Acetophenone oxime was characterized by its melting point (58–59 °C) and NMR spectrum. In addition to a correct melting point, the α,α,α-trideuterated compound was found to contain a methyl group with >95% deuterium content by NMR spectroscopy and ≥98% by mass spectrometry; the pentadeuteriophenyl oxime had 97.5 (NMR) and 98% (MS) deuterium content. NMR spectra were taken on Varian A-60 and HA-100 spectrometers. Mass spectra were run on an AEI-MS-902 mass spectrometer.[13] ESR spectra were taken on a Varian E-4 spectrometer with a variable temperature accessory. The hfsc are uncorrected, but they can be compared with those obtained with the same instrument for the perylene radical cation[14] in 98% sulfuric acid at 20 °C (found: 4.10, 3.10, and 0.45 G). Values of g were measured with respect to solid DPPH (taken as g = 2.0036).

Results and Discussion

We have previously analyzed the ESR spectra of aromatic iminoxy radicals in more detail than was done before[15,16] using *tert*-butyl peroxalate[17] (TBPO) as a convenient thermal source of *tert*-butoxy radicals in apolar solvents at ambient temperature, which in turn generate iminoxy radicals from the oximes.

This method enabled us to maintain a steady state of acetophenone iminoxy radicals for periods up to hours and to study them at leisure under high resolution. In addition to the previously reported a_N = 1.4 G (5 H, CH_3 and ortho H's), the spectra of (*Z*)-1 contain a small para H coupling (a_H^p = 0.56 G), indicating the presence of some unpaired spin density in the aromatic π-electron system. The coupling is removed by para substituents like OCH_3 (Figure 1). To explain the unpaired π-spin density in (*Z*)-1 and in other aromatic iminoxy radicals in which the oxygen atom and the phenyl group are in a *Z* position, the author has proposed a $\sigma \rightarrow \pi$ spin polarization mechanism at nitrogen and/or oxygen and a distri-

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