Benzyl Enol Ethers via Decarboxylation of α-Benzyloxy-β-lactones Derived from the Lithium α-Benzyloxy-α-lithioacetate Synthon

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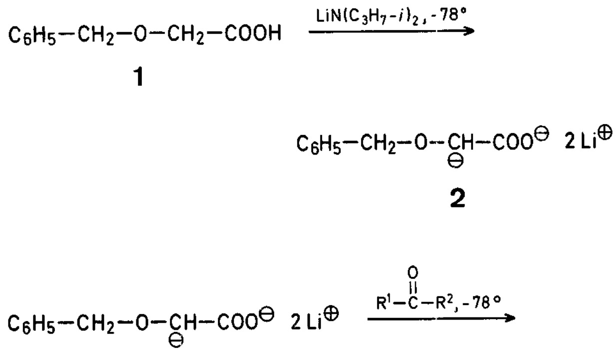
Sometime ago we showed[1] that β-lactones constitute convenient precursors to olefins on thermal decarboxylation. Furthermore, we demonstrated[2] that α-benzyloxyacetic acids **1** can be readily converted into the useful α-lithiocarboxylate synthons **2** by direct α-lithiation with lithium diisopropylamide at low temperature and that such synthons react with ketone electrophiles[3] to lead to the corresponding β-hydroxy acids.



$$\underset{\mathbf{1}}{C_6H_5-CH_2-O-CH_2-COOH} \xrightarrow{LiN(C_3H_7-i)_2,\ -78°} \underset{\mathbf{2}}{C_6H_5-CH_2-O-\underset{\ominus}{C}H-COO^{\ominus}\ 2\,Li^{\oplus}}$$

$$\underset{\mathbf{2}}{C_6H_5-CH_2-O-\underset{\ominus}{C}H-COO^{\ominus}\ 2\,Li^{\oplus}} \xrightarrow{R^1-\overset{O}{\overset{\|}{C}}-R^2,\ -78°}$$

2

	R^1	R^2
a	C_6H_5	H
b	$-(CH_2)_4-$	
c		
d	CH_3	CH_3
e	C_6H_5	C_6H_5

Based on these background facts, we have succeeded in preparing benzyl enol ethers **5** via the synthetic sequence shown below. In view of the fact that general methods for the preparation of enol ethers **5** are limited[4], the present sequence constitutes a convenient route to these useful compounds. The general procedures for the preparation of the α-benzyloxy-β-hydroxy acids **3**, the α-benzyloxy-β-lactones **4**, and the benzyl enol ethers **5** are described below and the results summarized in Tables 1–3, respectively.

General Preparation of α-Benzyloxy-β-hydroxy Acids (3):

A 50-ml, two-necked, round-bottomed flask, provided with a magnetic spinbar, a rubber septum and nitrogen inlet and outlet tubes, is flame-dried under a nitrogen atmosphere. The flask is charged with anhydrous tetrahydrofuran and the required amount of diisopropylamine to make a 1.0 molar solution. At −78° and while stirring magnetically the stoichiometric amount (equal to the quantity of the amine) of *n*-butyllithium in hexane is syringed slowly into the reaction flask. After warming up to room temperature and stirring for 10 min, the mixture is cooled to −78°. Half of the stoichiometric amount (one-fourth of the amount of amine) of the benzyloxyacetic acid (**1**) is added as a 1.0 molar solution in anhydrous tetrahydrofuran. After stirring at −78° for 30 min, an excess of the ketone or aldehyde electrophile (twice the amount of the acid) is added as a 3.0 molar solution in anhydrous tetrahydrofuran. The solution is stirred at 78° for 15 min to 12 h, poured on 2–3 volumes of crushed ice and transfered into a separatory funnel. After extraction with ether (2 × 15 ml) to remove neutral products, the aqueous layer is acidified with 20% hydrochloric acid to pH ~3 and extracted with ether (4 × 20 ml). The combined ether extracts are dried with magnesium sulfate and rota-evaporated (~30°/5–10 torr). The residue is recrystallized from the appropriate solvent. The yields, physical constants and spectral data are summarized in Table 1.

General Preparation of α-Benzyloxy-β-lactones (4):

The α-benzyloxy-β-hydroxy acid **3** (1 mmol) in anhydrous pyridine (10–20 ml) is placed into a 50 ml stoppered Erlenmeyer flask, cooled to 0°, and benzenesulfonyl chloride (2.5 mmol) is added. After storing overnight in the refrigerator, the mixture is poured onto 3–4 volumes of crushed ice and extracted with ether (4 × 15 ml). The combined ether extracts are washed with 10% sodium hydrogen carbonate (2 × 20 ml) and water (1 × 20 ml) and dried with magnesium sulfate. The solvent is rota-evaporated at 30°, first at 25 torr and finally at 1 torr. The residue is recrystallized from the appropriate solvent. When the β-lactone **4** failed to crystallize, it is purified by silica gel chromatography at ~ −20° [eluent: hexane/ether (1:1)]. The yields, physical constants, and spectral data are given in Table 2.

General Preparation of Benzyl Enol Ethers (5) via β-Lactone Decarboxylation:

The β-lactone (1.0 mmol) is placed into a 10-ml, one-necked, round-bottomed flask, provided with a magnetic spinbar and a gas outlet tube. After adding silica gel (2 g) and tetrachloromethane (10 ml) the mixture is stirred magnetically for 5 h at room temperature. The enol ether product, isolated by solvent rota-evaporation

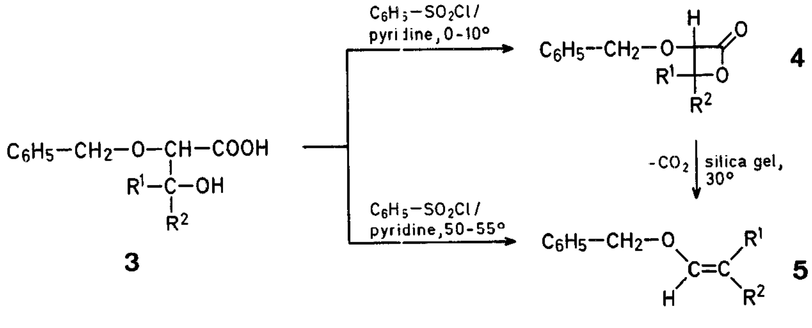


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Table 1. α-Benzyloxy-β-hydroxycarboxylic Acids **3**

Product	Yield [%]	m.p. (solvent)	Molecular formula[a]	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
3a	75	151–152° (dichloromethane/acetone)	$C_{16}H_{16}O_4$ (272.3)	3600–2400 (OH), 1715 (C=O)	7.45–7.05 (m, 2H, OH; 10H_{arom}); 4.9 (d, 1H, R^2); 4.4 (AB, 2H, CH_2O; $J=11$ Hz); 3.9 (d, 1H, CH)
3b	60	103–104° (hexane/ether)	$C_{14}H_{18}O_4$ (250.3)	3600–2500 (OH), 1720 (C=O)	7.15 (s, 2H, OH, 5H_{arom}); 4.45 (AB, 2H, CH_2O, $J=11$ Hz); 3.75 (s, 1H, CH); 1.7 [s, 8H, —$(CH_2)_4$—]
3c	53	155–156° (benzene/ether)	$C_{19}H_{24}O_4$ (316.4)	3580–2500 (OH), 1750 (C=O)	7.1 (s, 5H_{arom}); 6.25 (s, 2H, OH); 4.4 (AB, 2H, CH_2O, $J=11$ Hz); 4.3 (s, 1H, CH); 2.3–1.3 (m, 14H, R^1+R^2)
3d	50	61–63° (hexane/ether)	$C_{12}H_{16}O_4$ (224.3)	3600–2500 (OH), 1720 (C=O)	7.05 (s, 5H_{arom}); 6.2 (s, 2H, OH); 4.4 (AB, 2H, CH_2O, $J=11$ Hz); 3.55 (s, 1H, CH); 1.18 (s, 6H, R^1+R^2)
3e	32	168–169° (hexane/ethyl acetate)	$C_{22}H_{20}O_4$ (348.4)	3600–2400 (OH), 1720 (C=O)	7.6 (15H_{arom}); 6.4 (s, 2H, OH); 4.6 (s, 1H, CH); 4.4 (AB, 2H, CH_2O, $J=11$ Hz)

[a] The microanalyses showed the following maximum deviation from the calculated values: C, ±0.40; H, ±0.20. The mass spectra (70 eV) showed the appropriate M^+-H_2O and $M^+-H_2O-CO_2$ peaks.

Table 2. α-Benzyloxy-β-lactones **4**

Product	Yield [%]	m.p. (solvent)	Molecular formula[a]	I.R. (CCl_4) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]
4b	79	—[b]	$C_{14}H_{16}O_3$ (232.3)	1830 (C=O)	7.18 (s, 5H_{arom}); 4.65 (AB, 2H, CH_2O, $J=11$ Hz); 4.53 (s, 1H, CH); 2.1–1.5 [m, 8H, —$(CH_2)_4$—]
4c	90	83–84° (hexane/ether)	$C_{19}H_{22}O_3$ (298.4)	1830 (C=O)	7.2 (s, 5H_{arom}); 4.75 (AB, 2H, CH_2O, $J=11$ Hz); 4.2 (s, 1H, CH); 2.4–1.5 (m, 14H, R^1+R^2)
4d	84	40–41° (hexane/ether)	$C_{12}H_{14}O_3$ (206.2)	1830 (C=O)	7.12 (s, 5H_{arom}); 4.6 (AB, 2H, CH_2O, $J=11$ Hz); 4.3 (s, 1H, CH); 1.4 (s, 6H, R^1+R^2)

[a] The microanalyses showed the following maximum deviation from the calculated values: C, ±0.40; H, ±0.20. The mass spectra (70 eV) showed the appropriate M^+-CO_2 peaks.

[b] Purified by silica gel chromatography (~20°) eluent: hexane/ether (1:1).

Table 3. Enol Ethers **5**

Product	Yield [%]	b.p./torr (n_D^{20}) or m.p. (solvent)	Molecular formula[a]	I.R. (CCl_4) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]
5b	93	63–65°/0.05 (1.5356)	$C_{13}H_{16}O$ (188.3)	1685 ($>C=\overset{\vert}{C}-O$)	7.05 (s, 5H_{arom}); 5.9–5.7 (m, 1H, CH); 4.55 (s, 2H, CH_2O); 2.4–1.4 (m, 8H, R^1+R^2)
5c	90	130–140°/0.05[b] (1.5591)	$C_{18}H_{22}O$ (254.4)	1680 ($>C=\overset{\vert}{C}-O$)	7.05 (s, 5H_{arom}); 5.65 (s, 1H, CH); 4.5 (s, 2H, CH_2O); 2.1–1.4 (m, 14H, R^1+R^2)
5d	85	46–48°/0.05 (1.5120)	$C_{11}H_{14}O$ (162.2)	1685 ($>C=\overset{\vert}{C}-O$)	7.0 (s, 5H_{arom}); 5.6 (s, 1H, CH); 4.7 (s, 2H, CH_2O); 1.4, 1.5 (s, 3H, R^1, R^2)
5e	89	49.5–51° (hexane)	$C_{21}H_{18}O$ (286.4)	1670 ($>C=\overset{\vert}{C}-O$)	7.1 (s, 10H_{arom}); 6.95 (s, 5H_{arom}); 6.25 (s, 1H, CH); 4.75 (s, 2H, CH_2O):

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.40; H, ±0.20. The mass spectra (70 eV) showed the appropriate M^+ peaks.

[b] Molecular distillation bath temperature.

after removal the silica gel by filtration, is distilled at reduced pressure or recrystallized from the appropriate solvent. The reaction yields, physical constants, and spectral data are given in Table 3.

Direct Dehydrocarbonation of α-Benzyloxy-β-Hydroxy Acids (3): A 100-ml, one-necked, round-bottomed flask, provided with a spin-bar and condenser with a gas outlet tube which is protected with a $CaCl_2$ drying tube, is charged with the β-hydroxy-α-benzyloxycarboxylic acid **3** (2.0 mmol) in anhydrous pyridine (~15 ml). To this solution is added benzenesulfonyl chloride (5 mmol) and the mixture is stirred at 50–55° overnight. The dark mixture is poured onto 4–5 volumes of crushed ice and extracted with ether (2 × 15 ml). The combined ether extracts are washed with 10% hydrochloric acid (1 × 10 ml), then with saturated sodium hydrogen carbonate (1 × 10 ml), and finally with water (2 × 10 ml).

After drying over magnesium sulfate, the solvent is rota-evaporated at 30°/30 torr. The residue is purified by distillation at reduced pressure or recrystallized from the appropriate solvent. The yields are lower than via the β-lactone method.

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