

Titanocene(III)-promoted Reformatsky Additions

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Supporting Information

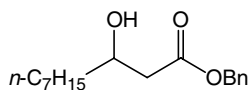
General

All reactions were performed in flame-dried glassware under an inert atmosphere of dry argon. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Unity 400 NMR (400 MHz for ^1H ; 100 MHz for ^{13}C) as solutions in CDCl_3 . Chemical shifts are given in ppm and are referenced to tetramethylsilane (0.00 ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), a (apparent) or br (broadened). Coupling constants, J , are reported in hertz. ^{13}C spectra are assigned with either a (+) or (-) symbol to indicate the orientation of the signal using an attached proton test (APT) pulse sequence. Signals with a (+) orientation have either zero or two attached protons; signals with a (-) signal have either one or three attached protons. Flash column chromatography was performed using 230-400 mesh silica gel (EM Science) and mixtures of ether and pentane or petroleum ether as eluant. Manganese powder, titanocene dichloride and all substrates are commercially available and used as received except for *n*-butyraldehyde and *iso*-butyraldehyde, which were distilled and stored under argon at -20 °C.

Cyclic Voltammetry

All voltammetric data was obtained on a Cypress Systems model CS-1090 potentiostat. The electrolytic mixture consisted of a 0.1 M solution of tetrabutylammonium tetrafluoroborate in freshly distilled and degassed tetrahydrofuran. The reference electrode consisted of a 0.01 M solution of silver nitrate immersed in acetonitrile. The working electrode was a glassy carbon electrode and the counter electrode was a platinum wire. The samples were run at a concentration of 5 mM at a scan rate of 100 mV/s. The data in Table 9 refers to the cathodic peak potential of the reduction observed in the voltammogram.

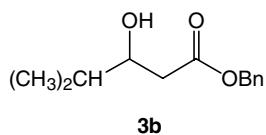
Optimized Procedure for Reformatsky addition:



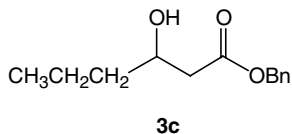
3a

Benzyl 3-hydroxynonanoate (3a). A flame-dried, 25 mL round bottom flask was charged with benzyl bromoacetate (158 μ L / 1.0 mmol), octanal (172 μ L / 1.1 mmol), manganese (220 mg / 4 mmol) and titanocene dichloride (550 mg / 2.2 mmol). The mixture was allowed to stir at ambient temperature for 30 minutes during which time the reaction color changed from red to dark green. At this point the reaction was shown to be complete by thin-layer chromatography. The reaction was quenched with 1 M potassium bisulfate (10 mL), diluted with 50 mL of water and extracted with ethyl ether (3 x 25 mL). The combined organic extracts were sequentially washed with aqueous sodium bicarbonate (30 mL), and brine (30 mL), dried (MgSO_4), filtered and concentrated. Column chromatography on silica gel eluting with 20 % ethyl ether/pentane afforded **3a**

as a colorless oil (217 mg / 78 %). ^1H NMR δ 0.88 (t, J = 7.1 Hz, 3 H), 1.26-1.34 (m, 12 H), 2.45 (dd, J = 9.0, 16.4 Hz, 1 H), 2.56 (dd, J = 3.1, 16.4 Hz, 1 H), 2.92 (br s, 1 H), 4.02 (m, 1 H), 5.15 (s, 2 H), 7.34-7.37 (m, 5 H); ^{13}C NMR δ 14.28 (-), 22.82 (+), 25.64 (+), 29.40 (+), 29.65 (+), 31.97 (+), 36.70 (+), 41.53 (+), 66.65 (+), 68.22 (-), 128.45 (-), 128.55 (-), 128.80 (-), 135.77 (+), 173.07 (+); IR (neat) 3464, 2926, 2856, 1725, 1455, 1163, 909, 732, 697; HRMS (EI) calculated for $\text{C}_{17}\text{H}_{26}\text{O}_3$ (M^+) 278.1882, found 278.1879.

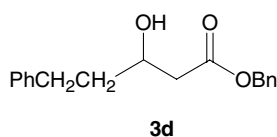


Benzyl 3-hydroxy-4-methylpentanoate (3b).ⁱ ^1H NMR δ 0.91 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 1.67-1.75 (m, 1 H), 2.46 (dd, J = 9.5, 16.3 Hz, 1 H), 2.58 (dd, J = 2.9, 16.3 Hz, 1 H), 2.86 (d, J = 4.0 Hz, 1 H), 3.78-3.84 (m, 1 H), 5.15 (s, 2 H), 7.33-7.43 (m, 5 H); ^{13}C NMR δ 17.93 (-), 18.53 (-), 33.35 (-), 38.71 (+), 66.73 (+), 72.89 (-), 128.48 (-), 128.57 (-), 128.81 (-), 135.77 (+), 173.48 (+).

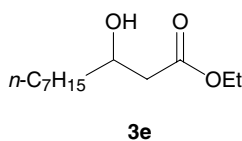


Benzyl 3-hydroxyhexanoate (3c).ⁱⁱ ^1H NMR δ 0.92 (t, J = 7.1 Hz, 3 H), 1.31-1.52 (m, 4 H), 2.45 (dd, J = 9.0, 16.5 Hz, 1 H), 2.55 (dd, J = 3.3, 16.5 Hz, 1 H), 2.95 (d, J = 4.0 Hz,

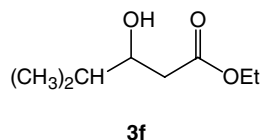
1 H), 4.01-4.06 (m, 1 H), 5.15 (s, 2 H), 7.31-7.39 (m, 5 H); ^{13}C NMR δ 14.14 (-), 18.83 (+), 38.80 (+), 41.54 (+), 66.65 (+), 67.90 (-), 128.44 (-), 128.55 (-), 128.74 (-), 135.74 (+), 173.05 (+).



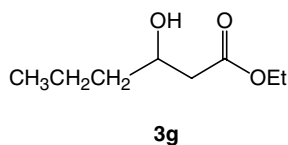
Benzyl 3-hydroxy-5-phenyl pentanoate (3d).ⁱⁱ ^1H NMR δ 1.72-1.81 (m, 1 H), 1.83-1.92 (m, 1 H), 2.52 (dd, $J = 8.2, 16.5$ Hz, 1 H), 2.59 (dd, $J = 4.0, 16.5$ Hz, 1 H), 2.72 (ddd, $J = 4.2, 6.9, 9.5$ Hz, 1 H), 2.85 (ddd, $J = 4.2, 5.5, 9.5$ Hz, 1 H), 3.12 (br s, 1 H), 4.10 (m, 1 H), 5.18 (s, 2 H), 7.20-7.41 (m, 10 H); ^{13}C NMR δ 31.77 (+), 38.14 (+), 41.41 (+), 66.57 (+), 67.24 (-), 125.93 (-), 128.32 (-), 128.45 (-), 128.49 (-), 128.67 (-), 135.54 (+), 141.71 (+), 172.78 (+).



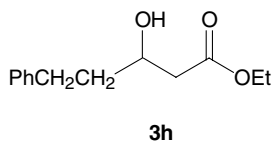
Ethyl 3-hydroxynonanoate (3e).ⁱⁱ ^1H NMR δ 0.88 (t, $J = 7.1$ Hz, 3 H), 1.24-1.58 (m, x H), 2.40 (dd, $J = 9.0, 16.3$ Hz, 1 H), 2.50 (dd, $J = 3.3, 16.3$ Hz, 1H), 3.10 (d, $J = 4.0$ Hz, 1 H), 3.99 (br m, 1 H), 4.17 (q, $J = 7.1$ Hz, 2 H); ^{13}C NMR δ 14.23 (-), 14.31 (-), 22.79 (+), 25.63 (+), 29.38 (+), 29.63 (+), 31.94 (+), 36.67 (+), 41.48 (+), 60.80 (+), 68.17 (-), 173.29 (+).



Ethyl 3-hydroxy-4-methylpentanoate (3f).ⁱⁱⁱ ^1H NMR δ 0.93 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.67-1.75 (m, 1 H), 2.40 (dd, J = 9.7, 16.3 Hz, 1 H), 2.50 (dd, J = 2.9, 16.3 Hz, 1 H), 2.95 (d, J = 2.9 Hz), 3.76- 3.80 (m, 1 H), 4.17 (q, J = 7.1 Hz, 2 H); ^{13}C NMR δ 14.07 (-), 17.65 (-), 18.27 (-), 33.11 (-), 38.47 (-), 60.59 (+), 72.63 (-), 173.41 (+).

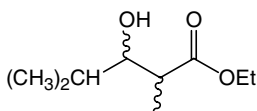


Ethyl 3-hydroxyhexanoate (3g).ⁱⁱ ^1H NMR δ 0.93 (t, J = 7.0 Hz, 3 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.35-1.58 (m, 4 H), 2.40 (dd, J = 9.0, 16.5 Hz, 1 H), 2.50 (dd, J = 3.3, 16.5 Hz, 1 H), 4.02 (br m, 1 H), 4.17 (q, J = 7.1 Hz, 2 H); ^{13}C NMR δ 14.08 (-), 14.28 (-), 18.81 (+), 38.77 (+), 41.51 (+), 60.81 (+), 67.90 (-), 173.28 (+).



Ethyl 3-hydroxy-5-phenylpentanoate (3h).^{iv} ^1H NMR δ 1.28 (t, J = 7.1 Hz, 3 H), 1.71-1.81 (m, 1 H), 1.82-1.91 (m, 1 H), 2.46 (dd, J = 8.2, 16.3 Hz, 1 H), 2.52 (dd, J = 3.9, 16.3 Hz, 1 H), 2.68-2.76 (m, 1 H), 2.81-2.88 (m, 1 H), 3.02 (dd, J = 1.4, 4.5 Hz, 1 H), 3.3 (br

s, 1 H), 4.01-4.08 (m, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 7.11-7.31 (m, 5 H); ^{13}C NMR δ 14.18 (-), 31.78 (+), 38.18 (+), 41.41 (+), 60.76 (+), 67.26 (-), 125.9 (-), 128.43 (-), 128.48 (-), 141.78 (+), 173.02 (+).



3i

Ethyl 3-hydroxy-2,4-dimethylpentanoate (3i). The stereochemistry of this reaction was determined by integration of the ^1H signal for the methine proton:^v *anti*-**3i** δ 3.36, *syn*-**3i** δ 3.56

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ⁱⁱ Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *J. Org. Chem.* **2001**, 65, 1702-1706.

ⁱⁱⁱ Kiyooka, S.; Shahid, K. A. *Bull. Chem. Soc. Jpn.* **2001**, 74, 1485-1495.

^{iv} Sumida, S.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, 122, 1310-1313.

^v Hena, M. A.; Terahuchi, S.; Kim, C-S.; Horiike, M.; Kiyooka, S. *Tetrahedron: Asymmetry* **1998**, 9, 1883-1890.