Catalytic, Asymmetric Feist-Benary Reactions

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Supporting Information

Starting Materials: 1,3-cyclohexadione, Proton Sponge®, ethyl bromopyruvate, TBABr, (DHQ)₂PYR, and (DHQD)₂PYR were purchased from Aldrich and used as received. 3-Bromo-2-ketoesters **6a-d** were prepared according to literature precedent.^{1,2,3} Dcinchona pyrimidine catalysts **4b-f**, and **5b-f** were prepared from the appropriate cinchona alkaloid and pyrimidinyl chloride, which were in turn prepared from commercially available carboxamidines and substituted malonates in accordance with the literature precedent.⁴

General procedure for formation of “interrupted” Feist-Benary product (3): 1,3-cyclohexadione (89 mg, 0.797 mmol), Proton Sponge® (171 mg, 0.797 mmol), and catalyst (0.0797 mmol) were dissolved in CH₂Cl₂ (8 mL) and cooled to –78 °C. Ethyl bromopyruvate (0.1 mL, 0.797 mmol) was then added dropwise, and the solution allowed to stir for 10 min at –78 °C. The reaction mixture was then concentrated and purified by flash chromatography on silica gel (CH₂Cl₂/MeOH, 100:1).

3-Hydroxy-4-oxo-hexahydrobenzofuran-3-carboxylic acid ethyl ester (3):

Enantiomers separated and quantified by analytical HPLC (Daicel Chiralpak ODH, 90:10 hexanes:*i*-propanol, 0.5 mL/min, 257 nm) $R_{t(R)} = 54$ min, $R_{t(S)} = 71$ min, data for (*R*)-isomer: $[\alpha]_D^{23} = +41.3$ (c 1.0, CH₂Cl₂); IR (neat) 3483, 2960, 1740, 1671 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.68 (d, J = 10.5 Hz, 1H), 4.46 (d, J = 10.5 Hz, 1H), 4.23 (q, J = 7.3 Hz, 3H), 4.07 (s, OH), 2.50 (t, J = 6.15 Hz, 2H), 2.29 (app. q, J = 4.4 Hz, 2H), 2.06-2.01 (m, 2H), 1.23 (t, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 194.0, 180.1, 173.5, 117.6, 88.7, 80.0, 63.2, 36.6, 24.3, 21.6, 14.2. Anal. Calcd. for C₁₁H₁₄O₅: C, 58.40; H, 6.24. Found: C, 58.53; H, 6.22.

General procedure for formation of substituted products (7a-d): 1,3-cyclohexadione (31 mg, 0.273 mmol), Proton Sponge® (59 mg, 0.273 mmol), TBABr (44 mg, 0.136 mmol), and catalyst **4c** (22 mg, 0.027 mmol) were in THF (2.7 mL) and cooled to –78 °C. The appropriate 3-bromo-2-ketoester **6** was then added dropwise and the reaction

¹ Okanya, J.; Hoffman, R.; Johnson, M.C. *J. Org. Chem.* **2002**, 67, 1102-1108.

² Coutrot, P.; Grison, C.; Tabyaoui, M.; Czernecki, S.; Valery, J. *J. Chem. Soc. Chem. Comm.* **1988**, 1515-1516.

³ Tsuboi, S.; Furutani, H.; Takeda, A.; Kawazoe, K.; Sato, S. *Bull. Chem. Soc. Japan.* **1987**, 60, 2475-9.

⁴ Bolm, C.; Gerlach, A.; Drauz, K.; Bommarius, A. U.S. Patent 6,180,551, 1998.

allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 10 min. The reaction mixture was then concentrated and purified by flash chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 100:1).

3-Hydroxy-2-methyl-4-oxo-hexahydrobenzofuran-3-carboxylic acid ethyl ester (7a):

Enantiomers separated and quantified by analytical HPLC (Daicel Chiralpak AD, 93:7 hexanes:*i*-propanol, 0.5 mL/min, 257 nm) $R_{\text{t}(2R,3R)} = 35\text{ min}$, $R_{\text{t}(2S,3S)} = 44\text{ min}$, data for (*R,R*)-isomer: $[\alpha]_{\text{D}}^{23} = +49.2$ (*c* 0.5, CH_2Cl_2); IR (neat) 3480, 2941, 1750 1634 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 4.89 (q, *J* = 6.6 Hz, 1H), 4.31-4.28 (m, 2H), 3.77 (s, OH), 2.51 (app. t, *J* = 6.6 Hz, 2H), 2.37-2.32 (m, 2H), 2.11-2.05 (m, 2H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 194.0, 180.1, 173.5, 117.6, 88.8, 80.0, 63.3, 36.6, 24.3, 21.6, 14.3, 13.6. Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_5$: C, 59.99; H, 6.71. Found: C, 59.53; H, 6.73.

3-Hydroxy-2-pentyl-4-oxo-hexahydrobenzofuran-3-carboxylic acid ethyl ester (7b):

Enantiomers separated and quantified by analytical HPLC (Daicel Chiralpak AD, 90:10 hexanes:*i*-propanol, 0.5 mL/min, 257 nm) $R_{\text{t}(2S,3S)} = 16\text{ min}$, $R_{\text{t}(2R,3R)} = 18\text{ min}$, data for (*R,R*)-isomer: $[\alpha]_{\text{D}}^{23} = +61.7$ (*c* 1.0, CH_2Cl_2); IR (neat) 3492, 2940, 1735, 1640 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 4.69 (t, *J* = 7.0 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.78 (s, OH), 2.50 (t, *J* = 6.6 Hz, 2H), 2.36-2.28 (m, 2H), 2.04 (app q, *J* = 6.1 Hz, 2H), 1.86-1.72 (m, 2H), 1.44-1.24 (m, 9H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 194.0, 180.0, 173.7, 117.9, 92.5, 79.8, 63.3, 36.6, 31.8, 28.1, 25.5, 24.3, 22.6, 21.6, 14.4, 14.2. Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{O}_5$: C, 64.84; H, 8.16. Found: C, 64.55; H, 8.17.

3-Hydroxy-2-isobutyl-4-oxo-hexahydrobenzofuran-3-carboxylic acid ethyl ester (7c):

Enantiomers separated and quantified by analytical HPLC (Daicel Chiralpak AD, 90:10 hexanes:*i*-propanol, 0.5 mL/min, 256 nm) $R_{\text{t}(2S,3S)} = 15\text{ min}$, $R_{\text{t}(2R,3R)} = 18\text{ min}$) data for (*R,R*)-isomer: $[\alpha]_{\text{D}}^{23} = +70.1$ (*c* 1.0, CH_2Cl_2); IR (neat) 3490, 2957, 2972, 1735, 1661, 1633 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 4.78 (t, *J* = 5.6 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.76 (s, OH), 2.50 (t, *J* = 6.5 Hz, 2H), 2.35-2.29 (m, 2H), 2.10-2.01 (m, 2H), 1.80-1.68 (m, 2H), 1.64-1.50 (m, 1H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 193.9, 180.0, 173.6, 117.8, 90.8, 80.0, 63.3, 36.7, 36.6, 25.0, 24.3, 23.0, 22.6, 21.6, 14.4. Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_5$: C, 63.81; H, 7.85. Found: C, 64.05; H, 7.97.

3-Hydroxy-2-phenyl -4-oxo-hexahydrobenzofuran-3-carboxylic acid ethyl ester (7d):

Enantiomers separated and quantified by analytical HPLC (Daicel Chiralpak AD, 90:10 hexanes:*i*-propanol, 0.5 mL/min, 259 nm) $R_{\text{t}(2S,3S)} = 20\text{ min}$, $R_{\text{t}(2R,3R)} = 27\text{ min}$, data for (*R,R*)-isomer: $[\alpha]_{\text{D}}^{23} = +37.0$ (*c* 1.0, CH_2Cl_2); IR (neat) 3484, 2932, 1744, 1652 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.39-7.36 (m, 3H), 7.30-7.20 (m, 2H), 5.78(s, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.39 (s, OH), 2.66 (q, *J* = 6.2 Hz, 2H), 2.45-2.38 (m, 2H), 2.24-2.12 (m, 2H), 1.35 (t, *J* = 7.5, 3H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 193.9, 180.3, 173.0, 132.7, 129.2, 128.6, 127.3, 117.7, 93.2, 80.8, 63.5, 36.7, 24.3, 21.6, 14.4. Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{O}_5$: C, 67.54; H, 6.00. Found: C, 67.70; H, 6.10.

The absolute and relative stereochemistry for compounds **3** and **7a-d** were assigned via an X-ray crystal structure analysis, including anomalous dispersion, of the following *p*-bromobenzyl ester. This compound was prepared using the procedure described for **7a-d**.