Catalytic, Asymmetric Preparation of Ketene Dimers from Acid Chlorides

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Supporting Information

General Experimental Procedure: For general experimental procedures, see previously cited work.[1]

General procedure for *In Situ* Ketene Formation and Dimerization: To TMSQN (0.25 mmol) in anhydrous CH_2Cl_2 (solvent volume) under argon was added Hünig's base (5.0 mmol), followed by the appropriate acid chloride (5.0 mmol). After stirring for Time A at room temperature, HN(OMe)Me (0.18 mL, 0.15 g, 2.5 mmol) and hydroxypyridine (0.024 g, 0.25 mmol) were added to the reaction mixture. The mixture was then stirred for Time B at room temperature, after which pH 7 buffer solution concentrate (10 mL) was added. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (4×50 mL). The combined organic layers were dried (Na_2SO_4), concentrated *in vacuo*, and the residue purified by flash chromatography on silica gel (EtOAc/hexanes).

General Procedure for Filtering Dimer Prior to Opening: Following Time A, the mixture was diluted with pentane (50 mL) and filtered through silica gel (2 g in a 2 cm flash chromatography column) at a flow rate of 100 mL/min. The silica gel was then washed with a 1:1 CH_2Cl_2:pentane mixture (100 mL) or until the yellow band reached the bottom of the column. To the resulting filtrate was added HN(OMe)Me (0.18 mL, 0.15 g, 2.5 mmol) and hydroxypyridine (0.024 g, 0.25 mmol). The mixture was stirred for Time B, after which pH 7 buffer solution concentrate (10 mL) was added. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (4×50 mL). The combined organic layers were dried (Na_2SO_4), concentrated *in vacuo*, and the residue purified by flash chromatography on silica gel (EtOAc/hexanes).

(S)-2-Methyl-3-oxo-pentanoic acid methoxy-methyl-amide, 2: Acid chloride = propionyl chloride, solvent volume = 50 mL, Time A = 6 h, Time B = 2 h, yield = 0.137 g, 79 %. This compound was previously characterized.[2] HPLC analysis (Daicel Chiralpak OD-H, 98:2 hexanes:*i*-propanol, 0.5 mL/min, 254 nm) showed a 97:3 mixture of enantiomers ($R_{t\ (R)}$ = 23.18 min, $R_{t\ (S)}$ = 25.41 min).

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[1] Calter, M. A.; Liao, W.; Struss, J. A. *J. Org. Chem.* **2001**, *66*, 7500-7504.

[2] Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308-5309.

(S)-2-Ethyl-3-oxo-hexanoic acid methoxy-methyl-amide (4a). Acid chloride = butyryl chloride, solvent volume = 50 mL, Time A = 6 h, Time B = 2 h, yield = 0.3423 g, 68 %. HPLC analysis (Daicel Chiralpak OD-H, 99:1 hexanes:*i*-propanol, 0.5 mL/min, 254 nm) of the purified compound showed a 96:4 mixture of enantiomers ($R_{t\,(S)}$ = 15.11 min; $R_{t\,(R)}$ = 16.45): $[\alpha]_D^{23}$ = -13.7° (*c* 1.00, $CHCl_3$); IR (neat film) 2964.2, 1716.7, 1663.3 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.69 (3H, s), 3.63 (app t, J = 3.2 Hz, 1H), 3.22 (s, 3H), 2.48-2.43 (m, 2H), 1.95 (app dp, J = 7.2, 14.6 Hz, 1H), 1.83 (app dp, J = 7.0, 14.1 Hz, 1H), 1.61 (app sextet, J = 7.3 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.6, 170.8, 61.1, 57.4, 42.5, 32.2, 21.4, 16.6, 13.4, 12.1. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found C, 59.90; H, 9.63; N, 7.14.

(S)-2-Isopropyl-5-methyl-3-oxo-hexanoic acid methoxy-methyl-amide (4b). Acid chloride = *iso*-valeryl chloride, solvent volume = 10 mL, Time A = 1 d, Time B = 1 d, yield = 0.3728 g, 65 %: $[\alpha]_D^{23}$ = -11.0° (*c* 1.00, $CHCl_3$); IR (neat film) 2959, 1717.2, 1658.9 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.70 (s, 3H), 3.55 (d, J = 9.9 Hz, 1H), 3.21 (s, 3H), 2.49-2.43 (m, 2H), 2.35 (dd, J = 6.58, 17.7 Hz), 2.15 (app septet, J = 6.62 Hz, 1H), 1.01-0.88 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.1, 170.0, 63.8, 61.2, 49.6, 32.2, 28.5, 23.5, 22.3, 22.2, 20.8, 20.3. Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found C, 62.86; H, 10.03; N, 6.38.

Optical Purity Assay for 4b. β-Ketoamide **4b** was reduced to the corresponding anti-β-hydroxyamide with potassium triethylborohydride using the conditions given for **2**.[2] The alcohol was then acylated by treatment with benzoyl chloride, pyridine, and DMAP for 4 d in CH_2Cl_2. HPLC analysis (Daicel Chiralpak OD-H, 99.9:0.01 hexanes:*i*-propanol, 0.2 mL/min, 254 nm) of the purified compound showed a 98:2 mixture of enantiomers ($R_{t\,(S)}$ = 27.21 min; $R_{t\,(R)}$ = 28.79.

(S)-2-*tert*-butyl-5,5-dimethyl-3-oxo-hexanoic acid methoxy-methyl-amide (4c). Acid chloride = *t*-butylacetyl chloride, solvent volume = 10 mL, Time A = 4 d, Time B = 2 d, yield = 0.3735 g, 58 %. HPLC analysis (Daicel Chiralpak OD-H, 99.99:0.01 hexanes:*i*-propanol, 0.5 mL/min, 254 nm) of the purified compound showed a 96:4 mixture of enantiomers ($R_{t\,(S)}$ = 17.45 min; $R_{t\,(R)}$ = 18.49): $[\alpha]_D^{23}$ = +11.4 (*c* 1.00, $CHCl_3$); IR (neat film) 2954, 1707.4, 1671.6 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.71 (s, 3H), 3.66 (s, 1H), 3.20 (s, 3H), 2.43 (d, J = 17.1 Hz, 1H), 2.35 (d, J = 17.0 Hz, 1H), 1.08 (s, 9H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.4, 170.5, 64.0, 61.0, 54.5, 34.7, 32.2, 30.7, 29.3, 28.3. Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.57; N, 5.44. Found C, 65.52; H, 10.72; N, 5.36.

(S)-3-Oxo-5-triisopropylsilanyloxy-2-triisopropylsilanyloxymethyl-pentanoic acid methoxy-methyl-amide (4d). Acid chloride = 3-(triisopropylsiloxy)propionyl chloride, solvent volume = 50 mL, Time A = 3 h, Time B = 2 h, yield = 0.1140 g, 88 %. HPLC analysis (Daicel Chiralpak OD-H, 99:1 hexanes:*i*-propanol, 0.5 mL/min, 254 nm) of the purified compound showed a 95.5:4.5 mixture of enantiomers ($R_{t\,(S)}$ = 9.72 min; $R_{t\,(R)}$ =

10.43): $[\alpha]_D^{23}$ = +3.2 (*c* 1.00, $CHCl_3$); IR (neat) 2942.3, 2890.7, 2866.1, 1720.8, 1666.7 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.19-4.11 (m, 3H), 3.97 (t, J = 6.9 Hz, 2H), 3.72 (s, 3H), 3.21 (s, 3H), 2.92 (dt, J = 7.0, 17.2 Hz, 1H), 2.78 (dt, J = 6.6, 17.2 Hz, 2H), 1.20-0.99 (m, 42H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.9, 169.0, 62.3, 61.3, 58.52, 58.46, 45.8, 32.2, 17.9, 17.86, 11.84, 11.78. Anal. Calcd for $C_{14}H_{27}NO_3$: C, 60.30; H, 10.70; N, 2.70. Found C, 60.19; H, 10.83; N, 2.62.

(S)-3-(Methoxy-methyl-carbamoyl)-4-oxo-heptanedioic dimethyl ester (4e). Acid chloride = 3-chlorocarbonyl-propionic acid methyl ester,[3] solvent volume = 50 mL, Time A = 3 h, Time B = 2 h, yield = 0.0973 g, 64 %. HPLC analysis (Daicel Chiralpak OD-H, 82:18 hexanes:*i*-propanol, 0.5 mL/min, 280 nm) of the purified compound showed a 96:4 mixture of enantiomers ($R_{t\,(S)}$ = 38.79 min; $R_{t\,(R)}$ = 42.39): $[\alpha]_D^{23}$ = -17.5° (*c* 1.00, $CHCl_3$); IR (neat) 2954, 1742, 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.32 (dd, J = 5.4, 8.5 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 3.24 (s, 3H), 2.98 (dd, J = 9, 17.4 Hz, 1H), 2.91-2.75 (m, 3H), 2.66-2.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.2, 172.6, 171.9, 168.9, 61.1, 51.8, 51.6, 51.1, 35.7, 32.3, 31.8, 27.3. Anal. Calcd for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84. Found C, 49.71; H, 6.73; N, 4.82.

[3] Ku, T. W.; McCarthy, M.E.; Weichman, B.M.; Gleason, J.G. *J. Med. Chem.* **1985**, *28*, 1847-1853.