A Highly Enantioselective Intramolecular Stetter Reaction

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Supporting Information

General Methods. All reaction were carried out under and atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Xylenes was distilled from CaH₂ and stored under argon. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, or KMnO₄ followed by heating.

Substrates **6**, **10-16**, **25** and **27** were prepared by known literature methods.^{1,2,3} Catalysts **7a-e**, **9a-b**, and **24** were prepared by literature methods.⁴ KHMDS was purchased from Aldrich Chemical Co. as a 0.5 M solution in toluene and used without purification. Racemic material was prepared either by stirring enantioenriched product in THF and aluminum oxide for 1 hour or by the method of Ciganek.¹ Absolute configuration of **8**, **17**, **18**, and **19** has been assigned based on comparison with literature values.⁵ The others were assigned by analogy.

Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ¹H NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ , ppm) from an internal standard tetramethylsilane (TMS) or deuterated chloroform (CDCl₃), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ¹³C NMR were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from (CDCl₃) taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Analytical high performance liquid chromatography (HPLC) was performed on a Dynamax model SD-200 HPLC equipped with a Dynamax model UV-1 variable wavelength UV detector using a Chiracel OD-H and AD (0.46 cm X 25 cm) chiral columns. Gas chromatography was performed on a Varian Cp 3800 gas chromatograph equipped with a flame ionization

¹ Ciganek, E. *Synthesis* **1995**, 1311.

² Bjornestedt, R.; Zhong, G.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 11720.

³ Claus, R. E.; Schreiber, S. L. *Organic Syntheses*, **1986**, *64*, 150.

⁴ Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1891.

⁵ Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta.* **1996**, *79*, 1899.

detector using a Chiraldex B-DM capillary gas chromatography column. Optical rotations were measured on an Autopol III automatic polarimeter in a 1 dm cell.

General procedure for the asymmetric intramolecular Stetter reaction: A flame-dried round bottom flask was charged with triazolium salt (0.2 eq) and 2 ml xylenes. To this solution was added KHMDS (0.5M in toluene) (0.2 eq.) via syringe and the solution was stirred at ambient temperature for 15 minutes. Substrate (1 eq.) was added and allowed to stir for 24 h at ambient temperature. The reaction was then poured into a column of silica gel and eluted with a suitable solution of ethyl acetate in hexanes (typically 1:6). Evaporation of solvent afforded analytically pure product.

(R)-(4-Oxo-chroman-3-yl)-acetic acid ethyl ester (8): According to the general procedure, 5.0 mg (0.012 mmol) of **9b** in 2 mL of xylenes was treated with 0.024 mL (0.012 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 14.0 mg (0.06 mmol) of **6** in 1 mL xylenes was added via syringe. Upon work-up 13.2 mg (94%) of desired ester was isolated as a colorless oil. Spectral data matched literature description.¹ $[\alpha]_D^{23} = -10^\circ$ (CH_2Cl_2); HPLC analysis - Chiracel AD column, 97:3 hexanes to isopropanol 0.5 ml/min. Major: 30.2 minutes, minor: 40.2 minutes.

(R)-(6-Methyl-4-oxo-chroman-3-yl)-acetic acid ethyl ester (17): According to the general procedure, 2.5 mg (0.006 mmol) of **9b** in 2 mL of xylenes was treated with 0.012 mL (0.012 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 15 mg (0.06 mmol) of **10** in 1 mL xylenes was added via syringe. Upon work-up 12.0 mg (80%) of desired ester was isolated as a colorless oil. Spectral data matched literature description.¹ $[\alpha]_D^{23} = -11^\circ$ (CH_2Cl_2); HPLC analysis - Chiracel AD column, 97:3 hexanes to isopropanol 0.5 ml/min. Major: 25.7 minutes, minor: 39.2 minutes.

(R)-(8-Methyl-4-oxo-chroman-3-yl)-acetic acid ethyl ester (18): According to the general procedure, 5.0 mg (0.012 mmol) of **9b** in 2 mL of xylenes was treated with 0.024 mL (0.012 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 15.0 mg (0.06 mmol) of **11** in 1 mL xylenes was added via syringe. Upon work-up 13.5 mg (90%) of desired ester was isolated as a colorless oil. Spectral data matched literature description.¹ $[\alpha]_D^{23} = -13^\circ$ (CH_2Cl_2); HPLC analysis - Chiracel AD column, 97:3 hexanes to isopropanol 0.5 ml/min. Major: 19.4 minutes, minor: 25.1 minutes.

(R)-(8-Methoxy-4-oxo-chroman-3-yl)-acetic acid ethyl ester (19): According to the general procedure, 2.5 mg (0.006 mmol) of **9b** in 2 mL of xylenes was treated with 0.012 mL (0.006 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 16.0 mg (0.06 mmol) of **12** in 1 mL xylenes was added via syringe. Upon work-up 15.0 mg (95%) of desired ester was isolated as a colorless oil. Spectral data matched literature description.¹ $[\alpha]_D^{23} = -15^\circ$ (CH_2Cl_2); HPLC analysis - Chiracel AD column, 97:3 hexanes to isopropanol 1.0 ml/min. Major: 27.8 minutes, minor: 42.2 minutes.

(S)-(4-Oxo-thiochroman-3-yl)-acetic acid methyl ester (20):

According to the general procedure, 5.0 mg (0.012 mmol) of **9b** in 2 mL of xylenes was treated with 0.024 mL (0.012 mmol) of KHMDS (0.5 M in toluene) and allowed to stir at ambient temperature for 15 min, to which was added 14.0 mg (0.06 mmol) of **13** in 1 mL xylenes via syringe. Upon work-up 9.0 mg (63%) of desired ester was isolated as a colorless oil: R_f (3:1 hexanes to ethyl acetate) = 0.42; $[\alpha]_D^{23} = -107.5^\circ$ (CH_2Cl_2); HPLC analysis - Chiracel AD column, 97:3 hexanes to isopropanol 0.5 ml/min. Major: 28.9 minutes, minor: 33.5 minutes; ^1H NMR (300 MHz, CDCl_3) δ 8.08 (dd, 1H, $J = 8.0, 1.4$ Hz), 7.83 (ddd, 1H, $J = 8.1, 7.1, 1.8$ Hz), 7.14 - 7.27 (m, 2H), 3.73 (s, 3H), 3.37 (ddd, 1H, $J = 9.0, 4.8, 2.0$ Hz), 3.34 (dd, 1H, $J = 12.8, 12.8$ Hz), 3.11 (m, 1H), 2.99 (dd, 1H, $J = 16.8, 5.2$ Hz), 2.59 (dd, 1H, $J = 16.6, 6.8$ Hz); ^{13}C NMR (300 MHz, CDCl_3) δ 194.3, 172.0, 141.6, 133.2, 130.4, 129.6, 127.3, 124.9, 52.0, 44.6, 34.1, 31.0; IR (NaCl) 2916, 1732, 1674, 1587, 1435, 1167 cm^{-1} ; HRMS (FAB+) calcd for $\text{C}_{12}\text{H}_{12}\text{O}_3\text{S}$, 237.0585. Found 237.0585.

(R)-(1-Methyl-4-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid ethyl ester (21):

According to the general procedure, 5.0 mg (0.012 mmol) of **9b** in 2 mL of xylenes was treated with 0.024 mL (0.012 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 14.0 mg (0.06 mmol) of **14** in 1 mL xylenes was added via syringe. Upon work-up 9.0 mg (64%) of desired ester was isolated as a light yellow oil; R_f (3:1 hexanes to ethyl acetate) = 0.25; $[\alpha]_D^{23} = -46.6^\circ$ (CH_2Cl_2); HPLC analysis - Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 ml/min. Major: 29.6 minutes, minor: 38.7 minutes; ^1H NMR (300 MHz, CDCl_3) δ 7.90 (dd, 1H, $J = 7.9, 1.6$ Hz), 7.41 (ddd, 1H, $J = 8.6, 7.1, 1.7$ Hz), 6.69-6.79 (m, 2H), 3.73 (s, 3H), 3.50 (dd, 1H, $J = 11.4, 5.4$ Hz), 3.33 (dd, 1H, $J = 12.2, 12.2$ Hz), 3.22 (m, 1H), 3.03 (dd, 1H, $J = 16.4, 4.86$ Hz), 3.00 (s, 3H), 2.36 (dd, 1H, $J = 14.4, 8.5$ Hz); ^{13}C NMR (400 MHz, CDCl_3) δ 194.1, 172.8, 135.5, 129.7, 129.0, 128.6, 117.4, 113.3, 56.0, 52.1, 43.3, 39.5, 31.8; IR (NaCl, CH_2Cl_2) 2953, 1738, 1674, 1605, 1498, 1342, 754 cm^{-1} ; HRMS (FAB+) calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_3$, 234.1130. Found 234.1123.

(R)-4-(3-Methoxycarbonylmethyl-4-oxo-3,4-dihydro-2H-quinolin-1-yl)-but-2-enoic acid methyl ester (22):

According to the general procedure, 5.0 mg (0.012 mmol) of **9b** in 2 mL of xylenes was treated with 0.024 mL (0.012 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 19.0 mg (0.06 mmol) of **15** in 1 mL xylenes was added via syringe. Upon work-up 13.7 mg (72%) of desired ester was isolated as a light yellow oil; R_f (3:1 hexanes to ethyl acetate) = 0.12; $[\alpha]_D^{23} = -20.8^\circ$ (CH_2Cl_2); HPLC analysis - Chiracel AD column, 90:10 hexanes to isopropanol 0.5 ml/min. Minor: 42.3 minutes, major: 45.7 minutes; ^1H NMR (300 MHz, CDCl_3) δ 7.91 (dd, 1H, $J = 8.2, 1.6$ Hz), 7.37 (ddd, 1H, $J = 8.5, 6.8, 1.5$ Hz), 6.92 (ddd, 1H, $J = 15.8, 15.8, 4.9$ Hz), 6.77 (ddd, 1H, $J = 8.1, 8.1, 0.7$ Hz), 6.60 (d, 1H, $J = 8.7$ Hz), 5.98 (ddd, 1H, $J = 15.7, 15.7, 1.86$ Hz), 4.16 (ddd, 1H, $J = 18.2, 4.2, 1.7$ Hz), 4.14 (ddd, 1H, $J = 18.1, 4.1, 1.8$ Hz), 3.72 (s, 6H), 3.52 (dd, 1H, $J = 11.8, 6.5$), 3.48 (dd, 1H, $J = 18.2, 11.8$ Hz), 3.23 (m, 1H), 3.02 (dd, 1H, $J = 16.8, 4.8$ Hz), 2.36 (dd, 1H, $J = 16.9, 8.1$ Hz); ^{13}C NMR (400 MHz, CDCl_3) δ 193.4, 172.4, 166.2, 142.3, 135.6, 128.7, 127.9, 122.7, 119.2,

117.7, 113.1, 53.9, 52.4, 51.9, 51.7, 42.8, 31.5; IR (NaCl) 2953, 1728, 1674, 1605, 1497, 1173, 754 cm^{-1} ; HRMS (FAB+) calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_5$, 318.1341. Found 318.1340.

(R)-(1-Oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid ethyl ester (23): According to the general procedure, 5.0 mg (1.2 mmol) of **24** in 2 mL of xylenes was treated with 0.024 mL (0.012 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 14.0 mg (0.06 mmol) of **16** in 1 mL xylenes was added via syringe. Upon work-up 12.5 mg (90%) of desired ester was isolated as a colorless oil; R_f (3:1 hexanes to ethyl acetate) = 0.47; $[\alpha]_D^{23} = +15.5^\circ$ (CH_2Cl_2); HPLC analysis - Chiracel AD column, 97:3 hexanes to isopropanol 0.5 ml/min. Minor: 21.6 minutes, major: 23.7 minutes; ^1H NMR (300 MHz, CDCl_3) δ 8.02 (dd, 1H, $J = 8.1, 1.2$ Hz), 7.46 (ddd, 1H, $J = 7.5, 7.5, 1.5$ Hz), 7.21 - 7.33 (m, 2H), 4.18 (q, 2H, $J = 6.5$ Hz), 2.93 - 3.19 (m, 4H), 2.42 (dd, 1H, $J = 18.3, 8.8$ Hz), 2.25 (dddd, 1H, $J = 3.0, 4.4, 4.4, 12.6$ Hz), 1.97 (m, 1H), 1.28 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (300 MHz, CDCl_3) δ 198.4, 172.7, 133.6, 129.0, 129.0, 128.9, 127.8, 126.8, 60.9, 45.2, 45.1, 35.5, 29.6, 14.6; IR (NaCl) 2983, 1730, 1678, 1599, 1161, 762 cm^{-1} ; HRMS (FAB+) calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$, 233.1178. Found 233.1167.

(R)-(2-Oxo-cyclopentyl)-acetic acid ethyl ester (28): According to the general procedure, 5 mg (0.013 mmol) of **24** in 2 mL of xylenes was treated with 0.026 mL (0.013 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 10.0 mg (0.065 mmol) of **27** in 1 mL xylenes was added via syringe. Upon work-up 9.0 mg (90%) of desired ester was isolated as a colorless oil: $[\alpha]_D^{23} = -65^\circ$ (CH_2Cl_2); Gas chromatography analysis - B-DM column with constant 110 $^\circ\text{C}$ oven temperature. Major: 19.6 minutes, minor: 20.5 min.

Spectral Data for **20**:

Spectral Data for **21**:

Spectral Data for **22**:

Spectral Data for **23**: