Isoxazole→Benzisoxazole Rearrangement Promoted Cascade Reactions Affording Stereodefined Polycycles

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Supporting Information

General Methods. All reaction utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry N₂. DME was distilled from Na and stored over 4 Å MS. Commercially available anhydrous, stabilizer-free THF (Kanto No. 41001) and Et₂O (Kanto No. 14547-95) were used without further purification. Diisopropylamine (DIPA) and triethylamine (NEt₃) were distilled from KOH and stored over 4 Å MS. Alkyl lithium reagents were purchased as solutions in hexane and tritrated with diphenylacetic acid (DPAA). Other reagents were used without further purification. Thin layer chromatography (TLC) was performed on Merck precoated plates (silica gel 60 F₂₅₄, Art 5715, 0.25 mm) and were visualized by fluorescence quenching under UV light or by staining with phosphomolybdic acid. Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates prepared from Merck Kieselgel 60 PF₂₅₄ (Art 7747). Column chromatography was performed on E. Merck Silica Gel 60 (230–400 Mesh) using a forced flow of 0.5–1.0 bar. Melting point (mp) determinations were performed by using a Yanaco MP-S3 instrument and are uncorrected. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) were measured on a JEOL JMN Lambda-400 spectrometer. Chemical shifts are expressed in parts per million (PPM) downfield from internal tetramethylsilane (δ = 0) and coupling constants are reported in hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on a Jasco IRA-202 spectrometer and are reported as wavenumbers (cm⁻¹).

Benzisoxazole 4. To **1** (473 mg, 1.50 mmol, 1.00 equiv) in 40 mL DME at $-78\text{ }^{\circ}\text{C}$ was added LDA (0.5 M in THF/Hexane, 6.0 mL, 3.0 mmol, 2.0 equiv) dropwise over 5 min. The resulting bright yellow solution was stirred 45 min at $-78\text{ }^{\circ}\text{C}$ before a solution of **3** (224 μL , 1.65 mmol, 1.10 equiv) was added in 100 mL DME. The mixture was warmed to $55\text{ }^{\circ}\text{C}$ and stirred 48 h. After cooling to rt, the reaction was quenched by addition of sat. aq. NH_4Cl (10 mL), diluted with H_2O (30 mL), and extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine (30 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. Flash chromatography on silica gel (3:1 hexanes/EtOAc) provided **4** (214 mg, 38% yield) as an off white foam.

^1H NMR (CDCl_3 , 400 MHz) δ 7.58–7.48 (m, 3 H), 7.26 (dt, 1 H, $J = 7.0, 1.0$), 5.04 (d, 1 H, $J = 0.7$), 5.00 (b d, 1 H, $J = 8.7$), 4.92 (s, 1 H), 4.39–4.26 (m, 2 H), 3.18 (dd, 1 H, $J = 12.6, 5.1$), 2.65–2.62 (m, 2 H), 2.57–2.47 (m, 1 H), 1.86 (dd, 1 H, $J = 12.6, 11.0$), 1.69 (s, 3 H), 1.34 (t, 3 H, $J = 7.1$), 1.16 (d, 3 H, $J = 6.6$)

^{13}C NMR (CDCl_3 , 100 MHz) δ 195.0, 177.0, 168.6, 163.0, 151.2, 140.7, 129.4, 123.1, 123.0, 122.2, 114.1, 109.8, 103.8, 88.0, 62.8, 59.8, 41.9, 39.2, 37.4, 17.4, 17.0, 14.3

IR (thin film) ν 2974, 1728, 1652, 1507, 1385, 1223, 1199, 1028, 753

EI-MS 381 m/z

Anal. calc'd for $\text{C}_{22}\text{H}_{23}\text{NO}_5$: C, 69.28; H, 6.08, N, 3.67; found C, 69.07, H, 5.76, N, 3.32

Olefin 8 . To **1** (47.2 mg, 0.150 mmol, 1.00 equiv) in 5 mL DME at $-78\text{ }^{\circ}\text{C}$ was added LDA (0.25 M in THF/Hexane, 1.2 mL, 0.30 mmol, 2.00 equiv) dropwise over 5 min. The resulting bright yellow solution was stirred 45 min at $-78\text{ }^{\circ}\text{C}$ before a solution of **7** (224 μL , 32.0 mg, 1.10 equiv) in 10 mL DME was added. The mixture was warmed to $50\text{ }^{\circ}\text{C}$ and stirred 48 h. After cooling to rt, the reaction was quenched by addition of sat. aq. NH_4Cl (5 mL), diluted with H_2O (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (20 mL), dried over Na_2SO_4 , and

concentrated under reduced pressure. Purification by preparative thin layer chromatography afforded **8** (24.7 mg, 45%.yield) as a pale oil.

¹H NMR (CDCl₃, 400 MHz) δ 7.58 (d, 1 H, J = 9.4), 7.53–7.50 (m, 2 H), 7.28–7.26 (m, 1 H), 5.84 (ddd, 1 H, J = 17.1, 8.6, 10.4), 5.38 (d, 1 H, J = 17.1), 5.28 (d, 1 H, J = 10.4), 5.08–5.02 (m, 1 H), 4.41–4.24 (m, 2 H), 3.21 (dd, 1 H, J = 12.5, 4.7), 2.65–2.62 (m, 2 H), 2.58–2.49 (m, 1 H), 1.81 (dd, 1 H, J = 12.5, 11.1), 1.34 (t, 3 H, J = 7.1), 1.17 (d, 3 H, J = 6.5)

¹³C NMR (CDCl₃, 100 MHz) δ 195.0, 176.9, 168.5, 163.0, 151.2, 134.1, 129.4, 123.2, 123.0, 122.1, 120.1, 109.8, 103.8, 86.5, 62.8, 59.9, 41.8, 40.5, 37.4, 17.0, 14.3

IR (thin film) δ 3540 (OH), 2925, 2855, 1730, 1654, 1378, 1222, 1197, 1022

Anal. calc'd for C₂₁H₂₁NO₅: C, 68.65; H, 5.76, N, 3.81; found C, 68.35, H, 5.73, N, 3.51.

Allene 10. To **1** (47.2 mg, 0.150 mmol, 1.00 equiv) in 5 mL DME at –78 °C was added LDA (0.25 M in THF/Hexane, 1.2 mL, 0.30 mmol, 2.0 equiv) dropwise over 5 min. The resulting bright yellow solution was stirred 20 min at –78 °C before a solution of **9** (224 μ L, 0.210 mmol, 1.10 equiv) was added in 15 mL DME. The mixture was warmed to 55 °C and stirred 12 h. After cooling to rt, the reaction was quenched by addition of sat. aq. NH₄Cl (5 mL), diluted with H₂O (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. TLC shows formation of one major, unstable product. Purification by preparative thin layer chromatography resulted in significant decomposition, however spectroscopically pure **9** (18.1 mg, 38%.yield) could be readily obtained.

¹H NMR (CDCl₃, 400 MHz) δ 7.76–7.74 (m, 1 H), 7.21–7.07 (m, 1 H), 7.00–6.93 (m, 2 H), 5.04 (dd, 2 H, J = 5.5, 1.6), 3.76–3.62 (m, 2 H), 3.38 (td, 1 H, J = 14.7, 1.6), 2.47–2.32 (m, 2 H), 2.11 (td, 1 H, J = 14.7, 5.8), 1.62–1.55 (m, 1 H), 0.71 (t, 3 H, J = 7.0), 0.67 (d, 3 H, J = 6.7)

¹³C NMR (100 MHz, CDCl₃) δ 195.3, 103.6, 173.8, 168.2, 163.8, 151.5, 131.1, 129.5, 123.2, 123.2, 123.1, 110.1, 106.4, 93.0, 62.6, 58.3, 42.2, 36.9, 36.1, 16.6, 13.9

Vinylogous Amide 19. A suspension of **4** (19 mg, 0.050 mmol) and Mo(CO)₆ (53 mg, 0.20 mmol, 4.0 equiv) in 4 ml CH₃CN and 1 ml H₂O was degassed by purging with argon under sonication. The clear suspension was warmed to 80 °C under N₂ and maintained at this temperature for 7 h. After cooling to rt, the reaction mixture was absorbed onto silica gel (2 g) and dried in the air for 12 h. Elution with EtOAc was followed by purification by preparative thin layer chromatography to afford **19** (15.2 mg, 80% yield) as a yellow oil.

¹H NMR (CDCl₃, 400 MHz) δ 10.61-10.39 (br s, 1 H), 7.47 (dd, 1 H, *J* = 7.8, 1.4), 7.41-7.37 (m, 1 H), 7.08 (dt, 1 H, *J* = 7.8, 1.2), 7.02 (dd, 1 H, *J* = 8.2, 1.0), 5.55-5.37 (br s, 1 H), 4.96 (s, 1 H), 4.75 (s, 1 H), 4.48 (dd, 1 H, *J* = 9.9, 5.4), 4.23-4.12 (m, 2 H), 3.30 (dd, 1 H, *J* = 13.0, 9.9), 2.66 (dd, 1 H, *J* = 18.1, 12.8), 2.42 (dd, 1 H, *J* = 18.1, 5.6), 2.32-2.24 (m, 1 H), 1.99 (dd, 1 H, *J* = 13.0, 5.4), 1.69 (s, 3 H), 1.18 (t, 3 H, *J* = 7.1), 0.96 (d, 3 H, *J* = 6.8)

¹³C NMR (100 MHz, CDCl₃) δ 195.6, 170.3, 153.4, 151.2, 144.3, 132.6, 122.6, 121.9, 118.1, 117.7, 110.1, 108.6, 97.6, 78.5, 60.8, 59.5, 43.0, 35.8, 33.2, 18.9, 15.9, 14.2

IR (thin film) ν 3383, 2928, 1728, 1628, 1568, 1483, 1268, 1202, 1010

EA calc'd for C₂₂H₂₅NO₅: C 68.91, H, 6.57, N, 3.65; found C 68.61, H 6.48, N 3.36

Compound 18. To **4** (13 mg, 0.034 mmol) in 3.5 mL glacial acetic acid at rt was added Zn (24 mg, 10.1 equiv). The mixture was heated to reflux for 10 h, during which time a grey precipitate formed. The reaction was cooled to rt, diluted with EtOAc (10 mL) and filter over a plug of Celite. Purification by preparative thin layer chromatography gave **18** (8.6 mg, 72% yield) as a yellow oil.

¹H NMR (CDCl₃, 400 MHz) δ 8.98 (s, 1 H), 7.18 (dd, 1 H, *J* = 7.5, 1.7), 7.07 (dt, 1 H, *J* = 7.7, 1.7), 6.87 (dd, 1 H, *J* = 8.0, 1.2), 6.74 (dt, 1 H, *J* = 7.4, 1.2), 5.19 (d, 1 H, *J* = 0.5), 5.07 (d, 1 H, *J* = 0.5), 4.99 (dd, 1 H, *J* = 11.1, 5.5), 4.12 (q, 2 H, *J* = 7.2), 3.55 (d, 2 H, *J*

= 2.7), 2.46-2.43 (m, 2 H), 2.29-2.22 (m, 1 H), 1.80 (s, 3 H), 1.71 (dd, 1 H, $J = 12.3$, 11.1), 1.05 (t, 3 H, $J = 7.5$), 1.04 (d, 3 H, $J = 7.3$);
 ^{13}C NMR (100 MHz, CDCl_3) δ 201.2, 176.0, 168.9, 155.1, 141.3, 131.1, 127.8, 126.3, 119.7, 117.3, 114.1, 113.8, 87.6, 62.3, 58.9, 41.1, 39.3, 37.5, 23.9, 17.4, 16.9, 13.8
 IR (thin film) ν 3192, 2916, 1728, 1620, 1369, 1202

Lactone 20. The unpurified **19** (13 mg, 0.034 mmol) was dissolved in 2 mL THF and treated with 2.0 M HCl (aq, 1 mL). The reaction was heated to 90 °C for 10 h, cooled to rt, and extracted with EtOAc (3 x 8 mL). The combined extracts were washed with brine (2 x 10 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. Purification by preparative thin layer chromatography gave **20** (7.1 mg, 60%, two steps) as a white solid.

^1H NMR (CDCl_3 , 400 MHz) δ 8.26 (dd, 1 H, $J = 8.1$, 0.7), 7.68 (dt, 1 H, $J = 7.2$, 0.7), 7.45–7.41 (m, 2 H), 5.08 (d, 1 H, $J = 0.7$), 5.00 (d, 1 H, $J = 0.7$), 4.94 (t, 1 H, $J = 8.7$), 3.47 (dd, 1 H, $J = 14.0$, 9.9), 3.40 (dd, 1 H, $J = 18.6$, 11.9), 2.87 (dd, 1 H, $J = 18.6$, 5.1), 2.55–2.45 (m, 1 H), 2.14 (dd, 1 H, $J = 14.0$, 7.9), 1.84 (s, 3 H), 1.34 (d, 3 H, $J = 6.8$)
 ^{13}C NMR (100 MHz, CDCl_3) δ 187.9, 177.5, 173.5, 172.6, 154.6, 142.4, 134.2, 126.9, 126.1, 125.0, 117.7, 115.0, 114.0, 81.8, 60.1, 35.4, 33.8, 33.3, 16.9, 16.5
 IR (thin film) ν 2923, 2851, 1753, 1697, 1515, 1464, 1405, 1180