Total Synthesis of (–)-Hennoxazole

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Supporting Information

General Information. Oxygen- or moisture-sensitive reactions were carried out in flame-dried or oven-dried glassware sealed with rubber septa under a positive pressure of dry nitrogen. Similarly sensitive liquids and solutions were transferred by gas-tight syringe or canula. Unless indicated otherwise, reagents and solvents were purchased and used without purification. Ether, THF, and CH₂Cl₂, were purified by passage through a bed of activated alumina.¹ Analytical TLC was performed with 0.25 mm silica gel 60 plates with 254 nm fluorescent indicator from SiliCycle. Plates were visualized under UV light and treatment with either acidic *p*-anisaldehyde stain or aqueous ceric ammonium molybdate solution followed by gentle heating. The term flash chromatography refers to preparative silica gel column chromatography as described by Still and co-workers.² Automated chromatography was accomplished using an Isco Combiflash System Sg 100c. Silica gel 60, 230–240 mesh, was purchased from SiliCycle (R10030B). Analytical high performance liquid chromatography (HPLC) was carried out on an Agilent 1100 chromatograph equipped with a variable wavelength detector. ¹H NMR spectra were recorded on a Bruker Avance 500 (500 MHz) spectrometer and are reported in ppm using tetramethylsilane (0.00 ppm) or solvent (CDCl₃: 7.24 ppm; acetone-d₆: 2.04 ppm) as an internal standard. Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ¹³C NMR spectra were recorded at 125 MHz and are reported in ppm using solvent as an internal standard (CDCl₃: 77.00 ppm, acetone-d₆: 206.00 ppm). Infrared spectra were recorded as thin films on NaCl plates on a Perkin-Elmer 710 Series Fourier transform spectrometer (FTIR). Melting points were determined with a Laboratory Devices Mel-Temp II apparatus equipped with an Fluke Model 51 K/J thermocouple and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter using the sodium (589, D line) lamp and are reported as follows: $[\alpha]_{\lambda}^{T\text{ }^{\circ}\text{C}}$ (c = g/100 mL, solvent). Combustion analyses were performed by Atlantic Microlab, Norcross, Georgia. High Resolution mass spectra (HRMS) were recorded at the Nebraska Center for Mass Spectrometry or at the University of Hawaii, Manoa.

(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, 1518.

(2) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem* **1978**, 43, 2923.

(Z,3*R*,4*S*)-2,4-dimethylhepta-1,5-dien-3-ol (4**)**³

Following the procedure reported by Williams,³ a 9:1 mixture of *syn:anti* products was obtained. Chiral gc (Chiraldex G-TA column, 30 m x 0.25 mm, 30 psi He, 50 °C, 1 °C/min ramp) indicated the *syn* diastereomer to be present in 95.4% ee but the *anti* diastereomer to be present in only 72.2% ee. The minor *anti* material was removed by chromatography on silver nitrate-impregnated silica gel⁴ to give pure title compound **4** as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 5.51 (dq, *J* = 15.4, 6.4 Hz, 1H), 5.40 (ddq, *J* = 15.3, 7.1, 1.2 Hz, 1H), 4.95 (s, 1H), 4.88 (s, 1H), 3.90 (dd, *J* = 4.5, 4.4 Hz, 1H), 2.36 (dq, *J* = 12.8, 6.7 Hz, 1H), 1.71 (s, 3H), 1.68 (d, 3H, *J* = 6.2 Hz), 1.56 (d, *J* = 3.7 Hz, 1H), 0.98 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 145.9, 133.6, 125.3, 111.6, 78.8, 39.7, 18.6, 18.1, 14.2 ppm.; IR (film) 3403, 2970, 2920, 2877, 1652, 1452, 1376, 1295, 1115, 1023, 981, 898, 557 cm⁻¹. [α]_D²⁴ = +5.4° (*c* = 1.01, CHCl₃). HRMS (EI): Exact mass calcd for C₉H₁₆O [M]⁺: 140.1201; Found: 140.1192.

(3) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924–4925.

(4) Li, T-S.; Li, J-T.; Li, H-Z *J. Chromatogr. A* **1995**, *715*, 372.

(*S*,3*Z*,6*Z*)-3,5-dimethylocta-3,6-dien-1-ol (5**)**³

The following procedure was adapted from Still⁵ and van Boom⁶ (Title compound **5** has also been prepared by Williams by a different route).³ To a 10 mL concentration flask was added KH (290 mg of a 35% dispersion in mineral oil, 2.383 mmol, 2.2 equiv). The white solid was washed in dry pentanes (3 x 5 mL) and suspended in dry THF (2 mL) at 0 °C. To this suspension was added allylic alcohol **4** (152 mg, 1.083 mmol, 1 equiv) *via* cannula in THF (1.2 mL), producing a cloudy yellow solution. Dibenzo-18-crown-6 (catalytic amt) was added as a white powder, followed by addition of Bu₃SnCH₂I⁷ (560 mg, 1.300 mmol, 1.2 equiv) *via* cannula in THF (0.8 mL). The solution became a light brown color and was warmed to rt. After 2 h, the solution was cooled to -78 °C. *n*-Butyllithium (1.1 mL of a 1.56 *M* in hexanes, 1.625 mmol, 1.5 equiv) was added dropwise *via* syringe down the cold wall of the flask, forming an orange solution. The solution was stirred at -78 °C for 2 h. The orange color gradually changed to a light brown and then became more yellow. The reaction mixture was partitioned between Et₂O (10 mL) and sat aq NH₄Cl (10 mL), and the layers were separated. The aqueous layer was extracted with Et₂O (2 x 10 mL), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield a clear, yellow oil and a red-brown precipitate. The product was purified *via* automated silica column chromatography (0 → 15% EtOAc/hexanes over 30 min, 110 g column; TLC: R_f = 0.42 in 15% EtOAc/hexanes, anisaldehyde stain) to provide homoallylic alcohol **5** (0.138 g, 83% yield) as a clear, colorless oil. Due to the volatility of alcohol **5**, it should not be exposed to pressures lower than 5 mm Hg. Chiral gc (Chiraldex G-TA column, 30 m x 0.25 mm, 30 psi He, 50 °C, 0.6 °C/min ramp) was not able to completely resolve a racemic sample, but was consistent with a product ee identical to that of the starting material ee of 95% (≥90% ee is the best confidence that can be estimated from the poorly resolved peaks): ¹H NMR (500 MHz, CDCl₃) δ 5.45-5.34 (m, 2H), 5.18 (d, 1H, *J* = 9.6 Hz), 3.72-3.62 (m, 2H), 3.12-3.03 (m, 1H), 2.37 (dt, *J* = 13.4, 6.4 Hz, 1H), 2.30 (dt, *J* = 13.4, 6.4 Hz, 1H), 1.72 (d, 3H, *J* = 1.2 Hz), 1.64 (d, *J* = 4.7 Hz, 3H), 1.34 (br s, 1H), 1.01 (d, *J* = 6.7 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 136.3, 133.2, 129.7, 122.8, 60.7, 35.4, 35.3, 23.5, 21.7, 17.9 ppm; IR (film) 3325, 2963, 2870, 1449, 1377, 1042, 968, 868 cm⁻¹; [α]_D²⁴ = -59.3° (*c* = 1.00, CHCl₃). HRMS (EI): Exact mass calcd for C₁₀H₁₈O [M]⁺: 154.1358; Found: 154.1358.

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(6) Ovaa, H.; Lastdrager, B.; Codée, J. D. C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Chem. Soc., Perkin Trans. I* **2002**, 2370–2377.

(7) (a) Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151–152. (b) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481–1486.

(*S*,2*E*,5*Z*,8*Z*)-5,7-dimethyldeca-2,5,8-trien-1-ol (6**)**

The following procedure was adapted from Parrain⁸ and Wavrin.⁹ A 25 mL concentration flask containing alcohol **5** (92.9 mg, 0.602 mmol, 1 equiv) in dry CH₂Cl₂ (6 mL) was cooled to 0 °C. Dess-Martin Periodinane (DMP) (0.332 g, 0.783 mmol, 1.3 equiv) was added, and the solution became a cloudy white. After 5 min, the solution was warmed to rt. After 1 h, a 1:1 mixture of sat aq Na₂S₂O₄ and sat aq NaHCO₃ (12 mL) was added to the crude mixture which was then stirred vigorously for 15 minutes. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 12 mL). The combined organics were washed with sat aq NaHCO₃ (5 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give a light yellow oil with a white precipitate. The residue was suspended in 20% Et₂O/pentane (5 mL) and filtered through a small plug of Celite (additional 5 mL rinse). The solvent was removed *in vacuo* to provide (*S*,3*Z*,6*Z*)-3,5-dimethylocta-3,6-dienal (**5a**) (0.116 g, with DMP contaminants) as a light yellow oil (TLC: R_f = 0.82, 15% EtOAc/hexanes, anisaldehyde stain) which was carried on without further purification. Due to the volatility of aldehyde **5a**, it should not be exposed to pressures lower than 5 mm Hg: ¹H NMR (500 MHz, CDCl₃) δ 9.57 (t, 1H, *J* = 2.4 Hz), 5.42–5.34 (m, 2H), 5.32 (d, 1H, *J* = 10.2 Hz), 3.12 (d, 2H, *J* = 2.4 Hz), 2.95 (ddq, 1H, *J* = 10.2, 9.1, 6.8 Hz), 1.76 (d, 3H, *J* = 1.3 Hz), 1.64 (d, 3H, *J* = 5.6 Hz), 1.03 (d, 3H, *J* = 6.8 Hz) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 199.5, 135.3, 134.8, 124.7, 123.3, 47.5, 35.8, 24.4, 21.4, 17.8 ppm; IR (film) 3022, 2966, 2927, 2870, 2717, 1726, 1450, 1379, 1238, 1170, 1120, 1048, 1017, 970, 857 cm⁻¹.

The following procedure was adapted from Lee.¹⁰ To a 10 mL concentration flask was added NaH (0.048 g of a 60% dispersion in oil, 1.205 mmol, 2.0 equiv). The white solid was washed in dry pentanes (3 x 1 mL) and suspended in dry THF (0.4 mL). To this suspension was added triethylphosphonoacetate (0.251 mL, 1.265 mmol, 2.1 equiv) dropwise *via* syringe, and the solid dissolved to give a light yellow solution. After 1 hr, the solution was cooled to 0 °C, and unpurified aldehyde **5a** (theoretical from above, 2.390 mmol, 1 equiv) was added *via* cannula in dry THF (0.5 mL), producing a bright yellow/orange solution. After 30 min, the solution was warmed to rt and after an additional 30 min, sat aq NH₄Cl (20 mL) was added along with Et₂O (20 mL), and the layers were separated. The aqueous layer was further extracted with Et₂O (2 x 10 mL), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield (*S*,2*E*,5*Z*,8*Z*)-ethyl 5,7-dimethyldeca-2,5,8-trienoate (**5b**) (0.270 g, with phosphate contaminants) as a clear, yellow oil (TLC: R_f = 0.80 in 20% EtOAc/hexanes, anisaldehyde stain) which was carried on without further purification. Due to the volatility of ethyl ester **5b**, it should not be exposed to pressures lower than 5 mm Hg: ¹H NMR (500 MHz, CDCl₃) δ 6.90 (dt, 1H, *J* = 15.6, 6.7 Hz), 5.82 (dt, 1H, *J* = 15.6, 1.4 Hz), 5.41–5.31 (m, 2H), 5.12 (d, 1H, *J* = 9.3 Hz), 4.18 (q, 2H, *J* = 7.1

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Hz), 2.95 (dd, 2H, $J = 6.7, 2.0$ Hz), 2.90 (m, 1H), 1.68 (d, 3H, $J = 1.0$ Hz), 1.63 (d, 3H, $J = 5.0$ Hz), 1.28 (t, 3H, $J = 7.1$ Hz), 1.01 (d, 3H, $J = 6.8$ Hz) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 166.6, 146.4, 135.7, 132.3, 129.7, 123.0, 122.0, 60.2, 35.6, 35.0, 23.5, 21.4, 17.9, 14.3 ppm; IR (film) 3022, 2966, 2927, 2870, 2717, 1725, 1450, 1379, 1048, 970, 857 cm^{-1} .

The following procedure was adapted from Fernandes.¹¹ To a 50 mL concentration flask containing ethyl ester **5b** as an unpurified mixture (theoretical from above, 2.390 mmol, 1 equiv) in dry CH_2Cl_2 (8.6 mL) at 0 °C was added DIBAL-H (1.99 mL of a 1.0 M solution in CH_2Cl_2 , 1.987 mmol, 3.3 equiv) dropwise *via* syringe. Some gas evolution was evident. After 1 hr, half-saturated Rochelle's salt (20 mL) and Et_2O (20 mL) was added and the mixture stirred vigorously overnight and allowed to come to rt. The layers were separated and the aqueous layer was further extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to yield a clear, yellow oil. The product was purified *via* automated silica column chromatography (0→15% EtOAc /hexanes, 10 g column; TLC: $R_f = 0.28$ in 20% EtOAc /hexanes, CAM stain) to provide title alcohol **6** (0.0827 g, 76% yield for three steps) as a clear, colorless oil. Due to the volatility of alcohol **6**, it should not be exposed to pressures lower than 5 mm Hg for more than several hours. When left overnight at 0.5 mm Hg for characterization purposes, partial product loss was observed: ^1H NMR (500 MHz, CDCl_3) δ 5.70-5.60 (m, 2H), 5.42-5.33 (m, 2H), 5.04 (d, 1H, $J = 9.4$ Hz), 4.13-4.07 (m, 2H), 3.05-2.97 (m, 1H), 2.82-2.69 (m, 2H), 1.67 (d, 3H, $J = 1.4$ Hz), 1.64 (d, $J = 3.9$ Hz, 3H), 1.33 (br s, 1H), 1.01 (d, 3H, $J = 6.7$ Hz) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 136.1, 131.6, 130.9, 130.5, 129.9, 122.7, 63.7, 35.4, 35.0, 23.4, 21.5, 17.9 ppm; IR (film) 3325, 2963, 2870, 1449, 1377, 1042, 968, 868 cm^{-1} ; $[\alpha]_{\text{D}}^{24} = -80.6^\circ$ ($c = 1.00$, CHCl_3); Anal calcd for $\text{C}_{12}\text{H}_{20}\text{O}$: C, 79.94%, H, 11.18%; Found: C, 79.72%, H, 11.35%. HRMS (EI): Exact mass calcd for $\text{C}_{12}\text{H}_{20}\text{O}$ $[\text{M}]^+$: 180.1514; Found: 180.1514.

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S10

(*S*,2*E*,5*Z*,8*Z*)-1-bromo-5,7-dimethyldeca-2,5,8-triene (3)

The following procedure was adapted from Corey.¹² To a 25 mL concentration flask containing alcohol **6** (0.0818 g, 0.454 mmol, 1 equiv) in dry THF (2 mL) was added Et₃N (0.253 mL, 1.815 mmol, 4 equiv). The solution was cooled to $-40\text{ }^{\circ}\text{C}$ and MsCl (0.105 mL, 1.361 mmol, 3 equiv) was added dropwise. A white precipitate formed immediately. After 50 min. at $-40\text{ }^{\circ}\text{C}$, the suspension was warmed to $0\text{ }^{\circ}\text{C}$. After 30 min, a solution of LiBr (0.394 g, 4.540 mmol, 10 equiv) in THF (4 mL) was added dropwise *via* canula. After 30 min, the flask was warmed to rt. And stirred for an additional 30 min. The reaction was quenched with ice-cold sat. aq. NaHCO₃ (15 mL) and diluted with pentane (5 mL). The layers were separated and the aqueous layer was further extracted with pentane (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield a clear, yellow oil. The product was purified *via* automated silica column chromatography (pentane, 4 g column (TLC: R_f = 0.89 in 20% EtOAc/hexanes, anisaldehyde stain) to provide bromide **3** (0.0958 g, 87% yield) as a clear, colorless oil. Due to the volatility of bromide **3**, it should not be exposed to pressures lower than 5 mm Hg for extended periods: ¹H NMR (500 MHz, CDCl₃) δ 5.75-5.67 (m, 2H), 5.42-5.32 (m, 2H), 5.06 (d, 1H, *J* = 8.9 Hz), 4.00-3.92 (m, 2H), 3.03-2.95 (m, 1H), 2.82-2.74 (m, 2H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.64 (d, 3H, *J* = 4.5 Hz), 1.01 (d, *J* = 6.8 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 136.0, 133.8, 131.4, 131.0, 127.2, 122.8, 35.4, 34.9, 33.3, 23.5, 21.5, 18.0 ppm; IR (film) 2964, 2927, 2868, 156, 1438, 1377, 1203, 965, 854, 580 cm⁻¹; [α]_D²⁴ = -69.3° (*c* = 1.00, CHCl₃); HRMS (EI): Exact mass calcd for C₁₂H₁₉Br [M]⁺: 242.0670; Found: 242.0663.

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S13

(3*S*,5*R*)-5-(2-(5-(*tert*-butyldimethylsilyl)-2-methyloxazol-4-yl)oxazol-4-yl)-3-hydroxy-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)-5-methoxypentan-1-one (9)

To a 10 mL flask containing bisoxazole methyl ether **8** (0.248 g, 0.388 mmol, 1 equiv) in CH₂Cl₂ (1.5 mL) under N₂ at –78 °C was added DIBAL-H (0.581 mL of a 1.0 M solution in CH₂Cl₂, 1.5 equiv) dropwise *via* syringe. After stirring for 1 h, the reaction was quenched by the addition of MeOH (7.5 mL). Rochelle's salt (10 mL of a 7:5 mixture of saturated solution and water) was added and the biphasic mixture was warmed to rt and stirred rapidly for 45 min. The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo* to give a colorless oil. This material was quickly subjected to flash chromatography (CH₂Cl₂ until the auxiliary was eluted then 30% Et₂O/CH₂Cl₂; TLC: R_f = 0.09 in 70% Et₂O/hexanes) to provide (*R*)-3-(2-(5-(*tert*-butyldimethylsilyl)-2-methyloxazol-4-yl)oxazol-4-yl)-3-methoxypropanal (**8a**) as a relatively unstable clear oil that was used immediately in the next step: ¹H NMR (500 MHz, CDCl₃) δ 9.83 (s, 1H), 7.67 (s, 1H), 4.81 (d, *J* = 7.6, 4.7 Hz, 1H), 3.38 (s, 3H), 3.03 (dd, *J* = 16.9, 7.7 Hz, 1H), 2.94 (dd, *J* = 16.9, 4.6 Hz, 1H), 2.55 (s, 3H), 0.96 (s, 9H), 0.34 (s, 6H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 200.0, 165.1, 156.8, 154.8, 140.8, 138.7, 135.2, 71.3, 56.9, 48.0, 26.3, 17.4, 13.6, –6.0 ppm.

To a 10 mL flask was added Sn(OTf)₂ (0.353 g, 0.847 mmol, 2.3 equiv) in a glove box. This tin compound was dissolved in CH₂Cl₂ (3.5 mL), the flask was cooled to –50 °C, *N*-ethyl piperidine (0.121 mL, 0.884 mmol, 2.4 equiv) was added dropwise *via* syringe, followed by (*S*)-*N*-acetyl-4-*i*-Pr-thiazolidinethione (0.122 g, 0.552 mmol, 1.5 equiv). The solution was stirred at –50 °C for 4.5 h to form the tin enolate and then was cooled to –110 °C in a liquid nitrogen/hexanes slurry before aldehyde **8a** (theoretical from above, 0.388 mmol, 1 equiv) was added *via* canula in CH₂Cl₂ (1.5 mL). The solution was kept between –90 and –100 °C for 2 h and was then warmed to –78 °C over 30 min and allowed to stir for an additional 30 min at –78 °C. The reaction was quenched with pH 7 buffer and filtered with CH₂Cl₂ (25 mL) through a plug of Celite into a separatory funnel containing sat. aq. NaHCO₃ (15 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 30 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo* to give a clear yellow oil. ¹H NMR integration of the unpurified product indicated a 3:1 diastereomer ratio. This material was purified *via* automated silica column chromatography (40→70% EtOAc/hexanes, 110 g column; TLC: R_f = 0.28 in 70% EtOAc/hexanes) to provide diastereomerically pure alcohol **9** (0.2142 g, 46% yield over two steps) as a clear, yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.65 (s, 1H), 5.15 (dd, *J* = 7.0, 6.8 Hz, 1H), 4.53 (dd, *J* = 7.2, 6.3 Hz, 1H), 4.33–4.26 (m, 1H), 3.57–3.47 (m, 3H), 3.39–3.30 (m, 1H), 3.34 (s, 3H), 3.03 (d, *J* = 11.1 Hz, 1H), 2.54 (s, 3H), 2.42–2.31 (m, 1H), 2.20–2.12 (m, 1H), 2.11–2.03 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 7.3 Hz, 3H), 0.95 (s, 9H), 0.38 (s, 6H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 202.8, 172.2, 165.0, 156.7, 154.7, 141.3, 138.9, 135.3, 75.1, 71.3, 66.4, 56.6, 45.4, 40.9, 30.7, 30.5, 26.5, 19.0, 17.7, 17.5, 13.7, –5.9 ppm; IR (film) 3420, 2958, 2930, 2855, 1696, 1616, 1583, 1469, 1363, 1314, 1157, 1094, 1036, 930, 844, 781, 730, 668 cm^{–1}; [α]_D²⁵ = +212.1° (*c* = 1.03, CHCl₃); HRMS (CI): Exact mass calcd for C₂₅H₄₀N₃O₅S₂Si [M + H]⁺: 554.2179; Found: 554.2181.

(S)-2-((R)-2-(2-(5-(*tert*-butyldimethylsilyl)-2-methyloxazol-4-yl)oxazol-4-yl)-2-methoxyethyl)-2,3-dihydro-6-methylpyran-4-one (10)

To a 10 mL flask containing alcohol **9** (0.2380 g, 0.431 mmol, 1 equiv) in DMF (2.7 mL) under an Ar atmosphere was added magnesium acetoacetate¹⁵ (0.195 mg, 0.861 mmol, 2 equiv) and imidazole (32.2 mg, 0.474 mmol, 1.1 equiv). After stirring for 29 h, the mixture was cooled to 0 °C in an ice bath, diluted with THF (3 mL), quenched with 7.5 mL of 2 M HCl, and stirred overnight. The layers were separated and the aqueous layer was extracted with EtOAc (4 x 20 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. This material was purified *via* automated silica column chromatography (55→80% EtOAc/hexanes, 110 g column; TLC: R_f = 0.40 in 80% EtOAc/hexanes) to provide dihydropyranone **10** (0.1215 g, 65% yield) as a clear colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 7.65 (s, 1H), 5.30 (s, 1H), 4.51–4.43 (m, 2H), 3.33 (s, 3H), 2.55 (s, 3H), 2.58–2.40 (m, 3H), 2.25 (ddd, *J* = 13.5, 6.0, 6.0 Hz, 1H), 1.97 (s, 3H), 0.95 (s, 9H), 0.38 (s, 6H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 192.4, 174.0, 165.1, 156.8, 154.8, 141.1, 138.8, 135.4, 104.8, 76.2, 72.6, 56.6, 40.6, 39.1, 26.3, 20.9, 17.5, 13.7, –6.00 ppm; IR (film) 2954, 2929, 2859, 1670, 1612, 1465, 1399, 1334, 1249, 1109, 1033, 842, 824, 781, 680 cm^{–1}; [α]_D²⁵ = –36.7° (*c* = 0.96, CHCl₃); HRMS (CI): Exact mass calcd for C₂₂H₃₃N₂O₅Si [M + H]⁺: 433.2159; Found: 433.2171.

(15) Ohta, S.; Tsujimura, A.; Okamoto, M. *Chem. Pharm. Bull.* **1989**, *21*, 2762–2768.

(2*R*,4*R*)-2-((*R*)-2-(2-(5-(*tert*-butyldimethylsilyl)-2-methyloxazol-4-yl)oxazol-4-yl)-2-methoxyethyl)-3,4-dihydro-6-methyl-2*H*-pyran-4-ol, *tert*-butyldimethylsilyl ether (11**)**

To a 10 mL flask containing dihydropyranone **10** (23.3 mg, 0.0539 mmol, 1 equiv) under an Ar atmosphere was added a solution of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (22.1 mg, 0.0593 mmol, 1.1 equiv) in a 1:1 mixture of THF/MeOH (0.77 mL). The suspension was cooled to -78°C and NaBH_4 (4.2 mg, 0.108 mmol, 2 equiv) was added as a solid in one portion. After 15 min, the flask was warmed to -50°C and then allowed to warm to -30°C over 1h. The reaction mixture was poured into pH 7 buffer (15 mL) and was diluted with Et_2O (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic layers were filtered through a plug of silica gel and concentrated *in vacuo* to give (2*R*,4*R*)-2-((*R*)-2-(2-(5-(*tert*-butyldimethylsilyl)-2-methyloxazol-4-yl)oxazol-4-yl)-2-methoxyethyl)-3,4-dihydro-6-methyl-2*H*-pyran-4-ol, *tert*-butyldimethylsilyl ether (**10b**) which was carried on immediately without any further purification: TLC: $R_f = 0.36$ in 80% EtOAc/hexanes.

To a 5 mL flask containing allylic alcohol **10b** (theoretical from above, 0.0593 mmol, 1 equiv) under an Ar atmosphere was added imidazole (10.8 mg, 0.162 mmol, 3 equiv) a catalytic amount of DMAP, and anhydrous DMF (0.5 mL). TBS-Cl (17.6 mg, 0.116 mmol, 2.2 equiv) was added and the reaction was stirred for 4 h. The solution was diluted with brine (5 mL) and EtOAc (5 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with water (2 x 8 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. This material was purified *via* flash chromatography (45% EtOAc/hexanes, TLC: $R_f = 0.31$ in 10% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$) to provide TBS ether **11** (18.6 mg, 70% yield over two steps) as a clear colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 7.63 (s, 1H), 4.46 (dd, $J = 8.0, 6.0$ Hz, 1H), 4.42 (s, 1H), 4.35 (dd, $J = 8.3, 7.0$ Hz, 1H), 3.86–3.78 (m, 1H), 3.29 (s, 3H), 2.54 (s, 3H), 2.26 (ddd, $J = 14.3, 8.7, 5.9$ Hz, 1H), 2.15 (ddd, $J = 12.7, 8.2, 4.3$ Hz, 1H), 1.95 (dd, $J = 13.0, 6.6$ Hz, 1H), 1.69 (s, 3H), 1.68–1.59 (m, 1H), 0.95 (s, 9H), 0.88 (s, 9H), 0.39 (s, 3H), 0.38 (s, 3H), 0.06 (s, 6H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 165.1, 156.6, 154.7, 152.0, 141.2, 139.1, 135.9, 101.3, 72.6, 71.5, 64.3, 56.3, 39.5, 37.6, 26.5, 25.9, 19.8, 18.2, 17.6, 13.8, $-4.7, -5.9$ ppm; IR (film) 2928, 2857, 1675, 1586, 1463, 1383, 1252, 1062, 837, 837, 780, 495 cm^{-1} ; $[\alpha]_D^{25} = +18.5^\circ$ ($c = 1.00, \text{CHCl}_3$); HRMS (CI): Exact mass calcd for $\text{C}_{28}\text{H}_{48}\text{N}_2\text{O}_5\text{Si}_2\text{Li}$ $[\text{M} + \text{Li}]^+$: 555.3262; Found: 555.3267.

(2*R*,4*R*,6*R*)-6-((*R*)-2-(2-(5-(*tert*-butyldimethylsilyl)-2-methyloxazol-4-yl)oxazol-4-yl)-2-methoxyethyl)-tetrahydro-2-methoxy-2-methyl-2*H*-pyran-4-ol, *tert*-butyldimethylsilyl ether (2**)**

To a 5 mL flask containing TBS ether **11** (4.8 mg, 0.0087 mmol, 1 equiv) in benzene (0.3 mL) under an Ar atmosphere was added MeOH (11 μ L, 30 equiv) and trimethyl orthoformate (5 μ L, 5 equiv). A spatula tip of PPTS was added in one portion and the reaction was stirred for 75 min. The reaction was quenched with sat. aq. NaHCO₃ (3 mL) and diluted with EtOAc (5 mL). The layers were separated and the aqueous phase was further extracted with EtOAc (2 x 10 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. This material was purified *via* flash chromatography (35% EtOAc/hexanes, TLC: R_f = 0.57 in 40% EtOAc/hexanes) to provide mixed methyl acetal **2** (5.1 mg, 88% yield) as a clear colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 7.62 (s, 1H), 4.45 (dd, *J* = 7.7, 6.4 Hz, 1H), 4.02–3.93 (m, 1H), 3.51–3.42 (m, 1H), 3.29 (s, 3H), 3.00 (s, 3H), 2.54 (s, 3H), 2.18–2.06 (m, 2H), 1.95 (dd, *J* = 12.8, 4.5 Hz 1H), 1.79 (d, *J* = 10.3 Hz, 1H), 1.31 (dd, *J* = 23.7, 11.6 Hz, 1H), 1.30 (s, 3H), 1.22 (dd, *J* = 23.6, 11.8 Hz, 1H), 0.95 (s, 9H), 0.87 (s, 9H), 0.39 (s, 3H), 0.38 (s, 3H), 0.04 (s, 6H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 165.1, 156.6, 154.8, 141.4, 139.1, 135.9, 99.6, 72.7, 65.8, 65.1, 56.3, 47.6, 45.3, 41.0, 40.3, 26.5, 25.8, 23.7, 18.0, 17.6, 13.8, –4.6, –5.9 ppm; IR (film) 2929, 2857, 1612, 1586, 1463, 1377, 1319, 1251, 1192, 1084, 1034, 930, 914, 870, 837, 779, 670, 580, 490 cm^{–1}; [α]_D²⁵ = –20.1° (*c* = 1.01, CHCl₃); HRMS (CI): Exact mass calcd for C₂₉H₅₂N₂O₆Si₂Li [M + Li]⁺: 587.3479; Found: 587.3523.

(2*R*,4*R*,6*R*)-6-((*R*)-2-(2-(5-(*tert*-butyldimethylsilyl)-2-((*S*,3*E*,6*E*,9*E*)-6,8-dimethylundeca-3,6,9-trienyl)oxazol-4-yl)oxazol-4-yl)-2-methoxyethyl)-tetrahydro-2-methoxy-2-methyl-2*H*-pyran-4-ol, *tert*-butyldimethylsilyl ether (12**)**

A 0.5 M solution of LiNEt₂ was prepared by addition of *n*BuLi (1.00 mL of a 2.72 M solution in hexanes, 2.72 mmol) to 25 mL concentration flask containing diethylamine (0.310 mL, 3.00 mmol) in THF (4.13 mL) at -78°C under an atmosphere of argon. After 5 min, the flask was warmed to 0°C . Mixed methyl acetal **2** (69.0 mg, 0.119 mmol, 1.0 equiv) in a 10 mL concentration flask was diluted with THF (2.0 mL). The solution was cooled to -78°C under an atmosphere of argon and the LiNEt₂ prepared above was added dropwise until a yellow color persisted (to remove any adventitious acid source—about 4 drops). After this zero point, LiNEt₂ (0.285 mL of a 0.5 M solution in THF, 0.143 mmol, 1.2 equiv) was added dropwise via gastight syringe. The reaction took on an bright orange/red color. After stirring at -78°C for 15 min, allylic bromide **3** (31.8 mg, 0.131 mmol, 1.1 equiv) was added dropwise *via* cannula in THF (1.65 mL) causing the reaction to become progressively lighter orange-yellow. After 15 min, the reaction was quenched with sat. aq. NaHCO₃ (5 mL), diluted with EtOAc (5 mL) and warmed to rt. The layers were separated and the aqueous phase was further extracted with EtOAc (3 x 5 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. This material was purified *via* automated silica column chromatography (0→20% EtOAc/hexanes, TLC: R_f = 0.62 in 30% EtOAc/hexanes) to provide protected hennoxazole **12** (67.7 mg, 77% yield) as a clear colorless oil along with unreacted starting material (4.6 mg, 7%) and doubly-alkylated product (6.1 mg, 6%): ¹H NMR (500 MHz, CDCl₃) δ 7.62 (s, 1H), 5.51-5.38 (m, 2H), 5.38-5.31 (m, 2H), 4.99 (d, 1H, *J* = 9.2 Hz), 4.45 (dd, 1H, *J* = 8.1, 6.0 Hz), 3.97 (dddd, *J* = 10.8, 10.8, 4.7, 4.7 Hz, 1H), 3.49-3.42 (m, 1H), 3.28 (s, 3H), 3.04-2.95 (m, 1H), 3.00 (s, 3H), 2.92 (t, *J* = 7.6 Hz, 2H), 2.71 (dd, *J* = 14.3, 6.1 Hz, 1H), 2.66 (dd, *J* = 14.3, 6.1 Hz, 1H), 2.51 (dt, *J* = 7.2, 6.7 Hz, 2H), 2.18-2.07 (m, 2H), 1.95 (ddd, 1H, *J* = 12.8, 4.7, 1.5 Hz), 1.97 (ddt, *J* = 12.3, 4.7, 2.4 Hz, 1H), 1.63 (d, *J* = 4.0 Hz, 3H), 1.60 (d, *J* = 1.4 Hz, 3H), 1.34 (dd, *J* = 12.6, 11.1 Hz, 1H), 1.28 (s, 3H), 1.22 (ddd, *J* = 11.8, 11.8, 11.8 Hz, 1H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.95 (s, 9H), 0.86 (s, 9H), 0.39 (s, 3H), 0.38 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 168.0, 156.6, 154.7, 141.3, 139.0, 136.1, 136.0, 132.0, 130.4, 129.5, 128.7, 122.5, 99.6, 72.7, 65.7, 65.1, 56.3, 47.6, 45.3, 41.0, 40.3, 35.3, 35.2, 30.0, 28.2, 26.5, 25.8, 23.7, 23.3, 21.4, 18.0, 17.9, 17.6, -4.6 , -5.9 ppm; IR (film) 2929, 2857, 1612, 1463, 1376, 1252, 1192, 1086, 969, 838, 778, 621, 525, 506, 489 cm⁻¹; [α]_D²⁵ = -40.3° (*c* = 1.01, CHCl₃); HRMS (CI): Exact mass calcd for C₄₁H₇₀N₂O₆Si₂Li [M + Li]⁺: 749.4933; Found: 749.4917.

Hennoxazole A (1)

To a 25 mL flask containing protected hennoxazole **12** (67.7 mg, 0.091 mmol, 1.0 equiv) in THF (6.0 mL) under Ar(g) was added TBAF (547 μ L of a 1.0 M solution in THF, 0.547 mmol, 6 equiv). The solution was stirred for 24 hr, after which, the reaction was concentrated *in vacuo* and purified *via* flash chromatography (0% $\rightarrow$ 100% EtOAc, TLC: R_f = 0.27 in 80% EtOAc/hexanes) to provide hennoxazole, **1** (46.2 mg, 99% yield) as a clear colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 8.13 (s, 1H), 7.63 (s, 1H), 5.50-5.38 (m, 2H), 5.37-5.31 (m, 2H), 4.99 (d, 1H, J = 9.2 Hz), 4.45 (t, 1H, J = 7.1 Hz), 4.04 (dddd, J = 10.8, 10.8, 4.5, 4.5 Hz, 1H), 3.61-3.54 (m, 1H), 3.31 (s, 3H), 3.07 (s, 3H), 3.03-2.95 (m, 1H), 2.90 (t, 2H, J = 7.6 Hz), 2.71 (dd, J = 14.4, 6.5 Hz, 1H), 2.66 (dd, J = 14.4, 6.0 Hz, 1H), 2.51 (dt, J = 7.2, 6.7 Hz, 2H), 2.22-2.15 (m, 1H), 2.11-2.03 (m, 2H), 1.97 (ddt, J = 12.3, 4.7, 2.2 Hz, 1H), 1.70 (br s, 1H), 1.63 (dd, J = 4.7, 1.0 Hz, 3H), 1.61 (d, J = 1.2 Hz, 3H), 1.32 (s, 3H), 1.31 (dd, J = 12.4, 11.1 Hz, 1H), 1.22 (ddd, J = 11.6, 11.6, 11.6 Hz, 1H), 0.98 (d, J = 6.9 Hz, 3H) ppm.; ^1H NMR (500 MHz, acetone- d_6) δ 8.41 (s, 1H), 8.00 (s, 1H), 5.53 (dt, J = 15.2, 6.6 Hz, 1H), 5.44 (dt, J = 15.3, 6.4 Hz, 1H), 5.39-5.29 (m, 2H), 4.95 (d, 1H, J = 9.4 Hz), 4.46 (dd, 1H, J = 8.1, 6.2 Hz), 3.92-3.84 (m, 1H), 3.67 (d, J = 5.0 Hz, 1H), 3.54-3.47 (m, 1H), 3.22 (s, 3H), 3.02 (s, 3H), 3.05-2.97 (m, 1H), 2.89 (t, 2H, J = 7.4 Hz), 2.74-2.64 (m, 2H), 2.50 (dt, J = 7.2, 6.7 Hz, 2H), 2.11-2.00 (m, 2H), 1.97 (ddd, J = 12.4, 4.7, 1.5 Hz, 1H), 1.88 (ddt, J = 12.3, 4.5, 2.3 Hz, 1H), 1.59 (s, 3H), 1.58 (s, 3H), 1.24 (s, 3H), 1.22 (dd, J = 12.3, 11.3 Hz, 1H), 1.10 (ddd, J = 11.7, 11.7, 11.7 Hz, 1H), 0.95 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 155.6, 141.8, 138.1, 136.1, 135.8, 132.0, 130.4, 130.3, 129.7, 128.4, 122.5, 99.5, 72.9, 65.8, 64.6, 56.5, 47.7, 44.9, 40.5, 40.3, 35.2, 29.9, 28.2, 23.6, 23.3, 17.9 ppm. ^{13}C NMR (125 MHz, acetone- d_6) δ 166.0, 156.3, 142.2, 139.5, 137.6, 136.9, 132.6, 131.3, 130.9, 130.0, 129.6, 122.8, 100.0, 73.1, 66.4, 64.2, 56.0, 47.7, 45.8, 41.5, 41.3, 35.8, 35.7, 30.2, 28.5, 23.9, 23.3, 21.6, 17.9 ppm; IR (film) 3401, 2958, 2929, 1632, 1579, 1449, 1375, 1229, 1189, 1108, 1048, 1025, 969, 917, 830, 774 cm^{-1} ; $[\alpha]_D^{25}$ = -46.8° (c = 0.635, CHCl_3); HRMS (CI): Exact mass calcd for $\text{C}_{29}\text{H}_{42}\text{N}_2\text{O}_6\text{Li}$ $[\text{M} + \text{Li}]^+$: 521.3203; Found: 521.3185.