Asymmetric Synthesis of the Carbocyclic Nucleoside Building Block (*R*)-(+)-4-Aminocyclopentenone using δ -Amino β -Ketophosphonates and Ring Closing Metathesis (RCM)

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Experimental

General Procedures. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless noted otherwise. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter and IR spectra were recorded, using NaCl plates or as KBr disks, on a Mattson 4020 FTIR. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400, operating at 400 and 100 MHz, respectively. HRMS were performed in the Department of Chemistry, Drexel University, Philadelphia, PA, using a Fissions ZAB HF double-focusing mass spectrometer. Elemental analyses were performed in the Department of Chemistry, University of Pennsylvania, Philadelphia, PA.

Dichloromethane was distilled over calcium hydride under an inert atmosphere. THF and ether were freshly distilled under argon from a purple solution of sodium and benzophenone ketyl. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. (*S*)-(+)-*N*-(Propylidene-*p*-toluenesulfinamide (**3a**),¹ (*S*)-(+)-*N*-(crotonylidene)-*p*-toluenesulfinamide (**3b**),¹ (*S_S*,*R*)-(+)-methyl-3-(*p*-toluenesulfinylamino)-hex-4-enonate (**4b**)² were prepared as previously described.

(*S_S*,*R*)-(+)-Methyl-3-(*p*-toluenesulfinylamino)-pent-4-enonate (4a**).** In a 250-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum and argon balloon was placed NaHMDS (1.0 M in THF, 16.6 mL, 16.6 mmol) in ether (40 mL) and the solution was cooled to -78 °C. To the reaction mixture was added methyl acetate (1.32 mL, 16.55 mmol) via syringe, the solution was stirred for 1 h and (+)-**3a** (2.13 g, 11.0 mmol) in ether (50 mL) at -78 °C was transferred via cannula. After stirring 3 h the reaction mixture was quenched at this temperature by addition of saturated aqueous NH_4Cl (20 mL). After warming to rt, H_2O (10 mL) was added and the solution was extracted with Et_2O (50 mL) and EtOAc (2 $\times$ 50 mL). The combined organic phases were washed with brine (20 mL), dried (MgSO_4), and concentrated. Flash chromatography (EtOAc :hexane, 1:1) afforded 2.56 g (87%) of a colorless oil; $[\alpha]_{\text{D}}^{20} +150.0$ (*c* 4.1, CHCl_3); IR (neat) 3197, 1737 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.14 (s, 3 H), 2.35-2.37 (m, 2 H), 3.37 (s, 3 H), 3.94-4.00 (m, 1 H), 4.55 (d, *J* = 7.2 Hz, 1 H), 4.94-4.97 (m, 1 H), 5.03-5.08 (m, 1 H), 5.61-5.70 (m, 1 H), 7.01 (d, *J* = 7.7 Hz, 2 H), 7.30-7.33 (m, 2 H); ^{13}C NMR (CDCl_3) δ 21.7, 40.7, 52.1, 53.7, 117.5, 125.9, 129.9, 138.1, 141.7, 142.3. HRMS Calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_3\text{NaS}$ (M+Na): 290.0827. Found: 290.0822.

(*S_S*,*R*)-(+)-Dimethyl-[2-oxo-4-(*p*-toluenesulfinylamino)-hex-5-enyl]-phosphonate (5a**).** In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum and argon balloon was placed dimethyl

methylphosphonate (1.14 mL, 10.47 mmol) in THF (50 mL). The solution was cooled to $-78\text{ }^{\circ}\text{C}$, *n*-BuLi (5.25 mL, 10.5 mmol, 2 M in cyclohexane) was added via syringe. After 15 min the anion was added to (+)-**4a** (0.56 g, 2.09 mmol) in THF (60 mL) in a separate 250-mL single-necked, round-bottom flask, via cannula, and cooled to $-78\text{ }^{\circ}\text{C}$. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h, quenched by addition of saturated aqueous NH_4Cl (10 mL), and H_2O (10 mL) was added. The solution was extracted with Et_2O (50 mL), EtOAc ($2 \times 50\text{ mL}$), the combined organic phases were washed with brine (20 mL), dried (MgSO_4), and concentrated. Chromatography (EtOAc) afforded a colorless oil which was subjected to Kugelrohr vacuum distillation ($60\text{ }^{\circ}\text{C}$ under 2.5 mm Hg), to remove excess dimethyl methylphosphonate, affording 0.625 g (83%) of a colorless oil; $[\alpha]_{\text{D}}^{20} +92.8$ (*c* 4.0, CHCl_3); IR (neat) 3194, 1714, cm^{-1} ; ^1H NMR (CDCl_3) δ 2.36 (s, 3 H), 2.91 (dd, $J = 3.9\text{ Hz}$, $J = 5.8\text{ Hz}$, 2 H), 2.98 (d, $J = 22.7\text{ Hz}$, 2 H), 3.69 (d, $J = 3.6\text{ Hz}$, 3 H), 3.72 (d, $J = 3.6\text{ Hz}$, 3 H), 4.21-4.24 (m, 1 H), 4.72 (d, $J = 7.2\text{ Hz}$, 1 H), 5.15 (d, $J = 10.4\text{ Hz}$, 1 H), 5.24 (d, $J = 17.2\text{ Hz}$, 1 H), 5.83-5.92 (m, 1 H), 7.23 (d, $J = 8.4\text{ Hz}$, 2 H), 7.52 (d, $J = 8.8\text{ Hz}$, 2 H); ^{13}C NMR (CDCl_3) δ 21.7, 41.7 (d, $^1J_{\text{CP}} = 126.8\text{ Hz}$), 49.9, 53.3, 117.4, 125.9, 129.9, 138.1, 141.7, 142.3, 200.2 (d, $^2J_{\text{CP}} = 5.9\text{ Hz}$); ^{31}P NMR (CDCl_3) δ 21.99. HRMS Calcd. for $\text{C}_{15}\text{H}_{23}\text{NO}_5\text{PS}(\text{M}+\text{H})$: 360.1035. Found: 360.1036.

(*S_S*,*R*)-(+)-Dimethyl-[2-oxo-4-(*p*-toluenesulfinylamino)-hept-5-enyl]-phosphonate (5b**).** Chromatography (EtOAc) gave 0.89 g (81%) of a colorless oil; $[\alpha]_{\text{D}}^{20} +73.1$ (*c* 1.8, CHCl_3); IR (neat) 3188, 1713 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.66 (dd, $J = 0.8\text{ Hz}$, $J = 6.4\text{ Hz}$, 3 H), 2.33 (s, 3 H), 2.84-2.86 (m, 2 H), 2.95 (d, $^2J_{\text{HP}} = 22.7\text{ Hz}$, 2 H), 3.66 (d, $^3J_{\text{HP}} = 4.2\text{ Hz}$, 3 H), 3.69 (d, $^3J_{\text{HP}} = 4.2\text{ Hz}$, 3 H), 4.15-4.21 (m, 1 H), 4.58 (d, $J = 6.0\text{ Hz}$, 1 H), 5.40-5.46 (m, 1 H), 5.66-5.74 (m, 1 H), 7.20 (d, $J = 7.6\text{ Hz}$, 2 H), 7.49 (d, $J = 7.6\text{ Hz}$, 2 H); ^{13}C NMR (CDCl_3) δ 18.2, 21.7, 41.7 (d, $^1J_{\text{CP}} = 126.9\text{ Hz}$), 50.3, 52.9, 53.4 (d, $^2J_{\text{CP}} = 5.9\text{ Hz}$), 125.9, 129.5, 129.9, 130.4, 141.6, 142.6, 200.5 (d, $^2J_{\text{CP}} = 5.8\text{ Hz}$); ^{31}P NMR (CDCl_3) δ 22.07. HRMS Calcd. for $\text{C}_{16}\text{H}_{24}\text{NO}_5\text{NaPS}(\text{M}+\text{Na})$: 396.1011. Found: 396.1020.

(*S_S*,*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-6-amino-4-oxo-octa-2,7-diene (6a**).** In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (+)-**5a** (0.56 g, 1.56 mmol) in THF (50 mL). The solution was cooled to $0\text{ }^{\circ}\text{C}$, acetaldehyde (0.88 mL, 15.6 mmol) was added, followed by DBU (0.467 mL, 3.12 mmol). After stirring for 1 h, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (3 mL), the solution was extracted with Et_2O (50 mL) and EtOAc ($2 \times 50\text{ mL}$). The combined organic phases were washed with brine (5 mL), dried (MgSO_4), and concentrated. Chromatography (EtOAc) afforded a colorless oil 0.406 g (94%); $[\alpha]_{\text{D}}^{20} +172.6$ (*c* 1.9, CHCl_3); IR (neat) 3216, 1665, 1629 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.79 (dd, $J = 1.7\text{ Hz}$, $J = 6.8\text{ Hz}$, 3 H), 2.33 (s, 3 H), 2.79 (d, $J = 5.8\text{ Hz}$, 2 H), 4.20-4.24 (m, 1 H), 4.75 (d, $J = 6.8\text{ Hz}$, 1 H), 5.11 (dt, $J = 1.0\text{ Hz}$, $J = 10.4\text{ Hz}$, 1 H), 5.20 (dt, $J = 1.0\text{ Hz}$, $J = 17.2\text{ Hz}$, 1 H), 5.82-5.90 (m, 1 H), 5.94 (d $\times$ quartet, $J = 1.8\text{ Hz}$, $J = 16.4\text{ Hz}$, 1 H), 6.67-6.76 (m, 1 H), 7.20-7.22 (m, 2 H), 7.50-7.52 (m, 2 H); ^{13}C NMR (CDCl_3) δ 18.7, 21.7, 45.8, 53.9, 117.3, 125.9, 129.9, 132.3, 138.5, 141.6, 142.5, 144.3, 198.2. HRMS Calcd. for $\text{C}_{15}\text{H}_{20}\text{NO}_2\text{S}(\text{M}+\text{H})$: 278.1215. Found: 278.1213.

(*S_S*,*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-6-amino-4-oxo-nona-2,7-diene (6b**).** Chromatography (EtOAc) gave 0.53 g (95%) of a oil: $[\alpha]_{\text{D}}^{20} +136.4$ (*c* 1.3, CHCl_3); IR (neat) 3202, 1665, cm^{-1} ; ^1H NMR (CDCl_3) δ 1.63 (dd, $J = 1.2\text{ Hz}$, $J = 6.4\text{ Hz}$, 3 H), 1.79

(dd, $J = 1.2$ Hz, $J = 7.2$ Hz, 3 H), 2.33 (s, 3 H), 2.74-2.77 (m, 2 H), 4.17-4.23 (m, 1 H), 4.67 (d, $J = 5.7$ Hz, 1 H), 5.42-5.49 (m, 1 H), 5.64-5.73 (m, 1 H), 5.94-5.99 (m, 1 H), 6.67-6.76 (m, 1 H), 7.20 (d, $J = 7.6$ Hz, 2 H), 7.50-7.52 (m, 2 H); ^{13}C NMR (CDCl_3) δ 18.2, 18.7, 21.7, 46.3, 53.5, 125.9, 129.3, 129.8, 130.9, 132.3, 141.5, 142.8, 144.2, 198.5. HRMS Calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}_2\text{NaS}(\text{M}+\text{Na})$: 314.1191. Found: 314.1197.

(R)-(-)-N-(p-Toluenesulfonyl)-6-amino-4-oxo-octa-2,7-diene (7a). In a 50-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon were placed (+)-**6a** (0.105 g, 0.380 mmol) and *m*-CPBA (77%) (0.127 g, 0.57 mmol) in CH_2Cl_2 (10 mL). After stirring at room temperature for 4 h, the reaction mixture was quenched by addition of saturated aqueous sodium bisulfite (2 mL). After stirring for 10 min H_2O (2 mL) was added and the solution was extracted with Et_2O (15 mL) and EtOAc (2×15 mL). The combined organic phases were washed with brine (5 mL), dried (MgSO_4), and concentrated. Flash chromatography (EtOAc) afforded 0.093 g (83%) of a colorless oil; $[\alpha]_{\text{D}}^{20} -31.1$ (c 1.2, CHCl_3); IR (neat) 3287, 1655 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.79 (dd, $J = 1.5$ Hz, $J = 6.9$ Hz, 3 H), 2.34 (s, 3 H), 2.67-2.81 (m, 2 H), 4.04-4.07 (m, 1 H), 4.88-4.96 (m, 2 H), 5.49 (d, $J = 8.1$ Hz, 1 H), 5.59-5.67 (m, 1 H), 5.92-5.96 (m, 1 H), 6.69-6.75 (m, 1 H), 7.19 (d, $J = 8.2$ Hz, 2 H), 7.64 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR (CDCl_3) δ 16.6, 19.7, 42.4, 51.0, 114.6, 125.4, 127.8, 130.0, 134.9, 136.0, 141.5, 142.5, 196.3. HRMS Calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_3\text{NaS}(\text{M}+\text{Na})$: 316.0983. Found: 316.0973.

(R)-(-)-N-(p-Toluenesulfonyl)-6-amino-4-oxo-nona-2,7-diene (7b). Chromatography (EtOAc) gave 0.054 g (85%) of a white solid, mp 73-74 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} -15.6$ (c 1.2, CHCl_3); IR (neat) 3274, 1661 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.37 (d, $J = 6.0$ Hz, 3 H), 1.79 (dd, $J = 1.5$ Hz, $J = 6.6$ Hz, 3 H), 2.34 (s, 3 H), 2.71-2.74 (m, 2 H), 3.96-4.01 (m, 1 H), 5.14-5.33 (m, 2 H), 5.40 (d, $J = 7.8$ Hz, 1 H), 5.91 (dd, $J = 1.5$ Hz, $J = 15.9$ Hz, 1 H), 6.66-6.78 (m, 1 H), 7.18 (d, $J = 8.4$ Hz, 2 H), 7.62 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (CDCl_3) δ 17.7, 18.6, 21.7, 44.8, 52.9, 127.5, 128.3, 129.5, 129.6, 132.1, 138.2, 143.3, 144.3, 198.6. HRMS Calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}_3\text{NaS}(\text{M}+\text{Na})$: 330.1140. Found: 330.1149.

(R)-(-)-N-(tert-Butylcarbonyl)-6-amino-4-oxo-nona-2,7-diene (8a). In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (+)-**6a** (0.48 g, 1.73 mmol) in anhydrous methanol (20 mL). The solution was cooled to 0 $^{\circ}\text{C}$, TFA (0.80 mL, 10.4 mmol) was added slowly via syringe, and after stirring at rt for 1 h, the solution was concentrated. Chromatography (EtOAc:hexane, 1:1, then MeOH) afforded an oil that was placed under high vacuum in a 100-mL, single-necked flask for 30 min. At this time THF (50 mL) was added, the solution cooled to 0 $^{\circ}\text{C}$, NEt_3 (0.72 mL, 5.18 mmol), DMAP (0.02 g), and di-*tert*-butyl dicarbonate (0.45 g, 2.07 mmol) were added in sequence. After stirring at 0 $^{\circ}\text{C}$ for 3 h, the reaction mixture was quenched by addition of H_2O (10 mL) and the solution was extracted with Et_2O (50 mL) and EtOAc (2×50 mL). The combined organic phases were washed with brine (10 mL), dried (MgSO_4), and concentrated. Flash chromatography (EtOAc) afforded a colorless oil 0.352 g (85%); $[\alpha]_{\text{D}}^{20} -30.5$ (c 0.4, CHCl_3); IR (neat) 3337, 1710 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.36 (s, 9 H), 1.82 (dd, $J = 1.6$ Hz, $J = 6.8$ Hz, 3 H), 2.68 (dd, $J = 6.0$ Hz, $J = 16.4$ Hz, 1 H), 2.83 (dd, $J = 4.0$ Hz, $J = 16.4$ Hz, 1 H), 4.41-4.45 (m, 1 H), 5.01 (dd, $J = 1.2$ Hz, $J = 10.4$ Hz, 1 H), 5.07-5.11 (m, 1 H), 5.19 (br.s., 1 H), 5.75-5.83 (m, 1 H), 6.02-6.06 (m, 1 H), 6.71-6.84 (m, 1 H); ^{13}C NMR (CDCl_3) δ 18.7, 28.7, 44.3, 50.0, 79.8, 115.4, 132.5, 138.1, 144.1, 155.6, 198.7; HRMS Calcd. for $\text{C}_{13}\text{H}_{21}\text{NO}_3\text{Na}$ (M+Na): 262.1419. Found: 262.1417.

(R)-(-)-N-(tert-Butylcarbonyl)-6-amino-4-oxo-nona-1,7-diene (8b). Chromatography (EtOAc) gave 0.134 g (89%) of an oil; $[\alpha]_D^{20}$ -11.4 (c 3.7, CHCl₃); IR (neat) 3354, 1700 cm⁻¹; ¹H NMR (CDCl₃) δ 1.35 (s, 9 H), 1.56 (dt, *J* = 1.2 Hz, *J* = 6.4 Hz, 3 H), 1.82 (dd, *J* = 1.2 Hz, *J* = 6.8 Hz, 3 H), 2.64 (dd, *J* = 2.0 Hz, *J* = 16.0 Hz, 1 H), 2.79 (dd, *J* = 4.8 Hz, *J* = 16.0 Hz, 1 H), 4.32-4.39 (m, 1 H), 5.12 (br.s., 1 H), 5.37-5.43 (m, 1 H), 5.48-5.57 (m, 1 H), 6.01-6.06 (m, 1 H), 6.74-6.83 (m, 1 H); ¹³C NMR (CDCl₃) δ 18.0, 18.7, 28.8, 45.0, 49.7, 79.6, 126.9, 130.9, 132.5, 143.9, 155.5, 199.0. HRMS Calcd. for C₁₄H₂₃NO₃Na(M+Na): 276.1576. Found: 276.1585.

(R)-(+)-4-(N-tert-butylcarbonyl)cyclopentenone (1). In a 1000-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, reflux condenser and argon balloon were placed (R)-(-)-**8a** (0.30 g, 1.255 mmol) and catalyst **I** (0.020 g, 0.025 mmol, 2 mol%) in CH₂Cl₂ (700 mL). The solution was refluxed for 18 h and concentrated. Chromatography (EtOAc:hexane, 1:1) gave 0.240 g (97%) of a white solid, mp 124-125 °C; $[\alpha]_D^{20}$ +69.6 (c 2.6, CHCl₃); IR (neat) 3326, 1720 cm⁻¹; ¹H NMR (CDCl₃) δ 1.44 (s, 9 H), 2.13 (d, *J* = 18.5 Hz, 1 H), 2.81 (dd, *J* = 6.5 Hz, *J* = 18.5 Hz, 1 H), 4.70 (d, *J* = 6.5 Hz, 1 H), 4.94 (br.s., 1 H), 6.21 (dd, *J* = 1.5 Hz, *J* = 6.5 Hz, 1 H), 7.51 (dd, *J* = 2.0 Hz, *J* = 5.5 Hz, 1 H); ¹³C NMR (CDCl₃) δ 28.7, 42.8, 51.4, 80.6, 135.6, 155.4, 162.6, 206.9. HRMS Calcd. For C₁₀H₁₆NO₃(M+H): 198.1130. Found: 198.1125.

(S_S,R)-(+)-N-(p-Toluenesulfinyl)-4-amino-cyclopentenone (9). In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, reflux condenser and argon balloon were placed (+)-**6a** (0.040 g, 0.144 mmol) and catalyst **I**, 0.006 g, 0.007 mmol, 5 mol %) in CH₂Cl₂ (50 mL). The solution was refluxed for 16 h, concentrated and chromatography (EtOAc:hexane, 1:1) gave 0.029 g (85%) of a colorless oil; $[\alpha]_D^{20}$ +146.2 (c 0.6, CHCl₃); IR (neat) 3200, 1718 cm⁻¹; ¹H NMR (CDCl₃) δ 2.03-2.08 (m, 1 H), 2.35 (s, 3 H), 2.43-2.49 (m, 1 H), 4.35 (d, *J* = 8.8 Hz, 1 H), 4.44-4.49 (m, 1 H), 6.12 (dd, *J* = 1.7 Hz, *J* = 5.6 Hz, 1 H), 7.25 (d, *J* = 7.9 Hz, 2 H), 7.51-7.54 (m, 2 H), 7.59 (dd, *J* = 2.4 Hz, *J* = 6.0 Hz, 1 H); ¹³C NMR (CDCl₃) δ 21.8, 43.5, 52.9, 126.3, 130.2, 135.7, 140.8, 142.3, 163.8, 206.4. HRMS Calcd. C₁₂H₁₃NO₂NaS(M+H): 258.0565. Found: 258.0567.

(R)-(+)-N-(p-Toluenesulfonyl)-4-aminocyclopentenone (10). In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, reflux condenser and argon balloon were placed (-)-**7a** (0.050 g, 0.17 mmol) and catalyst **I** (0.007 g, 7.9 μmol, 5 mol %) in CH₂Cl₂ (60 mL). The solution was refluxed for 18 h and concentrated. Chromatography (EtOAc) afforded 0.040 g (94%) of a white solid; mp 137-138 °C; $[\alpha]_D^{20}$ +7.0 (c 0.4, CHCl₃); IR (neat) 3200, 1718 cm⁻¹; ¹H NMR (CDCl₃) δ 1.88 (dd, *J* = 2.6 Hz, *J* = 19.2 Hz, 1 H), 2.38 (s, 3 H), 2.46 (dd, *J* = 6.8 Hz, *J* = 19.2 Hz, 1 H), 4.51-4.56 (m, 1 H), 5.05 (d, *J* = 9.2 Hz, 1 H), 6.12 (dd, *J* = 1.8 Hz, *J* = 5.6 Hz, 1 H), 7.26 (d, *J* = 8.3 Hz, 2 H), 7.29 (dd, *J* = 2.5 Hz, *J* = 5.6 Hz, 1 H), 7.69 (d, *J* = 8.3 Hz, 2 H); ¹³C NMR (CDCl₃) δ 22.0, 42.4, 53.9, 127.5, 130.4, 136.3, 137.5, 144.6, 161.3. HRMS Calcd. for C₁₂H₁₄NO₃S(M+H): 252.0694. Found: 252.0699.

(R)-(+)-4-Aminocyclopentenone hydrochloride (11). In a 50-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar and argon balloon were placed (+)-**1** (0.030 g, 0.152 mmol) in MeOH (5 mL). Hydrochloric acid (3 mL of 1.5 N HCl) was added to the solution and after 3 h at rt the solvent was removed to give 0.02 g (99%) of a white solid mp 170 dec [lit³ mp 170 dec]; $[\alpha]_D^{20}$ +62.4 (c 0.8, MeOH, [lit³ +61.5 (c 0.5, MeOH)]). Spectral properties were consistent with literature values.³

(1S,4R)-(+)-1-Methyl-4-(*N*-*tert*-butylcarbamoyl)-2-cyclopenten-1-ol (12). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (+)-**1** (0.0273 g, 0.139 mmol) in THF (5 mL). After the solution was cooled to -40 °C (acetonitrile–dry-ice bath), MeLi (1.6 M in THF, 0.217 mL) was added slowly via syringe. The reaction mixture was quenched after stirring at this temperature for 3 h by addition of saturated aqueous NH₄Cl (1 mL). The solution was extracted with Et₂O (5 mL), EtOAc (2 × 5 mL), and the combined organic phases were washed with brine (2 mL), dried (MgSO₄), and concentrated. Chromatography (EtOAc:hexane, 1:1) afforded 0.022 g (75%) of a colorless oil; $[\alpha]_D^{20} +84.3$ (*c* 0.7, CHCl₃); IR (neat) 3323, 1678 cm⁻¹; ¹H NMR (CDCl₃) δ 1.31 (s, 3 H), 1.36 (s, 9 H), 1.70 (dd, *J* = 2.4 Hz, *J* = 14.0 Hz, 1 H), 2.33 (dd, *J* = 8.0 Hz, *J* = 14.0 Hz, 1 H), 2.90 (br.s., 1 H, -OH), 4.33–4.39 (m, 1 H), 4.78 (br.s., 1 H, -NH), 5.62 (dd, *J* = 2.2 Hz, *J* = 5.5 Hz, 1 H), 5.77 (dd, *J* = 1.7 Hz, *J* = 5.5 Hz, 1 H); ¹³C NMR (CDCl₃) δ 27.5, 28.6, 47.8, 55.6, 79.6, 81.4, 132.2, 140.8, 155.5. HRMS Calcd. for C₁₁H₁₉NO₃Na(M+Na): 236.1262. Found: 236.1259.

(1S,4R)-(+)-4-(*N*-*tert*-Butylcarbamoyl)-2-cyclopenten-1-ol (2). In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon were placed (+)-**1** (0.289 g, 1.47 mmol) and cerium(III) chloride heptahydrate (2.18 g, 5.87 mmol) in MeOH (30 mL). The solution was stirred at rt for 30 min, cooled to 0 °C, and NaBH₄ (0.222 g, 5.87 mmol) was added in one portion. After being stirred at 0 °C for 3 h, the mixture was quenched by addition of H₂O (5 mL), and extracted with Et₂O (50 mL) and EtOAc (2 × 50 mL). The combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Flash chromatography (EtOAc) afforded a 0.221 g (76%) of a white solid mp 58–59 °C, [lit.⁴ mp 65 °C]; $[\alpha]_D^{20} +65.3$ (*c* 0.6, CHCl₃). Spectral properties are consistent with literature values.⁴

(S_s,4R,6R)-(+)-*N*-(*p*-Toluenesulfinyl)-6-aminoocta-2,7-dien-4-ol (13a). In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon were placed (+)-**6a** (0.182 g, 0.659 mmol) in CH₂Cl₂ (30 mL). This solution was cooled to -78 °C, lithium triethylborohydride (1.98 mL, 1.0 M in THF, 1.98 mmol) was added by syringe and the reaction mixture was stirred at -78 °C for 1 h. At this time the solution was quenched by addition of saturated aqueous NH₄Cl (2 mL), warmed to rt, and H₂O (5 mL) was added. The solution was extracted with Et₂O (30 mL), EtOAc (2 × 30 mL), and the combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Flash chromatography (EtOAc) afforded 0.140 g (76%) of a colorless oil; $[\alpha]_D^{20} +143.6$ (*c* 1.1, CHCl₃); IR (neat) 3372, 3225 cm⁻¹; ¹H NMR (CDCl₃) δ 1.52–1.58 (m, 4 H), 1.71–1.78 (m, 1 H), 2.32 (s, 3 H), 2.87 (br.s., 1 H), 4.01–4.05 (m, 1 H), 4.14 (br.s., 1 H), 4.50 (d, *J* = 6.4 Hz, 1 H), 5.09 (dt, *J* = 1.2 Hz, *J* = 10.4 Hz, 1 H), 5.19 (dt, *J* = 1.2 Hz, *J* = 17.2 Hz, 1 H), 5.34–5.40 (m, 1 H), 5.53–5.59 (m, 1 H), 5.77–5.85 (m, 1 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.50–7.52 (m, 2 H); ¹³C NMR (CDCl₃) δ 18.0, 21.7, 43.1, 54.9, 69.5, 116.3, 125.9, 127.1, 129.9, 133.8, 139.8, 141.7, 142.4. HRMS Calcd. for C₁₅H₂₂NO₂S(M+H): 280.1371. Found: 280.1370.

(S_s,4R,6R)-(+)-*N*-(*p*-Toluenesulfinyl)-6-aminonona-2,7-dien-4-ol (13b). Chromatography (EtOAc) gave 0.4 g (76%) of a colorless oil; $[\alpha]_D^{20} +118.6$ (*c* 0.9, CHCl₃); IR (neat) 3365, 3239 cm⁻¹; ¹H NMR (CDCl₃) δ 1.59–1.66 (m, 1 H), 1.67 (d, *J* = 6.9 Hz, 3 H), 1.74 (d, *J* = 6.9 Hz, 3 H), 1.79–1.87 (m, 1 H), 2.43 (s, 3 H), 2.49 (br.s., 1 H),

4.04-4.15 (m, 1 H), 4.17-4.25 (m, 1 H), 4.39 (d, $J = 5.7$ Hz, 1 H), 5.42-5.55 (m, 2 H), 5.60-5.81 (m, 2 H), 7.30 (d, $J = 8.1$ Hz, 2 H), 7.61 (d, $J = 8.1$ Hz, 2 H); ^{13}C NMR (CDCl_3) δ 17.9, 18.0, 21.6, 43.4, 54.1, 69.7, 125.7, 127.2, 128.0, 129.7, 132.1, 133.5, 141.5, 142.5. HRMS Calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_2\text{NaS}$ (M+Na): 316.1347. Found: 316.1344.

(*S*_s,1*R*,4*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-4-amino-2-cyclopenten-1-ol (14). In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, reflux condenser, and argon balloon were placed (+)-**13a** (0.031 g, 0.11 mmol) and catalyst **II** (0.005 g, 5 mol %) in CH_2Cl_2 (60 mL). The solution was refluxed for 18 h and concentrated. Chromatography (EtOAc) afforded 0.0245 g (93%) of a colorless oil; $[\alpha]_{\text{D}}^{20} +218.6$ (c 0.7, CHCl_3); IR (neat) 3327, 3219 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.89-1.93 (m, 2 H), 2.34 (s, 3 H), 3.93 (d, $J = 9.1$ Hz, 1 H), 4.46-4.52 (m, 1 H), 4.84-4.85 (m, 1 H), 5.88-5.90 (m, 1 H), 6.01-6.03 (m, 1 H), 7.22 (d, $J = 8.0$ Hz, 2 H), 7.50-7.52 (m, 2 H); ^{13}C NMR (CDCl_3) δ 21.7, 43.4, 58.6, 76.0, 129.32, 129.39, 130.0, 136.5, 137.9, 141.7. HRMS Calcd. for $\text{C}_{12}\text{H}_{16}\text{NO}_2\text{S}$ (M+H): 238.0901. Found: 238.0901.

(4*R*,6*R*)-(-)-6-(*N*-*tert*-butylcarbamoyl)octa-2,7-dien-4-ol (15). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (+)-**13a** (0.048 g, 0.173 mmol) in anhydrous methanol (3 mL). The solution was cooled to 0 °C, TFA (0.080 mL, 1.04 mmol) was added via syringe, and the reaction mixture was stirred at rt for 1 h. At this time the solution was concentrated, passed through a short column of silica gel (EtOAc:hexane, 1:1, then MeOH). The MeOH fraction was concentrated, placed under high vacuum for 30 min, THF (5 mL) was added, and the solution was cooled to 0 °C. At this time NEt_3 (0.072 mL, 0.518 mmol), DMAP (2 mg), and di-*tert*-butyl dicarbonate (0.045 g, 0.207 mmol) were added in sequence. The reaction mixture was stirred at 0 °C for 3 h, quenched by addition of H_2O (2 mL), and the solution was extracted with Et_2O (10 mL) and EtOAc (2 $\times$ 10 mL). The combined organic phases were washed with brine (2 mL), dried (MgSO_4), and concentrated. Chromatography (EtOAc:hexane, 1:1) afforded 0.032 g (77%) of a colorless oil; $[\alpha]_{\text{D}}^{20} -9.6$ (c 1.1, CHCl_3); IR (neat) cm^{-1} ; ^1H NMR (CDCl_3) δ 1.38 (s, 9 H), 1.44-1.47 (m, 1 H), 1.61-1.63 (m, 3 H), 1.66-1.70 (m, 1 H), 3.33 (br.s., 1 H), 4.02-4.08 (m, 1 H), 4.31 (br.s., 1 H), 4.76 (d, $J = 8.4$ Hz, 1 H), 5.04-5.07 (m, 1 H), 5.10-5.14 (m, 1 H), 5.42-5.48 (m, 1 H), 5.58-5.65 (m, 1 H), 5.71-5.80 (m, 1 H); ^{13}C NMR (CDCl_3) δ 19.2, 29.8, 44.5, 50.9, 70.2, 81.4, 116.1, 127.7, 134.6, 139.7, 158.0. HRMS Calcd. for $\text{C}_{13}\text{H}_{23}\text{NO}_3\text{Na}$ (M+Na): 264.1575. Found: 264.1580.

(1*R*,4*R*)-(+)-4-(*N*-*tert*-Butylcarbamoyl)-2-cyclopenten-1-ol (16). In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, reflux condenser, and argon balloon were placed (-)-**15** (0.020 g, 0.083 mmol) and catalyst **I** (0.004 g, 0.004 mmol, 5 mol%) in CH_2Cl_2 (60 mL). The reaction mixture was refluxed for 18 h and concentrated. Chromatography (EtOAc:hexane, 1:1) afforded 0.015 g, (91%) of a white solid mp 61-63 °C; $[\alpha]_{\text{D}}^{20} +180.8$ (c 0.7, CHCl_3), [lit.⁵ +182.1 (c 10.0 CHCl_3 + 1% EtOH)]; IR (neat) 3278, 1679 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.37 (s, 9 H), 1.60 (br.s., 1 H), 1.83-1.90 (m, 1 H), 2.08 (ddd, $J = 2.8$ Hz, $J = 7.6$ Hz, $J = 14.8$ Hz, 1 H), 4.39 (br.s., 1 H), 4.83 (br.s., 1 H), 4.88-4.91 (m, 1 H), 5.85-5.91 (m, 2 H); ^{13}C NMR (CDCl_3) δ 28.8, 42.6, 56.1, 76.4, 79.9, 136.4, 136.6, 155.7. HRMS Calcd. for $\text{C}_{10}\text{H}_{18}\text{NO}_3$ (M+H): 200.1286. Found: 200.1286.

References

1. Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555.
2. Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem.* **1995**, *60*, 7037.
3. Ramesh, N. G.; Klunder, A. J. H.; Zwanenburg, B. *J. Org. Chem.* **1999**, *64*, 3635.
4. Mulvihill, M. J.; Gage, J. L.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 3357.
5. Wu, Y.; Woster, P. M. *J. Med. Chem.* **1992**, *35*, 3196.