ANGEWANDTE CHEMIE
A Journal of the Gesellschaft Deutscher Chemiker

Supporting Information

for

Angew. Chem. Int. Ed. Z19405

69451 Weinheim, Germany

A Combined Intramolecular Diels-Alder/Intramolecular Schmidt Reaction Process: A Formal Synthesis of (±)-Stenine

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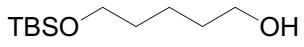
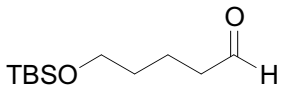
Supporting Information

Characterization of compounds **1-10** and
precursors to these compounds (15 pages)



A

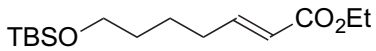
5-(*tert*-Butyldimethylsilanyloxy)-pentan-1-ol (A). Sodium hydride (60% dispersion in oil, 3.20 g, 63.4 mmol) was washed in triplicate with hexanes. After decanting the solvent the final time, dry THF was added (275 mL). The reaction mixture was cooled to 0 ºC, and 1,5-pentanediol was added slowly (6.0 g, 57.6 mmol). After stirring for 45 min at room temperature, the mixture was cooled to 0 ºC, and *tert*-butyldimethylchlorosilane (8.60 g, 57.6 mmol) was added cautiously. The mixture was allowed to acclimate to room temperature and stirred for an additional 45 min. The reaction was quenched upon addition of 10% aq K_2CO_3 and subsequently extracted with ether (4 x 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a yellow oil. Flash chromatography (15% EtOAc/hexane) gave 12.6 g (99%) of **A** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.37-1.45 (m, 2H), 1.52-1.63 (m, 4H), 1.71 (br s, 1H), 3.61-3.67 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ -4.9, 18.8, 22.4, 26.4, 32.8, 32.9, 63.3, 63.5; IR (neat) 3300, 2900, 1240 cm^{-1}; MS (CI) *m/z* 219 (M^++1), 161, 105, 92, 75, 69; HRMS calcd for $C_{11}H_{27}O_2Si$ (M^++1): 219.1780, found 219.1763.



B

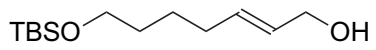
5-(*tert*-Butyldimethylsilanyloxy)-pentanal (B). A solution of oxalyl chloride (5.0 mL, 57.8 mmol) in dry CH_2Cl_2 (100 mL) was cooled to –78 ºC under an atmosphere of Ar. A solution of DMSO (8.20 mL, 116 mmol) in CH_2Cl_2 (10 mL) was added at a rate such that the reaction temperature remained below –65 ºC. After stirring for 5 min, a solution of alcohol **A** (12.6 g, 57.8 mmol) in CH_2Cl_2 (15 mL) was added slowly, and the resulting mixture was stirred for 15 min. Next, NEt_3 (40 mL, 289 mmol) was added slowly. After stirring the reaction for 10 additional min at –70 ºC, the cooling bath was removed and the reaction was allowed to warm for ca. 45 min. Upon reaching room temperature, water (100 mL) was added and stirring continued for 15 min. The reaction mixture was transferred to a separatory funnel, washed successively with 5% HCl (100

mL), saturated $NaHCO_3$ solution (100 mL), and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford an oil. Flash chromatography (15% EtOAc/hexane) gave 12.5 g (99%) of **B** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.50-1.57 (m, 2H), 1.69 (p, *J* = 7.6 Hz, 2H), 2.45 (dt, *J* = 7.3 Hz, 1.6 Hz, 2H), 3.62 (t, *J* = 6.2 Hz, 2H), 9.76 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ -4.98, 18.7, 19.0, 26.3, 32.5, 44.0, 62.9, 203.0; IR (neat) 2940, 1730 cm^{-1}; MS (CI) *m/z* 217 (M^++1), 154, 136; HRMS calcd for $C_{11}H_{25}O_2Si$ (M^++1): 217.1624, found 217.1609.



C

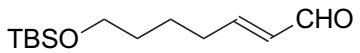
(*E*)-7-(*tert*-Butyldimethylsilanyloxy)-hept-2-enoic acid ethyl ester (C). A solution of **B** (5.10 g, 23.6 mmol) and (carbethoxymethylene)triphenylphosphorane (8.20 g, 23.6 mmol) in CH_2Cl_2 (175 mL) was heated to reflux for 18 h. The reaction was cooled to room temperature, diluted with water and extracted with pentane. The organic extract was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a yellow oil. Flash chromatography (15% EtOAc/hexane) gave 6.6 g (98%) of **C** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.84 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.50-1.54 (m, 4H), 2.19-2.24 (m, 2H), 3.59-3.62 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 5.83 (dd, *J* = 15.5 Hz, 1.3 Hz, 1H), 6.96 (dt, *J* = 15.6 Hz, *J* = 6.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ -4.9, 14.7, 18.7, 24.7, 26.3, 32.3, 32.6, 60.5, 63.1, 121.8, 149.5, 167.1; IR (neat) 2925, 1720, 1660 cm^{-1}; MS (CI) *m/z* 287 (M^++1), 229, 81; HRMS calcd for $C_{15}H_{31}O_3Si$ (M^++1): 287.2042, found 287.2063.



D

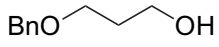
(*E*)-7-(*tert*-Butyldimethylsilanyloxy)-hept-2-en-1-ol (D). To a solution of **C** (11.2 g, 39.1 mmol) in diethyl ether (250 mL) was added DIBAL-H (1.0 M in hexanes, 86.0 mL, 86.1 mmol) at –78 ºC under Ar. The reaction was stirred at –20 ºC for 1 h and then warmed to room temperature. After stirring at room temperature for 2 h, an equal

volume of saturated aq potassium sodium tartrate was added slowly, and the resulting voluminous mixture was stirred for an additional 18 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 150 mL). The organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated to afford a colorless oil. Flash chromatography (15% EtOAc/hexane) gave 9.5 g (99%) of **D** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.42-1.56 (m, 5H), 2.07 (m, 2H), 3.62 (t, *J* = 6.4 Hz, 2H), 4.10 (d, *J* = 5.3 Hz, 2H), 5.61-5.74 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ -4.9, 18.8, 25.8, 26.4, 32.4, 32.7, 63.4, 64.2, 129.5, 133.7; IR (neat) 3330, 2930, 1470 cm^{-1}; MS (CI) *m/z* 245 (M^++1), 227, 187, 115; HRMS calcd for $C_{13}H_{29}O_2Si$ (M^++1): 245.1937, found 245.1930.



1

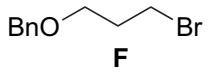
(*E*)-7-(*tert*-Butyldimethylsilanyloxy)-hept-2-enal (1). Aldehyde **1** was prepared from **D** using a Swern oxidation, as described for **B**. Flash chromatography (15% EtOAc/hexane) gave 7.1 g (99%) of **1** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.57 (m, 4H), 2.35 (m, 2H), 3.63 (m, 2H), 6.12 (dd, *J* = 15.6 Hz, 7.9 Hz, 1H), 6.86 (dt, *J* = 15.6 Hz, 6.7 Hz, 1H), 9.51 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ -4.9, 18.7, 24.6, 26.3, 32.5, 32.9, 63.0, 133.4, 159.1, 194.5; IR (neat) 2900, 1670, 1080 cm^{-1}; MS (CI) *m/z* 243 (M^++1), 185, 111, 75; HRMS calcd for $C_{13}H_{27}O_2Si$ (M^++1): 242.1780, found 243.1775.



E

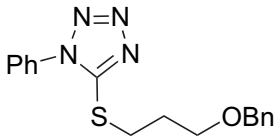
3-Benzyloxypropan-1-ol (E). Sodium hydride (60% dispersion in oil, 5.80 g, 116 mmol) was washed in triplicate with hexanes. After decanting the solvent the final time, dry DMF was added (150 mL). The reaction mixture was cooled to 0 ºC, and 1,3-propanediol (8.0 g, 105 mmol) was added slowly. After stirring for 10 min, benzyl bromide (12.5 ml, 105 mmol) was added cautiously. The mixture was allowed to acclimate to room temperature and stirred for 18 h. The reaction was quenched upon

addition of water (200 mL) and subsequently extracted with EtOAc (6 x 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a yellow oil. Flash chromatography (25% EtOAc/hexane) gave 17.3 g (92%) of **E** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (p, J = 6.1 Hz, 2H), 3.51 (br s, 1H) 3.61 (t, J = 6.1 Hz, 2H), 3.72 (m, 2H), 4.50 (s, 2H), 7.30 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 32.8, 60.9, 68.8, 73.5, 128.0, 128.8, 138.7; IR (neat) 3330, 2850, 1090 cm^{-1}; MS (CI) *m/z* 167 (M^++1), 91; HRMS calcd for $C_{10}H_{15}O_2$ (M^++1): 167.1072, found 167.1067.



F

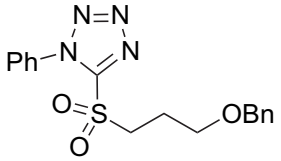
3-Benzyloxy-1-bromopropane (F). To a solution of alcohol **E** (10.2 g, 61.4 mmol) in dry CH_2Cl_2 (150 mL) was added CBr_4 (25.4 g, 76.7 mmol). After cooling the solution to 0 ºC, PPh_3 (29.0 g, 110 mmol) was added in portions. The resulting red solution was stirred at room temperature for 18 h. The solvent was removed under reduced pressure, and the precipitate washed several times with ether (6 x 100 mL) and filtered. The collective ether extracts were concentrated to afford a yellow oil. Flash chromatography (3% EtOAc/hexane) gave 14 g (99%) of **F** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (p, J = 6.3 Hz, 2H), 3.46 (t, J = 6.6 Hz, 2H), 3.53 (t, J = 5.8 Hz, 2H), 4.45 (s, 2H), 7.29 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 31.2, 33.5, 68.2, 73.6, 128.13, 128.15, 128.9, 138.8; IR (neat) 2820, 1090, 730, 690 cm^{-1}; MS (CI) *m/z* 228 (M^+-1), 91; HRMS calcd for $C_{10}H_{12}OBr$ (M^+-1): 227.0072, found 227.0067.



G

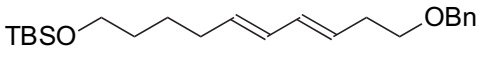
5-(3-Benzyloxypropylsulfanyl)-1-phenyl-1*H*-tetrazole (G). Sodium hydride (60% dispersion in oil, 3.70 g, 92.9 mmol) was washed in triplicate with hexanes. After decanting the solvent the final time, dry DMF was added (225 mL). The reaction mixture was cooled to 0 ºC, and 1-phenyl-1*H*-tetrazole-5-thiol (17.7 g, 77.4 mmol) was added

slowly. After stirring for 10 min, 3-benzyloxy-1-bromopropane **F** (13.8 g, 77.4 mmol) was added slowly, and the resulting solution was stirred for 18 h at room temperature. The reaction was quenched upon addition of water (500 mL) and subsequently extracted with EtOAc (6 x 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a yellow oil. Flash chromatography (25% EtOAc/hexane) gave 25 g (99%) of **G** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (p, *J* = 6.2 Hz, 2H), 3.53 (t, *J* = 7.0 Hz, 2H) 3.63 (t, *J* = 5.8 Hz, 2H), 4.52 (s, 2H), 7.32 (m, 5H), 7.56 (s, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 29.6, 30.8, 68.4, 73.5, 124.2, 128.11, 128.13, 128.8, 130.2, 130.5, 134.1, 138.5, 154.8; IR (neat) 2820, 1680, 1480 cm^{-1}; MS (CI) *m/z* 327 (M^++1), 173, 91, 84; HRMS calcd for $C_{17}H_{18}N_4OS$ (M^++1): 327.1280, found 327.1292.



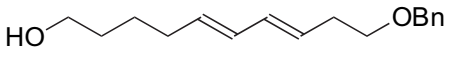
2

5-(3-Benzyloxy-propane-1-sulfonyl)-1-phenyl-1*H*-tetrazole (2). To a stirred solution of sulfide **G** (17.1 g, 52.4 mmol) in CH_2Cl_2 (400 mL) was added $NaHCO_3$ (13.2 g, 157 mmol) and *m*-CPBA (27.1 g, 157 mmol). The resulting mixture was stirred under an Ar atmosphere for 18 h and then quenched with 10% aq NaOH solution (150 mL). After extracting the aqueous layer with EtOAc (5 x 100 mL), the organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford an orange oil. Flash chromatography (25% EtOAc/hexane) gave 17.5 g (93%) of **2** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25-2.32 (m, 2H), 3.65 (t, *J* = 5.8 Hz, 2H), 3.90 (m, 2H), 4.52 (s, 2H), 7.32-7.38 (m, 5H), 7.60-7.70 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.4, 54.0, 67.5, 73.4, 125.6, 128.2, 128.3, 128.9, 130.1, 131.9, 133.4, 138.2, 153.9; IR (neat) 2820, 1580, 1480, 1320, cm^{-1}; MS (CI) *m/z* 359 (M^++1), 131; HRMS calcd for $C_{17}H_{19}N_4O_3S$ (M^++1): 359.1178, found 359.1182.



3

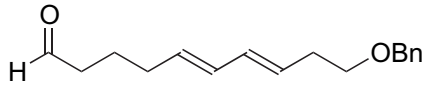
(5*E,7E*)-(10-Benzyloxy-deca-5,7-dienyloxy)-*tert*-butyldimethylsilane (3). A solution of sulfone **2** (10.0 g, 27.9 mmol) in THF (175 mL) was cooled to –78 ºC, and a solution of lithium bis(trimethylsilyl)amide (30.7 mL, 30.7 mmol) in THF (20 mL) was added slowly. The resulting solution was stirred at –65 ºC for 1 h, and then a solution of aldehyde **1** (6.90 g, 28.5 mmol) in THF (20 mL) was added at a rate such that the temperature remained below –65 ºC. The orange solution was stirred for an additional hour at –65 ºC and then allowed to acclimate to room temperature over 18 h. Water (150 mL) was added and the resulting mixture stirred for 1 h. The reaction was transferred to a separatory funnel, extracted with Et_2O (3 x 100 mL), dried (Na_2SO_4), filtered, and concentrated to afford a yellow oil. Flash chromatography (3% EtOAc/hexane) gave 9.6 g (90%) of **3** as a pale yellow oil. The ratio of (5*E,7E*)-**3**/(5*E*,7*Z*)-**3** was determined to be ca. 85:15 by ^{1}H NMR. (5*E,7E*)-**3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.93 (s, 9H), 1.37-1.49 (m, 2H), 1.52-1.59 (m, 2H), 2.08-2.13 (m, 2H), 2.39-2.44 (m, 2H), 4.55 (s, 2H), 5.57-5.65 (m, 2H), 6.01-6.14 (m, 2H), 7.28-7.37 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ -4.68, 18.8, 22.6, 26.4, 32.8, 33.1, 33.5, 63.6, 70.3, 73.3, 127.9, 128.0, 128.4, 128.7, 130.8, 132.7, 133.3, 138.9; IR (neat) 2900, 1450, 1090 cm^{-1}; MS (CI) *m/z* 375 (M^++1), 243, 91; HRMS calcd for $C_{23}H_{39}O_2Si$ (M^++1): 375.2719, found 375.2690. (5*E,7Z*)-**3**: ^{1}H NMR (400 MHz, $CDCl_3$, diagnostic peaks only) δ 2.51-2.56 (m, 2H), 4.56 (m, 2H), 5.33-5.42 (m, 1H), 5.65-5.75 (m, 1H), 6.34-6.42 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, diagnostic peaks only) δ 26.0, 28.8, 33.0, 63.4, 70.3, 125.7, 126.1, 128.0, 129.1, 130.9, 135.6.



H

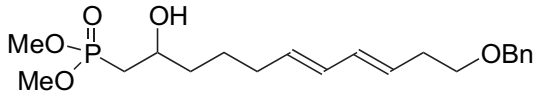
(5*E,7E*)-10-Benzyloxy-deca-5,7-dien-1-ol (H). To a stirred solution of diene **3** (5.70 g, 15.2 mmol) in ethanol (150 mL) was added pyridinium *p*-toluenesulfonate (1.10 g, 4.57 mmol). After stirring for 18 h, the solution was concentrated to give a viscous oil. Flash chromatography (25% EtOAc/hexane) gave 3.8 g (95%) of **H** as a colorless oil. The ratio of (5*E,7E*)-**H**/(5*E*,7*Z*)-**H** was determined to be ca. 85:15 by ^{1}H NMR. (5*E,7E*)-**H**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.63 (m, 5H), 2.11 (m, 2H), 2.40 (m, 2H), 3.53 (t, *J* = 6.8 Hz, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 4.54 (s, 2H), 5.62 (dt, *J* = 14.4 Hz, *J* = 6.9 Hz,

2H), 6.07 (m, 2H), 7.32 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.9, 32.6, 32.7, 33.5, 63.2, 70.3, 73.3, 128.0, 128.1, 128.6, 128.8, 130.9, 132.6, 133.0, 138.8; IR (neat) 3350, 2900, 1440, 1090 cm^{-1}; MS (CI) *m/z* 261 (M^++1), 243, 169, 91; HRMS calcd for $C_{17}H_{25}O_2$ (M^++1): 261.1855, found 261.1853. (5*E,7Z*)-**H**: ^{1}H NMR (400 MHz, $CDCl_3$, diagnostic peaks only) δ 2.42 (m, 2H), 5.37 (m, 1H), 5.71 (m, 1H), 6.34 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, diagnostic peaks only) δ 25.8, 28.8, 33.0, 70.2, 126.0, 126.2, 128.1, 130.8, 135.3.



I

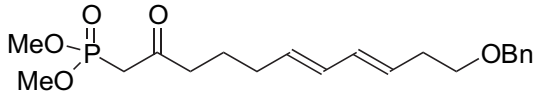
(5*E,7E*)-10-Benzyloxy-deca-5,7-dienal (I). Aldehyde **I** was prepared from **H** using a Swern oxidation, as described for **B**. Flash chromatography (15% EtOAc/hexane) gave 10 g (99%) of **I** as a yellow oil. The ratio of (5*E,7E*)- **I** /(5*E*,7*Z*)- **I** was determined to be ca. 85:15 by ^{1}H NMR. (5*E,7E*)- **I**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62-1.71 (m, 2H), 1.97–2.10 (m, 2H), 2.32-2.38 (m, 4H), 3.47 (t, *J* = 6.7 Hz, 2H), 4.46 (s, 2H), 5.45-5.61 (m, 2H), 5.95-6.07 (m, 2H), 7.25 (m, 5H), 9.67 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.0, 32.2, 33.5, 43.5, 70.2, 73.2, 127.9, 128.0, 128.8, 129.2, 131.7, 131.8, 132.3, 139.0, 202.6; IR (neat) 2800, 1695, 1080 cm^{-1}; MS (CI) *m/z* 259 (M^++1), 154, 136; HRMS calcd for $C_{12}H_{23}O_2$ (M^++1): 259.1698, found 259.1689. (5*E,7Z*)- **I**: ^{1}H NMR (400 MHz, $CDCl_3$, diagnostic peaks only) δ 2.49 (m, 2H), 5.33 (m, 1H), 6.33 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, diagnostic peaks only) δ 28.9, 32.5, 70.1, 126.6, 127.0, 127.9, 130.6, 134.1.



J

(6*E*,8*E*)-(11-benzyloxy-2-hydroxy-undeca-6,8-dienyl)-phosphonic acid dimethyl ester (J). To a cooled solution of dimethyl methyl phosphonate (2.60 mL, 23.8 mmol) in THF (25 mL) at -78 ºC was added *n*-butyllithium (1.6 M in hexanes, 15.5 mL, 23.3 mmol) slowly. The solution was stirred at -78 ºC for 1 h, and then aldehyde **I** (2.80 g, 10.8 mmol) was added as a solution in THF (10 mL). Stirring was continued at

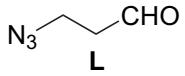
-78 ºC for 3h and then at 0 ºC for an additional hour. The reaction mixture was quenched at 0 ºC with saturated aq NH_4Cl solution, transferred to a separatory funnel, and extracted with EtOAc (3 x 100 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford a yellow oil. Flash chromatography (100% EtOAc) gave 3.8 g (92%) of β-hydroxyphosphonate **J** as a pale yellow oil. The ratio of (6*E,*8E)-**J**/(6*E*,8*Z*)-**J** was determined to be ca. 85:15 by ^{1}H NMR. (6*E,*8E)-**J**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39-1.56 (m, 4H), 1.90 (m, 1H), 1.95 (m, 1H), 2.01-2.14 (m, 2H), 2.33-2.40 (m, 2H), 3.48 (t, *J* = 6.8 Hz, 2H), 3.73 (d, *J* = 10.9 Hz, 6H), 3.87 (m, 1H), 3.96 (br s, 1H), 4.49 (s, 2H), 5.46-5.60 (m, 2H), 5.93-6.08 (m, 2H), 7.26 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.5, 32.7, 33.4, 38.1, 38.2, 52.6, 52.8, 66.5, 70.2, 73.2, 127.9, 128.0, 128.6, 128.7, 131.0, 132.9, 138.8; IR (neat) 3350, 2890, 1200 cm^{-1}; MS (CI) *m/z* 383 (M^++1), 357, 207, 91; HRMS calcd for $C_{20}H_{32}O_5P$ (M^++1): 383.198, found 383.1968. (6*E,*8Z)-**J**: ^{1}H NMR (400 MHz, $CDCl_3$, diagnostic peaks only) δ 2.46 (dd, *J* = 13.3 Hz, 8.0 Hz, 2H), 4.50 (s, 2H), 5.33 (m, 1H), 5.60 (m, 1H), 6.34 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, diagnostic peaks only) δ 28.8, 32.7, 33.0, 33.7, 38.1, 38.3, 52.7, 52.8, 66.5, 70.2, 127.9.



K

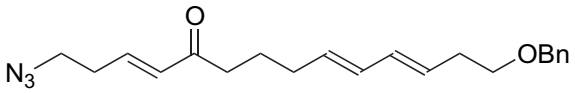
(6*E*,8*E*)-(11-Benzyloxy-2-oxo-undeca-6,8-dienyl)-phosphonic acid dimethyl ester (K). To a stirred solution of hydroxyphosphonate **J** (2.90 g, 7.58 mmol) in dry CH_2Cl_2 (50 mL) was added activated 4Å sieves, *N*-morpholine-*N*-oxide (1.30 g, 11.4 mmol) and TPAP (0.13 g, 0.38 mmol). After stirring the resulting black mixture for 72 h, the reaction mixture was filtered through Celite and washed with EtOAc. Concentration of the filtrate provided a black oil. Flash chromatography (100% EtOAc) gave 2.2 g (75%) of a yellow oil **K**. The ratio of (6*E,*8E)-**K**/(6*E*,8*Z*)-**K** was determined to be ca. 85:15 by ^{1}H NMR. (6*E,*8E)-**K**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64-1.73 (m, 2H), 2.05-2.19 (m, 2H), 2.36-2.41 (m, 2H), 2.59-2.63 (m, 2H), 3.05 (d, *J* = 22.7 Hz, 2H), 3.51 (t, *J* = 6.8 Hz, 2H), 3.75-3.77 (d, *J* = 11.2 Hz, 6H), 4.51 (s, 2H), 5.49-5.63 (m, 2H), 5.97-6.09 (m, 2H), 7.33 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.3, 32.0, 33.5, 41.1, 43.7, 53.4, 70.2, 73.3, 127.9, 128.1, 128.8, 129.1, 131.5, 132.0, 132.3, 138.8, 202.2; IR (neat)

2950, 1720, 1035 cm^{-1}; MS (CI) *m/z* 381 (M^++1), 345, 255, 91; HRMS calcd for $C_{20}H_{30}O_5P$ (M^++1): 381.1831, found 381.1836. (6*E*,8*Z*)-**K**: ^1H NMR (400 MHz, $CDCl_3$, diagnostic peaks only) δ 2.47-2.52 (m, 2H), 4.52 (s, 2H), 5.34-5.39 (m, 1H), 6.28-6.34 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, diagnostic peaks only) δ 28.8, 32.3, 42.4, 70.2, 126.4, 126.8, 130.5, 134.3.



L

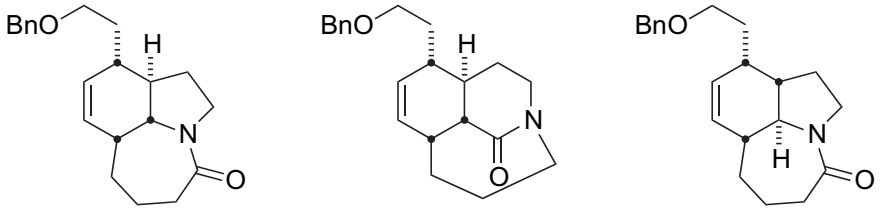
3-Azido-propionaldehyde (L).[1] To an ice-cooled solution of acetic acid (1.30 mL) and acrolein (0.60 mL, 8.92 mmol) was added NaN_3 (0.87 g, 13.4 mmol) in water (11 mL). The resulting mixture was stirred for 15 min and then quickly poured over saturated $NaHCO_3$ solution (caution – foaming!). The mixture was extracted with Et_2O (2 x 100 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure (no heat). The resulting yellow oil was placed on high vacuum for a few min to remove residual ether. This protocol afforded 880 mg of a pale yellow oil **L** in 98% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 2.71 (t, *J* = 6.3 Hz, 2H), 3.59 (t, *J* = 6.3 Hz, 2H), 9.77 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 43.0, 44.8, 200.1; IR (neat) 2045, 1690 cm^{-1}. **CAUTION: this compound has a high active nitrogen content and may be an explosion hazard. Use appropriate safety measures.**



4

(3*E*,9*E*,11*E*)-1-Azido-14-benzyloxy-tetradeca-3,9,11-trien-5-one (4). Prior to use, $Ba(OH)_2 \bullet 8H_2O$ was dried in a 140 ºC oven for 2 h (NOTE: drying of the hydroxide for shorter or longer periods of time resulted in lower overall yields of **4**). Phosphonate **K** (1.30 g, 3.42 mmol) was placed in a 100 mL flask with THF (30 mL) and $Ba(OH)_2 \bullet 8H_2O$ (0.86 g, 2.74 mmol). The mixture was stirred for 30-45 min, causing it to turn white in color. Aldehyde **L** (0.34 g, 3.42 mmol) was added slowly in 40:1 THF/H_2O (15 mL). After stirring the gelatinous material for 6 h, the solution was poured over saturated $NaHCO_3$ solution and extracted with EtOAc (4 x 100 mL). The extracts were dried

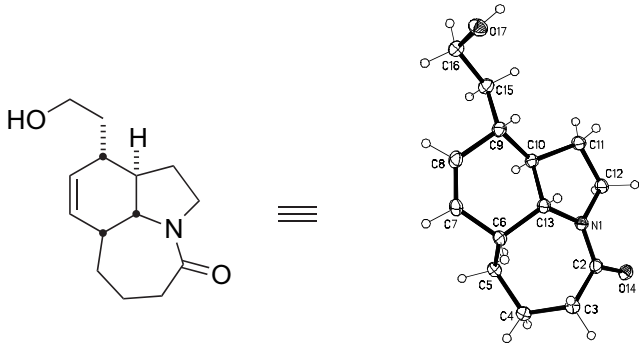
(Na_2SO_4), filtered, and concentrated to give a yellow oil. Flash chromatography (15% EtOAc/Hex) afforded 1.0 gram of a yellow oil **4** in 85% yield. The ratio of (3*E,9E,*11*E*)-**4**/(3*E*,9*E*,11*Z*)-**4** was determined to be ca. 85:15 by ^{1}H NMR. (3*E,*9*E,*11*E*)-**4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67-1.76 (m, 2H), 2.02-2.16 (m, 2H), 2.39-2.43 (m, 2H), 2.43-2.55 (m, 4H), 3.39 (t, *J* = 6.7 Hz, 2H), 3.49 (t, *J* = 6.8 Hz, 2H), 4.50 (s, 2H), 5.45-5.70 (m, 2H), 5.97-6.09 (m, 2H), 6.14 (d, *J* = 16.0 Hz, 1H), 6.73 (dt, *J* = 16.0 Hz, *J* = 6.8 Hz, 1H), 7.26-7.33 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.9, 32.2, 32.3, 33.5, 39.9, 50.0, 70.2, 73.3, 127.9, 128.0, 128.1, 128.8, 129.0, 131.3, 132.3, 132.4, 132.7, 142.2, 200.2; IR (neat) 2050, 1700, 1650, 1600 cm^{-1}; MS (FAB$^+$) *m/z* 354 (M^++1), 154, 136; HRMS calcd for $C_{21}H_{28}N_3O_2$ (M^++1): 354.2182, found 354.2162. (3*E*,9*E*,11*Z*)-**4**: ^{1}H NMR (400 MHz, $CDCl_3$, diagnostic peaks only): δ 5.34-5.38 (m, 1H), 6.28-6.35 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, diagnostic peaks only) δ14.6, 21.5, 27.4, 28.8, 32.6, 39.9, 60.8, 126.3, 126.8, 130.6, 134.6.



5 **6** **7**

Lactams 5, 6, and 7. To a flame dried 50 mL flask was added azidotriene **4** (0.25 g, 0.71 mmol) in CH_2Cl_2 (35 mL) and $MeAlCl_2$ (0.71 mL, 1.0 M soln in toluene, 0.71 mmol). Refluxing the yellow solution for 48 h produced a dark greenish solution that was cooled to room temperature and then poured over saturated aq $NaHCO_3$ solution (100 mL). Upon shaking, the dark solution turned yellow in color. The mixture was extracted with EtOAc (3 x 100 mL), the combined organic layers dried (Na_2SO_4), filtered, and concentrated to afford a yellow oil. Flash chromatography (100% EtOAc) afforded 100 mg (43%, viscous oil) of major isomer **5**, 56 mg (24%, viscous oil) of bridged lactam **6**, and 27 mg (12%, white solid) of minor isomer **7**. Major lactam **5** (R_f = 0.17): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39-1.48 (m, 3H), 1.54-1.64 (m, 2H), 1.72 (m, 2H), 1.85-1.93 (m, 2H), 2.13-2.16 (m, 1H), 2.28 (ddd, *J* = 13.2 Hz, 5.1 Hz, 1.7 Hz, 1H), 2.59 (dt, *J* = 13.4

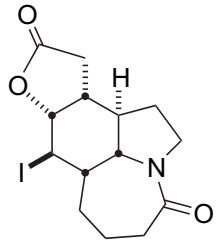
Hz, 6.7 Hz, 1H), 2.67 (m, 1H), 3.42 (m, 1H), 3.47-3.52 (m, 3H), 3.57 (t, *J* = 6.6 Hz, 1H), 4.51 (m, 2H), 5.53-5.59 (m, 1H), 5.63-5.66 (m, 1H), 7.31 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.2, 25.4, 26.8, 33.2, 33.4, 36.5, 38.0, 43.9, 45.9, 62.6, 68.0, 73.5, 128.01, 128.03, 128.8, 130.7, 130.9, 138.7, 171.5; IR (neat) 2840, 1625 cm^{-1}; MS (CI) *m/z* 326 (M^++1), 234, 91; HRMS calcd for $C_{21}H_{28}NO_2$ (M^++1): 326.2120, found 326.2129; Bridged lactam **6** (R_f = 0.63): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.64 (m, 4H), 1.72-2.01 (m, 5H), 2.19 (m, 1H), 2.36 (m, 1H), 2.48 (dt, *J* = 12.4 Hz, *J* = 4.8 Hz, 1H), 2.58 (dd, *J* = 10.0 Hz, *J* = 4.5 Hz, 1H), 2.89 (dt, *J* = 11.2 Hz, *J* = 4.2 Hz, 1H), 3.56 (t, *J* = 6.3 Hz, 2H), 3.69 (dt, *J* = 15.3 Hz, *J* = 4.2 Hz, 2H), 4.49 (m, 2H), 5.62-5.67 (m, 2H), 7.27-7.37 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.9, 25.4, 31.3, 32.2, 39.3, 39.9, 41.3, 53.4, 56.2, 56.8, 68.2, 73.6, 128.0, 128.1, 128.8, 132.6, 133.4, 138.8, 188.1; IR (neat) 2940, 1690 cm^{-1}; MS (FAB$^+$) *m/z* 326 (M^++1), 234, 91; HRMS calcd for $C_{21}H_{28}NO_2$ (M^++1): 326.2120, found 326.2122; Minor lactam **7** (R_f = 0.25). Mp: 85-88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-1.26 (m, 1H), 1.44-1.47 (m, 1H), 1.57-1.63 (m, 2H), 1.76-1.79 (m, 1H), 1.86-1.91 (m, 2H), 1.95-1.99 (m, 1H), 2.08-2.17 (m, 2H), 2.31 (t, *J* = 13.9 Hz, 1H), 2.59-2.67 (m, 2H), 3.00 (dd, *J* = 10.7 Hz, *J* = 9.3 Hz, 1H), 3.20-3.27 (m, 1H), 3.55-3.61 (m, 2H), 3.90 (dd, *J* = 11.6 Hz, *J* = 8.0 Hz, 1H), 4.52 (m, 2H), 5.37 (m, 1H), 5.75-5.79 (m, 1H), 7.28-7.36 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.2, 25.7, 30.8, 34.4, 37.0, 38.8, 45.1, 46.8, 47.2, 60.1, 68.7, 73.5, 128.1, 128.8, 131.3, 138.7, 175.3; IR (neat) 2820, 1600, 1430 cm^{-1}; MS (FAB$^+$) *m/z* 326 (M^++1), 234, 91; HRMS calcd for $C_{21}H_{28}NO_2$ (M^++1): 326.2120, found 326.2102.



M

10-(2-Hydroxyethyl)-1,2,6,7,7a,10,10a,10b-octahydro-5*H*-azepino[3,2,1-*hi*]indol-4-one (M). Ammonia (10 mL) was condensed into a solution of lactam **5** (250

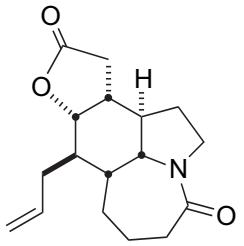
mg, 0.768 mmol) in THF (3 mL) at -78 ºC. Sodium was added, and upon stirring, the reaction mixture turned blue. The reaction was quenched with solid NH_4Cl, and the ammonia was allowed to evaporate. The resulting mixture was diluted with water (5 mL) and then extracted with CH_2Cl_2 (3 x 30mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a colorless oil. Flash chromatography (5% MeOH/CH_2Cl_2) afforded 180 mg (99% yield) of a white crystalline solid **M**. Mp 158-160 ◦C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.50 (m, 4H), 1.60-1.65 (m, 3H), 1.72-1.74 (m, 1H), 1.83-1.92 (m, 2H), 2.13-2.18 (m, 1H), 2.28 (ddd, *J* = 13.3 Hz, 5.1 Hz, 1.7 Hz, 1H), 2.64 (dt, *J* = 13.4 Hz, 6.7 Hz, 1H), 2.74 (m, 1H), 3.41-3.59 (m, 3H), 3.72-3.79 (m, 2H), 5.57-5.62 (m, 1H), 5.66-5.69 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.1, 25.4, 26.8, 33.1, 36.3, 36.5, 37.6, 43.9, 45.9, 60.4, 62.7, 130.7, 130.8, 171.6; IR (neat) 2920, 1600 cm^{-1}; MS (CI) *m/z* 236 (M^+-1), 111, 69; HRMS calcd for $C_{14}H_{22}NO_2$ (M^+-1): 236.1651, found 236.1640. Recrystallization from CH_2Cl_2/Hex gave white crystals (Mp 158-160 ◦C) that were subjected to single-crystal x-ray analysis.



9

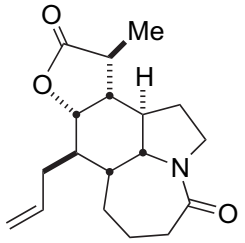
Iodolactam (9). Freshly prepared Jones reagent (8.0 N, 2.7 M) was added dropwise to an ice-cooled solution of alcohol **M** (100 mg, 0.425 mmol) in acetone (10 mL) until an orange color persisted. The solution was stirred for 3 h at 0 ºC and then 30 min at room temperature. After quenching with 2-propanol, the mixture was concentrated to afford a blue-green solid. To this material was added saturated aq $NaHCO_3$ solution (10 mL), THF (5 mL), Et_2O (5 mL), and solid $NaHCO_3$ (ca. 0.5 g). The mixture was cooled to 0 ºC, and then I_2 (0.32 g, 1.28 mmol) was added. The resulting reaction mixture was stirred for 2 h at 0 ºC and then at room temperature for 15 h. After adding saturated aq sodium thiosulfate solution, the solution was extracted with CH_2Cl_2 (3 x 50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a yellow oil. Flash

chromatography (5% MeOH/CH_2Cl_2) afforded 128 mg (80% yield) of a white solid **9**. Mp 187 °C (dec.), ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (m, 1H), 1.92 (m, 3H), 1.74-1.78 (m, 1H), 1.90-2.13 (m, 3H), 2.33-2.37 (m, 1H), 2.45 (dd, *J* = 18.0 Hz, 8.6 Hz, 1H), 2.64 (m, 2H), 2.88 (dd, *J* = 18.0 Hz, 10.0 Hz, 1H), 3.45 (m, 1H), 3.69 (dd, *J* = 11.6 Hz, 9.4 Hz, 1H), 3.78 (dd, *J* = 11.8 Hz, 9.0 Hz, 1H), 3.93 (t, *J* = 10.9 Hz, 1H), 4.94 (dd, *J* = 11.2 Hz, 9.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.2, 25.0, 27.9, 33.3, 33.6, 33.9, 38.0, 43.2, 44.2, 47.0, 60.6, 83.4, 171.4, 174.6; IR (neat) 1770, 1630 cm^{-1}; MS (EI) *m/z* 376 (M^++H), 248; HRMS calcd for $C_{14}H_{19}NO_2$ (M^++1): 376.0410, found 376.0405.



N

Allylated lactam (N). To a solution of lactam **9** (86 mg, 0.229 mmol) in degassed benzene (15 mL) was added allyltributyltin (0.14 mL, 0.459 mmol) and AIBN (8.0 mg, 0.0459 mmol). The solution was refluxed for 22 h, cooled to room temperature, and concentrated under reduced pressure to afford a colorless oil. Flash chromatography (5% MeOH/CH_2Cl_2) afforded 62 mg (93% yield) of a colorless oil **N**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42-1.80 (m, 6H), 1.90-2.03 (m, 3H), 2.10-2.16 (m, 1H), 2.35-2.50 (m, 4H), 2.60 (m, 1H), 2.87 (dd, *J* = 17.9 Hz, 10.0 Hz, 1H), 3.48 (m, 2H), 3.77 (dd, *J* = 12.1 Hz, 9.1 Hz, 1H), 4.60 (dd, *J* = 11.9 Hz, 9.3 Hz, 1H), 5.84-5.94 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.6, 23.6, 28.2, 33.5, 33.6, 34.3, 35.3, 37.7, 42.2, 44.7, 47.1, 60.8, 81.2, 119.1, 134.3, 171.5, 176.3; IR (neat) 1760, 1620 cm^{-1}; MS (EI) *m/z* 290 (M^++1), 246, 84; HRMS calcd for $C_{17}H_{24}NO_3$ (M^++1): 290.1756, found 290.1755.



10

Methylated lactam (10). To a cooled solution of allylated lactam **N** (0.16 g, 0.57 mmol) in THF (10 mL) at -78 ºC was added lithium bis(trimethylsilyl)amide (1.0 M in hexanes, 1.0 mL, 1.0 mmol) slowly. The solution was stirred at -78 ºC for 1 h, and then iodomethane (0.35 mL, 5.67 mmol) was added quickly. The yellow solution was stirred at -78 ºC for 40 min longer, and then the reaction was quenched with the addition of 20% aq HCl (ca. 6 mL). After warming to room temperature, the solution was extracted with CH_2Cl_2 (3 x 30mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford an off-white solid. Flash chromatography (50% EtOAc/50% Hex) afforded 0.13 mg (77% yield) of a white crystalline solid. An analytical sample was furnished by reverse-phase prep HPLC (50% acetonitrile/50% water/0.1% TFA). Mp: 119-121 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 7.1 Hz, 3H), 1.37-1.53 (m, 2H), 1.60-1.76 (m, 3H), 1.87-2.02 (m, 3H), 2.13-2.21 (m, 2H), 2.34-2.46 (m, 5H), 3.47 (m, 2H), 3.74 (dd, J = 12.2 Hz, J = 9.1 Hz, 1H), 4.43 (dd, J = 12.3 Hz, J = 9.4 Hz, 1H), 5.13 (m, 2H), 5.79-5.89 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.9, 22.5, 23.4, 28.2, 33.0, 34.1, 35.3, 40.2, 42.0, 44.7, 45.9, 47.5, 61.0, 78.7, 119.2, 134.2, 172.2, 178.9; IR (neat) 1779, 1639 cm^{-1}; MS (FAB$^+$) *m/z* 304 (M^++1), 154, 136; HRMS calcd for $C_{18}H_{26}NO_3$ (M^++1): 304.1908, found 304.1913. All spectroscopic and physical data of compound **10** were in agreement with published data.[2]

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[1] J. H. Boyer, *J. Am. Chem. Soc.* **1951**, *73*, 5248-5252.

[2] (a) C.Y. Chen, D. J. Hart, *J. Org. Chem.* **1990**, *55*, 6236-6240. (b) D. J. Hart, C.Y. Chen, *J. Org. Chem.* **1993**, *58*, 3840-3849.