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Supplementary Data for

A stereoselective synthesis of (+)-physoperuvine using a tandem aza-Claisen rearrangement and ring closing metathesis reaction

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1. General Experimental

All reagents and starting materials were obtained from commercial sources and used as received. Dry solvents were purified using a PureSolv 500 MD solvent purification system. Petroleum ethers refer to the fraction boiling at 40-60 °C. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to TMS (δ_H 0.00 and δ_C 0.0) or residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Mass spectra were obtained using a JEOL JMS-700 spectrometer. Infrared spectra were obtained using a JASCO FTIR 410 using a Golden Gate apparatus. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. Chiral HPLC was performed on an Agilent 1100 series instrument and were calibrated with the appropriate racemic mixture.

2. Experimental Procedures and Spectroscopic Data For All Compounds

6-Hepten-1-ol 8[1]

Ethyl 6-heptenoate **7** (2.5 g, 16.0 mmol) was dissolved in diethyl ether (200 mL) and cooled to –78 °C. DIBAL-H (1 M in hexane) (35 mL, 35.2 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 3 h, before warming to room temperature. The solution was cooled to 0 °C and quenched by the addition of a saturated solution of ammonium chloride (50 mL) and warmed to room temperature with vigorous stirring over 1 h producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (400 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (diethyl ether : petroleum ether, 3 : 7) gave 6-hepten-1-ol **8** (1.71 g, 94% yield) as a yellow oil. Spectroscopic data consistent with literature.[1] δ_H (400 MHz, $CDCl_3$) 1.32-1.47 (4H, m, 3-H_2 and 4-H_2), 1.53-1.62 (2H, m, 2-H_2), 2.06 (2H, q, *J* 6.6 Hz, 5-H_2), 3.63 (2H, t, *J* 6.6 Hz, 1-H_2), 4.93 (1H, d, *J* 10.0 Hz, 7-*H*H), 4.99 (1H, d, *J* 15.6 Hz, 7-H*H*), 5.80 (1H, ddt, *J* 15.6, 10.0, 6.6 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 25.2 (CH_2), 28.7 (CH_2), 32.6 (CH_2), 33.7 (CH_2), 62.8 (CH_2), 114.4 (CH_2), 138.9 (CH); *m/z* (Cl) 115 (MH^+, 100%), 97 (61), 95 (9), 83 (6).

Ethyl (2*E*)-2,8-nonadienoate 9[2]

Dimethyl sulfoxide (1.55 mL, 22.0 mmol) was added to a stirred solution of oxalyl chloride (1.07 mL, 12.28 mmol) in dichloromethane (100 mL) at –78 °C. The reaction mixture was stirred for 0.3 h before 6-hepten-1-ol **8** (1.0 g, 8.77 mmol) in dichloromethane (50 mL) was slowly added. The reaction mixture was stirred for a further 0.3 h before triethylamine (6.10 mL, 43.86 mmol) was added. This reaction mixture was stirred for 0.5 h at –78 °C and then allowed to warm to room temperature and stirred for a further 2 h. Meanwhile, a solution of lithium chloride (0.67 g, 15.79 mmol), triethyl phosphonoacetate (3.13 mL, 15.79 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (2.36 mL, 15.79 mmol) in acetonitrile (100 mL) was prepared and stirred for 1.0 h. The Swern solution was concentrated *in vacuo*, then the Horner Wadsworth Emmons solution was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by the addition of a saturated solution of ammonium chloride (50 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (4 × 75 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange oil. Purification by flash column chromatography (diethyl ether : petroleum ether, 3 : 97) yielded ethyl (2*E*)-2,8-nonadienoate **9** (1.34 g, 85% yield) as a yellow oil. Spectroscopic data consistent with literature.[2] δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.38-1.53 (4H, m, 5-H_2 and 6-H_2), 1.95-2.03 (2H, m, 7-H_2), 2.10-2.18 (2H, m, 4-H_2), 4.11 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.93-4.97 (1H, m, 9-*H*H), 4.97-5.04 (1H, m, 9-H*H*), 5.74-5.78 (1H, m, 8-H), 5.79-5.85 (1H, m, 2-H), 6.96 (1H, dt, *J* 15.6, 6.9 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 27.5 (CH_2), 28.4 (CH_2), 32.0 (CH_2), 33.5 (CH_2), 60.2 (CH_2), 114.7 (CH_2), 121.4 (CH), 138.6 (CH), 149.2 (CH), 166.8 (C); *m/z* (CI) 183.1382 (MH^+. $C_{11}H_{19}O_2$ requires 183.1385), 113 (8%), 97 (7), 81 (13), 71 (15).

(2*E*)-Nona-2,8-dien-1-ol 6[2]

Ethyl (2*E*)-2,8-nonadienoate **9** (2.0 g, 11.0 mmol) was dissolved in diethyl ether (200 mL) and cooled to –78 °C. DIBAL-H (1 M in hexane) (24 mL, 24.17 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 3 h, before warming to room temperature. The solution was cooled to 0 °C and quenched by the addition of a saturated solution of ammonium chloride (50 mL) and warmed to room temperature with vigorous stirring over 1 h producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (400 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in*

vacuo. Flash column chromatography using (diethyl ether : petroleum ether, 3 : 7) gave (2*E*)-nona-2,8-dien-1-ol **6** (1.56 g, 100% yield) as a pale yellow oil. Spectroscopic data consistent with literature.[2] δ_H (400 MHz, $CDCl_3$) 1.22 (1H, br s, OH), 1.38-1.42 (4H, m, 5-H_2 and 6-H_2), 2.02-2.10 (4H, m, 4-H_2 and 7-H_2), 4.09 (2H, t, *J* 4.9 Hz, 1-H_2), 4.92-4.96 (1H, m, 9-*H*H), 5.00 (1H, ddd, *J* 17.0, 3.4, 1.6 Hz, 9-H*H*), 5.60-5.74 (2H, m, 2-H and 3-H), 5.81 (1H, ddt, *J* 17.0, 10.2, 6.7 Hz, 8-H); δ_C (100 MHz, $CDCl_3$) 26.9 (CH_2), 27.1 (CH_2), 30.6 (CH_2), 32.2 (CH_2), 62.4 (CH_2), 112.9 (CH_2), 127.5 (CH), 131.9 (CH), 137.4 (CH); *m/z* (CI) 123.1169 (MH^+-H_2O. C_9H_{15} requires 123.1174), 109 (16%), 95 (12), 81 (63), 67 (17).

(1*S*)-(2',2',2'-Trichloromethylcarbonylamino)cyclohepta-2-ene 4[3]

(2*E*)-Nona-2,8-dien-1-ol **6** (0.5 g, 3.57 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.12 mL, 0.89 mmol) was then added to the solution followed by trichloroacetonitrile (0.53 mL, 5.35 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h under an argon atmosphere. The reaction mixture was then filtered through a short pad of silica gel and washed with diethyl ether (100 mL). The resulting filtrate was then concentrated to give allylic trichloroacetimidate **5**, which was used without further purification. Allylic trichloroacetimidate **5** was dissolved in dichloromethane (50 mL) under an argon atmosphere. (*S*)-COP-Cl **11** (10 mol%) (0.41g, 0.28 mmol) was then added to the solution and the reaction mixture was stirred at 45 °C for 3 days. The reaction mixture was diluted by adding dichloromethane (450 mL). Grubbs' catalyst (1st Generation) (0.23 g, 0.28 mmol) was then added and the reaction mixture was heated at 65 °C overnight. The mixture was cooled to room temperature and then filtered through a short pad of Celite® and washed with diethyl ether (400 mL). Concentration of the filtrate followed by flash column chromatography (dichloromethane : petroleum ether, 3 : 7) gave (1*S*)-1-(2',2',2'-trichloromethylcarbonylamino)cyclohepta-2-ene **4** (0.75 g, 82% yield) as a white solid. 84% ee determined by HPLC analysis using CHIRALPAK IB column (0.5% *i*PrOH : hexane at 0.5 mL/min), retention time: t_S= 21.5 min, and t_R= 22.1 min. Recrystallisation of **4** from ethyl acetate and petroleum ether (1 : 1) gave colourless crystals which were shown to have >99% ee using HPLC conditions described above. mp 105-106 °C (lit.[3] mp 105 °C); $[\alpha]_D^{23}$ –25.0 (*c* 1.0, $CHCl_3$); Spectroscopic data consistent with literature.[3] δ_H (400 MHz, $CDCl_3$) 1.39-1.49 (1H, m, 6-*H*H), 1.66-1.79 (3H, m, 6-H*H* and 7-H_2), 1.85-1.98 (2H, m, 5-H_2), 2.10-2.29 (2H, m, 4-H_2), 4.54-4.62 (1H, m, 1-H), 5.55-5.62 (1H, m, 2-H), 5.88-5.95 (1H, m, 3-H), 6.72 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 24.6 (CH_2), 25.2 (CH_2), 26.5 (CH_2), 31.1

(CH_2), 50.5 (CH), 90.8 (C), 130.5 (CH), 131.8 (CH), 158.8 (C); *m/z* (CI) 256.0060 (MH^+. $C_9H_{13}NO^{35}Cl_3$ requires 256.0063), 222 (18%), 95 (12).

(1*S*)-1-(*tert*-Butoxycarbonylamino)cyclohepta-2-ene 12[4]

(1*S*)-1-(2',2',2'-Trichloromethylcarbonylamino)cyclohepta-2-ene **4** (0.3 g, 1.17 mmol) was dissolved in 2 M sodium hydroxide (40 mL) and stirred vigorously for 12 h at room temperature. Di-*tert*-butyl dicarbonate (0.64 g, 2.94 mmol) was added and the solution was stirred for 6 h before a further portion of di-*tert*-butyl dicarbonate (0.64 g, 2.94 mmol) was added and the reaction mixture stirred for a further 12 h. The reaction mixture was then extracted with ethyl acetate (4 × 30 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (ethyl acetate : petroleum ether, 1 : 9) gave (1*S*)-1-(*tert*-butoxycarbonylamino)cyclohepta-2-ene **12** (0.24 g, 100% yield) as a white solid. mp 61-63 °C (lit.[4] mp 63-65 °C); ν_{max}/cm^{-1} (NaCl) 3334 (NH), 2925 (CH), 1679 (CO), 1516, 1367, 1246, 1166, 1016; $[\alpha]_D^{23}$ –9.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.32-1.38 (1H, m, 6-*H*H), 1.44 (9H, s, O^{t}Bu), 1.60-1.69 (3H, m, 6-H*H* and 7-H_2), 1.82-1.90 (2H, m, 5-H_2), 2.09-2.18 (2H, m, 4-H_2), 4.25-4.32 (1H, m, 1-H), 4.64 (1H, br s, NH), 5.53-5.56 (1H, m, 2-H), 5.77-5.79 (1H, m, 3-H); δ_C (100 MHz, $CDCl_3$) 24.8 (CH_2), 25.6 (CH_2), 26.0 (CH_2), 26.7 (CH_3), 32.6 (CH_2), 49.9 (CH), 83.4 (C), 129.9 (CH), 133.7 (CH), 153.3 (C); *m/z* (CI) 212 (MH^+, 10%), 156 (100), 155 (7), 112 (5), 81 (7), 69 (9).

(1*S*)-1-[*tert*-Butoxycarbonyl(methyl)amino]cyclohepta-2-ene 13

(1*S*)-1-(*tert*-Butoxycarbonylamino)cyclohepta-2-ene **12** (0.05 g, 0.2 mmol) was dissolved in THF (5 mL) and added to a solution of sodium hydride (0.03 g, 0.7 mmol, 60% in mineral oil) in THF (10 mL). After 0.5 h, iodomethane (0.08 mL, 1.4 mmol) was added and the reaction mixture was stirred for 5 h at room temperature. The mixture was then heated for 24 h under reflux. The solution was concentrated *in vacuo*, quenched with water and acidified with 1 M hydrochloric acid. The reaction mixture was extracted with ethyl acetate (4 × 30 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (ethyl acetate : petroleum ether, 2 : 8) gave (1*S*)-1-[*tert*-butoxycarbonyl(methyl)amino]cyclohepta-2-ene **13** (0.044 g, 84% yield) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 2921 (CH), 1692 (CO), 1386, 1364, 1313, 1134, 906; $[\alpha]_D^{23}$ +24.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.23-1.26 (1H, m, 6-*H*H), 1.39 (9H, s, O^{t}Bu), 1.61-1.68 (4H,

m, 5-*H*H, 6-H*H* and 7-H_2), 1.83-1.89 (1H, m, 5-H*H*), 1.95-2.05 (1H, m, 4-*H*H), 2.11-2.22 (1H, m, 4-H*H*), 2.69 (3H, s, NCH_3), 4.73-4.76 (1H, m, 1-H), 5.47-5.50 (1H, m, 2-H), 5.69-5.77 (1H, m, 3-H); δ_C (100 MHz, $CDCl_3$) 24.5 (CH_2), 25.8 (CH_2), 26.2 (CH_3), 26.3 (CH_2), 27.3 (CH_3), 30.4 (br, CH_2), 54.1 (br, CH), 77.0 (C), 129.5 (br, CH), 132.3 (br, CH), 153.3 (C); *m/z* (CI) 226.1806 (MH^+. $C_{13}H_{24}NO_2$ requires 226.1807), 198 (6%), 186 (11), 170 (100), 156 (6), 126 (5), 113 (9), 97 (11), 85 (25).

(1*S*)-1-[*tert*-Butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one 3

A mixture of (1*S*)-1-[*tert*-butoxycarbonyl(methyl)amino]cyclohepta-2-ene **13** (0.07 g, 0.3 mmol), 10% palladium on carbon (0.005 g), dichloromethane (5 mL), *tert*-butyl hydroperoxide (0.12 mL, 1.1 mmol, 5.0-6.0 M in decane) and anhydrous potassium carbonate (0.007 g, 0.05 mmol) was stirred at room temperature for 24 h. A further quantity of *tert*-butyl hydroperoxide (0.12 mL, 1.1 mmol, 5.0-6.0 M in decane) and 10% palladium on carbon (0.005 g) were added and the reaction mixture stirred for a further 24 h. The reaction mixture was filtered through a pad of silica which was subsequently washed with dichloromethane. After removal of solvent under reduced pressure, the crude material was purified by flash column chromatography using (diethyl ether : petroleum ether, 1 : 1) to give (1*S*)-1-[*tert*-butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one **3** (0.03 g, 45% yield) as a yellow oil. ν_{max}/cm^{-1} (NaCl) 2931 (CH), 1688 (CO), 1366, 1047, 877, 771; $[\alpha]_D^{23}$ –34.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, O^{t}Bu), 1.75-1.87 (3H, m, 6-*H*H and 7-H_2), 1.94-2.04 (1H, m, 6-H*H*), 2.48-2.65 (2H, m, 5-H_2), 2.69 (3H, s, NCH_3), 4.91-4.98 (1H, m, 1-H), 5.97 (1H, d, *J* 12.4 Hz, 3-H), 6.28 (1H, br d, *J* 12.4 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 26.6 (CH_3), 28.0 (CH_3), 29.1 (CH_2), 30.8 (CH_2), 41.8 (CH_2), 55.0 (br, CH), 78.5 (C), 130.3 (br, CH), 145.6 (br, CH), 153.8 (C), 201.5 (C); *m/z* (CI) 240.1604 (MH^+. $C_{13}H_{22}NO_3$ requires 240.1600), 200 (10%), 184 (100), 173 (15), 155 (15), 132 (18), 109 (39).

(1*S*)-1-[*tert*-Butoxycarbonyl(methyl)amino]cycloheptanone[5]

To a solution of (1*S*)-1-[*tert*-butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one **3** (0.06 g, 0.25 mmol) in methanol (8 mL) was added 10% palladium on carbon (0.004 g). The reaction mixture was allowed to stir under an atmosphere of hydrogen at room temperature for 18 h. The reaction mixture was filtered through a short pad of Celite®, which was washed with methanol and concentrated *in vacuo*. Flash column chromatography (diethyl ether : petroleum ether, 1 : 1) gave (1*S*)-1-[*tert*-butoxycarbonyl(methyl)amino]cycloheptanone (0.020 g, 66% yield) as a white solid. mp 65-66 °C (lit.[5] for opposite enantiomer, mp 68-69 °C); ν_{max}/cm^{-1}

(NaCl) 2916 (CH), 1699 (CO), 1674 (CO), 1446, 1363, 1319, 1155, 939; $[\alpha]_D^{23}$ +65.1 (*c* 1.0, $CHCl_3$); Spectroscopic data consistent with literature.[5] δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, O^{t}Bu), 1.46-1.78 (4H, m, 6-H_2 and 7-H_2), 1.88-1.91 (2H, m, 2-H_2), 2.32-2.56 (4H, m, 3-H_2 and 5-H_2), 2.68 (3H, s, NCH_3), 4.02-4.11 (1H, m, 1-H); δ_C (100 MHz, $CDCl_3$) 20.4 (br, CH_2), 27.2 (CH_3), 27.5 (CH_3), 29.7 (CH_2), 32.6 (br, CH_2), 39.2 (CH_2), 42.3 (CH_2), 55.9 (br, CH), 78.4 (C), 154.0 (C), 212.8 (C); *m/z* (EI) 241.1676 (M^+. $C_{13}H_{23}NO_3$ requires 241.1678), 185 (31%), 141 (17), 110 (39), 84 (29), 57 (98).

(+)-Physoperuvine 1[6]

A solution of (1*S*)-1-[*tert*-butoxycarbonyl(methyl)amino]cycloheptanone (0.03 g, 0.1 mmol) was dissolved in trifluoroacetic acid (0.5 mL) and stirred at room temperature for 0.5 h. The solvent was removed under vacuum, and the residue was made basic with aqueous sodium carbonate (10 mL, 1.0 M) then extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried, filtered and evaporated. Flash column chromatography (chloroform : methanol : ammonium hydroxide (30%), 5 : 4 : 1) gave (+)-physoperuvine **1** (0.01 g, 60% yield) as a white solid. mp 73-74 °C (lit.[6] mp 72-73 °C); $[\alpha]_D^{23}$ +18.3 (*c* 1.3, H_2O) (lit.[6] $[\alpha]_D^{25}$ +17.9 (*c* 1.3, H_2O)); Spectroscopic data consistent with literature.[6] δ_H (400 MHz, $CDCl_3$) 1.20-1.34 (1H, m, 6-*H*H), 1.52-1.82 (5H, m, 2-H_2, 6-H*H* and 7-H_2), 1.87-2.15 (4H, m, 3-H_2 and 5-H_2), 2.38 (3H, s, NCH_3), 3.12 (1H, br s, 1-H); *m/z* (CI) 142 (MH^+, 100%), 124 (39), 101 (5), 81 (9), 71 (12).

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