Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Stereoselective Synthesis of Pyrrolidines: Catalytic Oxidative Cyclisations Mediated by Osmium

Timothy J. Donohoe, Gwydion H. Churchill, Katherine M. P. Wheelhouse (née Gosby) and Paul A. Glossop

Contents

1. Experimental Details

Tetrahydrofuran, acetonitrile and toluene were purified prior to use by filtration through two activated alumina columns (activated basic aluminium oxide, Brockmann I, standard grade, ~ 150 mesh, 58 Å). Reagents obtained from Acros, Aldrich, Avocado, Fluka and Lancaster fine chemicals suppliers were used directly.

Flash column chromatography was carried out using silica gel 60 (0.040-0.063 mm) (Merck) using head pressure by means of head bellows. Thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (0.25 mm silica gel with fluorescent indicator UV_{254}). Visualisation was achieved by either the quenching of UV fluorescence or $KMnO_4$, or Vanillin stain.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE AV400 (400 MHz and 100.6 MHz), Bruker DPX400 (400 MHz and 100.6 MHz) or a Bruker AVANCE AV500 (500 MHz and 125.7 MHz) spectrometer. Signal positions were recorded in δ ppm with the abbreviations s, d, t, q, quin., sx, br and m denoting singlet, doublet, triplet, quartet, quintet, sextet, broad and multiplet respectively. All NMR chemical shifts were referenced to residual solvent peaks or to $SiMe_4$ as an internal standard. All coupling constants, *J*, are quoted in Hz.

Infra-red spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. Spectra were analysed either as thin films between NaCl plates, KBr disks or in a chloroform solution cell. Mass spectra (*m/z*) and HRMS were recorded under the conditions of electrospray (ESI), chemical (CI) and field (FI) ionisation. Melting points were obtained using a Leica VMTG heated-stage microscope and are uncorrected. "Petrol" refers to the fraction of petroleum ether boiling in the range 40-60 °C unless otherwise stated and "ether" refers to diethyl ether.

1.1 General Procedures

General Procedure 1: Henry reaction

KO^tBu (0.10 eq.) was added to a solution of $MeNO_2$ (3.00 eq.) and aldehyde (1.00 eq.) in a 1:1 mixture of ^{t}BuOH:THF (2.00 mL per mmol substrate) and stirred at room temperature for 1 h. The reaction was quenched by cautious addition of H_2O (25 mL) and the mixture extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to yield the crude product which was purified by flash column chromatography on silica gel as indicated.

General Procedure 2: THP formation

PPTS (0.10 eq.) was added to a solution of nitroalcohol (1.00 eq.) and dihydropyran (1.50 eq.) in CH_2Cl_2 (7.00 mL per mmol starting material). The reaction mixture was stirred at room temperature for 4 h, then quenched by addition of saturated aqueous $NaHCO_3$ (50 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the crude product which was purified by flash column chromatography on silica gel as indicated.

General Procedure 3: $LiAlH_4$ reduction followed by *N* protection

A solution of nitro compound (1.00 eq.) in Et_2O (2.50 mL per mmol substrate) was added dropwise to a refluxing suspension of $LiAlH_4$ (2.50 eq.) in Et_2O (2.50 mL per mmol substrate) over a period of 1 h. The resulting mixture was stirred at room temperature for 23 h, then quenched by dropwise addition of saturated aqueous Na_2SO_4 solution until effervescence ceased and a white precipitate formed. The resulting mixture was filtered through Celite® and the precipitate washed with Et_2O (3 x 20 mL). The filtrate was dried over Na_2SO_4, filtered and concentrated to give an oil which was dissolved in CH_2Cl_2 or DMF (1 mL per mmol substrate). TsCl or ZCl (1.10 eq.) and DMAP (2.0 eq.) were added and the reaction stirred at room temperature for 12 h. H_2O (20 mL) and Et_2O (20 mL) were added, the layers were separated and the

aqueous phase extracted with Et_2O (4 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to give the crude product which was purified by flash column chromatography on silica gel as indicated.

General Procedure 4: THP deprotection

The protected amino alcohol (1.00 eq.) and PPTS (0.10 eq.) were dissolved in EtOH (8 mL per mmol starting material) and heated to 55 °C for 4 h. The reaction mixture was then concentrated onto silica gel and purified by flash column chromatography as indicated.

General Procedure 5: "Aqueous" oxidative cyclisation

The protected amino alcohol (1.00 eq.) and $Me_3NO.2H_2O$ (5.00 eq.) were dissolved in a 9:1 mixture of acetone:H_2O (20 mL per mmol starting material) and the solution was cooled to 0 °C. *Trans*-cinnamic acid (10.0 eq.) and TFA (10 mL per mmol starting material) were added, followed immediately by $K_2OsO_4.2H_2O$ (5 mol% or 1 mol%, as indicated). The reaction was allowed to warm to room temperature and stirred for 16 h, then quenched by addition of solid Na_2SO_3 (13 mg, 0.10 mmol) and stirred for 30 minutes. The resulting mixture was cooled to 0 °C and neutralised by careful addition of aqueous NaOH (40% by mass, saturated with NaCl). EtOAc (20 mL) was added and the layers separated. The organic layer was washed with H_2O (20 mL) and the combined aqueous phases extracted with EtOAc (3 x 25 mL), then the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to give the crude product as a brown oil which was purified by flash column chromatography on silica gel, as indicated.

General Procedure 6: "Organic" oxidative cyclisation

The protected amino alcohol (1.00 eq.), CSA (6.00 eq.) and $Me_3NO.2H_2O$ (4.00 eq.) were dissolved in CH_2Cl_2 (50 mL per mmol starting material). *Trans*-cinnamic acid (10.0 eq.) was added, followed immediately by OsO_4 (5 mol% or 1 mol% as indicated) and the resulting solution was stirred at room temperature for 16 h. In the case of starting material remaining after this time, a further portion of CSA (6.00 eq.) was added and the reaction monitored by TLC until complete. The reaction was quenched by addition of solid Na_2SO_3 (13 mg, 0.10 mmol) and stirred for 30 minutes. The reaction mixture was washed with aqueous NaOH (2M, 25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to give the crude product which was purified by flash column chromatography on silica gel as indicated.

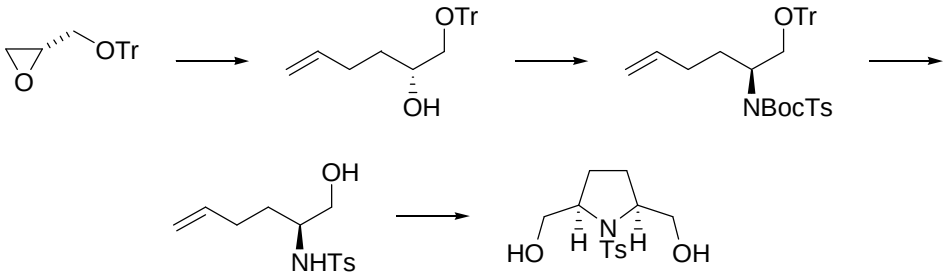
General Procedure 7: Combined deprotection of Boc and Tr groups

Trifluoroacetic acid (1.00 mL) was added at room temperature to a solution of the protected amino alcohol (1.00 eq.) in CH_2Cl_2 (1.00 mL) and stirred for 45 minutes.

MeOH (1.00 mL) was added and the reaction stirred for a further 1 h. Aqueous NaOH (2 M, 5 mL) was added and the reaction stirred for 5 minutes, then the mixture was partitioned with Et_2O (25 mL) and the aqueous layer extracted with Et_2O (3 x 25 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to give the crude product which was purified by flash column chromatography on silica gel as indicated.

Pyrrolidines

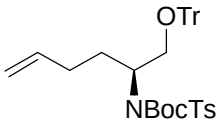
2. Data for starting materials and Pyrrolidines 4-10



3 **4**

Scheme 1: Synthesis of amino-alcohol **3** and pyrrolidine **4**

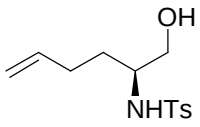
(*S*)-*tert*-butyl tosyl(1-(trityloxy)hex-5-en-2-yl)carbamate



Diisopropyl azodicarboxylate (1.36 g, 6.74 mmol) was added dropwise to a solution of (*R*)-1-(trityloxy)hex-5-en-2-ol (967 mg, 2.70 mmol), *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (1.83 g, 6.74 mmol) and triphenylphosphine (2.12 g, 8.09 mmol) at room temperature and the reaction stirred for 12 h, whereupon TLC analysis indicated complete consumption of starting material. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, eluting with 9:1 petrol-Et_2O then 8:2 petrol-Et_2O, R_f 0.26) to afford the protected amino alcohol (1.48 g, 2.42 mmol, 89%) as white plates.

m.p. 130-131 °C; **?**$_{max}$(KBr disk)/cm^{-1} 3060, 2980, 1727, 1492, 1449, 1395, 1354 1283, 1153, 1088, 1033; **d**$_H$ (400 MHz, $CDCl_3$) 7.91 (2 H, d, *J* 8.3), 7.43-7.41 (6 H, m), 7.32-7.23 (9 H, m), 7.08 (2 H, d, *J* 8.2), 5.82 (1 H, ddt, *J* 17.2, 10.4, 6.6), 5.05-4.98 (2 H, m), 4.88-4.85 (1 H, m), 3.55 (1 H, t, *J* 9.6), 3.32 (1 H, dd, *J* 9.6, 5.1), 2.36 (3 H, s), 2.16-2.10 (2 H, m), 1.99-1.93 (1 H, m), 1.80-1.71 (1 H, m), 1.27 (9 H, s); **d**$_C$ (100.6 MHz, $CDCl_3$) 159.8, 143.7, 143.6, 137.6, 128.9, 128.8, 128.4, 127.9, 127.8, 127.3, 127.0, 115.2, 87.1, 84.0, 64.4, 58.9, 30.8, 30.7, 27.9, 21.6; ***m/z*** (ESI^+) 670 (100%, M+MeCN+NH_4^+); **HRMS** (ESI^+) $C_{37}H_{41}NNaO_5S$ requires *MNa* 634.2598, found 634.2605 (-1.10 ppm); **[a]**$_D^{18}$ –17.9 (*c* 1, CH_2Cl_2).

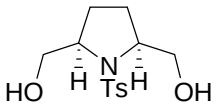
(*S*)-*N*-(1-hydroxyhex-5-en-2-yl)-4-methylbenzenesulfonamide 3



The protected amino alcohol (217 mg, 0.355 mmol) was subjected to General Procedure 7. Purification by flash column chromatography (SiO_2, eluting with 9:1 petrol-acetone then 7:3 petrol-acetone, R_f 0.29) gave protected amino alcohol **3** (80 mg, 0.297 mmol, 84%) as an oil.

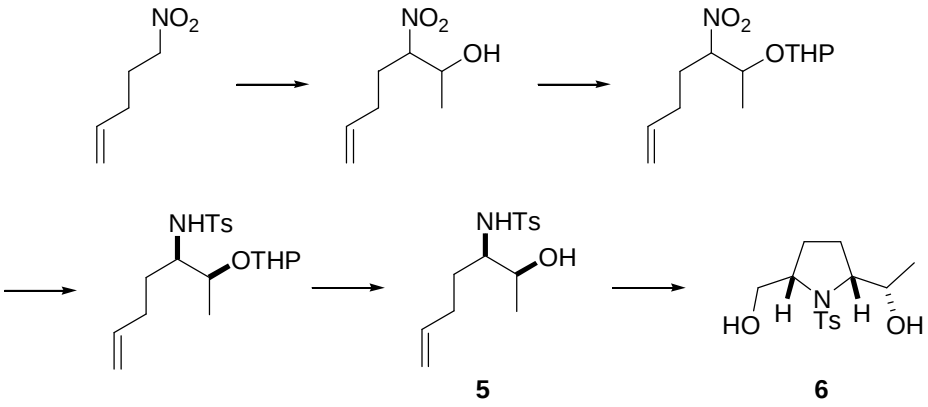
?$_{max}$(thin film)/cm^{-1} 3500, 3281, 2928, 1641, 1599, 1495, 1435, 1323, 1157, 1093; **d$_H$** (400 MHz, $CDCl_3$) 7.78 (2 H, d, *J* 8.3), 7.30 (2 H, d, *J* 8.4), 5.59 (1 H, ddt, *J* 16.9, 10.4, 6.6), 5.29 (1 H, d, *J* 8.1), 4.89-4.82 (2 H, m), 3.57 (1 H, dd, *J* 11.4, 3.8), 3.48 (1 H, dd, *J* 11.4, 5.1), 3.29-3.21 (1 H, m), 2.41 (3 H, s), 1.99-1.81 (2 H, m), 1.57-1.41 (2 H, m); **d$_C$** (100.6 MHz, $CDCl_3$) 143.6, 137.6, 137.3, 129.7, 127.1, 115.3, 64.5, 55.1, 30.9, 29.6, 21.5; ***m/z*** (ESI$^+$) 561 (78%, 2M+Na$^+$), 328 (100%, M+MeCN+NH_4^+); **HRMS** (ESI$^+$) $C_{13}H_{19}NNaO_3S$ requires *MNa* 292.0978, found 292.0975 (+1.07 ppm); **[a]$_D^{18}$** –2.4 (*c* 1, CH_2Cl_2).

(±)-((2*R*,5*S*)-1-tosylpyrrolidine-2,5-diyl)dimethanol 4



Amino alcohol **3** (70. mg, 0.26 mmol) was subjected to General Procedure 7. Purification by flash column chromatography (SiO_2, eluting with 7:3 petrol-acetone, R_f 0.25) afforded *pyrrolidine* **4** (59 mg, 0.21 mmol, 80%) as needles.

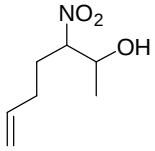
m.p. 105-106 °C; **?$_{max}$**(KBr disk)/cm^{-1} 3331, 2950, 1339, 1212, 1159, 1093; **d$_H$** (400 MHz, $CDCl_3$) 7.72 (2 H, d, *J* 8.3), 7.33 (2 H, d, *J* 8.3), 3.84 (2 H, dd, *J* 11.4, 4.0), 3.73-3.71 (2 H, m), 3.63 (2 H, dd, *J* 11.2, 4.8), 3.38 (2 H, br. s), 2.42 (3 H, s), 1.87-1.78 (2 H, m), 1.57-1.48 (2 H, m); **d$_C$** (100.6 MHz, $CDCl_3$) 144.1, 133.9, 129.9, 127.6, 65.5, 63.3, 27.2, 21.6; ***m/z*** (ESI$^+$) 344 (100%, M+MeCN+NH_4^+), 308 (20%, M+Na$^+$); **HRMS** (ESI$^+$) $C_{13}H_{20}NO_4S$ requires *MH* 286.1113, found 286.1114 (+0.5 ppm).



5 **6**

Scheme 2: Synthesis of amino-alcohol **5** and THF **6**

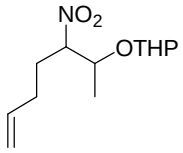
(±)-**3-Nitrohept-6-en-2-ol**



Acetaldehyde (191 mg, 4.34 mmol) was subjected to General Procedure 1. Purification by flash column chromatography (SiO_2, eluting with 4:1 petrol-EtOAc, R_f 0.20) furnished the *nitro alcohol* (670 mg, 4.21 mmol, 97%) as an oil consisting of a 1:1 mixture of diastereomers.

?$_{max}$(thin film)/cm^{-1} 3425, 1643, 1551, 1387, 1216; **d**$_H$ (400 MHz, $CDCl_3$) 5.75 (1 H, ddt, *J* 17.1, 10.1, 6.8), 5.08 (1 H, d, *J* 17.1), 5.06 (1 H, d, *J* 10.0), 4.47-4.40 (1 H, m), 4.24-4.18 (0.5 H, m), 4.15-4.09 (0.5 H, m), 2.35-2.01 (3 H, m), 1.94-1.81 (1 H, m), 1.71-1.64 (1 H, m), 1.29 (1.5 H, d, *J* 6.4), 1.26 (1.5 H, d, *J* 6.4); **d**$_C$ (100.6 MHz, $CDCl_3$) 135.8, 135.6, 116.8, 116.8, 93.1, 92.0, 68.4, 68.3, 30.1, 29.9, 29.7, 29.5, 19.9, 19.2; ***m/z*** (ESI$^-$) 158 (100%, $[M-H]^-$), 140 (10%, $[M-H-H_2O]^-$); **HRMS** (ESI$^-$) $C_7H_{12}NO_3$ requires *M-H* 158.0817, found 158.0816 (-0.7 ppm).

(±)-**2-(3-Nitrohept-6-en-2-yloxy)-tetrahydro-2*H*-pyran**

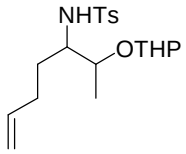


The above nitro alcohol (691 mg, 4.34 mmol) was subjected to General Procedure 2. Purification by flash column chromatography (SiO_2, eluting with 9:1 petrol-EtOAc, R_f 0.25) yielded *nitro compound* (976 mg, 4.01 mmol, 92%) as an oil consisting of a 1:1:1.5:1.5 mixture of 4 diastereomers.

?$_{max}$(thin film)/cm^{-1} 1643, 1553, 1380, 1202, 1125, 1077, 1024, **d**$_H$ (400 MHz, $CDCl_3$) 5.81-5.68 (1 H, m), 5.09-5.03 (2 H, m), 4.81-4.55 (1 H, m), 4.55-4.43 (1 H, m), 4.26-4.06 (1 H, m), 3.91-3.46 (2 H, m), 2.24-1.44 (10 H, m), 1.31 (1.5 H, d, *J* 6.4), 1.20 (0.6 H, d, *J* 6.3), 1.17 (0.9 H, d, *J* 6.3); **d**$_C$ (100.6 MHz, $CDCl_3$) 136.1, 136.0,

135.8, 135.7, 116.8, 116.7, 116.5, 101.4, 99.3, 95.6, 93.9, 92.5, 91.9, 91.4, 90.2, 76.4, 74.1, 71.1, 70.8, 62.9, 62.7, 62.5, 61.7, 30.8, 30.6, 30.5, 30.4, 30.1, 30.0, 29.8, 29.7, 29.0, 28.7, 28.4, 27.8, 25.4, 25.3, 25.2, 19.6, 18.6, 17.9, 15.0; ***m/z*** (FI) 244 (100%, $M+H^+$); **HRMS** (FI) $C_{12}H_{22}NO_4$ requires *MH* 244.1549, found 244.1539 (-3.9 ppm).

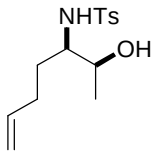
(±)-4-Methyl-*N*-(2-(tetrahydro-2*H*-pyran-2-yloxy)hept-6-en-3-yl)benzene sulfonamide



The above nitro compound (958 mg, 3.94 mmol) was subjected to General Procedure 3. Purification by flash column chromatography (SiO_2, eluting with 85:15 petrol-acetone, R_f 0.27) yielded the *protected amino alcohol* (935 mg, 2.54 mmol, 65%) as an oil consisting of a 4:4:1:1 mixture of 4 diastereomers.

?$_{max}$(thin film)/cm^{-1} 3454, 1641, 1327, 1162, 1094, 1075, 1025; **d_H** (400 MHz, $CDCl_3$) 7.72-7.70 (2 H, m), 7.30-7.26 (2 H, m), 6.01 (0.4 H, d, *J* 9.2), 5.81-5.62 (1 H, m), 5.13 (0.1 H, d, *J* 7.2), 4.98-4.89 (2 H, m), 4.75 (0.1 H, d, *J* 8.8), 4.70 (0.4 H, d, *J* 8.5), 4.55-4.53 (0.1 H, m), 4.49 (0.1 H, dd, *J* 5.6, 2.8), 4.33 (0.4 H, dd, *J* 5.2, 2.8), 4.19 (0.4 H, dd, *J* 7.3, 2.4), 4.01-3.96 (0.4 H, m), 3.86-3.81 (0.6 H, m), 3.65 (0.4 H, qd, *J* 6.5, 3.2), 3.47-3.40 (1 H, m), 3.38 (0.6 H, qd, *J* 6.6, 2.2), 3.25-3.15 (0.6 H, m), 3.06 (0.4 H, tdd, *J* 9.2, 4.2, 2.2), 2.42 (2.4 H, s), 2.41 (0.6 H, s), 2.25-1.61 (4 H, m), 1.58-1.33 (6 H, m), 1.12 (1.2 H, d, *J* 6.5), 1.03 (0.3 H, d, *J* 6.4), 1.00 (1.2 H, d, *J* 6.6), 0.98 (0.3 H, d, *J* 6.5); **d_C** (100.6 MHz, $CDCl_3$) 143.3, 143.0, 138.6, 138.4, 138.3, 137.8, 129.7, 129.5, 129.4, 127.2, 127.1, 127.0, 115.1, 114.8, 114.7, 100.6, 100.4, 99.7, 96.8, 77.5, 75.7, 75.2, 71.8, 65.2, 63.7, 63.1, 63.0, 57.8, 57.7, 57.3, 57.0, 31.7, 31.6, 31.0, 30.8, 29.9, 29.8, 28.4, 27.8, 25.3, 25.0, 22.6, 21.5, 21.4, 20.0, 18.2, 18.1, 17.9; ***m/z*** (ESI^-) 366 (100%, $[M-H]^-$); **HRMS** (ESI^-) $C_{19}H_{28}NO_4S$ requires *M-H* 366.1739, found 366.1734 (-1.5 ppm).

(±)-*N*-((2*R*,3*S*)-2-hydroxyhept-6-en-3-yl)-4-methyl benzenesulfonamide 5

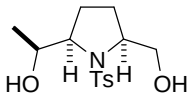


The protected amino alcohol (454 mg, 1.24 mmol) was subjected to General Procedure 4. Purification by flash column chromatography (SiO_2, eluting with 4:1 petrol-acetone, R_f 0.29) furnished *amino alcohol* **5** (323 mg, 1.14 mmol, 92%) as prisms (only a single diastereomer detectable by NMR spectroscopy).

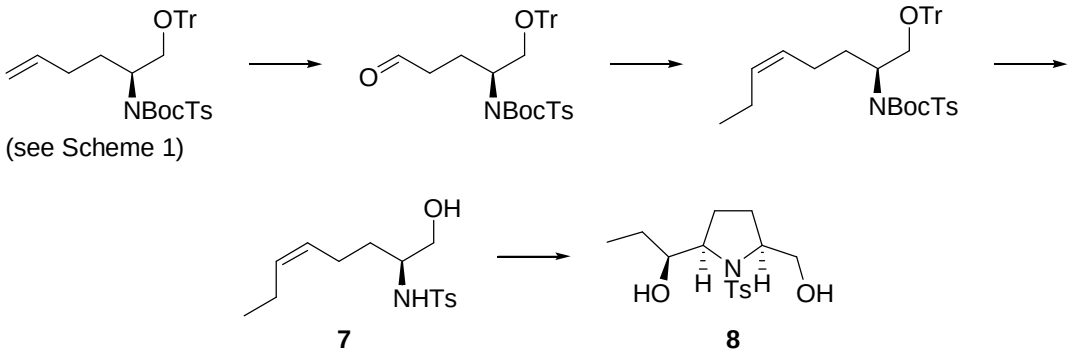
m.p. 85-85 °C; **?$_{max}$**(KBr disk)/cm^{-1} 3496, 3282, 1641, 1599, 1323, 1159, 1093; **d_H** (400 MHz, $CDCl_3$) 7.77 (2 H, d, *J* 8.3), 7.31 (2 H, d, *J* 8.2), 5.49 (1 H, ddt, *J* 17.0, 10.4,

6.5), 4.89 (1 H, dd, *J* 10.3, 1.6), 4.83 (1 H, dq, *J* 17.0, 1.6), 4.76 (1 H, d, *J* 8.4), 3.76 (1 H, qd, *J* 6.5, 3.0), 3.25-3.19 (1 H, m), 2.43 (3 H, s), 2.01-1.89 (1 H, m), 2.00 (1 H, br. s), 1.81-1.72 (1 H, m), 1.53-1.44 (1 H, m), 1.42-1.32 (1 H, m), 1.11 (3 H, d, *J* 6.5); **δ_C** (100.6 MHz, $CDCl_3$) 143.6, 137.6, 137.3, 129.7, 127.1, 115.4, 69.1, 58.6, 29.7, 28.8, 21.5, 18.4; ***m/z*** (ESI$^+$) 342 (100%, M+MeCN+NH_4^+); **HRMS** (ESI$^+$) $C_{14}H_{22}NO_3S$ requires *MH* 284.1320, found 284.1324 (+1.3 ppm).

(±)-(*RS*)-1-((2*SR*,5*RS*)-5-(hydroxymethyl)-1-tosylpyrrolidin-2-yl)ethanol 6

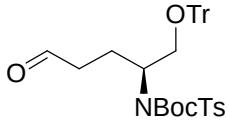


Amino alcohol **5** (315 mg, 1.11 mmol) was subjected to General Procedure 6. Purification by flash column chromatography (SiO_2, eluting with 3:2 petrol-acetone, R_f 0.30) afforded *pyrrolidine* **6** (301 mg, 1.01 mmol, 90%) as needles.
m.p. 120-121 °C; **?$_{max}$**(KBr disk)/cm^{-1} 3288, 1336, 1157, 1030; **δ_H** (400 MHz, $CDCl_3$) 7.72 (2 H, d, *J* 8.1), 7.33 (2 H, d, *J* 8.0), 4.33 (1 H, qd, *J* 6.6, 2.6), 3.89 (1 H, dd, *J* 11.1, 3.7), 3.78-3.72 (1 H, m), 3.62 (1 H, dd, *J* 11.1, 4.5), 3.53 (1 H, td, *J* 6.9, 2.6), 3.50 (2 H, br. s), 2.43 (3 H, s), 2.06-1.96 (1 H, m), 1.91-1.82 (1 H, m), 1.52-1.39 (2 H, m), 1.14 (3 H, d, *J* 6.6); **δ_C** (100.6 MHz, $CDCl_3$) 143.9, 134.1, 129.8, 127.5, 69.2, 67.1, 65.3, 62.7, 27.3, 23.9, 21.5, 19.3; ***m/z*** (ESI$^+$) 358 (100%, M+MeCN+NH_4^+), 322 (40%, M+Na^+); **HRMS** (ESI$^+$) $C_{14}H_{22}NO_4S$ requires *MH* 300.1270, found 300.1276 (+2.2 ppm).



Scheme 3: Synthesis of amino alcohol **7** and pyrrolidine **8**

(*S*)-*tert*-butyl-5-oxo-1-(trityoxy)pentan-2-yl(tosyl)carbamate

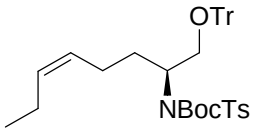


Osmium tetroxide (7.0 mg, 0.029 mmol) was added to a solution of the protected amino alcohol (350 mg, 0.572 mmol) in 4:1 THF:H_2O (4.0 mL) and stirred for 5 minutes.

Sodium periodate (612 mg, 2.86 mmol) was added and the reaction stirred for 2.5 h prior to quenching with Na_2SO_3 (13 mg, 0.10 mmol). H_2O (20 mL) was added and the mixture partitioned with Et_2O (20 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic layers washed with brine (25 mL) and dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash column chromatography (SiO_2, eluting with 3:2 petrol-Et_2O, R_f 0.20) afforded the ***aldehyde*** (228 mg, 0.371 mmol, 65%) as prisms.

m.p. 52-53 °C; **?**$_{max}$(KBr disk)/cm^{-1} 3059, 2927, 1727, 1598, 1492, 1449, 1354, 1153, 1089; **d**$_H$ (400 MHz, $CDCl_3$) 9.81 (1 H, s), 7.89 (2 H, d, *J* 8.3), 7.38-7.24 (15 H, m), 7.08 (2 H, d, *J* 8.1), 4.84-4.77 (1 H, m), 3.52 (1 H, t, *J* 9.1), 3.31 (1 H, dd, *J* 9.3, 5.1), 2.72-2.56 (2 H, m), 2.35 (3 H, s), 2.19-2.09 (1 H, m), 1.98-1.89 (1 H, m), 1.26 (9 H, s); **d**$_C$ (100.6 MHz, $CDCl_3$) 201.2, 143.9, 143.5, 137.2, 129.0, 128.8, 128.5, 127.9, 127.8, 127.3, 127.1, 87.2, 84.4, 64.6, 40.8, 27.8, 23.3, 21.6; ***m/z*** (ESI$^+$) 704 (40%, M+MeOH+MeCN+NH_4^+), 672 (100%, M+MeCN+NH_4^+); **HRMS** (ESI$^+$) $C_{36}H_{39}NNaO_6S$ requires *MNa* 636.2390, found 636.2390 (+0.00 ppm); **[a]**$_D^{18}$ –26.7 (*c* 1, CH_2Cl_2).

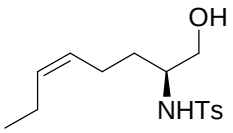
(*S*,*Z*)-*tert*-butyl tosyl(1-(1-trityloxy)oct-5-en-2-yl)carbamate



Propyltriphenylphosphonium bromide (227 mg, 0.589 mmol) was dried overnight at 55 °C under vacuum. Toluene (5 mL) was added and the suspension cooled to 0 °C prior to dropwise addition of KHMDS (0.5 M solution in toluene, 1.14 mL, 0.572 mmol). The resulting bright orange solution was warmed to room temperature and stirred for 20 minutes before cooling to –78 °C. A solution of the aldehyde (180 mg, 0.293 mmol) in THF (1 mL) was added dropwise and the reaction stirred for 3 h, whereupon TLC analysis indicated complete consumption of starting material. Saturated aqueous ammonium chloride (15 mL) and Et_2O (15 mL) were added and the mixture partitioned. The aqueous phase was extracted with Et_2O (3 x 25 mL) and the combined organic layers washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated. Flash column chromatography (SiO_2, eluting with 85:15 petrol-Et_2O, R_f 0.32) afforded the *protected amino alcohol* (152 mg, 0.238 mmol, 81%) as an oil.

?$_{max}$(thin film)/cm^{-1} 2962, 1728, 1598, 1449, 1354, 1282, 1152, 1088; **d**$_H$ (400 MHz, $CDCl_3$) 7.91 (2 H, d, *J* 8.1), 7.43-7.41 (6 H, m), 7.33-7.22 (9 H, m), 7.08 (2 H, d, *J* 8.3), 5.42-5.27 (2 H, m), 4.88-4.81 (1 H, m), 3.54 (1 H, t, *J* 8.8), 3.29 (1 H, dd, *J* 9.3, 5.1), 2.36 (3 H, s), 2.14-2.04 (2 H, m), 1.99 (2 H, quint., *J* 7.3), 1.91-1.82 (1 H, m), 1.72-1.65 (1 H, m), 1.26 (9 H, s), 0.94 (3 H, t, *J* 7.3); **d**$_C$ (100.6 MHz, $CDCl_3$) 143.7, 143.6, 137.6, 132.5, 128.9, 128.8, 128.4, 127.8, 127.7, 127.0, 87.0, 83.9, 64.6, 59.10, 31.5, 27.9, 24.4, 21.6, 20.5, 14.3; ***m/z*** (ESI$^+$) 698 (100%, M+MeCN+NH_4^+); **HRMS** (ESI$^+$) $C_{39}H_{45}NO_5NaS$ requires *MNa* 662.2916, found 662.2916 (+ 0.00 ppm); **[a]**$_D^{18}$ –17.7 (*c* 1, CH_2Cl_2).

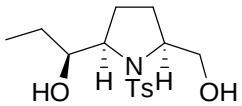
(*S*,*Z*)-*N*-(1-hydroxyoct-5-en-2-yl)-4-methylbenzenesulfonamide 7



The protected amino alcohol (302mg, 0.472 mmol) was subjected to General Procedure 7. Purification by flash column chromatography (SiO_2, eluting with 9:1 petrol-acetone then 7:3 petrol-acetone, R_f 0.35) gave *protected amino alcohol* **7** (127 mg, 0.427 mmol, 90%) as an oil.

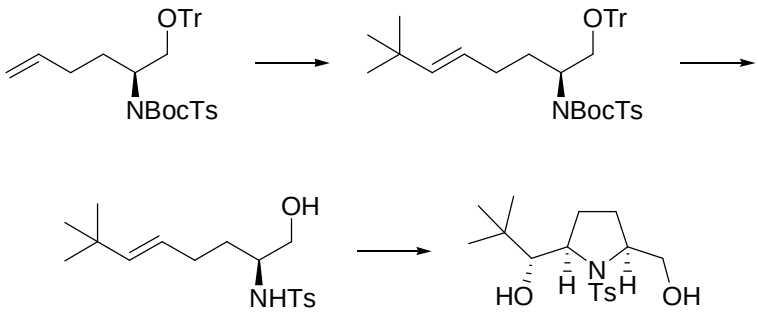
?$_{max}$(thin film)/cm^{-1} 3500, 3281, 2962, 1599, 1439, 1323, 1158, 1094; **d$_H$** (400 MHz, $CDCl_3$) 7.78 (2 H, d, *J* 8.3), 7.31 (2 H, d, *J* 8.4), 5.35-5.28 (1 H, m), 5.13-5.07 (1 H, m), 4.91 (1 H, d, *J* 7.8), 3.57 (1 H, dd, *J* 11.1, 3.8), 3.49 (1 H, dd, *J* 11.1, 5.1), 3.30-3.22 (1 H, m), 2.42 (3 H, s), 2.08 (1 H, br. s), 1.95-1.77 (4 H, m), 1.54-1.35 (2 H, m), 0.90 (3 H, t, *J* 7.6); **d$_C$** (100.6 MHz, $CDCl_3$) 143.6, 137.6, 132.8, 129.7, 127.3, 127.2, 64.6, 55.4, 31.9, 23.3, 21.5, 20.5, 14.2; ***m/z*** (ESI$^+$) 617 (90%, 2M+Na$^+$), 320 (100%, M+Na$^+$); **HRMS** (ESI$^+$) $C_{15}H_{23}NO_3NaS$ requires *MNa* 3201296, found 320.1291 (-1.5 ppm); **[a]$_D^{18}$** –3.3 (*c* 1, CH_2Cl_2).

(*S*)-1-((2*R*,5*S*)-5-(hydroxymethyl)-1-tosylpyrrolidin-2-yl)propan-1-ol 8



Amino alcohol **7** (78 mg, 0.26 mmol) was subjected to General Procedure 6. Purification by flash column chromatography (SiO_2, eluting with 3:1 petrol-acetone, R_f 0.19) afforded *pyrrolidine* **8** (67 mg, 0.22 mmol, 82%) as needles.

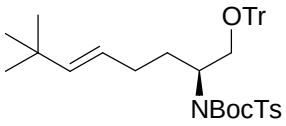
m.p. 109-110 °C; **?$_{max}$**(KBr disk)/cm^{-1} 3406, 1306, 1215, 1159, 1093; **d$_H$** (400 MHz, $CDCl_3$) 7.71 (2 H, d, *J* 8.3), 7.32 (2 H, d, *J* 8.4), 4.08-4.04 (1 H, m), 3.89 (1 H, dd, *J* 11.1, 3.5), 3.78-3.73 (1 H, m), 3.61 (1 H, dd, *J* 11.1, 4.3), 3.59-3.54 (1 H, m), 2.42 (3 H, s), 2.05-1.97 (1 H, m), 1.88-1.82 (1 H, m), 1.50-1.37 (4 H, m), 0.99 (3 H, t, *J* 7.4); **d$_C$** (100.6 MHz, $CDCl_3$) 143.9, 134.2, 129.9, 127.6, 74.9, 66.0, 65.6, 62.7, 27.5, 26.6, 24.1, 21.6, 10.6; ***m/z*** (ESI$^+$) 649 (100%, 2M+Na$^+$), 336 (60%, M+Na$^+$); **HRMS** (ESI$^+$) $C_{15}H_{23}NNaO_4S$ requires *MNa* 336.1216, found 336.1237 (+0.92 ppm); **[a]$_D^{18}$** +41.0 (*c* 1, CH_2Cl_2).



9 **10**

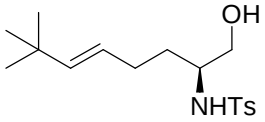
Scheme 4: Synthesis of amino-alcohol **9** and pyrrolidine **10**

(S,*E*)-*tert*-butyl7,7-dimethyl-1-(trityloxy)oct-5-en-2-yl(tosyl) carbamate



Grubbs second generation catalyst (26 mg, 0.303 mmol) was added to a solution of the protected amino alcohol (370 mg, 0.605 mmol) in 3,3-dimethyl-1-butene (5.00 mL) and stirred at 40 °C for 12 h. The reaction mixture was concentrated and purified by flash column chromatography (SiO_2, eluting with 85:15 petrol-Et_2O, R_f 0.25) to give the *protected amino alcohol* (401 mg, 0.60 mmol, 99%) as a pale brown oil. **?**$_{max}$(thin film)/cm^{-1} 2959, 1727, 1598, 1492, 1449, 1356, 1282, 1153, 1089; **d**$_H$ (400 MHz, $CDCl_3$) 7.91 (2 H, d, *J* 8.3), 7.43-7.40 (6 H, m), 7.30-7.22 (9 H, m), 7.08 (2 H, d, *J* 8.2), 5.46 (1 H, d, *J* 15.7), 5.30 (1 H, dt, *J* 15.7, 6.6), 4.86 (1 H, br. s), 3.54 (1 H, t), 3.30 (1 H, dd, *J* 9.3, 4.5), 2.36 (3 H, s), 2.06-2.01 (2 H, m), 1.91-1.86 (1 H, m), 1.75-1.66 (1 H, m), 1.26 (9 H, s), 0.99 (9 H, s); **d**$_C$ (100.6 MHz, $CDCl_3$) 150.8, 143.8, 143.6, 142.4, 128.9, 128.8, 128.4, 127.8, 127.0, 123.4, 87.0, 83.9, 64.4, 58.9, 32.8, 31.7, 29.7, 29.6, 27.9, 21.6; ***m/z*** (ESI^+) 726 (100%, M+MeCN+NH_4^+); **HRMS** (ESI^+) $C_{41}H_{49}NNaO_5S$ requires *MNa* 690.3224, found 690.3219 (+0.71 ppm); **[a]**$_D^{18}$ -11.8 (*c* 1, CH_2Cl_2).

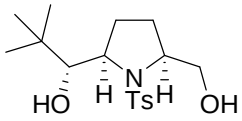
(*S*,*E*)-*N*-(1-hydroxy-7,7-dimethyloct-5-en-2-yl)-4-methyl benzene sulfonamide 9



The protected amino alcohol (300mg, 0.449 mmol) was subjected to General Procedure 7. Purification by flash column chromatography (SiO_2, eluting with 9:1 petrol-acetone then 7:3 petrol-acetone, R_f 0.32) gave the *protected amino alcohol* **9** (112 mg, 0.344 mmol, 77%) as an oil.

?$_{max}$(thin film)/cm^{-1} 3490, 3282, 2956, 1325, 1158, 1094; **d**$_H$ (400 MHz, $CDCl_3$) 7.78 (2 H, d, *J* 8.3), 7.31 (2 H, d, *J* 8.1), 5.28 (1 H, dt, *J* 15.4, 1.3), 5.14 (1 H, d, *J* 7.8), 5.06 (1 H, dt, *J* 15.7, 6.6), 3.58 (1 H, dd, *J* 11.4, 3.8), 3.48 (1 H, dd, *J* 11.4, 5.2), 3.26-3.19 (1 H, m), 2.28 (1 H, br. s), 2.42 (3 H, s), 1.89-1.75 (2 H, m), 1.53-1.37 (2 H, m), 0.92 (9 H, s); **d**$_C$ (100.6 MHz, $CDCl_3$) 143.5, 142.7, 137.5, 129.8, 127.2, 123.0, 64.6, 55.1, 32.7, 31.7, 29.6, 28.4, 21.5; ***m/z*** (ESI$^+$) 673 (70%, 2M+Na$^+$), 384 (45%, M+MeCN+NH_4^+), 348 (100%, M+Na$^+$); **HRMS** (ESI$^+$) $C_{17}H_{27}NNaO_3S$ requires *MNa* 348.1604, found 348.1598 (+1.75 ppm); **[a]**$_D^{18}$ –9.0 (*c* 1, CH_2Cl_2).

(*R*)-1-((2*R*,5*S*)-5-(hydroxymethyl)-1-tosylpyrrolidin-2-yl)-2,2-dimethylpropan-1-ol 10

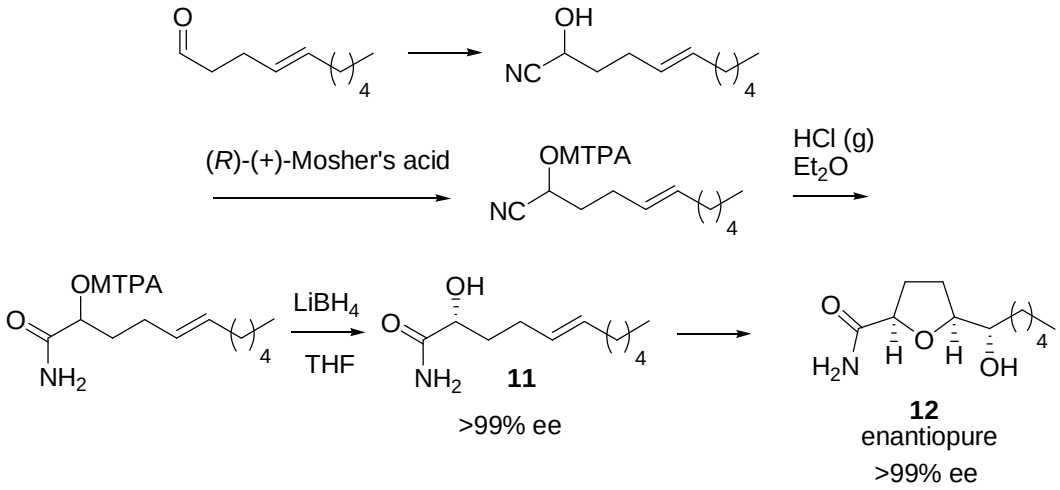


Amino alcohol **9** (84.0 mg, 0.26 mmol) was subjected to General Procedure 6. Purification by flash column chromatography (SiO_2, eluting with 3:1 petrol-acetone, R_f 0.28) afforded *pyrrolidine* **10** (70.0 mg, 0.21 mmol, 80%) as needles.
m.p. 155-156 °C; **?**$_{max}$(KBr disk)/cm^{-1} 3417, 2956, 1342, 1159, 1093; **d**$_H$ (400 MHz, $CDCl_3$) 7.71 (2 H, d, *J* 8.3), 7.34 (2 H, d, *J* 8.4), 4.10 (1 H, dd, *J* 11.6, 2.8), 3.85 (1 H, tt, *J* 8.3, 2.5), 3.65 (1 H, t, *J* 7.8), 3.52 (1 H, dd, *J* 11.6, 2.5), 3.21 (2 H, br. s), 2.91 (1 H, d, *J* 8.3), 2.45 (3 H, s), 2.17-2.07 (1 H, m), 1.83-1.76 (1 H, m), 1.53 (1 H, dd, *J* 12.6, 6.8), 1.31-1.21 (1 H, m), 0.94 (9 H, s); **d**$_C$ (100.6 MHz, $CDCl_3$) 144.9, 134.9, 130.0, 127.3, 78.6, 64.7, 63.1, 60.9, 35.3, 31.5, 26.0, 25.3, 21.6; ***m/z*** (ESI$^+$) 400 (100%, M+MeCN+NH_4^+); **HRMS** (ESI$^+$) $C_{17}H_{27}NNaO_4S$ requires *MNa* 364.1553, found 364.1554 (-0.33 ppm); **[a]**$_D^{18}$ +71.5 (*c* 1, CH_2Cl_2).

Tetrahydrofurans

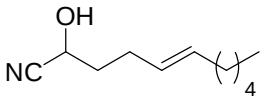
3. Data for amide 11 and THF 12

The amido-THF **12** was obtained by cyanohydrin formation followed by acidic hydrolysis to give racemic hydroxy-amide **11** (Scheme 5). Enantiopure **11** was obtained by chromatographic separation of the diastereomeric cyanohydrin (+)-MTPA esters, followed by acidic hydrolysis and reductive removal of the Mosher ester to give **11**. Cyclisation following the general procedure 5 then gave the tetrahydrofuran **12**. Enantiopurity was verified by comparison of the ^{19}F chemical shifts of the (+)-MTPA derivatives with racemic standards of amides **11** and **12**.



Scheme 5: Synthesis of hydroxy-amide **11** and THF **12**

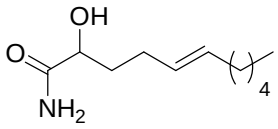
(±)-(*E*)-2-hydroxyoct-5-enenitrile



Triethylamine (265 µL, 1.94 mmol) was added to a stirred solution of *trans*-4-decenal (297 µL, 1.62 mmol) in dichloromethane (5 mL) under an atmosphere of argon. The solution was cooled to 0 °C and then TMSCN (216 µL, 1.62 mmol) was added dropwise over 2 min. The solution was allowed to warm to room temperature over 20 min and then stirred for 3 h. H_2O (3 mL) was added and the separated aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were concentrated *in vacuo* to approx. 5 mL and then 3M aqueous hydrochloric acid (1 mL) was added and the mixture was stirred at room temperature for 30 min. The separated aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the *cyanohydrin* (258 mg, 88%) as a colourless oil which was used without further purification.

?$_{max}$ (thin film)/cm^{-1} 3444, 2927, 2865, 1456, 1077; **d**$_H$ (400 MHz, $CDCl_3$) 5.54 (1 H, dt, *J* 15.1 and 6.7), 5.38 (1 H, dt, *J* 15.1 and 6.7), 4.49 (1 H, q, *J* 6.6), 2.90 (1 H, d, *J* 6.6), 2.26-2.20 (2 H, m), 2.02-1.97 (2 H, m) 1.95-1.88 (2 H, m), 1.39-1.23 (6 H, m), 0.89 (3 H, t, *J* 7.0); **d**$_C$ (100.6 MHz, $CDCl_3$) 133.3, 127.1, 119.9, 60.8, 34.8, 32.5, 31.4, 29.1, 27.6, 22.5, 14.1; **HRMS** (ESI^+) Calcd. for $C_{11}H_{19}NNaO$ ($M+Na^+$) 204.1359. Found 204.1360 (+ 0.5 ppm).

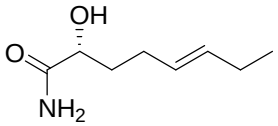
(±)-(*E*)-2-hydroxyoct-5-enamide 11



Triethylamine (1.06 mL, 7.78 mmol) was added to a stirred solution of *trans*-4-decenal (1.19 mL, 6.48 mmol) in dichloromethane (30 mL) under an atmosphere of argon. The solution was cooled to 0 °C and then TMSCN (0.86 mL, 6.48 mmol) was added dropwise over 2 min. The solution was allowed to warm to room temperature over 20 min and then stirred for 3 h. Water (10 mL) was added and the separated aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were concentrated *in vacuo* to approx. 10 mL. HCl (g) was bubbled through this solution for 6 h to give a pale green solution which was stirred for 24 h. The solution was degassed for 30 min with argon and then water (10 mL) and ethyl acetate (20 mL) were added. The separated aqueous layer was extracted with ethyl acetate (3 × 30 mL), washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the *hydroxy-amide* **11** (1.00g, 78%) which was recrystallised from hexanes/acetone to give colourless needles.

m.p. 137-140 °C; **?**$_{max}$ ($CHCl_3$)/cm^{-1} 3288 (br), 2919, 1635, 1090; **d**$_H$ (400 MHz, CD_3OD) 5.71-5.21 (2 H, m), 4.00 (1 H, dd, *J* 8.3, 3.8), 3.53-3.40 (1 H, m) 2.18-2.09 (2 H, m), 2.04-1.95 (2 H, m), 1.88-1.58 (4 H, m), 1.41-1.13 (4 H, m), 0.91 (3 H, t, *J* 6.82); **d**$_C$ (100.6 MHz, CD_3OD) 174.5, 131.4, 129.3, 71.1, 33.8, 32.6, 31.5, 29.4, 28.2, 22.6, 13.4; ***m/z*** (ESI^-) 198 (100%, $M-H^+$); **HRMS** (ESI^+) Calcd. for $C_{11}H_{21}NO_2Na$ ($M+Na^+$) 222.1465. Found 222.1462 (- 0.2 ppm).

(+)-(*R*)-(*E*)-2-hydroxyoct-5-enamide 11

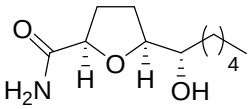


The enantiopure alcohol **11** was obtained as outlined in scheme 1 with identical data to the racemic compound. The absolute stereochemistry was assigned as R based on a moderate (30% ee) preference (for the same cyanohydrin as was used to give **5**) in an (*R*)-oxynitrilase catalysed cyanohydrin formation reaction.

Reference: F. Effenberger, Angew. Chem. Int. Ed. Engl., 1994, 33, 1555-1564.

[a]$_D^{21}$ +3.6 (*c* 0.3, MeOH).

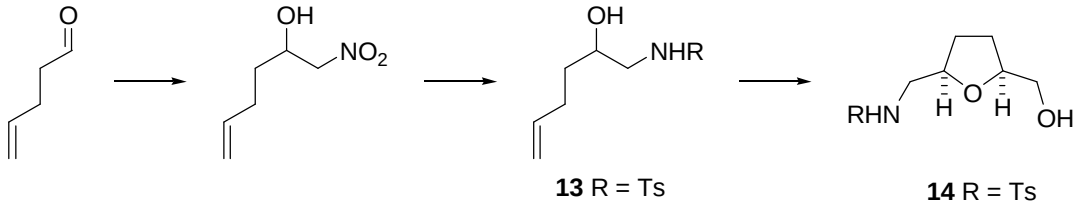
(+)-(2*R*,5*S*)-5-((*S*)-1-hydroxypropyl)tetrahydrofuran-2-carboxamide 12



The enantiopure hydroxy-amide **11** (30 mg, 0.15 mmol) was subjected to general procedure 5 to give a residue which was purified by chromatography on florisil® (200 mesh), eluting with 20-30% acetone in petroleum ether, to give the *tetrahydrofuran* **12** (24 mg, 75%) as a pale yellow oil. This reaction gave 80% yield for **12**, starting with (±)-**11**.

?$_{max}$ (thin film)/cm^{-}1 3380 (br), 2931, 1674; **d**$_{H}$ (400 MHz, $CDCl_3$) 7.38 (1 H, s), 5.98 (1 H, s), 4.40 (1 H, dd, *J* 9.0, 3.9), 4.03-3.86 (1 H, m), 3.64-3.52 (1 H, m), 2.70 (1 H, br s), 2.37-2.22 (1 H, m), 2.21-2.04 (1 H, m), 1.95-1.84 (1 H, m), 1.64-1.43 (3 H, m), 1.42-1.22 (5 H, m), 0.89 (3 H, t, *J* 7.1); **d**$_{C}$ (100.6 MHz, $CDCl_3$) 177.4, 84.1, 78.4, 72.3, 34.4, 31.8, 30.7, 26.9, 25.4, 22.6, 14.0; ***m/z*** (ESI^{-}) 214 (100%, M-H^{+}); **HRMS** (ESI^{+}) Calcd. for $C_{11}H_{21}NO_3Na$ (M+Na^{+}) 238.1414. Found 238.1405 (-3.7 ppm); **[a]**$_{D}^{21}$ +18.1 (*c* 0.07, MeOH).

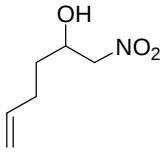
3.1 Data for starting materials and THFs 14-22



13 R = Ts **14** R = Ts

Scheme 6 : Synthesis of amino-alcohol **13** and THF **14**

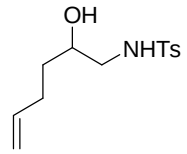
(±)-**1-Nitro-hex-5-en-2-ol**



4-Pentenal (1.00 g, 11.9 mmol) was subjected to General Procedure 1. Purification by flash column chromatography (SiO_2, eluting with 85:15 petrol-EtOAc, R_f 0.26) furnished the *nitro alcohol* (1.64 g, 11.3 mmol, 95%) as an oil.

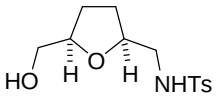
?$_{max}$(thin film)/cm^{-1} 3423, 1641, 1555, 1385; **d**$_{H}$ (400 MHz, $CDCl_3$) 5.80 (1 H, ddt, *J* 17.0, 10.2, 6.7), 5.08 (1 H, dd, *J* 17.1, 1.6), 5.04 (1 H, dd, *J* 10.2, 1.6), 4.46-4.31 (3 H, m), 2.61 (1 H, br. s), 2.31-2.15 (2 H, m), 1.70-1.53 (2 H, m); **d**$_{C}$ (100.6 MHz, $CDCl_3$) 137.0, 116.0, 80.5, 68.0, 32.6, 29.3; ***m/z*** (ESI^{-}) 144 (100%, [M-H]$^{-}$); **HRMS** (ESI^{-}) $C_6H_{10}NO_3$ requires *M-H* 144.0661, found 144.0659 (-0.8 ppm).

(±)-***N*-(2-Hydroxy-hex-5-enyl)-4-methyl-benzenesulfonamide 13**

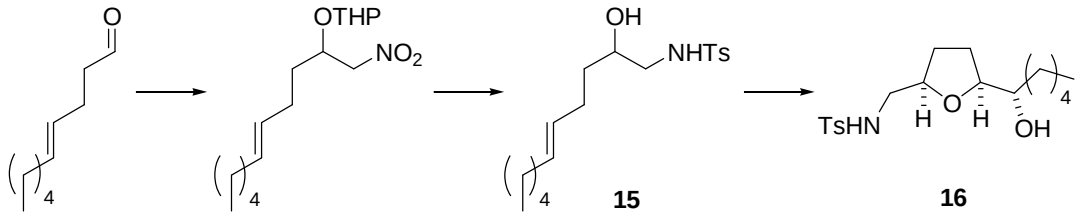


The above alcohol (350 mg, 2.41 mmol) was subjected to General Procedure 3, using TsCl. Purified by flash column chromatography (SiO_2, eluting with 3:2 petrol-EtOAc, R_f 0.31) gave ***amino alcohol* 13** (203 mg, 0.75 mmol, 31%) as a viscous oil. **?**$_{max}$(thin film)/cm^{-1} 3286, 1638, 1328, 1161; **d**$_H$ (400 MHz, $CDCl_3$) 7.74 (2 H, d, *J* 8.2), 7.31 (2 H, d, *J* 8.1), 5.80 (1 H, ddt, *J* 17.0, 10.2, 6.7), 5.30 (1 H, t, *J* 6.2), 5.00 (1 H, dd, *J* 17.1, 1.6), 4.95 (1 H, dd, *J* 10.2, 1.6), 3.74-3.68 (1 H, m), 3.06 (1 H, ddd, *J* 13.0, 7.3, 3.1), 2.80 (1 H, ddd, *J* 13.1, 8.1, 5.3), 2.50 (1 H, br. s), 2.42 (3 H, s), 2.19-2.02 (2 H, m), 1.52-1.46 (2 H, m); **d**$_C$ (100.6 MHz, $CDCl_3$) 143.5, 137.7, 136.6, 129.7, 127.1, 115.2, 69.9, 48.6, 33.5, 29.6, 21.5; ***m/z*** (ESI$^+$) 328 (100%, M+MeCN+NH_4^+), 292 (83%, M+Na^+); **HRMS** (ESI$^+$) $C_{13}H_{20}NO_3S$ requires *MH* 270.1164, found 270.1158 (-2.4 ppm).

(±)-*N*-(((2*RS*,5*SR*)-5-(hydroxymethyl)-tetrahydrofuran-2-yl)methyl)-4-methyl benzenesulfonamide 14

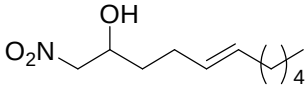


Amino alcohol **13** (269 mg, 1.00 mmol) was subjected to General Procedure 5. Purification by flash column chromatography (SiO_2, eluting with 3:2 petrol-acetone, R_f 0.30) furnished ***amino-THF* 14** (211 mg, 0.74 mmol, 74%) as a viscous oil. **?**$_{max}$(thin film)/cm^{-1} 3452, 3284, 1599, 1495, 1451, 1325, 1160, 1093; **d**$_H$ (400 MHz, $CDCl_3$) 7.69 (2 H, d, *J* 8.2), 7.23 (2 H, d, *J* 8.3), 6.18 (1 H, t, *J* 6.2), 4.02-3.94 (2 H, m), 3.65 (1 H, dd, *J* 11.8, 2.8), 3.41 (1 H, dd, *J* 11.8, 5.7), 3.35 (1 H, br. s), 3.06 (1 H, ddd, *J* 13.0, 6.2, 3.4), 2.86 (1 H, dt, *J* 13.0, 6.2), 2.35 (3 H, s), 1.90-1.76 (2 H, m), 1.69-1.62 (2 H, m); **d**$_C$ (100.6 MHz, $CDCl_3$) 143.0, 136.8, 129.5, 126.8, 80.2, 77.7, 64.4, 46.8, 28.1, 26.6, 21.3; ***m/z*** (ESI$^+$) 286 (100%, M+H^+); **HRMS** (ESI$^+$) $C_{13}H_{20}NO_4S$ requires *MH* 286.1113, found 286.1111 (-0.9 ppm).



Scheme 7: Synthesis of amino-alcohol **15** and THF **16**

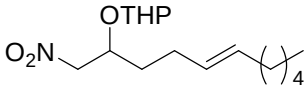
(±)-(*E*)-1-nitrooct-5-en-2-ol



Trans-4-decenal (771 mg, 5.00 mmol) was subjected to General Procedure 1. Purification by flash column chromatography (SiO_2, eluting with 9:1 petrol-acetone, R_f 0.26) furnished the *nitro alcohol* (1.07g, 4.95 mmol) as an oil.

?$_{max}$(thin film)/cm^{-1} 3428, 2927, 2856, 1557, 1454, 1383, 1200, 1098; **d**$_H$ (400 MHz, $CDCl_3$) 5.53-5.34 (2 H, m), 4.45-4.30 (3 H, m), 2.49 (1 H, br. s), 2.22-2.21 (2 H, m), 2.01-1.95 (2 H, m), 1.67-1.50 (2 H, m), 1.38-1.21 (6 H, m), 0.88 (3 H, t, *J* 7.1); **d**$_C$ (100.6 MHz, $CDCl_3$) 132.5, 128.1, 80.5, 68.1, 33.3, 32.5, 31.4, 29.1, 28.2, 22.5, 14.1; ***m/z*** (ESI^-) 214 (100%, $[M-H]^-$); **HRMS** (ESI^-) $C_{11}H_{20}NO_3$ requires *M-H* 214.1443, found 214.1452 (+4.1 ppm).

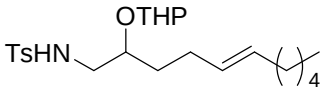
(±)- (*E*)-2-(1-nitrooct-5-en-2-yloxy)-tetrahydro-2*H*-pyran



The above nitroalcohol (850 mg, 3.95 mmol) was subjected to General Procedure 2. Purification by flash column chromatography (SiO_2, eluting with 97:3 petrol-EtOAc, R_f 0.20) yielded the *nitro compound* (1.129 g, 3.75 mmol, 95%) as an oil consisting of a 1:1 mixture of diastereomers.

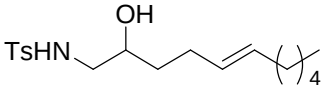
?$_{max}$(thin film)/cm^{-1} 2928, 2855, 1556, 1441, 1382, 1260, 1202, 1182, 1155, 1123, 1077, 1035; **d**$_H$ (400 MHz, C_6D_6) 5.44-5.19 (2 H, m), 4.58 (0.4 H, t, *J* 3.6), (0.6 H, t, *J* 3.6), 4.25-4.18 (1.5 H, m), 3.88 (0.5 H, dd, *J* 12.4, 8.3), 3.80-3.63 (2 H, m), 3.32-3.21 (1 H, m), 1.95 (3 H, q, *J* 6.8), 1.82 (1 H, q, *J* 6.8), 1.66-1.09 (14 H, m), 0.90 (1.5 H, t, *J* 6.9), 0.89 (1.5 H, t, *J* 7.0); **d**$_C$ (100.6 MHz, C_6D_6) 131.8, 131.7, 129.2, 129.0, 100.0, 98.1, 79.4, 78.5, 74.5, 73.6, 63.0, 62.4, 33.3, 32.9, 32.8, 31.8, 31.7, 31.2, 30.9, 29.6, 28.3, 28.1, 27.5, 25.5, 25.4, 22.9, 20.0, 19.6, 14.3; ***m/z*** (FI^+) 299 (100%, M^+); **HRMS** (FI^+) $C_{16}H_{29}NO_4$ requires *M* 299.2097, found 299.2090 (-2.3 ppm).

(±)-**(*E*)-4-methyl-*N*-(2-(tetrahydro-2*H*-pyran-2-yloxy)oct-5-enyl)benzenesulfonamide**



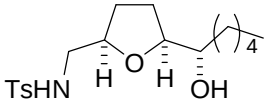
The above nitro compound (900 mg, 3.00 mmol) was subjected to General Procedure 3, using TsCl. Purification by flash column chromatography (SiO_2, eluting with 9:1 petrol-acetone, R_f 0.26) yielded the *protected amino alcohol* (759 mg, 1.79 mmol, 60%) as a colourless oil consisting of a 1:1 mixture of diastereomers. **?**$_{max}$(thin film)/cm^{-1} 3283, 2927, 2855, 1599, 1454, 1335, 1201, 1163, 1134, 1074, 1026; **d**$_H$ (400 MHz, $CDCl_3$) 7.75-7.71 (2 H, m), 7.31-7.27 (2 H, m), 6.16 (0.5 H, app. dd, *J* 8.1, 2.3), 5.46-5.23 (2 H, m), 4.96-4.78 (0.5 H, m), 4.48-4.46 (0.5 H, m), 4.30 (0.5 H, dd, *J* 7.5, 2.3), 4.01-3.95 (0.75 H, m), 3.87-3.81 (0.25 H, m), 3.73-3.67 (0.5 H, m), 3.56-3.40 (1.5 H, m), 3.14-3.03 (1 H, m), 2.89-2.71 (1 H, m), 2.42 (1.5 H, s), 2.41 (1.5 H, s), 2.09-1.61 (4 H, m), 1.54-1.39 (6 H, m), 1.33-1.22 (8 H, m), 0.89-0.82 (3 H, m); **d**$_C$ (100.6 MHz, $CDCl_3$) 143.4, 143.0, 137.1, 136.8, 131.8, 131.6, 129.7, 129.5, 128.9, 128.8, 128.7, 127.1, 127.0, 101.6, 97.8, 78.8, 74.6, 65.3, 63.2, 48.6, 47.6, 45.2, 41.3, 34.2, 33.2, 32.6, 32.5, 31.4, 31.3, 30.9, 29.2, 29.1, 28.6, 28.3, 25.2, 25.0, 22.6, 22.5, 21.5, 21.4, 20.0, 19.4, 14.1; ***m/z*** (ESI$^-$) 422 ([M-H]$^-$); **HRMS** (ESI$^-$) $C_{23}H_{36}NO_4S$ requires *M-H* 422.2360, found 422.2359 (+0.24 ppm).

(±)-(*E*)-*N*-(2-hydroxyoct-5-enyl)-4-methylbenzenesulfonamide 15

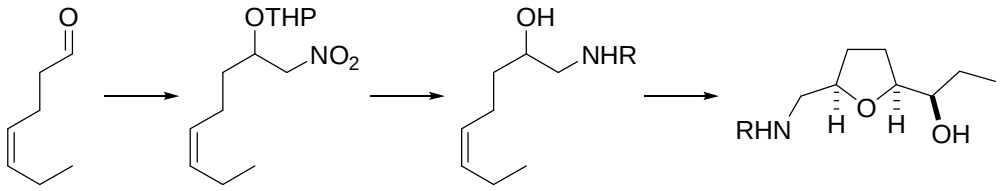


The protected amino alcohol (690 mg, 1.63 mmol) was subjected to General Procedure 4. Purification by flash column chromatography (SiO_2, eluting with 8:2 petrol-acetone, R_f 0.25) gave *amino alcohol* **15** (492 mg, 1.45 mmol, 89%) as an oil. **?**$_{max}$(thin film)/cm^{-1} 3500, 3283, 2926, 2856, 1599, 1454, 1327, 1160, 1092; **d**$_H$ (400 MHz, $CDCl_3$) 7.74 (2 H, d, *J* 8.3), 7.31 (2 H, d, *J* 8.2), 5.46-5.29 (2 H, m), 5.07 (1 H, dd, *J* 7.1, 5.3), 3.74-3.68 (1 H, m), 3.06 (1 H, ddd, *J* 12.9, 7.3, 3.0), 2.78 (1 H, ddd, *J* 12.9, 8.1, 5.1), 2.42 (3 H, s), 2.11-1.92 (4 H, m), 1.49-1.43 (2 H, m), 1.35-1.21 (6 H, m), 0.87 (3 H, t, *J* 7.0); **d**$_C$ (100.6 MHz, $CDCl_3$) 143.5, 136.7, 131.8, 129.8, 128.8, 127.1, 70.1, 48.6, 34.2, 32.5, 31.4, 29.2, 28.5, 22.5, 21.5, 14.1; ***m/z*** (ESI+) 701 (20%, 2M+Na$^+$), 398 (100%, M+MeCN+NH_4^+); **HRMS** (ESI$^+$) $C_{18}H_{29}NNaO_3S$ requires *MNa* 362.1760, found 362.1753 (+1.93 ppm).

(±)-N-(((2*RS*,5*SR*)-5-((*SR*)-1-hydroxypropyl)-tetrahydrofuran-2-yl)methyl)-4-methylbenzenesulfonamide 16



Protected amino alcohol **15** (0.212 g, 0.625 mmol) was subjected to General Procedure 5. Purification by flash column chromatography (SiO_2, eluting with 85:15 petrol-acetone, R_f 0.13) furnished ***amino-THF*** **16** (180 mg, 0.50 mmol, 80%) as pale yellow prisms. The ^1H NMR spectrum of this compound contains an impurity (ca. 5-10%); despite much effort, we were unable to separate or identify this compound.
m.p. 68-69 °C; **?**$_{max}$(thin film)/cm^{-1} 3500, 3282, 2930, 1599, 1495, 1455, 1327, 1160, 1091; **d**$_H$ (400 MHz, $CDCl_3$) 7.74 (2 H, d, *J* 8.3), 7.29 (2 H, d, *J* 8.2), 5.60 (1 H, t, *J* 5.9), 4.05-3.99 (1 H, m), 3.76-3.71 (1 H, m), 3.36 (1 H, dt, *J* 7.3, 5.1), 3.11 (1 H, ddd, *J* 12.9, 6.1, 3.5), 2.91 (1 H, dt, *J* 12.7, 6.1), 2.41 (3 H, s), 1.96-1.84 (2 H, m), 1.76-1.65 (2 H, m), 1.49-1.20 (8 H, m), 0.88 (3 H, t, *J* 6.9); **d**$_C$ (100.6 MHz, $CDCl_3$) 143.3, 137.0, 129.7, 127.1, 83.1, 77.5, 74.2, 47.1, 33.9, 31.8, 28.4, 27.9, 25.6, 22.6, 21.5, 14.1; ***m/z*** (ESI^+) 414 (100%, $M+MeCN+NH_4^+$), 378 (30%, $M+Na^+$); **HRMS** (ESI^+) $C_{18}H_{29}NNaO_4S$ requires *MNa* 378.1710, found 378.1705 (+1.24ppm).

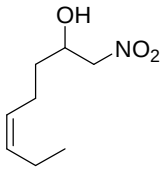


17 R = Ts
19 R = Z

18 R = Ts
20 R = Z

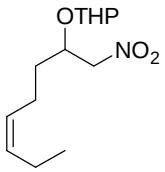
Scheme 8: Synthesis of amino-alcohols **17**, **19** and THFs **18** & **20**

(±)-***(Z)*-1-Nitrooct-5-en-2-ol**



Cis-4-heptenal (1.60 g, 14.3 mmol) was subjected to General Procedure 1. Purification by flash column chromatography (SiO_2, eluting with 9:1 petrol-acetone, R_f 0.22) furnished the ***nitro alcohol*** (2.43 g, 14.0 mmol, 98%) as an oil.
?$_{max}$(thin film)/cm^{-1} 3425, 1660, 1556, 1384, 1208, 1072; **d**$_H$ (400 MHz, $CDCl_3$) 5.46 (1 H, dt, *J* 10.6, 7.3), 5.31 (1 H, dt, *J* 10.5, 7.4), 4.46-4.36 (2 H, m), 4.35-4.30 (1 H, m), 2.58 (1 H, br. s), 2.22 (2 H, q, *J* 7.3), 2.06 (2 H, m), 1.67-1.49 (2 H, m), 0.97 (3 H, t, *J* 7.5); **d**$_C$ (100.6 MHz, $CDCl_3$) 133.5, 127.0, 80.6, 68.2, 33.4, 22.8, 20.5, 14.2; ***m/z*** (CI^+) 191 (100%, $M+NH_4^+$); **HRMS** (CI^+) $C_8H_{19}N_2O_3$ requires *MNH₄* 191.1396, found 191.1396 (+0.2 ppm).

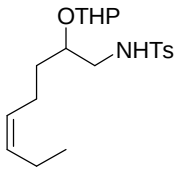
(±)-**(*Z*)-2-(1-Nitrooct-5-en-2-yloxy)-tetrahydro-2*H*-pyran**



The above nitroalcohol (2.16 g, 12.5 mmol) was subjected to General Procedure 2. Purification by flash column chromatography (SiO_2, eluting with 95:9 petrol-EtOAc, R_f 0.25) yielded the *tetrahydropyran* (2.90 g, 11.3 mmol, 90%) as an oil consisting of a 1:1 mixture of diastereomers.

?$_{max}$(thin film)/cm^{-1} 1660, 1556, 1383, 1202, 1182, 1156, 1124, 1077, 1035; **d$_H$** (400 MHz, C_6D_6) 5.41-5.33 (1 H, m), 5.27-5.12 (1 H, m), 4.56 (0.5 H, t, *J* 3.7), 4.89 (0.5 H, t, *J* 3.7), 4.25-4.15 (1.5 H, m), 3.91 (0.5 H, dd, *J* 12.4, 8.3), 3.80-3.63 (2 H, m), 3.31-3.20 (1 H, m), 1.96 (2 H, qu, *J* 7.6), 1.91-1.79 (2 H, m), 1.64-1.47 (2 H, m), 1.47-1.08 (6 H, m), 0.89 (1.5 H, t, *J* 7.5), 0.88 (1.5 H, t, *J* 7.5); **d$_C$** (100.6 MHz, C_6D_6) 132.8, 132.7, 128.1, 127.8, 100.0, 98.1, 79.4, 78.5, 74.6, 73.7, 63.1, 62.4, 33.5, 31.8, 31.2, 30.9, 25.5, 25.4, 23.0, 22.7, 20.9, 20.8, 20.0, 19.6, 14.5, 14.4; ***m/z*** (FI$^+$) 257 (100%, M$^+$); **HRMS** (FI$^+$) $C_{13}H_{23}NO_4$ requires *M* 257.1627, found 257.1627 (+0.0 ppm).

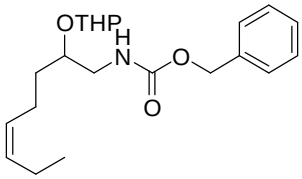
(±)-**(*Z*)-4-Methyl-*N*-(2-(tetrahydro-2*H*-pyran-2-yloxy)oct-5-enyl)benzenesulfonamide**



The tetrahydropyran (1.32 g, 5.10 mmol) was subjected to General Procedure 3, using TsCl. Purification by flash column chromatography (SiO_2, eluting with 9:1 petrol-acetone, R_f 0.21) yielded the *protected amino alcohol* (1.24 g, 3.26 mmol, 64%) as a colourless oil consisting of a 1:1 mixture of diastereomers.

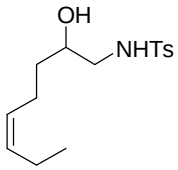
?$_{max}$(thin film)/cm^{-1} 3284, 1660, 1599, 1454, 1334, 1134, 1134, 1074, 1026; **d$_H$** (400 MHz, $CDCl_3$) 7.73 (1 H, d, *J* 8.2), 7.72 (1 H, d, *J* 8.2), 7.31-7.27 (2 H, m), 6.15 (0.5 H, app. dd, *J* 8.1, 2.1), 5.37-5.31 (1 H, m), 5.23-5.14 (1 H, m), 4.91 (0.5 H, t, *J* 6.0), 4.48-4.46 (0.5 H, m), 4.29-4.27 (0.5 H, m), 3.98-3.94 (0.5 H, m), 3.85-3.80 (0.5 H, m), 3.72-3.67 (0.5 H, m), 3.50-3.39 (1.5 H, m), 3.13-3.04 (1 H, m), 2.87 (0.5 H, dt, *J* 12.9, 5.9), 2.76 (0.5 H, ddd, *J* 12.6, 8.6, 2.4), 2.41 (1.5 H, s), 2.40 (1.5 H, s), 2.03-1.95 (4 H, m), 1.82-1.43 (8 H, m), 0.93 (3 H, t, *J* 7.5); **d$_C$** (100.6 MHz, $CDCl_3$) 143.3, 143.0, 137.0, 136.7, 132.5, 132.3, 129.6, 129.4, 127.8, 127.6, 127.0, 126.9, 101.5, 97.7, 78.8, 74.7, 65.2, 63.2, 47.3, 45.2, 33.3, 32.7, 31.3, 30.8, 25.1, 24.9, 22.9, 22.8, 21.4, 21.3, 20.4, 20.3, 19.9, 14.2, 14.1; ***m/z*** (ESI$^+$) 785 (40%, 2M+Na$^+$), 404 (100%, M+Na$^+$); **HRMS** (ESI$^+$) $C_{20}H_{31}NO_4NaS$ requires *MNa* 404.1872, found 404.1864 (-1.8 ppm).

(±)-**(*Z*)-Benzyl 2-(tetrahydro-2*H*-pyran-2-yloxy)oct-5-enylcarbamate**



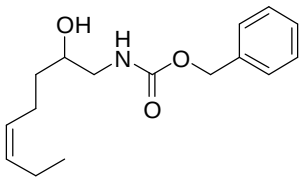
The tetrahydropyran (1.32 g, 5.10 mmol) was subjected to General Procedure 3, using ZCl. Purification by flash column chromatography (SiO_2, eluting with 9:1 petrol-acetone, R_f 0.21) yielded the *protected amino alcohol* (848 mg, 2.35 mmol, 46%) as a pale yellow oil consisting of a 1:1 mixture of diastereomers. **?**$_{max}$(thin film)/cm^{-1} 3348, 1725, 1656, 1518, 1245, 1134, 1075, 1027; **d**$_H$ (400 MHz, $CDCl_3$) 7.36-7.29 (5 H, m), 5.89 (1 H, br. s), 5.42-5.24 (2 H, m), 5.10 (2 H, s), 4.47-4.45 (0.5 H, m), 4.04-3.81 (1 H, m), 3.95-3.92 (0.5 H, m), 3.85-3.71 (0.5 H, m), 3.66-3.37 (2.5 H, m), 3.24-3.08 (1 H, m), 2.12-1.98 (4 H, m), 1.83-1.50 (8 H, m), 0.98-0.93 (3 H, m); **d**$_C$ (100.6 MHz, $CDCl_3$) 171.0, 135.3, 135.0, 132.4, 132.3, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 100.7, 78.5, 75.1, 66.4, 64.5, 45.5, 33.0, 32.8, 31.4, 31.1, 25.3, 25.1, 23.3, 23.0, 21.1, 20.5, 14.3; ***m/z*** (ESI^+) 745 (50%, $2M+Na^+$), 384 (100%, $M+Na^+$); **HRMS** (ESI^+) $C_{21}H_{31}NO_4Na$ requires *MNa* 384.2151, found 384.2140 (-2.8 ppm).

(±)-**(*Z*)-*N*-(2-Hydroxy-oct-5-enyl)-4-methylbenzenesulfonamide 17**



The protected amino alcohol (910 mg, 2.39 mmol) was subjected to General Procedure 4. Purification by flash column chromatography (SiO_2, eluting with 85:15 petrol-acetone, R_f 0.19) to give the *amino alcohol* **17** (621 mg, 2.09 mmol, 87%) as an oil. **?**$_{max}$(thin film)/cm^{-1} 3452, 3284, 1656, 1599, 1452, 1326, 1159, 1093; **d**$_H$ (400 MHz, $CDCl_3$) 7.74 (2 H, d, *J* 8.2), 7.31 (2 H, d, *J* 8.2), 5.42-5.36 (1 H, m), 5.29-5.23 (1 H, m), 4.96 (1 H, br. s), 3.74-3.68 (1 H, m), 3.06 (1 H, ddd, *J* 12.8, 7.3, 3.0), 2.79 (1 H, ddd, *J* 13.0, 8.0, 5.0), 2.43 (3 H, s), 2.10 (2 H, qu, *J* 7.3), 2.03 (1 H, br. s), 2.01 (2 H, qu, *J* 7.4), 1.46 (2 H, m), 0.94 (3 H, t, *J* 7.5); **d**$_C$ (100.6 MHz, $CDCl_3$) 143.5, 136.6, 132.9, 129.8, 127.7, 127.1, 70.2, 48.7, 34.4, 23.1, 21.5, 20.5, 14.3; ***m/z*** (ESI^+) 617 (100%, $2M+Na^+$), 612 (35%, $2M+NH_4^+$), 361 (20%, $M+MeCN+Na^+$), 315 (20%, $M+NH_4^+$), 298 (28%, $M+H^+$); **HRMS** (ESI^+) $C_{15}H_{24}NO_3S$ requires *MH* 298.1477, found 298.1466 (-3.5 ppm).

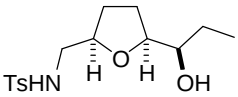
(±)-**(*Z*)-Benzyl 2-hydroxyoct-5-enylcarbamate 19**



The protected amino alcohol (635 mg, 1.76 mmol) was subjected to General Procedure 4. Purification by flash column chromatography (SiO_2, eluting with 85:15 petrol-acetone, R_f 0.25) furnished *amino alcohol* **19** (346 mg, 1.25 mmol, 71%) as a pale yellow oil.

?$_{max}$(thin film)/cm^{-1} 3418, 3280, 1701, 1659, 1531, 1260, 1145, 1096; **d$_H$** (400 MHz, $CDCl_3$) 7.36-7.30 (5 H, m), 5.44-5.38 (1 H, m), 5.35-5.29 (1 H, m), 5.16 (1 H, br. s), 5.11 (2 H, s), 3.76-3.69 (1 H, m), 3.41-3.36 (1 H, m), 3.09 (1 H, ddd, *J* 13.2, 7.1, 5.2), 2.16 (2 H, qu, *J* 7.8), 2.05 (2 H, qu, *J* 7.4), 1.96 (1 H, br. s), 1.54-1.48 (2 H, m), 0.96 (3 H, t, *J* 7.5); **d$_C$** (100.6 MHz, $CDCl_3$) 170.9, 136.4, 132.8, 128.5, 128.2, 128.1, 128.0, 71.1, 66.9, 47.0, 34.6, 23.3, 20.5, 14.3; ***m/z*** (ESI$^+$) 577 (100%, 2M+Na$^+$), 300 (98%, M+Na$^+$), 278 (80%, M+H$^+$); **HRMS** (ESI$^+$) $C_{16}H_{23}NO_3{}^{23}Na$ requires *MNa* 300.1576, found 300.1583 (+2.5 ppm).

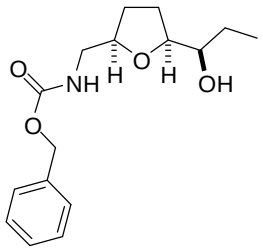
(±)-*N*-(((2*RS*,5*SR*)-5-((*RS*)-1-hydroxypropyl)-tetrahydrofuran-2-yl)methyl)-4-methyl benzenesulfonamide 18



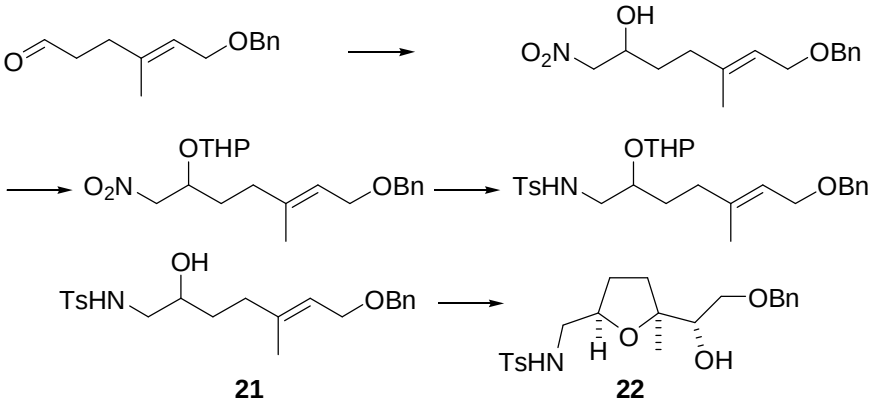
Protected amino alcohol **17** (149 mg, 0.50 mmol) was subjected to General Procedure 5. Purification by flash column chromatography (SiO_2, eluting with 7:3 petrol-acetone, R_f 0.28) furnished *amino-THF* **18** (140 mg, 0.45 mmol, 89%) as prisms.

m.p. 104-105 ºC; **?$_{max}$**(KBr disk)/cm^{-1} 3451, 3284, 1326, 1160, 1082; **d$_H$** (400 MHz, $CDCl_3$) 7.73 (2 H, d, *J* 8.1), 7.28 (2 H, d, *J* 8.0), 5.69 (1 H, br. s), 4.03-4.01 (1 H, m), 3.86-3.83 (1 H, m), 3.70-3.67 (1 H, m), 3.10 (1 H, d, *J* 12.2), 2.92 (1 H, dd, *J* 12.4, 5.2), 2.41 (3 H, s), 2.18 (1 H, d, *J* 7.8), 1.96-1.84 (2 H, m), 1.75-1.65 (2 H, m), 1.39-1.35 (2 H, m), 0.95 (3 H, t, *J* 7.2); **d$_C$** (100.6 MHz, $CDCl_3$) 143.1, 136.9, 129.5, 126.9, 82.8, 76.7, 73.1, 47.1, 28.4, 26.0, 23.9, 21.4, 10.3; ***m/z*** (ESI$^+$) 649 (100%, 2M+Na$^+$), 644 (20%, 2M+NH$_4^+$), 372 (10%, M+MeCN+NH$_4^+$), 336 (20%, M+Na$^+$), 314 (10%, M+H$^+$); **HRMS** (ESI$^+$) $C_{15}H_{23}NO_4{}^{23}NaS$ requires *MNa* 336.1245, found 336.1243 (-0.8 ppm).

(±)-Benzyl ((2*R*,5*S*)-5-((*R*)-1-hydroxypropyl)-tetrahydrofuran-2-yl) methyl carbamate 20



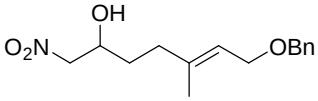
Amino alcohol **19** (139 mg, 0.50 mmol) was subjected to General Procedure 5. Purification by flash column chromatography (SiO_2, eluting with 4:1 petrol-acetone, R_f 0.25) furnished *amino-THF* **20** (113 mg, 0.39 mmol, 77%) as a viscous oil.
?$_{max}$(thin film)/cm^{-1} 3341, 1704, 1538, 1253, 1147, 1082; **d**$_H$ (400 MHz, $CDCl_3$) 7.36-7.30 (5 H, m), 5.20 (1 H, br. s), 5.11 (2 H, ABq, *J* 12.2), 4.04-3.99 (1 H, m), 3.90-3.86 (1 H, m), 3.71 (1 H, td, *J* 6.4, 2.9), 3.32-3.22 (2 H, m), 2.29 (1 H, br. s), 2.03-1.86 (2 H, m), 1.80-1.71 (1 H, m), 1.67-1.62 (1 H, m), 1.40 (2 H, qu, *J* 7.4), 0.99 (3 H, t, *J* 7.4); **d**$_C$ (100.6 MHz, $CDCl_3$) 170.6, 136.5, 128.5, 128.1, 128.0, 83.2, 78.4, 72.7, 66.9, 45.7, 28.6, 25.9, 23.5, 10.5; ***m/z*** (ESI$^+$) 609 (85%, 2M+Na$^+$), 316 (100%, M+Na$^+$), 294 (20%, M+H$^+$); **HRMS** (ESI$^+$) $C_{16}H_{23}NNaO_4$ requires *MNa* 316.1519, found 316.1520 (+0.2 ppm).



21 **22**

Scheme 9 : Synthesis of amino-alcohol **21** and THF **22**

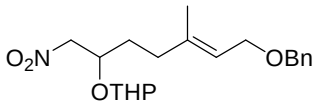
(±)-***(E)*-7-(Benzyloxy)-5-methyl-1-nitrohept-5-en-2-ol**



The geraniol derived aldehyde (873 mg, 4.00 mmol) was subjected to General Procedure 1. Purification by flash column chromatography (SiO_2, eluting with 3:2 petrol-EtOAc, R_f 0.23) furnished the *nitro alcohol* (754 mg, 2.70 mmol, 68%) as an oil.
?$_{max}$(thin film)/cm^{-1} 3407, 1671, 1554, 1383, 1203, 1069; **d**$_H$ (400 MHz, $CDCl_3$) 7.35-7.27 (5 H, m), 5.45 (1 H, tq, *J* 6.7, 1.2), 4.51 (2 H, s), 4.41-4.38 (2 H, m), 4.31-4.25

(1 H, m), 4.03 (2 H, d, *J* 6.8), 2.73 (1 H, br. s), 2.27-2.12 (2 H, m), 1.71-1.58 (2 H, m), 1.66 (3 H, s); δ_C (100.6 MHz, $CDCl_3$) 138.8, 138.3, 128.4, 127.8, 127.6, 122.1, 80.5, 72.3, 68.1, 66.4, 35.0, 31.4, 16.4; ***m/z*** (ESI$^-$) 278 (100%, $[M-H]^-$); **HRMS** (ESI$^-$) $C_{15}H_{20}NO_4$ requires *M-H* 278.1392, found 278.1385 (-2.8 ppm).

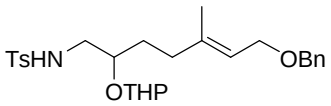
(±)-(*E*)-2-(7-(Benzyloxy)-5-methyl-1-nitrohept-5-en-2-yloxy)-tetrahydro-2*H*-pyran



The above nitroalcohol (731 mg, 2.62 mmol) was subjected to General Procedure 2. Purification by flash column chromatography (SiO_2, eluting with 85:15 petrol-EtOAc, R_f 0.26) yielded the *tetrahydropyran* (860 mg, 2.37 mmol, 90%) as an oil consisting of a 1:1 mixture of diastereomers.

ν_{max}(thin film)/cm^{-1} 1670, 1558, 1383, 1202, 1153, 1075, 1035; δ_H (400 MHz, $CDCl_3$) 7.35-7.25 (5 H, m), 5.99-5.97 (1 H, m), 4.67-4.63 (1 H, m), 4.50 (2 H, s), 4.66-4.64 (1 H, m), 4.45-4.37 (1 H, m), 4.35-4.27 (1 H, m), 4.02 (2 H, d, *J* 6.7), 3.90-3.74 (1 H, m), 3.53-3.43 (1 H, m), 2.17-2.10 (2 H, m), 1.92-1.68 (4 H, m), 1.66 (1.5 H, s), 1.64 (1.5 H, s), 1.58-1.50 (4 H, m); δ_C (100.6 MHz, $CDCl_3$) 139.0, 138.8, 138.5, 138.4, 128.4, 127.8, 127.6, 122.0, 121.8, 99.7, 98.9, 79.4, 78.5, 74.4, 73.9, 72.2, 72.1, 66.5, 66.1, 63.0, 62.8, 34.9, 34.7, 31.3, 30.8, 30.7, 29.9, 25.5, 25.1, 19.7, 19.5, 16.5, 16.4; ***m/z*** (FI$^+$) 363 (100%, M^+); **HRMS** (FI$^+$) $C_{20}H_{29}NO_5$ requires *M* 363.2046, found 363.2039 (-1.8 ppm).

(±)-(*E*)-*N*-(7-(Benzyloxy)-5-methyl-2-(tetrahydro-2*H*-pyran-2-yloxy)hept-5-enyl]-4-methyl-benzenesulfonamide

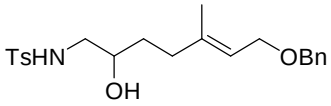


The tetrahydropyran (790 mg, 2.17 mmol) was subjected to General Procedure 3, using TsCl. Purification by flash column chromatography (SiO_2, eluting with 4:1 petrol-acetone, R_f 0.31) afforded the *protected amino alcohol* (271 mg, 0.57 mmol, 26%) as a colourless oil consisting of a 1:1 mixture of diastereomers.

ν_{max}(thin film)/cm^{-1} 3282, 1667, 1599, 1496, 1454, 1331, 1203, 1161; δ_H (400 MHz, $CDCl_3$) 7.73 (2 H, dd, *J* 8.3, 2.5), 7.34-7.27 (7 H, m), 6.13 (0.5 H, dd, *J* 8.1, 2.3), 5.39-5.32 (1 H, m), 4.80 (0.5 H, t, *J* 6.0), 4.49 (2 H, s), 4.49-4.47 (0.5 H, m), 4.31 (0.5 H, dd, *J* 7.4, 2.3), 4.01-3.98 (2 H, m), 3.97-3.94 (0.5 H, m), 3.87-3.82 (0.5 H, m), 3.72-3.67 (0.5 H, m), 3.49-3.40 (1.5 H, m), 3.14-3.02 (1 H, m), 2.88 (0.5 H, dt, *J* 12.7, 5.9), 2.79 (0.5 H, ddd, *J* 12.6, 2.5, 8.4), 2.41 (1.5 H, s), 2.40 (1.5 H, s), 2.07-1.95 (2 H, m), 1.82-1.39 (8 H, m), 1.60 (1.5 H, s), 1.58 (1.5 H, s); δ_C (100.6 MHz, $CDCl_3$) 143.4, 143.0, 139.5, 139.2, 138.5, 138.4, 137.1, 136.8, 129.8, 129.7, 129.5, 128.4, 127.8, 127.7, 127.6, 127.5, 127.1, 127.0, 121.6, 121.3,

101.6, 97.9, 79.0, 74.9, 72.2, 72.1, 66.5, 66.4, 65.2, 63.3, 47.6, 45.3, 35.2, 35.1, 31.4, 31.3, 30.9, 30.8, 25.2, 25.0, 21.5, 21.3, 20.0, 16.4, 16.3; ***m/z*** (ESI^-) 486 (100%, $[M-H]^-$); **HRMS** (ESI^-) $C_{27}H_{36}NO_5S$ requires *M-H* 486.2314, found 486.2314 (+0.0 ppm).

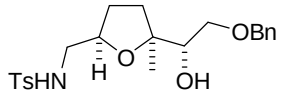
(±)-(*E*)-*N*-(7-(Benzyloxy)-2-hydroxy-5-methylhept-5-enyl)-4-methylbenzene sulphonamide 21



The above protected amino alcohol (230 mg, 0.47 mmol) was subjected to General Procedure 4. Purification by flash column chromatography (SiO_2, eluting with 7:3 petrol-acetone, R_f 0.33) furnished the *amino alcohol* **21** (174 mg, 0.43 mmol, 92%) as an oil.

?$_{max}$(thin film)/cm^{-1} 3443, 1660, 1326, 1159, 1091; **d**$_H$ (400 MHz, $CDCl_3$) 7.74 (2 H, d, *J* 8.3), 7.35-7.27 (7 H, m), 5.40 (1 H, t, *J* 6.7), 4.91 (1 H, t, *J* 5.4), 4.49 (2 H, s), 4.00 (2 H, d, *J* 6.7), 3.71-3.65 (1 H, m), 3.06 (1 H, ddd, *J* 12.9, 7.4, 3.1), 2.79 (1 H, ddd, *J* 13.0, 8.0, 5.2), 2.42 (3 H, s), 2.16-2.01 (3 H, m), 1.62 (3 H, s), 1.54 (2 H, m); **d**$_C$ (100.6 MHz, $CDCl_3$) 143.5, 139.6, 138.4, 136.7, 129.8, 128.4, 127.8, 127.6, 127.1, 121.6, 72.3, 70.1, 66.4, 48.6, 35.4, 32.3, 21.5, 16.4; ***m/z*** (ESI^-) 402 (100%, $[M-H]^-$); **HRMS** (ESI^-) $C_{22}H_{28}NO_4S$ requires *M-H* 402.1739, found 402.1734 (-1.3 ppm).

(±)-*N*-(((2*R*,5*S*)-5-((*R*)-2-(benzyloxy)-1-hydroxyethyl)-5-methyl-tetrahydrofuran-2-yl)methyl)-4-methylbenzenesulfonamide 22



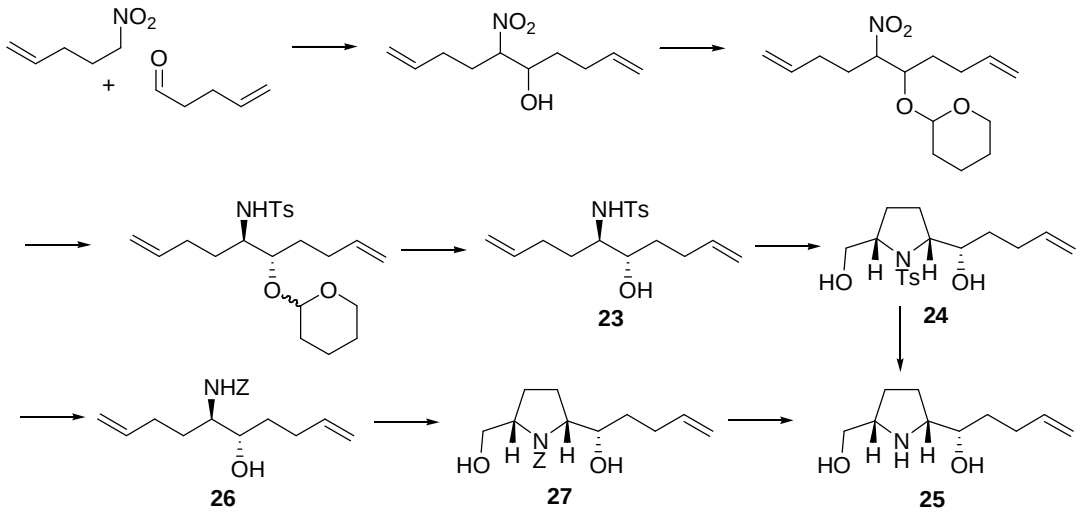
Amino alcohol **21** (98 mg, 0.24 mmol) was subjected to General Procedure 5. Purification by flash column chromatography (SiO_2, eluting with 7:3 petrol-acetone, R_f 0.19) furnished *amino-THF* **22** (76 mg, 0.18 mmol, 76%) as off-white prisms.

m.p. 78-80 °C; **?**$_{max}$(KBr disk)/cm^{-1} 3452, 3284, 1326, 1161, 1094; **d**$_H$ (400 MHz, $CDCl_3$) 7.72 (2 H, d, *J* 7.8), 7.39-7.31 (5 H, m), 7.27 (2 H, d, *J* 7.7), 5.73 (1 H, t, *J* 5.5), 4.56 (2 H, ABq, *J* 11.8), 4.17-4.12 (1 H, m), 3.70 (1 H, dd, *J* 8.6, 2.9), 3.59 (1 H, dd, *J* 9.5, 2.4), 3.46 (1 H, app. t, *J* 8.9), 3.09 (1 H, dt, *J* 12.4, 3.8), 2.97-2.91 (1 H, m), 2.87 (1 H, br. s), 2.41 (3 H, s), 2.22-2.15 (1 H, m), 2.03-1.94 (1 H, m), 1.84-1.75 (1 H, m), 1.62-1.55 (1 H, m), 1.08 (3 H, s); **d**$_C$ (100.6 MHz, $CDCl_3$) 143.1, 137.8, 137.1, 129.6, 128.5, 127.9, 127.8, 127.0, 84.4, 76.9, 75.4,

73.5, 70.9, 47.1, 34.7, 28.2, 22.7, 21.5; ***m/z*** (ESI$^+$) 478 (100%, M+MeCN+NH_4^+); **HRMS** (ESI$^+$) $C_{22}H_{30}NO_5S$ requires *MH* 420.1845, found 420.1837 (-1.8 ppm).

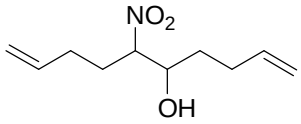
Mechanistic Studies

4. Data for competition substrates 23 and 26



Scheme 10: Synthesis of amino-alcohol substrates **23** & **26** and pyrrolidines **24**, **25** & **27**

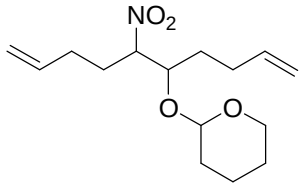
±)-**6-Nitrodeca-1,9-dien-5-ol**



5-Nitropent-1-ene (1.71g, 14.90 mmol) was added to 4-pentenal (1.47 mL, 14.90 mmol) and the neat mixture was stirred for 30 min at room temperature. Neutral alumina (5 g) was then added portionwise over 15 min to allow even adsorption. The pale yellow alumina was then left without stirring for 60 h and then filtered through cotton wool with dichloromethane (3 × 50 mL) to give a yellow oil which was purified by chromatography, eluting with 15% diethyl ether in petrol, to give the *nitroalcohol* (1.58 g, 53%) as a colourless oil consisting of a 1.6:1 mixture of diastereomers;

?$_{max}$ (thin film)/cm^{-1} 3445, 3080, 2926, 1642, 1550, 1448, 918; **d$_H$** (400 MHz, $CDCl_3$) *major diastereomer* 5.86-5.70 (2 H, m), 5.11-5.02 (4 H, m), 4.53-4.46 (1 H, m), 3.91 (1 H, br s), 2.30-2.01 (5 H, m), 1.92-1.84 (1 H, m), 1.68-1.51 (3 H, m); **d$_C$** (100.6 MHz, $CDCl_3$) 137.2, 135.9, 135.6, 116.9, 116.8, 115.9, 91.8, 91.2, 71.7, 71.3, 32.7, 32.2, 29.9, 29.8, 29.7, 29.5, 29.5, 27.03; **HRMS** (FI$^+$) Calcd. for $C_{10}H_{17}NO_3$ (M$^+$) 199.1208. Found 199.1203 (-2.5 ppm).

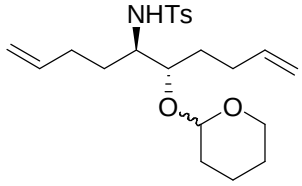
(±)-**2-(6-Nitrodeca-1,9-dien-5-yloxy)tetrahydro-2H-pyran**



The alcohol (0.77 g, 3.87 mmol) was subjected to General Procedure 2 to give a residue which was purified by chromatography, eluting with 15% diethyl ether in petrol to give the *acetal* (1.02 g, 93%) as a colourless oil consisting of a 1.6:1.6:1:1 mixture of diastereomers.

?$_{max}$ (thin film)/cm^{-1} 2944, 1553, 1125, 1035; **d**$_H$ (400 MHz, $CDCl_3$) 5.87-5.70 (2 H, m), 5.10-4.99 (4 H, m), 4.78-4.50 (2 H, m), 4.16-4.12 (? H, m), 4.09-4.03 (? H, m), 4.00-3.85 (1 H, m), 3.75-3.69 (? H, m), 3.53-3.47 (1 H, m), 2.30-2.02 (5 H, m), 1.93-1.47 (9 H, m); **d**$_C$ (100.6 MHz, $CDCl_3$) 137.8, 137.6, 137.4, 137.4, 136.2, 136.0, 135.6, 116.9, 116.8, 116.6, 116.5, 115.6, 115.5, 115.4, 115.2, 101.1, 99.2, 98.7, 97.2, 90.4, 90.2, 89.8, 78.8, 77.1, 76.0, 63.2, 63.1, 62.9, 62.6, 31.0, 30.8, 30.7, 30.6, 30.2, 30.2, 30.0, 29.8, 29.6, 29.3, 28.7, 28.3, 28.1, 28.0, 27.7, 27.3, 25.3, 25.2, 25.2, 19.8, 19.7, 19.6, 19.2; **HRMS** (FI) Calcd. for $C_{15}H_{25}NO_4$ (M^+) 283.1784. Found 283.1813 (-10 ppm).

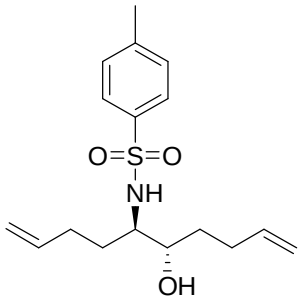
(±)-**4-Methyl-*N*-(6-(tetrahydro-2*H*-pyran-2-yloxy)deca-1,9-dien-5-yl)benzene sulfonamide**



The nitro acetal (1.80 g, 6.36 mmol) was subjected to General Procedure 3 to give a residue which was purified by chromatography, eluting with 10% acetone in petroleum ether to give the *sulfonamide* (1.56 g, 60%) as a pale yellow oil consisting of a 1:1 mixture of diastereomers.

?$_{max}$ (thin film)/cm^{-1} 3250 (br), 2944, 1715, 1441, 1161; **d**$_H$ (400 MHz, $CDCl_3$) *less polar diastereomer* 7.80 (2 H, d, *J* 8.4), 7.36 (2 H, d, *J* 8.4), 5.85-5.61 (2 H, m), 5.10-4.93 (5 H, m), 4.19 (1 H, dd, *J* 9.8, 5.1), 4.12-4.07 (1 H, m), 4.03 (1 H, dd, *J* 9.8, 5.1), 3.79 (1 H, br s), 3.65 (1 H, br s), 2.46 (3 H, s), 2.29-1.98 (6 H, m), 1.85-1.40 (8 H, m); **d**$_C$ (100.6 MHz, $CDCl_3$) 144.8, 138.1, 135.3, 132.8, 129.9, 127.8, 115.3, 115.2, 70.7, 70.2 (× 2), 69.5, 42.9, 36.5, 36.4, 33.9, 30.8, 30.5, 30.2, 21.7 ***m/z*** (ESI$^-$) 406 (25%, [M-H]$^-$), 322 (100%, M-$C_5H_9O^-$); **HRMS** (ESI$^-$) $C_{22}H_{32}NO_4S$ requires *M-H* 406.2047, found 406.2048 (+0.25 ppm).

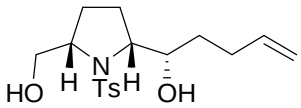
(±)-***N*-(6-Hydroxydeca-1,9-dien-5-yl)-4-methylbenzenesulfonamide 23**



The tetrahydropyran (146 mg, 0.36 mmol) was subjected to General Procedure 4 to give an oil which was purified by chromatography, eluting with 15% acetone in petroleum ether to give the *alcohol* **23** (93 mg, 80%) as a pale orange oil (single diastereomer by NMR spectroscopy).

?$_{max}$ (thin film)/cm^{-1} 3550, 3282, 2941, 1324, 1159; **d$_H$** (400 MHz, $CDCl_3$) 7.77 (2 H, d, *J* 8.1), 7.31 (2 H, d, *J* 8.1), 5.83-5.68 (1 H, m), 5.68-5.55 (1 H, m), 5.14-4.69 (5 H, m), 3.54 (1 H, app d, *J* 9.0), 3.31-3.15 (1 H, m), 2.44 (3 H, s), 2.26-2.11 (2 H, m), 2.11-1.94 (2 H, m), 1.70 (1 H, br s), 1.56-1.34 (4 H, m); **d$_C$** (100.6 MHz, $CDCl_3$) 143.5, 137.8, 137.7, 137.4, 129.7, 129.6, 127.1, 127.0, 115.3, 115.3, 72.9, 57.8, 32.1, 30.2, 29.7, 28.2, 21.5; **HRMS** (ESI$^+$) Calcd. for $C_{17}H_{25}NO_3SNa$ (M+Na$^+$) 346.1447. Found 346.1444 (-0.8 ppm).

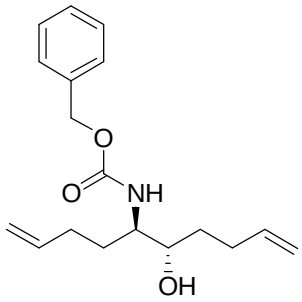
(±)-**1-(5-(hydroxymethyl)-1-tosylpyrrolidin-2-yl)pent-4-en-1-ol 24**



The amino alcohol **23** (42 mg, 0.13 mmol) was subjected to General Procedure 6 to give a residue which was purified by chromatography, eluting with 20% acetone in petroleum ether to give the *pyrrolidine* **24** (27 mg, 61%) as colourless prisms.

m.p. 120-122 °C; **?$_{max}$** ($CHCl_3$) 3385, 2930, 1341, 1159, 1093; **d$_H$** (400 MHz, $CDCl_3$) 7.73 (2 H, d, *J* 8.0), 7.34 (2 H, d, *J* 8.0), 5.85 (1 H, ddt, *J* 17.0, 10.3, 6.7), 5.07 (1 H, dd, *J* 17.0, 1.5), 5.00 (1 H, dd, *J* 10.6, 1.5), 4.18 (1 H, ddd, *J* 8.4, 4.6, 2.5), 3.90 (1 H, dd, *J* 11.1, 3.7), 3.77 (1 H, sx, *J* 8.4), 3.63 (1 H, dd, *J* 11.1, 4.6), 3.57 (1 H, dt, *J* 6.4, 2.5), 3.15 (2 H, br s), 2.45 (3 H, s), 2.37-2.25 (1 H, m), 2.21-2.09 (1 H, m), 2.09-1.96 (1 H, m), 1.93-1.80 (1 H, m), 1.58-1.38 (4 H, m); **d$_C$** (100.6 MHz, $CDCl_3$) 143.9, 138.2, 134.1, 129.9, 127.6, 115.1, 72.9, 66.2, 65.6, 62.7, 32.8, 30.5, 27.5, 24.2, 21.6; ***m/z*** (ESI$^+$) 701 (100%, 2M+Na$^+$), 362 (70%, M+Na$^+$), 340 (5%, M+H$^+$); **HRMS** (ESI$^+$) Calcd. for $C_{17}H_{25}NO_4SNa$ (M+Na$^+$) 362.1397. Found 362.1400 (+0.8 ppm).

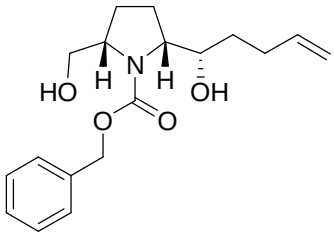
(±)-benzyl (5*R*,6*S*)-6-hydroxydeca-1,9-dien-5-ylcarbamate 26



The *carbamate* **26** was prepared *via* the same sequence used to prepare the sulfonamide, to give a white crystalline solid.

m.p. 124-126 °C; **?**$_{max}$ ($CHCl_3$)/cm^{-1} 3312, 2949, 1684, 1545, 1254, 1044; **d**$_H$ (400 MHz, $CDCl_3$) 7.38-7.32 (5 H, m), 5.87-5.76 (2 H, m), 5.15-5.01 (6 H, m), 4.87 (1 H, d *J* 8.4), 3.71-3.67 (2 H, m), 2.31-2.06 (4 H, m), 1.68-1.50 (5 H, m); **d**$_C$ (100.6 MHz, $CDCl_3$) 156.7, 138.1, 137.7, 136.4, 128.6, 128.2, 128.1, 115.3, 115.2, 74.0, 66.9, 55.4, 32.3, 30.3 (× 2), 28.4; ***m/z*** (ESI^+) 326 (40%, $M+Na^+$); **HRMS** (ESI^+) Calcd. for $C_{18}H_{25}NO_3Na$ ($M+Na^+$) 326.1727. Found 326.1727.

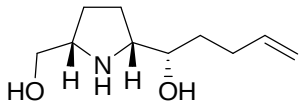
(±)-(2*SR*,5*RS*)-benzyl 2-(hydroxymethyl)-5-((*SR*)-1-hydroxypent-4-enyl)pyrrolidine-1-carboxylate



The carbamate **26** (75 mg, 0.247 mmol) was subjected to general procedure 5 to give a residue which was purified by chromatography, eluting with 20% acetone in petroleum ether to give the *pyrrolidine* **27** (27 mg, 34%) as a pale yellow oil.

?$_{max}$ (thin film)/cm^{-1} 3392, 2940, 1677, 1416, 1355, 1106; **d**$_H$ (400 MHz, $CDCl_3$) 7.39-7.32 (5 H, m), 5.81 (1 H, br s), 5.18-5.11 (2 H, m), 5.07-4.95 (2 H, m), 4.30-3.89 (4 H, m), 3.55 (1 H, br s), 3.18 (2 H, br s), 2.18-1.91 (6 H, m), 1.51-1.47 (2 H, m); **d**$_C$ (100.6 MHz, $CDCl_3$); ***m/z*** (ESI^+) 378 (100%, $M+CH_3CN+NH_4^+$), 342 (10%, $M+Na^+$); **HRMS** (ESI^+) Calcd. for $C_{18}H_{25}NO_4Na$ ($M+Na^+$) 342.1676. Found 342.1678 (+0.6 ppm).

(±)-(*SR*)-1-((2*RS*,5*SR*)-5-(hydroxymethyl)pyrrolidin-2-yl)pent-4-en-1-ol 25



Sodium pieces (~80 mg, 3.80 mmol) were added portionwise over 5 min to ammonia (3 mL) at -78 °C. The mixture was stirred until a dark blue/green colour was observed (~10 min) and then the sulphonamide **24** (49 mg, 0.152 mmol) in tetrahydrofuran (2

mL) was added dropwise over 5 min. The solution was stirred for 5 h and then quenched by addition of saturated aqueous NH_4Cl solution (2 mL). The mixture was then allowed to warm to room temperature and stirred for 30 min to allow evaporation of ammonia. Ethyl acetate (10 mL) was added and the separated aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the *amino-diol* **25** (21 mg, 75%) as a white solid which was recrystallised from petroleum ether 80-100 °C to give needles.

m.p. 135-137 °C; **?**$_{max}$ ($CHCl_3$) 3357, 2934, 1603, 1307; **d**$_H$ (400 MHz, $CDCl_3$) 5.85 (1 H, ddt, *J* 17.0, 10.3, 6.6), 5.06 (1 H, dq, *J* 17.0, 3.4, 1.7), 4.98 (1 H, dd, *J* 10.3, 1.7), 3.62-3.58 (2 H, m), 3.42-3.35 (2 H, m), 3.28 (1 H, dt, *J* 7.8, 3.7), 2.31-2.10 (5 H, m), 1.86-1.79 (1 H, m), 1.74-1.69 (2 H, m), 1.62-1.48 (3 H, m); **d**$_C$ (100.6 MHz, $CDCl_3$) 138.5, 114.8, 71.3, 65.8, 62.7, 58.6, 32.8, 30.4, 27.4, 23.6; **HRMS** (ESI^+) Calcd. for $C_{10}H_{20}NO_2$ ($M+H^+$) 186.1489. Found 186.1492 (+1.6 ppm).