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# Supporting Information



69451 Weinheim, Germany

# Part I
# Experimental

## Contents

# 1 General Procedures

Experimental techniques using flame dried glassware apparatus are standard unless otherwise indicated; reactions were carried out under nitrogen with dry, freshly distilled solvents. Dichloromethane was distilled from calcium hydride. n-BuLi in hexane (Aldrich) was titrated with benzyl-biphenyl-4-ylmethylene-amine and anhydrous menthol before use. All other reagents were purified in accordance with the instructions in 'Purification of Laboratory Chemicals' or used as obtained from commercial sources.

Temperatures of 0 °C were maintained using an ice-water bath and - 78 °C with an acetone and cardice.

Yields refer to chromatographically and spectroscopically pure compounds. All reactions were monitored by thin layer chromatography (TLC) using glass plates pre-coated with Merck silica gel 60 F254 or aluminium oxide 60 F254. Visualisation was by the quenching of UV fluorescence ($\nu_{max}$ = 254 nm) or by staining with ceric ammonium molybdate or potassium permanganate or Dragendorff's reagent (0.08 % w/v bismuth subnitrate and 2 % w/v KI in 3M aq. AcOH). Retention factors ($R_f$) are quoted to 0.01.

Melting points were obtained using a Reichert hot plate microscope with a digital thermometer attachment and are uncorrected.

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One spectrometer with internal referencing. Selected absorption maxima ($\nu_{max}$) are reported in wavenumbers ($cm^{-1}$).

Proton magnetic resonance spectra were recorded on Bruker Ultrashield 400 or 500. Proton assignments are supported by $^1$H-$^1$H spectra where necessary. Chemical shifts ($\delta_H$) are quoted in ppm and are referenced to the residual non-deuterated solvent peak. Coupling constants ($J$) are reported in Hertz to the nearest 0.5 Hz. Data are reported as follows: chemical shift, integration, multiplicity [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet; or as a combination of these (e.g. dd, dt, etc.)], coupling constant(s) and assignment. Diastereotopic protons are assigned as X and X′, where the ′ indicates the higher field proton.

Carbon magnetic resonance spectra were recorded on Bruker 400 or 500 spectrometers operating at 100 and 125 MHz respectively. Carbon spectra assignments are supported by DEPT editing and where necessary $^{13}$C-$^1$H (HMQC) correlations.

Chemical shifts ($\delta_C$) are quoted in ppm to the nearest 0.01 ppm, and are referenced to the deuterated solvent (7.26 ppm for $CHCl_3$ and 77.0 ppm for $^{13}$C of $CDCl_3$, 2.54 ppm for DMSO and 40.45 ppm for $^{13}$C of $d_6$-DMSO).

Phosphorus magnetic resonance spectra ($^{31}$P) were recorded on a DPX 400 MHz spectrometer. Chemical shifts ($\delta_P$) are quoted in ppm to the nearest 0.01 ppm and are referenced to $H_3PO_4$ (external).

Cyclopentadiene was prepared by cracking dicyclopentadiene at atmospheric pressure and collecting the monomer at 0 °C.

Library compounds were all purified by flash column chromatography and assessed for purity by LCMS using the UV trace (at 254 nm) and the total ion count. Compounds with purity greater than 85 % were screened in the biological assays.

LCMS spectra were recorded on an HP/Agilent MSD LC-MS APCI+ 120-1000 full gradient ACq T = 1 min 1$\mu$l. High resolution mass measurements were made by the EPSRC mass spectrometry service (Swansea) and reported mass values are within the error limits of 5 ppm mass units. Microanalyses were performed by the University of Cambridge Microanalytical Laboratory in the Department of Chemistry, and are quoted to the nearest 0.1 % for all elements except for hydrogen, which is quoted to the nearest 0.05 %. Reported atomic percentages are within the error limits of ± 0.4 %. Optical rotations were recorded on a Perkin Elmer 343 polarimeter. $[\alpha]_D^{25}$ values are reported in $10^{-1}$ deg $cm^2$ $g^{-1}$ at 589 nm, concentration (c) is given in $g(100mL)^{-1}$. All flash chromatography was carried out using slurry-packed Merck 9385 Kieselgel 60 silca gel.

The numbering on the pictures does not follow the IUPAC naming system and is simply used for the asigning of the $^1$H NMR and $^1$3C NMR.

2,2-Bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane[(*R*,*R*)-*tert*-Butyl bis (oxazoline)] catalyst was prepared according to Evans methodology.[1]

## 1.1 General methods for all branching pathways

### 1.1.1 Cleavage of the small molecule from solid support

The solid supported small molecule ( 100 mg) was dissolved in THF (0.5 ml) and HF·Pyr (50 $\mu$l, 1.77 mmol) was added. The vial sealed and agitated for 2.5 h, then quenched using trimethylethoxysilane. The vial was agitated for a further 30 min to ensure complete quenching. Then the solvent was filtered through a plug of silica gel and the solvent was removed in vacuo and the product purified by flash column chromatography (10:1 $CH_2Cl_2$: Methanol)

### 1.1.2 Cleavage of TIPS protecting group in solution phase

A plastic eppendorf vial containing the TIPS protected alcohol (1 equiv.) and THF (0.5 ml) at room temperature was charged with HF.Pyr (50 $\mu$L, 1.77 mmol). The vial was sealed and the solution agitated for 2.5 hours. The solution was quenched via addition of trimethylethoxysilane (0.32 ml) and agitated for a further 30 minutes. The solution was filtered through a plug of silica gel and the gel washed with $CH_2Cl_2$ (× 3), $CH_2Cl_2$: MeOH (1:1) (× 3) and $CH_2Cl_2$ (× 3) and the solvent removed *in vacuo*.

### 1.1.3 Determination of ee values - chiral shift reagents for pathway 1

To simplify the identification of the level of induced stereochemistry, the use of chiral shift reagents was introduced, by which method it was possible to estimate ee values from $^1$H NMR spectra. (S)-(+)-$\alpha$-methoxyphenylacetic acid in $C_6D_6$ was used, since under these conditions two distinctive peaks in the 1H NMR spectrum were clearly shown for the two enantiomers.

### 1.1.4 Determination of ee values - chiral HPLC

Other enantiomeric excess's were calculated using chiral HPLC.

### 1.1.5 General procedure for resin derivatisation

To prepare i-Pr(n-Bu)$_2$MgLi, a round bottom flask, equipped

with a magetic stirrer, containing i-PrMgCl (2.0 M in THF, 2 equiv.) and THF (quantity to result in 0.2 M solution of i-Pr(n-Bu)$_2$MgLi) at O °C was charged with n-BuLi (2.5 M solution in hexanes, 4 equiv.) and stirred for 30 mintues. The resulting clear yellow solution was added to a second round bottom flask, equipped with a magnetic stirrer, containing white copolymerised (74 % styrene, 1 % divinylbenzene, 25 % 4-bromostyrene) 4-bromopolystyrene beads (2.0 mmol/g, 1 equiv.) that had been previously swollen in THF (10 - 30 mL per gram of beads) for 15 minutes at 0 °C. The resutling mixture was stirred slowly for 5 hours, by which time the beads had turned golden in colour, then charged with i-Pr$_2$SiHCl (6 equiv.) and warmed to room temperature over two hours. The resulting white beads were filtered and washed sequentially with THF (3 × 5 minutes), $CH_2Cl_2$:MeOH (1:1, 3 × 5 minutes), and $CH_2Cl_2$ (5 × 5 minutes) then dried under reduced pressure to give free flowing white beads. Elemental analysis: Si 4.62 %

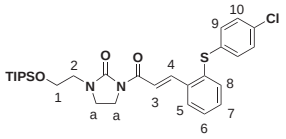
### 1.1.6 General procedure for alcohol loading

A dry fritted polpropylene column (Bruker), fitted with a Teflon stopcock and capped with a suba seal, containing the dry derivitised resin (1 equiv.) was evacuated and purged with nitrogen several times. The beads were swollen with $CH_2Cl_2$ (1mL/g beads) and the resulting suspension charged with TMSCl (6 equiv.) at room temperature and agitated occasionally over 30 minutes. The solution was drained and the beads washed with anhydrous $CH_2Cl_2$ (× 3). The beads were suspended in a solution of 1,3-dichloro-5,5-dimethylhydantoin (3 equiv.) and $CH_2Cl_2$ (1 mL/g beads) at room temperature and agitated occasionally over two hours. The solution drained and the beads washed with anhydrous $CH_2Cl_2$ (× 2). The beads were suspended in a solution of 2,6-lutidine (4 equiv.), DMAP (0.1 equiv.), the alcohol (1.1 equiv.) and $CH_2Cl_2$ (1.25 mL/g beads) at room temperature. The mixture was agitated and left to stand for 16 hours. The solution was drained and the leads washed with $CH_2Cl_2$ (× 3), $CH_2Cl_2$:MeOH (1:1, × 3) and THF (× 3). Air-drying under suction for two hours with occasional agitation followed by drying under high vacuum gave free flowing beads.

# 2 Solution phase synthesis of both enantiomers of gemmacin

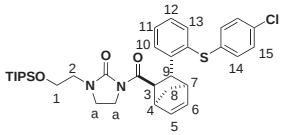
## 2.1 Preparation of enantioselective gemmacin

**1-3-[2-(4-Chloro-phenylsulfanyl)-phenyl]-acryloyl-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (5)** To a solution of the phosphonate (5.00 g, 10.8 mmol) in acetonitrile (50 ml) under nitrogen was added lithium bromide (946 mg, 11 mmol), DBU (2.17 ml, 11 mmol) and 2-(4-chlorothiophenyl)-benzaldehyde (2.73 g, 11 mmol). The solution was stirred for three hours and a yellow precipitate formed. The solvent was removed *in vacuo* and the solid dissolved in ethyl acetate and washed with saturated ammonium chloride solution, brine, dried ($MgSO_4$) and solvent removed *in vacuo*. The product was purified by flash column chromatography to yield the title compound as a white solid (3.20 g, 53 %).



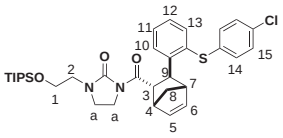

$R_f$ 0.33 ($SiO_2$; 10:3 40:60 petrol: ethyl acetate); $\nu_{max}$ (neat) 2942, 2865, 1721 (C=O), 1665 (C=O), 1615, 1475, 1374, 1355, 1266, 1107, 1092 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 8.34 (1H, d, *J* 15.5, H4), 8.04 (1H, d, *J* 15.5, H3), 7.81 (1H, dd, *J* 7.5, 2.0, H8), 7.39 (1H, m, H5), 7.36-7.28 (2H, m, ArH), 7.23 (2H, d, *J* 9.0, H9), 7.15 (2H, d, *J* 9.0, H10), 3.94 (2H, dd, *J* 8.0, 7.5, Ha), 3.91 (2H, t, *J* 5.0, H1), 3.66 (2H, dd, *J* 8.0, 7.5, Ha), 3.45 (2H, t, *J* 5.0, H2), 1.07 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 165.43 (C=O), 154.87 (C=O), 140.77 (C[4]H), 137.43 (C), 135.21 (C), 135.04 (C), 134.06 (C[5]H), 132.65 (C), 131.28 (C[9]H), 130.34 (C[8]H), 129.29 (C[10]H), 128.53 (CH), 127.89 (CH), 121.05 (C[3]H), 62.16 (C[1]$H_2$), 46.51 (C[2]$H_2$), 42.86 (C[a]$H_2$), 40.07 (C[a]$H_2$), 17.94 (C[TIPS]$H_3$), 11.84 (C[TIPS]H); LCMS (APCI+) 559 (M+H$^+$), HRMS (M+H)$^+$ found 559.2214 $C_{29}H_{40}N_2O_3ClSSi$ required 559.2212, Δ ppm +0.3, mp 106 -108 °C (40:60 petrol: ether).

**(1*S*, 2*R*, 3*R*, 4*R*)-1-3-[2-(4-Chloro-phenylsulfanyl)-phenyl]-bi-cyclo[2.2.1]hept-5-ene-2-carbonyl-3-(2-tri-isopropylsilanyloxy-ethyl)-imidazolidin-2-one (6)** To an oven dried round-bottomed flask was added 2,2-bis[2-[4(*S*)-*tert*-buty-1,3-oxazolinyl]]propane [(*s,s*)-*tert*-butyl bis(oxazoline)] (79 mg, 0.268 mmol), Cu(OTf)$_2$ (97 mg, 0.268 mmol) and 3Å molecular sieves followed by $CH_2Cl_2$ (5 ml). The solution was stirred for 40 minutes and developed a green colour. This was added to a solution of **5** (1.5 g, 2.68 mmol) followed by cyclopentadiene (4.4 ml, 53.6 mmol). The green reaction was stirred at room temperature for four days until complete by TLC. The solvent was removed *in vacuo* and the product purified by flash column chromatography to yield the title compound as a viscous oil (1.598 g, 95 %).



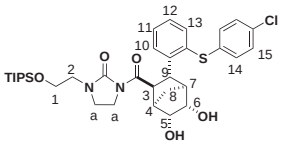

$R_f$ 0.22 ($SiO_2$; 10:3 hexane: ethyl acetate); $\nu_{max}$ (neat) 2942, 2865, 1720 (C=O), 1679 (C=O), 1474, 1436, 1389, 1354, 1333, 1261, 1242, 1107, 1091 cm$^{-1}$; $[\alpha]_D^{25}$ −39.1 (c 0.15, $CHCl_3$); $\delta_H$ (500 MHz; $CDCl_3$) 7.51 (1H, d, *J* 8.0, H10), 7.33-7.30 (2H, m, H11, H12), 7.22-7.15 (3H, m, H14, H13), 7.08 (2H, d, *J* 8.5, H15), 6.43 (1H, dd, *J* 5.5, 3.0, H6), 5.96 (1H, dd, *J* 5.5, 2.5, H5), 4.41 (1H, dd, *J* 5.0, 3.0, H3), 3.88-3.85 (2H, m, H1), 3.70-3.68 (2H, m, H9, Ha), 3.59-3.45 (2H, m, Ha), 3.45 (1H, ddd, *J* 14.0, 5.5, 4.5, H2), 3.38-3.37 (1H, m, Ha), 3.35 (1H, d, *J* 4.0, H4), 3.29-3.25 (1H, ddd, *J* 14.0, 5.5, 4.5, H2′), 2.93 (1H, s, H7), 1.94 (1H, d, *J* 9.0, H8), 1.54 (1H, dd, *J* 9.0, 1.5, H8′), 1.07 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 173.60 (C=O), 154.69 (C=O), 146.60 (C-Cl), 138.60 (C[6]H), 136.34 (C-C), 134.35 (C[5]H), 133.40 (C[13]H), 131.77 (C-S), 131.00 (C-S), 130.422 (C[14]H), 128.97 (C[15]H), 128.49 (C[10]H), 127.30 (C[11]H), 126.92 (C[12]H), 61.95 (C[1]$H_2$), 49.80 (C[7]H), 48.83 (C[3]H), 47.82 (C[8]$H_2$), 47.63 (C[4]H), 46.44 (C[2]$H_2$), 44.82 (C[9]H), 42.40 (C[a]$H_2$), 40.11 (C[a]$H_2$), 17.94 (C[TIPS]$H_3$), 11.86 (C[TIPS]H): HRMS (M+H)$^+$ found 625.2687 $C_{34}H_{46}N_2O_3ClSSi$ required 625.2681, Δ ppm +0.9.

**(1*R*, 2*S*, 3*S*, 4*S*)-1-3-[2-(4-Chloro-phenylsulfanyl)-phenyl]-bi-cyclo[2.2.1]hept-5-ene-2-carbonyl-3-(2-tri-isopropylsilanyloxy-ethyl)-imidazolidin-2-one (7)**



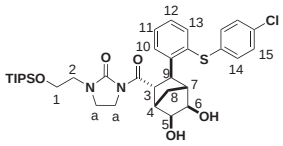
A viscous oil (704 mg, 62 %); $[\alpha]_D^{25}$ +41 (c 0.275, $CHCl_3$).

**(1*R*, 2*S*, 3*R*, 4*S*, 5*S*, 6*R*)-1-3-[2-(4-Chloro-phenylsulfanyl)-phenyl]-5,6-dihydroxy-bicyclo[2.2.1]-heptane-2-car-bonyl-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (8)** To a solution of **6** (1.5 g, 2.4 mmol) in acetone (100 ml) and water (10 ml) was added NMO (562 mg, 4.8 mmol) followed by a solution of $OsO_4$ (100 $\mu$l). The yellow reaction was stirred for 24 hours until complete by TLC. Saturated sodium thiosulfate solution (50 ml) was added and the reaction stirred for one hour. The reaction was extracted with $CH_2Cl_2$ and organic layer was washed with saturated sodium biocarbonate solution (50 ml), brine (50 ml), dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield the title compound as a yellow foam (1.32 g, 83 %).



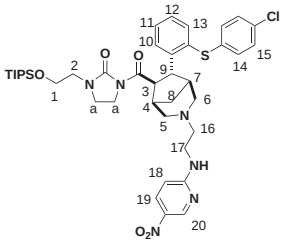
$R_f$ 0.19 ($SiO_2$; 10:1 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3449, 2940, 2864, 1725 (C=O), 1672 (C=O), 1474, 1388, 1354, 1261, 1091 $cm^{-1}$; $[\alpha]_D^{25}$ −28.0 (c 0.1, $CHCl_3$); $\delta_H$ (500 MHz; $CDCl_3$) 7.43 (1H, d, *J* 7.5, H10), 7.29-7.25 (2H, m, H11, H12), 7.20 (2H, d, *J* 8.5 H14), 7.15 (1H, t, *J* 7.0, H13), 7.08 (2H, d, *J* 8.5, H15), 4.31 (1H, dd, *J* 5.5, 4.5, H3), 4.08 (1H, d, *J* 5.5, H6), 3.99 (1H, d, *J* 5.5, H5), 3.86-3.84 (2H, m, H1), 3.81 (1H, d, *J* 5.5, H9), 3.79-3.66 (1H, m, Ha), 3.64-3.55 (2H, m, Ha), 3.43-3.38 (2H, m, Ha, H2), 3.34-3.30 (1H, m, H2′), 2.86 (2H, d, *J* 4.5, OH), 2.67 (1H, s, H4), 2.27 (1H, s, H7), 1.99 (1H, d, *J* 110, H8), 1.80 (1H, d, *J* 11.0, H8′), 1.06 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 172.39 (C=O), 154.23 (C=O), 145.09 (C-Cl), 135.95 (C-C), 134.29 (C[13]H), 132.25 (C-S), 132.04 (C-S), 130.49 (C[14]H), 128.08 (C[15]H), 128.43 (C[10]H), 127.18 (C[11]H), 126.98 (C[12]H), 74.07 (C[6]H), 70.33 (C[5]H), 62.02 (C[1]$H_2$), 51.12 (C[7]H), 49.33 (C[3]H), 47.29 (C[4]H), 46.51 (C[8]$H_2$), 42.28 (C[2]$H_2$), 42.08 (C[9]H), 40.04 (C[a]$H_2$), 32.54 (C[a]$H_2$), 17.95 (C[TIPS]$H_3$), 11.83 (C[TIPS]H); LCMS 659 ($M+H^+$); HRMS $(M+H)^+$ found 659.2736 $C_{34}H_{48}N_2O_5ClSSi$ required 659.2736, Δ ppm +0.0; mp 64-66 °C ($CH_2Cl_2$: MeOH).

**(1*S*, 2*R*, 3*S*, 4*R*, 5*R*, 6*S*)-1-3-[2-(4-Chloro-phenylsulfanyl)-phenyl]-5,6-dihydroxy-bicyclo[2.2.1]-heptane-2-car-bonyl-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (9)**



A yellow foam (571 mg, 84 %); $[\alpha]_D^{25}$ +35.3 (c 0.085, $CHCl_3$).

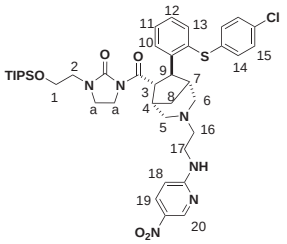
**(1*S*, 5*R*, 6*S*, 7*R*)-1-7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-[2-(5-nitro-pyridin-2-ylamino)-ethyl]-3-aza-bicyclo[3.2.1]octane-6-carbonyl-3-(2-tri-isopropylsilanyloxy-ethyl)-imidazolidin-2-one (10)** To a solution of **8** (300 mg, 0.46 mmol) in ethyl acetate (3.6 ml) and water (0.9 ml) at room temperature was added sodium periodate (149 mg, 0.69 mmol). The reaction was stirred for one hour and the solid removed by filtration. The solid was washed with methanol: ethyl acetate (3.5:6.5). Water was added to the filtrate and the organic layer separated. The organic layer was washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was dissolved in chloroform (5 ml) and 2-(2-aminoethylamino)-5-nitropyridine (83 mg, 0.46 mmol) was added. The reaction was stirred under nitrogen for 30 minutes and sodium triacetoxyborohydride (194 mg, 0.92 mmol) was added. The reaction was stirred overnight, then poured into water and extracted with chloroform. The organic layer was washed with brine, dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield the title compound as a yellow oil (252 mg, 68 %).



$R_f$ 0.35 ($SiO_2$; 10:4 toluene: ethyl acetate); $\nu_{max}$ (neat) 3287, 2941, 2867, 1723 (C=O), 1644 (C=O), 1603, 1473, 1318, 1289, 1248, 1108, 1091 $cm^{-1}$-1; $[\alpha]_D^{25}$ −37.5 (c 0.2, $CHCl_3$); $\delta_H$ (500 MHz; $CDCl_3$) 9.05 (1H, d, *J* 2.5, H20), 8.02 (1H, dd, *J* 9.5, 2.5, H19), 8.9 (1H, br s, NH), 7.49 (1H, d, *J* 8.0, H10), 7.39 (1H, d, *J* 7.5, H11), 7.36 (1H, t, *J* 6.0, H12), 7.25 (1H, d, *J* 7.5, H13), 7.10 (2H, d, *J* 8.5, H14), 6.89 (1H, d, *J* 9.5, H18), 6.78 (2H, d, *J* 8.5, H15), 4.83 (1H, d, *J* 7.0, H9), 4.52 (1H, dd, *J* 6.5, 6.0, H3), 3.89-3.86 (2H, m, H1), 3.85-3.83 (1H, m, Ha), 3.76-3.0 (1H, m, Ha), 3.59-3.55 (2H, m, Ha), 3.52-3.26 (4H, m, H2, H17), 2.99 (1H, s, H4), 2.55 (1H, d, *J* 12.0, H5), 2.52-2.44 (3H, m, H5′, H16), 2.42 (1H, d, *J* 11.0, H6), 2.28-2.26 (1H, m, H8), 2.0 (1H, d, *J* 10.0, H6′), 1.94 (1H, s, H7), 1.52 (1H, d, *J* 11.5, H8′), 1.06 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 173.02 (C=O), 161. 68 (C-N), 154.34 (C=O), 149.37 (C-Cl), 147.15 (C[20]H), 137.83 ($CNO_2$), 135.37 ([19]H), 134.79 (C-C), 132.25 (C-S), 132.40 (C-S), 131.22 (C[13]H), 139.51 (C[14]H), 129.02 (C[15]H), 128.91 (C[10]H), 127.16 (C[11]H), 126.99 (C[12]H), 125.29 (C[18]H), 61.73 (C[1]$H_2$), 57.21 (C[5]H), 56.46 (C[6]H), 54.52 (C[16]$H_2$), 54.32 (C[3]H), 46.52 (C[2]$H_2$), 44.17 (C[7]H), 44.00 (C[9]H), 42.42 (C[a]$H_2$), 40.79 (C[4]H), 40.38 (C[a]H),

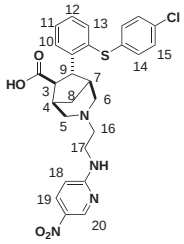
37.95 (C[8]$H_2$), 37.82 (C[2]$H_2$), 17.94 (C[TIPS]$H_3$), 11.82 (C[TIPS]H); LCMS (ES+) 806 (M+$H^+$); HRMS (M+H)$^+$ found 806.3411 $C_{41}H_{56}ClN_6O_5SSi$ required 806.3412, Δ ppm -0.1

**(1*R*, 5*S*, 6*R*, 7*S*)-1-7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-[2-(5-nitro-pyridin-2-ylamino)-ethyl]-3-aza-bicyclo[3.2.1]octane-6-carbonyl-3-(2-tri-isopropylsilanyloxy-ethyl)-imidazolidin-2-one (11)**



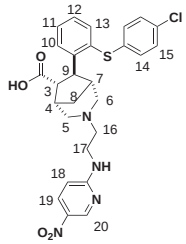
A yellow oil (230 mg, 75 %); $[\alpha]_D^{25}$ +38.0 (c 0.05, $CHCl_3$).

**(1*S*, 5*R*, 6*S*, 7*R*)-7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-[2-(5-nitro-pyridin-2-ylamino)-ethyl]-3-aza-bi-cyclo[3.2.1]octane-6-carboxylic acid (12)** To a solution of **10** (100 mg, 0.12 mmol) in THF (0.5 ml) and water (0.5 ml) was added lithium hydroxide (3 mg, 0.125 mmol). The reaction was heated at 50 °C for 48 hours, then acidified using pH 7 buffer and extracted with chloroform. The organic layer was reduced *in vacuo* and the crude product purified by flash column chromatography to yield the title compound as a yellow solid (43 mg, 67 %).



$R_f$ 0.05 ($SiO_2$; ethanol); $\nu_{max}$ (neat) 3241, 2939, 2791, 1604 (C=O), 1573, 1536, 1474, 1325, 1290, 1091 $cm^{-1}$; $[\alpha]_D^{25}$ +107.5 (c 0.04, $CHCl_3$); $\delta_H$ (500 MHz; MeOD) 8.92 (1H, d, *J* 2.5, H20), 7.96 (1H, dd, *J* 9.5, 2.5, H19), 7.46 (1H, d, *J* 8.0, H10), 7.34 (1H, t, *J* 8.5, H11), 7.26 (1H, d, *J* 8.0, H12), 7.18-7.14 (3H, m, H14, H13), 6.91-6.68 (3H, m, H15, H18), 4.45 (1H, d, *J* 5.5, H9), 3.68-3.64 (1H, m, H17), 3.47-3.43 (1H, m, H17), 3.29 (1H, t, *J* 6.0, H3), 3.13 (1H, d, *J* 11.0, H6), 2.95 (1H, br s, H5), 2.84-2.79 (2H, m, H16), 2.76 (1H, br s, H6′), 2.65 (1H, d, *J* 10.5, H7), 2.32 (1H, br s, H5′), 2.10-2.08 (1H, m, H8),1.91 (1H, br s, H4), 1.60 (1H, d, *J* 11.5, H8′); $\delta_C$ (125 MHz; MeOD) 179.53 (C=O), 161.61 (C-N), 149.17 (C-C), 145.98 (C[20]H), 136.31 (C-S), 135.05 (C-S), 134.00 ([19]H), 133.44 ($CNO_2$), 131.78 (C[13]H), 131.06 (C[14]H), 130.18 (C[15]H), 128.73 (C[10]H), 128.49 (C[11]H), 126.53 (C[12]H), 126.31 (C[18]H), 56.91 (C[5]H), 56.52 (C[6]H), 56.53 (C[3]H), 53.93 (C[16]$H_2$), 46.82 (C[7]H), 44.41 (C[9]H), 40.25 (C[4]H), 37.57 (C[8]$H_2$), 36.14 (C[17]$H_2$); LCMS (APCI+) 659 (M+$H^+$); HRMS (M+H)$^+$ found 539.1520 $C_{27}H_{28}N_4O_4SCl$ required 539.1516, Δ ppm -0.4; mp 99-102 °C (ethanol); HPLC - racemic compound inseparable under conditions tried. Columns: Chiralpak OD; AD; AS; AD-H. Solvent; 90:10 Hexane:IPA; 95:5 Hexane:IPA; 98:2 Hexane:IPA. Flow 1mL/min.

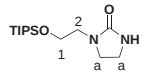
**(1*R*, 5*S*, 6*R*, 7*S*)-7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-[2-(5-nitro-pyridin-2-ylamino)-ethyl]-3-aza-bi-cyclo[3.2.1]octane-6-carboxylic acid (13)**



A yellow solid (54 mg, 86 %); $[\alpha]_D^{25}$ −105.0 (c 0.04, $CHCl_3$) HPLC - racemic compound inseparable under conditions tried. Columns: Chiralpak OD; AD; AS; AD-H. Solvent; 90:10 Hexane:IPA; 95:5 Hexane:IPA; 98:2 Hexane:IPA. Flow 1mL/min.

# 3 Synthesis of two carbon unit starting material

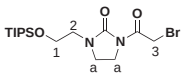
**1-(2-Triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (14)** A round-bottom flask, equipped with a magnetic stirrer, containing azeotroped ($CH_2Cl_2$/toluene) 1-(2-hydroxy-ethyl)-imaidazolidi-2-one (45.92 g, 0.35 mol), DMAP (2.93 g, 0.03 mol), $NEt_3$ (86.7 mL, 0.73 mol), $CaH_2$ (50 mg, 0.49 mmol) and $CH_2Cl_2$ (450 mL) was slowly charged with TIPSCl (53.2 mL, 0.29 mol) over 20 minutes. The mixture was stirred at room temperature for 16 hours. The resulting suspension was filtered, the filtrate poured carefully into ice water (500 mL) and the filtered solid dissolved in the resulting two phase mixture. The aqueous layer was extracted with $CH_2Cl_2$ (×2), the combined organic layers washed sequentially with saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride solution, dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by column chromatography to give the title compound as a colourless oil (42.9 g, 60 %).



$R_f$.035 ($SiO_2$; ethyl acetate); $\nu_{max}$ (neat) 3320, 2863, 1711, 1685 (C=O), 1276, 1105 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 4.73 (1H, br s, NH), 3.83 (2H, 2t, *J* 5.0, H1), 3.62 (2H, t, *J* 8.0, Ha), 3.39 (2H, t, *J* 8.0, Ha), 3.31 (2H, t, *J* 5.0, H2), 1.12-1.04 (21H, m, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 162.8 (C=O), 63.1 (C[1]$H_2$), 46. (C[2]$H_2$), 46.3 (C[a]$H_2$), 38.4 (C[a]$H_2$), 17.9 (C[TIPS]$H_3$), 11.9 (C[TIPS]H); HRMS (M+Na)$^+$ found 286.2062 $C_{14}H_{30}N_2O_3Si$ requires 286.4857, Δ ppm -4.8.

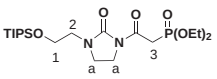
**1-(2-Bromo-acetyl)-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (15)** A round-bottom flask, equipped with a magnetic stirrer, containing **14** (13.76 g, 48 mmol) and THF (150 ml) at 0 °C was sequentially charged dropwise with bromoacetyl bromide (20 ml, 240 mmol) over 45 minutes followed by triethylamine (33 ml, 240 mmol) over 45 minutes. The reaction mixture was allowed to warm to room temperature and stirred for two hours. The reaction mixture was quenched by the addition of saturated aqueous sodium bicarbonate solution (150 ml) and stirred for one hour. The reaction mixture was extracted with ethyl

acetate (× 3), the combined organic layers washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography to give the title compound as a colourless oil (16.8 g, 86 %).



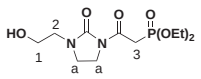

$R_f$ 0.44 ($SiO_2$; 2:8 ethyl acetate: 40:60 petrol); $\nu_{max}$ (neat) 2942, 2866, 1726 (C=O), 1683 (C=O), 1376, 1356, 1273, 1106, 917, 730 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 4.44 (2H, s, H3), 3.80-3.73 (4H, m, H1, Ha), 3.58-3.52 (2H, t, *J* 8.5, Ha), 3.34-3.29 (2H, t, *J* 5.0, H2), 1.23-0.64 (21H, s, TIPS); $\delta_C$ (100 MHz; $CDCl_3$) 166.0 (C=O), 154.0 (C=O), 61.8 (C[1]$H_2$), 46.4 (C[2]$H_2$), 42.7 (C[a]$H_2$), 40.0 (C[a]$H_2$), 28.3 (C[3]$H_2$), 17.8 (C[TIPS]$H_3$), 11.7 (C[TIPS]H); LCMS (APCI+) 407 ($M+H^+$); HRMS $(M+Na)^+$ found 429.11754 $C_{16}H_{31}N_2O_3SiBrNa$ requires 429.11795, Δ ppm +0.95.

**2-Oxo-2-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-1-yl]-ethyl-phosphonic acid diethyl ester (16)** A round-bottom flask, equipped with a magnetic stirrer, containing the **15** (16.0 g, 39 mmol) and triethyl phosphite (35 ml, 206 mmol) was refluxed at 155 °C for $3\frac{1}{2}$ hours. The unreacted triethyl phosphite was then removed *in vacuo* to give the crude product. The crude product was purified by flash column chromatography to give the title compound (17.5 g, 96 %) as a pale yellow solid.




$R_f$ 0.34 ($SiO_2$; ethyl acetate: $CH_2Cl_2$: MeOH 18:18:1); $\nu_{max}$ (neat) 2942, 2867, 1726 (C=O), 1677 (C=O), 1357, 1258, 1021, 882 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 4.19-4.09 (4H, m, $OC\underline{H_2}CH_3$), 3.88-3.76 (6H, m, H1, Ha, H3), 3.61-3.53 (2H, t, *J* 8.5, Ha), 3.41-3.35 (2H, t, *J* 5.5, H2), 1.33-1.26 (6H, t, *J* 7.2, $OCH_2C\underline{H_3}$), 1.12-0.99 (21H, m, TIPS); $\delta_C$ (100 MHz; $CDCl_3$) 165.1 (C=O), 154.3 (C=O), 62.4 ($CH_2$), 62.2 (C[1]$H_2$), 46.6 (C[2]$H_2$), 42.4 (C[a]$H_2$), 40.1 (C[a]$H_2$), 34.4 (C[3]$H_2$), 33.0 (C[3]$H_2$), 17.9 (C[TIPS]$H_3$), 16.3 (C[OEt]$H_3$), 16.4 (C[OEt]$H_3$), 11.8 (C[TIPS]H); LCMS (APCI+) 465 ($M+H^+$); HRMS $(M+H)^+$ found 465.2537 $C_{20}H_{42}N_2O_6SiP$ required 465.2550, Δ ppm −1.3; mp 30 °C (ethyl acetate: $CH_2Cl_2$: MeOH).

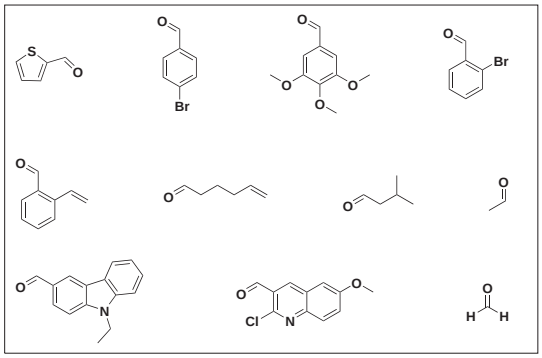
**2-Oxo-2-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-1-yl]-ethyl-phosphonic acid diethyl ester (1) 16** was cleaved using the standard cleavage conditions to yield a colourless oil (4.9 g, 93 %).




$R_f$ 0.12 ($SiO_2$; ethyl acetate: $CH_2Cl_2$: MeOH 18:18:4); $\nu_{max}$ (neat) 2946, 2874, 1726 (C=O), 1686 (C=O), 1355, 1251, 1016, 884 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 4.11 (1H, br s, OH), 4.06-3.95 (4H, m, $OC\underline{H_2}CH_3$), 3.74 (2H, d, *7.5*, H1), 3.72 (1H, s, H3), 3.68 (1H, s, H3′), 3.64-3.59 (2H, br s, Ha), 3.45 (2H, t, *8.0*, Ha), 3.28 (2H, t, *5.0*, H2), 1.20 (6H, t, *J* 7.0, $OCH_2C\underline{H_3}$); $\delta_C$ (100 MHz; $CDCl_3$) 164.7 (C=O), 154.5 (C=O), 62.5 (C[1]$H_2$), 59.73 (C[OEt]$H_2$), 46.4 (C[2]$H_2$), 41.6 (C[a]$H_2$), 40.0 (C[a]$H_2$), 34.0 (C[3]$H_2$), 33.0 (C[3]$H_2$), 16.2 (C[OEt]$H_3$), 16.1 (C[OEt]$H_3$); HRMS $(M+H)^+$ found 308.1135 $C_{11}H_{22}N_2O_6P$ required 308.1137, Δ ppm −0.2.

# 4 Horner Wadsworth Emmons Reaction

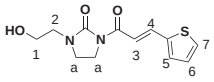
## 4.1 Building blocks used




### 4.1.1 General procedure on solid phase

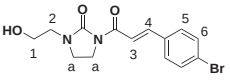
A test tube containing a suspension of the solid support immobilised phosphonate (**17**) (0.48 mmol/g, 1 equiv.), powered lithium bromide (2 equiv.) and dry DMF (10 mL/g beads) at room temperature was charged sequentially with DBU (2 equiv.) and the aldehyde (3 equiv.). The reaction was viciously agitated at room temperature for 48 hours. The beads were filtered and wsahed sequentially with DMF (× 3), $CH_2Cl_2$ (× 3), $CH_2Cl_2$:MeOH (1:1, × 3) and $CH_2Cl_2$ (× 3), air, dried under suction for 2 hours with occasional agitation, and then placed under high vacuum to give free flowing beads. A sample of the beads were cleaved using the standard cleavage conditions to give:

**1-(2-Hydroxy-ethyl)-3-(thiophen-2-yl-acryloyl)-imidazolidin-2-one (18)**




A white solid. $R_f$ 0.33 ($SiO_2$; 95:5 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3493 (OH), 1715 (C=O), 1640 (C=O) $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 8.02-7.95 (2H, 2d, *J* 5.5, H3, H4), 7.34 (3H, s, H5, H6, H7), 4.09 (2H, t, *J* 7.5, H1), 3.95 (2H, t, *J* 5.0, Ha), 3.65 (2H, t, *J* 7.5, H2), 3.43 (2H, t, *J* 5.0, Ha); $\delta_C$ (125 MHz; $CDCl_3$) 162.99 (C=O), 146.56 (C=O), 136.50 (C[4]H), 130.85 (CH), 128.37 (CH), 127.95 (CH), 117.14 (C[3]H), 60.95 (C[1]$H_2$), 46.81 (C[2]$H_2$), 42.35 (C[a]$H_2$), 40.15 (C[a]$H_2$); LCMS (APCI+) 267 ($M+H^+$): HRMS $(M+H)^+$ found 267.0809 $C_{12}H_{15}N_2O_3S$ requires 267.0803, Δ ppm +2.0; mp 154-156 °C ($CH_2Cl_2$: MeOH).

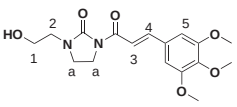
**1-[3-(4-Bromo-phenyl)-acryloyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (19)**




A white solid. $R_f$ 0.32 ($SiO_2$; 95:5 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3473 (OH), 1713 (C=O), 1660 (C=O), 1618 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.98 (1H, d, *J* 15.5, H4), 7.63 (1H, d, *J* 15.5, H3), 7.45-7.36 (4H, 2 × d, *J* 8.5, H5, H6), 3.91 (2H, t, *J* 8.0, H1), 3.78 (2H, t, *J* 5.0, Ha), 3.53 (2H, t, *J* 8.0, H2), 3.40 (2H, t, *J* 5.0, Ha), 1.87 (1H, br s,

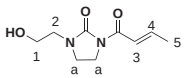
OH); $\delta_C$ (125 MHz; $CDCl_3$) 165.55 (C=O), 155.71 (C=O), 142.56 (C[4]H), 142.40 (C-C), 134.03 (C-Br), 131.99 (CH), 129.75 (CH), 129.44 (CH), 128.28 (CH), 124.27 (CH), 119.07 (C[3]H), 60.84 (C[1]$H_2$), 46.77 (C[2]$H_2$), 42.33 (C[a]$H_2$), 40.15 (C[a]$H_2$); LCMS (APCI+) 339 ($M+H^+$): HRMS $(M+Na)^+$ found 361.0174 $C_{14}H_{15}BrN_2O_3Na$ requires 361.0164, $\Delta$ ppm +2.7; mp 128-130 °C ($CH_2Cl_2$: MeOH).

### 1-(2-Hydroxy-ethyl)-3-[3-(3,4,5-trimethoxy-phenyl)-acryloyl]-imidazolidin-2-one (20)



A white solid. $R_f$ 0.33 ($SiO_2$; 95:5 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3453 (OH), 1704 (C=O), 1688 (C=O) $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.95 (1H, d, *J* 15.5, H4), 7.72 (1H, d, *J* 15.5, H3), 6.86 (2H, s, H5), 3.99 (2H, t, *J* 8.5, H1), 3.89 (3H, s, OMe) 3.87 (3H, s, OMe), 3.85 (3H, s, OMe), 3.63-3.58 (4H, m, H2, Ha), 3.48 (2H, t, *J* 5.0, Ha); $\delta_C$ (125 MHz; $CDCl_3$) 165.76 (C=O), 153.36 (C=O), 152.64 (C), 144.22 (C[4]H), 140.43 (CH), 130.65 (C), 117.71 (C[3]H), 107.49 (C[5]H), 105.62 (C[5]H), 60.92 (C[1]$H_2$), 56.22 (C[Me]$H_3$), 46.76 (C[2]$H_2$), 42.33 (C[a]$H_2$), 40.19 (C[a]$H_2$); LCMS (APCI+) 351 ($M+H^+$): HRMS $(M+H)^+$ found 351.1554 $C_{17}H_{23}N_2O_6$ requires 351.1556, $\Delta$ ppm −0.6; mp 190-192 °C ($CH_2Cl_2$: MeOH).

### 1-But-2-enoyl-3-(2-hydroxy-ethyl)-imidazolidin-2-one (21)

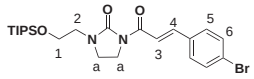


A yellow oil. $R_f$ 0.33 ($SiO_2$; 95:5 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3442 (OH), 1714 (C=O), 1662 (C=O), 1621 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.35 (1H, dq, *J* 15.0, 7.0, H4), 7.08 (1H, dq, *J* 15.0, 1.5, H3), 3.90 (2H, t, *J* 8.0, H1), 3.82 (2H, t, *J* 5.0, Ha), 3.56 (2H, t, *J* 8.0, H2), 3.44 (2H, t, *J* 5.0, Ha), 1.92 (3H, dd, *J* 7.0, 1.5, H5); $\delta_C$ (125 MHz; $CDCl_3$) 165.78 (C=O), 155.66 (C=O), 144.21 (C[4]H), 122.77 (C[3]H), 60.62 (C[1]$H_2$), 46.69 (C[2]$H_2$), 42.20 (C[a]$H_2$), 39.99 (C[a]$H_2$), 18.37 (C[5]$H_3$); LCMS (APCI+) 199 ($M+H^+$): HRMS $(M+H)^+$ found 199.1085 $C_9H_{15}N_2O_3$ required 199.1083, $\Delta$ ppm +1.0.

### 4.1.2 General procedure in solution phase

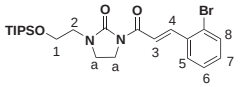
To a stirred solution of **16** (1.0 equiv.) and lithium bromide (1.2 equiv.) in dry MeCN under nitrogen was added DBU (1.2 equiv.) and the aldehyde (3.0 equiv.). The reaction was monitored by TLC and after 2.5 hours the solvent removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with sodium hydrogen carbonate solution (× 2), brine (× 2), dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield:

### 1-[3-(4-Bromo-phenyl)-acryloyl]-3-(2-triisopropyl-silanyloxy-ethyl)-imidazolidin-2-one (22)



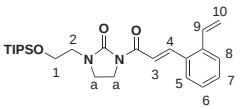
A white solid (210 mg, 81 %). $R_f$ 0.30 ($SiO_2$; 8:2 hexane: ethyl acetate); $\nu_{max}$ (neat) 2941, 2865, 1720 (C=O), 1644 (C=O), 1618, 1486, 1374, 1353, 1241, 1105 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 8.01 (1H, d, *J* 15.5, H4), 7.65 (1H, d, *J* 15.5, H3), 7.37 (4H, s, H5, H6), 3.80-3.90 (4H, m, H1, Ha), 3.54 (2H, t, *J* 8.0, H2), 3.36 (2H, t, *J* 5.0, Ha), 0.95 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 165.73 (C=O), 155.08 (C=O), 142.30 (C[4]H), 134.52 (C-C), 132.24 (CH), 130.05 (CH), 124.38 (C-Br), 119.07 (C[3]H), 62.41 (C[1]$H_2$), 46.90 (C[2]$H_2$), 43.11 (C[a]$H_2$), 40.41 (C[a]$H_2$), 18.12 ($CH_3$), 12.15 (CH); LCMS (APCI+) 495 ($M+H^+$): HRMS $(M+H)^+$ found 495.1689 $C_{23}H_{36}BrN_2O_3Si$ requires 495.1678, $\Delta$ ppm +2.1; mp 67-69 °C (hexane: ethyl acetate).

### 1-[3-(2-Bromo-phenyl)-acryloyl]-3-(2-triisopropyl-silanyloxy-ethyl)-imidazolidin-2-one (23)



A white solid (695 mg, 70 %); $R_f$ 0.34 ($SiO_2$; 10:3 hexane: ethyl acetate); $\nu_{max}$ (neat) 2942, 2866, 1719 (C=O), 1664 (C=O), 1611, 1567, 1465, 1436, 1381, 1364, 1265 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 8.17 (1H, d, *J* 15.5, H4), 8.05 (1H, d, *J* 15.5, H3), 7.76 (1H, dd, *J* 8.0, 1.5, H8), 7.60 (1H, d, *J* 8.0, H5), 7.31 (1H, apparent t, *J* 8.0, H6), 7.20 (1H, td, *J* 8.0, 1.5, H7), 3.99-3.95 (2H, m, Ha), 3.91 (2H, t, *J* 5.0, H1), 3.70-3.66 (2H, m, Ha), 3.46 (2H, t, *J* 5.0, H2), 1.06 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 165.34 (C=O), 154.85 (C=O), 141.91 (C[4]H), 135.22 (C-C), 133.26 (CH), 132.52 (C-Br), 130.87 (CH), 128.42 (CH), 127.58 (CH), 121.38 (C[3]H), 62.14 (C[1]$H_2$), 46.61 (C[2]$H_2$), 42.88 (C[a]$H_2$), 40.10 (C[a]$H_2$), 17.94 (C[TIPS]$H_3$), 11.84 (C[TIPS]H); LCMS (APCI+) 496 ($M+H^+$): HRMS $(M+H)^+$ found 495.1673 $C_{23}H_{35}N_2O_3SiBr$, required 495.1673, $\Delta$ ppm −0.1; mp 151-154 °C (hexane: ethyl acetate).

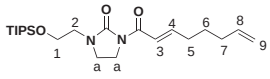
### 1-(2-Triisopropylsilanyloxy-ethyl)-3-[3-(2-vinyl-phenyl)-acryloyl]-imidazolidin-2-one (24)



A yellow oil (200 mg, 75 %); $R_f$ 0.28 ($SiO_2$; 10:3 hexane: ethyl acetate); $\nu_{max}$ (neat) 2942, 2865, 1720 (C=O), 1663 (C=O), 1614, 1374, 1354, 1268, 1241, 1107 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 8.14 (1H, d, *J* 15.5, H4), 7.98 (1H, d, *J* 15.5, H3), 7.67 (1H, dd, *J* 7.5, 1.0, ArH), 7.46 (1H, d, *J* 8.0, ArH), 7.31 (1H, td, *J* 8.0, 1.5, ArH), 7.25 (1H, td, *J* 7.5, 1.5, ArH), 7.11 (1H, dd, *J* 17.0, 11.0, H9), 5.62 (1H, dd, *J* 17.0, 1.5, H10), 5.39 (1H, dd, *J* 11.0, 1.0, H10′), 3.96-3.91 (2H, m, Ha), 3.88 (2H, t, *J* 5.0, H1), 3.67-3.62 (2H, m, Ha), 3.42 (2H, t, *J* 5.0, H2), 1.04 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 165.84 (C=O), 154.88 (C=O), 141.21 (C[4]H), 138.11 (C), 135.11 (CH), 134.39 (C), 129.72 (CH), 127.82 (CH), 127.37 (CH), 126.75 (C[9]H), 120.48 (C[3]H), 117.72 (C[10]$H_2$), 62.18 (C[1]$H_2$), 46.60 (C[2]$H_2$), 42.87 (C[a]$H_2$), 40.11 (C[a]$H_2$), 17.93 (C[TIPS]$H_3$), 11.83 (C[TIPS]H); LCMS (APCI+) 443

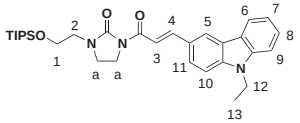
$(M+H^+)$: HRMS $(M+H)^+$ found 443.2726 $C_{25}H_{39}N_2O_3Si$, required 443.2724, Δ ppm -0.4.

### 1-Octa-2,7-dienoyl-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (25)



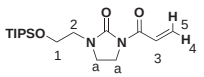

A colourless oil (136 mg, 67 %); $R_f$ 0.24 ($SiO_2$; 11:2 hexane: ethyl acetate); $\nu_{max}$ (neat) 2940, 2865, 1725 (C=O), 1671 (C=O), 1634, 1435, 1375, 1353, 1270, 1245, 1106 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.38 (1H, dt, *J* 15.5, 1.5, H3), 7.05 (1H, dt, *J* 15.5, 7.0, H4), 5.79 (1H, ddt, *J* 17.0, 10.0, 7.0, H8), 5.01 (1H, ddt, *J* 17.0, 2.0, 1.5, H9), 4.96 (1H, ddt, *J* 10.0, 2.0, 1.5, H9'), 3.90-3.86 (4H, m, H1, Ha), 3.62 (2H, dd, *J* 8.5, 7.5, Ha), 3.42 (2H, t, *J* 5.0, H2), 2.27 (2H, tdd, *J* 8.0, 7.0, 1.0, H5), 2.06 (2H, tdt, *J* 7.5, 7.0, 1.0, H7), 1.57 (2H, quintet, *J* 7.5, H6), 1.06 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 165.94 (C=O), 154.84 (C=O), 148.24 (C[4]H), 138.21 (C[8]H), 121.74 (C[3]H), 114.94 (C[9]H), 62.18 (C[1]$H_2$), 46.56 (C[2]$H_2$), 42.82 (C[a]$H_2$), 39.98 (C[a]$H_2$), 33.19 (C[7]$H_2$), 31.88 (C[5]$H_2$), 27.43 (C[6]$H_2$) 17.94 (C[TIPS]$H_3$), 11.84 (C[TIPS]H); LCMS (APCI+) 366 $(M+H^+)$: HRMS $(M+H)^+$ found 409.2881 $C_{22}H_{40}N_2O_3Si$, required 409.2881, Δ ppm +0.0.

### 1-[3-(9-Ethyl-9H-carbazol-3-yl)-acryloyl]-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (26)



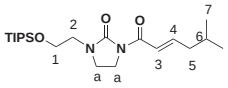

A yellow foam (138 mg, 24 %). $R_f$ 0.25 (hexane: ethyl acetate 3:1); $\nu_{max}$ (thin film) 2941 (s, CH), 2865 (s, CH), 1721 (s, C=O), 1660 (s, C=O) $cm^{-1}$; dH (400 MHz, $CDCl_3$) 8.34 (1H, s, ArH), 8.15 (1H, d, *J* 15.0, H3), 8.12 (1H, d, *J* 8.0, ArH), 8.03 (1H, d, *J* 15.0, H4), 7.76 (1H, d, *J* 8.0, ArH), 7.46 (1H, dd, *J* 8.0, 8.0, ArH), 7.37 (1H, d, *J* 8.0, ArH), 7.34 (1H, d, *J* 8.0, ArH), 7.25 (1H, dd, *J* 8.0, 8.0, ArH), 4.32 (2H, q, *J* 7.0, H12), 3.96 (2H, t, *J* 7.0, H1), 3.92 (2H, t, *J* 5.0, Ha), 3.64 (2H, t, *J* 7.0, Ha), 3.46 (2H, t, *J* 5.0, H2), 1.41 (3H, t, *J* 7.0, H13), 1.10-1.02 (21 H, m, (TIPS)); $\delta_C$ (100 MHz, $CDCl_3$) 166.4 (C=O), 155.2 (C=O), 145.3 (C[4]H), 141.2 (C-C), 140.4 (C-C), 126.5 (C-C), 126.3 (CH), 126.1 (CH), 123.3 (C-C), 123.0 (C-C), 121.3 (C[3]H), 120.7 (CH), 119.5 (CH), 115.2 (CH), 108.7 (CH), 108.6 (CH), 62.3 (C[1]$H_2$), 46.6 (C[2]$H_2$), 42.9 (C[a]$H_2$), 40.2 (C[a]$H_2$), 37.7 (C[12]$H_2$), 18.0 ($CH_3$), 13.8 (C[13]$H_3$), 11.8 (CH); HRMS $(ES^+)$ calculated for $C_{31}H_{43}N_3O_3Si$ $[M+H]^+$ 534.3146, found 534.3146.

### 1-Acryloyl-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (27)



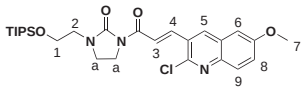

A viscous colourless oil (0.70 g, 98 %): $R_f$ 0.32 (hexane: ethyl acetate 4:1); $\nu_{max}$ (thin film) 2942 (s, CH), 2866 (s, CH), 1725 (s, C=O), 1672 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.62 (1H, dd, *J* 17.0, 10.0, H5), 6.47 (1H, dd, *J* 17.0, 2.0, H4), 5.77 (1H, dd, *J* 10.0, 2.0, H3), 3.91-3.86 (4H, m, C[1]$H_2$, Ha), 3.63 (2H, t, *J* 8.0, Ha), 3.42 (2H, t, *J* 5.0, H2), 1.14-1.01 (21H, m, (TIPS)); $\delta_C$ (100 MHz, $CDCl_3$) 165.6 (C=O), 154.6 (C=O), 129.2 (C[4,5]$H_2$), 128.5 (C[3]H), 62.1 (C[1]$H_2$), 46.5 (C[2]$H_2$), 42.8 (C[a]$H_2$), 39.9 (C[a]$H_2$), 17.9 ($CH_3$), 11.8 (CH); HRMS $(ES^+)$ calculated for $C_{17}H_{32}N_2O_3Si$ $[M+H]^+$ 341.2255, found 341.2257.

### 1-(5-Methyl-hex-2-enoyl)-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (28)




A colourless oil (3.30 g, 69 %): $R_f$ 0.41 (30-40 pet. ether:ethyl acetate 4:1); $\nu_{max}$ (thin film) 2943 (s, CH), 2867 (s, CH), 1726 (s, C=O), 1671 (s, C=O), 1634 (s, C=C) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.36 (1H, dt, *J* 15.0, 1.0, H4), 7.05 (1H, dt, *J* 15.0, 7.0, H3), 3.89-3.85 (4H, m, H1, Ha), 3.60 (2H, t, *J* 9.0, Ha), 3.41 (2H, t, *J* 5.0, H2), 2.14 (2H, app. dt, *J* 7.0, 1.0, H5), 1.77 (1H, septet, *J* 7.0, H6), 1.13-1.02 (21H, m, TIPS), 0.92 (6H, d, *J* 7.0, H7); $\delta_C$ (100 MHz, $CDCl_3$) 165.9 (C=O), 154.8 (C=O), 147.6 (C[4]H), 122.4 (C[3]H), 62.2 (C[1]$H_2$), 46.5 (C[2]$H_2$), 42.8 (C[a]$H_2$), 41.7 (C[5]$H_2$), 40.0 (C[a]$H_2$), 27.9 (C[6]H), 22.4 (C[7]$H_3$), 17.9 ($CH_3$), 11.8 (CH); HRMS $(ES^+)$ calculated for $C_{21}H_{40}N_2O_3Si$ $[M+H]^+$ 397.2881, found 397.2884.

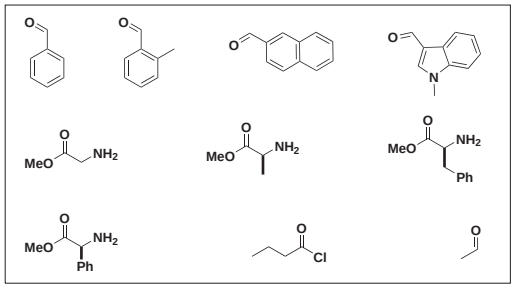
### 1-(3-(2-chloro-6-methoxyquinolin-3-yl)acryloyl)-3-(2-(triisopropylsilyloxy)ethyl)imidazolidin-2-one (29)




A white solid (940 mg, 81 %); $R_f$ 0.37 ($SiO_2$; 2:8 petrol: ethyl acetate); $\nu_{max}$ (neat) 2942, 2865, 1720 (C=O), 1666 (C=O), 1621, 1583, 1495, 1354, 1055, 729 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 8.39 (1H, s, H5), 8.21-8.20 (2H, m, H3, H4), 7.85 (1H, d, *J* 9.0, H9), 7.35 (1H, dd, *J* 9.0, 3.0, H8), 7.08 (1H, d, *J* 3.0, H6), 4.00-3.86 (7H, m, Ha, H1, H7), 3.66 (2H, t, *J* 8.5, Ha), 3.44 (2H, t, *J* 5.0, H2), 1.10 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 164.8 (C=O), 158.3 (C=O), 154.9 (C), 147.8 (C), 143.9 (C), 138.3 (C[4]H), 134.8 (CH), 129.6 (CH), 128.2 (C), 128.1 (C), 124.2 (CH), 122.5 (C[3]H), 105.2 (CH), 62.1 (C[1]$H_2$), 55.6 (C[OMe]), 46.6 (C[2]$H_2$), 42.9 (C[a]$H_2$), 40.1 (C[a]$H_2$), 17.9 (C[TIPS]$H_3$), 11.8 (C[TIPS]H); HRMS $(M+H)^+$ found 532.2395 $C_{27}H_{39}N_3O_4SiCl$, required 532.2393, Δ ppm +0.3; mp 156 °C (petrol: ethyl acetate).

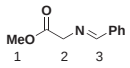
# 5 Branching pathway 1 1,3-Dipolar cycloadditions

## 5.1 Building blocks used



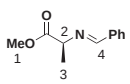
## 5.2 Synthesis of building blocks for the 1,3-dipolar cycloaddition

**(Benzylidene-amino)-acetic acid methyl ester (30)** A suspension of methyl glycinate hydrochloride (3.2 g, 25.3 mmol), benzaldehyde (2.1 mL, 21.1 mmol) and $MgSO_4$ (3.0 g, 25.3 mmol) in $CH_2Cl_2$ (30 mL) was stirred at 0 °C. TEA (3.5 mL, 25.3 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature and stirred overnight. $Et_2O$ (50 mL) was then added and the solution was filtered. The filtrate was washed with water (× 2), brine (× 2), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a colourless oil (3.54 g, 95 %).



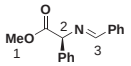
$\nu_{max}$ (thin film) 2953 (s, CH), 2851 (s, CH), 1740 (s, C=O), 1646 (s, C=N) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.28 (1H, s, H3), 7.77 (2H, dd, *J* 7.0, 2.0, ArH), 7.44-7.38 (3H, m, ArH), 4.41 (2H, s, H2), 3.76 (3H, s, H1); $\delta_C$ (125 MHz, $CDCl_3$) 170.5 (C=O), 165.5 (C[3]H), 135.6 (C-C), 131.3 (CH), 128.6 (CH), 128.5 (CH), 62.0 (C[2]$H_2$), 52.1 (C[1]$H_3$). Data consistant with literature values.[2]

**2-(Benzylidene-amino)-propionic acid methyl ester (31)** A suspension of L-alanine methyl ester hydrochloride (3.53 g, 25.3 mmol), benzaldehyde (2.1 mL, 21.1 mmol) and $MgSO_4$ (3.0 g, 25.3 mmol) in $CH_2Cl_2$ (50 mL) was stirred at 0 °C. TEA (3.5 mL, 25.3 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature and stirred overnight. $Et_2O$ (50 mL) was then added and the solution was filtered. The filtrate was washed with water (× 2) and brine (× 2), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a colourless oil (3.52 g, 87 %).



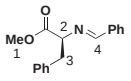
$\nu_{max}$ (thin film ) 2987 (s, CH), 2872 (s, CH), 1737 (s, C=O), 1642 (s, C=N) $cm^{-1}$;$[\alpha]_D^{25}$ −63.2 (c 0.97, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 8.31 (1H, s, H4), 7.78 (2H, d, *J* 7.0, ArH), 7.44-7.38 (3H, m, ArH), 4.16 (1H, q, *J* 7.0, H2), 3.74 (3H, s, H1), 1.53 (3H, d, *J* 7.0, H3); $\delta_C$ (100 MHz, $CDCl_33$) 173.0 (C=O), 163.0 (C[4]H) 135.7 (C-C), 131.1 (CH), 128.6 (CH), 128.5 (CH), 68.0 (C[2]H), 52.2 (C[1]$H_3$), 19.4 (C[3]$H_3$); m/z (APCI+) 192 (100 %, M+H+). Data in agreement with literature values. [2]

**(Benzylidene-amino)-phenyl-acetic acid methyl ester (32)** A suspension of (*S*)-(+)-2-phenylglycine methyl ester hydrochloride (5.10 g, 25.3 mmol), benzaldehyde (2.1 mL, 21.1 mmol) and $MgSO_4$ (3.0 g, 25.3 mmol) in $CH_2Cl_2$ (50 mL) was stirred at 0 °C. TEA (3.5 mL, 25.3 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature and stirred overnight. $Et_2O$ (50 mL) was then added and the solution was filtered. The filtrate was washed with water (× 2) and brine (× 2), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a white solid (5.08 g, 95 %).



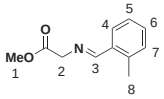
$\nu_{max}$ (thin film) 3029 (s, CH), 2952 (s, CH), 1738 (s, C=O), 1641 (s, C=N) $cm^{-1}$; $[\alpha]_D^{25}$ −41.6 (c 0.79, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 8.35 (1H, s, H3), 7.82 (2H, d, *J* 7.0, ArH), 7.51 (2H, d, *J* 7.0, ArH), 7.43-7.31 (6H, m, ArH), 5.21 (1H, s, H2), 3.75 (3H, s, H1); $\delta_C$ (100 MHz, $CDCl_3$) 171.5 (C=O), 163.8 (C[3]H) 138.1 (C-C), 135.7 (C-C), 131.2 (CH), 128.7 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 127.8 (CH), 76.5 (C[2]H), 52.5 (C[1]$H_3$); m/z (APCI+) 254 (92 %, M+H+); mp 48 °C. Data in agreement with literature values. [2]

**2-(Benzylidene-amino)-3-phenyl-propionic acid methyl ester (33)** A suspension of L-phenylalanine methyl ester hydrochloride (1.88 g, 8.72 mmol), benzaldehyde (0.74 mL, 7.26 mmol) and $MgSO_4$ (1.05 g, 8.72 mmol) in $CH_2Cl_2$ (20 mL) was stirred at 0 °C. TEA (1.22 mL, 8.72 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature and stirred for two days. $Et_2O$ (20 mL) was then added and the solution was filtered. The filtrate was washed with water (× 2) and brine (× 2), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a colourless oil (2.07 g, 89 %).



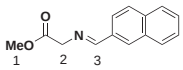
$R_f$ 0.37 (hexane: ethyl acetate 3:1); $\nu_{max}$ (thin film) 2952 (s, CH), 2849 (s, CH), 1736 (s, C=O), 1640 (s, C=N) $cm^{-1}$; $[\alpha]_D^{25}$ −206.7 (c 0.92, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.93 (1H, s, H4), 7.69 (2H, dd, *J* 6.0, 2.0, ArH), 7.45-7.36 (3H, m, ArH), 7.26-7.15 (5H, m, ArH), 4.18 (1H, dd, *J* 9.0, 5.0, H2), 3.75 (3H, s, H1), 3.38 (1H, dd, *J* 14.0, 5.0, H3), 3.15 (1H, dd, *J* 14.0, 9.0, H3′); $\delta_C$ (100 MHz, $CDCl_3$) 172.1 (C=O), 163.8 (C[4]H) 137.4 (C-C), 135.6 (C-C), 131.1 (CH), 129.7 (CH), 128.5 (CH), 128.5 (CH), 128.3 (CH), 126.6 (CH), 75.0 (C[2]H), 52.2 (C[1]$H_3$), 39.8 (C[3]$H_2$); m/z (APCI+) 268 (100 %, M+$H^+$). [2]

**[(2-Methyl-benzylidene)-amino]-acetic acid methyl ester (34)** A suspension of glycine methyl ester hydrochloride (2.61 g, 20.8 mmol), ortho-tolualdehyde (2.0 mL, 17.3 mmol) and $MgSO_4$ (2.50 g, 20.8 mmol) in $CH_2Cl_2$ (50 mL) was stirred at 0 °C. TEA (2.9 mL, 20.8 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature and stirred overnight. $Et_2O$ (100 mL) was then added and the solution was filtered. The filtrate was washed with water (× 2) and brine (× 2), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a crystalline solid (2.80 g, 75 %).



$\nu_{max}$ (thin film) 2953 (s, CH), 1737 (s, C=O), 1639 (s, C=N) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.57 (1H, s, H3), 7.90 (1H, d, *J* 7.0, ArH), 7.29 (1H, dd, *J* 7.0, 7.0, ArH), 7.21 (1H, dd, *J* 7.0, 7.0, ArH), 7.15 (1H, d, *J* 7.0, ArH), 4.41 (2H, s, H2), 3.75 (3H, s, H1), 2.49 (3H, s, H8); $\delta_C$ (100 MHz, $CDCl_3$) 170.6 (C=O), 164.0 (C[3]H) 138.0 (C-C), 133.6 (C-C), 130.8 (CH), 127.8 (CH), 126.2 (CH), 62.4 (C[2]$H_2$), 52.1 (C[1]$H_3$), 19.2 (C[8]$H_3$); m/z ($APCI^+$) 192 (100 %, M+H+); mp 45 °C.

**[(Naphthalen-2-ylmethylene)-amino]-acetic acid methyl ester (35)** A suspension of glycine methyl ester hydrochloride (1.0 g, 7.7 mmol), 2-naphtaldehyde (1.0 g, 6.4 mmol) and $MgSO_4$ (0.93 g, 7.7 mmol) in $CH_2Cl_2$ (25 mL) was stirred at 0 °C. TEA (1.1 mL, 7.7 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature and stirred overnight. $Et_2O$ (50 mL) was then added and the solution was filtered. The filtrate was washed with water (× 2) and brine (× 2), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as an off-white solid (1.33 g, 5.9 mmol, 91 %).

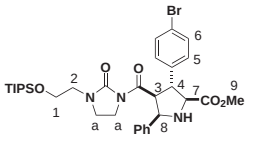


$\nu_{max}$ (thin film) 2953 (s, CH), 2881 (s, CH), 1723 (s, C=O), 1692 (s, C=N) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.45 (1H, s, H3), 8.09 (1H, s, ArH), 8.04 (1H, dd, *J* 9.0, 2.0, ArH), 7.92-7.83 (3H, m, ArH), 7.57-7.48 (2H, m, ArH), 4.48 (2H, s, H2), 3.80 (3H, s, H1); $\delta_C$ (100 MHz, $CDCl_3$) 170.6 (C=O), 165.5 (C[3]H) 135.0 (C-C), 133.3 (C-C), 133.0 (C-C), 130.6 (CH), 128.7 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 126.5 (CH), 123.9 (CH), 62.1 (C[2]$H_2$), 52.2 (C[1]$H_3$); m/z ($APCI^+$) 228 (90 %, M+H+) mp 84 °C.

## 5.3 General procedure for enantioselective 1,3-dipolar cycloaddition reaction

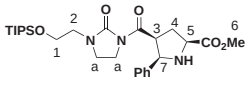
AgOAc (0.1 equiv.) and (*R*)-QUINAP (0.12 equiv.) were dissolved in THF at ambient temperature, a spatula of powdered molecular sieves (4 Å) was added. The reaction mixture was stirred for 1h. The imine (**30**-**35**) (1.5 equiv.) was added to the reaction mixture at -40 C, followed by the TIPS protected alkene (1 equiv.) and $iPr_2Net$ (0.3 equiv.). The reaction mixture was stirred at -78 °C for 6 hours and left at -25 °C overnight, after which the reaction mixture was concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:ethyl acetate 2:1).

**(2*S*, 3*R*, 4*S*, 5*R*)-3-(4-Bromo-phenyl)-4-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (36)**



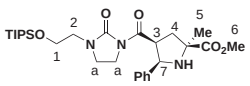
A colourless white foam (60 % ee); $[\alpha]_D^{25}$ −20.8 (c 1.22, $CHCl_3$). Data in agreement with racemic compound. EE calculated using chiral shift reagents, see general methods.

**(2*S*, 3*R*, 4*S*, 5*R*)-4-[2-Oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (37)**



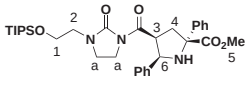
A colourless oil (65 % ee). $R_f$ 0.17 (hexane: ethyl acetate 1:1); $\nu_{max}$ (thin film /cm-1) 2943 (s, CH), 2866 (s, CH), 1722 (s, C=O), 1673 (s, C=O) $cm^{-1}$; $[\alpha]_D^{25}$ −22.6 (c 0.44, $CHCl_3$); $\delta_H$ (400 MHz, $C_6D_6$) 7.58 (2H, d, *J* 7.0, ArH), 7.16 (2H, dd, *J* 7.0, 7.0, ArH), 7.08 (1H, t, *J* 7.0 Hz, ArH), 5.07 (1H, ddd, *J* 8.0, 8.0, 7.0, H3), 4.67 (1H, d, *J* 8.0, H7), 3.83 (1H, dd, *J* 8.0, 8.0, H5), 3.65-3.54 (2H, m, H1), 3.49 (3H, s, H6), 3.23-3.13 (2H, m, Ha), 3.06-3.00 (1H, m, Ha), 2.97-2.84 (3H, m, H2, NH), 2.67-2.60 (1H, m, Ha), 2.48-2.41 (1H, m, H4), 2.27-2.20 (1H, m, H4), 1.13-1.03 (TIPS); $\delta_C$ (100 MHz, $C_6D_6$) 173.6 (C=O), 172.2 (C=O), 154.2 (C=O), 140.7 (C-C), 127.7 (CH), 127.4 (CH), 126.9 (CH), 66.2 (CH), 62.0 (C[1]$H_2$), 60.3 (CH), 51.3 (C[6]$H_3$), 47.9 (CH), 46.2 (C[2]$H_2$), 41.8 (C[a]$H_2$), 39.6 (C[a]$H_2$), 33.1 (C[4]$H_2$), 17.9 ($CH_3$), 11.9 (CH); HRMS ($ES^+$) calculated for $C_{27}H_{43}N_3O_5Si$ $[M+H]^+$ 518.3045, found 518.3043. EE calculated using chiral shift reagents, see general methods.

**(2*S*, 3*R*, 4*S*, 5*R*)-2-Methyl-4-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (38)**



A colourless oil (63 % ee). $R_f$ 0.31 (hexane:ethyl acetate 1:1); $\nu_{max}$ (thin film) 2943 (s, CH), 2866 (s, CH), 1723 (s, C=O), 1672 (s, C=O) $cm^{-1}$; $[\alpha]_D^{25}$ −23.3 (c 0.28, $CHCl_3$); $\delta_H$ (400 MHz, $C_6D_6$) 7.60 (2H, d, *J* 7.0, ArH), 7.16 (2H, dd, *J* 7.0, 7.0, ArH), 7.08 (1H, t, *J* 7.0, ArH), 5.22 (1H, ddd, *J* 8.0, 8.0, 6.0, H3), 4.92 (1H, d, *J* 8.0, H7), 3.64-3.52 (5H, m, H6, H1), 3.34-3.13 (4H, m, H2, Ha, NH), 3.04-2.98 (1H, m, Ha), 2.89 (1H, dt, *J* 10.0, 5.0, Ha), 2.62 (1H, dt, *J* 10.0, 5.0, Ha), 2.42 (1H, dt, *J* 10.0, 8.0, H4), 1.99 (1H, dd, *J* 13.0, 12.0, H4), 1.52 (3H, s, H5), 1.12-1.04 (21H, m, (TIPS); $\delta_C$ (100 MHz, $C_6D_6$) 176.4 (C=O), 172.3 (C=O), 154.1 (C=O), 140.8 (C-C), 127.7 (CH), 127.5 (CH), 126.9 (CH), 66.0 (C), 65.4 (CH), 62.0 (C[1]$H_2$), 51.6 (C[6]$H_3$), 48.8 (CH), 46.1 (C[2]$H_2$), 41.8 (C[a]$H_2$), 40.2 (C[a]$H_2$), 39.6 (C[4]$H_2$), 26.8 (C[5]$H_3$), 17.9 ($CH_3$), 11.9 (CH); HRMS ($ES^+$) calculated for $C_{28}H_{45}N_3O_5Si$ $[M+H]^+$ 532.3201, found 532.3201. EE calculated using chiral shift reagents, see general methods.

**(2*S*, 3*R*, 4*S*, 5*R*)-4-[2-Oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-2,5-diphenyl-pyrrolidine-2-carboxylic acid methyl ester (39)**

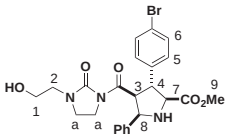


A colourless oil (60 % ee). $R_f$ 0.17 (hexane:ethyl acetate 3:1); $\nu_{max}$ (thin film) 2943 (s, CH), 2866 (s, CH), 1725 (s, C=O), 1670 (s, C=O) $cm^{-1}$; $[\alpha]_D^{25}$ −16.3 (c 0.23, $CHCl_3$); $\delta_H$ (400 MHz, $C_6D_6$) 8.01 (2H, d, *J* 7.0, ArH), 7.57 (2H, d, *J* 7.0, ArH), 7.30 (2H, dd, *J* 7.0, 7.0, ArH), 7.21-7.15 (3H, m, ArH), 7.10 (1H, t, *J* 7.0, ArH), 5.15 (1H, ddd, *J* 8.0, 8.0, 5.0, H3), 4.77 (1H, d, *J* 8.0, H6), 3.96 (1H, bs, NH), 3.68 (1H, dd, *J* 13.0, 5.0, H4), 3.60-3.48 (2H, m, H1), 3.45 (3H, s, H5), 3.29-3.19 (1H, m, Ha), 3.14-3.07 (1H, m, Ha), 2.99-2.92 (2H, m, H2), 2.68-2.58 (2H, m, Ha), 2.42 (1H, dt, *J* 9.0, 7.0, H4), 1.11-1.04 (21H, m, ((TIPS); $\delta_C$ (100 MHz, $C_6D_6$) 174.6 (C=O), 172.7 (C=O), 153.9 (C=O), 144.3 (C-C), 140.2 (C-C), 128.2 (CH), 127.6 (CH), 127.5 (CH) 127.1 (CH), 127.0 (CH), 126.8 (CH), 72.5 (C), 65.7 (CH), 62.0 (C[1]$H_2$), 52.1 (C[5]$H_3$), 48.9 (CH), 46.1 (C[2]$H_2$), 41.7 (C[a]$H_2$), 41.7 (C[a]$H_2$), 39.5 (C[4]$H_2$), 17.9 ($CH_3$), 11.9 (CH); HRMS ($ES^+$) calculated for $C_{33}H_{47}N_3O_5Si$ $[M+H]^+$ 594.3358, found 594.3358. EE calculated using chiral shift reagents, see general methods.

### 5.3.1 Racemic solid phase synthesis

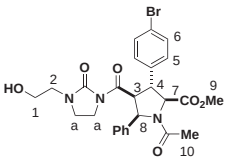
A suspension of the solid supported alkene (210 mg, 0.3 mmol/g), building block (**30-35**) (86 mg, 0.48 mmol) and silver acetate (80 mg, 0.48 mmol) in THF (3 mL), with a spatula of powdered molecular sieves was shaken at ambient temperature. DBU (0.07 mL, 0.48 mmol) was added, after which the reaction was left shaking overnight. The reaction mixture was diluted with $Et_2O$ and sat. aq. $NaHCO_3$ was added. The solution was then drained under positive nitrogen pressure and washed/drained with $CH_2Cl_2$ (× 3), $CH_2Cl_2$:methanol 1:1 (× 3) and THF (× 3). The beads were air-dried under suction for 2 hours and then placed under high vacuum for four days to give solid suported 1,3-dipolar cycloaddition product. 200 mg of resin was cleaved using the general procedure for deprotection of alcohols. The crude product was purified by filtration through a plug of silica with ethyl acetate to give:

**(2*S**, 3*R**, 4*S**, 5*R**)-3-(4-Bromo-phenyl)-4-[3-(2-hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (40)**



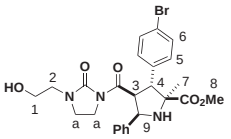
A white solid. $R_f$ 0.22 (ethyl acetate); $\nu_{max}$ (thin film) 3443 (b, OH), 2952 (s, CH), 1719 (s, C=O), 1670 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.42 (2H, d, *J* 7.0, ArH), 7.33 (2H, d, *J* 7.0, ArH), 7.29-7.19 (5H, m, ArH), 4.94 (1H, d, *J* 9.0, H8), 4.85 (1H, dd, *J* 9.0, 9.0, H3), 4.09 (1H, dd, *J* 9.0, 9.0, H4), 3.97 (1H, d, *J* 9.0, H7), 3.70-3.65 (5H, m, H1, H9), 3.45-3.38 (1H, m, Ha), 3.26-3.21 (2H, m, H2), 3.20-3.14 (1H, m, Ha), 2.94-2.87 (2H, m, Ha), 2.45 (1H, bs, NH); $\delta_C$ (125 MHz, $CDCl_3$) 172.7 (C=O), 170.6 (C=O), 154.8 (C=O), 139.8 (C-C), 139.3 (C-C), 131.7 (CH), 129.7 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 120.8 (C-Br), 67.2 (CH), 65.0 (CH), 60.6 (C[1]$H_2$), 57.9 (CH), 52.2 (C[9]$H_3$), 51.3 (CH), 46.5 (C[2]$H_2$), 42.0 (C[a]$H_2$), 39.7 (C[a]$H_2$); HRMS ($ES^+$) calculated for $C_{24}H_{26}BrN_3O_5$ $[M+H]^+$ 516.1129, found 516.1133; mp 65 °C (Ethyl acetate).

**(2*S**, 3*R**, 4*S**, 5*R**)-1-Acetyl-3-(4-bromo-phenyl)-4-[3-(2-hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (41)**



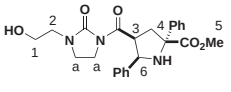
A white solid. $R_f$ 0.13 (ethyl acetate); IR (thin film) 3442 (b, OH), 2953 (s, CH), 1720 (s, C=O), 1678 (s, C=O), 1647 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.58 (2H, d, *J* 8.0, ArH), 7.42 (2H, d, *J* 8.0, ArH), 7.35 (2H, dd, *J* 8.0, 8.0, ArH), 7.28 (1H, t, *J* 8.0, ArH), 7.18 (2H, d, *J* 8.0, ArH), 5.64 (1H, d, *J* 9.0, H8), 4.82 (1H, dd, *J* 11.0, 9.0, H3), 4.46 (1H, d, *J* 11.0, H7), 4.18 (1H, dd, *J* 11.0, 11.0, H4), 3.87 (2H, t, *J* 5.0, H1), 3.68 (3H, s, H9), 3.57-3.40 (5H, m, H2, Ha), 3.20-3.13 (1H, m, Ha), 1.84 (3H, s, H10); $\delta_C$ (125 MHz, $CDCl_3$) 172.0 (C=O), 170.6 (C=O), 166.5 (C=O), 155.0 (C=O), 138.7 (C-C), 136.0 (C-C), 131.9 (CH), 129.9 (CH), 128.7 (CH), 128.4 (CH), 126.9 (CH), 121.6 (C-Br), 65.5 (CH), 63.4 (CH), 60.6 (C[1]$H_2$), 56.4 (CH), 52.3 (C[9]$H_3$), 46.5 (CH), 46.4 (C[2]$H_2$), 42.1 (C[a]$H_2$), 39.6 (C[a]$H_2$), 22.2 (C[10]H3); HRMS ($ES^+$) calculated for $C_{26}H_{28}BrN_3O_6$ $[M+H]^+$ 558.1234, found 558.1229; mp 224 °C (Ethyl acetate)

**(2*S**, 3*R**, 4*S**, 5*R**)-3-(4-Bromo-phenyl)-4-[3-(2-hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-2-methyl-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (42)**



A viscous oil. $\nu_{max}$ (thin film) 3337 (b, OH), 2951 (s, CH), 1720 (s, C=O), 1675 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.40 (2H, d, *J* 8.0, ArH), 7.34 (2H, d, *J* 8.0, ArH), 7.28-7.20 (3H, m, ArH), 7.15 (2H, d, *J* 8.0, ArH), 5.16 (1H, app. t, *J* 11.0, H3), 4.98 (1H, d, *J* 11.0, H9), 4.15 (1H, d, *J* 11.0, H4), 4.05 (1H, bs, NH), 3.75 (3H, s, H8), 3.71 (2H, t, *J* 5.0, H1), 3.75-3.68 (1H, m, Ha), 3.40 (1H, m, Ha), 3.29 (2H, t, *J* 5.0, H), 3.20-3.14 (1H, m, Ha), 2.95-2.88 (1H, m, Ha), 2.82-2.75 (1H, m, Ha), 1.27 (3H, s, H7); $\delta_C$ (100 MHz, $CDCl_3$) 174.9 (C=O), 170.5 (C=O), 155.0 (C=O), 140.0 (C-C), 136.7 (C-C), 131.3 (CH), 130.5 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 121.1 (C-Br), 68.7 (C), 62.5 (CH), 60.5 (C[1]$H_2$), 54.5 (CH), 54.2 (CH), 52.5 (C[8]$H_3$), 46.5 (C[2]$H_2$), 42.0 (C[a]$H_2$), 39.7 (C[a]$H_2$), 19.5 (C[7]$H_3$); HRMS ($ES^+$) calculated for $C_{25}H_{28}N_3O_5$ $[M+H]^+$ 530.1285, found 530.1286.

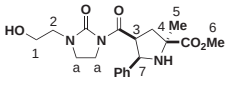
**(2*R*, 4*S*, 5*R*)-4-[3-(2-Hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-2,5-diphenyl-pyrrolidine-2-carboxylic acid methyl ester (43)**



A viscous oil. $\nu_{max}$ (thin film) 3443 (b, OH), 2923 (s, CH), 1723 (s, C=O), 1670 (s, C=O) $cm^{-1}$; $[\alpha]_D^{25}$ −24.6 (c 0.18, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.71 (2H, d, *J* 8.0, ArH),

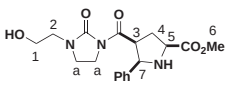
7.37-7.22 (8H, m, ArH), 4.76 (1H, app. q, $J$ 8.0, CH), 4.64 (1H, d, $J$ 8.0, CH), 3.77 (3H, s, H5), 3.65 (2H, t, $J$ 5.0, $CH_2$), 3.56-3.48 (1H, m, $CH_2$), 3.27 (1H, dd, $J$ 13.0, 5.0, $CH_2$), 3.18 (2H, t, $J$ 5.0, $CH_2$), 3.21-3.16 (1H, m, $CH_2$), 3.14-3.03 (1H, m, $CH_2$), 2.92-2.86 (2H, m, $CH_2$), 2.64 (1H, dd, $J$ 13.0, 7.0, $CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 174.7 (C=O), 172.8 (C=O), 154.9 (C=O), 142.5 (C-C), 139.0 (C-C), 128.4 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 126.5 (CH), 72.2 (C), 65.3 (C[1]$H_2$), 60.7 (CH), 52.9 (C[5]$H_3$), 48.8 (CH), 46.7 (C[2]$H_2$), 42.0 (C[a]$H_2$), 40.4 (C[a]$H_2$), 39.9 (C[4]$H_2$); HRMS ($ES^+$) calculated for $C_{24}H_{27}N_3O_5$ $[M+H]^+$ 438.2023, found 438.2023.

### (2*R**, 4*S**, 5*R**)-4-[3-(2-Hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-2-methyl-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (44)



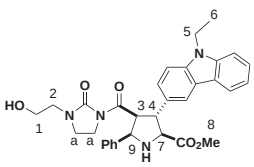
A viscous oil. $\nu_{max}$ (thin film) 3354 (b, OH), 2924 (s, CH), 2854 (s,CH), 1721 (s, C=O), 1668 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.29-7.20 (5H, m, ArH), 4.94-4.86 (2H, CH), 3.86 (3H, s, H6), 3.66 (2H, t, $J$ 5.0, H1), 3.51-3.46 (1H, m, Ha), 3.20 (2H, t, $J$ 5.0, H2), 3.21-3.16 (1H, m, Ha), 3.11-3.05 (1H, m, Ha), 2.92-2.83 (2H, m, Ha, H4), 2.09 (1H, dd, $J$ 13.0, 7.0, H4 $'$), 1.23 (3H, s, H5); $\delta_C$ (100 MHz, $CDCl_3$) 176.3 (C=O), 172.6 (C=O), 154.8 (C=O), 138.9 (C-C), 127.9 (CH), 127.6 (CH), 127.3 (CH), 66.5 (C), 65.4 (CH), 60.6 (C[1]$H_2$), 52.7 (C[6]$H_3$), 48.5 (CH), 46.7 (C[2]$H_2$), 42.0 (C[a]$H_2$), 40.1 (C[a]$H_2$), 39.8 (C[4]$H_2$), 26.4 (C[5]$H_3$); HRMS (ES+) calculated for $C_{19}H_{25}N_3O_5$ $[M+H]^+$ 376.1867, found 376.1865.

### (2*S**, 4*S**, 5*R**)-4-[3-(2-Hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (45)



A viscous oil. $\nu_{max}$ (thin film) 3405 (b, OH), 2952 (s, CH), 1723 (s, C=O), 1668 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.29-7.18 (5H, m, ArH), 4.82 (1H, dt, $J$ 8.0, 8.0, H3), 4.61 (1H, d, $J$ 8.0, H7), 3.95 (1H, t, $J$ 8.0, H5), 3.81 (3H, s, H6), 3.64 (2H, t, $J$ 5.0, H1), 3.52-3.45 (1H, m, Ha), 3.21 (2H, t, $J$ 5.0, H2), 3.21-3.16 (1H, m, Ha), 3.07-3.01 (1H, m, Ha), 2.92-2.85 (1H, m, Ha), 2.71 (1H, bs, NH), 2.59-2.53 (1H, m, H4), 2.40-2.33 (1H, m, H4); $\delta_C$ (100 MHz, $CDCl_3$) 173.8 (C=O), 172.7 (C=O), 154.9 (C=O), 138.9 (C-C), 127.8 (CH), 127.5 (CH), 127.2 (CH), 66.3 (CH), 60.5 (C[1]$H_2$), 60.1 (CH), 52.3 (C[6]$H_3$), 47.8 (CH), 46.6 (C[2]$H_2$), 41.9 (C[a]$H_2$), 39.8 (C[a]$H_2$), 33.1 (C[4]$H_2$); HRMS ($ES^+$) calculated for $C_{18}H_{23}N_3O_5$ $[M+H]^+$ 361.1638, found 361.1636.

### (2*S**, 3*R**, 4*S**, 5*R**)-3-(9-Ethyl-9H-carbazol-3-yl)-4-[3-(2-hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (46)

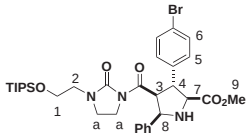


A colourless oil. $R_f$ 0.17 (ethyl acetate); $\nu_{max}$ (thin film) 3479 (b, OH), 2926 (s, CH), 1722 (s, C=O), 1673 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.08 (1H, d, $J$ 8.0, ArH), 8.06 (1H, d, $J$ 2.0, ArH), 7.48-7.18 (10H, m, ArH), 5.07 (1H, d, $J$ 9.0, H9), 5.00 (1H, dd, $J$ 9.0, 9.0, H3), 4.37-4.29 (3H, m, H4, H5), 4.15 (1H, d, $J$ 9.0, H7), 3.70 (2H, t, $J$ 5.0, H1), 3.65 (3H, s, H8), 3.46-3.40 (1H, m, Ha), 3.30-3.20 (2H, m, Ha), 3.16-3.11 (1H, m, Ha), 2.98-2.88 (2H, m, H2), 1.62 (1H, bs, NH), 1.41 (3H, t, $J$ 7.0, H6), 0.87 (1H, bs, OH); $\delta_C$ (100 MHz, $CDCl_3$) 173.3 (C=O), 171.1 (C=O), 155.0 (C=O), 140.2 (C-C), 140.1 (C-C), 139.1 (C-C), 130.4 (C-C), 127.9 (CH), 127.8 (CH), 127.7 (CH), 125.6 (CH), 123.0 (C-C), 122.7 (C-C), 120.5 (CH), 119.8 (CH), 118.7 (CH), 108.6 (CH), 108.3 (CH), 68.1 (CH), 65.2 (CH), 60.8 (C[1]$H_2$), 58.7 (CH), 52.5 (CH), 52.1 (C[8]$H_3$), 46.7 (C[5]$H_2$), 42.1 (C[2]$H_2$), 39.8 (C[a]$H_2$), 37.5 (C[a]$H_2$), 13.9 (C[6]$H_3$); HRMS ($ES^+$) calculated for $C_{32}H_{34}N_4O_5$ $[M+H]^+$ 555.2602, found 555.2603.

### 5.3.2 Racemic solution phase synthesis

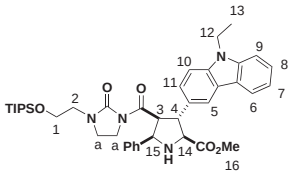
A solution of alkene (**22**-**29**) (1 equiv.), imine (**30**-**35**) (2 equiv.), and AgOAc (2 equiv.) in THF with a spatula of powdered molecular sieves was stirred at ambient temperature. DBU (2 equiv.) was added, after which the reaction was left to stir for 3 hours. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane : ethyl acetate 2:1) to yield:

### (2*S**, 3*R**, 4*S**, 5*R**)-3-(4-Bromo-phenyl)-4-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (36)



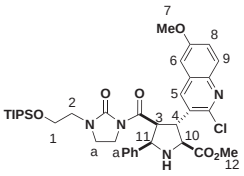
$R_f$ 0.14 (hexane: ethyl acetate: TEA 80:20:2); $\nu_{max}$ (thin film) 2944 (s, CH), 2866 (s, CH), 1725 (s, C=O), 1675 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $C_6D_6$) 7.70 (2H, d, $J$ 7.0, H6), 7.30 (2H, d, $J$ 7.0, H5), 7.28-7.21 (3H, m, ArH), 7.13 (2H, dd, $J$ 7.0, 7.0, ArH), 5.25 (1H, d, $J$ 9.0, H8), 5.20 (1H, dd, $J$ 9.0, 9.0, H3), 4.59 (1H, dd, $J$ 9.0, 9.0, H4), 3.99 (1H, d, $J$ 9.0, H7), 3.60-3.55 (2H, m, H1), 3.31 (3H, s, H9), 3.11-3.04 (3H, m, H2, Ha), 2.87 (1H, bs, NH), 2.82-2.72 (1H, m, Ha), 2.51-2.46 (2H, m, Ha), 1.11-1.01 (21H, m, TIPS); $\delta_C$ (125 MHz, $CDCl_3$) 172.8 (C=O), 170.6 (C=O), 154.1 (C=O), 140.0 (C-C), 139.2 (C-C), 131.7 (CH), 129.8 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 120.8 (C-Br), 67.3 (CH), 64.9 (CH), 62.2 (C[1]$H_2$), 57.8 (CH), 52.2 (C[9]$H_3$), 51.3 (CH), 46.3 (C[2]$H_2$), 42.4 (C[a]$H_2$), 39.6 (C[a]$H_2$), 18.0 ($CH_3$), 11.7 (CH); HRMS ($ES^+$) calculated for $C_{33}H_{46}BrN_3O_5Si$ $[M+H]^+$ 672.2463, found 672.2465 ; mp 104 °C (Ethanol)

**(2*S**, 3*R**, 4*S**, 5*R**)-3-(9-Ethyl-9H-carbazol-3-yl)-4-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (47)**



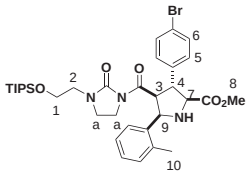

A viscous yellow oil (40 mg, 35 %). $R_f$ 0.16 (hexane: ethyl acetate 2:1); $\nu_{max}$ (thin film) 2944 (s, CH), 2866 (s, CH), 1723 (s, C=O), 1676 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.08 (1H, d, *J* 8.0, ArH), 8.06 (1H, d, *J* 2.0, ArH), 7.48-7.17 (10H, m, ArH), 5.09 (1H, d, *J* 9.0, H15), 5.04 (1H, dd, *J* 9.0, 9.0, H3), 4.37-4.29 (3H, m, H4, H12), 4.16 (1H, d, *J* 9.0, H14), 3.75 (2H, t, *J* 5.0, H1), 3.64 (3H, s, H16), 3.44-3.35 (1H, m, Ha), 3.27-3.18 (2H, m, Ha), 3.06-2.98 (1H, m, Ha), 2.95-2.85 (2H, m, H2), 1.71 (1H, bs, NH), 1.41 (3H, t, *J* 7.0, H13), 1.08-0.96 (21H, m, (TIPS)); $\delta_C$ (100 MHz, $CDCl_3$) 173.5 (C=O), 170.9 (C=O), 154.2 (C=O), 140.5 (C-C), 140.2 (C-C), 139.2 (C-C), 130.3 (C-C), 127.9 (CH), 127.7 (CH), 127.6 (CH), 125.7 (CH), 125.5 (CH), 123.1 (C-C), 122.8 (C-C), 120.6 (CH), 119.9 (CH), 118.7 (CH), 108.6 (CH), 108.3 (CH), 68.2 (CH), 67.0 (CH), 62.2 (C[1]$H_2$), 60.4 (CH), 52.4 (CH), 52.0 (C[16]H3), 46.4 (C[12]$H_2$), 42.4 (C[2]$H_2$), 39.6 (C[a]$H_2$), 37.5 (C[a]$H_2$), 17.9 ($CH_3$), 13.9 (C[13]$H_3$), 11.8 (CH); HRMS ($ES^+$) calculated for $C_{41}H_{54}N_4O_5Si$ $[M+H]^+$ 711.3936, found 711.3937.

**(2*S**, 3*R**, 4*S**, 5*R**)-3-(2-Chloro-6-methoxy-quinolin-3-yl)-4-[2-oxo-3-(2-triisopropylsilanyl-oxy-ethyl)-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (48)**



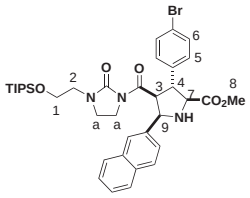

A yellow foam (185 mg, 93 %): $R_f$ 0.28 (hexane: ethyl acetate: TEA 60:40:2); $\nu_{max}$ (thin film) 2946 (s, CH), 2866 (s, CH), 1726 (s, C=O), 1674 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.13 (1H, s, ArH), 7.82 (1H, d, *J* 9.0, ArH), 7.38-7.22 (6H, m, ArH), 7.08 (1H, d, *J* 2.0, ArH), 5.20 (1H, dd, *J* 8.0, 8.0, H3), 5.02 (1H, d, *J* 8.0, H11), 4.73 (1H, dd, *J* 8.0, 8.0, H4), 4.13 (1H, d, *J* 8.0, H10), 3.92 (3H, s, H7), 3.73-3.72 (2H, m, H1), 3.73 (3H, s, H12), 3.45-3.39 (1H, m, Ha), 3.31-3.23 (2H, m, Ha), 3.21-3.13 (1H, m, Ha), 3.00-2.90 (2H, m, H2), 1.62 (1H, bs, NH), 1.07-0.98 (21H, m, (TIPS)); $\delta_C$ (100 MHz, $CDCl_3$) 172.7 (C=O), 170.8 (C=O), 158.2 (C=O), 154.0 (C=O), 148.7 (C-Cl), 142.7 (C-C), 139.3 (C-C), 135.7 (CH), 132.7 (C-C), 129.6 (CH), 128.5 (C-C), 128.0 (CH), 127.8 (CH), 127.6 (CH), 123.1 (CH), 104.8 (CH), 67.0 (C[3]H), 65.4 (C[11]H), 62.2 (C[1]$H_2$), 56.8 (C[10]H), 55.6 (C[7]$H_3$), 52.4 (C[12]H3), 49.0 (C[4]H), 46.4 (C[2]$H_2$), 42.4 (C[a]$H_2$), 39.7 (C[a]$H_2$), 17.9 ($CH_3$), 11.7 (CH); HRMS ($ES^+$) calculated for $C_{37}H_{49}ClN_4O_6Si$ $[M+H]^+$ 709.3183, found 709.3181.

**(2*S**, 3*R**, 4*S**, 5*R**)-3-(4-Bromo-phenyl)-4-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-5-o-tolyl-pyrrolidine-2-carboxylic acid methyl ester (48)**



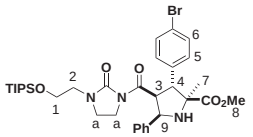

A viscous yellow oil (136 mg, 95 %): $R_f$ 0.11 (hexane: ethyl acetate 3:1); $\nu_{max}$ (thin film) 2943 (s, CH), 2866 (s, CH), 1725 (s, C=O), 1671 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.43 (2H, d, *J* 8.0, ArH), 7.30 (1H, d, *J* 7.0, ArH), 7.24 (2H, d, *J* 8.0, ArH), 7.18-7.00 (3H, m, ArH), 5.11 (1H, d, *J* 9.0, H9), 4.99 (1H, dd, *J* 9.0, 8.0, H3), 4.10 (1H, dd, *J* 9.0, 8.0, H4), 3.94 (1H, d, *J* 9.0 Hz, H7), 3.73-3.61 (2H, m, H1), 3.71 (3H, s, H8), 3.46-3.37 (1H, m, Ha), 3.26-3.15 (2H, m, Ha), 3.12-3.01 (2H, m, H2), 2.87 (1H, dt, *J* 9.0, 7.0, Ha), 2.41 (3H, H10), 1.07-0.98 (21H, m, (TIPS)); $\delta_C$ (100 MHz, $CDCl_3$) 172.6 (C=O), 171.7 (C=O), 153.9 (C=O), 140.2 (C-C), 137.1 (C-C), 136.6 (C-C), 131.8 (CH), 130.1 (CH), 129.5 (CH), 127.3 (CH), 126.3 (CH), 125.8 (CH), 120.8 (C-Br), 67.9 (CH), 62.1 (C[1]$H_2$), 61.7 (CH), 56.6 (CH), 52.6 (CH), 52.2 (C[8]$H_3$), 46.2 (C[2]$H_2$), 42.4 (C[a]$H_2$), 39.8 (C[a]$H_2$), 19.4 (C[10]$H_3$), 17.9 ($CH_3$), 11.8 (CH); HRMS ($ES^+$) calculated for $C_{34}H_{48}BrN_3O_5Si$ $[M+H]^+$ 686.2619, found 686.2616.

**(2*S**, 3*R**, 4*S**, 5*R**)-3-(4-Bromo-phenyl)-5-naphthalen-2-yl-4-[2-oxo-3-(2-triisopropylsilanyl-oxy-ethyl)-imidazolidine-1-carbonyl]-pyrrolidine-2-carboxylic acid methyl ester (49)**



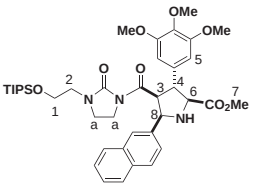

A yellow solid (137 mg, 96 %): $R_f$ 0.15 (hexane: ethyl acetate 3:1); $\nu_{max}$ (thin film) 2943 (s, CH), 2866 (s, CH), 1722 (s, C=O), 1675 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.80-7.76 (3H, m, ArH), 7.74 (1H, d, *J* 9.0, ArH), 7.49 (1H, dd, *J* 9.0, 2.0, ArH), 7.46-7.41 (4H, m, ArH), 7.27 (2H, d, *J* 8.0, ArH), 5.14 (1H, d, *J* 10.0, H9), 4.99 (1H, app. t, *J* 10.0, H3), 4.20 (1H, app. t, *J* 10.0, H4), 4.05 (1H, d, *J* 10.0, H7), 3.75-3.63 (2H, m, H1), 3.72 (3H, s, H8), 3.34-3.26 (2H, m, Ha), 3.11 (1H, dt, *J* 10.0, 5.0, Ha), 3.01-2.95 (1H, m, Ha), 2.73 (1H, dt, *J* 10.0, 3.0, H2), 2.50 (1H, dt, *J* 10.0, 7.0, H2′), 1.05-0.95 (21H, m, TIPS); $\delta_C$ (100 MHz, $CDCl_3$) 172.8 (C=O), 170.7 (C=O), 154.1 (C=O), 139.4 (C-C), 137.3 (C-C), 132.9 (C-C), 132.9 (C-C), 131.7 (CH), 129.8 (CH), 127.9 (CH), 127.5 (CH), 127.5 (CH), 126.6 (CH), 126.1 (CH), 126.0 (CH), 125.5 (CH), 120.8 (C-Br), 67.4 (CH), 65.1 (CH), 62.0 (C[1]$H_2$), 57.7 (CH), 52.2 (C[8]$H_3$), 51.2 (CH), 46.2 (C[2]$H_2$), 42.1 (C[a]$H_2$), 39.6 (C[a]$H_2$), 17.9 ($CH_3$), 11.8 (CH); HRMS ($ES^+$) calculated for $C_{37}H_{48}BrN_3O_5Si$ $[M+H]^+$ 722.2619, found 722.2621; mp 47 C (hexane: ethyl acetate)

**(2*S**, 3*R**, 4*S**, 5*R**)-3-(4-Bromo-phenyl)-2-methyl-4-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (50)**




A viscous colourless oil (114 mg, 83 %). $R_f$ 0.16 (hexane: ethyl acetate 3:1); $\nu_{max}$ (thin film) 2944 (s, CH), 2867 (s, CH), 1723 (s, C=O), 1676 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.39 (2H, d, *J* 8.0, ArH), 7.34 (2H, dd, *J* 7.0, 1.0, ArH), 7.28-7.19 (3H, m, ArH), 7.16 (2H, d, *J* 8.0, ArH), 5.20 (1H, app. t, *J* 10.0, H3), 5.00 (1H, d, *J* 10.0, H9), 3.36 (1H, d, *J* 10.0, H4), 3.87-3.78 (2H, m, H1), 3.76 (3H, s, H8), 3.41-3.32 (2H, m, Ha), 3.31-3.24 (2H, m, H2), 3.02 (1H, dt, *J* 9.0, 6.0, Ha), 2.79 (1H, dt, *J* 11.0, 6.0, Ha), 1.26 (3H, s, H7), 1.11-1.01 (21H, m, (TIPS)); $\delta_C$ (100 MHz, $CDCl_3$) 175.0 (C=O), 170.5 (C=O), 154.3 (C=O), 140.4 (C-C), 136.8 (C-C), 131.3 (CH), 130.6 (CH), 127.7 (CH), 127.7 (CH), 127.6 (CH), 121.0 (C-Br), 68.6 (C-CH3), 62.4 (CH), 62.2 (C[1]$H_2$), 54.3 (CH), 54.1 (CH), 52.4 (C[8]$H_3$), 46.4 (C[2]$H_2$), 42.5 (C[a]$H_2$), 39.6 (C[a]$H_2$), 19.8 (C[7]$H_3$), 17.9 ($CH_3$), 11.8 (CH); HRMS ($ES^+$) calculated for $C_{34}H_{48}BrN_3O_5Si$ $[M+H]^+$ 686.2619, found 686.2621.

**(2*S**, 3*R**, 4*S**, 5*R**)-5-Naphthalen-2-yl-4-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-3-(3,4,5-trimethoxy-phenyl)-pyrrolidine-2-carboxylic acid methyl ester (51)**

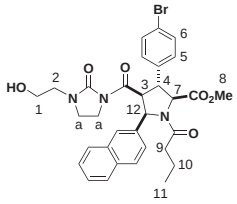



A yellow solid (5.72 g, 72 %). $R_f$ 0.23 (30-40 pet. ether: ethyl acetate 1:1); $\nu_{max}$ (thin film) 2942 (s, CH), 2866 (s, CH), 1722 (s, C=O), 1675 (s, C=O) $cm^{-1}$; $\delta_H$ (500 MHz, $C_6D_6$) 7.87-7.78 (3H, m, ArH), 7.77 (1H, d, *J* 8.0, ArH), 7.52 (1H, d, *J* 8.0, ArH), 7.49-7.45 (2H, m, ArH), 6.62 (2H, s, H5), 5.16 (1H, d, *J* 9.0, H8), 5.03 (1H, app. t, *J* 9.0, H3), 4.21 (1H, app. t, *J* 9.0, H4), 4.10 (1H, d, *J* 9.0, H6), 3.89 (6H, s, $OCH_3$), 3.84 (3H, s, $OCH_3$) 3.78-3.71 (1H, m, H1), 3.77 (3H, s, H7), 3.69-3.64 (1H, m, H1), 3.37-3.31 (2H, m, Ha), 3.17-3.12 (1H, m, Ha), 3.01-2.96 (2H, m, Ha, NH), 2.80-2.74 (1H, m, H2), 2.53-2.49 (1H, m, H2), 1.12-1.01 (21H, m, (TIPS)); $\delta_C$ (125 MHz, $CDCl_3$) 173.2 (C=O), 171.0 (C=O), 154.2 (C=O), 153.2 (C-C), 137.4 (C-C),136.9 (C-C), 136.1 (C-C), 132.9 (C-C), 127.9 (CH), 127.5 (CH), 127.4 (CH), 126.5 (CH), 126.1 (CH), 126.0 (CH), 125.6 (CH), 105.0 ($OCH_3$), 67.6 (CH), 65.3 (CH), 62.0 (C[1]$H_2$), 60.8 (CH), 57.6 (CH), 56.2 ($OCH_3$), 52.2 (C[7]$H_3$), 46.3 (C[2]$H_2$), 42.1 (C[a]$H_2$), 39.7 (C[a]$H_2$), 17.9 ($CH_3$), 11.8 (CH); HRMS (ES+) calculated for $C_{40}H_{55}N_3O_8Si$ $[M+H]^+$ 734.3831, found 734.3832; mp 53 °C (30-40 pet. ether: ethyl acetate 1:1).

### 5.3.3 General procedure for alkylation on solid phase

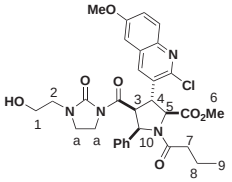
Solid-tagged pyrrolidine beads were swollen in $CH_2Cl_2$ (20 mL/g of beads). DMAP (1 equiv.) and pyridine (10 equiv.) were added, followed by acid chloride (10 equiv.). The reaction was left shaking for 3 days. The solution was drained under positive nitrogen pressure and washed/drained with $CH_2Cl_2$ (× 3), $CH_2Cl_2$:methanol 1:1 (× 3) and THF (× 3). The beads were air-dried under suction for 3 hours and placed under high vacuum for two days. A small portion of beads were cleaved using the standard cleavage method to give:

**(2*S**, 3*R**, 4*S**, 5*R**)-3-(4-Bromo-phenyl)-1-butyryl-4-[3-(2-hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-5-naphthalen-2-yl-pyrrolidine-2-carboxylic acid methyl ester (52)**



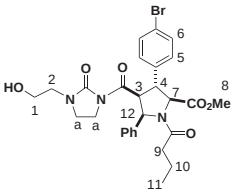

$\nu_{max}$ (thin film) 3447 (b, OH), 2922 (s, CH), 2851 (s, CH), 1721 (s, C=O), 1678 (s, C=O), 1651 (s, C=O) $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 8.07 (1H, s, ArH), 7.87-7.79 (3H, m, ArH), 7.73 (2H, d, *J* 8.0, ArH), 7.50-7.45 (2H, m, ArH), 7.42 (2H, d, *J* 8.0, ArH), 7.20 (2H, d, *J* 8.0, ArH), 5.83 (1H, d, *J* 9.0, H12), 4.87 (1H, dd, *J* 11.0, 9.0, H3), 4.51 (1H, d, *J* 11.0, H7), 4.25 (1H, app. t, *J* 12.0, H4), 3.93 (2H, t, *J* 5.0, H1), 3.72 (3H, s, H8), 3.67-3.56 (1H, m, Ha), 3.46-3.35 (4H, m, Ha, H2), 3.06-2.98 (1H, m, Ha), 2.24-2.16 (1H, m, H9), 1.89-1.83 (1H, m, H9′), 1.02-0.87 (2H, m, H10), 0.70 (3H, t, *J* 7.0, H11); $\delta_C$ (125 MHz, $CDCl_3$) 173.1 (C=O), 172.2 (C=O), 166.6 (C=O), 155.2 (C=O), 136.5 (C-C), 136.1 (C-C), 133.1 (C-C), 133.1 (C-C), 131.9 (CH), 129.9 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 126.4 (CH), 126.2 (CH), 126.2 (CH), 124.5 (CH), 121.6 (C-Br), 65.7 (CH), 62.9 (CH), 60.6 (C[1]$H_2$), 56.6 (CH), 52.3 (C[8]$H_3$), 46.4 (CH, C[2]$H_2$), 42.0 (C[a]$H_2$), 39.6 (C[a]$H_2$), 35.8 (C[9]$H_2$), 17.7 (C[10]$H_2$), 13.6 (C[11]$H_3$); m/z (APCI+) 638 (99 %, M+H+).

**(2*S**, 3*R**, 4*S**, 5*R**)-1-Butyryl-3-(2-chloro-6-methoxy-quinolin-3-yl)-4-[3-(2-hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (53)**




A white crystalline solid. $\nu_{max}$ (thin film) 2958 (s, CH), 2925 (s, CH), 1723 (s, C=O), 1677 (s, C=O), 1647 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.05 (1H, s, ArH), 7.86 (1H, d, *J* 9.0, ArH), 7.65 (2H, d, *J* 7.0, PhH), 7.40-7.28 (2H, m, ArH), 7.37 (2H, d, *J* 7.0, ArH), 7.03 (1H, d, *J* 2.0, ArH), 5.76 (1H, d, *J* 9.0, H10), 5.24 (1H, app. t, *J* 9.0, H4), 4.88 (1H, app. t, *J* 9.0, H3), 4.58 (1H, d, *J* 9.0, H5), 3.90-3.87 (5H, m, H6, H1), 3.73 (3H, s, $OCH_3$), 3.55-3.39 (5H, m, H2, Ha), 3.17-3.13 (1H, m, Ha), 2.23 (1H, dt, *J* 14.0, 7.0, H7), 1.92 (1H, dt, *J* 14.0, 7.0, H7′), 1.53 (2H, ddq, *J* 7.0, H8), 0.76 (3H, t, *J* 7.0, H9); $\delta_C$ (100 MHz, $CDCl_3$) 173.1 (C=O), 171.4 (C=O), 166.6 (C=O), 158.3 (C-C), 155.1 (C-C), 142.9 (C-C), 138.7 (C-C), 131.1 (CH), 129.6 (CH), 128.8 (CH), 128.5 (CH), 128.3

(C-C), 127.0 (CH), 123.4 (CH), 104.8 (CH), 68.0 (CH), 62.6 (CH), 60.5 (C[1]$H_2$), 55.6 ($OCH_3$), 55.3 (CH), 52.5 ($OCH_3$), 50.0 (CH), 46.4 (C[2]$H_2$), 42.1 (C[a]$H_2$), 39.7 (C[a]$H_2$), 35.8 (C[7]$_2$), 17.8 (C[8]$H_2$), 13.6 (C[9]$H_3$); HRMS ($ES^+$) calculated for $C_{32}H_{35}ClN_4O_7$ $[M+H]^+$ 623.2267, found 623.2263; mp 297 °C ($CH_2Cl_2$: Methanol 95:5)

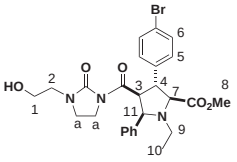



$\nu_{max}$ (thin film) 3448 (b, OH), 2922 (s, CH), 2852 (s, CH), 1720 (s, C=O), 1678 (s, C=O), 1647 (s, C=O) $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.58 (2H, d, *J* 7.0, ArH), 7.41 (2H, d, *J* 8.0, ArH), 7.35 (2H, dd, *J* 7.0, 7.0, ArH), 7.28 (1H, t, *J* 7.0, ArH), 7.18 (2H, d, *J* 8.0, ArH), 5.66 (1H, d, *J* 9.0, H12), 4.79 (1H, dd, *J* 12.0, 9.0, H3), 4.47 (1H, d, *J* 12.0, H7), 4.20 (1H, app. t, *J* 12.0, H4), 3.88 (2H, t, *J* 5.0, H1), 3.68 (3H, s, H8), 3.57-3.50 (3H, m, Ha), 3.50-3.39 (2H, m, H2), 3.20-3.13 (1H, m, Ha), 2.21-2.14 (1H, m, H9), 1.89-1.83 (1H, m, H9′), 1.53-1.43 (2H, m, H10), 0.73 (3H, t, J 7 Hz, H11); $\delta_C$ (125 MHz, $CDCl_3$) 173.0 (C=O), 172.2 (C=O), 166.6 (C=O), 155.1 (C=O), 138.9 (C-C), 136.1 (C-C), 131.9 (CH), 129.9 (CH), 128.7 (CH), 128.3 (CH), 126.9 (CH), 121.6 (C-Br), 65.6 (CH), 62.8 (CH), 60.7 (C[1]$H_2$), 56.5 (CH), 52.3 (C[8]$H_3$), 46.4 (C, CH, C[2]$H_2$), 42.1 (C[a]$H_2$), 39.6 (C[a]$H_2$), 35.8 (C[9]$H_2$), 17.7 (C[10]$H_2$), 13.6 (C[11]$H_3$); m/z (APCI+) 588 (99 %, M+H+).

### 5.3.4 General procedure for reductive amination on solid phase

Solid-tagged pyrrolidine beads were swollen in $CH_2Cl_2$:MeOH 1:2 (20 ml per gram of beads). Aldehyde (10 equiv.) was added followed by borane-pyridine complex (10 equiv.). The reaction was left shaking for 3 days. The solution was drained under positive nitrogen pressure and washed/drained with $CH_2Cl_2$:MeOH 1:1 (× 3), DMF:EtOH:$Et_3N$ 2:2:1 (× 3), $CH_2Cl_2$ (× 2), a solution of 8-hydroxyquinoline in $CH_2Cl_2$ (5 % w/v) (× 4) and $CH_2Cl_2$ (× 5). The beads were air-dried under suction for 3 hours and placed under high vacuum for two days. A small portion of beads were cleaved using the standard conditions to give:

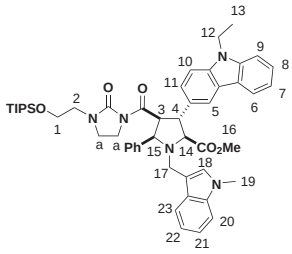
**(2*S**, 3*R**, 4*S**, 5*R**)-3-(4-Bromo-phenyl)-1-ethyl-4-[3-(2-hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (54)**




$\nu_{max}$ (thin film) 3462 (b, OH), 2922 (s, CH), 2851 (s, CH), 1721 (s, C=O), 1675 (s, C=O) $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.42 (2H, d, *J* 7.0, ArH), 7.38 (2H, d, *J* 8.0, ArH), 7.27-7.17 (5H, m, ArH), 4.73 (1H, dd, *J* 11.0, 11.0, H3), 4.47 (1H, d, *J* 11 Hz, H7), 4.33 (1H, dd, *J* 11.0, 11.0, H4), 3.79 (2H, t, *J* 5.0, H1), 3.65 (3H, s, H8), 3.62 (1H, d, *J* 11.0, H11), 3.46-3.38 (1H, m, Ha), 3.38-3.29 (2H, m, CHa), 3.24-3.18 (1H, m, Ha), 3.07-3.02 (1H, m, H2), 2.87-2.78 (1H, m, H2), 2.73-2.62 (2H, m, H9), 0.86 (H10); $\delta_C$ (125 MHz, $CDCl_3$) 173.2 (C=O), 169.5 (C=O), 155.1 (C=O), 141.4 (C-C), 138.0 (C-C), 131.6 (CH), 130.0 (CH), 128.5 (CH), 127.6 (CH), 127.5 (CH), 121.0 (C-Br), 71.6 (CH), 68.4 (CH), 60.9 (C[1]$H_2$), 55.5 (CH), 52.0 (C[8]$H_3$), 48.7 (CH), 42.2 (C[2]$H_2$), 39.7 (C[9]$H_2$), 11.7 (C[10]$H_3$); m/z (APCI+) 546 (99 %, M+H+).

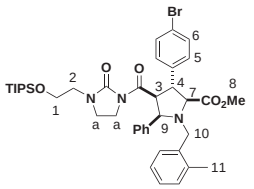
**General procedure for solution phase alkylation reactions** To a solution of pyrrolidine (**36-51**)) (1 equiv.) in DCE at ambient temperature was added 1-methylindole-3-carboxaldehyde (8 equiv.). The solution was stirred for 1.5 hours, after which $NaB(OAc)_3H$ (8 equiv.) was added and the reaction was stirred for 24 hours. The reaction mixture was poured into water, extracted with $CH_2Cl_2$, the organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:ethyl acetate 2:1) to give:

**(2*S**, 3*R**, 4*S**, 5*R**)-3-(9-Ethyl-9H-carbazol-3-yl)-1-(1-methyl-1H-indol-3-ylmethyl)-4-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (55)**



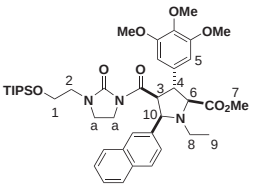

A colourless oil (17 mg, 48 %): $R_f$ 0.28 (hexane: ethyl acetate 2:1); $\nu_{max}$ (thin film) 2943 (s, CH), 2866 (s, CH), 1722 (s, C=O), 1678 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.06 (1H, d, *J* 8.0, ArH), 7.97 (1H, s, ArH), 7.57-7.17 (13H, m, ArH), 7.08 (1H, dd, *J* 8.0, 8.0, ArH), 6.91 (1H, s, ArH), 4.91 (1H, dd, *J* 9.0, 9.0, H3), 4.62-4.55 (2H, m, H4, H15), 4.28 (2H, q, *J* 7.0, H12), 4.03 (1H, d, *J* 9.0, H14), 3.81-3.77 (2H, m, H1), 3.77 (3H, s, H6), 3.71 (2H, s, H17), 3.37-3.3.18 (4H, m, $CH_2$), 3.19 (3H, s, H19), 3.08-3.00 (1H, m, $CH_2$), 2.84-2.76 (1H, m, $CH_2$), 1.37 (3H, t, *J* 7.0, H13), 1.07-0.99 (21H, m, (TIPS)); $\delta_C$ (100 MHz, CDCl3) 173.2 (C=O), 170.3 (C=O), 154.3 (C=O), 141.0 (C-C), 140.1 (C-C), 139.2 (C-C), 136.9 (C-C), 129.4 (CH), 129.4 (CH), 129.0 (C-C), 128.7 (C-C), 127.4 (CH), 127.2 (CH), 126.0 (CH), 125.4 (CH), 122.9 (C-C), 122.8 (C-C), 121.3 (CH), 120.6 (CH), 120.2 (CH), 119. 9 (CH), 118.9 (CH), 118.5 (CH), 109.4 (C-C), 108.7 (CH), 108.4 (CH), 108.2 (CH), 72.5 (CH), 68.4 (CH), 62.2 (C[1]$H_2$), 55.7 (CH), 51.1 (C[16]$H_3$), 49.6 (CH), 46.3 (C[12]$H_2$) 46.1 (C[17]$H_2$), 42.4 (C[2]$H_2$), 39.5 (C[a]$H_2$), 36.1 (C[a]$H_2$), 32.5 (C[19]$H_3$), 17.8 ($CH_3$), 13.7 (C[13]$H_3$), 11.7 (CH); HRMS ($ES^+$) calculated for $C_{51}H_{63}N_5O_5Si$ $[M+H]^+$ 854.4671, found 854.4675.

**(2*S**, 3*R**, 4*S**, 5*R**)-3-(4-Bromo-phenyl)-1-(2-methyl-benzyl)-4-[2-oxo-3-(2-triisopropylsilanyl-oxy-ethyl)-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (56)**



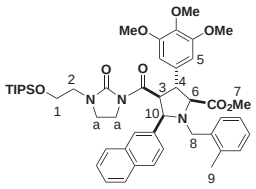

A yellow foam (60 mg, 98 %). $R_f$ 0.58 (30-40 pet. ether: ethyl acetate 2:1); $\nu_{max}$ (thin film) 2922 (s, CH), 2866 (s, CH), 1734 (s, C=O), 1711 (s, C=O), 1676 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $C_6D_6$) 7.41 (2H, d, *J* 7.0, ArH), 7.36 (2H, d, *J* 8.0, ArH), 7.22-7.15 (6H, m, ArH), 7.03-6.97 (2H, m, ArH), 6.92 (1H, dd, *J* 6.0, 2.0, ArH), 4.81 (1H, app. t, *J* 11.0, H3), 4.51 (1H, d, *J* 11.0, H9), 4.35 (1H, app. t, *J* 11.0, H4), 3.87-3.79 (3H, m, H7, H1), 3.66 (1H, d, *J* 13.0, H10), 3.55 (1H, d, *J* 13.0, H10′), 3.42-3.24 (4H, m, Ha, H2), 3.14 (3H, s, H8), 3.10-3.04 (1H, ddd, *J* 10.0, 6.0, 6.0, Ha), 2.82-2.75 (1H, ddd, *J* 10.0, 6.0, 6.0, Ha), 2.16 (3H, s, H11), 1.12-1.01 (21H, m, TIPS); $\delta_C$ (100 MHz, $CDCl_3$) 172.3 (C=O), 169.4 (C=O), 154.2 (C=O), 140.4 (C-C), 138.5 (C-C), 137.6 (C-C), 135.1 (C-C), 131.6 (CH), 130.9 (CH), 130.0 (CH), 129.7 (CH), 128.7 (CH), 127.5 (CH), 127.4 (CH), 121.0 (C-Br), 73.1 (CH), 70.5 (CH), 62.2 (C[1]$H_2$), 57.6 (C[10]$H_2$), 55.2 (CH), 51.3 (C[8]$H_3$), 49.2 (CH), 46.4 (C[2]$H_2$), 42.5 (C[a]$H_2$), 39.6 (C[a]$H_2$), 19.1 (C[11]$H_3$), 17.9 ($CH_3$), 11.8 (CH); HRMS ($ES^+$) calculated for $C_{41}H_{54}BrN_3O_5Si$ $[M+H]^+$ 776.3089, found 776.3088; m.p. 118 °C (30-40 pet. ether: ethyl acetate 2:1).

**(2*S**, 3*R**, 4*S**, 5*R**)-1-Ethyl-5-naphthalen-2-yl-4-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-3-(3,4,5-trimethoxy-phenyl)-pyrrolidine-2-carboxylic acid methyl ester (57)**




A viscous oil (2.66 g, 97 %). $R_f$ 0.22 (30-40 pet. ether: ethyl acetate 2:1); $\nu_{max}$ (thin film) 2942 (s, CH), 2866 (s, CH), 1723 (s, C=O), 1674 (s, C=O) $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.82-7.75 (4H, m, ArH), 7.70 (1H, dd, *J* 7.0, 1.0, ArH), 7.44-7.42 (2H, m, ArH), 6.57 (2H, s, H5), 4.92 (1H, app. t, *J* 11.0, H3), 4.68 (1H, d, *J* 11.0, H10), 4.42 (1H, app. t, *J* 11.0, H4), 3.84 (6H, s, $OCH_3$), 3.81 (2H, q, *J* 7.0, H8), 3.80 (3H, s, $OCH_3$), 3.72 (3H, s, H7), 3.70 (1H, d, *J* 11.0, H6), 3.47-3.40 (1H, m, H1), 3.33-3.26 (1H, m, H1), 3.21-3.13 (2H, m, Ha), 2.80-2.59 (4H, m, Ha, H2), 1.10-1.02 (21H, m, (TIPS)), 0.89 (3H, t, *J* 7.0, H8); $\delta_C$ (125 MHz, $CDCl_3$) 173.6 (C=O), 169.8 (C=O), 154.4 (C=O), 153.1 (COMe), 139.4 (COMe), 137.0 (C-C), 134.6 (C-C), 133.0 (C-C), 132.8 (C-C), 127.7 (CH), 127.6 (CH), 127.2 (CH), 127.0 (CH), 126.7 (CH), 125.8 (CH), 125.6 (CH), 105.1 (CH), 72.2 ($OCH_3$), 68.7 (CH), 62.0 (C[1]$H_2$), 60.7 (CH), 56.1 ($OCH_3$), 55.1 (CH), 52.0 ($OCH_3$), 49.6 (CH), 47.0 (C[2]$H_2$), 46.4 (C[a]$H_2$), 42.2 (C[a]$H_2$), 39.6 (C[8]$H_2$), 17.9 ($CH_3$), 12.1 (C[9]$H_3$), 11.8 (CH); HRMS ($ES^+$) calculated for $C_{42}H_{59}N_3O_8Si$ $[M+H]^+$ 762.4150, found 762.4184.

**(2*S**, 3*R**, 4*S**, 5*R**)-3-(4-Bromo-phenyl)-1-(2-methyl-benzyl)-4-[2-oxo-3-(2-triisopropylsilanyl-oxy-ethyl)-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (58)**

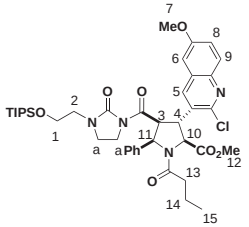



A viscous oil (2.84 g, 94 %). $R_f$ 0.37 (30-40 pet. ether: ethyl acetate 1:1); $\nu_{max}$ (thin film) 2942 (s, CH), 2865 (s, CH), 1725 (s, C=O), 1676 (s, C=O) $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.96-7.72 (5H, m, ArH), 7.46-7.43 (2H, m, ArH), 7.25-7.23 (1H, m, ArH), 7.01-6.97 (2H, m, ArH), 6.91-6.88 (1H, m, ArH), 6.57 (2H, s, H5), 4.96 (1H, app. t, *J* 11.0, H3), 4.68 (1H, d, *J* 11.0, H10), 4.45 (1H, app. t, *J* 11.0, H4), 3.91 (1H, d, *J* 13.0, H8), 3.85 (6H, s, $OCH_3$), 3.83-3.76 (2H, m, H1), 3.81 (3H, s, $OCH_3$), 3.70 (1H, d, *J* 13.0, H8′), 3.62 (1H, d, *J* 11.0, Ha), 3.48-3.42 (1H, m, Ha), 3.32-3.27 (1H, m, Ha), 3.17 (3H, s, H7), 3.17-3.11 (1H, m, Ha), 2.72-2.51 (2H, m, H2), 2.16 (3H, s, H9), 1.11-1.01 (21H, m, (TIPS)); $\delta_C$ (125 MHz, $CDCl_3$) 172.5 (C=O), 169.8 (C=O), 154.3 (C=O), 153.1 (COMe), 138.4 (COMe), 138.1 (C-C), 137.0 (C-C), 135.2 (C-C), 134.2 (C-C), 133.0 (C-C), 132.7 (C-C), 130.9 (CH), 129.7 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.0 (CH), 126.9 (CH), 126.0 (CH), 125.8 (CH), 125.7 (CH), 125.0 (CH), 105.1 (CH), 73.5 ($OCH_3$), 71.0 (CH), 62.0 (C[1]$H_2$), 60.7 (CH), 57.6 (C[8]$H_2$), 56.1 ($OCH_3$), 54.8 (CH), 51.3 ($OCH_3$), 50.2 (CH), 46.3 (C[2]$H_2$), 42.2 (C[a]$H_2$), 39.6 (C[a]$H_2$), 19.1 (C[9]$H_3$), 17.9 ($CH_3$), 11.8 (CH); HRMS ($ES^+$) calculated for $C_{48}H_{63}N_3O_8Si$ $[M+H]^+$ 838.4463, found 838.4462.

### 5.3.5 General procedure for solution phase acylation reactions

Acid Chloride (1.4 equiv.) was added to a solution of the pyrrolidine (**36**-**51**) (1 equiv.), DMAP (0.1 equiv.) and pyridine (1.5 equiv.) in $CH_2Cl_2$ at ambient temperature. The reaction was stirred for 5 hours, after which $Et_2O$ (20 mL) was added. The reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:ethyl acetate 1:1) to give:

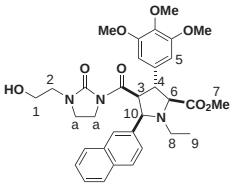
**(2*S**, 3*R**, 4*S**, 5*R**)- 1-Butyryl-3-(2-chloro-6-methoxy-quinolin-3-yl)-4-[2-oxo-3-(2-triiso-propylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylic acid methyl ester (59)**




A colourless oil (105 mg, 95 %): $R_f$ 0.33 (hexane: ethyl acetate 1:1); $\nu_{max}$ (thin film) 2944 (s, CH), 2867 (s, CH), 1749 (s, C=O), 1723 (s, C=O), 1679 (s, C=O), 1649 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.03 (1H, s, ArH), 7.83 (1H, d,

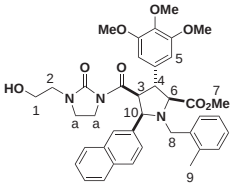
$J$ 9.0, ArH), 7.62 (2H, d, $J$ 7.0, ArH), 7.37-7.24 (4H, m, ArH), 6.98 (1H, d, $J$ 2.0, ArH), 5.75 (1H, d, $J$ 8.0, H11), 5.24 (1H, app. t, $J$ 8.0, H3), 4.85 (1H, app. t, $J$ 8.0, H4), 4.50 (1H, d, $J$ 8.0, H10), 3.90 (2H, t, $J$ 5.0 Hz, H1), 3.85 (3H, s, H7), 3.68 (3H, s, H12), 3.57-3.35 (5H, m, H2, Ha), 3.15-3.08 (1H, m, Ha), 2.28-2.17 (1H, m, H13), 1.93-1.85 (1H, m, H3′), 1.63-1.40 (2H, m, H14), 1.11-0.98 (21H, m, (TIPS)), 0.73 (3H, t, $J$ 7.0, H15); $\delta_C$ (100 MHz, $CDCl_3$) 173.0 (C=O), 171.4 (C=O), 166.5 (C=O), 158.3 (C-O), 154.4 (C=O), 148.6 (C-Cl), 142.9 (C-C), 138.8 (C-C), 136 (CH), 130.0 (C-C), 129.6 (CH), 128.7 (CH), 128.4 (C-C), 128.3 (CH), 126.9 (CH), 123.4 (CH), 104.8 (CH), 65.4 (C[3]H), 62.6 (C[11]H), 61.7 (C[1]$H_2$), 55.6 (C[7]$H_3$), 55.2 (C[10]HC=O), 52.5 (C[12]$H_3$), 46.5 (C[2]$H_2$), 42.9 (C[4]H), 42.5 (C[a]$H_2$), 39.6 (C[a]$H_2$), 35.7 (C[13]$H_2$), 17.9 ($CH_3$), 17.8 (C[14]$H_2$), 13.6 (C[15]$H_3$), 11.8 (CH); HRMS ($ES^+$) calculated for $C_{41}H_{55}ClN_4O_7Si$ $[M+H]^+$ 779.3601, found 779.3604.

**(2*S**, 3*R**, 4*S**, 5*R**)-1-Ethyl-4-[3-(2-hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-5-naphthalen-2-yl-3-(3,4,5-trimethoxy-phenyl)-pyrrolidine-2-carboxylic acid methyl ester (60)**




A white crystalline solid (31.6 mg, 73 %). $R_f$ 0.28 (ethyl acetate); $\nu_{max}$ (thin film) 2937 (s, CH), 2840 (s, CH), 1721 (s, C=O), 1676 (s, C=O) $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.84-7.78 (4H, m, ArH), 7.73 (1H, dd, $J$ 7.0, 1.0, ArH), 7.48-7.43 (2H, m, ArH), 6.58 (2H, s, H5), 4.87 (1H, app. t, $J$ 11.0, H3), 4.66 (1H, d, $J$ 11.0, H10), 4.44 (1H, app. t, $J$ 11.0, H4), 3.87 (6H, s, $OCH_3$), 3.82 (3H, s, $OCH_3$), 3.76-3.73 (5H, m, H8, H7), 3.71 (1H, d, $J$ 11.0, H6), 3.37-3.23 (3H, m, H1, Ha), 3.10-3.03 (1H, m, Ha), 2.82-2.68 (2H, m, H2), 2.68-2.55 (2H, m, Ha), 0.90 (3H, t, $J$ 7.0, H9); $\delta_C$ (125 MHz, $CDCl_3$) 173.5 (C=O), 169.9 (C=O), 155.1 (C=O), 153.1 (COMe), 139.1 (COMe), 137.0 (C-C), 134.7 (C-C), 133.1 (C-C), 132.8 (C-C), 127.7 (CH), 127.6 (CH), 127.3 (CH), 127.1 (CH), 126.8 (CH), 125.9 (CH), 125.7 (CH), 105.1 (CH), 72.1 ($OCH_3$), 68.9 (CH), 60.8 (C[1]$H_2$), 60.7 (CH), 56.2 ($OCH_3$), 55.4 (CH), 52.0 ($OCH_3$), 49.7 (CH), 46.8 (C[2]$H_2$), 46.6 (C[a]$H_2$), 42.0 (C[a]$H_2$), 39.7 (C[8]$H_2$), 11.9 (C[9]$H_3$); HRMS ($ES^+$) calculated for $C_{33}H_{39}N_3O_8$ $[M+H]^+$ 606.2810, found 606.2814; mp 73 °C (ethyl acetate).

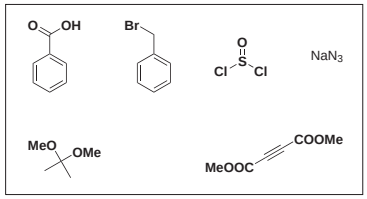
**(2*S**, 3*R**, 4*S**, 5*R**)-4-[3-(2-Hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-1-(2-methyl-benzyl)-5-naphthalen-2-yl-3-(3,4,5-trimethoxy-phenyl)-pyrrolidine-2-carboxylic acid methyl ester (61)**




A white crystalline solid (83.0 mg, 71 %). $R_f$ 0.28 (ethyl acetate); $\nu_{max}$ (thin film) 2947 (s, CH), 2841 (s, CH), 1721 (s, C=O), 1678 (s, C=O) $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.81-7.74 (5H, m, ArH), 7.47-7.43 (2H, m, ArH), 7.25-7.23 (1H, m, ArH), 7.01-6.96 (2H, m, ArH), 6.91-6.89 (1H, m, ArH), 6.56 (2H, s, H5), 4.91 (1H, app. t, $J$ 11.0, H3), 4.65 (1H, d, $J$ 11.0, H10), 4.46 (1H, app. t, $J$ 11.0, H4), 3.89 (1H, d, $J$ 13.0, H8), 3.84 (6H, s, $OCH_3$), 3.79 (3H, s, $OCH_3$), 3.76-3.68 (2H, m, H1), 3.66 (1H, d, $J$ 13.0, H8′), 3.61 (1H, d, $J$ 11.0, H6), 3.34-3.28 (2H, m, Ha), 3.24-3.19 (1H, m, Ha), 3.16 (3H, s, H7), 3.05-3.00 (1H, m, Ha), 2.64-2.58 (1H, m, H2), 2.50-2.45 (1H, m, H2), 2.16 (3H, s, H9); $\delta_C$ (125 MHz, $CDCl_3$) 172.4 (C=O), 169.8 (C=O), 155.1 (C=O), 153.1 (COMe), 138.4 (COMe), 137.9 (C-C), 137.0 (C-C), 135.1 (C-C), 134.3 (C-C), 133.0 (C-C), 132.6 (C-C), 130.9 (CH), 129.7 (CH), 127.7 (CH), 127.6 (CH), 127.6 (CH), 127.5 (CH), 127.1 (CH), 127.0 (CH), 125.8 (CH), 125.7 (CH), 125.0 (CH), 105.1 (CH), 73.5 ($OCH_3$), 71.2 (CH), 60.8 (C[1]$H_2$), 60.7 (CH), 57.6 (C[8]$H_2$), 56.1 ($OCH_3$), 54.9 (CH), 51.3 ($OCH_3$), 50.2 (CH), 46.6 (C[2]$H_2$), 42.0 (C[a]$H_2$), 39.8 (C[a]$H_2$), 19.1 (C[9]$H_3$); HRMS ($ES^+$) calculated for $C_{39}H_{43}N_3O_8$ $[M+H]^+$ 682.3123, found 682.3128; mp 78 °C (ethyl acetate).

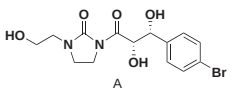
# 6 Branching Pathway 2 Dihydroxylation Reactions

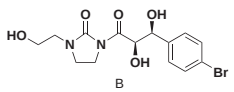
## 6.1 Building blocks used




## 6.2 Enantioselective dihydroxylation on solid support

To a sample-vial containing a suspension of solid support immobilised of alkene resin (0.77 mmol/g, 50 mg, 0.04 mmol) was charged sequentially with $K_3Fe(CN)_6$ (38 mg, 0.12 mmol), $K_2CO_3$ (16.9 mg, 0.12 mmol), $MeSO_2NH_2$ (5.5 mg, 0.06 mmol) in water (0.4 ml) and chiral ligand (2.9 mg, 4 $\mu$mol) in THF (0.4 ml). The suspension was charged with potassium osmate dihydrate (2.9 mg, 1.2 $\mu$mol) the sample-vials sealed. The mixture was vigorously agitated for 14 days at 4 °C. EtOAc and saturated sodium thiosulphate solution were added and mixture stirred for a further hour. The beads were washed with THF (× 3), $CH_2Cl_2$ (× 3), $CH_2Cl_2$:MeOH (× 3) and $CH_2Cl_2$ (× 3). The beads were air-dried under suction for 2 hours with occasional agitation, and then placed under high vacuum. A plastic eppendorf vial containing the immobilised resin bound alcohol beads (96 mg) and THF (0.5 ml) at room temperature was charged with HF.Pyr (50 $\mu$L, 1.77 mmol). The vial was sealed and agitated for 2.5 hours, then quenched with trimethylethoxysilane (0.32 ml). The vials were agitated for a further 30 minutes to ensure complete quenching. The solvent was filtered through a plug of silica gel and the resin washed with THF (× 3), $CH_2Cl_2$ (× 3), $CH_2Cl_2$: MeOH (1:1) (× 3) and $CH_2Cl_2$ (× 3) and the solvent was removed *in vacuo*. The spectral data was consistent with solution phase synthesis.



| | Solvent (1:1) | Chiral Catalyst | Yield | Enantiomeric excess |
|---|---|---|---|---|
| A | THF:Water | $(DHQD)_2PHAL$ (AD-mix $\beta$) | 63 % | 91 % |
| B | THF:Water | $(DHQD)_2PHAL$ (AD-mix $\alpha$) | 39 % | 90 % |

### 6.2.1 Racemic synthesis on solid support

**(*rac*)-1-[3-(4-Bromo-phenyl)-2,3-dihydroxy-propionyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one**
A test-tube containing a suspension of solid supported alkene (loading 0.36 mmol/g, 100 mg, 0.036 mmol), *N*-methyl morpholine-*N*-oxide (8 mg, 0.068 mmol), $H_2O$ (0.1 ml) and THF (0.9 ml) was charged with osmium tetroxide (2.5 wt % in 2-methyl-2-propanol). The test-tube was purged with nitrogen, sealed and agitated for 5 days. $Na_2S_2O_7$ solution and EtOAc were added the suspension agitated for a further 30 minutes. The beads were washed with THF (× 3), $CH_2Cl_2$:MeOH (× 3) and $CH_2Cl_2$ (× 3). Air-drying under suction for 2 hours with occasional agitation followed by drying under high vacuum yielded yellow beads (96 mg).

Following general method for the cleavage of the solid support gave the title compound as a white solid (10.2 mg, 76 %, loading 0.45 mmol/g). The spectral data was consistent with synthesized in solution.

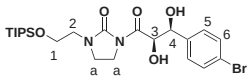
### 6.2.2 Enantioselective dihydroxylation reactions in solution phase

**2(*S*), 3(*R*)-1-[3-(4-Bromo-phenyl)-2,3-dihydroxy-propionyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one** To a round-bottomed flask, equipped with a magnetic stirring bar, containing the alkene (**22-29**) (194 mg, 0.39 mmol), methane sulfonamide (111 mg, 1.2 mmol), AD-mix $\beta$ (540 mg), $(DHQD)_2PHAL$ (31 mg, 0.04 mmol), $^t$BuOH (10 ml) and water (10 ml) was charged with osmium tetroxide (123 $\mu$L, 0.01 mmol). The mixture was stirred vigorously for 16 hours. The reaction mixture was quenched by the addition of $Na_2S_2O_7$ solution and stirred for a further 30 minutes. The quenched solution was diluted with EtOAc and the phases separated, the aqueous layer extracted with EtOAc (× 3), the combined organic layers washed with NaCl, dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude compound was purified by column chromatography ($R_f$ 0.50; $SiO_2$; 1:10 MeOH: $CH_2Cl_2$) to give the title compound as a white solid (109 mg, 92 %). The spectral data was constant with the racemic compound.

### 6.2.3 Racemic synthesis in solution phase

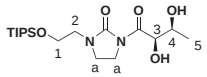
A round-bottom flask, equipped with a magnetic stirrer, containing the alkene (**22-29**) (1.5 g, 3.02 mmol), *N*-methyl morpholine-*N*-oxide (0.60 g, 5.14 mmol), acetone (75 ml) and water (7.5 ml) was charged with osmium tetroxide (2.5 wt% in 2-methyl-2-propanol, 0.92 ml, 0.09 mmol). The yellow mixture was stirred at room temperature for 12 hours. The reaction mixture was quenched by the addition of $Na_2S_2O_7$ solution (80 ml) and stirred for a further 30 minutes. The quenched reaction mixture was diluted with EtOAc and the phases separated. The aqueous layer was extracted with EtOAc (× 3), the combined organic layers washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude product was purified by column chromatography to give:

**(*rac*)-1-[3-(4-Bromo-phenyl)-2,3-dihydroxy-propionyl]-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (62)**



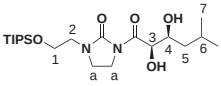

Isolated as a highly viscous clear oil (1.33 g, 83 %) that solidified on standing. $R_f$ 0.50 ($SiO_2$; 1:10 MeOH: $CH_2Cl_2$); $\nu_{max}$ (neat) 3504w, 3400w, 3170w br (alcohol) 1725s (amide), 1682s (amide), 1261m, 1104s, 765s cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.50-7.45 (2H, d, *J* 8.5, H6), 7.42-7.37 (2H, d, *J* 8.5, H5), 5.34-5.28 (1H, br s, H4), 5.17-5.11 (1H, br s, H3), 4.04-3.97 (1H, br d, *J* 5.7, OH), 3.94-3.83 (4H, m, H1, Ha), 3.75-3.66 (2H, m, Ha), 3.48-3.40 (2H, m, H2), 3.14-3.02 (1H, br d, *J* 5.5, OH), 1.19-0.99 (21H, m, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 172.6 (C=O), 154.4 (C=O), 140.0 (C-C), 131.2 (CH), 128.0 (CH), 121.4 (C-Br), 74.0 (CH), 73.2 (CH), 61.9 (C[1]$H_2$) 46.6 (C[2]$H_2$), 43.3 (C[a]$H_2$), 40.0 (C[a]$H_2$), 17.9 ($CH_3$), 11.8 (CH); HRMS found m/z (ESI-$H^+$) 529.1730 $C_{23}H_{38}{}^{79}BrN_2O_5Si^+$ required 529.1728, $\Delta$ppm +0.378; mp 66-68 °C (MeOH: $CH_2Cl_2$).

**(*rac*)-1-(2,3-Dihydroxy-butyryl)-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (63)**



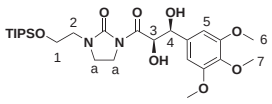

Isolated as a clear oil (103 mg, 95 %) after purification by column chromatography. $R_f$ 0.21 ($SiO_2$; 5:95 MeOH: $CH_2Cl_2$); $\nu_{max}$ (neat) 3466w br (alcohol) 2942m, 2867m, 1728s (amide), 1674s (amide), 1437w, 1356m, 1106s, 881m cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 5.03-4.86 (1H, dd, *J* 7.5, 2.0, H3), 4.18-4.09 (1H, m, H4), 4.01-3.95 (1H, d, *J* 7.5, OH), 3.91-3.79 (4H, m, H1, Ha), 3.68-3.60 (2H, m, Ha), 3.42-3.31 (2H, m, H2), 2.50-2.41 (1H, br s, OH), 1.32-1.25 (3H, d, *J* 6.5, H5), 1.12-0.94 (21H, m, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 173.5 (C=O), 154.4 (C=O), 73.8 (CH), 68.6 (CH), 61.9 (C[1]$H_2$) 46.5 (C[2]$H_2$), 43.2 (C[a]$H_2$), 39.8 (C[a]$H_2$), 19.8 (C[5]$H_3$), 17.9 ($CH_3$), 11.8 (CH); HRMS found m/z (ESI-$H^+$) 389.2467 $C_{18}H_{37}N_2O_5Si^+$ required 389.2466, $\Delta$ ppm +0.3.

**(*rac*)-1-(2,3-Dihydroxy-5-methyl-hexanoyl)-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (64)**



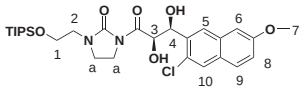

Isolated as a clear oil (96 mg, 89 %) after purification by column chromatography. $R_f$ 0.14 ($SiO_2$; 5:95 MeOH: $CH_2Cl_2$); $\nu_{max}$ (neat) 3448w (alcohol), 2944m, 2867m, 1731s (amide), 1673m (amide), 1356m, 1267s, 1103s, 882m cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 5.02-4.95 (1H, br s, H3), 4.11-4.01 (1H, br s, H4), 3.94-3.80 (5H, m, H1, Ha, OH), 3.71-3.62 (2H, t, *J* 8.5, Ha), 3.43-3.35 (2H, t, *J* 5.5, H2), 2.10-1.90 (1H, br s, OH), 1.18-1.73 (1H, m, H6), 1.63-1.51 (1H, m, H5), 1.50-1.38 (1H, m, H5′), 1.12-0.94 (21H, m, TIPS), 0.97-0.85 (2 x 3H, d, *J* 6.5, 5.5 H7); $\delta_C$ (125 MHz; $CDCl_3$) 173.8 (C=O), 154.3 (C=O), 73.3 (CH), 70.7 (CH), 61.9 (C[1]$H_2$) 46.5 (C[2]$H_2$), 43.3 (C[a]$H_2$), 43.1 (C[a]$H_2$), 39.9 (C[5]$H_2$), 24.4 (C[7]$H_3$), 23.3 (C[7]$H_3$), 21.9 (C[6]H), 17.8 ($CH_3$), 11.8 (CH); HRMS found m/z (ESI-$H^+$) 431.2936 $C_{21}H_{43}N_2O_5Si^+$ required 431.2936, $\Delta$ ppm +0.1.

**(*rac*)-1-[2,3-Dihydroxy-3-(3,4,5-trimethoxy-phenyl)-propionyl]-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (65)**



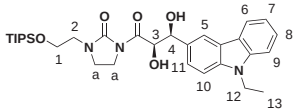
Isolated as a yellow oil (57 mg, 54 %) after purification by column chromatography. $R_f$ 0.28 ($SiO_2$; 5:95 MeOH: $CH_2Cl_2$); $\nu_{max}$ (neat) 3471w br (alcohol), 2941m, 2866m, 1728m (amide), 1675m (amide), 1429m, 1248m, 1123s, 732m $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.78-6.74 (2H, s, H5), 5.37-5.32 (1H, dd, *J* 7.0, 2.0, H4), 5.10-5.05 (1H, br d, *J* 4.5 H2), 4.03-3.97 (1H, d, *J* 7.0, OH), 3.94-3.75 (13H, m, H1, Ha, H6, H7), 3.73-3.58 (2H, m, Ha), 3.48-3.32 (2H, m, H2), 3.07-2,98 (1H, d, *J* 7.0, OH), 1.15-0.98 (21H, m, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 172.8 (C=o), 154.3 (C=0), 153.0 (C-C), 137.2 (C), 136.6 (C), 103.3 (C[5]H), 74.2 (CH), 73.7 (CH), 61.7 (C[1]$H_2$), 60.7 ($CH_3$), 56.1 ($CH_3$), 56.0 ($CH_3$), 46.5 (C[2]$H_2$), 43.1 (C[a]$H_2$), 39.9 (C[a]$H_2$), 17.8 ($CH_3$), 11.8 (CH); HRMS found m/z (ESI-H+) 558.3205 $C_{26}H_{48}N_3O_8Si^+$ required 558.3205, Δ ppm 0.0, mp 116-118 °C (MeOH; $CH_2Cl_2$).

**(*rac*)-1-[3-(3-Chloro-7-methoxy-naphthalen-2-yl)-2,3-dihydroxy-propionyl]-3-(2-triisopropylsilanyl-oxy-ethyl)-imidazolidin-2-one (66)**



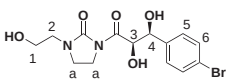
Isolated as a pale yellow oil (101 mg, 95 %) after purification by column chromatography. $R_f$ 0.22 ($SiO_2$; 5:95 MeOH: $CH_2Cl_2$); $\nu_{max}$ (neat) 3447 (alcohol), 2942m, 2866m, 1733s (amide), 1673m (amide), 1497s, 1272s, 1107s, 735m $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 8.44-8.36 (1H, s, H10), 7.88-7.82 (1H, d, *J* 9.5, H9), 7.36-7.29 (1H, dd, *J* 9.0, 2.5, H8), 7.11-7.08 (1H, d, *J* 2.5, H6), 5.61-5.57 (1H, m, H4), 5.23-5.18 (1H, dd, *J* 7.5, 4.0, H3), 4.89-4.84 (1H, d, *J* 7.5, OH), 3.99-3.82 (5H, m, H1, H7), 3.82-3.74 (2H, t, *J* 5.0, Ha), 3.71-3.57 (3H, m, Ha, OH), 3.34-3.20 (2H, m, Ha), 1.14-0.91 (21H, m, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 172.0 (C=O), 158.1 (C=O), 154.6 (C), 146.2 (C), 143.1 (C), 137.3 (CH), 131.8 (C), 129.4 (CH), 128.3 (C), 123.2 (CH), 105.4 (CH), 72.8 (CH), 70.5 (CH), 61.8 (C[1]$H_2$), 55.6 (C[7]$H_3$), 46.5 (C[2]$H_2$), 43.3 (C[a]$H_2$), 40.2 (C[a]$H_2$), 17.9 ($CH_3$), 11.8 (CH); HRMS found m/z (ESI-$H^+$) 566.2450 $C_{27}H_{41}N_3O_6{}^{35}ClSi^+$ required 566.2448, Δ ppm +0.4.

**(*rac*)-1-[3-(9-Ethyl-9H-carbazol-3-yl)-2,3-dihydroxy-propionyl]-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (67)**



Isolated as a white solid (71 mg, 67 %) after purification by column chromatography. $R_f$ 0.28 ($SiO_2$; 5:95 MeOH: $CH_2Cl_2$); $\nu_{max}$ (neat) 3447w br (alcohol), 2941m, 2866m, 1728s (amide), 1672m (amide), 1471m, 1271s, 1232s, 745m $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 8.29-8.17 (1H, s, ArylCH), 8.15-8.05 (1H, d, *J* 7.8. ArylCH), 7.67-7.61 (1H, dd, *J* 8.5, 1.5 ArylCH), 7.47-7.42 (1H, m, ArylCH), 7.41-7.35 (1H, m, ArylCH), 7.23-7.17 (1H, m, ArylCH), 5.50-5.47 (1H, dd, *J* 7.0, 3.0, H4), 5.39-5.34 (1H, dd, *J* 6.0, 2.5, H3), 4.39-4.31 (2H, q, *J* 7.0, H12), 4.09-4.03 (1H, d, *J* 7.0, OH), 3.92-3.84 (4H, m, H1, Ha), 3.69-3.55 (2H, m, Ha), 3.47-3.31 (2H, m, H2), 3.17-3.11 (1H, d, *J* 6.0, OH), 1.44-1.38 (3H, t, *J* 7.0, H13) 1.10-1.01 (21H, m, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 173.0 (C=O), 154.5 (C=O), 140.2 (C), 139.7 (C), 131.1 (C), 125.5 (CH), 124.4 (CH), 123.0 (C), 122.7 (C), 120.6 (CH), 118.7 (CH), 118.4 (CH), 108.4 (CH), 108.1 (CH), 74.6 (CH), 74.4 (CH), 61.9 (C[1]$H_2$), 46.5 (C[2]$H_2$), 43.2 (C[a]$H_2$), 39.9 (C[a]$H_2$), 37.5 (C[12]$H_2$), 17.9 (C[13]$H_3$), 13.8 ($CH_3$), 11.8 (CH); HRMS found m/z (ESI-$H^+$) 590.3021 $C_{31}H_{45}N_3O_5SiNa^+$ required 590.3021, Δppm +0.1, mp 64-65 °C (MeOH; $CH_2Cl_2$).

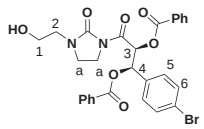
**(*rac*)-1-[3-(4-Bromo-phenyl)-2,3-dihydroxy-propionyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (68)** **62** cleaved using standard cleavage method.



$R_f$ 0.2 ($SiO_2$; 1:9 MeOH:$CH_2Cl_2$); $\nu_{max}$ (neat) 3397m bs (alcohol), 1714m (amide), 1671m (amide), 1264m, 1071s, 721m $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$:$CD_3OD$ (1:1)) 7.15-7.09 (4H, m, H5, H6), 5.09-5.06 (1H, d, *J* 2.0, H4), 4.80-4.77 (1H, *d*, J 2.0, H3), 3.65-3.56 (1H, m, Ha), 3.55-3.48 (1H, m, Ha′), 3.45-3.38 (2H, t, *J* 5.3 H1), 3.36-3.24 (2H, m, Ha), 3.16-3.03 (2H, m, H2); $\delta_C$ (125 MHz; $CDCl_3$:$CD_3OD$ (1:1)) 172.3 (C=O), 154.4 (C=O), 140.1 (C-C), 130.3 (CH), 127.6 (CH), 120.4 (C-Br), 73.9 (CH), 72.7 (CH), 58.7 (C[1]$H_2$), 45.5 (C[2]$H_2$), 41.8 (C[a]$H_2$), 39.3 (C[a]$H_2$); HRMS found m/z (ESI-$H^+$) 373.0395 $C_{14}H_{18}{}^{79}BrN_2O_5{}^+$ required 373.0394, Δppm +0.295; mp 132-135 °C (MeOH:$CH_2Cl_2$).

## 6.3 Diversity generating reactions from diols

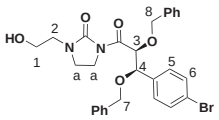
**(*rac*)-1-[2,3-Bis-benzoyloxy-3-(4-bromo-phenyl)-propionyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (69)** A round-bottom flask, equipped with a magnetic stirrer, containing **62** (50 mg, 0.09 mmol), EDC (40 mg, 0.11 mmol), DMAP (1.4 mg, 0.01 mmol) and $CH_2Cl_2$ (2 ml) at room temperature was charged with benzoic acid (34 mg, 0.21 mmol) in $CH_2Cl_2$ (1 ml). The mixture was stirred at room temperature for 6 hours. $NaHCO_3$ solution was added and the resulting phases separated, the aqueous layer extracted with $CH_2Cl_2$ (× 3), the organic layers combined, washed with NaCl solution, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography to give the TIPS protected title compound (50.2 mg, 78 %) as a white solid. Using the general method for cleavage of the TIPS group gave the title compound was obtained as a white solid (38 mg, 97 %) after flash column chromatography.



$R_f$ 0.34 ($SiO_2$; 1:9 MeOH: $CH_2Cl_2$); $\nu_{max}$ (neat) 2914w br (alcohol) 1718s (amide), 1395m, 1245s, 1068m, 710s $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 8.16-8.06 (2H, m, ArylCH), 8.06-8.04 (2H, m, ArylCH), 7.60-7.56 (4H, m, ArylCH), 7.55-7.43 (6H, m, 6 ArylCH), 6.85-6.83 (1H, d, *J* 2.5, H4), 6.72-6.70 (1H,

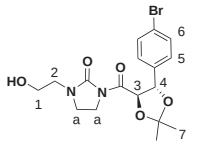
d, $J$ 2.5, H3), 3.95-3.84 (3H, m, H1, Ha), 3.75-3.66 (1H, m, Ha), 3.66-3.55 (2H, m, Ha), 3.59-3.44 (2H, m, H2); $\delta_C$ (100 MHz; $CDCl_3$) 166.3 (C=O), 165.7 (C=O), 165.6 (C=O), 155.0 (C=O), 135.4 (C-C), 133.5 (CH), 133.4 (CH), 131.5 (CH), 130.0 (CH), 129.9 (CH), 128.6 (C), 129.2 (C), 128.4 (2 × CH), 128.4 (CH), 128.2 (CH), 122.4 (C), 75.0 (CH), 73.3 (CH), 60.8 (C[1]$H_2$), 46.7 (C[2]$H_2$), 42.9 (C[a]$H_2$), and 39.8 (C[a]$H_2$); HRMS found m/z (ESI-$H^+$) 581.0920 $C_{28}H_{25}{}^{79}BrN_2O_7{}^+$ required 581.0918, $\Delta$ ppm +0.344; mp 77 °C (MeOH: $CH_2Cl_2$).

**(*rac*)-1-[2,3-Bis-benzyloxy-3-(4-bromo-phenyl)-propionyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (70)** A round-bottom flask, equipped with a magnetic stirrer, containing **62** (50 mg, 0.09 mmol), silver (I) oxide (218 mg, 0.94 mmol) and $CH_2Cl_2$ (2.5 ml) was charged with benzyl bromide (77 $\mu$L, 0.94 mmol). The mixture was heated at reflux for 16 hours. After this time period the solvent had evaporated leaving a black viscous oil that was taken up in $CH_2Cl_2$, filtered and the solvent removed *in vacuo*. The crude compound was purified by column chromatography to give the TIPS protected dibenzyl alcohol as a colourless oil (51.2 mg, 77 %). Using the general method for cleavage of the TIPS group gave the title compound as a colourless viscous oil (27 mg, 81 %) after flash column chromatography.



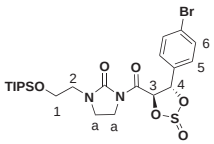

$R_f$ 0.4 ($SiO_2$; 1:9 MeOH: $CH_2Cl_2$); $\nu_{max}$ (neat) 3450w br (alcohol), 1721s (amide), 1486m, 1404m, 1258s, 1071s, 746m, 700m $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.51-7.49 (2H, m, ArylCH), 7.39-7.36 (2H, m, ArylCH), 7.34-7.25 (5H, m, ArylCH), 7.19-7.13 (3H, m, ArylCH), 6.96-6.92 (2H, m, ArylCH), 5.23-5.19 (1H, d, $J$ 3.5, H4), 4.88-4.85 (2H, d, $J$ 3.5, H3), 4.72-4.71 (1H, d, $J$ 12.5, H8), 4.70-4.64 (1H, d, $J$ 12.0, H7), 4.28-4.24 (1H, d, $J$ 12.0, H7′), 4.16-4.12 (1H, d, $J$ 12.5, H8′), 3.80-3.66 (3H, m, H1, Ha), 3.52-3.44 (1H, m, Ha), 3.44-3.37 (1H, m, HaB), 3.31-3.16 (3H, m, Ha, H2); $\delta_C$ (100 MHz; $CDCl_3$); 169.7 (C=O), 154.7 (C=O), 138.0 (CH), 137.4 (C), 137.2 (C), 129.6 (CH), 128.8 (CH), 128.1 (CH), 128.0 (CH), 128.0 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 121.6 (C), 81.0 (CH), 78.5 (CH), 72.9 ($CH_2$), 70.6 ($CH_2$), 60.8 (C[1]$H_2$), 46.6 (C[2]$H_2$), 42.8 (C[a]$H_2$), and 39.7 (C[a]$H_2$); HRMS found m/z (ESI-$H^+$) 553.1333 $C_{28}H_{30}{}^{79}BrN_2O_5{}^+$ required 553.1333, $\Delta$ ppm +0.000.

**(*rac*)-1-[5-(4-Bromo-phenyl)-2,2-dimethyl-[1,3]-dioxolane-4-carbonyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (71)** A round-bottom flask, equipped with a magnetic stirrer containing **62** (178 mg, 0.33 mmol), *p*-toluene sulphonic acid (3 mg, 0.02 mmol), powdered activated 4Å molecular sieves (10 mg) and DMF (0.67 ml) was charged with 2,2-dimethoxypropane (1.94 ml, 15.7 mmol). The mixture was at 100 °C for 2 hours. After this time period the reaction was complete by TLC ($SiO_2$2:8 EtOAc: Petrol). The mixture was allowed to cool to room temperature, diluted with ether, washed with water (× 3), the organic layer dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product that was purified by flash column chromatography to give the TIPS protected title compound (152 mg, 80 %) as a colourless oil. Using the general method for cleavage of the TIPS group gave the title compound as a white solid (20 mg, 87 %) after flash column chromatography.




$R_f$ 0.25 ($SiO_2$; EtOAc); $\nu_{max}$ (neat) 3423w br (alcohol), 2989w, 2921w, 1727m (amide), 1702m, 1682m, 1477w, 1414m, 1239m, 1044s, 1010s, 816m $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.45-7.49 (2H, m, H6), 7.28-7.33 (2H, m, H5), 5.49-5.53 (1H, d, $J$ 7.5, H4), 5.39-5.43 (1H, d, $J$ 7.5, H3), 3.95-3.82 (2H, m, Ha), 3.79-3.71 (2H, m, H1), 3.59-3.50 (2H, t, $J$ 8.0, Ha), 3.45-3.40 (1H, m, H2), 3.32-3.26 (1H, m, H2′), 1.59 (3H, s, H7), 1.58 (3H, s, H7′); $\delta_C$ (100 MHz; $CDCl_3$) 168.8 (C=O), 157.0 (C=O), 136.4 (C-C), 131.6 (CH), 128.6 (CH), 123.3 (C-Br), 111.4 (C-C), 79.6 (CH), 78.9 (CH), 60.7 (C[1]$H_2$), 46.6 (C[2]$H_2$), 42.4 (C[a]$H_2$), 39.9 (C[a]$H_2$), 27.1 ($CH_3$), 26.4 ($CH_3$); HRMS found m/z (ESI-$Na^+$) 435.0529 $C_{17}H_{21}{}^{79}BrN_2O_5Na^+$ required 435.0526, $\Delta$ ppm −0.689; mp 120-122 °C (EtOAc: Petrol).

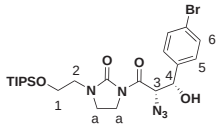
**(*rac*)-1-[5-(4-Bromo-phenyl)-2-oxo-2[4-[1,3,2]-dioxathiolane-4-carbonyl]]-3-(2-triisopropyl-silanyloxy-ethyl)-imidazolidin-2-one (72)** A round-bottom flask, equipped with a magnetic stirrer, containing **62** (281 mg, 0.53 mmol), pyridine (0.13 ml, 1.59 mmol) and $CH_2Cl_2$ (2 ml) at 0 °C was charged with thionyl chloride (0.05 ml, 0.69 mmol) over 15 minutes. The mixture was stirred at 0 °C for 1 hour. The mixture was filtered through a plug of silica gel, the silica washed with 1:1 EtOAc: Petrol and the solvent removed *in vacuo* to give the title compound (270 mg, 88 %) as a 1:2.5 mixture of diastereoisomers as a yellow oil. The cyclic sulphite was used without further purification.




$R_f$ 0.75 ($SiO_2$; EtOAc: Petrol 1:1); $\nu_{max}$ (neat) 2942m, 2866m, 1732s (amide), 1689m (amide), 1400w br, 1275m, 1217m, 735w $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.62-7.30 (8H, m, 2 × (4 × ArylCH) major and minor), 6.53-6.47 (1H, d, $J$ 3.5, H4 major), 6.44-6.40 (1H, d, $J$ 7.5, H4 minor), 5.97-5.93 (1H, d, $J$ 7.5, H3 minor), 5.70-5.67 (1H, d, $J$ 3.5, H3 major), 3.99-3.79 (8H, m, 2 × (H1 and Ha) major and minor), 3.76-3.61 (4H, m, 2 × Ha major and minor), 3.47-3.31 (4H, m, 2 × H2 major and minor), 1.16-0.95 (42H, m, 2 × TIPS major and minor); $\delta_C$ (120 MHz; $CDCl_3$) 166.3 (C=O, major), 164.9 (C=O, minor), 153.8 (C=O, major), 153.4 (C, major), 134.8 (C, major), 123.5 (CH, minor), 132.2 (CH, minor), 131.7 (CH, major), 129.4 (CH, major), 128.9 (CH, minor), 123.8 (C, minor), 123.3 (C, major), 85.7 (CH, major), 83.4 (CH, major), 82.4 (CH, minor), 82.0 (CH, minor), 61.8 (C[1]$H_2$, major and minor), 46.5 (C[2]$H_2$, major and minor), 43.2 (C[a]$H_2$, major), 42.9 (C[a]$H_2$, minor), 40.2 (C[a]$H_2$, major), 39.9 (C[a]$H_2$, minor), 17.9 ($CH_3$, major and minor), 11.8 (CH, major and minor); HRMS found m/z (ESI-$H^+$) 592.1510 $C_{23}H_{39}{}^{79}BrN_3O_6SSi^+$ required 592.107, $\Delta$ ppm +0.566.

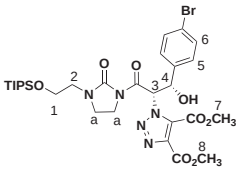
**(*rac*)-1-[2-Azido-3-(4-bromo-phenyl)-3-hydroxy-propionyl]-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (73)** A round-bottom flask, equipped with a magnetic stirrer containing **72** (77 mg, 0.13 mmol),

powdered activated 4Å molecular sieves (10 mg) and DMF (2 ml) at 0 °C was charged with sodium azide (14 mg, 0.2 mmol). The reaction mixture was stirred at 70 °C for 14 hours. The orange/brown solution was allowed to cool to room temperature, diluted with $Et_2O$, washed with saturated aqueous $NaHCO_3$ solution (× 3), washed with water (× 2), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography to give the title compound as an orange solid (40 mg, 42 %).



$R_f$ 0.34 ($SiO_2$; 3:7 EtOAc: Petrol); $\nu_{max}$ (neat) 3453w br (alcohol), 2943m, 2867m, 2105s (azide), 1733s (amide), 1685m (amide), 1271.4m, and 1110m $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.54-7.45 (2H, d, *J* 8.5, H6), 7.26-7.19 (2H, d, *J* 8.5, H5), 5.32-5.24 (1H, br d, *J* 6.5, H4), 4.97-4.92 (1H, d, *J* 6.5, H3), 4.15-3.97 (1H, br s, OH), 3.94-3.77 (4H, m, H1, Ha), 3.37-3.66 (2H, m, Ha), 3.49-3.37 (2H, m, H2), 1.18-0.98 (21H, m, TIPS); $\delta_C$ (500 MHz; $CDCl_3$) 171.05 (C=O), 154.47 (C=O), 134.55 (C-C), 131.65 (CH), 129.91 (CH), 122.79 (C-Br), 72.87 (C[3]H), 65.99 (C[4]H), 61.81 (C[1]$H_2$), 46.61 (C[2]$H_2$), 43.29 (C[a]$H_2$), 39.96 (C[a]$H_2$), 17.94 ($CH_3$), 11.84 (CH); HRMS found m/z (ESI-$H^+$) 554.1790 $C_{23}H_{37}{}^{79}BrN_5O_4Si^+$ required 554.1793, Δ ppm −0.541; mp 88-92 °C (EtOAc: Petrol).

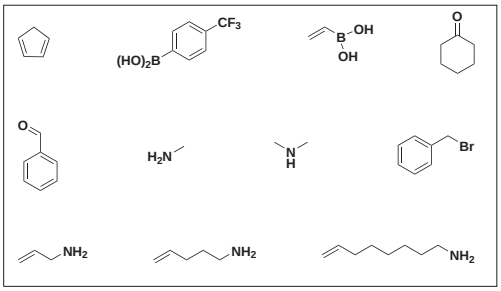
**(*rac*)-1-1-[(4-Bromo-phenyl)-hydroxy-methyl]-2-oxo-2-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-1-yl]-ethyl-1H-[1,2,3]triazole-4,5-dicarboxylic acid dimethyl ester (74)** A round bottom flask, equipped with a magnetic stirrer, containing the **73** (140 mg, 0.25 mmol) and toluene (1 ml) was charged with dimethyl acetylenedicarboxylate (0.15 ml, 1.25 mmol). The solution was stirred at 65 °C for 5 hours. After this time period the reaction was complete by TLC (3:7 EtOAc: Petrol). The solution was cooled to room temperature and the solvent was removed *in vacuo* to give the crude product that was purified by column chromatography to give the title compound (91 mg, 52 %) as a pale orange oil.



$R_f$ 0.14 ($SiO_2$; EtOAc: Petrol); $\nu_{max}$ (neat) 3446w br (alcohol), 2944m, 2867m, 1732s (amide), 1685m (amide), 1452m, 1271m, 1074m $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.53-7.42 (2H, d, *J* 8.5, H6), 7.44-7.40 (2H, d, *J* 8.5, H5), 6.47-6.42 (1H, d, *J* 10.0, H3), 5.95-5.89 (1H, dd, *J* 10.0 and 5.5, H4), 4.94-4.90 (1H, d, *J* 5.5, OH), 3.98-3.92 (6H, s, H7, H8), 3.90-3.86 (2H, t, *J* 5.0, H1), 3.78-3.64 (4H, m, Ha), 3.45-3.40 (2H, m, H2), 1.14-1.02 (21H, m, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 169.3 (C=O), 160.5 (C=O), 158.7 (C=O), 155.1 (C=O), 134.4 (C), 131.8 (CH), 130.4 (CH), 126.4 (C), 123.2 (C-Br), 71.4 (C[3]H), 63.0 (C[4]H), 61.7 (C[1]$H_2$), 53.3 ($CH_3$), 52.6 ($CH_3$), 46.6 (C[2]$H_2$), 43.4 (C[a]$H_2$), 39.8 (C[a]$H_2$), 17.9 ($CH_3$), 11.8 (CH); HRMS found m/z (ESI-$H^+$) 696.2064 $C_{29}H_{43}{}^{79}BrN_5O_8Si^+$ required 696.2059, Δ ppm +0.718.

# 7 Branching pathway 3 General Procedure Enantioselective Diels-Alder Reaction

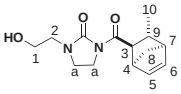
## 7.1 Building blocks used



## 7.2 Enantioselective Diels Alder reaction on solid support

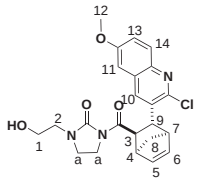
S-S-ligand (0.5 equiv.), copper (II) triflate (0.4 equiv.) and activated 4 Å molecular sieves in $CH_2Cl_2$ were stirred under nitrogen at room temperature to give a blue/green solution for 30 minutes and then added to the solid supported alkene (1 equiv.) which was suspended in $CH_2Cl_2$ (5 mL/g of beads). Freshly prepared cyclopentadiene (20 equiv.) was added to the reaction and the beads shaken for two weeks. The reaction was filtered and the beads washed with $CH_2Cl_2$ (× 3), $CH_2Cl_2$:MeOH (1:1, × 3), MeOH (× 3) and $CH_2Cl_2$ (× 3). The products were cleaved using the standard method.

**(1*S*, 2*S*, 3*R*, 4*R*)-1-(2-Hydroxy-ethyl)-3-(3-methyl-bicyclo[2.2.1]hept-5-ene-2-carbonyl)-imidazolidin-2-one (75)**



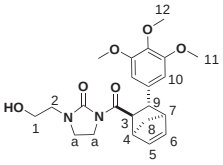
A yellow oil (35 mg, 79 %). $R_f$ 0.28 ($SiO_2$; 95:5 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3445 (OH), 1718s (C=O), 1672s (C=O) $cm^{-1}$; $\delta_H$ (500 MHz; $C_6D_6$) 6.47 (1H, dd, *J* 5.5, 3.0, H6), 6.09 (1H, dd, *J* 5.5, 3.0, H5), 4.07 (1H, t, *J* 3.5, H3), 3.66 (1H, br s, H4), 3.46-3.35 (4H, m, H1, Ha), 3.04-2.98 (2H, m, Ha), 2.61-2.51 (3H, m, H2, H7), 2.47 (1H, br s, H9), 1.80 (1H, br d, *J* 8.5, H8), 1.59 (1H, dd, *J* 8.5, 2.0, H8′), 1.22 (3H, d, *J* 7.0 , H10); $\delta_C$ (125 MHz; $C_6D_6$) 173.67 (C=O), 155.52 (C=O), 139.24 (C[6]H), 131.51 (C[5]H), 60.52 (C[1]$H_2$), 50.99 (C[3]H), 49.86 (C[4]H), 48.04 (C[7]H), 47.16 (C[8]$H_2$), 46.58 (C[2]$H_2$), 41.46 (C[a]$H_2$), 40.14 (C[a]$H_2$), 36.31 (C[9]H), 20.47 (C[10]$H_3$); LCMS (ES+) 265 ($M+H^+$); HRMS $(M+Na)^+$ found 287.1369 $C_{14}H_{20}N_2O_3Na$ required 287.1372, Δ ppm −1.02; diastereomeric ratio 89:11 (*endo:exo*); 71 % e.e.; HPLC: AD-H, 10% MeOH/IPA, flow 1ml/min; retention time (1*S*, 2*R*, 3*R*, 4*R*) enantiomer 1.00 min, 1*R*, 2*S*, 3*S*, 4*S* enantiomer 1.24 min.

**(1*S*, 2*R*, 3*R*, 4*R*)-1-[3-(2-Chloro-6-methoxy-quinolin-3-yl)-bi-cyclo[2.2.1]-hept-5-ene-2-carbonyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (76)**



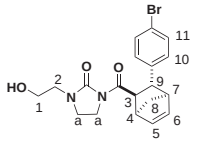
A yellow oil (50 mg, 53 %). $R_f$ 0.24 ($SiO_2$; 95:5 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3422 (OH), 1715 (C=O), 1674 (C=O), 1235s (C-O) $cm^{-1}$; $\delta_H$ (500 MHz; $C_6D_6$) 8.01 (1H, s, H10), 7.99 (1H, d, *J* 9.0, H14), 7.23 (1H, dd, *J* 9.0, 3.0, H13), 6.75 (1H, d, *J* 3.0, H11), 6.64 (1H, m, H6), 6.27 (1H, m, H5), 5.00 (1H, m, H3), 4.13 (1H, d, *J* 5.0, H9), 3.73 (1H, br s, H4), 3.50-3.37 (7H, m, H12, Ha, H1), 3.04-2.99 (3H, m, H7, Ha), 2.68-2.62 (2H, m, H2), 1.88 (1H, d, *J* 8.5, H8), 1.62 (1H, d, *J* 9.0, H8′); $\delta_C$ (125 MHz; $C_6D_6$) 172.67 (C=O), 158.23 (C), 155.52 (C=O), 149.92 (C), 142.47 (C), 138.41 (C[6]H), 136.63 (C), 133.96 (CH), 133.69 (C[5]H), 129.69 (CH), 128.68 (CH), 122.23 (CH), 105.09 (C[12]$H_3$), 60.32 (C[1]$H_2$), 54.92 (C[3]H), 49.68 (C[9]H), 48.17 (C[4]H), 47.86 (C[8]$H_2$), 47.25 (C[7]H), 44.90 (C[2]$H_2$), 41.46 (C[a]$H_2$), 40.20 (C[a]$H_2$); LCMS (ES+) 442 ($M+H^+$); HRMS $(M+Na)^+$ found 464.1342 $C_{23}H_{24}ClN_3O_4Na$ required 464.1353, $\Delta$ ppm −2.4; diastereomeric ratio 78:22 (*endo:exo*); 96 % e.e. ; HPLC: OJ-H, 20% MeOH/IPA, flow 1ml/min; retention time (1*S*, 2*R*, 3*R*, 4*R*) enantiomer 1.16 min, 1*R*, 2*S*, 3*S*, 4*S* enantiomer 1.28 min.

**(1*S*, 2*R*, 3*R*, 4*R*)-1-(2-Hydroxy-ethyl)-3-[3-(3,4,5-trimethoxy-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carbonyl]-imidazolidin-2-one (77)**



A yellow oil (63 %). $R_f$ 0.23 ($SiO_2$; 95:5 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3453 (OH), 1719 (C=O), 1676 (C=O), 1123 (C-O) $cm^{-1}$; $\delta_H$ (500 MHz; $C_6D_6$) 6.82 (2H, s, H10), 6.64 (1H, dd, *J* 5.5, 3.0, H6), 6.21 (1H, dd, *J* 5.5, 3.0, H5), 4.85 (1H, dd, *J* 5.0, 3.5, H9), 3.92 (3H, s, H12), 3.85 (1H, d, *J* 4.0, H3), 3.81 (1H, s, H4), 3.62 (1H, s, OH), 3.59 (6H, s, H11), 3.46-3.41 (4H, m, H1, Ha), 3.05-3.02 (3H, m, H2, H7), 2.75-2.59 (2H, m, Ha), 2.22 (1H, d, *J* 8.0, H8), 1.74 (1H, d, *J* 8.0, H8′); $\delta_C$ (125 MHz; $C_6D_6$)173.46 (C=O), 155.31 (C=O), 153.93 (C), 140.16 (C), 139.70 (C[10]H), 137.81 (C), 137.51 (C), 132.72 (C[6]H), 128.09 (C[5]H), 105.79 ($CH_3$), 60.30 (C[1]$H_2$), 55.74 ($CH_3$), 50.93 (C[3]H), 50.46 (C[9]H), 48.49 (C[8]$H_2$), 47.93 (C[4]H), 47.61 (C[7]H), 46.46 (C[2]$H_2$), 41.36 (C[a]$H_2$), 40.12 (C[a]$H_2$); LCMS (ES+) 417 ($M+H^+$); HRMS $(M+H)^+$ found 417.2021 $C_{22}H_{26}N_2O_6$ requires 417.2026, $\Delta$ ppm −1.1; diastereomeric ratio 79:21 (*endo:exo*); HPLC - racemic compound inseparable under conditions tried. Columns: Chiralpak OD; AD; AS; AD-H. Solvent; 90:10 Hexane:IPA; 95:5 Hexane:IPA; 98:2 Hexane:IPA. Flow 1mL/min.

**(1*S*, 2*R*, 3*R*, 4*R*)-1-[3-(4-Bromo-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carbonyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (78)**

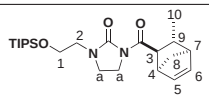
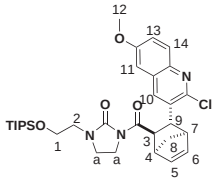
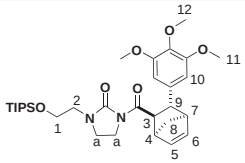
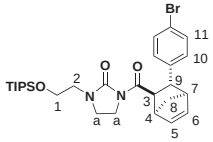


A white solid (64 %). $R_f$ 0.22 ($SiO_2$; 95:5 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3458 (OH), 1720 (C=O), 1671 (C=O) $cm^{-1}$; $\delta_H$ (500 MHz; $C_6D_6$) 7.34 (2H, d, *J* 8.5, H11), 7.12 (2H, d, *J* 8.5, H10), 6.52 (1H, dd, *J* 5.5, 3.0, H6), 6.14 (1H, dd, *J* 8.5, 3.0, H5), 4.62 (1H, dd, *J* 5.5, 3.0, H3), 3.79 (1H, s, H4), 3.72 (1H, br d , *J* 5.0, H9), 3.38-3.32 (4H, m, H1, Ha), 2.97 (2H, t, *J* 5.5, H2), 2.80 (1H, s, H7), 2.59-2.47 (2H, m, Ha), 1.94 (1H, d, *J* 8.5, H8), 1.61 (1H, d, *J* 8.5, H8′); $\delta_C$ (125 MHz; $C_6D_6$) 172.98 (C=O), 155.23 (C=O), 143.84 (C), 139.64 (C[6]H), 132.65 (C), 131.59 (C[5]H), 129.60 (C[11]H), 128.09 (C[10]H), 60.47 (C[1]$H_2$), 50.89 (C[3]H), 49.93 (C[9]H), 48.14 (C[8]$H_2$) 48.05 (C[4]H), 46.91 (C[7]H), 46.31 (C[2]$H_2$), 41.32 (C[a]$H_2$), 40.51 (C[a]$H_2$); LCMS (ES+) 407 ($M+H^+$); HRMS $(M+Na)^+$ found 427.0634 $C_{19}H_{21}BrN_2O_3Na$ requires 427.0633, $\Delta$ ppm +0.1; diastereomeric ratio 85:19 (*endo:exo*); 95.5 % e.e.; HPLC: OJ-H, 20% MeOH/IPA, flow 1ml/min; retention time (1*S*, 2*R*, 3*R*, 4*R*) enantiomer 1.15 min, 1*R*, 2*S*, 3*S*, 4*S* enantiomer 1.28 min.

### 7.2.1 General procedure for the enantioselective Diels Alder reaction in solution phase.

S-S-ligand (0.5 equiv.), copper (II) triflate (0.4 equiv.) and activated 4 Å molecular sieves in $CH_2Cl_2$ (8 mL) were stirred under nitrogen at room temperature to give a blue/green solution. The alkene (1 equiv.) was dissolved in $CH_2Cl_2$ (2 mL) and was added to the reaction followed by cyclopentadiene (20 equiv). The reaction was monitored by LCMS until complete conversion had occurred. The reaction was filtered and solvent removed *in vacuo*.[1] The crude product was purified by flash column chromatography to yield the desired products as brown oils.

[1]Diastereoselectivities were determined by NMR studies of the crude product

| Number | Product | *Endo*[a] | *Exo* | e.r. [b] |
|---|---|---|---|---|
| **79** |  | 89 | 11 | [c] |
| **80** |  | 81 | 19 | 98:2 |
| **81** |  | 79 | 21 | [d] |
| **82** |  | 87 | 13 | 83:17 |

[a]Determined from ratio of the integrals of the alkene protons between 5.9 and 6.7 ppm in the crude 500 MHz NMR

[b]calculated for the deprotect compound, NMR data matched that of the compound prepared on solid phase

[c]HPLC - racemic compound inseparable under conditions tried. Columns: Chiralpak OD; AD; AS; AD-H. Solvent; 90:10 Hexane:IPA; 95:5 Hexane:IPA; 98:2 Hexane:IPA. Flow 1mL/min.

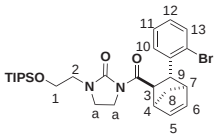
[d]HPLC - racemic compound inseparable under conditions tried. Columns: Chiralpak OD; AD; AS; AD-H. Solvent; 90:10 Hexane:IPA; 95:5 Hexane:IPA; 98:2 Hexane:IPA. Flow 1mL/min.

Cleavage of the TIPS group using the standard conditions generated products identical to the solid phase reaction.

### 7.2.2 General procedure for racemic Diels-Alder reaction

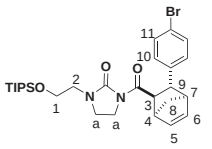
To a solution of **22-29** (1 equiv.) in $CH_2Cl_2$ (1 g in 10 ml) at −78 °C under an atmosphere of nitrogen was added dimethylaluminium chloride (1M in toluene, 1.4 equiv.) and cyclopentadiene (10 equiv.). The yellow reaction was stirred at −78 °C for one hour and then warmed to room temperature until complete by TLC. The reaction was quenched by addition of saturated ammonium chloride solution and extracted with $CH_2Cl_2$. The organic layer was washed with brine, dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield:

**(1*S**, 2*R**, 3*R**, 4*R**)-1-[3-(2-Bromo-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carbonyl]-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (83)**



A colourless oil (563 mg, 100 %); $R_f$ 0.34 ($SiO_2$; 10:2 hexane: ethyl acetate); $\nu_{max}$ (neat) 2942, 2865, 1720 (C=O), 1679 (C=O), 1482, 1467, 1432, 1391, 1354, 1333, 1262, 1243, 1107, 727 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.53 (1H, dd, *J* 7.0, 1.5, H13), 7.41 (1H, dd, *J* 7.5, 2.0, H10), 7.22 (1H, dt, *J* 7.5, 1.5, H11), 7.02 (1H, dt, *J* 7.5, 1.5, H12), 6.51 (1H, dd, *J* 5.5, 3.0, H6), 5.97 (1H, dd, *J* 5.5, 3.0, H5), 4.55 (1H, dd, *J* 5.0, 3.0, H9), 3.88-3.82 (2H, m, H1), 3.76 (2H, t, *J* 8.0, Ha), 3.58-3.53 (3H, m, Ha, H3), 3.40-3.37 (3H, m, H4, H2), 2.93 (1H, s, H7), 1.80 (1H, d, *J* 8.5, H8), 1.48 (1H, ddd, *J* 8.5, 2.0, 1.5, H8′), 1.04 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 172.75 (C=O), 154.86 (C=O), 143.04 (C), 138.62 (C[6]H), 133.16 (C[5]H), 133.06 (C[13]H), 127.93 (C[10]H), 127.93 (C[11]H), 127.24 (C[12]H), 126.20 (C), 61.87 (C[1]$H_2$), 50.30 (C[7]H), 47.75 (C[4]H), 47.28 (C[3]H), 47.06 (C[9]H), 46.47 (C[2]$H_2$), 42.55 (C[a]$H_2$), 40.25 (C[a]$H_2$), 17.94 (C[TIPS]$H_3$), 11.82 (C[TIPS]H); LCMS (ES+) 563 ($M+H^+$): HRMS $(M+Na)^+$ found 583.1969 $C_{28}H_{41}BrN_2O_3SiNa$ required 583.1968, Δ ppm +0.3.

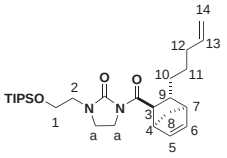
**(1*S**, 2*R**, 3*R**, 4*R**)-1-[3-(4-Bromo-phenyl)-bicyclo[2.2.1]-hept-5-ene-2-carbonyl]-3-(2-triisopropylsilanyloxy-ethyl) -imidazolidin-2-one (84)**



A colourless oil (3.07 g, 97 %); $R_f$ 0.33 ($SiO_2$; 10:2 hexane: ethyl acetate); $\nu_{max}$ (neat) 2941, 2865, 1723,(C=O), 1673 (C=O), 1488, 1413, 1383, 1354, 1264, 1246, 1107 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.39 (2H, d, *J* 7.5, H10), 7.25 (2H, d, *J* 7.5, H11), 6.50 (1H, dd, *J* 5.5, 3.0, H6), 5.92 (1H, dd, *J* 5.5, 3.0, H5), 4.31 (1H, dd, *J* 5.0, 3.0, H9), 3.90-3.76 (4H, m, H1, Ha), 3.63-51 (2H, m, Ha), 3.42-3.38 (3H, m, H3, H2), 3.31 (1H, d, *J* 4.5, H4), 2.91 (1H, s, H7), 1.91 (1H, d, *J* 8.5, H8), 1.54 (1H, d, *J* 8.5, H8′), 1.04 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 174.3 (C=O), 155.17 (C=O),

143.88 (C), 139.88 (C[6]H), 132.68 (C[5]H), 131.74 (C[10]H), 129.82 (C[11]H), 120.11 (C-Br), 62.32 (C[1]$H_2$), 50.68 (C[7]H), 50.07 (C[4]H), 48.23 (C[3]H), 46.90 (C[9]H), 46.58 (C[2]$H_2$), 43.05 (C[a]$H_2$), 40.63 (C[a]$H_2$), 18.32 (C[TIPS]$H_3$), 12.23 (C[TIPS]H); LCMS (ES+) 563 ($M+H^+$): HRMS $(M+Na)^+$ found 583.1962 $C_{28}H_{41}BrN_2O_3SiNa$ required 583.1968, Δ ppm −1.0.

**(1*S**, 2*S**, 3*R**, 4*R**)-1-(3-Pent-4-enyl-bicyclo-[2.2.1]hept-5-ene-2-carbon-yl)-3-(2-triisopropyl-silanyloxy-ethyl)-imidazolidin-2-one (85)**

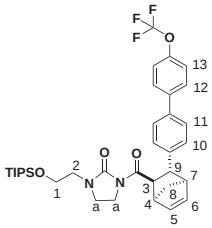


A colourless oil (107 mg, 94 %); $R_f$ 0.36 ($SiO_2$; 11:2 toluene: ethyl acetate); $\nu_{max}$ (neat) 2932, 2865, 1721 (C=O), 1676 (C=O), 1458, 1433, 1385, 1352, 1261, 1241, 1105 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.34 (1H, dd, *J* 5.5, 3.0, H6), 5.81-5.77 (2H, m, H5, H13), 4.98 (1H, dd, *J* 17.0, 2.0 H14), 4.91 (1H, dt, *J* 10.0, 1.0, H14′), 3.89 (2H, t, *J* 5.5, H1), 3.85-3.75 (2H, m, Ha), 3.70 (1H, dd, *J* 4.5, 3.5, H3), 3.59 (2H, m, Ha), 3.42 (2H, td, *J* 5.0, 1.0, H2), 3.24 (1H, s, H4), 2.61 (1H, s, H7), 2.03-2.00 (3H, m, H12, H9), 1.65 (1H, d, *J* 8.5, H8), 1.43-1.40 (5H, m, H10, H11, H8′), 1.06 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 174.81 (C=O), 154.82 (C=O), 139.15 (C[6]H), 139.01 (C[13]H), 131.52 (C[5]H), 114.33 (C[14]$H_2$), 62.03 (C[1]H), 49.98 (C[3]H), 47.61 (C[7]H), 47.53 (C[8]$H_2$), 47.37 (C[4]H), 46.49 (C[2]$H_2$), 42.67 (C[a]$H_2$), 42.19 (C[9]H), 40.22 (C[a]$H_2$), 35.19 (C[11]$H_2$), 34.05 (C[12]$H_2$), 28.18 (C[10]$H_2$), 17.95 (C[TIPS]$H_3$), 11.80 (C[TIPS]H); LCMS (APCI+) 475 ($M+H^+$); HRMS $(M+Na)^+$ found 497.3163 $C_{27}H_{46}N_2O_3SiNa$ required 497.3175, Δ ppm −2.4.

## 7.3 Diversity generating reactions from the norbornene

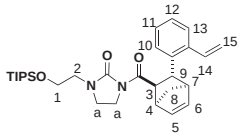
### 7.3.1 Suzuki Coupling

**(1*S**, 2*R**, 3*R**, 4*R**)-1-[3-(4′-trifluoromethoxy-biphenyl-4-yl)-bicyclo[2.2.1]hept-5-ene-2-carbonyl]-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (86)** To a solution of **84** (100 mg, 0.178 mmol), triphenylphosphine (2.3 mg, 5 mol%), palladium chloride (1.6 mg, 5 mol%), and 4-(trifluoromethoxy)phenylboronic acid (73 mg, 0.356 mmol) in DME (3 ml) was added 2 N sodium carbonate solution (3 ml). The reaction was heated to reflux for 2.5 hours (until complete by LCMS), cooled to room temperature, poured into water (15 ml) and extracted with ethyl acetate. The organic layer was washed with water, brine, dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield the title compounds as a yellow oil (116 mg, 100 %).



$R_f$ 0.50 ($SiO_2$; 10:3 hexane: ethyl acetate); $\nu_{max}$ (neat) 1724 (C=O), 1676 (C=O), 1256 (C-O) $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.54 (2H, d, *J* 8.5, H13), 7.45 (2H, d, *J* 8.0, H12), 7.35 (2H, d, *J* 8.0, H11), 7.24 (2H, d, *J* 8.0, H10), 6.51 (1H, dd, *J* 5.5, 2.5, H6), 5.95 (1H, dd, *J* 5.5, 2.5, H5), 4.36 (1H, dd, *J* 5.0, 3.0, H9), 3.89-3.80 (4H, m, H1, Ha), 3.64-3.55 (2H, m, Ha), 3.45 (1H, s, H4), 3.41-3.39 (3H, m, H3, H2), 2.99 (1H, s, H7), 1.95 (1H, d, *J* 8.5, H8), 1.55 (1H, d, *J* 9.0, H8) 1.02 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 174.87 (C=O), 154.76 (C=O), 144.98 (C), 139.61 (CH), 137.43 (C), 132.67 (CH), 128.28 (CH), 127.04 (CH), 121.17 (CH), 61.99 (C[1]$H_2$), 50.22 (C[9]H), 49.92 (C[4]H), 48.12 (C[8]$H_2$), 47.85 (C[7]H), 46.52 (C[2]$H_2$), 46.41 (C), 42.68 ($CH_2$), 40.26 ($CH_2$), 17.94 (C[TIPS]$H_3$), 11.83 (C[TIPS]H): LCMS (ES+) 643 ($M+H^+$); HRMS $(M+Na)^+$ found 665.3010 $C_{35}H_{45}N_2O_4F_3SiNa$ required 665.2998, Δ ppm +1.8.

**(1*S**, 2*R**, 3*R**, 4*R**)-1-(2-Triisopropylsilanyloxy-ethyl)-3-[3-(2-vinyl-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carbonyl]-imidazolidin-2-one (87)** To a solution of (**83**) (500 mg, 0.89 mmol), triphenylphosphine (40 mg, 10 mol%), palladium chloride (23 mg, 10 mol%), and vinylboronic acid (0.3 ml, 1.77 mmol) in dioxane (3 ml) was added 2 N sodium carbonate solution (5 ml). The reaction was heated to reflux for 2.5 hours (until complete by LCMS), cooled to room temperature, poured into water (15 ml) and extracted with ethyl acetate. The organic layer was washed with water, brine, dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield the title compounds as a yellow oil (200 mg, 44 %).



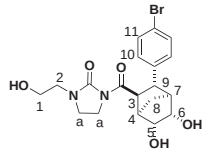
A colourless oil (200 mg, 44 %); $R_f$ 0.34 ($SiO_2$; 10:2 hexane: ethyl acetate); $\nu_{max}$ (neat) 2942, 2865, 1722 (C=O), 1675 (C=O), 1481, 1388, 1354, 1263, 1242, 1106 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.44 (1H, dd, *J* 7.5, 1.5, H13), 7.43 (1H, d, *J* 7.5, H10), 7.25 (1H, dt, *J* 7.5, 1.5, H12), 7.18 (1H, t, *J* 7.5, H11), 7.03 (1H, dd, *J* 17.0, 10.5, H14), 6.53 (1H, dd, *J* 5.5, 3.0, H6), 5.99 (1H, dd, *J* 5.5, 3.0, H5), 5.54 (1H, dd, *J* 17.0, 2.0, H15), 5.22 (1H, dd, *J* 10.5, 1.5, H15′), 4.37 (1H, dd, *J* 5.0, 3.5, H9), 3.90-3.87 (2H, m, H1), 3.86-3.78 (2H, m, Ha), 3.61-3.58 (2H, m, Ha), 3.53 (1H, d, *J* 4.5, H3), 3.42-3.39 (3H, m, H4, H2), 2.99 (1H, s, H7), 1.93 (1H, d, *J* 8.5, H8), 1.56 (1H, br d, *J* 8.5, H8′), 1.04 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 174.22 (C=O), 154.73 (C=O), 141.58 (C[14]H), 138.97 (C[6]H), 138.2 (C), 136.12 (C[5]H), 133.12 (C[13]H), 127.75 (C[10]H), 126.35 (CH), 126.20 (C), 125.81 (CH), 115.44 (C[15]$H_2$), 62.08 (C[1]$H_2$), 49.48 (C[3]H), 48.78 (C[9]H), 47.97 (C[8]$H_2$), 47.81 (C[4]H), 46.53 (C[2]$CH_2$), 43.37 (C[7]H), 42.69 (C[a]$CH_2$), 40.33 (C[a]$CH_2$), 17.93 (C[TIPS]$H_3$), 11.84 (C[TIPS]H); LCMS (APCI+) 509 ($M+H^+$); HRMS $(M+Na)^+$ found 531.3021 $C_{30}H_{44}N_2O_3SiNa$ required 531.3019, Δ ppm +0.4.

### 7.3.2 Dihydroxylation reaction solid phase

To a suspension of the solid supported norbornene (1 equiv.) in acetone and water (10:1, 5 mL/g of beads) was added NMO (2 equiv.) and the reaction stirred at room temperature under nitrogen. Osmium tetroxide 2.5 % solution in propanol

(3 mol%) was added and the reaction shaken for 48 hours. Aqueous sodium sulphate was added and the reaction shaken for 2 hours. The beads were filtered and washed with $CH_2Cl_2$ (× 3), $CH_2Cl_2$:MeoH (× 3), MeOH (× 3) and $CH_2Cl_2$ (× 3). The products were cleaved using the standard conditions to give:

**(1*R**, 2*S**, 3*R**, 4*S**, 5*S**, 6*R**)-1-[3-(4-Bromophenyl)-5,6-dihydroxy-bicyclo[2.2.1]heptane-2-carbonyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (88)**

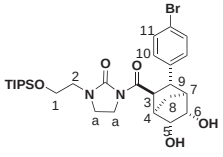


A white solid; $R_f$ 0.17 ($SiO_2$; 10:1 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3329 (OH), 2881, 1718 (C=O), 1670 (C=O), 1369, 1267, 1259, 1050 $cm^{-1}$; $\delta_H$ (500 MHz; 1:1 MeOD: $CDCl_3$) 7.37 (2H, d, *J* 8.5, H11), 7.08 (2H, d, *J* 8.5, H10), 4.04 (1H, dd, *J* 6.5, 4.5, H9), 3.93 (1H, d, *J* 6.0, H6), 3.94-3.83 (2H, m, Ha), 3.81 (1H, d, *J* 6.0, H5), 3.70 (2H, t, *J* 5.5, H1), 3.59-3.56 (2H, m, Ha), 3.38-3.36 (2H, m, H2), 3.28 (1H, d, *J* 6.5, H3), 2.64 (1H, s, H4), 2.31 (1H, s, H7), 1.98 (1H, d, *J* 11.0, H8), 1.69 (1H, d, *J* 11.0, H8′); $\delta_C$ (125 MHz; MeOD: $CDCl_3$) 172.91 (C=O), 154.77 (C=O), 143.71 (C-C), 131.33 (C[11]H), 129.42 (C[10]H), 119.56 (C-Br), 73.83 (C[6]H), 69.48 (C[5]H), 59.11 (C[1]$H_2$), 51.81 (C[3]H), 50.18 (C[7]H), 47.47 (C[4]H), 46.01 (C[2]$CH_2$), 43.34 (C[9]H), 41.66 (C[a]$CH_2$), 40.15 (C[a]$CH_2$), 32.41 (C[8]$H_2$); LCMS (ES+) 439 ($M+H^+$); HRMS $(M+H)^+$ found 439.0869 $C_{19}H_{23}BrN_2O_5$ required 439.0863, Δ ppm +1.4; mp 132-135 °C ($CH_2Cl_2$: MeOH).

### 7.3.3 Dihydroxylation reactions solution phase

To a solution of **84** (1 equiv.) in acetone and water (10:1) was added NMO (2 equiv.) and the reaction stirred at room temperature under nitrogen. Osmium tetroxide 2.5 % solution in propanol (3 mol%) was added and the reaction stirred until complete by TLC. Aqueous sodium sulphate was added and the reaction stirred for 30 minutes. The aqueous layer was extracted with ethyl acetate (× 3), dried ($MgSO_4$) and solvent removed *in vacuo*. The products were purified by flash column chromatography to yield:

**(1*R**, 2*S**, 3*R**, 4*S**, 5*S**, 6*R**)-1-[3-(4-Bromophenyl)-5,6-dihydroxy-bicyclo[2.2.1]heptane-2-carbonyl]-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (89)**



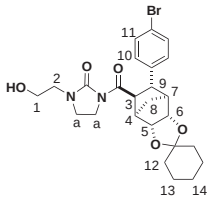
A white foam (895 mg, 93 %); $R_f$ 0.26 ($SiO_2$; 10:1 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3425 (OH), 2941, 2865, 1725 (C=O), 1669 (C=O), 1489, 1387, 1354, 1263, 1250, 1106, 1070, 1009 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.36 (2H, d, *J* 8.5, H11), 7.06 (2H, d, *J* 8.5, H10), 4.10-4.04 (2H, m, H3, H6), 3.91 (1H, d, *J* 6.0, H5), 3.86-3.79 (4H, m, Ha, H1), 3.60 (2H, t, *J* 5.5, H2), 3.48 (2H, s, OH), 3.45-3.30 (3H, m, Ha, H9), 2.71 (1H, s, H4), 2.34 (1H, s, H7), 1.90 (1H, d, *J* 10.5, H8), 1.73 (1H, d, *J* 10.5, H8′) 1.05 (21H, s TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 172.56 (C=O), 154.62 (C=O), 143.47 (C-C), 131.53 (C[11]H), 128.82 (C[10]H), 119.56 (C-Br), 74.43 (C[6]H), 70.29 (C[5]H), 62.01 (C[1]$H_2$), 51.49 (C[3]H), 50.53 (C[7]H), 47.65 (C[4]H), 46.56 (C[2]$H_2$), 43.38 (C[9]H), 42.61 (C[a]$H_2$), 40.18 (C[a]$H_2$), 32.76 (C[8]$H_2$), 17.94 (C[TIPS]$H_3$), 11.81 (C[TIPS]H); LCMS (ES+) 595 ($M+H^+$); HRMS $(M+H)^+$found 595.2196 $C_{28}H_{43}BrN_2O_5Si$ required 595.2197, Δ ppm −0.2.

Cleavage of the TIPS group using the standard conditions generated a white solid (40 mg, 70 %). Sprectra matched that of the solid phase route.

### 7.3.4 Acetal formations general procedure for solid phase synthesis

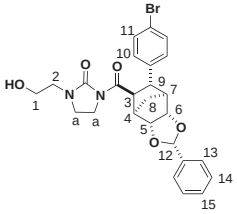
To a suspension of the diol (1 equiv.) in the aldehyde/ketone (10 equiv.) was added 4Å molecular sieves and catalytic *para*-toluene sulfonic acid. The reaction was shaken for two weeks then poured into water. The resin was separated from the excess reagents by filtration and washed with $CH_2Cl_2$ (× 3). The solid supported acetal (1 equiv.) was dissolved in THF (0.5 ml) and HF·Pyr (2.5 equiv.) was added. The vials were sealed and agitated for 2.5 h, then quenched using trimethylethoxysilane. The vials were agitated for a further 30 min to ensure complete quenching. The resin was removed by filtration and washed with $CH_2Cl_2$. The filtrate was filtered through a plug of silica gel (95:5 $CH_2Cl_2$: MeOH). The solvent was removed *in vacuo* and the product purified by flash column chromatography.

**(1*S**, 2*S**, 6*R**, 7*R**, 8*S**, 9*R**)-1-[9-(4-Bromo-phenyl)-4-cyclohexyl-3,5-dioxa-tri-cyclo[5.2.1.$0^{2,6}$]decane-8-carbonyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (90)**



A white foam. NMR data matched that of the solution phase reaction.

**(1*S**, 2*S**, 4*S**, 6*R**, 7*R**, 8*S**, 9*R**)-1-[9-(4-Bromo-phenyl)-4-phenyl-3,5-dioxa-tri-cyclo[5.2.1.$0^{2,6}$]decane-8-carbonyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (91)**

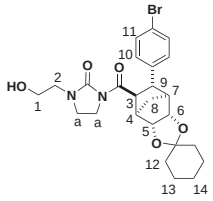


A colourless oil. NMR data matched that of the solution phase reaction.

### 7.3.5 Acetal formations general procedure for solution phase synthesis

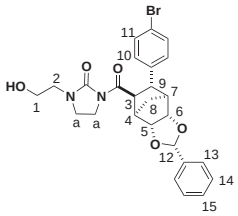
To a solution of **89** (1 equiv.) in the aldehyde/ketone (10 equiv.) was added 4Å molecular sieves and catalytic *para*-toluene sulfonic acid. The reaction was stirred until complete by LCMS then poured into water and extracted with $CH_2Cl_2$. The organic layer was dried ($MgSO_4$) and solvent removed *in vacuo*. The TIPS protected acetal (1 equiv.) was dissolved in THF (0.5 ml) and HF·Pyr (2.5 equiv.) was added. The vials were sealed and agitated for $2\frac{1}{2}$ hrs, then quenched using trimethylethoxysilane. The vials were agitated for a further 30 min to ensure complete quenching. Then the reaction mixture was filtered through a plug of silica gel (95:5 $CH_2Cl_2$: MeOH). The solvent was removed *in vacuo* and the product purified by flash column chromatography.

**(1*S**, 2*S**, 6*R**, 7*R**, 8*S**, 9*R**)-1-[9-(4-Bromo-phenyl)-4-cyclohexyl-3,5-dioxa-tri-cyclo[5.2.1.0$^{2,6}$]decane-8-carbonyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (90)**



A colourless oil (34 mg, 92 %); $R_f$ 0.32 ($SiO_2$; 95:5 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3265, 2929, 2857, 1718 (C=O), 1677 (C=O), 1480, 1447, 1390, 1359, 1270, 1100, cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.39 (2H, d, *J* 8.5, H11), 7.09 (2H, d, *J* 8.5, H10), 4.34 (1H, d, *J* 5.5, H5), 4.14 (1H, d, *J* 5.0, H6), 4.05 (1H, dd, *J* 6.0, 4.5, H9), 3.91-3.85 (2H, m, Ha), 3.81 (2H, t, *J* 5.0, H1), 3.61-3.54 (2H, m, Ha), 3.42 (2H, dt, *J* 5.5, 2.0, H2), 3.29 (1H, d, *J* 6.0, H3), 2.87 (1H, br d, *J* 3.0, H4), 2.50 (1H, s, H7), 1.93 (1H, dd, *J* 11.0, 1.5, H8), 1.70-1.30 (11H, m, H8′, CyH); $\delta_C$ (125 MHz; $CDCl_3$) 172.44 (C=O), 154.99 (C=O), 143.35 (C-C), 131.57 (C[11]H), 128.86 (C[10]H), 119.91 (C-Br), 109.96 (C), 81.50 (C[5]H), 77.89 (C[6]H), 60.80 (C[1]$H_2$), 50.88 (C[3]H), 47.13 (C[7]H), 46.77 (C[2]H2), 44.56 (C[4]H), 42.25 (C[9]H), 42.03 (C[a]$H_2$), 40.23 (C[a]H2), 35.19 (C[Cy]$H_2$), 33.62 (C[Cy]$H_2$), 32.48 (C[8]$H_2$), 25.24 (C[Cy]$H_2$), 24.09 (C[Cy]$H_2$), 23.65 (C[Cy]$H_2$); LCMS (ES+) 519 ($M+H^+$); HRMS $(M+H)^+$ found 519.1501 $C_{25}H_{32}BrN_2O_5$ required 519.1495, Δ ppm +1.3; mp 125 °C ($CH_2Cl_2$: MeOH).

**(1*S**, 2*S**, 4*S**, 6*R**, 7*R**, 8*S**, 9*R**)-1-[9-(4-Bromo-phenyl)-4-phenyl-3,5-dioxa-tri-cyclo[5.2.1.0$^{2,6}$]decane-8-carbonyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (91)**

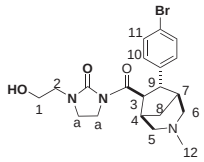


A white solid (10 mg, 47 %); $R_f$ 0.34 ($SiO_2$; 95:5 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 4337, 2932, 1724 (C=O), 1668 (C=O), 1489, 1395, 1355, 1263, 1066, 1009 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.54-7.49 (2H, m, ArH), 7.44-7.37 (5H, m, ArH), 7.12 (2H, d, *J* 8.5, H10), 5.63 (1H, s, H12), 5.31 (1H, s, OH), 4.42 (1H, d, *J* 5.5, H5), 4.25 (1H, d, *J* 5.5, H6), 4.13 (1H, dd, *J* 6.0, 4.5, H9), 3.93-3.89 (2H, m, Ha), 3.82 (2H, t, *J* 5.0, H1), 3.61-3.55 (2H, m, Ha), 3.42 (2H, t, *J* 5.0, H2), 3.35 (1H, d, *J* 6.0, H3), 3.04 (1H, s, H4), 2.67 (1H, s, H7), 2.12 (1H, d, *J* 11.0, H8), 1.76 (1H, d, *J* 11.0, H8′); $\delta_C$ (125 MHz; $CDCl_3$) 172.34 (C=O), 155.00 (C=O), 143.06 (C-C), 136.03 (C-C), 131.64 (CH), 129.53 (CH), 128.88 (CH), 128.42 (CH), 126.69 (CH), 120.04 (C-Br), 103.10 (C[12]H), 82.74 (C[5]H), 79.33 (C[6]H), 60.82 (C[1]$H_2$), 50.77 (C[3]H), 47.13 (C[7]H), 46.75 (C[2]H2), 44.45 (C[4]H), 42.34 (C[9]H), 42.26 (C[a]$H_2$), 40.26 (C[a]$H_2$), 32.84 (C[8]$H_2$); LCMS (APCI+) 527 ($M+H^+$); HRMS $(M+H)^+$ found 527.1183 $C_{26}H_{28}BrN_2O_5$ required 527.1182, Δ ppm +0.2. mp 125-126 °C.

### 7.3.6 General procedure for the oxidative cleavage, reductive amination reaction on solid support

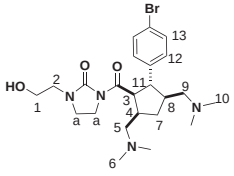
To a solution of the diol (1 equiv.) in THF: water (1:1, 6 mL/g of beads) was added sodium periodate (1.5 equiv.) at 0 °C. The reaction was shaken for 48 hours then the beads collected by filtration and dried under suction. The beads were suspended in dry $CH_2Cl_2$ (6 mL/g of beads) and methylamine 40 % solution in $H_2O$ (1 equiv.) was added. The reaction was shaken at room temperature for four hours then sodium triacetoxyborohydride (10 equiv.) was added and the reaction stirred overnight. The beads were collected by filtration and washed with $CH_2Cl_2$ (× 3), $CH_2Cl_2$:MeOH (1:1, × 3), THF (× 3) and DCM (× 3). The product was cleaved using the standard reactions conditions.

**(1*S**, 5*R**, 6*S**, 7*R**)-1-[7-(4-Bromo-phenyl)-3-methyl-3-aza-bicyclo[3.2.1]-octane-6-carbonyl]-3-(2-hydroxy-ethyl)-imida-zolidin-2-one (92)**



A yellow oil. NMR data matched that of the solution phase reaction.

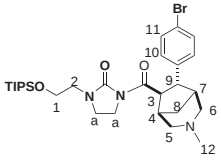
**(1*S**, 2*R**, 3*S**, 5*R**)-1-[2-(4-Bromo-phenyl)-3,5-bis-dimethylamino-methyl-cyclopentanecarbonyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (93)**



A yellow oil. NMR data matched that of the solution phase reaction.

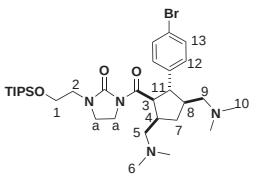
### 7.3.7 Oxidative cleavage, reductive amination reaction in solution phase

**(1$S^*$, 5$R^*$, 6$S^*$, 7$R^*$)-1-[7-(4-Bromo-phenyl)-3-methyl-3-aza-bicyclo[3.2.1]-octane-6-carbonyl]-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidin-2-one (94)** To a solution of **89** (140 mg, 0.2 mmol) in THF: water (1:1, 16 ml) was added sodium periodate (77 mg, 0.36 mmol) at 0 °C. The reaction was stirred for three hours then extracted with chloroform. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was dissolved in dry $CH_2Cl_2$ (10 ml) and methylamine 40 % solution in $H_2O$ (3 ml, 0.2 mmol) was added. The reaction was stirred at room temperature for one hour then sodium triacetoxyborohydride (593 mg, 2.8 mmol) was added and the reaction stirred overnight. The reaction was poured into water and extracted with chloroform. The organic layer was dried ($MgSO_4$), solvent removed *in vacuo* and the crude product purified by flash column chromatography to yield the title compound as a yellow oil (70 mg, 60 %).



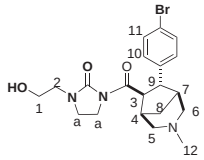

$R_f$ 0.38 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (neat) 2941, 2865, 1723 (C=O), 1681 (C=O), 1488, 1354, 1249, 1106 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 7.32 (2H, d, *J* 8.5, H11), 7.10 (2H, d, *J* 8.5, H10), 4.11-4.05 (2H, m, H1), 3.90-3.75 (4H, m, Ha), 3.55-3.49 (2H, m, H2), 4.30 (1H, d, *J* 6.0, H9), 4.17-4.06 (2H, m, H2), 3.32-3.27 (1H, m, H3), 3.14 (1H, d, *J* 8.5, H6), 2.87 (1H, s, H4), 2.77 (1H, d, *J* 11.5, H5), 2.43 (1H, d, *J* 10.0, H5′, H6′), 2.38 (3H, s, H12), 2.26 (1H, s, H7), 2.15-2.08 (1H, m, H8), 1.61 (1H, d, *J* 11.5, H8′), 0.99 (21H, s, TIPS); LCMS (APCI+) 594 ($M+H^+$).

**(1$S^*$, 2$R^*$, 3$S^*$, 5$R^*$)-1-[2-(4-Bromo-phenyl)-3,5-bis-dimethylamino-methyl-cyclopentanecarbonyl]-3-(2-triisopropyl-silanyloxy-ethyl)-imidazolidin-2-one (95)** To a solution of **89** (200 mg, 0.3 mmol) in THF: water (1:1; 16 ml) was added sodium periodate (77 mg, 0.36 mmol) at 0 °C. The reaction was stirred for three hours then extracted with chloroform. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was dissolved in dry $CH_2Cl_2$ (10 ml) and dimethylamine (3 ml, 2.8 mmol) was added. The reaction was stirred at room temperature for one hour then sodium triacetoxyborohydride (593 mg, 2.8 mmol) was added and the reaction stirred overnight. The reaction was poured into water and extracted with chloroform. The organic layer was dried ($MgSO_4$), solvent removed *in vacuo* and the crude product purified by flash column chromatography to yield the title compound as a yellow oil (117 mg, 61 %).



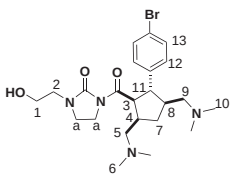

$R_f$ 0.37 ($SiO_2$; 10:2:0.1 $CHCl_3$: MeOH: $NEt_3$); $\nu_{max}$ (neat) 2942, 2865, 1765, 1722 (C=O), 1672 (C=O), 1461, 1413, 1397, 1355, 1252, 1105, 1010 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.38 (2H, d, *J* 8.5, H13), 7.14 (2H, d, *J* 8.5, H12), 4.38 (1H, dd, *J* 11.5, 9.5, H11), 3.85-3.79 (2H, m, H1), 3.69-3.56 (2H, m, Ha), 3.54-3.48 (1H, m, Ha), 3.44-3.37 (2H, m, H2), 3.33-3.27 (1H, m, Ha), 3.11 (1H, t, *J* 11.5, H3), 3.03 (1H, q, *J* 7.25, H8), 2.99-2.90 (1H, m, H4), 2.40 (1H, dt, *J* 13.0, 7.5, H5), 2.33-2.26 (2H, m, H9), 2.17 (6H, s, H6), 2.10 (6H, s, H10), 1.94 (1H, dd, *J* 12.0, 5.5, H5′), 1.36 (2H, t, *J* 7.5, H7), 1.03 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 173.09 (C=O), 155.05 (C=O), 141.17 (C-C), 131.47 (C[13]H), 129.84 (C[12]H), 119.94 (C-Br), 63.68 (C[5]$H_2$), 62.74 (C[9]$H_2$), 62.29 (C[1]$H_2$), 53.06 (C[3]H), 51.29 (C[11]H), 46.45 (C[2]$H_2$), 45.52 (C[6]$H_3$), 45.35 (C[10]$H_3$), 43.89 (C[4]H), 42.69 (C[a]$H_2$), 39.91 (C[a]$H_2$), 37.25 (C[8]H), 36.50 (H[7]$H_2$), 17.92 (C[TIPS]$H_3$), 11.81 (C[TIPS]H); LCMS (APCI+) 653 ($M+H^+$): HRMS $(M+H)^+$ found 651.3303 $C_{32}H_{56}BrN_4O_3Si$ required 651.3305, Δ ppm −0.5.

**(1$S^*$, 5$R^*$, 6$S^*$, 7$R^*$)-1-[7-(4-Bromo-phenyl)-3-methyl-3-aza-bicyclo[3.2.1]-octane-6-carbonyl]-3-(2-hydroxy-ethyl)-imida-zolidin-2-one (92)** The TIPS group was removed using the standard conditions to yield the title compound as a yellow oil (38 mg, 73 %).




$R_f$ 0.24 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (neat) 3452, 2936, 2778, 1721 (C=O), 1678 (C=O), 1488, 1440, 1375, 1353, 1249, 1158 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.38 (2H, d, *J* 8.0, H11), 7.16 (2H, d, *J* 8.5, H10), 4.14 (1H, d, *J* 7.0, H9), 4.09-4.04 (1H, m, H3), 3.95-3.84 (2H, m, Ha), 3.78 (2H, t, *J* 5.5, H1), 3.58-3.47 (2H, m, Ha), 3.44-3.32 (3H, m, H2, OH), 3.12 (1H, br d, *J* 10.4, H5), 2.93 (1H, s, H4), 2.84 (1H, d, *J* 11.5, H6), 2.40-3.33 (5H, m, H12, H5′, H6′), 2.30 (1H, br t, *J* 4.0, H7), 2.20-2.14 (1H, m, H8), 1.60 (1H, d, *J* 11.5, H8′); $\delta_C$ (125 MHz; $CDCl_3$) 172.22 (C=O), 155.27 (C=O), 131.56 (C[11]H), 128.87 (C[10]H), 119.71 (C-C), 62.16 (C[1]$H_2$), 60.52 (C[5]$H_2$), 57.66 (C[6]$H_2$), 56.56 (C[3]H), 46.77 (C[2]$H_2$), 46.63 (C[9]H), 45.41 (C[12]$H_3$), 42.19 (C[a]$H_2$), 42.07 (C[4]H), 40.43 (C[a]$H_2$), 39.76 (C[7]H), 37.72 (C[8]$H_2$); LCMS (APCI+) 438 ($M+H^+$); HRMS $(M+H)^+$ found 436.1243 $C_{20}H_{27}BrN_3O_3$ required 436.1236, Δ ppm −1.7.

**(1$S^*$, 2$R^*$, 3$S^*$, 5$R^*$)-1-[2-(4-Bromo-phenyl)-3,5-bis-dimethylamino-methyl-cyclopentanecarbonyl]-3-(2-hydroxy-ethyl)-imidazolidin-2-one (93)** The TIPS group was removed using the standard cleavage conditions to yield the title compound as a yellow oil (10 mg, 30 %)



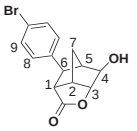

$R_f$ 0.39 ($SiO_2$; 10:2:0.1 $CHCl_3$: MeOH: $NEt_3$); $\nu_{max}$ (neat) 3421, 2941, 2818, 2766, 1720 (C=O), 1671 (C=O), 1482, 1457, 1443, 1414, 1397, 1376, 1354, 1255, 1071 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.39 (2H, d, *J* 8.5, H13), 7.15 (2H, d, *J* 8.5, H12), 4.34 (1H, dd, *J* 11.5, 9.5, H11), 3.79 (2H, t, *J*

5.0, H1), 3.73-3.63 (2H, m, Ha), 3.47-3.29 (4H, m, Ha, H2), 3.12 (1H, t, *J* 11.0, H3), 2.99-2.90 (1H, m, H8), 2.68 (1H, br d, *J* 6.5, H4), 2.40-2.30 (1H, m, H5), 2.20 (1H, d, *J* 10.5, H9), 2.11 (6H, s, H6), 2.10 (6H, s, H10), 2.04 (1H, d, *J* 8.5, H5′), 1.91 (1H, dd, *J* 12.5, 5.0, H9′), 1.14-1.09 (3H, m, H7, OH); $\delta_C$ (125 MHz; $CDCl_3$) 173.17 (C=O), 156.16 (C=O), 141.36 (C-C), 131.44 (C[13]H), 129.86 (C[12]H), 119.99 (C-Br), 63.93 (C[5]$H_2$), 62.86 (C[9]$H_2$), 61.10 (C[1]$H_2$), 53.29 (C[3]H), 51.31 (C[11]H), 46.97 (C[2]$H_2$), 45.78 (C[6]$H_3$), 45.43 (C[10]$H_3$), 44.12 (C[4]H), 42.40 (C[a]$H_2$), 40.08 (C[a]$H_2$), 37.25 (C[8]H), 36.49 (H[7]$H_2$); LCMS (APCI+) 495 ($M+H^+$): HRMS $(M+H)^+$ found 495.1963, $C_{23}H_{36}BrN_4O_3$ required 495.1971, $\Delta$ ppm −1.7.

### 7.3.8 General procedure for the epoxidation reaction on solid support

To a suspension of the solid supported norbornene (1 equiv.) in $CH_2Cl_2$ (5 mL/g of beads) under nitrogen was added mCPBA (4 equiv.). The reaction was shaken for 48 hours then the beads collected by filtration. The beads were washed with $CH_2Cl_2$ (× 5) and then suspended in methanol (10mL/g of beads) and heated to 65 °C for 24 hours. The beads were separated by filtration and the filtrate concentrated in vacuo to yield:

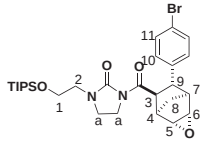
**(1*S**, 2*S**,, 3*S**, 6*S**, 7*R**, 9*R**)-9-(4-Bromophenyl)-2-hydroxy-4-oxa-tri-cyclo[4.2.1.0$^{3,7}$]-nonan-5-one (96)**




A colourless oil. NMR data matched that of the solution phase reaction.

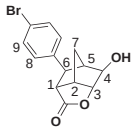
### 7.3.9 General procedure for the epoxidation reaction in solution phase

**(1*S**, 2*S**, 4*R**, 5*R**, 6*S**, 7*R**)-1-[7-(4-Bromophenyl)-3-oxa-tri-cyclo[3.2.1.0$^{2,4}$]octane-6-carbonyl]-3-(2-tri-isopropylsilanyloxy-ethyl)-imidazolidin-2-one (97)** To a solution **84** (100 mg, 0.18 mmol) in $CH_2Cl_2$ (10 mL) under nitrogen was added mCPBA (80 mg, 0.39 mmol). The reaction was stirred for four hours then washed with sodium bicarbonate solution and the organic layer dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield the compound as a colourless oil (90 mg, 86 %).




$R_f$ 0.40 ($SiO_2$; 10:3 hexane: ethyl acetate); $\nu_{max}$ (neat) 2944, 2864, 1725 (C=O), 1673 (C=O), 1490, 1418, 1390, 1361, 1262, 1247, 1108 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.46 (2H, d, *J* 8.5, H11), 7.10 (2H, d, *J* 8.0, H10), 4.52 (1H, d, *J* 5.0, H5), 3.89 (1H, s, H6), 3.85 (2H, t, *J* 5.5, H1), 3.65 (2H, dd, *J* 8.5, 7.5, Ha), 3.44 (2H, dd, *J* 8.5, 6.0, Ha), 3.34 (2H, t, *J* 5.0, H2), 3.23 (1H, td, *J* 4.5, 1.5, H4), 3.05 (1H, s, H9), 2.74 (1H, s, H7), 2.61 (1H, s, H3), 2.11 (1H, dd, *J* 11.5, 1.0, H8), 1.83 (1H, dd, *J* 11.5, 1.5, H8′), 1.08 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 179.19 (C=O), 1163.23 (C=O), 140.33 (C-C), 131.80 (C[11]H), 128.79 (C[10]H), 120.70 (C-Br), 86.83 (C[5]H), 77.83 (C[6]H), 62.93 (C[1]$H_2$), 49.54 (C[3]H), 47.84 (C[9]H), 46.93 (C[a]$H_2$), 46.47 (C[7]H), 46.27 (C[2]$H_2$), 44.93 (C[4]H), 38.55 (C[a]$H_2$), 31.34 (C[8]$H_2$), 17.97 (C[TIPS]$H_3$), 11.86 (C[TIPS]H); LCMS (ES+) 579 ($M+H^+$)

**(1*S**, 2*S**,, 3*S**, 6*S**, 7*R**, 9*R**)-9-(4-Bromophenyl)-2-hydroxy-4-oxa-tri-cyclo[4.2.1.0$^{3,7}$]-nonan-5-one (96)** A solution of **97** (50 mg, 86 $\mu$mol) in methanol (2.5 ml) was heated at 65 °C for six hours, cooled to room temperature and solvent removed *in vacuo*. The crude product was redissolved in $CH_2Cl_2$ and washed with brine. The organic layer was dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield the title compound as a colourless oil (20 mg, 75 %).



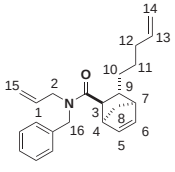

$R_f$ 0.34 ($SiO_2$; 1:1 hexane: ethyl acetate); $\nu_{max}$ (neat) 3449, 1777 (C=O), 1490, 1345, 1174, 1009 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.48 (2H, d, *J* 8.5, H9), 7.11 (2H, d, *J* 8.5, H8), 4.52 (1H, d, *J* 5.0, H3), 3.91 (1H, s, H1), 3.25 (1H, ddd, *J* 9.5, 5.0, 1.5, H4), 3.06 (1H, s, H6), 2.76 (1H, d, *J* 1.5, H5), 2.62 (1H, s, H2), 2.19 (1H, br s, OH), 2.11 (1H, d, *J* 11.5, H7), 1.85 (1H, dd, *J* 11.5, 1.5, H7′); $\delta_C$ (125 MHz; $CDCl_3$) 179.17 (C=O), 140.21 (C-C), 131.84 (C[9]H), 128.78 (C[8]H), 119.21 (C-Br), 86.79 (C[3]H), 77.90 (C[1]H), 49.59 (C[2]H), 47.82 (C[6]H), 46.40 (C[5]H), 44.93 (C[4]H), 31.31 (C[7]$H_2$); LCMS (APCI+) 350 ($M+MeCN+H^+$);

# 8 Diversity generating reactions preformed in solution phase

### 8.0.10 Alkylation reactions

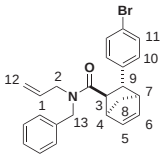
To a solution of the primary amide (1 equiv.) in DMF: THF (1:1) was added sodium hydride (2 equiv.) and the reaction stirred under nitrogen at 0 °C for one hour and then warmed to room temperature. The bromide (2 equiv.) was added and the reaction stirred at 40 °C for three hours. The reaction was cooled to room temperature and quenched with saturated ammonium chloride solution. The aqueous layer was extracted with ethyl acetate, which was washed with brine, dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield:

**(1*S**, 2*S**, 3*R**, 4*S**)-3-Pent-4-enyl-bicyclo[2.2.1]-hept-5-ene-2-carboxylic acid allyl-benzyl-amide (98)**



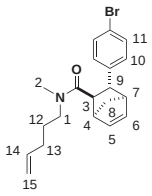
A yellow oil (80 mg, 41 %); $R_f$ 0.30 ($SiO_2$; 10:1 toluene: ethyl acetate); $\nu_{max}$ (neat) 2964, 2924, 1638 (C=O), 1453, 1413, 1333, 1214 $cm^{-1}$; $\delta_H$ (500 MHz; DMSO, 100 °C) 7.33 (2H, t, *J* 7.5, ArH), 7.25 (1H, t, *J* 7.5, ArH), 7.20 (2H, d, *J* 7.5, ArH), 6.22 (1H, dd, *J* 5.5, 3.0, H6), 5.83-5.74 (3H, m, H5, H1, H13), 5.15 (1H, d, *J* 10.0, H15), 5.12 (1H, d, *J* 17.5, H15′), 5.00-4.93 (2H, m, H14), 4.70 (1H, d, *J* 15.0, H16), 4.46 (1H, d, *J* 15.0, H16′), 4.10 (1H, dd, *J* 17.0, 5.0, H2), 3.90 (1H, d, *J* 14.0, H2′), 3.02 (1H, s, H4), 2.67 (1H, t, *J* 3.5, H3), 2.53 (1H, s, H7), 2.03-1.96 (3H, m, H12, H9), 1.56 (1H, d, *J* 8.5, H8), 1.44-1.31 (5H, m, H8′, H10, H11); $\delta_C$ (125 MHz; DMSO) 173.37 (C=O), 139.17 (C), 138.45 (CH), 131.89 (CH), 128.81 (CH), 127.35 (CH), 116.63 ($CH_2$), 114.76 ($CH_2$), 48.34 (CH), 47.69 (CH), 47.56 (CH), 46.82 (CH), 43.25 (CH), 35.08 ($CH_2$), 33.52 ($CH_2$), 28.04 ($CH_2$); LCMS (APCI+) 336 ($M+H^+$): HRMS $(M+H)^+$ found 336.2320 $C_{23}H_{30}NO$ required 336.2322, Δ ppm −0.7.

### (1*S**, 2*R**, 3*R**, 4*S**)–3-(4-Bromo-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid allyl-benzyl-amide(99)



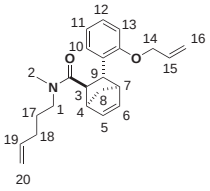

A yellow oil (33 mg, 87 %); $\nu_{max}$ (neat) 2978, 2929, 1642 (C=O), 1463, 1410, 1212 $cm^{-1}$; $\delta_H$ (500 MHz; DMSO, 90 °C) 7.43 (2H, d, *J* 8.0, H10), 7.34-7.29 (2H, m, ArH), 7.27-7.22 (1H, m, ArH), 7.20-7.12 (3H, m, ArH), 6.39 (1H, dd, *J* 5.5, 3.0, H6), 5.96 (1H, dd, *J* 5.5, 3.0, H5), 5.78-5.70 (1H, m, H1), 5.11 (1H, dd, *J* 10.5, 1.5, H12), 5.07 (1H, dd, *J* 17.5, 1.5, H12′), 4.71-4.68 (1H, m, H13), 4.47-4.41 (1H, m, H2), 4.08-4.04 (1H, m, H13′), 3.86-3.80 (1H, m, H2′), 3.22 (1H, d, *J* 4.0, H9), 2.99 (1H, s, H7), 2.90 (1H, s, H4), 2.51-2.50 (1H, m, H3), 1.75 (1H, d, *J* 8.5, H8), 1.44 (1H, d, *J* 8.5, H8′); LCMS (APCI+) 422 ($M+H^+$)

### (1*S**, 2*R**, 3*R**, 4*S**)–3-(4-Bromo-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid methyl-pent-4-enyl-amide (100)



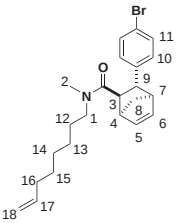

A colourless oil (79 mg, 82 %); $R_f$ 0.68 ($SiO_2$; 2:1 toluene: ethyl acetate); $\nu_{max}$ (DMSO) 2925, 2852, 1634 (C=O), 1486, 1457, 1376, 1259 $cm^{-1}$; $\delta_H$ (500 MHz; DMSO, 90 °C) 7.46 (2H, d, *J* 8.5, H11), 7.22 (2H, d, *J* 8.5, H10), 6.34 (1H, dd, *J* 5.0, 3.0, H6), 5.93 (1H, dd, *J* 5.0, 2.5, H5), 5.85-5.75 (1H, m, H14), 5.0 (1H, d, *J* 17.0, H15), 4.95 (1H, d, *J* 10.5, H15′), 3.40 (1H, dq, 8.5, 6.5, H9), 3.25-3.14 (4H, m, H2, H3), 3.98-2.86 (4H, m, H1, H4, H7), 2.00-1.95 (2H, m, H13), 1.78 (1H, d, *J* 8.5, H8), 1.61-1.49 (2H, m, H12), 1.46 (1H, d, *J* 8.5, H8′); LCMS (ES+) 375 ($M+H^+$)

### (1*S**, 2*R**, 3*R**, 4*S**)–3-(2-Allyloxy-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid methyl-pent-4-enyl-amide (101)



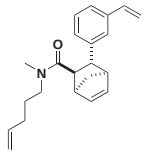

A pale yellow oil (164 mg, 67 %); $R_f$ 0.65 ($SiO_2$; 2:1 toluene: ethyl acetate); $\nu_{max}$ (DMSO) 3002, 1639 (C=O), 1491, 1451, 1405, 1241, 1015 $cm^{-1}$; $\delta_H$ (500 MHz; DMSO, 105 °C) 7.36 (1H, d, *J* 8.0, H10), 7.15 (1H, td, *J* 8.0, 2.0, H11), 6.96-6.91 (2H, m, H12, H13), 6.27 (1H, dd, *J* 5.5, 3.0, H6), 6.07-5.99 (1H, m, H15), 5.97 (1H, dd, *J* 5.5, 3.0, H5), 5.8-5.74 (1H, m, H19), 5.38 (1H, ddd, *J* 17.5, 3.5, 1.5, H16), 5.23 (1H, ddd, *J* 10.5, 3.0, 1.5, H16′), 4.98 (1H, dd, *J* 17.0, 1.5, H20), 4.93 (1H, ddd, *J* 10.5, 3.0, 1.0, H20′), 4.55-4.52 (2H, m, H14), 3.36 (2H, d, *J* 6.0, H1), 3.22 (1H, dd, *J* 5.0, 3.5, H3), 3.18-3.11 (2H, m, H9, H4), 2.87 (3H, s, H2), 2.82 (1H, s, H7), 1.94 (2H, dd, *J* 14.0, 6.5, H18), 1.74 (1H, d, *J* 8.1, H8), 1.60-1.47 (2H, m, H17), 1.39 (1H, ddd, *J* 8.5, 3.5, 1.5, H8′); LCMS (APCI+) 352 ($M+H^+$).

### (1*S**, 2*R**, 3*R**, 4*S**)–3-(4-Bromo-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid methyl-oct-7-enyl-amide (102)



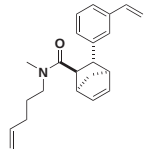

A pale yellow oil (92 mg, 88 %); $R_f$ 0.66 ($SiO_2$; 2:1 toluene: ethyl acetate); $\nu_{max}$ (DMSO) 2928, 1633 (C=O), 1489 $cm^{-1}$; $\delta_H$ (500 MHz; DMSO, 90 °C) 7.45 (2H, d, *J* 8.5, H10), 7.21 (2H, d, *J* 8.0, H11), 6.34 (1H, dd, *J* 5.5, 3.0, H6), 5.93 (1H, dd, *J* 5.0, 2.5, H5), 5.85-5.74 (1H, m, H17), 5.00 (1H, ddd, *J* 17.5, 3.5, 1.5, H18), 5.94 (1H, ddd, *J* 10.5, 3.0, 1.5, H18′), 3.43-3.34 (1H, m, H3), 3.22-3.13 (4H, m, H4, H1, H9), 2.90 (1H, s, H7), 2.87 (3H, s, H2), 2.01 (2H, dd, *J* 14.0, 7.0, H16), 1.78 (1H, d, *J* 8.5, H8), 1.45-1.15 (9H, m, H8′, H12, H13, H14, H15); LCMS (ES+) 417 ($M+H^+$).

### (1*S**, 2*R**, 3*R**, 4*S**)–3-(3-Vinyl-phenyl)-bicyclo-[2.2.1]hept-5-ene-2-carboxylic acid methyl-pent-4-enyl-amide (103)




A colourless oil (180 mg, 71 %); $R_f$ 0.34 ($SiO_2$; 9:1 toluene: ethyl acetate); LCMS (APCI+) 322 ($M+H^+$)

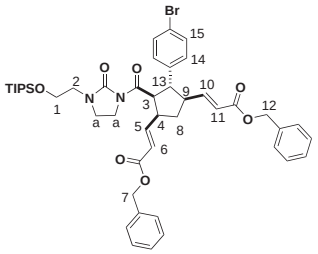
### (1*S**, 2*R**, 3*R**, 4*S**)–3-(3-Vinyl-phenyl)-bicyclo-[2.2.1]hept-5-ene-2-carboxylic acid methyl-pent-4-enyl-amide (103)



A colourless oil (180 mg, 71 %); $R_f$ 0.34 ($SiO_2$; 9:1 toluene: ethyl acetate); LCMS (APCI+) 322 ($M+H^+$)

### 8.0.11 Grubbs metathesis reactions

**(1$R^*$, 2$R^*$, 3$R^*$, 4$S^*$)–1-5-(2-Benzyloxycarbonyl-vinyl)-2-(4-bromo-phenyl)-3-[2-oxo-3-(2-triisopropylsilanyloxy-ethyl)-imidazolidine-1-carbonyl]-cyclopentyl-acrylic acid benzyl ester (104)** To a solution of **84** (40 mg, 88 $\mu$mol) in toluene (10 ml) under an atmosphere of ethylene was added benzyl acrylate (86 mg, 0.53 mmol). The reaction was stirred at 120 °C and Grubbs 2nd Generation catalyst (3 mg, 4.4 $\mu$mol) in toluene (6 ml) was added in three equal portions over six hours. After complete addition of the catalyst the reaction was stirred overnight and cooled to room temperature. The solvent was removed *in vacuo* and the crude product purified by flash column chromatography to yield the title compound as a colourless oil (25 mg, 33 %).

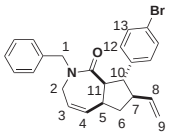


$R_f$ 0.22 ($SiO_2$; 10:1 toluene: ethyl acetate); $\nu_{max}$ (neat) 2942, 2865, 1719 (C=O), 1672 (C=O), 1414, 1393, 1355, 1261, 1162, 1105, 1009 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.42-7.26 (12H, m, ArH), 7.15-7.10 (2H, m, ArH), 6.89 (1H, dd, $J$ 15.5, 7.5, H10), 6.81 (1H, dd, $J$ 15.5, 9.5, H5), 5.85 (1H, d, $J$ 15.5, H11), 5.75 (1H, d, $J$ 15.5, H6), 5.18 (2H, d, $J$ 2.5, H7), 5.15 (2H, s, H12), 4.58 (1H, t, $J$ 10.5, H3), 3.81-3.75 (2H, m, H1), 3.68-3.62 (2H, m, Ha), 3.60-3.48 (2H, m, Ha), 3.46-3.40 (2H, m, H2), 3.24 (1H, td, $J$ 9.5, 6.0, H4), 3.15 (1H, ddd, $J$ 14.0, 6.5, 5.0, H9), 2.92-2.84 (1H, m, H13), 2.27 (1H, dt, $J$ 13.0, 7.0, H8), 1.72 (1H, dt, $J$ 11.5, 9.5, H8′), 1.06 (21H, s, TIPS); $\delta_C$ (125 MHz; $CDCl_3$) 171.00 (C=O), 165.88 (C=O), 165.71 (C=O), 154.17 (C), 149.04 (CH), 148.78 (CH), 139.60 (C), 136.11 (C), 135.96 (C), 131.71 (CH), 129.70 (CH), 128.53 (CH), 128.28 (CH), 128.18 (CH), 122.00 (CH), 121.88 (CH), 120.67 (C), 66.15 (C[12]$H_2$), 66.05 (C[7]$H_2$), 61.78 (C[1]$H_2$), 55.17 (C[3]H), 51.81 (C[4]H), 49.33 (C[9]H), 46.33 (C[a]$H_2$), 42.91 (C[13]H), 42.34 (C[a]$H_2$), 39.70 (C[2]$H_2$), 38.04 (C[8]$H_2$), 17.90 (C[TIPS]$H_3$) 11.79 (C[TIPS]H); LCMS (ES+) 857 ($M+H^+$): HRMS $(M+H)^+$ found 857.3194 $C_{46}H_{57}BrN_2O_7Si$ required 857.3191, $\Delta$ ppm +0.4.

### 8.0.12 General procedure for ring closing metathesis reactions

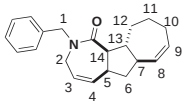
To a solution of the norbornene (**98-103**) (1 equiv.) in toluene (4 mg per ml) under an atmosphere of ethylene at 120 °C was added Grubbs 2nd generation catalyst (1 mol %) as a solution in toluene (1mg in 0.3 ml) in three equal portions over nine hours. The reaction was reflux overnight then cooled to room temperature. The solvent removed *in vacuo* and the crude product purified by flash column chromatography.

**(5a$S^*$, 7$R^*$, 8$R^*$, 8a$R^*$)–2-Benzyl-8-(4-bromo-phenyl)-7-vinyl-3,5a,6,7,8,8a-hexahydro-2H-cyclopenta[c]azepin-1-one (105)**



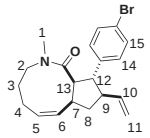
A colourless oil (13 mg, 65 %); $R_f$ 0.40 ($SiO_2$; 10:1 hexane: ethyl acetate); $\nu_{max}$ (neat) 2920, 2857, 1643 (C=O), 1489, 1423, 1224, 1009 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.42 (2H, d, $J$ 8.0, H13), 7.32-7.18 (7H, m, ArH), 5.97-5.88 (1H, m, H8), 5.79 (2H, s, H2), 4.98-4.92 (2H, m, H9), 4.73 (1H, d, $J$ 15.0, H3), 4.57 (1H, d, $J$ 15.0, H4), 4.16-4.10 (2H, m, H1), 3.46 (1H, dd, $J$ 9.5, 4.5, H11), 3.26-3.20 (1H, m, H10), 3.17-3.10 (1H, m, H5), 2.67-2.60 (1H, m, H7), 2.14 (1H, dt, $J$ 12.0, 6.0, H6), 1.54 (1H, dd, $J$ 24.5, 12.0, H6′); $\delta_C$ (125 MHz; $CDCl_3$) 171.83 (C=O), 144.28 (C-C), 140.16 (CH), 137.86 (C-C), 134.91 (CH), 131.51 (CH), 131.33 (CH), 129.42 (CH), 128.37 (CH), 128.33 (CH), 128.11 (C-Br), 127.22 (CH), 126.55 (CH), 114.45 (C[9]$H_2$), 54.26 (C[11]H), 51.41 (C[10]H), 51.32 (C[2]$H_2$), 50.81 (C[5]H), 43.10 (C[1]$H_2$), 42.27 (C[7]H), 40.12 (C[6]$H_2$); LCMS (APCI+) 422 ($M+H^+$): HRMS $(M+H)^+$ found 422.1111 $C_{24}H_{25}BrNO$ required 422.1114, $\Delta$ ppm −0.8.

**4-Benzyl-4-aza-tricyclo[8.5.0.0$^{2,8}$]pentadeca-6,11-dien-3-one (4)**



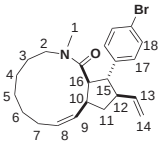
A colourless oil (20 mg, 54 %); $R_f$ 0.26 ($SiO_2$; 10:0.5 hexane: ethyl acetate); $\nu_{max}$ (neat) 2916, 2836, 1642 (C=O), 1439, 1416, 1219, 1199 $cm^{-1}$; $\delta_H$ (500 MHz; DMSO; 115 °C) 7.35-7.20 (5H, m, ArH), 5.90-5.65 (3H, m, CH), 4.67-4.35 (2H, m, CH), 4.15-3.90 (1H, m, CH), 3.40-2.91 (2H, m, CH), 2.60-1.79 (8H, m, CH), 1.45-1.15 (3H, m, CH); LCMS (APCI+) 308 ($M+H^+$):HRMS $(M+H)^+$ found 308.2008 $C_{21}H_{26}NO$ required 308.2009, $\Delta$ ppm −0.2.

**(2$R^*$, 3$R^*$, 3a$R^*$, 10a$S^*$)–3-(4-Bromo-phenyl)-5-methyl-2-vinyl-2,3,3a,5,6,7,8,10a-octahydro-1H-5-aza-cyclopentacyclononen-4-one (106)**



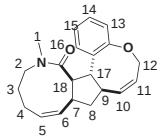
A colourless oil (42 mg, 86 %); $R_f$ 0.38 ($SiO_2$; 10:1 hexane: ethyl acetate); $\nu_{max}$ (neat) 2989, 1632 (C=O), 1486, 1410, 1261 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.39 (2H, d, $J$ 8.0, H15), 7.15 (2H, d, $J$ 8.0, H14), 5.72 (1H, ddd, $J$ 17.5, 10.5, 7.5, H10), 5.62 (1H, dtd, $J$ 10.5, 7.0, 1.5, H5), 5.41 (1H, dd, $J$ 10.5, 8.0, H6), 4.93 (1H, d, $J$ 17.5, H11), 4.90 (1H, d, $J$ 10.5, H11′), 3.67 (2H, t, $J$ 13.0, H2), 3.63 (1H, dd, $J$ 11.5, 9.0, H12), 3.45-3.32 (2H, m, H7, H13), 3.15 (1H, dd, $J$ 15.0, 4.5, H2′), 2.80 (3H, s, H1) 2.79-2.72 (1H, m, H9), 2.31-2.16 (3H, m, H4, H8), 1.83-1.74 (1H, m, H3), 1.72-1.64 (1H, m, H8′), 1.62-1.55 (1H, m, H3); $\delta_C$ (125 MHz; $CDCl_3$) 171.74 (C=O), 141.84 (C-C), 139.42 (C[10]H), 133.45 (C[6]H), 131.40 (C[15]H), 130.78 (C[5]H), 129.80 (C[14]H), 119.91 (C-Br), 115.27 (C[11]$H_2$), 55.66 (C[13]H), 52.90 (C[12]H), 51.48 (C[2]$H_2$), 50.76 (C[9]H), 40.44 (C[8]$H_2$), 38.50 (C[7]H), 33.26 (C[1]$H_3$), 28.22 (C[4]$H_2$), 25.86 (C[3]$H_2$); LCMS (APCI+) 374 ($M+H^+$).

**(2$R^*$, 3$R^*$, 3a$R^*$, 13a$S^*$)–3-(4-Bromo-phenyl)-5-methyl-2-vinyl-1,2,3,3a,5,6,7,8,9,10,11,13a-dodecahydro-5-aza-cyclopentacyclo-dodecen-4-one (107)**



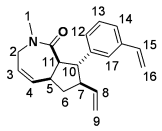
A colourless oil (40 mg, 69 %); $R_f$ 0.68 ($SiO_2$; 1:1 toluene: ethyl acetate); $\nu_{max}$ (neat) 2987, 1634 (C=O), 1486, 1413, 1260 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.39 (2H, d, $J$ 8.0, H18), 7.13 (2H, d, $J$ 8.5, H17), 5.75-5.65 (1H, m, H13), 5.49 (1H, dd, $J$ 15.0, 9.0, H9), 5.41 (1H, ddd, $J$ 15.0, 8.0, 6.0, H8), 4.90-4.85 (2H, m, H14), 4.40 (1H, ddd, $J$ 15.0, 11.5, 3.5, H15), 3.50 (1H, dd, $J$ 11.0, 9.5, H2), 3.30 (1H, t, $J$ 11, H2′), 3.07 (1H, quintet, $J$ 8.5, H10), 2.84 (3H, s, H1), 2.71-2.62 (1H, m, H12), 2.44 (1H, dt, $J$ 13.5, 4.0, H16), 2.20-2.13 (2H, m, H7), 2.02-1.95 (1H, m, H11), 1.73 (1H, dt, $J$ 11.5, 9.5, H11′), 1.59-1.20 (8H, m, H3, H4, H5, H6); $\delta_C$ (125 MHz; $CDCl_3$) 172.46 (C=O), 141.90 (C-C), 139.70 (C[13]H), 131.92 (C[9]H), 131.40 (C[18]H), 130.62 (C[8]H), 129.72 (C[17]H), 119.90 (C-Br), 115.07 (C[14]$H_2$), 54.21 (C[16]H), 53.30 (C[15]H), 51.08 (C[12]H), 45.05 (C[2]$H_2$), 43.37 (C[10]H), 39.10 (C[11]$H_2$), 34.04 (C[1]$H_3$), 31.53 (C[7]$H_2$), 26.78 (C[3]$H_2$), 24.92 (C[6]$H_2$), 24.70 (C[4]$H_2$), 23.13 (C[5]$H_2$); LCMS (APCI+) 416 ($M+H^+$): HRMS $(M+H)^+$ found 416.1591 $C_{23}H_{31}BrNO$ required 416.1589, Δ ppm +0.4.

**(1$R^*$, 2$R^*$, 9$R^*$, 11$S^*$)–17-Methyl-3,4-phenyl-5-oxa-17-azatricyclo[9.7.0.0$^{2,9}$] octadeca-7,12-dien-18-one (108)**



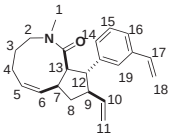
A colourless oil (5.4 mg, 11 %); $R_f$ 0.46 ($SiO_2$; 1:1 toluene: ethyl acetate); $\nu_{max}$ (DMSO) 2916, 1630 (C=O), 1486, 1448, 1260, 1101, 1007 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.34-7.30 (1H, m, H13), 7.21-7.14 (2H, m, H15, H16), 7.03 (1H, d, $J$ 7.5, H14), 5.71 (1H, ddd, $J$ 11.0, 8.0, 3.0, H11), 5.65-5.59 (1H, m, H5), 5.46 (1H, dd, $J$ 10.5, 8.0, H6), 5.38 (1H, br d, $J$ 11.0, H10), 5.04 (1H, d, $J$ 17.0, H12), 5.00-4.80 (1H, m, H12′), 4.36 (1H, dd, $J$ 16.5, 3.5, H18), 4.28-4.18 (1H, m, H17), 3.85 (1H, dd, $J$ 12.5, 9.5, H2), 3.73 (1H, t, $J$ 13.5, H2′), 3.41 (1H, dd, $J$ 12.0, 9.5, H7), 3.17 (1H, br d, $J$ 15.5, H9), 2.91 (3H, s, H1), 2.31-2.12 (3H, m, H4, H3), 1.85-1.75 (1H, m, H8), 1.61-1.50 (2H, m, H3′, H8′); LCMS (APCI+) 324 ($M+H^+$)

**(5a$S^*$, 7$R^*$, 8$R^*$, 8a$R^*$)–2-Methyl-7-vinyl-8-(3-vinyl-phenyl)-3,5a,6,7,8,8a-hexahydro-2H-cyclopenta[c]azepin-1-one (108)**



A colourless oil (10.3 mg, 21 %); $R_f$ 0.54 ($SiO_2$; 1:1 toluene: ethyl acetate); $\nu_{max}$ (DMSO) 2926, 2854, 1651 (C=O), 1486, 1345, 1316, 1260 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.28-7.17 (4H, m, H12, H13, H14, H17), 6.72 (1H, dd, $J$ 17.5, 11.0, H15), 6.06-6.04 (1H, m, H8), 5.95-5.85 (2H, m, H3, H4), 5.76 (1H, d, $J$ 17.5, H16), 5.24 (1H, d, $J$ 11, H16′), 4.95-4.92 (2H, m, H9), 4.30 (1H, dtd, $J$ 15.5, 5.5, 2.5, H2), 4.09 (1H, dd, $J$ 9.0, 4.5, H2′), 3.46 (1H, dd, $J$ 9.5, 4.5, H10), 3.18-3.12 (2H, m, H5, H11) 3.01 (3H, s, H1), 2.72-2.64 (1H, m, H7), 2.10 (1H, dt, $J$ 11.5, 5.5, H6), 1.49 (1H, dt, $J$ 13.5, 12.0, H6′); $\delta_C$ (125 MHz; $CDCl_3$) 172.21 (C=O), 145.71 (C-C), 140.51 (CH), 137.03 (CH), 135.56 (CH), 128.65 (CH), 127.28 (CH), 126.09 (CH), 125.91 (CH), 123.92 (CH), 114.37 (C[9]$H_2$), 113.71 (C[16]$H_2$), 54.08 (C[11]H), 51.66 (C[10]H), 50.94 (C[5]H), 45.82 (C[2]$H_2$), 42.42 (C[7]H), 40.04 (C[6]$H_2$), 35.65 (C[1]$H_3$); LCMS (APCI+) 294 ($M+H^+$): HRMS $(M+H)^+$ found 294.1863 $C_{20}H_{24}NO$ required 294.1858, Δ ppm +1.7.

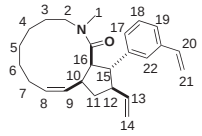
**(2$R^*$, 3$R^*$, 3a$R^*$, 10a$S^*$)–5-Methyl-2-vinyl-3-(3-vinyl-phenyl)-2,3,3a,5,6,7,8,10a-octahydro-1H-5-aza-cyclopentacyclononen-4-one (109)**



A colourless oil (15.9 mg, 31 %); $R_f$ 0.52 ($SiO_2$; 1:1 toluene: ethyl acetate); $\nu_{max}$ (DMSO) 3007, 2997, 1629 (C=O), 1261 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.29-7.17 (4H, m, H15, H16, H14, H17), 6.71 (1H, dd, $J$ 17.5, 11.0, H19), 5.77-5.72 (2H,

m, H10, H18), 5.62-5.60 (1H, m, H5), 5.42 (1H, dd, *J* 10.5, 7.25, H6), 5.22 (1H, d, *J* 11.0, H18′), 4.94 (1H, d, *J* 17.0, H11), 4.90 (1H, d, *J* 10.5, H11′), 3.72-3.65 (2H, m, H12, H2), 3.44-3.40 (2H, m, H2′, H13), 3.13 (1H, m, H7), 2.81 (3H, s, H1), 2.27-2.20 (3H, m, H9, H4), 1.80-1.70 (3H, m, H8, H3), 1.62-1.55 (1H, m,H8′); LCMS (APCI+) 322 ($M+H^+$).

**(2*R**, 3*R**, 3a*R**, 13a*S**)–5-Methyl-2-vinyl-3-(3-vinyl-phenyl)-1,2,3,3a,5,6,7,8,9,10,11,13a-dodecahydro-5-aza-cyclopentacyclo-dodecen-4-one (110)**



A colourless oil (5.5 mg, 11 %); $R_f$ 0.54 ($SiO_2$; 1:1 toluene: ethyl acetate); $\nu_{max}$ (DMSO) 2993, 1632 (C=O), 1481, 1410, 1302, 1259 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.28-7.12 (4H, m, H17, H18, H19, H22), 6.70 (1H, dd, *J* 17.5, 11.0, H20), 5.79-5.72 (2H, m, H21, H13), 5.52 (1H, dd, *J* 15.0, 8.5, H9), 5.40 (1H, dt, *J* 15.0, 7.0, H8), 5.22 (1H, d, *J* 10.5, H21′), 4.93-4.87 (2H, m, H14), 4.43 (1H, td, *J* 14.5, 3.8, H15), 3.54 (1H, dd, *J* 10.5, 9.5, H2), 3.41 (1H, t, *J* 9.5, H2′), 3.12-3.05 (1H, m, H10), 2.81 (3H, s, H1), 2.74-2.67 (1H, m, H12), 2.43 (1H, dt, *J* 14.0, 4.0, H16), 2.17-2.11 (2H, m, H7), 2.06-1.95 (1H, m, H11), 1.80 (1H, dd, *J* 22.0, 12.0, H11′), 1.58-1.54 (1H, m, H3), 1.53-1.40 (3H, m, H3′, H6), 1.32-1.21 (5H, m, H6, H5, H4); LCMS (APCI+) 363 ($M+H^+$).

# 9 Cleavage of compounds to synthesise carboxylic acids

## 9.1 General method for solid supports

To a solution of resin (1 equiv.) in acetonitrile: water (1:1, 2 mL/g of beads) was added lithium hydroxide (10 equiv.) and the reaction stirred at 65 °C for 16 hours and then cooled to room temperature. The beads were removed by filtration and washed with ether (× 3) and the aqueous layer was separated and neutralised using pH 7 buffer. The aqueous layer was then extracted with ether and the organic layer was dried ($MgSO_4$) and solvent removed *in vacuo*.

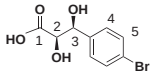
## 9.2 General method for solution phase synthesis

A round-bottom flask, equipped with a magnetic stirrer, containing the library compound (1 equiv.), lithium hydroxide (6 equiv.), THF (0.5 mL/200 mg of compound) and water (0.5 mL/200 mg of compound) was stirred at 50 °C for 5 hours. The resulting solution was cooled to room temperature and diluted with $Et_2O$ and $H_2O$ and acidified with aqueous 3N HCl solution. The aqueous layer was sequentially washed with $Et_2O$ (× 3), basified with aqueous 10 % NaOH solution and extracted with $Et_2O$ (× 3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*.

## 9.3 Library compounds generated using this methodology

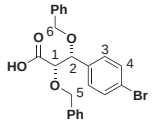
Compounds prepared using branching pathways 1,2,3 and 4 were cleaved after each step to generate carboxylic acids using the above methodology to generate compounds with purity greater than 80 % by NMR and LCMS:

**(*rac*)-3-(4-Bromo-phenyl)-2,3-dihydroxy-propionic acid (111)**



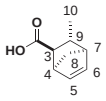
A viscous oil. $\nu_{max}$ (neat) 3407w br (OH), 2521w, 1742s (acid), 1489m, 1283m, 1107s, 727s $cm^{-1}$; $\delta_H$ (400 MHz; $CD_3OD$) 7.51-7.43 (2H, d, *J* 8.5, H5), 7.38-7.32 (2H, d, *J* 8.5, H6), 5.03-4.98 (1H, br s, H3), 4.25-4.21 (1H, d, *J* 3.0, H2); $\delta_C$ (125 MHz; $CD_3OD$) 174.1 (C=O), 140.8 (C-C), 130.6 (CH), 128.2 (CH), 120.6 (C-Br), 74.7 (CH), 73.6 (CH); HRMS found m/z (ESI-H+) 282.9572 $C_4H_9{}^{79}BrO_4Na^+$ required 282.9576, Δppm −1.4, mp 169-170 °C (Ether).

**(*rac*)-2,3-Bis-benzyloxy-3-(4-bromo-phenyl)-propionic acid (112)**



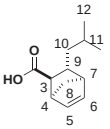
A viscous oil. $\nu_{max}$ (neat)/cm-1 2918w br, 1728m (carbonyl), 1487m, 1454m, 1072s, 1011m, 697m $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 7.51-7.45 (2H, d, *J* 8.3, H4), 7.30-7.17 (10H, m, H3, ArylH), 6.97-6.93 (2H, d, *J* 7.0, ArylH), 4.80-4.76 (1H, d, *J* 2.9, H2), 4.60-4.52 (2H, d, *J* 12.0, H5), 4.29-4.24 (2H, m, H6), 4.02-4.00 (1H, d, *J* 3.0, H1); $\delta_C$ (100 MHz; $CDCl_3$) 172.9 (C=O), 136.9 (C-C), 135.9 (C-C), 135.8 (C-C), 132.2 (CH), 131.6 (CH), 129.4 (CH), 128.4 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 122.3 (C-Br), 80.9 (C[1]H), 79.9 (C[2]H), 73.8 ($CH_2$), 71.5 ($CH_2$); HRMS found m/z (ESI-$H^+$) 458.0960 $C_{23}H_{25}{}^{79}BrNO_4{}^+$ required 458.0961, Δ ppm −0.3.

**(1*S**, 2*S**, 3*R**, 4*R**)–3-Methylbicyclo[2.2.2]oct-5-ene-2-carboxylic acid (113)**



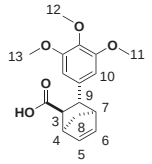
A white solid ; $\nu_{max}$ (neat) 2962, 1701 (C=O), 1273 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.30 (1H, dd, *J* 5.5, 3.0, H6), 6.06 (1H, dd, *J* 5.5, 3.0, H5), 3.15 (1H, s, H4), 2.50 (1H, s, H7), 2.44 (2H, t, *J* 4.5, H3), 1.86-1.83 (1H, m, H9), 1.58 (1H, d, *J* 8.5, H8), 1.43 (1H, dd, *J* 8.5, 1.5, H8′), 1.21 (3H, d, *J* 7.0, H10); LCMS (ES+) 153 ($M+H^+$). Data in agreement with literature values [3]

**(1*S**, 2*S**, 3*R**, 4*R**)–3-Isobutyl-bicyclo[2.2.1]-hept-5-ene-2-carboxylic acid (114)**



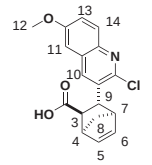
A colourless oil ; $\nu_{max}$ (DMSO) 3364, 2961, 1700 (C=O), 1318, 1261, 1220 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.30 (1H, dd, *J* 5.5, 3.0, H6), 6.06 (1H, dd, *J* 5.5, 3.0, H5), 3.15 (1H, s, H4), 2.50 (1H, s, H7), 2.44 (1H, dd, *J* 4.5, 3.5, H3), 1.85-83 (1H, m, H9), 1.57 (1H, d, *J* 8.5, H8), 1.47 (1H, dd, *J* 8.5, 1.5, H8′), 1.35-1.21 (3H, m, H10, H11), 1.21 (3H, d, *J* 7.0, H12), 0.88 (3H, d, *J* 7.0, H12); LCMS (ES+) 195 ($M+H^+$).

### (1*S**, 2*R**, 3*R**, 4*R**)–3-(3,4,5-Trimethoxy-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (115)



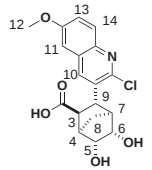
A colourless oil; $\nu_{max}$ (neat) 2941, 2838, 1699 (C=O), 1587, 1508, 1456, 1419, 1332, 1241, 1124 $cm^{-1}$; $\delta_H$ (500 MHz; MeOD) 6.35 (2H, s, H10), 6.18 (1H, dd, *J* 5.5, 3.0, H6), 5.93 (1H, dd, *J* 5.5, 3.0, H5), 3.63 (6H, s, H11), 3.58 (3H, s, H12), 3.12 (1H, dd, *J* 3.0, 1.5, H3), 3.07 (1H, s, H4), 2.79-2.74 (1H, m, H7), 2.73 (1H, dd, *J* 5.0, 1.5, H9), 1.57 (1H, d, *J* 8.5, H8), 1.37 (1H, dd, *J* 8.5, 1.5, H8′); LCMS (ES+) 305 ($M+H^+$).

### (1*S**, 2*R**, 3*R**, 4*R**)–3-(2-Chloro-6-methoxy-quinolin-3-yl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (116)



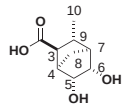
A colourless oil ; $\nu_{max}$ (neat) 2917, 1702 (C=O), 1622, 1496, 1230, 1183, 1040 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 8.07 (1H, s, H10), 7.87 (1H, d, *J* 9.0, H14), 7.26 (1H, dd, 9.0, 3.0, H13), 7.13 (1H, d, *J* 3.0, H11), 6.44 (1H, dd, *J* 5.5, 3.0, H6), 6.13 (1H, dd, *J* 5.5, 3.0, H5), 3.86 (3H, s, H12), 3.43 (1H, d, *J* 4.5, H3), 3.42 (1H, s, H4), 3.27 (1H, t, *J* 5.0, H9), 2.96 (1H, s, H7), 1.67 (1H, d, *J* 8.5, H8), 1.50 (1H, dd, *J* 8.5, 1.5, H8′); LCMS (ES+) 330 ($M+H^+$).

### (1*R**, 2*S**, 3*R**, 4*S**, 5*S**, 6*R**)–3-(2-Chloro-6-methoxy-quinolin-3-yl)-5,6-di-hydroxy-bicyclo-[2.2.1]heptane-2-carboxylic acid (117)



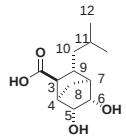
A white solid ; $\nu_{max}$ (DMSO) 2959, 1700 (C=O), 1461, 1260, 1098 $cm^{-1}$; $\delta_H$ (500 MHz; 1:1 MeOD: $CDCl_3$) 8.24 (1H, s, H10), 7.83 (1H, d, *J* 9.0, H14), 7.40 (1H, dd, 9.0, 3.0, H13), 7.28 (1H, d, *J* 3.0, H11), 3.48-3.40 (2H, m, H6, H5), 3.96 (3H, s, H12), 3.48 (1H, d, *J* 4.5, H3), 2.97 (1H, t, *J* 5.0, H9), 2.45 (1H, s, H4), 2.19 (1H, s, H7), 1.97 (1H, d, *J* 8.5, H8), 1.68 (1H, d, *J* 8.5, H8′); LCMS (ES+) 364 ($M+H^+$).

### (1*R**, 2*S**, 3*R**, 4*S**, 5*S**, 6*R**)–5,6-Dihydroxy-3-methyl-bicyclo[2.2.1]heptane-2-carboxylic acid (118)



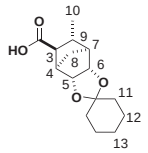
A colourless oil; $\nu_{max}$ (neat) 3353 (OH), 2962, 1702 (C=O), 1455, 1395, 1266, 1194, 1114, 1058 $cm^{-1}$; $\delta_H$ (500 MHz; 1:1 MeOD: $CDCl_3$) 3.73 (1H, s, H6), 3.70 (1H, s, H5), 2.36 (1H, s, H4), 2.09 (1H, t, *J* 5.0, H3), 1.80 (1H, s, H7), 1.77-1.69 (2H, m, H8, H9), 1.35 (1H, d, *J* 10.5, H8′), 0.94 (3H, d, *J* 7.0, H10); LCMS (ES-) 185 ($M-H^+$).

### (1*R**, 2*S**, 3*R**, 4*S**, 5*S**, 6*R**)–5,6-Dihydroxy-3-isobutyl-bicyclo[2.2.1]heptane-2-carboxylic acid (119)



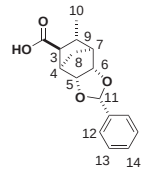
A colourless oil; $\nu_{max}$ (DMSO) 2950, 1662 (C=O), 1316, 1260 $cm^{-1}$; $\delta_H$ (500 MHz; 10:1 MeOD: $CDCl_3$) 3.91 (1H, s, H6), 3.83 (1H, s, H5), 2.46 (1H, s, H4), 2.20 (1H, d, *J* 4.5, H3), 1.78 (1H, s, H7), 1.82 (1H, d, *J* 8.5, H8), 1.79 (1H, d, *J* 6.0, H9), 1.51 (1H, sep, *J* 6.5, H11), 1.39 (1H, d, *J* 8.5, H8′), 1.20-1.12 (2H, m, H10), 0.87 (6H, d, *J* 6.5, H12); LCMS (ES-) 227 ($M-H^+$).

### (1*S**, 2*S**, 6*R**, 7*R**, 8*S**, 9*R**)–9-Methyl-4-cyclohexyl-3,5-dioxa-tricyclo[5.2.1.$0^{2,6}$] decane-8-carboxylic acid (120)



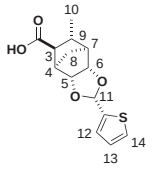
A colourless oil; $\nu_{max}$ (neat) 3202, 2933, 2863, 1700 (C=O), 1449, 1370, 1267, 1190, 1161, 1105, 1090, 1023 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 4.21 (1H, d, *J* 5.5, H6), 4.09 (1H, d, *J* 5.5, H5), 2.62 (1H, d, *J* 4.0, H4), 2.26 (1H, t, *J* 5.0, H3), 2.02 (1H, s, H7), 1.81-1.74 (2H, m, H8, H9), 1.70-1.61 (4H, m, CyH), 1.58-1.52 (4H, m, CyH), 1.44-1.36 (3H, m, CyH, H8′), 1.08 (3H, d, *J* 7.0, H10); $\delta_C$ (125 MHz; $CDCl_3$) 178.81 (C=O), 109.82 (C-C), 80.94 (C[5]H), 77.66 (C[6]H), 50.59 (C[3]H), 47.44 (C[7]H), 44.14 (C[4]H), 35.16 (CyC), 33.54 (C[9]H), 33.45 (CyC), 30.43 (C[8]$H_2$), 25.28 (CyC), 24.06 (CyC), 23.62 (CyC), 20.65 (C[10]H3); LCMS (APCI+) 267 ($M+H^+$): HRMS $(M+H)^+$ found 265.1433 $C_{15}H_{21}O_4$ required 265.1440, $\Delta$ ppm −3.0

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–9-Methyl-4-phenyl-3,5-dioxa-tricyclo[5.2.1.0$^{2,6}$] decane-8-carboxylic acid (121)**



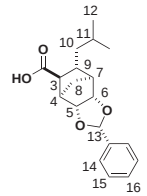
A yellow oil; $\nu_{max}$ (neat) 2953, 2889, 1698 (C=O), 1459, 1422, 1400, 1311, 1295, 1270, 1231, 1193, 1085, 1066, 1007 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.55-7.52 (2H, m, H12), 7.41-7.38 (3H, m, H13, H14), 5.61 (1H, s, H11), 4.71 (1H, br s, OH), 4.33 (1H, d, *J* 5.5, H6), 4.19 (1H, d, *J* 5.5, H5), 2.81 (1H, d, *J* 4.0, H4), 2.34 (1H, t, *J* 5.0, H3), 2.21 (1H, s, H7), 2.03 (1H, d, *J* 10.5, H8), 1.84 (1H, q, *J* 7.0, H9), 1.46 (1H, d, *J* 10.5, H8′), 1.12 (3H, d, *J* 7.0, H10); $\delta_C$ (125 MHz; $CDCl_3$) 178.82 (C=O), 136.01 (C-C), 129.54 (C[14]H), 128.42 (CH), 126.73 (CH), 103.06 (C[11]H), 82.23 (C[5]H), 79.07 (C[6]H), 50.61 (C[3]H), 47.39 (C[7]H), 44.08 (C[4]H), 33.70 (C[9]H), 30.80 (C[8]$H_2$) 20.61 (C[10]$H_3$); LCMS (ES-) 273 (M-H$^+$): HRMS (M+H)$^+$ found 273.1125 $C_{16}H_{17}O_4$ required 273.1127, Δ ppm −0.7.

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–9-Methyl-4-thiophen-2-yl-3,5-dioxa-tricyclo[5.2.1.0$^{2,6}$]decane-8-carboxylic acid (122)**



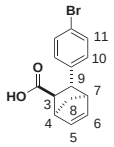
A yellow oil; $\nu_{max}$ (neat) 2896, 1697 (C=O), 1464, 1421, 1389, 1332, 1311, 1270, 1208, 1193, 1059, 1005 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.36 (1H, d, *J* 5.0, H14), 7.21 (1H, d, *J* 3.5, H12), 7.01 (1H, dd, *J* 5.0, 3.5, H13), 5.88 (1H, s, H11), 4.32 (1H, d, *J* 5.5, H6), 4.17 (1H, d, *J* 5.5, H5), 2.79 (1H, s, H4), 2.33 (1H, t, *J* 5.0, H3), 2.19 (1H, s, H7), 2.03 (1H, d, *J* 10.5, H8), 1.83 (1H, q, *J* 7.0, H9), 1.47 (1H, d, *J* 10.5, H8′), 1.11 (3H, d, *J* 7.0, H10); $\delta_C$ (125 MHz; $CDCl_3$) 183.09 (C=O), 139.29 (C-C), 127.02 (CH), 126.66 (CH), 126.51 (CH), 99.49 (C[11]H), 82.35 (C[5]H), 79.23 (C[6]H), 50.50 (C[3]H), 47.37 (C[7]H), 44.07 (C[4]H), 33.65 (C[9]H), 30.67 (C[8]$H_2$) 20.60 (C[10]$H_3$); LCMS (APCI+) 281 (M+H$^+$): HRMS (M+H)$^+$ found 279.0688 $C_{14}H_{15}O_4S$ required 279.0691, Δ ppm −1.1

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–9-Isobutyl-4-phenyl-3,5-dioxa-tricyclo[5.2.1.0$^{2,6}$] decane-8-carboxylic acid (123)**



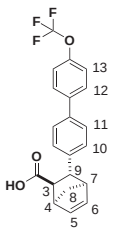
A pale yellow oil; $\nu_{max}$ (DMSO) 2977, 1709 (C=O), 1457, 1377, 1220 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.59-7.49 (2H, m, H14), 7.40-7.34 (3H, m, H15, H16), 5.58 (1H, s, H13), 4.30 (1H, d, *J* 5.5, H6), 4.16 (1H, d, *J* 5.5, H5), 2.78 (1H, d, *J* 4.0, H4), 2.35 (1H, t, *J* 5.0, H3), 2.25 (1H, s, H7), 1.97 (1H, d, *J* 10.5, H8), 1.80-1.78 (1H, m, H9), 1.68-1.64 (1H, m, H11), 1.40 (1H, d, *J* 10.5, H8′), 1.39-1.25 (2H, m, H10), 0.92 (6H, d, *J* 7.0, H12); LCMS (ES-) 315 (M-H$^+$).

**(1$S^*$, 2$R^*$, 3$R^*$, 4$R^*$)–3-(4-Bromo-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (124)**

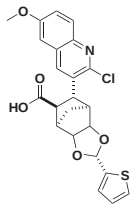
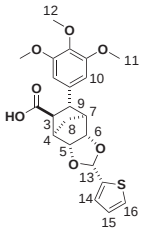
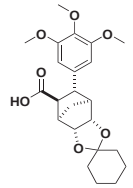
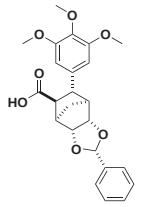
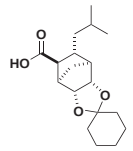
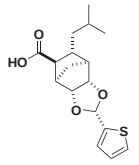
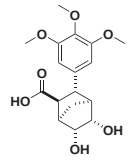


A white solid; $\nu_{max}$ (DMSO) 2977, 1710 (C=O), 1490, 1261, 1220 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.44 (2H, d, *J* 8.5, H11), 7.23 (2H, d, *J* 8.5, H10), 6.45 (1H, dd, *J* 5.5, 3.0, H6), 6.21 (1H, dd, *J* 5.5, 3.0, H5), 3.48 (1H, s, H4), 3.06-3.05 (2H, m, H9, H3), 3.00 (1H, s, H7), 1.76 (1H, d, *J* 8.5, H8), 1.60 (1H, d, *J* 8.5, H8′); LCMS (ES-) 291 (M-H$^+$).

**(1$S^*$, 2$R^*$, 3$R^*$, 4$R^*$)–3-(4′-Trifluoromethoxy-biphenyl-4-yl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (125)**



A colourless oil; $R_f$ 0.10 ($SiO_2$; 10:3 hexane: ethyl acetate); $\nu_{max}$ (neat) 2976 (OH), 1700 (C=O), 1256 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.57 (2H, d, *J* 8.5, H13), 7.49 (2H, d, *J* 8.0, H12), 7.41 (2H, d, *J* 8.0, H11), 7.27 (2H, d, *J* 8.5, H10), 6.46-6.44 (1H, m, H6), 6.22-6.20 (1H, m, H5), 3.35 (1H, s, H4), 3.13 (1H, d, *J* 5.0, H9), 3.09-3.08 (2H, m, H3, H7), 1.82 (1H, d, *J* 9.0, H8), 1.63 (1H, d, *J* 9.0, H8′); $\delta_C$ (125 MHz; $CDCl_3$) 180.04 (C), 148.58 (C), 143.57 (C), 139.63 (C), 139.20 (CH), 137.76 (C), 134.75 (CH), 128.36 (CH), 128.23 (CH), 128.01 (CH), 121.23 (CH), 52.15 (CH), 48.29 (CH), 47.33 (C[8]$H_2$), 47.25 (CH), 46.22 (CH); LCMS (ES+) 389 (M+H$^+$): HRMS (M+Na)$^+$ found 397.10240 $C_{21}H_{17}F_3O_3Na$ required 397.10275, Δ ppm −0.96.

| | Structure | LCMS |
|---|---|---|
| **126** |  | 457 (M+H$^+$) |
| **127** |  $\nu_{max}$ (neat) 2934, 2860, 1704 (C=O), 1588, 1509, 1451, 1241, 1123 cm$^{-1}$ | 433 (M+H$^+$) |
| **128** |  | 419 (M+H$^+$) |
| **129** |  | 443 (M+H$_2$O)$^+$ |
| **130** |  $\nu_{max}$ (DMSO) 2909, 1706 (C=O), 1416, 1304, 1220 cm$^{-1}$ | 309 (M+H$^+$) |
| **131** |  | 321 (M+H$^+$) |
| **132** |  $\nu_{max}$ (neat) 3380, 2939, 2861, 1708 (C=O), 1661, 1589, 1456, 1122 cm$^{-1}$ | 337 (M+H$^+$) |

# 10 Cleavage of compounds to synthesise alcohols

## 10.1 General method for solid supports

To a suspension of the resin (1 equiv.) in THF at 0 °C under nitrogen was added a solution of lithium borohydride hydride (5 equiv.) and the reaction stirred for twenty four hours. The reaction quenched using Rochelles salt and the beads removed by filtration. The aqueous layer was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$) and solvent removed *in vacuo*.

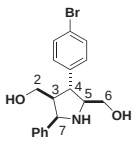
## 10.2 General method for solution phase synthesis

A round-bottom flask, equipped with a magnetic stirrer, containing the library compound (1 equiv.) was dissolved in THF (1 mL/ 100mg of compound) at 0 °C. $LiBH_4$ (2.0 M solution in THF, 6 equiv.) was added and the reaction mixture was stirred for 5h at 0 °C, then left at room temperature. Saturated aqueous Roche's salt (2 mL) was added and the reaction mixture was stirred for 30 minutes. The reaction mixture was then extracted with EtOAc, dried ($MgSO_4$) and concentrated *in vacuo*.

## 10.3 Library compounds generated using this methodology

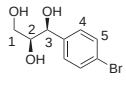
Compounds prepared using branching pathways 1,2,3 and 4 were cleaved after each step to generate carboxylic acids using the above methodology to generate compounds with purity greater than 80 % by NMR and LCMS:

### (2*S**, 3*R**, 4*S**, 5*R**)-[4-(4-Bromo-phenyl)-5-hydroxymethyl-2-phenyl-pyrrolidin-3-yl]-methanol (133)



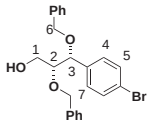
A white solid; $R_f$ 0.43 (30-40 pet. ether:ethyl acetate 1:1); $\nu_{max}$ (thin film) 3369 (b, OH), 2936 (s, CH) cm$^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.49 (2H, d, *J* 8.0, ArH), 7.47-7.34 (5H, m, ArH), 7.19 (2H, d, *J* 8.0, ArH), 4.90 (1H, s, NH), 4.62 (1H, dd, *J* 9.0, 7.0, H7), 4.23 (1H, dd, *J* 11.0, 3.0, H6), 3.60 (1H, dd, *J* 11.0, 1.0, H6), 3.51 (1H, app. t, *J* 11.0, H4), 3.33-3.22 (3H, m, H6, H3), 2.88-2.80 (1H, m, H5); $\delta_C$ (100 MHz, CDCl3) 137.8 (C-C), 136.6 (C-C), 132.4 (CH), 129.5 (CH), 129.1 (CH), 128.7 (CH), 128.0 (CH), 121.7 (C-Br), 73.1 (C[5]H), 72.6 (C[7]H), 61.2 (C[2]$H_2$), 60.4 (C[6]$H_2$), 51.2 (C[3]H), 46.7 (C[4]H); HRMS (ES$^+$) calculated for $C_{18}H_{20}BrNO_2$ [M+H]+ 362.0750, found 362.0748; mp 64 °C (30-40 pet. ether:ethyl acetate 1:1)

### (*rac*)-1-(4-Bromo-phenyl)-propane-1,2,3-triol (134)



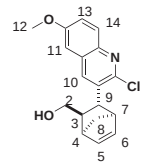
A colourless oil; $R_f$ 0.31 ($SiO_2$; 1:9 MeOH: $CH_2Cl_2$); $\nu_{max}$ (neat) 3416m, 3396m, 3086w br (alcohol), 2956w, 2868w, 1634s (amide), 1544m, 1054s, 729s $cm^{-1}$; $\delta_H$ (400 MHz; $CD_3OD$) 7.50-7.43 (2H, d, *J* 8.5, H5), 7.34-7.28 (2H, d, *J* 8.5, H4), 4.66-4.61 (1H, d, *J* 5.0, H3), 3.67-3.62 (1H, m, H2), 3.67-3.62 (1H, dd, *J* 4.5 11.0, H1), 3.57-3.51 (1H, dd, *J* 6.5, 11.0, H1*prime*); $\delta_C$ (125 MHz; $CD_3OD$) 141.6 (C-C), 130.8 (CH), 128.4 (CH), 120.9 (C-Br), 75.7 (CH), 73.1 (CH), 62.7 (C[1]$H_2$); HRMS found m/z (ESI-H+) 264.0234 $C_9H_{15}{}^{79}BrNO_3{}^+$ required 264.0230, Δ ppm +1.5, mp 94-95 °C (MeOH: $CH_2Cl_2$).

### (*rac*)-2,3-Bis-benzyloxy-3-(4-bromo-phenyl)-propan-1-ol (135)



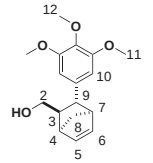

A viscous oil; $R_f$ 0.35 ($SiO_2$; 3:7 EtOAc: Petrol); $\nu_{max}$ (neat) 3457w br (alcohol), 2919w, 2867w, 1486w, 1454m, 1070s, 1011s, 735s, 697s $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 7.55-7.49 (2H, d, *J* 8.5, H5), 7.37-7.22 (12H, m, H4, ArylH), 4.81-4.75 (1H, d, *J* 11.5, H6), 4.64-4.57 (1H, d, *J* 11.5, H6), 4.56-4.49 (2H, m, H7, H3), 4.34-4.27 (1H, d, *J* 11.5, H7′), 3.72-3.62 (1H, q, *J* 6.0, H2), 3.56-3.45 (1H, m, H1), 3.39-3.29 (1H, m, H1′), 1,99-1.90 (1H, t, *J* 6.5, OH); $\delta_C$ (100 MHz; $CDCl_3$) 138.2 (C=O), 137.8 (C-C), 137.5 (C-C), 131.7 (CH), 129.3 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 122.1 (C-Br), 82.3 (CH), 81.6 (CH), 73.9 ($CH_2$), 71.0 ($CH_2$), 61.9 ($CH_2$); HRMS found m/z (ESI-$H^+$) 444.1168 $C_{23}H_{27}{}^{79}BrNO_3{}^+$ required 444.1169, Δ ppm −0.2.

### (1*S**, 2*R**, 3*R**, 4*R**)–[3-(2-Chloro-6-methoxy-quinolin-3-yl)-bicyclo[2.2.1]hept-5-en-2-yl]-methanol (136)



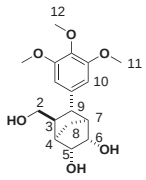

A colourless oil; $\nu_{max}$ (neat) 3277, 1852, 1391, 1116, 1066 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 8.08 (1H, s, H10), 7.89 (1H, d, *J* 9.0, H14), 7.33 (1H, dd, *J* 9.0, 3.0, H13), 7.07 (1H, d, *J* 3.0, H11), 6.49 (1H, dd, *J* 5.5, 3.0, H6), 6.23 (1H, dd, *J* 5.5, 3.0, H5), 3.94 (3H, s, H12), 3.67 (1H, dd, *J* 10.5, 6.0, H2), 3.50-3.45 (1H, m, H2′), 3.18 (1H, s, H4), 3.87 (1H, s, H7), 2.71-2.67 (1H, m, H3), 2.65 (1H, d, *J* 5.5, H9), 1.68 (1H, d, *J* 8.5, H8), 1.58 (1H, d, *J* 8.5, H8′); $\delta_C$ (125 MHz; $CDCl_3$) 158.22 (C), 142.02 (C-C), 138.39 (C[6]H), 136.11 (C), 134.26 (C[5]H), 134.17 (C[10]H), 129.43 (C[14]H), 122.36 (C[13]H), 105.02 (C[11]H), 66.28 (C[2]$H_2$), 55.58 (C[12]$H_3$), 49.92 (C[7]H), 47.73 (C[3]H), 46.15 (C[8]$H_2$), 45.08 (C[9]H), 44.29 (C[4]H); LCMS (ES+) 316 ($M+H^+$).

### (1*S**, 2*R**, 3*R**, 4*R**)–[3-(3,4,5-Trimethoxy-phenyl)-bicyclo[2.2.1]hept-5-en-2-yl]-methanol (137)



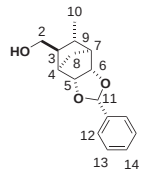

A colourless oil; $\nu_{max}$ (neat) 3421, 2939, 1587, 1509, 1462, 1420, 1330, 1240, 1126 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.55 (2H, s, H10), 6.38 (1H, dd, *J* 5.5, 3.0, H6), 6.16 (1H, dd, *J* 5.5, 3.0, H5), 3.86 (6H, s, H11, H13), 3.83 (3H, s, H12), 3.60 (1H, dd, *J* 9.0, 6.0, H2), 3.45 (1H, t, *J* 9.0, H2′), 3.06 (1H, s, H4), 2.87 (1H, m, H7), 2.37-2.34 (1H, m, H3), 2.12 (1H, d, *J* 4.6, H9), 1.79 (1H, d, *J* 8.5, H8), 1.62 (1H, br s, H8′); LCMS (ES+) 360 ($M+H^+$).

### (1*S**, 2*S**, 3*R**, 4*R**, 5*S**, 6*S**)–5-Hydroxymethyl-6-(3,4,5-trimethoxy-phenyl)-bicyclo[2.2.1]heptane-2,3-diol (138)



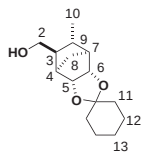

A colourless oil; $\nu_{max}$ (DMSO) 2910, 1587, 1507, 1461, 1410, 1325, 1260, 1126 $cm^{-1}$; LCMS (ES+) 325 ($M+H^+$).

### (1*S**, 2*S**, 4*S**, 6*R**, 7*R**, 8*S**, 9*S**)–(9-Methyl-4-phenyl-3,5-dioxa-tricyclo[5.2.1.$0^{2,6}$]dec-8-yl)-methanol (139)



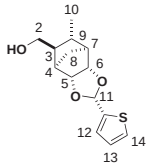

A colourless oil; $\nu_{max}$ (neat) 3420, 2957, 1458, 1403, 1220, 1087, 1064 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.55-7.51 (2H, m, H12), 7.40-7.38 (3H, m, H13, H14), 5.89 (1H, s, H11), 4.38 (1H, d, *J* 5.5, H6), 4.07 (1H, d *J* 5.5, H5), 3.63-3.56 (2H, m, H2), 2.55 (1H, s, H4), 2.14 (1H, s, H7), 1.92 (1H, d, *J* 10.5, H8), 1.65-1.61 (1H, m, H9), 1.40 (1H, d, *J* 10.5, H8′), 1.39-1.37 (1H, m, H3), 1.10 (3H, d, *J* 7.0, H10); LCMS (ES+) 261 ($M+H^+$).

### (1*S**, 2*S**, 6*R**, 7*R**, 8*S**, 9*S**)–(9-Methyl-4-cyclohexyl-2-yl-3,5-dioxa-tricyclo[5.2.1.$0^{2,6}$]dec-8-yl)-methanol (140)



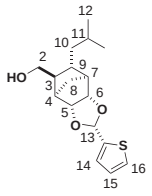

A colourless oil; $\nu_{max}$ (neat) 3421, 2934, 1449, 1370, 1097, 1023 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 4.29 (1H, d, *J* 5.5, H6), 3.97 (1H, d, *J* 5.5, H5), 3.77-3.52 (2H, m, H2), 2.38 (1H, s, H4), 1.95 (1H, s, H7), 1.72-1.62 (10H, m, CyH, H8, H9), 1.42-1.40 (2H, m, CyH), 1.30-1.28 (2H, m, H3, H8′), 1.06 (3H, d, *J* 7.0, H10); LCMS (APCI+) 253 ($M+H^+$).

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$S^*$)–(9-Methyl-4-thiophen-2-yl-3,5-dioxa-tricyclo[5.2.1.0$^{2,6}$]dec-8-yl)-methanol (141)**



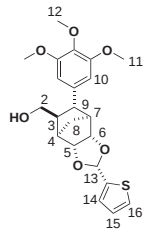
A yellow oil; $\nu_{max}$ (neat) 3421, 2955, 1546, 1444, 1393, 1329, 1202, 1063, 1003 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.36 (1H, d, $J$ 5.0, H14), 7.21 (1H, d, $J$ 3.5, H12), 7.01 (1H, dd, $J$ 5.0, 3.5, H13), 5.88 (1H, s, H11), 4.37 (1H, d, $J$ 5.5, H6), 4.06 (1H, d, $J$ 5.5, H5), 3.88-3.54 (2H, m, H2), 2.54 (1H, s, H4), 2.12 (1H, s, H7), 1.96 (1H, d, $J$ 10.5, H8), 1.63 (1H, m, H9), 1.40 (1H, d, $J$ 10.5, H8′), 1.33-1.30 (1H, m, H3), 1.10 (3H, d, $J$ 7.0, H10); LCMS (APCI+) 267 (M+H$^+$).

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$S^*$)–(9-Isobutyl-4-thiophen-2-yl-3,5-dioxa-tricyclo[5.2.1.0$^{2,6}$]dec-8-yl)-methanol (142)**



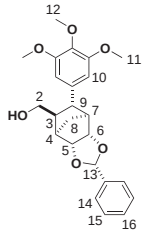
A yellow oil; $\nu_{max}$ (DMSO) 2911, 1393, 1306 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.36 (1H, d, $J$ 5.0, H16), 7.21 (1H, d, $J$ 3.5, H14), 7.00 (1H, m, H15), 5.88 (1H, s, H13), 4.41 (1H, d, $J$ 6.0, H6), 4.05 (1H, d, $J$ 5.5, H5), 3.6-3.63 (1H, m, H2), 3.51 (1H, t, $J$ 9.5, H2′), 2.55 (1H, s, H4), 2.21 (1H, s, H7), 1.94 (1H, d, $J$ 10.5, H8), 1-66-1.68 (2H, m, H11, H9), 1.36-1.19 (4H, m, H8′, H10, H3), 0.93 (6H, d, $J$ 10.0, H12); LCMS (ES+) 309 (M+H$^+$).

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$S^*$)–[4-Thiophen-2-yl-9-(3,4,5-trimethoxy-phenyl)-3,5--dioxa-tricyclo[5.2.1.0$^{2,6}$]dec-8-yl]-methanol (143)**



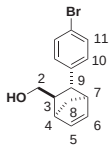
A yellow oil; $\nu_{max}$ (DMSO) 2967, 1261, 1019 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.37 (1H, d, $J$ 5.0, H16), 7.24 (1H, d, $J$ 3.5, H14), 7.03 (1H, dd, 5.0, 3.5, H15), 6.52 (2H, s, H10), 5.95 (1H, s, H13), 4.55 (1H, d, $J$ 5.5, H6), 4.24 (1H, d, $J$ 5.5, H5), 3.89-3.83 (10H, m, H11, H12, H2), 3.72 (1H, dd, $J$ 8.5, 2.2, H2′), 2.70 (1H, s, H4), 2.63 (1H, s, H7), 2.22-2.20 (1H, m, H3), 2.14-2.06 (2H, m, H8, H9), 1.63 (1H, d, $J$ 10.5, H8′); LCMS (ES+) 419 (M+H$^+$).

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$S^*$)–[4-Phenyl-9-(3,4,5-trimethoxy-phenyl)-3,5-dioxa-tricyclo-[5.2.1.0$^{2,6}$]dec-8-yl]-methanol (144)**

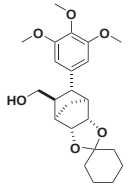
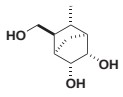
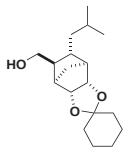
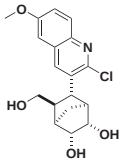
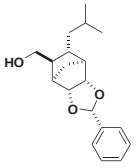
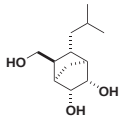


A colourless oil ; $\nu_{max}$ (DMSO) 2931, 1585, 1507, 1457, 1375, 1260 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.57-7.55 (2H, m, H14), 7.42-7.39 (3H, m, H15, H16), 6.52 (2H, s, H10), 5.67 (1H, s, H13), 4.55 (1H, d, $J$ 5.5, H6), 4.25 (1H, d, $J$ 5.5, H5), 3.91-3.80 (10H, m, H11, H12, H2), 3.74 (1H, dd, $J$ 11.0, 8.5, H2′), 2.78 (1H, s, H4), 2.57 (1H, s, H7), 2.27 (1H, t, $J$ 4.0, H3), 2.11-2.06 (2H, m, H8, H9), 1.60 (1H, d, $J$ 10.5, H8′); LCMS (APCI+) 413 (M+H$^+$).

**(1$S^*$, 2$R^*$, 3$R^*$, 4$R^*$)–[3-(4-Bromo-phenyl)-bicyclo[2.2.1]hept-5-en-2-yl] methanol (145)**

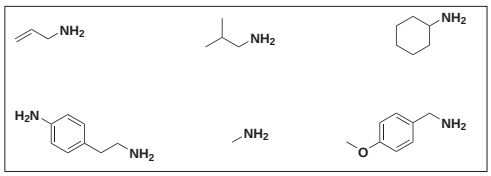


A colourless oil; $\nu_{max}$ (DMSO) 2910, 1489, 1305, 1260 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.43 (2H, d, $J$ 8.5, H11), 7.20 (2H, d, $J$ 8.5, H10), 6.37 (1H, dd, $J$ 5.5, 3.0, H6), 6.17 (1H, dd, $J$ 5.5, 3.0, H5), 3.60 (1H, dd, $J$ 10.5, 6.0, H2), 3.44 (1H, t, $J$ 9.0, H2′), 3.05 (1H, s, H4), 3.87 (1H, s, H7), 2.34-2.29 (1H, m, H3), 2.13 (1H, d, $J$ 4.0, H9), 1.74 (1H, d, $J$ 8.5, H8), 1.56 (1H, dd, $J$ 8.5, 1.5, H8′); LCMS (ES+) 332 (M+H$^+$).

| Structure | LCMS | Structure | LCMS |
|---|---|---|---|
|  **146** | 405 (M+H$^+$) |  **147** | 173 (M+H$^+$) |
|  **148** | 295 (M+H$^+$) |  **149** | 350 (M+H$^+$) |
|  **150** | 301 (M+H$^+$) |  **151** | 214 (M+H$^+$) |

# 11 Cleavage of compounds to synthesise amides

## 11.1 Building blocks used



## 11.2 General method for solid supports

To a suspension of the resin (1 equiv.) in toluene under nitrogen was added a solution of the amine (5 equiv.) and dimethyl aluminium chloride (1M in toluene, 5 equiv.). The reaction stirred for twenty four hours at 65 °C. The reaction was cooled and quenched using ammonium chloride solution and the beads removed by filtration. The aqueous layer was washed with toluene and the organic layer was washed with brine, dried ($MgSO_4$) and solvent removed *in vacuo*.

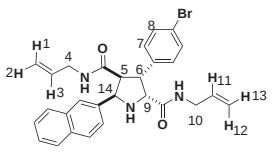
## 11.3 General method for solution phase synthesis

A round-bottom flask, equipped with a magnetic stirrer, containing the library compound (1 equiv.) in toluene was added a solution of the amine (3 equiv.) and dimethyl aluminium chloride (1M in toluene, 3 equiv.) in toluene and the reaction stirred at 65 °C under nitrogen for six hours. The reaction was cooled to room temperature and quenched using saturated ammonium chloride solution. The aqueous layer was extracted with toluene and the organic layer was washed with brine, dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography.

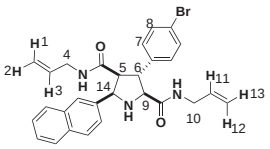
## 11.4 Library compounds generated using this methodology

Compounds prepared using branching pathways 1,2,3 and 4 were cleaved after each step to generate carboxylic acids using the above methodology to generate compounds with purity greater than 80 % by NMR and LCMS:

### 3-(4-Bromo-phenyl)-5-naphthalen-2-yl-pyrrolidine-2,4-dicarboxylic acid bis-allylamide (152)

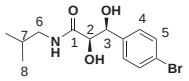


Off-white solid; (2*R**, 3*R**, 4*S**, 5*R**)-3-(4-Bromo-phenyl)-5-naphthalen-2-yl-pyrrolidine-2,4-dicarboxylic acid bis-allylamide (18 mg, 0.04 mmol, 36 %). $R_f$ 0.57 (ethyl acetate); $\nu_{max}$ (thin film) 3052 (s, CH), 2915 (s, CH), 1666 (s, C=O), 1648 (s, C=O), 1632 (s, C=O) $cm^{-1}$; $\delta_H$ (500 MHz, MeOD) 7.96 (1H, s, ArH), 7.94 (1H, d, *J* 9.0, ArH), 7.89-7.86 (2H, m, ArH), 7.64 (1H, dd, *J* 9.0, 2.0, ArH), 7.53 (2H, d, *J* 9.0, ArH), 7.52-7.50 (2H, m, ArH), 7.35 (2H, d, *J* 9.0, ArH), 5.79 (1H, ddt, *J* 17.0, 10.0, 5.0, H3), 5.46 (1H, ddt, *J* 17.0, 10.0, 5.0, H11), 5.10-5.05 (2H, m, H1, H12), 4.89 (1H, d, J 10 Hz, H14), 4.70 (1H, app. dq, *J* 10.0, 2.0, H13), 4.48 (1H, app. dq, *J* 17.0, 2.0, H2), 4.25 (1H, d, *J* 9.0, H9), 3.89-3.74 (3H, m, H4, H6), 3.53 (2H, app. dt, *J* 5.0, 2.0, H10), 3.37 (1H, app. t, *J* 10.0, H5); $\delta_C$ (125 MHz, MeOD) 172.9 (C=O), 171.7 (C=O), 138.8 (C-C), 136.5 (C-C), 135.1 (C[4]H), 134.9 (C-C), 134.8 (C-C), 134.6 (C[11]H), 133.1 (CH), 131.2 (CH), 130.0 (CH), 129.1 (CH), 128.7 (CH), 127.8 (CH), 127.6 (CH), 127.6 (CH), 125.8 (CH), 122.5 (C-Br), 116.4 (C[1,2]$H_2$), 115.4 (C[12,13]$H_2$), 68.3 (C[14]H), 68.1 (C[5]H), 63.5 (C[9]H), 56.7 (C[6]H), 42.6 ($CH_2$), 42.3 ($CH_2$); HRMS ($ES^+$) calculated for $C_{28}H_{28}BrN_3O_2$ $[M+H]^+$ 518.1438, found 518.1434; mp 179 °C (ethyl acetate).



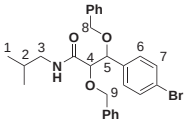
Off white solid; (2*S**, 3*R**, 4*S**, 5*R**)-3-(4-Bromo-phenyl)-5-naphthalen-2-yl-pyrrolidine-2,4-dicarboxylic acid bis-allylamide (12 mg, 21 %): $R_f$ 0.44 (ethyl acetate); $\nu_{max}$ (thin film) 3299 (s, CH), 3061 (s, CH), 1654 (s, C=O), 1635 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.88 (1H, s, ArH), 7.84-7.79 (1H, m, ArH), 7.82 (2H, d, *J* 8.0, ArH), 7.53-7.46 (3H, m, ArH), 7.47 (2H, d, *J* 8.0, ArH), 7.26 (2H, d, *J* 8.0, ArH), 5.90 (1H, ddt, *J* 17.0, 10.0, 5.0, H11), 5.27 (1H, dd, *J* 17.0, 1.0, H12), 5.17 (1H, dd, *J* 10.0, 1.0, H13), 5.04 (1H, d, *J* 8 Hz, C[14]H), 4.96 (1H, ddt, *J* 16.00, 10.0, 6.0, H3), 4.55 (1H, dd, *J* 9.0, 1.0, H2), 4.52 (1H, dd, *J* 16.0, 1.0, H1), 4.04-3.90 (4H, m, H9, H6, H10), 3.29-3.26 (2H, m, H4), 3.16 (1H, dd, *J* 8.0, 5.0, H5); $\delta_C$ (100 MHz, $CDCl_3$) 171.9 (C=O), 170.1 (C=O), 140.6 (C-C), 135.8 (C-C), 134.1 (CH), 133.2 (CH, C-C), 133.2 (C-C), 132.1 (CH), 129.6 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 126.4 (CH), 126.2 (CH), 126.1 (CH), 125.0 (CH), 121.1 (C-Br), 116.4 ($CH_2$), 116.3 ($CH_2$), 68.1 (CH), 65.6 (CH), 59.3 (CH), 51.6 (C[6]H), 42.0 ($CH_2$), 41.6 ($CH_2$); HRMS ($ES^+$) calculated for $C_{28}H_{28}BrN_3O_2$ $[M+H]^+$ 518.1438, found 518.1439; mp 112 °C (Ethyl acetate).

### (*rac*)-3-(4-Bromo-phenyl)-2,3-dihydroxy-*N*-isobutyl-propionamide (153)



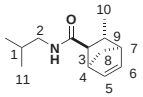
A pale orange oil; $R_f$ 0.15 ($SiO_2$; 1:1 EtOAc: Petrol); $\nu_{max}$ (neat) 3416m, 3396m, 3086w br (alcohol), 2956w, 2868w, 1634s (amide), 1544m, 1054s, 729s $cm^{-1}$; $\delta_H$ (400 MHz; $CD_3OD$) 7.52-7.42 (2H, d, *J* 8.5, H5), 7.38-7.33 (2H, d, *J* 8.5, H4), 5.00-4.97 (1H, d, *J* 3.0, H3), 4.10-4.07 (1H, d, *J* 3.0 , H2), 3.06-3.01 (2H, d, *J* 7.0, H6), 1.82-1.70 (1H, m, H7), 0.94-0.84 (6H, d, *J* 6.5, (H8); $\delta_C$ (125 MHz; $CD_3OD$) 173.3 (C=O), 141.3 (C-C), 130.6 (CH), 128.2 (CH), 120.6 (C-Br), 75.5 (CH), 73.3 (CH), 46.1 (C[6]$H_2$), 28.3 (C[7]H), 18.9 (C[8]$H_3$); HRMS found m/z (ESI-H+) 316.0546 $C_{13}H_{19}{}^{79}BrNO_3{}^+$ required 316.0543, Δ +1.1, mp 130-133 °C (EtOAc: Petrol).

### (*rac*)-2,3-Bis-benzyloxy-3-(4-bromo-phenyl)-*N*-isobutyl-propionamide (154)



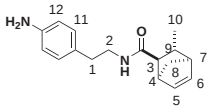
A viscous oil; $R_f$ 0.28 (SiO2; 7:3 EtOAc: Petrol); $\nu_{max}$ (neat) 3433m, 2999w, 2916w, 1656m (amide), 1437m, 1407m 1073s, 952s, 934m $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 7.51-7.43 (2H, d, *J* 8.5, H7), 7.00-6.93 (10H, m, H6, ArylH), 6.82-6.72 (2H, d, *J* 7.0, ArylH), 6.82-6.72 (1H, br m, NH), 4.90-4.84 (1H, d, *J* 2.0, H5), 4.51-4.46 (1H, d, *J* 11.5, H8), 4.35-4,21 (2H, 2 × d, *J* 11.5 11.5, H8′, H9), 4.17-4.12 (1H, d, *J* 11.5, H9′), 3.90-3.88 (1H, d, J 2.2, H7), 3.21-3.02 (2H, m, H3), 1.82-1.68 (1H, m, H2), 0.93-0.82 (6H, 2 × d, *J* 5.5, H1); $\delta_C$ (100 MHz; $CDCl_3$) 169.8 (C=O), 137.5 (C-c), 137.4 (C-C), 136.1 (C-C), 131.4 (CH), 129.1 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 121.8 (C-Br), 83.3 (CH), 80.5 (CH), 74.2 ($CH_2$), 71.8 ($CH_2$), 46.5 ($CH_2$), 28.4 (CH), 20.0 ($CH_3$); HRMS found m/z (ESI-$H^+$) 496.1481 $C_{27}H_{31}{}^{79}BrNO_3{}^+$ required 496.1482, Δ ppm −0.2.

### (1*S**, 2*S**, 3*R**, 4*R**)–3-Methyl-bicyclo[2.2.1]-hept-5-ene-2-carboxylic acid isobutyl-amide (155)



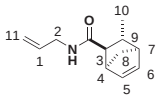
A colourless oil; $\nu_{max}$ (neat) 3297, 2957, 2870, 1644 (C=O), 1541, 1464, 1230 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.34 (1H, dd, *J* 5.5, 3.0, H6), 6.05 (1H, dd, *J* 5.5, 3.0, H5), 3.10-3.01 (3H, m, H2, H4), 2.50 (1H, s, H7), 2.31 (2H, t, *J* 4.0, H3), 1.79-1.74 (2H, m, H1, H9), 1.58 (1H, d, *J* 8.5, H8), 1.46 (1H, dd, *J* 8.5, 1.5, H8′), 1.20 (3H, d, *J* 7.0, H10), 0.90 (6H, d, *J* 6.5, H11); LCMS (ES+) 208 ($M+H^+$).

### (1*S**, 2*S**, 3*R**, 4*R**)–3-Methyl-bicyclo[2.2.1]-hept-5-ene-2-carboxylic acid[2-(4-amino-phenyl)-ethyl]-amide (156)



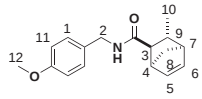
A colourless oil; $\nu_{max}$ (neat) 3288, 2956, 2866, 1637 (C=O), 1542, 1229 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.98 (2H, d, *J* 8.0, H12), 6.67 (2H, dd, *J* 9.0, 2.5, H11), 6.27 (1H, dd, *J* 5.5, 3.0, H6), 5.92 (1H, dd, *J* 5.5, 3.0, H5), 5.31 (1H, br s, NH), 3.63 (1H, br s, NH), 3.45-3.40 (2H, m, H2), 2.97 (1H, s, H4), 2.68 (2H, t, *J* 7.0, H1), 2.46 (1H, s, H7), 2.23 (1H, dd, *J* 4.5, 3.5, H3), 1.70-1.67 (1H, m, H9), 1.53 (1H, d, *J* 8.5, H8), 1.43 (1H, d, *J* 8.5, H8′), 1.15 (3H, d, 7.0, H10); LCMS (ES+) 271 ($M+H^+$).

### (1*S**, 2*S**, 3*R**, 4*R**)–3-Methyl-bicyclo[2.2.1]-hept-5-ene-2-carboxylic acid allylamide (157)



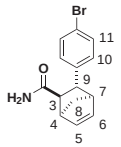
A colourless oil; $\nu_{max}$ (neat) 3288, 2956, 2866, 1637 (C=O), 1542, 1229 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 6.31 (1H, dd, *J* 5.5, 3.0, H6), 6.02 (1H, dd, *J* 5.5, 3.0, H5), 5.85 (1H, ddt, *J* 17.5, 10.5, 5.5, H1), 5.39 (1H, br s, NH), 5.15-5.08 (2H, m, H11), 3.85-3.80 (2H, m, H2), 3.04 (1H, s, H4), 2.54 (1H, s, H7), 2.29 (1H, dd, *J* 4.5, 3.5, H3), 1.80-1.73 (1H, m, H9), 1.55 (1H, d, *J* 8.5, H8), 1.46 (1H, ddd, *J* 8.5, 3.0, 1.5, H8), 1.17 (3H, d, *J* 7.0, H10); LCMS (ES+) 192 ($M+H^+$).

### (1*S**, 2*S**, 3*R**, 4*R**)–3-Methyl-bicyclo[2.2.1]-hept-5-ene-2-carboxylic acid 4-methoxy-benzyl-amide (158)



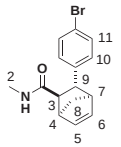
A colourless oil; $\nu_{max}$ (neat) 3320, 2956, 2868, 1645 (C=O), 1511, 1247 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.27 (2H, d, *J* 8.5, ArH), 7.18 (2H, d, *J* 8.5, ArH), 6.34 (1H, dd, *J* 5.5, 3.0, H6), 6.03 (1H, dd, *J* 5.5, 3.0, H5), 5.59 (1H, br s, NH), 4.34 (2H, dd, *J* 5.5, 3.5, H2), 3.81 (3H, s, H12), 3.06 (1H, s, H4), 2.50 (1H, s, H7), 2.32 (1H, dd, *J* 4.5, 3.5, H3), 1.80-1.73 (1H, m, H9), 1.59 (1H, d, *J* 8.5, H8), 1.42 (1H, ddd, *J* 8.5, 3.5, 2.0, H8′), 1.20 (3H, d, *J* 7.0, H10); LCMS (ES+) 272 ($M+H^+$).

### (1*S**, 2*R**, 3*R**, 4*R**)–3-(4-Bromo-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (159a)



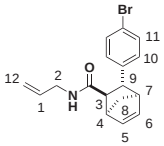
A white solid; $\nu_{max}$ 0.26 ($SiO_2$; 8:2 ethyl acetate: hexane); $\nu_{max}$ (neat) 3348, 3186, 2971, 1662 (C=O), 1610, 1489, 1400, 1333, 1292 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.44 (2H, d, *J* 10.5, H11), ), 7.21 (2H, d, *J* 10.5, H10), 6.46 (1H, dd, *J* 5.5, 3.0, H6), 6.20 (1H, dd, *J* 5.5, 3.0, H5), 5.35 (2H, br s, $NH_2$), 3.21 (1H, s, H4), 3.06 (1H, d, *J* 4.0, 1.0, H9), 3.03 (1H, s, H7), 2.84 (1H, dd, *J* 5.5, 3.5, H3), 1.78 (1H, d, *J* 8.5, H8), 1.66 (1H, d, *J* 8.5, H8′); $\delta_C$ (125 MHz; $CDCl_3$) 175.40 (C=O), 143.30 (C-C), 139.05 (C[6]H), 134.03 (C[5]H), 131.61 (C[11]H), 129.15 (C[10]H), 53.35 (C[3]H), 48.32 (C[7]H), 47.77 (C[9]H), 47.48 (C[8]$H_2$), 46.79 (C[4]H); LCMS (ES+) 309 ($M+H^+$), $(M+H)^+$ found 309.0599 $C_{14}H_{14}BrNO$ required 309.0597, Δ ppm +0.7; mp 128-129 °C (ethyl acetate: hexane).

### (1*S**, 2*R**, 3*R**, 4*R**)–3-(4-Bromo-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid methyl-amide (160)



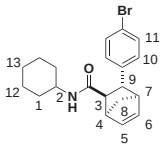
A white solid; $R_f$ 0.31 ($SiO_2$; 1:1 toluene: ethyl acetate); $\nu_{max}$ (DMSO) $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.40 (2H, br s, H11), 7.17 (2H, d, *J* 6.0, H10), 6.42 (1H, br s, H6), 6.14 (1H, br s, H5), 5.69 (1H, br s, NH), 3.16 (1H, s, H4), 3.04 (1H, d, *J* 9.0, H9), 2.98 (1H, s, H7), 2.77 (4H, br s, H3, H2), 1.71 (1H, d, *J* 4.5, H8), 1.60 (1H, d, *J* 4.5, 1.5, H8′); $\delta_C$ (100 MHz; $CDCl_3$) 173.94 (C=O), 143.61 (C-C), 138.71 (C[6]H), 134.13 (C[5]H), 131.52 (C[11]H), 129.18 (C[10]H), 119.78 (C-Br), 53.68 (C[3]H), 48.39 (C[7]H), 47.70 (C[8]$H_2$), 47.41 (C[9]H), 46.75 (C[4]H), 26.42 (C[2]$H_3$); LCMS (ES+)306 ($M+H^+$).

**(1*S**, 2*R**, 3*R**, 4*R**)–3-(4-Bromo-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid allylamide (161)**



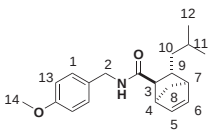
A white solid; $\nu_{max}$ (DMSO) 2930, 1659 (C=O), 1317, 1220 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.45 (2H, d, *J* 8.5, H11), 7.23 (2H, d, *J* 8.5, H10), 6.45 (1H, dd, *J* 5.5, 3.0, H6), 6.35 (1H, dd, *J* 5.5, 3.0, H5), 5.87-5.79 (1H, m, H1), 5.32 (1H, br s, NH), 5.18-5.13 (2H, m, H12), 3.93-3.85 (2H, m, H2), 3.19 (1H, s, H4), 3.06 (1H, d, *J* 4.5, H9), 3.01 (1H, s, H7), 2.80 (1H, dd, *J* 5.0, 3.5, H3), 1.77 (1H, d, *J* 8.5, H8), 1.63 (1H, dd, *J* 8.5, 1.5, H8′); $\delta_C$ (100 MHz; $CDCl_3$) 173.03 (C=O), 143.53 (C-C), 138.85 (C[6]H), 134.37 (C[1]H), 134.05 (C[5]H), 131.55 (C[11]H), 129.15 (C[10]H), 119. 83 (C-Br), 116.23 (C[12]$H_2$), 53.86 (C[3]H), 48.23 (C[7]H), 47.73 (C[8]$H_2$), 47.47 (C[9]H), 46.76 (C[4]H), 41.97 (C[2]$H_2$); LCMS (ES+) 332 ($M+H^+$): HRMS $(M+H)^+$ found 332.0641 $C_{17}H_{18}BrNO$ required 332.0645, Δ ppm −1.2; mp 95-96 °C ($CH_2Cl_2$).

**(1*S**, 2*R**, 3*R**, 4*R**)–3-(4-Bromo-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid cyclohexylamide (159b)**



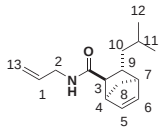
A white solid; $R_f$ 0.52 ($SiO_2$; 10:1 toluene: ethyl acetate); $\nu_{max}$ (neat) 3265, 2931, 2852, 1641 (C=O), 1556, 1487, 1453, 1009 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.43 (2H, d, *J* 10.5, H11), 7.18 (2H, d, *J* 10.5, H10), 6.42 (1H, dd, *J* 5.5, 3.0, H6), 6.15 (1H, dd, *J* 5.5, 3.0, H5), 5.30 (1H, br s, NH), 3.77-3.74 (1H, m, H2), 3.14 (1H, s, H4), 3.03 (1H, d, *J* 4.0, H9), 3.00 (1H, s, H7), 2.71 (1H, dd, *J* 5.0, 2.0, H3), 1.89 (2H, d, *J* 11.5, H1), 1.74 (1H, d, *J* 8.5, H8), 1.72-1.60 (4H, m, CyH, H8′), 1.38-1.34 (2H, m, CyH), 1.17-1.05 (3H, m, CyH); $\delta_C$ (125 MHz; $CDCl_3$) 172.18 (C=O), 143.78 (C-C), 138.73 (C[6]H), 134.05 (C[5]H), 131.51 (C[11]H), 129.16 (C[10]H), 119.76 (C-Br), 54.11 (C[3]H), 48.23 (C[7]H), 48.09 (C[9]H), 47.74 (C[8]$H_2$), 47.45 (C[2]H), 46.77 (C[4]H), 33.28 (C[cy]$H_2$), 33.20 (C[cy]$H_2$), 25.55 (C[cy]$H_2$), 24.88 (C[cy]$H_2$), 24.83 (C[cy]$H_2$); LCMS (ES+) 374 ($M+H^+$), HRMS $(M+H)^+$ found 374.1118 $C_{20}H_{24}BrNO$ required 374.1114, Δ ppm +1.1; mp 164-166 °C (toluene: ethyl acetate).

**(1*S**, 2*S**, 3*R**, 4*R**)–3-Isobutyl-bicyclo[2.2.1]-hept-5-ene-2-carboxylic acid 4-methoxy-benzylamide (162)**



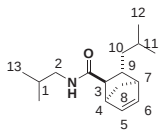
An orange oil; $R_f$ 0.32 ($SiO_2$; 10:2 toluene: ethyl acetate); $\nu_{max}$ (neat) 3270, 2956, 1633 (C=O), 1612, 1553, 1509, 1243, 1232, 1025 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.18 (2H, dd, *J* 6.5, 2.0, H13), 6.87 (2H, dd, *J* 6.5, 2.0, H1), 6.32 (1H, dd, *J* 5.5, 3.0, H6), 6.02 (1H, dd, *J* 5.5, 3.0, H5), 5.59 (1H, br s, NH), 4.39-4.30 (2H, m, H2), 3.81 (3H, s, H14), 3.04 (1H, s, H4), 2.58 (1H, s, H7), 2.35 (1H, dd, *J* 4.5, 3.5, H3), 1.79-1.77 (1H, m, H9), 1.68-1.66 (1H, m, H11), 1.54 (1H, d, *J* 8.0, H8), 1.45 (1H, dd, *J* 8.0, 3.0, H8′), 1.36-1.34 (2H, m, H10), 0.92 (3H, d, *J* 6.5, H12), 0.90 (3H, d, *J* 6.5, H12′); LCMS (ES+) 314 ($M+H^+$).

**(1*S**, 2*S**, 3*R**, 4*R**)–3-Isobutyl-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid allylamide (163)**



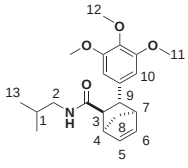
An orange oil; $R_f$ 0.31 ($SiO_2$; 10:2 toluene: ethyl acetate); $\nu_{max}$ (neat) 3303, 2959, 296, 2869, 1640 (C=O), 1548, 1234 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.34 (1H, dd, *J* 5.5, 3.0, H6), 6.05 (1H, dd, *J* 5.5, 3.0, H5), 5.86-5.79 (1H, m, H1), 5.42 (1H, br s, NH), 5.16 (1H, dd, *J* 17.0, 1.5, H13), 5.13 (1H, dd, *J* 10.5, 1.5, H13′), 3.90-3.82 (2H, m, H2), 3.06 (1H, s, H4), 2.59 (1H, s, H7), 2.35 (1H, dd, *J* 4.5, 3.5, H3), 1.77 (1H, dd, *J* 7.5, 6.0, H9), 1.68-1.63 (1H, m, H11), 1.55 (1H, d, *J* 8.5, H8), 1.45 (1H, dd, *J* 8.5, 1.5, H8′), 1.39-1.32 (2H, m, H10), 1.92 (3H, dd, *J* 6.5, H12), 1.91 (3H, dd, *J* 6.5, H12′); LCMS (ES+) 234 ($M+H^+$).

**(1*S**, 2*S**, 3*R**, 4*R**)–3-Isobutyl-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid isobutyl-amide (164)**



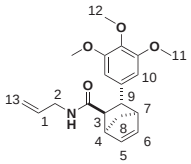
An colourless oil; $R_f$ 0.35 ($SiO_2$; 10:2 toluene: ethyl acetate); $\nu_{max}$ (neat) 3267, 2953, 2898, 2868, 1637 (C=O), 1557, 1466, 1160 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.34 (1H, dd, *J* 5.5, 3.0, H6), 6.05 (1H, dd, *J* 5.5, 3.0, H5), 5.42 (1H, br s, NH), 3.09-3.00 (3H, s, H2, H4), 2.58 (1H, s, H7), 2.32 (1H, dd, *J* 4.5, 3.5, H3), 1.75-1.71 (2H, m, H1, H9), 1.66 (1H, septet, *J* 6.5, H11), 1.54 (1H, d, *J* 8.5, H8), 1.45 (1H, dd, *J* 8.5, 1.5, H8′), 1.38-1.33 (2H, m, H10), 0.91-0.89 (12H, m, H12, H13); $\delta_C$ (125 MHz; $CDCl_3$) 174.35 (C=O), 138.62 (C[6]H), 133.28 (C[5]H), 53.38 (C[3]H), 47.56 (C[7]H), 47.15 (C[8]$H_2$), 46.73 (C[9]H), 46.02 (C[2]$H_2$), 45.89 (C[10]$H_2$), 42.28 (C[4]H), 28.56 (C[1]H), 26.86 (C[11]H), 23.86 (C[12]$H_3$), 22.77 (C[12]$H_3$), 20.08 (C[13]$H_3$); LCMS (ES+) 250 ($M+H^+$): HRMS $(M+H)^+$ found 250.2161 $C_{16}H_{28}NO$ required 250.2171, Δ ppm −4.1.

**(1*S**, 2*S**, 3*R**, 4*R**)–3-(3,4,5-Trimethoxy-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid isobutyl-amide (165)**



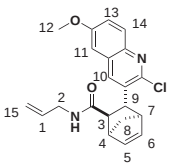
A colourless oil; $R_f$ 0.25 ($SiO_2$; 10:2 toluene: ethyl acetate); $\nu_{max}$ (neat) 3320, 2960, 1647 (C=O), 1587, 1509, 1462, 1240, 1127 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.55 (2H, s, H10), 6.45 (1H, dd, *J* 5.5, 3.0, H6), 6.19 (1H, dd, *J* 5.5, 3.0, H5), 5.45 (1H, br s, NH), 3.86 (6H, s, H11), 3.85 (3H, s, H12), 3.18 (1H, s, H4), 3.11-3.07 (2H, m, H2), 3.00-2.97 (2H, m, H7, H9), 2.81 (1H, dd, *J* 4.5, 3.5, H3), 1.83 (1H, d, *J* 8.5, H8), 1.76 (1H, septet, *J* 6.5, H1), 1.45 (1H, dd, *J* 8.5, 1.5, H8′), 0.91 (6H, d, *J* 6.5, H13); LCMS (APCI+) 360 ($M+H^+$).

### (1*S**, 2*S**, 3*R**, 4*R**)–3-(3,4,5-Trimethoxy-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid allylamide (166)



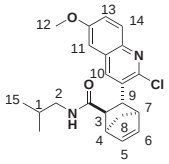
A colourless oil; $\nu_{max}$ (neat) 3312, 2962, 1642 (C=O), 1586, 1508, 1456, 1418, 1332, 1240, 1124 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.55 (2H, s, H10), 6.46 (1H, dd, *J* 5.5, 3.0, H6), 6.16 (1H, dd, *J* 5.5, 3.0, H5), 5.88-5.82 (1H, m, H1), 5.46 (1H, br s, NH), 5.17 (1H, d, *J* 17.0, H13), 5.13 (1H, dd, *J* 10.5, 1.0, H13′), 3.91-3.83 (11H, m, H11, H12, H2), 3.20 (1H, s, H4), 3.00-2.98 (2H, m, H7, H3), 2.83 (1H, dd, *J* 5.0, 3.5, H9), 1.84 (1H, d, *J* 8.5, H8), 1.65 (1H, d, *J* 8.5, H8′); LCMS (ES+) 344 ($M+H^+$).

### (1*S**, 2*S**, 3*R**, 4*R**)–3-(2-Chloro-6-methoxy-quinolin-3-yl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid allylamide (167)



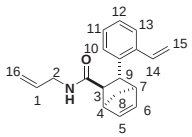
A white solid; $R_f$ 0.05 ($SiO_2$; 10:1 toluene: ethyl acetate); $\nu_{max}$ (neat) 2971, 1638 (C=O), 1374, 1238 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 7.98 (1H, s, H10), 7.89 (1H, d, *J* 9.0, H14), 7.34 (1H, dd, *J* 9.0, 3.0, H13), 7.07 (1H, d, *J* 3.0, H11), 6.55 (1H, dd, *J* 5.5, 3.0, H6), 6.26 (1H, dd, *J* 5.5, 3.0, H5), 5.86-5.81 (1H, m, H1), 5.54 (1H, br s, NH), 5.17 (1H, dd, *J* 17.0, 3.0, H15), 5.12 (1H, dd, *J* 11.5, 3.0, H15′), 3.94 (3H, s, H12), 3.90-3.87 (2H, m, H2), 3.41 (1H, d, *J* 5.0, H3), 3.31 (1H, s, H4), 3.09 (1H, s, H7), 3.03 (1H, dd, *J* 5.0, 3.5, H9), 1.75 (1H, d, *J* 8.5, H8), 1.63 (1H, d, *J* 8.5, H8′); $\delta_C$ (125 MHz; $CDCl_3$) 172.70 (C=O), 158.28 (C), 149.54 (C-C), 138.02 (C[6]H), 135.87 (C), 134.91 (C[5]H), 134.32 (C[10]H), 133.78 (C[1]H), 129.50 (C[14]H), 128.36 (C), 122.50 (C[13]H), 116.43 (C[15]$H_2$), 105.02 (C[11]H), 55.60 (C[12]$H_3$), 51.58 (C[3]H), 49.32 (C[7]H), 47.26 (C[8]$H_2$), 47.04 (C[9]H), 45.97 (C[4]H), 42.08 (C[2]$H_2$); LCMS (ES+) 369 ($M+H^+$): HRMS $(M+H)^+$ found 369.1368 $C_{21}H_{22}N_2O_2Cl$ required 369.1370, Δ ppm −0.4; mp 182-183 °C (toluene: ethyl acetate).

### (1*S**, 2*S**, 3*R**, 4*R**)–3-(2-Chloro-6-methoxy-quinolin-3-yl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid isobutyl-amide (168)



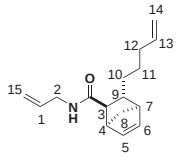
A colourless oil; $\nu_{max}$ (DMSO) 2987, 2910, 1618 (C=O), 1498, 1305, 1228 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 8.00 (1H, s, H10), 7.90 (1H, d, *J* 9.0, H14), 7.35 (1H, dd, 9.0, 3.0, H13), 7.07 (1H, d, *J* 3.0, H11), 6.55 (1H, dd, *J* 5.5, 3.0, H6), 6.26 (1H, dd, *J* 5.5, 3.0, H5), 5.47 (1H, br s, NH), 3.94 (3H, s, H12), 3.40 (1H, d, *J* 5.0, H3), 3.30 (1H, s, H4), 3.11-3.02 (4H, m, H9, H7, H2), 1.79-1.74 (2H, m, H8, H1), 1.63 (1H, d, *J* 8.5, H8′), 0.90 (6H, d, *J* 6.5, H15); LCMS (APCI+) 385 ($M+H^+$).

### (1*S**, 2*S**, 3*R**, 4*R**)–3-(2-Vinyl-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid allylamide (169)



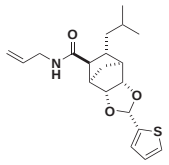
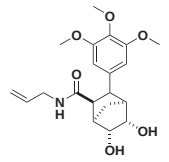
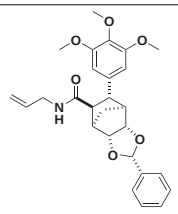
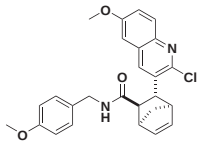
A cream solid; $R_f$ 0.24 ($SiO_2$; 10:3 toluene: ethyl acetate); $\nu_{max}$ (neat) 3292, 1641 (C=O), 1541, 1262, 1125 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.05 (1H, dd, *J* 7.5, 10, H10), 7.35 (1H, d, *J* 7.5, H13), 7.28 (1H, t, *J* 7.5, H11), 7.23 (1H, t, *J* 7.5, H12), 7.05 (1H, dd, *J* 17.0, 11.0, H14), 6.48 (1H, dd, *J* 5.5, 3.0, H6), 6.21 (1H, dd, *J* 5.5, 3.0, H5), 5.83-5.78 (1H, m, H1), 5.59 (1H, dd, *J* 17.0, 4.0, H15), 5.46 (1H, br s, NH), 5.28 (1H, dd, *J* 11.0, 1.5, H15′), 5.13 (1H, dd, *J* 17.0, 1.5, H16), 5.10 (1H, dd, *J* 10.5, 1.1, H16′), 3.88-3.80 (2H, m, H2), 3.26 (1H, d, *J* 5.0, H3), 3.19 (1H, s, H4), 2.96 (1H, s, H7), 2.85 (1H, dd, *J* 5.0, 3.5, H9), 1.83 (1H, d, *J* 8.5, H8), 1.59 (1H, dd, *J* 8.5, 1.5, H8′); $\delta_C$ (125 MHz; $CDCl_3$) 173.34 (C=O), 141.21 (C), 138.23 (C[6]H), 138.17 (C), 135.40 (CH), 134.59 (C[5]H), 134.43 (CH), 127.90 (CH), 126.58 (CH), 126.37 (CH), 125.37 (CH), 116.19 (C[16]$H_2$), 52.31 (C[3]H), 49.35 (C[9]H), 47.53 (C[7]H), 47.18 (C[8]$H_2$), 44.90 (C[4]H), 42.01 (C[2]$H_2$); LCMS (ES+) 280 ($M+H^+$): HRMS $(M+Na)^+$ found 302.1521 $C_{19}H_{21}NONa$ required 302.1521, Δ ppm +0.2.

### (1*S**, 2*S**, 3*R**, 4*R**)–3-Pent-4-enyl-bicyclo[2.2.1]-hept-5-ene-2-carboxylic acid allylamide (170)



A white solid; $R_f$ 0.25 ($SiO_2$; 10:1 toluene: ethyl acetate); $\nu_{max}$ (neat) 3064, 2972, 1641 (C=O), 1533, 1451, 1418, 1333, 1265, 1219, 1046 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.32 (1H, dd, *J* 5.5, 3.0, H6), 6.04 (1H, dd, *J* 5.5, 3.0, H5), 5.82-5.78 (2H, m, H13, H1), 5.46 (1H. br s, NH), 5.16 (1H, d, *J* 17.0, H15), 5.12 (1H, d, *J* 10.5, H15′), 5.01 (1H, dq, *J* 17.0, 1.5, H14), 4.95 (1H, dd, *J* 10.0, 1.0, H14′), 3.86-3.84 (2H, m, H2), 3.06 (1H, s, H4), 2.62 (1H, s, H7), 2.35 (1H, dd, *J* 4.5, 4.0, H3), 2.08 (2H, br d,

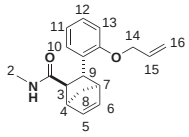
*J* 6.5, H12), 1.68-1.66 (1H, m, H9), 1.15-1.45 (6H, m, H8, H10, H11); $\delta_C$ (125 MHz; $CDCl_3$) 174.07 (C=O), 138.76 (C[6]H), 138.66 (C[13]H), 134. 59 (C[1]H), 133.18 (C[5]H), 115.98 (C[15]$H_2$), 114.33 (C[14]$H_2$), 43.12 (C[3]H), 47.13 (C[7]H), 47.10 (C[8]$H_2$), 46.51 (C[4]H), 44.23 (C[9]H), 41.80 (C[2]$H_2$), 35.69 (C[11]$H_2$), 33.90 (C[12]$H_2$), 27.95 (C[10]$H_2$); LCMS (APCI+) 246 ($M+H^+$): HRMS $(M+H)^+$ found 246.1852 $C_{16}H_{24}ON$ required 246.1852, $\Delta$ ppm +0.0; mp 34-35 °C (toluene: ethyl acetate).

| | Structure | LCMS |
|---|---|---|
| **171** |  | 362 ($M+H^+$) |
| **172** |  | 377 ($M+H^+$) |
| **173** |  | 466 ($M+H^+$) |
| **174** |  | 449 ($M+H^+$) |

## 11.5 Combined diels-alder and amide cleavage reactions

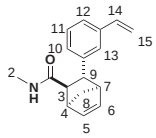
To a solution of HWE product (1 equiv.) in $CH_2Cl_2$ (25 mL/g) at -78 °C under nitrogen was added dimethylaluminium chloride (1M solution in hexane; 5 equiv.) and cyclopentadiene (20 equiv.). The yellow solution was stirred at -78 °C for one hour then allowed to warm to room temperature. After four hours toluene (25 mL/g) was added to the reaction followed by a solution of methylamine.HCl (10 equiv.) and dimethylaluminium chloride (4 equiv.) in toluene (20 ml). The reaction was stirred at 50 °C overnight and the reaction cooled to room temperature and quenched with ammonium chloride solution. The organic layer was separated, washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography to yield:

**(1$S^*$, 2$R^*$, 3$R^*$, 4$R^*$)–3-(2-Allyloxy-phenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid methylamide (175)**



A yellow oil (500 mg, 23 %); $R_f$ 0.24 ($SiO_2$; 1:1 toluene: ethyl acetate); $\nu_{max}$ (DMSO) 2992, 1668 (C=O), 1544, 1489, 1408, 1242 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.33 (1H, d, *J* 7.5, H10), 7.20 (1H, td, *J* 7.5, 1.5, H11), 6.97 (1H, td, *J* 7.5, 1.5, H12), 6.87 (1H, d, *J* 8.0, H13), 6.42 (1H, dd, *J* 5.5, 3.0, H6), 6.24 (1H, dd, *J* 5.5, 3.0, H5), 6.10-6.03 (2H, m, H15, NH), 5.41 (1H, dd, *J* 17.5, 1.5, H16), 5.31 (1H, dd, *J* 10.5, 1.0, H16′), 4.59-4.52 (2H, m, H14), 3.31 (1H, s, H4), 3.08 (1H, d, *J* 5.0, H9), 3.01 (1H, s, H7), 2.77-2.74 (4H, m, H3, H2), 1.81 (1H, d, *J* 8.5, H8), 1.58 (1H, dd, *J* 8.5, 1.5, H8′); $\delta_C$ (125 MHz; $CDCl_3$) 174.60 (C=O), 156.27 (C), 138.14 (C[6]H), 135.78 (C[13]H), 133.29 (C[5]H), 133.05 (C), 127.15 (CH), 126.42 (CH), 121.07 (CH), 117.87 (C[16]$H_2$), 111.58 (C[15]H), 69.28 (C[14]$H_3$), 53.60 (C[3]H), 48.48 (C[9]H), 47.41 (C[8]$H_2$), 46.56 (C[7]H), 41.81 (C[4]H), 26.20 (C[2]$H_2$); LCMS (APCI+) 284 ($M+H^+$): HRMS $(M+Na)^+$ found 306.1476 $C_{18}H_{21}NO_2Na$ required 306.1470, $\Delta$ ppm +2.1.

**(1$S^*$, 2$R^*$, 3$R^*$, 4$R^*$)–3-(3-Vinyl-phenyl)-bicyclo-[2.2.1]hept-5-ene-2-carboxylic acid methylamide (176)**



Colourless oil (300 mg, 17 %); $R_f$ 0.28 ($SiO_2$; 1:1 toluene: ethyl acetate); $\nu_{max}$ (neat) 3274, 3076, 2976, 1665 (C=O), 1262, 1556, 1411, 1341, 1295, 1233, 1106 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.33 (1H, s, H13), 7.28-7.18 (3H, m, H11, H10, H12), 6.75-6.68 (1H, m, H14), 6.44 (1H, dd, *J* 5.5, 3.0, H6), 6.18 (1H, dd, *J* 5.5, 3.0, H5), 5.76 (1H, d, *J* 17.0, H15), 5.67 (1H, br s, NH), 5.25 (1H, dd, *J* 11.0, 1.0, H15′), 3.19 (1H, s, H4), 3.04 (1H, d, *J* 5.5, H9), 3.01 (1H, s, H7), 3.29 (1H, dd, *J* 5.0, 3.5, H9), 2.78 (3H, d, *J* 5.0, H2), 1.81 (1H, d, *J* 8.5, H8), 1.59 (1H, dd, *J* 8.5, 1.5, H8′); LCMS (APCI+) 254 ($M+H^+$).

# 12 Cleavage of compounds to synthesise esters

## 12.1 General method for solid supports

To a suspension of the resin (1 equiv.) in (m)ethanol at 0 °C under nitrogen was added a sodium (m)ethoxide (5 equiv.) and the reaction stirred for twenty four hours. The reaction quenched using water and the beads removed by filtration. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with brine, dried ($MgSO_4$) and solvent removed *in vacuo*.

## 12.2 General method for solution phase synthesis

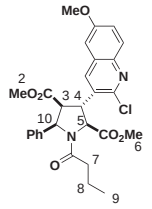
A round-bottom flask, equipped with a magnetic stirrer, containing the library compound (1 equiv.) was added a solution of sodium ethoxide (1.5 equiv.) in ethanol (10 mL/g of compound). The reaction was stirred at 0 °C for three hours

under nitrogen then a further portion of sodium ethoxide (1.5 equiv.) in ethanol (2 ml) was added and the reaction stirred until complete by TLC. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and solvent removed *in vacuo*.

## 12.3 Library compounds generated using this methodology

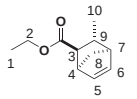
Compounds prepared using branching pathways 1,2,3 and 4 were cleaved after each step to generate carboxylic acids using the above methodology to generate compounds with purity greater than 80 % by NMR and LCMS:

### (2*S**, 3*R**, 4*S**, 5*R**)-1-Butyryl-3-(2-chloro-6-methoxy-quinolin-3-yl)-5-phenyl-pyrrolidine-2,4-dicarboxylic acid dimethyl ester (177)



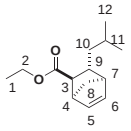

A colourless oil. $R_f$ 0.19 (ethyl acetate); $\nu_{max}$ (thin film) 2954 (s, CH), 2874 (s, CH), 1742 (s, C=O), 1647 (s, C=O), 1624 (s, C=O) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.01 (1H, s, ArH), 7.89 (1H, d, *J* 9.0, ArH), 7.76 (2H, d, *J* 7.0, ArH), 7.44-7.33 (4H, m, ArH), 7.03 (1H, s, ArH), 5.47 (1H, d, *J* 8.0, H10), 4.62 (2H, m, H3, H5), 4.10 (1H, m, H4), 3.92 (3H, s, $OCH_3$), 3.72 (3H, s, $OCH_3$), 3.25 (3H, s, $OCH_3$), 2.23-2.18 (1H, m, H7), 1.99-1.96 (1H, m, H7′), 1.59-1.52 (2H, m, H8), 0.79 (3H, t, *J* 7.0, H9); $\delta_C$ (125 MHz, $CDCl_3$) 172.9 (C=O), 171.0 (C=O), 168.0 (C=O), 158.5 (C-O), 148 (C-Cl), 143.0 (C-C), 137.7 (C-C), 136 (CH), 129.7 (CH), 128.8 (CH), 128.3 (C-C), 127.3 (CH), 127 (C-C), 123.7 (CH), 104.7 (CH), 65.5 (C[5]H), 63.2 (C[10]H), 55.6 ($CH_3$r), 55.5 (C[3]H), 52.6 (C[2]$H_3$), 52.0 (C[6]$H_3$), 43.5 (C[4]H), 35.7 (C[7]$H_2$), 17.9 (C[8]$H_2$), 13.7 (C[9]$H_3$); HRMS ($ES^+$) calculated for $C_{28}H_{29}ClN_2O_6$ $[M+H]^+$ 525.1787, found 525.1784.

### (1*S**, 2*S**, 3*R**, 4*R**)-3-Methyl-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid ethyl ester (178)



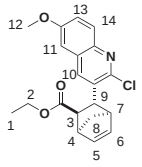

A colourless oil; $R_f$ 0.34 ($SiO_2$; 10:2 hexane: ethyl acetate); $\nu_{max}$ (neat) 2962, 1728 (C=O), 1463, 1178, 1033 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.26 (1H, dd, *J* 5.5, 3.0, H6), 5.99 (1H, dd, *J* 5.5, 3.0, H5), 4.10-4.05 (2H, m, H2), 3.11 (1H, s, H3), 2.47 (1H, s, H4), 2.37 (1H, t, *J* 4.0, H7), 1.85-1.82 (1H, m, H9), 1.55 (1H, d, *J* 8.5, H8), 1.43 (1H, dq, *J* 8.5, 1.5, H8′), 1.24 (3H, t, *J* 7.0, H1), 1.18 (3H, d, *J* 7.0, H10); $\delta_C$ (125 MHz; $CDCl_3$) 174.70 (C=O), 138.62 (C[6]H), 133.24 (C[5]H), 60.01 (C[2]$H_2$), 52.56 (C[3]H), 48.84 (C[7]H), 45.97 (C[8]$H_2$), 45.93 (C[4]H), 37.80 (C[9]H), 20.94 (C[10]$H_3$), 14.27 (C[1]$H_3$); LCMS (ES+) 181 $(M+H^+)$. Data agrees with literature values [4]

### (1*S**, 2*S**, 3*R**, 4*R**)-3-Isobutyl-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid ethyl ester (179)



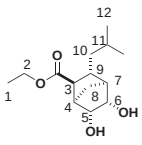

An colourless oil; $R_f$ 0.54 ($SiO_2$; 10:2 hexane: ethyl acetate); $\nu_{max}$ (neat) 2957, 1733 (C=O), 1467, 1367, 1333, 1178 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.27 (1H, dd, *J* 5.5, 3.0, H6), 6.00 (1H, dd, *J* 5.5, 3.0, H5), 4.10-4.05 (2H, m, H2), 3.11 (1H, s, H4), 2.55 (1H, s, H7), 2.40 (1H, dd, *J* 4.0, 3.5, H3), 1.85 (1H, m, H9), 1.53 (1H, septet, *J* 6.5, H11), 1.52 (1H, d, *J* 8.5, H8), 1.38 (1H, d, *J* 8.5, H8′), 1.32-1.27 (2H, m, H10), 1.23 (3H, t, *J* 7.0, H1), 0.93-0.89 (6H, m, H12); $\delta_C$ (125 MHz; $CDCl_3$) 174.80 (C=O), 138.50 (C[6]H), 133.42 (C[5]H), 60.02 (C[2]$H_2$), 51.44 (C[3]H), 47.40 (C[7]H), 46.40 (C[8]$H_2$), 45.95 (C[9]H), 45.67 (C[10]$H_2$), 41.23 (C[4]H), 26.83 (C[11]H), 23.09 (C[12]$H_3$), 22.71 (C[12]$H_3$), 14.26 (C[1]$H_3$); LCMS (ES+) 223 $(M+H^+)$; HRMS $(M+H)^+$ found 223.1709 $C_{14}H_{23}O_2$ required 223.1689, Δ ppm +4.9.

### (1*S**, 2*R**, 3*R**, 4*R**)-3-(2-Chloro-6-methoxy-quinolin-3-yl)-bicyclo[2.2.1]-hept-5-ene-2-carboxylic acid ethyl ester (180)




A cream solid; $R_f$ 0.62 ($SiO_2$; 10:1 toluene: ethyl acetate); $\nu_{max}$ (DMSO) 2989, 1727 (C=O), 1618, 1496, 1343, 1229, 1185 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.96 (1H, s, H10), 7.90 (1H, d, *J* 9.0, H14), 7.35 (1H, dd, 9.0, 3.0, H13), 7.08 (1H, d, *J* 3.0, H11), 6.53 (1H, dd, *J* 5.5, 3.0, H6), 6.18 (1H, dd, *J* 5.5, 3.0, H5), 4.19-4.12 (2H, m, H2), 3.94 (3H, s, H12), 3.50 (1H, d, *J* 5.0, H3), 3.37 (1H, s, H4), 3.18 (1H, t, *J* 4.5, H9), 3.08 (1H, s, H7), 1.73 (1H, d, *J* 8.5, H8), 1.61 (1H, d, *J* 8.5, H8′), 1.27 (3H, t, *J* 7.0, H1); $\delta_C$ (125 MHz; $CDCl_3$) 173.52 (C=O), 158.84 (C), 149.52 (C), 142.00 (C), 138.20 (C[6]H), 135.40 (C), 134.55 (C[10]H), 133.72 (C[5]H), 129.36 (C), 128.30 (C[14]H), 122.41 (C[13]H), 104.99 (C[11]H), 60.52 (C[2]$H_2$), 55.53 (C[12]$H_3$), 49.47 (C[3]H), 49.06 (C[7]H), 46.84 (C[4]H), 46.59 (C[8]$H_2$), 45.28 (C[9]H), 14.24 (C[1]$H_3$); LCMS (ES+) 358 $(M+H^+)$; HRMS $(M+H)^+$ found 358.1219 $C_{20}H_{21}ClNO_3$ required 358.1210, Δ ppm +2.5; mp 97-99 °C (toluene: ethyl acetate).

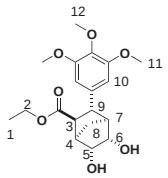
### (1*R**, 2*S**, 3*R**, 4*S**, 5*S**, 6*R**)-5,6-Dihydroxy-3-isobutyl-bicyclo[2.2.1]heptane-2-carboxylic acid ethyl ester (181)




A white foam; $\nu_{max}$ (neat) 2954, 1722 (C=O), 1464, 1385, 1299, 1254, 1184 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 4.16-4.12

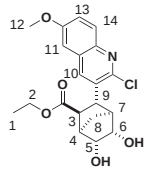
(2H, m, H2), 3.85 (1H, s, H6), 3.82 (1H, s, H5), 2.89 (2H, s, OH), 2.43 (1H, s, H4), 2.20 (1H, dd, *J* 10.0, 5.5, H3), 1.96 (1H, s, H7), 1.84 (1H, m, H8), 1.75 (1H, s, H9), 1.51 (1H, sep, *J* 6.5, H11), 1.38 (1H, d, *J* 10.5, H8′), 1.28-1.13 (5H, m, H1, H10), 0.89 (6H, d, *J* 6.5, H12); $\delta_C$ (125 MHz; $CDCl_3$) 173.84 (C=O), 74.13 (C[6]H), 70.48 (C[5]H), 60.52 (C[2]$H_2$), 50.83 (C[3]H), 48.96 (C[4]H), 47.09 (C[7]H), 45.05 (C[10]$H_2$), 38.00 (C[9]H), 30.99 (C[8]$H_2$), 25.93 (C[11]H), 22.82 (C[12]$H_3$), 22.60 (C[12]$H_3$), 14.23 (C[1]$H_3$); LCMS (ES+) 257 $(M+H^+)$; HRMS $(M+Na)^+$ found 279.1591 $C_{14}H_{23}O_4Na$ required 279.1596, Δ ppm −1.7.

### (1*R**, 2*S**, 3*R**, 4*S**, 5*S**, 6*R**)-5,6-Dihydroxy-3-(3,4,5-trimethoxy-phenyl)-bicyclo[2.2.1]heptane-2-carboxylic acid ethyl ester (182)



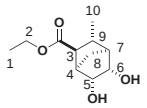
A yellow solid; $\nu_{max}$ (neat) 2971, 2910, 1724 (C=O), 1588, 1510, 1464, 1330, 1244, 1180, 1126 $cm^{-1}$; $\delta_H$ (500 MHz; MeOD: $CDCl_3$) 6.43 (2H, s, H10), 4.17-4.14 (2H, m, H2), 3.85-3.77 (11H, m, H6, H5, H11, H12), 2.95 (1H, d, *J* 6.0, H9), 2.73 (1H, dd, *J* 6.5, 4.5, H3), 2.54 (1H, s, H7), 2.35 (1H, s, H4), 1.95 (1H, d, *J* 10.5, H8), 1.61 (1H, dd, *J* 10.5, 1.5, H8′), 1.26 (3H, t, *J* 7.0, H1); $\delta_C$ (125 MHz; MeOD: $CDCl_3$) 173.84 (C=O), 153.04 (C-O), 153.00 (C-O), 140.35 (C-C), 103.88 (C[10]H), 73.54 (C[6]H), 69.82 (C[5]H), 60.93 (C[2]$H_2$), 60.70 (C[12]$H_3$), 55.92 (C[11]$H_3$), 52.60 (C[3]H), 49.66 (C[4]H), 46.94 (C[7]H), 44.79 (C[9]H), 32.21 (C[8]$H_2$), 14.04 (C[1]$H_3$); LCMS (ES+) 367 $(M+H^+)$; HRMS $(M+H)^+$ found 367.1773 $C_{19}H_{27}O_7$ required 367.1757, Δ ppm +4.4; mp 149-152 °C ($CH_2Cl_2$: MeOH).

### (1*R**, 2*S**, 3*R**, 4*S**, 5*S**, 6*R**)-3-(2-Chloro-6-methoxy-quinolin-3-yl)-5,6-dihydroxy-bicyclo-[2.2.1]heptane-2-carboxylic acid ethyl ester (183)



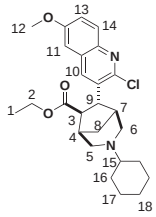
A yellow solid; $R_f$ 0.22 ($SiO_2$; 10:1 $CH_2Cl_2$: MeOH ); $\nu_{max}$ (DMSO) 3002 (OH), 2910, 1725 (C=O), 1618, 1590, 1496, 1383, 1342, 1230, 1185 $cm^{-1}$; $\delta_H$ (400 MHz; MeOD: $CDCl_3$) 8.00 (1H, s, H10), 7.76 (1H, d, *J* 9.0, H14), 7.31 (1H, dd, 9.0, 3.0, H13), 7.13 (1H, d, *J* 3.0, H11), 4.15 (2H, q, *J* 7.0, H2), 4.04 (1H, d, 6.0, H6), 3.96 (1H, d, *J* 5.0, H5), 3.89 (3H, s, H12), 3.47 (1H, d, *J* 6.0, H3), 3.04 (1H, dd, *J* 6.0, 4.5, H9), 2.61 (1H, s, H7), 2.26 (1H, s, H4) 1.96 (1H, dd, *J* 11.0, 1.5, H8), 1.57 (1H, d, *J* 11.0, H8′), 1.23 (3H, t, *J* 7.0, H1); $\delta_C$ (125 MHz; MeOD: $CDCl_3$) 173.10 (C=O), 158.46 (C), 148.76 (C), 141.69 (C), 135.16 (C), 134.18 (C[10]H), 128.35 (C), 128.35 (C[14]H), 122.89 (C[13]H), 105.15 (C[11]H), 73.17 (C[6]H), 69.59 (C[5]H), 60.98 (C[2]$H_2$), 55.29 (C[12]$H_3$), 50.25 (C[4]H), 48.85 (C[9]H), 47.12 (C[7]H), 42.42 (C[3]H), 31.14 (C[8]$H_2$), 13.75 (C[1]$H_3$); LCMS (ES+) 392 $(M+H^+)$; HRMS $(M+H)^+$ found 392.1267 $C_{20}H_{23}ClNO_5$ required 392.1265, Δ ppm +0.7; mp 183-186 °C ($CH_2Cl_2$: MeOH).

### (1*R**, 2*S**, 3*R**, 4*S**, 5*S**, 6*R**)-5,6-Dihydroxy-3-methyl-bicyclo[2.2.1]heptane-2-carboxylic acid ethyl ester (184)



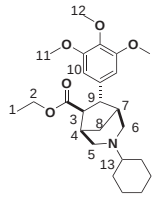
A white foam; $R_f$ 0.31 ($SiO_2$; 10:1 $CH_2Cl_2$: MeOH); $\nu_{max}$ (DMSO) 2911, 1722 (C=O), 1390, 1299, 1192 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 4.15 (2H, q, *J* 7.0, H2), 3.84 (1H, s, H6), 3.79 (1H, s, H5), 2.44 (1H, s, H4), 2.18 (1H, dd, *J* 9.0, 4.0, H3), 1.88 (1H, s, H7), 1.83 (1H, d, *J* 10.5, H8), 1.42 (1H, dd, *J* 10.5, 1.0, H8′), 1.34-1.31 (1H, m, H9), 1.25 (3H, t. *J* 7.0, H1), 1.02 (3H, d, *J* 7.0, H10); $\delta_C$ (125 MHz; $CDCl_3$) 173.80 (C=O), 73.83 (C[6]H), 70.23 (C[5]H), 60.56 (C[2]$H_2$), 51.95 (C[3]H), 50.53 (C[4]H), 47.23 (C[7]H), 34.67 (C[9]H), 30.55 (C[8]$H_2$), 20.89 (C[10]$H_3$), 14.26 (C[1]$H_3$); LCMS (APCI++) 214 $(M+H^+)$; HRMS $(M+Na)^+$ found 237.1124 $C_{11}H_{17}O_4Na$ required 237.1127, Δ ppm −1.0.

### (1*S**, 5*R**, 6*S**, 7*R**)-7-(2-Chloro-6-methoxy-quinolin-3-yl)-3-cyclohexyl-3-aza-bicyclo[3.2.1]octane-6-carboxylic acid ethyl ester (185)



Yellow oil; $R_f$ 0.42 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (DMSO) 2931, 1726 (C=O), 1464, 1365, 1264, 1187 $cm^{-1}$; $\delta_H$ (400 MHz $CDCl_3$) 7.87 (1H, d, *J* 9.0, H14), 7.85 (1H, s, H10), 7.30 (1H, dd, *J* 9.0, 2.5, H13), 7.04 (1H, d, *J* 2.5, H11), 4.30 (1H, d, *J* 6.0, H9), 4.17-4.06 (2H, m, H2), 3.90 (3H, s, H12), 3.27 (1H, t, *J* 6.0, H3), 3.15 (1H, dd, *J* 10.5, 3.5, H6), 3.04 (1H, dd, *J* 10.5, 3.5, H5), 2.71 (1H, d, *J* 4.5, H4), 2.46 (1H, d, *J* 10.0, H5′), 2.32 (1H, d, *J* 10.5, H6′), 2.25 (1H, br s, H15), 2.07 (1H, s, H7), 1.81-65 (5H, m, CyH, H8), 1.59-1.55 (1H, br d, *J* 10.5, CyH), 1.43 (1H, d, *J* 11.5, H8′), 1.26-1.0 (8H, m, H1, CyH); LCMS (ES+) 457 $(M+H^+)$.

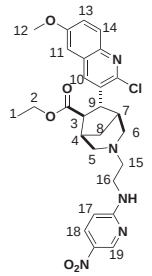
### (1*S**, 5*R**, 6*S**, 7*R**)-3-Cyclohexyl-7-(3,4,5-trimethoxy-phenyl)-3-aza-bi-cyclo[3.2.1]octane-6-carboxylic acid ethyl ester (186)



Colourless oil; $R_f$ 0.29 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (neat) 2930, 2853, 1727 (C=O), 1587, 1508, 1453, 1421, 1327,1242, 1226, 1127 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.59 (2H, s, H10), 4.19-4.12 (2H, m, H2), 3.86 (6H, s, H11), 3.82 (3H, s, H12), 3.76 (1H, d, *J* 5.5, H9), 2.99 (1H, d, *J* 10.5, H6), 2.80 (1H, t, *J* 6.0, H3), 2.76 (1H, dd, *J* 10.5, 3.5, H5), 2.56 (1H, d, *J* 3.5, H4), 2.43 (1H, d, *J* 10.5, H6′), 2.30 (1H, s, H7), 2.26 (1H, d, *J* 10.5, H5′), 2.21 (1H, br s,

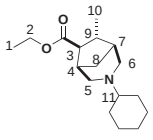
H13), 2.07-2.05 (1H, m, H8), 1.76-1.74 (3H, d, $J$ 8.5, CyH), 1.67 (1H, br s, CyH), 1.56-1.54 (2H, m, CyH, H8), 1.29 (3H, t, $J$ 7.0, H1), 1.27-1.17 (5H, m, CyH); $\delta_C$ (125 MHz; $CDCl_3$) 173.84 (C=O), 153.06 (C-O), 143.53 (C-O), 136.13 (C-C), 104.13 (C[10]H), 62.70 (C[13]H), 60.80 (C[12]$H_3$), 60.12 (C[2]$H_2$), 56.89 (C[5]$H_2$), 56.22 (C[3]H), 56.10 (C[11]$H_3$), 50.43 (C[6]$H_2$), 48.72 (C[9]H), 42.13 (C[7]H), 39.03 (C[4]H), 38.14 (C[8]$H_2$), 29.56 (C[Cy]$H_2$), 28.10 (C[Cy]$H_2$), 26.43 (C[Cy]$H_2$), 25.87 (C[Cy]$H_2$), 25.72 (C[Cy]$H_2$), 14.40 (C[1]$H_3$); LCMS (ES+) 431 ($M+H^+$); HRMS $(M+H)^+$ found 432.2755 $C_{25}H_{38}NO_5$ required 432.2750, $\Delta$ ppm +1.0.

### (1$S^*$, 5$R^*$, 6$S^*$, 7$R^*$)-7-(2-Chloro-6-methoxy-quinolin-3-yl)-3-[2-(5-nitro-pyridin-2-ylamino)-ethyl]-3-aza-bicyclo[3.2.1]octane-6-carboxylic acid ethyl ester (187)



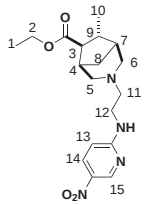
Yellow oil; $R_f$ 0.26 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (DMSO) 2946, 1717 (C=O), 1607, 1542, 1497, 1469, 1327, 1291, 1042 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 9.05 (1H, d, $J$ 3.5, H19), 8.07 (1H, dd, $J$ 9.5, 2.5, H18), 7.88 (1H, d, $J$ 7,5, H14), 7.86 (1H, s, H10), 7.32 (1H, dd, $J$ 9.0, 2.5, H13), 7.04 (1H, d, $J$ 2.5, H11), 6.87 (1H, br s, NH), 6.80 (1H, br d, $J$ 9.0, H17), 4.40 (1H, d, $J$ 6.0, H9), 4.18-4.14 (2H, m, H2), 3.90 (3H, s, H12), 3.55 (2H, br s, H16), 3.39 (1H, t, $J$ 6.0, H3), 3.14 (1H, d, $J$ 10.0, H6), 2.86-2.84 (2H, m, H4, H5), 2.80-2.65 (1H, m, H15), 2.60-2.54 (1H, m, H15′), 2.38 (1H, d, $J$ 9.5, H5′), 2.24-2.20 (2H, m, H6′, H7), 2.01-1.99 (1H, m, H8), 1.57 (1H, d, $J$ 11.5, H8′), 1.24 (3H, t, $J$ 7.0, H1); LCMS (ES+) 540 ($M+H^+$).

### (1$S^*$, 5$R^*$, 6$S^*$, 7$R^*$)-3-Cyclohexyl-7-methyl-3-aza-bicyclo[3.2.1]octane-6-carboxylic acid ethyl ester (188)



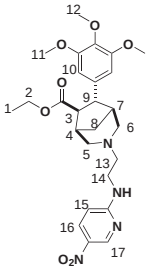
Colourless oil; $R_f$ 0.48 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (DMSO) 2931, 1725 (C=O), 1456, 1375, 1282, 1191, 1155 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 4.16-4.11 (2H, m, H2), 2.99 (1H, d, $J$ 9.0, H6), 2.65 (1H, d, $J$ 9.5, H5), 2.54-2.52 (1H, m, H9), 2.40 (1H, d, $J$ 3.5, H4), 2.33 (1H, d, $J$ 10.0, H6′), 2.21 (1H, t, $J$ 5.5, H3), 2.18-2.14 (2H, m, H5′, H11), 1.75-1.70 (5H, m, CyH, H7, H8), 1.63 (1H, br s, CyH), 1.55 (1H, m, CyH), 1.35 (1H, d, $J$ 10.5, H8′), 1.27 (3H, t, $J$ 7.0, H1), 1.27-1.07 (5H, m, CyH), 1.04 (3H, d, $J$ 7.0, H10); $\delta_C$ (125 MHz; $CDCl_3$) 174.49 (C=O), 62.76 (C[11]H), 59.76(C[2]$H_2$), 56.12 (C[5]$H_2$), 55.15 (C[3]H), 50.65 (C[6]$H_2$), 42.20 (C[7]H), 38.90 (C[4]H), 38.06 (C[9]H), 35.83 (C[8]$H_2$), 29.24 (CyC), 28.24 (CyC), 26.42 (CyC), 25.73 (CyC), 25.65 (CyC), 22.49 (C[10]$H_3$), 14.40 (C[1]$H_3$); LCMS (ES+) 280 ($M+H^+$).

### (1$S^*$, 5$R^*$, 6$S^*$, 7$R^*$)-7-Methyl-3-[2-(5-nitro-pyridin-2-ylamino)-ethyl]-3-aza-bicyclo[3.2.1]octane-6-carboxylic acid ethyl ester(189)



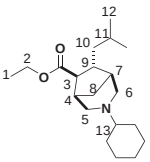
Brown oil, $R_f$ 0.31 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (neat) 3339, 2946, 2796, 1714 (C=O), 1601, 1529, 1497, 1472, 1320, 1289, 1260, 1114, 1030 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 9.03 (1H, d, $J$ 2.5, H15), 8.10 (1H, dd, $J$ 9.5, 2.5, H14), 6.82 (1H, br s, NH), 6.73 (1H, br s, H13), 4.15 (2H, t, $J$ 7.0, H2), 3.51-3.44 (2H, m, H12), 2.81 (1H, dd, $J$ 7.0, 3.5, H6), 2.76 (1H, br d, H5), 2.61 (1H, t, $J$ 6.5, H3), 2.56-2.54 (2H, m, H4, H6′), 2.47-2.42 (1H, m, H9), 2.41 (1H, dd, $J$ 6.0, 5.5, H5′), 2.24 (1H, d, $J$ 11.0, H11), 2.01 (1H, d, $J$ 10.0, H11′), 1.89-1.86 (1H, m, H8), 1.82 (1H, s, H7), 1.47 (1H, d, $J$ 11.5, H8′), 1.23 (3H, t, $J$ 7.0, H1), 1.04 (1H, d, $J$ 7.0, H10); LCMS (ES+) 363 ($M+H^+$).

### (1$S^*$, 5$R^*$, 6$S^*$, 7$R^*$)-3-[2-(5-Nitro-pyridin-2-ylamino)-ethyl]-7-(3,4,5-trimethoxy-phenyl)-3-aza-bicyclo[3.2.1]octane-6-carboxylic acid ethyl ester (190)



Brown oil; $R_f$ 0.26 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (DMSO) 2945, 1716 (C=O), 1608, 1547, 1500, 1469, 1328, 1290, 1126 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 9.05 (1H, s, H17), 8.13 (1H, dd, $J$ 9.5, 2.5, H16), 6.91 (1H, br s, H15), 6.76 (1H, br s, NH), 6.48 (2H, s, H10), 4.19-4.15 (2H, m, H2), 3.87 (6H, s, H11), 3.83 (3H, s, H12), 3.77 (1H, d, $J$ 6.0, H9), 3.54 (2H, br s, H14), 2.99 (1H, t, $J$ 6.0, H3), 2.94 (1H, d, $J$ 10.0, H6), 2.78 (1H, d, $J$ 10.5, H5), 2.72 (1H, d, $J$ 4.0, H4), 2.68-2.62 (1H, m, H13), 2.58-2.52 (1H, m, H13′), 2.39 (1H, s, H7), 2.32 (1H, d, $J$ 10.5, H6′), 2.22 (1H, d, $J$ 10.5, H5′), 2.12-2.10 (1H, m, H8), 1.66 (1H, d, $J$ 11.5, H8′), 1.24 (3H, t, $J$ 7.0, H1); LCMS (ES+) 514 ($M+H^+$).

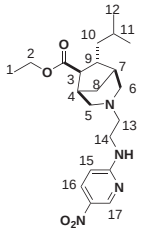
### (1$S^*$, 5$R^*$, 6$S^*$, 7$R^*$)-3-Cyclohexyl-7-isobutyl-3-aza-bicyclo[3.2.1]octane-6-carboxylic acid ethyl ester (3)



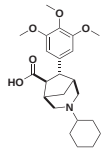
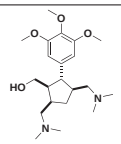
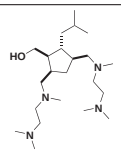
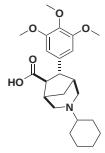
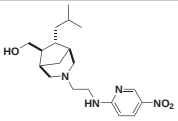
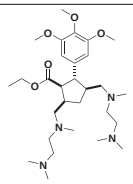
Yellow oil; $R_f$ 0.47 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (DMSO) 2972, 2910, 1724 (C=O), 1497, 1388, 1335, 1261, 1228 $cm^{-1}$;

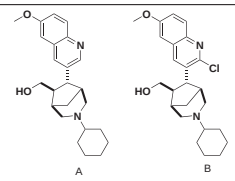
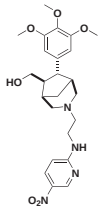
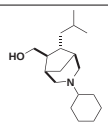
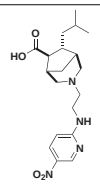
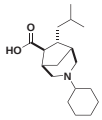
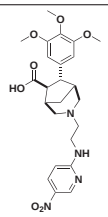
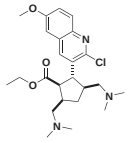
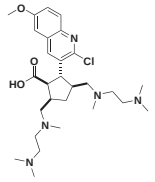
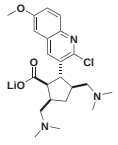
$\delta_H$ (400 MHz; $CDCl_3$) 4.14-4.07 (2H, m, H2), 2.94 (1H, dd, *J* 10.5, 4.0, H6), 2.59 (1H, d, *J* 10.5, H5), 2.49-2.45 (1H, m, H9), 2.40-2.35 (2H, m, H4, H6′), 2.23 (1H, t, *J* 5.5, H3), 2.17-2.10 (2H, m, H5′, H13), 1.77 (1H, s, H7), 1.68-1.64 (3H, m, CyH, H8), 1.62-1.53 (3H, m, CyH, H11), 1.33 (1H, d, *J* 10.5, H8′), 1.25 (3H, t, *J* 7.0, H1), 1.20-1.12 (8H, m, H10, CyH), 0.93 (3H, d, *J* 6.5, H12), 0.90 (3H, d, *J* 6.5, H12); LCMS (ES+) 457 ($M+H^+$).

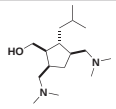
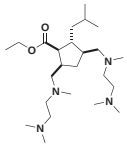
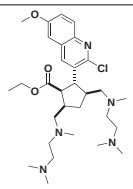
### (1*S**, 5*R**, 6*S**, 7*R**)-7-Isobutyl-3-[2-(5-nitro-pyridin-2-ylamino)-ethyl]-3-aza-bicyclo[3.2.1]octane-6-carboxylic acid ethyl ester (191)



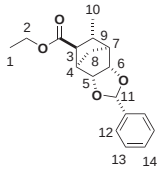

Orange oil; $R_f$ 0.31 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (DMSO) 2962, 2910, 1717 (C=O), 1607, 1539, 1464, 1327, 1291, 1261 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 9.00 (1H, s, H17), 8.07 (1H, dd, *J* 9.5, 2.5, H16), 6.87 (1H, br s, NH), 6.81 (1H, br d, *J* 8.0, H15), 4.15-4.10 (2H, m, H2), 3.47-3.44 (4H, m, H14, H9, H3), 2.76 (1H, d, *J* 11.0, H6), 2.62 (1H, d, *J* 10.5, H5), 2.56-2.52 (2H, m, H13, H4), 2.44-2.43 (1H, m, H13′), 2.26 (1H, d, *J* 10.5, H5′), 2.08 (1H, d, *J* 10.5, H6′), 1.85 (1H, s, H7), 1.82-1.78 (1H, m, H8), 1.44-1.35 (2H, m, H8′, H11), 1.27-1.17 (5H, m, H1, H10), 0.91 (3H, d, *J* 6.5, H12), 0.88 (3H, d, *J* 6.5, H12); LCMS (ES+) 405 ($M+H^+$).

| | **Structure** | LCMS |
|---|---|---|
| **192** |  | 404 ($M+H^+$) |
| **193** |  | 381 ($M+H^+$) |
| **194** |  | 385 ($M+H^+$) |
| **195** |  | 404 ($M+H^+$) |
| **196** |  | 363 ($M+H^+$) |
| **197** |  | 539 ($M+H^+$) |

| | Structure | LCMS |
|---|---|---|
| **198** |  A B | 381:426 ($M+H^+$) |
| **199** |  | 473 ($M+H^+$) |
| **200** |  | 280 ($M+H^+$) |
| **201** |  | 377 ($M+H^+$) |
| **202** |  | 294 ($M+H^+$) |
| **203** |  | 487 ($M+H^+$) |
| **204** |  | 448 ($M+H^+$) |
| **205** |  | 534 ($M+H^+$) |
| **206** |  | 426 ($M+Li^+$) |

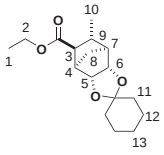
| | Structure | LCMS |
|---|---|---|
| **207** |  | 271 ($M+H^+$) |
| **208** |  | 426 ($M+H^+$) |
| **209** |  | 561 ($M+H^+$) |

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–9-Methyl-4-phenyl-3,5-dioxa-tricyclo[5.2.1.0$^{2,6}$]-decane-8-carboxylic acid ethyl ester (210)**



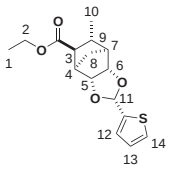
A colourless oil; $R_f$ 0.40 ($SiO_2$; 10:3 hexane: ethyl acetate); $\nu_{max}$ (neat) 2950, 1726 (C=O), 1459, 1400, 1375, 1265, 1187, 1087, 1026 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.55-7.51 (2H, m, H12), 7.41-7.38 (3H, m, H13, H14), 5.59 (1H, s, H11), 4.22-4.12 (4H, m, H2, H5, H6), 2.75 (1H, d, *J* 4.0, H4), 2.26 (1H, t, *J* 5.0, H3), 2.18 (1H, s, H7), 1.97 (1H, d, *J* 10.5, H8), 1.87 (1H, q, *J* 7.0, H9), 1.44 (1H, d, *J* 10.5, H8′), 1.30 (3H, t, *J* 7.0, H1), 1.10 (3H, d, *J* 7.0, H10); LCMS (ES+) 302 ($M+H^+$).

**(1$S^*$, 2$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–9-Methyl-4-cyclohexyl-3,5-dioxa-tricyclo[5.2.1.0$^{2,6}$]-decane-8-carboxylic acid ethyl ester (211)**



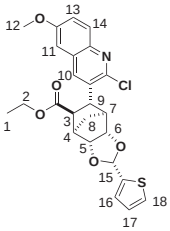
A colourless oil; $R_f$ 0.32 ($SiO_2$; 10:3 hexane: ethyl acetate); $\nu_{max}$ (neat) 2933, 1728 (C=O), 1449, 1370, 1182, 1161, 1105, 1091, 1034 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 4.16-4.07 (4H, m, H2, H5, H6), 2.57 (1H, d, *J* 4.0, H4), 2.19 (1H, t, *J* 5.0, H3), 1.99 (1H, s, H7), 1.76 (1H, d, *J* 10.5, H8), 1.68-1.60 (5H, m, H9, CyH), 1.54-1.52 (3H, m, H8′, CyH), 1.41-1.32 (4H, m, CyH), 1.27 (3H, t, *J* 7.0, H1), 1.04 (3H, d, *J* 7.0, H10); LCMS (ES+) 295 ($M+H^+$).

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–9-Methyl-4-thiophen-2-yl-3,5-dioxa-tricyclo[5.2.1.0$^{2,6}$]decane-8-carboxylic acid ethyl ester (212)**



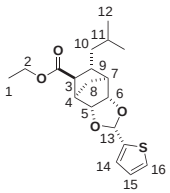
A yellow oil; $R_f$ 0.36 ($SiO_2$; 10:2 hexane: ethyl acetate); $\nu_{max}$ (neat) 2962, 1726 (C=O), 1541, 1445, 141, 1374, 1329, 1264, 1187, 1099 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.36 (1H, d, $J$ 5.0, H14), 7.21 (1H, d, $J$ 4.0, H12), 7.01 (1H, dd, $J$ 5.0, 4.0, H13), 5.87 (1H, s, H11), 4.20-4.15 (4H, m, H2, H5, H6), 2.74 (1H, s, H4), 2.26 (1H, t, $J$ 5.0, H3), 2.17 (1H, s, H7), 2.01 (1H, d, $J$ 10.0, H8), 1.56 (1H, q, $J$ 7.0, H9), 1.45 (1H, d, $J$ 10.0, H8′), 1.28 (3H, t, $J$ 7.0, H1), 1.08 (3H, d, $J$ 7.0, H10); LCMS (ES+) 309 (M+H$^+$).

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–9-(2-Chloro-6-methoxy-quinolin-3-yl)-4-thiophen-2-yl-3,5-dioxa-tricyclo[5.2.1.0$^{2,6}$]decane-8-carboxylic acid ethyl ester (213)**



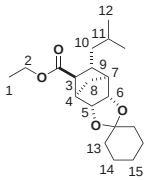
A yellow oil; $R_f$ 0.35 ($SiO_2$; 10:4 hexane: ethyl acetate); $\nu_{max}$ (neat) 2962, 1726 (C=O), 1541, 1445, 141, 1374, 1329, 1264, 1187, 1099 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.93-7.90 (2H, m, H10, H14), 7.38-7.36 (2H, m, H13, H18), 7.25 (1H, d, $J$ 3.5, H16), 7.09 (1H, d, $J$ 2.5, H11), 7.03 (1H, dd, $J$ 5.0, 4.0, H17), 5.98 (1H, s, H15), 4.56 (1H, d, $J$ 6.0, H6), 4.48 (1H, d, $J$ 6.0, H5), 4.23 (2H, q, $J$ 7.0, H2), 3.95 (3H, s, H12), 3.51 (1H, d, $J$ 5.5, H3), 3.07 (1H, t, $J$ 5.0, H9), 2.96 (1H, s, H4), 2.77 (1H, s, H7), 2.22 (1H, d, $J$ 11.0, H8), 1.64 (1H, d, $J$ 11.0, H8′), 1.27 (3H, t, $J$ 7.0, H1); LCMS (ES+) 486 (M+H$^+$).

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–9-Isobutyl-4-thiophen-2-yl-3,5-dioxa-tricyclo[5.2.1.0$^{2,6}$]decane-8-carboxylic acid ethyl ester (214)**



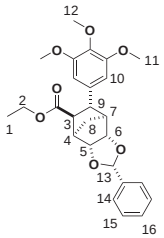
A yellow oil; $R_f$ 0.29 ($SiO_2$; 10:2 hexane: ethyl acetate); $\nu_{max}$ (DMSO) 2956, 1726 (C=O), 1259, 1180 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.35 (1H, d, $J$ 4.0, H16), 7.20 (1H, d, $J$ 3.5, H14), 7.00 (1H, dd, $J$ 4.0, 3.5, H15), 5.87 (1H, s, H13), 4.22-4.11 (4H, m, H6, H5, H2), 2.73 (1H, s, H4), 2.30 (1H, t, $J$ 5.0, H3), 2.20 (1H, s, H7), 1.99 (1H, d, $J$ 10.5, H8), 1.81 (1H, m, H9), 1.55 (1H, m, H11), 1.41 (1H, d, $J$ 10.5, H8′), 1.31-1.22 (5H, m, H1, H10), 0.91 (6H, d, $J$ 6.5, H12); $\delta_C$ (125 MHz; $CDCl_3$) 173.47 (C=O), 139.44 (C-C), 126.90 (CH), 126.56 (CH), 126.48 (CH), 99.39 (C[13]H), 82.62 (C[5]H), 79.54 (C[6]H), 60.58 (C[2]$H_2$), 49.68 (C[3]H), 45.86 (C[7]H), 44.76 (C[10]$H_2$), 44.10 (C[4]H), 36.35 (C[9]H), 31.06 (C[8]$H_2$), 26.05 (C[11]H), 22.89 (C[12]$H_3$), 22.61 (C[12]$H_3$), 14.26 (C[1]$H_3$); LCMS (ES+) 351 (M+H$^+$): HRMS (M+H)$^+$ found 351.1628 $C_{19}H_{27}O_4S$ required 351.1624, $\Delta$ ppm −1.1.

**(1$S^*$, 2$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–9-Isobutyl-4-cyclohexyl-2-yl-3,5-dioxa-tricyclo[5.2.1.0$^{2,6}$]decane-8-carboxylic acid ethyl ester (215)**



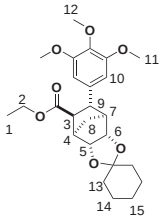
A colourless oil; $R_f$ 0.42 ($SiO_2$; 10:2 hexane: ethyl acetate); $\nu_{max}$ (DMSO) 2910, 1725 (C=O), 1451, 1369, 1305, 1261, 1162 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 4.17-4.10 (4H, m, H6, H5, H2), 2.55 (1H, s, H4), 2.21 (1H, t, $J$ 5.0, H3), 2.06 (1H, s, H7), 1.76-1.71 (2H, m, H8, H9), 1.65-1.60 (6H, m, CyH), 1.39-1.38 (2H, m, H10), 1.30-1.18 (5H, m, H8′, H1, H11), 0.88 (6H, d, $J$ 6.5, H12); $\delta_C$ (125 MHz; $CDCl_3$) 173.63 (C=O), 109.62 (C-C), 81.17 (C[5]H), 77.92 (C[6]H), 60.46 (C[2]$H_2$), 49.82 (C[3]H), 45.71 (C[7]H), 44.83 (C[10]$H_2$), 44.00 (C[4]H), 36.68 (C[9]H), 35.17 (C[Cy]$H_2$), 33.53 (C[Cy]$H_2$), 30.81 (C[8]$H_2$), 26.99 (C[11]H), 25.27 (C[Cy]$H_2$), 24.05 (C[Cy]$H_2$), 23.60 (C[Cy]$H_2$), 22.75 (C[12]$H_3$), 22.64 (C[12]$H_3$), 14.23 (C[1]$H_3$); LCMS (APCI+) 337 (M+H$^+$);

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–4-Phenyl-9-(3,4,5-trimethoxy-phenyl)-3,5-dioxa-tri-cyclo[5.2.1.0$^{2,6}$]decane-8-carboxylic acid ethyl ester (216)**



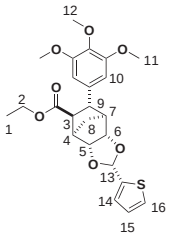
A colourless oil; $R_f$ 0.34 ($SiO_2$; 10:3 hexane: ethyl acetate); $\nu_{max}$ (DMSO) 2910, 1724 (C=O), 1588, 1509, 1462, 1305, 1244, 1125 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.55-7.54 (2H, m, H14), 7.41-7.39 (3H, m, H15, H16), 6.50 (2H, s, H10), 5.66 (1H, s, H13), 4.35 (1H, d, $J$ 5.5, H6), 4.29 (1H, d, $J$ 5.5, H5), 4.24 (2H, q, $J$ 7.0, H2), 3.86 (6H, s, H11), 3.84 (3H, s, H12), 3.03 (1H, d, $J$ 6.0, H9), 2.90 (1H, s, H4), 2.84 (1H, dd, 6.0, 4.5, H3), 2.74 (1H, s, H7), 2.15 (1H, d, $J$ 10.5, H8), 1.67 (1H, d, $J$ 10.5, H8′), 1.25 (3H, t, $J$ 7.0, H1); $\delta_C$ (125 MHz; $CDCl_3$) 173.11 (C=O), 153.29 (C-C), 129.61 (CH), 128.45 (CH), 126.67 (CH), 103.62 (CH), 103.26 (CH), 82.52 (C[5]H), 79.48 (C[6]H), 61.03 (C[11]$H_3$), 60.85 (C[2]$H_2$), 56.16 (C[12]$H_3$), 51.54 (C[3]H), 46.47 (C[7]H), 44.15 (C[4]H), 43.69 (C[9]H), 32.54 (C[8]$H_2$), 14.32 (C[1]$H_3$); LCMS (ES+) 455 (M+H$^+$): HRMS (M+H)$^+$ found 455.2066 $C_{26}H_{31}O_7$ required 455.2070, $\Delta$ ppm −0.8.

**(1$S^*$, 2$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–4-Phenyl-9-(3,4,5-trimethoxy-cyclohexyl)-3,5-dioxa-tri-cyclo-[5.2.1.0$^{2,6}$]decane-8-carboxylic acid ethyl ester (217)**



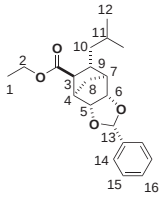
A colourless foam; $R_f$ 0.32 ($SiO_2$; 10:3 hexane: ethyl acetate); $\nu_{max}$ (neat) 2931, 1725 (C=O), 1587, 1509, 1461, 1420, 1369, 1332, 1260, 1242, 1125, 1100 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 6.47 (2H, s, H10), 4.27-4.18 (4H, m, H6, H5, H2), 3.85 (6H, s, H11), 3.83 (3H, s, H12), 2.98 (1H, d, $J$ 5.5, H9), 2.79 (1H, dd, $J$ 6.0, 4.5, H3), 2.73 (1H, d, $J$ 4.5, H4), 2.58 (1H, s, H7), 1.95 (1H, d, $J$ 10.5, H8), 1.73-1.40 (11H, m, H8′, CyH), 1.31 (3H, t, $J$ 7.0, H1); $\delta_C$ (125 MHz; $CDCl_3$) 173.25 (C=O), 153.24 (C-C), 110.13 (C), 103.95 (C[10]H), 81.27 (C[5]H), 78.08 (C[6]H), 60.91 (C[2]$H_2$), 60.82 (C[11]$H_3$), 56.14 (C[12]$H_3$), 51.46 (C[3]H), 46.51 (C[7]H), 44.24 (C[4]H), 43.58 (C[9]H), 35.18 (C[Cy]$H_2$), 33.60 (C[8]$H_2$), 32.17 (C[Cy]$H_2$), 25.25 (C[Cy]$H_2$), 24.07 (C[Cy]$H_2$), 23.62 (C[Cy]$H_2$), 14.28 (C[1]$H_3$); LCMS (ES+) 447 (M+H$^+$): HRMS (M+Na)$^+$ found 447.2367 $C_{25}H_{35}O_7Na$ required 447.2383, $\Delta$ ppm −3.5.

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–4-Thiophen-2-yl-9-(3,4,5-trimethoxy-phenyl)-3,5-dioxatricyclo[5.2.1.0$^{2,6}$]decane-8-carboxylic acid ethyl ester (218)**



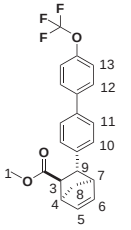
A yellow foam; $R_f$ 0.35 ($SiO_2$; 10:3 hexane: ethyl acetate); $\nu_{max}$ (neat) 2979, 2934, 2839, 1723 (C=O), 1587, 1508, 1461, 1330, 1240, 1184, 1124 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.38 (1H, d, $J$ 5.0, H16), 7.23 (1H, d, $J$ 3.5, H14), 7.01 (1H, dd, $J$ 5.0, 3.5, H15), 6.49 (2H, s, H10), 5.93 (1H, s, H13), 4.33 (1H, d, $J$ 5.5, H6), 3.28 (1H, d, $J$ 5.5, H5), 4.26-4.18 (2H, m, H2), 3.87 (6H, s, H11), 3.84 (3H, s, H12), 3.01 (1H, d, $J$ 6.0, H9), 2.89 (1H, br s, H4), 2.84 (1H, m, H3), 2.73 (1H, s, H7), 2.19 (2H, d, $J$ 11.5, H8), 1.71 (1H, d, $J$ 11.5, H8′), 1.31 (3H, t, $J$ 7.0, H1); LCMS (ES+) 461 (M+H$^+$).

**(1$S^*$, 2$S^*$, 4$S^*$, 6$R^*$, 7$R^*$, 8$S^*$, 9$R^*$)–9-Isobutyl-4-phenyl-3,5-dioxatricyclo[5.2.1.0$^{2,6}$] decane-8-carboxylic acid ethyl ester (219)**



A colourless oil; $R_f$ 0.35 ($SiO_2$; 10:2 hexane: ethyl acetate); $\nu_{max}$ (DMSO) 2987, 1719 (C=O), 1278, 1181, 1116 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.55-7.51 (3H, m, H16, H15), 7.41-7.38 (2H, m, H14), 5.59 (1H, s, H13), 4.22-4.10 (4H, m, H6, H5, H2), 2.75 (1H, br s, H4), 2.30 (1H, t, $J$ 5.0, H3), 2.25 (1H, s, H7), 1.97 (1H, d, $J$ 10.5, H8), 1.87-1.81 (1H, m, H9), 1.57-1.51 (1H, m, H11), 1.41 (1H, d, $J$ 10.5, H8′), 1.32-1.23 (5H, m, H1, H10), 0.93 (3H, d, $J$ 6.0, H12), 0.90 (3H, d, $J$ 6.0, H12′); LCMS (APCI+) 345 (M+H$^+$).

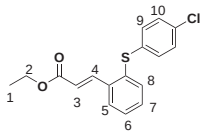
**(1$S^*$, 2$R^*$, 3$R^*$, 4$R^*$)–3-(4′-Trifluoromethoxy-biphenyl-4-yl)-bi-cyclo[2.2.1]hept-5-ene-2-carboxylic acid methyl ester (220**



A colourless oil; $R_f$ 0.51 ($SiO_2$; 11:1 hexane: ethyl acetate); $\nu_{max}$ (DMSO) 2989, 1730(C=O), 1496, 1306, 1257, 1224, 1167 cm$^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.57 (2H, d, $J$ 8.5, H13), 7.49 (2H, d, $J$ 8.0, H12), 7.40 (2H, d, $J$ 8.0, H11), 7.27-7.25 (2H, d, $J$ 8.5, H10), 6.44-6.41 (1H, m, H6), 6.14-6.12 (1H, m, H5), 3.68 (3H, s, H1), 3.31 (1H, s, H4), 3.13 (1H, d, $J$ 5.0, H9), 3.06 (1H, s, H7), 3.02 (1H, t, $J$ 5.0, H3), 1.80 (1H, d, $J$ 8.5, H8), 1.60 (1H, d, $J$ 8.5, H8′); $\delta_C$ (125 MHz; $CDCl_3$) 174.69 (C=O), 148.55 (C), 143.88 (C), 139.66 (C), 139.09 (C), 137.63 (CH), 136.79 (C), 134.68 (CH), 128.38 (CH), 128.26 (CH), 128.26 (CH), 119.51 (CH), 52.11 (C[3]H), 51.96 (C[9]H), 48.41 (C[4]H), 47.31 (C[7]H), 47.21 (C[8]$H_2$), 46.24 (C[1]$H_3$); LCMS (ES+) 389 (M+H$^+$): HRMS (M+Na)$^+$ found 411.1184 $C_{22}H_{19}O_3F_3Na$ required 411.1173, $\Delta$ ppm −1.0.

# 13 Preparation of analogues in solution phase for SAR analysis

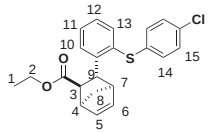
**3-[2-(4-Chloro-phenylsulfanyl)-phenyl]acrylic acid ethyl ester (221)** To a solution of triethylphosphonacetate (4 ml, 18.8 mmol), lithium bromide (1.6 g, 18.8 mmol) and DBU (3.7 ml, 18.8 mmol) in acetonitrile (40 ml) under nitrogen was added 2-(4-chlorophenylthio)benzaldehyde (4.68 g, 18.8 mmol). The solution was stirred for three hours until complete by TLC, then saturated ammonium chloride solution was added. The reaction was extracted with ethyl acetate and the organic layer washed with brine, dried ($MgSO_4$) and solvent removed *in vacuo* to yield the title compound as a yellow solid (5.86 g, 98 %).



$R_f$ 0.45 ($SiO_2$; 3:1 40:60 petrol: ether); $\nu_{max}$ (neat) 2989, 2901, 1711 (C=O), 1633, 1473, 1315, 1180, 1090 cm$^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 8.20 (1H, d, $J$ 16.0, H4), 7.62 (1H, dd, $J$ 9.0, 5.0, H8), 7.37-7.30 (3H, m, H5, H6, H7), 7.24 (2H, d, $J$ 8.5, H9), 7.17 (2H, d, $J$ 8.5, H10), 6.35 (1H, d, $J$

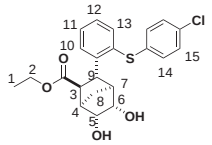
16.0, H3), 4.24 (2H, q, $J$ 7.0, H2), 1.31 (3H, t, $J$ 7.0, H1); $\delta_C$ (125 MHz; $CDCl_3$) 166.49 (C=O), 141.70 (C[4]H), 136.46 (C), 135.44 (C), 134.54 (CH), 133.83 (C), 133.00 (CH), 131.58 (CH), 130.55 (CH), 128.46 (CH), 127.42 (CH), 120.75 (C[3]H), 60.56 (C[2]$H_2$), 14.29 (C[1]$H_3$); $(M+H)^+$ found 319.0573 $C_{17}H_{16}O_2SCl$ requires 319.0560, $\Delta$ ppm +4.1

**(1$S^*$, 2$R^*$, 3$R^*$, 4$R^*$)–3-[2-(4-Chloro-phenylsulfanyl)-phenyl]-bi-cyclo[2.2.1]hept-5-ene-2-carboxylic acid ethyl ester (222)** To a solution of **221** (5.70 g, 17.9 mmol) in $CH_2Cl_2$ (140 ml) at - 78 °C under nitrogen was added dimethylaluminium chloride (17.9 ml, 17.9 mmol) and cyclopentadiene (13.0 ml, 179 mmol). The reaction was stirred for one hour then allowed to warm to room temperature for four hours until complete by TLC. The reaction was quenched by addition of saturated ammonium chloride solution (200 ml), the organic layer was separated and washed with brine. The organic layer was dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield the title compound as a yellow foam (5.38 g, 78 %).



$R_f$ 0.22 (Si; 3:1 40:60 petrol: ether); $\nu_{max}$ (neat) 3060, 2977, 1730 (C=O), 1474, 1160, 1091 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 7.40 (1H, d, $J$ 7.5, ArH), 7.32-7.29 (2H, m, ArH), 7.25-7.23 (2H, m, ArH), 7.18-7.15 (3H, m, ArH), 6.38 (1H, dd, $J$ 5.0, 3.0, H6), 6.10 (1H, dd, $J$ 5.5, 3.0, H5), 4.10-3.95 (2H, m, H2), 3.53 (1H, d, $J$ 5.0, H9), 3.28 (1H, s, H4), 3.13 (1H, t, $J$ 4.5, H3), 2.77 (1H, s, H7), 1.78 (1H, d, $J$ 8.5, H8), 1.50 (1H, d, $J$ 8.5, H8′), 1.17 (3H, t, $J$ 7.0, H1); $\delta_C$ (125 MHz; $CDCl_3$) 173.96 (C=O), 145.06 (C-Cl), 138.68 (C[6]H), 135.27 (C-S), 134.97 (C-S), 134.33 (C[5]H), 133.81 (C[13]H), 132.57 (C-C), 131.49 (C[14]H), 129.22 (C[15]H), 128.13 (C[10]H), 127.08 (C[11]H), 126.64 (C[12]H), 60.33 (C[2]$H_2$), 50.19 (C[7]H), 49.99 (C[3]H), 46.58 (C[8]$H_2$), 46.51 (C[4]H), 45.78 (C[9]H), 14.23 (C[1]$H_3$); LCMS (APCI+) 385 ($M+H^+$): HRMS $(M+H)^+$ found 385.1041 $C_{22}H_{22}O_2ClS$ required 385.1029, $\Delta$ ppm +3.1.

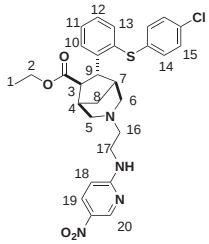
**(1$R^*$, 2$S^*$, 3$R^*$, 4$S^*$, 5$S^*$, 6$R^*$)–3-[2-(4-Chloro-phenylsulfanyl)-phenyl]-5,6-dihydroxy-bicyclo-[2.2.1]heptane-2-car-boxylic acid ethyl ester (223)** To a solution of **222** (5.3 g, 13.8 mmol) in acetone (200 ml) and water (20 ml) was added NMO (3.2 g, 27.6 mmol) and osmium tetroxide (2.5 mol% solution in pentane; 0.1 ml). The reaction was stirred for four hours until complete by TLC and then quenched with saturated sodium sulfite solution (200 ml). The aqueous layer was extracted with ethyl acetate (2 × 300 ml) and the organic layer was dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield the title compound as a white foam (5.30 g, 92 %).



$R_f$ 0.19 ($SiO_2$; 10:1 $CH_2Cl_2$: MeOH); $\nu_{max}$ (neat) 3379 (OH), 2976, 1724 (C=O), 1474, 1176, 1091, 1031 $cm^{-1}$; $\delta_H$ (400 MHz; 9:1 $CDCl_3$: MeOD) 7.29-7.22 (5H, m, ArH), 7.18-7.12 (3H, m, ArH), 4.05 (2H, q, $J$ 7.0, H2), 4.02 (1H, d, $J$ 5.5, H5), 3.96 (1H, d, $J$ 5.5, H6), 3.54 (1H, d, $J$ 6.0, H9), 2.97 (1H, dd, $J$ 6.0, 4.5, H3), 2.87 (2H, br s, OH), 2.59 (1H, d, $J$ 2.5, H4), 2.15 (1H, s, H7), 1.93 (1H, d, $J$ 11.0, H8), 1.62 (1H, d, $J$ 11.0, H8′), 1.19 (3H, t, $J$ 7.0, H1); $\delta_C$ (125 MHz; 9:1 $CDCl_3$:MeOD) 173.03 (C=O), 144.72 (C-Cl), 135.200 (C-S), 134.45 (C-S), 133.80 (C[13]H), 132.69 (C-C), 131.42 (C[14]H), 129.29 (C[15]H), 128.16 (C[10]H), 127.32 (C[11]H), 126.29 (C[12]H), 73.76 (C[6]H), 70.28 (C[5]H), 60.86 (C[2]$H_2$), 51.35 (C[7]H), 49.94 (C[3]H), 47.21 (C[4]H), 42.71 (C[9]H), 31.64 (C[8]$H_2$), 14.16 (C[1]$H_3$); LCMS (APCI+) 418 ($M+Na^+$): HRMS $(M+Na)^+$ found 441.0885 $C_{22}H_{23}O_4SClNa$ required 441.0903, $\Delta$ ppm −4.1.

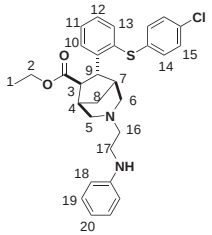
**General Procedure for oxidative cleavage reductive amination reactions** To a solution of **223** (1.0 equiv.) in THF: water (1:1) was added sodium periodate (1.8 equiv.) at 0 °C. The reaction was stirred for three hours then extracted with chloroform. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was dissolved in dry $CH_2Cl_2$ and the amine (1.0 equiv.) was added. The reaction was stirred at room temperature for one hour then sodium triacetoxyborohydride (2.0 equiv.) was added and the reaction stirred overnight. The reaction was poured into water and extracted with chloroform. The organic layer was dried ($MgSO_4$), solvent removed *in vacuo* and the crude product purified by flash column chromatography to yield:

**(1$S^*$, 5$R^*$, 6$S^*$, 7$R^*$)–7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-[2-(5-nitropyridin-2-ylamino)-ethyl]-3-aza-bicyclo[3.2.1]-octane-6-carboxylic acid ethyl ester (224)**



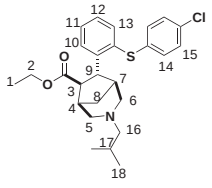
Yellow oil, (52 mg, 38 %). $R_f$ 0.32 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (DMSO) 2976, 1716 (C=O), 1601, 1529, 1320, 1201 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 9.04 (1H, d, $J$ 2.5, H20), 8.02 (1H, dd, $J$ 9.0, 2.0, H19), 7.41 (1H, d, $J$ 8.0, H10), 7.36 (2H, d, $J$ 4.0, H11, H12), 7.21-7.17 (1H, m, H13), 7.13 (2H, d, $J$ 8.0, H15), 6.95 (1H, br s, NH), 6.84 (2H, d, $J$ 8.0, H14), 6.78 (1H, d, $J$ 9.0, H18), 4.57 (1H, d, $J$ 6.0, H9), 4.19-4.08 (2H, m, H2), 3.51 (1H, m, H17), 3.36 (1H, m, H17′), 3.31 (1H, t, $J$ 6.0, H3), 2.77-2.75 (2H, m, H4, H7), 2.62 (1H, d, $J$ 8.5, H5), 2.58-2.51 (2H, m, H16), 2.38 (1H, d, $J$ 10.5, H6), 2.12 (1H, m, H8), 1.95 (1H, d, $J$ 10.0, H6′), 1.90 (1H, s, H8), 1.53 (1H, d, $J$ 11.0, H8′), 1.23 (3H, t, $J$ 7.0, H1); $\delta_C$ (125 MHz; $CDCl_3$) 174.39 (C=O), 161.49 (C-N), 148.42 (C-Cl), 146. 95 (C[20]H), 136.29 (C-$NO_2$), 135.26 (C[19]H), 135.11 (C-C), 132.96 (C-S), 131.85 (C-S), 131.50 (C[13]H), 129.52 (C[12]H), 129.15 (C[14]H), 129.04 (C[15]H), 127.14 (C[10]H), 126.52 (C[11]H), 60.75 (C[2]$H_2$), 57.29 (C[5]$H_2$), 56.68 (C[6]$H_2$), 54.55 (C[16]$H_2$), 54.06 (C[3]H), 45.42 (C[9]H), 44.08 (C[7]H), 40.49 (C[4]H), 37.80 (C[17]$H_2$), 31.64 (C[8]$H_2$), 14.36 (C[1]$H_3$); LCMS (APCI+) 567 ($M+H^+$); HRMS $(M+H)^+$ found 567.1829 $C_{29}H_{32}N_4O_4ClS$ required 567.1833, $\Delta$ ppm −0.6; MRSA 15 - $MIC_{50}$: > 64 $\mu$g/ml, MRSA 16 - $MIC_{50}$: > 64 $\mu$g/ml.

**(1$S^*$, 5$R^*$, 6$S^*$, 7$R^*$)–7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-(2-phenyl-amino-ethyl)-3-aza-bicyclo[3.2.1]octane-6-carboxylic acid ethyl ester (225)**



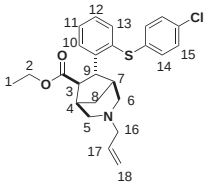
Colourless oil (58.5 mg, 47 %); $R_f$ 0.48 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (DMSO) 2951, 2927, 2850, 1721 (C=O), 1603, 1475, 1290 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.45 (1H, d, *J* 8.0, H10), 7.38-7.34 (2H, m, H11, H12), 7.23-7.11 (3H, m, H13, H19), 7.10 (2H, d, *J* 8.5, H14), 6.85 (2H, d, *J* 7.5, H18), 6.76 (2H, d, *J* 8.5, H15), 6.71 (1H, t, *J* 7.0, H20), 4.95 (1H, br s, NH), 4.66 (1H, d, *J* 6.0, H9), 4.15 (2H, ddq, *J* 47.0, 11.0, 7.0, H2), 3.26 (1H, t, *J* 6.0, H3), 3.05-3.03 (1H, m, H17), 2.98-2.95 (1H, m, H17′), 2.92 (1H, d, *J* 12.5, H6), 2.74 (1H, d, *J* 3.0, H4), 2.60-2.58 (1H, m, H16), 2.54-2.51 (1H, m, H16′), 2.41 (1H, d, *J* 8.0, H5), 2.25 (1H, d, *J* 11.0, H6′), 2.11 (1H, dd, *J* 11.0, 5.5, H8), 1.83 (1H, d, *J* 10.0, H5′), 1.79 (1H, s, H7), 1.47 (1H, d, *J*11.0, H8′), 1.22 (3H, t, *J* 7.0, H1); $\delta_C$ (125 MHz; $CDCl_3$) 173.47 (C=O), 149.79 (C-Cl), 135.44 (C[10]H), 133.08 (C-S), 131.43 (C-S), 130.48 (CH), 129.77 (CH), 129.08 (CH), 128.95 (CH), 128.80 (CH), 126.84 (CH), 126.68 (CH), 116.77 (C), 113.34 (C[18]H), 60.52 (C[2]$H_2$), 58.03 (C[5]$H_2$), 56.66 (C[6]$H_2$), 55.54 (C[16]$H_2$), 54.31 (C[3]H), 45.46 (C[9]H), 44.10 (C[7]H), 40.01 (C[17]$H_2$), 39.78 (C[4]H), 37.26 (C[8]$H_2$), 14.43 (C[1]$H_3$); LCMS (APCI+) 521 ($M+H^+$): HRMS $(M+H)^+$ found 521.2027 $C_{30}H_{34}ClN_2O_2S$ required 521.2030, Δ ppm −0.5; MRSA 15 - $MIC_{50}$: > 64 μg/ml, MRSA 16 - $MIC_{50}$: > 64 μg/ml.

**(1$S^*$, 5$R^*$, 6$S^*$, 7$R^*$)–7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-isobutyl-3-aza-bicyclo[3.2.1]octane-6-carboxylic acid ethyl ester (226)**



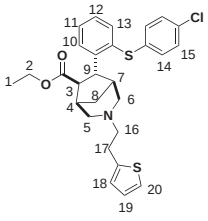
A yellow solid, (32 mg, 30 %); $R_f$ 0.22 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (DMSO) 2965, 1711 (C=O), 1471, 1385, 1254, 1218 $cm^{-1}$; $\delta_H$ (500 MHz; $CDCl_3$) 7.40 (1H, dd, *J* 8.0, 1.0, H10), 7.37 (1H, d, *J* 7.5, H12), 7.33 (1H, d, *J* 7.5, H11), 7.22 (2H, d, *J* 8.5, H14), 7.18 (1H, td, *J* 7.5, 1.5, H13), 7.12 (2H, d, *J* 8.5, H15), 4.51 (1H, d, *J* 6.5, H9), 4.10-4.02 (2H, m, H2), 3.21 (1H, t, *J* 6.0, H3), 3.07 (1H, d, *J* 10.5, H6), 2.64 (1H, dd, *J* 9.0, 4.5, H7), 2.60 (1H, dd, *J* 10.0, 3.5, H5), 2.04 (1H, d, *J* 11.0, H6′), 2.10-1.94 (3H, m, H8, H16), 1.82 (1H, d, *J* 10.0, H5′), 1.81-1.79 (1H, m, H4), 1.65-1.63 (1H, m, H17), 1.41 (1H, d, *J* 11.0, H8′), 1.19 (3H, t, *J* 7.0, H1), 0.86 (3H, d, *J* 6.0, H18), 0.84 (3H, d, *J* 6.5, H18′); $\delta_C$ (125 MHz; $CDCl_3$) 173.36 (C=O), 149.27 (C-Cl), 136.66 (C-C), 134.81 (C[10]H), 133.50 (C-S), 131.83 (C-S), 130.33 (C[15]H), 128.99 (C[14]H), 128.68 (C[13]H), 126.64 (C[11]H), 126.36 (C[12]H), 66.34 (C[16]$H_2$), 60.08 (C[2]$H_2$), 59.92 (C[5]$H_2$), 56.73 (C[6]$H_2$), 53.40 (C[3]$H_2$), 45.70 (C[9]H), 44.53 (C[7]H), 38.80 (C[4]H), 36.87 (C[8]$H_2$), 25.52 (C[17]H), 20.89 (C[18]$H_3$), 20.51 (C[18′]$H_3$), 14.20 (C[1]$H_3$); LCMS (APCI+) 458 ($M+H^+$); HRMS $(M+H)^+$ found 458.1915 $C_{26}H_{33}ClNO_2S$ required 458.1921, Δ ppm −1.2; mp 85-87 °C ($CHCl_3$; MeOH); MRSA 15 - $MIC_{50}$: > 64 μg/ml, MRSA 16 - $MIC_{50}$: > 64 μg/ml.

**(1$S^*$, 5$R^*$, 6$S^*$, 7$R^*$)–3-Allyl-7-[2-(4-chloro-phenylsulfanyl)-phenyl]-3-aza-bicyclo[3.2.1]octane-6-carboxylic acid ethyl ester (227)**



Colourless oil (55 mg, 53 %); $R_f$ 0.39 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (DMSO) 2906, 2794, 1721 (C=O), 1475 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 7.36-7.32 (3H, m, ArH), 7.22 (2H, d, *J* 8.5, H15), 7.16.13 (3H, m, ArH), 5.77-5.68 (1H, m, H17), 5.13 (1H, dd, *J* 17.0, 1.5, H18), 5.04 (1H, dd, *J* 9.0, 1.0, H18′), 4.49 (1H, d, *J* 6.0, H9), 4.11-4.02 (2H, m, H2), 3.23 (1H, t, *J* 6.0, H3), 3.08 (1H, d, *J* 10.5, H6), 2.94-2.85 (2H, m, H16), 2.72 (1H, dd, *J* 10.0, 4.0, H5), 2.64 (1H, d, *J* 4.0, H7), 2.01 (1H, d, *J* 10.5, H6′), 1.96-1.93 (2H, m, H8, H5′), 1.83 (1H, s, H4), 1.39 (1H, d, *J* 11.5, H8′), 1.19 (3H, t, *J* 7.0, H1); $\delta_C$ (100 MHz; $CDCl_3$) 173.39 (C=O), 148.55 (C-Cl), 136.23 (C-C), 136.19 (C[10]H), 134.22 (C[17]H), 134.03 (C-S), 132.1 (C-S), 130.95 (C[15]H), 129.07 (C[14]H), 128.33 (C[13]H), 126.67 (C[11]H), 126.28 (C[12]H), 116.40 (C[18]$H_2$), 60.65 (C[16]H2), 60.07 (C[2]$H_2$), 59.73 (C[5]$H_2$), 55.45 (C[6]$H_2$), 52.93 (C[3]$H_2$), 45.85 (C[9]H), 44.43 (C[7]H), 38.84 (C[4]H), 36.54 (C[8]$H_2$), 14.20 (C[1]$H_3$); LCMS (APCI+) 442 ($M+H^+$); HRMS $(M+H)^+$ found 442.1607 $C_{25}H_{29}ClNO_2S$ required 442.1608, Δ ppm −0.1; MRSA 15 - $MIC_{50}$: > 64 μg/ml, MRSA 16 - $MIC_{50}$: > 64 μg/ml.

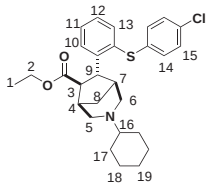
**(1$S^*$, 5$R^*$, 6$S^*$, 7$R^*$)–7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-(2-thio-phen-2-yl-ethyl)-3-aza-bicyclo[3.2.1]octane-6-car-boxylic acid ethyl ester (228)**



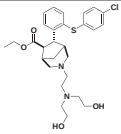
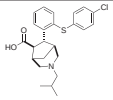
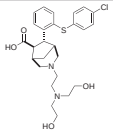
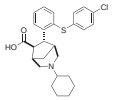
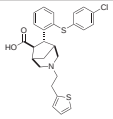
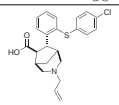
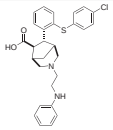
Colourless oil (87 mg, 72 %); $R_f$ 0.15 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (DMSO) 2941, 2784, 1719 (C=O), 1475, 1221 (APCI+); $\delta_H$ (400 MHz; $CDCl_3$) 7.39-7.29 (3H, m, ArH), 7.22 (2H, d, *J* 8.5, H15), 7.17 (1H, td, *J* 7.5, 1.5, H13), 7.12 (2H, d, *J* 8.5, H14), 7.07 (1H, dd, *J* 5.0, 1.0, H20), 6.89 (1H, dd, *J* 5.0, 3.5, H19), 6.82 (1H, d, *J* 3.5, H18), 4.51 (1H, d, *J* 6.0, H9), 4.04 (2H, q, *J* 7.0, H2), 3.24 (1H, t, *J* 6.0, H3, H5), 2.87 (2H, t, *J* 7.0, H17), 2.75 (1H, dd, *J* 10.0, 3.5, H6), 2.67 (1H, d, *J* 3.5, H4), 2.56 (1H, t, *J* 6.5, H16), 2.10 (1H, d, *J* 10.5, H5′), 2.04 (1H, d, *J* 10.0, H6′), 1.98-1.96 (1H, m, H8), 1.85 (1H, s, H7), 1.43 (1H, d, *J* 11.5, H8′), 1.18 (3H, t, *J* 7.0, H1); $\delta_C$ (100 MHz; $CDCl_3$) 173.31 (C=O), 148.85 (C-Cl), 143.47 (C-C), 136.55 (C-C), 134.59 (C[10]H), 133.75

(C-S), 131.94 (C-S), 130.59 (C[15]H), 129.08 (C[14]H), 128.57 (C[13]H), 126.75 (C[11]H), 126.63 (C[20]H), 126.30 (C[12]H), 124.43 (C[19]H), 122.99 (C[18]H), 60.13 (C[16]$H_2$), 60.07 (C[2]$H_2$), 59.82 (C[5]$H_2$), 59.28 (C[17]$H_2$), 55.55 (C[6]$H_2$), 52.99 (C[3]$H_2$), 45.76 (C[9]H), 44.43 (C[7]H), 38.53 (C[4]H), 36.65 (C[8]$H_2$), 27.74 (C[16]$H_2$), 14.34 (C[1]$H_3$); LCMS (APCI+) 512 ($M+H^+$); HRMS $(M+Na)^+$ found 534.1306 $C_{28}H_{30}ClNO_2SNa$ required 534.1304, $\Delta$ ppm +0.4; MRSA 15 - $MIC_{50}$: > 64 $\mu$g/ml, MRSA 16 - $MIC_{50}$: > 64 $\mu$g/ml.

### (1*S**, 5*R**, 6*S**, 7*R**)–7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-cyclohexyl-3-aza-bicyclo[3.2.1]-octane-6-carboxylic acid ethyl ester (229)

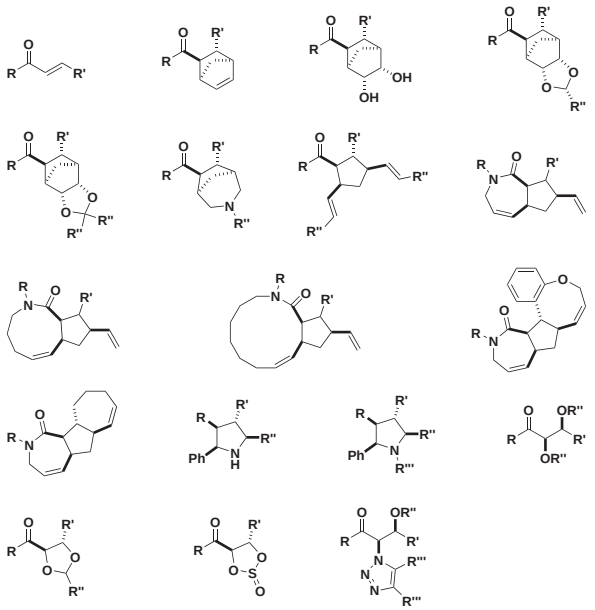


Colourless oil (66 mg, 57 %); $R_f$ 0.16 ($SiO_2$; 10:1 $CHCl_3$: MeOH); $\nu_{max}$ (DMSO) 2930, 1718 (C=O), 1466, 1378, 1256 $cm^{-1}$;$\delta_H$ (500 MHz; $CDCl_3$) 7.35-7.30 (3H, m, ArH), 7.23 (2H, d, *J* 8.5, H15), 7.16-7.14 (3H, m, H13, H14), 4.51 (1H, d, *J* 6.0, H9), 4.13-4.04 (2H, m, H2), 3.20 (1H, t, *J* 6.0, H3), 3.10 (1H, d, *J* 10.5, H6), 2.73-2.69 (2H, m, H5, H4), 2.43 (1H, dd, *J* 10.5, 10.0, H6′), 2.31 (1H, s, H5′), 1.98-1.96 (1H, m, H8), 1.91 (1H, s, H7), 1.59-1.57 (4H, br s, H8′, CyH), 1.59-1.36 (2H, m, CyH), 1.15-1.11 (7H, m, H1, CyH); $\delta_C$ (125 MHz; $CDCl_3$) 173.83 (C=O), 148.35 (C-Cl), 136.21 (C-C), 134.22 (C[10]H), 133.85 (C-S), 132.15 (C-S), 130.85 (C[15]H), 129.10 (C[14]H), 128.45 (C[13]H), 126.77 (C[11]H), 126.26 (C[12]H), 62.88 (C[16]H), 60.29 (C[2]$H_2$), 55.62 (C[5]$H_2$), 52.96 (C[3]$H_2$), 51.04 (C[6]$H_2$), 46.05 (C[9]H), 44.18 (C[7]H), 38.85 (C[4]H), 36.18 (C[8]$H_2$), 28.87 (C[17]$H_2$), 28.70 (C[17′]$H_2$), 26.28 (C[18]$H_2$), 25.53 (C[18′]$H_2$), 20.97 (C[19]$H_2$), 14.26 (C[1]$H_3$); LCMS (APCI+) 484 ($M+H^+$); HRMS $(M+H)^+$ found 484.2076 $C_{28}H_{35}ClNO_2S$ required 484.2077, $\Delta$ ppm −0.3; MRSA 15 - $MIC_{50}$: > 64 $\mu$g/ml, MRSA 16 - $MIC_{50}$: > 64 $\mu$g/ml.

| | Structure | Mass (mg) | Yield (%) |
|---|---|---|---|
| **230** |  A colourless Oil MRSA 15 and 16 $MIC_{50}$: > 64 $\mu$g/ml | 98 | 68 |
| **231** |  A colourless oil $\nu_{max}$ (DMSO) 2976, 1700 (C=O) 1650, 1471, 1261, 1091 $cm^{-1}$ MRSA 15 and 16 $MIC_{50}$: > 64 $\mu$g/ml | 6.3 | 67 |
| **232** |  A colourless oil $\nu_{max}$ (DMSO) 2988, 2901, 1710 (C=O), 1476, 1314, 1261, 1183 $cm^{-1}$ MRSA 15 and 16 $MIC_{50}$: > 64 $\mu$g/ml | 4.6 | 17 |
| **233** |  A yellow oil $\nu_{max}$ (DMSO) 2926, 1711 (C=O), 1658, 1582, 1476, 1380 $cm^{-1}$ MRSA 15 and 16 $MIC_{50}$: > 64 $\mu$g/ml | 7.8 | 41 |
| **234** |  A yellow oil $\nu_{max}$ (DMSO) 2966, 1706 (C=O), 1469, 1385, 1254 $cm^{-1}$ MRSA 15 and 16 $MIC_{50}$: > 64 $\mu$g/ml | 12.5 | 65 |
| **235** |  White Solid, mp 61-62 °C $\nu_{max}$ (DMSO) 2901, 1711 (C=O), 1469, 1529, 1320, 1201 $cm^{-1}$ MRSA 15 and 16 $MIC_{50}$: > 64 $\mu$g/ml | 7.1 | 51 |
| **236** |  Yellow Oil $\nu_{max}$ (DMSO) 2976, 1706 (C=O), 1598, 1509, 1471 $cm^{-1}$ MRSA 15 and 16 $MIC_{50}$: > 64 $\mu$g/ml | 6.6 | 34 |

# 14 Core Skeletal Structures

18 Core structures synthesised were synthesised in the library.



# 15 PCA analysis

In order to assess the diversity of the small molecule collection, we calculated 184 physicochemical and topological molecular descriptors properties (e.g. size, polarity, charges, degree of branching) using MOE 2005.06 [MOE (Molecular Operating Environment); Chemical Computing Group Inc.: Montreal, Quebec, Canada]. Structures were washed (ionized to formal charge, acids and bases protonated according to neutral pH) and PEOE partial charges[5] were assigned for the calculation of descriptors involving partial surface charges. Subsequently, principal component analysis (PCA) of the resulting property space was performed for visualization and numerical diversity estimation using Statistica 6.[6] Numerical diversity values were calculated as the product of the standard deviations of the first three principal components, which gives an estimate of the average size of chemical space occupied per compound in this representation. To gauge the degree of overall diversity obtained in our diversityoriented synthesis we compared the diversity of our library to the chemical space spanned by benchmark collections: (1) the MDL Drug Data Report (MDDR) database [MDL Drug Data Report, Elsevier MDL, http://www.mdli.com] and (2) a focused library of histamine H3 receptor antagonists (where a common biphenyl scaffold was functionalized at two positions).[7]

# 16 Screening Data

*Standardised antimicrobial activity of gemmacin*: performed by Dr Derek F. J. Brown (Clinical Microbiology and Public Health Laboratory, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QW, United Kingdom). gemmacin was dissolved in DMSO at a concentration of $10^4$ $\mu$g/ml and stock solutions further diluted to $10^3$ $\mu$g/ml in water. Organisms tested were Cambridge culture collection isolates of *Staphylococcus aureus* (7), *Enterococcus spp* (5), *Enterobacteriaceae* (7), P*seudomonas aeruginosa* (2), *Acinetobacter sp* (1), *Streptococcus spp* (11), *Heamophilus influenzae* (6), *Moraxella catarrhalis* (2) and yeasts (7). Stock solutions of agents were used to prepare a twofold dilution series of 0.03-64 g/ml in IsoSensitest agar (with 5 % defibrinated horse blood and 20 g/ml NAD for streptococci, *Haemophilus influenzae*, *Moraxella catarrhalis* and yeasts). Organisms were inoculated onto plates at a concentration of approximately $10^4$ cfu/spot. Plates were incubated at 35-37 °C for 24 h in air. The minimum inhibitory concentration (MIC) endpoints were read as the lowest concentration showing no visible growth. The lowest concentration showing a marked antibacterial effect as seen by a significant reduction in growth (MAE) was also recorded.

| Species | Strain | Antimicrobial activity (g/ml) | |
|---|---|---|---|
| | | MIC | MAE |
| *S. aureus* | NCTC 6571 | 32 | 32 |
| | ATCC 29213 | 32 | 32 |
| | ATCC 25923 | 32 | 32 |
| | NCTC 12493 MRSA | 32 | 16 |
| | Mu50 GISA | 32 | 16 |
| | EMRSA 15 | 32 | 16 |
| | EMRSA 16 | 32 | 16 |
| *E. faecalis* | ATCC 29212 | 64 | 32 |
| | vanA 56059 | 64 | 32 |
| | vanB 78097 | 64 | 32 |
| *E. faecium* | vanA 56001 | 64 | 32 |
| | vanB 129036 | 64 | 32 |
| *E. coli* | NCTC 10418 | >64 | >64 |
| | ATCC 29212 | >64 | >64 |
| | ESBL CTX-M 42037 | >64 | >64 |
| | ESBL CTX-M-15 42039 | >64 | >64 |
| *Enterobacter sp* | AmpC 66086 | >64 | >64 |
| | ESBL CTX-M-9 42033 | >64 | >64 |
| *Klebsiella sp* | 78065 | >64 | >64 |
| *Acinetobacter sp* | 165041 | >64 | >64 |
| *P. aeruginosa* | NCTC 10662 | >64 | >64 |
| | ATCC 27853 | >64 | >64 |
| *S. pneumoniae* | ATCC 49619 | 64 | 32 |
| | 110040 | 64 | 64 |
| | 110041 | 64 | 64 |
| Strep Group A | 110070 | >64 | 64 |
| | 110071 | >64 | 64 |
| Strep Group B | 110097 | >64 | >64 |
| | 110098 | >64 | >64 |
| Strep Group G | 152043 | >64 | 64 |
| | 152045 | >64 | 64 |
| *S. oralis* | 152019 | >64 | 64 |
| | 152025 | >64 | >64 |
| *S. intermedius* | 152022 | >64 | 64 |
| *S. parasanguis* | 152027 | 64 | 64 |
| *H. influenzae* | 110026 | >64 | >64 |
| | 110027 | >64 | >64 |
| | 3034 | >64 | >64 |
| | 3037 | >64 | >64 |
| *M. catarrhalis* | 110001 | 16 | 1 |
| | 110002 | 16 | 1 |
| *C. albicans* | ATCC 90028 | >64 | 8 |
| *C. parapsilosis* | 107002 | >64 | 8 |
| *C. lusitaniae* | 107003 | >64 | 64 |
| *C. tropicalis* | 107011 | >64 | 64 |
| *C. glabrata* | 107012 | >64 | >64 |
| *C. guilliermondii* | 107028 | >64 | >64 |

# 17 Screening against EMRSA 15 and 16

Bacterial Growth Assays. Overnight (stationary-phase) cultures of *S. aureus* strains (EMRSA 15 and EMRSA 16) were grown in Luria Broth (10 g $l^{-1}$ tryptone, 5 g $l^{-1}$ Yeast Extract, 5 g $l^{-1}$ NaCl, pH 7.0) at 37 °C in 25 ml Universal tubes mounted in a rolling drum. These cultures were used to inoculate aliquots (200 $\mu$l) of LB dispensed into the central 60 wells of a 96-well polystyrene microtitre plate. The outside wells were filled with water. Each well was also supplemented with the compound of interest at the indicated concentration. Control wells were supplemented with DMSO alone. The plates were then taped to the surface of an orbital platform and incubated at 37 °C to ensure good aeration of the cultures. Each hour, the plates were removed for spectrophotometric determination (absorbance was measured at 595 nm) of the cell density. After this, the plates were returned as soon as

possible to the orbital shaker to ensure continuous aeration and growth. In this way, growth curves could be constructed for each strain in the presence of the appropriate compounds. This allowed the assessment of the effects of these compounds on (i) the growth rate during exponential-phase growth, and (ii) the final optical density achieved by each culture during the stationary-phase. All experiments were performed independently in triplicate. $MIC_{50}$ = Minimum Inhibitory Concentration required to inhibit the growth of 50 % of organisms after 8 h when the control has reached the stationary-phase.

## 18 Human Cell Cytotoxicity Assay

Cell cytotoxicity was determined using the CCK8 assay (Dojinodo Molecular Technologies, Gaithersburg, MD, USA), which measures the reduction of WST-8, a water soluble tetrazolium salt by dehydrogenases in viable cells. HEK cells in Dulbecco's modified Eagle's medium supplemented with 10 % heat-inactivated fetal bovine serum, 2 mM L-glutamine, and 50 units/ml penicillin and streptomycin, were seeded out at 200,000 per well of a 96-well plate and allowed to grow overnight at 37 °C with 5 % $CO_2$. The plates were incubated for 48 hours and then each well was also supplemented with gemmacin (dissolved in PBS buffer with 5 % DMSO) at the indicated concentration. Two different controls were used: (i) wells containing PBS buffer with no media and (ii) media with PBS buffer. The plates were then incubated in a $CO_2$ incubator at 37 °C for 48 hours. The media was removed and replaced with fresh HEK media (100 $\mu$l) and CCK8 solution (10 $\mu$l) was added to each well and incubated for 2 hours at 37 °C. Absorbance was measured at 450 nm. The CCK8 assay measures viable cells as a per cent of control cells. All experiments were performed independently in triplicate.

## 19 Membrane Disrupter Assay

An overnight (stationary-phase) culture of EMRSA 16 was grown in brain-heart infusion (BHI) culture at 37 °C, and then aliquoted into eight 25 ml Universal tubes and maintained in the shaking water bath. The number of viable bacteria in each tube was estimated by spectrophotometric optical density by taking an aliquot of 200 $\mu$l of culture and diluting it with 800 $\mu$l of BHI media and measuring optical density at 600 nm on a spectrophotometer. Four different experiments in duplicate were carried out, and the vials were inoculated with either: DMSO (negative control), gemmacin at inhibitory concentration (34 $\mu$g $ml^{-1}$), gemmacin at sub-inhibitory concentration (4 $\mu$g $ml^{-1}$), or nothing (negative control). After two hours incubation, optical density was determined again. To remove the test compounds, cultures were spun down on a centrifuge at 8000 rpm for four minutes and the media removed. The cells were re-suspended in TES buffer (10 mM Tris-HCl [pH 7.5], 1 mM EDTA and 100 mM NaCl), spun down on a centrifuge at 8000 rpm for four minutes and the buffer removed. The cells were re-suspended in NaCl buffer (7.1 g NaCl in 50 ml TES buffer), and optical density determined again. The bacteria were then treated with 10 $\mu$l of lysostaphin and shaken in a waterbath at 37 °C for 30 minutes. Lysostaphin specifically digests the pentaglycine bridge between peptidoglycan strands in the *S. aureus* cell wall, leading to a cell wall weakening and a reduction in optical density, but does not disrupt the cellular membrane resulting in cell lysis. Optical density was tested again. Finally, 100 $\mu$l of 20 % sarkosyl was added to the samples which is a detergent sufficient to disrupt *S. aureus* cell membranes and lyse the cells. Optical density was tested again.

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