Supporting information

Enantioselective Total Synthesis of the Highly Selective Sphingosine-1-Receptor VPC01091 by Heck Desymmetrization of a Non-Activated Cyclopentene-Fused Spiro-Pyrrolidinone

Ismat Ullah Khan, a,b Shivashankar Katella, b Abbas Hassan a and Carlos Roque Duarte Correia*,b

a Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan
b Institute of Chemistry, State University of Campinas, Josue de Castro St., Campinas (Brazil), 13083-970, Email: roque@iqm.unicamp.br, Homepage: www.correia-group.com.

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1. General Informations

All of the Heck-Matsuda arylation reactions were performed in 4 mL screw-top vessels under an air atmosphere. Reaction temperatures different from room temperature are reported as the temperature of the heat transfer medium surrounding the vessel. Bottle grade solvents were used for Heck-Matsuda arylation reactions without any previous treatment (drying or distillation). Methanol refers to >99.8% and acetonitrile refers to >99.5%, both were purchased from synthesis. Pd(TFA)$_2$ (Palladium(II)trifluoroacetate) refers to >97% (Strem chemicals). Ligands L$_1$, L$_3$, L$_4$ and L$_5$ were purchased from Sigma-Aldrich and used as received. Ligands L$_2$, L$_6$ and L$_7$ were prepared by procedure recently reported by our group.$^1$ DTBMP (2,6-ditertiarybutyl-4-methylpyridine)$^2$ and arenediazonium salts$^3$ were prepared by the literature procedures.

Normally, the general laboratory techniques were used. Moisture and air sensitive reactions were performed in oven-dried glassware fitted with air-tight rubber septum and under an inert (nitrogen) atmosphere. Standard syringe techniques were used to handle the reagents and solvents. Elevated temperatures were obtained by using a stirrer-hotplate and heating block.

Analytical thin layer chromatography was performed on Merck® TLC silica gel 60 F$_{254}$ plates, 0.25mm thickness and eluted with ethylacetate/n-hexane mixtures. To visualize TLC, ultraviolet light ($\lambda = 254$nm), KMnO$_4$ and PMA (phosphomolybdic acid) solutions were used.

The crude products obtained were purified by flash column chromatography using Merck® Silica gel 60 (230-400 mesh), eluting with ethylacetate/n-hexane. Solvents used for chromatography were technical grade and were distilled before to use. $^1$HNMR spectra were taken on Bruker® 250, 400, 500 and 600 MHz and $^{13}$CNMR spectra at 100, 125 and 150 MHz instruments. At the methodology optimization stage, 1,3-bis(trifluoromethyl)-5-bromobenzene was used as an internal standard for the determination of chemical yields by $^1$H NMR. The chemical shift values were recorded in parts per million (ppm) relative to the residual signals of the deuterated NMR solvents used as references (CDCl$_3$; $^1$H: $\delta$ = 7.27 ppm, $^{13}$C: $\delta$ = 77.26 ppm. (CD$_3$)$_2$SO; $^1$H: $\delta$ = 2.50 ppm, $^{13}$C: $\delta$ = 39.52 ppm). The multiplicities of the signals are denoted by s (singlet), d (doublet), t (triplet), q (quartet), sept (septate) bs (broad singlet), td (triplet of doublet), dt (doublet of triplet) dd (double doublet) and m (multiplet).
For determining enantiomeric ratios (er), compounds were analysed on Agilent technologies 1260 infinity instrument with an UV detector and Daicel Chiralpak® chiral columns as stationary phase. Isopropyl alcohol and n-hexane as an eluent stated with each product.

Optical rotations (\(\alpha\)) were measured on a Perkin Elmer Model 341 polarimeter at 20 °C using a quartz glass cell (10 mm path length). Specific rotations \([\alpha]_{D}^{20}\) are given in [deg cm\(^{-1}\) g\(^{-1}\) dm\(^3\)] and the concentration of the samples is expressed in [g/100 mL].

Exact ESI mass spectra were recorded on a Waters Xevo Q-TOF using electrospray ion source, positive mode, (ESI) and (TOF) analyzer. Mass calibration was carried out directly before the measurement of the sample using clusters of sodium formate. The major signals are quoted in m/z.

Melting points were determined on Thomas-Hoover Capillary Melting Point Apparatus, Model 6427-H10.

### 2. Substrates Synthesis

![Substrate Synthesis Diagram]

**Figure 1.** Substrate (4) Synthesis
Ethyl-2,2-bis(allyl)-2-nitroacetate (ii)

Experimental Procedure:

To a solution of Ethyl-2-nitroacetate (i) (100 mol%, 15.03 mmol, 2.00 g, 1.67 mL) in dry THF (75 mL, 0.2 M) were added Allylacetate (210 mol%, 31.56 mmol, 3.4 mL) and Pd(PPh₃)₄ (10 mol%, 1.50 mmol, 1.73 g). After stirring for 15 minutes, DIPEA (210 mol%, 31.56 mmol, 4.80 g, 5.50 mL) was added and the reaction mixture was stirred under N₂ atmosphere at 50 °C for 8 h. The progress of the reaction was checked by TLC using 2:8 ethylacetate/n-hexane. On completion of the reaction, the reaction mixture was filtered over celite-bed and washed with THF (2 × 100 mL). The filterate was concentrated at low pressure on rotary evaporator, the residue obtained was dissolved in DCM (75 mL) and washed with NaHCO₃ aq. solution (75 mL). The aq. layer was extracted with DCM (2 × 75 mL). The combined organic layers were dried on anhydrous Na₂SO₄ and concentrated at low pressure on rotary evaporator. The product obtained was purified by flash column chromatography using 2:98 ethylacetate/n-hexane (less polar eluent was used for column as the PPh₃ in the reaction mixture and the product have very similar Rf values.)

Compound (ii) was obtained as yellow oil; 96% yield (3.07 g).

¹H NMR (400 MHz, CDCl₃) δ 5.67 – 5.57 (m, 2 H), 5.22 – 5.17 (m, 4 H), 4.26 (q, J = 7.1 Hz, 2 H), 2.99 – 2.86 (m, 4 H), 1.28 (t, J = 7.2 Hz, 3 H).

¹³C NMR (100 MHz, CDCl₃) δ 166.2, 129.6, 121.6, 95.0, 63.0, 38.2, 14.1.
Ethyl-2-allyl-2-aminopent-4-enoate (iii)

Experimental Procedure:\textsuperscript{5}

To a solution of Ethyl-2,2-bis(allyl)-2-nitroacetate (ii) (100 mol\%, 10.80 mmol, 2.30 g) in isopropanol (100 mL, 0.1 M) in a 250 mL 1 N round bottom flask, activated zinc (3,000 mol\%, 324.03 mmol, 21.19 g) was added. Then AcOH (4000 mol\%, 432.00 mmol, 24.7 mL) was added slowly (in 10 minutes) and the reaction mixture was stirred at 25 °C for 1 h. The progress of the reaction was checked by TLC. On completion of the reaction, the reaction mixture was filtered and washed with ethylacetate. The solvent and excess AcOH were removed at low pressure on rotary evaporator. The residue obtained was dissolved in EtOAc (100 mL) and washed with 100 mL NaHCO\textsubscript{3} aq. The aq. layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried on anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated at low pressure on rotary evaporator to a pure product.

Compound (iii) was obtained as Colourless oil; 92\% yield (1.82 g).

\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) δ 5.75 – 5.68 (m, 2 H), 5.17 – 5.14 (m, 4 H), 4.20 (q, J = 7.1 Hz, 2 H), 2.58 (dd, J = 13.5, 6.5 Hz, 2 H), 2.29 (dd, J = 13.5, 8.3 Hz, 2 H), 1.29 (t, J = 7.1 Hz, 3 H).

\textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}) δ 175.1, 132.8, 119.8, 61.4, 60.7, 44.3, 14.6.

2-Allyl-2-aminopent-4-en-1-ol (vi)

Experimental Procedure:\textsuperscript{6}

An oven dried flask was purged with N\textsubscript{2}, LiAlH\textsubscript{4} (200 mol\%, 16.36 mmol, 0.62 g) was taken in THF (40.00 mL THF), which was then cooled to 0 °C. The solution of the ester (iii) (100 mol\%, 8.18 mmol, 1.5 g) in 20 mL dry THF was added dropwise (via syringe in 15 minutes) to the flask containing LiAlH\textsubscript{4} and stirred for 1 h at 0 °C. The progress of the reaction was checked by TLC using 1:1 ethylacetate/n-hexane. On completion of the reaction, the reaction mixture was diluted two fold with THF (by adding 40 mL THF) and quenched
according to the Fieser procedure (by successive addition of water (0.4 mL/mmol LiAlH₄), 10% NaOH (0.4 mL/mmol LiAlH₄), and water (1.2 mL/mmol LiAlH₄) dropwise). The whole reaction mixture was dried over anhydrous MgSO₄, filtered, and concentrated. The crude product was purified by flash column chromatography using 1:9 ethylacetate/n-hexane as an eluent.

Compound (vi) was obtained as a white solid; 89% yield (1.03 g).

**1H NMR** (600 MHz, CDCl₃) δ 5.87 – 5.79 (m, 2 H), 5.15 – 5.11 (m, 4 H), 3.35 (s, 2 H), 2.21 – 2.12 (m, 4 H).

**13C NMR** (150 MHz, CDCl₃) δ 133.7, 119.1, 68.4, 55.1, 42.1.

**HRMS (ESI+)** calculated for (C₈H₁₅NO + H⁺): 142.1232, found: 142.1238.

**4,4-Diallyloxazolidin-2-one (iv)**

**Experimental Procedure:**

To a solution of 2-Allyl-2-aminopent-4-en-1-ol (vi) (100 mol%, 9.21 mmol, 1.30 g) in dry DCM (45 mL) at 0 °C was added triethylamine (200 mol%, 18.42 mmol, 2.57 mL). A solution of triphosgene (50 mol%, 4.61 mmol, 1.37 g) in dry DCM (45 mL) was added dropwise to the reaction mixture in 1 h. The reaction mixture was stirred further for 2 h at 0 °C. The progress of the reaction was checked by TLC by using 1:1 ethylacetate/n-hexane. On completion of the reaction, ether (70 mL) was added to the clear solution which resulted in appearance of white precipitate. The solids were filtered through a sintered glass crucible and washed with DCM. The filtrate was concentrated at low pressure on a rotary evaporator to nearly 15–20 mL. The resulting oil was loaded onto a small pad of silica gel (5 cm length) in a sintered glass crucible and washed slowly with ethylacetate. The filtrate was then concentrated on a rotatory evaporator to provide pure 4,4-Diallyloxazolidin-2-one (iv).

Compound (iv) was obtained as light yellow oil; 96% yield (1.48 g).

**1H NMR** (600 MHz, CDCl₃) δ 5.80 – 5.74 (m, 2 H), 5.24 – 5.18 (m, 4 H), 4.13 (s, 2 H), 2.38 (dd, J = 14.0, 7.1 Hz, 2 H), 2.32 (dd, J = 14.0, 7.7 Hz, 2 H).

**13C NMR** (150 MHz, CDCl₃) δ 159.5, 131.4, 120.8, 73.1, 59.9, 43.1.

**HRMS (ESI+)** calculated for (C₉H₁₃NO₂ + H⁺): 168.1024, found: 168.1022.
**Experimental Procedure:**

To a solution of 4,4-Diallyloxazolidin-2-one (iv) (100 mol%, 7.18 mmol, 1.20 g) in DCM (75 mL, 0.1 M) were added triethylamine (250 mol%, 17.95 mmol, 2.50 mL), 4-dimethylaminopyridine (50 mol%, 3.59 mmol, 0.44 g). (Boc)$_2$O (300 mol%, 21.54 mmol, 4.70 g) dissolved in 35 mL DCM was added dropwise at 0 °C. After stirring for 5 minutes at 0 °C, the reaction mixture was warmed to room temperature, and stirred further for 1 h. The progress of the reaction was checked by TLC by using 2:8 ethylacetate/n-hexane. On completion of the reaction, the volatiles were removed at low pressure on rotary evaporator. The residue obtained was diluted with ethylacetate (100 mL). The organic layer was washed with 2 N HCl aq. solution (2 × 100 mL), saturated NaHCO$_3$ aqueous solution (2 × 100 mL), brine (2 × 100 mL). The organic layer was dried over anhydrous MgSO$_4$, concentrated under reduced pressure on rotary evaporator. The residue obtained was purified by flash column chromatography (using ethylacetate/n-hexane, 1:10 to 3:7).

Compound (v) was obtained as colourless oil; 93% yield (1.79 g).

$^1$H NMR (600 MHz, CDCl$_3$) δ 5.74 – 5.67 (m, 2 H), 5.24 – 5.18 (m, 4 H), 4.08 (s, 2 H), 2.88 (dd, $J = 14.1, 7.3$ Hz, 2 H), 2.34 (dd, $J = 14.1, 7.4$ Hz, 2 H), 1.56 (s, 9 H).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 152.9, 149.7, 130.9, 121.3, 84.1, 68.8, 63.7, 41.5, 28.2; HRMS (ESI+) calculated for (C$_{14}$H$_{21}$NO$_4$ + H$^+$): 268.1549, found: 268.1554.

**Experimental Procedure:**

$^t$er$^t$-Butyl-2-oxo-3-oxa-1-azaspiro[4.4]non-7-ene-1-carboxylate (4)

term-Butyl-2-oxo-3-oxa-1-azaspiro[4.4]non-7-ene-1-carboxylate (4)

Experimental Procedure:

$t$er$^t$-Butyl-4,4-diallyl-2-oxooxazolidine-3-carboxylate (vi) (100 mol%, 3.74 mmol, 1.00 g) was dissolved in 1200 mL DCM. To deoxygenate DCM, N$_2$ was bubbled through the solution
for 30 minutes. After that Grubbs-II catalyst (2.5 mol%, 0.18 mmol, 0.16 g) was added and stirred under N\textsubscript{2} at room temperature for overnight. The progress of the reaction was checked by TCL using 3:7 ethylacetate/n-hexane. On completion of the reaction, the solvent was evaporated at low pressure on rotary evaporator. The residue obtained was purified by flash column chromatography using 1:9 ethylacetate/n-hexane.

Compound (4) was obtained as off white solid; 93% yield (1.68 g).

\textbf{\textsuperscript{1}H NMR} (600 MHz, CDCl\textsubscript{3}) \(\delta\) 5.67 (s, 2 H), 4.17 (s, 2 H), 3.17 (d, \(J = 15.2\) Hz, 2 H), 2.47 (d, \(J = 15.1\) Hz, 2 H), 1.52 (s, 9 H).

\textbf{\textsuperscript{13}C NMR} (150 MHz, CDCl\textsubscript{3}) \(\delta\) 152.9, 149.6, 128.3, 84.3, 77.9, 67.0, 44.0, 28.3.

\textbf{HRMS (ESI+)} calculated for (C\textsubscript{12}H\textsubscript{17}NO\textsubscript{4} + H\textsuperscript{+}): 240.1236, found: 240.1227.

\textbf{M.P.}: 85 – 87 °C.
3. Synthesis and Characterization of Products

3.1 General procedure for the Heck-Matsuda arylation reactions using arenediazonium salts:

To a 4 mL screw-top vial containing a magnetic stir-bar was added Pd(TFA)$_2$ (5 mol%, 0.005 mmol, 0.00166 g), ligand (pyrazine-bisoxazoline, 7.5 mol%, 0.0075 mmol, 0.00248 g) and 0.25 mL of 2:8 acetonitrile/methanol (0.4 M). The resulting light orange colored solution was then stirred at 60 °C for 8 minutes to result in the formation of ligand-catalyst complex. After 8 minutes stirring at 60 °C, it was cooled to room temperature. Then the olefin (4) (100 mol%, 0.1 mmol, 0.0239 g), DTBMP (2,6-di-tert-butyl-4-methylpyridine) (100 mol%, 0.1 mmol, 0.0205 g) were added to it, followed by the addition of the appropriate arenediazonium salt 5a-5l (120 mol%, 0.12 mmol). The progress of the reaction was monitored by TLC using 2:8 ethylacetate/n-hexane and stained by PMA (phosphomolybdic acid) solution. On complete consumption of the olefin shown by TLC, the reaction mixture was filtered through a short pad of silica gel in 24 mL plastic syringe and washed with 1:1 ethylacetate/n-hexane to remove the polar impurities. The resulting filtrate was concentrated at low pressure on rotary evaporator. The crude product obtained was purified by flash column chromatography using 1:9 ethylacetate/n-hexane as eluent to afford the Heck products with yield up to 93%. To determine the chemical yield by $^1$HNMR, 1,3-bis(trifluoromethyl)-5-bromobenzene (1 eq, 0.0293 g, 17.2 μL for 0.1 mmol of substrate) was added to the crude reaction mixture as an internal standard and the olefinic protons signal was compared with the one proton signal of the internal standard.

$\text{(5R,8R)-}t_{-}\text{Butyl-8-(4methoxyphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3a)}$

Compound 3a was obtained as a colorless crystalline solid (30.4 mg, 0.088 mmol, 88% isolated yield); 92:8 dr (determined by NMR).

The enantiomeric ratio (er) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IA-3 column (4.6 mm × 250 mm) at 25 °C, 1:99 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: $t_R =$
28.72 min (major), 44.50 min (minor); minor diastereomer: $t_R = 26.18$ min (major), 32.67 min (minor)).

**$^1$H NMR (500 MHz, CDCl$_3$):** $\delta$ 7.03 (d, $J = 8.6$ Hz, 2 H), 6.86 (d, $J = 8.7$ Hz, 2 H), 6.07 (dd, $J = 5.5$, 2.3 Hz, 1 H), 5.80 (dd, $J = 5.5$, 2.3 Hz, 1 H), 4.27 – 4.23 (m, 1 H), 4.20 (d, $J = 8.8$ Hz, 1 H), 4.05 (d, $J = 8.8$ Hz, 1 H), 3.80 (s, 3 H), 2.97 (dd, $J = 14.2$, 9.2 Hz, 1 H), 1.90 (dd, $J = 14.2$, 4.2 Hz, 1 H), 1.55 (s, 9 H).

**$^{13}$C NMR (125 MHz, CDCl$_3$):** $\delta$ 158.7, 152.6, 149.5, 139.7, 136.3, 131.2, 128.2, 114.4, 84.2, 73.9, 73.8, 55.6, 49.8, 45.0, 28.3.

**HRMS (ESI+)** calculated for (C$_{19}$H$_{23}$NO$_5$ + H$^+$): 346.1654, found: 346.1644.

**[α]$^20_D$ (c 2.86, CHCl$_3$) = +184.2.**

**M.P.:** 154 – 157 °C

![Compound 3b](image)

(5R,8R)-tert-Butyl-8-(2-methoxyphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3b)

Compound 3b was obtained as a white solid (29.4 mg, 0.085 mmol, 85% isolated yield); 95:5 dr determined by NMR.

**The enantiomeric ratio (er) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IA-3 column (4.6 mm × 250 mm) at 25 °C, 1:99 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: $t_R = 30.33$ min (major), 36.29 min (minor); minor diastereomer: $t_R = 22.71$ min (major), 25.67 min (minor)).

**$^1$H NMR (500 MHz, CDCl$_3$):** $\delta$ 7.23 (td, $J = 8.1$, 8.0, 1.7 Hz, 1 H), 6.96 (dd, $J = 7.7$, 1.6 Hz, 1 H), 6.94 – 6.87 (m, 2 H), 6.07 (dd, $J = 5.6$, 2.4 Hz, 1 H), 5.83 (dd, $J = 5.5$, 2.2 Hz, 1 H), 4.51 – 4.45 (m, 1 H), 4.12 (d, $J = 8.8$ Hz, 1 H), 3.96 (d, $J = 8.8$ Hz, 1 H), 3.84 (s, 3 H), 2.96 (dd, $J = 14.1$, 9.5 Hz, 1 H), 1.94 (dd, $J = 14.1$, 3.8 Hz, 1 H), 1.56 (s, 9 H).

**$^{13}$C NMR (125 MHz, CDCl$_3$):** $\delta$ 157.3, 152.8, 149.5, 138.3, 132.5, 131.8, 128.2, 127.0, 120.6, 110.7, 84.1, 73.8, 73.7, 55.4, 44.6, 43.1, 28.3.

**HRMS (ESI+)** calculated for (C$_{19}$H$_{23}$NO$_5$ + H$^+$): 346.1654, found: 346.1650.

**[α]$^20_D$ (c 2.90, CHCl$_3$) = +128.7.**
**M.P.:** 70 – 73 °C.

(5R,8R)-**tert**-Butyl-2-oxo-8-(4-(trifluoromethyl)phenyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3c)

Compound 3c was obtained as a colorless crystalline solid (20.3 mg, 0.053 mmol, 53% isolated yield); 88:12 dr determined by NMR. The enantiomeric ratio (er) was determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 10:90 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: \(t_R = 35.08\) min (major), 30.13 min (minor); minor diastereomer: \(t_R = 57.44\) min (major), 38.71 min (minor)).

\[^1H\text{ NMR (500 MHz, CDCl}_3\text{)}:\] \(\delta 7.58 \ (d, J = 8.1 \text{ Hz, 2 H}), 7.25 \ (d, J = 8.1 \text{ Hz, 2 H}), 6.11 \ (dd, J = 5.5, 2.2 \text{ Hz, 1 H}), 5.88 \ (dd, J = 5.5, 2.3 \text{ Hz, 1 H}), 4.41 – 4.38 \ (m, 1 H), 4.24 \ (d, J = 8.9 \text{ Hz, 1 H}), 4.05 \ (d, J = 8.9 \text{ Hz, 1 H}), 3.05 \ (dd, J = 14.3, 9.2 \text{ Hz, 1 H}), 1.90 \ (dd, J = 14.3, 4.6 \text{ Hz, 1 H}), 1.57 \ (s, 9H).\)

\[^{13}C\text{ NMR (125 MHz, CDCl}_3\text{)}:\] \(\delta 152.3, 149.6, 148.3, 138.7, 132.1, 129.5 \ (q, J = 32.6 \text{ Hz}), 127.7, 126.0 \ (q, J = 3.6 \text{ Hz}), 124.4 \ (q, J = 269.6 \text{ Hz}), 84.4, 73.7, 73.7, 50.5, 44.8, 28.3.\)

HRMS (ESI+) calculated for \((\text{C}_{19}\text{H}_{20}\text{F}_3\text{NO}_4^+ + \text{H}^+): 384.1423,\) found: 384.1417.

\([\alpha]_{D}^{20}\) (c 1.05, CHCl\(_3\)) = +154.8.

**M.P.:** 139 – 143 °C.

(5R,8R)-**tert**-Butyl-2-oxo-8-(3-(trifluoromethyl)phenyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3d)

Compound 3d was obtained as a yellow sticky material (16.1 mg, 0.042 mmol, 42% isolated yield); 89:11 dr determined by NMR. The enantiomeric ratio (er) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 10:90 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: \(t_R = 44.85\) min (major), 40.13 min (minor); minor diastereomer: \(t_R = 64.60\) min (major), 45.17 min (minor)).

\[^1H\text{ NMR (500 MHz, CDCl}_3\text{)}:\] \(\delta 7.58 \ (d, J = 8.1 \text{ Hz, 2 H}), 7.25 \ (d, J = 8.1 \text{ Hz, 2 H}), 6.11 \ (dd, J = 5.5, 2.2 \text{ Hz, 1 H}), 5.88 \ (dd, J = 5.5, 2.3 \text{ Hz, 1 H}), 4.41 – 4.38 \ (m, 1 H), 4.24 \ (d, J = 8.9 \text{ Hz, 1 H}), 4.05 \ (d, J = 8.9 \text{ Hz, 1 H}), 3.05 \ (dd, J = 14.3, 9.2 \text{ Hz, 1 H}), 1.90 \ (dd, J = 14.3, 4.6 \text{ Hz, 1 H}), 1.57 \ (s, 9H).\)

\[^{13}C\text{ NMR (125 MHz, CDCl}_3\text{)}:\] \(\delta 152.3, 149.6, 148.3, 138.7, 132.1, 129.5 \ (q, J = 32.6 \text{ Hz}), 127.7, 126.0 \ (q, J = 3.6 \text{ Hz}), 124.4 \ (q, J = 269.6 \text{ Hz}), 84.4, 73.7, 73.7, 50.5, 44.8, 28.3.\)

HRMS (ESI+) calculated for \((\text{C}_{19}\text{H}_{20}\text{F}_3\text{NO}_4^+ + \text{H}^+): 384.1423,\) found: 384.1417.

\([\alpha]_{D}^{20}\) (c 1.05, CHCl\(_3\)) = +154.8.
min (major), 35.94 min (minor); minor diastereomer: $t_R = 40.46$ min (major), min $51.32$ (minor).

**$^1$H NMR (600 MHz, CDCl$_3$)**: $\delta$ 7.5 – 7.43 (m, 2 H), 7.36 – 7.30 (m, 2 H), 6.10 (dd, $J = 5.5, 2.3$ Hz, 1 H), 5.88 (dd, $J = 5.5, 2.3$ Hz, 1 H), 4.40 – 4.37 (m, 1 H), 4.24 (d, $J = 8.9$ Hz, 1 H), 4.05 (d, $J = 8.9$ Hz, 1 H), 3.04 (dd, $J = 14.4, 9.2$ Hz, 1 H), 1.90 (dd, $J = 14.4, 4.7$ Hz, 1 H), 1.55 (s, 9 H).

**$^{13}$C NMR (150 MHz, CDCl$_3$)**: $\delta$ 152.3, 149.4, 145.2, 138.7, 132.2, 131.3 (q, $J = 32.2$ Hz), 130.7, 129.5, 124.2 (q, $J = 272.3$ Hz), 124.0 (q, $J = 3.8$ Hz), 123.9 (q, $J = 3.8$ Hz), 84.3, 73.7, 73.6, 50.5, 44.8, 28.2.

**HRMS (ESI+)** calculated for (C$_{19}$H$_{20}$F$_3$NO$_4$ + H$^+$): 384.1423, found: 384.1414.

$\lbrack \alpha \rbrack_{D}^{20} (c$ 1.516, CHCl$_3$) = +188.0.

(5R,8R)-tert-Butyl-2-oxo-8-(p-tolyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3e)

Compound 3e was obtained as a colorless crystalline solid (29.6 mg, 0.09 mmol, 90% isolated yield); 94:6 dr determined by NMR.

The **enantiomeric ratio (er)** determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 5:95 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: $t_R = 77.71$ min (major), 84.38 min (minor); minor diastereomer: $t_R = 99.28$ min (major), 121.64 min (minor)).

**$^1$H NMR (500 MHz, CDCl$_3$)**: $\delta$ 7.13 (d, $J = 7.8$ Hz, 2 H), 7.00 (d, $J = 8.0$ Hz, 2 H), 6.08 (dd, $J = 5.5, 2.3$ Hz, 1 H), 5.80 (dd, $J = 5.5, 2.2$ Hz, 1 H), 4.28 – 4.25 (m, 1 H), 4.20 (d, $J = 8.8$ Hz, 1 H), 4.05 (d, $J = 8.8$ Hz, 1 H), 2.99 (dd, $J = 14.2, 9.2$ Hz, 1 H), 2.34 (s, 3 H), 1.92 (dd, $J = 14.2, 4.2$ Hz, 1 H), 1.56 (s, 9 H).

**$^{13}$C NMR (125 MHz, CDCl$_3$)**: $\delta$ 152.6, 149.5, 145.2, 138.7, 132.2, 131.3 (q, $J = 32.2$ Hz), 130.7, 129.5, 124.2 (q, $J = 272.3$ Hz), 124.0 (q, $J = 3.8$ Hz), 123.9 (q, $J = 3.8$ Hz), 84.3, 73.9, 50.2, 44.9, 29.9, 28.3, 21.2.

**HRMS (ESI+)** calculated for (C$_{19}$H$_{23}$NO$_4$ + H$^+$): 330.1705, found: 330.1700.

$\lbrack \alpha \rbrack_{D}^{20} (c$ 1.459, CHCl$_3$) = +218.9.

**M.P.:** 115 – 118 °C.
(5R,8R)-tert-Butyl-8-(4-isopropylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3f)

Compound 3f was obtained as a white solid (30.7 mg, 0.0.86 mmol, 86% isolated yield); 95:5 dr determined by NMR.

The enantiomeric ratio (er) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IA-3 column (4.6 mm × 250 mm) at 25 °C, 1:99 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: \( t_R = 14.32 \) min (major), 16.30 min (minor); minor diastereomer: \( t_R = 34.92 \) min (major), 21.90 min (minor)).

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.18 (d, \( J = 8.1 \) Hz, 2 H), 7.04 (d, \( J = 8.1 \) Hz, 2 H), 6.09 (dd, \( J = 5.5, 2.3 \) Hz, 1 H), 5.81 (dd, \( J = 5.5, 2.3 \) Hz, 1 H), 4.28 – 4.25 (m, 1 H), 4.21 (d, \( J = 8.8 \) Hz, 1 H), 4.07 (d, \( J = 8.8 \) Hz, 1 H), 2.98 (dd, \( J = 14.2, 9.3 \) Hz, 1 H), 2.89 (sept, \( J = 6.9 \) Hz, 1 H), 1.95 (dd, \( J = 14.3, 4.2 \) Hz, 1 H), 1.56 (s, \( J = 6.2 \) Hz, 9 H), 1.25 (d, \( J = 7.0 \) Hz, 6 H)

\(^1\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 152.6, 149.5, 147.6, 141.5, 139.5, 131.2, 127.2, 127.0, 84.1, 73.9, 73.8, 50.2, 44.8, 33.9, 28.2, 24.2.

HRMS (ESI+) calculated for (C\(_{21}\)H\(_{27}\)NO\(_4\) + H\(^+\)): 358.2018, found: 358.2003.

\([\alpha]^{20}_D\) (c 1.91, CHCl\(_3\)) = +221.2.

M.P.: 97 – 99 °C.

(5R,8R)-tert-Butyl-8-(4-hexylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3g)

Compound 3g was obtained as a yellow sticky material (34.4 mg, 0.086 mmol, 86% isolated yield); 94:6 dr determined by NMR.

The enantiomeric ratio (er) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 5:95 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: \( t_R = 55.21 \) min (major), 60.17 min (minor); minor diastereomer: \( t_R = 84.65 \) min (major), 97.28 min (minor)).
**1H NMR (500 MHz, CDCl₃):** δ 7.13 (d, J = 8.0 Hz, 2 H), 7.02 (d, J = 8.0 Hz, 2 H), 6.09 (dd, J = 5.5, 2.3 Hz, 1 H), 5.80 (dd, J = 5.5, 2.2 Hz, 1 H), 4.28 – 4.25 (m, 1 H), 4.21 (d, J = 8.8 Hz, 1 H), 4.06 (d, J = 8.8 Hz, 1 H), 2.98 (dd, J = 14.2, 9.2 Hz, 1 H), 2.58 (t, J = 8.0 Hz, 2 H), 1.94 (dd, J = 14.2, 4.2 Hz, 1 H), 1.63 – 1.58 (m, 2 H), 1.56 (s, 9 H), 1.35 – 1.27 (m, 6 H), 0.89 (t, J = 6.6 Hz, 3 H).

**13C NMR (125 MHz, CDCl₃):** δ 152.6, 149.6, 141.8, 141.4, 139.6, 131.2, 129.0, 127.4, 127.1, 84.2, 73.9, 50.3, 44.9, 35.8, 32.0, 31.7, 29.3, 28.3, 22.8, 14.3.

HRMS (ESI+) calculated for (C₂₄H₃₃NO₄ + H⁺): 400.2472, found: 400.2488.

[α]D²⁰ (c 1.14, CHCl₃) = +88.1.

(5R,8R)-t-Butyl-8-(4-octylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3h)

Compound 3h was obtained as a light brown solid (39.8 mg, 0.093 mmol, 93% isolated yield); 95:5 dr determined by NMR.

The enantiomeric ratio (er) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 10:90 isopropanol/n-hexane (0.5 mL/min) as mobile phase. (Major diastereomer: tᵣ = 56.41 min (major), 59.54 min (minor); minor diastereomer: tᵣ = 73.95 min (major), 65.37 min (minor)).

**1H NMR (600 MHz, CDCl₃):** δ 7.13 (d, J = 8.0 Hz, 2 H), 7.02 (d, J = 8.0 Hz, 2 H), 6.09 (dd, J = 5.5, 2.3 Hz, 1 H), 5.80 (dd, J = 5.5, 2.2 Hz, 1 H), 4.28 – 4.25 (m, 1 H), 4.21 (d, J = 8.8 Hz, 1 H), 4.06 (d, J = 8.8 Hz, 1 H), 2.98 (dd, J = 14.2, 9.3 Hz, 1 H), 2.58 (t, J = 7.8 Hz, 2 H), 1.94 (dd, J = 14.2, 4.2 Hz, 1 H), 1.66 – 1.59 (m, 2 H), 1.56 (s, 9 H), 1.34 – 1.25 (m, 10 H), 0.89 (t, J = 7.0 Hz, 3 H).

**13C NMR (150 MHz, CDCl₃):** δ 152.6, 149.5, 141.8, 141.4, 139.6, 131.2, 129.0, 127.1, 84.2, 73.9, 50.3, 44.8, 37.6, 35.8, 32.1, 31.7, 29.7, 29.6, 29.5, 28.3, 22.9, 14.3.

HRMS (ESI+) calculated for (C₂₆H₃₇NO₄ + H⁺): 428.2801, found: 428.2807.

[α]D²⁰ (c 1.90, CHCl₃) = +145.0

M.P.: 55 – 57 °C.
(5R,8R)-tert-Butyl-8-(4-fluorophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3i)

Compound 3i was obtained as a yellow solid (28.3 mg, 0.085 mmol, 85% isolated yield); 89:11 dr determined by NMR.

**The enantiomeric ratio (er)** determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IA-3 column (4.6 mm × 250 mm) at 25 °C, 1:99 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: \( t_R = 29.47 \) min (major), 44.57 min (minor); minor diastereomer: \( t_R = 26.95 \) min (major), 33.52 min (minor)).

**1H NMR (500 MHz, CDCl3):** \( \delta 7.09 – 6.99 \) (m, 4 H), 6.08 (dd, \( J = 5.5, 2.2 \) Hz, 1 H), 5.83 (dd, \( J = 5.4, 2.2 \) Hz, 1 H), 4.31 – 4.29 (m, 1 H), 4.21 (d, \( J = 8.8 \) Hz, 1 H), 4.04 (d, \( J = 8.8 \) Hz, 1 H), 3.00 (dd, \( J = 14.2, 9.2 \) Hz, 1 H), 1.89 (dd, \( J = 14.3, 4.4 \) Hz, 1 H), 1.56 (s, \( J = 8.3 \) Hz, 9H).

**13C NMR (125 MHz, CDCl3):** \( \delta 161.7 \) (d, \( J = 245.4 \) Hz), 152.2, 149.3, 139.7 (d, \( J = 2.9 \) Hz), 131.3, 128.5 (d, \( J = 7.9 \) Hz), 115.6 (d, \( J = 21.3 \) Hz), 114.2, 73.6, 49.7, 44.8, 29.7, 28.1.

**HRMS (ESI+)** calculated for \( (\text{C}_{18}\text{H}_{20}\text{FNO}_4^+) \): 334.1454, found: 334.1442.

**\([\alpha]_D^{20}\)** (c 0.99, CHCl3) = +167.8.

**M.P.:** 68 – 71 °C.

(5R,8R)-tert-Butyl-8-(4-chlorophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3j)

Compound 3j was obtained as a white solid (29.0 mg, 0.083 mmol, 83% isolated yield); 90:10 dr determined by NMR.

**The enantiomeric ratio (er)** determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IB-3 column (4.6 mm × 250 mm) at 25 °C, 5:95 isopropanol/n-hexane (0.6 mL/min) as mobile phase. (Major diastereomer: \( t_R = 21.61 \) min (major), 24.48 min (minor); minor diastereomer: \( t_R = 26.82 \) min (major), 28.40 min (minor)).

**1H NMR (500 MHz, CDCl3):** \( \delta 7.31 \) (d, \( J = 8.4 \) Hz, 2 H), 7.07 (d, \( J = 8.4 \) Hz, 2 H), 6.10 (dd, \( J = 5.5, 2.2 \) Hz, 1 H), 5.86 (dd, \( J = 5.5, 2.2 \) Hz, 1 H), 4.32 – 4.30 (m, 1 H), 4.23 (d, \( J = 8.8 \) Hz, 1 H),
4.06 (d, $J = 8.8$ Hz, 1 H), 3.03 (dd, $J = 14.3, 9.2$ Hz, 1 H), 1.90 (dd, $J = 14.3, 4.4$ Hz, 1 H), 1.58 (s, $J = 7.4$ Hz, 9 H).

$^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 152.4, 149.5, 142.7, 139.0, 132.8, 131.8, 129.1, 128.6, 84.3, 73.7, 50.0, 44.8, 30.4, 28.2.

HRMS (ESI+) calculated for (C$_{18}$H$_{20}$ClNO$_4$ + H$^+$): 350.1159, found: 350.1146.

$[^{20}\alpha]_{D}$ (c 2.49, CHCl$_3$) = +237.1.

M.P.: 125 – 127 °C.

(5R,8R)-tert-Butyl-8-(4-bromophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3k)

Compound 3k was obtained as a light yellow solid (32.3 mg, 0.082 mmol, 82% isolated yield); 92:8dr determined by NMR.

The enantiomeric ratio (er) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 10:90 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: $t_R = 65.73$ min (major), 76.69 min (minor); minor diastereomer: $t_R = 69.79$ min (major), 61.58 min (minor)).

$^1$H NMR (500 MHz, CDCl₃): $\delta$ 7.44 (d, $J = 8.4$ Hz, 2 H), 7.00 (d, $J = 8.4$ Hz, 2H), 6.07 (dd, $J = 5.5, 2.3$ Hz, 1 H), 5.84 (dd, $J = 5.5, 2.3$ Hz, 1 H), 4.30 – 4.26 (m, 1 H), 4.21 (d, $J = 8.8$ Hz, 1 H), 4.04 (d, $J = 8.8$ Hz, 1 H), 3.01 (dd, $J = 14.3, 9.2$ Hz, 1 H), 1.88 (dd, $J = 14.3, 4.5$ Hz, 1 H), 1.55 (s, 9 H).

$^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 152.4, 149.5, 143.3, 139.0, 132.1, 131.8, 129.0, 120.8, 84.3, 73.7, 50.1, 44.8, 44.0, 28.3.

HRMS (ESI+) calculated for (C$_{18}$H$_{20}$BrNO$_4$ + H$^+$): 394.0654, found: 394.0640.

$[^{20}\alpha]_{D}$ (c 0.77, CHCl$_3$) = +158.7.

M.P.: 136 – 139 °C.
(5R,8R)-tert-Butyl-8-(3-bromophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3l)

Compound 3l was obtained as a yellow sticky material (28.4 mg, 0.072 mmol, 72% isolated yield); >98:2 dr determined by NMR.

The enantiomeric ratio (er) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm x 250 mm) at 25 °C, 15:85 isopropanol/n-hexane (1.0 mL/min) as mobile phase. Major diastereomer: \( t_R = 42.79 \) min (major), 39.68 min (minor).

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.39 – 7.05 (m, 4 H), 6.08 (dd, \( J = 5.5, 2.3 \) Hz, 1 H), 5.85 (dd, \( J = 5.5, 2.3 \) Hz, 1 H), 4.31 – 4.28 (m, 1 H), 4.23 (d, \( J = 8.9 \) Hz, 1 H), 4.06 (d, \( J = 8.9 \) Hz, 1 H), 3.01 (dd, \( J = 14.3, 9.2 \) Hz, 1 H), 1.90 (dd, \( J = 14.3, 4.6 \) Hz, 1 H), 1.56 (s, 9 H).

\(^1^3\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 152.4, 149.5, 146.6, 138.9, 132.0, 130.6, 130.4, 130.2, 126.0, 123.2, 84.4, 73.7, 50.4, 44.8, 29.9, 28.3.

HRMS (ESI+) calculated for (C\(_{18}\)H\(_{20}\)BrNO\(_4\) + H\(^+\)): 394.0654, found: 394.0650.

\([\alpha]_D^{20}\) (c 0.82, CHCl\(_3\)) = +146.3.

4. Application of the methodology for the Enantioselective Total Synthesis of the Highly Selective Sphingosine-1-Receptor, VPC01091

The Highly Selective Sphingosine-1-Receptor, VPC01091 was prepared by a short and concise way involving four steps starting from the spirosubstrate, 4 with the 62% overall yield
**tert-Butyl-((1R,4R)-1-(hydroxymethyl)-4-(4-octylphenyl)cyclopent-2-en-1-yl)carbamate (12)**

**Experimental procedure:**

To a solution of pyrolidinone 3h (0.1 mmol, 0.0428 g) in 2 mL methanol was added Cs₂CO₃ (0.12 mmol, 0.0391 g) and stirred at 25 °C for 24 h. On completion, the reaction was quenched with H₂O and extracted with ethyl acetate. The combined organic layers were washed with brine, dried on MgSO₄ and concentrated on rotary evaporator. The crude product was purified by flash column chromatography using 1:9 to 2:8 ethyl acetate/n-hexane as an eluent.

Compound 12 was obtained as a white solid (32.9 mg, 0.082 mmol, 82% isolated yield).

**1H NMR** (600 MHz, CDCl₃): δ 7.12 (d, J = 8.1 Hz, 2 H), 7.08 (d, J = 8.1 Hz, 2 H), 6.03 (dd, J = 5.6, 1.9 Hz, 1 H), 5.95 (dd, J = 5.5, 2.5 Hz, 1 H), 4.93 (s, 1 H), 4.16 – 4.13 (m, 1 H), 3.79 (s, 2 H), 2.59 – 2.56 (m, 3 H), 1.94 (dd, J = 14.0, 6.7 Hz, 1 H), 1.62 – 1.57 (m, 2 H), 1.47 (s, 9 H), 1.33 – 1.26 (m, 10 H), 0.89 (t, J = 7.0 Hz, 3 H).

**13C NMR** (150 MHz, CDCl₃): δ 156.2, 141.8, 141.4, 139.0, 133.0, 128.8, 127.3, 80.2, 70.5, 49.8, 49.7, 43.6, 35.8, 32.1, 31.8, 29.7, 29.6, 29.5, 28.6, 22.9, 14.3.

**HRMS (ESI+)** calculated for (C₂₅H₃₉NO₃ + H⁺): 402.3008, found: 402.2998.

[α]²⁰_D (c 0.541, CHCl₃) = +90.2.

**M.P.:** 77 – 80 °C.

**tert-Butyl-((1S,3S)-1-(hydroxymethyl)-3-(4-octylphenyl)cyclopentyl)carbamate (13)**

**Experimental procedure:**

To a suspension of the tert-Butyl(1-(hydroxymethyl)-4-(4-octylphenyl)cyclopent-2-en-1-yl)carbamate 12 (0.0418 g, 0.1 mmol) in methanol (1 mL) was added Pd/C (5%, 0.0045 mmol, 0.011 g) and stirred at room temperature under H₂ atmosphere for 6 h. The progress of the reaction was checked by TLC using 3:7 ethyl acetate/n-hexane. On completion of the reaction,
the reaction mixture was filtered through a short pad of silica gel and concentrated under reduced pressure on rotary evaporator to provide the pure product.

Compound 13 was obtained as a white solid (38.3 mg, 0.095 mmol, 95% isolated yield); 96:4 dr determined by HPLC.

The enantiomeric ratio (er) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IA-3 column (4.6 mm × 250 mm) at 25 °C, 1:99 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: $t_R = 22.19$ min (major), $19.32$ min (minor); minor diastereomer: $t_R = 24.78$ min (major), $17.98$ min (minor)).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.15 (d, $J = 8.1$ Hz, 2 H), 7.11 (d, $J = 8.1$ Hz, 2 H), 4.87 (s, 1 H), 3.74 (dd, $J = 34.7$, 10.9 Hz, 2 H), 3.35 – 3.27 (m, 1 H), 2.57 (app. t, $J = 7.7$ Hz, 2 H), 2.32 (dd, $J = 13.7$, 7.4 Hz, 1 H), 2.20 – 2.07 (m, 2 H), 1.86 – 1.66 (m, 3 H), 1.63 – 1.57 (m, 2 H), 1.47 (s, $J = 4.9$ Hz, 9 H), 1.32 – 1.27 (m, 10 H), 0.89 (t, $J = 6.9$ Hz, 3 H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 156.5, 141.6, 141.1, 128.6, 127.0, 80.3, 70.3, 65.2, 43.9, 43.8, 36.6, 35.8, 33.2, 32.1, 31.8, 29.7, 29.6, 29.5, 28.6, 22.9, 14.4.

HRMS (ESI+) calculated for (C$_{25}$H$_{41}$NO$_3$+H$^+$): 404.3165, found: 404.3184.

$\lbrack\alpha\rbrack_{D}^{20}$ (c 2.67, MeOH) = +16.09.

M.P.: 58 – 61 °C.

((1S,3S)-1-Amino-3-(4-octylphenyl)cyclopentyl)methanol Hydrochloride (2b, VPC01091)

Experimental procedure: $^{12}$

Compound 13 (0.0436 g, 0.1 mmol) was dissolved in a carefully pre-mixed methanol and acetyl chloride (4:1, 5 ml), and stirred at 25 °C for 16 h. Upon completion of the reaction, the solvent was evaporated. The residue was dissolved in 10% NaOH aqueous solution and extracted with DCM. The combined organic layers were dried on Na$_2$SO$_4$, filtered and concentration on rotary evaporator into pure 2b (VPC01091).

Compound 2b (VPC01091) was obtained as a white solid (25.8 mg, 0.085 mmol, 85% isolated yield.)
$^{1}$H NMR (400 MHz, DMSO): δ 7.14 (d, $J = 8.2$ Hz, 2 H), 7.10 (d, $J = 8.2$ Hz, 2 H), 3.53 – 3.46 (m, 2 H), 3.44 – 3.34 (m, 1 H), 2.54 – 2.50 (m, 2 H), 2.12 – 2.00 (m, 3 H), 1.78 – 1.46 (m, 5 H), 1.32 – 1.14 (m, 10 H), 0.85 (t, $J = 6.83$ Hz, 3 H).

$^{13}$C NMR (100 MHz, DMSO): δ 140.9, 140.1, 128.2, 126.7, 65.6, 63.7, 42.8, 41.5, 34.7, 33.7, 33.0, 31.2, 31.0, 28.8, 28.7, 28.6, 22.0, 13.9.

HRMS (ESI+) calculated for (C$_{20}$H$_{33}$NO $^+$): 304.2640, found: 304.2646.

$[\alpha]_{D}^{20}$ (c 2.36, MeOH) = +2.
5. Chiral Chromatographic data:

(5R,8R)-tert-Butyl-8-(4-methoxyphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3a)
(5R, 8R)-tert-Butyl-8-(2-methoxyphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3b)
(5R,8R)-tert-Butyl 2-oxo-8-(4-(trifluoromethyl)phenyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3c)
(5R,8R)-tert-Butyl 2-oxo-8-(3-(trifluoromethyl)phenyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3d)
(5R,8R)-tert-Butyl 2-oxo-8-(p-tolyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3e)
(5R,8R)-tert-Butyl 8-(4-isopropylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3f)
(5R,8R)-\textit{tert}-Butyl 8-((4-hexylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3g)
(5R,8R)-tert-Butyl 8-(4-octylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate

(3h)
(5R,8R)-tert-Butyl 8-(4-fluorophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3i)
(5R,8R)-tert-Butyl 8-(4-chlorophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3j)
(5R,8R)-tert-Butyl 8-(4-bromophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3k)
(5R,8R)-tert-Butyl 8-(3-bromophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3l)
**tert-Butyl ((1S,3S)-1-(hydroxymethyl)-3-(4-octylphenyl)cyclopentyl)carbamate (13)**

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</table>
6. NMR Spectra
Ethyl-2,2-bis(allyl)-2-nitroacetate (ii)

K004
K004

°CdCl3/Av400Mhz
mar31ismH1

1H (ppm)

1.26 1.28 1.30
2.86 2.88 2.90
4.23 4.25 4.27
5.57 5.59 5.60

13C

14.08 38.25 62.96
76.94 77.26 77.58
95.03 121.61 129.59
166.17

O

N

O

i

O

N

O

i

O

i
Ethyl-2-allyl-2-aminopent-4-enoate (iii)
2-Allyl-2-aminopent-4-en-1-ol (iv)

K014
Ismat - K014 - CDCl3 - Avance 600 MHz - fev25ismH2 - 1H

42.08
55.09
68.35
119.11
133.68

H
O
N
2

H
O
N
2

iv
4,4-Diallyloxazolidin-2-one (v)

[Diagram of the molecule]

f1 (ppm)

K015
Ismat - K015 - CDCl3 - Avance 600 MHz - fev25ismH3 - 1H

[Chemical shifts and resonances]

[Diagram of the molecule]

f1 (ppm)

K015
Ismat - K015 - CDCl3 - Avance 600 MHz - fev25ismH3 - 13C

[Chemical shifts and resonances]
*tert*-Butyl-4,4-diallyl-2-oxooxazolidine-3-carboxylate (vi)
**tert-Butyl-2-oxo-3-oxa-1-azaspiro[4.4]non-7-ene-1-carboxylate (4)**

![Chemical Structure of tert-Butyl-2-oxo-3-oxa-1-azaspiro[4.4]non-7-ene-1-carboxylate (4)](image)

**K033**

Ismat - K033 - CDCl3 - Avance 600 MHz - tc25simH5 - 1H

**K033**

Ismat - K033 - CDCl3 - Avance 600 MHz - tc25simH5 - 13C
(5R,8R)-tert-Butyl 8-(4-methoxyphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3a)
(5R,8R)-tert-Butyl 8-(2-methoxyphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3b)
(5R,8R)-**tert**-Butyl 2-oxo-8-(4-(trifluoromethyl)phenyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3c)
(5R,8R)-tert-Butyl 2-oxo-8-(3-(trifluoromethyl)phenyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3d)
(5R,8R)-tert-Butyl 2-oxo-8-(p-tolyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3e)
(5R,8R)-tert-Butyl 8-(4-isopropylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3f)
(5R,8R)-tert-Butyl 8-(4-hexylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3g)
(5R,8R)-tert-Butyl 8-(4-octylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate(3h)
(5R,8R)-tert-Butyl 8-(4-fluorophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3i)
(5R,8R)-tert-Butyl 8-(4-chlorophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3j)
(5R,8R)-tert-Butyl 8-(4-bromophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3k)
(5R,8R)-tert-Butyl 8-(3-bromophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3l)
**tert-Butyl ((1R,4R)-1-(hydroxymethyl)-4-(4-octylphenyl)cyclopent-2-en-1-yl)carbamate (12)**

![NMR spectra of compound 12](image)

**1H NMR** (CDCl₃, Avance 600 MHz)

- **f1 (ppm)**:
  - 12.42
  - 9.18
  - 2.33
  - 1.00
  - 3.05
  - 1.94
  - 1.01
  - 0.89
  - 0.94
  - 0.92
  - 1.99
  - 1.98

**13C NMR** (CDCl₃, Avance 600 MHz)

- **f1 (ppm)**:
  - 14.33
  - 22.90
  - 28.64
  - 29.49
  - 29.61
  - 29.72
  - 31.77
  - 32.13
  - 35.80
  - 43.57
  - 49.74
  - 49.80
  - 70.46
  - 77.05
  - 77.26
  - 77.47
  - 80.21
  - 127.28
  - 128.82
  - 133.02
  - 138.96
  - 141.38
  - 141.75
  - 156.20

**Chemical Structure**

- **OH**
- **NHBoc**
- **n-oct**
tert-Butyl ((1S,3S)-1-(hydroxymethyl)-3-(4-octylphenyl)cyclopentyl)carbamate (13)
7.1. Relative stereochemistry assignment by $^1$H-$^1$H NOESY experiment

The relative stereochemistry of the major isomer of Heck adduct 3a was determined by 2D $^1$H-$^1$H NOESY, (Figure 2), on the basis of the presence of the key cross signals of H$^1$ with H$^4$ and H$^6$, but no cross signal with H$^3$. Similarly, the presence of the key cross signal of H$^2$ with H$^3$, but no cross signals with H$^4$ and H$^6$.

**Figure 2.** 2D $^1$H-$^1$H NOESY and stereochemical assignment for the Heck product 3a.
7.2. NOE increments and stereochemical assignment for the Heck product 3a.

The $H^1$ (which is syn to aromatic ring) is shielded by aromatic ring and is observed in $^1$H NMR spectrum at 1.9 ppm as a doublet of doublet with coupling constants of 14.2 and 4.2 Hz while the $H^2$ (which is trans to aromatic ring) appears at 3.0 ppm as a doublet of doublet with coupling constant of 14.2 and 9.2 Hz. In order to confirm the relative position of aromatic ring, we performed NOE (Nuclear Overhauser Effect) experiments with the Heck adduct 3a by irradiating the methylene hydrogens ($H^1$ and $H^2$). Irradiating the $H^1$, induced an NOE increment 1.4% in $H^6$, 0.7% in $H^3$ and 3.1% in $H^4$, indicating the greater proximity between $H^1$ and $H^4$. Similarly irradiating the $H^2$, induced no NOE in $H^4$, 0.2% in $H^6$ and 3.9% in $H^3$ indicating the greater proximity between $H^1$ and $H^3$. The NOE increments, confirmed the relative stereochemistry of the Heck adduct deduced from 2D $^1$H-$^1$H NOESY, (Figure 3), which was further confirmed by the X-rays crystallographic data for 3a given in Figure 4.
8. Absolute Configuration of Heck product 3a

The absolute stereochemistry of the Heck product, 3a was attributed by X-ray crystallographic analysis while all the other Heck products were attributed in analogy.

8.1. X-rays Crystallographic Data for Compound 3a

Data sets for the Heck product 3a were collected with a Bruker APEX CCD detector diffractometer. Programs used: data collection, APEX2 (Bruker, 2010); cell refinement: SAINT (Bruker, 2010); data reduction: SAINT (Bruker, 2010); program(s) used to solve structure: SHELXS97\textsuperscript{13} (Sheldrick, 2008); program(s) used to refine structure: SHELXL2014/\textsuperscript{7}\textsuperscript{13}.
(Sheldrick, 2014); and graphics, Mercury 3.5.1 (Build RC5, 2014). Thermals ellipsoids are shown with 50% probability, R-values are given for observed reflections, and wR\textsuperscript{2} values are given for all reflections. Single-crystals were obtained from ethanol. The enantiomeric ratio was 99:1 (determined as stated for compound 3a). Crystallographic data for structure 3a in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1497742

Compound-3a: CCDC 1497742

Formula: C\textsubscript{19} H\textsubscript{23} N\textsubscript{1} O\textsubscript{5} 

Unit Cell Parameters: a 12.0073(4) b 5.9225(2) c 13.6415(4) P2\textsuperscript{1}

Crystal data

\[
\begin{array}{ll}
C_{19}H_{23}NO_5 & V = 913.97 (5) \text{ Å}^3 \\
M_r = 345.38 & Z = 2
\end{array}
\]
**Monoclinic, P2₁**

\( a = 12.0073 (4) \ \text{Å} \)

\( b = 5.9225 (2) \ \text{Å} \)

\( c = 13.6415 (4) \ \text{Å} \)

\( \beta = 109.584 (1)^\circ \)

\( \mu = 0.75 \ \text{mm}^{-1} \)

\( T = 296 \ \text{K} \)

\( 0.32 \times 0.32 \times 0.13 \ \text{mm} \)

---

**Data collection**

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<th>Bruker APEX CCD detector diffractometer</th>
<th>3241 independent reflections</th>
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<tbody>
<tr>
<td>Absorption correction: multi-scan SADABS (Bruker, 2010)</td>
<td>3228 reflections with ( I &gt; 2\sigma(I) )</td>
</tr>
<tr>
<td>( T_{\text{min}} = 0.673, T_{\text{max}} = 0.753 )</td>
<td>( R_{\text{int}} = 0.028 )</td>
</tr>
<tr>
<td>30012 measured reflections</td>
<td>( \theta_{\text{max}} = 68.1^\circ )</td>
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---

**Refinement**

\( R[F^2 > 2\sigma(F^2)] = 0.040 \)

\( wR(F^2) = 0.098 \)

\( S = 1.09 \)

3241 reflections

242 parameters

1 restraint

H-atom parameters constrained

\( \Delta \rho_{\text{max}} = 0.25 \ \text{e} \ \text{Å}^{-3} \)

\( \Delta \rho_{\text{min}} = -0.24 \ \text{e} \ \text{Å}^{-3} \)


Absolute structure parameter: 0.03 (2)
9. References


