

Supplementary Material for Organic & Biomolecular Chemistry  
Supplementary data

# **Chemical Variation of Natural Product-Like Scaffolds: Design and Synthesis of Spiroketal Derivatives**

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Supplementary information

## Synthesis of ynals (5) and (6)

### General procedure for the synthesis of (2S)-2-Benzyloxymethyl-oxirane and (2S)-2-(4-Bromo-benzyloxymethyl)-oxirane

To a stirred suspension of NaH (60% dispersion in mineral oil, 1.2 eq) in anhydrous DMF (2.4 M) at 0 °C was added a solution of (*R*)-glycidol in anhydrous DMF (6.1 M with rinsing x 2). The resultant white suspension was stirred until effervescence ceased, and then either BnBr or *p*-BrBnBr (1.4 eq) and TBAI (spatula) were added, sequentially. The reaction mixture was then allowed to warm to ambient temperature over 18 h, poured into distilled water and extracted with Et<sub>2</sub>O (x 3). The recombinant organic extracts were then washed with distilled water (x 2) and brine (x 1), dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resultant crude was purified by gravimetric column chromatography on silica, using 3:7 Et<sub>2</sub>O and petroleum ether as eluent.

**(2S)-2-Benzyloxymethyl-oxirane:** a pale, yellow oil (98%); *R<sub>f</sub>* 0.62 (1:1 Et<sub>2</sub>O: petroleum ether);  $[\alpha]_{\text{D}}^{25}$  -2.6 (*c* 1.22, CHCl<sub>3</sub>);  $\nu_{\text{max}}$ (film)/cm<sup>-1</sup> 2997, 2863, 1496, 1454, 1253, 1206, 1092, 909, 846, 733 and 697;  $\delta_{\text{H}}$ (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 7.29-7.36 (5 H, m, *Ar*), 4.55-4.64 (2 H, m, -OCH<sub>2</sub>Ph), 3.77 (1 H, dd, *J* 11.5 and 3.1, *H*<sub>1A</sub>), 3.45 (1 H, dd, *J* 11.4 and 5.8, *H*<sub>1B</sub>), 3.18-3.19 (1 H, m, *H*<sub>2</sub>), 2.79 (1 H, t, *J* 4.8, *H*<sub>3A</sub>) and 2.62 (1 H, dd, *J* 5.0 and 2.7, *H*<sub>3B</sub>);  $\delta_{\text{C}}$ (100 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 137.9, 128.4, 127.7, 73.3, 70.8, 50.8 and 44.3; *m/z* (+EI) calc. for C<sub>10</sub>H<sub>12</sub>O (M<sup>+</sup>) 164.0837, found 164.0837.

**(2S)-2-(4-Bromo-benzyloxymethyl)-oxirane:** a clear, colourless oil (96%); *R<sub>f</sub>* 0.24 (1:4 Et<sub>2</sub>O: petroleum ether);  $[\alpha]_{\text{D}}^{25}$  +7.2 (*c* 0.50, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$ (film)/cm<sup>-1</sup> 3051, 2999, 2862, 1593, 1487, 1252, 1203, 1161, 1134, 1091, 1069, 901, 838, 795, 762, and 697;  $\delta_{\text{H}}$ (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 7.47 (2 H, d, *J* 8.3, *Ar*), 7.22 (2 H, d, *J* 8.2, *Ar*), 4.49-4.58 (2 H, m, -OCH<sub>2</sub>Ph), 3.79 (1 H, dd, *J* 11.5 and 2.8, *H*<sub>1A</sub>), 3.42 (1 H, dd, *J* 11.5 and 5.9, *H*<sub>1B</sub>), 3.16-3.20 (1 H, m, *H*<sub>2</sub>), 2.80 (1 H, t, *J* 4.4, *H*<sub>3A</sub>) and 2.60-2.62 (1 H, m, *H*<sub>3B</sub>);  $\delta_{\text{C}}$ (100 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 137.0, 131.5, 129.3, 121.6, 72.5, 70.9, 50.8 and 44.2; *m/z* (+ESI) calc. for C<sub>10</sub>H<sub>11</sub>BrNaO<sub>2</sub> (MNa<sup>+</sup>) 264.9840, found 264.9795.

### General procedure for the synthesis of (2S)-1-Benzyloxy-5-trimethylsilylanyl-pent-4-yn-2-ol and (2S)-1-(4-Bromo-benzyloxy)-5-trimethylsilylanyl-pent-4-yn-2-ol

To a stirred solution of TMS-acetylene (1.5 eq) in anhydrous THF (0.2-0.4 M) at -78 °C was added *n*-BuLi (1.5 eq). After stirring at -78 °C for 30 min, BF<sub>3</sub>·THF (1.5 eq) was added. After stirring at -78 °C for a further 30 min, a pre-prepared solution of either (2S)-2-Benzyloxymethyl-oxirane or (2S)-2-(4-Bromo-benzyloxymethyl)-oxirane in anhydrous THF (1.2-2.4 M with rinsing x 2) was added dropwise, and the reaction left to reach ambient temperature, with stirring, over 18 h. The reaction was then quenched with a saturated, aqueous solution of NH<sub>4</sub>Cl and extracted with Et<sub>2</sub>O (x 3). The recombinant organic extracts were washed with distilled water (x 2) and brine (x 1), dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resultant crude was purified by gravimetric column chromatography on silica, using 1:4 Et<sub>2</sub>O and petroleum ether as eluent.

**(2S)-1-Benzyloxy-5-trimethylsilylanyl-pent-4-yn-2-ol:** a pale, yellow oil (quant.); *R<sub>f</sub>* 0.61 (1:1 Et<sub>2</sub>O: petroleum ether);  $[\alpha]_{\text{D}}^{25}$  +16.4 (*c* 1.04, CHCl<sub>3</sub>);  $\nu_{\text{max}}$ (film)/cm<sup>-1</sup> 3429, 3032, 2959, 2176, 1497, 1409, 1364, 1249, 1204, 1097, 1028, 838, 758, 735 and 697;  $\delta_{\text{H}}$ (600 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 7.30-7.37 (5 H, m, *Ar*), 4.58 (2 H, s, -OCH<sub>2</sub>Ph), 3.92-3.99 (1 H, m, *H*<sub>2</sub>), 3.61 (1 H, dd, *J* 9.5 and 4.0, *H*<sub>1A</sub>), 3.51 (1 H, dd, *J* 9.5 and 6.5, *H*<sub>1B</sub>), 2.52 (1 H, dd, *J* 16.9 and 6.0, *H*<sub>3A</sub>), 2.49 (1 H, dd, *J* 16.9 and 6.9, *H*<sub>3B</sub>), 2.40 (1 H, d, *J* 4.8, *OH*) and 0.14 (9 H, s, -Si(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$ (150 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 137.9, 128.4, 127.8, 127.7, 102.5, 87.3, 73.4, 72.8, 68.8, 25.0 and -0.01; *m/z* (+ESI) calc. for C<sub>15</sub>H<sub>22</sub>O<sub>2</sub>NaSi (MNa<sup>+</sup>) 285.1287, found 285.1275.

**(2S)-1-(4-Bromo-benzyloxy)-5-trimethylsilylanyl-pent-4-yn-2-ol:** a clear, faint-yellow oil (quant.); *R<sub>f</sub>* 0.16 (3:7 Et<sub>2</sub>O: petroleum ether);  $[\alpha]_{\text{D}}^{25}$  +96.1 (*c* 1.09, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$ (film)/cm<sup>-1</sup> 3427, 2958, 2176, 1594, 1488, 1406, 1349, 1248, 1202, 1096, 1070, 1031, 1011, 832, 802, 795, 759 and 698;  $\delta_{\text{H}}$ (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 7.48 (2 H, d, *J* 8.3, *Ar*), 7.21 (2 H, d, *J* 8.3, *Ar*), 4.52 (2 H, s, -OCH<sub>2</sub>Ph), 3.91-3.98 (1 H, m, *H*<sub>2</sub>), 3.59 (1 H, dd, *J* 9.5 and 4.0, *H*<sub>1A</sub>), 3.45-3.51 (1 H, m, *H*<sub>1B</sub>), 2.48-2.51 (2 H, m, *H*<sub>3</sub>), 2.34 (1 H, d, *J* 4.8, *OH*) and 0.14 (9 H, s, -Si(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$ (100 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 136.9, 131.6, 129.3, 121.7, 102.3, 87.5, 72.8, 72.6, 68.8, 25.0 and -0.01; *m/z* (+ESI) calc. for C<sub>15</sub>H<sub>22</sub>BrO<sub>2</sub>Si (MH<sup>+</sup>) 341.0572, found 341.0468; calc. for C<sub>15</sub>H<sub>21</sub>BrNaO<sub>2</sub>Si (MNa<sup>+</sup>) 363.0392, found 363.0281.

### General procedure for the synthesis of (2S)-1-Benzyloxy-pent-4-yn-2-ol and (2S)-1-(4-Bromo-benzyloxy)-pent-4-yn-2-ol

To a stirred solution of either (2S)-1-Benzyloxy-5-trimethylsilylanyl-pent-4-yn-2-ol or (2S)-1-(4-Bromo-benzyloxy)-5-trimethylsilylanyl-pent-4-yn-2-ol in anhydrous MeOH (0.6 M) was added solid, anhydrous K<sub>2</sub>CO<sub>3</sub> (5.0 eq). After stirring at ambient temperature for 2 h the reaction mixture was then filtered through a pad of silica, and concentrated *in vacuo*.

The resultant crude was purified by gravimetric column chromatography on silica, using 1:4 Et<sub>2</sub>O and petroleum ether as eluent.

**(2S)-1-Benzyloxy-pent-4-yn-2-ol:** a clear, colourless oil (85%); *R<sub>f</sub>* 0.49 (1:1 Et<sub>2</sub>O: petroleum ether);  $[\alpha]_D^{25} +12.1$  (*c* 0.62, CHCl<sub>3</sub>);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3417, 3293, 3032, 2119, 1605, 1496, 1364, 1252, 1206, 1074, 1028, 841, 737 and 697;  $\delta_{\text{H}}$ (600 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 7.27-7.37 (5 H, m, *Ar*), 4.58 (2 H, s, -OCH<sub>2</sub>Ph), 3.95-4.18 (1 H, m, *H*<sub>2</sub>), 3.62 (1 H, dd, *J* 9.7 and 4.0, *H*<sub>1A</sub>), 3.52 (1 H, dd, *J* 9.4 and 6.6, *H*<sub>1B</sub>), 2.44-2.50 (3 H, m, *H*<sub>3</sub> and *OH*) and 2.03 (1 H, t, *J* 2.7, *H*<sub>5</sub>);  $\delta_{\text{C}}$ (150 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 137.8, 128.5, 127.8, 127.7, 80.2, 73.5, 72.8, 70.6, 68.8 and 23.5; *m/z* (+ESI) calc. for C<sub>12</sub>H<sub>14</sub>NaO<sub>2</sub> (MNa<sup>+</sup>) 213.0891, found 213.0884.

**(2S)-1-(4-Bromo-benzyloxy)-pent-4-yn-2-ol:** a clear, faint-green oil (96%); *R<sub>f</sub>* 0.26 (1:1 Et<sub>2</sub>O: petroleum ether);  $[\alpha]_D^{25} +8.1$  (*c* 1.09, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3414, 3298, 2910, 1593, 1488, 1361, 1252, 1203, 1096, 1069, 831, 802 and 795;  $\delta_{\text{H}}$ (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 7.48 (2 H, d, *J* 8.3, *Ar*), 7.21 (2 H, d, *J* 8.3, *Ar*), 4.52 (2 H, s, -OCH<sub>2</sub>Ph), 3.94-4.17 (1 H, m, *H*<sub>2</sub>), 3.60 (1 H, dd, *J* 9.5 and 3.9, *H*<sub>1A</sub>), 3.51 (1 H, dd, *J* 9.5 and 6.4, *H*<sub>1B</sub>), 2.46 (2 H, dd, *J* 6.3 and 2.6, *H*<sub>3</sub>), 2.39 (1 H, d, *J* 4.8, *OH*) and 2.03 (1 H, t, *J* 2.6, *H*<sub>5</sub>);  $\delta_{\text{C}}$ (100 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 136.8, 131.6, 129.3, 121.7, 80.1, 72.9, 72.6, 70.7, 68.7 and 23.5; *m/z* (+ESI) calc. for C<sub>12</sub>H<sub>13</sub>BrNaO<sub>2</sub> (MNa<sup>+</sup>) 290.9997, found 290.9933.

#### General procedure for the synthesis of (1S)-(1-Benzyloxymethyl-but-3-ynyloxy)-triethyl-silane and (1S)-[1-(4-Bromo-benzyloxymethyl)-but-3-ynyloxy]-triethyl-silane

To a stirred solution of either (2S)-1-Benzyloxy-pent-4-yn-2-ol or (2S)-1-(4-Bromo-benzyloxy)-pent-4-yn-2-ol in anhydrous THF (0.4-0.6 M) was added, first imidazole (2.4 eq), then TESCl (1.05 eq) at ambient temperature. After stirring at ambient temperature for 18 h, the reaction mixture was then filtered through a pad of silica, and concentrated *in vacuo*. The resultant crude was purified by gravimetric column chromatography on silica, using 1:4 Et<sub>2</sub>O and petroleum ether as eluent.

**(1S)-(1-Benzyloxymethyl-but-3-ynyloxy)-triethyl-silane:** a clear, colourless oil (85%); *R<sub>f</sub>* 0.89 (1:1 Et<sub>2</sub>O: petroleum ether);  $[\alpha]_D^{25} +0.6$  (*c* 1.06, CHCl<sub>3</sub>);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3309, 2953, 1496, 1238, 1092, 733 and 697;  $\delta_{\text{H}}$ (600 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 7.27-7.34 (5 H, m, *Ar*), 4.56 (2 H, s, -OCH<sub>2</sub>Ph), 3.95-3.99 (1 H, m, *H*<sub>2</sub>), 3.48-3.54 (2 H, m, *H*<sub>1</sub>), 2.50 (1 H, ddd, *J* 16.6, 5.7 and 2.6, *H*<sub>3A</sub>), 2.38 (1 H, ddd, *J* 16.6, 5.7 and 2.6, *H*<sub>3B</sub>), 1.96 (1 H, t, *J* 2.5, *H*<sub>5</sub>), 0.96 (9 H, t, *J* 8.0, -OSi(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>) and 0.63 (6 H, q, *J* 8.0, -OSi(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$ (150 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 138.3, 128.3, 127.6, 127.5, 81.2, 73.4, 73.4, 70.0, 69.8, 24.7, 6.8 and 4.8; *m/z* (+ESI) calc. for C<sub>18</sub>H<sub>28</sub>NaO<sub>2</sub>Si (MNa<sup>+</sup>) 327.1756, found 327.1764.

**(1S)-[1-(4-Bromo-benzyloxymethyl)-but-3-ynyloxy]-triethyl-silane:** a clear, faint-yellow liquid (97%); *R<sub>f</sub>* 0.92 (1:1 Et<sub>2</sub>O: petroleum ether);  $[\alpha]_D^{25} +2.5$  (*c* 1.25, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3310, 2954, 2911, 1593, 1488, 1239, 1203, 1070, 833, 803, 795 and 740;  $\delta_{\text{H}}$ (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 7.46 (2 H, d, *J* 8.3, *Ar*), 7.21 (2 H, d, *J* 8.2, *Ar*), 4.47 (2 H, s, -OCH<sub>2</sub>Ph), 3.96-3.99 (1 H, m, *H*<sub>2</sub>), 3.46-3.54 (2 H, m, *H*<sub>1</sub>), 2.49 (1 H, ddd, *J* 16.7, 6.4 and 2.6, *H*<sub>3A</sub>), 2.37 (1 H, ddd, *J* 19.3, 6.4 and 2.6, *H*<sub>3B</sub>), 1.96 (1 H, t, *J* 2.6, *H*<sub>5</sub>), 0.96 (9 H, t, *J* 8.0, -OSi(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>) and 0.62 (6 H, q, *J* 8.0, -OSi(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$ (100 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 137.4, 131.4, 129.2, 121.4, 81.1, 73.5, 72.6, 70.0, 68.0, 24.7, 6.8 and 4.9; *m/z* (+ESI) calc. for C<sub>18</sub>H<sub>28</sub>BrO<sub>2</sub>Si (MH<sup>+</sup>) 383.1042, found 383.1062; calc. for C<sub>18</sub>H<sub>27</sub>BrNaO<sub>2</sub>Si (MNa<sup>+</sup>) 405.0861, found 405.0888.

#### General procedure for the synthesis of (5S)-6-Benzyloxy-5-triethylsilanyloxy-hex-2-ynal 5 and (5S)-6-(4-Bromo-benzyloxy)-5-triethylsilanyloxy-hex-2-ynal 6

To a stirred solution of either (1S)-(1-Benzyloxymethyl-but-3-ynyloxy)-triethyl-silane or (1S)-[1-(4-Bromo-benzyloxymethyl)-but-3-ynyloxy]-triethyl-silane in anhydrous THF (0.3-1.7 M) at -78 °C was added *n*-BuLi (1.1 eq). After stirring at -78 °C for 1 h, the reaction mixture was then treated with a solution of *N*-formylmorpholine (1.5 eq) in anhydrous THF (0.5-1.0 M), and allowed to reach ambient temperature over 18 h. The reaction mixture was then quenched with a saturated, aqueous solution of NH<sub>4</sub>Cl and extracted with Et<sub>2</sub>O (x 3). The recombinant organic extracts were washed with distilled water (x 2) and brine (x 1), dried over anhydrous MgSO<sub>4</sub>, filtered and then concentrated *in vacuo*. The resultant crude was then purified by gravimetric column chromatography on silica, using 1.4 Et<sub>2</sub>O and petroleum ether (bp 30-40°C).

**(5S)-6-Benzyloxy-5-triethylsilanyloxy-hex-2-ynal 5:** a clear, yellow liquid (87%); *R<sub>f</sub>* 0.60 (1:4 Et<sub>2</sub>O: petroleum ether);  $[\alpha]_D^{25} -5.2$  (*c* 1.19, CHCl<sub>3</sub>);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2954, 2910, 2203, 1671, 1496, 1238, 1112, 736 and 699;  $\delta_{\text{H}}$ (600 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 9.15 (1 H, s, *H*<sub>6</sub>), 7.27-7.34 (5 H, m, *Ar*), 4.55 (2 H, s, -OCH<sub>2</sub>Ph), 4.01-4.06 (1 H, m, *H*<sub>2</sub>), 3.50 (1 H, dd, *J* 9.7 and 4.9, *H*<sub>1A</sub>), 3.45 (1 H, dd, *J* 9.7 and 6.2, *H*<sub>1B</sub>), 2.74 (1 H, dd, *J* 17.3 and 5.3, *H*<sub>3A</sub>), 2.61 (1 H, dd, *J* 17.4 and 6.0, *H*<sub>3B</sub>), 0.96 (9 H, t, *J* 8.0, -OSi(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>) and 0.62 (6 H, q, *J* 8.0, -OSi(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$ (150 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 176.9, 137.9, 128.4, 127.7, 127.6, 96.8, 73.5, 73.1, 69.3, 51.4, 30.3, 6.7 and 4.8; *m/z* (+ESI) calc. for C<sub>19</sub>H<sub>28</sub>NaO<sub>3</sub>Si (MNa<sup>+</sup>) 355.1705, found 355.1705.

**(5S)-6-(4-Bromo-benzyloxy)-5-triethylsilanyloxy-hex-2-ynal 6:** a clear, faint-yellow oil (65%);  $R_f$  0.12 (3:7 DCM: petroleum ether);  $[\alpha]_D^{25}$  -4.8 ( $c$  1.05,  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2954, 2911, 2203, 1669, 1594, 1488, 1239, 1203, 1138, 1093, 1070, 804, 740, 727, 699 and 675;  $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$  9.16 (1 H, s,  $H_6$ ), 7.47 (2 H, d,  $J$  8.3,  $A_r$ ), 7.20 (2 H, d,  $J$  8.3,  $A_r$ ), 4.49 (2 H, s,  $-\text{OCH}_2\text{Ph}$ ), 4.01-4.05 (1 H, m,  $H_2$ ), 3.43-3.52 (2 H, m,  $H_1$ ), 2.73 (1 H, dd,  $J$  17.3 and 5.8,  $H_{3A}$ ), 2.61 (1 H, dd,  $J$  17.3 and 5.8,  $H_{3B}$ ), 0.96 (9 H, t,  $J$  8.0,  $-\text{OSi}(\text{CH}_2\text{CH}_3)_3$ ) and 0.62 (6 H, q,  $J$  7.9,  $-\text{OSi}(\text{CH}_2\text{CH}_3)_3$ );  $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$  176.8, 137.0, 131.5, 129.3, 121.6, 95.8, 82.8, 73.3, 72.7, 69.2, 25.5, 6.7 and 4.8;  $m/z$  (+ESI) calc. for  $\text{C}_{19}\text{H}_{28}\text{BrO}_3\text{Si}$  ( $\text{MH}^+$ ) 411.0991, found 411.1024; calc. for  $\text{C}_{19}\text{H}_{27}\text{BrNaO}_3\text{Si}$  ( $\text{MNa}^+$ ) 433.0810, found 433.0811.

## Compound (32)

**For the experimental procedure see experimental part of the article: procedure for the synthesis of aldehydes (30a-c)**

**1,7-Dioxa-spiro[5.5]undecane-2-carbaldehyde (32):** a clear, colourless oil (quant.);  $R_f$  0.52 (1:1 EtOAc: petroleum ether);  $\delta_{\text{H}}(600 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$  9.65 (1 H, s), 4.06 (1 H, dd,  $J$  12.1 and 2.6), 3.61-3.65 (2 H, m), 1.78-1.98 (3 H, m), 1.42-1.76 (7 H, m), 1.41 (1 H, td,  $J$  12.1 and 4.5) and 1.30-1.34 (1 H, m);  $\delta_{\text{C}}(150 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$  202.4, 96.0, 74.3, 60.6, 35.3, 35.0, 25.3, 25.1, 18.3 and 17.9;  $m/z$  (+EI) calc. for  $\text{C}_{10}\text{H}_{17}\text{O}_3$  ( $\text{MH}^+$ ) 185.1, found 185.0.

## Compounds (34a-b)

**General procedure for the synthesis of spiroketal-derived amines (34a-b)**

To a stirred solution of spiroketal aldehyde **32** in anhydrous DCM (0.15 M) was added the requisite amine (3 eq). The resultant reaction suspension was left stirring under a positive argon atmosphere for 2 h, then EtOAc and distilled water were added, and the subsequent aqueous phase extracted with EtOAc (x 3). The recombinant organic extracts were washed with distilled water (x 1) and brine (x 1), dried over anhydrous  $\text{MgSO}_4$ , filtered and then evaporated *in vacuo*. The resultant crude was redissolved in anhydrous DCM and polymer supported borohydride (load: ca. 2 mmol/g, 2 eq) was added. The reaction was stirred at room temperature over 18 h, and then the mixture was filtered and evaporated *in vacuo* to afford the pure secondary amine product.

**(1,7-Dioxa-spiro[5.5]undec-2-ylmethyl)-(3-morpholin-4-yl-propyl)-amine (34a):** a colourless oil (80%);  $R_f$  0.25 (7:3 EtOAc: MeOH);  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3350, 3330, 3313, 2945, 1645, 1726, 1310, 1689, 1556, 1278, 1229, 1210, 1125, 1078, 1047, 834 and 750;  $\delta_{\text{H}}(600 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$  3.73-3.77 (1 H, m,  $H_9$ ), 3.62-3.68 (4 H, m,  $-\text{CH}_2\text{-N}(-\text{CH}_2\text{-CH}_2)_2\text{O}$ ), 3.52-3.55 (2 H, m,  $H_1$ ), 2.55-2.72 (4 H, m,  $H_{10}$  and  $H_{12}$ ), 2.30-2.40 (6 H, m,  $-\text{CH}_2\text{-N}(-\text{CH}_2\text{-CH}_2)_2\text{O}$ ), 1.25-1.91 (13 H, m), 1.04-1.24 (1 H, m);  $\delta_{\text{C}}(150 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$  95.3, 68.3, 66.9, 60.4, 57.2, 56.8, 55.2, 48.3, 40.7, 35.7, 35.5, 30.2, 28.8, 26.9, 25.3 and 18.7;  $m/z$  (+ESI) calc. for  $\text{C}_{17}\text{H}_{33}\text{N}_2\text{O}_3$  ( $\text{MH}^+$ ) 313.2491, found 313.2486; calc. for  $\text{C}_{17}\text{H}_{32}\text{N}_2\text{NaO}_3$  ( $\text{MNa}^+$ ) 335.2311, found 335.2315.

**(1,7-Dioxa-spiro[5.5]undec-2-ylmethyl)-pyridin-2-ylmethyl-amine (34b):** a colourless oil (90%);  $R_f$  0.30 (7:3 EtOAc: MeOH);  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ : 3350, 2939, 1645, 1726, 1290, 1672, 1527, 1278, 1229, 1210, 1181, 1141, 1118, 1070, 1047, 811 and 737;  $\delta_{\text{H}}(600 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$  8.48-8.53 (1 H, m,  $A_r$ ), 7.58 (1 H, t,  $J$  7.6,  $A_r$ ), 7.22 (1 H, d,  $J$  7.8,  $A_r$ ), 7.09-7.11 (1 H, m,  $A_r$ ), 3.91-3.92 (2 H, m,  $H_{11}$ ), 3.79-3.82 (1 H, m,  $H_9$ ), 3.53-3.56 (2 H, m,  $H_1$ ), 2.66 (1 H, dd,  $J$  9.1 and 8.0,  $H_{10A}$ ), 2.61 (1 H, dd,  $J$  11.9 and 3.8,  $H_{10B}$ ), 1.68-2.18 (4 H, m), 1.38-1.67 (7 H, m), 1.31 (1 H, td,  $J$  12.1 and 4.5) and 1.12-1.28 (1 H, m);  $\delta_{\text{C}}(150 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$  161.9, 149.2, 136.6, 122.1, 121.1, 95.3, 68.5, 60.5, 55.3, 54.6, 47.8, 35.7, 28.7, 25.3 and 18.6;  $m/z$  (+ESI) calc. for  $\text{C}_{16}\text{H}_{24}\text{N}_2\text{NaO}_2$  ( $\text{MNa}^+$ ) 299.1735, found 299.1721.

## Compounds (47) and (48)

**For the experimental procedure see experimental part of the article: general procedure for the synthesis of spiroketal-derived carbamates (35a-b), (36a-b) and (37a-b)**

**Pyridin-2-ylmethyl-carbamic acid 1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester (47):** a colourless oil (90%);  $R_f$  0.40 (EtOAc);  $[\alpha]_D^{25}$  -1.2 ( $c$  0.98,  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3320, 2942, 1721, 1592, 1572, 1520, 1439, 1336, 1247, 1229, 1212, 1182, 1150, 1097, 1079, 1062, 1047, 849, 808 and 755;  $\delta_{\text{H}}(600 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$  8.52 (1 H, d,  $J$  4.6,  $A_r$ ), 7.68 (1 H, t,  $J$  6.9,  $A_r$ ), 7.31 (1 H, d,  $J$  8.1,  $A_r$ ), 7.21-7.23 (1 H, m,  $A_r$ ), 5.90 (1 H, s,  $-\text{O}(\text{CO})\text{NH}-$ ), 4.46-4.53 (2 H, m,  $H_{11}$ ), 4.09-4.13 (1 H, m,  $H_{10A}$ ), 4.03-4.06 (1 H, m,  $H_{10B}$ ), 3.82-3.84 (1 H, m,  $H_9$ ), 3.58-3.63 (1 H, m,  $H_{1A}$ ), 3.50-3.54 (1 H, m,  $H_{1B}$ ), 1.77-1.85 (2 H, m,  $H_{3A}$  and  $H_{7A}$ ), 1.35-1.58 (9 H, m,  $H_2$ ,  $H_{3B}$ ,  $H_4$ ,  $H_6$ ,  $H_{7B}$  and  $H_{8A}$ ), 1.20-1.25 (1 H, m,  $H_{8B}$ );  $\delta_{\text{C}}(150 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$  157.1, 156.9, 148.8, 137.2, 122.6, 122.1, 95.6, 68.0, 67.6, 60.4, 45.9, 35.5, 35.0, 26.8, 25.2, 18.4 and 18.2;  $m/z$  (+ESI) calc. for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{NaO}_4$  ( $\text{MNa}^+$ ) 343.1634 found 343.1607.

**(3-Morpholin-4-yl-propyl)-carbamic acid 1,7-dioxaspiro[5.5]undec-2-ylmethyl ester (48):** a colourless oil (90%);  $R_f$  0.50 (EtOAc);  $[\alpha]_D^{25} +7.6$  ( $c$  0.14,  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$ (film)/ $\text{cm}^{-1}$  3334, 2941, 2870, 2812, 1706, 1593, 1523, 1449, 1336, 1257, 1229, 1212, 1182, 1117, 1097, 1062, 1047, 918, 863, 808 and 777;  $\delta_{\text{H}}$ (600 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 5.90 (1 H, s, -O(CO)NH-), 4.01-4.05 (2 H, m,  $H_{10}$ ), 3.80-3.84 (1 H, m,  $H_9$ ), 3.62-3.73 (5 H, m,  $H_{1A}$  and -N(- $\text{CH}_2\text{-CH}_2$ ) $_2$ O), 3.55-3.57 (1 H, m,  $H_{1B}$ ), 3.25-3.27 (2 H, m,  $H_{11}$ ), 2.40-2.44 (6 H, m, - $\text{CH}_2\text{-N(-CH}_2\text{-CH}_2$ ) $_2$ O), 1.83-1.86 (2 H, m,  $H_{3A}$  and  $H_{7A}$ ), 1.64-1.69 (2 H, m,  $H_{12}$ ), 1.41-1.61 (8 H, m,  $H_2$ ,  $H_{3B}$ ,  $H_{4A}$ ,  $H_6$ ,  $H_{7B}$  and  $H_{8A}$ ), 1.33-1.39 (1 H, m,  $H_{4B}$ ), 1.20-1.25 (1 H, m,  $H_{8B}$ );  $\delta_{\text{C}}$ (150 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 156.7, 95.6, 67.7, 67.6, 67.0, 60.4, 57.4, 53.6, 40.5, 35.5, 35.1, 26.9, 25.3, 18.5 and 18.3;  $m/z$  (+ESI) calc. for  $\text{C}_{18}\text{H}_{33}\text{N}_2\text{O}_5$  ( $\text{MH}^+$ ) 357.2389, found 357.2397.

### Compound (46)

For the experimental procedure see experimental part of the article: general procedure for the synthesis of spiroketal-derived sulfonamides (45a-d)

**Methanesulfonylamino-acetic acid 1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (46):** a clear, colourless oil (quant. over two steps);  $R_f$  0.20 (1:1 EtOAc: petroleum ether);  $[\alpha]_D^{25} +0.3$  ( $c$  0.65,  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$ (film)/ $\text{cm}^{-1}$  3296, 2941, 1749, 1325, 1212, 1079, 1047, 993, 845, 808 and 758;  $\delta_{\text{H}}$ (600 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 4.91 (1 H, s, -NH), 4.21 (1 H, dd,  $J$  11.3 and 7.0,  $H_{10A}$ ), 4.15 (1 H, dd,  $J$  11.3 and 3.5,  $H_{10B}$ ), 4.00 (2 H, d,  $J$  5.4,  $H_{11}$ ), 3.86-3.90 (1 H, m,  $H_9$ ), 3.58-3.64 (2 H, m,  $H_1$ ), 3.02 (3 H, s, - $\text{NHSO}_2\text{CH}_3$ ), 1.75-1.91 (2 H, m,  $H_{3A}$  and  $H_{7A}$ ), 1.50-1.63 (7 H, m,  $H_2$ ,  $H_{3B}$ ,  $H_{4A}$ ,  $H_{6A}$ ,  $H_{7B}$  and  $H_{8A}$ ), 1.43-1.48 (1 H, m,  $H_{4B}$ ), 1.35-1.40 (1 H, m,  $H_{6B}$ ) and 1.22-1.29 (1 H, m,  $H_{8B}$ );  $\delta_{\text{C}}$ (150 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 169.6, 95.7, 68.5, 67.0, 60.5, 44.3, 41.4, 35.4, 35.0, 26.7, 25.2, 18.5 and 18.2;  $m/z$  (+ESI) calc. for  $\text{C}_{13}\text{H}_{24}\text{NO}_6\text{S}$  ( $\text{MH}^+$ ) 322.1324, found 322.1301, calc. for  $\text{C}_{13}\text{H}_{23}\text{NNaO}_6\text{S}$  ( $\text{MNa}^+$ ) 344.1144, found 344.1122.