Switching between novel samarium(II)-mediated cyclizations by a simple change in alcohol cosolvent

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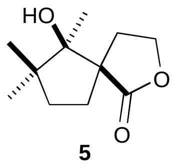
Experimental

General Experimental Considerations have been described previously.[1]

General Samarium(II) Cyclisation Procedure A



5

rel-(5R, 6R)-6-hydroxy-6,7,7-trimethyl-2-oxa-spiro[4.4]nonan-1-one 5

Dry MeOH (1.4 ml) was added to a stirred solution of $\mathrm{SmI_2}$ (0.1 M in THF, 5.10 ml, 0.510 mmol, 4 eq) at 0°C and the resulting solution was stirred for 10 min. (*E*)-3-(3,3-Dimethyl-4-oxo-pentylidene)-dihydro-furan-2-one **4** (25 mg, 0.127 mmol, 1 eq), in THF (0.5 ml) was added, and the resultant solution stirred at 0°C for 2 h. The reaction was quenched by opening to the air, followed by the addition of aqueous saturated NaCl (10 ml). The aqueous layer was separated and extracted with 80% EtOAc in petroleum ether (40-60°C) (4 x 15 ml). The combined organic extracts were dried ($\mathrm{MgSO_4}$), and concentrated *in vacuo* to give the crude product. Purification by column chromatography (eluting with 40% EtOAc in petroleum ether (40-60°C)), gave *rel*-(5R, 6R)-6-hydroxy-6,7,7-trimethyl-2-oxa-spiro[4.4]nonan-1-one **5** (15.8 mg, 0.08 mmol, 63%) as a white crystalline solid: mp 87 – 90°C (20% EtOAc in petroleum ether (40-60°C)): ν_{max} (neat)/cm^{-1} 3431s (OH), 1733s (C=O), 1471m, 1376m, 1221m, 1199m and 1026m; δ_H (400 MHz, $\mathrm{CDCl_3}$) 0.87 (3H, s, $\mathrm{C}H_3$), 1.02 (3H, s, $\mathrm{C}H_3$), 1.10 (3H, s, $\mathrm{C}H_3$), 1.52 – 1.59 (1H, m, 1H from $\mathrm{C(CH_3)_2C}H_2$), 1.66 – 1.72 (1H, m, 1H from $\mathrm{C(CH_3)_2CH_2C}H_2$), 1.84 – 1.91 (1H, m, 1H from $\mathrm{C(CH_3)_2C}H_2$), 2.02 – 2.07 (1H, m, 1H from $\mathrm{OCH_2C}H_2$), 2.15 – 2.23 (1H, m, 1H from $\mathrm{C(CH_3)_2CH_2C}H_2$), 2.34 – 2.42 (1H, m, 1H from $\mathrm{OCH_2C}H_2$), 4.09 – 4.15 (1H, m, 1H from $\mathrm{OC}H_2$), 4.23 – 4.28 (1H, m, 1H from $\mathrm{OC}H_2$) and 4.65 (1H, s, $\mathrm{O}H$); δ_C (100 MHz, $\mathrm{CDCl_3}$) 19.3 ($C\mathrm{H_3}$), 24.0 ($C\mathrm{H_3}$), 27.6 ($C\mathrm{H_3}$), 33.2 ($\mathrm{C(CH_3)_2CH_2}C\mathrm{H_2}$), 35.1 ($\mathrm{OCH_2}C\mathrm{H_2}$), 38.7, ($\mathrm{C(CH_3)_2}C\mathrm{H_2}$), 46.0 ($C\mathrm{(CH_3)_2}$),

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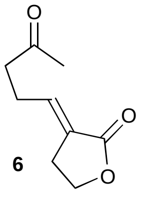
[1] Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, *68*, 3190.

55.2 (*C*C(O)), 65.8 (O*C*H_2), 84.8 (*C*(OH)CH_3) and 183.3 (*C*(O)); *m/z* (EI mode) 198 (($M^{+\bullet}$) 10%), 180 (25), 170 (20), 153 (40), 138 (25), 128 (95), 112 (100), 99 (100), 85 (100), 83 (100), 55 (25) and 43 (55); (Found: C, 66.82; H, 9.35; $C_{11}H_{18}O_3$ requires C, 66.64; H, 9.15).

General Oxidation/Olefination Procedure B

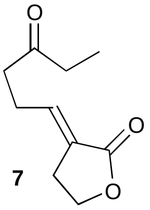


6

(*E*)-3-(4-Oxo-pentylidene)-dihydro-furan-2-one 6

DMSO (681 ml, 9.60 mmol, 4 eq) was added to a stirred solution of $(COCl)_2$ (419 ml, 4.80 mmol, 2 eq) in CH_2Cl_2 (10 ml) at –78°C and the resulting solution was stirred for 10 min. 1,4-Pentanediol (250 mg, 2.40 mmol, 1 eq) was then added as a solution in CH_2Cl_2 (10 ml) and the resultant solution stirred for a further 30 min. Triethylamine (3.44 ml, 24.0 mmol, 10 eq) was then added. After 2 h (1-butyrolactonylidene)triphenylphosphorane (1.66 g, 4.80 mmol, 2 eq) was added as a solution in CH_2Cl_2 (20 ml) and the reaction mixture allowed to warm to room temperature and stirred for 16 h. Aqueous saturated $NaHCO_3$ (10 ml) was then added, and the aqueous layer was separated and extracted with 80% EtOAc in petroleum ether (40-60°C) (4 x 20 ml). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product. Purification by column chromatography (eluting with 25% EtOAc in petroleum ether (40-60°C)), gave (*E*)-3-(4-oxo-pentylidene)-dihydro-furan-2-one **6** (399 mg, 2.37 mmol, 99%) as a yellow oil: n_{max} (neat)/cm^{-1} 1739s (lactone C=O), 1716s (ketone C=O), 1681s (C=C), 1405m, 1383m, 1238m, 1190m, 1038m, 1021m and 997m; d_H (400 MHz, $CDCl_3$) 2.19 (3H, s, C(O)C*H_3*), 2.46 (2H, apparent q, *J* 7.1, C*H_2*CH=C), 2.67 (2H, t, *J* 7.1 C*H_2*C(O)), 2.96 (2H, dt, *J* 2.9, 7.5, C*H_2*CH_2O), 4.41 (2H, t, *J* 7.5, C*H_2*O) and 6.64 (1H, tt, *J* 2.9, 7.5, C*H*=C); d_C (100 MHz, $CDCl_3$) 24.5 (*C*H_2CH=C), 25.5 (CH=C*C*H_2), 30.4 (C(O)*C*H_3), 41.8 (*C*H_2C(O)), 65.9 (*C*H_2O), 126.9 (CH=*C*), 138.9 (*C*H=C), 171.5 (*C*(O)O) and

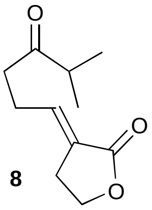
207.0 (*C*(O)); *m/z* (EI mode) 168 ((M$^{+\bullet}$) 10%), 125 (60), 111 (5), 83 (100), 79 (15) and 47 (20); (Found: (M$^{+\bullet}$), 168.0785. $C_9H_{12}O_3$ requires *M*, 168.0786).



7

(*E*)-3-(4-Oxo-hexylidene)-dihydro-furan-2-one 7

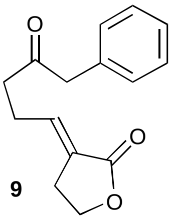
As for general procedure B. Hexane-1,4-diol (180 mg, 1.52 mmol, 1 eq), after oxidation and reaction with (1-butyrolactonylidene)triphenylphosphorane (1.05 g, 3.04 mmol, 2 eq) for 16 h and purification of the crude product mixture by column chromatography (eluting with 80% EtOAc in petroleum ether (40-60°C)), gave (*E*)-3-(4-oxo-hexylidene)-dihydro-furan-2-one **7** (115 mg, 0.63 mmol, 42%) as a pale yellow oil: n_{max} (neat)/cm^{-1} 1747s (ester C=O), 1709s (ketone C=O), 1679s (C=C), 1374m, 1352m, 1211m and 1022m; d_H (400 MHz, $CDCl_3$) 1.08 (3H, t, *J* 7.4, CH_3), 2.43 – 2.50 (4H, m, 2H from CH_2CH_3, 2H from CH_2CH=C), 2.64 (2H, t, *J* 7.1, CH_2C(O)), 2.93 (2H, dt, *J* 3.0, 7.5, CH_2CH_2O), 4.40 (2H, t, *J* 7.5, CH_2O) and 6.63 (1H, tt, *J* 3.0, 7.6, C*H*=C); d_C (100 MHz, $CDCl_3$) 8.1 (CH_3), 24.5 (CH_2CH=C), 25.5 (CH_2C=CH), 36.4 (CH_2CH_3), 40.5 (CH_2C(O)), 65.9 (CH_2O), 126.8 (CH=*C*), 139.1 (*C*H=C), 171.6 (*C*(O)O) and 209.9!(*C*(O)); *m/z* (EI mode) 182 ((M$^{+\bullet}$) 45%), 153 (10), 125 (100), 109 (15), 97 (15), 81 (50), 57 (65) and 53 (20); (Found: (M$^{+\bullet}$), 182.0942. $C_{10}H_{14}O_3$ requires *M*, 182.0943).



8

(*E*)-3-(5-Methyl-4-oxo-hexylidene)-dihydro-furan-2-one 8

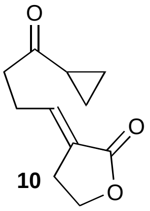
As for general procedure B. 5-Methyl-hexane-1,4-diol (200 mg, 1.51 mmol, 1 eq), after oxidation and reaction with (1-butyrolactonylidene)triphenylphosphorane (1.05 g, 3.03 mmol, 2 eq) for 16 h and purification of the crude product mixture by column chromatography (eluting with 80% EtOAc in petroleum ether (40-60°C)), gave (*E*)-3-(5-methyl-4-oxo-hexylidene)-dihydro-furan-2-one **8** (196 mg, 1.00 mmol, 66%) as a pale yellow oil: n_{max} (neat)/cm^{-1} 2970w, 1749s (ester C=O), 1707s (ketone C=O), 1680s (C=C), 1468m, 1381m, 1215m, 1194m and 1026m; d_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.45 (3H, d, *J* 7.0, $CH(CH_3)_2$), 2.47 (2H, apparent q, *J* 8.8, $CH_2CH=C$), 2.65 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 2.79 (2H, t, *J* 6.4, $CH_2C(O)$), 2.94 – 3.00 (2H, m, CH_2CH_2O), 4.40 (2H, t, *J* 7.4, CH_2O) and 6.63 (1H, tt, *J* 2.9, 7.6, $CH=C$); d_C (100 MHz, $CDCl_3$) 18.6 ($CH(CH_3)_2$), 18.7 ($CH(CH_3)_2$), 24.6 ($CH_2CH=C$), 25.5 (CH_2CH_2O), 38.5 ($CH_2C(O)$), 41.3 ($CH(CH_3)_2$), 65.9 (CH_2O), 122.6 ($CH=C$), 139.3 ($CH=C$), 171.6 ($C(O)O$) and 213.2 ($C(O)$); *m/z* (EI mode) 196 (($M^{+\bullet}$) 35%), 153 (25), 125 (100), 109 (30), 81 (50), 79 (30) and 43 (50); (Found: ($M^{+\bullet}$), 196.1100. $C_{11}H_{16}O_3$ requires *M*, 196.1099).



9

(*E*)-3-(4-Oxo-5-phenyl-pentylidene)-dihydro-furan-2-one 9

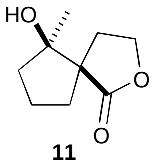
As for general procedure B. 5-Phenyl-pentane-1,4-diol (100 mg, 0.56 mmol, 1 eq), after oxidation and reaction with (1-butyrolactonylidene)triphenylphosphorane (385 mg, 1.11 mmol, 2 eq) for 16 h and purification of the crude product mixture by column chromatography (eluting with 40% EtOAc in petroleum ether (40-60°C)), gave (*E*)-3-(4-oxo-5-phenyl-pentylidene)-dihydro-furan-2-one **9** (78 mg, 0.34 mmol, 61%) as a yellow oil: n_{max} (neat)/cm^{-1} 2917s, 1751s (lactone C=O), 1717s (ketone C=O), 1681s (C=C), 1497m, 1454m, 1438m, 1412m, 1382m, 1360m, 1194m, 1030m and 961m; d_H (400 MHz, $CDCl_3$) 2.43 (2H, apparent q, *J* 7.1, $CH_2CH=C$), 2.67 (2H, t, *J* 7.1 C*H*$_2$C(O)), 2.91 (2H, dt, *J* 3.0, 7.4, C*H*$_2$C=CH), 3.72 (2H, s, C*H*$_2$Ph), 4.38 (2H, t, *J* 7.4, C*H*$_2$O), 6.57 (1H, tt, *J* 3.0, 7.4, C*H*=C), 7.20 – 7.22 (1H, m, Ar C*H*), 7.26 – 7.32 (2H, m, 2 x Ar C*H*) and 7.34 – 7.38 (2H, m, 2 x Ar C*H*); d$_C$ (100 MHz, CDCl$_3$) 24.5 (*C*H$_2$CH=C), 25.4 (*C*H$_2$C=CH), 40.2 (*C*H$_2$C(O)), 50.7 (*C*H$_2$Ph), 65.8 (*C*H$_2$O), 127.0 (CH=*C*), 127.7 (Ar *C*H), 129.3 (2 x Ar *C*H), 129.7 (2 x Ar *C*H), 134.2 (Ar *C*), 138.8 (*C*H=C), 171.5 (*C*(O)O) and 206.9 (*C*(O)); *m/z* (EI mode) 244 ((M$^{+\bullet}$) 37%), 223 (5), 205 (2), 176 (5), 153 (100), 125 (45), 119 (65), 91 (100), 81 (50), 65 (40) and 41 (22); (Found: (M$^{+\bullet}$), 244.1099. $C_{15}H_{16}O_3$ requires *M*, 244.1099).



10

(*E*)-3-(4-Oxo-4-cyclopropyl-butylidene)-dihydro-furan-2-one 10

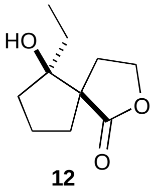
As for general procedure B. 1-Cyclopropyl-butane-1,4-diol (408 mg, 2.45 mmol, 1 eq), after oxidation and reaction with (1-butyrolactonylidene)triphenylphosphorane (1.70g, 4.92mmol, 2 eq) for 16 h and purification of the crude product mixture by column chromatography (eluting with 50% EtOAc in petroleum ether (40-60°C)), gave (*E*)-3-(4-oxo-4-cyclopropyl-butylidene)-dihydro-furan-2-one **10** (111 mg, 0.57 mmol, 48%) as a white crystalline solid: mp 67 – 69°C (20% Et$_2$O in petroleum ether (30-40°C): n$_{max}$ (neat)/cm^{-1} 2951m, 2899m, 1738s (lactone C=O), 1693s (ketone C=O), 1678s (C=C), 1496m, 1311m and 815m; d$_H$ (400 MHz, CDCl$_3$) 0.79 - 0.85 (2H, m, CH(OH)CHC*H*$_2^A$), 0.94 - 0.98 (2H, m, CH(OH)CHC*H*$_2^B$), 1.78 - 1.90 (1H, m, CH(OH)C*H*), 2.40 (2H, apparent q, *J* 7.3, C*H*$_2$CH=C), 2.72 (2H, t, *J* 7.3, C*H*$_2$C(O)), 2.86 (2H, apparent q, *J* 7.4, C*H*$_2$C=CH), 4.30 (2H, t, *J* 7.4, C*H*$_2$O) and 6.60 (1H, tt, *J* 1.6, 7.3, C*H*=C); d$_C$ (100 MHz, CDCl$_3$) 9.3 (C(OH)CH*C*H$_2^A$), 9.4 (C(OH)CH*C*H$_2^B$), 19.0 (CH(OH)*C*H), 22.7 (*C*H$_2$CH=C), 23.5 (*C*H$_2$C=CH), 39.6 (*C*H$_2$C(O)), 63.9 (*C*H$_2$O), 124.7 (CH=*C*), 137.3 (*C*H=C), 169.6 (*C*(O)O) and 207.3 (*C*(O)); *m/z* (EI mode) 194 ((M$^{+\bullet}$), 28%), 125 (100), 85 (50), 83 (76), 69 (83), 47 (16) and 41 (39); (Found: (M$^{+\bullet}$) 194.0942. $C_{11}H_{14}O_3$ requires *M*, 194.0943).



11

rel-(5R, 6R)-6-Hydroxy-6-methyl-2-oxa-spiro[4.4]nonan-1-one 11[2]

As for general procedure A. (*E*)-3-(4-Oxo-pentylidene)-dihydro-furan-2-one **6** (50 mg, 0.30 mmol, 1 eq), after a reaction time of 2 h and purification of the crude product mixture by column chromatography (eluting with 50% EtOAc in petroleum ether (40-60°C)), gave *rel*-(5R, 6R)-6-hydroxy-6-methyl-2-oxa-spiro[4.4]nonan-1-one **11** (36 mg, 0.21 mmol, 71%) as a clear, colourless oil: n_{max} (neat)/cm^{-1} 3480bs (OH), 2971s, 2874s, 1758s (C=O), 1450m, 1376s, 1302w, 1200m, 1149m, 1103m, 1030m, 1001m, 958m and 937m; d_H (400 MHz, $CDCl_3$) 1.23 (3H, s, C(OH)CH_3), 1.58 – 1.75 (3H, m, 1H from C$H_2CH_2CH_2$C(OH), 1H from CH_2CH_2C(OH), 1H from CH_2C(OH)), 1.88 (1H, ddd, *J* 3.0, 6.7, 12.7, 1H from CH_2CH_2O), 1.92 – 1.99 (2H, m, 1H from C$H_2CH_2CH_2$C(OH), 1H from CH_2CH_2C(OH)), 2.22 – 2.31 (2H, m, 1H from CH_2C(OH), 1H from CH_2CH_2O), 3.60 (1H, s, O*H*), 4.15 (1H, dt, *J* 6.7, 9.0, 1H from CH_2O) and 4.27 (1H, dt, *J* 3.0, 9.0, 1H from CH_2O); d_C (100 MHz, $CDCl_3$) 20.7 (*C*H_2CH_2C(OH)), 23.3 (*C*H_3), 32.4 (*C*H_2CH_2O), 34.1 (*C*H_2C(OH)), 39.0 (*C*$H_2CH_2CH_2$C(OH)), 55.0 (*C*C(O)), 65.8 (*C*H_2O), 82.2 (*C*(OH)) and 182.0 (*C*(O)); *m/z* (EI mode) 170 (($M^{+\bullet}$) 7%), 155 (2), 128 (7), 112 (40), 99 (100), 72 (25), 53 (10) and 43 (35); (Found: ($M^{+\bullet}$), 170.0942. $C_9H_{14}O_3$ requires *M*, 170.0943).



12

rel-(5R, 6R)-6-Ethyl-6-hydroxy-2-oxa-spiro[4.4]nonan-1-one 12

As for general procedure A. 3-(*E*)-(4-Oxo-hexylidene)-dihydro-furan-2-one **7** (40 mg, 0.22 mmol, 1 eq), after a reaction time of 1 h and purification of the crude product

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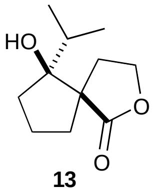
[2] Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453.

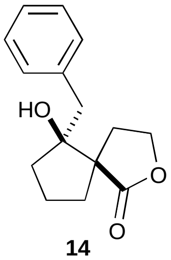
mixture by column chromatography (eluting with 60% EtOAc in petroleum ether (40-60°C)), gave *rel*-(5R, 6R)-6-ethyl-6-hydroxy-2-oxa-spiro[4.4]nonan-1-one **12** (24 mg, 0.13 mmol, 60%) as a yellow oil: n_{max} (neat)/cm^{-1} 3477bs (OH), 2968s, 1740s (C=O), 1371s, 1190s, 1032m, 1022m and 962m; d_H (400 MHz, CDCl$_3$) 0.90 (3H, t, *J* 7.4, C*H*$_3$), 1.43 – 1.52 (2H, m, 1H from C*H*$_2$CH$_3$, 1H from C*H*$_2$C), 1.54 – 1.62 (1H, m, 1H from C*H*$_2$CH$_3$), 1.63 – 1.69 (1H, m, 1H from C*H*$_2$CH$_2$C), 1.72 – 1.78 (1H, m, 1H from C*H*$_2$C(OH)), 1.85 – 1.96 (3H, m, 1H from C*H*$_2$CH$_2$O, 1H from C*H*$_2$C, 1H from C*H*$_2$CH$_2$C), 2.20 – 2.26 (2H, m, 1H from C*H*$_2$C(OH), 1H from C*H*$_2$CH$_2$O), 3.92 (1H, s, O*H*), 4.15 (1H, dt, *J* 6.8, 9.2, 1H from C*H*$_2$O) and 4.28 (1H, dt, *J* 2.7, 9.2, 1H from C*H*$_2$O); d_C (100 MHz, CDCl$_3$) 8.7 (*C*H$_3$), 20.7 (*C*H$_2$CH$_2$C), 29.1 (*C*H$_2$CH$_3$), 30.2 (*C*H$_2$CH$_2$O), 34.7 (*C*H$_2$C(OH)), 36.9 (*C*H$_2$C), 54.0 (*C*), 65.7 (*C*H$_2$O), 85.1 (*C*(OH)) and 182.9 (*C*(O)); *m/z* (CI mode, isobutane) 185 ((M + H)$^+$ 100%), 167 (80), 155 (2), 139 (1), 123 (2), 99 (2), 85 (5) and 71 (5); (Found: (M + H)$^+$, 185.1178. $C_{10}H_{17}O_3$ requires *M*, 185.1178).



13

rel-(5R, 6S)-6-Hydroxy-6-isopropyl-2-oxa-spiro[4.4]nonan-1-one 13

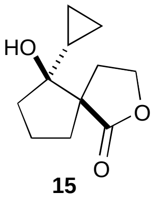
As for general procedure A. 3-(*E*)-(5-Methyl-4-oxo-hexylidene)-dihydro-furan-2-one **8** (50 mg, 0.26 mmol, 1 eq), after a reaction time of 2 h and purification of the crude product mixture by column chromatography (eluting with 60% EtOAc in petroleum ether (40-60°C)), gave *rel*-(5R, 6S)-6-hydroxy-6-isopropyl-2-oxa-spiro[4.4]nonan-1-one **13** (24 mg, 0.12 mmol, 47%) as a white crystalline solid: mp 43 – 46°C (petroleum ether (40-60°C)): n_{max} (neat)/cm^{-1} 3446bs (OH), 2966s, 1734s (C=O), 1470m, 1441m, 1371m, 1186m and 1018m; d_H (400 MHz, CDCl$_3$) 0.75 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 0.93 (3H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.40 – 1.45 (1H, m, 1H from C*H*$_2$C), 1.65 – 1.70 (1H, m, 1H from C*H*$_2$CH$_2$C), 1.77 – 1.83 (3H, m, 1H from C*H*(CH$_3$)$_2$, 1H from C*H*$_2$C(OH)), 1.91 – 1.98 (2H, m, 1H from C*H*$_2$C, 1H from C*H*$_2$CH$_2$C) 1H from C*H*$_2$CH$_2$O), 2.20 – 2.28 (2H, m, 1H from C*H*$_2$C(OH)), 1H from C*H*$_2$CH$_2$O), 4.15 (1H, dt, *J* 5.4, 9.1, 1H from C*H*$_2$O), 4.32 (1H, s, O*H*) and 4.33 (1H, dt, *J* 1.7, 9.1, 1H from C*H*$_2$O); d_C (100 MHz, CDCl$_3$) 17.4 (CH(*C*H$_3$)$_2$), 18.4 (CH(*C*H$_3$)$_2$), 20.8 (*C*H$_2$CH$_2$C), 30.8 (*C*H$_2$CH$_2$O), 33.7 (*C*H(CH$_3$)$_2$), 35.5 (*C*H$_2$C(OH)), 38.2 (*C*H$_2$C), 52.8 (*C*), 65.6 (*C*H$_2$O), 87.2 (*C*(OH)) and 183.9(*C*(O)); *m/z* (EI mode) 198 (($M^{+\bullet}$) 5%), 180 (3), 155 (100), 152 (5), 127 (10), 99 (45), 83 (80), 71 (15), 55 (20) and 43 (17); (Found: ($M^{+\bullet}$), 198.1257. $C_{11}H_{18}O_3$ requires *M*, 198.1256).



14

rel-(5R, 6S)-6-Benzyl-6-hydroxy-2-oxa-spiro[4.4]nonan-1-one 14

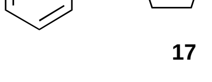
As for general procedure A. (*E*)-3-(4-Oxo-5-phenyl-pentylidene)-dihydro-furan-2-one **9** (40 mg, 0.17 mmol, 1 eq), after a reaction time of 2 h and purification of the crude product mixture by column chromatography (eluting with 50% EtOAc in petroleum ether (40-60°C)), gave *rel*-(5R, 6S)-6-benzyl-6-hydroxy-2-oxa-spiro[4.4]nonan-1-one **14** (27 mg, 0.12 mmol, 68%) as a white crystalline solid: mp 70 – 72˚C (petroleum ether (40-60°C)): n_{max} (neat)/cm^{-1} 3428bs (OH), 3026w, 2978w, 1752s, (C=O), 1456m, 1380m, 1225m, 1183m and 1033m; d_H (400 MHz, CDCl$_3$) 1.61 – 1.80 (4H, m, C*H*$_2$CH$_2$C(OH), C*H*$_2$CH$_2$CH$_2$C(OH)), 1.89 – 1.98 (2H, m, 1H from C*H*$_2$C(OH), 1H from C*H*$_2$CH$_2$O), 2.21 – 2.29 (1H, m, 1H from C*H*$_2$C(OH)), 2.46 – 2.54 (1H, m, 1H from C*H*$_2$CH$_2$O), 2.78 (2H, apparent s, C*H*$_2$Ph), 3.78 (1H, s, O*H*), 4.17 (1H, apparent dt, *J* 2.6, 9.0, 1H from C*H*$_2$O), 4.32 (1H, apparent dt, *J* 2.6, 9.0, 1H from C*H*$_2$O) and 7.14 – 7.24 (5H, m, Ar C*H*); d_C (100 MHz, CDCl$_3$) 20.4 (*C*H$_2$C), 31.9 (*C*H$_2$CH$_2$O), 34.6 (*C*H$_2$C(OH)), 36.6 (*C*H$_2$CH$_2$C(OH)), 41.9 (*C*H$_2$Ph), 54.6 (*C*), 65.6 (*C*H$_2$O), 84.5 (*C*(OH)), 127.1 (Ar *C*H), 128.5 (2 x Ar *C*H), 130.7 (2 x Ar *C*H), 137.2 (Ar *C*) and 182.0 (*C*(O)); *m/z* (EI mode) 246 (($M^{+\bullet}$) 5%), 156 (15), 155 (100), 111 (65), 92 (95), 91 (60), 55 (20) and 41 (15); (Found: ($M^{+\bullet}$), 246.1257. $C_{15}H_{18}O_3$ requires *M*, 246.1256).



15

rel-(5R, 6S)-6-Cyclopropyl-6-hydroxy-2-oxa-spiro[4.4]nonan-1-one 15

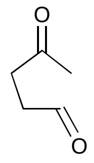
As for general procedure A. (*E*)-3-(4-Oxo-4-cyclopropyl-butylidene)-dihydro-furan-2-one **10** (30mg, 0.16 mmol, 1 eq), after a reaction time of 2 h and purification of the crude product mixture by column chromatography (eluting with 20% EtOAc in petroleum ether (40-60°C)), gave *rel*-(5R, 6S)-6-cyclopropyl-6-hydroxy-2-oxa-spiro[4.4]nonan-1-one **15** (15mg, 0.08 mmol, 49%) as a white crystalline solid: mp 57 – 59°C (20% Et_2O in petroleum ether (30-40°C): n_{max} (neat)/cm^{-1} 3050(OH), 2759w, 1743s (C=O), 1384m, 1182m, 1076m, 1018m and 953m; d_H (400 MHz, $CDCl_3$) 0.27 - 0.37 (3H, m, 2H from C(OH)CHCH_2^A, 1H from C(OH)CHCH_2^B), 0.46 - 0.50 (1H, m, 1H from C(OH)CHCH_2^B), 0.80 - 0.83 (1H, m, C(OH)C*H*), 1.63 - 1.83 (4H, m, 1H from CH_2C(OH), 3H from CH_2), 1.89 - 1.97 (2H, m, 1H from CH_2CH_2O, 1H from CH_2), 2.26 - 2.28 (1H, m, 1H from CH_2C(OH)), 2.50 - 2.55 (1H, m, 1H from CH_2CH_2O), 3.62 (1H, s, O*H*), 4.20 (1H, dt, *J* 7.2, 8.5, 1H from CH_2O) and 4.29 - 4.34 (1H, td, *J* 4.2, 8.5, 1H from CH_2O); d_C (100 MHz, $CDCl_3$) -0.67 (C(OH)CH*C*H_2^A), 0.0 (C(OH)CH*C*H_2^B), 14.2 (C(OH)*C*H), 19.9 (*C*H_2), 31.4 (*C*H_2CH_2O), 34.3 (*C*H_2C(OH)), 36.6 (*C*H_2), 54.2 (*C*C(O)), 65.3 (*C*H_2O), 82.2 (*C*(OH)) and 182.1 (*C*(O)); *m/z* (EI mode) 196 (($M^{+\bullet}$), 26%), 112 (79), 99 (59), 98 (32), 85 (65), 83 (100), 69 (50) 48 (19) and 41 (24); (Found: ($M^{+\bullet}$) 196.1100. $C_{11}H_{16}O_3$ requires *M*, 196.1099).



17

1-Benzyl-3-(diethoxyphosphinyl)-pyrrolidin-2-one 17

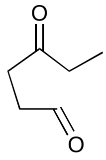
A solution of LDA was prepared by the addition of diisopropylamine (802 μl, 5.70 mmol, 2 eq) to a stirred solution of ^{n}BuLi (2.5 M in Hexanes, 2.85 ml, 5.70 mmol, 2 eq) in THF (2.5 ml) at –5ºC, and the resultant solution was stirred for 30 min. A solution of 1-benzyl-pyrrolidin-2-one (500 mg, 2.85 mmol, 1 eq) in THF (3ml) was then added *via* cannula, and the temperature raised to 15ºC and the solution stirred for 10 min. A solution of diethylchlorophosphate (420 μl, 2.85 mmol, 1 eq) in THF (2 ml) was then added *via* cannula, whereupon the temperature rose to 25ºC. The resulting solution was stirred at room temperature for 3 h. The solution was then acidified to pH 1 (2 M aqueous HCl), and the aqueous layer was separated and extracted with CH_2Cl_2 (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography (50% EtOAc in petroleum ether (40-60°C) to remove non-polar impurities, then with 50% EtOAc in MeCN) gave 1-benzyl-3-(diethoxyphosphinyl)-pyrrolidin-2-one **17** (481 mg, 1.55 mmol, 54%) as a brown oil: ν_{max} (neat)/cm^{-1} 2983s, 2909s, 1693s (C=O), 1496m, 1455m, 1440m, 1258m (P=O), 1164w, 1059m (P–O) and 961m; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1, OCH_2CH_3), 1.29 (3H, t, *J* 7.1, OCH_2CH_3), 2.19 – 2.37 (2H, m, CH_2CHP), 2.94 (1H, ddd, J_{HP}, 22.0, *J* 5.3, 10.2, C*H*P), 3.12 – 3.18 (1H, m, 1H from CH_2N), 3.33 (1H, apparent q, *J* 7.7, 1H from CH_2N), 4.08 – 4.23 (4H, m, 2 x OCH_2), 4.36 (1H, d, *J* 14.8, AB system, 1H from CH_2Ph), 4.46 (1H, d, *J* 14.8, AB system, 1H from CH_2Ph), 7.15 – 7.23 (3H, m, 3 x Ar C*H*) and 7.24 – 7.28 (2H, m, 2 x Ar C*H*); δ_C (100 MHz, $CDCl_3$) 16.8 (d, J_{CP} 4.1, OCH_2CH_3), 16.8 (d, J_{CP} 4.1, OCH_2CH_3), 20.6 (d, J_{CP} 3.9, NCH_2CH_2), 41.4 (d, J_{CP} 141.2, C*H*P), 45.7 (d, J_{CP} 3.9, NCH_2), 47.4 (CH_2Ph), 62.7 (d, J_{CP} 6.6, OCH_2), 63.4 (d, J_{CP} 6.6, OCH_2), 128.0 (Ar *C*H), 128.5 (2 x Ar *C*H), 129.1 (2 x Ar *C*H), 136.4 (Ar *C*) and 169.7 (d, J_{CP} 4.0 *C*(O)); δ_P (81MHz, $CDCl_3$) 24.4; *m/z* (EI mode) 311 (($M^{+\bullet}$) 80%), 282 (10), 254 (5), 238 (2), 220 (15), 179 (15), 174 (40), 145 (20), 119 (25), 91 (100), 83 (30), 65 (10) and 47 (7); (Found: ($M^{+\bullet}$), 311.1285. $C_{15}H_{22}O_4NP$ requires *M*, 311.1286).



18

4-Oxo-pentanal 18[3]

To a stirred solution of 3-acetylpropanol (5.00 g, 50.0 mmol, 1 eq) in CH_2Cl_2 (150 ml) at room temperature was added pyridinium chlorochromate (16.2 g, 75.0 mmol, 1.5 eq) and the resulting solution stirred for 16 h. The reaction mixture was passed through a plug of silica and concentrated *in vacuo* to give the crude product. Purification by column chromatography (eluting with CH_2Cl_2) gave 4-oxo-pentanal **18** (3.53 g, 35.3 mmol, 71%) as a clear, colourless oil: n_{max} (neat)/cm^{-1} 2729s, 1716bs (2 x C=O), 1428bs, 1170w, 1132w, 1080w, 961m and 879m; d_H (400 MHz, $CDCl_3$) 2.23 (3H, s, C*H*$_3$), 2.77 (4H, s, 2 x C*H*$_2$) and 9.83 (1H, s, C*H*O); d_C (100 MHz, $CDCl_3$) 30.2 (*C*H$_3$), 35.9 (*C*H$_2$C(O)CH$_3$), 27.8 (*C*H$_2$CHO), 200.8 (*C*HO) and 206.8 (*C*(O)); *m/z* (CI mode, isobutane) 101 ((M + H)$^+$ 20%), 57 (100) and 56 (10); (Found: (M + H)$^+$, 101.0602. $C_5H_9O_2$ requires *M*, 101.0603).



19

4-Oxo-hexanal 19[4]

DMSO (361 ml, 5.08 mmol, 4 eq) was added to a stirred solution of $(COCl)_2$ (222 ml, 2.54 mmol, 2 eq) in CH_2Cl_2 (10 ml) at –78°C and the resulting solution was stirred for 10 min. Hexane-1,4-diol (150 mg, 1.27 mmol, 1 eq) was then added as a solution in CH_2Cl_2 (5 ml) and the resultant solution stirred for a further 30 min. Triethylamine (1.82 ml, 12.7 mmol, 10 eq) was then added and the reaction mixture was allowed to warm to room temperature and stir for 2 h. Aqueous saturated $NaHCO_3$ (5 ml) was

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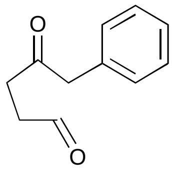
[3] Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830.

[4] Takeoka, G. R.; Buttery, R. G.; Perrino, C. T. *J. Agric. Food Chem.* **1995**, 43, 22.

then added, and the aqueous layer was separated and extracted with EtOAc (4 x 10 ml). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product. Purification by column chromatography (eluting with 80% EtOAc in petroleum ether (40-60°C)) gave 4-oxo-hexanal **19** (103 mg, 0.90 mmol, 73%) as a pale yellow oil: n_{max} (neat)/cm^{-1} 2980s, 1735s (aldehyde C=O), 1719s (ketone C=O), 1459s, 1420s, 1116m and 1089m; d_H (400 MHz, $CDCl_3$) 1.01 (3H, t, *J* 7.3, $C(O)CH_2CH_3$), 2.41 (2H, q, *J* 7.3, $C(O)CH_2$), 2.64 – 2.72 (4H, m, 2 x CH_2) and 9.70 (1H, s, C*H*O); d_C (100 MHz, $CDCl_3$) 8.2 (CH_3), 34.6 (CH_2), 36.3 ($C(O)CH_2$), 37.9 (CH_2), 200.9 (*C*HO) and 209.6 (*C*(O)); *m/z* (CI mode, isobutane) 127 (10%), 115 ($(M + H)^+$ 100), 99 (95), 97 (5) and 71 (5); (Found: $(M + H)^+$, 115.0759. $C_6H_{11}O_2$ requires *M*, 115.0759).



20

4-Oxo-5-phenyl-pentanal 20[5]

DMSO (261 ml, 3.68 mmol, 4 eq) was added to a stirred solution of $(COCl)_2$ (161 ml, 1.84 mmol, 2 eq) in CH_2Cl_2 (7 ml) at –78°C and the resulting solution was stirred for 10 min. 5-Phenyl-pentane-1,4-diol (165 mg, 0.92 mmol, 1 eq) was then added as a solution in CH_2Cl_2 (3 ml) and the resultant solution stirred for a further 30 min. Triethylamine (1.32 ml, 9.2 mmol, 10 eq) was then added and the reaction mixture was allowed to warm to room temperature and stir for 2 h. Aqueous saturated $NaHCO_3$ (5 ml) was then added, and the aqueous layer was separated and extracted with EtOAc (4 x 10 ml). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product. Purification by column chromatography (eluting with 20% EtOAc in petroleum ether (40-60°C)) gave 4-oxo-5-phenyl-pentanal **20** (116 mg, 0.66 mmol, 72%) as a pale yellow oil: n_{max} (neat)/cm^{-1} 2826m, 2727m, 1702bs (2 x C=O), 1603m, 1584m, 1498m, 1454m, 1413m, 1092m, 1036m and 1002w; d_H (400 MHz, $CDCl_3$) 2.64 – 2.72 (4H, m, 2 x CH_2), 3.69 (2H, s,

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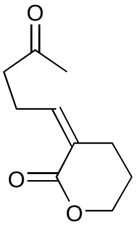
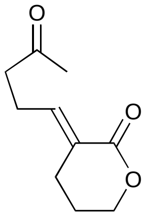
[5] Brown, E.; Paterne, M. *Bull. Soc. Chim. Fr.* **1974**, 1001.

C*H*$_2$Ph), 7.14 – 7.35 (5H, m, 5 x Ar C*H*) and 9.71 (1H, s, C*H*O); d$_C$ (100 MHz, CDCl$_3$) 34.4 (*C*H$_2$), 37.9 (*C*H$_2$), 50.4 (*C*H$_2$Ph), 127.5 (Ar *C*H), 129.2 (2 x Ar *C*H), 129.8 (2 x Ar *C*H), 134.4 (Ar *C*), 200.7 (*C*HO) and 206.6 (*C*(O)); *m/z* (EI mode) 176 (($M^{+\bullet}$) 20%), 165 (5), 148 (5), 117 (3), 115 (3), 85 (100), 65 (15), 57 (10) and 51 (5); (Found: ($M^{+\bullet}$), 176.0836. $C_{11}H_{12}O_2$ requires *M*, 176.0837).

General Horner-Wittig Olefination Procedure C


21*Z*

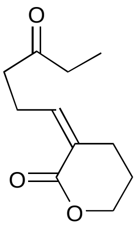

21*E*

(*Z*)-3-(4-Oxo-pentylidene)-tetrahydro-pyran-2-one 21*Z* and (*E*)-3-(4-Oxo-pentylidene)-tetrahydro-pyran-2-one 21*E*

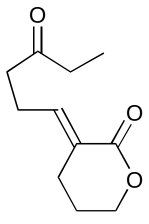
K_2CO_3 (643 mg, 4.65 mmol, 1.1 eq) was added to a solution of 18-crown-6 (1.23 g, 4.65 mmol, 1.1 eq) and 3-(diethoxyphosphinyl)-tetrahydro-pyran-2-one **16** (1.00 g, 4.23 mmol, 1 eq) in THF (50 ml) at room temperature, and the resultant solution stirred for 2 h. 4-Oxo-pentanal **18** (509 mg, 5.08 mmol, 1.2 eq) in THF (10 ml) was then added and the solution stirred for 16 h. Aqueous saturated NH_4Cl (30 ml) was then added dropwise, and the aqueous layer was separated and extracted with Et_2O (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography (eluting with EtOAc) gave (*Z*)-3-(4-oxo-pentylidene)-tetrahydro-pyran-2-one **21*Z*** (301 mg, 1.65 mmol, 39%) as a pale yellow oil: n$_{max}$ (neat)/cm^{-1} 2928s, 2861s, 1733s (C=O), 1635s (C=C), 1478m, 1449m, 1116m, 1061m, 1028m and 976m; d$_H$ (400 MHz, CDCl$_3$) 1.72 –1.76 (2H, m, OCH$_2$C*H*$_2$), 1.99 (3H, s, C(O)C*H*$_3$), 2.39 (2H, dt, *J* 1.6, 5.2, CH=CC*H*$_2$), 2.46 (2H, t, *J* 7.0, C*H*$_2$C(O)), 2.65 (2H, apparent q, *J* 7.0, C*H*$_2$CH=C), 4.11 (2H, t, *J* 5.4, OC*H*$_2$) and 5.93 (1H, tt, *J* 1.6, 7.5, C*H*=C); d$_C$ (100

MHz, $CDCl_3$) 23.7 (OCH_2CH_2), 24.5 ($CH_2CH=C$), 29.7 ($CH=CCH_2$), 30.1 ($C(O)CH_3$), 43.2 ($CH_2C(O)$), 69.1 (OCH_2), 126.2 ($CH=C$), 146.1 ($CH=C$), 165.9 ($C(O)O$) and 208.5 ($C(O)$).

Further elution gave (*E*)-3-(4-oxo-pentylidene)-tetrahydro-pyran-2-one **21*E*** (120 mg, 0.66 mmol, 16%) as a pale yellow oil: n_{max} (neat)/cm^{-1} 2901s, 1727s (C=O), 1636s (C=C), 1479m, 1438m, 1313m, 1274m, 1159m, 1129m, 1073m and 967m; d_H (400 MHz, $CDCl_3$) 1.75 –1.81 (2H, m, CH_2CH_2O), 2.01 (3H, s, $C(O)CH_3$), 2.24 (2H, apparent q, *J* 7.2, $CH_2CH=C$), 2.42 (2H, dt, *J* 2.1, 7.2, $CH=CCH_2$), 2.47 (2H, t, *J* 7.2, $CH_2C(O)$), 4.15 (2H, t, *J* 5.3, CH_2O) and 6.75 (1H, tt, *J* 2.1, 7.3, $CH=C$); d_C (100 MHz, $CDCl_3$) 22.6 ($CH_2CH=C$), 23.0 (CH_2CH_2O), 24.0 ($CH=CCH_2$), 30.4 ($C(O)CH_3$), 42.0 ($CH_2C(O)$), 69.0 (CH_2O), 126.9 ($CH=C$), 144.5 ($CH=C$), 166.8 ($C(O)O$) and 207.3 ($C(O)$); *m/z* (EI mode) 182 (($M^{+\bullet}$) 15%), 164 (1), 139 (100), 125 (5), 111 (10), 93 (15), 84 (15), 67 (15) and 43 (35); (Found: ($M^{+\bullet}$), 182.0942. $C_{10}H_{14}O_3$ requires *M*, 182.0943).



22*Z*

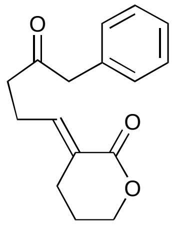


22*E*

(*Z*)-3-(4-Oxo-hexylidene)-tetrahydro-pyran-2-one 22*Z* and (*E*)-3-(4-Oxo-hexylidene)-tetrahydro-pyran-2-one 22*E*

As for general procedure C. Reaction of 3-(diethoxyphosphinyl)-tetrahydro-pyran-2-one **16** (207 mg, 0.88 mmol, 1 eq) with 4-oxo-hexanal **19** (100 mg, 0.88 mmol, 1 eq) for 18 h, after purification by column chromatography (eluting with 80% EtOAc in petroleum ether (40-60°C)), gave (*Z*)-3-(4-Oxo-hexylidene)-tetrahydro-pyran-2-one **22*Z*** (29 mg, 0.15 mmol, 17%) as a yellow oil: n_{max} (neat)/cm^{-1} 2974w, 1709s (C=O), 1633s (C=C), 1398m, 1375m, 1124m and 1072m; d_H (400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.3, CH_2CH_3), 1.85 (2H, apparent quintet, *J* 6.6, OCH_2CH_2), 2.36 (2H, q, *J* 7.3, CH_2CH_3), 2.48, (2H, dt, *J* 1.6, 7.1, $CH=CCH_2$), 2.53 (2H, t, *J* 7.1 $CH_2C(O)$), 2.76 (2H, apparent q, *J* 7.1, C*H*$_2$CH=C), 4.21 (2H, t, *J* 5.5, C*H*$_2$O) and 6.03 (1H, tt, *J* 1.6, 7.6, C*H*=C); d_C (100 MHz, CDCl$_3$) 8.2 (*C*H$_3$), 23.7 (OCH$_2$*C*H$_2$), 24.6 (*C*H$_2$CH=C), 29.7 (CH=C*C*H$_2$), 30.1 (*C*H$_2$CH$_3$), 41.8 (*C*H$_2$C(O)), 69.1 (*C*H$_2$O), 126.1 (CH=*C*), 146.4 (*C*H=C), 166.0 (*C*(O)O) and 211.2 (*C*(O)).

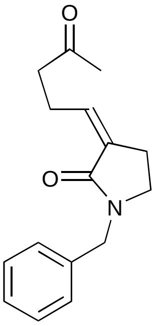
Further elution gave (*E*)-3-(4-Oxo-hexylidene)-tetrahydro-pyran-2-one **22*E*** (76 mg, 0.39 mmol, 44%) as a yellow oil: n_{max} (neat)/cm^{-1} 2974m, 1704s (C=O), 1632s (C=C), 1394m, 1254m, 1169m and 1074m; d_H (400 MHz, CDCl$_3$) 1.00 (3H, t, *J* 7.3, CH$_2$C*H*$_3$), 1.86 (2H, apparent quintet, *J* 6.6, C*H*$_2$CH$_2$O), 2.33 (2H, apparent t, *J* 7.4, C*H*$_2$CH=C), 2.38 (2H, q, *J* 7.3, C*H*$_2$CH$_3$), 2.52 (2H, dt, *J* 2.3, 7.4, CH=CC*H*$_2$), 2.54 (2H, t, *J* 7.4, C*H*$_2$C(O)), 4.26 (2H, t, *J* 5.8, C*H*$_2$O) and 6.84 (1H, tt, *J* 2.3, 7.4, C*H*=C); d_C (100 MHz, CDCl$_3$) 8.1 (CH$_2$*C*H$_3$), 22.7 (*C*H$_2$CH=C), 23.0 (CH$_2$CH$_2$O), 24.0 (CH=C*C*H$_2$), 36.4 (*C*H$_2$CH$_3$), 40.6 (*C*H$_2$C(O)), 69.0 (*C*H$_2$O), 126.8 (CH=*C*), 144.8 (*C*H=C), 166.9 (*C*(O)O) and 210.1 (*C*(O)); *m/z* (EI mode) 196 ((M$^{+\bullet}$) 55%), 167 (10), 139 (100), 125 (20), 111 (30), 93 (50), 67 (40), 57 (65) and 41 (25); (Found: (M$^{+\bullet}$), 196.1100. C$_{11}$H$_{16}$O$_3$ requires *M*, 196.1099).



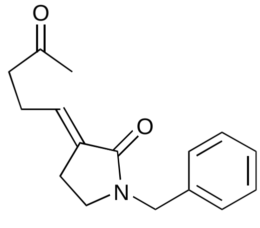
23*E*

(*E*)-3-(4-Oxo-5-phenyl-pentylidene)-tetrahydro-pyran-2-one 23*E*

As for general procedure C. Reaction of 3-(diethoxyphosphinyl)-tetrahydro-pyran-2-one **16** (135 mg, 0.57 mmol, 1 eq) with 4-oxo-5-phenyl-pentanal **20** (100 mg, 0.57 mmol, 1 eq) for 18 h, after purification by column chromatography (eluting with 80% EtOAc in petroleum ether (40-60°C)), gave (*E*)-3-(4-Oxo-5-phenyl-pentylidene)-tetrahydro-pyran-2-one **23*E*** (68 mg, 0.26 mmol, 46%) as a yellow oil: n_{max} (neat)/cm^{-1} 2897w, 1707s (C=O), 1632s (C=C), 1496m, 1396m, 1259m, 1167m and 1074m; d_H (400 MHz, CDCl$_3$) 1.84 (2H, apparent quintet, *J* 6.5, C*H*$_2$CH$_2$O), 2.29 (2H, apparent q, *J* 7.2, C*H*$_2$CH=C), 2.46 (2H, apparent t, *J* 7.2, CH=CC*H*$_2$), 2.56 (2H, t, *J* 7.2, C*H*$_2$C(O)), 3.62 (2H, s, C*H*$_2$Ph), 4.22 (2H, t, *J* 5.4, C*H*$_2$O), 6.78 (1H, tt, *J* 2.4, 7.2, C*H*=C) and 7.05 – 7.32 (5H, m, Ar C*H*); d$_C$ (100 MHz, $CDCl_3$) 22.7 (*C*H$_2$CH=C), 23.0 (*C*H$_2$CH$_2$O), 24.0 (CH=C*C*H$_2$), 40.3 (*C*H$_2$C(O)), 50.7 (*C*H$_2$Ph), 69.0 (*C*H$_2$O), 126.9 (CH=*C*), 127.6 (Ar *C*H), 129.2 (2 x Ar *C*H), 129.8 (2 x Ar *C*H), 134.3 (Ar *C*), 144.4 (*C*H=C), 166.8 (*C*(O)O) and 207.1 (*C*(O)); *m/z* (EI mode) 258 (($M^{+\bullet}$) 35%), 184 (2), 167 (100), 139 (30), 121 (15), 91 (70), 65 (15) and 55 (10); (Found: ($M^{+\bullet}$), 258.1256. $C_{16}H_{18}O_3$ requires *M*, 258.1256).



24*Z*



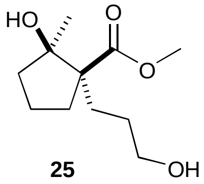
24*E*

(*Z*)-1-Benzyl-3-(4-oxo-pentylidene)-pyrrolidin-2-one 24*Z* and (*E*)-1-Benzyl-3-(4-oxo-pentylidene)-pyrrolidin-2-one 24*E*

18-Crown-6 (500 mg, 1.90 mmol, 5 eq) was added to a solution of 1-benzyl-3-(diethoxyphosphinyl)-pyrrolidin-2-one **17** (118 mg, 0.38 mmol, 1 eq) in THF (3 ml) at –78ºC. The resultant solution was stirred for 5 min before addition of KHMDS (0.5 M in PhMe, 0.76 ml, 0.38 mmol, 1 eq). After 30 min, a solution of 4-oxo-pentanal **18** (45 mg, 0.45 mmol, 1.2 eq) in THF (3 ml) was added *via* cannula, and the solution was left to warm to room temperature and stir for 18 h. Aqueous saturated NH_4Cl (10 ml) was then added dropwise, and the aqueous layer was separated and extracted with Et_2O (3 x 20 ml). The combined organic extracts were washed with H_2O (dist.) (2 x 10 ml), dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography (eluting with 80% EtOAc in petroleum ether (40-60°C)) gave (*Z*)-1-benzyl-3-(4-oxo-pentylidene)-pyrrolidin-2-one **24*Z*** (16 mg, 0.06 mmol, 16%) as a pale yellow oil: n$_{max}$ ($CDCl_3$ sol$^{\underline{n}}$)/cm^{-1} 2255s, 1714m (ketone C=O), 1677m (amide C=O), 1651m (C=C), 1440w, 1425w, 1383w, 1278w, 1162w and 1094w; d$_H$ (400 MHz, $CDCl_3$) 2.01 (3H, s, C(O)C*H*$_3$), 2.44 (2H, t, *J* 7.1, C*H*$_2$C(O)), 2.48 (2H, dt, *J* 2.4, 5.1, CH=CC*H*$_2$), 2.90 (2H, apparent q, *J* 7.2, C*H*$_2$CH=C), 3.06

(2H, t, *J* 5.1, CH_2N), 4.34 (2H, s, CH_2Ph), 5.76 (1H, tt, *J* 2.4, 7.8, C=C*H*) 7.07 – 7.14 (3H, m, 3 x Ar C*H*) and 7.16 – 7.22 (2H, m, 2 x Ar C*H*); d_C (100 MHz, $CDCl_3$) 21.7 (*C*H_2CH=C), 25.8 (CH=C*C*H_2), 30.0 (C(O)*C*H_3), 44.0 (*C*H_2C(O)), 44.1 (*C*H_2N), 47.2 (*C*H_2Ph), 127.9 (Ar *C*H), 128.6 (2 x Ar *C*H), 129.1 (2 x Ar *C*H), 130.8 (Ar *C*), 135.3 (*C*H=C), 136.9 (CH=*C*), 168.7 (*C*(O)N) and 209.0 (*C*(O)).

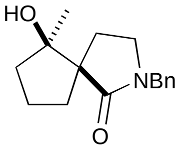
Further elution gave (*E*)-1-benzyl-3-(4-oxo-pentylidene)-pyrrolidin-2-one **24*E*** (52 mg, 0.20 mmol, 53%) as a pale yellow oil: n_{max} ($CDCl_3$ sol^{n})/cm^{-1} 2920m, 1714s (ketone C=O), 1680 (amide C=O) 1670s (C=C), 1495m, 1448m, 1427m, 1360w, 1286m, 1256m and 1165w; d_H (400 MHz, $CDCl_3$) 2.00 (3H, s, C(O)CH_3), 2.30 (2H, apparent q, *J* 7.4, CH_2CH=C), 2.44 (2H, t, *J* 7.2, CH_2C(O)), 2.52 (2H, dt, *J* 2.7, 6.6, CH=CCH_2), 3.13 (2H, t, *J* 6.6, CH_2N), 4.38 (2H, s, CH_2Ph), 6.23 (1H, tt, *J* 2.7, 7.4, C*H*=C) 7.08 – 7.14 (3H, m, 3 x Ar C*H*) and 7.15 – 7.19 (2H, m, 2 x Ar C*H*); d_C (100 MHz, $CDCl_3$) 22.1 (CH=C*C*H_2), 23.6 (*C*H_2CH=C), 30.5 (C(O)*C*H_3), 42.4 (*C*H_2C(O)), 44.1 (*C*H_2N), 47.5 (*C*H_2Ph), 128.0 (Ar *C*H), 128.7 (2 x Ar *C*H), 129.1 (2 x Ar *C*H), 132.9 (Ar *C*), 131.4 (*C*H=C), 136.8 (CH=*C*), 168.6 (*C*(O)N) and 207.8 (*C*(O)); *m/z* (EI mode) 257 (($M^{+\bullet}$) 45%), 256 (1), 214 (70), 186 (20), 171 (7), 170 (5), 118 (10), 104 (4), 91 (100), 65 (12) and 43 (22); (Found: ($M^{+\bullet}$), 257.1417. $C_{16}H_{19}O_2N$ requires *M*, 257.1416).



25

rel-(1R, 2R)-Methyl-2-hydroxy-1-(3-hydroxy-propyl)-2-methyl-cyclopentanoate 25

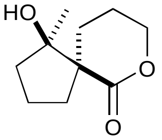
As for general procedure A. A 1:1 mixture of (*Z*)-3-(4-oxo-pentylidene)-tetrahydro-pyran-2-one **21*Z*** and (*E*)-3-(4-oxo-pentylidene)-tetrahydro-pyran-2-one **21*E*** (50 mg, 0.27 mmol, 1 eq) after a reaction time of 30 min and purification of the crude product mixture by column chromatography (eluting with 80% EtOAc in CH_2Cl_2), gave *rel*-(1R, 2R)-methyl-2-hydroxy-1-(3-hydroxy-propyl)-2-methyl-cyclopentanoate **25** (47 mg, 0.22 mmol, 81%) as a clear, colourless oil: n_{max} (neat)/cm^{-1} 3392bs (OH), 2953s, 1714s (C=O), 1452m, 1261m, 1194m, 1173m, 1122m, 1055m and 1007m; d$_H$ (400 MHz, CDCl$_3$) 1.22 – 1.38 (2H, m, 1H from C*H*$_2$CH$_2$OH, 1H from C*H*$_2$), 1.33 (3H, s, C*H*$_3$), 1.45 – 1.57 (2H, m, 1H from C*H*$_2$CH$_2$OH, 1H from C*H*$_2$), 1.59 – 1.66 (1H, m, 1H from C*H*$_2$C(OH)), 1.69 – 1.82 (4H, m, 4H from C*H*$_2$), 2.35 – 2.42 (1H, m, 1H from C*H*$_2$C(OH)), 3.55 – 3.61 (2H, m, C*H*$_2$O) and 3.65 (3H, s, OC*H*$_3$); d$_C$ (100 MHz, CDCl$_3$) 20.1 (*C*H$_2$), 23.6 (C(OH)*C*H$_3$), 29.2 (*C*H$_2$), 31.0 (*C*H$_2$), 31.6 (*C*H$_2$C(OH)), 40.1 (*C*H$_2$), 52.2 (O*C*H$_3$), 60.5 (*C*), 63.4 (*C*H$_2$O), 83.4 (*C*(OH)) and 176.6 (*C*(O)); *m/z* (CI mode, isobutane) 217 ((M + H)$^+$ 25%), 199 (100), 185 (40), 171 (35), 167 (30), 156 (5), 139 (10), 113 (10), 97 (15) and 85 (25); (Found: (M + H)$^+$, 217.1438. C$_{11}$H$_{21}$O$_4$ requires *M*, 217.1440).



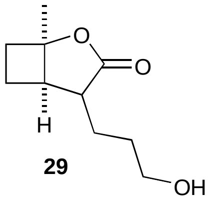
26

rel-(5R, 6R)-2-Benzyl-6-hydroxy-6-methyl-2-aza-spiro[4.4]nonan-1-one 26

As for general procedure A. (*E*)-1-Benzyl-3-(4-oxo-pentylidene)-pyrrolidin-2-one **24*E*** (50 mg, 0.19 mmol, 1 eq) after a reaction time of 3 h and purification of the crude product mixture by column chromatography (eluting with 10% EtOAc in petroleum ether (40-60°C)), gave *rel*-(5R, 6R)-2-benzyl-6-hydroxy-6-methyl-2-aza-spiro[4.4]nonan-1-one **26** (4.60 mg, 0.02 mmol, 9%) as a clear, colourless oil: n$_{max}$ (CDCl$_3$ sol$^{\underline{n}}$)/cm^{-1} 3012s (OH), 2397m, 2256w, 1661w (C=O), 1598w, 1525w, 1483w, 1420w, 1382w, 1215s and 1098w; d$_H$ (400 MHz, CDCl$_3$) 1.17 (3H, s, C(OH)C*H*$_3$), 1.50 – 1.67 (4H, m, 1H from C*H*$_2$CC(OH), 1H from C*H*$_2$C(OH), 1H from C*H*$_2$CH$_2$C(OH), 1H from NC(O)CC*H*$_2$), 1.82 – 1.96 (3H, m, 1H from C*H*$_2$CC(OH), 1H from C*H*$_2$CH$_2$C(OH), 1H from NC(O)CC*H*$_2$), 2.25 – 2.31 (1H, m, 1H from C*H*$_2$C(OH)), 3.04 – 3.16 (2H, m, NC*H*$_2$), 4.36 (1H, apparent d, *J* 14.6, AB system, 1H from C*H*$_2$Ph), 4.47 (1H, apparent d, *J* 14.6, AB system, 1H from C*H*$_2$Ph), 4.97 (1H, d, *J* 1.5, O*H*), 7.15 – 7.22 (3H, m, 3 x Ar C*H*) and 7.23 – 7.29 (2H, m, 2 x Ar C*H*); d$_C$ (100 MHz, CDCl$_3$) 20.7 (*C*H$_2$CH$_2$C(OH)), 23.0 (C(OH)*C*H$_3$), 29.6 (*C*H$_2$CC(O)N), 34.4 (*C*H$_2$C(OH)), 39.0 (*C*H$_2$CC(OH)), 44.0 (C(O)N*C*H$_2$), 47.1 (*C*H$_2$Ph), 56.2 (*C*), 82.9 (*C*(OH)), 128.1 (Ar *C*H), 128.4 (2 x Ar *C*H), 129.2 (2 x Ar *C*H), 136.5 (Ar *C*) and 178.4 (*C*(O)N); *m/z* (EI mode) 259 (($M^{+\bullet}$) 20%), 241 (5), 216 (5), 201 (2), 188 (50), 175 (5), 149 (2), 121 (3), 114 (7), 84 (100), 83 (65) and 47 (30); (Found: ($M^{+\bullet}$), 259.1571. $C_{16}H_{21}O_2N$ requires *M*, 259.1572).



28



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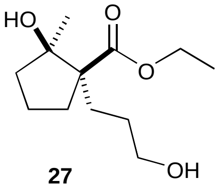


27

***rel*-(1R, 5R)-1-Hydroxy-1-methyl-7-oxa-spiro[4.5]decan-6-one 28** and ***rel*-(1R, 4R/S, 5R)-4-(3-Hydroxy-propyl)-1-methyl-2-oxa-bicyclo[3.2.0]heptan-3-one 29** and ***rel*-(1R, 2R)-Ethyl-2-hydroxy-1-(3-hydroxy-propyl)-2-methyl-cyclopentanoate 27**

Dry EtOH (3 ml) was added to a stirred solution of SmI_2 (0.1 M in THF, 11 ml, 1.10 mmol, 4 eq) at 0°C and the resulting solution was stirred for 10 min. A 2.5:1 mixture of (*Z*)-3-(4-oxo-pentylidene)-tetrahydro-pyran-2-one **21*Z*** and (*E*)-3-(4-oxo-pentylidene)-tetrahydro-pyran-2-one **21*E*** (50 mg, 0.27 mmol, 1 eq) in THF (1 ml) was added, and the resultant solution stirred at 0°C for 40 min. The reaction was quenched by opening to the air, followed by the addition of aqueous saturated NaCl (10 ml). The aqueous layer was separated and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification by column chromatography (eluting with 30% EtOAc in CH_2Cl_2), gave *rel*-(1R, 5R)-1-hydroxy-1-methyl-7-oxa-spiro[4.5]decan-6-one **28** (6 mg, 0.03 mmol, 12 %) as a pale yellow oil: n_{max} (neat)/cm^{-1} 3417bs (OH), 2962s, 1714s (C=O), 1450m, 1394m, 1263m, 1146s and 962s; d_H (400 MHz, $CDCl_3$) 1.19 (3H, s, CH_3), 1.55 – 1.66 (3H, m, 3H from CH_2), 1.75 – 1.95 (6H, m, 1H from CH_2C(OH), 5H from CH_2), 2.23 – 2.28 (1H, m, 1H from CH_2C(OH)), 4.22 – 4.29 (1H, m, 1H from CH_2O), 4.33 – 4.39 (1H, m, 1H from CH_2O) and 4.65 (1H, s, O*H*); d_C (100 MHz, $CDCl_3$) 19.1 (CH_2), 19.8 (CH_2), 21.7 (CH_3), 26.8 (CH_2), 34.8 (CH_2C(OH)), 37.1 (CH_2), 53.8 (*C*), 68.8 (CH_2O), 82.4 (*C*(OH)) and 176.5 (*C*(O)); *m/z* (EI mode) 184 (($M^{+\bullet}$) 5%), 166 (5), 151 (2), 126 (30), 113 (100), 84 (45), 83 (70), 67 (20) and 43 (40); (Found: ($M^{+\bullet}$), 184.1099. $C_{10}H_{16}O_3$ requires *M*, 184.1099).

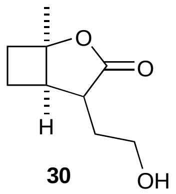
Further elution then gave *rel*-(1R, 4R/S, 5R)-4-(3-hydroxy-propyl)-1-methyl-2-oxa-bicyclo[3.2.0]heptan-3-one **29** (5 mg, 0.03 mmol, 10%) as a clear, colourless oil:

Characterised as a single diastereoisomer

n_{max} ($CDCl_3$ sol$^{\underline{n}}$)/cm^{-1} 3011s (OH), 2402m, 1755m (C=O), 1514w, 1420w, 1225s and 1015w; d_H (400 MHz, $CDCl_3$) 1.42 (3H, s, CCH_3), 1.49 – 1.66 (4H, m, 1H from $CH_2CH_2CH_2OH$, 2H from CH_2CH_2OH, 1H from CCH_2CH_2CH), 1.73 – 1.78 (1H, m, 1H from $CH_2CH_2CH_2OH$), 2.10 – 2.20 (3H, m, 3H from CCH_2CH_2CH), 2.45 – 2.47 (1H, m, CH_2CHCH), 2.54 (1H, dt, *J* 2.7, 5.9, CHC(O)) and 3.61 (2H, t, *J* 5.7, CH_2OH); d_C (100 MHz, $CDCl_3$) 21.4 (CH_2), 24.8 (CCH_3), 29.1 ($CH_2CH_2CH_2OH$), 30.7 (CH_2CH_2OH), 33.5 (CH_2), 45.1 (CH_2CHCH), 49.6 (CHC(O)), 62.7 (CH_2OH), 87.0 ($C(CH_3)O$) and 180.6 (C(O)); *m/z* (CI mode, isobutane) 185 ((M + H)$^+$ 100), 167 (15), 139 (2), 129 (10), 97 (3), 85 (85) and 71 (7); (Found: (M + H)$^+$, 185.1177. $C_{10}H_{17}O_3$ requires *M*, 185.1178).

Further elution then gave *rel*-(1R, 2R)-ethyl-2-hydroxy-1-(3-hydroxy-propyl)-2-methyl-cyclopentanoate **27** (20 mg, 0.09 mmol, 41%) as a clear, colourless oil: n_{max} (neat)/cm^{-1} 3406bs (OH), 2958m, 1709s (C=O), 1446m, 1369m, 1265m, 1180m, 1122m, 1055m and 1030m; d_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.1, CH_2CH_3), 1.22 – 1.29 (1H, m, 1H from CH_2), 1.30 (3H, s, C(OH)CH_3), 1.37 – 1.42 (1H, m, 1H from CH_2), 1.47 – 1.53 (2H, m, CH_2), 1.58 – 1.79 (5H, m, 1H from CH_2C(OH) 4H from CH_2), 2.33 – 2.41 (1H, m, 1H from CH_2C(OH)), 3.50 – 3.60 (2H, m, CH_2OH) and 4.11 (2H, q, *J* 7.1, OCH_2CH_3); d_C (100 MHz, $CDCl_3$) 14.7 (OCH_2CH_3), 20.0 (CH_2), 23.6 (C(OH)CH_3), 29.2 (CH_2), 30.9 (CH_2), 31.6 (CH_2C(OH)), 40.1 (CH_2), 60.3 (CC(O)), 61.0 (OCH_2CH_3), 63.4 (CH_2OH), 83.3 (C(OH)) and 176.1 (C(O)); *m/z* (CI mode, isobutane) 231 ((M + H)$^+$ 100), 213 (100), 185 (70), 167 (90), 139 (30), 113 (5), 99 (5), 85 (5) and 81 (2); (Found: (M + H)$^+$, 231.1585. $C_{12}H_{23}O_4$ requires *M*, 231.1596).

General Cyclobutane-forming Procedure D


30

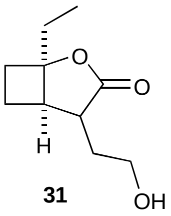
rel-(1R, 4R/S, 5R)-4-(2-Hydroxy-ethyl)-1-methyl-2-oxa-bicyclo[3.2.0]heptan-3-one 30

Dry ^{t}BuOH (6.5 ml) was added to a stirred solution of SmI_2 (0.1 M in THF, 24 ml, 2.40 mmol, 4 eq) at 0°C and the resulting solution was stirred for 10 min. (*E*)-3-(4-Oxo-pentylidene)-dihydro-furan-2-one **6** (100 mg, 0.60 mmol, 1 eq) in THF (2 ml) was added, and the resultant solution stirred at 0°C for 4 h. The reaction was quenched by opening to the air, followed by the addition of aqueous saturated NaCl (10 ml). The aqueous layer was separated and extracted with 80% EtOAc in petroleum ether (40-60°C) (4 x 15 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification by column chromatography (eluting first with 80% EtOAc in petroleum ether (40-60°C), then with 30% Et_2O in $CHCl_3$), gave *rel*-(1R, 4R/S, 5R)-4-(2-hydroxy-ethyl)-1-methyl-2-oxa-bicyclo[3.2.0]heptan-3-one **30** (65 mg, 0.38 mmol, 64%) as a clear, colourless oil:

Characterised as a mixture of diastereoisomers

ν_{max} (neat)/cm^{-1} 3406bs (OH), 2941m, 1745s (C=O), 1383m, 1250m, 1174m, 1122m, 1057m and 949m; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, CH_3 from minor), 1.43 (3H, s, CH_3 from major), 1.64 – 2.23 (12H, m, 3 x CH_2 from minor, 3 x CH_2 from major), 2.48 – 2.50 (1H, m, CH_2C*H*CHC(O) from major), 2.70 (1H, dt, *J* 2.8, 7.5, CH_2CHC*H*C(O) from major), 2.79 – 2.91 (2H, m, 2 x C*H* from minor) and 3.60 – 3.77 (4H, m, CH_2OH from minor, CH_2OH from major); δ_C (100 MHz, $CDCl_3$) 17.2 (*C*H_2 from minor), 21.5 (*C*H_2 from major), 23.7 (*C*H_3 from minor),), 24.8 (*C*H_3 from major), 29.0 (*C*H_2 from minor), 32.2 (*C*H_2 from major), 33.4 (*C*H_2 from minor), 35.3 (*C*H_2 from major), 42.3 (*C*H from minor), 43.2 (*C*H from minor), 45.2 (*C*HCHC(O) from major), 47.2 (CH*C*HC(O) from major), 60.9 (*C*H_2OH from major), 61.7

(*C*H_2OH from minor), 87.5 (*C*(CH_3)O from major), 88.1 (*C*(CH_3)O from minor), 180.1 (*C*(O) from minor) and 181.2 (*C*(O) from major); *m/z* (CI mode, isobutane) 341 (35%), 209 (15), 171 ((M + H)$^+$ 100), 153 (70), 115 (20) and 109 (5); (Found: (M + H)$^+$, 171.1021. $C_9H_{15}O_3$ requires *M*, 171.1021).



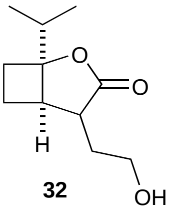
31

rel-(1R, 4R/S, 5R)-1-Ethyl-4-(2-hydroxy-ethyl)-2-oxa-bicyclo[3.2.0]heptan-3-one 31

As for general procedure D. (*E*)-3-(4-Oxo-hexylidene)-dihydro-furan-2-one **7** (40 mg, 0.22 mmol, 1 eq), after reaction time of 1 h and purification of the crude product mixture by column chromatography (eluting with 60% EtOAc in petroleum ether (40-60°C)) gave *rel*-(1R, 4R/S, 5R)-1-ethyl-4-(2-hydroxy-ethyl)-2-oxa-bicyclo[3.2.0]heptan-3-one **31** (12 mg, 0.07 mmol, 31%) as a clear, colourless oil:

Characterised as a mixture of diastereoisomers

n_{max} (neat)/cm^{-1} 3406bs (OH), 2941m, 1743s (C=O), 1462m, 1209m, 1132m, 1115m, 1024m and 943m; d_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.4, C*H_3* from minor), 0.88 (3H, t, *J* 7.4, C*H_3* from major), 1.61 – 2.19 (16H, m, 4 x C*H_2* from minor, 4 x C*H_2* from major), 2.47 – 2.50 (1H, m, C*H*CHC(O) from major), 2.71 (1H, dt, *J* 3.0, 7.6, CHC*H*C(O) from major), 2.81 – 2.88 (1H, m, C*H*CHC(O) from minor), 2.91 – 2.98 (1H, m, CHC*H*C(O) from minor) and 3.58 – 3.77 (4H, m, C*H_2*OH from minor, C*H_2*OH from major); d_C (100 MHz, $CDCl_3$) 7.9 (*C*H_3 from minor), 8.0 (*C*H_3 from major), 16.9 (*C*H_2 from minor), 21.8 (*C*H_2 from major), 29.2 (*C*H_2 from minor), 30.3 (*C*H_2 from minor), 30.4 (*C*H_2 from minor), 30.6 (*C*H_2 from major), 31.5 (*C*H_2 from major), 35.3 (*C*H_2 from major), 41.4 (*C*HCHC(O) from minor), 42.8 (CH*C*HC(O) from minor), 43.3 (*C*HCHC(O) from major), 47.2 (CH*C*HC(O) from major), 61.0 (*C*H_2OH from major), 61.7 (*C*H_2OH from minor), 90.3 (*C*(CH_2CH_3)O from major), 91.2 (*C*(CH_2CH_3)O from minor), 180.4 (*C*(O) from minor) and 181.5 (*C*(O) from major); *m/z* (CI mode, isobutane) 223 (5%), 199 (15), 185 ((M + H)$^+$ 100), 183 (50), 167 (20), 115 (15), 113 (2) and 81 (5); (Found: (M + H)$^+$, 185.1179. $C_{10}H_{17}O_3$ requires *M*, 185.1178).



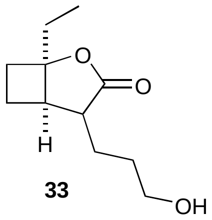
32

***rel*-(1R, 4R/S, 5R)-4-(2-Hydroxy-ethyl)-1-isopropyl-2-oxa-bicyclo[3.2.0]heptan-3-one 32**

As for general procedure D. (*E*)-3-(5-methyl-4-oxo-hexylidene)-dihydro-furan-2-one **8** (50 mg, 0.26 mmol, 1 eq), after reaction time of 1 h and purification of the crude product mixture by column chromatography (eluting with 50% EtOAc in petroleum ether (40-60°C)) gave *rel*-(1R, 4R/S, 5R)-4-(2-hydroxy-ethyl)-1-isopropyl-2-oxa-bicyclo[3.2.0]heptan-3-one **32** (28 mg, 0.14 mmol, 54%) as a clear, colourless oil:

Characterised as a mixture of diastereoisomers

ν_{max} (neat)/cm^{-1} 3410bs (OH), 2962m, 1743s (C=O), 1470m, 1236m, 1209m, 1167m, 1053m and 947m; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.9, CH_3), 0.85 (3H, d, *J* 6.9, CH_3), 0.87 (3H, d, *J* 6.9, CH_3), 0.91 (3H, d, *J* 6.9, CH_3), 1.58 – 2.22 (14H, m, 3 x CH_2 from minor, 3 x CH_2 from major, C*H*(CH_3)$_2$ from minor, C*H*(CH_3)$_2$ from major), 2.52 – 2.54 (1H, m, C*H* from minor), 2.70 – 2.73 (1H, m, C*H* from minor), 2.81 (1H, dt, *J* 1.7, 8.1, C*H* from major), 2.97 (1H, apparent q, *J* 8.1, C*H* from major) and 3.58 – 3.79 (4H, m, C*H*$_2$OH from minor, C*H*$_2$OH from major); δ_C (100 MHz, $CDCl_3$) 14.8 (*C*H_3), 14.9 (*C*H_3), 14.9 (*C*H_3), 15.0 (*C*H_2), 15.2 (*C*H_3), 20.4 (*C*H_2), 27.7 (*C*H_2), 27.9 (*C*H_2), 28.6 (*C*H_2), 32.5 (*C*H(CH_3)$_2$), 33.5 (*C*H(CH_3)$_2$), 33.9 (*C*H_2), 39.1 (*C*H from major), 40.5 (*C*H from minor), 41.5 (*C*H from major), 46.0 (*C*H from minor), 59.7 (*C*H_2OH from minor), 60.2 (*C*H_2OH from major), 91.3 (*C*CH from minor), 92.2 (*C*CH from major). 179.3 (*C*(O) from major) and 180.2 (*C*(O) from minor); *m/z* (CI mode, isobutane) 397 (20%), 237 (15), 199 ((M + H)$^+$ 100), 181 (45), 153 (15) and 95 (35); (Found: (M + H)$^+$, 199.1336. $C_{11}H_{19}O_3$ requires *M*, 199.1334).



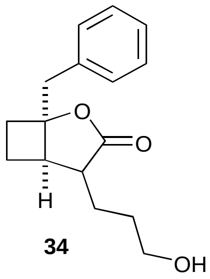
33

rel-(1R, 4R/S, 5R)-1-Ethyl-4-(3-hydroxy-propyl)-2-oxa-bicyclo[3.2.0]heptan-3-one 33

As for general procedure D. A 2:1 mixture of (*E*)-3-(4-oxo-hexylidene)-tetrahydro-pyran-2-one **22*E*** and (*Z*)-3-(4-oxo-hexylidene)-tetrahydro-pyran-2-one **22*Z*** (40 mg, 0.20 mmol, 1 eq), after reaction time of 1 h and purification of the crude product mixture by column chromatography (eluting with 80% EtOAc in petroleum ether (40-60°C)) gave *rel*-(1R, 4R/S, 5R)-1-ethyl-4-(3-hydroxy-propyl)-2-oxa-bicyclo[3.2.0]heptan-3-one **33** (20 mg, 0.10 mmol, 50%) as a clear, colourless oil:

Characterised as a mixture of diastereoisomers

n_{max} (neat)/cm^{-1} 3413bs (OH), 2939m, 1747s (C=O), 1460m, 1207m, 1055m, 1022m and 941m; d_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.4, C*H*$_3$ from minor), 0.88 (3H, t, *J* 7.4, C*H*$_3$ from major), 1.45 – 2.17 (20H, m, 5 x C*H*$_2$ from minor, 5 x C*H*$_2$ from major), 2.42 – 2.46 (1H, m, C*H*CHC(O) from major), 2.52 – 2.56 (1H, m, CHC*H*C(O) from major), 2.61 – 2.68 (1H, m, C*H*CHC(O) from minor), 2.90 (1H, apparent q, *J* 8.0, CHC*H*C(O) from minor) and 3.59 – 3.62 (4H, m, C*H*$_2$OH from minor, C*H*$_2$OH from major); d_C (100 MHz, $CDCl_3$) 7.9 (*C*H$_3$ from minor), 8.1 (*C*H$_3$ from major), 16.3 (*C*H$_2$), 21.7 (*C*H$_2$), 22.6 (*C*H$_2$), 29.0 (*C*H$_2$), 30.3 (*C*H$_2$), 30.4 (*C*H$_2$), 30.6 (*C*H$_2$), 30.7 (*C*H$_2$), 31.5 (*C*H$_2$), 31.6 (*C*H$_2$), 41.1 (CH*C*HC(O) from minor), 43.1 (*C*HCHC(O) from major), 44.4 (*C*HCHC(O) from minor), 49.5 (CH*C*HC(O) from major), 62.7 (*C*H$_2$OH from major), 62.8 (*C*H$_2$OH from minor), 89.7 (*C*(CH_2CH_3)O from major), 90.4 (*C*(CH_2CH_3)O from minor), 179.8 (*C*(O) from minor) and 180.9 (*C*(O) from major); *m/z* (CI mode, isobutane) 200 (10%), 199 ((M + H)$^+$ 100), 181 (10), 169 (2), 129 (5), 115 (2), 85 (10) and 71 (10); (Found: (M + H)$^+$, 199.1335. $C_{11}H_{19}O_3$ requires *M*, 199.1334).



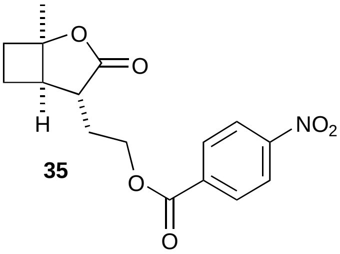
34

rel-(1S, 4R/S, 5R)-1-Benzyl-4-(3-hydroxy-propyl)-2-oxa-bicyclo[3.2.0]heptan-3-one 34

As for general procedure D. (*E*)-3-(4-Oxo-5-phenyl-pentylidene)-tetrahydro-pyran-2-one **23*E*** (20 mg, 0.08 mmol, 1 eq), after reaction time of 2.5 h and purification of the crude product mixture by column chromatography (eluting with 80% EtOAc in petroleum ether (40-60°C)) gave *rel*-(1S, 4R/S, 5R)-1-benzyl-4-(3-hydroxy-propyl)-2-oxa-bicyclo[3.2.0]heptan-3-one **34** (7 mg, 0.03 mmol, 34%) as a clear, colourless oil:

Characterised as a mixture of diastereoisomers

n_{max} (neat)/cm^{-1} 3408bs (OH), 2941m, 1747s (C=O), 1454m, 1261m, 1171m, 1053m and 947; d_H (400 MHz, $CDCl_3$) 0.60 – 0.70 (1H, m, 1H from CH_2 from major), 1.13 – 1.20 (1H, m, 1H from CH_2 from major), 1.30 – 1.99 (9H, m, C*H* from minor, 2 x CH_2 from minor, 2 x CH_2 from major), 2.12 – 2.26 (4H, m, CH_2 from minor, CH_2 from major), 2.34 – 2.40 (1H, m, C*H* from major), 2.49 – 2.55 (1H, m, C*H* from major), 2.82 (1H, d, *J* 14.1, AB system, 1H from CH_2Ph from minor), 2.83 (1H, d, *J* 14.2, AB system, 1H from CH_2Ph from major), 2.95 (1H, apparent q, *J* 7.8, C*H* from minor), 3.03 (1H, d, *J* 14.1, AB system, 1H from CH_2Ph from minor), 3.09 (1H, d, *J* 14.2, AB system, 1H from CH_2Ph from major), 3.35 – 3.45 (2H, m, CH_2OH from major), 3.46 – 3.52 (2H, m, CH_2OH from minor) and 7.13 – 7.29 (10H, m, Ar C*H* from minor, Ar C*H* from major); d_C (100 MHz, $CDCl_3$) 15.3 (CH_2), 20.4 (CH_2), 20.9 (CH_2), 26.4 (CH_2), 29.2 (CH_2), 29.8 (CH_2), 30.0 (CH_2), 31.0 (CH_2), 39.8 (*C*H from minor), 40.7 (*C*H from major), 42.2 (*C*H$_2$Ph from minor), 42.3 (*C*H$_2$Ph from major), 42.7 (*C*H from minor), 48.1 (*C*H from major), 61.2 (*C*H_2OH from major), 61.3 (*C*H_2OH from minor), 87.7 (*C*(CH_2Ph)O from major), 87.8 (*C*(CH_2Ph)O from minor), 125.9 (Ar *C*H from minor), 126.0 (Ar *C*H from major), 127.4 (2 x Ar *C*H from major), 127.5 (2 x Ar *C*H from minor), 128.8 (2 x Ar *C*H from minor), 129.2 (4 (2 x Ar *C*H from major), 134.3 (Ar *C* from minor), 134.5 (Ar *C* from major), 178.2 (*C*(O) from minor) and 179.2 (*C*(O) from major); *m/z* (EI mode) 260 (($M^{+\bullet}$) 10%), 232 (5), 214 (20), 186 (20), 169 (70), 141 (40), 123 (100), 91 (80), 81 (40), 67 (20) and 41 (15); (Found: ($M^{+\bullet}$), 260.1412. $C_{16}H_{20}O_3$ requires *M*, 260.1412).

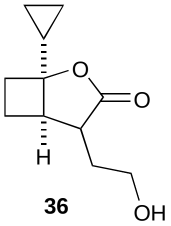


35

rel-(1R, 4R, 5R)-Ethyl-2-(1-methyl-3-oxo-2-oxa-bicyclo[3.2.0]hept-4-yl)-4-nitrobenzoate 35

4-Nitrobenzoyl chloride (46 mg, 0.25 mmol, 2 eq) was added to a stirred solution of 4-(2-hydroxy-ethyl)-1-methyl-2-oxa-bicyclo[3.2.0]heptan-3-one **30** (21 mg, 0.12 mmol, 1 eq) in pyridine (1 ml) at room temperature. The solution was stirred for 2 h before addition of H_2O (dist.) (1 ml). The aqueous layer was separated and extracted with EtOAc (4 x 10 ml). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product. Purification by column chromatography (eluting with 30% Et_2O in $CHCl_3$) gave *rel*-(1R, 4R, 5R)-ethyl-2-(1-methyl-3-oxo-2-oxa-bicyclo[3.2.0]hept-4-yl)-4-nitrobenzoate **35** (20 mg, 0.06 mmol, 51%) as white crystals: mp 130 – 133°C (in EtOH): n_{max} (golden gate)/cm^{-1} 2954w, 1743s (lactone C=O), 1724s (ester C=O), 1520s, 1344m, 1269s, 1236s, 1119s, 1103s, 1011m, 958s, 877s and 839s; d_H (400 MHz, $CDCl_3$) 1.43 (3H, s, CH_3), 1.63 – 1.68 (1H, m, 1H from CCH_2CH_2CH), 1.93 – 2.02 (1H, m, 1H from C$H_2$$CH_2$O), 2.10 – 2.28 (4H, m, 3H from CCH_2CH_2CH, 1H from C$H_2$$CH_2$O), 2.51 – 2.56 (1H, m, C*H*CHC(O)), 2.70 (1H, dt, *J* 3.0, 6.1, CHC*H*C(O)), 4.37 – 4.48 (2H, m, CH_2O), 8.14 (2H, apparent dt, *J* 1.9, 8.9, 2 x Ar C*H*) and 8.23 (2H, apparent dt, *J* 1.9, 8.9, 2 x Ar

C*H*); d$_C$ (100 MHz, $CDCl_3$) 21.4 (1C from C*C*H$_2$*C*H$_2$CH), 24.7 (*C*H$_3$), 31.3 (*C*H$_2$CH$_2$O), 33.6 (1C from C*C*H$_2$*C*H$_2$CH), 44.6 (*C*HCHC(O)), 46.9 (*C*HC(O)), 63.6 (*C*H$_2$O), 86.9 (*C*(CH$_3$)O), 124.0 (2 x Ar *C*H), 131.2 (2 x Ar *C*H), 135.6 (Ar C(O)*C*), 151.1 (Ar *C*NO$_2$), 164.9 (Ar *C*(O)) and 179.7 (*C*(O)O); *m/z* (CI mode, isobutane) 320 ((M + H)$^+$ 100), 290 (50), 171 (15), 153 (10), 138 (5), 120 (25), 113 (5), 97 (5), 85 (5) and 71 (10); (Found: (M + H)$^+$, 320.1135. $C_{16}H_{18}O_6N$ requires *M*, 320.1134).



36

rel-(1S, 4R/S, 5R)-1-Cyclopropyl-4-(2-hydroxy-ethyl)-2-oxa-bicyclo[3.2.0]heptan-3-one 36

As for general procedure E. (*E*)-3-(4-Oxo-4-cyclopropyl-butylidene)-dihydro-furan-2-one **10** (50 mg, 0.26 mmol, 1 eq), after reaction time of 2.5 h and purification of the crude product mixture by column chromatography (eluting with 50% EtOAc in petroleum ether (40-60°C), then with 30% Et$_2$O in CHCl$_3$) gave *rel*-(1S, 4R/S, 5R)-1-cyclopropyl-4-(2-hydroxy-ethyl)-2-oxa-bicyclo[3.2.0]heptan-3-one **36** (36 mg, 0.18 mmol, 70%) as a clear, colourless oil:

Characterised as a mixture of diastereoisomers

n$_{max}$ (neat)/cm^{-1} 3413bs (OH), 2943m, 1743s (C=O), 1238m, 1167m, 1051m and 945m; d$_H$ (400 MHz, CDCl$_3$) 0.28 – 0.32 (4H, m, OCCH(C*H*$_2$)$_2^A$ from minor, OCCH(C*H*$_2$)$_2^A$ from major), 0.46 – 0.52 (4H, m, OCCH(C*H*$_2$)$_2^B$ from minor, OCCH(C*H*$_2$)$_2^B$ from major), 1.02 – 1.10 (2H, m, OCC*H*(CH$_2$)$_2$ from minor, OCC*H*(CH$_2$)$_2$ from major), 1.62 – 2.12 (12H, m, 3 x C*H*$_2$ from minor, 3 x C*H*$_2$ from major), 2.42 – 2.46 (1H, m, C*H* from major), 2.67 – 2.71 (1H, m, C*H* from major), 2.81 – 2.88 (2H, m, 2 x C*H* from minor), 3.57 – 3.62 (1H, m, 1H from C*H*$_2$OH from minor) and 3.68 – 3.78 (3H, m, 1H from C*H*$_2$OH from minor, C*H*$_2$OH from major); d$_C$ (100 MHz, CDCl$_3$) –0.4 (OCH(*C*H$_2$)$_2^{AB}$), –0.3 (OCH(*C*H$_2$)$_2^{AB}$), –0.1 (OCH(*C*H$_2$)$_2^{AB}$),

0.0 (OCH(CH$_2$)$_2$^{AB}), 14.0 (OCH(CH$_2$)$_2$), 14.6 (OCH(CH$_2$)$_2$), 15.1 (CH_2), 20.0 (CH_2), 27.2 (CH_2), 27.5 (CH_2), 28.4 (CH_2), 33.4 (CH_2), 39.1 (CH), 40.7 (CH), 41.4 (CH), 45.1 (CH), 59.1 (CH$_2$OH), 59.8 (CH$_2$OH), 88.4 (CCH), 89.1 (CCH), 178.3 (C(O)) and 179.3 (C(O)); *m/z* (CI mode, isobutane) 197 ((M + H)$^+$ 100), 179 (10), 169 (1), 151(2), 135 (2), 15 (5), 93 (2), 85 (2) and 71 (2); (Found: (M + H)$^+$, 197.1177. $C_{11}H_{17}O_3$ requires *M*, 197.1178).