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

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 SmI₂ (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 (MgSO₄), 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, CDCl₃) 0.87 (3H, s, CH₃), 1.02 (3H, s, CH₃), 1.10 (3H, s, CH₃), 1.52 – 1.59 (1H, m, 1H from C(CH₃)₂CH₂), 1.66 – 1.72 (1H, m, 1H from C(CH₃)₂CH₂CH₂), 1.84 – 1.91 (1H, m, 1H from C(CH₃)₂CH₂), 2.02 – 2.07 (1H, m, 1H from OCH₂CH₂), 2.15 – 2.23 (1H, m, 1H from C(CH₃)₂CH₂CH₂), 2.34 – 2.42 (1H, m, 1H from OCH₂CH₂), 4.09 – 4.15 (1H, m, 1H from OCH₂), 4.23 – 4.28 (1H, m, 1H from OCH₂) and 4.65 (1H, s, OH); δ_{C} (100 MHz, CDCl₃) 19.3 (CH₃), 24.0 (CH₃), 27.6 (CH₃), 33.2 (C(CH₃)₂CH₂CH₂), 35.1 (OCH₂CH₂), 38.7, (C(CH₃)₂CH₂), 46.0 (C(CH₃)₂),

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

55.2 (CC(O)), 65.8 (OCH₂), 84.8 (C(OH)CH₃) and 183.3 (C(O)); *m/z* (EI mode) 198 ((M⁺) 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; C₁₁H₁₈O₃ requires C, 66.64; H, 9.15).

General Oxidation/Olefination Procedure B

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

DMSO (681 μ l, 9.60 mmol, 4 eq) was added to a stirred solution of (COCl)₂ (419 μ l, 4.80 mmol, 2 eq) in CH₂Cl₂ (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 CH₂Cl₂ (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-butylolactonylidene)triphenylphosphorane (1.66 g, 4.80 mmol, 2 eq) was added as a solution in CH₂Cl₂ (20 ml) and the reaction mixture allowed to warm to room temperature and stirred for 16 h. Aqueous saturated NaHCO₃ (10 ml) was then added, and the aqueous layer was separated and extracted with 80% EtOAc in petroleum ether (40-60 $^{\circ}\text{C}$) (4 x 20 ml). The combined organic extracts were dried (MgSO₄), and concentrated *in vacuo* to give the crude product. Purification by column chromatography (eluting with 25% EtOAc in petroleum ether (40-60 $^{\circ}\text{C}$)), gave (*E*)-3-(4-oxo-pentylidene)-dihydro-furan-2-one **6** (399 mg, 2.37 mmol, 99%) as a yellow oil: ν_{max} (neat)/cm⁻¹ 1739s (lactone C=O), 1716s (ketone C=O), 1681s (C=C), 1405m, 1383m, 1238m, 1190m, 1038m, 1021m and 997m; δ_{H} (400 MHz, CDCl₃) 2.19 (3H, s, C(O)CH₃), 2.46 (2H, apparent q, *J* 7.1, CH₂CH=C), 2.67 (2H, t, *J* 7.1 CH₂C(O)), 2.96 (2H, dt, *J* 2.9, 7.5, CH₂CH₂O), 4.41 (2H, t, *J* 7.5, CH₂O) and 6.64 (1H, tt, *J* 2.9, 7.5, CH=C); δ_{C} (100 MHz, CDCl₃) 24.5 (CH₂CH=C), 25.5 (CH=CCH₂), 30.4 (C(O)CH₃), 41.8 (CH₂C(O)), 65.9 (CH₂O), 126.9 (CH=C), 138.9 (CH=C), 171.5 (C(O)O) and

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

(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: $\nu_{\max}$ (neat)/ cm^{-1} 1747s (ester $C=O$), 1709s (ketone $C=O$), 1679s ($C=C$), 1374m, 1352m, 1211m and 1022m; δ_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, $CH=C$); δ_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 ($CH=C$), 171.6 ($C(O)O$) and 209.9 ($C(O)$); m/z (EI mode) 182 ((M^{+}) 45%), 153 (10), 125 (100), 109 (15), 97 (15), 81 (50), 57 (65) and 53 (20); (Found: (M^{+}) , 182.0942. $C_{10}H_{14}O_3$ requires M , 182.0943).

(*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: ν_{max} (neat)/cm⁻¹ 2970w, 1749s (ester C=O), 1707s (ketone C=O), 1680s (C=C), 1468m, 1381m, 1215m, 1194m and 1026m; δ_{H} (400 MHz, CDCl₃) 1.11 (3H, d, *J* 7.0, CH(CH₃)₂), 1.45 (3H, d, *J* 7.0, CH(CH₃)₂), 2.47 (2H, apparent q, *J* 8.8, CH₂CH=C), 2.65 (1H, septet, *J* 7.0, CH(CH₃)₂), 2.79 (2H, t, *J* 6.4, CH₂C(O)), 2.94 – 3.00 (2H, m, CH₂CH₂O), 4.40 (2H, t, *J* 7.4, CH₂O) and 6.63 (1H, tt, *J* 2.9, 7.6, CH=C); δ_{C} (100 MHz, CDCl₃) 18.6 (CH(CH₃)₂), 18.7 (CH(CH₃)₂), 24.6 (CH₂CH=C), 25.5 (CH₂CH₂O), 38.5 (CH₂C(O)), 41.3 (CH(CH₃)₂), 65.9 (CH₂O), 122.6 (CH=C), 139.3 (CH=C), 171.6 (C(O)O) and 213.2 (C(O)); *m/z* (EI mode) 196 ((M⁺) 35%), 153 (25), 125 (100), 109 (30), 81 (50), 79 (30) and 43 (50); (Found: (M⁺), 196.1100. C₁₁H₁₆O₃ requires *M*, 196.1099).

(*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: ν_{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; δ_{H} (400 MHz, CDCl₃) 2.43 (2H, apparent q, *J* 7.1, CH₂CH=C), 2.67 (2H, t,

J 7.1 $\text{CH}_2\text{C}(\text{O})$), 2.91 (2H, dt, *J* 3.0, 7.4, $\text{CH}_2\text{C}=\text{CH}$), 3.72 (2H, s, CH_2Ph), 4.38 (2H, t, *J* 7.4, CH_2O), 6.57 (1H, tt, *J* 3.0, 7.4, $\text{CH}=\text{C}$), 7.20 – 7.22 (1H, m, Ar *CH*), 7.26 – 7.32 (2H, m, 2 x Ar *CH*) and 7.34 – 7.38 (2H, m, 2 x Ar *CH*); $\square_{\text{C}}$ (100 MHz, CDCl_3) 24.5 ($\text{CH}_2\text{CH}=\text{C}$), 25.4 ($\text{CH}_2\text{C}=\text{CH}$), 40.2 ($\text{CH}_2\text{C}(\text{O})$), 50.7 (CH_2Ph), 65.8 (CH_2O), 127.0 ($\text{CH}=\text{C}$), 127.7 (Ar *CH*), 129.3 (2 x Ar *CH*), 129.7 (2 x Ar *CH*), 134.2 (Ar *C*), 138.8 ($\text{CH}=\text{C}$), 171.5 ($\text{C}(\text{O})\text{O}$) and 206.9 ($\text{C}(\text{O})$); *m/z* (EI mode) 244 ((M^+) 37%), 223 (5), 205 (2), 176 (5), 153 (100), 125 (45), 119 (65), 91 (100), 81 (50), 65 (40) and 41 (22); (Found: (M^+) , 244.1099. $\text{C}_{15}\text{H}_{16}\text{O}_3$ requires *M*, 244.1099).

(*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% Et₂O in petroleum ether (30-40°C): $\square_{\text{max}}$ (neat)/cm⁻¹ 2951m, 2899m, 1738s (lactone C=O), 1693s (ketone C=O), 1678s (C=C), 1496m, 1311m and 815m; $\square_{\text{H}}$ (400 MHz, CDCl_3) 0.79 $\square$ 0.85 (2H, m, $\text{CH}(\text{OH})\text{CHCH}_2^{\text{A}}$), 0.94 $\square$ 0.98 (2H, m, $\text{CH}(\text{OH})\text{CHCH}_2^{\text{B}}$), 1.78 $\square$ 1.90 (1H, m, $\text{CH}(\text{OH})\text{CH}$), 2.40 (2H, apparent q, *J* 7.3, $\text{CH}_2\text{CH}=\text{C}$), 2.72 (2H, t, *J* 7.3, $\text{CH}_2\text{C}(\text{O})$), 2.86 (2H, apparent q, *J* 7.4, $\text{CH}_2\text{C}=\text{CH}$), 4.30 (2H, t, *J* 7.4, CH_2O) and 6.60 (1H, tt, *J* 1.6, 7.3, $\text{CH}=\text{C}$); $\square_{\text{C}}$ (100 MHz, CDCl_3) 9.3 ($\text{C}(\text{OH})\text{CHCH}_2^{\text{A}}$), 9.4 ($\text{C}(\text{OH})\text{CHCH}_2^{\text{B}}$), 19.0 ($\text{CH}(\text{OH})\text{CH}$), 22.7 ($\text{CH}_2\text{CH}=\text{C}$), 23.5 ($\text{CH}_2\text{C}=\text{CH}$), 39.6 ($\text{CH}_2\text{C}(\text{O})$), 63.9 (CH_2O), 124.7 ($\text{CH}=\text{C}$), 137.3 ($\text{CH}=\text{C}$), 169.6 ($\text{C}(\text{O})\text{O}$) and 207.3 ($\text{C}(\text{O})$); *m/z* (EI mode) 194 ((M^+) , 28%), 125 (100), 85 (50), 83 (76), 69 (83), 47 (16) and 41 (39); (Found: (M^+) 194.0942. $\text{C}_{11}\text{H}_{14}\text{O}_3$ requires *M*, 194.0943).

rel-(5R, 6R)-6-Hydroxy-6-methyl-2-oxa-spiro[4.4]nonan-1-one 11²

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: ν_{max} (neat)/cm⁻¹ 3480bs (OH), 2971s, 2874s, 1758s (C=O), 1450m, 1376s, 1302w, 1200m, 1149m, 1103m, 1030m, 1001m, 958m and 937m; δ_{H} (400 MHz, CDCl₃) 1.23 (3H, s, C(OH)CH₃), 1.58 – 1.75 (3H, m, 1H from CH₂CH₂CH₂C(OH), 1H from CH₂CH₂C(OH), 1H from CH₂C(OH)), 1.88 (1H, ddd, *J* 3.0, 6.7, 12.7, 1H from CH₂CH₂O), 1.92 – 1.99 (2H, m, 1H from CH₂CH₂CH₂C(OH), 1H from CH₂CH₂C(OH)), 2.22 – 2.31 (2H, m, 1H from CH₂C(OH), 1H from CH₂CH₂O), 3.60 (1H, s, OH), 4.15 (1H, dt, *J* 6.7, 9.0, 1H from CH₂O) and 4.27 (1H, dt, *J* 3.0, 9.0, 1H from CH₂O); δ_{C} (100 MHz, CDCl₃) 20.7 (CH₂CH₂C(OH)), 23.3 (CH₃), 32.4 (CH₂CH₂O), 34.1 (CH₂C(OH)), 39.0 (CH₂CH₂CH₂C(OH)), 55.0 (CC(O)), 65.8 (CH₂O), 82.2 (C(OH)) and 182.0 (C(O)); *m/z* (EI mode) 170 ((M⁺) 7%), 155 (2), 128 (7), 112 (40), 99 (100), 72 (25), 53 (10) and 43 (35); (Found: (M⁺), 170.0942. C₉H₁₄O₃ requires *M*, 170.0943).

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

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: ν_{max} (neat)/cm⁻¹ 3477bs (OH), 2968s, 1740s (C=O), 1371s, 1190s, 1032m, 1022m and 962m; δ_{H} (400 MHz, CDCl₃) 0.90 (3H, t, *J* 7.4, CH₃), 1.43 – 1.52 (2H, m, 1H from CH₂CH₃, 1H from CH₂C), 1.54 – 1.62 (1H, m, 1H from CH₂CH₃), 1.63 – 1.69 (1H, m, 1H from CH₂CH₂C), 1.72 – 1.78 (1H, m, 1H from CH₂C(OH)), 1.85 – 1.96 (3H, m, 1H from CH₂CH₂O, 1H from CH₂C, 1H from CH₂CH₂C), 2.20 – 2.26 (2H, m, 1H from CH₂C(OH), 1H from CH₂CH₂O), 3.92 (1H, s, OH), 4.15 (1H, dt, *J* 6.8, 9.2, 1H from CH₂O) and 4.28 (1H, dt, *J* 2.7, 9.2, 1H from CH₂O); δ_{C} (100 MHz, CDCl₃) 8.7 (CH₃), 20.7 (CH₂CH₂C), 29.1 (CH₂CH₃), 30.2 (CH₂CH₂O), 34.7 (CH₂C(OH)), 36.9 (CH₂C), 54.0 (C), 65.7 (CH₂O), 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. C₁₀H₁₇O₃ requires *M*, 185.1178).

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)): ν_{max} (neat)/cm⁻¹ 3446bs (OH), 2966s, 1734s (C=O), 1470m, 1441m, 1371m, 1186m and 1018m; δ_{H} (400 MHz, CDCl₃) 0.75 (3H, d, *J* 6.7, CH(CH₃)₂), 0.93 (3H, d, *J* 6.7, CH(CH₃)₂), 1.40 – 1.45 (1H, m, 1H from CH₂C), 1.65 – 1.70 (1H, m, 1H from CH₂CH₂C), 1.77 – 1.83 (3H, m, 1H from CH(CH₃)₂, 1H from CH₂C(OH)), 1.91 – 1.98 (2H, m, 1H from CH₂C, 1H from CH₂CH₂C), 1H from CH₂CH₂O), 2.20 – 2.28 (2H, m, 1H from CH₂C(OH)), 1H from CH₂CH₂O), 4.15 (1H,

dt, J 5.4, 9.1, 1H from CH_2O), 4.32 (1H, s, OH) and 4.33 (1H, dt, J 1.7, 9.1, 1H from CH_2O); $\square_{\text{C}}$ (100 MHz, CDCl_3) 17.4 ($\text{CH}(\text{CH}_3)_2$), 18.4 ($\text{CH}(\text{CH}_3)_2$), 20.8 ($\text{CH}_2\text{CH}_2\text{C}$), 30.8 ($\text{CH}_2\text{CH}_2\text{O}$), 33.7 ($\text{CH}(\text{CH}_3)_2$), 35.5 ($\text{CH}_2\text{C}(\text{OH})$), 38.2 (CH_2C), 52.8 (C), 65.6 (CH_2O), 87.2 ($\text{C}(\text{OH})$) and 183.9 ($\text{C}(\text{O})$); m/z (EI mode) 198 ((M^+) 5%), 180 (3), 155 (100), 152 (5), 127 (10), 99 (45), 83 (80), 71 (15), 55 (20) and 43 (17); (Found: (M^+) , 198.1257. $\text{C}_{11}\text{H}_{18}\text{O}_3$ requires M , 198.1256).

***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)): $\square_{\text{max}}$ (neat)/ cm^{-1} 3428bs (OH), 3026w, 2978w, 1752s, (C=O), 1456m, 1380m, 1225m, 1183m and 1033m; $\square_{\text{H}}$ (400 MHz, CDCl_3) 1.61 – 1.80 (4H, m, $\text{CH}_2\text{CH}_2\text{C}(\text{OH})$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{OH})$), 1.89 – 1.98 (2H, m, 1H from $\text{CH}_2\text{C}(\text{OH})$, 1H from $\text{CH}_2\text{CH}_2\text{O}$), 2.21 – 2.29 (1H, m, 1H from $\text{CH}_2\text{C}(\text{OH})$), 2.46 – 2.54 (1H, m, 1H from $\text{CH}_2\text{CH}_2\text{O}$), 2.78 (2H, apparent s, CH_2Ph), 3.78 (1H, s, OH), 4.17 (1H, apparent dt, J 2.6, 9.0, 1H from CH_2O), 4.32 (1H, apparent dt, J 2.6, 9.0, 1H from CH_2O) and 7.14 – 7.24 (5H, m, Ar CH); $\square_{\text{C}}$ (100 MHz, CDCl_3) 20.4 (CH_2C), 31.9 ($\text{CH}_2\text{CH}_2\text{O}$), 34.6 ($\text{CH}_2\text{C}(\text{OH})$), 36.6 ($\text{CH}_2\text{CH}_2\text{C}(\text{OH})$), 41.9 (CH_2Ph), 54.6 (C), 65.6 (CH_2O), 84.5 ($\text{C}(\text{OH})$), 127.1 (Ar CH), 128.5 (2 x Ar CH), 130.7 (2 x Ar CH), 137.2 (Ar C) and 182.0 ($\text{C}(\text{O})$); m/z (EI mode) 246 ((M^+) 5%), 156 (15), 155 (100), 111 (65), 92 (95), 91 (60), 55 (20) and 41 (15); (Found: (M^+) , 246.1257. $\text{C}_{15}\text{H}_{18}\text{O}_3$ requires M , 246.1256).

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% Et₂O in petroleum ether (30-40°C): ν_{max} (neat)/cm⁻¹ 3050(OH), 2759w, 1743s (C=O), 1384m, 1182m, 1076m, 1018m and 953m; δ_{H} (400 MHz, CDCl₃) 0.27 $\square$ 0.37 (3H, m, 2H from C(OH)CHCH₂^A, 1H from C(OH)CHCH₂^B), 0.46 $\square$ 0.50 (1H, m, 1H from C(OH)CHCH₂^B), 0.80 $\square$ 0.83 (1H, m, C(OH)CH), 1.63 $\square$ 1.83 (4H, m, 1H from CH₂C(OH), 3H from CH₂), 1.89 $\square$ 1.97 (2H, m, 1H from CH₂CH₂O, 1H from CH₂), 2.26 $\square$ 2.28 (1H, m, 1H from CH₂C(OH)), 2.50 $\square$ 2.55 (1H, m, 1H from CH₂CH₂O), 3.62 (1H, s, OH), 4.20 (1H, dt, *J* 7.2, 8.5, 1H from CH₂O) and 4.29 $\square$ 4.34 (1H, td, *J* 4.2, 8.5, 1H from CH₂O); δ_{C} (100 MHz, CDCl₃) $\square$ 0.67 (C(OH)CHCH₂^A), 0.0 (C(OH)CHCH₂^B), 14.2 (C(OH)CH), 19.9 (CH₂), 31.4 (CH₂CH₂O), 34.3 (CH₂C(OH)), 36.6 (CH₂), 54.2 (CC(O)), 65.3 (CH₂O), 82.2 (C(OH)) and 182.1 (C(O)); *m/z* (EI mode) 196 ((M⁺), 26%), 112 (79), 99 (59), 98 (32), 85 (65), 83 (100), 69 (50) 48 (19) and 41 (24); (Found: (M⁺) 196.1100. C₁₁H₁₆O₃ requires *M*, 196.1099).

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

A solution of LDA was prepared by the addition of diisopropylamine (802 μ l, 5.70 mmol, 2 eq) to a stirred solution of ⁿBuLi (2.5 M in Hexanes, 2.85 ml, 5.70 mmol, 2 eq) in THF (2.5 ml) at -5°C , 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 15°C and the solution stirred for 10 min. A solution of diethylchlorophosphate (420 μ l, 2.85 mmol, 1 eq) in THF (2 ml) was then added *via* cannula, whereupon the temperature rose to 25°C . 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 ($40-60^{\circ}\text{C}$) 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, CHP), 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 CH) and 7.24 – 7.28 (2H, m, 2 x Ar CH); 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, CHP), 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 CH), 128.5 (2 x Ar CH), 129.1 (2 x Ar CH), 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^+) 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^+), 311.1285. $\text{C}_{15}\text{H}_{22}\text{O}_4\text{NP}$ requires M , 311.1286).

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: ν_{max} (neat)/ cm^{-1} 2729s, 1716bs (2 x C=O), 1428bs, 1170w, 1132w, 1080w, 961m and 879m; δ_{H} (400 MHz, CDCl_3) 2.23 (3H, s, CH_3), 2.77 (4H, s, 2 x CH_2) and 9.83 (1H, s, CHO); δ_{C} (100 MHz, CDCl_3) 30.2 (CH_3), 35.9 ($\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 27.8 (CH_2CHO), 200.8 (CHO) and 206.8 ($\text{C}(\text{O})$); m/z (CI mode, isobutane) 101 ($(\text{M} + \text{H})^+$ 20%), 57 (100) and 56 (10); (Found: $(\text{M} + \text{H})^+$, 101.0602. $\text{C}_5\text{H}_9\text{O}_2$ requires M , 101.0603).

4-Oxo-hexanal **19**⁴

DMSO (361 μl , 5.08 mmol, 4 eq) was added to a stirred solution of $(\text{COCl})_2$ (222 μl , 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

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 (MgSO₄), 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: ν_{max} (neat)/cm⁻¹ 2980s, 1735s (aldehyde C=O), 1719s (ketone C=O), 1459s, 1420s, 1116m and 1089m; δ_{H} (400 MHz, CDCl₃) 1.01 (3H, t, *J* 7.3, C(O)CH₂CH₃), 2.41 (2H, q, *J* 7.3, C(O)CH₂), 2.64 – 2.72 (4H, m, 2 x CH₂) and 9.70 (1H, s, CHO); δ_{C} (100 MHz, CDCl₃) 8.2 (CH₃), 34.6 (CH₂), 36.3 (C(O)CH₂), 37.9 (CH₂), 200.9 (CHO) 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. C₆H₁₁O₂ requires *M*, 115.0759).

4-Oxo-5-phenyl-pentanal **20**⁵

DMSO (261 μ l, 3.68 mmol, 4 eq) was added to a stirred solution of (COCl)₂ (161 μ l, 1.84 mmol, 2 eq) in CH₂Cl₂ (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 CH₂Cl₂ (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 NaHCO₃ (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 (MgSO₄), 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: ν_{max} (neat)/cm⁻¹ 2826m, 2727m, 1702bs (2 x C=O), 1603m, 1584m, 1498m, 1454m, 1413m, 1092m, 1036m and 1002w; δ_{H} (400 MHz, CDCl₃) 2.64 – 2.72 (4H, m, 2 x CH₂), 3.69 (2H, s,

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

CH_2Ph), 7.14 – 7.35 (5H, m, 5 x Ar CH) and 9.71 (1H, s, CHO); δ_{C} (100 MHz, CDCl_3) 34.4 (CH_2), 37.9 (CH_2), 50.4 (CH_2Ph), 127.5 (Ar CH), 129.2 (2 x Ar CH), 129.8 (2 x Ar CH), 134.4 (Ar C), 200.7 (CHO) and 206.6 (C(O)); m/z (EI mode) 176 ((M^+) 20%), 165 (5), 148 (5), 117 (3), 115 (3), 85 (100), 65 (15), 57 (10) and 51 (5); (Found: (M^+) , 176.0836. $\text{C}_{11}\text{H}_{12}\text{O}_2$ requires M , 176.0837).

General Horner-Wittig Olefination Procedure C

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

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 **21Z** (301 mg, 1.65 mmol, 39%) as a pale yellow oil: δ_{max} (neat)/ cm^{-1} 2928s, 2861s, 1733s (C=O), 1635s (C=C), 1478m, 1449m, 1116m, 1061m, 1028m and 976m; δ_{H} (400 MHz, CDCl_3) 1.72 – 1.76 (2H, m, OCH_2CH_2), 1.99 (3H, s, $\text{C}(\text{O})\text{CH}_3$), 2.39 (2H, dt, J 1.6, 5.2, $\text{CH}=\text{CCH}_2$), 2.46 (2H, t, J 7.0, $\text{CH}_2\text{C}(\text{O})$), 2.65 (2H, apparent q, J 7.0, $\text{CH}_2\text{CH}=\text{C}$), 4.11 (2H, t, J 5.4, OCH_2) and 5.93 (1H, tt, J 1.6, 7.5, $\text{CH}=\text{C}$); δ_{C} (100

MHz, CDCl₃) 23.7 (OCH₂CH₂), 24.5 (CH₂CH=C), 29.7 (CH=CCH₂), 30.1 (C(O)CH₃), 43.2 (CH₂C(O)), 69.1 (OCH₂), 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 **21E** (120 mg, 0.66 mmol, 16%) as a pale yellow oil: ν_{max} (neat)/cm⁻¹ 2901s, 1727s (C=O), 1636s (C=C), 1479m, 1438m, 1313m, 1274m, 1159m, 1129m, 1073m and 967m; δ_{H} (400 MHz, CDCl₃) 1.75 –1.81 (2H, m, CH₂CH₂O), 2.01 (3H, s, C(O)CH₃), 2.24 (2H, apparent q, *J* 7.2, CH₂CH=C), 2.42 (2H, dt, *J* 2.1, 7.2, CH=CCH₂), 2.47 (2H, t, *J* 7.2, CH₂C(O)), 4.15 (2H, t, *J* 5.3, CH₂O) and 6.75 (1H, tt, *J* 2.1, 7.3, CH=C); δ_{C} (100 MHz, CDCl₃) 22.6 (CH₂CH=C), 23.0 (CH₂CH₂O), 24.0 (CH=CCH₂), 30.4 (C(O)CH₃), 42.0 (CH₂C(O)), 69.0 (CH₂O), 126.9 (CH=C), 144.5 (CH=C), 166.8 (C(O)O) and 207.3 (C(O)); *m/z* (EI mode) 182 ((M⁺) 15%), 164 (1), 139 (100), 125 (5), 111 (10), 93 (15), 84 (15), 67 (15) and 43 (35); (Found: (M⁺), 182.0942. C₁₀H₁₄O₃ requires *M*, 182.0943).

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

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 **22Z** (29 mg, 0.15 mmol, 17%) as a yellow oil: ν_{max} (neat)/cm⁻¹ 2974w, 1709s (C=O), 1633s (C=C), 1398m, 1375m, 1124m and 1072m; δ_{H} (400 MHz, CDCl₃) 0.99 (3H, t, *J* 7.3, CH₂CH₃), 1.85 (2H, apparent quintet, *J* 6.6, OCH₂CH₂), 2.36 (2H, q, *J* 7.3, CH₂CH₃), 2.48, (2H, dt, *J* 1.6, 7.1, CH=CCH₂), 2.53 (2H, t, *J* 7.1 CH₂C(O)), 2.76 (2H,

apparent q, J 7.1, $\text{CH}_2\text{CH}=\text{C}$), 4.21 (2H, t, J 5.5, CH_2O) and 6.03 (1H, tt, J 1.6, 7.6, $\text{CH}=\text{C}$); δ_{C} (100 MHz, CDCl_3) 8.2 (CH_3), 23.7 (OCH_2CH_2), 24.6 ($\text{CH}_2\text{CH}=\text{C}$), 29.7 ($\text{CH}=\text{CCH}_2$), 30.1 (CH_2CH_3), 41.8 ($\text{CH}_2\text{C}(\text{O})$), 69.1 (CH_2O), 126.1 ($\text{CH}=\text{C}$), 146.4 ($\text{CH}=\text{C}$), 166.0 ($\text{C}(\text{O})\text{O}$) and 211.2 ($\text{C}(\text{O})$).

Further elution gave (*E*)-3-(4-Oxo-hexylidene)-tetrahydro-pyran-2-one **22E** (76 mg, 0.39 mmol, 44%) as a yellow oil: δ_{max} (neat)/ cm^{-1} 2974m, 1704s ($\text{C}=\text{O}$), 1632s ($\text{C}=\text{C}$), 1394m, 1254m, 1169m and 1074m; δ_{H} (400 MHz, CDCl_3) 1.00 (3H, t, J 7.3, CH_2CH_3), 1.86 (2H, apparent quintet, J 6.6, $\text{CH}_2\text{CH}_2\text{O}$), 2.33 (2H, apparent t, J 7.4, $\text{CH}_2\text{CH}=\text{C}$), 2.38 (2H, q, J 7.3, CH_2CH_3), 2.52 (2H, dt, J 2.3, 7.4, $\text{CH}=\text{CCH}_2$), 2.54 (2H, t, J 7.4, $\text{CH}_2\text{C}(\text{O})$), 4.26 (2H, t, J 5.8, CH_2O) and 6.84 (1H, tt, J 2.3, 7.4, $\text{CH}=\text{C}$); δ_{C} (100 MHz, CDCl_3) 8.1 (CH_2CH_3), 22.7 ($\text{CH}_2\text{CH}=\text{C}$), 23.0 ($\text{CH}_2\text{CH}_2\text{O}$), 24.0 ($\text{CH}=\text{CCH}_2$), 36.4 (CH_2CH_3), 40.6 ($\text{CH}_2\text{C}(\text{O})$), 69.0 (CH_2O), 126.8 ($\text{CH}=\text{C}$), 144.8 ($\text{CH}=\text{C}$), 166.9 ($\text{C}(\text{O})\text{O}$) and 210.1 ($\text{C}(\text{O})$); m/z (EI mode) 196 ($(\text{M}^{+\bullet})$ 55%), 167 (10), 139 (100), 125 (20), 111 (30), 93 (50), 67 (40), 57 (65) and 41 (25); (Found: $(\text{M}^{+\bullet})$, 196.1100. $\text{C}_{11}\text{H}_{16}\text{O}_3$ requires M , 196.1099).

23E

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

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 **23E** (68 mg, 0.26 mmol, 46%) as a yellow oil: δ_{max} (neat)/ cm^{-1} 2897w, 1707s ($\text{C}=\text{O}$), 1632s ($\text{C}=\text{C}$), 1496m, 1396m, 1259m, 1167m and 1074m; δ_{H} (400 MHz, CDCl_3) 1.84 (2H, apparent quintet, J 6.5, $\text{CH}_2\text{CH}_2\text{O}$), 2.29 (2H, apparent q, J 7.2, $\text{CH}_2\text{CH}=\text{C}$), 2.46 (2H, apparent t, J 7.2, $\text{CH}=\text{CCH}_2$), 2.56 (2H, t, J 7.2,

$\text{CH}_2\text{C}(\text{O})$), 3.62 (2H, s, CH_2Ph), 4.22 (2H, t, J 5.4, CH_2O), 6.78 (1H, tt, J 2.4, 7.2, $\text{CH}=\text{C}$) and 7.05 – 7.32 (5H, m, Ar CH); δ_{C} (100 MHz, CDCl_3) 22.7 ($\text{CH}_2\text{CH}=\text{C}$), 23.0 ($\text{CH}_2\text{CH}_2\text{O}$), 24.0 ($\text{CH}=\text{CCH}_2$), 40.3 ($\text{CH}_2\text{C}(\text{O})$), 50.7 (CH_2Ph), 69.0 (CH_2O), 126.9 ($\text{CH}=\text{C}$), 127.6 (Ar CH), 129.2 (2 x Ar CH), 129.8 (2 x Ar CH), 134.3 (Ar C), 144.4 ($\text{CH}=\text{C}$), 166.8 ($\text{C}(\text{O})\text{O}$) and 207.1 ($\text{C}(\text{O})$); m/z (EI mode) 258 ($(\text{M}^{+\bullet})$ 35%), 184 (2), 167 (100), 139 (30), 121 (15), 91 (70), 65 (15) and 55 (10); (Found: $(\text{M}^{+\bullet})$, 258.1256. $\text{C}_{16}\text{H}_{18}\text{O}_3$ requires M , 258.1256).

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

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 -78°C . 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 **24Z** (16 mg, 0.06 mmol, 16%) as a pale yellow oil: δ_{max} (CDCl_3 solⁿ)/ cm^{-1} 2255s, 1714m (ketone $\text{C}=\text{O}$), 1677m (amide $\text{C}=\text{O}$), 1651m ($\text{C}=\text{C}$), 1440w, 1425w, 1383w, 1278w, 1162w and 1094w; δ_{H} (400 MHz, CDCl_3) 2.01 (3H, s, $\text{C}(\text{O})\text{CH}_3$), 2.44 (2H, t, J 7.1, $\text{CH}_2\text{C}(\text{O})$), 2.48 (2H, dt, J 2.4, 5.1, $\text{CH}=\text{CCH}_2$), 2.90 (2H, apparent q, J 7.2, $\text{CH}_2\text{CH}=\text{C}$), 3.06

(2H, t, J 5.1, CH_2N), 4.34 (2H, s, CH_2Ph), 5.76 (1H, tt, J 2.4, 7.8, $\text{C}=\text{CH}$) 7.07 – 7.14 (3H, m, 3 x Ar CH) and 7.16 – 7.22 (2H, m, 2 x Ar CH); δ_{C} (100 MHz, CDCl_3) 21.7 ($\text{CH}_2\text{CH}=\text{C}$), 25.8 ($\text{CH}=\text{CCH}_2$), 30.0 ($\text{C}(\text{O})\text{CH}_3$), 44.0 ($\text{CH}_2\text{C}(\text{O})$), 44.1 (CH_2N), 47.2 (CH_2Ph), 127.9 (Ar CH), 128.6 (2 x Ar CH), 129.1 (2 x Ar CH), 130.8 (Ar C), 135.3 ($\text{CH}=\text{C}$), 136.9 ($\text{CH}=\text{C}$), 168.7 ($\text{C}(\text{O})\text{N}$) and 209.0 ($\text{C}(\text{O})$).

Further elution gave (*E*)-1-benzyl-3-(4-oxo-pentylidene)-pyrrolidin-2-one **24E** (52 mg, 0.20 mmol, 53%) as a pale yellow oil: δ_{max} (CDCl_3 solⁿ)/ cm^{-1} 2920m, 1714s (ketone $\text{C}=\text{O}$), 1680 (amide $\text{C}=\text{O}$) 1670s ($\text{C}=\text{C}$), 1495m, 1448m, 1427m, 1360w, 1286m, 1256m and 1165w; δ_{H} (400 MHz, CDCl_3) 2.00 (3H, s, $\text{C}(\text{O})\text{CH}_3$), 2.30 (2H, apparent q, J 7.4, $\text{CH}_2\text{CH}=\text{C}$), 2.44 (2H, t, J 7.2, $\text{CH}_2\text{C}(\text{O})$), 2.52 (2H, dt, J 2.7, 6.6, $\text{CH}=\text{CCH}_2$), 3.13 (2H, t, J 6.6, CH_2N), 4.38 (2H, s, CH_2Ph), 6.23 (1H, tt, J 2.7, 7.4, $\text{CH}=\text{C}$) 7.08 – 7.14 (3H, m, 3 x Ar CH) and 7.15 – 7.19 (2H, m, 2 x Ar CH); δ_{C} (100 MHz, CDCl_3) 22.1 ($\text{CH}=\text{CCH}_2$), 23.6 ($\text{CH}_2\text{CH}=\text{C}$), 30.5 ($\text{C}(\text{O})\text{CH}_3$), 42.4 ($\text{CH}_2\text{C}(\text{O})$), 44.1 (CH_2N), 47.5 (CH_2Ph), 128.0 (Ar CH), 128.7 (2 x Ar CH), 129.1 (2 x Ar CH), 132.9 (Ar C), 131.4 ($\text{CH}=\text{C}$), 136.8 ($\text{CH}=\text{C}$), 168.6 ($\text{C}(\text{O})\text{N}$) and 207.8 ($\text{C}(\text{O})$); m/z (EI mode) 257 ((M^+) 45%), 256 (1), 214 (70), 186 (20), 171 (7), 170 (5), 118 (10), 104 (4), 91 (100), 65 (12) and 43 (22); (Found: (M^+), 257.1417. $\text{C}_{16}\text{H}_{19}\text{O}_2\text{N}$ requires M , 257.1416).

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 **21Z** and (*E*)-3-(4-oxo-pentylidene)-tetrahydro-pyran-2-one **21E** (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: δ_{max} (neat)/ cm^{-1} 3392bs (OH), 2953s,

1714s (C=O), 1452m, 1261m, 1194m, 1173m, 1122m, 1055m and 1007m; δ_{H} (400 MHz, CDCl_3) 1.22 – 1.38 (2H, m, 1H from $\text{CH}_2\text{CH}_2\text{OH}$, 1H from CH_2), 1.33 (3H, s, CH_3), 1.45 – 1.57 (2H, m, 1H from $\text{CH}_2\text{CH}_2\text{OH}$, 1H from CH_2), 1.59 – 1.66 (1H, m, 1H from $\text{CH}_2\text{C}(\text{OH})$), 1.69 – 1.82 (4H, m, 4H from CH_2), 2.35 – 2.42 (1H, m, 1H from $\text{CH}_2\text{C}(\text{OH})$), 3.55 – 3.61 (2H, m, CH_2O) and 3.65 (3H, s, OCH_3); δ_{C} (100 MHz, CDCl_3) 20.1 (CH_2), 23.6 ($\text{C}(\text{OH})\text{CH}_3$), 29.2 (CH_2), 31.0 (CH_2), 31.6 ($\text{CH}_2\text{C}(\text{OH})$), 40.1 (CH_2), 52.2 (OCH_3), 60.5 (C), 63.4 (CH_2O), 83.4 ($\text{C}(\text{OH})$) and 176.6 ($\text{C}(\text{O})$); m/z (CI mode, isobutane) 217 ($(\text{M} + \text{H})^+$ 25%), 199 (100), 185 (40), 171 (35), 167 (30), 156 (5), 139 (10), 113 (10), 97 (15) and 85 (25); (Found: $(\text{M} + \text{H})^+$, 217.1438. $\text{C}_{11}\text{H}_{21}\text{O}_4$ requires M , 217.1440).

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 **24E** (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: μ_{max} (CDCl_3 solⁿ)/ cm^{-1} 3012s (OH), 2397m, 2256w, 1661w (C=O), 1598w, 1525w, 1483w, 1420w, 1382w, 1215s and 1098w; δ_{H} (400 MHz, CDCl_3) 1.17 (3H, s, $\text{C}(\text{OH})\text{CH}_3$), 1.50 – 1.67 (4H, m, 1H from $\text{CH}_2\text{CC}(\text{OH})$, 1H from $\text{CH}_2\text{C}(\text{OH})$, 1H from $\text{CH}_2\text{CH}_2\text{C}(\text{OH})$, 1H from $\text{NC}(\text{O})\text{CCH}_2$), 1.82 – 1.96 (3H, m, 1H from $\text{CH}_2\text{CC}(\text{OH})$, 1H from $\text{CH}_2\text{CH}_2\text{C}(\text{OH})$, 1H from $\text{NC}(\text{O})\text{CCH}_2$), 2.25 – 2.31 (1H, m, 1H from $\text{CH}_2\text{C}(\text{OH})$), 3.04 – 3.16 (2H, m, NCH_2), 4.36 (1H, apparent d, J 14.6, AB system, 1H from CH_2Ph), 4.47 (1H, apparent d, J 14.6, AB system, 1H from CH_2Ph), 4.97 (1H, d, J 1.5, OH), 7.15 – 7.22 (3H, m, 3 x Ar CH) and 7.23 – 7.29 (2H, m, 2 x Ar CH); δ_{C} (100 MHz, CDCl_3) 20.7 ($\text{CH}_2\text{CH}_2\text{C}(\text{OH})$), 23.0 ($\text{C}(\text{OH})\text{CH}_3$), 29.6 ($\text{CH}_2\text{CC}(\text{O})\text{N}$), 34.4 ($\text{CH}_2\text{C}(\text{OH})$), 39.0 ($\text{CH}_2\text{CC}(\text{OH})$), 44.0 ($\text{C}(\text{O})\text{NCH}_2$), 47.1 (CH_2Ph), 56.2 (C), 82.9 ($\text{C}(\text{OH})$), 128.1 (Ar CH), 128.4 (2 x Ar CH), 129.2 (2 x Ar CH), 136.5 (Ar C)

and 178.4 (C(O)N); m/z (EI mode) 259 ((M^{+}) 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^{+}), 259.1571. $C_{16}H_{21}O_2N$ requires M , 259.1572).

***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 **21Z** and (*E*)-3-(4-oxo-pentylidene)-tetrahydro-pyran-2-one **21E** (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: ν_{max} (neat)/ cm^{-1} 3417bs (OH), 2962s, 1714s (C=O), 1450m, 1394m, 1263m, 1146s and 962s; δ_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, OH); δ_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^{+}) 5%), 166 (5), 151 (2), 126 (30), 113 (100), 84 (45), 83 (70), 67 (20) and 43 (40); (Found: (M^{+}), 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

$\nu_{\max}$ (CDCl₃ solⁿ)/cm⁻¹ 3011s (OH), 2402m, 1755m (C=O), 1514w, 1420w, 1225s and 1015w; δ_{H} (400 MHz, CDCl₃) 1.42 (3H, s, CCH₃), 1.49 – 1.66 (4H, m, 1H from CH₂CH₂CH₂OH, 2H from CH₂CH₂OH, 1H from CCH₂CH₂CH), 1.73 – 1.78 (1H, m, 1H from CH₂CH₂CH₂OH), 2.10 – 2.20 (3H, m, 3H from CCH₂CH₂CH), 2.45 – 2.47 (1H, m, CH₂CHCH), 2.54 (1H, dt, *J* 2.7, 5.9, CHC(O)) and 3.61 (2H, t, *J* 5.7, CH₂OH); δ_{C} (100 MHz, CDCl₃) 21.4 (CH₂), 24.8 (CCH₃), 29.1 (CH₂CH₂CH₂OH), 30.7 (CH₂CH₂OH), 33.5 (CH₂), 45.1 (CH₂CHCH), 49.6 (CHC(O)), 62.7 (CH₂OH), 87.0 (C(CH₃)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. C₁₀H₁₇O₃ 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: $\nu_{\max}$ (neat)/cm⁻¹ 3406bs (OH), 2958m, 1709s (C=O), 1446m, 1369m, 1265m, 1180m, 1122m, 1055m and 1030m; δ_{H} (400 MHz, CDCl₃) 1.22 (3H, t, *J* 7.1, CH₂CH₃), 1.22 – 1.29 (1H, m, 1H from CH₂), 1.30 (3H, s, C(OH)CH₃), 1.37 – 1.42 (1H, m, 1H from CH₂), 1.47 – 1.53 (2H, m, CH₂), 1.58 – 1.79 (5H, m, 1H from CH₂C(OH) 4H from CH₂), 2.33 – 2.41 (1H, m, 1H from CH₂C(OH)), 3.50 – 3.60 (2H, m, CH₂OH) and 4.11 (2H, q, *J* 7.1, OCH₂CH₃); δ_{C} (100 MHz, CDCl₃) 14.7 (OCH₂CH₃), 20.0 (CH₂), 23.6 (C(OH)CH₃), 29.2 (CH₂), 30.9 (CH₂), 31.6 (CH₂C(OH)), 40.1 (CH₂), 60.3 (CC(O)), 61.0 (OCH₂CH₃), 63.4 (CH₂OH), 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. C₁₂H₂₃O₄ requires *M*, 231.1596).

General Cyclobutane-forming Procedure D

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

Dry ^tBuOH (6.5 ml) was added to a stirred solution of SmI₂ (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 (MgSO₄) 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% Et₂O in CHCl₃), 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

$\bar{\nu}_{\text{max}}$ (neat)/cm⁻¹ 3406bs (OH), 2941m, 1745s (C=O), 1383m, 1250m, 1174m, 1122m, 1057m and 949m; δ_{H} (400 MHz, CDCl₃) 1.37 (3H, s, CH₃ from minor), 1.43 (3H, s, CH₃ from major), 1.64 – 2.23 (12H, m, 3 x CH₂ from minor, 3 x CH₂ from major), 2.48 – 2.50 (1H, m, CH₂CHCHC(O) from major), 2.70 (1H, dt, *J* 2.8, 7.5, CH₂CHCHC(O) from major), 2.79 – 2.91 (2H, m, 2 x CH from minor) and 3.60 – 3.77 (4H, m, CH₂OH from minor, CH₂OH from major); δ_{C} (100 MHz, CDCl₃) 17.2 (CH₂ from minor), 21.5 (CH₂ from major), 23.7 (CH₃ from minor), 24.8 (CH₃ from major), 29.0 (CH₂ from minor), 32.2 (CH₂ from major), 33.4 (CH₂ from minor), 35.3 (CH₂ from major), 42.3 (CH from minor), 43.2 (CH from minor), 45.2 (CHCHC(O) from major), 47.2 (CHCHC(O) from major), 60.9 (CH₂OH from major), 61.7

(CH₂OH from minor), 87.5 (C(CH₃)O from major), 88.1 (C(CH₃)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. C₉H₁₅O₃ requires *M*, 171.1021).

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

ν_{max} (neat)/cm⁻¹ 3406bs (OH), 2941m, 1743s (C=O), 1462m, 1209m, 1132m, 1115m, 1024m and 943m; δ_{H} (400 MHz, CDCl₃) 0.86 (3H, t, *J* 7.4, CH₃ from minor), 0.88 (3H, t, *J* 7.4, CH₃ from major), 1.61 – 2.19 (16H, m, 4 x CH₂ from minor, 4 x CH₂ from major), 2.47 – 2.50 (1H, m, CHCHC(O) from major), 2.71 (1H, dt, *J* 3.0, 7.6, CHCHC(O) from major), 2.81 – 2.88 (1H, m, CHCHC(O) from minor), 2.91 – 2.98 (1H, m, CHCHC(O) from minor) and 3.58 – 3.77 (4H, m, CH₂OH from minor, CH₂OH from major); δ_{C} (100 MHz, CDCl₃) 7.9 (CH₃ from minor), 8.0 (CH₃ from major), 16.9 (CH₂ from minor), 21.8 (CH₂ from major), 29.2 (CH₂ from minor), 30.3 (CH₂ from minor), 30.4 (CH₂ from minor), 30.6 (CH₂ from major), 31.5 (CH₂ from major), 35.3 (CH₂ from major), 41.4 (CHCHC(O) from minor), 42.8 (CHCHC(O) from minor), 43.3 (CHCHC(O) from major), 47.2 (CHCHC(O) from major), 61.0 (CH₂OH from major), 61.7 (CH₂OH from minor), 90.3 (C(CH₂CH₃)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).

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

$\nu_{\max}$ (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, $CH(CH_3)_2$ from minor, $CH(CH_3)_2$ from major), 2.52 – 2.54 (1H, m, CH from minor), 2.70 – 2.73 (1H, m, CH from minor), 2.81 (1H, dt, J 1.7, 8.1, CH from major), 2.97 (1H, apparent q, J 8.1, CH from major) and 3.58 – 3.79 (4H, m, CH_2OH from minor, CH_2OH from major); δ_C (100 MHz, $CDCl_3$) 14.8 (CH_3), 14.9 (CH_3), 14.9 (CH_3), 15.0 (CH_2), 15.2 (CH_3), 20.4 (CH_2), 27.7 (CH_2), 27.9 (CH_2), 28.6 (CH_2), 32.5 ($CH(CH_3)_2$), 33.5 ($CH(CH_3)_2$), 33.9 (CH_2), 39.1 (CH from major), 40.5 (CH from minor), 41.5 (CH from major), 46.0 (CH from minor), 59.7 (CH_2OH from minor), 60.2 (CH_2OH from major), 91.3 (CCH from minor), 92.2 (CCH 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. C₁₁H₁₉O₃ requires *M*, 199.1334).

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

ν_{max} (neat)/cm⁻¹ 3413bs (OH), 2939m, 1747s (C=O), 1460m, 1207m, 1055m, 1022m and 941m; δ_{H} (400 MHz, CDCl₃) 0.85 (3H, t, *J* 7.4, CH₃ from minor), 0.88 (3H, t, *J* 7.4, CH₃ from major), 1.45 – 2.17 (20H, m, 5 x CH₂ from minor, 5 x CH₂ from major), 2.42 – 2.46 (1H, m, CHCHC(O) from major), 2.52 – 2.56 (1H, m, CHCHC(O) from major), 2.61 – 2.68 (1H, m, CHCHC(O) from minor), 2.90 (1H, apparent q, *J* 8.0, CHCHC(O) from minor) and 3.59 – 3.62 (4H, m, CH₂OH from minor, CH₂OH from major); δ_{C} (100 MHz, CDCl₃) 7.9 (CH₃ from minor), 8.1 (CH₃ from major), 16.3 (CH₂), 21.7 (CH₂), 22.6 (CH₂), 29.0 (CH₂), 30.3 (CH₂), 30.4 (CH₂), 30.6 (CH₂), 30.7 (CH₂), 31.5 (CH₂), 31.6 (CH₂), 41.1 (CHCHC(O) from minor), 43.1 (CHCHC(O) from major), 44.4 (CHCHC(O) from minor), 49.5 (CHCHC(O) from major), 62.7 (CH₂OH from major), 62.8 (CH₂OH from minor), 89.7 (C(CH₂CH₃)O from major), 90.4 (C(CH₂CH₃)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).

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 **23E** (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

$\nu_{\max}$ (neat)/ cm^{-1} 3408bs (OH), 2941m, 1747s (C=O), 1454m, 1261m, 1171m, 1053m and 947; δ_{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, CH 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, CH from major), 2.49 – 2.55 (1H, m, CH 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, CH 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 CH from minor, Ar CH from major); δ_{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 (CH from minor), 40.7 (CH from major), 42.2 (CH_2Ph from minor), 42.3 (CH_2Ph from major), 42.7 (CH

from minor), 48.1 (CH from major), 61.2 (CH₂OH from major), 61.3 (CH₂OH from minor), 87.7 (C(CH₂Ph)O from major), 87.8 (C(CH₂Ph)O from minor), 125.9 (Ar CH from minor), 126.0 (Ar CH from major), 127.4 (2 x Ar CH from major), 127.5 (2 x Ar CH from minor), 128.8 (2 x Ar CH from minor), 129.2 (4 (2 x Ar CH 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⁺) 10%), 232 (5), 214 (20), 186 (20), 169 (70), 141 (40), 123 (100), 91 (80), 81 (40), 67 (20) and 41 (15); (Found: (M⁺), 260.1412. C₁₆H₂₀O₃ requires *M*, 260.1412).

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 H₂O (dist.) (1 ml). The aqueous layer was separated and extracted with EtOAc (4 x 10 ml). The combined organic extracts were dried (MgSO₄), and concentrated *in vacuo* to give the crude product. Purification by column chromatography (eluting with 30% Et₂O in CHCl₃) 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): ν_{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; δ_{H} (400 MHz, CDCl₃) 1.43 (3H, s, CH₃), 1.63 – 1.68 (1H, m, 1H from CCH₂CH₂CH), 1.93 – 2.02 (1H, m, 1H from CH₂CH₂O), 2.10 – 2.28 (4H, m, 3H from CCH₂CH₂CH, 1H from CH₂CH₂O), 2.51 – 2.56 (1H, m, CHCHC(O)), 2.70 (1H, dt, *J* 3.0, 6.1, CHCHC(O)), 4.37 – 4.48 (2H, m, CH₂O), 8.14 (2H, apparent dt, *J* 1.9, 8.9, 2 x Ar CH) and 8.23 (2H, apparent dt, *J* 1.9, 8.9, 2 x Ar

CH); δ_{C} (100 MHz, CDCl_3) 21.4 (1C from $\text{CCH}_2\text{CH}_2\text{CH}$), 24.7 (CH_3), 31.3 ($\text{CH}_2\text{CH}_2\text{O}$), 33.6 (1C from $\text{CCH}_2\text{CH}_2\text{CH}$), 44.6 ($\text{CHCHC}(\text{O})$), 46.9 ($\text{CHC}(\text{O})$), 63.6 (CH_2O), 86.9 ($\text{C}(\text{CH}_3)\text{O}$), 124.0 (2 x Ar CH), 131.2 (2 x Ar CH), 135.6 (Ar $\text{C}(\text{O})\text{C}$), 151.1 (Ar CNO_2), 164.9 (Ar $\text{C}(\text{O})$) and 179.7 ($\text{C}(\text{O})\text{O}$); m/z (CI mode, isobutane) 320 ($(\text{M} + \text{H})^+$ 100), 290 (50), 171 (15), 153 (10), 138 (5), 120 (25), 113 (5), 97 (5), 85 (5) and 71 (10); (Found: $(\text{M} + \text{H})^+$, 320.1135. $\text{C}_{16}\text{H}_{18}\text{O}_6\text{N}$ requires M , 320.1134).

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-butyldiene)-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% Et₂O 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

δ_{max} (neat)/ cm^{-1} 3413bs (OH), 2943m, 1743s ($\text{C}=\text{O}$), 1238m, 1167m, 1051m and 945m; δ_{H} (400 MHz, CDCl_3) 0.28 – 0.32 (4H, m, $\text{OCCH}(\text{CH}_2)_2^{\text{A}}$ from minor, $\text{OCCH}(\text{CH}_2)_2^{\text{A}}$ from major), 0.46 – 0.52 (4H, m, $\text{OCCH}(\text{CH}_2)_2^{\text{B}}$ from minor, $\text{OCCH}(\text{CH}_2)_2^{\text{B}}$ from major), 1.02 – 1.10 (2H, m, $\text{OCCH}(\text{CH}_2)_2$ from minor, $\text{OCCH}(\text{CH}_2)_2$ from major), 1.62 – 2.12 (12H, m, 3 x CH_2 from minor, 3 x CH_2 from major), 2.42 – 2.46 (1H, m, CH from major), 2.67 – 2.71 (1H, m, CH from major), 2.81 – 2.88 (2H, m, 2 x CH from minor), 3.57 – 3.62 (1H, m, 1H from CH_2OH from minor) and 3.68 – 3.78 (3H, m, 1H from CH_2OH from minor, CH_2OH from major); δ_{C} (100 MHz, CDCl_3) -0.4 ($\text{OCH}(\text{CH}_2)_2^{\text{AB}}$), -0.3 ($\text{OCH}(\text{CH}_2)_2^{\text{AB}}$), -0.1 ($\text{OCH}(\text{CH}_2)_2^{\text{AB}}$),

0.0 (OCH(CH₂)₂^{AB}), 14.0 (OCH(CH₂)₂), 14.6 (OCH(CH₂)₂), 15.1 (CH₂), 20.0 (CH₂), 27.2 (CH₂), 27.5 (CH₂), 28.4 (CH₂), 33.4 (CH₂), 39.1 (CH), 40.7 (CH), 41.4 (CH), 45.1 (CH), 59.1 (CH₂OH), 59.8 (CH₂OH), 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. C₁₁H₁₇O₃ requires *M*, 197.1178).