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8-Oxabicyclo[3.2.1]oct-6-en-3-one as a Module for the Synthesis of β-Alkoxy-δ-valerolactones Relevant to Natural Products and Drugs

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Abstract. The enantioselective synthesis of all four stereoisomeric *cis*-3,5 and *trans*-3,5-substituted β-alkoxy-δ-valerolactones was accomplished starting from 8-oxabicyclo[3.2.1]oct-6-en-3-one. © 1997 Elsevier Science Ltd.

Functionalized tetrahydropyrans are chiral building blocks of numerous natural products. For example, the spongistatins[1], phorboxazoles[2] or mevinic acids[3] contain substituted tetrahydropyran or valerolactone rings with defined stereochemistry which is essential for biological activity[4] (Fig.1).

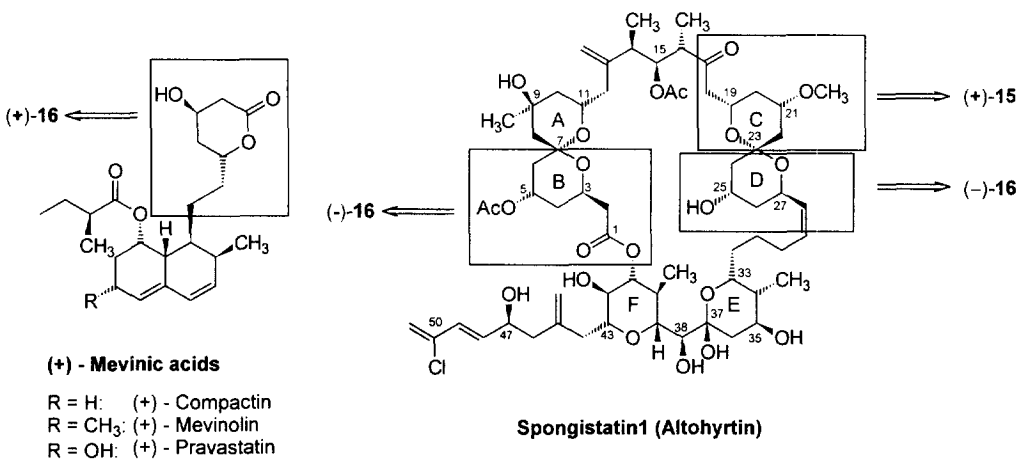
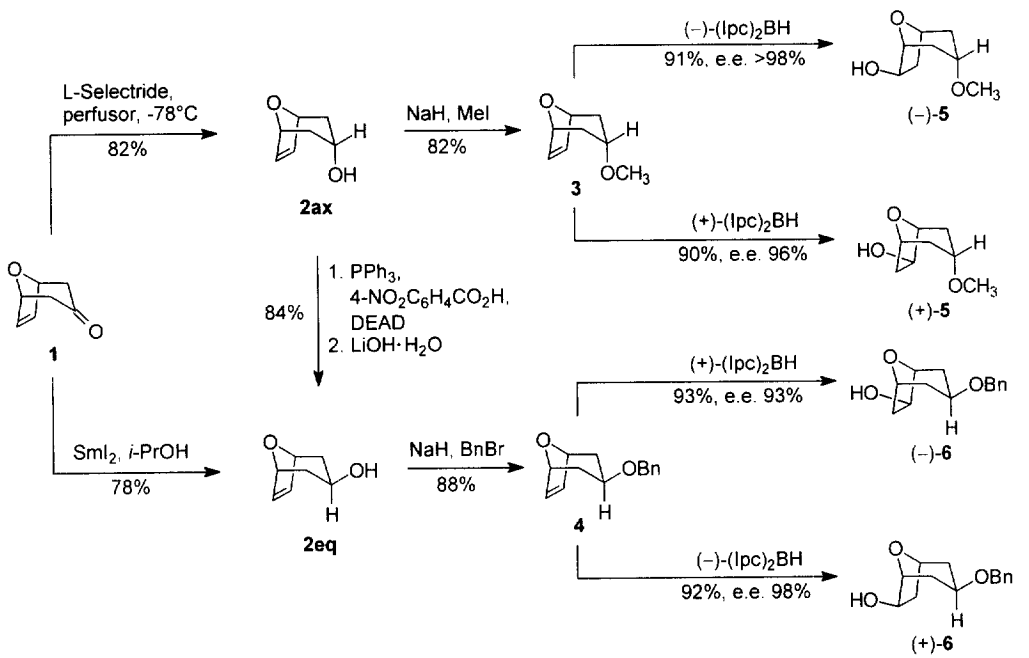


Figure 1. Some current targets of organic synthesis

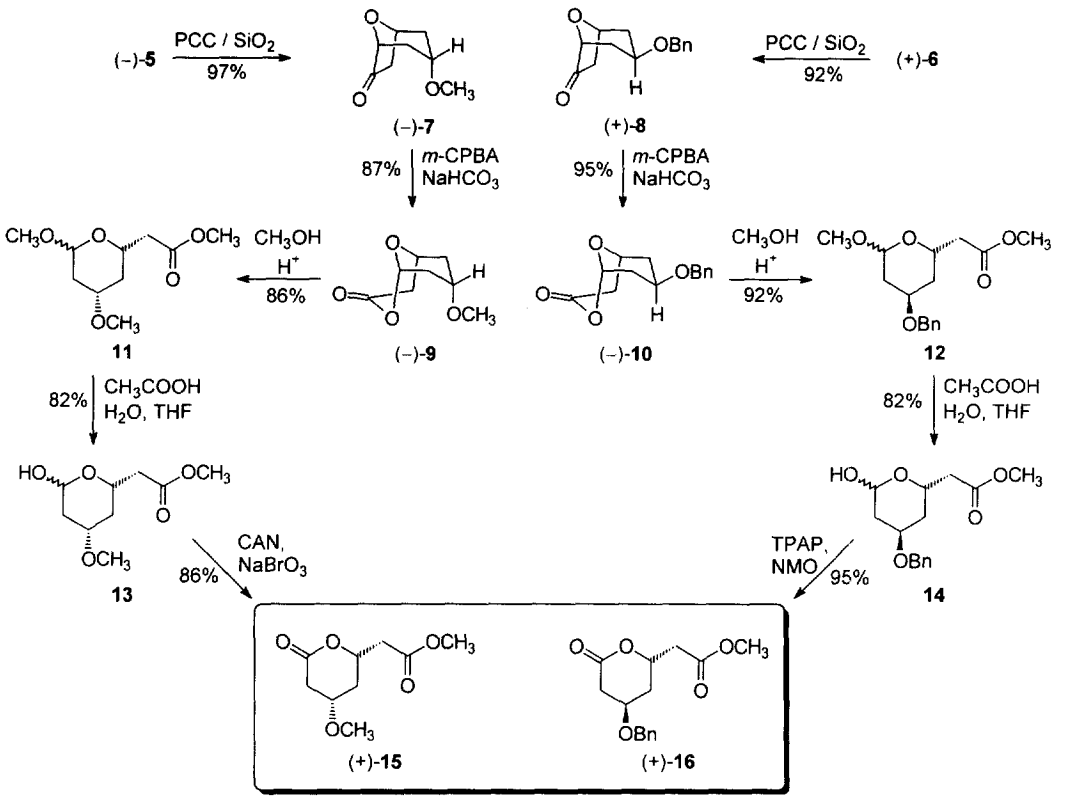
It occurred to us that *cis*-3,5 or *trans*-3,5-substituted β-alkoxy- and β-hydroxy-δ-valerolactones should be readily accessible from 8-oxabicyclo[3.2.1]oct-6-en-3-one (**1**) by desymmetrization and stereoselective transformations based on combined substrate and reagent control. The bicyclic ketone **1**,[5] was reduced selectively to the *endo*-**2ax** and *exo*-**2eq** alcohol[6] by L-Selectride[®] and samarium diiodide,[7] respectively. Etherification of the resulting alcohols afforded the epimeric ethers **3** and **4** which, like their precursor ketone **1**, are σ-symmetric. Desymmetrization was accomplished by asymmetric hydroboration.[8] Thus all four stereoisomeric alcohols (−)-**5**, (+)-**5**, (−)-**6** and (+)-**6** are accessible in excellent optical[9] and chemical yield.



Scheme 1.

The following sequence (Scheme 2) is representative and was executed with methoxy alcohol (−)-**5** and also benzyloxy alcohol (+)-**6**. PCC oxidation was straightforward and gave bicyclic ketones (−)-**7** and (+)-**8**, respectively. Baeyer-Villiger oxidation furnished the bicyclic lactones (−)-**9** and (−)-**10**, which were opened to the monocyclic anomers **11** and **12** by acidic methanolysis. The resulting methoxyacetals were cleaved to the corresponding hemiacetals **13**, **14** using a mixture of acetic acid and tetrahydrofuran as a solvent. Finally, oxidation to the required target compounds succeeded with established oxidation agents.

In summary we have developed a simple modular approach to some key intermediates of current interest from one single starting material **1**. The synthesis of lactone (+)-**15** is relevant to that of ring C in spongistatin. Lactone (−)-**16** appears in ring B and D of spongistatin[10] and its enantiomer (+)-**16** in three current blockbuster drugs, i. e. Zocor® and Mevacor® (Merck Sharp & Dohme), as well as Mevalotin® (Sankyo).



Scheme 2.

EXPERIMENTAL

General. Melting points: Büchi apparatus. – Infrared spectra: Perkin-Elmer 1710 spectrometer. – ^1H NMR spectra: Bruker WP 200 SY or AM 400 spectrometer, solvent $CDCl_3$ unless otherwise stated. – ^{13}C NMR spectra: Bruker WP 200 SY or a Bruker AM 400. – Microanalyses were performed in the Department of Organic Chemistry of the University of Hannover. – Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30 - 60 μm). – Analytical t.l.c. was carried out on aluminum-backed 0.2-mm silica gel 60 F_{254} plates (E. Merck). – E (ethyl ether). PE (light petroleum, bp 40 – 60 °C). MTBE (methyl *t*-butyl ether).

endo-*8-Oxabicyclo[3.2.1]oct-6-en-3-ol* (**2ax**). At -78°C, 18 mL (18 mmol) of a 1 M L-Selectride® solution in THF was added slowly *via* perfusor to a solution of 1.86 g (15.0 mmol) of bicyclic ketone **1**[5] in 15 mL of abs. THF. The solution was stirred for 1 h at -78°C, then allowed to warm up to ambient temperature and stirred for another hour. At 0°C, 16 mL (81.0 mmol) of 20% aqueous NaOH and 8 mL (80.0 mmol) of 30% H_2O_2 were added slowly. The mixture was neutralized with 2 M H_2SO_4, the aqueous phase was saturated with NaCl and extracted continuously for 24 h with MTBE. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (eluent: MTBE) afforded **2ax** (1.55 g, 12.3 mmol, 82%) as white crystals. mp 134-135°C. ^1H NMR (200 MHz, $CDCl_3$, TMS) δ 6.48 (s, 2 H), 4.76 (d, J = 4 Hz, 2 H), 3.98 (m, 1 H), 2.28 (ddd, J = 15 Hz, J = 5 Hz, J = 4 Hz, 2 H), 1.74 (dd, J = 15 Hz, J = 1 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ 135.71 (=CH), 77.62 (CH), 65.21 (CHOH), 35.98 (CH_2); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3424, 2952, 1400, 1340, 1288, 1228, 1180, 1052, 1036, 960, 856; HRMS calcd for $C_7H_{10}O_2$ (M^+) 126.0681,

found 126.0681.

exo-*8-Oxabicyclo[3.2.1]oct-6-en-3-ol* (**2eq**) *(via SmI_2-reduction).* Successful preparation strictly demands absence of oxygen. Therefore all used appliances (syringes, needles, flasks, etc.) have to be well dried and flushed with argon or nitrogen. Samarium (17 g, 114 mmol) was transferred under argon into a flask and activated by heating and evacuating with a high vacuum pump. After cooling to ambient temperature 1.2-diiodoethane (28.07 g, 100.4 mmol) was added, the flask was evacuated once more without heating and 182 mL of absolute THF was injected at 0°C. Under stirring the mixture was allowed to warm to rt. When the solution became deep blue (~ 45 min) it was heated to reflux. Then a separately prepared solution of **1** (6.172 g, 48.98 mmol) and *i*-PrOH (3.81 ml, 49.0 mmol) in 49 mL of absolute THF was added after argon had been bubbled through for 15 min. After 3 h refluxing the reaction was terminated by dilution with water. The organic layer was successively washed with H_2O, 2 N HCl and saturated $Na_2S_2O_3$ solution. Insoluble material was removed by filtration. The combined aqueous layers were extracted, first with EtOAc (5x 30 mL) and then continuously with MTBE over 20 h. The organic layers were combined, dried ($MgSO_4$) and volatile compounds were removed under reduced pressure. The residue was purified by chromatography (700 g silica gel, EtOAc) to yield 4.81 g of **2eq** (38.2 mmol, 78%) as a crude orange to brown oil which crystallized in the freezer to a light yellow solid, mp 43-44°C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 6.10 (s, 2 H), 4.79 (d, J = 3.6 Hz, 2 H), 3.85 (tt, J = 9.7 Hz, J = 6.3 Hz, 1 H), 3.43 (bs, 1H), 1.91 (dd, J = 13 Hz, J = 6.3 Hz, 2 H), 1.60 (ddd, J = 13 Hz, J = 9.7 Hz, J = 3.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 130.8 (=CHR), 78.0 ($OCHR_2$), 63.8 ($HOCHR_2$), 35.4 (CH_2); ν_{max} ($CHCl_3$)/cm^{-1} 3600, 3080, 3000, 2956, 2920, 1620, 1424, 1256, 1152, 1108, 1040; HRMS calcd for $C_7H_{10}O_2$ (M^+) 126.0676, found 126.0681.

endo-*3-Methoxy-8-oxabicyclo[3.2.1]oct-6-ene* (**3**). A solution of 149 mg (1.18 mmol) of alcohol **2ax** in 2 mL of abs. THF was added at 0°C to 150 mg (3.75 mmol) of sodium hydride. After 15 min of reflux, 0.75 mL (11.9 mmol) of methyl iodide was added at 0°C. The reaction mixture was refluxed for 22 h, diluted with sat. ammonium chloride, extracted with E and dried over $MgSO_4$. Removal of the solvent *in vacuo* and purification by column chromatography (EtOAc/cyclohexane, 1 : 2) yielded **3** (136 mg, 0.97 mmol, 82%). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 6.25 (d, J = 0.7 Hz, 2 H), 4.68 (d, J = 4 Hz, 2 H), 3.51 (m, 1 H), 3.22 (s, 3 H), 2.13 (ddd, J = 15 Hz, J = 4 Hz, J = 2 Hz, 2 H), 1.72 (dd, J = 15 Hz, J = 1 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ 133.61 (=CH), 77.39 (CH), 73.86 (CHOR), 56.26 (CH_3) 31.58 (CH_2); ν_{max}($CHCl_3$)/cm^{-1} 3000, 2948, 2924, 2880, 2824, 1372, 1344, 1280, 1236, 1076, 1036, 1032; 960, 888, 848, HRMS calcd for $C_8H_{12}O_2$ (M^+) 140.0837, found 140.0838.

exo-*3-Benzyloxy-8-oxabicyclo[3.2.1]oct-6-ene* (**4**). To a solution of **2eq** (3.96 g, 31.4 mmol) and a catalytic amount of (n-Bu)$_4$NI in 150 mL of dry THF was added NaH (2.93 g of a 60% suspension, 73.25 mmol) under argon atmosphere. The mixture was refluxed under vigorous stirring. After 1 hour benzyl bromide (7.50 mL, 62.9 mmol) was injected dropwise. The mixture was heated overnight and terminated by careful addition of water. The aqueous layer was extracted with EtOAc(4x 50 mL), the combined organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. Flash chromatography of the residue (400 g silica gel, EtOAc) yielded 5.94 g (27.5 mmol, 87.5%) of **4** as a light yellow solid, mp 62 - 64°C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.33-7.28 (m, 5 H), 6.09 (s, 2 H), 4.81 (d, J = 3.6 Hz, 2 H), 4.47 (s, 2 H), 3.68 (tt, J = 9.6 Hz, J = 6.3 Hz, 1 H), 1.96 (dd, J = 13 Hz, J = 6.3 Hz, 2 H), 1.73 (ddd, J = 13 Hz, J = 9.6 Hz, J = 3.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.7 (Ar-C), 130.9 (=CHR), 128.3 (*m*-Ar-C), 127.5 (*o*-Ar-C), 127.4 (*p*-Ar-C), 78.0 ($OCHR_2$), 70.9 ($OBnCHR_2$), 69.7 (OCH_2Ar), 32.6 (CH_2); ν_{max}(KBr)/cm^{-1} 3084, 2952, 2912, 1452, 1360, 1116, 1076, 1040, 752, 704; HRMS calcd for $C_{14}H_{16}O_2$ (M^+) 216.1134, found 216.1150.

General Procedure for Asymmetric Hydroboration. To a 8.5 M solution of (+)- or (-)-α-pinene (3.8 eq) in abs. THF was added BH_3·DMS (1.5 eq) dropwise. Stirring was stopped after 5 min yielding voluminous crystals of (-)- or (+)-(Ipc)$_2$BH overnight. Crystallization was completed in an ice-bath after 2 h. The remaining solution was removed *via* syringe, the solid was powdered under an argon atmosphere, washed twice with abs. E and dried *in vacuo*. At -25°C a highly concentrated solution (3.1 M - 7 M, depending on the substrate) of the alkene (1 eq) in abs. THF was added to the enantiopure borane. The heterogeneous reaction mixture was stirred for 2 h at this temperature, then stored for 2-3 weeks in the freezer (-15 to -5°C) and shaken occasionally. To the resulting homogeneous oil was added methanol (3.8 eq), 3 N NaOH (3 eq) and 30% H_2O_2 (4 eq) at 0°C. The mixture was stirred for 1 h at rt, poured into water and extracted with MTBE.

The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (MTBE).

(1S,3S,5R,6S)-3-Methoxy-8-oxabicyclo[3.2.1]octan-6-ol (−)-**5**. Prepared according to the general procedure described above from **3** (3.40 g, 24.3 mmol). Yield 3.50 g (22.2 mmol, 91%) of colourless solid, mp 49°C, $[\alpha]_D^{15}$ = -10.3° (c = 1, $CHCl_3$), e.e. > 98%. ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 4.59 (dd, *J* = 7.1 Hz, *J* = 2.0 Hz, 1 H), 4.47 (m, 1 H), 4.10 (m, 1 H), 3.45 (m, 1 H), 3.27 (s, 3 H), 2.75 (dd, *J* = 13.1 Hz, *J* = 7.1 Hz, 1 H), 2.63 (bs, 1 H) 1.90 (m, 3 H), 1.74 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 82.41 (*C*HCOH), 75.56 (CHOH), 74.48 (CH), 73.11 (CHCOR), 56.21 (CH_3), 41.60 (*C*H_2COH), 34.06 (CH_2), 32.49 (CH_2); $\nu_{max}(CHCl_3)/cm^{-1}$ 3592, 3000, 2952, 2928, 2876, 2824, 1232, 1216, 1180, 1100, 1072, 1052, 940, 924, 864, 844; HRMS calcd for $C_8H_{14}O_3$ (M^+) 158.0943, found 158.0939.

(1R,3R,5S,6R)-3-Methoxy-8-oxabicyclo[3.2.1]octan-6-ol (+)-**5**. Prepared from **3** (420 mg, 3.00 mmol) yielded in 426 mg (2.70 mmol, 90%) of colourless solid, mp 49-50°C, $[\alpha]_D^{20}$ = + 9.9° (c = 1, $CHCl_3$), e.e. 96%.

(1S,3R,5R,6S)-3-Benzyloxy-8-oxabicyclo[3.2.1]octan-6-ol (+)-**6**. Prepared according to the general procedure described above from **4** (4.50 g, 20.8 mmol). Yield: 4.47 g (19.1 mmol, 92%) of a crude colourless oil which crystallized in the refrigerator, mp 60-61°C, $[\alpha]_D^{20}$ = +5.1°, (c = 1.0, $CHCl_3$), e.e. = 98%. ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.37-7.25 (m, 5 H,), 4.59 (dd, *J* = 7.5 Hz, *J* = 2.5 Hz, 1 H), 4.50 (s, 2 H), 4.23 (m, 1 H), 4.18 (dd, *J* = 7.2 Hz, *J* = 2.5 Hz, 1 H), 3.50 (dddd, *J* = 10.6 Hz, *J* = 10.6 Hz, *J* = 5.3 Hz, *J* = 5.3 Hz, 1 H), 2.18 (dd, *J* = 14 Hz, *J* = 7.5 Hz, 1 H), 2.04 (m, 2 H), 1.86 (m, 2 H), 1.66 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.3 (Ar-C), 128.4 (*m*-Ar-C), 127.6 (*p*-Ar-C), 127.5 (*o*-Ar-C), 82.7 (*C*HCOH), 74.8 (CHOH), 74.7 (CH), 69.7 (O*C*H_2Ar), 69.4 (CHOBn), 41.3 (CH_2), 37.1 (CH_2), 35.3 (CH_2); ν_{max}(KBr)/cm^{-1} 3420, 3064, 3032, 2948, 2924, 2852, 1496, 1452, 1368, 1316, 1296, 1224, 1176, 1156, 1100, 1044, 998, 868, 762, 696; HRMS calcd for $C_{14}H_{18}O_3$ (M^+) 234.1252, found 234.1256.

(1R,3S,5S,6R)-3-Benzyloxy-8-oxabicyclo[3.2.1]octan-6-ol (−)-**6**. Prepared from **4** (400 mg, 1.85 mmol). Yield 405 mg (1.73 mmol, 93%) of (−)-**6**, colourless oil, $[\alpha]_D^{20}$ = -5.0° (c = 1.0, $CHCl_3$), e.e. 93%.

General Procedure for PCC Oxidation. A 0.2 M solution of the alcohol in abs. DCM was added to a 0.3 M suspension of PCC (1.5 eq) on silica (2 mmol / g) at 0°C. The suspension was stirred for 1 h at 0°C and at rt overnight, filtered over a short dry silica column and eluted with E. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (EtOAc/cyclohexane, 1 : 2).

(1S,3S,5R)-3-Methoxy-8-oxabicyclo[3.2.1]octan-6-one (−)-**7**. Prepared according to the general procedure described above from (−)-**5** (158.0 mg, 1.0 mmol). Yield 151.2 mg (0.97 mmol, 97%) of colourless solid, mp 35-36°C, $[\alpha]_D^{20}$ = -7.2° (c = 1.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 4.74 (dd, *J* = 7.9 Hz, *J* = 4.1 Hz, 1 H), 3.95 (m, 1 H), 3.62 (m, 1 H), 3.21 (s, 3 H), 2.70 (d, *J* = 17.0 Hz, 1 H), 2.56 (dd, *J* = 17.0 Hz, *J* = 7.9 Hz, 1 H), 2.15-2.24 (m, 2 H), 1.99 (ddd, *J* = 14.6 Hz, *J* = 4.1 Hz, *J* = 4.0 Hz, 1 H) 1.88 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 215.19 (CO), 77.14 (*C*HCO), 73.65 (CH), 72.93 (*C*HOCH$_3$), 55.74 (CH_3), 42.37 (*C*H_2CO), 33.97 (CH_2), 32.72 (CH_2); $\nu_{max}(CHCl_3)/cm^{-1}$ 2928, 2880, 2828, 1756, 1416, 1228, 1176, 1156, 1096, 1052, 1028, 1008, 968, 948, 924, 884, 848, 824; HRMS calcd for $C_8H_{12}O_3$ (M^+) 156.0786, found 156.0780.

(1S,3R,5R)-3-Benzyloxy-8-oxabicyclo[3.2.1]octan-6-one (+)-**8**. Prepared according to the general procedure described above from (+)-**6** (1.50 g, 6.46 mmol). Yield: 1.45 g (6.25 mmol, 97%) of colourless solid, mp 44-45°C, $[\alpha]_D^{19}$ = +4.4°, (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.36-7.24 (m, 5 H), 4.82 (m, 1 H), 4.49 (d, *J* = 12 Hz, 2 H), 4.14 (m, 1 H), 3.76 (dddd, *J* = 11.2 Hz, *J* = 11.2 Hz, *J* = 5.6 Hz, *J* = 5.6 Hz, 1 H), 2.66 (dd, *J* = 17.8 Hz, *J* = 8.1 Hz, 1 H), 2.26 (dd, *J* = 13.2 Hz, *J* = 5.6 Hz, 1 H), 2.21 (d, *J* = 17.8 Hz, 1 H), 2.65 (dd, *J* = 13.2 Hz, *J* = 5.6 Hz, 1 H), 1.97 (ddd, *J* = 13.2 Hz, *J* = 11.2 Hz, *J* = 3.7 Hz, 1 H), 1.80 (ddd, *J* = 13.2 Hz, *J* = 11.2 Hz, *J* = 4.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 215.0 (CO), 138.0 (Ar-C), 128.5 (*m*-Ar-C), 127.6 (*p*-Ar-C), 127.5 (*o*-Ar-C), 76.6 (CHCO), 73.5 (CH), 70.1 (O*C*H_2Ar), 69.1 (CHOBn), 41.9 (*C*H_2CO), 36.3 (CH_2), 35.5 (CH_2); ν_{max}(KBr)/cm^{-1} 3032, 2992, 2964, 2868, 1748, 1496, 1456, 1424, 1408, 1368, 1340, 1320, 1296, 1240, 1212, 1176, 1148, 1096, 1060, 1028, 988, 752, 696; HRMS calcd for $C_{14}H_{16}O_3$ (M^+) 232.1089, found 232.1099.

General Procedure for Baeyer-Villiger Oxidation. The ketone was dissolved in dry DCM (0.075M solution). $NaHCO_3$ (2.1 eq) and *m*-CPBA (1.8 eq) were added successively at 0°C under argon atmosphere.

The cooling bath was removed after 1 h and the reaction was stirred overnight. Dilution with 200 mL of DCM and removal of insoluble solids by filtration was followed by evaporation of the filtrate. The residue was dissolved in 500 mL of MTBE, washed with 10% NaOH and brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield a colourless solid which was purified by flash chromatography.

(1S,5S,7S)-7-Methoxy-2,9-dioxabicyclo[3.3.1]nonan-3-one (−)-**9**. Prepared according to the general procedure described above from (−)-**7** (156 mg, 1.00 mmol). Yield 149 mg (0.870 mmol, 87%) of colourless solid, mp 86-88°C, $[\alpha]_D^{20}$ = -43.0° (c = 1.5, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 5.73 (m, 1 H), 4.45 (m, 1 H), 3.76 (m, 1 H), 3.29 (s, 3 H), 2.95 (ddd, *J* = 17.7 Hz, *J* = 8.3 Hz, *J* = 1.0 Hz, 1 H), 2.58 (d, *J* = 17.7 Hz, 1 H), 2.40 (ddd, *J* = 15.1 Hz, *J* = 4.2 Hz, *J* = 2.0 Hz, 1 H), 2.20 (ddd, *J* = 14.6 Hz, *J* = 4.5 Hz, *J* = 1.0 Hz, 1 H) 1.97-2.02 (m, 1 H), 1.84 (ddd, *J* = 15.1 Hz, *J* = 3.5 Hz, *J* = 3.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 166.37 (CO), 96.90 (*C*H(OR)$_2$), 70.66 (*C*HOCH$_3$), 65.90 (CHOR), 55.45 (CH_3), 33.72 (*C*H$_2$COO), 33.18 (CH_2), 30.91 (CH_2); $\nu_{max}(CHCl_3)/cm^{-1}$ 1744, 1340, 1308, 1284, 1232, 1176, 1104, 1016, 968, 784; HRMS calcd for $C_8H_{12}O_4$ (M^+) 172.0736, found 172.0734, Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found C, 55.81; H, 6.97.

(1S,5S,7R)-7-Benzyloxy-2,9-dioxabicyclo[3.3.1]nonan-3-one (−)-**10**. Prepared according to the general procedure described above from (+)-**8** (3.50 g, 15.1 mmol): Yield (after purification (200 g silica gel, E/PE)): 3.545 g (14.24 mmol, 95%) of a colourless solid, mp 72-72°C, $[\alpha]_D^{20}$ = -53.6° (c = 0.95, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.43-7.26 (m, 5 H), 5.90 (bd, J = 2.4 Hz, 1 H), 4.58 (m, 1 H), 4.55 (s, 2 H), 3.95 (dddd, *J* = 11 Hz, *J* = 11 Hz, *J* = 5.1 Hz, *J* = 5.1 Hz, 1 H), 3.09 (ddd, *J* = 18.3 Hz, *J* = 8.4 Hz, *J* = 1.2 Hz, 1 H), 2.57 (ddd, *J* = 13.2 Hz, *J* = 5.1 Hz, *J* = 2.1 Hz, 1 H), 2.50 (d, *J* = 18.3 Hz, 1 H), 2.17 (ddd, *J* = 13.2 Hz, *J* = 5.1 Hz, *J* = 2.4 Hz, 1 H), 2.06 (ddd, *J* = 13.2 Hz, *J* = 11.0 Hz, *J* = 2.4 Hz, 1 H), 1.81 (ddd, *J* = 13.2 Hz, *J* = 11.0 Hz, *J* = 2.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 166.4 (C=O), 137.7 (Ar-C), 128.5 (*m*-Ar-C), 127.9 (*p*-Ar-C), 127.6 (*o*-Ar-C), 99.3 (CH(OR)$_2$), 70.5 (OCH_2Ar), 67.9 ($OCHR_2$), 66.3 ($OCHR_2$), 37.0 (CH_2), 36.8 (CH_2), 34.9 (CH_2); ν_{max}(KBr)/cm^{-1} 3064, 2980, 2960, 2924, 2856, 1740, 1720, 1496, 1456, 1396, 1376, 1360, 1232, 1164, 1120, 1088, 1032, 980, 956, 820, 749, 696; HRMS calcd for $C_{14}H_{16}O_4$ (M^+) 248.1037, found 248.1049.

General Procedure for Acidic Methanolysis. A 0.3 M solution of the bicyclic lactone in abs. methanol with a catalytic amount of conc. H_2SO_4 was stirred for 24 h at rt. The reaction mixture was diluted with E and poured into sat. $NaHCO_3$ solution. The aqueous phase was extracted several times with E and the combined organic layers were dried ($MgSO_4$). Removal of the solvent and column chromatography afforded the methylacetal as an anomeric mixture.

(4,6-Dimethoxy-tetrahydropyran-2-yl)-acetic acid methyl ester (**11**). Prepared according to the general procedure described above from (−)-**9** (1.20 g, 7.00 mmol). Yield 1.31 g (6.00 mmol, 86%) of colourless oil, α : β = 8.5 : 1. Analytical data for predominating α-anomer: ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 4.84 (d, *J* = 3.3 Hz, 1 H), 4.18 (m, 1 H), 3.71 (s, 3 H), 3.67 (m, 1 H), 3.340 (s, 3 H), 3.337 (s, 3 H), 2.57 (dd, *J* = 15.4 Hz, *J* = 9.0 Hz, 1 H), 2.47 (dd, *J* = 15.4 Hz, *J* = 4.4 Hz, 1 H), 2.15 (m, 1 H), 2.07 (m, 1 H), 1.43 (m, 1 H), 1.21 (ddd, *J* = 11.8 Hz, *J* = 11.8 Hz, *J* = 11.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) 171.51 (COOR), 99.07 (*C*H(COR)$_2$), 75.08 (*C*HOCH$_3$), 64.50 (CH), 55.48 (CH_3), 54.66 (CH_3), 51.69 (CH_3), 40.74 (*C*H$_2$COOR) 37.07 (CH_2), 35.78 (CH_2); $\nu_{max}(CHCl_3)/cm^{-1}$ 3000, 2936, 1736, 1436, 1264, 1152, 1124, 1080, 1044, 972; HRMS calcd for $C_{10}H_{18}O_5$ (M^+) 218.1154, found 218.1148.

(4-Benzyloxy-6-methoxy-tetrahydropyran-2-yl)-acetic acid methyl ester (**12**). Prepared according to the general procedure described above from (−)-**10** (600 mg, 2.42 mmol). Yield: 654 mg (2.22 mmol, 92%) of a colourless oil, β : α = 4.5 : 1. Analytical data for the predominating β-anomer: ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.38-7.32 (m, 5 H), 4.73 (dd, *J* = 9.7 Hz, *J* = 2.2 Hz, 1 H), 4.54 (s, 2 H), 4.33 (m, 1 H), 3.93 (m, 1 H), 3.69 (s, 3 H), 3.45 (s, 3 H), 2.63 (dd, *J* = 15.0 Hz, *J* = 8.3 Hz, 1 H), 2.47 (dd, *J* = 15 Hz, *J* = 5 Hz, 1 H), 2.08 (m, 1 H), 1.92 (m, 1 H), 1.50 (ddd, *J* = 13.2 Hz, *J* = 9.7 Hz, *J* = 3.2 Hz, 1 H), 1.40 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 171.4 (COOR), 138.4 (Ar-C), 128.4 (*m*-Ar-C), 127.4 (*o*-and *p*-Ar-C), 99.6 (*C*H(COR)$_2$), 71.9 (CHOBn), 70.3 (OCH_2Ar), 67.5 (CH), 56.1 (CH_3), 51.6 (CH_3), 40.6 (CH_2), 35.4 (CH_2), 34.4 (CH_2); ν_{max} ($CHCl_3$)/cm^{-1} 3064, 2952, 2932, 1736, 1496, 1436, 1340, 1304, 1276, 1228, 1164, 1144, 1096, 1036, 992; MS (RT): M^+ = 294 (24.4), 244 (8), 203 (9.7), 186 (19.8), 171 (27.5), 156 (32), 143 (26.7), 138 (16.5), 124 (29.6), 107 (29), 91 (100), 79 (30.4), 67 (27.9).

General Procedure for Acetal Cleavage. A 0.06 M solution of the methylacetal in a solvent mixture of 60% acetic acid and THF (3:2 v/v) was heated (70°C for substrate **11**, 50°C for **12**) for 96 to 108 h. The reaction mixture was diluted with E and washed successively with water, sat. $NaHCO_3$ solution (2×) and brine. The combined aqueous layers were extracted with E, dried ($MgSO_4$), concentrated and purified by column chromatography (EtOAc/cyclohexane, 1 : 2).

(6-Hydroxy-4-methoxy-tetrahydropyran-2-yl)-acetic acid methyl ester (**13**). Prepared according to the general procedure described above from **11** (118 mg, 0.541 mmol). Yield 90.6 mg (0.444 mmol, 82%) of white solid, mp 43-45°C, α : β = 5 : 1. Analytical data for predominating α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 5.42 (d, *J* = 2.6 Hz, 1 H), 4.44 (m, 1 H), 3.76 (m, 1 H), 3.70 (s, 3 H), 3.36 (s, 3 H), 2.57 (dd, *J* = 15.5 Hz, *J* = 8.5 Hz, 1 H), 2.47 (dd, *J* = 15.5 Hz, *J* = 4.8 Hz, 1 H), 2.19 (m, 1 H), 2.11 (m, 1 H) 1.42 (m, 1 H), 1.24 (ddd, *J* = 11.8 Hz, *J* = 11.6 Hz, *J* = 11.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) 171.78 (COOR), 92.71 (HOCHCOR), 71.71 (*C*HOCH$_3$), 64.70 (CH), 55.50 (CH$_3$), 51.82 (CH$_3$), 40.69 (*C*H$_2$COOR) 37.22 (CH$_2$), 35.84 (CH$_2$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3592, 3008, 2952, 1736, 1436, 1404, 1376, 1328, 1264, 1232,1180, 1152, 1132, 1180, 1080, 1060, 988; HRMS calcd for $C_9H_{15}O_4$ (M^+) 204.0998, found 204.0999.

(6-Hydroxy-4-benzyloxy-tetrahydropyran-2-yl)-acetic acid methyl ester (**14**). Prepared according to the general procedure described above from **12** (210 mg, 0.710 mmol). Yield: 165 mg (0.59 mmol, 82%) of a colourless oil which crystallized in the refrigerator to a white solid, mp 43-45°C, as an anomeric mixture α : β = 1.3 : 1. Analytical data for the predominating α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.42-7.30 (m, 5 H), 5.18 (bs, 1 H), 4.62 (m, 1 H) 4.53 (d, *J* = 2.4 Hz, 2 H), 3.99 (m, 1 H), 3.70 (s, 3 H), 2.61 (dd, *J* = 15.3 Hz, *J* = 6.9 Hz, 1 H), 2.48 (dd, *J* = 15.3 Hz, *J* = 6.1 Hz, 1 H), 2.07 (m, 2 H), 1.81 (dd, *J* = 14.5 Hz, *J* = 2.6 Hz, 1 H), 1.51 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 171.45 (COOR), 137.39 (Ar-C), 128.47 (*m*-Ar-C), 127.69 (*o*-Ar-C), 127.44 (*p*-Ar-C), 92.52 (CHOH), 71.80 (CHOBn), 70.91 (OCH$_2$Ar), 60.69 (CH), 51.70 (CH$_3$), 40.51 (CH$_2$), 34.23 (CH$_2$), 33.39 (CH$_2$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3592, 3492, 3004, 2952, 2932, 1736, 1496, 1440, 1340, 1132, 1108, 1092, 1072, 1048, 996, 976; MS (RT): M^+ = 280 (0.83), 263 (1.94), 231 (0.66), 189 (1.06), 171 (3.80), 156 (9.70), 138 (2.21), 108 (18.39), 91 (100), 77 (10.66).

(2S,4S)-(4-Methoxy-6-oxo-tetrahydropyran-2-yl)-acetic acid methyl ester (+)-**15**. To a suspension of 44.4 mg (0.294 mmol) of sodium bromate and 16.0 mg (0.029 mmol) of ceric ammonium nitrate in 3.0 mL of a solvent mixture (acetonitrile/water, 7 : 3) was added a solution of 60.0 mg (0.294 mmol) of lactol **13** in 0.6 mL of the solvent mixture. The reaction mixture was refluxed for 4 h, diluted with E and washed with sat. $NaHCO_3$ and brine. The combined aqueous layers were extracted with E, the organic layers were dried (Na_2SO_4) and concentrated. Recrystallization from cyclohexane/E (1 : 1) afforded 51.2 mg (0.253 mmol, 86%) of (+)-**15** as a white solid, mp 57-58°C, $[\alpha]_D^{25}$ = +16.7° (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 4.67 (m, 1 H), 3.81 (m, 1 H), 3.73 (s, 3 H), 3.36 (s, 3 H), 2.89 (dd, *J* = 17.0 Hz, *J* = 1.1 Hz, 1 H), 2.84 (dd, *J* = 17.0 Hz, *J* = 1.1 Hz, 1 H), 2.64 (dd, *J* = 16.7 Hz, *J* = 6.1 Hz, 1 H), 2.57 (dd, *J* = 16.7 Hz, *J* = 6.8 Hz, 1 H), 2.42 (dddd, *J* = 13.8 Hz, *J* = 6.7 Hz, *J* = 3.2 Hz, *J* = 1.1 Hz, 1 H), 1.61 (ddd, *J* = 13.8 Hz, *J* = 11.6 Hz, *J* = 8.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) 170.10 (CO), 169.66(CO), 73.05 (*C*HOCH$_3$), 72.10 (CH), 56.10 (CH$_3$), 52.09 (CH$_3$), 40.03 (*C*H$_2$COOR), 36.00 (CH$_2$), 34.22 (CH$_2$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2956, 2932, 1736, 1440, 1232, 1196, 1176, 1136, 1092,1052; HRMS calcd for $C_9H_{14}O_5$ (M^+) 202.0841, found 202.0849.

(2S,4R)-(4-Benzyloxy-6-oxo-tetrahydropyran-2-yl)-acetic acid methyl ester (+)-**16**. Lactol **14** (93.0 mg, 0.332 mmol) was dissolved with activated molecular sieves (3 Å) and N-methylmorpholine N-oxide (59 mg, 0.50 mmol) in 2 mL of absolute DCM. After addition of TPAP[11] (6 mg, 0.016 mmol) under argon atmosphere the mixture was stirred for 4 h at rt. For separation of the product the mixture was passed through a short column and eluated with MTBE. After concentration *in vacuo* the residue was purified by chromatography (10 g silica gel, MTBE) affording 87.6 mg (0.315 mmol, 95%) of (+)-**16** as a colourless oil which crystallized in the refrigerator, mp 38-39°C, $[\alpha]_D^{20}$ = +1.7° (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.40-7.28 (m, 5H), 5.09 (m, 1 H), 4.55 (d, *J* = 2.2 Hz, 2 H), 4.02 (m, 1 H), 3.69 (s, 3 H), 2.80 (ddd, *J* = 17.4 Hz, *J* = 3.5 Hz, *J* = 1.7 Hz, 1 H), 2.78 (dd, *J* = 16.1 Hz, *J* = 6.4 Hz, 1 H), 2.68 (dd, *J* = 17.4 Hz, *J* = 4.6 Hz, 1 H), 2.63 (dd, *J* = 16.1 Hz, *J* = 6.4 Hz, 1 H), 2.25 (ddd, *J* = 14.4 Hz, *J* = 6.4 Hz, *J* = 1.7 Hz, 1 H), 1.77 (ddd, *J* = 14.4 Hz, *J* = 11.7 Hz, *J* = 3.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 169.97 (CO) 169.27 (CO), 137.37 (Ar-C), 128.47 (*m*-Ar-C), 127.88 (*p*-Ar-C), 127.52 (*o*-Ar-C), 72.14 (CH), 70.37 (OCH$_2$Ar), 68.83 (CHOBn), 51.93 (CH$_3$), 39.81 (CH$_2$), 35.75 (CH$_2$), 32.55 (CH$_2$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3040, 2956, 2924, 2864, 1736, 1604, 1436,

1436, 1388, 1252, 1232, 1060; HRMS calcd for $C_{15}H_{18}O_5$ (M^+) 278.1154, found 278.1154. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.72; H, 6.52. Found C, 64.52; H, 6.50.

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