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Chemoenzymatic Synthesis of Enantiomerically Pure β,γ-Disubstituted γ-Lactones

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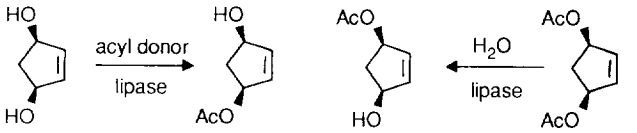
Abstract: The synthesis of enantiomerically pure β,γ-disubstituted γ-lactones is described based on the lipase-catalysed asymmetrisation of the *cis*-cyclopent-2-ene-1,4-diol derivatives **1** or **3**. The cyclopentanones **7** and *ent*-**7** have been obtained *via* epoxidation of the chiral monoacetates **2** or *ent*-**2**, respectively, followed by protecting group interconversion and oxidation. Baeyer-Villiger oxidation of **7** and *ent*-**7** and subsequent acidic methanolysis furnished the title compounds **9** and *ent*-**9**, respectively.

The lactone skeleton is found in many natural products. Therefore, lactones are attractive target molecules in organic synthesis. Furthermore, due to their rich functionality, lactones are versatile intermediates in the synthesis of natural and synthetic bioactive compounds. Many efforts have been made to synthesise the lactone skeleton.[1] Particularly, the synthesis of lactones in enantiomerically pure form is of special interest by using various approaches of asymmetric synthesis. The synthesis of enantiomerically pure lactones based on biocatalytic processes as one of the most challenging tasks has been realised, for instance by oxidation of prochiral diols with horse liver alcohol dehydrogenase,[2] by the microbial Baeyer-Villiger oxidation of racemic or prochiral cyclic ketones,[3] by lipase-catalysed lactonisation of hydroxy carboxylic esters[4] or kinetic resolution of hydroxy lactones.[5] The lipase-catalysed transesterification of the *meso*-diol **1**[6a-c] or hydrolysis of its corresponding *meso*-diacetate **3**[6c,7] were recently investigated in this laboratory and by others. These asymmetrisations represent an easy access to the enantiomerically pure monoacetates **2** or *ent*-**2** (Scheme 1).



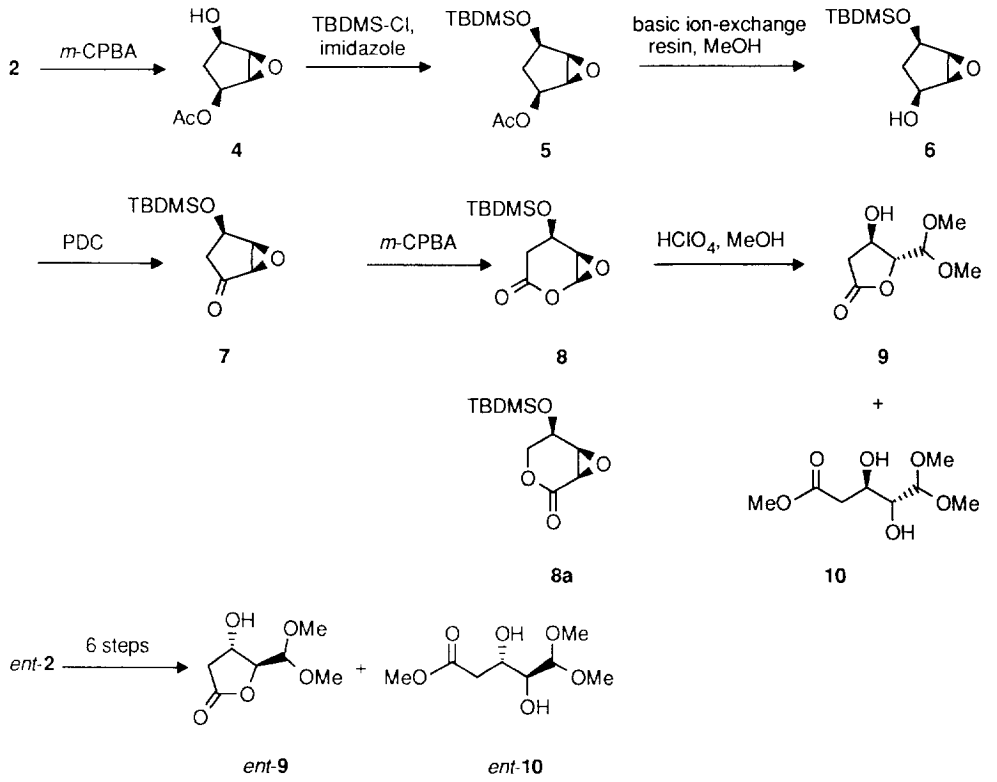
1 **2** *ent*-**2** **3**

Scheme 1

The latter chiral monoacetates have been used as versatile building blocks for the synthesis of prostaglandins,[8] carbocyclic nucleoside analogues,[9] methyl jasmonate,[10] 1,3-dideoxynojirimycin,[11] and brefeldin A.[12]

In this paper will be reported on the synthesis of enantiomerically pure β,γ-disubstituted γ-lactones based on the lipase-catalysed asymmetrisation of the *meso*-diol **1** or its corresponding diacetate **3** (Scheme 2).

Stereoselective epoxidation of the enantiomerically pure monoacetate **2** with *m*-chloroperbenzoic acid (*m*-CPBA) yielded the *cis*-epoxyalcohol **4** in high yield. Alternatively, **2** could be obtained by a lipase-catalysed asymmetrisation of the corresponding epoxy-diol.[6a] Silylation of the monoacetate **4** with *tert*-butyldimethylsilyl chloride (TBDMS chloride) afforded the silyl ether **5** which was subsequently deacetylated furnishing the silyloxy alcohol **6**. This protecting group interconversion was carried out due to the expected higher stability of the TBDMS group compared with the acetate group for the intended further transformations. In addition, the lower polarity of the resulting compounds allowed their extractive work-up from aqueous solutions. Oxidation of the silyloxy alcohol **6** by pyridinium dichromate (PDC) afforded the epoxy-cyclopentanone **7** in high yield.



Scheme 2

Baeyer-Villiger oxidation of **7** by *m*-CPBA, the key step in this synthetic sequence, furnished the epoxy-δ-lactone **8** in a highly regioselective manner and almost quantitative chemical yield. The corresponding regioisomeric lactone **8a** could not be detected in the reaction mixture. The NMR spectra of **8** support its structure. The acetal carbon shows a chemical shift at 76.58 ppm which is low compared with other data for normal acetals. However, this low value is in the same range as found for a similar epoxy-lactone.[13] The lactone **8** was sensitive against water which is an additive of commercial *m*-CPBA. Therefore, a solution of *m*-CPBA in dichloromethane was dried with sodium sulphate before using as oxidising agent. Furthermore, **8** was decomposed by chromatography on silica gel. The procedure avoiding wet *m*-CPBA and chromatography furnished almost analytically pure **8**. γ,δ-Epoxy-δ-lactones have been non-stereoselectively prepared by epoxidation of the corresponding enol-lactones with dimethyldioxirane.[13] Finally, acidic methanolysis of **8** afforded the lactone **9** in 85 % yield and the open-chain dihydroxy ester **10** in 11 % yield as a by-product.

Analogously, this synthetic protocol was applied on the enantiomeric monoacetate *ent*-**2** leading to the enantiomeric γ-lactone *ent*-**9** and the corresponding β,γ-dihydroxy ester *ent*-**10**. The γ-lactones **9** and *ent*-**9** represent derivatives of the enantiomeric 2-deoxy-*L*- and *D*-ribonolactones, respectively. *D*-2-Deoxy-ribonolactone derivatives have been synthesised based on multistep synthesis starting from *D*-ribonolactone.[14]

In summary, the enantiomerically pure γ-lactones **9** and *ent*-**9** have been prepared based on the enantiomeric monoacetates **2** and *ent*-**2**, respectively. These lactones can be useful chiral building blocks. They exhibit different types of functional groups for selective synthetic transformations in order to obtain further substituted γ-lactones or acyclic derivatives.

Experimental

General. All reactions were monitored by thin-layer chromatography on glass plates coated with a 0.25 mm layer of silica gel. Compounds were visualised with a 3.5 % solution of molybdatophosphoric acid in ethanol. Flash chromatography was performed with silica gel 60 (0.063-0.040 mm). ^{1}H NMR spectra were recorded in $CDCl_3$ at 200 MHz on a Bruker WP SY or at 300 MHz on a Varian Gemini 300 spectrometer. ^{13}C NMR spectra were obtained at 75 MHz on a Varian Gemini 300 spectrometer. *J* values are given in Hz. EI mass spectra were measured at 70 eV on the GC/MS-Datensystem HP 5985 B. FAB mass spectra were recorded on the Autospec VG. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

(1*R*,2*R*,4*S*,5*S*)-(−)-2-Hydroxy-6-oxabicyclo[3.1.0]hex-4-yl acetate (4). A solution of **2** (3.00 g, 21.1 mmol) in dichloromethane (200 ml) was treated with *m*-CPBA (10.90 g, 63.3 mmol) and stirred at rt for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed through a pad (5 × 3 cm, h × w) of silica gel with hexane-ethyl acetate (2:1) containing 1 % (v/v) of acetic acid. The fractions containing

crude **4** were combined and purified by flash chromatography with the same eluent to furnish **4** (3.20 g, 96 %) as a colourless oil. $[\alpha]_D^{20}$ = –31.0 (*c* 1.0, $CHCl_3$); {Ref.[6a] $[\alpha]_D^{20}$ = –31.2 (*c* 1.0, $CHCl_3$)}.

(1*S*,2*S*,4*R*,5*R*)-(+)-2-Hydroxy-6-oxabicyclo[3.1.0]hex-4-yl acetate (*ent*-4). $[\alpha]_D^{20}$ = +31.5 (*c* 1.0, $CHCl_3$).

(1*R*,2*R*,4*S*,5*S*)-(–)-2-*tert*-Butyldimethylsilyloxy-6-oxabicyclo[3.1.0]hex-4-yl acetate (5). A solution of **4** (4.35 g, 27.5 mmol) in DMF (20 ml) was treated with imidazole (7.48 g, 110 mmol) and TBDMS chloride (8.29 g, 55 mmol) and stirred at rt for 3 h. The reaction mixture was diluted with hexane-diethyl ether (1:1, 50 ml) and washed three times with water. The organic solution was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was distilled to yield **5** as colourless crystals (6.75 g, 90 %). Bp 120-130°C (1 Pa, Kugelrohr); mp 45-50°C; $[\alpha]_D^{20}$ = –4.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 4.88 (ddd, 1, *J* = 9, 9, 1.5), 4.15 (ddd, 1, *J* = 9, 9, 1.5), 3.55 (dd, 1, *J* = 4, 1.5), 3.42 (dd, 1, *J* = 4, 1.5), 2.17 (ddd, 1, *J* = 12.5, 7.5, 7.5), 2.04 (s, 3), 1.44 (ddd, 1, *J* = 12.5, 8.5, 8.5), 0.88 (s, 9), 0.08 (s, 3), 0.06 (s, 3); ^{13}C NMR: δ –4.77, –4.72, 18.13, 20.90, 25.81, 31.25, 54.61, 57.59, 70.53, 71.96, 171.15. MS (*m/z*) 215 (M^+ – *t*-Bu), 197, 173, 155, 131, 129, 117, 101, 75 (100); calcd.: C 57.32, H 8.88 for $C_{13}H_{24}O_4Si$, found: C 57.24, H 9.00.

(1*S*,2*S*,4*R*,5*R*)-(+)-2-*tert*-Butyldimethylsilyloxy-6-oxabicyclo[3.1.0]hex-4-yl acetate (*ent*-5). Yield: 96 %; $[\alpha]_D^{20}$ = +4.8 (*c* 1.0, $CHCl_3$).

(1*R*,2*R*,4*S*,5*S*)-(+)-2-*tert*-Butyldimethylsilyloxy-6-oxabicyclo[3.1.0]hexan-4-ol (6). A solution of **5** (2.88 g, 10.6 mmol) in MeOH (50 ml) was treated with the basic ion-exchange resin Wofatit SBW (OH^-) (10 g) and stirred at rt for 48 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography with hexane-ethyl acetate (2:1) and subsequently distilled furnishing **6** as colourless crystals (1.93 g, 80 %). Bp 160°C (2 Pa, Kugelrohr); mp 37-39°C; $[\alpha]_D^{20}$ = +3.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 4.02 (m, 1), 3.43 (dd, 1, *J* = 2.5, 1.5), 3.37 (dd, 1, *J* = 2.5, 1.5), 2.74, (d, 1, *J* = 9.5), 2.09 (ddd, 1, *J* = 12.5, 7.5, 7.5), 1.28 (ddd, 1, *J* = 12.5, 8.5, 8.5), 0.84 (s, 9), 0.04 (s, 3), 0.02 (s, 3); ^{13}C NMR δ –4.76, –4.69, 18.11, 25.79, 35.14, 57.30, 58.59, 70.41, 70.67. MS (*m/z*) 173 (M^+ – *t*-Bu), 155, 131, 75 (100); calcd.: C 57.34, H 9.63 for $C_{11}H_{22}O_3Si$, found: C 57.30, H 9.61.

(1*S*,2*S*,4*R*,5*R*)-(–)-2-*tert*-Butyldimethylsilyloxy-6-oxabicyclo[3.1.0]hexan-4-ol (*ent*-6). Yield 84 %; $[\alpha]_D^{20}$ = –3.3 (*c* 1.0, $CHCl_3$).

(1*R*,2*R*,5*R*)-(–)-2-*tert*-Butyldimethylsilyloxy-6-oxabicyclo[3.1.0]hexan-4-one (7). A solution of **6** (2.00 g, 8.7 mmol) in dry dichloromethane (50 ml) was treated with PDC (9.80 g, 26 mmol) and stirred at rt for 18 h. The reaction mixture was diluted with diethyl ether (50 ml) and filtrated through celite. The solvents were removed under reduced pressure and the residue was purified by flash chromatography with hexane-diethyl ether (4:1). Kugelrohr distillation yielded **7** as colourless crystals (1.73 g, 87 %). Bp 125°C (50 Pa); mp 26-28°C $[\alpha]_D^{20}$ = –9.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 4.40 (ddd, 1, *J* = 7, 7, 1.5); 3.85 (dd, 1, *J* = 2.5, 1.5), 3.38 (d, 1, *J* = 2.5), 2.32 (dd, 2, *J* =5, 7), 0.90 (s, 9), 0.12 (s, 3), 0.09 (s, 3); ^{13}C NMR δ –4.73, 18.76, 25.72, 39.53, 56.48,

59.78, 67.46, 205.27. MS (*m/z*) 171 (M^+ – *t*-Bu), 143, 129 (100), 101, 75; calcd.: C 57.85, H 8.83 for $C_{11}H_{20}O_3Si$, found: C 57.95, H 8.94.

(1*S*,2*S*,5*S*)-(+)-2-*tert*-Butyldimethylsilyloxy-6-oxabicyclo[3.1.0]hexan-4-one (*ent*-7). Yield 80 %; $[\alpha]_D^{20}$ = +9.8 (*c* 1.0, $CHCl_3$).

(1*S*,5*R*,6*R*)-(−)-5-*tert*-Butyldimethylsilyloxy-2,7-dioxabicyclo[4.1.0]heptan-3-one (8). A 0.2 M solution of *m*-CPBA in dichloromethane (80 ml, dried for 2 h with Na_2SO_4) was treated with **7** (1.00 g, 4.4 mmol) and allowed to stand at rt for 24 h. The reaction mixture was washed with a saturated solution of sodium thiosulphate (4 × 20 ml), a saturated solution of sodium bicarbonate (1 × 20 ml) and water (1 × 20 ml). The organic phase was dried (Na_2SO_4) and concentrated to dryness to yield **8** (1.07 g, 100 %) as a homogeneous white solid which gave reasonable analytical data without further purification. $[\alpha]_D^{20}$ = −32.9 (*c* 1.0, $CHCl_3$); ^1H NMR δ 5.15 (d, 1, *J* = 3), 4.35 (dd, 1, *J* = 8, 8), 3.30 (m, 1), 2.63 (d, 2, *J* = 8), 0.85 (s, 9), 0.08 (s, 3), 0.06 (s, 3); ^{13}C NMR δ −4.75, −4.71, 17.97, 25.60, 37.11, 54.70, 64.36, 76.58, 166.64. MS (*m/z*) 187 M^+ – *t*-Bu), 159, 145, 129, 117 (100), 101, 89, 75; calcd.: C 54.06, H 8.25 for $C_{11}H_{20}O_4Si$, found: C 53.53, H 8.34.

(1*R*,5*S*,6*S*)-(+)-5-*tert*-Butyldimethylsilyloxy-2,7-dioxabicyclo[4.1.0]heptan-3-one (*ent*-8). Yield 100 %; $[\alpha]_D^{20}$ = +28.9 (*c* 1.0, $CHCl_3$).

(4*R*,5*R*)-(+)-5-Dimethoxymethyl-4-hydroxydihydrofuran-2-one (9) and (3*R*,4*R*)-(+)-3,4-Dihydroxy-5,5-dimethoxypentanoic acid methyl ester (10). A solution of **8** (1.07 g, 4.4 mmol) in MeOH (50 ml) was treated with 70 % $HClO_4$ (0.070 ml) and allowed to stand at rt for 24 h and at 50°C for a further 4 h. The reaction mixture was treated with triethyl amine (2.5 ml) and concentrated under reduced pressure. The residue was purified by flash chromatography with hexane-ethyl acetate (1:2) to furnish **9** (0.615 g, 85 %) and **10** (0.099 g, 11 %) both as colourless oils.

9: $[\alpha]_D^{20}$ = +16.1 (*c* 1.15, $CHCl_3$); ^1H NMR δ 4.56 (m, 1), 4.36 (d, 1, *J* = 3.5), 4.30 (d, 1, *J* = 3.5), 3,44 (s, 3), 3.43 (s, 3), 2.87 (dd, 1, *J* = 18, 7), 2.56 (d, 1, *J* = 3.5), 2.38 (dd, 1, *J* = 18, 3); ^{13}C NMR δ 37.81, 56.28, 57.72, 67.48, 86.23, 104.27, 175.73. MS (*m/z*) 145 (M^+ – OMe), 127, 99, 85, 75 (100); calcd.: C 47.72, H 6.86 for $C_7H_{12}O_5$, found: C 47.33, H 6.92.

10: $[\alpha]_D^{20}$ = +31.0 (*c* 1.0, $CHCl_3$); ^1H NMR δ 4.37 (d, 1, *J* = 5), 4.06 (m, 1), 3.65 (s, 3), 3.55 (m, 1), 3.42 (s, 3), 3.40 (s, 3), 3.33 (d, 1, *J* = 4), 2.58 (dd, 2, *J* = 8, 4), 2.55 (d, 1, *J* = 4); ^{13}C NMR δ 37.18, 51.82, 55.21, 55.37, 68.46, 72.68, 104.59, 173.32. MS (FAB) (*m/z*) 177 (M^+ – OMe, 159 (100), 145; calcd.: C 46.15, H 7.74 for $C_8H_{16}O_6$, found: C 45.82, H 7.80.

(4*S*,5*S*)-(−)-5-Dimethoxymethyl-4-hydroxydihydrofuran-2-one (*ent*-9). Yield 81 %;$[\alpha]_D^{20}$ = −15.2 (*c* 1.3, $CHCl_3$).

(3*S*,4*S*)-(−)-3,4-Dihydroxy-5,5-dimethoxypentanoic acid methyl ester (*ent*-10). Yield 17 %; $[\alpha]_D^{20}$ = −28.8 (*c* 1.0, $CHCl_3$).

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