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Lipase Mediated Desymmetrization of *Meso* 2,6-Di(acetoxymethyl)-tetrahydropyran-4-one Derivatives. An Innovative Route to Enantiopure 2,4,6-Trifunctionalized C-Glycosides

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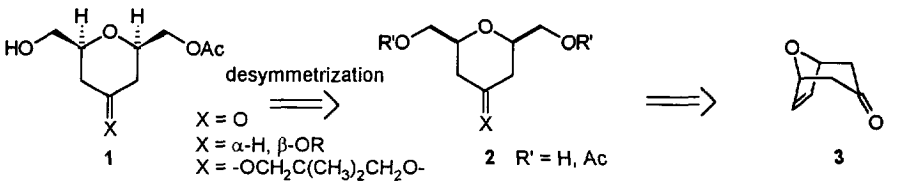
Abstract: The desymmetrization of several *meso*-configurated 2,4,6-trifunctionalized tetrahydropyrans was studied. Amongst the derivatives investigated the conformationally more rigid spiro ketal **8b** afforded hydroxy-acetate (-)-**12** in excellent chemical yield and enantiomeric excess. The absolute configuration of the resulting 2,4,6-trifunctionalized C-glycosides was established by X-ray crystal diffraction.

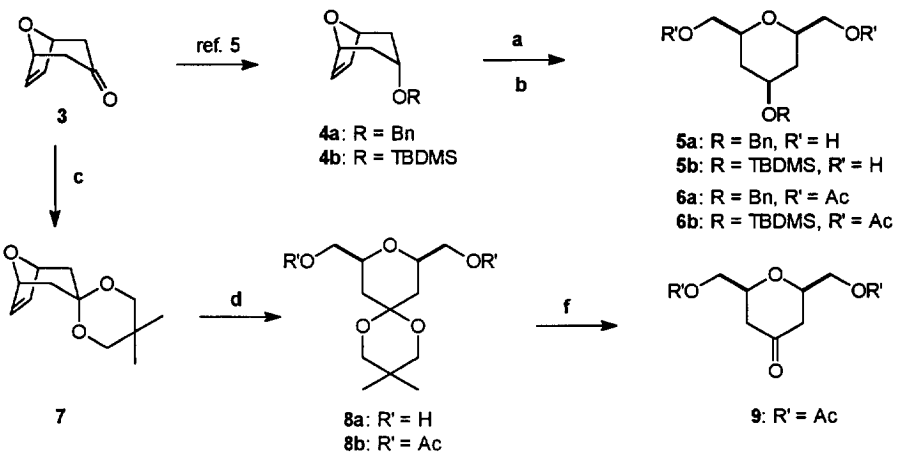
As part of an ongoing program aimed at the enantioselective synthesis of substituted tetrahydropyran subunits (e.g. **1**) as chiral building blocks of marine macrolide natural products such as the bryostatins[1], we envisioned *meso* substrates represented by general structure **2** as suitable precursors (Scheme 1). Prochiral molecules of type **2** are available from 8-oxabicyclo[3.2.1]oct-6-en-3-one **3** by functionalization and oxidative cleavage of the C-C double bond.



Scheme 1

It occurred to us that the differentiation between the two enantiotopic groups (either hydroxymethyl or acetoxymethyl) in σ-symmetric compounds **2** should be feasible using an enzymatic approach[2] to give in theory enantiopure 2,4,6-trifunctionalized C-glycosides in 100% chemical yield. The desymmetrization of *meso* substrates has recently become a powerful methodology in the *de novo* synthesis of enantiomerically pure compounds.[3]

The synthesis of *meso* substrates **5a/b**, **6a/b**, **8a/b** and **9** is straightforward and outlined in Scheme 2. Starting from readily available oxabicyclic ketone[4] **3** and following already established procedures, *endo*-benzyl ether[5a] **4a** and TBDMS-ether[5b] **4b** were prepared from **3**. Access to the crystalline *meso* diols **5a** and **5b** was gained through ozonolysis and *in situ* reduction with $NaBH_4$ (100 % and 95 % yield, respectively). Successive acetylation furnished *meso* diacetates **6a** and **6b** in high yield.



a) i. O_3, $MeOH/CH_2Cl_2$ (4:1) -78 to -20 °C, then $NaBH_4$, 0 °C to r.t., 100 %; ii. Ac_2O, cat. 4-DMAP, py, r.t., 95 %; **b)** i. O_3, $MeOH/CH_2Cl_2$ (4:1) -78 to -20 °C, then $NaBH_4$, 0 °C to r.t., 95 %; ii. AcCl, py, 0 °C to r.t., 84 %; **c)** 2,2,5,5-Tetramethyl-1,3-dioxane, cat. p-TsOH, 35-45 mm Hg, 6 d, 50 % (borsm 88 %); **d)** i. O_3, $MeOH/CH_2Cl_2$ (4:1) -78 to -20 °C, then $NaBH_4$, -20 to 0 °C, 98 %; ii. Ac_2O, cat. 4-DMAP, py, r.t., 91 %; **f)** Acetone, cat. $Pd(CH_3CN)_2Cl_2$, r.t., 72 %.

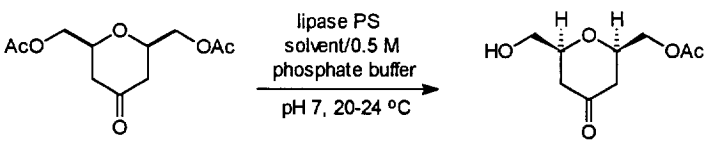
Scheme 2

In order to circumvent problems with the oxidative fission of the C-C double bond in ketone **3** the carbonyl group of the acid labile bicyclic structure[6] was protected *via* a suitably engineered transketalization procedure. An excess of 2,2,5,5-tetramethyl-1,3-dioxane in the presence of a catalytic amount of *p*-TsOH at reduced pressure afforded crystalline tricyclic ketal **7** in 50 % isolated yield, together with 43 % of recovered starting material **3**. Application of the ozonolysis protocol furnished in almost quantitative yield (98 %) *meso* diol **8a** which could be converted into diacetate **8b** (91 %). Deprotection and regeneration of the carbonyl functionality to give **9** was best carried out through Pd^{II}-assisted transketalization[7] with a large excess of acetone (72 % isolated yield). The reaction sequences outlined in Scheme 2 allow the synthesis of *meso* diols and *meso* diacetates of the 2,4,6-trisubstituted tetrahydropyran series in multigram quantities.

In preliminary studies *meso* diols **5b** and **8a** as well as *meso* diacetates **6b**, **8b** and **9** were submitted to the action of various esterases and lipases in transesterification and hydrolysis reactions, respectively. Amongst enzymes investigated briefly (see Experimental), lipase PS from *Pseudomonas cepacia* (Amano) was found to be the most promising biocatalyst in terms of conversion of starting materials and selectivity towards

monofunctionalization. The observed degree of monofunctionalization was especially high in hydrolysis, whereas in transesterification reactions significant amounts of *meso* diacetates were isolated. This phenomenon was attributed to the poor solubility of the investigated *meso* diols in organic solvents. Consequently, lipase PS catalysed hydrolysis reactions of *meso* diacetates (e.g. **9**) were investigated more closely.

Preparative hydrolysis reactions were performed in a heterogeneous mixture of an organic solvent and a 0.5 molar phosphate buffer solution at room temperature, with a pH-stat[8] maintaining the pH value at 7 by automatic addition of 1 molar NaOH (Scheme 3). The enantiomeric purity of the monoacetate **(-)-10** was easily determined by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$ and by ^{1}H NMR of the corresponding Mosher esters[9] prepared from *S*-MTPA-Cl (see Experimental). The absolute configuration was established by X-ray crystallographic analysis of a derivative bearing a heavy atom (see below).



9 **(-)-10**

Scheme 3

Table 1: Lipase PS Mediated Hydrolysis of *meso* Diacetate **9**

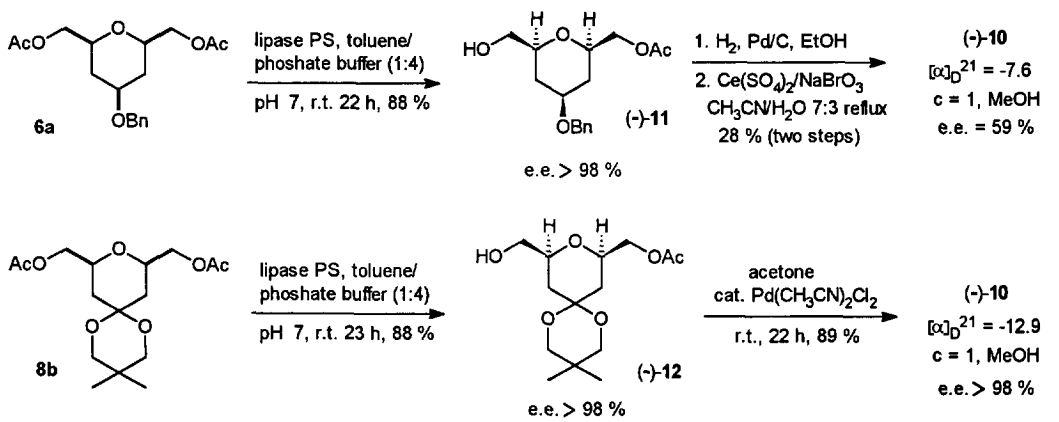
#	Solvent	Solvent/buffer	Units/mmol	Time [h]	Yield [%][a]	$[\alpha]_D$[b]	e.e. [%]
1	MTB-ether	4 : 1	1500	32	85	-6.4	50
2	toluene	2.5 : 1	1500	92	88	-8.5	66
3	toluene	1 : 2.3	1700	24	78	-8.8	68
4	toluene	1 : 4	1000	43	80	-9.1	70
5	petrolether	1 : 4	1500	24	80	-8.2	64
6	-	buffer only[c]	1500	78	43	-7.5	59

[a] Isolated yield of pure **(-)-10**, [b] c = 1, MeOH. [c] 0.06 molar solution of **9** in phosphate buffer

As can be seen from Table 1, the influence of the organic cosolvent on the enantioselectivity of the lipase PS catalyzed hydrolysis of diacetate **9** was relatively low. Values for the enantiopurity of monoacetate **(-)-10** range from 50 to 70 % e.e. with best results obtained in the system toluene/phosphate buffer. Within this system a marginal influence of the ratio of cosolvent to phosphate buffer on the enantioselectivity of the hydrolysis reaction was observed. Although the hydrolysis was only moderately pro-*S* selective with lipase PS, hydrolysis of the second acetate to the corresponding diol was actually quite slow under the reaction conditions. Interestingly the observed e.e. values in lipase PS catalyzed hydrolysis reactions were almost independent of the % conversion of starting material.

To improve the enantioselectivity for the conversion of *meso* diacetate **9** into desired monoacetate[10] the "enriched racemates" of (-)-**10** were incubated with some esterases and lipases in the presence of acylating agents [PLE, esterase from pig liver, Fluka; CCL from *Candida cylindracea* (now classified as *Candida rugosa*), Sigma; lipase PS; isopropenyl acetate and vinyl acetate]. Again lipase PS was found to be the most active biocatalyst and again the enantioselectivity of the enzyme in this "kinetic resolution" was found to be only moderate. At best monoacetate (-)-**10** was obtained in 70 % e.e. starting from 58 % e.e. with 25 % conversion of starting material (lipase PS, isopropenyl acetate, 45 °C, 24 h).

In contrast, structurally similar *meso* diacetates *lacking* the free carbonyl group i.e. the benzyl ether **6a** and the ketal **8b** could be desymmetrized upon the action of lipase PS in a 4:1 mixture of 0.5 molar phosphate buffer and toluene at pH 7. The corresponding 2,4,6-trifunctionalized C-glycosides (-)-**11** and (-)-**12** were obtained in high chemical and excellent optical yield (Scheme 4). It was interesting to note that (as in the case of substrate **9**) only very small amounts of *meso* diols **5a** and **8a** were formed in the lipase PS catalyzed hydrolysis reactions. Upon scale up (3.5 g, 10.5 mmol) no loss of either chemical or optical yield in the desymmetrization of **8b** was observed. The enantiopurity of the monoacetates was determined by ^{1}H NMR for (-)-**11** in the presence of (+)-Eu(hfc)$_3$ and for (-)-**12** *via* the Mosher ester prepared from *S*-MTPA-Cl.



Scheme 4

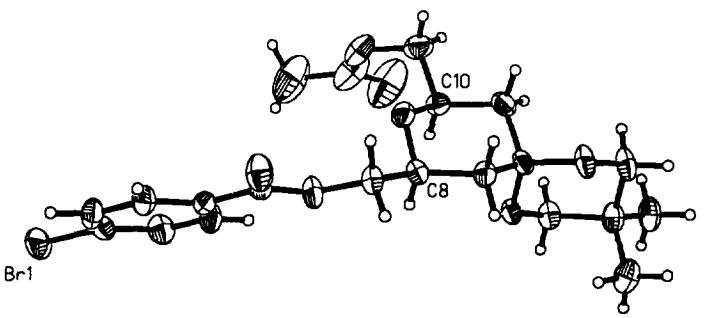
To confirm the absolute configuration of C-glycoside derivative (-)-**11** the monoacetate was converted into keto-monoacetate (-)-**10** by debenzylation and successive oxidation of the secondary alcohol.[11] The yield of product was rather low (28 %, two steps) and partial racemization through intermolecular acetate scrambling, presumably in the oxidation step, occurred as e.e.-determination of the product revealed. Regeneration of the keto carbonyl from the ketal (-)-**12** was more straightforward. Pd^{II}-mediated transketalization in acetone furnished (-)-**10** in high chemical yield and without racemization. The e.e. of the isolated product by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$ was shown to be higher than 98 %. In comparison to the ketone substrate **9**,

significantly higher pro-*S* selectivity was accomplished with both benzyl ether **6a** and ketal derivative **8b** as substrates.

Similar improvements of the enantioselectivity by changing a ketone into a ketal functionality have been reported by Hemmerle and Gais[12a] for the desymmetrization of *meso* cyclopentanone derivatives: With the unmasked keto group hydrolysis using porcine pancreatic lipase (PPL) gave moderate selectivity (e.e. 50 %), upon modification of the latter by ketalisation a remarkable increase of selectivity up to 94 % e.e. was observed (similar results in HLADH mediated reactions have been reported by Jones *et al.*[12b]). Recently, Kazlauskas[13] proposed an empirical rule that predicts which enantiomer of a primary alcohol reacts faster in reactions catalyzed by lipase from *Pseudomonas cepacia*. However, primary alcohols and acetates with an oxygen atom attached to the stereocenter had to be excluded from the rule presumably due to high conformational flexibility which allows the substrate to adopt different reactive conformers thus decreasing the ability of the enzyme to bind selectively and discriminate one enantiotopic group. We suggest that increased conformational mobility of keto substrate **9** caused by the sp^2 carbon atom in the ring is responsible for the moderate selectivity (70 % e.e.).[14] In striking contrast, conformationally more rigid ketal **8b** and benzyl ether **6b** (all three substituents of the tetrahydropyran ring can adopt equatorial positions) were desymmetrized with significantly higher stereoselectivity (> 98 % e.e.) by the action of lipase PS.

A *p*-bromobenzoyl derivative was prepared from enantiopure alcohol (-)-**12** by standard methods (*p*-bromobenzoyl chloride, cat. 4-DMAP, pyridine, CH_2Cl_2). Repeated recrystallization of the crude material from petrolether/ether yielded single crystals (mp 97-98 °C). With this heavy atom derivative in hand the absolute stereochemistry of monoacetate (-)-**12** - and thus ketone (-)-**10** and benzyl ether (-)-**11** - was established.[15] Figure 1 shows the ORTEP drawing of *p*-bromobenzoyl ester of monoalcohol (-)-**12**.

Figure 1: Single-crystal X-ray structure of *p*-bromobenzoyl ester of alcohol (-)-**12**.



In conclusion, starting from 8-oxabicyclo[3.2.1]oct-en-3-one we have outlined an efficient and innovative construction of enantiopure 2,4,6-trifunctionalized C-glycosides of relevance in a wide variety of biologically active natural products.[16]

Experimental

General: Melting points: Büchi apparatus, not corrected. Optical rotations: Perkin-Elmer 241 automatic polarimeter. Infrared spectra: Perkin-Elmer 1710 spectrometer. ^{1}H NMR spectra were recorded at 200 MHz and ^{13}C NMR spectra at 50 MHz (Bruker WP 200) in $CDCl_3$ (APT, Attached Proton Test: spin echo base selection of multiplicitites of ^{13}C signals with quaternary C and CH_2 carbon atoms giving positive signals "+" while CH and CH_3 carbon atoms giving negative signals "-"). Low and High resolution (MS, MS-FAB, HRMS): Finnigan MAT 312 spectrometer, 70 eV at r.t. (unless otherwise stated) with relative intensities in parenthesis. Elemental analysis: Heräus CHN-Rapid. Preparative column chromatography: silical gel from J. T. Baker (partical size: 30-60 μm). Analytical TLC: Merck silica plates (aluminium baked 0.2 mm, 60 F_{254}). All Reactions were carried out under nitrogen in dried glassware except enzyme catalysed reactions. CH_2Cl_2 was distilled from CaH_2 prior to use, methanol from magnesium. Petrolether (PE) refers to light petroleum (bp 30-60 °C) and ether to diethyl ether, distilled prior to use. Enzymes were obtained as stated and were used without further purifications.

Preparation of *meso* Diols and Diacetates

General Procedure for Ozonolysis with *in situ* Reduction. The olefin was dissolved in a 4:1 mixture of dried methanol and CH_2Cl_2 (0.2 molar), cooled to -78 °C and ozone (~ 3 % in an O_2-stream) was bubbled through the solution until saturation with ozone occurred (blue colour). Excess of ozone was removed by bubbling nitrogen through the reaction mixture, the cooling bath was removed and the colourless solution was allowed to warm up to -20 °C. Upon portionwise addition of solid $NaBH_4$ (2.2 eq) the reaction mixture gradually warmed up to 0 °C. After stirring 1 h at 0 °C the suspension was carefully neutralized to pH 7 with 10 % aq. H_2SO_4, the volatile solvents were removed and the white residue was treated with saturated NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (5x), the combined organic layers were dried (Na_2SO_4) and evaporated to yield the crude product as a colourless solid.

5a: Prepared according to the general procedure described above from **4a** (4.33 g, 20 mmol). Yield 5.05 g (100 %) of a colourless solid, mp 92-93 °C (for analytical purposes the crude product was recrystallized from ether to give crystals, mp 100-101 °C). IR ($CHCl_3$) ν 3468, 3396, 2948, 2920, 1360, 1144,1036 cm^{-1}; ^{1}H NMR δ 7.45-7.25 (m, 5 H), 4.55 (s, 2H), 3.75-3.42 (m, 7 H), 2.78 (b s, 2 H), 1.96 (dd, ^2J = 12 Hz, ^3J = 5 Hz, 2 H), 1.28 (q, $^{2/3}J$ = 12 Hz, 2 H); ^{13}C NMR δ 139.96 (+, Ar-C), 129.35 (-, Ar-C), 128.79 (-, Ar-C), 128.60 (-, Ar-C), 77.74 (-, $OCHR_2$), 75.88 (-, $BnOCHR_2$), 70.71 (+, OCH_2Ph), 66.46 (+, CH_2OH), 35.10 (+, CH_2); MS *m/z* (90 °C) no M^+, 221 (31.3, M-CH_3O), 157 (6.5), 146 (10.2), 115 (30.6) 91 (100); Anal. Calcd for $C_{14}H_{20}O_4$ C: 66.65, H: 7.99 Found C: 66.60, H: 7.91.

6a: To a solution of *meso* diol **5a** (4.07 g, 17.3 mmol) and 4-DMAP (60 mg) in dry pyridine (10.5 ml) at r.t. was added dropwise acetic anhydride (4.5 ml, 48 mmol). The reaction was terminated after 5 h by diluting with ether (500 ml) and the resulting mixture was washed successively with H_2O, 2N HCl and brine. The organic layer was dried ($MgSO_4$), evaporated in vacuo to afford a yellow oil which was purified by column chromatography (180 g silica gel, petrolether/ether ~ 2:1) to yield 5.53 g of **6a** as a viscous oil (95 %). IR (neat) ν 1740, 1245 1096, 1073, 1023 cm^{-1}; ^1H NMR δ 7.40-7.25 (m, 5 H), 4.58 (s, 2 H), 4.12 (d, ^2J = 5 Hz, 4 H), 3.72-3.52 (m, 3 H), 2.10 (s, 6 H), 2.08-1.97 (m, 2 H), 1.34 (q, $^{2/3}J$ = 12 Hz, 2 H); ^{13}C NMR δ 170.83 (+, $OCOCH_3$), 138.16 (+, Ar-C), 128.39 (-, Ar-C), 127.62 (-, Ar-C), 127.47 (-, Ar-C), 73.73 (-, $BnOCHR_2$), 73.56 (-, $OCHR_2$), 69.70 (+, OCH_2Ph), 66.60 (+, CH_2OAc), 33.95 (+, CH_2), 20.83 (-, $OCOCH_3$); MS-FAB *m/z* 337 (M+1, 100), 335 (M-1, 35).

7: Freshly distilled oxabicyclic ketone **3** (5.58 g, 45 mmol) was dissolved in 65 ml of 2,2,5,5-tetramethyl-1,3-dioxane.[17] *p*-TsOH•$2H_2O$ (375 mg, 1.8 mmol) was added and the orange coloured solution was stirred at r.t. for 3.5 days under reduced pressure (~ 35-45 mm Hg) to remove liberated acetone. Additional 2,2,5,5-tetramethyl-1,3-dioxane (15 ml) and *p*-TsOH•$2H_2O$ (93 mg, 0.45 mmol) were added and stirring under reduced pressure was continued. After 6 days the reaction was quenched with triethylamine (0.5 ml). The bulk of the 2,2,5,5-tetramethyl-1,3-dioxane (64 ml) was recoverd by distillation under reduced pressure (29 °C/~15 mm, dry ice cooled trap) and the dark residue was chromatographed (500 g silica gel, solvent gradient: petrolether/ether ~ 1:1 to ether/methanol 10:1) to afford 4.70 g of pure **7** (50 %) as colourless crystals, mp 67-67.5 °C and 2.69 g of starting material **3** (43 %, contaminated with 6 % of 7). IR (KBr) ν 2955, 2864,1362, 1345, 1281, 1164, 1103 cm^{-1}; ^1H NMR δ 6.15 (s, 2 H), 4.78 (d, ^3J = 4 Hz, 2 H), 3.43 (s, 4 H), 2.21 (d, ^2J = 14 Hz, 2 H), 1.98 (dd, ^2J = 14 Hz, ^3J = 4 Hz, 2 H), 0.94 (s, 6 H); ^{13}C NMR δ 132.35 (-, RHC=C), 96.12 (+, R_2CO_2), 77.12 (-, $OCHR_2$), 69.48 (+, OCH_2), 69.45 (+, OCH_2), 36.48 (+, CH_2), 29.75 (+, CR_4), 22.64 (-, CH_3); MS *m/z* 210 (M^+, 13.4), 181 (26.5), 128 (100), 95 (18.0); Anal. Calcd for $C_{12}H_{18}O_3$ C: 68.55, H: 8.63 Found C: 68.48, H: 8.44.

8a: Prepared according to the general procedure described above from **7** (4.21 g, 20 mmol). Yield 4.81 g (98 %) of a colourless solid/foam, mp 60-64 °C. IR ($CHCl_3$) ν 3604, 3448, 2960, 2932, 2872, 1224, 1136, 1088 cm^{-1}; ^1H NMR δ 3.82-3.53 (m, 8 H), 3.52 (s, 2 H), 3.50 (s, 2 H), 2.10 (d, ^2J = 12 Hz, 2 H), 1.33 (t, $^{2/3}J$ = 12 Hz, 2H), 0.96 (s, 6 H); ^{13}C NMR δ 96.33 (+, R_2CO_2), 74.48 (-, $OCHR_2$), 69.97 (+, OCH_2R), 69.61 (+, OCH_2R), 65.40 (+, CH_2OH), 34.15 (+, CR_4), 30.04 (+, CH_2), 22.50 (-, CH_3); MS *m/z* (60 °C) no M^+, 215 (100), 158 (54.1), 129 (18.6), 85 (26.2), 71 (44.6), 69 (75.8); HRMS Calcd. for $C_{11}H_{19}O_4$ (M-31): 215.1283, Found: 215.1284.

8b: Acetic anhydride (5.2 ml, 55 mmol) was added dropwise to a solution of *meso* diol **8a** (4.81 g, 19.5 mmol) and 4-DMAP (73 mg) in dry pyridine (11 ml) at r.t. After stirring at r.t. for 5 h the reaction was quenched with

H_2O (0.5 ml). Ether (600 ml) was added and the organic layer was successively washed with H_2O, 2N HCl (2x) and brine. The ether solution was dried ($MgSO_4$), concentrated in vacuo and afforded after flash chromatography (200 g silica gel, petrolether/ether 2:3) 5.87 g of a colourless solid, mp 59.5-60 °C (91 %). IR (KBr) ν 2966, 1737, 1362, 1265, 1239, 1168, 1052 cm^{-1}; ^1H NMR δ 4.11 (d, ^3J = 5 Hz, 4 H), 3.87-3.75 (m, 2 H), 3.54 (s, 2 H), 3.00 (s, 2 H), 2.19 (d, ^2J = 13 Hz, 2H), 2.09 (s, 6 H), 1.37 (t, $^{2/3}J$ = 13 Hz, 2 H); ^{13}C NMR δ 170.88 (+, $OCOCH_3$), 95.99 (+, R_2CO_2), 72.01 (-, $OCHR_2$), 70.21 (+, OCH_2), 69.83 (+, OCH_2), 66.59 (+, CH_2OAc), 34.66 (+, CH_2), 30.32 (+, CR_4), 22.59 (-, CH_3), 20.90 (-, $OCOCH_3$); MS *m/z* (80 °C) no M^+, 271 (M-29, 8.3), 257 (57.2), 229 (13.9), 157 (71.2), 128 (30.2), 101 (100); Anal. Calcd for $C_{16}H_{26}O_7$ C: 58.17, H: 7.99 Found C: 58.13, H: 7.77.

9: A solution of ketal **8b** (915 mg, 2.77 mmol) and $Pd(CH_3CN)_2Cl_2$ (47 mg, 0.18 mmol) in acetone (75 ml) was protected from light and stirred at r.t. for 66 h. After addition of pyridine (60 µml) and concentration in vacuo flash chromatography (30 g silica gel, petrolether/ether) of the residue yielded 488 mg (72 %) of a colourless oil which crystallized in the refrigerator, mp 56-57 °C. IR (KBr) ν 1734, 1387, 1245, 1046 cm^{-1}; ^1H NMR δ 4.23-4.17 (m, 4 H), 4.01-3.86 (m, 2 H), 2.46-2.38 (m, 4 H), 2.02 (s, 6 H); ^{13}C NMR δ 204.52 (+, R_2C=O), 170.54 (+, -$OCOCH_3$), 74.49 (-, $OCHR_2$), 65.73 (+, CH_2OAc), 43.47 (+, CH_2), 20.69 (-, -$OCOCH_3$); MS *m/z* (80 °C) no M^+; 184 (M-60, 11.8), 171 (17.8), 124 (28.9), 111 (100); Anal. Calcd for $C_{11}H_{16}O_6$ C: 54.09, H: 6.60 Found C: 54.03, H: 6.53.

Typical Procedure for Enzyme Screening. *Hydrolysis:* 10 mg of diacetate (**6b**, **8b**, or **9**) were dissolved in 1 ml of a biphasic reaction system consisting of 50 mM phosphate buffer (pH 7) and organic solvent (toluene) (1:1) in 1.5 ml Eppendorf tubes and incubated in a thermoshaker (Eppendorf, Hamburg, Germany) at 37 °C and 1300 rpm, and then 200 U enzyme (PLE, pig liver esterase, Fluka; *Rhizopus delemar* lipase, Amano D; *Aspergillus niger* lipase, Amano F-AP 15; *Pseudomonas cepacia* lipase, Amano PS) were added. *Transesterification:* 10 mg of diol (**5b** or **8a**) were dissolved in 1 ml of organic solvent (toluene, THF or MTB-ether) in 1.5 ml Eppendorf tubes in the presence of a twofold excess of vinyl acetate and incubated in a thermoshaker at 37° C and then the same enzymes as for hydrolysis were added. The reaction progress was monitored by TLC. Preparative hydrolyses were performed in a pH-stat system (Metrohm, Buchs, Switzerland) with automatic titration of released acetic acid. Best results in hydrolysis reactions were achieved with lipase PS giving monoacetates with negative rotation values whereas hydrolysis of **8b** and **9** with pig liver esterase gave higher proportions of diols with monoacetates having positive rotation values. Transesterifications were carried out at 37 °C in 10 ml glass stoppered round bottom flasks in an oil bath stirred at 400 rpm. In a typical experiment 0.5 mmol of **8a**, vinyl acetate (1 mmol) and 1500 U lipase PS in toluene (3 ml) were used. It was generally observed that acylation resulted in lower enantioselectivity and higher formation of diacetate. Lowering the temperature to 25 or 4 °C gave no improvement (data not shown).

Determination of Enantiomeric Excess for Optically Active Monoacetates (-)-10, (-)-11 and (-)-12

(-)-10: (a) The e.e. for compound **(-)-10** could be determined by ^{1}H NMR analysis in the presence of chiral shift reagent (+)-Eu(hfc)$_3$. The acetyl signals showed a significant difference in their chemical shift values which allowed a calculation of the integration area after resolution enhancement. (b) The e.e. of monoacetate **(-)-10** could also be determined by ^{1}H NMR analysis of its (*R*)-MTPA ester prepared by standard methods (*S*-MTPA-Cl, cat. 4-DMAP, pyridine, CH_2Cl_2). ^{1}H NMR δ 7.59-7.52 (m, 2 H), 7.47-7.38 (m, 3 H), 4.50 (dd, ^2J = 12 Hz, ^3J = 4 Hz, 1 H), 4.39 (dd, ^2J = 12 Hz, ^3J = 5.5 Hz, 1 H), 4.18-4.15 (m, 2 H), 4.04-3.86 (m, 2 H), 3.57 (m, 3 H), 2.42-2.33 (m, 4 H), 2.05 (s, 3 H). (*R*)-MTPA esters of **(-)-10** with d.e. lower than 98 % showed a signal at 2.04 ppm for the acetyl group of the diastereomer.

(-)-11: The e.e. for monoacetate **(-)-11** was determined by ^{1}H NMR analysis in the presencs of chiral shift reagent (+)-Eu(hfc)$_3$. The acetyl signals showed a significant difference in their chemical shift values which allowed a calculation of the integration area after resolution enhancement.

(-)-12: The e.e. of compound **(-)12** was determined by ^{1}H NMR analysis of its (*R*)-MTPA ester prepared by standard methods (*S*-MTPA-Cl, cat. 4-DMAP, pyridine, CH_2Cl_2). ^{1}H NMR δ 7.62-7.53 (m, 2 H), 7.45-7.38 (m, 3 H), 4.45 (dd, ^2J = 11.5 Hz, ^3J = 4 Hz, 1 H), 4.30 (dd, ^2J = 11.5 Hz, ^3J = 6 Hz, 1 H), 4.08 (d, ^3J = 5 Hz, 2 H) 3.93-3.73 (m, 2 H), 3.57 (m, 3 H), 3.51 (s, 2 H), 3.46 (s, 2 H), 2.24-2.11 (m, 2 H), 2.03 (s, 3 H), 1.37-1.23 (m, 2 H), 0.97 (s, 3 H), 0.94 (s, 3 H). (*R*)-MTPA esters of **(-)-12** with d.e. lower than 98 % showed a signal at 2.01 ppm for the acetyl group of the diastereomer.

Preparation of Optically Active 2,4,6-Trifunctionalized C-Glycosides

General Procedure for Lipase PS Mediated Hydrolysis of ***9***. To *meso* diacetate **9** (0.5 to 3.5 mmol) dissolved in the chosen solvent was added 0.5 molar phosphate buffer solution. The vigorously stirred biphasic reaction mixture was incubated with indicated amounts of lipase PS at r.t. (20-24 °C) and the pH was maintained at 7 by automatic addition of 1 molar NaOH (pH-stat) until the reaction was terminated by addition of ethanol/acetone (1:1). The mixture was extracted 6 times with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to afford a crude mixture which was purified by column chromatography (solvent gradient: ether to ether/methanol 20:1) to afford monoacetate **(-)-10** in reported yields as a colourless, highly viscous oil. IR (neat) *v* 3456, 1740, 1724, 1370, 1239, 1094, 1044 cm^{-1}; ^{1}H NMR δ 4.20 (d, ^3J = 4.5 Hz, 2 H), 4.00-3.57 (m, 4 H), 2.60-2.26 (m, 4 H), 2.12 (s, 3 H), 1.79 (broad s, 1 H); ^{13}C NMR δ 205.75 (+, R_2C=O), 170.73 (+, -OCOCH$_3$), 77.14 (-, OCHR$_2$), 74.41 (-, OCHR$_2$), 65.74 (+, CH_2OAc), 64.69 (+, CH_2OH), 43.33 (+, CH_2), 42.90 (+, CH_2), 20.61 (-, OCOCH$_3$); MS *m/z* (50 °C) 202 (M$^+$, 1.1), 172 (26.5), 171 (32), 142 (42.5), 129 (91.3), 111 (100); HRMS Calcd. for $C_8H_{11}O_4$ (M-31): 171.0657, Found: 171.0657.

(-)-11: *Meso* diacetate **6a** (650 mg, 1.94 mmol) was dissolved in toluene (4 ml) and 16 ml of 0.5 molar phosphate buffer (pH 7) solution. The vigorously stirred suspension was incubated at r.t. (18-21 °C) with 145 mg of lipase PS until after 22 h the reaction was stopped by addition of 6 ml of ethanol/acetone (1:1). The reaction mixture was extracted with ether (3x 70 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (25 g silica gel, ether) to afford 503 mg of **(-)-11** as colourless, highly viscous oil (88 %). $[\alpha]_D^{21}$ = -4.7 (c = 1, MeOH), e.e. > 98 %; IR (neat) ν 3457, 1740, 1366, 1246, 1093, 1080, 1044 cm^{-1}; ^1H NMR δ 7.40-7.25 (m, 5 H), 4.58 (s, 2 H), 4.12 (d, ^3J = 5 Hz, 2 H), 3.72-3.41 (m, 5 H), 2.27 (b s, 1 H), 2.10 (s, 3 H), 2.10-1.94 (m, 2 H), 1.33 (q, $^{2/3}J$ = 12 Hz, 2 H); ^{13}C NMR δ 170.77 (+, $OCOCH_3$), 138.31 (+, Ar-C), 128.27 (-, Ar-C) 127.48 (-, Ar-C), 127.37 (-, Ar-C), 76.25 (-, $OCHR_2$), 73.77/73.42 (-, $OCHR_2$), 69.50 (+, OCH_2Ph), 66.58/65.51 (+, CH_2OH and CH_2OAc), 34.04 (+, CH_2), 33.47 (+, CH_2), 20.71 (-, $OCOCH_3$); MS-FAB *m/z* 295 (M+1, 100), 293 (M-1, 18), 229 (15), 187 (22), 165 (18), 127 (42).

(-)-12: *Meso* diacetate **8b** (3.46 g, 10.5 mmol) was dissolved in toluene (21 ml) and 84 ml of 0.5 molar phosphate buffer (pH 7) solution. The vigorously stirred suspension was incubated at r.t. (22-24 °C) with 785 of mg lipase PS. After 6 and 19.5 h 3 ml of 1N NaOH solution were added and the reaction was quenched after 23 h total by addition of 50 ml ethanol/acetone (1:1). The milky suspension was extracted with ether (4x 150 ml) and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to yield a crude mixture which was readily separated by column chromatography (150 g silica gel). Petrolether/ether (1:3) furnished the starting material **8b** (0.9 mmol) and ether as eluent afforded 2.65 g of pure **(-)-12** as a colourless, highly viscous oil (88 % yield, 96 % borsm). $[\alpha]_D^{22}$ = -6.1 (c = 1, MeOH), e.e. > 98 %; IR (neat) ν 3473, 2957, 2872,1741, 1366, 1246, 1138, 1093, 1044 cm^{-1}; ^1H NMR δ 4.12 (d, ^3J = 5 Hz, 2 H), 3.91-3.79 (m, 1 H), 3.76-3.54 (m, 3 H), 3.52-3.47 (m, 4 H), 2.65 (broad s, 1 H), 2.15 (d, ^2J = 12.5 Hz, 2 H), 2.08 (s, 3 H), 1.37 (t, $^{2/3}J$ = 12.5 Hz, 2 H), 0.99 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR δ 171.02 (+, $OCOCH_3$), 96.21 (+, R_2CO_2), 74.56 (-, $OCHR_2$), 71.98 (-,$OCHR_2$), 70.20 (+, OCH_2R), 69.82 (+, OCH_2R), 66.66 (+, CH_2OAc); 65.52 (+, CH_2OH), 35.16 (CH_2); 33.88 (+, CH_2), 30.73 (+, CR_4), 22.65 (-, CH_3), 22.56 (-, CH_3), 20.89 (-, $OCOCH_3$); MS *m/z* (60 °C) no M^+, 257 (M-31, 27.9), 215 (47.5), 157 (69.8), 128 (21.1), 101 (43.6), 69 (100); HRMS Calcd. for $C_{13}H_{21}O_5$ (M-31): 257.1389, Found: 257.1390.

(-)-10 from **(-)-12**: To a solution of **(-)-12** (2.58 g, 8.96 mmol, e.e. > 98 %) in acetone (900 ml) was added $Pd(CH_3CN)_2Cl_2$ (258 mg, 0.89 mmol). The orange coloured solution (protection from light) was stirred at r.t. for 19 h until the reaction was stopped by addition of pyridine (180 µml). After concentration of the reaction mixture in vacuo (to ~ 20 ml) the residue was diluted with ether (20 ml), the insoluble material was removed by filtration and the filtrate was evaporated to give a crude product which was immediately chromatographed (110 g silica gel, solvent gradient: ether to ether/methanol 20:1). 1.60 g of pure **(-)-10** (89 %) was obtained as a colourless, highly viscous oil; $[\alpha]_D^{22}$ = -12.9 (c = 1, MeOH), e.e. > 98 %. Spectroscopic data see above.

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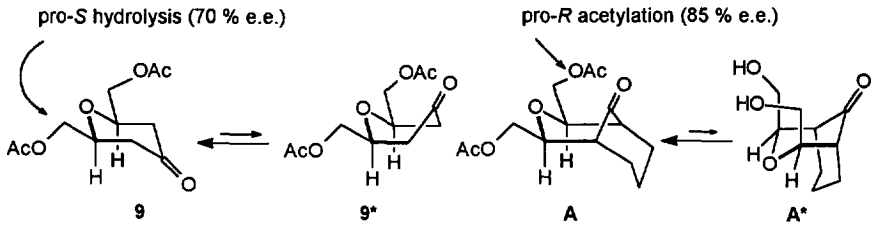

Thus, a changeover from pro-*S* selectivity (70 % e.e. in **9**) to pro-*R* selectivity (85 % e.e. in **A**) is observed. The propano bridge in **A** forces a boat-like oxacyclohexanone moiety with reduced mobility leading to an exposed position of the carbonyl group, whereas **9** should adopt a chair conformation preferentially, but not exclusively.

15. The structure was solved by direct methods and refined with a full matrix least-squares method. Crystal data for *p*-bromobenzoyl ester of (-)-**12**: $C_{21}H_{27}BrO_7$, M: 471.34, monoclinic, space group $P2_1$, a = 1105.3 (6) pm, b = 696.5 (3) pm, c = 1411.5 (8) pm, β = 94.44 (7)°, V = 1.0834 (10) nm^3, T = 193 (2) K, Z = 2, Mo-K_α = 71.073 pm, R_{int} = 0.0531 over 3324 independent reflections, absolute structure parameter 0.017 (8).

16. A recent application is described elswhere: Lampe, T. F. J; Hoffmann, H. M. R. *Tetrahedron Lett.* **1996**, *37*, in press.

17. 2,2,5,5-Tetramethyl-1,3-dioxane was prepared on a molar scale from 2,2-dimethoxypropane and 2,2-dimethyl-1,3-propandiol in the presence of catalytic amounts *p*-TsOH·H_2O (74 % yield); cf. Bruice, T. C.; Piszkiewicz, D. *J. Am. Chem. Soc.*, **1967**, *89*, 3568.

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