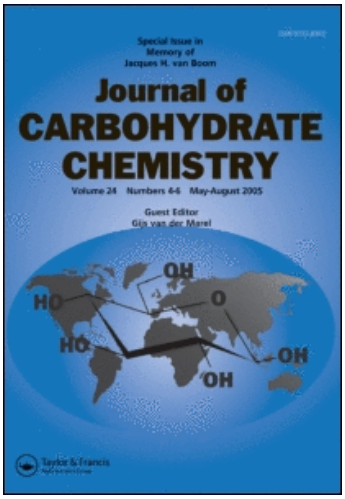

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Alkylating γ-Lactone-Opening: A Short Synthesis of Benzyl 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-*D*-glucofuranuronate

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ALKYLATING γ-LACTONE-OPENING: A SHORT SYNTHESIS OF BENZYL 3-O-BENZYL-1,2-O-ISOPROPYLIDENE-α-D-GLUCOFURANURONATE

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ABSTRACT

γ-Lactones were reacted with barium oxide/barium hydroxide/benzyl bromide in dimethylformamide to result in simultaneous benzylation of the γ-hydroxyl group and esterification of the carboxylic acid. A suitable protecting group for an α-hydroxyl function proved to be the tetrahydropyranyl group. The title compound was thus obtained in four steps from D-glucurono-6,3-lactone.

INTRODUCTION

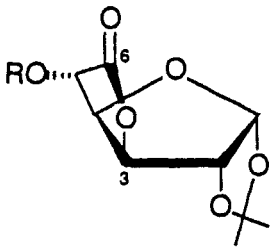
The synthesis of protected γ-hydroxy carboxylic acid derivatives from γ-lactones is often hampered by readily occurring relactonization. Thus, lactone-opening of 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone (**1**) with an alcohol under slightly basic conditions furnishes the carboxylic ester, which, however, cannot be isolated due to reformation of the stable γ-lactone.[1,2] One possibility to circumvent this difficulty is to lock the open chain by formation of amides which are not prone to relactonization and subsequently block the γ-hydroxyl

group. We encountered this problem in a programme directed to synthetic heparin saccharides where we needed an access to uronic acid derivatives having a permanent protective group at the 3-hydroxyl group such as uronic ester **2**. This type of compound as e.g. the methyl ester analogue of **2**[4] has been prepared previously from the corresponding hexose by oxidation of the terminal hydroxyl group. In order to avoid this oxidation step the direct functionalization of γ-lactones and especially glucuronolactone **1** was investigated.

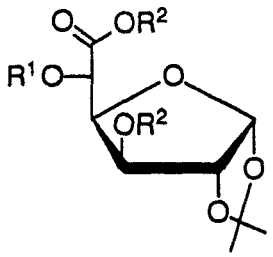
RESULTS AND DISCUSSION

1,2-O-Isopropylidene-α-D-glucofuranurono-6,3-lactone (**1**) which is readily available from D-glucofuranurono-6,3-lactone[5] was blocked at its only free hydroxyl function with different temporary protecting groups. Thus, standard transformation of **1** using isopropenyl methyl ether and catalytic amounts of phosphorous oxychloride furnished the crystalline MME-acetal **3** in 84% yield, reaction of **1** with dihydropyran and p-toluenesulfonic acid yielded the tetrahydropyranyl acetal **4** as 3:2 mixture of diastereomers in 95% yield. With t-butyldimethylsilyl chloride[6] silyl ether **5** was obtained in 88% yield. The allyl ether **6** was prepared from **1** following the trichloroacetimidate procedure.[7] Trityl ether **8** was obtained employing tritylpyridinium tetrafluoroborate[8] in 89% yield, or also using the less reactive trityl chloride, albeit in lower yield (62%). In the NMR spectrum of **8** the enormous upfield shift of H-4 (δ 2.80) caused by the shielding effect of the trityl group is remarkable.

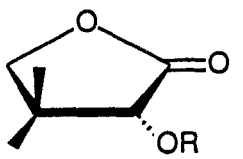
Reactions of the above mentioned fully blocked glucurono lactones with barium oxide/barium hydroxide/benzyl bromide in dimethylformamide were investigated, a reagent system that has potential for alkylation[9] as well as esterification.[10] The MME group of **3** was labile under these reaction conditions, whereas the allyl derivative **6** did not react at all, even under forcing conditions. Trityl derivative **8** could be lactone-opened to **9** in low yield (8.6%), despite the fairly drastic reaction conditions (13 h of sonication) no full conversion of **8** was achieved. The silyl ether **5** furnished the desired benzylated uronic



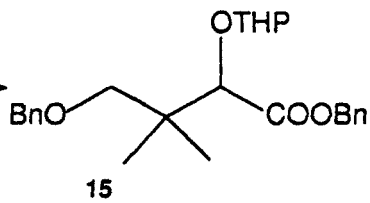
1 R = H
3 R = MME
4 R = THP
5 R = TBDMS
6 R = All
8 R = Tr



	R^1	R^2
2	H	Bn
9	Tr	Bn
10	TBDMS	Bn
11	Bn	Bn
12	THP	Bn



13 R = H
14 R = THP



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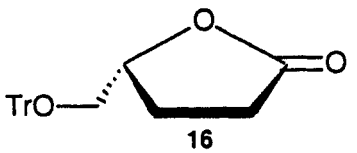

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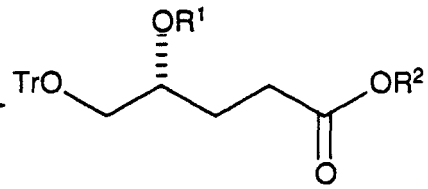

	R^1	R^2
17	Bn	Bn
18	H	Bn
19	Bn	H

MME = methoxy methyl ethyl, THP = tetrahydropyranyl,
TBDMS = t-butyldimethylsilyl, All = allyl, Tr = trityl, Bn = benzyl.

Scheme 1

ester **10** in 20% yield, however, the t-butyldimethylsilyl group was cleaved to some extent giving rise to the 5-O-benzylated by-product **11**. The best results were obtained with the THP derivative **4** which upon treatment with barium oxide/barium hydroxide/benzyl bromide for 21 h at room temperature gave 28% of lactone-opened product **12**. The pair of diastereomers, with respect to the THP group, was separated by chromatography to facilitate the NMR characterization of the compounds. In general, the moderate yields were due to the heterogeneous reaction conditions and the formation of poorly soluble barium glucuronates. After the basic treatment of alkylating lactone-opening no other products due to epimerization at the α-carbon could be detected.

The THP group of **12** could be removed selectively to give title compound **2** in 85% yield, making this intermediate available in four steps from glucurono-6,3-lactone.

To demonstrate the usefulness of alkylating lactone-opening to other γ-lactones, D-pantolactone (**13**) was converted to its THP ether **14**,[11] and one diastereomer was lactone-opened to furnish benzylated ester **15** in 32% yield. Similarly, commercially available lactone **16** was opened upon sonication to give **17** in 30.5% yield.Without sonication, 13.6% of **17** were isolated, along with γ-hydroxy ester **18** (18.5%) starting material **16** (9%), and γ-benzyloxy acid **19** (4%), showing that under these reaction conditions the esterification proceeds faster than the benzylation of the γ-hydroxyl group. γ-Hydroxy ester **18** was stable enough to be isolated and characterized, but slowly relactonized to **16** upon standing.

In conclusion, γ-lactones can be ring-opened achieving alkylation of the γ-hydroxyl group and esterification of the carboxyl group in one step with barium oxide/barium hydroxide/ benzyl bromide in DMF. Despite the moderate yields this conversion may be interesting to prepare chiral building blocks from the numerous γ-lactones commercially available at low cost.

EXPERIMENTAL

General Procedures. Solvents and reagents were obtained from Fluka (puriss. p.a.). Evaporation: Büchi rotary evaporator. TLC: pre-

coated silica gel 60 F - 254 plates (Merck), detection by UV light(254 nm) and spraying with a 10 % solution of concd H_2SO_4 in MeOH followed by heating. Medium pressure liquid chromatography (MPLC): Lobar columns, LiChroprep Si 60 (40-63µm,Merck) at 2-5 bar (Labomatic MD 80/100 pump). *Sonication*: TEC-15, frequency 33 kHz, the bath filled with water warmed up from room temperature to ca. 50°C within 2.5 h. IR: Nicolet 7199 FT-IR spectrophotometer. MS: MS 9 updated with Finnagan ZAB console, data system SS 200, VG Altrichem (EI: 70 eV); MM 7070 F, data system 2050, VG Altrichem (CI: NH_3). ^{1}H-NMR: Bruker AS 250 (250 MHZ) or Bruker HX-270 (270 MHZ), chemical shifts in ppm relative to tetramethylsilane as internal standard.

1,2-O-Isopropylidene-5-O-(1-methoxy-1-methyl-ethyl)-α-D-glucofuranurono-6,3-lactone (3). To a stirred solution of **1** (5.0 g, 23.1 mmol) in dichloromethane (40 mL) and isopropenyl methyl ether (4.4 mL, 46.2 mmol) were added two drops of $POCl_3$ at 0°C. After 70 min at 0°C and 70 min at room temperature 4 drops of triethylamine were added. The mixture was concentrated to a syrup, dissolved in ethyl acetate/hexane containing 1% of triethylamine, and filtered through a pad of silica gel. Upon addition of hexane colourless crystals of **3** (5.593 g, 84%) were obtained: mp 118-119°C; $[\alpha]_D^{20}$ +77.0° (c 0.5, dioxane); MS (EI) 273 (1%, M-·CH_3), 257 (4%, M-·OCH_3), 215 (2%, M^+-$^+C(CH_3)_2OCH_3$), 201 (9%, M-·CH_3 - CH_2=$C(CH_3)OCH_3$), 73 (100%, $(CH_3)_2C$=OCH_3^+); ^{1}H NMR (DMSO) δ 6.05 (d, $J_{1,2}$ = 4.0 Hz, H-1), 4.97-4.77 (m, 4H, H-2, H-3, H-4, H-5), 3.26 (s, 3H, OCH_3), 1.36 (s, 6H, 2 CH_3), 1.45, 1.29 (2s, 6H, isopropylidene CH_3).

Anal. Calcd for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99. Found: C, 54.31; H, 7.00.

1,2-O-Isopropylidene-5-O-(tetrahydro-2H-pyran-2-yl)-α-D-glucofuranurono-6,3-lactone (4). To a solution of **1** (10.0 g, 46.3 mmol) in dichloromethane (100 mL) and dihydropyran (DHP, 8.3 mL, 91.6 mmol) was added p-toluenesulfonic acid (0.4 g, 2.1 mmol) at 0°C. After stirring for 90 min at 0°C triethylamine (1mL) was added. Extraction with dichloromethane from ice water/bicarbonate solution and MPLC (acetone/hexane 1:3) of the crude product furnished 13.2 g (95%) of sirupy **4**; $[\alpha]_D^{20}$ + 46.4 ° (c 0.5, dioxane); IR (film) 1804 (lactone C=O), 1146 (ester), 1095 and 1031 (ether); MS (EI) 158 (2%, M^+-$(CH_3)_2C$=O - DHP), 85 (100%, $DHPH^+$); MS (CI) 318 (14%, M + NH_4^+), 234

(3%, M + NH_4^+-DHP), 85 (68%, $DHPH^+$); ^1H NMR ($CDCl_3$) δ 6.05, 6.03 (2d ~ t, $J_{1,2}$ = 3.9 Hz, H-1), 4.80, 4.60 (2 d, $J_{4,5}$ = 4.2, 4.3 Hz, H-5, integral 2:3) 1.53, 1.35 (2 s, isopropylidene CH_3).

Anal. Calcd for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71. Found: C, 56.16; H 6.93

5-O-(tert-Butyldimethylsilyl)-1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone (5). To a solution of **1** (5.0 g, 23.1 mmol) in dry DMF (20 mL) were added 4-dimethylaminopyridine (DMAP, 0.3 g, 2.5 mmol) and t-butyldimethylsilyl chloride (TBDMSCl, 4.3 g, 28.5 mmol). After stirring for 16 h the same amounts of DMAP and TBDMSCl together with DMF (10 mL) were added and the mixture was stirred for 27 h. Extraction with dichloromethane gave a brown syrup which was chromatographed (MPLC, ethyl acetate/hexane 1:3) to yield colourless crystals of **5** (6.7 g, 88%): mp 118-119 °C; $[\alpha]_D^{20}$ + 44.2 ° (c 0.5, dioxane); MS (EI) 315 (10%, M-·CH_3), 273 (28%, M-·$C(CH_3)_3$), 257 (2%, M-$(CH_3)_3CH$ -·CH_3), 215 (68%, M-·$C(CH_3)_3$- $(CH_3)_2C{=}O$), 75 (100%, $(CH_3)_2SiOH^+$); ^1H NMR ($CDCl_3$) δ 6.02 (d, $J_{1,2}$ = 3.6 Hz, H-1), 4.81 (dd, $J_{4,5}$ = 4.2 Hz, H-4), 4.78 (d, H-2), 4.73 (d, $J_{3,4}$ = 2.9 Hz, H-3), 4.52 (d, H-5), 1.53, 1.34 (2s, 6H, isopropylidene CH_3), 0.96 (s, 9H, t-butyl), 0.21, 0.18 (2s, 2 Si-CH_3).

Anal. Calcd for $C_{15}H_{26}O_6Si$: C, 54.52; H,7.93. Found: C, 54.53; H, 8.12

5-O-Allyl-1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone (6). To a solution of **1** (10.0 g, 46.3 mmol) in dry dichloromethane (150 mL) were added allyl trichloroacetimidate (20.0 g, 92.5 mmol), cyclohexane (150 mL), and dropwise trifluoromethane sulfonic acid (triflic acid, 0.5 mL, 8.13 mmol). After stirring overnight cyclohexane (50 mL) and triflic acid (0.1 mL, 1.63 mmol) were added. 22 h later the reaction was completed as judged by TLC. The reaction mixture was filtered, diluted with ether and successively washed with 2% sodium bicarbonate solution and water. Evaporation of organic solvents and MPLC (ethyl acetate/hexane 2:9) furnished two fractions (3.5 g and 8.6 g) which were rechromatographed, separately, (ethylacetate/hexane 1:2) to give pure **6** (9.86 g, 83%) : mp 69-70 °C from ether/hexane; IR (KBr) 1796 (C=O), 1626 (C=C), 1392, 1382, (-CH_3), 1170, 1150 (ester), 1095, 1035)(C-O-C); MS (EI) 256 (2%, M^+), 241 (11%, M-·CH_3), 215 (6%, M-·All), 200 (2%, M-·CH_3-All), 157 (16%, M-All-

$(CH_3)_2C=O$), 41 (100%, $^+CH_2-CH=CH_2$); ^1H NMR ($CDCl_3$) δ 6.04 (d, $J_{1,2}$=3.7 Hz, H-1), 4.95 (dd, H-4), 4.81 (d, H-2), 4.78 (d, $J_{3,4}$=3.0 Hz, H-3), 4.33 (d, $J_{4,5}$=4.2 Hz, H-5) 1.52, 1.35 (2s, 6H, isopropylidene CH_3), allyl: 5.99 (dddd), 5.39 (dddd ~ dq), 5.31 (dddd ~ dq),4.40 (dddd ~ ddt), 4.34 (ddd ~ ddt).

Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.16; H, 6.37.

1,2-O-Isopropylidene-5-O-triphenylmethyl-α-D-glucofuranurono-6,3-lactone (8). A: To a solution of **1** (2.0 g, 9.25 mmol) in pyridine (15 mL) was added triphenylmethyl chloride (trityl chloride, 3.87 g, 13.9 mmol). After keeping the mixture at 60°C for 24 h, more trityl chloride (1,29 g, 4.6 mmol) was added, and again the mixture heated to 60°C for 24 h. Extraction with ether from ice/water gave a crude product from which trityl alcohol was removed by crystallization from acetone/hexane. A second crystallization gave pure **8**(1.45 g, 34%) The mother liquor of this crystallization was chromatographed (MPLC, acetone/hexane 2:7) to yield another lot of crystalline **8** (1.2 g, 28%).

B: To a solution of **1** (530 mg, 2.44 mmol) in dry acetonitrile (10 mL) and dry pyridine (0.4 mL, 4.88 mmol) was added trityl pyridinium tetrafluoroborate (2.0 g, 4.88 mmol). The mixture was kept at 60°C for 16 h, diluted with ether (30 mL) and filtered. The filtrate was concentrated, crystallization from acetone/hexane furnished pure **8** (884 mg, 79%), from the mother liquors a second crop of **8** (107 mg, 9.6 %) was obtained: mp 211-212°C, $[\alpha]_D^{20}$ + 14.4° (c 0.5, dioxane); IR (KBr) 1803 (C=O), 1230 (ester), 748, 709 (monosubstituted phenyl); MS (EI) 381 (3%, M-·C_6H_5), 323 (2%, 381-$(CH_3)_2C=O$), 259 (6%, $^+OC(C_6H_5)_3$), 243 (100%, $^+C(C_6H_5)_3$), 165 (6%, 243-C_6H_6); ^1H NMR ($CDCl_3$) δ 7.69-7.64 (m, 6H, aromatic), 7.47-7.22 (m,9H, aromatic), 5.86 (d, H-1), 4.62 (d, $J_{1,2}$ = 3.2 Hz, H-2), 4.33 (d, H-5), 4.32 (d, H-3), 2.80 (dd, $J_{3,4}$=2.9 Hz, $J_{4,5}$=3.9 Hz, H-4), 1.24, 1.21 (2s, 6H, isopropylidene CH_3).

Anal.Calcd for $C_{28}H_{26}O_6$:C, 73.35; H, 5.72. Found: C, 73.31; H, 5.59.

Benzyl 3-O-Benzyl-1,2-O-isopropylidene-5-O-triphenylmethyl-α-D-glucofuranuronate (9). To a solution of **8** (1.0 g, 2.18 mmol) in dry DMF (20 mL) were added barium oxide (1.31 g, 8.54 mmol), barium hydroxide octahydrate (0.39 g, 0.91 mmol), and benzyl bromide (1.97 mL, 16.4 mmol). After 5 h of sonication the same amounts of BaO

and $Ba(OH)_2 \times 8H_2O$ were added together with benzyl bromide (1.8 mL, 15 mmol). The sonication was continued for 8 h, dichloromethane (150 mL) was added, and the orange mixture was filtered over a pad of Speedex. The filtrate was extracted with ether from ice/water, and the crude product was chromatographed (MPLC, acetone/hexane 1:9, then 1:3). Compound **9** (124 mg, 8.6%) was obtained as a syrup, along with crystalline starting material **8** (211 mg, 21%). **9**: IR (film) 1743 (C=O), 1600, 1493 (aromat); MS (EI) 413 (3%, M-·$C(C_6H_5)_3$), 243 (64%, $^+C(C_6H_5)_3$), 165 (22%, 243-C_6H_6), 91 (100%, C_7H_7); ^1H NMR ($CDCl_3$) δ 7.41-7.36 (m,7H,aromatic), 7.30-7.16 (m,16H, aromatic), 6.92-6.87 (m,2H, aromatic), 5.79 (d,$J_{1,2}$=3.7 Hz,H-1), 4.72 (s, 2H, CH_2 ester), 4.63 (dd, $J_{4,5}$=8.1 Hz, H-4), 4.52 (d, $J_{2,3}$ < 0.5 Hz, H-2), 4.44 (d,H-5), 4.38 , 4.05 (2d, 2H, J = 11.4 Hz, CH_2 ether), 4.14 (d, $J_{3,4}$=3.1 Hz, H-3), 1.54, 1.30 (2s, 6H, isopropylidene CH_3).

Benzyl 3-O-Benzyl-5-O-(tert-butyldimethylsilyl)-1,2-O-isopropylidene-α-D-glucofuranuronate (10). To a solution of **5** (1.0 g, 3.03 mmol) in dry DMF (20 mL) were added barium oxide (1.0 g, 6.5 mmol), barium hydroxide octahydrate (0.3 g, 1.9 mmol), and benzyl bromide (1 mL, 8.3 mmol) at 0°C. After stirring for 80 min at room temperature the suspension was diluted with acetone (50 mL) and filtered over a pad of Speedex. The filtrate was concentrated and chromatographed (MPLC, acetone/hexane 1:3) to yield **10** (314 mg, 19.6 %) as a syrup; MS (EI) 305 (1%, M-·C_7H_7-tBu$(CH_3)_2$SiOH), 91 (100%, C_7H_7); MS (CI) 546 (30%, M+ NH_4^+), 529 (68%, M+H^+), 488 (11%, 546-$(CH_3)_2C$=O), 108 (100%, C_7H_7OH), 91 (94%, $C_7H_7^+$); ^1H NMR ($CDCl_3$), δ 7.44-7.23 (m, 10H, aromatic), 5.99 (d, $J_{1,2}$=3.7 Hz, H-1), 5.33, 5.20 (2d, 2H, J=12.3 Hz, CH_2 ester), 4.73, 4.62 (2d, 2H, J=11.7 Hz, CH_2 ether), 4.65 (d, H-2), 4.62 (d, H-5), 4.49 (dd, $J_{4,5}$=8.8 Hz, H-4), 4.16 (d, $J_{3,4}$=3.2 Hz, H-3), 1.58, 1.38 (2s, 6H, isopropylidene CH_3), 0.92 (s, 9H, t-butyl), 0.03, 0.00 (2s, 6H, Si-CH_3).

Anal. Calcd for $C_{29}H_{40}O_7Si$: C, 65.88; H,7.63. Found: C, 66.03; H,7.78.

In a second fraction syrupy **benzyl 3,5-di-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranuronate (11)** (160 mg, 10.5 %) was obtained; MS (EI) 413 (1.5%. M^+-·C_7H_7), 355 (1%, 413-$(CH_3)_2C$=O), 91 (100%,·C_7H_7); MS (CI) 522 (33%, M+ NH_4^+), 505 (5%, M+H^+), 464 (17%, 522-$(CH_3)_2C$=O), 108 (100%, C_7H_7OH), 91 (86%, C_7H_7); ^1H NMR (CDC13) δ

7.37-7.16 (m, 15H, aromatic), 5.93 (d, $J_{1,2}$=3.7Hz, H-1), 5.26, 5.17 (2d, 2H, J=12.4 Hz, CH_2 ester), 4.63, 4.48 (2d, 2H, J=11.8 Hz, CH_2 ether), 4.51, 4.38 (2d, 2H, J=11.1 Hz, CH_2 ether), 4.58 (d, H-2), 4.47 (dd, H-4), 4.36 (d, $J_{4,5}$=9.2 Hz, H-5), 4.12 (d, $J_{3,4}$=4.1 Hz, H-3), 1.46, 1.30 (2s, 6H, isopropylidene CH_3)

Benzyl 3-O-Benzyl-1,2-O-isopropylidene-5-O-(tetrahydro-2H-pyran-2-yl)-α-D-glucofuranuronate (12). To a solution of **4** (1.0 g, 3.3 mmol) in dry DMF (20 mL) were added barium oxide (2.0 g, 13 mmol), barium hydroxide octahydrate (0.6 g, 3.8 mmol), and benzyl bromide (1 mL, 8.3 mmol). The mixture was stirred for 5 h at room temperature and more benzyl bromide was added (2 mL, 16.6 mmol). After 16 h acetone (100 ml) and triethylamine (2 mL) were added to the red-brown suspension. Filtration through a pad of silica gel, washing with acetone/hexane 1:2 (80 mL) and evaporation of solvents followed by chromatography of the residual syrup (MPLC, ethyl acetate/hexane 1:2) gave **12** (460 mg, 28%) as a syrup; IR (film) 1746 (C=O), 1604, 1585, 1497 (aromat), 1262, 1213 (ester), 1170, 1125, 1077 (ether), 746, 698 (monosubstituted phenyl); MS (EI) 413 (3%, M-·$O(CH_2)_5$), 414 (1%, M^+ - DHP), 323 (M-DHP-·C_7H_7), 356 (M^+-DHP-$(CH_3)_2C$=O), 91 (100%, ·C_7H_7), 85 (60%, DHP-H^+).

The two diastereomers, with respect to the tetrahydropyranyl, moiety could be separated by MPLC (ethyl acetate/hexane 1:9); diastereomer **I**: syrup; ^{1}H NMR ($CDCl_3$) δ 7.36-7.25 (m, 10 H, aromatic), 5.937 (d, $J_{1,2}$= 3.8 Hz, H-1), 5.28, 5.18 (2d, 2H, J=12.5 Hz, CH_2 ester), 4.76 (d, H-5), 4.67, 4.61 (2d, 2H, J=10.8 Hz, CH_2 ether), 4.615 (d, H-2), 4.61 (~dd, 1H, -OC<u>H</u>-O tetrahydropyranyl=THP), 4.44 (dd, $J_{4,5}$=9.0 Hz, H-4), 4.14 (d, $J_{3,4}$=3.3 Hz, H-3), 3.74(ddd, O-C<u>H</u>$_{ax}$<u>H</u>$_{eq}$ THP), 3.30 (ddd ~ dt, -OCH$_{ax}$<u>H</u>$_{eq}$ THP), 1.83 - 1.40 (m, 6H, THP), 1.49, 1.32 (2s, 6H, isopropylidene CH_3); diastereomer **II**: syrup; ^{1}H NMR ($CDCl_3$) δ 7.41-7.26 (m, 10 H, aromatic) 5.944 (d, $J_{1,2}$=3.7 Hz, H-1)), 5.34, 5.09 (2d, 2H, J=12.4 Hz, CH_2 ester), 4.68, 4.44 (2d, 2H, J=11.4 Hz, 4.56 (dd ~ t, 1H, -OC<u>H</u>-O THP), 4.46 (dd, H-4) (d, $J_{3,4}$=3.1 Hz, H-3), 4.08 (d, $J_{4,5}$=9.5 Hz, H-5), 3.66 (ddd, -OC<u>H</u>$_{ax}$<u>H</u>$_{eq}$ THP), 3.19 (ddd ~ dt, -OCH$_{ax}$<u>H</u>$_{eq}$ THP), 1.81-1.41 (m, 6H, THP), 1.49, 1.32 (2s, 6H, isopropylidene CH_3).

Benzyl 3-O-Benzyl-1,2-O-isopropylidene-α-D-glucofuranuronate (2). A solution of **12** (256 mg, 0.51 mmol) in methanol (5 mL) was

stirred at room temperature for 4 h together with Amberlite IR 120 (H^+, ca. 1 mL). Filtration, evaporation of solvent and chromatography (MPLC, acetone/hexane 1:3) gave **2** (181 mg, 85 %) as a syrup; $[\alpha]_D^{20}$ - 6.8° (c 0.5, dioxane); MS (EI) 415 (2%, $M+H^+$), 357 (1.5%, $M+H^+-(CH_3)_2C=O$), 323 (5%, $M-\cdot C_7H_7$), 265 (5%, $M-\cdot C_7H_7$ - $(CH_3)_2C=O$), 91 (100%, C_7H_7); ^1H NMR ($CDCl_3$) δ 7.36 - 7.26 (m, 10H, aromatic), 6.02 (d, $J_{1,2}$=3.9 Hz, H-1), 5.24, 5.18 (2d, 2H, J=12.0 Hz, CH_2 ester), 4.62 (dd, $J_{4,5}$=5.5 Hz, $J_{5,5-OH}$=9.6 Hz, H-5) 4.58 (d, H-2), 4.54, 4.39 (2d, 2H, J=11.2 Hz, CH_2 ether), 4.47 (dd, $J_{3,4}$=3.8 Hz, H-4), 4.03 (d, H-3), 3.47 (d, 5-OH), 1.47, 1.32 (2s, 6H, isopropylidene CH_3).

Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.76; H, 6.38.

2-O-(Tetrahydro-2H-pyran-2-yl)-D-pantolactone (14). To a solution of **13** (5.0 g, 38.4 mmol) in dichloromethane (50 mL) and dihydropyran (6.9 mL, 76 mmol) was added p-toluenesulfonic acid (330 mg, 1.7 mmol) at 0°. After 25 min at 0° the mixture was extracted with dichloromethane from $NaHCO_3$ solution, washed with water, and dried over $MgSO_4$. The residue was chromatographed (MPLC, ethyl acetate/hexane 1:9 -> 1:4) to furnish the two diastereomers of **14** with respect to the tetrahydropyranyl moiety (diastereomer **I**: 5.23 g, 63.5%; diastereomer **II**: 2.835 g, 34.4 %). Diastereomer **I**: syrup; $[\alpha]_D^{20}$ + 147.6° (c 0.5, dioxane); IR (film) 1789 (C=O), 1127, 1094 (C-O-C); MS (EI) 186 (1%, $M-2\cdot CH_2$), 114 (5%, $M-OTHP^+$), 85 (100%, $DHP-H^+$); ^1H NMR ($CDCl_3$) δ 5.16 (dd~t, -OCH-O THP), 4.15 (s, H-2), 4.01 (d, $J_{4a,4b}$=8.8 Hz, H-4a), 3.92 (d, H-4b), 3.87, 3.56 (2 ddd, $-OCH_2$ THP), 1.85-1.51 (m, 6H, CH_2 THP), 1.22, 1.14 (2s, 6H, 2 CH_3).

Anal.Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.59; H, 8.50.

Diastereomer **II**: syrup; $[\alpha]_D^{20}$-132.8° (c 0.5, dioxane); IR (film) 1791 (C=O), 1126, 1094 (C-O-C); MS (EI) 186 (1%, $M-2\cdot CH_2$), 114 (6%, $M-OTHP^+$), 85 (100%, $DHP-H^+$); ^1H NMR ($CDCl_3$) δ 4.85 (dd~t, -OCH-O THP), 4.22 (s, H-2), 4.21 (ddd, $OCH_{ax}H_{eq}$ THP), 3.98 (d, $J_{4a,4b}$=8.5 Hz, H-4a), 3.89 (d, H-4b), 3.55 (ddd, $OCH_{ax}H_{eq}$ THP), 1.99-1.86 (m, 1H, THP), 1.76-1.71 (m, 2H, THP), 1.68-1.52 (m, 3H, THP), 1.21, 1.11 (2s, 6H, $2CH_3$).

Anal.Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.64; H, 8.36.

Benzyl 4[R]-Benzyloxy-3,3-dimethyl-2-[(tetrahydro-2H-pyran-2-yl)oxy] butyrate (15). To a solution of **14** (diastereomer **I**, 1.0 g, 4.7 mmol) in DMF (25 mL) were added barium oxide (2.81 g, 18.3 mmol), barium hydroxide octahydrate (840 mg, 2 mmol), and benzyl bromide (4.2 mL, 35 mmol) at 0°. After 130 min of sonication, dichloromethane (200 mL) was added, and the mixture was filtered through a pad Speedex. Evaporation of solvents, extraction with ether from water, drying (Na_2SO_4) and concentration followed by MPLC (ethyl acetate/hexane 1:9) furnished **15** (623 mg, 32%) as a syrup, $[\alpha]_D^{20}$ + 68.8° (c 0.5, dioxane); IR (film) 1742 (C=O), 1258, 1196 (ester), 1078 (C-O-C), 738, 697 (monosubstituted phenyl); MS (EI) 327 (4%,M+H$^+$-·THP), 237 (2%, M-DHP-·C_7H_7), 221 (M-DHP-·OC7H7), 91 (88%,·C_7H_7), 85 (100%, DHP-H$^+$); ^{1}H NMR ($CDCl_3$) δ 7.38- 7.26 (m, 10 H, aromatic), 5.15, 5.07 (2d, 2H, J=12.3Hz, CH_2 ester), 4.58 (dd~t, -OC<u>H</u>-O THP), 4.43 (s, 2H, CH_2 ether), 4.35 (s, H-2), 3.80 (ddd, OC<u>H</u>$_{ax}$H$_{eq}$ THP), 3.95 (m$_c$, OCH$_{ax}$<u>H</u>$_{eq}$ THP), 3.41 (d, $J_{4a,4b}$=8.8 Hz, H-4a), 3.21 (d, H-4b), 1.04, 1.01 (2s, 6H, 2 CH_3).

Anal.Calcd for $C_{25}H_{32}O_5$: C, 72.79; H 7.82. Found: C, 73.00; H, 7.92.

Benzyl 4[R]-Benzyloxy-5-trityloxy-valerate (17). To a solution of **16** (1.0 g, 2.8 mmol) in DMF (25 mL) were added barium oxide (1.67 g, 10.9 mmol), barium hydroxide octahydrate (0.5 g, 1.2 mmol), and benzyl bromide (2 mL, 16.7 mmol). After 7.5 h of sonication, barium oxide (1.67 g, 10.9 mmol) and benzyl bromide (2.8 ml, 23.3 mmol) were added, and then sonication was continued for 14 h. The mixture was diluted with dichloromethane (50 mL) and filtered through a pad of Speedex. The filtrates were extracted with ether from ice/water, and the crude product was chromatographed (MPLC, ethyl acetate/hexane 1:9 -> 1:3) to give **17** (470 mg, 30.5 %) as a syrup; $[\alpha]_D^{20}$ +19.2° (c 0.5, dioxane); IR (film) 1735 (C=O), 1600, 1492 (aromat), 1214 (ester), 1077 (C-O-C), 746, 700 (monosubstituted phenyl); MS (EI) 260 (20%, TrOH), 183 (94%, TrOH-C_6H_5), 105 (100%, $C_6H_5CO^+$), 91 (68%, ·C_7H_7), 77 (60%, $C_6H_5^+$); ^{1}H NMR ($CDCl_3$) δ 7.47-7.19 (m, 25H, aromatic), 5.05 (s, 2H, CH_2 ester), 4.65, 4.44 (2d, 2H, J=11.6 Hz, CH_2 ether), 3.57 (m$_c$, 1H, H-4), 3.23 (dd, $J_{4,5a}$=5.2 Hz, H-5a), 3.13 (dd, $J_{4,5b}$=4.4 Hz, $J_{5a,5b}$=10.4 Hz, H-5b), 2.40 (m$_c$, 2H, H-2), 1.97-1.83 (m, 2H, H-3).

Anal.Calcd for $C_{38}H_{36}O_4$: C, 81.99; H, 6.52. Found: C, 81.92; H, 6.65.

When the same mixture (without a second addition of BaO and benzyl bromide) was stirred at room temperature without sonication for 47 h the usual work-up gave **17** (210 mg, 13.6 %) along with **benzyl 4[R]-hydroxy-5-trityloxy-valerate (18**, 240 mg, 18.5 %), starting material **16** (90 mg, 9%), and **4[R]-benzyloxy-5-trityloxy valeric acid (19**, 50 mg, 4%). **18**: syrup; IR (film) 3450 (OH), 1734 (C=O), 1596, 1492 (aromat), 1217 (ester), 1073 (C-O-C), 747, 702 (monosubstituted phenyl); MS (EI) 358 (12%, M^+-C_7H_7OH), 281 (24%, M^+-C_7H_7OH-·C_6H_5), 243 (100%, Tr^+), 165 (46%, 243-C_6H_6), 91 (14%, ·C_7H_7); ^1H NMR ($CDCl_3$) δ 7.44 - 7.21 (m, 20H, aromatic), 5.09 (s, 2H, CH_2 ester), 3.08 (m, 1H, H-4), 3.18 (dd, $J_{4,5a}$=3.8 Hz, H-5a), 3.05 (dd, $J_{4,5b}$= 7.0 Hz, $J_{5a,5b}$=9.8 Hz, H-5b), 2.54-2.38 (m, 3H, H-2 + 4-O<u>H</u>), 1.82-1.68 (m, 2H, H-3).

Anal. Calcd for $C_{31}H_{30}O_4$: C, 79.80; H, 6.48. Found: C, 79.62; H, 6.42

19: Syrup; $[\alpha]_D^{20}$ +13.5° (c 0.2, dioxane); IR (film) 2600 (COOH), 1710 (C=O), 1595, 1492 (aromat), 1216 (ester), 1077 (C-O-C), 746, 702 (monosubstituted phenyl); MS (EI) 243 (100%, Tr^+), 223 (10%, M^+ -Tr), 165 (40%, Tr^+ - C_6H_6), 91 (85%, C_7H_7); ^1H NMR ($CDCl_3$) δ 7.48 - 7.19 (m, 20H, aromatic), 4.70, 4.47 (2d, 2H, J=11.5Hz, CH_2 ether), 3.61 (m_c, 1H, H-4), 3.25 (dd, $J_{4,5a}$=5.2 Hz, H-5a), 3.17 (dd, $J_{4,5b}$=4.8 Hz, $J_{5a,5b}$=10.4 Hz, H-5b), 2.39 (m_c, 2H, H-2), 1.93-1.86 (m, 2H, H-3).

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