Novel Chiral Glycerol Analogues Building Blocks. Application to the Synthesis of Bioactive Glycoglycerolipid Analogues

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Abstract: Monoacylglycosylglycerols show anti-tumor promoting effects: in order to study the role of the ester function we have prepared by simple methods (*R*)-1-*O*-benzyl-1,2-decandiol, (*R*)-3-*O*-benzyl-1-*O*-hexyl-*sn*-glycerol, and (*R*)-1-*O*-benzyl-5-oxo-1,2-decandiol; these optically active compounds are building blocks for the synthesis of monohexanoylglycosylglycerol isosters.

Key words: glycolipids, antitumor agents, isosters, building blocks, synthons

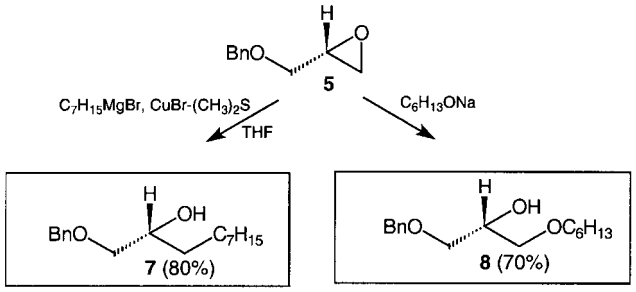
Monoacylglycosylglycerols have been reported to have significant anti-tumor promoting effects;[1] in particular, among the different derivatives, compounds **1b** and **1c**, both bearing a hexanoyl chain on the glycerol C-1, are the most active.[2,3]

In the course of a project aimed at ascertaining the structural features responsible for the cancer chemopreventing activity, in order to study the role of the ester function in modulating this activity, we have planned to prepare the acylglucosyl- and galactosylglycerol analogues **2b-c, 3b-c** and **4b-c** in which the chain is linked to the glycosylglycerol skeleton through bonds metabolically more stable than the ester linkage.

In this paper, the preparation of compounds **7, 8** and **9**, suitably protected at the primary hydroxy group, i.e. the proper isosters of 1-*O*-hexanoyl-*sn*-glycerol **1a**, which are required for the synthesis of the target compounds by glycosidation at the secondary hydroxyl, is described.

To obtain the compounds with the desired C-2 configuration, the commercially available (*R*)-benzylglycydol **5** and (*R*)-γ-hydroxymethyl-γ-butyrolactone **6** were chosen as starting material for the synthesis of alkyl and ether isosters **2a** and **3a** or of the carbonylic isoster **4a**, respectively.

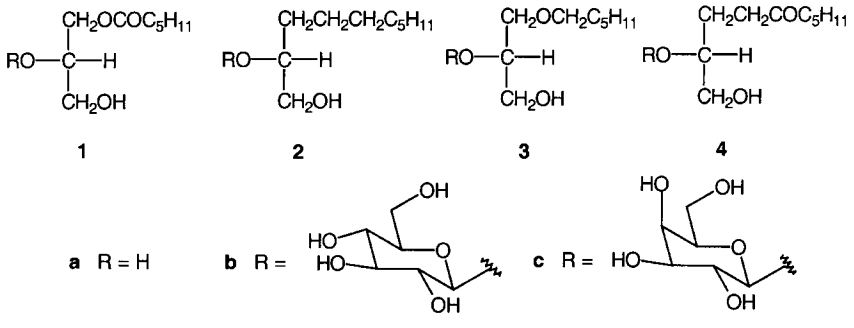
(*R*)-1-*O*-Benzyldecan-1,2-diol[4] **7** was obtained in 80% yield from **5** by reaction with 1-heptylmagnesiumbromide and copper (I) bromide-dimethyl sulfide complex; the same protected epoxyalcohol **5** afforded the desired (*R*)-hexylether[5] **8** (70% yield) by reaction with sodium in hexanol (Scheme 1).[6]

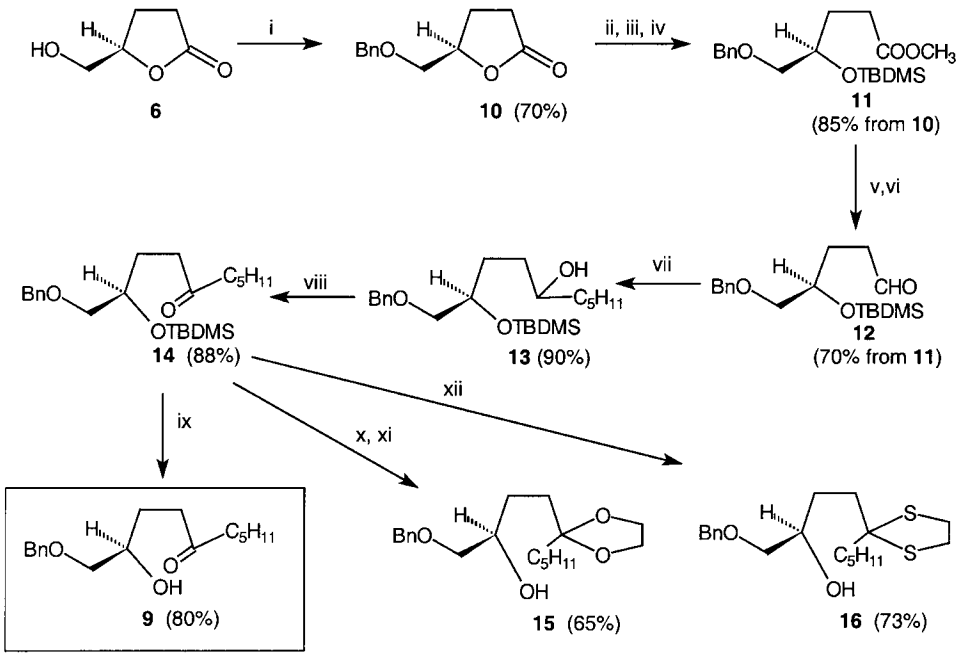


Scheme 1

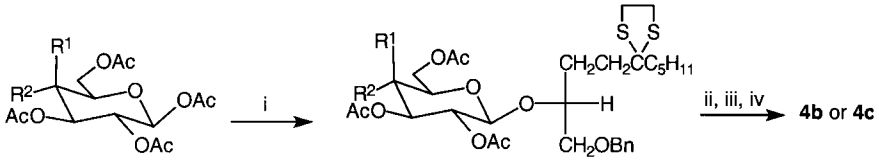
In turn, for the synthesis of isoster **9**, (*R*)-lactone **6**, after reaction with benzyl trichloroacetimidate to the corresponding benzylether[7] **10**, was converted into its methyl ester and protected as silylether giving compound **11**.[8] $LiAlH_4$ reduction of the ester function, followed by pyridium chlorochromate (PCC) oxidation afforded (*R*)-aldehyde **12,**[9] which was transformed in secondary alcohol **13,**[10] by treatment with 1-bromopentyl magnesium. Then, oxidation of **13** with PCC afforded 5-ketone **14**, and deprotection of the silylether with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran gave compound **9**[11] in 26% overall yield from lactone **6** (Scheme 2).

Since compound **9** is a synthon for the above mentioned glycosylation reactions, and it is prone to an intramolecular cyclization reaction to give a six-membered cyclic





Scheme 2 Reagents: i. $Cl_3CC(=NH)OCH_2Ph$, CF_3SO_2OH, CH_2Cl_2/ hexane, 0 °C, 0.5h; ii. N NaOH, rt, 1h; iii. CH_3I, TBABr, CH_3COCH_3, rt, 8h; iv. TBDMSCl, imidazole, THF, rt, 15h; v. $LiAlH_4$,THF, rt, 4h; vi. PCC, AcONa, CH_2Cl_2, rt, 1h; vii. $C_5H_{11}MgBr$, Et_2O, rt, 4h; viii. PCC, AcONa, CH_2Cl_2, rt, 1h; ix. TBAF, THF, rt, 8h; x. ethylene glycol, $(EtO)_3CH$, BF_3/Et_2O, C_6H_6, reflux, 4h; xi. TBAF, THF, rt, 8h; xii. $HSCH_2CH_2SH$, BF_3/Et_2O, CH_2Cl_2, rt, 0.5h.



17. $R^1 = OAc$, $R^2 = H$
18. $R^1 = H$, $R^2 = OAc$
19. $R^1 = OAc$, $R^2 = H$ (70%)
20. $R^1 = H$, $R^2 = OAc$ (65%)

Scheme 3 Reagents: i. **16**, BF_3/Et_2O, CH_2Cl_2, 0 °C to rt, 5h; ii. NBS, acetone/H_2O, 0 °C; iii. MeONa, MeOH; iv. H_2, Pd/C, MeOH/AcOH.

hemiacetal, we protected the carbonyl function by synthesizing both (*R*)-ketal **15**[12,13] and (*R*)-thioketal **16**[14] (Scheme 2).

As an illustration of the applicability of these novel glycerol analogues building blocks, we report the synthesis of compounds **4b** and **4c**. Several attempts of glycosylation between ketal **15** and β-D-galactose pentaacetate, or the corresponding α-trichloroacetimidate, in the presence of BF_3-ethyl etherate, or between **15** and peracetylated methyl β-D-thiogalactopyranoside under dimethyl(methylthio)sulfonium tetrafluoroborate promotion, resulted in very low yields of glycosylation product and decomposition of acceptor **15**.

To circumvent the problem, we successfully turned our attention to thioketal **16**; the glycosylation product **19**[15] was obtained in 70% yield from **16** and β-D-galactose pentaacetate **17** in dichloromethane (0 °C to r.t.) in the presence of BF_3-ethyl etherate (1 equiv). Using the same procedure, starting from β-D-glucose pentaacetate **18,** the corresponding glucoconjugate **20**[16] was obtained in 65% yield. After conventional deprotection methods the glycoglycerolipid analogues **4b** and **4c** were recovered[17] (Scheme 3).

In conclusion, we have reported an approach, which provides a general access to glycerol analogues building blocks; the described simple synthetic routes for compounds **7-9** are, in fact, generalizable to whatever chain lengths and, besides the described synthesis of glycoconjugates, also appropriate for the obtention of other glycerol containing compounds, as for example, the PAF (platelet antiaggregating factor)[18] and the ALP (alkyllysophospholipid)[19] and their isosters[20] in which the 1-position of the glycerol should be selectively modified.

Acknowledgement

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References and Notes

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(4) (*R*)-*1-O-Benzyl-1,2-decandiol* **7** was prepared as reported for a similar compound differing in the chain length (Iguchi, K.; Kitade, M.; Kashiwagi, T.; Yamada, Y. *J. Org. Chem.* **1993**, *58*, 5690) in 80% yield from (*R*)-benzylglycidol **5** (1g, FLUKA), oil; $[\alpha]_D$ - 4.0 (*c* 1 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ_H 0.84 (t, 3H, C*H*$_3$), 1.20-1.36 (m, 12H, C*H*$_2$), 1.36-1.50 (m, 2H, C*H*$_2$-3), 2.50-2.58 (m, 1H, exchang.), 3.27 (m, 1H, C*H*-OBn), 3.45 (m, 1H, C*H*-OBn), 3.74-3.82 (m, 1H, C*H*-O), 4.50 (s, 2H, C*H*$_2$Ph), 7.20-7.38 (m, 5H, Ar). m/z (EI) 264 (M^+), 246, 217, 181, 173, 143, 122, 91.

(5) (*R*)-*3-O-Benzyl-1-O-hexyl-sn-glycerol* **8** was prepared as described for the analogue 1-methylether (Waagen, V.; Hollingsaeter, I.; Partali, V.; Thorstad, O.; Anthonsen, T. *Tetrahedron: Asym.* **1993**, *4*, 2265) in 70% yield from **5** (1g), oil; $[\alpha]_D$ +3.9 (*c* 1 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500MHz): δ_H 0.90 (t, 3H, CH_3), 1.22-1.38 (m, 6H, C*H*$_2$), 1.52-1.60 (m, 2H, C*H*$_2$-CH_2-O), 2.76-2.80 (m, 1H, exchang.), 3.38-3.58 (m, 6H, C*H*$_2$-O), 3.96-4.00 (m, 1H, C*H*-O), 4.54 (s, 2H, C*H*$_2$Ph), 7.22-7.36 (m, 5H, Ar). m/z (EI) 267 (MH^+), 233, 217, 187, 181, 163, 142, 113, 107.

(6) To ascertain whether the high optical purity of the starting material **5** remained unchanged in the products **7** and **8**, ^1H NMR analysis of the MTPA-esters of the corresponding optically active and racemic compounds was performed (Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512). Racemic **7** and **8** were prepared starting from (*R,S*)-benzylglycidol (FLUKA). The MTPA-derivative of racemic **7** showed as significant signals two multiplets centered at 4.40 and 4.48 ppm due to the OC*H*$_2$Ph protons. In the spectrum of the MTPA derivative of (*R*)-**7** the signal at 4.40 ppm was not detectable. In the case of the MTPA derivative of (*R,S*)-**8**, the ^1H NMR spectrum showed two multiplets centered at 4.42 and 4.52 ppm due to the OC*H*$_2$Ph protons. The same signals for the (*R*)-**8** derivative were present in a 2/98 ratio indicating a 96% ee.

(7) *5-Benzyloxymethyl-dihydrofuran-2-one* **10**. The benzylation was carried out with benzyl trichloroacetimidate in presence of trifluoromethanesulphonic acid (Nicolaou, K.C.; Raja Reddy, K.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558) in 70% yield from *(R)*-**6** (5g, FLUKA). $[\alpha]_D$ -17.5 (*c* 1.6 $CHCl_3$) (lit.+18 for *(S)*-isomer, Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251). ^1H NMR ($CDCl_3$, 500MHz): δ_H 2.06-2.14 (m, 1H, C*H*-3), 2.22-2.30 (m, 1H, C*H*-3), 2.40-2.50 (m, 1H, C*H*-2), 2.56-2.66 (m, 1H, C*H*-2), 3.56 (m, 1H, C*H*-OBn), 3.66 (m, 1H, C*H*-OBn), 4.55 (s, 2H, C*H*$_2$Ph), 4.62-4.67 (m, 1H, *CH*-O), 7.22-7.40 (m, 5H, Ar).

(8) *Methyl* (*R*)-*5-O-benzyl-4-O-tert-butyldimethylsilyl-4,5-dihydroxypentanoate* **11**. Lactone **10** was transformed into the crude methylester (Takeda, K.; Nakajima, A.; Yoshi, E. *Synlett* **1997**, 255) which was immediately treated with *t*-butyldimethylsilyl chloride and imidazole in THF (r.t., 15 h) to afford the silylether **11** (85% from **10**). ^1H NMR ($CDCl_3$, 500MHz): δ_H 0.0 (s, 6H, C*H*$_3$Si), 0.88 (s, 9H, (CH_3)$_3$C), 1.74-1.82 (m, 1H, C*H*-3), 1.90-1.98 (m, 1H, C*H*-3), 2.34-2.46 (m, 2H, C*H*$_2$), 3.34 (m, 1H, C*H*-OBn), 3.40 (m, 1H, C*H*-OBn), 3.66 (s, 3H, C*H*$_3$-O), 3.86-3.92 (m, 1H, C*H*-O), 4.50-4.52 (m, 2H, C*H*$_2$Ph), 7.32-7.34 (m, 5H, Ar).

(9) (*R*)-*5-O-Benzyl-4-O-tert-butyldimethylsilyl-4,5-dihydroxypentanal* **12**. Methylester **11** was reduced with $LiAlH_4$ (r.t., 4 h) in THF to afford the corresponding alcohol that was oxidized (r.t., 1 h) with pyridinium chlorochromate (PCC) in presence of sodium acetate in dichloromethane. Filtration through a Florisil pad and evaporation of the solvents afforded the aldehyde **12** (70% from **11**), oil. $[\alpha]_D$+15.8 (*c* 2 $CHCl_3$). ^1H NMR ($CDCl_3$, 500MHz):δ_H 0.0 (s, 6H, C*H*$_3$Si), 0.90 (s, 9H, (CH_3)$_3$C), 1.76-1.84 (m, 1H, C*H*-3), 1.88-1.98 (m, 1H, C*H*-3), 2.48 (t, 2H, C*H*-2), 3.32 (m, 1H, C*H*-OBn), 3.40 (m, 1H, C*H*-OBn), 3.86-3.92 (m, 1H, C*H*-O), 4.46-4.50 (m, 2H, C*H*$_2$Ph), 7.22-7.36 (m, 5H, Ar), 9.74 (s, 1H, C*H*O). IR ($CHCl_3$) ν_{max} 1730 cm^{-1}.

(10) (*2R*),(*5R,S*)-*1-O-Benzyl-2-O-tert-butyldimethylsilyl-1,2,5-decantriol* **13**. Aldehyde **12** was treated with pentyl magnesium bromide in diethyl ether (r.t., 4 h) to afford the secondary alcohol **13** in 90% yield. ^1H NMR ($CDCl_3$, 500MHz): δ_H 0.0 (s, 6H, (CH_3)$_2$Si), 0.90-0.98 (m, 12H, (CH_3)$_3$C and C*H*$_3$), 1.20-1.80 (m, 12H, C*H*$_2$), 3.32-3.44 (m, 2H, C*H*$_2$-OBn), 3.52-3.62 (m, 1H, C*H*-OH), 3.84-3.92 (m, 1H, C*H*-O), 4.50 (s, 2H, C*H*$_2$Ph), 7.20-7.36 (m, 5H, Ar).

(11) (*R*)-*1-O-Benzyl-5-oxo-1,2-decandiol* **9**. Title compound was obtained by oxidation of **13** with PCC to ketone **14** and deprotection of silyl ether with TBAF (Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972,** *94*, 6190) (70% from **13**, oil). $[\alpha]_D$ +3.3 (*c* 1 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500MHz): δ_H 0.92 (t, 3H, C*H*$_3$), 1.20-1.36 (m, 4H, C*H*$_2$), 1.50-1.60 (m, 2H, C*H*$_2$), 1.60-1.70 (m, 1H, C*H*-3), 1.70-1.80 (m, 1H, C*H*-3), 2.36 (t, 2H, C*H*$_2$CO), 2.48-2.62 (m, 2H, C*H*$_2$CO), 3.32 (m, 1H, C*H*-OBn), 3.46 (m, 1H, C*H*-OBn), 3.74-3.80 (m, 1H, C*H*-O), 4.50 (s, 2H, C*H*$_2$Ph), 7.22-7.40 (m, 5H, Ar). m/z (APCI) 279 (MH^+), 261.

(12) (*R*)-*1-O-Benzyl-5-ethylendioxy-1,2-decandiol* **15.** The ketal was prepared from ketone **14** with diethylene glycol under boron trifluoride-ethyl etherate catalysis (Derguini, F.; Linstrumelle, G. *Tetrahedron Lett.* **1984**, *25*, 5763 and Hase, T.A.; Ourika, A.; Holmberg, C. *J. Org. Chem.* **1981**, *46*, 3137). The silylether was removed by reaction with TBAF (ref 11) affording **15** in 65% yield from **14**. $[\alpha]_D$+0.6 (*c* 2 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500MHz): δ_H 0.84 (t, 3H, C*H*$_3$), 1.18-1.36 (m, 6H, C*H*$_2$), 1.44-1.58 (m, 4H, C*H*$_2$), 1.60-1.70 (m, 1H, C*H*), 1.74-1.84 (m, 1H, C*H*), 2.70 (br s, 1H, exchang.), 3.33 (dd, 1H, $J_{H1a,1b}$ 9 Hz, $J_{H1a,2}$ 7.5 Hz, H-1a), 3.47 (dd, 1H, $J_{H1b,2}$ 3 Hz, H-1b), 3.78 (m, 1H, H-2), 3.86 (br s, 4H, *CH*$_2$-O), 4.54 (s, 2H, C*H*$_2$Ph), 7.20-7.40 (m, 5H, Ar).

(13) The optical purity of (*R*)-**9** was determined by ^1H NMR analysis of the MTPA-ester[6] of (*R*)-**15**. (*R,S*)-**15** was prepared by PCC oxidation of (*R*)-**15**, followed by $NaBH_4$ reduction in methanol. In the spectrum of the racemic derivative two signals centered at 4.42 and 4.52 ppm, due to the OC*H*$_2$Ph protons, were present, whereas in the spectrum of the (*R*)-**15**-derivative the signal at 4.42 ppm was not detectable.

(14) (*R*)-*1-O-Benzyl-5-ethylenedithio-1,2-decandiol* **16**. The thioketal was prepared in one step procedure from ketone **14** by reaction in dichloromethane with 1,2-ethandithiol in the presence of 0.2 equiv of boron trifluoride-diethyl ether (73%, oil). $[\alpha]_D$ -1.4 (*c* 1 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz):δ_H 0.87 (t, 3H, C*H*$_3$), 1.27 (m, 4H, C*H*$_2$), 1.45 (m, 2H, C*H*$_2$), 1.64 (m, 2H, C*H*$_2$), 1.88 (m, 3H, C*H*$_2$ and C*H*), 2.12 (m, 1H, C*H*), 2.32 (br s, 1H, exchang.), 3.24 (s, 4H, C*H*$_2$-S), 3.33 (dd, 1H, $J_{H1a,1b}$ 9.5 Hz, $J_{H1a,2}$ 9.5 Hz, H-1a), 3.51 (dd, 1H, $J_{H1b,2}$ 2.5 Hz, H-1b), 3.80 (m, 1H, H-2), 4.54 (s, 2H, C*H*$_2$Ph), 7.22-7.40 (m, 5H, Ar).

(15) (*R*)-*1-O-Benzyl-2-O-(2,3,4,6-tetra-O-acetyl-*β*-D-galacto-pyranosyl)-5-ethylenedithio-1,2-decandiol* **19**. $[\alpha]_D$ -3 (*c* 1 in

$CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ_H 0.85 (t, 3H, C*H*$_3$), 1.22-1.32 (m, 4H, C*H*$_2$), 1.40 (m, 2H, C*H*$_2$), 1.65-1.88 (m, 6H, C*H*$_2$), 1,94, 1,97, 2,05, 2,10 (4 s, 12H, 4 C*H*$_3$CO), 3.22 (br s, 4H, C*H*$_2$-S), 3.44 (dd, 1H, $J_{H1a,1b}$ 10.0 Hz, $J_{H1a,2}$ 6.0 Hz, H-1a), 3.62 (dd, 1H, $J_{H1b,2}$ 4.5Hz, H-1b), 3.72 (m, 1H, H-2), 3.82 (dd, 1H, $J_{H'5,6a} = J_{H'5,6b}$ 6.5 Hz, H'-5), 4.02-4.10 (m, 2H, H'-6a,6b), 4.49 (s, 2H, C*H*$_2$Ph), 4.55 (d, 1H, $J_{H'1,2}$ 8Hz, H'-1), 4.96 (dd, 1H, $J_{H'2,3}$ 10 Hz, $J_{H'3,4}$ 3 Hz, H'-3), 5.17 (dd, 1H, H'-2), 5.33 (br d, 1H, H'-4), 7.18-7.36 (m, 5H, Ar). m/z (CI/NH_3) 702 $[M+NH_4]^+$.

(16) *(R)-1-O-Benzyl-2-O-(2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosyl)-5-ethylenedithio-1,2-decandiol* **20**. $[\alpha]_D$ -6 (*c* 1 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ_H 0.85 (t, 3H, C*H*$_3$), 1.20-1.32 (m, 4H, C*H*$_2$), 1.40 (m, 2H, C*H*$_2$), 1.68-1.90 (m, 6H, C*H*$_2$), 1.96, 1.98, 2.02, 2.04 (4 s, 12H, 4 C*H*$_3$CO), 3.18-3.26 (m, 4H, C*H*$_2$-S), 3.44 (dd, 1H, $J_{H1a,1b}$ 10.0 Hz, $J_{H1a,2}$ 5.5 Hz, H-1a), 3.57-3.64 (m, 2H, H-1b and H'-5), 3.72 (m, 1H, H-2), 4.03 (dd, 1H, $J_{H'6a,6b}$ 12.5 Hz, $J_{H'5,6a}$ 2.5 Hz, H'-6a), 4.16 (dd, 1H, $J_{H'5,6b}$ 4.5 Hz, H'-6b), 4.51 (s, 2H, C*H*$_2$Ph), 4.59 (d, 1H, $J_{H'1,2}$ 8Hz, H'-1), 4.96 (dd, 1H, $J_{H'2,3}$ 9.5 Hz, H'-2), 5.04 (dd, 1H, $J_{H'3,4} = J_{H'4,5}$ = 10Hz, H'-4), 5.15 (dd, 1H, H'-3), 7.20-7.36 (m, 5H, Ar). m/z (CI/NH_3) 702 $[M+NH_4]$+.

(17) Compounds **19** and **20** were deprotected as follows. The thioketal group was removed by adding dropwise at 0 °C a solution of NBS in acetone to a solution of the substrate (0.25 g) in acetone (97% acetone+3% H_2O) until disappeance of the starting compound. After removal of the acetates with the Zemplen reaction (MeONa/MeOH), the benzyl ether was quantitatively hydrogenolyzed in MeOH with Pd/C as catalyst. The mixture was filtered over Celite, evaporated to dryness, and diluted with water. This solution was treated with Dowex 50 × 8 (H^+ form) under reduced pressure (12 mm Hg) at 50 °C for 10 min; after filtration, the solution was lyophilized affording the desired **4b** and **4c**. *(R)-2-O-(β-D-glucopyranosyl)-5-oxo-1,2-decandiol* **4b**. $[\alpha]_D$ -20 (c 0.5 in H_2O). ^1H NMR (D_2O, 500 MHz): δ_H 0.70 (t, 3H, CH_3), 1.02-1.18 (m, 4H, C*H*$_2$), 1.36 (m, 2H, C*H*$_2$), 1.63 (m, 2H, C*H*$_2$), 2.37 (m, 2H, C*H*$_2$-6), 2.53 (m, 2H, C*H*$_2$-4), 3.10 (dd, 1H, $J_{H'1,2}$ 8Hz, $J_{H'2,3}$ 9 Hz, H'-2), 3.16-3.34 (m, 3H, H'-3,4,5), 3.43 (dd, 1H, $J_{H1a,1b}$ 12.0 Hz, $J_{H1a,2}$ 6.0 Hz, H-1a), 3.56-3.46 (m, 2H, H-1b and H'-6a), 3.63 (m, 1H, H-2), 3.72 (dd, 1H, $J_{H'6a,6b}$ 12 Hz, $J_{H'6b,5}$ 1,5 Hz, H'-6b), 4.31 (d, 1H, H'-1). m/z (CI/NH_3) 368 $[M+NH_4]^+$. *(R)-2-O-(β-D-galactopyranosyl)-5-oxo-1,2-decandiol* **4c**. $[\alpha]_D$ -5 (c 0.5 in H_2O). ^1H NMR (D_2O, 500 MHz): δ_H 0. 70 (t, 3H, CH_3), 1.02-1.18 (m, 4H, C*H*$_2$), 1.38 (m, 2H, C*H*$_2$), 1.63 (m, 2H, C*H*$_2$), 2.37 (m, 2H, C*H*$_2$-6), 2.53 (m, 2H, C*H*$_2$-4), 3.30-3.61 (m, 7H, H-1a,1b and H'-2,3,5,6a,6b); 3.64 (m, 1H, H-2), 3.74 (br s, 1H, $J_{H'3,4}$ 3 Hz, H'-4), 4.25 (d, 1H, $J_{H'1,2}$ 8.0 Hz, H'-1). m/z (CI/NH_3) 368 $[M+NH_4]^+$.

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