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Article

Synthesis of 3,4-Di-*O*-benzyl-1-*O*-methyl-L-galactitol, a Key Precursor of the C_{33}-C_{37} Fragment of Calyculins

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3,4-Di-*O*-benzil-1-*O*-metil-L-galactitol (**3**) foi sintetizado em 7 etapas a partir de 1,2:3,4-di-*O*-isopropilideno-α-D-galactopiranose (**4**). A síntese envolve a metilação do HO-6 de **4**, seguida de metanólise para a mistura do 6-*O*-metil-α-D-galactopiranosídeo de metila (**6**, produto principal) e do análogo β-furanosídico **8**. O composto **6** foi convertido no derivado 3,4-*O*-isopropilidênico **9** e o grupo OH livre foi protegido na forma do éter metoxietoximetílico (MEM). A remoção quimiosseletiva do acetonídeo por hidrólise, seguida de benzilação forneceu o 3,4-di-*O*-benzil-2-*O*-metoxietoximetil-6-*O*-metil-α-D-galactopiranosídeo de metila (**12**). A hidrólise ácida simultânea do glicosídeo metílico e do grupo MEM de **12** levou a **13** que foi então reduzido com boroidreto de sódio à molécula alvo **3**.

3,4-Di-*O*-benzyl-1-*O*-methyl-L-galactitol (**3**) has been synthesized in a seven step sequence starting from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**). The synthesis involves the methyllation of HO-6 of **4**, followed by methanolysis to the mixture of the corresponding methyl 6-*O*-methyl-α-D-galactopyranoside (**6**, major product) and the β-furanoside analog (**8**). Compound **6** was converted into the 3,4-*O*-isopropylidene derivative **9**, and the free HO-group was protected as the methoxyethoxymethyl (MEM) ether. Chemoselective removal of the acetonide by hydrolysis, followed by benzylation gave the methyl 3,4-di-*O*-benzyl-2-*O*-methoxyethoxymethyl-6-*O*-methyl-α-D-galactopyranoside (**12**). Simultaneous acid hydrolysis of the methyl glycoside and MEM group of **12** led to **13**, which was then reduced with sodium borohydride to the target molecule **3**.

Keywords: calyculins, secondary metabolites, marine sponge, galactose diacetonide, L-galactitol derivative.

Introduction

The calyculins A-H are the secondary metabolites isolated from the Japonese marine sponge *Discodermia calyx* which exhibited varied biological activities, including antitumor, smooth muscle contractile and tumor promotion[1,2]. The basic structure of these polyketides differ mainly by a methyl group on C-32 and the geometry of C-2,3 and C-6,7 olefins. From the same sponge four new calyculins have been isolated more recently[3], and also calyculins A, B, E and F and a mixture of calyculinamides A and B have been isolated from the New-Zeeland deep-water marine sponge *Lamellomorpha strongylata*[4]. Hydrolysis of calyculins affored 2,3-dihydroxy-4-dimethylamino-5-methoxypentanoic acid (**2b**), the C_{33}-C_{37} fragment of the molecule, which has a (2*S*, 3*S*, 4*S*) configuration. The synthesis of its enantiomer from (*S*)-pyroglutaminol provided the conclusive evidence on the absolute configuration of calyculins[5].

Many efforts have been directed towards the synthesis of calyculins, and a carbohydrate approach to the synthesis of **2a** has been reported[6a]. In this case a D-lyxose derivative[6b], previously synthesized by van Boom[7], was employed as starting material, and the pentitol derivative **1** was an advanced intermediate in the sequence (Scheme 1). In connection with our project on the enantiospecific synthesis of naturally occurring hydroxy amino acids from carbohydrates[8,9] we wish to report here the synthesis of a conveniently protected L-galactitol derivative **3**, an analog of **1** having one more carbon atom, as key intermediate for the synthesis of **2a**. In our strategy we started from inexpensive and readily available D-galactose, and all the steps to **3** were high yielding.

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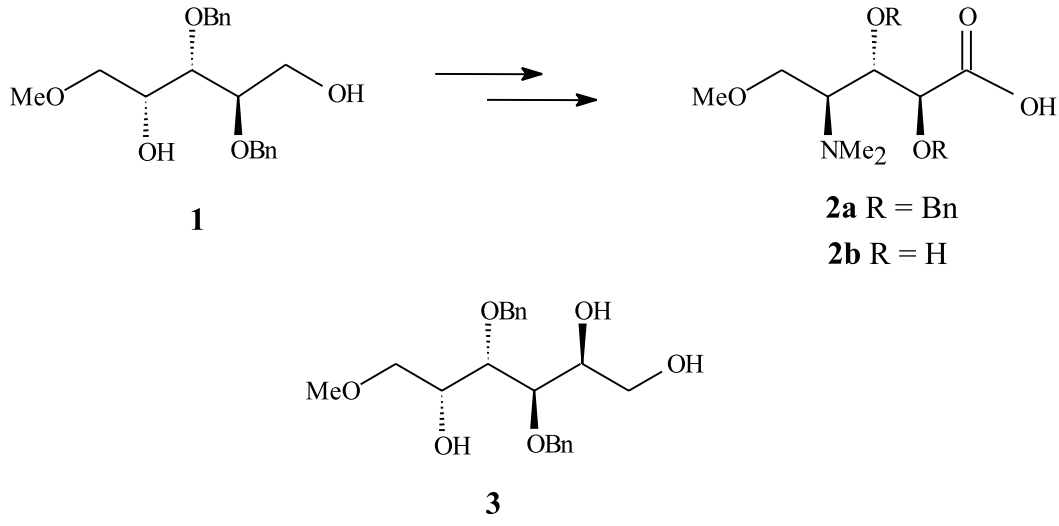


Scheme 1.

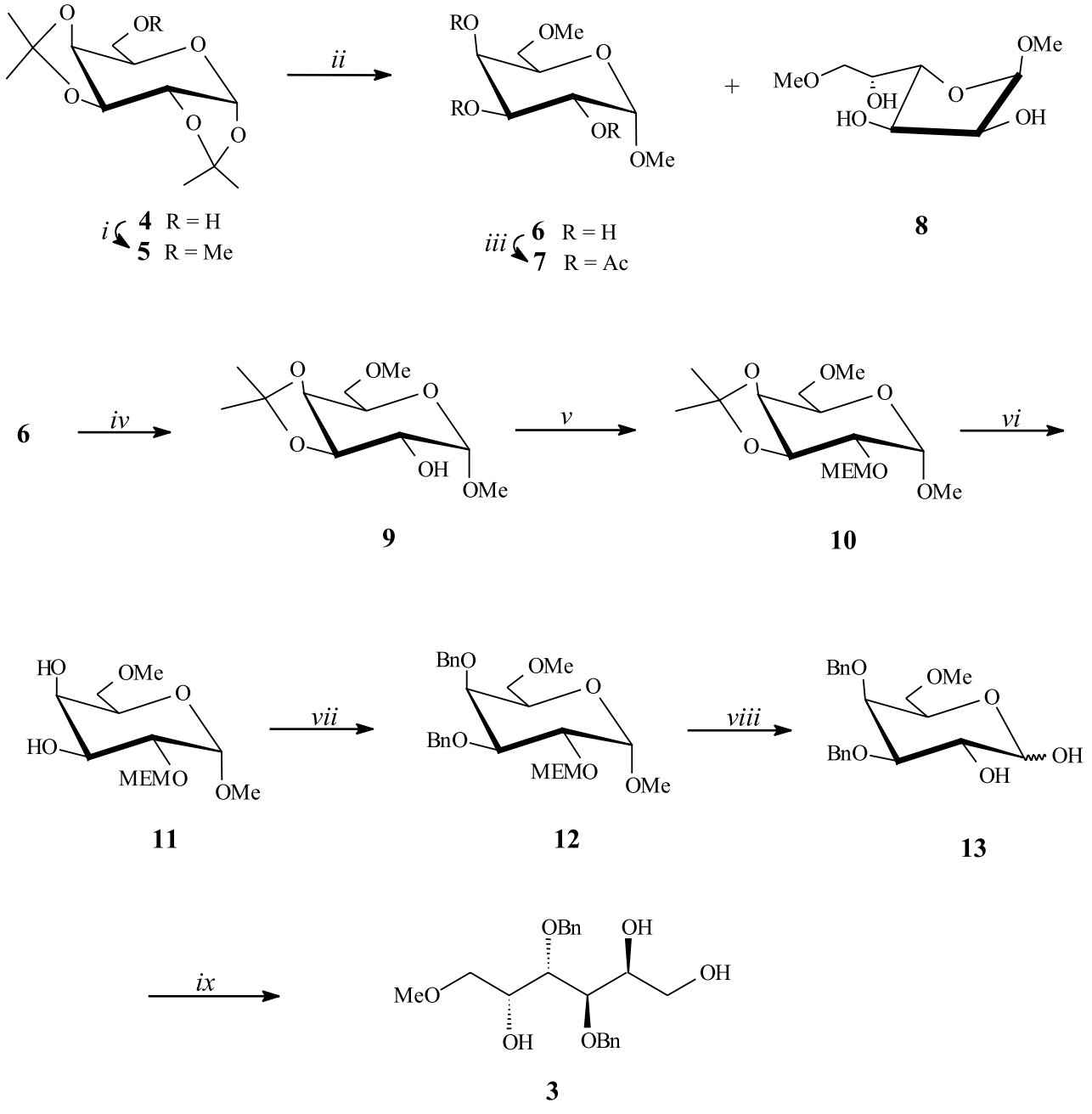
Results and discussion

Acid catalyzed acetonation of D-galactose[10] afforded the diacetonide **4** in quantitative yield. The crude 1,2:3,4-di-*O*-isopropylidene derivative **4** was methylated using methyl iodide in the presence of potassium hydroxide suspended in tetrahydrofuran (THF) to give the 6-*O*-methyl ether **5** in 90% yield (Scheme 2). The ^{1}H NMR spectrum of **5** showed that the sugar ring was strongly distorted from the regular $^4C_1$ conformation because of the two fused five-membered isopropylidene rings. Thus, unusual coupling constant values of 2.3 and 7.9 Hz were respectively observed between trans (H-2, H-3) and cis (H-3, H-4) coupled protons. This result was in agreement with previous reports on derivatives of **4**[11].

Treatment of **5** with a solution of aqueous HCl in methanol under reflux, led to the removal of the acetal protecting groups and to the formation of two methyl glycosides. The one which showed by TLC lower R_f value was the major product and crystallized from the reaction mixture upon neutralization and concentration. The $J_{1,2}$ value (3.7 Hz) in the ^{1}H-NMR spectrum of this major product suggested that it was the methyl α-pyranoside isomer. However, the other signals of the sugar ring were overlapped as a complex multiplet, and in order to establish firmly its structure the compound was acetylated under standard conditions to afford the tri-*O*-acetyl derivative **7**. Its ^{1}H-NMR spectrum confirmed, on the basis of the *J* and chemical shift values, the methyl α-D-galactopyranoside structure for **7**. For example, as expected, H-3 gave a double doublet having a large $J_{2,3}$ (10.7 Hz) and a small $J_{3,4}$ (3.3 Hz) coupling constant values, whereas H-4 gave only small *J* values. The ^{13}C NMR spectrum of **6** was also coincident with the spectrum reported for methyl α-D-galacto-pyranoside[12], except for the downfield shift of the C-6 signal due to methylation,[13] and for the additonal signal of the methyl ether carbon.

The structure of the minor product of methanolysis was established as methyl 6-*O*-methyl-β-D-galactofuranoside (**8**), on the basis of its spectral data. Thus, the small $J_{1,2}$ value (1.6 Hz) indicates a trans relationship for H-1 and H-2, and hence a β-furanoside ring[14]. The ^{13}C-NMR spectrum of **8** showed a large downfield shift for the C-2 and C-4 signals, in agrement with δ values observed for other alkyl and aryl β-D-galactofuranosides[14,15]. Particularly, such a spectrum greatly resembles that of methyl β-D-galactopyranoside, with difference between the C-6 signals, which appeared shifted downfield in **8** because of the methylation of the HO-6 group.

The hydroxyl groups at C-3 and C-4 of compound **6** were transiently protected by isopropylidenation with acetone in the presence of *p*-toluenesulphonic acid and anhydrous $CuSO_4$ to afford the 3,4-*O*-isopropropylidene derivative **9** in 87% yield. The remaining free hydroxyl group at C-2 was derivatized as the MEM acetal on treatment of **9** with 2-methoxyethoxymethyl chloride (MEM chloride) and *N*,*N*-diisopropylethylamine (EDPA). The 2-*O*-MEM derivative **10** was obtained in 90% yield, after purification by column chromatography. As the 3,4-*O*-isopropylidene acetal is rather labile under acidic conditions we decided to replace it by a more stable protecting group, which could resist the further reactions needed for the synthesis of **2a**. For this purpose, it was required the chemoselective removal of such an



Scheme 2. *Reagentes and conditions*: *i)* Mel-KOH, THF (90%); *ii)* HCl-MeOH, reflux, 48 h (**6**: 69%, **8**: 13%); *iii)* Ac_2O-C_5H_5N, rt, 16 h (quantitative); *iv)* $Me_2CO/CuSO_4$, PTSA, 16 h (87%); *v)* MEMCl,CH_2Cl_2-EDPA (90%); *vi)* AcOH-MeOH, reflux, 24 h (quantitative); *vii)* BnBr, NaH (81% from **10**); *viii)* HCl-CH_3CN, 82 °C, 16 h; *ix)* $NaBH_4$, MeOH (**3**, 70% from **12**).

isopropylidene acetal in the presence of other two ketal functions (the MEM and the methyl glycoside). From the several reagents and conditions attempted, the best results were achieved by heating **10** with a acetic acid-methanol-water solution under reflux for 24 h. The chromatographically homogeneous crude **11** was employed for the next step. Benzylation of **11** by treatment with benzyl bromide and sodium hydride in a sealed tube, under N_2 atmosphere, afforded 3,4-di-*O*-benzyl derivative **12** (81% yield from **10**). Its ^{1}H-NMR spectrum showed a complex pattern between 4.97-4.57 ppm due to the AB-system of the methylene groups of the benzyl substituents and the MEM-acetal overlapped with H-1.

Complete hydrolysis of the MEM-protecting group and the methyl glycoside was performed on treatment of **12** with a solution of 5:1 4M HCl-acetonitrile at 82 ºC

overnigth, to afford oily compound **13**. The ^{13}C-NMR spectrum showed that **13** was actually a mixture of α : β anomers. Their ratio was established as 2 : 1 on the basis of the integral of the anomeric signals, which were assigned by comparison with the same signals of galactopyranose[12]. Reduction of the anomeric center of **13** with sodium borohydride in methanol led to the target alditol derivative **3**, in 70% yield from **12**. Its ^{13}C NMR spectrum was adquired by employing the DEPT pulse sequence, facilitating the assignment of the C-1 resonance. This appeared in the region of the benzyl methylene carbons; whereas C-6 resonates at higher field, similar to the hydroxymethyl carbon of galactitol[12].

For the synthesis of **2a** from **3** we propose as next steps the protection of HO-5,6, substitution of HO-2 by Me_2N with change of the C-2 configuration, deprotection of HO-5,6, and oxidative degradation of the glycol system. We expect that this oxidation should occur under smoother conditions than those employed for the oxidation of **1**, and hence to improve the poor yield (38%) obtained in this step in the reported synthesis[6b] of **2a** .

Experimental

General

Melting points (mp) were determined with a Fisher-Johns apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed on 0.2 mm silica gel 60 F_{254} (Merck) aluminium supported plates. Visualization of the spots was effected by charring with a solution of 5% sulfuric acid in EtOH, containing 0.5% *p*-anisaldehyde. Column chromatography was performed with silica gel 60 (230-400 mesh, Merck). Optical rotations were measured with a Perkin-Elmer Model 343 digital polarimeter in the solvent indicated in each individual case. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC 200 spectrometer in $CDCl_3$ solutions (unless otherwise indicated) with TMS as an internal standard.

*6-O-Methyl-1,2:3,4-di-O-isopropyliden-α-D-galacto-pyranose (**5**).*

To a solution of the diacetonide **4**[10] (3.20 g, 12.3 mmol) in dry tetrahydrofuran (THF, 25 mL) was added freshly powdered potassium hydroxide (1.50 g, 26.5 mmol). The suspension was stirred under a nitrogen atmosphere, and iodomethane (0.88 mL, 14.10 mmol) was added. The stirring was maintained, at room temperature, for 16 h. The liquid was decanted and the solid residue was washed twice with THF. The liquids were combined and upon addition of water (15 mL) the solution was extracted with ether (4 x 25 mL). The organic layer was washed with water, dried ($MgSO_4$) and concentrated. The residue, which showed by TLC a main spot having R_f 0.55 (3:1 hexane-EtOAc) was purifed by column chromatography (8:1 hexane-EtOAc) to afford **5** (3.03 g, 90%) as a colorless oil; $[\alpha]^{20}_D$ -71 (*c* 1.2, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 5.52 (d, 1H, $J_{1,2}$ 5.1 Hz, H-1), 4.58 (dd, 1H, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 3.9 Hz, H-3), 4.30 (dd, 1H, $J_{1,2}$ 5.1, $J_{2,3}$ 2.4 Hz, H-2), 4.23 (dd, 1H, $J_{4,5}$ 1.9 Hz, H-4), 3.95 (ddd, 1H, $J_{5,6}$ 5.0, $J_{5,6'}$ 6.8 Hz, H-5), 3.59 (dd, 1H, $J_{6,6'}$ 9.6 Hz, H-6), 3.51 (dd, 1H, $J_{5,6'}$ 6.8, $J_{6,6'}$ 9.6 Hz, H-6´), 3.38 (s, 3H, OCH_3), 1.53, 1.44, 1.33, 1.31, (4 s, 12H, 2 C(CH_3)$_2$); ^{13}C- NMR (50.3 MHz, $CDCl_3$) δ: 108.9, 108.1 (2 *C*Me_2), 96.1 (C-1), 71.1, 71.0, 70.4, 70.3, 66.4 (C-2, 3, 4, 5, 6), 58.8 (O*C*H_3), 25.7, 24.6, 24.2 (C(*C*H_3)$_2$). Anal. calcd for $C_{13}H_{22}O_6$: C, 56.81; H, 8.01. Found: C, 57.09; H, 8.33

*Methyl 6-O-methyl-α-D-galactopyranoside (6) and methyl 6-O-methyl-β-D-galactofuranoside (**8**).*

A solution of compound **5** (1.00 g, 3.64 mmol) in MeOH (10 mL) containing concentrated aqueous HCl (0.1 mL) was heated under reflux for 48 h. The resulting solution was neutralized with AG3-X4 resin and concentrated. Crystallization from 1:1 EtOAc-ether affored **6** (0.40 g, 53%) as colorless crystals; mp 138 ºC; $[\alpha]^{20}_D$ +151 (*c* 0.8, MeOH); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 4.85 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.05-3.68 (m, 6H, H-2, 3, 4, 5, 6, 6´), 3.44, 3.43 (2 s, CH_3O); ^{13}C-NMR (50.3 MHz, D_2O) δ: 100.3 (C-1), 72.6, 70.2, 70.0, 69.5, 68.8 (C-2-6), 59.1, 56.0 (O*C*H_3). Anal. calcd for $C_8H_{16}O_6$: C, 46.02; H, 7.67. Found: C, 46.30; H, 7.60.

Acetylation of **6** (25 mg, 0.12 mmol) with pyridine (1 mL) and acetic anhydride (0.8 mL) overnight, afforded after the usual work-up the 2,3,4-tri-*O*-acetyl derivative **7** in quantitative yield; R_f 0.47 (1:4 PhMe-EtOAc); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 5.45 (bd, 1H, $J_{3,4}$ 3.3, $J_{4,5}$ < 1 Hz, H-4) 5.35 (dd, 1H, $J_{2,3}$ 10.7 Hz, H-3), 5.15 (dd, 1H, $J_{1,2}$ 3.5 Hz, H-2), 4.99 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.12 (t, $J_{5,6} \approx J_{5,6'}$ 6.0 Hz, H-5), 3.51-3.35 (m, 2H, H-6,6´), 3.41, 3.33 (2 s, 6H, 2 CH_3O), 2.13, 2.07, 1.97 (3 s, 9H, 3 CH_3CO).

Concentration of the mother liquors of crystallization of **6** gave a syrup (0.35 g) which was chromatographed using EtOAc as solvent, to afford an additional crop of **6** (0.12 g, 69% overall yield). From further fractions of the column, the furanoside **8** was isolated (0.10 g, 13%); $[\alpha]^{20}_D$ -72 (*c* 0.8, MeOH); ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 5.22, 5.01, 4.67 (3 d, *J* 4.4 Hz, 3 *H*O), 4.61 (d, $J_{1,2}$ 1.6 Hz, H-1), 3.83-3.66 (m, 4H, H-2, 3, 4, 5), 3.37 (m, 2H, H-6, 6´), 3.26, 3.24

(2 s, 6H, 2 C*H*$_3$O); ^{1}H-NMR (200 MHz, D_2O) δ: 4.83 (bs, 1H, H-1), 4.00-3.85 (m, 4H, H-2, 3, 4, 5), 3.52 (m, 2H, H-6, 6´), 3.34 (s, 6H, 2 C*H*$_3$O); ^{13}C-NMR (50.3 MHz, DMSO-d_6) δ: 108.6 (C-1), 82.3, 81.7 (C-2, 4), 76.4, 73.7, 67.8 (C-3, 5,6), 58.1, 54.1 (2 OC*H*$_3$); ^{13}C-NMR (50.3 MHz, D_2O) δ: 109.0 (C-1), 83.9 (C-4), 81.6 (C-2), 77.4 (C-3), 74.1 (C-6), 69.8 (C-5), 59.3, 55.8 (*C*H$_3$O). Anal. calcd for $C_8H_{16}O_6$: C, 46.02; H, 7.67. Found: C, 45.43; H, 8.02.

*Methyl 3,4-O-isopropylidene-6-O-methyl-α-D-galacto-pyranoside (**9**).*

Powdered, anhydrous $CuSO_4$ (1.60 g, 10.0 mmol) was added to a solution of **6** (0.44 g, 2.11 mmol) in dry acetone (16 mL). A small crystal of *p*-toluensulphonic acid was added and the mixture was vigorously stirred at room temperature for 16 h. The solid was filtered and the filtrate neutralized with AG 3-X4 resin. Evaporation of acetone led to a chromatographically homogenous syrup (R_f 0.54, 4:1 EtOAc-PhMe) which crystallized spontaneously. Compound **9** (0.46 g, 87%) gave mp 99-100 ºC; $[\alpha]^{20}_D$ +134 (*c* 0.9, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 4.78 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 4.26-4.11 (m, 3H, H-3, 4, 5), 3.80 (ddd, 1H, $J_{2,3}$ 10.0, $J_{2,HO}$ 6.2 Hz, H-2), 3.64 (d, 2H, $J_{5,6}$ 6.0 Hz, 2 H-6), 3.47, 3.43 (2 s, 6H, 2 OC*H*$_3$), 2.34 (d, 1H, *H*O), 1.51, 1.35 (2 s, 6H, (C*H*$_3$)$_2$C); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 109.6 (*C*Me$_2$), 98.6 (C-1), 76.2, 73.4, 72.1, 69.6, 67.2 (C-2-6), 59.3, 55.5 (2 *C*H$_3$O), 27.8, 26.0 ((*C*H$_3$)$_2$). Anal. calcd for $C_{11}H_{20}O_6$: C, 53.10; H, 8.05. Found: C, 53.28; H, 8.07

*Methyl 3,4-O-isopropylidene-2-O-methoxyethoxymethyl-6-O-methyl-α-D-galacto pyranoside (**10**).*

Compound **9** (0.42 g, 1.69 mmol) was dissolved in a mixture of anhydrous CH_2Cl_2 (4.0 mL) and *N*,*N*-diisopropylethylamine (EDPA, 2.3 mL). The solution was cooled to 0 ºC (ice-water bath) and stirred for 10 min, then methoxyethoxymethyl chloride (MEMCl, 0.75 g, 6.02 mmol) was added. The solution was refluxed for 3 h, when TLC showed complete conversion of **6** into a product of higher mobility (R_f 0.58, 4:1 EtOAc-PhMe). The mixture was diluted with CH_2Cl_2 (25 mL) and washed with 2N aqueous HCl, water, and saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated. Purification by column chromatography (3:1 EtOAc-hexane) afforded oily **10** (0.51 g, 90%); $[\alpha]^{20}_D$ +62 (*c* 0.8, $CHCl_3$), ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 4.92, 4.83 (2 d, 2H, *J* 6.9 Hz, OC*H*$_2$O), 4.84 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1), 4.31-4.24 (m, 2H), 4.18-3.52 (m, 8H), 3.43 (x2), 3.38 (2 s, 9H, 3 OC*H*$_3$); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ:109.2 (*C*Me$_2$), 98.7 (C-1), 95.5 (OC*H*$_2$O), 75.6, 75.3, 73.8 (C-2, 3, 4), 72.0, 71.5 (OC*H*$_2$-*C*H$_2$O), 66.9 (C-9), 66.3 (C-5), 59.2, 58.9, 55.4 (3 *C*H$_3$O), 28.1, 26.3 ((*C*H$_3$)$_2$C). Anal. calcd for $C_{15}H_{28}O_8$: C, 53.57; H, 8.33. Found: C, 53.31; H, 8.40

*Methyl 3,4-di-O-benzyl-2-O-methoxyethoxymethyl-6-O-methyl-α-D-galactopyranoside (**12**).*

A solution of **10** (0.26 g, 0.78 mmol) in 1: 1: 0.01 acetic acid-methanol-water (5 mL) was stirred under reflux for 24 h. The mixture was neutralized by addition of 1M aqueous NaOH, and then concentrated. The residue was suspended in EtOAc, filtered and the solid was washed several times with hot EtOAc. The solution was concentrated to afford **11** as a chromatographically homogeneous oil (R_f 0.35, 20:1 EtOAc-MeOH); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 4.88, 4.75 (2 d, 2H, *J* 7.2 Hz, OC*H*$_2$O), 7.85 (d, 1H, H-1), 4.00-3.52 (m, 6H, H-2, 3, 4, 5, 6, 6´), 3.40 (x2), 3.36 (2 s, 9H, 3 OC*H*$_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 98.9 (C-1), 96.8 (OC*H*$_2$O), 78.4, 72.6, 71.6, 69.9 68.8, 68.3, 67.8 (C-2-6 and OC*H*$_2$-*C*H$_2$O), 59.4, 59.0, 55.2 (3 *C*H$_3$O).

Crude **11** was dissolved in anhydrous DMF (2 mL) and to the solution, cooled to 0 ºC, benzyl bromide (0.24 mL, 2.02 mmol) and sodium hydride (48 mg, 2.00 mmol) were successively added. After 15 h of stirring at room temperature, the mixture was treated with MeOH (2 mL) for 1 h and then concentrated in vacuum. The residue was extracted with CH_2Cl_2 (3 x 15 mL) and the solvent evaporated. Purification by column chromatography (6:1 PhMe-EtOAc) afforded oily **12** (0.30 g, 81% from **10**); $[\alpha]^{20}_D$ + 17 (*c* 1.1, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.33 (m, 10H aromatic), 4.97, 4.85 (2 d, 2H, *J* 6.9 Hz, OC*H*$_2$O), 4.96, 4.57 (2 d, 2H, *J* 11.7 Hz, PhC*H*$_2$), 4.91 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.76, 4.70 (2 d, 2H, *J* 11.9 Hz, PhC*H*$_2$), 4.21 (dd, $J_{2,3}$ 9.5 Hz, H-2), 3.92-3.77 (m, 3H), 3.69-3.45 (m, 6H), 3.43, 3.36, 3.30 (3 s, 9H, 3 OC*H*$_3$); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 138.6, 128.3, 128.1, 127.5, 127.4 (C-aromatic), 99.5 (C-1), 96.5 (OC*H*$_2$O), 78.6, 75.2, 75.0, 69.1 (C-2, 3, 4, 5), 74.7, 73.0 (PhC*H*$_2$), 71.6, 71.5 (OC*H*$_2$C*H*$_2$O), 67.1 (C-6), 59.0, 58.9, 55.2 (3 OC*H*$_3$). Anal. calcd for $C_{26}H_{36}O_8$.0.5H_2O: C, 64.33; H, 7.63. Found: C, 64.38; H, 7.93.

*3,4-Di-O-benzyl-1-O-methyl-L-galactitol (**3**).*

A solution of **12** (0.28 g, 0.59 mmol) in 5:1 4M HCl-acetonitrile (8 mL) was heated at 82 ºC overnight. The solution was concentrated to dryness and the residue was extracted with CH_2Cl_2 (30 mL) and treated with solid $NaHCO_3$ (1 g). The suspension was filtered and

concentrated to give syrupy **13**, R_f 0.50 (20: 1 CH_2Cl_2-MeOH); ^{13}C- NMR (50.3 MHz, $CDCl_3$) δ: 138.1, 128.6, 128.3, 127.9, 127.8 (C-aromatic), 97.4 (C-1 β), 92.8 (C-1α, ratio α: β 2:1), 79.2, 74.7, 74.6, 74.1, 72.5, 71.9, 71.3, 69.6, 69.1, 59.1

Crude **13** (0.2 g, 0.53 mmol) was dissolved in MeOH (1.5 mL) and $NaBH_4$ (24 mg, 0.6 mmol) was added. The solution was stirred overnight at room temperature and then neutralized with Dowex 50W (H^+) resin. Concentration of the solution gave a residue which was dissolved in MeOH (5 ml) and the solvent evaporated. This procedure was repeated twice in order to remove boric acid. Compound **3** (0.15 g, 70% from **12**) crystallized upon addition of 20:1 CH_2Cl_2-MeOH; mp 92-93 ºC, $[\alpha]^{20}_D$ -2 (*c* 1.0, MeOH); ^{1}H-NMR (200 MHz, $(CD_3)_2CO + D_2O$) δ: 7.39-7.23 (m, 10 H-aromatic), 4.77, 4.75, 7.63, 4.56 (4 d, 4H, *J* 11.3 Hz, 2 PhCH_2), 4.05-3.86 (m, 3H), 3.81 (dd, 1H, *J* 1.8, *J* 7.6 Hz), 3.66 (m, 2H), 3.50, 3.42 (2 d, 2H, *J* 10.3 Hz), 3.25 (s, 3H, OCH_3).

^{13}C-NMR (50.3 MHz, $(CD_3)_2CO$ + D_2O) δ: 139.6, 129.1, 128.8, 128.7, 128.3 (C-aromatic), 78.8, 78.6 (C-3, 4), 74.9, 74.8, 74.6 (C-1, 2 PhCH_2), 72.1, 69.8 (C-2, 5), 63.9 (C-6), 58.9 (CH_3O). Anal. calcd for $C_{21}H_{28}O_6$: C, 67.02; H, 6.65. Found: C, 66.95; H, 6.82.

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References

1. (a) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780-2781; (b) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930-3932.
2. Suganuma, M.; Fujiki, H.; Furuya-Suguri, H.; Yoshizawa, S.; Yasumoto, S.; Kato, Y.; Fusetani, N.; Sugimura, T. *Cancer Res.* **1990**, *50*, 3521-3525.
3. Matsunaga, S.; Wakimoto, T.; Fusetani, N. *J. Org. Chem.* **1997**, *62*, 2640-2642.
4. Dumdei, E.J.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Org. Chem.* **1997**, *62*, 2636-2639.
5. Hamada, Y.; Tanada, Y.; Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 5983-5986.
6. (a) Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem*. **1996**, *61*, 6139-6152; (b) Ogawa, A. K.; DeMattei, J. A.; Scarlato, G. R.; Tellew, J. E.; Chong, L. S.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6153-6161, and references therein.
7. Veeneman, G. H.; Gomes, L. J. F.; van Boom, J. H. *Tetrahedron* **1989**, *45*, 7433-7448.
8. Di Nardo, C.; Varela, O. *J. Org. Chem.* **1999**, *64*, 6119-6125.
9. Varela, O. *Pure Appl. Chem.* **1997**, *69*, 621-626.
10. (a) Calinaud, P.; Gelas, J. In Hanessian, S. Ed. *Preparative Carbohydrate Chemistry*, Marcel Dekker, New York, 1996, p. 21; (b) Schmidt, O. T. *Methods Carbohydr. Chem.*, **1963**, *2*, 318-325.
11. Cone, C.; Hough, L. *Carbohydr. Res.*, **1965**, *1*, 1-9.
12. Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.*, **1983**, *41*, 27-66.
13. Perlin, A. S. *MTP Int. Rev. Sci., Org. Chem. Ser. 1*, **1976**, *7*, 1-34.
14. Marino, C.; Varela, O.; Lederkremer, R. M. *Carbohydr. Res.*, **1989**, *190*, 65-76.
15. Varela, O.; Marino, C.; Lederkremer, R. M. *Carbohydr. Res.*, **1986**, *155*, 247-251.

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