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# Investigation of Different Synthetic Approaches towards Methyl 2,6-Dideoxy-α-D-*arabino*- and -α-D-*lyxo*-hexopyranosides

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New synthetic routes for making available different methyl 2,6-dideoxyhexopyranosides are reported. Starting with methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-manno- and -α-D-talo-pyranoside the respective methyl 2,6-dideoxy-α-D-*arabino*- and α-D-*lyxo*-hexopyranosides were obtained. The investigation of different synthetic approaches, including the selective monoalkylation of vicinal diols, using tin–ether intermediates, and the radical induced mono-deoxygenation of cyclic thionocarbonates, is described. In the *talo* series an unusual intramolecular acetal migration was observed. The migration product was used in the synthesis of some methyl 2,6-dideoxy-α-D-*lyxo*-hexopyranosides.

Owing to their occurrence in Nature we were interested in the synthesis of methyl 2,6-dideoxyhexopyranosides.[1] They are found as the carbohydrate aglycones in a variety of antibiotic compounds.[2a,b] Many of those antibiotics show antitumor activity and are active against gram positive bacteria but they are also very toxic. Thus their synthesis could provide useful material for further studies of biological and medical interest. Our aim was to develop short synthetic sequences towards the sugar aglycones starting with a common chiral precursor. Under these investigations methyl 6-deoxy-2,3-*O*-isopropylidine-α-D-mannopyranoside **1** has been found to be a useful starting material (Fig. 1). Different synthetic approaches from **1**, yielding the methyl glycosides of five naturally occurring carbohydrate antibiotics, are now described.

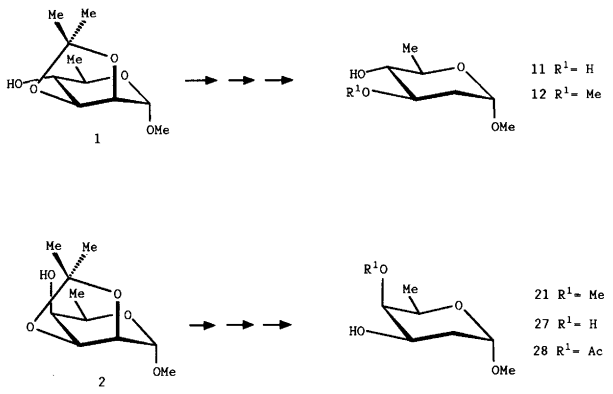


*Fig. 1.*

## Results and discussion

In order to synthesize methyl 2,6-dideoxy-α-D-*arabino*-hexopyranosides, namely the methyl glycosides of D-olivose **11**[3a–c,4a] and D-oleandrose **12**,[4a,b] the benzyl ether **3** was prepared.[5] Using **3**, two different synthetic routes were investigated. The first one made use of the activation of the equatorial OH-3 by the dibutyltin oxide method.[6] After optimization of the reaction conditions the 3-*O*-methyl ether **4** and 3-*O*-benzyl ether **5** were obtained (95% and 86%, respectively) (Fig. 2). Preparation of the intermediate dibutyltin ether in methanol led in all cases to only partial transformation in the following alkylation reaction, but unchanged starting diol could be recovered. The best results were obtained when preparing the tin ether intermediate in toluene with azeotropic removal of water and with activation of the alkylation reaction with tetrabutylammonium iodide.[7] It is interesting to note that no methylation at OH-2 was observed, whereas the 2,4-di-*O*-benzyl ether **6** (10%) was obtained in the benz-

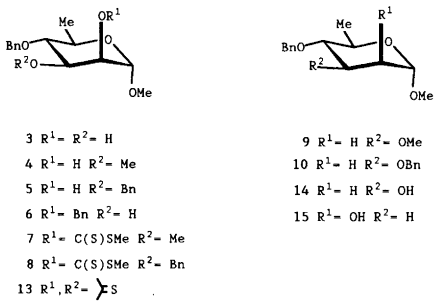


*Fig. 2.*

ylation reaction under similiar conditions. An attempt to use bis(tributyltin) oxide instead of dibutyltin oxide did not improve the regioselectivity of the benzylation. The subsequent deoxygenation at C-2 for **4** and **5** could be achieved via the xanthogenates **7** and **8** (91% and 83%), followed by radical deoxygenation using tributyltin hydride ($Bu_3SnH$) to yield the 2,6-dideoxy-sugars **9** and **10** (71% and 66%). Because of their toxicity, the use of tin compounds in the synthesis of substances with biological and medicinal applications is rather inappropriate. In those cases tris (trimethylsilyl)silane (TTMSS)[8] can be used as a substitute as exemplified by the synthesis of the 2,6-dideoxy-sugar **9** (84%). Finally, methyl α-D-olivoside **11** and methyl α-D-oleandroside **12** were obtained after debenzylation of **9** and **10** under standard hydrogenation conditions (90% yield each).

Another route towards 2,6-dideoxygenated sugars might be via cyclic 2,3-*O*-thionocarbonates by applying radical induced mono-deoxygenation.[9] This was attempted, preparing the 2,3-thionocarbonate **13**[10] (81%) from diol **3**. However, treating **13** with 3 equivalents of $Bu_3SnH$ in refluxing toluene yielded two main products. The regioselectivity of this reaction was low (4 : 3), giving the 2,6-dideoxy sugar **14** (41%) and the 3,6-dideoxygenated isomer **15** (30%). Although **14** could be transformed into the 3-*O*-methyl ether **9** (85%) by methylation with MeI–NaH, this route yields the antibiotic sugar **12** in lower yield than the method described above.

To obtain the D-*lyxo* isomers of methyl 2,6-dideoxy-hexopyranosides, **1** was transformed into its epimer **2** using the oxidation/reduction sequence as described by Eis *et al.*[11] Methylation or benzylation at OH-4 and hydrolysis of the isopropylidene protecting group yielded the diols **16** and **17** (67% and 87%) from the alcohol **2**. Different routes to achieve deoxygenation at C-2 using **16** and **17** were investigated (Fig. 3). Aspinall *et al.*[12] obtained a mixture of isomeric benzyl ethers when treating the benzyl α-L-enantiomer of **17** with

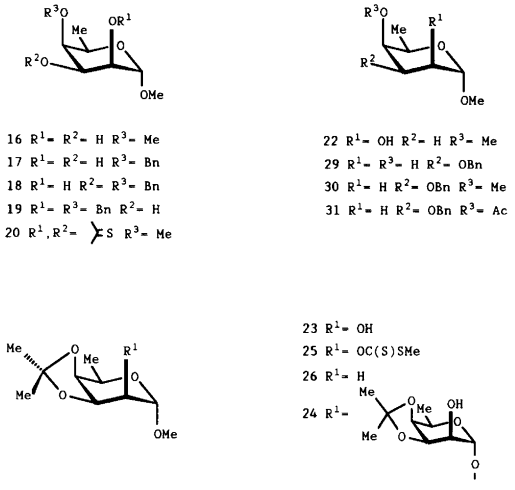


*Fig. 3.*

bis(tributyltin) oxide followed by benzyl bromide. A similiar attempt to activate **17** with dibutyltin oxide resulted in the formation of the 3,4-di-*O*-benzyl ether **18** (55%) and the 2,4-di-*O*-benzyl ether **19** (36%). Even the high total yield did not make this route very attractive, owing to a tedious separation procedure and a moderate yield of the desired 3,4-di-*O*-benzyl ether **18**. It was therefore decided to proceed via the cyclic 2,3-thionocarbonate **20** which could be synthesized by using thiocarbonyldiimidazole (TCDI) in refuxing THF (73%). As in the *manno* series regioselectivity in the reaction of **20** with $Bu_3SnH$ in refluxing toluene was low (3 : 2) but favored the 2,6-dideoxygenated sugar, thus giving methyl α-D-chromoside A **21**[13a–c] through a short synthesis. The yields were, however, only moderate (37% for **21** and 26% for **22**) and therefore a more expedient approach towards 2,6-dideoxy-α-D-*lyxo*-hexopyranosides seemed desirable.

It has been described[14] that direct isopropylidenation of methyl 6-deoxy-α-L-talopyranoside yields the 3,4-*O*-isopropylidene compound as the major product. On isopropylidenation of the α-D-enantiomer two products were obtained. The major product proved to be the 3,4-*O*-isopropylidene compound **23** (60%), while compound **2** was obtained in 21% yield. The formation of **2** prompted us to investigate the possibility of a more direct synthesis of **23** via an acetal migration.[15] Such a migration indeed took place when **2** was treated with concentrated sulfuric acid in acetone under anhydrous conditions. In addition to **23** (74%) small amounts of **2** (8%) and of the disaccharide **24** (6%) were obtained. Thus, an easy access to an OH-2 talopyranoside was established. Deoxygenation of **23** was performed via the xanthogenate **25** (88%) and successive radical deoxygenation with TMSS yielded the 2,6-dideoxy-sugar **26** (79%). The subsequent hydrolysis of the isopropylidene protecting group was performed under mild conditions to avoid the formation of a methyl β-glycoside. The best results were obtained using methanolic HCl which gave methyl α-D-olioside **27**[13,16] in 81% yield. To obtain the methyl α-D-glycosides of chromose A **21** and chromose D **28**,[16,17] the diol **27** was benzylated regioselectively at OH-3 (83%) using activation via an intermediate dibutyltin ether and tetrabutylammonium iodide as a catalyst.[13a] The benzyl ether **29** was then methylated or acylated to yield the fully protected compounds **30** (79%) and **31** (86%) respectively. Both sugars could be debenzylated under standard hydrogenation conditions to yield methyl α-D-chromoside A **21** (88%) and methyl α-D-chromoside D **28** (86%).

The reported investigations show the synthetic potential of a carbohydrate-derived synthon, namely methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside **1**, allowing the preparation of the five target compounds **11**, **12**, **21**, **27** and **28**. In contrast with the rather individual routes reported for the synthesis of these sugar aglycones, broad access to dideoxygenated hexopyranosides was established by using a common chiral precursor.

## Experimental

*General methods.* For experimental details see Ref. 5. All compounds not described in detail show spectroscopic properties in full agreement with the assigned structures. In the *talo* series it is possible to distinguish between OH-2 and OH-3 substitution by comparing the $^{13}C$ NMR data. The compounds having a free OH-2 show typical values around 101.9–103.6 ppm for the anomeric carbon atom, whereas 2-*O*-substitution results in lower resonances (95.8–98.6 ppm) for C-1. The following mixtures (v/v) were used for TLC and flash and column chromatography: A (ethyl acetate–hexane 1 : 1), B (ethyl acetate–hexane 1 : 2), C (ethyl acetate–hexane 1 : 3), D (diethyl ether–hexane (5 : 4), E (dichloromethane–hexane 7 : 3), F (dichloromethane–hexane–diethyl ether 10 : 4 : 1).

*General procedure 1: synthesis of mono-xanthogenates* **7**, **8** *and* **25**. A suspension of NaH (1.5 mmol) in 5 ml THF was cooled to 0°C under nitrogen. A mixture of the alcohol (1.0 mmol) and imidazole (10 mg) in 10 ml THF was then added dropwise. The suspension was allowed to warm to room temperature for 15 min, and then $CS_2$ (3.0 mmol) was added followed, after an additional 15 min, by $CH_3I$ (2.0 mmol). When TLC indicated the complete consumption of the starting alcohol (15–45 min) acetic acid was added to destroy the excess of NaH. The suspension was filtered, the solvent was removed and the residue was extracted with 15 ml ether. The ether was washed with sat. $NaHCO_3$ (5 ml) and water (2 × 10 ml) and dried over $MgSO_4$. After the removal of the solvents the remainder was purified by flash chromatography to yield the xanthogenates. For physical data of the compounds **7**, **8** and **25** see below.

*General procedure 2: deoxygenation of mono-xanthogenates* **7**, **8** *and* **25**. A solution of the xanthogenate (1.0 mmol) in 10 ml of toluene was heated to 80°C under nitrogen. A mixture of TTMSS (1.2 mmol) and azoisobutyronitrile (AIBN) (0.1 mmol) in 5 ml toluene was added dropwise over 20 min. When TLC indicated the reaction to be complete (2–4 h), the mixture was evaporated *in vacuo* and the residue submitted to flash chromatography with an appropriate eluant to yield the deoxy sugars **9**, **10** and **26**. Reductions with tributyltin hydride were performed as described above at 110°C using 3.0 equiv. of $Bu_3SnH$ and 0.1 equiv. AIBN. For physical data of the compounds **9**, **10** and **26** see below.

*Methyl 4-*O*-benzyl-6-deoxy-3-*O*-methyl-α-*D*-mannopyranoside* (**4**). A mixture of **3**[5] (0.80 g) and dibutyltin oxide (0.74 g) in 30 ml of abs. toluene was refluxed with azeotropic removal of water for 16 h. The resulting solution was concentrated to about 15 ml and $CH_3I$ (5 ml) and tetrabutylammonium iodide (1.10 g) were added. The mixture was stirred at 40°C for 18 h after which time TLC showed complete consumption of the starting material. The mixture was evaporated and the residue submitted to flash chromatography on silica gel (eluant A) to yield 0.82 g (95%) of **4** as a syrup ($R_f = 0.38$, A) with $[\alpha]_D + 87.5°$ (*c* 0.55). $^1H$ NMR: δ 1.31 (d, 3 H, *J* 6.2 Hz, $CH_3$), 2.44 (d, 1 H, *J* 2.2 Hz, OH), 3.35 (s, 3 H, $CH_3O$-1), 3.36 (t, 1 H, *J* 9.2 Hz, H-4), 3.49 (s, 3 H, $CH_3O$-3), 3.54 (dd, 1 H, *J* 9.0, 3.4 Hz, H-3), 3.68 (dq, 1 H, *J* 9.6, 6.2 Hz, H-5), 4.04 (ddd, 1 H, *J* 3.4, 2.2, 1.6 Hz, H-2), 4.70 (d, 1 H, *J* 1.6 Hz, H-1), 4.73 (dd, 2 H, $CH_2O$-4), 7.35 (m, 5 H, ArH). $^{13}C$ NMR: δ 17.9 (C-6), 54.7 ($CH_3O$-1), 57.4 ($CH_3O$-3), 67.0, 67.8 (C-2 and C-5), 75.1 ($CH_2O$-4), 79.8, 81.7 (C-3 and C-4), 100.0 (C-1), 127.6–138.5 (Ar).

*Methyl 3,4-di-*O*-benzyl-6-deoxy-α-*D*-mannopyranoside* (**5**) *and methyl 2,4-di-*O*-benzyl-6-deoxy-α-*D*-mannopyranoside* (**6**). A mixture of **3** (536 mg) and dibutyltin oxide (498 mg) in 20 ml abs. toluene was refluxed with azeotropic removal of water for 18 h. The mixture was concentrated to about 10 ml. Thereafter, tetrabutylammonium iodide (738 mg) and benzyl bromide (855 mg) were added and the mixture was heated at 90°C for 1 h. After evaporation under reduced pressure the residue was chromatographed on silica gel (eluant A) to yield the 2,4-di-*O*-benzyl ether **6** (80 mg, 10%, $R_f = 0.78$, A) which was characterized by comparision of its spectra with literature data.[18] Further elution yielded **5** (620 mg, 86%) as a chromatographically homogeneous ($R_f = 0.64$, A) syrup, $[\alpha]_D + 45.8°$ (*c* 1.3). $^1H$ NMR: δ 1.34 (d, 3 H, *J* 6.0 Hz, $CH_3$), 2.44 (br s, 1 H, OH), 3.36 (s, 3 H, $CH_3O$-1), 3.47 (t, 1 H, *J* 9.2 Hz, H-4), 3.84 (dd, 1 H, *J* 8.8, 3.4 Hz, H-3), 4.04 (dd, 1 H, *J* 3.4, 1.6 Hz, H-2), 4.70 (m, 3 H), 4.78 (dd, 2 H, $CH_2O$), 7.34 (m, 10 H, ArH). $^{13}C$ NMR: δ 18.6 (C-6), 54.9 ($CH_3O$-1), 67.2 and 68.6 (C-2 and C-5), 72.0 and 75.3 (2 × $CH_2O$), 79.9 and 80.0 (C-3 and C-4), 99.8 (C-1), 127.1–137.7 (Ar).

*Methyl 4-*O*-benzyl-6-deoxy-3-*O*-methyl-2-*O*-[(methylthio)thiocarbonyl]-α-*D*-mannopyranoside* (**7**). The alcohol **4** (460 mg) was processed according to general procedure 1 and the residue purified by column chromatography on silica gel (eluant E) to yield 552 mg (91%) of **7** as a chromatographically homogeneous syrup ($R_f = 0.52$, E) with $[\alpha]_D + 10.2°$ (*c* 1.8). $^1H$ NMR: δ 1.34 (d, 3 H, *J* 6.2 Hz, $CH_3$), 2.59 (s, 3 H, $SCH_3$), 3.37 (s, 3 H, $CH_3O$-1), 3.42 (t, 1 H, *J* 9.4 Hz, H-4) 3.44 (s, 3 H, $CH_3O$-3), 3.75 (dq, 1 H, *J* 9.2, 6.2 Hz, H-5), 3.76 (dd, 1 H, *J* 9.6, 3.4 Hz, H-3), 4.77 (d, 1 H, *J* 1.6 Hz, H-1), 4.80 (dd, 2 H, $CH_2O$-4), 6.10 (dd, 1 H, *J* 3.4, 1.6 Hz, H-2), 7.35 (m, 5 H, ArH). $^{13}C$ NMR: δ 18.0 (C-6), 19.0 ($SCH_3$), 54.9 ($CH_3O$-1), 57.7 ($CH_3O$-3), 67.4 (C-5), 75.2 ($CH_2O$-4), 76.8 (C-2), 80.0, 80.2 (C-3 and C-4), 97.5 (C-1), 127.0–138.5 (Ar), 215.9 (C=S).

*Methyl 3,4-di-*O*-benzyl-6-deoxy-2-*O*-[(methylthio)thiocarbonyl]-α-*D*-mannopyranoside* (**8**). The alcohol **5** (802 mg) was treated as described in general procedure 1. Flash chromatography (eluant A) yielded **8** (835 mg, 83%) as a syrup, $[\alpha]_D + 4.0°$ (*c* 1.25). $^1H$ NMR: δ 1.35

(d, 3 H, *J* 6.2 Hz, $CH_3$), 2.60 (s, 3 H, $SCH_3$), 3.37 (s, 3 H, $CH_3O$-1), 3.49 (t, 1 H, *J* 9.2 Hz, H-4), 3.78 (dq, 1 H, *J* 9.2, 6.2 Hz, H-5), 4.04 (dd, 1 H, *J* 9.2, 3.4 Hz, H-3), 4.68 and 4.74 (2 × dd, 4 H, $2 \times CH_2O$), 4.78 (br s, 1 H, H-1), 6.15 (dd, 1 H, *J* 3.4, 1.8 Hz, H-2), 7.32 (m, 10 H, ArH). $^{13}C$ NMR: δ 18.4 (C-6), 19.3 ($SCH_3$), 55.0 ($CH_3O$-1), 67.6 (C-5), 71.8 (C-2), 75.3 ($CH_2O$), 77.3 and 78.0 ($CH_2O$ and C-3), 80.1 (C-4), 97.4 (C-1), 127.2–138.0 (Ar), 215.6 (C=S).

*Methyl 4-*O*-benzyl-2,6-dideoxy-3-*O*-methyl-*α*-*D*-arabino-hexopyranoside* (**9**). The xanthogenate **7** (300 mg) was processed according to general procedure 2 and the residue was submitted to column chromatography using a hexane–ether gradient (starting with pure hexane and ending with eluant D) to yield 179 mg (84%) of **9** as a colorless syrup ($R_f = 0.61$, D), $[\alpha]_D + 125°$ (*c* 0.5). $^1H$ NMR: δ 1.29 (d, 3 H, *J* 6.2 Hz, $CH_3$), 1.56 (ddd, 1 H, *J* 13.2, 11.4, 3.8 Hz, H-$2_{ax}$), 2.27 (ddd, 1 H, *J* 13.2, 5.2, 1.4 Hz, H-$2_{eq}$), 3.03 (t, 1 H, *J* 9.2 Hz, H-4), 3.31 (s, 3 H, $CH_3O$-1), 3.44 (s, 3 H, $CH_3O$-3), 3.67 (m, 2 H), 4.75 (dd, 1 H, *J* 3.8, 1.4 Hz, H-1), 4.78 (dd, 2 H, $CH_2O$-4), 7.34 (m, 5 H, ArH). $^{13}C$ NMR: δ 18.1 (C-6), 35.1 (C-2), 54.4 ($CH_3O$-1), 57.1 ($CH_3O$-3), 66.9 (C-5), 74.9 ($CH_2O$-4), 78.9 (C-3), 84.1 (C-4), 98.2 (C-1), 127.5–138.7 (Ar).

**9** was also prepared by methylation of **14** in THF using NaH–MeI (85%). The resulting syrup showed the same physical data as described above.

*Methyl 3,4-di-*O*-benzyl-2,6-dideoxy-*α*-*D*-arabino-hexopyranoside* (**10**). The xanthogenate **8** (770 mg) was treated as described in general procedure 2. After chromatography (solvent D) 385 mg (66%) of **10** was obtained as a chromatographically homogeneous ($R_f = 0.65$, D) syrup with $[\alpha]_D + 82.1°$ (*c* 1.5). $^1H$ NMR: δ 1.32 (d, 3 H, *J* 6.2 Hz, $CH_3$), 1.69 (ddd, 1 H, *J* 13.0, 11.4, 3.7 Hz, H-$2_{ax}$), 2.32 (ddd, 1 H, *J* 13.0, 5.0, 1.3 Hz, H-$2_{eq}$), 3.16 (t, 1 H, *J* 9.6 Hz, H-4), 3.33 (s, 3 H, $CH_3O$-1), 3.72 (dq, 1 H, *J* 9.6, 6.2 Hz, H-5), 3.95 (ddd, 1 H, *J* 11.4, 9.6, 5.0 Hz, H-3), 4.70–4.97 (m, 5 H), 7.34 (m, 10 H, ArH). $^{13}C$ NMR: δ 18.7 (C-6), 36.0 (C-2), 54.5 ($CH_3O$-1), 67.1 (C-5), 71.7 and 75.7 ($2 \times CH_2O$), 77.4 (C-3), 84.2 (C-4), 98.0 (C-1), 127.0–138.1 (Ar).

*Methyl 2,6-dideoxy-*α*-*D*-arabino-hexopyranoside* (**11**). A mixture of **10** (101 mg) and 10% Pd–C (20 mg) in 5 ml of ethyl acetate was stirred under a hydrogen atmosphere for 24 h. Filtration over a short silica gel column (ethyl acetate as the eluant) and evaporation of solvents gave **11** (43 mg, 90%) as a colorless syrup ($R_f = 0.28$, EtOAc), $[\alpha]_D + 131°$ (*c* 0.45) {Lit.[3c] $[\alpha]_D + 120°$ (*c* 2.0, $H_2O$)}. $^1H$ NMR data were in agreement with those given.[3c] $^{13}C$ NMR: δ 18.4 (C-6), 38.2 (C-2), 54.9 ($CH_3O$-1), 67.5 and 69.3 (C-3 and C-5), 78.0 (C-4), 98.2 (C-1).

*Methyl 2,6-dideoxy-3-*O*-methyl-*α*-*D*-arabino-hexopyranoside* (**12**). A mixture of **9** (335 mg) and 10% Pd–C (50 mg) in 10 ml of ethyl acetate was stirred under a hydrogen atmosphere for 36 h. After filtration over a short silica gel column (eluant *D*) the solvents were evaporated off to give 198 mg (90%) of **12** as a chromatographically homogeneous syrup ($R_f = 0.28$, D), $[\alpha]_D + 1.01°$ (*c* 1.6) {Lit.[4a] $[\alpha]_D + 104.2°$ (*c* 0.57)}. Spectroscopic data were in in full agreement with those reported.[4a]

*Methyl 4-*O*-benzyl-2,6-dideoxy-*α*-*D*-arabino-hexopyranoside* (**14**) *and methyl 4-*O*-benzyl-3,6-dideoxy-*α*-*D*-arabino-hexopyranoside* (**15**). A solution of **13**[10] (170 mg) in 10 ml toluene under a nitrogen atmosphere was heated under reflux. A mixture of AIBN (10 mg) and tributyltin hydride (480 mg) in 10 ml of toluene was added over a period of 45 min (the addition was repeated with half the amounts after 2 h). When all the starting material had reacted (TLC), the mixture was evaporated *in vacuo* and the remainder was submitted to flash chromatography (solvent D) to yield 57 mg (41%) of **14** ($R_f = 0.27$, D) and 42 mg (30%) of **15** ($R_f = 0.21$, D). Physical data for compound **14**: $[\alpha]_D + 92.2°$ (*c* 1.0). $^1H$ NMR: δ 1.34 (d, 3 H, *J* 6.4 Hz, $CH_3$), 1.68 (ddd, 1 H, *J* 12.8, 11.4, 1.4 Hz, H-$2_{ax}$), 2.15 (ddd, 1 H, *J* 12.8, 5.2, 1.2 Hz, H-$2_{eq}$), 2.99 (t, 1 H, *J* 9.2 Hz, H-4), 3.30 (s, 3 H, $CH_3O$-1), 3.70 (dq, 1 H, *J* 9.2, 6.4 Hz, H-5), 3.99 (ddd, 1 H, *J* 11.4, 9.2, 5.2 Hz, H-3), 4.74 (br s, 1 H, H-1), 4.75 (dd, 2 H, $CH_2O$-4), 7.34 (m, 5 H, ArH). $^{13}C$ NMR: δ 18.3 (C-6), 37.6 (C-2), 54.6 ($CH_3O$-1), 66.8 and 68.7 (C-3, C-5), 75.0 ($CH_2O$-4), 86.4 (C-4), 98.2 (C-1), 127.6–138.2 (Ar).

*Methyl 6-deoxy-4-*O*-methyl-*α*-*D*-talopyranoside* (**16**). To a mixture of **2** (0.74 g), KOH (0.76 g) and DMSO (15 ml) was added MeI (1.44 g) dropwise with stirring at 10°C. Stirring was continued at room temperature for 1 h, the mixture was diluted with $CH_2Cl_2$ (15 ml) and washed with water (5 × 15 ml). The organic phase was dried with $MgSO_4$, filtered and evaporated under reduced pressure to yield the 4-*O*-methyl ether as a homogeneous syrup ($R_f = 0.55$, D). The crude syrup was dissolved in 50 ml of dry chloroform, and 90% aqueous trifluoroacetic acid (TFA) was added (1 ml). After 1 h the mixture was evaporated *in vacuo* and co-distilled with water and toluene. The residue was submitted to flash chromatography (eluant A) on $SiO_2$ to yield **16** (0.39 g, 67%) as colorless needles (from B), m.p. 76–77°C; $[\alpha]_D + 119.2°$ (*c* 2.8). $^1H$ NMR: δ 1.21 (d, 3 H, *J* 6.6 Hz, $CH_3$), 3.25 (s, 3 H, $CH_3O$-1), 3.33 (br s, 2 H, 2 × OH), 3.51 (s, 3 H, $CH_3O$-4), 3.55 (m, 2 H), 3.68 (t, 1 H, *J* 3.2 Hz, H-3), 3.75 (q, 1 H, *J* 6.6 Hz, H-5), 4.63 (s, 1 H, H-1). $^{13}C$ NMR: δ 16.7 (C-6), 54.9 ($CH_3O$-1), 62.5 ($CH_3O$-4), 65.7, 66.6 and 70.7 (C-2, C-3 and C-5), 83.4 (C-4), 101.9 (C-1).

*Methyl 4-*O*-benzyl-6-deoxy-*α*-*D*-talopyranoside* (**17**). To a mixture of **2** (0.83 g) and KOH (0.85 g) in 20 ml DMSO was added benzyl bromide (1.30 g) dropwise. After 2 h methanol (2 ml) was added to destroy the excess of reagent and after an additional 30 min $CH_2Cl_2$ (60 ml)

and water (20 ml) were added. The organic layer was separated and washed with water (5 × 20 ml). After being dried with $MgSO_4$ the mixture was co-evaporated several times with water and finally toluene. The syrupy residue obtained could be used directly and was treated as described for **16**. The remainder was purified by flash chromatography on silica gel to yield **17** (0.89 g, 87%) as a syrup ($R_f$ = 0.56, A) with $[\alpha]_D$ + 98.8° (*c* 1.8). $^1$H NMR: δ 1.26 (d, 3 H, *J* 6.6 Hz, $CH_3$), 3.01 (d, 1 H, *J* 10.4 Hz, OH), 3.35 (s, 3 H, $CH_3O$-1), 3.43 (d, 1 H, *J* 12.0 Hz, OH), 3.62 (m, 2 H), 3.84 (m, 2 H), 4.73 (dd, 2 H, $CH_2O$-4), 4.74 (s, 1 H, H-1), 7.35 (m. 5 H, ArH).

*Methyl 3,4-di-*O*-benzyl-6-deoxy-*α*-*D*-talopyranoside* (**18**) *and methyl 2,4-di-*O*-benzyl-6-deoxy-*α*-*D*-talopyranoside* (**19**). To a solution of **17** (210 mg) in 10 ml toluene was added bis(tributyltin) oxide (467 mg) and the mixture was refluxed with azeotropic removal of water for 16 h. The solution was concentrated to about 5 ml, benzyl bromide (333 mg) and tetrabutylammonium bromide (288 mg) were added and the mixture was kept at 90°C for 5 h. The solvent was removed and the residue submitted to column chromatography (eluant D) to yield **18** (151 mg, 55%) as a syrup ($R_f$ = 0.46, D), $[\alpha]_D$ + 47.3°(*c* 0.85). $^1$H NMR: δ 1.24 (d, 3 H, *J* 6.6 Hz, $CH_3$), 3.35 (s, 3 H, $CH_3O$-1), 3.68 (br s, 1 H), 3.74 (t, 1 H, *J* 2.8 Hz, H-3), 3.83 (q, 1 H, *J* 6.6 Hz, H-5), 3.98 (br s, 1 H), 4.22 (br s, 1 H), 4.74 and 4.79 (2 × dd, 4 H, 2 × $CH_2O$), 4.80 (br s, 1 H, H-1), 7.35 (m, 10 H, ArH). $^{13}$C NMR: δ 17.4 (C-6), 55.2 ($CH_3O$-1), 66.4 (C-5), 67.9 (C-2), 69.8 ($CH_2O$), 74.4 and 75.5 (C-3 and $CH_2O$), 78.8 (C-4), 102.5 (C-1), 127.0–137.6 (Ar). Further elution gave **19** (98 mg, 36%) as a syrup ($R_f$ = 0.36, D).

*Methyl 6-deoxy-4-*O*-methyl-2,3-*O*-thiocarbonyl-*α*-*D*-talopyranoside* (**20**). A solution of **16** (500 mg) and TCDI (580 mg) in 20 ml of dry THF was refluxed under a nitrogen atmosphere for 2 h. The solvent was removed and the residue purified by flash chromatography on silica gel (eluant A) to yield a syrup ($R_f$ = 0.68, A) which crystallized on treatment with diisopropyl ether to give 444 mg (73%) of **20**, m.p. 138–140°C; $[\alpha]_D$ + 34.7° (*c* 0.5). $^1$H NMR: δ 1.35 (d, 3 H, *J* 6.4 Hz, $CH_3$), 3.35 (dd, 1 H, *J* 5.0, 1.0 Hz, H-4), 3.40 (s, 3 H, $CH_3O$-1), 3.58 (s, 3 H, $CH_3O$-4), 3.84 (dq, 1 H, *J* 6.4, 1.0 Hz, H-5), 4.56 (dd, 1 H, *J* 7.1, 1.0 Hz, H-2), 5.04 (t, 1 H, *J* 7.0 Hz, H-3), 5.05 (br s, 1 H, H-1). $^{13}$C NMR: δ 16.2 (C-6), 55.4 ($CH_3O$-1), 62.4 and 63.4 ($CH_3O$-4 and C-5), 75.1, 77.7 and 78.0 (C-2, C-3 and C-4), 95.7 (C-1), 189.6 (C=S).

*Methyl 2,6-dideoxy-4-*O*-methyl-*α*-*D*-*lyxo*-hexopyranoside* (**21**). A mixture of **30** (120 mg) and 10% Pd-on-charcoal (20 mg) in 5 ml of ethyl acetate was stirred under a hydrogen atmosphere for 24 h. Filtration of the reaction mixture through a short silica gel column and evaporation of the solvent afforded **21** (70 mg, 88%) which crystallized on standing, m.p. 97–98°C; $[\alpha]_D$ + 163° (*c* 1.0) {Lit.[13b] m.p. 95–96°C; $[\alpha]_D$ + 168° (*c* 0.6)}. $^1$H NMR data were in accordance with those given in the literature.[13b] C NMR: δ 17.8 (C-6), 34.4 (C-2), 55.0 ($CH_3O$-1), 62.3 ($CH_3O$-4), 66.1, 66.2 (C-3, C-5), 81.5 (C-4), 98.4 (C-1).

**21** was also prepared (37%) by treating **20** with $Bu_3SnH$ as described for the synthesis of **14**, to give material showing the same physical data as given above.

*Methyl 6-deoxy-3,4-*O*-isopropylidene-*α*-*D*-talopyranoside* (**23**) *and methyl 6-deoxy-2-*O*-(6-deoxy-3,4-*O*-isopropylidene-*α*-*D*-talopyranosyl)-3,4-*O*-isopropylidene-*α*-*D*-talopyranoside* (**24**). To a well-stirred solution of **2** (1.64 g) in 50 ml dry acetone was added dropwise a solution of 0.12 ml sulfuric acid in 2.5 ml acetone. After 1 h dry $Na_2CO_3$ was added, the solution was filtered and evaporated *in vacuo* and the residue was submitted to column chromatography on silica gel (eluant A). Three compounds were isolated: 135 mg (8%) of **2** ($R_f$ = 0.56, A), 1.21 g (74%) of **23** as a chromatographically homogeneous syrup ($R_f$ = 0.32, A), $[\alpha]_D$ + 80.0° (*c* 1.6). $^1$H NMR: δ 1.24 (d, 3 H, *J* 6.6 Hz, $CH_3$), 1.35 and 1.51 [2 s, 6 H, $C(CH_3)_2$], 2.60 (br s, 1 H, OH), 3.42 (s, 3 H, $CH_3O$-1), 3.67 (dd, 1 H, *J* 5.6, 3.4 Hz, H-2), 3.78 (dq, 1 H, *J* 6.6, 1.6 Hz, H-5), 4.09 (dd, 1 H, *J* 7.4, 1.6 Hz, H-4), 4.49 (dd, 1 H, *J* 7.4, 3.4 Hz, H-3), 4.63 (d, 1 H, *J* 5.6 Hz, H-1). $^{13}$C NMR: δ 16.4 (C-6), 25.7 and 26.6 [$C(CH_3)_2$], 55.5 ($CH_3O$-1), 65.2 (C-5), 68.9 (C-2), 73.7 (C-3), 76.3 (C-4), 101.4 (C-1), 109.5 [$C(CH_3)_2$]. Further elution yielded the disaccharide **24** (105 mg, 6%) as a syrup ($R_f$ = 0.10, A). The isopropylidene derivative **23** was also synthesized (60% yield), by treating methyl 6-deoxy-α-D-talopyranoside with 2,2-dimethoxypropane and pyridinium *p*-toluenesulfonate (PPTS) in acetone as the solvent, showing the same physical data as given above. In addition, compound **2** was obtained in a 21% yield.

*Methyl 6-deoxy-3,4-*O*-isopropylidene-2-*O*-[(methylthio)-thiocarbonyl]-*α*-*D*-talopyranoside* (**25**). The alcohol **23** (1.18 g) was treated according to general procedure 1, to yield 1.41 g (88%) of **25** as a syrup ($R_f$ = 0.60, E) after flash chromatography (eluant E), $[\alpha]_D$ + 105.4° (*c* 1.1). $^1$H NMR: δ 1.26 (d, 3 H, *J* 6.6 Hz, $CH_3$), 1.33 and 1.53 [2 s, 6 H, $C(CH_3)_2$], 2.60 (s, 3 H, $SCH_3$), 3.41 (s, 3 H, $CH_3O$-1), 3.89 (dq, 1 H, *J* 6.6, 1.8 Hz, H-5), 4.17 (dd, 1 H, *J* 7.4, 1.8 Hz, H-4), 4.75 (dd, 1 H, *J* 7.4, 3.0 Hz, H-3), 4.92 (d, 1 H, *J* 6.2 Hz, H-1), 5.79 (dd, 1 H, *J* 6.2, 3.0 Hz, H-2). $^{13}$C NMR: δ 16.2 (C-6), 19.9 ($SCH_3$), 25.9 and 26.7 [$C(CH_3)_2$], 55.5 ($CH_3O$-1), 66.1 (C-5), 71.7 (C-2), 76.5 (C-3), 79.0 (C-4), 98.3 (C-1), 110.2 [$C(CH_3)_2$], 215.3 (C=S).

*Methyl 2,6-dideoxy-3,4-*O*-isopropylidene-*α*-*D*-talopyranoside* (**26**). A solution of **25** (1.12 g) in 60 ml toluene was processed according to general procedure 2. After 2 h the mixture was evaporated *in vacuo* and the residue was submitted to column chromatography (eluant F) to give 0.58 g (79%) of **26** as a colorless syrup ($R_f$ = 0.44, F), $[\alpha]_D$ + 61.0° (*c* 1.55) {Lit.[16] $[\alpha]_D$ + 59.2° (*c* 0.9,

$CH_2Cl_2$)}. $^1$H NMR data were in accordance with those given in the literature.[16] $^{13}$C NMR: δ 16.7 (C-6), 25.8 and 27.3 [$C(CH_3)_2$], 30.9 (C-2), 55.0 ($CH_3O$-1), 60.5 (C-5), 70.6 (C-3), 75.6 (C-4), 97.2 (C-1), 108.3 [$C(CH_3)_2$].

*Methyl 2,6-dideoxy-α-*D*-lyxo-hexopyranoside* (**27**). To a solution of **26** (0.54 g) in 50 ml of dry MeOH was added 2 ml methanolic HCl and the solution was left at +4°C for 16 h. The solution was neutralized with ion-exchange resin (Ionenaustauscher III, Merck), filtered and evaporated *in vacuo*, and the residue was purified by flash chromatography on silica gel with ether as the eluant to yield **27** (0.36 g, 81%) as a syrup, $[\alpha]_D$ + 118° (*c* 0.6) {Lit.[16] $[\alpha]_D$ + 125.2° (*c* 0.8, $CH_2Cl_2$)}. $^{13}$C NMR: δ 17.4 (C-6), 33.2 (C-2), 55.1 ($CH_3O$-1), 65.6, 66.0 (C-3, C-5), 71.2 (C-4), 98.4 (C-1). $^1$H NMR data were in accordance with those reported.[16]

*Methyl 4-*O*-acetyl-2,6-dideoxy-α-*D*-lyxo-hexopyranoside* (**28**). A mixture of **31** (205 mg) and 10% Pd-on-charcoal (40 mg) in 10 ml ethyl acetate was stirred under a hydrogen atmosphere for 24 h. The mixture was filtered and purified by chromatography (ethyl acetate as the eluant) to yield 121 mg (86%) of **28** as a colorless syrup ($R_f$ = 0.20, EtOAc) which crystallized on treatment with eluant B, m.p. 87–89°C; $[\alpha]_D$ + 130.1° (*c* 0.85) {Lit.[17a] m.p. 89°C; $[\alpha]_D$ + 129° (*c* 0.5)}. $^{13}$C NMR: δ 17.4 (C-6), 21.5 (OAc), 33.3 (C-2), 55.2 ($CH_3O$-1), 64.6 and 65.0 (C-3, C-5), 73.0 (C-4), 98.5 (C-1), 170.9 (C=O). $^1$H NMR data were in accordance with those reported.[16]

*Methyl 3-*O*-benzyl-2,6-dideoxy-α-*D*-lyxo-hexopyranoside* (**29**). A mixture of **27** (0.48 g) and dibutyltin oxide (0.73 g) in 40 ml of toluene was refluxed with azeotropic removal of water for 16 h. The mixture was cooled and concentrated to about 20 ml. Benzyl bromide (1.26 g) and tetrabutylammonium iodide (1.09 g) were added and the mixture was kept at 90°C for 2 h. The solvent was removed and the residue purified by column chromatography (eluant B) to yield **29** (0.62 g, 83%) as a colorless syrup ($R_f$ = 0.45, B), $[\alpha]_D$ + 115° (*c* 0.72) {Lit.[19] $[\alpha]_D$ + 83° (*c* 2.5)}. $^1$H NMR: δ 1.32 (d, 3 H, *J* 6.6 Hz, $CH_3$), 1.95 (m, 2 H), 2.12 (br s, 1 H, OH), 3.32 (s, 3 H, $CH_3O$-1), 3.84 (m, 3 H), 4.59 (s, 2 H, $CH_2O$-3), 4.82 (d, 1 H, *J* 3.2 Hz, H-1), 7.34 (m, 5 H, ArH). $^{13}$C NMR: δ 17.4 (C-6), 30.4 (C-2), 55.1 ($CH_3O$-1), 65.5 (C-5), 68.8, 70.1 (C-4, $CH_2O$-3), 73.0 (C-3), 98.4 (C-1), 127.0–137.3 (Ar).

*Methyl 3-*O*-benzyl-2,6-dideoxy-4-*O*-methyl-α-*D*-lyxo-hexopyranoside* (**30**). The benzyl ether **29** (218 mg) was methylated with NaH–MeI in THF in the usual manner to yield 183 mg (79%) of **30** as a syrup ($R_f$ = 0.55, C) after chromatography on silica gel (eluant C), $[\alpha]_D$ + 114.6° (*c* 0.5) {Lit.[17a] $[\alpha]_D$ + 108° (*c* 0.58)}. $^1$H NMR: δ 1.27 (d, 3 H, *J* 6.4 Hz, $CH_3$), 1.93 (ddd, 1 H, *J* 12.6, 5.0, 1.2 Hz, H-$2_{eq}$), 2.08 (ddd, 1 H, *J* 12.6, 11.8, 3.6 Hz, H-$2_{ax}$), 3.30 (s, 3 H, $CH_3O$-1), 3.34 (d, 1 H, *J* 2.4 Hz, H-4), 3.63 (s, 3 H, $CH_3O$-4), 3.79 (q, 1 H, *J* 6.4 Hz, H-5), 3.85 (ddd, 1 H, *J* 11.8, 5.0, 2.4 Hz, H-3), 4.61 (s, 2 H, $CH_2O$-3), 4.82 (d, 1 H, *J* 3.6 Hz, H-1), 7.34 (m, 5 H, ArH). $^{13}$C NMR: δ 17.7 (C-6), 31.1 (C-2), 55.0 ($CH_3O$-1), 61.5 ($CH_3O$-4), 66.5 (C-5), 70.4 and 74.9 (C-3 and $CH_2O$-3), 78.7 (C-4), 98.7 (C-1), 126.7–137.9 (Ar).

*Methyl 4-*O*-acetyl-3-*O*-benzyl-2,6-dideoxy-α-*D*-lyxo-hexopyranoside* (**31**). The benzyl ether **29** (160 mg) was acetylated with acetic anhydride–triethylamine–DMAP in $CH_2Cl_2$ to yield 160 mg (86%) of **31**, $[\alpha]_D$ + 160.2° (*c* 0.5) {Lit.[17a] $[\alpha]_D$ + 168° (*c* 0.38)}. $^1$H NMR: δ 1.18 (d, 3 H, *J* 6.6 Hz, $CH_3$), 1.92 (dd, 2 H, *J* 12.5, 5.6 Hz, H-$2_{eq}$), 2.02 (ddd, 1 H, *J* 12.5, 11.6, 3.8 Hz, H-$2_{ax}$), 2.18 (s, 3 H, OAc), 3.33 (s, 3 H, $CH_3O$-1), 3.90 (ddd, 1 H, *J* 11.6, 5.6, 2.6 Hz, H-3), 3.94 (q, 1 H, *J* 6.6 Hz, H-5), 4.55 (dd, 2 H, $CH_2O$-3), 4.85 (d, 1 H, *J* 3.8 Hz, H-1), 5.34 (d, 1 H, *J* 2.6 Hz, H-4), 7.31 (m, 5 H, ArH). $^{13}$C NMR: δ 17.5 (C-1), 21.8 (OAc), 31.8 (C-2), 55.1 ($CH_3O$-1), 64.8 (C-5), 69.1, 70.3 and 71.4 (C-3, C-4 and $CH_2O$-4), 98.6 (C-6), 127.0–137.4 (Ar), 169.8 (C=O).

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