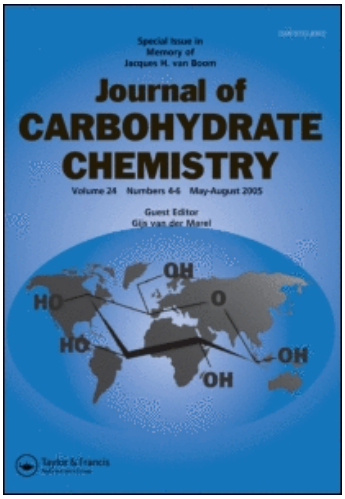


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# Synthesis of Methyl 2,3,6-Trideoxy-4-*C*-(2,5-dimethoxybenzyl)-α-l-*threo*-hex-2-enopyranoside

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# SYNTHESIS OF METHYL 2,3,6-TRIDEOXY-4-*C*-(2,5-DIMETHOXYBENZYL)-α-L-*threo*-HEX-2-ENOPYRANOSIDE

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## ABSTRACT

Methyl 2,3-*O*-protected α-L-lyxopyranosid-4-uloses (**9** and **19**), obtained from L-rhamnose (**8**), react with 2,5-dimethoxybenzyllithium to afford, with high stereoselectivity, compounds **10a** and **20a**, respectively. After protection of the 4-OH group, ethers **10b** and **20b** were transformed *via vic*-diol deoxygenation reactions into the title compound **3** and its 4-*O*-benzyl derivative **17**. The configuration at C-4 in the alcohol **10a** and the acetate of its regioisomer **12b** has been established by single crystal X-ray analysis.

## INTRODUCTION

Anthracycline antibiotics, a significant group of anticancer agents,[1] have long been important targets in synthetic organic chemistry.[2] One of the versatile strategies for the synthesis of the aglycone portion of an antibiotic, *e.g.*, daunomycinone (**1**), involves coupling of the AB and CD fragments to yield in a convergent manner a tetracyclic skeleton.[3] Consequently numerous synthetic methods for the suitably protected AB building block **2** have been developed. Introduction of chirality into the synthetic route has

often relied on enantiopure substrates derived from natural sources. To this end carbohydrates have been used extensively.[4]

In our approach we have focused on the novel sugar synthon, 4-*C*-substituted 2,3-unsaturated pyranoside **3,** which can be regarded as an advanced intermediate, comprising the stereogenic centre at C-4 corresponding to the one at C-9 in the target molecule, for the synthesis of an AB building block **2** of daunomycinone (**1**) (Scheme 1).

Our attempt to obtain compound **3** by addition of 2,5-dimethoxybenzyllithium (**4**) to methyl 2,3,6-trideoxy-α-L-hex-2-enopyranosid-4-ulose (**5**) was frustrated by the unfavourable regioselectivity, which resulted predominantly in the 1,4-adduct **6** instead of the desired 1,2-adduct **7**[5] (Scheme 2). Now we report on a highly stereoselective, efficient synthesis of 2,3-unsaturated pyranoside **3** with a (4*S*) configuration from L-rhamnose (**8**), a readily available sugar.

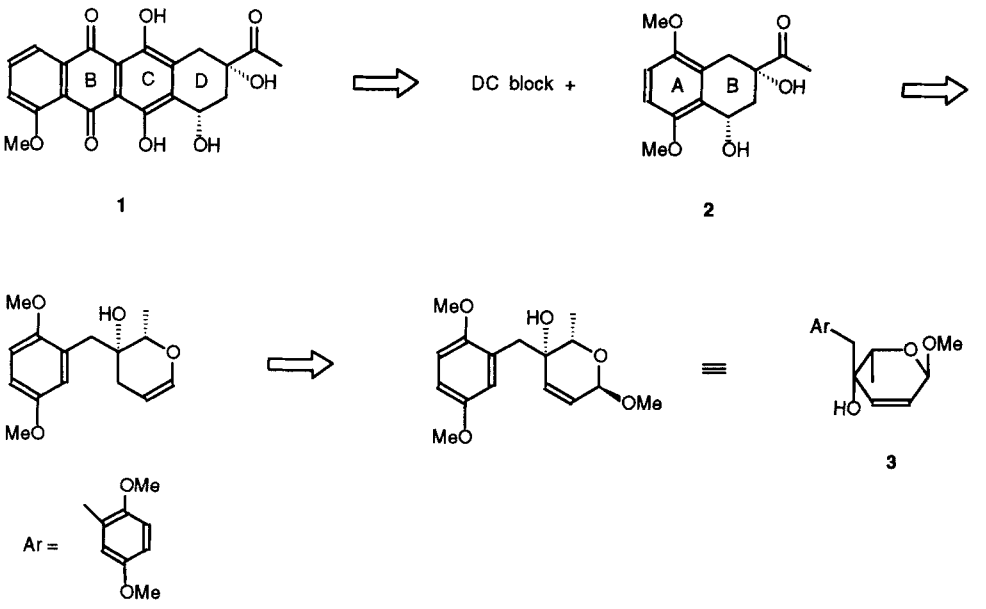


## RESULTS AND DISCUSSION

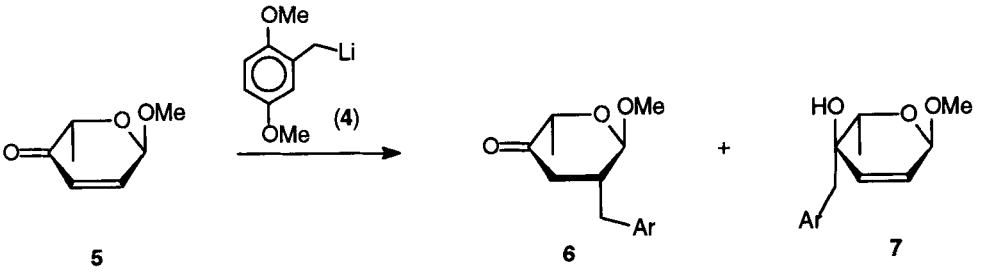
L-Rhamnose (**8**) was transformed, according to literature procedures,[6] into the ketopyranoside **9**. Reaction of ketone **9** with 2,5-dimethoxybenzyllithium (**4**) afforded alcohol **10a** as a single product. Steric hindrance of the 2,3-*O*-isopropylidene moiety prevented the approach of **4** to the carbonyl group from the α-side of the pyranoside ring, hence the α-*talo* configuration was assigned to product **10a**. Nevertheless the structure of alcohol **10a** and acetate **12b** (*vide infra*) were unequivocally confirmed by single crystal X-ray analysis.

Treatment of alcohol **10a** with pyridinium *p*-toluenesulfonate (PPTS) in wet methanol gave products of removal (**11a**) and rearrangement (**12a**) of the isopropylidene group (Scheme 3). Compound **12a** turned out to be stable even under more forcing conditions of hydrolysis. The same rearrangement product has also been obtained, as the acetyl derivative **12b**, by reacting **10a** with acetyl chloride. The ease of the isopropylidene group migration confirmed the all-*cis* configuration of the hydroxyl groups in the pyranoside moiety of **10a**.

To avoid migration of the 2,3-*O*-isopropylidene group to the thermodynamically more stable 3,4-isomer the hydroxyl at C-4 was protected as a benzyl (**10b**) or *p*-



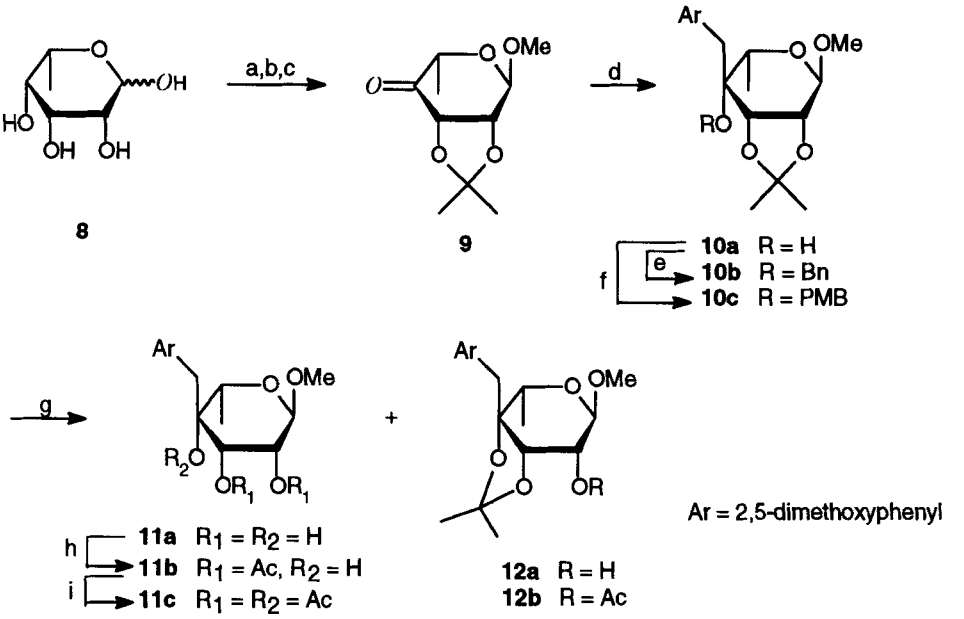

**Scheme 1**




**Scheme 2**

methoxybenzyl (PMB) (**10c**) ether. It is worth mentioning that the reactions of alcohol **10a** with *p*-methoxybenzyl chloride and with benzyl bromide catalyzed with tetrabutylammonium iodide were remarkably slow (reflux, 2.5 h and 22 h, respectively) in comparison with other sterically hindered alcohols.[7]

Surprisingly, the *p*-methoxybenzyl ether **10c** was not stable under PPTS-methanol treatment yielding a mixture of compounds **11a** and **12a**, similar to the mixture obtained




a. MeOH/HCl; b. $(CH_3)_2C(OCH_3)_2$, PPTS; c. $RuO_2$, $NaIO_4$; d. **4**, THF/ether, -70 °C; e. NaH, BnBr, $Bu_4NI$; f. NaH, PMBCl, $Bu_4NI$; g. MeOH, PPTS; h. $Ac_2O$, pyr.; i. AcCl, rt.

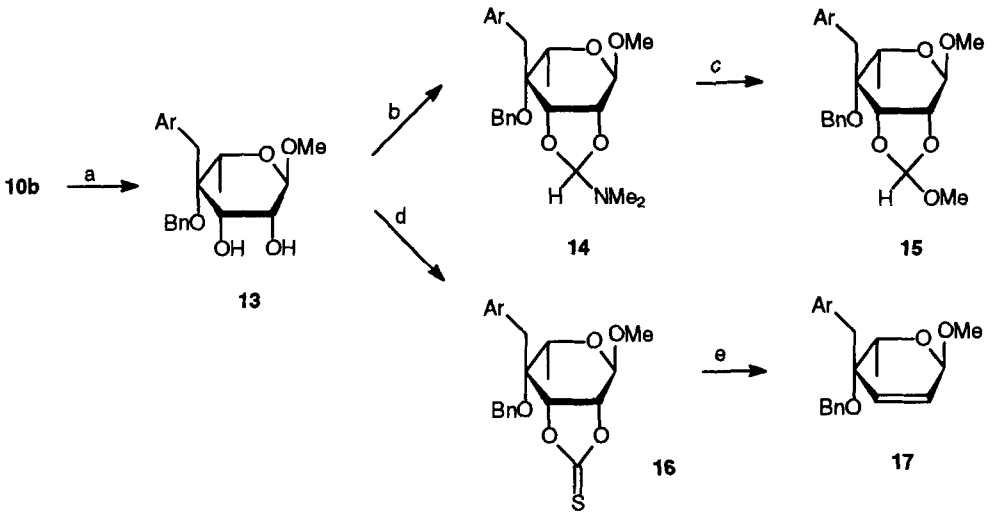
**Scheme 3**



under these conditions directly from the alcohol **10a**. On the other hand the same reagent removed only the isopropylidene group of benzyl ether **10b** yielding diol **13** (Scheme 4).

Two procedures for the deoxygenation of *vic*-diol **13** were examined (Scheme 4). Quaternization of the aminodioxolane **14** with methyl iodide followed by pyrolysis[8] failed, yielding as the main product orthoester **15**. However, the use of the Corey-Winter reaction,[9] *i.e.* cleavage of thiocarbonate **16** by refluxing with triethyl phosphite gave efficiently the desired 2,3-unsaturated pyranoside **17** with a protected 4-OH group.

Since the removal of the benzyl group in **17** proved to be difficult, to obtain the 2,3-unsaturated pyranoside **3** with free 4-OH group we turned to a cyclic orthoester as the 2,3-*O*-protecting group since this is compatible with the required transformations and can eventually be removed with concomitant deoxygenation at C-2 and C-3. Thus, L-rhamnose (**8**) was transformed into the orthoester **18**. Oxidation of the hydroxy group[6b]



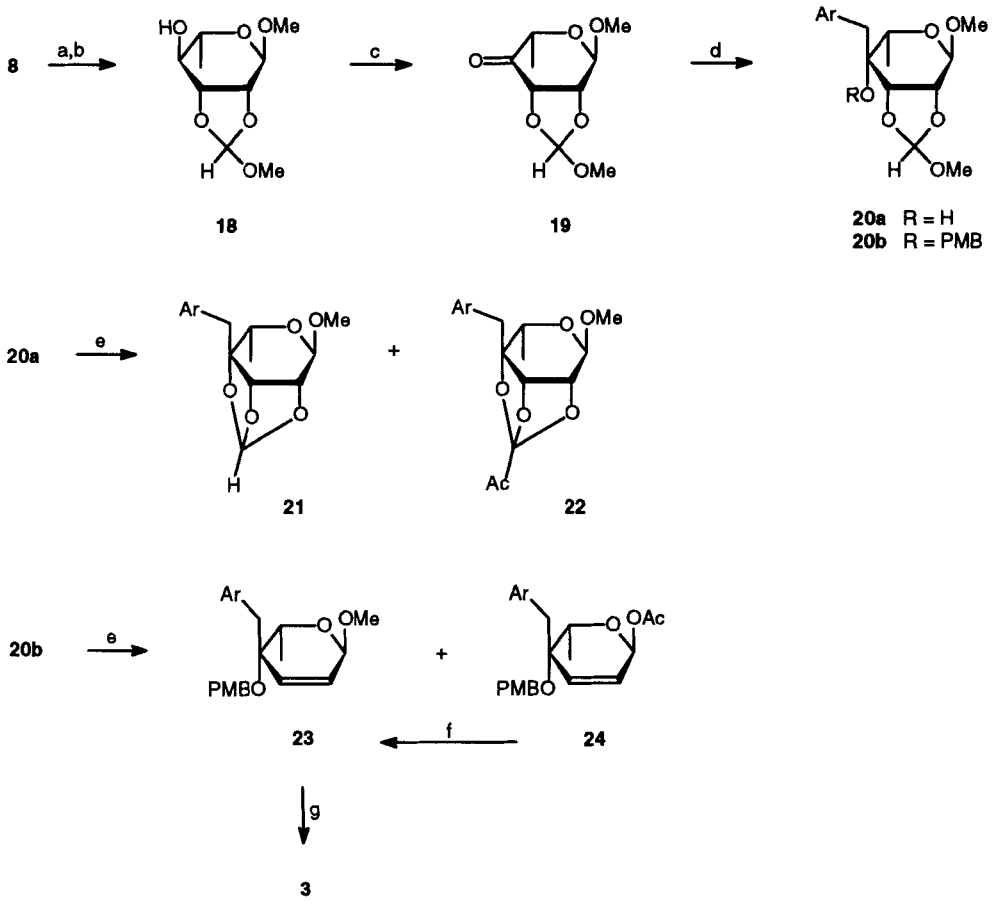

a. PPTS, MeOH; b. $HC(OMe)_2NMe_2$; c. MeI, $PhCH_3$, Δ; d. $Im_2C{=}S$, $PhCH_3$, Δ; e. $HP(OEt)_3$, Δ.

**Scheme 4**



and addition of 2,5-dimethoxybenzyllithium (**4**) to the resulting ketone **19** afforded, with complete stereoselectivity, alcohol **20a**. The assignment of the configuration at C-4 in **20a** is based on stereochemical considerations and analogy to the firmly established course of addition to the carbonyl group in the related ketone **9** (Scheme 5). Refluxing orthoester **20a** in acetic anhydride led to intramolecular cyclization involving the 4-OH group instead of deoxygenation. The structures of the isolated products of this reaction have been deduced from their $^1$H NMR spectra[10] as cyclic orthoesters of formic (**21**) and pyruvic (**22**) acid.

To avoid the undesirable participation of the 4-OH group the latter was protected as the PMB ether **20b**. Refluxing **20b** in acetic anhydride gave deoxygenation product **23** accompanied by **24**, a product of partial acetolysis of the glycosidic OMe group. The latter could be quantitatively converted back into methyl glycoside by treatment with methanolic hydrogen chloride.[11] The PMB protecting group in **23** was conveniently removed by use of 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) in wet dichloromethane[12] affording the title compound **3** in an excellent (over 80%) yield.




a. MeOH, HCl; b. $HC(OMe)_3$; c. $RuO_2$, $NaIO_4$; d. 4, THF/ether, -70 °C;
e. $Ac_2O$, 140 °C; f. HCl/MeOH; g. DDQ, $CH_2Cl_2$.

**Scheme 5**

In conclusion, starting from the readily available monosaccharide (**8**) an efficient, stereoselective route to an advanced intermediate **3** (or **17**) of the AB building block **2** of daunomycinone (**1**) has been developed.

**Crystal Structure of Compounds 10 and 12b**

The crystallographic X-ray analysis of **10a** and **12b** was carried out in order to confirm the proposed configuration at C-4, which could not be deduced from their $^1H$

NMR spectra, and to determine the conformation of the pyranoside and dioxolane moieties.

The ORTEP drawings with atom numbering of **10a** and **12b** are given in Fig. 1 (A and B). Table 1 lists selected torsion angles in **10a** and **12b**. Inspection of drawings A and B in Fig.1 reveals that in both compounds the configuration on C-4 is (*R*), thereby vindicating our assignment based on stereochemical considerations and our conclusion that acetate **12b** arose following migration of the isopropylidene group to the 3,4-position.

Location of the rings junction in **10a** and **12b** at C2 - C3 and C3 - C4, respectively, has little influence on the conformation of the dioxolane ring, but has strongly affected the conformation of the pyranoside moiety. Asymmetry parameters[13] of dioxolane ring in **10a** $\Delta C_2^{2,O3} = 8.04°$, $\Delta C_s^2 = 10.02°$ and **12b**: $\Delta C_2^{3,O4} = 4.11°$, $\Delta C_s^{O4} = 8.12°$, indicate that the five membered rings in both compounds have similar, half-chair conformations with a dominant $C_2$ axis passing through O4 (**10a**) or O5 (**12b**). On the other hand the conformations of the tetrahydropyran rings in **10a** and **12b** differ considerably. According to the asymmetry parameters $\Delta C_s^2 = 5.49°$ and $\Delta C_2^{2,3} = 10.85°$ the pyranoside moiety of **10a** can be described as a distorted chair conformation, flattened at the C-2 and puckered at C-5, whereas the values $\Delta C_2^1 = 14.3°$ and $\Delta C_2^{2,3} = 14.45°$ calculated for **12b** indicate conformation departing from the ideal skew-boat. In the crystal structure of **10a** the C-4 hydroxyl group, which occupies an axial position, forms weak intramolecular hydrogen bonds with O1 and O3 (depicted by the dashed lines in Fig. 1A) as well as intermolecular hydrogen bond with O2 (methoxy group). Their geometries are shown in Table 2.

It should be pointed out that calculated, by the PC MODEL routine,[14] the vicinal coupling constant values $J_{1,2}$ and $J_{2,3}$ for the dihedral angles determined by X-ray analysis are in qualitative agreement with those obtained experimentally. Therefore it can be inferred that in solution compounds **10a** and **12b** occur in the conformations close to those found in the solid state, *i.e.*, chair and skew-boat, respectively.

## EXPERIMENTAL

**General methods**. Melting points were determined on a Büchi 535 apparatus in capillary tubes and are uncorrected. $^1$H NMR spectra were recorded in $CDCl_3$ on a Varian

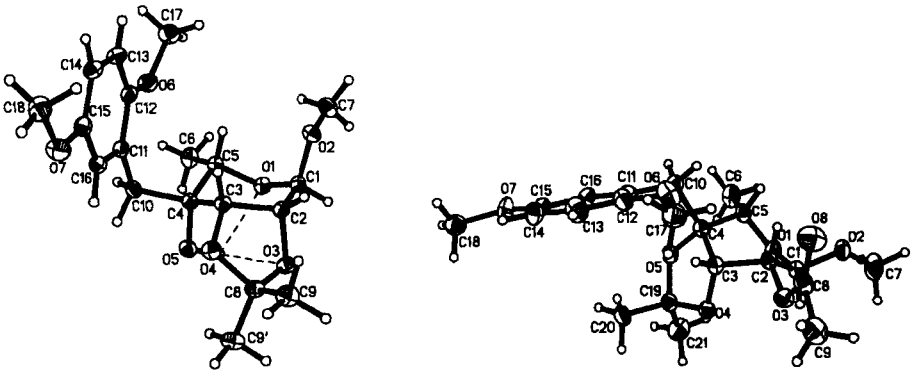



**Figure 1.** ORTEP drawings of **10a** (A) and **12b** (B) showing numbering of atoms

**Table 1.** Selected torsional angles[a] in the solid state structures of **10a** and **12b**.

| | **10a** | **12b** |
|---|---|---|
| O1-C1-C2-C3 | -34.6(3) | 38.3(4) |
| C1-C2-C3-C4 | 32.7(3) | -62.2(4) |
| C2-C3-C4-C5 | -46.8(3) | 22.2(4) |
| C3-C4-C5-O1 | 64.4(2) | 37.4 |
| C4-C5-O1-C1 | -72.0(3) | -65.6(4) |
| C5-O1-C1-C2 | 55.1(3) | 24.9(4) |
| C2-O3-C8-O4 | 30.9(3) | - |
| C3-C8-O4-C3 | -7.0(3) | - |
| C8-O4-C3-C2 | -17.4(2) | - |
| O4-C3-C2-O3 | 35.2(2) | - |
| C3-C2-O3-C8 | -40.6(2) | - |
| C3-O4-C13-O5 | - | 25.7(3) |
| O4-C19-O5-C4 | - | -11.1(3) |
| C19-O5-C4-C3 | - | -6.7(3) |
| O5-C4-C3-O4 | - | 21.9(3) |
| C4-C3-O4-C19 | - | -29.6(3) |

a. Atom numbering as in Fig. 1.

**Table 2.** Hydrogen bonds distances [Å] and angles [°] for **10a**[a]

| | Distance O···O | Distance O-H | Distance H···O | Angle O-H···O |
|---|---|---|---|---|
| O(5)-H(5)···O(1) | 2.721(2) | 0.959(33) | 2.189(31) | 114(3) |
| O(5)-H(5)···O(3) | 3.026(2) | 0.959(33) | 2.590(31) | 108(2) |
| O(5)-H(5)···O(2)[b] | 3.254(2) | 0.959(33) | 2.467(36) | 139(3) |

a. Atom numbering as in Fig. 1A.
b. Symmetry operation used to generate equivalent atom: 0.5+x, 0.5-y, 1.0-z

Gemini 200, Varian Gemini 2000 or Bruker AM 500 spectrometers using TMS as an internal reference. IR spectra were recorded for $CHCl_3$ solutions with Perkin Elmer FT IR, 1725X or Nicolet FT-IR Impact 410 spectrometers. Mass spectra (MS) and high resolution mass spectra (HRMS) were obtained using a Finnigan MAT 8200. Chromatography refers to column chromatography on Merck Kieselgel 60 (230-400 mesh). Analytical thin-layer chromatography was performed using pre-coated aluminum plates (Merck Kieselgel 60 $F_{254}$) and visualized with UV light or acidic molybdate (IV) - cerium sulfate reagent. Solvents and reagents were purified before use according to standard procedures[15].

**X-Ray Structure Determination of 10a and 12b**. Colourless crystals of compounds **10a** (platy with dimensions 0.7 x 0.4 x 0.25 mm) and **12b** (columnar, with dimensions 0.4 x 0.3 x 0.25 mm), obtained from hexane-ethyl acetate solution, were mounted on KUMA KM-4 κ-axis single crystal diffractometer. Graphite monochromatized Cu Kα radiation was used to collect the data. Unit cell parameters were obtained by the least-squares treatment of 25 reflections with $20 \leq 2\theta \leq 25°$. 2391 (**10a**) and 2508 (**12b**) reflections were collected at room temperature up to to $2\theta < 150°$ (**10a**) and $2\theta < 140°$ (**12b**), respectively, including Friedel opposites. 2041 and 1803 of them were classified as observed [$I > 2\sigma(I)$] for **10a** and **12b,** respectively. Data were corrected for Lorenz-polarization factors but not for absorption. Structures were solved using direct methods from SHELXS-86 program.[16] Almost all heavy atoms were found on the E-maps. The rest of them and the remaining hydrogen atoms were located during subsequent Δρ syntheses. Structures were then refined basing on $F^2$ by application of SHELXL-93 program.[17] The

absolute configurations for both structures were verified on the basis of the calculated Flack parameter.[18] In the last cycle of full matrix refinement of **10a** all the non-hydrogen atoms positions were refined together with their anisotropic displacement parameters and the hydrogen atoms positions with their isotropic thermal coefficients.

The $\Delta\rho$ maps obtained after anisotropic refinement of the **12b** model revealed some additional maxima in the vicinity of methyl groups. They were interpreted as a partial disorder of the structure. In the last cycle of full matrix refinement all non-hydrogen atom positions of the ordered part of the molecule were refined together with their anisotropic displacement parameters. The hydrogen atoms were placed in their calculated positions with their isotropic thermal coefficients refined. The disordered methoxy groups carbon atoms were refined together with their isotropic displacement parameters. The common isotropic displacement parameters for hydrogen atoms of each disordered group were varied. The data collection and refinement details are shown in Table 3.



**Methyl 6-Deoxy-4-*C*-(2,5-dimethoxybenzyl)-2,3-*O*-isopropylidene-α-L-talopyranoside (10a).** To a finely cut lithium wire (2.8 g, 0.4 mol) suspended in THF (24 mL) cooled to -15 °C under Ar was added slowly, with stirring, ethyl 2,5-dimethoxybenzyl ether (11.8 g, 60 mmol) in ether (12 mL). After completion of addition, stirring was continued for 1 h at -10 °C and the dark brown solution of 2,5-dimethoxybenzyllithium was transferred *via* syringe to a solution of ketone **9** (7 g, 32 mmol) in ether (100 mL) and hexane (50 mL) cooled to -70 °C. Stirring was continued for 1 h, the reaction mixture warmed to -30 °C and quenched with sat. aq. $NH_4Cl$, washed twice with $NH_4Cl$ solution, water, brine and dried ($MgSO_4$). After evaporation of the solvents unreacted **9** and 2,5-dimethoxytoluene[20] were removed by bulb-to-bulb distillation at 110 °C/0.1 Torr. The oily residue was dissolved in ethyl acetate and triturated with hexane to give crystalline **10a** (4.2 g, 35.6%). Mother liquors were filtered through a silica gel column and concentrated to give a second crop of **10a** (2.1g, 17.8%) , mp 92.5 - 93.5 °C; $^1$H NMR (500 MHz) δ 6.82 (d, J = 2.8 Hz, 1H, aromatic H-6), 6.77 (d, J = 8.8 Hz, 1H, aromatic H-3), 6.74 (dd, 1H, aromatic H-4), 4.88 (d, $J_{1,2}$ = 2.5 Hz, 1H, H-1), 4.16 (d, $J_{2,3}$ = 6.8 Hz, 1H, H-3), 3.98 (dd, 1H, H-2); 3.77, 3.76 and 3.39 (3·s, 3·3H, 3·$OCH_3$), 3.76 (q, $J_{5,6}$ = 6.4 Hz, 1H, H-5), 2.90 and 2.73 (AB, $J_{gem}$ = 13.6 Hz, $CH_2$), 2.87 (d, J = 0.7 Hz, 1H, OH), 1.51 and 1.28 (2·s, 2·3H, $C(CH_3)_2$), 1.55 (d, 3H, $CH_3$). IR 3552, 1504, 1466, 1384, 1089 cm$^{-1}$. MS: *m/z*

**Table 3.** Data Collection and Processing Parameters of Compounds **10a** and **12b**.[19]

| Compound | **10a** | **12b** |
|---|---|---|
| Empirical formula | $C_{19}H_{28}O_7$ | $C_{21}H_{30}O_8$ |
| Formula weight | 368.41 | 410.45 |
| Temperature | 293(2) K | 293(2) K |
| Wavelength | 1.54178Å | 1.54051Å |
| Crystal system | Orthorhombic | Monoclinic |
| Space group | $P2_12_12_1$ | $P\ 2_1$ |
| Unit cell dimensions | a = 9.6353(12) Å<br>b = 11.848(2) Å<br>c = 16.602(2) Å | a = 10.9130(10) Å<br>b = 7.8550(10) Å<br>c = 13.177(2) Å<br>β = 103.230(10)° |
| Volume | 1895.3(4) $Å^3$ | 1099.6(2) $Å^3$ |
| Z | 4 | 2 |
| Density (calculated) | 1.291 $Mg/m^3$ | 1.240 $Mg/m^3$ |
| Absorption coefficient | 0.813 $mm^{-1}$ | 0.789 $mm^{-1}$ |
| F(000) | 792 | 440 |
| Crystal size | 0.7 x 0.4 x 0.25 mm | 0.4 x 0.3 x 0.25 mm |
| Theta range for data collection | 4.58 to 75.14 ° | 3.44 to 70.00° |
| Index ranges | -3≤h≤12, -3≤k≤14, -5≤l≤20 | -13≤h≤11, -8≤k≤9, -15≤l≤16 |
| Reflections collected | 2391 | 2508 |
| Independent reflections | 2225 [$R_{int}$ = 0.0306] | 2358 [$R_{int}$ = 0.0457] |
| Absorption correction | Not applied | Not applied |
| Refinement method | Full-matrix least-squares on $F^2$ | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 2222 / 0 / 348 | 2358 / 3 / 279 |
| Goodness-of-fit on $F^2$ | 1.073 | 1.024 |
| Final R indices [$I>2\sigma(I)$] | R = 0.0288, wR2 = 0.0847 | R = 0.0441, wR2 = 0.1179 |
| R indices (all data) | R = 0.0326, wR2 = 0.0974 | R = 0.0626, wR2 = 0.1291 |
| Weights | $w=1/[\sigma(Fo^2)+(0.0607P)^2+0.0986P]$ where $P=(Fo^2+2Fc^2)/3'$ | $w=1/[\sigma^2(Fo^2)+(0.0793P)^2+0.1024P]$ where $P=(Fo^2+2Fc^2)/3$ |
| Absolute structure parameter | -0.1(2) | 0.0(3) |
| Extinction coefficient | 0.0059(5) | 0.059(4) |
| Largest diff. peak and hole | 0.185 and -0.110 $e.Å^{-3}$ | 0.236 and -0.249 $e.Å^{-3}$ |

151, 152 (100), 185, 217, 368. HRMS Calcd for $C_{19}H_{28}O_7$ ($M^+$): 368.18350. Found: 368.18330.

**Methyl 4-*O*-Benzyl-6-deoxy-4-*C*-(2,5-dimethoxybenzyl)-2,3-*O*-isopropylidene-α-L-talopyranoside (10b)**. Sodium hydride (50% suspension in oil, 300 mg, 6.25 mmol) was added under Ar to a solution of **10a** (1.84 g, 5 mmol) in THF (7.5 mL). After stirring for 10 min, benzyl bromide (1.025 g, 6 mmol) and $Bu_4NI$ (370 mg, 1 mmol) were added. The reaction mixture was refluxed for 22 h, then cooled, poured into water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried ($MgSO_4$). After evaporation of solvents the residue was chromatographed (eluent hexane-ethyl ether 7:3 v/v) through a silica gel column to afford **10b** (2.25 g, 98.1%) as a pale yellow oil. $^1H$ NMR (200 MHz) δ 7.40 - 7.23 (m, 5H, aromatic), 6.93 (m, 1H, aromatic H-6), 6.75 (m, 2H, aromatic H-3, H-4), 4.98 and 4.82 (AB, $J_{gem}$ = 11.25 Hz, O-$CH_2$), 4.89 (d, $J_{1,2}$ = 6.65 Hz, 1H, H-1), 4.42 (bd, $J_{2,3}$ = 6.6 Hz, 1H, H-3); 4.04 (t, 1H, H-2); 3.97 (q, 1H, H-5); 3.68, 3.66 and 3.40 (3·s, 3·3H, 3·$OCH_3$); 3.22 and 3.08 (AB, $J_{gem}$ = 13.8 Hz, $CH_2$), 1.53 and 1.36 (2·s, 2·3H, $C(CH_3)_2$), 1.48 (d, $J_{5,6}$ = 6.7 Hz, 3H, $CH_3$). IR 1604, 1501, 1466, 1097 $cm^{-1}$. MS: *m/z* 242 (29), 185 (29), 151 (100), 121 (15), 91 (82). HRMS Calcd for $C_{26}H_{34}O_7$ ($M^+$): 458.230448. Found: 458.230457.

**Methyl 6-Deoxy-2,3-*O*-isopropylidene-4-*C*-(2,5-dimethoxybenzyl)-4-*O*-(4-methoxybenzyl) -α-L-talopyranoside (10c)**. Sodium hydride (50% suspension in oil, 320 mg, 6.67 mmol) was added under Ar to a solution of **10a** (1.76 g, 4.6 mmol) in THF (10 mL). After stirring for 10 min *p*-methoxybenzyl chloride (900 mg, 5.75 mmol) and $Bu_4NI$ (170 mg, 0.46 mmol) were added. The reaction mixture was refluxed for 2.5 h, then cooled, poured into water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried ($MgSO_4$). After evaporation of solvents the residue was chromatographed (benzene-ethyl acetate 95:5 v/v) through a silica gel column to afford **10c** (2.16 g, 95.6%) as a pale yellow oil. $^1H$ NMR (200 MHz) δ 7.32 - 7,27 (m, 2H, aromatic), 6.94 - 6.75 (m, 5H, aromatic), 4.90 and 4.73 (AB, $J_{gem}$= 10.5 Hz, O-$CH_2$), 4.88 (d, $J_{1,2}$ = 6.4 Hz, 1H, H-1), 4.41 (d, $J_{3,4}$ = 6.6 Hz, 1J, H-3), 4.03 (t, 1H, H-2), 3.95 (q, $J_{5,6}$ = 6.7 Hz, 1H, H-5), 3.80, 3.71, 3.68 and 3.48 (4·s, 4·3H, 4·$OCH_3$), 3.22 and 3.07 (AB, $J_{gem}$ = 13.9 Hz, $CH_2$), 1.54 and 1.36 (2·s, 2·3H, $C(CH_3)_2$), 1.47 (d, 3H, $CH_3$). IR 1614, 1588, 1503, 1097 $cm^{-1}$.

**Methyl 2-*O*-Acetyl-6-deoxy-3,4-*O*-isopropylidene-4-*C*-(2,5-dimethoxybenzyl)-α-L-talopyranoside (12b).** A solution of **10a** (1.79 g, 4.8 mmol) and acetyl chloride (5 mL) was left at rt for 1.5 h. The reaction mixture was diluted with ethyl acetate, washed with sodium bicarbonate, water, brine and dried ($MgSO_4$). Evaporation of solvent and flash chromatography (hexane-ethyl acetate 1:1) of the residue afforded **12b** (1.17 g, 58.7%). Recrystallization from hexane gives **12b** mp 108.5 - 109 °C; $^1$H NMR (200 MHz) δ 6.80 - 6.77 (m, 3H, aromatic), 4.97 (dd, $J_{2,3}$ = 6.3, $J_{1,2}$ = 2.2 Hz, 1H, H-2), 4.70 (d, 1H, H-1), 4.17 (bd, 1H, H-3); 3.80 (q, $J_{5,6}$ = 6.4 Hz, 1H, H-5), 3.77, 3.74 and 3.38 (3·s, 3·3H, 3·$OCH_3$), 3.94 and 2.71 (AB, $J_{gem}$ = 13.9 Hz, -$CH_2$), 2.13 (s, 3H, OAc), 1.48 and 0.97 (2·s, 2·3H, $C(CH_3)_2$), 1.27 (d, 3H, $CH_3$); IR 1743, 1500, 1373, 1244, 1060 cm$^{-1}$; MS: *m/z* 410.0 (64), 260.4 (12), 259.0 (81), 250.0 (17), 200.9 (14), 169.0 (65), 159.2 (21); HRMS Calcd for $C_{21}H_{30}O_8$ ($M^+$): 410.194062. Found: 410.193766.

**Methyl 2,3-Di-*O*-acetyl-6-deoxy-4-*C*-(2,5-dimethoxybenzyl)-α-L-talopyranoside (11b).** A solution of **10a** (1.0 g, 2.7 mmol) and PPTS (200 mg, 0.8 mmol) in MeOH (40 mL) was refluxed for 3 h. The solvent was evaporated and the residue co-evaporated twice with toluene and treated with acetic anhydride (5 mL) and pyridine (5 mL). After the usual work-up the mixture was flash-chromatographed (eluent hexane-ethyl acetate 1:1 v/v) to give **12b** (83 mg, 7.5%) and **11b** (1.02 g, 91.2%). $^1$H NMR (200 MHz) δ 6.82 - 6.67 (m, 3H, aromatic), 5.20 (dd, $J_{2,3}$ = 3.7, $J_{1,2}$ = 1.7 Hz, 1H, H-2), 5.05 (d, 1H, H-3); 4.61 (bd, 1H, H-1), 3.93 (q, $J_{5,6}$ = 6.4 Hz, 1H, H-5), 3.75, 3.73 and 3.34 (3·s, 3·3H, 3·$OCH_3$), 2.87 and 2.78 (AB, $J_{gem}$ = 14.2 Hz, 2H, $CH_2$), 2.12 and 1.81 (2·s, 2·3H, 2·OAc), 1.39 (d, 3H, $CH_3$); IR 3570, 1752, 1500, 1372, 1136, 1078 cm$^{-1}$.

**Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-4-*C*-(2,5-dimethoxybenzyl)-α-L-talopyranoside (11c).** A solution of **11b** (900 mg, 2.2 mmol) and acetyl chloride (10 mL) was left at rt for 3 days, then the reaction mixture was poured onto crushed ice mixed with solid sodium carbonate. The product was extracted with ethyl acetate, the organic layer washed with water, brine and dried ($MgSO_4$). After evaporation of the solvent the residue was crystallized from ether to give **11c** (490 mg, 49.4%): mp 128 - 129 ° C; $^1$H NMR (200 MHz) δ 6.83 - 6.67 (m, 3H, aromatic), 5.71 (d, $J_{2,3}$ = 2.9 Hz, 1H, H-3), 5.00 (dd, $J_{1,2}$ = 6.1 Hz, 1H, H-2); 4.70 (d, 1H, H-1), 4.25 (q, $J_{5,6}$ = 6.4 Hz, 1H, H-5), 3.76, 3.75 and 3.40 (3·s,

3·3H, 3·$OCH_3$), 3.52 and 3.41 (AB, $J_{gem}$ = 14.4 Hz, 2H, $CH_2$), 2.08, 2.05 and 2.04 (3·s, 3·3H, 3·OAc), 1.11 (d, 3H, $CH_3$); IR 1751, 1503, 1371, 1257, 1055 $cm^{-1}$. MS *m/z*: 454 (35), 394 (40), 260 (100), 231 915), 151 (60), 121 (23), 43 (52). HRMS Calcd for $C_{22}H_{30}O_{10}$ ($M^+$): 454.183898. Found: 454.184937.

**Methyl 4-*O*-Benzyl-6-deoxy-4-*C*-(2,5-dimethoxybenzyl)-α-L-talopyrano-side (13)**. A solution of **10b** (2.0 g, 4.4 mmol) and PPTS (332 mg, 1.3 mmol) in methanol (70 mL) was refluxed for 3.5 h. The reaction mixture was concentrated to dryness, dissolved in dichloromethane and washed with sodium bicarbonate, water, brine and dried ($MgSO_4$). Evaporation of the solvent left **13** (1.83 g, 100%) as a yellow oil, homogenous by TLC, which was used in the next step without purification.

**Methyl 4-*O*-Benzyl-6-deoxy-4-*C*-(2,5-dimethoxybenzyl)-2,3-*O*-thiocarbo-nyl-α-L-talopyranoside (16)**. A solution of diol **13** (1.1 g, 2.6 mmol) and thiocarbonyldiimidazole (1 g, 7.3 mmol) in toluene (30 mL) was refluxed for 3.5 h. The reaction mixture was cooled, diluted with ethyl acetate (50 mL), washed thoroughly with water, brine, dried and concentrated. Upon trituration of the residue with ether, thiocarbonate **16** (1.06 g, 87.6%) solidified as a grayish powder. $^1H$ NMR (200 MHz) δ 7.46 - 7.29 (m, 5H, aromatic), 6.81 - 6.77 (m, 3H, aromatic), 5.06 (d, $J_{1,2}$ = 3.3 Hz, 1H, H-1), 5.01 (d, $J_{2,3}$ = 8.1 Hz, 1H, H-3), 5.00 and 4.86 (AB, $J_{gem}$ = 11.2 Hz, 2H, $OCH_2$), 4.54 (dd, 1H, H-2); 3.81, 3.75 and 3.34 (3·s, 3·3H, 3·$OCH_3$), 3.80 (q, 1H, H-5); 3.42 and 3.03 (AB, $J_{gem}$ = 13.3 Hz, 2H, $CH_2$), 1.50 (d, $J_{5,6}$ = 6.4 Hz, 3H, $CH_3$); IR 1503, 1456, 1317, 1279, 756 $cm^{-1}$; MS: *m/z* 460.1 (10); 242.2 (11); 216.5 (10), 151.3 (100); 121.2 (20); 91.4 (94). HRMS Calcd for $C_{24}H_{28}O_7S$ ($M^+$): 460.155569. Found: 460.156357.

**Methyl 4-*O*-Benzyl-6-deoxy-4-*C*-(2,5-dimethoxybenzyl)-α-L-*threo*-hex-2-eno-pyranoside (17)**. A solution of thiocarbonate **16** (775 mg, 1.68 mmol) in triethyl phosphite (5 mL) was refluxed for 4.5 h, then concentrated. The residue was chromatographed using ether-hexane (1:1 v/v) solution through a short silica gel column to give, on solvent evaporation, **17** (556 mg, 85.8%) as a pale yellow oil. $^1H$ NMR (200 MHz) δ 7.30 - 7.22 (m, 5H, aromatic), 6.91 - 6.85 (m, 1H, aromatic), 6.80 - 6.70 (m, 2H, aromatic), 6.02 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 3.1 Hz, 1H, H-2), 5.72 (dd, $J_{1,3}$ = 0.9 Hz, 1H, H-3), 4.89 (bd, 1H, H-1); 4.67 and 4.41 (AB, $J_{gem}$ = 12.0 Hz, 2H, $OCH_2$), 4.13 (q, $J_{5,6}$ = 6.6 Hz,

1H, H-5), 3.73, 3.64 and 3.42 (3·s, 3·3H, 3·$OCH_3$), 2.92 and 2.80 (AB, $J_{gem}$ = 13.5 Hz, 2H, $CH_2$), 1.40 (d, 3H, $CH_3$); IR 1603, 1502, 1465, 1116, 1037, 964 $cm^{-1}$; MS: *m/z* 151.3 (55), 121.2 (19), 111.3 (40); 91.1 (100). HRMS Calcd for $C_{23}H_{28}O_5$ ($M^+$): 384.19377. Found: 384.193769.

**Methyl 4-*C*-(2,5-Dimethoxybenzyl)-6-deoxy-2,3-*O*-methoxymethylidene-α-L-talopyranoside (20a)**. A solution of 2,5-dimethoxybenzyllithium (**4**) prepared as described above from 12 g (61 mmol) of ethyl 2,5-dimethoxybenzyl ether was slowly added to a cooled to -70 ° C solution of **19** (7.8 g, 35.7 mmol) in THF-ether (1:1, 100 mL). Stirring was continued for 1.5 h and the reaction mixture quenched with saturated aqueous $NH_4Cl$, washed 3 times with $NH_4Cl$ solution, then with water, brine and dried ($MgSO_4$). After evaporation of solvents the residue was chromatographed through a silica gel (300 g) column (eluent hexane - diethyl ether 8:2) to give unreacted **19** (1.72 g, 22%) and **20a** (5.9 g, 56.1%, conversion 82%) as a mixture of epimers, from which the major isomer crystallized out, mp 79 - 80 °C. $^1H$ NMR (200 MHz) δ 6.83 - 6.70 (m, 3H, aromatic); 5.86 (s, 1H, $HCO_3$); 4.01 (bs, 1H, H-1); 4.33 (d, $J_{2,3}$ = 5.9 Hz, 1H, H-30; 4.01 (dd, $J_{1,2}$ = 0.9 Hz, 1H, H-2); 3.80, 3.77, 3.37 and 3.28 (4·s, 4·3H, 4·$OCH_3$); 3.73 (q, 1H, H-5); 2.99 (bs, 1H, OH); 2.87 and 2.76 (AB, $J_{gem}$ = 13.6 Hz, $CH_2$); 1.37 (d, $J_{5,6}$ = 6.4 Hz, 3H, $CH_3$). IR 3556, 1502, 1232, 1062, 995 $cm^{-1}$. MS: *m/z* 370.3 (44), 186.9 (100), 152.5 (71), 151.3 (66), 137.2 (18), 127.1 (12), 121.3 (28), 117.3 (15), 99.2 (28), 87.1 (38). HRMS Calcd for $C_{18}H_{26}O_8$ ($M^+$) 370.16276. Found: 370.16205.

Minor epimer: $^1H$ NMR (200 MHz) δ 5.57 (s, 1H, HC ); 4.98 (d, $J_{1,2}$ = 2,2 Hz, 1H, H-1); 4.66 (d, $J_{2,3}$ = 6.8 Hz, 1H, H-3); 4.14 (dd, 1H, H-2); 3.79, 3.78, 3.40 and 3.29 (4·s, 4·3H, 4·$OCH_3$); 2.99 (bs, 2H, $CH_2$); 1.45 (d, $J_{5,6}$ = 6.4 Hz, 3H, $CH_3$).

**Methyl 6-Deoxy-4-*O*-(4-methoxybenzyl)-4-*C*-(2,5-dimethoxybenzyl)-2,3-*O*-methoxymethylidene-α-L-talopyranoside (20b)**. Sodium hydride (50% suspension in oil, 500 mg, 10.4 mmol) was added under Ar to a solution of **20a** (3.44 g, 9.2 mmol) in THF (20 mL). After stirring for 10 min, 4-methoxybenzyl chloride (1.63g, 10.4 mmol) and $Bu_4NI$ (340 mg, 0.92 mmol) were added. The reaction mixture was refluxed for 2.5 h, then cooled, poured into water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried ($MgSO_4$). After evaporation of solvents the residue was chromatographed (eluent hexane - ethyl acetate 7:3 v/v) through silica gel column to

afford **20b** (4.52 g, 99.2%) as a solid mass consisting of two epimers (TLC). The latter was dissolved in ether and triturated with hexane to give the major epimer as colourless crystals, mp 69.5 - 70.5 °C. $^1$H NMR (200 MHz) δ 7.36 - 7.28 (m, 2H, aromatic); 6.91 - 6.72 (m, 5H, aromatic); 5.88 (s, 1H, $HCO_3$); 4.91 (d, $J_{1,2}$ = 2.8 Hz, 1H, H-1); 4.86 (bs, 2H, $OCH_2$); 4.52 (d, $J_{2,3}$ = 6.8 Hz, 1H, H-3); 4.09 (dd, 1H, H-2); 3.81 (q, 1H, H-5); 3.81, 3.76, 3.71, 3.38 and 3.32 (5·s, 5·3H, 5·$OCH_3$); 3.25 and 3.04 (AB, $J_{gem}$ = 15.5 Hz, 2H, $CH_2$); 1.45 (d, $J_{5,6}$ = 6.4 Hz, 3H, $CH_3$). IR 1502, 1242, 1065 cm$^{-1}$. MS: *m/z* 272.3 (22), 151.1 (17), 121.5 (100). HRMS Calcd for $C_{26}H_{34}O_9$ ($M^+$): 490.220276. Found: 490.219665.

Minor epimer: $^1$H NMR (200 MHz) δ 5.74 (s, 1H, $HCO_3$); 5.00 (d, $J_{1,2}$ = 6.6 Hz, 1H, H-1); 4.83 and 4.64 (AB, $J_{gem}$ = 10.4 Hz, 2H, $CH_2$); 4.38 (d, $J_{2,3}$ = 5.9 Hz, 1H, H-3); 4.06 (dd, 1H, H-2); 3.79, 3.71, 3.63, 3.52 and 3.44 (5·s, 5·3H, 5·$OCH_3$); 3.27 and 3.00 (AB, $J_{gem}$ = 14.0 Hz, 2H, $CH_2$); 1.54 (d, $J_{5,6}$ = 6.4 Hz, 3H, $CH_3$).

**Methyl 6-Deoxy 4-*C*-(2,5-dimethoxybenzyl)-4-*O*-(4-methoxybenzyl)-α-L-*threo*-hex-2--enopyranoside (23)**. A solution of **20b** (a mixture of epimers, 4.0 g, 8.1 mmol) in acetic anhydride (20 mL) was refluxed under Ar for 3 h. After concentration to dryness the residue was dissolved in methanolic hydrogen chloride (2% v/v, 10 mL) and left for 1 h. The mixture was then neutralized with triethylamine, concentrated and the residue flash-chromatographed (eluent hexane-ethyl acetate 8:2 v/v) to give **23** (2.13 g, 63%). $^1$H NMR (200 MHz) δ 7.22 - 7.12 (m, 2H, aromatic); 6.90 - 6.71 (m, 5H, aromatic); 5.99 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 3.1 Hz, 1H, H-2); 5.71 (dd, $J_{1,3}$ = 1.1 Hz, 1H, H-3); 4.88 (dd, 1H, H-1); 4.60 and 4.31 (AB, $J_{gem}$ = 11.2 Hz, 2H, $OCH_2$); 4.12 (q, $J_{5,6}$ = 6.5 Hz, 1H, H-5); 3.78, 3.72, 3.64 and 3.42 (4·s, 4·3H, 4·$OCH_3$); 2.91 and 2.77 (AB, $J_{gem}$ = 13.5 Hz, 2H, $CH_2$); 1.39 (d, 3H, $CH_3$). IR 1506, 1244, 1111, 962 cm$^{-1}$. MS *m/z*: 272 (20), 151 (15), 121 (100). HRMS Calcd for $C_{24}H_{30}O_6$ ($M^+$): 414.20423. Found: 414.203829.

In a separate experiment **20a** was refluxed with acetic anhydride under Ar, concentrated to dryness and the residue flash-chromatographed (eluent hexane - ethyl acetate 8:2 v/v) to yield **23** (30%) and 1-*O*-acetyl-6-deoxy-4-*C*-(2,5-dimethoxybenzyl)-4-*O*-(4-methoxybenzyl)-α-L-*threo*-hex-2-enopyranose (**24**) (47%). $^1$H NMR (200 MHz) δ 7.23 - 7.10 (m, 2H, aromatic); 6.89 - 6.70 (m, 5H, aromatic); 6.29 (bd, 1H, H-1); 6.03 (dd, $J_{2,3}$ = 10.1, $J_{1,2}$ = 3.2 Hz, 1H, H-2); 5.87 (bd, 1H, H-3); 4.58 and 4.31 (AB, $J_{gem}$ =

11.2 Hz, 2H, $OCH_2$); 4.14 (q, $J_{5,6}$ = 6.4 Hz, 1H, H-5); 3.78, 3.75 and 3.66 (3·s, 3·3H, 3·$OCH_3$); 2.95 and 2.80 (AB, $J_{gem}$ = 13.5 Hz, 2H, $CH_2$); 1.40 (d, 3H, $CH_3$). IR 1732, 1612, 1502, 1246, 1036 $cm^{-1}$.

**Methyl 6-Deoxy-4-*C*-(2,5-dimethoxybenzyl)-α-L-*threo*-hex-2-enopyrano-side (3).** 2,3-Dichloro-5,6-dicyano-1,4-quinone (DDQ) (1.18 g, 5.2 mmol) was added at rt to a stirred solution of **23** (1.96 g, 4.73 mmol) in $CH_2Cl_2$ (22.5 mL) and water (1.1 mL). After 1 h the reaction mixture was filtered through Celite, evaporated and flash-chromatographed (eluent hexane - ethyl acetate 7:3 v/v) affording **3** (1.15 g, 82.7%). $^1H$ NMR (200 MHz) δ 6.90 - 6.66 (m, 3H, aromatic); 5.87 (bd, $J_{2,3}$ = 10.6 Hz, 1H, H-3); 5.73 (dd, $J_{1,2}$ = 2.9 Hz, 1H, H-2); 4.90 (bd, 1H, H-1); 4.05 (q, $J_{5,6}$ = 6.4 Hz, 1H, H-5); 3.78, 3.76 and 3.42 (3·s, 3·3H, 3·$OCH_3$); 2.94 and 2.65 (AB, $J_{gem}$ = 13.7 Hz, 2H, $CH_2$); 1.33 (d, 3H, $CH_3$). IR 3498, 1502, 1047, 964 $cm^{-1}$. MS *m/z*: 152 (100), 151 (30), 137 (25), 121 (15). HRMS Calcd for $C_{16}H_{22}O_5$ ($M^+$): 294.146724. Found: 294.146645.



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10. $^1$H NMR (200 MHz): **21**: δ 6.83 - 6.70 (m, 3H, aromatic), 6.14 (bs, 1H, $HCO_3$), 4.94 - 4.88 (m, 2H, H-1, H-3), 3.86 (q, $J_{5,6}$ = 6.4 Hz, 1H, H-5), 3.80, 3.76 and 3.36 (3·s, 3·3H, 3·$OCH_3$), 3.77 (dd, $J_{2,3}$ = 6.4, $J_{1,2}$ = 2.0 Hz, 1H, H-2), 2.90 and 3.81 (AB, $J_{gem}$ = 14.0 Hz, 2H, $CH_2$), 1.45 (d, 3H, $CH_3$). **22**: δ 6.80 - 6.68 (m, 3H, aromatic), 5.44 (bd, $J_{2,3}$ = 5.3 Hz, 1H, H-3), 4.94 (bd, 1H, H-2), 4.70 (bs, 1H, H-1), 4.24 (q, $J_{5,6}$ = 6.8 Hz, 1H, H-5), 3.76, 3.75 and 3.43 (3·s, 3·3H, 3·$OCH_3$), 3.43 and 3.30 (AB, $J_{gem}$ = 15.9 Hz, 2H, $CH_2$), 2.08 (s, 3H, $COCH_3$), 1.36 (d, 3H, $CH_3$)

11. A small amount of β-anomer was isolated from the reaction mixture, $^1$H NMR (200 MHz) δ 7.23 – 7.10 (m, 2H, aromatic), 6.90 - 6.70 (m, 5H, aromatic), 5.95 (dd, $J_{2,3}$=10.3 Hz, $J_{1,2}$=0.9 Hz, 1H, H-2), 5.75 (dd, $J_{1,3}$=1.5 Hz, 1H, H-3), 4.42 (m, 1H, H-1), 4.72 and 4.49 (AB, $J_{gem}$=11.5 Hz, 2H, $OCH_2$), 3.76 (q, 1H, H-5), 3.79, 3.75, 3.68 and 3.49 (4xs, 4x3H, 4x$OCH_3$), 2.29 and 2.75 (AB, $J_{gem}$=13.5 Hz), 1.38 (d, $J_{5,6}$=6.4 Hz, 3H, $CH_3$).

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19. The atomic coordinates have been deposited with the Cambridge X-ray Data Centre and may be obtained, on request, from the Director, Cambridge X-ray Data Centre, University Chemical Lab, Lensfield Road, Cambridge, CB2 1EW, UK.

20. During the preparation of 2,5-dimethoxybenzyllithium side products were formed : 2,5-dimethoxytoluene, 1,2-bis-(2,5-dimethoxyphenyl)ethane and 2,5-dimethoxybenzyl alcohol were isolated and identified by their IR and $^1$H NMR spectra.