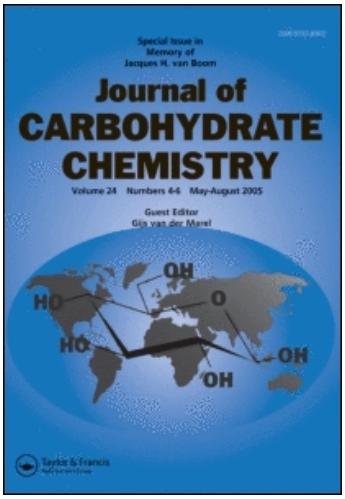

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THE FIRST SYNTHESIS OF A *RIBO*-HEXOS-5-ULOSE: THE L-ENANTIOMER[1]

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ABSTRACT

The title compound, previously unreported in either enantioform, and its 2,6-di-*O*-benzyl derivative have been synthesized through a stereocontrolled epimerization at C-2 of 6-*O*-protected methyl 3,4-*O*-isopropylidene-5-*C*-methoxy-β-D-galactopyranosides. The epimerization, performed through a high yielding sequence of oxidation-reduction owing to the cooperative role of the equatorial C-1 aglycon and the steric hindrance of the isopropylidene group, turned out to be completely diastereoselective. Whereas the unprotected L-*ribo*-hexos-5-ulose exists, as proved by NMR in D_2O, in five main tautomeric forms in a ratio of about 4:2:2:1:1, only two anomeric 1,4-furanosic forms are present at equilibrium in its 2,6-di-*O*-benzyl derivative, in ratios ranging from 10:1 to 7:3, depending on the prevalence of D_2O or CD_3CN in the solvent mixture.

INTRODUCTION

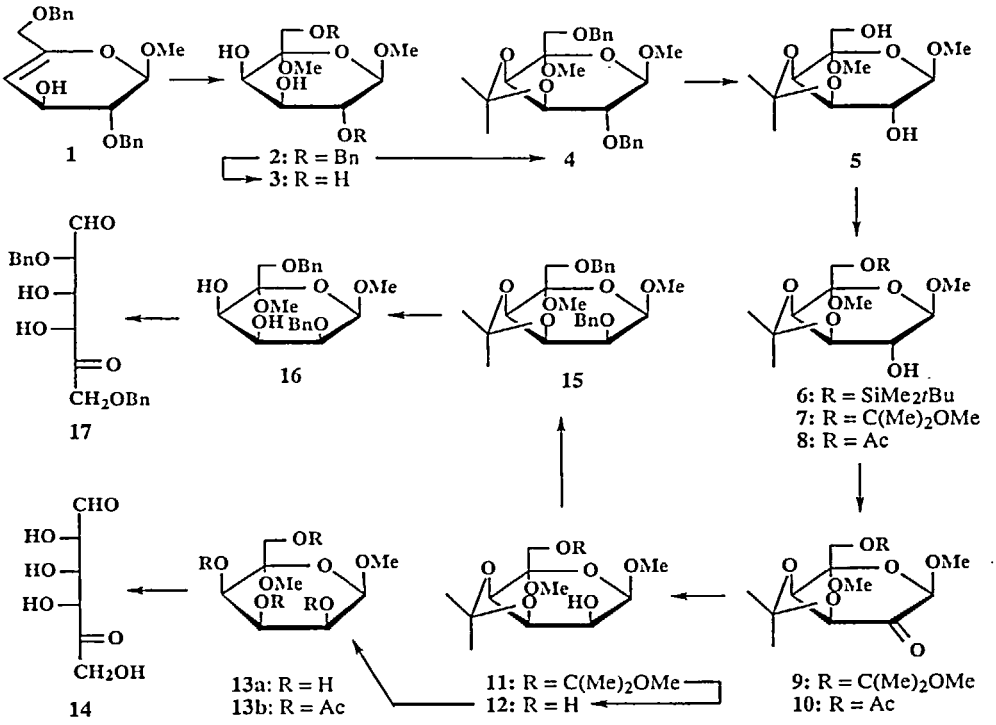
Little was known before the start of the present decade about the chemistry of hexos-5-uloses (5-ketoaldoses). At the end of the eighties only the D-*xylo* form had been prepared in its free form[2] and used in an interesting biomimetic synthesis of the biologically relevant *myo*-inositol. During the present decade interest has been rising in

these polyfunctional versatile synthons and the complexity of their tautomeric equilibria.[3] Of the eight possible stereoisomeric forms four have so far been synthesized, the D-*xylo*,[2,4b] the L-*arabino*,[4a] the D-*lyxo*,[5a,3b] and the L-*lyxo*[4c] ones, and selectively used as starting materials for stereoselective approaches to 1-deoxy-azapyranoses[5] (nojirimycin analogues) and protected polyhydroxycyclopentanes.[6] Only for the *ribo* series was neither of its enantiomers known. In a general project aimed at making available all possible stereoisomers of hexos-5-ulose we are now describing a synthesis of its L-*ribo* form.

The synthetic approach we used (Scheme) was based on the stereoselective epimerization at C-2 of suitably protected derivatives of methyl 5-*C*-methoxy-β-D-galactopyranoside (**3**),[7] the 1β,5α-bis-methyl pyranoside anomer of L-*arabino*-hexos-5-ulose hemihydrate, diastereoselectively obtained in good yield through epoxidation-methanolysis followed by debenzylation[4a] of the glycal **1**, in turn easily prepared from methyl β-D-galactopyranoside.[8]

RESULTS AND DISCUSSION

The 3,4,6-tri-*O*-protected derivative **7** was an ideal precursor for the planned synthesis, since its 5-demethoxy analogue had been obtained in high yield directly from methyl β-D-galactopyranoside through an acid catalyzed reaction with 2,2-dimethoxypropane under equilibrating conditions.[9] However, later work[10] showed that the same reaction, when applied to **3**, gave disappointingly low yields. This difficulty was circumvented by a three-step sequence starting from methyl 2,6-di-*O*-benzyl-5-*C*-methoxy-β-D-galactopyranoside (**2**), the product directly obtained in the epoxidation-methanolysis of **1**.[4a] The bis-glycoside **2** was acetonated with 2,2-dimethoxypropane and TsOH to give the acetonide **4** (88%), that was debenzylated through catalytic hydrogenation with $Pd(OH)_2$ on charcoal in ethyl acetate (quant yield) to the diol **5**. The methoxyisopropylation of **5** with 2-methoxypropene (1.1 eq) and pyridinium tosylate/4 Å molecular sieves in CH_2Cl_2 led to **7** with almost complete regioselectivity (83%, isolated yield), the sole other isolated product being unreacted **5**, recovered in 16% yield. Nevertheless, when a greater excess of 2-methoxypropene was used (1.5 eq) in order to push the acetonation of **5** toward completion, substantial amounts of its 2,6-di-*O*-(1-methoxy-1-methylethyl) derivative **18** were formed together with **7** (**18**:**7** ratio ≈ 1:1, ^{13}C NMR), indicating thus a rather low difference in reactivity between the primary (OH-6) and the secondary (OH-2) alcoholic functions of **5**.

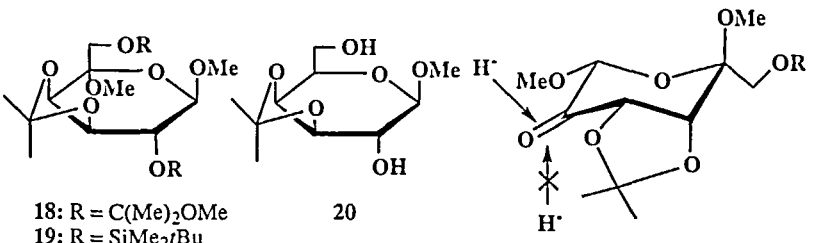


Scheme

A similar behaviour was also observed in the silylation of **5** with *t*-butyldimethylchlorosilane. When imidazole was used as the catalyst, according to the more general protocol,[11] a mixture of the 6-*O*-*t*-butyldimethylsilyl ether **6** and of the 2,6-di-*O*-silylated derivative **19** was obtained in isolated yields of 44 and 19%, respectively. With the milder catalytic system dimethylaminopyridine/triethylamine[12] the silylation was almost completely regioselective, but the formation of **6** was very slow, only about 30% being formed after 6 days of reaction at room temperature.

Another satisfactory method for the protection of the OH-6 function of **5** was found in a lipase mediated acetylation. As previously observed in the 3,4-*O*-isopropylidene-D-galactopyranoside series,[13] the lipases from *Pseudomonas species* (LPS) and from *Candida Antarctica* (N 435) proved to be able to promote in a regiospecific manner an acetyl transfer from vinyl acetate in organic solvents (THF or TBDME) to the 6-OH group, leading to the 6-*O*-acetate **8** in excellent isolated yields (92 and 95%, respectively). The acetylation rate was, however, much slower (7 days) than in the case of the 5-demethoxylated analogue **20**[13] (48 h). A marked reduction of the

reactivity of the primary OH-6 function of **5** with respect to that of **20** was also evidenced by the complete absence of reactivity of **5** toward trityl chloride, even under forcing conditions, whereas in the case of **20** the expected 6-trityl derivative was formed in reasonable yield.[14] As previously discussed[10] the reduced reactivity of the OH-6 group of **5** compared to **20** may be attributed to steric hindrance related to its resemblance to a neopentyl hydroxyl, rather than to the presence of appreciable conformational differences between **5** and **20**.



18: R = $C(Me)_2OMe$
19: R = $SiMe_2tBu$

20

($^4C_1$)-**9**: R = $C(Me)_2OMe$
($^4C_1$)-**10**: R = Ac

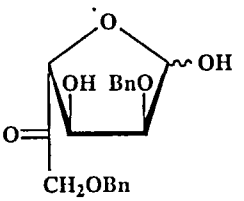
Derivatives **7** and **8** were used for performing a stereocontrolled epimerization at C-2 through a simple oxidation-reduction sequence. In both cases C-2 oxidation was efficiently carried out with the TPAP/NMO system,[15] that led in quantitative yields to the keto derivatives **9** and **10**. An analytical sample of **10** was obtained by crystallization, but in the case of syrupy **9** purification was not possible because of its instability over silica. Nevertheless, the subsequent reduction with $NaBH_4$ in MeOH was satisfactorily performed on crude **9**, a clean and rapid (10 min) reaction took place in a stereospecific manner, leading to the bis-glycoside **11** isolated, after flash chromatography, in good yield (88%). Similarly, the acetyl derivative **10** was converted into **12** (90% yield), the acetyl group being removed by saponification during work-up. The L-*ribo* configuration of **11** and **12** was firmly assigned on the basis of the ^1H NMR vicinal coupling constants relative to H-1, H-2 and H-3. In particular, the low values of $J_{1,2}$ and $J_{2,3}$, respectively of 3.4 and 4.8 Hz for **11** and 3.1 and 4.7 Hz for **12**, points to an axial-equatorial-axial orientation for the above protons, whereas in the case of L-*arabino* bis-glycosides, as for instance **8**, the axial-axial-axial orientation of the same protons gives higher values of $J_{1,2}$ and $J_{2,3}$, respectively of 8.4 and 7.7 Hz.

A tentative explanation for the complete stereoselectivity of the reduction of **9** and **10** required a knowledge of their conformational situation, that was not deducible from NMR analysis because of the absence of significant vicinal proton coupling constants. Nevertheless, an approximate estimation of the conformational preference of **9** and **10** was made through molecular mechanics calculations[16] that led to a value of about 4.5 kcal/mole in favour of the $^4C_1$ conformer. Following this hypothesis, the reduction is

controlled by the C-1 equatorial anomeric substituent[17] and by the steric hindrance of the 3,4-*O*-isopropylidene group, both playing a cooperative role in directing hydride attack exclusively equatorially from the α face.

In order to obtain a simplified model for the analysis of the tautomeric equilibrium of the target compound **14**, its 2,6-di-*O*-benzyl derivative **17** was prepared through the simple sequence depicted in the Scheme. The diol **12**, obtained by reduction followed by saponification of **10** and by demethoxyisopropylation of **11** with pyridinium tosylate in MeOH (90% yield after flash chromatography), was di-*O*-benzylated with benzyl bromide in THF in the presence of KOH/18-crown-6 and traces of H_2O^{18} to give **15** in 70% isolated yield. The deacetonation of **15** (TsOH/MeOH, room temp 2 h) gave **16**, purified by flash chromatography (85%, isolated yield), that was hydrolyzed with CF_3COOH in CH_3CN/H_2O (60 °C, 6 h) and, finally, submitted to flash chromatography to give analytically pure **17** (73% yield) as an amorphous solid, homogeneous in TLC analysis. The preparation of **14** was performed by subjecting the deacetonated product **13a**, obtained from **12** by de-*O*-isopropylidenation with Amberlist 15 resin (88% yield), to an acid hydrolytic treatment with Dowex 50 W resin (H^+ form) (83% yield). The direct acid hydrolysis of **12** gave a complex mixture of products incorporating acetone. The target dicarbonyl monose, L-*ribo*-hexos-5-ulose (**14**) was obtained as an amorphous, semisolid and highly hygroscopic material, that resisted all attempts at crystallization.

The NMR analysis (CD_3CN/D_2O) of 2,6-di-*O*-benzyl-L-*ribo*-hexos-5-ulose (**17**) revealed the presence of only two tautomers in ratios ranging from 10:1 to 7:3, depending on the prevalence of D_2O or CD_3CN in the solvent mixtures. The presence of two separated carbon signals at δ 208.8 and δ 209.2, unequivocally due to two ketonic functions, and of two anomeric signals, respectively, at δ 97.2 and δ 100.8, suggested for both tautomers a furanose structure of type **17**, arising from hemiacetalization of the OH-4 group with the C-1 aldehydic function.



17 α,β

The tautomeric equilibrium of **14** was, as expected, much more complicated; in pure D_2O a complex mixture of at least 5 tautomers was observed, in a ratio that, on the basis of the integration of the anomeric proton signals (experimental), was about 4:2:2:1:1. Also in this case, a strong dependence of the ratios of tautomers on the composition of CD_3CN/D_2O solvent mixtures, was found. A specific study aimed at the

attribution of the structures of the α,β-furanose anomers of **17**, and of the five principal tautomers of **14** is presently under investigation and will be presented in a forthcoming paper.

EXPERIMENTAL

General methods. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 20±2 °C. ^{1}H NMR spectra (internal TMS) were recorded with a Bruker AC 200 instrument at 200 MHz. First-order spectral analysis was performed whenever possible, otherwise spectra were simulated with PANIC (Bruker) or LAOCN-5 (QCPE QCMP 049) computer programs. Chemical shifts and coupling constants values were confirmed, when necessary, with COSY or J-RES experiments. ^{13}C NMR spectra were recorded with the same spectrometer at 50 MHz. Assignments were made with the aid of DEPT and HETCOR experiments. All reactions were followed by TLC on Kieselgel 60 F_{254} with detection by UV light and/or with ethanolic 10% phosphomolybdic or sulphuric acid, and heating. Kieselgel 60 (Merck, 230-400 mesh) was used for flash chromatography. Solvents were distilled and stored over 4 Å molecular sieves activated at least 24 h at 400 °C. $MgSO_4$ was used as the drying agent for solutions.

Methyl 2,6-Di-*O*-benzyl-3,4-*O*-isopropylidene-5-*C*-methoxy-β-D-galactopyranoside (4). A solution of 2[4a] (2.61 g, 6.45 mmol) and *p*-toluenesulfonic acid (40 mg, 0.23 mmol) in 2,2-dimethoxypropane (13 mL) was stirred for 3 h at room temperature. An excess of triethylamine (0.5 mL) was added to the reaction mixture, which after 30 min additional stirring, was concentrated under reduced pressure and repeatedly co-evaporated with toluene (3 x 30 mL). The crude reaction product (2.88 g) was flash chromatographed on silica gel (9:1 hexane/EtOAc) to give pure **4** (2.53 g, 88% yield), as a syrup, R_f 0.73 (1:1 hexane/EtOAc); $[\alpha]_D$ +4.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR (CD_3CN) δ 1.35 (s, 6 H, 2 x C(CH_3)$_2$), 3.31 (s, 3 H, OCH_3-5), 3.32 (dd, 1 H, $J_{1,2}$ = 8.2 Hz, $J_{2,3}$ = 7.0 Hz, H-2) 3.50 (s, 3 H, OCH_3-1), 3.55 (d, 1 H, $J_{6,6'}$ = 10.5 Hz, H-6'), 3.74 (d, 1 H, H-6), 4.17 (dd, 1 H, $J_{3,4}$ = 5.3 Hz, H-3), 4.18 (d, 1 H, H-4), 4.51 (d, 1 H, H-1), 4.53 and 4.58 (AB system, 2 H, J_{AB} = 11.9 Hz, CH_2Ph), 4.74 and 4.79 (AB system, 2 H, J_{AB} = 12.0 Hz, CH_2Ph), 7.28-7.39 (m, 10 H, aromatic H); ^{13}C NMR (CD_3CN) δ 26.71 and 28.30 [C(CH_3)$_2$], 48.51 (OCH_3-5), 57.12 (OCH_3-1), 67.35 (C-6), 73.88 and 73.98 (2 x CH_2Ph), 75.85 (C-4), 78.73 (C-3), 80.23 (C-2), 99.46 (C-1), 99.82 (C-5), 110.02 [C(CH_3)$_2$], 129.20-128.30 (aromatic CH), 139.34 and 139.78 (aromatic C).

Anal. Calcd for $C_{25}H_{32}O_7$ (444.5): C, 67.55; H, 7.26. Found: C, 67.10; H, 7.00.

Methyl 3,4-*O*-Isopropylidene-5-*C*-methoxy-β-D-galactopyranoside (5). A solution of **4** (2.63 g, 5.90 mmol) in EtOAc (40 mL) containing 400 mg of 10% $Pd(OH)_2$ on charcoal, was stirred at room temperature under H_2 for 3 h until the starting material had disappeared (TLC analysis 3:7 hexane/EtOAc). The suspension was filtered over Celite and concentrated under reduced pressure to give **5** as a white amorphous solid (1.68 g, quantitative yield), mp 118-119 °C (EtOAc/hexane); R_f 0.34 (3:7 hexane/EtOAc); $[\alpha]_D$ -57.2° (*c* 1.3, $CHCl_3$), identical with a previously prepared[10] authentic sample.

Methyl 6-*O*-*t*-Butyldimethylsilyl-3,4-*O*-isopropylidene-5-*C*-methoxy-β-D-galactopyranoside (6) and Methyl 2,6-Di-*O*-*t*-butyldimethylsilyl-3,4-*O*-isopropylidene-5-*C*-methoxy-β-D-galactopyranoside (19). A solution of **5** (300 mg, 1.14 mmol), *t*-butyldimethylchlorosilane (TBDMCS) (207 mg, 1.37 mmol) and imidazole (204 mg, 3.00 mmol) in DMF (1.5 mL) was stirred for 5 h at room temperature. The reaction mixture was diluted with petroleum ether (30 mL) and washed with saturated aq $NaHCO_3$ (3 x 30 mL) and saturated aq NaCl (30 mL). The organic phase, dried and concentrated under reduced pressure, gave a crude product (321 mg), which was purified by flash chromatography on silica gel (7:3 hexane/EtOAc) to give **6** (189 mg, 44% yield) and **19** (108 mg, 19% yield).

Compound 6: syrup, R_f 0.60 (3:7 hexane/EtOAc); $[\alpha]_D$ -26.8° (*c* 1.1, $CHCl_3$); ^1H NMR (CD_3CN) δ 0.05 and 0.06 (2 s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $C(CH_3)_3$), 1.27 and 1.42 (2 s, 6 H, $C(CH_3)_2$), 3.28 (s, 3 H, OCH_3-5), 3.31 (dd, 1H, $J_{1,2}$ = 8.3 Hz, $J_{2,3}$ = 7.4 Hz, H-2) 3.43 (s, 3 H, OCH_3-1), 3.63 (d, 1 H, $J_{6,6'}$ = 10.9 Hz, H-6'), 3.78 (d, 1 H, H-6), 3.97 (dd, 1 H, $J_{3,4}$ = 5.2 Hz, H-3), 4.06 (d, 1 H, H-4), 4.33 (d, 1 H, H-1); ^{13}C NMR (CD_3CN) δ -5.40 and -5.33 [$Si(CH_3)_2$], 18.82 [$C(CH_3)_3$], 26.10 [$C(CH_3)_3$], 26.60 and 28.44 [$C(CH_3)_2$], 48.26 (OCH_3-5), 57.31 (OCH_3-1), 60.54 (C-6), 73.10 (C-2), 75.31 (C-4), 78.93 (C-3), 99.53 (C-1), 100.56 (C-5), 110.09 [$C(CH_3)_2$].

Anal. Calcd for $C_{17}H_{34}O_7Si$ (378.5): C, 53.94; H, 9.05. Found: C, 54.02; H, 9.10.

Compound 19: syrup, R_f 0.83 (3:7 hexane/EtOAc); $[\alpha]_D$ -24.5° (*c* 0.9, $CHCl_3$); ^1H NMR (CD_3CN) δ 0.06, 0.07, 0.09 and 0.09 (4 s, 12 H, 2 x $Si(CH_3)_2$), 0.89 and 0.90 (2 s, 18 H, 2 x $C(CH_3)_3$), 1.28 and 1.43 (2 s, 6 H, $C(CH_3)_2$), 3.30 (s, 3 H, OCH_3-5), 3.39 (dd, 1 H, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 7.1 Hz, H-2) 3.44 (s, 3 H, OCH_3-1), 3.64 (d, 1H, $J_{6,6'}$ = 10.9 Hz, H-6'), 3.80 (d, 1 H, H-6), 3.96 (dd, 1 H, $J_{3,4}$ = 5.2 Hz, H-3), 4.08 (d, 1 H, H-4), 4.29 (d, 1 H, H-1); ^{13}C NMR (CD_3CN) δ -5.42, -5.36, -4.47, and -4.25, [2 x $Si(CH_3)_2$], 18.77 and 18.84 [2 x$C(CH_3)_3$], 26.10 [2 x $C(CH_3)_3$], 26.71 and 28.60 [$C(CH_3)_2$], 48.20 (OCH_3-5), 57.35 (OCH_3-1), 60.58 (C-6), 75.22 and 75.44 (C-4 and C-2), 80.18 (C-3), 99.98 (C-1), 100.36 (C-5), 109.86 [$C(CH_3)_2$].

Anal. Calcd for $C_{23}H_{48}O_7Si_2$ (492.8): C, 56.05; H, 9.82. Found: C, 56.35; H, 9.97.

Methyl 3,4-*O*-Isopropylidene-5-*C*-methoxy-6-*O*-(1-methoxy-1-methylethyl)-β-D-galactopyranoside (7). A mixture of **5** (600 mg, 2.27 mmol) in 30 mL of anhydrous CH_2Cl_2, powdered 4 Å molecular sieves (480 mg) and pyridinium *p*-toluenesulfonate (85.5 mg, 0.33 mmol), was stirred for 20 minutes at 0 °C, and treated with a solution of 2-methoxypropene in dry CH_2Cl_2 (0.234 mL, 2.49 mmol). After 5.5 h solid Na_2CO_3 (213 mg, 2.01 mmol) was added, and the reaction mixture was stirred for 10 min. The suspension was filtered through Celite and the solvent was evaporated under reduced pressure to give a crude residue (750 mg), which was purified by flash-chromatography on silica gel (1:1 hexane/EtOAc) to give unreacted **5** (96 mg, 16% yield) and **7** (630 mg, 83% yield), R_f 0.3 (1:1 hexane/EtOAc); $[\alpha]_D$ -36.7° (*c* 1.9, $CHCl_3$), identical to the sample previously described by us.[10]

Methyl 6-*O*-Acetyl-3,4-*O*-isopropylidene-5-*C*-methoxy-β-D-galactopyranoside (8). a) With Novozym 435 in TBME. Into a reaction vessel were introduced 100 mg (0.38 mmol) of **5**, 400 μL of vinyl acetate, 20 mL of *t*-butyl methyl ether and 500 mg of commercially available Novozym N435 (a lipase from *Candida Antarctica* immobilized on a macroporous polypropylenic resin, supplied by Novo Nordisk Bioindustriale S.r.l. Italia). The mixture was shaken on an orbit shaker at 43 °C. The reaction course was monitored by TLC (3:7 hexane/EtOAc) and, after 8 days, the enzyme was filtered off. The solvent was evaporated under reduced pressure leaving a crude residue (177 mg) which was purified by flash chromatography on silica gel (1:1 hexane/EtOAc) to give **8** as a white solid (110 mg, 95% yield); mp 95-96 °C (hexane); R_f 0.52 (7:3 hexane/EtOAc); $[\alpha]_D$ -60.1° (*c* 0.8, $CHCl_3$); ^1H NMR (CD_3CN) δ 1.28 and 1.42 (2 s, 6 H, $C(CH_3)_2$), 2.02 (s, 3 H, CH_3CO), 3.27 (s, 3 H, OCH_3-5), 3.34 (dd, 1 H, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 7.7 Hz, H-2), 3.46 (s, 3 H, OCH_3-1), 3.97 (d, 1 H, $J_{6,6'}$ = 11.9 Hz, H-6'), 4.01 (dd, 1 H, $J_{3,4}$ = 5.3 Hz, H-3), 4.05 (d, 1 H, H-4), 4.33 (d, 1 H, H-1), 4.38 (d, 1 H, H-6); ^{13}C NMR (CD_3CN) δ 20.88 (CH_3CO), 26.47 and 28.28 [$C(CH_3)_2$], 48.79 (OCH_3-5), 57.53 (OCH_3-1), 60.79 (C-6), 72.63 (C-2), 75.59 (C-4), 78.74 (C-3), 99.24 (C-5), 99.48 (C-1), 110.59 [$C(CH_3)_2$], 171.90 ($COCH_3$).

Anal. Calcd for $C_{13}H_{22}O_8$ (306.3): C, 50.98; H, 7.24. Found: C, 51.36; H, 7.26.

b) With *Pseudomonas Species* lipase (LPS). The product **8** was obtained by the method described above under a), with the following reagents: 0.38 mmol of **5**, 7 mL of vinyl acetate, 500 mg of LPS [supplied by Amano Mitsubishi Italia s.p.a. and supported before use on Hyflo Supercell (1:3 w/w) in 0.1 M phosphate buffer (pH 7.0, 10 mL) and dried *in vacuo* (0.1 mm Hg) for 48 h] and 3 mL of THF. After 8 days the reaction mixture was submitted to the work-up described in a), and the residue (150 mg) was flash chromatographated on silica gel (1:1 hexane/EtOAc) to give pure **8** (108 mg, 93% yield).

Methyl 3,4-*O*-Isopropylidene-5-*C*-methoxy-6-*O*-(1-methoxy-1-methylethyl)-β-D-*lyxo*-hexopyranosid-2-ulose (9). A solution of **7** (746 mg, 2.22 mmol) in 15 mL of

anhydrous CH_2Cl_2 and pre-dried 4-methylmorpholine-*N*-oxide (NMO) (432 mg, 3.69 mmol) containing 4 Å powdered molecular sieves (400 mg) was stirred for 30 min at room temperature. Tetrapropylammonium perruthenate (TPAP) (117 mg, 0.33 mmol) was added and the reaction was followed by TLC analysis until completion (30 min). The suspension was filtered through Celite and the solvent was evaporated under reduced pressure to give a crude residue (725 mg, quantitative yield), consisting of **9** exclusively (NMR), as a syrup, R_f 0.50 (1:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.36, 1.39, 1.40 and 1.46 (4 s, 12 H, 2 x $C(CH_3)_2$), 3.25 (s, 3 H, $C(CH_3)_2OCH_3$), 3.46 (s, 3 H, OCH_3-5), 3.57 (s, 3 H, OCH_3-1), 3.65 (d, 1 H, $J_{6,6'}$ = 10.6 Hz, H-6'), 3.70 (d, 1 H, H-6), 4.56 (m, 2 H, H-3 and H-4), 5.00 (s, 1 H, H-1); ^{13}C NMR (CD_3CN) δ 24.11, 24.29, 25.52 and 26.70 (2 x $C(CH_3)_2$), 48.64 [$C(CH_3)_2OCH_3$ and OCH_3-5], 56.50 (OCH_3-1), 57.25 (C-6), 76.02 and 77.60 (C-3 and C-4), 95.57 (C-1), 98.73 (C-5), 100.23 [$C(CH_3)_2OCH_3$], 111.11 [$C(CH_3)_2$], 198.72 (C-2). The product was not further characterized because of its instability on silica gel, but was directly used for the subsequent reduction reaction.

Methyl 6-*O*-Acetyl-3,4-*O*-isopropylidene-5-*C*-methoxy-β-D-*lyxo*-hexopyranosyid-2-ulose (10). The product **10** was obtained by the method described above for **9**, with the following amounts: 628 mg (2.05 mmol) of **8**, in 12 mL of anhydrous CH_2Cl_2, 370 mg of 4 Å powdered molecular sieves, 442 mg (3.42 mmol) of NMO and 72 mg (0.204 mmol) of TPAP. After 60 min the reaction mixture was submitted to the work-up described for **9** to give a solid crude residue (576 mg, quantitative yield) constituted (NMR) exclusively by **10**. Compound **10** was a crystalline solid, mp 109-111 °C (hexane); R_f 0.47 (1:1 hexane/EtOAc); $[\alpha]_D$ -97.2° (*c* 0.73, $CHCl_3$); ^{1}H NMR (CD_3CN) δ 1.33 and 1.35 (2 s, 6 H, $C(CH_3)_2$), 2.05 (s, 3 H, CH_3CO), 3.39 (s, 3 H, OCH_3-5), 3.50 (s, 3 H, OCH_3-1), 4.03 (d, 1 H, $J_{6,6'}$ = 12.1 Hz, H-6'), 4.45 (d, 1 H, H-6), 4.48 (d, 1 H, $J_{3,4}$ = 5.8 Hz, H-4), 4.59 (dd, 1 H, $J_{1,3}$ = 0.9 Hz, H-3), 5.03 (d, 1 H, H-1); ^{13}C NMR (CD_3CN) δ 20.83 (CH_3CO), 25.99 and 27.18 [$C(CH_3)_2$], 49.79 (OCH_3-5), 57.20 (OCH_3-1), 60.31 (C-6), 77.26 (C-3), 79.40 (C-4), 96.47 (C-1), 98.83 (C-5), 111.90 [$C(CH_3)_2$], 170.83 ($COCH_3$), 199.23 (C-2).

Anal. Calcd for $C_{13}H_{20}O_8$ (304.2): C, 51.31; H, 6.62. Found: C, 51.19; H, 7.06.

Methyl 3,4-*O*-Isopropylidene-5-*C*-methoxy-6-*O*-(1-methoxy-1-methylethyl)-β-D-talopyranoside (11). To a solution of **9** (596 mg, 1.78 mmol) in MeOH (20 mL) $NaBH_4$ (494 mg, 13.14 mmol) was added at 0 °C, and the reaction mixture was stirred at rt for 10 min until TLC analysis revealed a complete disappearance of the starting material. The solution was treated with H_2O (20 mL), the mixture was stirred for 15 min and extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were dried and concentrated *in vacuo* to leave a crude residue (554 mg) which was flash chromatographed on silica gel (7:3 hexane/EtOAc) to give pure **11** (530 mg, 88% yield),

as a syrup, R_f 0.30 (9:1 CH_2Cl_2/Et_2O); $[\alpha]_D$ -78.3° (*c* 1.1, $CHCl_3$); ^1H NMR (CD_3CN) δ 1.27, 1.30, 1.31, and 1.43 (4 s, 6 H, 2 x $C(CH_3)_2$), 3.18 (s, 3 H, $C(CH_3)_2CH_3$), 3.24 (s, 3 H, OCH_3-5), 3.36 (s, 3 H, OCH_3-1), 3.45 (d, 1 H, $J_{6,6'}$ = 10.3 Hz, H-6'), 3.50 (dd, 1 H, H-6), 3.82 (dd, 1 H, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 4.8 Hz, H-2), 4.32 (ddd, 1 H, $J_{3,4}$ = 7.6 Hz, $J_{1,3}$ = 0.9 Hz, H-3), 4.33 (d, 1 H, H-4), 4.66 (dd, 1 H, H-1); ^{13}C NMR (CD_3CN) δ 23.71, 24.58, 24.71 and 25.05 [2 x $C(CH_3)_2$], 48.41 (OCH_3-5), 49.04 [$C(CH_3)_2OCH_3$], 56.45 (OCH_3-1), 58.54 (C-6), 65.79 (C-2), 72.24 (C-3), 73.76 (C-4), 98.68 (C-1), 98.86 (C-5), 100.99 [$C(CH_3)_2OCH_3$], 110.55 [$C(CH_3)_2$].

Anal. Calcd for $C_{15}H_{28}O_8$ (336.4): C, 53.56; H, 8.39. Found: C, 53.39; H, 8.85.

Methyl 3,4-*O*-Isopropylidene-5-*C*-methoxy-β-D-talopyranoside (12). From **10:** The product **12** was obtained by the method described above for **11**, with the following reagents: 483 mg (1.59 mmol) of **10** in MeOH (20 mL) and 441 mg (11.6 mmol) of $NaBH_4$. After 2 h the reaction mixture was submitted to the work-up described for **11** and the crude reaction product (426 mg) was flash chromatographated on silica gel (7:3; 1:1 hexane/EtOAc) to give pure **12** (336 mg, 80% yield), as a syrup, R_f 0.40 (3:7 hexane/EtOAc); $[\alpha]_D$ -64.8° (*c* 1.67, $CHCl_3$); ^1H NMR (CD_3CN) δ 1.28 and 1.42 (2 s, 6 H, $C(CH_3)_2$), 3.24 (s, 3 H, OCH_3-5), 3.35 (s, 3 H, OCH_3-1), 3.47 (d, 1 H, $J_{6,6'}$ = 12.2 Hz, H-6'), 3.64 (d, 1 H, H-6), 3.82 (dd, 1 H, $J_{1,2}$ = 3.1 Hz, $J_{2,3}$ = 4.7 Hz, H-2), 4.27 (d, 1 H, H-4), 4.32 (ddd, 1 H, $J_{3,4}$ = 7.5 Hz, $J_{1,3}$ = 0.8 Hz, H-3), 4.65 (dd, 1 H, H-1); ^{13}C NMR (CD_3CN) δ 25.06 and 25.64 [$C(CH_3)_2$], 48.43 (OCH_3-5), 56.72 (OCH_3-1), 59.32 (C-6), 65.71 (C-2), 72.34 (C-3), 73.51 (C-4), 98.51 (C-1), 99.22 (C-5), 110.83 [$C(CH_3)_2$].

Anal. Calcd for $C_{11}H_{20}O_7$ (264.3): C, 49.99; H, 7.63. Found: C, 49.92; H, 7.40.

From **11:** To a solution of **11** (646 mg, 1.92 mmol) in MeOH (14 mL) pyridinium *p*-toluenesulfonate (17 mg, 0.067 mmol) was added. The mixture was stirred for 4 h at room temperature until the starting material had completely reacted (TLC). The solution was neutralized with solid Na_2CO_3, stirred for 15 min, and the crude reaction product (551 mg) was directly submitted to flash chromatography to give pure **12** (457 mg, 90% yield).

Methyl 5-*C*-Methoxy-β-D-talopyranoside (13a). To a solution of **12** (200 mg, 0.76 mmol) in MeOH (12 mL) Amberlist 15 (wet) ion-exchange resin (750 mg) was added. The mixture was shaken on an orbit shaker at room temperature. The reaction course was monitored by TLC (9:1 AcOEt/MeOH) and, after 3 h, the resin was filtered off. The solvent was evaporated under reduced pressure to leave a crude residue (150 mg, 88%), consisting of **13a** exclusively (NMR), as a white hygroscopic solid, mp 73-76 °C (Et_2O); R_f 0.32 (9:1 EtOAc/MeOH); $[\alpha]_D$ -100.8° (*c* 0.78, 1:1 CH_3CN/H_2O); ^1H NMR (CD_3CN/D_2O) δ 3.25 (s, 3 H, OCH_3-5), 3.45 (s, 3 H, OCH_3-1), 3.63 (d, 1 H, $J_{6,6'}$ = 12.3 Hz, H-6'), 3.68 (d, 1 H, $J_{3,4}$ = 3.4 Hz, $J_{2,4}$ = 1.3 Hz, H-4), 3.72 (d, 1 H, H-6), 3.81 (dd, 1

H, $J_{2,3}$ = 3.1 Hz, H-3), 3.85 (ddd, 1 H, $J_{1,2}$ = 1.3 Hz, H-2), 4.50 (d, 1 H, H-1); ^{13}C NMR (CD_3CN/D_2O) δ 48.81 (OCH_3-5), 57.54 (OCH_3-1), 57.77 (C-6), 66.05 (C-4), 69.97 (C-3), 71.73 (C-2), 98.26 (C-1), 102.58 (C-5).

Methyl 2,3,4,6-Tetra-*O*-acetyl-5-*C*-methoxy-β-D-talopyranoside (13b). A sample of **13a** (50 mg, 0.22 mmol) was dissolved in dry pyridine (3 mL), treated with Ac_2O (2 mL) and left at rt for 24 h. The reaction mixture was repeatedly co-evaporated *in vacuo* with toluene (3 x 10 mL) to leave a crude residue of **13b** (76 mg, 87%), an analytical sample of which was obtained through flash chromatography on silica gel (7:3 petroleum ether/EtOAc), as a syrup, R_f 0.58 (3:7 hexane/EtOAc); $[\alpha]_D$ -97.8° (*c* 1.4, $CHCl_3$); ^{1}H NMR (CD_3CN) δ 1.89, 1.95, 2.04 and 2.05 (4 s, 12 H, C*H*$_3$CO), 3.34 (s, 3 H, OCH_3-5), 3.49 (s, 3 H, OCH_3-1), 4.17 (d, 1 H, $J_{6,6'}$ = 12.3 Hz, H-6'), 4.25 (d, 1 H, H-6), 4.81 (d, 1 H, $J_{1,2}$ = 1.7 Hz, H-1), 5.10 (d, 1 H, $J_{3,4}$ = 3.7 Hz, $J_{2,4}$ = 0.9 Hz, H-4), 5.21 (dd, 1 H, $J_{2,3}$ = 3.6 Hz, H-3), 5.32 (ddd, 1 H, H-2); ^{13}C NMR (CD_3CN) δ 20.98 and 20.73 (4 x *C*H$_3$CO), 49.27 (OCH_3-5), 57.46 (OCH_3-1), 58.93 (C-6), 66.21 (C-4), 66.92 (C-3), 67.46 (C-2), 93.30 (C-1), 100.69 (C-5), 170.33, 170.67, 170.67 and 171.03 (4 x CH$_3$*CO*).

Anal. Calcd for $C_{16}H_{24}O_{11}$ (392.4): C, 48.98; H, 6.17. Found: C, 49.10; H, 6.20.

Methyl 2,6-Di-*O*-benzyl-3,4-*O*-isopropylidene-5-*C*-methoxy-β-D-talopyranoside (15). To a solution of **12** (384 mg, 1.45 mmol) in THF containing 0.5% of H_2O (16 mL) was added KOH (280 mg, 5.72 mmol), 18-crown-6 (14.8 mg, 0.06 mmol) and benzyl bromide (0.50 mL, 4.24 mmol). The reaction mixture was stirred for 5 h at room temperature, then treated with MeOH (10 mL). After 30 min stirring, the solvent was evaporated *in vacuo*, and the residue was partitioned between CH_2Cl_2 and H_2O (4 x 100 mL). The combined organic phases were dried and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1:1 hexane/EtOAc) to give pure **15** (451 mg, 70% yield), as a slightly yellow syrup, R_f 0.59 (1:1 hexane/EtOAc); $[\alpha]_D$ -11.0° (*c* 1.54, $CHCl_3$); ^{1}H NMR (CD_3CN) δ 1.33 and 1.43 (2 s, 6 H, C(C*H*$_3$)$_2$), 3.21 (s, 3 H, OCH_3-5), 3.37 (s, 3 H, OCH_3-1), 3.53 (d, 1H, $J_{6,6'}$ = 10.5 Hz, H-6'), 3.65 (d, 1 H, H-6), 3.83 (dd, 1 H, $J_{1,2}$ = 2.9 Hz, $J_{2,3}$ = 4.5 Hz, H-2), 4.33 (d, 1 H, $J_{3,4}$ = 7.6 Hz, H-4), 4.50 (ddd, 1 H, $J_{1,3}$ = 0.9 Hz, H-3), 4.54 and 4.56 (AB system, 2 H, J_{AB} = 12.0 Hz, C*H*$_2$Ph), 4.60 and 4.67 (AB system, 2 H, J_{AB} = 11.6 Hz, C*H*$_2$Ph), 4.76 (dd, 1 H, H-1), 7.30-7.40 (m, 10 H, aromatic H); ^{13}C NMR (CD_3CN) δ 25.21 and 25.88 [C(*C*H$_3$)], 48.48 (OCH_3-5), 56.41 (OCH_3-1), 67.56 (C-6), 71.32 (C-3), 73.26 (C-4), 73.08 and 73.79 (2 x *C*H$_2$Ph), 74.37 (C-2), 97.71 (C-1), 98.92 (C-5), 110.50 [*C*(CH$_3$)$_2$], 129.17-128.52 (aromatic CH), 139.44 and 139.52 (aromatic C).

Anal. Calcd for $C_{25}H_{32}O_7$ (444.5): C, 67.55; H, 7.26. Found: C, 67.31; H, 7.50.

Methyl 2,6-Di-*O*-benzyl-5-*C*-methoxy-β-D-talopyranoside (16). A solution of **15** (326 mg, 0.73 mmol) and TsOH (42 mg, 0.23 mmol) in MeOH (10 mL) was stirred at

room temperature until TLC analysis (9:1 EtOAc/MeOH) revealed complete disappearance of **15** (2 h). The solution was neutralized with solid Na_2CO_3, stirred for 15 min and then concentrated to give a crude residue (392 mg) which, after flash chromatography on silica gel (9:1 EtOAc/MeOH), gave pure **16** (251 mg, 85% yield), as a syrup, R_f 0.31 (6:4 hexane/EtOAc); $[\alpha]_D$ -67.4° (*c* 1.4, $CHCl_3$); ^1H NMR (CD_3CN) δ 3.20 (s, 3 H, OCH_3-5), 3.45 (s, 3 H, OCH_3-1), 3.54 (d, 1 H, $J_{6,6'}$ = 10.4 Hz, H-6), 3.58 (m, 1 H, H-2), 3.67 (d, 1 H, H-6'), 3.86 (m, 2 H, H-3 and H-4), 4.45 and 4.54 (AB system, 2 H, $J_{A,B}$ = 11.9 Hz, CH_2Ph), 4.55 (m, 1 H, H-1), 4.67 and 4.77 (AB system, 2 H, $J_{A,B}$ = 11.2 Hz, CH_2Ph), 7.30-7.37 (m, 10 H, aromatic H); ^{13}C NMR (CD_3CN) δ 48.94 (OCH_3-5), 57.51 (OCH_3-1), 66.12 (C-6), 66.51 (C-4), 71.01 (C-3), 73.90 and 76.35 (2 x CH_2Ph), 80.25 (C-2), 98.94 (C-1), 102.37 (C-5), 128.65-129.84 (aromatic CH), 139.08 (aromatic C).

Anal. Calcd for $C_{22}H_{28}O_7$ (404.5): C, 65.33; H, 6.98. Found: C, 65.53; H, 7.00.

2,6-Di-*O*-benzyl-L-*ribo*-hexos-5-ulose (17). A solution of **16** (210 mg 0.52 mmol) in 1:2 H_2O/CH_3CN (6 mL) and CF_3COOH (0.8 mL) was stirred at 60 °C until the reaction was complete (TLC). After 7 h the solvent was evaporated under reduced pressure and coevaporated repeatedly with toluene (3 x 30 mL) giving a residue (202 mg), which was purified by flash chromatography on silica gel (6:4 hexane/EtOAc) to give **17** (136 mg, 73% yield), as a white amorphous solid, mp 120-124 °C (hexane/EtOAc); R_f 0.31 (1:1 hexane/EtOAc); $[\alpha]_{D\infty}$ -20.5° (*c* 0.7, $CHCl_3$); ^1H NMR (CD_3CN) δ major anomer 3.68 (dd, $J_{1,2}$ = 1.1 Hz, $J_{2,3}$ = 4.5 Hz, H-2), 4.32 (dd, $J_{3,4}$ = 6.6 Hz, H-3), 4.25 (d, H-4), 5.27 (d, H-1); minor anomer 3.71 (dd, $J_{1,2}$ = 4.2 Hz, $J_{2,3}$ = 5.3 Hz, H-2), 4.19 (dd, $J_{3,4}$ = 3.7 Hz, H-3), 4.55 (d, H-4), 5.30 (d, H-1); ^{13}C NMR (CD_3CN) δ major anomer 73.14 (C-3), 73.71 (C-6), 82.87 (C-4), 85.95 (C-2), 100.82 (C-1), 209.17 (C-5); minor anomer 72.23 (C-3), 74.16 (C-6), 77.88 (C-4), 86.79 (C-2), 97.22 (C-1), 208.82 (C-5).

Anal. Calcd for $C_{20}H_{22}O_6$ (358.4): C, 67.03; H, 6.19. Found: C, 66.98; H, 6.19.

L-*ribo*-Hexos-5-ulose (14). To a solution of **13** (270 mg 1.20 mmol) in H_2O (15 mL) was added Dowex 50 WX2 200-400 mesh (1.68 g). The mixture was shaken on an orbit shaker at 50 °C, and the reaction course was monitored by TLC (i-PrOH). After 52 h the resin was filtered off, the solvent was evaporated under reduced pressure to leave a crude residue (177 mg, 83%) consisting (NMR, D_2O) exclusively of **14**, as a syrup. $[\alpha]_{D\infty}$ +2.3° (*c* 1.9, D_2O). The ^1H NMR spectra of **14** in D_2O revealed the presence of five tautomers on the basis of 5 doublets [δ 4.84 (J = 4.8 Hz) 40%; δ 4.85 (J = 6.1 Hz) 20%; δ 5.04 (J = 8.4 Hz) 10%; δ 5.22 (J = 0.9 Hz) 20%; δ 5.34 (J = 4.1 Hz) 10%] in the anomeric region of proton spectrum.

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REFERENCES AND NOTES

1. Part 10 of the series, " Rare and Complex Saccharides from D-galactose and other Milk-derived Carbohydrates". For part 9 see ref. 4c.
2. a) D. E. Kiely and H. G. Fletcher Jr., *J. Am. Chem. Soc,* **90**, 3289 (1968); b) D. E. Kiely and H. G. Fletcher, *J. Org. Chem.*, **34**, 1386 (1969).
3. a) J. M. Riordan, P. E. Morris, Jr. and D. E. Kiely, *J. Carbohydr. Chem.*, **12**, 865 (1993); b) D. E. Kiely, R. E. Harry-O'Kuru, P. E. Morris, Jr., D. W. Morton and J. M. Riordan, *J. Carbohydr. Chem.*, **16**, 1159 (1997).
4. a) P. L. Barili, G. Berti, G. Catelani and F. D'Andrea, *Gazz. Chim. Ital.*, **122**, 135 (1992); b) P. L. Barili, G. Berti, G. Catelani, F. D'Andrea and F. De Rensis, *Tetrahedron,* **53**, 8665 (1997); c) P. L. Barili, G. Berti, G. Catelani, F. D'Andrea, F. De Rensis and G. Goracci, *J. Carbohydr. Chem.*, **17**, 1167 (1998).
5. a) E. W. Baxter and A. B. Reitz, *J. Org. Chem.*, **59**, 3175 (1994); b) P. L. Barili, G. Berti, G. Catelani, F. D'Andrea, F. De Rensis and L. Puccioni, *Tetrahedron*, **53**, 3407 (1997).
6. M. Adinolfi, G. Barone, A. Iadonisi and L. Mangoni, *Tetrahedron Lett.*, **39**, 2021 (1998).
7. An alternative name of **3**, according to the more recent rules could be methyl (*5R*)-5-methoxy-α-L-*arabino*-hexopyranoside.
8. P. L. Barili, G. Berti, G. Catelani and F. D'Andrea, *Carbohydr. Res.*, **190**, 13 (1989).
9. P. L. Barili, G. Berti, G. Catelani, F. Colonna and A. Marra, *Tetrahedron Lett.*, **27**, 2307 (1986).
10. M. C. Bergonzi, G. Catelani, F. D'Andrea and F. De Rensis, *Carbohydr. Res.*, **311**, 231 (1998).
11. E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
12. S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, **2**, 99 (1979).
13. P. L. Barili, G. Catelani, F. D'Andrea and E. Mastrorilli, *J. Carbohydr. Chem.*, **16**, 1001 (1997).
14. A. Levy, H. M. Flowers and N. Sharon, *Carbohydr. Res.*, **4**, 305 (1967).
15. S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 639 (1994).
16. PC MODEL, Serena Software, P.O. Box 3076, Bloomington, IN 47402, USA, (1990).
17. F. W. Lichtenthaler, E. Kaji and S. Weprek, *J. Org. Chem*, **50**, 3505 (1985).
18. M. Bessodes, J. Shamsazar and K. Antonakis, *Synthesis*, **7**, 560 (1988).