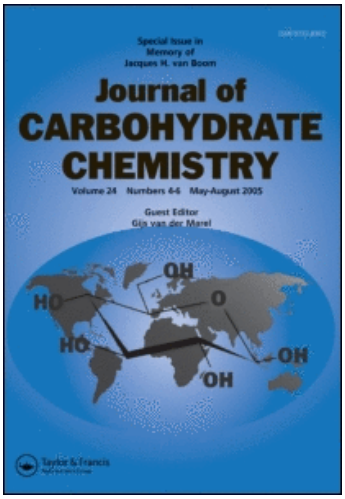

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Silver Zeolite as Promoter in Glycoside Synthesis. The Synthesis of 2-Deoxy-β-D-Glycopyranosides

Per J. Garegg[ab]; Petra Ossowski[a]; Sabine Köpper[c]; Joachim Thiem[c]
[a] Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm, Stockholm, Sweden [b] Department of Organic Pharmaceutical Chemistry, Uppsala Biomedical Center, Uppsala, Sweden [c] Westfälische Wilhelms-Universität Münster, Organisch-Chemisches Institut, Münster, Federal Republic of Germany

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SILVER ZEOLITE AS PROMOTER IN GLYCOSIDE SYNTHESIS. THE SYNTHESIS OF 2-DEOXY-β-D-GLYCOPYRANOSIDES

Per J. Garegg*, Sabine Köpper**, Petra Ossowski*, and Joachim Thiem**
*Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm, S-106 91 Stockholm, Sweden. **Westfälische Wilhelms-Universität Münster, Organisch-Chemisches Institut, Orléans-Ring 23, D-4400 Münster, Federal Republic of Germany.

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ABSTRACT

The use of silver zeolite as a promoter for the preparation of β-linked 2-deoxyglycosides and disaccharides of biological relevance has been explored. Starting from benzoylated glycosyl bromides, the total yield of glycosides varies from 54 to 84% and the α:β ratio from 0.25 to 1.18.

RESULTS AND DISCUSSION

A generally applicable, efficient synthesis of β-linked 2-deoxyhexopyranosides remains a problem in synthetic carbohydrate chemistry.[1-3] Recent progress in this field includes the use of 1,2-*trans* 2-bromo-2-deoxy-β-D-glycopyranosyl bromides.[2-4] In these glycosylations, the 2-bromo substituent directs the anomeric outcome by means of neighbouring group participation and the consequent formation of an intermediate bromonium ion. Nucleophilic attack must therefore come from the β-side.[4] In the *digitoxose* (2,6-dideoxy-α-D-*ribo*-hexopyranose) series, advantage has been taken of a urethane or a p-methoxybenzoate group in the axial 3-position participating in the reaction at the anomeric centre, leading to stereoselective β-D-glycoside formation.[5,6] None of these methods, however, has the desired simplicity of allowing the use, as starting material, an acylated glycosyl halide, obtainable directly from the parent sugar in an essentially one-step operation.

Present address for PJG : Department of Organic Pharmaceutical Chemistry, Uppsala Biomedical Center, Box 574, S-751 23 Uppsala, Sweden.

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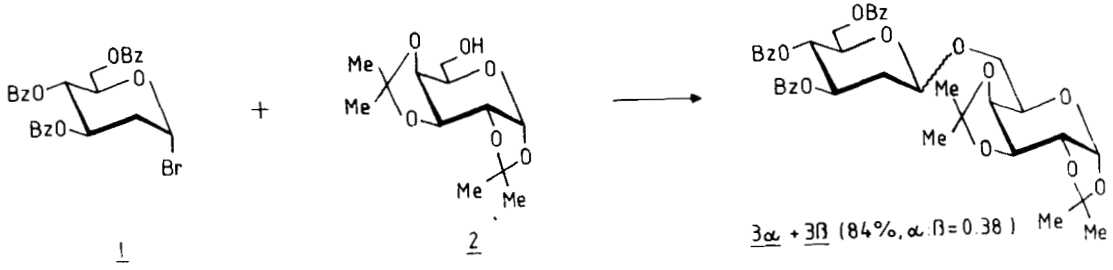
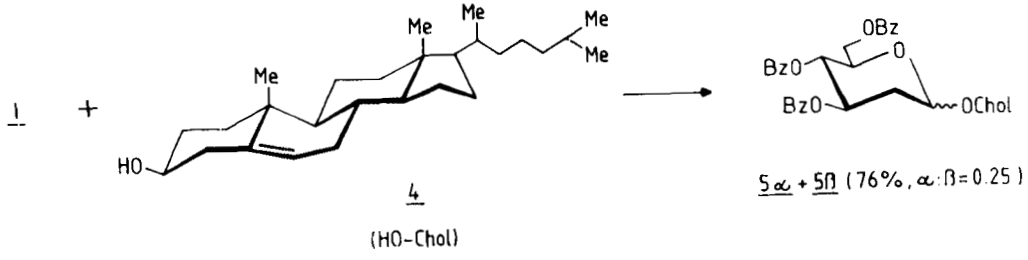




We have previously demonstrated that silver zeolite is a useful promoter for the synthesis of β-D-mannopyranosides from α-D-mannopyranosyl halides carrying a non-participating 2-substituent.[7] An obvious extension of this work is the use of the same promoter in the synthesis of β-D- (β-L-) 2-deoxypyranosides since no participation may occur from the 2-position. In the present paper we present an examination of this possibility.

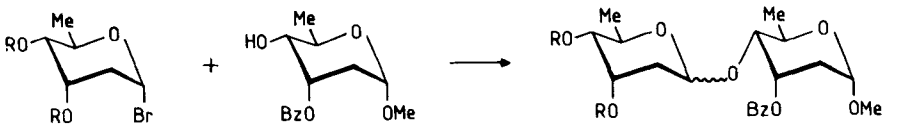
The results obtained are shown in the schemes. Starting from benzoylated β-D-glycosyl bromides, the yields of glycosides isolated varied from 54 to 84% and the α:β ratio from 0.25 to 1.18. In some reactions, the simultaneous formation of α-D-2,3-dideoxy-hex-2-enopyranosides was observed. The stereoselectivity would seem to be better in the 2-deoxy-*arabino*-hexopyranosyl series than in the corresponding *ribo* series. In the latter, the higher yields and stereoselectivity appear to be given by the benzoylated glycosyl bromides rather than by the acetylated ones.

The easy availability of the glycosyl donors described here, should make this method a useful addition to the existing ones for the synthesis of 2-deoxy-β-D- (β-L-) hexopyranosides.

EXPERIMENTAL

General methods. Concentrations were performed under vacuum at a bath temperature below 40 °C. Reactions were monitored by TLC on silica gel foils FG_{254} (Merck). The spots were visualised with UV light and otherwise by spraying with sulfuric acid and charring. Preparative TLC was performed using "Fertigplatten" silica gel 60 F_{254} of 0.25 and 0.5 mm thickness (Merck). Silica gel 60 (Merck) was used for column chromatography, normally operated in the flash mode.[8] Optical rotations were recorded at 589 nm in 10 cm cuvettes at 20-22 °C using Perkin-Elmer 241 and 243 polarimeters. ^{1}H NMR spectra were recorded using Bruker WH 270 (270 MHz), WA 300 (300 MHz), and WM 400 (400 MHz) instruments. ^{13}C NMR spectra were recorded on a JEOL JNM FX 100 instrument (25 MHz). ^{1}H and ^{13}C NMR data recorded for all new compounds were invariably in accordance with the postulated structures and are available (from J.T.) upon request.

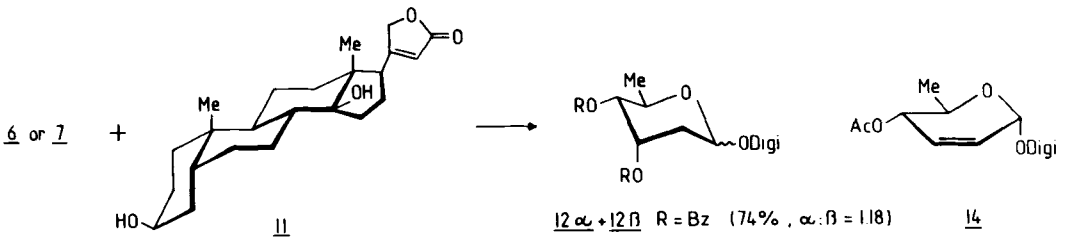
1,2:3,4-Di-O-isopropylidene-6-O-(3,4,6-tri-O-benzoyl-2-deoxy-α- and β-D-*arabino*-hexopyranosyl)-α-D-galactopyranose (3α and 3β). A solution of bromide 1[9] (540 mg, 1.0 mmol) and alcohol component 2 (130 mg, 0.5 mmol) in dichloromethane (10 ml) was stirred with silver zeolite (1.0 g) at room temperature in the dark, under rigorous exclusion of moisture for 5 h. Following dilution with dichloromethane and filtration, the solution was washed with sodium hydrogencarbonate, dried ($MgSO_4$), filtered and concentrated. Separation and purification of the products was done by means of silica gel chromatography (toluene -ethyl acetate 6:1) to give 3α (79 mg, 23%) and 3β (220 mg, 61%). Compound 3α had $[\alpha]_D$ +34° (c 0.8, CH_2Cl_2). ^{13}C NMR data ($CDCl_3$): δ 97.0 (C-1'), $J_{C1',H1'}$ 170.9 Hz.



6 R = Bz
7 R = Ac

8

9α + 9β R = Bz (54%, α:β = 1.16)
10α + 10β R = Ac (52%, α:β = 2.30)



11
(HO-Digi)

12α + 12β R = Bz (74%, α:β = 1.18)
13α + 13β R = Ac (41%, α:β = 1.0)

14

15 R = Bz
16 R = Ac

17

^{1}H NMR data (400 MHz, C_6D_6): δ 4.85 (dd, 1 H, $J_{1',2'ax}$ 3.5 Hz, $J_{1',2'eq}$ 1.0 Hz, H-1'). Compound 3β had $[\alpha]_D$ -37° (c 1.5, CH_2Cl_2), ^{13}C NMR data ($CDCl_3$): δ 100.3 (C-1'), $J_{C1',H1'}$ 158.7 Hz. ^{1}H NMR data (400 MHz, C_6D_6): δ 4.45 (dd, 1 H, $J_{1',2'ax}$ 9.5 Hz, $J_{1',2'eq}$ 1.7 Hz, H-1').

Cholesterin-3-yl 3,4,6-tri-O-benzoyl-2-deoxy-α- and -β-D-arabino-hexopyranoside (5α and 5β). A solution of bromide 1[9] (540 mg, 1.0 mmol) and alcohol component 4 (193 mg, 0.5 mmol) was treated with silver zeolite (1.0 g) for 48 h and then worked up as described above. Separation and purification of the products by means of silica gel chromatography (toluene) yielded 5α (63 mg, 15%) and 5β (257 mg, 61%) which both crystallised from methanol - dichloromethane. Compound 5α had m.p. 214-216 °C, $[\alpha]_D$ +40° (c 1.0, CH_2Cl_2), ^{13}C NMR ($CDCl_3$): δ 95.0 (C-1'). ^{1}H NMR (400 MHz C_6D_6): δ 4.92 (dd, 1 H, $J_{1',2'ax}$ 3.0 Hz, $J_{1',2'eq}$ 1.0 Hz, H-1'). Compound 5β had m.p. 182-184 °C, $[\alpha]_D$ -42° (c 0.6, CH_2Cl_2), ^{13}C NMR ($CDCl_3$): δ 98.1 (C-1'). ^{1}H NMR (400 MHz, C_6D_6): δ 4.51 (dd, 1 H, $J_{1',2'ax}$ 9.2 Hz, $J_{1',2'eq}$ 1.7 Hz, H-1').

Anal. Calcd. for $C_{54}H_{68}O_8$ (845.1): C, 76.7; H, 8.11. Found for 5α: C, 75.9; H, 7.99. Found for 5β: C, 76.4; H, 8.08.

3,4-Di-O-benzoyl-α-D-ribo-2,6-dideoxy-hexopyranosyl bromide (6). A solution of 1,3,4-tri-O-benzoyl-β-D-ribo-hexopyranose (115 mg, 0.25 mmol) in dry benzene (2.5 ml) was treated with trimethylsilyl bromide (0.067 ml, 0.5 mmol) for 1 h at room temperature. Following freeze-drying, the residue was coevaporated twice with dry benzene. The slightly yellow, labile syrupy product was used immediately in the next reaction step. The NMR data of 6 were identical to those reported.[10]

Methyl 3-O-benzoyl-2,6-dideoxy-α-D-ribo-hexopyranoside (8). A solution of methyl α-D-digitoxoside[11] (200 mg, 1.23 mmol) and trimethyl orthobenzoate (674 mmol, 8.4 mmol) in dry tetrahydrofuran (8 ml) was stirred at room temperature for 10 min. After the addition of a small amount of p-toluenesulfonic acid, stirring was continued for 12 h. Water (0.5 ml) and sodium hydrogencarbonate were added to give a slightly basic mixture. This was diluted with ethyl acetate. The organic layer was washed twice with water, dried ($MgSO_4$), filtered and concentrated. The product was purified by silica gel column chromatography (hexane -ethyl acetate 3:1) to give a colourless syrup (272 mg, 83%) consisting of a mixture of 8 and the isomeric 4-O-benzoate in a ratio of 2:1 (from ^{1}H NMR). The syrup partly crystallised at room temperature and the crystals were washed with hexane to yield 8 (122 mg, 37%). A second crystallisation of the mother liquor gave an additional amount of 8 (58 mg, 17%). Compound 8 had m.p. 91-92 °C, $[\alpha]_D$ +17° (c 1.0, ethyl actetate), ^{1}H NMR data (400 MHz, C_6D_6): δ 1.36 (d, 3 H, $J_{5,6}$ 6.3 Hz, H-6), 1.47 (ddd, 1 H, $J_{1,2ax}$ 4.5 Hz, H-2_{ax}'), 1.87 (d, 1 H, $J_{4,4\text{-OH}}$ 7.0 Hz, 4-OH), 2.09 (ddd, 1 H, $J_{1,2eq}$ 9.6 Hz, H-2_{eq}'),4.39 (dd, 1 H, H-1).

Anal. Calcd. for $C_{14}H_{18}O_5$ (266.3): C, 63.2; H, 6.81. Found: C, 63.3; H, 6.82.

Methyl 3-O-benzoyl-4-O-(3,4-di-O-benzoyl-2,6-dideoxy-α- and β-D-ribo-hexopyranosyl)-2,6-dideoxy-α-D-ribo-hexopyranoside (9α and 9β). A solution of bromide 6 (100 mg, 0.24 mmol) and alcohol component 8 (30 mg, 0.11 mmol) in dichloromethane (3 ml) was treated with silver zeolite (100 mg) for 12 h and then worked up as described above. Separation and purification of the products was done by means of silica gel chromatography (toluene -ethyl acetate 5:1). The fastest moving-fraction contained methyl 3-O-benzoyl-4-O-(4-O-benzoyl-2,3,6-trideoxy-α-D-erythro-hex-2-enopyranosyl)-2,6-dideoxy-α-D-ribo-hexopyranoside 15 (9.5 mg, 18%), $[\alpha]_D$ +167° (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, 3 H, $J_{5',6'}$ 6.3 Hz, H-6'), 1.34 (d, 3 H, $J_{5,6}$ 6.2 Hz, H-6), 4.88 (dd, 1 H, $J_{1,2ax}$ 4.0 Hz, $J_{1,2eq}$ 0.8 Hz, H-1), 5.27 (ddd, 1 H, $J_{1',2'}$ 1.0 Hz, $J_{1',3'}$ 2.6 Hz, $J_{1',4'}$ 1.6 Hz, H-1'). The second fraction contained 9β (16.4 mg, 25%), amorphous material, softening range 57-62 °C, $[\alpha]_D$ +166° (c 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (d, 3 H, $J_{5',6'}$ 6.3 Hz), H-6'), 1.29 (d, 3 H, $J_{5,6}$ 6.3 Hz, H-6), 4.70 (dd, 1 H, $J_{1,2ax}$ 4.0 Hz, $J_{1,2eq}$ 1.0 Hz, H-1), 5.04 (dd, $J_{1',2'ax}$ 9.4 Hz, $J_{1',2'eq}$ 2.0 Hz, H-1'). The third fraction contained 9α (19.3 mg, 29%), amorphous material, softening range 49-52 °C, $[\alpha]_D$ + 191° (c 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24

(d, 3 H, $J_{5',6'}$ 6.4 Hz, H-6'), 1.37 (d, 3 H, $J_{5,6}$ 6.2 Hz, H-6), 4.75 (dd, 1 H, $J_{1,2ax}$ 4.4 Hz, $J_{1,2eq}$ 1.0 Hz, H-1), 5.15 (d, 1 H, $J_{1',2'a}$ 3.2 Hz, $J_{1',2'e}$ 2.2 Hz, H-1').

Methyl 4-O-(3,4-di-O-acetyl-2,6-dideoxy-α- and -β-D-ribo-hexopyranosyl)-3-O-benzoyl-2,6-dideoxy-α-D-ribo-hexopyranoside (10α and 10β). A solution of bromide 7[10] (107 mg, 0.36 mmol) and alcohol component 8 (50 mg, 0.18 mmol) in dichloromethane (4 ml) was treated with silver zeolite (100 mg) first at -40 °C, then at room temperature for 24 h and subsequently worked up as described above. Separation and purification of the products by means of TLC (hexane -ethyl acetate 2:1, 2 developments) gave methyl 4-O-(4-O-acetyl-2,3,6-trideoxy-α-D-erythro-hex-2-enopyranosyl)-3-O-benzoyl-2,6-dideoxy-α-D-ribo-hexopyranoside (16, 30 mg, 40%), $[\alpha]_D$ +147° (c 1.3, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (d, 3 H, $J_{5',6'}$ 6.2 Hz, H-6'), 1.30 (d, 3 H, $J_{5,6}$ 6.2 Hz, H-6), 1.96 (s, 3 H, OAc), 4.77 (dd, 1 H, $J_{1,2ax}$ 4.2 Hz, $J_{1,2eq}$ 0.8 Hz, H-1), 5.23 (ddd, 1 H, $J_{1',2'}$ 1.3 Hz, $J_{1',3'}$ 2.8 Hz, $J_{1',4'}$ 1.6 Hz, H-1').

Anal. Calcd. for $C_{22}H_{28}O_8$ (420.5): C, 62.9; H, 6.71. Found: C, 62.9; H, 6.78.

Also obtained was 10α (27 mg, 31%), $[\alpha]_D$ 172 ° (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, 3 H, $J_{5',6'}$ 6.3 Hz, H-6'), 1.39 (d, 3 H, $J_{5,6}$ 6.2 Hz, H-6), 1.86 and 2.01 (both s, both 3 H, 2 OAc), 4.77 (dd, 1 H, $J_{1,2ax}$ 4.1 Hz, $J_{1,2eq}$ 0.8, H-1), 5.10 (dd, 1 H, $J_{1',2'ax}$ 4.0 Hz, $J_{1',2'eq}$ 1.0 Hz, H-1')

Anal. Calcd. for $C_{24}H_{32}O_{10}$ (480.5): C, 60.0; H, 6.71. Found: C, 60.0; H, 6.73.

Another fraction contained 10β: (18 mg, 21%, containing a 25% contamination by 10α). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.06 (d, 3 H, $J_{5',6'}$ 6.2 Hz, H-6'), 1.27 (d, 3 H, $J_{5,6}$ 6.2 Hz, H-6'), 1.95 and 2.07 (both s, both 3 H, 2 OAc), 4.69 (dd, $J_{1,2ax}$ 3.8 Hz, $J_{1,2eq}$ 0.8 Hz, H-1), 4.87 (dd, 1 H, $J_{1',2'ax}$ 9.3 Hz, $J_{1',2'eq}$ 3.0 Hz, H-1').

Digitoxigenin-3-yl 3,4-di-O-benzoyl-2,6-dideoxy-α- and β-D-ribo-hexopyranoside (12α and 12β). A solution of bromide 6 (420 mg, 1.0 mmol) and digitoxigenin (11, 187 mg, 0.5 mmol) in dichloromethane (10 ml) was treated with silver zeolite (1.0 g) for 30 min, and then worked up as described above after first having added a few drops of 2,4,6-trimethylpyridine to the reaction mixture. Separation and purification of the products by means of TLC (toluene - ethyl acetate 3:1, 3 developments) gave 12α (142 mg, 40%), $[\alpha]_D$ +107° (c 1.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 1.24 (d, 3 H, $J_{5',6'}$ 6.3 Hz, H-6'), 5.05 (dd, 1 H, $J_{1',2'ax}$ 3.4 Hz, $J_{1',2'eq}$ 2.1 Hz, H-1'). Also obtained was 12β (120 mg, 34%), $[\alpha]_D$ +73° (c 0.7, CH_2Cl_2). ^{1}H NMR (400 MHz $(CD_3)_2CO$): δ 1.26 (d, 3 H, $J_{5',6'}$ 6.2 Hz, H-6'), 5.21 (dd, 1 H, $J_{1',2'ax}$ 9.2 Hz, $J_{1',2'eq}$ 2.2 Hz, H-1').

Anal. Calcd. for $C_{43}H_{52}O_9$ (712.9): C, 72.5; H, 7.35. Found for 12α: C, 71.7; H, 7.60. Found for 12β: C, 73.0; H, 7.53.

Digitoxigenin 3-yl 3,4-di-O-acetyl-2,6-dideoxy-α- and β-D-ribo-hexopyranoside (13α and 13β). A solution of bromide 7[10] (107 mg, 0.36 mmol) and digitoxi-

genin (11, 70 mg, 0.18 mmol) in dichloromethane -nitromethane - toluene 1:1:2, 4 ml) was treated with silver zeolite (370 mg) first at -40 °C, then at room temperature for 24 h and subsequently worked up as described above. Separation and purification of the products by means of silica gel chromatography (hexane - ethyl acetate 1:1) gave digitoxigenin-3-yl 4-O-acetyl-2,3,6-trideoxy-α-D-erythro-hex-2-enopyranoside (14, 50 mg, 53%) m.p. 85-87 °C, $[\alpha]_D$ 62° (c 3.0, $CHCl_3$).[12] Also obtained were 13α and 13β (43 mg, 41%) as a 1:1 mixture (according to ^1H NMR). For a previous preparation as well as ^{13}C and ^1H NMR data for 13α, 13β and 14, see references 12 and 13.

Methyl 4-O-(3-O-acetyl-2,3,6-trideoxy-α-D-erythro-hexopyranosyl)-3-O-benzoyl-2,6-dideoxy-α-D-ribo-hexopyranoside (17). A solution of 15 (18 mg, 0.04 mmol) in ethanol (1.5 ml) was stirred with a small amount of 10% palladium on charcoal in a hydrogen atmosphere for 24 h. The mixture was filtered through celite and concentrated. Purification by means of TLC (hexane - ethyl acetate 3:1, 2 developments) gave 17 (13 mg, 72%), $[\alpha]_D$ +181° (c 0.3,$CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, 1 H, $J_{5',6'}$ 6.2 Hz, H-6'), 1.35 (d, 1 H, $J_{5,6}$ 6.2 Hz, H-6), 3.44 (s, 3 H, OAc), 4.76 (dd, 1 H, $J_{1,2ax}$ 4.0 Hz, $J_{1,2eq}$ 0.8 Hz, H-1), 5.07 (dd, $J_{1',2'ax}$ 3.0 Hz, $J_{1',2'eq}$ 0.8 Hz, H-1').
Anal. Calcd. for $C_{22}H_{32}O_{10}$ (422.5): C, 62.6; H, 7.16. Found C, 62.4; H, 7.20.

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