ORGANIC LETTERS

2000
Vol. 2, No. 13
1839−1842

β-Glycosides of 2,3-Diazido-2,3-dideoxy-D-mannose, a Synthetic Precursor of a Rare Bacterial Cell-Wall Building Unit†

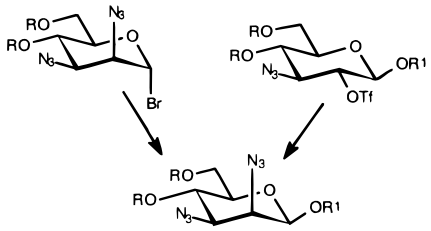
Zoltán Szurmai,*,‡,§,|| János Rákó,§ Károly Ágoston,§ Alain Danan,‡ and Daniel Charon‡

Equipe "Endotoxines" du C.N.R.S. (U.R.A. 1116), Université de Paris-Sud, Centre d'Etudes Pharmaceutiques, 92296 Châtenay-Malabry, France, and Institute of Biochemistry, Faculty of Sciences, University of Debrecen, P.O. Box 55, H-4010 Debrecen, Hungary

szurmaiz@tigris.klte.hu

Received April 4, 2000

ABSTRACT



2,3-Diazido-2,3-dideoxy-β-D-mannopyranoside derivatives were synthesized in order to prepare β-glycosides of 2,3-diacetamido-2,3-dideoxy-D-mannuronic acid, a rare moiety of bacterial oligosaccharides. A direct glycosyl donor, 4,6-di-*O*-acetyl-2,3-diazido-2,3-dideoxy-α-D-mannopyranosyl bromide, was prepared, and its synthetic capacity was tested in glycosylation reactions. An indirect route was also elaborated: 3-azido-3-deoxy-β-D-glucopyranosides were converted into β-D-mannopyranosides. The *cis vicinal* diazido function successfully tolerated the conditions of mild acidic hydrolysis, tritylation, Jones oxidation, TEMPO oxidation, acetolysis, and bromination with $TiBr_4$.

2,3-Diacetamido-2,3-dideoxy-D-mannuronic acid is a constituent of the cell-wall of microorganisms[1,2] where it is linked by a β-glycosidic bond to another monosaccharide unit. To prepare bacterial oligosaccharides containing this rare mannuronic unit—bearing in mind the difficulties inherent in 1,2-*cis* glycosylations—we investigated the synthetic methods which would lead to a 2,3-diacetamido-β-mannosidic linkage.

Despite the fact that many new highly effective glycosylation methods have been elaborated over the past two decades,[3−6] β-mannosylation is still a challenge in carbohydrate chemistry.[7,8] 2-Acetamido-2-deoxy-β-mannosides as natural compounds have been synthesized rather frequently,[9−13]

† Dedicated to Professor András Lipták on the occasion of his 65th birthday.

‡ Université de Paris-Sud.

§ University of Debrecen.

|| Address correspondence to this author at the University of Debrecen. Fax: (36)-52-512913.

(1) Caroff, M.; Lebbar, S.; Szabó, L. XIVth International Carbohydrate Symposium, Stockholm, Sweden, 1988; Abstract A 22.

(2) Knirel, Y. A.; Vinogradov, E. V.; Shashkov, A. S.; Dmitrijev, B. A.; Kochetkov, N. K. *Carbohydr. Res.* **1982**, *104*, C4−C7.

(3) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−173.

(4) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235.

(5) Sinaÿ, P. *Pure Appl. Chem.* **1991**, *63*, 519−528.

(6) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531.

(7) Kaji, E.; Lichtenthaler, F. W. *Trends Glycosci. Glycotechnol.* **1993**, *5*, 121−142.

(8) Barresi, F.; Hindsgaul, O. *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neill, R. A., Eds.; Harwood Academic Publishers: 1996; pp 251−276.

(9) David, S.; Malleron, A.; Dini, C. *Carbohydr. Res.* **1989,** *188*, 193−200.

(10) Paulsen, H.; Lorentzen, J. P. *Carbohydr. Res.* **1984**, *133*, C1−C4. Paulsen, H.; Lorentzen, J. P. *Carbohydr. Res.* **1986**, *150*, 63−90.

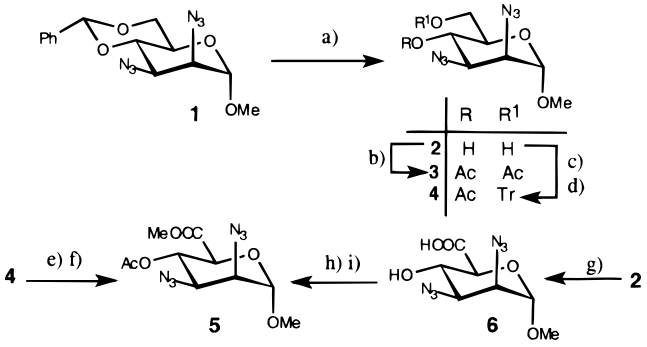
10.1021/ol0058893 CCC: $19.00
Published on Web 06/01/2000

but to our best knowledge, there is no method in the literature for the preparation of β-linked 2,3-diacetamido-*manno* derivatives. For this reason, we report the synthesis and the synthetic capacity of 4,6-di-*O*-acetyl-2,3-diazido-2,3-dideoxy-α-D-mannopyranosyl bromide, a halide capable of forming 1,2-*cis* glycosides. On the other hand, we show an indirect route via 3-azido-3-deoxy-β-D-glucopyranosides, which have been converted into the target compounds.

For the synthesis of 2,3-diacetamido-2,3-dideoxy-β-D-mannopyranoside derivatives, mannosyl bromide **8** was prepared as a "direct" glycosyl donor. The key compound in the reaction sequence was methyl 2,3-diazido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannopyranoside (**1**) which was synthesized from methyl α-D-glucopyranoside on a relatively large scale according to the slightly modified method of Guthrie and Murphy.[14,15]

Compound **1** was hydrolyzed, and the resulting methyl 2,3-diazido-2,3-dideoxy-α-D-mannopyranoside (**2**) was conventionally acetylated into **3**. Compound **1** was also converted in three steps (via **2**) into methyl (methyl 4-*O*-acetyl-2,3-diazido-2,3-dideoxy-α-D-mannopyranosid)uronate (**5**) by Jones oxidation of the corresponding 6-*O*-trityl derivative (**4**).[16] The structure of **5** was ascertained by its ^{1}H NMR spectrum in which the singlet of COOMe (3.77 ppm) and the doublet of H-5 were clearly identified. With the aim of obtaining a derivative of diamino mannuronic acid, which could be a convenient acceptor for further glycosylation, the diol (**2**) was selectively oxidized at the C-6 hydroxy group with sodium hypochlorite and catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under phase transfer conditions.[17] The free acid (**6**) was obtained crystalline with an isolated yield of 73%. Upon esterification with methanol and subsequent acetylation, it led to **5**, identical with the product obtained by Jones oxidation (Scheme 1).

Scheme 1[a]

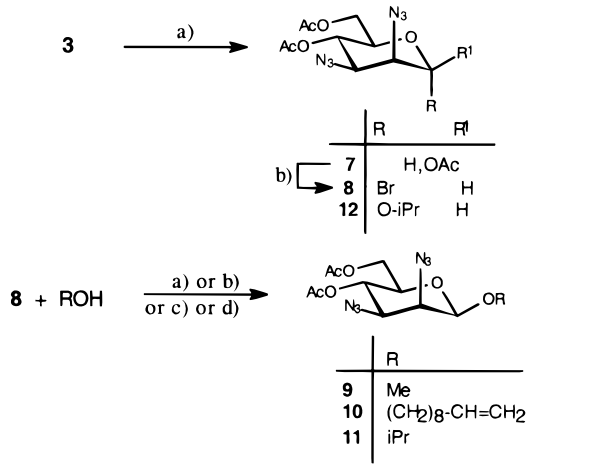


[a] (a) 60% AcOH, 94%; (b) Py, Ac_2O, 91%; (c) Py, TrCl; (d) Py, Ac_2O, 55% for two steps; (e) CrO_3, H_2SO_4, CH_2Cl_2/acetone; (f) Bu_4NBr, MeI, CH_2Cl_2/H_2O, 79% for two steps; (g) TEMPO, NaOCl, 73%; (h) MeOH, H^+, resin; (i) Py, Ac_2O, 94% for two steps.

Acetolysis of the glycosidic methyl group in compound **3** afforded the corresponding 1-*O*-acetate (**7**). The reaction of **7** with $TiBr_4$ (2 equiv) in dry CH_2Cl_2 at room temperature gave glycosyl donor **8**. The potentiality of uronide **5** to lead to uronyl donor was actively tested but without success; therefore only bromide **8** was used as glycosyl donor. The reaction of bromide **8** with methanol, 9-decen-1-ol, and 2-propanol in the presence of Ag-silicate in dry CH_2Cl_2 exclusively yielded β-anomers (**9**, **10**, and **11**), respectively. The β-anomeric configurations were clearly demonstrated by the $[\alpha]_D$ values and the NMR data. In the ^{13}C NMR spectra, the $J_{C-1,H-1}$ values were in the range of 157−158 Hz, respectively.

Surprisingly, when the $HgBr_2$ promoter was used in dry CH_2Cl_2, and either methanol or 2-propanol was present in excess, the observed β:α ratios were 20:1 and 10:1 (by TLC), respectively. The reaction of compound **8** with 2-propanol in the presence of $Hg(CN)_2$ still gave the β-mannoside (**11**) as the main product. These experiments showed that the coupling of bromide **8** with reactive aglycons yielded mainly β-mannosides. If the promoters were effective enough and the nucleophiles were present in extremely high quantities, the reaction had an S_N2 character producing 1,2-*cis* glycosidic linkages. Decreasing the activity of the promoters [Ag-silicate → $HgBr_2$ → $Hg(CN)_2$] the β:α selectivity also decreased (Scheme 2).

Scheme 2[a]



[a] (a) Ac_2O, H_2SO_4, 80%; (b) $TiBr_4$, CH_2Cl_2, 90%; (c) Ag-silicate, CH_2Cl_2, 76−82%; (d) $HgBr_2$, CH_2Cl_2, 4 Å, 70−79%; (e) $Hg(CN)_2$, toluene/$MeNO_2$, 33%.

The availability of bromide **8** was tested by its reaction with **13**,[18] as a model compound, using different promoters.

(11) Micheli, E.; Nicotra, F.; Panza, L.; Ronchetti, F.; Toma, L. *Carbohydr. Res.* **1985**, *139*, C1−C3.

(12) Classon, B.; Garegg, P. J.; Oscarson, S.; Tidén, A.-K. *Carbohydr. Res.* **1991**, *216*, 187−196.

(13) Kaji, E.; Lichtenthaler, F. W.; Osa, Y.; Takahashi, K.; Matsui, E.; Zen, S. *Chem. Lett.* **1992**, 707−710.

(14) Guthrie, R. D.; Murphy, D. *J. Chem. Soc.* **1965**, 5288−5294 .

(15) Guthrie, R. D.; Murphy, D. *J. Chem. Soc.* **1965**, 6956−6960.

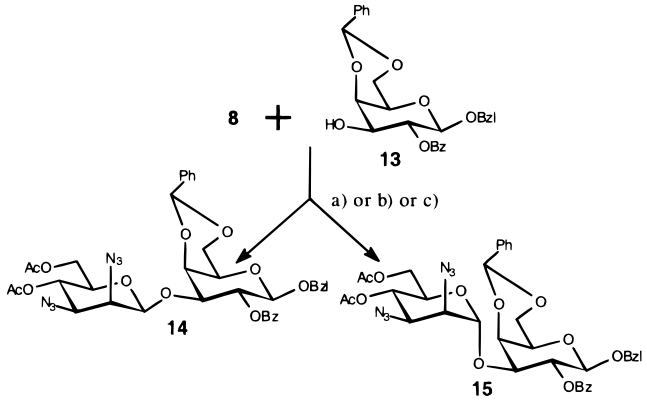
(16) Steffan, W.; Vogel, C.; Kristen, H. *Carbohydr. Res.* **1990**, *204*, 109−120.

(17) Davis, N. J.; Flitsch, S. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 359−368.

(18) Chittenden, G. J. F.; Buchanan, J. G. *Carbohydr. Res.* **1969**, *11*, 379−385.

Ag-silicate or $HgBr_2$ yielded a mixture of the corresponding disaccharides (**14** and **15**), with opposite β:α selectivity (7:2 and 1:2). In the case of Ag-triflate, only the α-disaccharide (**15**) was obtained in 80% yield. The configurations of the interglycosidic linkages were determined by the $[\alpha]_D$ values and NMR data. The $J_{C-1',H-1'}$ values were 173 Hz for the α-disaccharide (**15**) and 162 Hz for the β-one (**14**) (Scheme 3).

Scheme 3[a]

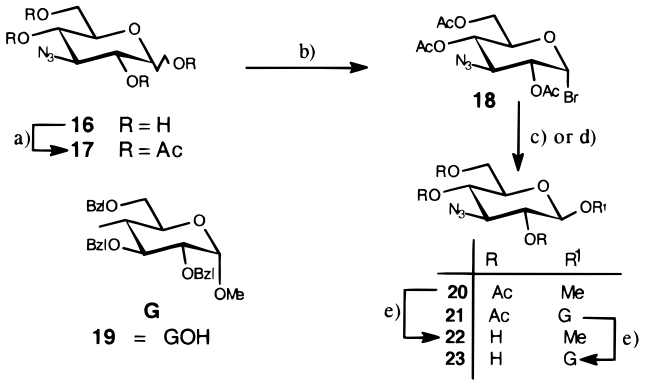


[a] (a) Ag-silicate, CH_2Cl_2, β:α = 7:2; (b) $HgBr_2$, CH_2Cl_2, 4 Å β:α = 1:2; (c) AgOTf, CH_2Cl_2/toluene, 4 Å only α.

From the above results it is predictable that mannosyl bromide **8** cannot be used as a glycosyl donor to undertake the stereoselective synthesis of complex oligosaccharides. However, it can be of great use in preparing the simple glycosides of 2,3-diacetamido-2,3-dideoxy-D-mannuronic acid.

To overcome the difficulties inherent in the "direct" method, an "indirect" synthetic route was also elaborated (Scheme 4). According to the literature, 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**16**)[19] was

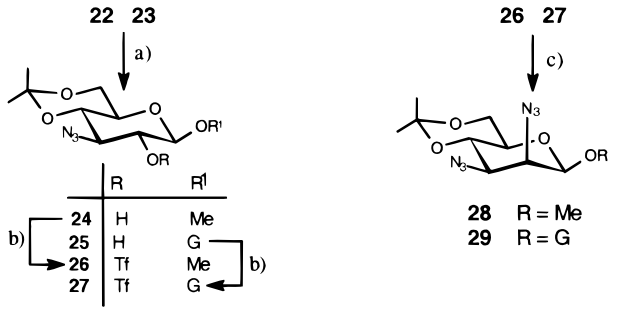
Scheme 4[a]



[a] (a) Py, Ac_2O, 94%; (b) $TiBr_4$, CH_2Cl_2, 91%, %; (c) $HgBr_2$, CH_2Cl_2, 4 Å, 92%; (d) AgOTf, CH_2Cl_2/toluene, 4 Å, 88%; (e) NaOMe, MeOH, 84−88%.

prepared from D-glucose in a five-step reaction sequence. Acidic hydrolysis (→ **16**) followed by conventional acetylation (→ **17**) and then bromination with $TiBr_4$ (2 equiv) gave α-bromide **18**, which was reacted with methanol and unreactive glucose derivative **19** to give compounds **20** and **21**, separately. The donor's neighboring-group-active acyloxy substituent on C-2 governed the stereospecific formation of the β-D-glucosides. In the case of compound **19**, the highly effective silver triflate promoter assured that disaccharide **21** would be obtained in high yield. Deacylation (**20** → **22** and **21** → **23**) followed by isopropylidenation (**22** → **24** and **23** → **25**) yielded the key 2-OH compounds, suitable for changing the configurations on C-2. Thus, compounds **24** and **25** were reacted with trifluoromethanesulfonic anhydride and then converted into the diazido β-mannosides (**24** → **26** → **28** and **25** → **27** → **29**) in good yields (Scheme 5). All

Scheme 5[a]



[a] (a) 2,2-Dimethoxypropane, pTsOH, 85−92%; (b) Py, Tf_2O; (c) NaN_3, DMF, 78−84% for two steps.

compounds gave satisfactory microanalytical and/or spectroscopic data.[20]

(19) Brimacombe, J. S.; Bryan, J. G. H.; Husain, A.; Stacey, M.; Tolley, M. S. *Carbohydr. Res.* **1967**, *3*, 318−324.

(20) Compound **3**: mp 83 °C (from EtOH); $[\alpha]_D$ +111.7° (*c* 0.80 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.77 (s, 1 H, H-1), 3.43 (s, 3 H, OMe); ^{13}C NMR δ 98.1 (C-1, $J_{C-1,\ H-1}$ 172 Hz). Compound **5**: mp 100−101 °C (EtOH); $[\alpha]_D$ +122.1° (*c* 0.63 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.88 (d, 1 H, $J_{1,2}$ = 2.9 Hz, H-1), 4.24 (d, 1 H, $J_{4,\ 5}$ 8.3 Hz, H-5), 3.77 (s, 3 H, COOMe), 3.48 (s, 3 H, OMe). Compound **7**: $[\alpha]_D$ +59.3° (*c* 0.77 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.10 (d, 0.62 H, $J_{1,2}$ = 1 Hz, H-1α), 5.80 (bs, 0.38 H, H-1β). Compound **8**: ^1H NMR ($CDCl_3$) δ 6.42 (d, 1 H, $J_{1,2}$ = 1.4 Hz, H-1), 2.16 and 2.10 (2s, each 3 H, 2 OAc). Compound **9**: mp 115−117 °C (from EtOH); $[\alpha]_D$ −67.2° (*c* 0.95 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.56 (s, 1 H, H-1), 3.51 (s, 3 H, OMe); ^{13}C NMR δ 101.0 (C-1, $J_{C-1,H-1}$ = 158 Hz). Compound **10**: $[\alpha]_D$ −63.5° (*c* 0.70 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.62 (s, 1 H, H-1); ^{13}C NMR δ 100.08 (C-1, $J_{C-1,H-1}$ = 158 Hz). Compound **11**: $[\alpha]_D$ −86.4° (*c* 0.57 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.71 (d, 1 H, $J_{1,2}$ < 1 Hz, H-1); ^{13}C NMR δ 98.17 (C-1, $J_{C1,\ H-1}$ = 157 Hz). Compound **14**: $[\alpha]_D$ −11° (c 0.60 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.79 (bs, 1 H, H-1′), 4.59 (d, 1 H, $J_{1,2}$ = 7.8 Hz, H-1); ^{13}C NMR δ 99.60 (C-1, $J_{C-1,H-1}$ = 161 Hz) and 99.15 (C-1′, $J_{C-1',H-1'}$ = 162 Hz). Compound **15**: $[\alpha]_D$ +106° (*c* 0.28 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.98 (bs, 1 H, H-1′), 4.63 (d, 1 H, $J_{1,2}$ = 8.1 Hz, H-1); ^{13}C NMR δ 98.87 (C-1, $J_{C-1,H-1}$ = 61 Hz), 93.03 (C-1′, $J_{C-1',H-1'}$ = 173 Hz). Compound **18**: ^1H NMR ($CDCl_3$) δ 6.63 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1); ^{13}C NRM δ 87.00 (C-1), 61.27 (C-3), 60.88 (C-6). Compound **20**: $[\alpha]_D$ −15.4° (*c* 0.41 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.39 (d, 1 H, $J_{1,2}$ = 7.8 Hz, H-1), 3.50 (s, 3 H, OMe). Compound **21**: $[\alpha]_D$ −4.5° (c 0.24 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.57 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 4.38 (d, 1 H, $J_{1',2'}$ = 8.1 Hz, H-1′), 3.37 (s, 3 H, OMe); ^{13}C NMR δ 100.25 (C-1′) 98.43 (C-1), 67.43 (C-6), 64.17 (C-3′), 61.70 (C-6′), 55.43 (OMe). Compound **24**: $[\alpha]_D$ −19.8° (*c* 0.50 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.28 (d, 1 H, $J_{1,2}$ = 7.3 Hz, H-1), 3.56

In summary, it is obvious that both synthetic routes have their advantages and disadvantages. In the case of the direct one, different β-glycosides can be prepared using the same donor (**8**). Unfortunately, unreactive aglycons with high stereoselectivity cannot be mannosylated in good yields. From this point of view, the indirect[9,11,12,21−26] route is more useful; the *gluco*-donor's (**18**) neighboring-group-active substituent on C-2 allows the stereospecific construction of the β-glycosidic linkages. The crucial step of this sequence, namely changing the configuration of C-2, has been successfully carried out by nucleophilic substitution reactions. The only disadvantage is that the complete reaction sequence has to be accomplished for every target compound. The carboxylic function of the mannuronic moiety is introduced at a later stage of the synthesis by the $Pt-O_2$ system,[10] TEMPO oxidation,[17] or Jones oxidation, as was successfully shown for the conversion of methyloside **2** into methyl uronate **5**.

Acknowledgment. The authors thank Dr. Ladislas Szabó, Dr. Patricia Szabó, Dr. László Szilágyi, and Mrs. Michelle Mondange for their interest and help. Financial support from the French Government and, in part, from the Hungarian National Foundation (OTKA T015543) is gratefully acknowledged.

OL0058893

(s, 3 H, OMe); ^{13}C NRM δ 104.32 (C-1), 64.61 (C-3), 62.07 (C-6), 57.41 (OMe). Compound **25**: $[\alpha]_D$ +17.9° (*c* 0.18 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.53 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 4.48 (d, 1 H, $J_{1',2'}$ = 7.0 Hz, H-1′), 3.34 (s, 3 H, OMe); ^{13}C NMR δ 103.67 (C-1′) 98.26 (C-1), 68.41 (C-6), 64.62 (C-3′), 61.94 (C-6′), 55.29 (OMe). Compound **28**: $[\alpha]_D$ −53.9° (*c* 0.20 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.54 (d, 1 H, $J_{1,2}$ = 1.4 Hz, H-1), 3.57 (s, 3 H, OMe), 1.54 and 1.43 (2 s, each 3 H, 2Me); ^{13}C NMR δ 101.55 (C-1, $J_{C-1,H-1}$ = 159 Hz), 100.36 (Me-C-Me), 62.01 (C-6), 63.30 and 60.56 (C-2,3), 57.31 (OMe), 28.91 and 18.98 (2Me). Compound **29**: $[\alpha]_D$ −18.6° (*c* 0.29 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.68 (d, 1 H, $J_{1,2}$ = 3.4 Hz, H-1), 4.53 (bs, 1 H, H-1′), 3.46 (s, 3 H, OMe), 1.53 and 1.47 (2s, each 3 H, 2Me); ^{13}C NMR δ 100.61 (C-1′, $J_{C-1',H-1'}$ = 160 Hz), 100.07 (Me-C-Me), 98.31 (C-1, $J_{C-1,H-1}$ = 171 Hz), 68.02 (C-6), 61.82 (C-6′), 63.47 and 60.28 (C-2′and C-3′), 55.39 (OMe), 28.91 and 18.95 (2Me).

(21) Borén, H. B.; Ekborg, G.; Eklind, K.; Garegg, P. J.; Pilotti, Å.; Swahn, C. G. *Acta Chem. Scand.* **1973**, *27*, 2639−2644.
(22) Kochetkov, N. K.; Dmitriev, B. A.; Malysheva, N. N.; Chernyak, A. Y.; Klimov, E. M.; Bayramova, N. E.; Torgov, V. I. *Carbohydr. Res.* **1975**, *45*, 283−290.
(23) Warren, C. D.; Auge, C.; Laver, M.; Suzuki, S.; Power, D.; Jeanloz, R. W. *Carbohydr. Res.* **1980**, *82*, 71−83.
(24) Liu, K. K.-C.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 1892−1894.
(25) Alais, J.; David, S. *Carbohydr. Res.* **1990**, *201*, 69−77.
(26) Günther, W.; Kunz, H. *Carbohydr. Res.* **1992**, *228*, 217−241.