Stereodivergent Synthesis of D,D- and L,L-*glycero*-β-*allo*-Heptopyranoses on a Dioxanone Scaffold

Nagarjuna Palyam, Izabella Niewczas, Marek Majewski*

Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon, SK, S7N 5C9, Canada
Fax +1(306)9664730; E-mail: marek.majewski@usask.ca

Received: 05.06.2012; Accepted after revision: 20.07.2012

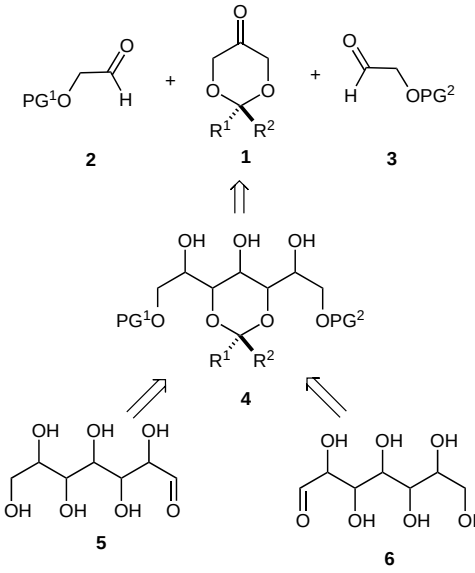
Abstract: We report a stereodivergent synthesis of both enantiomers of *glycero-allo*-heptose from 2,2-dimethyl-1,3-dioxan-5-one, a readily available nonchiral scaffold, and from two different synthetic equivalents of glyoxal: dimethoxyacetaldehyde and 1,3-dithiane-2-carboxaldehyde. The short synthetic sequence involves first a proline-mediated, and then a lithium enolate mediated aldol reaction at the α- and α′-positions of the dioxanone ring, respectively, and demonstrates the complementary nature of organocatalysis and metal enolate based methods.

Key words: aldol reaction, organocatalysis, carbohydrates, heterocycles, stereoselective synthesis

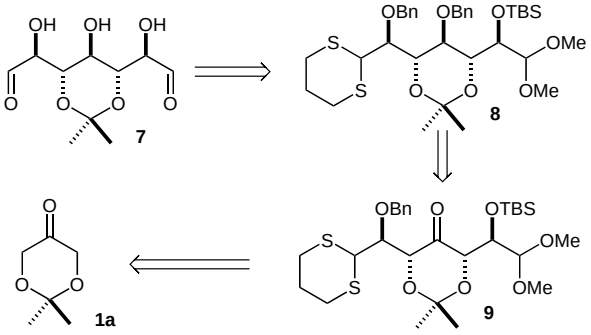
The use of symmetry in carbohydrate chemistry fascinated chemists for a long time and, over the years, manifested itself in elegant solutions to synthetic and analytical problems to mention only the classic intellectual *tour de force* known as Fischer's deduction of glucose stereochemistry.[1] During studies aimed at developing new approaches to the synthesis of higher carbohydrates we became attracted to the possibility of constructing both enantiomers of an odd-carbon higher sugar from one symmetrical precursor: 2,2-dialkyl-1,3-dioxan-5-one (**1**, dioxanone).[2] Thus an aldoheptose (**5** or **6**) could, in principle, be constructed from three building blocks: a dioxanone **1** and two different synthetic equivalents of glyoxal **2** and **3** (Scheme 1). Aldoheptoses are synthetic targets of interest and considerable literature exists on their isolation, synthesis, and biological significance.[3]

The sequence in which the two terminal hydroxyls in the key intermediate **4** are deprotected dictates which isomer of the carbohydrate will be produced. The control of stereochemistry rests in the choice of the method for discrimination between the two enantiotopic nucleophilic sites in the ketone (C4 or C6), the relative stereochemistry of both aldol reactions (*syn* or *anti*), and the disposition of both newly attached side chains on the ring (*cis* or *trans*). A combination of these elements such that **4** has C_S symmetry would lead to compounds **5** and **6** being enantiomers, that is, to a stereodivergent synthesis.

The utility of dioxanones as versatile synthetic building blocks has been demonstrated before.[2,4,5] Recently, we have reported on two consecutive aldol reactions involving these compounds.[4e] In the current project, aimed at a synthesis of D,D- and L,L-*glycero*-β-*allo*-heptoses following the strategy summarized in Scheme 1, we have focused our attention on compound **8** which is synthetically equivalent to the *meso*-dialdehyde **7** and should be accessible by reduction of the corresponding double aldol derivative **9** (Scheme 2).



Scheme 1 Aldoheptose–dioxanone retrosynthetic analysis

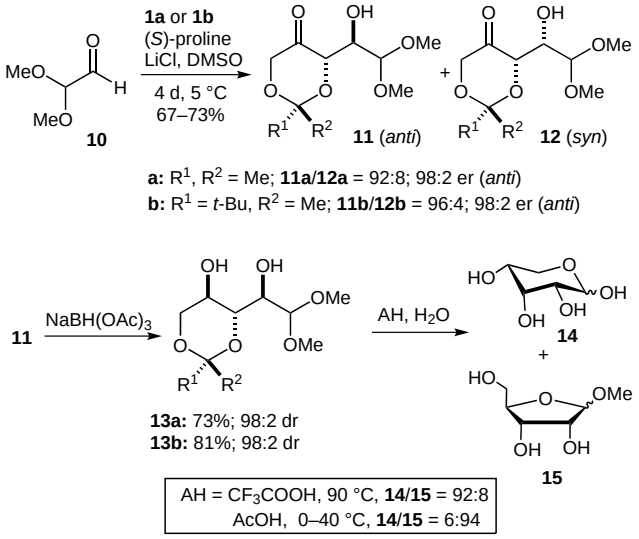


Scheme 2 Key intermediates – latent symmetry and retrosynthesis

Organocatalytic aldol reactions involving dioxanones and dimethoxyacetaldehyde, that is synthetically equivalent to a protected glyoxal (Scheme 1), have been reported before.[6] In our hands this reaction, catalyzed by (*S*)-proline, proceeded in good yield and high selectivity affording the *anti*-aldol **11** as the major product (Scheme 3). Compound **11** is a derivative of D-ribose, and in order to confirm the

SYNLETT 2012, 23, 2367–2370
Advanced online publication: 24.08.2012
DOI: 10.1055/s-0032-1290461; Art ID: ST-2012-S0479-L

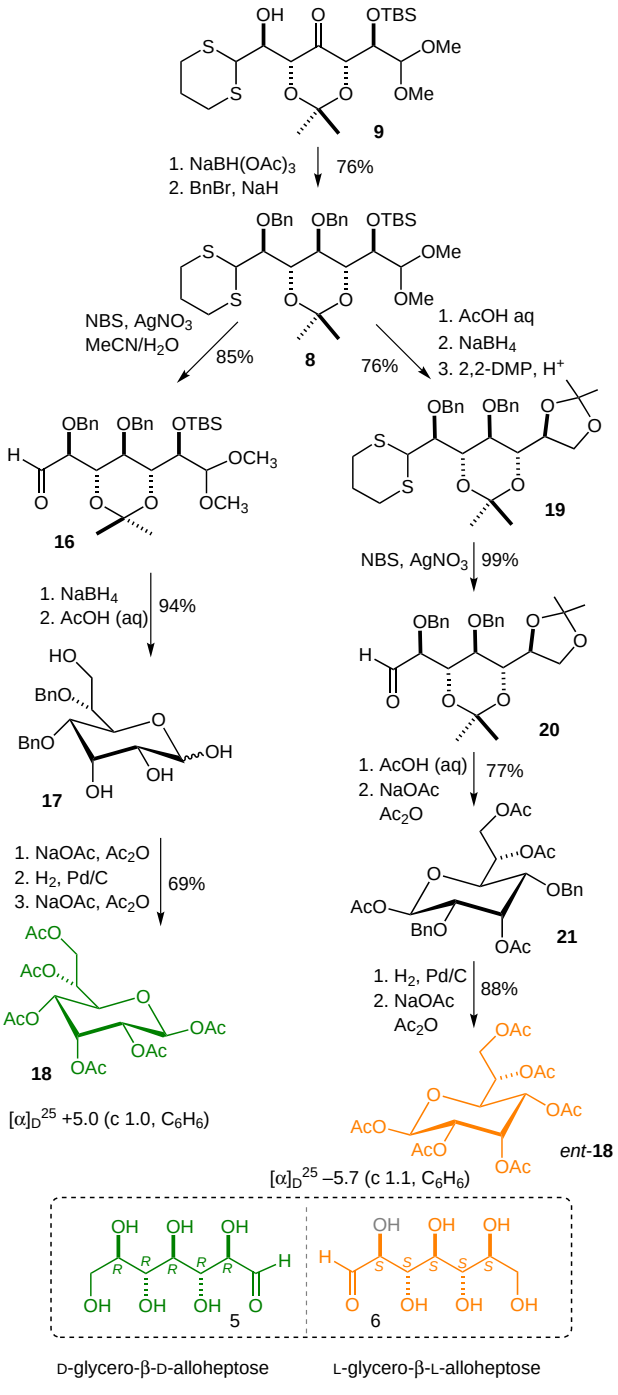
structure we have subjected this compound to reduction followed by hydrolysis. As expected, based on the literature precedents, the reduction gave selectively the *syn*-diol **13**.[6] Hydrolysis of the diol yielded selectively D-ribopyranose (**14**) or the corresponding methyl-D-ribofuranoside (**15**) in high yield depending on the reaction conditions (Scheme 3).



Scheme 3 Organocatalytic aldol reaction of dioxanones

Compound **8**, corresponding to the key intermediate **4** in Scheme 1, was synthesized from **11** via a sequence involving protection and LDA-mediated aldol addition to give the corresponding monoprotected bisaldol **9** followed by a reduction of the ketone carbonyl and benzylation using the methods described before.[4e] The unmasking of one of the two aldehyde groups embedded in compound **8** played the central role in carrying out the stereodivergent synthesis of both enantiomers of *glycero-allo*-heptose (Scheme 4). Dithiane hydrolysis of compound **8** using Corey's protocol (NBS/$AgNO_3$ in aq MeCN)[7] gave the corresponding aldehyde **16**. This compound was reduced to the corresponding alcohol and then both acetal groups as well as the *tert*-butyldimethylsilyl (TBS) group were removed by hydrolysis to give compound **17**. Acetylation followed by debenzylation and yet another acetylation afforded the hexaacetate of D-*glycero*-β-D-*allo*-heptopyranose (**18**) in 22% overall yield in eleven steps starting from dioxanone **1**.

A similar approach was applied in the synthesis of the L-enantiomer (*ent*-**18**, Scheme 4). Intermediate **8** was subjected to hydrolysis followed by $NaBH_4$-mediated reduction of the aldehyde intermediate and protection of the resulting tetraol moiety using 2,2-dimethoxypropane. The subsequent hydrolysis of the dithiane moiety in compound **19** gave the aldehyde **20** that was subjected to a 'one-pot' acid-catalyzed ketal deprotection–cyclization followed by acetylation to afford compound **21** (α/β = 14:86, 77% overall yield). Debenzylation followed by further acetylation gave the hexaacetate of L-*glycero*-β-L-*allo*-heptopyranose (*ent*-**18**) in 20% overall yield in 13 steps starting from dioxanone **1**. The opposite signs of optical rotation values of **18** and *ent*-**18** were observed, and the specific rotation value was in good agreement with that reported for D-*glycero*-D-*allo*-heptose.[3g] The identical ^1H and ^{13}C NMR spectroscopic data for both compounds confirmed the stereodivergent synthesis of the L,L- and D,D-isomers.



Scheme 4 Stereodivergent synthesis of *glycero-allo*-heptoses

In summary, both enantiomers of *glycero*-β-*allo*-heptopyranose (**18** and *ent*-**18**) were synthesized starting from the readily available dioxanone **1**. Further expansion of the

scope of this methodology into synthesis of sialic acids is under investigation.

Compound 11

2,2-Dimethoxyacetaldehyde (**2a**, 60% aq solution, 2.90 g, 16.9 mmol), (*S*)-proline (530 mg, 4.60 mmol), and LiCl (645 mg; 15.4 mmol) were added to a solution of **1a** (2.00 g, 14.4 mmol) in dry DMSO (5 mL). The resulting mixture was flushed with nitrogen, stirred at r.t. for 15 min to dissolve all the reactants and refrigerated at 5 °C until the reaction was complete as shown by TLC (ca. 72 h). A sat. NH_4Cl solution and EtOAc were added with vigorous stirring, the mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine. The organic phase was dried (Na_2SO_4) and concentrated to afford the crude product. The ratio of diastereomers was measured by ^{1}H NMR spectroscopy on the crude product and was found to be *anti*/*syn* = 92:8. Purification by flash column chromatography (hexane–EtOAc = 7: 3) provided the *anti*-aldol adduct **11** (2.4 g, 67%) as a pale yellow oil. The enantiomeric ratio (er) was measured by ^{1}H NMR spectroscopy in C_6D_6 with Eu(tfc)$_3$ as a shift reagent. $[\alpha]_D^{25}$ –134 (*c* 1.15, $CHCl_3$; 96% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.65 (d, *J* = 6.8 Hz, 1 H), 4.44 (dd, J_1 = 1.3 Hz, J_2 = 3.1 Hz, 1 H), 4.25 (dd, J_1 = 1.5 Hz, J_2 = 16.7 Hz, 1 H), 4.07 (dd, J_1 = 3.1 Hz, J_2 = 6.8 Hz, 1 H), 3.99 (d, *J* = 16.7 Hz, 1 H), 3.43 (s, 3 H), 3.38 (s, 3 H), 2.42 (br s, 1 H), 1.47 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.5, 103.4, 100.5, 76.3, 71.2, 67.1, 55.4, 54.3, 25.0, 23.0. HRMS (CI, NH_3): *m/z* calcd for $(C_{10}H_{18}O_6 + NH_4)^+$ $[M + NH_4]^{+*}$: 252.1447; found: 252.1451. LRMS (CI, NH_3): *m/z* (%) = 252 (20) $[M + 18]^+$, 238 (22), 220 (56), 206(44), 188 (70), 152 (100), 148 (28). IR (KBr): 3377, 1747 cm^{-1}.

Compound 8

A solution of *n*-BuLi (4.80 mL, 10.1 mmol, 2.1 M solution in hexanes, 3.3 equiv) was added dropwise to a stirred solution of diisopropylamine (1.57 mL, 11.1 mmol, 3.6 equiv) in THF (10 mL) at 0 °C under nitrogen. After 30 min, a solution of TBS-protected **11** (1.07 g, 3.07 mmol, 1.00 equiv) in THF (5 mL) was added slowly, and the mixture was stirred for 2 h at –78 °C. Dithiane carboxaldehyde (1.82 g, 12.3 mmol, 4.0 equiv) in dry THF (5 mL) was added, and the mixture was stirred at –78 °C for 30 min. The reaction was quenched with concentrated phosphate buffer (pH 7.5; 15 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were rinsed with sat. solution of $NaHCO_3$, NaCl, and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the diastereoselectivity of the reaction was determined by ^{1}H NMR spectroscopy on the crude product by integration of the peaks at δ = 3.43 and 3.35 ppm and was found to be *anti-anti-trans*/*anti-anti-cis* aldols = 9:91. The crude reaction mixture was fractionated by flash column chromatography (5–10% EtOAc in hexane) to give compound **9** as a colorless oil (1.33 g, 87%). $[\alpha]_D^{24}$ –3 (*c* 0.33, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.50 (d, *J* = 7.4 Hz, 1 H), 4.37–4.33 (m, 2 H), 4.31–4.27 (m, 1 H), 4.11–4.04 (m, 2 H), 3.73 (br s, 1 H), 3.39 (s, 3 H), 3.35 (s, 3 H), 3.20–3.10 (m, 2 H), 2.75–2.67 (m, 1 H), 2.64–2.56 (m, 1 H), 2.04–1.95 (m, 2 H), 1.50 (s, 3 H), 1.47 (s, 3 H), 0.84 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.8, 105.5, 98.9, 79.8, 77.9, 76.0, 74.4, 56.0, 55.9, 44.6, 28.9, 28.8, 28.4, 26.0, 25.9, 20.6, 18.3, –4.4, –4.5 ppm. HRMS (CI): *m/z* calcd for $C_{21}H_{40}O_7S_2Si$ [M + H]: 497.2065; found: 497.2078. LRMS (CI, NH_3): *m/z* (%) = 497 (56) $[M^+ + 1]$, 465 (44), 407 (8), 366 (17), 334 (98), 317 (100), 276 (44), 185 (20), 159 (32), 119 (72), 75 (84). IR (KBr): 3487, 1709 cm^{-1}.

AcOH (3.2 mL) and NaBH(OAc)$_3$ (1.1 g, 5.2 mmol, 2 equiv) were added at –20 °C to the solution of β-hydroxyketone **9** (1.3 g, 2.6 mmol, 1.0 equiv) in dry CH_2Cl_2 (20 mL). The mixture was stirred at –20 °C for 12 h and then kept at that temperature for 3 d (TLC controlled). The reaction was quenched with a sat. $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 100 mL).The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give the crude diol. Diastereoselectivity of the reaction was measured by integrating peaks at δ = 3.45 and 3.56 ppm and was found to be *syn*/*anti* = 2:98. The crude product was purified by flash column chromatography using silica gel (hexane–EtOAc = 8:2) to give pure diol **9a** as a colorless oil (1.11 g, 85%). $[\alpha]_D^{25}$ +23 (*c* 1, C_6H_6) and $[\alpha]_D^{25}$ +7 (*c* 1.05, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.93 [br s, 1 H (OH)], 4.25 (d, *J* = 3.8 Hz, 1 H), 4.24 (d, *J* = 2.6 Hz, 1 H), 4.20 (br s, 1 H), 4.06 (dd, J_1 = 2.6 Hz, J_2 = 7.8 Hz, 1 H), 3.90 (dd, J_1 = 7.8 Hz, J_2 = 9.2 Hz, 1 H), 3.88 (dd, J_1 = 1.0 Hz, J_2 = 9.1 Hz, 1 H), 3.84 (dd, J_1 = 1.0 Hz, J_2 = 3.8 Hz, 1 H), 3.80 (dd, J_1 = 9.1 Hz, J_2 = 9.2 Hz, 1 H), 3.56 (s, 3 H), 3.42 (s, 3 H), 3.12–3.02 (m, 2 H), 2.84–2.79 (m, 1 H), 2.72–2.67 (m, 1 H), 2.07–1.96 (m, 2 H), 1.45 (s, 3 H), 1.32 (s, 3 H), 0.88 (s, 9 H), 0.10 (s, 3 H) 0.07 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 106.8, 98.7, 80.8, 76.2, 72.3, 70.5, 65.0, 58.6, 56.5, 47.5, 29.5, 29.1, 28.8, 26.2, 26.0, 19.5, 18.4, –4.2, –4.8 ppm. HRMS (CI, Na): *m/z* calcd for $(C_{21}H_{42}O_7S_2Si + Na)^+$ [M + Na]$^+$: 521.2039; found: 521.2038. IR (KBr): 3457 (br), 2991, 2928, 2854, 1463, 1380, 1255, 1166, 1151, 1070, 1001, 836, 779, 731 cm^{-1}.

The diol **9a** (0.6 g, 1.2 mmol) in dry THF (10 mL) was added to a stirred suspension of NaH (80% w/w, 91 mg, 23.0 mmol) in dry THF (5 mL) at 0 °C under inert atmosphere. The resulting mixture was stirred at 0 °C for 15 min, benzyl bromide (0.32 mL, 2.6 mmol) and catalytic amount of TBAI (20 mg) were then added. The resulting mixture was stirred at ambient temperature for 12 h. After TLC showed no starting material, the reaction was quenched with an aq sat. $NaHCO_3$ solution and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to yield the crude product which was purified by flash chromatography using SiO_2; hexane–EtOAc (5–10%) to give pure **8** (0.73 g, 89%). $[\alpha]_D^{25}$ +14 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.22 (m, 10 H), 4.87 (dd, J_1 = 5.5 Hz, J_2 = 11.6 Hz, 2 H), 4.77 (t, *J* = 12.0 Hz, 2 H), 4.45 (d, *J* = 10.1 Hz, 1 H), 4.28 (d, *J* = 9.4 Hz, 1 H), 4.25 (d, *J* = 8.2 Hz, 1 H), 4.05 (t, *J* = 9.9 Hz, 1 H), 4.00 (t, *J* = 9.7 Hz, 1 H), 3.69 (d, *J* = 8.2 Hz, 1 H), 3.62 (d, *J* = 9.7 Hz, 1 H), 3.28 (s, 3 H), 3.27 (s, 3 H), 2.71 (m, 1 H), 2.61 (m, 2 H), 2.36 (m, 1 H), 1.94 (m, 1 H), 1.76 (m, 1 H), 1.46 (s, 3 H), 1.40 (s, 3 H), 0.88 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9, 138.3, 128.3, 128.2, 128.1, 127.5, 127.3, 127.0, 105.6, 99.3, 81.7, 75.5, 74.7, 74.0, 73.7, 72.5, 71.1, 55.9, 54.8, 49.9, 40.6, 30.0, 29.4, 26.0, 19.2, 18.5, –4.2, –4.6. HRMS (CI, Na): *m/z* calcd for $(C_{35}H_{54}O_7S_2Si + Na)^+$ [M + Na]$^+$: 701.2978; found: 701.2989. IR (KBr): 3060, 2993, 2928, 2854, 1457, 1380, 1095, 1076, 1000, 836, 778, 697 cm^{-1}.

Spectroscopic Data for Compound 18

β-Anomer

$[\alpha]_D^{24}$ 5.1 (*c* 1.0, C_6H_6). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.93 (d, *J* = 8.6 Hz, 1 H), 5.65 (t, *J* = 3.0 Hz, 1 H), 5.19 (ddd, J_1 = 2.8 Hz, J_2 = 4.6 Hz, J_3 = 7.2 Hz 1 H), 5.00 (dd, J_1 = 2.9 Hz, J_2 = 10.4 Hz, 1 H), 4.92 (dd, J_1 = 3.0 Hz, J_2 = 8.6 Hz, 1 H), 4.25 (dd, J_1 = 4.4 Hz, J_2 = 11.8 Hz, 1 H), 4.17 (dd, J_1 = 2.9 Hz, J_2 = 10.4 Hz, 1 H), 4.11 (dd, J_1 = 7.2 Hz, J_2 = 11.8 Hz, 1 H), 2.14 (s, 3 H), 2.09 (s, 3 H), 2.08 (s, 3 H), 2.01 (s, 6 H), 1.98 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 170.1, 169.96, 169.3, 169.3, 169.2, 90.3, 72.5, 69.9, 68.4, 68.1, 66.9, 61.8, 21.17, 21.14, 20.95, 20.93, 20.78, 20.75. HRMS (CI, NH_3): *m/z* calcd for $(C_{19}H_{26}O_{13} + NH_4)^+$: 480.1717; found: 480.1715. LRMS (CI, NH_3): *m/z* (%) = 480 (100) $[M + 18]^+$, 403 (52), 215 (2), 152 (8), 139 (9), 110 (8), 77 (7), 60 (41). IR (KBr): 3476 (w), 2965, 1749, 1433, 1370, 1216, 1048, 948, 914, 601 cm^{-1}.

Spectroscopic Data for Compound *ent*-19

β-Anomer

$[\alpha]_D^{24}$ –5.7 (*c* 1.1, C_6H_6). HRMS (CI, NH_3): *m/z* calcd for $(C_{19}H_{26}O_{13} + NH_4)^+$: 480.1717; found: 480.1710. The NMR and IR spectra were identical with these of compound **18**.

Acknowledgment

The authors thank NSERC (Canada) and the University of Saskatchewan for financial support and the Saskatchewan Structural Sciences Centre for help in analytical measurements.

References

(1) Roth, K.; Hoeft-Schleeh, S. *Chem. Unserer Zeit* **2002**, *36*, 390.
(2) Review: Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1304.
(3) (a) Fraser-Reid, B. O.; Tatsuta, K.; Thiem, J. *Glycoscience Chemistry and Chemical Biology*, 2nd ed.; Springer: Berlin, **2008**, 861–956. (b) Davies, D. A. L. *Nature (London)* **1957**, *180*, 1129. (c) Davies, D. A. L. *Biochem. J.* **1957**, *67*, 253. (d) MacLennan, A. P.; Davies, D. A. L. *Bull. Soc. Chim. Biol.* **1960**, *42*, 1373. (e) Slein, M. W.; Schnell, G. W. *Proc. Soc. Exp. Biol.* **1953**, *82*, 734. (f) Missale, G.; Colajacomo, A.; Bologna, I. *Boll. Soc. Ital. Biol. Sper.* **1960**, *36*, 1885. (g) Pratt, J. W.; Richtmyer, N. K. *J. Am. Chem. Soc.* **1955**, *77*, 6326. Heptoses reviews:. (h) Kosma, P. *Curr. Org. Chem.* **2008**, *12*, 1021. (i) Hansson, J.; Oscarson, S. *Curr. Org. Chem.* **2000**, *4*, 535. (j) Eidels, L.; Osborn, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1673; and references cited therein. Heptoses synthesis:. (k) Jaipuri, F. A.; Collet, B. Y. M.; Pohl, N. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1707. (l) Prenner, R. H.; Binder, W. H.; Schmid, W. *Liebigs Ann. Chem.* **1994**, *1*, 73. (m) Guezlek, H.; Graziani, A.; Kosma, P. *Carbohydrate Res.* **2005**, *340*, 2808. (n) Hricoviniova, Z. *Tetrahedron: Asymmetry* **2002**, *13*, 1567.
(4) (a) Majewski, M.; Nowak, P. *J. Org. Chem.* **2000**, *65*, 5152. (b) Majewski, M.; Nowak, P. *Tetrahedron: Asymmetry* **1998**, *9*, 2611. (c) Majewski, M.; Niewczas, I.; Palyam, N. *Synlett* **2006**, 2387. (d) Palyam, N.; Niewczas, I.; Majewski, M. *Tetrahedron Lett.* **2007**, *48*, 9195. (e) Niewczas, I.; Majewski, M. *Eur. J. Org. Chem.* **2009**, 33. (f) Palyam, N.; Majewski, M. *J. Org. Chem.* **2009**, *74*, 4390.
(5) Selected articles: (a) Markert, M.; Mahrwald, R. *Chem.–Eur. J.* **2008**, *14*, 40; and references cited therein. (b) Aungst, R. A.; Funk, R. L. *J. Am. Chem. Soc.* **2001**, *123*, 9455. (c) Enders, D.; Narine, A. *J. Org. Chem.* **2008**, *73*, 7857. (d) Calderon, F.; Doyaguez, E. G.; Fernandez-Mayoralas, A. *J. Org. Chem.* **2006**, *71*, 6258. (e) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1753.
(6) (a) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329. (b) Suri, J. T.; Mitsumori, S.; Alberthofer, K.; Tanaka, F.; Barbas, C. F. III. *J. Org. Chem.* **2006**, *71*, 3822.
(7) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

