DOI: 10.1002/cjoc.201180487

Bromodimethylsulfonium Bromide Catalyzed Synthesis of Methyl 2-Dexoy-4,6-*O*-benzylidene Galactopyranoside from Galactal and the Rapid Route to 2,3- and 2,6-Dideoxygalactopyranoses

Ding, Ning[a](丁宁) Chun, Yuexing[b](淳月兴) Zhang, Wei[a](张伟) Li, Yingxia*,[a](李英霞)

[a] *Department of Medicinal Chemistry, Fudan University, 826 Zhangheng Road, Shanghai 201203, China*
[b] *School of Medicine and Pharmacy, Ocean University of China, Qingdao, Shandong 266003, China*

4,6-*O*-Benzylidenation of *D*-galactal with $PhCH(OCH_3)_2$ catalyzed by bromodimethylsulfonium bromide leads to methyl 2-dexoy-4,6-*O*-benzylidene galactopyranoside efficiently, which serves as a key intermediate to the ready preparation of 2,3- and 2,6-dideoxy galactopyranosides.

Keywords deoxysugars, bromodimethylsulfonium bromide, synthetic methods, galactal, carbohydrate

Introduction

Deoxysugars, monosaccharides in which one or more hydroxyl groups is/are replaced with hydrogen atoms, are an important class of carbohydrates that occur widely in natural products.[1-3] For example, 2-deoxy-*D*-ribose is present in DNA as the skeletal sugar component. 2-Keto-3-deoxy-*D*-manno-octulosonic acid (KDO) is an essential component of lipopolysaccharides in Gram-negative bacteria.[4] 2,6-Dideoxy-hexoses are frequently present in antibiotics and anti-cancer agents such as anthracyclines, angucyclines, aureolic acid antibiotics, cardiac glycoside, enediynesm macrolides, and pluramycins.[3] In this context, the ready synthesis of such sugars has the potential of being used for the creation of vaccine candidates, antibiotics and other small molecule drugs.

So far a variety of approaches for the synthesis of deoxysugars have been developed either through multistep transformations of relatively economical common sugars[3,5] or alternatively, through non-carbohydrate precursors.[6] However, many of these methods either employed expensive reagents or performed extensive protecting group manipulations.

Glycals are extremely useful carbohydrate derivatives, finding uses in oligosaccharide synthesis and for many other synthetic purposes as chiral building blocks.[7] Selective 4,6-*O*-protection of a glycal is particularly useful since it allows manipulation of the remaining 3-hydroxyl group. Moreover, 4,6-*O*-benzylidene protection is particularly desirable since regioselective cleavage of the benzylidene group,[8] which may be performed at any later point in a synthetic sequence, allows selective access to either the 4- or 6-hydroxyl group as desired. However, direct 4,6-*O*-benzylidenation of glycal is messy and very low yielding due to the acid sensitivity of the enol ether functionality.[9]

As part of our continuing interest in studying the structure-activity relationships of deoxysugars as anticancer agents, we present here a concise and practical protocol for the preparation of 2,3- and 2,6-dideoxy galactopyranoses from *D*-galactal.

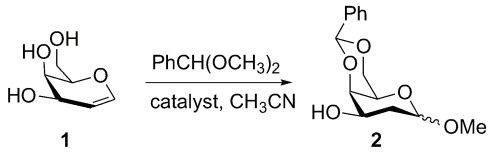
Results and Discussion

In a routine experiment, 4,6-*O*-benzylidenation of *D*-galactal **1** with benzaldehyde dimethylacetal in acetonitrile at room temperature catalyzed by 10-camphorsulfonic acid (CSA), which is a commonly used protonic acid catalyst, formed very messy products (Table 1, Entry 1). To our surprise, further experiment showed that when the stronger acid *p*-toluenesulfonic acid monohydrate (*p*-TsOH•H_2O) was employed as the catalyst instead of CSA under the above condition, methyl 2-dexoy-4,6-*O*-benzylidene galactopyranoside **2** was provided as a major product (55%, Table 1, Entry 2). This result was interesting since an early report[10] described the reaction of *D*-glucal in benzaldehyde dimethylacetal with *p*-TsOH•H_2O as catalyst furnished 2,3-unsaturated Ferrier rearranged product (methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-*D*-erythro-hex-2-enopyranoside) in 90% yield. Because that compound **2** is an extremely useful building block for the synthesis of deoxysugars, a more efficient synthesis of compound

* E-mail: liyx417@fudan.edu.cn; Tel./Fax: 0086-021-51980120
Received April 29, 2011; accepted September 5, 2011.

2 would be valuable. Thus the next effort is to improve the yielding of compound **2**.

Table 1 Synthesis of methyl 2-dexoy-4,6-*O*-benzylidene galactosylpyranose **2**[a]



1 2

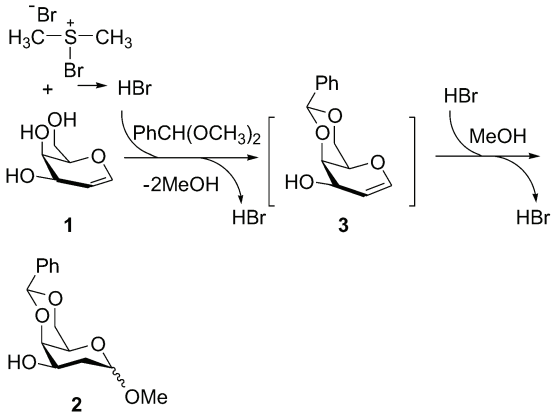
Entry	Reagent	Catalyst	Time	Yield/% (α : β)
1	$PhCH(OCH_3)_2$	CSA	—	messy products
2	$PhCH(OCH_3)_2$	*p*-TsOH•H_2O	30 min	55 (5 : 2)
3	$PhCH(OCH_3)_2$	BDMS	10 min	87 (3 : 1)
4	PhCHO	CSA	—	messy products
5	PhCHO	*p*-TsOH•H_2O	—	messy products
6	PhCHO	BDMS	—	messy products

[a] The catalyst (0.1 equiv.) was added to a stirred solution of *D*-galactal **1** (1.0 equiv.) and $PhCH(OCH_3)_2$ (1.5 equiv.) or PhCHO (1.5 equiv.) in dry acetonitrile at room temperature. The reaction was monitored by TLC. After the full conversion of **1**, Et_3N was added to quench the reaction. The reaction mixture was then concentrated and purified by silica gel column chromatography.

Since Meerwein's discovery of bromodimethylsulfonium bromide (BDMS), it has gained considerable interest in the field of organic chemistry, due to its easy handling and low cost, as well as its varied applications both as a catalyst and as an effective reagent.[11] Recently, Khan and co-workers demonstrated the usefulness of BDMS as a mild catalyst for *O*,*O*-isopropylidenation of free sugars.[12] They claimed that BDMS may generate dry HBr in the medium upon reaction with the sugars, and the *in situ*-generated HBr catalyzed the isopropylidenation reaction of sugars into the corresponding *O*,*O*-isopropylidene derivatives. Inspired by this report, we investigated the effect of BDMS as the catalyst on the benzylidenation of *D*-galactal. To our delight, BDMS drove the reaction of galactal **1** and $PhCH(OCH_3)_2$ to provide compound **2** more efficiently than *p*-TsOH•H_2O. As shown in Table 1, in this case not only the yield of compound **2** was improved but also the reaction time was shortened (Entry 3).

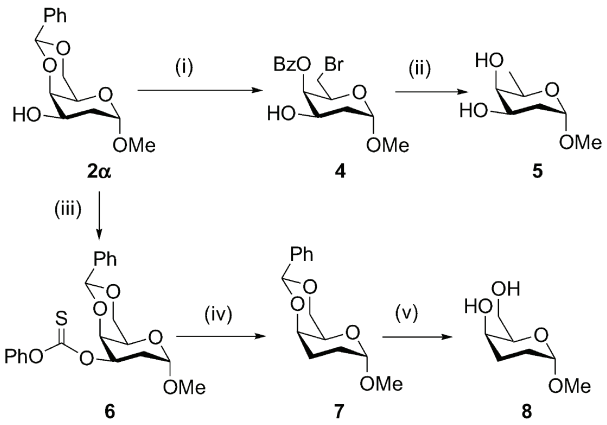
We propose the formation of compound **2** was through a two-step conversion. The first step is 4,6-*O*-benzylidenation of **1** catalyzed by the *in situ*-generated HBr, which formed intermediate **3** and released two molecules of methanol. In the presence of HBr catalyst, intermediate **3** was unstable due to the acid sensitivity of the enol ether functionality but was trapped by a methanol molecule rapidly to form the stable product **2** (Scheme 1). Further experiments confirmed the importance of the presence of methanol molecules, as employing benzaldehyde instead of benzaldehyde dimethylacetal in the above reaction provided messy products (Table 1, Entries 4, 5, 6).

Scheme 1 The formation of **2** from **1** catalyzed by BDMS



With compound **2** in hand, deoxysugars were readily prepared. The α/β isomers of **2** can be easily separated by silica gel column chromatography. To facilitate the characterization and purification of the intermediates and products, **2α** was used as the key intermediate. Treatment of compound **2α** (1 equiv.) by NBS (1.25 equiv.), AIBN (0.05 equiv.) and barium carbonate (0.6 equiv.) in CCl_4 at 70 ℃ (Hanessian-Hullar reaction)[13] afforded compound **4** in 68% yield. The 4-*O*-benzoyl and 6-bromo groups were then removed by $LiAlH_4$ in THF simultaneously to provide 2,3-dideoxygalactosylpyranoside (**5**) in 83% yield. The preparation of 2,3-dideoxygalactosylpyranoside **8** was achieved through a radical deoxygenation procedure (Barton-McCombie reaction)[14] to remove the 3-OH on **2** (71% over two steps), followed by the cleavage of the 4,6-*O*-benzylidene group through hydrogenation in the presence of $Pd(OH)_2$ (92%).

Scheme 2 Synthesis of α-methyl 2,6- and 2,3-dideoxygalactosylpyranoside (**5** and **8**)



Reagents and conditions: (i) **2α** (1 equiv.), NBS (1.25 equiv.), AIBN (0.05 equiv.), $BaCO_3$ (0.6 equiv.), CCl_4, 70 ℃, 1 h, 68%; (ii) $LiAlH_4$ (5 equiv.), THF, 1 h, 83%; (iii) PhOC=SCl, DMAP, CH_2Cl_2, 12 h, 96%; (iv) Bu_3SnH (1.6 equiv.), AIBN (0.2 equiv.), toluene, 80 ℃, 2 h, 74%; (v) $Pd(OH)_2$, H_2, CH_3OH, 30 ℃, 92%

CHINESE JOURNAL OF CHEMISTRY

Conclusions

In conclusion, BDMS was discovered to be an efficient catalyst to drive the 4,6-*O*-benzylidenation of *D*-galactal with $PhCH(OCH_3)_2$ to afford methyl 2-dexoy-4,6-*O*-benzylidene galactopyranoside without Ferrier rearrangement, which serves as a key intermediate for ready preparation of 2,3- and 2,3-dideoxygalactosylpyranosides.

Experimental

General methods

All commercial reagents and solvents were used as received without further purification unless specified. Reaction solvents were distilled from CaH_2 for dichloromethane and from sodium metal and benzophenone for tetrahydrofuran. Flash column chromatography was performed on silica gel (200—300 mesh, Qingdao, China). ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker Avance 400 MHz spectrometer with tetramethylsilane (TMS) as an internal standard at room temperature. Mass spectra were obtained on a Waters Q-TOF micro mass spectrometer (Waters).

Synthesis of methyl 4,6-*O*-benzylidene-2-dexoy-*D*-galactopyranoside (2)

Compound **1** (146.1 mg, 1.0 mmol) was dissolved in dry acetone (10 mL), then benzaldehyde dimethyl acetal (228.3 mg, 1.5 mmol) and BDMS (22.0 mg, 0.1 mmol) were added. After stirring at room temperature for 10 min, the reaction mixture was neutralized by addition of solid K_2CO_3 and then evaporated to dryness. The silica gel column chromatography of the residue furnished **2** (231.5 mg, 87%) as a foamy solid. Compound **2α**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.50—7.48 (m, 2H, ArH), 7.40—7.38 (m, 3H, ArH), 5.61 (s, 1H, PhCH), 4.95 (s, 1H, H-1), 4.30 (dd, J=12.3, 1.2 Hz, 1H, H-6a), 4.13—4.07 (m, 3H, H-4, H-3, H-6b), 3.65 (s, 1H, H-5), 3.36 (s, 3H, OCH_3), 2.23 (d, J=10.5 Hz, 1H, 3-OH), 1.98 (m, 2H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.8, 129.1, 128.2, 126.3, 101.1 (PhCH), 99.4 (C-1), 74.8 (C-4), 70.0 (C-6), 64.4 (C-3), 62.5 (C-5), 55.0 (OCH_3), 33.7 (C-2); ESI-MS *m*/*z* (%): 289.1 (M+Na, 65), 555.2 (M_2+Na, 55). Compound **2β**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.52—7.50 (m, 2H, ArH), 7.37—7.36 (m, 3H, ArH), 5.60 (s, 1H, PhCH), 4.39 (d, J=8.3 Hz, 1H, H-1), 4.37 (d, J=10.1 Hz, 1H, H-6a), 4.11 (dd, J=12.3, 1.6 Hz, 1H, H-6b), 3.83—3.81 (m, 1H, H-3), 3.53 (s, 3H, OCH_3), 3.38 (s, 1H, H-5), 2.13—1.82 (m, 2H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 129.2, 128.1, 126.5, 101.3 (PhCH), 101.2 (C-1), 73.8 (C-4), 69.6 (C-6), 68.2 (C-3), 66.8 (C-5), 56.6 (OCH_3), 35.6 (C-2); ESI-MS *m*/z (%): 289.1 (M+Na, 70), 555.2 (M_2+Na, 55).

Synthesis of methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2-deoxy-*α*-*D*-galactopyranoside (4)

A solution of methyl 4,6-*O*-benzylidene-2-dexoy-*α*-*D*-galactosylpyranoside (**2α**) (600.0 mg, 2.3 mmol) in CCl_4 (40 mL) was treated with freshly recrystallized *N*-bromosuccinimide (601.5 mg, 3.4 mmol) and $BaCO_3$ (266.4 mg, 1.4 mmol). The solution was deoxygenated by sparging with argon for 1 h and then AIBN (18.5 mg, 0.1 mmol) was added. The reaction mixture was heated at 65 ℃ for 1.5 h. After the mixture was cooled to room temperature and filtered, it was dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel to give **4** (529.7 mg, 68%) as a white foamy solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.09 (dd, J=8.3, 1.2 Hz, 2H, ArH), 7.61 (t, J=7.5 Hz, 1H, ArH), 7.48 (dd, J=7.9, 7.5 Hz, 2H, ArH), 5.55 (d, J=3.2 Hz, 1H, H-4), 4.99 (d, J=2.0 Hz, 1H, H-1), 4.38—4.35 (m, 1H); 4.18—4.16 (m, 1H), 3.46—3.44 (m, 5H, OCH_3, H-6ab), 2.04—2.02 (m, 2H, H-2ab); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.0, 133.6, 129.8, 128.6, 99.0, 71.0, 69.5, 65.1, 55.2, 33.1, 30.5; ESI-MS *m*/*z*: 367.1 (M+Na), 711.1 (M_2+Na).

Synthesis of methyl 2,6-di-deoxy-*α*-*D*-galactopyranoside (5)

A solution of methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2-deoxy-*α*-*D*-galactopyranoside (**4**) (140.0 mg, 0.4 mmol) in THF (5 mL) was treated with $LiAlH_4$ (77 mg, 2.0 mmol). The reaction mixture was stirred at room temperature for 12 h. EtOAc (20 mL) was added dropwise to quench the reaction. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **5** (54.6 mg, 83%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.78 (d, J=3.5 Hz, 1H, H-1), 3.98—4.01 (m, 1H, H-3), 3.92 (dd, J=12.9, 6.7 Hz, 1H, H-5), 3.63 (s, 1H, H-4), 3.33 (s, 3H, OCH_3), 2.0—2.2 (bm, 2H, OH), 1.92 (dd, J=13.3, 5.7 Hz, 1H, H-2a), 1.78 (ddd, J=12.9, 12.9, 3.5 Hz, 1H, H-2b), 1.29 (d, J=6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 98.6, 71.2, 65.8, 65.4, 54.9, 32.7, 16.7; ESI-MS *m*/*z*: 185.2 (M+Na, 100), 347.2 (M_2+Na, 85).

Synthesis of methyl 4,6-*O*-benzylidene-2-dexoy-3-*O*-phenylthiocarbonate-*α*-*D*-galactopyranoside (6)

Phenyl chlorothionoformate (103.6 mg, 0.6 mmol) and DMAP (147.0 mg, 1.2 mmol) were added sequentially to a flame-dried round-bottom flask containing a solution of compound **2** (160.0 mg, 0.6 mmol) in anhydrous dichloromethane (25 mL). The reaction solution was stirred at room temperature for 2 h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **6** (390.0 mg, 96%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.50—7.08 (m, 10H, ArH), 5.80—5.78 (m, 1H, H-3), 5.65 (s, 1H, PhCH), 5.06 (d, J=2.0 Hz, 1H, H-1), 4.58 (d, J=2.7 Hz, 1H, H-4), 4.32 (d, J=12.5 Hz, 1H, H-6a), 4.13 (d, J=12.5 Hz, 1H, H-6b), 3.74 (s, 1H, H-5), 3.40 (s, 3H, OCH_3), 2.46 (ddd, J=12.1, 12.1, 3.5 Hz, 1H, H-2a), 2.18 (dd, J=12.5, 5.1 Hz, 1H, H-2b); ESI-MS *m*/*z* (%): 425.2 (M+Na, 100), 827.3 (M_2+Na, 75).

Synthesis of methyl 4,6-*O*-benzylidene-2,3-di-deoxy-*α*-*D*-galactopyranoside (7)

To a solution of compound **6** (50.0 mg, 0.12 mmol) in toluene (10 mL) was added tributyltin hydride (70.0 mg, 0.24 mmol) and AIBN (6.0 mg, 0.04 mmol), and the mixture was heated at reflux for 3 h. Solvent was then removed under reduced pressure, and the resulting residue was purified by silica gel flash chromatography to give **7** (23.0 mg, 74%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54 (dd, J=7.7, 2.0 Hz, 2H, ArH), 7.39—7.33 (m, 3H, ArH), 5.57 (s, 1H, PhCH), 4.87 (bs, 1H, H-1), 4.22 (dd, J=12.1, 1.1 Hz, 1H, H-6a), 4.06 (dd, J=12.1, 1.6 Hz, 1H, H-6b), 3.97 (bs, 1H, H-5), 3.63 (d, J=1.1 Hz, 1H, H-4), 3.41 (s, 3H, OCH_3), 2.11—1.14 (m, 4H, H-2ab, H-3ab); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 128.9, 128.1, 126.6, 101.1, 98.6, 71.5, 70.5, 62.1, 54.8, 23.7, 23.2; ESI-MS *m*/*z* (%): 273.1 (M+H, 10), 523.2 (M_2+Na, 100).

Synthesis of methyl 2,3-di-deoxy-*α*-*D*-galactopyranoside (8)

To a solution of compound **7** (20.0 mg, 0.08 mmol) in MeOH (5 mL) and CH_2Cl_2 (5 mL) was added $Pd(OH)_2$/C (75% wt% Pd dry basis on carbon, 25.0 mg), and the mixture was hydrogenated at r.t. for 12 h. The suspension was filtered through Celite pad. The filter cake was rinsed with CH_2Cl_2MeOH (10 mL, 1∶1). The combined filtrate and washings were concentrated under reduced pressure to give **8** (12.0 mg, 92%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.70 (bs, 1H, H-1), 3.98—3.70 (m, 4H, H4, H-5, H-6ab), 3.34 (s, 3H, OCH_3), 2.97 (bs, 1H, OH), 2.41 (bs, 1H, OH), 2.12—1.49 (m, 4H, H-2ab, H-3ab); ESI-MS *m*/*z* (%): 185.2 (M+Na, 100), 347.2 (M_2+Na, 35). The NMR data of compound **8** was identical to those reported by Mocerino *et al.*[15]

Acknowledgement

This work is sponsored by National Natural Science Foundation of China (No. 21002014) and the Startup Foundation for Young Teachers, School of Pharmacy, Fudan University.

References

[1] He, X.; Agnihotri, G.; Liu, H.-W. *Chem*. *Rev*. **2000**, *100*, 4615.
[2] He, X. M.; Liu, H.-W. *Curr*. *Opin*. *Chem*. *Biol*. **2002**, *6*, 590.
[3] Hou, D.; Lowary, T. L. *Carbohydr*. *Res*. **2009**, *344*, 1911.
[4] Raetz, C. R. *Annu*. *Rev*. *Biochem*. **1990**, *59*, 129.
[5] (a) Chang, C.-W. T.; Clark, T.; Ngaara, M. *Tetrahedron Lett*. **2001**, *42*, 6797; (b) Zhang, G.; Shi, L.; Liu, Q.; Wang, J.; Liu, X. *Tetrahedron* **2007**, *63*, 9705; (c) Sánchez-Roselló, M.; Puchlopek, A. L. A.; Morgan, A. J.; Miller, S. J. *J*. *Org*. *Chem*. **2008**, *73*, 1774; (d) Engers, D. W.; Bassindale, M. J.; Pagenkopf, B. L. *Org*. *Lett*. **2004**, *6*, 663; (e) Csuk, R.; Prell, E.; Reiβmann, S. *Tetrahedron* **2008**, *64*, 9417; (f) Yang, Z.; Yu, B. *Carbohydr*. *Res*. **2001**, *333*, 105.
[6] (a) Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Winssinger, N.; Hughes, R.; Bando, T. *Angew*. *Chem*., *Int*. *Ed*. **1999**, *38*, 240; (b) Cutchins, W. W.; McDonald, F. E. *Org*. *Lett*. **2002**, *4*, 749; (c) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew*. *Chem*., *Int*. *Ed*. **2004**, *43*, 2152; (d) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752; (e) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J*. *Am*. *Chem*. *Soc*. **2004**, *126*, 3428; (f) Haukaas, M. H.; O'Doherty, G. A. *Org*. *Lett*. **2002**, *4*, 1771; (g) Andreana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G. *Org*. *Lett*. **2002**, *4*, 3875; (h) Zhu, L.; Kedenburg, J. P.; Xian, M.; Wang, P. G. *Tetrahedron Lett*. **2005**, *46*, 811.
[7] Ferrier, R. J.; Hoberg, J. O. *Adv*. *Carbohydr*. *Chem*. *Biochem*. **2003**, *58*, 55.
[8] Garreg, P. J. In *Preparative Carbohydrate Chemistry*, Ed.: Hannesian, S., Marcel Dekker, New York, **1997**, pp. 53—67.
[9] (a) Sharma, M.; Brown, R. K. *Can*. *J*. *Chem*. **1966**, *44*, 2825; (b) Feast, A. A.; Overend, W. G.; Williams, N. R. *J*. *Chem*. *Soc*. **1965**, 7378; (c) Lemieux, R. U.; Fraga, E.; Watanabe, K. A. *Can*. *J*. *Chem*. **1968**, *46*, 61; (d) Fraser-Reid, B.; Walker, D. L.; Tam, S. Y.-K.; Holder, N. L. *Can*. *J*. *Chem*. **1973**, *51*, 3950; (e) Champers, D. J.; Evans, G. R.; Fairbanks, A. J. *Tetrahedron*: *Asymmetry* **2003**, *14*, 1767; (f) Sakakibara, T.; Ito, T.; Kotaka, C.; Kajihara, Y.; Watanabe, Y.; Fujioka, A. *Carbohydr*. *Res*. **2008**, *343*, 2740; (g) Osborn, H. M. I.; Meo, P.; Nijjar, R. K. *Tetrahedron*: *Asymmetry* **2005**, *16*, 1935.
[10] Florent, J.-C.; Monneret, C. *Synthesis* **1982**, 29.
[11] Choudhury, L. H.; Parvin, T.; Khan, A. T. *Tetrahedron* **2009**, *65*, 9513.
[12] Khan, A. T.; Khan, M. M. *Carbohydr*. *Res*. **2010**, *345*, 154.
[13] Crich, D.; Yao, Q.; Bowers, A. A. *Carbohydr*. *Res*. **2006**, *341*, 1748.
[14] Baer, H. H. *Pure Appl*. *Chem*. **1989**, *61*, 1217.
[15] Mocerino, M.; Stick, R. V. *Aust*. *J*. *Chem*. **1990**, *43*, 1183.

(E1104295 Lu, Y.; Zheng, G.)

