Carbohydrate Research 344 (2009) 1020–1023

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Note

Convenient approaches to synthesis of furanoid sugar-aza-crown ethers from *C*-ribosyl azido aldehyde via a reductive amination/amidation

Yu-Chi Hsieh [a], Jiun-Ly Chir [b], Wei Zou [c], Hsiu-Han Wu [a], An-Tai Wu [a,*]

[a] *Department of Chemistry, National Changhua University of Education, Changhua 50058, Taiwan*
[b] *Biotechnology Center in Southern Taiwan, Academia Sinica, 2F., No. 22, Lane 31, Sec. 1, Huandong Road, Sinshih Township, Tainan County 744, Taiwan*
[c] *Institute for Biological Sciences, National Research Council of Canada, 100 Sussex Drive, Ottawa, Ontario, Canada K1A 0R6*

ARTICLE INFO

Article history:
Received 11 February 2009
Received in revised form 2 March 2009
Accepted 7 March 2009
Available online 12 March 2009

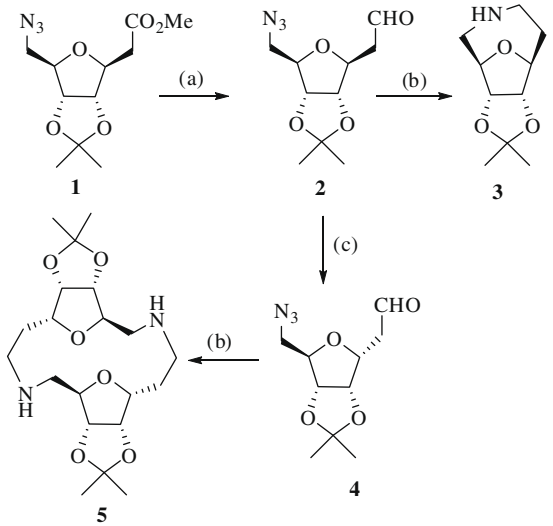
Keywords:
Furanoid
Sugar-aza-crown ether
Amination
Amidation

ABSTRACT

A short and highly efficient route to the α-anomer of a furanoid sugar-aza-crown ether was developed by a one-pot reductive amination of an α-anomer *C*-ribosyl azido aldehyde. In addition, the β-anomer furanoid sugar-aza-crown ether was synthesized from a linear disaccharide precursor via amidation and then followed by microwave-assisted amide reduction.

In recent years, new sugar-based molecular receptors such as sugar-aza-crown (SAC)[1] ethers have received attention, especially pyranoid-based SAC ethers, because of applicable functions such as metal chelation, host–guest recognition, and chemosensors. They are easily obtained by reducing the amide bond in cyclic pyranoid sugar amino acids (SAAs), which have been extensively synthesized by many groups.[2–8] Xie et al. reported a short and highly efficient route to pyranoid SAC ethers through the one-pot Staudinger/aza-Wittig reaction of azido aldehydes for macrocyclization.[9] In addition, modified pyranoid SAC ethers with bispyrenyl have also been synthesized and applied to sensing and recognizing Cu^{2+} cation.[10] Therefore, we are interested in the synthesis of furanoid SAC ethers. In this paper, we adopt two strategies to synthesize α- and β-anomer furanoid SAC ethers, respectively. One approach involves converting a *C*-ribosyl azido aldehyde monomer directly into α-anomer SAC ether by one-pot reductive amination; the other is the conversion of a linear disaccharide precursor to the SAA by intramolecular amidation and reduction of the amide bonds to obtain the β-anomer furanoid SAC ether.

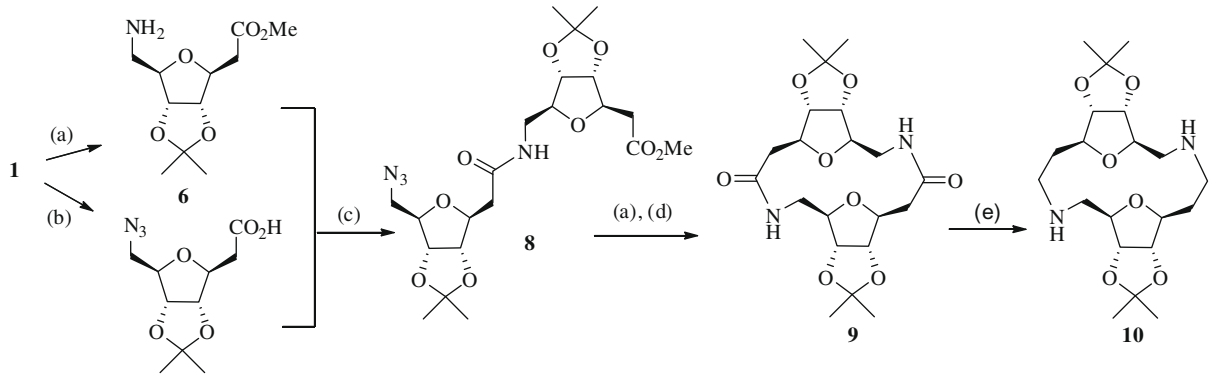
The preparation of furanoid SAC ethers, starting from the readily available aza-*C*-riboside **1**,[11] is outlined in Scheme 1. The reaction of **1** with DIBAL-H at −78 °C produced the β-anomer *C*-ribosyl azido aldehyde **2** in 64% yield. We intended to use the reductive amination strategy for this cyclodimerization. Unfortunately, when treating the azido aldehyde **2** under palladium-catalyzed hydrogenation, the β-anomer *C*-riboside favored intramolecular cyclization leading to the formation of the tricyclic lactam[12] **3** in 65% yield. Because the cyclodimerization was based on the anomeric configuration, the epimerization of the β-anomer to the α-anomer of *C*-riboside for dimercyclization should be



Scheme 1. Reagents and conditions: (a) DIBAL-H, −78 °C, CH_2Cl_2; (b) H_2, Pd/C, MeOH; (c) $Zn(OAc)_2$, NaOMe, MeOH.

* Corresponding author. Fax: +1 886 4 7211 190.
E-mail address: antai@cc.ncue.edu.tw (A.-T. Wu).

0008-6215/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2009.03.008



Scheme 2. Reagents and conditions: (a) H_2, Pd/C, MeOH; (b) NaOH, THF, H_2O; (c) DEPC, Et_3N, DMF; (d) K_2CO_3, MeOH; (e) LAH, THF, microwave.

performed. Accordingly, **2** was treated overnight with 4% NaOMe and $Zn(OAc)_2$[13] to obtain the α-anomer *C*-ribosyl azido aldehyde **4** in 75% yield with about 15% starting material remaining. Furthermore, following reduction of the *C*-ribosyl azido aldehyde **4**, under palladium-catalyzed hydrogenation, the compound spontaneously underwent intermolecular reductive amination. We observed the desired dimer α-anomer furanoid SAC ether **5** in 80% yield and no imine intermediate or remaining polymers were observed during the reaction. Interestingly, the results of our study are inconsistent with the study performed by Xie et al.[9] They performed reduction of the *C*-glucosyl azido aldehydes bearing different protection groups under palladium-catalyzed hydrogenation, but imine intermediates (pyranoid derivatives) were the major products with a trace of amine products. This dissimilarity probably arises from the steric hindrance derived from backbone-based groups (protecting groups or sugar rings) applied during the hydrogenation process. The α-anomer furanoid SAC ether **5** was characterized by NMR and mass spectra.

The requisite β-anomer furanoid SAC ether, however, can be synthesized from its linear disaccharide, which is the conventional process for synthesizing similar cyclic homooligomers,[1] as shown in Scheme 2. Accordingly, the aza-*C*-riboside **1** was subjected to reduction by hydrogenation and hydrolysis, respectively, to produce the corresponding amino ester **6** in 92% yield and the azido acid **7** in 90% yield. With these two *C*-ribosides in hand, the coupling of the amino ester **6** and the azido acid **7** was carried out with diethyl phosphoryl cyanide (DEPC) and Et_3N in DMF to obtain the linear disaccharide **8** in 81% yield. The azido group in the linear disaccharide **8** was reduced by catalytic hydrogenation, which produced an amino ester intermediate. After filtration and removal of the solvent, the intermediate was treated with K_2CO_3 in MeOH, which resulted in intramolecular amidation with the ester leading to the desired β-anomer furanoid SAA **9** as a major product in 76% yield, and a trace amount of the starting material **8**. Furthermore, we tried to synthesize the more flexible amine-linked β-anomer furanoid SAC ether **10** by reducing the amide bonds. Next, we used classical reduction conditions such as BH_3·THF or LAH under reflux after a long reaction time, but they were totally inert to reduction. This is probably due to the intramolecular hydrogen bond interaction between the NH groups and oxygen atoms of the SAC ether **9**. Finally, reducing the amide bonds of **9** with microwave irradiation and excess LAH was found to be successful for obtaining the desired β-anomer furanoid SAC ether **10** in 67% yield.

A comparison of the ^{1}H NMR spectra in $CDCl_3$ of the α-anomer furanoid SAC ether **5** and the β-anomer furanoid SAC ether **10** is shown in Figure 1. In the ^{1}H NMR spectra, the H-1 of the α-anomer furanoid SAC ether **5** appears as a multiplet at δ 2.41–2.66, H-2 was observed as a doublet of a doublet at δ 4.27 (J = 12.6, 3.9 Hz), and H-5 was observed as a broad doublet at δ 3.68 (J = 9.9 Hz). Two H-7 protons were observed at different field strengths as multiplets at δ 3.08 and 2.47. On the other hand, H-1 of the β-anomer furanoid SAC **10** was observed at more downfield strengths as a multiplet at δ 2.62–2.88 than that of α-anomer. H-2 and H-5 of the β-anomer overlap and were observed as a multiplet at δ 3.97–4.02. The H-5 in both cases showed an obvious shift difference of 0.31 ppm. The ^{13}C NMR spectra further supported the shift difference with the carbon (C-5) signals of the α- and β-anomer furanoid SAC (**5** and **10**) at around δ 79.4 and δ 85.5, respectively. The structures of all the products were in accord with spectroscopic data and analyses.

In summary, we described an efficient method for the synthesis of α- and β-anomer furanoid SAC ethers from aza-*C*-riboside via reductive amination and amidation, respectively. The resulting furanoid-based SAC ethers, a new class of molecular receptors, probably can lead to easy access for applications in chemosensors. We consider the fluorescent derivatives of furanoid-based SACs to

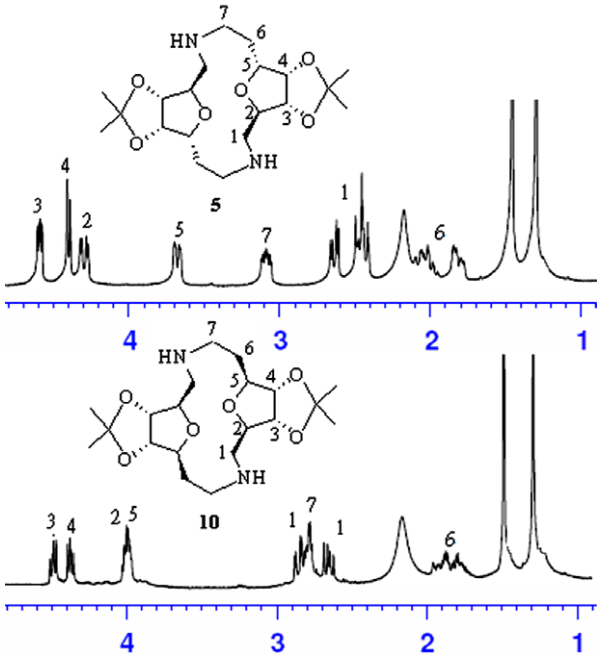


Figure 1. ^{1}H NMR spectra of α-anomer furanoid SAC ether **5** and β-anomer furanoid SAC ether **10** ($CDCl_3$; 298 K).

be synthesized and further examined with ligands such as cation metals to demonstrate their application.

1. Experimental

1.1. General methods

All reagents were obtained from commercial suppliers and were used without further purification. DCM was distilled over CaH_2. MeOH was distilled over magnesium and iodine. Analytical thin-layer chromatography was performed using silica gel 60 F254 plates (Merck). The ^1H and ^{13}C NMR spectra were recorded with a Bruker AM 300 spectrometer. Chemical shifts are given in ppm with residual $CHCl_3$ or CD_3OD as reference. Mass spectra were recorded under fast atom bombardment (FAB) or electron spray interface (ESI) conditions. Microwave reactions were carried out in a Milestone Start S with a maximum power of 300 W and 50 mL process flask.

1.2. Methyl 2-*C*-(5-azido-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribofuranosyl) acetaldehyde (2)

To a solution of **1** (3.58 g, 13 mmol) in dry CH_2Cl_2 (100 mL) was added 1 M solution of DIBALH (30 mL, 2.5 equiv) at −78 °C. The reaction mixture was stirred at the temperature for 1 h. MeOH (16 mL) was added and stirred for 10 min at −78 °C. Saturated NaCl (2 mL), Et_2O (50 mL) and $MgSO_4$ (1.07 g) were subsequently added. The mixture was stirred at room temperature for 1 h and then was filtered through Celite. The solvent was removed and the crude product was purified by chromatography (hexanes–EtOAc 5:1) to give **2** (2.01 g, 64%) as a colorless oil; R_f 0.34 (EtOAc–hexanes 1:2.5); ^1H NMR (300 MHz, $CDCl_3$) δ: 9.71 (t, J = 1.5 Hz, 1H), 4.54 (dd, J = 6.9, 4.5 Hz, 1H), 4.40 (dd, J = 6.6, 5.1 Hz, 1H), 4.30–4.25 (m, 1H), 4.03 (q, J = 4.2 Hz, 1H), 3.49 (dd, J = 13.2, 3.6 Hz, 1H), 3.28 (dd, J = 13.2, 4.5 Hz, 1H), 2.74–2.69 (m, 2H), 1.47 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.3, 115.1, 84.2, 82.9, 81.8, 79.4, 52.0, 46.8, 27.2, 25.3; HRMS (FAB): calcd for $C_{10}H_{16}N_3O_4$ (M+H), m/z 242.1141; found m/z 242.1138.

1.3. Methyl 2-*C*-(5-azido-5-deoxy-2,3-di-*O*-isopropylidene-α-D-ribofuranosyl) acetaldehyde (4)

To a solution of **2** (1.04 g, 4.32 mmol) and $Zn(OAc)_2$ (4.7 g, 6.0 equiv) was added 0.7 M solution of NaOMe in MeOH (15 mL). The mixture was stirred overnight, and then neutralized by adding HOAc. The mixture was extracted with EtOAc, filtered, and concentrated. The resulting residue was purified by silica column chromatography (hexanes–EtOAc 5:1) to give **4** (0.78 g, 75%) as a colorless oil; R_f 0.34 (hexanes–EtOAc 2.5:1); ^1H NMR (300 MHz, $CDCl_3$) δ: 9.78 (d, J = 1.2 Hz, 1H), 4.77–4.60 (m, 2H), 4.42–4.16 (m, 2H), 3.39–3.28 (m, 2H), 2.86–2.83 (m, 2H), 1.44 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.9, 112.9, 83.2, 82.6, 81.2, 76.2, 51.6, 43.6, 26.1, 24.7; HRMS (FAB): calcd for $C_{10}H_{16}N_3O_4$ (M+H), m/z 242.1141; found m/z 242.1137.

1.4. Furanoid sugar-aza-crown (5)

A mixture of **4** (0.95 g, 3.94 mmol) and 10% Pd–C (0.1 g) in methanol (20 mL) was stirred under H_2 atmosphere (balloon pressure) for 24 h until the starting material was completely consumed. The reaction mixture was filtered and the filtrate was concentrated. Purification by chromatography (EtOAc–MeOH 3:1) gave **5** (0.63 g, 80%) as a pale yellow solid; mp: 182 °C; R_f 0.21 (EtOAc–MeOH 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ: 4.57 (dd, J = 6.0, 5.7 Hz, 2H), 4.38 (d, J = 6.0 Hz, 2H), 4.27 (dd, J = 12.6, 3.9 Hz, 2H), 3.68 (d, J = 9.9 Hz, 2H), 3.11–3.05(m, 3H), 2.63 (dd, J = 12.0, 3.9 Hz, 2H), 2.49–2.47 (m, 4H), 2.04–1.99 (m, 3H), 1.83–1.78 (m, 2H), 1.43 (s, 6H), 1.24 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 112.6, 83.5, 82.7, 81.8, 79.4, 48.7, 48.4, 27.7, 26.2, 25.3; HRMS (FAB): calcd for $C_{20}H_{34}N_2O_6$ (M+H), m/z 398.2417; found m/z 399.2501.

1.5. Methyl 2-*C*-(5-amino-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribofuranosyl)acetate (6)

A mixture of **1** (1.72 g, 6.34 mmol) and 10% Pd–C (0.17 g) in methanol (20 mL) was stirred under H_2 atmosphere (balloon pressure) for 40 min when the starting material was completely consumed. The reaction mixture was filtered and the filtrate was concentrated. Purification by chromatography (DCM–MeOH 10:1) gave **6** (1.43 g, 92%) as a yellow oil; R_f 0.2 (DCM–MeOH 10:1); ^1H NMR (300 MHz, $CDCl_3$) δ: 4.52–4.43 (m, 2H), 4.23–4.18 (m, 1H), 3.88 (m, 1H), 3.66 (s, 3H, CO_2Me), 2.91–2.73 (m, 2H), 2.64–2.52 (m, 2H), 1.50 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.9, 114.7, 85.5, 84.2, 82.4, 80.3, 51.8, 44.0, 38.1, 27.4, 25.5; HRMS (FAB): calcd for $C_{11}H_{20}NO_5$ (M+H), m/z 246.1341; found m/z 246.1343.

1.6. Methyl 2-*C*-(5-azido-5-deoxy-2,3-di-*O*-isopropylidene-β-D-ribofuranosyl)acetic acid (7)

To a solution of **1** (5.32 g, 0.02 mol) in THF (10 mL) was added 1 M aqueous $NaOH_{(aq)}$ (5 mL). The mixture was stirred overnight, then Amberlite® IR-120 (H^+) was added to neutralize, and the mixture was filtered and concentrated. The resulting residue was purified by silica chromatography (hexanes–EtOAc 3:1) to give **7** (4.65 g, 90%) as a colorless oil; R_f 0.31 (hexanes–EtOAc 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ: 4.57–4.52 (m, 2H), 4.28–4.26 (m, 1H), 4.08–4.07 (m, 1H), 3.52 (dd, J = 12.9, 3.6 Hz, 1H), 3.33 (dd, J = 12.9, 4.5 Hz, 1H), 2.73–2.70 (m, 2H), 1.52 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.8, 115.0, 84.1, 83.0, 81.9, 80.6, 52.2, 37.9, 27.3, 25.4; HRMS (FAB): calcd for $C_{10}H_{16}N_3O_5$ (M+H), m/z 258.1090; found m/z 258.1086.

1.7. Linear furanoid sugar amino acid (8)

To a solution of amine **6** (1.90 g, 7.75 mmol) and acid **7** (2.00 g, 7.77 mmol) in DMF (20 mL) under nitrogen atmosphere, DEPC (1.7 mL, 1.5 equiv) and Et_3N (3 mL, 3 equiv) were added at 0 °C. The solution was allowed to warm to room temperature and stirred for two days. Then, the mixture was partitioned in EtOAc–H_2O (1:1), the organic layer was washed with brine, and the aqueous layers were combined and extracted with EtOAc. The organic layers were combined, dried, filtered, and concentrated. The resulting residue was purified by silica column chromatography (hexanes–EtOAc 3:1) to give **8** (3.03 g, 81%) as a brown oil; R_f 0.33 (hexanes–EtOAc 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ: 4.54–4.46 (m, 4H), 4.16 (d, J = 4.5 Hz, 2H), 4.07–4.00 (m, 2H), 3.67 (s, 3H), 3.57–3.52 (m, 2H), 3.40–3.32 (m, 2H), 2.69–2.52 (m, 4H), 1.48 (s, 3H), 1.44 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.1, 169.8, 115.0, 114.7, 84.2, 83.9, 83.0, 82.8, 82.4, 81.9, 81.3, 80.4, 52.1, 51.8, 40.9, 40.1, 37.3, 27.4, 27.3,25.4; HRMS (ESI): calcd for $C_{21}H_{32}N_4O_9$ (M^+), m/z 484.2169; found m/z 484.2176.

1.8. Cyclic furanoid sugar amino acid (9)

A mixture of **8** (1.72 g, 3.57 mmol) and 10% Pd–C (0.17 g) in methanol (20 mL) was stirred under H_2 atmosphere (balloon pressure) for 40 min when the starting material was completely consumed. The reaction mixture was filtered and the filtrate was

concentrated. The crude product was dissolved in MeOH and K_2CO_3 (0.74 g, 5.35 mmol) was added. The mixture was stirred at room temperature for 24 h. Then Amberlite® IR-120 (H^+) was added to neutralize, and the mixture was filtered and concentrated. Purification by chromatography (EtOAc–MeOH 20:1) gave **9** (1.32 g, 87%) as a yellow solid. Mp 234 °C (decomp.); R_f 0.57 (EtOAc–MeOH 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.62 (s, 1H), 6.60 (s, 1H), 4.67 (dd, J = 4.2, 7.2 Hz, 2H), 4.41 (dd, J = 7.2, 5.4 Hz, 2H), 4.12–4.07 (m, 2H), 3.93–3.82 (m, 5H), 3.19–3.13 (m, 2H), 2.56 (t, J = 3.9 Hz, 3H), 1.45 (s, 6H), 1.26 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 115.1, 83.7, 83.1, 81.3, 81.1, 40.2, 39.4, 27.2, 25.3; HRMS (ESI): calcd for $C_{20}H_{30}N_2O_8$ (M^+), m/z 426.2002; found m/z 426.2007.

1.9. Furanoid sugar-aza-crown (10)

To a solution of **9** (0.127 g, 0.30 mmol) in dry THF (35 mL) was added LAH (68 mg, 6 equiv) at 0 °C. After stirring for 5 min, the mixture was stirred at 70 °C under 300 W microwave irradiation for 6 h. Then the mixture was filtered, concentrated, and extracted with EtOAc. The solvent was removed and the crude was purified by chromatography (EtOAc–MeOH 3:1) to give **10** (0.08 g, 67%) as a yellow solid. Mp 143 °C; R_f 0.09 (EtOAc–MeOH 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.75 (s, 1H), 4.49 (dd, J = 6.9, 4.5 Hz, 2H), 4.37 (dd, J = 6.9, 4.8 Hz, 2H), 4.02–3.97 (m, 3H), 2.88–2.77 (m, 5H), 2.66 (dd, J = 11.7, 7.5 Hz, 2H), 1.96–1.77 (m, 7H), 1.49 (s, 6H), 1.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 114.9, 85.5, 84.7, 83.0, 82.5, 51.0, 47.2, 30.6, 27.3, 25.4; HRMS (FAB): calcd for $C_{20}H_{35}N_2O_6$ (M+H), m/z 399.2495; found m/z 399.2499.

Acknowledgment

This work was supported by the National Science Council of Taiwan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.03.008.

References

1. Ménand, M.; Blais, J.-C.; Hamon, L.; Valéry, J.-M.; Xie, J. *J. Org. Chem.* **2005**, *70*, 4423–4430.
2. Fuchs, E. F.; Lehmann, J. *Carbohydr. Res.* **1976**, *49*, 267–273.
3. Suhara, Y.; Hildreth, J. E. K.; Ichikawa, Y. *Tetrahedron Lett.* **1996**, *37*, 1575–1578.
4. Suhara, Y.; Ichikawa, M.; Hildreth, J. E. K.; Ichikawa, Y. *Tetrahedron Lett.* **1996**, *37*, 2549–2552.
5. Wessel, H. P.; Mitchell, C. M.; Lobato, C. M.; Schmid, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2712–2713.
6. Müller, G.; Kitas, E.; Wessel, H. P. *J. Chem. Soc., Chem. Commun.* **1995**, 2425–2426.
7. Szabo, L.; Smith, B. L.; McReynolds, K. D.; Parrill, A. L.; Morris, E. R.; Gervay, J. *J. Org. Chem.* **1998**, *63*, 1074–1078.
8. Locardi, E.; Stöckle, M.; Gruner, S.; Kessler, H. *J. Am. Chem. Soc.* **2001**, *123*, 8189–8196.
9. Ménand, M.; Blais, J. C.; Valéry, J. M.; Xie, J. *J. Org. Chem.* **2006**, *71*, 3295–3298.
10. Xie, J.; Ménand, M.; Maisonneuve, S.; Métivier, R. *J. Org. Chem.* **2007**, *72*, 5980–5985.
11. van Well, R. M.; Overkleeft, H. S.; Overhand, M.; Carstenen, E. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2000**, *41*, 9331–9335.
12. Wu, A. T.; Wu, P. J.; Zou, W.; Chir, J. L.; Chang, Y. C.; Tsai, S. Y.; Guo, C. Q.; Chang, W. S.; Hsieh, Y. C. *Carbohydr. Res.* **2008**, *343*, 2887–2893.
13. Wang, Z.; Shao, H.; Lacroix, E.; Wu, S. H.; Jennings, H. J.; Zou, W. *J. Org. Chem.* **2003**, *68*, 8097–8105.