DOI: 10.1002/ejoc.201001045

Straightforward Synthesis of Diverse 1-Deoxyazapyranosides via Stereocontrolled Nucleophilic Additions to Six-Membered Cyclic Nitrones

Ting-Hao Chan,[a] Yi-Fan Chang,[a] Jung-Jung Hsu,[a] and Wei-Chieh Cheng*[a]

Keywords: Diastereoselectivity / Natural products / Nucleophilic addition / Alkaloids / Grignard reaction

A systematic study of diastereoselective nucleophilic addition of Grignard reagents to six-membered chiral tri-*O*-benzyl cyclic nitrones is described. With all eight chiral cyclic nitrones and asymmetric reaction conditions in hand, a practical methodology is established for the preparation of diverse 1-deoxyazapyranosides bearing various stereogenic centers.

Introduction

Naturally occurring or synthetic 1-deoxyazapyranosides (piperidine-based alkaloids) bearing multihydroxy groups with proper configurations possess various biological activities to modulate carbohydrate-processing enzymes and thus are utilized for therapeutic studies, especially in the treatment of various diseases such as diabetes, cancer, and viral infections, and lysosomal storage disorders.[1] For example, DMJ is a specific inhibitor of Golgi mannosidase I to block conversion of high mannose to complex oligosaccharides; Miglitol is for the treatment of type II diabetes; and Amigal (DGJ) is a chemical chaperone for Fabry disease (Figure 1). Due to their versatile biological behaviors, many of the synthetic efforts are toward the preparation of these molecules and their derivatives.[2–4]

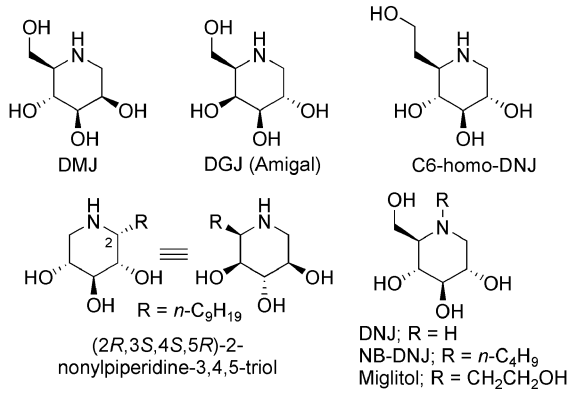


Figure 1. Examples of biologically interesting 1-deoxyazapyranosides (polyhydroxylated piperidines).

[a] Genomics Research Center, Academia Sinica,
128, Academia Road, Sec. 2, Taipei 115, Taiwan
Fax: +886-2-2789-8771
E-mail: wcheng@gate.sinica.edu.tw

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001045.

Five-membered cyclic nitrones have been extensively applied in synthetic chemistry, especially for the preparation of pyrrolodine-based molecules.[5–7] In our previous reports,[6] we developed a concise method to prepare various azafuranosides, such as DMDP, ADMDP, and their isomers, by using five-membered cyclic nitrones as key intermediates.[6]

In contrast, the use of six-membered tri-*O*-benzyl chiral cyclic nitrones[7–9] as key intermediates to study their diastereoselective nucleophilic additions towards the synthesis of 1-deoxyazapyranosides has scarcely been investigated[10b] (Figure 2). Perhaps the systematic preparation of chiral six-membered cyclic nitrones is not available; thus, their synthetic study and application are limited.

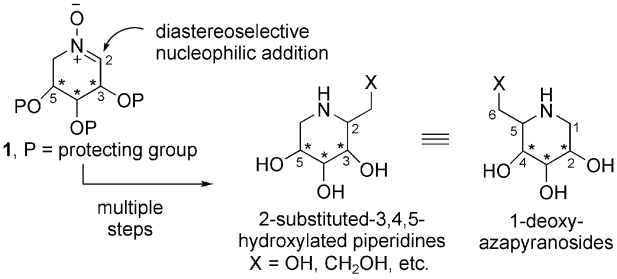


Figure 2. General synthetic criteria and the relationship between 1-deoxyazapyranosides and polyhydroxylated piperidines.

To extend our research interests and create a practical synthetic method for various polyhydroxylated piperidines, in this communication we report new synthetic routes to prepare all eight enantiopure tri-*O*-benzyl six-membered cyclic nitrones (Figure 3) that undergo diastereoselective nucleophilic additions with Grignard reagents. With proper stereocontrol, highly diverse 1-deoxyazapyranosides will be prepared to demonstrate the flexibility of this new synthetic strategy.

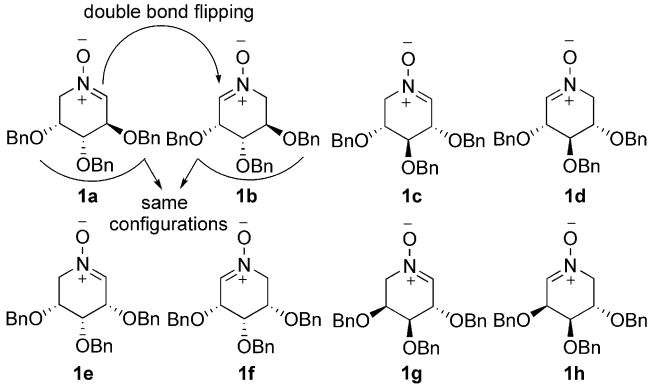
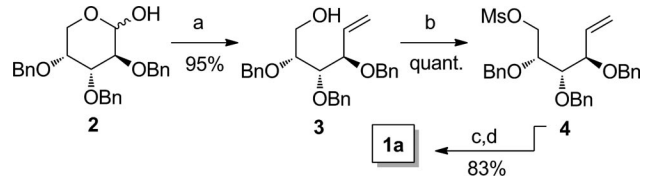


Figure 3. Chemical structures of all eight six-membered tri-*O*-benzyl chiral cyclic nitrones **1a**–**h**.

Results and Discussion

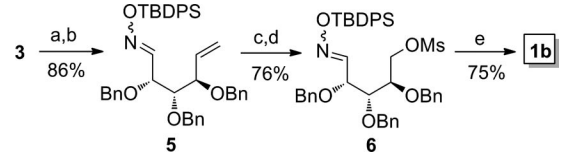
In our model study for the preparation of cyclic nitrone **1a**, the Wittig olefination of 2,3,4-tri-*O*-benzyl-D-arabinopyranoside (**2**) followed by mesylation gave alkene **4** in an overall 95% yield over the two steps. After ozonolysis of **4**, hydroxylamine[10,11] was directly added to obtain **1a** in 85% yield, and the overall yield was 79% for the four steps (Scheme 1).



Scheme 1. Preparation of **1a** through method A. Reagents and conditions: (a) $MePPh_3Br$, *n*BuLi, THF, –78 °C → room temp.; (b) MsCl, Et_3N, DCM; (c) O_3, MeOH/DCM, –78 °C, then DMS; (d) $H_2NOH{\cdot}HCl$, $NaHCO_3$, MeOH, reflux.

Compared with Tamura's method[8] or our previous modified conditions,[12] this new method possesses several merits should be addressed: (1) a multigram-scale synthesis of nitrones can be achieved; (2) the procedure is practical and reagents are inexpensive; (3) the overall yield for four steps is improved to 79%. Gratifyingly, cyclic nitrones **1c**, **1e**, and **1g** were obtained in 45–71% overall yield by using this approach from the corresponding 2,3,4-tri-*O*-benzyl-aldopyranoses (Scheme 1, method A). However, if applying this approach to prepare **1b**, **1d**, **1f**, and **1h**, the use of expensive D-lyxose, L-xylose, L-ribose, and L-lyxose, respectively, as the starting material is inevitable (see the Supporting Information).

To circumvent this dilemma and to develop more practical methodology, our initial attempts to reduce *O*-TBDPS oxime to the amine did not work well due to the extremely sensitive conditions required for oxime reduction (<10% yield; see the Supporting Information).[13] After reinvestigation, the problem was finally overcome by switching both functional groups before the intramolecular cyclization. Oxidation of alkene **3** followed by oxime formation with $NH_2OTBDPS$ gave **5** (86%). Treatment of **5** with the successive transformations (ozonolysis, reduction, mesylation, and deprotection with concomitant cyclization) generated **1b** smoothly in a yield of 57% over the four steps from **5** (Scheme 2). Likewise, cyclic nitrones **1d**, **1f**, and **1h** were prepared in 30–35% overall yield (see the Supporting Information).

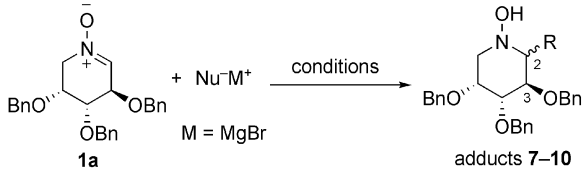


Scheme 2. New approach (method B) for the preparation of **1b** by double-bond flipping. Reagents and conditions: (a) DMSO, $(COCl)_2$, DCM, $(iPr)_2EtN$, –78 °C → room temp.; (b) $H_2NOTBDPS$, PPTS, $MgSO_4$, toluene, reflux; (c) 1. O_3, MeOH, –78 °C, then Me_2S; 2. $NaBH_4$, MeOH, 0 °C → room temp.; (d) MsCl, Et_3N, DCM; (e) TBAF, THF, reflux.

Notably, cyclic nitrones **1a** and **1b** are all from the same starting material **2** and the only difference is that the unsaturated double bond is on the right side in **1a** and that is on the left side in **1b** (Figure 3). All eight cyclic nitrones **1a**–**h** were systematically prepared through methods A and B, and it is the first time that all of them have been prepared from only four inexpensive chiral pools, including D- and L-arabinose, D-xylose, and D-ribose. With all eight cyclic nitrones **1a**–**h** in hand, we had the privilege to comprehensively investigate their diastereoselective chemistry in nucleophilic additions and also to investigate their further synthetic applications.

As shown in Table 1, we utilized **1a** as our representative model to investigate the asymmetric addition under various conditions. Satisfactorily, all reactions proceeded in good

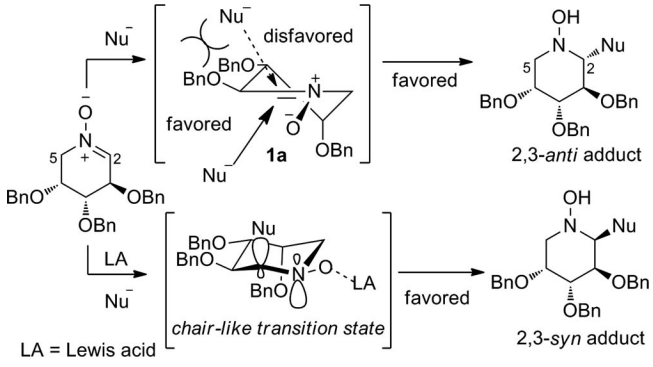
Table 1. Diastereoselective nucleophilic addition of Grignard reagents to cyclic nitrone **1a**.



Entry	Nu	Conditions	Product, yield [%][a]	Ratio *anti*:*syn*[b,c]
1	*i*Pr	THF, 0 °C	**7**, 79	≥95:5[d]
2	Bn	THF, 0 °C	**8**, 93	≥95:5[d]
3	allyl	THF, 0 °C	**9**, 81	77:23
4	vinyl	THF, 0 °C	**10**, 86	66:33
5	vinyl	THF, –78 °C	**10**, 83	62:38
6	vinyl	THF, Et_2AlCl, –78 °C	**10**, 85	19:81
7	vinyl	DCM, Et_2AlCl, –78 °C	**10**, 83	10:90
8	vinyl	DCM, $(iBu)_2AlCl$, –78 °C	**10**, 80	5:95

[a] Isolated yield. [b] Determined by NMR spectroscopic analysis. [c] Configuration assigned after hydrogenolysis or reductive cleavage of the N–O bond. [d] Ref.[12]

yields (79–93%). The assignment of the configurations of the adducts by NMR spectroscopic analysis was carried out after the reductive cleavage of the N–O bond (Zn/AcOH) or after catalytic hydrogenation [$Pd(OH)_2$, H_2] because of the broad signal peaks caused by the *N*-hydroxy group.[14] When a bulky nucleophile such as isopropylMgBr or BnMgBr was adopted, corresponding adduct **7** or **8** (2,3-*anti* adduct; $J_{2,3}$ = 9.0 Hz) was exclusively obtained (Table 1, Entries 1 and 2). The use of a smaller nucleophile such as vinylMgBr gave diastereoisomers, and the ratio was not affected dramatically by the reaction temperature (Table 1, Entries 4 and 5). The results could be rationalized by using the proposed model in Scheme 3, where a nucleophile favors approach to **1a** from the less sterically hindered side to afford the 2,3-*anti* adduct as the exclusive or major product.



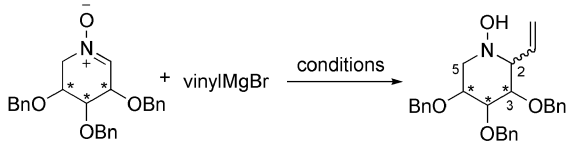
Scheme 3. Proposed mechanism for a nucleophile attacking **1a** with or without premixing Lewis acid (LA).

Compounds **1a**, **1b**, **1c**, and **1e** are the corresponding enantiomers of **1g**, **1h**, **1d**, and **1f**, respectively; thus, we could conveniently use the former four cyclic nitrones as representative substrates for an extensive diastereoselectivity study. Vinylmagnesium bromide (vinylMgBr) was chosen as our model nucleophile because of the versatile synthetic utility of the vinyl moiety[15] (Table 2).

As expected, all the addition reactions in Table 2 proceeded in good yield (71–87%). For the results of 2,3-*syn* and 2,3-*anti* selectivity, the reaction of **1b** with vinylMgBr exhibited excellent *anti* selectivity (Table 2, Entry 1; ≥95:5 *dr*). Using the same reaction conditions, compound **1e** was completely converted into single *anti* adduct **13** (Table 2, Entry 5). In contrast, when **1c** was converted into adduct **12**, the minor 2,3-*syn* isomer was observed (Table 2, Entry 3; 83:17 *dr*). Analysis of the results in Tables 1 and 2 showed that the facial selectivity is significantly affected by the steric hindrance effect of the *O*-benzyl groups at C3 and C4 and less influenced by the *O*-benzyl substituent at C5.

Interestingly, when **1a** was pretreated with a Lewis acid[16] followed by the addition of vinylMgBr (Table 1, Entries 6–8), the diastereoselectivity was significantly changed, and the ratio of isomers was dependent on the reaction conditions such as the Lewis acid and solvent. When a noncoordinating solvent (DCM) was utilized instead of a coordinating solvent (THF), more 2,3-*syn* isomer was observed (Table 1, Entries 6 and 7). In addition, when the bulky Lewis acid ($iBu)_2AlCl$ was used (Table 1, Entry 8), adduct **10** was produced as the 2,3-*syn* isomer with the highest excess observed for our study (Table 1, Entry 8; ≥95 *dr*). To explain this observation, we proposed a mechanistic pathway based on the antiperiplanar lone pair theory (stereoelectronic effect),[17] in which the Lewis acid chelates to the oxygen of the nitrone moiety to generate a chair-like transition state as the favored form, and subsequently, a nucleophile readily attacks the axial position to yield a major 2,3-*syn* adduct (Scheme 3).

Table 2. Stereocontrolled nucleophilic additions to various cyclic nitrones.



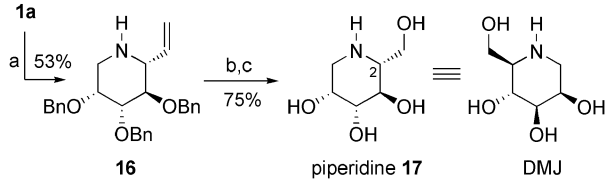
Entry	Cyclic nitrone	Conditions	Product, yield [%][a]	Ratio[b,c] *anti*/*syn*
1	**1b**	THF, –78 °C	**11**, 87	≥95:5
2	**1b**	DCM, $(iBu)_2AlCl$, –78 °C	**11**, 85	33:67
3	**1c**	THF, –78 °C	**12**, 71	83:17
4	**1c**	DCM, $(iBu)_2AlCl$, –78 °C	**12**, 75	5:95
5	**1e**	THF, –78 °C	**13**, 73	≥95:5
6	**1e**	DCM, $(iBu)_2AlCl$, –78 °C	**13**, 72	≥95:5
7	**1g**	THF, –78 °C	**14**, 85	63:37
8	**1h**	THF, –78 °C	**15**, 83	≥95:5

[a] Isolated yield. [b] Determined by NMR spectroscopic analysis. [c] Configuration assigned after hydrogenolysis or reductive cleavage of the N–O bond.

When cyclic nitrones **1b**, **1c**, and **1e** were tested, a similar trend of Lewis acid induced reversal of diastereoselectivity was observed (Table 2), except in the case of **1e**. Only one single adduct **13** possessing a 2,3-*anti* configuration was obtained from **1e**, no matter whether the Lewis acid was premixed or not (Table 2, Entries 5 and 6). Presumably, the steric hindrance effect of three tri-*O*-benzyl substituents (all *syn* configurations) imposes **1e** into a stable conformation, which cannot be twisted in the presence of a Lewis acid.

The valuable information encouraged us to challenge the new strategy for the preparation of various biologically interesting piperidines, also called 1-deoxyazapyranosides. In our first case study, piperidine **17** (DMJ) was efficiently prepared in 75% yield from intermediate **16** (Scheme 4). Following a similar approach, other DMJ-based analogues, such as **18** (5-epi-DMJ), **19** (6-homo-5-epi-DMJ), **20** (6-homo-DMJ), and more complicated derivatives **21**–**24**, were also prepared (Figure 4), and the synthesis of their intermediates is described in the Supporting Information. Piperidines **19**, **20**, and **22**–**24** are new azasugar-based molecules and have not been reported yet. Next, we turned to synthesize various enantiopure 1-deoxyazapyranosides with divergent stereocenters to demonstrate the generality of this new

approach. As illustrated in Figure 5, L-DMJ (**25**), DNJ (**26**), DGJ (**27**), and 5-epi-DGJ (**28**) were prepared in 35–54% overall yield from **1g**, **1d**, and **1h**, respectively, through a similar synthetic route. Obviously, as long as an appropriate tri-*O*-benzyl cyclic nitrone is chosen from our nitrone library (**1a**–**h**), the most desired 1-deoxyazapyranoside should be generated after concise transformations with stereocontrolled nucleophilic addition as the key step.



Scheme 4. Reagents and conditions: (a) 1. VinylMgBr, THF, 0 °C; 2. excess Zn, AcOH, room temp.; (b) 1. $(Boc)_2O$, Et_3N, DCM; 2. O_3, MeOH/DCM, –78 °C, then DMS; 3. $NaBH_4$, MeOH; 4. 10% HCl(aq.), MeOH, 70 °C; (c) H_2(g), $Pd(OH)_2$/C, 10% HCl(aq.)/MeOH, room temp.

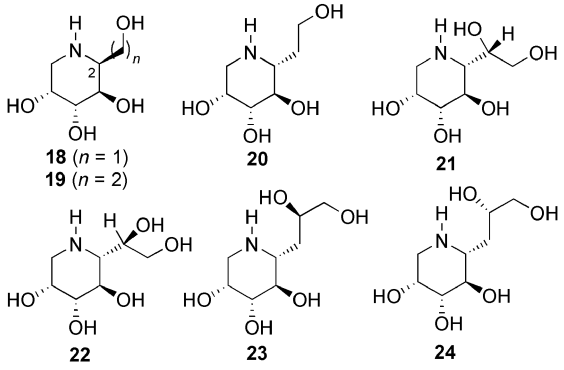


Figure 4. Chemical structures of DMJ-based analogues **18**–**24** prepared from **1a**.

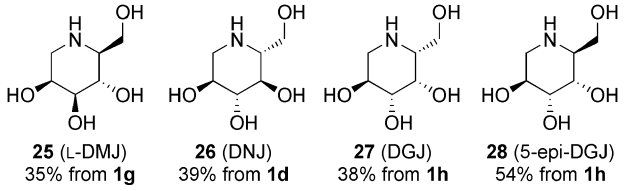


Figure 5. Chemical structures and total yields of 1-deoxyazapyranosides **25**–**28** prepared from the corresponding cyclic nitrones.

Conclusions

We have successfully developed practical methods to efficiently prepare enantiopure six-membered tri-*O*-benzyl cyclic nitrones with divergent stereocenters from aldopentoses. This is the first time that all eight chiral cyclic nitrones **1a**–**h** were prepared as key intermediates so that their diastereoselectivity and synthetic applications could be systematically studied. Using these cyclic nitrones and stereocontrolled synthesis, 12 examples of diverse 1-deoxyazapyranosides including enantiomers were synthesized to demonstrate the generality and flexibility of this new approach. We are applying this method to prepare biologically interesting molecules to systematically modulate sugar-processing enzymes, and the results will be published in due course.

Supporting Information (see footnote on the first page of this article): Experimental details, compound characterization data, and copies of the NMR spectra.

Acknowledgments

We thank the National Science Council and the Academia Sinica for financial support.

[1] a) A. E. Stütz, *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*, Wiley-VCH, Weinheim, **1999**; b) W. Zou, *Curr. Top. Med. Chem.* **2005**, *5*, 1363–1391 and references cited therein.
[2] a) A. Kato, N. Kato, E. Kano, I. Adachi, K. Ikeda, L. Yu, T. Okamoto, Y. Banba, H. Ouchi, H. Takahata, N. Asano, *J. Med. Chem.* **2005**, *48*, 2036–2044; b) M. S. M. Pearson, M. Mathe-Allainmat, V. Fargeas, J. Lebreton, *Eur. J. Org. Chem.* **2005**, 2159–2191; c) H. Takahata, Y. Banba, H. Ouchi, H. Nemoto, *Org. Lett.* **2003**, *5*, 2527–2529; d) C. McDonnell, L. Cronin, J. L. O'Brien, P. V. Murphy, *J. Org. Chem.* **2004**, *69*, 3565–3568; e) C. Boglio, S. Stahlke, S. Thorimbert, M. Malacria, *Org. Lett.* **2005**, *7*, 4851–4854.
[3] Examples of the synthesis of 1-deoxyazasugars: a) D. D'Alonzo, A. Guaragna, G. Palumbo, *Curr. Med. Chem.* **2009**, *16*, 473–505; b) K. Afarinkia, A. Bahar, *Tetrahedron: Asymmetry* **2005**, *16*, 1239–1287; c) P. Szolcsányi, T. Gracza, M. Koman, N. Prónayová, T. Liptaj, *Chem. Commun.* **2000**, 471–472.
[4] M. Sugiyama, Z. Hong, P.-H. Liang, S. M. Dean, L. J. Whalen, W. A. Greenberg, C.-H. Wong, *J. Am. Chem. Soc.* **2007**, *129*, 14811–14817.
[5] For a recent review, see: J. Revuelta, S. Cicchi, A. Goti, A. Brandi, *Synthesis* **2007**, 485–504 and references cited therein.
[6] a) E.-L. Tsou, Y.-T. Yeh, P.-H. Liang, W.-C. Cheng, *Tetrahedron* **2008**, *65*, 93–100; b) E.-L. Tsou, S.-Y. Chen, M.-H. Yang, S.-C. Wang, T.-R. R. Cheng, W.-C. Cheng, *Bioorg. Med. Chem.* **2008**, *16*, 10198–10204.
[7] For representative papers, see: a) P. Merino, I. Delso, T. Tejero, F. Cardona, M. Marradi, E. Faggi, C. Parmeggiani, A. Goti, *Eur. J. Org. Chem.* **2008**, 2929–2947; b) S. Cicchi, M. Marradi, P. Vogel, A. Goti, *J. Org. Chem.* **2006**, *71*, 1614–1619; c) S. Desvergnes, S. Py, Y. Vallee, *J. Org. Chem.* **2005**, *70*, 1459–1462.
[8] O. Tamura, A. Toyao, H. Ishibashi, *Synlett* **2002**, 1344–1346.
[9] While this manuscript was in preparation, an independent work for the synthesis of tri-*O*-benzyl cyclic nitrones **1a**, **1g**, and **1e** by using NH_2OMe as the key reagent was reported:W.-B. Wang, M.-H. Huang, Y.-X. Li, P.-X. Rui, X.-G. Hu, W. Zhang, J.-K. Su, Z.-L. Zhang, J.-S. Zhu, W.-H. Xu, X.-Q. Xie, Y.-M. Jia, C.-Y. Yu, *Synlett* **2010**, 488–492.
[10] a) S. Desvergnes, S. Py, Y. Vallee, *J. Org. Chem.* **2005**, *70*, 1459–1462; b) A. Peer, A. Vasella, *Helv. Chim. Acta* **1999**, *82*, 1044–1065.
[11] C.-Y. Yu, M.-H. Huang, *Org. Lett.* **2006**, *8*, 3021–3024.
[12] Y.-F. Chang, C.-W. Guo, T.-H. Chan, Y.-W. Pan, E.-L. Tsou, W.-C. Cheng, *Mol. Diversity* **2010**, in press.
[13] J. M. Tronchet, G. Zosimo-Landolfo, N. Bizzozero, D. Cabrini, F. Habashi, E. Jean, *J. Carbohydr. Chem.* **1988**, *7*, 169–186.

[14] S. A. Ali, S. M. A. Hashmi, M. I. M. Wazeer, *Spectrochim. Acta Part A* **1999**, *55A*, 1445–1452.
[15] R. Badorrey, C. Cativiela, M. D. Diaz-de-Villegas, R. Diez, J. A. Galvez, *Eur. J. Org. Chem.* **2003**, 2268–2275.
[16] For representative papers, see: a) P. Merino, V. Mannucci, T. Tejero, *Eur. J. Org. Chem.* **2008**, 3943–3959; b) M. Ueda, H. Miyabe, M. Teramachi, O. Miyata, T. Naito, *J. Org. Chem.* **2005**, *70*, 6653–6660.
[17] R. V. Stevens, *Acc. Chem. Res.* **1984**, *17*, 289–296.

Received: July 23, 2010
Published Online: September 13, 2010

