ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2015, **51**, 13957

Received 8th July 2015,
Accepted 27th July 2015

DOI: 10.1039/c5cc05651a

www.rsc.org/chemcomm

ortho-(Methyltosylaminoethynyl)benzyl glycosides as new glycosyl donors for latent-active glycosylation†

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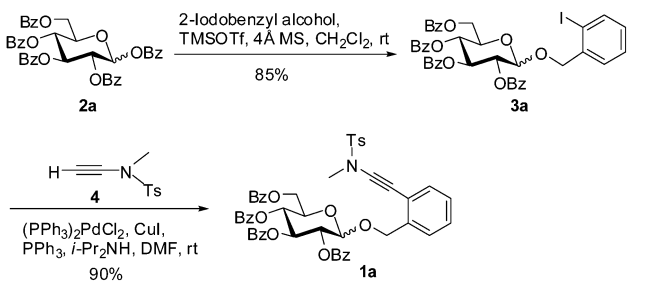
A new glycosylation protocol employing *ortho*-(methyltosylaminoethynyl)benzyl glycosides as glycosyl donors and TMSOTf as the catalyst is disclosed. These donors can be readily prepared from the corresponding 'latent' *ortho*-iodobenzyl glycosides *via* a Sonogashira coupling, thus providing a new approach for the 'latent-active' synthesis of glycans.

New glycosylation methods are continuously developed with efforts to construct the extremely diverse glycosidic linkages occurring in glycans and glycoconjugates in an efficient and economical manner.[1] In the last decade, much interest has been devoted to the investigation of glycosylation protocols based on activation of the C≡C triple bonds. Thus, propargyl glycosides and 1,2-orthoesters (under the catalysis of AuX_3),[2,3] glycosyl alkynoates (under the promotion of $Hg(OTf)_2$),[4] dipropargylcyanoacetates (under the catalysis of $AuCl_3/AgSbF_6$),[5] as well as alkynyl-containing thioglycosides (under the catalysis of Au(I) complexes),[6] are disclosed to be effective donors in certain glycosylation reactions. Especially, glycosyl *ortho*-alkynylbenzoates (under the catalysis of a gold(I) complex, such as PPh_3AuNTf_2 and PPh_3AuOTf) have been found to have wide applications in the synthesis of complex glycans and glycoconjugates;[7,8] and the general mechanism of this glycosylation reaction has been largely elucidated.[7c–e] During the course of these studies, we tried glycosyl *ortho*-alkynylbenzyl glycosides as donors, which would have the advantage of easy manipulation of the protecting groups, but found no glycosylation took place under similar conditions wherein the corresponding *ortho*-alkynylbenzoates underwent glycosylation. We envisioned introduction of an electron-rich substituent on the alkyne moiety to facilitate the desired glycosylation pathway. Here we report *ortho*-(methyltosylaminoethynyl)benzyl glycosides as a new type of glycosyl donors which can be activated by a catalytic amount of TMSOTf under mild conditions and their applicability in the 'latent-active' synthesis of glycans.

The desired glycosyl *ortho*-(methyltosylaminoethynyl)benzyl glycosides could be easily prepared from the corresponding *ortho*-iodobenzyl glycosides *via* a Sonogashira coupling with ynamide **4**.[9–11] Taking the preparation of perbenzoyl glucopyranoside **1a** as an example (Scheme 1), *ortho*-iodobenzyl glucopyranoside **3a** was obtained *via* condensation of perbenzoylated glucose **2a** with 2-iodobenzyl alcohol under the action of TMSOTf, which was then subjected to coupling with ynamide **4** in the presence of $(PPh_3)_2PdCl_2$ and CuI in i-Pr_2NH/DMF to provide the desired *ortho*-(methyltosylaminoethynyl)benzyl glucoside **1a** in high yield (90%).[10] Manipulation of the protecting groups on the iodobenzyl glycoside **3a** followed by Sonogashira coupling would lead to (methyltosylaminoethynyl)benzyl glucopyranosides bearing different protecting group patterns, such as **1c** (Table 2). (Methyltosylaminoethynyl)benzyl rhamnopyranoside **1b** and 2-deoxy-glucopyranoside **1d** were similarly prepared by Sonogashira coupling as the key step (see ESI† for details). All these glycosides were found to be stable when stored at room temperature.

With the perbenzoyl glucoside **1a** as a potential donor and cholesterol **5a** as an acceptor, a variety of π-acids and Lewis acids (0.1 eq.) were screened as promoters for the desired



Scheme 1 Preparation of *ortho*-(methyltosylaminoethynyl)benzyl glucopyranoside **1a**.

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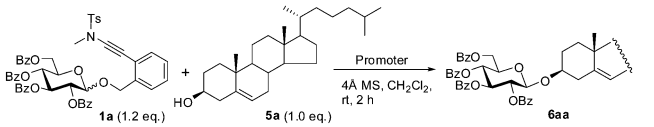
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5cc05651a

Table 1 Screening of promoters for the glycosylation of *ortho*-(methyltosylaminoethynyl)benzyl glucoside **1a** with cholesterol **5a**



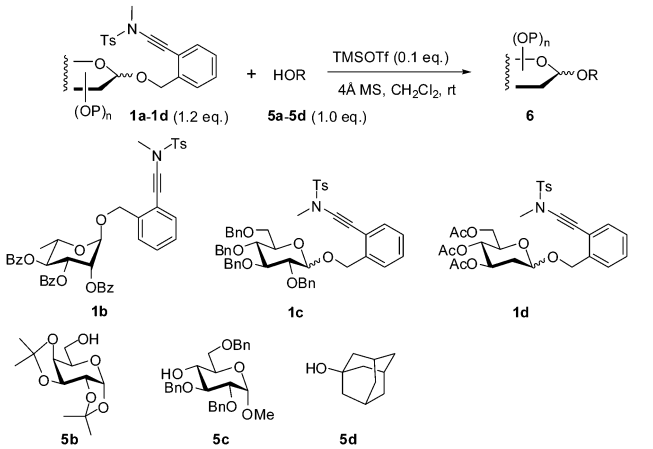
Entry	Promoter (0.1 eq.)	Isolated yield (%)
1	PPh_3AuNTf_2	43
2	TMSOTf	91
3	$Bi(OTf)_3$	83
4	$In(OTf)_3$	67
5	$Cu(OTf)_2$	46
6	$Sc(OTf)_3$	17
7	BF_3OEt_2 (1.2 eq.)	21
8	$SnCl_4$	26
9	$PtCl_2$	16
10	$AuBr_3$	Trace
11	CuI or LiOTf	No reaction

glycosylation reaction in the presence of 4 Å MS in CH_2Cl_2 at room temperature (Table 1). Surprisingly, PPh_3AuNTf_2, the effective catalyst for the glycosylation of glycosyl *ortho*-alkynylbenzoates,[7] could not catalyze the present coupling effectively, providing the desired β-glucoside **6aa** in only 43% yield (entry 1). The major by-product arose from the nucleophilic addition of cholesterol **5a** onto the ynamide moiety.[11a,e] TMSOTf turned out to be the most effective catalyst, wherein the coupled glycoside **6aa** was obtained in a high yield of 91% (entry 2). $Bi(OTf)_3$, $In(OTf)_3$, and $Cu(OTf)_2$ were shown to be better catalysts than PPh_3AuNTf_2, leading to **6aa** in 83%, 67%, and 46% yield, respectively (entries 3–5). $Sc(OTf)_3$, BF_3OEt_2, $SnCl_4$, and $PtCl_2$ were found to be ineffective for this coupling (16–26%) (entries 6–9), whereas the coupling partners stayed inert in the presence of $AuBr_3$, CuI, and LiOTf (entries 10 and 11).

Next, we investigated briefly the scope of the TMSOTf-catalyzed glycosylation reaction with *ortho*-(methyltosylaminoethynyl)benzyl glycosides as donors (Table 2). Four representative glycosides **1a–1d** and four alcohols **5a–5d** were selected as coupling partners, and all the reactions were carried out under fixed conditions (0.1 eq. TMSOTf, 4 Å MS, CH_2Cl_2, rt, 2 h). The couplings of perbenzoyl-glucopyranoside **1a** with all the four alcohols led to the coupled glycosides in excellent yields (>91%) and with complete β-selectivity (entries 1–4), testifying the participation of the neighbouring group in the glycosylation.[1] Similarly, the couplings of 2,3,4-tri-*O*-benzoyl-L-rhamnopyranoside **1b** with alcohols **5a–5d** provided the corresponding α-L-rhamnosides in a fully stereocontrolled manner in high yields (88–95%; entries 5–8). As expected, the corresponding glycosylation reactions of perbenzyl-glucopyranoside **1c** and 2-deoxy-glucopyranoside **1d**, in the absence of a neighboring participating group, led to the coupled glycosides in high yields (83–99%), albeit in a pair of the α- and β-anomers (Table 2, entries 11–16).[12,13] It was noted that the reactions with the hindered glucose-4-OH derivative **5c** as the acceptor were devoid of the addition of alcohol onto the ynamide moiety, therefore the unglycosylated **5c** could be fully recovered.

In fact, the addition of alcohol onto the ynamide moiety became a serious problem when the alcohol to be glycosylated

Table 2 Glycosylation with *ortho*-(methyltosylaminoethynyl)benzyl glycosides **1a–1d** as donors under the catalysis of TMSOTf

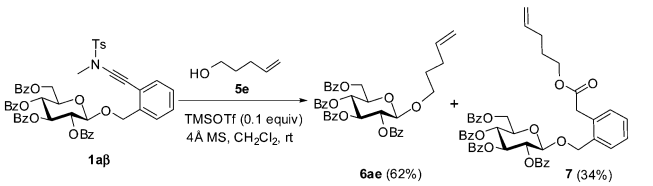


Entry	Donor	Acceptor	Product	Yield[a] [%]	α/β[b]
1	**1a**	**5a**	**6aa**	91	β only
2		**5b**	**6ab**	91	β only
3		**5c**	**6ac**	98	β only
4		**5d**	**6ad**	94	β only
5	**1b**	**5a**	**6ba**	90	α only
6		**5b**	**6bb**	95	α only
7		**5c**	**6bc**	88	α only
8		**5d**	**6bd**	91	α only
9	**1c**	**5a**	**6ca**	95	1 : 1
10		**5b**	**6cb**	93	1.5 : 1
11		**5c**	**6cc**	85	1.2 : 1
12		**5d**	**6cd**	89	1.2 : 1
13	**1d**	**5a**	**6da**	93	1.8 : 1
14		**5b**	**6db**	99	2.5 : 1
15		**5c**	**6dc**	83	10 : 1
16		**5d**	**6dd**	89	3 : 1

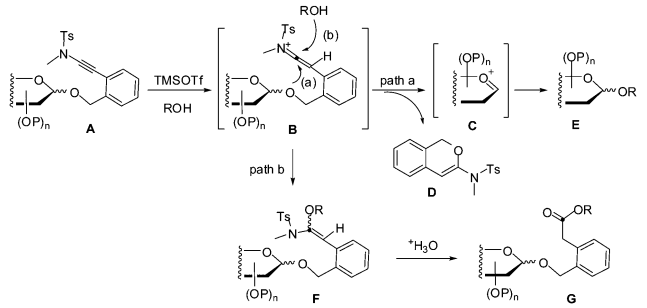
[a] Isolated yield. [b] The α/β ratio was determined by ^{1}H NMR spectroscopic measurement.

is highly reactive. Thus, the condensation of **1a** with 4-penten-1-ol **5e** under the catalysis of TMSOTf delivered the coupled glycoside **6ae** in only 62% yield, while ester **7**, which was derived from the corresponding adduct during workup, was isolated in 34% yield (Scheme 2).[11]

Based on these experimental findings and the nature of ynamides,[9,11] a plausible mechanism for the present TMSOTf-catalyzed glycosylation reaction with *ortho*-(methyltosylaminoethynyl)benzyl glycosides as donors was proposed (Scheme 3). Thus, keteniminium cation **B** was generated from *ortho*-(methyltosylaminoethynyl)benzyl glycoside **A** in the presence of ROH and TMSOTf (wherein HOTf[14] was produced *in situ*).[15] An intramolecular nucleophilic addition of the anomeric oxygen onto



Scheme 2 The coupling of *ortho*-(methyltosylaminoethynyl)benzyl glucopyranoside **1a** with 4-penten-1-ol (**5e**).

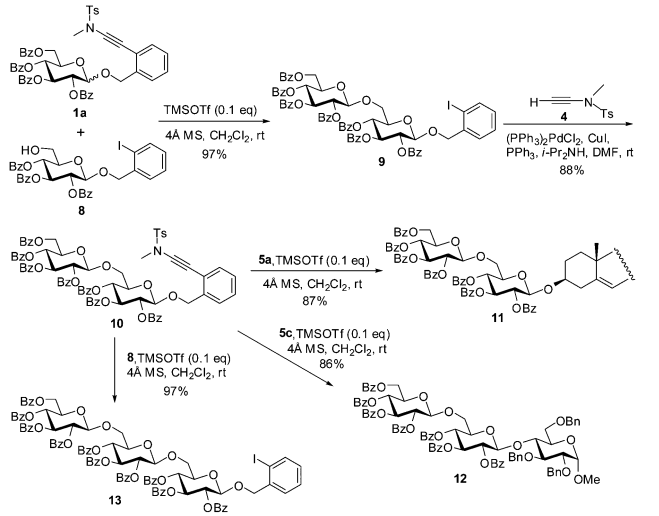


Scheme 3 A plausible mechanism for the glycosylation with *ortho*-(methyltosylaminoethynyl)benzyl glycosides as donors under the catalysis of TMSOTf.

the keteniminium led to sugar oxocarbenium ion **C** and 1*H*-isochromene **D** which was indeed characterized (path a). Sugar oxocarbenium ion **C** underwent glycosylation in the presence of ROH to provide glycoside **E**.[1e] Alternatively, keteniminium cation **B** could be attacked by the alcohol ROH, giving rise to alkoxy-substituted enamine intermediate **F** (path b). Hydrolysis of the enamine **F** during workup provided ester **G.**

Given the fact that the *ortho*-(methyltosylaminoethynyl)-benzyl glycoside donors are readily prepared from the *ortho*-iodobenzyl glycosides, which are inactive in the glycosylation reactions of the former, these donors could be applied to the expeditious synthesis of oligosaccharides based on the 'latent-active' strategy.[16] The previous donors applicable in the 'latent-active' synthesis of glycans include *p*-acetamidophenyl thioglycosides (*vs. p*-nitrophenyl thioglycosides),[17] *n*-pentenyl glycosides (*vs.* 4,5-dibromopentyl glycosides),[18] vinyl glycoside (*vs.* 1-methyl-2-propenyl glycosides),[19] 2-(hydroxycarbonyl)benzyl glycosides (*vs.* 2-(benzyloxycarbonyl)benzyl glycosides),[20] and *S*-benzimidazolyl glycosides (*vs. N*-anisoylated *S*-benzimidazolyl glycosides).[21] To demonstrate the feasibility of applying the present glycosylation protocol to the 'latent-active' assembly of glycans, the 'active' *ortho*-(methyltosylaminoethynyl)-benzyl glycoside **1a** was coupled with the 'latent' *ortho*-iodobenzyl glucoside derivative **8** in the presence of TMSOTf (0.1 eq.) to provide β-(1→6)-disaccharide **9** (97%), which was then converted into the 'active' *ortho*-(methyltosylaminoethynyl)benzyl disaccharide **10** *via* Sonogashira coupling with ynamide **4** (88%) (Scheme 4). Subsequent glycosylation of disaccharide **10** with cholesterol **5a** or glucose-4-OH derivative **5c** under similar glycosylation conditions furnished cholesterol 3-*O*-β-disaccharide **11** and β-trisaccharide **12** in 87% and 86% yields, respectively. In addition, glycosylation of disaccharide **10** with the 'latent' *ortho*-iodobenzyl glucoside acceptor **8** provided the 'latent' *ortho*-iodobenzyl trisaccharide **13** in 97% yield, which could be used for further elongation of the glycans *via* the iterative Sonogashira coupling/glycosylation sequence.

In conclusion, *ortho*-(methyltosylaminoethynyl)benzyl glycosides have been disclosed as a new type of glycosyl donors under the catalysis of TMSOTf. These shelf-stable donors are readily prepared from the corresponding *ortho*-iodobenzyl glycosides *via* Sonogashira coupling with ynamide **4**. The expeditious assembly of glycans *via* the 'latent-active' strategy using the present protocol has been demonstrated. These



Scheme 4 Assembly of oligosaccharides **11–13** by the 'latent-active' strategy using *ortho*-(methyltosylaminoethynyl)benzyl glycosides as donors and *ortho*-iodobenzyl glycosides as acceptors.

promising preliminary results shall warrant further elaboration and application of this new glycosylation method.

Financial support from the Ministry of Science and Technology of China (2012ZX09502-002), the National Natural Science Foundation of China (21432012), the Fundamental Research Funds for the Central Universities (WY1514052), and the Shanghai Pujiang Program (15PJ1401500) is gratefully acknowledged.

Notes and references

1 (*a*) X. Zhu and R. R. Schmidt, *Angew. Chem., Int. Ed.*, 2009, **48**, 1900–1934; (*b*) M. J. McKay and H. M. Nguyen, *ACS Catal.*, 2012, **2**, 1563–1595; (*c*) B. Yu, J. Sun and X. Yang, *Acc. Chem. Res.*, 2012, **45**, 1227–1236; (*d*) S. S. Nigudkar and A. V. Demchenko, *Chem. Sci.*, 2015, **6**, 2687–2704; (*e*) L. Bohe and D. Crich, *Carbohydr. Res.*, 2015, **403**, 48–59; (*f*) Y. Yang, X. Zhang and B. Yu, *Nat. Prod. Rep.*, 2015, DOI: 10.1039/C5NP00033E.

2 (*a*) S. Hotha and S. Kashyap, *J. Am. Chem. Soc.*, 2006, **128**, 9620–9621; (*b*) S. K. Mamidyala and M. G. Finn, *J. Org. Chem.*, 2009, **74**, 8417–8420; (*c*) S. R. Vidadala, S. A. Thadke and S. Hotha, *J. Org. Chem.*, 2009, **74**, 9233–9236; (*d*) S. R. Vidadala, G. Gayatri, G. N. Sastry and S. Hotha, *Chem. Commun.*, 2011, **47**, 9906–9908; (*e*) A. K. Kayastha and S. Hotha, *Chem. Commun.*, 2012, **48**, 7161–7163; (*f*) A. K. Kayastha and S. Hotha, *Beilstein J. Org. Chem.*, 2013, **9**, 2147–2155.

3 (*a*) G. Sureshkumar and S. Hotha, *Tetrahedron Lett.*, 2007, **48**, 6564–6568; (*b*) G. Sureshkumara and S. Hotha, *Chem. Commun.*, 2008, 4282–4284; (*c*) A. Y. Shaikh, G. Sureshkumar, D. Pati, S. S. Guptab and S. Hotha, *Org. Biomol. Chem.*, 2011, **9**, 5951–5959; (*d*) S. A. Thadke, B. Mishra and S. Hotha, *Org. Lett.*, 2013, **15**, 2466–2469; (*e*) S. A. Thadke, B. Mishra and S. Hotha, *J. Org. Chem.*, 2014, **79**, 7358–7371; (*f*) B. V. Rao, S. Manmode and S. Hotha, *J. Org. Chem.*, 2015, **80**, 1499–1505.

4 H. Imagawa, A. Kinoshita, T. Fukuyama, H. Yamamoto and M. Nishizawa, *Tetrahedron Lett.*, 2006, **47**, 4729–4731.

5 S. R. Koppolu, R. Niddana and R. Balamurugan, *Org. Biomol. Chem.*, 2015, **13**, 5094–5097.

6 (*a*) F. Yang, Q. Wang and B. Yu, *Tetrahedron Lett.*, 2012, **53**, 5231–5234; (*b*) S. Adhikari, K. N. Baryal, D. Zhu, X. Li and J. Zhu, *ACS Catal.*, 2013, **3**, 57–60.

7 (*a*) Y. Li, Y. Yang and B. Yu, *Tetrahedron Lett.*, 2008, **49**, 3604–3608; (*b*) Y. Li, X. Yang, Y. Liu, C. Zhu, Y. Yang and B. Yu, *Chem. – Eur. J.*, 2010, **16**, 1871–1882; (*c*) Y. Zhu and B. Yu, *Angew. Chem., Int. Ed.*, 2011, **50**, 8329–8332; (*d*) Y. Tang, J. Li, Y. Zhu, Y. Li and B. Yu, *J. Am.*

Chem. Soc., 2013, **135**, 18396–18405; (*e*) Y. Zhu and B. Yu, *Chem. – Eur. J.*, 2015, **21**, 8771–8780.

8 (*a*) Y. Yang, Y. Li and B. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 12076–12077; (*b*) Y. Li and B. Yu, *Chem. Commun.*, 2010, **46**, 6060–6062; (*c*) W. Yang, J. Sun, W. Lu, Y. Li, L. Shan, W. Han, W.-D. Zhang and B. Yu, *J. Org. Chem.*, 2010, **75**, 6879–6888; (*d*) Y. Ma, Z. Li, H. Shi, J. Zhang and B. Yu, *J. Org. Chem.*, 2011, **76**, 9748–9756; (*e*) Q. Zhang, J. Sun, Y. Zhu, F. Zhang and B. Yu, *Angew. Chem., Int. Ed.*, 2011, **50**, 4933–4936; (*f*) Y. Li, J. Sun and B. Yu, *Org. Lett.*, 2011, **13**, 5508–5511; (*g*) J. Yu, J. Sun and B. Yu, *Org. Lett.*, 2012, **14**, 4022–4025; (*h*) J. Zhang, H. Shi, Y. Ma and B. Yu, *Chem. Commun.*, 2012, **48**, 8679–8681; (*i*) J. Yu, J. Sun, Y. Niu, R. Li, J. Liao, F. Zhang and B. Yu, *Chem. Sci.*, 2013, **4**, 3899–3905; (*j*) G. Xiao and B. Yu, *Chem. – Eur. J.*, 2013, **19**, 7708–7712; (*k*) S. Nie, W. Li and B. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 4157–4160; (*l*) J. Li and B. Yu, *Angew. Chem., Int. Ed.*, 2015, **54**, 6618–6621; (*m*) X. Zhang, Y. Zhou, J. Zuo and B. Yu, *Nat. Commun.*, 2015, **6**, 5879, DOI: 10.1038/ncomms6879.

9 (*a*) C. A. Zificsak, J. A. Mulder, R. P. Hsung, C. Rameshkumar and L.-L. Wei, *Tetrahedron*, 2001, **57**, 7575–7606; (*b*) G. Evano, A. Coste and K. Jouvin, *Angew. Chem., Int. Ed.*, 2010, **49**, 2840–2859.

10 (*a*) Y.-P. Wang and R. L. Danheis, *Tetrahedron Lett.*, 2011, **52**, 2111–2114; (*b*) M. R. Tracey, Y. Zhang, M. O. Frederick, J. A. Mulder and R. P. Hsung, *Org. Lett.*, 2011, **13**, 5508–5511.

11 (*a*) M. C. B. Jaimes, V. Weingand, F. Rominger and A. S. K. Hashmi, *Chem. – Eur. J.*, 2013, **19**, 12504–12511; (*b*) Y. Kong, K. Jiang, J. Cao, L. Fu, L. Yu, G. Lai, Y. Cui, Z. Hu and G. Wang, *Org. Lett.*, 2013, **15**, 422–425; (*c*) T. Okitsu, K. Nakata, K. Nishigaki, N. Michioka, M. Karatani and A. Wada, *J. Org. Chem.*, 2014, **79**, 5914–5920; (*d*) D. Fujino, H. Yorimitsu and A. Osuka, *J. Am. Chem. Soc.*, 2014, **136**, 6255–6258; (*e*) S. Kramer, K. Dooleweerdt, A. T. Lindhardt, M. Rottländer and T. Skrydstrup, *Org. Lett.*, 2009, **11**, 4208–4211.

12 D. Hou and T. L. Lowary, *Carbohydr. Res.*, 2009, **344**, 1911–1940.

13 E. Juaristi and G. Cuevas, *The Anomeric Effect*, CRC Press, 1994, pp. 183–194.

14 T. T. Dang, F. Boeck and L. Hintermann, *J. Org. Chem.*, 2011, **76**, 9353–9361.

15 Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer and A. Davis, *Org. Lett.*, 2005, **7**, 1047–1050.

16 (*a*) T. C. Shiao and R. Roy, *Top. Curr. Chem.*, 2011, **301**, 69–108; (*b*) J. T. Smoot and A. V. Demchenko, *Adv. Carbohydr. Chem. Biochem.*, 2009, **62**, 161–250; (*c*) G. J. Boons, *Tetrahedron*, 1996, **52**, 1095–1121.

17 (*a*) R. Roy, F. O. Andersson and M. Letellier, *Tetrahedron Lett.*, 1992, **33**, 6053–6056; (*b*) L. Huang, Z. Wang and X. Huang, *Chem. Commun.*, 2004, 1960–1961.

18 B. Fraser-Reid, U. E. Udodong, Z. F. Wu, H. Ottosson, J. R. Merritt, C. S. Rao, C. Roberts and R. Madsen, *Synlett*, 1992, 927–942.

19 (*a*) G.-J. Boons and S. Isles, *Tetrahedron Lett.*, 1994, **35**, 3593–3596; (*b*) P. Wang, P. Haldar, Y. Wang and H. Hu, *J. Org. Chem.*, 2007, **72**, 5870–5873.

20 K. S. Kim, J. H. Kim, Y. J. Lee, Y. J. Lee and J. Park, *J. Am. Chem. Soc.*, 2001, **123**, 8477–8481.

21 S. J. Hasty, M. A. Kleine and A. V. Demchenko, *Angew. Chem., Int. Ed.*, 2011, **50**, 4197–4201.

