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A diversity oriented one-pot synthesis of novel iminosugar *C*-glycosides†

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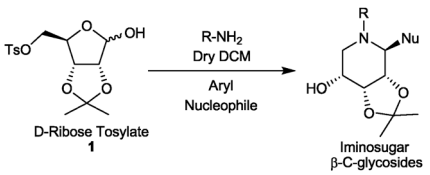
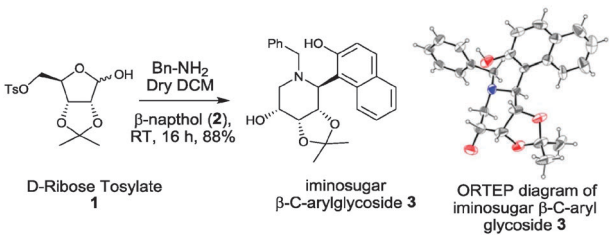
A mild and highly efficient one-pot method has been developed for the stereoselective synthesis of structurally diverse novel iminosugar *C*-aryl glycosides. The generality of this methodology is demonstrated with a wide variety of aryl nucleophiles and amines. The synthetic potential of this methodology is further shown in the domino synthesis of iminosugar based hybrid molecules.

Ever since the discovery of iminosugars as potent glycosidase inhibitors, they have evoked considerable interest at the interface between medicinal chemistry, glycobiology and organic synthesis.[1] The broad spectrum of biological activities displayed by iminosugars has widened their scope towards the inhibition of various enzymes of medicinal interest such as glycosyltransferases, glycogen phosphorylases, nucleoside-processing enzymes and metalloproteinases.[1,2] Moreover, iminosugars serve as potential molecules in probing active sites as well as the allosteric interactions with carbohydrate-processing enzymes (CPEs).[1] Thus, because of their biomimetic properties, iminosugars are becoming important lead molecules for drug development in a variety of therapeutic areas including diabetes, viral infections and tumor metastases. Recent biological studies have suggested that the presence of alkyl/aryl substituents on iminosugars often leads to an increase in potency and specificity.[3] This is further supported by the enhanced anticancer as well as the ceramide glucosyltransferase inhibitory activities displayed by *N*-alkylated iminosugars.[4] As a consequence, there has been ever-growing interest towards achieving a simple, general and reliable synthesis of various *N*-/*C*1-alkyl/aryl substituted iminosugars for a wide spectrum of biological evaluations.[5]

In this communication, we report a mild and highly efficient method for the diversity oriented one-pot synthesis of novel iminosugar *C*-aryl glycosides *via* stereoselective arylation of *in situ* generated iminium ions with various aryl nucleophiles (Scheme 1).



Scheme 1 Synthesis of novel iminosugar β-*C*-aryl glycosides.



Scheme 2 Synthesis of novel iminosugar β-*C*-aryl glycosides **3** from **1**.

Thus, treatment of D-ribose tosylate **1** at room temperature with benzyl amine and subsequent stereoselective arylation of the *in situ* generated iminium ions with β-naphthol (**2**) resulted in the isolation of a functionalized iminosugar β-*C*-glycoside **3** as the only product in 88% yield (Scheme 2).[6] The structure and stereochemistry of the iminosugar β-*C*-glycoside **3** was unambiguously confirmed using single crystal X-ray analysis.[7a] Encouraged by the efficacy of this transformation, the generality of this reaction was tested using a wide variety of amines and carbon nucleophiles and the results are summarized in Table 1.

Stereoselective arylation of the *in situ* generated iminium ions, derived from tosylate **1** using various amines, with resorcinol (**4**) resulted in the isolation of the corresponding iminosugar β-*C*-glycosides **5**, **6**, **7** and **8** respectively in very good yields (Table 1, entry 1). Similarly iminium ions, derived from benzylamine and tosylate **1**, on arylation with pyrogallol (**9**) and *m*-amino phenol (**11**) afforded the corresponding iminosugar β-*C*-glycosides **10** and **12**, respectively, in 84% and 80% yield (Table 1, entries 2 and 3). Under similar reaction conditions, the heteroaromatics such as indole (**13**) and pyrrole (**15**) underwent a smooth reaction to

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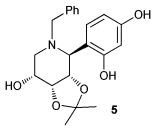
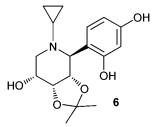
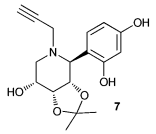
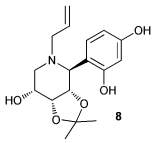
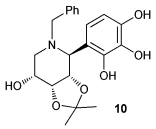
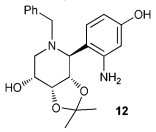
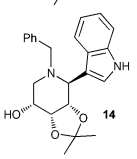
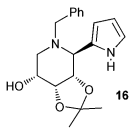
† Electronic supplementary information (ESI) available: Representative experimental procedure and characterization of reaction products. CCDC 931863–931865. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc48370c

Table 1 One-pot synthesis of iminosugar β-*C*-aryl glycosides

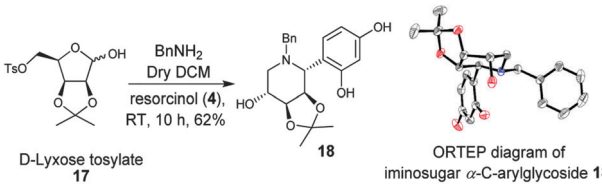
Entry	Nucleophile	Time (h)	Product	Yield[a] (%)
1	 4	11	 5	92[b]
		20	 6	80[c]
		10	 7	84[d]
		12	 8	89[e]
2	 9	14	 10	84[b]
3	 11	8	 12	80[b]
4	 13	10	 14	60[b]
5	 15	7	 16	68[b]

[a] Yield of the pure isolated product. [b] Iminium ion derived from benzyl amine. [c] Cyclopropyl amine. [d] Propargyl amine. [e] Allylamine.

give the corresponding iminosugar β-*C*-glycosides **14** and **16**, respectively, in good yields with a high degree of stereoselectivity (Table 1, entries 4 and 5).

Intriguingly, tosylate **17** derived from D-lyxose is also found to undergo similar transformations with equal ease. Thus, the reaction of D-lyxose tosylate derivative **17** with benzylamine and subsequent arylation of the *in situ* generated iminium ions with resorcinol (**4**) afforded the corresponding iminosugar α-*C*-aryl glycoside **18** in good yield with excellent stereoselectivity (Scheme 3). The structure and stereochemistry of the iminosugar α-*C*-aryl glycoside **18** was unambiguously confirmed using single crystal X-ray analysis.[7b]

The synthetic utility of this methodology was further explored in the domino synthesis of skeletally challenging iminosugar based hybrid molecules.[8,9] The indolo[2,3-*a*]quinolizidine ring system is one of the most important structural subunits present in a wide variety of biologically active alkaloids exhibiting anticancer, antibacterial, antifertility, and antitussive activities.[10] For the construction of this



Scheme 3 Synthesis of iminosugar α-*C*-aryl glycoside **18** from D-lyxose tosylate **17**.

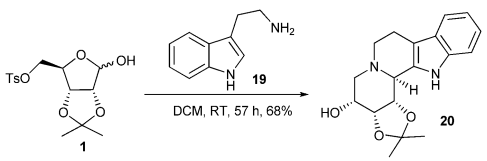
polycyclic framework, several multi-step approaches have been reported based on diastereoselective vinylogous Mannich reaction,[11] Bischler–Napieralski reaction,[12] Fischer indole synthesis[13] and asymmetric Pictet–Spengler reaction.[14]

Using our new methodology, a domino reaction based strategy[15] has been developed for the stereoselective synthesis of novel polyhydroxy indolo[2,3-*a*]quinolizidine derivatives. Thus, exposure of D-ribose tosylate **1** to tryptamine (**19**) at room temperature resulted in a smooth domino cyclization *via* iminium ions to furnish the corresponding iminosugar based hybrid molecule **20** in good yield (Scheme 4). The structure and stereochemistry of the hybrid molecule **20** was unambiguously confirmed using single crystal X-ray analysis (Fig. 1).[7c]

The versatility of this domino reaction was further tested with various aryl amino acid derivatives such as L-tryptophan methyl ester (**21**), L-3,4-dihydroxyphenylalanine methyl ester (**23**), and histidine methyl ester (**25**), and the results are summarized in Table 2. All amino acid derivatives underwent a smooth domino reaction to give the corresponding hybrid iminosugar molecules **22**, **24** and **26** respectively in excellent yields (Table 2, entries 1–3).

Similarly, the reaction of tosylate **17**, derived from D-lyxose, with L-tryptophan methyl ester (**21**) and L-3,4-dihydroxyphenylalanine methyl ester (**23**), under similar reaction conditions, afforded the corresponding highly functionalized hybrid molecules **27** and **28**, respectively, in good yields (Table 2, entry 4 and 5).

A plausible mechanism for the formation of iminosugar based hybrid molecules from tosylate **1** is shown in Scheme 5. It is believed that the tosylate **1** on treatment with tryptamine **19** would lead to the formation of the imine intermediate **1A**, which on subsequent SN_2 displacement of tosylate would lead to the corresponding cyclic



Scheme 4 Domino synthesis of iminosugar based hybrid molecule.

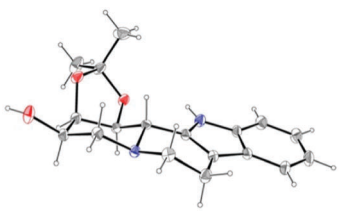
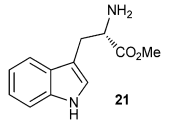
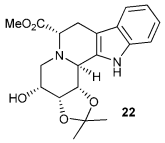
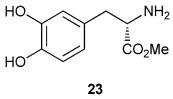
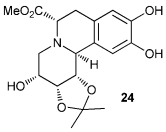
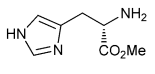
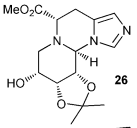
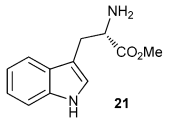
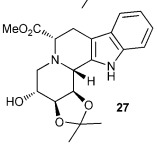
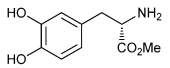
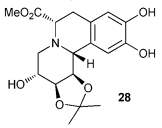
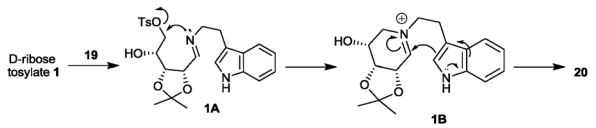


Fig. 1 ORTEP diagram of the iminosugar based hybrid molecule **20**.

Table 2 Domino synthesis of iminosugar based hybrid molecules

Entry	Nucleophile	Time (h)	Product	Yield[a] (%)
1	 21	16	 22	83
2	 23	10	 24	88
3	 25	7	 26	94
4	 21	48	 27	74[b]
5	 23	47	 28	78[b]

[a] Yield of the pure isolated product. [b] Tosylate **17** derived from D-lyxose was used.



Scheme 5 Plausible mechanism for the formation of hybrid molecule.

iminium ion intermediate **1B**. The cyclic iminium ion intermediate **1B** would then undergo Pictet–Spengler reaction with the electron rich indole moiety to furnish the hybrid molecule **20**.

In summary, we have developed a simple and highly efficient method for the synthesis of novel iminosugar *C*-aryl glycosides in very good yields. This one-pot method is highly diastereoselective and several sensitive functional groups such as –OH, –NH_2, ester, cyclopropyl, propargyl, and alkene are found to be stable under the reaction conditions. The present diversity oriented approach provides an easy access to a wide variety of iminosugar *C*-aryl glycosides at room temperature. The synthetic potential of this methodology is further exemplified in the domino synthesis of synthetically challenging iminosugar based hybrid molecules.[16]

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Notes and references

1 P. Compain and O. R. Martin, *Iminosugars: From Synthesis to Therapeutic applications*, John Wiley & Sons, Hoboken, 2007, p. 467; G. B. Fodor and B. Colasanti, *The Pyridine and Piperidine Alkaloids, Chemistry and Pharmacology*, Alkaloids: Chemical and Biological Perspectives, ed. S. W. Pelletier, Wiley-Interscience, New York, 1985, vol. 3, p. 1; N. Asano, R. J. Nash, R. J. Molyneux and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 2000, **11**, 1645; E. S. H. Ashry, N. Rashed and A. H. S. Shobier, *Pharmazie*, 2000, **55**, 331.

2 P. Compain, C. Decroocq, J. Iehl, M. Holler, D. Hazelard, T. M. Barrag, C. O. Mellet and J.-F. Nierengarten, *Angew. Chem., Int. Ed.*, 2010, **49**, 5753; H.-J. Wu, C.-W. Ho, T.-P. Ko, S. D. Popat, C.-H. Lin and A. H.-J. Wang, *Angew. Chem., Int. Ed.*, 2010, **49**, 337.

3 P. Compain and O. R. Martin, *Iminosugars: From Synthesis to Therapeutic Applications*, Wiley-VCH, Weinheim, Germany, 2007, p. 63; R. J. Nash, A. Kato, C.-Y. Yu and G. W. J. Fleet, *Future Med. Chem.*, 2011, **3**, 1513; G. Horne, F. X. Wilson, J. Tinsley, D. H. Williams and R. Storer, *Drug Discovery Today*, 2011, **16**, 107; N. Asano, *Curr. Top. Med. Chem.*, 2003, **3**, 471; Y. Ichikawa, Y. Igarashi, M. Ichikawa and Y. Suhara, *J. Am. Chem. Soc.*, 1998, **120**, 3007.

4 M. G. Szczepina, B. D. Johnston, Y. Yuan, B. Svensson and B. M. Pinto, *J. Am. Chem. Soc.*, 2004, **126**, 12458; T. D. Butters, L. A. G. M. van den Broek, G. W. J. Fleet, T. M. Krulle, M. R. Wormald, R. A. Dwek and F. M. Platt, *Tetrahedron: Asymmetry*, 2000, **11**, 113; T. D. Butters, R. A. Dwek and F. M. Platt, *Chem. Rev.*, 2000, **100**, 4683; N. L. Segraves and P. Crews, *J. Nat. Prod.*, 2005, **68**, 118.

5 P. Compain, V. Chagnault and O. R. Martin, *Tetrahedron: Asymmetry*, 2009, **20**, 652; B. G. Davis, *Tetrahedron: Asymmetry*, 2009, **20**, 672 and the references cited therein; K. Afarinkia and A. Bahar, *Tetrahedron: Asymmetry*, 2005, **16**, 1239; A. Aravind, M. G. Sankar, B. Varghese and S. Baskaran, *J. Org. Chem.*, 2009, **74**, 2858; A. Aravind, P. S. Kumar, M. G. Sankar and S. Baskaran, *Eur. J. Org. Chem.*, 2011, 6980; P. S. Kumar, A. Banerjee and S. Baskaran, *Angew. Chem., Int. Ed.*, 2010, **49**, 804; M. Yokoyama, T. Akiba, Y. Ochiai, A. Momotake and H. Togo, *J. Org. Chem.*, 1996, **61**, 6079; E.-R. van Rijssel, T. P. M. Goumans, G. Lodder, H. S. Overkleeft, G. A. van der Marel and D. C. Codée, *Org. Lett.*, 2013, **15**, 3026.

6 For *C*-nucleosidation of five membered cyclic imine in the presence of Brønsted acid see. B. Han, B. Jaun, R. Krishnamurthy and A. Eschenmoser, *Org. Lett.*, 2004, **6**, 3691; B. Han, V. Rajwanshi, J. Nandy, R. Krishnamurthy and A. Eschenmoser, *Synlett*, 2005, 744; For addition of organometallic reagents to five membered cyclic imines see: G. B. Evans, R. H. Furneaux, G. J. Gainsford, V. L. Schramm and P. C. Tyler, *Tetrahedron*, 2000, **56**, 3053; G. B. Evans, R. H. Furneaux, H. Hausler, J. S. Larsen and P. C. Tyler, *J. Org. Chem.*, 2004, **69**, 2217; G. B. Evans, R. H. Furneaux, G. J. Gainsford, J. C. Hanson, G. A. Kicska, A. A. Sauve, V. L. Schramm and P. C. Tyler, *Med. Chem.*, 2003, **46**, 155.

7 (*a*) CCDC 931863; (*b*) CCDC 931865; (*c*) CCDC 931864.

8 Hybrid approach in drug discovery has gained interest in developing novel molecules with a dual mode of biological function to effectively target multifactorial diseases. For reviews see, M. Decker, *Curr. Med. Chem.*, 2011, **18**, 1464; B. Meunier, *Acc. Chem. Res.*, 2008, **41**, 69; P. G. Baraldi, D. Preti, F. Fruttarolo, M. A. Tabrizi and R. Romagnoli, *Bioorg. Med. Chem.*, 2007, **15**, 17.

9 F. Sébastien and G. Bérubé, *Expert Opin. Drug Discovery*, 2013, **8**, 1029; L. K. Gediya and V. C. O. Njar, *Expert Opin. Drug Discovery*, 2009, **4**, 1099; J. J. Walsh and A. Bell, *Curr. Pharm. Des.*, 2009, **15**, 2970; J. Tang, K. Maddali, C. D. Dreis, Y. Y. Sham, R. Vince, Y. Pommier and Z. Wang, *ACS Med. Chem. Lett.*, 2011, **2**, 63; J. F. Billing and U. J. Nilsson, *Tetrahedron*, 2005, **61**, 863.

10 R. T. Brown, in *Indole and Biogenetically Related Alkaloids*, ed. J. D. Phillipson and M. H. Zenk, Academic Press, London, 1980, ch. 9; R. T. Brown, in *The Chemistry and Biology of Isoquinoline Alkaloids*, ed. J. D. Phillipson, M. F. Roberts and M. H. Zenk, Springer-Verlag, Berlin, 1985, p. 204; H. Waldmann, M. Braun, M. Weymann and M. Gewehr, *Tetrahedron*, 1993, **49**, 397; A. I. Meyers, *Tetrahedron*, 1992, **48**, 2589; H. H. Wasserman and G.-H. Kuo, *Tetrahedron*, 1992, **48**, 7071; R. L. Beard and A. I. Meyers, *J. Org. Chem.*, 1991, **56**, 2091.

11 A. Deiters, K. Chen, C. T. Early and S. F. Martin, *J. Am. Chem. Soc.*, 2003, **125**, 4541.

12 A. Deiters and S. F. Martin, *Org. Lett.*, 2002, **4**, 3243.

13 R. S. Fornicola, K. Subburaj and J. Montgomery, *Org. Lett.*, 2002, **4**, 615.

14 J. Stöckigt, A. P. Antonchick, F. Wu and H. Waldmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 8538. and the references cited therein.

15 L. F. Tietze and K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006; L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; L. F. Tietze and N. Rackelmann, *Pure Appl. Chem.*, 2004, **76**, 1967.

16 The biological significance of the iminosugar *C*-glycosides and hybrid molecules are being evaluated and will be reported in due course.