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Iminosugars from α,β-epoxyamides. Part 1: Synthetic approach to hydroxylated piperidine derivatives

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Abstract—A new synthetic route towards iminosugars starting from chiral epoxyamides is described. The strategy, by which a single precursor, the α,β-epoxyamide obtained from 6-*O*-trityl-2,3-*O*-isopropylidene-D-ribose and a sulphur ylide, can be transformed into different iminosugars, is based on the combination of a regioselective epoxide opening and stereospecific intramolecular displacements.
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Iminosugars have been the object of an intense research effort during last years,[1,2] due to their remarkable biological activities such as selective glycosidase and glycosyltransferases inhibitors. Several studies have confirmed the value of these compounds in inhibiting the human immunodeficiency virus (HIV) replication.[3] It has also been demonstrated their therapeutic applications for the treatment of hyperglycemia and disorders related to these conditions such as obesity and diabetes.[4] These useful biological properties have prompted the search for more efficient and/or more selective compounds and iminosugar derivatives of great structural diversity have been prepared[3,5] or isolated from natural sources.[6,7]

Homoiminosugars (also named homoazasugars), with an additional anomeric hydroxymethyl such as α-HMJ and β-HMJ (homomannojirimycins) as well as some glycosides, are natural products and their syntheses have preceded their isolation from cultivated plants; this incorporated substituent might provide additional selectivity.[8,9] It has been also described that monomethyl amides analogues showed strong competitive inhibition against glucosaminidases[8] (Fig. 1).

This paper reports the synthesis of piperidinic homoiminosugars precursors from chiral epoxyamides.

The syntheses of α,β-epoxyamides in a highly stereoselective manner by reaction of monosaccharides, properly functionalized, with stabilized sulfonium ylides, have been performed by our group in the last years.[10,11] These systems with a high degree of functionality represent new, readily available, optically active building blocks for use in synthesis. Our preliminary studies showed these epoxyamides as precursors of C-glycosides, by intramolecular cyclisation by oxirane ring opening.[12] Now, our strategy is leading to synthesize azasugars and related products.

Since the epoxyamide **1** is obtained in quantitative yield with complete stereoselectivity,[13] firstly we started with this easily available D-ribose derivative (only three steps from D-ribose) to reach our objectives. Two strategies were established (Scheme 1).

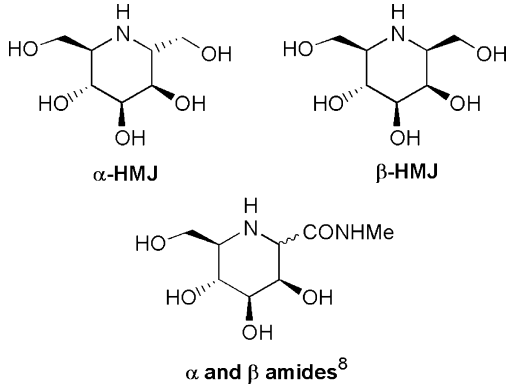

Figure 1.

Keywords: iminosugar; azasugar; hydroxylated piperidines; epoxyamide; C-glycosides; sulphur ylides.
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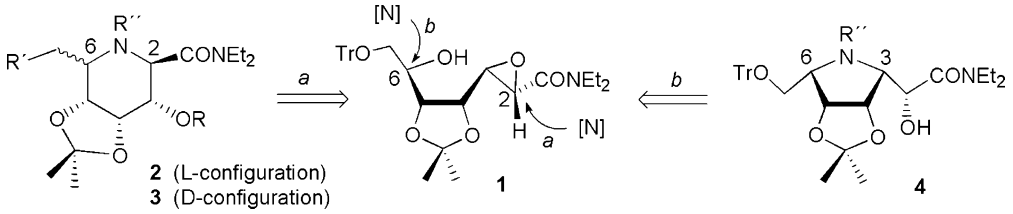


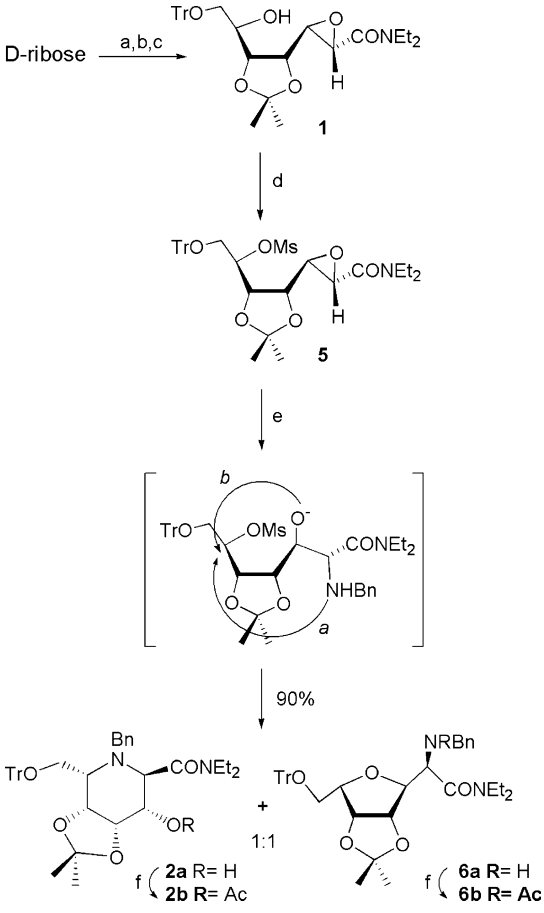
Scheme 1.

(*a*) Cyclisation by nucleophilic displacement on C-6: Introduction of the heteroatom (nitrogen) at C-2 by a regioselective opening[14] of the epoxide group in **1**, hydroxy group transformation at C-6, with configurational inversion or retention and intramolecular cyclisation to piperidines **2** and **3** by stereospecific displacement of a good leaving group at C-6.

(*b*) Cyclisation by nucleophilic displacement on C-3: Introduction of the heteroatom at C-6 in **1**, with subsequent 5-*exo* cyclisation to afford the functionalized pyrrolidines **4**.

In this paper we describe the development of the first strategy (*a*). The protected polyhydroxypiperidines can be prepared alternatively by means of two synthetic routes: (a) previous transformation at C-6 and subsequent epoxide opening (Scheme 2) and (b) epoxide opening followed by selective hydroxyl group protection (Schemes 3 and 5).

In the first approach, the epoxyamide **1** was treated with mesyl chloride in pyridine at 0°C giving the mesylated product **5**. The oxirane ring of **5** was opened with complete regioselectivity by benzyl amine with subsequent intramolecular displacement of mesyl group giving the imino sugar **2a** and the C-glycoside **6a** (only two steps from the epoxyamide **1** and five from D-ribose). The formation of these products can be justified by the mechanism depicted in Scheme 2 (via *a*→**2a**, via *b*→**6a**). The acetylation of **2a** and **6a** in the usual manner afforded the products **2b** and **6b**. Characteristic features of the ^{1}H and ^{13}C NMR spectra and COSY experiments, provided strong evidence for the proposed structures of **2a**, **2b**, **6a** and **6b**.

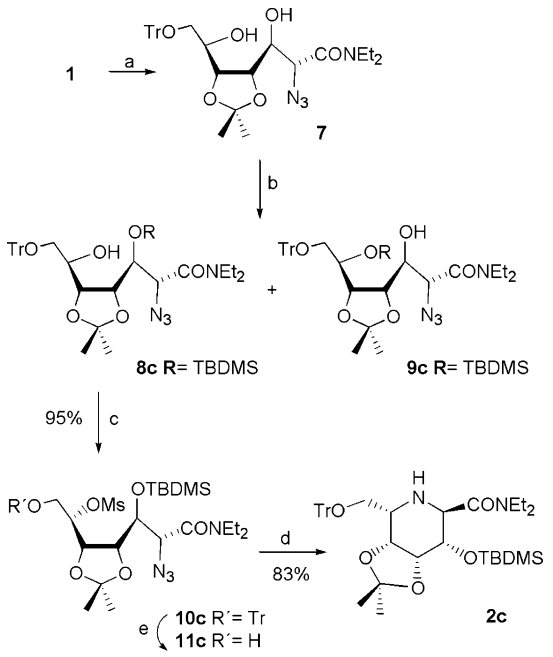


Scheme 2. *Reagents and conditions*: (a) Me_2CO, H^+; (b) TrCl, py; (c) $Me_2S^+CH_2CONEt_2,Cl^-$, 20% NaOH (aq) CH_2Cl_2; (d) MsCl, py; (e) H_2NBn, MeOH; (f) Ac_2O, py.

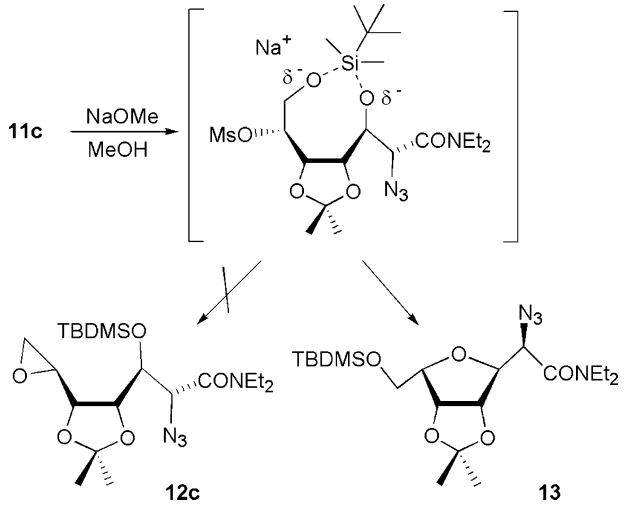
In order to avoid the formation of C-glycoside **6a** an alternative route was developed (Scheme 3). The epoxide **1** was treated with sodium azide in AcOH/DMF to give the azide derivative **7** with complete regioselectivity. The selective protection of the OH group on C-3 was achieved with TBDMSOTf and 2,6-lutidine in methylene chloride at 0°C (**8c**:**9c**, 2:1). The transformation of **8c** into the mesylate **10c** with mesyl chloride in pyridine (95% yield) and the further treatment of the azide group with Ph_3P in THF, followed by addition of water, gave the functionalized homoiminosugar **2c** in 83% yield.

The formation of a D-epimer of **2c** was intended via the formation of the epoxide **12c**. Preliminary assays toward the formation of the terminal epoxide from product **11c** failed but gave the C-glycoside **13**, which could be characterized by spectroscopic data. The formation of **13** can be justified by a 1,7 O→O migration of the TBDMS group in basic media[15] and further attack of O-C3 with intramolecular substitution of the mesyl group (Scheme 4).

The silyl group migration was avoided when **7** was protected with the triisopropylsilyl ether (TIPS).[16] The regioselectivity observed was higher to that of TBDMS group (Table 1). Selective protection with other groups were tested: treatment of **7** with *t*-butyldiphenylsilyl chloride afforded **9e** as the major product; this opposite regioselectivity can be justified by a π-π stacking interaction with the trityl group. The reaction with benzyl bromide yielded a mixture 1:1 of benzylated products.



Scheme 3. *Reagents and conditions*: (a) NaN_3, AcOH, DMF; (b) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C; (c) MsCl, py, 0°C; (d) i-Ph_3P, THF; ii-H_2O; (e) 2% TFA in CH_2Cl_2.

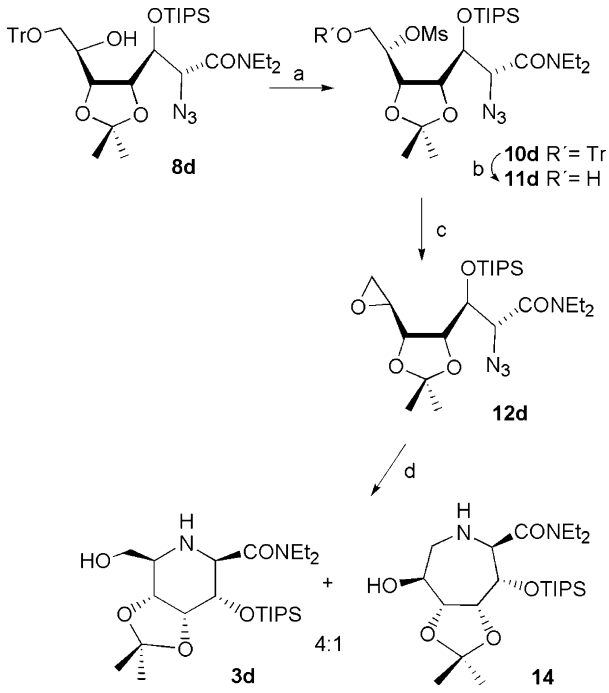


Scheme 4.

Table 1. Regioselectivity in the hydroxyl group protection

Series	R	Reactive	Relation products **8**:**9**
c	TBDMS	TBDMSOTf	2:1
d	TIPS	TIPSOTf	3:1
e	TBDPS	TBDPSCl	0:1
f	Bn	BnBr	1:1

The formation of epoxide **12d** from the derivated **11d** was accomplished as depicted in Scheme 5. The mesylation of **8d** followed by the deprotection of trityl group afforded **11d**. The treatment of **11d** with solid sodium methoxide in $CDCl_3$, permitted us to monitorize the



Scheme 5. *Reagents and conditions*: (a) MsCl, py, 0°C; (b) 2% TFA in CH_2Cl_2; (c) 1 M solid NaOMe in $CHCl_3$; (d) i-Ph_3P, $CHCl_3$; ii-H_2O.

reaction by ^1H NMR, showing the epoxide formation according to the signals (ppm) at 3.44 (m, H-6), 2.61 and 2.84 (2dd, H-7,7′). When the azide group was reduced with $Ph_3P/CHCl_3$ followed by water addition, the subsequent intramolecular oxirane opening led to the 6-*exo* product **3d** as the more favoured over the 7-*endo* product **14** by a ratio of 4:1. The structural assignments for **3d** and **14** were based on their NMR spectroscopic data: 2.75 (m, H-6), 3.42, 3.76 (m, H-7,7′) and 58.0 (C-6), 63.0 (C-7) for **3d**; 3.85 (m, H-6), 2.93 (m, H-7,7′) and 71.02 (C-6), 46.34 (C-7) for **14**.

The present syntheses of **2a**, **2c** and **3d** from the ribose derivative **1** have demonstrated the utility of α,β-epoxyamides in the formation of hydroxylated piperidines. Summing up, we have reported an efficient methodology for the preparation of iminosugars based on the combination of a regioselective epoxide opening and a stereospecific cyclisation. The scope of this strategy can still be enhanced by the use of different monosaccharide starting materials.

Acknowledgements

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