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.

Iminosugars have been the object of an intense research effort during last years, 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. It has also been demonstrated their therapeutic applications for the treatment of hyperglycemia and disorders related to these conditions such as obesity and diabetes. These useful biological properties have prompted the search for more efficient and/or more selective iminosugars and iminosugar derivatives of great structural diversity have been prepared or isolated from natural sources.

Homoiminosugars (also named homoaazasugars), 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. It has been also described that monomethyl amides analogues showed strong competitive inhibition against glucosaminidases (Fig. 1).

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

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 regioslective 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\(^\circ\)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.

In order to avoid the formation of C-glycoside 6a an alternative route was developed (Scheme 3). The epoxyamide 1 was treated with sodium azide in AcOH/DMF to give the azide derivative 7 with complete regioslectivity. The selective protection of the OH group on C-3 was achieved with TBDMSOTf and 2,6-lutidine in methylene chloride at 0\(^\circ\)C (8c:9c, 2:1). The transformation of 8c into the mesylate 10c with mesyl chloride at 0\(^\circ\)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$_3$P in THF, followed by addition of water, gave the functionalized homoiminosugar 2e 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 11e 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 trisopropylsilyl 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 \(\pi\)-\(\pi\) 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) NaN₃, AcOH, DMF; (b) TBDMSOTf, 2,6-lutidine, CH₂Cl₂, 0°C; (c) MsCl, py, 0°C; (d) i-Ph₃P, THF; ii-H₂O; (e) 2% TFA in CH₂Cl₂.

Scheme 5. Reagents and conditions: (a) MsCl, py, 0°C; (b) 2% TFA in CH₂Cl₂; (c) 1 M solid NaOMe in CHCl₃; (d) i-Ph₃P, CHCl₃; ii-H₂O.

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 CDCl₃, permitted us to monitorize the 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'p37). When the azide group was reduced with Ph₃P/CHCl₃ 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 ω,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.

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