Divergent synthesis of various iminocyclitols from D-ribose†

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A very efficient route to the diastereoselective synthesis of polyhydroxy pyrrolidines, piperidines and azepanes from an aldehyde derivative of ribose is reported. Asymmetric $\alpha$-amination of aldehydes using proline catalysed hydrazination is the key step in the synthesis. The method utilizes the stereocenters present in ribose and the extra carbon atoms present in the target molecules are incorporated using Wittig reactions. The incorporation of the amino group is carried out asymmetrically to account for additional stereocenters. This synthetic route to iminocyclitols has the potential to be extended for the synthesis of a large class of such compounds starting from other sugar derived aldehydes.

Introduction

Iminocyclitols are sugar analogues with a secondary or tertiary amino group replacing the oxygen atom in the ring. These compounds, consisting of a 5, 6 or 7 membered polyhydroxy N-heterocyclic frameworks are generally referred to as iminosugars or azasugars (Fig. 1). They are potential inhibitors of various carbohydrate processing enzymes and are key to the development of therapeutics for a wide range of diseases such as diabetes, cancer and viral infections including AIDS. Dihydroxymethyl-3,4-dihydroxy pyrrolidine (DMDP, 1a) along with its isomers are first among the pyrrolidine class of iminosugars to be isolated from natural sources. They are known to inhibit both $\alpha$- and $\beta$-glycosidases. 1- and 2-deoxynojirimycin derivatives 2a, 2b, 3a and 3b are among the 6-membered iminosugars, which exhibit inhibitory activity towards $\alpha$-glucosidases and ceramide glucosyltransferases (CGT). Compounds 4a and 4b are polyhydroxyazepane derivatives and are examples of 7-membered iminocyclitols, which have received relatively less attention in terms of synthesis and evaluation of inhibitory activity. Stereoselective routes to the synthesis of these compounds are of great interest and significance due to their potential in therapeutics.

Incorporation of an amino group stereoselectively into a cyclic or linear polyhydroxy system is the important step in most of the reported syntheses of these compounds. The incorporation of the amino group is achieved by nucleophilic displacement of a leaving group with azide anions or with alkyl amines. These routes are generally limited to the possibility of synthesizing only one diastereomer of the molecule from a starting compound. It will therefore, be useful to have strategies, where at least two diastereomers of the target molecules can be synthesized from the same intermediate by switching a chiral catalyst to generate new stereocentres with control. The incorporation of additional carbon atoms into a synthetic intermediate is achieved either by Wittig reaction or using organometallic reagents in general. Generation of new stereocentres during or after the incorporation of additional carbon atoms on a synthetic intermediate is often done through the asymmetric induction offered by the existing stereocentres within the intermediate.

We report here a divergent method for the synthesis of various iminocyclitols starting from ribose. The method opens...
up the possibility of synthesizing target molecules with higher number of carbon atoms and stereocentres than the starting material used. Wittig reactions were used to incorporate additional carbon atoms and organocatalytic asymmetric amination of aldehydes was used for the generation of new chiral centres functionalized with nitrogen atoms. The use of \( \alpha \)- and \( \beta \)-proline separately as catalysts offers the possibility to generate two different diastereomers with high selectivity. Although, proline catalysed asymmetric amination has been used widely in synthesis, it has not been explored to the same extent in carbohydrate chemistry.

**Results and discussion**

Our strategy towards the synthesis of these molecules is based on the synthesis of an amino alcohol derivative with a suitably positioned leaving group (mesylate). These amino alcohols are prepared by proline catalyzed asymmetric amination of aldehydes derived from ribose. A nucleophile substitution of the mesylate group by the free amino group leading to the formation of 5, 6 or 7 membered rings was expected (Scheme 1).

The syntheses of the 5-membered iminocyclitols 1a and 1b were achieved from the aldehyde 9, synthesized from the commercially available ribose derivative 5 (Scheme 2). Wittig reaction of 5 using methyldiphenylphosphonium bromide yielded the alkene 6. The secondary hydroxyl group in 6 was converted to a mesylate to get 7 in very high yield. Hydroboration/oxidation of 7 gave the primary alcohol 8, which on Swern oxidation yielded the aldehyde 9 (Scheme 2).

The aldehyde 9 was treated with dibenzyl azodicarboxylate in the presence of both \( \alpha \)- and \( \beta \)-proline (0.1 equiv.) in separate reactions to get the hydrazino aldehydes, which were reduced to the corresponding primary alcohols 10a and 10b in one-pot. The diastereomeric ratios of these compounds were estimated using chiral HPLC and were established by comparing the chromatograms with that of a 1 : 1 mixture of the diastereomers obtained through reactions catalyzed by \( \alpha \)-proline. The asymmetric \( \alpha \)-hydrazination reaction follows a very ordered transition state, which is similar to the one proposed by List and Jorgensen. The orientation of the carboxylic acid function of proline decides the outcome of the reaction and thus the stereochemistry of the products. While \( \alpha \)-proline prefers the attack on the \( Re \)-face, the reaction using \( \beta \)-proline proceeds on the \( Si \)-face. While asymmetric hydrazination catalyzed by \( \alpha \)-proline gave 10a as a single diastereomer, the reaction catalyzed by \( \beta \)-proline yielded 10b and 10a in a 90 : 10 ratio. The lower selectivity achieved in one of these \( \alpha \)-functionalization reactions is expected and is accounted for based on the influence of the stereochemistry of the \( \beta \)-carbon. Such differences in selectivity during asymmetric hydrazination using \( \alpha \)- and \( \beta \)-proline on the same substrate can be more prominent depending on the nature of the substrate. Similar observations in the case of proline catalyzed aldol reactions have extensively been studied.

Hydrogenolysis of the hydrazino groups in 10a and 10b using freshly prepared RANEY® Ni and H2 yielded the corresponding amino compounds, which underwent immediate cyclization by displacing the mesylate to give the pyrrolidine derivatives 11a and 11b in 78% and 73% yields respectively. The targeted iminocyclitols 1a and 1b were obtained in overall yields of 27% and 21%, respectively by acidolysis of the proline. The diastereomeric ratios of these compounds were estimated using chiral HPLC. Similar observations in the case of proline catalyzed aldol reactions have extensively been studied.

The deoxynojirimycin derivatives 2a and 2b were synthesized using a similar strategy as the one used for the synthesis of 1a and 1b through 9. An aldehyde derivative 16 was prepared from 6 by using a different strategy for protecting and activating the hydroxyl groups. Accordingly, the secondary hydroxyl group in 6 was protected using MOMCl to get 12 in 89% yield. The TBDPS group in 12 was removed with TBAF to get the primary alcohol 13, which was treated with MsCl to get 14. Hydroboration/oxidation of 14 gave the primary alcohol 15, which on Swern oxidation yielded the required aldehyde 16 (Scheme 4). Following the strategy used for the synthesis of 1a and 1b from 9, 2a and 2b were synthesized from 16 with overall yields of 19% and 17%, respectively (Scheme 5). The diastereoselectivity of the \( \alpha \)-proline catalyzed reaction was very high (95 : 5) in favour of 17a. However, the corresponding \( \beta \)-proline catalyzed reaction was only moderately selective. It has to be noted that the \( \alpha \)-proline catalyzed reaction on 16 proceeded to give 17a and 17b as a 60 : 40 mixture. Although 17a
and 17b are not separable by column chromatography, the iminocyclitol derivatives 18a and 18b are separated easily. If 2a and 2b are required to be synthesized, use of D-proline as a catalyst and separation of 18a and 18b are preferred. The stereochemistry of 2a and 2b was confirmed using NMR studies\textsuperscript{18} and the spectral data were also found to match with those reported in the literature.\textsuperscript{7i,10d}

The homonojirimycin derivatives 3a and 3b and the 7-hydroxymethyl-3,4,5-trihydroxyazepane derivatives 4a and 4b were synthesized by increasing the number of carbon atoms in the ribose derivative 5 by two through a Wittig reaction using the stabilized ylide, Ph\textsubscript{3}P=CHCOOEt. The \(\alpha,\beta\)-unsaturated ester obtained was reduced using Pd/C and \(\text{H}_2\) to get the hydroxy ester 19 in 85\% yield (Scheme 6). The secondary hydroxyl group was converted to a mesylate using MsCl in the presence of triethylamine to get 20. The ester group in 20 was reduced using DIBAL-H to get the aldehyde 21 required for the preparation of 3a and 3b (Scheme 6).

Hydrazination of 21 under similar conditions used for the synthesis of 10 from 9, using both L- and D-proline yielded 22a and 22b in good yields. Unlike the \(\alpha\)-functionalization of 9 and 16, the reaction of the aldehyde 21 proceeded with very high diastereoselectivity with L- and D-proline. The absence of inherent chirality on the \(\beta\)-carbon atom allows the asymmetric

Scheme 3 Synthesis of 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine derivatives 1a and 1b.

Scheme 4 Synthesis of aldehyde 16.

Scheme 5 Synthesis of deoxynojirimycin derivatives 2a and 2b.

Scheme 6 Synthesis of aldehyde 21.

Scheme 7 Synthesis of deoxynojirimycin derivatives 2a and 2b.
induction to be controlled entirely by proline. The amine generated by hydrogenolysis of 22 with RANEY® Ni did not undergo cyclization in situ unlike the reaction of 17. The crude reaction mixture had to be heated in the presence of triethylamine to displace the mesylate and get the piperidine derivatives 23a and 23b. It may be assumed that the secondary mesylate was difficult to be displaced in the presence of an adjacent O-TBDPS group. The homonojirimycin derivatives 3a and 3b were obtained by acidolysis of 23a and 23b, respectively using 4 N HCl in EtOAc (Scheme 7). Detailed NMR analysis of the benzyl derivatives of 3a and 3b prepared by the dibenzylation of 23 confirmed their structures to be as given in Scheme 7.18

The aldehyde 27 required for the preparation of 4a and 4b was prepared from 19 by using a different protection and activation strategy for the hydroxyl groups. Similar to the preparation of aldehyde 16, the primary hydroxyl group was converted to a mesylate and the adjacent secondary hydroxyl group was protected as a MOM derivative to get 27 (Scheme 8). Asymmetric hydrazination of 27 using l- and p-proline proceeded in good yield and high diastereoselectivity, as in the case of 22a and 22b, to give 28a and 28b, respectively (Scheme 9).17 Hydrogenolysis followed by cyclization using triethylamine yielded the azepane derivatives 29a and 29b from 28a and 28b, respectively. Acidolysis of 29a and 29b gave the target molecules 4a and 4b in overall yields of 20% and 19% (Scheme 9). Dibenzyl derivatives made from 29 were analyzed using NMR spectroscopy to confirm the stereochemistry of 4a and 4b.18

Conclusions

We have developed a divergent strategy for synthesizing various iminocyclitols from ribose and have successfully applied this in the synthesis of 5, 6 and 7 membered iminosugars. The absolute configuration of the stereocenter bearing the imino group is switched by changing the catalyst from l-proline to p-proline. While most of these reactions proceeded with very high diastereoselectivity, induction by the adjacent chiral centres reduced the diastereoselectivity achieved in the
reactions catalyzed by D-proline in two of the examples. In comparison with other methods available for the synthesis of similar compounds, the current strategy allows the preparation of target molecules with increased number of carbon atoms and stereocenters to that of the starting compounds. The method reported here has the potential to be a very useful strategy for making a large number of iminocyclitols by varying the sugar unit used as the starting compound. It provides a general method for the synthesis of imino and aza-sugars from a lower sugar homolog.

**Experimental section**

**General experimental methods**

All the commercially available reagents were used directly without any further purification. All the reactions were carried out under an inert atmosphere unless otherwise mentioned. Acetonitrile was distilled initially from phosphorus pentoxide and subsequently from calcium hydride; DCM was distilled from calcium hydride. Yields reported are for purified compounds using column chromatography. All the reactions were monitored by analytical thin layer chromatography carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as a visualizing agent and ninhydrin, 5% H2SO4 as a staining agent. Merck silica gel (particle size 60–200 mesh) was used for column chromatography. All proton NMR spectra were recorded at either 400 or 500 MHz; 100–120 and 1H NMR (500 MHz, CDCl3): δ 7.64–7.66 (m, 4H), 7.45–7.37 (m, 6H), 6.01 (dd, J = 16.6, 10.3, 6.3 Hz, 1H), 5.40 (d, J = 17.1 Hz, 1H), 5.27 (d, J = 10.3 Hz, 1H), 4.69 (t, J = 6.5 Hz, 1H), 4.15 (dd, J = 8.6, 6.3 Hz, 1H), 3.86 (dd, J = 10.3, 2.9 Hz, 1H), 3.82–3.78 (m, 1H), 3.71 (bs, 1H), 2.55 (bs, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 1.07 (s, 9H) ppm; 13C NMR (125 MHz, CDCl3): δ 135.6, 134.1, 129.9, 127.8, 117.7, 108.7, 78.9, 77.5, 69.9, 65.3, 27.8, 26.9, 25.5, 19.4 ppm; IR vmax (thin film): 3460, 2030, 1585 cm⁻¹; HRMS (ESI-TOF) m/z [M + Na]⁺ calc for C23H32NaO6SSi 449.2124; found 449.2128.

**Procedure for mesylation of 6 to get 7.** Triethylamine (0.6 mL, 4.4 mmol, 2.2 equiv.) followed by mesyl chloride (0.17 mL, 2.2 mmol, 1.1 equiv.) were added to a stirred solution of 6 (0.85 g, 2 mmol, 1 equiv.) in dichloromethane (10 mL) at 0 °C, and stirred the reaction mixture for 2 h at room temperature. After the complete disappearance of 6 on TLC, the reaction mixture was quenched with water. The organic layer was extracted with dichloromethane (2 × 10 mL), and the combined organic phases were washed with water (1 × 20 mL), dried over anhydrous Na2SO4, filtered, concentrated, and purified by column chromatography.

The same procedure was used for the preparation of 14, 20 and 26.

**Compound 7.** Column chromatography (petroleum ether/EtOAc, 8:2); oily liquid (0.96 g, 1.9 mmol, 95%); [α]20D = −0.45 (c 0.20, CHCl3); 1H NMR (500 MHz, CDCl3): δ 7.68–7.64 (m, 4H), 7.45–7.37 (m, 6H), 5.79 (dd, J = 17.1, 8.6, 6.8 Hz, 1H), 5.35 (d, J = 18.6 Hz, 1H), 5.28–5.25 (m, 1H), 4.74–4.71 (m, 1H), 4.68 (t, J = 6.8 Hz, 1H), 4.51–4.48 (m, 1H), 3.98–3.95 (m, 1H), 3.92–3.88 (m, 1H), 3.02 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.07 (s, 9H) ppm; 13C NMR (125 MHz, CDCl3): δ 135.7, 132.8, 132.7, 132.4, 130.1, 130.0, 129.7, 127.8, 119.5, 109.0, 81.9, 78.0, 76.3, 63.0, 39.3, 27.0, 26.8, 25.0, 19.2 ppm; IR vmax (thin film): 3072, 1589 cm⁻¹; HRMS (ESI-TOF) m/z [M + Na]⁺ calc for C30H30NaO6Si 527.1900; found 527.1897.

**Compound 14.** Column chromatography (petroleum ether/EtOAc, 6:4); oily liquid (0.56 g, 1.8 mmol, 90%); [α]20D = +93.34 (c 0.4, CHCl3); 1H NMR (500 MHz, CDCl3): δ 5.91–5.84 (m, 1H), 5.41 (d, J = 17.2 Hz, 1H), 5.26 (d, J = 10.3 Hz, 1H), 4.71 (t, J = 6.5 Hz, 1H), 4.66 (d, J = 6.9 Hz, 1H), 4.64 (d, J = 6.9 Hz, 1H), 4.53 (dd, J = 10.9, 2.3 Hz, 1H), 4.34 (dd, J = 10.8, 4.0 Hz, 1H), 4.26 (dd, J = 7.7, 6.5 Hz, 1H), 3.68–3.69 (m, 1H), 3.39 (s, 3H), 3.02 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H) ppm; 13C NMR (125 MHz, CDCl3): δ 133.1, 118.0, 108.9, 97.3, 78.0, 76.1, 75.2, 70.0, 56.3, 37.3, 27.6, 25.2 ppm; IR vmax (thin film): 2988, 1643, 1546 cm⁻¹; HRMS (ESI-TOF) m/z [M + Na]⁺ calc for C28H29NaO6Si 333.0984; found 333.0987.

**Compound 20.** Column chromatography (petroleum ether/EtOAc, 9:1); oily liquid (1.04 g, 1.8 mmol, 95%); [α]20D = −1.08 (c 0.74, CHCl3); 1H NMR (500 MHz, CDCl3): δ 7.70–7.68 (m, 4H), 7.44–7.37 (m, 6H), 4.76 (m, 1H), 4.39 (t, J = 6.6 Hz, 1H), 4.22–4.18 (m, 1H), 4.13 (q, J = 7.4 Hz, 2H), 3.99–3.98 (m, 2H), 3.06 (s, 3H), 2.52–2.38 (m, 2H), 2.03–1.96 (m, 1H), 1.77–1.69 (m, 1H), 1.29 (s, 3H), 1.26–1.23 (m, 6H), 1.07 (s, 9H) ppm; 13C NMR (125 MHz, CDCl3): δ 173.1, 135.7, 132.8, 130.0, 129.9, 127.9, 127.8, 108.5, 80.6, 76.2, 75.0, 63.4, 60.4, 39.4,
30.9, 27.6, 26.8, 25.5, 24.9, 19.3, 14.3 ppm; IR ν_{max} (thin film): 3072, 1737, 1589 cm\(^{-1}\); HRMS (ESI-TOF) m/z [M + Na]\(^{+}\) calc'd for C\(_{4}\)H\(_{12}\)NaO\(_{3}\)S\(_{2}\) 601.2267; found 601.2270.

**Compound 26.** Column chromatography (petroleum ether/EtOAc, 1:1); oily liquid (0.73 g, 1.9 mmol, 95%); [\(\delta_{D}^{2} \pm 1.1 (c \ 0.35, \text{CHCl}_3)\); \(^{1}H\) NMR (500 MHz, CDCl\(_{3}\)): \(\delta 4.76 (d, J = 6.8 \text{ Hz, } 1H)\), 4.58 (dd, \(J = 11 \text{ Hz, } 1H\)), 4.35 (dd, \(J = 10.9, 3.4 \text{ Hz, } 1H\)), 4.21–4.17 (m, 1H), 4.17–4.13 (m, 1H), 4.11 (q, \(J = 6.8 \text{ Hz, } 2H\)), 3.79 (d, \(J = 7.9 \text{ Hz, } 1H\)), 3.40 (s, 3H), 3.03 (s, 3H), 2.56–2.50 (m, 1H), 2.44–2.37 (m, 1H), 1.99–1.92 (m, 1H), 1.80–1.72 (m, 1H), 1.38 (s, 3H), 1.30 (s, 3H), 1.23 (t, \(J = 6.9 \text{ Hz, } 3H\) ppm); \(^{13}C\) NMR (125 MHz, CDCl\(_{3}\)): \(\delta 173.2, 108.4, 96.7, 76.5, 75.2, 74.4, 69.7, 60.4, 56.4, 37.3, 31.1, 28.0, 25.6, 24.9, 14.2 ppm; IR \(\nu_{max}\) (thin film): 1734 cm\(^{-1}\); HRMS (ESI-TOF) m/z [M + Na]\(^{+}\) calc'd for C\(_{12}\)H\(_{24}\)O\(_{8}\)S 329.1273; found 329.1275.

**Procedure for hydroboration followed by oxidation of 7 to get 8.** Borane (1 M solution in THF – 4 mL, 4 mmol, 2 equiv.) was added to the stirred solution of 7 (1.00 g, 2 mmol, 1 equiv.) in THF at 0 °C under a nitrogen atmosphere, and stirred for 2 h. After the disappearance of 7 on TLC, 2 N NaOH (8 mL, 16 mmol) and then 30% H\(_{2}\)O\(_{2}\) (8 mL) were added and stirring was continued for further 30 min at 0 °C. The reaction was quenched with saturated ammonium chloride, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic phases were dried over Na\(_{2}\)SO\(_{4}\), filtered, concentrated and purified by column chromatography.

The same procedure was used for the preparation of 15 from 14.

**Compound 8.** Column chromatography (petroleum ether/EtOAc, 7:3); oily liquid (0.57 g, 1.44 mmol, 72%); [\(\delta_{D}^{2} \pm 0.877 (c \ 0.23, \text{CHCl}_3)\); \(^{1}H\) NMR (500 MHz, CDCl\(_{3}\)): \(\delta 7.69–7.66 (m, 4H), 7.43–7.37 (m, 6H), 4.77–4.75 (m, 1H), 4.40–4.35 (m, 2H), 4.02–3.95 (m, 2H), 3.79–3.73 (m, 2H), 3.03 (s, 3H), 1.88–1.69 (m, 2H), 1.30 (s, 3H), 1.37 (s, 3H), 1.08 (s, 9H) ppm); \(^{13}C\) NMR (125 MHz, CDCl\(_{3}\)): \(\delta 135.7, 132.7, 130.1, 130.0, 127.9, 127.8, 108.6, 81.1, 76.2, 75.2, 63.3, 61.0, 39.5, 32.3, 27.5, 26.9, 25.4, 19.2 ppm; IR \(\nu_{max}\) (thin film): 3486, 3080, 1546 cm\(^{-1}\); HRMS (ESI-TOF) m/z [M + Na]\(^{+}\) calcd for C\(_{15}\)H\(_{28}\)NaO\(_{9}\)S 538.2295; found 538.2299.

**Procedure for asymmetric \(\alpha\)-hydrazination of 9 to get 10.** The aldehyde 9 (1.04 g, 2 mmol, 1 equiv.) in dry acetonitrile (15 mL) was treated with dibenzylazodicarboxylate (0.59 g, 2 mmol, 1 equiv.) and proline (either \(d\) or \(l\), 0.02 g, 10 mol%) at 0 °C. The mixture was stirred for 2 h and the temperature was raised to 20 °C over a period of 1 h. The mixture was stirred until the solution turned colorless from yellow (1 to 2 h) and was cooled to 0 °C and then treated with sodium borohydride (0.05 g) in ethanol (15 mL). The stirring was continued for 5 min and the reaction was quenched with saturated ammonium chloride solution (20 mL). The organic layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic phases were dried over anhydrous Na\(_{2}\)SO\(_{4}\), filtered, concentrated, and purified by column chromatography.

**Note:** The hydrazine derivatives give complex NMR spectra at room temperature due to the existence of rotamers.
The same procedure was used for the preparation of 17, 22 and 28.

**Compound 10a.** Column chromatography (petroleum ether/EtOAc, 8:2); oily liquid (1.13 g, 1.38 mmol, 69%); \[a]_{D}^{25} = +4.6° (c 0.46, CHCl3); \(^1H\) NMR (500 MHz, CDCl3): \( \delta \) 7.72–7.64 (m, 4H), 7.42–7.24 (m, 16H), 6.74 (bs, 1H), 5.30–5.05 (m, 4H), 4.86–4.36 (m, 2H), 4.30–4.09 (m, 3H), 3.73–3.55 (m, 2H), 3.16–3.03 (m, 3H), 2.66 (bs, 1H), 1.19–1.06 (m, 15H) ppm; \(^13C\) NMR (125 MHz, CDCl3): \( \delta \) 152.6, 151.9, 151.3, 133.1, 132.9, 132.8, 130.3, 130.1, 129.9, 129.8, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 128.7, 127.7, 127.6, 127.5, 127.4, 126.9, 68.4, 68.2, 67.8, 64.9, 62.6, 60.0, 59.8, 58.7, 53.5, 39.4, 39.1, 26.9, 26.8, 25.4, 25.3, 19.4, 19.3 ppm; IR \( \nu_{\text{max}} \) (thin film): 3464, 3378, 1717, 1588 cm\(^{-1}\); HRMS (ESI-TOF) \( m/z \) [M + Na\(^+\)] \(^{c}+\) c played for \( C_{24}H_{27}N_{2}O_{12}S_{2} \) 843.2959; found 843.2962.

**Compound 17a.** Column chromatography (petroleum ether/EtOAc, 1:1); oily liquid (0.91 g, 1.46 mmol, 73%); \[a]_{D}^{25} = +22.85° (c 0.14, CHCl3); \(^1H\) NMR (500 MHz, CDCl3): \( \delta \) 7.39–7.13 (m, 10H), 5.33–5.05 (m, 4H), 4.53–4.16 (m, 8H), 3.94–3.84 (m, 1H), 3.61 (bs, 1H), 3.28 (s, 3H), 2.99–2.93 (d, 3H), 1.42 (s, 3H), 1.29 (s, 3H) ppm; \(^13C\) NMR (125 MHz, CDCl3): \( \delta \) 159.2, 152.8, 151.3, 151.5, 151.4, 151.3, 128.9, 128.7, 128.6, 128.3, 128.0, 127.9, 127.6, 127.4, 126.9, 68.4, 68.2, 67.8, 64.9, 62.6, 60.0, 59.8, 58.7, 53.5, 39.4, 39.1, 26.9, 26.8, 25.4, 25.3, 19.4, 19.3 ppm; IR \( \nu_{\text{max}} \) (thin film): 3464, 3378, 1717, 1588 cm\(^{-1}\) HRMS (ESI-TOF) \( m/z \) [M + Na\(^+\)] \(^{c}+\) c played for \( C_{24}H_{27}N_{2}O_{12}S_{2} \) 843.2959; found 843.2962.

**Compound 22a.** Column chromatography (petroleum ether/EtOAc, 7:3); oily liquid (1.21 g, 1.46 mmol, 73%); \[a]_{D}^{25} = +23.5° (c 1.6, CHCl3); \(^1H\) NMR (500 MHz, CDCl3): \( \delta \) 7.68–7.65 (m, 4H), 7.44–7.30 (m, 16H), 7.11–7.03 (m, 1H), 5.22–5.12 (m, 4H), 4.70–4.64 (m, 1H), 4.29–4.20 (m, 2H), 4.14–4.05 (m, 1H), 3.96–3.88 (m, 2H), 3.50–3.42 (m, 2H), 3.01–2.97 (m, 3H), 1.76–1.47 (m, 2H), 1.32–1.23 (m, 6H), 1.06 (s, 9H) ppm; \(^13C\) NMR (125 MHz, CDCl3): \( \delta \) 159.1, 158.7, 156.9, 156.2, 136.0, 135.7, 135.6, 135.6, 135.3, 132.7, 132.6, 130.2, 130.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 127.4, 115.9, 115.8, 115.7, 115.6, 115.3, 115.2, 113.0, 108.7, 108.5, 105.6, 90.8, 81.5, 75.4, 75.3, 74.8, 68.6, 68.4, 68.1, 63.5, 63.3, 61.8, 61.6, 59.9, 58.7, 39.6, 39.5, 39.4, 27.2, 27.1, 26.9, 24.8, 24.6, 19.3 ppm; IR \( \nu_{\text{max}} \) (thin film): 3473, 1721, 1588 cm\(^{-1}\); HRMS (ESI-TOF) \( m/z \) [M + Na\(^+\)] \(^{c}+\) c played for \( C_{18}H_{25}N_{2}O_{14}S_{6} \) 857.3115; found 857.3115.
Procedure for the hydrogenation of compound 10 to get 11. Freshly prepared RANEY® nickel (around 0.80 g, pre-washed with absolute ethanol) was added to the stirred solution of 10 (2 mmol) in dry methanol (15 mL) followed by 40 drops of acetic acid. The reaction mixture was hydrogenated at atmospheric pressure for 16 h at room temperature. After the complete disappearance of the starting material on TLC, the reaction mixture was passed over Celite and concentrated, and purified by column chromatography.

The same procedure was used for the preparation of 18 from 17. Compounds 23 and 29 were also prepared using a similar procedure, however refluxing with triethylamine (2 equiv.) was required for the desired cyclization to occur.

**Compound 11a.** Chromatography (petroleum ether/EtOAc, 4 : 6); oily liquid (0.65 g, 1.46 mmol, 73%); [a]$_D^{25}$ = +12.3 (c 0.31, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.81–7.67 (m, 4H, Ar–H), 7.43–7.33 (m, 6H, Ar–H), 5.67–5.96 (m, 2H, C$_2$H$_2$, C$_3$H$_2$), 3.98–3.83 (m, 4H, C$_2$H$_3$, C$_3$H$_3$), 3.31–3.08 (m, 1H, C$_2$H$_3$), 2.96–2.93 (m, 1H, C$_2$H$_3$), 1.41 (s, 3H, C$_2$H), 1.27 (s, 3H, C$_3$H), 1.04 (s, 9H, (CH$_3$)$_3$C–Si) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 135.7 (C–Ar), 133.0 (C–Ar), 132.9 (C–Ar), 129.8 (C–Ar), 127.8 (C–Ar), 127.7 (C–Ar), 112.3 (C–9), 81.8 (C–3), 79.4 (C–2), 66.3 (C–6), 62.8 (C–6), 60.2 (C–1), 60.0 (C–4), 26.8 ([C$_3$H$_3$]$_2$C–Si), 26.2 (C–8), 24.3 (C–7), 19.2 (C–Si) ppm; IR $\nu_{max}$ (thin film): 3407, 3470, 1669 cm$^{-1}$; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for C$_{20}$H$_{28}$N$_2$O$_6$Si 419.1932; found 419.1870.

**Compound 11b.** Chromatography (petroleum ether/EtOAc, 4 : 6); oily liquid (0.65 g, 1.46 mmol, 73%); [a]$_D^{25}$ = +12.3 (c 0.24, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.71–7.67 (m, 4H, Ar–H), 7.43–7.33 (m, 6H, Ar–H), 4.67–4.64 (m, 2H, C$_2$H$_2$, C$_3$H$_2$), 3.98–3.83 (m, 4H, C$_2$H$_3$, C$_3$H$_3$), 3.11–3.08 (m, 1H, C$_2$H$_3$), 2.96–2.93 (m, 1H, C$_2$H$_3$), 1.41 (s, 3H, C$_2$H), 1.27 (s, 3H, C$_3$H), 1.04 (s, 9H, (CH$_3$)$_3$C–Si) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 135.7 (C–Ar), 133.6 (C–Ar), 133.6 (C–Ar), 133.4 (C–Ar), 129.7 (C–Ar), 127.7 (C–Ar), 127.6 (C–Ar), 111.4 (C–9), 82.3 (C–8), 81.2 (C–2), 63.6 (C–5), 62.7 (C–6), 61.7 (C–1), 60.9 (C–4), 26.9 ([C$_3$H$_3$]$_2$C–Si), 25.6 (C–8), 23.9 (C–7), 19.3 (C–Si) ppm; IR $\nu_{max}$ (thin film): 3407, 3470, 1669 cm$^{-1}$; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for C$_{20}$H$_{28}$N$_2$O$_6$Si 419.1932; found 419.1870.

**Compound 18a.** Chromatography (DCM/MeOH, 95 : 5); oily liquid (0.37 g, 1.5 mmol, 75%); [a]$_D^{25}$ = +14.8 (c 0.6, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.68–7.65 (m, 4H, Ar–H), 7.41–7.33 (m, 6H, Ar–H), 5.40–4.48 (m, 1H, C$_3$H), 4.53–4.43 (m, 1H, C$_3$H), 3.64–3.60 (m, 2H, C$_2$H$_3$), 3.41–3.36 (m, 1H, C$_3$H), 3.18–3.12 (m, 2H, CH$_2$), 2.76–2.74 (m, 1H, C$_3$H), 2.02–1.99 (m, 1H, C$_3$H), 1.81–1.77 (m, 1H, C$_3$H), 1.42 (s, 3H, C$_3$H), 1.34–1.28 (s, 3H, C$_2$H), 1.03 (s, 9H, (CH$_3$)$_3$C–Si) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.2 (C–Ar), 134.1 (C–Ar), 132.3 (C–Ar), 131.9 (C–Ar), 128.2 (C–Ar), 126.2 (C–Ar), 126.1 (C–Ar), 126.8 (C–Ar), 126.3 (C–3), 70.3 (C–3), 70.1 (C–2), 63.1 (C–7), 62.2 (C–6), 50.5 (C–1), 46.4 (C–5), 30.5 (C–4), 28.2 (C–12), 27.9 ([C$_3$H$_3$]$_2$C–Si), 25.3 (C–11), 20.0 (C–Si) ppm; IR $\nu_{max}$ (thin film): 3408, 3071, 1670 cm$^{-1}$; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for C$_{20}$H$_{28}$N$_2$O$_6$Si 456.2570; found 456.2572.

**Compound 18b.** Chromatography (DCM/MeOH, 95 : 5); oily liquid (0.37 g, 1.5 mmol, 76%); [a]$_D^{25}$ = −30.7 (c 0.27, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.82 (d, $J$ = 6.9 Hz, 1H, –O–CH$_2$–O–), 4.71 (d, $J$ = 6.8 Hz, 1H, –O–CH$_2$–O–), 4.56 (d, $J$ = 8.5 Hz, 1H, C$_3$H), 4.48–4.45 (m, 1H, C$_3$H), 4.20–4.18 (m, 1H, C$_3$H), 3.77 (dd, $J$ = 11.4, 2.8 Hz, 1H, C$_3$H), 3.62 (dd, $J$ = 10.9, 6.6 Hz, 1H, C$_3$H); 3.39 (s, 3H, –OCH$_3$–), 3.38–3.30 (m, 3H, C$_2$H$_2$, C$_3$H$_2$), 2.07–1.94 (m, 2H, C$_2$H$_2$), 1.54 (s, 3H, C$_3$H), 1.37 (s, 3H, C$_2$H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 108.3 (C–12), 96.0 (–O–CH$_2$–O–), 78.4 (C–4), 74.0 (C–3), 71.8 (C–5), 64.0 (C–7), 55.9 (–OCH$_3$–), 55.2 (C–1), 45.1 (C–6), 32.5 (C–2), 25.7 (C–11), 23.5 (C–10) ppm; IR $\nu_{max}$ (thin film): 3439 cm$^{-1}$; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for C$_{17}$H$_{26}$N$_2$O$_4$ 262.1654; found 262.1651.

**Compound 29a.** Chromatography (DCM/MeOH, 95 : 5); oily liquid (0.33 g, 1.28 mmol, 64%); [a]$_D^{25}$ = +18.6...
(c 0.22, CHCl3); 1H NMR (500 MHz, CDCl3): δ 4.84 (d, J = 6.8 Hz, 1H, −O−CH2−O−), 4.71 (d, J = 6.3 Hz, 1H, −O−CH2−O−), 4.41 (q, J = 8.0 Hz, 1H, C3H), 4.19 (dd, J = 8.0, 2.8 Hz, 1H, C6H), 3.91 (dd, J = 5.7, 2.2 Hz, 1H, C3H), 3.51 (dd, J = 10.3, 4.5 Hz, 1H, C3H), 3.38 (s, 3H, −OCH3), 3.32−3.23 (m, 2H, C2H), 2.64 (d, J = 14.8 Hz, 1H, C6H), 2.56−2.52 (m, 1H, C1H), 1.91−1.88 (m, 2H, C2H), 1.47 (s, 3H, C4D), 1.33 (s, 3H, C3H) ppm; 13C NMR (125 MHz, CDCl3): δ 109.8 (C-12), 79.5 (−O−CH2−O−), 80.6 (C-4), 76.3 (C-3), 76.1 (C-5), 65.7 (C-7), 56.3 (−OCH3), 55.7 (C-1), 48.3 (C-6), 35.8 (C-2), 26.6 (C-11), 24.0 (C-10) ppm; IR v∞max (thin film): 3401 cm⁻¹; HRMS (ESI-TOF) m/z [M + H]⁺ cale. for C3H4NO2, 262.1654; found 262.1655.

Procedure for acidolysis of 11 to get 1. 4 N HCl in ethyl acetate (4 mL) was added to the cyclic amino alcohol 11a or 11b (0.44 g, 1 mmol, 1 equiv.), and stirred for 24 h at room temperature. After the disappearance of the starting material on TLC, the ethyl acetate was decanted carefully and the white solid was washed with fresh ethyl acetate (3 × 5 mL) and concentrated.

The same procedure was used for the preparation of 2 and 3 and from 18 to 19, respectively.

**Compound 1a.** White solid; (0.161 g, 0.81 mmol, 81%); [α]25D = +6.3 (c 0.18, MeOH): mp 158−159 °C; 1H NMR (400 MHz, D2O): δ 3.95 (bs, 1H, C3H), 3.91 (dd, J = 6.3, 3.4 Hz, 1H, C1H), 3.87 (dd, J = 5.9, 3.2 Hz, 1H, C6H), 3.80−3.78 (m, 2H, C2H), 3.72 (dd, J = 16, 4.5 Hz, 1H, C1H), 3.65−3.59 (m, 1H, C1H), 3.40 (dt, J = 8.5, 2.3 Hz, 1H, C6H), 1.78−1.73 (m, 2H, C2H) ppm; 13C NMR (100 MHz, D2O): δ 72.0 (C-3), 70.1 (C-4), 62.2 (C-7), 61.8 (C-6), 58.2 (C-5), 57.5 (C-3) ppm; IR v∞max (KBr): 3356 cm⁻¹; HRMS (ESI-TOF) m/z [M + H]⁺ − (HCl)⁺ cale. for C3H4NO2, 164.0923; found 164.0923.

**Compound 1b.** White solid; (0.165 g, 0.83 mmol, 83%); [α]25D = +23.1 (c 0.4, H2O) [lit.66 [α]25D = −25.5 (c 0.90, H2O)] mp 122−125 °C; 1H NMR (500 MHz, D2O): δ 4.25−4.23 (m, 1H, C1H), 4.17 (dd, J = 9.1, 4.0 Hz, 1H, C3H), 3.91−3.85 (m, 2H, C6H), 3.82−3.73 (m, 2H, C2H), 3.68−3.65 (m, 1H, C6H), 3.56−3.53 (m, 1H, C1H) ppm; 13C NMR (125 MHz, D2O): δ 71.2 (C-3), 70.3 (C-4), 62.4 (C-7), 61.8 (C-6), 58.2 (C-5), 57.5 (C-3) ppm; IR v∞max (KBr): 3356 cm⁻¹; HRMS (ESI-TOF) m/z [M + H]⁺ − (HCl)⁺ cale. for C3H4NO2, 164.0923; found 164.0923.

**Compound 2a.** White solid; (0.08 g, 0.41 mmol, 83%); [α]25D = −35.2 (c 0.43, MeOH) [lit.71 [α]25D = −37.7 (c 1.00, MeOH)] mp 152−153 °C; 1H NMR (500 MHz, D2O): δ 4.01 (bs, 1H, C3H), 3.86−3.85 (m, 1H, C1H), 3.77−3.73 (m, 3H, C6H, C2H), 3.19−3.11 (m, 1H, C6H), 3.12−3.10 (m, 1H, C1H), 2.98−2.96 (m, 1H, C1H) ppm; 13C NMR (125 MHz, D2O): δ 69.9 (C-3), 65.4 (C-4), 64.6 (C-5), 57.7 (C-7), 54.7 (C-2), 41.6 (C-6) ppm; IR v∞max (KBr): 3436 cm⁻¹; HRMS (ESI-TOF) m/z [M + H]⁺ − (HCl)⁺ cale. for C3H4NO2, 164.0923; found 164.0923.

**Compound 2b.** White solid; (0.08 g, 0.42 mmol, 84%); [α]25D = −23.4 (c 0.4, MeOH) [lit.70 [α]25D = −21.7 (c 0.8, MeOH)] mp 153−155 °C; 1H NMR (400 MHz, D2O): δ 4.10−4.09 (m, 1H, C3H), 4.02−4.01 (m, 1H, C1H), 3.74 (m, 2H, C2H, C3H), 3.71 (t, J = 3.2 Hz, 1H, C7H), 3.37 (dd, J = 13.7, 3.0 Hz, 1H, C1H, C3H), 3.26 (dt, J = 1.3, 6.8 Hz, 1H, C1H), 3.13 (dd, J = 13.7, 1.8 Hz, 1H, C1H) ppm; 13C NMR (100 MHz, D2O): δ 69.8 (C-3), 65.2 (C-4), 64.5 (C-5), 57.5 (C-7), 54.6 (C-2), 41.4 (C-6) ppm; IR v∞max (KBr): 3436 cm⁻¹; HRMS (ESI-TOF) m/z [M + H]⁺ − (HCl)⁺ cale. for C3H4NO2, 164.0923; found 164.0924.
1.30 (s, 3H), 1.24 (t, \( J = 7.0 \) Hz, 1H), 3.92 (dd, \( J = 11.0, 2.45 \) Hz, 1H), 3.87 (dd, \( J = 11.0, 4.25 \) Hz, 1H), 3.71–3.61 (m, 1H), 3.34 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.07 (s, 9H) ppm; \( ^{13} \text{C} \) NMR (125 MHz, CDCl\(_3\)): \( \delta = 135.8, 135.7, 134.3, 133.6, 133.4, 129.6, 129.7, 127.6, 117.9, 108.4, 96.9, 78.7, 77.4, 76.5, 50.6, 27.6, 26.9, 25.3, 19.3 ppm; IR \( \nu_{\text{max}} \) (thin film): 3460, 1590 cm\(^{-1}\), 1735, 1587 cm\(^{-1}\), 1589, 1472 cm\(^{-1}\).

**Compounds 24.** Column chromatography (petroleum ether/EtOAc, 9.5 : 0.5); oily liquid (0.92 g, 1.7 mmol, 85%); \([M + Na]^+ \) calcd for C\(_{27}\)H\(_{38}\)NaO\(_5\)Si 493.2386; found 493.2381.

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**Notes and references**

1. (a) G. Horne and R. Storer, *Drug Discovery Today*, 2011, 16, 107; (b) A. E. Stutz, *Iminosugars as Glycosidase Inhibitors, Nojirimycin and Beyond*, Wiley-VCH, Weinheim, 1999; (c) P. E. Compain and O. R. Martin, *Iminosugars, From Synthesis to Therapeutic Applications*, Wiley-VCH, Weinheim, 2007.

2. (a) B. Andersen, A. Rassov, N. Westergaard and K. Lundgren, *Biochem. J.*, 1999, 342, 545; (b) R. J. Bernack and W. Korytnyk, *Cancer Metastasis Rev.*, 1985, 4, 81; (c) T. D. Butters, R. A. Dwek and F. M. Platt, *Chem. Rev.*, 2000, 100, 4683; (d) F. Chery, L. Cronin, J. L. O’Brien and P. V. Murphy, *Tetrahedron*, 2004, 60, 6597; (e) B. D. Walker, M. Kowalski, W. C. Goh, K. Kozarsky, M. Krieger, C. Rosen, L. Rohrshneider, W. A. Haseltine and J. Sodroski, *Proc. Natl. Acad. Sci. U. S. A.*, 1987, 84, 8120; (f) H. Paulson and I. Brockhausen, *Glycoconjugate J.*, 2001, 18, 867.

3. (a) A. Weter, J. Jadot, G. Dardenne, M. Marlier and J. Casimir, *Phytochemistry*, 1976, 15, 747; (b) S. Takayama, R. Martin, J. Wu, K. Laslo, G. Siuzdak and C.-H. Wong, *J. Am. Chem. Soc.*, 1997, 119, 8146; (c) A. Schäfer, G. Klich, M. Schreiber, H. Paulsen and J. Thiem, *Carbohydr. Res.*, 1998, 313, 107.

4. (a) C. Boucheron, V. Desvergnes, P. Compain, O. Martin, R. A. Lavi, M. Mackeen, M. R. Wormald, D. A. Dwek and T. D. Butters, *Tetrahedron: Asymmetry*, 2005, 16, 1747; (b) T. M. Jespersen, W. Dong, M. R. Sierks, T. Skrydstrup, I. Lundt and M. Bols, *Angew. Chem., Int. Ed. Engl.*, 1994, 7779; (c) N. Asano, H. Kizu, K. Oseki, E. Tomioka, K. Matsui, M. Okamoto and M. Baba, *J. Med. Chem.*, 1995, 38, 2349.

5. (a) F. Moris-Varás, X.-H. Qian and C.-H. Wong, *J. Am. Chem. Soc.*, 1996, 118, 764; (b) G. F. Painter, P. J. Eldridge and A. Falshaw, *Bioorg. Med. Chem.*, 2004, 12, 225; (c) F. Popowycz, S. Gerber-Lemaire, C. Schütz and P. Vogel, *Helv. Chim. Acta.*, 2004, 87, 806.

6. (a) M. E. Bouillon and S. G. Pyne, *Tetrahedron Lett.*, 2014, 55, 475; (b) A. A. Ansari and Y. D. Vankar, *J. Org. Chem.*, 2013, 78, 9383; (c) B. J. Ayers, N. Ngo, S. F. Jenkinson, R. F. Martínez, Y. Shimada, I. Adachi, A. C. Weymouth-Wilson, A. Kato and G. W. J. Fleet, *J. Org. Chem.*, 2012, 77, 76.3, 63.8, 60.4, 56.1, 31.1, 28.0, 25.6, 25.2, 14.2 ppm; IR \( \nu_{\text{max}} \) (thin film): 3472, 1735 cm\(^{-1}\); HRMS (ESI-TOF) m/z [M + Na]^+ calcd for C\(_{14}\)H\(_{26}\)NaO\(_7\) 329.1576; found 329.1571.
12 (a) B. List, *J. Am. Chem. Soc.*, 2002, **124**, 5656; (b) N. K. Kumaragurubharan, A. Juhl, A. Bogevig and K. A. Jorgensen, *J. Am. Chem. Soc.*, 2002, **124**, 6254; (c) A. Bogevig, K. Juhl, N. Kumaragurubharan, W. Zhuang and K. A. Jorgensen, *Angew. Chem., Int. Ed.*, 2002, **41**, 1790; (d) R. O. Duthaler, *Angew. Chem., Int. Ed.*, 2003, **42**, 975.

13 (a) A. Nuzzi, A. Massi and A. Dondoni, *Org. Lett.*, 2008, **10**, 4485; (b) R. Ait-Youcef, K. Sbargoud, X. Moreau and C. Greck, *Synlett*, 2009, 3007; (c) Y. Nishikawa, M. Kitajima, N. Kogure and H. Takayama, *Tetrahedron*, 2009, **65**, 1608; (d) R. Ait-Youcef, X. Moreau and C. Greck, *J. Org. Chem.*, 2010, **75**, 5312; (e) R. Petakamsetty, R. P. Das and R. Ramapanicker, *Tetrahedron*, 2014, **70**, 9554.

14 (a) P. Kumar, V. Jha and R. G. Gonnade, *J. Org. Chem.*, 2013, **78**, 11756; (b) V. Jha, N. B. Kondekar and P. Kumar, *Org. Lett.*, 2010, **12**, 2762; (c) A. Desmarchelier, V. Coeffard, X. Moreau and C. Greck, *Tetrahedron*, 2014, **70**, 2491.

15 (a) V. Jha, S. V. Kaulookkar and P. Kumar, *Eur. J. Org. Chem.*, 2014, 4897; (b) S. V. Kaulookkar, V. Jha, G. Jogdandb and P. Kumar, *Org. Biomol. Chem.*, 2014, **12**, 4454; (c) V. Jha and P. Kumar, *RSC Adv.*, 2014, **4**, 3238; (d) S. P. Kotkar, V. B. Chavan and A. Sudalai, *Org. Lett.*, 2008, **9**, 1001.

16 W. J. Choi, H. R. Moon, H. O. Kim, B. N. Yoo, J. A. Lee, D. H. Shin and L. S. Jeong, *J. Org. Chem.*, 2004, **69**, 2634.

17 The diastereomeric ratio of these compounds was estimated using chiral HPLC and was established by comparing the chromatograms with that of a 1:1 mixture of the diastereomers obtained through reactions catalyzed by dL-proline (given in the ESI†).

18 Synthesis of the benzyl derivatives and the NMR spectral analysis are provided in the ESL†.