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## Glycal mediated synthesis of piperidine alkaloids: fagomine, 4-*epi*-fagomine, 2-deoxynojirimycin, and an advanced intermediate, iminoglycal†

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Glucal and galactal are transformed into 2-deoxyglycolactams, which are important building blocks in the synthesis of biologically active piperidine alkaloids, fagomine and 4-*epi*-fagomine. In one of the strategies, reduction of 2-deoxyglycolactam-N-Boc carbonyl by lithium triethylborohydride (Super-Hydride®) has been exploited to generate lactamol whereas reduction followed by dehydration was utilized as the other strategy to functionalize the C<sub>1</sub>–C<sub>2</sub> bond in the iminosugar substrate. The strategies provide the formal synthesis of 2-deoxynojirimycin, nojirimycin and nojirimycin B. DFT studies were carried out to determine the reason for the failure of the formation of the 2-deoxygalactonojirimycin derivative. Further, DFT studies suggest that phenyl moieties of protecting groups and lone pairs of oxygen in carbamate group plays a vital role in deciphering the conformational space of the reaction intermediates and transition-state structures through cation–π or cation–lone pair interactions. The influence of these interactions is more pronounced at low temperature when the entropy factor is small.

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## Introduction

Polyhydroxylated alkaloids are of considerable interest as potential therapeutic agents, they are also used as an important tool to understand biological recognition processes.<sup>1</sup> Hence, their synthesis and biological activity studies have assumed significance. These occur in the species of *Streptomyces*, family Leguminosae, Solanaceae, and Convolvulaceae and possess therapeutic potential.<sup>1</sup> Nojirimycin **1** (Fig. 1) was the first natural polyhydroxylated piperidine alkaloid isolated from a *Streptomyces* filtrate in 1966 by Inouye *et al.*<sup>2</sup> 1,2-Dideoxy-iminosugars exemplify a small but essential class of glycosidase inhibitors.<sup>3</sup> One of the members of this family, fagomine **5a**, was isolated from the seeds of Japanese buckwheat *Fagopyrum esculentum australe* Moench<sup>4</sup> and also from the seeds of *Castanospermum australe*<sup>5</sup> (Leguminosae). It has also been reported that 4-*epi*-fagomine **5b** (Fig. 1) acts as a potent glycosidase inhibitor.<sup>6</sup> The batzellasides **6** are a novel class of C-alkylated iminosugars originally isolated from *Batzella* sp., a marine sponge from Madagascar<sup>7a</sup> and are active against *Staphylococcus epidermidis*. Their unique structural features

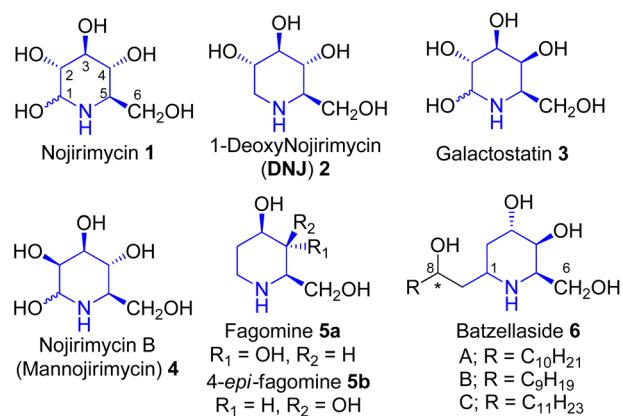


Fig. 1 Some common piperidine alkaloids of therapeutic value.

resemble an intriguing extension of the iminosugar frameworks, hence their synthesis<sup>7b,c</sup> has attracted the attention of researchers who practice contemporary drug discovery.

## Results and discussion

Reported synthesis of fagomine and 4-*epi*-fagomine involves either use of carbohydrate building blocks<sup>8,9</sup> or non-carbohydrate precursors.<sup>10</sup> Although nojirimycin **1** is very active glycosidase inhibitor,<sup>2b</sup> it has been observed that the deoxy derivatives displays a broad range of activities and are much more stable than nojirimycin **1** itself thereby attracting

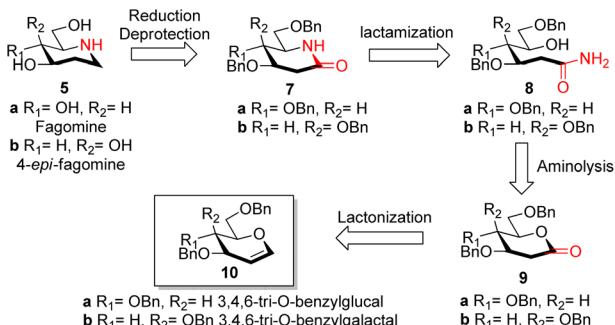
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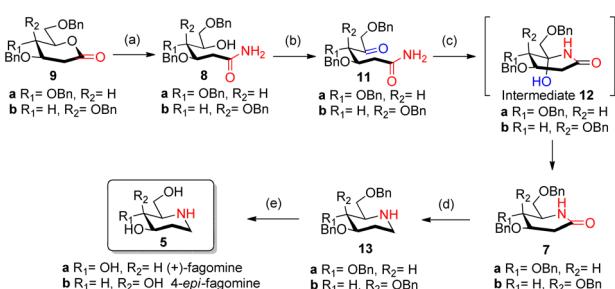
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**Scheme 1** Retrosynthetic plan for the synthesis of fagomine **5a** and 4-*epi*-fagomine **5b**.

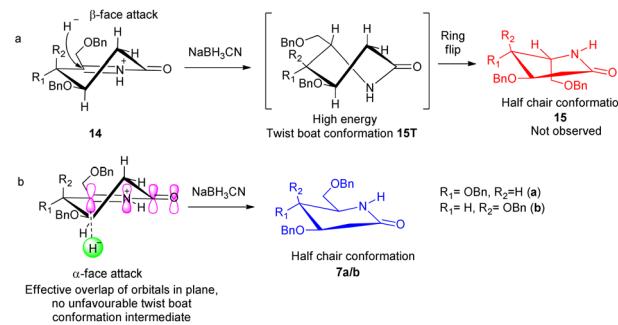


**Scheme 2** Synthesis of fagomine **5a** and 4-*epi*-fagomine **5b**; reagents and conditions: (a)  $\text{NH}_3$  in  $\text{CH}_3\text{OH}$  7 N solution, (6 h, 82% **8a**), (11 h, 96% **8b**); (b)  $\text{AC}_2\text{O}/\text{DMSO}$ , (23 h, 59% **11a**), (26 h, 64% **11b**); (c)  $\text{HCOOH}/\text{NaBH}_3\text{CN}$ ,  $\text{CH}_3\text{CN}$  reflux, (4.5 h, 59% **7a**), (4.5 h, 59% **7b**). (d)  $\text{LiAlH}_4/\text{THF}$  reflux, (4 h, 49% **13a**), (2 h, 41% **13b**); (e) ref.<sup>8</sup> ( $\text{H}_2, \text{Pd/C, EtOH, HCl}$ , 85%).

interest of synthetic chemists on the synthesis of deoxynojirimycin.<sup>11</sup>

We have designed the synthesis of fagomine **5a** and 4-*epi*-fagomine **5b** using carbohydrate building blocks as shown in Scheme 1. Fagomine **5a** and 4-*epi*-fagomine **5b** could be synthesized by deprotection and reduction of the corresponding 2-deoxyglycolactams **7a/b**. By lactamization of delta-hydroxy amides **8a/b**, 2-deoxyglycolactams **7a/b** could be obtained. Delta-Hydroxy amides **8a/b** could be accessed by aminolysis of 2-deoxyglycolactones **9a/b** which in turn could be obtained from readily available tri-O-benzyl-D-glucal **10a** or tri-O-benzyl-D-galactal **10b** respectively (Scheme 1). Nitrogen from ammonia is the source of the heteroatom in our planned synthesis of piperidine alkaloids.

With our research interests in sesquiterpene lactones<sup>12a</sup> and sugar-derived 2-deoxy-delta-lactone transformations,<sup>12b-d</sup> 2-deoxyglycolactones **9a/b** were readily synthesized from glycals **10a/b** by known literature protocol.<sup>13</sup> Further manipulating 2-deoxyglycolactone **9a/b** we thought that by using Pandit's method<sup>14a</sup> we could open the 2-deoxyglycolactone **9a/b** with 7 N methanolic ammonia. Hence, the treatment of lactones **9a/b** with methanolic ammonia (aminolysis) furnished the ring-opened compound delta-hydroxy amides **8a** (82%) and **8b** (96%) from 2-deoxyglycolactones **9a** and **9b** respectively (Scheme 2). With this



**Fig. 2** Stereochemical course of the reduction of Schiff base **14**; (a)  $\beta$ -face attack of the hydride, (b)  $\alpha$ -face attack of the hydride.

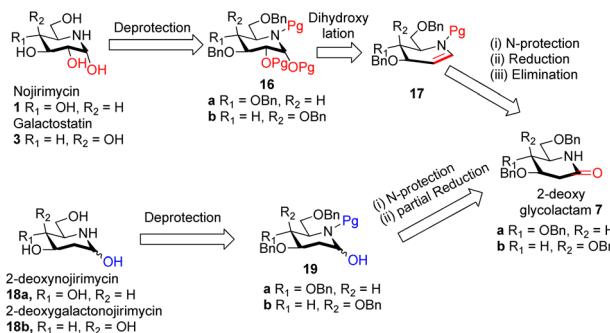
step nitrogen atom is incorporated in the molecule by cleavage of C-O bond in 2-deoxyglycolactone **9**.

$\delta$ -Hydroxy amides **8a/b** under Albright Goldmann oxidation condition *i.e.*  $\text{Ac}_2\text{O}$  and  $\text{DMSO}$  at  $rt$  provided the desired  $\delta$ -keto amides **11a/b** which without purification was carried on for the next step. The crude of the above reaction was then treated with formic acid and  $\text{NaBH}_3\text{CN}$ , to furnish the desired 2-deoxyglycolactams **7a/b**. This crucial step comprises an intramolecular reductive amination, which involved condensation of the amine with the ketone to furnish the cyclized product. Formic acid complexes with the ketone carbonyl and increases its electrophilicity to facilitate the attack of amine, leading to the formation of a new C-N bond. The iminium ion **14** formed *in situ* after dehydration from the intermediate **12a/b** undergoes  $\text{NaBH}_3\text{CN}$  reduction to form the desired 2-deoxyglycolactams **7a/b** (Fig. 2).

It is noteworthy here to describe the stereochemical course of the reduction of Schiff base **14**. The mechanism of this step presumably involves a hydride donation by the  $\text{NaBH}_3\text{CN}$  reagent to the acyliminium ion **14a/b**, initially formed by an acid-catalyzed dehydration of the hydroxy lactam substrates **12a/b**. Attack of hydride can take place from the  $\beta$ -face as well as from the  $\alpha$ -face leading to the formation of 2-deoxyglycolactam.<sup>14a</sup> The 2-deoxyglycolactam adopts a stable half chair conformation.<sup>14b</sup> Here the reduction is governed by the stereoelectronically controlled transition states. Attack of hydride from the  $\beta$ -face results in an unfavorable twist boat conformation **15T** which then flips to a favorable half chair conformation **15** (Fig. 2(a)). However, as **15a/b** was not formed it indicates that hydride approaches from the  $\alpha$ -face of the piperidine ring, in which hydride orbital overlaps effectively with the orbitals of the double bond which in turn are in conjugation with the lactam carbonyl. Moreover, during  $\alpha$ -face hydride attack there is no formation of twist boat conformation transition state, instead this directly leads to the formation of 2-deoxyglycolactam product in stable half chair conformation **7a/b** (Fig. 2(b)). None of the other products being formed and the NMR of the products **7a/b** supports the stereoselective reduction step.

Reduction of the carbonyl group of 2-deoxyglycolactam **7a/b** shall furnish the desired benzyl protected fagomine **13a** and 4-*epi*-fagomine **13b** which was successfully achieved by carrying





**Scheme 3** Retrosynthetic plan for the synthesis of nojirimycin **1**, galactostatin **3**, 2-deoxynojirimycin **18a** and 2-deoxygalactonojirimycin **18b**.

out the reaction in THF with slow addition of  $\text{LiAlH}_4$  at  $0^\circ\text{C}$  and then to rt and finally reflux for around 4 h to yield benzyl protected fagomine **13a** in 49% and benzyl protected *4-epi*-fagomine **13b** in 41% respectively from the corresponding 2-deoxyglycolactams **7a/b** (Scheme 2). Finally, following the reported procedure by Shipman *et al.*<sup>8a</sup> or Vankar *et al.*<sup>8b</sup> benzyl deprotection can be carried out to furnish fagomine **5a** and *4-epi*-fagomine **5b** respectively in 12% and 13% overall yields from the corresponding 2-deoxyglycolactones **9a/b**.

Intrigued by the amazing chemistry of 2-deoxyglycolactams **7a/b**, we envisioned that 2-deoxyglycolactams **7a/b** can be utilized to synthesize an advanced intermediate *viz.* iminoglycal **17** from which the biologically important piperidine alkaloids such as nojirimycin and its analog 2-deoxynojirimycin derivative can be readily synthesized. Iminoglycals were obtained as important reaction products<sup>15a,b</sup> or were intermediates<sup>15c</sup> synthesized which are utilized further for C–O<sup>15d</sup> or C–C bond forming reactions at C-1 of the piperidine nucleus, for the synthesis of natural products like (+)-deoxoprosophylline,<sup>15e,f</sup> (+)-fagomine,<sup>8a</sup> (–)-1-*epi*-adenophorine<sup>15g</sup> and potential immunosuppressant compounds.<sup>15h</sup> Although many syntheses of nojirimycin are reported,<sup>11a</sup> it is noteworthy to mention that synthesis of 2-deoxynojirimycin derivative is less known, so far we came across only two references.<sup>7b,c</sup> Hence, we formulated a retrosynthetic plan for its synthesis from a common intermediate as shown in Scheme 3.

We visualized that N-protected iminoglycal **17** can be readily obtained in 3 steps from 2-deoxyglycolactam **7** by (i) N-protection, (ii) reduction of the carbonyl (iii) elimination. Appropriate stereoselective dihydroxylation of **17** will furnish protected nojirimycin or galactostatin derivative which on deprotection will give the desired nojirimycin **1** and galactostatin **3**. On the other hand, 2-deoxyglycolactamol **19** can be obtained by (i) N-protection and (ii) partial reduction of the carbonyl group of 2-deoxyglycolactam **7**. 2-Deoxynojirimycin **18a** or 2-deoxygalactonojirimycin **18b** can be synthesized from **19a/b** by deprotection reaction condition.

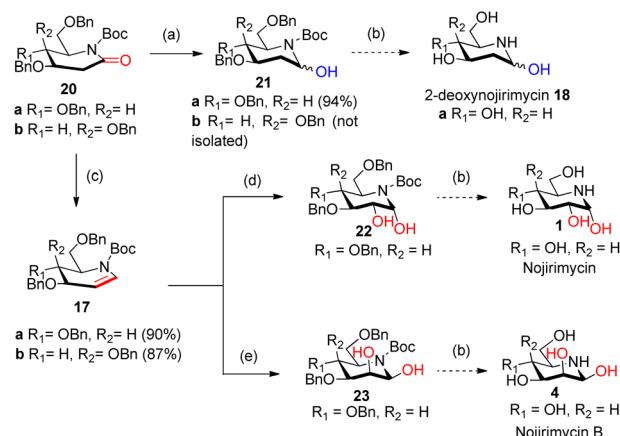
To achieve the N-protection of 2-deoxyglycolactam **7a/b** various conditions were tried such as  $\text{Boc}_2\text{O}$ , Py, DMAP, rt<sup>16a</sup> (Table 1, ESI†). Finally, by following the reaction condition<sup>16b</sup>  $\text{Boc}_2\text{O}$ , DCM,  $\text{NET}_3$ , DMAP (cat), 0 °C then rt (Table 1, ESI†) 2-

deoxyglycolactam-N-Boc derivative **20a/b** formation in 95% and 79% respectively from **7a** and **7b** was achieved.

Our idea was then to partially reduce the carbonyl group of 2-deoxyglycolactams **7a/b** and also to subsequently bring the dehydration of the lactamol hydroxy group. To proceed for that we started with 2-deoxyglycolactams **7a/b** and treated with  $\text{NaBH}_4$  in MeOH following the reported procedure<sup>16c</sup> carried out on the similar type of substrates (Table 2, ESI†). However, in all the cases even with 2-deoxyglycolactam-N-Boc **20a/b** and also under varying conditions and solvents desired product was not formed (Table 2, ESI†).

During our literature survey in the synthesis of fagomine, 4-*epi*-fagomine, and nojirimycin, we visualized that so far Super-Hydride or  $\text{LiBHET}_3$  are used mainly for three purposes (i) regioselective epoxide ring opening<sup>10c,17</sup> (ii) reduction of the ester to alcohol<sup>18</sup> and (iii) displacement of triflate  $-\text{OTf}$  by hydride.<sup>9a</sup> There are hardly any references for the use of Super-Hydride in the reduction of amide carbonyl and which is utilized in the synthesis of piperidine alkaloids. On extensive search we came across only three references using Super-Hydride in the reduction of carbonyl but it is not used on iminosugar substrate.<sup>19</sup> This inspired us to use Super-Hydride in our synthetic strategy of iminosugar. As we proposed in our retrosynthetic plan in partial reduction of amide carbonyl and also partial reduction followed by elimination of OH group to introduce a double bond *i.e.* to generate an iminoglycal **18a/b**, we took advantage of Super-Hydride here to play the double role. With fine-tuning of the reaction conditions using Super-Hydride the reaction shall proceed to furnish the desired products **21a** and **17a/b** (Scheme 4).

2-Deoxygluconolactam-N-Boc **20a** was treated with Super-Hydride in toluene<sup>19a,b</sup> at  $-76^\circ\text{C}$  for 1 h, and then with  $\text{NH}_4\text{Cl}$



**Scheme 4** Synthesis of 2-deoxynojirimycin **18a**, nojirimycin **1** and nojirimycin B **4**; reagents and conditions: (a) (i) Super-Hydride, toluene,  $-76^\circ\text{C}$  1 h; (ii)  $\text{NH}_4\text{Cl}$ ,  $-76^\circ\text{C}$  to rt; (b) (i) aq. HCl, MeOH, heat; (ii)  $\text{H}_2$ , Pd–C (10%), AcOH; (c) (i) Super-Hydride, toluene,  $-76^\circ\text{C}$ , 30 min; (ii) TFAA, DIPEA, DMAP (cat),  $-76^\circ\text{C}$  to rt; (d) ( $\text{DHQD}_2\text{AQN}$  (5 mol%),  $\text{K}_3\text{Fe}(\text{CN})_6$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{K}_2\text{OsO}_2(\text{OH})_4$  (5.59 mol%),  $\text{CH}_3\text{SO}_2\text{NH}_2$ , *t*-butyl alcohol:  $\text{H}_2\text{O}$  (1:1) 0 °C for 66 h; (e) ( $\text{DHQD}_2\text{AQN}$  (5 mol%),  $\text{K}_3\text{Fe}(\text{CN})_6$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{K}_2\text{OsO}_2(\text{OH})_4$  (5.59 mol%),  $\text{CH}_3\text{SO}_2\text{NH}_2$ , *t*-butyl alcohol:  $\text{H}_2\text{O}$  (1:1) 0 °C for 60 h.



(sat) solution at  $-76\text{ }^{\circ}\text{C}$  to rt furnished the desired 2-deoxygluconolactamol **21a** in 94% yield. The  $^1\text{H}$  NMR spectrum of 2-deoxygluconolactamol **21a**  $\delta_{\text{H}}$  5.64 brs represents H1 protons deshielded due to  $-\text{OH}$  and also by N atom. Reduction happened chemoselectively at  $\delta$ -lactam carbonyl only, as the CO group of Boc was observed intact at 156.7 ppm in  $^{13}\text{C}$  NMR spectrum. However, when 2-deoxygalactonolactam-*N*-Boc **20b** was treated with Super-Hydride under similar conditions, desired product 2-deoxygalactonolactamol **21b** could not be formed but starting material was recovered (Scheme 4). Interestingly, during our literature survey we observed that 3,4-di-*epi*-isomer of **21a** was utilized by Yoda *et al.*<sup>7b,c</sup> for the synthesis of (+)-batzellaside B 6 and its C8-epimer. By known methods *viz.* aq. HCl, MeOH,  $76\text{ }^{\circ}\text{C}$ , and then hydrogenolysis with  $\text{H}_2$ , Pd–C (10%), AcOH can easily furnish the desired product 2-deoxy-nojirimycin **18a** from **21a**.

It was then necessary to reduce and dehydrate both *in situ* the 2-deoxyglycolactam-*N*-Boc **20** to generate iminoglycal **17a/b**. This was achieved when 2-deoxyglycolactam-*N*-Boc **20a/b** was subjected to reaction conditions<sup>19a,c</sup> by treating with Super-Hydride, in toluene at  $-76\text{ }^{\circ}\text{C}$  for 30 min, and then with TFAA and base DIPEA in presence of catalytic DMAP, then raising the temperature from  $-76\text{ }^{\circ}\text{C}$  to rt, starting material was consumed in 12 h, with 90% **17a** and 87% **17b** respectively from **20a** and **20b** (Scheme 4). It was noteworthy that carrying out the reaction at  $-76\text{ }^{\circ}\text{C}$  or  $-70\text{ }^{\circ}\text{C}$  had no profound effect on the yields of the products, we preferred carrying the reaction at lower temperature ( $-76\text{ }^{\circ}\text{C}$ ) to the reported reaction condition<sup>19c</sup> at  $-70\text{ }^{\circ}\text{C}$ . In  $^1\text{H}$  NMR spectrum of iminoglycal **17a**,  $\delta_{\text{H}}$  7.11–6.93 (m, 1H), 5.10–4.90 (m, 1H), corresponds to vinylic protons,  $^{13}\text{C}$  NMR  $\delta_{\text{C}}$  101.5 indicates the chemical shift of  $\beta$ -carbon of enamine which is shielded by N atom. The other enamine  $\alpha$ -carbon signal is merged with the aromatic carbons which appear in the range 128.6–126.6 ppm. However, in this case by  $^{13}\text{C}$  NMR isomeric mixture of products could be predicted possibly due to the presence of a Boc group which attains different conformation, in the plane of piperidine ring and out of the plane of the piperidine ring.

To further extensively understand the reaction step for the selective conversion of **20a** to **21a** (Scheme 4), we performed the Density Functional Theory (DFT) calculations for this step of reaction involving both the substrates **20a** and **20b**. We have come up with the following explanation for the above selective conversions. The formation of 2-deoxygalactonolactamol **21b** that could not be isolated under the conditions (a) given in Scheme 4 is endergonic. However, the formation of **17b** under condition (c) (ii) from **20b** further suggests that **21b** is in dynamic equilibrium with **20a** under condition (a), as the subsequent treatment of **21b** formed *in situ* with TFAA and base DIPEA in the presence of catalytic DMAP condition (c) (ii) gives the desired dehydrated product **17b**. To further elaborate the above point, a relative DFT studies involving the substrates **20a** and **20b** for this particular step of the reaction was performed. The computational details are provided in the ESI<sup>†</sup>.

Two different pathways corresponding to the approach of the Super-Hydride to the *re*- and *si*-faces of the prochiral substrates (**20a/b**) have been investigated. Both modes of approach are

associated with two different conformations ( $\text{C}_1$  and  $\text{C}_2$ ) of reactant and product complexes and the transition state geometry (see, computational details section (ESI<sup>†</sup>) for more details). Results of the gas-phase calculations are provided in Tables 3 and 4 (see ESI<sup>†</sup>) for **20a** and **20b** respectively. Please refer to Fig. S1 and S2 in the ESI<sup>†</sup> for the optimized gas-phase transition state geometries involving **20a** and **20b**. The results of gas-phase calculations reveal that the conformation  $\text{C}_2$  is significantly more stable than the conformation  $\text{C}_1$ . Therefore, the free energy profile diagrams and all the further analyses are exclusively based on conformation  $\text{C}_2$ . Furthermore, the solvent-phase calculations were performed only on conformation  $\text{C}_2$ . The results of the solvent phase calculations are provided in Table 5 (see ESI<sup>†</sup>) and the optimized solvent-phase transition state geometries are represented in Fig. S3 (see ESI<sup>†</sup>).

Therefore, two different pathways (each with two different conformations of reactant and product complexes and transition-state geometries) have been investigated for both the substrates, **20a** and **20b** (Fig. S1 and S2 in ESI<sup>†</sup>). Results of the gas-phase calculations are provided in Tables 3 and 4 in the ESI<sup>†</sup> for **20a** and **20b**, respectively. Tables 3 and 4<sup>†</sup> reveals that conformation 2 for each mode of approach for both the substrates are energetically favorable. Therefore, the free energy profile diagrams and all the further analyses for both the substrates exclusively involve conformation 2. It is to be noted that the solvent-phase calculations were performed only on conformation 2 for both the pathways for the two substrates.

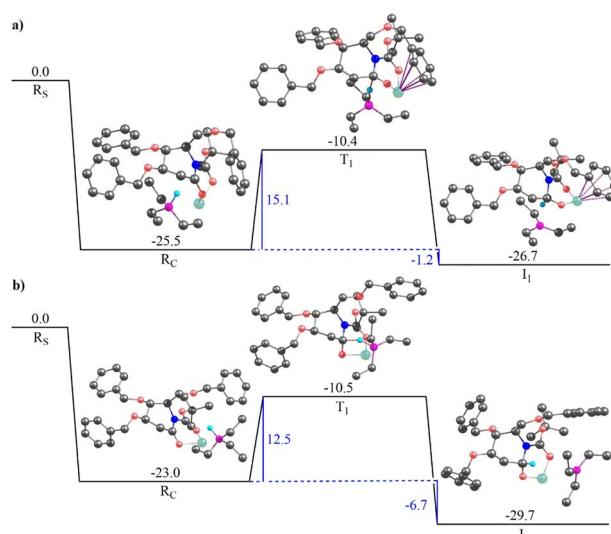


Fig. 3 The gas-phase free energy profile for reduction of 2-deoxygluconolactam-*N*-Boc **20a** to 2-deoxygluconolactam-*N*-Boc **21a** representing approach of the Super-Hydride to: (a) *re*-face of **20a** and (b) *si*-face of **20a**.  $R_s$ ,  $R_C$ ,  $T_1$ ,  $I_1$  represent infinitely separated reactants, the reactant complex, the transition state geometry, and the product complex, respectively. Hydrogen atoms that are not part of the reaction coordinate have been removed for clarity. All the values are in  $\text{kcal mol}^{-1}$ . Hydrogen atoms that are not part of the reaction coordinate have been removed for clarity. Color codes: black – carbon, coral – oxygen, cyan – hydrogen, light green – lithium, fuchsia – boron, blue – nitrogen. The dotted pink lines represent cation–π interaction and dotted maroon lines represent bond breaking/bond forming.



The results of the solvent phase calculations are provided in Table 5, ESI.†

Fig. 3 illustrates the gas-phase free energy profile for the conversion of 2-deoxygluconolactam-*N*-Boc **20a** to 2-deoxygluconolactam-*N*-Boc **21a** involving both the *re*- and *si*-face pathways. A very strong interaction between the Super-Hydride and **20a** has been observed, as the reactant complex in the pathway shown in Fig. 3(a) (for the *re*-face approach) is 25.5 kcal mol<sup>-1</sup> lower in energy than the infinitely separated reactants. Besides, the reactant complex for the *si*-face approach is 2.5 kcal mol<sup>-1</sup> less stable as compared to the *re*-face reactant complex. The subsequent barriers for the conversion to 2-deoxygluconolactam-*N*-Boc **21a** for the *re*- and *si*-face approaches are 15.1 and 12.5 kcal mol<sup>-1</sup>, respectively. However, the relative energies of two transition state geometries with respect to the infinitely separated reactants are almost the same. Further, the product complex for the *si*-face pathway was found to be 3.0 kcal mol<sup>-1</sup> more stable than the *re*-face approach (Fig. 3). Notably, both the pathways lead to stable product complexes (the intermediates for the next step of the reaction) with the reaction step being exergonic. Thus, one would expect that both the pathways are feasible for **20a** in the given condition, which leads to product **21a** that we were able to isolate.

The solvent phase calculations (employing toluene as solvent) for **20a** reveal a more distinct trend. The *re* face pathway is kinetically favorable with a lower (by 2.5 kcal mol<sup>-1</sup>) barrier as compared to the *si*-face pathway (Fig. S4a and b in ESI†). The reactant complexes for both the pathways are almost of the same energy. However, the product complex obtained for the *si*-face approach is 3.7 kcal mol<sup>-1</sup> lower in energy than the *re*-face product, depicting the *si*-face pathway is thermodynamically favorable. Moreover, both the pathways reveal the process being exergonic with thermally stable product complexes, which could be isolated after subsequent hydrolysis.

Fig. 4 illustrates the gas-phase free energy profile for the reduction of 2-deoxygalactonolactam-*N*-Boc **20b** by Super-Hydride. The reactant complex for the *re*-face pathway, in this case, is 7.8 kcal mol<sup>-1</sup> lower in energy than the *si*-face reactant complex, which according to the Boltzmann distribution law substantiates for more than 99.99% of the population in this microstate. Thus, any further chemical conversion is possible only through the *re*-face reactant complex, and hence it rules out the *si*-face pathway for the reduction of the **20b** using Super-Hydride. The subsequent barrier for the reduction of the 2-deoxygalactonolactam-*N*-Boc **20b** (through *re*-face approach) is 19.6 kcal mol<sup>-1</sup>, with the overall reaction step being endergonic by 7.8 kcal mol<sup>-1</sup>. The solvent-phase calculations also reproduce the gas-phase findings with slightly altered energy values (Fig. S4c and d, ESI†). The reactant complex for the *re* face approach in the solvent-phase was obtained to be 4.8 kcal mol<sup>-1</sup> lower in energy than the *si* face reactant complex, which accounts for this microstate being occupied by about 99.99% of the total population (as per the Boltzmann distribution law). Thus, the solvent-phase results also indicate the selective reduction through the *re* face of the substrate **20b**. The obtained barrier for the *re* face approach in the solvent-phase was obtained to be 17.6 kcal mol<sup>-1</sup>. Importantly, this barrier with

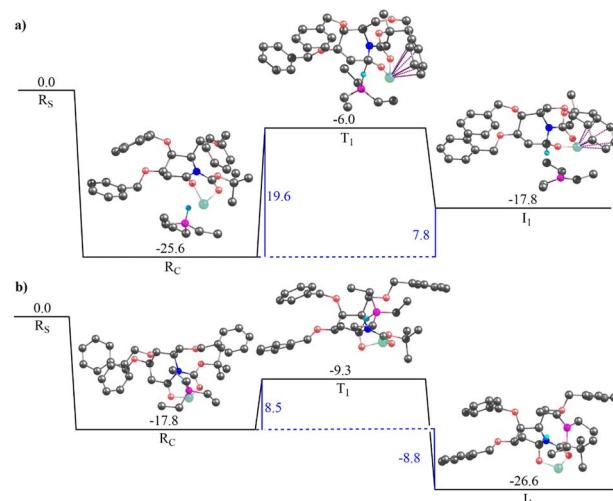


Fig. 4 The gas-phase free energy profile for reduction of 2-deoxygalactonolactam-*N*-Boc **20b** to 2-deoxygalactonolactam-*N*-Boc **21b** representing approach of the Super-Hydride to: (a) *re*-face of **20b** and (b) *si*-face of **20b**.  $R_s$ ,  $R_c$ ,  $T_1$ ,  $I_1$  represent infinitely separated reactants, the reactant complex, the transition state geometry, and the product complex, respectively. Hydrogen atoms that are not part of the reaction coordinate have been removed for clarity. All the values are in kcal mol<sup>-1</sup>. Hydrogen atoms that are not part of the reaction coordinate have been removed for clarity. Color codes: black – carbon, coral – oxygen, cyan – hydrogen, light green – lithium, fuchsia – boron, blue – nitrogen. The dotted pink lines represent cation–π interaction and dotted maroon lines represent bond breaking/bond forming.

respect to the infinitely separated reactants is merely 0.1 kcal mol<sup>-1</sup>. Thus, it could be deduced that the barrier is easily surmountable at the reaction temperature ( $-76$  °C). However, the product complex obtained for this pathway in the solvent-phase is 3.8 kcal mol<sup>-1</sup> higher in energy than the reactant complex, implying that the reaction of **20b** with Super-Hydride is endergonic by 3.8 kcal mol<sup>-1</sup>. This suggests that the product is significantly unstable in the case of 2-deoxygalactonolactam-*N*-Boc, and that is why it could not be isolated experimentally.

These results corroborate our original hypothesis that, **20a** a relatively stable product under the condition (a) given in Scheme 4, and hence the corresponding 2-deoxygluconolactam-*N*-Boc **21a** could be isolated experimentally. However, **20b** forms an unstable product complex, which converts back into the reactant under condition (a) Scheme 4, and thus could not be separated under the applied experimental conditions. However, the product was not extensively unstable and the barrier height was also surmountable at the given temperature. Therefore, when the conditions for the forthcoming step (TFAA and base DIPEA, catalytic DMAP then to rt) were enforced immediately, a successful conversion of **21b** to **17b** was achieved. Thereby provides the reason why 2-deoxygluconolactam-*N*-Boc **21a** could be isolated, whereas 2-deoxygalactonolactam-*N*-Boc **21b** could not be.

By synthesizing the iminoglycal **17a/b** we have functionalized the C-1 and C-2 position of iminosugar, which can grant access to the synthesis of various other biologically active



piperidine alkaloids. As per our retrosynthetic plan dihydroxylation of iminoglycal can procure nojirimycin **1** and nojirimycin B **4** (mannojirimycin) (Scheme 4). Following the very well-established condition for dihydroxylation<sup>20a</sup> with AD-mix  $\alpha$  and AD-mix  $\beta$  (commercial reagent) in *t*-butyl alcohol–H<sub>2</sub>O (1 : 1) 0 °C for 4 days, resulted in complete recovery of starting material. Strong chelating ligands and using methane sulfonamide are known to accelerate the dihydroxylation reaction which prompted us to try this reaction condition by using strong chelating ligands (DHQ)<sub>2</sub>AQN and (DHQD)<sub>2</sub>AQN.<sup>20b,21</sup> To our surmise, on treating iminoglycal **17a** with (DHQ)<sub>2</sub>AQN (5 mol%), with K<sub>3</sub>Fe(CN)<sub>6</sub> as oxidant and K<sub>2</sub>CO<sub>3</sub> as a base, K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub> (5.59 mol%) CH<sub>3</sub>SO<sub>2</sub>NH<sub>2</sub> as an additive in *t*-butyl alcohol : H<sub>2</sub>O (1 : 1) 0 °C, was completed in 66 h, furnished the protected derivative of nojirimycin **22**. However, even after purification by preparative thin layer chromatography (PTLC) it was difficult to obtain the pure product nojirimycin **22** and it was contaminated with some uncharacterized impurities due to which the peaks in NMR were not very distinct for analysis. But the LC-MS and HRMS were in good agreement with the desired product nojirimycin derivative **22**. Similarly, by treating iminoglycal **17a** with (DHQD)<sub>2</sub>AQN (5 mol%), with K<sub>3</sub>Fe(CN)<sub>6</sub>, K<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub> (5.59 mol%) CH<sub>3</sub>SO<sub>2</sub>NH<sub>2</sub> in *t*-butyl alcohol : H<sub>2</sub>O (1 : 1) 0 °C for 60 h, furnished the protected derivative of nojirimycin **23**. Similar to nojirimycin derivative **22** in this case also it was difficult to purify the nojirimycin derivative **23** by PTLC and it was contaminated with some uncharacterized impurities. Nojirimycin derivative **22** and **23** can be readily converted to nojirimycin **1** and nojirimycin B **4** by known methods of Boc deprotection and dehydrogenation as reported in the synthesis of nojirimycin and deoxynojirimycin.

All the attempts for the dihydroxylation of the iminoglycal **17b** by following the same conditions as that for iminoglycal **17a** with (DHQD)<sub>2</sub>AQN as well as (DHQ)<sub>2</sub>AQN could not furnish the desired product. Probably we could reason that, the axial OBN group at C-4 in the case of iminoglycal **17b** blocks the approach of Osmium from  $\beta$ -face and  $\alpha$ -face is blocked by Boc group, which is already occupying the  $\alpha$ -face (Boc group placed trans to C-4 OBN group to minimize steric interaction). The situation is different in iminoglycal **17a** where the OBN group at C-4 is in equatorial position doesn't hinder the entry of osmium atom from either of the facial attack, also the Boc group maintains the more stable equatorial position in the plane of the piperidine ring without hampering the dihydroxylation process.

By following the known reaction conditions, generally, Boc deprotection is obtained in quantitative yields<sup>10c</sup> and debenzylation are obtained in yields of 85%<sup>8a</sup> utilizing assumption for final deprotection (Boc deprotection and debenzylation) starting from glucolactam **7a** 2-deoxynojirimycin **21a** can be readily obtained in 76%, and in 22% starting from 2-deoxygluconolactone **9a**. Similarly, nojirimycin **1** can be synthesized in 22% from 2-deoxygluconolactam **7a** and in 6% starting from 2-deoxygluconolactone **9a**. Likewise nojirimycin B or mannojirimycin **4** can be synthesized in 52% from 2-deoxygluconolactam **7a** and in 15% starting from 2-deoxygluconolactone **9a**. Initially, once again we tried to

ascertain the failure of the dihydroxylation reaction with iminoglycal **17b** using DFT studies but we observed that incorporating the heavier Os atom and bulky ligands made the calculation process very slow and time-consuming. DFT calculations for this problem still deserves attention for some more interesting results which will be undertaken in the future.

## Conclusions

We have successfully synthesized fagomine and 4-*epi*-fagomine from 2-deoxygluconolactone and 2-deoxygalactonolactone, respectively from chiral pool approach employing less expensive reagents and easy to handle reaction conditions. By slight variation in reaction condition employing Super-Hydride, we have synthesized iminoglycal and functionalized the C-1 and C-2 position of iminosugar, which can serve as a handle for the synthesis of various other biologically active molecules. The partially reduced product by Super-Hydride *i.e.* 2-deoxynojirimycin derivative can be utilized for the synthesis of epimers of natural products such as batzellasides. Thus, the use of Super-Hydride opens a new route for the synthesis of different iminosugars. Also, formal synthesis of nojirimycin, nojirimycin B, and 2-deoxynojirimycin has been achieved. From the DFT studies, we could reason the failure of the formation of 2-deoxygalactonojirimycin *via* Super-Hydride reduction of 2-deoxygalactonolactam to 2-deoxygalactonolactamol.

## Experimental

### General methods

The FT-IR spectra were recorded on a FT-IR-8300 Shimadzu spectrometer and are reported in cm<sup>-1</sup>. NMR spectra were recorded on Bruker ACF 200 or AV200 (200 MHz for <sup>1</sup>H NMR and 50 MHz for <sup>13</sup>C NMR) or AV400 (400 MHz for <sup>1</sup>H NMR and 100 MHz for <sup>13</sup>C NMR) or JEOL ECX 400 (400 MHz for <sup>1</sup>H NMR and 100 MHz for <sup>13</sup>C NMR) or Bruker DRX-500 (500 MHz for <sup>1</sup>H NMR and 125 MHz for <sup>13</sup>C NMR) spectrometers using CDCl<sub>3</sub> as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in <sup>1</sup>H NMR and CDCl<sub>3</sub> (77.0 ppm) in <sup>13</sup>C NMR, respectively. Chemical shifts are expressed in parts per million (ppm) and coupling constants ( $\mathcal{J}$ ) in hertz (Hz). Mass spectra were recorded on LC-MS/MSTOF API QSTAR PULSAR spectrometer, samples introduced by infusion method using the Electrospray Ionization Technique (ESI). HRMS (ESI) of samples was taken on an Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. Analytical thin-layer chromatography (TLC) were performed on 0.2 mm coated Merck pre-coated silica gel (EM 60-F254) plates. Visualization was accomplished with UV light (254 nm) and exposure to either ethanolic phosphomolybdc acid (PMA) or *p*-anisaldehyde–acetic acid–sulfuric acid charring reagent followed by heating. PTLC separations were carried out on 0.25 mm E. Merck silica gel plates (60F254). All the melting points reported are recorded in an open capillary using Büchi melting point apparatus B-540 and are uncorrected. Optical rotations were recorded on Jasco P-2000 polarimeter Na-lamp,  $\lambda$  = 589 nm. Flash chromatography was performed with Combi-Flash R<sub>f</sub> 200i equipped with UV/VIS and ELSD, Isco Teledyne



Inc., USA using RediSep® column ( $\text{SiO}_2$ ). All other chemicals were of analytical grade. Chemical nomenclature was generated using ChemDraw.

#### Procedure for the synthesis $\delta$ -hydroxy amides

*(3R,4R)-3,4,6-Tris(benzyloxy)-5-hydroxyhexanamide (8a) and (3R,4S)-3,4,6-tris(benzyloxy)-5-hydroxyhexanamide (8b).* 2-Deoxygluconolactone **9a/b** (1.0 g, 2.32 mmol) was dissolved in methanolic ammonia solution (7 N, 22 mL) and was stirred at room temperature for 1.5 h. After completion of the reaction (TLC), the reaction mixture was concentrated *in vacuo* (inside a fume hood, taking necessary precautions for ammonia gas) followed by purification by  $\text{SiO}_2$  column chromatography (EtOAc–petroleum ether, 6 : 4) to afford **8a/b**.

*(3R,4R)-3,4,6-Tris(benzyloxy)-5-hydroxyhexanamide (8a).* Colorless solid; 859 mg, 82%; mp 74–76 °C;  $R_f$  0.26 (EtOAc–petroleum ether, 1 : 1);  $[\alpha]_D^{20} +14.27$  (c 1.43,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ):  $\nu_{\text{max}}$  3473, 3374, 3201, 3012, 2869, 1673, 1615, 1404, 1216, 1072, 1028, 908, 747, 698, 667  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.37–7.23 (m, 15H, 3 Ph-H), 5.65 (brs, 1H, NH), 5.22 (brs, 1H, NH), 4.66–4.60 (m, 2H,  $\text{CH}_2\text{Ph}$ ), 4.60–4.47 (m, 4H,  $\text{CH}_2\text{Ph}$ ), 4.31–4.23 (m, 1H,  $\text{H}_3$ ), 3.95 (brs, 1H,  $\text{H}_5$ ), 3.69–3.65 (m, 1H,  $\text{H}_4$ ), 3.65–3.60 (m, 2H,  $\text{H}_6$ ), 3.06 (brs, 1H, OH), 2.64–2.56 (m, 1H,  $\text{H}_{2a}$ ), 2.56–2.47 (m, 1H,  $\text{H}_{2b}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 173.2 (C<sub>1</sub>), 138.0, 137.8, 137.6 (ArC), 128.5, 128.5, 128.3, 128.3, 128.0, 127.9, 127.8 (ArCH), 78.1 (C<sub>4</sub>), 76.7 (C<sub>3</sub>), 73.5 ( $\text{CH}_2\text{Ph}$ ), 73.3 ( $\text{CH}_2\text{Ph}$ ), 71.1 (C<sub>6</sub>), 70.8 (C<sub>5</sub>), 37.2 (C<sub>2</sub>); ESI-MS  $m/z$  450.2240 [M + H]<sup>+</sup>; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{27}\text{H}_{31}\text{NO}_5\text{Na}^+$  [M + Na]<sup>+</sup> 472.2094, found 472.2087.

*(3R,4S)-3,4,6-Tris(benzyloxy)-5-hydroxyhexanamide (8b).* Yellowish gum; 1.08 g, 96%;  $R_f$  0.19 (EtOAc–petroleum ether, 1 : 1);  $[\alpha]_D^{20} +2.92$  (c 1.2,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ):  $\nu_{\text{max}}$  3660, 3372, 3019, 2872, 1736, 1454, 1216, 1101, 1064, 908, 755, 698, 668  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.33–7.25 (m, 15H), 6.00 (brs, 1H), 5.51 (brs, 1H), 4.79–4.48 (m, 6H), 4.18–4.10 (m, 1H), 3.95 (brs, 1H), 3.76–3.72 (m, 1H), 3.60–3.44 (m, 2H), 2.83 (brs, 1H), 2.68–2.47 (m, 2H), 1.80 (brs, 1H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 173.5, 137.7, 137.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 78.7, 77.2, 74.0, 73.4, 72.9, 71.0, 69.8, 37.6; ESI-MS  $m/z$  450.4348 [M + H]<sup>+</sup>, 472.4115 [M + Na]<sup>+</sup>; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{27}\text{H}_{31}\text{NO}_5\text{Na}^+$  [M + Na]<sup>+</sup> 472.2094, found 472.2088. Data was in good agreement with the previous report.<sup>22</sup>

#### Procedure for the synthesis $\delta$ -keto amides

*(3R,4R)-3,4,6-Tris(benzyloxy)-5-oxohexanamide (11a) and (3R,4S)-3,4,6-tris(benzyloxy)-5-oxohexanamide (11b).* To a solution of **8a/b** (1 g, 2.2 mmol) in dry dimethyl sulfoxide (8 mL, 0.11 M) and acetic anhydride (5 mL, 0.05 M) was stirred under an inert atmosphere for 23–26 h in a well-ventilated hood. Water (50 mL) was added and the mixture was stirred for another 30 min during which a yellow oil precipitated. The water layer was then removed and the residue was dissolved in dichloromethane and extracted with water (4 × 10 mL). The organic layer was then washed with brine (2 × 10 mL). The organic layer was dried with anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The product [**11a** (587 mg, 59%) **11b** (637 mg, 64%)] was used without further purification for the subsequent reactions.

#### Procedure for the synthesis of 2-deoxyglycolactam

*(5R,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)piperidin-2-one (7a) and (5S,6R)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)piperidin-2-one (7b).* Crude compound **11a/b** (582 mg, 1.302 mmol) was dissolved in  $\text{CH}_3\text{CN}$  (20 mL) and HCOOH (3.8 mL) was added to the reaction mixture followed by  $\text{NaBH}_3\text{CN}$  (177 mg, 2 eq.) and the reaction mixture was refluxed at 85 °C for 4.5 h. The reaction mixture was then cooled in an ice-bath and was quenched by slowly adding aq. HCl solution (0.1 N, 30 mL). After stirring for another 15 minutes, EtOAc (50 mL) and then saturated aq.  $\text{NaHCO}_3$  solution (50 mL) was added to it slowly taking necessary precautions from the brisk effervescence. The addition of  $\text{NaHCO}_3$  solution was continued under cold conditions if the effervescence doesn't cease. The water layer was separated and extracted with EtOAc (2 × 25 mL), the combined organic fractions were pooled and then washed with brine (1 × 30 mL) and dried (anhydrous  $\text{Na}_2\text{SO}_4$ ). After concentration *in vacuo*, the resulting crude was purified by  $\text{SiO}_2$  column chromatography (EtOAc–petroleum ether, 4 : 6) to afford **7a** as a colourless solid and **7b** as semi-solid.

*(5R,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)piperidin-2-one (7a).* Colorless needles (crystallization by EtOAc–petroleum ether) 329 mg, 59%; m.p. 73–75 °C [Lit<sup>23</sup> m.p. 73–75 °C];  $R_f$  0.32 (EtOAc–petroleum ether, 1 : 1);  $[\alpha]_D^{20} +16.78$  (c 1.02,  $\text{CHCl}_3$ ); [Lit<sup>23</sup>  $[\alpha]_D^{20} +17$  (c 1,  $\text{CHCl}_3$ )]; IR ( $\text{CHCl}_3$ ):  $\nu_{\text{max}}$  3396, 3019, 2868, 1666, 1455, 1215, 1100, 755, 699, 669  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.34–7.23 (m, 15H, 3 Ph-H), 6.33 (brs, 1H, NH), 4.79 (d,  $J$  = 11.5 Hz, 1H,  $\text{CH}_2\text{Ph}$ ), 4.65–4.60 (m, 1H,  $\text{CH}_2\text{Ph}$ ), 4.58–4.51 (m, 2H,  $\text{CH}_2\text{Ph}$ ), 4.47–4.43 (m, 2H,  $\text{CH}_2\text{Ph}$ ), 3.88 (dt,  $J$  = 5.3, 7.2 Hz, 1H,  $\text{H}_3$ ), 3.63–3.51 (m, 3H,  $\text{H}_{6a}$ ,  $\text{H}_5$ ,  $\text{H}_4$ ), 3.42–3.35 (m, 1H,  $\text{H}_{6b}$ ), 2.79 (dd,  $J$  = 5.3, 17.2 Hz, 1H,  $\text{H}_{2e}$ ), 2.48 (dd,  $J$  = 7.6, 17.4 Hz, 1H,  $\text{H}_{2a}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 169.8 (C<sub>1</sub>), 137.8, 137.7, 137.5 (ArC), 128.5, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6 (ArCH), 75.7 (C<sub>4</sub>), 75.5 (C<sub>3</sub>), 73.6 ( $\text{CH}_2\text{Ph}$ ), 73.3 ( $\text{CH}_2\text{Ph}$ ), 71.7 ( $\text{CH}_2\text{Ph}$ ), 71.0 (C<sub>6</sub>), 54.9 (C<sub>5</sub>), 35.2 (C<sub>2</sub>); ESI-MS  $m/z$  432.78 [M + H]<sup>+</sup>, 454.57 [M + Na]<sup>+</sup>, 470.74 [M + K]<sup>+</sup>; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{27}\text{H}_{29}\text{NO}_4^+$  [M + Na]<sup>+</sup> 454.1993, found 454.1993. Data was in good agreement with the previous report.<sup>23</sup>

*(5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)piperidin-2-one (7b).* Semi-solid; 332 mg, 59%;  $R_f$  0.21 (EtOAc–petroleum ether, 4 : 6);  $[\alpha]_D^{20} +29.43$  (c 1.1,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ):  $\nu_{\text{max}}$  3395, 3017, 2926, 1663, 1454, 1216, 1114, 756, 698, 668  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.40–7.23 (m, 15H), 6.06 (s, 1H), 4.94 (d,  $J$  = 11.6 Hz, 1H), 4.68–4.53 (m, 3H), 4.50–4.38 (m, 2H), 4.00 (brs., 1H), 3.84 (ddd,  $J$  = 1.6, 6.3, 10.7 Hz, 1H), 3.62–3.46 (m, 3H), 2.93–2.61 (m, 2H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 170.2, 138.1, 137.7, 137.4, 128.6, 128.5, 128.4, 128.0, 128.0, 127.9, 127.8, 127.5, 75.6, 73.8, 73.6, 71.7, 70.9, 70.6, 54.2, 33.7; ESI-MS  $m/z$  432.39 [M + H]<sup>+</sup>, 454.39 [M + Na]<sup>+</sup>; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{27}\text{H}_{30}\text{NO}_4^+$  [M + H]<sup>+</sup> 432.2169, found 432.2170. Data was in good agreement with the previous report.<sup>22</sup>

**Preparation of tri-O-benzyl fagomine/(2R,3R,4R)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)piperidine (13a) and tri-O-benzyl 4-*epi*-fagomine/(2R,3S,4R)-3,4-bis(benzyloxy)-2-(benzyloxy-methyl)piperidine (13b).** To a solution of **7a/b** (256 mg, 0.594 mmol) in THF (15 mL), LAH (68 mg, 1.8 mmol,



3 eq.) was added. The reaction mixture was stirred for 4 h at 70 °C under the nitrogen atmosphere. The mixture was then brought to room temperature and poured into a mixture of diethyl ether and ice water (1 : 1, 100 mL). After stirring for 15 min, 0.5 M aq. NaOH (75 mL) was added and the mixture was stirred for another 10 minutes. The water layer was then separated and extracted with diethyl ether (3 × 50 mL), the organic fractions were pooled, washed with brine, and finally dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The crude product was purified by SiO<sub>2</sub> column chromatography (EtOAc–petroleum ether, 1 : 1) to afford **13a/b**.

*Tri-O-benzyl-4-epifagomine/(2R,3R,4R)-3,4-bis(benzyloxy)-2-(benzyloxy-methyl)piperidine (13a).* Yellow syrup; 120 mg, 49%; R<sub>f</sub> 0.12 (EtOAc–petroleum ether, 1 : 1); [α]<sub>D</sub><sup>20</sup> +21.76 (c 1.1, CHCl<sub>3</sub>); [Lit<sup>a</sup> [α]<sub>D</sub><sup>18</sup> +30.5 (c 1.90, CHCl<sub>3</sub>)]; IR (CHCl<sub>3</sub>): ν<sub>max</sub> 3151, 3017, 2922, 1398, 1220, 1099, 772, 669, 615 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.40–7.20 (m, 15H, 3 Ph-H), 4.93 (d, J = 10.8 Hz, 1H, CH<sub>2</sub>Ph), 4.70 (d, J = 11.8 Hz, 1H, CH<sub>2</sub>Ph), 4.63 (d, J = 11.5 Hz, 1H, CH<sub>2</sub>Ph), 4.57–4.49 (m, 1H, CH<sub>2</sub>Ph), 4.49–4.40 (m, 2H, CH<sub>2</sub>Ph), 3.71 (dd, J = 2.5, 9.0 Hz, 1H, H<sub>6a</sub>), 3.60–3.46 (m, 2H, H<sub>6b</sub>, H<sub>3</sub>), 3.32 (t, J = 9.2 Hz, 1H, H<sub>4</sub>), 3.09–2.99 (m, 1H, H<sub>1e</sub>), 2.70 (ddd, J = 2.5, 6.3, 9.3 Hz, 1H, H<sub>5</sub>), 2.55 (dt, J = 2.3, 12.7 Hz, 1H, H<sub>1a</sub>), 2.30 (brs., 1H, NH), 2.18–2.06 (m, 1H, H<sub>2e</sub>), 1.56–1.41 (m, 1H, H<sub>2a</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 138.7, 138.6, 138.1 (ArC), 128.4, 128.3, 128.3, 128.0, 127.8, 127.7, 127.6, 127.6, 127.5 (ArCH), 82.4 (C<sub>3</sub>), 80.7 (C<sub>4</sub>), 75.1 (CH<sub>2</sub>Ph), 73.3 (CH<sub>2</sub>Ph), 71.5 (CH<sub>2</sub>Ph), 70.6 (C<sub>6</sub>), 60.0 (C<sub>5</sub>), 43.5 (C<sub>1</sub>), 32.0 (C<sub>2</sub>); ESI-MS m/z 418.42 [M + H]<sup>+</sup>; HRMS (ESI) m/z calcd for C<sub>27</sub>H<sub>32</sub>NO<sub>3</sub><sup>+</sup> [M + H]<sup>+</sup> 418.2377, found 418.2378. Data was in good agreement with the previous report.<sup>8a</sup>

*Tri-O-benzyl-4-epifagomine/(2R,3S,4R)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)piperidine (13b).* Yellow syrup; 102 mg, 41%; R<sub>f</sub> 0.12 (EtOAc–petroleum ether); [α]<sub>D</sub><sup>20</sup> −4.07 (c 1.0, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>): ν<sub>max</sub> 3302, 3089, 3066, 3019, 2929, 1455, 1365, 1216, 1088, 751, 699, 669 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.39–7.20 (m, 15H, 3 Ph-H), 4.94 (d, J = 11.5 Hz, 1H, CH<sub>2</sub>Ph), 4.68–4.55 (m, 3H, CH<sub>2</sub>Ph), 4.52–4.37 (m, 2H, CH<sub>2</sub>Ph), 3.93 (brs, 1H, H<sub>4</sub>), 3.57–3.49 (m, 1H, H<sub>6a</sub>), 3.49–3.43 (m, 1H, H<sub>3</sub>), 3.43–3.36 (m, 1H, H<sub>6b</sub>), 3.27 (brs, 1H, NH), 3.16–3.04 (dd, J = 2.0, 13.3 Hz, 1H, H<sub>1e</sub>), 2.78 (t, J = 6.8 Hz, 1H, H<sub>5</sub>), 2.57 (dt, J = 2.9, 12.9 Hz, 1H, H<sub>1a</sub>), 2.05–1.87 (m, 1H, H<sub>2a</sub>), 1.79 (d, J = 10.0 Hz, 1H, H<sub>2e</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 139.0, 138.6, 138.0 (ArC), 128.3, 128.2, 128.1, 128.1, 127.9, 127.7, 127.4, 127.2 (ArCH), 79.6 (C<sub>3</sub>), 74.0, 73.3, 73.2 (C<sub>4</sub>), 70.3 (C<sub>6</sub>), 70.0, 58.7 (C<sub>5</sub>), 44.1 (C<sub>1</sub>), 27.6 (C<sub>2</sub>); ESI-MS m/z 418.30 [M + H]<sup>+</sup>; HRMS (ESI) m/z calcd for C<sub>27</sub>H<sub>32</sub>NO<sub>3</sub><sup>+</sup> [M + H]<sup>+</sup> 418.2377, found 418.2377.

**Preparation of *tert*-butyl(2R,3R,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-6-oxopiperidine-1-carboxylate (20a) and *tert*-butyl(2R,3S,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-6-oxopiperidine-1-carboxylate (20b).** 2-Deoxyglycolactam **7a/b** (150 mg, 0.35 mmol) was dissolved in DCM (10 mL), Et<sub>3</sub>N (48.8 μL, 0.35 mmol) was added and cooled to 0 °C, Boc<sub>2</sub>O (152 mg, 0.70 mmol) was then added followed by DMAP (43 mg, 0.35 mmol) and stirred at 25 °C till completion of the reaction (TLC). The reaction mixture was evaporated to dryness and subjected to SiO<sub>2</sub> column chromatography (EtOAC–Et<sub>3</sub>N–petroleum ether, 5 : 2 : 93) to afford **20a/b**.

*tert*-Butyl(2R,3R,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-6-oxopiperidine-1-carboxylate (20a). Pale yellow oily syrup; 175 mg, 95%; R<sub>f</sub> 0.76 (EtOAc–petroleum ether, 1 : 1); [α]<sub>D</sub><sup>25</sup> −49.53 (c 1.12, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>): ν<sub>max</sub> 3021, 2978, 2402, 2360, 1767, 1718, 1511, 1220, 1034, 789, 734, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.37–7.17 (m, 15H), 4.70–4.59 (m, 2H), 4.59–4.47 (m, 3H), 4.45 (s, 2H), 4.07–3.99 (m, 1H), 3.86 (td, J = 5.5, 8.5 Hz, 1H), 3.67 (dd, J = 6.9, 9.3 Hz, 1H), 3.53 (dd, J = 4.1, 9.3 Hz, 1H), 2.86 (dd, J = 4.9, 16.8 Hz, 1H), 2.64 (dd, J = 8.9, 16.5 Hz, 1H), 1.48 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 169.5, 152.1, 137.7, 137.7, 128.4, 128.4, 127.9, 127.9, 127.8, 127.7, 127.6, 127.4, 83.3, 76.3, 75.4, 73.2, 72.2, 71.6, 70.3, 58.9, 37.5, 27.9; ESI-MS m/z 554.23 [M + Na]<sup>+</sup>; HRMS (ESI) m/z calcd for C<sub>32</sub>H<sub>37</sub>NO<sub>6</sub>Na [M + Na]<sup>+</sup> 554.2513, found 554.2513.

*tert*-Butyl(2R,3S,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-6-oxopiperidine-1-carboxylate (20b). Pale yellow oily syrup; 146 mg, 79%; R<sub>f</sub> 0.57 (EtOAc–petroleum ether, 1 : 1); flash chromatography (EtOAC–Et<sub>3</sub>N–petroleum ether, 5 : 2 : 93); [α]<sub>D</sub><sup>25</sup> +1.16 (c 1.14, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>): ν<sub>max</sub> 3014, 2362, 1741, 1707, 1657, 1516, 1265, 1033, 812, 759, 674 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ = 7.44–7.17 (m, 15H), 4.93–4.75 (m, 1H), 4.72–4.56 (m, 3H), 4.47 (d, J = 1.8 Hz, 2H), 4.42–4.27 (m, 1H), 4.14 (dd, J = 1.7, 4.1 Hz, 1H), 3.95–3.82 (m, 2H), 3.81–3.66 (m, 1H), 3.06–2.87 (m, 1H), 2.81–2.64 (m, 1H), 1.45 (s, 9H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ = 168.5, 152.4, 138.0, 137.9, 137.8, 128.4, 128.3, 127.8, 127.6, 127.4, 83.7, 73.6, 73.4, 73.2, 73.0, 71.3, 68.9, 57.0, 36.9, 27.7; ESI-MS m/z 554.27 [M + Na]<sup>+</sup>; HRMS (ESI) m/z calcd for C<sub>32</sub>H<sub>37</sub>NO<sub>6</sub>Na<sup>+</sup> [M + Na]<sup>+</sup> 554.2513, found 554.2521.

*tert*-Butyl(2R,3R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-6-hydroxypiperidine-1-carboxylate (21a). N-Boc protected lactam **20a** (100 mg, 0.188 mmol) was dissolved in dry toluene (5.0 mL) and cooled to −76 °C under inert atmosphere, and Super-Hydride (1.0 M in THF, 0.21 mL, 1.12 eq.) was added slowly dropwise over a period of 10 min, and stirred at −76 °C for 1 h. Saturated NH<sub>4</sub>Cl solution (4.0 mL) was added and stirred further for 1.5 h at −76 °C, and then temp was raised to room temperature and stirred at room temperature for 10 h. Reaction mixture was then treated with 10% Na<sub>2</sub>CO<sub>3</sub> solution (4 mL) and DCM (10 mL) was added to the reaction mixture. The organic layer was separated, and the aq. layer was extracted with DCM (3 × 5 mL). All the organic layers were pooled together, dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), concentrated *in vacuo* and finally purified by SiO<sub>2</sub> column chromatography (EtOAC–Et<sub>3</sub>N–petroleum ether, 5 : 1 : 44) to afford **21a** as a viscous oil (94 mg, 94%); R<sub>f</sub> 0.38 (EtOAc–petroleum ether, 3 : 7); [α]<sub>D</sub><sup>25</sup> −47.44 (c 1.21, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>): ν<sub>max</sub> 3741, 3019, 2362, 2334, 1692, 1531, 1216, 757, 695, 672 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 7.30–7.25 (m, 15H), 5.64 (brs, 1H), 4.71–4.48 (m, 6H), 4.05–4.01 (m, 2H), 3.85–3.68 (m, 2H), 3.62–3.50 (m, 1H), 2.26–2.15 (m, 1H), 2.04–1.90 (m, 1H), 1.69 (brs, 1H), 1.46 (s, 9H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 156.6, 138.1, 138.0, 137.4, 128.5, 128.3, 127.7, 127.6, 80.7, 77.2, 74.7, 73.2, 72.9, 71.7, 71.4, 30.9, 28.3; ESI-MS m/z 556.27 [M + Na]<sup>+</sup>; HRMS (ESI) m/z calcd for C<sub>32</sub>H<sub>39</sub>NO<sub>6</sub>Na<sup>+</sup> [M + Na]<sup>+</sup> 556.2670, found 556.2670.

**Preparation of *tert*-butyl(2R,3R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydropyridine-1(2H)-carboxylate (17a)**



and *tert*-butyl(2*R*,3*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (**17b**). *N*-Boc protected lactams **20a/b** (136 mg, 0.26 mmol) was dissolved in dry toluene (3 mL) and cooled to  $-76\text{ }^{\circ}\text{C}$  under inert atmosphere, and Super-Hydride (1.0 M in THF, 0.3 mL, 1.1 eq.) was added slowly dropwise over a period of 10 min, and stirred at  $-76\text{ }^{\circ}\text{C}$  for 30 min. TFAA (0.31 mL, 2.2 mmol) was added followed by the addition of DIPEA (68  $\mu\text{L}$ , 1.5 mmol) and a catalytic amount of DMAP ( $\sim$ 5 mg). The temperature was then raised from  $-76\text{ }^{\circ}\text{C}$  to room temperature in 8 h and stirred further for 3 h at  $25\text{ }^{\circ}\text{C}$ . Water was added (10 mL), the organic layer was separated, washed with water ( $2 \times 10$  mL), dried (anhydrous  $\text{Na}_2\text{SO}_4$ ), concentrated, and purified by  $\text{SiO}_2$  column chromatography (EtOAc-Et<sub>3</sub>N-petroleum ether, 3 : 2 : 95) to afford **17a/b**.

*tert*-Butyl(2*R*,3*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (**17a**). Viscous oil (119 mg, 90%);  $R_f$  0.57 (EtOAc-petroleum ether, 1 : 1);  $[\alpha]_D^{25} -97.97$  (c 1.10,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ):  $\nu_{\text{max}}$  3739, 3426, 2362, 2334, 1645, 1547, 1365, 924, 800, 699  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.35–7.24 (m, 15H), 7.11–6.93 (m, 1H), 5.10–4.90 (m, 1H), 4.74–4.56 (m, 3H), 4.52–4.39 (m, 4H), 4.19–4.13 (m, 1H), 3.86–3.57 (m, 3H), 1.54–1.49 (m, 9H); <sup>13</sup>C NMR (125 MHz,  $\text{CDCl}_3$ , mixture of isomers):  $\delta$  152.7, 152.2, 138.8, 138.6, 138.3, 138.0, 128.6, 128.5, 128.4, 128.2, 127.7, 127.4, 127.3, 126.9, 126.6, 101.5, 81.4, 81.3, 77.9, 77.8, 75.6, 75.1, 73.1, 72.9, 72.9, 72.8, 72.7, 71.9, 71.5, 71.2, 71.1, 70.9, 70.7, 70.4, 70.2, 68.4, 66.9, 66.8, 66.5, 66.0, 28.2, 28.0, 27.8; ESI-MS  $m/z$  538.27 [ $\text{M} + \text{Na}$ ]<sup>+</sup>; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{32}\text{H}_{37}\text{NO}_5\text{Na}$  [ $\text{M} + \text{Na}$ ]<sup>+</sup> 538.2564, found 538.2564.

*tert*-Butyl(2*R*,3*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (**17b**). Pale yellow viscous oil; 115 mg, 87%; purification by  $\text{SiO}_2$  column chromatography (EtOAc-Et<sub>3</sub>N-petroleum ether, 3 : 2 : 95);  $R_f$  0.57 (EtOAc-petroleum ether, 1 : 1);  $[\alpha]_D^{25} -56.21$  (c 1.13,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ):  $\nu_{\text{max}}$  3740, 3620, 2362, 2334, 1647, 1547, 1367, 921, 821, 678  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.29 (s, 1H), 7.36–7.22 (m, 15H), 4.93–4.73 (m, 3H), 4.73–4.61 (m, 3H), 4.49–4.32 (m, 2H), 4.05–3.92 (m, 2H), 3.75 (dd,  $J = 3.9, 5.1$  Hz, 1H), 3.50 (q,  $J = 7.2$  Hz, 1H), 1.50–1.44 (m, 9H); <sup>13</sup>C NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.9, 138.8, 138.3, 137.5, 128.6, 128.5, 128.2, 128.1, 128.1, 127.7, 127.7, 127.6, 127.5, 127.4, 110.5, 84.6, 75.5, 75.1, 72.9, 71.5, 68.4, 67.7, 27.7; ESI-MS  $m/z$  538.08 [ $\text{M} + \text{Na}$ ]<sup>+</sup>; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{32}\text{H}_{37}\text{NO}_5\text{Na}$  [ $\text{M} + \text{Na}$ ]<sup>+</sup> 538.2564, found 538.2565.

*tert*-Butyl(2*R*,3*R*,5*R*,6*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5,6-dihydroxypiperidine-1-carboxylate (**22**). (DHQ)<sub>2</sub>AQN (5.0 mg, 0.0058 mmol, 5 mol%),  $\text{K}_3\text{Fe}(\text{CN})_6$  (118 mg, 0.358 mmol, 3 eq.),  $\text{K}_2\text{CO}_3$  (114 mg, 0.826 mmol, 70 eq.), and  $\text{K}_2\text{OsO}_2(\text{OH})_4$  (2.5 mg, 0.0068 mmol, 5.59 mol%) were dissolved in *tert*-butyl alcohol and water (6 mL each) at room temperature.  $\text{CH}_3\text{SO}_2\text{NH}_2$  (23 mg, 0.242 mmol, 2.0 eq.) was added. The solution was cooled to  $0\text{ }^{\circ}\text{C}$  and Boc-iminoglycal **17a** was added (61 mg, 0.118 mmol). The mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 66 h. In the work up,  $\text{Na}_2\text{SO}_3$  (200 mg) was slowly added and the suspension was warmed to room temperature with vigorous stirring. EtOAc was added and the aq. layer was further extracted with ethyl acetate ( $2 \times 5$  mL), the combined organic layers

were washed with 2 M NaOH (20 mL). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*, which on preparative TLC separation (EtOAc-petroleum ether, 7 : 3) furnished **22** (20 mg, 30%),  $R_f$  0.21 (EtOAc-petroleum ether, 7 : 3);  $[\alpha]_D^{25} -13.33$  (c 1.1%,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ )/ $\text{cm}^{-1}$  3443, 3064, 2927, 2859, 2362, 2334, 1690, 1499, 1368, 1086, 757, 699, 669; <sup>1</sup>H NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.26 (m, 15H), 5.65–5.52 (m, 1H), 4.70–4.41 (m, 6H), 4.24–4.04 (m, 1H), 3.95–3.89 (m, 1H), 3.85–3.80 (m, 1H), 3.75–3.63 (m, 2H), 3.58–3.45 (m, 1H), 2.68 (brs, 1H), 1.68 (brs, 1H), 1.48–1.40 (m, 9H); <sup>13</sup>C NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  153.9, 138.0, 137.3, 137.3, 128.6, 128.5, 128.4, 128.4, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 87.9, 81.6, 81.3, 78.5, 77.2, 73.3, 73.0, 72.4, 64.1, 61.3, 28.3; ESI-MS  $m/z$  572.26 [ $\text{M} + \text{Na}$ ]<sup>+</sup>; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{32}\text{H}_{39}\text{NO}_7\text{Na}$  [ $\text{M} + \text{Na}$ ]<sup>+</sup> 572.2619, found 572.2619.

*tert*-Butyl(2*R*,3*R*,5*S*,6*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5,6-dihydroxypiperidine-1-carboxylate (**23**). (DHQD)<sub>2</sub>AQN (4.16 mg, 0.00485 mmol, 5 mol%),  $\text{K}_3\text{Fe}(\text{CN})_6$  (96 mg, 0.291 mmol, 3 eq.),  $\text{K}_2\text{CO}_3$  (93.7 mg, 0.679 mmol, 70 eq.), and  $\text{K}_2\text{OsO}_2(\text{OH})_4$  (2 mg, 0.00543 mmol, 5.59 mol%) were dissolved in *tert*-butyl alcohol and water (5 mL each) at room temperature,  $\text{CH}_3\text{SO}_2\text{NH}_2$  (18.43 mg, 0.194 mmol, 2.0 eq.) was added. The solution was cooled to  $0\text{ }^{\circ}\text{C}$  and Boc-iminoglycal **17a** was added (50 mg, 0.097 mmol). The mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 60 h. In the work up  $\text{Na}_2\text{SO}_3$  (200 mg) was slowly added and the suspension was warmed to room temperature with vigorous stirring. The aq. layer was further extracted with EtOAc ( $2 \times 10$  mL), the combined organic layers were washed with 2 M NaOH (20 mL). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*, which on preparative TLC separation (EtOAc-petroleum ether, 2 : 8) furnished **23** (38 mg, 71%),  $R_f$  0.23 (EtOAc-petroleum ether, 7 : 3);  $[\alpha]_D^{25} -18.79$  (c 1.15%,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ )/ $\text{cm}^{-1}$  3445, 3060, 2930, 2860, 2365, 2340, 1692, 1490, 1364, 1080, 750, 690, 667; <sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39–7.24 (m, 15H), 5.69–5.56 (m, 1H), 4.69–4.48 (m, 6H), 4.19–4.08 (m, 1H), 3.99–3.93 (m, 1H), 3.87–3.85 (m, 2H), 3.78–3.69 (m, 1H), 3.63–3.55 (m, 1H), 2.68 (brs, 1H), 1.75 (brs, 1H), 1.53–1.47 (m, 9H); <sup>13</sup>C NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  155.4, 138.2, 137.9, 137.7, 128.6, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.7, 127.5, 81.2, 81.1, 78.4, 77.2, 77.0, 73.1, 73.0, 72.8, 71.6, 65.7, 28.3; ESI-MS  $m/z$  572.27 [ $\text{M} + \text{Na}$ ]<sup>+</sup>; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{32}\text{H}_{39}\text{NO}_7\text{Na}$  [ $\text{M} + \text{Na}$ ]<sup>+</sup> 572.2619, found 572.2621.

## Author contributions

H. R. C. performed synthesis of all the compounds; M. K. T. performed DFT analysis of selected compounds; A. K. B. conceptualised the idea as well as critically analysed all experiments as well as corrected the manuscript. All authors searched literature and drafted the manuscript.

## Conflicts of interest

There are no conflicts to declare.



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