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Synthesis of iminosugar derivatives presenting naphthyl and alkylamine interacting groups and binding to somatostatin receptors

Stephen Barron\textsuperscript{a} and Paul V. Murphy\textsuperscript{b}

The synthesis of 1-deoxynojirimycin (DNJ) derivatives presenting a 2-naphthylmethyl and an alkyl amino sidechain from L-sorbose is described. The synthetic derivatives were tested for their ability to inhibit the binding of somatostatin-14 to human recombinant somatostatin receptors (hSSTRs). One DNJ derivative showed selective binding for hSSTR5 over hSSTR4. The presence of benzyl groups and acetates on the oxygen atoms of the iminosugar scaffold led to increased affinity for both hSSTR5 and hSSTR4. Ligand-lipophilicity efficiencies (LLEs) are calculated for the iminosugar derivatives. The LLE values are significantly higher for iminosugar derivatives where hydroxyl groups are not protected, as compared to where they are benzylated. This indicates that leaving hydroxyl groups free or without multiple benzyl groups could be important for drug discovery research based on sugar scaffolds.

Introduction

Carbohydrate scaffolds have been of interest in medicinal chemistry.\textsuperscript{1} Each functional group inherent on the scaffold provides a specific location where groups involved in interactions can be placed. As a consequence various carbohydrate scaffolds have been investigated, and these include sugar amino acids\textsuperscript{2} as well as other monosaccharides\textsuperscript{3} and disaccharides.\textsuperscript{4} Research has included solid phase syntheses of libraries centred on the carbohydrate scaffold.\textsuperscript{5} These carbohydrate frameworks and their derivatives have found application in peptidomimetic and glycomimetic and other research.\textsuperscript{6,7} Iminosugars, which are analogues of the monosaccharides where the ring oxygen atom of a saccharide is replaced by a nitrogen atom, have also been investigated in this regard. The use of iminosugars, such as 1-deoxynojirimycin 2 (DNJ, Fig. 1), gives additional features compared to their oxygen containing counterparts, in that the ring nitrogen atom would be protonated at physiological pH and attachment of interacting groups to the ring nitrogen are possible. The latter possibility has been investigated,\textsuperscript{8} including by the synthesis of the somatostatin mimetic 5, which showed activity for the human somatostatin receptor (hSSTR) 4 but not for hSSTR5.\textsuperscript{9} This dipeptide mimetic presented both lysine and tryptophan sidechains which are found in somatostatin. In 5, lysine’s butyramino side chain is grafted via the iminosugar C-6 alcohol group whereas the tryptophan sidechain was grafted to the scaffold via the ring nitrogen. The iminosugar 4, which is the tri-O-benzylated derivative of 5, is analogous to pyranoside derivatives such as 3, the latter being introduced by Hirschmann and collaborators.\textsuperscript{10}

Here, we present the synthesis and biological evaluation of DNJ derivatives 6-8 where the iminosugar presents the 2-naphthylmethyl group and an alkyl amine group. The naphthalene residue is introduced as a replacement for the indole residue and in this compound there is only a one carbon spacer between the naphthalene group and the piperidine nitrogen. The use of naphthalene as an isostere for sugar based peptidomimetics was studied previously by Hirschmann and co-workers.\textsuperscript{11} A naphthalene group provides a π-cloud for intermolecular interactions similar to those expected for the indole residue and would be expected to increase liophilicity. The pentylamine chain, which mimics...
that of the lysine sidechain, is attached directly to the piperidine ring with the methylene and oxygen spacer between the ring and pentyalamino group in 5 being deleted in 6-8. As well as the compound with free OH groups 6, the tri-O-benzylated and tri-O-acetylated derivatives 7 and 8 are described.

Results and discussion

Firstly, molecular modelling was used to estimate low energy conformations for 6, and to compare these with 5. In the low energy structure for 5, which had been generated by a conformational search using Macromodel, the tryptophan and lysine side chains had previously been shown to have overlap with those in sandostatin, whose solution structure has been determined, and which acts on SSTRs. Macromodel was again employed and a conformational search, using the OPLSA force field, on 6 yielded the low energy conformer shown in figure 2. In this conformer the naphthyl group and alkyl group are stacked. This is similar to that of the low energy structure for 5 where the indole and alkyl group also showed stacking. However, in the case of 6 the distance between the amino group and the aromatic group is reduced compared to that in 5. An observation from the calculated structures was that while a hydrogen bond was possible in 5 between the iminosugar 4-OH group and the iminosugar oxygen atom at C-6, this possibility was removed for 6. As a consequence the pharmacophoric naphthalene and alkylamino chain, while keeping a stacked orientation, adopted a different orientation with respect to the piperidine ring in 6 than in 5.

Meanwhile, the synthesis of the target compounds was commenced from 9 (Scheme 1) which is readily prepared from L-sorbose. In previous work the oxidation of 9 to its aldehyde was carried out using the Swern oxidation. Here the hypervalent iodine oxidant IBX was found to deliver a more facile and higher yielding oxidation (>97%, Scheme 1). The use of elevated temperatures (stirring at 70 °C in EtOAc), is necessary due to the poor solubility of IBX. This can be problematic when sensitive substrates or products are involved, but this was not the case here. The next step was a Wittig reaction. The precursor 10 to the required Wittig reagent was obtained by the reaction of benzyl alcohol and 1,4-dibromobutane in the presence of sodium hydroxide (65%) and subsequent treatment of the product with triphenylphosphine (74%) to give 10. The reaction of 10 with NaHMDS gave the required Wittig reagent and its reaction with the aldehyde obtained from oxidation of L-sorbose in THF gave an alkene intermediate (46%). Catalytic hydrogenation of this alkene gave 11 (91%). Next, the regioselective deprotection of the acetonide derived from the primary alcohol of sorbose was performed using 60% aq acetic acid at 80 °C to generate a diol (73%). This diol was converted to a cyclic sulfite by reaction with thionyl chloride and pyridine in CH2Cl2. Subsequent reaction of this cyclic sulfite with sodium azide gave the primary azide 12 (90% over two steps). The remaining acetonide protecting group was then removed from 12 by its reaction with the Dowex 50WX8 resin in acetonitrile and water; the mixture was heated at reflux and gave the desired deprotected sorbose derivative 13 (52%). Compound 13 adopted an acyclic structure, similar to that observed previously for related sorbose derivatives. Evidence for this structural assignment for 13 was supported by a signal at δ 208.6 in the 13C-NMR spectrum, which corresponds to the ketone C=O group. The next step involved a one pot catalytic hydrogenation of the azide to give the primary amine. This amine then reacted in situ with the ketone group of the open chain form of the sorbose derivative to generate an imine. The piperidine 14 (80%) is formed from this imine after further in situ catalytic hydrogen addition. The next problem to be addressed was the introduction of both the amine functionality in the alkyl chain of 14 and the 2-naphthylmethyl group onto the piperidine ring nitrogen atom. It was decided to postpone introduction of the 2-naphthylmethyl group until later in the synthesis. This was because the 2-naphthylmethyl group, used as a protecting group for alcohols, is susceptible to both acid catalysed hydrolysis and catalytic hydrogenolysis. Hence, the orthogonal protection of the iminosugar hydroxy groups and piperidine nitrogen were first carried out. The carbamate 15 was thus formed by reaction of 14 with di-tert-butyldicarbonate and DIPEA in CH2Cl2 (86%). The free alcohol groups of 15 were then acetylated using acetic anhydride, pyridine and a catalytic amount of DMAP to give 16 (94%).

Fig. 2 Space filling models of low energy structures of 5 (left) and 6 (right). Structures were obtained by a conformational search using Macromodel.

Next the de-O-benzylation of 16 was carried out by treating it with a mixture of palladium on carbon as well as palladium hydroxide on carbon in EtOAc under hydrogen (90%). In our hands, this unusual catalyst mixture was needed as the use of either palladium or palladium hydroxide on carbon individually
were not effective. Subsequently, the alcohol product was mesylated and the crude mesylate exposed to sodium azide in DMF to furnish the primary azide 17 in 84% yield. With the amine that would ultimately be introduced now masked as an azide, it was time to approach the attachment of the 2-naphthyl methyl group. The t-BOC group was first cleaved from using formic acid and the resulting free piperidine nitrogen atom was then coupled with 2-(bromomethyl) naphthalene using DIPEA as a base, in DMF to give 18 (83%, two steps, Scheme 2). The de-O-acetylation of 18 was initially attempted with sodium methoxide in methanol. However, the 2-naphthyl group was found to be cleaved during treatment of the subsequent mixture with the Amberlite acidic ion exchange resin. Acidification with an acidic ion exchange resin is often used after reaction with methoxide in methanol. This problem was overcome by reacting 18 in MeOH in the presence of Ambersep 900 OH resin, which led to the isolation of 19 (86%) without the need for treatment with the acidic ion exchange resin. Afterwards, the reduction of the azide was accomplished under hydrogen in the presence of palladium on carbon in MeOH, giving the target compound 6 (37%). The catalytic hydrogenation of 15 directly gave 7 (94%). Finally, tri-O-benzylolation of 16 using sodium hydride and benzyl bromide in DMF, followed by catalytic hydrogenation of the product gave 8 (28% over two steps).

With 6-8 in hand, they were were tested\(^1\) for their ability to inhibit the binding of radiolabelled somatostatin-14 to human recombinant SSTR4\(^19\) and SSTR5\(^20\) in vitro and the results are summarized in Table 1. Included in the Table are \(K_i\) data for 4 and 5, which were previously determined. Somatostatin displayed \(K_i\) values of <2.0 nM for these receptors. Compound 6 showed binding hSSTR5 (\(K_i = 36 \mu M\)) but there was no evidence for binding to hSSTR4. The presence of benzyl groups on the scaffold gave a ligand 8, which showed improved affinity for hSSTR5 (\(K_i = 2 \mu M\)) and also for hSSTR4 (\(K_i = 1.9 \mu M\)). The presence of acetate groups in 7 also led to affinity increases for both receptors compared with 6, although 7 was less potent towards hSSTR4 (\(K_i = 5.4 \mu M\)) and hSSTR5 (\(K_i = 7.7 \mu M\)) than 8. The activity displayed for 6, which showed selective binding for hSSTR5 is contrary to that found for 5, the latter showing selective binding towards hSSTR4. The precise reason for this finding is not clear. This could be due to the spacing between the \(\pi\)-cloud and alkylamino chain being altered as indicated by the modeling. Alternatively the change in orientation the iminosugar scaffold in 6 when compared with 5 with respect to the pharmacophoric groups as discussed above could also lead to the different biological properties between 5 and 6, particularly if the scaffold also had interactions. Compound 8 showed a slight improvement over 4 for both receptor subtypes, indicating again interaction of at least one of the benzyl groups in SSTR binding sites.

The achievement of high potency (low value for \(K_i\)) for molecules is highly desirable in medicinal chemistry. Lipophilicity (Log P) is also important as it influences a compound’s water solubility, its ability to move through cell membranes, its clearance, its selectivity, and whether it has non-specific toxicity. In addition to the \(K_i\) values, the Log P values of compounds 4-8 have been calculated\(^{21}\) and are listed in Table 1. For orally available drugs, a Log P between 2 and 3 has been stated as optimal, with a value < 5 being considered as necessary. Compound 6 is estimated to be more lipophilic than 5 and less so than 4, 7 and 8. Compound 6 was water soluble despite the presence of the more lipophilic naphthalene group. The ligand-lipophilicity efficiency LLE\(^{23}\) defined as \(pK_i\cdot\text{LogP}\), allows both potency and lipophilicity to be considered in a single parameter. Drug candidates normally have an LLE value > 6. The calculated LLE values for 4-8 are shown in Table 1. The data suggests that the tri-O-benzylated 4 and 8 would not be drug-like. On the other hand, there may be some promise in commencing a medicinal chemistry programme based on 5 or 6 (or another related compound) where some OH groups on the scaffold are kept free.

Table 1. Binding of 4-8 at Somatostatin Receptors

<table>
<thead>
<tr>
<th>Compd</th>
<th>(K_i) [(\mu M)] (hSSTR4)</th>
<th>(K_i) [(\mu M)] (hSSTR5)</th>
<th>LogP</th>
<th>LLE(^b) (hSSTR4)</th>
<th>LLE(^b) (hSSTR5)</th>
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</thead>
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<td>5</td>
<td>7.58</td>
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<td>0.48</td>
<td>5.01</td>
<td>-</td>
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<td>Not active</td>
<td>34</td>
<td>1.57</td>
<td>-</td>
<td>2.89</td>
</tr>
<tr>
<td>7</td>
<td>5.4</td>
<td>7.7</td>
<td>2.89</td>
<td>2.37</td>
<td>2.22</td>
</tr>
<tr>
<td>8</td>
<td>1.9</td>
<td>2.0</td>
<td>8.67</td>
<td>-2.94</td>
<td>-2.97</td>
</tr>
</tbody>
</table>

\(^a\) Calculator Plugins were used for Log P prediction and calculation, Marvin 6.2, 2014, ChemAxon (http://www.chemaxon.com). LogP for each compound was estimated using the physicochemical property prediction, which is based on published methods.\(^{24}\)

\(^b\) LLE = Ligand-Lipophilicity Efficiency = \(pK_i\cdot\text{LogP}\).
Conclusions

A synthetic route from L-sorbose to ligands for somatostatin receptors based on the 1-deoxyxojirimycin scaffold is described. This route facilitated the introduction of an acid sensitive 2-naphthylmethyl pharmacophoric group on the piperidine ring nitrogen atom as well as the lysine alkylamino side chain. The iminosugars generated herein showed activity for somatostatin receptors, with selectivity for hSSTR5 over hSSTR4 being observed for one compound. Somatostatin regulates, through binding to its receptors a number of processes including the release of growth hormone and other pituitary hormones. This research provides a basis for further development of iminosugar derivatives that can potentially modulate the function of somatostatin and its receptors. Attaining ligands for the different hSSTR sub-types has been of interest. Improvement of potency of iminosugar derivatives while keeping lipophilicity in the desired range would be important. Achieving success in this regard will depend on improving the synthetic chemistry to enable a more facile synthesis of iminosugar derivatives in order that potency and other physicochemical properties can be optimised.

Experimental

General Experimental Conditions: Optical rotations were determined at the sodium D line at 20°C using Schmidt and Haensch UniPol L1000. NMR spectra were recorded with a 500 MHz spectrometer. Chemical shifts are reported relative to internal Me₂Si in CDCl₃ (δ 0.0) or HOD for D₂O (δ 4.80) or CD₃OD (δ 3.31) for ¹H and Me₂Si in CDCl₃ (δ 0.0) or CDCl₃ (δ 77.0) or CD₃OD (δ 49.05) for ¹³C. ¹H NMR signals were assigned with the aid of COSY and ¹³C NMR signals were assigned with the aid of DEPT, gHSQC and/or gHMBCAD. Coupling constants are reported in hertz (Hz). The IR spectra were recorded using thin film with a PerkinElmer Spectrum 100 FT-IR spectrometer with an ATR attachment. High resolution mass measurements were obtained using a Waters LCT Premier XE. Silica gel (pore size 60 Å, particle size 40-60 μm 230-400 mesh particle size) was purchased from Sigma-Aldrich. Dichloromethane, MeOH, THF and DMF reaction solvents were obtained from a Pure Solv™ solvent purification system. Acetonitrile (Chromasolv for HPLC grade, >99.9%) and anhydrous pyridine were obtained from Sigma-Aldrich. All hydrogenation reactions were carried out at ambient pressure.

2,3:4,6-Di-O-isopropylidene-(2R,3S,4S,5S)-2-(5-(benzoxyl)pentyl)-5-(hydroxymethyl)tetrahydrofuran-2,3,4-triol 11: To alcohol 98 (8.4 g, 32.3 mmol) in EtOAc (200 mL) was added IBX (18.1 g, 96.8 mmol). This suspension was stirred at 70 °C while being left open to air for 4 h and was then filtered through a sintered glass funnel. The solid residue was washed with EtOAc and the solvent was removed under reduced pressure to give the aldehyde intermediate (6.4 g, 97%, Rf: 0.1, EtOAc-petroleum ether, 1:1), which was used in the next step without further purification. To a suspension of 10 (14.5 g, 29 mmol) in dry THF (50 mL) at -78°C under a N₂ atmosphere, was added dropwise 1 M sodium bis(trimethylsilyl)amide in THF (30 mL, 30 mM). The reaction mixture was stirred at -78 °C for 30 min, 0 °C for 30 min and at room temperature for a further 30 min. The mixture was cooled again to -78 °C and a solution of the aldehyde intermediate (4.95 g, 19 mmol) in dry THF (20 mL) was added. The reaction mixture was allowed to attain room temperature, while stirring, over 15 h and then quenched with sat'd aq NH₄Cl at 0 °C. The layers were separated and the aq layer was extracted with EtOAc (x 3). The combined organic layers were washed with water (x 3) and brine, dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. Flash chromatography of the residue (EtOAc-petroleum ether, 1:2, Rf: 0.2) gave the intermediate alkene as a pale yellow oil (3.53 g, 91%)—NMR spectra were determined at the sodium D line at 20°C using a PerkinElmer Spectrum 100 FT-IR spectrometer with an ATR attachment. High resolution mass measurements were obtained using a Waters LCT Premier XE. Silica gel (pore size 60 Å, particle size 40-60 μm 230-400 mesh particle size) was purchased from Sigma-Aldrich. Dichloromethane, MeOH, THF and DMF reaction solvents were obtained from a Pure Solv™ solvent purification system. Acetonitrile (Chromasolv for HPLC grade, >99.9%) and anhydrous pyridine were obtained from Sigma-Aldrich. All hydrogenation reactions were carried out at ambient pressure.

2,3:4,6-Di-O-isopropylidene-(2R,3S,4S,5S)-5-(azidomethyl)-2-(5-(benzoxyl)pentyl)tetrahydrofuran-2,3,4-triol 12: A solution of 11 (1 g, 2.5 mmol) in 60% acetic acid-water (100 mL) was stirred at 60 °C for 1 h. The solvent was removed under reduced pressure and flash chromatography (EtOAc-petroleum ether, 1:2, Rf: 0.47) gave the title compound (1.67 g, 91%)—NMR spectra were determined at the sodium D line at 20°C using a PerkinElmer Spectrum 100 FT-IR spectrometer with an ATR attachment. High resolution mass measurements were obtained using a Waters LCT Premier XE. Silica gel (pore size 60 Å, particle size 40-60 μm 230-400 mesh particle size) was purchased from Sigma-Aldrich. Dichloromethane, MeOH, THF and DMF reaction solvents were obtained from a Pure Solv™ solvent purification system. Acetonitrile (Chromasolv for HPLC grade, >99.9%) and anhydrous pyridine were obtained from Sigma-Aldrich. All hydrogenation reactions were carried out at ambient pressure.

2,3:4,6-Di-O-isopropylidene-(2R,3S,4S,5S)-2-(5-(benzoxyl)pentyl)-5-(hydroxymethyl)tetrahydrofuran-2,3,4-triol 11: To alcohol 98 (8.4 g, 32.3 mmol) in EtOAc (200 mL) was added IBX (18.1 g, 96.8 mmol). This suspension was stirred at 70 °C while being left open to air for 4 h and was then filtered through a sintered glass funnel. The solid residue was washed with EtOAc and the solvent was removed under reduced pressure to give the aldehyde intermediate (6.4 g, 97%, Rf: 0.1, EtOAc-petroleum ether, 1:1), which was used in the next step without further purification. To a suspension of 10 (14.5 g, 29 mmol) in dry THF (50 mL) at -78°C under a N₂ atmosphere, was added dropwise 1 M sodium bis(trimethylsilyl)amide in THF (30 mL, 30 mM). The reaction mixture was stirred at -78 °C for 30 min, 0 °C for 30 min and at room temperature for a further 30 min. The mixture was cooled again to -78 °C and a solution of the aldehyde intermediate (4.95 g, 19 mmol) in dry THF (20 mL) was added. The reaction mixture was allowed to attain room temperature, while stirring, over 15 h and then quenched with sat'd aq NH₄Cl at 0 °C. The layers were separated and the aq layer was extracted with EtOAc (x 3). The combined organic layers were washed with water (x 3) and brine, dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. Flash chromatography of the residue (EtOAc-petroleum ether, 1:2, Rf: 0.2) gave the intermediate alkene as a pale yellow oil (3.53 g, 91%)—NMR spectra were determined at the sodium D line at 20°C using a PerkinElmer Spectrum 100 FT-IR spectrometer with an ATR attachment. High resolution mass measurements were obtained using a Waters LCT Premier XE. Silica gel (pore size 60 Å, particle size 40-60 μm 230-400 mesh particle size) was purchased from Sigma-Aldrich. Dichloromethane, MeOH, THF and DMF reaction solvents were obtained from a Pure Solv™ solvent purification system. Acetonitrile (Chromasolv for HPLC grade, >99.9%) and anhydrous pyridine were obtained from Sigma-Aldrich. All hydrogenation reactions were carried out at ambient pressure.
solution of SOCl₂ (238 mg, 0.15 mL, 2 mmol) in dry CH₂Cl₂ (7 mL). After stirring for 1 h, the reaction mixture was washed with water (x 3) and brine. The organic layer was dried (Na₂SO₄), filtered, and the solvent was removed at 30 °C under reduced pressure. The residue was dissolved in dry DMF (40 mL) and sodium azide (333 mg, 5.1 mmol) was added. The reaction mixture was stirred at 105 °C under N₂ for 16 h. After being allowed to cool to room temperature, the mixture was diluted with water and then extracted with EtOAc (x 3). The combined organic layers were then washed with water (x 3) and brine, dried (Na₂SO₄), filtered, and the solvent was removed under reduced pressure. Flash chromatography of the residue (EtOAc-petroleum ether, 1:1; Rf 0.53) gave the title compound (490 mg, 90%) as a white solid; ¹H NMR (500 MHz, CDCl₃): δ 7.37-7.32 (m, 4H, Ar H), 7.30-7.26 (dd, 1H, Ar H), 4.49 (s, 2H, CH₂Ph), 4.32 (td, J = 5.6 Hz, J = 2.8 Hz, 1H, H-5), 4.22 (s, 1H, H-3), 4.19 (t, J = 3.2 Hz, 1H, H-4), 3.63 (dd, J = 12.8 Hz, J = 6.3 Hz, 1H, CH₂), 3.52 (dd, J = 12.8 Hz, J = 5.2 Hz, 1H, CH₂OH), 1.58-1.36 (m, 2H, 2 x CH₂), 1.33 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 138.6 (Ar C), 128.3, 127.6, 127.5 (each Ar CH), 115.3 (C-2), 111.1 (CH(CH₃)), 87.1 (C-3), 78.4 (C-5), 70.6 (C-4), 72.9 (CH₂Ph), 70.3 (CH₃), 49.5 (CH₂O), 38.0 (CH₂), 29.6 (CH₂), 27.4, 26.6 (each CH₂), 26.3 (CH₂), 23.7 (CH₃); ESI-HRMS: Found 374.1710 required 374.1692 [M+Na⁺].

2-(5-azidopentyl)-1-(tert-butoxycarbonyl)piperidine-3,4,5-triyl triacetate 16. DMAP (3 mg, 0.0247 mmol) was added to a solution of 15 (112 mg, 0.274 mmol) in acetic anhydride-pyridine (1:1, 10 mL), under N₂. After stirring for 4 h at room temperature, the reaction was diluted with EtOAc, followed by water. The layers were separated and the aq layer was extracted with EtOAc (x 2). The combined organic layers were washed with water (x 3) and brine, dried (Na₂SO₄), filtered, and the solvent was removed under reduced pressure. Flash chromatography of the residue (EtOAc-petroleum ether, 1:2; Rf 0.34) gave the title compound (138 mg, 94%) as a white solid; ¹H NMR (500MHz, CDCl₃): δ 7.35-7.31 (m, 4H, Ar H), 7.30-7.25 (m, 1H, Ar H), 4.96 (m, 1H, Ar H)-4.4, 4.7 (overlapping signals, 2H, CH₂Ph), 4.35 (m, 1H, H-2), 4.23 (d, J = 14.9 Hz, H-6a), 3.46 (t, J = 6.6 Hz, 2H, CH₂), 2.38 (d, J = 14.4 Hz, 1H, H-6b), 2.55 (s, 1H, OH), 1.92-1.82 (m, 1H, CH₂), 1.65-1.52 (overlapping signals, 3H, CH₂H & CH₂OH), 1.48-1.28 (overlapping signals, 13H, 2 x CH₂ & 3 x tert-butyl); ¹³C NMR (125 MHz, CDCl₃): δ 157.3 (C=O), 138.5 (Ar C), 128.4, 127.7, 127.5 (each Ar CH), 80.2 (tert-Bu C), 72.9 (CH₂Ph), 71.9 (C-3), 70.5 (CH₂), 70.0 (2s, C-3 and C-4), 57.9 (C-2), 40.5 (C-6), 29.6 (CH₂), 29.1 (CH₂), 28.4 (CH₃), 26.4 (CH₂), 26.0 (CH₃); ESI-HRMS: Found 432.2364 required 432.2362 [M+Na⁺].

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To a solution of azide 19 (13 mg, 0.03 mmol) in MeOH (1 mL) was added 10% Pd-C (4 mg). After stirring under H₂ for 20 min, the mixture was filtered through celite. The solvent was removed under reduced pressure and flash chromatography of the residue (CHCl₃-MeOH-satd aq NH₄OH, 8:3:0.4) gave the title compound (4 mg, 37%) as a white solid; §H NMR (500 MHz, CDCl₃): δ 7.84-7.80 (m, 3H, Ar H), 7.76 (s, 1H, Ar H), 7.49 (dd, 1H, Ar H), 7.47-7.42 (m, 2H, Ar H), 4.20 (d, 1H, J = 13.4 Hz, CHHNaph), 3.43 (dd, 1H, J = 10.3 Hz, J = 9.3 Hz, CH₂, H-5), 3.34 (t, 1H, J = 9.2 Hz, H-3, partially obscured by NMR solvent peak), 3.27 (dd, 1H, J = 13.4 Hz, CHHNaph), 3.23 (t, 2H, J = 6.9 Hz, CH₂N₃), 3.14 (t, 1H, J = 9.0 Hz, H-4), 2.88 (dd, 1H, J = 11.5 Hz, J = 4.8 Hz, H-6a), 2.23 (dt, 1H, J = 9.5 Hz, J = 3.7 Hz, H-2), 1.97-1.83 (overlapping signals, 3H, H-6b and CH₂), 1.63-1.49 (overlapping signals, 4H, 2CH₂), 1.42-1.32 (m, 2H, CH₂); §C NMR (125 MHz, CDCl₃): δ 138.0, 135.0, 134.3, 129.1, 128.7 (2s), 128.5, 128.0, 127.1, 126.7 (Ar C and CH), 80.8 (C-4), 73.7 (C-3), 70.8 (C-5), 67.2 (C-7), 58.1 (C-6), 57.1 (CH₂N₃), 52.5, 30.0, 28.8, 28.4, 24.1 (each CH₂); ESI-HRMS: found 385.2241 required 385.2240 [M+Na]⁺.


To a solution of azide 19 (13 mg, 0.03 mmol) in MeOH (1 mL) was added 10% Pd-C (4 mg). After stirring under H₂ for 20 min, the mixture was filtered through celite. The solvent was removed under reduced pressure and flash chromatography of the residue (CHCl₃-MeOH-satd aq NH₄OH, 8:3:0.4) gave the title compound (4 mg, 37%) as a white solid; §H NMR (500 MHz, CDCl₃): δ 7.84-7.78 (m, 3H, Ar H), 7.76 (s, 1H, Ar H), 7.51-7.41 (m, 3H, Ar H), 4.20 (d, 1H, J = 13.4 Hz, CHHNaph), 3.43 (dd, 1H, J = 10.5 Hz, J = 9.2 Hz, J = 4.8 Hz, H-1H, H-5), 3.34 (t, 1H, J = 9.2 Hz, H-1H, H-3 partially obscured by NMR solvent peak), 3.28 (d, 1H, J = 13.4 Hz, CHHNaph), 3.15 (t, 1H, J = 9.0 Hz, H-4), 2.88 (dd, 1H, J = 11.5 Hz, J = 4.8 Hz, H-6a), 2.82 (t, 2H, J = 6.6 Hz, CH₂N₃), 2.25 (dt, 1H, J = 9.4 Hz, J = 3.7 Hz, H-2), 1.99-1.86 (overlapping signals, 3H, H-6b and CH₂), 1.68-1.50 (overlapping signals, 4H, 2CH₂), 1.45-1.33 (m, 1H, CH₂); §C NMR (125 MHz, CDCl₃): δ 138.0, 134.9, 134.3, 129.1, 128.7, 128.4, 127.9, 127.2, 126.7 (Ar C and CH), 80.8 (C-4), 73.7 (C-3), 70.8 (C-5), 67.0 (C-2), 58.0 (C-6), 57.6 (CH₂N₃), 41.1 (CH₂N₃), 29.7, 28.7, 28.0, 24.1 (each CH₂); ESI-HRMS: found 359.2339 required 359.2235 [M+Na]⁺.


To a solution of azide 19 (13 mg, 0.03 mmol) in MeOH (1 mL) was added 10% Pd-C (4 mg). After stirring under H₂ for 20 min, the mixture was filtered through celite. The solvent was removed under reduced pressure and flash chromatography of the residue (CHCl₃-MeOH-satd aq NH₄OH, 8:3:0.4) gave the title compound (4 mg, 37%) as a white solid; §H NMR (500 MHz, CDCl₃): δ 7.84-7.78 (m, 3H, Ar H), 7.76 (s, 1H, Ar H), 7.51-7.41 (m, 3H, Ar H), 4.20 (d, 1H, J = 13.4 Hz, CHHNaph), 3.43 (dd, 1H, J = 10.5 Hz, J = 9.2 Hz, J = 4.8 Hz, H-1H, H-5), 3.34 (t, 1H, J = 9.2 Hz, H-1H, H-3 partially obscured by NMR solvent peak), 3.28 (d, 1H, J = 13.4 Hz, CHHNaph), 3.15 (t, 1H, J = 9.0 Hz, H-4), 2.88 (dd, 1H, J = 11.5 Hz, J = 4.8 Hz, H-6a), 2.82 (t, 2H, J = 6.6 Hz, CH₂N₃), 2.25 (dt, 1H, J = 9.4 Hz, J = 3.7 Hz, H-2), 1.99-1.86 (overlapping signals, 3H, H-6b and CH₂), 1.68-1.50 (overlapping signals, 4H, 2CH₂), 1.45-1.33 (m, 1H, CH₂); §C NMR (125 MHz, CDCl₃): δ 138.0, 134.9, 134.3, 129.1, 128.7, 128.4, 127.9, 127.2, 126.7 (Ar C and CH), 80.8 (C-4), 73.7 (C-3), 70.8 (C-5), 67.0 (C-2), 58.0 (C-6), 57.6 (CH₂N₃), 41.1 (CH₂N₃), 29.7, 28.7, 28.0, 24.1 (each CH₂); ESI-HRMS: found 359.2339 required 359.2235 [M+Na]⁺.
J = benzylated intermediate as a white solid (12 mg, 0.018 mmol, mixture was filtered through celite and the solvent was water (x 3) and brine, dried (Na2SO4). After stirring for 16 h and was then poured on to ice. The mixture was stirred in dry DMF (1.5 mL) at 0 °C under N2. After stirring for 5 min, benzyl bromide (14 μL, 0.12 mmol), was added dropwise. The mixture was stirred, first at 0 °C and then allowing it to attain room temperature, for 16 h and was then poured on to ice. The mixture was washed with water (x 3) and brine, dried (Na2SO4), filtered and the solvent was removed under reduced pressure. Flash chromatography of the residue (EtOAc-petroleum ether, 1:7; Rf = 0.19) gave the benzylated intermediate as a white solid (12 mg, 0.018 mmol, 60%); 1H NMR (CDCl3, 500 MHz): δ 7.18-7.33 (m, 1H, Ar H), 7.21 (d, J = 8.3 Hz, 2H, Ar H), 7.15 (d, J = 8.4 Hz, 2H, Ar H), 7.63 (s, 1H, Ar H), 7.50-7.45 (m, 2H, Ar H), 7.40 (dd, J = 4.8 Hz, J = 1.5 Hz, 1H, Ar H), 7.27-7.22 (m, 2H, Ar H), 7.16-7.08 (m, 5H, Ar H), 4.98 (overlapping signals, 2H, 2xCH2Ph), 4.82 (d, J = 11.1 Hz, 1H, CHPh), 4.50 (d, J = 11.5 Hz, 1H, CHPh), 4.43 (d, J = 11.2 Hz, 1H, CHPh), 4.08 (d, J = 13.5 Hz, 1H, CH/HNaph), 3.60-3.52 (overlapping signals, 2H, H-5, H-4), 3.48 (t, J = 9.0 Hz), 1H, H-3), 3.29 (d, J = 13.5 Hz, 1H, CH/HNaph), 3.19 (t, J = 7.0 Hz, 2H, CH2NPh), 2.97 (dd, J = 11.8 Hz, J = 4.2 Hz, 1H, H-6a), 2.43 (dt, J = 9.3 Hz, J = 3.9 Hz, 1H, H-2), 1.95 (dd, J = 11.6 Hz, J = 10.1 Hz, 1H, H-6b), 1.88-1.76 (m, 2H, CH2), 1.55-1.46 (overlapping signals, 3H, CH2 and CH3). 1H NMR (CDCl3, 125 MHz): δ 138.9, 138.5, 138.3, 136.6, 133.4, 132.8, 128.4 (2s), 128.2, 128.1, 128.0, 127.9, 127.7 (3s), 127.5, 127.0, 126.5, 126.0, 125.6 (Ar C and CH), 87.6 (C-4), 79.9 (C-3), 78.0 (C-5), 75.4, 75.3, 72.5 (each CH2Ph), 64.7 (C-2), 55.6 (CH2Naph), 53.9 (C-6), 51.4 (CH2Naph), 28.9, 28.7, 27.2, 23.4 (each CH3); ESI-HRMS: Found 655.3641 required 655.3648 [M+H]+.

To this intermediate (11 mg, 0.017 mmol) in EtOAc-MeOH (2:1, 1.5 mL) was added 10% Pd-C (5 mg). The reaction mixture was stirred under H2 for 30 min. The mixture was filtered through celite and the solvent was removed under reduced pressure. Flash chromatography of the residue (EtOAc-MeOH-satd aq NaHCO3, 8:2:0.1; Rf = 0.17) furnished the title compound (5 mg, 47%); 1H NMR (CDCl3, 500 MHz): δ 7.87-7.84 (m, 1H, Ar H), 7.81 (d, J = 8.5 Hz, 2H, Ar H), 7.68 (s, 1H, Ar H), 7.52-7.45 (m, 2H, Ar H), 7.41 (dd, J = 8.5 Hz, J = 1.5 Hz, 1H, Ar H), 7.35-7.24 (m, 10H, Ar H), 7.09 (dd, J = 7.7 Hz, J = 1.8 Hz, 2H, Ar H), 7.06-7.01 (m, 3H, Ar H), 4.94 (2d, J = 11.1 Hz, 2H, 2xCH2Ph), 4.77 (d, J = 11.0 Hz, 1H, CHPh), 4.47 (d, J = 11.9 Hz, 1H, CH/HNaph), 4.40 (d, J = 11.9 Hz, 1H, CHPh), 4.13 (d, J = 13.3 Hz, 1H, CH/HNaph), 3.54-3.43 (overlapping signals, 3H, H-3, H-4, 3.26 (d, J = 13.3 Hz, 1H, CH/HNaph), 2.92 (dd, J = 11.8 Hz, J = 4.2 Hz, 1H, H-6a), 2.58 (t, J = 7.3 Hz, 2H, CH2NPh), 2.36 (dt, J = 9.0 Hz, J = 3.8 Hz, 1H, H-2), 1.91-1.78 (overlapping signals, 3H, H-6b, CH2), 1.57-1.48 (m, 1H, CH/HNaph), 1.47-1.36 (overlapping signals, 3H, CH2 and CH3), 1.30-1.18 (m, 2H, CH2), 1.3-C-NMR (CDCl3, 125 MHz): δ 140.3, 140.0, 139.7, 138.0, 135.0, 134.4, 129.4 (2s), 129.2 (2s), 129.1, 129.0 (2s), 128.8 (2s), 128.7, 128.6, 128.3, 127.7, 127.1, 126.8 (Ar C and CH), 88.8 (C-4), 81.3 (C-3), 79.2 (C-5), 76.4, 76.2, 73.5 (each CH2Ph), 66.4 (C-2), 57.0 (CH2Naph), 55.1 (C-6), 42.3 (CH2Naph), 33.1, 29.0, 28.4, 24.9 (each CH2); ESI-HRMS: Found 629.3755 required 629.3743 [M+H]+.

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Notes and references

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† This assay was conducted at Cerep (www.cerep.com). These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/


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