JOC*Article*

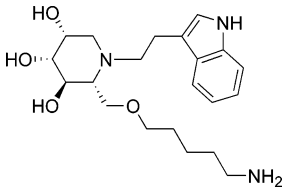
Synthesis of Somatostatin Mimetics Based on the 1-Deoxymannojirimycin Scaffold

Sebastien G. Gouin and Paul V. Murphy*

Centre for Synthesis and Chemical Biology, UCD School of Chemistry and Chemical Biology, Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland

paul.v.murphy@ucd.ie

Received July 14, 2005



A novel synthesis of somatostatin mimetics based on the 1-deoxymannojirimycin (DMJ) scaffold has been developed. This involved development of a route suitable for the strategic grafting of pharmacophoric tryptophan and lysine side chains to the nitrogen atom of the piperidine ring and to the primary hydroxyl group of DMJ, respectively. The novel peptidomimetics were found to bind with higher affinity to sst4 receptors than to sst5 receptors.

1. Introduction

There has been recent progress in the application of pyranosides and related scaffolds as platforms for drug discovery since the first experimental application by researchers at the University of Pennsylvania, which showed that novel ligands (peptide β-turn mimetics) for peptide hormone receptors could be developed based on β-D-glucopyranose.[1] In this example, pharmacophoric groups, which correspond to amino acid side chains, were grafted to the pyranose, which acted as a replacement for the peptide backbone. Interest in this area has since extended[2] to the wider application of pyranosides as peptidomimetics[3] and as scaffolds for the solid-phase synthesis of prospecting combinatorial libraries.[4] There has been interest in syntheses of pyranose-based sugar amino acids (SAAs)[5] and incorporation of such motifs into molecules of biological interest. Investigations have included (amino)sugar scaffolds, including L-sugars,[6] sugar amino acids,[7] and disaccharides.[8] Although no drug has yet been developed, potent ligands for receptors have been identified[9] and it has been shown that pyranoside derivatives can have improved cellular permeability over

(1) (a) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Smith, A. B., III; Strader, C. D.; Cascieri, M. A.; Candelore, M. R.; Donaldson, C.; Vale, W.; Maechler, L. *J. Am. Chem. Soc.* **1992**, *114*, 9217. (b) Nicolaou, K. C.; Salvino, J. M.; Raynor, K.; Pietranico, S.; Reisine, T.; Freidinger, R. M.; Hirschmann, R. In *Peptides − Chemistry, Structure, and Biology*, Proceedings of the 11th American Peptide Symposium; Rivier, J. E., Marshall, G. R., Eds.; ESCOM: Leiden, 1990; pp 881−884. (c) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakepseare, W. C.; Sprengler, P. A.; Hamley, P.; Smith, A. B.; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. R.; Strader, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 12550.

(2) For reviews of sugar scaffolds see: (a) Sofia, M. J. *Mol. Diversity* **1998**, *3*, 75. (b) Sofia, M. J. *Med. Chem. Res.* **1998**, *8*, 362. (c) Sofia, M. J.; Silva, D. J. *Curr. Opin. Drug Discov. Dev.* **1999**, *2*, 365. (d) Schweizer, F.; Hindsgaul, O. *Curr. Opin. Chem. Biol.* **1999**, *3*, 29. (e) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491. (f) Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 231. (g) Marcaurelle, L. A.; Seeberger, P. H. *Curr. Opin. Chem. Biol.* **2002**, *6*, 289. (h) Chakraborty, T. K.; Srinivasu, P.; Tapadar, S.; Mohan, B. K. *J. Chem. Sci.* **2004**, *116*, 187. (i) Schweizer, F. *Trends Glycosci. Glycotechnol.* **2003**, *15*, 315.

(3) The first nonpeptidal peptidomimetic was reported in 1986, which recognized the opiate receptor for which it was designed. See: Belanger, P. C.; Dufresne, C. *Can. J. Chem.* **1986**, *64*, 1514.

(4) (a) Wunberg, T.; Kallus, C.; Opatz, T.; Henke, S.; Schmidt, W.; Kunz, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2503. (b) Sofia, M. J.; Hunter, R.; Chan, T. Y.; Vaughan, A.; Dulina, R.; Wang, H. M.; Gange, D. *J. Org. Chem.* **1998**, *63*, 2802. (c) Jain, R.; Kamau, M.; Wang, C.; Ippolito, R.; Wang, H.; Dulina, R.; Anderson, J.; Gange, D.; Sofia, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2185. (d) Opatz, T.; Kallus; C.; Wunberg, T.; Schmidt, W.; Henke, S.; Kunz, H. *Carbohydr. Res.* **2002**, *337*, 2089. (e) Opatz, T.; Kallus, C.; Wunberg, T.; Schmidt, W.; Henke, S.; Kunz, H. *Eur. J. Org. Chem.* **2003**, 1527. (f) Opatz, T.; Kallus, C.; Wunberg, T.; Kunz, H. *Tetrahedron* **2004**, *60*, 8613.

(5) (a) Graf von Roedern, E.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 670. (b) Kessler, H.; Diefenbach, B.; Finsinger, D.; Geyer, A.; Gurrath, M.; Goodman, S. L.; Holzemann, G.; Haubner, R.; Jonczyk, A.; Muller, G.; Graf von Roedern, E.; Wermuth, J. *Lett. Pept. Sci.* **1995**, *2*, 155.

(6) Hirschmann, R.; Cichy-Knight, M. A.; van Rijn, R. D.; Sprengler, P. A.; Spoors, P. G.; Shakespeare, W. C.; Pietranico-Cole, S.; Barbosa, J.; Liu, J.; Yao, W.; Roher, S.; Smith, A. B., III. *J. Med. Chem.* **1998**, *41*, 1382.

(7) Graf von Roedern, E.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156.

10.1021/jo051454n CCC: $30.25
Published on Web 09/13/2005

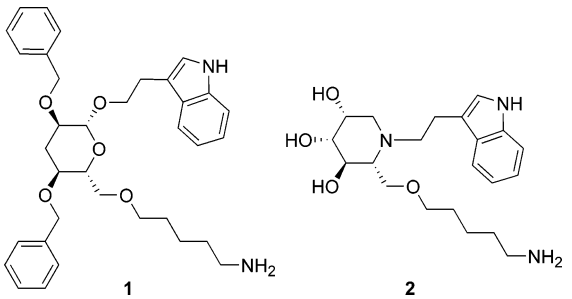
peptides.[10] Both of these are objectives for peptidomimetic research.[11] Progress is continually dependent on advances in synthetic carbohydrate chemistry both in solution and on solid phase. These include the development of orthogonal protecting group strategies, strategies for regioselective manipulation of pyranoside hydroxyl groups, and the chemoselective manipulation of functional groups.

The application of iminosugar-based scaffolds as peptidomimetics has been less well-developed although some work has been carried out by Le Merrer and co-workers[12] and, more recently, by researchers from our group.[13] This is presumably because such scaffolds are not as readily available as pyranosides and the synthesis of iminosugars is not trivial.[14] Iminosugars themselves have been of significant interest as glycosidase inhibitors[15] and some have found clinical use.[16] The use of iminosugars as scaffolds for bioorganic and medicinal chemistry offers the possibility, not available to pyranosides, of incorporating a charged hydrogen bond donor through protonation of the ring nitrogen atom which would occur at physiological pH. In addition, pharmacophoric groups can be grafted to the nitrogen atom. Herein we describe an approach to the synthesis of somatostatin mimetics derived from 1-deoxymannojirimycin.

2. Results and Discussion

2.1. Design of Somatostatin Mimetics. Somatostatin is a cyclic peptide that regulates the release of growth hormone and other pituitary hormones and plays a role in neuronal transmission. A number of receptor subtypes for this hormone have been identified. The somatostatin antagonist **1**, developed by Hirschmann and co-workers, is based on the β-D-glucopyranoside scaffold (Chart 1). We proposed the working out of a synthesis of **2**, a structural analogue of **1**, from 1-deoxymannojirimycin (DMJ) scaffold. This required the development of a strategy for grafting the pharmacophoric tryptophan and lysine side chains to the nitrogen atom of the piperidine ring and to the primary hydroxyl group, respectively. The piperidine **2** lacks the benzyl groups found in **1** and in iminosugars synthesized by Le Merrer. The branching positions on the scaffold would lead to a different spatial distance between the indole and pentylamino groups.

CHART 1



2.2. Synthesis of Somatostatin Mimetics. The synthesis of **2** commenced from **3** which was prepared, as previously described,[17] from DMJ.[18,19] Preliminary efforts to introduce a TIPS or TBDPS group on the primary hydroxyl group of **3** were unsuccessful. However, the reaction of **3** in acetone using a catalytic amount of PPTS gave, in a regioselective manner, **4** in 70% yield.[20] The formation of the diacetonide **5** was also observed; the yield of **5** varied from 2 to 10% in a number of experiments. The TBS group was then introduced regioselectively at the primary hydroxyl group to give **6** using TBSCl and imidazole in DMF. The introduction of the benzyl or methoxyphenylmethyl (MPM) protecting at the remaining free hydroxyl group of **6** was not achieved in our hands; however, the MOM protecting group was introduced to this hydroxyl group by the reaction of **6** with MOMCl, diisopropylethylamine (DIPEA) in dichloromethane giving **7** in 89% yield (Scheme 1).

Conditions for the regioselective removal of protecting groups from **7** were investigated next (Scheme 2). It was possible to remove the TBS protecting group using TBAF in THF to give **9**; however, the yield was only 47%. This was due to the basicity of the TBAF, which led to the removal of the CBz group as well. Indeed it has recently been shown that TBAF can remove carbamate protecting groups.[21] The removal of the TBS group was, however, achieved in a selective fashion using HF-pyridine and **9** was obtained in 75% yield after 18 h. Selective deprotection of the CBz group by stirring a mixture of **7** and Pd−C in THF in the presence of H_2 gave **8** in a quantitative yield.

Grafting of the alkylamino side chain to the primary hydroxyl group of **9** was explored next. The triflate **12**

(8) For some recent syntheses of disaccharide libraries see: (a) Sofia, M. J.; Allanson, N.; Hatzenbuhler, N. T.; Jain, R.; Kakarla, R.; Kogan, N.; Liang, R.; Liu, D. S.; Silva, D. J.; Wang, H. M.; Gange, D.; Anderson, J.; Chen, A.; Chi, F.; Dulina, R.; Huang, B. W.; Kamau, M.; Wang, C. W.; Baizman, E.; Branstrom, A.; Bristol, N.; Goldman, R.; Han, K. H.; Longley, C.; Midha, S.; Axelrod, H. R. *J. Med. Chem.* **1999**, *42*, 3193. (b) Baizman, E. R.; Branstrom, A. A.; Longley, C. B.; Allanson, N.; Sofia, M. J.; Gange, D.; Goldman, R. C. *Microbiology-SGM* **2000**, *146*, 3129. (c) Castoldi, S.; Cravini, M.; Micheli, F.; Piga, E.; Russo, G.; Seneci, P.; Lay, L. *Eur. J. Org. Chem.* **2004**, 2853. (d) Venot, A.; Swayze, E. E.; Griffey, R. H. Boons, G.-J. *ChemBioChem* **2004**, *5*, 1228.

(9) Prasad, V.; Birzin, E. T.; McVaugh, C. T.; van Rijn, R. D.; Rohrer, S. P.; Chicci, G.; Underwood, D. J.; Thornton, E. R.; Smith, A. B., III; Hirschmann, R. *J. Med. Chem.* **2003**, *46*, 1858.

(10) El Oualid, F.; Burm, B. E. A.; Leroy, I. M.; Cohen, L. H.; van Boom, J. H.; van den Elst, H.; Overkleeft, H. S.; van der Marel, G. A.; Overhand, M. *J. Med. Chem.* **2004**, *47*, 3920.

(11) Hirschmann, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1278.

(12) (a) Le Merrer, Y.; Poitout, L.; Depezay, J.-C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M.-J. *Bioorg. Med. Chem. Lett.* **1997**, *6*, 11667. (b) Le Merrer, Y.; Poitout, L.; Depezay, J.-C. In *Methods in Molecular Medicine*: *Peptidomimetics Protocols*. Kazmierski., W. M., Ed.; Humana Press Inc.: Totowa, NJ, 1999; Vol. 23.

(13) (a) Chery, F.; Murphy, P. V. *Tetrahedron Lett.* **2004**, *45*, 2067. (b) Chery, F.; Cronin, L.; O' Brien, J. L.; Murphy, P. V. *Tetrahedron* **2004**, *60*, 6597.

(14) For a recent review on synthesis of iminosugars containing six-membered rings see: Afarinkia, K.; Bahar, A. *Tetrahedron Asymmetry* **2005**, *16*, 1239.

(15) For reviews on glycosidase inhibition by iminosugars and related compounds see: (a) Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994**, 135. (b) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199. (c) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340. (d) Heightman, T. D.; Vasella A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750. (e) Lillelund V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515. (f) Greimel, P.; Spreitz, J.; Stutz, A. E.; Wrodnigg, T. M. *Curr. Top. Med. Chem.* **2003**, *3*, 513. (g) Asano, N.; Nash R. J.; Molyneaux, R. J.; Fleet, G. W. J. *Tetrahedron Asymmetry* **2000**, *11*, 1645.

(16) Kingma, P. J.; Menheere, P. P.; Sels, J. A.; Nieuwenhuijzen Kruseman, A. C. *Diabetes Care* **1992**, *15*, 478.

(17) Paulsen, H.; Matzke, M.; Orthen, B.; Nuck, R.; Reutter, W. *Liebigs Ann. Chem.* **1990**, 953.

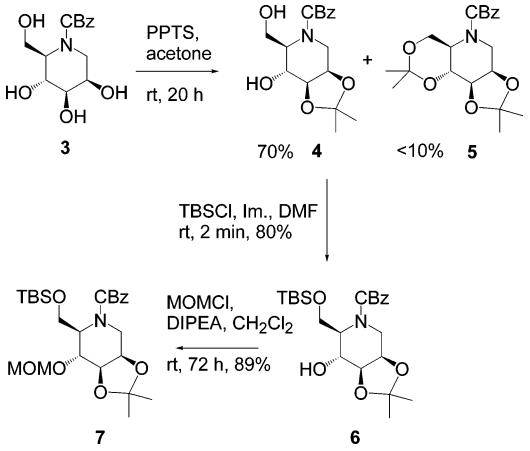
(18) For a synthesis of DMJ from our own group see: O'Brien J. L.; Tosin, M.; Murphy, P. V. *Org Lett.* **2001**, *3*, 3353.

(19) For a five-step synthesis of DMJ from D-fructose see: Spreitz, J.; Stütz, A. E.; Wrodnigg, T. *Carbohydr. Res.* **2002**, *337*, 183.

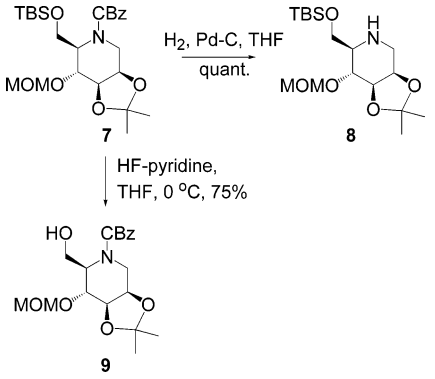
(20) Schueller, A. M.; Heiker, F. R.; Bayer, A.-G. *Carbohydr. Res.* **1990**, *203*, 308.

(21) Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039.

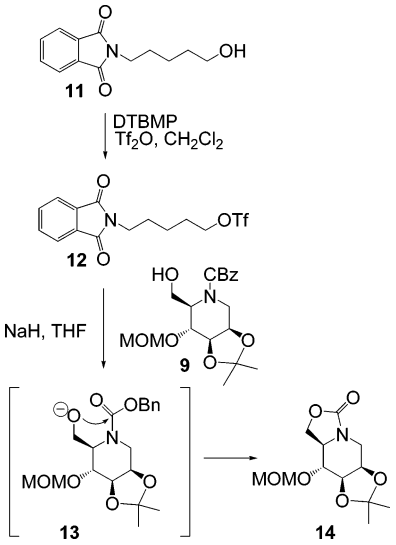
SCHEME 1



SCHEME 2

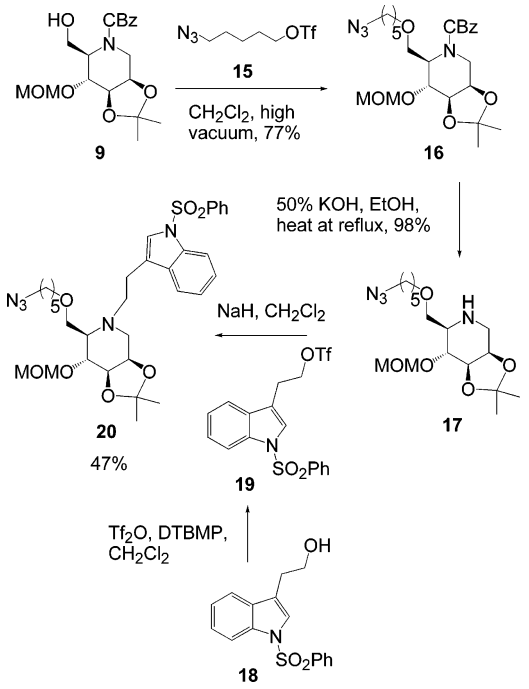


SCHEME 3



was first prepared from phthalamide derivative **11**[1c] and attempts to use this as an electrophile in reactions with **9** were unsuccessful. The attempted reaction of **12** with **9** in the presence of sodium hydride led to formation of the cyclic carbamate **14**[22] which occurs via **13** (Scheme 3). Attempts to effect the desired alkylation reaction of **12** in absence of base were not successful.

SCHEME 4



The azide derivative **15** was freshly prepared as described previously,[1c,6] and the alkylation of **9** with this electrophile in dichloromethane gave **16** in 77% yield. This experiment was conducted in absence of base and under vacuum, according to the protocol previously described by Hirschmann and co-workers.[6] The CBz group was removed in the presence of the azide group and the other protecting groups by heating **16** in ethanolic potassium hydroxide to give **17**. The triflate **19**, freshly prepared from its alcohol precursor **18**,[1c] on reaction with **17** in the presence of sodium hydride gave the indole derivative **20** in 47% yield (Scheme 4).

Next, the benzensulfonyl group was removed from **20** by heating in the presence of 5 M aqueous NaOH−EtOH; the azide was converted to the amine using catalytic hydrogenation to give **21**. The MOM and isopropylidene groups were finally removed under acidic conditions to give the target compound **2** (Scheme 5).

2.3. Biological Evaluation. Compounds **2** and **21** were investigated for their effects in an in vitro nonselective sst receptor binding assay[23] and in in vitro selective sst4[24] and sst5[25] receptor binding assays. The results are summarized in Table 1. In the nonselective assay the K_i values determined for **2** and **21** were 26 and 21 μM, respectively. Both iminosugar derivatives showed preferential binding to sst4 receptors than to sst5 receptors. Compounds **2** and **21** inhibited binding of the control to sst4 receptors by 46% and 48% (both at 1.0 μM), respectively, whereas they did not show any binding to sst5 receptors at this concentration, and only displayed significant inhibition of the binding at 1.0×10^{-4} M.

(22) For a previous observation of a related cyclic carbamate see: Fellows, L. E.; Bell, E. A.; Lynn, D. G.; Pilkiewicz, F.; Miura, I.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1979**, 977.

(23) Brown, P. J.; Lee, A. B.; Norman, M. G.; Presky, D. H.; Schonbrunn, A. *J. Biol. Chem.* **1990**, *265*, 17995.

(24) Rohrer, L.; Raulf, F.; Bruns, C.; Buettner, R.; Hofstaedter, F.; Schüle, R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 4196.

(25) Yamada, Y.; Kagimoto, S.; Kubota, A.; Yasuda, K.; Masuda, K.; Someya, Y.; Ihara, Y.; Li, Q.; Imura, H.; Seino, S. *Biochem. Biophys. Res. Commun.* **1993**, *195*, 844.

SCHEME 5

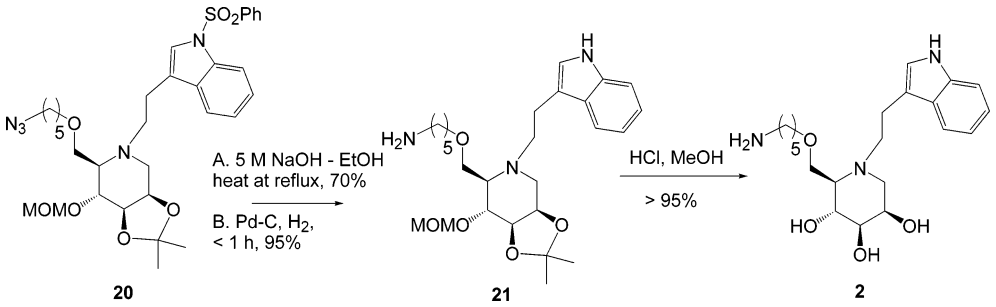


TABLE 1. Binding of Iminosugar Derivatives at Somatostatin Receptors

compd	sst (nonspecific) K_i (μM)	sst4 (% inhibition at 1.0×10^{-6} M)	sst5 (% inhibition at 1.0×10^{-6} M)	sst5 (% inhibition at 1.0×10^{-5} M)	sst5 (% inhibition at 1.0×10^{-4} M)
2	26	46	<5	22	78
21	21	48	<5	26	78

2.4. Summary and Conclusions. A synthesis of somatostatin mimetics based on the DMJ has been developed which facilitated strategic grafting of pharmacophoric tryptophan and lysine side chains to the nitrogen atom of the piperidine ring and to the primary hydroxyl group of DMJ, respectively. The synthetic compounds showed preferential affinity for sst4 receptors when compared to sst5 receptors. It may be possible to enhance affinity for somatostatin receptors by introducing other pharmacophoric groups at other hydroxyl groups of the DMJ scaffold, as has been shown by Hirschmann and co-workers for pyranoside scaffolds. Development of strategies for regioselective synthesis of such compounds from DMJ and other iminosugars is underway. It seems interesting that **2** has significant binding to sst4 receptors even though it is lacking in benzyl groups of **1** and the spatial relationships between the indole and pentylamino group would also be different from **1**.

3. Experimental Section

***N*-Benzyloxycarbonyl-1,5-dideoxy-1,5-imino-2,3-*O*-isopropylidene-D-mannitol 4.** The benzyloxycarbonyl derivative **3** (387 mg, 1.3 mmol) was dissolved in acetone (10 mL) and PPTS monohydrate (10 mg, 0.05 mmol) was added. The mixture was stirred at room temperature for 14 h and the solvent was then removed under diminished pressure. Chromatography of the residue (EtOAc−cyclohexane, 3:1 as eluant) gave, in order of elution, **5** (5 mg) as a white solid and **4** (307 mg, 70%) as a colorless oil. Analytical data for **4**: $[\alpha]_D$ −55 (c = 0.4, DMSO-d_6). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 7.37 (5H, s, aromatic H), 5.27 (1H, d, $J_{4,OH}$ 4 Hz, O*H*), 5.07 (2H, m, CH_2OCO), 4.75 (1H, br s, O*H*), 4.27 (1H, ddd, $J_{2,3}$ 4 Hz, $J_{1,2}$ 6 Hz, $J_{1',2}$ 8 Hz, H-2), 4.07 (1H, br s, H-1), 3.97 (1H, t, $J_{2,3}$ 4 Hz, $J_{3,4}$ 4 Hz, H-3), 3.87 (1H, br s, H-4), 3.60−3.67 (2H, m, H-6,6′), 3.48 (1H, br s, H-5), 2.93 (1H, br s, H-1′), 1.39 (3H, s, CH_3), 1.26 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 160.5, 160.0 (each s, each C=O), 142.3 (s, aromatic *C*), 133.8, 133.2, 132.9 (each d, each aromatic *C*H), 113.9 (s), 83.1, 76.0, 75.7, 71.9 (d), 71.7 (t), 64.4 (t), 63.9, 63.6, 63.5 (each d), 47.9, 47.5 (each t), 27.2, 27.1 (each q). ES−HRMS: found 338.1604 $[M + H]^+$; $C_{17}H_{24}NO_6$ requires 338.1619. Analytical data for *N*-benzyloxycarbonyl-1,5-dideoxy-2,3:4,6-di-O-isopropylidene-1,5-imino-D-mannitol **5**: $[\alpha]_D$ −78 (c = 0.8, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.36 (5H, s, aromatic H), 5.20−5.07 (2H, CH_2OCO), 4.37−4.22 (3H, m, H-1, H-2, H-6′), 4.15 (1H, dd, $J_{2,3}$ 8 Hz, $J_{3,4}$ 8 Hz, H-3), 4.03 (1H, dd, $J_{3,4}$ 8 Hz, $J_{4,5}$ 11 Hz, H-4), 3.70 (1H, t, $J_{5,6}$ 11 Hz, $J_{6,6'}$ 11 Hz, H-6), 3.38 (1H, dt, $J_{4,5}$ 11 Hz, $J_{5,6}$ 11 Hz, $J_{5,6'}$ 4 Hz, H-5), 2.96 (1H, m, H-1′), 1.52, 1.49, 1.46, 1.33 (12H, s, each CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 156.0 (s, C=O), 136.0 (s, aromatic *C*), 128.7, 128.3, 128.2 (each d, each aromatic *C*H), 110.0, 99.6 (each s), 75.5, 72.0, 71.9 (each d), 67.7, 63.0 (each t), 50.2, 42.7 (each d), 29.0, 26.8, 24.2, 19.2 (each q). ES−HRMS: found 378.1917 $[M + H]^+$; $C_{20}H_{28}NO_6$ requires 378.1933.

***N*-Benzyloxycarbonyl-6-*O*-*tert*-butyldimethylsilyl-1,5-dideoxy-1,5-imino-2,3-*O*-isopropylidene-D-mannitol 6**. To acetonide **4** (317 mg, 0.94 mmol) were added anhydrous DMF (3 mL) and imidazole (256 mg, 3.8 mmol) and to this mixture was added, dropwise, a solution of TBSCl (283 mg, 1.9 mmol) in DMF (1.5 mL). After 2 min of stirring under nitrogen at room temperature, the mixture was diluted with water (50 mL) and extracted with diethyl ether (3 × 50 mL). The organic layer was then dried ($MgSO_4$) and filtered, and the solvent removed under diminished pressure. Chromatography (EtOAc−cyclohexane, 1:4 as eluant) gave **6** as a colorless oil (339 mg, 80%); $[\alpha]_D$ −71 (c = 0.6, CH_2Cl_2). ^{1}H NMR (DMSO-d_6, 500 MHz, 90 °C): δ (ppm) 7.35 (5H, s, aromatic H), 5.10 (2H, s, CH_2OCO), 5.04 (1H, d, $J_{OH,4}$ 6 Hz, O*H*), 4.29 (1H, ddd, $J_{1,2}$ 7 Hz, $J_{1',2}$ 4 Hz, $J_{2,3}$ 7 Hz, H-2), 4.07 (1H, dd, $J_{1,1'}$ 13 Hz, $J_{1,2}$ 7 Hz, H-1), 4.01 (1H, t, $J_{2,3}$ 7 Hz, $J_{3,4}$ 7 Hz, H-3), 3.92−3.81 (3H, m, H-4,6,6′), 3.59 (1H, dt, $J_{4,5}$ 3.5 Hz, $J_{5,6}$ 7 Hz, H-5), 2.93 (1H, dd, $J_{1,1'}$ 13 Hz, $J_{1',2}$ 4 Hz, H-1′), 1.41 (3H, s, CH_3), 1.30 (3H, s, CH_3), 0.86 (9H, s, $(CH_3)_3$CSi), −0.01 (6H, 2s, $(CH_3)_2$Si). ^{13}C NMR (DMSO-d_6, 75 MHz, 90 °C): δ (ppm) 154.8 (s, C=O), 136.8 (s, aromatic *C*), 128.2−127.2 (each d, each aromatic *C*H), 108.5 (s), 77.7, 70.5, 66.5 (each d), 66.3, 60.7 (each t), 58.0, 42.4 (each d), 27.2, 27.1, 25.6, 24.8, 24.7 (each q), 17.7 (s), −5.6 (q). ES−HRMS: found 452.2478 $[M + H]^+$; $C_{23}H_{38}NO_6Si$ requires 452.2468.

***N*-Benzyloxycarbonyl-6-*O*-*tert*-butyldimethylsilyl-1,5-dideoxy-1,5-imino-2,3-*O*-isopropylidene-4-methoxymethyl-D-mannitol 7**. To acetonide **6** (305 mg, 0.068 mmol) were added anhydrous CH_2Cl_2 (9 mL), DIPEA (942 μL, 5.4 mmol), and molecular sieves (300 mg) and the mixture was stirred for 30 min under nitrogen at room temperature. Then MOMCl (411 μL, 5.4 mmol) was added and stirring continued for 19 h. The solvent was then removed under diminished pressure and chromatography (EtOAc−cyclohexane, 4:96 to 3:97 gradient elution) of the residue gave **7** as a colorless oil (299 mg, 89%); $[\alpha]_D$ +70 (c = 0.5, DMSO). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 7.36 (5H, m, aromatic H), 5.20−5.00 (2H, s, CH_2OCO), 4.80 (1H, s, C*H*H′OMe), 4.60 (1H, s, CH*H*′OMe), 4.33 (1H, m, H-2), 4.17 (1H, t, $J_{2,3}$ 7 Hz, $J_{3,4}$ 7 Hz, H-3), 4.01 (2H, m, H-1, 4), 3.90−3.70 (3H, m, H-4,6,6′), 3.27 (3H, m, CH_2OCH_3), 3.01

(1H, m, H-1′), 1.41 (3H, s, CH_3), 1.28 (3H, s, CH_3), 0.83 (9H, s, (CH_3)$_3$CSi), −0.03 (6H, s, (CH_3)$_2$Si). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 154.8, 154.4 (each s, C=O), 136.5 (s, aromatic *C*), 128.2−127.4 (each d, each aromatic *C*H), 108.7 (s), 95.3 (t), 75.8 (d), 70.8, 70.3, 70.0 (each d), 66.4, 66.3, 60.4, 59.8 (each t), 56.1 (d), 55.2 (q), 42.4 (d), 27.2, 27.1, 25.6, 24.8, 24.7 (each q), 17.6 (s), −5.7 (q). ES−HRMS: found 496.2750 [M + H]$^+$, $C_{25}H_{42}NO_7Si$ requires 496.2731.

6-*O*-*tert*-Butyldimethylsilyl-1,5-dideoxy-1,5-imino-2,3-*O*-isopropylidene-4-methoxymethyl-*D*-mannitol 8. Acetonide **7** (23 mg, 0.046 mmol) was added to THF (2.5 mL) containing 10% Pd−C (5 mg) and the mixture was stirred for 4 h under an atmosphere of hydrogen at room temperature. Filtration and removal of solvent under diminished pressure afforded **8** as a colorless oil (17 mg, quantitative); [α]$_D$ −34 (*c* = 0.5, DMSO). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 4.79 (1H, d, *J* 6 Hz, C*H*H′OMe), 4.60 (1H, d, *J* 6 Hz, CH*H*′OMe), 4.06 (1H, m, H-2), 3.97 (1H, dd, $J_{2,3}$ 5 Hz, $J_{3,4}$ 7 Hz, H-3), 3.68 (2H, m, H-6,6′), 3.54 (1H, dd, $J_{3,4}$ 7 Hz, $J_{4,5}$ 3 Hz, H-4), 3.30 (3H, m, CH$_2$OCH_3), 3.17 (1H, d, $J_{1,1'}$ 14 Hz, H-1), 2.84 (1H, d, $J_{1,1'}$ 14 Hz, H-1′), 2.33 (1H, br s, H-5), 1.41 (3H, s, CH_3), 1.28 (3H, s, CH_3), 0.87 (9H, s, (CH_3)$_3$CSi), 0.03 (6H, s, (CH_3)$_2$Si). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 107.8 (s), 95.3 (t), 79.4, 74.1, 73.8, 62.1, 58.0 (each d), 55.0 (q), 42.4 (d), 27.7, 26.4, 25.5 (each q), 17.7 (s), −5.7 (q). ES−HRMS: found 362.2374 [M + H]$^+$; $C_{17}H_{36}NO_5Si$ requires 362.2363.

***N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-2,3-O-isopropylidene-4-methoxymethyl-D-mannitol 9**. Acetonide **7** (25 mg, 0.05 mmol) was added to anhydrous THF (1 mL) to which had been pre-added a stock solution (0.2 mL) of HF-pyridine:pyridine:THF (2:4:10). The resulting mixture was stirred for 50 h under nitrogen at room-temperature. Then saturated aqueous $NaHCO_3$ (2.5 mL) was added and the resulting mixture was stirred again for 10 min. The mixture was then diluted with EtOAc (5 mL), the organic layer separated, dried ($MgSO_4$), and filtered, and the solvent removed under diminished pressure. Chromatography (EtOAc−cyclohexane, 3:7 to 1:1) gave **9** as a colorless oil (14 mg, 75%); [α]$_D$ −25 (*c* = 0.7, DMSO). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 7.37−7.35 (5H, m, aromatic H), 5.09 (2H, s, CH_2OCO), 4.78 (1H, m, O*H*), 4.75 (1H, s, C*H*H′OMe), 4.65 (1H, s, CH*H*′OMe), 4.30 (1H, m, H-2), 4.15 (1H, t, $J_{2,3}$ 7 Hz, $J_{3,4}$ 7 Hz, H-3), 4.00 (2H, m, H-1,4), 3.79−3.60 (4H, m, H-1,5,6,6′), 3.30 (3H, m, CH$_2$OCH_3), 3.01 (1H, m, H-1′), 1.42 (3H, s, CH_3), 1.29 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 154.9, 154.6 (each s, C=O), 136.6 (s, aromatic *C*), 128.3, 127.7, 127.3 (each d, each aromatic *C*H), 108.7 (s), 95.3 (t), 76.0, 71.0, 70.2, 69.8 (each d), 66.9, 66.2 (each t), 58.7, 58.3, 56.4 (each d), 55.2 (q), 41.5, 40.0 (each d), 28.9, 27.0, 25.0 (each q). ES−HRMS: found 382.1886 [M + H]$^+$; $C_{19}H_{28}NO_7$ requires 382.1881.

6-*O*-(5′-Azidopentyl)-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-2,3-*O*-isopropylidene-4-methoxymethyl-D-mannitol 16. To a stirred solution of 5-azido-1-pentanol (23 mg, 178 μmol) and 2,6-di-*tert*-butyl-4-methylpyridine (37 mg, 180 μmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C was added, dropwise, triflic anhydride (29 μL, 180 μmol). The mixture was stirred at room temperature for 15 min, then poured into water (12 mL) and extracted with CH_2Cl_2 (3 × 12 mL). The organic phases were combined and dried ($MgSO_4$) and solvent removed under diminished pressure to a volume approximating 25 mL. The concentration of the triflate solution was then ca. 8 mM. Some of this solution (6.5 mL, 52.5 μmol) was added to **9** (20 mg, 52.5 μmol) and the reaction mixture concentrated under diminished pressure and then placed under high vacuum for 2 h. This procedure was repeated (×3) and the residue kept under high vacuum for 12 h. Chromatography (EtOAc−cyclohexane, 1:4) gave **16** as a colorless oil (20 mg, 77%); [α]$_D$ −36 (*c* 0.3, DMSO). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 7.37−7.29 (5H, m, aromatic H), 5.09 (2H, m, CH_2OCO), 4.76 (1H, d, *J* 7 Hz, C*H*H′OMe), 4.61 (1H, d, *J* 7 Hz, CH*H*′OMe), 4.32 (1H, m, $J_{2,3}$ 7 Hz, H-2), 4.15 (1H, t, $J_{2,3}$ 7 Hz, $J_{3,4}$ 7 Hz, H-3), 3.95 and 3.60 (5H, each m, H-1,4,5,6), 3.29 (3H, s, CH$_2$-OCH_3), 3.26 (4H, m, CH_2N$_3$, CH$_2$CH_2O), 2.97 (1H, m, H-1′), 1.50−1.23 (12H, m, CH_2, CH_3). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 154.9, 154.6 (each s, each C=O), 136.6 (s, aromatic *C*), 128.3, 127.8, 127.4 (each d, each aromatic *C*H), 108.8 (s), 95.4 (t), 75.6, 71.4 (each d), 70.0 (2s, d and t), 68.0, 66.4 (each t), 55.2 (q), 54.4 (d), 50.5, 40.1, 28.4, 27.9 (each t), 26.9, 24.8 (each q), 22.8 (t). ES−HRMS: found 493.2659 [M + H]$^+$; $C_{24}H_{37}N_4O_7$ requires 493.2662.

6-*O*-(5′-azidopentyl)-1,5-dideoxy-1,5-imino-2,3-*O*-isopropylidene-4-methoxymethyl-D-mannitol 17. Azide **16** (48 mg, 9.7 mmol) was dissolved in 50% KOH and ethanol (1:1, 2 mL) and the mixture heated at reflux for 15 h. Water was then added (20 mL) and the compound was extracted with CH_2Cl_2 (20 mL). The organic layer was dried ($MgSO_4$) and filtered, and solvent removed under diminished pressure to give **17** as a colorless oil (34 mg, 98%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 4.92 (1H, d, *J* 6 Hz, C*H*H′OMe), 4.66 (1H, d, *J* 7 Hz, CH*H*′OMe), 4.16 (1H, m, H-2), 4.02 (1H, dd, $J_{2,3}$ 5 Hz, $J_{3,4}$ 7 Hz, H-3), 3.63−3.37 (9H, m, H-1,4,6,6′, CH$_2$CH_2O, CH$_2$OCH_3), 3.29 (2H, t, *J* 7 Hz, CH_2N$_3$), 2.96 (1H, dd, $J_{1,1'}$ 15 Hz, $J_{1',2}$ 2 Hz, H-1′), 2.49 (1H, ddd, *J* 3 Hz, *J* 5 Hz, *J* 10 Hz, H-5), 1.80 (1H, s, N*H*), 1.66−1.37 (12H, overlapping signals, CH_2 and CH_3). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 109.2 (s), 96.4 (t), 80.5, 75.8, 74.4 (each d), 71.1, 70.5 (each t), 57.8 (d), 56.1 (q), 51.5 (t), 45.9 (d), 29.3, 28.8 (each t), 28.2, 26.7 (each q), 23.5 (t). ES−HRMS: found 359.2311 [M + H]$^+$, $C_{16}H_{31}N_4O_5$ requires 359.2294.

6-*O*-(5′-Azidopentyl)-1,5-dideoxy-1-(*N*-phenylsulfonylindol-3-yl)ethyl-1,5-imino-2,3-*O*-isopropylidene-4-methoxymethyl-D-mannitol 20. Triflic anhydride (332 μmol) was added dropwise to a stirring solution of alcohol **18** (52 μL, 332 μmol) and 2,6-di-*tert*-butyl-4-methylpyridine (68 mg, 332 μmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C. The mixture was stirred at room temperature for 20 min and was then poured into water (20 mL) and extracted with CH_2Cl_2 (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum to a volume ca. 10 mL. The concentration of the triflate **19** in solution was ca. 33 mM. This solution (3.5 mL, 118 μmol) was added to a flask containing **17** (22 mg, 61 μmol) and NaH (13 mg, 325 μmol, 60% dispersion) in CH_2Cl_2 (0.75 mL) at 0 °C, which had been pre-stirred for 30 min, and the resulting mixture was stirred under nitrogen at room temperature for 16 h. Water (20 mL) was poured into the solution which was then extracted with CH_2Cl_2 (20 mL). The organic layer was dried ($MgSO_4$) and concentrated in a vacuum. Chromatography (EtOAc−cyclohexane, 1:3) gave **20** as a colorless oil (20 mg, 47%); [α]$_D$ −18 (*c* = 0.5, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.97 (1H, d, *J* 8 Hz, aromatic H), 7.86 (2H, d, *J* 7 Hz, aromatic H), 7.54−7.20 (7H, m, aromatic H), 4.81 (1H, d, *J* 6 Hz, C*H*H′OMe), 4.72 (1H, d, *J* 7 Hz, CH*H*′OMe), 4.32 (1H, m, H-2), 4.19 (1H, dd, $J_{2,3}$ 5 Hz, $J_{3,4}$ 6 Hz, H-3), 3.91 (1H, t, $J_{2,3}$ 5 Hz, $J_{3,4}$ 5 Hz, H-4), 3.56 (1H, dd, $J_{5,6}$ 5 Hz, $J_{6,6'}$ 10 Hz, H-6), 3.53 (1H, dd, $J_{5,6'}$ 5 Hz, $J_{6,6'}$ 10 Hz, H-6′), 3.41 (3H, s, CH$_2$-OCH_3), 3.37 (2H, t, *J* 6 Hz, CH$_2$CH_2O), 3.18 (2H, t, *J* 7 Hz, CH_2N$_3$), 3.05−2.92 (6H, m, H-1, H-5, NCH_2CH_2), 1.60−1.33 (12H, m, CH_2 and CH_3). ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 138.5, 135.2, 133.5, 131.2, 129.1, 126.6, 124.6, 123.2, 123.0, 121.3, 119.4, 113.7 (aromatic C and CH), 109.1 (s), 96.4 (t, *C*H$_2$-OMe), 76.6, 73.7, 72.8 (each d), 70.9, 69.3 (each t), 61.9 (d), 55.8 (q), 53.7, 51.3, 50.0, 29.1, 28.6 (each t), 27.4, 25.5 (each q), 23.4, 22.8 (each t). ES−HRMS: found 642.2973 [M + H]$^+$; $C_{32}H_{44}N_5O_7S$ requires 642.2961.

1,5-Dideoxy-6-*O*-(5′-iminopentyl)-*N*-[(indol-3-yl)ethyl]-1,5-imino-2,3-*O*-isopropylidene-4-methoxymethyl-D-mannitol 21. Azide **20** (25 mg, 39 μmol) was dissolved in a mixture of 5 M NaOH (850 μL) and EtOH (5 mL) and the mixture heated at reflux for 2 h. The ethanol was removed under diminished pressure, water (20 mL) was added, and the product was then extracted into CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with water (20 mL), dried ($MgSO_4$) and filtered, and solvent removed to give the intermediate as a colorless oil (14 mg, 70%); [α]$_D$ −15 (*c* = 0.3,

CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.95 (1H, s, NH), 7.60 (1H, d, *J* 8 Hz, aromatic H), 7.35 (1H, d, *J* 9 Hz, aromatic H), 7.18 (1H, t, *J* 7 Hz, *J* 7 Hz, aromatic H), 7.10 (1H, t, *J* 8 Hz, *J* 8 Hz, aromatic H), 7.04 (1H, d, *J* 2 Hz, indole H), 4.82 (1H, d, *J* 6 Hz, C*H*H′OMe), 4.72 (1H, d, *J* 6 Hz, CH*H*′OMe), 4.35 (1H, m, H-2), 4.20 (1H, t, $J_{2,3}$ 5 Hz, $J_{3,4}$ 6 Hz, H-3), 3.93 (1H, t, $J_{3,4}$ 6 Hz, $J_{4,5}$ 5 Hz, H-4), 3.64 (1H, dd, $J_{5,6}$ 5 Hz, $J_{6,6'}$ 10 Hz, H-6), 3.58 (1H, dd, $J_{5,6'}$ 5 Hz, $J_{6,6'}$ 10 Hz, H-6′), 3.40 (5H, m, CH_2CH_2O and CH_2OCH_3), 3.20−2.88 (6H, m, H-1,1′ and NCH_2CH_2), 2.73 (1H, dd, $J_{1,1'}$ 10 Hz, $J_{1,2}$ 5 Hz, H-5), 1.60−1.33 (12H, m, CH_2 and CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 136.5, 129.3, 122.2, 121.7, 119.4, 119.0, 114.9, 111.29 (each aromatic C and CH), 109.3 (s), 96.4 (t), 78.0, 74.1, 73.2 (each d), 71.1, 69.5 (each t), 62.0 (d), 56.1 (q), 55.1 (t), 51.5 (d), 50.5, 29.9, 29.4, 28.9 (each t), 27.7, 25.9 (each q), 23.7, 23.1 (each t). ES−HRMS: found 502.3036 $[M + H]^+$ $C_{26}H_{40}N_5O_5$ requires 502.3029. This intermediate (2.2 mg, 4.4 μmol) was dissolved in MeOH (2 mL) and 10% Pd−C was added. The resulting mixture was stirred at room temperature for 45 min under an atmosphere of hydrogen. The mixture was then filtered through Celite and the solvent removed under diminished pressure to provide **21** as a colorless oil; $[\alpha]_D$ −10 (c = 0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.15 (1H, s, NH), 7.60 (1H, d, *J* 8 Hz, aromatic H), 7.35 (1H, d, *J* 8 Hz, aromatic H), 7.18 (1H, t, *J* 8 Hz, aromatic H), 7.10 (1H, t, *J* 8 Hz, aromatic H), 7.06 (1H, s, aromatic H), 4.82 (1H, d, *J J* 6 Hz, C*H*H′OMe), 4.72 (1H, d, *J* 6 Hz, CH*H*′OMe), 4.35 (1H, m, H-2), 4.19 (1H, t, $J_{2,3}$ 6 Hz, $J_{3,4}$ 6 Hz, H-3), 3.93 (1H, t, $J_{3,4}$ 6 Hz, $J_{4,5}$ 6 Hz, H-4), 3.64 (1H, dd, $J_{5,6}$ 5 Hz, $J_{6,6'}$ 10 Hz, H-6), 3.58 (1H, dd, $J_{5,6'}$ 5 Hz, $J_{6,6'}$ 10 Hz, H-6′), 3.36 (5H, m, CH_2CH_2O and CH_2OCH_3), 3.11−2.88 (6H, m, H-1,1′ and NCH_2CH_2), 2.74 (1H, dd, $J_{4,5}$ 6 Hz, $J_{5,6}$ 5 Hz, H-5), 2.63 (1H, t), 1.60−1.33 (12H, m, CH_2 and CH_3), ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 136.5, 127.9 (each s, aromatic *C*), 122.1, 122.0, 121.8, 119.0, 114.8 (each d, aromatic *C*H), 111.2 (s, aromatic C), 109.3 (s), 96.4 (t), 74.1, 73.2, 71.4 (each d), 69.3 (t), 62.0 (d), 56.0, 55.0 (each q), 50.5 (t), 42.4, 29.8, 27.7 (each t), 25.9, 23.8 (each q), 23.1 (t). ES−HRMS: found 476.3136 $[M + H]^+$; $C_{26}H_{42}N_3O_5$ requires 476.3124.

1,5-Dideoxy-*N*-(indol-3-yl)ethyl-6-O-(5′-iminopentyl)-1,5-imino-D-mannitol 2. Indole **21** (1.2 mg, 2.53 μmol) was dissolved in MeOH (250 μL) and a solution of 30% HCl (25 μL) was added. The mixture was stirred at room temperature for 2 h and the solvent was then removed under diminished pressure. The residue was freeze-dried (x2) giving the compound as a hygroscopic white solid (1.3 mg, quant); $[\alpha]_D$ −36 (c = 0.3, DMSO). ^{1}H NMR (D_2O, 300 MHz): δ (ppm) 7.72 (1H, d, *J* 8 Hz, aromatic H), 7.55 (1H, d, *J* 8 Hz, aromatic H), 7.37 (1H, s, aromatic H), 7.30 (1H, t, *J* 8 Hz, aromatic H), 7.22 (1H, t, *J* 8 Hz, aromatic H), 4.30 (1H, s, H-5), 3.90−3.73 (6H, m, H-6,6′, CH_2O and CH_2Ar), 3.50−3.25 (7H, m, H-1,1′,2,3,4 and CH_2N), 2.78 (2H, m, CH_2), 1.46 (2H, m, CH_2), 1.13 (4H, m, $2CH_2$). ^{13}C NMR (D_2O, 75 MHz): δ (ppm) 139.3, 129.0, 127.0, 125.1, 122.4, 121.0, 114.9, 110.5, 74.7, 73.7, 68.5, 68.2, 65.6, 57.4, 55.8, 42.0, 30.4, 29.2, 24.9, 21.9. ES−HRMS: found 392.2563 $[M + H]^+$; $C_{21}H_{34}N_3O_4$ requires 392.2549.

Biological Evaluation. The assays were carried out at Cerep[26] as previously described.[23] Compounds were evaluated for their ability to inhibit somatostatin binding to sst receptors from AtT-20 cells (nonselective assay), to human recombinant sst4[24] receptors (CHO cells), and to human recombinant sst5[25] receptors (HEK-293 cells). The IC_{50} values (concentration causing a half-maximal inhibition of control-specific binding) and Hill coefficients (n_H) were determined by nonlinear regression analysis of competition curves using Hill equation curve fitting. The inhibition constants (K_i) were calculated from the Cheng Prusoff equation ($K_i = IC_{50}/(1 + (L/K_D)$, where L is the concentration of radioligand in the assay, and K_D is the affinity of the radioligand for the receptor).

Acknowledgment. The authors thank Geraldine Fitzpatrick for NMR spectra and Dr. Dilip Rai for high resolution mass spectrometry measurements. Funding was provided by the European Commission through a Marie Curie IntraEuropean Fellowship (proposal No. 514958) to S.G.G. P.V.M. thanks the Science Foundation Ireland and the Program for Research in Third-Level Institutions (PRTLI), administered by the HEA (of Ireland) for funding.

Supporting Information Available: General experimental conditions, analytical data for **14,** and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051454N

(26) See http://www.cerep.fr.