De Novo Design and Synthesis of Somatostatin Non-Peptide Peptidomimetics Utilizing β-D-Glucose as a Novel Scaffolding

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Abstract: Non-peptide peptidomimetics of the peptide hormone somatostatin (SRIF) were designed and synthesized, utilizing β-D-glucose as a novel scaffolding. Such compounds resemble conventional peptide analogs in that they retain critical amino acid side chains but differ in that they are devoid of both the peptide backbone and amide surrogates. Structure–activity relationships resulting from systematic deletion or modification of the side chains of **4a** were consistent with expectations, with the exception that analogs **8a** and **8b**, lacking an indole side chain, bound to the SRIF receptor. A possible explanation for this unexpected result and its potential implications are discussed. Unexpectedly we also found that the primary amino group of Lys[9] is not required for SRIF receptor binding or activation. Taken together, the results reported herein, and those described elsewhere,[1,2] support the validity of the concept of non-peptide scaffolding and also demonstrate that non-peptidal peptidomimetics can provide unexpected biological information not previously available from natural ligands or their peptidal analogs.

Introduction

Poor oral bioavailability, displayed by innumerable peptides of potential therapeutic value, has generated an intensive search for peptidomimetics[1,3] in which the backbone amide bonds are systematically replaced, generally by amide surrogates, with the expectation that stability to proteolytic enzymes will be enhanced. Replacement of L- by D-amino acids at cleavage sites or freezing presumed bioactive conformations through the introduction of conformational constraints[4] can achieve the same goal. These manipulations generate a class of structures which we call peptidal peptidomimetics to emphasize their close structural resemblance to peptides. Such structural modifications can indeed result in analogs with increased biological half-lives and have sometimes also enhanced potency. This approach has serious limitations, however: aside from the fact that a given replacement of an amide bond at one position of a peptide may not be permissible at an equivalent position in another series, this strategy has not solved the bioavailability problem partly because of the presence of residual peptide bonds. Importantly, there is evidence that the poor oral bioavailability of peptides is not due solely to their susceptibility to cleavage by peptidases or to their size, since even small, cyclic peptides which are stable to proteolytic enzymes frequently display unacceptably low oral bioavailability due to poor transport properties and/or biliary secretion.[3e,5] The fact that the N-methylated peptide cyclosporin, in olive oil solution, displays good oral activity suggested to us[3e,2c] that the NH groups of backbone amide bonds may contribute to the bioavailability problems. Striking experimental support for this hypothesis in relation to passive transport has been provided very recently by Conradi and collaborators.[6]

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Merck Research Laboratories, West Point.

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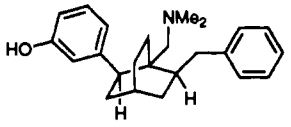
As early as 1977, Walter[7] pointed out that there is no compelling evidence for direct participation of the amide backbone elements in receptor occupation or activation. This astute observation was reinforced by the design and synthesis by Freidinger and co-workers of a potent retro-enantio analog of an SRIF-related cyclic hexapeptide[8] and—with hindsight—by the existence of morphine, now known to bind to receptors for which the natural ligands are peptides. That morphine contains no amide bonds has been known since 1925.[9] These considerations suggested to us an alternative approach toward the design of peptidomimetics, wherein the entire amide backbone of a β-turn is replaced by novel scaffoldings devoid of amide bonds or their isosteric replacements.[1,3e] This approach allows consideration of a host of diverse, rigid structures as scaffolds to which the amino acid side chains (or homologs) required for binding can be attached. We refer to such structures as non-peptidal peptidomimetics with novel scaffolding. The successful implementation of this approach would bridge the gap between peptidal peptidomimetics and compounds, such as morphine, which reproduce the binding interactions of the natural peptide without recognizable atom for atom correspondence of the pharmacophoric groups (these compounds have been termed "limetics," i.e., ligand mimetics[10]).

In 1980, the design of non-peptide peptidomimetics using novel scaffolds was insightfully anticipated by Farmer,[3a] who proposed, but did not explore, the attachment of side chains to a cyclohexane ring. While several novel scaffolds mimicking β-turns have been reported during the second half of the 80s,[11] these early compounds incorporated at most one β-turn-derived side chain and thus were not designed to bind to any particular receptor. To our knowledge, compound **1** was the first non-peptide peptidomimetic with novel scaffolding which is recognized by the receptor (opiate) for which it had been designed,[12] with an IC_{50} of 225 nM in the ^{3}H-naloxone binding assay.



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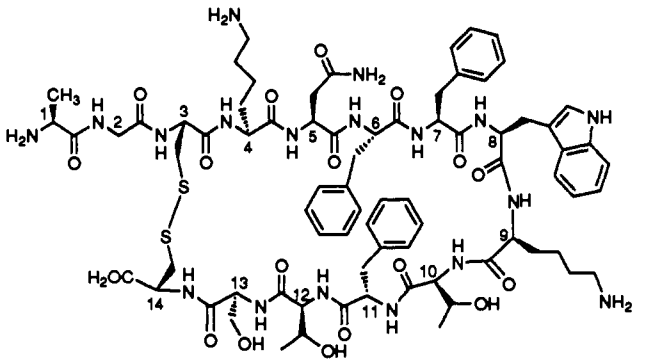
The peptide hormone somatostatin (SRIF) **2**,[13] a cyclic tetradecapeptide which inhibits the release of several hormones including growth hormone (GH), has attracted attention as a potential therapeutic agent.[14] Its very short biological half-life led to the design and synthesis of longer acting peptidal peptidomimetics such as seglitide (MK-678) and octreotide. The latter became the first SRIF-related marketed drug. To date, no SRIF analog possessing adequate oral bioavailability has been described. SRIF contains a β-turn composed of the tetrapeptide sequence Phe-Trp-Lys-Thr.[15] This tetrapeptide retains the ability to elicit SRIF-like biological effects as long as the side chains of these four amino acids are constrained in nearly the same orientation as in the bioactive conformation of SRIF. For example, cyclic hexapeptides, typified by c-(Phe-D-Trp-Lys-Thr-Phe-Pro) **3**, are potent agonists.[16] In these structures, the dipeptide building block Phe-Pro, or its conformational equivalent Phe-N-Me-Ala, allows the side chains of the four amino acids that comprise the β-turn to assume conformations which permit both binding and agonism. In addition, the aromatic side chain of the Phe-Pro dipeptide provides a favorable hydrophobic interaction with the SRIF receptor. For example, the equivalent peptide with an Ala-Pro replacing the Phe-Pro linkage is about 23-fold



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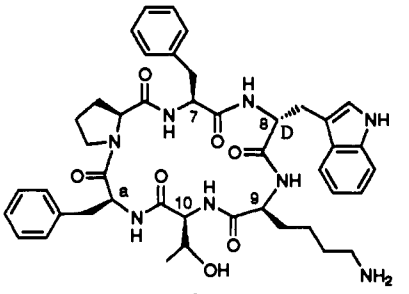

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less potent in inhibiting GH release in vitro, despite a similar conformation as demonstrated by NMR and CD measurements.[16] Importantly, Veber concluded that the Phe of the Phe-Pro dipeptide (subsequently referred to herein as Phe^a) does not correspond to Phe^{11} of SRIF, but that it replaces the hydrophobic region defined by Asn^5 and Thr^{12} of SRIF.[17] Phe^a added about 2.5–3.0 kcal mol^{-1} to binding. In contrast, Phe^6 and Phe^{11} of SRIF were thought to contribute no significant enhancement of binding but instead to stabilize the bioactive conformation via hydrophobic stacking.[15a] Several lines of evidence are consistent with this analysis. In the model for the solution conformation of SRIF developed by Veber and associates,[15] which is consistent

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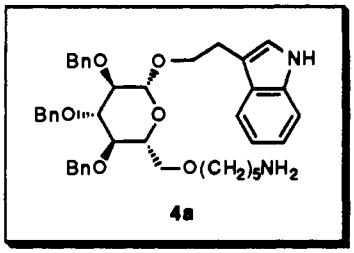
also with the structure–activity relationships (SARs) reported by Vale, Rivier, and collaborators,[18] the side chains of Phe^6 and Phe^{11} are within bonding distance. Moreover, Phe^6 is shielded in the ^{1}H NMR spectrum by another Phe, presumed to be Phe^{11}, based on the model and other evidence. While [Ala^6]SRIF and [Ala^{11}]SRIF were shown by Rivier and collaborators[18] to display <1% and 3%, respectively, of the potency of SRIF, a bicyclic analog wherein a cystine bridge replaced both Phe^6 and Phe,^{11} thereby stabilizing the bioactive conformation, was found to be highly active.[15]

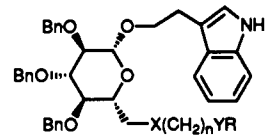
The ubiquitous D-glucose appeared as an attractive option for a non-peptide scaffolding in the design of an SRIF mimetic. The pyranoside of glucose offers several advantages over other sugars including its well defined conformation, the ability to position the required side chains in an equatorial disposition around the pyran ring, the requisite enantiomeric purity of a starting material, and the vast array of synthetic knowledge already gathered.[19,20]

Molecular modeling (*vide infra*) suggested to us that in the simple tribenzyl glycoside **4a** the substituents at C-2, C-1, and

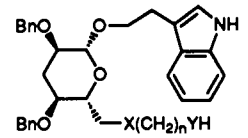


4a

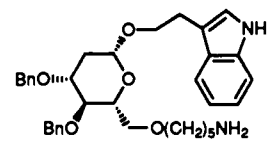
C-6 held the promise of providing appropriately positioned replacements for the critical Phe-Trp-Lys side chains respectively and also that the benzyl group at C-4 may be able to mimic Phe^a. Since Thr^{10} of SRIF can be replaced by Ala without loss of potency,[18] and Thr^{10} of **3** can be replaced by Val^{5a} or Gly,[21] the side chain of Thr^{10} was not incorporated into the design of **4a**. We describe herein the synthesis and the biological properties of **4a** which, being readily accessible, was chosen as the initial target. We report also the synthesis of the 3-deoxy sugar **5a** in which the C-3 benzyloxy substituent, lacking a counterpart in **3**, was deleted and which was therefore expected to display receptor affinity at least equal to **4a**. In order to lend support for the validity of the



4a n = 5, X = O, Y = NH, R = H
4b n = 4, X = O, Y = NH, R = H
4c n = 6, X = O, Y = NH, R = H
4d n = 5, X = O, Y = NH, R = Ac
4e n = 5, X = NH, Y = O, R = H
4f n = 4, X = NH, Y = O, R = H
4g n = 6, X = NH, Y = O, R = H



5a n = 5, X = O, Y = NH
5b n = 6, X = O, Y = NH
5c n = 5, X = NH, Y = O
5d n = 6, X = NH, Y = O



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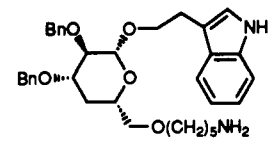

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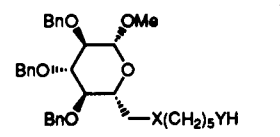
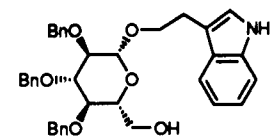


8a X = O, Y = NH
8b X = NH, Y = O



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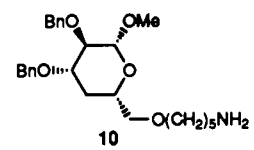

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design, we also synthesized and sought to predict the binding affinities of the 2- and 4-deoxy analogs (**6** and **7**, respectively) and of compounds lacking the Trp^8 and Lys^9 mimetic side chains (**8** and **9**) as well as for the analog **4d** in which the primary amino group is acetylated. The biological results from the binding assays (*vide infra*) were generally in accord with our predictions, except for compound **8**. This latter anomaly led us to synthesize analog **10** (*vide infra*). Finally, we report the synthesis and biological activities of compounds in which the C-6 side chain is attached via nitrogen rather than oxygen (**4e–g**, **5c,d**, and **8b**).

Molecular Modeling

The first step in designing our SRIF mimetics was the recognition that the solution conformation of SRIF is believed to include a type I β-turn involving Phe^7-Trp^8-Lys^9-Thr^{10}, whereas the solution conformation of D-Trp^8-SRIF may contain a type II' β-turn. In its bioactive conformation, the side chains of SRIF in $i+1$ and $i+2$ positions are thought to assume a relationship resembling that found in D-Trp^8-SRIF.[15] This analysis is consistent with the known structure–activity relationships (SARs) and with ^{1}H NMR studies.[15] Moreover, extensive NMR and modeling studies[22] on the highly active cyclic hexapeptide **3** (L-363 301) and its analogs have revealed the presence of a type II' β-turn in solution. In **3**, the Phe-Pro amide bond exists in a cis arrangement, holding the peptide in the desired conformation.

A local minimum of the tribenzyl sugar **4a** was initially located using MacroModel[23] and the MM2 force field.[24] This structure was then superimposed on the solution structure of hexapeptide

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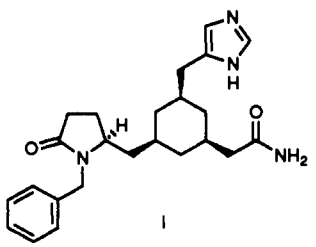
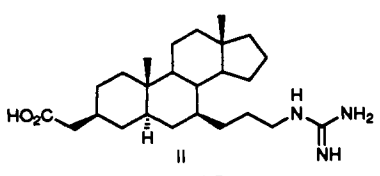
(19) In a conceptually similar approach, the synthesis of a thyrotropin-releasing hormone mimic I which employed a cyclohexane scaffold was reported (Olson, G. L.; Cheung, H.-C.; Voss, M. E.; Hill, D. E.; Kahn, M.; Madison, V. S.; Cook, C. M.; Sepinwall, J.; Vincent, G. In *Proc. Biotechnol. (USA)*; Conference Management Corporation: Norwalk, 1989; p S.348). Compound **I** bound to the low-affinity TRH receptors in the CNS. Significantly, it was found to be orally bioavailable.



I

(20) Elsewhere, our group has reported the use of the cyclopentanoperhydrophenanthrene steroid skeleton as a peptidomimetic scaffolding.[2a,b] Compound **II** bound to the fibrinogen receptor on blood platelets (GP IIb/IIIa) with an IC_{50} of ca. 100 μM.



II

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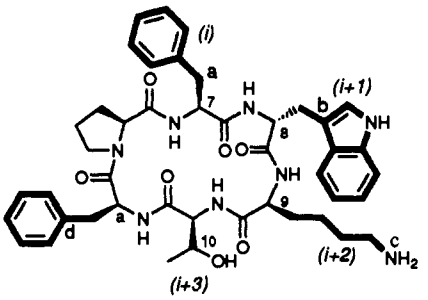
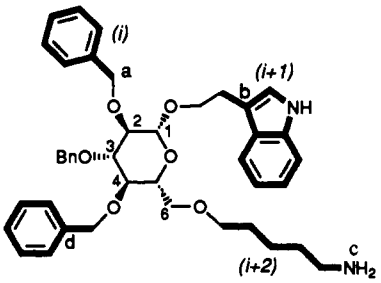


Cyclic hexapeptide L-363,301 (3)



Non-peptide mimetic **4a**, derived from β-D-glucose

Distances between labelled atoms (Å)						
	a-b	a-c	a-d	b-c	b-d	c-d
L-363,301 (3)	7.1	11.3	9.2	7.3	9.2	14.1
Peptidomimetic **4a**	5.6	10.6	8.0	6.6	10.3	13.5

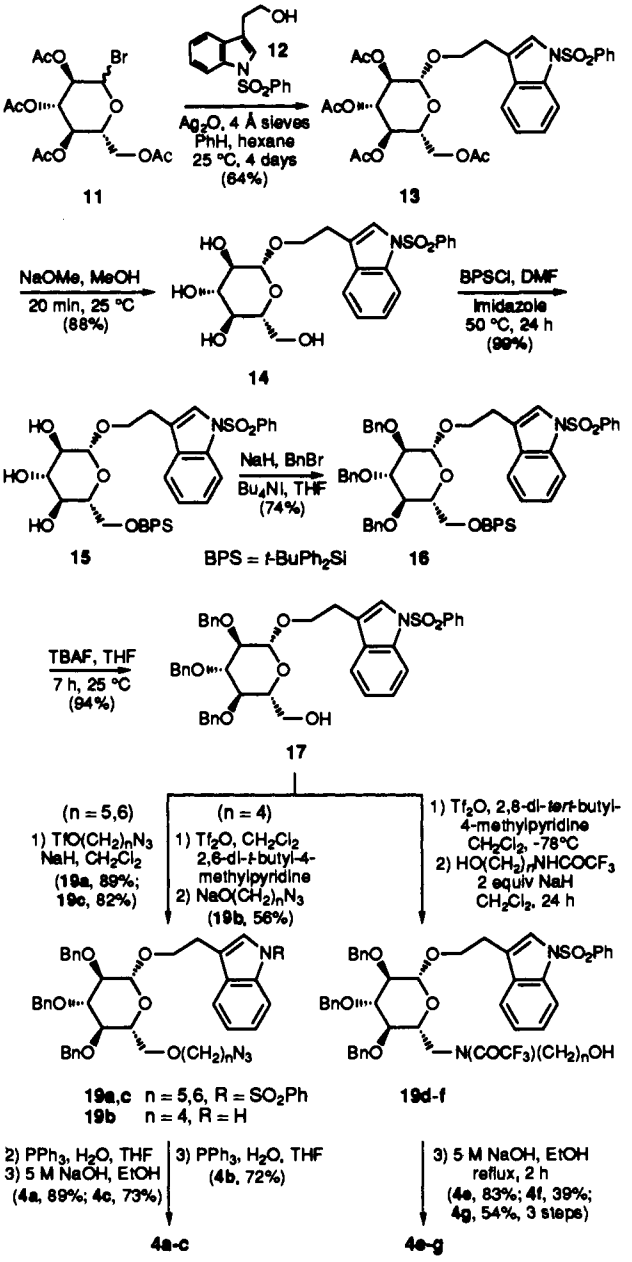
Figure 1. Overlap of a local minimum of **4a** with the bioactive conformation of **3**.

3. A local minimum of sugar **4a** overlaps quite well with the bioactive conformation of **3** (Figure 1).

Synthesis

The initial target, **4a**, was synthesized in eight steps from tetra-*O*-acetyl-α-D-glucopyranosyl bromide **11**[25] (Scheme I). Koenigs–Knorr coupling[26] of *N*-phenylsulfonyl tryptophol **12** with **11** yielded tetraacetate **13** as the desired β-isomer in 64% yield. A nonpolar solvent system and 1 equiv of silver(I) oxide, rather than a catalytic amount, were necessary in order to inhibit α-isomer and orthoester formation. The four acetyl groups were removed by methanolysis to afford the tetraol **14** which was selectively protected at the primary hydroxyl to give *tert*-butyldiphenylsilyl ether **15**. The remaining hydroxyls were then benzylated to afford **16**. Desilylation with tetrabutylammonium fluoride gave alcohol **17**. Conversion[27] to the corresponding triflate, followed by displacement of the triflate with the presumed dianion of 5-trifluoroacetamido-1-pentanol (**18a**),[28] unexpectedly afforded **19d** rather than its regioisomer in good overall yield.[29] Simultaneous cleavage of the benzenesulfonamide and trifluoroacetamide groups was accomplished with aqueous sodium hydroxide in ethanol at reflux to yield **4e**. Similar sequences using 4-trifluoroacetamido-1-pentanol (**18b**)[28] and 6-trifluoro-

Scheme I



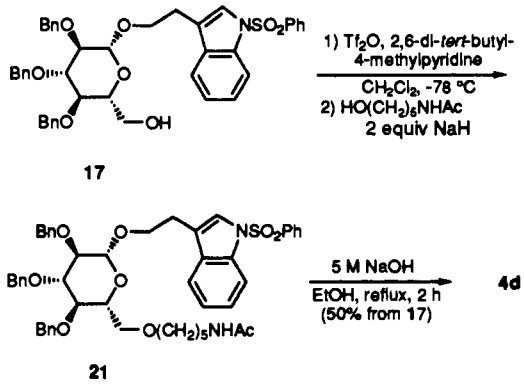
acetamido-1-pentanol (**18c**)[30] furnished analogs **4f** and **4g**.[29] The correct lysine side-chain analogs **4a–c** were successfully prepared by employing an azide as a masked amine (Scheme I).

To construct the N-acylated C-6 side-chain analog (**4d**), 5-acetamido-1-pentanol (**20**)[32] was treated with 2 equiv of NaH and allowed to react with the triflate derived from **17** to provide **21** (Scheme II). Selective deprotection of the benzenesulfonamide with aqueous sodium hydroxide in ethanol at reflux afforded compound **4d** in 50% yield for the three steps.

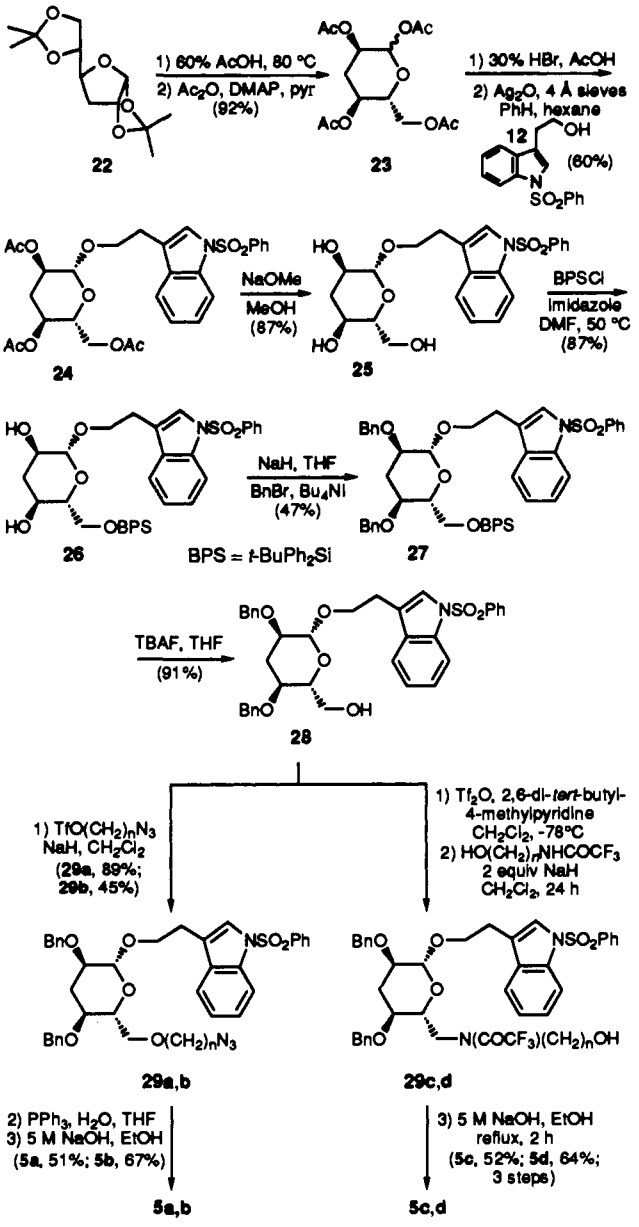
The syntheses of the three possible mono-deoxy analogues of **4** were then undertaken. The 3-deoxy analogue **5** was synthesized in nine steps from diacetone D-glucose (Scheme III). The key building block, 1,2,4,6-tetra-*O*-acetyl-3-deoxy-β-D-glucopyranoside (**23**), was accessible by the known Barton deoxygenation of diacetone D-glucose (**22**)[32] followed by deprotection in aqueous acetic acid. Peracetylation of the crude mixture then gave the

(25) Jeremias, C. G.; Lucas, G. B.; Mackenzie, C. A. *J. Am. Chem. Soc.* **1948**, *70*, 2598.
(26) Magus, V. *Carbohydr. Res.* **1979**, *76*, 261.
(27) Binkley, R. W.; Ambrose, M. G. *J. Carbohydr. Chem.* **1984**, *3*, 1.
(28) Zarytova, V. F.; Ivanova, E. M.; Kutyavin, I. V.; Segeev, D. S.; Sil'nikov, V. N.; Shishkin, G. V. *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* **1989**, 3. Lokhov, S. G.; Podyminogin, M. A.; Sergeev, D. S.; Sil'nikov, V. N.; Kutyavin, I. V.; Shishkin, G. V.; Zarytova, V. P. *Bioconjugate Chem.* **1992**, *3*, 414.
(29) Compounds **4e** and **5c** were originally incorrectly formulated with an oxygen-linked C-6 side chain in ref 1a (e.g., structures **3** and **4**), 1b (e.g., structures **II** and **III**), and 1c (e.g., structures **1a** and **1b**).
(30) Barker, R.; Olsen, K. W.; Shaper, J. H.; Hill, R. L. *J. Biol. Chem.* **1972**, *247*, 7135. Chipowsky, S.; Lee, Y. C. *Carbohydr. Res.* **1973**, *31*, 339.
(31) Wojcik, B.; Adkins, H. *J. Am. Chem. Soc.* **1934**, *56*, 2419. Fernandez, S.; Menendez, E.; Vicente, G. *Synthesis* **1991**, 713.
(32) Iacono, S.; Rasmussen, J. R. *Org. Synth.* **1985**, *64*, 57.

Scheme II



Scheme III



tetraacetate **23** in high yield as an ca. 1:2 mixture of α/β anomers which could be separated by crystallization. The use of high temperatures in the deprotection step ensures the formation of only trace amounts of the corresponding furan isomers.[33] The synthesis then parallels that of the tribenzyl sugar **4**. Thus, Koenigs–Knorr coupling via the bromide as before produced triacetate **24**. Methanolysis gave triol **25** which was protected to give silyl ether **26**, converted to the dibenzyl ether **27** and desilylated, affording alcohol **28**. Attempted introduction of the lysine mimicking side chain as before using both **18a** and **18c** again provided the N-linked sugar analogs **5c** and **5d** instead of the desired O-linked analogs **5a** and **5b**.[29] Again the desired analogs **5a,b** were obtained by employing the azide protected side chain (Scheme III).

Preparation of the 2-deoxy compound **6** (Scheme IV) entailed benzylation of glucal **30**, followed by removal of the silyl protecting group.[34] The resulting alcohol (**32**) was then deprotonated using sodium hydride and a catalytic amount of 15-crown-5 ether, followed by coupling with the triflate of 5-phthalimido-1-pentanol (**33**) to install the protected amine side chain in 86% yield. Using a variation on a procedure introduced by Danishefsky and co-workers,[35] stereospecific epoxidation of the resulting enol ether **34** with dimethyldioxirane and subsequent zinc chloride-promoted opening with sulfonyltryptophol **12** led to fully substituted sugar **35**. Deoxygenation at the C-2 position was effected by the Barton xanthate reduction procedure,[36] to give compound **36**. Sequential removal of the phthalimido and sulfonyl groups afforded the target compound **6**.

The 4-deoxy analogue **7** was synthesized from the known tribenzoate **37**[37] (Scheme V). Deoxygenation at the 4-position was effected via the corresponding xanthate. In order to avoid benzoyl migration, the xanthate was formed by generation of the anion of **37** with sodium hexamethyldisilazane in the presence of carbon disulfide, followed by addition of methyl iodide. Barton deoxygenation[36] afforded the deoxy tribenzoate derivative **38**[38] in 80% yield. The latter was converted to the corresponding acetate **39** by reaction with acetic anhydride and boron trifluoride etherate. Koenigs–Knorr coupling of **39** with tryptophol **12**, via the bromide, yielded exclusively β-anomer **40**. Methanolysis of the benzoate groups followed by primary hydroxyl silylation afforded diol **42**. Benzylation of the two remaining hydroxyls and desilylation gave **44**. Attempts to generate the C-6 triflate of **44** led, however, to undesired elimination products. This was not entirely unexpected since the C-5 proton of **44** is more accessible than the corresponding protons of the analogous intermediates in the syntheses of **4** and **5**.

To circumvent this problem, the phthalimidopentyl triflate used previously (Scheme IV) could be efficiently coupled with **44** in the presence of sodium hydride in dichloromethane to provide the protected intermediate **45** in 76% yield. Reaction of **45** with sodium methoxide in methanol at reflux removed both the phthaloyl and benzenesulfonyl groups to yield the desired 4-deoxy compound **7** (Scheme V).

The des-tryptophol analogue **8** was synthesized in three steps from methyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**46**)[39] by a procedure analogous to that described for the preparation of **4** and **5** (Scheme VI). Here again, conversion to the triflate and coupling with the presumed dianion of 5-trifluoroacetamido-1-pentanol (**18a**) afforded **47b**, whereupon base-mediated deprotection gave **8b** in 72% yield. The desired analog **8a** could be prepared as shown in Scheme VI.

The des-aminopentane analogue **9** was prepared by removal of the indole protecting group from **17** with aqueous sodium hydroxide in ethanol at reflux (Scheme VII).

(33) This is an improvement on a much lower-yielding procedure: RajanBabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522.

(34) Blackburne, I. D.; Fredericks, P. M.; Buthrie, R. D. *Aust. J. Chem.* **1976**, *29*, 381.

(35) Danishefsky, S. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

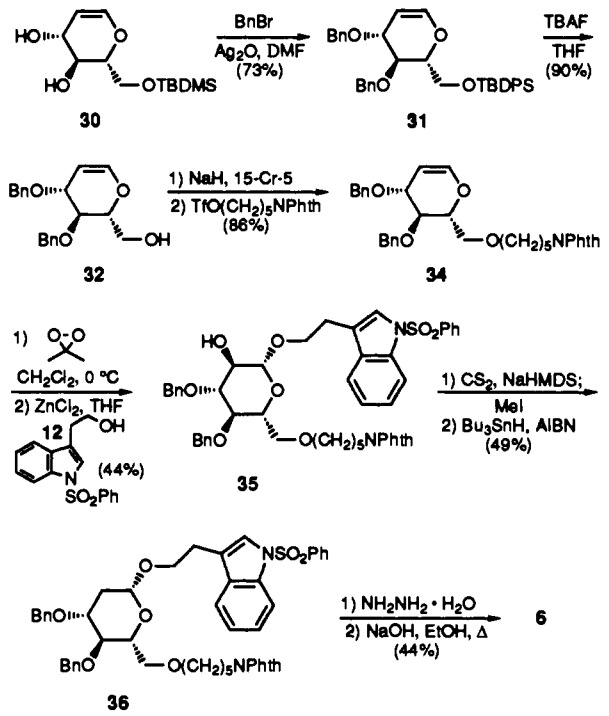
(36) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans 1* **1975**, 1574.

(37) Williams, J. M.; Richardson, A. C. *Tetrahedron* **1967**, *23*, 1369.

(38) Street, I. P.; Armstrong, C. R.; Withers, S. G. *Biochemistry* **1986**, *25*, 6021.

(39) Bhattacharjee, S. S.; Gorin, P. A. J. *Can. J. Chem.* **1969**, *47*, 1195. Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990.

Scheme IV



Compound **10**, which is based on the 4-deoxy scaffold and lacks also the indole functionality, was elaborated from methyl β-D-glucopyranoside (**48**) (Scheme VIII). Selective acetonide formation gave **49** which underwent benzylation to afford the dibenzyl ether (**50**). Deprotection of the acetonide with acidic Amberlyst 15 ion exchange resin gave diol **51** which could be selectively protected at the primary hydroxyl to furnish silyl ether **52**. Barton deoxygenation then gave the 4-deoxy derivative (**53**). Desilylation of **53**, affording alcohol **54**, was followed by coupling with the phthalimidoltriflate of 5-amino-1-pentanol to give phthalimide **55** in 89% yield. Liberation of the free amine using sodium methoxide in methanol at reflux then afforded **10** in 75% yield.

Biological Results

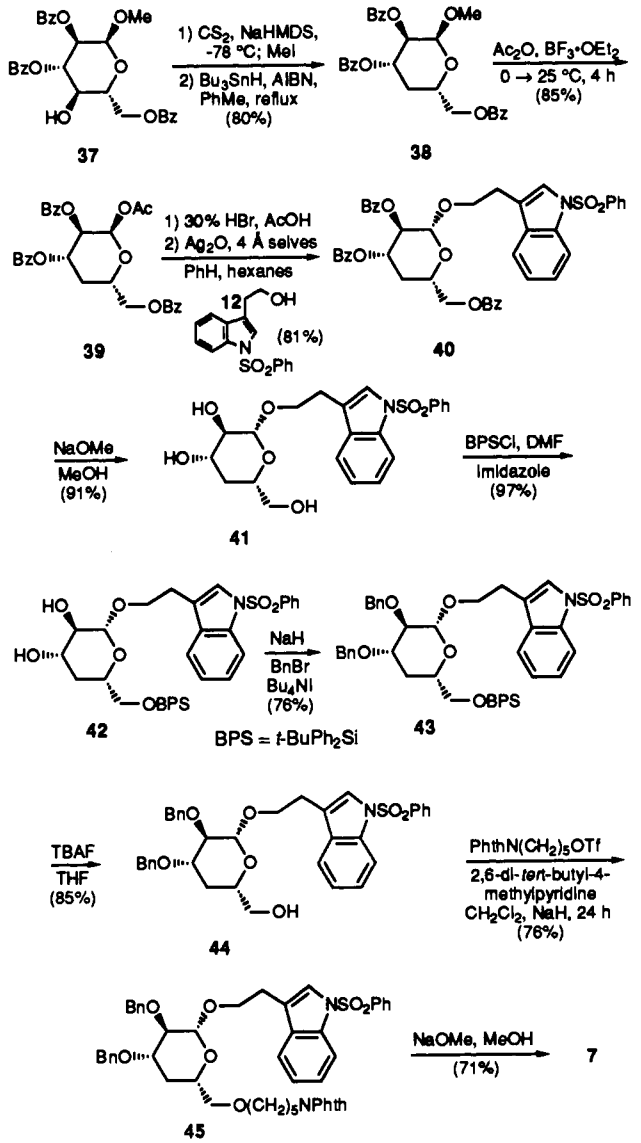
Binding Assays. The carbohydrate peptidomimetics **4e–9**, **5c–d**, **8b**, and **9** were initially tested *in vitro* at the University of Pennsylvania[1a,29] on membranes from a subclone of the AtT-20 cell line (AtT-20/D16-16v) using [^{125}I]CGP 23996 (des-Ala^1, Gly^2-desamino-Cys^3[Tyr^{11}]dicarba^{3,4}-somatostatin) as the ligand. Binding studies on pituitary and cerebral cortex membranes gave similar IC_{50} values.[1a,29] Later on, selected compounds and all subsequently prepared analogs were tested at Panlabs, Inc. where ^{125}I-Tyr^{11}-SRIF was employed as the radio ligand and a different subclone of the AtT-20 cell line (AtT-20/D16) was used (Table I).

Discussion

The designed mimetic **4a** bound in a dose-dependent manner to the SRIF receptor (IC_{50} 15 μM, ^{125}I-Tyr^{11}-SRIF ligand). Interestingly, the C-6 side-chain isomer **4e**, the first mimetic synthesized, also bound to the SRIF receptor in a dose-dependent manner with an IC_{50} of 9.5 μM, using ^{125}I-CGP-23996 as a radiolabeled ligand (Table I).[1,29] This was an encouraging result given the novelty of the design. Furthermore, the 3-deoxy analog **5c**, which lacks the unnecessary benzyloxy group at C-3, was found to be almost an order of magnitude more potent than **4e** (1.3 μM) in displacing ^{125}I-CGP-23996 binding to membranes from AtT-20/D16-16v cells.[1,29] Subsequently IC_{50} values of 14 and 10 μM were obtained for **4e** and **5c**, respectively, when ^{125}I-Tyr^{11}-SRIF was used as the ligand and a different subclone (AtT-20/D16) of the cell line was employed. Independently, Papageorgiou and co-workers[40] reported an IC_{50} of 16 μM with our compound **5c**, using rat cortex membranes with ^{125}I-Tyr^3-octreotide as radiolabelled ligand. The differing affinities of **5c** obtained by the three laboratories may reflect the use of three different radioligands which may differ in affinity for SRIF receptor subtypes.[41] In addition, the particular receptors employed by the three laboratories may also reflect differing SRIF receptor populations. As Table I indicates, overall the agreement in the observed binding affinities between laboratories was excellent.

It is noteworthy that we have consistently found the cyclic hexapeptides L-363 301 (**3**) and MK-678 to have a lower binding affinity than SRIF in these assays,[42,1a] whereas they were more potent than SRIF in inhibiting GH, insulin, and glucagon release in vivo and in inhibiting GH release *in vitro*.[5a] Diverse receptor subtypes may also explain this unexpected divergence between the relative binding affinities of these three peptides on the one hand and their *in vivo* and *in vitro* potencies on the other.

Scheme V

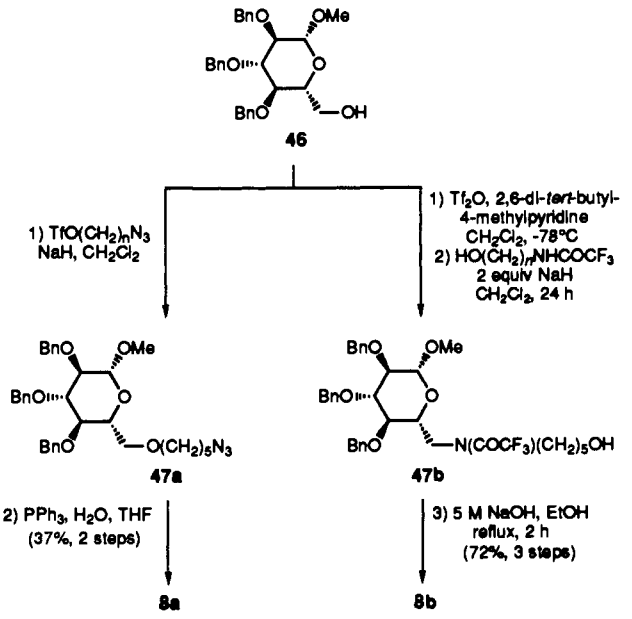


(40) Papageorgiou, C.; Haltiner, R.; Bruns, C.; Petcher, T. J. *Biorg. Med. Chem. Lett.* **1992**, *2*, 135.

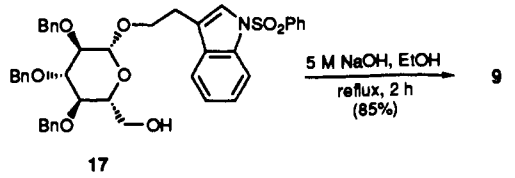
(41) Sreedharan, S. P.; Kodama, K. T.; Peterson, K. E.; Goetzl, E. J. *J. Biol. Chem.* **1989**, *264*, 949. He, H.-T.; Johnson, K.; Thermos, K.; Reisine, T. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 1480. Kimura, N.; Hayafuji, C.; Kimura, N. *J. Biol. Chem.* **1989**, *264*, 7033. Rens-Domiano, S.; Law, S. F.; Yamada, Y.; Seino, S.; Bell, G. I.; Reisine, T. *Mol. Pharmacol.* **1992**, *42*, 28.

(42) Reisine, T. University of Pennsylvania, unpublished results.

Scheme VI



Scheme VII



Importantly, in a functional assay compound **5c** was found to inhibit GRF-induced GH release by cultured rat anterior pituitary cells with an IC_{50} of 3 μM (Figure 2a); thus **5c** is an SRIF agonist, albeit a weak one, at its pituitary receptor.[1b,29] Subsequently, **5a** was also found to be an SRIF agonist.[43] That **5a** and **5c** both acted as SRIF agonists strongly suggests that the binding is specific and that the SRIF receptor recognizes the molecules as SRIF mimetics. This is the most significant evidence supporting the relevance of the design. This agonism runs counter to the prevailing opinion that designed peptidomimetics with novel scaffolding are unlikely to achieve the degree of fit required for agonism at the endocrine receptor (see however ref 12). For **5c**, the maximum level of inhibition of stimulated GH release (found at 50 μM) was only about half that seen with an optimal level of SRIF, suggesting the possibility that **5c** is a partial agonist. Indeed, Figure 2b shows that at high concentrations of SRIF in the presence of a constant concentration (5 μM) of **5c**, the latter decreases SRIF-induced inhibition of stimulated GH release, which is consistent with partial agonism. This would be noteworthy because no compound, peptidal or non-peptidal, has been described which displays antagonism at the SRIF receptor.[44] There is, however, an alternative explanation for the results revealed in Figure 2, that **5c** is an SRIF agonist which in addition stimulates GH release by a mechanism which is not blocked by SRIF.[45] This alternative, which would be equally noteworthy, is now being investigated.

Further evidence supporting the relevance of the design stems from the similarities between the SARs of the pyranosides and those of the corresponding cyclic hexapeptides. As shown in Figure 3, the effects of side-chain modifications on potency with **3** strikingly parallel the effects on the binding affinities of the corresponding changes on **5a**.

That compound **9** does not bind to the SRIF receptor is consistent with the known importance of the Lys^9 side chain of SRIF.[47] Probing the length of the Lys^9-mimicking side chain revealed that upon increasing the length of the linker from 5 to 6 methylenes, the effect on binding depended somewhat on the presence or absence of a 3-substituent. However, shortening this chain to four methylenes reduced the affinity.

(43) Cheng, K.; Smith, R. G. Merck Research Laboratories, private communication.
(44) Brown, P. J.; Schonbrann, A. *J. Biol. Chem.* **1993**, *268*, 6668.
(45) The authors are indebted to Dr. Paul S. Anderson (Merck Research Laboratories) for suggesting this possibility. See: Smith, R. G.; Cheng, K.; Schoen, W. R.; Pong, S.-S.; Hickey, G.; Jacks, T.; Butler, B.; Chan, W. W.-S.; Chaung, L.-Y. P.; Judith, F.; Taylor, J.; Wyvratt, M. J.; Fisher, M. H. *Science* **1993**, *260*, 1643 and references cited therein.

Scheme VIII

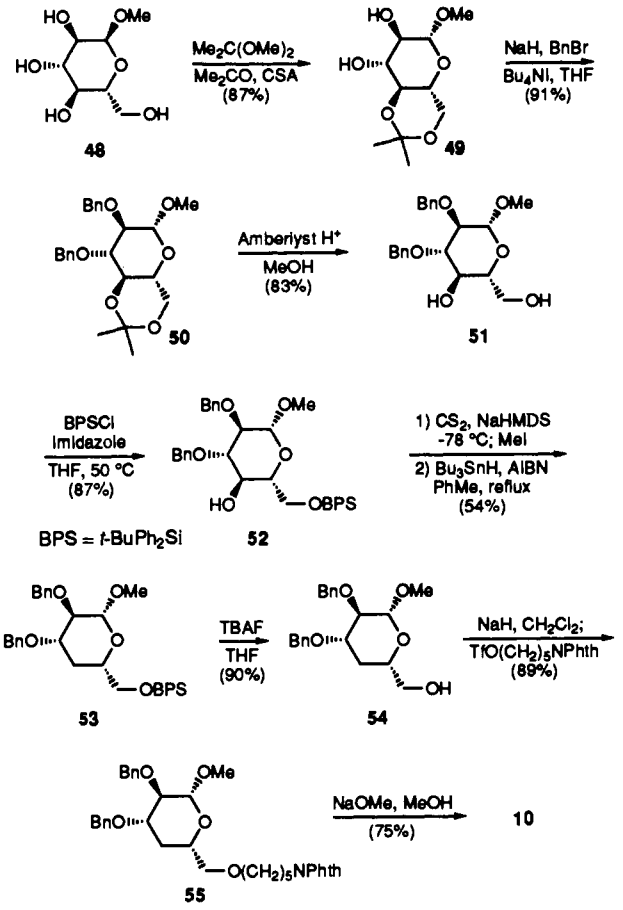


Table I. *In Vitro* SRIF Binding Affinities of Selected Peptides and Peptidomimetics **4–10**

peptide				$IC_{50}^a(IC_{50}^b)$ μM	
2 (SRIF)				0.00083 (0.0093)	
3 (L-363,301)				NT (0.019)	
MK-678[c]				0.0023	
N-Ac-MK-678				0.05	
sugar analog				$IC_{50}^a(IC_{50}^b)$ μM	
O-linked	N-linked	*n*	R	O-linked	N-linked
4a	**4e**	5	H	15.0	14.0 (9.5)
4b	**4f**	4	H	NT	NT [d]
4c	**4g**	6	H	11.0	5.1
4d		5	Ac	*e*	
5a	**5c**	5	H	8.4	10.0 (1.3)[f]
5b	**5d**	6	H	6.6	34.0
6		5	H	35.0	
7		5	H	47.0	
8a	**8b**	5	H	5.9	54.0 (4.2)
9				NT (*g*)	
10		5	H	*e*	

[a] ^{125}I-Tyr^{11}-SRIF. [b] ^{125}I-CGP-23996. [c] *c*-(*N*-Me-Ala-Tyr-D-Trp-Lys-Val-Phe). [d] Lower affinity than that of **4e** at a concentration of 2×10^{-5} M; dose-response curve not obtained. [e] <20% at 10^{-4} M. [f] 1.6×10^{-5} M using ^{125}I-Tyr^3-octreotide on rat cortex membranes.[40] [g] 0% at 10^{-5} M.

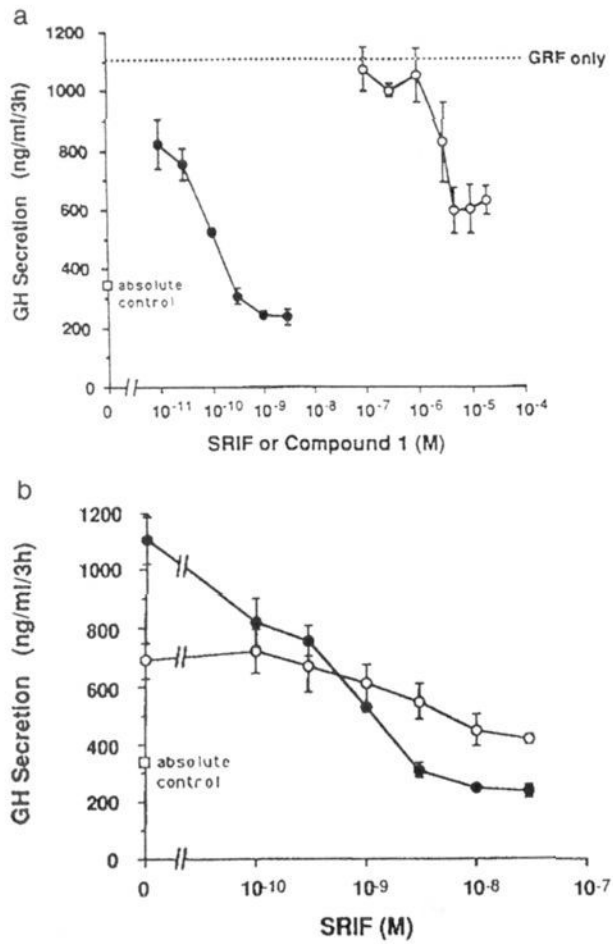
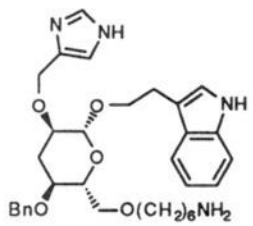


Figure 2. Functional assay: (a) The effect of SRIF (●) and **5c** (○) on GH secretion stimulated by a constant amount of (1 nM) of GRF.[46] (b) The effect of SRIF on the inhibition of GH secretion induced by a constant dose (1 nM) of GRF in the presence (○) and absence (●) of a constant concentration (*5 μM*) of **5c**.[46]

Subsequent to the submission and review of this paper, we synthesized **56** containing an imidazole functionality at the 2-position, partly in an effort to improve water solubility and also because it was known that the His[7]-analog of **3** displayed a 1.6-fold increase in potency.[48] Indeed the binding affinity of **56** to the SRIF receptor using ^{125}I-Tyr^{11}-SRIF as the radio ligand was 1.9 μM, the best to date in this protocol, providing further striking



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parallelism between the SARs of our sugars and the peptides.

It has been suggested that the 2-benzyloxy group of our compounds **4** and **5** mimics Phe[6] of SRIF and that the 4-benzyloxy group mimics Phe[11] of SRIF.[49] However, we believe that the 2-benzyloxy group of **4a** mimics Phe[7] and the 4-benzyloxy group mimics Phe[8] of the cyclic hexapeptide **3**. This interpretation is also consistent with the fact that **56** has a higher affinity for the SRIF receptor than **5a**. Moreover, the binding affinities of the 2- and 4-deoxy analogs are instructive. If the 2-benzyloxy group of **4** and **5** mimicked Phe[6] of SRIF itself, then deletion of this group would be expected to lead to complete loss of binding affinity, because Ala[6][SRIF] reportedly has <1% of the activity of SRIF.[18] In fact, the 2-deoxy analog **6** has an IC_{50} of 35 μM (i.e., **4a** is only 2.3-fold more potent than **6**). The observed binding affinity of **6** is, however, not unreasonable if the C-2 benzyl substituent mimics Phe[7] of **5** since Ala[7][SRIF] retains 3% of the potency of SRIF.[18] Similarly, the 4-deoxy analog **7** had an IC_{50} of 47 μM (*i.e., its affinity was about one-third that of* **4a**), *not* inconsistent with the retention of activity when Phe[8] of the cyclic hexapeptide **3** is replaced by Ala, albeit with a 23-fold decrease

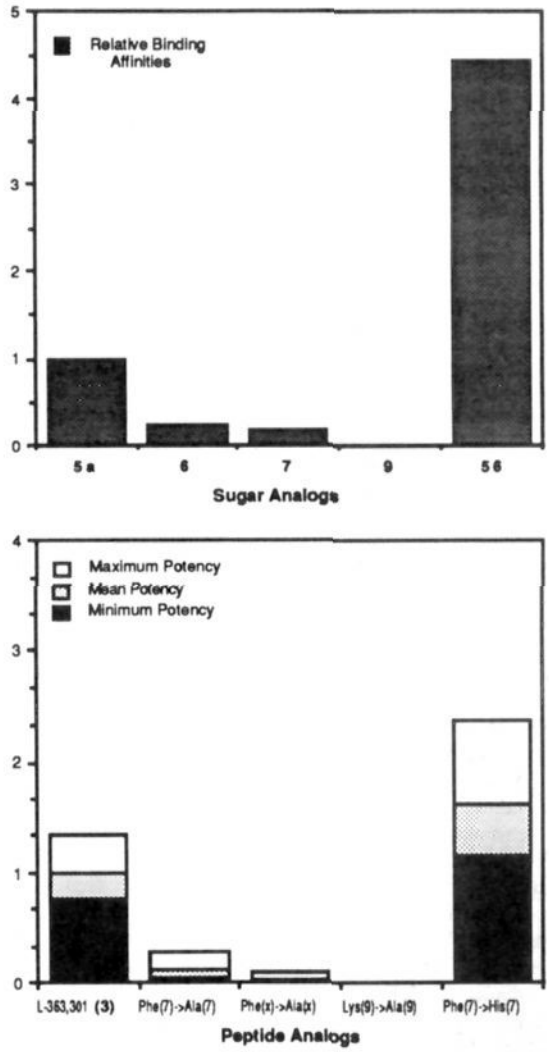

Figure 3. *Comparison of relative binding affinities (AtT-20 membranes,* ^{125}I-Tyr^{11}-SRIF radio label) of sugars vs potencies[48] (GH release inhibition in vitro) of the corresponding peptides (see text).

(46) Details of the procedure are provided in the Experimental Section, also see: (a) Vale, W.; Rivier, J.; Ling, N.; Brown, M. *Metabolism* **1978**, *27*, 1391. (b) Vale, W.; Vaughan, J.; Jolley, D.; Yamamoto, G.; Bruhn, T.; Seifert, H.; Perrin, M.; Thorner, M.; Rivier, J. In *Methods in Enzymology: Hormone Action: Neuroendocrine Peptides*; Conn, P. M., Ed.; Academic: Orlando, 1986; p 389.

(47) Nutt, R. F.; Veber, D. F.; Curley, P. E.; Saperstein, R.; Hirschmann, R. *Int. J. Peptide Protein Res.* **1983**, *21*, 66 and references cited therein.

(48) Nutt, R. F.; Veber, D. F. Merck Research Laboratories, private communication.

(49) After an abstract of part of this work was presented, Papageorgiou et al. (Sandoz)[41] proposed, based on their independent findings, that the C-2 benzyl group of **5c** was not correctly oriented to mimic the Phe7 residue of somatostatin. The results presented here suggest otherwise. It should be pointed out that our modeling hypothesis, unlike that of Sandoz, is based not on the bioactive conformation of the flexible peptide hormone itself, which is replete with uncertainty, but on the conformation of the relatively inflexible cyclic hexapeptide L-363,301, which is well established by solution NMR, molecular modeling, and SARs.

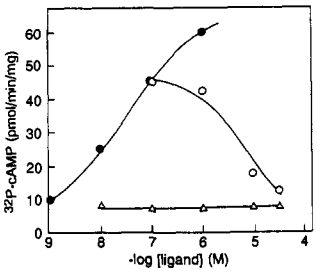

Figure 4. β_2-Adrenergic receptor functional assay: effect of isoproterenol (●) and **5c** (△) on adenylate cyclase induced c-AMP formation; inhibition by **5c** of isoproterenol-induced c-AMP formation (○).[53]

in potency. If the 4-benzyloxy group mimicked Phe[11] of SRIF, no loss of binding affinity would be expected, since Phe[11] is believed to be important to binding only indirectly by stabilizing the bioactive conformation of SRIF (evidence for this, as pointed out earlier, comes from a highly active bicyclic analog of SRIF wherein a cystine bridge replaced both Phe[6] and Phe[11], thereby stabilizing the bioactive conformation).[15] Thus, comparison of the deoxy analog binding affinities with those of the relevant peptides suggests that the substituents of compounds **4** and **5** mimic the interactions that were intended.

Among the analogs of the lead compound **4a**, only mimetics **8a** and **8b**, in which the Trp[8]-mimicking side chain has been replaced by a methoxy substituent, gave binding affinities to the SRIF receptor which were at variance with our expectations. Compound **8a** binds to the AtT-20 cells with an IC_{50} of 5.9 μM, and **8b** binds to the AtT-20 cells with IC_{50}s of 51 and 4.2 μM, depending on the cell subclone and the radioligand employed. We had not expected this analog to bind at all because [Ala[8]]-SRIF reportedly has less than 1% of the activity of SRIF as an agonist.[18] Importantly, we found that the latter peptide did not bind to the SRIF receptor (i.e., it is not an SRIF antagonist). A possible explanation for the unexpected binding of **8a** and **8b** is that the 4-benzyloxy substituent can attain proximity to the lysine side chain, mimicking the role of Trp[8] in SRIF, in which close proximity of Trp[8] to Lys[9] is thought to be a feature of the bioactive conformation.[50] To test this tentative hypothesis, we synthesized **10**, lacking both the indole and the 4-benzyloxy substituents. This compound, indeed, does not bind to the SRIF receptor.[51] These results may suggest that the indole side chain in **4a–g** and **5a–d**—unlike the tryptophan residue in the peptides—may contribute very little to binding.

It has generally been assumed that the free primary amino group of Lys[9] is required for peptides to activate the SRIF receptor.[18,47] We were therefore surprised to find that the *N*-acetyl analogue of MK-678[52] (seglitide), which we synthesized as a control compound, did bind to the SRIF receptor, although with an affinity 1/20 that of MK-678. Importantly, this peptide proved to be an SRIF agonist in a functional assay demonstrating that a free primary amino group is not required either for binding or receptor activation. This result makes the SRIF agonism of **4e** and **5c** less surprising. Acetylation of the amino group of **4a** to afford **4d** likewise resulted in a reduction of binding affinity, generating in this case a compound that does not bind at 10^{-4} μM.

We have previously reported that **4e** and **5c** bind to the β_2-adrenergic receptor, albeit weakly.[1,29] In a functional assay, **5c** proved to be a β_2-adrenergic receptor antagonist (Figure 4). The *N*-acetyl compound **4d**, unlike **4e** and **5c**, did not bind to the β_2-adrenergic receptor. Both **4a** and **5a** also bind weakly to the β_2-adrenergic receptor (IC_{50}s 90 and 500 μM, respectively), and **5a** is a pure antagonist in a functional assay. We also reported earlier that **4e** and **5c** bind to the NK-1 (SP) receptor (IC_{50} 120 and 180 nM, respectively).[1,29] We have subsequently discovered that analogs **4a** and **5a** bind with similar affinities (IC_{50} 150 and 500 nM, respectively).

Several results indicate that the design of **5a** was not optimal. These include the relatively weak binding affinities, the absence of shielding by the indole side chain of the lysine side chain in the NMR,[15b] the binding of analogs **8a** and **8b** possibly indicating that the indole side chain may not be optimally oriented, and the observation that a conformational search[52b] revealed that the lowest energy structures had conformations very different from those which overlap best with L-363,301 (**3**). The conformation associated with these low-energy structures is consistent with the concept of hydrophobic collapse proposed by Rich.[54] Therefore our future efforts to increase the binding affinity will focus partly on preventing hydrophobic collapse and partly on optimizing the geometry of the existing side chains.

Conclusion

We have described the design, synthesis, and biological properties of compounds **4a** and **5a**, *de novo*-designed peptidomimetics embodying a novel scaffolding. These compounds bind to the SRIF receptor in a dose-dependent manner, with affinity in the μM range. The original design hypotheses are supported by systematic deletion and modification of each of the side chains postulated to be involved in binding and most notably by the fact that **5a** can act as an SRIF agonist. Further, our results confirm that hydrogen bonding to the peptide backbone is not required for either binding to or activation of the SRIF receptor. Finally, we have shown that only three of the four side chains of the β-turn of SRIF are required for binding and receptor activation. Taken together, the results reported herein, and those relating to the binding of several of our sugars at the SP receptor,[1] support the validity of the concept of designed non-peptide scaffolding and also demonstrate that non-peptidal peptidomimetics can provide unexpected biological information not previously available from the natural ligands, their peptidal analogs, or amide surrogates.

Experimental Section[55,56]

***N*-(Phenylsulfonyl)tryptophol (12). (a) (1) 1-*O*-*tert*-Butyldimethylsilyl 2-(3-Indolyl)ethanol.** A solution of trytophol (5.0 g, 31 mmol) in DMF (30 mL) was treated with imidazole (4.64 g, 68 mmol) and cooled to 0 °C. *tert*-Butyldimethylsilyl chloride (5.14 g, 34.1 mmol) was added, and the mixture stirred at room temperature for 16 h. The mixture was then diluted with ethyl acetate (100 mL) and washed with water (2 × 100 mL), and the aqueous solutions were extracted with ethyl acetate (200 mL). The combined organic layers were dried over sodium sulfate, filtered,

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(51) In functional assays[48] similar to those performed with **5c**, both **8b** and **56** also proved to be SRIF agonists; however, **56** was more potent than either **5c** or **8b**.

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(55) **Materials and Methods.** Reactions were carried out in flame-dried glassware under an argon atmosphere, unless otherwise noted. Ether and THF were distilled from sodium and benzophenone. Acetonitrile, benzene, and dichloromethane were distilled from calcium hydride. Dimethylformamide was dried over barium oxide and distilled. All other solvents were HPLC grade. Analytical thin-layer chromatography was performed on E. Merck 0.25-mm precoated silica gel plates. Merck 60–200 mesh silica gel was used for flash column chromatography. ^1H and ^{13}C NMR spectra were obtained with a Brucker AM500 spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane (δ = 0) for proton spectra and relative to chloroform-*d* (δ = 77.0), acetone-d_6 (δ = 29.8), or methanol-d_4 (δ = 49.0) for carbon spectra. Coupling constants are given in hertz. Melting points were recorded on a Thomas Hoover Uni-Melt apparatus and are corrected. Infrared spectra were determined using a Perkin-Elmer 781 spectrophotometer. High-resolution mass spectra were measured on a VG 70/70 Micromass or VG ZAB-E spectrometer. Microanalyses were performed by Robertson Microlit Laboratories Inc., Madison, NJ. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter.

(56) Complete spectral details are available as supplementary material.

and concentrated *in vacuo*. Flash chromatography (30% ether/petroleum ether) gave the title compound (8.43 g, 99% yield) as a colorless oil: ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.08, 127.62, 122.08, 121.75, 119.12, 118.79, 112.84, 111.04, 63.89, 28.98, 25.98, 18.34, -5.29; high-resolution mass spectrum (CI, NH_3) m/z 276.1750 [$(M + H)^+$; calcd for $C_{16}H_{25}NOSi$ 276.1783].

(b) 1-(*O*-*tert*-Butyldimethylsilyl)-2-[3-(1-*N*-phenylsulfonyl)indolyl]-ethanol. A suspension of sodium hydride (1.91 g, 60% oil dispersion) in dry DMF (64 mL) was cooled to 0 °C and a solution of 1-(*O*-*tert*-butyldimethylsilyl)-2-(3-indolyl)ethanol (8.43 g, 30.6 mmol) in DMF (30 mL) was added. The mixture was stirred at room temperature for 30 min, recooled to 0 °C, and treated dropwise with benzenesulfonyl chloride (5.30 mL, 39.7 mmol). The reaction was then stirred at room temperature for 16 h, quenched with saturated aqueous ammonium chloride (100 mL), and extracted with ether (3 × 200 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (30% ether/petroleum ether) afforded the title compound (7.37 g, 79% yield) as a colorless oil: ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.10, 133.55, 131.21, 129.12, 126.65, 124.56, 123.42, 122.00, 120.31, 119.57, 113.59, 62.51, 28.51, 25.87, 18.22, -5.44; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) m/z 433.1920 [$(M + NH_4)^+$; calcd for $C_{22}H_{29}NSO_3Si$ 433.1971].

(c) *N*-(Phenylsulfonyl)tryptophol (12). Tetrabutylammonium fluoride (21 mL, 1 M in THF) was added to a solution of 1-(*O*-*tert*-butyldimethylsilyl)-2-[3-(1-*N*-phenylsulfonyl)indolyl]ethanol (6.6 g, 22 mmol) in THF (100 mL), and the reaction stirred at room temperature for 16 h. The mixture was then diluted with ethyl acetate (100 mL) and extracted with water (2 × 100 mL). The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (40% ethyl acetate/petroleum ether) furnished **11** (4.00 g, 84% yield) as a pale yellow oil which crystallized upon standing: mp 63–64 °C; ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.79, 134.99, 133.55, 130.78, 129.00, 126.43, 124.63, 123.39, 123.05, 119.67, 119.38, 61.40, 28.07; high-resolution mass spectrum (CI, NH_3) m/z 301.0748 (M^+; calcd for $C_{16}H_{15}NO_3S$ 301.0772).

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (13). A solution of **12** (537 mg, 1.78 mmol) in dry benzene (3 mL) was added to a suspension of powdered, activated 4 Å molecular sieves (0.89 g) and silver(I) oxide (412 mg, 17.8 mmol) in dry hexane (9 mL) at room temperature. A solution of bromide **11**[25] (804 mg, 1.95 mmol) in dry benzene (3 mL) was then added, the flask was covered with aluminum foil, and the mixture allowed to stir for 2 days at room temperature. More silver(I) oxide (206 mg, 8.9 mmol) and benzene (1 mL) were added, and the reaction was stirred at room temperature for an additional 2 days. After filtration through Celite, concentration *in vacuo* and recrystallization (ethyl acetate/petroleum ether) afforded pure **13** (580 mg) as a white solid. Concentration of the filtrate *in vacuo* and flash chromatography (5% ether/dichloromethane) afforded **13** admixed with the α anomer and the corresponding ortho ester. Further flash chromatography (70% ether/petroleum ether) then gave an additional 134 mg of pure **13** (64% total yield): mp 145–146 °C; $[\alpha]^{25}_D$ -16° (*c* 0.14, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.66, 170.24, 169.34, 138.24, 135.08, 133.70, 130.94, 129.22, 126.73, 124.75, 123.56, 123.21, 119.57, 119.42, 113.65, 106.61, 100.70, 72.87, 71.16, 68.75, 68.39, 61.91, 25.31, 20.72, 20.57, 20.43; high-resolution mass spectrum (CI, NH_3) m/z 649.2021 [$(M + NH_4)^+$; calcd for $C_{30}H_{33}NO_{12}S$ 649.2054]. Anal. Calcd for $C_{30}H_{33}NO_{12}S$: C, 57.04; H, 5.27. Found: C, 56.75; H, 5.30.

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl β-D-Glucopyranoside (14). Sodium methoxide (221 mg, 4.09 mmol) was added to a suspension of **13** (3.22 g, 5.12 mmol) in methanol (26 mL) at room temperature. After 20 min, the resultant solution was diluted with methanol (26 mL) and neutralized with Amberlyst 15 ion exchange resin. The resin was quickly removed by filtration to avoid formation of the methyl glucoside. Concentration and flash chromatography (5:1:1 dichloromethane/methanol/acetone) afforded **13** (2.09, 88% yield) as a white foam: $[\alpha]^{25}_D$ -23° (*c* 0.09, acetonitrile); ^{13}C NMR (125 MHz, acetone-d_6) δ 139.40, 136.57, 134.87, 132.21, 130.31, 127.67, 125.41, 125.30, 124.07, 121.33, 120.56, 114.35, 104.07, 78.07, 77.53, 74.93, 71.73, 68.76, 63.00, 49.72, 25.92; high-resolution mass spectrum (CI, NH_3) m/z 481.1656 [$(M + NH_4)^+$; calcd for $C_{22}H_{25}NO_8S$ 481.1634].

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 6-*O*-*tert*-Butyldiphenylsilyl-β-D-glucopyranoside (15). At room temperature a stirred solution of **14** (7.11 g, 15.4 mmol) in dry DMF (51 mL) was treated with imidazole (2.93 g, 43.1 mmol) followed by *tert*-butyldiphenylsilyl chloride (5.58 g, 21.6 mmol). The solution was heated at 50 °C for 24 h. After concentration *in vacuo*, the mixture was diluted with ethyl acetate (250 mL) and washed with water (100 mL). The organic phase was then washed with brine (100 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (5% methanol/dichloromethane) provided pure **15** (9.15 g, 85% yield) as a white foam: $[\alpha]^{25}_D$ -26° (*c* 0.14, acetonitrile); ^{13}C NMR (125 MHz, acetone-d_6) δ 206.17, 138.97, 136.39, 136.30, 135.95, 134.83, 134.60, 134.47, 132.13, 130.45, 130.41, 130.26, 128.47, 127.59, 125.40, 125.01, 124.04, 121.24, 120.60, 114.31, 104.11, 78.17, 77.76, 74.94, 71.14, 68.93, 64.72, 27.12, 26.10, 19.82; high-resolution mass spectrum (CI, NH_3) m/z 684.2532 [$(M - OH)^+$; calcd for $C_{38}H_{43}NO_8SSi$: 684.2449]. Anal. Calcd for $C_{38}H_{43}NO_8SSi$: C, 65.03; H, 6.18. Found: C, 64.96; H, 6.28.

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-β-D-glucopyranoside (16). A solution of **15** (1.62 g, 2.31 mmol) in THF (7 mL) was added to a stirred suspension of sodium hydride (323 mg, 60% oil dispersion, 8.08 mmol) in THF (5 mL) at 0 °C. After the mixture was stirred for 1 h at room temperature and recooled to 0 °C, benzyl bromide (1.09 mL, 9.24 mmol) was added dropwise followed by tetrabutylammonium iodide (85 mg, 0.23 mmol). The reaction was then allowed to stir for 3 days at room temperature. The resultant suspension was diluted with saturated aqueous ammonium chloride (3 mL) at 0 °C and extracted with ether (2 × 80 mL). The combined extracts were washed with saturated aqueous ammonium chloride (30 mL) and brine (30 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (20% ether/petroleum ether) afforded **16** (1.66 g, 74% yield) as a white foam: $[\alpha]^{25}_D$ -7.0° (*c* 0.12, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.58, 138.47, 138.32, 138.19, 135.83, 135.35, 135.23, 133.64, 133.58, 133.18, 130.96, 129.60, 129.13, 128.39, 128.30, 127.97, 127.90, 127.72, 127.66, 127.55, 127.51, 126.63, 124.77, 123.38, 123.16, 119.74, 119.57, 113.71, 103.62, 84.71, 82.55, 77.66, 75.81, 75.79, 75.10, 74.80, 68.53, 62.80, 26.78, 25.90, 19.29; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) m/z 972.4071 [$(M + H)^+$; calcd for $C_{59}H_{61}NO_8SSi$ 972.3970].

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-β-D-glucopyranoside (17). Tetrabutylammonium fluoride (1 M in THF, 2.4 mL, 2.4 mmol) was added to a stirred solution of **16** (1.55 g, 1.60 mmol) in THF (8 mL) at room temperature. After 7 h the reaction mixture was diluted with ethyl acetate (70 mL), washed with water (30 mL) and brine (30 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (30% ethyl acetate/petroleum ether) afforded **17** (1.10 g, 94% yield) as a clear oil: $[\alpha]^{25}_D$ -13° (*c* 0.14, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.48, 138.21, 138.13, 137.95, 135.09, 133.60, 130.92, 129.10, 128.40, 128.30, 128.25, 128.22, 127.98, 127.90, 127.82, 127.76, 127.55, 126.58, 124.72, 123.57, 123.12, 119.61, 119.31, 113.66, 103.59, 84.39, 82.25, 77.37, 75.56, 75.16, 74.99, 74.75, 68.60, 61.77, 25.57; high-resolution mass spectrum (CI, NH_3) m/z 734.2743 [$(M + H)^+$; calcd for $C_{43}H_{43}NO_8S$ 734.2774]. Anal. Calcd for $C_{43}H_{43}NO_8S$: C, 70.37; H, 5.91. Found: C, 70.30; H, 6.08.

2-(*N*-Phenylsulfonylindol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-6-O-(5-azidopentyl)-β-D-glucopyranoside (19a). Sodium azide (19.0 g, 292 mmol) was added to a stirred solution of 5-bromo-1-pentanol (8.6 g, 51 mmol) in DMSO (160 mL). The resultant mixture was stirred at room temperature for 2.5 h, diluted with water (100 mL), and extracted with diethyl ether (2 × 100 mL). The combined organic solutions were washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered through a plug of silica gel, and concentrated *in vacuo* to afford the azide (5.1 g, 75% yield) as a light yellow oil.

A stirred solution of above 5-azido-1-pentanol (280 mg, 2.17 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (441 mg, 2.17 mmol) in dichloromethane (9 mL) was treated dropwise with triflic anhydride (0.36 mL, 2.17 mmol). After 10 min the mixture was poured into brine (40 mL) and extracted with dichloromethane (2 × 40 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resultant triflate was used without purification in the next step.

Sodium hydride (12.4 mg, 0.31 mmol, 60% dispersion in oil) was added to a solution of alcohol **17** (225 mg, 0.309 mmol) and crude azido triflate (161 mg, equivalent to 0.62 mmol) in dichloromethane (4 mL) at room temperature. The mixture was stirred for 24 h, diluted with dichloromethane (40 mL), and poured into saturated aqueous ammonium chloride (40 mL). The aqueous phase was extracted with dichloromethane (2 × 40 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash

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chromatography (15% ethyl acetate/hexane) furnished **19a** (248 mg, 95% yield) as a colorless oil: $[\alpha]^{25}_D$ +1.3° (*c* 0.48, $CHCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.56, 138.31, 138.28, 138.22, 135.18, 133.60, 130.96, 129.13, 128.42, 128.35, 128.28, 128.00, 127.85, 127.82, 127.77, 127.57, 127.51, 126.67, 124.74, 123.47, 123.11, 119.65, 119.44, 113.72, 103.74, 84.64, 82.25, 77.93, 75.66, 74.97, 74.90, 74.75, 71.40, 69.70, 68.76, 51.29, 29.18, 28.66, 25.71, 23.41; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 867.3532 [(M + Na)$^+$; calcd for $C_{48}H_{52}N_4O_8S$: 867.3403].

2-(1*H*-Indol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-(5-aminopentyl)-β-D-glucopyranoside (4a). A stirred solution of azide **19a** (31 mg, 0.037 mmol) in THF (2 mL) and water (0.032 mL, 0.58 mmol) was treated with triphenylphosphine (25 mg, 0.095 mmol). The mixture was heated at reflux for 2.5 h, cooled, and concentrated *in vacuo*. Flash chromatography (10% methanol/dichloromethane) furnished the corresponding amine (26 mg, 86% yield) as a colorless oil: $[\alpha]^{25}_D$ −1.5° (*c* 1.12, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 2920 (s), 2870 (s), 1505 (w), 1455 (s), 1370 (s), 1180 (s), 1125 (s), 1075 (s), 910 (w), 695 (m), 595 (m), 570 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 1 H), 7.89 (dd, *J* = 8.5, 0.9 Hz, 2 H), 7.39–7.21 (m, 22 H), 4.96 (d, *J* = 10.9 Hz, 1 H), 4.91 (d, *J* = 10.9 Hz, 1 H), 4.84 (d, *J* = 10.9 Hz, 1 H), 4.78 (d, *J* = 11.3 Hz, 1 H), 4.67 (d, *J* = 10.8 Hz, 1 H), 4.65 (d, *J* = 11.0 Hz, 1 H), 4.47 (d, *J* = 7.8 Hz, 1 H), 4.26 (dt, *J* = 9.5, 6.9 Hz, 1 H), 3.90 (dt, *J* = 9.5, 7.1 Hz, 1 H), 3.75–3.62 (m, 4 H), 3.56 (dt, *J* = 9.4, 6.5 Hz, 1 H), 3.49–3.44 (m, 3 H), 3.06 (t, *J* = 6.9 Hz, 2 H), 2.68 (t, *J* = 6.9 Hz, 2 H), 1.91 (br s, 2 H), 1.66–1.58 (m, 2 H), 1.50–1.34 (m, 4 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.49, 138.23, 138.14, 135.25, 133.56, 133.20, 132.08, 131.56, 131.90, 130.09, 129.08, 128.52, 128.32, 128.23, 127.93, 127.79, 127.52, 126.59, 124.67, 123.39, 123.06, 119.60, 119.40, 113.62, 103.65, 84.56, 82.17, 77.85, 75.60, 74.91, 74.80, 74.68, 71.56, 69.56, 68.68, 41.88, 33.18, 29.37, 25.63, 23.36; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 819.3687 [(M + H)$^+$; calcd for $C_{48}H_{54}N_2O_8S$: 819.3679].

The above amine (26 mg, 0.032 mmol) was dissolved in ethanol (4 mL) and treated with 5 M aqueous sodium hydroxide (0.65 mL). The resultant mixture was heated at reflux for 3 h, cooled, diluted with brine, and poured into dichloromethane (30 mL). The aqueous layer was extracted with dichloromethane (2 × 40 mL), and the combined organic solutions were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (10% methanol/dichloromethane) afforded **4a** (19.7 mg, 91% yield) as a colorless oil: $[\alpha]^{25}_D$ +13.3° (*c* 0.03, $CHCl_3$); IR ($CHCl_3$) 3009 (s), 2930 (m), 2860 (m), 1450 (w), 1360 (w), 1200 (s), 1062 (s), 920 (w), 690 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.75 (br s, 1 H), 7.59 (d, *J* = 7.9 Hz, 1 H), 7.38–7.24 (m, 16 H), 7.17 (t, *J* = 7.2 Hz, 1 H), 7.10 (t, *J* = 7.2 Hz, 1 H), 7.07 (s, 1 H), 4.93 (d, *J* = 10.9 Hz, 1 H), 4.89 (d, *J* = 11.0 Hz, 1 H), 4.85 (d, *J* = 11.0 Hz, 1 H), 4.80 (d, *J* = 10.9 Hz, 1 H), 4.71 (d, *J* = 11.0 Hz, 1 H), 4.57 (d, *J* = 11.0 Hz, 1 H), 4.48 (d, *J* = 7.8 Hz, 1 H), 4.18 (dt, *J* = 9.4, 7.1 Hz, 1 H), 3.88 (dt, *J* = 9.4, 7.1 Hz, 1 H), 3.68–3.64 (m, 2 H), 3.55–3.35 (m, 6 H), 3.12 (t, *J* = 7.1 Hz, 2 H), 2.43 (br t, *J* = 7.1 Hz, 2 H), 1.59–1.54 (m, 2 H), 1.52–1.45 (m, 2 H), 1.37–1.28 (m, 4 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.48, 138.20, 138.05, 136.14, 130.90, 128.97, 128.45, 128.37, 128.07, 127.88, 127.61, 127.40, 122.47, 121.87, 119.17, 118.64, 112.15, 111.44, 103.70, 84.62, 82.29, 77.88, 77.21, 75.68, 74.97, 74.79, 74.56, 71.03, 70.46, 69.51, 66.80, 29.69, 28.89, 28.64, 25.77, 22.95; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 701.3561 [(M + Na)$^+$; calcd for $C_{42}H_{50}N_2O_6$: 701.3567].

2-(1*H*-Indol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-(4-azidobutyl)-β-D-glucopyranoside (19b). Sodium azide (15.1 g, 270 mmol) was added to a stirred solution of 4-bromo-1-butanol (6.8 g, 44 mmol) in DMSO (110 mL). The resultant mixture was stirred at room temperature for 2.5 h, diluted with water (100 mL), and extracted with diethyl ether (2 × 100 mL). The combined organic solutions were washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered through a plug of silica gel, and concentrated *in vacuo* to afford the azide (3.6 g, 67% yield) as a light yellow oil.

Alcohol **17** (0.164 g, 0.223 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.06 g, 0.29 mmol) were dissolved in dichloromethane (5 mL) and triflic anhydride (0.041 mL, 0.246 mmol) was added dropwise. The mixture was stirred at room temperature for 10 min, diluted with dichloromethane (40 mL), and poured into brine (40 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated. The resultant white solid was redissolved in dichloromethane (3 mL) and treated sequentially with the above 4-azido-1-butanol (0.13 g, 1.21 mmol), sodium hydride (0.045 g, 1.13 mmol, 60% dispersion in oil), and 15-crown-5 (10 mg, 0.045 mmol). The mixture was then stirred for 24 h, diluted with dichloromethane (40 mL), and poured into saturated aqueous ammonium chloride (40 mL). The aqueous phase was extracted with dichloromethane (2 × 20 mL), and the combined organic solutions were washed with brine (40 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (15% ethyl acetate/hexane) gave **19b** (85.2 mg, 56% yield) as a colorless oil: $[\alpha]^{25}_D$ +10.2° (*c* 0.3, CH_2Cl_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.60, 138.56, 138.24, 136.17, 128.43, 128.28, 128.04, 127.90, 127.86, 127.78, 127.60, 127.53, 122.12, 121.96, 119.29, 118.73, 112.81, 111.10, 103.71, 84.70, 82.33, 77.99, 75.69, 74.97, 74.84, 74.69, 70.97, 70.05, 69.76, 51.29, 26.88, 25.84, 25.81; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 690.3438 [(M + H)$^+$; calcd for $C_{41}H_{46}N_4O_6$: 690.3417].

2-(1*H*-Indol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-(4-aminobutyl)-β-D-glucopyranoside (4b). A solution of azide **19b** (0.037 g, 0.056 mmol) in THF (3 mL) was treated sequentially with water (0.025 mL, 1.39 mmol) and triphenylphosphine (0.29 g, 0.11 mmol). The mixture was then heated at 60 °C for 6 h, cooled, and concentrated *in vacuo*. Flash chromatography (10% methanol/dichloromethane) gave **4b** (26.6 mg, 72% yield) as a colorless oil: $[\alpha]^{25}_D$ +8.4° (*c* 0.22, CH_2Cl_2); IR (CH_2Cl_2) 3700 (w), 3487 (m), 3028 (m), 3020 (m), 2918 (s), 2878 (s), 1608 (w), 1498 (w), 1277 (m), 1212 (m), 1072 (s), 1465 (s), 1371 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (br s, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.34–7.60 (m, 18 H), 7.09 (br s, 1 H), 4.92 (d, *J* = 10.9 Hz, 1 H), 4.86 (d, *J* = 10.9 Hz, 1 H), 4.83 (d, *J* = 11.0 Hz, 1 H), 4.79 (d, *J* 10.9 Hz, 1 H), 4.66 (d, *J* = 11.0 Hz, 1 H), 4.61 (d, *J* = 10.9 Hz, 1 H), 4.45 (d, *J* = 7.8 Hz, 1 H), 4.24 (dt, *J* = 9.3, 6.9 Hz, 1 H), 3.89 (dt, *J* = 9.3, 7.1 Hz, 1 H), 3.12 (t, *J* = 6.9 Hz, 2 H), 2.66 (t, *J* = 6.8 Hz, 2 H), 1.62–1.47 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.55, 137.49, 137.21, 135.11, 127.34, 127.27, 127.20, 126.96, 126.80, 126.67, 126.49, 126.45, 121.18, 120.75, 118.09, 117.59, 111.69, 110.04, 102.60, 83.61, 81.28, 76.09, 74.59, 73.90, 73.73, 73.63, 70.42, 68.88, 68.51, 40.90, 29.29, 26.00, 24.69; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 665.3590 [(M + H)$^+$; calcd for $C_{41}H_{48}N_2O_6$: 665.3582].

2-(*N*-Phenylsulfonylindol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-(6-azidohexyl)-β-D-glucopyranoside (19c). Sodium azide (2.93 g, 450 mmol) was added to a stirred solution of 6-bromo-1-hexanol (1.36 g, 7.5 mmol) in DMSO (20 mL). The resultant mixture was stirred at room temperature for 2.5 h, diluted with water (50 mL), and extracted with diethyl ether (2 × 50 mL). The combined organic solutions were washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered through a plug of silica gel, and concentrated *in vacuo* to afford the azide (1.01 g, 94% yield) as a colorless oil.

A stirred solution of 6-azido-1-hexanol from above (0.087 g, 0.61 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.125 g, 0.061 mmol) in dichloromethane (5 mL) was treated with triflic anydride (0.1 mL, 0.61 mmol) at room temperature. After 15 min the solution was diluted with dichloromethane (20 mL) and poured into saturated aqueous sodium bicarbonate (20 mL). The organic phase was washed with brine, dried over magnesium sulfate, filtered, and concentrated to afford a white semisolid which was used without purification. A solution of the alcohol **17** (0.3 g, 0.41 mmol) and the crude triflate in dichloromethane (3 mL) was treated with sodium hydride (0.024 g, 0.6 mmol, 60% dispersion in oil) followed by 15-crown-5 (10 mg, 0.045 mmol). The mixture was then stirred at ambient temperature for 48 h, diluted with dichloromethane (25 mL), and poured into saturated aqueous ammonium chloride (20 mL). The aqueous phase was extracted with dichloromethane (2 × 20 mL), and the combined organic solutions were washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (15% ethyl acetate/hexane) furnished **19c** (302 mg, 86% yield) as a colorless oil: $[\alpha]^{25}_D$ −4.8° (*c* 1.06, CH_2Cl_2); IR (CH_2Cl_2) 3030 (m), 2991 (w), 2920 (m), 2932 (m), 2110 (s), 1720 (w), 1609 (w), 1450 (s), 1372 (s), 1252 (s), 1212 (w), 1180 (s), 1122 (s), 1091 (s), 1071 (s), 892 (w), 692 (br), 600 (s), 573 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 1 H), 7.83 (dd, *J* = 8.5, 1.1 Hz, 2 H), 7.50–7.16 (m, 22 H), 4.91 (d, *J* = 10.9 Hz, 1 H), 4.85 (d, *J* = 10.9 Hz, 1 H), 4.78 (d, *J* = 10.9 Hz, 1 H), 4.73 (d, *J* = 11.0 Hz, 1 H), 4.61 (d, *J* = 10.9 Hz, 1 H), 4.41 (d, *J* = 7.7 Hz, 1 H), 4.20 (dt, *J* = 9.4, 7.1 Hz, 1 H), 3.83 (dt, *J* = 9.4, 7.5 Hz, 1 H), 3.69–3.56 (m, 4 H), 3.53–3.48 (m, 1 H), 3.43–3.40 (m, 3 H), 3.19 (t, *J* = 6.9 Hz, 2 H), 3.01 (t, *J* = 7.0 Hz, 2 H), 1.63–1.20 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.56, 138.37, 138.27, 138.23, 135.17, 133.59, 130.96, 129.12, 128.41, 128.33, 128.27, 127.99, 127.84, 127.75, 127.57, 127.56, 126.66, 124.72, 123.46, 123.11, 119.64, 119.44, 113.70, 103.74, 84.64, 82.24, 77.93, 75.66, 74.96, 74.89, 74.73, 71.52, 69.65, 68.75, 51.33, 29.48, 28.72, 26.52, 25.73, 25.71; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 881.3538 [(M + Na)$^+$; calcd for $C_{49}H_{54}N_4O_8S$: 881.3560].

2-(1*H*-Indol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-(6-aminohexyl)-β-D-glucopyranoside (4c). A solution of azide **19c** (0.234 g, 0.272 mmol) in THF (15 mL) was treated sequentially with water (0.12 mL, 6.67 mmol) and triphenylphosphine (0.142 g, 0.54 mmol) and then heated to 60 °C for 4 h. The mixture was then cooled and concentrated to a gum. Flash chromatography (10% methanol/dichloromethane) gave the requisite amine (190 mg, 84% yield) as a colorless oil: $[\alpha]^{25}_D$ −1.7° (*c* 0.52, $CHCl_3$); IR (CH_2Cl_2) 3730 (w), 3045 (m), 2940 (m), 1610 (w), 1450 (m), 1426 (s), 1372 (m), 1271 (s), 1183 (s), 1180 (s), 1115 (s), 1091 (s), 1076 (s), 900 (s), 730 (br s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 1 H), 7.83 (apparent d, *J* = 7.4 Hz, 2 H), 7.49–7.44 (m, 3 H), 7.37–7.14 (m, 17 H), 4.90 (d, *J* = 10.9 Hz, 1 H), 4.85 (d, *J* = 10.9 Hz, 1 H), 4.78 (d, *J* = 10.9 Hz, 1 H), 4.72 (d, *J* = 11.0 Hz, 1 H), 4.61 (d, *J* = 10.9 Hz, 1 H), 4.59 (d, *J* = 11.0 Hz, 1 H), 4.41 (d, *J* = 7.8 Hz, 1 H), 4.20 (dt, *J* = 9.6, 6.9 Hz, 1 H), 3.83 (dt, *J* = 9.6, 7.2 Hz, 1 H), 3.67 (apparent t, *J* = 9.0 Hz, 2 H), 3.63–3.60 (m, 1 H), 3.58 (apparent t, *J* = 9.3 Hz, 2 H), 3.49 (dt, *J* = 9.4, 6.5 Hz, 1 H), 3.41 (t, *J* = 6.7 Hz, 2 H), 3.39–3.37 (m, 1 H), 3.00 (t, *J* = 6.9 Hz, 2 H), 2.99–2.97 (br t, *J* = 7.0 Hz, 2 H), 1.57–1.25 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.24, 133.60, 129.13, 128.41, 128.34, 128.27, 128.00, 127.85, 127.84, 127.56, 126.67, 124.74, 123.47, 123.12, 119.68, 113.71, 103.73, 84.65, 82.25, 77.95, 75.65, 74.97, 74.90, 74.74, 71.64, 69.65, 68.76, 29.55, 26.60, 25.88, 25.71; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 833.3827 [(M + H)$^+$; calcd for $C_{49}H_{56}N_2O_8S$: 833.3845].

A solution of the above amine (0.248 g, 0.30 mmol) in ethanol (22.5 mL) was treated with 5 M aqueous potassium hydroxide (4.5 mL) and heated to reflux. After 5 h the mixture was cooled, diluted with saturated aqueous ammonium chloride (30 mL), and poured into dichloromethane (30 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic solutions were washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. Flash chromatography (10% methanol/dichloromethane) furnished **4c** (179 mg, 87% yield) as a colorless oil: $[\alpha]^{25}_D$ +9.4° (*c* 0.25, $CHCl_3$); IR (CH_2Cl_2) 3700 (br), 3026 (s), 2980 (s), 2925 (m), 2860 (m), 2085 (m), 1610 (w), 1440 (s), 1421 (s), 1365 (s), 1255 (s), 1175 (s), 1120 (s), 1085 (s), 1075 (s), 980 (w), 890 (s), 700 (br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.49 (br s, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.26–7.15 (m, 16 H) 7.07 (t, *J* = 8.0 Hz, 1 H), 7.00 (t, *J* = 7.1 Hz, 1 H), 6.92 (s, 1 H), 4.84 (d, *J* = 11.0 Hz, 1 H), 4.77 (d, *J* = 10.9 Hz, 1 H), 4.76 (d, *J* = 10.9 Hz, 1 H), 4.70 (d, *J* = 10.9 Hz, 1 H), 4.59 (d, *J* = 11.0 Hz, 1 H), 4.49 (d, *J* = 11.0 Hz, 1 H), 4.38 (d, *J* = 7.8 Hz, 1 H), 4.08 (dt, *J* 9.3, 6.9 Hz, 1 H), 3.77 (dt, *J* = 9.3, 7.1 Hz, 1 H), 3.62–3.28 (m, 8 H), 3.03 (t, *J* = 7.3 Hz, 2 H), 2.67 (t, *J* = 7.5 Hz, 2 H), 1.48–1.37 (m, 4 H), 1.17–1.13 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.54, 138.48, 138.11, 136.15, 128.39, 128.32, 128.27, 128.03, 127.84, 127.75, 127.54, 127.47, 122.20, 121.79, 119.12, 118.64, 112.16, 111.23, 103.68, 84.65, 82.29, 78.09, 75.62, 74.91, 74.83, 74.68, 71.37, 70.26, 69.77, 39.74, 29.35, 27.37, 26.13, 25.83, 25.42; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 715.3753 [(M + Na)$^+$; calcd for $C_{43}H_{52}N_2O_6$: 715.3723].

5-(Trifluoroacetamido)-1-pentanol (18a).[28] A solution of 5-amino-1-pentanol (1.00 g, 9.69 mmol) in methanol (8 mL) was cooled to 0 °C and treated with triethylamine (3.28 mL, 23.5 mmol), followed by dropwise addition of trifluoroacetic anhydride (1.88 mL, 13.4 mmol). The reaction mixture was stirred at room temperature for 16 h. Concentration and flash chromatography (60% ethyl acetate/petroleum ether) then furnished **18a** (1.7 g, 89% yield) as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 1 H), 3.66 (m, 2 H), 3.37 (dd, *J* = 13.3, 6.8 Hz, 2 H), 1.77 (s, 1 H), 1.66–1.58 (m, 4 H), 1.47–1.41 (m, 2 H); high-resolution mass spectrum (CI, CH_4) *m/z* 200.0901 [(M + H)$^+$; calcd for $C_7H_{13}F_3NO_2$ 200.0696].

2-(1*H*-Indol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-6-aminio-6-deoxy-6-*N*-(5-hydroxypentyl)-β-D-glucopyranoside (4e). A stirred solution of **17** (196 mg, 0.27 m mol) in dry dichloromethane (2.7 mL) was cooled to −78 °C and treated with 2,6-di-*tert*-butyl-4-methylpyridine (880 mg, 0.427 mmol) followed by triflic anhydride (58 μL, 0.347 mmol). The mixture was stirred for 15 min at −78 °C, warmed to room temperature over 20 min, then poured into saturated aqueous sodium bicarbonate (20 mL), and extracted with ethyl acetate (60 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (3 × 20 mL) and brine (20 mL) and dried over magnesium sulfate. Filtration and concentration *in vacuo* provided crude triflate which was used without purification.

A solution of 5-(trifluoroacetamido)-1-pentanol (**18a**) (265 mg, 1.3 mmol) in THF (10 mL) was added to a stirred suspension of sodium hydride (123 mg, 3.07 mmol, 60% oil dispersion) in THF (17 mL) at 0 °C. After 10 min the suspension was warmed to room temperature, stirred for 1 h, and recooled to 0 °C, and a solution of the above triflate (0.574 mmol) in dichloromethane (25 mL) was added dropwise. The reaction was stirred at 0 °C for 30 min and then at room temperature for 24 h, cooled to 0 °C, quenched with saturated aqueous ammonium chloride (10 mL), and extracted with ethyl acetate (2 × 150 mL). The combined extracts were washed with water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (2% methanol/dichloromethane) afforded an inseparable mixture of compounds, presumably **19d** and its benzenesulfonamide deprotected counterpart, which was used directly in the next step.

A stirred solution of the above mixture in ethanol (6 mL) was treated with 5 M aqueous NaOH (2 mL, 10 mmol), and the reaction mixture was heated to reflux for 2 h, cooled, and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (40 mL), and the solution was washed with water (15 mL) and brine (15 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (5% methanol/dichloromethane) afforded **4e** (150 mg, 83% yield for 3 steps) as a pale yellow oil: $[\alpha]^{25}_D$ +3.2° (*c* 0.31, acetonitrile); UV (1.14×10^{-4} M, acetonitrile) λ_{max} 289.6 (ϵ 4.17×10^3), 280.8 (4.97×10^3), 220.0 (2.4×10^4) nm; IR (film) 3420 (w), 3300 (w), 3063 (w), 3033 (w), 2938 (m), 2860 (m), 1495 (w), 1455 (m), 1360 (m), 1210 (w), 1072 (s), 1026 (m), 910 (w), 538 (s), 495 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.59 (d, *J* = 7.9 Hz, 1 H), 7.33–7.04 (m, 19 H), 4.90 (d, *J* = 10.9 Hz, 1 H), 4.85 (d, *J* = 11.1 Hz, 1 H), 4.80 (d, *J* = 11.0 Hz, 1 H), 4.77 (d, *J* = 10.9 Hz, 1 H), 4.64 (d, *J* = 11.0 Hz, 1 H), 4.60 (d, *J* = 11.1 Hz, 1 H), 4.48 (d, *J* = 7.8 Hz, 1 H), 4.21 (ddd, *J* = 9.4, 6.7, 6.7 Hz, 1 H), 3.89 (ddd, *J* = 9.4, 7.3, 7.3 Hz, 1 H), 3.64 (dd, *J* = 9.0, 9.0 Hz, 1 H), 3.56 (t, *J* = 6.4 Hz, 2 H), 3.51–3.47 (m, 1 H), 3.42 (t, *J* = 9.2 Hz, 2 H), 3.11 (t, *J* = 7.0 Hz, 2 H), 2.96 (dd, *J* = 12.3, 2.6 Hz, 1 H), 2.66 (dd, *J* = 12.3, 7.8 Hz, 1 H), 2.62–2.54 (m, 2 H), 1.93 (s, 2 H), 1.54–1.44 (m, 4 H), 1.38–1.32 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.57, 138.49, 138.14, 136.17, 128.43, 128.36, 128.29, 128.02, 127.88, 127.82, 127.60, 127.56, 127.50, 122.14, 121.96, 119.30, 118.68, 112.60, 111.13, 103.67, 84.61, 82.45, 79.70, 77.20, 75.68, 74.99, 74.73, 73.82, 70.25, 62.63, 50.52, 49.59, 32.36, 29.28, 25.86, 23.31; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 679.3700 [(M + H)$^+$; calcd for $C_{42}H_{50}N_2O_6$ 679.3747].

4-(Trifluoroacetamido)-1-butanol (18b).[28] Trifluoroacetylation of 4-amino-1-butanol (0.700 g, 7.86 mmol) as described for **18a** followed by flash chromatography (55% ethyl acetate/hexane) afforded **18b** (1.32 g, 85% yield) as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (s, 1 H), 3.72 (dd, *J* = 10.2, 5.8 Hz, 2 H), 3.40 (dd, *J* = 12.6, 6.3 Hz, 2 H), 1.99 (t, *J* = 4.2 Hz, 1 H), 1.78–1.70 (m, 2 H), 1.68–1.62 (m, 2 H); high-resolution mass spectrum (CI, CH_4) *m/z* 186.0732 [(M + H)$^+$; calcd for $C_6H_{11}F_3NO_2$ 186.0742].

2-(1*H*-Indol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-6-amino-6-deoxy-6-*N*-(4-hydroxybutyl)-β-D-glucopyranoside (4f). A solution of 4-(trifluoroacetamido)-1-butanol (**18b**) (425 mg, 2.29 mmol) in THF (10 mL) was added to a stirred suspension of sodium hydride (60% dispersion in oil, 210 mg, 5.27 mmol) in THF (28 mL) at 0 °C. After 10 min the suspension was warmed to room temperature, stirred for 1 h, and recooled to 0 °C. Crude triflate (0.27 mmol), prepared as described for **4e**, was dissolved in dichloromethane (16 mL) and added dropwise. The reaction was stirred at 0 °C for 1 h and then at room temperature for 24 h, cooled to 0 °C, quenched with saturated aqueous ammonium chloride (10 mL), and extracted with ethyl acetate (2 × 150 mL). The combined extracts were washed with water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (3% methanol/dichloromethane) afforded an inseparable mixture of compounds, presumably **19e** and its benzenesulfonamide deprotected counterpart, which was used directly in the next step.

A stirred solution of the above mixture in ethanol (11 mL) was treated with 2.5 M aqueous NaOH (7.0 mL, 17.5 mmol), and the reaction mixture was heated to reflux for 2 h, cooled to room temperature, and concentrated *in vacuo*. The residue was taken up in dichloromethane (60 mL), and the solution was washed with brine (20 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (5% methanol/dichloromethane) provided **4f** (148 mg, 39%) as a pale yellow oil: IR (film) 3435 (w), 3310 (w), 2930 (m), 2870 (m), 1502 (w), 1460 (m), 1364 (m), 1215 (w), 1075 (s), 1032 (sh), 1012 (sh), 913 (m), 815 (w), 740 (s), 700 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.59 (d, *J* = 7.9 Hz, 1 H), 7.33–7.21 (m, 15 H), 7.19–7.16 (m, 2 H), 7.12–7.09 (m, 1 H), 7.04 (d, *J* = 2.1 Hz, 1 H), 4.90 (d, *J* = 10.9 Hz, 1 H), 4.86 (d, *J* = 11.1 Hz, 1 H), 4.78 (d, *J* = 11.1 Hz, 1 H), 4.76 (d, *J* = 10.9 Hz, 1 H), 4.63 (d, *J* = 11.0 Hz, 1 H), 4.58 (d, *J* = 11.1 Hz, 1 H), 4.46 (d, *J* = 7.8 Hz, 1 H), 4.20 (ddd, *J* = 9.5, 6.7, 6.7 Hz, 1 H), 3.89 (ddd, *J* = 9.5, 7.3, 7.3 Hz, 1 H), 3.62 (apparent t, *J* = 9.0 Hz, 1 H), 3.53 (t, *J* = 5.3 Hz, 2 H), 3.46 (ddd, *J* = 9.5, 4.4, 2.9 Hz, 1 H), 3.41 (dd, *J* = 9.1,

7.9 Hz, 1 H), 3.36 (apparent t, J = 9.2 Hz, 1 H), 3.11 (t, J = 6.9 Hz, 2 H), 2.93 (dd, J = 12.3, 2.9 Hz, 1 H), 2.63 (dd, J = 12.3, 7.9 Hz, 1 H), 2.59 (t, J = 5.7 Hz, 2 H), 1.61 (m, 2 H), 1.55 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.50, 138.46, 138.07, 136.15, 128.43, 128.35, 128.28, 127.98, 127.87, 127.82, 127.59, 127.53, 127.46, 122.15, 121.95, 119.29, 118.67, 112.60, 111.14, 103.61, 84.58, 82.38, 79.73, 75.66, 74.97, 74.69, 73.36, 70.20, 62.54, 50.32, 49.49, 32.11, 28.10, 25.85; high-resolution mass spectrum (Cl, NH_3) m/z 665.3640 [$(M + H)^+$; calcd for $C_{41}H_{49}N_2O_6$ 665.3590].

2-(1*H*-Indol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-6-amino-6-deoxy-6-*N*-(6-hydroxyhexyl)-β-D-glucopyranoside (4g). A solution of 6-trifluoroacetamido-1-hexanol (**18c**) (145.0 mg, 0.680 mmol) in THF (2 mL) was added to a suspension of sodium hydride (60.0 mg, 1.50 mmol, 60% dispersion in oil) in THF (2 mL) at 0 °C. The mixture was stirred at room temperature for 1.5 h, cooled to 0 °C, and treated with a solution of the triflate derived from **17** (0.136 mmol), prepared as described for the synthesis of **4e**, in dichloromethane (4 mL). The reaction mixture was then stirred at room temperature for 48 h, cooled to 0 °C, quenched with saturated aqueous ammonium chloride (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (5% methanol/dichloromethane) afforded an inseparable mixture of compounds, presumably **19f** and its benzenesulfonamide deprotected counterpart, which was used directly in the next step.

A stirred solution of the above mixture in ethanol (6 mL) was treated with 5 N aqueous sodium hydroxide (2 mL) and heated to reflux for 2 h. Cooling followed by concentration *in vacuo* gave an oily residue which was taken up in water (5 mL) and extracted with dichloromethane (3 × 5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (6% methanol/dichloromethane) furnished **4g** as a colorless oil (36.4 mg, 54% yield): $[\alpha]^{25}_D$ −18° (c 0.18, acetonitrile); UV (1.72 × 10^{-4} M, acetonitrile) λ_{max} 290.0 (ϵ 1.02 × 10^3), 281.2 (1.13 × 10^3), 228.4 (1.39 × 10^3) nm; IR (film) 3440 (m), 3310 (m), 3060 (m), 3030 (m), 2930 (s), 2860 (s), 2240 (w), 1497 (w), 1455 (s), 1360 (m), 1210 (w), 1070 (s), 910 (s), 740 (s), 700 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (br s, 1 H), 7.59 (d, J = 7.9 Hz, 1 H), 7.33–7.00 (m, 19 H), 4.91 (d, J = 10.9 Hz, 1 H), 4.86 (d, J = 11.1 Hz, 1 H), 4.80 (d, J = 11.3 Hz, 1 H), 4.78 (d, J = 11.1 Hz, 1 H), 4.65 (d, J = 11.0 Hz, 1 H), 4.60 (d, J = 11.1 Hz, 1 H), 4.47 (d, J = 7.8 Hz, 1 H), 4.21 (dt, J = 9.4, 6.8 Hz, 1 H), 3.86 (dt, J = 9.4, 7.6 Hz, 1 H), 3.64 (t, J = 9.0 Hz, 1 H), 3.55 (t, J = 6.6 Hz, 2 H), 3.51–3.40 (m, 3 H), 3.12 (t, J = 7.2 Hz, 2 H), 2.96–2.13 (dd, J = 12.2, 2.6 Hz, 1 H), 2.68–2.51 (m, 3 H), 1.87 (br s, 2 H), 1.51–1.41 (m, 4 H), 1.33–1.25 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.47, 138.39, 138.05, 136.11, 128.39, 128.34, 128.27, 128.02, 127.96, 127.88, 127.80, 127.59, 127.55, 127.40, 122.10, 121.87, 119.21, 118.62, 112.32, 111.13, 103.61, 84.55, 82.38, 79.77, 75.69, 75.00, 74.72, 73.91, 70.25, 62.67, 50.64, 49.61, 32.55, 29.78, 26.97, 25.81, 25.55; high-resolution mass spectrum (Cl, CH_4) m/z 693.3946 (M^+; calcd for $C_{43}H_{50}N_2O_6$ 693.3903).

5-Acetamido-1-pentanol (20).[32] A solution of 5-amino-1-pentanol (0.650 g, 6.31 mmol) in methanol (15 mL) was cooled to 0 °C and treated with triethylamine (1.62 mL, 11.6 mmol) followed by acetic anhydride (0.891 mL, 9.45 mmol). The reaction mixture was stirred at room temperature overnight. TLC analysis (8% methanol/dichloromethane) then revealed some unreacted material, so additional triethylamine (1.6 mL, 11.6 mmol) and acetic anhydride (0.9 mL, 9.5 mmol) were added at room temperature and the solution was stirred 16 h further. Concentration *in vacuo* and flash chromatography (7% methanol/dichloromethane) afforded **20** (1 g, 94% yield) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (s, 1 H), 3.62 (t, J = 6.4 Hz, 2 H), 3.23 (dd, J = 12.9, 7.0 Hz, 2 H), 2.87 (s, 1 H), 1.97 (s, 3 H), 1.60–1.50 (m, 4 H), 1.43–1.37 (m, 2 H); high-resolution mass spectrum (Cl, CH_4) m/z 146.1164 [$(M + H)^+$; calcd for $C_7H_{16}NO_2$ 146.1181].

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-(5-acetamidopentyl)-β-D-glucopyranoside (4d). A solution of 5-acetamido-1-pentanol (177 mg, 1.22 mmol) in THF (8 mL) was added to a stirred suspension of sodium hydride (60% dispersion in oil, 108 mg, 2.70 mmol) in THF (20 mL) at 0 °C. After 10 min the mixture was stirred at room temperature for 1.5 h and cooled to 0 °C. The triflate derived from **17** (0.245 mmol), prepared as described for the synthesis of **4a**, was dissolved in dichloromethane (20 mL) and slowly added dropwise. The reaction was stirred at 0 °C for 1 h and at room temperature for 24 h, then was cooled to 0 °C, quenched with saturated aqueous ammonium chloride (10 mL), and diluted with ethyl acetate (150 mL). The organic layer was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (3% methanol/dichloromethane) afforded an inseparable mixture of compounds, presumably **21** and its benzenesulfonamide deprotected counterpart, which was used directly in the next step.

A stirred solution of the above mixture in ethanol (4 mL) was treated with 5 N aqueous NaOH (2 mL, 10 mmol) and then heated to reflux for 2 h, cooled, and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (40 mL), and the resultant solution was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (4% methanol/dichloromethane) provided **4d** (88 mg, 50% yield) as a colorless oil: $[\alpha]^{25}_D$ +14.5° (c 0.53, $CHCl_3$); IR (film) 3300 (s), 3090 (w), 3065 (m), 3035 (m), 2940 (s), 2870 (s), 1960 (w), 1885 (w), 1815 (w), 1662 (s), 1550 (m), 1500 (m), 1458 (s), 1369 (s), 1285 (m), 1213 (m), 1070 (s), 914 (w), 810 (w), 742 (s), 700 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1 H), 7.59 (d, J = 8.1 Hz, 1 H), 7.34–7.21 (m, 16 H), 7.19–7.16 (m, 1 H), 7.12–7.08 (m, 1 H), 7.03 (d, J = 2.2 Hz, 1 H), 5.41 (s, 1 H), 4.92 (d, J = 10.9 Hz, 1 H), 4.85 (d, J = 11.0 Hz, 1 H), 4.83 (d, J = 11.0 Hz, 1 H), 4.78 (d, J = 11.0 Hz, 1 H), 4.66 (d, J = 11.0 Hz, 1 H), 4.59 (d, J = 11.0 Hz, 1 H), 4.45 (d, J = 7.8 Hz, 1 H), 4.22 (ddd, J = 9.4, 6.9, 6.9 Hz, 1 H), 3.86 (ddd, J = 9.4, 7.5, 7.5 Hz, 1 H), 3.68 (dd, J = 10.9, 1.8 Hz, 1 H), 3.64 (apparent t, J = 9.0 Hz, 1 H), 3.59 (dd, J = 10.9, 5.1 Hz, 1 H), 3.55 (apparent t, J = 9.0 Hz, 1 H), 3.51–3.39 (m, 4 H), 3.17–3.13 (m, 2 H), 3.12 (t, J = 7.2 Hz, 2 H), 1.91 (s, 3 H), 1.58–1.53 (m, 2 H), 1.48–1.42 (m, 2 H), 1.38–1.32 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.06, 138.57, 138.22, 136.21, 128.41, 128.35, 128.27, 128.03, 127.87, 127.84, 127.76, 127.59, 127.55, 127.49, 122.18, 121.81, 119.14, 118.61, 112.46, 111.19, 103.68, 84.68, 82.33, 78.04, 77.20, 75.67, 74.93, 74.83, 74.67, 71.42, 70.06, 69.71, 39.56, 29.29, 25.76, 23.61, 23.27; high-resolution mass spectrum (Cl, NH_3) m/z 721.3790 [$(M + H)^+$; calcd for $C_{44}H_{53}N_2O_7$ 721.3852].

1,2,4,6-Tetra-*O*-acetyl-3-β-D-glucopyranoside (23). A solution of 3-deoxydiacetone-D-glucose (**22**) (27.5 g, 113 mmol) in 60% aqueous acetic acid (200 mL) was heated at 90 °C for 1 h, cooled, and concentrated *in vacuo*, and the residue was azeotroped with dry benzene (4 × 20 mL). A solution of the concentrate in dry pyridine (250 mL) was treated with acetic anhydride (107 mL, 1.13 mol) and DMAP (2 mol%, 275 mg) and stirred at room temperature for 30 min. After concentration *in vacuo* the residue was diluted with water (40 mL) and extracted with dichloromethane (3 × 40 mL), and the combined extracts were then washed with brine (40 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Recrystallization from ether afforded the pure β-anomer (11.3 g) as a fine white powder. Concentration of the filtrate and flash chromatography (45% ethyl acetate/hexane) gave a mixture of α- and β-anomers as a colorless gum (23.0 g, total yield 91.7%). β-Anomer **23**: mp 127–128 °C (ether) [lit.[57] 129–130 °C (ethyl acetate)]; $[\alpha]^{25}_D$ −17.1° (c 1.05, CH_3OH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.69, 169.43, 169.31, 169.19, 93.06, 75.68, 67.33, 65.00, 62.07, 32.69, 20.92, 20.77; high-resolution mass spectrum (Cl, NH_3) m/z 350.1412 [$(M + NH_4)^+$; calcd for $C_{14}H_{20}O_9Cl$ 350.1450]. Anal. Calcd for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.65; H, 6.16.

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 2,4,6-Tri-*O*-acetyl-3-deoxy-β-D-glucopyranoside (24). Hydrobromic acid (30% in acetic acid, 3 mL, 14.0 mmol) was added to **23** (750 mg, 2.26 mmol) at 0 °C. After 10 min, the solution was warmed to room temperature, stirred for 30 min, diluted with ether (20 mL), poured into a mixture of ice, and saturated aqueous sodium bicarbonate (25 mL). An additional 30 mL of ether was added, and the layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate (3 × 25 mL), water, and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude bromide was used without purification in the next step: high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) m/z 370.0470 [$(M + NH_4)^+$; calcd for $C_{12}H_{17}BrO$ 370.0494].

A solution of *N*-(benzenesulfonyl)tryptophol (**12**) (1.20 g, 4.0 mmol) in dry benzene (4 mL) was added to a stirred suspension of activated, powdered 4 Å molecular sieves (1.33 g) in dry hexane (11 mL) at room temperature. A solution of the bromide (2.26 mmol) in dry benzene (4 mL) was introduced, followed by silver(I) oxide (523 mg, 2.26 mmol). The reaction vessel was covered with aluminum foil, and the mixture was stirred for 3 days and then filtered through Celite. Concentration and flash chromatography (10:1 dichloromethane/ether) provided pure **24** (781 mg, 60% yield) as a white foam: mp 49–51 °C; $[\alpha]^{25}_D$ −12° (c 0.21, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.80, 169.47, 133.68, 131.06, 129.20, 126.72, 124.73, 123.56, 123.16, 119.84, 119.50, 113.66, 106.62, 102.09, 75.03, 68.46, 68.38, 65.83, 62.65, 32.92, 25.37, 20.87, 20.79; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) m/z 573.1623 (M^+; calcd for $C_{28}H_{31}NO_{10}S$ 573.1669).

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 3-Deoxy-β-D-glucopyranoside (25). Sodium methoxide (55.2 mg, 1.02 mmol) was added to a suspension of **24** (735 mg, 1.28 mmol) in methanol (6.4 mL). The mixture was stirred at room temperature for 90 min, diluted with methanol (6 mL), and neutralized with Amberlyst 15 ion exchange resin. The resin was quickly filtered. Concentration *in vacuo* and flash chromatography (12:1:1 dichloromethane/acetone/methanol) afforded pure **25** (498 mg, 87% yield) as a white solid: mp 55–57 °C; $[\alpha]^{25}_D$ −26° (*c* 0.25, methanol); ^{13}C NMR (500 MHz, CD_3OD) δ 139.40, 136.57, 135.02, 132.62, 130.38, 127.89, 125.65, 125.30, 124.36, 121.74, 120.63, 114.70, 106.49, 81.82, 69.41, 69.37, 66.27, 62.95, 40.72, 26.32; high-resolution mass spectrum (Cl, NH_3) *m/z* 465.1627 [(M + NH_4)$^+$; calcd for $C_{22}H_{25}NO_7S$ 465.1685].

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 3-Deoxy-6-*O*-(*tert*-butyldiphenylsilyl)-β-D-glucopyranoside (26). A stirred solution of **25** (779 mg, 1.74 mmol) in dry DMF (17 mL, 0.1 M) was treated with imidazole (260 mg, 3.83 mmol) followed by *tert*-butyldimethylsilyl chloride (0.541 mL, 2.09 mmol). The solution was heated at 50 °C for 24 h, cooled, diluted with ethyl acetate (250 mL), and washed with water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (3% methanol/dichloromethane) provided pure **26** (1.04 g, 87% yield) as a white foam: $[\alpha]^{25}_D$ −24° (*c* 0.46, acetonitrile); ^{13}C NMR (125 MHz, acetone-d_6) δ 138.24, 135.54, 135.51, 135.14, 133.65, 132.46, 132.38, 130.97, 130.00, 129.17, 128.30, 127.86, 126.65, 124.79, 123.42, 123.13, 119.67, 119.34, 113.73, 104.73, 77.34, 68.83, 68.58, 68.28, 66.11, 37.34, 26.77, 25.45, 19.09; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 686.2651 [(M + H)$^+$; calcd for $C_{38}H_{43}NO_7SSi$ 686.2607]. Anal. Calcd for $C_{38}H_{43}O_7NSSi$: C, 66.54; H, 6.32. Found: C, 66.18; H, 6.14.

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 3-Deoxy-2,4-di-*O*-benzyl-6-*O*-(*tert*-butyldiphenylsilyl)-β-D-glucopyranoside (27). A stirred suspension of sodium hydride (4.63 mmol, 185 mg, 60% oil dispersion) in THF (5 mL) was cooled to 0 °C and a solution of **26** (1.27 g, 1.85 mmol) in THF (10 mL) was added. After 10 min the reaction mixture was warmed to room temperature, stirred for 1 h, recooled to 0 °C, and treated with benzyl bromide (5.55 mmol, 0.660 mL) followed by tetrabutylammonium iodide (68 mg, 0.185 mmol). The reaction was then warmed to room temperature, stirred for 3 days, and quenched with saturated aqueous ammonium chloride (3 mL) at 0 °C. The mixture was diluted with ether (80 mL), washed with water (2 × 30 mL) and brine (30 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (25% ether/petroleum ether) furnished pure **27** (760 mg, 47% yield) as a white foam: $[\alpha]^{25}_D$ −2.7° (*c* 0.66, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.68, 138.32, 138.08, 135.72, 135.56, 135.18, 133.74, 133.54, 133.49, 131.06, 129.52, 129.10, 128.36, 128.30, 127.66, 127.63, 127.59, 127.51, 127.45, 126.63, 124.69, 123.47, 123.12, 119.94, 119.57, 113.67, 105.11, 79.10, 75.27, 72.68, 72.06, 71.37, 68.18, 63.23, 34.99, 26.77, 25.80, 19.29; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 865.3419 (M$^+$; calcd for $C_{52}H_{55}NO_7SSi$ 865.3468).

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 3-Deoxy-2,4-di-*O*-benzyl-β-D-glucopyranoside (28). Tetrabutylammonium fluoride (1.0 M in THF, 1.17 mmol, 1.17 mL) was added to a stirred solution of **27** (675 mg, 0.780 mmol) in THF (10 mL). The solution was stirred for 2 h, diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (60% ether/petroleum ether) afforded pure **28** (445 mg, 91% yield) as a pale yellow oil: $[\alpha]^{25}_D$ +2.5° (*c* 0.44, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.44, 138.30, 137.82, 135.15, 133.63, 131.03, 129.15, 128.49, 128.35, 127.89, 127.79, 127.63, 127.58, 126.68, 124.75, 123.65, 123.15, 119.80, 119.38, 113.73, 105.19, 78.18, 75.02, 72.71, 72.23, 71.29, 68.38, 62.38, 34.83, 25.61; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 627.2370 (M$^+$; calcd for $C_{36}H_{37}NO_7S$ 627.2291).

2-(*N*-Phenylsulfonylindol-3-yl)ethyl 2,4-Di-*O*-benzyl-3-deoxy-6-*O*-(5-azidopentyl)-β-D-glucopyranoside (29a). 5-Azido-1-pentanol (280 mg, 2.17 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (441 mg, 2.17 mmol) were dissolved in dichloromethane (9 mL), and triflic anhydride (0.36 mL, 2.17 mmol) was added dropwise. After 10 min the mixture was poured into brine (40 mL) and extracted with dichloromethane (2 × 40 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The triflate was used without purification in the next step.

Sodium hydride (16 mg, 0.40 mmol, 60% dispersion in oil) was added to a solution of alcohol **28** (120 mg, 0.198 mmol) and azido triflate (105 mg, equivalent to 0.40 mmol) in dichlormethane (3 mL) at room temperature. The mixture was stirred for 24 h, diluted with dichloromethane (40 mL), and poured into saturated ammonium chloride (40 mL). The aqueous phase was extracted with dichloromethane (2 × 40 mL), and the combined organic solutions were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (15% ethyl acetate/hexane) afforded **29a** (121 mg, 83% yield) as a colorless oil: $[\alpha]^{25}_D$ +4.0° (*c* 0.24, $CHCl_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.52, 138.23, 137.00, 135.07, 133.59, 131.09, 129.14, 128.43, 128.31, 127.78, 127.68, 127.50, 126.70, 126.69, 124.70, 123.54, 123.09, 119.71, 119.48, 113.70, 105.26, 78.01, 74.92, 72.67, 72.25, 71.38, 71.24, 69.96, 68.41, 51.30, 34.97, 29.15, 28.66, 25.65, 23.39; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 761.2973 [(M + Na)$^+$; calcd for $C_{41}H_{46}N_4O_7S$: 761.2985].

2-(1*H*-Indol-3-yl)ethyl 2,4-Di-*O*-benzyl-3-deoxy-6-*O*-(5-aminopentyl)-β-D-glucopyranoside (5a). A stirred solution of azide **29a** (80 mg, 0.109 mmol) in THF (5.2 mL) and water (0.083 mL, 1.49 mmol) was treated with triphenylphosphine (65 mg, 0.248 mmol), heated at reflux for 2.5 h, cooled, and concentrated *in vacuo*. Flash chromatography (10% methanol/dichloromethane) furnished the corresponding amine (70 mg, 90% yield) as a colorless oil: $[\alpha]^{25}_D$ +6.4° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 3028 (m), 2940 (s), 2875 (m), 1450 (s), 1370 (s), 1280 (w), 1178 (s), 1122 (m), 1070 (m), 695 (w), 597 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.9 Hz, 1 H), 7.86 (d, *J* = 7.7 Hz, 2 H), 7.53–7.45 (m, 3 H), 7.40–7.23 (m, 14 H), 4.68 (d, *J* = 12.0 Hz, 1 H), 4.61 (d, *J* = 11.5 Hz, 1 H), 4.55 (d, *J* = 12.0 Hz, 1 H), 4.43 (d, *J* = 11.5 Hz, 1 H), 4.23 (dt, *J* = 9.5, 6.7 Hz, 1 H), 3.85 (dt, *J* = 9.5, 7.1 Hz, 1 H), 3.74 (d, *J* = 10.2 Hz, 1 H), 3.60 (dd, *J* = 10.7, 4.7 Hz, 1 H), 3.53–3.42 (m, 4 H), 3.33–3.29 (m, 1 H), 3.03 (t, *J* = 6.9 Hz, 2 H), 2.86 (br s, 2 H), 2.72 (br s, 2 H), 2.52 (dt, *J* = 12.2, 4.1 Hz, 1 H), 1.62–1.47 (m, 4 H), 1.40–1.35 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.51, 138.25, 138.00, 135.13, 133.66, 133.58, 131.05, 129.11, 128.40, 128.27, 127.76, 127.69, 127.62, 127.46, 126.65, 124.68, 123.54, 123.09, 119.91, 119.48, 105.21, 77.97, 74.96, 72.64, 72.18, 71.34, 71.21, 69.94, 68.39, 39.70, 34.94, 28.89, 25.59, 23.44, 23.26; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 713.3241 [(M + H)$^+$; calcd for $C_{41}H_{48}N_2O_7S$: 713.3260].

The above amine (14 mg, 0.020 mmol) was dissolved in ethanol (2.2 mL) and treated with 5 M aqueous sodium hydroxide (0.36 mL). The resultant mixture was heated at reflux for 3 h, cooled, diluted with brine, and poured into dichloromethane (40 mL). The aqueous layer was extracted with dichloromethane (2 × 40 mL) and the combined organic solutions were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (10% methanol/dichloromethane) afforded **5a** (7 mg, 61% yield) as a colorless oil: $[\alpha]^{25}_D$ −12.4° (*c* 0.11, $CHCl_3$); IR ($CHCl_3$) 3684 (w), 3624 (w), 3019 (s), 1525 (m), 1478 (w), 1425 (m), 1210 (s), 1046 (m), 929 (s), 760 (s), 669 (s), 626 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (br s, 1 H), 7.58 (d, *J* = 7.8 Hz, 1 H), 7.34–7.25 (m, 11 H), 7.14 (t, *J* = 7.5 Hz, 1 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 7.04 (s, 1 H), 4.77 (d, *J* = 11.8 Hz, 1 H), 4.60 (d, *J* = 12.0 Hz, 1 H), 4.57 (d, *J* = 11.6 Hz, 1 H), 4.44 (d, *J* = 7.5 Hz, 1 H), 4.39 (d, *J* = 11.5 Hz, 1 H), 4.16 (dt, *J* = 9.3, 7.3 Hz, 1 H), 3.85 (dt, *J* = 9.3, 7.2 Hz, 1 H), 3.70 (d, *J* = 10.4 Hz, 1 H), 3.51 (dd, *J* = 10.6, 5.8 Hz, 1 H), 3.46–3.36 (m, 4 H), 3.35–3.29 (m, 1 H), 3.11 (t, *J* = 7.2 Hz, 2 H), 2.68 (br t, *J* = 7.1 Hz, 2 H), 2.53–2.49 (dt, *J* = 12.3, 4.7 Hz, 1 H), 1.56–1.42 (m, 5 H), 1.36–1.25 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.53, 137.86, 136.12, 128.45, 128.38, 127.86, 127.82, 127.72, 127.62, 127.12, 123.06, 122.02, 119.32, 118.62, 112.26, 111.63, 105.43, 77.49, 75.28, 72.79, 71.34, 71.79, 71.05, 70.39, 68.85, 39.21, 34.65, 27.54, 26.16, 25.72, 22.51; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 573.3313 [(M + H)$^+$; calcd for $C_{35}H_{44}N_2O_5$: 573.3328].

2-(*N*-Phenylsulfonylindol-3-yl)ethyl 2,4-Di-*O*-benzyl-3-deoxy-6-*O*-(6-azidohexyl)-β-D-glucopyranoside (29b). 6-Azido-1-hexanol (6 mg, equivalent to 0.040 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (8 mg, 0.040 mmol) were dissolved in dichloromethane (0.7 mL) and triflic anhydride (0.007 mL, 0.040 mmol) was added dropwise. After 10 min the mixture was poured into brine (2 mL) and extracted with dichloromethane (3 × 2 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The triflate was used without purification in the next step.

Sodium hydride (1 mg, 0.025 mmol, 60% dispersion in oil) was added to a solution of alcohol **28** (6.3 mg, 0.01 mmol) and azido triflate (11 mg, equivalent to 0.040 mmol) in dichloromethane (1.2 mL) at room temperature. The mixture was stirred for 4 h and poured into water (2 mL). The aqueous phase was extracted with dichloromethane (3 × 2 mL), and the combined organic solutions were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Thin-layer chromatography (0.5 mm plate, 30% ethyl acetate/hexane) afforded **29b** (3.2 mg, 45% yield) as a colorless oil: $[\alpha]^{25}_D$ +6.2° (*c* 0.45, CH_2Cl_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.54, 138.32, 138.04, 135.16, 133.58, 131.06, 129.13,

128.41, 128.30, 127.78, 127.69, 127.66, 127.49, 126.69, 124.69, 123.54, 123.09, 119.87, 119.48, 113.69, 105.26, 78.03, 74.96, 72.67, 72.29, 71.52, 71.27, 69.94, 68.41, 51.35, 34.99, 29.48, 28.75, 26.53, 25.72, 25.66; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 775.3132 [(M + Na)$^+$; calcd for $C_{42}H_{48}N_4O_7S$: 775.3142].

2-(1*H*-Indol-3-yl)ethyl 2,4-Di-*O*-benzyl-3-deoxy-6-*O*-(6-aminohexyl)-β-D-glucopyranoside (5b). A solution of azide **29b** (0.16 g, 0.21 mmol) in THF (13.3 mL) was treated sequentially with water (0.093 mL, 5.16 mmol) and triphenylphosphine (0.112 g, 0.43 mmol). The mixture was then heated at 60 °C for 5 h, cooled to room temperature, and concentrated *in vacuo*. Flash chromatography (10% methanol/dichloromethane) gave the corresponding amine (142.3 mg, 92% yield) as a colorless oil: $[\alpha]^{25}_D$ +7.0° (*c* 1.7, $CHCl_3$); IR (CH_2Cl_2) 3680 (w), 3045 (m), 2938 (s), 2880 (s), 1606 (m), 1582 (m), 1450 (s), 1370 (s), 1260 (s), 1208 (m), 1180 (s), 1090 (s), 1075 (s), 590 (m), 570 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 1 H), 7.76 (d, *J* = 7.9 Hz, 1 H), 7.76 (d, *J* = 8.4 Hz, 1 H), 7.43–7.13 (m, 17 H), 4.58 (d, *J* = 12.0 Hz, 1 H), 4.52 (d, *J* = 11.5 Hz, 1 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 4.36 (d, *J* = 11.5 Hz, 1 H), 4.33 (d, *J* = 7.5 Hz, 1 H), 4.13 (dt, *J* = 9.5, 6.8 Hz, 1 H), 3.75 (dt, *J* = 9.51, 7.2 Hz, 1 H), 3.65 (d, *J* = 10.4 Hz, 1 H), 3.51 (dd, *J* = 10.7, 4.7 Hz, 1 H), 3.44–3.32 (m, 4 H), 3.20 (m, 1 H), 2.93 (t, *J* = 6.9 Hz, 2 H), 2.55 (t, *J* = 7.0 Hz, 2 H), 2.41 (dt, *J* = 12.3, 4.2 Hz, 1 H), 1.53–1.42 (m, 7 H), 1.34–1.18 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.30, 138.06, 137.81, 134.93, 133.32, 130.82, 128.87, 128.15, 128.04, 127.51, 127.45, 127.40, 127.23, 126.43, 124.43, 123.29, 122.84, 119.63, 119.24, 113.43, 105.01, 76.49, 74.72, 72.41, 72.05, 71.42, 71.03, 69.66, 68.14, 41.80, 34.77, 33.26, 29.34, 26.45, 25.75, 25.37; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 727.3436 [(M + H)$^+$; calcd for $C_{36}H_{46}N_2O_5$: 727.3417].

A solution of the above amine (0.119 g, 0.16 mmol) in ethanol (15 mL) was treated with 5 M aqueous potassium hydroxide (3 mL) and then heated to reflux. After 5 h the mixture was cooled, diluted with saturated aqueous ammonium chloride (25 mL), and poured into dichloromethane (30 mL). The aqueous phase was extracted with dichloromethane (4 × 10 mL), and the combined organic solutions were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (15% methanol/dichloromethane) furnished **5b** (80.9 mg, 73% yield) as a colorless oil: $[\alpha]^{25}_D$ +11.8° (*c* 0.43, CH_2Cl_2); IR (CH_2Cl_2) 3681 (w), 3436 (m), 3025 (m), 2918 (s), 2862 (s), 1729 (m), 1609 (m), 1458 (s), 1251 (m), 1098 (s), 1076 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (br s, 1 H), 7.49 (d, *J* = 8.6 Hz, 1 H), 7.27–7.16 (m, 11 H), 7.05 (apparent t, *J* = 7.1 Hz, 1 H), 6.98 (apparent t, *J* = 5.9 Hz, 1 H), 6.93 (s, 1 H), 4.67 (d, *J* = 11.8 Hz, 1 H), 4.51 (d, *J* = 11.8 Hz, 1 H), 4.49 (d, *J* = 11.4 Hz, 1 H), 4.36 (d, *J* = 7.6 Hz, 1 H), 4.31 (d, *J* = 11.4 Hz, 1 H), 4.07 (dt, *J* = 9.5, 7.3 Hz, 1 H), 3.75 (dt, *J* = 9.5, 7.5 Hz, 1 H), 3.44–3.21 (m, 6 H), 3.02 (t, *J* = 7.4 Hz, 2 H), 2.63 (br t, *J* = 6.9 Hz, 2 H), 2.42 (dt, *J* = 12.3, 4.7 Hz, 1 H), 1.49–1.35 (m, 6 H), 1.18–1.1 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.70, 138.04, 136.20, 128.42, 128.31, 127.75, 127.71, 127.58, 127.50, 122.27, 121.78, 119.11, 118.71, 112.42, 111.22, 105.30, 77.92, 75.09, 72.70, 72.40, 71.31, 71.09, 70.00, 69.93, 39.76, 34.91, 29.29, 27.37, 26.09, 25.82, 25.42; high-resolution mass spectrum (FAB *m*-nitrobenzyl alcohol) *m/z* 609.3332 [(M + Na)$^+$; calcd for $C_{36}H_{46}N_2O_5$: 609.3305].

2-(1*H*-Indol-3-yl)ethyl 2,4-Di-*O*-benzyl-3,6-dideoxy-6-amino-6-*N*-(5-hydroxypentyl)-β-D-glucopyranoside (5c). Triflic anhydride (126 μL, 0.748 mmol) was added to a stirred solution of **28** (360 mg, 0.575 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (189 mg, 0.92 mmol) in dichloromethane (3 mL) at −78 °C. After 20 min at −78 °C, the mixture was allowed to warm to room temperature over 20 min. The resultant suspension was poured into saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The oily crude triflate was used without purification in the next step.

A solution of 5-(trifluoroacetamido)-1-pentanol (**18a**) (687 mg, 3.45 mmol) in THF (16 mL) was added to a stirred suspension of sodium hydride (8.63 mmol, 345 mg, 60% dispersion in oil) in THF (20 mL) at 0 °C. After 10 min the mixture was allowed to warm to room temperature, stirred for 90 min, recooled to 0 °C, and treated with a solution of crude triflate (0.575 mmol) in dichloromethane (22 mL). The suspension was stirred for 30 min at 0 °C and then at room temperature for an additional 24 h. The reaction was quenched at 0 °C with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate, and the extracts were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (gradient elution, 1 → 2% methanol/dichloromethane) afforded an inseparable mixture of compounds, presumably **29c** and its benzenesulfonamide deprotected counterpart, which was used directly in the next step.

A stirred solution of the above mixture in ethanol (6 mL) was treated with 5 N NaOH (1 mL, 5 mmol), heated at reflux for 2 h, cooled, and concentrated *in vacuo*. The residue was taken up in dichloromethane, and the resultant solution was washed with 2 N HCl. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (8% methanol/dichloromethane) gave pure **5c** (172 mg, 52% yield for three steps) as a colorless oil: $[\alpha]^{25}_D$ +17° (*c* 0.15, acetonitrile); UV (6.5 × 10^{-5} M, acetonitrile) λ_{max} 281.2 (ε 6.2 × 10^3), 218.8 (3.62 × 10^4) nm; IR (film) 3325 (m), 3065 (w), 3035 (w), 3015 (w), 2940 (s), 2870 (s), 1500 (w), 1458 (m), 1354 (w), 1220 (w), 1076 (s), 1030 (m), 745 (s), 700 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1 H), 7.57 (d, *J* = 7.7 Hz, 1 H), 7.31–7.23 (m, 10 H), 7.17–7.14 (m, 1 H), 7.11–7.07 (m, 1 H), 7.04 (d, *J* = 2.0 Hz, 1 H), 4.71 (d, *J* = 11.8 Hz, 1 H), 4.57 (d, *J* = 11.7 Hz, 1 H), 4.56 (d, *J* = 11.9 Hz, 1 H), 4.46 (d, *J* = 7.5 Hz, 1 H), 4.40 (d, *J* = 11.5 Hz, 1 H), 4.20 (ddd, *J* = 13.8, 9.4, 6.8 Hz, 1 H), 3.87 (ddd, *J* = 14.9, 9.3, 7.4 Hz, 1 H), 3.55–3.50 (m, 3 H), 3.32–3.26 (m, 2 H), 3.11 (t, *J* = 7.2 Hz, 2 H), 3.02 (dd, *J* = 12.4, 2.9 Hz, 1 H), 2.68 (dd, *J* = 12.4, 8.1 Hz, 1 H), 2.67–2.57 (m, 2 H), 2.50 (ddd, *J* = 12.3, 4.8, 4.8 Hz, 1 H), 2.20 (s, 3 H), 1.57–1.44 (m, 5 H), 1.36–1.30 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.61, 137.92, 136.14, 128.41, 128.27, 127.79, 127.70, 127.53, 127.49, 122.18, 121.84, 119.18, 118.67, 112.56, 111.12, 105.22, 105.18, 76.53, 75.14, 74.28, 72.69, 70.99, 69.91, 62.45, 50.69, 49.49, 34.86, 32.28, 29.16, 25.80, 23.27; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 573.3314 [(M + H)$^+$; calcd for $C_{35}H_{44}N_2O_5$ 573.3328].

2-(1*H*-Indol-3-yl)ethyl 2,4-Di-*O*-benzyl-3,6-dideoxy-6-amino-6-*N*-(6-hydroxyhexyl)-β-D-glucopyranoside (5d). A solution of 6-(trifluoroacetamido)-1-hexanol (**18c**) (147 mg, 0.690 mmol) in THF (1 mL) was added to a suspension of sodium hydride (60% oil dispersion, 69.0 mg, 1.73 mmol) in THF (3 mL) at 0 °C. The mixture was stirred at room temperature for 1 h, recooled to 0 °C, and treated with a solution of the crude triflate derived from **28** (0.115 mmol), prepared as described for the synthesis of **5c**, in dry dichloromethane (5 mL). The reaction mixture was then warmed to room temperature, stirred for 48 h, and quenched at 0 °C with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*, affording an inseparable mixture of compounds, presumably **29d** and its benzenesulfonamide deprotected counterpart, which was used directly in the next step.

A stirred solution of the above mixture in ethanol (6 mL) was treated with 5 N sodium hydroxide (2 mL), heated to reflux for 2 h, cooled, and concentrated *in vacuo*. The oily residue was taken up in water and extracted with dichloromethane, and the organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (5% methanol/dichloromethane) gave **5d** (56 mg, 64% yield for two steps) as a colorless oil: $[\alpha]^{25}_D$ +13° (*c* 0.12, acetonitrile); UV (1.23 × 10^{-4} M, acetonitrile) λ_{max} 289.6 (ε 1.78 × 10^3), 280.8 (1.37 × 10^3), 228.0 (2.63 × 10^3) nm; IR (film) 3300 (br), 3060 (w), 3030 (w), 2930 (s), 2860 (m), 1450 (m), 1350 (w), 1070 (s), 740 (s), 700 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (br s, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.35–7.04 (m, 14 H), 4.71 (d, *J* = 11.8 Hz, 1 H), 4.60 (d, *J* = 11.6 Hz, 1 H), 4.57 (d, *J* = 11.9 Hz, 1 H), 4.47 (d, *J* = 7.6 Hz, 1 H), 4.41 (d, *J* = 11.5 Hz, 1 H), 4.20 (dt, *J* = 9.4, 6.8 Hz, 1 H), 3.87 (dt, *J* = 9.3, 7.6 Hz, 1 H), 3.56 (t, *J* = 10.0 Hz, 1 H), 3.52 (m, 1 H), 3.12 (t, *J* = 6.9 Hz, 2 H), 3.04 (d, *J* = 2.8 Hz, 1 H), 3.02 (d, *J* = 2.8 Hz, 1 H), 2.70–2.48 (m, 4 H), 2.05 (br s, 2 H), 1.54 (q, *J* = 11.6 Hz, 1 H), 1.48–1.26 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.61, 137.95, 136.14, 128.40, 128.27, 127.77, 127.69, 127.53, 127.49, 122.12, 121.85, 119.19, 118.68, 112.54, 111.10, 105.24, 76.87, 76.74, 75.17, 74.37, 72.70, 71.00, 69.92, 62.71, 50.81, 49.58, 34.90, 32.53, 29.67, 26.94, 25.81, 25.53; high-resolution mass spectrum (Cl, CH_4) *m/z* 587.3557 [(M + H)$^+$; calcd for $C_{36}H_{47}N_2O_5$ 587.3485].

5-Phthalimido-1-pentanol (33). A solution of 5-amino-1-pentanol (5.00 g, 48.5 mmol) in benzene (150 mL) was treated with *N*-carbethoxyphthalimide (11.0 g, 50.2 mmol) and stirred at room temperature for 5 h. Concentration *in vacuo* and flash chromatography (25% ethyl acetate/petroleum ether) gave **33** (9.6 mg, 84% yield) as a clear, colorless oil: ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.39, 133.78, 131.96, 123.05, 62.34,

37.74, 32.03, 28.22, 22.93; high-resolution mass spectrum (CI, NH_3) m/z 234.1108 [(M + H)$^+$; calcd for $C_{13}H_{15}NO_3$ 234.1129].

3,4-Di-*O*-Benzyl-6-*O*-(5-phthalimidopentyl)-D-glucal (34). 5-Phthalimidopentyl triflate was prepared as follows: A stirred solution of 5-phthalimido-1-pentanol (**33**) (1.32 g, 4.67 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.960 g, 4.67 mmol) in dry dichloromethane (10 mL) was treated with triflic anhydride (0.784 mL, 4.67 mmol). After 10 min at room temperature, the mixture was diluted with water (100 mL) and extracted with dichloromethane (2 × 200 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*, affording a yellow solid which was used without purification in the next reaction.

Sodium hydride (60% dispersion in oil, 0.20 g, 5.06 mmol) was added to a solution of alcohol **32** (1.27 g, 3.89 mmol), 5-phthalimidopentyl triflate (4.67 mmol), and 15-crown-5 (20 mg, 2.3 mol %), in methylene chloride (100 mL) at 0 °C. After stirring for 24 h at room temperature, the mixture was poured into water. The aqueous layer was extracted with methylene chloride (3 × 50 mL), and the combined extracts were washed with water, dried over magnesium sulfate, and concentrated *in vacuo*. Flash chromatography (3% ether/methylene chloride) provided **34** (1.82 g, 86% yield) as a colorless oil: $[\alpha]^{25}_D$ −8.2° (*c* 0.70, $CHCl_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) d 168.4, 144.8, 138.4, 138.3, 133.9, 132.2, 128.4, 127.9, 127.8, 127.6, 123.2, 99.9, 76.8, 75.8, 74.5, 73.8, 71.4, 70.5, 69.2, 37.9, 29.2, 28.5, 23.5; high-resolution mass spectrum (CI, NH_3) m/z 541.2483 (M$^+$; calcd for $C_{33}H_{35}NO_6$ 541.2464).

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 3,4-Di-*O*-benzyl-6-*O*-(5-phthalimidopentyl)-β-D-glucopyranoside (35). A solution of dimethyldioxirane[58] in acetone (1.2 equiv, ca. 0.05 M) was added dropwise to glycal **34** (1.53 g, 2.80 mmol) in dichloromethane (26 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and concentrated *in vacuo*. To a solution of the crude epoxide and **12** (1.15 g, 3.82 mmol) in THF (12 mL) at −78 °C was added $ZnCl_2$ (1.0 M in *ether*, 5.6 mL, 5.6 mmol), and the mixture was allowed to stir at −78 °C for 1 h. The solution was then slowly warmed to room temperature and stirred 18 h. The mixture was poured into saturated aqueous sodium bicarbonate (50 mL) and extracted with ethyl acetate (3 × 50 mL), and the combined extracts were washed with water, dried over magnesium sulfate, and concentrated *in vacuo*. Flash chromatography (45% ethyl acetate/hexane) gave **35** (1.05 g, 44% yield) as a colorless oil: $[\alpha]^{25}_D$ −8.1° (*c* 1.8 $CHCl_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 168.4, 138.6, 138.2, 135.1, 133.8, 133.7, 132.1, 131.0, 129.1, 128.4, 127.9, 127.8, 127.7, 126.7, 124.7, 123.5, 123.1, 119.7, 119.4, 113.7, 102.8, 84.4, 76.5, 75.1, 71.5, 69.6, 68.7, 37.8, 29.2, 28.4, 25.4, 23.5; high-resolution mass spectrum (Cl, NH_3) m/z 662.2774 (M$^+$; calcd for $C_{35}H_{42}SO_7$ 662.2775).

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 2-Deoxy-3,4-di-*O*-benzyl-6-*O*-(5-phthalimidopentyl)-β-D-glucopyranoside (36). A solution of **35** (0.455 g, 0.530 mmol) in THF (10 mL) was cooled to −78 °C and treated with carbon disulfide (27 μL, 0.583 mmol) followed by sodium bis(trimethylsilyl)amide (0.6 M in *toluene*, 0.953 mL, 0.572 mmol). After 20 min methyl iodide (59 μL, 0.640 mmol) was added, and the solution was stirred for 5 min at −78 °C and then at room temperature for 45 min. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*, affording the crude xanthate as a pale yellow oil (0.462 g, 92% yield) which was used without purification in the next step.

To a solution of the crude xanthate (0.462 g, 0.487 mmol) and AIBN (10 mg) in toluene (8 mL) was added tributyltin hydride (0.214 mL, 0.795 mmol), and the reaction mixture heated to reflux for 4 h, cooled, and concentrated *in vacuo*. The residue was taken up in acetonitrile (30 mL) and washed with petroleum ether (5 × 10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to an oil. Flash chromatography (20% ethyl acetate/petroleum ether) gave **36** (0.296 g, 72% yield) as a colorless oil: $[\alpha]^{25}_D$ −10° (*c* 1.1 $CHCl_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 23.5, 25.5, 28.4, 29.2, 36.7, 37.9, 68.1, 70.0, 71.4, 75.0, 75.2, 78.2, 79.3, 99.9, 113.6, 119.6, 123.1, 123.5, 124.7, 126.7, 127.7, 128.0, 128.4, 129.2, 131.1, 132.1, 133.6, 133.8, 135.1, 138.3, 138.5, 168.4; high-resolution mass spectrum (Cl, NH_3) m/z 814.3287 (M$^+$; calcd for $C_{44}H_{50}SO_8N_2$ 814.3289).

2-(1*H*-Indol-3-yl)ethyl 2-Deoxy-3,4-di-*O*-benzyl-6-*O*-(5-aminopentyl)-β-D-glucopyranoside (6). A solution of hydrazine (0.2 M in *MeOH*, 6 mL) was added to **36** (0.034 g, 0.043 mmol). After stirring for 16 h, the reaction mixture was concentrated *in vacuo*, the residue was dissolved in ethanol (4 mL), and 5 N Na*H* (0.90 mL) was added. The mixture was heated at reflux for 4 h, cooled, and extracted with methylene chloride (3 × 10 mL). The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to an oil. Flash chromatography (11% methanol/methylene chloride) afforded **6** (11 mg, 44%) as a pale yellow oil; $[\alpha]^{25}_D$ −15° (*c* 0.62, $CHCl_3$); IR ($CHCl_3$) 3490 (m), 3345 (br, m), 3020 (m), 2945 (s), 2882 (s), 1625 (w), 1500 (w), 1459 (m), 1370 (m), 1230 (w), 1100 (s), 695 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (br s, 1 H), 7.49 (d, *J* = 7.9 Hz, 1 H), 7.19–7.31 (m, 11 H), 7.10 (t, *J* = 7.1 Hz, 1 H), 7.00 (t, *J* = 8.0 Hz, 1 H), 6.97 (s, 1 H), 4.83 (d, *J* = 11.1 Hz, 1 H), 4.59 (d, *J* = 11.7 Hz, 1 H), 4.51 (d, *J* = 11.0 Hz), 4.50 (d, *J* = 11.7, 1 H), 4.39 (d, *J* = 9.7 Hz, 1 H), 4.00 (apparent q, *J* = 7.3 Hz, 1 H), 3.67 (apparent q, *J* = 7.3 Hz, 1 H), 3.60 (d, *J* = 9.0 Hz, 1 H), 3.56 (m, 1 H), 3.46 (dd, *J* = 10.8, 5.3 Hz), 3.31 (m, 4 H), 2.98 (t, *J* = 7.2 Hz, 2 H), 2.50 (t, *J* = 7.3 Hz, 2 H), 2.28 (m, 2 H), 1.57 (q, *J* = 10 Hz, 1 H), 1.42 (m, 4 H), 1.19 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 138.3, 138.2, 136.2, 128.4, 128.0, 127.7, 127.5, 122.3, 121.8, 119.1, 118.7, 112.0, 111.4, 99.9, 79.3, 78.2, 74.9, 71.4, 71.0, 69.9, 69.8, 39.7, 36.7, 28.8, 27.6, 25.7, 23.1; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) m/z 573.3371 [(M + H)$^+$; calcd for $C_{35}H_{44}N_2O_5$ 573.3328].

Methyl 2,3,6-Tri-*O*-benzoyl-4-deoxy-α-D-glucopyranoside (38). A solution of **37** (5.00 g, 9.87 mmol) in THF (100 mL) was cooled to −78 °C and treated with carbon disulfide (0.45 mL, 7.48 mmol) followed by sodium bis(trimethylsilyl)amide (1.0 M in THF, 10.5 mL, 51.8 mmol). After 20 min methyl iodide (2.10 mL, 33.7 mmol) was added, and the solution was stirred for 5 min at −78 °C and then at room temperature for 45 min. The reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*, affording the crude xanthate as a pale yellow oil (5.70 g, 97% yield) which was used without purification in the next step. Purification of an analytical sample by flash chromatography (20% ethyl acetate/petroleum ether) gave white crystals: mp 72–73 °C; $[\alpha]^{25}_D$ +140° (*c* 0.13, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.10, 165.73, 165.53, 133.37, 133.13, 129.90, 129.75, 129.70, 129.21, 128.90, 128.37, 128.23, 96.94, 76.25, 71.83, 70.45, 67.36, 62.58, 55.60, 19.18; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) m/z 597.1286 [(M + H)$^+$; calcd for $C_{30}H_{28}O_9S_2$ 597.1253].

Tributyltin hydride (6.68 mL, 24.8 mmol) was added to a solution of the crude xanthate (5.70 g, 9.55 mmol) and AIBN (50 mg) in toluene (120 mL), and the reaction mixture was then heated to reflux for 4 h, cooled, and concentrated *in vacuo*. The residue was taken up in acetonitrile (200 mL) and extracted with petroleum ether (5 × 100 mL). The acetonitrile solution was dried over sodium sulfate, filtered, and concentrated *in vacuo*, affording a clear, colorless oil which solidified on standing. Flash chromatography (20% ethyl acetate/petroleum ether) gave **38** (3.60 g, 82% yield) as a white solid: mp 119–120 °C (lit.[39] mp 119–120 °C); $[\alpha]^{25}_D$ +121° (*c* 0.17, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.23, 166.09, 165.81, 133.22, 133.16, 133.09, 129.84, 129.67, 129.62, 129.41, 128.42, 128.35, 128.32, 97.82, 72.57, 68.38, 66.05, 65.33, 55.32, 33.16; high resolution mass spectrum (Cl, NH_3) m/z 536.1902 [(M + NH_4)$^+$; calcd for $C_{28}H_{30}N_1O_8$ 536.1919].

Acetyl 2,3,6-Tri-*O*-benzoyl-4-deoxy-α-D-glucopyranoside (39). A solution of glycoside **38** (0.50 g, 1.1 mmol) in acetic anhydride (3.0 mL, 32 mmol) was cooled to 0 °C and treated with boron trifluoride etherate (0.1 mL). The reaction mixture was then stirred at room temperature for 4 h, diluted with ethyl acetate, and poured into ice-cold saturated sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*, affording **39** (0.45 g, 85% yield) as a colorless which crystallized upon standing as white needles: mp 123–124 °C; $[\alpha]^{25}_D$ +123° (*c* 0.19, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.87, 166.16, 165.54, 133.35, 133.29, 133.22, 129.71, 129.66, 129.58, 129.35, 129.02, 128.42, 128.39, 90.32, 71.59, 71.36, 70.78, 68.12, 68.05, 65.57, 32.76, 20.86, 20.80; high-resolution mass spectrum (Cl, NH_3) m/z 536.1902 [(M + NH_4)$^+$; calcd for $C_{29}H_{26}O_9$: 536.1919].

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 2,3,6-Tri-*O*-benzoyl-4-deoxy-β-D-glucopyranoside (40). A stirred solution of acetate **39** (0.137 g, 0.29 mmol) in dichloromethane (3 mL) was cooled to 0 °C and treated with 30% hydrogen bromide in acetic acid (0.07 mL, 0.33 mmol). The reaction mixture was stirred at room temperature for 4 h, diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*, furnishing a colorless oil which solidified upon standing. Recrystallization (ether/petroleum ether) gave the bromide (0.15 g, 100% yield) as white crystals: mp 134–135 °C; $[\alpha]^{25}_D$ +114° (*c* 0.10, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.11, 165.64, 165.53, 133.65, 133.35, 133.32, 130.01, 129.78, 126.69,

129.49, 129.31, 128.75, 128.48, 128.42, 88.85, 71.54, 70.78, 68.63, 65.05, 32.16; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 539.0661 [(M + H)$^+$; calcd for $C_{27}H_{23}O_7Br$ 539.0705].

A solution of the above bromide (0.40 g, 0.814 mmol) in hexane and benzene (2:3, 17 mL) was added to a mixture of activated, powdered 4Å molecular sieves (0.83 g), protected tryptophol **12** (0.37 g, 1.23 mmol), and silver(I) oxide (0.83 g, 3.58 mmol) in a flask wrapped with aluminum foil. The mixture was stirred at room temperature for 2 days, filtered through Celite, and concentrated *in vacuo* to furnish a colorless oil. Flash chromatography (50% ether/petroleum ether) then gave **40** (0.50 g, 81% yield) as a colorless solid: mp 76–78 °C; $[\alpha]^{25}_D$ +28° (*c* 0.12, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.20, 165.89, 165.42, 135.03, 133.55, 133.24, 133.22, 133.06, 130.86, 129.72, 129.67, 129.62, 129.49, 129.32, 129.12, 128.42, 128.37, 128.31, 126.67, 124.58, 123.43, 123.06, 119.42, 119.35, 113.56, 101.42, 72.53, 71.56, 69.75, 68.80, 65.81, 33.00, 25.60; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 759.2108 (M$^+$; calcd for $C_{43}H_{37}NO_{10}S$ 759.2138).

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 4-Deoxy-β-D-glucopyranoside (41). A solution of tribenzoate **40** (120 mg, 0.158 mmol) in methanol (20 mL) was treated with sodium methoxide (0.027 g, 0.507 mmol) and then stirred for 16 h. The mixture was neutralized with Amberlyst 15 ion exchange resin and filtered, and the filtrate was concentrated *in vacuo* to yield a tan solid. Flash chromatography (10% methanol/dichloromethane) gave **41** (65 mg, 91% yield) as a white solid: mp 64–65 °C; $[\alpha]^{25}_D$ −29° (*c* 0.15, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.19, 135.14, 133.74, 131.04, 129.23, 126.70, 124.83, 123.68, 123.22, 119.74, 119.31, 113.76, 102.92, 76.09, 72.75, 70.72, 68.72, 65.04, 33.75, 25.40; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 447.1389 (M$^+$; calcd for $C_{22}H_{25}NO_7S$ 447.1352).

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 4-Deoxy-6-(*O*-*tert*-butyldimethylsilyl)-β-D-glucopyranoside (42). A solution of triol **41** (0.24 g, 0.536 mmol) in DMF (6 mL) was treated with imidazole (73 mg, 1.07 mmol) followed by *tert*-butyldiphenylsilyl chloride (0.17 mL, 0.643 mmol). The reaction mixture was then heated at 70 °C for 48 h, cooled, quenched with methanol (5 mL), and concentrated *in vacuo*. The residue was extracted with ethyl acetate, and the extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resultant pale yellow oil was purified by flash chromatography (3% methanol/dichloromethane) to give **42** (0.36 g, 97% yield) as a colorless oil: $[\alpha]^{25}_D$ −24 °C (*c* 0.37, acetonitrile); UV (1.75×10^{-4} M, acetonitrile) λ_{max} 253.2 (ε 1.53×10^3), 212.0 (2.58×10^3) nm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.22, 135.55, 135.52, 133.64, 133.33, 129.69, 129.66, 129.16, 127.65, 126.65, 124.76, 123.49, 123.15, 119.75, 119.41, 113.71, 102.80, 76.24, 72.66, 70.82, 68.64, 66.09, 34.75, 26.75, 25.48, 19.20; high-resolution mass spectrum (Cl, NH_3) *m/z* 703.2929 [(M + NH_4)$^+$; calcd for $C_{38}H_{47}N_2O_7SSi$ 703.2873].

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 2,3-Di-*O*-benzyl-4-deoxy-6-(*O*-*tert*-butyldimethylsilyl)-β-D-glucopyranoside (43). A solution of diol **42** (0.50 g, 0.729 mmol) in THF (7 mL) was added to a stirred suspension of sodium hydride (73.0 mg, 3.04 mmol, 60% oil dispersion) in THF (3 mL) at 0 °C, and the reaction was stirred at room temperature for 30 min. The mixture was recooled to 0 °C, and benzyl bromide (0.26 mL, 2.2 mmol) was added dropwise. After 3 days at room temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ether. The extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (33% ether/petroleum ether) afforded **43** (0.73 g, 76% yield) as a colorless oil: $[\alpha]^{25}_D$ −5.6° (*c* 0.16, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.64, 138.31, 135.58, 135.54, 135.19, 133.54, 133.46, 130.99, 129.70, 129.67, 129.10, 128.33, 128.20, 127.95, 127.66, 127.62, 127.54, 127.44, 126.62, 124.70, 123.42, 123.11, 119.74, 119.51, 113.69, 103.84, 82.95, 76.74, 74.89, 72.24, 68.55, 66.22, 33.66, 26.80, 25.80, 19.23; high-resolution mass spectrum (Cl, NH_3) *m/z* 883.3898 [(M + NH_4)$^+$; calcd for $C_{52}H_{59}N_2O_7SSi$ 883.3812].

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 2,3-Di-*O*-benzyl-4-deoxy-β-D-glucopyranoside (44). A solution of silyl ether **43** (0.37 g, 0.427 mmol) in THF (11 mL) was treated with tetrabutylammonium fluoride (1.33 mL, 1.0 M in THF, 1.33 mmol) and stirred at room temperature for 3 h. The solution was then diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (33% petroleum ether/ethyl acetate) gave **44** (0.43 g, 85% yield) as a colorless oil: $[\alpha]^{25}_D$ −4.4° (*c* 0.32, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.54, 138.19, 135.14, 133.61, 130.99, 129.12, 128.32. 128.20, 127.92, 127.60, 127.56, 127.49, 126.63, 124.72, 123.58, 123.13, 119.69, 119.37, 113.69, 103.84, 82.74, 78.11, 74.93, 72.29, 72.19, 68.65, 65.12, 32.61, 25.65; high-resolution mass spectrum (Cl, CH_4) *m/z* 645.2675 [(M + NH_4)$^+$; calcd for $C_{36}H_{41}N_2O_7S$ 645.2634].

2-(*N*-(Phenylsulfonyl)indol-3-yl)ethyl 2,3-Di-*O*-benzyl-4-deoxy-6-*O*-(5-phthalimidopentyl)-β-D-glucopyranoside (45). 5-Phthalimidopentyl triflate was prepared as follows: A stirred solution of 5-phthalimido-1-pentanol (**33**) (39.1 mg, 0.168 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (34.5 mg, 0.168 mmol) in dry dichloromethane (1.5 mL) was treated with triflic anhydride (28.3 μL, 0.168 mmol). After 10 min at room temperature, the mixture was diluted with water (25 mL) and extracted with dichloromethane (2 × 50 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*, affording a yellow solid which was used without purification in the next reaction.

Sodium hydride (60% dispersion in oil, 51 mg, 1.3 mmol) was added to a solution of alcohol **44** (150 mg, 0.240 mmol), 5-phthalimidopentyl triflate (1.37 mmol), and 2,6-di-*tert*-butyl-4-methylpyridine (282 mg, 1.39 mmol) in dichloromethane (1.5 mL) at 0 °C. The reaction mixture was stirred for 48 h at room temperature, quenched with saturated aqueous ammonium chloride, and extracted with dichloromethane, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (20% ethyl acetate/petroleum ether) gave **45** (158 mg, 78% yield) as a colorless oil: $[\alpha]^{25}_D$ −2.5° (*c* 0.36, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.37, 138.61, 138.31, 135.19, 133.83, 133.56, 132.13, 131.03, 129.11, 128.31, 128.19, 127.96, 127.63, 127.51, 127.44, 126.65, 124.68, 123.51, 123.12, 119.78, 119.49, 113.70, 103.85, 82.83, 78.23, 74.90, 73.10, 72.16, 71.39, 70.95, 68.68, 37.86, 33.94, 29.67, 29.11, 28.36, 25.75, 23.41; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 865.3201 [(M + Na)$^+$; calcd for $C_{49}H_{50}N_2O_9SNa$ 865.3134].

2-(1*H*-Indol-3-yl)ethyl 2,3-Di-*O*-benzyl-6-*O*-(5-aminopentyl)-β-D-glucopyranoside (7). Sodium methoxide (40 mg, 0.740 mmol) was added to a solution of **45** (150 mg, 0.178 mmol) in methanol (8 mL), and the reaction mixture was then heated at reflux for 24 h, cooled, poured into water (100 mL), and extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (10% methanol/dichloromethane) afforded **7** (72.0 mg, 71% yield) as a colorless oil: $[\alpha]^{25}_D$ +3.9° (*c* 1.8, acetonitrile); UV (1.57×10^{-4} M, acetonitrile) λ_{max} 280.0 (ε 1.41×10^3), 224.8 (1.66×10^3) nm; IR ($CHCl_3$) 3350 (br), 3060 (w), 2930 (m), 2860 (m), 1630 (m), 1590 (m), 1560 (m), 1450 (m), 1400 (m), 1270 (m), 1100 (s), 740 (s), 700 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (br m, 1 H), 7.48 (d, *J* = 7.8 Hz, 1 H), 7.36–6.93 (m, 15 H), 4.62–4.49 (m, 4 H), 4.32 (d, *J* = 7.7 Hz, 1 H), 4.11 (dt, *J* = 9.4, 6.7 Hz, 1 H), 3.78 (dt, *J* = 9.2, 7.4 Hz, 1 H), 3.52 (m, 4 H), 3.26 (m, 2 H), 3.22 (t, *J* = 7.2 Hz, 1 H), 3.13 (t, *J* = 7.8 Hz, 1 H), 3.00 (t, *J* = 7.0 Hz, 2 H), 2.00 (ddd, *J* = 6.7, 5.2, 1.4 Hz, 1 H), 1.29 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.11, 138.10, 130.75, 130.59, 129.31, 128.92, 128.84, 128.57, 128.44, 123.70, 122.24, 119.40, 112.82, 112.31, 105.01, 84.13, 79.55, 75.76, 74.12, 73.12, 72.53, 72.18, 71.29, 41.05, 34.54, 30.38, 29.90, 27.07, 24.72; high-resolution mass spectrum (Cl, NH_3) *m/z* 573.3301 [(M + H)$^+$; calcd for $C_{35}H_{45}N_2O_5$ 573.3328].

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(5-azidopentyl)-β-D-glucopyranoside (47a). At room temperature a solution of 5-azido-1-pentanol (0.18 g, 1.40 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.3 g, 1.46 mmol) in dichloromethane (10 mL) was treated dropwise with triflic anhydride (0.240 mL, 1.43 mmol). After 15 min the mixture was diluted with dichloromethane (40 mL) and poured into saturated aqueous sodium bicarbonate (50 mL). The organic phase was washed with brine (2 × 20 mL), dried over magnesium sulfate, filtered, and concentrated, affording a light yellow solid which was used without purification. The alcohol **46** (0.2 g, 0.429 mmol) and the crude triflate were dissolved in dichloromethane (2 mL) and treated with sodium hydride (0.025 g, 0.625 mmol, 60% dispersion in oil). The mixture was stirred for 48 h, diluted with dichloromethane (40 mL), and poured into saturated aqueous ammonium chloride (40 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL) and the combined organic solutions were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (15% ethyl acetate/hexane) provided **47a** (0.126 g, 51% yield) as a white solid: mp 69–70 °C (MeOH/CH_2Cl_2); $[\alpha]^{25}_D$ +7.7° (*c* 0.75, $CHCl_3$; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.59, 138.53, 138.27, 128.42, 128.35, 128.33, 128.07, 127.88, 127.83, 127.76, 127.60, 127.50, 104.73, 84.63, 82.32, 77.96, 75.67, 74.97, 74.84, 74.72, 71.41, 69.70, 57.08, 51.35, 29.22, 28.69, 23.44; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 598.2880 [(M + Na)$^+$; calcd for $C_{33}H_{39}N_3O_6$: 598.2893].

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(5-aminopentyl)-β-D-glucopyranoside

(**8a**). Azide **47a** (0.126 g, 0.219 mmol) was dissolved in THF (12 mL) and treated with water (0.096 mL, 5.33 mmol) followed by triphenylphosphine (0.114 g, 0.44 mmol). The mixture was then heated at 60 °C for 12 h, cooled, and concentrated *in vacuo*. Flash chromatography (10% methanol/dichloromethane) afforded **8a** (87.3 mg, 73% yield) as a white solid: mp 79–80 °C; $[\alpha]^{25}_D$ +6.8° (*c* 1.85, $CHCl_3$); IR (CH_2Cl_2) 3700 (w), 3040 (s), 2980 (s), 2920 (s), 2860 (m), 1420 (s), 1350 (m), 1260 (s), 1140 (m), 1060 (s), 890 (s), 700 (br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.25 (m, 15 H), 4.92 (d, *J* = 10.9 Hz, 1 H), 4.91 (d, *J* = 11.0 Hz, 1 H), 4.85 (d, *J* = 10.9 Hz, 1 H), 4.78 (d, *J* = 11.0 Hz, 1 H), 4.70 (d, *J* = 10.9 Hz, 1 H), 4.61 (d, *J* = 10.9 Hz, 1 H), 4.29 (d, *J* = 7.8 Hz, 1 H), 3.70–3.40 (m, 8 H), 3.56 (s, 3 H), 2.66 (t, *J* = 6.9 Hz, 2 H), 1.61–1.56 (m, 4 H), 1.46–1.35 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.58, 138.52, 138.25, 128.39, 128.31, 128.05, 127.85, 127.84, 127.73, 127.58, 127.55, 104.71, 84.61, 82.30, 77.94, 75.65, 74.95, 74.83, 74.70, 71.63, 69.61, 57.07, 42.02, 33.47, 29.48, 23.45; high-resolution mass spectrum (FAB, *m*-nitrobenzyl alcohol) *m/z* 572.2997 $[(M + Na)^+$; calcd for $C_{33}H_{43}O_6N$: 572.2988].

Methyl 2,3,4-Tri-*O*-benzyl-6-amino-6-deoxy-6-*N*-(5-hydroxypentyl)-β-D-glucopyranoside (8b). A stirred solution of **46** (800 mg, 1.71 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (632 mg, 3.08 mmol) in dichloromethane (9 mL) was cooled to −78 °C and treated with triflic anhydride (0.345 mL, 2.05 mmol). After 15 min the mixture was warmed to room temperature over 20 min, poured into saturated aqueous sodium bicarbonate (20 mL), and extracted with ethyl acetate (50 mL). The organic layer was washed with additional bicarbonate solution and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*, affording crude triflate which was used in the next step without further purification.

A solution of 5-(trifluoroacetamido)-1-pentanol (**18a**) (1.7 g, 8.6 mmol) in THF (35 mL) was added to a stirred suspension of sodium hydride (855 mg, 21.4 mmol, 60% oil dispersion) in THF (60 mL) at 0 °C. After 10 min the suspension was warmed to room temperature, stirred for 1 h, and recooled to 0 °C. A solution of the crude triflate (1.71 mmol) in dichloromethane (60 mL) was then added, and stirring continued at 0 °C for 30 min and at room temperature for 24 h. The reaction mixture was quenched at 0 °C with saturated aqueous ammonium chloride and extracted with ethyl acetate, and the combined organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification through a small plug of silica gel (30% ethyl acetate/petroleum ether) gave crude **47b** which was used immediately in the next step.

A stirred solution of the above crude **47b** in ethanol (10 mL) was treated with 5 N NaOH (3 mL, 15 mmol) at room temperature and then heated at reflux for 2 h, cooled, and concentrated *in vacuo*. The residue was diluted with dichloromethane and washed with 2 N HCl. The aqueous layer was extracted with dichloromethane (3 × 50 mL), and the combined organic solutions were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Recrystallization (ethyl acetate/petroleum ether) furnished pure **8b** (675 mg, 72% yield from **46**) as a white solid: mp 95–95.5 °C; $[\alpha]^{25}_D$ +9.3° (*c* 0.15, acetonitrile); IR (film) 3280 (m), 3095 (w), 3065 (w), 3035 (w), 2935 (s), 2915 (s), 2860 (s), 1496 (w), 1454 (m), 1404 (w), 1393 (w), 1358 (m), 1214 (m), 1115 (s), 1072 (s), 1037 (m), 1027 (m), 1009 (m), 911 (w), 826 (w), 747 (s), 696 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.24 (m, 15 H), 4.92 (d, *J* = 7.5 Hz, 1 H), 4.90 (d, *J* = 7.6 Hz, 1 H), 4.85 (d, *J* = 11.0 Hz, 1 H), 4.78 (d, *J* = 11.0 Hz, 1 H), 4.70 (d, *J* = 11.0 Hz, 1 H), 4.60 (d, *J* = 11.0 Hz, 1 H), 4.32 (d, *J* = 7.8 Hz, 1 H), 3.66–3.59 (m, 3 H), 3.56 (s, 3 H), 3.48–3.36 (m, 3 H), 2.94 (dd, *J* = 12.5, 2.1 Hz, 1 H), 2.68 (dd, *J* = 12.0, 6.8 Hz, 1 H), 2.64–2.53 (m, 2 H), 1.71 (s, 2 H), 1.59–1.53 (m, 2 H), 1.51–1.45 (m, 2 H), 1.42–1.36 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.55, 138.47, 138.17, 128.39, 128.33, 128.03, 127.95, 127.85, 127.77, 127.60, 127.57, 104.72, 84.56, 82.45, 79.74, 75.66, 75.02, 74.74, 74.16, 62.62, 57.20, 50.69, 49.72, 32.49, 29.65, 23.37; high-resolution mass spectrum (Cl, NH_3) *m/z* 550.3179 $[(M + H)^+$; calcd for $C_{33}H_{43}O_6N$ 550.3168].

2-(1*H*-Indol-3-yl)ethyl 2,3,4-Tri-*O*-benzyl-β-D-glucopyranoside (9). A stirred solution of **17** (100 mg, 0.136 mmol) in ethanol (3 mL) was treated with 5 N NaOH (1 mL), then heated at reflux for 2 h, cooled, and concentrated *in vacuo*. The residue was diluted with dichloromethane and washed with 2 N HCl, and the aqueous layer was extracted with dichloromethane. The combined organic solutions were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (25% ethyl acetate/petroleum ether) furnished **9** (68 mg, 85% yield) as a colorless oil: $[\alpha]^{25}_D$ −2.5° (*c* 1.37, acetonitrile); UV (2.89 × 10^{-4} M, acetonitrile) λ_{max} 289.6 (ε 3.56 × 10^3), 281.2 (4.24 × 10^3), 222.4 (1.01 × 10^4) nm; IR (film) 3575 (sh), 3435 (m), 3085 (sh), 3065 (w), 3035 (w), 2925 (m), 2880 (m), 1500 (w), 1455 (m), 1360 (w), 1310 (w), 1150 (sh), 1085 (s), 1030 (s), 920 (w), 810 (w), 740 (s), 700 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.33–7.24 (m, 15 H), 7.20–7.17 (m, 2 H), 7.11 (t, *J* = 7.8 Hz, 1 H), 7.01 (d, *J* = 1.8 Hz, 1 H), 4.91 (d, *J* = 10.9 Hz, 1 H), 4.85 (d, *J* = 10.9 Hz, 1 H), 4.80 (d, *J* = 10.9 Hz, 1 H), 4.79 (d, *J* = 11.0 Hz, 1 H), 4.64 (d, *J* = 11.0 Hz, 1 H), 4.63 (d, *J* = 11.0 Hz, 1 H), 4.49 (d, *J* = 7.8 Hz, 1 H), 4.22 (ddd, *J* = 9.4, 6.7, 6.7 Hz, 1 H), 3.90–3.82 (m, 2 H), 3.72–3.67 (m, 1 H), 3.65 (apparent t, *J* = 9.1 Hz, 1 H), 3.56 (apparent t, *J* = 9.3 Hz, 1 H), 3.42 (apparent t, *J* = 8.1 Hz, 1 H), 3.35 (ddd, *J* = 9.5, 4.3, 2.8 Hz, 1 H), 3.11 (t, *J* = 7.0 Hz, 2 H), 1.87 (dd, *J* = 7.6, 5.9 Hz, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 138.52, 138.44, 137.98, 136.17, 128.46, 128.36, 128.29, 128.05, 128.00, 127.89, 127.86, 127.60, 127.57, 127.45, 122.09, 122.01, 119.34, 118.68, 112.60, 111.13, 103.69, 84.49, 82.34, 77.57, 75.64, 75.04, 75.01, 74.75, 70.25, 62.04, 25.86; high-resolution mass spectrum (Cl, NH_3) *m/z* 611.3043 $[(M + NH_4)^+$; calcd for $C_{37}H_{39}O_6N$ 611.3121].

Methyl 2,3-Di-*O*-benzyl-4,6-di-*O*-isopropylidene-β-D-glucopyranoside (50). A solution of glucoside **49** (2.5 g, 10.7 mmol) in THF (100 mL) was added to a suspension of sodium hydride (0.94 g, 23.5 mmol) in THF (50 mL) at 0 °C. The reaction was stirred at room temperature for 1 h and cooled to 0 °C, and benzyl bromide (2.8 mL, 24 mmol) was then added dropwise, followed by tetrabutylammonium iodide (100 mg). The mixture was stirred at room temperature for 24 h, quenched with saturated aqueous ammonium chloride, and extracted with ether, and the extracts washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (10% ethyl acetate/petroleum ether) afforded **50** as a colorless oil (4.02 g, 91% yield): $[\alpha]^{25}_D$ −2.0° (*c* 0.15, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.81, 138.54, 128.26, 128.17, 127.98, 127.85, 127.58, 127.46, 105.16, 99.24, 82.14, 81.27, 75.19, 74.77, 74.27, 69.79, 62.25, 57.32, 29.14, 19.09; high-resolution mass spectrum (Cl, NH_3) *m/z* 415.2137 $[(M + H)^+$; calcd for $C_{24}H_{31}O_6$ 415.2120].

Methyl 2,3-Di-*O*-benzyl-β-D-glucopyranoside (51). Amberlyst 15 ion exchange resin (0.5 g) was added to a solution of **50** (1.00 g, 2.4 mmol) in methanol (50 mL), and the mixture was stirred at room temperature for 4 h, filtered, and concentrated *in vacuo*. Flash chromatography (6% methanol/dichloromethane) gave **51** (0.75 g, 83% yield) as a white foam: $[\alpha]^{25}_D$ +16° (*c* 0.15, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.48, 138.34, 128.49, 128.46, 128.30, 127.99, 127.83, 127.76, 127.62, 104.85, 83.82, 81.87, 75.13, 74.90, 74.57, 70.18, 62.30, 57.20; high-resolution mass spectrum (Cl, NH_3) *m/z* 392.2043 $[(M + NH_4)^+$; calcd for $C_{21}H_{30}NO_6$ 392.2072].

Methyl 2,3-Di-*O*-benzyl-6-(*O*-*tert*-butyldiphenylsilyl)-β-D-glucopyranoside (52). A solution of **51** (3.30 g, 8.81 mmol) and imidazole (0.84 g, 12.3 mmol) in a mixture of THF (150 mL) and DMF (25 mL) was treated with *tert*-butyldiphenylsilyl chloride (2.80 mL, 10.6 mmol) and heated at 50 °C for 24 h. The reaction mixture was quenched with methanol (5 mL) and concentrated *in vacuo*. The resultant oil was taken up in ethyl acetate, and the solution was washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (10% ethyl acetate/petroleum ether) furnished **52** (5.40 g, 100% yield) as a colorless oil: $[\alpha]^{25}_D$ +7.3° (*c* 0.22, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.71, 138.62, 135.69, 135.61, 129.73, 128.50, 128.34, 128.03, 127.99, 127.78, 127.72, 127.69, 127.62, 104.68, 84.22, 81.93, 75.30, 74.89, 74.67, 71.62, 64.44, 56.86, 26.79, 19.25; high-resolution mass spectrum (Cl, NH_3) *m/z* 630.3296 $[(M + NH_4)^+$; calcd for $C_{37}H_{48}NO_6Si$ 630.3251].

Methyl 2,3-Di-*O*-benzyl-4-deoxy-6-(*O*-*tert*-butyldiphenylsilyl)-β-D-glucopyranoside (53). A solution of **52** (0.33 g, 0.54 mmol) in THF (20 mL) was cooled to −78 °C and treated with sodium bis(trimethylsilyl)-amide (0.66 mL, 1.0 M in THF, 0.66 mmol) followed by carbon disulfide (46 μL, 0.77 mmol). After 15 min methyl iodide (137 μL, 2.20 mmol) was added, and the solution was stirred 15 min further at −78 °C and then at room temperature for 45 min. The reaction mixture was quenched with water (2 mL) and extracted with ether. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* affording the crude xanthate as a yellow oil which was used without purification.

A solution of crude xanthate (6.06 g, 8.62 mmol) and a catalytic amount of AIBN (ca. 50 mg) in toluene (350 mL) was treated with tributyltin hydride (7.0 mL, 26 mmol) and then heated at reflux for 3 h, cooled, and concentrated *in vacuo*. The residue was taken up in acetonitrile and extracted with petroleum ether (5 × 100 mL). The acetonitrile layer was dried over sodium sulfate, filtered, and concentrated

in vacuo. Flash chromatography (8% ethyl acetate/petroleum ether) gave **53** (3.60 g, 78% yield for two steps) as a colorless oil: $[\alpha]^{25}_D$ +2.7° (*c* 0.15, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.91, 138.65, 135.60, 135.55, 133.48, 133.44, 129.66, 128.29, 128.22, 127.95, 127.63, 127.60, 127.49, 127.43, 104.81, 82.99, 78.32, 74.82, 72.20, 72.15, 66.22, 56.73, 33.62, 26.78, 19.22; high-resolution mass spectrum (Cl, NH_3) *m/z* 614.3256 [$(M + NH_4)^+$; calcd for $C_{37}H_{48}NO_5Si$ 614.3301].

Methyl 2,3-Di-*O*-benzyl-4-deoxy-β-D-glucopyranoside (54). A solution of **53** (3.60 g, 6.02 mmol) in THF (125 mL) was treated with tetrabutylammonium fluoride (1.0 M in THF, 6.1 mmol, 6.1 mL) at room temperature, stirred for 4 h, poured into water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (50% ethyl acetate/petroleum ether) afforded **54** (2.03 g, 94% yield) as a colorless oil: $[\alpha]^{25}_D$ +8.0° (*c* 0.15, acetonitrile); ^{13}C NMR (500 MHz, $CDCl_3$) δ 138.71, 138.47, 128.33, 128.28, 128.00, 127.62, 127.58, 127.55, 104.95, 82.81, 78.07, 74.92, 72.26, 72.13, 65.20, 57.19, 32.65; high-resolution mass spectrum (Cl, NH_3) *m/z* 359.1827 [$(M + H)^+$; calcd for $C_{21}H_{27}O_5$ 359.1858].

Methyl 2,3-Di-*O*-benzyl-4-deoxy-6-*O*-(5-phthalimidopentyl)-β-D-glucopyranoside (55). A solution of 5-phthalimido-1-pentanol (0.66 g, 2.83 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.58 g, 2.83 mmol) in dry dichloromethane (21 mL) was treated with triflic anhydride (0.48 mL, 2.83 mmol) at room temperature, stirred for 10 min, poured into water, and extracted with dichloromethane. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The freshly generated triflate was then dissolved in dry dichloromethane (21 mL), 2,6-di-*tert*-butyl-4-methylpyridine (0.58 g, 2.83 mmol) was added, and the solution was cooled to 0 °C. A solution of **54** (1.0 g, 2.79 mmol) in dichloromethane (21 mL) was introduced, followed after 20 min by NaH (60% oil dispersion, 0.25 g, 6.25 mmol). The reaction mixture was stirred at room temperature for 24 h, quenched with saturated aqueous ammonium chloride, and extracted with dichloromethane, and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (50% ethyl acetate/petroleum ether) gave **55** (1.42 g, 89% yield) as a colorless oil: $[\alpha]^{25}_D$ +11° (*c* 0.11, acetonitrile); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.38, 138.87, 138.64, 133.84, 132.17, 128.30, 128.25, 128.02, 127.63, 127.48, 123.14, 104.85, 82.91, 78.24, 74.86, 73.15, 72.19, 71.42, 70.92, 56.97, 37.90, 33.94, 29.15, 28.38, 23.44; high-resolution mass spectrum (Cl, NH_3) *m/z* 591.3014 [$(M + NH_4)^+$; calcd for $C_{34}H_{43}O_7N_2$ 591.3070].

Methyl 2,3-Di-*O*-benzyl-4-deoxy-6-*O*-(5-aminopentyl)-β-D-glucopyranoside (10). A solution of phthalimide **55** (0.79 g, 1.38 mmol) in methanol (100 mL) was treated with sodium methoxide (0.23 g, 4.26 mmol), heated at reflux for 4 h, cooled, and concentrated *in vacuo*. The residue was taken up in water and extracted with dichloromethane, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (10% methanol/dichloromethane) furnished **10** (0.46 g, 75% yield) as a white foam: $[\alpha]^{25}_D$ +8.9° (*c* 0.18, acetonitrile); UV (2.03×10^{-4} M, acetonitrile) λ_{max} 276.4 (ϵ 1.54×10^3), 257.6 (2.26×10^3) nm; IR (film) 3330 (br), 3080 (w), 3020 (w), 2930 (s), 2870 (s), 1650 (s), 1550 (m), 1450 (m), 1370 (m), 1300 (s), 1210 (m), 1185 (m), 1100 (br), 1000 (w), 900 (w), 740 (s), 700 (s), 670 (w), 640 (w) cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.76–7.74 (m, 1 H), 7.35–7.13 (m, 9 H), 4.74–4.49 (m, 4 H), 4.14 (d, *J* = 7.7 Hz, 1 H), 3.53–3.36 (m, 9 H), 3.20 (m, 2 H), 3.07 (t, *J* = 7.8 Hz, 1 H), 1.99 (ddd, *J* = 2.8, 5.3, 1.7 Hz, 1 H), 1.50–1.18 (m, 9 H); ^{13}C NMR (125 MHz, CD_3OD) δ 140.18, 139.99, 138.83, 131.94, 130.83, 130.49, 129.28, 129.18, 128.99, 128.83, 128.69, 128.55, 128.49, 105.98, 84.04, 79.56, 75.73, 74.05, 73.04, 72.49, 72.12, 57.24, 40.94, 34.53, 30.30, 29.81, 24.64; high-resolution mass spectrum (Cl, NH_3) *m/z* 444.2783 [$(M + H)^+$; calcd for $C_{26}H_{38}NO_5$ 444.2749].

Biological Assays. Binding affinity data were obtained following the procedure of Raynor and Reicine[59] employing either AtT-20 mouse pituitary cells (ATCC no. CCL 89) and ^{125}I-Tyr^{11}-SRIF as the ligand or AtT-20/D16-16 cells, a subclone of the former cell line, and ^{125}I-CGP-23996 as the ligand.

The SRIF functional assays were performed in the following manner: For the curve in Figure 2a, rat anterior pituitary cells were dissociated, established in primary culture, and used in a somatostatin bioassay as described in ref 46. After 3 days in culture, wells were washed and either SRIF or **5c** were added to triplicate wells at multiple concentrations in serum free medium with 0.1% bovine serum albumin containing 1 nM growth hormone releasing factor (GRF). Sugar **5c** was dissolved in DMSO; equivalent amounts of DMSO were added with all treatments so that all cells were incubated in a final concentration of 0.2% DMSO. Three hours later the media were collected and stored for future GH radioimmunoassay with reagents provided by the National Hormone and Pituitary Program of NIDDK. Analogue **5c** exhibits ~10^{-5} the agonist potency of SRIF and ca. 55% of the efficacy. For the curve in Figure 2a, cultured rat anterior pituitary cells prepared and used as described above were incubated with 1 nM GRF and various concentrations of SRIF in the presence of a constant concentration (5 μM) of **5c** and in the absence of **5c**.

The β_2-adrenergic functional assay was performed following the procedure described in ref 52.

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Supplementary Material Available: Complete spectral data for **4–10**, **12–18**, **20**, **23–28**, **33–36**, **38–45**, and **50–55** (26 pages). Ordering information is given on any current masthead page.