JOC Article

Novel Chimeric Scaffolds to Extend the Exploration of Receptor Space: Hybrid β-D-Glucose−Benzoheterodiazepine Structures for Broad Screening. Effect of Amide Alkylation on the Course of Cyclization Reactions

Leïla Abrous,[†] Patrick A. Jokiel,[‡] Sarah R. Friedrich,[§] John Hynes, Jr.,[||] Amos B. Smith, III,* and Ralph Hirschmann*

University of Pennsylvania, Department of Chemistry, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323

rfh@sas.upenn.edu

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New molecular platforms which are hybrids of two scaffolds—namely, β-D-glucose and benzodiazepine, each able to bind several proteins—were designed, synthesized and functionalized to serve as probes for broad biological screening. Herein, we describe the syntheses and chemical properties of these novel chimeric scaffolds. Attempted cyclization of the functionalized analogues (−)-**96** and (−)-**97** afforded the corresponding dimers (−)-**98** and (−)-**99**, respectively, under a variety of reaction conditions, even at concentrations of only 0.001 N. Consideration of factors affecting the conformation of amide bonds and their effects on cyclization reactions led us to alkylate the amide bond. As expected, the cyclization of the *N*-methyl derivative (−)-**110** afforded exclusively the unimolecular cyclization product (+)-**111**. These compounds are only now undergoing broad screening and represent therefore at present a "prospecting library."

Introduction

The design and synthesis of novel molecular platforms which can project substituents into multiple regions of receptor space remains an important goal in the search for new leads for drug discovery. Platforms that have been called promiscuous because of their ability to bind multiple protein targets include the so-called tricyclic scaffold[1] and the steroids. Benzodiazepines have attracted much attention because of their ability to bind not only G-protein coupled receptors, but also enzymes such as farnesyl transferase, reverse transcriptase, and γ-secretase,[2] and they can modulate ion channels.[3] Similarly, research carried out in our laboratories has demonstrated that the β-D-glucose scaffold can also bind diverse proteins by virtue of radial symmetry.[4] Thus, a fully substituted β-D-glucose was designed to bind a receptor of the peptide hormone somatostatin-14 as an agonist. Lead optimization, a modest effort by industrial standards, led to a K_I of 53 nM.[5] Without any formal screening, the same lead was found serendipitously also to be a β_2 andrenergic blocking agent and a substance P antagonist at the NK-1 receptor. Synthesis of analogues then led to a ligand at the latter receptor with an IC_{50} of 10 nM. Remarkably, a closely related congener of the original glucoside was found to block a protein−protein interaction.[6]

[†] Present address: Wyeth-Ayerst Research, Pearl River, NY 10965.
[‡] Present address: Pharmacopeia, Inc. P.O. Box 5350 Princeton, NJ 08543.
[§] Present address: GlaxoSmithKline Pharmaceuticals, Collegeville, PA 19426.
[||] Present address: Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08453.

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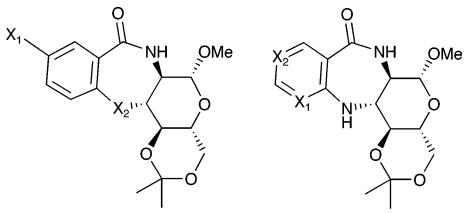
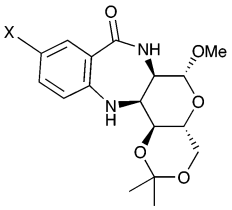
Scaffolds such as those mentioned above are useful, because adequate specificity and potency can generally be achieved efficiently via modulation of the substituents[1−5] as long as the desired and the unwanted biological effects are the result of the interaction of the ligand with different macromolecules. Indeed, Nature herself allows a degree of promiscuity in the physiologic compounds which she releases in humans.[7]

Given the biological relevance of the β-D-glucose and benzodiazepine scaffolds, the hybrid scaffold described herein lends itself well to the development of "prospecting" small molecule libraries, a descriptor coined by Bartlett.[8]

Scaffold Design. In a preliminary report,[9] we described the design and synthesis of hybrids of two promiscuous scaffolds: benzoheterodiazepines and β-D-glucose. While the molecular bases for the interaction of a given platform with diverse receptors has not been defined, we speculate that aromaticity and nonplanarity are structural elements common to such platforms.[10] We refer to such structural features as "elements of privilege". The benzodiazepine portion of the hybrid scaffold contributes aromaticity and nonplanarity, and the β-D-glucose component adds a third ring as well as chiral centers via the C1, C4, and C6 positions of the sugar. These centers provide points of attachment for diverse side chains, facilitating their projection into areas of receptor space previously inaccessible to the classical benzodiazepines. Herein we report in detail the design and synthesis of the *trans*-fused benzodiazepine−sugar hybrids (+)-**1** and (−)-**2**, the *trans*-fused benzoxazepine−sugar hybrid (−)-**3**, the 2- and 4-pyridyldiazepine−sugar hybrids (−)-**4** and (−)-**5**, and the *cis*-fused benzodiazepine−sugar hybrids **6** and (−)-**7** (Scheme 1). Comparison of the minimized structures[11] of (−)-**2**, (−)-**7**, and the benzodiazepine-derived drug Valium (Figure 1) suggests that the former have the potential for increased sampling of receptor space relative to the classical benzodiazepines. In addition, we describe our efforts toward the controlled introduction of functionality, with emphasis placed on functionalizing the carbohydrate hydroxyls and the aniline and lactam nitrogens of the benzodiazepine scaffold. The relative reactivities of these nucleophilic sites are discussed. Monosaccharides, as

SCHEME 1





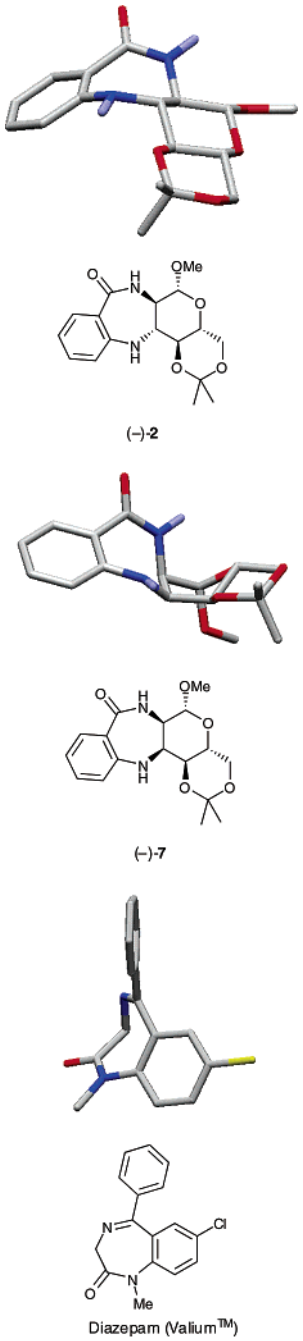


FIGURE 1. Minimized structures of (−)-**2**, (−)-**7**, and diazepam.

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(7) Thus, the target of cortrisol is the glucocorticoid receptor, but it activates also the mineralocorticoid receptor. The reverse is true of aldosterone, which targets primarily the latter receptor. Interestingly, the manmade 1-dehydrocortisol (prednisolone) is more selective than cortisol.

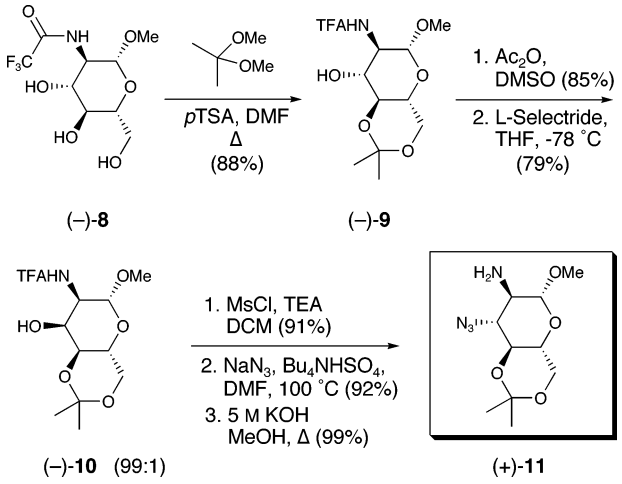
previously pointed out,[4b] represent an attractive building block, due to the ready availability of diastereomers. Thus, we have usefully employed the L-mannose[12] and the L-glucose scaffolds.[13] Broad-screen biological evaluation of functionalized targets is currently in progress;[14] the results of these binding studies will be reported in due course.

Results and Discussion

Scaffold Synthesis. General Strategy. Our approach to the various tricyclic hybrids entails the union of two coupling partners: a suitably functionalized amino sugar is acylated with a benzoic acid derivative followed by an intramolecular S_NAr reaction to generate the benzoheterodiazepine ring. In the following sections, we describe the synthesis of the requisite amino sugar intermediates and their conversion to the tricyclic hybrids.

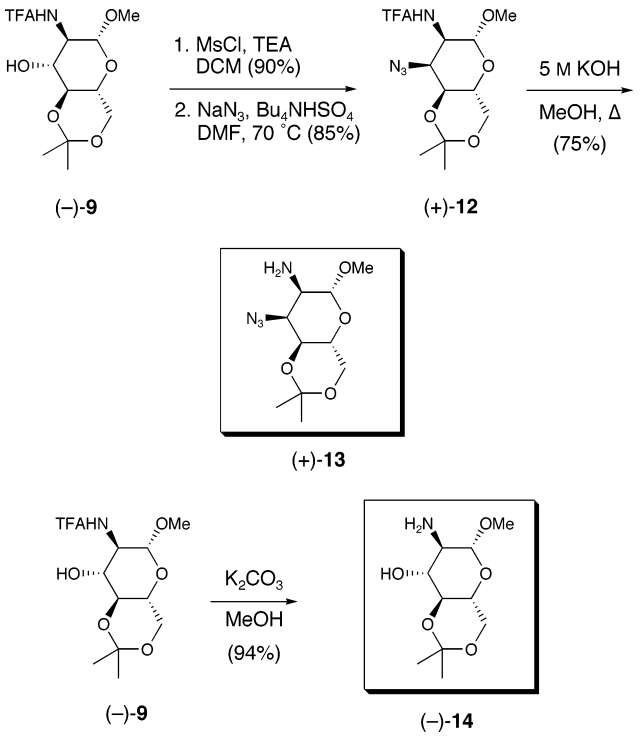
Synthesis of 2-Amino-*β*-glycoside Building Blocks. *β*-Glycosides (+)-11, (+)-13, and (−)-14. Amino sugar (+)-**11**, an intermediate in the synthesis of the *trans*-fused benzodiazepine−sugar hybrid (+)-**1**, was prepared in six steps from the known triol (−)-**8**.[15] Treatment of (−)-**8** (Scheme 2) with 2,2-dimethoxypropane and

SCHEME 2



p-toluenesulfonic acid (*p*TSA) in DMF at reflux gave (−)-**9** in 88% yield. Oxidation of the remaining C(3) hydroxyl (Ac_2O, DMSO) provided the corresponding ketone. Diastereoselective reduction was then effected using L-Selectride to furnish alcohol (−)-**10** in 67% yield for the two steps with a dr of 99:1 in favor of the C(2), C(3) cis isomer. Activation of the C(3) hydroxyl as the mesylate (MsCl, TEA, DCM) followed by treatment with sodium azide at 100 °C led to the azide. The trifluoroacetyl protecting group was then removed by methanolysis to provide the amino sugar building block (+)-**11** in 83% yield for the three steps.

SCHEME 3



Similarly, amino sugar (+)-**13**, the required building block for the synthesis of the *cis*-fused benzodiazepine−sugar hybrid (−)-**7**, was prepared in three steps from compound (−)-**9** in 57% overall yield (Scheme 3), while amino sugar (−)-**14** was prepared in 94% yield from (−)-**9** via methanolysis of the trifluoroacetamide functionality.

Synthesis of *Trans*-Fused Tricyclic Hybrids: Benzodiazepine−Sugar (+)-1, Benzoxazepine−Sugar (−)-3, and the 2- and 4-Pyridyldiazepine−Sugars (−)-4 and (−)-5. With the requisite amino sugars (+)-**11** and (−)-**14** in hand, we constructed a variety of *trans*-fused tricyclic hybrids as depicted in Scheme 4 and Table 1. Our initial attempt to elaborate the chimeric 1,4-benzodiazepin-5-one (−)-**2** involved acylation of (+)-**11** by **15** to afford the amide **19** in 93% yield. Subsequent azide reduction, using the Staudinger protocol,[16] provided amine **20**. Since attempts to effect ring closure of **20** were unsuccessful using either metal catalysis or heating, we explored the cyclization of congener (−)-**22**, incorporating an activating *p*-nitro group. Toward this end, amide (+)-**21**, prepared in 95% yield via acylation of (+)-**11** (EDAC, **16**, DCM, 0 °C), followed by Staudinger reduction, led to (−)-**22** in 74% yield. Cyclization of (−)-**22** now proceeded in 70% yield by heating in dilute acetonitrile to provide (+)-**1**. The dimer (+)-**28** was formed in appreciable amounts, when the reaction was carried out at concen-

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(12) Hirschmann, R.; Hynes, J., Jr.; Cichy-Knight, M. A.; van Rijn, R. D.; Sprengeler, P. A.; Spoors, P. G.; Shakespeare, W. C.; Pietranico-Cole, S.; Barbosa, J.; Liu, J.; Yao, W.; Rohrer, S.; Smith, A. B., III. *J. Med. Chem.* **1998**, *41*, 1382−1391.
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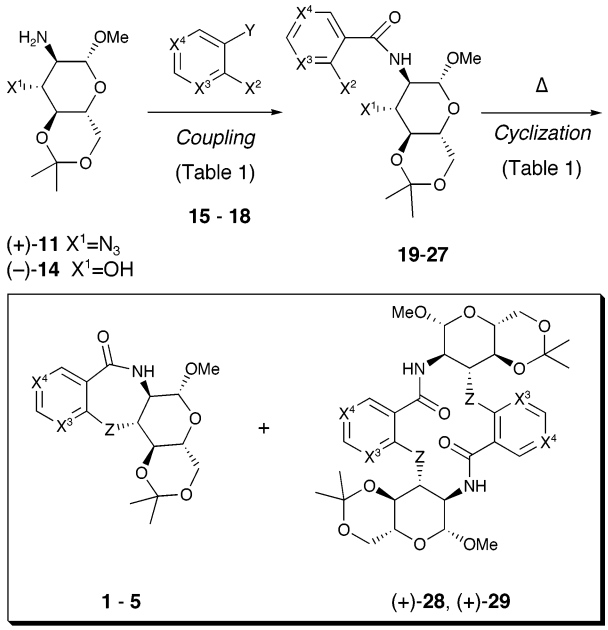
SCHEME 4



Acylating Agents 15 - 18:

Number	X^2	X^3	X^4	Y
15	F	CH	CH	COCl
16	F	CH	C-NO_2	CO_2H
17	Cl	N	CH	COCl
18	Cl	CH	N	CO_2H

Cyclization Precursors 19 - 27:

Number	X^1	X^2	X^3	X^4
19	N_3	F	CH	CH
20	NH_2	F	CH	CH
(+)-**21**	N_3	F	CH	C-NO_2
(–)-**22**	NH_2	F	CH	C-NO_2
(–)-**23**	OH	F	CH	C-NO_2
(–)-**24**	N_3	Cl	N	CH
(–)-**25**	NH_2	Cl	N	CH
(–)-**26**	N_3	Cl	CH	N
(–)-**27**	NH_2	Cl	CH	N

Cyclization Products 1-5, 28, 29:

Number	X^3	X^4	Z
(+)-**1**	CH	C-NO_2	NH
(–)-**2**	CH	CH	NH
(–)-**3**	CH	C-NO_2	O
(–)-**4**	N	CH	NH
(–)-**5**	CH	N	NH
(+)-**28**	CH	C-NO_2	NH
(+)-**29**	CH	C-NO_2	O

trations above 0.005 M (Table 1). The structure of (+)-**1** was confirmed by single-crystal X-ray analysis.

The corresponding benzoxazepine–sugar scaffold was prepared in an analogous fashion. Cyclization of (–)-**23** (Scheme 4) to establish the benzoxazepine ring system led to extensive dimerization, even under significantly higher dilution than the cyclization of (–)-**22**. Basic conditions (CsF, DMF, 100 °C) resulted in the formation of the tricyclic hybrid (–)-**3** in 38% yield. The dimer (+)-**29** was formed in 25% yield. Alternatively, treatment with potassium carbonate in DMF at 25 °C gave exclusively (+)-**29** in 75% yield. A rationalization for the formation of such macrocyclic structures is provided in the final section of this account. Single-crystal X-ray analysis again confirmed the structure of (–)-**3**.

In a similar fashion, the syntheses of (–)-**4** and (–)-**5** (Scheme 4) were achieved from (–)-**25** and (–)-**27** in 36% and 71% yield, respectively. Again, CsF was required to effect cyclization. Presumably, the reaction pathway involves an initial *ipso*-substitution[17] of the aryl chloride to give the more reactive aryl fluoride.

Synthesis of the *Cis*-Fused Benzodiazepine-Sugar Tricyclic Hybrid (–)-7. Our initial approach to a *cis*-fused sugar-benzodiazepine is depicted in Scheme 5. Azide (–)-**30** was prepared in 99% yield by coupling amino sugar (+)-**13** with acid **16** exploiting the sequence illustrated in Table 1. Staudinger reduction of the azide using trimethylphosphine at −78 °C afforded (–)-**31** in 43% yield.[18] Nitroamide (–)-**31**, however, failed to yield **6** under either neutral (MeCN, Δ) or basic (NaH, THF) conditions.

We therefore turned to the approach illustrated in Scheme 6, employing imine formation followed by reduction. The requisite cyclization precursor (–)-**32** was prepared via acylation of the primary amine of (–)-**14**, followed by oxidation of the C(3) hydroxyl (Ac_2O, DMSO); the overall yield of (–)-**32** was 53%. Palladium-catalyzed hydrogenolysis afforded the free amine which underwent intramolecular condensation to give the imine intermediate. Hydrogenation resulted in a 20% yield of the desired *cis*-fused tricycle (–)-**7** accompanied by 5% of the *trans*-fused congener (–)-**2**.

Scaffold Functionalization: (1) Esterification of the Pyranose Hydroxyls. The pyranose diols (+)-**33** and (+)-**34** comprise powerful synthons that permit controlled derivatization. We first examined functionalization by acylation, given the abundance of effective methods for acylation of alcohols and amines. While the resulting esters would be potentially labile in vivo, congeners that prove to be interesting on the basis of in vitro screening could be converted into more stable derivatives. A variety of acyl substituents were effectively introduced selectively at the primary hydroxyl. For example, acetonide (+)-**1** was treated with 5% hydrochloric acid in THF to afford the benzodiazepine–sugar diol (+)-**33** in 99% yield (Table 2). Acylation of the primary hydroxyl of (+)-**33** with pyrazinoyl chloride[19] then furnished the pyrazine ester (+)-**35** in 72% yield. In general, use of collidine gave higher selectivity for the primary

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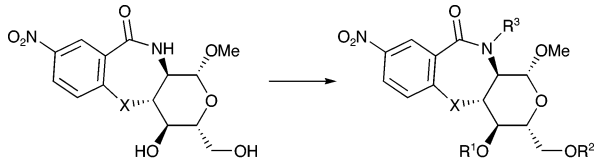
(18) See the Supporting Information for more details.
(19) Prepared by reaction of commercially available pyrazine-2-carboxylic acid with thionyl chloride in benzene at reflux and purified by sublimation. Cynamon, M. H.; Gimi, R.; Gyenes, F.; Sharpe, C. A.; Bergmann, K. E.; Han, H. J.; Gregor, L. B.; Rapolu, R.; Luciano, G.; Welch, J. T. *J. Med. Chem.* **1995**, *38*, 3902.

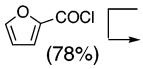
TABLE 1. Coupling of Amino Sugars with Functionalized Benzoic and Nicotinic Acid Derivatives and Subsequent Cyclization

entry	amino sugar	coupling conditions	coupling product (%)	cyclization conditions	cyclization product (%)
1	(+)-**11**	**15**, TEA, DCM, 0 °C	**19** (93)	MeCN, Δ	NR
2		**16**, EDAC, DCM, 0 °C	(+)-**21** (95)	MeCN, Δ (0.0025 M)	(+)-**1** (70)
3				MeCN, Δ (0.005 M)	(+)-**1** (52) (+)-**28** (>5)
4				MeCN, Δ (0.01 M)	(+)-**1** (42) (+)-**28** (>10)
5				MeCN, Δ (0.02 M)	(+)-**1** (30) (+)-**28** (>20)
6	(−)-**14**	**16**, DMTMM, THF, r.t.	(−)-**23** (93)	CsF, DMF, 100 °C (0.01 M)	(−)-**3** (38) (+)-**29** (25)
7				K_2CO_3, DMF, rt	(+)-**29** (75)
8	(+)-**11**	**17**, DIPEA, DCM, 0°C	(−)-**24** (99)	CsF, DMF, 100°C (c = 0.01 M)	(−)-**4** (36)
9		**18**, DCC, DCM, 0°C	(−)-**26** (33)	CsF, DMF, 75 °C (c = 0.01 M)	(−)-**5** (71)

TABLE 2. Functionalization of Diols (+)-33 and (+)-34

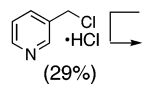


(+)-**33** X=NH
(+)-**34** X=O



(78%)

(+)-**35** X=NH, R^1=H, R^2=pyrazolyl, R^3=H
(+)-**36** X=NH, R^1=H, R^2=acetyl, R^3=H
(−)-**37** X=NH, R^1=R^2=acetyl, R^3=H
(−)-**38** X=NH, R^1=H, R^2=2-furoyl, R^3=H
(+)-**39** X=NH, R^1=R^2=2-furoyl, R^3=H
(−)-**40** X=O, R^1=H, R^2=acetyl, R^3=H
(−)-**41** X=O, R^1=R^2=acetyl, R^3=H
(−)-**42** X=O, R^1=R^2=R^3=acetyl
(−)-**47** X=O, R^1=H, R^2=benzoyl, R^3=H
(−)-**48** X=O, R^1=H, R^2=nicotinoyl, R^3=H
(+)-**53** X=NH, R^1=R^2=nicotinoyl, R^3=H
(−)-**64** X=NH, R^1,R^2=CH(3-pyridyl), R^3=H
(−)-**65** X=NH, R^1,R^2=CH(*p*-anisyl), R^3=H
(−)-**66** X=O, R^1,R^2=CH(phenyl), R^3=H
(+)-**67** X=NH, R^1=R^2=R^3=methyl



(29%)

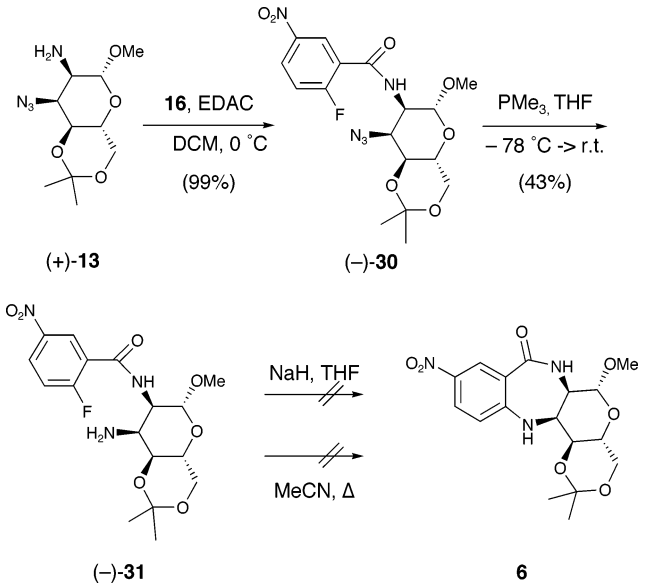
(−)-**68** X=NH, R^1=H, R^2=3-picolyl, R^3=H
(−)-**69** X=NH, R^1=R^2=3-picolyl, R^3=H
(−)-**70** X=NH, R^1=H, R^2=benzyl, R^3=H

entry	diol	conditions	product (%)
1	(+)-**33**	pyrazinoyl chloride (1 equiv), collidine, −40 °C	(+)-**35** (72)
2	(+)-**33**	acetyl chloride (1 equiv), collidine, −40 °C	(+)-**36** (89)
3	(+)-**33**	acetyl chloride (3 equiv), TEA, 0°	(−)-**37** (85)
4	(+)-**33**	2-furoyl chloride (1 equiv), collidine, −40 °C	(−)-**38** (71)
5	(+)-**34**	acetyl chloride (5 equiv), TEA, DCM, 0 °C	(−)-**40**, (−)-**41**, (−)-**42** (82)
6	(+)-**34**	benzoyl chloride (1 equiv), collidine, −40 °C	(−)-**47** (28)
7	(+)-**34**	nicotinic acid, BOP, HOAt, DMAP, DIPEA, DMF	(−)-**48** (42)
8	(+)-**33**	nicotinic acid (4 equiv), DIPCDI, HOAt, NMP, 60 °C	(+)-**53** (70)
9	(+)-**33**	3-pyridyl carboxaldehyde, pTSA, DMF, Δ	(−)-**64** (74)
10	(+)-**33**	*p*-anisaldehyde, $ZnCl_2$, sonication	(−)-**65** (88)
11	(+)-**34**	benzaldehyde dimethyl acetal, pTSA, DMF, Δ	(−)-**66** (98)
12	(+)-**33**	NaH, MeI (3 equiv), DMF	(+)-**67** (54)
13	(+)-**33**	3-picolyl chloride·HCl, NaH, TBAI, DMF−THF	(−)-**68** (24)
14	(+)-**33**	(1) $(Bu_2SnO)_n$, benzene, Δ; (2) BnBr, TBAI, benzene, Δ	(−)-**70** (82)

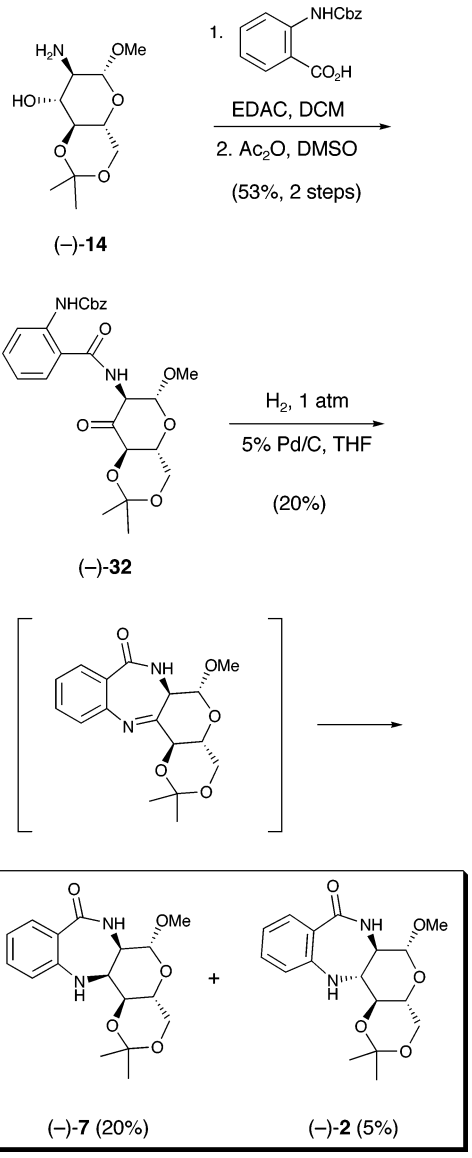
hydroxyl than did Hünig's base.[20] The same protocol was used to prepare the benzodiazepine-sugar derived monoacetyl (+)-**36** (89%) and 2-furoyl (−)-**38** (71%) derivatives. Monoacetate (+)-**33** was then converted to the diacetylated congener (−)-**37** in 85% yield on exposure to an additional equivalent of acetyl chloride. Similarly, furoyl ester (−)-**38** was converted via treatment with an ad-

(20) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791.

SCHEME 5



SCHEME 6



ditional equivalent of 2-furoyl chloride to the difuroyl derivative (+)-**39** in 78% yield. Of note, the aniline nitrogen was not acylated under these conditions. This series of constructs appends pyrazine and furan heterocycles to the scaffold, which may differ in their ability to bind diverse receptors.[5]

We also investigated the treatment of the benzoxazepine−sugar diol (+)-**34** [obtained in 99% yield via hydrolysis of the acetonide protecting group in (−)-**3**] with an excess of acetyl chloride (5 equiv) in the presence of triethylamine (Table 2). A mixture of the mono-, di-, and triacetylated derivatives (−)-**40**, (−)-**41**, and (−)-**42**, respectively, was obtained in a combined yield of 82%.

Having demonstrated the chemoselective introduction of diverse acyl groups at the primary hydroxyl of diols (+)-**33** and (+)-**34**, we undertook the synthesis of a series of mixed diacyl derivatives **43**−**46** (Figure 2).[21] Concerned that these targets might be prone to acyl migration, the C-6 monobenzoyl compound (−)-**47** (Table 2) was subjected to the conditions employed for the second acylation (pyridine, 25 °C, 17 h). No migration of the benzoyl substituent was observed. Encouraged by this result, we proceeded with the synthesis of mixed diacyl derivatives. We were particularly interested in the incorporation of side chains bearing basic heterocycles, namely pyridine, as these constructs would have the potential to interact with biological receptors via such noncovalent interactions as hydrogen bonding and salt bridge formation. Moreover, we have recently demonstrated significant differences between benzene and pyridine rings on $\pi-\pi$ interactions.[5] Unfortunately, all attempts to introduce a nicotinoyl substituent at the C(4) hydroxyl of (−)-**47** under diverse conditions proved unsuccessful, leading only to the recovery of starting material.

Since the selective introduction of a nicotinoyl substituent onto the C(4) hydroxyl was unsuccessful, we sought to generate a mixture of C(4) and C(6) nicotinate derivatives employing more forcing conditions. To this end, diol (+)-**34** was subjected to a series of vigorous coupling protocols (BOP, HOAt, DIPEA, cat. DMAP, and DMF). Pleasingly, only the C(6) hydroxyl was acylated furnishing the mononicotinate (−)-**48** in a moderate yield (42%). We speculate that the aniline functionality in (+)-**33** may participate in the acylation of the C-4 hydroxyl.

Due to the difficulties encountered in the introduction of a second acyl substituent onto (−)-**47**, along with the problem of extensive dimer formation in the synthesis of (−)-**3**, we focused our efforts on the preparation of analogues **49**−**52** (Figure 2) which contain the benzodiazepine scaffold. Introduction of the nicotinoyl substituent at C-6 again proved challenging. No reaction was observed employing the coupling conditions used successfully in the preparation of (−)-**47** and (−)-**48**. Moreover, treatment of (+)-**33** with nicotinic anhydride prepared in situ [nicotinic acid, EDCI, HOAt, DMF; then (+)-**33**, DMAP] yielded only the recovered diol. However, the coupling conditions developed by Rich et al.[22] for the preparation of hindered tertiary amides [nicotinic acid (4 equiv), DIPCDI, HOAt, NMP, 60 °C], led to acylation

(21) In addition to providing a diverse collection of compounds for broad screening, exploring the synthesis of mixed diacyl derivatives will address the important chemical question of stability to acyl migration.

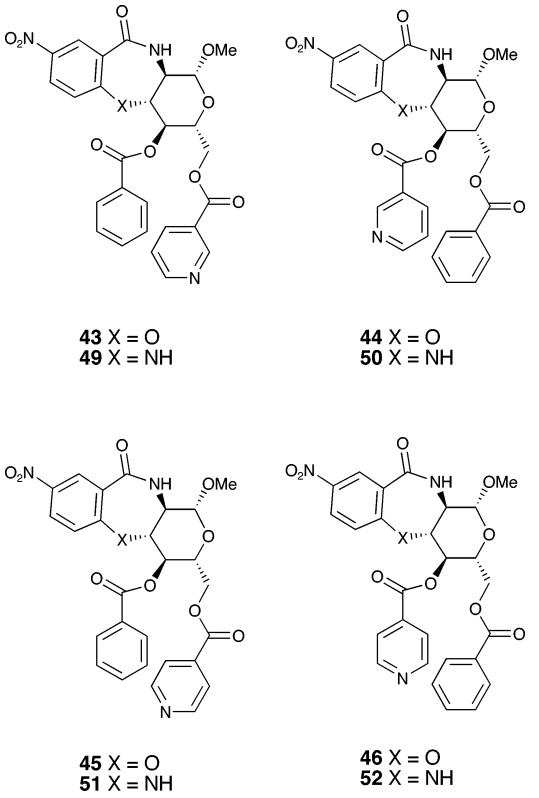


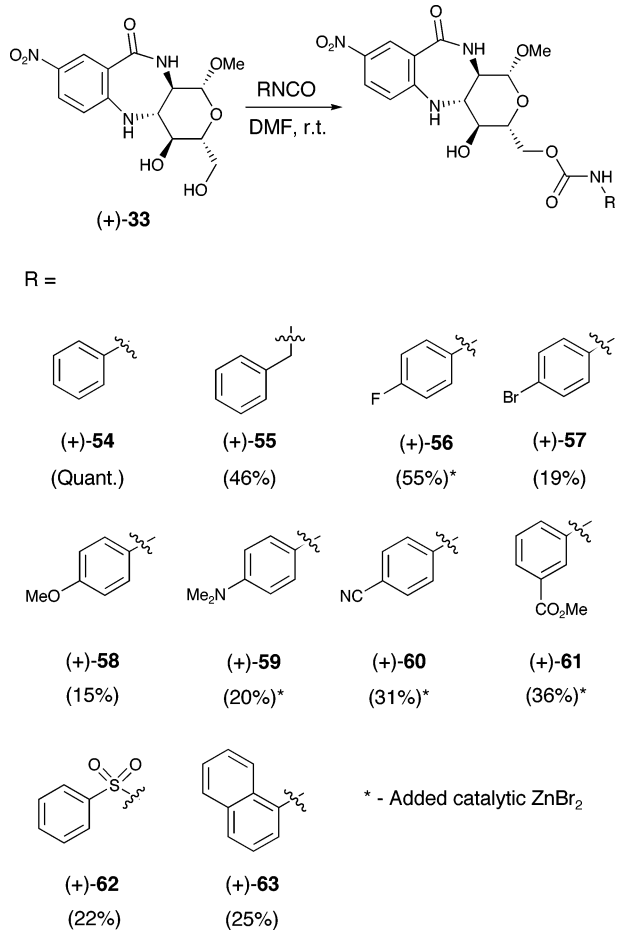
FIGURE 2. Proposed mixed diacyl derivatives **43**−**46** and **49**−**52**.

of both hydroxyls, affording (+)-**53** (Table 2) in 70% yield. Unfortunately, treatment of (+)-**33** with 1 equiv of nicotinic acid, isonicotinic acid, 3-pyrrolecarboxylic acid, and 3-tryptophancarboxylic acid employing the above Rich protocol was unsuccessful.

(2) Derivatization via Carbamate Formation. Due to these difficulties, the reaction of diol (+)-**33** with isocyanates was explored. A variety of commercially available isocyanates were employed leading to selective acylation of the primary hydroxyl to furnish carbamate derivatives **54**−**63** (Scheme 7). Although the reaction with phenyl isocyanate proceeded under neutral conditions to give the phenyl carbamate (+)-**54** in quantitative yield, more substituted isocyanates proved to be much less reactive. Addition of a catalytic amount of anhydrous $ZnBr_2$[23] significantly improved the efficiency of acylation, without compromising selectivity for the C-6 hydroxyl. A trace amount of C-4 acylated product was isolated from the reaction of (+)-**33** with *p*-methoxyphenyl isocyanate.

(3) Acetal Derivatives. The C(4) and C(6) hydroxyls of glucose derivatives form a single acetal with the R substituent of the acetal equatorially disposed in the resulting trans-fused chair conformer. Thus, acetal derivatives of diols typified by (+)-**33** (Scheme 7) serve as rigid templates for the spatial projection of a variety of functional groups. Table 2 contains a series of acetal derivatives of the diols (+)-**33** and (+)-**34**. The 3-pyridyl acetal (−)-**64** (Table 2) was obtained in 74% yield upon treatment of (+)-**33** with 3-pyridyl carboxaldehyde. Sonication of (+)-**33** with *p*-anisaldehyde and freshly fused zinc chloride led to (−)-**65** in 88% yield. Similarly, the benzylidene acetal (−)-**66** was prepared in nearly quantitative yield from the corresponding oxazepine-sugar diol (+)-**34** employing transacetalization conditions (benzaldehyde dimethyl acetal, *p*TSA, DMF, Δ). Little decomposition was observed on incubation with simulated gastric juice at 37 °C for 2 h.[24] Thus, we anticipate that the acetal derivatives will possess adequate stability after oral administration.

SCHEME 7



(4) Ether Derivatives. As noted above, the aforementioned ester and acetal derivatives are potentially labile under physiological conditions. Ether derivatives of the pyranose hydroxyls would overcome this problem, but chemoselectivity was expected to become a problem. Indeed, treatment of (+)-**33** with sodium hydride and methyl iodide afforded predominantly the trimethylated product (+)-**67** (Table 2) in 54% yield. Fortunately, introduction of substituents larger than methyl proceeded with excellent selectivity for the hydroxyls over the aniline nitrogen. For example, alkylation of diol (+)-**33** with 3-picolyl chloride hydrochloride (1 equiv, NaH, TBAI, DMF−THF) furnished the C-6 monoalkylated product (−)-**68**, accompanied by a minor amount of the C-4 alkylated product in a combined yield of 24%, the

(22) Raman, P.; Stokes, S. S.; Angell, Y. M.; Flentke, G. R.; Rich, D. H. *J. Org. Chem.*, **1998**, *63*, 5734−5735.

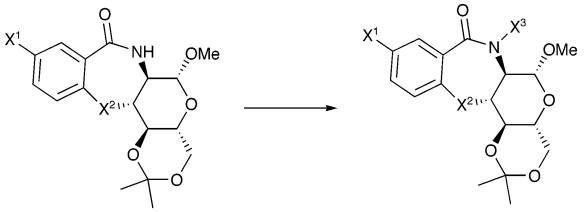
(23) Berrier, J. V. Process for Preparing Carbamates. European Patent EP0967199, 1999.

(24) Compounds (−)-**64**, (−)-**65**, and (−)-**66** were incubated at 37 °C in pH 1 buffer (hydrochloric acid, Fisher Chemical Co.). Minimal decomposition was observed by reverse phase HPLC (Zorbax SE 5911 column, 9.6 × 250 mm; 35% MeCN/H_2O) after 2 h.

balance being starting material. A trace amount of the O,O-dialkylated analogue (−)-**69** was also formed and was separable from the monoalkyl derivatives by flash chromatography. Treatment of the monoalkylated mixture with an excess (3 equiv) of 3-picolyl chloride·HCl then gave (−)-**69** in 29% yield. No N-alkylation of the aniline was observed. The monobenzylated secondary alcohol (−)-**70** (Table 2) was prepared in 82% yield via alkylation of the intermediate stannylidene acetal[25] of diol (+)-**33** with benzyl bromide (3 equiv) [TBAI, benzene, Δ].

(5) Derivatization of the Nitrogens of the Seven-Membered Ring. In addition to the sugar functionalization sites, the two nitrogens of the benzodiazepine ring offer additional points for selective derivatization (Table 3). Treatment of (+)-**1** with an excess of benzyl bromide afforded the dibenzylated adduct (+)-**71** in 90% yield, along with a minor amount (5%) of the monobenzyl derivative (+)-**72**. Selective debenzylation of the aniline nitrogen in (+)-**71**, accompanied by hydrolysis of the acetonide protecting group, was easily effected by treatment with wet chloroform to yield (+)-**73** in nearly quantitative yield. Similarly, treatment of (+)-**1** with an excess of NaH and MeI in THF furnished the dimethylated heterocycle (+)-**74** in 94% yield. On the other hand, acylation could be achieved selectively at the more basic aniline nitrogen. Treatment of (+)-**1** with an excess of trifluoroacetic anhydride furnished the trifluoroacetamide (+)-**75** in 74% yield.

TABLE 3. Synthesis of Benzoheterodiazepine Derivatives



(+)-**1** X^1=NO_2, X^2=NH
(−)-**3** X^1=NO_2, X^2=O

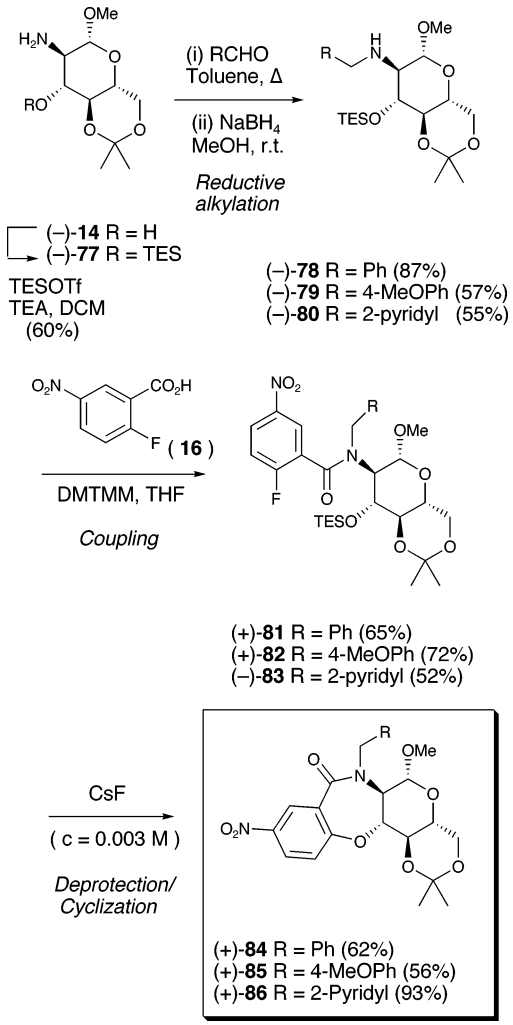
$CHCl_3$, H_2O (82%, 2 steps)

(+)-**71** X^1=NO_2, X^2=N-Bn, X^3=Bn
(+)-**72** X^1=NO_2, X^2=N-Bn, X^3=H
(+)-**73** X^1=NO_2, X^2=NH, X^3=Bn (No acetonide)
(+)-**74** X^1=NO_2, X^2=N-Me, X^3=Me
(+)-**75** X^1=NO_2, X^2=N-TFA, X^3=H
(−)-**2** X^1=H, X^2=NH, X^3=H
(−)-**76** X^1=Cl, X^2=O, X^3=H

entry	starting material	conditions	product (%)
1	(+)-**1**	BnBr (3.1 equiv), TBAI, THF, 0 °C	(+)-**71** (90), (+)-**72** (5)
2	(+)-**1**	NaH, MeI (4 equiv), THF	(+)-**74** (94)
3	(+)-**1**	$(COCF_3)_2O$, TEA, DCM, 0 °C	(+)-**75** (74)
4	(+)-**1**	H_2, 5% Pd/C, MeOH isoamyl-ONO, DMF, 40 °C	(−)-**2** (42, two steps)
5	(−)-**3**	H_2, 5% Pd/C, MeOH *tert*-butyl-ONO, MeCN, $CuCl_2$, 0 °C → rt	(−)-**76** (35, two steps)

In an alternative approach to analogues containing diverse alkyl groups at the lactam nitrogen, we reacted the secondary amino sugars with acid **16** (Scheme 8),

SCHEME 8

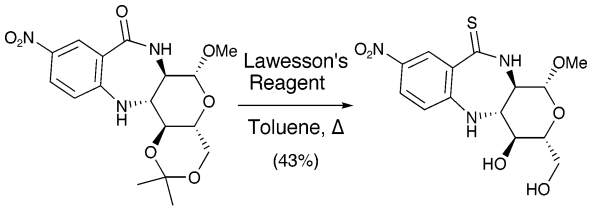


followed by cyclization to establish the respective tricyclic structure. This protocol was applied to the preparation of analogues **84**−**86** (Scheme 8), containing benzyl, *p*-methoxybenzyl, and 2-picolyl substituents, respectively, on the lactam nitrogen. Thus, the C(3) hydroxyl of amino sugar (−)-**14** was protected as the TES ether to furnish (−)-**77** in 60% yield. Reductive alkylation afforded the secondary amino sugars **78**−**80**, which were coupled to acid **16** in the presence of 4-(4,6-dimethoxy[1.3.5]triazin-2-yl)-4-methylmorpholinium chloridehydrate (DMTMM) to give the tertiary amides **81**−**83**. Heating the latter in dilute DMF in the presence of CsF (5 equiv) effected cleavage of the TES ether, followed by S_NAr cyclization to furnish the alkylated tricycles **84**−**86**. No dimer formation was observed upon cyclization of **81**−**83**.

(6) Derivatization via the Aromatic Nitro Group. The aromatic nitro group was also used successfully to introduce diversity. Reduction of the nitro group in (+)-**1** (Table 3) was achieved by catalytic hydrogenation to afford the air-sensitive aniline, which was directly subjected to reductive deamination using the method of Doyle[26] [isoamyl nitrite, DMF, 40 °C] to afford (−)-**2** in 42% yield for the two steps. Alternatively, exchange of

(25) (a) For a review: David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643. (b) Boons, G.-J.; Castle, G. H.; Clase, J. A.; Grice, P.; Ley, S. V.; Pinel, C. *Synlett* **1993**, 913.

SCHEME 9



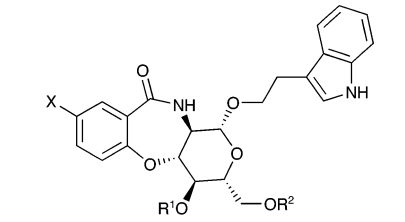
(+)-**1** (–)-**87**

the nitro functionality in (−)-**3** for a halogen via the Sandmeyer reaction[27] was also explored (Table 3). Catalytic hydrogenation as with (+)-**1**, followed in turn by diazotization [*tert*-butyl nitrite, MeCN, 0 °C → rt] and treatment of the resulting diazonium species with copper (II) chloride furnished the aryl chloride (−)-**76**. The resulting aryl chlorides hold considerable potential for further substitution via Buchwald/Hartwig chemistry.[28]

The lactam carbonyl represents the final site for potential functionalization. Preparation of the corresponding thiolactam from (+)-**1** using Lawesson's reagent[29] proceeded to give (−)-**87** in 43% yield after a mild acidic workup (Scheme 9). Further elaboration of the thiolactam can be envisioned.

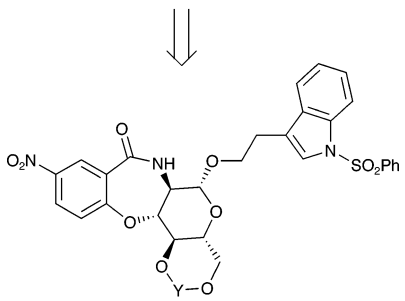
Toward the Synthesis of a Small Library of Compounds Based on the Tricylic Hybrid Scaffold. Having secured access to the tricyclic hybrids **1**−**7** in which the anomeric hydroxyl is methylated and the C4 and C6 hydroxyls (sugar numbering) are protected as acetals, we sought to construct a series of small libraries functionalized at C1, C4, and C6. A tryptophan-mimicking indole residue was chosen as the anomeric substituent (Scheme 10).

SCHEME 10



88

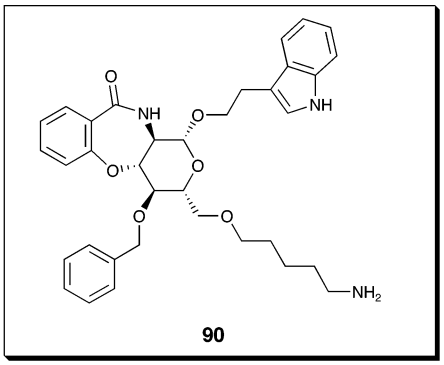
X = H, NO_2
R^1, R^2 = heterocyclic, amino acid-mimicking side chains



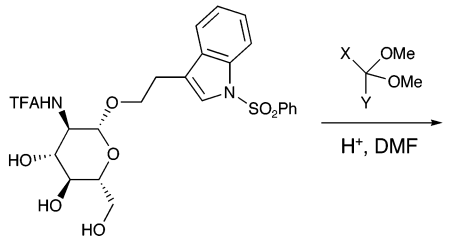
89

Y = isopropylidene, benzylidene

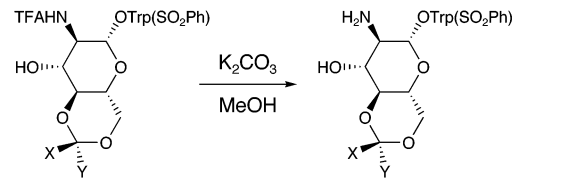
SCHEME 11



90



(–)-**91**



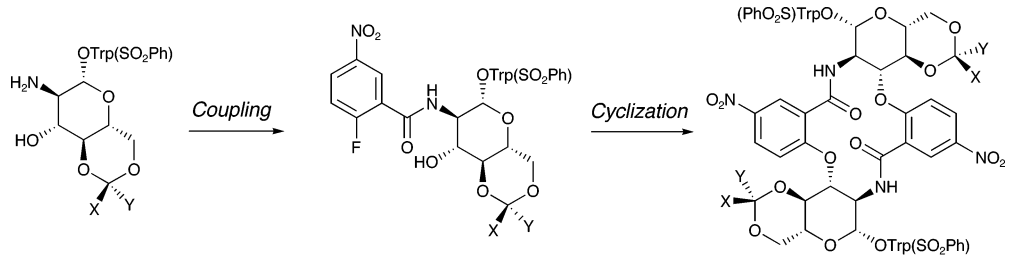
(–)-**92** X = Ph, Y = H
(–)-**93** X = Y = Me (84%)

(–)-**94** X = Ph, Y = H (56%, 2 steps)
(–)-**95** X = Y = Me (Quant.)

Initial efforts were directed toward the synthesis of compound **90**, as earlier efforts in our sugar peptidomimetics found that similar substitution of the β-D-glucose scaffold led to a ligand for hNK-1 with an IC_{50} of 240 nM.[4b] For the synthesis of **90**, amino sugars (−)-**94** and (−)-**95** were each prepared in two steps from known triol (−)-**91**, exploiting the methodology of Cichy-Knight (Scheme 11).[30] *N*-Acylation of (−)-**94** and (−)-**95** provided cyclization precursors (−)-**96** and (−)-**97** (Table 4). Attempted S_NAr cyclization of these substrates employing diverse conditions resulted instead in the exclusive formation of the 14-membered macrocycles (−)-**98** and (−)-**99**, the products of two consecutive S_NAr reactions. Structural assignments of (−)-**98** and (−)-**99** were complicated by their C_2 axes of symmetry. In addition, mass spectrometric analysis gave divergent results.[31] To establish unequivocally the structure of the cyclization products, chemical transformation to a system lacking this element of symmetry was undertaken. To this end, partial hydrolysis of the acetonide protecting groups in

(26) Doyle, M. P.; Dellaria, J. F., Jr.; Siegfried, B.; Bishop, S. W. *J. Org. Chem.* **1977**, *42*, 3494.
(27) Doyle, M. P.; Siegfried, B.; Dellaria, J. F., Jr. *J. Org. Chem.* **1977**, *42*, 2426.
(28) For a review, see: Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.
(29) Pedersen, B. S.; Lawesson, S. O. *Tetrahedron* **1979**, *35*, 2433.
(30) Cichy-Knight, M. Ph.D. Dissertation, University of Pennsylvania, 1997.

TABLE 4. Coupling of Amino Sugars (−)-94 and (−)-95 with Functionalized Benzoic Acid Derivatives and Subsequent Cyclization



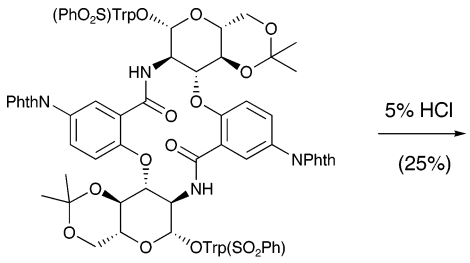
(−)-**94** X=Ph, Y=H
(−)-**95** X=Y=Me

(−)-**96** X=Ph, Y=H
(−)-**97** X=Y=Me

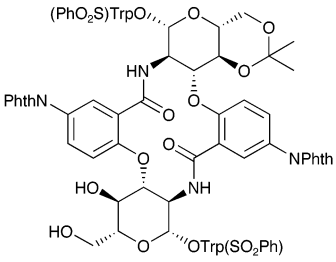
(−)-**98** X=Ph, Y=H
(−)-**99** X=Y=Me

entry	amino sugar	coupling conditions	coupling product (%)	cyclization conditions	cyclization product (%)
1	(−)-**94**	**16**, EDAC, DCM, 0 °C	(−)-**96** (75)	CsF, DMF, 60 °C (c = 0.03 M)	(−)-**98** (45)
2				CsF, DMF, 25 °C (c = 0.03 M)	(−)-**98** (38)
3				CsF, DMSO, 25 °C (c = 0.03 M)	(−)-**98** (37)
4				CsF, DMA, 90 °C (c = 0.03 M)	(−)-**98** (45)
5				K_2CO_3, DMF, 25 °C (c = 0.03 M)	(−)-**98** (62)
6	(−)-**95**	**16**, DMTMM, THF, rt	(−)-**97** (90)	CsF, DMF, 90 °C (c = 0.03 M)	(−)-**99** (30)
7				K_2CO_3, DMF, 25 °C (c = 0.01 M)	(−)-**99** (75)

SCHEME 12



(+)-**100**

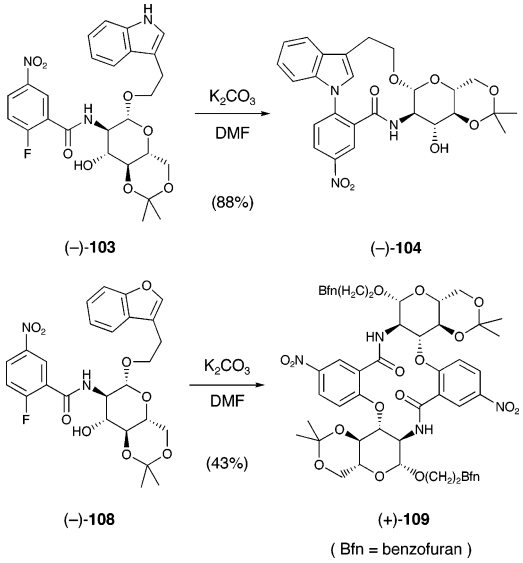


(+)-**101**

(+)-**100**[32] (Scheme 12) was achieved with 5% HCl (aq). Both unchanged starting material and the monoacetonide (+)-**101** were isolated, respectively, in 17% and 25% yield. The ^{1}H and ^{13}C NMR spectra of (+)-**101** are consistent with the elimination of the C_2 symmetry axis inherent in the starting material. While the formation of dimeric products was not unexpected, the exclusive formation of dimers under the conditions of high dilution was unexpected.[33]

To understand why (−)-**96** and (−)-**97** favor the intermolecular reaction manifold, we modeled the *s-cis* and *s-trans* conformers of (−)-**97** for the global minimum conformations.[34] As anticipated, the resultant computations suggest that the *s-trans* amide bond is greatly favored (ΔE_{calc} = 4.5 kcal/mol). Intermolecular S_NAr reaction via the *s-trans* conformation thus predominates.[35]

Factors Influencing the Conformation of Amide Bonds and Their Effect on Cyclization Reactions. To inhibit dimer formation, we therefore sought to modify the conformation of the amide bond. In 1998, Scherer et al.[36] determined the conformation of secondary amide bonds in 399 protein structures. The frequency of the



(−)-**103** (−)-**104**

(−)-**108** (+)-**109**

(Bfn = benzofuran)

(31) Under chemical ionization (CI) conditions, a molecular ion having the same mass-to-charge ratio as the desired product was observed. Under electrospray ionization (ESI) conditions, a molecular ion corresponding to dimer formation was observed under both positive and negative ionization conditions. Signals corresponding to dimerization of molecules in the mass spectrometer is not uncommon under ESI conditions.

(32) Details regarding the preparation of compound (+)-**100** are presented in the Supporting Information.

(33) Even under conditions of very high dilution (c = 0.001 N), only dimer formation was observed.

(34) Monte Carlo conformational searches were performed on MacroModel Version 6.0, using the MM2 force field and the Polak-Ribiere conjugate gradient as algorithm.

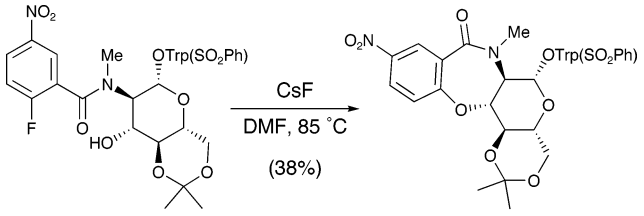
(35) We also synthesized the glucosamine derivative (−)-**103**, which afforded the macrocycle (−)-**104** on treatment with potassium carbonate in DMF. Similarly, (−)-**108** gave only the dimeric (+)-**109** under conditions of high dilution. For details, see the Supporting Information.

trans conformer was found to be 99.97%. On the other hand, the frequency of *cis*-prolyl bonds in protein structures was 4.8%.[36] Further, Beausoleil reported that amide linkages *N*-terminal to proline possess energetically similar *cis* and *trans* isomers that are separated by a significant barrier.[37] Williams and Deber made the significant observation that proline and sarcosine have similar effects on amide bond conformation.[38] Taken together, these and other publications demonstrate that the instability of *cis* amide bonds is greatly reduced in all tertiary amide bonds, a conclusion that is also consistent with the calculations by Zimmerman and Scheraga using the Empirical Conformational Energy Program for Peptides (ECEPP).[39] Deber also investigated factors that favor the cyclization of peptide chains and identified amino acid residues typified by proline and sarcosine as building blocks that facilitate ring closure.[40] Finally, Veber et al. reported that the amide bond between Phe and the respective amino acid of *c*-(Phe-Pro-Phe-D-Trp-Lys-Val) and of *c*-(Phe-*N*-Me-Ala-Phe-D-Trp-Lys-Val) have the *cis* conformation.[41]

For these reasons, we examined the effect of alkylation of the lactam nitrogen on the course of the cyclization reaction (Scheme 13). We prepared the *N*-methyl amide derivative (−)-**110** and examined the subsequent S_NAr reaction. As expected, cyclization of the *N*-methyl derivative (−)-**110** afforded the benzoxazepine−sugar hybrid (+)-**111** on treatment with cesium fluoride in DMF in an unoptimized yield of 38% (Scheme 13).[42] No dimer formation was observed.

As demonstrated earlier in Scheme 8, alkylation of the amide nitrogen was effective in promoting the intramolecular cyclization of the methyl glycosides **81**−**83** to furnish the corresponding *N*-alkylated tricyclic hybrids **84**−**86**. The cyclization of the *N*-picolyl derivative (−)-**83**, in particular, proceeded in very high yield.

SCHEME 13



(−)-**110** *Exclusively Unimolecular* (+)-**111**

Conclusions

The synthesis of the chimeric benzoheterodiazepine β-D-glucopyranoside scaffold, a template from which to project a variety of substituents into previously unexplored receptor space, has been achieved. A rationale for the difficulties encountered [i.e., the influence of amide rotational isomerism on the course of cyclization of constructs such as (−)-**96**, (−)-**97**, and (−)-**103**] in the synthesis of more functionalized analogues, has been developed and this rationale verified experimentally. Finally, the synthesis of a minilibrary based on the benzoheterodiazepine hybrid scaffold is underway in our laboratory and will be reported in due course, in conjunction with the results from broad biological screening.

Experimental Section

Methyl 2-Deoxy-4,6-*O*-isopropylidene-*N*-(trifluoroacetamido)-β-D-allosamine (−)-10. Freshly distilled acetic anhydride (3.5 mL) was added in one portion, at rt, to a stirred solution of (−)-**9** in DMSO (anhydrous, 7 mL). The reaction flask was covered in aluminum foil, stirred overnight, and then diluted with ether (150 mL) and washed with H_2O (100 mL). The aqueous wash was extracted with ether (2 × 100 mL), and the combined ether extracts were dried over $MgSO_4$, filtered, and concentrated. Residual DMSO was removed by vacuum distillation. Flash chromatography (2.5% MeOH/DCM) gave 84 mg (85% yield) of the ketone as an off-white solid: $[\alpha]^{20}_D$ −25.5 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 3400, 3010, 2900, 1740, 1540, 1380, 1240, 1180, 1130, 1100, 840, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.53 (s, 3 H), 1.56 (s, 3 H), 3.51 (m, 1 H), 3.58 (s, 3 H), 4.00 (dd, $J^1 = J^2 = 10.5$ Hz, 1 H), 4.13 (dd, $J = 10.9$ and 5.3 Hz, 1 H), 4.50 (d, $J = 7.9$ Hz, 1 H), 4.70 (dd, $J = 10.1$ and 1.4 Hz, 1 H), 4.76 (dd, $J^1 = J^2 = 8.3$ Hz, 1 H), 6.90 (d, $J = 7.9$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 158.9, 104.5, 100.3, 76.2, 67.9, 62.1, 60.5, 57.3, 30.1, 28.7, 19.0; high-resolution mass spectrum (CI, NH_3) *m*/*z* 270.0977 [$(M)^+$, calcd for $C_{12}H_{16}N_6F_3$ 270.0967].

The ketone (103 mg, 0.315 mmol) was azeotropically dried with benzene (3 × 5 mL) and dissolved in THF (anhydrous, 6.5 mL). The solution was sparged with argon and cooled to −78 °C, and L-Selectride (1.0 M solution in THF, 0.63 mL, 0.63 mmol) was added dropwise via syringe over 10 min. The resultant yellow solution was stirred 4 h at −78 °C, and then quenched with distilled H_2O (4 mL), followed by an excess of $NaHCO_3$ (250 mg). The suspension was stirred overnight at rt and then transferred to a separatory funnel. The layers were separated, and the aqueous phase was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated to give the crude product as a yellow oil. Flash chromatography (2.5% MeOH/DCM) gave 138 mg (79% yield) of (−)-**10** as a white solid: mp 118−120 °C: $[\alpha]^{20}_D$ −73.4 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3600, 3600−3200, 3430, 3000, 2910, 1745, 1545, 1380, 1180, 875 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 3 H), 1.53 (s, 3 H), 2.55 (br m, 1 H), 3.50 (s, 3 H), 3.71 (m, 1 H), 3.82 (m, 2 H), 3.99 (m, 1 H), 4.14 (m, 2 H), 4.60 (d, $J = 8.1$ Hz, 1 H), 6.81 (br t, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9 (q, $J^{C-F} = 37$ Hz), 100.8, 99.9, 71.2, 68.4, 64.3, 62.2, 57.1, 52.5, 28.9, 19.2; high-resolution mass spectrum (CI, NH_3) *m*/*z* 347.1441 [$(M + NH_4)^+$, calcd for $C_{12}H_{18}NO_6F_3$ 347.1430].

Methyl 2-Deoxy-3-azido-4,6-*O*-isopropylidene-β-D-glucosamine (+)-11. To a stirred solution of (−)-**10** (0.95 g, 2.9 mmol) in DCM (50 mL) at 0 °C were added TEA (0.80 mL, 5.8 mmol) and methanesulfonyl chloride (0.45 mL, 5.8 mmol).

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After being stirred for 2 h at 0 °C, the reaction was warmed to rt, and stirring was continued for 18 h. The mixture was diluted with DCM (50 mL) and shaken with 5% HCl (aq, 50 mL) and H_2O (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (40% ethyl acetate/hexanes) gave 1.07 g (91% yield) of the mesylate as a white solid: mp 160 °C dec; $[\alpha]^{20}_D$ −108.9 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3700−3200, 3010, 1735, 1550, 1375, 1180, 930 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 3 H), 1.55 (s, 3 H), 3.16 (s, 3 H), 3.53 (s, 3 H), 3.83 (m, 3 H), 4.03 (dd, J = 9.9 and 4.3 Hz, 1 H), 4.20 (ddd, J = 8.5, 8.5, 2.8 Hz, 1 H), 4.65 (d, J = 8.5 Hz, 1 H), 5.14 (dd, $J^1 = J^2$ = 2.5 Hz, 1 H), 6.62 (br m, 1 H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 159.1 (q, J^{C-F} = 37 Hz), 101.4, 100.5, 79.0, 70.8, 66.1, 63.2, 57.2, 54.5, 39.3, 29.2, 19.3; high-resolution mass spectrum (CI, NH_3) *m*/*z* 425.1208 [(M + NH_4)$^+$, calcd for $C_{13}H_{24}F_3N_2O_6$ 425.1205]. Anal. Calcd for $C_{13}H_{20}F_3NO_6$: C, 38.33; H, 4.95; N, 3.44. Found: C, 38.63; H, 4.71; N, 3.32.

To a solution of the mesylate (2.26 g, 5.5 mmol) in DMF (25 mL) were added sodium azide (1.44 g, 22 mmol) and tetrabutylammonium hydrogen sulfate (cat., 100 mg). (CAUTION: hydrazoic acid is generated under these conditions—the use of a blast shield is recommended.) The reaction mixture was heated at 100 °C for 36 h. The reaction was cooled to rt, diluted with ethyl acetate (100 mL), and washed with H_2O (75 mL), and the aqueous layer further extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (33% ethyl acetate/hexanes) gave 1.74 g (92% yield) of the azide as a white solid: mp 218−220 °C; $[\alpha]^{20}_D$ +1.3 (*c* 0.46, $CHCl_3$); IR ($CHCl_3$) 3450, 2110, 1735, 1550, 1090, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 3 H), 1.55 (s, 3 H), 3.34 (dt, J = 10.9, 8.1 Hz, 1 H), 3.42 (ddd, J = 9.8, 9.8, 5.3 Hz, 1 H), 3.51 (s, 3 H), 3.65 (dd, $J^1 = J^2$ = 9.5 Hz, 1 H), 3.82 (dd, $J^1 = J^2$ = 10.7 Hz, 1 H), 3.99 (dd, J = 10.9, 5.3 Hz, 1 H), 4.10 (dd, J = 10.8, 9.6 Hz, 1 H), 4.77 (d, J = 8.2 Hz, 1 H), 6.60 (br m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5 (q, J^{C-F} = 37 Hz), 100.6, 100.1, 73.7, 68.1, 62.1, 60.9, 57.3, 56.8, 28.9, 19.0; high-resolution mass spectrum (CI, NH_3) *m*/*z* 372.1499 [(M + NH_4)$^+$, calcd for $C_{12}H_{21}F_3N_5O_5$ 372.1495].

To a stirred solution of the azide (0.60 g, 1.75 mmol) in MeOH (10 mL) was added 5 M KOH (aq, 1 mL), and the mixture was heated at reflux for 24 h. The reaction was cooled to rt and concentrated in vacuo. Flash chromatography (33% ethyl acetate/hexanes) gave 0.44 g (99% yield) of (+)-**11** as a yellow oil: $[\alpha]^{20}_D$ +2.9 (*c* 0.65, $CHCl_3$); IR ($CHCl_3$) 3400, 3005, 2895, 2120, 1375, 1270, 1100, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 3 H), 1.55 (s, 3 H), 1.57 (br s, 2 H), 2.67 (dd, J = 10.1, 7.8 Hz, 1 H), 3.35 (m, 2 H), 3.55 (s, 3 H), 3.69 (t, J = 9.5 Hz, 1 H), 3.82 (dd, $J^1 = J^2$ = 10.5 Hz, 1 H), 3.96 (dd, $J^1 = J^2$ = 5.3 Hz, 1 H), 4.19 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 105.7, 100.0, 73.3, 68.4, 65.3, 62.3, 57.4, 56.4, 56.4, 29.0, 19.0; high-resolution mass spectrum (CI, NH_3) *m*/*z* 259.1406 [(M + H)$^+$, calcd for $C_{10}H_{19}N_4O_4$ 259.1402]. Anal. Calcd for $C_{10}H_{18}N_4O_4$: C, 46.48; H, 7.03; N, 21.69. Found: C, 46.51; H, 6.94; N, 21.42.

Methyl 2-Deoxy-3-azido-4,6-*O*-isopropylidene-*N*-(trifluoroacetamido)-*β*-D-allosamine (+)-12. A solution of (−)-**9** (9.52 g, 28.9 mmol) in DCM (296 mL) was cooled to 0 °C, and TEA (12.4 mL, 88.8 mmol) was added, followed by addition of methanesulfonyl chloride (4.6 mL, 59.3 mmol). The reaction mixture was warmed to rt over 1 h and then stirred for an additional 2 h. The mixture was diluted with DCM (500 mL), washed with 5% HCl (aq, 500 mL) and brine (500 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (5% MeOH/DCM) to give the mesylate (10.6 g, 90% yield) as a white solid: $[\alpha]^{20}_D$ −26.8 (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 3400, 3000, 2900, 1740, 1550, 1360, 1260, 1180, 1130, 1100, 970, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 3 H), 1.49 (s, 3 H), 3.04 (s, 3 H), 3.38 (ddd, J = 10.0, 10.0, 5.4 Hz, 1 H), 3.48 (s, 3 H), 3.68 (m, 1 H), 3.76 (dd, $J^1 = J^2$ = 9.5 Hz, 1 H), 3.80 (dd, $J^1 = J^2$ = 10.6 Hz, 1 H), 3.98 (dd, J = 10.9, 5.4 Hz, 1 H), 4.79 (d, J = 8.2 Hz, 1 H), 4.87 (dd, $J^1 = J^2$ = 9.7 Hz, 1 H), 6.78 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 120.0, 100.9, 100.1, 78.5, 72.0, 66.7, 61.8, 56.5, 51.5, 38.4, 28.9, 19.1; high-resolution mass spectrum (CI, NH_3) *m*/*z* 425.0960 [(M + NH_4)$^+$, calcd for $C_{13}H_{24}F_3N_2O_8S$ 425.1206].

To a solution of the mesylate (425 mg, 1.1 mmol) in DMF (4.6 mL) was added sodium azide (279.5 mg, 4.3 mmol), followed by a catalytic amount of tetrabutylammonium hydrogen sulfate. (CAUTION: hydrazoic acid is generated under these conditions—the use of a blast shield is recommended.) The reaction mixture was heated to 70 °C for 48 h, cooled to rt, and then diluted with H_2O (15 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (33% ethyl acetate/hexanes) gave 307 mg (85% yield) of (+)-**12** as a white solid: $[\alpha]^{20}_D$ +20 (*c* 0.27, $CHCl_3$); IR ($CHCl_3$) 3390, 3000, 2900, 2100, 1725, 1540, 1450, 1370, 1150, 1040, 940, 880, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 3 H), 1.49 (s, 3 H), 3.44 (s, 3 H), 3.84 (s, 3 H), 3.98 (dd, J = 9.4, 3.8 Hz, 1 H), 4.04 (ddd, J = 8.5, 8.5, 3.6 Hz, 1 H), 4.15 (dd, $J^1 = J^2$ = 3.2 Hz, 1 H), 4.42 (d, J = 8.2 Hz, 1 H), 6.43 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6 (q, J^{C-F} = 37.7 Hz, 1 H), 115.7, 100.3, 100.1, 72.1, 65.2, 62.1, 60.4, 57.0, 51.3, 28.8, 18.9; high-resolution mass spectrum (CI, NH_3) *m*/*z* 372.1261 [(M + NH_4)$^+$, calcd for $C_{12}H_{21}F_3N_5O_5$ 372.1495].

Methyl 2,3-Deoxy-3-azido-4,6-*O*-isopropylidene-*N*-(2-fluoro-5-nitrobenzamido)-*β*-D-glucopyranoside (+)-21. To a stirred suspension of amine (+)-**11** (101.8 mg, 0.39 mmol) and acid **16** (135 mg, 0.47 mmol) was added a solution of EDAC (105 mg, 0.51 mmol) in DCM (1.0 mL) via cannula. After the addition was complete, the reaction mixture became homogeneous. The mixture was stirred for 45 min at 0 °C and then warmed to rt, diluted with DCM (25 mL), and washed with H_2O (25 mL). The aqueous wash was further extracted with DCM (3 × 25 mL). The combined DCM extracts were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (2% MeOH/DCM) gave 160 mg (95% yield) of (+)-**21** as a white solid: mp 211−213 °C dec; $[\alpha]^{20}_D$ +6.1 (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) 3460, 3005, 2110, 1685, 1635, 1535, 1480, 1355, 1095, 855 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 3 H), 1.56 (s, 3 H), 3.40 (m, 1 H), 3.51 (s, 3 H), 3.55 (m, 1 H), 3.67 (dd, $J^1 = J^2$ = 9.5 Hz, 1 H), 3.84 (dd, $J^1 = J^2$ = 10.5 Hz, 1 H), 4.00 (dd, J = 10.9, 5.4 Hz, 1 H), 4.21 (dd, J = 10.7, 9.5 Hz, 1 H), 4.91 (d, J = 8.2 Hz, 1 H), 6.89 (dd, J = 11.4, 8.1 Hz, 1 H), 7.35 (dd, J = 10.3, 9.1 Hz, 1 H), 8.40 (ddd, J = 7.3, 4.3, 3.0 Hz, 1 H), 8.96 (dd, J = 6.5, 2.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, J^{C-F} = 257 Hz), 161.4, 144.8, 128.7 (d, J^{C-F} = 11.4 Hz), 128.2 (d, J^{C-F} = 3.9 Hz), 122.3 (d, J^{C-F} = 14.7 Hz), 117.7 (d, J^{C-F} = 27.6 Hz), 101.3, 100.0, 73.6, 68.1, 62.2, 61.6, 57.2, 28.9, 19.0; high-resolution mass spectrum (CI, NH_3) *m*/*z* 425.1429 [(M)$^+$, calcd for $C_{17}H_{20}FN_5O_7$ 425.1347].

Methyl 2,3-Deoxy-3-amino-4,6-*O*-isopropylidene-*N*-(2-fluoro-5-nitrobenzamido)-*β*-D-glucosamine (−)-22. To a solution of (+)-**21** (153 mg, 0.383 mmol) in THF (10 mL) was added H_2O (100 *μ*L), followed by triphenylphosphine (141 mg, 0.54 mmol), and the reaction mixture was heated at 55 °C for 48 h. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (2.5% MeOH/DCM) to give 106.7 mg (74% yield) of (−)-**22** as a yellow solid: mp 166−168 °C; $[\alpha]^{20}_D$ −21.0 (*c* 0.31, $CHCl_3$); IR ($CHCl_3$) 3460, 3005, 1680, 1635, 1535, 1355, 1200, 1095, 860 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 3 H), 1.55 (s, 3 H), 1.58 (br s, 2 H), 3.25 (dd, J = 10.4, 9.1 Hz, 1 H), 3.38−3.51 (m, 2 H), 3.52 (s, 3 H), 3.81 (m, 1 H), 3.83 (dd, $J^1 = J^2$ = 10.6 Hz, 1 H), 3.97 (dd, J = 11.0, 5.7 Hz, 1 H), 6.66 (dd, $J^1 = J^2$ = 9.4 Hz, 1 H), 7.34 (dd, J = 10.4, 9.2 Hz, 1 H), 8.39 (ddd, J = 9.0, 4.1, 3.1 Hz, 1 H), 9.00 (dd, J = 6.5, 2.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, J^{C-F} = 257 Hz), 161.4, 144.8, 128.5, 128.5, 122.7 (d, J^{C-F} = 14.9 Hz), 117.6 (d, J^{C-F} = 27.9 Hz), 102.3, 99.8, 75.1, 68.6, 62.2, 58.4, 56.9, 54.8, 29.1, 19.2; high-resolution mass

spectrum (CI, NH_3) *m/z* 400.1533 [$(M + H)^+$, calcd for $C_{17}H_{23}FN_3O_7$ 400.1520].

Methyl 2-Deoxy-4,6-*O*-isopropylidene-*N*-(2-fluoro-5-nitrobenzamido)-*β*-D-glucosamine (−)-23. To a solution of (−)-**14** (320 mg, 1.37 mmol) in THF (anhydrous, 10 mL) was added acid **16** (212 mg, 1.15 mmol). The resulting solution was stirred for 15 min at rt, and DMTMM (0.382 g, 1.38 mmol) was added in portions to give a white suspension. Stirring was maintained for 4 h at rt, and the mixture was concentrated in vacuo. The residue was purified by flash chromatography to give 428 mg (93% yield) of (−)-**23** as a white foam: $[\alpha]^{20}_D$ −36.1 (*c* 0.13, CH_2Cl_2); IR (thin film) 3400, 3060, 2890, 2880, 1650, 1525, 1480, 1350, 1090, 940, 850, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 3 H), 1.52 (s, 3 H), 3.35 (ddd, J = 10.0, 10.0, 5.4 Hz, 1 H), 3.50 (s, 3 H), 3.62 (dd, $J^1 = J^2$ = 9.3 Hz, 1 H), 3.73 (m, 1 H), 3.81 (m, 1 H), 3.95 (dd, J = 10.8, 5.4 Hz, 1 H), 4.07 (dd, $J^1 = J^2$ = 9.3 Hz, 1 H), 4.69 (d, J = 8.2 Hz, 1 H), 6.83 (br s, 1 H), 7.31 (dd, $J^1 = J^2$ = 9.7 Hz, 1 H), 8.35 (m, 1 H), 8.96 (dd, J = 6.5, 2.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, J^{C-F} = 258 Hz), 161.9 (d, J^{C-F} = 3 Hz), 144.8, 128.7 (d, J^{C-F} = 11.4 Hz), 122.3, 117.6 (d, J^{C-F} = 27.8 Hz), 101.7, 99.9, 74.4, 71.6, 67.3, 62.0, 59.2, 57.1, 29.0, 19.1; high-resolution mass spectrum (CI, NH_3) *m/z* 381.1293 [$(M + H)^+$, calcd for $C_{17}H_{21}N_2O_8$ 381.1297].

Tricyclic Hybrid (+)-1. A solution of (−)-**22** (86.8 mg, 0.20 mmol) in acetonitrile (80 mL, c = 0.0025 M) was heated at 80 °C for 48 h. The mixture was concentrated in vacuo and purified by flash chromatography (50% ethyl acetate/hexanes) to give 34.5 mg (70% yield) of (+)-**1** as yellow crystals: mp 150−152 °C; $[\alpha]^{20}_D$ +29.3 (*c* 0.45, $CHCl_3$); IR ($CHCl_3$) 3405, 3005, 1665, 1620, 1535, 1515, 1345, 1130, 1100, 860 cm^{-1}; UV (ϵ_{356} = 14,762); ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 3 H), 1.60 (s, 3 H), 3.51 (m, 2 H), 3.58 (dd, $J^1 = J^2$ = 9.3 Hz, 1 H), 3.66 (s, 3 H), 3.69 (dd, $J^1 = J^2$ = 9.4 Hz, 1 H), 3.85 (dd, $J^1 = J^2$ = 10.5 Hz, 1 H), 4.03 (dd, J = 11.0, 5.5 Hz, 1 H), 4.49 (d, J = 7.8 Hz, 1 H), 5.26 (br s, 1 H), 6.69 (d, J = 9.1 Hz, 1 H), 7.29 (br s, 1 H), 8.09 (dd, J = 9.1, 2.7 Hz, 1 H), 9.08 (d, J = 2.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 149.6, 139.5, 131.4, 127.7, 118.8, 115.4, 102.5, 100.6, 72.1, 68.0, 61.7, 59.8, 57.6, 56.7, 29.0, 19.2; high-resolution mass spectrum (CI, NH_3) *m/z* 397.1727 [$(M + NH_4)^+$, calcd for $C_{17}H_{25}N_4O_7$ 397.1724].

Tricyclic Hybrid (−)-3. Cesium fluoride (22 mg, 0.15 mmol) was added to a stirred solution of alcohol (−)-**23** (39 mg, 0.097 mmol) in DMF (dry, 10 mL) at 100 °C. The resulting orange-yellow solution was stirred for 7 h at 100 °C. The reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (5% MeOH/DCM) to give 14 mg (38% yield) of (−)-**3** as a white solid, accompanied by 9 mg (25% yield) of the dimer (+)-**29**. For (−)-**3**: $[\alpha]^{20}_D$ −113 (*c* 0.686, $CHCl_3$); IR ($CHCl_3$) 2920, 2840, 1650, 1620, 1520, 1350, 1250, 990, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 3 H), 1.58 (s, 3 H), 3.41 (ddd, J = 10.0, 10.0, 5.3 Hz, 1 H), 3.60 (m, 1 H), 3.87 (dd, $J^1 = J^2$ = 10.5 Hz, 1 H), 3.93 (dd, $J^1 = J^2$ = 9.4 Hz, 1 H), 4.02 (dd, J = 10.9, 5.3 Hz, 1 H), 4.18 (dd, $J^1 = J^2$ = 8.8 Hz, 1 H), 4.94 (d, J = 7.9 Hz, 1 H), 7.18 (d, J = 9.0 Hz, 1 H), 4.94 (d, J = 7.9 Hz, 1 H), 7.18 (d, J = 9.0 Hz, 1 H), 7.24 (s, 1 H), 8.25 (dd, J = 9.0, 2.9 Hz, 1 H), 9.16 (d, J = 2.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 160.9, 142.9, 130.1, 128.2, 122.1, 120.7, 102.6, 100.3, 81.8, 71.5, 67.5, 61.8, 58.2, 57.6, 28.9, 19.0; high-resolution mass spectrum (CI, NH_3) *m/z* 381.1293 [$(M + H)^+$, calcd for $C_{17}H_{21}N_2O_8$ 381.1297].

2,3-Deoxy-3-azido-4,6-*O*-isopropylidene-*N*-(2-chloro-3-nicotinamido)-*β*-D-glucosamine (−)-24. To a solution of acyl chloride **17** (0.28 g, 1.6 mmol) in DCM (3 mL) at 0 °C was added Hünig's base (0.42 mL, 2.4 mmol) followed by slow addition of a solution of (+)-**11** (0.21 g, 0.80 mmmol) in DCM (5 mL). The mixture was diluted with DCM (24 mL) and washed with H_2O (3 × 10 mL), and the aqueous layer was extracted with DCM (2 × 15 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (5% MeOH/DCM) gave 0.33 g of (−)-**24** (99% yield) as a white solid: $[\alpha]^{20}_D$ −8.10 (*c* 0.63, $CHCl_3$); IR ($CHCl_3$) 3426, 2920, 1684, 1600, 1576, 1508, 1251, 1160, 1004, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 3 H), 1.54 (s, 3 H), 3.44 (m, 2 H), 3.53 (s, 3 H), 3.64 (dd, $J^1 = J^2$ = 9.7 Hz, 1 H), 3.81 (dd, $J^1 = J^2$ = 10.5 Hz, 1 H), 3.98 (dd, J = 10.8 and 5.4 Hz, 1 H), 4.27 (dd, $J^1 = J^2$ =10.1 Hz, 1 H), 4.91 (d, J = 8.2 Hz, 1 H), 6.61 (d, J = 7.7 Hz, 1 H), 7.35 (dd, J = 4.8, 2.8 Hz, 1 H), 8.06 (dd, J = 5.7, 2.0 Hz, 1 H), 8.48 (dd, J = 2.9, 1.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 151.2, 147.1, 139.1, 131.0, 122.8, 101.2, 99.9, 73.5, 68.0, 62.2, 61.7, 57.5, 57.3, 28.9, 18.9; high-resolution mass spectrum (FAB) *m/z* 398.1231 [$(M + H)^+$, calcd for $C_{16}H_{21}ClN_5O_5$ 398.1231].

2-Deoxy-4,6-*O*-isopropylidene-*N*-(2-chloro-3-nicotinamido)-*β*-D-glucosamine (−)-25. To a solution of (−)-**24** (0.33 g, 0.83 mmol) in THF (16 mL) were added triphenylphosphine (0.52 g, 1.9 mmol) and H_2O (0.8 mL, 0.05 mmol). The reaction flask was fitted with a reflux condenser and heated at 65 °C for 19 h. The mixture was concentrated under reduced pressure, and the residue was azeotropically dried with benzene (10 mL). Flash chromatography (33% ethyl acetate/hexanes) provided 0.28 g (91% yield) of (−)-**25**: $[\alpha]^{20}_D$ −21.0 (*c* 1.23, $CHCl_3$); IR ($CHCl_3$) 3410, 3290, 2930, 2870, 1660, 1580, 1400, 1090, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 3 H), 1.49 (s, 3 H), 1.61 (s, 2 H), 3.17 (dd, $J^1 = J^2$ = 9.3 Hz, 1 H), 3.30 (m, 1 H), 3.38 (dd, $J^1 = J^2$ = 9.3 Hz, 1 H), 3.47 (s, 3 H), 3.67 (dd, J = 10.2, 8.7 Hz, 1 H), 3.76 (dd, $J^1 = J^2$ = 10.4 Hz, 1 H), 3.89 (dd, J = 5.6, 5.2 Hz, 1 H), 4.60 (d, J = 8.3 Hz, 1 H), 6.98 (d, J = 8.7 Hz, 1 H), 7.25 (dd, J = 4.8, 2.8 Hz, 1 H), 7.91 (dd, J = 5.8, 1.8 Hz, 1 H), 8.37 (dd, J = 2.9, 1.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 150.6, 146.9, 138.9, 131.6, 122.5, 102.2, 99.6, 74.6, 68.4, 62.0, 58.1, 56.8, 54.3, 28.9, 19.0; high-resolution mass spectrum (FAB) *m/z* 372.1326 [$(M + H)^+$, calcd for $C_{16}H_{23}ClN_3O_5$ 372.1326].

2-Pyridyldiazepine Tricyclic Hybrid (−)-4. Cesium fluoride (39.1 mg, 0.11 mmol) was added to a stirred solution of (−)-**25** (21.9 mg, 0.11 mmol) in DMF (10 mL, c = 0.01 M), and the mixture was heated at 100 °C for 5 days. The mixture was poured into $NaHCO_3$ (saturated aqueous, 5 mL), and the resultant mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and K_2CO_3, filtered and concentrated in vacuo. The residue was purified by preparative TLC (500 μm, 10% MeOH/DCM) to give 12.0 mg (36% yield) of (−)-**4** as a white solid: $[\alpha]^{20}_D$ −57.6 (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) 3386, 3017, 1636, 1590, 1510, 1450, 1380, 1210, 1090, 920, 850, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 3 H), 1.55 (s, 3 H), 3.46 (m, 2 H), 3.49 (m, 1 H), 3.58 (s, 3 H), 3.71 (d, J = 9.3 Hz, 1 H), 3.71 (d, J = 9.3 Hz, 1 H), 3.82 (dd, $J^1 = J^2$ = 10.6 Hz, 1 H), 3.95 (dd, J = 10.8, 5.4 Hz, 1 H), 4.38 (d, J = 7.4 Hz, 1 H), 5.67 (s, 1 H), 6.81 (s, 1 H), 8.22 (dd, J = 2.8, 1.8 Hz, 1 H), 8.48 (dd, J = 9.0, 1.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 156.4, 152.5, 143.3, 114.9, 110.7, 102.7, 100.5, 71.8, 68.3, 61.8, 57.9, 57.8, 57.4, 28.9, 19.0; high-resolution mass spectrum (FAB) *m/z* 336.1548 [$(M + H)^+$, calcd for $C_{16}H_{22}N_3O_5$ 336.1559].

2,3-Deoxy-3-azido-4,6-*O*-isopropylidene-*N*-(6-chloro-3-nicotinamido)-*β*-D-glucosamine (−)-26. To a solution of (+)-**11** (92.1 mg, 0.35 mmol) in DCM (10 mL) were added *N*,*N*-dicyclohexylcarbodiimide (DCC, 77.2 mg, 0.37 mmol) and acid **18** (54.5 mg, 0.35 mmol) at 0 °C. The mixture was gradually warmed to rt, and the resultant suspension was concentrated in vacuo. The residue was recrystallized from ethanol (absolute, 50 mL) to give 45.2 mg (33% yield) of (−)-**26** as a white solid: $[\alpha]^{20}_D$ −7.0 (*c* 0.49, $CHCl_3$); IR ($CHCl_3$) 2160, 1640, 1570, 1080, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 3 H), 1.51 (s, 3 H), 3.32 (m, 2 H), 3.45 (m, 1 H), 3.51 (s, 3 H), 3.59 (dd, $J^1 = J^2$ = 9.5 Hz, 1 H), 3.79 (dd, $J^1 = J^2$ = 10.5 Hz, 1 H), 3.96 (dd, J = 10.8 and 5.4 Hz, 1 H), 4.30 (dd, $J^1 = J^2$ = 10.1 Hz, 1 H), 4.94 (d, J = 8.2 Hz, 1 H), 6.41 (d, J = 7.6 Hz, 1 H), 7.35 (d, J = 5.4 Hz, 1 H), 8.54 (d, J = 5.4 Hz, 1 H), 8.80 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 151.9, 150.5, 140.9, 130.7, 124.9, 101.0, 99.9, 73.6, 68.0, 62.2, 61.5, 57.7, 57.4, 28.9, 18.9; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 398.1224 [$(M + H)^+$, calcd for $C_{16}H_{21}ClN_5O_5$ 398.1231].

Methyl 2-Deoxy-4,6-*O*-isopropylidene-*N*-(6-chloro-3-nicotinamido)-*β*-D-glucosamine (−)-27. To a stirred solution of (−)-**26** (25.5 mg, 0.064 mmol) in THF (1.3 mL) were added triphenylphosphine (44.1 mg, 0.17 mmol) and H_2O (12.8 μL). The reaction flask was fitted with a Dean−Stark trap and condenser and heated at 65 °C for 12 h. The mixture was concentrated in vacuo, and the residue was azeotropically dried with benzene (5 mL). Preparative TLC (500 μm, 10% MeOH/DCM) provided 20.9 mg (88% yield) of (−)-**27** as a white solid: $[\alpha]^{20}_D$ −17.9 (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 3400, 3000, 2100, 1690, 1220, 1090, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 3 H), 1.49 (s, 3 H), 1.69 (s, 2 H), 3.29 (dd, $J^1 = J^2 = 9.7$ Hz, 1 H), 3.38 (m, 2 H), 3.49 (s, 1 H), 3.63 (dd, $J = 10.3$, 8.4 Hz, 1 H), 3.77 (dd, $J^1 = J^2 = 10.3$ Hz, 1 H), 3.92 (dd, $J = 10.6$, 5.3 Hz, 1 H), 4.68 (d, $J = 8.2$ Hz, 1 H), 6.40 (d, $J = 8.3$ Hz, 1 H), 7.33 (d, $J = 5.4$ Hz, 1 H), 8.51 (d, $J = 5.4$ Hz, 1 H), 8.79 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 151.7, 150.7, 140.7, 130.9, 124.9, 102.1, 99.8, 74.8, 68.6, 62.2, 58.7, 56.9, 54.2, 29.1, 19.1; high-resolution mass spectrum (FAB) *m*/*z* 406.0941 [$(M + Cl)^-$, calcd for $C_{16}H_{21}Cl_2N_3O_5$ 406.0936].

4-Pyridyldiazepine Tricyclic Hybrid (−)-5. Cesium fluoride (anhydrous, 16 mg, 0.045 mmol) was added to a stirred solution of amine (−)-**27** (3.2 mg, 0.009 mmol) in DMF (dry, 0.9 mL), and the mixture was heated at 75 °C for 12 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (10% MeOH/DCM) to give 2.0 mg (71% yield) of (−)-**5** as a white solid: $[\alpha]^{20}_D$ −36.0 (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 3360, 3010, 1636, 1590, 1456, 1370, 1215, 1089, 852, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 3 H), 1.56 (s, 3 H), 3.42 (dd, $J = 7.4$ and 1.3 Hz, 1 H), 3.47 (m, 2 H), 3.58 (s, 3 H), 3.65 (dd, $J^1 = J^2 = 9.4$ Hz, 1 H), 3.82 (dd, $J^1 = J^2 = 10.6$ Hz, 1 H), 4.00 (dd, $J = 11.0$, 5.5 Hz, 1 H), 4.38 (d, $J = 7.6$ Hz, 1 H), 4.99 (s, 1 H), 6.21 (s, 1 H), 6.48 (d, $J = 5.8$ Hz, 1 H), 8.27 (d, $J = 5.8$ Hz, 1 H), 9.18 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 155.9, 151.4, 111.8, 102.6, 100.5, 71.9, 70.5, 68.0, 61.7, 58.9, 57.3, 56.6, 29.6, 28.9, 19.2; high-resolution mass spectrum (FAB) *m*/*z* 336.1564 [$(M + H)^+$, calcd for $C_{16}H_{22}N_3O_5$ 336.1559].

Methyl 2-Deoxy-3-azido-4,6-*O*-isopropylidene-*N*-(2-fluoro-5-nitrobenzamido)-*β*-D-allosamine (−)-30. A solution of EDAC (101 mg, 0.47 mmol) in DCM (4 mL) was slowly added to a stirred solution of amino sugar (+)-**13** (46.6 mg, 0.18 mmol) and acid **16** (40 mg, 0.22 mmol) in DCM (3.6 mL) at 0 °C. Stirring was continued for 30 min, and the mixture was then warmed to rt, diluted with DCM, and washed with $NaHCO_3$ (saturated aqueous, 100 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2% MeOH/DCM) gave 76 mg (99% yield) of (−)-**30** as a white solid: $[\alpha]^{20}_D$ −0.44 (*c* 0.64, $CHCl_3$); IR ($CHCl_3$) 3050, 3000, 2900, 2120, 1680, 1530, 1350, 1270, 1200, 1100, 840, 800−650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 1 H), 1.51 (s, 3 H), 3.45 (s, 3 H), 3.83 (m, 2 H), 3.96 (m, 2 H), 4.25 (dd, $J^1 = J^2 = 3.2$ Hz, 1 H), 4.33 (m, 2 H), 4.50 (d, $J = 8.3$ Hz, 1 H), 6.94 (m, 1 H), 7.34 (dd, $J = 10.4$, 9.0 Hz, 1 H), 8.36 (dd, $J^1 = J^2 = 2.5$ Hz, 1 H), 8.95 (dd, $J = 6.5$, 2.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, $J^{C-F} = 257$ Hz), 160.5 (d, $J^{C-F} = 3$ Hz), 144.7, 128.6 (d, $J^{C-F} = 4.0$ Hz), 117.6 (d, $J^{C-F} = 27.5$ Hz), 100.7, 99.9, 72.9, 72.9, 65.2, 62.2, 61.4, 56.9, 51.6, 28.8, 28.7, 18.9; high-resolution mass spectrum (CI, NH_3) *m*/*z* 426.1427 [$(M + H)^+$, calcd for $C_{17}H_{21}FN_5O_7$ 426.1425].

Methyl 2-Deoxy-4,6-*O*-isopropylidene-*N*-[(*o*-benzyloxycarbonylamino)benzoyl]-*β*-D-ribohex-3-ulosamine (−)-32. To a stirred solution of amino sugar (−)-**14** (1.03 g, 4.4 mmol) in DCM (10 mL) at 0 °C was added a solution of *N*-Cbz-protected anthranilic acid (1.4 g, 5.3 mmol) and EDAC (1.1 g, 5.8 mmol) in DCM (5 mL). The mixture was warmed to rt, diluted with DCM, and then washed with $NaHCO_3$ (saturated) and brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (50% ethyl acetate/hexanes) gave 1.7 g (82% yield) of the N-acylated product as a white solid: $[\alpha]^{20}_D$ −10.4 (*c* 0.22, $CHCl_3$); IR (thin film) 3331, 2993, 2883, 1735, 1636, 1588, 1525, 1450, 1214, 1094, 1043, 855 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 3 H), 1.48 (s, 3 H), 2.15 (s, 1 H), 3.26 (ddd, $J = 10.0$, 10.0, 5.3 Hz, 1 H), 3.44 (s, 1 H), 3.55 (dd, $J^1 = J^2 = 9.3$ Hz, 1 H), 3.63 (m, 1 H), 3.77 (dd, $J^1 = J^2 = 10.5$ Hz, 1 H), 3.91 (dd, $J = 10.7$, 5.3 Hz, 1 H), 3.97 (dd, $J^1 = J^2 = 9.3$ Hz, 1 H), 4.64 (d, $J = 8.1$ Hz, 1 H), 5.14 (s, 2 H), 6.70 (d, $J = 7.2$ Hz, 1 H), 6.91 (t, $J = 7.5$ Hz, 1 H), 7.36 (m, 10 H), 8.24 (d, $J = 8.4$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 153.7, 139.5, 136.1, 132.8, 128.5, 128.3, 128.2, 127.6, 127.1, 127.0, 122.1, 120.2, 101.7, 99.9, 74.5, 71.6, 67.1, 66.9, 65.3, 62.0, 58.5, 57.0, 29.0, 19.1; high-resolution mass spectrum (CI, NH_3) *m*/*z* 509.1905 [$(M + Na)^+$, calcd for $C_{25}H_{30}N_2O_8Na$ 509.1900].

To a stirred solution of the coupled product (100 mg, 0.25 mmol) in DMSO (anhydrous, 7 mL) was added, in a single portion, acetic anhydride (distilled, 3.5 mL) at rt. The reaction flask was covered in aluminum foil, stirred overnight, and then diluted with ether (150 mL) and washed with H_2O (100 mL). The aqueous wash was extracted with ether (2 × 100 mL), and the combined ether extracts were dried over $MgSO_4$, filtered, and concentrated. Residual DMSO was removed by vacuum distillation. Flash chromatography (2.5% MeOH/DCM) gave 63 mg (65% yield) of (−)-**32** as an off white solid: $[\alpha]^{20}_D$ −7.1 (*c* 0.7, $CHCl_3$); IR (thin film) 3342, 2062, 2994, 2882, 1737, 1648, 1589, 1524, 1450, 1214, 1097, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 3 H), 1.44 (s, 3 H), 3.44 (s, 3 H), 3.45 (m, 1 H), 3.88 (dd, $J^1 = J^2 = 10.4$ Hz, 1 H), 3.99 (dd, $J = 10.9$, 5.3 Hz, 1 H), 4.36 (dd, $J = 10.3$, 1.4 Hz, 3 H); 4.62 (d, $J = 7.9$ Hz, 1 H), 4.75 (dd, $J^1 = J^2 = 9.4$ Hz, 1 H), 5.08 (s, 2 H), 6.90 (dd, $J^1 = J^2 = 8.5$ Hz, 1 H), 7.27 (m, 5 H), 7.58 (dd, $J = 7.9$, 1.4 Hz, 1 H), 7.79 (d, $J = 8.4$ Hz, 1 H), 8.25 (d, $J = 7.9$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 173.9, 169.1, 153.5, 140.0, 136.2, 132.8, 128.4, 128.1, 128.0, 127.6, 121.6, 119.6, 104.7, 100.3, 75.8, 67.1, 66.6, 62.4, 61.2, 57.3, 40.5, 28.7, 20.9, 18.7; high-resolution mass spectrum (CI, NH_3) *m*/*z* 507.1755 [$(M + Na)^+$, calcd for $C_{25}H_{28}N_2O_8Na$ 507.1744].

Methyl 2-Deoxy-3-amino-4,6-*O*-isopropylidene-*N*-(*o*-aminobenzoyl)-*β*-D-allosamine-1,4-benzodiazepin-5-one (−)-7. A solution of (−)-**32** (89 mg, 0.18 mmol) in THF (18 mL) was sparged with argon and then charged with a catalytic amount of 5% palladium on activated carbon (dry). The reaction flask was repeatedly (3×) evacuated and sparged with hydrogen. The reaction was stirred 24 h at rt under hydrogen atmosphere. Upon completion, the reaction mixture was repeatedly (3×) evacuated and sparged with argon and then filtered through Celite 545. The filtrate was concentrated in vacuo, and the residue was purified by preparatory TLC (500 μm, 5% MeOH/DCM) to afford 12 mg (20% yield) of (−)-**7** as a beige solid accompanied by 4 mg (5% yield) of (−)-**2**. For (−)-**7**: $[\alpha]^{20}_D$ −48.7 (*c* 0.115, $CHCl_3$); IR ($CHCl_3$) 3300, 2900, 2850, 1620, 1480, 1200, 990, 850, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 3 H), 1.60 (s, 3 H), 3.32 (m, 1 H), 3.52 (s, 3 H), 3.89 (m, 5 H), 4.58 (br s, 1 H), 4.67 (d, $J = 8.0$ Hz, 1 H), 6.40 (br s, 1 H), 6.25 (d, $J = 8.0$ Hz, 1 H), 6.92 (t, $J = 7.2$ Hz, 1 H), 7.29 (m, 1 H), 8.75 (d, $J = 2.7$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 148.2, 134.0, 132.9, 119.9, 118.5, 117.6, 102.3, 100.0, 70.6, 65.3, 62.5, 58.3, 57.5, 55.6, 28.9, 19.1; high-resolution mass spectrum (CI, NH_3) *m*/*z* 334.1521 [$(M)^+$, calcd for $C_{17}H_{22}N_2O_5$ 334.1529].

Methyl 2-Deoxy-3-amino-*O*-6-acylpyrazine-*N*-(*o*-aminobenzoyl)-α-D-glucosamine Benzodiazepinone (+)-35. A solution of diol (+)-**33** (3.1 mg, 0.009 mmol) in 2,4,6-collidine (180 μL) was cooled to −40 °C. Freshly sublimed pyrazinoyl chloride (1.4 mg, 0.009 mmol) was added, and the reaction mixture was warmed gradually to rt overnight. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography to give 2.9 mg (72% yield) of (+)-**35** as a yellow solid: $[\alpha]^{20}_D$ +121.8 (*c* 0.055, MeOH); IR (thin film) 3400, 2900, 2850, 1720, 1630, 1310, 1140, 960 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 3.30 (m, 1 H), 3.47 (ddd, $J = 10.5$, 10.5, 3.3 Hz, 1 H), 3.53 (s, 3 H), 3.68 (dd, $J^1 = J^2 = 9.9$ Hz, 1 H), 3.87 (br dd, $J = 11.8$, 5.3 Hz, 1 H), 3.98 (ddd, $J = 9.9$, 5.3, 2.6 Hz, 1 H), 4.66 (dd, $J = 10.5$, 5.3 Hz, 1 H), 4.72 (d, $J = 8.1$

Hz, 1 H), 4.78 (dd, J = 12.0, 5.2 Hz, 1 H), 5.18 (br s, 1 H), 6.77 (br s, 1 H), 7.10 (d, J = 10.5 Hz, 1 H), 8.02 (dd, J = 10.5, 3.3 Hz, 1H), 8.78 (br s, 1 H), 8.83 (m, 1 H), 9.24 (d, J = 1.4 Hz, 1 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 164.4, 151.6, 148.8, 146.8, 145.6, 144.5, 131.1, 127.5, 120.1, 120.0, 116.7, 102.8, 75.4, 70.1, 65.0, 64.9, 64.8, 56.9, 56.4; high-resolution mass spectrum (CI, NH_3) m/z 480.0943 [(M + Cl)$^-$, calcd for $C_{19}H_{19}N_5O_8Cl$ 480.0922].

Methyl 2-Deoxy-3-amino-*O*-6-acetyl-*N*-(*o*-aminobenzoyl)- α-D-glucosamine benzodiazepinone (+)-36. A solution of diol (+)-**33** (10 mg, 0.03 mmol) in 2,4,6-collidine (300 μL) was cooled to −40 °C. After the solution was stirred for 20 min, acetyl chloride (2.5 μL, 0.035 mmol) was added. The mixture was stirred an additional 3 h at −40 °C,warmed to rt, and concentrated in vacuo. Flash chromatography (5% MeOH/DCM) afforded 7.2 mg (89% yield) of (+)-**36** as a yellow solid: $[\alpha]^{20}_D$ +0.5 (c 0.2, $CHCl_3$); IR (thin film) 3390, 3100, 2930, 1645, 1330, 1120, 1080, 830, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 3.37 (m, 2 H), 3.49 (dd, $J^1 = J^2$ = 9.2 Hz, 1 H), 3.56 (ddd, J = 9.6, 9.6, 2.4 Hz, 1 H), 3.60 (s, 3 H), 4.19 (dd, J = 12.4, 2.4 Hz, 1 H), 4.38 (d, J = 7.8 Hz, 1 H), 4.78 (dd, J = 12.7, 2.6 Hz, 1 H), 5.64 (s, 1 H), 6.64 (d, J = 9.0 Hz, 1 H), 6.83 (s, 1 H), 8.03 (dd, J = 9.0, 2.7 Hz, 1 H), 9.01 (d, J = 2.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) (lactam carbonyl C not obsd due to long relax time) δ 174.7, 171.4, 150.3, 139.2, 131.0, 128.2, 119.1, 115.5, 102.5, 73.0, 70.1, 62.0, 57.3, 30.5, 21.0; high-resolution mass spectrum (CI, NH_3) m/z 382.1238 [(M + H)$^+$, calcd for $C_{16}H_{20}N_3O_8$ 382.1250].

Methyl 2-Deoxy-3-amino-*O*-4,6-diacetyl-*N*-(*o*-aminobenzoyl)-α-D-glucosamine Benzodiazepinone (−)-37. A solution of diol (+)-**33** (44.7 mg, 0.132 mmol) was dissolved in DMF (anhydrous, 6.6 mL) and cooled to 0 °C, and TEA (370 μL, 2.6 mmol) was added. After 5 min, acetyl chloride (28 μL, 0.40 mmol) was added, and the reaction was stirred overnight at rt. The reaction was quenched with H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (50% ethyl acetate/hexanes) gave 51.3 mg (85% yield) of (−)-**37** as a yellow solid: $[\alpha]^{20}_D$ −7.6 (c 0.145, $CHCl_3$); IR (thin film) 3300, 2900, 2350, 1785, 1650, 1600, 1330, 1240, 1040, 740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12 (s, 3 H), 2.22 (s, 3H), 3.50 (br m, 1 H), 3.61 (m, 1 H), 3.63 (s, 3 H), 3.84 (m, 1 H), 4.22 (dd, J = 9.4, 2.5 Hz, 1 H), 4.40 (d, J = 8.1 Hz, 1 H), 4.47 (dd, J = 11.3, 3.8 Hz, 1 H), 4.96 (dd, $J^1 = J^2$ = 9.5 Hz, 1 H), 6.13 (s, 1 H), 6.59 (d, J = 9.0 Hz, 1 H), 6.82 (br s, 1 H), 8.05 (d, J = 9.0 Hz, 1 H), 9.09 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 170.6, 139.6, 131.4, 127.7, 118.8, 114.9, 102.4, 76.5, 72.7, 69.9, 62.0, 61.6, 57.8, 57.5, 29.7, 20.9, 20.7; high-resolution mass spectrum (CI, NH_3) m/z 458.0971 [(M + Cl)$^-$, calcd for $C_{18}H_{21}N_3O_9Cl$ 458.0966].

Methyl 2-Deoxy-3-amino-*O*-6-(2-furoyl)-*N*-(*o*-aminobenzoyl)-α-D-glucosamine Benzodiazepinone (−)-38. To a solution of diol (+)-**33** (4.9 mg, 0.0144 mmol) in 2,4,6-collidine (1 mL) at −40 °C was added 2-furoyl chloride (1.5 μL, 0.015 mmol). The reaction mixture was warmed to rt over 20 min and concentrated in vacuo. The residue was purified by preparative TLC (500 μm, 5% MeOH/DCM) to give 4.4 mg (71% yield) of (−)-**38** as a white solid: $[\alpha]^{20}_D$ −12.5 (c 0.120, $CHCl_3$); IR ($CHCl_3$) 3316, 2922, 2851, 1713, 1649, 1463, 1322, 1298, 1171, 1122, 1081, 762, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34−3.66 (m, 8 H), 4.13 (br s, 1 H), 4.45 (m, 1 H), 5.10 (d, J = 8.2 Hz, 1 H), 5.30 (s, 1 H), 5.62 (s, 1 H), 6.31 (s, 1 H), 6.79 (d, J = 9.0 Hz, 1 H), 7.40 (d, J = 3.0 Hz, 1 H), 7.81 (s, 1 H), 8.05 (dd, J = 9.0, 3.0 Hz, 1 H), 9.1 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 161.6, 155.2, 149.0, 147.6, 140.7, 138.8, 134.9, 132.4, 125.5, 114.7, 115.9, 101.9, 74.8, 72.1, 63.7, 61.9, 56.7; high-resolution mass spectrum (CI, NH_3) m/z 433.1123 [(M)$^+$, calcd for $C_{19}H_{19}N_3O_9$ 433.1121].

Methyl 2-Deoxy-3-amino-*O*-4,6-di(2-furoyl)-*N*-(*o*-aminobenzoyl)-α-D-glucosamine Benzodiazepinone (+)-39. To a solution of monofuroyl derivative (−)-**38** (2.1 mg, 0.0048 mmol) in 2,4,6-collidine (1 mL) at −40 °C was added 2-furoyl chloride (0.4 μL, 0.052 mmol). The reaction mixture was warmed to rt over 20 min and concentrated in vacuo. The residue was purified by preparative TLC (500 μm, 5% MeOH/DCM) to give 1.9 mg (78% yield) of (+)-**39** as a yellow solid: $[\alpha]^{20}_D$ +4.7 (c 0.15, $CHCl_3$); IR ($CHCl_3$) 3350, 2926, 2853, 1723, 1656, 1614, 1471, 1324, 1296, 1179, 1121, 1074, 759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.56 (ddd, J = 8.5, 8.5, 1.2 Hz, 2 H), 3.62 (s, 3 H), 3.75 (ddd, J = 9.0, 9.0, 1.2 Hz, 1 H), 4.12 (m, 1 H), 4.47 (m, 2 H), 4.61 (dd, J = 12.1, 2.7 Hz, 1 H), 5.22 (dd, $J^1 = J^2$ = 9.5 Hz, 1 H), 6.29 (br s, 1 H), 6.49 (dd, J = 3.5, 1.7 Hz, 1 H), 6.55 (dd, J = 3.6, 1.7 Hz, 1 H), 6.63 (d, J = 9.0 Hz, 1 H), 6.76 (br s, 1 H), 7.17 (d, J = 3.5 Hz, 1 H), 7.33 (d, J = 3.5 Hz, 1 H), 7.63 (s, 1 H), 8.03 (dd, J = 9.0, 2.7 Hz, 1 H), 9.08 (d, J = 2.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 159.6, 158.0, 149.9, 148.2, 146.9, 142.6, 139.7, 131.3, 127.7, 121.1, 119.0, 118.8, 115.0, 112.7, 112.0, 102.3, 72.6, 71.2, 62.5, 61.9, 57.8, 57.4; high-resolution mass spectrum (CI, NH_3) m/z 527.1182 [(M)$^+$, calcd for $C_{24}H_{21}N_3O_{11}$ 527.1176].

Methyl 2-Deoxy-6-*O*-acetyl-*N*-(*o*-hydroxybenzoyl)-β-D-glucosamine oxazepinone (−)-40. To a stirred solution of diol (+)-**34** (150 mg, 0.439 mmol) in DCM (10 mL) at 0 °C was added TEA (370 μL, 2.6 mmol) followed by acetyl chloride (154 μL, 2.2 mmol). The solution was warmed to rt, stirred overnight, and concentrated in vacuo, and the residue was purified by flash chromatography (50% ethyl acetate/hexanes) to afford 34.5 mg (82% yield) of a mixture of isomeric acylation products (−)-**40**, (−)-**41**, and (−)-**42**. For (−)-**40**: $[\alpha]^{20}_D$ −16.0 (c 0.2, $CHCl_3$); IR ($CHCl_3$) 3450, 2900, 2850, 1720, 1680, 1650, 1450, 1330, 1250, 1080, 1020 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 3 H), 3.02 (d, J = 3.7 Hz, 1 H), 3.55 (dd, $J^1 = J^2$ = 8.6 Hz, 1 H), 3.59 (m, 1 H), 3.61 (s, 3 H), 3.85 (m, 1 H), 4.07 (dd, $J^1 = J^2$ = 8.9 Hz, 1 H), 4.32 (d, J = 7.9 Hz, 1 H), 4.39 (dd, J = 12.3, 2.2 Hz, 1 H), 4.59 (dd, J = 12.3, 4.1 Hz, 1 H), 6.48 (s, 1 H), 7.19 (d, J = 9.0 Hz, 1 H), 8.28 (dd, J = 9.0, 2.9 Hz, 1 H), 9.25 (d, J = 2.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 163.1, 161.1, 143.3, 130.5, 128.4, 121.5, 102.2, 84.3, 74.0, 68.3, 62.5, 57.4, 57.3, 29.6, 20.7; high-resolution mass spectrum (ESI) m/z 417.0721 [(M + Cl)$^-$, calcd for $C_{16}H_{18}N_2O_9Cl$ 417.0700].

Methyl 2-Deoxy-3-amino-6-*O*-benzoyl-*N*-(2-hydroxy-5-nitrobenzoyl)-β-D-glucosamine Benzodiazepinone (−)-47. To a stirred solution of (+)-**34** (11 mg, 0.032 mmol) in 2,4,6-collidine (0.65 mL) at −40 °C was added benzoyl chloride (3.7 μL, 0.032 mmol). The reaction mixture was warmed to rt, stirred for 15 h, and concentrated in vacuo. Preparative TLC (500 μm, 5% MeOH/DCM) gave 4.0 mg (28% yield) of (−)-**47** as a yellow, waxy solid: $[\alpha]^{20}_D$ −44.5 (c 0.20, $CHCl_3$); IR (thin film) 3366, 3199, 3072, 2923, 2853, 1718, 1653, 1617, 1522, 1451, 1337, 1276, 1245, 1130, 1083, 748, 713 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.56 (dd, $J^1 = J^2$ = 8.6 Hz, 1 H), 3.62 (s, 3 H), 3.73 (ddd, J = 9.9, 2.3, 2.3 Hz, 1 H), 3.93 (dd, $J^1 = J^2$ = 9.8 Hz, 1 H), 4.12 (dd, $J^1 = J^2$ = 8.9 Hz, 1 H), 4.37 (d, J = 8.0 Hz, 1 H), 4.64 (dd, J = 12.3, 2.2 Hz, 1 H), 4.84 (dd, J = 12.3, 4.3 Hz, 1 H), 6.60 (br s, 1 H), 7.16 (d, J = 9.0 Hz, 1 H), 7.47 (t, J = 7.8 Hz, 2 H), 7.62 (t, J = 7.4 Hz, 1 H), 8.09 (d, J = 8.3 Hz, 2 H), 8.26 (dd, J = 9.0 and 2.9 Hz, 1 H), 9.23 (d, J = 2.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 163.2, 161.2, 143.3, 133.6, 130.6, 129.9, 129.4, 128.6, 128.5, 121.6, 121.0, 102.3, 84.4, 74.4, 68.5, 63.1, 57.5, 57.4; high-resolution mass spectrum (ESI) m/z 479.0869 [(M + Cl)$^-$, calcd for $C_{21}H_{20}ClN_2O_9$ 479.0857].

Methyl 2-Deoxy-3-amino-6-*O*-nicotinoyl-*N*-(2-hydroxy-5-nitrobenzoyl)-β-D-glucosamine benzodiazepinone (−)-48. To a stirred solution of (+)-**34** (4.2 mg, 0.012 mmol) in DMF (anhydrous, 200 μL) were added nicotinic acid (1.5 mg, 0.012 mmol), DIPEA (8 μL, 0.05 mmol), BOP coupling reagent (11 mg, 0.024 mmol), HOAt (4.9 mg, 0.036 mmol), and a catalytic amount of DMAP. The resultant bright yellow mixture was stirred for 20 h at rt and concentrated in vacuo to give a brown residue. Preparative TLC (500 μm, 5% MeOH/DCM) gave 2.0 mg (42% yield) of (−)-**48** as a white powder: $[\alpha]^{20}_D$ −62.5 (c 0.080, $CHCl_3$); IR (thin film) 3406, 3183, 3061, 2920, 2849,

1725, 1659, 1619, 1593, 1512, 1436, 1355, 1284, 1239, 1127, 1082, 1041 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.13 (br s, 1 H), 3.56 (dd, $J^1 = J^2 = 8.6$ Hz, 1 H), 3.61 (s, 3 H), 3.77 (ddd, $J = 9.8, 2.4, 2.4$ Hz, 1 H), 3.96 (dd, $J^1 = J^2 = 9.1$ Hz, 1 H), 4.11 (dd, $J^1 = J^2 = 9.0$ Hz, 1 H), 4.37 (d, $J = 7.9$ Hz, 1 H), 4.73 (dd, $J = 12.2, 2.3$ Hz, 1 H), 4.80 (dd, $J = 12.2, 4.5$ Hz, 1 H), 6.49 (br s, 1 H), 7.19 (d, $J = 9.0$ Hz, 1 H), 7.43 (dd, $J = 8.0, 4.9$ Hz, 1 H), 8.28 (dd, $J = 9.0, 2.9$ Hz, 1 H), 8.34 (ddd, $J = 7.9, 1.9, 1.9$ Hz, 1 H), 8.82 (dd, $J = 4.9, 1.7$ Hz, 1 H), 9.26 (d, $J = 2.8$ Hz, 1 H), 9.28 (d, $J = 1.9$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 163.1, 161.1, 160.2, 153.9, 151.1, 143.4, 137.3, 130.7, 128.5, 125.5, 123.4, 121.6, 120.8, 102.3, 84.5, 74.0, 68.6, 57.5, 57.4; high-resolution mass spectrum (ESI) *m/z* 480.0830 [$(M + Cl)^-$, calcd for $C_{20}H_{19}ClN_3O_9$ 480.0810].

Methyl 2-Deoxy-3-amino-4,6-*O*-dinicotinoyl-*N*-(*o*-hydroxybenzoyl)-*β*-D-glucosamine benzodiazepinone (+)-53. To a stirred solution of diol (+)-**33** (15 mg, 0.044 mmol) in NMP (peptide synthesis grade, 0.15 mL) in a 1-dram vial were added nicotinic acid (22 mg, 0.18 mmol), diisopropyl carbodiimide (DIPCDI, 28 μL, 0.18 mmol), and HOAt (25 mg, 0.18 mmol). The vial was closed, and the mixture was stirred 17.5 h at 60 °C. The reaction mixture was loaded directly onto a silica gel column and purified by flash chromatography (5% MeOH/DCM) to give 17 mg (70% yield) of (+)-**53** as a yellow foam: $[\alpha]^{20}_D$ +78.3 (*c* 0.925, $CHCl_3$); IR (thin film) 3349, 3300, 3188, 3080, 2925, 2854, 1733, 1699, 1653, 1615, 1591, 1549, 1506, 1482, 1423, 1325, 1283, 1196, 1122, 1079, 1025, 991, 966, 915, 827, 739, 701 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 3.62 (s, 3 H), 3.79 (ddd, $J = 8.6, 8.6, 3.2$ Hz, 1 H), 4.31 (t, $J = 9.3$ Hz, 1 H), 4.39−4.43 (m, 1 H), 4.57 (dd, $J = 12.2, 4.8$ Hz, 1 H), 4.67 (dd, $J = 12.2, 3.0$ Hz, 1 H), 4.94 (d, $J = 8.0$ Hz, 1 H), 5.54 (dd, $J^1 = J^2 = 9.6$ Hz, 1 H), 6.81 (br s, 1 H), 6.91 (d, $J = 9.2$ Hz, 1 H), 7.48 (dd, $J = 7.9, 4.8$ Hz, 1 H), 7.54 (dd, $J = 8.0, 4.8$ Hz, 1 H), 7.56 (br s, 1 H), 8.01 (dd, $J = 9.1, 2.8$ Hz, 1 H), 8.28 (ddd, $J = 7.9, 1.8, 1.8$ Hz, 1 H), 8.38 (d, $J = 8.0$ Hz, 1 H), 8.76−8.78 (m, 1 H), 8.81 (d, $J = 3.5$ Hz, 1 H), 9.13 (s, 1 H), 9.21 (s, 1 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 167.8, 166.1, 165.4, 154.8, 154.5, 151.3, 151.1, 151.0, 139.7, 138.0, 137.5, 130.4, 127.6, 126.5, 124.4, 124.3, 120.8, 120.7, 118.6, 102.8, 73.2, 72.8, 64.2, 63.5, 57.1, 56.3; high-resolution mass spectrum (ESI) *m/z* 550.1576 [$(M + H)^+$, calcd for $C_{26}H_{24}N_5O_9$ 550.1574].

Methyl 2-Deoxy-3-amino-6-*O*-(phenylcarbamate)-*N*-(2-amino-5-nitrobenzoyl)-*β*-D-glucosamine Benzodiazepinone (+)-54. Diol (+)-**33** (2.0 mg, 0.0060 mmol) was dissolved in DMF (anhydrous, 100 μL), and phenyl isocyanate (1 μL, 0.009 mmol) was added. The resulting yellow solution was stirred 18 h at rt and then concentrated in vacuo. Preparative TLC (500 μm, 10% MeOH/DCM) gave 4.0 mg (99% yield) of (+)-**54** as a yellow solid: $[\alpha]^{20}_D$ +83.6 (*c* 0.11, MeOH); IR (thin film) 3335, 3082, 2954, 2925, 1700, 1636, 1613, 1541, 1507, 1445, 1320, 1227, 1158, 1123, 1057, 966, 914, 821, 749 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 3.38 (ddd, $J = 8.2, 3.4, 3.4$ Hz, 1 H), 3.55 (s, 3 H), 3.62 (dd, $J^1 = J^2 = 9.4$ Hz, 1 H), 3.67 (dd, $J^1 = J^2 = 9.4$ Hz, 1 H), 3.78 (ddd, $J = 9.3, 2.2, 2.2$ Hz, 1 H), 4.43 (dd, $J = 11.7, 2.1$ Hz, 1 H), 4.49 (dd, $J = 12.1, 4.4$ Hz, 1 H), 4.67 (d, $J = 8.0$ Hz, 1 H), 5.20 (br s, 1 H), 6.85 (br s, 1 H), 7.03 (t, $J = 7.4$ Hz, 1 H), 7.07 (br s, 1 H), 7.10 (d, $J = 9.2$ Hz, 1 H), 7.29 (d, $J = 8.4$ Hz, 1 H), 7.30 (d, $J = 8.4$ Hz, 1 H), 7.56 (d, $J = 8.2$ Hz, 2 H), 8.01 (dd, $J = 9.0, 2.7$ Hz, 1 H), 8.79 (br s, 1 H), 8.84 (dd, $J^1 = J^2 = 2.7$ Hz, 1 H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 170.1, 155.9, 152.2, 140.1, 139.6, 131.1, 129.8, 128.4, 124.2, 120.4, 119.9, 119.6, 102.9, 76.4, 70.5, 65.6, 64.6, 57.2, 56.9; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 481.1335 [$(M + Na)^+$, calcd for $C_{21}H_{22}N_4O_8Na$ 481.1346].

Methyl 2-Deoxy-3-amino-4,6-*O*-(3-pyridylacetal)-*N*-(*o*-aminobenzoyl)-*β*-D-glucosamine benzodiazepinone (−)-64. To a stirred solution of diol (+)-**33** (18.3 mg, 0.05 mmol) in DMF (anhydrous, 540 μL) was added 3-pyridyl carboxaldehyde (13.2 μL, 0.14 mmol), followed by *p*TSA (20 mg, 0.065 mmol). A reflux condenser was affixed, and the mixture was brought to reflux. After being stirred overnight at 100 °C, the mixture was poured into ethyl acetate (10 mL) and washed with 1 N NaOH (aq., 2 × 5 mL). The combined aqueous washes were adjusted to pH 5−6 with acetic acid and re-extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was passed through a short column of silica gel, eluting with 5% MeOH/DCM, to give 20.0 mg (74%) of (−)-**64** as a yellow solid: $[\alpha]^{20}_D$ −22.4 (*c* 0.165, $CHCl_3$); IR ($CHCl_3$) 3400, 2900, 2850, 1720, 1630, 1310, 1140, 960 cm^{-1}; ^1H NMR (500 MHz, MeOH-d_4) δ 3.49 (dd, $J^1 = J^2 = 8.8$ Hz, 1 H), 3.58 (s, 3 H), 3.71 (ddd, $J = 8.8, 8.8, 5.9$ Hz, 1 H), 3.76 (dd, $J^1 = J^2 = 9.9$ Hz, 1 H), 3.80 (dd, $J = 13.2, 10.2$ Hz, 1 H), 3.87 (dd, $J^1 = J^2 = 7.9$ Hz, 1 H), 4.39 (dd, $J = 7.9, 5.3$ Hz, 1 H), 4.68 (d, $J = 8.1$ Hz, 1 H), 5.80 (s, 1 H), 6.99 (d, $J = 9.9$ Hz, 1 H), 7.47 (dd, $J = 9.8, 4.0$ Hz, 1 H), 8.04 (dd, $J = 9.9, 1.4$ Hz, 1 H), 8.56 (d, $J = 3.9$ Hz, 1 H), 8.73 (s, 1 H), 8.78 (d, $J = 1.4$ Hz, 1 H) (amido, amine NH's not obsd due to exchange with CD_3OD); ^{13}C NMR (125 MHz, MeOH-d_4) δ 164.4, 151.6, 148.8, 146.8, 145.6, 144.5, 131.1, 127.5, 120.1, 120.0, 116.7, 102.8, 101.6, 75.4, 70.1, 65.0, 64.9, 64.8, 56.9, 56.4; high-resolution mass spectrum (CI, NH_3) *m/z* 429.1411 [$(M + H)^+$, calcd for $C_{20}H_{21}N_4O_7$ 429.1410].

Methyl 2-Deoxy-3-amino-4,6-*O*-dimethyl-*N*-(2-amino-5-nitrobenzoyl)-*N*-methyl-*β*-D-glucosamine Benzodiazepinone (+)-67. To a stirred solution of diol (+)-**33** (4.0 mg, 0.012 mmol) in DMF (100 μL) at 0 °C was added iodomethane (3.2 μL, 0.052 mmol), followed by sodium hydride (60% dispersion in mineral oil, 14 mg, 0.65 mmol). The reaction was stirred overnight at rt, poured into H_2O, and extracted with DCM. Combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% MeOH/DCM) gave 2.4 mg (54% yield) of (+)-**67** as a yellow solid: $[\alpha]^{20}_D$ +156 (*c* 0.08, $CHCl_3$); IR (thin film) 2900, 2850, 1620, 1480, 1440, 1300, 1030, 880, 750, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.12 (s, 3 H), 3.28 (m, 1 H), 3.35 (m, 1 H), 3.40 (s, 3 H), 3.54 (s, 3 H), 3.62 (s, 3 H), 3.62−3.68 (m, 4 H), 4.61 (d, $J = 7.7$ Hz, 1 H), 5.81 (br s, 1 H), 6.65 (d, $J = 8.9$ Hz, 1 H), 8.11 (dd, $J = 8.9, 2.7$ Hz, 1 H), 8.59 (d, $J = 2.7$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 148.2, 141.5, 128.5, 127.3, 124.8, 119.9, 101.0, 70.7, 63.5, 60.6, 59.3, 57.8, 56.4, 29.7, 28.6, 14.1; high-resolution mass spectrum (CI, NH_3) *m/z* 382.1603 [$(M + H)^+$, calcd for $C_{17}H_{24}N_3O_7$ 382.1614].

Methyl 2-Deoxy-3-amino-6-*O*-(3-picolyl)-*N*-(2-amino-5-nitrobenzoyl)-*β*-D-glucosamine Benzodiazepinone (−)-68. A solution of (+)-**33** (10 mg, 0.029 mmol) in DMF (anhydrous, 200 μL) was added to a stirred suspension of sodium hydride (anhydrous powder, 3.5 mg, 0.15 mmol) and 3-picolyl chloride·HCl (9.5 mg, 0.058 mmol) via syringe. A crystal of TBAI was added, and the resultant red mixture was stirred for 17 h at rt. The mixture was quenched with NH_4Cl (50 mg) and concentrated in vacuo to give a yellow-orange residue, which was purified by preparative TLC (500 μm, 10% MeOH/DCM) to give 3.2 mg (24% combined yield) of (−)-**68** accompanied by a minor amount of the C-6 alkylated isomer, which was removed using semi-prep HPLC {Waters NovaPak Silica 6 μm, 19 × 300 mm, 50% IPA/hexanes, t_R [(−)-**68**] = 34.75 min, flow rate = 10 mL/min} to give 2.0 mg of purified (−)-**68** as a yellow solid: $[\alpha]^{20}_D$ −22.2 (*c* 0.045, $CHCl_3$); IR (thin film) 3322, 3181, 3078, 2953, 2918, 2852, 1657, 1648, 1642, 1632, 1613, 1585, 1548, 1534, 1477, 1463, 1435, 1317, 1247, 1125, 1068, 913, 829, 791 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.39 (dd, $J^1 = J^2 = 8.2$ Hz, 1 H), 3.47 (d, $J = 9.0$ Hz, 1 H), 3.57 (s, 3 H), 3.64−3.73 (m, 2 H), 3.75−3.81 (m, 2 H), 3.94 (dd, $J = 9.8, 4.1$ Hz, 1 H), 4.35 (d, $J = 7.7$ Hz, 1 H), 4.61 (d, $J = 12.2$ Hz, 1 H), 4.70 (d, $J = 12.2$ Hz, 1 H), 5.72 (br s, 1 H), 6.45 (br s, 1 H), 6.70 (d, $J = 9.0$ Hz, 1 H), 7.36 (br s, 1 H), 7.69 (d, $J = 8.0$ Hz, 1 H), 8.06 (dd, $J = 9.0, 2.6$ Hz, 1 H), 8.63 (br s, 2 H), 9.08 (d, $J = 2.7$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 150.2, 149.0, 139.3, 136.8, 131.4, 131.1, 129.2, 127.7, 118.7, 114.8, 102.3, 73.5, 71.6, 71.4, 70.9, 68.1, 61.8, 57.2, 55.7; high-resolution mass spectrum (ESI) *m/z* 453.1380 [$(M + Na)^+$, calcd for $C_{20}H_{22}N_3O_7Na$ 453.1386].

Methyl 2-Deoxy-3-amino-4,6-*O*-bis(3-picolyl)-*N*-(2-amino-5-nitrobenzoyl)-β-D-glucosamine Benzodiazepinone (−)-69. A solution of (−)-**68** (6.1 mg, 0.014 mmol; accompanied by a minor amount of the C-6 alkylated isomer) in DMF (anhydrous, 200 μL) was added to a stirred suspension of sodium hydride (99%, anhydrous powder, 2.2 mg, 0.070 mmol) and 3-picolyl chloride·HCl (7.2 mg, 0.044 mmol) via syringe. A crystal of TBAI was added, and the resultant red mixture was stirred for 20 h at rt. The mixture was quenched with NH_4Cl (50 mg) and concentrated in vacuo to give a red residue, which was purified by preparative TLC (500 μm, 10% MeOH/DCM) to give 3.2 mg (29% yield) of (−)-**69** as a yellow solid: $[\alpha]^{20}_D$ −10 (*c* 0.060, $CHCl_3$); IR (thin film) 2922, 2855, 1658, 1606, 1477, 1316, 1259, 1121, 1069, 831, 793, 722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.37 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1 H), 3.48 (dd, $J^1 = J^2 = 9.3$ Hz, 1 H), 3.59 (s, 3 H), 3.63−3.64 (m, 1 H), 3.73 (dd, $J^1 = J^2 = 9.4$ Hz, 1 H), 3.88 (dd, *J* = 11.6, 1.8 Hz, 1 H), 3.96 (dd, *J* = 11.5, 2.9 Hz, 1 H), 4.34 (d, *J* = 7.8 Hz, 1 H), 4.61 (d, *J* = 12.2 Hz, 1 H), 4.67 (d, *J* = 12.1 Hz, 1 H), 4.78 (d, *J* = 12.2 Hz, 1 H), 4.86 (d, *J* = 12.2 Hz, 1 H), 5.93 (d, *J* = 9.0 Hz, 1 H), 6.47 (br s, 1 H), 7.33 (dd, *J* = 7.7, 4.7 Hz, 1 H), 7.39 (dd, *J* = 7.6, 4.9 Hz, 1 H), 7.65 (d, *J* = 7.5 Hz, 1 H), 7.74 (d, *J* = 7.5 Hz, 1 H), 7.96 (dd, *J* = 9.0, 2.7 Hz, 1 H), 8.60 (br m, 1 H), 8.66 (br m, 2 H), 8.73 (br m, 2 H), 8.98 (d, *J* = 2.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 150.4, 149.8, 149.5, 149.3, 149.2, 136.2, 135.6, 132.8, 132.6, 131.0, 127.7, 124.0, 123.4, 118.5, 102.3, 75.9, 75.7, 71.4, 71.0, 61.1, 59.2, 57.1, 55.8, 24.2, 19.7; high-resolution mass spectrum (ESI) *m*/*z* 544.1793 $[(M + Na)^+$, calcd for $C_{26}H_{27}N_5O_7Na$ 544.1808].

Methyl 2-Deoxy-3-amino-6-*O*-benzyl-*N*-(2-amino-5-nitrobenzoyl)-β-D-glucosamine Benzodiazepinone (−)-70. A solution of (+)-**33** (6.3 mg, 0.018 mmol) and dibutyltin oxide (4.6 mg, 0.018 mmol) was heated at reflux in benzene overnight with azeotropic removal of water. The mixture was concentrated to ca. 1 mL and TBAI (cat.) was added, followed by benzyl bromide (4.6 mL, 0.04 mmol). The resulting solution was brought to reflux, stirred for 24 h, cooled to rt, and concentrated in vacuo. Flash chromatography gave 6.4 mg (82% yield) of (−)-**70**: $[\alpha]^{20}_D$ −31.1 (*c* 0.045 $CDCl_3$); IR ($CDCl_3$) 3320, 2910, 2820, 1620, 1400, 1310, 1120, 1060, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.65 (br s, 1 H), 3.46 (dd, $J^1 = J^2 =$ 9.0 Hz, 1 H), 3.55 (s, 3 H), 3.69 (m, 3 H), 3.91 (m, 1 H), 4.33 (d, *J* = 7.8 Hz, 1 H), 4.58 (d, *J* = 11.7 Hz, 1 H), 4.63 (d, *J* = 11.7 Hz, 1 H), 5.55 (br s, 1 H), 6.44 (br s, 1 H), 6.66 (d, *J* = 9.0 Hz, 1 H), 7.36 (m, 5 H), 8.06 (dd, *J* = 9.0, 2.7 Hz, 1 H), 9.08 (d, *J* = 2.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 150.2, 139.4, 136.7, 131.4, 128.8, 127.9, 127.8, 127.7, 118.8, 115.0, 102.3, 72.9, 72.7, 71.2, 61.9, 57.3, 55.6, 29.7; high-resolution mass spectrum (ESI) *m*/*z* 428.1472 $[(M - H)^-$, calcd for $C_{21}H_{22}N_3O_7$ 428.1458].

Methyl 2-Deoxy-3-amino-4,6,-*O*-isopropylidene-*N*-(*o*-aminobenzoyl)-*N*,*N*-dibenzyl-β-D-glucosamine Benzodiazepinone (+)-71. To a stirred solution of (+)-**1** (15.1 mg, 0.04 mmol) in THF (600 μL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 3.6 mg, 0.09 mmol). The mixture was stirred for 20 min at 0 °C, and benzyl bromide (15 μL, 0.125 mmol) was added, followed by TBAI (cat.). The mixture was stirred at rt overnight, quenched with saturated NH_4Cl, poured into water (5 mL), and extracted with DCM (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (33% ethyl acetate/hexanes) provided 20.1 mg (90% yield) of (+)-**71** as a bright yellow solid: $[\alpha]^{20}_D$ +448 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3005, 2925, 2890, 2840, 2395, 1650, 1600, 1530, 1440, 1380, 1200, 1090, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 3 H), 1.49 (s, 3 H), 3.10 (m, 1 H), 3.21 (s, 3 H), 3.34 (m, 1 H), 3.50 (dd, $J^1 = J^2 = 9.2$ Hz, 1 H), 3.61 (m, 2 H), 3.82 (dd, *J* = 11.0, 5.4 Hz, 1 H), 4.40 (d, *J* = 15.2 Hz, 1 H), 4.53 (d, *J* = 15.2 Hz, 1 H), 4.57 (d, *J* = 10.0 Hz, 1 H), 4.68 (d, *J* = 15.2 Hz, 1 H), 5.21 (d, *J* = 15.7 Hz, 1 H), 7.12 (d, *J* = 7.0 Hz, 1 H), 7.18 (m, 2 H), 7.26 (m, 4 H), 7.30 (m, 2 H), 7.37 (m, 2 H), 8.11 (dd, *J* = 8.8, 2.7 Hz, 1 H), 8.50 (d, *J* = 2.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 149.6, 143.2, 137.6, 137.2, 133.5, 128.6, 128.0, 128.0, 127.9, 127.7, 127.4, 126.5, 125.9, 122.9, 100.2, 99.4, 74.0, 67.7, 66.7, 62.1, 62.0, 56.4, 55.8, 46.0, 29.2, 19.2; high-resolution mass spectrum (CI, NH_3) *m*/*z* 560.2396 $[(M + H)^+$, calcd for $C_{31}H_{34}N_3O_7$ 560.2397].

Methyl 2-Deoxy-3-amino-*N*-(*o*-aminobenzoyl)-*N*-benzylamide-β-D-glucosamine Benzodiazepinone (+)-73. A solution of (+)-**71** (11.6 mg, 0.02 mmol) in wet $CHCl_3$ was stirred at rt for 2 h and concentrated in vacuo. Flash chromatography (5% MeOH/DCM) gave the acetonide deprotection product, which was stirred overnight in wet $CHCl_3$ to give 7.3 mg (82% yield, two steps) of (+)-**73** as a yellow solid: $[\alpha]^{20}_D$ +143 (*c* 0.065 CH_2Cl_2); IR (thin film) 3327, 2916, 2839, 1621, 1491, 1445, 1323, 1070, 745 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 1.87 (m, 1 H), 2.77 (d, *J* = 4.8 Hz, 1 H), 3.13 (m, 1 H), 3.28 (dd, $J^1 = J^2 = 11.5$ Hz, 1 H), 3.40 (s, 3 H), 3.53 (m, 1 H), 3.75 (dd, *J* = 11.5, 7.9 Hz, 1 H), 3.78 (m, 2 H), 3.79 (m, 1 H), 4.26 (d, *J* = 16.0 Hz, 1 H), 4.70 (d, *J* = 7.9 Hz, 1 H), 5.13 (br s, 1 H), 5.56 (d, *J* = 16.0 Hz, 1 H), 6.78 (d, *J* = 8.8 Hz, 1 H), 7.35 (m, 4 H), 8.10 (dd, *J* = 8.8, 2.7 Hz, 1 H), 8.57 (d, *J* = 2.7 Hz, 1 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 168.6, 148.7, 141.1, 137.7, 128.6, 128.6, 128.5, 127.5, 127.3, 127.1, 124.2, 120.3, 100.0, 75.0, 71.3, 65.3, 62.2, 58.3, 55.8, 45.8, 29.6; high-resolution mass spectrum (ESI) *m*/*z* 464.1224 $[(M + Cl)^-$, calcd for $C_{21}H_{23}N_3O_7Cl$ 464.1224].

Methyl 2-Deoxy-3-amino-4,6-*O*-isopropylidene-*N*-(*o*-aminobenzoyl)-*N*,*N*-dimethyl-β-D-glucosamine Benzodiazepinone (+)-74. To a stirred solution of (+)-**1** (11.0 mg, 0.03 mmol) in THF (600 μL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 11.6 mg, 0.29 mmol). The resultant suspension was stirred for 20 min at 0 °C, and iodomethane (7.2 μL, 0.12 mmol) was added. The mixture was warmed to rt, quenched with NH_4Cl (saturated aqueous, 5 mL), and poured into H_2O (5 mL). The resulting solution was extracted with DCM (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% MeOH/DCM) gave 11.0 mg (94% yield) of (+)-**74** as a yellow solid: $[\alpha]^{20}_D$ +223 (*c* 0.4 $CHCl_3$); IR ($CHCl_3$) 3100, 2950, 2890, 1650, 1600, 1520, 1490, 1340, 1220, 1000, 800−650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 3 H), 1.48 (s, 3 H), 3.10 (s, 3 H), 3.11 (s, 3 H), 3.28 (m, 1 H), 3.52 (s, 3 H), 3.53 (m, 2 H), 3.69 (m, 2 H), 3.92 (dd, *J* = 11.0, 5.3 Hz, 1 H), 4.66 (d, *J* = 7.8 Hz, 1 H), 7.01 (d, *J* = 8.9 Hz, 1 H), 8.22 (dd, *J* = 8.9, 2.8 Hz, 1 H), 8.49 (d, *J* = 2.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 151.2, 142.2, 130.9, 127.0, 126.4, 121.0, 100.9, 99.4, 74.4, 68.1, 67.1, 62.2, 60.8, 56.4, 41.6, 29.2, 28.2, 19.1; high-resolution mass spectrum (CI, NH_3) *m*/*z* 408.1770 $[(M + H)^+$, calcd for $C_{19}H_{26}N_3O_7$ 408.1771].

Methyl 2-Deoxy-3-amino-4,6-*O*-isopropylidene-*N*-(*o*-aminobenzoyl)-*N*-trifluoroacetamide-β-D-glucosamine Benzodiazepinone (+)-75. To a stirred solution of (+)-**1** (35.0 mg, 0.092 mmol) in DCM (10 mL) at 0 °C was added TEA (76 μL, 0.55 mmol) followed by trifluoroacetic anhydride (39 μL, 0.27 mmol). The reaction mixture was warmed to rt, stirred for 3.5 h, and then concentrated in vacuo. Flash chromatography (50% ethyl acetate/hexanes) gave 33.5 mg (74% yield) of (+)-**75** as a yellow solid: $[\alpha]^{20}_D$ +12 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3020, 2890, 1680, 1540, 1350, 1220, 1160, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 6 H), 3.01 (m, 1 H), 3.42 (m, 1 H), 3.56 (s, 3 H), 3.57 (m, 1 H), 3.71 (dd, $J^1 = J^2 = 10.5$ Hz, 1 H), 3.96 (dd, *J* = 10.9, 5.1 Hz, 1 H), 4.70 (d, *J* = 7.6 Hz, 1 H), 5.04 (m, 1 H), 6.87 (s, 1 H), 7.42 (d, *J* = 8.3 Hz, 1 H), 8.45 (dd, *J* = 8.5, 2.6 Hz, 1 H), 8.63 (d, *J* = 2.6 Hz, 1 H); (trifluoroacetamide carbonyl C not obsd due to long relax time) ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 149.0, 138.0, 136.5, 131.0, 127.0, 125.5, 117.0, 115.0, 101.5, 100.1, 70.0, 64.5, 62.0, 57.5, 56.5, 29.0, 19.0; high-resolution mass spectrum (CI, NH_3) *m*/*z* 493.1546 $[(M + NH_4)^+$, calcd for $C_{19}H_{24}F_3N_4O_8$ 493.1547].

Tricyclic Hybrid (−)-2. To a stirred solution of (+)-**1** (10 mg, 0.026 mmol) in MeOH (1 mL) was added a catalytic amount of 5% palladium on activated carbon. The reaction vessel was repeatedly evacuated and purged with argon and

then hydrogen. The suspension was stirred under hydrogen for 1 h and then repeatedly evacuated and purged with argon. The reaction mixture was filtered through Celite, and the filter cake was washed with MeOH. The pale green filtrate was concentrated maintaining the water bath at 25 °C in the dark. The light- and air-sensitive aniline was rapidly transferred to a 5 mL conical flask and taken up in DMF (100 μL). In a separate flask, a solution of isoamyl nitrite (5.3 μL, 0.04 mmol) in DMF (160 μL) was heated to 40 °C, and the aniline solution was added slowly via cannula. Stirring was maintained for 5 h, and H_2O (5 mL) was added to the resultant red mixture. The layers were separated, and the aqueous phase was extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative TLC (500 μm, 5% MeOH/DCM) to give 3.6 mg (42% yield, two steps) of (−)-**2** as a yellow oil: $[\alpha]^{20}_D$ −59 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) 3010, 2910, 1630, 1480, 1370, 1200, 1090, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 3 H), 1.58 (s, 3 H), 3.48 (m, 2 H), 3.59 (s, 3 H), 3.75 (dd, $J^1 = J^2 = 9.3$ Hz, 1 H), 3.83 (dd, $J^1 = J^2 = 10.5$ Hz, 1 H), 4.00 (dd, $J = 10.9$ and 5.3 Hz, 1 H), 4.40 (d, $J = 7.5$ Hz, 1 H), 4.57 (s, 1 H), 6.33 (s, 1 H), 6.69 (d, $J = 8.1$ Hz, 1 H), 6.88 (dd, $J^1 = J^2 = 6.1$ Hz, 1 H), 7.29 (dd, $J = 15.2$, 1.6 Hz, 1 H), 8.17 (dd, $J = 8.1$, 1.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 146.0, 133.0, 134.0, 119.0, 118.5, 103.0, 100.5, 72.0, 68.5, 62.0, 60.0, 58.0, 57.5, 30.0, 29.0, 19.0; high-resolution mass spectrum (CI, NH_3) *m*/*z* 335.1612 [(M + H)$^+$, calcd for $C_{17}H_{23}N_2O_5$ 335.1607].

Methyl 2-Deoxy-4,6-*O*-isopropylidene-*N*-(2-hydroxy-5-chlorobenzoyl)-β-D-glucosamine Benzodiazepinone (−)-76. To a solution of (−)-**3** (35.8 mg, 0.094 mmol) in methanol (3 mL) was added a catalytic amount of 5% palladium on activated carbon. The reaction vessel was repeatedly evacuated and purged with argon and then hydrogen. The suspension was stirred under hydrogen for 1 h and then repeatedly evacuated and purged with argon. The reaction mixture was filtered through Celite, and the filter cake was washed with MeOH. Concentration of the combined filtrates followed by flash chromatography (5% MeOH/DCM) furnished 28.8 mg (87% yield) of the aniline: $[\alpha]^{20}_D$ −103 (*c* 0.06, $CHCl_3$); IR ($CHCl_3$) 3020, 1630, 1530, 1500, 1410, 1260, 1160, 940, 800, 650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 3 H), 1.55 (s, 3 H), 3.33 (ddd, $J = 10.0$, 10.0, 5.3 Hz, 1 H), 3.48 (m, 1 H), 3.55 (s, 3 H), 3.59 (br s, 2 H), 3.82 (m, 2 H), 3.97 (m, 2 H), 4.34 (d, $J = 8.0$ Hz, 1 H), 6.29 (s, 1 H), 6.75 (dd, $J = 8.5$, 2.9 Hz, 1 H), 6.87 (d, $J = 8.5$ Hz, 1 H), 7.43 (d, $J = 2.9$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 149.3, 142.1, 122.9, 121.9, 121.0, 117.9, 102.7, 100.1, 81.5, 71.5, 68.2, 62.0, 58.8, 57.3, 29.0, 19.1; high-resolution mass spectrum (CI, NH_3) *m*/*z* 351.1567 [(M + H)$^+$, calcd for $C_{17}H_{23}N_2O_6$ 351.1556].

A solution of *tert*-butyl nitrite (5.3 μL, 0.0445 mmol) and copper(II) chloride (anhydrous, 4.8 mg, 0.0356 mmol) in acetonitrile (anhydrous, 120 μL) was cooled to 0 °C, and the aniline (10.4 mg, 0.0297 mmol) was added over 15 min. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (50% ethyl acetate/hexanes) to give 6.8 mg (40% yield) of (−)-**76**: $[\alpha]^{20}_D$ −41.8 (*c* 0.225, $CHCl_3$); IR ($CHCl_3$) 2900, 2820, 1660, 1590, 1460, 1200, 990, 920, 840, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 3 H), 1.57 (s, 3 H), 3.35 (ddd, $J = 10.0$, 10.0, 5.3 Hz, 1 H), 3.52 (m, 1 H), 3.57 (s, 3 H), 3.86 (m, 2 H), 4.00 (m, 2 H), 4.33 (d, $J = 7.8$ Hz, 1 H), 6.36 (s, 1 H), 7.00 (d, $J = 8.6$ Hz, 1 H), 7.36 (dd, $J = 8.6$, 2.7 Hz, 1 H), 8.21 (d, $J = 2.7$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 155.6, 133.7, 132.8, 128.5, 122.4, 102.7, 100.2, 81.2, 71.6, 68.0, 62.0, 58.8, 57.5, 29.7, 29.0, 19.1; high-resolution mass spectrum (CI, NH_3) *m*/*z* 370.1042 [(M + H)$^+$, calcd for $C_{17}H_{21}ClNO_6$ 370.1057].

Methyl 2-Deoxy-3-triethylsilyl-4,6-*O*-isopropylidene-β-D-glucosamine (−)-77. A stirred solution of amino sugar (−)-**14** (197 mg, 0.845 mmol) in DCM (dry, 40 mL) was cooled to −78 °C, and TEA (0.59 mL, 4.2 mmol) was added dropwise via syringe. Triethylsilane trifluoromethanesulfonate (0.57 mL, 2.5 mmol) was added, and the mixture was stirred for 2 h at −78 °C and then brought to rt. The solvent was removed under reduced pressure to give a yellow oily residue. Flash chromatography (hexanes−ethyl acetate, 1:1) gave 175 mg (60% yield) of (−)-**77** as a colorless, viscous oil: $[\alpha]^{20}_D$ −36.8 (*c* 0.226, $CHCl_3$); IR (thin film) 3394, 3314, 2993, 2954, 2912, 2876, 2837, 1458, 1381, 1200, 1173, 1147, 1125, 1100, 1085, 1017, 949, 857, 806, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.58−0.71 (m, 6 H), 0.96 (t, $J = 7.9$ Hz, 9 H), 1.40 (s, 3 H), 1.46 (s, 3 H), 1.59 (br s, 2 H), 2.77 (t, $J = 8.3$ Hz, 1 H), 3.22 (ddd, $J = 9.9$, 9.9, 5.4 Hz, 1 H), 3.48 (t, $J = 4.5$ Hz, 2 H), 3.52 (s, 3 H), 3.78 (dd, $J^1 = J^2 = 10.6$ Hz, 1 H), 3.90 (dd, $J = 10.7$, 5.4 Hz, 1 H), 4.17 (d, $J = 7.9$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 105.5, 99.4, 75.4, 74.0, 67.6, 62.2, 58.8, 57.3, 29.1, 18.9, 6.9, 5.1; high-resolution mass spectrum (ESI) *m*/*z* 370.2018 [(M + Na)$^+$, calcd for $C_{16}H_{33}NO_5SiNa$ 370.2025].

Methyl 2-Deoxy-3-triethylsilyl-4,6-*O*-isopropylidene-*N*-benzyl-β-D-glucosamine (−)-78. Amino sugar (−)-**77** (175 mg, 0.504 mmol) was dissolved in toluene (10 mL), and benzaldehyde (0.15 mL, 1.5 mmol) was added via syringe. The reaction flask was fitted with a Dean−Stark trap and condenser, and the mixture was heated at reflux, with azeotropic removal of water, for 14 h. Concentration gave a viscous yellow oil, which was taken up in MeOH−$CHCl_3$ (1:1, 14 mL). Sodium borohydride (34 mg, 0.91 mmol) was added to the stirred solution in portions over 10 min. The resulting mixture was stirred 1 h at rt and then concentrated. The residue was treated with DCM (4 × 2 mL). The combined DCM washings were concentrated, and the residue was purified by flash chromatography (20% ethyl acetate in hexanes) to furnish 193 mg (87% yield) of (−)-**78** as a colorless, viscous oil: $[\alpha]^{20}_D$ −64.5 (*c* 1.28, $CHCl_3$); IR (thin film) 3357, 3063, 3027, 2993, 2953, 2910, 2875, 1495, 1456, 1381, 1309, 1272, 1240, 1202, 1177, 1122, 1091, 1011, 955, 885, 862, 805, 740, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.61−0.74 (m, 6 H), 0.99 (t, $J = 7.9$ Hz, 9 H), 1.41 (s, 3 H), 1.45 (s, 3 H), 1,74 (br s, 1 H), 2.52 (dd, $J = 8.1$, 2.4 Hz, 1 H), 3.47 (dd, $J = 9.3$, 2.0 Hz, 1 H), 3.52 (s, 3 H), 3.73 (dd, $J^1 = J^2 = 10.2$ Hz, 1 H), 3.79 (ddd, $J = 9.8$, 9.8, 4.8 Hz, 1 H), 3.89−3.96 (m, 3 H), 4.15 (br m, 1 H), 4.50 (d, $J = 8.1$ Hz, 1 H), 7.23 (t, $J = 7.5$ Hz, 1 H), 7.31 (t, $J = 7.5$ Hz, 2 H), 7.36 (d, $J = 7.5$ Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 128.3, 127.9, 126.7, 103.7, 99.2, 72.7, 69.9, 63.4, 62.6, 60.9, 56.9, 51.1, 28.8, 19.1, 7.0, 5.3; high-resolution mass spectrum (ESI) *m*/*z* 460.2500 [(M + Na)$^+$, calcd for $C_{23}H_{39}NO_5SiNa$ 460.2496].

Methyl 2-Deoxy-3-triethylsilyl-4,6-*O*-isopropylidene-*N*-4-methoxybenzyl-β-D-glucosamine (−)-79. Amino sugar (−)-**77** (36.8 mg, 0.106 mmol) was dissolved in toluene (HPLC grade, 10 mL) and *p*-anisaldehyde (15 μL, 0.13 mmol) was added. The mixture was concentrated on the rotary evaporator, and more toluene (10 mL) was added. This sequence was repeated four times to give the crude imine as a viscous oil. The imine was dissolved in methanol (HPLC, 2 mL), and $NaBH_4$ (20 mg, 0.53 mmol) was added in portions to the stirred solution over 5 min. The mixture was stirred 1 h at rt to complete the reaction and concentrated. The residue was purified by preparative TLC (500 μm, 50% ethyl acetate in hexanes) to give 28 mg (57% yield) of (−)-**79** as a viscous yellow oil: $[\alpha]^{20}_D$ −11.3 (*c* 0.14, $CHCl_3$); IR (thin film) 3332, 2993, 2954, 2876, 2835, 1612, 1513, 1465, 1381, 1246, 1201, 1174, 1097, 1075, 1042, 1008, 861, 818, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.56−0.67 (m, 6 H), 0.92 (t, $J = 7.9$ Hz, 9 H), 1.40 (s, 3 H), 1.46 (s, 3 H), 1.80 (br s, 1 H), 2.59 (dd, $J^1 = J^2 = 8.5$ Hz, 1 H), 3.19 (ddd, $J = 10.1$, 10.1, 5.0 Hz, 1 H), 3.49 (dd, $J = 16.3$, 8.4 Hz, 2 H), 3.54 (s, 3 H), 3.78 (d, $J = 13.0$ Hz, 1 H), 3.79 (s, 3 H), 3.90 (dd, $J = 10.8$, 5.3 Hz, 1 H), 3.97 (d, $J = 12.8$ Hz, 1 H), 4.27 (d, $J = 7.9$ Hz, 1 H), 6.84 (d, $J = 8.6$ Hz, 2 H), 7.22 (d, $J = 8.5$ Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.0, 129.5, 113.8, 106.8, 99.4, 74.3, 74.1, 67.3, 64.6, 62.2, 57.1, 55.3, 53.3, 29.3, 29.0, 18.9, 6.9, 5.1; high-resolution mass spectrum (ESI) *m*/*z* 468.2769 [(M + Na)$^+$, calcd for $C_{24}H_{41}NO_6SiNa$ 468.2781].

Methyl 2-Deoxy-3-triethylsilyl-4,6-*O*-isopropylidene-*N*-2-picolyl-*β*-D-glucosamine (−)-80. Amino sugar (−)-**77** (45.2 mg, 0.130 mmol) was dissolved in toluene (HPLC grade, 10 mL), and 2-pyridyl carboxaldehyde (15 μL, 0.16 mmol) was added. The mixture was concentrated on the rotary evaporator, and more toluene (10 mL) was added. This sequence was repeated four times to give the crude imine as a white solid. The imine was dissolved in methanol (HPLC, 2 mL), and $NaBH_4$ (25 mg, 0.65 mmol) was added in portions to the stirred solution over 5 min. The mixture was stirred 24 h at rt to complete the reaction and concentrated. The residue was purified by preparative TLC (500 μm, 50% ethyl acetate in hexanes) to give 31 mg (55% yield) of (−)-**80** as a viscous yellow oil: $[\alpha]^{20}_D$ −13.6 (*c* 0.155, $CHCl_3$); IR (thin film) 3320, 3061, 2993, 2954, 2876, 1592, 1570, 1472, 1435, 1381, 1265, 1236, 1175, 1100, 1049, 1009, 942, 861, 818, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.60−0.72 (m, 6 H), 0.94 (t, *J* = 7.8 Hz, 9 H), 1.41 (s, 3 H), 1.46 (s, 3 H), 2.60 (dd, *J* = 9.1, 8.0 Hz, 1 H), 3.21 (ddd, *J* = 9.9, 9.9, 5.3 Hz, 1 H), 3.50 (s, 3 H), 3.50−3.53 (m, 1 H), 3.60 (dd, $J^1 = J^2$ = 9.0 Hz, 1 H), 3.77 (dd, $J^1 = J^2$ = 10.5 Hz, 1 H), 3.90 (dd, *J* = 10.7, 5.3 Hz, 1 H), 4.00 (d, *J* = 14.5 Hz, 1 H), 4.16 (d, *J* = 14.5 Hz, 1 H), 4.30 (d, *J* = 7.8 Hz, 1 H), 7.12 (dd, $J^1 = J^2$ = 6.2 Hz, 1 H), 7.27 (d, *J* = 8.3 Hz, 1 H), 7.60 (dd, $J^1 = J^2$ = 7.7 Hz, 1 H), 8.54 (d, *J* = 4.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 136.0, 122.0, 121.6, 106.7, 99.4, 74.4, 74.1, 67.3, 65.2, 62.2, 58.8, 57.0, 54.9, 29.0, 18.9, 6.9, 5.1; high-resolution mass spectrum (ESI) *m*/*z* 461.2448 [(M + Na)$^+$, calcd for $C_{22}H_{38}N_2O_5SiNa$ 461.2450].

Methyl 2-Deoxy-3-triethylsilyl-4,6-*O*-isopropylidene-*N*-(2-fluoro-5-nitrobenzamido)-*N*-(benzyl)-*β*-D-glucosamine (+)-81. To a solution of (−)-**78** (25.5 mg, 0.0583 mmol) in THF (anhydrous, 600 μL) was added acid **16** (9.0 mg, 0.049 mmol), and the mixture was stirred for 5 min at rt. DMTMM (17 mg, 0.060 mmol) was added, and the resulting white suspension was stirred 19 h at rt and then diluted with ethyl acetate (5 mL). The suspension was filtered through Celite, and the filter cake was washed with EtOAc (3 × 2 mL). The combined filtrates were concentrated, and the residue was purified by preparative TLC (500 μm, 25% ethyl acetate/hexanes) to give 22 mg (65% yield) of (+)-**81** as a white foam: $[\alpha]^{20}_D$ +38.6 (*c* 0.14, $CHCl_3$); IR (thin film) 3072, 2937, 2870, 1647, 1585, 1535, 1451, 1423, 1373, 1345, 1255, 1205, 1172, 1127, 1082, 1004, 948, 853, 797, 730; ^1H NMR (500 MHz, $CDCl_3$, complex spectrum due to slow rotational isomerism) δ 0.77 (app. q, *J* = 8.0 Hz, 6 H, major + minor), 1.03 (t, *J* = 8.0 Hz, 9 H, major + minor), 1.39 (s, 1 H, minor), 1.41 (s, 2 H, major), 1.46 (s, 2 H, major), 1.53 (s, 2 H, minor), 1.84−1.87 (m, 5 H, major + minor), 2.76 (br s, 2 H, major + minor), 3.20 (s, 1 H, major + minor), 3.27 (br m, 1 H, major + minor), 3.40−3.42 (br m, 1 H, major + minor), 3.61 (dd, $J^1 = J^2$ = 10.4 Hz, 1 H, major + minor), 3.74−3.83 (m, 4 H, major), 3.83−3.93 (m, 4 H, major + minor), 3.84−3.93 (m, 2 H, minor), 3.98 (dd, *J* = 9.6 and 4.6 Hz, 1 H, major + minor), 4.08 (s, 1 H, major + minor), 4.52 (d, *J* = 17.9 Hz, 1 H, major), 4.56 (d, *J* = 17.9 Hz, 1 H, minor), 4.71 (d, *J* = 8.0 Hz, 1 H, major + minor), 4.77 (br s, 1 H, major), 4.82 (d, *J* = 17.5 Hz, 1 H, major + minor), 4.96 (d, *J* = 7.3 Hz, 1 H, major + minor), 5.49 (d, *J* = 15.6 Hz, 1 H, major + minor), 7.05−7.10 (m, 2 H, major + minor), 7.15 (t, *J* = 7.5 Hz, 1 H, major + minor), 7.33 (t, *J* = 8.6 Hz, 1 H, major + minor), 7.36−7.37 (m, 2 H, major + minor), 7.89 (br s, 1 H, major), 8.05−8.08 (br m, 1 H, major + minor), 8.31 (br s, 1 H, minor); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 165.8, 162.4, 162.0, 160.3, 160.0, 143.7, 137.6, 128.3, 127.3, 127.2, 127.0, 126.7, 126.6, 126.4, 126.0, 125.2, 116.7, 116.5, 73.8, 72.4, 72.2, 63.7, 62.8, 62.5, 62.0, 58.7, 56.1, 55.9, 50.7, 31.9, 28.7, 28.5, 19.2, 19.1, 7.1, 7.0, 5.3, 5.1; high-resolution mass spectrum (ESI) *m*/*z* 627.2488 [(M + Na)$^+$, calcd for $C_{30}H_{41}FN_2O_8SiNa$ 627.2514].

Methyl 2-Deoxy-3-triethylsilyl-4,6-*O*-isopropylidene-*N*-(2-fluoro-5-nitrobenzamido)-*N*-(4-methoxybenzyl)-*β*-D-glucosamine (+)-82. To a solution of (−)-**79** (28 mg, 0.060 mmol) in THF (anhydrous, 0.70 mL) was added acid **16** (9.3 mg, 0.050 mmol), and the mixture was stirred for 5 min at rt. DMTMM (17 mg, 0.060 mmol) was added, and the resulting white suspension was stirred 14 h at rt and then diluted with EtOAc (5 mL). The suspension was filtered through Celite, and the filter cake was washed with EtOAc (3 × 2 mL). The combined filtrates were concentrated to give the crude product as a yellow residue. Preparative TLC (500 μm, 25% ethyl acetate/hexanes) furnished 27 mg (72% yield) of (+)-**82** as a white foam: $[\alpha]^{20}_D$ +5.7(*c* 0.75, $CHCl_3$); IR (thin film) 3084, 2994, 2956, 2877, 2842, 1650, 1613, 1585, 1533, 1514, 1448, 1349, 1247, 1201, 1176, 1125, 1094, 1017, 857, 809, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, complex spectrum due to slow rotational isomerism) δ 0.59−0.80 (br m, 6 H, major + minor), 1.01 (t, *J* = 7.8 Hz, 9 H, major + minor), 1.40 (s, 3 H, major + minor), 1.42 (s, 3 H, major + minor), 1.47 (s, 1 H, minor), 2.91 (br s, 3 H, major + minor), 2.94 (ddd, *J* = 9.9, 9.9, 5.4 Hz, 1 H, major + minor), 3.28−3.32 (br m, 1 H, major + minor), 3.38−3.41 (br m, 1 H, major + minor), 3.52 (br d, *J* = 18.0 Hz, 1 H, major + minor), 3.60 (dd, $J^1 = J^2$ = 10.6 Hz, 1 H, major + minor), 3.74 (dd, $J^1 = J^2$ = 5.5 Hz, 1 H, major + minor), 3.77−3.80 (br m, 2 H, major + minor), 3.82 (s, 3 H, major + minor), 3.89−3.92 (br m, 1 H, major + minor), 4.04−4.07 (br m, 1 H, major + minor), 4.37−4.49 (br m, 1 H, major + minor), 6.78 (d, *J* = 8.3 Hz, 1 H, minor), 6.92 (d, *J* = 8.6 Hz, 2 H, major + minor), 7.08 (d, *J* = 8.5 Hz, minor H), 7.23 (d, *J* = 8.4 Hz, minor H), 7.38 (d, *J* = 8.2 Hz, 2 H, major + minor), 8.15 (br s, 1 H, minor), 8.25 (ddd, *J* = 9.0, 3.5 and 3.5 Hz, 1 H, major + minor), 8.37 (br s, 1 H, major); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.1, 158.7, 158.5, 129.6, 129.1, 128.6, 127.7, 126.5, 125.8, 124.8, 116.6, 116.4, 113.7, 113.6, 103.6, 99.6, 99.5, 98.8, 98.4, 73.8, 72.6, 72.3, 72.2, 72.1, 69.7, 63.7, 63.3, 62.9, 62.8, 62.6, 62.5, 61.9, 58.5, 56.9, 56.0, 55.9, 55.3, 55.2, 50.4, 50.2, 29.6, 28.7, 28.6, 28.5, 19.2, 19.1, 7.0, 6.9, 5.3, 5.2, 5.0; high-resolution mass spectrum (ESI) *m*/*z* 657.2620 [(M + Na)$^+$, calcd for $C_{31}H_{43}FN_2O_9SiNa$ 657.2601].

Methyl 2-Deoxy-3-triethylsilyl-4,6-*O*-isopropylidene-*N*-(2-fluoro-5-nitrobenzamido)-*N*-(2-picolyl)-*β*-D-glucosamine (−)-83. To a solution of (−)-**80** (26.4 mg, 0.0602 mmol) in THF (anhydrous, 0.7 mL) was added acid **16** (9.3 mg, 0.050 mmol), and the mixture was stirred for 5 min at rt. DMTMM (17 mg, 0.060 mmol) was added, and the resulting white suspension was stirred for 48 h at rt. The reaction mixture was diluted with ethyl acetate (2 mL) and filtered through Celite. The filter cake was washed with ethyl acetate (3 × 2 mL), and the combined filtrates were concentrated to give the crude product as a yellow residue. Preparative TLC (500 μm, 50% ethyl acetate/hexanes) furnished 16 mg (52% yield) of (−)-**83** as a white foam: $[\alpha]^{20}_D$ −28.4 (*c* 0.80, $CHCl_3$); IR (thin film) 3084, 2993, 2956, 2877, 1651, 1533, 1448, 1373, 1350, 1259, 1242, 1201, 1125, 1094, 1017, 857, 810, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, complex spectrum due to slow rotational isomerism) δ 0.64−0.73 (br m, 6 H, major + minor), 0.99 (t, *J* = 7.8 Hz, 9 H, major + minor), 1.26 (s, 1 H, minor), 1.38 (s, 3 H, major), 1.41 (s, 3 H, major), 1.43 (s, 1 H, minor), 1.48 (s, 1 H, minor), 1.62 (br s, 1 H, minor), 2.61 (dd, $J^1 = J^2$ = 6.2 Hz, 1 H, minor), 2.88 (br s, 3 H, major), 3.12 (ddd, *J* = 9.8, 9.8 and 5.4 Hz, 1 H, major + minor), 3.30 (dd, $J^1 = J^2$ = 8.9 Hz, 1 H, major + minor), 3.43−3.50 (br m, 2 H, major + minor), 3.61 (dd, $J^1 = J^2$ = 10.6 Hz, 1 H, major), 3.66 (dd, $J^1 = J^2$ = 6.3 Hz, 1 H, minor), 3.74 (dd, $J^1 = J^2$ = 10.4 Hz, 1 H, minor), 3.79 (dd, *J* = 10.8 and 5.4 Hz, 1 H, major + minor), 3.91−3.93 (br m, 1 H, minor), 4.12−4.15 (br m, 2 H, major), 4.25 (br d, *J* = 15.3 Hz, 1 H, major + minor), 4.50−4.54 (br m, 1 H, major), 4.64−4.68 (br m, 1 H, minor), 4.79 (br s, 1 H, minor), 5.47 (br s, 1 H, minor), 5.61 (d, *J* = 15.4 Hz, 1 H, major + minor), 5.76 (br m, 1 H, minor), 7.13−7.16 (br m, 1 H, minor), 7.23−7.24 (br m, 2 H, major + minor), 7.56 (br s, 1 H, minor), 7.65 (ddd, *J* = 7.7, 7.7, 1.6 Hz, 1 H, minor), 7.73−7.75 (br m, 2 H, major), 8.26 (ddd, *J* = 9.0, 3.5, 3.5 Hz, 1 H, major + minor), 8.39 (br m, 1 H, minor), 8.42 (dd, *J* = 5.5, 2.8 Hz, 1 H, major + minor), 8.54 (br d, *J* = 4.7 Hz, 1 H, major + minor); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 157.4, 149.2, 148.7, 143.6, 136.9, 136.5,

126.5, 126.4, 126.3, 125.8, 125.7, 125.5, 125.4, 123.9, 122.7, 122.6, 117.5, 117.3, 117.2, 117.0, 100.6, 99.5, 74.7, 71.7, 69.9, 66.9, 66.8, 66.5, 66.4, 62.1, 61.7, 56.3, 47.7, 29.7, 29.0, 28.9, 18.8, 18.7, 7.0, 6.8, 5.3, 5.0; high-resolution mass spectrum (ESI) *m/z* 606.2656 [(M + H)$^+$, calcd for $C_{29}H_{41}FN_3O_8Si$ 606.2647].

***N*-Benzyl Tricyclic Hybrid (+)-84.** To a solution of cyclization precursor (+)-**81** (30.2 mg, 0.0499 mmol) in DMF (anhydrous, 16 mL, $c = 0.003$ M) was added CsF (anhydrous, 38.0 mg, 0.250 mmol). The mixture was sparged 5 min with argon and heated at 90 °C for 22 h. Solvent was removed by vacuum distillation to give the crude product as a bright yellow residue. Preparative TLC (500 μm, 50% ethyl acetate/hexanes) furnished 15 mg (62% yield) of (+)-**84** as a white solid: $[\alpha]^{20}_D$ +5.9 (*c* 0.17, $CHCl_3$); IR (thin film) 2989, 2918, 2849, 1653, 1458, 1375, 1339, 1268, 1199, 1087, 944, 846 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3 H), 1.44 (s, 3 H), 3.33 (s, 3 H), 3.44 (ddd, $J = 9.4, 9.4, 4.9$ Hz, 1 H), 3.79 (dd, $J^1 = J^2 = 10.6$ Hz, 1 H), 3.86 (dd, $J = 10.7, 4.9$ Hz, 1 H), 4.27 (d, $J = 7.7$ Hz, 1 H), 4.59 (d, $J = 14.9$ Hz, 1 H), 4.89 (s, 1 H), 5.23 (d, $J = 13.8$ Hz, 1 H), 5.74 (s, 1 H), 7.05 (d, $J = 9.1$ Hz, 1 H), 7.25−7.26 (m, 2 H), 7.30−7.34 (m, 1 H), 7.36−7.38 (m, 2 H), 8.21 (d, $J = 9.4$ Hz, 1 H), 8.88 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 139.2, 138.7, 136.2, 132.1, 128.8, 128.4, 128.4, 128.1, 126.9, 118.7, 116.1, 100.1, 99.0, 70.9, 67.1, 62.5, 56.9, 53.0, 31.9, 29.0, 14.1; high-resolution mass spectrum (ESI) *m/z* 469.1597 [(M − H)$^-$, calcd for $C_{24}H_{25}N_2O_8$ 469.1611].

***N*-(4-Methoxybenzyl) Tricyclic Hybrid (+)-85.** To a solution of cyclization precursor (+)-**82** (27 mg, 0.043 mmol) in DMF (anhydrous, 14 mL, $c = 0.003$ M) was added CsF (anhydrous, 28.3 mg, 0.186 mmol). The mixture was sparged 5 min with argon and heated at 90 °C for 24 h. Solvent was removed by vacuum distillation to give the crude product as a bright yellow residue. Preparative TLC (500 μm, 50% ethyl acetate/hexanes) furnished 12 mg (56% yield) of (+)-**85** as a white, waxy solid: $[\alpha]^{20}_D$ +42.0 (*c* 0.60, $CHCl_3$); IR (thin film) 3084, 2938, 2888, 2836, 1654, 1613, 1583, 1513, 1441, 1373, 1345, 1267, 1247, 1223, 1203, 1175, 1091, 1029, 1004, 946, 914, 885, 855, 724 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 3 H), 1.48 (s, 3 H), 3.00 (ddd, $J = 9.8, 9.8, 5.4$ Hz, 1 H), 3.46 (dd, $J^1 = J^2 = 9.5$ Hz, 1 H), 3.50 (s, 3 H), 3.62−3.69 (m, 2 H), 3.84 (s, 3 H), 3.87 (dd, $J = 10.9, 3.8$ Hz, 1 H), 4.03−4.08 (m, 2 H), 4.72 (d, $J = 7.8$ Hz, 1 H), 5.75 (d, $J = 15.6$ Hz, 1 H), 6.92 (d, $J = 8.7$ Hz, 2 H), 7.08 (d, $J = 8.8$ Hz, 1 H), 7.30 (d, $J = 8.6$ Hz, 2 H), 8.31 (dd, $J = 8.8, 2.8$ Hz, 1 H), 8.66 (d, $J = 2.8$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 159.4, 156.0, 144.8, 130.4, 129.0, 128.9, 127.8, 126.6, 123.7, 114.5, 99.9, 84.8, 70.7, 67.1, 61.7, 60.0, 56.4, 55.3, 44.8, 29.7, 28.9, 19.0; high-resolution mass spectrum (ESI) *m/z* 523.1681 [(M + Na)$^+$, calcd for $C_{25}H_{28}N_2O_9Na$ 523.1693].

***N*-(2-Picolyl) Tricyclic Hybrid (+)-86.** To a solution of cyclization precursor (−)-**83** (16 mg, 0.04328 mmol) in DMF (anhydrous, 10 mL, $c = 0.003$ M) was added CsF (anhydrous, 24 mg, 0.16 mmol). The mixture was sparged 5 min with argon and heated at 90 °C for 2.5 h. Solvent was removed by vacuum distillation to give the crude product as a yellow solid. Flash chromatography (50% ethyl acetate/hexanes) gave 11 mg (93% yield) of (+)-**86** as a white solid: $[\alpha]^{20}_D$ +69.6 (*c* 0.135, $CHCl_3$); IR (thin film) 2992, 2925, 2853, 1657, 1615, 1591, 1526, 1474, 1346, 1306, 1267, 1223, 1203, 1174, 1150, 1091, 1003, 944, 886, 855 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 3 H), 1.51 (s, 3 H), 3.24 (ddd, $J = 9.8, 9.8, 5.4$ Hz, 1 H), 3.47 (s, 3 H), 3.53 (dd, $J^1 = J^2 = 9.5$ Hz, 1 H), 3.66−3.74 (m, 2 H), 3.94 (dd, $J = 10.9, 5.4$ Hz, 1 H), 4.32−4.37 (m, 2 H), 5.22 (d, $J = 7.7$ Hz, 1 H), 5.60 (d, $J = 15.5$ Hz, 1 H), 7.05 (d, $J = 8.8$ Hz, 1 H), 7.25−7.28 (m, 1 H), 7.55 (d, $J = 7.8$ Hz, 1 H), 7.71 (ddd, $J = 7.7, 7.7, 1.7$ Hz, 1 H), 8.29 (dd, $J = 8.8, 2.8$ Hz, 1 H), 8.58 (br d, $J = 3.4$ Hz, 1 H), 8.64 (d, $J = 2.8$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 157.2, 156.3, 149.0, 144.6, 137.4, 130.0, 127.9, 127.8, 126.6, 123.6, 123.1, 100.1, 84.9, 71.0, 67.0, 61.9, 60.0, 56.4, 47.6, 29.7, 28.9, 19.0; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 472.1722 [(M + H)$^+$, calcd for $C_{23}H_{26}N_3O_8$ 472.1720].

Methyl 2-Deoxy-*N*-(*o*-hydroxybenzothioyl)-β-D-glucosamine-oxazepinthione (−)-87. To a solution of (+)-**1** (12 mg, 0.035 mmol) in freshly distilled toluene was added Lawesson's reagent (15 mg, 0.037 mmol) and the mixture heated at reflux for 24 h. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (10% MeOH/DCM) to give 5.3 mg (43% yield) of (−)-**87**: $[\alpha]^{20}_D$ −140 (*c* 0.5, MeOH-d_4); IR (thin film) 3300−2920, 2850, 1705, 1580, 1500, 1320, 1150, 990, 850, 400 cm^{-1}; ^{1}H NMR (500 MHz, MeOH-d^4) δ 3.33 (m, 1 H), 3.49 (dd, $J = 10.9, 7.9$ Hz, 1 H), 3.53 (s, 3 H), 3.59 (dd, $J^1 = J^2 = 9.4$ Hz, 1 H), 3.71 (dd, $J = 12.0, 5.1$ Hz, 1 H), 3.87 (dd, $J = 12.0, 2.3$ Hz, 1 H), 4.48 (dd, $J = 10.8, 9.1$ Hz, 1 H), 4.67 (d, $J = 7.9$ Hz, 1 H), 4.80 (m, 1 H), 7.28 (s, 1 H), 8.28 (dd, $J = 8.8, 2.9$ Hz, 1 H), 8.81 (d, $J = 2.9$ Hz, 1 H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 167.6, 152.2, 128.4, 121.4, 116.0, 114.9, 111.7, 87.8, 79.0, 64.5, 55.3, 48.5, 47.0, 43.7; high-resolution mass spectrum (ESI) *m/z* 355.0591 [(M − H)$^-$, calcd for $C_{14}H_{16}N_2O_7S$ 355.0599].

2-(1-Phenylsulfonylindol-3-yl)ethyl 2-Deoxy-4,6-*O*-benzylidene-*N*-trifluoroacetamido-β-D-glucosamine (−)-92. To a stirred solution of triol (−)-**91** (6.6 g, 12 mmol) in DMF (120 mL) were added benzaldehyde dimethyl acetal (6.6 g, 43 mmol) and PPTS (1.2 g, 4.8 mmol). The mixture was heated at 85 °C for 2 h, cooled to rt, poured into H_2O (1 L), and extracted with ethyl acetate (3 × 200 mL). Combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% MeOH/DCM) furnished 6.4 g (85% yield) of (−)-**92** as a white solid: $[\alpha]^{20}_D$ −42.3 (*c* 1.24, acetone); IR (thin film) 3500−3200, 3000, 2920, 2840, 1540, 1350, 1170, 1080, 850 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 2.56 (dd, $J^1 = J^2 = 2.3$ Hz, 1 H), 2.94−2.97 (m, 2 H), 3.46 (ddd, $J = 9.7, 9.7, 5.0$ Hz, 1 H), 3.60 (dd, $J^1 = J^2 = 9.2$ Hz, 1 H), 3.79 (dd, $J^1 = J^2 = 10.2$ Hz, 1 H), 3.88 (ddd, $J = 9.8, 6.1, 6.1$ Hz, 1 H), 3.93 (dd, $J^1 = J^2 = 8.9$ Hz, 1 H), 4.00 (dd, $J^1 = J^2 = 9.3$ Hz, 1 H), 4.09 (ddd, $J = 9.8, 7.2, 7.2$ Hz, 1 H), 4.25 (dd, $J = 10.3, 5.0$ Hz, 1 H), 4.87 (d, $J = 8.4$ Hz, 1 H), 5.64 (s, 1 H), 7.25 (t, $J = 7.5$ Hz, 1 H), 7.33 (t, $J = 7.9$ Hz, 1 H), 7.35 (d, $J = 1.9$ Hz, 2 H), 7.36 (d, $J = 2.0$ Hz, 1 H), 7.48 (d, $J = 2.0$ Hz, 1 H), 7.50 (d, $J = 4.2$ Hz, 1 H), 7.55−7.58 (m, 3 H), 7.60 (s, 1 H), 7.65 (t, $J = 7.4$ Hz, 1 H), 7.97−7.99 (m, 3 H), 8.54 (d, $J = 9.2$ Hz, 1 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 139.0, 135.9, 134.8, 132.0, 130.3, 129.5, 129.0, 128.7, 127.6, 127.2, 125.4, 124.9, 124.0, 120.8, 120.5, 114.3, 102.2, 102.1, 82.5, 71.5, 69.2, 67.3, 58.0, 30.1, 30.0, 29.2, 26.0 (trifluoroacetamide carbonyl, CF_3 C's not obsd due to long relax time); high-resolution mass spectrum (ESI) *m/z* 681.1302 [(M + Cl)$^-$, calcd for $C_{31}H_{29}ClF_3N_2O_8S$ 681.1285].

2-(1-Phenylsulfonylindol-3-yl)ethyl-2-deoxy-4,6-*O*-benzylidene-*N*-(2-fluoro-5-nitrobenzamido)-β-D-glucosamine (−)-96. To a solution of (−)-**94** (4.1 g, 6.7 mmol) and acid **16** (1.36 g, 7.37 mmol) in DCM (135 mL) at 0 °C was added a solution of ethyl (dimethylamino)propylcarbodiimide (EDAC, 1.54 g, 8.04 mmol) in DCM (135 mL). Stirring was continued for 0.5 h. The reaction mixture was warmed to rt, diluted with DCM, and washed with saturated $NaHCO_3$ (aq) and brine. The organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (5% MeOH/DCM) gave 3.5 g (75% yield) of (−)-**96** as a white foam: $[\alpha]^{20}_D$ −12.8 (*c* 3.0, $CHCl_3$); IR (thin film) 3500−3100, 2840, 1650, 1620, 1520, 1450, 1350, 1175, 1090, 990, 850 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89−2.97 (m, 2 H), 3.36 (br s, 1 H), 3.55−3.68 (m, 3 H), 3.81−3.87 (m, 2 H), 4.25 (ddd, $J = 9.8, 6.0, 6.0$ Hz, 1 H), 4.33 (dd, $J^1 = J^2 = 8.9$ Hz, 1 H), 4.39 (dd, $J = 10.5, 4.6$ Hz, 1 H), 5.03 (d, $J = 8.3$ Hz, 1 H), 5.58 (s, 1 H), 6.74 (dd, $J = 13.0, 6.3$ Hz, 1 H), 7.13−7.16 (m, 2 H), 7.24 (dd, $J = 10.5, 9.0$ Hz, 1 H), 7.36−7.42 (m, 6 H), 7.49−7.51 (m, 4 H), 7.73−7.75 (m, 1 H), 7.77−7.80 (m, 2 H), 8.31 (ddd, $J = 9.1, 4.2, 3.0$ Hz, 1 H), 8.74 (dd, $J = 6.5, 3.0$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 162.1, 161.7, 144.5, 138.1, 136.9, 134.8, 133.6, 130.8, 129.2, 129.1, 128.6, 128.5, 128.2, 127.9, 126.4, 124.4, 123.3, 123.0, 121.7, 121.6, 119.6, 119.3, 117.8, 117.6, 113.3, 101.9, 100.0, 81.7, 77.3, 70.6, 68.6, 66.3, 59.4, 25.1; high-resolution

mass spectrum (CI, NH_3) *m/z* 740.1659 [$(M + H)^+$, calcd for $C_{36}H_{32}FN_3O_{10}S$ 740.1690].

2-(1-Phenylsulfonylindol-3-yl)ethyl 2-Deoxy-4,6,-*O*-isopropylidene-*N*-(2-fluoro-5-nitrobenzamido)-*β*-D-glucosamine (−)-97. To a stirred solution of (−)-**95** (204 mg, 0.406 mmol) in THF (anhydrous, 3 mL) was added acid **16** (63 mg, 0.34 mmol). After the mixture was stirred for 10 min at rt, DMTMM (112 mg, 0.406 mmol) was added. The resultant white suspension was stirred for 2.5 h at rt. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (50% ethyl acetate/hexanes) to give 247 mg (90% yield) of (−)-**97** as a white foam: $[\alpha]^{20}_D$ −7.7 (*c* 0.93, $CHCl_3$); IR (thin film) 3419, 3085, 2993, 2924, 2887, 1661, 1629, 1584, 1531, 1479, 1448, 1350, 1267, 1175, 1121, 1087, 1041, 857, 837, 745, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 3 H), 1.55 (s, 3 H), 2.92 (m, 2 H), 3.38 (ddd, J = 10.0, 10.0, 5.4 Hz, 1 H), 3.64 (dd, $J^1 = J^2$ = 9.3 Hz, 1 H), 3.79−3.84 (m, 1 H), 3.84 (dd, $J^1 = J^2$ = 10.5 Hz, 1 H), 3.97 (dd, J = 10.8, 5.4 Hz, 1 H), 4.11 (dd, $J^1 = J^2$ = 9.4 Hz, 1 H), 4.23 (dd, J = 6.0, 3.7 Hz, 1 H), 4.90 (d, J = 8.3 Hz, 1 H), 6.68 (dd, J = 13.1, 6.5 Hz, 1 H), 7.15 (ddd, J = 9.0, 9.0, 1.7 Hz, 1 H), 7.23 (d, J = 9.1 Hz, 1 H), 7.36 (s, 1 H), 7.38−7.42 (m, 5 H), 7.50 (t, J = 7.5 Hz, 1 H), 7.74 (d, J = 6.7 Hz, 2 H), 7.78 (d, J = 7.3 Hz, 2 H), 8.32 (ddd, J = 4.1, 4.1, 3.0 Hz, 1 H), 8.76 (dd, J = 6.5, 3.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 162.1, 161.9, 144.5, 138.1, 134.8, 133.7, 130.8, 129.2, 128.6, 128.5, 127.9, 126.6, 124.5, 123.4, 123.1, 121.7, 121.6, 119.7, 119.4, 117.9, 113.3, 100.3, 99.9, 74.4, 71.3, 68.5, 67.3, 61.9, 59.3, 25.2, 19.0; high-resolution mass spectrum (ESI) *m/z* 692.1670 [$(M + Na)^+$, calcd for $C_{32}H_{32}FN_5O_{10}SNa$ 692.1690].

Dimeric Macrocyle (−)-98. Cesium fluoride (350 mg, 9.3 mmol) was added to a stirred solution of (−)-**96** (140 mg, 0.35 mmol) in DMF (anhydrous, 46 mL), and the mixture was heated at 60 °C for 24 h. Concentration in vacuo gave a yellow residue, which was purified by flash chromatography (5% MeOH/DCM) to give 720 mg (45% yield) of (−)-**98** as a yellow solid: $[\alpha]^{20}_D$ −113 (c 0.686, $CHCl_3$); IR ($CHCl_3$) 3200, 3100−3000, 2840, 1650, 1610, 1520, 1350, 1250, 990, 850, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.82−2.88 (m, 2 H), 2.92−2.98 (m, 2 H), 3.54 (ddd, J = 10.0, 7.5, 7.5 Hz, 2 H), 3.80 (ddd, J = 9.6, 9.6, 4.8 Hz, 2 H), 3.96−4.01 (m, 4 H), 4.16 (dd, $J^1 = J^2$ = 9.3 Hz, 2 H), 4.22−4.26 (m, 2 H), 4.51 (dd, J = 10.5, 4.8 Hz, 2 H), 5.51 (d, J = 8.0 Hz, 2 H), 5.79 (s, 2 H), 7.04−7.08 (m, 4 H), 7.32 (t, J = 7.5 Hz, 6 H), 7.39−7.43 (m, 8 H), 7.45 (t, J = 7.5 Hz, 2 H), 7.53−7.56 (m, 4 H), 7.64−7.68 (m, 6 H), 7.82 (d, J = 9.3 Hz, 2 H), 8.01 (dd, J = 9.3, 3.0 Hz, 2 H), 8.34 (d, J = 6.8 Hz, 2 H), 8.48 (d, J = 3.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 161.9, 144.5, 138.2, 134.7, 133.6, 130.6, 129.2, 129.1, 128.5, 128.3, 127.4, 126.4, 124.4, 123.5, 123.0, 121.1, 119.4, 119.0, 113.4, 101.7, 99.2, 80.6, 80.4, 68.6, 68.5, 66.7, 59.6, 25.1; high-resolution mass spectrum (ESI) *m/z* 1417.3376 [$(M + Na)^+$, calcd for $C_{72}H_{62}N_6O_{20}S_2Na$ 1417.3358].

Dimeric Macrocyle (−)-99. Representative procedure: A solution of (−)-**97** (63 mg, 0.16 mmol) and K_2CO_3 (111 mg, 0.803 mmol) in DMF (anhydrous, 16 mL) was stirred 18 h at rt. The solvent was removed by vacuum distillation to furnish the crude product as a yellow residue. Flash chromatography (50% ethyl acetate/hexanes) gave 44 mg (75% yield) of (−)-**99** as a yellow solid: mp 145−150 °C; $[\alpha]^{20}_D$ −25.0 (*c* 0.660, $CHCl_3$); IR (thin film) 3396, 3199, 3068, 2994, 2940, 2888, 2812, 2704, 1662, 1533, 1481, 1447, 1350, 1296, 1175, 1122, 1087, 986, 842, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.57 (s, 6 H), 1.61 (s, 6 H), 2.84 (ddd, J = 16.1, 5.4, 5.4 Hz, 2 H), 2.95−3.01 (m, 2 H), 3.46 (ddd, J = 10.0, 10.0, 7.5 Hz, 2 H), 3.63 (ddd, J = 9.7, 9.7, 5.3 Hz, 2 H), 3.94−3.99 (m, 4 H), 4.05−4.09 (m, 4 H), 4.16−4.21 (m, 2 H), 5.43 (dd, $J^1 = J^2$ = 9.7 Hz, 2 H), 5.46 (d, J = 7.9 Hz, 2 H), 7.13−7.21 (m, 4 H), 7.36−7.39 (m, 8 H), 7.48 (t, J = 7.5 Hz, 2 H), 7.76 (m, 4 H), 7.88 (d, J = 9.3 Hz, 2 H), 8.19 (dd, J = 9.3, 3.0 Hz, 2 H), 8.39 (d, J = 6.8 Hz, 2 H), 8.45 (d, J = 3.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 162.4, 142.9, 138.3, 134.8, 133.7, 130.8, 130.7, 129.2, 128.8, 128.6, 127.3, 126.5, 124.7, 123.3, 123.3, 121.3, 120.5, 119.4, 119.1, 113.5, 100.3, 99.1, 81.4, 73.8, 68.5, 67.6, 62.0, 59.7, 29.0, 25.0, 18.9; high-resolution mass spectrum (ESI) *m/z* 1321.3358 [$(M + Na)^+$, calcd for $C_{64}H_{62}N_6O_{20}S_2Na$ 1321.3260].

Bis(phthalimide-protected) Aniline (+)-100. To a solution of (−)-**99** (175 mg, 0.261 mmol) in glacial acetic acid (35 mL) was added 10% Pd on activated carbon (175 mg). The resulting black suspension was purged with argon and then stirred under hydrogen (1 atm) at rt for 4 h. The resulting aniline (126 mg, 0.203 mmol) was dissolved in toluene (freshly distilled, 10 mL), and phthalic anhydride (60 mg, 0.41 mmol) was added. The flask was fitted with a Dean−Stark trap and condenser, and the mixture was heated at reflux, with azeotropic removal of water, for 8.5 h. Concentration in vacuo gave the crude product as yellow residue. Purification by preparatory TLC (500 μm, 5% MeOH/DCM) gave 120 mg (69% yield, two steps) of (+)-**100** as a yellow solid: mp 225−228 °C; $[\alpha]^{20}_D$ +55.6 (*c* 1.16, $CHCl_3$); IR (thin film) 3399, 3062, 2992, 2926, 2886, 1721, 1662, 1540, 1492, 1447, 1420, 1377, 1285, 1267, 1227, 1202, 1174, 1099, 1020, 988, 855, 744, 718, 686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 6 H), 1.56 (s, 6 H), 2.97 (t, J = 7.0 Hz, 4 H), 3.41 (ddd, J = 10.0, 10.0, 7.5 Hz, 2 H), 3.62 (ddd, J = 9.8, 9.8, 5.3 Hz, 2 H), 3.90−3.95 (m, 4 H), 3.99−4.06 (m, 4 H), 4.15 (ddd, J = 9.7, 9.7, 7.5 Hz, 2 H), 5.47 (dd, $J_1 = J_2$ = 9.7 Hz, 2 H), 5.53 (d, J = 7.9 Hz, 2 H), 7.20 (t, J = 7.2 Hz, 2 H), 7.27 (t, J = 7.2 Hz, 2 H), 7.38 (t, J = 7.8 Hz, 4 H), 7.45−7.48 (m, 4 H), 7.50 (d, J = 2.9 Hz, 2 H), 7.52 (d, J = 2.8 Hz, 2 H), 7.74 (dd, J = 5.5 and 3.0 Hz, 4 H), 7.83 (d, J = 8.5 Hz, 4 H), 7.86 (s, 2 H), 7.87−7.90 (m, 4 H), 7.94 (d, J = 8.3 Hz, 2 H), 8.06 (d, J = 2.8 Hz, 2 H), 8.69 (d, J = 6.9 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 164.1, 157.6, 134.3, 133.7, 131.8, 131.5, 131.0, 129.4, 129.2, 128.4, 126.7, 126.6, 124.7, 123.7, 123.6, 123.1, 121.6, 120.2, 119.5, 119.4, 113.7, 99.9, 80.6, 74.2, 69.3, 67.3, 62.2, 60.0, 29.1, 25.5, 19.1; high-resolution mass spectrum (ESI) *m/z* 1521.4140 [$(M + Na)^+$, calcd for $C_{80}H_{70}N_6O_{20}S_2Na$ 1521.3984].

Mono(phthalimide-protected) Aniline (+)-101. To a stirred solution of (+)-**100** (12 mg, 0.0080 mmol) in THF (1 mL) was added 5% HCl (aq, 122 μL). The mixture was stirred 4.5 h at rt and then concentrated. Water was removed by azeotropic distillation with benzene (2 × 3 mL). The crude residue was purified by preparative TLC (500 μm, 5% MeOH/DCM) to give 3 mg (25% yield) of (+)-**101** as a yellow solid: $[\alpha]^{20}_D$ +39.2 (*c* 0.355, $CHCl_3$); IR (thin film) 3398, 3122, 3058, 2923, 2853, 1720, 1653, 1539, 1491, 1447, 1378, 1281, 1230, 1174, 1098, 719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.55 (s, 6 H), 2.36 (dd, $J^1 = J^2$ = 6.5 Hz, 1 H), 2.85 (ddd, J = 16.6, 5.6, 5.6 Hz, 1 H), 2.95 (ddd, J = 13.5, 13.5, 6.9 Hz, 3 H), 3.29−3.31 (m, 2 H), 3.60 (ddd, J = 9.9, 9.9, 5.3 Hz, 1 H), 3.71−3.73 (m, 1 H), 3.90−4.09 (m, 8 H), 4.12−4.23 (m, 3 H), 5.35 (dd, $J^1 = J^2$ = 9.7 Hz, 1 H), 5.47 (dd, $J^1 = J^2$ = 8.1 Hz, 2 H), 5.52 (d, J = 8.1 Hz, 1 H), 7.06 (t, J = 4.7 Hz, 2 H), 7.20 (t, J = 7.5 Hz, 1 H), 7.26 (t, J = 7.8 Hz, 1 H), 7.30−7.35 (m, 5 H), 7.39 (d, J = 7.5 Hz, 1 H), 7.42 (d, J = 6.1 Hz, 1 H), 7.44−7.51 (m, 5 H), 7.54 (s, 1 H), 7.65−7.69 (m, 3 H), 7.73 (d, J = 3.1 Hz, 1 H), 7.74 (d, J = 2.9 Hz, 2 H), 7.75 (d, J = 3.0 Hz, 1 H), 7.79 (d, J = 9.0 Hz, 1 H), 7.84−7.89 (m, 7 H), 7.94 (d, J = 8.3 Hz, 1 H), 7.96 (d, J = 2.8 Hz, 1 H), 8.54 (d, J = 6.8 Hz, 1 H), 8.72 (d, J = 6.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 166.7, 163.9, 157.8, 157.6, 138.4, 137.6, 135.1, 134.9, 134.2, 134.2, 133.8, 133.7, 131.8, 131.8, 131.4, 131.1, 131.1, 130.6, 129.3, 129.2, 129.2, 128.8, 128.3, 126.7, 126.6, 126.6, 124.9, 124.7, 124.6, 123.7, 123.7, 123.6, 123.6, 123.4, 123.3, 123.1, 121.9, 120.6, 120.5, 120.4, 119.6, 119.6, 119.4, 119.3, 119.2, 113.6, 113.3, 99.9, 99.6, 99.3, 83.4, 80.9, 75.4, 74.0, 71.5, 68.9, 68.2, 67.3, 62.8, 59.8, 59.3, 29.7, 29.0, 25.5, 25.4, 19.0; high-resolution mass spectrum (ESI) *m/z* 1481.3688 [$(M + Na)^+$, calcd for $C_{77}H_{66}N_6O_{20}S_2Na$ 1481.3671].

2-(Indol-3-yl)ethyl-2-deoxy-4,6-*O*-isopropylidene-*β*-D-glucosamine (−)-102. To a solution of (−)-**95** (21 mg, 0.042 mmol) in absolute ethanol (4 mL) was added 5 M NaOH (aq, 0.71 mL, 3.6 mmol) via syringe. The resulting solution was heated at reflux for 1 h. The mixture was concentrated in

vacuo, and the residue was azeotropically dehydrated with benzene (2 × 25 mL). Purification by preparative TLC (500 μm, 5% MeOH/DCM) afforded 14 mg (90% yield) of (−)-**102** as a white solid: $[\alpha]^{20}_D$ −36.3 (*c* 3.6, $CHCl_3$); IR (thin film) 3364, 3057, 2993, 2884, 2247, 1587, 1457, 1428, 1382, 1267, 1201, 1175, 1093, 1052, 1010, 910, 851, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 3 H), 1.51 (s, 3 H), 1.69 (br s, 2 H), 2.75 (dd, *J* = 9.4, 8.0 Hz, 1 H), 3.04−3.13 (m, 3 H), 3.24 (ddd, *J* = 9.9, 9.9, 5.4 Hz, 1 H), 3.42 (dd, $J^1 = J^2 = 9.2$ Hz, 1 H), 3.58 (dd, $J^1 = J^2 = 9.1$ Hz, 1 H), 3.76−3.83 (m, 2 H), 3.90 (dd, *J* = 10.8, 5.4 Hz, 1 H), 4.18−4.22 (m, 1 H), 4.24 (d, *J* = 8.0 Hz, 1 H), 7.05 (s, 1 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* = 8.1 Hz, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 8.10 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 127.5, 122.2, 122.0, 119.3, 118.7, 112.5, 111.3, 104.2, 99.8, 73.9, 73.1, 70.2, 67.4, 62.1, 58.0, 29.0, 25.6, 19.1; high-resolution mass spectrum (ESI) *m/z* 385.1729 [(M + Na)$^+$, calcd for $C_{19}H_{26}N_2O_5Na$ 385.1740].

2-(Indol-3-yl)ethyl-2-deoxy-4,6-*O*-isopropylidene-*N*-(2-fluoro-5-nitrobenzamido)-β-D-glucosamine (−)-103. Acid **16** (8.0 mg, 0.041 mmol) was suspended in DCM (dry, 0.5 mL) and cooled to −78 °C. DIPEA (14 μL, 0.082 mmol) was added via syringe, followed by the sequential addition of HATU (16 mg, 0.041 mmol) and HOAt (7.0 mg, 0.049 mmol). The mixture was stirred 10 min at rt, and amino sugar (−)-**102** (15 mg, 0.041 mmol) was added in portions. The reaction mixture was allowed to warm to rt gradually over 20 h. The resultant yellow solution was concentrated in vacuo, and the crude residue was purified by prep TLC (500 μm, 5% MeOH/DCM) to afford 16 mg (73% yield) of the N-coupled product (−)-**103** as a yellow solid: $[\alpha]^{20}_D$ −21.9 (*c* 0.54, $CHCl_3$); IR (thin film) 3406, 3082, 2996, 2942, 2887, 1661, 1628, 1532, 1479, 1457, 1422, 1350, 1265, 1201, 1175, 1117, 1086, 1039, 924, 837, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 3 H), 1.54 (s, 3 H), 3.01 (dd, $J^1 = J^2 = 6.6$ Hz, 2 H), 3.36 (ddd, *J* = 9.9, 9.9, 5.4 Hz, 1 H), 3.55 (br s, 1 H), 3.65 (dd, $J^1 = J^2 = 9.3$ Hz, 1 H), 3.75−3.86 (m, 3 H), 3.96 (dd, *J* = 10.8, 5.4 Hz, 1 H), 4.04 (br dd, $J^1 = J^2 = 9.4$ Hz, 1 H), 4.21 (ddd, *J* = 9.7, 9.7, 6.5 Hz, 1 H), 4.80 (d, *J* = 8.3 Hz, 1 H), 6.66 (dd, *J* = 11.7, 6.7 Hz, 1 H), 6.99 (s, 1 H), 7.01 (d, *J* = 5.7 Hz, 1 H), 7.04 (d, *J* = 6.7 Hz, 1 H), 7.08−7.13 (m, 2 H), 7.48 (d, *J* = 8.2 Hz, 1 H), 7.95 (br s, 1 H), 8.24 (ddd, *J* = 8.9, 3.6, 3.6 Hz, 1 H), 8.72 (dd, *J* = 6.4, 2.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 162.0 (d, $J^{C-F} = 9.9$ Hz), 144.4, 135.9, 128.2 (d, $J^{C-F} = 11.3$ Hz), 127.8 (d, $J^{C-F} = 3.6$ Hz), 127.4, 122.1, 121.8, 119.1, 118.5, 117.4, 117.2, 112.4, 110.8, 100.7, 99.9, 74.3, 71.5, 70.0, 67.2, 61.9, 59.2, 29.0, 25.4, 19.0; high-resolution mass spectrum (ESI) *m/z* 552.1763 [(M + Na)$^+$, calcd for $C_{26}H_{28}FN_3O_8Na$ 552.1758].

Macrocycle (−)-104. To a solution of amide (−)-**103** (13 mg, 0.025 mmol) in DMF (dry, 2.5 mL) was added K_2CO_3 (anhydrous, 17 mg, 0.125 mmol). The resulting suspension was stirred 23 h at rt, and the mixture was concentrated in vacuo to give the crude product as an orange solid. Purification by prep TLC (500 μm, 5% MeOH/DCM) furnished 11 mg (88% yield) of (−)-**104** as a bright yellow solid: $[\alpha]^{20}_D$ −107 (*c* 0.55, $CHCl_3$); IR (thin film) 3349, 3281, 3078, 2923, 2852, 1724, 1650, 1605, 1582, 1523, 1489, 1453, 1375, 1343, 1264, 1201, 1174, 1126, 1094, 1006, 939, 855, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 1.47 (s, 3 H), 2.65 (br s, 1 H), 2.96 (ddd, *J* = 9.8, 9.8, 5.5 Hz, 1 H), 3.04−3.07 (m, 2 H), 3.19 (dd, $J^1 = J^2 = 9.4$ Hz, 1 H), 3.37 (ddd, *J* = 10.3, 10.3, 5.3 Hz, 1 H), 3.52 (dd, $J^1 = J^2 = 9.5$ Hz, 2 H), 3.74 (dd, $J^1 = J^2 = 10.6$ Hz, 1 H), 3.84 (dd, *J* = 10.8, 5.5 Hz, 1 H), 4.02−4.10 (m, 1 H), 4.29−4.35 (m, 1 H), 4.60 (d, *J* = 8.7 Hz, 1 H), 7.11 (s, 1 H), 7.31 (quint, *J* = 7.4 Hz, 2 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.65 (d, *J* = 7.5 Hz, 1 H), 8.51 (dd, *J* = 8.7, 2.5 Hz, 1 H), 8.79 (d, *J* = 2.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 146.3, 141.2, 135.8, 133.7, 130.1, 128.0, 127.8, 126.9, 126.4, 123.7, 121.9, 119.2, 114.7, 110.0, 104.2, 99.8, 73.8, 73.4, 70.4, 66.5, 61.8, 56.6, 28.9, 25.7, 19.0; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 532.1690 [(M + Na)$^+$, calcd for $C_{26}H_{27}N_3O_8Na$ 532.1696].

2-(Benzofuran-3-yl)ethyl 2-Deoxy-*N*-trifluoroacetamido-β-D-glucosamine (−)-106. A suspension of 2-(2-benzofuranyl)-ethanol (3.50 g, 21.6 mmol), Ag_2CO_3 (3.57 g, 12.9 mmol), and powdered, freshly activated 3 Å MS (1.9 g) in DCM (dry, 25 mL) was cooled to 0 °C. To this stirred solution was added, via cannula, a solution of glycosyl bromide (+)-**105** (3.360 g, 6.163 mmol) in DCM (dry, 25 mL). The resulting suspension was warmed to rt, and stirring was maintained for 20 h. The reaction mixture was filtered through Celite, and the filter cake was washed with DCM (4 × 50 mL). The combined filtrates were condensed under reduced pressure to give the crude product as a viscous orange oil. Purification by flash chromatography eluting first with 25% ethyl acetate in hexanes, then 25% ethyl acetate in hexanes, afforded 3.360 g (57% yield) of the glycosidation product as a white solid: mp 145−147 °C; $[\alpha]^{20}_D$ −15.2 (*c* 0.690, $CHCl_3$); IR (thin film) 3314, 3113, 2958, 2894, 1752, 1560, 1454, 1368, 1226, 1168, 1077, 1041, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.02 (s, 3 H), 2.03 (s, 3 H), 2.96 (dd, $J^1 = J^2 = 6.4$ Hz, 2 H), 3.70 (ddd, *J* = 9.9, 4.8, 2.5 Hz, 1 H), 3.78 (dd, *J* = 9.8, 7.0 Hz, 1 H), 3.96 (ddd, *J* = 19.3, 19.3, 18.6 Hz, 1 H), 4.15 (dd, *J* = 12.4, 2.3 Hz, 1 H), 4.17−4.20 (m, 1 H), 4.27 (dd, *J* = 12.3, 4.8 Hz, 1 H), 4.67 (d, *J* = 8.2 Hz, 1 H), 5.10 (dd, $J^1 = J^2$= 9.5 Hz, 1 H), 5.24 (dd, $J^1 = J^2 = 9.3$ Hz, 1 H), 6.25 (d, *J* = 8.8 Hz, 1 H), 7.23 (t, *J* = 7.4 Hz, 1 H), 7.29 (t, *J* = 7.6 Hz, 1 H), 7.45 (s, 1 H), 7.46 (d, *J* = 7.3 Hz, 1 H), 7.52 (d, *J* = 7.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 163.2, 161.3, 157.3, 143.3, 133.6, 130.6, 129.9, 128.5, 121.2, 102.3, 84.4, 74.4, 68.4, 63.1, 57.5, 57.4, 31.9, 24.2, 22.7, 20.8; high-resolution mass spectrum (ESI) *m/z* 568.1428 [(M + Na)$^+$, calcd for $C_{24}H_{26}F_3NO_{10}Na$ 568.1408].

The glycosidation product (116 mg, 0.213 mmol) was dissolved in methanol (HPLC, 1 mL), and sodium methoxide solution (30 wt. % in methanol) was added dropwise via syringe. The reaction was quenched after 2 h by the addition of solid NH_4Cl (40 mg, 0.75 mmol). The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between water (5 mL) and EtOAc (5 mL) in a separatory funnel. The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated to afford the crude product as an oily residue. Flash chromatography, eluting with hexanes:ethyl acetate (1:1) gave 30.0 mg (37%) of triol (−)-**106** as a white solid: mp 183−185 °C dec; $[\alpha]^{20}_D$ −17.6 (*c* 0.625, MeOH); IR (thin film) 3389, 3279, 3119, 2928, 2888, 1700, 1569, 1453, 1212, 1186, 1076, 1032, 744 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.85 (dd, $J^1 = J^2 = 6.5$ Hz, 2 H), 3.10−3.16 (m, 2 H), 3,42−3.43 (br m, 1 H), 3.48−3.57 (m, 2 H), 3.70 (ddd, *J* = 9.9, 9.9, 6.6 Hz, 2 H), 4.02 (ddd, *J* = 9.9, 9.9, 6.6 Hz, 1 H), 4.49 (d, *J* = 8.4 Hz, 1 H), 4.55 (br s, 1 H), 5.09 (br s, 1 H), 5.18 (br s, 1 H), 7.22 (t, *J* = 7.4 Hz, 1 H), 7.28 (t, *J* = 7.0 Hz, 1 H), 7.51 (d, *J* = 7.4 Hz, 1 H), 7.61 (d, *J* = 7.3 Hz, 1 H), 7.67 (s, 1 H), 9.18 (d, *J* = 9.1 Hz, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.7 (q, $J^{C-F} = 35.7$ Hz), 154.9, 142.8, 128.2, 124.6, 122.8, 120.1, 117.6, 117.3, 111.6, 100.5, 77.6, 73.8, 70.9, 67.9, 61.3, 56.5, 23.8; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 442.1084 [(M + Na)$^+$, calcd for $C_{18}H_{20}F_3NO_7Na$ 442.1090].

2-(Benzofuran-3-yl)ethyl 2-Deoxy-4,6,-*O*-isopropylidene-β-D-glucosamine (−)-107. To a solution of (−)-**106** (881 mg, 2.10 mmol) in DMF (anhydrous, 20 mL) were added *p*TSA (40 mg, 0.21 mmol) and 2,2-dimethoxypropane (1.3 mL, 10.5 mmol). The mixture was stirred 2 h at rt and then partitioned between cold water (100 mL) and EtOAc (100 mL). The layers were separated, and the organic phase was extracted with cold water (100 mL) and saturated $NaHCO_3$ (50 mL), dried over Na_2SO_4, and concentrated to give the crude product as a viscous, yellow oil. Flash chromatography, eluting with hexanes/ethyl acetate (2:1), gave 854 mg (89%) of the acetonide-protected compound as a white solid: mp 195−197 °C dec; $[\alpha]^{20}_D$ −32.8 (*c* 0.80, $CHCl_3$); IR (thin film) 3413, 3324, 3117, 2995, 2925, 2887, 1705, 1560, 1453, 1369, 1265, 1216, 1184, 1095, 1037, 850, 745 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ

1.32 (s, 3 H), 1.49 (s, 3 H), 2.94 (ddd, J = 6.7, 6.7, 1.1 Hz, 2 H), 3.25 (ddd, J = 9.8, 9.8, 5.5 Hz, 1 H), 3.60 (dd, $J^1 = J^2$ = 9.2 Hz, 2 H), 3.75−3.90 (m, 5 H), 4.09 (ddd, J = 9.7, 6.7, 6.7 Hz, 1 H), 4.76 (d, J = 8.3 Hz, 1 H), 7.23 (t, J = 7.4 Hz, 1 H), 7.29 (t, J = 7.7 Hz, 1 H), 7.46 (d, J = 8.2 Hz, 1 H), 7.60−7.62 (m, 2 H), 8.46 (br d, J = 8.5 Hz,m 1 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.9 (q, J = 36.4 Hz), 156.0, 143.2, 129.0, 124.9, 123.1, 120.4, 117.9, 111.8, 101.9, 100.0, 75.1, 71.9, 71.8, 69.0, 68.3, 62.5, 58.0, 29.3, 24.6, 19.3; high-resolution mass spectrum (ESI) m/z 482.1414 [(M + Na)$^+$, calcd for $C_{21}H_{24}F_3NO_7Na$ 482.1398].

To a solution of TFA-protected amino sugar (821 mg, 1.79 mmol) in methanol (HPLC, 45 mL) were added distilled H_2O (4 mL) and K_2CO_3 (742 mg, 5.37 mmol). The mixture was stirred 24 h at rt and then concentrated to minimum volume on the rotary evaporator. The aqueous residue was transferred to a separatory funnel and extracted with DCM (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, and concentrated to give the crude product as a white foam. Purification by chromatography gave 599 mg (92% yield) of amino sugar (−)-**107** as a white solid: mp 130−132 °C; $[\alpha]^{20}_D$ −35.5 (c 0.65, $CHCl_3$); IR (thin film) 3476, 3375, 3309, 3114, 3061, 2992, 2940, 2882, 1576, 1453, 1381, 1266, 1201, 1176, 1092, 1067, 1053, 1014, 856, 747 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 3 H), 1.50 (s, 3 H), 2.09 (br s, 2 H), 2.76 (dd, J = 9.4, 8.0 Hz, 1 H), 2.97−3.05 (m, 2 H), 3.25 (ddd, J = 9.9, 9.9, 5.3 Hz, 1 H), 3.43 (dd, $J^1 = J^2$ = 9.2 Hz, 1 H), 3.57 (dd, $J^1 = J^2$ = 9.2 Hz, 1 H), 3.76−3.82 (m, 2 H), 3.90 (dd, J = 10.8, 5.4 Hz, 1 H), 4.20 (ddd, J = 9.5, 9.5, 6.5 Hz, 1 H), 4.26 (d, J = 7.9 Hz, 1 H), 7.24 (t, J = 7.4 Hz, 1 H), 7.29 (t, J = 7.6 Hz, 1 H), 7.46 (d, J = 8.2 Hz, 1 H), 7.50 (s, 1 H), 7.56 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 24.2, 29.0, 57.8, 62.1, 67.4, 69.2, 73.6, 73.9, 99.7, 104.7, 111.5, 117.0, 119.5, 122.3, 124.2, 128.3, 141.9, 155.2; high-resolution mass spectrum (ESI) m/z 364.1745 [(MH)$^+$, calcd for $C_{19}H_{25}NO_6$ 364.1758].

2-(Benzofuran-3-yl)ethyl 2-Deoxy-4,6,-*O*-isopropylidene-*N*-(2-fluoro-5-nitrobenzamido)-β-D-glucosamine (−)-108. To a solution of amino sugar (−)-**107** (13 mg, 0.036 mmol) in THF (dry, 2 mL) was added carboxylic acid **16** (6.0 mg, 0.030 mmol), and the resulting mixture was stirred for 10 min at rt. DMTMM (10 mg, 0.036 mmol) was added, and the resulting white suspension was stirred at rt for 1 h. The reaction mixture was concentrated, and the residue was taken up in EtOAc (0.5 mL) and purified by preparatory TLC (500 μm, 5% MeOH in DCM) to give 15 mg of amide (−)-**108** (78%) as a white solid: mp 232 °C dec; $[\alpha]^{20}_D$ −22.8 (c 0.75, $CHCl_3$); IR (thin film) 3398, 3314, 3117, 3084, 2993, 2925, 2885, 1654, 1628, 1584, 1531, 1477, 1453, 1349, 1265, 1200, 1175, 1120, 1087, 1040, 923, 857, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 3 H), 1.54 (s, 3 H), 2.94 (dd, $J^1 = J^2$ = 6.5 Hz, 2 H), 3.33 (d, J = 2.7 Hz, 1 H), 3.37 (ddd, J = 10.0, 10.0, 5.3 Hz, 1 H), 3.63 (dd, $J^1 = J^2$ = 9.3 Hz, 1 H), 3.67−3.73 (m, 1 H), 3.79−3.85 (m, 2 H), 3.96 (dd, J = 10.8, 5.4 Hz, 1 H), 4.09 (ddd, J = 9.8, 9.8, 2.8 Hz, 1 H), 4.24 (ddd, J = 9.7, 9.7, 6.0 Hz, 1 H), 4.86 (d, J = 8.3 Hz, 1 H), 6.62 (q, J = 6.3 Hz, 1 H), 7.12−7.15 (m, 1 H), 7.17−7.21 (m, 2 H), 7.39 (s, 1 H), 7.46−7.48 (m, 1 H), 88.31−8.34 (m, 1 H), 8.80 (dd, J = 6.5, 3.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 161.8, 142.0, 128.5 (d, J^{C-F} = 11.4 Hz), 128.19, 128.16, 128.0, 124.1, 122.3, 119.4, 117.6, 117.4, 116.9, 111.1, 100.5, 99.9, 74.4, 71.4, 68.9, 67.3, 62.0, 59.3, 44.0, 29.0, 24.0, 19.1; high-resolution mass spectrum (ESI) m/z 553.1574 [(M + Na)$^+$, calcd for $C_{26}H_{27}FN_2O_9Na$ 553.1598].

Dimeric Macrocycle (+)-109. Cyclization precursor (−)-**108** (15 mg, 0.028 mmol) was dissolved in DMF (anhydrous, 5 mL). Potassium carbonate (anhydrous, 19 mg, 0.14 mmol) was added, and the resulting yellow solution was stirred for 8.5 h at rt. The reaction mixture was concentrated in vacuo to give the crude product as a yellow, waxy residue. Purification by preparatory TLC, eluting with hexanes−ethyl acetate (1:1), gave 6.0 mg of (+)-**109** (43% yield) as a yellow solid: $[\alpha]^{20}_D$ +81.2 (c 0.085, $CHCl_3$); IR (thin film) 3411, 3117, 3076, 1665, 1615, 1581, 1544, 1521, 1480, 1453, 1346, 1289, 1228, 1201, 1172, 1097, 1029, 940, 856, 748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (s, 6 H), 1.62 (s, 6 H), 2.94 (dd, $J^1 = J^2$ = 6.2 Hz, 4 H), 3.29−3.34 (m, 2 H), 3.62 (ddd, J = 9.8, 9.8, 5.4 Hz, 2 H), 3.90−3.95 (m, 4 H), 3.99 (dd, $J^1 = J^2$ = 9.4 Hz, 2 H), 4.08 (dd, J = 11.0, 5.3 Hz, 2 H), 4.23 (ddd, J = 10.0, 6.3, 6.3 Hz, 2 H), 5.37 (d, J = 8.0 Hz, 2 H), 5.43 (dd, $J^1 = J^2$ = 9.8 Hz, 2 H), 7.07−7.11 (m, 4 H), 7.21−7.22 (m, 2 H), 7.39 (s, 2 H), 7.43 (dd, J = 5.5, 2.2 Hz, 2 H), 7.78 (d, J = 9.3 Hz, 2 H), 8.20 (dd, J = 9.3, 2.9 Hz, 2 H), 8.23 (d, J = 7.1 Hz, 2 H), 8.56 (d, J = 2.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 162.2, 155.1, 143.0, 141.9, 128.7, 127.8, 127.6, 124.1, 122.3, 121.3, 120.0, 119.2, 116.6, 111.3, 100.2, 99.6, 81.0, 73.9, 69.2, 67.4, 62.1, 59.9, 29.1, 24.2, 19.1; high-resolution mass spectrum (ESI) m/z 1043.3139 [(M + Na)$^+$, calcd for $C_{52}H_{52}N_4O_{18}Na$ 1043.3174].

***N*-Methyl Tricyclic Hybrid (+)-111.** To a solution of the cyclization precursor (−)-**110** (8.0 mg 0.012 mmol) in DMF (anhydrous, 5 mL, c = 0.0025 M) was added CsF (3.0 mg, 0.018 mmol). The resultant mixture was heated at 85 °C for 19 h, and the solvent was removed by vacuum distillation to give a yellow residue. Preparative TLC (500 μm, 5% MeOH/DCM) gave 3 mg (38% yield) of (+)-**111** as a yellow solid: $[\alpha]^{20}_D$ +22.0 (c 0.15, $CHCl_3$); IR (thin film) 2924, 2854, 1650, 1615, 1525, 1472, 1455, 1344, 1267, 1175, 1089, 881, 855, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 3 H), 1.54 (s, 3 H), 2.97 (dd, $J^1 = J^2$ = 6.8 Hz, 1 H), 3.00 (s, 3 H), 3.29 (ddd, J = 9.7, 9.7, 5.4 Hz, 1 H), 3.58−3.63 (m, 1 H), 3.75 (dd, $J^1 = J^2$ = 10.6 Hz, 2 H), 3.82 (ddd, J = 9.1, 6.8, 6.8 Hz, 1 H), 3.94 (dd, J = 10.9, 5.3 Hz, 1 H), 4.16 (ddd, J = 9.2, 6.8, 6.8 Hz, 1 H), 4.31 (dd, $J^1 = J^2$ = 6.7 Hz, 1 H), 4.54 (dd, J = 11.1, 9.3 Hz, 1 H), 4.81 (d, J = 7.8 Hz, 1 H), 7.10 (d, J = 8.8 Hz, 1 H), 7.22 (t, J = 7.1 Hz, 1 H), 7.34 (ddd, J = 8.4, 8.4, 1.2 Hz, 1 H), 7.39 (s, 1 H), 7.43 (t, J = 8.2 Hz, 2 H), 7.51−7.54 (m, 2 H), 7.85−7.87 (m, 2 H), 7.97 (d, J = 8.4 Hz, 1 H), 8.31 (dd, J = 8.8, 2.8 Hz, 1 H), 8.62 (d, J = 2.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 162.1, 161.9, 144.4, 138.0, 134.7, 133.7, 130.8, 129.1, 128.4, 128.3, 127.7, 126.5, 124.5, 123.3, 123.0, 122.0, 121.8, 119.7, 119.4, 117.8, 117.6, 113.3, 100.4, 99.8, 74.4, 68.4, 67.2, 61.9, 59.0, 28.9, 25.1, 19.0; high-resolution mass spectrum (ESI) m/z 686.1804 [(M + Na)$^+$, calcd for $C_{33}H_{33}N_2O_{10}Na$ 686.2724].

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Supporting Information Available: Experimental procedures and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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