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Synthesis of Isofagomine–Pyrrolidine Hybrid Sugars and Analogues of (−)-Steviamine and (+)-Hyacinthacine C_5 Using 1,3-Dipolar Cycloaddition Reactions

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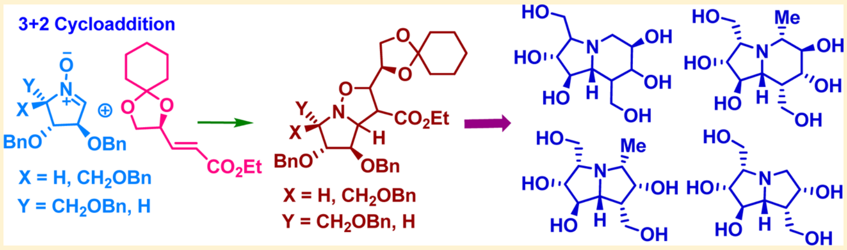
S Supporting Information



ABSTRACT: Highly regioselective 1,3-dipolar cycloadditions between D-arabinose-derived nitrones and D-mannitol-derived *trans*-olefins have been utilized to synthesize isofagomine–pyrrolidine hybrid sugars, hydroxymethylated analogues of (−)-steviamine and analogues of (+)-hyacinthacine C_5. All of the new compounds were subsequently tested against several commercially available glycosidases, and some of them showed good and selective glycosidase inhibition.

INTRODUCTION

Among the biomolecules, carbohydrates[1] have been identified as a ubiquitous and diverse class of molecules that are essential for all living forms to perform the key roles in cell recognition, reproduction, communication events, bacterial adhesion, protein folding, etc. The synthesis and degradation of these glycans are catalyzed by glycosyl transferases[2] and glycosidases,[3] respectively, which are thus responsible for maintaining a balanced level of glycoconjugates required in cellular processes. Over the past several years, the growing importance of polyhydroxylated sugar mimics, mainly imino- and azasugars, has been attributed to their ability to inhibit glycosidases and glycosyl transferases, which makes them potential therapeutics against diabetes,[4a−e] cancer,[4f−j] viral infections such as HIV,[4k−m] and lysosomal storage disorders.[4n,o] In addition to the naturally occurring compounds, several analogues have been designed and synthesized so as to improve the selectivity, specificity, and potency of the parent molecules.[5] In view of this, we and others[6] have reported syntheses of hybrid sugar mimics (Figure 1), as hybrid molecules are known to bear two or more molecular domains and their combination results in different or improved physical, chemical, or biological properties.[7] Also, these molecules may display dual modes of action, as different moieties may not act on the same target.

Isofagomine **7** (Figure 2), a synthetic azasugar, was observed to be a potent and selective inhibitor of β-glucosidase (K_i = 0.11 μM, sweet almonds).[8] The molecule was designed considering that it could act as an apparent transition state analogue by mimicking the oxycarbenium intermediate, where the nitrogen atom at the anomeric carbon has a positive charge. Its tartarate salt was found to be an active-site inhibitor of glucocerebrosidase by increasing its activity in N370S fibroblasts following several mechanisms.[9] Different stereoisomers and derivatives of isofagomine **8**−**10** (Figure 2) have shown significant inhibition property.[10] However, still there is a need to develop modified isofagomine molecules as promising pharmaceutical agents. On the other hand, pyrrolidines[11] **11**−**14** (Figure 2) are a class of small iminosugars and several derivatives of pyrrolidines have been isolated from nature and also synthesized as good glycosidase inhibitors. These strong enzyme inhibitors showing broad spectrum activity have emerged as sought-after scaffolds for drug design.[12]

In continuation with our ongoing research in synthesizing structurally diverse sugar mimics as glycosidase inhibitors,[14] we herein report syntheses of hybrid molecules where the designed templates bear an azasugar unit akin to isofagomine and a pyrrolidine unit (Figure 3). These targets consequently aim at studying the combined effect of both types of molecules on glycosidase inhibitory potency. In addition to the monocyclic N-heterocycles, unnatural indolizidine and pyrrolizidine analogues, reported by many groups,[5g] have also gained considerable attention in recent years owing to better inhibitory activity in comparison to their parent molecules in some cases. Modifications in position of the hydroxyl groups, ring size, stereochemistry, and introductions of different substituents in

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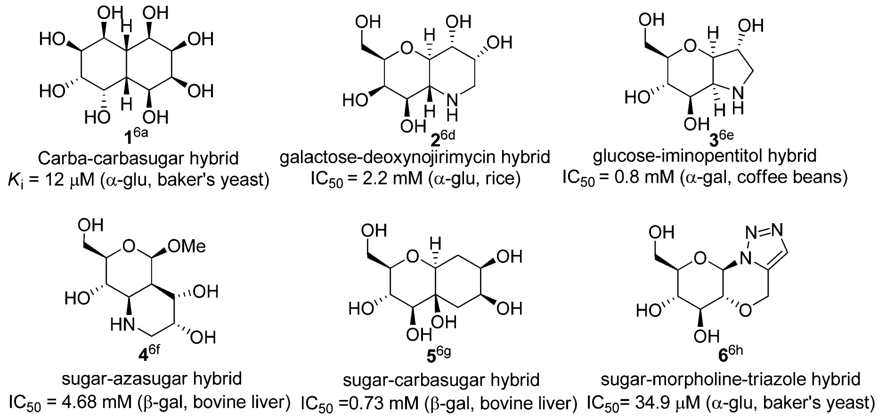


Figure 1. Hybrid molecules as glycosidase inhibitors.

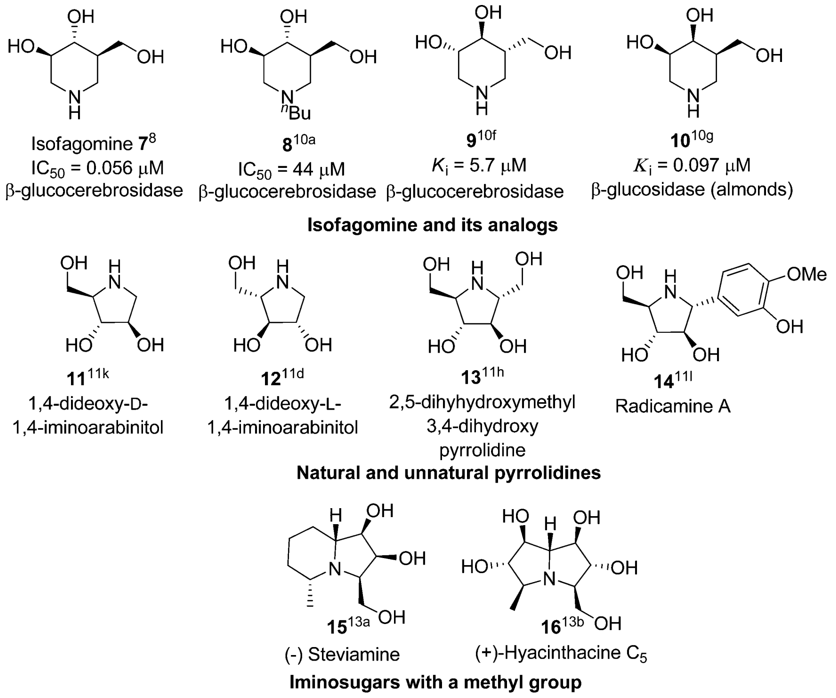


Figure 2. Examples of azasugars, pyrrolidines, and methylated iminosugars.

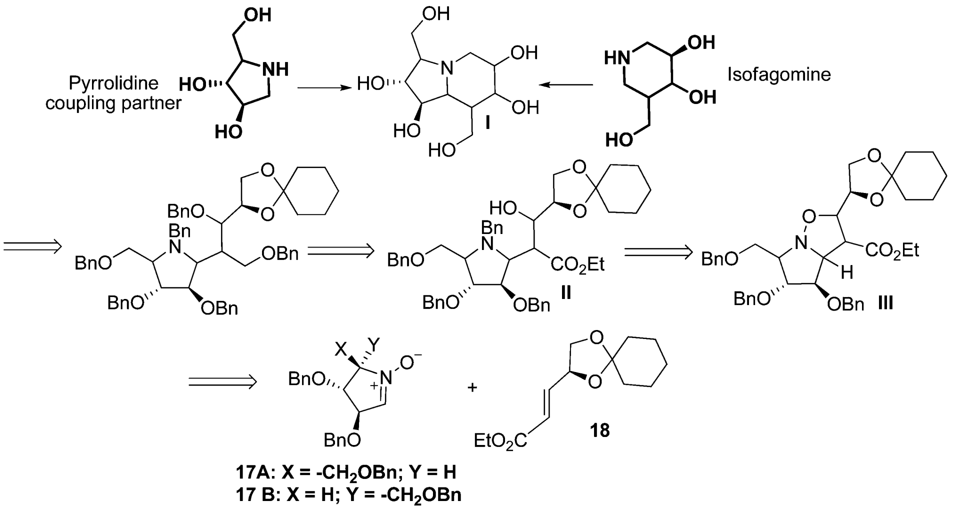


Figure 3. Retrosynthetic analysis toward the designed hybrids.

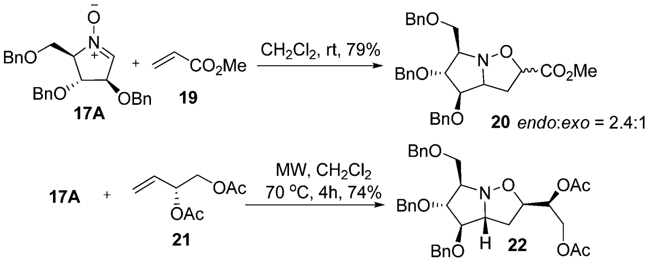
these molecules have been found to make a difference in reactivity pattern with increased selectivity for a better understanding of the structure−activity relationships. Among these derivatives, methyl- and hydroxymethyl-substituted analogues have displayed commendable glycosidase inhibition. Thus, we have used common synthetic intermediates to obtain analogues of (−)-steviamine **15** (Figure 2), a naturally occurring α-galactosaminidase inhibitor (chicken liver, IC_{50} = 814 μM), and (+)-hyacinthacine C_5 **16** (Figure 2), an α-glucosidase inhibitor (rat intestinal maltase at IC_{50} = 77 μM).[13] While the analogue of (−)-steviamine bears additional hydroxyl and hydroxymethyl groups, the analogues of (+)-hyacinthacine C_5 bear a hydroxymethyl group at C7 in place of a hydroxyl group. All of the synthetic targets have been correspondingly tested against commercially available glycosidases.

■ RESULTS AND DISCUSSION

From retrosynthetic analysis (Figure 3), it was envisaged that the target **I** could be readily derived from intermediate **II**, which can be obtained from the oxazolidine derivative **III**. This intermediate can, in turn, be obtained via 1,3-dipolar cycloaddition of nitrones **17A** and **17B**[15] with the disubstituted *trans*-olefin **18**.

In our synthetic endeavor, D-arabinose-derived chiral nitrones were reacted with the *trans*-olefin **18**, a dipolarophile that had not been reported earlier in 1,3-dipolar cycloadditions where the olefin bears an ester and a highly sterically hindered protected diol. This dipolarophile (i.e., **18**) can be considered to bear combined functionalities of the dipolarophiles **19**[15h] and **21**[15k] reported earlier (Scheme 1), where the regioselectivity followed the coefficient matching of the frontier orbitals in the cycloaddition reaction, resulting in the substituent being α to the oxygen atom on the oxazolidine cycloadduct. We anticipated that the presence of an electronegative atom at the β position of the conjugated olefin bearing a sterically hindered protecting group, such as cyclohexylidene acetal, would compel the dipolarophile **18** to follow regioselectivity opposite to that observed with simple acrylates.[15h] Thus, we expected a competition among the two substituents on the olefin following electronic and steric effects to eventually guide regioselectivity in the cycloaddition reaction.

Scheme 1. Literature-Based Cycloadditions with Nitrone 17A



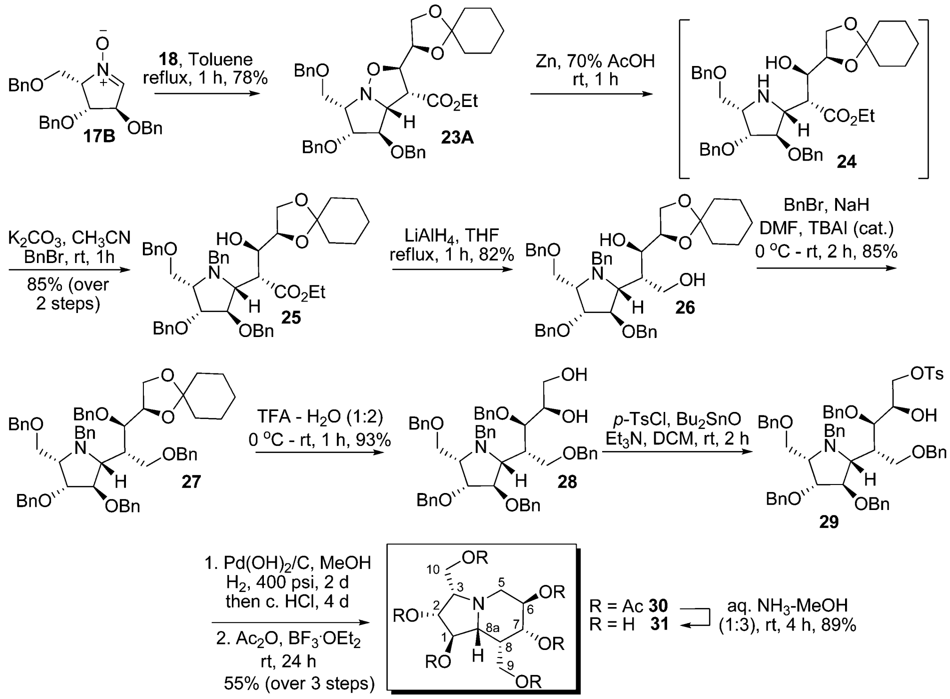
The chiral nitrones **17A,B** were synthesized from the common synthon 2,3,5-tri-*O*-benzylated D-arabinose following literature procedures.[16] Dipolarophile **18** was prepared from a D-mannitol-derived aldehyde, which was subsequently converted to the unsaturated ester by a Wittig−Horner reaction to give the (*E*)-olefin as the only product.[17] The 1,3-dipolar cycloaddition reaction (Scheme 2) was brought about by heating the two components, viz. **17B** and **18**, in toluene under reflux for 1 h. The crude ^{1}H NMR spectrum showed it to be a cycloadduct formed in a 9:1 ratio (combined yield 88%).[23] The major product was separated through silica gel column chromatography, and the structure was proved to be the expected cycloadduct **23A** on the basis of its spectral characteristics.[23] However, the minor isomer could not be procured in pure form from column chromatography. Hence, compound **23A** was further used for the synthetic sequence of zinc-mediated N−O cleavage under acidic conditions to give the cyclic amine **24** bearing a secondary hydroxyl group. However, lactam formation from **24** was not observed as reported by Goti et al.[15h] for the cycloadducts with ethyl acrylate or substituted acrylates. This clearly suggested that the dipolar cycloaddition followed reversal of coefficients due to the electronic and steric effects of the cyclohexylidene-protected diol on the dipolarophile **18**. The secondary amine **24** was selectively protected with a benzyl group using potassium carbonate and benzyl bromide to form **25**, which was subsequently reduced with $LiAlH_4$. The formation of compound **26** was established on the basis of its ^{1}H NMR spectrum and other spectral details.[23] Its −OH groups were protected as benzyl ethers using benzyl bromide and a catalytic amount of *n*-Bu_4NI to give **27**. The cyclohexylidene acetal group was removed under acidic conditions, and the so formed diol **28** was selectively converted to a primary tosylate in the presence of a secondary hydroxyl group using *p*-toluenesulfonyl chloride and a catalytic amount of dibutyltin oxide. The crude tosylate **29** was then dissolved in dry methanol and treated with $Pd(OH)_2/C$ for 48 h under hydrogen atmosphere at 400 psi until HRMS showed the presence of cyclized product with deprotected primary hydroxyl groups. At this stage concentrated HCl was added to the reaction mixture to make a 1.5 M solution in methanol and then this mixture was stirred in the high-pressure Parr reactor for another 96 h. After complete deprotection of the benzyl ethers, the crude product was dissolved in acetic anhydride and a catalytic amount of $BF_3\cdot Et_2O$ was added for peracetylation. The resulting hexaacetate **30** was then subjected to 1D and 2D NMR studies for structure elucidation. The peracetylated product **30** was deprotected using aqueous ammonia in methanol, which formed acetamide as the only side product. The pure compound **31** was isolated by washing away the so formed acetamide with distilled chloroform.

The formation of product **30** was confirmed by its ^{1}H NMR spectrum, and the protons were assigned from the ^{1}H−^{1}H COSY spectrum. In addition, DEPT-135 analysis for the carbons led to assignment of the methylene carbons. The stereochemistry at the newly generated stereocenters of the six-membered ring in the hybrid structure was established on the basis of NOE and decoupling studies.[23]

Owing to the importance of the methyl substitution (vide supra), we turned our attention to synthesize the methyl-substituted analogues **32**−**34** (Figure 4) from the intermediate diol **28**. The retrosynthetic analysis of these target molecules is shown in Figure 4. The key steps involved in making these molecules were oxidative cleavage, methyl Grignard addition, and cyclization via reductive amination.

The synthesis of compound **32** started with the intermediate diol **28** (Scheme 3) in which the primary hydroxyl group was selectively protected as trityl ether **35** using trityl chloride and triethylamine, followed by protection of the secondary hydroxyl group as a benzyl ether to afford compound **36** in 95% yield.

Scheme 2. Synthetic Approach toward Compound 31



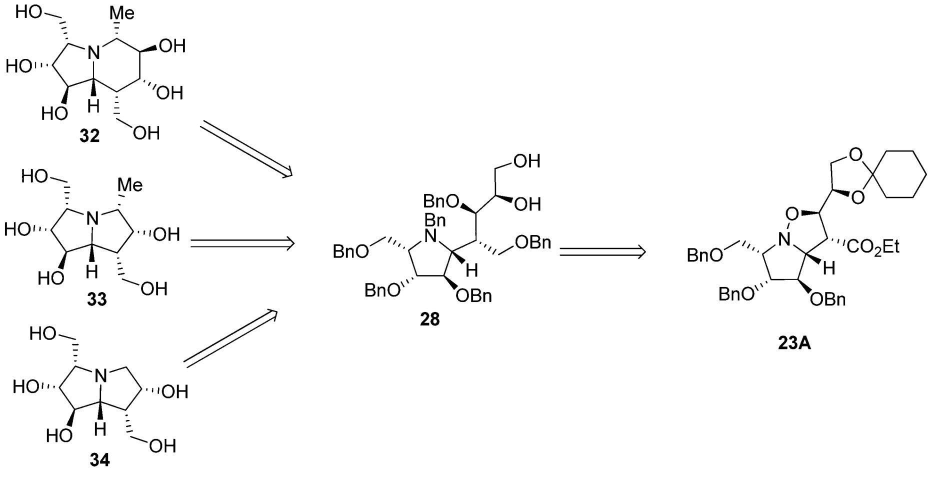


Figure 4. Retrosynthetic analysis for compounds **32**–**34**.

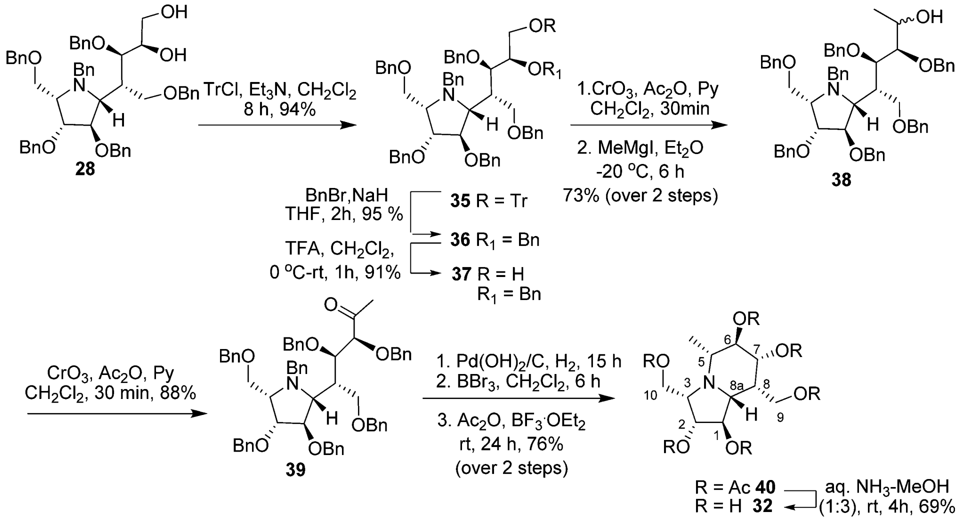
Selective deprotection of the trityl group using trifluoroacetic acid furnished the corresponding free primary hydroxyl group. Next, oxidation of the primary hydroxyl group in **37** using the CrO_3/Ac_2O/pyridine system[18] gave the desired aldehyde, which was immediately reacted with 3 equiv of methylmagnesium iodide[19] at −20 °C to give an inseparable mixture of addition products **38**. Oxidation of this diastereomeric mixture (10:1 ratio) using CrO_3 gave the corresponding keto compound **39**, which was subjected to reductive cycloamination[20] to afford a mixture of the cyclized product, monodebenzylated product, and didebenzylated product, as confirmed by its ESI-HRMS data (*m*/*z* 804.4260, 714.3793, 624.3347). The benzyl ether groups were then deprotected with BBr_3[21] in dichloromethane (6 h) to yield the final compound **32**, which was peracetylated using acetic anhydride and $BF_3{\cdot}Et_2O$ to give compound **40**.

The structure of product **40** was confirmed by ^1H NMR, and the protons were assigned from the ^1H–^1H COSY. The stereochemistry of the newly generated stereocenters was determined by NOE and decoupling studies.[23]

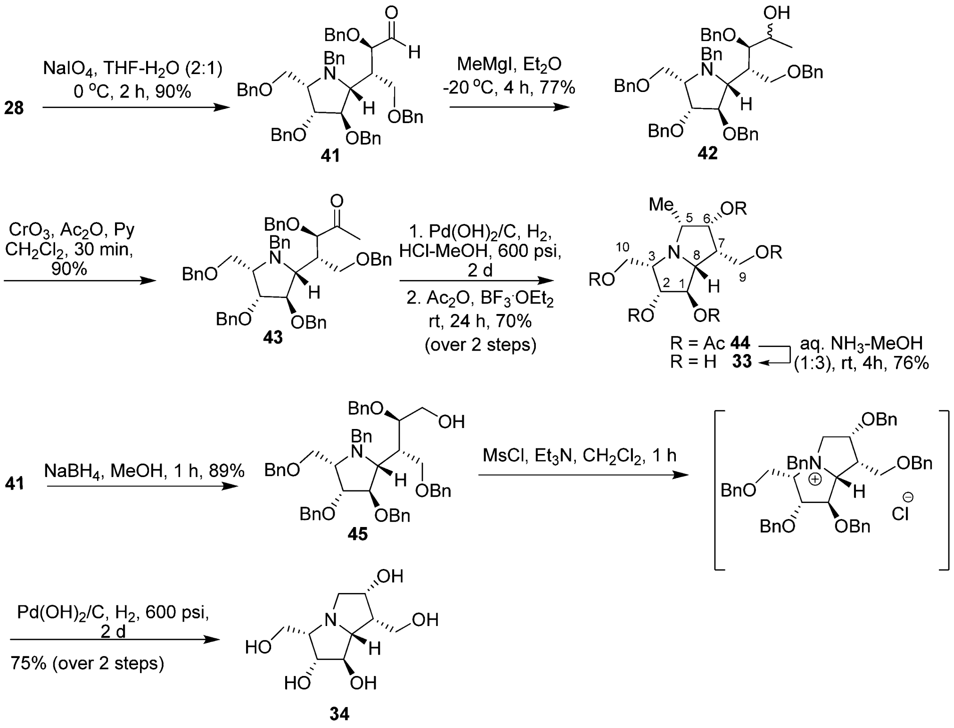
To obtain the pyrrolizidine analogue **33** (Scheme 4), the diol **28** was oxidatively cleaved with sodium periodate to give the corresponding aldehyde **41**, which was further treated with 3 equiv of MeMgI to give a mixture of diastereomers **42** in a 10:1.2 ratio. Oxidation of the secondary hydroxyl group afforded the corresponding ketone **43**. The desired target molecule **33** was obtained by reductive amination and benzyl ether deprotection under $Pd(OH)_2/C$, H_2 conditions. The corresponding acetyl derivative **44** was obtained by treating the crude product with acetic anhydride and $BF_3{\cdot}Et_2O$. The stereochemistry was confirmed by ^1H–^1H COSY and NOE studies and decoupling experiments.[22,23]

It is interesting to note that both compounds **40** and **44** underwent highly stereoselective hydrogenation through the β face of the intermediate iminium ions formed in situ during

Scheme 3. Synthetic Approach toward Compound 32



Scheme 4. Synthetic Approach toward Compounds 33 and 34



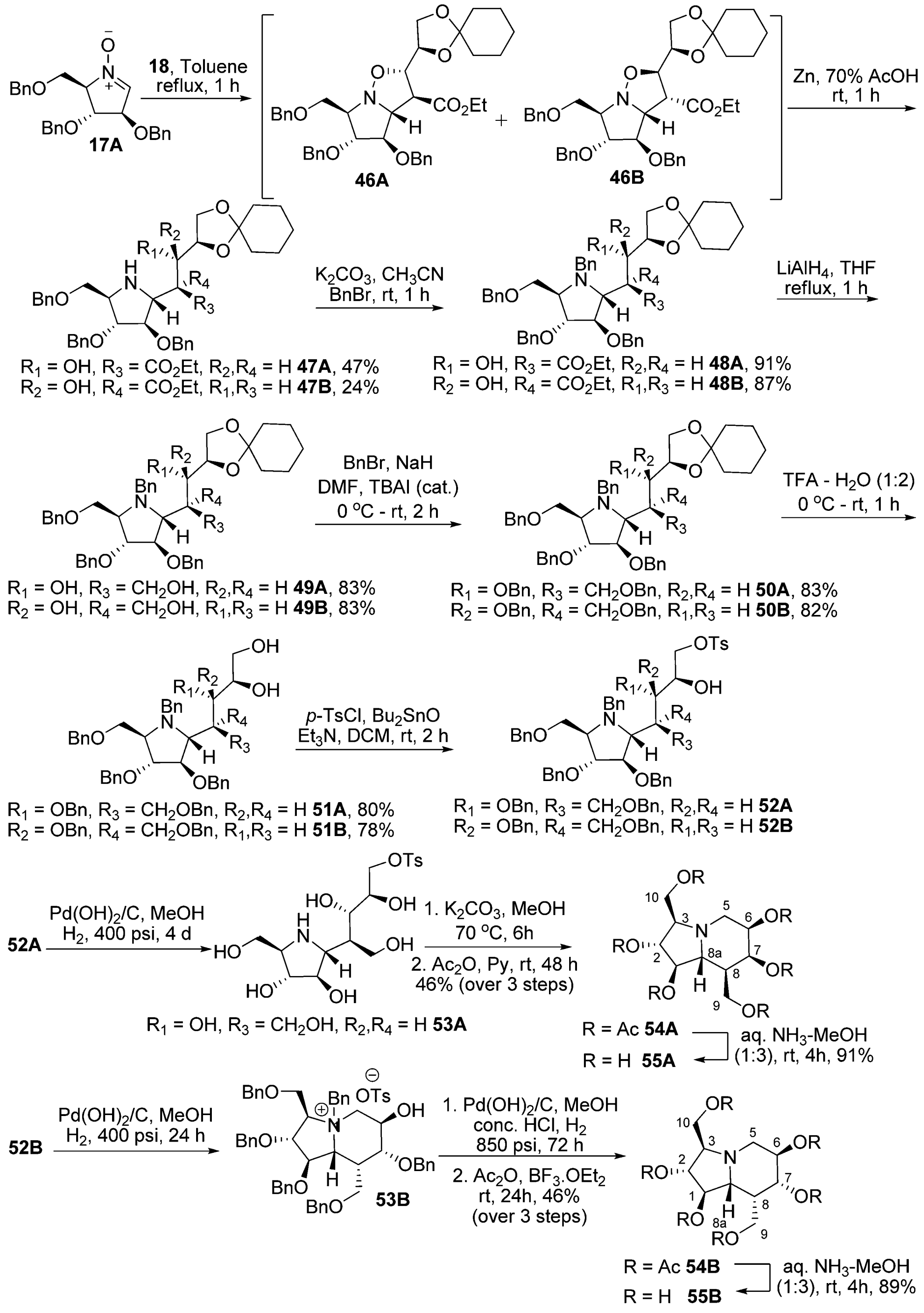
reductive amination. This seems to be guided by the stereochemistry of the substituent at C-3 rather than at C-6.[20b]

Synthesis of another pyrrolizidine analogue **34** (Scheme 4) began with aldehyde **41**, which was reduced with sodium borohydride in MeOH to give compound **45**. The primary hydroxyl group was then converted to its mesylate by treatment with MsCl and triethylamine, which upon cyclization and global deprotection under hydrogenation conditions gave the target molecule **34**.

Synthesis of the isomers of the bicyclic hybrid molecule **31** (Scheme 2) (namely **55A,B**) was started with the nitrone **17A** (Scheme 5), where a cycloaddition reaction with **18** gave a mixture of products **46** that was difficult to separate by column chromatography. Thus, the diastereomeric mixture was subjected to reductive cleavage of the N−O bond by Zn-AcOH (vide supra) and, by careful chromatographic separation, compounds **47A,B** were obtained in a 2:1 ratio. The spectral data of compounds **47A,B**[23] suggested that formation of the cycloadducts **46** followed reversal of regioselectivity, as was observed in the formation of compound **23A** and discussed earlier. The synthetic sequence was continued using the two pyrrolidines separately.

The secondary amine of compound **47A** was protected by selective benzylation in the presence of potassium carbonate, and the ester **48A** was subsequently reduced with $LiAlH_4$. The diol **49A** was then protected as the corresponding benzyl ethers to give **50A**, which was subsequently subjected to removal of the cyclohexylidene acetal with aqueous trifluoroacetic acid. The pure diol **51A** was selectively tosylated at the primary position, and the less polar product, obtained after the usual

Scheme 5. Synthetic Approaches toward Hybrid Molecules 55A,B



workup, was subjected to one-pot N-debenzylation and cyclization under hydrogenolysis conditions in the presence of a catalytic amount of tetrabutylammonium iodide at 400 psi pressure in a Parr reactor. Unlike the immediate formation of the bicyclic compound **31** (Scheme 2), compound **52A** underwent complete debenzylation only under these conditions. Formation of the uncyclized but completely deprotected intermediate **53A** was confirmed by the HRMS data of a sample from the reaction mixture. To obtain the bicyclic target molecule, the catalyst was removed from the reaction mixture and the crude product was dissolved in methanol and treated with 4 equiv of potassium carbonate. The reaction mixture was heated to reflux for 6 h, after which formation of indolizidine **55A** was confirmed by the HRMS data. Acetylation of the so formed crude polyhydroxylated compound was done using a 1:1 mixture of acetic anhydride and pyridine. The peracetylated product **54A** was purified, and the structure of this bicyclic compound was elucidated using 1D and 2D NMR spectroscopy. Again, the pure target molecule **55A** was obtained by ammonolysis in good yields (Scheme 5).

Following a similar sequence of reactions, the minor cycloadduct **47B** was converted to the diol **51B**. When the corresponding monotosylate **52B** was subjected to hydrogenolysis under general conditions, the bicyclic salt **53B** was obtained in 24 h and its formation was confirmed by HRMS analysis. Complete deprotection of this salt was achieved under a hydrogen atmosphere at 850 psi pressure ($Pd(OH)_2/C$, H_2) for 72 h, and the so obtained polyhydroxylated indolizidine was subsequently acetylated under acidic conditions. The peracetylated compound **54B** was utilized for structure determination

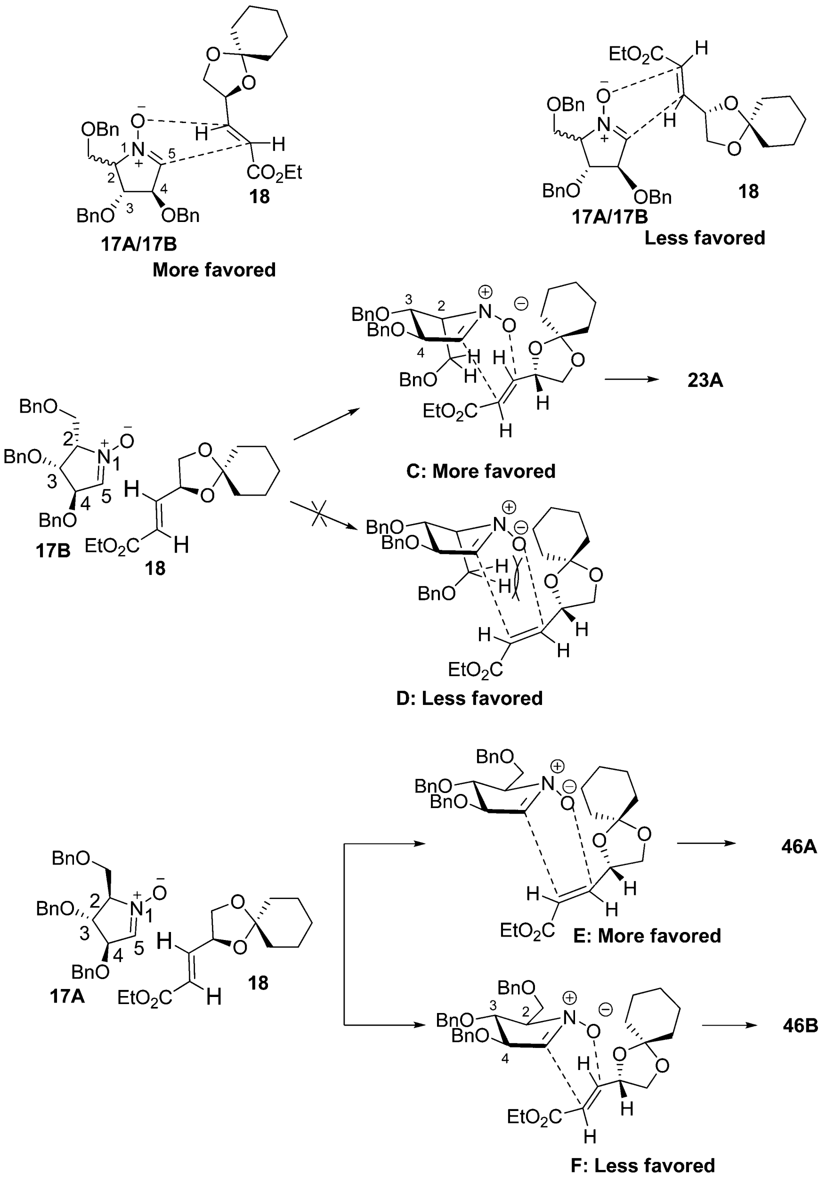


Figure 5. Proposed transition models for stereochemical outcomes of cycloaddition reactions.

and subsequently deacetylated in aqueous ammonia−methanol medium to yield the pure indolizidine **55B**. The absolute stereochemistries of the newly generated stereocenters were determined by spectroscopic studies (see the Supporting Information).

The formation of the target molecules thus gives insight into the regio- and stereoselectivity of 1,3-dipolar cycloaddition reactions. The absence of lactam formation after N−O bond cleavage of cycloadducts suggests that cycloadditions followed reversal of coefficients due to electronic and steric effects of the cyclohexylidene-protected diol on the dipolarophile **18** (Figure 5). From the absolute stereochemistry of **31** it is concluded that nitrone **17B** underwent a cycloaddition reaction such that dipolarophile **18** approached from the bottom face which is anti to the benzyloxy group at the 4-position of **17B**. Also, the addition occurred by an endo approach of ester, as the more bulky substituent (i.e., the cyclohexylidene group trans to this ester on the olefin) would prefer to be in an exo position. Thus, the favored approach is as shown in transition state **C**; the transition state **D** is not favored, as it involves steric repulsion between exocyclic methylene protons of the nitrone and the ketal oxygen of the dipolaraphile. On the other hand, a cycloaddition reaction between **17A** and **18** followed similar regioselectivity but the dipolarophile approached in both the endo and exo orientations, with respect to the ester group. This observation may be justified by the structural difference between nitrones **17A** and **17B**. The benzyloxymethyl group at the C-2 position of nitrone **17A** is in a β orientation, and thus steric hindrance for the bulky protected diol in **18** is reduced during the cycloaddition reaction (Figure 5). Hence, both approaches of dipolarophile **18** are allowed for cycloaddition with nitrone **17A**.

Glycosidase Inhibition Studies. The polyhydroxylated hybrid target molecules **31**−**34** and **55A,B** were then tested against a few commercially available glycosidases: viz., α-glucosidase (yeast), β-glucosidase (almonds), α-galactosidase (coffee beans), β-galactosidase (bovine liver), α-mannosidase (Jack beans), β-mannosidase (*Helix pomatia*), and α-L-fucoside (bovine liver). The IC_{50} values in μM of these compounds have been summarized in Table 1. Among the newly synthesized

Table 1. Glycosidase Inhibition of Synthesized Compounds: IC_{50} Values (μM)[a]

enzyme	31	32	33	34	55A	55B
α-glucosidase (yeast)	NI	11.4	NI	NI	NI	NI
β-glucosidase (almonds)	NI	115	NI	NI	NI	NI
α-galactosidase (coffee beans)	NI	NI	68.0	5.4	101.0	NI
β-galactosidase (bovine liver)	17.1	40.0	NI	82.9	NI	61.3
α-mannosidase (Jack beans)	NI	NI	NI	NI	NI	27.6
β-mannosidase (*Helix pomatia*)	NI	NI	NI	NI	62.9	85.0
α-fucosidase (bovine liver)	NI	NI	13	NI	NI	NI

[a] NI − No inhibition.

compounds, **31** showed very good and selective inhibition of β-galactosidase (bovine liver) with an IC_{50} value of 17.1 μM. On the other hand, its isomer **55A** inhibited α-galactosidase (coffee beans) and β-mannosidase (*Helix pomatia*) with IC_{50} values of 101.0 and 62.9 μM, respectively. It is noteworthy that compound **55A** showed no inhibition of β-glucosidase (almonds) and β-galactosidase (bovine liver) as displayed by its parent molecule **10**. Compound **55B** showed good inhibition of β-galactosidase (bovine liver) and mannosidases at low micromolar levels. Thus, the pyrrolidine units on the isofagomine molecule in the novel hybrid compounds have shown significant variation in their inhibition against glycosidases which highly depends on the stereochemistry of the hydroxyl groups. The fully substituted indolizidine **32** showed good yet nonselective inhibition against α-glucosidase (yeast), β-glucosidase (almonds) and β-galactosidase (bovine liver). Pyrrolizidine analogue **33** showed selectivity against α-galactosidase (coffee beans) with IC_{50} = 68 μM and also showed good inhibition against α-L-fucosidase (bovine liver) with IC_{50} = 13 μM. The nonmethyl analogue **34** showed inhibition against both α- and β-galactosidases with IC_{50} = 5.4 and 82.9 μM, respectively.

■ CONCLUSION

In conclusion, we have efficiently utilized 1,3-dipolar cycloaddition reactions of sugar-derived cyclic nitrones with a disubstituted unsymmetric olefin as dipolarophile to obtain novel pyrrolidine−isofagomine hybrid systems and related indolizidine and pyrrolizidine analogues. The cycloadduct reaction followed a reversal of regioselectivity in comparison to acrylates, and this provided the platform for synthesizing the newly designed molecules. The newly synthesized compounds have been further tested against commercially available glycosidases to study their enzymatic activity.

■ EXPERIMENTAL SECTION

General Experimental Methods. All solvents and common reagents were purified by established procedures; IR spectra were recorded with FTIR as a thin film, and values are expressed in cm^{-1}. Mass spectra were recorded by Q-Tof using the electrospray ionization (ESI) method. Column chromatography was performed on silica gel (100−200 mesh) using hexane and ethyl acetate as eluents. Thin-layer chromatography (TLC) was performed on silica gel plates made by using grade G silica gel or silica gel precoated on aluminum plates. The ^1H NMR (400 or 500 MHz) and ^{13}C NMR (100 or 125 MHz) spectra were referenced with respect to the residual solvent signals (7.26 ppm for ^1H and 77.0 ppm for ^{13}C in $CDCl_3$; 4.79 ppm for ^1H and uncorrected for ^{13}C in D_2O). Chemical shifts (δ) are reported in ppm, and the abbreviations used for denoting multiplicities are as follows: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dq (doublet of quartets), m (multiplets). The concentration (c) for specific rotation is calculated in grams per 100 mL.

(2*R*,3*R*,3a*R*,4*R*,5*R*,6*S*)-Ethyl 4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(1,4-dioxaspiro[4.5]decan-2-yl)hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (23A). A mixture of compound **17B** (2.0 g, 4.790 mmol) and **18** (1.15 g, 4.790 mmol) in an equimolar ratio was taken up in toluene (10 mL) and heated to reflux for 1 h. After complete consumption of the starting material on TLC, the reaction mixture was brought to room temperature and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to give **23A**: yield 2.455 g, 78%; R_f = 0.7 (4/6 hexane/EtOAc); $[\alpha]_D^{28}$ = +42.88° (c = 0.23, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2923.2, 2853.4, 1733.5, 1621.0, 1453.3, 1366.6, 1094.5, 1025.0; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (t, J = 7.3 Hz, 3H), 1.30−1.66 (m, 10H), 3.38 (t, J = 8.6 Hz, 1H), 3.72−3.88 (m, 4H), 3.90−4.04 (m, 3H), 4.16 (dd, J = 1.2, 5.6 Hz, 1H), 4.31−4.36 (m, 4H), 4.46−4.57 (m, 6H), 7.21−7.33 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.2, 14.2, 24.0, 24.1, 25.3, 35.1, 35.9, 51.0, 60.9, 65.3, 68.0, 68.8, 69.0, 72.4, 72.8, 73.1, 73.5, 73.6, 75.7, 78.1, 81.5, 81.7, 82.9,110.1, 127.4, 127.6, 127.8, 127.8, 127.9, 128.1, 128.4, 128.5, 128.5, 128.6, 128.8, 137.4, 138.0, 138.4, 170.2; HRMS calcd for $C_{39}H_{48}NO_8$ $[M + H]^+$ 658.3374, found 658.3384, calcd for $C_{39}H_{47}NaNO_8$ $[M + Na]^+$ 680.3199, found 680.3198.

(2*R*,3*R*)-Ethyl 2-((2*R*,3*R*,4*R*,5*S*)-1-Benzyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl)-3-hydroxy-3-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)propanoate (25). Compound **23A** (10.0 g, 15.160 mmol) was taken up in 70% aqueous acetic acid (94 mL), and to it was added dried zinc dust (19.36 g, 296.0 mmol). The reaction mixture was stirred at room temperature and was then filtered to remove the solid by consecutive washing with water. The filtrate was then neutralized with 5 M NaOH, the compound was extracted by workup with dichloromethane (3 × 75 mL), and the combined layers were washed with brine solution and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the crude product was used without further purification. The crude secondary amine **24** (500.0 mg, 0.758 mmol) was dissolved in dry acetonitrile (10 mL), and to it was added anhydrous potassium carbonate (214.0 mg, 1.516 mmol) and benzyl bromide (0.1 mL, 0.834 mol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h and then diluted with water. The compound was extracted with ethyl acetate (3 × 10 mL), and the extracts were washed with brine and then dried over anhydrous sodium sulfate. Removal of the solvent by vacuum evaporation gave the crude product, which was purified by column chromatography to afford compound **25**: yield 483.2 mg, 85%; R_f = 0.6 (7/3 hexane/EtOAc); $[\alpha]_D^{28}$ = −21.3° (c = 0.375, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3395.3, 2921.4, 2852.4, 1735.0, 1597.1, 1454.2, 1022.4; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17−1.69 (m, 13H), 2.56−2.65 (m, 1H), 3.30 (dd, J = 4.5, 7.6 Hz, 1H), 1.26−1.61 (m, 1H), 3.14 (dd, J = 4.6, 6.7 Hz, 1H), 3.24−3.31 (m, 1H), 3.40 (dd, J = 1.8, 10.4 Hz, 1H), 3.53 (dd, J = 3.4, 10.4 Hz, 1H), 3.76 (d, J = 13.8 Hz, 1H), 3.81−3.87 (m, 1H), 3.94−4.02 (m, 2H), 4.03−4.10 (m, 1H), 4.16 (dd, J = 4.6, 9.2 Hz, 1H), 4.19−4.30 (m, 2H), 4.36−4.56 (m, 6H), 4.58−4.69 (m, 2H), 4.74 (d, J = 12.0 Hz, 1H), 7.19−7.39 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 23.9, 24.0, 25.2, 29.8, 35.0, 36.2, 44.8, 53.6, 57.6, 60.6, 64.0, 65.6, 66.0, 71.6, 72.5, 72.7, 73.1, 73.4, 77.8, 82.5, 83.7, 109.6, 127.0, 127.3, 127.5, 127.6, 127.7, 127.7, 127.8, 128.0, 128.3, 128.4, 128.4, 128.5, 128.7, 128.9, 128.3, 138.4, 138.4, 138.6, 172.7; HRMS calcd for $C_{46}H_{56}NO_8$ $[M + H]^+$ 750.4000, found 750.4009.

(1*R*,2*S*)-2-((2*R*,3*R*,4*R*,5*S*)-1-Benzyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl)-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)propane-1,3-diol (26). To a suspension of $LiAlH_4$ (113 mg, 3.60 mmol) in dry THF (8.0 mL) was added dropwise a solution of compound **25** (900 mg, 1.200 mmol) in dry THF (7.0 mL) at 0 °C, and the reaction mixture was heated to reflux for 1 h. After the reaction was complete (TLC monitoring), it was quenched with ethyl acetate, ice, and 30% NaOH solution. The reaction mixture was stirred at room temperature for 1 h. The colloidal residue was removed by filtration on a sintered-glass funnel and the solvent evaporated in vacuo to give the crude product, which was purified by column chromatography: yield 697 mg, 82%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +10.5° (*c* = 2.48, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3415.8, 3062.9, 2928.5, 2856.4, 1602.1, 1494.2, 1451.5, 1093.8, 1027.9; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28−1.72 (m, 10 H), 2.08−2.16 (m, 1H), 3.21 (d, *J* = 6.4 Hz, 1H), 3.36−3.44 (m, 2H), 3.55 (dd, *J* = 3.1, 10.4 Hz, 1H), 3.63 (d, *J* = 13.5 Hz, 1H), 3.75 (dd, *J* = 3.4, 9.5 Hz, 1H), 3.95−4.04 (m, 3H), 4.17−4.22 (m, 2H), 4.33−4.44 (m, 4H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.54−4.58 (m, 2H), 4.64 (dd, *J* = 7.6, 9.5 Hz, 1H), 4.80 (d, *J* = 11.6 Hz, 1H), 7.13−7.37 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 24.1, 25.1, 35.4, 35.9, 46.6, 53.0, 57.2, 63.7, 65.1, 67.9, 68.2, 72.9, 73.6, 76.2, 79.6, 83.0, 85.0, 110.3, 127.4, 127.6, 127.8, 127.9, 128.0, 128.4, 128.5, 128.5, 128.6, 128.7, 137.5, 138.0, 138.1, 138.5; HRMS calcd for $C_{44}H_{54}NO_7$ $[M + H]^+$ 708.3895, found 708.3907.

(2*S*,3*R*,4*R*,5*R*)-1-Benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-((1*R*,2*S*)-1,3-bis(benzyloxy)-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)propan-2-yl)pyrrolidine (27). The diol **26** (300 mg, 0.423 mmol) was dissolved in dry DMF (10 mL), and to it were added sodium hydride (60% suspension in paraffin oil, 40.8 mg, 1.060 mmol), benzyl bromide (0.15 mL, 1.271 mmol), and a catalytic amount of tetrabutylammonium iodide (0.02 mmol) at 0 °C. After the reaction mixture was stirred at room temperature for 2 h, it was quenched with ice and the usual workup with ethyl acetate (3 × 10 mL) was followed. The organic phase was washed with brine solution and then dried over anhydrous sodium sulfate. In vacuo removal of the solvent gave the crude compound, which was purified by column chromatography: yield 320 mg, 85%; R_f = 0.8 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = −12.0° (*c* = 1, CH_2Cl_2), IR (ν_{max}/cm^{-1}) 2921.7, 2852.7, 1601.4, 1452.1, 1021.0; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34−1.36 (m, 2H), 1.53−1.60 (m, 8H), 2.65−2.66 (m, 1H), 3.21−3.22 (m, 1H), 3.37 (dd, *J* = 2.5, 10.1 Hz, 1H), 3.53 (dd, *J* = 4.0, 10.1 Hz, 1H), 3.66 (d, *J* = 14.7 Hz, 1H), 3.77−3.87 (m, 4H), 3.99−4.02 (m, 2H), 4.10 (t, *J* = 6.3 Hz, 1H), 4.32−4.44 (m, 6H), 4.49−4.54 (m, 3H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.63−4.69 (m, 3H), 7.07−7.39 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 24.2, 25.3, 34.8, 36.4, 40.1, 53.5, 58.0, 60.9, 66.0, 66.4, 69.2, 72.5, 72.9, 72.9, 73.3, 74.8, 79.6, 83.6, 84.2, 109.1, 126.3, 127.4, 127.5, 127.6, 127.7, 127.9, 127.9, 128.2, 128.2, 128.3, 128.4, 138.7, 138.8, 138.9, 140.5. 39.9, 54.7, 59.7, 61.3, 64.4, 66.4, 69.2, 72.6, 73.3, 73.3, 73.6, 79.9, 82.8, 83.8, 126.5, 127.5, 127.6, 127.6, 127.7, 127.8, 128.0, 128.3, 128.3, 128.4, 128.5, 128.5, 138.0, 138.2, 138.5, 138.5, 140.7; HRMS calcd for $C_{58}H_{66}NO_7$ $[M + H]^+$ 888.4834, found 888.4833.

(2*R*,3*R*,4*S*)-4-((2*R*,3*R*,4*R*,5*S*)-1-Benzyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl)-3,5-bis(benzyloxy)pentane-1,2-diol (28). Compound **27** (700 mg, 0.788 mmol) was dissolved in a trifluoroacetic acid/water mixture (1/2, 14.2 mL), at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. On complete consumption of the reactants, the product was extracted with ethyl acetate (3 × 15 mL) and then washed with brine solution. The combined organic layers were dried over anhydrous sodium sulfate, and removal of solvent by vacuum evaporation gave the crude product, which was purified by column chromatography: yield 592.1 mg, 93%; R_f = 0.2 (8/2 hexane/EtOAc), $[\alpha]_D^{28}$ = −8.25° (*c* = 0.97, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3398.7, 2922.7, 2853.5, 1601.1, 1452.8, 1092.3, 1023.5; ^1H NMR (500 MHz, $CDCl_3$) δ 2.10−2.20 (m, 1H), 2.68−2.76 (m, 1H), 3.33 (dd, *J* = 2.9, 9.7 Hz, 1H), 3.36−3.39 (m, 1H), 3.54 (dd, *J* = 4.9, 9.8 Hz, 1H), 3.58−3.68 (m, 2H), 3.72−3.81 (m, 5H), 3.86 (d, *J* = 15.2 Hz, 1H), 3.94 (dd, *J* = 3.2, 9.8 Hz, 1H), 4.03 (d, *J* = 15.2 Hz, 1H), 4.16 (t, *J* = 5.8 Hz, 1H), 4.33−4.12 (m, 5H), 4.45 (d, *J* = 11.4 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 4.52 (s, 2H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 7.08−7.13 (m, 2H), 7.17−7.37 (m, 28 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.9, 54.7, 59.7, 61.3, 64.4, 66.4, 69.2, 72.6, 73.3, 73.3, 73.6, 79.9, 82.8, 83.8, 126.5, 127.5, 127.6, 127.6, 127.7, 127.8, 128.0, 128.3, 128.3, 128.4, 128.5, 128.5, 138.0, 138.2, 138.5, 138.5, 140.7; HRMS calcd for $C_{52}H_{58}NO_7$ $[M + H]^+$ 808.4208, found 808.4214.

(1*R*,2*R*,3*S*,6*R*,7*R*,8*S*,8a*R*)-3,8-Bis(acetoxymethyl)octahydroindolizine-1,2,6,7-tetrayl Tetraacetate (30). The diol **28** (200 mg, 0.247 mmol) was dissolved in dry dichloromethane (4 mL), and to it were added *p*-toluenesulfonyl chloride (52.8 mg, 0.30 mmol), dry triethylamine (0.060 mL, 0.408 mmol), and dibutyltin oxide (0.02 mmol) at room temperature. The mixture was stirred for 4 h, and then on completion of the reaction (TLC monitoring), it was diluted with water. The organic layer was separated, and the aqueous phase was washed with dichloromethane (2 × 5 mL) and brine solution and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the crude product was subsequently dissolved in dry methanol (10 mL) and treated with $Pd(OH)_2/C$ (91 mg, 40% w/w) and tetrabutylammonium iodide (0.1 mmol). The reaction mixture was exposed to a hydrogen atmosphere at 400 psi for 2 days in a Parr reactor. After complete formation of the bicyclic compound as monitored by HRMS, concentrated HCl was added to make a 1 M solution and the reaction mixture was stirred for another 4 days at the same pressure. After complete formation of the polyhydroxylated product, the catalyst was removed by filtration through a sintered funnel and the solvent was removed in vacuo to give the crude product. The residue was dissolved in acetic anhydride (2 mL) and treated with a catalytic amount of $BF_3{\cdot}Et_2O$ (0.2 mL). The reaction mixture was stirred at room temperature for 1 day, and on completion of hexaacetylation, it was neutralized with a saturated aqueous solution of sodium bicarbonate. The compound was extracted with dichloromethane (3 × 10 mL), and the organic layer was washed with brine and then dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue purified by column chromatography to give **30**: yield 68 mg, 55% (over three steps); R_f = 0.6 (2/8 hexane/EtOAc); $[\alpha]_D^{28}$ = −21.3° (*c* = 0.375, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3023.4, 2923.5, 1742.5, 1596.2, 1405.2, 1192.3, 1039.1; ^1H NMR (500 MHz, $CDCl_3$) δ 2.01 (s, 3H, $-OCOCH_3$), 2.02 (s, 3H, $-OCOCH_3$), 2.08 (s, 3H, $-OCOCH_3$), 2.09 (s, 3H, $-OCOCH_3$), 2.12 (s, 3H, $-OCOCH_3$), 2.13 (s, 3H, $-OCOCH_3$), 2.29−2.32 (m, H-8), 2.84 (dd, *J* = 2.3, 12.7 Hz, H-5ax), 3.09 (dd, *J* = 2.4, 12.9 Hz, H-5eq), 3.32 (dd, *J* = 2.5, 8.3 Hz, H-8a), 3.67−3.70 (m, H-3), 4.04−4.11 (m, H-9, H-9′), 4.26 (dd, *J* = 3.9, 11.8 Hz, H-10), 4.78 (dd, *J* = 4.9, 11.9 Hz, H-10′), 4.89−4.91 (m, H-7), 5.13−5.20 (m, H-6), 5.33−5.36 (m, H-2), 5.44−5.48 (m, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 21.0, 21.1, 21.2, 21.3, 21.3, 39.1, 50.0, 59.3, 60.0, 61.5, 62.1, 67.7, 71.376.1, 76.5, 170.0, 170.3, 170.3, 170.5, 170.6, 170.7; HRMS calcd for $C_{22}H_{32}NO_{12}$ $[M + H]^+$ 502.1919, found 502.1920.

(1*R*,2*R*,3*S*,6*R*,7*S*,8*R*,8a*R*)-3,8-Bis(hydroxymethyl)octahydroindolizine-1,2,6,7-tetraol (31). The peracetylated compound **30** (15 mg, 0.030 mmol) was dissolved in a mixture of 30% aqueous ammonia/methanol (1/3, 2.0 mL), and this mixture was stirred at room temperature for 4 h. After complete consumption of starting material, the solvent was removed under reduced pressure and the residue washed several times with distilled chloroform, discarding the washings. The residue was then analyzed spectroscopically, which was pure enough to carry out biological studies: yield 6.6 mg, 89%; R_f = 0.4 (8/2 EtOAc/MeOH); $[\alpha]_D^{28}$ = −39.0° (*c* = 0.1, MeOH); IR (ν_{max}/cm^{-1}) 3412.3, 2925.5, 2854.1, 1633.0, 1462.2, 1370.1, 1043.6; ^1H NMR (400 MHz, D_2O) δ 1.77 (s, OH), 2.20 (br s, 1H), 2.70 (br s, 1H), 3.08 (br s, 1H), 3.04−3.05 (m, 1H), 3.72−3.82 (br m, 7H), 3.93 (s, 2H), 4.39 (br s, 1H); ^{13}C NMR (100 MHz, D_2O) δ 33.6, 40.5, 60.0, 60.4, 62.6, 62.9, 67.8, 68.3, 69.0, 69.6; HRMS calcd for $C_{10}H_{20}NO_6$ $[M + H]^+$ 250.1285, found 250.1286.

(2*R*,3*R*,4*S*)-4-((2*R*,3*R*,4*R*,5*S*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-3,5-bis(benzyloxy)-1-(trityloxy)pentan-2-ol (35). To a solution of diol **28** (300 mg, 0.371 mmol) in dichloromethane (5 mL) at 0 °C were added triethylamine (0.258 mL, 1.113 mmol) and trityl chloride (182 mg, 0.445 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred for 5 h at room temperature, diluted with water, and extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude product by column chromatography afforded **35** as a colorless liquid: yield 366.3 mg, 94%; R_f = 0.6 (6/4 hexane/EtOAc); $[\alpha]_D^{28}$ = −11.3° (*c* = 1.85, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3464.6, 3029.8, 2867.7, 1494.5, 1451.2, 1364.2; ^1H NMR (500 MHz, $CDCl_3$) δ 2.81−2.84 (m, 1H), 3.14 (bs, 1H), 3.31−3.35 (m, 2H), 3.37−3.39 (m, 1H), 3.45 (dd, *J* = 3.5 Hz, 9.5 Hz, 1H), 3.56 (dd, *J* = 4.5 Hz, 10.0 Hz, 1H), 3.70−3.74 (m, 2H), 3.86−3.92 (m, 3H), 3.98−4.00 (m, 1H), 4.05 (bs, 1H), 4.15−4.18 (m, 2H), 4.21−4.25 (m, 1H), 4.30−4.39 (m, 2H), 4.41−4.48 (m, 3H), 4.53−4.60 (m, 2H), 4.66−4.71 (m, 2H), 6.89 (d, *J* = 7.0 Hz), 7.07−7.10 (m, 2H), 7.16−7.20 (m, 3H), 7.21−7.34 (m, 30H), 7. 35−7.38 (m, 2H), 7.48−7.49 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.1, 53.8, 58.9, 61.1, 65.2, 66.1, 69.2, 71.9, 72.5, 72.7, 73.0, 73.2, 73.5, 78.9, 83.4, 84.0, 86.7, 127.1, 127.5, 127.6, 127.8, 127.9, 128.1, 128.3, 128.4, 128.9, 138.4, 138.7, 140.7, 144.1; HRMS calcd for $C_{71}H_{72}NO_7$ $[M + H]^+$ 1050.5309, found 1050.5300.

(2*S*,3*R*,4*R*,5*R*)-1-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)-methyl)-5-((2*S*,3*R*,4*R*)-1,3,4-tris(benzyloxy)-5-(trityloxy)-pentan-2-yl)pyrrolidine (36). Compound **35** (300 mg, 0.285 mmol) was benzylated with sodium hydride (15 mg, 0.571 mmol) and benzyl bromide (0.07 mL, 0.571 mmol) using a procedure similar to that followed to make compound **27** to give **36** as a colorless liquid: yield 315 mg, 95%; R_f = 0.8 (9:1 hexane/EtOAc); $[\alpha]_D^{28}$ = −24.0° (*c* = 1.25, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3029.6, 2869.0, 1494.8, 1451.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.71−2.73(m, 1H), 3.21−3.23 (m, 1H), 3.34−3.38 (m, 2H), 3.53−3.63 (m, 3H), 3.77 (t, *J* = 9.5 Hz, 1H), 3.81−3.86 (m, 2H), 3.94−3.97 (m, 1H), 4.06 (t, *J* = 6.5 Hz, 1H), 4.12−4.15 (m, 1H), 4.20−4.22 (m, 1H), 4.30−4.48 (m, 11H), 4.75 (d, *J* = 11.5 Hz, 1H), 6.84 (m, 2H), 6.99 (m, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.15−7.34 (m, 40H), 7.46−7.48 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.0, 53.2, 58.1, 61.2, 63.8, 66.1, 69.8, 72.3, 72.4, 72.5, 72.7, 73.4, 74.0, 78.4, 80.3, 83.8, 84.5, 86.7, 126.2, 126.6, 126.9, 127.0, 127.1, 127.2, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.9, 130.8, 138.5, 138.7, 139.0, 139.1, 139.2, 140.8, 144.3 HRMS calcd for $C_{78}H_{78}NO_7$ $[M + H]^+$ 1140.5778, found 1140.5770

(2*R*,3*R*,4*S*)-4-((2*R*,3*R*,4*R*,5*S*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-2,3,5-tris(benzyloxy)-pentan-1-ol (37). To a solution of compound **36** (300 mg, 0.262 mmol) in dry dichloromethane (5 mL) was added trifluoroacetic acid (0.0604 mL, 0.788 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then neutralized with saturated aqueous K_2CO_3 solution. The reaction mixture was extracted with dichloromethane (3 × 20 mL), and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude product which was further purified by column chromatography: colorless liquid; yield 216 mg, 91%; R_f = 0.6 (6/4 hexane/EtOAc); $[\alpha]_D^{28}$ = −18.3° (*c* = 0.6, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3029.6, 2923.9, 2855.5, 1495.5, 1453.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (br s, 1H), 2.68−2.71 (m, 1H), 3.24−3.26 (m, 1H), 3.37 (dd, *J* = 2.5 Hz, 10.0 Hz, 1H), 3.54−3.57 (m, 1H), 3.66−3.71 (m, 2H), 3.79−3.87 (m, 5H), 4.00−4.02 (m, 1H), 4.06−4.09 (m, 1H), 4.21(d, *J* = 14.5 Hz, 1H), 4.29−4.57 (m, 11H), 4.75 (d, *J* = 11.0 Hz, 1H), 7.13−7.29 (m, 35H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.8, 39.4, 53.8, 58.3, 61.2, 61.4, 66.0, 69.7, 71.8, 72.3, 72.6, 73.0, 73.4, 74.4, 79.7, 80.8, 83.7, 84.3, 126.4, 127.3, 127.4, 127.5, 127.6. 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 138.4, 138.5, 138.6, 138.9, 140.5; HRMS calcd for $C_{59}H_{64}NO_7$ $[M + H]^+$ 898.4688, found 898.4683.

(3*R*,4*R*,5*S*)-5-((2*R*,3*R*,4*R*,5*S*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-3,4,6-tris(benzyloxy)-hexan-2-ol (38). To a solution of chromium trioxide (68 mg, 0.668 mmol) in 4 mL of anhydrous dichloromethane to 0 °C were added pyridine (0.107 mL, 0.105 g, 2.004 mmol) and acetic anhydride (0.06 mL, 0.066 g, 0.668 mmol) followed by slow addition of a solution of alcohol **37** (0.300 g, 0.334 mmol) in 2 mL of dichloromethane. After 15 min of stirring, the black solution was poured into ethyl acetate (10 mL) and the mixture was filtered through a sintered-glass funnel. The filtrate was concentrated in vacuo and passed through a short column packed with silica gel to afford the intermediate aldehyde. To this crude aldehyde (400 mg, 0.494 mmol) in anhydrous ether at −20 °C was added 3 equiv of methylmagnesium iodide (prepared using a literature procedure[19]), and the mixture was stirred for 4 h at the same temperature. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate (2 × 30 mL), and the combined organic layers were washed with water and brine and dried over Na_2SO_4. After removal of the solvent, purification by column chromatography gave compound **38** as a 10/1 mixture of diastereomers: yield 222 mg, 73%; R_f = 0.6 (6/4 hexane/EtOAc); IR (ν_{max}/cm^{-1}) 3488.9, 2922.8, 2857.3, 1495.7, 1453.4; ^{1}H NMR (500 MHz, $CDCl_3$, 10/1.2 mixture of diastereomers) δ 1.12 (d, *J* = 6.5 Hz, 3H, major isomer), 1.23 (d, *J* = 6.5 Hz, 3H, minor isomer), 2.70 (t, *J* = 7.5 Hz, 1H, major isomer), 2.83−2.89 (m, 1H, minor isomer), 3.23−3.26 (m, 2H, both isomers), 3.33−3.35 (m, 1H, both isomers), 3.48−3.53 (m, 1H, both isomers), 3.58−3.63(m, 2H, both isomers), 3.63−3.69 (m, 1H, both isomers), 3.81 (dd, *J* = 3.0, 10.0 Hz, major isomer, 1H), 3.86 (dd, *J* = 3.5, 10.0 Hz, 1H, minor isomer), 3.90−3.92 (m, 1H, both isomers), 3.94−3.96 (m, 1H, both isomers), 4.03−4.12 (m, 3H, both isomers), 4.28−4.62 (m, 11H, both isomers), 4.73 (d, *J* = 11.0 Hz, 1H, minor isomer), 4.80 (d, *J* = 11.0 Hz, 1H, major isomer), 7.10−7.31 (m, 35H, both isomers); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5, 29.8, 39.4, 54.1, 58.4, 61.4, 66.0, 67.0, 69.8, 72.3, 72.6, 73.0, 73.3, 73.7, 74.4, 81.1, 82.7, 83.4, 84.3, 126.5, 127.4, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 138.1, 138.4, 138.6, 138.7, 140.5; HRMS calcd for $C_{60}H_{66}NO_7$ $[M + H]^+$ 912.4830, found 912.4839.

(3*S*,4*R*,5*S*)-5-((2*R*,3*R*,4*R*,5*S*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-3,4,6-tris(benzyloxy)-hexan-2-one (39). To a solution of chromium trioxide (56 mg, 0.568 mmol) in 4 mL of anhydrous dichloromethane at 0 °C were added pyridine (0.122 mL, 0.119 g, 2.272 mmol) and acetic anhydride (0.07 mL, 0.075 g, 0.754 mmol) followed by slow addition of a solution of alcohol **38** (0.300 g, 0.378 mmol) in 2 mL of dichloromethane. After 15 min of stirring, the black solution was poured into ethyl acetate (10 mL) and the mixture was filtered through a sintered-glass funnel. The filtrate was concentrated in vacuo and passed through a short column packed with silica gel to afford the ketone **39** as a colorless liquid: yield 350 mg, 88%; R_f = 0.7 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = −26.0° (*c* = 0.5, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3062.5, 2922.5, 2854.9, 1718.1, 1495.7, 1453.3, 1353.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.0 (s, 3H), 2.78−2.82 (m, 1H), 3.23−3.25 (m, 1H), 3.35 (dd, *J* = 2.5, 10.0 Hz, 1H), 3.54 (dd, *J* = 4.0, 10.0 Hz, 1H), 3.68 (d, *J* = 14.5 Hz, 1H), 3.75−3.78 (m, 1H), 3.84−3.87 (m, 2H), 4.05−4.07 (m, 1H), 4.12 (t, *J* = 6.0 Hz, 1H), 4.22−4.55(m, 15H), 7.10−7.30 (m, 35H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7, 39.3, 53.8, 58.4, 61.2, 66.1, 69.4, 72.3, 72.5, 72.7, 72.8, 73.3, 73.7, 80.3, 83.6, 84.2, 86.0, 126.3, 127.3, 127.4, 127.5, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 137.7, 138.0, 138.6, 138.7, 138.9, 140.6, 209.7; HRMS calcd for $C_{60}H_{64}NO_7$ $[M + H]^+$ 910.4683, found 910.4680.

(1*R*,2*R*,3*S*,5*R*,6*R*,7*R*,8*S*,8a*R*)-3,8-Bis(acetoxymethyl)-5-methyloctahydroindolizine-1,2,6,7-tetrayl Tetraacetate (40). To compound **39** (0. 300 g, 0.330 mmol) dissolved in MeOH (6 mL) was added $Pd(OH)_2/C$ (90 mg, 30% w/w), and the mixture was stirred under a hydrogen atmosphere for 1 day at 600 psi pressure. TLC (4/2 hexane/EtOAc) showed complete consumption of the starting material and formation of a cyclized product, which was confirmed by mass spectrometry. The catalyst was filtered off, and the solvent was evaporated under reduced pressure. The crude product (385 mg) was dissolved in dichloromethane (4 mL) and cooled to 0 °C, followed by addition of 6 equiv of BBr_3 in dichloromethane, and the mixture was stirred for 6 h. After complete deprotection of the reaction, which was confirmed by ESI-HRMS analysis (*m*/*z* 264.1440), the reaction mixture was quenched with methanol (10 mL). Then the solvent was removed under reduced pressure. The residue was dissolved in acetic anhydride (4 mL), and this solution was treated with a catalytic amount of $BF_3{\cdot}Et_2O$ and stirred at room temperature for 12 h. The product was extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was removed by vacuum evaporation and the crude product purified by column chromatography as a colorless liquid: yield 129 mg, 76%; R_f = 0.6 (6/4 hexane/EtOAc); $[\alpha]_D^{28}$ = −21.3° (*c* = 0. 75, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2925.4, 2853.7, 1744.1, 1371.8, 1230.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.5 Hz), 1.97 (s, 3H, $-OCOCH_3$), 2.00 (s, 3H, $-OCOCH_3$), 2.07 (s, 3H, $-OCOCH_3$), 2.10 (s, 3H, $-OCOCH_3$), 2.11 (s, 3H, $-OCOCH_3$), 2.15 (s, 3H, $-OCOCH_3$), 2.20−2.24 (m, H-8), 2.98 (dq, *J* = 2.5, 6.5 Hz, H-5), 3.36 (dd, *J* = 2.0, 9.5 Hz, H8a), 3.74−3.77 (m, H-3), 4.12−4.13 (m, H10,10′), 4.25 (dd, *J* = 3.5, 12.0 Hz, H-9), 4.79−4.86 (m, H-7, H-9), 5.14 (t, *J* = 2.5 Hz, H-6), 5.5 (t, *J*

= 7.5 Hz, H-2), 5.52−5.56 (m, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 20.8, 20.9, 21.0, 21.2, 21.3, 38.6, 53.6, 55.5, 59.1, 61.7, 62.3, 70.6, 72.2, 75.9, 76.0, 169.9, 170.2, 170.4, 170.6, 170.7, 170.8; HRMS calcd for $C_{23}H_{34}NO_{12}$ [M + H]$^+$ 516.2081, found 516.2080.

(1*R*,2*R*,3*S*,5*R*,6*R*,7*R*,8*S*,8a*R*)-3,8-Bis(hydroxymethyl)-5-methyloctahydroindolizine-1,2,6,7-tetraol (32). This compound was synthesized from **40** using the same procedure as was followed for preparing compound **31**: yield 69%; $[\alpha]_D^{28}$ = −26.6° (*c* = 0.075, MeOH); IR (ν_{max}/cm^{-1}) 3364.0, 2924.8, 1633.7, 1401.5; ^{1}H NMR (400 MHz, D_2O) δ 1.07 (d, *J* = 6.0 Hz, 3H), 2.02 (br s, 1H), 2.73−2.84 (m, 1H), 3.12−3.25 (m, 2H), 3.50 (br s, 1H), 3.60−3.79 (m, 5H), 4.05−4.09 (m, 1H), 4.22−4.26 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 14.3, 43.9, 54.7, 56.6, 57.0, 59.7, 63.9, 72.2, 72.5, 76.2, 77.7; HRMS calcd for $C_{11}H_{22}NO_6$ [M + H]$^+$ 264.1447, found 264.1445.

(2*R*,3*S*)-3-((2*R*,3*R*,4*R*,5*S*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-2,4-bis(benzyloxy)butanal (41). To the diol **28** (200 mg, 0.247 mmol) dissolved in dry THF (2 mL) was added a solution of sodium periodate (106 mg, 0.495 mmol) in 0.84 mL of water dropwise with ice cooling. The reaction mixture was stirred for 30 min at room temperature. After completion of the reaction (TLC monitoring), the residue was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give the crude aldehyde, which was purified by column chromatography to afford **41** as a colorless liquid: yield 175 mg, 90%; R_f = 0.8 (8:2 hexane/EtOAc); $[\alpha]_D^{28}$ = −11.6° (*c* = 1.2, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2921.9, 2858.0, 1727.5, 1495.8, 1453.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.83−2.87 (m, 1H), 3.25−3.29 (m, 2H), 3.51−3.54 (m, 1H), 3.61−3.68 (m, 2H), 3.78−3.89 (m, 3H), 4.11−4.13 (m, 2H), 4.29−4.66(m, 11H), 7.17−7.38 (m, 30H), 9.46 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.8, 54.6, 60.0, 61.0, 66.4, 68.3, 72.0, 72.5, 72.9, 73.2, 82.9, 83.2, 83.4, 126.6, 127.4, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 128.4, 137.7, 138.3, 138.5, 140.3, 201.5; HRMS calcd for $C_{51}H_{54}NO_6$ [M + H]$^+$ 776.3999, found 776.3951.

(3*R*,4*S*)-4-((2*R*,3*R*,4*R*,5*S*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-3,5-bis(benzyloxy)pentan-2-ol (42). To aldehyde **41** (300 mg, 0.386 mmol) in anhydrous ether at −20 °C was added 3 equiv of methylmagnesium iodide (prepared using a literature procedure[19]), and the mixture was stirred for 4 h at the same temperature. The reaction mixture was quenched by the addition of a saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate (2 × 30 mL), and the combined organic layers were washed with water and brine and dried over Na_2SO_4. After removal of the solvent, purification by column chromatography yielded compound **42** as a 10:1.2 mixture of diastereomers: yield 238 mg, 77%; R_f = 0.6 (6/4 hexane/EtOAc); IR (ν_{max}/cm^{-1}) 3437.4, 2864.9, 1495.6, 1453.3, 1364.3; ^{1}H NMR (400 MHz, $CDCl_3$, 10/2 mixture of diasteromers) δ 1.17 (d, *J* = 6.3 Hz, 3H, major isomer), 1.25 (d, *J* = 6.3 Hz, 3H, minor isomer), 2.83−2.87 (m, 1H, both isomers), 3.25−3.29 (m, 2H, both isomers), 3.51−3.54 (q, *J* = 4.5 Hz, 1H, major isomer), 3.61−3.68 (m, 2H, both isomers), 3.78−3.89 (m, 3H, both isomers), 4.11−4.13 (m, 2H, both isomers), 4.29−4.38 (m, 5H, both isomers), 4.40−4.45(m, 3H, both isomers), 4.59−4.66 (m, 2H, both isomers), 7.17−7.33 (m, 30H, both isomers); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 20.1, 39.0, 39.5, 54.2, 54.3, 58.7, 61.2, 67.8, 69.7, 72.7, 73.3, 73.7, 82.5, 82.6, 83.0, 83.7, 84.3, 127.4, 127.5, 127.6, 127.7, 127.9, 128.3, 138.0, 138.4, 138.6, 140.2; HRMS calcd for $C_{52}H_{58}NO_6$ [M + H]$^+$ 792.4264, found 792.4262.

(3*R*,4*S*)-4-((2*R*,3*R*,4*R*,5*S*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-3,5-bis(benzyloxy)pentan-2-one (43). This compound was synthesized from **42** using the same procedure as was followed for preparing compound **39**: yield 280 mg, 90%; R_f = 0.7 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = −25.7° (*c* = 1.4, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3029.7, 2861.9, 1711.6, 1495.7, 1453.4, 1355.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.84−3.89 (m, 1H), 3.18−3.21 (m, 1H), 3.30 (dd, *J* = 3.0, 10.0 Hz, 1H), 3.51 (q, *J* = 5.0 Hz, 1H), 3.61 (t, *J* = 10.0 Hz, 1H), 3.68−3.71 (m, 2H), 3.89 (q, *J* = 3.5 Hz, 1H), 3.97 (d, *J* = 14.5 Hz, 1H), 4.07−4.10 (m, 2H), 4.28 (d, *J* = 11.5 Hz, 1H), 4.30−4.44 (m, 5H), 4.48−4.59 (m, 4H), 4.66 (d, *J* = 11.5 Hz, 1H), 7.15−7.38 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.2, 41.1, 54.3, 59.0, 60.8, 66.2, 69.1, 72.3, 72.4, 72.5, 72.9, 73.2, 83.2, 83.6, 85.8, 126.6, 127.4, 127.5, 127.8, 128.1, 128.2, 128.3, 128.4, 137.7, 138.6, 138.9, 140.1, 210.3; HRMS calcd for $C_{52}H_{56}NO_6$ [M + H]$^+$ 790.4108, found 790.4100.

(1*R*,2*R*,3*S*,5*R*,6*R*,7*S*,7a*R*)-3,7-Bis(acetoxymethyl)-5-methylhexahydro-1*H*-pyrrolizine-1,2,6-triyl Triacetate (44). To compound **43** (300 mg, 0.330 mmol) dissolved in methanol (6 mL) was added $Pd(OH)_2/C$ (90 mg, 30% w/w), and the mixture was stirred in the presence of hydrogen at 700 psi for 24 h. When a single spot was observed on TLC, concentrated HCl dissolved in methanol (2 mL) was added and the mixture was further stirred for 2 days. The final product formation was confirmed by ESI-HRMS data (*m*/*z* 234.1340), and the crude product was peracetylated using acetic anhydride and $BF_3{\cdot}Et_2O$ in 8 h to give the acetylated compound **44**: yield 129 mg, 70%; R_f = 0.3 (6/4 hexane/EtOAc); $[\alpha]_D^{28}$ = −16.0° (*c* = 0.75, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2924.9, 1741.3, 1371.8, 1230.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, *J* = 7 Hz, CH_3), 1.98 (s, 3H, $-OCOCH_3$), 2.03 (s, 3H, $-OCOCH_3$), 2.06 (s, 3H, $-OCOCH_3$), 2.11 (s, 3H, $-OCOCH_3$), 2.13 (s, 6H, $-OCOCH_3$), 2.74−2.80 (m, H-7), 3.37−3.39 (m, H-5), 3.82−3.87 (m, H-3, H-10′), 4.01−4.11 (m, H-8, H-9, H-10), 4.30−4.34 (m, H-9′), 5.32−5.30 (m, H-6, H-2), 5.44−5.47 (m, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2, 20.8, 20.9, 21.0, 21.2, 29.7, 45.1, 54.7, 60.0, 60.1, 62.6, 64.2, 75.0, 75.2, 169.7, 170.1, 170.3, 170.7, 170.9; HRMS calcd for $C_{20}H_{30}NO_{10}$ [M + H]$^+$ 444.1870, found 444.1878.

(1*R*,2*R*,3*S*,5*R*,6*R*,7*S*,7a*R*)-3,7-Bis(hydroxymethyl)-5-methylhexahydro-1*H*-pyrrolizine-1,2,6-triol (33). This compound was synthesized from **44** using the same procedure as was followed for preparing compound **31**: yield 30 mg, 76%; R_f = 0.4 (8/2 EtOAc/MeOH); $[\alpha]_D^{28}$ = +46.6° (*c* = 0.15, MeOH); IR (ν_{max}/cm^{-1}) 3369.1, 2935.9, 1579.9, 1409.6, 1170.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (d, *J* = 7 Hz, 3H), 2.58−2.64 (m, 1H), 3.47−3.49 (m, 1H), 3.67−3.73 (m, 4H), 3.86−3.90 (m, 1H), 4.17 (bs, 1H), 4.21−4.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.4, 46.2, 56.5, 58.0, 62.3, 70.2, 73.0, 73.8, 77.1; HRMS calcd for $C_{10}H_{20}NO_5$ [M + H]$^+$ 234.1341, found 234.1340.

(2*R*,3*S*)-3-((2*R*,3*R*,4*R*,5*S*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-2,4-bis(benzyloxy)butan-1-ol (45). To a stirred solution of aldehyde **41** (100 mg, 0.128 mmol) in methanol (2.0 mL) cooled to 0 °C was added $NaBH_4$ (7.3 mg, 0.193 mmol). The reaction mixture was stirred at room temperature for 1 h, and after completion of the reaction, it was quenched with saturated ammonium chloride solution (10.0 mL). The reaction mixture was concentrated under vacuum to remove methanol. The aqueous phase was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were washed with water and brine and dried over Na_2SO_4. Purification through column chromatography furnished compound **45** as a colorless liquid: yield 90.0 mg, 89%; R_f = 0.6 (4/1 hexane/EtOAc); $[\alpha]_D^{28}$ = −21.5° (*c* = 1.95, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3455.3, 3029.2, 2864.4, 1495.4, 1453.2, 1363.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.69−2.72 (m, 1H), 3.14 (br s, 1H), 3.25−3.28 (m, 1H), 3.38 (dd, *J* = 2.5, 10.0 Hz, 1H), 3.54 (dd, *J* = 4.5, 10.0 Hz, 1H), 3.62−3.72 (m, 4H), 3.79−3.88 (m, 3H), 3.95 (dd, *J* = 2.0, 10.0 Hz, 1H), 4.11−4.14 (m, 1H), 4.36−4.70 (m, 11H), 7.17−7.37 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.9, 54.3, 58.6, 61.3, 61.6, 65.8, 69.9, 71.2, 72.5, 72.8, 73.3, 73.4, 80.5, 83.4, 84.2, 126.6, 127.5, 127.6, 127.7, 127.9, 128.2, 128.2, 128.3, 128.4, 138.0, 138.5, 138.7, 140.1; HRMS calcd for $C_{51}H_{56}NO_6$ [M + H]$^+$ 778.4108, found 778.4109.

(1*R*,2*R*,3*S*,6*R*,7*S*,7a*R*)-3,7-Bis(hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,6-triol (34). To a stirred solution of alcohol **45** (300 mg, 0.385 mmol) in dichloromethane (7.0 mL) at 0 °C was added triethylamine (0.12 mL, 0.546 mmol), followed by slow addition of methanesulfonyl chloride (0.031 mL, 0.262 mmol) and a catalytic amount of DMAP (0.1 mmol). After 30 min, a very polar spot was observed on TLC and the reaction mixture was neutralized with saturated aqueous sodium bicarbonate solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product (340 mg) was dissolved in aqueous HCl/MeOH, and to this solution was added $Pd(OH)_2/C$ (120 mg, 35% w/w). The reaction mixture was stirred under a hydrogen atmosphere (1 atm) for 2 days, and on complete deprotection, the catalyst was removed by vacuum filtration over Celite and the reaction mixture was passed through a Dowex (50X) basic resin column to give compound **34** as a viscous brown liquid: yield 50.0 mg, 75% (over two steps); R_f = 0.6 (8/2 EtOAc/MeOH); $[\alpha]^{28}_{D}$ = +20.0° (c = 0.15, MeOH); IR (ν_{max}/cm^{-1}) 3356.0, 2927.0, 1637.7, 1401.3; ^1H NMR (500 MHz, D_2O) δ 2.74(br s, 1H), 3.19–3.23 (m, 1H), 3.40 (d, J = 13.5 Hz, 1H), 3.57–3.65 (m, 2H), 3.81–3.90 (m, 3H), 4.05 (br s, 1H), 4.21–4.26 (m, 2H), 4.39–4.43 (m, 1H), 4.94 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.6, 57.1, 57.6, 60.6, 68.9, 70.7, 74.1, 77.2, 85.7; HRMS calcd for $C_9H_{18}NO_5$ [M + H]$^+$ 220.1185, found 220.1189.

Cycloaddition of Nitrone 17A and Compound 18. A mixture of **17A** (2.0 g, 4.790 mmol) and **18** (1.15 g, 4.790 mmol) was reacted following a procedure similar to that for compound **23A**. The mixture of compounds obtained after purification was reduced with zinc by the procedure for the synthesis of **24**. The two compounds **47A,B** were separated by column chromatography.

*(2S,3S)-Ethyl 2-((3R,4R,5R)-3,4-Bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-3-hydroxy-3-((R)-1,4-dioxaspiro[4.5]decan-2-yl)propanoate (**47A**):* yield 1.485 g, 47%; R_f = 0.5 (7/3 hexane/EtOAc); $[\alpha]^{28}_{D}$ = −1.22° (c = 1.64, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3390.6, 2928.7, 2853.0, 1725.0, 1618.5, 1496.4, 1451.9, 1365.5, 1093.4, 1027.4; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3H), 1.30–1.39 (m, 2H), 1.54–1.62 (m, 8H), 2.73–2.76 (m, 1H), 3.36 (dd, J = 4.3 Hz, 9.2 Hz, 1H), 3.54–3.63 (m, 2H), 3.77 (s, 1H), 3.86 (d, J = 11 Hz, 1H), 3.92–4.13 (m, 7H), 4.40 (d, J = 11.9 Hz, 1H), 4.42 (d, J = 11.9 Hz, 1H), 4.47–4.51 (m, 3H), 4.54 (d, J = 11.9 Hz, 1H), 7.25–7.39 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 24.0, 24.0, 25.3, 35.2, 36.1, 48.8, 60.7, 63.2, 66.2, 66.9, 70.9, 72.2, 73.2, 76.3, 78.0, 86.2, 86.3, 110.2, 127.6, 127.7, 127.8, 127.8, 127.9, 128.0, 128.0, 128.1, 128.2, 128.5, 128.5, 128.6, 128.6, 128.8, 137.9, 138.0; HRMS calcd for $C_{39}H_{50}NO_8$ [M + H]$^+$ 660.3531, found 660.3531.

*(2R,3R)-Ethyl 2-((2R,3R,4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-3-hydroxy-3-((R)-1,4-dioxaspiro[4.5]decan-2-yl)propanoate (**47B**):* yield 758.5 mg, 24%; R_f = 0.4 (7/3 hexane/EtOAc); $[\alpha]^{28}_{D}$ = −10.46° (c = 2.49, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3396.1, 2923.7, 2854.6, 1725.9, 1601.8, 1452.1, 1368.5, 1093.5, 1025.4; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (t, J = 7.2 Hz), 1.30–1.41 (m, 2H), 1.49–1.63 (m, 8H), 2.84 (dd, J = 5.2 Hz, 6.8 Hz, 1H), 3.41–3.52 (m, 3H), 3.64 (dd, J = 5.2 Hz, 7 Hz, 1H), 3.84–3.87 (m, 1H), 3.91–3.94 (m, 2H), 4.03 (dd, J = 2.5 Hz, 6.7 Hz, 1H), 4.06–4.13 (m, 4H), 4.86–4.60 (m, 7H), 7.26–7.34 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 24.0, 24.1, 25.3, 35.1, 35.8, 49.8, 60.5, 60.8, 61.0, 65.7, 69.8, 70.2, 71.9, 72.5, 73.3, 85.4, 87.0, 110.2, 127.8, 127.8, 127.9, 128.0, 128.5, 128.5, 138.1, 138.2, 138.2, 172.1; HRMS calcd for $C_{39}H_{50}NO_8$ [M + H]$^+$ 660.3531, found 660.3541.

(2*S*,3*S*)-Ethyl 2-((2*R*,3*R*,4*R*,5*R*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-3-hydroxy-3-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)propanoate (48A). This compound was synthesized from **47A** using the procedure followed for obtaining compound **24** from **23**: yield 830 mg, 91%; R_f = 0.5 (9/1 hexane/EtOAc); $[\alpha]^{28}_{D}$ = −4.29° (c = 0.7, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3402.4, 3030.4, 2926.4, 2854.5, 1729.8, 1602.2, 1494.5, 1451.8, 1095.1, 1063.8; ^1H NMR (500 MHz, $CDCl_3$): 1.10 (t, J = 7.2 Hz, 3H), 1.26–1.55 (m, 10H), 2.98 (dd, J = 6.3 Hz, 9.5 Hz, 1H), 2.80–3.35 (m, 1H), 3.50 (dd, J = 4.3 Hz, 9.8 Hz, 1H), 3.56 (dd, J = 6 Hz, 9.8 Hz, 1H), 3.60–3.62 (m, 2H), 3.67–3.70 (m, 1H), 3.82 (dd, J = 6 Hz, 8.3 Hz, 1H), 3.90 (dd, J = 6 Hz, 14 Hz), 3.99–4.13 (m, 4H), 4.17 (d, J = 13.5 Hz, 1H), 4.36 (d, J = 12.0 Hz, 1H), 4.42–4.56 (m, 5H), 4.61 (d, J = 3.5 Hz, 1H), 7.21–7.34 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 23.9, 24.0, 25.2, 35.0, 35.9, 50.2, 51.0, 60.6, 62.7, 65.8, 67.1, 67.6, 71.2, 71.9, 73.2, 73.3, 78.4, 84.8, 85.1,110.3, 127.0, 127.7, 127.8, 128.1, 128.2, 128.4, 128.4, 128.6, 137.2, 138.1, 138.3, 138.6, 171.5; HRMS calcd for $C_{46}H_{56}NO_8$ [M + H]$^+$ 750.4000, found 750.4008.

(2*R*,3*R*)-Ethyl 2-((2*R*,3*R*,4*R*,5*R*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-3-hydroxy-3-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)propanoate (48B). This compound was synthesized from **47B** using the same procedure as was followed to obtain compound **25**: yield 953 mg, 87%; R_f = 0.5 (7/3 hexane/EtOAc); $[\alpha]^{28}_{D}$ = −38.46° (c = 1.56, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3398.7, 2930.7, 2856.6, 1727.3, 1603.5, 1496.5, 1452.9, 1095.4, 1028.2; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3H), 1.30–1.33 (m, 2H), 1.47–1.72 (m, 8H), 3.31 (dd, J = 4.0, 8.0 Hz, 1H), 3.37 (dd, J = 3.2, 10.0 Hz, 1H), 3.53–3.59 (m, 3H), 3.64 (dd, J = 4.2 Hz, 9.4 Hz, 1H), 4.00 (t, J = 7.3 Hz, 1H), 4.05–4.10 (m, 3H), 4.13–4.16 (m, 1H), 4.29 (dd, J = 13.2 Hz, 1H), 4.36–4.46 (m, 7H), 4.54 (d, J = 12.3 Hz, 1H), 7.20–7.32 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 24.1, 25.4, 35.2, 35.5, 43.0, 51.6, 60.8, 62.1, 64.9, 65.1, 69.7, 70.5, 71.0, 72.2, 73.3, 76.6, 82.0, 85.2, 109.9, 127.4, 127.6, 127.7, 127.7, 127.9, 128.0, 128.3, 128.4, 128.4, 128.7, 128.7, 137.1, 137.1, 171.8; HRMS calcd for $C_{46}H_{56}NO_8$ [M + H]$^+$ 750.4000, found 750.4004.

(1*S*,2*R*)-2-((2*R*,3*R*,4*R*,5*R*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)propane-1,3-diol (49A). This compound was synthesized from **48A** using the same procedure as was followed for preparing compound **26**: yield 650 mg, 83%; R_f = 0.6 (6/4 hexane/EtOAc); $[\alpha]^{28}_{D}$ = −28.65° (c = 1.85, CH_2Cl_2), IR (ν_{max}/cm^{-1}) 3403.2, 2930.2, 2856.8, 1602.6, 1494.5, 1451.4, 1095.2, 1027.3; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34–1.66 (m, 10H), 2.19–2.21 (m, 1H), 3.42–3.45 (m, 2H), 3.54 (t, J = 4.9 Hz, 1H), 3.60–3.71 (m, 3H), 3.82 (dd, J = 4.1, 11.8 Hz, 1H), 3.84–3.87 (d, J = 4.3 Hz, 1H), 4.42–4.44 (m, 3H), 4.48 (s, 2H), 4.56 (d, J = 11.8 Hz, 1H), 7.24–7.34 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 24.1, 25.2, 35.1, 36.3, 42.4, 51.7, 61.9, 62.6, 66.3, 66.7, 67.7, 71.5, 71.7, 73.4, 74.1, 83.5, 85.5, 110.1, 127.2, 127.7, 127.7, 127.9, 128.1, 128.1, 128.3, 128.4, 128.5, 128.6, 137.3, 137.9, 138.1, 138.4; HRMS calcd for $C_{44}H_{54}NO_7$ [M + H]$^+$ 708.3895, found 708.3900.

(1*R*,2*S*)-2-((2*R*,3*R*,4*R*,5*R*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)propane-1,3-diol (49B). This compound was synthesized from **48B** using the same procedure as was followed for making of compound **26**: yield 700 mg, 83%, R_f = 0.5 (6/4 hexane/EtOAc); $[\alpha]^{28}_{D}$ = −30.83° (c = 1.2, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3399.0, 2926.8, 2854.7, 1602.6, 1451.2, 1096.4, 1027.3; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26–1.71 (m, 10H), 2.54–2.56 (m, 1H), 3.18 (br s, 1H), 3.30 (t, J = 5.6 Hz, 1H), 3.43 (dd, J = 2.7 Hz, 6.1 Hz, 1H), 3.50 (d, J = 13.5 Hz, 1H), 3.58 (d, J = 5.8 Hz, 2H), 3.67–3.75 (m, 2H), 3.97–4.00 (m, 2H), 4.13–4.15 (m, 2H), 4.24 (dt, J = 2.0, 6.6 Hz, 1H), 4.32–4.36 (m, 3H), 4.39–4.48 (m, 4H), 4.57 (d, J = 12.4 Hz, 1H), 7.22–7.33 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 24.1, 25.3, 35.3, 35.6, 39.7, 51.6, 61.9, 62.5, 64.8, 65.7, 69.5, 70.3, 71.1,73.4, 76.4, 82.4, 85.6, 109.7, 127.3, 127.6, 127.7, 127.8, 128.2, 128.3, 128.5, 128.6, 128.7, 137.1, 137.4, 138.0; HRMS calcd for $C_{44}H_{54}NO_7$ [M + H]$^+$ 708.3895, found 708.3904.

(2*R*,3*R*,4*R*,5*R*)-1-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-((1*S*,2*R*)-1,3-bis(benzyloxy)-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)propan-2-yl)pyrrolidine (50A). This compound was synthesized from **49A** using the same procedure as was followed for synthesizing compound **27**: yield 620 mg, 83%; R_f = 0.6 (9/1 hexane/EtOAc); $[\alpha]^{28}_{D}$ = −31.72° (c = 1.45, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2929.4, 2855.6, 1604.6, 1495.2, 1453.0, 1096.0, 1027.8; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40–1.65 (m, 10H), 2.20–2.22 (m, 1H), 3.39–3.42 (m, 2H), 3.49 (t, J = 8.9 Hz, 1H), 3.63 (t, J = 9.2 Hz, 1H), 3.67–3.70 (m, 2H), 3.89–3.93 (m, 4H), 3.98–4.04 (m, 2H), 4.10 (d, J = 3.7 Hz, 1H), 4.23–4.47 (m, 9H), 4.57 (d, J = 11.0 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 7.24–7.33 (m, 30 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1, 24.2, 25.4, 34.9, 36.4, 41.0, 45.1, 51.1, 62.3, 66.1, 66.4, 67.1, 70.7, 71.7, 73.0, 73.1, 75.1, 79.0, 82.9, 85.5, 109.0, 126.3, 126.5, 126.7, 127.2, 127.5, 127.5, 127.7, 127.9, 127.9, 128.0, 128.2, 128.3, 128.3, 128.4, 128.4, 128.6, 130.6, 138.5, 138.6, 138.7, 138.8, 139.3, 139.8; HRMS calcd for $C_{58}H_{66}NO_7$ [M + H]$^+$ 888.4834, found 888.4837.

(2*R*,3*R*,4*R*,5*R*)-1-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-((1*R*,2*S*)-1,3-bis(benzyloxy)-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)propan-2-yl)pyrrolidine (50B). This compound was synthesized from **49B** using the same procedure as was followed for obtaining compound **27**: yield 675 mg, 82%; R_f = 0.6 (9/1 hexane/EtOAc); $[\alpha]^{28}_{D}$ = −15.5° (c = 2.0, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2926.5, 2855.0, 1602.5, 1494.2, 1452.4, 1095.0, 1026.1; ^1H NMR (500 MHz,

$CDCl_3$) δ 1.27−1.70 (m, 10H), 2.14−2.15 (m, 1H), 3.32−3.34 (m, 1H), 3.38 (dd, *J* = 2.5 Hz, 6.1 Hz, 1H), 3.49−3.57 (m, 4H), 3.69−3.78 (m, 3H), 3.98−4.02 (m, 2H), 4.07−4.09 (m, 1H), 4.30 (d, *J* = 11.9 Hz, 1H), 4.36−4.52 (m, 10H), 4.85 (d, *J* = 11.3 Hz, 1H), 7.13−7.31 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 24.2, 25.4, 35.3, 36.6, 43.2, 51.4, 62.5, 65.1, 66.2, 67.0, 68.0, 71.3, 71.7, 73.2, 74.5, 78.4, 79.5, 83.9, 88.0, 109.7, 126.4, 127.3, 127.6, 127.6, 127.9, 128.1, 128.1, 128.3, 128.4, 128.4, 138.4, 138.5, 138.6, 139.0, 139.8; HRMS calcd for $C_{58}H_{66}NO_7$ $[M + H]^+$ 888.4834, found 888.4835.

(2*R*,3*S*,4*R*)-4-((2*R*,3*R*,4*R*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-3,5-bis(benzyloxy)-pentane-1,2-diol (51A). This compound was synthesized from **49A** using the same procedure as was followed for obtaining compound **28**: yield 435 mg, 80%; R_f = 0.5 (6/4 hexane/EtOAc); $[\alpha]_D^{28}$ = −31.0° (*c* = 2.0, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3395.4, 2920.5, 2853.8, 1602.4, 1494.4, 1452.8, 1067.6, 1023.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30−2.33 (m, 1H), 3.41−3.44 (m, 1H), 3.51−3.54 (m, 2H), 3.64−3.72 (m, 5H), 3.84−3.92 (m, 4H), 4.00 (s, 1H), 4.09 (d, *J* = 4.3 Hz, 1H), 4.24 (d, *J* = 11.3 Hz, 1H), 4.33 (d, *J* = 11.3 Hz), 4.40 (s, 4H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.48−4.51 (m, 4H), 7.23−7.33 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.7, 51.9, 62.8, 64.1, 65.9, 66.2, 67.2, 71.1, 71.6, 71.7, 73.3, 73.8, 79.6, 83.1, 86.1, 126.9, 127.6, 127.7, 127.7, 127.8, 127.9, 127.9, 128.0, 128.2, 128.4, 128.4, 128.5, 128.6, 138.1, 138.2, 138.1, 138.4, 138.5, 139.2; HRMS calcd for $C_{52}H_{58}NO_7$ $[M + H]^+$ 808.4208, found 808.4201.

(2*R*,3*R*,4*S*)-4-((2*R*,3*R*,4*R*)-1-Benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)-3,5-bis(benzyloxy)-pentane-1,2-diol (51B). This compound was synthesized from **50B** using the same procedure as was followed for synthesizing compound **28**: yield 460 mg, 78%; R_f = 0.5 (6/4 hexane/EtOAc); $[\alpha]_D^{28}$ = −22.96° (*c* = 1.35, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3400.4, 2920.1, 2853.6, 1603.7, 1495.5, 1453.4, 1070.7, 1027.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47−2.49 (m, 1H), 3.31−3.35 (m, 1H), 3.49−3.59 (m, 4H), 3.73−3.76 (m, 2H), 3.79−3.86 (m, 2H), 3.89 (d, *J* = 3.4 Hz, 1H), 3.97 (s, 1H), 4.07 (d, *J* = 14.1 Hz, 1H), 4.28 (d, *J* = 11.6 Hz, 1H), 4.33−4.44 (m, 6H), 4.47−4.51 (m, 3H), 4.54 (d, *J* = 11.0 Hz, 1H), 7.13−7.30 (m, 30H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 42.6, 52.4, 62.8, 64.8, 66.2, 66.8, 69.3, 71.1, 71.4, 72.7, 73.3, 73.5, 74.2, 78.4, 83.3, 86.5, 127.1, 127.6, 127.6, 127.7, 127.7, 127.9, 128.0, 128.1, 128.2, 128.2, 128.3, 128.4, 128.5, 128.6, 137.9, 138.2, 138.3, 138.3, 138.4; HRMS calcd for $C_{52}H_{58}NO_7$ $[M + H]^+$ 808.4208, found 808.4205.

(1*R*,2*R*,3*R*,6*R*,7*S*,8*R*,8a*R*)-3,8-Bis(acetoxymethyl)octahydro-indolizine-1,2,6,7-tetrayl Tetraacetate (54A). Compound **51A** (300 mg, 0.371 mmol) was dissolved in dry dichloromethane (5.5 mL), and to this solution was added *p*-toluenesulfonyl chloride (72 mg, 0.41 mmol), dry triethylamine (0.081 mL, 0.556 mmol), and dibutyltin oxide (0.02 mmol) at room temperature. This mixture was stirred for 4 h, and then on completion of the reaction (TLC monitoring), it was diluted with water (5 mL). The organic layer was separated and the aqueous phase washed with dichloromethane (2 × 5 mL) and brine solution and then dried over anhydrous sodium sulfate. The crude product was dissolved in dry methanol (10 mL), to this solution were added $Pd(OH)_2/C$ (180 mg, 60% w/w) and a catalytic amount of tetrabutylammonium iodide (0.2 mmol), and the reaction mixture was stirred under a H_2 atmosphere at 400 psi for 4 days. On complete deprotection of the benzyl groups, the reaction mixture was filtered on Celite and the solvent removed under reduced pressure. The crude product was dissolved in methanol (4 mL), to this solution was added potassium carbonate (204.8 mg, 1.484 mmol), and then this mixture was heated to reflux for 6 h. On completion of reaction (TLC monitoring), the solvent was removed in vacuo and the residue dissolved in 1/1 mixture of acetic anhydride and pyridine (2 mL). The reaction mixture was stirred at room temperature for 48 h, and then the product was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine solution and dried over anhydrous sodium sulfate. The solvent was removed by vacuum evaporation and the crude product purified by column chromatography: yield 90 mg, 46% (over three steps); R_f = 0.6 (2/8 hexane/EtOAc); IR (ν_{max}/cm^{-1}) 3023.4, 2923.5, 1742.5, 1596.2, 1405.2, 1192.3, 1039.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (s, 3H, $-OCOCH_3$), 2.07 (s, 3H, $-OCOCH_3$), 2.12 (s, 6H, $-OCOCH_3$), 2.14 (s, 3H, $-OCOCH_3$), 2.21 (s, 3H, $-OCOCH_3$), 3.35−3.39 (m, H-9), 3.56−3.61 (m, H-5), 3.85 (dd, *J* = 4.0 Hz, 11.6 Hz, H-9′), 3.93−4.00 (m, H-3, H-5′), 4.09 (dd, *J* = 4.9 Hz, 10.1 Hz, H-10), 4.27−4.28 (m, H-8a), 4.37 (dd, *J* = 4.9 Hz, 11.0 Hz, H-10′), 4.99−5.02 (m, H-2, H-7), 5.21−5.23 (m, H-1, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 21.1, 21.2, 23.0, 34.8, 62.0, 62.6, 63.7, 67.2, 67.9, 68.9, 70.6, 75.9; HRMS calcd for $C_{22}H_{32}NO_{12}$ $[M + H]^+$ 502.1919, found 502.1920.

(1*R*,2*R*,3*R*,6*R*,7*R*,8*S*,8a*R*)-3,8-Bis(acetoxymethyl)octahydro-indolizine-1,2,6,7-tetrayl Tetraacetate (54B). Compound **51B** (300 mg, 0.371 mmol) was dissolved in dry dichloromethane (5.5 mL), and to this solution was added *p*-toluenesulfonyl chloride (72 mg, 0.41 mmol), dry triethylamine (0.081 mL, 0.556 mmol), and dibutyltin oxide (0.02 mmol) at room temperature. This mixture was stirred for 4 h, and then on completion of reaction (TLC monitoring), it was diluted with water (5 mL). The organic layer was separated and the aqueous phase washed with dichloromethane (2 × 5 mL) and brine solution and then dried over anhydrous sodium sulfate. The crude product was dissolved in dry methanol (10 mL), to this solution were added $Pd(OH)_2/C$ (180 mg, 60% w/w) and a catalytic amount of tetrabutylammonium iodide (0.2 mmol), and the reaction mixture was stirred under a H_2 atmosphere at 400 psi for 24 h. The pressure of the Parr reactor was elevated to 850 psi, and the reaction was allowed to continue for another 72 h. After completion of the reaction, the catalyst was removed by filtration over Celite and the filtrate was concentrated under vacuum. The crude product was dissolved in acetic anhydride (2 mL), to this solution was added a catalytic amount of $BF_3 \cdot Et_2O$, and the mixture was stirred at room temperature for 24 h. The reaction mixture was neutralized with a saturated solution of sodium bicarbonate, and the product was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine solution and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by column chromatography: yield 90.0 mg, 46% (over three steps); R_f = 0.6 (2:8 hexane/EtOAc); IR (ν_{max}/cm^{-1}) 3023.4, 2923.5, 1742.5, 1596.2, 1405.2, 1192.3, 1039.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.01 (s, 3H, $-OCOCH_3$), 2.02 (s, 3H, $-OCOCH_3$), 2.05 (s, 3H, $-OCOCH_3$), 2.07 (s, 3H, $-OCOCH_3$), 2.10 (s, 6H, $-OCOCH_3$), 2.40−2.44 (m, H-5), 2.61−2.63 (m, H-8), 3.06 (dd, *J* = 1.6, 6.1 Hz, H-8a), 3.28−3.31 (m, H-5′), 3.33−3.35 (m, H-3), 4.16 (dd, *J* = 4.9, 11.9, Hz, H-9), 4.24−4.31 (m, H-9′, H-10), 4.43 (d, *J* = 11.3 Hz, H-10′), 4.78−4.85 (m, H-6, H-7), 4.98 (dd, *J* = 1.7, 2.3 Hz, H-2), 5.35 (dd, *J* = 2.2, 6.4 Hz, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 21.0, 21.1, 21.2, 39.1, 48.5, 59.5, 61,2, 64.6, 65.6, 67.8, 73.2, 77.4, 79.6, 169.7, 170.3, 170.4, 170.6, 171.0; HRMS calcd for $C_{22}H_{32}NO_{12}$ $[M + H]^+$ 502.1919, found 502.1920.

(1*R*,2*R*,3*R*,6*R*,7*S*,8*R*,8a*R*)-3,8-Bis(hydroxymethyl)octahydro-indolizine-1,2,6,7-tetraol (55A). This compound was synthesized from **54A** using a procedure similar to that followed to obtain compound **31**: yield 6.8 mg, 91%; R_f = 0.4 (8/2 EtOAc/MeOH); $[\alpha]_D^{28}$ = −14.0° (*c* = 0.05, MeOH); IR (ν_{max}/cm^{-1}) 3412.5, 2925.2, 2854.2, 1633.0, 1462.0, 1370.0, 1043.6; ^{1}H NMR (400 MHz, D_2O) δ 1.79 (s, OH), 2.28 (br s, 1H), 3.17−3.46 (m, 5H), 3.71−3.80 (m, 5H), 3.95−4.00 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 38.6, 58.1, 61.6, 61.9, 66.5, 67.7, 70.2, 71.8, 74.6, 77.5; HRMS calcd for $C_{10}H_{20}NO_6$ $[M + H]^+$ 250.1285, found 250.1288.

(1*R*,2*R*,3*R*,6*R*,7*R*,8*S*,8a*R*)-3,8-Bis(hydroxymethyl)octahydro-indolizine-1,2,6,7-tetraol (55B). This compound was synthesized from **54B** using a procedure similar to that followed to obtain compound **31**: yield 6.6 mg, 89%; R_f = 0.4 (8/2 EtOAc/MeOH); $[\alpha]_D^{28}$ = −20.0° (*c* = 0.05, MeOH); IR (ν_{max}/cm^{-1}) 3412.0, 2925.4, 2854.5, 1633.2, 1462.1, 1369.8, 1043.2; ^{1}H NMR (400 MHz, D_2O) δ 1.76 (s, OH), 2.11 (br s, 1H), 2.40 (br s, 1H), 2.87−2.88 (m 2H), 3.04−3.05 (m, 1H), 3.45−3.54 (m, 2H), 3.65−3.69 (m, 4H), 3.80−3.82 (m, 1H), 4.02 (br s, 1H); ^{13}C NMR (100 MHz, D_2O) δ 40.8, 51.0, 56.8, 59.1, 65.2, 68.0, 68.1, 72.0, 76.7, 78.6; HRMS calcd for $C_{10}H_{20}NO_6$ $[M + H]^+$ 250.1285, found 250.1286.

General Procedure for Enzyme Inhibition Assay. All of the enzymes and their corresponding substrates have been obtained from Sigma-Aldrich Chemical Co. The inhibition studies of compounds

31−**34** and **55A,B** have been determined by measuring residual hydrolytic activities of the glycosidases. The substrates, i.e. the corresponding *p*-nitrophenyl glycopyranosides, and enzymes were prepared as 0.025 M solutions in the respective pH buffer solutions of the corresponding enzyme. A mixture of 100 μL of enzyme solution, 200 μL of a 1 mg mL^{-1} aqueous solution of the test compound, and 100 μL of the appropriate buffer solution of the optimum pH for the enzyme was incubated at 37 °C for 1 h, after which 100 μL of the substrate solution was added and allowed to react for 10 min. The reaction mixture was quenched using 2.5 mL of 0.05 M borate buffer (pH 9.8). In all cases, a series of control experiments in the absence of test compound and a series of blank experiments without the enzyme or test compounds were run. The absorbance of the liberated *p*-nitrophenol in each reaction (both test and control reactions) was recorded using a spectrophotometer at 405 nm. The ratio of the difference in the observed absorbances of the control and test reactions to the observed absorbance of the control reaction was calculated to obtain the percent inhibition. The corresponding IC_{50} values, which is the concentration of the test compound that causes 50% inhibition of the enzyme, was calculated from the percent inhibition.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H and ^{13}C NMR and additional spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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