JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

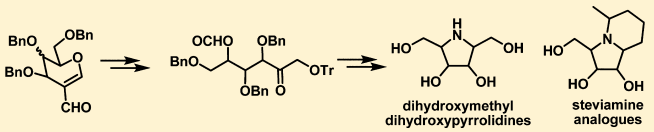
Synthesis of Dihydroxymethyl Dihydroxypyrrolidines and Steviamine Analogues from C-2 Formyl Glycals

Alafia A. Ansari and Yashwant D. Vankar*

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh 208 016, India

Supporting Information

ABSTRACT: Synthesis of dihydroxymethyl dihydroxypyrrolidines from C-2 formyl D-glycals has been described via a common dicarbonyl intermediate. The hence obtained pyrrolidines have been further utilized for the synthesis of some steviamine analogues. The newly synthesized molecules have been evaluated for glycosidase inhibition against 6 commercially available enzymes and found to be active in the micromolar range, where one of the steviamine analogues showed good and selective inhibition of β-mannosidase (*Helix pomatia*).



INTRODUCTION

Iminosugars form an important class of compounds with interesting structures and immense biological significance, especially as glycosidase inhibitors,[1] making them important targets for organic synthesis. Synthesis of naturally occurring monocyclic and bicyclic iminosugars and design and synthesis of their analogues is of utmost importance,[2] since glycosidase inhibitors are useful for the treatment of diseases such as diabetes,[3a] Gaucher's disease,[3b] Fabry's disease,[3b] AIDS,[3c,d] etc. Among the monocyclic iminosugars, numerous 5-, 6-, and 7-membered compounds, either naturally occurring or synthetic, have been reported in the literature as potent glycosidase inhibitors.[4] Further, among 5-membered iminosugars, pyrrolidines such as 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP) **1**, 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) **2**, codonopsinine **3**, and radicamine A **4** (Figure 1) are popular examples of inhibitors.[2a] DMDP **1** was the first pyrrolidine iminosugar to be isolated from natural sources[5a] and is a good inhibitor of both α- and β-glucosidases.[5b] As a consequence, several synthetic routes toward DMDP and its analogues have been reported in the literature.[6]

Among the bicyclic compounds, indolizidines such as lentiginosine **5**, swainsonine **6**, and castanospermine **7** (Figure 2) are of continued interest, owing to their biological importance and therapeutic value.[2d] As a result, several syntheses of these molecules and their analogues have been reported in the literature.[7] More recently, (−)-steviamine **8** has been isolated from the leaves of *Stevia rebaudiana*[8a] and was found to be a good β-galactosidase inhibitor (IC_{50} = 35 μM, rat intestinal lactase) and a weak inhibitor of α-galactosaminidase,[8b] which may provide leads for the treatment of cancer.[8c] This molecule has also attracted the attention of organic chemists, and a few synthesis have been reported in the recent past.[8b,d,e]

In continuation with our efforts in the design and synthesis of new glycosidase inhibitors,[2a,9] we became interested in designing a new general strategy for the synthesis of dihydroxymethyl dihydroxypyrrolidines, to utilize them in the synthesis of steviamine analogues, and to evaluate their glycosidase inhibitory behavior.

RESULTS AND DISCUSSION

C-2 formyl glycals are versatile synthons in organic chemistry,[10a] as has been illustrated in the synthesis of sugar β-amino acids,[10b] iminosugars,[10c,d] potential anticancer[10e] and anti-inflammatory compounds,[10f] and other important intermediates.[10g−j] We envisaged the synthesis of polyhydroxylated pyrrolidines from C-2 formyl glycals, using a simple and efficient strategy as outlined in the retrosynthesis (Scheme 1). The key steps of the synthesis would include dihydroxylation, oxidative cleavage of the resulting diol to ketoformate, followed by reduction and double nucleophilic displacement by amine.

Synthesis of the monocyclic azasugars commenced from 3,4,6-tri-*O*-benzyl-D-glucal **9a** (Scheme 2), which was converted to the vinyl aldehyde **10a**, using the Vilsmeier−Haack reaction.[11,12a] Reduction of **10a** was carried out using sodium borohydride in methanol resulting in the corresponding allylic alcohol **11a**.[12b] The primary hydroxyl group in alcohol **11a** was protected using trityl chloride and triethylamine as a base, giving trityl ether **12a** in 92% yield (Scheme 2). The olefin moiety was now subjected to dihydroxylation using OsO_4 and NMO,[13] giving a mixture of diols **13a** (*dr* = 5.5:1) in almost quantitative yield. The diols were not stable during column chromatography, and hence only a small portion was purified for analytical purpose, by quickly filtering through a short silica gel column and immediate evaporation. The crude mixture was subsequently exposed to oxidative cleavage using sodium metaperiodate in CH_3CN/H_2O (4:1) medium at room temperature. The reaction proceeded to completion in a facile manner, when sodium metaperiodate was added in portions over 2 h, followed by vigorous stirring for 3 h at room temperature to afford compound **14a** in 74% yield (over 2 steps). The keto-formate **14a** typically showed a peak at δ 7.83 in ^{1}H NMR spectrum corresponding to −OC*H*O proton and peaks

Received: July 25, 2013
Published: August 28, 2013

   dx.doi.org/10.1021/jo401613v | *J. Org. Chem.* 2013, 78, 9383−9395

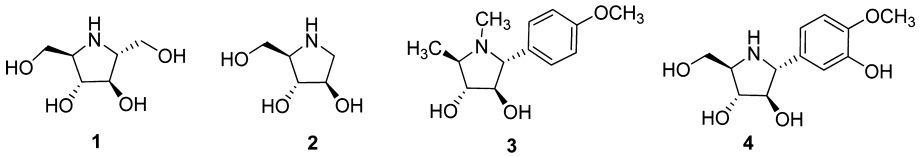


Figure 1. Pyrrolidine glycosidase inhibitors.

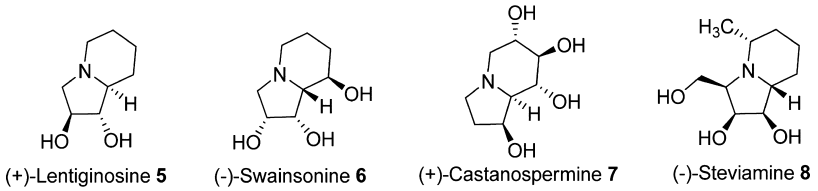
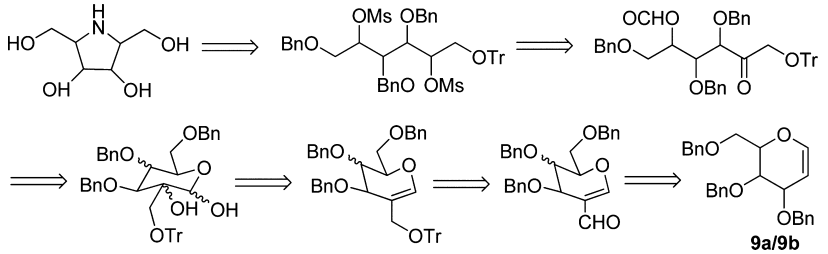
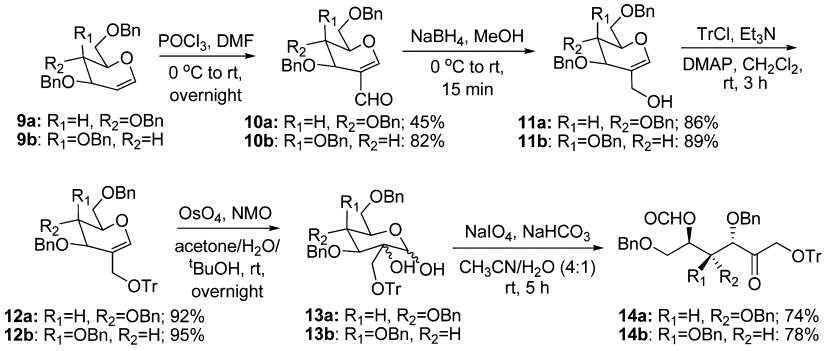


Figure 2. Indolizidine glycosidase inhibitors.

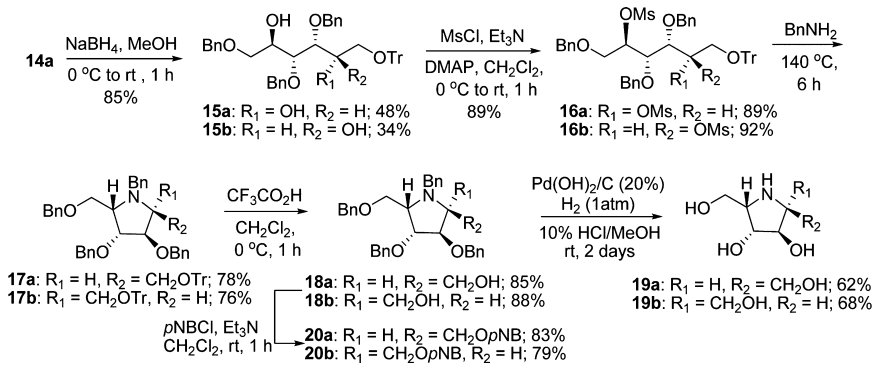
Scheme 1



Scheme 2



Scheme 3



at δ 207 and 160 ppm in ^{13}C NMR spectrum corresponding to ketone and formate groups, respectively.[14] Using the same series of reactions as described above, C-2 formyl galactal **10b**, obtained from 3,4,6-tri-*O*-benzyl-D-galactal **9b**,[11] was converted to ketoformate **14b.**

Compound **14a** was then reduced using $NaBH_4$ in methanol, affording a 1.8:1 mixture of diols **15a** and **15b** (Scheme 3). The diols were chromatographically separated and then converted to compounds **16a** and **16b** using mesyl chloride and triethylamine and a catalytic amount of DMAP at 0 °C. The dimesylates were

dx.doi.org/10.1021/jo401613v | J. Org. Chem. 2013, 78, 9383−9395

then treated with neat benzylamine for double nucleophilic displacements leading to pyrrolidines **17a** and **17b**, respectively. The reaction took place only at around 140 °C, probably because both the mesylate groups are secondary in nature causing sufficient steric hindrance for two displacement reactions. Attempts for double nucleophilic displacement using *tert*-butyl carbamate, benzyl carbamate, or tosylamine failed, possibly because of the reduced nucleophilicity of these amines as compared to benzylamine. The formation of **17a** and **17b** was confirmed by the disappearance of the 2 mesylate peaks at δ 2.9 in ^{1}H NMR spectrum and appearance of 2 characteristic doublets corresponding to $-NCH_2Ph$ at δ 3.9.[14] The trityl protecting group was removed using 3 equiv of trifluoroacetic acid in dichloromethane at 0 °C. The resulting alcohols **18a** and **18b** were then completely deprotected using $Pd(OH)_2/C$ under 1 atm H_2 pressure, in acidic medium for 2 days to obtain **19a**[15a] and **19b**[15b] in 10.4 and 8.4% overall yield from C-2 formyl glucal **10** using simple organic transformations.

The protection of compounds **18a** and **18b** was initially attempted with acetate protecting group in order to study the stereochemistry of the newly generated stereocenters. However, the ^{1}H NMR spectra of the resulting products did not help in stereochemical analysis since the required protons were found to merge with other protons. This problem was overcome by switching to PNB protection. Hence, alcohols **18a** and **18b** were converted to the corresponding *p*-nitrobenzoate analogues **20a** and **20b** using *p*-nitrobenzoyl chloride and triethylamine (Scheme 3). Their stereochemistry was analyzed by ^{1}H NMR, COSY, NOE, and decoupling experiments (Figure 3).[14] (**20a**: NOE experiment of H-5/H-2, H-4/H-2, $J_{2,3}$ = 4.3 Hz; **20b**: NOE experiment of H-2/H-4, H-2/H-5, $J_{2,3}$ = 11.3 Hz)[14]

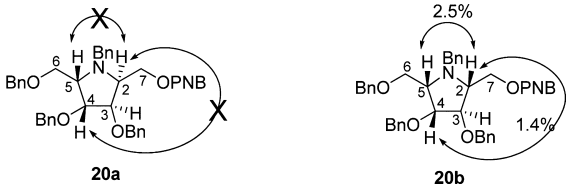


Figure 3. NOE correlations of compounds **20a** and **20b**.

Reduction of **14b** gave a 1.3:1 mixture of diols **21a** and **21b**, as shown in Scheme 4. Following the same sequence of steps as described earlier, viz. mesylation, double nucleophilic displacement using benzyl amine, followed by complete deprotection, pyrrolidines **25a** and **25b** were obtained in 9.5 and 10.6% overall yields, respectively, from D-galactal **9b**.

The alcohols **24a** and **24b** were converted to PNB analogue **26a** and acetate **26b**, respectively, in order to study stereochemistry of new stereocenters (Figure 4) (**26a**: NOE experiment of H-2/H-4, H-2/H-5; **26b**: NOE experiment of H-2/H-4, H-2/H-5; $J_{2,3}$ = 2.8 Hz).[14]

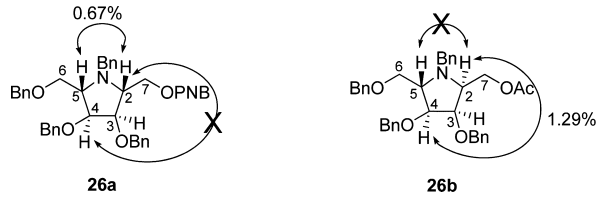
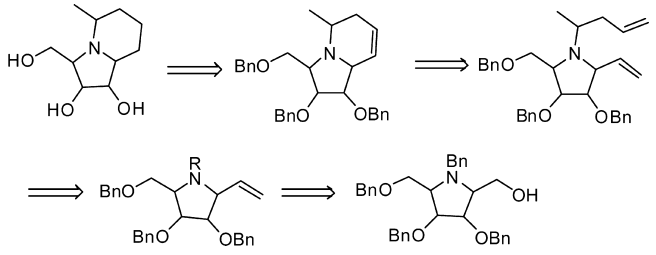


Figure 4. NOE correlations of compounds **26a** and **26b**.

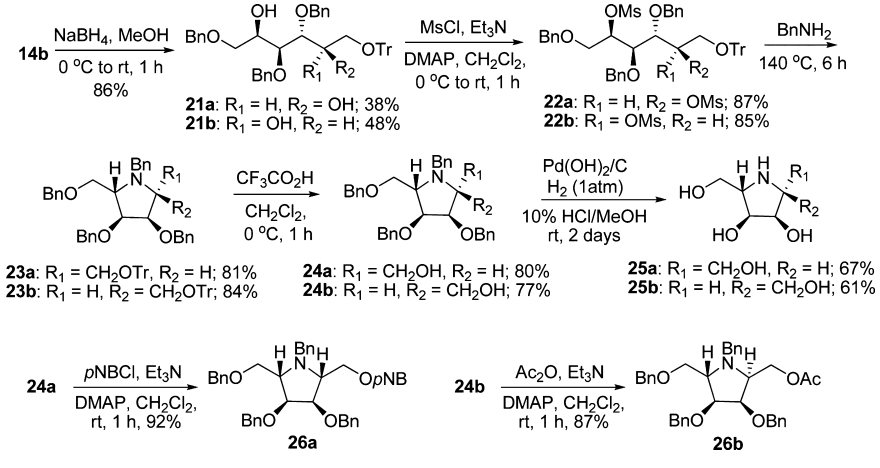
Because of its interesting biological properties, the recently isolated (−)-steviamine **8** has garnered considerable interest among glycochemists and glycobiologists. With this easy and practical synthesis at hand, which allowed us to prepare pyrrolidines in a scalable manner, we next targeted synthesis of steviamine analogues. The retrosynthetic plan is illustrated in Scheme 5. The key steps involved are aza-Michael addition of the secondary amine on crotonaldehyde followed by Wittig olefination and ring closing metathesis.

Scheme 5



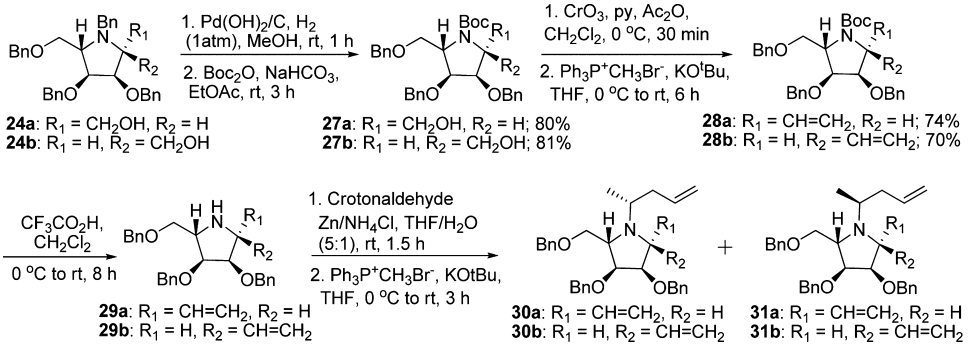
Compounds **24a** and **24b** were converted to Boc amines in order to reduce the nucleophilicity of the amine group for facilitation of further reactions. The benzyl group on the amine was removed successfully using $Pd(OH)_2/C$ and 1 atm H_2

Scheme 4

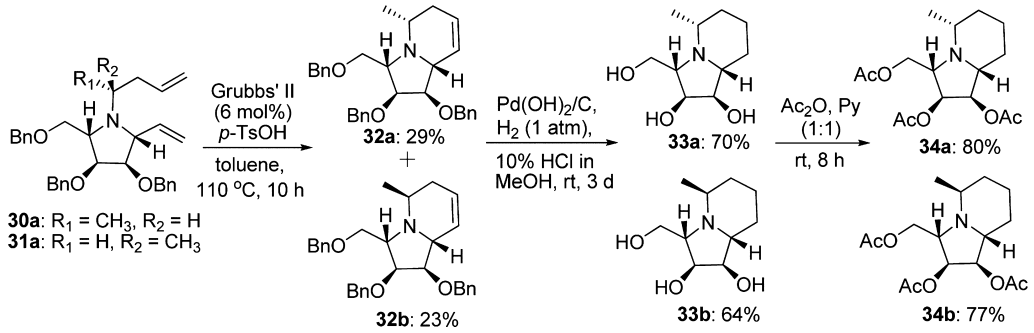


dx.doi.org/10.1021/jo401613v | J. Org. Chem. 2013, 78, 9383−9395

Scheme 6



Scheme 7



(Scheme 6) in just one hour, without affecting any of the benzyl ethers present in the compound.[16] The crude amine was subsequently protected as *tert*-butylcarbamate using Boc_2O in the presence of Na_2CO_3 to obtain **27a** and **27b**. The ^1H NMR spectrum of **27a** and **27b** showed a sharp singlet peak at δ 1.2 ppm, which is characteristic of *tert*-butyl protons, and the ^{13}C NMR spectrum showed peaks at 156 and 30 ppm,[14] corresponding to carbonyl group and *tert*-butyl carbons of carbamate, respectively. Next, the free primary alcohol was oxidized using CrO_3–Py–Ac_2O reagent system,[17] and the resulting aldehyde was subjected to Wittig olefination using methyl triphenylphosphonium bromide and KO^{t}Bu resulting in alkenes **28a** and **28b**. The carbamate protection was then removed using trifluoroacetic acid in dichloromethane at room temperature over 8 h. The free amine so obtained was studied for aza-Michael reaction with crotonaldehyde using different conditions. Addition of bases such as KO^{t}Bu or NaH did not help in conversion even under reflux. The zinc/NH_4Cl system[18] worked best for this reaction in terms of yield, reaction time, and cleaner reaction profile. The reaction furnished the aldehydes, which were unstable and hence immediately converted to dienes **30a**/**31a** and **30b**/**31b** using Wittig salt and KO^{t}Bu. These dienes were chromatographically inseparable at this stage, and hence the mixtures were subjected to ring-closing metathesis reaction.

Ring-closing metathesis of the resulting dienes proved to be a formidable task. Using Grubbs' first or second generation catalyst at room temperature and even reflux in toluene did not give the desired products. However, the mixture of dienes **30a** and **31a** underwent smooth ring-closing metathesis reaction with 6 mol % of Grubbs' second generation catalyst in the presence of 2 equiv of *p*-TsOH,[19] in refluxing toluene, giving the products **32a** and **32b** in 1.2:1 ratio and total 52% yield over 4 steps (Scheme 7). The so obtained cyclized products were easily separable by column chromatography. Each isomer **32a** and **32b** was then subjected to one-pot double bond reduction and deprotection of benzyl groups, using $Pd(OH)_2/C$ in 10% HCl/MeOH under 1 atm H_2 for 3 days to afford steviamine analogues **33a** and **33b** in 70 and 64% yields, respectively.

The free hydroxyl groups were protected as acetates using a 1:1 mixture of acetic anhydride and pyridine over 8 h (Scheme 7), hence affording **34a** and **34b** for stereochemistry studies (Figure 5) (NOE experiments of **34a**: H-8a/H-5, H-8a/H-3; **34b**: H-3/H-5, H-3/H-8a).[14]

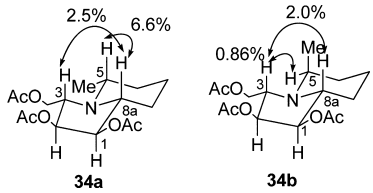


Figure 5. NOE correlations of acetates **34a** and **34b**.

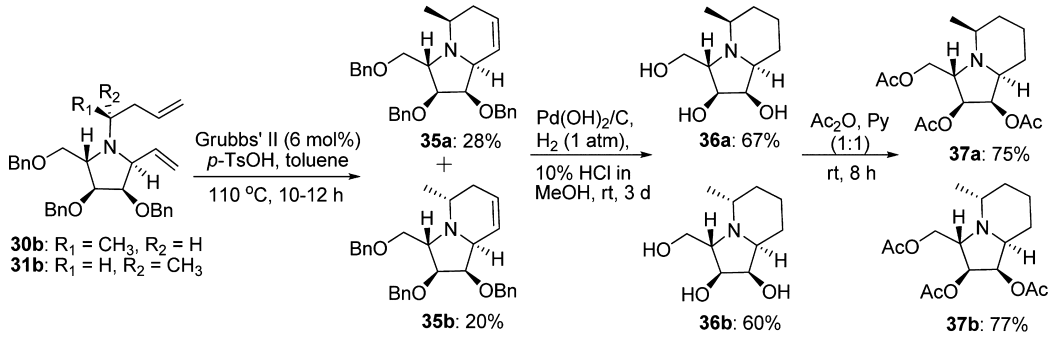
The other mixture of dienes **30b** and **31b** was subjected to ring-closing metathesis (Scheme 8) to obtain ring-closed products **35a** and **35b** in 1.4:1 ratio and total 48% yield over 4 steps. On hydrogenation as shown in Scheme 8, steviamine analogues **36a** and **36b** were obtained.

Again, acetates **37a** and **37b** were prepared from **36a** and **36b**, respectively, to carry out stereochemical studies (Figure 6) (NOE experiments of **34a**: H-8a/H-5, H-5/H-3; **34b**: H-5/H-3, H-5/H-8a).[14]

Inhibition Studies. The synthesized dihydroxymethyl dihydroxypyrrolidines and steviamine analogues were tested against six commercially available enzymes, and the inhibitory values (IC_{50}) are listed in Table 1. Pyrrolidine **19a** showed good activity against β-mannosidase (*Helix pomatia*, IC_{50} = 40 μM), but it was not selective, while pyrrolidine **19b** is already reported

dx.doi.org/10.1021/jo401613v | J. Org. Chem. 2013, 78, 9383–9395

Scheme 8



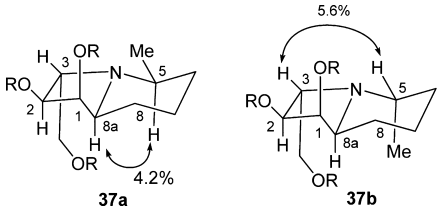


Figure 6. NOE correlations of acetates **37a** and **37b**.

in literature to be a good yet nonselective glycosidase inhibitor.[15b] On the other hand, compounds **25a** and **25b** showed a broad range of inhibition properties. Among steviamine analogues, **33a** and **36a** were found to be good inhibitors of β-mannosidase (*Helix pomatia*) with an IC_{50} of 45.6 and 45.9 μM, respectively, but **36a** was more selective in nature. The inversion of stereochemistry of methyl substituent at C-5 in **36a** and **36b** has proved detrimental to the inhibition against galactosidases. However, steviamine analogues **33a** and **36a** are good inhibitors of β-mannosidase, while **33b** and **36b** do not show inhibition activity. Even though the structure of **33b** is more similar to that of **36a**, the methyl group at C-5 position is equatorially oriented in **33a** and **36a** and axially oriented in **33b** and **36b**, respectively, indicating that axial methyl group could adversely affect mannosidase binding because of more steric hindrance. Hence it is possible that steviamine analogues without methyl group could be better inhibitors. Moreover, all the steviamine analogues except **36a** showed preferable affinity toward galactosidases. This is probably due to the β-configuration of the hydroxyl groups at C-1 and C-2, which is comparable to similar configurations at C-1 and C-2 of (−)-steviamine, a good β-galactosidase inhibitor. Compound **33b**, which differs from (−)-steviamine only in the configuration of hydroxymethyl group at C-3, shows activity toward β-galactosidase from bovine liver, while (−)-steviamine is inactive toward this enzyme.[8d] These results indicate that structural modifications in naturally occurring glycosidase inhibitors can lead to different and/or improved activity.

CONCLUSION

In conclusion, we have devised a new strategy for the construction of pyrrolidine azasugars from C-2 formyl glycals, which has been successfully employed for the synthesis of four dihydroxymethyl dihydroxypyrrolidines viz. **19a**, **19b**, **25a**, and **25b**. This strategy can be further utilized for the preparation of other pyrrolidine azasugars. Further, four novel analogues of steviamine, **33a**, **33b**, **36a**, and **36b** have been synthesized using aza-Michael addition and ring-closing metathesis as key steps. All the molecules obtained were examined for glycosidase inhibition against six commercially available enzymes, of which **36a** was found to be a good and selective β-mannosidase inhibitor, while the other steviamine analogues showed affinity toward galactosidases.

EXPERIMENTAL SECTION

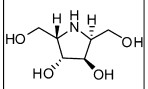
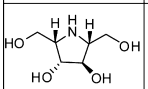
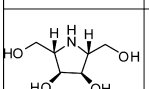
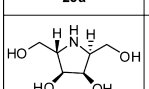
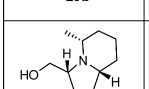
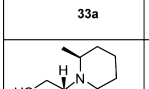
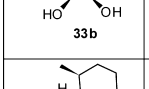
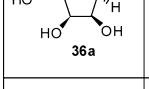
General Experimental Methods. All experiments have been performed in oven-dried apparatus and under nitrogen atmosphere in dry solvents, unless indicated otherwise. Commerical grade solvents were dried by known methods, and dry solvents were stored over 4 Å molecular sieves. IR spectra were recorded as a thin film and expressed in cm^{-1}. High resolution mass spectra were recorded by Q-TOF using electrospray ionization (ESI) method. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded using $CDCl_3$ or D_2O as a solvent. Chemical shifts have been reported in ppm downfield to tetramethylsilane and coupling constants expressed in Hertz (Hz); splitting patterns have been assigned as s (singlet), d (doublet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), quin (quintet), m (multiplet), or br (broad). The NMR peaks of compounds **20a**, **20b**, **26a**, **26b**, **34a**, **34b**, **37a**, and **37b** were assigned with the help of ^1H, COSY, NOE and homonuclear decoupling experiments. Optical rotations were measured at 28 °C in indicated solvents. TLC plates were prepared using thin layers of silica gel on microscopic slides, and visualization of spots was effected by exposure to iodine or spraying with 10% H_2SO_4 and charring. Column chromatography was performed over silica gel (100−200 Mesh) using hexane and ethyl acetate as eluents.

*(2R,3S,4R)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(trityloxymethyl)-3,4-dihydro-2H-pyran (**12a**).* To a stirred solution of alcohol **11a** (1.5 g, 3.37 mmol) in dry CH_2Cl_2 (15 mL) at room temperature under N_2 atmosphere was added Et_3N (1.17 mL, 8.42 mmol), followed by trityl chloride (1.135 g, 4.04 mmol), and a catalytic amount of 4-dimethylaminopyridine (DMAP) (41 mg, 0.38 mmol), and the mixture was stirred for 3 h. On completion of reaction, saturated $NaHCO_3$ solution (10 mL) was added, and the mixture was stirred for 10 min. Extraction was done with CH_2Cl_2 (3 × 10 mL), and combined organic extracts were washed with water (1 × 30 mL) and brine (1 × 30 mL) and then dried over Na_2SO_4. Concentration in vacuo gave a crude residue, which was purified by column chromatography to obtain 2.13g (92%) of **12a** as a colorless thick oil: R_f = 0.7 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = +10.9 (*c* 2.65, CH_2Cl_2); IR (neat) ν_{max} 3030, 2922, 2868, 1667, 1492, 1449, 1088, 1068, 1028, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46−7.44 (m, 6H), 7.32−7.20 (m, 22H), 7.02−7.01 (m, 2H), 6.47 (s, 1H), 4.75 (d, *J* = 11.3 Hz, 1H), 4.64 (d, *J* = 11.3 Hz, 1H), 4.54 (s, 2H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.46 (d, *J* = 11.0 Hz, 1H), 4.38 (d, *J* = 5.2 Hz, 1H), 4.26−4.23 (m, 1H), 3.89 (dd, *J* = 5.5, 7.3 Hz, 1H), 3.77 (dd, *J* = 5.5, 10.6 Hz, 1H), 3.74−3.69 (m, 2H), 3.58 (d, *J* = 10.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 142.8, 138.3, 138.1, 138.0, 128.8, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.5, 127.0, 111.0, 86.8, 76.9, 75.1, 74.3, 73.5, 73.4, 72.6, 68.4, 61.7; HRMS calcd for $C_{47}H_{44}NaO_5$ $[M + Na]^+$ 711.3086, found 711.3080.

*(4S,5R,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-(trityloxymethyl)tetrahydro-2H-pyran-2,3-diol (**13a**).* Compound **12a** (1.5 g, 2.18 mmol) was dissolved in acetone/^{t}BuOH/H_2O (14 mL, 5:1:1). NMO (280 mg, 2.4 mmol) was added to it, followed by a

dx.doi.org/10.1021/jo401613v | J. Org. Chem. 2013, 78, 9383−9395

Table 1. IC_{50} (μM) Values of the Synthesized Compounds against Tested Glycosidases[a]

Compound	E1	E2	E3	E4	E5	E6
 19a	143.8±26.0	NI	108.4±19.6	250.3±15.8	NI	40.0±11.4
 19b	26.8±5.1	60.4±7.1	132.7±8.5	NI	NI	NI
 25a	NI	77.6±11.4	59.9±3.2	NI	NI	103.4±6.7
 25b	NI	NI	76.6±5.4	NI	82.8±7.7	521.8±20.2
 33a	269.2±11.8	NI	116.7±22.6	276.5±25.2	103.3±13.2	45.6±1.7
 33b	416.3±12.3	NI	105.2±13.4	107.8±4.7	85.8±11.5	NI
 36a	NI	NI	NI	812.9±97.1	NI	45.9±2.1
 36b	386.7±10.1	NI	218.0±3.5	412.6±5.3	NI	NI

[a]**E1** = α-glucosidase (Baker's yeast), **E2** = β-glucosidase (almonds), **E3** = α-galactosidase (coffee beans), **E4** = β-galactosidase (bovine liver), **E5** = α-mannosidase (Jack beans), **E6** = β-mannosidase (*Helix pomatia*).

catalytic amount of OsO_4 (0.02 mmol), and the mixture was stirred overnight at room temperature. Saturated sodium metabisulphite (10 mL) was then added to it, and stirring was continued for 1 h, followed by filtration of the reaction mixture through a Celite pad. The filtrate was extracted with ethyl acetate (3 × 15 mL), and combined organic extracts were washed with brine (1 × 30 mL), dried over Na_2SO_4, and concentrated under a vacuum. The crude product was used as such without purification for the next step, while a small portion was taken and purified by passing through a short silica gel column for analytical purpose. Compound **13a** was a thick viscous liquid: R_f = 0.6 (hexane/EtOAc = 2:1); IR (neat) ν_{max} 3405, 3086, 2924, 2878, 1647, 1492, 1449, 1238, 1097; ^{1}H NMR (500 MHz, $CDCl_3$, 5.5:1 mixture of isomers) δ 7.47−7.44 (m, 6H, both isomers), 7.34−7.12 (m, 22H, both isomers), 7.13−7.10 (m, 2H, both isomers), 5.47 (d, J = 2.7 Hz, 1H, major isomer), 5.34 (d, J = 10.7 Hz, 1H, minor isomer), 4.86−4.35 (m, 6H, both isomers), 4.10 (dt, J = 3.3, 9.4 Hz, 1H, major isomer), 4.05−4.01 (m, 1H, minor isomer), 3.96 (d, J = 8.8 Hz, 1H, major isomer), 3.90−3.70 (m, 4H, minor isomer), 3.65−3.48 (m, 4H, major isomer, 1H, minor isomer), 3.51−3.48 (m, 1H, minor isomer), 3.41 (t, J = 9.1 Hz, 1H, major isomer), 3.37−3.31 (m, 1H, both isomers), 3.07 (s, 1H, minor isomer), 2.94 (s, 1H, major isomer); ^{13}C NMR (125 MHz, $CDCl_3$, 5.5:1 mixture of isomers) δ 143.6, 143.3, 143.1, 142.8, 138.6, 138.3, 138.2, 137.9, 128.9−127.2 (m, aromatic C), 100.0, 93.4, 88.8, 87.3, 85.9, 82.2, 80.7, 76.7, 76.5, 76.1, 76.0, 75.9, 75.7, 75.4, 75.1, 74.8, 74.5, 73.3, 70.8, 68.9, 68.6, 63.8, 62.3, 62.0; HRMS (ESI) calcd for $C_{47}H_{46}NaO_7$ $[M + Na]^+$ 745.3141, found 745.3143.

*(2R,3R,4S)-1,3,4-Tris(benzyloxy)-5-oxo-6-(trityloxy)hexan-2-yl formate (**14a**).* The crude diol **13a** was dissolved in CH_3CN/H_2O (4:1) mixture (20 mL). Sodium metaperiodate (1.4 g, 6.54 mmol) was added to the vigorously stirred solution in portions over 2 h at room temperature, followed by stirring for another 3 h. The reaction mixture was then filtered, and the filtrate was extracted with CH_2Cl_2 (3 × 15 mL). Combined organic extracts were washed once with brine (1 × 30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by a short silica gel column to afford 1.17g (74% over 2 steps) of **14a** as a colorless oil: R_f = 0.6 (hexane/EtOAc = 7:3); $[\alpha]_D^{28}$ = +0.8 (c 2.50, CH_2Cl_2); IR (neat) ν_{max} 3031, 2869, 1726, 1596, 1492, 1450, 1169, 1095, 1028, 746, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.48−7.39 (m, 6H), 7.31−7.17 (m, 20H), 7.09−7.07 (m, 2H), 7.05−7.03 (m, 2H), 5.22−5.20 (m, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.41−4.28 (m, 5H), 4.23 (d, J = 2.7 Hz, 1H), 4.19 (d, J = 11.3 Hz, 1H), 4.03 (d, J = 18.0 Hz, 1H), 3.94 (d, J = 18.0 Hz, 1H), 3.77 (dd, J = 2.4, 11.3 Hz, 1H), 3.68 (dd, J = 4.6, 11.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 159.9, 143.3, 137.6, 137.1, 136.4, 128.9, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.3, 87.4, 82.3, 77.4, 74.6, 73.9, 73.3, 71.5, 69.5, 67.8; HRMS (ESI) calcd for $C_{47}H_{44}NaO_7$ $[M + Na]^+$ 743.2985, found 743.2987.

*(2R,3R,4R,5S)-1,3,4-Tris(benzyloxy)-6-(trityloxy)hexane-2,5-diol (**15a**) and (2R,3R,4R,5R)-1,3,4-Tris(benzyloxy)-6-(trityloxy)hexane-*

dx.doi.org/10.1021/jo401613v | J. Org. Chem. 2013, 78, 9383−9395

*2,5-diol (**15b**).* The dicarbonyl compound **14a** (1.12 g, 1.56 mmol) was dissolved in dry MeOH (15 mL) and cooled to 0 °C. Then, $NaBH_4$ (185 mg, 4.88 mmol) was added to the reaction mixture in portions over 15 min, and stirring was continued for 1 h. Subsequently, aq. NH_4Cl (10 mL) was added dropwise to the reaction mixture until the effervescence ceased. Extraction was done using CH_2Cl_2 (3 × 15 mL), and the extracts were washed with brine (1 × 30 mL) and dried over Na_2SO_4. Removal of solvent under a vacuum furnished a crude residue, which was subjected to column chromatography to separate the 2 isomers. **15a**: Yield 540 mg, 48%; R_f = 0.6 (hexane/EtOAc = 2:1); $[\alpha]_D^{28}$ = +25.7 (*c* 0.35, CH_2Cl_2); IR (neat) ν_{max} 3467, 2923, 2867, 1493, 1450, 1089, 1069, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42−7.40 (m, 4H), 7.33−7.22 (m, 24H), 7.09−7.08 (m, 2H), 4.51−4.44 (m, 5H), 4.37 (d, *J* = 10.9 Hz, 1H), 4.07 (br s, 1H), 4.00 (br s, 1H), 3.90 (dd, *J* = 2.1, 7.3 Hz, 1H), 3.79 (dd, *J* = 2.1, 7.3 Hz, 1H), 3.61 (dd, *J* = 3.4, 9.4 Hz, 1H), 3.55 (dd, *J* = 5.2, 9.4 Hz, 1H), 3.41 (dd, *J* = 3.9, 9.4 Hz, 1H), 3.28 (dd, *J* = 5.5, 9.1 Hz, 1H), 2.86 (d, *J* = 4.6 Hz, 1H), 2.79 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 137.9, 137.8, 128.8, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.2, 86.8, 78.1, 77.9, 73.6, 73.4, 71.2, 70.1, 69.9, 64.8; HRMS calcd for $C_{46}H_{46}NaO_6$ $[M + Na]^+$ 717.3192, found 717.3193.

15b: Yield 385 mg, 34%; R_f = 0.6 (hexane/EtOAc = 2:1); $[\alpha]_D^{28}$ = +10.0 (*c* 0.20, CH_2Cl_2); IR (neat) ν_{max} 3428, 2922, 2854, 1492, 1449, 1071, 745, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42−7.40 (m, 6H), 7.32−7.16 (m, 22H), 7.10−7.08 (m, 2H), 4.56−4.46 (m, 5H), 4.37 (d, *J* = 11.3 Hz, 1H), 4.11 (br s, 1H), 4.05 (br s, 1H), 3.92 (dd, *J* = 2.4, 4.8 Hz, 1H), 3.70−3.61 (m, 3H), 3.31 (dd, *J* = 5.8, 9.1 Hz, 1H), 3.12 (dd, *J* = 7.3, 9.1 Hz, 1H), 2.94 (br s, 1H), 2.83 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 138.0, 137.8, 128.7, 128.5, 128.4, 128.0, 127.9, 127.8, 127.3 127.1, 86.8, 78.4, 78.1, 76.8, 74.4, 73.6, 73.5, 71.2, 71.0, 69.7, 64.4; HRMS calcd for $C_{46}H_{46}NaO_6$ $[M + Na]^+$ 717.3192, found 717.3191.

*(2R,3S,4S,5S)-1,3,4-Tris(benzyloxy)-6-(trityloxy)hexane-2,5-diyl dimethanesulfonate (**16a**).* To a stirred solution of diol **15a** (950 mg, 1.37 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C under N_2 atmosphere was added Et_3N (0.95 mL, 6.85 mmol), followed by DMAP (2 mg, 0.02 mmol) and MsCl (0.26 mL, 3.43 mmol). The reaction was allowed to stir at the same temperature for 1 h, following which aq. $NaHCO_3$ (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and combined organic extracts were washed with water (1 × 20 mL) and brine (1 × 20 mL) and then dried over Na_2SO_4. Concentration in vacuo gave an oily residue, which was purified by column chromatography to give 1.03 g (89%) of compound **16a** as a colorless oil: R_f = 0.6 (hexane/EtOAc = 2:1); $[\alpha]_D^{28}$ = +16.0 (*c* 1.75, CH_2Cl_2); IR (neat) ν_{max} 3529, 3031, 2935, 1597, 1493, 1449, 1353, 1174, 1090, 917, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44−7.43 (m, 6H), 7.34−7.23 (m, 20H), 7.20−7.19 (m, 2H), 7.14−7.12 (m, 2H), 5.11 (quin, *J* = 3.7 Hz, 1H), 5.02 (quin, *J* = 3.7 Hz, 1H), 4.54−4.51 (m, 5H), 4.48 (d, *J* = 11.6 Hz, 1H), 3.99 (t, *J* = 4.0 Hz, 1H), 3.92 (t, *J* = 4.0 Hz, 1H), 3.86 (dd, *J* = 2.7, 11.3 Hz, 1H), 3.77 (dd, *J* = 6.7, 11.3 Hz, 1H), 3.58 (dd, *J* = 3.7, 11.0 Hz, 1H), 3.52 (dd, *J* = 7.3, 11.0 Hz, 1H), 2.95 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 137.4, 137.3, 137.2, 128.8, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.3, 87.6, 81.4, 81.3, 78.3, 78.2, 74.3, 74.2, 73.5, 68.7, 62.6, 38.8; HRMS calcd for $C_{48}H_{50}NaO_{10}S_2$ $[M + Na]^+$ 873.2743, found 873.2749.

*(2R,3S,4S,5R)-1,3,4-Tris(benzyloxy)-6-(trityloxy)hexane-2,5-diyl dimethanesulfonate (**16b**).* The same procedure used to convert **15a** to **16a** was employed for 570 mg (0.838 mmol) of **15b** to obtain 668 mg (92%) of **16b** as a thick viscous liquid: R_f = 0.6 (hexane/EtOAc = 2:1); $[\alpha]_D^{28}$ = +4.0 (*c* 1.25, CH_2Cl_2); IR (neat) ν_{max} 3407, 2924, 1597, 144, 1356, 1175, 1089, 970, 913, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.38 (m, 6H), 7.34−7.21 (m, 22H), 7.03−6.99 (m, 2H), 4.91−4.85 (m, 2H), 4.69 (s, 2H), 4.53−4.43 (m, 3H), 4.16 (dd, *J* = 4.2, 6.1 Hz, 1H), 4.01 (d, *J* = 11.3 Hz, 1H), 3.91 (dd, *J* = 3.4, 11.3 Hz, 1H), 3.79 (t, *J* = 3.7 Hz, 1H), 3.70 (dd, *J* = 7.0, 11.3 Hz, 1H), 3.61 (dd, *J* = 2.7, 11.3 Hz, 1H), 3.19 (dd, *J* = 5.2, 11.3 Hz, 1H), 2.96 (s, 3H), 2.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 137.5, 137.3, 137.2, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.3, 87.1, 82.2, 81.7, 78.7, 77.7, 75.2, 74.3, 73.5, 68.7, 62.5, 38.5, 38.4; HRMS calcd for $C_{48}H_{54}NO_{10}S_2$ $[M + NH_4]^+$ 868.3184, found 868.3183.

*(2S,3R,4R,5S)-1-Benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(trityloxymethyl)-pyrrolidine (**17a**).* Compound **16a** (1.03 g, 1.22 mmol) was dissolved in 8 mL of benzylamine and heated up to 140 °C for 6 h. The reaction mixture was cooled to room temperature, and 1 N HCl (15 mL) was added to it. Extraction was done using EtOAc (3 × 10 mL) followed by washing of organic layer with brine and drying over Na_2SO_4. Concentration under a vacuum gave a residue, which was purified by column chromatography to give 1.03 g (78%) of **17a** as a pale yellow oil: R_f = 0.7 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = −12.7 (*c* 0.55, CH_2Cl_2); IR (neat) ν_{max} 3377, 1596, 1449, 1408, 1088, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45−7.43 (m, 6H), 7.35−7.34 (m, 2H), 7.30−7.12 (m, 25H), 6.95−6.94 (m, 2H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.62 (t, *J* = 4.6 Hz, 1H), 4.57−4.48 (m, 4H), 4.29 (t, *J* = 7.3 Hz, 1H), 3.99 (d, *J* = 14.3 Hz, 1H), 3.78 (dd, *J* = 4.6, 9.7 Hz, 1H), 3.57−3.47 (m, 3H), 3.29−3.28 (m, 2H), 3.20 (dd, *J* = 4.6, 11.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 140.1, 138.9, 138.7, 129.1, 128.3, 128.2, 128.0, 127.7, 127.6, 127.4, 126.8, 126.4, 87.7, 83.8, 83.1, 73.4, 72.9, 70.3, 60.8, 59.3, 52.8; HRMS calcd for $C_{53}H_{52}NO_4$ $[M + H]^+$ 766.3896, found 766.3898.

*(2S,3R,4R,5R)-1-Benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(trityloxymethyl)-pyrrolidine (**17b**).* In a similar manner, as described for **17a** above, compound **16b** (665 mg, 0.787 mmol) was converted to pyrrolidine **17b** (460 mg, 0.60 mmol, 76%) as a pale yellow oil: R_f = 0.7 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = +20.0 (*c* 0.35, CH_2Cl_2); IR (neat) ν_{max} 3029, 1493, 1450, 1364, 1093, 1072, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28−7.11 (m, 35H), 4.56−4.50 (m, 2H), 4.38 (s, 2H), 4.30 (d, *J* = 12.0 Hz, 1H), 4.20 (d, *J* = 12.3 Hz, 1H), 3.94−3.85 (m, 3H), 3.74−3.66 (m, 2H), 3.45 (dd, *J* = 4.9, 9.4 Hz, 1H), 3.34−3.31 (m, 1H), 3.13 (dd, *J* = 4.9, 8.3 Hz, 1H), 3.00−2.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 139.4, 138.5, 138.4, 129.3, 128.7, 128.4, 128.3, 128.2, 128.1, 127.7, 127.6, 127.5, 127.4, 126.9, 126.7, 86.4, 82.7, 82.2, 73.3, 71.5, 70.8, 69.7, 65.9, 65.0, 59.7; HRMS calcd for $C_{53}H_{52}NO_4$ $[M + H]^+$ 766.3896, found 766.3898.

*((2S,3R,4R,5S)-1-Benzyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-pyrrolidin-2-yl)methanol (**18a**).* The trityl ether **17a** (800 mg, 1.046 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C under N_2 atmosphere. To this solution was added trifluoroacetic acid (0.40 mL, 5.23 mmol), and the mixture was stirred at the same temperature for 1 h. Solvent was evaporated, and the residue diluted with EtOAc (10 mL) and quenched with satd. $NaHCO_3$ solution (10 mL). The compound was extracted with EtOAc (3 × 10 mL), and the organic layer washed with brine (1 × 25 mL) and dried over Na_2SO_4. Concentration in vacuo gave a residue, which was purified by column chromatography to give 464 mg (85%) of **18a** as a pale yellow oil: R_f = 0.3 (hexane/EtOAc = 3:1); $[\alpha]_D^{28}$ = −20.0 (*c* 1.50, CH_2Cl_2); IR (neat) ν_{max} 3444, 3029, 2864, 1495, 1453, 1363, 1207, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.23 (m, 20H), 4.77 (d, *J* = 11.9 Hz, 1H), 4.63 (d, *J* = 11.9 Hz, 1H), 4.56−4.51 (m, 4H), 4.46 (d, *J* = 14.9 Hz, 1H), 4.22 (t, *J* = 7.0 Hz, 1H), 3.85 (s, 2H), 3.67−3.60 (m, 3H), 3.47 (dd, *J* = 1.8, 10.0 Hz, 1H), 3.39−3.36 (m, 1H), 3.32−3.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 128.5, 128.4, 127.7, 127.6, 127.0, 84.5, 83.2, 77.6, 73.4, 73.0, 72.7, 66.2, 63.5, 60.3, 58.2, 52.7; HRMS calcd for $C_{34}H_{38}NO_4$ $[M + H]^+$ 524.2801, found 524.2803.

*((2R,3R,4R,5S)-1-Benzyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-pyrrolidin-2-yl)methanol (**18b**).* The same method for deprotection of **17a** was used for 710 mg (0.928 mmol) of trityl ether **17b** to obtain 427 mg (88%) of **18b** as a pale yellow oil: R_f = 0.3 (hexane/EtOAc = 3:1); $[\alpha]_D^{28}$ = +20.0 (*c* 0.15, CH_2Cl_2); IR (neat) ν_{max} 3324, 2920, 2851, 1602, 1495, 1453, 1364, 1094, 1027, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 20H), 4.60−4.56 (m, 2H), 4.50−4.47 (m, 2H), 4.43 (s, 2H), 4.04 (t, *J* = 3.3 Hz, 1H), 3.99 (dd, *J* = 3.0, 5.5 Hz, 1H), 3.91 (d, *J* = 14.0 Hz, 1H), 3.78 (d, *J* = 14.0 Hz, 1H), 3.59 (dd, *J* = 6.4, 9.1 Hz, 1H), 3.47−3.44 (m, 2H), 3.40−3.34 (m, 2H), 2.98 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 138.3, 138.2, 138.0, 128.8, 128.5, 128.4, 128.0, 127.8, 127.6, 127.2, 82.7, 81.8, 73.4, 72.2, 72.0, 70.3, 69.7, 65.1, 60.9, 58.4; HRMS calcd for $C_{34}H_{38}NO_4$ $[M + H]^+$ 524.2801, found 524.2795.

*(2S,3R,4R,5S)-2,5-Bis(hydroxymethyl)pyrrolidine-3,4-diol (**19a**).* Compound **18a** (120 mg, 0.23 mmol) was dissolved in 10% HCl/MeOH (3 mL). To this solution was added $Pd(OH)_2/C$ (20% w/w, 30 mg). The solution was degassed and subsequently stirred vigorously under 1 atm of H_2 (balloon) for 2 days, after which it was filtered

dx.doi.org/10.1021/jo401613v | J. Org. Chem. 2013, 78, 9383−9395

through a Celite pad and washed with MeOH. The solvent was evaporated, and the residue dissolved in 5 mL of MeOH and passed through Amberlite IRA 120 (H^+) resin. The eluent was evaporated, and residue washed repeatedly with EtOAc/Hexane (1:1) to obtain 23 mg (62%) of **19a**. Spectral data was found to be identical with the data reported in the literature.[15a]

*(2S,3R,4R,5R)-2,5-Bis(hydroxymethyl)pyrrolidine-3,4-diol (**19b**).* Using the same procedure for complete deprotection of **18a** to **19a**, **18b** (100 mg, mmol) gave 68% (21 mg) of **19b** as a pale yellow oil. Data was found to be matching with the literature report.[15b]

*((2S,3R,4S,5S)-1-Benzyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-pyrrolidin-2-yl)methyl 4-nitrobenzoate (**20a**).* To a solution of alcohol **18a** (60 mg, 0.115 mmol) in dry CH_2Cl_2 (2 mL) under N_2 at room temperature was added 4-nitrobenzoyl chloride (32 mg, 0.172 mmol) along with Et_3N (0.05 mL, 0.344 mmol) and a catalytic amount of DMAP, following which the reaction mixture was stirred for 1 h. The reaction was then treated with satd. $NaHCO_3$ solution (2 mL) and extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic extracts were washed with H_2O (1 × 5 mL) and brine (1 × 5 mL) and finally dried over Na_2SO_4. The solvent was evaporated, and the residue purified by column chromatography to afford 64 mg (83%) of **20a** as a colorless oil: R_f = 0.6 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = −12.0 (*c* 0.50, CH_2Cl_2); IR (neat) ν_{max} 2918, 2854, 1723, 1605, 1526, 1495, 1453, 1346, 1272, 1101, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19−8.17 (m, 2H, Ar*H*), 8.04−8.02 (m, 2H, Ar*H*), 7.31−7.19 (m, 20H, Ar*H*), 4.71−4.49 (m, 8H, H-7, H-7′, $-OCH_2Ph$), 4.35−4.31 (m, 1H, H-3), 4.24−4.20 (m, 1H, H-4), 4.07 (dd, *J* = 3.0, 14.3 Hz, 1H, $-NCH_2Ph$), 3.89 (dd, *J* = 2.7, 14.3 Hz, 1H, $-NCH_2Ph$), 3.69−3.60 (m, 2H, H-2, H-6), 3.48 (dt, *J* = 2.7, 9.8 Hz, 1H, H-6′), 3.30 (td, *J* = 3.0, 6.4 Hz, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 150.4, 139.4, 138.5, 138.4, 138.3, 135.9, 130.6, 128.4, 128.3, 128.1, 127.7, 127.6, 127.5, 127.4, 126.9, 123.5, 83.2, 82.6, 73.5, 73.0, 72.6, 67.1, 64.2, 60.7, 58.8, 53.0; HRMS calcd for $C_{41}H_{41}N_2O_7$ [M + H]$^+$ 673.2914, found 673.2912.

*((2R,3R,4S,5S)-1-Benzyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-pyrrolidin-2-yl)methyl 4-nitrobenzoate (**20b**).* Using the same procedure as described for protection of **18a**, alcohol **18b** (45 mg, 0.086 mmol) was converted to its *p*NB ester **20b** (46 mg, 79%), which was a colorless oil: R_f = 0.6 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = +23.0 (*c* 0.65, CH_2Cl_2); IR (neat) ν_{max} 3029, 2919, 2857, 1724, 1606, 1527, 1495, 1453, 1346, 1271, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14−8.12 (m, 2H, Ar-*H*), 7.94−7.92 (m, 2H, Ar-*H*), 7.32−7.19 (m, 20H, Ar-*H*), 4.54−4.46 (m, 5H, $-OCH_2Ph$), 4.41 (d, *J* = 12.3 Hz, 1H, $-OCH_2Ph$), 4.22 (dd, *J* = 8.0, 11.3 Hz, 1H, H-3), 4.08−4.02 (m, 3H, H-4, H-7, H-7′), 3.87−3.83 (m, 2H, $-NCH_2-$), 3.78 (dd, *J* = 7.7, 9.1 Hz, 1H, H-6), 3.51 (dd, *J* = 4.9, 9.1 Hz, 1H, H-6′), 3.45 (t, *J* = 4.9, 7.4 Hz, 1H, H-5), 3.25−3.22 (m, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 150.4, 139.5, 138.4, 138.2, 137.9, 135.6, 130.7, 128.9, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 127.2, 123.4, 82.5, 82.3, 73.5, 72.7, 71.1, 69.7, 68.3, 66.3, 59.7; HRMS calcd for $C_{41}H_{41}N_2O_7$ [M + H]$^+$ 673.2914, found 673.2911.

*(2R,3R,4R)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(trityloxymethyl)-3,4-dihydro-2H-pyran (**12b**).* Following the same procedure for the preparation of **12a** from **11a**, compound **12b** (3.20 g, 95%) was obtained from **11b** (2.18 g, 4.90 mmol) as a colorless oil: R_f = 0.6 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = +16.4 (*c* 2.20, CH_2Cl_2); IR (neat) ν_{max} 3030, 2870, 1665, 1492, 1450, 1090, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47−7.46 (m, 6H), 7.36−7.23 (m, 22H), 7.16 (br s, 2H), 6.39 (s, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 11.4 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.55−4.49 (m, 2H), 4.44−4.41 (m, 2H), 4.35 (br s, 1H), 4.02 (s, 1H), 3.84−3.80 (m, 1H), 3.75 (d, *J* = 10.3 Hz, 1H), 3.68 (d, *J* = 8.9 Hz, 1H), 3.58 (d, *J* = 10.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 142.2, 138.7, 138.3, 138.1, 128.8, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 127.0, 111.0, 86.8, 75.9, 73.5, 73.4, 73.2, 72.5, 71.6, 68.4, 62.0; HRMS calcd for $C_{47}H_{44}NaO_5$ [M + Na]$^+$ 711.3086, found 711.3086.

*(4S,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-(trityloxymethyl)tetrahydro-2H-pyran-2,3-diol (**13b**).* The method for dihydroxylation of **12a** to **13a** was used for compound **12b** (3.20 g, 4.65 mmol). Compound **13b** was a thick colorless viscous liquid: R_f = 0.6 (hexane/EtOAc = 2:1); IR (neat) ν_{max} 3423 (br), 3061, 2925, 1493, 1449, 1064 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 4.4:1 mixture of isomers) δ 7.34−7.12 (m, 28H, both isomers), 6.97−6.95 (m, 2H, both isomers), 5.41 (s, 1H, major isomer), 5.23 (d, *J* = 10.7 Hz, 1H, minor isomer), 4.75−4.56 (m, 3H, both isomers), 4.53−4.38 (m, 2H, major isomer, 3H, minor isomer), 4.33−4.28 (m, 1H, both isomers), 4.25−4.18 (m, 1H, both isomers), 4.05 (d, *J* = 6.1 Hz, 1H, minor isomer), 3.98 (d, *J* = 10.4 Hz, 1H, major isomer), 3.83−3.80 (m, 2H, major isomer, 1H, minor isomer), 3.75 (dd, *J* = 1.2, 3.0 Hz, 1H, minor isomer), 3.63 (d, *J* = 10.4 Hz, 1H, major isomer), 3.58−3.53 (m, 2H, both isomers), 3.48−3.45 (m, 1H, minor isomer), 3.38 (s, 1H, major isomer), 3.20 (s, 1H, major isomer), 2.55 (d, *J* = 7.0 Hz, 1H, minor isomer); ^{13}C NMR (125 MHz, $CDCl_3$, 5.5:1 mixture of isomers) δ 143.6, 142.8, 138.8, 138.7, 138.6, 138.0, 137.9, 128.7−127.1 (m, aromatic C), 100.8, 94.0, 88.6, 87.3, 82.6, 78.4, 75.8, 75.2, 75.0, 74.7, 74.5, 73.9, 73.6, 73.4, 71.4, 69.5, 69.1, 68.7, 68.2, 63.1, 62.1; HRMS (ESI) calcd for $C_{47}H_{46}NaO_7$ [M + Na]$^+$ 745.3141, found 745.3143.

*(2R,3S,4S)-1,3,4-Tris(benzyloxy)-5-oxo-6-(trityloxy)hexan-2-yl formate **14b**.* The same procedure for oxidative cleavage of **13a** to **14a** was followed for crude **13b** to afford **14b** (2.61 g, 78% after 2 steps) as a viscous liquid: R_f = 0.6 (hexane/EtOAc = 7:3); $[\alpha]_D^{28}$ = −7.1 (*c* 1.40, CH_2Cl_2); IR (neat) ν_{max} 3061, 3031, 2924, 2870, 1728, 1493, 1451, 1173, 1098, 737, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.40−7.39 (m, 6H), 7.27−7.20 (m, 22H), 7.10−7.06 (m, 30H), 5.34 (d, *J* = 4.2 Hz, 1H), 4.48 (dd, *J* = 2.4, 11.3 Hz, 1H), 4.44 (dd, *J* = 2.1, 11.3 Hz, 1H), 4.40 (br s, 2H), 4.35−4.33 (m, 2H), 4.14 (dd, *J* = 2.4, 4.9 Hz, 1H), 4.11−4.09 (m, 1H), 4.04 (dd, *J* = 2.7, 18.0 Hz, 1H), 3.98 (dd, *J* = 2.7, 18.0 Hz, 1H), 3.65 (ddd, *J* = 2.4, 5.2, 10.7 Hz, 1H), 3.57 (ddd, *J* = 2.4, 4.3, 10.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 160.5, 143.3, 137.5, 137.4, 136.7, 128.8−127.1 (m, aromatic), 87.4, 81.0, 78.2, 74.5, 73.2, 72.7, 72.3, 69.7, 68.2; HRMS calcd for $C_{47}H_{44}NaO_7$ [M + Na]$^+$ 743.2985, found 743.2982.

*(2R,3S,4R,5R)-1,3,4-Tris(benzyloxy)-6-(trityloxy)hexane-2,5-diol **21a** and (2R,3S,4R,5S)-1,3,4-Tris(benzyloxy)-6-(trityloxy)hexane-2,5-diol (**21b**).* The procedure followed for the reduction of compound **14a** was followed for 2.60 g (3.62 mmol) of **14b**, to provide **21a** and **21b**, which were separated by column chromatography.

21a: Yield 950 mg, 38%; R_f = 0.4 (hexane/EtOAc = 7:3); $[\alpha]_D^{28}$ = −2.2 (*c* 1.85, CH_2Cl_2); IR (neat) ν_{max} 3435, 3060, 2925, 2870, 1597, 1493, 1449, 1397, 1323, 1210, 1073, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44−7.42 (m, 6H), 7.35−7.21 (m, 22H), 7.08−7.06 (m, 2H), 4.74 (d, *J* = 11.3 Hz, 1H), 4.63 (d, *J* = 11.0 Hz, 1H), 4.55−4.51 (m, 2H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.31 (d, *J* = 10.7 Hz, 1H), 4.09−4.01 (m, 2H), 3.96 (dd, *J* = 1.2, 7.6 Hz, 1H), 3.78 (dd, *J* = 1.8, 7.6 Hz, 1H), 3.55 (dd, *J* = 6.4, 9.4 Hz, 1H), 3.46 (dd, J = 6.1, 9.4 Hz, 1H), 3.39 (dd, *J* = 6.1, 9.1 Hz, 1H), 3.12 (dd, *J* = 7.3, 8.8 Hz, 1H), 2.51 (d, *J* = 7.3 Hz, 1H), 2.39 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 138.0, 137.8, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.1, 86.9, 77.5, 74.6, 74.5, 73.4, 71.5, 69.8, 69.5, 64.6; HRMS calcd for $C_{46}H_{46}NaO_6$ [M + Na]$^+$ 717.3192, found 717.3198.

21b: Yield 1.19 g, 48%; R_f = 0.3 (hexane/EtOAc = 7:3); $[\alpha]_D^{28}$ = −7.7 (*c* 2.85, CH_2Cl_2); IR (neat) ν_{max} 3432, 3060, 2926, 2871, 1597, 1492, 1449, 1397, 1212, 1074, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43−7.41 (m, 6H), 7.30−7.21 (m, 22H), 7.06−7.05 (m, 2H), 4.64−4.59 (m, 2H), 4.51−4.44 (m, 3H), 4.38 (d, *J* = 11.0 Hz, 1H), 4.08−4.04 (m, 2H), 3.87 (t, *J* = 3.5 Hz, 1H), 3.78 (dd, *J* = 3.7, 7.0 Hz, 1H), 3.57−3.50 (m, 2H), 3.45 (dd, *J* = 3.0, 9.7 Hz, 1H), 3.28 (dd, *J* = 6.7, 9.7 Hz, 1H), 3.19 (br s, 1H), 2.85 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 138.0, 137.8, 128.8, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.1, 86.8, 80.5, 77.9, 73.8, 73.7, 73.4, 71.1, 70.8, 70.2, 64.9;HRMS calcd for $C_{46}H_{46}NaO_6$ [M + Na]$^+$ 717.3192, found 717.3195.

*(2R,3R,4S,5R)-1,3,4-Tris(benzyloxy)-6-(trityloxy)hexane-2,5-diyl dimethanesulfonate (**22a**).* The diol **21a** (950 mg, 1.37 mmol) was converted to dimesylate using the same method as for **15a** to **16a**, to afford 1.01 g (87%) of **22a** as a colorless oil: R_f = 0.3 (hexane/EtOAc = 7:3); $[\alpha]_D^{28}$ = −8.1 (*c* 2.65, CH_2Cl_2); IR (neat) ν_{max} 3400, 3061, 2934, 2874, 1597, 1492, 1449, 1357, 1175, 1095, 917 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41−7.39 (m,6H), 7.34−7.22 (m, 22H), 7.17−7.15 (m, 2H), 5.03 (br s, 1H), 4.79−4.76 (m, 2H), 4.66 (d, *J* = 11.0 Hz, 1H), 4.61 (d, *J* = 11.0 Hz, 1H), 4.47−4.40 (m, 3H), 4.20 (dd, *J* = 2.7, 6.1 Hz, 1H), 3.87−3.81 (m, 2H), 3.73−3.71 (m, 2H), 3.27 (dd, *J* = 5.1, 11.6 Hz, 1H), 2.91 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1,

dx.doi.org/10.1021/jo401613v | J. Org. Chem. 2013, 78, 9383−9395

137.4, 137.3, 128.8−127.4 (m, aromatic C), 87.4, 81.5, 81.4, 77.9, 77.8, 74.7, 74.5, 73.5, 69.7, 63.6, 38.7, 38.4; HRMS calcd for $C_{48}H_{50}NaO_{10}S_2$ $[M + Na]^+$ 873.2743, found 873.2748.

*(2R,3R,4S,5S)-1,3,4-Tris(benzyloxy)-6-(trityloxy)hexane-2,5-diyl dimethanesulfonate (**22b**).* The diol **21b** (1.15 g, 1.66 mmol) was converted to dimesylate using the same method as for **15a** to **16a**, to afford 1.19 g (85%) of **22b** as a colorless oil: R_f = 0.3 (hexane/EtOAc = 7:3); $[\alpha]_D^{28}$ = −0.4 (*c* 2.35, CH_2Cl_2); IR (neat) ν_{max} 3433, 3030, 2934, 2874, 1597, 1449, 1356, 1174, 1092, 917 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41−7.38 (m, 6H), 7.33−7.21 (m, 22H), 7.17−7.14 (m, 2H), 5.20−5.18 (m, 1H), 5.09 (dd, *J* = 5.2, 8.8 Hz, 1H), 4.60 (d, *J* = 11.0 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.52−4.49 (m, 3H), 4.43 (d, *J* = 10.6 Hz, 1H), 3.96−3.92 (m, 2H), 3.80 (dd, *J* = 5.8, 11.0 Hz, 1H), 3.74 (dd, *J* = 3.7, 11.3 Hz, 1H), 3.55 (dd, *J* = 2.4, 11.3 Hz, 1H), 3.47 (dd, *J* = 6.7, 11.0 Hz, 1H), 2.98 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 137.2, 137.1, 128.7−127.3 (m, aromatic C), 87.3, 81.4, 80.8, 77.6, 77.5, 75.1, 73.7, 72.7, 69.5, 63.1, 39.2, 38.6; HRMS calcd for $C_{48}H_{50}NaO_{10}S_2$ $[M + Na]^+$ 873.2743, found 873.2747.

*(2S,3S,4R,5R)-1-Benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(trityloxymethyl)pyrrolidine (**23a**).* The procedure for double nucleophilic displacement as used for **16a** to **17a** was followed for 1.00 g (1.18 mmol) of **22a**, to obtain 728 mg (81%) of **23a** as a yellow liquid: R_f = 0.6 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = −9.2 (*c* 1.20, CH_2Cl_2); IR (neat) ν_{max} 3397, 3029, 1598, 1493, 1449, 1088, 1061, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42−7.36 (m, 6H), 7.30−7.17 (m, 29H), 4.48−4.41 (m, 4H), 4.32 (s, 2H), 3.97 (d, *J* = 13.5 Hz, 1H) 3.86 (d, *J* = 13.5 Hz, 1H), 3.75−3.72 (m, 2H), 3.30−3.19 (m, 4H), 3.02−2.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 139.7, 138.6, 138.4, 129.4, 128.8, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 127.4, 126.9, 86.5, 78.1, 78.0, 73.1, 71.9, 71.2, 66.7, 66.0, 64.7, 59.9; HRMS calcd for $C_{53}H_{52}NO_4$ $[M + H]^+$ 766.3896, found 766.3891.

*(2S,3S,4R,5S)-1-Benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(trityloxymethyl)pyrrolidine (**23b**).* The procedure for double nucleophilic displacement as used for **16a** to **17a** was followed for 1.19 g (1.40 mmol) of **22b**, to obtain 902 mg (84%) of **23b** as a yellow liquid: R_f = 0.6 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = +3.6 (*c* 1.10, CH_2Cl_2); IR (neat) ν_{max} 3401, 3029, 2918, 2862, 1597, 1493, 1450, 1204, 1090, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.37 (m, 6H), 7.28−7.18 (m, 29H), 4.50−4.42 (m, 4H), 4.34 (br s, 2H), 3.99 (d, *J* = 13.1 Hz, 1H), 3.88 (d, *J* = 13.1 Hz, 1H), 3.77−3.73 (m, 2H), 3.31−3.21 (m, 4H), 3.03−2.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 138.6, 138.5, 129.4, 128.8, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 127.4, 126.9, 86.5, 78.1, 78.0, 73.1, 71.9, 71.2, 66.7, 66.0, 64.7, 59.9; HRMS calcd for $C_{53}H_{52}NO_4$ $[M + H]^+$ 766.3896, found 766.3899.

*((2R,3R,4S,5S)-1-Benzyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-pyrrolidin-2-yl)methanol (**24a**).* Using the procedure for deprotection of trityl ether in **17a** to give **18a**, compound **24a** (390 mg, 80%) was obtained from trityl ether **23a** (715 mg, 0.935 mmol), as a pale yellow oil: R_f = 0.5 (hexane/EtOAc = 3:2); $[\alpha]_D^{28}$ = −8.2 (*c* 2.05, CH_2Cl_2); IR (neat) ν_{max} 3205, 3031, 1670, 1454, 1202, 1133 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44−7.21 (m, 20H), 4.72 (d, *J* = 12.5 Hz, 1H), 4.59−4.53 (m, 3H), 4.49−4.43 (m, 3H), 4.29 (d, *J* = 12.8 Hz, 1H), 4.13 (dd, *J* = 4.2, 7.9 Hz, 1H), 4.10−4.08 (m, 1H), 3.90 (dd, *J* = 8.2, 10.4 Hz, 1H), 3.83 (td, *J* = 3.0, 7.9 Hz, 1H), 3.71 (dd, *J* = 3.0, 10.1 Hz, 1H), 3.63 (br s, 1H), 3.59−3.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 137.3, 131.2, 129.0, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 78.3, 73.6, 72.6, 68.1, 61.8, 59.0; HRMS calcd for $C_{34}H_{38}NO_4$ $[M + H]^+$ 524.2801, found 524.2802.

*((2S,3R,4S,5S)-1-Benzyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-pyrrolidin-2-yl)methanol (**24b**).* Using the procedure for deprotection of trityl ether in **17a** to give **18a**, compound **24b** (446 mg, 77%) was obtained from trityl ether **23b** (850 mg, 1.11 mmol), as a pale yellow oil: R_f = 0.5 (hexane/EtOAc = 3:2). $[\alpha]_D^{28}$ = +24.3 (*c* 0.70, CH_2Cl_2); IR (neat) ν_{max} 3424, 3292, 2865, 1601, 1494, 1453, 1117, 1045, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.20 (m, 20H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.51−4.42 (m, 3H), 4.14−4.09 (m, 2H), 4.01 (d, *J* = 6.1 Hz, 1H), 3.97−3.93 (m, 2H), 3.76 (br s, 2H), 3.45 (dd, *J* = 3.4, 7.1 Hz, 1H), 3.37 (dd, *J* = 3.7, 9.7 Hz, 1H), 3.27−3.24 (m, 1H), 3.21 (dd, *J* = 7.4, 9.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1, 138.3, 138.1, 137.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.4, 126.9, 78.9, 77.8, 73.4, 71.8, 71.3, 67.8, 61.6, 58.4, 52.7; HRMS calcd for $C_{34}H_{38}NO_4$ $[M + H]^+$ 524.2801, found 524.2802.

*(2S,3S,4R,5R)-2,5-Bis(hydroxymethyl)pyrrolidine-3,4-diol (**25a**).* The same method for complete deprotection of **18a** to **19a** was followed for **24a** (95 mg, 0.18 mmol), affording 20 mg (67%) of **25a** as a yellow liquid: R_f = 0.4 (MeOH/EtOAc = 1:4); $[\alpha]_D^{28}$ = +21.3 (*c* 0.40, CH_3OH). IR (neat) ν_{max} 3349, 3062, 1237, 1100, 1028 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.21−4.20 (m, 1H), 4.14 (dd, *J* = 4.0, 9.1 Hz, 1H), 3.88−3.82 (m, 2H), 3.77 (dd, *J* = 8.3, 12.0 Hz, 1H), 3.71 (dd, *J* = 5.7, 12.6 Hz, 1H), 3.63 (ddd, *J* = 3.4, 4.9, 8.3 Hz, 1H), 3.51 (ddd, *J* = 3.4, 5.7, 9.1 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 71.2, 70.1, 62.2, 61.7, 58.1, 57.5; HRMS calcd for $C_6H_{14}NO_4$ $[M + H]^+$ 164.0923, found 164.0922.

*(2S,3S,4R,5S)-2,5-Bis(hydroxymethyl)pyrrolidine-3,4-diol (**25b**).* The same method for complete deprotection of **18a** to **19a** was followed for **24b** (105 mg, 0.20 mmol), affording 21 mg (61%) of **25b** as a yellow liquid: R_f = 0.4 (MeOH/EtOAc = 1:4); $[\alpha]_D^{28}$ = +7.5 (*c* 0.80, CH_3OH); IR (neat) ν_{max} 3344, 3062, 1100, 1025 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.27 (dd, *J* = 3.0, 4.2 Hz, 1H), 4.19 (s, 1H), 3.93−3.87 (m, 2H), 3.81−3.72 (m, 2H), 3.65 (br s, 1H), 3.57 (ddd, *J* = 3.0, 5.8, 7.8 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 71.9, 70.6, 62.7, 62.2, 58.6, 57.9; HRMS calcd for $C_6H_{14}NO_4$ $[M + H]^+$ 164.0923, found 164.0918.

*((2R,3R,4S,5S)-1-Benzyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-pyrrolidin-2-yl)methyl-4-nitrobenzoate (**26a**).* In the same way as **18a** was converted to **20a**, compound **24a** (45 mg, 0.086 mmol) was transformed to **26a** (53 mg, 92%), which was a colorless oil: R_f = 0.6 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = +27.5 (*c* 3.35, CH_2Cl_2); IR (neat) ν_{max} 3375, 3029, 2862, 1725, 1606, 1526, 1453, 1347, 1273, 1101, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10−8.09 (m, 2H, Ar*H*), 7.94−7.92 (m, 2H, Ar*H*), 7.34−7.14 (m, 20H, Ar*H*), 4.64−4.55 (m, 3H, −OCH_2Ph), 4.47 (dd, *J* = 4.5, 11.5 Hz, 1H, H-7), 4.35−4.30 (m, 2H, −OCH_2Ph), 4.23 (d, *J* = 12.0 Hz, 1H, −OCH_2Ph), 4.18 (dd, *J* = 3.7, 11.5 Hz, 1H, H-7′), 4.02 (d, *J* = 8.0 Hz, 1H, −NCH_2Ph), 3.95−3.94 (m, 1H, H-4), 3.86−3.81 (m, 2H, H-3, −NCH_2Ph), 3.46−3.43 (m, 1H, H-2), 3.26−3.23 (m, 1H, H-5), 3.04 (dd, *J* = 4.3, 9.7 Hz, 1H, H-6), 2.98 (dd, *J* = 7.4, 9.7 Hz, 1H, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 150.4, 139.2, 138.3, 138.2, 137.8, 135.6, 130.6, 129.0, 128.4, 128.3, 128.0, 127.8, 127.6, 127.4, 127.2, 123.4, 77.9, 77.0, 73.1, 71.5, 71.0, 66.8, 65.2, 64.7, 59.4; HRMS calcd for $C_{41}H_{41}N_2O_7$ $[M + H]^+$ 673.2914, found 673.2917.

*((2S,3R,4S,5S)-1-Benzyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-pyrrolidin-2-yl)methyl acetate (**26b**).* The alcohol **24b** (40 mg, 0.076 mmol) was dissolved in dry CH_2Cl_2 (2 mL). To this solution was added Et_3N (0.012 mL, 0.09 mmol), Ac_2O (0.02 mL, 0.19 mmol), and a catalytic amount of DMAP, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with satd. $NaHCO_3$ solution, followed by extraction with CH_2Cl_2 (3 × 2 mL). Organic layer was then washed with H_2O (1 × 5 mL) and brine (1 × 5 mL) and then dried over Na_2SO_4. Concentration in vacuo gave a residue, which was purified by column chromatography to yield (37 mg, 87%) of **26b** as a colorless oil: R_f = 0.4 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = +7.5 (*c* 0.80, CH_2Cl_2); IR (neat) ν_{max} 3062, 3029, 2860, 1739, 1453, 1237, 1100, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.19 (m, 20H, Ar*H*), 4.68−4.54 (m, 5H, −OCH_2Ph, H-7), 4.44−4.39 (m, 3H, H-7′, −OCH_2Ph), 4.10−4.03 (m, 2H, H-3, −NCH_2Ph), 3.94−3.91 (m, 2H, H-4, −NCH_2Ph), 3.55 (td, *J* = 2.7, 7.0 Hz, 1H, H-2), 3.30 (dd, *J* = 8.2, 14.3 Hz, 1H, H-6), 3.23−3.19 (m, 2H, H-5, H-6′), 1.85 (s, 3H, OCOCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 140.1, 138.8, 138.4, 138.3, 128.4−126.8 (m, aromatic), 79.8, 78.3, 73.3, 72.1, 71.8, 70.6, 66.6, 63.1, 60.7, 53.4, 21.1; HRMS calcd for $C_{36}H_{40}NO_5$ $[M + H]^+$ 566.2906, found 566.2903.

*(2S,3S,4R,5R)-tert-Butyl 3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(hydroxymethyl)pyrrolidine-1-carboxylate (**27a**).* Compound **24a** (870 mg, 1.66 mmol) was dissolved in dry CH_3OH (10 mL), and $Pd(OH)_2/C$ (20% w/w, 44 mg) was added to it. The mixture was degassed and then vigorously stirred under 1 atm of H_2 pressure (balloon) for 1 h. On complete consumption of starting material (TLC monitoring), the reaction mixture was filtered through Celite. Filtrate was evaporated to obtain the crude amine, which was used without purification for the next step.

dx.doi.org/10.1021/jo401613v | J. Org. Chem. 2013, 78, 9383−9395

The amine was dissolved in EtOAc (8 mL). To this solution were added Boc_2O (0.42 mL, 1.83 mmol) and solid Na_2CO_3 (528 mg, 4.98 mmol), and the mixture was stirred for 3 h at room temperature. The reaction mixture was then diluted with EtOAc (5 mL) followed by addition of H_2O (8 mL). It was then extracted with EtOAc (3 × 5 mL), washed with brine (1 × 15 mL), and dried over Na_2SO_4. Evaporation of solvent gave a residue, which on column chromatography afforded 708 mg (80%) of **27a** as a colorless oil: R_f = 0.6 (hexane/EtOAc = 7:3); $[\alpha]_D^{28}$ = +5.1 (*c* 2.15, CH_2Cl_2); IR (neat) ν_{max} 3447, 2928, 2867, 1694, 1496, 1454, 1394, 1365, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 1.7:1 mixture of rotamers) δ 7.32−7.29 (m, 13H, both rotamers), 7.25−7.22 (m, 2H, both rotamers), 4.55−4.53 (m, 3H, both rotamers), 4.46−4.41 (m, 3H, both rotamers), 4.21 (br s, 1H, major rotamer), 4.11−3.97 (m, 2H, both rotamers), 3.90−3.86 (m, 2H major rotamer, 3H minor rotamer), 3.75 (br s, 1H, major rotamer), 3.50−3.45 (m, 2H, both rotamers), 3.02 (br s, 1H, minor rotamer), 1.47−1.40 (m, 9H, both rotamers); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 138.0, 137.7, 137.0, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.6, 80.6, 80.3, 78.2, 78.0, 77.8, 77.5, 73.4, 71.9, 71.7, 68.6, 68.4, 64.4, 63.0, 61.8, 61.4, 28.4; HRMS calcd for $C_{32}H_{40}NO_6$ $[M + H]^+$ 534.2850, found 534.2853.

*(2S,3S,4R,5S)-tert-Butyl 3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(hydroxymethyl)pyrrolidine-1-carboxylate (**27b**).* The same procedure employed for the preparation of **27a** from **24a** was used for the conversion of **24b** (950 mg, mmol) to give **27b** (785 mg, 81%) as a colorless oil: R_f = 0.6 (hexane/EtOAc = 7:3); $[\alpha]_D^{28}$ = +27.5 (*c* 2.40, CH_2Cl_2); IR (neat) ν_{max} 3455, 2974, 2928, 2867, 1693, 1496, 1454, 1391, 1366, 1255, 1113, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.34−7.25 (m, 13H, both rotamers), 7.23−7.21 (m, 2H, both rotamers), 4.74−4.66 (m, 1H, both rotamers), 4.55−4.48 (m, 5H, both rotamers), 4.45−4.40 (m, 2H, both rotamers), 4.28 (dd, *J* = 4.5, 8.0 Hz, 1H, one rotamer), 4.25 (dd, *J* = 4.5, 8.5 Hz, 1H, one rotamer), 4.16−4.09 (m, 3H, both rotamers), 4.05−3.97 (m, 2H, both rotamers), 3.94 (dd, *J* = 2.5, 6.5 Hz, 1H, one rotamer), 3.88−3.85 (m, 1H, one rotamer), 3.82 (dd, *J* = 4.0, 9.5 Hz, 1H, one rotamer), 3.61 (dd, *J* = 3.0, 10.0 Hz, 1H, one rotamer), 3.56−3.28 (m, 1H, both rotamers), 3.46−3.44 (m, 1H, one rotamer), 3.36 (dd, *J* = 7.0, 9.5 Hz, 1H, one rotamer), 1.47 (s, 9H, one rotamer), 1.40 (s, 9H, one rotamer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 154.2, 138.2, 137.8, 137.6, 137.5, 137.0, 128.5−127.5 (m, aromatic), 80.5, 80.3, 78.7, 77.2, 73.4, 72.3, 72.1, 71.9, 71.8, 69.3, 68.6, 61.8, 61.7, 60.9, 60.8, 59.5, 59.3, 28.5, 28.4; HRMS calcd for $C_{32}H_{40}NO_6$ $[M + H]^+$ 534.2850, found 534.2856.

*(2S,3S,4R,5R)-tert-Butyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-vinylpyrrolidine-1-carboxylate (**28a**).* To a well-stirred, ice-cooled suspension of CrO_3 (210 mg, 2.10 mmol) in dry CH_2Cl_2 (5 mL), under N_2 atmosphere, was added Ac_2O (0.40 mL, 4.19 mmol), and pyridine (0.67 mL, 8.38 mmol). After stirring for 15 min, alcohol **27a** (700 mg, 1.31 mmol) dissolved in dry CH_2Cl_2 (3 mL) was added at 0 °C, and the mixture was stirred with gradual warming to room temperature over 1 h. On completion of reaction (TLC monitoring), the reaction mixture was quickly passed through a short silica gel column and washed down with EtOAc (25 mL). Concentration of eluent gave crude aldehyde, which was used as such without purification for the next step.

To a stirred suspension of methyl triphenylphosphonium bromide (1.029 g, 2.88 mmol) in dry THF (3 mL) under N_2 atmosphere, was added potassium *tert*-butoxide (368 mg, 3.28 mmol), and the mixture was stirred at room temperature for half an hour. The formation of ylide was indicated by a bright yellow colored solution. Then the aldehyde dissolved in dry THF (2 mL) was added dropwise to this mixture at 0 °C. Stirring was continued over 3 h, following which the contents were poured into cold water (5 mL). The extraction was done using EtOAc (3 × 5 mL), and combined organic extracts were washed with brine (1 × 10 mL). Drying over Na_2SO_4 and concentration in vacuo gave a crude residue, which was purified by column chromatography, to yield 515 mg of **28a** (74%, over 2 steps) as a colorless oil: R_f = 0.7 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = −1.3 (*c* 0.75, CH_2Cl_2); IR (neat) ν_{max} 3331, 2976, 2929, 1692, 1453, 1391, 1105 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 3.5:1 mixture of rotamers) δ 7.36−7.18 (m, 15H, both rotamers), 6.14−6.07 (m, 1H, major rotamer), 5.70 (br s, 1H, minor rotamer), 5.32−5.05 (m, 1H, both rotamers), 4.75−4.40 (7H, both rotamers), 4.31 (t, *J* = 8.5 Hz, 1H, major rotamer), 4.15−4.11 (m, 1H, both rotamers), 4.06 (d, *J* = 4.0 Hz, 1H, minor rotamer), 4.02 (d, *J* = 4.0 Hz, 1H, major rotamer), 3.95 (dd, *J* = 2.7, 6.7 Hz, 1H, minor rotamer), 3.79 (br s, 1H, minor rotamer), 3.65−3.47 (m, 2H, major rotamer), 3.34−3.30 (m, 1H, minor rotamer), 1.41 (br s, 9H, major rotamer), 1.38 (s, 9H, minor rotamer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 138.3, 138.0, 136.0, 135.3, 128.5−127.5 (m, aromatic), 118.5, 117.9, 80.0, 79.9, 78.7, 78.0, 77.7, 73.2, 72.2, 71.7, 71.5, 69.5, 68.7, 62.6, 61.9, 61.7, 61.5, 53.5, 28.5, 28.4; HRMS calcd for $C_{33}H_{40}NO_5$ $[M + H]^+$ 530.2901, found 530.2901.

*(2S,3S,4R,5S)-tert-Butyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-vinylpyrrolidine-1-carboxylate (**28b**).* In a similar manner as described above for **28a**, compound **28b** (535 mg, 70%) was obtained from **27b** (770 mg, 1.44 mmol) as a colorless oil: R_f = 0.7 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = +14.2 (*c* 0.85, CH_2Cl_2); IR (neat) ν_{max} 3332, 2976, 2928, 2867, 1694, 1454, 1408, 1392, 1366, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 2.5:1 mixture of rotamers) δ 7.37−7.25 (m, 13H, both rotamers), 7.20−7.18 (m, 2H, both rotamers), 6.15−6.07 (m, 1H, both rotamers), 5.34−5.16 (m, 2H, both rotamers), 4.75−4.40 (m, 6H major rotamer, 7H minor rotamer), 4.32 (t, *J* = 8.5 Hz, 1H, major rotamer), 4.16−4.12 (m, 2H major rotamer, 1H, minor rotamer), 4.07 (d, *J* = 4.0 Hz, 1H, minor rotamer), 4.03 (d, *J* = 4.0 Hz, 1H, major rotamer), 3.95 (dd, *J* = 2.5, 6.5 Hz, 1H, minor rotamer), 3.59 (dd, *J* = 2.5, 9.5 Hz, 1H, major rotamer), 3.54 (dd, *J* = 2.5, 9.5 Hz, 1H, minor rotamer), 3.48 (dd, *J* = 6.5, 9.5 Hz, 1H, major rotamer), 3.32 (dd, *J* = 7.0, 9.5 Hz, 1H, minor rotamer), 1.42 (s, 9H, major rotamer), 1.39 (s, 9H, minor rotamer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 153.5, 138.5, 138.3, 138.2, 138.0, 137.9, 136.0, 135.3, 128.5−127.5 (m, aromatic), 118.6, 118.0, 80.0, 79.9, 78.6, 77.9, 77.6, 73.3, 73.2, 72.1, 71.7, 71.6, 71.5, 69.5, 68.7, 62.6, 61.9, 61.7, 61.4, 28.5; HRMS calcd for $C_{33}H_{40}NO_5$ $[M + H]^+$ 530.2901, found 530.2904.

General Procedure for the Aza-Michael Reaction and Wittig Olefination Followed by Ring-Closing Metathesis to Obtain Compounds 32a, 32b, 35a, and 35b. An amine **28a** or **28b** (600 mg, 1.13 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C, CF_3COOH (0.26 mL, 3.39 mmol) was added, and the mixture was stirred with gradual warming to room temperature for 8 h. Once the starting material was consumed (TLC monitoring), the solvent was evaporated, and the crude amine used as such for the next reaction. The crude amine was dissolved in THF (2 mL), crotonaldehyde (0.18 mL, 2.26 mmol) was added, and to this solution Zn (368 mg, 5.65 mmol) and saturated NH_4Cl solution (5 mL) were added, and the mixture was stirred vigorously for 3 h. The reaction mixture was then diluted with EtOAc (5 mL) and washed with water (1 × 10 mL). Extraction with EtOAc (3 × 5 mL) and evaporation of the solvent gave crude aldehydes, which were used without purification for the Wittig reaction.

To a stirred suspension of methyl triphenyl phosphonium bromide (887 mg, 2.49 mmol) in dry THF (3 mL) under N_2 at room temperature was added KO^{t}Bu (390 mg, 3.40 mmol), and the mixture was stirred for 1 h. To the resulting bright yellow mixture was added the crude aldehyde dissolved in dry THF (2 mL), and the mixture was stirred for 2 h. The reaction mixture was poured into ice−water and extracted with EtOAc (3 × 5 mL). Organic extracts were dried and concentrated. The crude diene mixture was dissolved in dry toluene under N_2 atmosphere, and to this solution was added Grubbs' second generation catalyst (58 mg, 0.067 mmol) and *p*TSA (440 mg, 2.26 mmol), and the mixture was heated to 100−110 °C, for 10−12 h. The solvent was removed by evaporation, and the residue purified by column chromatography.

*(1R,2S,3S,5R,8aR)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-5-methyl-1,2,3,5,6,8a-hexahydroindolizine (**32a**).* Yield 29% (148 mg), colorless oil: R_f = 0.7 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = +23.3 (*c* 1.50, CH_2Cl_2); IR (neat) ν_{max} 2922, 1697, 1640, 1454, 1363, 1206, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.25 (m, 15H), 5.97−5.90 (m, 1H), 5.81−5.73 (m, 1H), 4.71−4.63 (m, 2H), 4.57−4.50 (m, 2H), 4.42 (s, 2H), 4.06 (dt, *J* = 2.4, 6.7 Hz, 1H), 3.89 (dd, *J* = 2.4, 5.8 Hz, 1H), 3.51 (dd, *J* = 6.7, 9.8 Hz, 1H), 3.07 (dd, *J* = 5.5, 9.1 Hz, 1H), 2.77−2.71 (m, 1H), 2.25−2.12 (m, 3H), 1.68 (br s, 1H), 1.05−1.04 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.1, 136.7, 135.7, 128.5, 128.3, 127.9, 127.8, 127.7, 127.6, 119.1, 115.5, 85.2, 82.5, 71.9, 71.6, 71.0, 57.5, 53.3, 32.3; HRMS calcd for $C_{31}H_{35}NNaO_3$ $[M + Na]^+$ 492.2515, found 492.2516.

dx.doi.org/10.1021/jo401613v | *J. Org. Chem.* 2013, 78, 9383−9395

*(1R,2S,3S,5S,8aR)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-5-methyl-1,2,3,5,6,8a-hexahydroindolizine (**32b**).* Yield 23% (118 mg), colorless oil: R_f = 0.7 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = +41.0 (*c* 2.20, CH_2Cl_2); IR (neat) ν_{max} 2922, 1695, 1638, 1496, 1454, 1363, 1206, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.25 (m, 15H), 5.91−5.88 (m, 1H), 5.82−5.78 (m, 1H), 4.71−4.68 (m, 2H), 4.63−4.52 (m, 3H), 4.48 (s, 2H), 4.35 (dd, *J* = 2.4, 6.5 Hz, 1H), 4.26 (dd, *J* = 3.1, 8.2 Hz, 1H), 3.92 (br s, 1H), 3.50 (dd, *J* = 6.7, 9.8 Hz, 1H), 3.39 (d, *J* = 11.2 Hz, 1H), 3.14 (d, *J* = 11.2 Hz, 1H), 2.50 (dd, *J* = 5.5, 8.2 Hz, 1H), 2.25 (*J* = 5.5, 8.2 Hz, 1H), 1.15−1.14 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.2, 136.5, 135.8, 128.5, 128.3, 127.9, 127.8, 127.7, 127.6, 121.2 119.6, 82.3, 81.3, 71.9, 71.6, 71.0, 57.6, 53.5, 32.3; HRMS calcd for $C_{31}H_{35}NNaO_3[M + Na]^+$ 492.2515, found 492.2512.

*(1R,2S,3S,5S,8aS)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-5-methyl-1,2,3,5,6,8a-hexahydroindolizine (**35a**).* Yield 28% (144 mg), colorless oil: R_f = 0.7 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = −4.8 (*c* 1.40, CH_2Cl_2); IR (neat) ν_{max} 2922, 1695, 1638, 1496, 1454, 1363, 1206, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.22 (m, 15H), 5.91−5.88 (m, 1H), 5.82−5.78 (m, 1H), 4.49−4.34 (m, 7H), 4.18−4.13 (m, 2H), 4.01−3.99 (m, 2H), 3.91−3.87 (m, 1H), 3.84 (dd, *J* = 4.0, 8.6 Hz, 1H), 3.39 (dd, *J* = 2.8, 10.3 Hz, 1H), 3.32−3.30 (m, 1H), 1.15−1.14 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.7, 136.4, 136.2, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.6, 127.4, 127.3, 126.6, 108.7, 85.6, 83.5, 74.8, 73.4, 69.3, 58.1, 51.9, 34.7; HRMS calcd for $C_{31}H_{35}NNaO_3[M + Na]^+$ 492.2515, found 492.2511.

*(1R,2S,3S,5R,8aS)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-5-methyl-1,2,3,5,6,8a-hexahydroindolizine (**35b**).* Yield 20% (103 mg), colorless oil: R_f = 0.7 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = −11.5 (*c* 0.90, CH_2Cl_2); IR (neat) ν_{max} 2925, 1698, 1640, 1495, 1453, 1361, 1208, 1095 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.22 (m, 15H), 5.91−5.84 (m, 2H), 4.27−4.09 (m, 4H), 3.92−3.70 (m, 7H), 3.12 (dt, *J* = 2.1, 5.2 Hz, 1H), 3.06 (dd, *J* = 8.7, 14.3 Hz, 1H), 2.84−2.78 (m, 1H), 2.28−2.24 (m, 1H), 1.10−1.08 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 138.0, 136.5, 135.8, 128.5, 128.3, 127.9, 127.8, 127.7, 127.6, 115.5, 114.0, 84.2, 82.6, 71.9, 71.3, 57.5, 53.3, 32.9; HRMS calcd for $C_{31}H_{35}NNaO_3[M + Na]^+$ 492.2515, found 492.2517.

*(1R,2S,3S,5R,8aR)-3-(Hydroxymethyl)-5-methyloctahydroindolizine-1,2-diol (**33a**).* Compound **32a** (40 mg, 0.085 mmol) was dissolved in dry CH_3OH (2 mL), and $Pd(OH)_2/C$ (8 mg, 20% w/w) was added. The mixture was stirred under 1 atm of H_2 (balloon) overnight, following which 1 N HCl (1 mL) was added, and subsequently the mixture was stirred under 1 atm of H_2 for 2 days. The catalyst was filtered through a Celite bed and washed with MeOH. The solvent was removed under a vacuum, and residue washed repeatedly with hexane. The compound was purified by washing with excess of 50% EtOAc/Hexane solution. The solvent was decanted, and the residue left behind was dried under a vacuum to afford pure compound **33a** (12 mg, 70%) as a pale yellow liquid: R_f = 0.3 (EtOAc); $[\alpha]_D^{28}$ = −2.2 (*c* 0.40, CH_3OH). IR (neat) ν_{max} 3349, 3062, 1237, 1100, 1028 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.20−4.19 (m, 2H), 4.02−4.00 (m, 2H), 3.90 (dd, *J* = 8.5, 11.3 Hz, 1H), 3.46−3.44 (m, 1H), 2.62 (br s, 1H), 1.77 (br s, 2H), 1.65−1.56 (m, 4H), 1.28−1.26 (m, 3H); ^{13}C NMR (125 MHz, D_2O) δ 77.1, 70.2, 62.6, 62.3, 56.5, 46.2, 28.3, 26.4, 23.2, 9.4; HRMS calcd for $C_{10}H_{20}NO_3$ $[M + H]^+$ 202.1443, found 202.1437.

*(1R,2S,3S,5S,8aR)-3-(Hydroxymethyl)-5-methyloctahydroindolizine-1,2-diol (**33b**).* Following the same procedure for **33a**, compound **33b** was obtained from **32b** (32 mg, 0.068 mmol), in 64% yield (9 mg), as a pale yellow liquid: R_f = 0.3 (EtOAc); $[\alpha]_D^{28}$ = −7.9 (*c* 0.20, CH_3OH). IR (neat) ν_{max} 3353, 3060, 1420, 1232, 1101, 1029 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.04 (br s, 1H), 3.65−3.64 (m, 2H), 3.58−3.56 (m, 2H), 3.41 (d, *J* = 13.7 Hz, 1H), 3.25−3.20 (m, 1H), 1.80−1.55 (m, 5H), 1.46 (br s, 1H), 1.25−1.23 (m, 3H); ^{13}C NMR (125 MHz, D_2O) δ 77.2, 70.7, 62.1, 60.6, 57.6, 47.5, 29.2, 26.1, 20.8, 10.2; HRMS calcd for $C_{10}H_{20}NO_3$ $[M + H]^+$ 202.1443, found 202.1437.

*(1R,2S,3S,5S,8aS)-3-(Hydroxymethyl)-5-methyloctahydroindolizine-1,2-diol (**36a**).* Using the procedure employed to obtain **33a**, compound **36a** was obtained from **35a** (45 mg, 0.096 mmol), in 67% yield (13 mg), as a pale yellow liquid: R_f = 0.3 (EtOAc); $[\alpha]_D^{28}$ = +3.1 (*c* 0.55, CH_3OH). IR (neat) ν_{max} 3353, 3060, 1420, 1232, 1101, 1029 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.25−4.22 (m, 1H), 4.06 (br s, 1H), 3.77−3.74 (m, 2H), 3.49 (br s, 1H), 3.17 (br s, 1H), 2.02 (br s, 1H), 1.77−1.49 (m, 6H), 1.07−1.06 (m, 3H); ^{13}C NMR (125 MHz, D_2O) δ 77.9, 72.5, 63.9, 59.7, 57.0, 43.9, 29.6, 25.7, 22.5, 14.3; HRMS calcd for $C_{10}H_{20}NO_3$ $[M + H]^+$ 202.1443, found 202.1441.

*(1R,2S,3S,5R,8aS)-3-(Hydroxymethyl)-5-methyloctahydroindolizine-1,2-diol (**36b**).* Following the same procedure for **33a**, compound **36b** was obtained from **35b** (28 mg, 0.059 mmol), in 60% yield (7 mg), as a colorless oil: R_f = 0.3 (EtOAc); $[\alpha]_D^{28}$ = −2.2 (*c* 0.40, CH_3OH). IR (neat) ν_{max} 3351, 3064, 1229, 1101, 1027 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.20−4.19 (m, 2H), 4.02−3.85 (m, 3H), 3.41−3.37 (m, 1H), 2.69 (br s, 1H), 1.90−1.75 (m, 2H), 1.65−1.56 (m, 4H), 1.28−1.26 (m, 3H); ^{13}C NMR (125 MHz, D_2O) δ 76.9, 70.1, 62.6, 62.3, 56.5, 46.2, 28.3, 26.4, 23.2, 11.2; HRMS calcd for $C_{10}H_{20}NO_3$ $[M + H]^+$ 202.1443, found 202.1440.

*(1R,2S,3S,5R,8aR)-3-(Acetoxymethyl)-5-methyloctahydroindolizine-1,2-diyl diacetate (**34a**).* The triol **33a** (20 mg, 0.061 mmol) was stirred at room temperature in acetic anhydride−pyridine mixture (1:1, 2 mL) for 8 h, following which solvent was evaporated, and residue was purified by column chromatography to afford 26 mg (80%) of acetate **34a** as a pale yellow liquid: R_f = 0.4 (hexane/EtOAc = 3:1); $[\alpha]_D^{28}$ = +9.5 (*c* 0.20, CH_2Cl_2); IR (neat) ν_{max} 3062, 3029, 2860, 1739, 1453, 1237, 1100, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46 (t, *J* = 6.6 Hz, 1H, H-2), 5.37 (t, *J* = 6.6 Hz, 1H, H-1), 4.32 (t, *J* = 10.6 Hz, 1H, H-9), 4.12−4.01 (m, 2H, H-3, H-9′), 3.38 (ddd, *J* = 2.8, 6.6, 13.7 Hz, 1H, H-5), 2.81−2.74 (m, 1H, H-8a), 2.11 (s, 3H, −OCOCH_3), 2.07 (s, 3H, −OCOCH_3), 2.04 (s, 3H, −OCOCH_3), 1.80−1.70 (m, 2H, H-6, H-6′), 1.61−1.58 (m, 1H, H-7), 1.46−1.41 (m, 1H, H-7′), 1.26−1.21 (m, 5H, H-8, H-8′, −CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.7, 170.3, 75.2, 62.6, 60.1, 54.7, 45.1, 29.7, 28.3, 23.4, 21.2, 21.0, 20.8, 11.2; HRMS calcd for $C_{16}H_{26}NO_6$ $[M + H]^+$ 328.1760, found 328.1763.

*(1R,2S,3S,5S,8aR)-3-(Acetoxymethyl)-5-methyloctahydroindolizine-1,2-diyl diacetate (**34b**).* Following the same procedure for **34a**, compound **34b** was obtained from **33b** (18 mg, 0.055 mmol), in 77% yield (23 mg) as a colorless oil: R_f = 0.4 (hexane/EtOAc = 3:1); $[\alpha]_D^{28}$ = +2.2 (*c* 1.80, CH_2Cl_2); IR (neat) ν_{max} 3065, 3039, 2858, 1740, 1238, 1100, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.54 (dd, *J* = 8.0, 9.1 Hz, 1H, H-1), 5.25 (m, 1H, H-2), 5.14 (m, 1H, H-9), 4.25 (dd, *J* = 3.4, 12.0 Hz, 1H, H-9′), 3.76−3.74 (m, 1H, H-3), 3.36 (dd, *J* = 2.0, 9.1 Hz, 1H, H-5), 2.98 (ddd, *J* = 2.3, 8.0, 12.6 Hz, 1H, H-8a), 2.15 (s, 3H, −OCOCH_3), 2.10 (s, 3H, −OCOCH_3), 2.07 (s, 3H, −OCOCH_3), 1.76−1.72 (m, 1H, H-6), 1.59−1.48 (m, 3H, H-6′, H-7, H-7′), 1.38−1.22 (m, 2H, H-8, H-8′), 1.09 (m, 3H, −CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.7, 170.2, 76.0, 62.3, 61.7, 59.1, 55.5, 53.5, 38.6, 29.7, 21.3, 21.2, 21.0, 14.8; HRMS calcd for $C_{16}H_{26}NO_6$ $[M + H]^+$ 328.1760, found 328.1758.

*(1R,2S,3S,5S,8aS)-3-(Acetoxymethyl)-5-methyloctahydroindolizine-1,2-diyl diacetate (**37a**).* Following the same procedure for **34a**, compound **37a** was obtained from **36a** (25 mg, 0.076 mmol), in 75% yield (30 mg) as a colorless oil: R_f = 0.4 (hexane/EtOAc = 3:1); $[\alpha]_D^{28}$ = +12.5 (*c* 1.00, CH_2Cl_2); IR (neat) ν_{max} 3058, 3030, 1738, 1428, 1240, 1103, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46−5.43 (m, 1H, H-1), 5.34 (t, *J* = 6.7 Hz, 1H, H-2), 4.90−4.89 (m, 1H, H-9), 4.77 (dd, *J* = 4.5, 11.9 Hz, 1H, H-9′), 3.69−3.66 (m, 1H, H-3), 3.32 (dd, *J* = 2.4, 8.2 Hz, 1H, H-8a), 2.83 (dd, *J* = 2.4, 12.8 Hz, 1H, H-5), 2.11 (s, 3H, −OCOCH_3), 2.09 (s, 3H, −OCOCH_3), 2.02 (s, 3H, −OCOCH_3), 1.75−1.62 (m, 2H, H-8, H-8′), 1.56−1.43 (m, 3H, H-7, H-7′, H-6), 1.28−1.26 (m, 1H, H-6′), 1.09 (m, 3H, −CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.4, 170.0, 76.1, 62.0, 61.5, 59.9, 59.3, 49.9, 39.1, 29.7, 21.3, 21.2, 20.8, 14.8; HRMS calcd for $C_{16}H_{26}NO_6$ $[M + H]^+$ 328.1760, found 328.1760.

*(1R,2S,3S,5R,8aS)-3-(Acetoxymethyl)-5-methyloctahydroindolizine-1,2-diyl diacetate (**37b**).* Following the same procedure for **33a**, compound **37b** was obtained from **36b** (12 mg, 0.037 mmol), in 77% yield (15 mg) as a colorless oil: R_f = 0.4 (hexane/EtOAc = 3:1); $[\alpha]_D^{28}$ = −32.8 (*c* 0.80, CH_2Cl_2); IR (neat) ν_{max} 3059, 3028, 1742, 1430, 1236, 1103, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.14 (dd, *J* = 6.7, 14.3 Hz, 1H, H-1), 5.00−4.99 (m, 2H, H-2, H-9), 4.95 (br s, 1H, H-9′), 4.18 (dd, *J* = 2.4, 8.2 Hz, 1H, H-3), 3.20 (d, *J* = 11.3 Hz, 1H, H-8a), 2.76 (dd, *J* = 2.1, 6.7 Hz, 1H, H-5), 2.13 (s, 3H, −OCOCH_3), 2.10 (s, 3H, −OCOCH_3), 2.04 (s, 3H, −OCOCH_3), 1.72−1.65 (m, 2H, H-6, H-6′),

dx.doi.org/10.1021/jo401613v | J. Org. Chem. 2013, 78, 9383−9395

1.60−1.52 (m, 2H, H-7, H-7′), 1.44−1.40 (m, 1H, H-8), 1.27−1.21 (m, 1H, H-8′), 1.12 (m, 3H, $-CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 170.6, 169.9, 71.1, 62.5, 60.7, 59.6, 58.5, 32.6, 21.2, 21.1, 20.9, 15.8; HRMS calcd for $C_{16}H_{26}NO_6$ $[M + H]^+$ 328.1760, found 328.1761.

General Procedure for Enzyme Inhibition Assay. All the enzymes and their corresponding substrates have been procured from Sigma-Aldrich Chemical Co. The inhibition studies of compounds (**19a**, **19b**, **25a**, **25b**, **33a**, **33b**, **36a**, **36b**) have been determined by measuring residual hydrolytic activities of the glycosidases. The substrates and enzymes were prepared as 0.025 M solutions in the respective pH buffer solutions of the corresponding enzyme. In all cases, the substrates used were the corresponding *p*-nitrophenyl glycopyranosides. The incubation mixture consisted of 100 μL of enzyme solution, 200 μL of 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. After incubation at 37 °C for 1 h, 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, control experiments were run simultaneously in the absence of test compound. A series of blank experiments for the substrate were also carried out in the respective buffer solutions without the enzyme or test compounds. The absorbance of the liberated *p*-nitrophenol in each reaction (both test and control reactions) was recorded using spectrophotometer at 405 nm. Percentage inhibition was calculated as the ratio of the difference in the observed absorbances of the control and test reactions to the observed absorbance of the control reaction. Results have thus been reported as IC_{50} values, which is the concentration of the test compound that causes 50% inhibition of the enzyme. The assays were performed in triplicate, and the IC_{50} values have been reported as mean ± standard deviation, in Table 1.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*Fax: 0091-512-259 0007. E-mail: vankar@iitk.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Department of Science and Technology, New Delhi, for a J. C. Bose National Fellowship (JCB/SR/S2/JCB-26/2010) to Y.D.V. We also thank the Council of Scientific and Industrial Research (CSIR), New Delhi for financial support [Grant No. 02(0124)/13/EMR-II)]. A.A.A. thanks the CSIR, New Delhi, for a Senior Research Fellowship.

■ DEDICATION

Dedicated to Professor M. Periasamy on the occasion of his 60th birthday.

■ REFERENCES

(1) (a) Stutz, A. E. *Iminosugars as Glycosidase Inhibitors. Nojirimycin and Beyond*; Wiley-VCH: Weinheim, 1999. (b) Compain, P. E.; Martin, O. R. *Iminosugars. From Synthesis to Therapeutic Applications*; Wiley-VCH: Weinheim, 2007.

(2) (a) Lahiri, R.; Ansari, A. A.; Vankar, Y. D. *Chem. Soc. Rev.* **2013**, *42*, 5102−5118. (b) Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett, G. W.; Timmer, M. S. M. *Eur. J. Org. Chem.* **2010**, 1615−1637. (c) Davis, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 652−671. (d) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem.—Eur. J.* **2009**, *15*, 7808−7821. (e) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625−649.

(3) (a) Andersen, B.; Rassov, A.; Westergaard, N.; Lundgren, K. *Biochem. J.* **1999**, *342*, 545−550. (b) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683−4696. (c) Chery, F.; Cronin, L.; O'Brien, J. L.; Murphy, P. V. *Tetrahedron* **2004**, *60*, 6597−6608. (d) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrshneider, L.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci. U. S. A.* **1987**, *84*, 8120−8124.

(4) For example, see: (a) Boucheron, C.; Desvergnes, V.; Compain, P.; Martin, O. R.; Lavi, A.; Mackeen, M.; Wormald, M. R.; Dwek, D. A.; Butters, T. D. *Tetrahedron: Asymmetry* **2005**, *16*, 1747−1756. (b) Jespersen, T. M.; Dong, W.; Sierks, M. R.; Skrydstrup, T.; Lundt, I.; Bols, M. *Angew. Chem., Int. Ed. Engl.* **1994**, 1778−1779. (c) Asano, N.; Kizu, H.; Oseki, K.; Tomioka, E.; Matsui, K.; Okamoto, M.; Baba, M. *J. Med. Chem.* **1995**, *38*, 2349−2356. (d) Moris-Varas, F.; Qian, X.-H.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 7647−7652. (e) Painter, G. F.; Eldridge, P. J.; Falshaw, A. *Bioorg. Med. Chem.* **2004**, *12*, 225−232. (f) Popowycz, F.; Gerber-Lemaire, S.; Schütz, C.; Vogel, P. *Helv. Chim. Acta* **2004**, *87*, 800−810.

(5) (a) Welter, A.; Jadot, J.; Dardenne, G.; Marlier, M.; Casimir, J. *Phytochemistry* **1976**, *15*, 747−749. (b) Takayama, S.; Martin, R.; Wu, J.; Laslo, K.; Siuzdak, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 8146−8151.

(6) (a) Kumar, V.; Ramesh, N. G. *Tetrahedron* **2006**, *62*, 1877−1885. (b) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999−1002. (c) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem.—Eur. J.* **2006**, *12*, 6607−6620. (d) García-Moreno, M. I.; Aguilar, M.; Mellet, C. O.; García Fernandez, J. M. *Org. Lett.* **2006**, *8*, 297−299. (e) Li, Y.-X.; Huang, M.-H.; Yamashita, Y.; Kato, A.; Jia, Y.-M.; Wang, W.-B.; Fleet, G. W. J.; Nash, R. J.; Yu, C.-Y. *Org. Biomol. Chem.* **2011**, *9*, 3405−3414.

(7) (a) Nemr, A. E. *Tetrahedron* **2000**, *56*, 8579−8629. (b) Cardona, F.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2006**, 1551−1565. (c) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520−542.

(8) (a) Michalik, A.; Hollinshead, J.; Jones, L.; Fleet, G. W. J.; Yu, C.-Y.; Hu, X.-G.; van Well, R.; Horne, G.; Wilson, F. X.; Kato, A.; Jenkinson, S. F.; Nash, R. J. *Phytochem. Lett.* **2010**, *3*, 136−138. (b) Hu, X.-G.; Bartholomew, B.; Nash, R. J.; Wilson, F. X.; Fleet, G. W. J.; Nakagawa, S.; Kato, A.; Jia, Y.-M.; van Well, R.; Yu, C.-Y. *Org. Lett.* **2010**, *12*, 2562−2565. (c) Greco, M.; De Mitri, M.; Chiriaco, F.; Leo, G.; Brienza, E.; Maffia, M. *Cancer Lett.* **2009**, *283*, 222−229. (d) Jiangseubchatveera, N.; Bouillon, M. E.; Liawruangrath, B.; Liawruangrath, S.; Nash, R. J.; Pyne, S. G. *Org. Biomol. Chem.* **2013**, *11*, 3826−3833. (e) Chronowska, A.; Gallienne, E.; Nicolas, C.; Kato, A.; Adachi, I.; Martin, O. R. *Tetrahedron Lett.* **2011**, *52*, 6399−6402.

(9) (a) Reddy, B. G.; Vankar, Y. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 2001−2004. (b) Doddi, V. R.; Vankar, Y. D. *Eur. J. Org. Chem.* **2008**, 5583−5589. (c) Doddi, V. R.; Kokatla, H. P.; Pal, A. P. J.; Basak, R. K.; Vankar, Y. D. *Eur. J. Org. Chem.* **2008**, 5731−5739. (d) Kumari, N.; Vankar, Y. D. *Org. Biomol. Chem.* **2009**, *7*, 2104−2109. (e) Pal, A. P. J.; Gupta, P.; Reddy, Y. S.; Vankar, Y. D. *Eur. J. Org. Chem.* **2010**, 6957−6966. (f) Reddy, Y. S.; Kancharla, P. K.; Roy, R.; Vankar, Y. D. *Org. Biomol. Chem.* **2012**, *10*, 2760−2773 and references cited therein.

(10) (a) Ramesh, N. G.; Balasubramaniam, K. K. *Eur. J. Org. Chem.* **2003**, 4477−4487. (b) Rawal, G. K.; Rani, S.; Kumari, N. *J. Org. Chem.* **2009**, *74*, 5349−5355. (c) Gupta, P.; Vankar, Y. D. *Eur. J. Org. Chem.* **2009**, 1925−1933. (d) Reddy, Y. S.; Kancharla, P. K.; Roy, R.; Vankar, Y. D. *Org. Biomol. Chem.* **2012**, *10*, 2760−2773. (e) Sagar, R.; Park, J.; Koh, M.; Park, S. B. J. *Org. Chem.* **2009**, *74*, 2171−2174. (f) Bharate, S. B.; Mahajan, T. R.; Gole, Y. R.; Nambiar, M.; Matan, T. T.; Kulkarni-Almeida, A.; Balachandran, S.; Junjappa, H.; Balakrishnan, A.; Vishwakarma, R. A. *Bioorg. Med. Chem.* **2008**, *16*, 7167−7176. (g) Kim, Y.; Kim, J.; Oh, K.; Lu, D.-S.; Park, S. B. *ACS Med. Chem. Lett.* **2012**, *3*, 151−154. (h) Sridhar, P. R.; Sudharani, C. *RSC Adv.* **2012**, *2*, 8596−8598. (i) Maiti, D. K.; Halder, S.; Pandit, P.; Chatterjee, N.; Joarder, D. D.; Pramanik, N.; Saima, Y.; Patra, A.; Maiti, P. K. *J. Org. Chem.* **2009**, *74*, 8086−8097. (j) Gupta, A.; Vankar, Y. D. *Tetrahedron* **2000**, *56*, 8525−8531.

(11) Vilsmeier, A.; Haack, A. *Chem. Ber.* **1927**, *60*, 119−122.

(12) (a) Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron Lett.* **1991**, *32*, 3875. (b) Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron* **1995**, *51*, 255−272.
(13) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973−1976.
(14) Please see the Supporting Information.
(15) (a) Hong, Z.; Liu, L.; Sugiyama, M.; Fu, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 8352−8353. (b) Liu, K. K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C.-H. J. *Org. Chem.* **1991**, *56*, 6280−6289.
(16) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **2002**, *58*, 341−354.
(17) Garegg, P. J.; Samuelsson, B. *Carbohydr. Res.* **1978**, *67*, 267−270.
(18) Jing-Ping, K.; Yu-Juan, L.; Xu-Yang, L.; Ji-Zhen, L. *Chem. Res. Chin. Univ.* **2009**, *25*, 461−464.
(19) Wright, D. L.; Shulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847−1850.