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# Total Synthesis of L-(+)-Swainsonine and Other Indolizidine Azasugars from D-Glucose

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A total synthesis of L-(+)-swainsonine, a potent and specific inhibitor of naringinase, along with the syntheses of six unnatural indolizidine azasugars are reported by starting from D-glucose. L-(+)-Swainsonine was synthesized in 14 steps in 17 % overall yield. Further, two of the indolizidine analogues were found to be good glycosidase inhibitors at micromolar concentrations. In all of these syntheses, the key step was an intramolecular $S_N2$ reaction.


## Introduction

Since 1966 more than 100 azasugars have been isolated from various plants and microorganisms.[1] Owing to their potent glycosidase inhibition activity, a large number of structural analogues[2] have also been prepared and tested as therapeutically potent inhibitors. Two of these synthetic analogues, polyhydroxylate piperidines Miglitol[3] and Miglustat,[4] have been approved as drugs against Type-2 diabetes and Gaucher's disease, respectively. Among these azasugars, the indolizidine class of glycosidase inhibitors has attracted much attention due to their potent and selective glycosidase inhibition activities. Thus, whereas D-(–)-swainsonine (**1**; Figure 1) shows anticancer activity,[5] (+)-castanospermine is a potent antiviral agent[6] and (+)-lentiginosine is an amyloglucosidase inhibitor.[7] To obtain more-potent as well as more-selective inhibitors, a large number of swainsonine analogues have been synthesized[8] and evaluated for their glycosidase inhibition activity. It is well established that changes in the configuration of chiral centers change the inhibition activity of the resultant molecule; for example, L-(+)-swainsonine is a potent inhibitor of naringinase at submicromolar concentration, whereas D-(–)-swainsonine does not inhibit naringinase.[9] Similarly, addition of a substituent in the indolizidine core of swainsonine changes its selectivity as well as its potency.[10] Pearson et al. [11] reported the synthesis and glycosidase inhibition study of D-(–)-swainsonine analogues with an additional substituent in the indolizidine core, and they found that some of the analogues were more potent than D-(–)-swainsonine in their ability to inhibit jack bean α-mannosidase. Many other analogues are documented in the literature.[12]

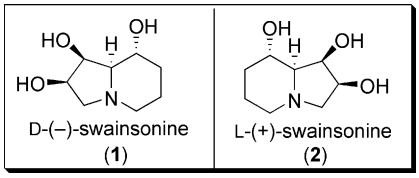


Figure 1. Enantiomers of swainsonine.

It is believed that inhibitors of naringinase, which process nonmammalian sugars, might be useful in controlling diseases caused by mycobacteria.[13] Although a number of molecules[2c,8,14] have been reported as naringinase inhibitors, only a few of them (Figure 2) show good inhibition activity. While we were preparing this manuscript, Fleet[14e] et al. reported the total synthesis of L-(+)-swainsonine along with the synthesis of an analogue showing inhibition activity at nanomolar concentrations. Apart from this, Fleet et al.[9] earlier synthesized L-(+)-swainsonine from octanolactone, whereas Hirama et al.[15] synthesized it from substituted butyrolactone. Recently, O'Doherty et al.[16] reported the de novo synthesis of this molecule from furan and bu-

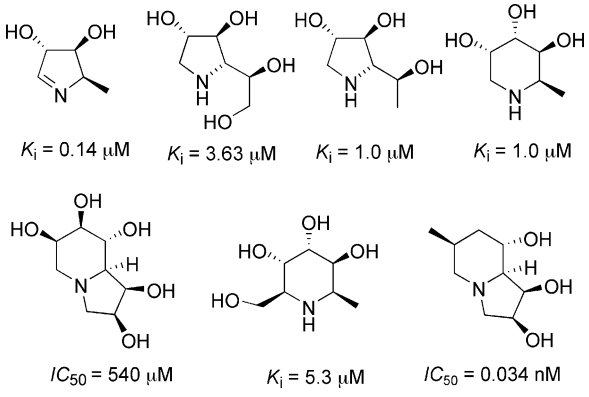


Figure 2. Naringinase inhibitors.

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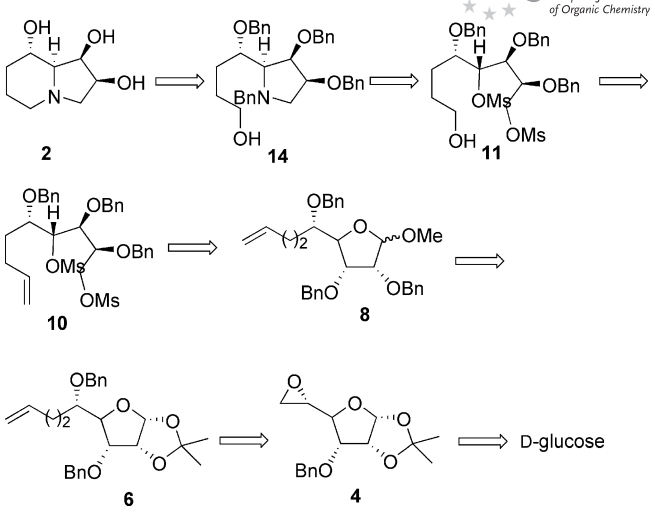
tyrolactone. In addition, a racemic synthesis of swainsonine is also reported in literature.[17] In continuation of our efforts to obtain pharmacologically promising glycosidase inhibitors[18] and our interest in the functionalization of sugars[19] in an effort to obtain glycosidase inhibitors, we hereby report the synthesis of L-(+)-swainsonine and a few analogues of swainsonine with an additional hydroxymethyl substituent. It was reported that an extra hydroxymethyl substituent in azasugars enhances the interaction with the active site of glycosidases, and it provides conformational flexibility to the molecule as well.[20]

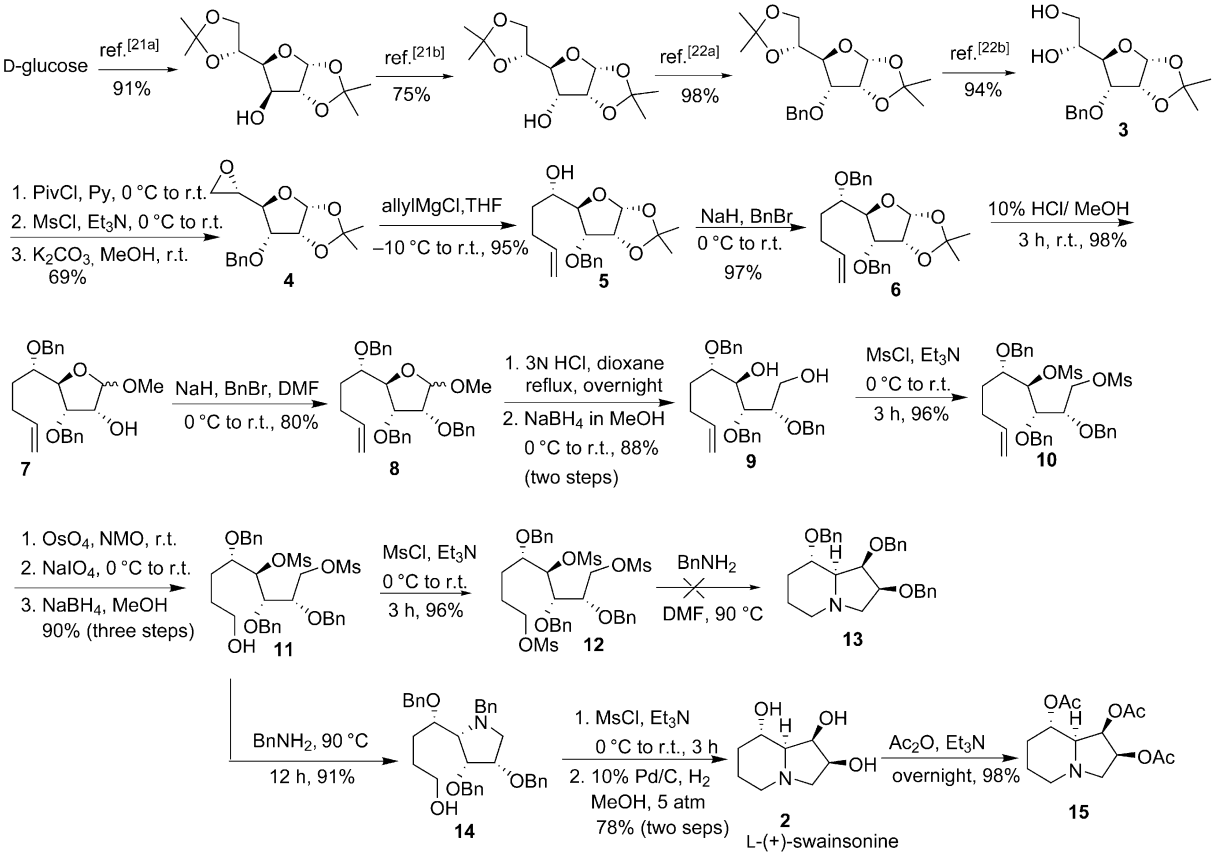
Retrosynthetic analysis for L-(+)-swainsonine (**2**) is shown in Scheme 1. This involves two crucial intramolecular $S_N2$ cyclizations leading to the formation of two rings successively. The stereochemically significant epoxide **4** could be readily assembled from D-(+)-glucose following the manipulation of the exocylic 1,2-diol unit.




Scheme 1. Retrosynthetic analysis.

As outlined in Scheme 2, diol **3** was obtained from D-glucose following literature procedures.[21a,21b,22a,22b] However, the configuration at C-5 needed to be inverted, and this was achieved by converting diol **3** into epoxide **4** in 69% overall yield[23] through sequential treatment of this diol with pivaloyl chloride (to form the ester of the primary alcohol), followed by treatment with mesyl chloride/$Et_3N$. The corresponding mesylate was then treated with $K_2CO_3$ in methanol.

Regiospecific ring opening[24] of epoxide **4** with allylmagnesium chloride at –10 °C gave alcohol **5** in 95% yield (Scheme 2), which was characterized by the presence of an internal olefinic proton at $\delta$ = 5.81 ppm and the C-1 proton at $\delta$ = 5.72 ppm in its $^1$H NMR spectrum apart from other spectroscopic data.[25] The free hydroxy group was protected as a benzyl ether by using NaH/benzyl bromide[22a] to give **6** in 97% yield. Removal of the isopropylidene group and introduction of a methoxy group at the anomeric carbon atom was carried out by treating **6** with 10% HCl in MeOH, which afforded **7** in excellent yield. Again, the free




Scheme 2.

hydroxy group so liberated was protected as a benzyl ether and compound **8** was obtained in 80% yield. The acetal group in compound **8** was deprotected by using 3 N HCl in refluxing dioxane followed by the reduction of the hemiacetal group with $NaBH_4$ to form diol **9** in 88% yield.[26] Formation of the diol was confirmed from its $^1H$ NMR spectroscopic data, which showed the disappearance of the OMe peak and further indicated the formation of a single diastereomer. Diol **9** was converted into dimesylate **10** with mesyl chloride and $Et_3N$ in an excellent yield, which was characterized by the presence of two mesyl peaks as a singlet at $\delta$ = 2.93 ppm. The double bond was cleaved with $OsO_4$ and $NaIO_4$[27] to give the corresponding aldehyde. Reduction of this aldehyde with $NaBH_4$ gave hydroxy dimesylate **11** in 90% yield. Initially, it was anticipated that treatment of trimesylate **12**, obtained from dimesylate **11** upon treatment with MsCl/$Et_3N$, with benzylamine would directly afford[28] desired bicyclic moiety **13**. However, this reaction was not clean, and it led to the formation of several products from which we could not isolate any pure compound. We therefore decided to proceed with compound **11** in two steps. Thus, **11** was heated with neat benzylamine at 90 °C for 12 h, which afforded compound **14** in 91% yield. Disappearance of the two mesylate group signals and integration of the phenyl protons in its $^1H$ NMR spectrum along with other spectroscopic data[25] confirmed the formation of the pyrrolidine ring. This cyclization, as a consequence of the intramolecular $S_N2$ reaction, inverted[29] the configuration at the stereocenter of the secondary mesylate. This was further confirmed by nOe experiments of bicyclic triacetate **15** obtained later (vide infra). In order to construct the second ring, alcohol **14** was treated with MsCl/$Et_3N$ in $CH_2Cl_2$; a very polar compound, most likely a quaternary ammonium chloride salt,[30] was isolated, which upon hydrogenolysis[16] with 10% Pd/C in MeOH at 5 atm $H_2$ gave desired compound **2** in 78% yield.

The spectral and analytical data of L-(+)-swainsonine were in complete agreement with the literature data. The structure was further confirmed by analyzing the $^1H$ and $^{13}C$ NMR, COSY, and nOe spectroscopic data of its acetate derivative **15**. In the nOe experiment (Figure 3), irradiation of the H-5 proton did not show any enhancement in the H-2, H-3, or H-4 protons. In contrast, irradiation of the H-3 proton enhanced the signal for the H-2 and H-4 protons. These observations confirmed the absolute stereochemistry of L-(+)-swainsonine triacetate and consequently that of L-(+)-swainsonine.

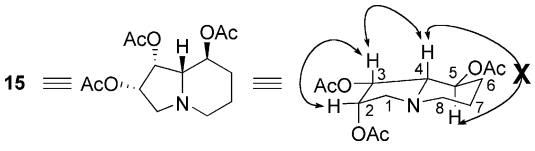
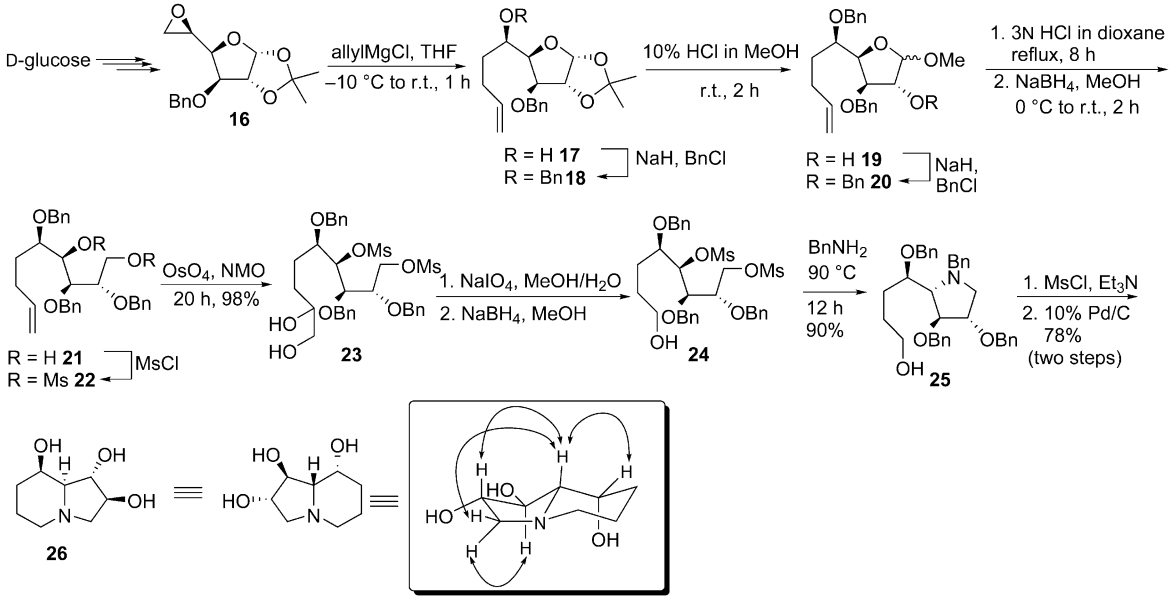



Figure 3. nOe correlations.

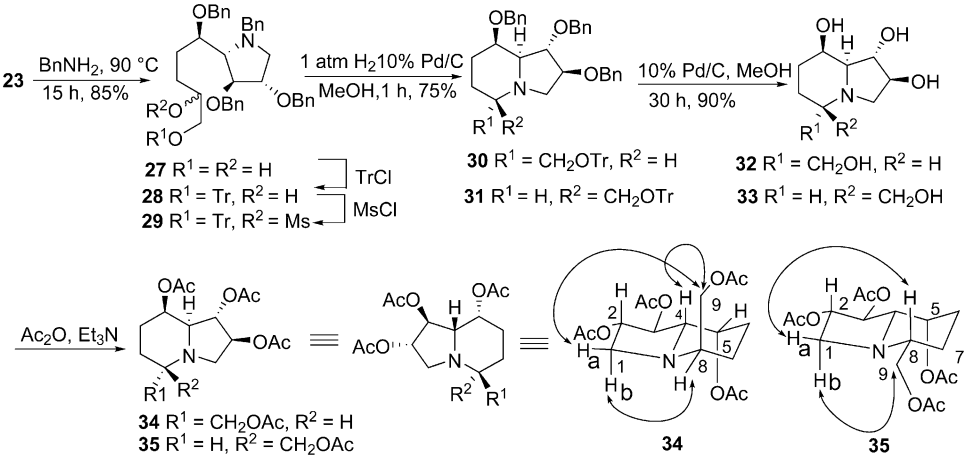
A known analogue of swainsonine, viz. **26**, having a *trans* 1,2-diol unit in the pyrrolidine ring and a 5β-OH group is known to be an inhibitor of cytosolic β-D-galactosidase of human liver.[32] We hereby report its new synthesis, as shown in Scheme 3, from epoxide **16** having the β-configuration, which was obtained from D-glucose according to a literature procedure.[31] The sequence of reactions followed were essentially the same as that used for the synthesis of L-(+)-swainsonine (Scheme 2). The structures of the intermediate products and **26** were confirmed by $^1H$ and $^{13}C$ NMR, COSY, and nOe spectroscopic analysis.[25]

In order to obtain the indolizidine azasugars with an additional hydroxymethyl substituent, dimesylate **23** was heated in neat benzylamine at 90 °C for 15 h to afford pyrrolidine derivative **27** (Scheme 4) in 85% yield. The primary




Scheme 3.

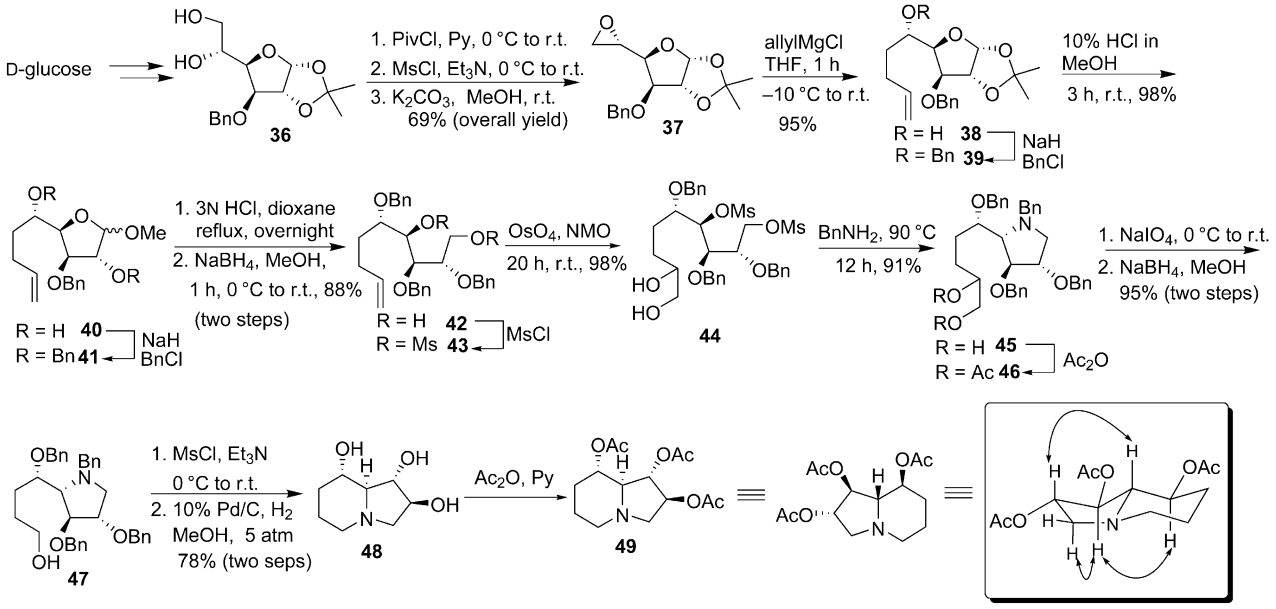



Scheme 4.

hydroxy group of **27** was protected as a trityl ether followed by mesylation of the secondary hydroxy group. Treatment of mesylate **29** with a half-weight equivalent of 10% Pd/C in methanol under 1 atm $H_2$ afforded two diastereomeric cyclized products **30** and **31**. These diastereomers were chromatographically separated and separately detritylated and hydrogenolyzed in one pot by treating with 10% Pd/C in TFA/MeOH (2:3) at 5 atm $H_2$ for 30 h to afford **32** and **33**, respectively. The absolute stereochemistry and structures of these molecules were confirmed from the spectroscopic data of their acetate derivatives **34** and **35**,[25] respectively.

In the case of **34**, nOe interactions between the H-4 and H-9 protons confirmed the *S* configuration of the newly generated chiral center, which was further confirmed by the nOe between the H-1a and H-9 protons. So, the configuration of the newly generated chiral center of **35** is *R*. This was further supported by the nOe interactions between the pseudoequatorial H-1a and H-8 protons and the pseudoaxial H-1b and H-9 protons.

To obtain the other set of isomers, epoxide **37** (Scheme 5) with the inverted configuration at C-5 was prepared. For this purpose, diol **36** was treated with pivaloyl chloride followed by treatment with mesyl chloride to get the corresponding mesyl ester, which was treated with $K_2CO_3$ in methanol to afford desired epoxide **37** in 69% overall yield. By using the same sequence of reactions as employed for the synthesis of **26**, dimesylate **44** was obtained from **37** in excellent yield. Upon treatment with benzylamine at 90 °C, dimesylate **44** gave pyrrolidine-derived diol **45** in 91% yield, which was cleaved by treating with $NaIO_4$ followed by reduction with $NaBH_4$ to give **47** in 95% yield. This hydroxy derivative of pyrrolidine was treated with MsCl/$Et_3N$ followed by hydrogenolysis with Pd/C at 5 atm $H_2$ to give **48**

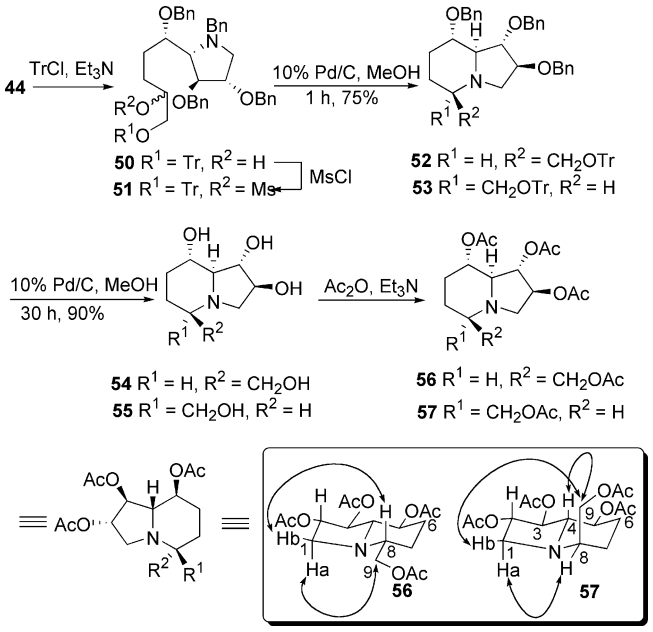



Scheme 5.

in 78% yield, which was characterized by the $^1H$ and $^{13}C$ NMR, COSY, and nOe spectroscopic data of its acetate derivative **49**.[25]

The other set of isomers with a hydroxymethyl substituent viz. **54** and **55** were obtained from compound **44** in an analogous manner to that shown in Scheme 6.[25]




Scheme 6.

The absolute stereochemistry of the molecules was confirmed from the spectroscopic data of their acetate derivatives **56** and **57**. Thus, in the case of **56**, nOe interactions between the H-1b and H-8 protons confirmed the *R* configuration of the newly generated chiral center, which was further supported by the nOe interaction between the H-1a and H-9 protons. Similarly, in **57** nOe interactions between the H-1b and H-9 protons confirmed the reverse *S* configuration of the newly generated chiral center, which was further confirmed by the nOe interaction between the pseudoaxial H-1a and H-8 protons.

The inhibitory activities of compounds **32**, **33**, **54**, and **55**, all of which have an extra hydroxymethyl substituent, towards six commercially available enzymes were then evaluated (Table 1). Of these four indolizidine azasugars, compounds **33** and **55** showed good inhibition activity against α-glucosidase obtained from baker's yeast. Interestingly, the same enzyme was not inhibited by **26**. Thus, the extra hydroxymethyl substituent plays an important role in the inhibition activity of the indolizidine azasugars.

Table 1. $IC_{50}$ values for compounds **32**, **33**, **54** and **55**.[a]

| Enzymes | 32 | 33 | 54 | 55 |
|---|---|---|---|---|
| α-Mannosidase (Jack beans) | NI | NI | NI | NI |
| β-Glucosidase (Almonds) | NI | NI | NI | NI |
| α-Galactosidase (Green coffee) | NI | NI | NI | NI |
| α-Glucosidase (Baker's yeast) | NI | 56 μM | NI | 30.15 μM |
| β-Galactosidase (Bovine liver) | NI | NI | NI | NI |

[a] NI: no inhibition at a concentration of 3 mM; optimal pH of the enzymes at 37 °C.

## Conclusion

In conclusion, short and efficient syntheses of L-(+)-swainsonine and indolizidine azasugars were achieved from D-glucose, a cheap and commercially available starting material. Enzyme inhibition activities showed the significance of the extra hydroxymethyl substituent.

## Experimental Section

**(3a*R*,6*R*,6a*R*)-6-Benzyloxy-2,2-dimethyl-5-[(2*S*)-oxiran-2-yl]tetrahydrofuro[2,3-*d*][1,3]dioxole (4):** To a solution of diol **3** (5 g, 16.1 mmol) in $CH_2Cl_2$ (50 mL) was added pyridine (1.9 mL, 24.2 mmol) and PivCl (2.3 mL, 18.7 mmol) at 0 °C. The mixture was stirred at ambient temperature for 8 h and then diluted with $Et_2O$ (50 mL). The organic layer was washed with 1 N HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (50 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was dissolved in $CH_2Cl_2$ (50 mL) and treated with triethylamine (4.4 mL, 31.7 mmol) at 0 °C, followed by the addition of MsCl (2.5 mL, 32.1 mmol) and DMAP (0.09 g, 0.078 mmol). The mixture was stirred overnight at room temperature and then poured into saturated aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$ ($3 \times 50$ mL). The combined organic layer was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude mesylate was dissolved in methanol (100 mL) and $K_2CO_3$ (4.8 g, 35.0 mmol) was added, and the mixture was stirred overnight at room temperature. The mixture was concentrated and diluted with brine (100 mL), extracted with $Et_2O$ ($3 \times 100$ mL), dried with $MgSO_4$, and concentrated in vacuo. Purification by column chromatography gave **4** (3.24 g, 69% overall yield) as a colorless semisolid. $[\alpha]_D^{25} = +32$ ($c = 0.5$, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3031, 2988, 1496, 1455, 1252, 860 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.38–7.28 (m, 5 H), 5.69 (d, $J$ = 3.6 Hz, 1 H), 4.79 (d, $J$ = 11.9 Hz, 1 H), 4.62 (d, $J$ = 11.9 Hz, 1 H), 4.56 (t, $J$ = 3.8, 7.8 Hz, 1 H), 4.03 (dd, $J$ = 3.9, 9.0 Hz, 1 H), 3.78 (dd, $J$ = 4.4, 9.0 Hz, 1 H), 3.08 (m, 1 H), 2.87 (dd, $J$ = 2.6, 5.4 Hz, 1 H), 2.78 (dd, $J$ = 4.4, 5.6 Hz, 1 H), 1.58 (s, 3 H), 1.35 (s, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 137.3, 128.5, 128.1, 128.0, 113.2, 104.1, 79.0, 72.4, 51.0, 44.2, 29.6, 26.8, 26.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{20}O_5$ [M + Na]$^+$ 315.1208; found 315.1201.

**(1*S*)-1-{(3a*R*,6*R*,6a*R*)-6-Benzyloxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl}pent-4-en-1-ol (5):** To a stirred suspension of a mixture of Mg (65.73 mg, 27.39 mmol) in THF (10 mL) and a catalytic amount of $I_2$ at 0 °C was added allyl chloride (0.66 mL, 8.21 mmol). After disappearance of the iodine color, the solution was further cooled to –10 °C and epoxide **4** (2.0 g, 6.84 mmol) in THF (5 mL) was added dropwise. After 1 h of stirring, the reaction mixture was quenched with aqueous $NH_4Cl$ (15 mL) and extracted with ethyl acetate ($2 \times 15$ mL). The combined organic layers was washed with brine (15 mL), dried with $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography to obtain colorless viscous liquid **5** (2.17 g, 95%). $[\alpha]_D^{25} = +61.3$ ($c = 0.75$, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3435, 3065, 2985, 2933, 1640, 1454, 1373, 1309, 1217, 1130, 1024, 912, 886, 739, 699 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.40–3.29 (m, 5 H), 5.85–5.76 (m, 1 H), 5.73 (d, $J$ = 3.4 Hz, 1 H), 5.07–4.96 (m, 2 H), 4.76 (d, $J$ = 11.7 Hz, 1 H), 4.59

(d, $J$ = 11.7 Hz, 1 H), 4.56 (d, $J$ = 3.9 Hz, 1 H), 3.98 (dd, $J$ = 2.4, 9.0 Hz, 1 H), 3.86 (dd, $J$ = 4.4, 9.0 Hz, 1 H), 3.62 (m, 1 H), 2.26–2.11 (m, 2 H), 1.72–1.61 (m, 2 H), 1.59 (s, 3 H), 1.36 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 138.1, 137.5, 128.4, 128.0, 114.9, 113.1, 104.2, 80.8, 76.6, 72.3, 69.3, 33.7, 29.9, 26.9, 26.5 ppm. HRMS (ESI): calcd. for $C_{19}H_{26}O_5$ [M + H]$^+$ 335.1858; found 335.1849.

**(3a*R*,6*R*,6a*R*)-6-Benzyloxy-5-[(1*S*)-1-benzyloxypent-4-enyl]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (6):** NaH (60% suspension in paraffin oil, 0.29 g, 11.97 mmol) was added in small portions to a stirred solution of **5** (2.00 g, 5.98 mmol) in DMF (40 mL). After 30 min, benzyl chloride (0.82 mL, 6.58 mmol) was added dropwise, and the reaction mixture was stirred for 4 h at room temperature. The reaction mixture was poured into ice, and it was then extracted with diethyl ether (60 mL) followed by washing with water (3 × 50 mL), dried with $MgSO_4$ and concentrated in vacuo, which gave a crude product. Purification of the crude product by column chromatography gave colorless semi solid **6** (2.46 g, 97% yield). $[\alpha]_D^{25}$ = +94 ($c$ = 0.5, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3030, 2983, 2930, 1640, 1495, 1375, 1214, 1167, 1072, 1023, 1167, 738, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.36–7.23 (m, 10 H), 5.78 (m, 2 H), 5.03–4.95 (m, 2 H), 4.68 (d, $J$ = 11.7 Hz, 1 H), 4.56 (t, $J$ = 3.9 Hz, 1 H), 4.53 (d, $J$ = 11.7 Hz, 1 H), 4.43 (d, $J$ = 11.7 Hz, 1 H), 4.38 (d, $J$ = 11.7 Hz, 1 H), 4.10 (dd, $J$ = 2.6, 8.8 Hz, 1 H), 3.83 (dd, $J$ = 4.4, 8.8 Hz, 1 H), 3.54 (dt, $J$ = 2.6, 6.5 Hz, 1 H), 2.14 (m, 2 H), 1.84–1.75 (m, 2 H), 1.58 (s, 3 H), 1.35 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 138.5, 138.2, 137.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.5, 114.8, 112.7, 104.1, 79.9, 76.6, 76.3, 72.3, 71.9, 30.0, 29.7, 26.8, 26.6 ppm. HRMS (ESI): calcd. for $C_{26}H_{32}O_5$ [M + H$^+$] 425.2328; found 425.2313.

**(3*R*,4*S*)-4-Benzyloxy-5-[(1*S*)-1-benzyloxypent-4-enyl]-2-methoxytetrahydrofuran-3-ol (7):** A solution of **6** (2.30 g, 5.42 mmol) in 10% HCl in methanol (50 mL) was stirred at room temperature for 3 h. The reaction mixture was quenched by adding $NaHCO_3$ (5 g), and the mixture was then concentrated in vacuo followed by the addition of ice water to the residue. The residue was then extracted with ethyl acetate (3 × 30 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification of the product by column chromatography afforded colorless thick oil **7** (2.11 g, 98% yield). $[\alpha]_D^{25}$ = –4.06 ($c$ = 0.25, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3464, 3064, 3030, 2925, 1640, 1605, 1496, 1362, 1257, 1103, 737, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.35–7.21 (m, 10 H), 5.78 (m, 1 H), 5.02 (d, $J$ = 1.7 Hz, 2 H), 4.87 (s, 1 H), 4.64–4.46 (m, 5 H), 4.18–4.06 (m, 2 H), 4.02 (s, 1 H), 3.46–3.40 (m, 2 H), 3.36 (s, 3 H), 2.61 (br. s, 1 H), 2.24–2.12 (m, 2 H), 1.64–1.59 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 138.4, 128.6, 128.3, 128.2, 127.9, 127.7, 127.5, 127.4, 114.7, 107.9, 84.0, 82.8, 79.5, 79.0, 76.6, 72.8, 72.7, 72.5, 29.7, 29.5 ppm. HRMS (ESI): calcd. for $C_{24}H_{30}O_5$ [M + H]$^+$ 399.2179; found 399.2172.

**(3*R*,4*R*)-3,4-dibenzyloxy-2-[(1*S*)-1-benzyloxypent-4-enyl]-5-methoxytetrahydrofuran (8):** NaH (60% suspension in paraffin oil, 0.361 g, 15.04 mmol) was added in small portions to a stirred solution of **7** (2.0 g, 5.02 mmol) in DMF (40 mL). After 30 min, benzyl bromide (0.60 mL, 6.58 mmol) was added dropwise, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into ice and extracted with diethyl ether (3 × 30 mL) followed by washing with water (3 × 50 mL). The solution was then dried with $MgSO_4$ and concentrating in vacuo. The crude product was purified by column chromatography to afford colorless semisolid **8** (1.96 g, 80% yield). $[\alpha]_D^{25}$ = +24 ($c$ = 0.5, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3063, 3029, 1639, 1496, 1359, 1258, 1103, 1027, 912, 736, 697 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.38–7.25 (m, 15 H), 5.81–5.74 (m, 1 H), 5.01–4.92 (m, 3 H), 4.69 (d, $J$ = 12.2 Hz, 1 H), 4.59–4.56 (m, 2 H), 4.49 (d, $J$ = 11.7 Hz, 1 H), 4.32 (d, $J$ = 11.7 Hz, 1 H), 4.22 (dd, $J$ = 5.4, 7.5 Hz 1 H), 4.01 (dd, $J$ = 4.4, 7.5 Hz, 1 H), 3.85 (d, $J$ = 4.3 Hz, 1 H), 3.43–3.38 (m, 2 H), 3.32 (s, 3 H), 2.33–2.12 (m, 2 H), 1.70–1.67 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 138.9, 138.5, 137.7, 128.4, 128.1, 128.0, 127.8, 127.6, 127.3, 114.6, 105.7, 82.8, 79.2, 78.0, 72.3, 72.3, 55.0, 29.8, 29.5 ppm. HRMS (ESI): calcd. for $C_{31}H_{36}O_5$ [M + H]$^+$ 489.2641; found 489.2638.

**(2*S*,3*R*,4*R*,5*S*)-2,3,5-Tribenzyloxynon-8-en-1,4-diol (9):** Compound **8** was dissolved in *p*-dioxane (30 mL). To this solution was added 3 N HCl (10 mL). The reaction mixture was heated at reflux overnight and then neutralized with solid $NaHCO_3$ at 0 °C. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The hemiacetal product was dissolved in methanol (30 mL) and cooled to 0 °C. To this solution was added $NaBH_4$ (0.31 g, 7.02 mmol), and the reaction mixture was stirred at room temperature for 2 h. The mixture was then diluted with water (40 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. Purification by silica gel column chromatography afforded **9** (1.45 g, 88% yield) as a viscous liquid. $[\alpha]_D^{25}$ = +54 ($c$ = 0.5, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3434, 3063, 3030, 2929, 1720, 1639, 1605, 1496, 1398, 1271, 1068, 912, 735, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.35–7.25 (m, 15 H), 5.77 (m, 1 H), 5.03–4.96 (m, 2 H), 4.78 (d, $J$ = 11.2 Hz, 1 H), 4.79–4.69 (d, $J$ = 11.7 Hz, 1 H), 4.63 (d, $J$ = 11.7 Hz, 1 H), 4.57 (d, $J$ = 11.3 Hz, 1 H), 4.35 (d, $J$ = 11.4 Hz, 1 H), 4.26 (d, $J$ = 11.4 Hz, 1 H), 3.93 (m, 1 H), 3.88 (br. s, 2 H), 3.72 (dd, $J$ = 2.6, 8.0 Hz, 1 H), 3.66 (dt, $J$ = 2.2, 6.3 Hz, 1 H), 2.60 (br. s, 2 H), 2.10 (m, 2 H), 1.73 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 138.3, 138.0, 128.4, 128.3, 127.9, 127.8, 127.7, 114.9, 79.8, 79.6, 73.4, 72.2, 72.0, 71.9, 61.2, 29.9, 29.4 ppm. HRMS (ESI): calcd. for $C_{30}H_{36}O_5$ [M + H]$^+$ 477.2641; found 477.2639.

**(2*S*,3*S*,4*R*,5*S*)-2,3,5-Tribenzyloxynon-8-en-1,4-diyl Dimethanesulfonate (10):** To a stirred solution of diol **9** (1.3 g, 2.73 mmol) in $CH_2Cl_2$ (15 mL) at 0 °C was added $Et_3N$ (0.832 mL, 6.00 mmol) followed by MsCl (0.41 mL, 5.73 mmol) and a catalytic amount of DMAP. After 2 h, aqueous $NaHCO_3$ (20 mL) was added, and the organic layer was washed with water (2 × 20 mL), followed by brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification by silica gel column chromatography afforded colorless viscous liquid **10** (1.65 g, 96% yield). $[\alpha]_D^{25}$ = –28 ($c$ = 0.25, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3064, 3031, 2936, 1745, 1640, 1496, 1355, 1174, 1069, 938, 825, 747, 699 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.35–7.25 (m, 15 H), 5.77 (m, 1 H), 5.04 (dd, $J$ = 1.9, 7.8 Hz, 1 H), 4.95 (d, $J$ = 1.4 Hz, 1 H), 4.90 (m, 1 H), 4.76 (d, $J$ = 10.9, 1 H), 4.71 (d, $J$ = 10.7, 1 H), 4.64 (d, $J$ = 2.2 Hz, 1 H), 4.57 (d, $J$ = 11.2, 1 H), 4.51 (d, $J$ = 1.7 Hz, 1 H), 4.48 (d, $J$ = 1.9, 1 H), 4.42–4.36 (m, 2 H), 3.90 (m, 1 H), 3.81–3.76 (m, 2 H), 2.93 (s, 6 H), 2.03 (m, 2 H), 1.59 (m, 2 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 137.9, 137.7, 136.6, 128.7, 128.5, 128.3, 128.2, 128.0, 127.7, 115.1, 84.2, 76.2, 75.8, 73.1, 72.6, 67.8, 38.9, 37.6, 30.3, 28.6 ppm. HRMS (ESI): calcd. for $C_{39}H_{40}O_9S_2$ [M + Na]$^+$ 656.2011; found 656.2010.

**(2*S*,3*S*,4*R*,5*S*)-2,3,5-Tribenzyloxy-8-hydroxyoctan-1,4-diyl Dimethanesulfonate (11):** To a stirred solution of **10** (1.50 g, 2.37 mmol) in THF/$H_2O$ (4:1, 10 mL) was added NMO (0.305 g, 2.60 mmol) followed by a catalytic amount of $OsO_4$ at room temperature. The reaction mixture was stirred for 20 h, and the volatile substances were then removed in vacuo to afford a crude brown oil product, which was used in the next step without further purification. To a

mixture of diol and MeOH/$H_2O$ (6:1, 20 mL) at 0 °C was added $NaIO_4$(0.56 g, 2.63 mmol), and the solution was stirred for 1 h. The reaction mixture was filtered followed by evaporation of methanol in vacuo and then $H_2O$ (10 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo to afford a brownish viscous liquid. This crude product was dissolved in MeOH (20 mL) and cooled to 0 °C followed by the addition of $NaBH_4$ (0.16 g, 3.5 mmol). The reaction mixture was stirred for 1 h at room temperature followed by the addition of a saturated aqueous solution of $NH_4Cl$ (10 mL) and then extraction with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine(30 mL), dried with $MgSO_4$, and concentrated in vacuo to afford a colorless viscous liquid, which was purified by silica gel column chromatography to get **11** (1.35 g, 90% yield). $[\alpha]_D^{25}$ = –50 (*c* = 0.1, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3563, 3444, 3088, 3031, 2937, 2873, 1666, 1496, 1454, 1352, 1211, 1172, 1065, 936, 824, 746, 700 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.36–7.25 (m, 15 H), 5.07 (dd, *J* = 1.7, 8.0 Hz, 1 H), 4.77 (d, *J* = 11.0 Hz, 1 H), 5.72 (d, *J* = 11.7 Hz, 1 H), 4.64 (dd, *J* = 1.9, 11.4 Hz, 1 H), 4.59 (d, *J* = 11.2 Hz, 1 H), 4.47 (d, *J* = 10.5 Hz, 1 H), 4.40 (d, *J* = 11.2 Hz, 1 H), 4.39 (dd, *J* = 3.2, 11.2 Hz, 1 H), 3.89 (dt, *J* = 2.4, 4.9, 7.8 Hz, 1 H), 3.82 (m, 2 H), 3.47 (m, 2 H), 2.95 (s, 3 H), 2.93 (s, 3 H), 1.49 (m, 4 H) ppm. (100 MHz, $CDCl_3$): $\delta$ = 137.9, 136.8, 136.7, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.7, 84.2, 77.6, 76.3, 75.7, 72.9, 72.7, 72.5, 67.8, 62.1, 39.0, 37.7, 27.4, 27.1 ppm. HRMS (ESI): calcd. for $C_{31}H_{40}O_{10}S_2$ $[M + H]^+$ 637.2141; found 637.2138.

**(2*S*,3*S*,4*R*,5*S*)-2,3,5-Tribenzyloxyoctan-1,4,8-triyl Trimethanesulfonate (12):** Prepared by the same procedure as that used for the preparation of compound **11**. Yield: 96%. $[\alpha]_D^{25}$ = –40 (*c* = 0.25, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3099, 3031, 2936, 1497, 1351, 1205, 973, 701 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34–7.26 (m, 15 H), 4.90 (t, *J* = 5.1 Hz, 1 H), 4.70–4.63 (m, 3 H), 4.52 (dt, *J* = 7.0, 11.7 Hz, 2 H), 4.45–4.38 (m, 2 H), 4.28 (dd, *J* = 4.4, 11.2 Hz, 1 H), 4.12 (m, 2 H), 3.93 (t, *J* = 4.8 Hz, 1 H), 3.86–3.83 (m, 1 H), 3.62 (m, 1 H), 2.95 (s, 3 H), 2.95 (s, 3 H), 2.91 (s, 3 H), 1.71–1.64 (m, 4 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 137.6, 136.6, 136.4, 128.8, 128.6, 128.4, 128.1, 127.8, 84.2, 75.9, 75.4, 73.3, 72.7, 72.3, 69.7, 67.2, 60.3, 42.8, 39.0, 37.6, 31.5, 27.0, 24.3, 14.3 ppm. HRMS (ESI): calcd. for $C_{32}H_{42}O_{12}S_3$[M + H]$^+$ 715.1838; found 715.1833.

**(4*S*)-4-[(3*R*,4*S*)-1-Benzyl-3,4-dibenzyloxypyrrolidin-2-yl]-4-benzyloxybutan-1-ol (14):** Dimesylate **11** (1.0 g, 1.57 mmol) was dissolved in benzylamine (5 mL) and stirred for 12 h at 90 °C. To this reaction mixture was added 1 N HCl (10 mL), and the mixture was then extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel column chromatography to afford colorless semisolid **14** (0.78 g, 91% yield). $[\alpha]_D^{25}$ = +30 (*c* = 0.5, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3429, 3061, 2929, 2865, 1604, 1495, 1453, 1263, 1210, 1144, 1062, 1027, 734, 698 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34–7.25 (m, 20 H), 4.76 (d, *J* = 11.7 Hz, 1 H), 4.60 (d, *J* = 7.0 Hz, 1 H), (d, *J* = 8.0 Hz,1 H), 4.44 (m, 3 H), 4.30 (d, *J* = 13.6 Hz, 1 H), 4.11 (dd, *J* = 4.8, 7.4 Hz, 1 H), 3.95 (q, *J* = 4.1, 8.5 Hz, 1 H), 3.85 (m, 1 H), 3.54 (t, *J* = 6.8 Hz, 2 H) 3.38 (d, *J* = 13.6 Hz, 1 H), 3.21 (dd, *J* = 3.4, 7.8 Hz, 1 H), 3.12 (dd, *J* = 3.8, 11.0 Hz, 1 H), 2.31 (m, 2 H), 1.76–1.65 (m, 4 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 139.5, 138.8, 138.4, 128.4, 128.2, 128.1, 127.7, 127.5, 126.7, 80.0, 79.6, 72.6, 71.7, 71.4, 65.6, 62.7, 60.7, 54.4, 49.4, 27.4 ppm. HRMS (ESI): calcd. for $C_{36}H_{41}NO_4$ $[M + H]^+$ 552.3114; found 552.3111.

**(1*R*,2*S*,8*S*,8a*S*)-Octahydroindolizin-1,2,8-triol (2):** To a stirred solution of **14** (0.60 g, 1.08 mmol) in DCM (10 mL) at 0 °C was added $Et_3N$ (0.16 mL, 6.00 mmol) followed by MsCl (0.15 mL, 5.73 mmol). After 1 h, aqueous $NaHCO_3$ (10 mL) was added, and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic layer was washed with brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude product was dissolved in 40% $CF_3CO_2H$ in MeOH and 10% Pd/C (300 mg) was added. The reaction mixture was subjected to 5 atm $H_2$ for 30 h at room temperature. The catalyst was filtered off through Celite, and concentrated in vacuo followed by purification by passing through anion exchange resin to afford **2** (149 mg, 78% yield). $[\alpha]_D^{25}$ = +81 (*c* = 0.85, MeOH) {ref.[16] $[\alpha]_D^{25}$ = +75 (*c* = 0.92, MeOH); ref.[15] $[\alpha]_D^{25}$ = +84.3 (*c* = 1.02, $H_2O$)}. M.p. 142–143 °C (lit.[9] m.p. 143–144 °C). IR (thin film): $\tilde{\nu}$ = 3305, 2937, 2858, 1578, 1413, 1342, 1261, 1219, 1143, 1085, 1024, 933 $cm^{-1}$. $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ = 4.34 (td, *J* = 2.9, 5.6 Hz, 1 H), 2.27 (dd, *J* = 3.4, 5.8 Hz, 1 H), 3.85 (ddd, *J* = 4.6, 9.5, 10.9, 1 Hz), 3.12–3.05 (m, 2 H), 2.77 (dd, *J* = 7.8, 11.0 Hz, 1 H), 2.23 (dt, *J* = 3.4, 12.4 Hz, 1 H), 2.15 (m, 1 H), 2.06 (m, 1 H), 1.77 (m, 1 H), 1.66 (qt, *J* = 4.2, 8.8 Hz, 1 H), 1.34–1.25 (m, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 77.9, 73.4, 72.8, 69.3, 65.3, 56.0, 36.6, 26.9 ppm. HRMS (ESI): calcd. for $C_8H_{15}NO_3$ $[M + H]^+$ 174.1130; found 174.1125.

**(1*R*,2*S*,8*S*,8a*S*)-Octahydroindolizine-1,2,8-triyl Triacetate (15):** To a stirred solution of **2** (50 mg, 0.28 mmol) in pyridine (2 mL) was added $Ac_2O$ (0.1 mL, 1.10 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred for 12 h at room temperature. Pyridine was removed in vacuo followed by workup with water (5 mL) and extraction with ethyl acetate (3 × 5 mL). The combined organic layer was washed with brine (5 mL), dried with $MgSO_4$, and concentrated in vacuo followed by purification by silica gel chromatography to afford pure triacetate **15** (84.68 mg, 98% yield). $[\alpha]_D^{25}$ = +28 (*c* = 0.25, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 2944, 2854, 2802, 11743, 1374, 1256, 1045, 901 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.52 (dd, *J* = 4.4, 6.6 Hz, 1 H), 5.21 (dt, *J* = 1.7, 8.0 Hz, 1 H), 4.95 (m, 1 H), 3.16 (dd, *J* = 1.6, 11.2 Hz 1 H), 3.05 (br. td, *J* = 2.9, 5.8, 10.7 Hz, 1 H), 2.58 (dd, *J* = 7.8, 11.2 Hz, 1 H), 2.16–2.08 (m, 1 H), 2.08 (s, 3 H), 2.03 (s, 3 H), 1.99 (s, 3 H), 1.94–1.89 (m, 1 H), 1.78–1.71 (m, 3 H), 1.28–1.18 (m, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 170.1, 169.9, 70.1, 69.7, 69.2, 68.0, 59.2, 51.7, 29.7, 23.2, 20.9, 20.5, 20.4 ppm. HRMS (ESI): calcd. for $C_{14}H_{21}NO_6$ $[M + H]^+$ 300.1147; found 300.1143.

**(2*S*,3*R*,4*R*,5*R*)-2,3,5-Tribenzyloxy-8,9-dihydroxynonane-1,4-diyl Dimethanesulfonate (23):** To a stirred solution of **22** (3.0 g, 5.74 mmol) in THF/$H_2O$ (4:1, 20 mL) was added NMO (0.71 g, 5.20 mmol) followed by a catalytic amount of $OsO_4$ at room temperature. The reaction mixture was stirred for 20 h and then treated with $Na_2S_2O_5$ (1.36 g, 6.88 mmol). The reaction mixture was further stirred for 1 h and then extracted with EtOAc (2 × 50 mL). The combined organic layer was washed with 1 N HCl, water, and finally brine, and it was then dried with $MgSO_4$ and concentrated in vacuo to give a crude product that was purified by silica gel column chromatography to afford vacuous liquid **23** (3.09 g, 98% yield). $[\alpha]_D^{25}$ = +3.6 (*c* = 0.6, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3434, 3063, 2927, 2870, 1605, 1495, 1453, 1355, 1208, 1096, 1027, 912 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.31 (m, 15 H), 5.20 (m, 1 H), 4.85 (dd, *J* = 3.6, 11.2 Hz, 1 H), 4.68 (dd, *J* = 4.6, 11.4 Hz, 1 H), 4.60 (d, *J* = 11.0 Hz, 1 H), 4.52 (d, *J* = 11.2 Hz, 1 H), 4.46 (d, *J* = 11.4 Hz, 1 H), 4.40 (d, *J* = 4.6 Hz, 2 H), 4.29 (t, *J* = 11.4 Hz, 1 H), 3.80 (m, 1 H), 3.74 (m, 1 H), 3.63 (m, 1 H), 3.52 (m, 1 H), 3.44 (m, 1 H), 3.31 (m, 1 H), 3.00 (s, 3 H), 2.93 (s, 3 H), 2.02 (br. s, 2 H), 1.63 (m, 3 H), 1.55 (m, 1 H) ppm. $^{13}C$ NMR (100 MHz): $\delta$ = 137.3,

137.2, 136.9, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 82.2, 78.5, 76.3, 75.0, 72.8, 72.0, 71.2, 67.8, 66.6, 39.1, 37.3, 28.9, 28.3, 25.9, 25.2 ppm. HRMS (ESI): calcd. for $C_{32}H_{42}O_{11}S_2$ [M + H]$^+$ 667.2247; found 667.2232.

**(5*R*)-5-[(3*S*,4*S*)-1-Benzyl-3,4-dibenzyloxypyrrolidin-2-yl]-5-benzyloxypentan-1,2-diol (27):** Prepared by the same procedure as that used for the preparation of **14**. Yield: 3.00, 85%. $[\alpha]_D^{25}$ = +25 (*c* = 1.0, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3411, 3086, 3062, 3029, 2923, 1670, 1495, 1453, 1393, 1092, 1072, 736, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.35–7.24 (m, 20 H), 4.73 (dd, *J* = 1.9, 11.2 Hz, 1 H), 4.54–4.43 (m, 6 H), 4.02 (dd, *J* = 2.9, 8.0 Hz, 1 H), 3.95 (dd, *J* = 3.4, 13.1 Hz, 1 H), 3.88 (d, *J* = 4.1 Hz, 1 H), 3.55–3.44 (m, 4 H), 3.35 (m, 1 H), 3.15 (dd, *J* = 4.8, 10.4 Hz, 1 H), 3.05 (d, *J* = 3.6 Hz, 1 H), 2.59 (dd, *J* = 4.4, 10.7 Hz, 1 H), 2.02 (m, 1 H), 1.52–1.41 (m, 4 H) ppm. $^{13}$C NMR (100 MHz): $\delta$ = 138.2, 128.7, 128.3, 128.1, 127.6, 127.0, 84.5, 81.0, 72.0, 71.6, 71.4, 70.6, 66.6, 60.1, 57.6, 30.2, 26.6, 26.4 ppm. HRMS (ESI): calcd. for $C_{37}H_{43}NO_5$ [M + H]$^+$ 582.3219; found 582.3206.

**(5*R*)-5-[(3*S*,4*S*)-1-Benzyl-3,4-dibenzyloxypyrrolidin-2-yl]-5-benzyloxy-1-trityloxypentan-2-ol (28):** A solution of diol **27** (1.5 g, 1.82 mmol) in $CH_2Cl_2$ (20 mL) was treated with TrCl (0.75 mL, 2.73 mmol) and $Et_3N$ (0.76 mL, 5.65 mmol). The reaction mixture was stirred for 8 h and then $H_2O$ (20 mL) was added. The reaction mixture was extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layer was washed with brine(30 mL), dried with $MgSO_4$, and concentrated in vacuo to afford the crude tritylated product, which was purified by silica gel chromatography to give a colorless viscous tritylated product (1.7 g, 80% yield). $[\alpha]_D^{25}$ = +1.50 (*c* = 0.4, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3582, 3445, 3085, 30360, 3029, 2923, 2866, 2794, 1670, 1598, 1493, 1450, 1367, 1212, 1092, 1074, 1028, 901, 737, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.43–7.21 (m, 35 H), 4.74 (dd, *J* = 1.3, 11.2 Hz, 1 H), 4.51–4.40 (m, 5 H), 3.98 (d, *J* = 12.9 Hz, 2 H), 3.85 (s, 1 H), 3.46 (d, *J* = 12.9 Hz, 2 H), 3.11–2.99 (m, 4 H), 2.55 (dd, *J* = 3.2, 6.1 Hz, 1 H), 2.02–1.94 (m, 1 H), 1.56–1.54 (m, 1 H), 1.40 (m, 2 H), 1.25 (s, 1 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 144.0, 128.7, 128.3, 128.0, 127.8, 127.6, 127.5, 126.9, 1269, 86.5, 81.1, 72.1, 71.7, 71.4, 70.5, 60.2, 57.5, 30.6 ppm. HRMS (ESI): calcd. for $C_{56}H_{57}NO_5$ [M + H]$^+$ 824.4315; found 824.4305.

**(5*R*)-5-[(3*S*,4*S*)-1-Benzyl-3,4-dibenzyloxypyrrolidin-2-yl]-5-benzyloxy-1-trityloxypentan-2-yl Methanesulfonate (29):** To a stirred solution of **28** (1.50 g, 1.82 mmol) in $CH_2Cl_2$ (30 mL) at 0 °C was added $Et_3N$ (0.29 mL, 2.17 mmol) followed by MsCl (0.15 mL, 2.00 mmol) and a catalytic amount of DMAP. After 4 h, aqueous $NaHCO_3$ (20 mL) was added, and the organic layer was washed with $H_2O$ (2 × 40 mL) followed by brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification by silica gel column chromatography afforded a colorless viscous liquid (1.51 g, 92% yield). $[\alpha]_D^{25}$ = +6.0 (*c* = 0.9, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3060, 3030, 2928, 1702, 1493, 1451, 1362, 1265, 1090, 1027, 907, 739, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.43–7.21 (m, 35 H), 4.69 (dd, *J* = 3.4, 11.4 Hz, 2 H), 4.49–4.35 (m, 6 H), 3.94 (m, 2 H), 3.81 (d, *J* = 3.9 Hz, 1 H), 3.46 (dd, *J* = 4.8, 13.2 Hz, 1 H), 3.13 (m, 1 H), 3.00 (d, *J* = 10.5 Hz, 1 H), 2.81 (s, 3 H), 2.54 (dd, *J* = 4.1, 10.4 Hz, 1 H), 1.93 (m, 2 H), 0.84 (m,1 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 143.5, 142.6, 142.4, 139.2, 138.4, 138.2, 138.1, 128.9, 128.6, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 127.1, 126.9, 86.9, 84.9, 84.8, 83.2, 82.8, 80.8, 79.3, 78.9, 72.2, 72.2, 72.1, 71.6, 71.5, 71.4, 71.3, 70.5, 65.1, 60.1, 57.6, 38.5, 29.0, 28.8, 26.4, 26.2 ppm. HRMS (ESI): calcd. for $C_{56}H_{57}NO_7S$ [M + H]$^+$ 902.4090; found 902.4078.

**(1*S*,2*S*,5*R*,8*R*,8a*S*)-1,2,8-Tribenzyloxy-5-trityloxymethyloctahydroindolizine (30):** Mesylate derivative **29** (1.4 g, 1.55 mmol) in methanol (30 mL) was stirred under an atmosphere of $H_2$ in the presence of 10% Pd/C (560 mg) at room temperature for 1 h. The reaction mixture was filtered through Celite to remove the catalyst and then concentrated in vacuo. At this stage, diastereomers **30** and **31**[26] were separated by silica gel chromatography to give pure bicyclic product **30** (0.43 g, 38% yield). $[\alpha]_D^{25}$ = +5.3 (*c* = 0.6, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 3366, 3060, 3030, 2926, 1600, 1492, 1450, 1359, 1206, 1152, 1089, 1028, 744, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.44–7.11 (m, 30 H), 4.53 (d, *J* = 12.4 Hz, 1 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.37–4.28 (m, 3 H), 4.21 (d, *J* = 11.2 Hz, 1 H), 4.08 (dd, *J* = 2.6, 9.2 Hz, 1 H), 3.83 (dd, *J* = 2.6, 6.1 Hz, 1 H), 3.66 (br. s, 1 H), 3.28 (dd, *J* = 5.4, 9.2 Hz, 1 H), 3.17 (d, *J* = 10.7 Hz, 1 H), 3.08 (dd, *J* = 6.1, 15.6 Hz, 1 H), 2.34 (dd, *J* = 6.8, 10.5 Hz, 1 H), 2.23 (m, 1 H), 2.10–2.03 (m, 2 H), 1.70 (m, 1 H), 1.57 (m, 1 H), 1.28 (m, 1 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 137.2, 137.0, 125.5, 128.3, 128.1, 127.9, 127.7, 127.5, 126.7, 79.4, 79.3, 76.2, 75.6, 74.4, 73.2, 72.1, 71.1, 68.8, 39.3, 38.6, 37.2, 29.6, 22.0 ppm. HRMS (ESI): calcd. for $C_{49}H_{49}NO_4$ [M + H]$^+$ 716.3740; found 716.3732.

**(1*S*,2*S*,5*S*,8*R*,8a*S*)-5-(Hydroxymethyl)octahydroindolizine-1,2,8-triol (32):** The indolizidine derivative (0.4 g, 0.55 mmol) in 40% TFA methanol (30 mL) was stirred under 5 atm of $H_2$ in the presence of 10% Pd/C (300 mg) at room temperature for 30 h. The reaction mixture was filtered through Celite to remove the catalyst and concentrated in vacuo. The residue was purified by passing through a Dowex basic resin (109 mg, 90% yield). $[\alpha]_D^{25}$ = +19.2 (*c* = 1.0, MeOH). IR (thin film): $\tilde{\nu}$ = 3397, 3031, 2929, 1665, 1415, 1336, 1278, 1211, 1059, 738, 699 cm$^{-1}$. $^1$H NMR (400 MHz, $D_2O$): $\delta$ = 4.14 (m, 3 H), 3.88 (br. d, *J* = 4.1 Hz, 1 H), 3.72 (dd, *J* = 4.6, 12.6 Hz, 1 H), 3.64 (m, 1 H), 3.59 (s, 1 H), 3.27 (s, 1 H), 3.13 (br. d, *J* = 11.7 Hz, 1 H), 1.91 (t, *J* = 5.8 Hz, 1 H), 1.73 (m, 2 H), 1.62 (dd, *J* = 5.6, 14.6 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz, $D_2O$): $\delta$ = 76.6, 74.4, 67.4, 63.4, 59.8, 58.9, 56.7, 24.8, 20.9 ppm. HRMS (ESI): calcd. for $C_9H_{17}NO_4$ [M + H]$^+$ 204.1236; found 204.1224.

**(1*S*,2*S*,5*R*,8*R*,8a*S*)-5-(Acetoxymethyl)octahydroindolizine-1,2,8-triyl Triacetate (34):** Polyhydroxy derivative **32** (50 mg, 0.24 mmol) in pyridine and acetic anhydride (1:0.5, 2 mL) was stirred for 20 h at room temperature The reaction mixture was dissolved in $CH_2Cl_2$ (5 mL) and washed with water (2 × 4 mL) and brine (3 mL), dried with $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography to give the pure tetraacetate derivative (84 mg, 97% yield). $[\alpha]_D^{25}$ = +2.3 (*c* = 0.3, $CH_2Cl_2$). IR (thin film): $\tilde{\nu}$ = 2960, 2927, 2855, 1739, 1651, 1551, 1428, 1374, 1260, 1104, 1028 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 5.06 (dd, *J* = 2.9, 6.8 Hz, 1 H), 5.03 (d, *J* = 2.6 Hz, 1 H), 4.99 (m, 1 H), 4.29 (dd, *J* = 5.8, 11.4 Hz, 1 H), 4.08 (dd, *J* = 6.1, 11.4 Hz,1 H) 3.25 (dd, *J* = 6.8, 10.9 Hz, 2 H), 3.05 (dd, *J* = 2.2, 11.0 Hz, 1 H), 2.88 (dd, *J* = 2.4, 6.8 Hz, 1 H), 2.16 (s, 3 H), 2.09 (s, 3 H), 2.07 (s, 3 H), 2.06 (s, 3 H), 1.90 (m, 2 H), 1.56 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.8, 170.7, 170.5, 170.0, 77.4, 76.1, 66.2, 61.9, 60.3, 55.2, 52.9, 23.6, 21.1, 21.0, 20.8, 20.7 ppm. HRMS (ESI): calcd. for $C_{17}H_{25}NO_7$ [M + H]$^+$ 372.1658; found 372.1638.

**Supporting Information** (see footnote on the first page of this article): All spectroscopic data for the remaining unknown compounds; detailed experimental procedure for the evaluation of enzyme inhibition activity of **32**, **33**, **54**, and **55**.

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