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Stereoselective Total Syntheses of (+)-Castanospermine and Neu5Ac Methyl Ester

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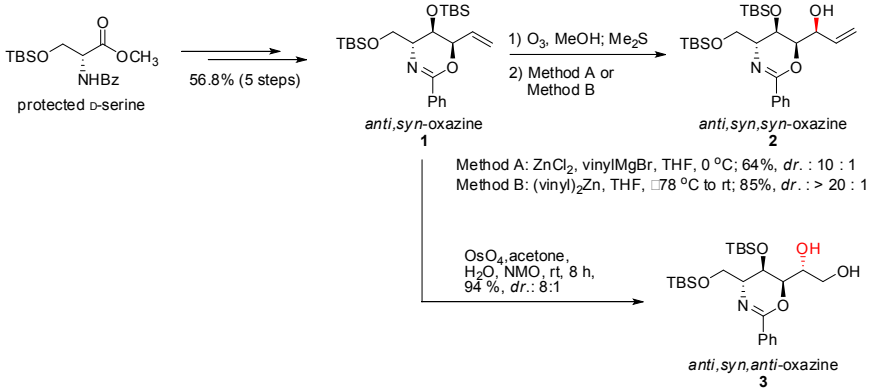
Supporting Information Placeholder

ABSTRACT

Concise and stereocontrolled total syntheses of (+)-castanospermine and Neu5Ac methyl ester were achieved from diastereomerically enriched *anti*,*syn*,*syn*-1,3-oxazine and *anti*,*syn*,*anti*-1,3-oxazine, respectively. The key step in this strategy was the stereoselective $BF_3{\cdot}OEt_2$-mediated allylation.

INTRODUCTION

Aiming to synthesize biologically active and useful compounds, we have developed facile synthetic strategies for the polyhydroxylated alkaloids containing more than three contiguous stereogenic centers,[1,2] for example, the piperidines D-fagomine,[2b] (+)-1-deoxynojirimycin,[1e] (+)-1-deoxygalactonojirimycin,[1c] (−)-1-deoxygulonojirimycin,[1c] and (−)-1-deoxymannojirimycin;[1a] the pyrrolidines DAB-1,[2b] (+)-DMDP,[1e] (+)-DGDP,[1a] and (+)-radicamine B;[1d] a pyrrolizidine (+)-hyacinthacine A_2;[1f] and an indolizidine (−)-lentiginosine;[1h] using *anti*,*syn*-1,3-oxazine **1**, *anti*,*syn*,*syn*-1,3-oxazine **2**, and *anti*,*syn*,*anti*-1,3-oxazine **3** as diastereomerically enriched chiral building blocks (Scheme 1).



Scheme 1. Our previous research regarding chiral *anti,syn*-1,3-oxazine **1**, *anti,syn,syn*-1,3-oxazine **2**, and *anti,syn,anti*-1,3-oxazine **3**.

Polyhydroxylated alkaloids isolated from plants and microorganisms act as glycosidase inhibitors by mimicking natural saccharide molecules.[3] Among such polyhydroxylated

alkaloids, an indolizidine alkaloid (+)-castanospermine (**4**) (Figure 1), isolated from *Castanospermum australe* in 1981,[4] is particularly important because of its antiviral activity against the human immunodeficiency virus (HIV), herpes simplex virus (HSV), and hepatitis C virus (HCV), as well as its glycosidase inhibitory effects.[5] In particular, a semi-synthetic derivative, celgosivir, has been evaluated by Aventis for the treatment of HCV.[6] Thus, many schemes for total syntheses of (+)-castanospermine (**4**),[7,8,9] have been reported.

Neu5Ac (*N*-acetylneuraminic acid) belongs to a class of acidic monosaccharides with a nine-carbon skeleton found at the terminal positions of glycoproteins, glycolipids, and oligosaccharides.[10] It is involved in virus–cell interactions, cell differentiation, cell growth, and also plays a role in some pathologies, such as inflammatory diseases, cancer metastasis, and viral infections.[11] Neuraminidase is an enzyme that cleaves the terminal sialic acid residues in glycoproteins and glycolipids.[12] This process is essential for the growth of new viruses and their emission via the respiratory system.[13] Zanamivir and oseltamivir are the best examples of neuraminidase inhibitors which prevent such viral growth.[14] Because of the importance of these type of compounds, many synthetic routes to Neu5Ac have been reported.[15] Herein, we describe the total syntheses of (+)-castanospermine (**4**) and Neu5Ac methyl ester (**5**) via stereoselective allylations from *anti*,*syn*,*syn*-1,3-oxazine **2** and *anti*,*syn*,*anti*-1,3-oxazine **3**, respectively.

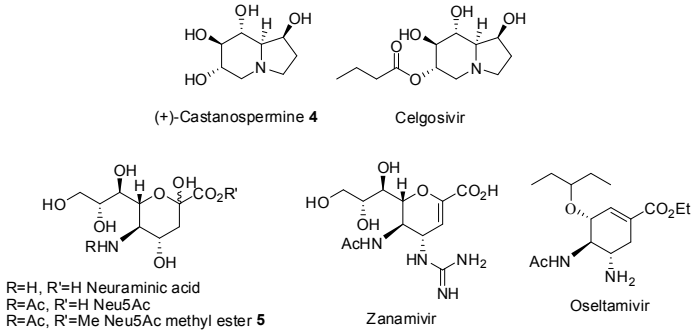
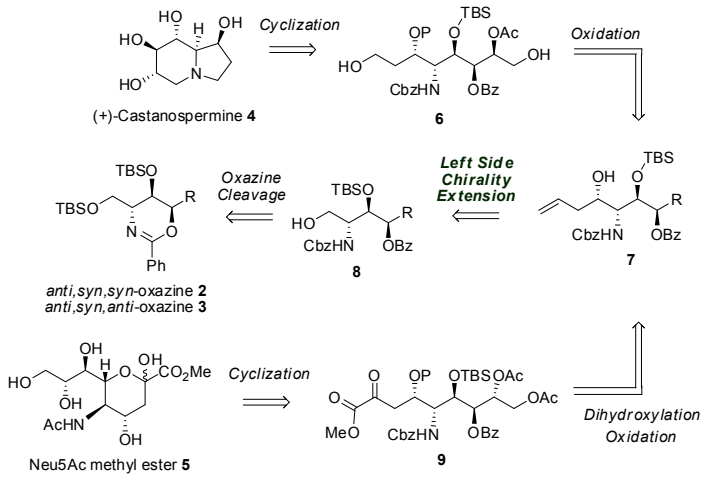


Figure 1. Structures of (+)-castanospermine (**4**) and NeuAc methyl ester (**5**).

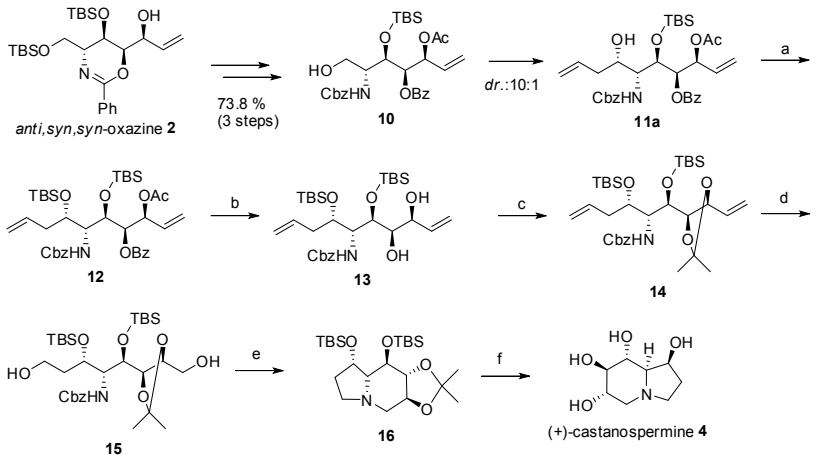
Recently, we reported the stereoselective allylation reactions to acyclic α-amino-β-hydroxy aldehydes.[16] There are several examples in the literature for the use of cyclic α-amino-β-hydroxy aldehydes which have four contiguous stereocenters in the total syntheses of the members of castanospermine family and their congeners. Nevertheless, reactions to acyclic aldehydes which have four contiguous stereocenters have not been reported yet. *Thus, this is the first report wherein stereoselectivities are achieved in cases of the linear and chiral α-amino-β-hydroxy aldehydes which have four contiguous stereocenters.*

RESULTS AND DISCUSSION



Scheme 2. Retrosynthetic analysis of (+)-castanospermine (**4**) and NeuAc methyl ester (**5**)

According to our retrosynthetic analysis (Scheme 2) (+)-castanospermine (**4**) could be obtained by two successive cyclizations from compound **6**, which contains two primary alcohol moieties. Compound **6** could be derived from the conversion of the terminal olefins of homoallylic alcohol **7**, which contains five contiguous stereogenic centers in its structure. Neu5Ac methyl ester (**5**) can be obtained by the acid-catalyzed *O*-cyclization of α-keto ester **9** which in turn could be prepared from homoallylic alcohol **7** via dihydroxylation followed by oxidation and esterification. Homoallylic alcohol **7** could be converted by aldehyde oxidation and Lewis acid-mediated allylation from primary alcohol **8** which in turn could be obtained from the previously reported *anti*,*syn*,*syn*-1,3-oxazine **2**, and *anti*,*syn*,*anti*-1,3-oxazine **3**.

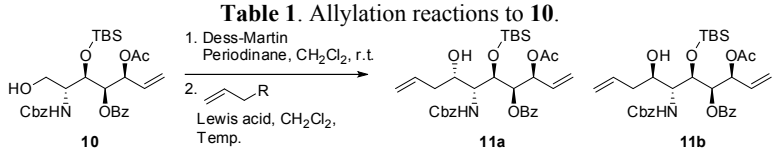


Scheme 3. Total synthesis of (+)-castanospermine (**4**). Reagents and conditions: (a) TBSCl, imidazole, dimethylformamide (DMF), 50 °C, 24 h, 82%; (b) NaOMe, MeOH, 0 °C, 12 h, 79%; (c) 2,2-dimethoxypropane, pyridinium *p*-toluenesulfonate (PPTS), DMF, 60 °C, 12 h, 63%; (d) O_3, MeOH, then $NaBH_4$, 0 °C, 3 h, 56%; (e) i. MsCl, triethylamine (TEA), CH_2Cl_2, 0 °C, 1 h; ii. $Pd(OH)_2$, H_2, rt, 12 h; iii. TEA, MeOH, reflux, 12 h, 64%; and (f) 1 N HCl, MeOH, rt, 12 h, then DOWEX-50WX8-100, 89%.

Total synthesis of (+)-castanospermine (4). To begin with, primary alcohol **10** was prepared by our previously reported method from *anti*,*syn*,*syn*-1,3-oxazine **2** (Scheme 3).[1g] The results of allylation to the aldehyde obtained after Dess–Martin oxidation of corresponding primary alcohol **10** are shown in Table 1. $SnCl_4$-mediated reaction with allyltrimethylsilane as a nucleophile afforded stereoisomers **11a** and **11b** with low diastereoselectivity (entry 1). $TiCl_4$-mediated reaction with allyltrimethylsilane afforded amino alcohols **11a** and **11b** in a 3:1 ratio (entry 2), while $MgBr_2{\cdot}OEt_2$ and $ZnCl_2$-mediated reaction using allyltrimethylsilane as a

nucleophile did not proceed (entries 3 and 4). However, $MgBr_2 \cdot OEt_2$-mediated reaction with allyltributyltin afforded the corresponding products with 2:1 diastereoselectivity (entry 5). The reaction mediated by $BF_3 \cdot OEt_2$ with allyltributyltin afforded *syn*-alcohol **11a** as the major diastereomer (**11a**/**11b** = 10:1) in 76% yield (entry 6).

Table 1. Allylation reactions to **10**.

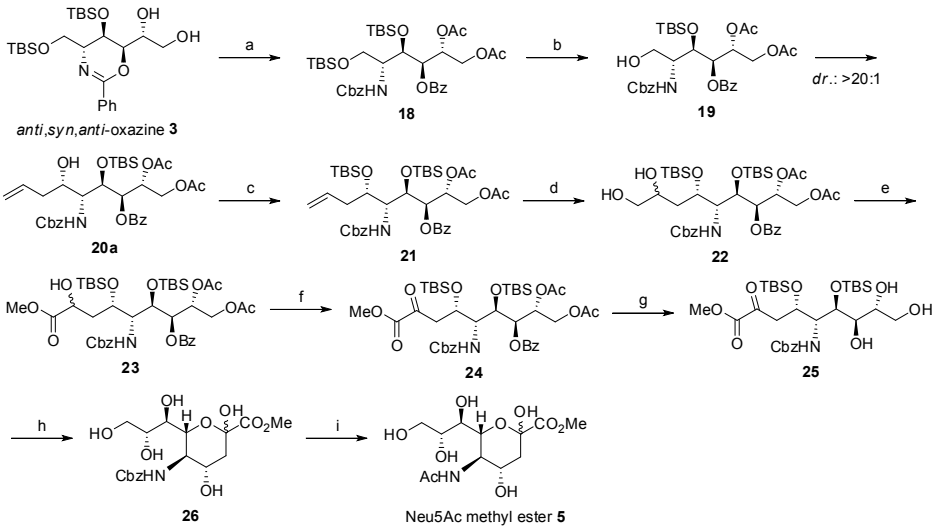


Entry	R	Lewis acid	Temp.	Time (h)	Ratio (**11a**:**11b**) [a]	Yield (%) [b]
1	$SiMe_3$	$SnCl_4$	−78 °C	1	1:1.5	72
2	$SiMe_3$	$TiCl_4$	−78 °C	3	3:1	57
3	$SiMe_3$	$MgBr_2 \cdot OEt_2$	0 °C	12	−	N.R.
4	$SiMe_3$	$ZnCl_2$	0 °C	12	−	N.R.
5	$SnBu_3$	$MgBr_2 \cdot OEt_2$	0 °C	12	2:1	52
6	$SnBu_3$	$BF_3 \cdot OEt_2$	−78 °C	1	10:1	76

[a] Ratios were determined by ^1H NMR analysis.
[b] Yields refer to two-step yields of mixed isomers.

Thus, obtained *syn*-alcohol **11a** was protected by an acetyl group. Our attempts to synthesize diol **6** were not successful. The reason for this failure might be the migration of the secondary benzoyl and acetyl groups onto the newly generated primary hydroxyl groups.[17] To avoid this, we changed the protecting group to the one with a low probability of migration.

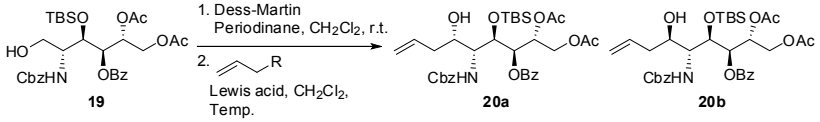
Accordingly, *syn*-alcohol **11a** was protected by a TBS group (Scheme 3). The secondary benzoyl and acetyl groups of resulting **12** were deprotected using NaOMe at 0 °C in 79% yield. Secondary diol **13** was then protected as acetonide with 2,2-dimethoxypropane. Primary diol **15** was successfully obtained by reductive ozonolysis of acetonide-protected **14**, with little migration of the acetonide group. Primary diol **15** was then transformed into its primary dimesyl derivative, which on hydrogenolysis and subsequent treatment with triethylamine afforded protected castanospermine **16**. Finally, removal of all the protecting groups of **16** by treatment with 1 N HCl yielded **4**·**HCl** salt, which was neutralized by ion-exchange chromatography to afford synthetic (+)-castanospermine (**4**) at 89% yield. The optical rotation of synthetic **4**, $[\alpha]_D^{20}$ +78.3 (*c* 0.1, H_2O), was consistent with the reported value, $[\alpha]_D^{25}$ +76.9 (*c* 0.1, H_2O),[8g] thus confirming its absolute configuration. Spectroscopic (^1H and ^{13}C NMR) data and other properties of synthetic (+)-castanospermine (**4**) were in good agreement with the reported ones.[8g]



Scheme 4. Total synthesis of Neu5Ac methyl ester (**5**). Reagents and conditions: (a) i. Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 2 h, 93%; ii. CbzCl, 0.6 M aqueous $NaHCO_3$, CH_2Cl_2, 50 °C, 48 h, 80%; and (b) HF–pyr., pyridine, THF, 0 °C, 12 h, 92%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 20 min, 93%; (d) OsO_4, NMO, acetone/H_2O, 0 °C, 8 h, 91%; (e) i. TEMPO, $NaClO_2$, NaClO, phosphate buffer, toluene, 50 °C; ii. MeI, K_2CO_3, DMF, 67%; and (f) Dess–Martin periodinane, CH_2Cl_2, rt; (g) NaOMe, MeOH, 0 °C, 68% from **23**; and (h) 50% aq. HF, MeCN, 0 °C, 46%; and (i) H_2/$Pd(OH)_2$, Ac_2O, THF, 51%.

Total synthesis of Neu5Ac methyl ester (5). To begin the total synthesis of Neu5Ac methyl ester (**5**), the diol in *anti,syn,anti*-1,3-oxazine **3** was protected with Ac_2O (Scheme 4). Under Schotten–Baumann conditions with CbzCl and $NaHCO_3$ in CH_2Cl_2/H_2O at 50 °C, the 1,3-oxazine ring was cleaved to give benzyl carbamate **18**. The primary silyl ether of benzyl carbamate **18** was cleaved by HF·pyridine to furnish primary alcohol **19**. The results of the allylation to corresponding aldehyde, obtained after the Dess–Martin oxidation of primary alcohol **19** are shown in Table 2. The reactions mediated by $SnCl_4$ and $TiCl_4$ with allyltrimethylsilane afforded isomers **20a** and **20b** with low diastereoselectivity (entries 1 and 2). $MgBr_2·OEt_2$ and $ZnCl_2$-mediated reactions using allyltrimethylsilane did not proceed (entries 3 and 4). However, $MgBr_2·OEt_2$-mediated reaction with allyltributyltin as the nucleophile afforded the corresponding products with 1.6:1 diastereoselectivity (entry 5). The reaction mediated by $BF_3·OEt_2$ with allyltributyltin afforded *syn*-alcohol **20a** as the major diastereomer (**20a**/**20b** > 20:1) in 83% yield (entry 6).

Table 2. Allylation reactions to **19**.



Entry	R	Lewis acid	Temp.	Time (h)	Ratio (**20a**:**20b**)[a]	Yield (%)[b]
1	$SiMe_3$	$SnCl_4$	−78 °C	1	1.2:1	68
2	$SiMe_3$	$TiCl_4$	−78 °C	3	1.4:1	78
3	$SiMe_3$	$MgBr_2·OEt_2$	0 °C	12	–	N.R.
4	$SiMe_3$	$ZnCl_2$	0 °C	12	–	N.R.
5	$SnBu_3$	$MgBr_2·OEt_2$	0 °C	12	1.6:1	72
6	$SnBu_3$	$BF_3·OEt_2$	−78 °C	1	>20:1	83

[a] Ratios were determined by ^1H NMR analysis.
[b] Yields refer to two-step yield of the mixed isomers.

The newly introduced hydroxyl group of **20a** was protected with TBS group using TBSOTf

and 2,6-lutidine to give **21** (Scheme 4). Subsequently, dihydroxylation of **21** was carried out using OsO_4 to result in diol **22**.

To introduce the α-keto ester functionality and obtain **24**, we planned to employ the methoxyallene strategy reported by Bressel and Reissig.[15d] However, when corresponding aldehyde of diol **22** was treated with lithiated methoxyallene (10 equiv.) the desired product was not be obtained. The reason for this failure was thought to be the instability of both acetyl and benzoyl esters toward nucleophiles. Hence, an oxidation strategy was adopted. Aldehyde which was obtained via Swern oxidation of **22** was subjected to Pinnick oxidation expecting the formation of α-keto acid moiety. However, no reaction was observed. Nonetheless, introduction of an α-keto methyl ester via oxidation with 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) has been reported by Yao *et al*.[18] Thus, we decided to employ these reaction conditions, since the substrates used in their work are similar to the presents ones. Diol **22** was treated with TEMPO, tetra-*n*-butylammonium bromide (TBAB), KBr, and $Ca(ClO)_2$ in CH_3CN and sat. $NaHCO_3$ solution to obtain the corresponding α-keto carboxylic acid. Contrary to our expectation, the reaction furnished aldehyde moiety via an oxidative cleavage. To avoid this side reaction, we changed the solvent and reagents, as reported by Shibuya *et al*.[19] Treatment of diol **22** with TEMPO, $NaClO_2$, NaClO, and phosphate buffer (pH = 6.8) in toluene at 50 °C for 24 h gave the desired α-hydroxy acid, which was directly subjected to esterification with MeI to afford α-hydroxy ester **23**, which was then subjected to Dess–Martin oxidation to afford α-keto ester **24** (Scheme 4).

Subsequently, to obtain pyranoside methyl ester **26**, several reaction conditions were tested. First, TBS desilylation of **24** with TBAF, followed by deprotection of the benzoyl and acetyl groups was attempted, but in vain. We considered that the free hydroxyl group at the β-position of the carbonyl might be involved in a retro aldol reaction under basic conditions, thus preventing the formation of expected product **26**. Therefore, deprotection of the benzoyl and acetyl groups was carried out before the deprotection of the TBS groups. The afforded triol **25** was subjected to several test reactions. TBS deprotection reactions with TBAF and Amberlyst-15 did not yield the target compound. When 50% aq. HF was used, the TBS group was removed, and cyclization occurred to afford pyranoside methyl ester **26** (Scheme 4). Maintaining the reaction temperature at 0 °C was a crucial factor for preventing the side reactions. Finally, exchange of the amino protecting group via palladium-catalyzed hydrogenation in the presence of Ac_2O was conducted. When THF was used as solvent, reaction was successful and afforded Neu5Ac methyl ester (**5**) in 51% yield. The optical rotation of synthetic **5**, $[\alpha]_D^{20}$ –24.5 (*c* 0.2, MeOH), was consistent with the reported value, $[\alpha]_D^{20}$ −23.4 (*c* 1.0, MeOH),[15f] thus confirming its absolute configuration. The spectroscopic (^1H and ^{13}C NMR) data and other properties of synthetic Neu5Ac methyl ester (**5**) were in good agreement with the reported ones.[15c]

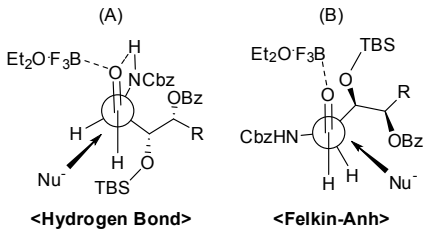


Figure 2. Proposed mechanism of stereoselective allylations.

The possible transition states for the nucleophilic allylations are summarized in Figure 2. Allylations to the aldehydes would proceed via the hydrogen bonding (Figure 2A), and not the Felkin–Anh model (Figure 2B), which would result in *syn*-alcohol **11a** and **20a**. Similar hydrogen bonding effects mediated by $BF_3{\cdot}OEt_2$ were previously observed.[16a,20]

CONCLUSION

In conclusion, we have described new procedures for the diastereoselective allylations to the acyclic and chiral aldehydes which have four contiguous stereocenters. The diastereoselectivity during the allylations was predominantly controlled by $BF_3 \cdot OEt_2$. We took advantage of this reaction and various other known transformations to synthesize (+)-castanospermine (**4**) and Neu5Ac methyl ester (**5**). The main advantage of this strategy is its high versatility, which could allow the preparation of a wide range of biologically active polyhydroxylated alkaloids. Further results of the allylation to acyclic and chiral α-amino aldehydes will be reported in future studies.

EXPERIMENTAL SECTION

General information. Commercially available reagents were used without additional purification, unless otherwise stated. All non-aqueous reactions were performed under an argon atmosphere with commercial-grade reagents and solvents, unless otherwise stated. THF was distilled from sodium and benzophenone (indicator). CH_2Cl_2 was distilled from calcium hydride. Optical rotations were measured using a Jasco P1020 polarimeter in the specified solvent. Specific rotations are reported in 10^{-1} deg cm^2/g and concentrations in g/100 mL. IR spectra were obtained using an FT-IR spectrometer. ^1H and $^{13}C\{^1H\}$ NMR spectroscopic data were recorded using an FT-NMR spectrometer at 75, 101, 300, or 400 MHz. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or deuterated chloroform ($CDCl_3$) as the internal standards, and the coupling constants are reported in hertz. High-resolution mass spectroscopic (HRMS) data were obtained using an Agilent 6530 Accurate-Mass Q-TOF liquid chromatography (LC)/MS high-resolution mass spectrometer equipped with a magnetic sector–electric sector double-focusing analyzer. Flash chromatographic separation was performed using mixtures of hexanes and ethyl acetate or methanol and chloroform as the eluents.

Total synthesis of (+)-castanospermine (4). *(3S,4R,5R,6R,7R)-3-Acetoxy-6-(((benzyloxy)carbonyl)amino)-5-((tert-butyldimethylsilyl) oxy)-7-hydroxydeca-1,9-dien-4-yl benzoate* (**11a**). To a solution of primary alcohol **10** (54 mg, 0.09 mmol) in anhydrous dichloromethane (0.9 mL), Dess–Martin periodinane (59 mg, 0.14 mmol) was added at room temperature. The reaction mixture was stirred at ambient temperature for 2 h. The mixture was diluted with Et_2O, and then saturated $NaHCO_3$ (53 mg, 0.63 mmol) and $Na_2S_2O_3$ (172 mg, 0.354 mmol) were added, and the heterogeneous mixture was stirred at room temperature until the organic layer was clear. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting substance was immediately used without further purification. A solution of $BF_3 \cdot OEt_2$ (0.05 mL, 0.14 mmol) was slowly added to a solution of the above in anhydrous CH_2Cl_2 (0.9 mL) at –78 °C. This solution was stirred for 5 min at the same temperature, and allyltributyltin (0.08 mL, 0.18 mmol) was added dropwise to this reaction mixture at –78 °C. The mixture was stirred at –78 °C until a thin-layer chromatography (TLC) plate indicated the complete reaction. The reaction was diluted with ethyl acetate and quenched with aqueous saturated $NaHCO_3$, and the organic phase was washed with saturated brine, dried with $MgSO_4$, and then concentrated *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 4:1) gave **11a** (42 mg, 0.068 mmol, 76% yield) as a colorless oil. $R_f = 0.33$ (hexanes:ethyl acetate = 4:1); $[\alpha]_D^{20}$ −16.6 (*c* 0.15, $CHCl_3$); IR (neat) ν_{max} 3449, 2930, 2857, 1724, 1500, 1452, 1371, 1271, 1228, 1108, 1026, 936, 839, 778, 712; ^1H

NMR ($CDCl_3$, 300 MHz) δ 7.97–8.09 (m, 2 H), 7.53–7.63 (m, 1 H), 7.29–7.50 (m, 7 H), 5.75–5.93 (m, 2 H), 5.02–5.66 (m, 9 H), 4.36 (dd, *J* = 7.5, 3.1 Hz, 1 H), 4.27 (t, *J* = 6.9 Hz, 1 H), 3.73 (dd, *J* = 8.3, 2.9 Hz, 1 H), 2.35 (dt, *J* = 14.3, 7.2 Hz, 1 H), 2.23 (dt, *J* = 14.3, 7.2 Hz, 1 H), 2.16 (s, 3 H), 0.69–0.81 (m, 9 H), −0.09 to 0.09 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 165.8, 155.9, 136.5, 133.7, 133.3, 131.9, 129.8, 128.5, 128.1, 119.1, 118.5, 74.4, 74.2, 72.5, 69.6, 66.9, 53.3, 38.2, 25.7, 20.9, 17.9, −4.5, −4.6; HRMS (EI+) [$(M+H)^+$] *m/z* calcd for $C_{33}H_{46}NO_8Si$ 612.2987; found 612.2989.

(3S,4R,5R,6R,7R)-3-Acetoxy-6-(benzyloxycarbonylamino)-5-(tert-butyldimethylsilyloxy)-7-hydroxydeca-1,9-dien-4-yl benzoate (**11b**). R_f = 0.25 (hexanes:ethyl acetate = 4:1); $[\alpha]_D^{20}$ 7.5 (*c* 0.2, $CHCl_3$); IR (neat) ν_{max} 3452, 3069, 2929, 2857, 1726, 1509, 1229, 1122, 1026, 838, 777, 712; ^1H NMR ($CDCl_3$, 300M Hz) δ 7.99–8.08 (m, 2 H), 7.52–7.62 (m, 1 H), 7.37–7.47 (m, 2 H), 7.22–7.36 (m, 5 H), 5.73–5.94 (m, 3 H), 5.66 (t, *J* = 5.3 Hz, 1 H), 4.95–5.43 (m, 7 H), 4.30 (dd, *J*=4.9, 3.0 Hz, 1 H), 3.72–3.86 (m, 2 H), 2.38–2.52 (m, 1 H), 2.14–2.31 (m, 1 H), 2.02 (s, 3 H), 0.75–0.88 (m, 9 H), −0.04 to 0.12 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0, 166.0, 156.1, 136.5, 134.2, 133.3, 132.4, 129.8, 128.5, 128.4, 127.9, 119.3, 119.1, 74.6, 72.8, 71.4, 70.0, 66.7, 57.4, 38.9, 25.7, 20.9, 18.0, −4.3, −4.4; HRMS (EI+) [$(M+H)^+$] *m/z* calcd for $C_{33}H_{46}NO_8Si$ 612.2987; found 612.2987.

(3S,4R,5R,6R,7S)-3-Acetoxy-6-(benzyloxycarbonylamino)-5,7-bis(tert-butyldimethylsilyloxy)deca-1,9-dien-4-yl benzoate (**12**). To a solution of **11a** (50 mg, 0.09 mmol) in dimethylformamide (DMF, 0.9 mL), TBSCl (42 mg, 0.27 mmol) and imidazole (21 mg, 0.27 mmol) were added at 40 °C. After 12 h, the reaction mixture was washed with H_2O, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 30:1) gave **12** (41 mg, 0.074 mmol, 82% yield) as a colorless oil. R_f = 0.5 (hexanes:ethyl acetate = 6:1); $[\alpha]_D^{20}$ 8.6 (*c* 0.2, $CHCl_3$); IR (neat) ν_{max} 2929, 2857, 1726, 1502, 1256, 1229, 1092, 1027, 836, 777, 712; ^1H NMR ($CDCl_3$, 300M Hz) δ 7.86–8.03 (m, 2 H), 7.41–7.52 (m, 1 H), 7.21–7.41 (m, 6 H), 5.58–5.89 (m, 3 H), 5.36–5.55 (m, 2 H), 4.89–5.33 (m, 6 H), 4.07 (dd, *J* = 8.8, 2.1 Hz, 1 H), 3.97 (t, *J* = 6.5 Hz, 1 H), 3.87 (dd, *J* = 9.9, 9.1 Hz, 1 H), 2.14 (t, *J* = 6.7 Hz, 2 H), 1.72–1.86 (m, 3 H), 0.66–0.92 (m, 18 H), −0.07 to 0.29 (m, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 165.9, 156.1, 136.8, 133.3, 132.9, 132.6, 130.2, 129.6, 128.4, 128.3, 128.0, 120.1, 118.7, 74.6, 73.5, 71.4, 71.1, 67.0, 54.6, 39.2, 26.0, 25.8, 25.7, 20.9, 18.4, 18.0, −2.8, −3.1, −3.5, −4.5; HRMS (EI+) [$(M+H)^+$] *m/z* calcd for $C_{39}H_{60}NO_8Si_2$ 726.3852; found 726.3853.

Benzyl (5S,6R,7R)-5-allyl-7-((1R,2S)-1,2-dihydroxybut-3-enyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ylcarbamate (**13**). To a solution of **12** (240 mg, 0.33 mmol) in methanol (3.3 mL), NaOMe (0.04 mL, 0.165 mmol; 4.4 M solution in methanol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 12 h, and, then, NH_4Cl was added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated $NaHCO_3$ and brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification by silica gel column chromatography (hexanes:ethyl acetate = 15:1) gave **13** (151 mg, 0.26 mmol, 79% yield) as a colorless oil. R_f = 0.4 (hexanes:ethyl acetate = 4:1); $[\alpha]_D^{20}$ 32 (*c* 0.07, $CHCl_3$); IR (neat) ν_{max} 3438, 2954, 2929, 2857, 1709, 1502, 1254, 1218, 1079, 923, 836, 778; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.42 (m, 5 H), 5.87 (ddd, *J* = 17.3, 10.4, 6.9 Hz, 1 H), 5.73 (ddt, *J* = 16.3, 10.9, 7.3 Hz, 1 H), 4.95–5.37 (m, 7 H), 4.25 (q, *J* = 6.8 Hz, 2 H), 3.63 (t, *J* = 9.3 Hz, 1 H), 3.36–3.54 (m, 3 H), 2.51 (d, *J* = 8.8 Hz, 1 H), 2.24 (t, *J* = 6.8 Hz, 2 H), 0.84–0.94 (m, 18 H), 0.03–0.13 (m, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 138.2, 136.4, 133.6, 128.6, 128.2, 118.1, 117.0,

75.8, 72.5, 69.3, 69.1, 67.1, 54.6, 39.6, 25.9, 25.9, 18.2, 18.0, −4.3, −4.8, −4.9; HRMS (EI+) [(M+H)$^+$] *m/z* calcd for $C_{30}H_{54}NO_6Si_2$ 580.3484; found 580.3492.

Benzyl (5S,6R,7R)-5-allyl-7-((4R,5S)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ylcarbamate (**14**). To a solution of **13** (130 mg, 0.23 mmol) in DMF (2.3 mL), 2,2-dimethoxypropane (0.3 mL, 2.3 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 22 mg, 0.05 mmol) were added at 60 °C. The reaction mixture was stirred at 60 °C for 12 h, and then, distilled water was added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification by silica gel column chromatography (hexanes:ethyl acetate = 30:1) gave **14** (90 mg, 0.145 mmol, 63% yield) as a colorless oil. R_f = 0.6 (hexanes:ethyl acetate = 6:1); $[\alpha]_D^{20}$ −10.2 (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3443, 2955, 2929, 2857, 1729, 1499, 1254, 1208, 1076, 1032, 925, 836, 776; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.43 (m, 5 H), 5.65–5.93 (m, 2 H), 4.89–5.22 (m, 7 H), 4.12 (dd, *J* = 8.2, 5.8 Hz, 1 H), 3.96–4.07 (m, 2 H), 3.91 (dd, *J* = 10.0, 5.9 Hz, 1 H), 3.79 (dd, *J* = 10.1, 9.4 Hz, 1 H), 2.15–2.28 (m, 2 H), 1.35–1.42 (m, 6 H), 0.83–0.94 (m, 18 H), −0.06 to 0.13 (m, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.3, 138.7, 136.6, 133.4, 128.5, 128.4, 128.2, 118.1, 115.9, 109.4, 83.8, 75.0, 74.4, 70.4, 66.9, 56.0, 39.1, 27.8, 27.2, 26.0, 18.2, 18.0, −4.3, −4.5, −4.6; HRMS (EI+) [(M+H)$^+$] *m/z* calcd for $C_{33}H_{57}NO_6Si_2$ 620.3797; found 620.3805.

Benzyl (5S,6R,7R)-5-(2-hydroxyethyl)-7-((4R,5S)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ylcarbamate (**15**). Compound **14** (63 mg, 0.1 mmol) was dissolved in dry methanol (1 mL) and cooled to −78 °C. Ozone was then passed through the solution until the reaction was complete. The reaction mixture was quenched with $NaBH_4$ (43 mg, 1 mmol) and allowed to warm to room temperature for 3 h. Then, and distilled water was added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification was carried out using silica gel column chromatography (hexanes:ethyl acetate = 4:1), giving **15** (35 mg, 0.056 mmol, 56% yield) as a colorless oil. R_f = 0.4 (hexanes:ethyl acetate = 2:1); $[\alpha]_D^{20}$ −9.4 (*c* 0.08, $CHCl_3$); IR (neat) ν_{max} 3439, 2929, 2857, 1717, 1506, 1254, 1214, 1069, 837, 777, 698; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.42 (m, 5 H), 5.21 (d, *J* = 12.1 Hz, 1 H), 5.07 (d, *J* = 9.8 Hz, 1 H), 5.00 (d, *J* = 12.1 Hz, 1 H), 4.28 (t, *J* = 6.8 Hz, 1 H), 4.13 (dd, *J* = 6.9, 2.5 Hz, 1 H), 3.95 (dd, *J* = 9.7, 7.0 Hz, 1 H), 3.79 (t, *J* = 9.8 Hz, 1 H), 3.67 (t, *J* = 6.3 Hz, 2 H), 3.45–3.61 (m, 3 H), 1.73 (q, *J* = 6.4 Hz, 2 H), 1.35–1.46 (m, 6 H), 0.81–0.96 (m, 18 H), 0.01–0.16 (m, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.7, 136.3, 128.6, 128.4, 109.3, 83.1, 74.7, 71.4, 68.4, 67.2, 65.2, 59.2, 57.0, 37.2, 29.7, 27.5, 26.9, 26.0, 26.0, 18.2, 18.0, −4.4, −4.6; HRMS (EI+) [(M+H)$^+$] *m/z* calcd for $C_{31}H_{58}NO_8Si_2$ 628.3695; found 628.3694.

(3aS,8S,8aR,9R,9aR)-8,9-Bis(tert-butyldimethylsilyloxy)-2,2-dimethyloctahydro-[1,3]dioxolo[4,5-f]indolizine (**16**). To a solution of **15** (43mg, 0.08 mmol) in CH_2Cl_2 (0.8 ml), MsCl (0.02 ml, 0.24 mmol), and triethylamine (TEA, 0.04 ml, 0.24 mmol) were added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and then, $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. The resulting substance was immediately used without further purification. The resulting substance was dissolved in dry methanol (0.8 mL) and hydrogenated overnight in the presence of 20% $Pd(OH)_2$/C (43 mg) at room temperature. The catalyst was

removed by filtration through Celite and the filtrate was evaporated under reduced pressure. TEA was added to a solution of the reaction mixture at room temperature for 12 h. Subsequently, the reaction solvent was evaporated under reduced pressure. Purification using silica gel column chromatography (hexanes:ethyl acetate = 20:1) yielded **16** (24 mg, 0.051 mmol, 64% yield) as a colorless oil. R_f= 0.4 (hexanes:ethyl acetate = 6:1); $[\alpha]_D^{20}$ 11.2 (*c* 0.25, $CHCl_3$); IR (neat) ν_{max} 2953, 2928, 2856, 2790, 1728, 1472, 1371, 1254, 1232, 1168, 1114, 1057, 907, 837, 778, 675; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.37 (ddd, *J* = 6.8, 4.5, 1.5 Hz, 1 H), 4.00 (td, *J* = 9.2, 5.0 Hz, 1 H), 3.56 (t, *J* = 9.0 Hz, 1 H), 3.30 (t, *J* = 9.2 Hz, 1 H), 3.18 (dd, *J* = 10.9, 5.0 Hz, 1 H), 3.14 (td, *J* = 8.5, 1.7 Hz, 1 H), 2.17 - 2.27 (m, 2 H), 2.07 (dd, *J* = 9.0, 4.5 Hz, 1 H), 2.00 (dd, *J* = 10.8, 9.3 Hz, 1 H), 1.79–1.91 (m, 1 H), 1.37–1.43 (m, 6 H), 0.85–0.93 (m, 18 H), 0.05–0.14 (m, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 110.1, 84.9, 73.3, 71.1, 70.2, 69.4, 57.3, 51.5, 35.4, 29.7, 26.9, 26.8, 25.9, 25.8, 18.5, 18.3, −4.6, −4.9, −5.1; HRMS (EI+) [$(M+H)^+$] *m/z* calcd for $C_{23}H_{48}NO_4Si_2$ 458.3116; found 458.3124.

(1S,6S,7R,8R,8aR)-Octahydroindolizine-1,6,7,8-tetraol, (+)-Castanospermine (**4**). A 1 N solution of HCl (0.5 ml) was added to a solution of **16** (20 mg, 0.04 mmol) in MeOH (0.5 mL). After stirring the reaction mixture for 24 h, the solvent was removed *in vacuo*, furnishing **4·HCl** as a white solid. Further purification after the treatment of **4·HCl** with an ion-exchange resin (DOWEX-50WX8-100) afforded (+)-castanospermine **4** (6 mg, 0.0.36 mmol, 89% yield) as a white solid. $[\alpha]_D^{20}$ 78.3 (*c* 0.1, H_2O); IR (neat) ν_{max} 3349, 2925, 2851, 1659, 1598, 1444, 1375, 1133, 1090, 1007, 624; ^{1}H NMR (D_2O, 300 MHz) δ 4.34 (ddd, *J* = 6.6, 4.2, 1.8 Hz, 1 H), 3.53 (td, *J* = 10.6, 5.2 Hz, 1 H), 3.52 (t, *J* = 9.5 Hz, 1 H), 3.24 (t, *J* = 9.2 Hz, 1 H), 3.15 (dd, *J* = 11.1, 5.1 Hz, 1 H), 3.09 (td, *J* = 8.7, 2.2 Hz, 1 H), 2.24 (dddd, *J* = 14.2, 9.6, 7.0, 2.4 Hz, 1 H), 2.24 (q, *J* = 9.2 Hz, 1 H), 2.11 (t, *J*=10.4 Hz, 6 H), 2.10 (dd, *J* = 9.9, 4.3 Hz, 1 H), 1.57–1.74 (m, 1 H); ^{13}C NMR (D_2O, 75 MHz) δ 78.4, 71.2, 69.5, 69.0, 68.3, 54.7, 51.5, 32.3; HRMS (EI+) [$(M+H)^+$] *m/z* calcd for $C_8H_{16}NO_4$ 190.1074; found 190.1081.

Total synthesis of Neu5Ac methyl ester (5). (*R)-1-((4R,5R,6R)-5-((tert-Butyldimethylsilyl)oxy)-4-(((tert-butyldimethylsilyl)oxy)methyl)-2-phenyl-5,6-dihydro-4H-1,3-oxazin-6-yl)ethane-1,2-diyl diacetate*. Acetic anhydride (0.43 mL, 4.54 mmol) and 4-DMAP (22.2 mg, 0.18 mmol) were added to a solution of diol **3** (450 mg, 0.91 mmol) in CH_2Cl_2 (9.1 mL) and pyridine (0.12 mL) and stirred for 2 h. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phase was washed with a saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated *in vacuo*. Purification by silica gel column chromatography afforded the diacetate (490.7 mg, 0.85 mmol, 93% yield); R_f = 0.47 (hexanes:ethyl acetate = 6:1); $[\alpha]_D^{20}$ +31.3 (*c* 0.2, $CHCl_3$); IR (neat) ν_{max}: 3726, 3704, 3624, 3597, 3019, 2957, 2928, 2857, 1752, 1688, 1660, 1614, 1592, 1472, 1256, 1218, 835, 759, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77–7.82 (m, 2 H), 7.27–7.38 (m, 3 H), 5.18 (ddd, *J* = 8.6, 3.5, 2.3 Hz, 1 H), 4.71 (dd, *J* = 12.5, 2.3 Hz, 1 H), 4.34–4.37 (m, 1 H), 4.31–4.33 (m, 1 H), 4.17 (s, 1 H), 3.92 (dd, *J* = 10.4, 3.7 Hz, 1 H), 3.65 (dd, *J* = 7.9, 3.7 Hz, 1 H), 3.45 (dd, *J* = 10.4, 8.1 Hz, 1 H), 2.00 (s, 3 H), 1.99 (s, 3 H), 0.82 (s, 9 H), 0.75 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H), −0.03 (s, 3 H), −0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.7, 169.7, 154.9, 133.3, 130.6, 128.1, 127.2, 71.4, 69.5, 64.7, 63.1, 60.8, 26.0, 25.7, 21.0, 20.8, 18.2, 17.9, −4.2, −4.9, −5.4, −5.5; HRMS (EI+) [$(M)^+$] *m/z* calcd for $C_{29}H_{49}NO_7Si_2$ 579.3048; found 579.3046.

(2R,3R,4R,5R)-3-(Benzoyloxy)-5-(((benzyloxy)carbonyl)amino)-4,6-bis((tert-butyldimethylsilyl)oxy)hexane-1,2-diyl diacetate (**18**). A solution of the diacetate (479 mg, 0.83 mmol) in CH_2Cl_2 (5.5 mL) was treated with $NaHCO_3$ (5.5 mL, 0.60 M aqueous solution, 3.30

mmol) and the resulting mixture was cooled to 0 °C. Then, a solution of benzyl chloroformate (0.47 mL, 3.31 mmol) was added dropwise. The resulting mixture was stirred at 50 °C for 24 h and additional benzyl chloroformate (0.47 mL, 3.31 mmol) was added. The resulting mixture was stirred for another 24 h until the reaction was complete, as monitored by TLC. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel column chromatography afforded carbamate **18** (486 mg, 0.66 mmol, 80% yield) as a colorless oil; R_f = 0.45 (hexanes:ethyl acetate = 4:1); $[\alpha]_D^{20}$ +6.6 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max}: 3726, 3704, 3623, 3598, 3020, 2958, 2930, 2857, 1749, 1726, 1219, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, *J* = 7.3 Hz, 2 H), 7.49–7.55 (m, 1 H), 7.34–7.41 (m, 2 H), 7.18–7.30 (m, 5 H), 5.54 (t, *J* = 5.3 Hz, 1 H), 5.31 (sxt, *J* = 2.6 Hz, 1 H), 5.09 (d, *J* = 6.7 Hz, 1 H), 4.94–5.05 (m, 2 H), 4.50 (dd, *J* = 12.3, 2.4 Hz, 1 H), 4.26 (t, *J* = 4.5 Hz, 1 H), 4.19 (dd, *J* = 12.2, 6.5 Hz, 1 H), 3.90 (tdd, *J* = 6.5, 5.5 Hz, 1 H), 3.72–3.82 (m, 2 H), 1.98 (s, 3 H), 1.96 (s, 3 H), 0.84 (s, 9 H), 0.76 (s, 9 H), 0.03 (d, *J* = 2.0 Hz, 6 H), 0.00 (s, 3 H), −0.10 (s, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.6, 170.1, 165.4, 156.2, 136.6, 133.4, 129.8, 128.6, 128.4, 127.8, 72.3, 70.4, 69.9, 66.5, 61.7, 61.0, 55.2, 25.9, 25.8, 21.0, 20.1, 18.2, 18.0, −0.0, −4.4, −4.8, −5.5; HRMS (FAB+) $[M + H]^+$ *m/z* calcd for $C_{37}H_{58}NO_{10}Si_2$ 732.3599; found 732.3599.

(2R,3R,4R,5R)-3-(Benzoyloxy)-5-(((benzyloxy)carbonyl)amino)-4-((tert-butyldimethylsilyl)oxy)-6-hydroxyhexane-1,2-diyl diacetate (**19**). To a solution of carbamate **18** (463 mg, 0.63 mmol) in THF (6.3 mL) and pyridine (2.11 mL), HF·pyridine (0.63 mL, 1.0 M solution in THF, 0.63 mmol) was added. Then, the reaction mixture was quenched with $NaHCO_3$. The aqueous phase was extracted with Et_2O. The combined organic phase was washed with aqueous $CuSO_4$ and H_2O, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography gave **19** (358 mg, 0.58 mmol, 92% yield) as a colorless oil. R_f = 0.50 (hexanes:ethyl acetate = 1:1) $[\alpha]_D^{20}$ +2.3 (*c* 0.5, $CHCl_3$); IR(neat) ν_{max}: 3725, 3704, 3624, 3599, 3020, 1725, 1220, 768 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz) δ 8.02 (d, *J* = 7.3 Hz, 2 H), 7.56–7.62 (m, 1 H), 7.42–7.49 (m, 2 H), 7.28–7.38 (m, 5 H), 5.54–5.61 (m, 2 H), 5.30 (dt, *J* = 7.4, 3.6 Hz, 1 H), 5.11 (s, 2 H), 4.58 (dd, *J* = 12.2, 2.9 Hz, 1 H), 4.27–4.36 (m, 2 H), 4.20 (dt, *J* = 11.6, 2.9 Hz, 1 H), 4.12 (q, *J* = 7.1 Hz, 1 H), 3.77–3.91 (m, 2 H), 2.73 (dd, *J* = 8.5, 2.8 Hz, 1 H), 2.04 (s, 6 H), 0.74 (s, 9 H), 0.03 (s, 3 H), −0.11 (s, 3 H); ^{13}C NMR(101 MHz, $CDCl_3$) δ 170.7, 170.4, 165.7, 156.1, 136.3, 133.5, 129.8, 128.6, 128.5, 128.1, 72.9, 72.8, 70.5, 66.9, 61.8, 61.5, 53.6, 25.7, 20.8, 20.7, 17.9, −4.6, −4.8; HRMS (EI+) $[(M)^+]$ *m/z* calcd for $C_{31}H_{43}NO_{10}Si$ 617.2656; found 617.2653.

(2R,3R,4R,5R,6S)-3-(Benzoyloxy)-5-(((benzyloxy)carbonyl)amino)-4-((tert-butyldimethylsilyl)oxy)-6-hydroxynon-8-ene-1,2-diyl diacetate (**20a**). To a solution of primary alcohol **19** (341 mg, 0.55 mmol) in CH_2Cl_2 (5.5 mL), Dess–Martin periodinane (820 mg, 1.93 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with Et_2O, and, then, saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ were added, and the heterogeneous mixture was stirred at room temperature until the organic layer was clear. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo* to give the crude aldehyde. To the solution of the crude aldehyde in CH_2Cl_2 (5.5 mL), $BF_3{\cdot}OEt_2$ (0.08 mL, 0.66 mmol) was carefully added at −78 °C. After stirring for 5 min, $AllylSnBu_3$ (0.51 mL, 1.66 mmol) was slowly added at the same temperature. Once TLC indicated that the reaction had completed, the reaction mixture was quenched with $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography gave **20a** (294 mg, 0.45 mmol, 81% yield) as a colorless oil. R_f = 0.50 (hexanes:ethyl acetate = 2:1); $[\alpha]_D^{20}$ +9.8 (*c* 1.0, $CHCl_3$);

IR(neat) ν_{max}: 3726, 3704, 3623, 3599, 3019, 2925, 2855, 1725, 1218, 771 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz) δ 7.96–8.04 (m, 2 H), 7.60 (t, *J* = 7.1 Hz, 1 H), 7.46 (t, *J* = 7.5 Hz, 2 H), 7.29–7.40 (m, 5 H), 5.90 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H), 5.66 (dd, *J* = 8.2, 3.4 Hz, 1 H), 5.57 (d, *J* = 7.7 Hz, 1 H), 5.05–5.25 (m, 5 H), 4.57 (dd, *J* = 12.1, 2.9 Hz, 1 H), 4.47 (t, *J* = 6.8 Hz, 1 H), 4.37 (dd, *J* = 12.0, 8.1 Hz, 1 H), 4.30 (dd, *J* = 8.2, 1.2 Hz, 1 H), 3.83 (d, *J* = 7.6 Hz, 1 H), 3.15 (s, 1 H), 2.39 (dt, *J* = 13.7, 6.7 Hz, 1 H), 2.26 (dt, *J* = 14.0, 7.1 Hz, 1 H), 2.05 (s, 3 H), 2.01–2.04 (m, 3H), 0.71 (s, 9 H), 0.01 (s, 3 H), −0.14 (s, 3H); ^{13}C NMR($CDCl_3$, 101 MHz) δ 170.7, 170.4, 165.7, 156.0, 136.3, 133.8, 129.8, 128.6, 128.1, 118.5, 74.5, 73.1, 70.4, 69.2, 66.9, 61.2, 53.2, 38.3, 31.9, 29.7, 29.4, 25.6, 22.7, 20.8, 17.8, 14.1, −4.5, −4.8; HRMS (EI+) [$(M)^+$] *m/z* calcd for $C_{34}H_{47}NO_{10}Si$ 657.2969; found 657.2969.

(2R,3R,4R,5R,6R)-3-(Benzoyloxy)-5-(((benzyloxy)carbonyl)amino)-4-((tert-butyldimethylsilyl)oxy)-6-hydroxynon-8-ene-1,2-diyl diacetate (**20b**). R_f = 0.35 (hexanes:ethyl acetate = 2:1); $[\alpha]_D^{20}$ +3.6 (*c* 0.3, $CHCl_3$); IR (neat) ν_{max}: 3726, 3704, 3623, 3599, 3019, 1725, 1218, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, *J* = 7.6 Hz, 2 H), 7.49 (t, *J* = 7.3 Hz, 1 H), 7.34 (t, *J* = 7.6 Hz, 2 H), 7.15–7.24 (m, 5 H), 5.78 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H), 5.64 (t, *J* = 4.8 Hz, 1 H), 5.33 (quin, *J* = 3.5 Hz, 1 H), 5.18 (d, *J* = 8.7 Hz, 1 H), 5.09 (d, *J* = 12.6 Hz, 2 H), 4.90–5.00 (m, *J* = 5.3 Hz, 2 H), 4.49 (dd, *J* = 12.2, 2.2 Hz, 1 H), 4.25 (dd, *J* = 5.2, 3.1 Hz, 1 H), 4.19 (dd, *J* = 12.1, 7.2 Hz, 1 H), 3.83 (td, *J* = 8.6, 2.7 Hz, 1 H), 3.66 (t, *J* = 8.2 Hz, 1 H), 2.36–2.44 (m, 2 H), 2.15 (quin, *J* = 7.5 Hz, 1 H), 1.97 (s, 3 H), 1.92 (s, 3 H), 0.70 (s, 9 H), 0.00 (s, 3 H), −0.12 (s, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.7, 170.4, 165.7, 156.3, 134.1, 133.5, 129.8, 128.6, 128.4, 127.8, 119.1, 73.3, 71.4, 70.0, 66.7, 61.9, 57.9, 39.0, 29.7, 25.7, 21.0, 20.7, 17.9, −0.1, −4.4, −4.7; HRMS (EI+) [$(M)^+$] *m/z* calcd for $C_{34}H_{47}NO_{10}Si$ 657.2969; found 657.2964.

(2R,3R,4R,5R,6S)-3-(Benzoyloxy)-5-(((benzyloxy)carbonyl)amino)-4,6-bis((tert-butyldimethylsilyl)oxy)non-8-ene-1,2-diyl diacetate (**21**). To a solution of compound **20a** (301 mg, 0.45 mmol) in CH_2Cl_2 (4.7 mL), *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.38 mL, 1.64 mmol) and 2,6-lutidine (0.19 mL, 1.64 mmol) were added at 0 °C and stirred at room temperature for 20 min. The reaction was quenched with NH_4Cl, diluted with EtOAc, and the organic phase was washed with saturated brine, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography gave product **21** (323 mg, 0.42 mmol, 93% yield) as a colorless oil. R_f = 0.51 (hexanes:ethyl acetate = 4:1); $[\alpha]_D^{20}$ +21.2 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max} 3725, 3704, 3623, 3599, 3019, 2926, 2854, 1724, 1217, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83–7.93 (m, 2 H), 7.38–7.45 (m, 1 H), 7.24–7.31 (m, 2 H), 6.99–7.22 (m, 5 H), 5.66 (ddt, *J* = 17.8, 9.8, 7.5 Hz, 1 H), 5.50 (dd, *J* = 8.1, 2.8 Hz, 1 H), 5.24 (ddd, *J* = 8.2, 5.3, 3.3 Hz, 1 H), 4.80–4.98 (m, 4 H), 4.25 (dd, *J* = 12.3, 3.3 Hz, 1 H), 3.90–4.04 (m, 3 H), 3.78 (ddd, *J* = 10.0, 7.5, 2.1 Hz, 1 H), 2.01–2.17 (m, 2 H), 1.93 (s, 3 H), 1.83 (s, 3 H), 0.75 (s, 9 H), 0.72 (s, 9 H), −0.09 to 0.13 (m, 12 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.6, 169.6, 165.6, 156.0, 136.7, 133.3, 133.2, 129.7, 128.4, 128.2, 128.0, 118.7, 71.7, 71.4, 69.7, 66.8, 62.2, 54.7, 39.5, 26.0, 25.9, 21.0, 20.6, 18.0, –3.2, –4.3; HRMS (FAB+) [$(M + H)^+$] *m/z* calcd for $C_{40}H_{62}NO_{10}Si_2$ 772.3912; found 772.3914.

(2R,3R,4R,5R,6S)-3-(Benzoyloxy)-5-(((benzyloxy)carbonyl)amino)-4,6-bis((tert-butyldimethylsilyl)oxy)-8,9-dihydroxynonane-1,2-diyl diacetate (**22**). OsO_4 in *t*-BuOH (2.5% wt., 0.19 mL, 0.02 mmol) and NMO (8.7 mg, 0.75 mmol) were added to a solution of **21** (288 mg, 0.37 mmol) in acetone/H_2O (5:1) solvent (1.86 mL) at 0 °C. After 8 h, the reaction mixture was poured into a solution of saturated aq. Na_2SO_4. The mixture was washed with EtOAc. The filtrate was washed with brine, dried with $MgSO_4$, and evaporated *in vacuo*. Purification by

silica gel chromatography gave diol **22**. (271 mg, 0.34 mmol, 93% yield) as a colorless oil. R_f = 0.45 (hexanes:ethyl acetate = 1:1); $[\alpha]_D^{20}$ +23.0 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max}: 3726, 3704, 3623, 3600, 3020, 2952, 2926, 2855, 1725, 1218, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86–7.95 (m, 2 H), 7.42–7.52 (m, 1 H), 7.28–7.35 (m, 2 H), 7.14–7.28 (m, 5 H), 5.55 (quind, *J* = 3.8, 1.6 Hz, 1 H), 5.33 (tdt, *J* = 9.0, 5.0, 3.2 Hz, 1 H), 4.98–5.07 (m, 1 H), 4.86–4.98 (m, 1 H), 4.33 (dtd, *J* = 12.2, 4.0, 1.2 Hz, 1 H), 4.26 (dq, *J* = 9.5, 2.0 Hz, 1 H), 4.10–4.18 (m, 1 H), 3.91–4.09 (m, 2 H), 3.63–3.74 (m, 1 H), 3.41 (qd, *J* = 11.0, 3.4 Hz, 1 H), 3.25 (ddd, *J* = 13.5, 11.2, 7.1 Hz, 1 H), 1.98 (d, *J* = 1.3 Hz, 3 H), 1.88 (s, 3 H), 1.37–1.53 (m, 2 H), 0.81 (d, *J* = 2.2 Hz, 9 H), 0.74 (d, *J* = 4.5 Hz, 9 H), 0.14 (d, *J* = 2.4 Hz, 3 H), 0.06 (d, *J* = 4.5 Hz, 3 H), −0.05 to 0.02 (m, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.7, 170.6, 170.0, 169.8, 165.5, 156.9, 156.4, 136.5, 136.4, 133.4, 129.7, 128.5, 128.2, 71.7, 71.5, 69.8, 68.9, 67.2, 67.0, 66.9, 62.2, 56.1, 54.7, 38.1, 37.6, 26.0, 21.0, 20.7, 18.4, 18.0, −3.5, −3.9; HRMS (ESI) calcd for $C_{40}H_{63}NNaO_{12}Si_2$ $[M + Na]^+$ 828.3786, found 828.3788.

(2R,3R,4R,5R,6S)-3-(Benzoyloxy)-5-(((benzyloxy)carbonyl)amino)-4,6-bis((tert-butyldimethylsilyl)oxy)-8-hydroxy-9-methoxy-9-oxononane-1,2-diyl diacetate (**23**). To a mixture of diol **22** (142 mg, 0.18 mmol) and TEMPO (1.4 mg, 0.09 mmol) in toluene and phosphate buffer (pH = 6.8), solid $NaClO_2$ (3.5 M in water, 0.3 mL, 1.06 mmol) and NaOCl (0.168 M in water, 0.52 mL, 0.08 mmol) were slowly added. The mixture was vigorously stirred at 55 °C for 24 h. The reaction was quenched with phosphate buffer (pH = 2.1) and the aqueous phase was extracted with EtOAc. The organic phase was washed with saturated brine, dried with $MgSO_4$, and concentrated *in vacuo*. The afforded the crude α-hydroxy acid in DMF (1.76 mL), which was treated with K_2CO_3 (366 mg, 2.65 mmol) and MeI (2 M solution in THF, 1.32 mL, 2.65 mmol). When TLC indicated that reaction had completed, the reaction mixture was quenched with NH_4Cl and extracted with EtOAc. The organic layer was then washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography gave α-hydroxy ester **23** (100 mg, 0.12 mmol, 68% yield) as a colorless oil. R_f = 0.53 (hexanes:ethyl acetate = 2:1); $[\alpha]_D^{20}$ +17.6 (*c* 0.4, $CHCl_3$); IR(neat) ν_{max}: 3725, 3705, 3023, 3599, 3019, 1722, 1217, 769 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz) δ 7.82–7.94 (m, 2 H), 7.37–7.45 (m, 1 H), 7.24–7.30 (m, 2 H), 7.10–7.23 (m, 5 H), 5.49–5.55 (m, 1 H), 5.26–5.32 (m, 1 H), 4.91–4.99 (m, 1 H), 4.81–4.87 (m, 1 H), 4.20–4.29 (m, 2 H), 4.12–4.20 (m, 1 H), 4.01–4.11 (m, 1 H), 3.96 (sxt, *J* = 5.8 Hz, 1 H), 3.84 (t, *J* = 9.4 Hz, 1 H), 3.53–3.61 (m, 3 H), 1.93 (s, 3 H), 1.82 (d, *J* = 4.4 Hz, 3 H), 1.43–1.57 (m, 2 H), 0.69–0.80 (m, 18 H), −0.17 to 0.18 (m, 12 H); ^{13}C NMR($CDCl_3$, 101 MHz) δ 175.2, 170.6, 169.6, 165.7, 156.4, 136.5, 133.2, 129.7, 128.5, 128.2, 128.1, 128.0, 71.7, 71.4, 71.2, 69.5, 68.8, 68.6, 67.7, 67.0, 62.2, 56.4, 52.7, 52.6, 39.9, 29.7, 26.0, 25.9, 21.0, 20.7, 18.5, 18.4, 18.2, 18.0, −3.1, −3.4, −3.8, −4.2, −4.3; HRMS (ESI) calcd for $C_{41}H_{63}NNaO_{13}Si_2$ $[M + Na]^+$ 856.3736, found 856.3749.

(2R,3R,4R,5R,6S)-3-(Benzoyloxy)-5-(((benzyloxy)carbonyl)amino)-4,6-bis((tert-butyldimethylsilyl)oxy)-9-methoxy-8,9-dioxononane-1,2-diyl diacetate (**24**). To a solution of α-hydroxy ester **23** (150 mg, 0.18 mmol) in CH_2Cl_2 (1.8 mL), Dess–Martin periodinane (381 mg, 0.90 mmol) and $NaHCO_3$ (8.0 mg, 0.09 mmol) were added at room temperature. The reaction mixture was stirred at ambient temperature for 40 min. The mixture was diluted with Et_2O, and, then, saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ were added and the heterogeneous mixture was stirred at room temperature until the organic layer was clear. The organic layer was washed with brine, dried with $MgSO_4$ and concentrated *in vacuo* to give α-keto ester **24**. Then, α-keto ester **24** was directly used for the next step without further purification.

Methyl (4S,5R,6R,7R,8R)-5-(((benzyloxy)carbonyl)amino)-4,6-bis((tert-butyldimethylsilyl)oxy)-

7,8,9-trihydroxy-2-oxononanoate (**25**). NaOMe (0.01 mL, 0.05 mmol; 4.4 M solution in methanol) was added to a solution of α-keto ester **24** in methanol (1.8 mL) at 0 °C. The reaction mixture was stirred at room temperature for 5 h. After TLC indicated that the reaction had completed, the reaction mixture was quenched with NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography gave **25** (7.0 mg, 0.11 mmol, 60% yield for two steps) as a colorless oil. R_f = 0.31 (hexanes:ethyl acetate = 2:1); $[\alpha]_D^{20}$ +1.2 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3726, 3705, 3623, 3599, 3019, 1716, 1218, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.21–7.33 (m, 5 H), 5.10 (d, *J* = 12.2 Hz, 1 H), 4.93 (d, *J* = 12.2 Hz, 1 H), 4.68–4.75 (m, 1 H), 4.59 (d, *J* = 8.4 Hz, 1 H), 3.92–4.01 (m, 2 H), 3.73–3.79 (m, 3 H), 3.72 (s, 3 H), 3.65–3.70 (m, 1 H), 3.57–3.65 (m, 1 H), 3.50–3.57 (m, 1 H), 1.96–2.11 (m, 2 H), 0.74–0.84 (m, 18 H), −0.05 to 0.02 (m, 12 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.2, 170.1, 157.8, 136.0, 128.5, 128.1, 95.3, 71.4, 69.5, 68.5, 67.3, 64.0, 54.8, 53.1, 39.9, 25.9, 25.6, 18.3, 17.8, −4.2, −4.8, −5.3, −5.4; HRMS (FAB+) calcd for $C_{30}H_{53}NNaO_{10}Si_2$ $[M + Na]^+$ 666.3106, found 666.3107.

Methyl (2S,4S,5R,6R)-5-(((benzyloxy)carbonyl)amino)-2,4-dihydroxy-6-((1R,2R)-1,2,3-trihydroxypropyl)tetrahydro-2H-pyran-2-carboxylate (**26**). HF (0.02 mL, 0.47 mmol) was added to a solution of **25** (3.1 mg, 0.05 mmol) in CH_3CN (1.57 mL) at 0 °C. The reaction mixture was stirred at same temperature for 6 h. After TLC indicated that the reaction had completed, the reaction mixture was quenched with $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography gave pyranoside **26** (1.2 mg, 0.02 mmol, 46% yield) as a colorless oil. R_f = 0.40 (chloroform:methanol = 4:1); $[\alpha]_D^{20}$ +6.0 (*c* 0.1, $CHCl_3$); IR (neat) ν_{max}: 3725, 3704, 3623, 3594, 2936, 2830, 1712, 1512, 1246, 1034 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.37 (d, *J* = 7.70 Hz, 5 H), 5.07–5.18 (m, 2 H), 3.97–4.09 (m, 2 H), 3.80 (s, 3 H), 3.66–3.74 (m, 1 H), 3.57–3.66 (m, 2 H), 2.23 (dd, *J* = 13.0, 4.8 Hz, 1 H), 1.90 (t, *J* = 12.0 Hz, 1 H); ^{13}C NMR (CD_3OD, 101 MHz) δ 158.3, 136.8, 128.1, 127.5, 95.3, 70.9, 70.6, 68.8, 66.6, 66.3, 63.5, 54.2, 51.7, 39.4; HRMS (ESI) calcd for $C_{18}H_{26}NO_{10}$ $[M + H]^+$ 416.1557, found 416.1557.

Methyl (2S,4S,5R,6R)-5-acetamido-2,4-dihydroxy-6-((1R,2R)-1,2,3-trihydroxypropyl)tetrahydro-2H-pyran-2-carboxylate, *Neu5Ac methyl ester* (**5**). A mixture of pyranoside **26** (32 mg, 0.08 mmol), Ac_2O (0.01 mL, 0.10 mmol), and 20% $Pd(OH)_2/C$ (15 mg) in THF (1 mL) was stirred under 2 atm of H_2 for 4 h at room temperature. The mixture was filtered through a pad of Celite, concentrated *in vacuo*, and purified by silica gel column chromatography, affording Neu5Ac methyl ester **5** (1.3 mg, 0.04 mmol) in 51% yield as a colorless oil. R_f = 0.38 ($CHCl_3$:MeOH:AcOH:H_2O = 60:30:3:5); $[\alpha]_D^{20}$ −24.5 (*c* 0.2, MeOH); IR (neat) ν_{max}: 3725, 3704, 3624, 3596, 3019, 2928, 2857, 1752, 1660, 1614, 1591, 1256, 1218, 758 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 4.07 (dd, *J* = 10.5, 5.1 Hz, 1 H), 4.02 (dd, *J* = 10.4, 1.5 Hz, 1 H), 3.84 (t, *J* = 9.8 Hz, 2 H), 3.80 (s, 3 H), 3.68–3.74 (m, 1 H), 3.65 (dd, *J* = 11.2, 5.6 Hz, 1 H), 3.51 (d, *J* = 8.7 Hz, 1 H), 2.24 (dd, *J* = 12.8, 5.0 Hz, 1 H), 2.02 (s, 3 H), 1.84 (dd, *J* = 12.8, 11.2 Hz, 1 H); ^{13}C NMR (CD_3OD, 101 MHz) δ 175.5, 173.6, 142.9, 95.3, 70.7, 70.3, 68.6, 66.3, 63.3, 52.7, 51.9, 39.5, 29.4, 21.4; HRMS (ESI) calcd for $C_{12}H_{22}NO_9$ $[M + H]^+$ 324.1295, found 324.1298.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Failed Reactions Schemes and copies of ^{1}H and ^{13}C NMR spectra for **11a**, **11b**, **12**, **13**, **14**, **15**, **16**, **18**, **19**, **20a**, **20b**, **21**, **22**, **23**, **24**, **25**, **26**, **4**, and **5**.

References

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