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New asymmetric strategy for the total synthesis of naturally occurring (+)-alexine and (−)-7-*epi*-alexine

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ABSTRACT

A novel and highly convenient process is described for the asymmetric synthesis of polyhydroxylated pyrrolizidine alkaloids, (+)-alexine [(1*R*,2*R*,3*R*,7*S*,7a*S*)-3-hydroxymethyl-1,2,7-trihydroxypyrrolizidine] and (−)-7-*epi*-alexine [(1*R*,2*R*,3*R*,7*R*,7a*S*)-3-hydroxymethyl-1,2,7-trihydroxypyrrolizidine], as the potent glycosidase inhibitors by featuring the efficient and stereodefined elaboration of the functionalized pyrrolidine derivatives, which were, in turn, prepared via stereoselective manipulation of the homochiral allyl alcohol precursors derived from L-xylose.

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1. Introduction

Polyhydroxylated monocyclic and bicyclic alkaloids can be viewed as sugar mimics in which the ring oxygen is replaced by nitrogen;[1] the biological properties inhibiting various glycosidases in a reversible and competitive manner[2] and uses as chemotherapeutic agents have ensured an escalating interest in synthesizing both naturally occurring and synthetic compounds,[3] since such glycosidase inhibitors proved to have the potential to produce antiviral, insect antifeedant, antidiabetic, and anticancer effects as well as immune modulatory properties. Noteworthy members among this class of compounds are polyhydroxylated pyrrolizidines such as the alexines (**1**),[4] represented by the parent alkaloid (**1b**), australine (**2**) (the 7a epimer of **1b**),[5] and casuarine (**3**)[6] (Fig. 1) exhibiting viral and retroviral[7] including anti-HIV[8] activity together with powerful glycosidase inhibitory properties.[9] Recently, a new series of hyacinthacines were isolated from bluebells (*Hyacinthoides non-scripta*)[10] and grape hyacinths (*Muscari armeniacum*)[11] by Asano and co-workers. Hyacinthacine B_2 (**4**), for example, was found to be a selective inhibitor of β-glucosidase and β-galactosidase and, in addition, proved to inhibit rat intestinal lactase in a competitive manner with an IC_{50} value of 3.6 μM.[11] There is a significant structural resemblance to (2*R*,3*R*,4*R*,5*R*)-2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine, DMDP (**5**), known as a strong glycosidase inhibitor occurring in some spp. *Derris* and *Lonchocarpus* (Leguminosae).[12] These are also a unique subset of pyrrolizidine alkaloids possessing contiguous stereogenic centers. The presence of a hydroxymethyl function to the ring nitrogen [C(3)],[4c] however, distinguishes these groups from the larger class of necine bases such as dihydroxyheliotridane (**6**), which bear carbon substituents at C(1). Alexines have 5 chiral centers; 7 of the 32 stereoisomers have been isolated as natural products from plants.[10,11,13] The biological potential, which varies substantially with the number, position, and stereochemistry of the hydroxyl groups into the pyrrolizidine skeleton, and the complexity of five adjacent stereogenic centers have led to a large number of subsequent papers on their synthesis.[14] However, in contrast to the synthetic endeavors on the alexines, to our knowledge, there are only two syntheses of the parent alkaloid, alexine (**1b**), based on an optical resolution method by Fleet et al.[4b] and our redundant synthetic strategy.[14h] Thus, the method is very limited to special ways. With these considerations in mind, we wish to describe

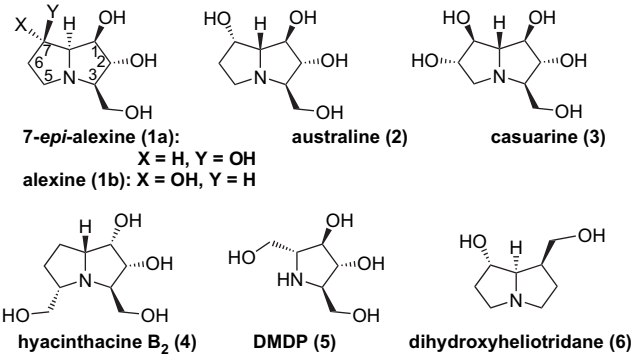

Figure 1. Structures of selected polyhydroxylated alkaloids.

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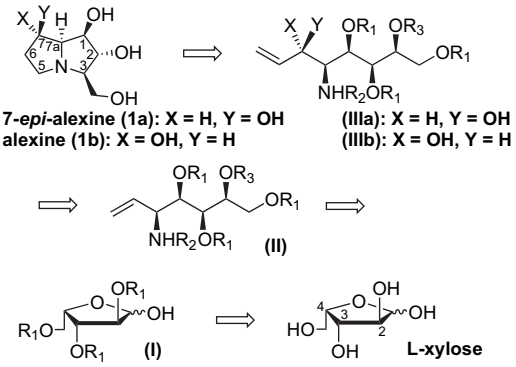


Figure 2. General retrosynthesis.

herein an efficient and stereodefined asymmetric synthesis of **1b** together with its 7-*epi* isomer **1a** by means of stereoselective elaboration of the functionalized homochiral allyl alcohol precursor derived from L-xylose.

In formulating the synthetic plan for **1**, we recognized that the absolute configurations at C(1) and C(2) are the same as the configurations at the corresponding centers C(2) and C(3) of L-xylose (Fig. 2). Further, we envisioned that the stereogenic center of C(7a) would originate from the nucleophilic addition to the aminal derivative of 2,3,5-tri-*O*-protected L-xylose (**I**), allowing the synthesis of the amino alcohol intermediate (**II**). Meanwhile, the remaining stereogenic center C(7) of **1** would have to be independently set in an asymmetric carbon-extension reaction to provide the corresponding allyl alcohol (**III**).

2. Results and discussion

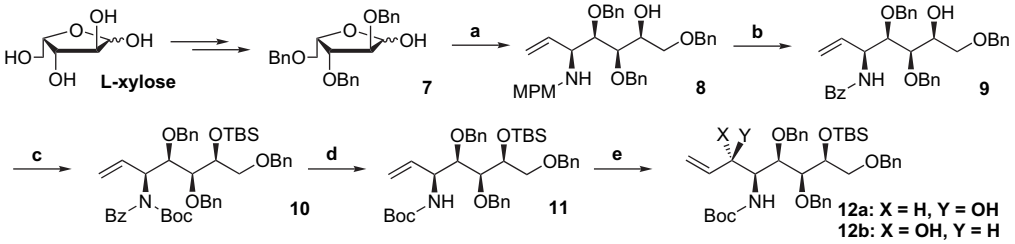
As shown in Scheme 1, starting 2,3,5-tri-*O*-benzyl-L-xylose (**7**) was initially prepared from L-xylose through a three-step sequence; methyl glycosilation, benzyl protection with NaH, and hydrolysis of the corresponding methyl furanoside.[15] Nucleophilic addition of vinylmagnesium chloride to the furanosylamine intermediate derived from **7** with 4-methoxybenzylamine (MPM amine) gave the labile amino alcohol **8** as a single isomer.[16] For the purpose of facility in the pyrrolizidine ring construction at the final stage together with reducing formation of by-products,[17] an attempt to obtain the *N*-Boc derivative was designed and elaborated through promising treatments of **8** upon replacing the MPM function via the benzoyl (Bz) group. Thus, **8** was effected with BzCl, which on successive treatment with cerium ammonium nitrate (CAN) gave rise to the amide **9** in 77% two-step yield. Compound **9** thus obtained was further stepwisely submitted to protection reactions with TBSCl followed by $(Boc)_2O$, leading to the *N*-Boc amide **10**. Then, chemoselective deprotection of the Bz group in 1,1,3,3-tetramethylguanidine at 130 °C yielded the pure NHBoc carbamate **11** in 98% yield without racemization as well as thermal decomposition. The olefinic part in **11** was then cleaved via dihydroxylation to afford the aldehyde intermediate, which on treatment with vinyl-Grignard reagent at −78 °C, resulted in the preparation of the fully functionalized allylic alcohol **12a** or **12b** with fortunately almost complete stereoselectivity.[18] It is reasonable to presume that the obtained product could be **12a**, since the reaction would proceed simply in terms of the Cram's non-chelation transition structure through the attack on the carbonyl group from the less hindered face.

In light of the above outcome, we turned our attention to the construction of a pyrrolizidine ring system. After protection of the hydroxyl group of **12a** with MOMCl, **13a** thus obtained was subjected to the following reactions of desilylation, mesylation, and *t*-BuOK-promoted cyclization, leading to the pyrrolidine intermediate **14a** in 82% yield (three steps). Then, **14a** was regioselectively hydroborated with 9-BBN to give the primary alcohol **15a** as a sole product. Compound **15a** prepared in this way was, in turn, submitted to the subsequent reactions of mesylation again and $BF_3\cdot OEt_2$-induced Boc-deprotection accompanied with the simultaneous reactions of deprotection of MOM group and nitrogen-induced cyclization under the conditions developed in our laboratory,[19] to provide the desired pyrrolizidine structure **16a** directly in 84% overall yield from **15a**. Finally, removal of the three benzyl-protecting groups in **16a** was effectively conducted with 10% Pd on carbon in the presence of $HCOONH_4$ in MeOH at 60 °C to complete the total synthesis of **1a** in 82% yield.

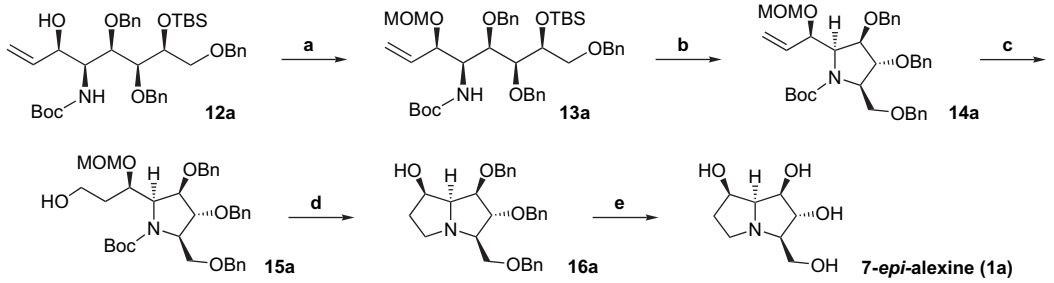
Unambiguous proof of the stereochemistry of the generated stereocenter in **12a** came, at this stage, from the comparison of its spectral data with those of the reported value,[4b] resulting in the conclusion that obtained **1a** should be 7-*epi*-alexine {$[\alpha]_D^{23}$ −11.0 (*c* 1.00, H_2O) [lit. $[\alpha]_D^{20}$ −10.6 (*c* 0.56, H_2O)][4b]} (Scheme 2).

Having obtained and characterized synthetic 7-*epi*-alexine (**1a**), we attempted the asymmetric preparation of **12b** containing the reverse stereochemistry at C(6) required to synthesize natural (+)-alexine (**1b**). The results from our survey are described in Scheme 3. After oxidation of **12a** with tetrapropylammonium perruthenate(TPAP)/NMO reagent,[20] we were delighted to find through detailed investigation of stereoselective reduction that the Luche reagent in MeOH at low temperature could effect these reactions beneficially, bringing about the desired reduction product **12b** predominantly (**12a**/**12b**=4:96, determined by ^1H NMR) in a reverse stereoselective manner. We postulate at present that this high stereoselective performance would be attributed to the steric demand of the $CeCl_3$-mediated six-membered metal-chelating structure (Fig. 3).[21] It would proceed through the preferential attack of H^- to the carbonyl function from the right face of this six-membered model due to the shielding effect of the three large functional groups described below.

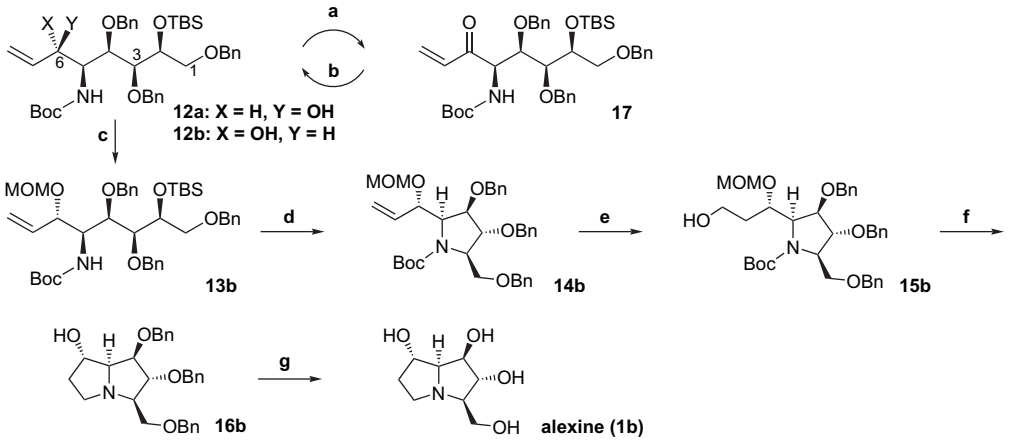
With the compound **12b** in hand as a main product, we attempted the total synthesis of **1b** based on the same synthetic strategy as mentioned above. Fortunately, it has become apparent that the major diastereomer **13b** obtained from the protection of this diastereomer mixture with MOMCl was easily separated from **13a** by column chromatography on silica gel (**13a**: R_f=0.45, **13b**: R_f=0.60 hexane/EtOAc=5:1, respectively). Then, **13b** was



Scheme 1. Reagents and conditions: (a) (i) $MPMNH_2$, MS 4 Å, toluene, reflux; (ii) CH_2=CHMgCl, THF, −78 °C to 0 °C, 2 h; 75% (two steps); (b) (i) BzCl, CH_2Cl_2; 89%; (ii) CAN, MeOH; 86%; (c) (i) TBSCl, imidazole, DMF; 89%; (ii) Boc_2O, Et_3N, DMAP, CH_2Cl_2; 92%; (d) $(Me_2N)_2C$=NH, reflux, 130 °C, 8 h; 98%; (e) (i) OsO_4, NMO, acetone; 94%; (ii) $NaIO_4$, THF/H_2O (1:1); (iii) CH_2=CHMgCl, THF, −78 °C; 95% (two steps).



Scheme 2. Reagents and conditions: (a) MOMCl, *i*-Pr_2NEt; 98%; (b) (i) Bu_4NF, THF; 98%; (ii) MsCl, Et_3N, CH_2Cl_2; (iii) *t*-BuOK, THF; 84% (two steps); (c) (i) 9-BBN, H_2O_2 (34.5%), 3 N NaOH, THF; 94%; (d) (i) MsCl, Et_3N, CH_2Cl_2; (ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C; 84%; (e) Pd/C (10%), HCO_2NH_4, MeOH, reflux, 2 h; 82%.



Scheme 3. Reagents and conditions: (a) TPAP, NMO, MS 4 Å, CH_2Cl_2; 92%; (b) $NaBH_4$, $CeCl_3$, MeOH, −45 °C; 80%; (c) MOMCl, *i*-Pr_2NEt; 4% (**13a**); 96% (**13b**); (d) (i) Bu_4NF, THF; 91%; (ii) MsCl, Et_3N, CH_2Cl_2; (iii) *t*-BuOK, THF; 87% (two steps); (e) 9-BBN, H_2O_2 (34.5%), 3 N NaOH, THF; 97%; (f) (i) MsCl, Et_3N, CH_2Cl_2; (ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C; 84% (two steps); (e) Pd/C(10%), HCO_2NH_4, MeOH; reflux 2 h; 83%.

desilylated with Bu_4NF and the product was further treated under the cyclization conditions to lead to the pyrrolidine derivative **14b** in 87% two-step yield. Compound **14b** thus prepared was successively effected by hydroboration with 9-BBN and advantageous $BF_3{\cdot}OEt_2$-mediated cyclization again after mesylation of **15b**, providing the desired alexine tri-benzylether **16b** in high yield. Finally, debenzylation of **16b** under the same reaction conditions as mentioned above complete the total synthesis of (+)-alexine (**1b**). The spectral data of synthetic **1b**, together with the optical rotation of which matches that of the reported value {$[\alpha]_D^{23}$ +40.4 (*c* 0.33, H_2O) [lit. $[\alpha]_D^{20}$ +40.0 (*c* 0.25, H_2O)][4a]}, were completely identical to those of the natural product.[4a] Compounds **1a** and **1b** were obtained in 15 and 17 steps, and 21 and 16% overall yield from 2,3,5-tri-*O*-benzyl-L-xylose (**7**), respectively.

3. Conclusions

In summary, an efficient and novel synthetic pathway to natural (+)-alexine and (−)-7-*epi*-alexine has been established by featuring the efficient and stereodefined elaboration of the functionalized homochiral allyl alcohols prepared from L-xylose in excellent overall yields, respectively. This process was substantially performed under mild conditions through the entire sequence and represents an easily accessible pathway to widespread pyrrolidine and pyrrolizidine types of alkaloidal sugar mimics. Further syntheses based on this strategy are currently underway.

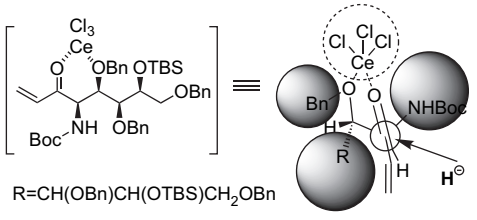


Figure 3. Six-membered chelation model.

4. Experimental section

4.1. General

All solvents and reagents were of reagent grade quality from Aldrich Chemical Company, Fluka, Acros or Wako Pure Chemicals and used without any further purification. Melting points were measured on an automated melting point system (MPA 100, Stanford Research Systems). Fourier transform infrared (FTIR) spectra were recorded on a Shimadzu FTIR-8200A spectrometer. The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra operating at the frequencies of 300 and 75 MHz, respectively, were measured with a JEOL JNM-AL300 spectrometer in chloroform-*d* ($CDCl_3$) unless otherwise stated. Chemical shifts are reported in parts per million (ppm) relative to TMS as internal standard (δ=0 ppm) for ^1H NMR, and $CDCl_3$ was used as internal standard (δ=77.0) for ^{13}C NMR. The coupling constants are reported in hertz (Hz). Optical rotations were measured in 1 dm path length cell of 2 mL capacity using a JASCO Model DIP-1000 polarimeter at a wavelength of 589 nm. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm Merck silica gel 60-F_{254} precoated silica gel plates by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in methanol followed by heating. Column chromatography was performed on Kanto Chemical silica gel 60N eluting with the indicated solvent

system. The non-crystalline compounds were shown to be homogeneous by chromatographic methods and characterized by NMR, IR, high resolution mass spectra (HRMS), and microanalysis. High-pressure liquid chromatography (HPLC) was carried out using a Shimadzu Model LC-10AD or 10AT intelligent pump and SPD-10A UV detector. HRMS were recorded on a JEOL JMS-T100CS spectrometer. Microanalyses were performed with a JSL Model JM 10.

4.2. Experimental procedures

*4.2.1. (2S,3R,4R,5S)-1,3,4-Tris(benzyloxy)-5-(4-methoxybenzylamino)hept-6-en-2-ol (**8**)*

A solution of **7** (0.481 g, 1.144 mmol) and 4-methoxybenzylamine (0.157 g, 1.144 mmol) in toluene (9.5 mL) was refluxed for 8 h in the presence of molecular sieves (4 Å, 0.5 g). Filtration and evaporation of the volatiles gave a crude anomeric mixture of the aminal (0.617 g) as a yellow oil, which was not purified further. Vinylmagnesium chloride (1.48 M solution in THF, 3.1 mL, 4.576 mmol) was added dropwise to a solution of this aminal in THF (6 mL) under nitrogen at −78 °C. The reaction mixture was gradually warmed to 0 °C and stirred for 2 h. It was quenched by the addition of saturated NH_4Cl (5 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydride Na_2SO_4, and concentrated to give the crude amino alcohol, which was purified by column chromatography (silica gel, hexane/EtOAc=5:1) to give **8** (0.486 g, 75%) as a pale yellow oil. $[\alpha]_D^{24}$ −11.7 (*c* 1.0, $CHCl_3$); IR (NaCl) 2864 (C–H), 1247 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.15 (m, 17H, Ar*H*), 6.84–6.79 (m, 2H, Ar*H*), 5.78 (m, 1H, CH_2=C*H*), 5.23–5.09 (m, 2H, CH_2=CH), 4.65–4.61 (m, 3H, PhCH_2 and C*H*), 4.60–4.30 (m, 6H, 3PhCH_2), 4.09 (dd, *J*=5.8, 8.3 Hz, 1H, C*H*), 3.84–3.40 (m, 4H, CH_2 and 2C*H*), 3.74 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 158.9 (*C*), 141.0 (CH_2=CH), 138.6 (*C*), 138.5 (*C*), 138.4 (*C*), 137.7 (*C*H), 130.9 (*C*H), 129.9 (*C*H), 129.6 (2*C*H), 128.5 (*C*H), 128.4 (2*C*H), 128.3 (*C*H), 128.2 (*C*H), 128.1 (2*C*H), 127.9 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 127.6 (2*C*H), 127.5 (*C*H), 126.9 (*C*H), 117.4 (CH_2=CH), 114.0 (*C*H), 113.8 (*C*H), 81.0 (*C*H), 75.7 (*C*H), 73.8 (CH_2), 73.5 (*C*H_2), 66.1 (CH_2), 65.2 (*C*H), 58.2 (*C*H), 55.2 (CH_3), 49.9 (CH_2); HRMS (ESI^+) *m*/*z* calcd for $C_{36}H_{41}NO_5$+H: 568.3063, found 568.3042.

*4.2.2. N-((3S,4R,5R,6S)-4,5,7-Tris(benzyloxy)-6-hydroxyhept-1-en-3-yl)benzamide (**9**)*

4.2.2.1. Protection with BzCl. To a solution of **8** (1.663 g, 2.929 mmol) in CH_2Cl_2 (2 mL) was added a solution of benzoyl chloride (1.323 g, 8.788 mmol) in CH_2Cl_2 (1 mL) and stirred for 3 h. Then, the mixture was quenched by the addition of saturated aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydride Na_2SO_4, and concentrated in vacuo. The residue was chromatographed (silica gel, hexane/EtOAc=5:1) to give the MPM-benzylamide (1.751 g, 89%) as a pale yellow oil. $[\alpha]_D^{28}$ −12.3 (*c* 1.0, $CHCl_3$); IR (NaCl) 3402 (O–H), 2864 (C–H), 1625 (C=O), 1247 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.05 (m, 22H, Ar*H*), 6.81–6.77 (m, 2H, Ar*H*), 6.48 (m, 1H, C*H*), 5.78 (m, 1H, CH_2=CH), 5.18–3.90 (m, 12H, CH_2=CH, 4PhCH_2 and 3C*H*), 3.77 (s, 3H, CH_3), 3.78–3.48 (m, 3H, CH_2 and C*H*), 2.65 (m, 1H, O*H*); ^{13}C NMR ($CDCl_3$) δ 168.8 (*C*=O), 158.8 (*C*), 138.3 (CH_2=CH), 138.0 (*C*), 137.2 (*C*), 134.5 (*C*), 129.4 (*C*H), 129.1 (*C*H), 128.4 (2*C*H), 128.3 (2*C*H), 128.0 (3*C*H), 127.9 (2*C*H), 127.8 (*C*H), 127.7 (2*C*H), 127.6 (2*C*H), 127.5 (2*C*H), 127.8 (3*C*H), 127.7 (2*C*H), 126.7 (*C*H), 126.9 (*C*H), 119.5 (*C*H_2=CH), 113.7 (*C*H), 79.4 (*C*H), 77.3 (*C*H), 74.6 (*C*H_2), 74.1 (*C*H_2), 73.3 (*C*H_2), 71.4 (*C*H_2), 70.0 (*C*H), 62.6 (*C*H), 55.2 (CH_3), 54.3 (CH_2); HRMS (ESI^+) *m*/*z* calcd for $C_{43}H_{45}NO_6$+Na: 694.3145, found 694.3131.

4.2.2.2. Deprotection of MPM group. To a solution of the above benzylamide (0.213 g, 0.317 mmol) in MeOH (2.7 mL) was added cerium ammonium nitrate (CAN) (0.521 g, 0.951 mmol) slowly at 0 °C and stirred for 4 h at room temperature. Then, the mixture was quenched by the addition of water (5 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydride Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc=3:2) to give the benzylamide **9** (0.150 g, 86%) as a white solid; mp 104.7–104.9 °C. $[\alpha]_D^{27}$ −53.0 (*c* 1.0, $CHCl_3$); IR (KBr) 3402 (O–H), 2961 (C–H), 1658 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79–7.77 (m, 2H, Ar*H*), 7.52–7.46 (m, 3H, Ar*H*), 7.34–7.17 (m, 15H, Ar*H*), 6.84 (d, *J*=9.0 Hz, 1H, N*H*), 5.98 (ddd, *J*=17.2, 10.4, 4.8 Hz, 1H, CH_2=C*H*), 5.28–5.24 (m, 2H, CH_2=CH), 5.02 (m, 1H, C*H*), 4.80 (dd, *J*=10.8 Hz, 1H, PhCH_2), 4.78 (dd, *J*=11.0 Hz, 1H, PhCH_2), 4.68 (dd, *J*=10.8 Hz, 1H, PhCH_2), 4.50 (dd, *J*=11.0 Hz, 1H, PhCH_2), 4.49 (dd, *J*=11.8 Hz, 1H, PhCH_2), 4.42 (dd, *J*=11.8 Hz, 1H, PhCH_2), 4.09 (m, 1H, C*H*), 4.04 (dd, *J*=8.4, 1.8 Hz, 1H, C*H*), 3.68 (dd, *J*=8.4, 1.8 Hz, 1H, C*H*), 3.54 (dd, *J*=9.5, 6.6 Hz, 1H, CH_2), 3.42 (dd, *J*=9.5, 6.1 Hz, 1H, CH_2), 2.47 (d, *J*=7.5 Hz, 1H, O*H*); ^{13}C NMR ($CDCl_3$) δ 166.8 (*C*=O), 138.1 (2*C*), 138.0 (*C*), 137.9 (*C*), 136.3 (CH_2=CH), 134.4 (*C*H), 131.5 (2*C*H), 128.6 (*C*H), 128.4 (2*C*H), 128.3 (2*C*H), 128.1 (3*C*H), 127.9 (2*C*H), 127.8 (3*C*H), 127.7 (2*C*H), 127.6 (*C*H), 127.0 (*C*H), 115.8 (CH_2=CH), 81.9 (*C*H), 79.5 (*C*H), 75.2 (2CH_2), 73.1 (*C*H), 71.1 (*C*H), 69.3 (*C*H_2), 52.1 (*C*H_2); HRMS (ESI^+) *m*/*z* calcd for $C_{35}H_{37}NO_5$+Na: 574.2569, found 574.2578. Anal. Calcd for $C_{35}H_{37}NO_5$: C, 76.20; H, 6.76; N, 2.54. Found: C, 76.28; H, 6.88; N, 2.68.

*4.2.3. tert-Butyl benzoyl((3S,4R,5S,6S)-4,5,7-tris(benzyloxy)-6-(tert-butyldimethylsilyloxy)hept-1-en-3-yl)carbamate (**10**)*

4.2.3.1. Protection with TBSCl. A solution of **9** (0.230 g, 0.417 mmol), imidazole (0.057 g, 0.834 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl) (0.094 g, 0.625 mmol) in DMF (0.5 mL) was stirred for 12 h. It was quenched by the addition of water (5 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydride Na_2SO_4, and concentrated in vacuo. The combined organic layers were washed with brine (5 mL), dried over anhydride Na_2SO_4, and concentrated in vacuo. The residue was chromatographed (silica gel, hexane/EtOAc=15:1) to give the TBS-ether (0.246 g, 89%) as a colorless oil. $[\alpha]_D^{27}$ −55.6 (*c* 1.0, $CHCl_3$); IR (NaCl) 2856 (C–H), 1658 (C=O), 1253 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77–7.73 (m, 2H, Ar*H*), 7.47–7.43 (m, 3H, Ar*H*), 7.28–7.22 (m, 15H, Ar*H*), 6.77 (d, *J*=9.0 Hz, 1H, N*H*), 5.95 (ddd, *J*=16.7, 10.4, 5.0 Hz, 1H, CH_2=C*H*), 5.26–5.22 (m, 2H, CH_2=CH), 4.95 (m, 1H, C*H*), 4.77 (dd, *J*=10.8 Hz, 1H, PhCH_2), 4.75 (dd, *J*=11.6 Hz, 1H, PhCH_2), 4.64 (dd, *J*=10.8 Hz, 1H, PhCH_2), 4.60 (dd, *J*=11.6 Hz, 1H, PhCH_2), 4.42 (dd, *J*=11.9 Hz, 1H, PhCH_2), 4.36 (dd, *J*=11.9 Hz, 1H, PhCH_2), 4.20 (m, 1H, C*H*), 4.05 (d, *J*=7.5 Hz, 1H, C*H*), 3.70 (d, *J*=3.0 Hz 1H, C*H*), 3.65 (dd, *J*=9.5, 6.0 Hz, 1H, CH_2), 3.42 (dd, *J*=9.5, 6.0 Hz, 1H, CH_2), 0.91 (s, 9H, 3CH_3), 0.10 (d, *J*=7.0 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.8 (*C*=O), 138.7 (*C*), 138.3 (2*C*), 138.2 (*C*), 136.6 (CH_2=CH), 134.5 (2*C*H), 131.4 (2*C*H), 128.5 (2*C*H), 128.3 (2*C*H), 128.2 (2*C*H), 128.1 (2*C*H), 127.7 (2*C*H), 127.6 (2*C*H), 127.4 (*C*H), 127.3 (*C*H), 127.3 (*C*H), 127.0 (*C*H), 115.7 (CH_2=CH), 80.8 (*C*H), 80.7 (*C*H), 75.1 (*C*H), 74.5 (*C*H_2), 73.2 (*C*H), 72.9 (*C*H_2), 71.2 (*C*H_2), 52.6 (*C*H_2), 26.0 (2CH_3), 25.6 (*C*H_3), 18.2 (*C*), −3.9 (*C*H_3), −4.6 (*C*H_3); HRMS (ESI^+) *m*/*z* calcd for $C_{41}H_{51}NO_5$-Si+Na: 688.3434, found 688.3386.

4.2.3.2. Protection with $(Boc)_2O$. A solution of the above TBS-ether (0.371 g, 0.557 mmol), Et_3N (0.564 g, 5.571 mmol), $(Boc)_2O$ (0.608 g, 2.786 mmol), and DMAP (0.340 g, 2.786 mmol) was stirred for 12 h. It was quenched by the addition of water (5 mL) and extracted with ethyl acetate (10×3 mL). The combined organic layers were washed with brine (5 mL), dried over anhydride

Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc=20:1) to give **10** (0.392 g, 92%) as a viscous oil. $[\alpha]_D^{24}$ +14.9 (*c* 0.8, $CHCl_3$); IR (NaCl) 2858 (C–H), 1732 (C=O), 1674 (C=O), 1252 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46–7.21 (m, 20H, Ar*H*), 6.19 (m, 1H, CH_2=C*H*), 5.32–5.18 (m, 2H, CH_2=C*H*), 4.79–4.56 (m, 3H, PhCH_2 and C*H*), 4.52–4.46 (m, 2H, PhCH_2), 4.43–4.39 (m, 2H, PhCH_2), 4.16 (dt, *J*=10.9, 2.2 Hz, 1H, C*H*), 3.76 (dd, *J*=10.9, 2.2 Hz, 1H, C*H*), 3.67 (dd, *J*=1.8, 6.3 Hz, 1H, CH_2), 3.49 (dd, *J*=6.3, 9.4 Hz, 1H, CH_2), 0.98 (s, 9H, $3CH_3$), 0.92 (s, 9H, $3CH_3$), 0.04 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$) δ 173.6 (*C*=O), 156.3 (*C*=O), 139.0 (C), 138.7 (2*C*), 138.6 (*C*), 136.6 (CH_2=CH), 134.5 (*C*H), 130.9 (2*C*H), 128.3 (*C*H), 128.2 (*C*H), 128.1 (3*C*H), 128.0 (2*C*H), 127.9 (2*C*H), 127.8 (*C*H), 127.7 (2*C*H), 127.6 (2*C*H), 127.5 (2*C*H), 127.4 (2*C*H), 127.3 (*C*H), 127.0 (*C*H), 120.5 (CH_2=CH), 83.9 (*C*H), 82.8 (*C*H), 79.5 (*C*), 73.7 (*C*H), 73.2 (*C*H), 72.6 (CH_2), 72.5 (CH_2), 72.1 (CH_2), 27.7 (CH_3), 27.2 (CH_3), 26.0 (CH_3), 25.8 ($3CH_3$), 18.2 (*C*), −4.5 (CH_3), −4.7 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{46}H_{59}NO_7Si$+Na: 788.3959, found 788.3914.

4.2.4. *tert*-Butyl (3*S*,4*R*,5*S*,6*S*)-4,5,7-tris(benzyloxy)-6-(*tert*-butyldimethylsilyloxy)hept-1-en-3-ylcarbamate (**11**)

A solution of **10** (0.255 g, 0.333 mmol) and 1,1,3,3-tetramethylguanidine (0.383 g, 3.329 mmol) was stirred at 130 °C for 8 h. After concentration of the reaction mixture in vacuo, column chromatographic purification (silica gel, hexane/EtOAc=10:1) gave **11** (0.216 g, 98%) as a colorless oil. $[\alpha]_D^{27}$ −37.1 (*c* 0.6, $CHCl_3$); IR (NaCl) 2858 (C–H), 1717 (C=O), 1253 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.21 (m, 15H, Ar*H*), 5.85 (m, 1H, CH_2=C*H*), 5.27–5.14 (m, 3H, CH_2=CH and C*H*), 4.78 (d, *J*=11.6 Hz, 1H, PhCH_2), 4.71 (d, *J*=11.6 Hz, 1H, PhCH_2), 4.60 (d, *J*=10.8 Hz, 1H, PhCH_2), 4.55 (d, *J*=10.8 Hz, 1H, PhCH_2), 4.44 (d, *J*=12.0 Hz, 1H, PhCH_2), 4.40 (d, *J*=12.0 Hz, 1H, PhCH_2), 4.11 (m, 1H, C*H*), 3.89 (d, *J*=7.1 Hz, 1H, C*H*), 3.66 (dd, *J*=7.8, 2.8 Hz, 1H, C*H*), 3.60 (m, 1H, CH_2), 3.42 (dd, *J*=9.5, 6.0 Hz, 1H, CH_2), 1.41 (s, 9H, $3CH_3$), 0.90 (s, 9H, $3CH_3$), 0.07 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$) δ 155.5 (*C*=O), 139.0 (*C*), 138.4 (*C*), 138.3 (*C*), 137.3 (CH_2=CH), 128.2 (3CH), 128.1 (*C*H), 128.0 (2*C*H), 127.9 (2*C*H), 127.8 (2*C*H), 127.7 (2*C*H), 127.6 (*C*H), 127.5 (*C*H), 127.3 (*C*H), 115.2 (CH_2=CH), 81.0 (*C*H), 80.4 (*C*), 79.3 (CH_2), 77.2 (*C*H), 75.2 (*C*H), 74.5 (*C*H), 72.9 (CH_2), 71.3 (CH_2), 53.4 (CH_2), 28.4 ($3CH_3$), 26.0 ($3CH_3$), 18.2 (*C*), −3.9 (CH_3), −4.6 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{39}H_{55}NO_6Si$+Na: 684.3696, found 684.3650.

4.2.5. *tert*-Butyl (3*S*,4*S*,5*R*,6*S*,7*S*)-5,6,8-tris(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-3-hydroxyoct-1-en-4-ylcarbamate (**12a**)

4.2.5.1. Dihydroxylation. To a solution of **11** (0.147 g, 0.222 mmol) and 4-methylmorpholine *N*-oxide (50 wt% in H_2O, 0.039 g, 0.333 mmol) in acetone (0.5 mL) was added OsO_4 (0.05 M in THF, 0.06 mL, 0.003 mmol) and stirred for 12 h. Evaporation of the volatiles gave a crude mixture, which was chromatographed (silica gel, hexane/EtOAc=7:3) to give the diol (0.145 g, 94%) as a colorless oil (2.3:1 diastereomer mixture determined by ^1H NMR). IR (NaCl) 3441 (O–H), 3031 (C–H), 2858 (C–H), 1713 (C=O), 1253 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32–7.22 (m, 15H, Ar*H*), 5.22 (d, *J*=9.0 Hz, 1H, N*H*), 4.86 (d, *J*=10.8 Hz, 1H, PhCH_2), 4.81 (d, *J*=11.7 Hz, 1H, PhCH_2), 4.62 (d, *J*=11.7 Hz, 1H, PhCH_2), 4.61 (d, *J*=10.8 Hz, 1H, PhCH_2), 4.46 (d, *J*=11.9 Hz, 1H, PhCH_2), 4.41 (d, *J*=11.9 Hz, 1H, PhCH_2), 4.34 (d, *J*=8.1 Hz, 1H, C*H*), 3.97 (m, 1H, C*H*), 3.72–3.60 (m, 5H, $2CH_2$ and C*H*), 3.50–3.48 (m, 2H, CH_2), 2.39 (d, *J*=9.9 Hz, 1H, O*H*),1.39 (s, 9H, $3CH_3$), 0.90 (s, 9H, $3CH_3$), 0.06 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$) δ (major isomer) 157.2 (*C*=O), 138.9 (*C*), 138.5 (*C*), 138.3 (*C*), 128.4 (2*C*H), 128.3 (2*C*H), 128.2 (3*C*H), 128.1 (2*C*H), 127.7 (2*C*H), 127.5 (2*C*H), 127.3 (2*C*H), 80.7 (*C*H), 80.4 (*C*), 76.8 (CH_2), 75.4 (*C*H), 74.3 (CH_2), 73.0 (*C*H), 71.5 (CH_2), 71.4 (*C*H), 71.1 (*C*H), 62.6 (*C*H), 52.5 (*C*H), 28.2 ($3CH_3$), 26.0 ($3CH_3$), 18.2 (*C*), −4.2 (CH_3), −4.4 (CH_3); ^{13}C NMR ($CDCl_3$) δ (minor isomer) 157.2 (*C*=O), 138.6 (*C*), 138.5 (*C*), 138.4 (*C*), 128.4 (3CH), 128.3 (3*C*H), 128.2 (3*C*H), 128.1 (3*C*H), 127.6 (3*C*H), 127.4 (2*C*H), 127.2 (2*C*H), 80.5 (*C*), 80.3 (*C*H), 76.7 (*C*H), 75.4 (*C*H), 74.1 (CH_2), 72.9 (*C*H), 71.3 (CH_2), 71.4 (*C*H), 71.0 (*C*H), 62.6 (*C*H), 52.3 (*C*H), 28.1 (CH_3), 25.8 (CH_3), 17.8 (CH_3), −4.1 (CH_3), −4.6 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{39}H_{57}NO_8Si$+Na: 718.3751, found 718.3748.

4.2.5.2. Cleavage and nucleophilic addition. To a solution of the above diol (0.449 g, 0.645 mmol) in THF (0.9 mL) was added a solution of sodium periodate (0.690 g, 3.226 mmol) in H_2O (0.9 mL) and stirred for 4 h. The mixture was extracted with ether (10×3 mL) and evaporated in vacuo to give the crude aldehyde (0.428 g) as a yellow oil, which was used without further purification. Vinylmagnesium chloride (1.47 M solution in THF, 1.70 mL, 2.581 mmol) was added dropwise at −78 °C to a solution of the aldehyde in THF (6 mL) under nitrogen and the reaction mixture was stirred for 3 h. It was quenched by the addition of saturated NH_4Cl (5 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydride Na_2SO_4, and concentrated to give the crude amino alcohol, which was purified by column chromatography (silica gel, hexane/EtOAc=9:1) to give **12a** (0.424 g, 95%) as a colorless oil. $[\alpha]_D^{24}$ −3.1 (*c* 1.0, $CHCl_3$); IR (NaCl) 3443 (O–H), 1713 (C=O), 1253 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29–7.25 (m, 15H, Ar*H*), 5.79 (m, 1H, CH_2=C*H*), 5.22–5.18 (m, 3H, CH_2=CH and C*H*), 4.85 (d, *J*=10.8 Hz, 1H, PhCH_2), 4.71 (d, *J*=11.1 Hz, 1H, PhCH_2), 4.60 (d, *J*=10.8 Hz, 1H, PhCH_2), 4.55 (d, *J*=11.1 Hz, 1H, PhCH_2), 4.44 (d, *J*=12.0 Hz, 1H, PhCH_2), 4.40 (d, *J*=12.0 Hz, 1H, PhCH_2), 4.17 (m, 1H, C*H*), 4.08 (m, 1H, C*H*), 3.66–3.60 (m, 2H, CH_2 and C*H*), 3.48 (m, 1H, CH_2), 3.35 (m, 1H, C*H*), 1.61 (s, 9H, $3CH_3$), 0.91 (s, 9H, $3CH_3$), 0.07 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$) δ 155.7 (*C*=O), 138.9 (*C*), 138.6 (*C*), 138.4 (*C*), 135.5 (CH_2=CH), 128.3 (2*C*H), 128.2 (2*C*H), 128.1 (2*C*H), 128.0 (2*C*H), 127.9 (2*C*H), 127.6 (3CH), 127.3 (*C*H), 127.2 (*C*H), 119.7 (CH_2=CH), 80.4 (*C*), 80.1 (*C*H), 78.2 (*C*H), 76.8 (*C*H), 74.2 (*C*H), 73.9 (CH_2), 72.9 (CH_2), 71.5 (CH_2), 54.5 (CH_2), 28.4 ($3CH_3$), 28.3 ($3CH_3$), 18.3 (*C*), −3.9 (CH_3), −4.6 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{40}H_{57}NO_7Si$+Na: 714.3802, found 714.3798.

4.2.6. *tert*-Butyl (3*S*,4*S*,5*R*,6*R*,7*S*)-5,6,8-tris(benzyloxy)-7-hydroxy-3-(methoxymethoxy)oct-1-en-4-ylcarbamate (**13a**)

To a solution of **12a** (0.151 g, 0.218 mmol) in *N*,*N*-diisopropylethylamine (0.2 mL) was added chloromethyl methyl ether (0.035 g, 0.102 mmol) and stirred for 12 h. It was quenched by the addition of water (5 mL) and extracted with ethyl acetate (10×3 mL). The combined organic layers were washed with brine (5 mL), dried over anhydride Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc=9:1) to give the MOM-ether **13a** (0.160 g, quant.) as a viscous oil. $[\alpha]_D^{27}$ −26.0 (*c* 0.8, $CHCl_3$); IR (NaCl) 1713 (C=O), 1253 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29–7.20 (m, 15H, Ar*H*), 5.73 (m, 1H, CH_2=C*H*), 5.27–5.17 (m, 2H, CH_2=CH), 5.04 (d, *J*=10.0 Hz, 1H, CH_2), 4.83 (d, *J*=10.7 Hz, 1H, PhCH_2), 4.74 (d, *J*=11.8 Hz, 1H, PhCH_2), 4.66 (d, *J*=6.7 Hz, 1H, PhCH_2), 4.61 (d, *J*=11.8 Hz, 1H, PhCH_2), 4.54 (d, *J*=6.7 Hz, 1H, PhCH_2), 4.45 (d, *J*=10.7 Hz, 1H, PhCH_2), 4.38 (d, *J*=10.0 Hz, 1H, CH_2), 4.13–4.09 (m, 2H, 2*C*H), 3.98 (d, *J*=7.7 Hz, 1H, C*H*), 3.91 (d, *J*=7.7 Hz, 1H, C*H*), 3.71 (dd, *J*=7.7, 3.5 Hz, 1H, C*H*), 3.55–3.50 (m, 2H, CH_2), 3.34 (s, 3H, CH_3), 1.44 (s, 9H, $3CH_3$), 0.90 (s, 9H, $3CH_3$), 0.07 (d, *J*=2.9 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$) δ 155.7 (*C*=O), 138.9 (*C*), 138.6 (*C*), 138.4 (*C*), 135.5 (CH_2=CH), 128.3 (2*C*H), 128.2 (3CH), 128.1 (2*C*H), 127.9 (2*C*H), 127.6 (2*C*H), 127.3 (*C*H), 127.2 (*C*H), 127.1 (*C*H), 127.0 (*C*H), 119.7 (CH_2=CH), 93.8 (CH_2), 80.2 (*C*), 80.0 (*C*H), 78.2 (*C*H), 76.8 (*C*H), 74.2 (*C*H), 73.9 (CH_2), 72.9 (*C*H), 71.5 (CH_2), 71.4 (CH_2), 55.6 (CH_3), 54.5 (CH_2), 28.4 ($3CH_3$), 28.3 ($3CH_3$),

18.3 (*C*), −3.9 (*CH*$_3$), −4.4 (*CH*$_3$); HRMS (ESI$^+$) *m*/*z* calcd for $C_{42}H_{61}NO_8Si$+Na: 758.4064, found 758.4007.

4.2.7. (2R,3R,4R,5S)-tert-Butyl 3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-((S)-1-(methoxymethoxy)allyl)pyrrolidine-1-carboxylate (**14a**)

4.2.7.1. Deprotection of TBSCl. To a solution of **13a** (1.285 g, 1.747 mmol) in THF (43.6 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 3.5 mL, 3.5 mmol) and stirred for 3 h. The mixture was quenched by the addition of saturated $NaHCO_3$ (5 mL) and extracted with ethyl acetate (20×3 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydride Na_2SO_4, and concentrated to give the crude alcohol, which was purified by column chromatography (silica gel, hexane/EtOAc=3:1) to give the alcohol (1.063 g, 98%) as a white solid; mp 86.3–87.0 °C. $[\alpha]_D^{27}$ −30.9 (*c* 1.0, $CHCl_3$); IR (KBr) 3412 (O–H), 1715 (C=O), 1167 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29–7.20 (m, 15H, Ar*H*), 5.73 (m, 1H, CH_2=C*H*), 5.27–5.17 (m, 2H, C*H*$_2$=CH), 5.03 (d, *J*=10.0 Hz, 1H, C*H*$_2$), 4.82 (d, *J*=10.8 Hz, 1H, PhC*H*$_2$), 4.76 (d, *J*=11.2 Hz, 1H, PhC*H*$_2$), 4.67 (d, *J*=6.8 Hz, 1H, PhC*H*$_2$), 4.61 (d, *J*=11.2 Hz, 1H, PhC*H*$_2$), 4.56 (d, *J*=6.8 Hz, 1H, PhC*H*$_2$), 4.48 (d, *J*=10.8 Hz, 1H, PhC*H*$_2$), 4.45 (d, *J*=10.0 Hz, 1H, C*H*$_2$), 4.11 (m, 1H, C*H*), 3.99–3.95 (m, 3H, 3C*H*), 3.69 (dd, *J*=8.0, 1.8 Hz, 1H, C*H*), 3.55 (m, 1H, C*H*$_2$), 3.40 (m, 1H, C*H*$_2$), 3.37 (s, 3H, C*H*$_3$), 2.49 (d, *J*=9.0 Hz, 1H, O*H*), 1.40 (s, 9H, 3C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 156.0 (*C*=O), 138.4 (*C*), 138.1 (*C*), 138.0 (*C*), 135.3 (CH_2=CH), 128.4 (*C*H), 128.3 (2*C*H), 128.2 (3*C*H), 127.8 (2*C*H), 127.7 (2*C*H), 127.6 (2*C*H), 127.5 (*C*H), 127.4 (*C*H), 127.3 (*C*H), 119.8 (*C*H$_2$=CH), 93.9 (*C*H$_2$), 80.3 (*C*), 79.9 (*C*H), 79.0 (*C*H), 78.1 (*C*H), 74.7 (*C*H$_2$), 74.1 (*C*H$_2$), 73.1 (*C*H), 71.4 (*C*H), 69.3 (*C*H$_2$), 55.6 (*C*H$_3$), 54.1 (*C*H$_2$), 28.4 (3*C*H$_3$); HRMS (ESI$^+$) *m*/*z* calcd for $C_{36}H_{47}NO_8$+Na: 644.3199, found 644.3177. Anal. Calcd for $C_{36}H_{47}NO_8$: C, 69.54; H, 7.62; N, 2.25. Found: C, 69.48; H, 7.57; N, 2.32.

4.2.7.2. Mesylation and cyclization. To a solution of the above alcohol (1.063 g, 1.710 mmol) and Et_3N (0.346 g, 3.420 mmol) in CH_2Cl_2 (8.6 mL) was added methanesulfonyl chloride (0.300 g, 2.621 mmol) and stirred for 12 h. The mixture was quenched by the addition of 0.5% aq HCl (3 mL) and extracted with CH_2Cl_2 (20×3 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydride Na_2SO_4, and concentrated to give the crude mesylate (1.197 g), which was not purified further. A solution of this mesylate in THF (5.0 mL) was added dropwise at 0 °C to a suspension of *t*-BuOK (0.294 g, 2.621 mmol) in THF (1.0 mL) under nitrogen and gradually warmed to room temperature. After the mixture was stirred for 12 h, it was quenched by the addition of H_2O (5 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydride Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc=9:1) to give **14a** (0.863 g, 84%) as a colorless oil. $[\alpha]_D^{26}$ −51.8 (*c* 1.0, $CHCl_3$); IR (NaCl) 2858 (C–H), 1713 (C=O), 1217 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34–7.22 (m, 15H, Ar*H*), 5.73 (m, 1H, CH_2=C*H*), 5.20–5.14 (m, 2H, C*H*$_2$=CH), 4.76 (d, *J*=11.8 Hz, 1H, PhC*H*$_2$), 4.65 (d, *J*=11.8 Hz, 1H, PhC*H*$_2$), 4.57 (d, *J*=9.4 Hz, 1H, PhC*H*$_2$), 4.54 (d, *J*=15.8 Hz, 1H, PhC*H*$_2$), 4.49 (d, *J*=15.8 Hz, 1H, PhC*H*$_2$), 4.44 (d, *J*=9.3 Hz, 1H, C*H*), 4.36 (d, *J*=9.4 Hz, 1H, PhC*H*$_2$), 4.28–4.24 (m, 2H, C*H*), 4.02 (m, 1H, C*H*), 3.90 (m, 1H, C*H*), 3.76 (d, *J*=9.3 Hz, 1H, C*H*), 3.74 (m, 1H, C*H*), 3.20 (s, 3H, C*H*$_3$), 1.42 (s, 9H, 3C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 154.9 (*C*=O), 138.6 (*C*), 136.0 (*C*), 135.5 (*C*), 128.3 (CH_2=*C*H), 128.2 (*C*H), 128.1 (3*C*H), 128.0 (3*C*H), 127.8 (2*C*H), 127.7 (2*C*H), 127.6 (*C*H), 127.5 (*C*H), 127.4 (*C*H), 127.3 (*C*H), 117.8 (*C*H$_2$=CH), 86.2 (*C*H), 83.3 (*C*H$_2$), 80.4 (*C*), 75.3 (*C*H), 73.1 (*C*H), 72.0 (*C*H), 71.1 (*C*H), 61.1 (*C*H$_2$), 60.1 (*C*H$_2$), 59.7 (*C*H$_2$), 55.6 (*C*H$_3$), 54.1 (*C*H$_2$), 28.2 (3*C*H$_3$); HRMS (ESI$^+$) *m*/*z* calcd for $C_{36}H_{45}NO_7$+Na: 626.3094, found 626.3102.

4.2.8. (2R,3R,4R,5S)-tert-Butyl 3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-((S)-3-hydroxy-1-(methoxymethoxy)propyl)pyrrolidine-1-carboxylate (**15a**)

To a solution of **14a** (0.863 g, 1.430 mmol) in THF (1.8 mL) was added 9-BBN (0.5 M solution in THF, 5.7 mL, 2.85 mmol) under nitrogen at 0 °C and stirred for 12 h at room temperature. After the mixture was quenched by the addition of H_2O (0.2 mL), a solution of 3 N aq NaOH (1.5 mL) and hydrogen peroxide solution (34.5 wt % in H_2O, 1.5 mL) was added dropwise at 0 °C and stirred for further 4 h at room temperature. The mixture was quenched by the addition of water (5 mL) and extracted with ethyl acetate (20×3 mL). The combined organic layers were washed with brine (10 mL), dried over anhydride Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc=5:1) to give the primary alcohol **15a** (0.834 g, 94%) as a viscous oil. $[\alpha]_D^{22}$ −7.0 (*c* 1.0, $CHCl_3$); IR (NaCl) 3586 (O–H), 1693 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39–7.22 (m, 15H, Ar*H*), 4.75 (d, *J*=11.6 Hz, 1H, PhC*H*$_2$), 4.69 (d, *J*=10.1 Hz, 1H, PhC*H*$_2$), 4.64 (d, *J*=10.1 Hz, 1H, PhC*H*$_2$), 4.59 (d, *J*=11.6 Hz, 1H, PhC*H*$_2$), 4.49 (d, *J*=12.3 Hz, 1H, PhC*H*$_2$), 4.45 (d, *J*=12.3 Hz, 1H, PhC*H*$_2$), 4.43–4.39 (m, 2H, C*H*$_2$), 4.15 (d, *J*=2.0 Hz, 1H, C*H*), 4.11–3.96 (m, 2H, C*H*), 3.88–3.86 (m, 2H, C*H*$_2$), 3.76 (d, *J*=9.3 Hz, 1H, C*H*), 3.68–3.64 (m, 2H, C*H*$_2$), 3.25 (s, 3H, C*H*$_3$), 2.83 (br, 1H, O*H*), 2.04–1.64 (m, 2H, C*H*$_2$), 1.42 (s, 9H, 3C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 155.7 (*C*=O), 138.4 (2*C*), 137.6 (*C*), 128.3 (3*C*H), 128.2 (2*C*H), 128.1 (2*C*H), 128.0 (2*C*H), 127.7 (3*C*H), 127.5 (2*C*H), 127.3 (*C*H), 97.1 (*C*H$_2$), 83.1 (*C*H$_2$), 80.4 (*C*), 76.1 (*C*H), 75.3 (*C*H), 73.0 (*C*H$_2$), 72.9 (*C*H), 72.7 (*C*H$_2$), 72.2 (*C*H), 71.0 (*C*H$_2$), 60.1 (*C*H$_2$), 59.7 (*C*H$_2$), 55.9 (*C*H$_3$), 34.4 (*C*H$_2$), 28.2 (3*C*H$_3$); HRMS (ESI$^+$) *m*/*z* calcd for $C_{36}H_{47}NO_8$+Na: 644.3199, found 644.3198.

4.2.9. (1S,5R,6R,7R,7aS)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)hexahydro-1H-pyrrolizin-1-ol (**16a**)

To a solution of **15a** (0.070 g, 0.112 mmol) and Et_3N (0.023 g, 0.224 mmol) in CH_2Cl_2 (1.1 mL) was added methanesulfonyl chloride (0.020 g, 0.168 mmol) and stirred for 1 h. The mixture was quenched by the addition of 0.5% aq HCl (3 mL) and extracted with CH_2Cl_2 (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydride Na_2SO_4, and concentrated to give the crude mesylate (0.079 g), which was used without further purification. To a solution of this mesylate in CH_2Cl_2 (1.5 mL) was added 0.5 mL of $BF_3{\cdot}OEt_2/CH_2Cl_2$ (1:3) solution at −20 °C and warmed to 0 °C. After the mixture was stirred for 3 h, it was quenched by the addition of saturated aq $NaHCO_3$ (1 mL) and stirred for additional 2 h. It was diluted with water (5 mL) and extracted with CH_2Cl_2 (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydride Na_2SO_4, and concentrated in vacuo. The residue was chromatographed (silica gel, chloroform/MeOH=5:1) to give **16a** (0.043 g, 84%) as a pale yellow oil. $[\alpha]_D^{22}$ −1.9 (*c* 1.0, $CHCl_3$); IR (NaCl) 3582 (O–H), 2863 (C–H), 1693 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39–7.22 (m, 15H, Ar*H*), 4.72–4.20 (m, 7H, 3PhC*H*$_2$ and C*H*), 3.89–3.56 (m, 4H, C*H*$_2$ and 2C*H*), 1.87–1.67 (m, 3H, C*H*$_2$ and C*H*), 1.33–1.26 (m, 4H, C*H*$_2$ and 2C*H*); ^{13}C NMR ($CDCl_3$) δ 138.4 (*C*), 137.6 (*C*), 137.5 (*C*), 128.5 (2*C*H), 128.4 (2*C*H), 128.3 (3*C*H), 128.1 (2*C*H), 127.9 (2*C*H), 127.5 (2*C*H), 127.2 (2*C*H), 83.2 (*C*H), 81.0 (*C*H), 77.6 (*C*H), 77.2 (*C*H), 73.0 (*C*H$_2$), 72.9 (*C*H$_2$), 72.7 (*C*H$_2$), 72.2 (*C*H), 71.0 (*C*H$_2$), 68.3 (*C*H$_2$), 37.2 (*C*H$_2$); HRMS (ESI$^+$) *m*/*z* calcd for $C_{29}H_{33}NO_4$+H: 460.2488, found 460.2481.

4.2.10. (1R,2R,3R,7S,7aS)-3-(Hydroxymethyl)hexahydro-1H-pyrrolizine-1,2,7-triol (7-epi-alexine) (**1a**)

To a solution of **16a** (0.043 g, 0.0936 mmol) and ammonium formate (0.006 g, 0.150 mmol) in MeOH (1.0 mL) was added 10% Pd on carbon (0.15 g) and refluxed for 2 h. The mixture was filtered through a pad of Celite with MeOH and concentrated. Finally, the water solution of the crude product was passed through Dowex

50WX-8 (H^+ form), which was first eluted with water (20 mL), and then with 0.7 M NH_4OH (20 mL) followed by 1.4 M NH_4OH (10 mL). Alkaline fractions were concentrated in vacuo to give **1a** (0.014 g, 82%) as a syrup. The spectral data of synthetic **1a** thus obtained were identical in all respects with those of the previously synthesized compound.[4b] $[\alpha]_D^{23}$ −11.0 (*c* 1.0, H_2O) {lit. $[\alpha]_D^{20}$ −10.6 (*c* 0.56, H_2O)};[4b] IR (NaCl) 3427 (O–H), 2862 (C–H) cm^{-1}; ^1H NMR (D_2O) δ 4.38 (br, 1H, C*H*), 4.13 (t, *J*=8.0 Hz, 1H, C*H*), 3.87–3.76 (m, 3H, CH_2 and C*H*), 3.38 (dd, *J*=3.7, 8.5 Hz, 1H, C*H*), 3.08 (m, 1H, C*H*), 2.88–2.86 (m, 2H, C*H*), 1.79–1.77 (m, 2H, C*H*); ^{13}C NMR (D_2O) δ, 77.5 (*C*H), 75.3 (*C*H), 72.3 (*C*H), 67.0 (*C*H), 64.2 (*C*H), 59.2 (CH_2), 46.7 (CH_2), 34.2 (CH_2); HRMS (ESI^+) *m*/*z* calcd for $C_8H_{15}NO_4$+H: 190.1079, found 190.1075.

*4.2.11. tert-Butyl (4R,5R,6S,7S)-5,6,8-tris(benzyloxy)-7-(tert-butyldimethylsilyloxy)-3-oxooct-1-en-4-ylcarbamate (**17**)*

To a solution of **12a** (0.010 g, 0.0145 mmol), molecular sieves (4 Å, 0.002 g) and NMO (97%, 0.003 g, 0.0216 mmol) in CH_2Cl_2 (0.20 mL) was added TPAP (0.002 g, 0.00569 mol) and stirred for 12 h. The mixture was filtered through a pad of Celite with CH_2Cl_2 and concentrated. The residue was chromatographed (silica gel, hexane/EtOAc=20:1) to give **17** (0.009 g, 92%) as a colorless oil. $[\alpha]_D^{25}$ −14.0 (*c* 0.4, $CDCl_3$); IR (NaCl) 3032 (C–H), 2961 (C–H), 1717 (C=O), 1658 (ArH), 1614 (C=O), 1254 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29–7.21 (m, 15H, Ar*H*), 6.62 (dd, *J*=17.2, 10.4 Hz, 1H, CH_2=CH), 6.11 (d, 1H, *J*=17.2 Hz, CH_2=C*H*), 5.70 (d, *J*=7.0 Hz, 1H, N*H*), 4.70 (d, *J*=11.0 Hz, 1H, PhCH_2), 4.65 (d, *J*=3.0 Hz, 1H, C*H*), 4.61 (d, *J*=11.0 Hz, 1H, PhCH_2), 4.37–4.35 (m, 3H, PhCH_2), 4.25 (t, *J*=3.0 Hz, 1H, CH_2), 4.02 (m, 1H, C*H*), 3.79 (dd, *J*=10.1, 3.1 Hz, 1H, CH_2), 3.48 (t, *J*=4.2 Hz, 1H, C*H*), 3.35 (dd, *J*=11.0, 7.0 Hz, 1H, CH_2), 1.44 (s, 9H, 3CH_3), 0.88 (s, 9H, 3CH_3), 0.03 (d, *J*=1.1 Hz, 6H, 2CH_3); ^{13}C NMR ($CDCl_3$) δ 197.6 (C=O), 152.8 (*C*=O), 139.2 (*C*), 138.9 (*C*), 138.4 (*C*), 135.3 (CH=CH), 128.8 (2*C*H), 128.5 (*C*H), 128.3 (*C*H), 128.2 (2*C*H), 128.1 (*C*H), 128.0 (2*C*H), 127.8 (*C*H), 127.6 (2*C*H), 127.5 (*C*H), 127.3 (*C*H), 127.2 (*C*H), 119.7 (CH_2=CH), 86.5 (*C*H), 80.6 (*C*), 77.2 (*C*H), 77.0 (*C*H), 74.7 (*C*H), 72.8 (CH_2), 71.0 (CH_2), 56.1 (CH_2), 54.0 (CH_2), 28.4 ($3CH_3$), 26.1 ($3CH_3$), 18.2 (*C*), −4.3 (CH_3), −4.5 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{40}H_{55}NO_7Si$+Na: 712.3646, found 712.3688.

*4.2.12. tert-Butyl (3S,4S,5R,6R,7S)-5,6,8-tris(benzyloxy)-7-hydroxy-3-(methoxymethoxy)oct-1-en-4-ylcarbamate (**13b**)*

4.2.12.1. Reduction with the Luche reagent. To a solution of **17** (0.010 g, 0.0145 mmol) and powdered $CeCl_3$ heptahydrate (0.016 g, 0.0435 mmol) in MeOH (0.15 mL) was added $NaBH_4$ (0.002 g, 0.0435 mmol) at −45 °C and stirred for 2 h. It was quenched by the addition of saturated $NaHCO_3$ (2 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydride Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc=9:1) to give the diastereomer mixture of **12** (0.008 g, 80%) as a colorless oil. IR (NaCl) 3443 (O–H), 1713 (C=O), 1253 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ (major isomer) 7.29–7.24 (m, 15H, Ar*H*), 5.93 (m, 1H, CH_2=C*H*), 5.26–5.23 (m, 3H, CH_2=CH and C*H*), 4.85 (d, *J*=10.8 Hz, 1H, PhCH_2), 4.71 (d, *J*=11.1 Hz, 1H, PhCH_2), 4.60 (d, *J*=10.8 Hz, 1H, PhCH_2), 4.55 (d, *J*=11.1 Hz, 1H, PhCH_2), 4.44 (d, *J*=12.0 Hz, 1H, PhCH_2), 4.40 (d, *J*=12.0 Hz, 1H, PhCH_2), 4.17 (m, 1H, C*H*), 4.08 (m, 1H, C*H*), 3.65–3.61 (m, 2H, CH_2 and C*H*), 3.48 (m, 1H, CH_2), 3.35 (m, 1H, C*H*), 1.61 (s, 9H, 3CH_3), 0.91 (s, 9H, 3CH_3), 0.07 (s, 6H, 2CH_3); ^{13}C NMR ($CDCl_3$) δ (major isomer) 155.7 (*C*=O), 138.9 (*C*), 138.6 (*C*), 138.4 (*C*), 135.5 (CH=*C*H), 128.3 (2*C*H), 128.2 (2*C*H), 128.1 (2*C*H), 128.0 (2*C*H), 127.9 (2*C*H), 127.6 (2*C*H), 127.3 (2*C*H), 127.2 (*C*H), 119.7 (*C*H_2=CH), 80.1 (*C*), 79.1 (*C*H_2), 78.2 (*C*H), 77.2 (*C*H), 74.2 (*C*H), 72.9 (*C*H), 71.5 (*C*H_2), 71.4 (CH_2), 55.6 (CH_2), 54.5 (CH_2), 28.4 ($3CH_3$), 28.3 ($3CH_3$), 18.3 (*C*), −3.9 (CH_3), −4.6 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{40}H_{57}NO_7Si$+Na: 714.3802, found 714.3772.

4.2.12.2. Protection with MOMCl. To a solution of the above mixture (0.035 g, 0.0507 mmol) in *N*,*N*-diisopropylethylamine (0.2 mL) was added chloromethyl methyl ether (0.008 g, 0.102 mmol) and stirred for 12 h. It was quenched by the addition of water (5 mL) and extracted with ethyl acetate (10×3 mL). The combined organic layers were washed with brine (5 mL), dried over anhydride Na_2SO_4, and concentrated in vacuo. The crude products of two diastereomers were separated by column chromatography (silica gel, hexane/EtOAc=9:1) to give **13a** (0.002 g, 4%, R_f=0.45, hexane/EtOAc=5:1) and **13b** (0.036 g, 96%, R_f=0.60, hexane/EtOAc=5:1) as a viscous oil, respectively. Compound **13a**: see Section 4.2.6. Compound **13b**: $[\alpha]_D^{24}$ +15.6 (*c* 0.7, $CHCl_3$); IR (NaCl) 2872 (C–H), 1713 (C=O), 1217 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.26 (m, 15H, Ar*H*), 5.76 (m, 1H, CH_2=C*H*), 5.28–5.24 (m, 2H, CH_2=CH), 5.04 (d, *J*=13.2 Hz, 1H, CH_2), 4.83 (d, *J*=10.8 Hz 1H, PhCH_2), 4.74 (d, *J*=11.8 Hz, 1H, PhCH_2), 4.66 (d, *J*=6.7 Hz, 1H, PhCH_2), 4.61 (d, *J*=11.8 Hz, 1H, PhCH_2), 4.54 (d, *J*=6.7 Hz, 1H, PhCH_2), 4.45 (d, *J*=10.7 Hz, 1H, PhCH_2), 4.38 (d, *J*=10.0 Hz, 1H, CH_2), 4.13–4.09 (m, 2H, C*H*), 3.98 (d, *J*=7.7 Hz, 1H, C*H*), 3.91 (d, *J*=7.7 Hz, 1H, C*H*), 3.71 (dd, *J*=7.7, 3.5 Hz, 1H, C*H*), 3.55–3.51 (m, 2H, CH_2), 3.34 (s, 3H, CH_3), 1.44 (s, 9H, 3CH_3), 0.90 (s, 9H, 3CH_3), 0.07 (d, *J*=2.9 Hz, 6H, 2CH_3); ^{13}C NMR ($CDCl_3$) δ 155.5 (*C*=O), 139.2 (*C*), 138.9 (*C*), 138.4 (*C*), 136.3 (CH=CH), 128.5 (2*C*H), 128.3 (2*C*H), 128.2 (2*C*H), 128.1 (2*C*H), 127.8 (2*C*H), 127.6 (2*C*H), 127.5 (*C*H), 127.3 (*C*H), 127.2 (*C*H), 119.7 (*C*H_2=CH), 86.5 (CH_2), 80.6 (*C*), 79.1 (*C*H_2), 77.2 (*C*H), 77.0 (*C*H), 74.7 (*C*H), 74.4 (*C*H), 72.8 (*C*H), 71.1 (CH_2), 71.0 (CH_2), 56.1 (CH_3), 54.0 (CH_2), 28.4 ($3CH_3$), 26.1 ($3CH_3$), 18.2 (*C*), −3.9 (CH_3), −4.5 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{42}H_{61}NO_8Si$+Na: 758.4064, found 758.4018.

The same procedure gave the desilylated compound, pyrrolizidines **14b**, **15b**, **16b**, and (+)-alexine (**1b**) from the corresponding MOM-ether **13b** (yields are given in Scheme 3). The spectral data of synthetic **1b** thus obtained were identical in all respects with those of the natural[4a] and synthesized compound.[4b]

*4.2.12.2.1. Desilylated compound of **13b**.* $[\alpha]_D^{25}$ +6.5 (*c* 0.3, $CHCl_3$); IR (NaCl) 3412 (O–H), 2872 (C–H), 1715 (C=O), 1028 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32–7.24 (m, 15H, Ar*H*), 5.73 (m, 1H, CH_2=C*H*), 5.25–5.21 (m, 2H, CH_2=CH), 5.00 (d, *J*=10.0 Hz, 1H, CH_2), 4.82 (d, *J*=10.8 Hz, 1H, PhCH_2), 4.76 (d, *J*=11.2 Hz, 1H, PhCH_2), 4.67 (d, *J*=6.8 Hz, 1H, PhCH_2), 4.61 (d, *J*=11.2 Hz, 1H, PhCH_2), 4.56 (d, *J*=6.8 Hz, 1H, PhCH_2), 4.48 (d, *J*=10.8 Hz, 1H, PhCH_2), 4.45 (d, *J*=10.0 Hz, 1H, CH_2), 4.11 (m, 1H, C*H*), 4.01–3.93 (m, 3H, 3C*H*), 3.69 (dd, *J*=8.0, 1.8 Hz, 1H, C*H*), 3.55 (m, 1H, CH_2), 3.40 (m, 1H, CH_2), 3.37 (s, 3H, CH_3), 2.49 (d, *J*=9.0 Hz, 1H, O*H*), 1.40 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$) δ 155.6 (*C*=O), 138.7 (*C*), 138.5 (*C*), 138.1 (*C*), 135.9 (CH=*C*H), 128.4 (2*C*H), 128.3 (3*C*H), 128.2 (3*C*H), 128.0 (3*C*H), 127.9 (*C*H), 127.7 (*C*H), 127.6 (*C*H), 127.5 (*C*H), 119.6 (*C*H_2=CH), 86.3 (*C*H_2), 80.6 (*C*), 79.3 (*C*H), 78.1 (*C*H), 77.2 (*C*H), 74.9 (*C*H), 74.1 (*C*H), 73.1 (*C*H_2), 71.4 (CH_2), 69.2 (CH_2), 56.1 (CH_3), 53.7 (CH_2), 28.3 ($3CH_3$); HRMS (ESI^+) *m*/*z* calcd for $C_{36}H_{47}NO_8$+Na: 644.3199, found 644.3168.

*4.2.12.2.2. Compound **14b**.* $[\alpha]_D^{24}$ −13.7 (*c* 0.5, $CHCl_3$); IR (NaCl) 2872 (C–H), 1713 (C=O), 1217 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.01 (m, 15H, Ar*H*), 5.93 (m, 1H, CH_2=C*H*), 5.21–5.14 (m, 2H, CH_2=CH), 4.74–4.45 (m, 8H, 3PhCH_2 and CH_2), 4.37–4.16 (m, 4H, 4C*H*), 3.91–3.65 (m, 3H, CH_2 and C*H*), 3.24 (s, 3H, CH_3), 1.43 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$) δ 154.6 (*C*=O), 138.5 (*C*), 138.3 (*C*), 138.2 (*C*), 136.9 (CH=*C*H), 128.3 (2*C*H), 128.0 (3*C*H), 127.8 (*C*H), 127.7 (2*C*H), 127.6 (2*C*H), 127.5 (2*C*H), 127.3 (*C*H), 127.2 (*C*H), 127.0 (*C*H), 118.1 (*C*H_2=CH), 94.9 (*C*H), 86.5 (CH_2), 80.2 (*C*), 77.2 (*C*H), 76.2 (*C*H), 74.9 (*C*H), 73.1 (*C*H), 73.0 (2CH_2), 72.5 (CH_2), 60.5 (CH_3), 55.8 (CH_2), 28.4 ($3CH_3$); HRMS (ESI^+) *m*/*z* calcd for $C_{36}H_{45}NO_7$+Na: 626.3094, found 626.3063.

*4.2.12.2.3. Compound **15b**.* $[\alpha]_D^{25}$ +9.4 (*c* 0.8, $CHCl_3$); IR (NaCl) 3584 (O–H), 2872 (C–H), 1693 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32–

7.28 (m, 15H, Ar*H*), 4.68 (d, *J*=13.8 Hz, 1H, PhCH_2), 4.60 (d, *J*=13.2 Hz, 1H, PhCH_2), 4.59 (d, *J*=13.8 Hz, 1H, PhCH_2), 4.60 (d, *J*=13.2 Hz, 1H, PhCH_2), 4.53 (d, *J*=11.6 Hz, 1H, PhCH_2), 4.51 (d, *J*=11.6 Hz, 1H, PhCH_2), 4.49–4.45 (m, 2H, CH_2), 4.25 (t, *J*=5.1 Hz, 1H, CH_2), 4.15 (m, 1H, CH_2), 4.10 (t, *J*=6.8 Hz, 1H, CH_2), 4.00 (dd, *J*=11.1, 7.2 Hz, 1H, C*H*), 3.66–3.56 (m, 5H, CH_2 and 3C*H*), 3.33 (s, 3H, CH_3), 2.83 (br, 1H, O*H*), 1.91–1.87 (m, 2H, CH_2), 1.42 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$) δ 154.6 (*C*=O), 138.5 (*C*), 138.3 (*C*), 137.9 (*C*), 136.9 (CH_2=CH), 128.3 (2*C*H), 128.2 (2*C*H), 128.1 (*C*H), 128.0 (*C*H), 127.9 (*C*H), 127.8 (3*C*H), 127.7 (2*C*H), 127.6 (2*C*H), 127.5 (*C*H), 118.1 (CH_2=CH), 94.2 (*C*H), 80.1 (*C*), 78.8 (CH_2), 78.6 (CH_2), 77.2 (*C*H), 73.1 (CH_2), 73.0 (*C*H), 72.5 (*C*H), 70.1 (*C*H), 69.1 (*C*H), 60.5 (CH_2), 55.8 (CH_2), 37.2 (CH_2), 28.4 (3CH_3); HRMS (ESI$^+$) *m*/*z* calcd for $C_{36}H_{47}NO_8$+Na: 644.3199, found 644.3235.

4.2.12.2.4. Compound ***16b****.* $[\alpha]_D^{23}$ +1.8 (*c* 0.7, $CHCl_3$); IR (NaCl) 3584 (O–H), 2872 (C–H), 1693 (C=O), 1365 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39–7.22 (m, 15H, Ar*H*), 4.72–4.20 (m, 7H, 3PhCH_2 and C*H*), 3.89–3.51 (m, 4H, CH_2 and 2C*H*), 1.99–1.95 (m, 3H, CH_2 and C*H*), 1.33–1.26 (m, 4H, CH_2 and 2C*H*); ^{13}C NMR ($CDCl_3$) δ 138.4 (*C*), 137.6 (*C*), 137.3 (*C*), 128.5 (2*C*H), 128.4 (2*C*H), 128.3 (2*C*H), 128.2 (3*C*H), 128.1 (*C*H), 128.0 (*C*H), 127.9 (2*C*H), 127.5 (2*C*H), 77.6 (*C*H), 77.2 (*C*H), 73.0 (CH_2), 72.9 (CH_2), 72.7 (CH_2), 72.2 (*C*H), 73.0 (*C*H), 68.3 (*C*H), 62.7 (CH_2), 47.2 (CH_2), 37.2 (CH_2); HRMS (ESI$^+$) *m*/*z* calcd for $C_{29}H_{33}NO_4$+H: 460.2488, found 460.2497.

*4.2.12.2.5. Alexine (****1b****).* Mp 161.7–163.2 °C; (lit. mp 162–163 °C);[4a] $[\alpha]_D^{23}$ +40.4 (*c* 0.3, H_2O) {lit. $[\alpha]_D^{20}$ +40.0 (*c* 0.25, H_2O)};[4a] IR (KBr) 3425 (O–H), 2858 (C–H) cm^{-1}; ^{1}H NMR (D_2O) δ 4.47 (m, 1H, C*H*), 4.21 (d, *J*=6.2 Hz, 1H, C*H*), 3.77–3.75 (m, 2H, CH_2), 3.69 (d, 1H, *J*=6.2 Hz, 1H, C*H*), 3.55 (dd, *J*=8.5, 3.7 Hz, 1H, C*H*), 3.00–2.96 (m, 3H, C*H*), 2.08 (m, 1H, C*H*), 1.85 (m, 1H, C*H*); ^{13}C NMR (D_2O) δ 77.2 (*C*H), 75.3 (*C*H), 71.2 (*C*H), 69.8 (*C*H), 64.2 (*C*H), 59.2 (CH_2), 45.5 (CH_2), 34.8 (CH_2); HRMS (ESI$^+$) *m*/*z* calcd for $C_8H_{15}NO_4$+H: 190.1079, found 190.1077.

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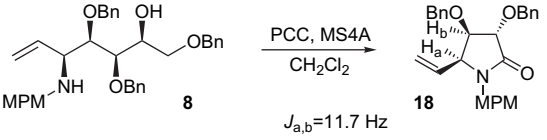
16. The addition of organometallic compounds to glycosylamines introduced by Nicotra et al.[16a] is an efficient and versatile method to obtain functionalized pyrrolidines. The synthetic applications of this reaction have been demonstrated both by our group[14h,16b,c] and by others[16d–f] for the synthesis of glycosidase or glycosyltransferase inhibitors. (a) Lay, L.; Nicotra, F.; Paganini, A.; Pangrazio, C.; Panza, L. *Tetrahedron Lett.* **1993**, *34*, 4555; (b) Yoda, H.; Yamazaki, H.; Kawauchi, M.; Takabe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2669; (c) Yoda, H.; Asai, F.; Takabe, K. *Synlett* **2000**, 1001; (d) Hashimoto, M.; Terashima, S. *Chem. Lett.* **1994**, 1001; (e) Behr, J.-B.; Mvondo-Evina, C.; Phung, N.; Guillerm, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1597; (f) Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1999**, *40*, 9375; The absolute configuration of the newly created stereogenic center of **8** was easily characterized to be *S* after derivatization to the corresponding vinyl lactam **18** as shown below.



The observed vicinal coupling constant ($J_{a,b}$) of protons (H_a,H_b) was 11.7 Hz, which indicates the lactam **18** occupies the cis-relation.[16a,b]
17. Initially we investigated the direct pyrrolizidine ring formation employing the *N*-benzylated derivative of **15a** via the quaternary ammonium salt, however, these reactions resulted in the formation of a complex mixture including *N*-mesylated compounds and gave the desired product **16a** in very low yield (10∼15%).
18. Determined by ^{13}C NMR analysis. Only trace amounts of minor stereoisomer were detected. The configuration of the newly generated stereocenter of the product was exactly determined to be *R*, and hence the obtained compound was **12a**, by comparing its ^{1}H and ^{13}C NMR spectral data with those of the reported value[4b] after completion of the synthesis of 7-*epi*-alexine **1a**.
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