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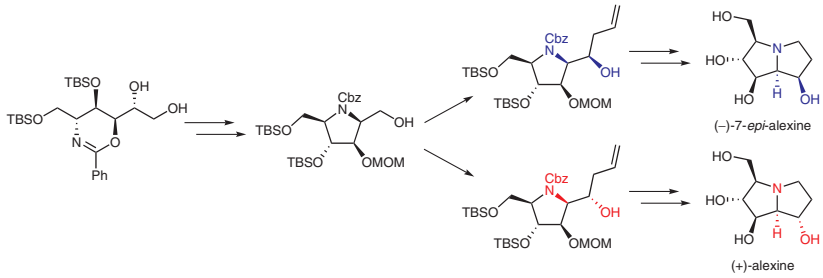
Total Syntheses of (–)-7-*epi*-Alexine and (+)-Alexine Using Stereoselective Allylation

In-Soo Myeong[a]
Changyoung Jung[a]
Won-Hun Ham[*a,b]

[a] School of Pharmacy, Sungkyunkwan University, Seobu-ro 2066, Suwon-si, Gyeonggi-do 16419, Republic of Korea
whham@skku.edu
[b] Yonsung Fine Chemicals Co., Ltd., Sujeong-ro 207, Jangan-myeon, Hwaseong-si, Gyeonggi-do 18581, Republic of Korea



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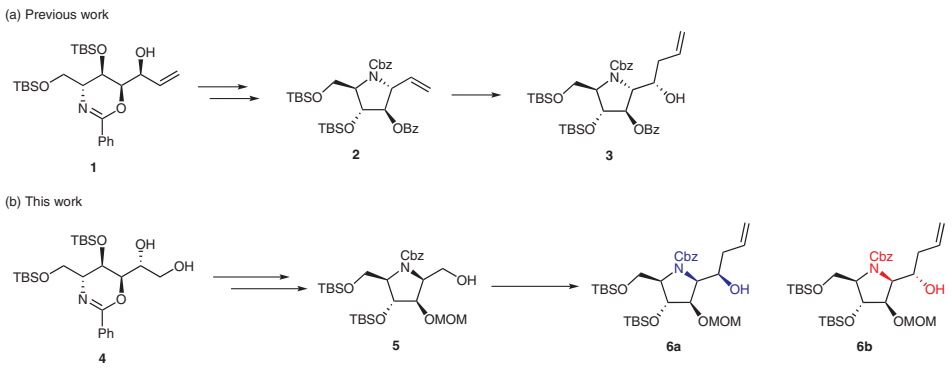
Abstract Total syntheses of (–)-7-*epi*-alexine and (+)-alexine were achieved by using stereoselective allylation via a functionalized pyrrolidine obtained from an extended chiral 1,3-oxazine. The synthetic strategies include pyrrolidine formation via oxazine cleavage and diastereoselective allylations of a pyrrolidine aldehyde. (–)-7-*epi*-Alexine and (+)-alexine were synthesized from *anti*,*syn*,*anti*-oxazine in 12 steps.

Key words allylation, alkaloids, amino alcohols, diastereoselectivity, asymmetric synthesis, cyclization

With the aim of synthesizing biologically active and important compounds, our research group has synthesized polyhydroxylated alkaloids using extended chiral 1,3-oxazines.[1] Recently, we reported the synthesis of a novel chiral building block, functionalized pyrrolidine **2**, from *anti*,*syn*,*syn*-oxazine **1**, and successfully extended the chirality to the synthesis of pyrrolidine **3** (Scheme 1).[2] In this work, the synthesis of functionalized pyrrolidine **5** from *anti*,*syn*,*anti*-oxazine **4** and stereoselective allylation of functionalized pyrrolidine **5** were achieved.

(+)-Alexine (**7**, Figure 1) is a naturally occurring tetrahydroxylated pyrrolizidine, whose isolation from *Alexa leiopetal* was reported in 1988.[3] Polyhydroxylated pyrrolizidine alkaloids are a class of sugar mimics wherein an oxygen atom in the ring is replaced by a nitrogen atom.[4] (+)-Alexine (**7**) and its structurally related congeners have attracted interest due to their significant biological activities, including potent inhibitory activity toward glycosidases and antiviral and antiretroviral activities.[5] Due to their biological activities and structural features, many syntheses of (+)-alexine (**7**) and (–)-7-*epi*-alexine (**8**) have been reported.[6] Our main tactic involved individual *syn*- and *anti*-selective allylations. Herein we report the stereocontrolled total syntheses of (+)-alexine (**7**) and (–)-7-*epi*-alexine (**8**).

Our retrosynthetic analyses are shown in Scheme 2. (–)-7-*epi*-Alexine (**8**) could be derived from the cyclization of **6a**, which could be obtained via stereoselective allylation of the functionalized pyrrolidine **5**. Functionalized pyrrolidine **5** could be derived from *anti*,*syn*,*syn*-oxazine **4**.



Scheme 1 Syntheses involved in previous work and this work

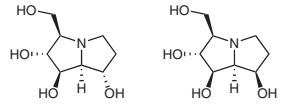
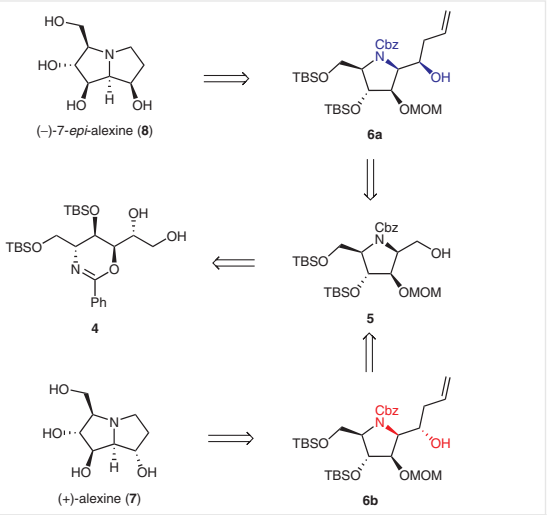


Figure 1 Structures of alexine (**7**) and 7-*epi*-alexine (**8**)



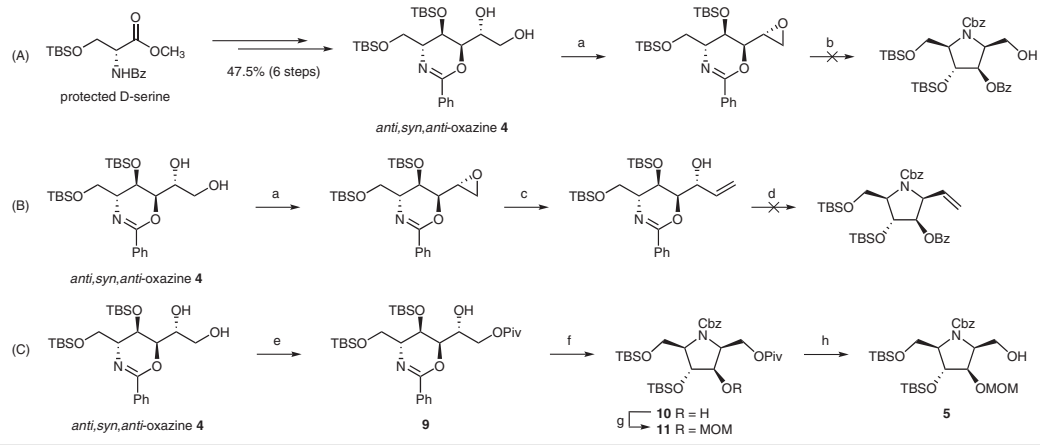
Scheme 2 Retrosynthetic analyses of (–)-*epi*-alexine (**8**) and (+)-alexine (**7**)

Through the same series of transformations, (+)-alexine (**7**) could be obtained via compounds **6b**, **5**, and **4**.

The preparation of **5** is shown in Scheme 3, and begins with *anti*,*syn*,*anti*-oxazine **4**, which was prepared using previously reported methods.[1a,7] To obtain the pyrrolidine ring via oxazine ring cleavage, we tested various methods. Primary selective monotosylation of the diol **4** and base treatment furnished an epoxide.[8] We then tried to synthesize the pyrrolidine ring using Pd-catalyzed hydrogenation via cleavage of the oxazine ring and epoxide ring opening, but only decomposition products were obtained (Scheme 3A). The epoxide derived from the diol **4** was treated with dimethylsulfonium methylide to generate allylic alcohol.[9] Drawing from our previously reported method,[2] we attempted the oxazine ring cleavage with CbzCl, but the desired product was not obtained, and the dimethylsulfonium methylide reaction gave a very low yield of allylic alcohol (Scheme 3B). Primary selective pivaloylation of the diol **4** furnished compound **5** (Scheme 3C).[10] Mesylation of **4** was carried out with $Pd(OH)_2/C$ under H_2 to afford the pyrrolidine **10**. The secondary alcohol **10** was protected by a methoxymethyl (MOM) group, and the pivaloyl group was deprotected using DIBAL-H,[11] to furnish the primary alcohol **5** (Scheme 3C).

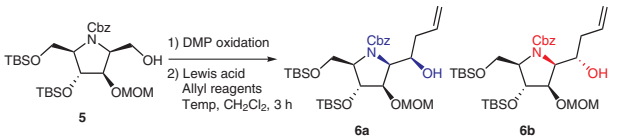
The results of the allylation of the aldehyde after Dess–Martin oxidation of the corresponding primary alcohol **5** are shown in Table 1. The reaction mediated by $SnCl_4$ with allyltributyltin afforded **6a**/**6b** in a 10:1 ratio and in 57% yield (entry 1). The reaction mediated by $TiCl_4$ resulted in the same **6a**/**6b** ratio as in entry 1, but in lower yield (entry 2). The $MgBr_2{\cdot}OEt_2$ reaction using allyltributyltin as the nucleophile afforded **6a**/**6b** in a 15:1 ratio and in 78% yield (entry 3). The reaction mediated by $BF_3{\cdot}OEt_2$ furnished **6a**/**6b** in a 1:6 ratio and in 73% yield (entry 4). The reaction using allylmagnesium bromide with no Lewis-acid afforded **6a**/**6b** in a 6:1 ratio and in 42% yield (entry 5).

The transition states for the allylation reactions are shown in Figure 2. Additions to the aldehyde derived from **5** mediated by $SnCl_4$, $TiCl_4$, and $MgBr_2{\cdot}OEt_2$ could proceed via the α-chelation model (Figure 2A), which results in the *syn*-alcohol **6a** (entries 1–3). Addition to the aldehyde derived



Scheme 3 Synthesis of **5**. *Reagents and conditions*: (a) 1. TsCl, Bu_2SnO, Et_3N, 2 h; 2. K_2CO_3, MeOH, r.t., 1 h, 75% (2 steps); (b) $Pd(OH)_2/C$, H_2 (80 psi), r.t., 24 h; (c) Me_3SI, 2 h, *n*-BuLi, THF, 12%; (d) 1. MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 90%; 2. CbzCl, 0.6 M aq $NaHCO_3$, CH_2Cl_2, 50 °C, 48 h; (e) PivCl, pyridine, CH_2Cl_2, 0 °C, 1 h, 91%; (f) 1. MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 93%; 2. $Pd(OH)_2/C$, H_2 (80 psi), r.t., 24 h; 3. CbzCl, Et_3N, CH_2Cl_2, r.t., 1 h, 66% (2 steps); (g) MOMCl, DIPEA, DMAP, CH_2Cl_2, 40 °C, 24 h, 83% (h) DIBAL-H, CH_2Cl_2, –78 °C, 1 h, 85%.

Table 1 Allylation Reactions to Afford **6**



Entry	Lewis acid	Allyl reagent	Temp	Ratio **6a**/**6b**[a]	Yield (%)[b]
1	$SnCl_4$	$AllylSnBu_3$	–78 °C	10:1	57
2	$TiCl_4$	$AllylSnBu_3$	–78 °C	10:1	34
3	$MgBr_2{\cdot}OEt_2$	$AllylSnBu_3$	0 °C	15:1	78
4	$BF_3{\cdot}OEt_2$	$AllylSnBu_3$	–78 °C	1:6	73
5	NA[c]	AllylMgBr	–78 °C	6:1	42

[a] Ratios were determined by ^1H NMR spectroscopy.
[b] Yields refer to the two-step yields of the mixed isomers.
[c] NA = Non Addition.

from **5** mediated by $BF_3{\cdot}OEt_2$ could proceed via the Felkin–Anh model (Figure 2B), which results in the *anti*-alcohol **6b** (entry 4).

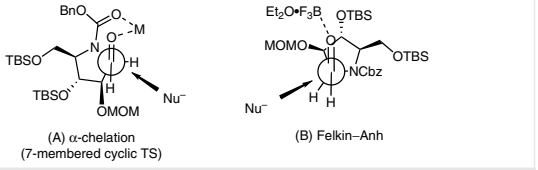
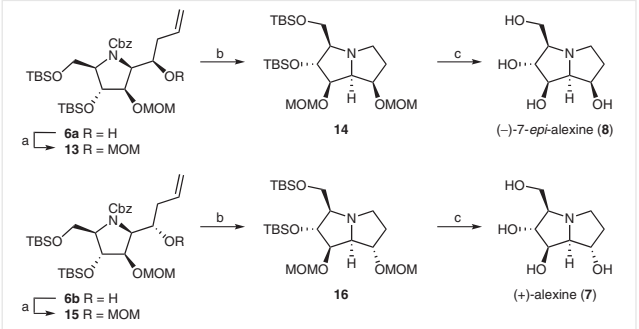


Figure 2 Proposed transition states for the allylations

The resulting allylation products **6a** and **6b** were used in the syntheses of (–)-*epi*-alexine (**8**) and (+)-alexine (**7**), respectively, as shown in Scheme 4, which further confirmed the relative stereochemistries of **6a** and **6b**. Allylation products **6a** and **6b** were first protected with a MOM group. Ozonolysis and hydrogenolysis of **13** and **15** afforded pyrrolizidine compounds **14** and **16**, respectively. Global deprotections of **14** and **16** with 1 N aq HCl furnished **8** and **7** as HCl salts (**8**·HCl and **7**·HCl), which were neutralized with an ion-exchange resin to afford (–)-*epi*-alexine (**8**) and (+)-alexine (**7**), respectively. The spectroscopic (^1H and ^{13}C NMR) data and other properties of the synthesized (–)-*epi*-alexine (**8**) and (+)-alexine (**7**) were in good agreement with the previously reported values.[6d] The optical rotation of **8**, $[\alpha]_D^{20}$ –10.7 (*c* 0.4, H_2O), was similar to the reported value, $[\alpha]_D^{23}$ –11.0 (*c* 1.0, H_2O),[6d] thereby confirming its absolute configuration. The optical rotation of **7**, $[\alpha]_D^{20}$ +40.7 (*c* 0.4, H_2O), was also similar to the reported value, $[\alpha]_D^{23}$ +40.4 (*c* 0.3, H_2O),[6d] which confirmed its absolute configuration. Thus, (–)-*epi*-alexine (**8**) and (+)-alexine (**7**) were synthesized from *anti*,*syn*,*anti*-oxazine **4**, in 14.6% and 15.1% yields, respectively, in 12 steps.



Scheme 4 Syntheses of (–)-*epi*-alexine (**8**) and (+)-alexine (**7**). *Reagents and conditions*: (a) MOMCl, DIPEA, DMAP, CH_2Cl_2, 40 °C, 24 h, 83–85%; (b) 1. O_3, MeOH, –78 °C, then Me_2S; 2. $Pd(OH)_2/C$, H_2, r.t., 24 h, 66–69%; (c) 1 N aq HCl, MeOH, 40 °C, 3 h, then DOWEX 50X-8 200, 87–90%.

In summary, (–)-7-*epi*-alexine (**8**) and (+)-alexine (**7**) were synthesized from *anti*,*syn*,*anti*-oxazine **4** via formation of pyrrolidines, stereoselective allylation, and pyrrolizidine cyclization. Notably, *syn*- and *anti*-selective allylations were successfully carried out by using $MgBr_2{\cdot}OEt_2$ and $BF_3{\cdot}OEt_2$, respectively. Further applications of using functionalized pyrrolidines are currently in progress.

Commercially available reagents were used without additional purification, unless stated otherwise. Unless stated otherwise, all non-aqueous reactions were performed under an argon atmosphere by using commercial-grade reagents and solvents. THF was distilled from sodium and benzophenone (as an indicator). CH_2Cl_2 was distilled from CaH_2. Optical rotations were measured with a Jasco P1020 polarimeter, in the solvent reported alongside the data. Specific rotations are reported in 10^{-1} deg·cm^2/g, and concentrations in g/100 mL. IR spectra were obtained using a Jasco FT/IR-4100 spectrophotometer. ^1H and ^{13}C NMR spectroscopic data were recorded at the Yonsung R&D center using a Bruker FT-NMR 300 MHz spectrometer. Chemical shift values are reported in ppm relative to TMS or $CDCl_3$ as the internal standards, and coupling constants are reported in Hz. Mass spectroscopic data were obtained using an Agilent 6530 Accurate-Mass Q-TOF LC/MS high-resolution mass spectrometer equipped with a magnetic sector–electric sector double-focusing analyzer. Flash chromatographic separations were performed using mixtures of hexanes and EtOAc or MeOH and $CHCl_3$ as the eluents.

(*R*)-2-{(4*R*,5*R*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-[(*tert*-butyldimethylsilyloxy)methyl]-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl}-2-hydroxyethyl Pivalate (9)

To a solution of **4** (0.5 g, 0.86 mmol) in CH_2Cl_2 (8.6 mL) was added pyridine (1 mL) followed by PivCl (0.16 mL, 1.29 mmol). The reaction mixture was stirred at 0 °C for 1 h and quenched with sat. aq NH_4Cl solution (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (20 mL). The combined organic layers were washed successively with $CuSO_4$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting substance was purified by column chromatography (silica gel, hexanes–EtOAc, 15:1); this afforded **9**.

Yield: 0.45 g (0.78 mmol, 91%); colorless oil; R_f = 0.4 (hexanes–EtOAc, 6:1); $[\alpha]_D^{20}$ +26.8 (*c* 0.2, $CHCl_3$).

IR (neat): 2956, 2930, 2858, 1733, 1657, 1472, 1337, 1281, 1256, 1138, 1004, 836, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.77 (m, 2 H), 7.17–7.31 (m, 3 H), 4.38 (dd, *J* = 11.8, 2.5 Hz, 1 H), 4.29 (t, *J* = 2.2 Hz, 1 H), 4.24 (dd, *J* = 11.8, 4.9 Hz, 1 H), 4.01–4.09 (m, *J* = 8.9, 4.6, 2.3 Hz, 1 H), 3.98 (dd, *J* = 8.8, 1.8 Hz, 1 H), 3.83 (dd, *J* = 10.3, 3.5 Hz, 1 H), 3.55 (dt, *J* = 7.3, 3.1 Hz, 1 H), 3.38 (dd, *J* = 10.4, 7.6 Hz, 1 H), 2.53–2.70 (m, 1 H), 1.09 (s, 9 H), 0.68–0.76 (m, 18 H), –0.14 to 0.03 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.2, 154.7, 133.3, 130.6, 128.1, 127.3, 72.5, 68.4, 65.9, 64.6, 63.4, 60.6, 39.0, 27.2, 25.9, 25.7, 18.3, 18.0, –4.5, –4.7, –5.4.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{54}NO_6Si_2$: 580.3484; found: 580.3485.

Benzyl (2*R*,3*R*,4*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-4-hydroxy-5-(pivaloyloxymethyl)pyrrolidine-1-carboxylate (10)[12]

To a solution of **9** (350 mg, 0.6 mmol) in CH_2Cl_2 (6 mL), Et_3N (0.2 mL, 1.2 mmol), followed by MsCl (0.1 mL, 1.2 mmol) at 0 °C were added. The reaction mixture was stirred at 0 °C for 1 h and quenched with sat. aq $NaHCO_3$ solution (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting substance was purified by column chromatography (silica gel, hexanes–EtOAc, 10:1); this afforded mesylate (368 mg, 0.56 mmol, 93%); colorless oil. $Pd(OH)_2/C$ (70 mg, 0.1 mmol) was added to a solution of the mesylate in MeOH (6 mL) under an H_2 atmosphere at r.t. The reaction mixture was stirred for 24 h. The mixture was filtered through a pad of Celite and concentrated *in vacuo*. The resulting substance was immediately used without further purification. To a solution of above resulting substance in CH_2Cl_2 (6 mL), CbzCl (0.19 mL, 1.1 mmol) and Et_3N (0.18 mL, 1.1 mmol) were added. The reaction mixture was stirred at r.t. for 1 h and quenched with sat. aq NH_4Cl solution (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting substance was purified by column chromatography (silica gel, hexanes–EtOAc, 15:1); this afforded **10**.

Yield: 226 mg (0.37 mmol, 66%); colorless oil. R_f = 0.6 (hexanes–EtOAc, 4:1); $[\alpha]_D^{20}$ –11.0 (*c* 1.0, $CHCl_3$).

IR (neat): 3443, 2955, 2928, 2857, 1709, 1463, 1408, 1362, 1283, 1254, 1130, 1094, 837, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.40 (m, 5 H), 5.17 (s, 2 H), 4.51–4.68 (m, 1 H), 4.33 (t, *J*=8.2 Hz, 1 H), 3.87–4.25 (m, 5 H), 3.63–3.86 (m, 2 H), 1.20 (s, 9 H), 0.81–0.94 (m, 18 H), 0.02–0.15 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.7, 178.5, 136.5, 128.5, 128.0, 127.9, 78.1, 76.1, 69.2, 67.1, 62.6, 61.4, 60.9, 38.8, 27.1, 25.9, 25.7, 18.4, 17.9, –4.7, –4.8, –5.5, –5.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{31}H_{55}NO_7Si_2$: 609.3517; found: 609.3516.

Benzyl (2*R*,3*R*,4*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-4-(methoxymethoxy)-5-(pivaloyloxymethyl)pyrrolidine-1-carboxylate (11)[12]

To a solution of **10** (240 mg, 0.4 mmol) in CH_2Cl_2 (4 mL) were added DMAP (5 mg, 0.04 mmol) and DIPEA (0.15 mL, 0.8 mmol), followed by MOMCl (0.07 mL, 0.8 mmol). The reaction mixture was stirred at 40 °C for 24 h and then quenched with H_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting substance was purified by column chromatography (silica gel, hexanes–EtOAc, 20:1) to give compound **11**.

Yield: 218 mg (0.33 mmol, 83%); colorless oil; R_f = 0.7 (hexanes–EtOAc, 4:1); $[\alpha]_D^{20}$ –10.0 (*c* 1.0, $CHCl_3$).

IR (neat): 2955, 2930, 2896, 2857, 1711, 1471, 1406, 1361, 1329, 1281, 1255, 1220, 1151, 1101, 1046, 1004, 838, 773 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.40 (m, 5 H), 5.01–5.30 (m, 2 H), 4.66 (s, 2 H), 4.23–4.45 (m, 4 H), 3.92–4.02 (m, 1 H), 3.63–3.83 (m, 3 H), 3.40 (s, 3 H), 1.08–1.23 (m, 9 H), 0.82–0.95 (m, 18 H), –0.05 to 0.16 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.0, 155.9, 136.6, 128.5, 128.0, 127.9, 97.3, 82.3, 74.4, 73.5, 67.0, 66.7, 62.8, 61.8, 61.2, 58.2, 57.5, 55.9, 38.7, 27.2, 25.9, 25.7, 18.3, 17.9, –4.6, –4.9, –5.5.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{33}H_{59}NO_8Si_2$: 653.3779; found: 653.3779.

Benzyl (2*R*,3*R*,4*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-5-(hydroxymethyl)-4-(methoxymethoxy)pyrrolidine-1-carboxylate (5)[12]

To a solution of **11** (456 mg, 0.651 mmol) in CH_2Cl_2 (6.5 mL) was added 1.0 M DIBAL-H in cyclohexane (1.63 mL, 1.632 mmol). The reaction mixture was stirred at –78 °C for 1 h and then quenched with sat. aq potassium sodium tartrate (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting substance was purified by column chromatography (silica gel, hexanes–EtOAc, 6:1) to give compound **5**.

Yield: 315 mg (0.55 mmol, 85%); colorless oil; R_f = 0.3 (hexanes–EtOAc, 4:1); $[\alpha]_D^{20}$ +0.1 (*c* 1.0, $CHCl_3$).

IR (neat): 2953, 2928, 2895, 2856, 1708, 1471, 1412, 1356, 1256, 1219, 1099, 1044, 1005, 837, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.40 (m, 5 H), 4.99–5.29 (m, 2 H), 4.38–4.79 (m, 3 H), 4.25–4.37 (m, 1 H), 3.51–4.24 (m, 7 H), 3.40 (s, 3 H), 0.82–0.93 (m, 18 H), –0.06 to 0.14 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.1, 136.2, 128.6, 128.2, 128.0, 98.0, 97.2, 83.6, 83.3, 74.0, 73.8, 67.5, 67.3, 67.0, 64.1, 62.8, 61.3, 60.0, 59.9, 56.2, 56.0, 25.9, 25.7, 18.3, 17.9, –4.6, –4.9, –5.5, –5.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{28}H_{51}NO_7Si_2$: 569.3204; found: 569.3204.

Benzyl (2*R*,3*R*,4*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-5-[(*R*)-1-hydroxybut-3-enyl]-4-(methoxymethoxy)pyrrolidine-1-carboxylate (6a)[12]

To a solution of **5** (162 mg, 0.284 mmol) in CH_2Cl_2 (6 mL) was added DMP (241 mg, 0.569 mmol). The reaction mixture was stirred at r.t. for 1 h and quenched with sat. aq $Na_2S_2O_3$ (10 mL) and sat. aq $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The aldehyde was immediately used in the next step without further purification. $MgBr_2{\cdot}OEt_2$ (110 mg, 0.43 mmol) was added to a solution of the above aldehyde in CH_2Cl_2 (6 mL) at 0 °C. This solution was stirred for 5 min at 0 °C, and allyltributyltin (0.19 mL, 0.57 mmol) was then added dropwise at 0 °C over 3 h. The reaction was quenched with sat. aq $NaHCO_3$ (10 mL), diluted with Et_2O, and the organic phase was

washed with brine. After drying over $MgSO_4$, the solvent was evaporated *in vacuo*. Purification by column chromatography (silica gel, hexanes–EtOAc, 10:1) afforded the product **6a**.

Yield: 127 mg (0.206 mmol, 73%); colorless oil; R_f = 0.55 (hexanes–EtOAc, 4:1); $[\alpha]_D^{20}$ –7.2 (*c* 0.1, $CHCl_3$).

IR (neat): 3442, 2954, 2858, 2359, 1706, 1471, 1397, 1255, 1103, 1008, 838, 778, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.41 (m, 5 H), 5.73–6.16 (m, 1 H), 4.86–5.29 (m, 4 H), 4.62–4.83 (m, 3 H), 4.02–4.50 (m, 3 H), 3.67–4.00 (m, 3 H), 3.53 (ddd, *J* = 6.3, 3.9, 1.7 Hz, 1 H), 3.39 (s, 3 H), 2.07–2.54 (m, 2 H), 0.81–0.96 (m, 18 H), 0.01–0.16 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 156.3, 136.1, 128.6, 128.3, 116.2, 98.1, 83.0, 74.2, 73.9, 70.8, 70.2, 67.6, 64.9, 64.2, 62.7, 61.6, 56.4, 40.0, 26.0, 25.7, 18.5, 17.8, –4.2, –4.7, –5.5, –5.6.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{31}H_{56}NO_7Si_2$: 610.3590; found: 610.3591.

Benzyl (2*R*,3*R*,4*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-5-[(*S*)-1-hydroxybut-3-enyl]-4-(methoxymethoxy)pyrrolidine-1-carboxylate (6b)[12]

Yield: 111 mg (0.18 mmol, 63%); colorless oil; R_f = 0.45 (hexanes–EtOAc, 4:1); $[\alpha]_D^{20}$ +9.4 (*c* 1.0, $CHCl_3$).

IR (neat): 2953, 2929, 2895, 2857, 1686, 1471, 1409, 1353, 1297, 1254, 1218, 1097, 1078, 1033, 1002, 836, 773 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.39 (m, 5 H), 5.74–6.05 (m, 1 H), 4.97–5.23 (m, 4 H), 4.60–4.81 (m, 2 H), 3.95–4.44 (m, 5 H), 3.63–3.82 (m, 3 H), 3.41 (s, 3 H), 2.28–2.39 (m, 1 H), 2.10–2.24 (m, 1 H), 0.82–0.91 (m, 18 H), –0.04 to 0.12 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3, 136.4, 136.3, 128.5, 128.1, 127.8, 116.2, 97.1, 84.4, 73.9, 70.5, 68.4, 67.4, 65.6, 61.4, 56.2, 38.8, 25.9, 25.7, 18.2, 17.9, –4.7, –4.9, –5.4, –5.6.

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{31}H_{55}NO_7Si_2$: 609.3517; found: 609.3516.

Benzyl (2*R*,3*R*,4*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-4-(methoxymethoxy)-5-[(*R*)-1-(methoxymethoxy)but-3-enyl]pyrrolidine-1-carboxylate (13)[12]

To a solution of **6a** (85 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) was added DIPEA (0.10 mL, 0.6 mmol) followed by MOMCl (0.05 mL, 0.6 mmol). The reaction mixture was stirred at 40 °C for 24 h and quenched with sat. aq $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting substance was purified by column chromatography (silica gel, hexanes–EtOAc, 15:1) to yield compound **13**.

Yield: 82 mg (0.13 mmol, 83%); colorless oil; R_f = 0.50 (hexanes–EtOAc, 6:1); $[\alpha]_D^{20}$ +3.6 (*c* 0.1, $CHCl_3$).

IR (neat): 2954, 2888, 2857, 2349, 1709, 1472, 1405, 1355, 1254, 1098, 1045, 917, 837, 777, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.40 (m, 5 H), 5.61–6.03 (m, 1 H), 5.09–5.24 (m, 2 H), 4.92–5.09 (m, 2 H), 4.54–4.77 (m, 4 H), 4.19–4.40 (m, 3 H), 4.01 (dd, *J* = 5.5, 2.6 Hz, 1 H), 3.80 (s, 3 H), 3.32–3.47 (m, 6 H), 2.26–2.51 (m, 2 H), 0.81–0.95 (m, 18 H), –0.04 to 0.15 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 136.7, 128.5, 128.0, 116.4, 97.4, 97.3, 84.6, 75.3, 68.5, 67.1, 62.1, 56.0, 55.8, 36.0, 26.0, 25.7, 18.3, 17.9, –4.7, –4.8, –5.2, –5.5.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{33}H_{60}NO_8Si_2$: 654.3852; found: 654.3856.

Benzyl (2*R*,3*R*,4*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-4-(methoxymethoxy)-5-[(*S*)-1-(methoxymethoxy)but-3-enyl]pyrrolidine-1-carboxylate (15)[12]

Yield: 84 mg (0.133 mmol, 85%); colorless oil; R_f = 0.45 (hexanes–EtOAc, 6:1); $[\alpha]_D^{20}$ –13.9 (*c* 1.0, $CHCl_3$).

IR (neat): 2953, 2929, 2896, 2857, 1707, 1471, 1407, 1257, 1219, 1102, 1045, 916, 839, 773 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.39 (m, 5 H), 5.81–6.04 (m, 1 H), 4.95–5.23 (m, 4 H), 4.53–4.76 (m, 4 H), 4.33–4.41 (m, 1 H), 4.04–4.25 (m, 2 H), 3.99 (dd, *J* = 6.0, 2.5 Hz, 1 H), 3.67–3.90 (m, 3 H), 3.42 (s, 3 H), 3.33 (s, 3 H), 2.26–2.52 (m, 2 H), 0.82–0.91 (m, 18 H), –0.03 to 0.12 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.7, 136.7, 135.9, 128.4, 127.9, 116.4, 97.4, 97.2, 84.1, 76.4, 73.9, 73.6, 68.3, 67.1, 62.5, 61.3, 56.0, 55.7, 37.0, 25.9, 25.7, 18.2, 17.8, –4.7, –4.9, –5.3, –5.5.

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{33}H_{59}NO_8Si_2$: 653.3779; found: 653.3777.

(1*R*,2*R*,3*R*,7*R*,7a*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-[(*tert*-butyldimethylsilyloxy)methyl]-1,7-bis(methoxymethoxy)hexahydro-1*H*-pyrrolizine (14)

Compound **13** (60 mg, 0.1 mmol) was dissolved in MeOH (3 mL) and cooled to –78 °C. Ozone was then passed through the solution until the reaction was complete. The reaction mixture was quenched with Me_2S (0.07 mL, 1.0 mmol) and warmed to r.t.. The solvent was then evaporated *in vacuo*. Purification by short silica gel chromatography afforded a crude aldehyde product. $Pd(OH)_2/C$ (10 mg, 0.01 mmol) was added to a solution of the above product in MeOH (3 mL) under a H_2 atmosphere at 0 °C. The reaction mixture was stirred for 3 h. The mixture was filtered through a pad of Celite and concentrated *in vacuo*. Purification by column chromatography (silica gel, $CHCl_3$–MeOH, 20:1) afforded **14**.

Yield: 33 mg (0.07 mmol, 66%); colorless oil; R_f = 0.40 ($CHCl_3$–MeOH, 9:1); $[\alpha]_D^{20}$ +5.2 (*c* 0.2, $CHCl_3$).

IR (neat): 2954, 2930, 2857, 2359, 1738, 1472, 1362, 1254, 1151, 1103, 1044, 920, 837, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.58–4.73 (m, 4 H), 4.17 (td, *J* = 4.0, 2.5 Hz, 1 H), 4.09 (dd, *J* = 7.3, 6.5 Hz, 1 H), 3.94 (t, *J* = 6.5 Hz, 1 H), 3.75–3.89 (m, 2 H), 3.29–3.47 (m, 8 H), 3.00 (td, *J* = 7.7, 4.3 Hz, 1 H), 2.88 (td, *J* = 8.3, 3.1 Hz, 1 H), 1.80–2.07 (m, 2 H), 0.83–0.95 (m, 18 H), 0.02–0.11 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 98.0, 95.8, 84.6, 68.3, 66.8, 61.6, 55.8, 55.6, 45.9, 33.1, 25.9, 25.7, 18.2, 17.9, –4.3, –4.7, –5.4, –5.4.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{52}NO_6Si_2$: 506.3328; found: 506.3324.

(1*R*,2*R*,3*R*,7*S*,7a*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-[(*tert*-butyldimethylsilyloxy)methyl]-1,7-bis(methoxymethoxy)hexahydro-1*H*-pyrrolizine (16)

Yield: 35 mg (0.073 mmol, 69%); colorless oil; R_f = 0.35 ($CHCl_3$–MeOH, 9:1); $[\alpha]_D^{20}$ –2.0 (*c* 0.3, $CHCl_3$).

IR (neat): 2952, 2930, 2856, 1257, 1219, 1153, 1110, 839, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.61–4.75 (m, 4 H), 4.25 (q, *J* = 6.5 Hz, 1 H), 4.08 (dd, *J* = 3.5, 2.6 Hz, 1 H), 3.87 (dd, *J* = 4.3, 1.7 Hz, 1 H), 3.71–3.81 (m, 2 H), 3.32–3.50 (m, 7 H), 3.02 (dt, *J* = 8.4, 7.2 Hz, 1 H), 2.75–2.94 (m, 2 H), 2.24–2.39 (m, 1 H), 1.91–2.08 (m, 1 H), 0.81–0.95 (m, 18 H), 0.01–0.14 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 96.4, 96.1, 81.6, 74.8, 72.7, 68.8, 62.2, 55.8, 55.5, 46.6, 35.0, 29.7, 25.9, 25.7, 18.3, 17.9, –4.6, –4.7, –5.4, –5.5.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{24}H_{52}NO_6Si_2$: 506.3328; found: 506.3331.

(1*R*,2*R*,3*R*,7*R*,7a*S*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,7-triol [(–)-7-*epi*-Alexine; 8]

To a solution of **14** (33 mg, 0.07 mmol) in MeOH (3 mL) at r.t., 1 N aq HCl solution (3 mL) was added. The reaction mixture was stirred for 6 h. The solvent was removed *in vacuo*, furnishing the HCl salt of **2** (**2**·HCl) as a white solid. This was purified on an ion-exchange column (DOWEX 50WX8-200). The column was washed with MeOH (20 mL) and H_2O (20 mL) to remove products not containing amines, and then with 6 M aq NH_4OH (60 mL) to yield a solution of compound **8**. Evaporation of the solvent afforded product **8**.

Yield: 12 mg (0.06 mmol, 90%); white solid; $[\alpha]_D^{20}$ –10.7 (*c* 0.4, H_2O).

IR (neat): 3338, 2919, 2309, 1558, 1437, 1109, 1046, 791, 598 cm^{-1}.

^{1}H NMR (300 MHz, D_2O): δ = 4.47 (td, *J* = 3.9, 1.5 Hz, 1 H), 4.22 (t, *J* = 8.1 Hz, 1 H), 3.81–3.96 (m, 3 H), 3.52 (dd, *J* = 8.3, 4.2 Hz, 1 H), 3.21 (ddd, *J* = 11.6, 9.4, 6.3 Hz, 1 H), 2.92–3.05 (m, 2 H), 1.75–1.94 (m, 2 H).

^{13}C NMR (75 MHz, D_2O): δ = 77.4, 75.0, 72.0, 66.0, 63.5, 59.0, 45.7, 33.7.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{16}NO_4$: 190.1074; found: 190.1076.

(1*R*,2*R*,3*R*,7*S*,7a*S*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,7-triol [(+)-Alexine; 7]

Yield: 11.6 mg (0.058 mmol, 87%); white solid; $[\alpha]_D^{20}$ +40.7 (*c* 0.4, H_2O).

IR (neat): 3338, 2922, 2865, 2844, 1456, 1346, 1054, 1032, 1013 cm^{-1}.

^{1}H NMR (300 MHz, D_2O): δ = 4.48 (td, *J* = 6.9, 5.3 Hz, 1 H), 4.22 (t, *J* = 7.0 Hz, 1 H), 3.78–3.87 (m, 3 H), 3.49 (dd, *J* = 7.5, 5.3 Hz, 1 H), 2.94–3.16 (m, 3 H), 2.21 (dtd, *J* = 12.6, 6.3, 4.0 Hz, 1 H), 1.79 (ddt, *J* = 12.7, 9.6, 7.3 Hz, 1 H).

^{13}C NMR (75 MHz, D_2O): δ = 75.7, 75.4, 70.6, 69.9, 64.7, 58.5, 46.0, 33.9.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{16}NO_4$: 190.1074; found: 190.1075.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611566.

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