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Total Synthesis of (+)-Alexine by Utilizing a Highly Stereoselective [3+2] Annulation Reaction of an *N*-Tosyl-α-Amino Aldehyde and a 1,3-Bis(silyl)propene

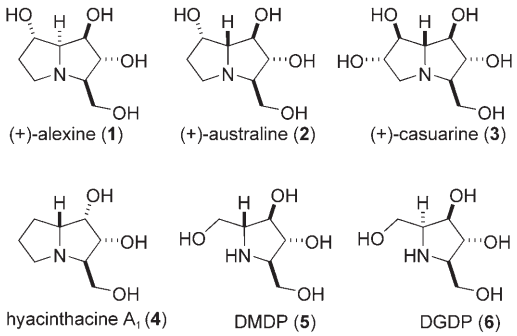
Martina Dressel,[a] Per Restorp,[a] and Peter Somfai*[a, b]

Abstract: A novel route towards the polyhydroxylated pyrrolizidine alkaloid (+)-alexine has been developed. A key step in this synthesis is a highly stereoselective [3+2] annulation reaction of *N*-Ts-α-amino aldehyde **7a** (Ts = tosyl) and 1,3-bis(silyl)propene **8a** for the construction of the polyhydroxylated pyrrolidine subunit of the target molecule. Previous synthetic strategies rely on carbohydrates that require several protecting-group manipulations, thereby making the total number of steps relatively high. The [3+2] annulation strategy compares favorably with carbohydrate-based syntheses and constitutes a highly efficient entry to polyhydroxylated alkaloids.

Keywords: annulation · asymmetric synthesis · natural products · nitrogen heterocycles · silanes

Introduction

Polyhydroxylated pyrrolidine and pyrrolizidine alkaloids are a class of naturally occurring compounds, primarily isolated from plants throughout the world, that have attracted considerable attention owing to their significant biological activity.[1] Many of these alkaloids exhibit diverse biological activities, including powerful glycosidase inhibitory properties and antiviral and antiretroviral activities, and are, therefore, potential chemotherapeutic drug targets for HIV and cancer therapy.[2] Noteworthy members of this important class of compounds are (+)-alexine ((+)-**1**), (+)-australine ((+)-**2**), (+)-casuarine ((+)-**3**), and hyacinthacine A_1 (**4**), which are all structurally related and differ only in relative stereochemistry (compare **1** and **2**) and the level of hydroxylation (compare **3** and **4**). Formally, compounds **1**–**4** can be derived from the monocyclic glycosidase inhibitors 2,5-dideoxy-2,5-imino-D-mannitol, DMDP (**5**) and 2,5-dideoxy-2,5-imino-D-glucitol, DGDP (**6**).



Biological screenings of these compounds have demonstrated that the substitution pattern and stereochemistry of the hydroxy groups in the pyrrolizidine skeleton have a significant impact on their biological activity.[2] Therefore, a number of synthetic routes leading to natural as well as unnatural isomers of pyrrolizidine alkaloids have been developed. Owing to the structural resemblance to sugars, synthetic routes to alexine ((+)-**1**) and several of their structurally related congeners have exploited the intrinsic chirality and highly oxygenated architecture of carbohydrates as starting materials.[3]

Although the use of sugar-derived precursors minimizes the need to introduce the requisite stereocenters and hydroxy moieties, several of these syntheses are impractical owing to the large number of synthetic steps, the need for extensive protecting group manipulations, and the apparent lack of stereochemical flexibility. To meet the demands for

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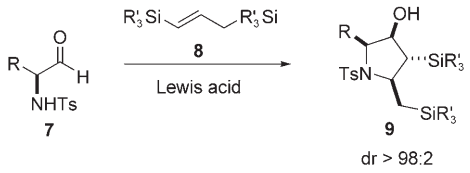
higher synthetic efficiency, focused and divergent asymmetric routes from achiral starting materials have been developed that, to date, mainly rely on stereoselective reductions of pyrroles,[4] Sharpless asymmetric amino-hydroxylations[5] and dihydroxylations,[6] ring-closing metathesis,[7] and tandem [4+2]/[3+2] cycloaddition reactions of nitroalkenes.[8] Recently, a synthesis of polyhydroxylated pyrrolidine alkaloids based on asymmetric allylic alkylations of butadiene epoxide with amines was reported by Trost et al.[9]

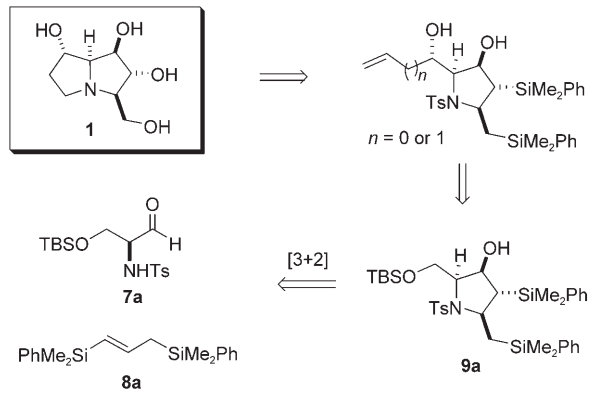
The Lewis acid promoted addition of allylsilanes to aldehydes (Sakurai–Hosomi allylation) is an important method for stereoselective C–C bond formation.[10] Allylsilanes can also function as synthetic equivalents of 1,2- and 1,3-dipoles in [3+2] annulation reactions with activated aldehydes,[11] imines,[12] and chlorosulfonyl isocyanates.[13] These approaches have been well studied and provide efficient entries to five-membered heterocyclic ring systems, mainly functionalized 2-pyrrolidone (γ-lactam)[13] and THF[11] subunits. In contrast, the corresponding [3+2] annulation reaction to afford functionalized pyrrolidines has only received scarce attention.[12,14] Recently, we reported that highly functionalized pyrrolidines **9**, containing four contiguous stereocenters can be prepared by a [3+2] annulation reaction of protected α-amino aldehydes **7** and 1,3-bis(silyl)propenes **8** (Scheme 1).[15] The efficiency of the method was also demonstrated by a straightforward synthesis of DGDP (**6**). We now wish to describe our efforts to apply this novel annulation methodology to the synthesis of the polyhydroxylated pyrrolizidine alkaloid (+)-alexine ((+)-**1**).



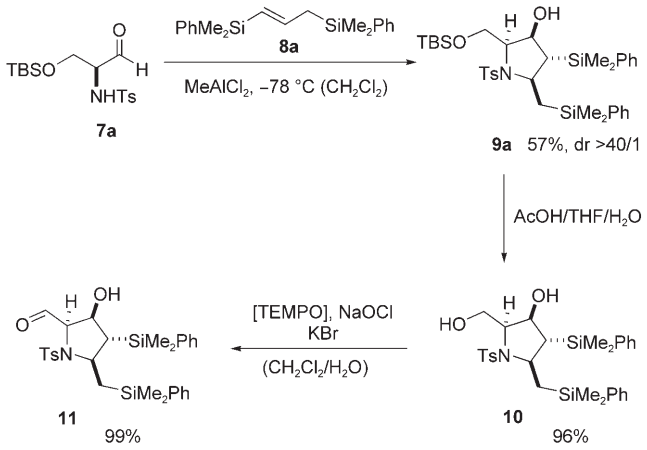
Scheme 1. The stereoselective synthesis of functionalized pyrrolidines **9**.

Results and Discussion

Carbon–silicon bonds can be oxidized to carbon–oxygen bonds with retention of configuration in which the reaction requires proper selection of the substituents on the Si nucleus.[16] With this in mind, it was reasoned that our recently developed [3+2] annulation methodology would be an ideal starting point for an expedient synthesis of (+)-alexine ((+)-**1**). Accordingly, we envisioned that pyrrolidine **9a**, which is readily available from aldehyde **7a**[17] and silane **8a** by a [3+2] annulation reaction, would serve as an advanced intermediate towards compound **1** (Scheme 2). Notably, four of the stereocenters required for compound **1** are introduced in this step with excellent selectivity. It was then reasoned that the remaining C7 stereocenter of (+)-**1** could be introduced by a substrate-controlled nucleophilic allylation or vinylation of the corresponding aldehyde **11**. The synthesis of (+)-**1** commenced with aldehyde **7a** and silane **8a**, which smoothly underwent a highly stereoselective [3+2] annulation reaction to afford pyrrolidine **9a** as a single diastereomer (Scheme 3).[15] Desilylation under acidic conditions then

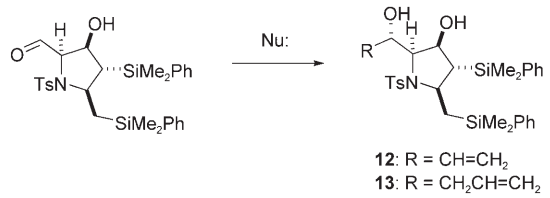


Scheme 2. Retrosynthetic analysis of (+)-alexine ((+)-**1**).



Scheme 3. Synthesis of aldehyde **11**.

afforded diol **10** in an excellent yield. The synthesis then required a chemoselective oxidation of the primary hydroxy group in **10**, thus setting the stage for introducing the C7 stereocenter. After screening several methods, it was found that 2,2,6,6-tetramethylpiperidinyl-*N*-oxyl (TEMPO)/NaOCl cleanly furnished aldehyde **11**[18] in a quantitative yield with no sign of oxidation of the secondary alcohol or aldehyde epimerization.[17] At this point, the substrate-controlled diastereoselective additions to aldehyde **11** were examined (Scheme 4). It was envisioned that the correct C7 stereochemistry required for (+)-**1** could be installed by a Felkin–Anh-controlled addition to **11** in which the (−)-sulfonamide moiety acts as the large group and exerts the major stereodirecting effect.[19] Alternatively, a chelation-controlled nucleophilic addition to a six-membered cyclic chelate, as previ-



Scheme 4. Allylation/vinylation of **11**.

ously described for $TiCl_4$-promoted additions of allylsilanes to α-alkoxy aldehydes, is also expected to furnish the correct C7 stereochemistry.[20] In this event, treatment of aldehyde **11** with vinylmagnesium bromide at −78 °C afforded pyrrolidine **12** in excellent yields but as an inseparable mixture of C7 stereoisomers (Scheme 4 and Table 1, entry 1). Lowering the reaction temperature to −100 °C resulted in only a marginal improvement in the diastereoselectivity (Table 1, entry 2). However, treatment of aldehyde **11** with allyltrimethylsilane and $TiCl_4$ afforded pyrrolidine **13** in 70% yield as a single detectable stereoisomer. The use of the less reactive Lewis acid analogue $TiCl_2(OiPr)_2$ resulted in similar stereoselectivity but a somewhat diminished yield. Additionally, the reaction temperature had to be increased to −50 °C to ensure full conversion of **11** (Table 1, entry 4). Further attempts to optimize this reaction by employing other monodentate and chelating Lewis acids (BF_3·OEt_2 and $MeAlCl_2$) gave inferior results.

Table 1. Stereoselective allylation/vinylation of aldehyde **11**.

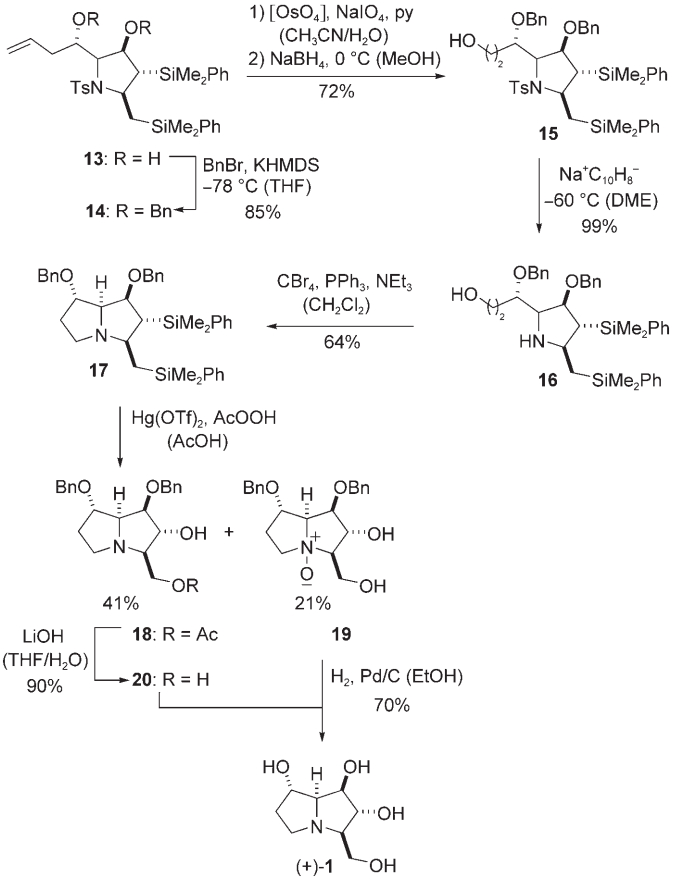
Entry	Nu:	Lewis acid	*T* [°C]	dr[a] (Yield [%])[b]	Product
1[c]	CH_2=CHMgBr	n/a[d]	−78	86:14 (90)	**12**[e]
2[c]	CH_2=CHMgBr	n/a	−100	90:10 (85)	**12**[e]
3[f]	CH_2=$CHCH_2TMS$	$TiCl_4$	−78	>95:5 (70)	**13**
4[g]	CH_2=$CHCH_2TMS$	$TiCl_2(OiPr)_2$	−78 to −50	>95:5 (56)	**13**

[a] Determined by ^{1}H NMR analysis of the crude reaction mixtures. [b] Yield of the isolated product after flash chromatography. [c] Vinylmagnesium bromide (5 equiv) was added to a solution of aldehyde **11** in Et_2O at the indicated temperature. [d] n/a = non applicable. [e] Product not fully characterized. [f] Allyltrimethylsilane (3 equiv) was added to a solution of aldehyde **11** and $TiCl_4$ (1.5 equiv) in CH_2Cl_2. [g] Allyltrimethylsilane (3 equiv) was added to a solution of aldehyde **11** and $TiCl_2(OiPr)_2$ (3 equiv) in CH_2Cl_2.

To complete the synthesis, the vinyl moiety in **13** must be cleaved followed by insertion of the pyrrolizidine ring system. Initially it was planned to perform this sequence without protecting the secondary hydroxy groups in **13**, the argument being that sufficient chemoselectivity to perform this should be inherent in the system. However, all attempts to put this strategy into practice failed. Treating compound **13** with O_3 or OsO_4/$NaIO_4$ only yielded complex mixtures without any trace of the desired product.[21] As a result, the alcohol moieties in **13** were protected as benzyl ethers, which furnished pyrrolidine **14** in an excellent yield (Scheme 4). The cleavage of the terminal olefin moiety in **14** by using a Lemieux–Johnson oxidation[22] was straightforward and the resultant aldehyde was reduced in situ to give alcohol **15** in a 72% yield over two steps. Removal of the tosyl group then gave amine **16** in excellent yield.

Different conditions were evaluated for the 5-*exo-tet* ring closure of **16** into pyrrolizidine **17**. It has recently been reported that MsCl (MsCl = mesyl chloride) also effects this cyclization in other similar systems, with the reaction proceeding by a selective mesylation of the primary hydroxy group followed by ring closure.[4] However, treatment of **16** with MsCl at 0 °C only gave a complex mixture of products, perhaps indicating that, for the present case, the mesylation suffers from poor chemoselectively. Instead, the cyclization could be accomplished by converting the primary hydroxy moiety in **16** into the corresponding alkylbromide followed by cyclization to afford the pyrrolizidine **17** in good yields.

Having synthesized **17**, only two steps remained to complete the synthesis of (+)-**1**: a stereospecific Tamao–Fleming oxidation of the Me_2PhSi groups and removal of the benzyl ethers. It is known that the oxidation of dimethylphenylsilyl moieties to the corresponding alcohols can be accomplished in a one-pot procedure by treatment with a suitable electrophile (Br_2 or Hg^{2+} ion) in AcOOH/AcOH.[16,23] Alternatively, the oxidation can be performed in a two-step sequence by transforming the dimethylphenylsilyl moieties into the corresponding silylfluorides by using BF_3·AcOH or HBF_4·OEt_2 in CH_2Cl_2 or AcOH, followed by oxidation to the corresponding alcohols by using H_2O_2. The latter protocol is reported to be less prone to oxidize tertiary amines.[21] Initial attempts to oxidize **17** by using Br_2 (generated in situ from KBr) in AcOOH/AcOH yielded a complex mixture of products with no sign of the formation of **18**. Instead, we turned our attention to the two-step procedures described above, which have previously been successfully used for oxidation of dimethylphenylsilyl moieties in the presence of tertiary amines.[24] However, treatment of **17** with BF_3·AcOH or HBF_4·OEt_2 in CH_2Cl_2 or AcOH at ambient temperature gave only starting material, whereas higher reaction temperatures resulted in the rapid decomposition of **17**. Similarly, the use of $Hg(OTf)_2$/AcOOH in TFA/$CHCl_3$/AcOH (Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid), which has been recently applied in the total synthesis of (+)-casuarine, only returned the starting material.[25] Interestingly, a similar procedure with $Hg(OTf)_2$/AcOOH in AcOH at ambient temperature resulted in the chemoselective oxidation of the primary silyl group. When the reaction time was prolonged, pyrrolizidine **18** and *N*-oxide **19** could be isolated in satisfying yields. Hydrolysis of **18** gave alcohol **20**, and finally, treating compounds **19** and **20** to H_2 and Pd/C gave (+)-**1** in good yields (Scheme 5).



Scheme 5. The synthetic pathway towards (+)-alexine ((+)-**1**). py = pyridine.

Conclusion

We have completed the first asymmetric, non-carbohydrate-based total synthesis of the polyhydroxylated pyrrolizidine alkaloid (+)-alexine ((+)-**1**) in twelve steps from the serine-derived aldehyde **7a** with an overall yield of 6%. The key steps in the synthesis are a highly stereoselective [3+2] annulation of *N*-Ts-α-amino aldehydes (Ts = tosyl) and 1,3-bis-(silyl)-propenes, a highly selective substrate-controlled Sakurai–Hosomi allylation, and a stereospecific Fleming–Tamao oxidation of the dimethylphenylsilyl moieties. The ^{13}C NMR data, melting point, and the optical rotation (160–161 °C, $[\alpha]_D^{20} = +39$ ($c = 0.08$ in H_2O)) were in good agreement with the published data for natural (+)-alexine (162–163 °C, $[\alpha]_D^{20} = +40$ ($c = 0.25$ in H_2O)).[1a] However, all proton signals in the ^{1}H NMR spectrum were shifted $\delta = 0.2$–0.3 ppm downfield when compared with the data published by Nash et al.[1a] Similar observations have been described previously and have been ascribed to the particular pH value of the NMR sample and the method used for its purification.[4d,7]

To date, two total syntheses of (+)-alexine have been detailed in the literature,[3a,d] both of which rely on carbohydrates as the starting materials. As a result, several protecting-group manipulations are required, which makes the total number of steps relatively high (20 steps with a 4% overall yield[3a] and 26 steps with a 4% overall yield[3d]). Thus, it can be seen that the [3+2] annulation strategy presented herein compares favorably and constitutes a highly efficient entry to polyhydroxylated alkaloids.

Experimental Section

General methods: All air- and moisture-sensitive reactions were carried out in flame-dried flasks under nitrogen. The liquid reagents were transferred by using oven-dried syringes. THF and CH_2Cl_2 were dried by using a glass-contour solvent-dispensing system. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or D_2O by using the residual signal of $CHCl_3$ (^{1}H NMR $\delta = 7.26$ ppm, ^{13}C NMR $\delta = 77.0$ ppm) or H_2O (^{1}H NMR $\delta = 4.79$ ppm) as the internal standard. Analytical TLC plates were visualized by using UV light, phosphomolybdic acid/cerium sulfate, and/or Draggendorff reagent.

(2*S*,3*R*,4*R*,5*R*)-4-[Dimethyl(phenyl)silyl]-5-{[dimethyl-(phenyl)silyl]methyl}-2-methyl-1-tosylpyrrolidin-3-(*tert*-butyldimethylsilanoyl) (9a): $MeAlCl_2$ (1 M in hexanes, 6.98 mL) was added by using a syringe to a stirred solution of aldehyde **7a** (2.08 g, 5.82 mmol) in CH_2Cl_2 (100 mL), which was cooled to −78 °C, followed by the addition of **8a** (1.98 g, 6.40 mmol). The resulting mixture was stirred at −78 °C for 2 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, filtered, and then evaporated to give a colorless oil. Flash chromatography (silica gel, pentane/EtOAc 5:1) of the residue yielded **9a** as a white solid (2.25 g, 58%). $[\alpha]_D^{25} = -3.4$ ($c = 0.55$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.56$ (d, $J = 8.2$ Hz, 2H), 7.45–7.23 (m, 12H), 3.99 (dd, $J = 10.1$, 4.7 Hz, 1H), 3.87 (m, 2H), 3.80 (ddd, $J = 8.8$, 5.9, 3.1 Hz, 1H), 3.52 (m, 1H), 3.45 (d, $J = 3.3$ Hz, 1H), 2.42 (s, 3H), 1.69 (dd, $J = 15.7$, 8.8 Hz, 1H), 1.47 (t, $J = 5.7$ Hz, 1H), 1.18 (dd, $J = 15.7$, 3.1 Hz, 1H), 0.89 (s, 9H), 0.27 (s, 3H), 0.26 (s, 3H), 0.10 (s, 6H), 0.06 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 143.4$, 139.2, 136.6, 135.4, 134.0, 133.9, 129.6, 129.3, 128.8, 127.9, 127.7, 127.6, 75.1, 64.1, 62.8, 60.3, 39.6, 26.7, 25.8, 21.5, 18.0, −1.5, −1.8, −4.0, −4.2, −5.4, −5.5 ppm; IR (neat): $\tilde{\nu} = 3490$, 2950, 1350, 1160 cm^{-1}; MS (ESI): *m*/*z* (%): 690 (100) $[M+Na]^+$; HRMS (FAB): *m*/*z* calcd for $C_{35}H_{53}NO_4SSi_3$: 690.2895 $[M+Na]^+$; found: 690.2899.

(2*S*,3*R*,4*R*,5*R*)-2-(Hydroxymethyl)-4-[dimethyl(phenyl)silyl]-5-{[dimethyl(phenyl)silyl]methyl}-1-tosylpyrrolidin-3-ol (10): Pyrrolidine **9a** (1.06 g, 1.58 mmol) was dissolved in AcOH/THF/H_2O (3:1:1, 25 mL) and stirred for 15 h at RT. The solvents were removed in vacuo. Flash chromatography (pentane/EtOAc 1:1) of the residue afforded pyrrolidine **10** as a colorless oil (840 mg, 96%). $[\alpha]_D^{25} = -23.4$ ($c = 0.47$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.61$ (m, 2H), 7.51 (m, 2H), 7.39–7.19 (m, 8H), 7.52 (m, 2H), 3.97 (m, 1H), 3.84 (m, 3H), 3.42 (m, 1H), 2.55 (dd, $J = 7.1$, 5.9 Hz, 1H), 2.44 (s, 3H), 2.38 (d, $J = 4.5$ Hz, 1H), 1.76 (dd, $J = 14.7$, 8.7 Hz, 1H), 1.43 (t, $J = 5.3$ Hz, 1H), 1.37 (dd, $J = 14.7$, 3.3 Hz, 1H), 0.33 (s, 3H), 0.32 (s, 3H), 0.04 (s, 3H), −0.07 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 145.2$, 140.6, 137.6, 136.1, 135.4, 135.3, 131.3, 131.1, 130.5, 129.6, 129.4, 129.2, 76.8, 65.3, 64.1, 61.9, 41.8, 28.8, 23.1, 0.04, −0.36, −2.0, −3.4 ppm; IR (neat): $\tilde{\nu} = 3443$, 2953, 2923, 1427, 1341, 1250, 1159, 1112, 1034, 815 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{29}H_{39}NO_4SSi_2$: 576.2031 $[M+Na]^+$; found: 576.2028.

(2*S*,3*R*,4*R*,5*R*)-3-Hydroxy-4-[dimethyl(phenyl)silyl]-5-{[dimethyl-(phenyl)silyl]methyl}-1-tosylpyrrolidine-2-carbaldehyde (11): Pyrrolidine **10** (405 mg, 0.73 mmol) and 2,2,6,6-tetramethylpiperidinoxyl radical (1.14 mg, 0.07 mmol) were dissolved in CH_2Cl_2 (20 mL). KBr (95.7 mg, 0.80 mmol) was dissolved in an aqueous solution of $NaHCO_3$ (5% w/w, 40 mL) and added to the reaction mixture. The vigorously stirred two-layer mixture was cooled to 0 °C and an aqueous solution of NaOCl (496 μL, 0.80 mmol, 10% w/w) was slowly added. After complete conversion of the alcohol (TLC control) the phases were separated and the

aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were successively washed with an aqueous solution of $NaHCO_3$ (5% w/w, 10 mL) and brine (10 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvents yielded a white solid (400 mg, 99%), which was used in the following allylation without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=9.63 (d, J=3.0 Hz, 1H), 7.64–7.62 (m, 2H), 7.52 (m, 2H), 7.41–7.28 (m, 8H), 7.06–7.05 (m, 2H), 4.27 (dd, J=5.4, 1.6 Hz, 1H), 3.94 (dt, J=10.7, 2.8 Hz, 1H), 3.64 (dd, J=5.4, 2.7 Hz, 1H), 2.44 (s, 3H), 1.87 (m, 1H), 1.69 (dd, J=14.7, 2.6 Hz, 1H), 1.43 (t, J=1.8 Hz, 1H), 1.37 (dd, J=14.7, 3.3 Hz, 1H), 0.29 (s, 3H), 0.28 (s, 3H), −0.1 (s, 3H), −0.3 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=201.8, 144.2, 138.5, 135.6, 134.6, 134.0, 133.6, 133.6, 129.9, 129.7, 128.0, 128.0, 128.0, 76.8, 71.4, 60.8, 42.6, 28.0, 21.5, −1.6, −2.5, −3.9, −5.7 ppm.

(2*S*,3*R*,4*R*,5*R*)-2-[(*S*)-1-Hydroxybut-3-enyl]-4-[dimethyl(phenyl)silyl]-5-{[dimethyl(phenyl)silyl]methyl}-1-tosylpyrrolidin-3-ol (13): $TiCl_4$ (42 μL, 0.39 mmol) was added to a solution of **11** (160 mg, 0.3 mmol) in CH_2Cl_2 (8 mL) at −78°C. Allyltrimethylsilane (140 μL, 0.9 mmol) was then added and the resulting mixture was stirred at −78°C for 1.5 h. The reaction was quenched with a saturated solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to give a yellowish oil. The residue was then purified with flash chromatography (pentane/EtOAc 4:1) to give pyrrolidine **13** as a colorless oil (115 mg, 70%). $[\alpha]_D^{25}$=−19.5 (c=0.19 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.57 (m, 2H), 7.48 (m, 2H), 7.37 (m, 4H), 7.29 (m, 4H), 7.16 (m, 2H), 5.77 (tdd, J=17.3, 10.2, 7.0 Hz, 1H), 5.12 (m, 2H), 4.26 (m, 1H), 3.85 (m, 4H), 3.15 (t, J=5.2 Hz, 1H), 2.92 (d, J=3.5 Hz, 1H), 2.44 (m, 5H), 1.44 (m, 2H), 0.32 (s, 3H), 0.31 (s, 3H), −0.03 (s, 3H), −0.12 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=143.8, 139.2, 136.3, 134.7, 134.3, 133.9, 133.8, 129.9, 129.5, 128.9, 128.0, 127.8, 118.2, 75.1, 70.9, 65.0, 60.5, 41.3, 37.8, 29.0, 21.5, −1.8, −2.4, −3.9, −4.5 ppm; IR (neat): $\tilde{\nu}$=3420, 2954, 2904, 1427, 1347, 1250, 1162, 1112, 817 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{32}H_{43}NO_4SSi_2$: 616.2344 $[M+Na]^+$; found: 616.2340.

(2*S*,3*R*,4*R*,5*R*)-3-(Benzyloxy)-2-[(*S*)-1-(benzyloxy)but-3-enyl]-4-[dimethyl(phenyl)silyl]-5-{[dimethyl(phenyl)silyl]methyl}-1-tosylpyrrolidine (14): Potassium hexamethyldisilazide (KHMDS) (2.5 mL, 0.5 M solution in PhMe) was added to a solution of **13** (250 mg, 0.42 mmol) and BnBr (Bn=benzyl; 200 μL, 1.68 mmol) in THF (10 mL) at −78°C and the resulting mixture was stirred at −78°C for 1 h and at 0°C. The reaction was quenched with a saturated solution of NH_4Cl (10 mL) and extracted with Et_2O (3×15 mL). The combined organic phases were dried, filtered, and evaporated. Flash chromatography of the residue (pentane/EtOAc 10:1) afforded pyrrolidine **14** as a colorless oil (260 mg, 85%). $[\alpha]_D^{25}$=−6.1 (c=0.28 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.56 (d, J=8.2 Hz, 2H), 7.37–7.12 (m, 20H), 6.90 (d, J=6.5 Hz, 2H), 6.00 (m, 1H), 5.09 (d, J=17.1 Hz, 1H), 5.03 (d, J=10.1 Hz, 1H), 4.53 (d, J=11.1 Hz, 1H), 4.42 (d, J=11.1 Hz, 1H), 4.24 (d, J=12.1 Hz, 1H), 3.92 (d, J=12.1 Hz, 1H), 3.84 (m, 2H), 3.74 (dt, J=7.9, 3.5 Hz, 1H), 3.10 (dd, J=9.3, 6.1 Hz, 1H), 2.68 (m, 1H), 2.52 (m, 1H), 2.38 (s, 3H), 1.44 (dd, J=9.2, 7.4 Hz, 1H), 0.96 (m, 2H), 0.34 (s, 3H), 0.23 (s, 3H), 0.05 (s, 3H), −0.16 ppm (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz): δ=143.3, 140.1, 138.7, 137.8, 136.9, 135.9, 134.0, 133.6, 129.6, 129.3, 128.5, 128.0, 127.8, 127.6, 127.5, 127.4, 127.2, 127.1, 116.8, 80.4, 78.1, 72.3, 71.5, 63.0, 58.5, 39.4, 37.3, 29.5, 21.5, −2.2, −3.3, −3.5, −4.9 ppm; IR (neat): $\tilde{\nu}$=3067, 2954, 2925, 1640, 1349, 1264, 1164, 1112, 818, 756, 700 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{46}H_{55}NO_4SSi_2$: 796.3283 $[M+Na]^+$; found: 796.3270.

(*S*)-3-(Benzyloxy)-3-[(2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-[dimethyl(phenyl)silyl]-5-({[dimethyl(phenyl)silyl]methyl}pyrrolidin-2-yl)propan-1-ol (15): Pyridine (55 μL, 0.64 mmol), $NaIO_4$ (350 mg, 1.6 mmol), and OsO_4 (0.5 mL of a solution of 25 mg OsO_4/mL in MeCN) were added to a solution of **14** (250 mg, 0.32 mmol) in CH_3CN/H_2O (1:1, 10 mL) and the solution was stirred for 3 h at RT. Et_2O (10 mL) was added to the reaction mixture and the phases were separated. The aqueous phase was extracted with Et_2O (3×10 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvent removed in vacuo. The crude product was dissolved in MeOH (15 mL) and the solution was cooled to 0°C. $NaBH_4$ was added and the stirring was continued for 20 min. The solution was filtered through a Celite pad, diluted with H_2O (15 mL) and extracted with Et_2O (3×15 mL). The combined organic phases were dried, filtered, and evaporated. The residue was purified with flash chromatography (pentane/EtOAc 10:1) to afford pyrrolidine **15** as a colorless crystalline solid (175 mg, 72%). M.p. 49–50°C; $[\alpha]_D^{25}$=−4.0 (c=0.25 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.60 (d, J=8.3 Hz, 2H), 7.41–7.18 (m, 20H), 6.91 (d, J=8.0 Hz, 2H), 4.57 (d, J=11.2 Hz, 1H), 4.48 (d, J=11.2 Hz, 1H), 4.14 (d, J=12.1 Hz, 1H), 3.99–3.94 (m, 3H), 3.91–3.89 (m, 1H), 3.83–3.79 (m, 2H), 3.22 (dd, J=7.8, 6.1 Hz, 1H), 2.42 (s, 3H), 2.14–2.09 (m, 1H), 1.96–1.91 (m, 1H), 1.46 (dd, J=7.8, 6.4 Hz, 1H), 1.15–1.10 (m, 1H), 1.06–1.02 (m, 1H), 0.35 (s, 3H), 0.28 (s, 3H), 0.06 (s, 3H), −0.06 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=143.4, 139.8, 138.3, 137.7, 136.8, 134.1, 133.8, 129.6, 129.4, 129.0, 128.7, 128.5, 128.3, 128.3, 128.2, 128.0, 128.0, 127.9, 127.9, 127.7, 127.7, 127.6, 127.5, 127.5, 81.1, 72.4, 71.4, 62.9, 60.4, 60.0, 59.1, 38.9, 33.9, 29.2, 21.6, 21.1, 14.2, −2.1, −3.2, −3.9, −4.6 ppm; IR (neat): $\tilde{\nu}$=3484, 2954, 2876, 1349, 1248, 1164, 1112, 819, 735, 700 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{45}H_{55}NO_5SSi_2$: 778.3412 $[M+H]^+$; found: 778.3416.

(*S*)-3-(Benzyloxy)-3-(2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-[dimethyl(phenyl)silyl]-5-({[dimethyl(phenyl)silyl]methyl}pyrrolidin-2-yl)propan-1-ol (16): A deep-green solution of sodium naphthalenide in dimethoxyethane (2.5 mL) was added to a solution of **15** (120 mg, 0.15 mmol) in dimethoxyethane (4 mL, freshly distilled over Na) at −60°C until the green color persisted and stirring was continued for 10 min. The reaction was quenched with a saturated solution of NH_4Cl (10 mL) and extracted with Et_2O (3×15 mL). The combined organic phases were dried, filtered, and evaporated. Purification of the residue with flash chromatography (pentane/EtOAc 1:1) afforded pyrrolidine **16** as a colorless oil (90 mg, 99%). $[\alpha]_D^{25}$=+27.6 (c=1.5 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.38–7.13 (m, 20H), 4.53 (d, J=11.5 Hz, 1H), 4.36 (d, J=11.5 Hz, 1H), 4.22 (d, J=11.5 Hz, 1H), 4.02 (m, 2H), 3.73 (m, 2H), 3.49 (m, 1H), 3.08 (m, 1H), 2.56 (dd, J=9.3, 3.3 Hz, 1H), 1.91 (m, 2H), 1.28 (m, 2H), 0.97 (dd, J=15.1, 2.7 Hz, 1H), 0.88 (m, 1H), 0.78 (dd, J=15.1, 11.2 Hz, 1H), 0.32 (s, 3H), 0.31 (s, 3H), 0.29 (s, 3H), 0.25 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=139.0, 138.8, 138.4, 137.1, 133.8, 133.5, 129.3, 128.8, 128.2, 127.9, 127.7, 127.4, 127.4, 127.4, 127.3, 82.8, 71.1, 69.7, 69.1, 58.3, 58.1, 44.1, 35.7, 26.0, −2.4, −2.8, −4.3, −4.5 ppm; IR (neat): 3067, 2925, 2856, 1455, 1264, 1112, 736, 701 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{38}H_{49}NO_3Si_2$: 624.3324 $[M+H]^+$; found: 624.3314.

(1*R*,2*R*,3*R*,7*S*,7a*S*)-1,7-Bis(benzyloxy)hexahydro-2-[dimethyl(phenyl)silyl]-3-{[dimethyl(phenyl)silyl]methyl}-1*H*-pyrrolizine (17): NEt_3 (54 μL, 0.39 mmol), PPh_3 (100 mg, 0.39 mmol), and CBr_4 (127 mg, 0.39 mmol) were added to a solution of **16** (80 mg, 0.13 mmol) in CH_2Cl_2 (7 mL) and the solution was stirred at RT for 1 h. The reaction was quenched by the addition of MeOH (2 mL) and the solvents were removed in vacuo. Purification of the residue by flash chromatography (pentane/EtOAc 1:1) afforded **17** as a colorless oil (50 mg, 64%). $[\alpha]_D^{25}$=+14.5 (c=0.5 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.42 (m, 4H), 7.27 (m, 14H), 7.07 (m, 2H), 4.51 (d, J=11.8 Hz, 1H), 4.37 (d, J=11.8 Hz, 1H), 4.32 (m, 1H), 4.12 (d, J=11.5 Hz, 1H), 4.04 (d, J=11.5 Hz, 1H), 3.82 (dd, J=5.6, 4.9 Hz, 1H), 3.13 (dd, J=5.6, 2.9 Hz, 1H), 3.03 (dt, J=10.6, 3.0 Hz, 1H), 2.59 (m, 2H), 2.18 (m, 1H), 1.83 (m, 1H), 1.47 (dd, J=9.6, 4.9 Hz, 1H), 1.32 (m, 1H), 0.89 (m, 1H), 0.31 (s, 3H), 0.28 (s, 3H), 0.27 (s, 3H), 0.26 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=139.7, 138.6, 138.0, 133.9, 133.6, 129.1, 128.6, 128.3, 128.1, 127.8, 127.5, 127.4, 127.2, 127.1, 83.9, 78.1, 75.1, 71.6, 71.1, 58.8, 45.5, 40.5, 33.6, 19.7, −2.3, −2.6, −3.6, −3.8 ppm; IR (neat): $\tilde{\nu}$=2955, 2923, 2361, 1250, 1114, 835 cm^{-1} HRMS (ESI): m/z: calcd for $C_{38}H_{47}NO_2Si_2$: 606.3218 $[M+H]^+$; found: 606.3199.

(1*R*,2*R*,3*R*,7*S*,7a*S*)-1,7-Bis(benzyloxy)hexahydro-3-(hydroxymethyl)-1*H*-pyrrolizin-2-ol (20) and (1*R*,2*R*,3*R*,7*S*,7a*S*)-1,7-bis(benzyloxy)hexahydro-3-(hydroxymethyl)-1*H*-pyrrolizin-2-ol-*N*-oxide (19): $Hg(OTf)_2$ (65.7 mg, 0.15 mmol) was added to a solution of **17** (23.3 mg, 38.0 μmol) in AcOH (1.5 mL) at RT. The reaction mixture was stirred for 1 h before AcOOH (4 mL, 32% solution in AcOH) was added. The solution was stirred at RT for 5 d. EtOAc (10 mL) was added and the reaction mixture was cooled to 0°C. Saturated $Na_2S_2O_3$ (10 mL) was added dropwise and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic phases were washed with H_2O (10 mL), saturated $NaHCO_3$ (1 M,

15 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and the solvents were removed in vacuo. The residue was purified by flash chromatography (EtOAc+1% $iPrNH_2$→EtOAc/MeOH 20:1+1% $iPrNH_2$) to give **18** (6.4 mg, 41%) and **19** (3.0 mg, 21%) as colorless oils.

*Compound **19***: ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.28–7.21 (m, 10H), 4.54 (s, 2H), 4.45 (d, J=11.7 Hz, 1H), 4.38 (d, J=11.7 Hz, 1H), 4.31–4.23 (m, 3H), 3.94 (dd, J=7.4, 4.4 Hz, 1H), 3.88 (dd, J=6.8, 4.4 Hz, 1H), 3.60 (t, J=5.6 Hz, 1H), 3.08–3.04 (m, 1H), 2.92–2.87 (m, 1H), 2.80–2.76 (m, 1H), 2.18–2.12 (m, 1H), 2.02 (s, 3H), 1.93–1.86 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=171.0, 138.2, 137.9, 137.6, 128.5, 128.4, 127.8, 127.7, 127.7, 127.6, 84.3, 78.4, 78.4, 72.4, 71.6, 71.3, 64.4, 62.7, 47.1, 33.4, 20.9 ppm.

*Compound **20***: Compound **18** (6.0 mg, 14.6 μmol) was dissolved in THF/H_2O (2 mL, 1:1) and LiOH (6.1 mg, 0.15 mmol) was added. The reaction mixture was stirred for 15 min before removing the solvents in vacuo. Flash chromatography of the residue afforded **20** as a colorless oil (4.8 mg, 90%). $[\alpha]_D^{25}$=+32.5 (c=0.08 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.34–7.21 (m, 10H), 4.64 (d, J=11.8 Hz, 1H), 4.56 (d, J=11.8 Hz, 1H), 4.51 (d, J=11.7 Hz, 1H), 4.44 (d, J=11.7 Hz, 1H), 4.36–4.32 (m, 1H), 4.17 (dd, J=6.5, 3.4 Hz, 1H), 3.91 (dd, J=6.3, 3.4 Hz, 1H), 3.87 (d, J=5.6 Hz, 2H), 3.86 (t, J=5.6 Hz, 1H), 3.09–3.05 (m, 1H), 2.93–2.91 (m, 2H), 2.32–2.25 (m, 1H), 2.00–1.96 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=138.1, 137.7, 128.7, 128.5, 128.4, 127.9, 127.8, 127.8, 127.7, 115.0, 83.8, 79.9, 76.4, 72.3, 72.2, 71.7, 97.6, 61.0, 46.5, 33.7; IR (neat): $\tilde{\nu}$=2953, 2920, 2364, 1250, 838 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{22}H_{27}NO_4$: 370.2013 $[M+H]^+$; found: 370.2004.

(+)-Alexine ((+)-1): Pd/C was added to a mixture of **14** (2 mg, 4.86 μmol) and **15** (2 mg, 5.41 μmol) in EtOH (2 mL). The reaction mixture was stirred under an atmosphere of H_2 at RT for 16 h. The reaction mixture was filtered over Celite and the solvent was removed in vacuo, affording (+)-**1** as a white solid (1.3 mg, 70%). M.p.=160–161 °C; $[\alpha]_D^{20}$=+39.0 (c=0.08 in H_2O); ^{1}H NMR (D_2O, 500 MHz): δ=4.53–4.49 (m, 1H), 4.26 (t, J=7.6 Hz, 1H), 3.89–3.88 (m, 2H), 3.87–3.84 (m, 1H), 3.48 (t, J=6.6 Hz, 1H,), 3.12–3.07 (m, 2H), 3.03–2.98 (m, 1H), 2.28–2.23 (m, 1H), 1.86–1.78 ppm (m, 1H); ^{13}C NMR (D_2O, 125 MHz, CH_3CN as internal standard): δ=76.3, 75.8, 71.5, 70.4, 65.6, 59.0, 46.8, 34.6 ppm; HRMS (ESI): m/z: calcd for $C_8H_{15}NO_4$: 190.1074 $[M+H]^+$; found: 190.1073.

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