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Extremely high regio- and stereoselective C–C bond formation of substituted γ-hydroxylactams: synthesis of macronecines based on their structural duality

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ABSTRACT

With a view to develop a new synthetic entry for the necine bases, treatment of functionalized γ-hydroxylactams was found to undergo quite high regio- and diastereoselective carbon–carbon bond formation reactions, affording the corresponding structurally dualistic alkylated lactams in satisfactory yields. The reaction was further applied to the practical and efficient synthesis of (±)-macronecine [(1*S**,2*R**,7a*R**)-1-hydroxymethyl-2-hydroxypyrrolizidine] and (±)-2-*epi*-macronecine [(1*S**,2*S**,7a*R**)-1-hydroxymethyl-2-hydroxypyrrolizidine].

1. Introduction

Pyrrolizidine alkaloids, which comprise a unique family of bicyclic heterocycles with diverse oxygenation patterns on the azabicyclo[3.3.0]octane skeleton, are widely distributed throughout the plant kingdom and found in the animal kingdom as well.[1] Over the past several decades, these compounds have attracted great interest from organic chemists because of their potent mutagenic, teratogenic, and carcinogenic activities[2,3] as well as their synthetic challenges for further elaboration of architecturally complicated natural products.[4] Noteworthy members among this class of compounds are the necines, alexines,[5] and the new series of hyacinthacines, which were recently isolated from bluebells (*Hyacinthoides non-scripta*)[6] and grape hyacinths (*Muscari armeniacum*)[7] by Asano and co-workers as selective inhibitors of β-glucosidase and β-galactosidase (Fig. 1). Among them, the compounds bearing particular substituents of the C(1)-positions on the pyrrolizidine ring systems allow us to distinguish the necines from the others bearing the hydroxymethyl substituents at C(3)-positions.

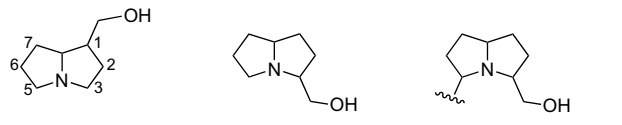

Figure 1. Structures of selected pyrrolizidine alkaloids.

The necine family of the pyrrolizidine alkaloids may be divided into three different classes according to their structural features (Fig. 2). In the first class of the necines, such as laburnine (**1a**), macronecine (**1b**), and hastanecine (**1d**), each of these molecules bears a free hydroxyl group in their side chain. The second class of the necine derivatives such as farfugine (**1e**) possesses external ester groups, while macrocyclic lactones such as retrorsine (**1f**) represent the third class of them. Their structural and stereochemical properties coupled with their diverse and potentially useful characteristics have made them so far inviting targets for synthesis. With these considerations in mind, we report here the expeditiously synthetic application of the γ-hydroxylactams to macronecine (**1b**)[8] and 2-*epi*-macronecine (**1c**) as well as the research of their fascinating duality for regio- and diastereoselective carbon–carbon bond formation, which were, in turn, prepared via the corresponding monoterpene lactone precursor.

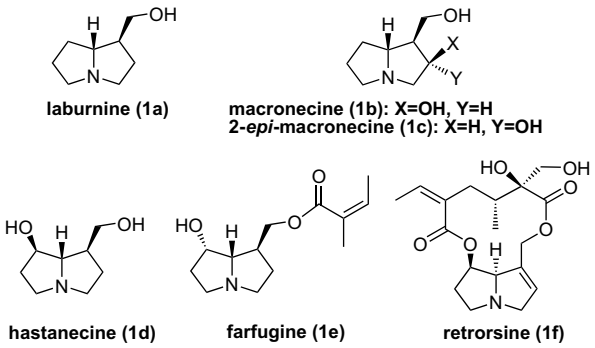

Figure 2. Structures of selected necine bases.

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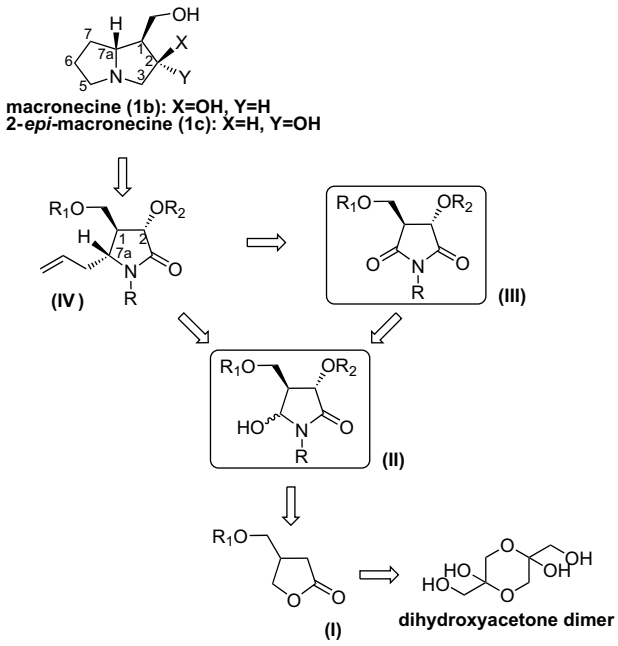


Figure 3. General retrosynthesis.

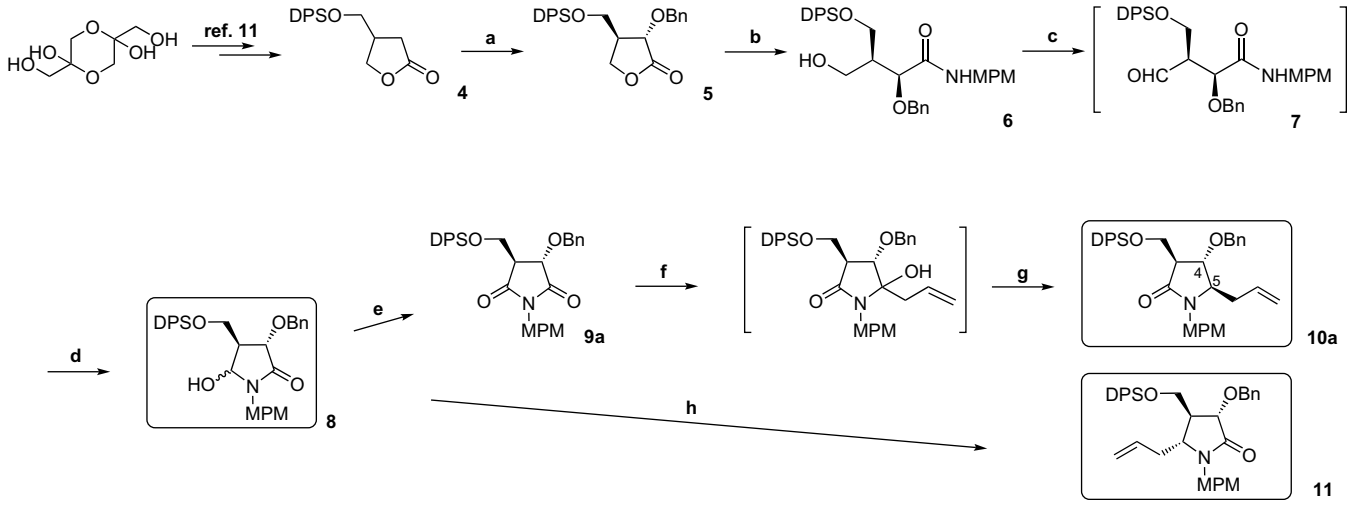
Our synthetic plan for macronecine (**1b**) and 2-*epi*-macronecine (**1c**) is shown in Figure 3. We envisaged that the pyrrolizidine ring would be constructed from lactam (**IV**). The stereogenic center of C(7a) on (**IV**) would originate from the regio- and stereoselective nucleophilic allylation of two different precursors, hydroxylactam (**II**) and imide (**III**). The relative stereochemistry at C(1) and C(2) could be constructed through sequential treatments of the monoterpene lactone (**I**) prepared from dihydroxyacetone dimer.

2. Results and discussion

As shown in Scheme 1, the starting terpene lactone **4** was prepared from dihydroxyacetone dimer according to our procedure.[9] The lactone **4** was oxygenated with 2-phenylsulfonyl-3-phenyloxaziridine[10] in the presence of lithium hexamethyldisilazide (LiHMDS) at −78 °C to give the *trans*-disubstituted lactone as an extremely predominant product.[11] The hydroxylated lactone was subsequently protected with BnBr followed by separation of the resulting mixture from both the minor stereoisomer and side-products by silica gel column chromatography to give the pure lactone **5**. Ring opening reaction of **5** with *p*-methoxybenzylamine ($MPMNH_2$) proceeded smoothly to form the amide alcohol **6** in 97% yield and the following Swern oxidation of **6** with diisopropylethylamine gave rise to **7** without epimerization at α-position of the aldehyde.[12] Unfortunately, intramolecular cyclization of **7** did not proceed under mild basic and acidic conditions, which employed Et_3N and *p*-TsOH, respectively. The use of $BF_3\cdot OEt_2$ in THF, however, promoted the cyclization to provide **8** in 77% yield (two steps). The lactam **8** was subsequently converted into the imide **9a** via PCC oxidation.

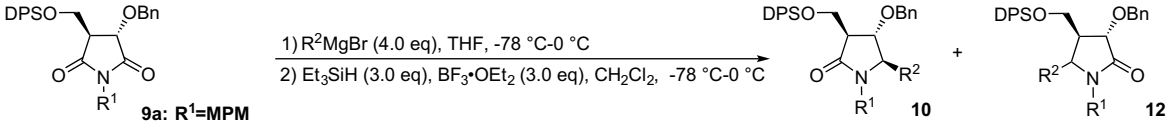
With the two substrates **8** and **9a** in hand, regio- and diastereoselective nucleophilic allylation was examined. According to our established procedure,[13] the imide **9a** was treated with allyl Grignard reagent at low temperature to give the quaternary hydroxylactam with complete regioselectivity. Reductive deoxygenation of the hydroxylactam via the *N*-acyliminium ion intermediate, which was performed with Et_3SiH in the presence of $BF_3\cdot OEt_2$, afforded the allylated lactam as the extremely diastereoselective product (99:1 regioselectivity, 98% de determined by ^1H NMR). This compound was determined based on the coupling constant of ^1H NMR to be the β,γ-*trans*-substituted lactam **10a** ($J_{H4,H5}$=3.7 Hz) shown in Scheme 1.[14]

Interested in this excellent regio- and diastereoselectivity, we applied the other alkyl Grignard reagents to this type of successive nucleophilic addition/deoxygenation reactions (Table 1). Interestingly, whereas the reactions with the *N*-larger substituted imide **9a** gave the alkylated products **10a**–**d** predominantly together with the small amount of regioisomers (entries 1–4), the reactions with the smaller *N*-methyl imide **9b** afforded **10e**–**h** with complete regioselectivity and excellent diastereoselectivity (entries 5–8). In each case, the initial Grignard addition afforded the adducts as an approximately 1:1 mixture of diastereomers. This type of Grignard reaction/reductive deoxygenation sequence with mono-substituted imide has been reported.[15] Both the high regioselectivity on Grignard addition and the trans-diastereoselectivity on reductive deoxygenation were also observed and these selectivities were attributed to the chelation between the oxygen atom of BnO substituent and the reagents.[16] Our results may support their reaction mechanism[17] and extend the utility of this strategy to



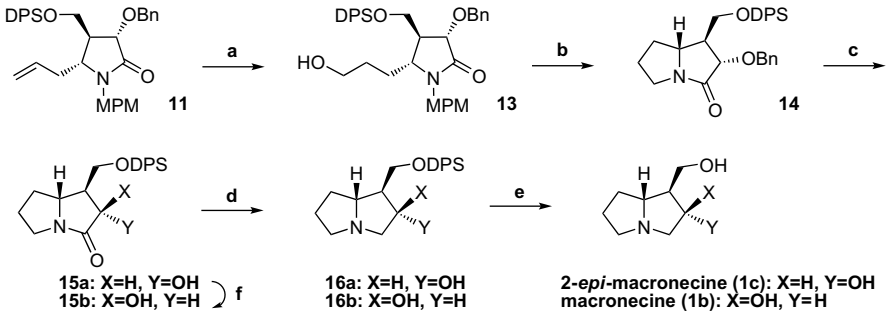
Scheme 1. Reagents and conditions: (a) (i) LiHMDS, 2-phenylsulfonyl-3-phenyloxaziridine, THF, −78 °C; (ii) BnBr, Ag_2O, EtOAc, 46% (two steps); (b) $MPMNH_2$, MeOH, 97%; (c) $(COCl)_2$, DMSO, $(i\text{-}Pr)_2NEt$, THF, −78 °C to 0 °C; (d) $BF_3\cdot OEt_2$, THF, 0 °C, 96% (two steps); (e) PCC, CH_2Cl_2, 93%; (f) 3-bromopropene, Mg, THF, −78 °C to 0 °C; (g), Et_3SiH, $BF_3\cdot OEt_2$, −78 °C to 0 °C, 74% (two steps); (h) allyltrimethylsilane, $BF_3\cdot OEt_2$, CH_2Cl_2, −78 °C to −20 °C, 99%.

Table 1
Regio- and diastereoselective alkylation of **9**



Entry	Imide (**9**)	R^2	Yield/%[a] (conversion yield)[b]	Regioselectivity (**10**:**12**)[c]	Diastereoselectivity of **10**/% de[d]
1	**9a**	CH_2=$CHCH_2$	74	99:1	98 (**10a**)
2	**9a**	Me	87	97:3	99 (**10b**)
3[b]	**9a**	*n*-C_3H_7	54 (81)	98:2	99 (**10c**)
4	**9a**	*n*-C_9H_{19}	51 (61)	99:1	99 (**10d**)
5	**9b**	CH_2=$CHCH_2$	69	100:0	92 (**10e**)
6	**9b**	Me	99	100:0	99 (**10f**)
7	**9b**	*n*-C_3H_7	88	100:0	99 (**10g**)
8	**9b**	*n*-C_9H_{19}	60	100:0	99 (**10h**)

[a] Combined and isolated yield of **10** and **12** in two steps.
[b] Conversion yield was calculated on the basis of the recovery of the starting material.
[c] The ratio of **10** and **12** was calculated from ^{1}H NMR.
[d] The diastereomeric excess was determined by ^{1}H NMR.



Scheme 2. Reagents and conditions: (a) 9-BBN, H_2O_2 (34.5%), 3 N NaOH, THF, 84%; (b) (i) TsCl, pyridine; (ii) CAN, MeCN/H_2O=2:1; (iii) NaH, THF, 73% (three steps); (c) $Pd(OH)_2$/C, H_2, EtOH, 95%; (d) BH_3·THF, THF, 67% (**16a**), 89% (**16b**); (e) 3% HCl/MeOH, quant. (**1c**), 62% (**1b**); (f) (i) Tf_2O, pyridine, CH_2Cl_2; (ii) CsOAc, 18-crown-6, toluene, 70% (two steps); (iii) K_2CO_3, MeOH, 93%.

the syntheses of more complicated natural products and their analogs such as 1-homoaustraline.[18]

Since the Grignard addition/deoxygenation sequence gave **10a**, we next examined the direct allylation of the hydroxylactam **8** with allyltrimethylsilane. Whereas the reaction employing the corresponding hydroxylactams derived from tartaric acid gave the products with moderate cis-selectivity[13c,19] or no diastereoselectivity,[20] the reaction of **8** gave the trans-stereoisomer **11** in 95% yield with complete diastereoselectivity.[21] To the best our knowledge, this excellent diastereoselective reaction is the first example of the allylation with disubstituted hydroxylactam containing hydroxymethyl and hydroxyl substituents. These results demonstrate that the allylation of the hydroxylactam **8** and the imide **9** realizes their synthetically fascinating duality for regio- and stereocontrolled carbon–carbon bond formation.

With these results in hand, we attempted the formation of the pyrrolizidine ring system toward the synthesis of **1b** and **1c** (Scheme 2). Thus, **11** was regioselectively hydroborated with 9-BBN to give the primary alcohol **13**, which was, in turn, submitted to the tosylation, deprotection of the MPM group, and the intramolecular cyclization to provide the desired bicyclic compound **14** in 73% yield (three steps). After hydrogenation reaction of **14** with $Pd(OH)_2$/C under H_2 atmosphere followed by reduction of **15a**, desilylation of **16a** with 3% HCl/MeOH led to the completion of the synthesis of (±)-2-*epi*-macronecine (**1c**). In order to accomplish the synthesis of **1b**, we turn next to the preparation of **15b** containing the reverse stereochemistry at C(2). Inversion of the configuration at C(2) was achieved via the triflate intermediate with cesium acetate in the presence of 18-crown-6 followed by hydrolysis,[22] affording the alcohol **15b** in 65% isolated yield (three steps). Finally, two-step sequence through the same procedures for **15a** allowed the construction of (±)-macronecine (**1b**), which showed analytical and spectroscopic data in complete accordance with those of authentic samples.[8]

3. Conclusions

In summary, we have completed the practical synthesis of macronecines. Highlight of the synthesis is the efficient elaboration of the hydroxylactam intermediate prepared from the monoterpene lactone precursor, which demonstrates the synthetically fascinating duality for regio- and stereocontrolled carbon–carbon bond formation. This synthetic strategy will find applications in the synthesis of biologically important pyrrolizidine and/or indolizidine alkaloids. Current efforts to expand the scope of synthetic application to more complicated natural products are in progress.

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 ^{1}H 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 ^{1}H NMR, and $CDCl_3$ was used as internal standard (δ=77.0) for ^{13}C NMR. The coupling constants are reported in hertz (Hz). 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. 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. (3S,4S*)-3-(Benzyloxy)-4-((tert-butyldiphenylsilyloxy)-methyl)dihydrofuran-2(3H)-one (**5**)*

To a stirred solution of LiHMDS [prepared from hexamethyldisilazane (910 mg, 5.64 mmol) and *n*-BuLi (1.66 M in hexane, 2.5 mL, 4.23 mmol) in THF (20 mL) under nitrogen at −78 °C] was added a solution of the lactone **4** (1.00 g, 2.82 mmol) in THF (8.0 mL). After the mixture was stirred for 10 min, a solution of 2-phenylsulfonyl-3-phenyloxaziridine (813 mg, 3.10 mmol) was added, and the reaction mixture was further stirred for 1 h at the same temperature. It was quenched by the addition of saturated aq NH_4Cl (10 mL) and extracted with EtOAc (30 mL). The organic extract was washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was roughly purified by column chromatography (silica gel, toluene/EtOAc=15:1 to 8:1). This operation was performed more two times to give the crude product (1.88 g), which was used without further purification. A solution of the combined crude product (1.88 g), benzyl bromide (1.30 g, 7.59 mmol), and silver(I) oxide (1.41 g, 6.07 mmol) in EtOAc (10 mL) was stirred for 48 h. After filtration through a pad of Celite with EtOAc and concentration, the crude product was purified by column chromatography (silica gel, hexane/EtOAc=15:1) to give **5** (1.68 g, 46%) as a colorless oil. IR (NaCl) 2900 (C–H), 1788 (C=O), 1589 (C=C), 1111 (C–O), 1011 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.60–7.57 (m, 4H, Ar*H*), 7.46–7.28 (m, 11H, Ar*H*), 5.03 (d, *J*=11.4 Hz, 1H, CH_2), 4.65 (d, *J*=11.4 Hz, 1H, CH_2), 4.37 (t, *J*=8.1 Hz, 1H, CH_2), 4.23 (d, *J*=8.1 Hz, 1H, C*H*), 4.15 (t, *J*=8.7 Hz, 1H, CH_2), 3.77 (dd, *J*=10.5, 3.6 Hz, 1H, CH_2), 3.69 (dd, *J*=10.5, 3.6 Hz, 1H, CH_2), 2.69 (m, 1H, C*H*), 1.03 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 175.2 (*C*), 137.0 (*C*), 135.5 (*C*H), 132.6 (*C*), 130.0 (*C*H), 128.4 (*C*H), 128.1 (*C*H), 128.0 (*C*H), 127.8 (*C*H), 73.7 (*C*H), 72.3 (CH_2), 67.1 (CH_2), 60.8 (CH_2), 44.3 (*C*H), 26.8 (CH_3), 19.2 (*C*); HRMS (ESI^+) *m*/*z* calcd for $C_{28}H_{32}O_4Si$+Na: 483.1968, found 483.1959.

4.2.2. (2S,3S*)-2-(Benzyloxy)-4-(tert-butyldiphenylsilyloxy)-3-(hydroxymethyl)-N-(4-methoxybenzyl)butanamide (**6**)*

A solution of **5** (742 mg, 1.61 mmol) and *p*-methoxybenzylamine ($MPMNH_2$) (0.23 mL, 1.77 mmol) in MeOH (6.0 mL) was stirred for 24 h. The mixture was concentrated and chromatographed (silica gel, hexane/EtOAc=2:1 to 1:1) to give the amide **6** (929 mg, 97%) as a viscous oil. IR (NaCl) 3414 (N–H), 3400 (O–H), 1651 (C=O), 1612 (C=C), 1249 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, *J*=7.3 Hz, 4H, Ar*H*), 7.43–7.22 (m, 9H, Ar*H*), 7.11–7.09 (m, 4H, Ar*H*), 6.87–6.79 (m, 3H, N*H*, Ar*H*), 4.44 (d, *J*=11.2 Hz, 1H, CH_2), 4.37 (d, *J*=11.2 Hz, 1H, CH_2), 4.37 (dd, *J*=14.4, 5.1 Hz, 1H, CH_2), 4.28 (dd, *J*=14.4, 5.5 Hz, 1H, CH_2), 4.01 (d, *J*=6.8 Hz, 1H, C*H*), 3.89–3.80 (m, 4H, CH_2), 3.76 (s, 3H, CH_3), 2.88 (br s, 1H, O*H*), 2.15 (m, 1H, C*H*), 1.04 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 172.1 (*C*), 159.0 (*C*), 136.6 (*C*), 135.5 (*C*H), 133.2 (*C*), 129.8 (*C*H), 129.7 (*C*), 129.0 (*C*H), 128.5 (*C*H), 128.3 (*C*H), 128.1 (*C*H), 127.7 (*C*H), 114.1 (*C*H), 79.2 (*C*H), 73.5 (CH_2), 62.3 (CH_2), 61.6 (CH_2), 55.2 (*C*H), 47.1 (CH_3), 42.5 (CH_2), 26.8 (CH_3), 19.1 (*C*); HRMS (ESI^+) *m*/*z* calcd for $C_{36}H_{43}NO_5Si$+Na: 620.2808, found 620.2760.

4.2.3. (3S,4S*)-3-(Benzyloxy)-4-((tert-butyldiphenylsilyloxy)-methyl)-5-hydroxy-1-(4-methoxybenzyl)-pyrrolidin-2-one (**8**)*

To a stirred solution of oxalyl chloride (0.043 mL, 0.50 mmol) in CH_2Cl_2 (1.0 mL) was added DMSO (0.047 mL, 0.67 mmol) under nitrogen at −78 °C and stirred for 15 min. Then, a solution of **6** (85.0 mg, 0.142 mmol) in CH_2Cl_2 (1.5 mL) was added to this mixture and further stirred for 15 min. (*i*-Pr)$_2$EtN (0.19 mL, 1.4 mmol) was added and warmed to 0 °C. After stirring for 15 min, the mixture was quenched by the addition of saturated aq NH_4Cl (5 mL) and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was roughly passed through column chromatography (silica gel, EtOAc) to give the crude aldehyde **7** (87.7 mg), which was used without further purification. To a solution of the above aldehyde was added $BF_3\cdot OEt_2$ (0.023 mL, 0.18 mmol) at 0 °C and stirred for 30 min. It was quenched by the addition of saturated aq $NaHCO_3$ (5 mL) and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc=5:2) to give the hydroxylactam **8** (80.9 mg, 96%) as a colorless oil. IR (NaCl) 3370 (O–H), 1690 (C=O), 1514 (C=C), 1112 (C–O), 1075 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.63–7.60 (m, 4H, Ar*H*), 7.50–7.15 (m, 30H, Ar*H*), 6.87 (m, 2H, Ar*H*), 6.80–6.77 (m, 2H, Ar*H*), 5.18 (d, *J*=11.3 Hz, 1H, CH_2), 5.07 (m, 1H, C*H*), 5.06 (d, *J*=11.6 Hz, 1H, CH_2), 4.89 (d, *J*=14.3 Hz, 1H, CH_2), 4.87 (d, *J*=14.3 Hz, 1H, CH_2), 4.74 (m, 1H, C*H*), 4.70 (d, *J*=11.6 Hz, 1H, CH_2), 4.60 (d, *J*=11.6 Hz, 1H, CH_2), 4.39 (d, *J*=8.2 Hz, 1H, C*H*), 4.14–3.99 (m, 6H, C*H*, CH_2), 3.89 (dd, *J*=10.6, 5.0 Hz, 1H, CH_2), 3.79 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.65–3.63 (m, 2H, O*H*), 2.32 (m, 1H, C*H*), 2.16 (m, 1H, C*H*), 1.04 (s, 9H, C(CH_3)$_3$), 0.93 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.8 (2*C*), 159.0 (*C*), 158.9 (*C*), 137.5 (2*C*), 135.42 (2*C*H), 135.38 (2*C*H), 135.36 (*C*H), 135.33 (*C*H), 132.8 (*C*), 132.7 (*C*), 132.2 (*C*), 132.0 (*C*), 130.0 (*C*H), 129.9 (*C*H), 129.73 (*C*H), 129.67 (*C*H), 129.6 (2*C*H), 128.19 (*C*H), 128.16 (*C*H), 127.94 (*C*H), 127.87 (*C*H), 127.83 (*C*H), 127.80 (*C*H), 127.64 (2*C*H), 127.61 (2*C*H), 114.0 (2*C*H), 80.5 (*C*H), 80.1 (*C*H), 75.9 (*C*H), 75.1 (*C*H), 72.8 (CH_2), 72.7 (CH_2), 60.8 (CH_2), 59.7 (CH_2), 55.1 (CH_3), 55.0 (CH_3), 51.4 (*C*H), 45.8 (*C*H), 43.0 (CH_2), 42.4 (CH_2), 26.7 (CH_3), 26.6 (CH_3), 19.0 (*C*), 18.9 (*C*). Anal. Calcd for $C_{36}H_{41}NO_5Si$: C, 72.57; H, 6.94; N, 2.35. Found: C, 72.28; H, 6.61; N, 2.73.

4.2.4. (3S,4S*)-3-(Benzyloxy)-4-((tert-butyldiphenylsilyloxy)-methyl)-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (**9a**)*

A mixture of **8** (472 mg, 0.791 mmol), PCC (205 mg, 0.949 mmol), and MS 4 Å (300 mg) in CH_2Cl_2 (8.0 mL) was stirred for 2 h. After filtration through a pad of Celite with Et_2O and concentration, the crude product was purified by column chromatography (silica gel, hexane/EtOAc=7:1) to give the imide **9a** (438 mg, 93%) as a colorless oil. IR (NaCl) 2858 (C–H), 1713 (C=O), 1250 (C–O), 1113 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55–7.27 (m, 17H, Ar*H*), 6.79–6.74 (m, 2H, Ar*H*), 4.99 (d, *J*=11.5 Hz, 1H, CH_2), 4.72 (d, *J*=11.5 Hz, 1H, CH_2), 4.65 (d, *J*=5.5 Hz, 2H, CH_2), 4.51 (d, *J*=4.4 Hz, 1H, C*H*), 4.19 (dd, *J*=10.1, 2.6 Hz, 1H, CH_2), 3.71 (s, 3H, CH_3), 3.69 (dd, *J*=10.1, 2.8 Hz, 1H, CH_2), 2.75 (ddd, *J*=4.4, 2.8, 2.6 Hz, 1H, C*H*), 0.85 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 175.6 (*C*), 174.8 (*C*), 159.2 (*C*), 136.9 (*C*), 135.5 (*C*H), 135.4 (*C*), 132.5 (*C*), 132.3 (*C*), 130.1 (*C*H), 129.9 (*C*H), 129.8 (*C*H), 128.5 (*C*H), 128.1 (2*C*H), 127.7 (*C*H), 114.0 (*C*H), 74.1 (*C*H),

73.2 (CH_2), 60.0 (CH_2), 55.2 (CH_3), 50.3 (*C*H), 41.8 (CH_2), 26.5 (CH_3), 19.0 (*C*); HRMS (ESI^+) *m*/*z* calcd for $C_{36}H_{39}NO_5Si$+Na: 616.2495, found 616.2463.

4.2.5. (3S*,4S*,5R*)-5-Allyl-4-(benzyloxy)-3-((tert-butyldiphenylsilyloxy)methyl)-1-(4-methoxybenzyl)-pyrrolidin-2-one (**10a**)

To a stirred solution of **9a** (260 mg, 0.438 mmol) in THF (1.0 mL) were added magnesium (43.0 mg, 17.5 mmol) and allyl bromide (212 mg, 1.75 mmol) in THF (0.40 mL) under nitrogen at −78 °C and gradually warmed to 0 °C. The mixture was quenched by the addition of saturated aq NH_4Cl (5.0 mL) and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was roughly purified by column chromatography (silica gel, hexane/EtOAc=3:1) to give the crude hydroxylactam (276 mg), which was used without further purification. To a solution of the above product and Et_3SiH (0.21 mL, 1.31 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of $BF_3\cdot OEt_2$ (0.16 mL, 1.31 mmol) in CH_2Cl_2 (0.70 mL) at −78 °C and gradually warmed to 0 °C. Then, it was quenched by the addition of saturated aq $NaHCO_3$ (5.0 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc=20:1) to give the lactam **10a** (324 mg, 74%) as a colorless oil. IR (NaCl) 2932 (C–H), 1686 (C=O), 1248 (C–O), 1113 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71–7.64 (m, 4H, Ar*H*), 7.42–7.16 (m, 13H, Ar*H*), 6.83–6.80 (m, 2H, C*H*), 5.69–5.55 (m, 1H, C*H*), 5.05 (dd, *J*=9.7, 1.5 Hz, 1H, CH_2), 5.04 (dd, *J*=18.0, 1.5 Hz, 1H, CH_2), 4.95 (d, *J*=15.0 Hz, 1H, CH_2), 4.50 (d, *J*=11.7 Hz, 1H, CH_2), 4.40 (d, *J*=11.7 Hz, 1H, CH_2), 4.15 (dd, *J*=5.4, 3.7 Hz, 1H, C*H*), 4.09 (dd, *J*=10.3, 5.3 Hz, 1H, CH_2), 4.01 (d, *J*=15.0 Hz, 1H, CH_2), 3.93 (dd, *J*=10.3, 3.5 Hz, 1H, CH_2), 3.47 (ddd, *J*=7.8, 4.2, 3.7 Hz, 1H, C*H*), 2.75 (ddd, *J*=5.4, 5.3, 3.7 Hz, 1H, C*H*), 2.49–2.41 (m, 1H, CH_2), 2.26–2.16 (m, 1H, CH_2), 1.07 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 172.3 (*C*), 158.9 (*C*), 137.8 (*C*), 135.7 (*C*H), 135.6 (*C*H), 133.2 (*C*), 132.9 (*C*, *C*H), 129.7 (*C*H), 129.2 (*C*H), 128.3 (*C*, *C*H), 127.7 (2*C*H), 118.6 (CH_2), 114.0 (*C*H), 78.1 (*C*H), 71.4 (CH_2), 62.1 (CH_2), 61.7 (*C*H), 55.2 (CH_3), 52.3 (*C*H), 43.7 (CH_2), 26.9 (CH_3), 19.3 (*C*). Anal. Calcd for $C_{39}H_{45}NO_4Si$: C, 75.57; H, 7.32; N, 2.26. Found: C, 75.24; H, 7.32; N, 2.28.

4.2.6. (3S*,4S*)-3-(Benzyloxy)-4-((tert-butyldiphenylsilyloxy)-methyl)-1-methylpyrrolidine-2,5-dione (**9b**)

A solution of **5** (195 mg, 0.423 mmol) and methylamine in H_2O (40%, 1.0 mL) in THF (1.0 mL) was stirred for 30 min. The mixture was concentrated and chromatographed (silica gel, $CHCl_3$/MeOH=20:1) to give the amide (194 mg, 93%) as a white powder. Mp 116–118 °C; IR (NaCl) 3456 (N–H), 3402 (O–H), 2858 (C–H), 1668 (C=O), 1111 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66–7.63 (m, 4H, Ar*H*), 7.45–7.16 (m, 11H, Ar*H*), 6.57–6.55 (m, 1H, N*H*), 4.49 (d, *J*=11.4 Hz, 1H, CH_2), 4.40 (d, *J*=11.4 Hz, 1H, CH_2), 3.96 (d, *J*=6.9 Hz, 1H, C*H*), 3.89–3.77 (m, 4H, C*H*, CH_2, O*H*), 2.81 (m, 1H, CH_2), 2.77 (d, *J*=5.1 Hz, 3H, CH_3), 2.16–2.06 (m, 1H, CH_2), 1.04 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 173.0 (*C*), 136.8 (*C*), 135.6 (*C*H), 135.5 (*C*), 133.3 (*C*), 133.2 (*C*), 129.7 (*C*H), 128.6 (*C*H), 128.2 (*C*H), 127.9 (*C*H), 127.7 (*C*H), 79.3 (*C*H), 73.5 (CH_2), 62.5 (CH_2), 61.7 (CH_2), 47.1 (CH_3), 26.8 (CH_3), 25.7 (*C*H), 19.2 (*C*). Anal. Calcd for $C_{29}H_{37}NO_4Si$: C, 70.84; H, 7.58; N, 2.85. Found: C, 70.61; H, 7.36; N, 3.23.

To a stirred solution of oxalyl chloride (0.35 mL, 4.0 mmol) in CH_2Cl_2 (7.0 mL) was added DMSO (0.38 mL, 5.4 mmol) under nitrogen at −78 °C and stirred for 15 min. Then, a solution of the above amide (660 mg, 1.34 mmol) in CH_2Cl_2 (8.0 mL) was added to this mixture and further stirred for 15 min. (*i*-Pr)$_2$EtN (1.48 mL, 10.7 mmol) was added and warmed to 0 °C. After stirring for 15 min, the mixture was quenched by the addition of saturated aq NH_4Cl (10 mL) and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was roughly passed through column chromatography (silica gel, EtOAc) to give the crude aldehyde (758 mg), which was used without further purification. To a solution of the above aldehyde in THF (20 mL) was added $BF_3\cdot OEt_2$ (0.18 mL, 1.5 mmol) at 0 °C and stirred for 1 h. It was quenched by the addition of saturated aq $NaHCO_3$ (10 mL) and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc=3:1 to 1:1) to give the hydroxylactam (599 mg, 91%) as a colorless oil. IR (NaCl) 3369 (O–H), 2858 (C–H), 1686 (C=O), 1113 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64–7.56 (m, 4H, Ar*H*), 7.47–7.25 (m, 12H, Ar*H*), 6.87 (m, 2H, Ar*H*), 7.47–7.25 (m, 12H, Ar*H*), 5.18–5.14 (m, 1H, C*H*), 5.11 (d, *J*=11.6 Hz, 1H, CH_2), 4.98 (d, *J*=11.6 Hz, 1H, CH_2), 4.80 (dd, *J*=10.4, 3.3 Hz, 1H, CH_2), 4.65 (d, *J*=11.6 Hz, 1H, CH_2), 4.55 (d, *J*=11.6 Hz, 1H, CH_2), 4.10–4.02 (m, 2H, C*H*), 3.90 (dd, *J*=10.7, 5.5 Hz, 1H, C*H*), 3.77 (dd, *J*=10.4, 4.4 Hz, 1H, CH_2), 3.69 (dd, *J*=10.4, 4.8 Hz, 1H, CH_2), 2.93 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 2.75 (d, *J*=10.4 Hz, 1H, O*H*), 2.47–2.39 (m, 1H, C*H*), 2.20–2.15 (m, 1H, C*H*), 1.05 (s, 9H, CH_3), 1.01 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.2 (*C*), 171.8 (*C*), 137.5 (*C*), 135.6 (*C*H), 135.5 (3*C*H), 132.9 (*C*), 132.7 (*C*), 130.2 (2*C*), 129.9 (*C*H), 128.4 (*C*H), 128.3 (*C*H), 128.1 (*C*H), 128.0 (2*C*H), 127.8 (*C*H), 127.7 (*C*H), 84.2 (*C*H), 83.8 (*C*H), 74.5 (*C*H), 72.7 (CH_2), 72.6 (CH_2), 61.0 (CH_2), 51.6 (CH_3), 45.4 (*C*H), 27.3 (CH_3), 26.8 (CH_3), 19.2 (*C*), 19.1 (*C*). Anal. Calcd for $C_{29}H_{35}NO_4Si$: C, 71.13; H, 7.20; N, 2.86. Found: C, 71.49; H, 6.85; N, 3.12.

A mixture of the hydroxylactam (111 mg, 0.227 mmol), PDC (102 mg, 0.272 mmol), and MS 4 Å (170 mg) in CH_2Cl_2 (1.0 mL) was stirred for 3 h. After filtration through a pad of Celite with Et_2O and concentration, the crude product was purified by column chromatography (silica gel, hexane/EtOAc=5:1 to 1:1) to give the imide **9b** (109 mg, 98%) as a colorless oil. IR (NaCl) 2858 (C–H), 1713 (C=O), 1113 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–7.57 (m, 4H, Ar*H*), 7.30–7.48 (m, 2H, Ar*H*), 5.01 (d, *J*=11.6 Hz, 2H, CH_2), 4.75 (d, *J*=11.6 Hz, 1H, CH_2), 4.49 (d, *J*=3.8 Hz, 1H, C*H*), 4.17 (dd, *J*=2.7, 10.1 Hz, 1H, CH_2), 3.74 (dd, *J*=2.8, 10.1 Hz, 1H, CH_2), 3.05 (s, 3H, CH_3), 2.76–2.79 (m, 1H, C*H*), 0.93 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$): δ 175.9 (*C*), 175.6 (*C*), 136.9 (*C*), 135.5 (2*C*H), 132.6 (*C*), 132.3 (*C*), 130.0 (*C*), 129.9 (*C*H), 129.9 (*C*H), 128.6 (*C*H), 128.2 (*C*H), 127.9 (*C*H), 127.8 (*C*H), 74.3 (*C*H), 73.2 (CH_2), 60.5 (CH_2), 50.5 (CH_3), 26.3 (CH_3), 24.7 (*C*H), 19.1 (*C*). Anal. Calcd for $C_{29}H_{33}NO_4Si$: C, 71.42; H, 6.82; N, 2.87. Found: C, 71.39; H, 6.87; N, 3.20.

4.2.7. General procedure for Grignard reaction/reductive deoxygenation

To a stirred solution of **9** (0.114 mmol) in THF (0.40 mL) was added Grignard reagent (0.456 mmol) under nitrogen at −78 °C and gradually warmed to 0 °C. The mixture was quenched by the addition of saturated aq NH_4Cl (3.0 mL) and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was roughly purified by column chromatography (silica gel, hexane/EtOAc) to give the crude, which was used without further purification. To a solution of the above product and Et_3SiH (0.342 mmol) in CH_2Cl_2 (0.60 mL) was added a solution of $BF_3\cdot OEt_2$ (0.342 mmol) at −78 °C and gradually warmed to 0 °C. Then, it was quenched by the addition of saturated aq $NaHCO_3$ (3.0 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc) to give the lactam **10** as a colorless oil.

4.2.7.1. (3S,4S*,5R*)-4-(Benzyloxy)-3-((tert-butyldiphenylsilyloxy)-methyl)-1-(4-methoxybenzyl)-5-methylpyrrolidin-2-one (**10b**).* IR (NaCl) 3011 (C–H), 1686 (C=O), 1248 (C–O), 1113 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71–7.63 (m, 4H, Ar*H*), 7.45–7.16 (m, 15H, Ar*H*), 6.83–6.80 (m, 2H, Ar*H*), 4.88 (d, *J*=14.8 Hz, 1H, CH_2), 4.51 (d, *J*=11.7 Hz, 1H, CH_2), 4.44 (d, *J*=11.7 Hz, 1H, CH_2), 4.14 (dd, *J*=10.1, 4.6 Hz, 1H, CH_2), 4.04 (d, *J*=14.8 Hz, 1H, CH_2), 3.98 (dd, *J*=5.6, 3.3 Hz, 1H, C*H*), 3.92 (dd, *J*=10.1, 3.3 Hz, 1H, CH_2), 3.47 (dt, *J*=6.6, 3.3 Hz, 1H, C*H*), 2.72 (dd, *J*=4.6, 3.3 Hz, 1H, C*H*), 1.18 (d, *J*=6.6 Hz, 3H, CH_3), 1.05 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 172.0 (*C*), 158.9 (*C*), 137.8 (*C*), 135.7 (*C*H), 135.6 (*C*H), 133.3 (*C*), 132.9 (*C*), 129.7 (*C*H), 128.6 (*C*H), 127.7 (*C*H), 127.4 (*C*H), 114.0 (*C*H), 81.2 (*C*H), 71.7 (*C*H_2), 61.8 (*C*H), 58.0 (*C*H), 55.2 (*C*H_3), 43.4 (*C*H_2), 26.9 (*C*H_3), 19.3 (*C*), 18.7 (*C*H_3). /INS> Anal. Calcd for $C_{37}H_{43}NO_4Si$: C, 74.84; H, 7.30; N, 2.36. Found: C, 74.95; H, 7.12; N, 2.36.

4.2.7.2. (3S,4S*,5R*)-4-(Benzyloxy)-3-((tert-butyldiphenylsilyloxy)-methyl)-1-(4-methoxybenzyl)-5-propylpyrrolidin-2-one (**10c**).* IR (NaCl) 2992 (C–H), 1682 (C=O), 1248 (C–O), 1113 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.64 (m, 4H, ArH), 7.43–7.39 (m, 5H, ArH), 7.38–7.15 (m, 6H, ArH), 6.83–6.80 (m, 2H, ArH), 4.92 (d, *J*=15.0 Hz, 1H, CH_2), 4.51 (d, *J*=11.6 Hz, 1H, CH_2), 4.38 (d, *J*=11.6 Hz, 1H, CH_2), 4.09–4.03 (m, 2H, C*H*, O*H*), 3.96 (d, *J*=15.0 Hz, 1H, CH_2), 3.95 (dd, *J*=10.4, 3.7 Hz, 1H, CH_2), 3.77 (s, 3H, CH_3), 3.37 (dt, *J*=9.0, 3.3 Hz, 1H, C*H*), 2.78–2.74 (m, 1H, C*H*), 1.67–1.58 (m, 1H, 2CH_2), 1.40–1.15 (m, 3H, 2CH_2), 1.06 (s, 9H, C(CH_3)$_3$), 0.84 (t, *J*=7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.8 (*C*), 137.8 (*C*), 135.7 (*C*H), 135.6 (*C*H), 133.3 (*C*), 132.9 (*C*), 129.7 (*C*H), 128.4 (*C*H), 127.7 (2*C*H), 127.5 (*C*H), 81.2 (*C*H), 72.4 (*C*H_2), 62.2 (*C*H_2), 60.8 (*C*H_2), 52.1 (*C*H_3), 26.8 (*C*H_3), 19.3 (*C*H), 18.6 (*C*). Anal. Calcd for $C_{39}H_{47}NO_4Si$: C, 75.32; H, 7.62; N, 2.25. Found: C, 75.47; H, 7.55; N, 2.29.

4.2.7.3. (3S,4S*,5R*)-4-(Benzyloxy)-3-((tert-butyldiphenylsilyloxy)-methyl)-1-(4-methoxybenzyl)-5-nonylpyrrolidin-2-one (**10d**).* IR (NaCl) 2993 (C–H), 1688 (C=O), 1248 (C–O), 1113 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71–7.64 (m, 4H, Ar*H*), 7.45–7.41 (m, 13H, Ar*H*), 6.84–6.79 (m, 2H, Ar*H*), 4.91 (d, *J*=14.9 Hz, 1H, CH_2), 4.52 (d, *J*=11.6 Hz, 1H, CH_2), 4.38 (d, *J*=11.6 Hz, 1H, CH_2), 4.11–4.05 (m, 2H, 2C*H*), 3.97 (d, *J*=14.9 Hz, 1H, CH_2), 3.95 (dd, *J*=10.3, 3.5 Hz, 1H, CH_2), 3.77 (s, 3H, CH_3), 3.36 (dt, *J*=9.2, 3.5 Hz, 1H, C*H*), 2.77–2.73 (m, 1H, C*H*), 1.71–1.64 (m, 1H, CH_2), 1.31–1.19 (m, 15H, CH_2), 1.06 (s, 9H, C(CH_3)$_3$), 0.89 (t, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.0 (*C*), 158.9 (C), 137.8 (*C*), 135.7 (*C*H), 135.6 (*C*H), 133.2 (C), 132.9 (*C*), 129.8 (*C*H), 129.2 (*C*H), 128.5 (CH), 128.3 (CH), 127.7 (2*C*H), 127.5 (*C*), 114.0 (CH), 78.5 (*C*H), 71.2 (*C*H_2), 62.4 (*C*H_2), 62.3 (*C*H), 55.2 (*C*H_3), 52.4 (*C*H), 43.6 (*C*H_2), 31.8 (*C*H_2), 31.3 (*C*H_2), 29.5 (3CH_2), 29.3 (*C*H_2), 26.9 (*C*H_3), 24.5 (*C*H_2), 22.6 (*C*H_2), 19.3 (*C*), 14.1 (*C*H_3). Anal. Calcd for $C_{45}H_{59}NO_4Si$: C, 76.55; H, 8.42; N, 1.98. Found: C, 76.49; H, 8.45; N, 2.04.

4.2.7.4. (3S,4S*,5R*)-5-Allyl-4-(benzyloxy)-3-((tert-butyldiphenylsilyloxy)methyl)-1-methylpyrrolidin-2-one (**10e**).* IR (NaCl) 2858 (C–H), 1690 (C=O), 1113 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.62 (m, 4H, Ar*H*), 7.44–7.24 (m, 11H, Ar*H*), 5.75–5.61 (m, 1H, C*H*), 5.11–5.06 (m, 2H, CH_2), 4.57 (d, *J*=11.6 Hz, 1H, CH_2), 4.45 (d, *J*=11.6 Hz, 1H, CH_2), 4.09 (t, *J*=3.6 Hz, 1H, C*H*), 3.96–3.93 (m, 2H, CH_2), 3.54 (dt, *J*=8.2, 3.6 Hz, 1H, C*H*), 2.84 (s, 3H, CH_3), 2.74–2.69 (m, 1H, C*H*), 2.53–2.45 (m, 1H, CH_2), 2.29–2.19 (m, 1H, CH_2), 1.05 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 172.1 (*C*), 137.8 (*C*), 135.7 (*C*H), 133.2 (*C*H), 129.7 (*C*H), 128.4 (*C*H), 127.69 (*C*H), 127.68 (*C*H), 127.67 (*C*H), 118.7 (*C*H_2), 78.3 (*C*H), 71.3 (*C*H_2), 64.7 (*C*H), 62.3 (*C*H_2), 52.2 (*C*H_3), 35.9 (*C*H_2), 27.8 (*C*H_3), 26.8 (*C*H_3), 19.2 (*C*). Anal. Calcd for $C_{32}H_{39}NO_3Si$: C, 74.81; H, 7.65; N, 2.73. Found: C, 74.50; H, 7.45; N, 2.70.

4.2.7.5. (3S,4S*,5R*)-4-(Benzyloxy)-3-((tert-butyldiphenylsilyloxy)-methyl)-1,5-dimethylpyrrolidin-2-one (**10f**).* IR (NaCl) 2858 (C–H), 1690 (C=O), 1113 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.68–7.62 (m, 4H, Ar*H*), 7.44–7.24 (m, 11H, Ar*H*), 4.57 (d, *J*=11.5 Hz, 1H, CH_2), 4.48 (d, *J*=11.5 Hz, 1H, CH_2), 4.02 (dd, *J*=10.3, 5.3 Hz, 1H, CH_2), 3.93 (dd, *J*=3.7, 3.5 Hz, 1H, C*H*), 3.91 (dd, *J*=10.3, 3.5 Hz, 1H, CH_2), 3.53 (dq, *J*=6.6, 3.5 Hz, 1H, C*H*), 2.81 (s, 3H, CH_3), 2.68 (ddd, *J*=5.5, 3.7, 3.5 Hz, 1H, C*H*), 1.13 (d, *J*=6.6 Hz, 3H, CH_3), 1.04 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 172.2 (*C*), 158.9 (*C*), 137.9 (*C*), 135.7 (*C*H), 135.6 (*C*H), 133.3 (*C*), 133.0 (*C*), 129.8 (*C*H), 129.2 (*C*H), 128.5 (*C*), 128.4 (*C*H), 127.7 (*C*H, *C*), 127.5 (*C*H), 114.0 (*C*H), 78.8 (*C*H), 71.1 (*C*H_2), 62.4 (*C*H_2), 62.2 (*C*H), 55.2 (*C*H_3), 52.5 (*C*H), 43.6 (*C*H_2), 26.9 (*C*H_3), 19.3 (*C*), 17.9 (*C*H_2), 14.0 (*C*H_3). Anal. Calcd for $C_{30}H_{37}NO_3Si$: C, 73.88; H, 7.65; N, 2.87. Found: C, 74.09; H, 7.36; N, 2.94.

4.2.7.6. (3S,4S*,5R*)-4-(Benzyloxy)-3-((tert-butyldiphenylsilyloxy)-methyl)-1-methyl-5-propylpyrrolidin-2-one (**10g**).* IR (NaCl) 2858 (C–H), 1693 (C=O), 1113 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.68–7.62 (m, 4H, Ar*H*), 7.45–7.24 (m, 11H, Ar*H*), 4.58 (d, *J*=11.7 Hz, 1H, CH_2), 4.43 (d, *J*=11.7 Hz, 1H, CH_2), 3.99 (dd, *J*=3.3, 3.1 Hz, 1H, C*H*), 3.95 (d, *J*=4.6 Hz, 1H, CH_2), 3.94 (d, *J*=5.5 Hz, 1H, CH_2), 3.42 (dt, *J*=8.8, 3.1 Hz, 1H, C*H*), 2.81 (s, 3H, CH_3), 2.72 (ddd, *J*=5.5, 4.6, 3.3 Hz, 1H, C*H*), 1.74–1.60 (m, 1H, 2CH_2), 1.41–1.23 (m, 3H, 2CH_2), 1.05 (s, 9H, C(CH_3)$_3$), 0.92 (t, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.9 (*C*), 137.8 (*C*), 135.7 (*C*H), 135.6 (*C*H), 133.2 (*C*), 133.0 (*C*), 129.7 (*C*H), 128.4 (*C*H), 127.7 (2*C*H), 127.5 (*C*H), 79.0 (*C*H), 71.1 (*C*H_2), 65.4 (*C*H), 62.6 (*C*H_2), 52.3 (*C*H_3), 33.9 (*C*H_2), 26.9 (*C*H_3), 19.3 (*C*), 18.1 (*C*H_2), 14.1 (*C*H_2). Anal. Calcd for $C_{32}H_{41}NO_3Si$: C, 74.52; H, 8.01; N, 2.72. Found: C, 74.36; H, 7.76; N, 2.67.

4.2.7.7. (3S,4S*,5R*)-4-(Benzyloxy)-3-((tert-butyldiphenylsilyloxy)-methyl)-1-methyl-5-nonylpyrrolidin-2-one (**10h**).* IR (NaCl) 2856 (C–H), 1690 (C=O), 1113 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.67–7.62 (m, 4H, Ar*H*), 7.45–7.25 (m, 11H, Ar*H*), 4.58 (d, *J*=11.7 Hz, 1H, CH_2), 4.43 (d, *J*=11.7 Hz, 1H, CH_2), 3.95 (d, *J*=5.3 Hz, 1H, CH_2), 3.94 (d, *J*=4.2 Hz, 1H, CH_2), 3.41 (dt, *J*=8.8, 3.1 Hz, 1H, C*H*), 2.81 (s, 3H, CH_3), 2.73–2.69 (m, 1H, C*H*), 1.71–1.68 (m, 1H, CH_2), 1.39–1.26 (m, 15H, CH_2), 1.04 (s, 9H, C(CH_3)$_3$), 0.89 (t, *J*=6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.0 (*C*), 137.8 (*C*), 135.7 (*C*H), 135.6 (*C*H), 133.2 (C), 133.0 (*C*), 129.8 (*C*H), 128.4 (*C*H), 127.7 (2*C*H), 127.6 (*C*H), 78.8 (*C*H), 71.1 (*C*H_2), 65.5 (*C*H), 62.6 (*C*H_2), 52.3 (*C*H_3), 31.9 (*C*H_2), 31.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.3 (*C*H_2), 27.7 (*C*H_2), 26.9 (*C*H_3), 24.8 (*C*H_2), 22.7 (*C*H_2), 19.3 (*C*), 14.1 (*C*H_3). Anal. Calcd for $C_{38}H_{53}NO_3Si$: C, 76.08; H, 8.90; N, 2.33. Found: C, 75.98; H, 8.79; N, 2.44.

4.2.8. (3S,4S*,5R*)-5-Allyl-3-(benzyloxy)-4-((tert-butyldiphenylsilyloxy)methyl)-1-(4-methoxybenzyl)pyrrolidin-2-one (**11**)*

To a stirred solution of **8** (927 mg, 1.56 mmol) and allyltrimethylsilane (0.99 mL, 6.2 mmol) in CH_2Cl_2 (15 mL) was added a solution of $BF_3{\cdot}OEt_2$ (0.77 mL, 6.2 mmol) at −78 °C and gradually warmed to −20 °C. The mixture was quenched by the addition of saturated aq $NaHCO_3$ (5 mL) and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc=4:1) to give 11 (959 mg, 99%) as a colorless oil. IR (NaCl) 1693 (C=O), 1514 (C=C), 1113 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.47 (m, 4H, Ar*H*), 7.44–7.23 (m, 11H, Ar*H*), 7.13–7.10 (m, 2H, Ar*H*), 6.79–6.76 (m, 2H, Ar*H*), 5.44 (m, 1H, C*H*), 5.13–4.99 (m, 4H, CH_2), 4.77 (d, *J*=11.7 Hz, 1H, CH_2), 4.23 (d, *J*=5.5 Hz, 1H, C*H*), 3.86 (d, *J*=14.8 Hz, 1H, CH_2), 3.75 (s, 3H, CH_3), 3.64 (dd, *J*=10.6, 4.7 Hz, 1H, CH_2), 3.51 (dd, *J*=10.7, 4.2 Hz, 1H, CH_2), 3.29 (m, 1H, C*H*), 2.26–2.23 (m, 2H, CH_2, C*H*), 2.15 (m, 1H, CH_2), 0.95 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 172.7 (*C*), 159.0 (*C*), 138.1 (*C*),

135.5 (*C*H), 133.0 (*C*), 132.8 (*C*), 132.5 (*C*H), 129.80 (*C*H), 129.3 (*C*H), 128.3 (*C*H), 128.02 (*C*H), 127.67 (*C*H), 127.6 (*C*H), 118.9 (CH_2), 114.1 (*C*H), 76.8 (*C*H), 72.5 (CH_2), 61.3 (CH_2), 55.2 (CH_3), 54.3 (*C*H), 45.5 (*C*H), 43.4 (CH_2), 35.9 (CH_2), 26.8 (CH_3), 19.1 (*C*); HRMS (ESI^+) *m*/*z* calcd for $C_{39}H_{45}NO_4Si$+Na: 642.3016, found 642.3057.

4.2.9. (3S*,4S*,5R*)-3-(Benzyloxy)-4-((tert-butyldiphenylsilyloxy)methyl)-5-(3-hydroxypropyl)pyrrolidin-2-one (**13**)

To a solution of **11** (834 mg, 1.34 mmol) in THF (10 mL) was added 9-BBN (0.5 M solution in THF, 3.0 mL, 1.5 mmol) under nitrogen and stirred for 1 h. After the mixture was quenched by the addition of 3 N aq NaOH (10 mL) and hydrogen peroxide solution (34.5 wt % in H_2O, 10 mL) was added dropwise at 0 °C and stirred for further 3 h at room temperature. The mixture was quenched by the addition of saturated aq $Na_2S_2O_3$ (20 mL) and extracted with EtOAc (3×30 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/acetone=2:1 to 3:2) to give the primary alcohol **13** (719 mg, 84%) as a colorless oil. IR (NaCl) 3210 (O–H), 1682 (C=O), 1514 (C=C), 1112 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–7.47 (m, 4H, Ar*H*), 7.51–7.25 (m, 11H, Ar*H*), 7.11 (d, *J*=8.5 Hz, 2H, Ar*H*), 6.76 (d, *J*=8.5 Hz, 2H, Ar*H*), 5.09 (d, *J*=11.7 Hz, 1H, CH_2), 5.00 (d, *J*=14.6 Hz, 1H, CH_2), 4.75 (d, *J*=11.7 Hz, 1H, CH_2), 4.16 (d, *J*=5.5 Hz, 1H, C*H*), 3.84 (d, *J*=14.6 Hz, 1H, CH_2), 3.74 (s, 3H, CH_3), 3.59 (dd, *J*=10.2, 5.1 Hz, 1H, CH_2), 3.51–3.47 (m, 3H, CH_2), 3.25 (m, 1H, C*H*), 2.11 (m, 1H, C*H*), 1.62–1.55 (m, 2H, CH_2), 1.38–1.20 (m, 2H, CH_2), 0.95 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 172.5 (*C*), 158.9 (*C*), 138.0 (*C*), 135.5 (*C*H), 133.0 (*C*), 132.8 (*C*), 129.8 (*C*H), 129.3 (*C*H), 128.3 (*C*H), 128.1 (*C*H), 127.9 (*C*H), 127.7 (*C*H), 114.0 (*C*H), 77.2 (*C*H), 72.5 (2CH_2), 62.4 (*C*H_2), 61.9 (*C*H_2), 55.19 (*C*H), 55.16 (*C*H_3), 45.6 (*C*H), 43.4 (*C*H_2), 27.4 (*C*H_2), 26.7 (*C*H_3), 19.1 (*C*). Anal. Calcd for $C_{39}H_{47}NO_5Si$: C, 73.43; H, 7.43; N, 2.20. Found: C, 73.59; H, 7.57; N, 2.59.

4.2.10. (1S*,2S*,7aR*)-2-(Benzyloxy)-1-((tert-butyldiphenylsilyloxy)methyl)tetrahydro-1H-pyrrolizin-3(2H)-one (**14**)

To a solution of **13** (71.1 mg, 0.111 mmol) in pyridine (1.3 mL) was added *p*-toluenesulfonyl chloride (117 mg, 0.613 mmol) at 0 °C and stirred for 6 h. The mixture was quenched by the addition of 3% HCl (5 mL) and extracted with EtOAc (2×5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was roughly purified by column chromatography (silica gel, hexane/EtOAc=3:1 to 1:1) to give the crude tosylate (98.6 mg), which was used without further purification. A solution of this tosylate and CAN (243 mg, 4.44 mmol) in MeCN/H_2O=2:1 (6.0 mL) was stirred for 2 h. The mixture was quenched by the addition of water and extracted with EtOAc (3×5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was roughly purified by column chromatography (silica gel, hexane/EtOAc=2:1 to 1:2) to give the crude deprotected amide (57.9 mg), which was used without further purification. To a solution of this amide in THF (3.0 mL) was added NaH (55 wt %, 48.4 mg, 1.11 mmol) under nitrogen at 0 °C and stirred for 30 min under the same temperature. After the solution was warmed to room temperature and stirred for 20 min, it was quenched by the addition of water (5 mL) and extracted with EtOAc (3×5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc=3:1 to 1:1) to give **14** (40.6 mg, 73%) as a colorless oil. IR (NaCl) 1701 (C=O), 1113 (C–O), 1074 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (dd, *J*=7.9, 1.7 Hz, 4H, Ar*H*), 7.47–7.22 (m, 11H, Ar*H*), 5.09 (d, *J*=11.7 Hz, 1H, CH_2), 4.64 (d, *J*=11.7 Hz, 1H, CH_2), 4.32 (d, *J*=10.1 Hz, 1H, CH_2), 3.81 (dd, *J*=10.7, 3.1 Hz, 1H, CH_2), 3.73 (dd, *J*=10.7, 6.1 Hz, 1H, CH_2), 3.67–3.54 (m, 2H, CH_2), 3.07 (m, 1H, C*H*), 2.20 (m, 1H, C*H*), 2.07–1.93 (m, 3H, CH_2, CH_2), 1.41 (m, 1H, CH_2), 1.04 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 172.7 (*C*), 138.0 (*C*), 135.5 (*C*H), 133.2 (*C*), 129.8 (*C*H), 128.3 (*C*H), 128.0 (*C*H), 127.8 (*C*H), 127.6 (*C*H), 79.5 (*C*H), 72.5 (CH_2), 62.0 (CH_2), 59.5 (*C*H), 52.9 (*C*H), 41.3 (CH_2), 31.6 (CH_2), 26.8 (CH_3), 26.0 (CH_2), 19.2 (*C*). Anal. Calcd for $C_{31}H_{37}NO_3Si$: C, 74.51; H, 7.46; N, 2.80. Found: C, 74.62; H, 7.39; N, 3.19.

4.2.11. (1S*,2S*,7aR*)-1-((tert-Butyldiphenylsilyloxy)methyl)-2-hydroxytetrahydro-1H-pyrrolizin-3(2H)-one (**15a**)

A mixture of **14** (78.9 mg, 0.158 mmol) and Pearlman's catalyst (31.2 mg) in EtOH (9.0 mL) was stirred under hydrogen atmosphere for 23 h. The mixture was filtered through a pad of Celite with EtOH and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc=1:1 then $CHCl_3$/MeOH=15:1) to give **15a** (61.8 mg, 95%) as a white powder. Mp 119–120 °C; IR (NaCl) 3281 (O–H), 1684 (C=O), 1113 (C–O), 1057 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66–7.63 (m, 4H, Ar*H*), 7.46–7.26 (m, 6H, Ar*H*), 4.44 (d, *J*=9.9 Hz, 1H, C*H*), 3.95 (dd, *J*=10.4, 3.7 Hz, 1H, CH_2), 3.84 (dd, *J*=10.4, 6.8 Hz, 1H, CH_2), 3.66–3.54 (m, 2H, C*H*), 3.29 (br s, 1H, O*H*), 3.07 (m, 1H, C*H*), 2.18–1.93 (m, 4H, CH_2, CH_2, C*H*), 1.47 (m, 1H, CH_2), 1.07 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 173.8 (*C*), 135.5 (*C*H), 133.2 (*C*), 129.8 (*C*H), 127.8 (*C*H), 73.9 (*C*H), 62.6 (*C*H_2), 60.3 (*C*H), 55.0 (*C*H), 41.5 (*C*H_2), 31.5 (*C*H_2), 26.9 (*C*H_3), 26.2 (*C*H_2), 19.2 (*C*). Anal. Calcd for $C_{24}H_{31}NO_3Si$: C, 70.38; H, 7.63; N, 3.42. Found: C, 70.58; H, 7.53; N, 3.42.

4.2.12. (1S*,2S*,7aR*)-2-Hydroxy-1-(hydroxymethyl)tetrahydro-1H-pyrrolizin-3(2H)-one (**16a**)

To a solution of **15a** (40.4 mg, 0.0986 mmol) in THF (1.2 mL) was added borane–tetrahydrofuran complex (0.99 M solution in THF, 0.97 mL, 0.96 mmol) and stirred for 18 h. The mixture was quenched by the addition of MeOH (5 mL) and concentrated. To the residue was added MeOH (10 mL) and stirred under reflux for 4 h. The solution was concentrated to give the crude amine, which was purified by column chromatography (silica gel, hexane/acetone=3:1) to give **16a** (26.2 mg, 67%) as a colorless oil. IR (NaCl) 3500 (O–H), 1113 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68–7.64 (m, 4H, Ar*H*), 7.49–7.38 (m, 6H, Ar*H*), 4.47 (dt, *J*=8.3, 6.6 Hz, 1H, C*H*), 3.77 (d, *J*=6.2 Hz, 2H, CH_2), 3.56 (dd, *J*=10.5, 6.3 Hz, 1H, CH_2), 3.48 (m, 1H, CH_2), 3.16–3.07 (m, 2H, C*H*, CH_2), 2.76 (dd, *J*=10.1, 9.2 Hz, 1H, CH_2), 2.19–1.82 (m, 5H, CH_2, CH_2, C*H*, O*H*), 1.65 (m, 1H, CH_2), 1.07 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 135.6 (*C*H), 132.9 (*C*), 130.0 (*C*H), 127.9 (*C*H), 74.1 (*C*H), 72.5 (*C*H), 67.7 (*C*H_2), 64.6 (*C*H_2), 63.9 (*C*H_2), 55.4 (*C*H), 31.1 (*C*H_2), 26.9 (*C*H_3), 24.2 (*C*H_2), 19.1 (*C*). Anal. Calcd for $C_{24}H_{33}NO_2Si$: C, 72.86; H, 8.41; N, 3.54. Found: C, 72.68; H, 8.22; N, 3.63.

4.2.13. (1S*,2S*,7aR*)-1-(Hydroxymethyl)hexahydro-1H-pyrrolizin-2-ol (2-epi-macronecine) (**1c**)

A solution of **16a** (15.3 mg, 0.0387 mmol) in 3% HCl/MeOH (2.0 mL) was stirred for 1.5 h. After concentration, the residue was dissolved in 3% HCl (5.0 mL) and washed with EtOAc (5 mL). The water extract was concentrated and the residue was passed through Dowex 50WX-8 (H^+ form), which was first eluted with water (20 mL), and then 0.3 M NH_4OH (20 mL) followed by 0.7 M NH_4OH (20 mL). Alkaline fractions were concentrated in vacuo to give **1c** (6.2 mg, quant.) as a white powder. Mp 94–96 °C; IR (NaCl) 3300 (O–H), 2910 (O–H), 1112 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.33 (m, 1H, C*H*), 3.80 (dd, *J*=11.1, 3.9 Hz, 1H, CH_2), 3.64 (dd, *J*=11.1, 5.1 Hz, 1H, CH_2), 3.42–3.30 (m, 2H, C*H*, CH_2), 2.94 (m, 1H, CH_2), 2.68 (m, 1H, CH_2), 2.47 (t, *J*=9.3 Hz, 1H, CH_2), 2.01–1.86 (m, 2H, C*H*, CH_2), 1.82–1.56 (m, 3H, CH_2); ^{13}C NMR (CD_3OD) δ 74.7 (*C*H), 67.7 (*C*H), 63.0 (*C*H_2), 61.9 (*C*H_2), 56.4 (*C*H_2), 56.2 (*C*H), 33.3 (*C*H_2), 26.3 (*C*H_2).

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.36; H, 9.93; N, 9.06.

4.2.14. *(1S*,2R*,7aR*)-1-((tert-Butyldiphenylsilyloxy)methyl)-2-hydroxytetrahydro-1H-pyrrolizin-3(2H)-one (**15b**)*

To a solution of **15a** (6.7 mg, 0.0164 mmol) and pyridine (0.050 mL, 0.65 mmol) in CH_2Cl_2 (1.0 mL) was added trifluoromethanesulfonic anhydride (0.050 mL, 0.26 mmol) at 0 °C and stirred for 1 h at room temperature. It was quenched by the addition of water (5 mL) and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated to give the crude triflate, which was used without further purification. To a solution of the above product and 18-crown-6 (4.0 mg, 0.015 mmol) in toluene (0.5 mL) was added CsOAc (4.0 mg, 0.21 mmol) and stirred for 1 h. The reaction was quenched by the addition of water (5 mL) and extracted with EtOAc (10 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/acetone=3:1 to 2:1) to give the acetate (5.7 mg, 70%). IR (NaCl) 1736 (C=O), 1703 (C=O), 1232 (C–O), 1113 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65–7.60 (m, 4H, Ar*H*), 7.48–7.36 (m, 6H, Ar*H*), 5.50 (d, *J*=9.6 Hz, 1H, C*H*), 3.82 (dd, *J*=10.5, 6.3 Hz, 1H, CH_2), 3.78 (m, 1H, C*H*), 3.63 (dd, *J*=10.5, 8.4 Hz, 1H, CH_2), 3.53 (dt, *J*=12.3, 7.5 Hz, 1H, CH_2), 3.14 (m, 1H, CH_2), 2.35 (dq, *J*=13.2. 7.5 Hz, 1H, CH_2), 2.19–2.02 (m, 3H, CH_2, CH_2, C*H*), 1.37 (m, 1H, CH_2), 1.05 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 169.5 (*C*), 169.2 (*C*), 135.5 (*C*H), 133.0 (*C*), 129.9 (*C*H), 127.8 (*C*H), 76.2 (*C*H), 64.2 (*C*H), 61.0 (*C*H_2), 47.8 (*C*H), 41.1 (*C*H_2), 31.5 (*C*H_2), 27.1 (*C*H_2), 26.8 (*C*H_3), 20.5 (*C*H_3), 19.1 (*C*). Anal. Calcd for $C_{26}H_{33}NO_4Si$: C, 69.14; H, 7.36; N, 3.10. Found: C, 69.12; H, 7.14; N, 3.27.

A mixture of the acetate (41.3 mg, 0.0826 mmol) and K_2CO_3 (40.0 mg) in MeOH (3.0 mL) was stirred for 45 min. The mixture was roughly purified by silica gel column chromatography (hexane/acetone=2:1) and concentrated. The residue was purified by column chromatography (silica gel, hexane/acetone=3:1 to 2:1) to give **15b** (31.4 mg, 93%) as colorless needles. Mp 162–164 °C; IR (NaCl) 3330 (O–H), 1680 (C=O), 1111 (C–O), 1072 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66 (dd, *J*=7.7, 1.7 Hz, 4H, Ar*H*), 7.46–7.35 (m, 6H, Ar*H*), 4.35 (br d, *J*=5.9 Hz, 1H, C*H*), 4.20 (br s, 1H, O*H*), 4.01–3.90 (m, 2H, CH_2), 3.83 (m, 1H, C*H*), 3.45 (dt, *J*=11.3, 7.9 Hz, 1H, CH_2), 3.10 (m, 1H, CH_2), 2.20–1.97 (m, 4H, CH_2, C*H*), 1.32 (m, 1H, CH_2), 1.06 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 173.4 (*C*), 135.6 (*C*H), 133.3 (*C*), 129.8 (*C*H), 127.8 (*C*H), 76.5 (*C*H), 64.5 (*C*H), 61.7 (*C*H_2), 49.1 (*C*H), 40.6 (*C*H_2), 31.5 (*C*H_2), 27.1 (*C*H_2), 26.9 (*C*H_3), 19.1 (*C*). Anal. Calcd for $C_{24}H_{31}NO_3Si$: C, 70.38; H, 7.63; N, 3.42. Found: C, 70.10; H, 7.42; N, 3.52.

The same procedure gave the pyrrolizidine **16b** and (±)-macronecine (**1b**) from the corresponding amide **15b** (yields are given in Scheme 2). The spectral data of synthetic **1b** thus obtained were identical in all respects with those of the natural and synthesized compound.[8]

4.2.15. *(1S*,2R*,7aR*)-2-Hydroxy-1-(hydroxymethyl)tetrahydro-1H-pyrrolizin-3(2H)-one (**16b**)*

IR (NaCl) 3474 (O–H), 1112 (C–O), 1078 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (d, *J*=7.3 Hz, 4H, Ar*H*), 7.44–7.37 (m, 6H, Ar*H*), 4.35 (m, 1H, C*H*), 4.02 (dd, *J*=10.4, 7.0 Hz, 1H, CH_2), 3.74 (dd, *J*=10.4, 6.7 Hz, 1H, CH_2), 3.64–3.53 (m, 2H, 2CH_2), 3.21 (d, *J*=9.7 Hz, 1H, O*H*), 3.15–2.91 (m, 3H, C*H*, 2CH_2), 2.20–1.97 (m, 3H, C*H*, CH_2), 1.86–1.68 (m, 2H, CH_2), 1.06 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 135.6 (*C*H), 133.2 (*C*), 129.9 (*C*H), 127.8 (*C*H), 75.5 (*C*H), 73.1 (*C*H), 70.3 (*C*H_2), 65.6 (*C*H_2), 62.2 (*C*H_2), 53.8 (*C*H), 30.8 (*C*H_2), 26.8 (*C*H_3), 24.4 (*C*H_2), 19.1 (*C*). Anal. Calcd for $C_{24}H_{33}NO_2Si$: C, 72.86; H, 8.41; N, 3.54. Found: C, 72.76; H, 8.52; N, 3.57.

4.2.16. *(1S*,2R*,7aR*)-1-(Hydroxymethyl)hexahydro-1H-pyrrolizin-2-ol (macronecine) (**1b**)*

Mp 109–110 °C; IR (NaCl) 3363 (O–H), 2933 (O–H), 1038 (O–H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.50 (t, *J*=3.9 Hz, 1H, C*H*), 3.91 (dd, *J*=11.4, 4.8 Hz, 1H, CH_2), 3.84 (dd, *J*=11.4, 6.9 Hz, 1H, CH_2), 3.59 (m, 1H, C*H*), 3.22 (d, *J*=11.4 Hz, 1H, CH_2), 3.00 (dt, *J*=10.8, 6.6 Hz, 1H, CH_2), 2.71 (dd, *J*=11.4, 3.9 Hz, 1H, CH_2), 2.60 (dt, *J*=10.8, 6.3 Hz, 1H, CH_2), 1.97 (m, 1H, C*H*), 1.90–1.77 (m, 3H, CH_2, CH_2), 1.54 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$) δ 75.6 (*C*H), 64.5 (*C*H), 62.8 (*C*H_2), 60.8 (*C*H_2), 54.7 (*C*H_2), 52.2 (*C*H), 31.0 (*C*H_2), 25.5 (*C*H_2). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.09; H, 9.70; N, 9.05.

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11. Only trace amounts of minor stereoisomer were detected by ^1H NMR.
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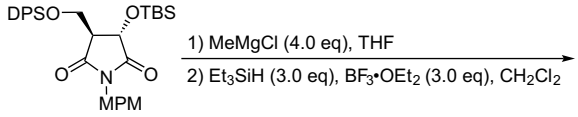
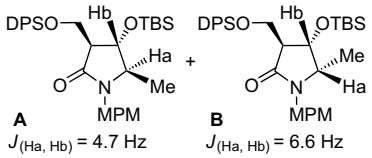
14. To determine the stereochemistry of allylated lactam **10a** unambiguously, we prepared the compound **A** and **B** under the same reaction conditions, providing almost non-stereoselective results as described below. The coupling constants of these compounds were indicated to be 4.7 (trans-form) and 6.6 (cis-form) Hz, respectively.





74% yield
97:3 regioselectivity, 8% de (*cis*-selective)

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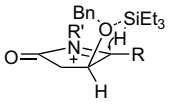
16. In Ref. 15, they suggest that the regioselectivity on Grignard addition is controlled by both the complex induced proximity effects (cis-directing effect) between benzyloxy group and Grignard reagent and steric effects (trans-directing effect). They also explained that the diastereoselectivity on reductive deoxygenation is influenced by the chelation between the benzyloxy group on *N*-acyliminium ion intermediate and the triethylsilane supporting the *syn*-addition (see below).



17. As shown in Ref. 14, we observed the similar regioselectivity on the reaction of the imide containing TBS protecting group, which is generally recognized as a non-chelation substituent. This result indicates that the regioselectivity would be controlled by not only the complex induced proximity effects but also some other unclarified factors.
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