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Stereoselective Synthesis of Nitrogen-Containing Heterocycles *via* Nickel-Catalyzed Cyclization of 1,3-Diene and Aldehyde: Formal Total Synthesis of (-)-Elaeokanine C

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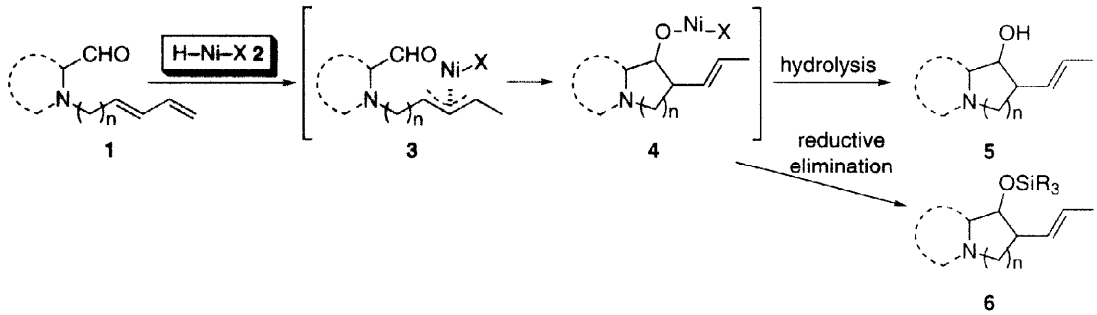
Abstract: Stereoselective syntheses of pyrrolidine, piperidine, pyrrolizidine and indolizidine skeletons were accomplished by nickel-catalyzed cyclization of 1,3-diene and aldehyde in a chain. A formal total synthesis of an Elaeocarpus alkaloid, (-)-Elaeokanine C, in the naturally occurring form was achieved using this cyclization.

The first example of nickel-promoted co-oligomerization of 1,3-diene was reported by Reed in 1954,[1] where 1,5-cyclooctadiene was produced by the reaction of two molecules of butadiene with $Ni(CO)_4$ in the presence of $P(OPh)_3$. Since then, although many efforts to investigate the nickel-promoted or -catalyzed oligomerization of 1,3-dienes and multiple bonds had been made,[2] synthetic utilization of these processes was restricted due to the difficulty to control the regio- and stereoselectivity. On the other hand, the intramolecular versions of this process are useful for regio- and stereoselective ring construction, and a few excellent examples for [4+4] cycloaddition of bis-dienes,[3] [4+2] cycloaddition of dienynes,[4] cocyclization of bis-dienes in the presence of hydrosilanes, and cyclization of dienynes with isocyanides[5] have been reported. Recently, we reported a novel nickel-promoted or -catalyzed cyclization of 1,3-diene and a carbonyl group in a chain to afford the five- to seven-membered cycloalkanes in a stereoselective manner *via* an π-allylnickel intermediate.[6] During the course of our investigation, we found that a hydride nickel complex played an important role in the cyclization. The versatility of this cyclization encouraged us to apply this approach to the synthesis of nitrogen-containing heterocycles,[7] because construction of these is very important for the synthesis of naturally occurring substrates and biologically active substances. Our plan is shown in Scheme 1.

Scheme 1



Reaction of 1,3-diene **1** with a hydride nickel complex **2**, generated by the reduction of $Ni(acac)_2$ with DIBAL-H in the presence of Ph_3P, would give π-allylnickel complex **3**, which would react with the aldehyde moiety in the side chain to give complex **4**. After hydrolysis of the reaction mixture, nitrogen-containing heterocycles **5**

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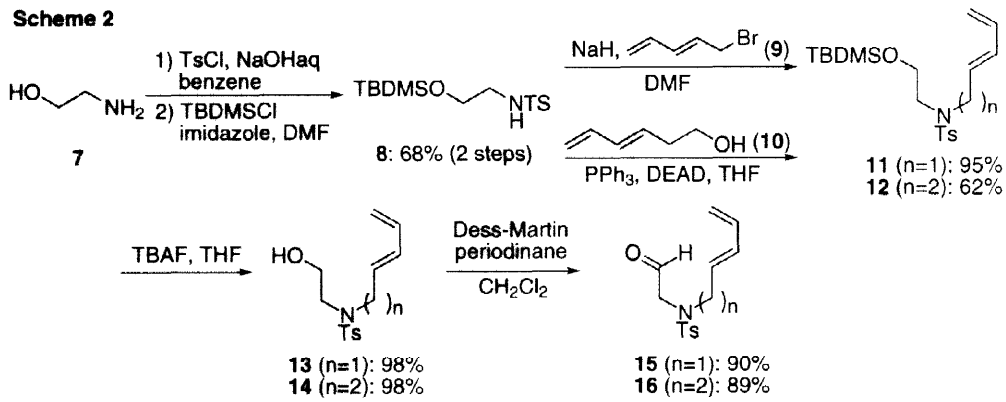
would be obtained stereoselectively. In this cyclization, the use of a hydride nickel complex **2** (X=R_3Si), generated by the oxidative addition of R_3SiH to zerovalent nickel complex, would enable reductive elimination of **6** from complex **4**, and it was expected that the cyclization would proceed catalytically in the nickel complex.

Synthesis of Monocyclic Nitrogen-Containing Heterocycles

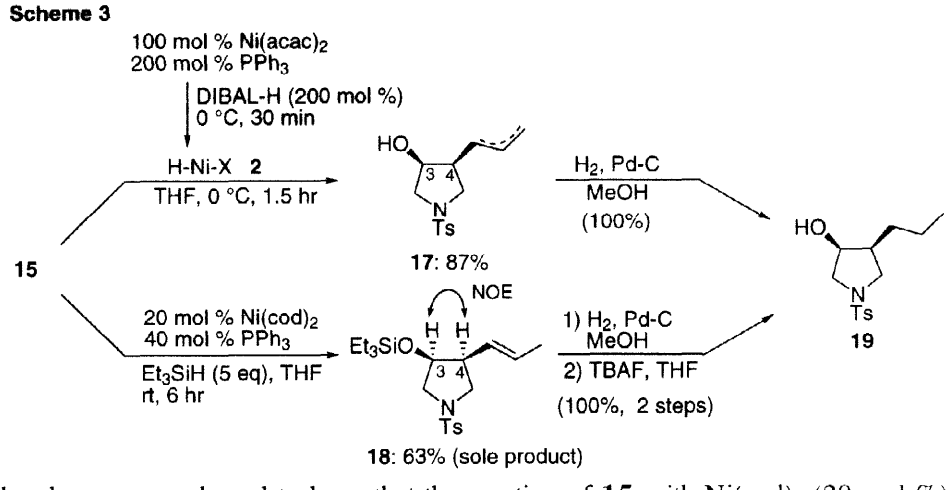
To examine the feasibility of the above plan, we investigated the synthesis of monocyclic nitrogen-containing heterocycles using nickel-promoted cyclization. The starting dienes **15** and **16** were synthesized as shown in Scheme 2. The tosylamide **8**, which was easily prepared from 2-aminoethanol **7**, was converted into **11** by the coupling reaction with **9**[8] using NaH in DMF or into **12** by the Mitsunobu reaction[9] with **10**.[10] After deprotection of the TBDMS group, the corresponding alcohol **13** or **14** was transformed into **15** or **16** by the oxidation with Dess-Martin periodinane,[11] respectively.

Scheme 2



First, we examined the cyclization of **15** giving the pyrrolidine derivative using a stoichiometric amount of hydride nickel complex generated from $Ni(acac)_2$ and DIBAL-H. To a THF solution of hydride nickel complex **2**, generated *in situ* by treatment of $Ni(acac)_2$ (100 mol %) and PPh_3 (200 mol %) with DIBAL-H (200 mol %), was added a solution of **15** in THF at 0 °C, and the mixture was stirred at the same temperature for 1.5 hours. Hydrolysis of the reaction mixture with 10% HCl at 0 °C afforded pyrrolidine derivatives **17** as an inseparable mixture in 87% yield. Hydrogenation of **17** with Pd on charcoal produced saturated alcohol **19** as a sole product, which suggested that two stereocenters at C3 and C4 of pyrrolidine rings in the cyclized products **17** were produced in a stereoselective manner in this cyclization.

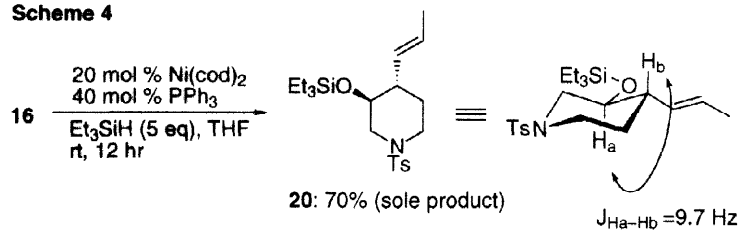
Scheme 3



On the other hand, we were pleased to learn that the reaction of **15** with $Ni(cod)_2$ (20 mol %) and PPh_3 (40 mol %) in the presence of Et_3SiH provided pyrrolidine derivative **18** as a sole product, whose stereochemistry was unequivocally determined from the NOE experiment. Hydrogenation of **18** with Pd on charcoal followed

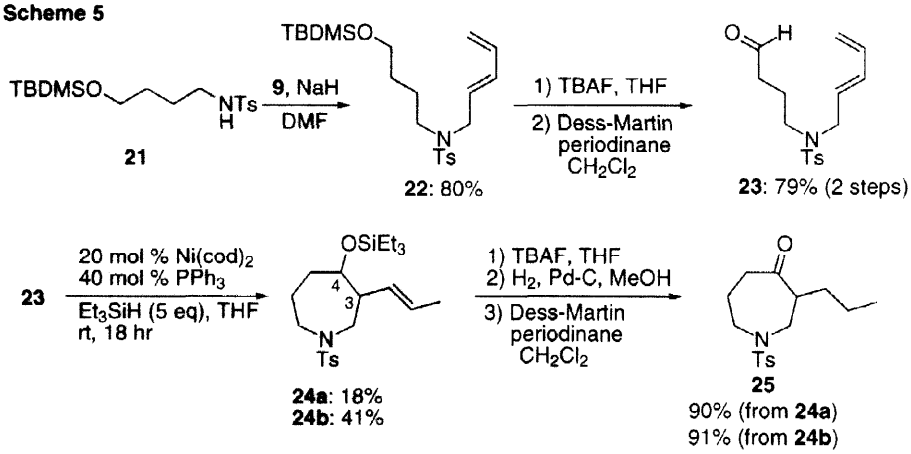
by deprotection of the triethylsilyl group afforded the above alcohol **19**, which indicates that the reaction using a catalytic amount of hydride nickel complex showed the same stereoselectivity as that using a stoichiometric amount of hydride nickel complex. Encouraged by these results, our investigation was focused on the reaction using a catalytic amount of nickel complex, and the cyclizations of various substrates were examined. The construction of piperidine ring from **16** was also fruitful. Thus, treatment of **16** with $Ni(cod)_2$ (20 mol %), PPh_3 (40 mol %), and Et_3SiH (5 eq.) in THF afforded piperidine derivative **20** in 70 % yield as a sole product. The stereochemistry of **20** was determined by the coupling constants of H_a and H_b on the NMR spectrum.

Scheme 4



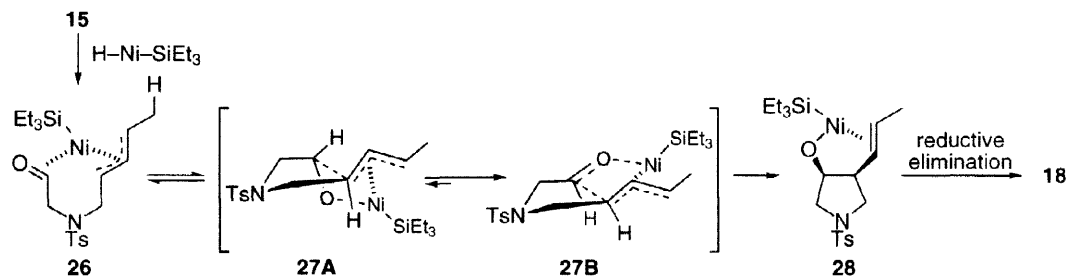
On the other hand, the cyclization of **23**, which was prepared from **21** in a similar procedure to that above, afforded perhydroazepine derivatives **24a** and **24b** in yields of 18% and 41%, respectively. Although the stereochemistries of these cyclized products could not be determined, it was thought that these products were stereoisomers with respect to C3- and C4-substituents on the perhydroazepine ring. The perhydroazepines **24a** and **24b** were transformed into ketone **25**, which was fully characterized by ^1H- and ^{13}C-NMR, IR, MS and elemental analysis. It was noteworthy that this cyclization was applicable to the construction of a seven-membered ring containing the keto-carbonyl group.

Scheme 5



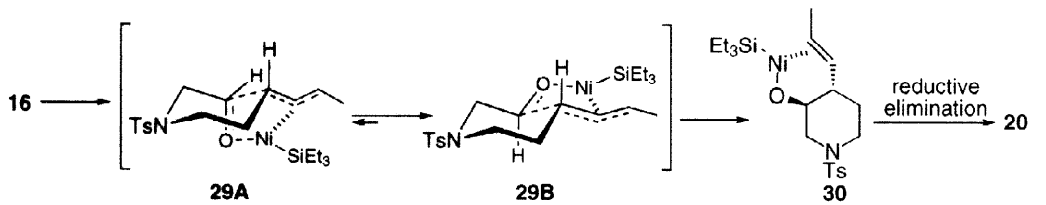
A possible explanation for the stereoselectivity in this cyclization is described in Scheme 6. In the cyclization affording the pyrrolidine derivative **18**, a hydride nickel complex, generated by the oxidative addition of Et_3SiH to zerovalent nickel complex, reacted with **15** to form π-allylnickel complex **26**.

Scheme 6



The reaction of π-allylnickel moiety in **26** with aldehyde in a chain produced cyclized π-complex **28** in a stereoselective manner. During this conversion, we might consider the two intermediates **27A** and **27B**, in which the former would afford an *anti*-isomer of **28** with respect to C3- and C4-substituents, and the latter would give **28**. It was considered that **27B** was more preferable than **27A**, because these intermediates reminded us of the stability in the bicylo[3.3.0]octane system, where a *cis*-bicyclo[3.3.0]octane (analogous to **27B**) was more stable than a *trans*-one. As a result, it is thought that the pyrrolidine derivative **18** was produced stereoselectively in this cyclization. Similarly, in view of the stability in the bicyclo[4.3.0]nonane (hydrindan) system, the intermediate **29B** might be more stable than **29A**, thus giving **20** stereoselectively in the cyclization of piperidine system (Scheme 7).

Scheme 7



On the other hand, each intermediate in the perhydroazepine system might have almost the same stability because they are more flexible than that in the pyrrolidine or piperidine system, which would result in the production of two isomers with regard to the C3- and C4-substituents.

Synthesis of Pyrrolizidine Derivatives

Having established the stereoselective construction of monocyclic heterocycles, we tried to synthesize the pyrrolizidine derivative using this cyclization. The starting diene **33** was easily prepared in an optically active form (>99% ee)[12] by the coupling reaction of (*S*)-pyroglutamic acid derivative **31**[13] with **9** followed by deprotection of the ethoxyethyl group and oxidation with Dess-Martin reagent (Scheme 8).

Scheme 8

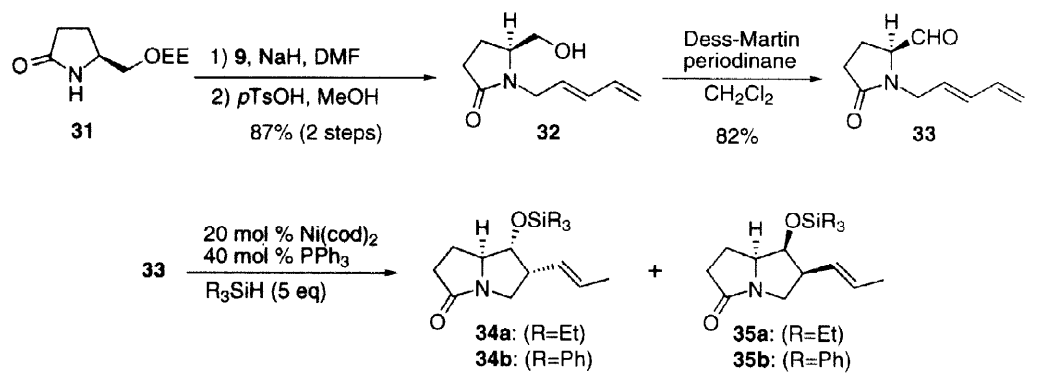


Table 1. Cyclization of **33** under the various conditions

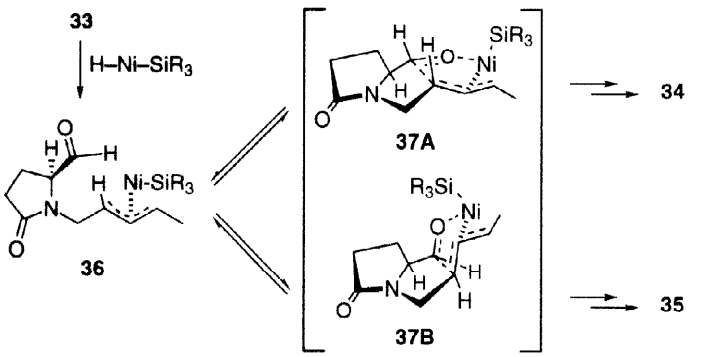
run	solvent	R_3SiH	temp	time (hr)	yield (%) (**34**+**35**)	ratio (**34**/**35**)	ee (%)[a] (**34**/**35**)
1	toluene	Et_3SiH	rt	13.5	64	3.3/1	97/96
2	THF	Et_3SiH	rt	12.5	75	4.4/1	97/95
3	DMF	Et_3SiH	rt	13	75	3.7/1	97/94
4	CH_3CN	Et_3SiH	rt	94	30	6.5/1	95/93
5	THF	Ph_3SiH	rt	1	77	7.6/1	93/97
6	THF	Ph_3SiH	0 °C	1.5	81	9.1/1	97/99

[a] The ee of **34** or **35** was determined by HPLC analysis (DAICEL CHIRALCEL OD, hexane/ ^{i}PrOH=9/1) of the corresponding benzoate, respectively.

Treatment of **33** with 20 mol % $Ni(cod)_2$ and 40 mol % PPh_3 in the presence of Et_3SiH in degassed toluene at room temperature for 13.5 hr provided pyrrolizidine derivatives **34a** and **35a** in yields of 49% and 15% (Table 1, run 1), whose stereochemistries were determined by X-ray analysis of the corresponding alcohols, respectively. The enantiomeric excesses of **34a** and **35a** were determined to be 97% ee and 96% ee by HPLC analysis, indicating that the optical purity of the starting material **33** was completely retained during cyclization. Although various solvents were investigated in the cyclization of **33** using Et_3SiH as a hydride source, the ratio of **34a** to **35a** was not improved. On the other hand, we were very surprised to learn that the use of Ph_3SiH as a hydride source accelerated the reaction rate and improved the ratio of **34** to **35**. The cyclization of **33** with 20 mol % $Ni(cod)_2$ and 40 mol % PPh_3 in the presence of Ph_3SiH in THF was completed within 1 hr at room temperature to give **34b** in 68% yield (93% ee) and **35b** in 9% yield (97% ee). Furthermore, the cyclization of **33** at 0 ℃ gave **34b** in 73% yield (97% ee) and **35b** in 8% yield (99% ee).

These results indicate that the formation of **34** *via* **37A**, which has both a trialkylsiloxy group and a 1-propenyl group on the convex face of the eventual 5-5 bicyclic framework, is preferable to that of **35** *via* **37B**, in which both groups are on the concave face. In the reaction using Ph_3SiH as a hydride source, it is thought that the difference in stability between **37A** and **37B** was greater than that in the reaction using Et_3SiH, and that the selectivity of **34** to **35** was improved.

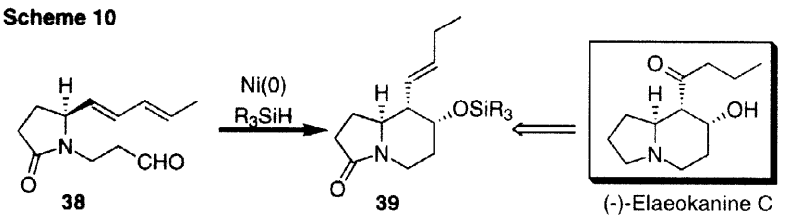
Scheme 9



Synthesis of Indolizidine Derivative —Formal Total Synthesis of (-)-Elaeokanine C

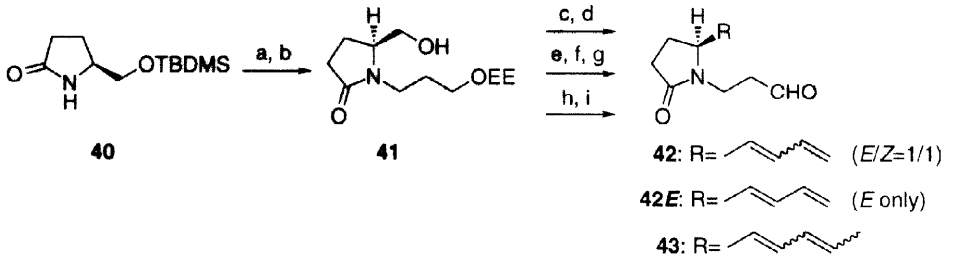
We turned our attention to the synthesis of a natural product. If the cyclization of **38**, which has a substituent on the 1,3-diene moiety, proceeds in a manner similar to the above-mentioned reaction, we should obtain the indolizidine derivative **39**, which could be easily converted into the Elaeocarpus alkaloid, (-)-Elaeokanine C.[14,15]

Scheme 10



The substrates were synthesized as shown in Scheme 11. Initially, the cyclization of **42**, which does not have a methyl group on the terminus of the 1,3-diene moiety, was carried out under similar conditions, and the indolizidine derivatives **45a** and **46a** were obtained in yields of 40% and 38%, respectively (Table 2, run 1). The stereochemistries of **45a** and **46a** were determined by the coupling constants of H_a and H_b, or H_b and H_c from the NMR spectra of **45a** and **46a**, respectively (Figure 1).

Scheme 11[a]



[a] (a) NaH, $Br(CH_2)_3OEE$ (**44**), 89%. (b) TBAF, 87%. (c) (1) Dess-Martin ox.; (2) $CH_2=CHCH_2PPh_3Br$ ^tBuOK; (3) *p*TsOH, MeOH, 23% (3 steps). (d) Dess-Martin ox., 83%. (e) (1) Swern ox.; (2) $Ph_3P=CHCO_2Et$; (3) DIBAL-H, 30% (3 steps). (f) (1) Dess-Martin ox.; (2) Ph_3PCH_3Br, BuLi; (3) *p*TsOH, MeOH, 33% (3 steps). (g) Dess-Martin ox., 86%. (h) (1) Dess-Martin ox.; (2) $CH_3CH=CHCH_2PPh_3Br$, (3) *p*TsOH, MeOH, 46% (3 steps). (i) Dess-Martin ox., 86%.

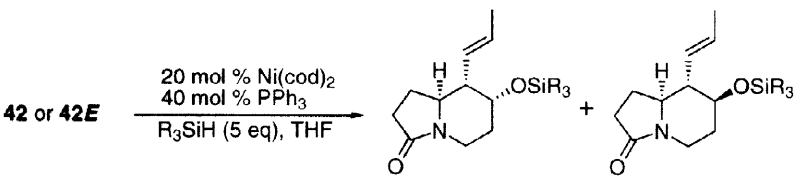
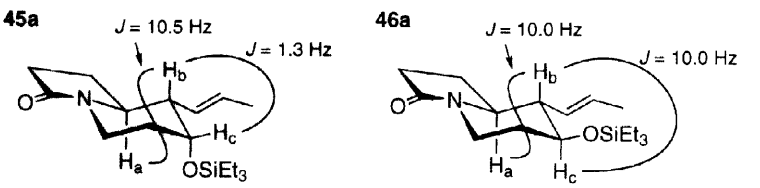


Table 2. Cyclization of **42** under various conditions

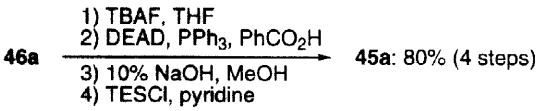
run	substrate	R_3SiH	temp	time (hr)	yield (%) **45**	**46**
1	**42**	Et_3SiH	rt	12	40	38
2	**42**	Ph_3SiH	0 °C	1	39	43
3	**42*E***	Et_3SiH	rt	12	42	40

Figure 1



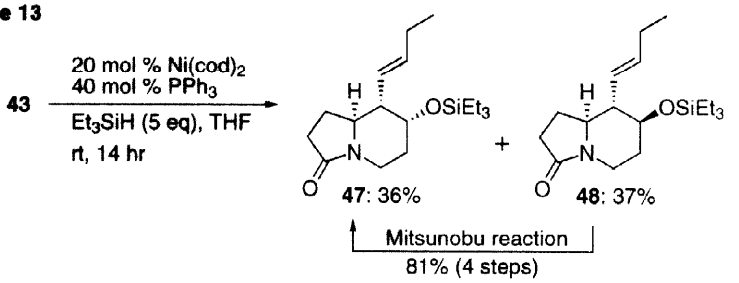
Unfortunately, the use of Ph_3SiH did not improve the ratio of **45b** to **46b** in the construction of the indolizidine skeleton (run 2). To investigate whether the stereoisomers of the cyclized product were produced from the geometric isomers with regard to the 1,3-diene moiety in **42**, the cyclization of **42*E*** was examined. As a result, **45a** and **46a** were obtained in the same ratio as in the cyclization of **42**, which indicates that the geometry of the 1,3-diene moiety does not affect the stereochemistry of the cyclized product. However, we were pleased to find that **46a** was easily transformed into **45a** in 80% yield (4 steps) *via* Mitsunobu inversion (Scheme 12).

Scheme 12



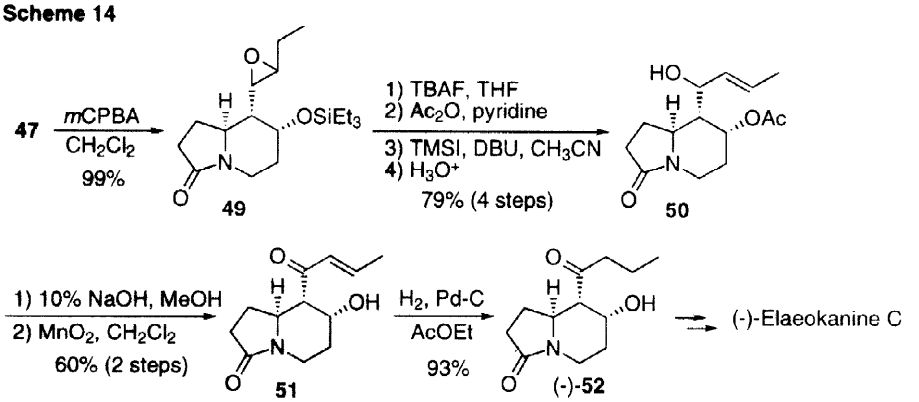
Next, the cyclization of **43**, which has a methyl group on the 1,3-diene moiety, was examined for the synthesis of (-)-Elaeokanine C (Scheme 13). As expected, indolizidine derivatives **47** and **48** were obtained in good yields, and the conversion of **48** to **47** was achieved in 81% yield (4 steps).

Scheme 13



Thus, we tried to synthesize (-)-Elaeokanine C from **47** (Scheme 14). Epoxidation of **47** with *m*CPBA gave epoxide **49** as two inseparable diastereomers. Attempts to rearrange epoxide **49** into the allyl alcohol were fruitless, perhaps due to the bulkiness of the triethylsilyl group. After the triethylsilyl group was replaced by an acetyl group, treatment with TMSI-DBU[16] followed by acidic work-up gave the desired allyl alcohol **50** in 79% yield (4 steps). Deprotection of the acetyl group followed by selective oxidation of the allylic alcohol gave enone **51** as a sole product, which was successively subjected to catalytic hydrogenation with Pd on charcoal to produce (-)-**52**. The total synthesis of (+)-Elaeokanine C (unnatural antipode) from (+)-**52** has been previously reported by Koizumi and co-workers,[15j,k] and all of the spectral data of the synthetic (-)-**52** were identical to those reported for (+)-**52**, except for the sign of $[\alpha]_D$.

Scheme 14



$[\alpha]_D^{24}$ -109.2 (*c* 1.1, $CHCl_3$)

lit. $[\alpha]_D^{26}$ +113.4 (*c* 1.0, $CHCl_3$)

In conclusion, pyrrolidine, piperidine, pyrrolizidine and indolizidine skeletons were successfully constructed in a stereoselective manner by the nickel-catalyzed cyclization of 1,3-diene and aldehyde in a chain. In addition, we applied this method to the formal total synthesis of (-)-Elaeokanine C, which is the first synthesis of this compound in the naturally occurring form.

EXPERIMENTAL SECTION

All manipulations were performed under an argon atmosphere unless otherwise mentioned. THF was distilled under an argon atmosphere from sodium benzophenone ketyl, or was purchased from Kanto Chemical Co., Inc., and used without further purification. All other solvents were distilled under an argon atmosphere from sodium benzophenone ketyl (toluene), CaH_2 (CH_2Cl_2 and DMF), or P_2O_5 (CH_3CN). All other reagents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (70-230 mesh), and flash chromatography was performed on silica gel 60 (230-400 mesh) using the

indicated solvent.

(3*E*)-6-Aza-8-*tert*-butyldimethylsilyloxy-6-(*p*-toluenesulfonyl)-1,3-octadiene (11). To a suspension of NaH (60% wt dispersion in mineral oil, 66.5 mg, 1.66 mmol) in DMF (1 ml) was added a solution of **8** (435 mg, 1.32 mmol) in DMF (4 ml) at 0 ℃, and the mixture was stirred at room temperature for 1 h. A solution of **9** (291 mg, 1.98 mmol) in DMF (2 ml) was added to the mixture at 0 ℃, and the mixture was stirred at room temperature for 20 min. To the mixture was added saturated aq. NH_4Cl and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/Et_2O=8/1) to give **11** (497 mg, 95%) as a colorless oil. IR (neat) 1654, 1600, 1346, 1160 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.9 Hz, 2 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 6.25 (ddd, *J* = 16.7, 10.2, 10.2 Hz, 1 H), 6.09 (dd, *J* = 14.9, 10.2 Hz, 1 H), 5.50 (dt, *J* = 14.9, 6.8 Hz, 1 H), 5.13 (dd, *J* = 16.7, 1.6 Hz, 1 H), 5.08 (dd, *J* = 10.2, 1.6 Hz, 1 H), 3.92 (d, *J* = 6.8 Hz, 2 H), 3.72 (t, *J* = 6.4 Hz, 2 H), 3.22 (t, *J* = 6.4 Hz, 2 H), 2.42 (s, 3 H), 0.87 (s, 9 H), 0.03 (s, 6 H); EI-MS *m/z* 395 (M^+), 338 (M^+-*t*-Bu), 327, 281, 213, 199, 182, 155, 91; EI-HRMS calcd for $C_{16}H_{24}NO_3SSi$ (M^+-*t*-Bu) 338.1242, found 338.1238.

(3*E*)-7-Aza-9-*tert*-butyldimethylsilyloxy-7-(*p*-toluenesulfonyl)-1,3-nonadiene (12). To a solution of **8** (1.52 g, 4.61 mmol) in THF (6 ml) were added PPh_3 (1.43 g, 5.45 mmol), a solution of **10** (411 mg, 4.19 mmol) in THF (4 ml), and diethyl azodicarboxylate (0.73 ml, 4.64 mmol), and the mixture was stirred at room temperature for 2.5 h. To the mixture was added saturated aq. NH_4Cl, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/Et_2O=10/1, 5/1) to give **12** (1.06 g, 62%) as a colorless oil. IR (neat) 1654, 1600, 1342, 1160 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 6.25 (ddd, *J* = 16.9, 10.3, 10.3 Hz, 1 H), 6.04 (dd, *J* = 15.0, 10.3 Hz, 1 H), 5.54 (dt, *J* = 15.0, 7.3 Hz, 1 H), 5.10 (dd, *J* = 16.9, 1.2 Hz, 1 H), 5.00 (dd, *J* = 10.3, 1.2 Hz, 1 H), 3.74 (t, *J* = 6.2 Hz, 2 H), 3.26 (t, *J* = 6.2 Hz, 2 H), 3.24 (t, *J* = 7.3 Hz, 2 H), 2.42 (s, 3 H), 2.36 (dt, *J* = 7.3, 7.3 Hz, 2 H), 0.87 (s, 9 H), 0.04 (s, 6 H); EI-MS *m/z* 394 (M^+-Me), 352, 342, 272, 256, 172, 155, 115, 81; EI-HRMS calcd for $C_{20}H_{32}NO_3SSi$ (M^+-Me) 394.1873, found 394.1874.

(5*E*)-3-Aza-3-(*p*-toluenesulfonyl)-5,7-octadien-1-ol (13). To a solution of **11** (486 mg, 1.23 mmol) in THF (5 ml) was added TBAF (1 *M* solution in THF, 1.9 ml, 1.90 mmol) at 0 ℃, and the mixture was stirred at the same temperature for 15 min. To the mixture was added saturated aq. NH_4Cl, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=2/1, 1/1) to give **13** (339 mg, 98%) as a colorless oil. IR (neat) 3528, 1654, 1600, 1334, 1158 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 6.25 (ddd, *J* = 16.6, 10.1, 10.1 Hz, 1 H), 6.11 (dd, *J* = 14.8, 10.1 Hz, 1 H), 5.51 (dt, *J* = 14.8, 6.8 Hz, 1 H), 5.17 (dd, *J* = 16.6, 1.6 Hz, 1 H), 5.11 (dd, *J* = 10.1, 1.6 Hz, 1 H), 3.90 (d, *J* = 6.8 Hz, 2 H), 3.73 (t, *J* = 5.4 Hz, 2 H), 3.22 (t, *J* = 5.4 Hz, 2 H), 2.44(s, 3 H), 2.16 (br s, 1 H); EI-MS *m/z* 281 (M^+), 250 (M^+-CH_2OH), 184, 155, 126, 91, 67; EI-HRMS calcd for $C_{13}H_{16}NO_2S$ (M^+-CH_2OH) 250.0882, found 250.0861.

(6*E*)-3-Aza-3-(*p*-toluenesulfonyl)-6,8-nonadien-1-ol (14). In a similar manner to that for the synthesis of **13** from **11**, **14** (713 mg, 98%) was synthesized from **12** (1.01 g, 2.47 mmol) and TBAF (1 *M* solution in THF, 3.7 ml, 3.70 mmol). IR (neat) 3526, 1652, 1598, 1336, 1156, 1088 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 6.26 (ddd, *J* = 16.8, 10.3, 10.3 Hz, 1 H), 6.06 (dd, *J* = 15.0, 10.3 Hz, 1 H), 5.56 (dt, *J* = 14.9, 7.4 Hz, 1 H), 5.12 (d, *J* = 16.8 Hz, 1 H), 5.00 (d, *J* = 10.3 Hz, 1H), 3.76 (t, *J* = 5.1 Hz, 2 H), 3.24 (t, *J* = 5.1 Hz, 2 H), 3.22 (t, *J* = 7.4 Hz, 2 H), 2.43 (s, 3 H), 2.36 (dt, *J* = 7.4, 7.4 Hz, 2 H), 2.19 (br s, 1 H); EI-MS *m/z* 296 (M^++H), 295 (M^+), 264, 228, 155, 91, 56; EI-HRMS calcd for 295.1228 $C_{15}H_{21}NO_3S$, found 295.1214.

(5*E*)-3-Aza-3-(*p*-toluenesulfonyl)-5,7-octadienal (15). To a suspension of Dess-Martin reagent (343 mg, 0.810 mmol) in CH_2Cl_2 (3 ml) was added a solution of **13** (114 mg, 0.450 mmol) in CH_2Cl_2 (4.4 ml) at 0 ℃, and the mixture was stirred at room temperature for 1 h. To the mixture were added saturated aq. $NaHCO_3$ and 10% aq. $Na_2S_2O_3$ at 0 ℃. After stirring for 20 min, the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/Et_2O=1/1) to give **15** (102 mg, 90%) as a colorless oil. IR

(neat) 1734, 1654, 1598, 1342, 1160 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.58 (t, J = 1.3 Hz, 1 H), 7.70 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 8.3 Hz, 2 H), 6.26 (ddd, J = 16.8, 10.2, 10.2 Hz, 1 H), 6.09 (dd, J = 15.0, 10.2 Hz, 1 H), 5.51 (dt, J = 15.0, 6.9 Hz, 1 H), 5.19 (d, J = 16.8 Hz, 1 H), 5.14 (d, J = 10.2 Hz, 1 H), 3.85 (d, J = 6.9 Hz, 2 H), 3.80 (d, J = 1.3 Hz, 2 H), 2.45 (s, 3 H); EI-MS m/z 279 (M^+), 278, 198, 184, 155, 139, 123, 91; EI-HRMS calcd for $C_{14}H_{17}NO_3S$ 279.0937, found 279.0944.

(6*E*)-3-Aza-3-(*p*-toluenesulfonyl)-6,8-nonadienal (16). A crude product, which was prepared from **14** (121 mg, 0.409 mmol) and Dess-Martin reagent (347 mg, 0.818 mmol) in a similar manner to that for the synthesis of **15** from **13**, was purified by column chromatography on silica gel (hexane/Et_2O=1/1) to give **16** (107 mg, 89%) as a colorless oil. IR (neat) 1734, 1654, 1598, 1342, 1160 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.61 (t, J = 1.4 Hz, 1 H), 7.79 (d, J = 8.3 Hz, 2 H), 7.32 (d, J = 8.3 Hz, 2 H), 6.25 (ddd, J = 16.9, 10.2, 10.2 Hz, 1 H), 6.05 (dd, J = 15.0, 10.2 Hz, 1 H), 5.53 (dt, J = 15.0, 7.1 Hz, 1 H), 5.12 (d, J = 16.9 Hz, 1 H), 5.03 (d, J = 10.2 Hz, 1 H), 3.82 (d, J = 1.4 Hz, 2 H), 3.26 (t, J = 7.1 Hz, 2 H), 2.44 (s, 3 H), 2.32 (dt, J = 7.1, 7.1 Hz, 2 H); EI-MS m/z 293 (M^+), 266 (M^+-C_5H_7), 226, 212, 155, 139, 91, 81; EI-HRMS calcd for $C_{10}H_{12}NO_3S$ (M^+-C_5H_7) 226.0538, found 226.0538.

(3*E*)-6-Aza-10-*tert*-Butyldimethylsilyloxy-6-(*p*-toluenesulfonyl)-1,3-decadiene (22). In a similar manner to that for the synthesis of **11** from **8**, **22** (516 mg, 80%) was synthesized from **21** (543 mg, 1.52 mmol), **9** (344 mg, 2.34 mmol), and NaH (78.9 mg, 2.00 mmol). IR (neat) 1654, 1598, 1340, 1160 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 2 H), 7.30 (d, J = 8.3 Hz, 2 H), 6.23 (ddd, J = 16.7, 10.2, 10.2 Hz, 1 H), 6.11 (dd, J = 14.7, 10.2 Hz, 1 H), 5.47 (dt, J = 14.7, 6.7 Hz, 1 H), 5.15 (d, J = 16.7 Hz, 1 H), 5.08 (d, J = 10.2 Hz, 1 H), 3.83 (d, J = 6.7 Hz, 2 H), 3.57 (t, J = 6.1 Hz, 2 H), 3.13 (t, J = 6.9 Hz, 2 H), 2.42 (s, 3 H), 1.40-1.65 (m, 4 H), 0.87 (s, 9 H), 0.029 (s, 6 H); EI-MS m/z 408 (M^+-Me), 366, 342, 300, 284, 268, 202, 187, 155, 130, 115, 91; EI-HRMS calcd for $C_{21}H_{34}NO_3SSi$ 408.2009, found 408.1989.

(5*E*)-3-Aza-3-(*p*-toluenesulfonyl)-5,7-octadienal (23). In a similar manner to that for the synthesis of **13** from **11**, (7*E*)-5-aza-5-(*p*-toluenesulfonyl)-7,9-decadien-1-ol (333 mg, 89%) was synthesized from **22** (519 mg, 1.22 mmol) and TBAF (1 *M* solution in THF, 1.9 ml, 1.90 mmol). IR (neat) 3534, 1654, 1600, 1334, 1158 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2 H), 7.29 (d, J = 8.3 Hz, 2 H), 6.24 (ddd, J = 16.8, 10.2, 10.2 Hz, 1 H), 6.10 (dd, J = 14.8, 10.2 Hz, 1 H), 5.47 (dt, J = 14.8, 6.9 Hz, 1 H), 5.15 (d, J = 16.8 Hz, 1 H), 5.09 (d, J = 10.2 Hz, 1 H), 3.83 (d, J = 6.9 Hz, 2 H), 3.64 (dt, J = 5.0, 5.6 Hz, 2 H), 3.15 (t, J = 6.9 Hz, 2 H), 2.42 (s, 3 H), 1.47-1.70 (m, 4 H), 1.34 (t, J = 5.0 Hz, 1 H); EI-MS m/z 309 (M^+), 250, 184, 155, 126, 91, 67; EI-HRMS calcd for $C_{16}H_{23}NO_3S$ 309.1417, found 309.1435. The alcohol (184 mg, 0.595 mmol) was oxidized with Dess-Martin reagent (505 mg, 1.19 mmol) to give **23** (164 mg, 90%) as a colorless oil. IR (neat) 1722, 1654, 1600, 1336, 1158 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.77 (t, J = 1.5 Hz, 1 H), 7.68 (d, J = 8.3 Hz, 2 H), 7.30 (d, J = 8.3 Hz, 2 H), 6.23 (ddd, J = 16.7, 10.2, 10.2 Hz, 1 H), 6.10 (dd, J = 14.6, 10.2 Hz, 1 H), 5.44 (dt, J = 14.6, 6.7 Hz, 1 H), 5.17 (d, J = 16.7 Hz, 1 H), 5.09 (d, J = 10.2 Hz, 1 H), 3.81 (d, J = 6.7 Hz, 2 H), 3.13 (t, J = 6.9 Hz, 2 H), 2.54 (td, J = 7.0, 1.5 Hz, 2 H), 2.42 (s, 3 H), 1.84 (tt, J = 7.0, 6.9 Hz, 2 H); EI-MS m/z 307 (M^+), 250, 224, 152, 134, 108, 67; EI-HRMS calcd for $C_{16}H_{21}NO_3S$ 307.1250, found 307.1258.

(5*S*)-5-Hydroxymethyl-1-[(2*E*)-2,4-pentadienyl]-2-pyrrolidinone (32). A crude product, which was prepared from **31** (937 mg, 5.01 mmol), **9** (956 mg, 6.49 mmol) and NaH (253 mg, 6.31 mmol) in a similar manner to that for the synthesis of **11** from **8**, was purified by column chromatography on silica gel (hexane/AcOEt=3/1, 2/1, 1/1) to give alkylated product (1.12 g, 89%) as a colorless oil. IR (neat) 1686, 1657, 1604, 1134 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.30 (ddd, J = 16.6, 10.5, 9.7 Hz, 1 H), 6.16 (dd, J = 14.9, 10.5 Hz, 1 H), 5.61 (ddd, J = 14.9, 7.5, 5.6 Hz, 1 H), 5.18 (dd, J = 16.6, 1.6 Hz, 1 H), 5.09 (dd, J = 9.7, 1.6 Hz, 1 H), 4.69 (q, J = 5.6 Hz, 1 H), 4.28 (m, 1 H), 3.38-3.79 (m, 6 H), 2.48 (m, 1 H), 2.32 (m, 1 H), 2.11 (m, 1 H), 1.87 (m, 1 H), 1.28 (d, J = 5.6 Hz, 3 H), 1.19 (t, J = 7.1 Hz, 3 H); EI-MS m/z 253 (M^+), 207, 181, 164, 152, 98, 84, 67, 45 ; EI-HRMS calcd for $C_{14}H_{23}NO_3$ 253.1679, found 253.1680. To a solution of the product (497 mg, 1.96 mmol) in MeOH (20 ml) was added *p*-TsOH·H_2O (18.6 mg, 97.8 μmol), and the solution was stirred at room temperature for 15 h. To the solution was added saturated aq. $NaHCO_3$, and MeOH was removed. The aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel to give **32** (334 mg, 94%) as a colorless oil. IR (neat) 3374, 1664, 1600, 1174 cm^{-1}; ^1H NMR (270 MHz,

$CDCl_3$) δ 6.29 (ddd, *J* = 16.3, 10.2, 10.2 Hz, 1 H), 6.17 (dd, *J* = 14.8, 10.2 Hz, 1 H), 5.59 (ddd, *J* = 14.8, 7.6, 5.5 Hz, 1 H), 5.18 (dd, *J* = 16.3, 1.9 Hz, 1 H), 5.08 (dd, *J* = 10.2, 1.7 Hz, 1 H), 4.28 (dd, *J* = 15.5, 5.5 Hz, 1 H), 3.78 (dd, *J* = 11.7, 3.1 Hz, 1 H), 3.59-3.69 (m, 2 H), 3.55 (d, *J* = 11.7 Hz, 1 H), 3.10 (br s, 1 H), 2.45 (ddd, *J* = 17.1, 9.7, 4.7 Hz, 1 H), 2.31 (ddd, *J* = 17.1, 9.8, 5.3 Hz, 1 H), 1.90-2.16 (m, 2 H); EI-MS *m/z* 181 (M^+), 164, 150, 139, 124, 98, 84, 67; EI-HRMS calcd for $C_{10}H_{15}NO_2$ 181.1090, found 181.1077.

(5*S*)-5-Formyl-1-[(2*E*)-2,4-pentadienyl]-2-pyrrolidinone (33). A crude product, which was prepared from **32** (67.5 mg, 0.372 mmol) and Dess-Martin reagent (206 mg, 0.484 mmol) in a similar manner as above, was purified by column chromatography on silica gel (AcOEt) to give **33** (59.3 mg, 89%) as a colorless oil. IR (neat) 2711, 1732, 1686, 1651, 1602 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.57 (d, *J* = 2.4 Hz, 1 H), 6.29 (ddd, *J* = 16.7, 10.1, 10.1 Hz, 1 H), 6.14 (dd, *J* = 14.9, 10.1 Hz, 1 H), 5.44 (ddd, *J* = 14.9, 7.7, 6.3 Hz, 1 H), 5.21 (dd, *J* = 16.7, 1.4, 1 H), 5.12 (dd, *J* = 10.1, 1.4 Hz, 1 H), 4.28 (dd, *J* = 15.3, 6.3 Hz, 1 H), 4.12 (ddd, *J* = 9.3, 4.3, 2.4 Hz, 1 H), 3.74 (dd, *J* = 15.3, 7.7 Hz, 1 H), 2.40-2.49 (m, 2 H), 2.28 (m, 1 H), 1.90-2.13 (m, 1 H); EI-MS *m/z* 179 (M^+), 150, 124, 113, 84, 67, 44; EI-HRMS calcd for $C_{10}H_{13}NO_2$ 179.0931, found 179.0916.

(5*S*)-1-[3-(1-Ethoxyethoxy)propyl]-5-hydroxymethyl-2-pyrrolidinone (41). A crude product, which was prepared from **40** (278 mg, 1.21 mmol) and **44** (383 mg, 1.81 mmol), was purified by column chromatography on silica gel (hexane/AcOEt=1/1, AcOEt) to give (5*S*)-5-*tert*-butyldimethylsilyloxymethyl-1-[3-(1-ethoxyethoxy)propyl]-2-pyrrolidinone (387 mg, 89%) as a colorless oil. IR (neat) 1690, 1112 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.65 (q, *J* = 5.4 Hz, 1 H), 3.54-3.75 (m, 6 H), 3.35-3.54 (m, 2 H), 3.10 (m, 1 H), 2.44 (ddd, *J* = 16.6, 8.9, 8.9 Hz, 1 H), 2.28 (ddd, *J* = 16.6, 9.6, 4.8 Hz, 1 H), 2.05 (m, 1 H), 1.69-1.95 (m, 3 H), 1.29 (d, *J* = 5.4 Hz, 3 H), 1.19 (t, *J* = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.048 (s, 3 H), 0.044 (s, 3 H); EI-MS *m/z* 344 (M^+-Me), 314, 302, 286, 270, 258, 314, 142, 73 ; EI-HRMS calcd for $C_{17}H_{34}NO_4Si$ (M^+-Me) 344.2257, found 344.2257. The product (346 mg, 0.960 mmol) was desilylated with TBAF (1*M* solution in THF, 1.5 ml, 1.50 mmol) to give **41** (206 mg, 87%) as a colorless oil. IR (neat) 3392, 1666, 1058 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.65 (q, *J* = 5.8 Hz, 1 H), 3.84 (br d, *J* = 11.5 Hz, 1 H), 3.25-3.73 (m, 8 H), 2.85 (br s, 1 H), 2.47 (ddd, *J* = 15.6, 10.0, 7.1 Hz, 1 H), 2.30 (ddd, *J* = 15.6, 9.8, 5.8 Hz, 1 H), 1.77-2.20 (m, 4 H), 1.29 (d, *J* = 5.8 Hz, 3 H), 1.19 (t, *J* = 7.0 Hz, 3 H); EI-MS *m/z* 228 (M^+-OH), 214 (M^+-CH_2OH), 200, 172, 156, 142; EI-HRMS calcd for $C_{11}H_{20}NO_3$ (M^+-CH_2OH) 214.1459, found 214.1444.

(5*S*)-1-(3-Formylethyl)-5-(1,3-butadienyl)-2-pyrrolidinone (42). A crude product, which was prepared from **41** (164 mg, 0.667 mmol) and Dess-Martin reagent (566 mg, 1.33 mmol), was dissolved in THF (1 ml). To the cooled solution was added a solution of ylide, which was prepared from allyltriphenylphosophonium bromide (385 mg, 1.00 mmol) and ^{t}BuOK (168 mg, 1.50 mmol) in THF (5 ml), and the mixture was stirred at room temperature for 1 h. To the mixture was added saturated aq. NH_4Cl at 0 ℃, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was treated with *p*-TsOH·H_2O (11.6 mg, 60.9 μmol) in MeOH (1.5 ml) to give (5*S*)-5-(1,3-butadienyl)-1-(3-hydroxypropyl)-2-pyrrolidinone (30.3 mg, 23%, 3 steps) as an inseparable mixture of isomers (*E*/*Z*=1/1). IR (neat) 3414, 1668, 1604, 1258 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*E*)-isomer: δ 6.34 (ddd, *J* = 16.9, 10.3, 10.3 Hz, 1 H), 6.23 (dd, *J* = 15.0, 10.3 Hz, 1 H), 5.50 (dd, *J* = 15.0, 8.9 Hz, 1 H), 5.34 (d, *J* = 16.9 Hz, 1 H), 5.25 (d, *J* = 10.3 Hz, 1 H), 4.04 (ddd, *J* = 8.9, 7.9, 7.9 Hz, 1 H), 3.40-3.70 (m, 4 H), 3.21 (m, 1 H), 2,35-2.55 (m, 2 H), 2.28 (m, 1 H), 1.80 (m, 1 H), 1.55-1.65 (m, 2 H) (*Z*)-isomer: δ 6.64 (ddd, *J* = 16.9, 10.9, 10.9 Hz, 1 H), 6.22 (dd, *J* = 15.0, 9.8 Hz, 1 H), 5.28 (dd, *J* = 9.8, 9.5 Hz, 1 H), 5.27 (d, *J* = 16.9 Hz, 1 H), 5.18 (d, *J* = 10.9 Hz, 1 H), 4.57 (ddd, *J* = 9.5, 7.2, 7.2 Hz, 1 H), 3.40-3.70 (m, 4 H), 3.21 (m, 1 H), 2.35-2.55 (m, 2 H), 2.28 (m, 1 H), 1.80 (m, 1 H), 1.55-1.65 (m, 2 H); EI-MS *m/z* 195(M^+), 178, 167, 164, 150, 140, 136, 122, 94, 67, 59. The alcohol was oxidized with Dess-Martin reagent (281 mg, 0.663 mmol) to give **42** (82.2 mg, 83%) as an inseparable mixture of isomers (*E*/*Z*=1/1). IR (neat) 1722, 1682, 1604 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*E*)-isomer: δ 9.76 (t, *J* = 1.5 Hz, 1 H), 6.34 (ddd, *J* = 16.8, 10.5, 10.5 Hz, 1 H), 6.25 (dd, *J* = 15.1, 10.5 Hz, 1 H), 5.50 (dd, *J* = 15.1, 8.3 Hz, 1 H), 5.36 (d, *J* = 16.8 Hz, 1 H), 5.17 (d, *J* = 10.5 Hz, 1 H), 4.11 (ddd, *J* = 8.3, 5.8, 5.8 Hz, 1 H), 3.71 (m, 1 H), 3.31 (m, 1 H), 2.78 (m, 1 H), 2.61 (m, 1 H), 2.2-2.46 (m, 3 H), 1.74 (m, 1 H) (*Z*)-isomer: δ 9.76 (t, *J* = 1.5 Hz, 1 H), 6.71 (ddd, *J* = 16.7, 10.9, 10.9 Hz, 1 H), 6.22 (dd, *J* = 10.9, 10.9 Hz, 1 H), 5.28 (dd, *J* = 10.9, 9.4 Hz, 1 H), 5.27 (d, *J* = 16.7 Hz, 1 H), 5.25 (d, *J* = 10.9 Hz, 1 H), 4.26 (ddd, *J*

= 9.4, 6.8, 6.8 Hz, 1 H), 3.71 (m, 1 H), 3.31 (m, 1 H), 2.78 (m, 1 H), 2.61 (m, 1 H), 2.2-2.46 (m, 3 H), 1.74 (m, 1 H).

(5*S*)-5-[(*E*)-1,3-Butadienyl]-1-(3-formylethyl)-2-pyrrolidinone (42*E*). To a solution of oxalyl chloride (1.6 ml, 18.3 mmol) in CH_2Cl_2 (35 ml) was added a solution of DMSO (1.3 ml, 18.3 mmol) in CH_2Cl_2 (7 ml) at -78 ℃, and the mixture was stirred at the same temperature for 10 min. To the mixture was added a solution of **41** (3.00 g, 12.2 mmol) in CH_2Cl_2 (8 ml) at -78 ℃, and the mixture was stirred at the same temperature for 10 min. To the mixture was added triethylamine (17 ml, 122 mmol) at -78 ℃ and the temperature was raised to 0 ℃ for 2 h. After usual work up, the crude product was dissolved in benzene (50 ml). To the solution was added Ph_3CHCO_2Et (4.25 g, 12.2 mmol), and the mixture was refluxed for 12 h. The solvent was removed, and the residue was dissolved in toluene and CH_2Cl_2 (toluene:CH_2Cl_2=2:1, 27 ml). To the solution was added DIBAL-H (1.02 *M* solution in toluene, 29.5 ml, 30.0 mmol) at -78 ℃, and the mixture was stirred at the same temperature for 2 h. To the mixture was added a small amount of MeOH at -78 ℃, and the solution was stirred at 0 ℃. To the mixture was added 50% aq. potassium sodium (+)-tartarate tetrahydrate, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (AcOEt, AcOEt/MeOH=20/1) to give (5*S*)-1-[3-(1-ethoxyethoxy)propyl]-5-[(*E*)-3-hydroxy-1-propenyl]-2-pyrrolidinone (1.00 g, 30%, 3 steps). To a suspension of Dess-Martin reagent (2.35 g, 5.53 mmol) in CH_2Cl_2 (22 ml) was added a solution of the alcohol (1.00 g, 3.69 mmol) in CH_2Cl_2 (8 ml) at 0 ℃, and the mixture was stirred at room temperature for 30 min. After usual work up, the crude product was dissolved in THF (1 ml). The solution was added to a cooled solution of ylide, which was prepared from Ph_3PMeBr (1.32 g, 3.69 mmol) and BuLi (1.64 *M* solution in hexane, 2.25 ml, 3.69 mmol) in THF (5 ml), and the mixture was stirred at 0 ℃ for 1 h. To the mixture was added saturated aq. NH_4Cl at 0 ℃, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was treated with *p*-TsOH·H_2O (21.1 mg, 0.111 mmol) in MeOH (1.5 ml) to give (5*S*)-5-[(*E*)-1,3-butadienyl]-1-(3-hydroxypropyl)-2-pyrrolidinone (238 mg, 33%, 3 steps) as a colorless oil. The alcohol (43.7 mg, 0.224 mmol) was oxidized with Dess-Martin reagent (143 mg, 0.336 mmol) to give **42*E*** (37.4 mg, 86%) as a colorless oil, whose spectral data were identical with those of above mentioned **42*E***.

(5*S*)-1-(2-Formylethyl)-5-(1,3-pentadienyl)-2-pyrrolidinone (43). In a similar manner to that for the synthesis of **42** for **41**, a crude product, which was prepared from **41** (1.49 g, 6.09 mmol) and Dess-Martin reagent (3.66 g, 7.92 mmol), was dissolved in THF (5 ml). To the cold solution was added a solution of ylide, which was prepared from crotyltriphenylphosophonium bromide (2.42 g, 6.09 mmol) and ^{t}BuOK (68. mmol, 6.09 mmol) in THF (15 ml), and the mixture was stirred at room temperature for 1 h. After usual work up, the crude product was treated with *p*-TsOH·H_2O (11.6 mg, 60.9 μmol) in MeOH (10 ml) to give (5*S*)-1-(3-hydroxypropyl)-5-(1,3-pentadienyl)-2-pyrrolidinone (582 mg, 46%, 3 steps) as an inseparable mixture of isomers. IR (neat) 3404, 1668, 1655, 1160 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.95-6.60 (m, 4 H), 4.56 (ddd, *J* = 9.9, 6.7, 6.7 Hz, 3/8 H), 3.95-4.17 (m, 5/8 H), 3.76 (t, *J* = 6.7 Hz, 1 H), 3.38-3.65 (m, 3 H), 3.14-3.30 (m, 1 H), 2.20-2.58 (m, 3 H), 1.78 (dd, *J* = 7.2, 1.7 Hz, 3 H), 1.50-1.71 (m, 3 H); EI-MS *m/z* 209 (M^+), 194, 192, 178, 168, 164, 150, 142, 136, 111, 98, 84, 67, 59; EI-HRMS calcd for $C_{12}H_{19}NO_2$ 209.1435, found 209.1454 In a similar manner as above, the alcohol (56.5 g, 0.270 mmol) was oxidized with Dess-Martin reagent (149 mg, 0.351 mmol) to give **43** (48.3 mg, 86%) as an inseparable mixture of isomers. IR (neat) 2728, 1722, 1682, 1656 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.76 (t, *J* = 5.3 Hz, 1 H), 5.08-6.60 (m, 4 H), 4.61 (m, 3/8 H), 4.03-4.17 (m, 5/8 H), 3.70 (m, 1 H), 3.33 (m, 1 H), 2.77 (m, 1 H), 2.60 (m, 1 H), 2.19-2.48 (m, 3H), 1.65-1.83 (m, 4 H); EI-MS *m/z* 207 (M^+), 192, 189, 178, 194, 150, 148, 136, 134, 122, 108, 97, 82, 67, 55; EI-HRMS calcd for $C_{12}H_{17}NO_2$ 207.1247, found 207.1234.

The General Procedure for the Cyclization Using Ni(cod)$_2$ and triethylsilane. To a stirred solution of Ni(cod)$_2$ (0.0560 mmol) and PPh_3 (0.112 mmol) in degassed-THF (3 ml) were added Et_3SiH (1.41 mmol) and a solution of aldehyde (0.280 mmol) in degassed-THF (4 ml) at 0 ℃. The mixture was stirred at room temperature. To the mixture was added saturated aq. NH_4Cl at 0 ℃, and the mixture was stirred at the same temperature for 20 min. The aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel to give the cyclized product.

(3*S,4*S**)-4-[(*E*)-1-Propenyl)]-1-(*p*-toluenesulfonyl)-3-triethylsilyloxypyrrolidine (18).**

A crude product, which was prepared from $Ni(cod)_2$ (12.5 mg, 45.4 μmol), PPh_3 (23.9 mg, 91.1 μmol), Et_3SiH (0.18 ml, 1.13 mmol), and **15** (63.4 mg, 0.227 mmol), was purified by column chromatography on silica gel (hexane/AcOEt=10/1, 5/1) to give **18** (56.0 mg, 63%) as a colorless solid. IR (nujol) 1654, 1346, 1164, 1068 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2 H), 7.29 (d, J = 8.3 Hz, 2 H), 5.48 (dq, J = 15.5, 6.3 Hz, 1 H), 5.28 (ddq, J = 15.5, 8.1, 1.0 Hz, 1 H), 4.08 (dd, J = 3.5, 3.5 Hz, 1 H), 3.49 (dd, J = 11.1, 3.7 Hz, 1 H), 3.46 (dd, J = 8.9, 7.6 Hz, 1 H), 3.17 (dd, J = 11.1, 0.9 Hz, 1 H), 3.09 (dd, J = 10.9, 8.9 Hz, 1 H), 2.56 (dddd, J = 8.1, 7.6, 3.6, 3.6 Hz, 1 H), 2.42 (s, 3 H), 1.62 (dd, J = 6.3, 1.0 Hz, 3 H), 0.81 (t, J = 7.9 Hz, 9 H), 0.48 (q, J = 7.9 Hz, 6 H); EI-MS m/z 395 (M^+), 380, 367, 240, 211, 183, 155, 139, 115, 91, 42; EI-HRMS calcd for $C_{20}H_{33}NO_3SSi$ 395.1963, found 395.1950; mp 75-76 ℃; Anal. Calcd for $C_{20}H_{33}NO_3SSi$: C, 60.72; H, 8.41; N, 3.54; S, 8.10. Found: C, 60.61; H, 8.33; N, 3.42; S, 8.12.

(3*S,4*S**)-3-Hydroxy-4-propyl-1-(*p*-toluenesulfonyl)pyrrolidine (19).** IR (neat) 3512, 1598, 1336, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 4.15 (m, 1 H), 3.47 (dd, J = 9.4, 7.9 Hz, 1 H), 3.41 (dd, J = 11.4, 3.7 Hz, 1 H), 3.34 (br d, J = 11.4 Hz, 1 H), 2.94 (dd, J = 10.8, 9.4 Hz, 1 H), 2.41 (s, 3 H), 1.93 (m, 1 H), 1.72 (br s, 1 H), 1.15-1.50 (m, 4 H), 0.86 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 134.1, 129.6, 127.4, 71.6, 56.5, 50.5, 43.9, 28.4, 21.5, 21.0, 14.0; EI-MS m/z 283 (M^+), 240, 214, 198, 184, 155, 128, 91, 44; EI-HRMS calcd for $C_{14}H_{21}NO_3S$ 283.1230, found 283.1218.

(3*S,4*R**)-4-[(*E*)-1-Propenyl]-1-(*p*-toluenesulfonyl)-3-triethylsilyloxypiperidine (20).** A crude product, which was prepared from $Ni(cod)_2$ (15.4 mg, 56.0 μmol), PPh_3 (29.4 mg, 0.112 mmol), Et_3SiH (0.23 ml, 1.41 mmol), and **16** (82.1 mg, 0.280 mmol), was purified by column chromatography on silica gel (hexane/Et_2O=8/1, 5/1) to give **20** (80.8 mg, 70%) as a colorless solid. IR (nujol) 1596, 1344, 1172, 1108 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, J = 8.2 Hz, 2 H), 7.32 (d, J = 8.2 Hz, 2 H), 5.42 (dq, J = 15.3, 6.4 Hz, 1 H), 5.28 (dd, J = 15.3, 7.7 Hz, 1 H), 3.76 (ddd, J = 11.0, 4.9, 1.9 Hz, 1 H), 3.70 (br d, J = 11.9 Hz, 1 H), 3.41 (ddd, J = 9.7, 9.7, 4.9 Hz, 1 H), 2.41 (s, 3 H), 2.18 (ddd, J = 11.9, 12.2, 2.5 Hz, 1 H), 2.05 (dd, J = 11.0, 9.7 Hz, 1 H), 1.74 (m, 1 H), 1.68 (br d, J = 13.8 Hz, 1 H), 1.64 (d, J = 6.4 Hz, 3 H), 1.51 (dddd, J = 13.8, 12.2, 12.2 4.9 Hz, 1 H), 0.93 (t, J = 8.0 Hz, 9 H), 1.14 (q, J = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 133.3, 131.9, 129.5, 127.6, 126.5, 71.1, 52.4, 47.0, 45.6, 29.6, 21.4, 17.9, 6.7, 4.9; EI-MS m/z 409 (M^+), 380, 254, 155, 115, 87; EI-HRMS calcd for $C_{21}H_{35}NO_3SSi$ 409.2089, found 409.2071; mp 75-76 ℃; Anal. Calcd for $C_{21}H_{35}NO_3SSi$: C, 61.57; H, 8.61; N, 3.42; S, 7.83. Found: C, 61.62; H, 8.62; N, 3.37; S, 7.79.

1-Aza-3-[(*E*)-1-propenyl]-1-(*p*-toluenesulfonyl)-4-triethylsilyloxycycloheptane (24a and 24b). A crude product, which was prepared from $Ni(cod)_2$ (22.3 mg, 0.0811 mmol), PPh_3 (42.5 mg, 0.162 mmol), Et_3SiH (0.32 ml, 2.00 mmol), and **23** (82.1 mg, 0.280 mmol), was purified by preparative thin layer chromatography on silica gel (hexane/Et_2O=20/1) to give **24a** (31.1 mg, 18%) and **24b** (70.7 mg, 41%) as the colorless oils, respectively. **24a**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 2 H), 7.28 (d, J = 8.3 Hz, 2 H), 5.49 (dq, J = 15.6, 6.3 Hz, 1 H), 5.35 (ddq, J = 15.6, 8.3, 1.3 Hz, 1 H), 3.97 (br d, J = 5.8 Hz, 1 H), 3.61 (ddd, J = 12.5, 7.3, 7.3 Hz, 1 H), 3.43 (dd, J = 14.1, 3.5 Hz, 1 H), 2.99 (ddd, J = 12.5, 6.3, 6.3 Hz, 1 H), 2.93 (dd, J = 14.1, 10.8 Hz, 1 H), 2.41 (s, 3 H), 3.37 (m, 1 H), 1.80-2.00 (m, 2 H), 1.60-1.75 (m, 2 H), 1.65 (dd, J = 6.3, 1.3 Hz, 3 H), 0.92 (t, J = 7.8 Hz, 9 H), 0.54 (q, J = 7.8 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 136.9, 130.9, 129.5, 126.9, 126.4, 72.6, 50.8, 48.3, 47.8, 32.3, 26.7, 21.4, 18.1, 6.9, 4.9. **24b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 7.9 Hz, 2 H), 7.29 (d, J = 7.9 Hz, 2 H), 5.52 (dq, J = 15.4, 6.3 Hz, 1 H), 5.44 (ddq, J = 15.4, 8.1, 1.1 Hz, 1 H), 3.62 (ddd, J = 8.0, 5.6, 2.4 Hz, 1 H), 3.23-3.32 (m, 2 H), 3.18 (dd, J = 14.2, 6.8 Hz, 1 H), 3.12 (m, 1 H), 2.4 1 (s, 3 H), 2.30 (m, 1 H), 1.90 (m, 1 H), 1.63-2.82 (m, 2 H), 1.68 (dd, J = 6.3, 1.1 Hz, 3 H), 1.57 (m, 1 H), 0.92 (t, J = 8.0 Hz, 9 H), 0.54 (q, J = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 135.8, 130.8, 129.5, 127.1, 127.0, 74.8, 50.6, 48.1, 47.3, 32.1, 21.5, 21.4, 18.1, 6.8, 4.9.

4-Aza-2-propyl-4-(*p*-toluenesulfonyl)cycloheptanone (25). IR (neat) 1704, 1598, 1338, 1158 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 8.2 Hz, 2 H), 3.67-3.70 (m, 2 H), 2.89 (ddd, J = 13.4, 9.0, 4.5 Hz, 1 H), 2.82 (dd, J = 14.4, 9.8 Hz, 1 H), 2.68 (m, 1 H), 2.56 (ddd, J = 13.4, 9.3, 4.5 Hz, 1 H), 2.47 (m, 1 H), 2.40 (s, 3 H), 1.77-1.87 (m, 2 H), 1.56 (m, 1 H), 1.27-1.40 (m, 3 H), 0.88 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.2, 143.5, 135.8, 129.8, 127.0, 53.4, 50.6, 50.1, 40.6, 31.4, 25.4, 21.4, 20.1, 13.9; EI-MS m/z 309 (M^+), 295, 280, 267, 240, 155, 125, 112; EI-HRMS

calcd for $C_{16}H_{23}NO_3S$ 309.1405, found 309.1399; mp 76-77 °C; Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53; S, 10.36. Found: C, 62.01; H, 7.53; N, 4.41; S, 10.28.

(3*R*,4*R*,5*S*)-1-Aza-3-[(*E*)-1-propenyl]-4-triethylsilyloxybicyclo[3.3.0]octan-8-one (34a). IR (neat) 1702, 1652, 1104 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.41-5.57 (m, 2 H), 3.74-3.86 (m, 3 H), 2.94 (ddd, *J* = 11.7, 7.7, 1.1 Hz, 1 H), 2.54-2.72 (m, 2 H), 2.26-2.40 (m, 2 H), 1.59-1.70 (m, 1 H), 1.68 (dd, *J* = 6.3, 1.5 Hz, 3 H), 0.95 (t, *J* = 7.8 Hz, 9 H), 0.65 (q, *J* = 7.8 Hz, 6 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.1, 127.9, 127.5, 78.6, 68.5, 48.4, 46.4, 33.9, 26.2, 18.0, 6.63, 4.67; EI-MS *m/z* 295 (M^+), 226, 163, 115, 97; EI-HRMS calcd for $C_{16}H_{29}NO_2Si$ 295.1970, found 295.1973.

(3*S*,4*S*,5*S*)-1-Aza-3-[(*E*)-1-propenyl]-4-triethylsilyloxybicyclo[3.3.0]octan-8-one (35a). IR (neat) 1694, 1655, 1116 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.56 (dq, *J* = 15.3, 5.9 Hz, 1 H), 5.44 (ddq, *J* = 15.3, 7.7, 0.74 Hz, 1 H), 3.88-4.01 (m, 2 H), 3.29 (dd, *J* = 10.9, 10.9 Hz, 1 H), 3.17 (ddd, *J* = 10.9, 8.6, 0.88 Hz, 1 H), 2.92 (ddd, *J* = 18.2, 8.6, 3.1 Hz, 1 H), 2.64 (m, 1 H), 2.39 (ddd, *J* = 16.5, 9.8, 3.5 Hz, 1 H), 1.87-2.17 (m, 2 H), 1.69 (dd, *J* = 5.9, 0.74 Hz, 3 H), 0.94 (t, *J* = 7.8 Hz, 9 H), 0.59 (q, *J* = 7.8 Hz, 6 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.3, 128.2, 128.0, 74.5, 67.1, 50.9, 45.0, 34.2, 19.2, 17.9, 6.81, 5.03; EI-MS *m/z* 295 (M^+), 226, 163, 115, 97; EI-HRMS calcd for $C_{16}H_{29}NO_2Si$ 295.1963, found 295.1958.

(3*R*,4*R*,5*S*)-1-Aza-3-[(*E*)-1-propenyl]-4-triphenylsilyloxybicyclo[3.3.0]octan-8-one (34b). IR (neat) 1698, 1654, 1590, 1118 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.58-7.67 (m, 6 H), 7.35-7.51 (m, 9 H), 5.67 (ddq, *J* = 15.4, 8.7, 1.5 Hz, 1 H), 5.44 (dq, *J* = 15.4, 6.3 Hz, 1 H), 4.07 (dd, *J* = 6.3, 4.0 Hz, 1 H), 3.84 (ddd, *J* = 8.7, 7.0, 4.0 Hz, 1 H), 3.80 (dd, *J* = 11.6, 7.2 Hz, 1 H), 3.03 (ddd, *J* = 11.6, 7.8, 0.9 Hz, 1 H), 2.58 (ddd, *J* = 15.0, 7.5, 7.5 Hz, 1 H), 2.46 (m, 1 H), 2.16 (ddd, *J* = 16.4, 9.2, 1.5 Hz, 1 H), 1.81 (m, 1 H), 1.70 (dd, *J* = 6.3, 1.5 Hz, 3 H), 1.32 (m, 1 H) ; EI-MS *m/z* 439 (M^+), 362, 259, 181, 105, 97; EI-HRMS calcd for $C_{28}H_{29}NO_2Si$ 439.1992, found 439.2016.

(3*S*,4*S*,5*S*)-1-Aza-3-[1-(*E*)-propenyl]-4-triphenylsilyloxybicyclo[3.3.0]octan-8-one (35b). IR (neat) 1692, 1648, 1558, 1116 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.55-7.65 (m, 6 H), 7.33-7.49 (m, 9 H), 5.45 (dq, *J* = 15.5, 5.8 Hz, 1 H), 5.35 (dd, *J* = 15.5, 7.0 Hz, 1 H), 4.25 (dd, *J* = 3.0, 3.0 Hz, 1 H), 3.90 (ddd, *J* = 7.2, 7.2, 2.4 Hz, 1 H), 3.48 (dd, *J* = 10.3, 10.3 Hz, 1 H), 3.24 (dd, *J* = 10.3, 10.3 Hz, 1 H), 2.94 (m, 1 H), 2.56 (ddd, *J* = 16.7, 9.7, 9.7 Hz, 1 H), 2.31 (ddd, *J* = 16.7, 10.1, 2.9 Hz, 1 H), 1.97 (m, 1 H), 1.65 (m, 1 H), 1.46 (d, *J* = 5.8 Hz, 3 H); EI-MS *m/z* 439 (M^+), 362, 259, 181, 163, 105, 97, 77; EI-HRMS calcd for $C_{28}H_{29}NO_2Si$ 439.1975, found 439.1983.

(7*R*,8*S*,8a*S*)-8-[(*E*)-1-Propenyl]-7-triethylsilyloxyindolizidin-3-one (45a) and (7*S*,8*S*,8a*S*)-8-[(*E*)-1-Propenyl]-7-triethylsilyloxyindolizidin-3-one (46a) from 42. A crude product, which was prepared from $Ni(cod)_2$ (22.0 mg, 80.0 μmol), PPh_3 (23.1 mg, 0.160 mmol), Et_3SiH (0.32 ml, 2.00 mmol) and **42** (77.3 mg, 0.400 mmol), was purified by preparative thin layer chromatography on silica gel (hexane/AcOEt=3/1) to give **45a** (49.8 mg, 40%) and **46a** (46.4 mg, 38%) as the colorless oils, respectively. **45a**: IR (neat) 1694, 1654, 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.53 (dq, *J* = 15.4, 6.4 Hz, 1 H), 5.38 (ddq, *J* = 15.4, 8.9, 1.4 Hz, 1 H), 3.98 (br s, 1 H), 3.91 (ddd, *J* = 12.9, 5.4, 1.5 Hz, 1 H), 3.65 (ddd, *J* = 10.5, 7.4, 7.4 Hz, 1 H), 3.03 (ddd, *J* = 12.9, 12.9, 3.4 Hz, 1 H), 2.65 (d, *J* = 6.9 Hz, 1 H), 2.62 (d, *J* = 6.9 Hz, 1 H), 2.06 (dddd, *J* = 13.6, 7.4, 6.9, 6.9 Hz, 1 H), 1.75 (ddd, *J* = 10.5, 8.9, 1.8 Hz, 1 H), 1.70 (m, 1 H), 1.69 (dd, *J* = 6.4, 1.4 Hz, 3 H), 1.51-1.57 (m, 2 H), 0.95 (t, *J* = 8.0 Hz, 9 H), 0.55 (q, *J* = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 129.7, 127.9, 68.8, 54.7, 53.1, 34.1, 32.4, 30.3, 23.6, 18.1, 6.82, 4.93; EI-MS *m/z* 309 (M^+), 280, 253, 228, 209, 195, 171, 143, 136, 122, 115, 87; EI-HRMS calcd for $C_{17}H_{31}NO_2Si$ 309.2118, found 309.2112. **46a**: IR (neat) 1694, 1655, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57 (dq, *J* = 15.2, 6.4 Hz, 1 H), 5.10 (ddq, *J* = 15.2, 9.2, 1.5 Hz, 1 H), 4.12 (ddd, *J* = 13.3, 5.2, 1.8 Hz, 1 H), 3.35 (ddd, *J* = 10.0, 10.0, 4.2 Hz, 1 H), 3.21 (ddd, *J* = 10.0, 7.2, 7.2 Hz, 1 H), 2.65 (ddd, *J* = 13.3, 13.3, 2.8 Hz, 1 H), 2.25-2.40 (m, 2 H), 2.08 (m, 1 H), 1.86 (br d, *J* = 13.3 Hz, 1 H), 1.73 (ddd, *J* = 10.0, 10.0, 9.2 Hz, 1 H), 1.69 (dd, *J* = 6.4, 1.5 Hz, 3 H), 1.59-1.67 (m, 1 H), 1.45 (m, 1 H), 0.94 (t, *J* = 8.0 Hz, 9 H), 0.56 (q, *J* = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 129.5, 128.8, 72.5, 59.2, 56.1, 37.6, 34.0, 30.3, 23.4, 18.2, 6.73, 4.98; EI-MS *m/z* 309 (M^+), 280, 254, 228, 209, 195, 171, 143, 136, 122, 115 ; EI-HRMS calcd for $C_{17}H_{31}NO_2Si$ 309.2124, found 309.2124.

(7*R*,8*S*,8a*S*)-8-[(*E*)-1-Propenyl]-7-triphenylsilyloxyindolizidin-3-one (45b) and (7*S*,8*S*,8a*S*)-8-[(*E*)-1-Propenyl]-7-triphenylsilyloxyindolizidin-3-one (46b). A crude product, which

was prepared from $Ni(cod)_2$ (10.1 mg, 36.4 μmol), PPh_3 (19.1 mg, 72.8 μmol), Ph_3SiH (237 mg, 0.910 mmol) and **42** (77.3 mg, 0.400 mmol), was purified by column chromatography on silica gel (hexane/AcOEt=1/1) to give inseparable mixture of **45b** and **46b** (67.7 mg, 82%, **45b/46b**=1/1.1). ^1H NMR (500 MHz, $CDCl_3$) **45b**: δ 7.60-7.63 (m, 6 H), 7.42-7.46 (m, 3 H), 7.36-7.40 (m, 6 H), 5.45 (dq, *J* = 15.4, 6.1 Hz, 1 H), 5.36 (dd, *J* = 15.4, 8.7 Hz, 1 H), 4.24 (br s, 1 H), 4.04 (ddd, *J* = 13.5, 5.0, 1.7 Hz, 1 H), 3.87 (ddd, *J* = 10.6, 7.5, 7.5 Hz, 1 H), 3.17 (ddd, *J* = 12.9, 12.9, 3.0 Hz, 1 H), 2.23-2.42 (m, 2 H), 2.01 (m, 1 H), 1.89 (br d, *J* = 12.9 Hz, 1 H), 1.78 (m, 1 H), 1.58-1.69 (m, 1 H), 1.50-1.60 (m, 1 H), 1.53 (d, *J* = 6.1 Hz, 3 H) **46b**: δ 7.60-7.63 (m, 6 H), 7.42-7.46 (m, 3 H), 7.36-7.40 (m, 6 H), 5.63 (dq, *J* = 15.1, 6.5 Hz, 1 H), 4.84 (dd, *J* = 15.1, 9.1 Hz, 1 H), 3.89 (m, 1 H), 3.67 (ddd, *J* = 10.8, 10.8, 4.3 Hz, 1 H), 3.07 (ddd, *J* = 10.8, 7.1, 7.1 Hz, 1 H), 2.47 (ddd, *J* = 13.3, 13.3, 2.2 Hz, 1 H), 2.23-2.42 (m, 2 H), 2.13 (m, 1 H), 1.95 (ddd, *J* = 9.8, 9.8, 9.8 Hz, 1 H), 1.65-1.75 (m, 1 H), 1.60 (d, *J* = 6.5 Hz, 3 H), 1.41 (m, 1 H).

(7*R*,8*S*,8a*S*)-8-[(*E*)-1-Butenyl]-7-triethylsilyloxyindolizidin-3-one (47) and (7*S*,8*S*,8a*S*)-8-[(*E*)-1-Butenyl]-7-triethylsilyloxyindolizidin-3-one (48). A crude product, which was prepared from $Ni(cod)_2$ (12.1 mg, 44.0 μmol), PPh_3 (23.1 mg, 88.1 μmol), Et_3SiH (0.175 ml, 1.10 mmol) and **43** (45.6 mg, 0.220 mmol), was purified by preparative thin layer chromatography on silica gel (hexane/AcOEt=3/1) to give **47** (25.5 mg, 36%) and **48** (26.5 mg, 37%) as the colorless oils, respectively. **47**: IR (neat) 1696, 1656, 1058 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.56 (dt, *J* = 5.5, 6.3 Hz, 1 H), 5.35 (ddt, *J* = 15.5, 9.0, 1.3 Hz, 1 H), 3.98 (br s, 1 H), 3.90 (ddd, *J* = 13.0, 5.3, 1.3 Hz, 1 H), 3.63 (ddd, *J* = 10.5, 7.2, 7.2 Hz, 1 H), 3.03 (ddd, *J* = 13.0, 13.0, 3.3 Hz, 1 H), 2.31 (d, *J* = 7.2 Hz, 1 H), 2.29 (d, *J* = 7.2 Hz, 1 H), 2.04 (dq, *J* = 6.3, 7.3 Hz, 2 H), 2.02 (m, 1 H), 1.74 (ddd, *J* = 10.6, 8.9, 1.7 Hz, 1 H), 1.69 (br d, *J* = 13.6 Hz, 1 H), 1.50-1.56 (m, 2 H), 0.97 (t, *J* = 7.3 Hz, 3 H), 0.95 (t, *J* = 8.0 Hz, 9 H), 0.58 (q, *J* = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 135.2, 127.3, 69.8, 54.7, 53.2, 34.1, 32.4, 30.3, 25.7, 23.5, 13.5, 6.84, 4.94; EI-MS *m/z* 323 (M^+), 294, 267, 238, 228, 209, 171, 136, 115, 96; EI-HRMS calcd for $C_{18}H_{33}NO_2Si$ 323.2252, found 323.2224; $[\alpha]_D^{21}$ -90.6 (*c* 1.02, $CHCl_3$). **48**: IR (neat) 1698, 1654, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57 (dt, *J* = 15.3, 6.3 Hz, 1 H), 5.08 (dd, *J* = 15.3, 8.9 Hz, 1 H), 4.11 (ddd, *J* = 13.3, 5.0, 1.5 Hz, 1 H), 3.49 (ddd, *J* = 10.2, 9.9, 4.1 Hz, 1 H), 3.20 (ddd, *J* = 9.2, 7.2, 7.2 Hz, 1 H), 2.64 (ddd, *J* = 13.3, 13.3, 2.5 Hz, 1 H), 2.35 (ddd, *J* = 17.1, 5.1, 5.1 Hz, 1 H), 2.29 (dd, *J* = 17.1, 9.3 Hz, 1 H), 2.06 (m, 1 H), 2.03 (dq, *J* = 6.3, 7.5 Hz, 2 H), 1.85 (br d, *J* = 12.9 Hz, 1 H), 1.72 (ddd, *J* = 9.9, 9.9, 8.9 Hz, 1 H), 1.63 (m, 1 H), 1.43 (m, 1 H), 0.98 (t, *J* = 7.5 Hz, 3 H), 0.92 (t, *J* = 8.0 Hz, 9 H), 0.55 (q, *J* = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 136.5, 126.5, 72.6, 59.2, 56.0, 37.6, 34.0, 30.3, 25.8, 23.3, 13.4, 6.8, 5.0; EI-MS *m/z* 323 (M^+), 294, 267, 238, 228, 209, 171, 136, 115, 96; EI-HRMS calcd for $C_{18}H_{33}NO_2Si$ 323.2275, found 323.2270; $[\alpha]_D^{26}$ -47.9 (*c* 1.18, $CHCl_3$).

Transformation of 48 into 47 by Mitsunobu Reaction. To a solution of an alcohol (46.4 mg, 0.220 mmol), which was prepared from **48** by desilylation with TBAF, in THF (4 ml) were added PPh_3 (300 mg, 1.14 mmol), benzoic acid (140 mg, 1.14 mmol), and diethyl azodicarboxylate (0.18 ml, 1.14 mmol), and the mixture was stirred at room temperature for 2 h. To the mixture was added saturated aq. $NaHCO_3$, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated, which was dissolved in MeOH (1 ml). To the solution was added 10% aq. NaOH (1 ml) at 0 ℃, and the mixture was stirred at room temperature for 4.5 h. The aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (AcOEt, AcOEt/MeOH=10/1) to give (7*R*,8*S*,8a*S*)-7-hydroxy-8-[(*E*)-1-propenyl]indolizidin-3-one (40.6 mg, 93%, 2 steps). To a solution of the deacylated product (40.6 mg, 0.194 mmol) in pyridine (1 ml) was added Et_3SiCl (50 μl, 0.298 mmol) at 0 ℃, and the mixture was stirred at room temperature for 14 h. To the mixture was added saturated aq. NH_4Cl at 0 ℃, and the aqueous layer was extracted with AcOEt. The organic layer was washed with 10% HCl, saturated aq. $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (AcOEt, AcOEt/MeOH=10/1) to give **47** (62.6 mg, 100%).

(7*R*,8*R*,8a*S*)-8-(1,2-Epoxybutyl)-7-triethylsilyloxyindolizidin-3-one (49). To a solution of **47** (143 mg, 0.442 mmol) in CH_2Cl_2 (5 ml) was added *m*CPBA (226 mg, 1.31 mmol) at 0 ℃, and the mixture was stirred at room temperature for 6 h. To the mixture were added saturated aq. $NaHCO_3$ and saturated aq. $Na_2S_2O_3$ at 0 ℃. After the mixture was stirred at room temperature for 2 h, the aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue

was purified by column chromatography on silica gel (AcOEt) to give **49** (149 mg, 99%) as an inseparable mixture of isomers. IR (neat) 1694, 1234 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.27 (br s, 3/4 H), 4.17 (br s, 1/4 H), 3.85-3.95 (m, 2/4 H), 3.91 (dd, *J* = 13.0, 5.5 Hz, 3/4 H), 3.73 (ddd, *J* = 10.6, 7.6, 7.6 Hz, 3/4 H), 3.04 (ddd, *J* = 13.0, 12.8, 3.1 Hz, 3/4 H), 3.01 (ddd, *J* = 12.8, 12.8, 3.8 Hz, 1/4 H), 2.80 (dd, *J* = 8.4, 2.1 Hz, 1/4 H), 2.75 (dt, *J* = 2.1, 5.5 Hz, 3/4 H), 2.68 (dt, *J* = 2.1, 6.1 Hz, 1/4 H), 2.66 (dd, *J* = 8.6, 2.1 Hz, 3/4 H), 2.30-2.35 (m, 2 H), 2.18 (m, 1 H), 1.35-1.90 (m, 6 H), 1.00 (t, *J* = 7.5 Hz, 3/4 H), 0.97 (t, *J* = 8.0 Hz, 9 H) , 0.96 (t, *J* = 7.6 Hz, 9/4 H), 0.64 (q, *J* = 8.0 Hz, 6 H); EI-MS *m/z* 339 (M^+), 323, 310, 280, 225, 136, 115, 87; EI-HRMS calcd for $C_{18}H_{33}NO_3Si$ 339.2232, found 339.2234.

(7*R*,8*R*,8a*S*)-7-Acetoxy-8-[(*E*)-1-hydroxy-2-butenyl]indolizidin-3-one (50). After desilylation of **49** with TBAF, the product (63.2 mg, 0.281 mmol) was dissolved in pyridine (1 ml). To the solution were added Ac_2O (53 μl, 0.480 mmol) and DMAP (1.7 mg, 13.9 μmol), and the mixture was stirred at room temperature for 6 h. After usual work up, the residue was purified by column chromatography on silica gel (AcOEt/MeOH=15/1) to give acetylated product (75.2 mg, 100%) as an inseparable mixture of isomers. IR (neat) 1740, 1690, 1240 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.32 (br s, 14/19 H), 5.29 (br s, 5/19 H), 4.03 (dd, *J* =13.9, 6.1 Hz, 5/19 H), 4.01 (dd, *J* = 13.5, 6.0 Hz, 14/19 H), 3.83 (ddd, *J* = 10.6, 7.0, 7.0 Hz, 5/19 H), 3.51 (ddd, *J* = 10.8, 7.5, 7.5 Hz, 14/19 H), 2.90 (ddd, *J* = 13.9, 13.9, 3.2 Hz, 5/19 H), 2.87 (ddd, *J* = 13.5, 13.5, 3.2 Hz, 14/19 H), 2.80 (dt, *J* = 2.2, 5.7 Hz, 14/19 H), 2.70 (dt, *J* = 2.0, 5.6 Hz, 5/19 H), 2.61 (dd, *J* = 7.9, 2.2 Hz, 14/19 H), 2.57 (dd, *J* = 7.9, 2.0 Hz, 5/19 H), 2.35-2.43 (m, 2 H), 2.25 (m, 1 H), 2.11 (s, 42/19 H), 2.10 (s, 15/19 H), 2.07 (m, 14/19 H), 1.95 (m, 5/19 H), 1.47-1.70 (m, 4 H), 1.23 (m, 14/19 H), 1.12 (m, 5/19 H), 1.02 (t, *J* = 7.5 Hz, 42/19 H), 0.96 (t, *J* = 7.4 Hz, 15/19 H); EI-MS *m/z* 268 (M^++H), 238, 207, 196, 178, 166, 150, 138, 96, 84; EI-HRMS calcd for $C_{14}H_{22}NO_4$ (M^++H) 268.1554, found 268.1559. To a solution of the acetate (96.0 mg, 0.359 mmol) in CH_3CN (2 ml) were added TMSI (0.11 ml, 0.773 mmol) and DBU (0.27 ml, 1.81 mmol) at 0 ℃, and the mixture was refluxed for 6.5 h. To the mixture was added 1% HCl at 0 ℃, and the mixture was stirred at the same temperature for 30 min. The aqueous layer was extracted with AcOEt. The organic layer was washed with saturated aq. $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (AcOEt/MeOH=20/1) to give **50** (75.4 mg, 79%) as an inseparable mixture. IR (neat) 3394, 1738, 1668, 1654 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.71 (dq, *J* = 15.1, 6.1 Hz, 16/21 H), 5.61 (dq, *J* = 14.8, 6.4 Hz, 5/21 H), 5.54 (ddd, *J* = 15.1, 7.4, 1.2 Hz, 16/21 H), 5.45-5.51 (m, 1H), 5.21 (br s, 5/21 H), 3.95-4.19 (m, 2 H), 3.72 (ddd, *J* = 10.5, 6.7, 6.7 Hz, 16/21 H), 3.70 (ddd, *J* = 10.6, 6.6, 6.6 Hz, 5/21 H), 2.87 (ddd, *J* = 13.2, 13.2, 3.2 Hz, 16/21 H), 2.82 (ddd, *J* = 12.3, 12.3, 3.4 Hz, 5/21 H), 2.20-2.48 (m, 3 H), 2.10 (s, 48/21 H), 2.05 (s, 15/21 H), 2.04 (br s, 1 H), 1.99 (m, 1 H), 1.72 (dd, *J* = 6.1, 1.2 Hz, 48/21 H), 1.69 (dd, *J* = 6.4, 1.3 Hz, 15/21 H), 1.45-1.70 (m, 3 H) ; EI-MS *m/z* 267 (M^+), 249, 224, 207, 190, 164, 153, 136, 107, 96, 84; EI-HRMS calcd for $C_{14}H_{21}NO_4$ 267.1457, found 267.1444.

(7*R*,8*S*,8a*S*)-7-Hydroxy-8-(2-butenoyl)indolizidin-3-one (51). To a solution of **50** (54.2 mg, 0.203 mmol) in MeOH (1 ml) was added 10% aq. NaOH (0.1 ml) at 0 ℃, and the mixture was stirred at the same temperature for 1.5 h. The aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (AcOEt/MeOH=20/1) to give deacylated product (42.8 mg, 94%) as a colorless oil. IR (neat) 3344, 1664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (dq, *J* = 15.0, 6.4 Hz, 3/4 H), 5.74 (dq, *J* = 15.4, 6.6 Hz, 1/4 H), 5.65 (dd, *J* = 15.0 , 6.2 Hz, 3/4 H), 5.61 (dd, *J* = 15.4, 6.2 Hz, 1/4 H), 4.44 (br s, 1 H), 4.37 (m, 3/4 H), 4.27 (m, 1/4 H), 4.05 (ddd, *J* = 10.9, 7.4 , 7.4 Hz, 1 H) , 3.94 (ddd, *J* = 12.8, 5.3, 1.0 Hz, 1 H), 3.32 (br s, 1 H), 3.10 (ddd, *J* = 12.8, 12.8, 3.3 Hz, 3/4 H), 3.04 (ddd, *J* = 12.8, 12.8, 3.4 Hz, 1/4 H), 2.77 (br d, *J* = 4.7 Hz, 1 H), 2.25-2.43 (m, 3 H), 1.83 (br d, *J* = 13.8 Hz, 1 H), 1.75 (d, *J* = 6.4 Hz, 9/4 H), 1.72 (d, *J* = 6.6 Hz, 3/4 H), 1.40-1.70 (m, 3 H) ; EI-MS *m/z* 225 (M^+), 207, 192, 182, 178, 164, 153, 136, 125, 110, 98, 84, 71; EI-HRMS calcd for $C_{12}H_{19}NO_3$ 225.1370, found 225.1375. To a solution of the product (42.8 mg, 0.190 mmol) was added MnO_2 (496 mg, 0.700 mmol), and the mixture was stirred at room temperature for 23 h. After the catalyst was filtered off, the filtrate was concentrated. The residue was purified by column chromatography on silica gel (AcOEt/MeOH=15/1) to give **51** (27.3 mg, 64%) as a colorless solid. IR (nujol) 3284, 1675, 1660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.01 (dq, *J* = 15.6, 6.9 Hz, 1H), 6.25 (dq, *J* = 15.6, 1.5 Hz, 1 H), 4.30 (br s, 1 H), 4.07 (ddd, *J* = 10.7, 7.2, 7.2 Hz, 1 H), 3.98 (ddd, *J* = 13.2, 5.6, 1.3 Hz, 1 H), 3.13 (ddd, *J* = 13.2, 13.2, 3.4 Hz, 1 H), 3.11 (br s, 1 H), 2.72 (dd, *J* = 10.7, 1.7 Hz, 1 H), 2.35-2.40 (m,

2 H), 2.20 (m, 1 H), 1.98 (dd, J = 6.9, 1.5 Hz, 3 H), 1.93 (br d, J = 14.1 Hz, 1 H), 1.51-1.60 (m, 2 H); EI-MS *m/z* 223 (M^+), 205, 178, 164, 124, 111, 95, 83, 69, 55; EI-HRMS calcd for $C_{12}H_{17}NO_3$ 223.1229, found 223.1249; mp 158-160 ℃; $[\alpha]_D^{21}$ -129.5 (*c* 1.09, $CHCl_3$).

(7*R*,8*S*,8a*S*)-8-Butyryl-7-hydroxyindolizidin-3-one (52). To a solution of **51** (25.6 mg, 0.115 mmol) in AcOEt (2 ml) was added 10% Pd-C (6.1 mg, 5.73 mmol), and the mixture was stirred under hydrogen (1 atm) at room temperature for 18 h. After the catalyst was filtered off, the filtrate was concentrated. The residue was purified by column chromatography on silica gel (AcOEt/MeOH=15/1) to give **52** (24.2 mg, 93%) as a colorless solid, whose spectral data were identical with those reported by Koizumi, except for the sign of $[\alpha]_D$. $[\alpha]_D^{24}$ -109.2 (*c* 1.1, $CHCl_3$).

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