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APPLICATION OF SAMARIUM DIIODIDE-PROMOTED REDUCTIVE CARBON-NITROGEN BOND CLEAVAGE REACTION TO 3-OXOPYRROLIDINE DERIVATIVES: ALTERNATIVE SYNTHESIS OF A COCCINELLID ALKALOID, (-)-ADALININE†

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Abstract – Samarium diiodide-promoted reductive deamination reaction was applied to 5,5-disubstitued 3-oxopyrrolidines to provide 4,4-disubstituted 4-aminobutan-2-one derivatives, where the carbon-nitrogen bond cleavage took place at the desired position, regioselectively. This strategy was exploited in the synthesis of a coccinellid alkaloid, (-)-adalinine.

INTRODUCTION

In 1999, we have developed a novel carbon-nitrogen bond cleavage reaction of α-amino carbonyl compounds by using samarium diiodide (SmI_2) as a one-electron transfer reagent.[1] Thereafter, this strategy was recognized to be a general and widely applicable synthetic tool for the synthesis of various types of naturally occurring alkaloids,[2] in which proline derivatives have mainly been employed as the chiral starting materials. The plausible mechanism for the fragmentation was depicted in Figure 1 as exemplified by the reaction of α-amino esters with samarium diiodide, where samarium-containing 5-membered intermediates might be involved as the active species.

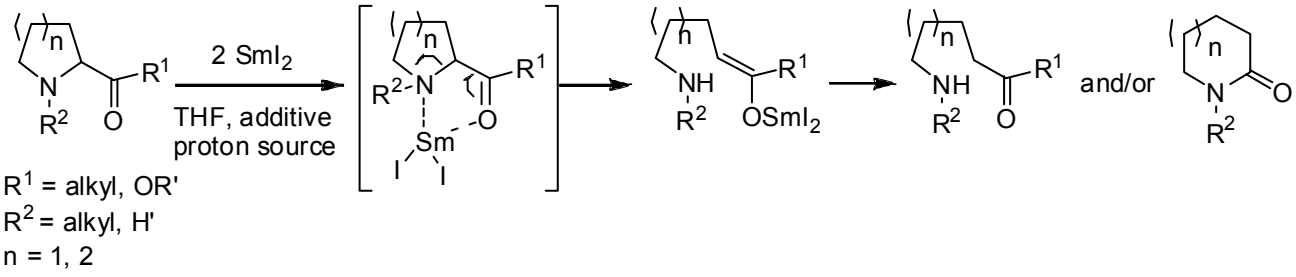


Figure 1. Proposed mechanism for a regioselective C-N bond fragmentation of α-aminocarbonyl compounds with SmI_2

To extend the usefulness of this strategy, we decided to apply a SmI_2-promoted fragmentation reaction to a 3-oxopyrrolidine derivative with expectation of a bond cleavage between the 1(N) and 2(C) positions, siteselectively, since an obtained product would be a suitable precursor for the synthesis of coccinellid alkaloids adalinine (**1**) and adaline (**2**) as shown in Figure 2.

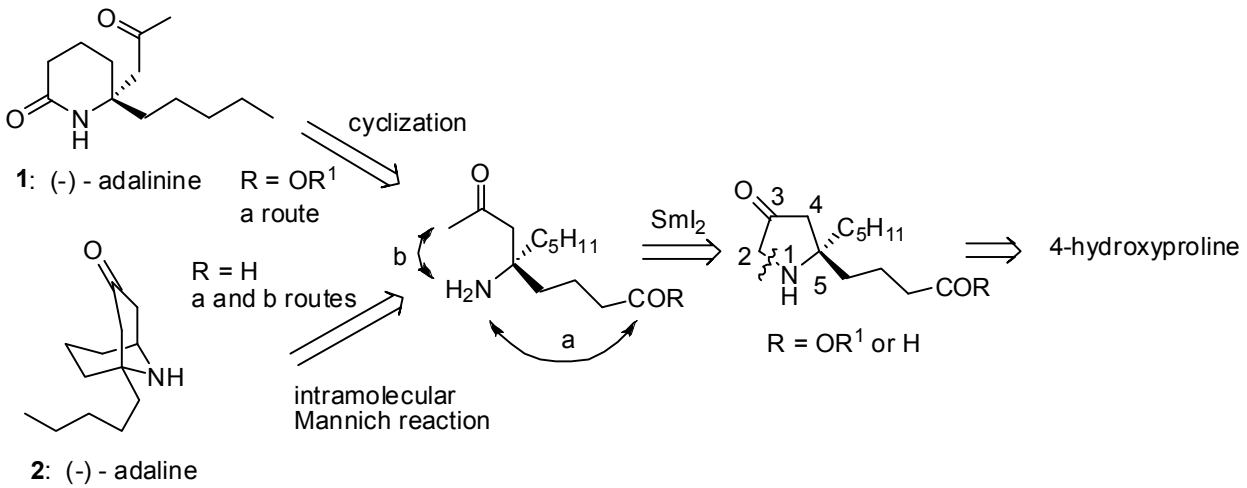
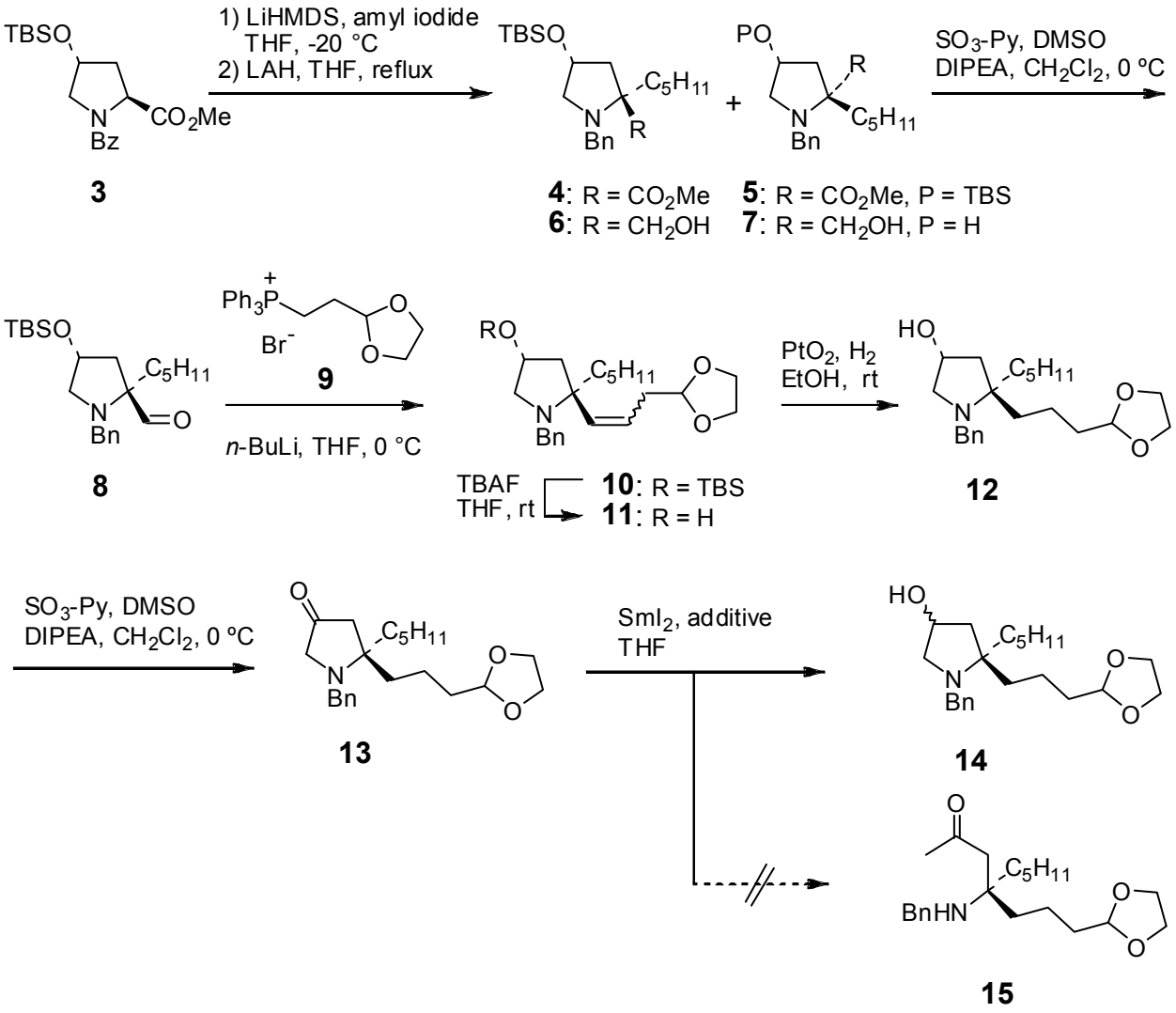


Figure 2. Synthetic plan for coccinellid alkaloids

RESULTS AND DISCUSSION‡

Thus, the precursors having a quaternary carbon center at the 5-position for a SmI_2-promoted fragmentation reaction were prepared starting from (4*R*)-hydroxyproline as follows.

First, we decided to synthesize a 3-oxopyrrolidine derivative possessing (1,3-dioxolan-2-yl)propyl group at the 5-position as the precursor for the synthesis of (-)-adalinine (**1**).[3] Alkylation of methyl (4*R*)-[*N*-benzoyl-4-*tert*-butyldimethylsilyloxy]prolinate (**3**)[4] with amyl iodide in the presence of LiHMDS in THF gave alkylated compounds as an inseparable mixture of diastereoisomers (**4** and **5**) in 99% yield, in a ratio of *ca*. 3:2. Reduction of the mixture with $LiAlH_4$ afforded *N*-benzylated alcohols (**6** and **7**) in 45 and 22% yields from **3**, respectively, where desilylation of the secondary hydroxyl group on 2*S*-isomer (**7**) occurred leading to determination of its stereostructure.[5] Swern oxidation of 2*R*-derivative (**6**), followed by Wittig condensation of the resulting aldehyde (**8**) with the phosphonium bromide (**9**) gave alkene (**10**) in 90% yield. After desilylation of **10** with TBAF, the resulting alcohol (**11**) was reduced to the secondary alcohol (**12**) by catalytic reduction over platinum oxide. Oxidation of **12** with sulfur trioxide gave the desired ketone (**13**) in 66% yield from **10**. With the requisite precursor in hand, we attempted a SmI_2-promoted carbon-nitrogen bond cleavage reaction of **13** in appropriate solvent in the presence of several kinds of additives. However, the desired fragmentation product (**15**) was not obtained under the reaction conditions investigated, and an inseparable mixture of the reduction products (**14**) was isolated as the major products (Scheme 1).



Scheme 1. SmI_2-promoted fragmentation of **13**

It would be conceivable, based upon examination of proposed reaction mechanism for a regioselective carbon-nitrogen bond fragmentation of α-amino carbonyl compounds with SmI_2, that a participation of samarium metal in forming a cyclic intermediate between carbonyl and amino functions might play an important role to accelerate the fragmentation as shown in Figure 1. However, a formation of such samarium-involved 5-membered intermediate seems to be sterically disfavor for **13** leading to reduction of ketone carbonyl to give the corresponding secondary alcohols **14** as the major products (Figure 3).

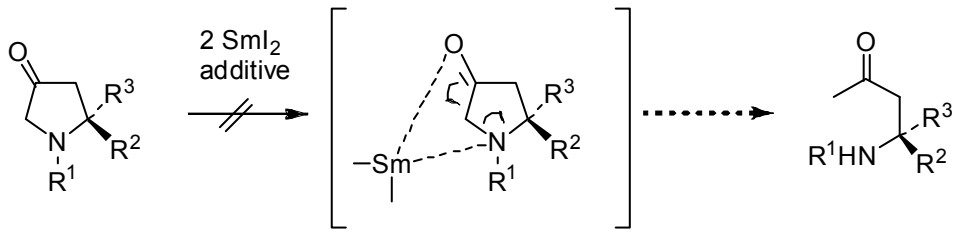
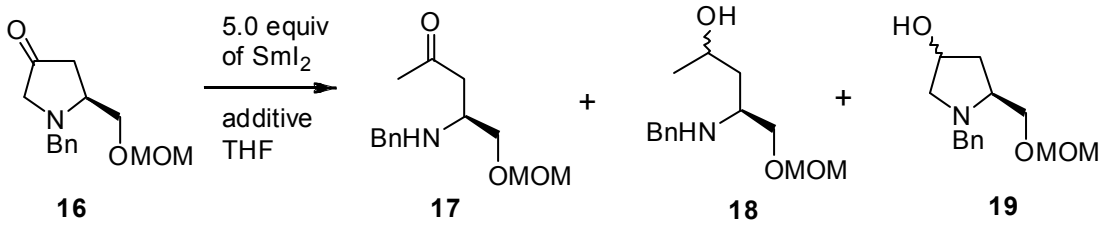


Figure 3. Reaction of 3-oxopyrrolidines with SmI_2

Given these considerations, we sought to prepare the known 3-oxopyrrolidine derivative (**16**)[6] having a functional group at the 5-position that can generate a reasonably tight coordination with samarium metal. SmI_2-promoted carbon-nitrogen bond cleavage reaction of **16** was investigated under several reaction conditions, and the results obtained were summarized in Table 1.

Treatment of **16** with 5 equivalents of SmI_2 in THF in the presence of HMPA and MeOH as an additive and a proton source, respectively, at 0 °C for 5 min afforded the secondary alcohols (**19**) in 88% yield (Entry 1). By changing the proton source to *N,N*-dimethylaminoethanol (DMEA), the similar reaction gave the fragmentation product with further reduction of the carbonyl group to furnish the secondary amine (**18**), as an inseparable mixture of the diastereoisomers, in 42% yield (Entry 2).

Table 1. SmI_2-promoted C-N fragmentation of **16**



16 **17** **18** **19**

Entry	Additive (equiv)	Time	Temp. (°C)	Product	Yield (%)
1	HMPA (5.0) + MeOH (2.5)	5 min	0	**19**	88
2	DMEA (10.0)	10 min	0	**18**	42
3	MeOH (2.5)	1 h	0	**17**	44
4	MeOH (2.5)	3 h	-78	**19**	63

By using MeOH as a proton source in the absence of HMPA, the desired ketone (**17**) could be isolated from the reaction mixture in 44% yield. When this reaction was carried out at -78 °C for 3 h, the reduction product (**19**) was again isolated in 63% yield. Similar reaction at room temperature afforded the reduction product (**19**) as the sole isolable product. It is reasonably assumed that the reaction of **16** with SmI_2 would probably proceed through the chelation intermediate to facilitate the desired fragmentation as depicted in Figure 4.

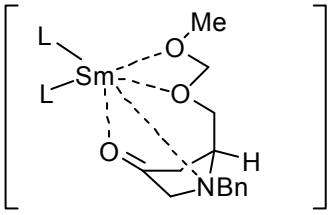
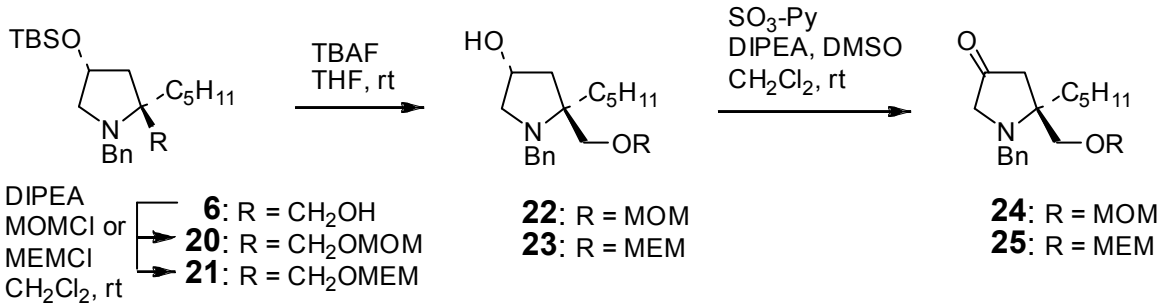


Figure 4. Assumed chelation intermediate for the fragmentation of **16**

Next, we attempted to find the best proton source for 5,5-disubstituted 3-oxopyrrolidine derivative having

a similar substitution pattern to the target natural product.

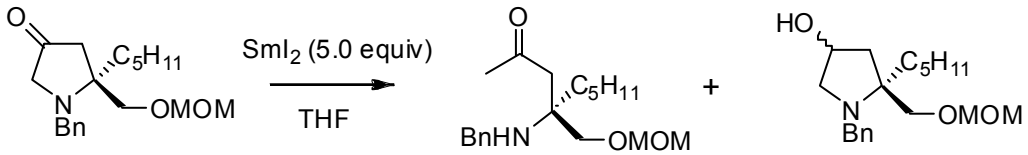
The ketone (**24**) as the model compound was prepared as follows. Methoxymethylation of **6** gave its MOM ether (**20**), which on treatment with TBAF afforded the secondary alcohol (**22**). Oxidation of **22** provided the desired ketone (**24**). The corresponding MEM ether (**25**) was also prepared from **6** by the similar procedures via **21** and **23**, as described for **24**.



Scheme 2. Preparation of **24** and **25**

First, the fragmentation of **24** was carried out by using SmI_2 (5.0 equivalents) in THF-HMPA at 0 °C for 15 h, however, only decomposition of the starting material was observed (Entry 1). We note in advance that proton sources play an important role in this fragmentation reaction. We, therefore, decided to find the best proton source in THF solution by screening, and the results obtained were summarized in Table 2.

Table 2. Screening of proton sources for SmI_2-promoted fragmentation

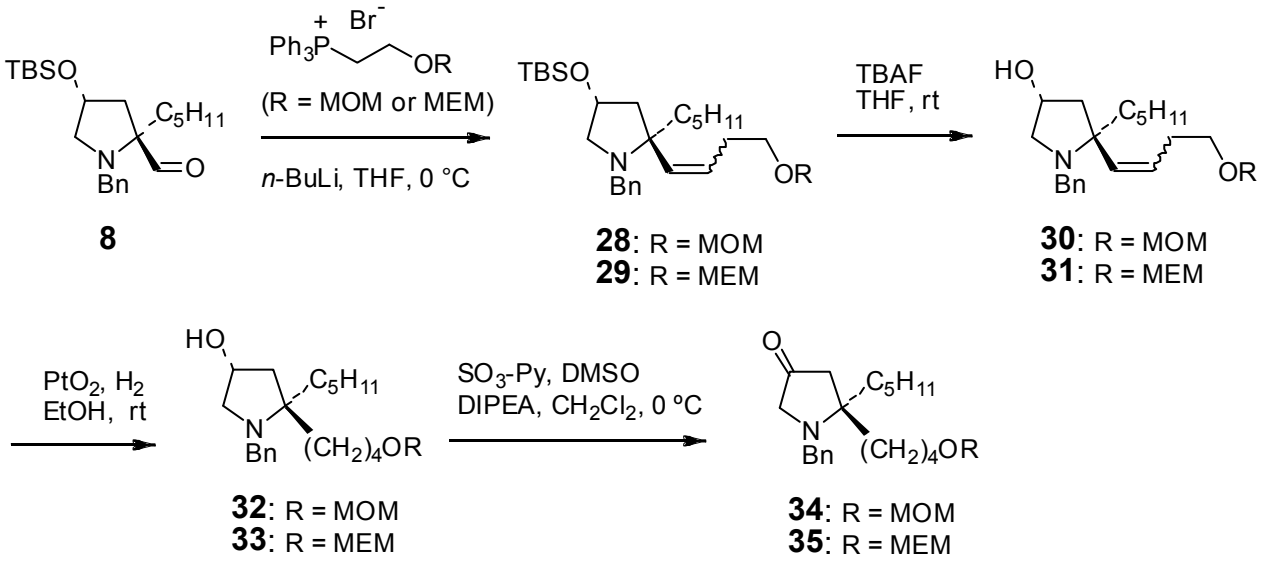


24 **26** **27**

Entry	Additive (equiv)	Time	Temperature	Products (yield)
1	HMPA (5.0) + MeOH (2.5)	15 h	0 °C	decompose
2	DMEA (10)	10 min	0 °C	**27** (75%)
3	MeOH (2.5)	2 h	0 °C	**26** (trace), **27** (50%)
4	NiI_2 (0.05)	6 h	0 °C to rt	**27** (25%), **24** (58%)
5	NiI_2 (0.05) + MeOH (2.5)	4 h	0 °C	**27** (43%)
6	HMPA (5.0)+ MeOH (2.5)	5 min	0 °C	**27** (85%)
7	HMPA (5.0) + *tert*-BuOH (2.5)	6 h	0 °C	**27** (68%)
8	*tert*-BuOH (2.5)	15 h	0 °C	**27** (10%)
9	*tert*-BuOH (2.5)	2 h	reflux	**27** (60%)
10	H_2O (2.5)	2 h	0 °C	**26** (50%)

With the presence of MeOH as the proton donor in THF-HMPA, the reaction of **24** with SmI_2 (5.0 equivalents) at 0 °C for 5 min gave the secondary alcohols (**27**) as an inseparable diastereoisomeric mixture in 85% yield in a ratio of ca. 1:1 (Entry 6). As can be seen in Table 2, almost all of proton sources; such as *N,N*-dimethylethanolamine (DMEA), *tert*-BuOH and the combination of those proton sources were also found to be ineffective for this fragmentation (Entries 2, 4, 5, 7-9). When MeOH (2.5 equiv) was employed as the proton source in THF solution, formation of the desired product (**26**) was observed in a trace amount (< 3%) (Entry 3). However, the yield of **26** could not be improved under the variety of reaction conditions attempted by the use of MeOH, unfortunately. We are very pleased to find that the choice of water as a proton source afforded the desired carbon-nitrogen bond cleavage product (**26**) in moderate yield (Entry 10). Although the pivotal role was still unclear at present, it has been recognized that the use of water as the proton donor sometimes induced profound impact on variety of factors; such as the reaction rate, mechanism, and stereoselectivity for SmI_2-mediated one-electron transfer reactions.[7]

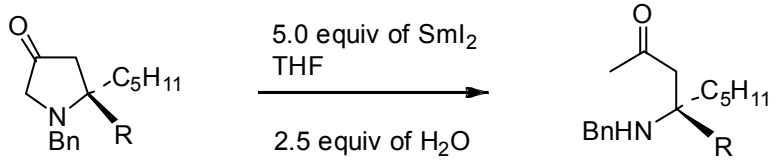
Since a methoxymethyl protecting group of the primary alcohol in **16** and **24** was found to be effective for the expected fragmentation, we further investigated a possibility of other types of protecting groups expecting a formation of chelation intermediate by employing water as the proton donor. Thus, the compounds having a MOM or MEM group were prepared as depicted in Scheme 3.



Scheme 3. Preparation of the starting material for SmI_2-promoted fragmentation

Again, the attempted fragmentation of the compounds (**24**, **25**, **34** and **35**) with SmI_2 provided the corresponding carbon-nitrogen cleavage products in moderate yields, and the results were summarized in Table 3. Although the exact reason was not clear at present, the use of water as a proton source furnished the desired product in reasonable yields.

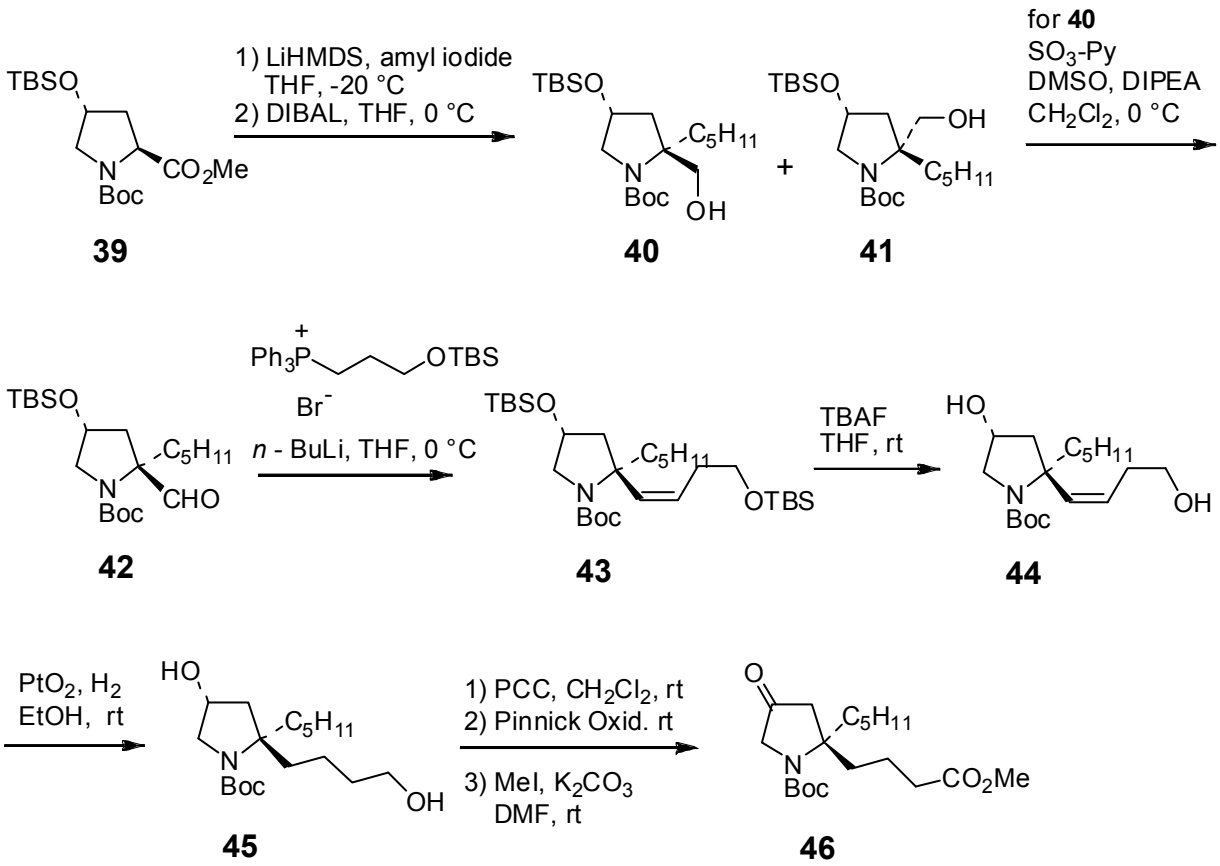
Table 3. Fragmentation reactions for 3-oxopyrrolidine derivatives



24: R = CH_2OMOM
25: R = CH_2OMEM
35: R = $(CH_2)_4OMOM$
36: R = $(CH_2)_4OMEM$

26: R = CH_2OMOM (50%)
36: R = CH_2OMEM (58%)
37: R = $(CH_2)_4OMOM$ (45%)
38: R = $(CH_2)_4OMEM$ (53%)

These results obviously indicated that formation of a chelation intermediate between samarium metal and heteroatoms on the protecting groups seems to play an important role to take place a SmI_2-promoted bond cleavage reaction.

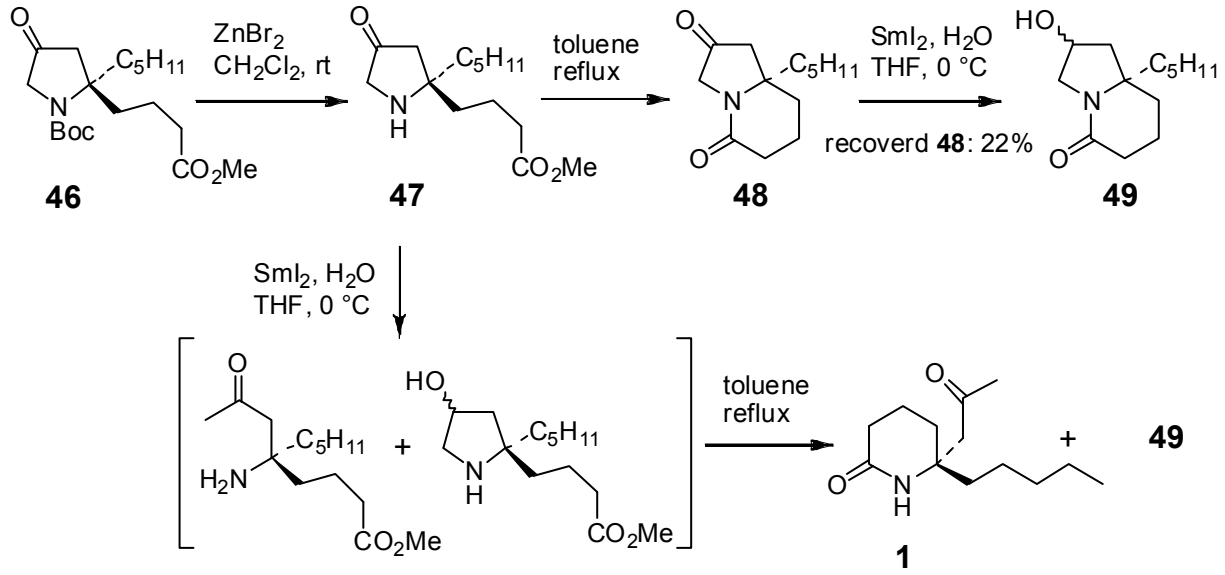


Scheme 4. Preparation of the starting material for the synthesis of adalinine

Given these considerations, we assumed that an ester might also serve as a suitable functional group to generate a chelation intermediate with samarium metal. Therefore, we decided to synthesize a precursor having an ester function on the side chain for SmI_2-promoted carbon-nitrogen bond cleavage reaction in

the synthesis of adalinine (Scheme 4). Alkylation of the known ester (**39**)[8] with amyl iodide in the presence of LiHMDS in THF, followed by reduction of a mixture of diastereoisomeric esters with DIBAL gave primary alcohols (**40** and **41**) in 51% and 33% yield, respectively. Oxidation of the major alcohol (**40**) with SO_3-Py and subsequent Wittig reaction of the resulting aldehyde (**42**) with the phosphonium salt afforded (*Z*)-olefin (**43**) in 87% yield. After deprotection of the silyl group of **43** on treatment with TBAF, the olefinic diol (**44**) was hydrogenated over platinum oxide to provide the saturated diol (**45**). Oxidation of both hydroxyl groups of **45**, followed by Pinnick oxidation[9] of the resulting aldehyde with $NaClO_2$ gave the corresponding acid. Finally, esterification of the acid with methyl iodide in the presence of potassium carbonate furnished the desired ester (**46**) in 39% yield from **45**.

With the requisite carbonyl compound (**46**) in hand, a SmI_2-promoted carbon-nitrogen bond cleavage reaction was attempted. The desired precursor thus obtained was subjected to SmI_2-mediated reductive carbon-nitrogen bond cleavage reaction exploiting water as the proton donor by two routes (Scheme 5).



Scheme 5. Synthesis of (-)-adalinine (**1**)

Removal of *N*-Boc group of the ester (**46**) by treatment with $ZnBr_2$ gave the amine (**47**), which was heated in toluene to furnish the lactam (**48**) in 86% yield from **46**. Treatment of **48** with 5.0 equivalents of SmI_2 in THF in the presence of 2.5 equivalents of water at 0 °C for 3 h, however, afforded the reduction product (**49**) as the major product in 61% yield as a mixture of diastereoisomers, together with 22% of the recovered starting material (**48**). On the other hand, a similar treatment of the amine (**47**) with 5.0 equivalents of SmI_2 in THF in the presence of 2.5 equivalents of water at 0 °C for 30 min generated two products, which, without separation, were heated at reflux in toluene to give (-)-adalinine (**1**), in 16% yield from **46**, together with the bicyclic compound (**49**) in 38% yield. The spectroscopic data for the

synthesized compound (**1**) including its specific optical rotation were comparable to the authentic specimen previously prepared by us $[\alpha]_D$ -24.2 (*c* 1.50, CH_2Cl_2), {lit.[4d] $[\alpha]_D$ -28.3 (*c* 1.6, CH_2Cl_2)}.

In summary, we were able to establish an alternative stereoselective chiral synthesis of (-)-adalinine (**1**) by employing a SmI_2-promoted reductive carbon-nitrogen bond cleavage reaction of a 3-oxopyrrolidine derivative as a key reaction. In this synthesis, we assumed that the formation of samarium-involved chelation intermediate would play an important role for the desired fragmentation. It is noteworthy that water was the best proton source for this reaction, although the reasons remained unclear. This methodology seems to be applicable to various types of 3-oxo-pyrrolidine and -piperidine derivatives, and its application is now under investigation in our laboratory.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on JEOL LAMBDA-270 (^{1}H-NMR: 270 MHz, ^{13}C-NMR: 67.8 MHz) instrument for solutions in $CDCl_3$ unless otherwise noted, and chemical shifts are reported on the δ scale from internal TMS. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Yanaco-MT5.

Methyl (2*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-1-benzoyl-2-pentyl-L-prolinate (4) and methyl (2*R*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-1-benzoyl-2-pentyl-L-prolinate (5). To a stirred solution of methyl (2*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-1-benzoyl-L-prolinate (**3**) (10.0 g, 27.6 mmol) in THF (150 mL) was added a solution of LiHMDS (1.6 M in THF, 26.0 mL, 41.3 mmol) at -40 °C, and the mixture was stirred for a further 2 h. To this solution was added a solution of 1-iodopentane (10.9 g, 55.1 mmol) in THF (30.0 mL) and the whole mixture was gradually warmed up to 0 °C and stirred for 4 h at the same temperature. After treatment with saturated aqueous NH_4Cl solution, the mixture was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which, without separation, was used in the next step. Analytical sample of each ester was obtained by careful separation using column chromatography on silica gel. Elution with *n*-hexane:AcOEt (8:1 v/v) afforded **4** and **5**.

Ester 4; $[\alpha]_D^{26}$ +58.8 (*c* 1.0, $CHCl_3$); IR (thin film): 2954, 2929, 2858, 1744, 1643, 1404, 1271, 1149, 1113, 838, 779 cm^{-1}; ^{1}H NMR δ: 7.53-7.51 (m, 2H), 7.46-7.38 (m, 3H), 4.48 (pent, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 3.73 (dd, *J* = 7.0, 10.2 Hz, 1H), 3.37 (dd, *J* = 8.0, 10.2 Hz, 1H), 2.52-2.44 (m, 1H), 2.21 (dd, *J* = 6.7, 13.2 Hz, 1H), 2.08 (dd, *J* = 9.0, 13.2 Hz, 1H), 1.98-1.91 (m, 1H), 1.56-1.52 (m, 1H), 1.44-1.23 (m, 5H), 0.90 (t, *J* = 6.7 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H); ^{13}C NMR δ: 171.5, 169.1, 136.2, 130.3, 128.3, 127.4, 68.5, 68.0, 58.0, 52.4, 43.0, 32.8, 31.9, 25.7, 23.1, 22.7, 18.0, 14.1, -4.85, -4.92; MS

(*m/z*): 434 (M^++1); HRMS *m/z* (CI) calcd for $C_{24}H_{40}NO_4Si$ (M^++1): 434.2721, found: 434.2726.

Ester 5; mp 98-100 °C; $[\alpha]_D^{21}$ -10.8 (*c* 1.0, $CHCl_3$); IR (thin film):2952, 2928, 2856, 1732, 1625, 1405, 1259, 1123, 1085, 1004, 927, 835, 775, 706 cm^{-1}; ^1H NMR δ: 7.46-7.40 (m, 5H), 4.38 (pent, *J* = 6.0 Hz, 1H), 3.77 (s, 3H), 3.65 (dd, *J* = 6.0, 10.6 Hz, 1H), 3.41 (dd, *J* = 5.8, 10.6 Hz, 1H), 2.61-2.53 (m, 1H), 2.28 (dd, *J* = 6.1, 13.1 Hz, 1H), 2.17 (dd, *J* = 6.3, 13.1 Hz, 1H), 2.00-1.93 (m, 1H), 1.46-1.18 (m, 6H), 0.91 (t, *J* = 6.7 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H); ^{13}C NMR δ: 174.1, 168.1, 137.5, 129.5, 128.4, 126.4, 69.2, 68.7, 58.5, 52.4, 44.8, 34.0, 31.8, 25.6, 23.8, 22.6, 17.9, 14.0, -4.87, -4.97; MS (*m/z*): 434 (M^++1); *Anal.* Calcd for $C_{24}H_{39}NO_4Si$: C, 66.47; H, 9.06; N, 3.23. Found: C, 66.41; H, 9.04; N, 3.25.

(2*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-1-benzyl-2-hydroxymethyl-2-pentylpyrrolidine (6) and (2*R*,4*R*)-1-benzoyl-4-hydroxy-2-hydroxymethyl-2-pentylpyrrolidine (7). To a suspension of $LiAlH_4$ (3.45 g, 90.9 mmol) in refluxing THF (110 mL) was added slowly a solution of a mixture of esters (**4** and **5**) obtained above in THF (20.0 mL), and the whole mixture was stirred for a further 30 min. After cooling to rt, the mixture was diluted with THF and carefully treated with water and 20% aqueous KOH solution. The insoluble material was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with *n*-hexane:AcOEt (6:1 v/v) gave the alcohol (**6**) (6.5 g, 60%) as a colorless oil; $[\alpha]_D^{19}$ -45.4 (*c* 1.0, $CHCl_3$); IR (thin film): 3434, 2954, 2929, 2857, 1470, 1463, 1255, 1127, 837, 776 cm^{-1}; ^1H NMR δ: 7.38-7.24 (m, 5H), 4.23-4.16 (m, 1H), 3.82 (d, *J* = 12.8 Hz, 1H), 3.40-3.32 (m, 3H), 3.11 (dd, *J* = 6.7, 9.3 Hz, 1H), 2.46 (dd, *J* = 6.7, 9.3 Hz, 1H), 2.16 (dd, *J* = 8.1, 13.3 Hz, 1H), 1.78-1.71 (m, 2H), 1.48-1.18 (m, 6H), 0.91 (t, *J* = 6.7 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR δ: 139.6, 128.6, 128.5, 127.0, 69.5, 66.5, 63.6, 59.6, 51.5, 41.9, 32.8, 32.1, 25.8, 24.1, 22.6, 17.9, 14.1, -4.80, -4.86; MS (*m/z*): 392 (M^++1); HRMS *m/z* calcd (CI) for $C_{23}H_{42}NO_2Si$ (M^++1): 392.2984, found: 392.2985.

Further elution with *n*-hexane:AcOEt (1:1 v/v) afforded the diol (**7**) (3.1g, 40%) as a colorless oil; $[\alpha]_D^{18}$ +14.6 (*c* 1.0, $CHCl_3$); IR (thin film): 3361, 2954, 2931, 2859, 1455, 1042, 735, 698 cm^{-1}; ^1H NMR δ: 7.32-7.27 (m, 4H), 7.25-7.23 (m, 1H), 4.22-4.14 (m, 1H), 3.86 (d, *J* = 13.2 Hz, 1H), 3.64 (br s, 1H), 3.48-3.42 (m, 3H), 2.98 (br s, 1H), 2.86 (d, *J* = 10.2 Hz, 1H), 2.72 (dd, *J* = 4.2, 10.2 Hz, 1H), 2.20 (dd, *J* = 6.4, 14.4 Hz, 1H), 1.87 (d, *J* = 14.4 Hz, 1H), 1.44-1.40 (m, 1H), 1.36-1.20 (m, 6H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ: 139.8, 128.5, 128.3, 127.0, 69.1, 65.9, 63.9, 60.3, 51.4, 43.5, 33.2, 32.8, 24.0, 22.6, 14.1; MS (*m/z*): 278 (M^++1); HRMS *m/z* (CI) calcd for $C_{17}H_{28}NO_2$ (M^++1): 278.2145, found: 278.2120.

(2*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-1-benzyl-2-pentyl-2-pyrrolidinecarboxaldehyde (8). To a stirred solution of **6** (3.79 g, 9.69 mmol) in CH_2Cl_2 (50.0 mL) were successfully added DMSO (4.13 mL, 58.2 mmol), DIPEA (14.0 mL, 77.5 mmol), and sulfur trioxide-pyridine complex (6.30 g, 38.8 mmol) at

0 °C under argon. The mixture was gradually warmed to rt, and stirred at the same temperature for 2 h. The mixture was treated with water and extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane:AcOEt, (30:1 v/v) afforded the aldehyde (**8**) (3.6 g, 95%) as a colorless oil; $[\alpha]_D^{24}$ -3.0 (*c* 1.1, $CHCl_3$); IR (thin film): 2954, 2929, 2857, 2802, 1728, 1470, 1462, 1379, 1255 cm^{-1}; ^1H NMR δ: 9.35 (s, 1H), 7.30 (d, *J* = 4.4 Hz, 4H), 7.24-7.21 (m, 1H), 4.39-4.33 (m, 1H), 3.75 (dd, *J* = 13.6, 16.6 Hz, 2H), 3.02 (dd, *J* = 6.3, 9.5 Hz, 1H), 2.61 (dd, *J* = 4.5, 9.5 Hz, 1H), 2.26 (dd, *J* = 7.3, 13.4 Hz, 1H), 1.81 (dd, *J* = 4.4, 13.4 Hz, 2H), 1.73-1.66 (m, 1H), 1.34-1.23 (m, 6H), 0.91 (t, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), -0,01 (s, 3H); ^{13}C NMR δ: 201.5, 139.6, 128.3, 128.1, 126.9, 71.6, 70.2, 59.9, 52.2, 40.4, 32.6, 29.4, 25.8, 24.4, 22.6, 18.0, 14.1, -4.9; MS (*m/z*): 390 (M^++1); HRMS (CI) *m/z* calcd for $C_{23}H_{40}NO_2Si$ (M^++1): 390.2832, found: 390.2828.

(2*S*,4*R*)-4-(*tert*-Butyldimethylsiloxy)-1-benzyl-2-[3-(1,3-dioxolan-2-yl)propenyl]-2-pentylpyrrolidine (10). To a stirred solution of 2-(3,3-dioxolan-2-yl)ethyltriphenylphosphonium bromide (**9**) (682 mg, 1.54 mmol) in THF (10.0 mL) was added dropwise a solution of *n*-BuLi (1.59 M in *n*-hexane, 0.93 mL, 1.49 mmol) at 0 °C under argon, and the resulting mixture was stirred for a further 1 h. To this mixture was added a solution of **8** (413 mg, 1.06 mmol) in THF (6.0 mL), and the whole mixture was stirred for 1 h at the same temperature. The mixture was treated with brine and the insoluble materials were removed by filtration. The filtrate was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane:AcOEt, (15:1 v/v) afforded the olefin (**10**) (452 mg, 90%) as a colorless oil; $[\alpha]_D^{19}$ -19.9 (*c* 1.1, $CHCl_3$); IR (thin film): 2954, 2929, 2857, 1471, 1255, 1134, 1121, 1048, 914, 837, 776 cm^{-1}; ^1H NMR δ: 7.34-7.27 (m, 4H), 7.23-7.18 (m, 1H), 5.65 (d, *J* = 12.1 Hz, 1H), 5.52-5.45 (m, 1H), 4.90 (t, *J* = 4.9 Hz, 1H), 4.33 (sept, *J* = 3.7 Hz, 1H), 4.01-3.95 (m, 2H), 3.91-3.84 (m, 2H), 3.71 (d, *J* = 13.4 Hz, 1H), 3.59 (d, *J* = 13.4 Hz, 1H), 2.92 (dd, *J* = 6.6, 9.9 Hz, 1H), 2.72-2.69 (m, 2H), 2.51 (dd, *J* = 3.9, 9.9 Hz, 1H), 2.24 (dd, *J* = 7.6, 13.1 Hz, 1H), 1.94 (dd, *J* = 3.9, 13.1 Hz, 1H), 1.76-1.69 (m, 1H), 1.64-1.57 (m, 1H), 1.50-1.24 (m, 6H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.00 (s, 3H), -0.03 (s, 3H); ^{13}C NMR δ: 140.7, 136.1, 128.3, 128.1, 126.4, 124.6, 104.0, 70.1, 66.7, 65.0, 59.5, 52.4, 45.9, 34.7, 33.7, 32.8, 25.8, 24.7, 22.8, 18.0, 14.1, -4.8; MS (*m/z*): 473 (M^+); HRMS *m/z* (EI) calcd for $C_{28}H_{47}NO_3Si$ (M^+): 473.3310, found: 473.3325.

(3*R*,5*S*)-1-Benzyl-5-[3-(1,3-dioxolan-2-yl)propenyl]-5-pentylpyrrolidin-3-ol (11). To a stirred solution of **10** (2.5 g, 5.28 mmol) in THF (50.0 mL) was added TBAF (1.0 M in THF, 7.9 mL, 7.9 mmol) at rt, and the resulting solution was stirred overnight. Removal of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane:AcOEt, (2:1 v/v) afforded the

alcohol (**11**) (1.7g, 89%) as a colorless oil; $[\alpha]_D^{19}$ +19.4 (*c* 1.1, $CHCl_3$); IR (thin film): 3422, 2953, 2931, 2871, 1455, 1137, 1030, 943, 842, 737, 700 cm^{-1}; ^1H NMR δ: 7.32-7.27 (m, 4H), 7.24-7.20 (m, 1H), 5.74 (dd, *J* = 1.9, 12.2 Hz, 1H), 5.55-5.49 (m, 1H), 4.91 (t, *J* = 4.8 Hz, 1H), 4.28-4.18 (m, 1H), 4.04-3.95 (m, 2H), 3.92-3.84 (m, 2H), 3.80 (d, *J* = 13.3 Hz, 1H), 3.47 (d, *J* = 13.3 Hz, 1H), 2.71 (dd, *J* = 5.2, 10.1 Hz, 1H), 2.64 (d, *J* = 10.1 Hz, 1H), 2.61-2.57 (m, 2H), 2.42 (dd, *J* = 7.2, 13.9 Hz, 1H), 1.96 (d, *J* = 13.9 Hz, 1H), 1.89 (br s, 1H), 1.77-1.65 (m, 2H), 1.56-1.44 (m, 1H), 1.42-1.24 (m, 5H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ: 140.2, 135.4, 128.4, 128.3, 126.7, 124.8, 103.9, 69.8, 66.4, 65.0, 59.1, 51.9, 46.5, 36.8, 33.9, 32.5, 24.2, 22.7, 14.1; MS (*m/z*): 288 (M^+-71); HRMS *m/z* (EI) calcd for $C_{17}H_{22}NO_3$ (M^+-71): 288.1599, found: 288.1578.

(3*R*,5*S*)-1-Benzyl-5-[3-(1,3-dioxolan-2-yl)propyl]-5-pentylpyrrolidin-3-ol (12). A solution of **11** (1.69 g, 4.73 mmol) in EtOH (10.0 mL) in the presence of PtO_2 (53.7 mg, 0.24 mmol) was stirred at rt overnight. After removal of the insoluble materials by filtration, the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane:AcOEt, (2:1 v/v) afforded the alcohol (**12**) (1.4 g, 80%) as a colorless oil; $[\alpha]_D^{25}$ +13.3 (*c* 1.0, $CHCl_3$); IR (thin film): 3447, 2952, 2931, 2871, 1455, 1142, 1029, 736, 699 cm^{-1}; ^1H NMR δ: 7.32-7.27 (m, 4H), 7.25-7.19 (m, 1H), 4.87 (t, *J* = 4.7 Hz, 1H), 4.20-4.12 (m, 1H), 4.02-3.94 (m, 2H), 3.90-3.84 (m, 2H), 3.74 (d, *J* = 13.3 Hz, 1H), 3.45 (d, *J* = 13.3 Hz, 1H), 2,76 (dd, *J* = 5.0, 9.8 Hz, 1H), 2.62 (d, *J* = 9.8 Hz, 1H), 2.07 (dd, *J* = 7.1, 14.1 Hz, 1H), 1.84 (br s, 1H), 1.73-1.63 (m, 3H), 1.58-1.49 (m, 3H), 1.47-1.39 (m, 4H), 1.37-1.24 (m, 5H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ: 140.1, 128.13, 128.10, 126.5, 104.3, 69.5, 64.7, 64.3, 58.5, 51.1, 43.1, 35.8, 34.7, 34.5, 32.5, 23.9, 22.6, 20.6, 19.1, 14.1; MS (*m/z*): 361 (M^+); HRMS *m/z* (EI) calcd for $C_{22}H_{35}NO_3$ (M^+): 361.2590, found: 361.2617.

(5*R*)-1-Benzyl-5-[3-(1,3-dioxolan-2-yl)propyl]-5-pentylpyrrolidin-3-one (13). To a stirred solution of **12** (1.33 g, 3.68 mmol) in CH_2Cl_2 (25.0 mL) were successfully added DMSO (1.57 mL, 22.1 mmol), DIPEA (5.27 mL, 29.5 mmol), and sulfur trioxide-pyridine complex (2.40 g, 14.7 mmol) at 0 °C under argon. The mixture was gradually warmed to rt, and stirred at the same temperature for 2 h. The mixture was treated with water and extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane:AcOEt, (4:1 v/v) afforded the ketone (**13**) (1.2 g, 93%) as a colorless oil; $[\alpha]_D^{27}$ +4.3 (*c* 1.0, $CHCl_3$); IR (thin film): 2952, 2931, 2871, 1754, 1456, 1142, 1029, 943, 735, 699 cm^{-1}; ^1H NMR δ: 7.29-7.34 (m, 4H), 7.21-7.26 (m, 1H), 4.87 (t, *J* = 4.6 Hz, 1H), 4.00-3.92 (m, 2H), 3.89-3.65 (m, 4H), 3.10-3.03 (m, 2H), 2.41-2.32 (m, 2H), 1.73-1.51 (m, 8H), 1.49-1.25 (m, 6H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ: 214.5, 139.2, 128.4, 128.1, 127.0, 104.3, 64.9, 64.1, 58.7, 51.5, 45.9, 34.6, 34.5, 34.3,

32.6, 24.1, 22.7, 18.9, 14.1; MS (*m/z*): 359 (M^+); HRMS *m/z* (EI) calcd for $C_{22}H_{35}NO_3$ (M^+): 359.2465, found: 359.2460.

(3*RS*,5*S*)-1-Benzyl-5-(3-[1,3]dioxolan-2-yl-propyl)-5-pentyl-pyrrolidin-3-ol (14). To a stirred solution of **13** (198 mg, 0.55 mmol) in THF (6 mL) was added a solution of SmI_2 (0.2 M in THF, 13.8 mL, 2.75 mmol) (prepared from Sm metal and 1,2-diiodoethane) at 0 °C in the presence of suitable proton source(s) (MeOH or *N,N*-dimethylethanolamine or HMPA + MeOH), and the resulting mixture was stirred for 3 h at the same temperature. Saturated aqueous $NaHCO_3$ solution and Et_2O were added to the mixture, and the whole mixture was filtered through a pad of Celite to remove insoluble materials. The filtrate was extracted with Et_2O, and the ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane:AcOEt, (3:1 v/v) afforded the ketone (**14**) (90-92% yield) as an inseparable mixture of alcohols; IR (thin film): 3488, 2953, 2931, 2871, 1607, 1456, 1409, 1141, 1029, 943, 736, 699 cm^{-1}; ^1H NMR δ: 7.38-7.28 (m, 4H), 7.25-7.18 (m, 1H), 4.90-4.81 (m, 1H), 4.25-4.10 (m, 1H), 4.02-3.93 (m, 2H), 3.92-3.81 (m, 2H), 3.75 (d, *J* = 13.2 Hz, 0.5 H), 3.66-3.51 (m, 1H), 3.46 (d, *J* = 13.2 Hz, 0.5 H), 2.81-2.71 (m, 1H), 2.77-2.48 (m, 1H), 2.16-1.91 (m, 1H), 1.77-1.18 (m, 16H), 0.92-0.87 (m, 3H).

(4*S*)-4-Benzylamino-5-(methoxymethoxy)pentan-2-one (17). Reductive carbon-nitrogen bond cleavage reaction for **16** (200 mg, 0.80 mmol) was carried out by using the same procedure [SmI_2 (0.2 M in THF, 8.8 mL, 1.77 mmol)] as for the synthesis of **14** to give **17** (90 mg, 45%) as a colorless oil; $[\alpha]_D^{28}$ -6.2 (*c* 1.5, $CHCl_3$); IR (thin film): 3062, 3028, 2928, 2887, 1712, 1454, 1360, 1150, 1111, 1042, 918, 738, 700 cm^{-1}; ^1H NMR δ: 7.33-7.29 (m, 4H), 7.25-7.22 (m, 1H), 4.65-4.53 (s, 2H), 3.84-3.76 (m, 2H), 3.56 (ddd, *J* = 5.0, 9.8, 14.8 Hz, 2H), 3.35 (s, 3H), 3.32-3.27 (m, 1H), 2.65 (d, *J* = 6.4 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR δ: 208.0, 140.2, 128.4, 128.1, 127.0, 96.7, 68.9, 55.4, 53.2, 51.4, 46.1, 30.7; MS (*m/z*): 252 (M^++1); HRMS *m/z* (CI) calcd for $C_{14}H_{22}NO_3$ (M^++1): 252.1599, found: 252.1622.

(2*RS*)-4-(Benzylamino)-1,3,4-trideoxy-5-*O*-(methoxymethyl)-D-*glycero*-pentitol (18). IR (thin film): 3404, 3028, 2931, 2886, 2824, 1651, 1495, 1455, 1375, 1339, 1213, 1150, 1108, 1042, 919, 748, 700 cm^{-1}; ^1H NMR δ: 7.35-7.24 (m, 5H), 4.62 (s, 2H), 4.15-4.05 (m, 1H), 3.96 (d, *J* = 12.8 Hz, 0.66H), 3.95 (d, *J* = 12.8 Hz, 0.33H), 3.77-3.45 (m, 4H), 3.38 (s, 1/3xMe), 3.36 (s, 2/3xMe), 3.27-2.95 (m, 1H), 1.78 (dd, *J* = 4.0, 9.2 Hz, 0.33H), 1.74 (dd, *J* = 3.6, 8.8 Hz, 0.66H), 1.60-1.52 (m, 1H), 1.163 (d, *J* = 6.4 Hz, 1/3xMe), 1.157 (d, *J* = 6.0 Hz, 2/3xMe).

(3*RS*, 5*S*)-1-Benzyl-5-[(methoxymethoxy)methyl]pyrrolidin-3-ol (19). Since **19** was isolated as a

mixture of diastereoisomers, its ^{1}H NMR measurement afforded a heavily overlapped spectrum. Thus, **19** was oxidized by the same procedure as described for the preparation of **13** to give **16**.

(2*S*,4*R*)-1-Benzyl-4-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)methyl-2-pentylpyrrolidine (20). A solution of **6** (6.33 g, 16.2 mmol), MOMCl (2.46 mL, 32.4 mmol), and DIPEA (7.05 mL, 40.5 mmol) in CH_2Cl_2 (80.0 mL) was stirred overnight under argon. The mixture was treated with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane:AcOEt, (15:1 v/v) afforded the MOM ether (**20**) (6.5 g, 94%) as a colorless oil; $[\alpha]_D^{26}$ +8.6 (*c* 1.0, $CHCl_3$); IR (thin film): 3062, 3026, 2953, 2929, 2857, 2822, 1463, 1254, 1150, 1110, 1048, 919, 836, 775, 733, 698 cm^{-1}; ^{1}H NMR δ: 7.37-7.28 (m, 4H), 7.23-7.20 (m, 1H), 4.64 (d, *J* = 13.2 Hz, 1H), 4.62 (d, *J* = 13.2 Hz, 1H), 4.38-4.32 (m, 1H), 3.80-3.74 (m, 2H), 3.51-3.43 (m, 2H), 3.40 (s, 3H), 2.93 (dd, *J* = 6.4, 9.4 Hz, 1H), 2.64 (dd, *J* = 3.9, 9.4 Hz, 1H), 2.05 (dd, *J* = 7.5, 13.2 Hz, 1H), 1.79 (dd, *J* = 4.6, 13.2 Hz, 1H), 1.26-1.27 (m, 8H), 0.91 (t, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 3H), -0.02 (s, 3H); ^{13}C NMR δ: 141.0, 128.04, 128.02, 128.3, 96.8, 72.9, 69.9, 64.9, 60.7, 55.3, 52.3, 43.1, 33.2, 32.8, 25.8, 24.2, 22.7, 18.0, 14.1, -4.9; MS (*m/z*): 361 (M^+-74); HRMS *m/z* (EI) calcd for $C_{22}H_{39}NOSi$(M^+-74): 361.2801, found: 361.2826.

(3*R*,5*S*)-1-Benzyl-5-[(methoxymethoxy)methyl]-5-pentylpyrrolidin-3-ol (22). To a stirred solution of **20** (6.47 g, 14.9 mmol) inTHF (50.0 mL), was added TBAF (1.0 M in THF, 15.0 mL, 14.9 mmol) at 0 °C, and the resulting mixture was stirred overnight at rt. Removal of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane:AcOEt, (3:1 v/v) afforded the MOM ether (**22**) (4.7g, 98%) as a colorless oil; $[\alpha]_D^{26}$ +41.2 (*c* 1.0, $CHCl_3$); IR (thin film): 3420, 3085, 3061, 3027, 2931, 2870, 2860, 2823, 2796, 1454, 1214, 1148, 1110, 1046, 968, 918, 738, 699 cm^{-1}; ^{1}H NMR δ: 7.32-7.27 (m, 4H), 7.24-7.19 (m, 1H), 4.62 (s, 2H), 4.23-4.16 (m, 1H), 4.01 (d, *J* = 13.4 Hz, 1H), 3.48 (d, *J* = 13.4 Hz, 1H), 3.51-3.43 (m, 2H), 2.85 (dd, *J* = 4.7, 9.8 Hz, 1H), 2.69 (d, *J* = 9.8 Hz, 1H), 2.14 (dd, *J* = 6.7, 14.1 Hz, 1H), 1.97 (br s, 1H), 1.83 (d, *J* = 14.1 Hz, 1H), 1.67-1.60 (m, 1H), 1.54-1.45 (m, 2H), 1.41-1.27 (m, 5H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR δ: 140.4, 128.0, 1827.9, 126.3, 96.5, 71.8, 69.2, 64.4, 60.0, 55.1, 51.8, 42.9, 34.4, 32.3, 23.8, 22.4, 13.9; MS (*m/z*): 322 (M^++1); HRMS *m/z* (CI) calcd for $C_{19}H_{32}NO_3$ (M^++1): 322.2382, found: 322.2411.

(5*S*)-1-Benzyl-5-[(methoxymethoxy)methyl]-5-pentylpyrrolidin-3-one (24), Oxidation of **22** (1.16 g, 3.61 mmol) using DMSO (1.54 mL, 21.7 mmol), DIPEA (5.16 mL, 28.9 mmol), and sulfur trioxide-pyridine complex (2.35 g, 14.5 mmol), was carried out according to the same procedure as described for

the synthesis of **13** to give the ketone (**24**) (1.1 g, 95%) as a colorless oil; $[\alpha]_D^{26}$ +88.7 (*c* 1.0, $CHCl_3$); IR (thin film): 3087, 3061, 3028, 2931, 2869, 2823, 1757, 1455, 1151, 1111, 1048, 965, 918, 738, 699 cm^{-1}; ^1H NMR δ: 7.33-7.28 (m, 4H), 7.24-7.21 (m, 1H), 4.59 (dd, *J* = 6.6, 15.2 Hz, 2H), 4.06 (d, *J* = 13.2 Hz, 1H), 3.83 (d, *J* = 10.0 Hz, 1H), 3.57 (d, *J* = 13.2 Hz, 1H), 3.53 (d, *J* = 10.0 Hz, 1H), 3.37 (s, 3H), 3.18 (s, 2H), 2.45-2.39 (m, 2H), 1.67-1.46 (m, 3H), 1.39-1.26 (m, 5H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR δ: 213.7, 139.3, 128.4, 128.1, 127.0, 96.7, 72.8, 64.1, 60.5, 55.7, 52.2, 46.2, 33.7, 32.5, 23.8, 22.6, 14.1; MS (*m/z*): 320 (M^++1); HRMS *m/z* (CI) calcd for $C_{19}H_{30}NO_3$ (M^++1): 320.2226, found: 320.2254.

(4*S*)-4-Benzylamino-4-[(methoxymethoxy)methyl]nonan-2-one (26). Sm-promoted fragmentation of **24** (100 mg, 0.31 mmol) with SmI_2 (0.1 M in THF, 15.7 mL, 1.57 mmol) in the presence of H_2O (14 μL, 0.78 mmol) was carried out by the same procedure as described for the preparation of **17** to give **26** (50 mg, 50%) as a colorless oil; $[\alpha]_D^{21}$ +5.8 (*c* 0.8, $CHCl_3$); IR (thin film): 2952, 2931, 2871, 1708, 1467, 1454, 1357, 1149, 1110, 1045, 734, 699 cm^{-1}; ^1H NMR δ: 7.36-7.29 (m, 4H), 7.26-7.21 (m, 1H), 4.60 (s, 2H), 3.66 (d, *J* = 3.5 Hz, 2H), 3.56 (d, *J* = 3.0 Hz, 2H), 3.35 (s, 3H), 2.68-2.60 (m, 2H), 2.19 (s, 3H), 1.57-1.53 (m, 2H), 1.41-1.22 (m, 6H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ: 208.6, 140.9, 128.4, 128.2, 126.8, 96.8, 71.2, 58.1, 55.5, 46.7, 46.0, 34.4, 32.4, 32.2, 22.7, 22.5, 14.1; MS (*m/z*): 322 (M^++1); HRMS *m/z* (CI) calcd for $C_{19}H_{32}NO_3$ (M^++1): 322.2382, found: 322.2354.

(3*RS*, 5*R*)-1-Benzyl-5-[(methoxymethoxy)methyl]-5-pentylpyrrolidin-3-ol (27). Since **27** was isolated as a mixture of diastereoisomers, its ^1H NMR measurement afforded a heavily overlapped spectrum. Thus, **27** was oxidized by the same procedure as described for the preparation of **13** to give **24**.

(2*S*,4*R*)-1-Benzyl-4-(*tert*-butyldimethylsilyloxy)-2-[(2-methoxyethoxymethoxy)methyl)-2-pentyl-pyrrolidine (21). A solution of **6** (2.00 g, 5.12 mmol), MEMCl (1.46 mL, 12.8 mmol), and DIPEA (3.20 mL, 17.9 mmol) in CH_2Cl_2 (25.0 mL) was stirred overnight under argon. The mixture was treated with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane:AcOEt, (15:1 v/v) afforded the MEM ether (**21**) (1.8 g, 72%) as a colorless oil; $[\alpha]_D^{23}$ +8.6 (*c* 1.0, $CHCl_3$); IR (thin film): 3062, 3026, 2953, 2929, 2857, 1462, 1254, 1115, 1048, 836, 775, 773, 698 cm^{-1}; ^1H NMR δ: 7.37 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 4.78-4.72 (m, 2H), 4.42-4.31 (m, 1H), 3.83-3.72 (m, 4H), 3.60-3.47 (m, 4H), 3.42 (s, 3H), 2.95 (dd, *J* = 6.4, 9.3 Hz, 1H), 2.66 (dd, *J* = 3.8, 9.3 Hz, 1H), 2.07 (dd, *J* = 7.5, 13.1 Hz, 1H), 1.81 (dd, *J* = 3.8, 13.1 Hz, 1H), 1.67-1.55 (m, 2H), 1.51-1.31 (m, 6H), 0.93 (t, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), -0,.02 (s, 3H); ^{13}C NMR δ: 141.1, 128.09, 128.05, 126.4, 95.3, 73.1, 69.9, 66.9, 66.7,

65.0, 60.8, 59.0, 52.3, 43.2, 33.2, 32.8, 25.9, 24.3, 22.7, 18.0, 14.2, -4.5, -4.8; MS (*m/z*): 480 (M^++1); HRMS *m/z* (CI) calcd for $C_{27}H_{50}NO_4Si$ (M^++1): 480.3509, found: 480.3506.

(3*R*,5*S*)-1-Benzyl-5-[(2-methoxyethoxymethoxy)methyl)-5-pentylpyrrolidin-3-ol (23). Desilylation of **21** (1.63 g, 3.40 mmol) with TBAF (1.0 M in THF, 5.1 mL, 5.1 mmol) in THF (20.0 mL) was carried out by the same procedure as described for the preparation of **22** to give **23** (1.2 g, 95%) as a colorless oil; $[\alpha]_D^{24}$ +37.2 (*c* 1.0, $CHCl_3$); IR (thin film): 3442, 3085, 3061, 3027, 2930, 2871, 1454, 1157, 1115, 1049, 979, 849, 737, 699 cm^{-1}; ^1H NMR δ: 7.31-7.28 (m, 4H), 7.24-7.18 (m, 1H), 4.71 (s, 2H), 4.20-4.17 (m, 1H), 3.98 (d, *J* = 13.4 Hz, 1H), 3.75-3.69 (m, 2H), 3.59-3.56 (m, 2H), 3.53-3.45 (m, 2H), 3.47 (d, *J* = 13.4 Hz, 1H), 3.40 (s, 3H), 2.84 (dd, *J* = 4.8, 9.8 Hz, 1H), 2.67 (d, *J* = 9.8 Hz, 1H), 2.12 (dd, *J* = 6.8, 14.1 Hz, 2H), 1.81 (d, *J* = 14.1 Hz, 1H), 1.66-1.59 (m, 1H), 1.52-1.46 (m, 2H), 1.41-1.26 (m, 5H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR δ: 140.6, 128.23, 128.22, 126.7, 95.9, 72.2, 71.8, 69.8, 67.1, 64.4, 60.1, 59.1, 51.8, 43.1, 34.9, 32.6, 24.0, 22.7, 14.1; MS (*m/z*): 366 (M^++1); HRMS (CI) *m/z* calcd for $C_{21}H_{36}NO_4$ (M^++1): 366.2644, found: 366.2666.

(5*S*)-1-Benzyl-5-[(2-methoxyethoxymethoxy)methyl]-5-pentylpyrrolidin-3-one (25). Oxidation of **23** (1.07 g, 2.93 mmol) with DMSO (1.25 mL, 17.6 mmol), DIPEA (4.20 mL, 23.4 mmol) and sulfur trioxide-pyridine complex (1.87 g, 11.7 mmol) was carried out by the same procedure as described for the preparation of **24** to give **25** (1.1 g, 100%) as a colorless oil; $[\alpha]_D^{20}$ +82.2 (*c* 1.0, $CHCl_3$); IR (thin film): 3086, 3062, 3028, 2930, 2871, 2817, 1756, 1455, 1178, 1114, 1050, 982, 849, 772, 738, 699 cm^{-1}; ^1H NMR δ: 7.33-7.28 (m, 4H), 7.26-7.19 (m, 1H), 4.75-4.65 (m, 2H), 4.06 (d, *J* = 13.3 Hz, 1H), 3.85 (d, *J* = 10.0 Hz, 1H), 3.72-3.68 (m, 2H), 3.60-3.55 (m, 4H), 3.39 (s, 3H), 3.17 (s, 2H), 2.47 (d, *J* = 12.4 Hz, 1H), 2.35 (d, *J* = 12.4 Hz, 1H), 1.66-1.44 (m, 3H), 1.40-1.24 (m, 5H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ: 213.7, 139.3, 128.4, 128.1, 127.0, 95.6, 72.8, 71.7, 67.2, 64.1, 60.5, 59.0, 52.2, 46.2, 33.8, 32.5, 23.8, 22.6, 14.1; MS (*m/z*): 364 (M^++1); HRMS *m/z* (CI) calcd for $C_{21}H_{34}NO_4$ (M^++1): 364.2488, found: 364.2515.

(4*S*)-4-Benzylamino-4-[(2-methoxyethoxymethoxy)methyl)-nonan-2-one (36). Sm-promoted fragmentation of **26** (200 mg, 0.55 mmol) with SmI_2 (0.2 M in THF, 13.8 mL, 2.75 mmol) in the presence of H_2O (25 μL, 1.38 mmol) was carried out by the same procedure as described for the preparation of **26** to give **36** (117mg, 58%) as a colorless oil; $[\alpha]_D^{24}$ +9.8 (*c* 1.2, $CHCl_3$); IR (thin film): 2953, 2931, 2872, 1707, 1455, 1362, 1116, 1048, 736, 699 cm^{-1}; ^1H NMR δ: 7.35-7.28 (m, 5H), 7.25-7.20 (m, 1H), 4.70 (s, 2H), 3.75-3.66 (m, 4H), 3.58-3.53 (m, 4H), 3.38 (s, 3H), 2.69 (d, *J* = 12.1 Hz, 1H), 2.62 (d, *J* = 12.1 Hz, 1H), 2.17 (s, 3H), 1.56-1.48 (m, 2H), 1.39-1.23 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ: 208.6, 140.9, 128.4, 128.2, 126.8, 95.9, 71.7, 71.3, 67.0, 59.0, 58.1, 46.7, 46.0, 34.4, 32.4, 32.2, 22.7, 22.6, 14.1; MS (*m/z*): 366 (M^++1); HRMS *m/z* (CI) calcd for $C_{21}H_{36}NO_4$ (M^++1): 366.2644, found: 366.2647.

(2*S*,4*R*)-1-Benzyl-4-(*tert*-butyldimethylsilyloxy)-2-[(4-methoxymethoxy)but-1-enyl]-2-pentyl-pyrrolidine (28). Wittig reaction of **8** (3.58 g, 9.20 mmol) with 3-(methoxymethoxy)-propyltriphenylphosphonium bromide (5.32 g, 12.0 mmol) and *n*-BuLi (1.54 M in *n*-hexane, 7.20 mL, 7.2 mmol) was carried out by the same procedure as for the preparation of **10** to give the olefin (**28**) (3.6 g, 83%) as a colorless oil; $[\alpha]_D^{24}$ -13.5 (*c* 1.2, $CHCl_3$); IR (thin film): 3086, 3062, 2953, 2929, 2857, 2822, 2797, 1470, 1378, 1254, 1149, 1112, 1037, 918, 836, 775, 732, 698 cm^{-1}; ^1H NMR δ: 7.34-7.27 (m, 4H), 7.23-7.19 (m, 1H), 5.58 (d, *J* = 12.1 Hz, 1H), 5.46-5.39 (m, 1H), 4.64 (s, 2H), 4.36-4.31 (m, 1H), 3.73 (d, *J* = 13.5 Hz, 1H), 3.62 (d, *J* = 13.5 Hz, 1H), 3.57 (t, *J* = 6.9 Hz, 2H), 3.38 (s, 3H), 2.91 (dd, *J* = 7.1, 9.8 Hz, 1H), 2.65-2.52 (m, 3H), 2.24 (dd, *J* = 7.6, 13.0 Hz, 1H), 1.96 (dd, *J* = 3.7, 13.0 Hz, 1H), 1.77-1.60 (m, 2H), 1.51-1.28 (m, 6H), 0.91 (t, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR δ: 140.7, 135.1, 128.3, 128.1, 127.6, 126.4, 96.4, 70.1, 67.5, 66.8, 59.5, 55.2, 52.4, 46.0, 34.9, 32.8, 29.4, 25.8, 24.7, 22.8, 18.0, 14.1, -4.8; MS (*m/z*): 475 (M^+); HRMS *m/z* calcd (EI) for $C_{28}H_{49}NO_3Si(M^+)$: 475.3482, found: 475.3459.

(3*R*,5*S*)-1-Benzyl-5-[(4-methoxymethoxy)but-1-enyl]-5-pentylpyrrolidin-3-ol (30). Desilylation of **28** (2.18 g, 4.60 mmol) with TBAF (1.0 M in THF, 6.9 mL, 6.9 mmol) in THF (6.9 mL) was carried out by the same procedure as described for the preparation of **22** to give **30** (1.6g, 95%) as a colorless oil; $[\alpha]_D^{24}$ +20.4 (*c* 1.0, $CHCl_3$); IR (thin film): 3425, 3084, 3061, 2952, 2931, 2870, 2822, 2797, 1495, 1454, 1379, 1364, 1208, 1149, 1112, 1033, 919, 832, 735, 699 cm^{-1}; ^1H NMR δ: 7.32-7.27 (m, 4H), 7.23-7.19 (m, 1H), 5.63 (d, *J* = 12.2 Hz, 1H), 5.48-5.44 (m, 1H), 4.63 (s, 2H), 4.23-4.20 (m, 1H), 3.80 (d, *J* = 13.3 Hz, 1H), 3.56 (t, *J* = 6.8 Hz, 2H), 3.44 (d, *J* = 13.3 Hz, 1H), 3.36 (s, 3H), 2.69 (dd, *J* = 5.3, 10.2 Hz, 1H), 2.63 (dd, *J* = 1.9, 10.2 Hz, 1H), 2.51-2.45 (m, 2H), 2.41 (dd, *J* = 7.3, 13.8 Hz, 1H), 2.09 (br s, 1H), 1.94 (dd, *J* = 2.9, 13.8 Hz, 1H), 1.78-1.64 (m, 2H), 1.55-1.23 (m, 6H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ: 140.2, 134.2, 128.4, 128.3, 127.9, 126.7, 96.4, 69.7, 67.4, 66.6, 59.2, 55.2, 52.0, 46.6, 37.0, 32.5, 29.6, 24.2, 22.7, 14.1; MS (*m/z*): 362 (M^++1); HRMS *m/z* (CI) calcd for $C_{22}H_{36}NO_3(M^+$+1): 362.2695, found: 362.2673.

(3*R*,5*S*)-1-Benzyl-5-[(4-methoxymethoxy)butyl]-5-pentylpyrrolidin-3-ol (32). Catalytic reduction of **30** (1.88 g, 5.21 mmol) over PtO_2 (59.1 mg, 0.26 mmol) was carried out by the same procedure as described for the preparation of **12** to give **32** (1.2 g, 61%) as a colorless oil; $[\alpha]_D^{23}$ +14.6 (*c* 1.0, $CHCl_3$); IR (thin film): 3437, 3085, 3061, 3027, 2932, 2870, 2822, 2794, 1495, 1454, 1364, 1212, 1151, 1112, 1044, 920, 772, 736, 698 cm^{-1}; ^1H NMR δ: 7.30-7.27 (m, 4H), 7.20-7.25 (m, 1H), 4.63 (s, 2H), 4.20-4.11 (m, 1H), 3.75 (d, *J* = 13.3 Hz, 1H), 3.55 (t, *J* = 6.5 Hz, 2H), 3.46 (d, *J* = 13.3 Hz, 1H), 3.37 (s, 3H), 2.77 (dd, *J* = 5.0, 9.9 Hz, 1H), 2.63 (dd, *J* = 1.8, 9.9 Hz, 1H), 2.07 (dd, *J* = 7.1, 14.0 Hz, 1H), 1.86 (br s, 1H), 1.71 (dd, *J* = 2.2, 14.1 Hz, 1H), 1.68-1.47 (m, 6H), 1.46-1.26 (m, 8H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR

δ: 140.6, 128.3, 128.2, 126.7, 96.4, 69.8, 67.8, 64.3, 58.7, 55.1, 51.2, 43.3, 36.0, 34.7, 32.6, 30.6, 24.0, 22.8, 21.4, 14.2; MS (*m/z*): 364 (M^++1); HRMS *m/z* (CI) calcd for $C_{22}H_{38}NO_3$(M^++1): 364.2851, found: 364.2854.

(5*R*)-1-Benzyl-5-[(4-methoxymethoxy)butyl]-5-pentylpyrrolidin-3-one (34). Oxidation of **32** (1.15 g, 3.17 mmol) using DMSO (1.4 mL, 19.0 mmol), DIPEA (4.50 mL, 25.4 mmol), and sulfur trioxide-pyridine complex (2.02 g, 12.7 mmol), was carried out according to the same procedure as described for the synthesis of **13** to give the ketone (**34**) (938 mg, 82%) as a colorless oil; $[\alpha]_D^{22}$ -5.1 (*c* 1.0, $CHCl_3$); IR (thin film): 3086, 3062, 3028, 2932, 2870, 2823, 2795, 1754, 1495, 1455, 1403, 1365, 1211, 1149, 1111, 1044, 919, 769, 735, 698 cm^{-1}; ^{1}H NMR δ: 7.33-7.28 (m, 4H), 7.25-7.21 (m, 1H), 4.62 (s, 2H), 3.76 (d, *J* = 13.4 Hz, 1H), 3.72 (d, *J* = 13.4 Hz, 1H), 3.55 (t, *J* = 6.3 Hz, 2H), 3.36 (s, 3H), 3.07 (s, 2H), 2.36 (s, 2H), 1.69-1.56 (m, 6H), 1.55-1.24 (m, 8H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ: 214.6, 139.2, 128.4, 128.1, 127.0, 96.4, 67.6, 64.1, 58.8, 55.2, 51.5, 46.0, 34.64, 36.56, 32.6, 30.4, 24.2, 22.7, 21.2, 14.1; MS (*m/z*): 362 (M^++1); HRMS *m/z* (CI) calcd for $C_{22}H_{36}NO_3$(M^++1): 362.2695, found: 362.2673.

(2*S*,4*R*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-2-[4-(2-methoxyethoxymethoxy)but-1-enyl]-2-pentyl-pyrrolidine (29). Wittig reaction of **8** (2.12 g, 5.45 mmol) with 3-[(2-methoxyethoxy)methoxy]-propyltriphenylphosphonium bromide (4.00 g, 8.18 mmol) and *n*-BuLi (1.59 M in *n*-hexane, 4.80 mL, 7.63 mmol) was carried out by the same procedure as for the preparation of **10** to give the olefin (**29**) (1.9 g, 68%) as a colorless oil; $[\alpha]_D^{19}$ -11.4 (*c* 1.0, $CHCl_3$); IR (thin film): 2954, 2929, 2858, 1471, 1378, 1363, 1254, 1119, 1097, 1046, 915, 836, 774, 734, 699 cm^{-1}; ^{1}H NMR δ: 7.35-7.29 (m, 4H), 7.24-7.20 (m, 1H), 5.58 (d, *J* = 12.1 Hz, 1H), 5.45-5.39 (m, 1H), 4.74 (s, 2H), 4.33 (sept, *J* = 3.7 Hz, 1H), 3.72-3.69 (m, 3H), 3.63-3.56 (m, 5H), 3.41 (s, 3H), 2.91 (dd, *J* = 6.9, 10.0 Hz, 1H), 2.64-2.56 (m, 2H), 2.53 (dd, *J* = 3.9, 10.0 Hz, 1H), 2.23 (dd, *J* = 7.6, 13.0 Hz, 1H), 1.96 (dd, *J* = 3.8, 13.0 Hz, 1H), 1.77-1.69 (m, 1H), 1.66-1.59 (m, 1H), 1.51-1.25 (m, 6H), 0.91 (t, *J* = 7.0 Hz, 3H), 0.87 (s. 9H), 0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR δ: 140.7, 135.1, 128.2, 128.1, 127.7, 126.4, 95.5, 71.8, 70.1, 67.6, 66.83, 66.75, 59.5, 59.0, 52.4, 46.0, 34.9, 32.8, 29.4, 25.8, 24.7, 22.8, 18.0, 14.1, -4.8; MS (*m/z*): 520 (M^++1); HRMS *m/z* (CI) calcd for $C_{30}H_{54}NO_4Si$(M^++1): 520.3822, found: 520.3828.

(3*R*,5*S*)-1-Benzyl-5-[4-(2-methoxyethoxymethoxy)but-1-enyl]-5-pentylpyrrolidin-3-ol (31). Desilylation of **29** (1.38 g, 2.66 mmol) with TBAF (1.0 M in THF, 4.0 mL, 4.0 mmol) in THF (30.0 mL) was carried out by the same procedure as described for the preparation of **22** to give **31** (955 mg, 89%) as a colorless oil; $[\alpha]_D^{19}$ +18.7 (*c* 1.0, $CHCl_3$); IR (thin film): 3450, 2952, 2931, 2871, 1495, 1454, 1365, 1200, 1117, 1097, 1074, 1039, 849, 774, 734, 699 cm^{-1}; ^{1}H NMR δ: 7.32-7.27 (m, 4H), 7.24-7.20 (m, 1H), 5.65 (d, *J* = 12.2 Hz, 1H), 5.48-5.41 (m, 1H), 4.73 (s, 2H), 4.27-4.20 (m, 1H), 3.81 (d, *J* = 13.3 Hz, 1H),

3.73-3.67 (m, 2H), 3.61-3,56 (m, 4H), 3.44 (d, *J* = 13.3 Hz, 1H), 3.40 (s, 3H), 2.69 (dd, *J* = 5.0, 10.2 Hz, 1H), 2.65 (dd, *J* = 1.9, 10.2 Hz, 1H), 2.47 (ddd, *J* = 1.9, 7.1, 8.6 Hz, 2H), 2.41 (dd, *J* = 7.1, 13.8 Hz, 1H), 1.96 (dd, *J* = 2.6, 13.8 Hz, 1H), 1.89 (br s, 1H), 1.77-1.64 (m, 2H), 1.56-1.26 (m, 6H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ: 140.3, 134.2, 128.4, 128.3, 128.0, 126.7, 95.5, 71.8, 69.7, 67.4, 66.8, 66.5, 59.2, 59.0, 52.0, 46.5, 37.0, 32.5, 29.6, 24.2, 22.7, 14.1; MS (*m/z*): 406 (M^++1); HRMS *m/z* (CI) calcd for $C_{24}H_{40}NO_4$(M^++1): 406.2957, found: 406.2942.

(3*R*,5*S*)-1-Benzyl-5-[4-(2-methoxyethoxymethoxy)butyl]-5-pentylpyrrolidin-3-ol (33). Catalytic reduction of **31** (1.28 mg, 3.16 mmol) over PtO_2 (21.5 mg, 0.09 mmol) was carried out by the same procedure as described for the preparation of **12** to give **33** (818 mg, 64%) as a colorless oil; $[\alpha]_D^{18}$ +11.2 (*c* 1.0, $CHCl_3$); IR (thin film): 3441, 3085, 3061, 3027, 2932, 2871, 2816, 1495, 1454, 1365, 1244, 1200, 1117, 1097, 1048, 982, 849, 736, 698 cm^{-1}; ^{1}H NMR δ: 7.30-7.27 (m ,4H), 7.25-7.20 (m, 1H), 4.73 (s, 2H), 4.20-4.11 (m, 1H), 3.74 (d, *J* = 13.3 Hz, 1H), 3.71-3.69 (m, 2H), 3.59-3.56 (m, 4H), 3.45 (d, *J* = 13.3 Hz, 1H), 3.40 (s, 3H), 2.77 (dd, *J* = 5.0, 9.9 Hz, 1H), 2.62 (dd, *J* = 1.9, 9.9 Hz, 1H), 2.06 (dd, *J* = 7.0, 14.0 Hz, 1H), 1.85 (br s, 1H), 1.70 (dd, *J* = 1.9, 14.0 Hz, 1H), 1.59 (pent, *J* = 6.6 Hz, 2H), 1.55-1.46 (m, 3H), 1.45-1.24 (m, 9H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ: 140.6, 128.3, 128.2, 126.7, 95.5, 71.8, 69.7, 67.8, 66.7, 64.4, 59.0, 58.7, 51.2, 43.3, 35.9, 34.7, 32.6, 30.6, 24.0, 22.7, 21.4, 14.2; MS (*m/z*): 407 (M^+); HRMS *m/z* (EI) calcd for $C_{24}H_{41}NO_4$(M^+): 407.3035, found: 407.3046.

(5*R*)-1-Benzyl-5-[4-(2-methoxyethoxymethoxy)butyl]-5-pentylpyrrolidin-3-one (35). Oxidation of **33** (818 mg, 2.01 mmol) using DMSO (0.86 mL, 12.1 mmol), DIPEA (2.87 mL, 16.1 mmol), and sulfur trioxide-pyridine complex (1.31 g, 8.04 mmol), was carried out according to the same procedure as described for the synthesis of **13** to give the ketone (**35**) (596 mg, 73%) as a colorless oil; $[\alpha]_D^{22}$ -5.1 (*c* 1.0, $CHCl_3$); IR (thin film): 3085, 3062, 3028, 2932, 2871, 1754, 1495, 1455, 1365, 1244, 1175, 1116, 1096, 1046, 981, 736, 699 cm^{-1}; ^{1}H NMR δ: 7.33-7.30 (m, 4H), 7.25-7.21 (m, 1H), 4.71 (s, 2H), 3.75-3.65 (m, 4H), 3.62-3.52 (m, 4H), 3.39 (s, 3H), 3.06 (s, 2H), 2.35 (s, 2H), 1.63-1.57 (m, 6H), 1.55-1.28 (m, 8H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ: 214.4, 139.1, 128.4, 128.1, 127.0, 95.5, 71.8, 67.6, 66.7, 64.1, 59.0, 58.7, 51.5, 46.0, 34.7, 34.6, 32.6, 30.3, 24.2, 22.6, 21.2, 14.1; MS (*m/z*): 406 (M^++1); HRMS *m/z* (CI) calcd for $C_{24}H_{40}NO_4$(M^++1): 406.2957, found: 406.2927.

(4*R*)-4-Benzylamino-4-[(4-methoxymethoxy)butyl]-nonan-2-one (37). Sm-promoted fragmentation of **35** (189 mg, 0.52 mmol) with SmI_2 (0.1 M in THF, 26.2 mL, 2.62 mmol) in the presence of H_2O (24 μL, 1.31 mmol) was carried out by the same procedure as described for the preparation of **26** to give **37** (86 mg, 45%) as a colorless oil; $[\alpha]_D^{20}$ +0.7 (*c* 1.01, $CHCl_3$); IR (thin film): 2931, 2870, 1707, 1607, 1455, 1356, 1148, 1111, 1044, 920, 733, 699 cm^{-1}; ^{1}H NMR δ: 7.35-7.28 (m, 4H), 7.24-7.20 (m, 1H), 4.61 (s,

2H), 3.61-3.50 (m, 4H), 3.35 (s, 3H), 2.55 (s, 2H), 2.17 (s, 3H), 1.82 (br s, 1H), 1.43-1.65 (m, 6H), 1.25-1.42 (m, 8H), 0.89 (t, J = 6.3 Hz, 3H); ^{13}C NMR δ: 208.7, 141.0, 128.4, 128.3, 126.8, 96.5, 67.7, 57.6, 55.1, 47.8, 46.0, 36.2, 36.1, 32.4, 32.2, 30.2, 23.0, 22.7, 20.0, 14.1; MS (*m/z*): 408 (M^+-117); HRMS *m/z* (EI) calcd for $C_{16}H_{24}NO$ (M^+-117): 246.1881, found: 246.1858.

(4*R*)-4-Benzylamino-4-[4-(2-methoxyethoxymethoxy)butyl]-nonan-2-one (38). Sm-promoted fragmentation of **36** (150 mg, 0.37 mmol) with SmI_2 (0.2 M in THF, 9.3 mL, 1.85 mmol) in the presence of H_2O (17 μL, 0.93 mmol) was carried out by the same procedure as described for the preparation of **26** to give **38** (80 mg, 53%) as a colorless oil; $[\alpha]_D^{18}$ -1.3 (*c* 2.0, $CHCl_3$); IR (thin film): 2931, 2870, 1708, 1609, 1455, 1364, 1117, 1047, 849, 735, 699 cm^{-1}; ^{1}H NMR δ: 7.35-7.26 (m, 4H), 7.27-7.18 (m, 1H), 4.71 (s, 2H), 3.75-3.42 (m, 8H), 3.39 (s, 3H), 2.57 (s, 2H), 2.17 (s, 3H), 1.44-1.71 (m, 6H), 1.41-1.16 (m, 8H), 0.89 (t, J = 6.2 Hz, 3H); ^{13}C NMR δ: 208.7, 140.8, 128.4, 128.3, 126.8, 95.5, 71.8, 67.8, 66.7, 59.0, 57.7, 47.8, 45.9, 36.2, 36.0, 32.4, 32.2, 30.2, 23.0, 22.6, 20.0, 14.1; MS (*m/z*): 408 (M^++1); HRMS *m/z* (CI) calcd for $C_{24}H_{42}NO_4$ (M^++1): 407.3090, found: 407.3114.

***tert*-Butyl (2*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-2-hydroxymethyl-2-pentylpyrrolidine-1-carboxylate (40) and *tert*-butyl (2*R*,4*R*)-4-hydroxy-2-hydroxymethyl-2- pentylpyrrolidine-1-carboxylate (41).** To a stirred solution of methyl (2*S*,4*R*)-1-*tert*-butoxycarbonyl-4-(*tert*-butyldimethylsilyloxy)-L-prolinate (**39**) (5.8 g, 16.2 mmol) in THF (90 mL) was added a solution of LiHMDS (1.6 M in THF, 20 mL, 32.3 mmol) at -20 °C, and the mixture was stirred for a further 2 h. To this solution was added a solution of 1-iodopentane (8.02 g, 40.5 mmol) in THF (20 mL) and the whole mixture was gradually warmed up to 0 °C and stirred for 4 h at the same temperature. After treatment with saturated aqueous NH_4Cl solution, the mixture was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which, without separation, was used in the next step. Analytical sample of each ester was obtained by careful separation using column chromatography on silica gel. Elution with *n*-hexane:AcOEt (10:1 v/v) afforded each esters.

Less polar ester; $[\alpha]_D^{26}$ +18.2 (*c* 1.0, $CHCl_3$); IR (thin film): 2955, 2931, 2856, 1746, 1704, 1471, 1463, 1434, 1393, 1366, 1318, 1254, 1150, 1129, 1102, 1047, 1006, 910, 838, 777, 735, 672 cm^{-1}; ^{1}H NMR δ: 4.44-4.37 (m, 1H), 3.95-3.78 (m, 1H), 3.70 (s, 3H), 3.15-3.08 (m, 1H), 2.30-1.96 (m, 3H), 1.93-1.79 (m, 1H), 1,49-1.21 (m, 6H), 1,42 (s, 9H), 0.92-0.88 (m, 12H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR δ: 175.06, 174.98, 153.7, 153.5, 79.9, 79.5, 68.5, 67.9, 67.3, 66.9, 55.4, 54.9, 52.01, 51.95, 44.8, 43.7, 35.0, 33.8, 32.0, 31.9, 28.3, 28.2, 25.7, 25.6, 23.1, 22.9, 22.5, 17.9, 14.01, 13.96, -4.9, -5.0; MS (*m/z*): 430 (M^++1); HRMS *m/z* (CI) calcd for $C_{22}H_{44}NO_5Si$ (M^++1): 430.2988, found: 430.3017.

More polar ester; $[\alpha]_D^{23}$ +7.9 (*c* 1.0, $CHCl_3$); IR (thin film): 2956, 2931, 2859, 1747, 1703, 1472, 1391,

1366, 1255, 1166, 1122, 1080, 1031, 1007, 837, 777 cm^{-1}; ^1H NMR δ: 4.35-4.23 (m, 1H), 3.71-3.61 (m, 1H), 3.70 (s, 3H), 3.45-3.29 (m, 1H), 2.31-2.02 (m. 3H), 1.85-1.77 (m, 1H), 1.43 (s, 9H), 1.32-1.15 (m, 6H), 0.91-0.85 (m, 12H), 0.46 (s, 3H), 0.42 (s, 3H); ^{13}C NMR δ: 175.1, 174.8, 154.0, 153.9, 79.9, 79.4, 68.8, 68.2, 67.7, 67.3, 63.4, 56.1, 56.0, 52.0, 46.1, 44.8, 35.5, 34.4, 31.9, 31.8, 28.4, 28.3, 25.73, 25.67, 23.4, 23.1, 22.5, 18.0, 14.0, 13.9, -4.9, -5.0; MS (*m/z*): 430 (M^++1); HRMS *m/z* (CI) calcd for $C_{22}H_{44}NO_5Si$ (M^++1): 430.2988, found: 430.3004.

To a stirred solution of the mixture obtained above in THF (100 mL) was added dropwise DIBAL (1.02 M in *n*-hexane, 48.0 mL, 48.6 mmol) at -40 °C, and the resulting solution was gradually warmed to 0 °C and stirred for 5 h at the same temperature. After the mixture was treated with saturated aqueous NH_4Cl solution, the whole mixture was stirred for a further 30 min. The insoluble material was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with *n*-hexane:AcOEt (5:1 v/v) gave the alcohol (**41**) (2.1 g, 33 %) as a colorless oil; $[\alpha]_D^{26}$ -5.2 (*c* 1.0, $CHCl_3$); IR (thin film): 3402, 2956, 2930, 2859, 1696, 1672, 1472, 1398, 1366, 1255, 1173, 1077, 837, 776 cm^{-1}; ^1H NMR δ: 5.15 (d, *J* = 8.8 Hz, 1H), 4.28-4.22 (m, 1H), 3.97-3.81 (m, 1H), 3.72-3.63 (m, 1H), 3.49-3.33 (m, 2H), 2.30-2.07 (m, 1H), 1.97-1.61 (m, 3H), 1.47 (s, 9H), 1.36-1.04 (m, 6H), 0.91-0.87 (m, 12H), 0.10 (m, 6H), 0.08 (s, 3H); ^{13}C NMR δ: 155.6, 154.5, 79.9, 69.2, 68.7, 68.6, 68.0, 67.5, 66.5, 58.1, 57.1, 45.2, 44.0, 35.6, 33.3, 32.2, 32.1, 28.48, 28.44, 25.7, 23.6, 22.6, 22.5, 17.9, 14.01, 13.98, -4.87, -4.92; MS (*m/z*): 402 (M^++1); HRMS *m/z* (CI) calcd for $C_{21}H_{44}NO_4Si$ (M^++1): 402.3039, found: 402.3013.

Further elution with the same solvent system afforded the diastereoisomeric alcohol (**40**) (3.3 g, 51 %) as a colorless oil; $[\alpha]_D^{23}$ +0.8 (*c* 1.0, $CHCl_3$); IR (thin film): 3403, 2956, 2930, 2859, 1697, 1671, 1471, 1398, 1366, 1254, 1174, 1133, 1095, 1047, 919, 837, 776 cm^{-1}; ^1H NMR δ: 5.15 (dd, *J* = 2.1, 9.3 Hz, 1H), 4.39-4.23 (m, 1H), 3.84-3.34 (m, 3H), 3.24 (dd, *J* = 3.8, 11.6 Hz, 1H), 2.19-2.02 (m, 1H), 1.94-1.80 (m, 2H), 1.64 (dd, *J* = 6.0, 6.8 Hz, 1H), 1.47 (s, 9H), 1.40-1.09 (m, 6H), 0.89-0.86 (m, 12H), 0.06 (s, 6H); ^{13}C NMR δ: 155.9, 80.1, 68.9, 68.6, 67.8, 56.9, 42.3, 32.4, 32.2, 28.4, 25.7, 24.0, 22.7, 17.9, 14.1, -4.8, -4.9; MS (*m/z*): 402 (M^++1); HRMS *m/z* (CI) calcd for $C_{21}H_{44}NO_4Si$ (M^++1): 402.3039, found: 402.3052.

(2*S*,4*R*)1-*tert*-Butoxycarbonyl-4-(*tert*-butyldimethylsilyloxy)-2-pentyl-2-pyrrolidinecarboxaldehyde (42). Oxidation of **40** (5.95 g, 14.8 mmol) with DMSO (6.30 mL, 88.8 mmol), DIPEA (21.0 mL, 118.4 mmol), and sulfur trioxide-pyridine complex (9.60 g, 59.3 mmol), was carried out by the same procedure as for the preparation of **8** to give the aldehyde (**42**) (5.5 g, 92%) as a colorless oil; $[\alpha]_D^{24}$ -13.3 (*c* 1.2, $CHCl_3$); IR (thin film): 2956, 2930, 2859, 1738, 1698, 1471, 1392, 1367, 1255, 1153, 1101, 1078, 1040, 911, 838, 777 cm^{-1}; ^1H NMR δ: 9.50 (br s, 1H), 4.35-4.28 (m, 1H), 3.89-3.72 (m, 1H), 3.27-3.15 (m, 1H),

2.17-1.80 (m, 4H), 1.44 (s, 9H), 1.37-1.26 (m, 6H), 0.92-0.88 (m, 12H), 0.08 (s, 6H). 0.04 (s, 3H); ^{13}C NMR δ: 200.9, 199.7, 153.9, 153.3, 80.9, 80.1, 70.7, 70.6, 69.1, 68.4, 55.7, 55.6, 41.6, 40.4, 32.9, 32.2, 32.1, 32.0, 28.3, 28.2, 25.7, 22.6, 22.5, 17.9, 14.03, 13.97, -4.88, -4.95, -5.00; MS (*m/z*): 422 (M^++Na); HRMS *m/z* (ESI) calcd for $C_{21}H_{41}NO_4SiNa$ (M^++Na): 422.2703, found: 422.2715.

***tert*-Butyl (2*S*,4*R*)-4-*tert*-butyldimethylsilyloxy-2-{[(1*Z*)-4-*tert*-butyldimethylsilyloxy]but-1-en-1-yl}-2-pentylpyrrolidine-1-carboxylate (43).** Wittig reaction of **42** with [3-(*tert*–butyldimethylsilyl)-oxypropyl]triphenylphosphonium bromide (3.75 g, 7.26 mmol) and *n*-BuLi (1.65 M in *n*-hexane, 4.3 mL, 7.04 mmol) was carried out by the same procedure as described for the synthesis of **28** to provide the olefin (**43**) (2.3 g, 87%) as a colorless oil; $[\alpha]_D^{26}$ -25.5 (*c* 1.0, $CHCl_3$); IR (thin film): 2956, 2929, 2897, 2858, 1704, 1692, 1472, 1463, 1389, 1364, 1255, 1173, 1131, 1102, 1037, 1006, 920, 837, 776 cm^{-1}; ^{1}H NMR δ: 5.62-5.67 (m, 1H), 5.19-5.25 (m, 1H), 4.21-4.28 (m, 1H), 3.56-3.78 (m, 3H), 3.10-3.18 (m, 1H), 2.21-2.27 (m, 2H), 2.13-2.19 (m, 1H), 1.98-2.11 (m, 2H), 1.69-1.85 (m, 1H), 1.44 (s, 9H), 1.09-1.41 (m, 6H), 0.88-0.89 (m, 21H), 0.05-0.06 (m, 12H); ^{13}C NMR δ: 154.0, 152.9, 138.1, 136.9, 126.34, 126.30, 79.4, 78.8, 68.5, 67.9, 65.4, 64.9, 63.0, 62.9, 55.4, 55.1, 46.8, 45.8, 39.1, 37.8, 32.3, 32.0, 31.6, 28.5, 25.9, 25.8, 23.8, 23.7, 22.74, 22.68, 18.3, 18.0, 14.1, 14.0, -4.80, -4.86, -4.94, -5.29; MS (*m/z*): 556 (M^++1); HRMS *m/z* (CI) calcd for $C_{30}H_{62}NO_4Si_2$ (M^++1): 556.4217, found: 556.4240.

***tert*-Butyl (2*S*,4*R*)-4-Hydroxy-2-[(1*Z*)-4-hydroxybut-1-en-1-yl]-2-pentylpyrrolidine-1-carboxylate (44).** Desilylation of **43** (2.26 g, 4.08 mmol) with TBAF (1.0 M in THF, 12.2 mL, 12.2 mmol) in THF (20.0 mL) was carried out by the same procedure as described for the preparation of **22** to give diol (**44**) (1.3 g, 100 %) as a colorless oil; $[\alpha]_D^{22}$ -38.1 (*c* 1.0, $CHCl_3$); IR (thin film): 3403, 2957, 2930, 2871, 1669, 1454, 1401, 1366, 1253, 1171, 1067, 1006, 863, 772 cm^{-1}; ^{1}H NMR δ: 5.64 (dt, *J* = 1.8, 12.1 Hz, 1H), 5.29-5.19 (m, 1H), 4.42-4.34 (m, 1H), 3.88-3.75 (m, 1H), 3.66 (d, *J* = 5.1 Hz, 2H), 3.29-3.18 (m, 1H), 2.31-1.71 (m, 8H), 1.44 (s. 9H), 1.40-1.17 (m, 6H), 0.94-0.84 (m, 3H); ^{13}C NMR δ: 154.3, 153.2, 138.1, 137.1, 124.6, 123.7, 80.0, 79.3, 67.4, 66.7, 65.6, 65.2, 62.3, 62.1, 55.0, 46.1, 45.7, 39.1, 37.7, 32.1, 31.9, 31.2, 30.8, 28.5, 23.6, 23.4, 22.7, 14.1, 14.0; MS (*m/z*): 327 (M^+); HRMS *m/z* (EI) calcd for $C_{18}H_{33}NO_4$ (M^+): 327.2409, found: 327.2391.

***tert*-Butyl (2*S*,4*R*)-4-Hydroxy-2-(4-hydroxybut-1-yl]-2-pentylpyrrolidine-1-carboxylate (45).** Catalytic reduction of **44** (1.33 g, 4.08 mmol) over PtO_2 (45 mg, 0.20 mmol) was carried out by the same procedure as described for the preparation of **12** to give **45** (931 mg, 70%) as a colorless oil; $[\alpha]_D^{22}$ -3.1 (*c* 1.0, $CHCl_3$); IR (thin film): 3402, 2953, 2931, 2864, 1664, 1477, 1455, 1409, 1366, 1251, 1172, 1140, 1072, 1007, 922, 862, 772, 734, 646 cm^{-1}; ^{1}H NMR δ: 4.36-4.30 (m. 1H), 3.76-3.58 (m, 3H), 3.23 (pent, *J* = 6.0 Hz, 1H), 2.81 (br s, 1H), 2.34 (br s, 1H), 2.11-1.48 (m, 8H), 1.44 (d, *J* = 10.6 Hz, 9H), 1.38-1.10 (m,

8H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ: 154.5, 153.6, 79.7, 79.0, 67.9, 67.1, 66.0, 65.5, 62.6, 62.1, 56.24, 56.20, 43.9, 43.0, 39.5, 39.1, 38.3, 36.9, 33.1, 32.3, 32.1, 28.6, 28.5, 23.9, 23.7, 22.7, 20.7, 20.2, 14.1, 14.0; MS (*m/z*): 329 (M^+); HRMS *m/z* (EI) calcd for $C_{18}H_{35}NO_4$ (M^+): 329.2566, found: 329.2558.

***tert*-Butyl (2*R*)-2-(4-methoxy-4-oxobutyl)-4-oxo-2-pentylpyrrolidine-1-carboxylate (46).** To a stirred mixture of PCC (647 mg, 2.94 mmol), powdered molecular sieves (300 mg) and CH_2Cl_2 (6.00 mL) was added a solution of **45** (324 mg, 0.98 mmol) in CH_2Cl_2 (4.00 mL) at rt, and the resulting mixture was stirred for a further 30 min at the same temperature. Insoluble materials were removed by filtration through a pad of Celite, and the filtrate was concentrated to leave a residue, which was then dissolved into a mixture of *tert*-BuOH (4.00 mL) and THF (4.00 mL). To this solution were successively added 2-methyl-2-butene (0.83 mL, 7.84 mmol), $NaClO_2$ (266 mg, 2.94 mmol) and a solution of $NaH_2PO_4 \cdot 2H_2O$ (459 mg, 2.94 mmol) in H_2O (3.0 mL) at rt. After being stirred at rt for 2 h, the mixture was treated with saturated aqueous NH_4Cl solution and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was dissolved into DMF (5.00 mL). To this solution was added K_2CO_3 (271 mg, 1.96 mmol) and then MeI (275 mL, 4.41 mmol), and the whole mixture was stirred for 3 h at rt. The mixture was treated with brine and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane:AcOEt (4:1 v/v) gave the ester (**46**) (136 mg, 39%) as a colorless oil; $[\alpha]_D^{22}$ -4.3 (*c* 1.0, $CHCl_3$); IR (thin film): 2956, 2930, 2860, 1763, 1740, 1703, 1455, 1439, 1393, 1367, 1256, 1170, 1138, 1107, 994, 873, 772 cm^{-1}; ^{1}H NMR δ: 3.89 (s, 1H), 3.82 (s, 1H), 3.67 (s, 3H), 2.70-2.47 (m, 2H), 2.43-2.27 (m, 2H), 2.26-2.17 (m, 1H), 2.05 (br s, 1H), 1.89-1.56 (m, 4H), 1.48 (d, J = 19.5 Hz, 9H), 1.37-1.08 (m, 8H), 0.92-0.84 (m, 3H); ^{13}C NMR δ: 210.3, 209.5, 173.7, 173.4, 154.2, 153.1, 80.7, 79.8, 64.8, 64.3, 56.6, 56.5, 51.5, 48.0, 47.2, 39.7, 39.2, 38.3, 37.8, 33.9, 33.8, 32.0, 31.8, 28.44, 28.37, 23.5, 23.3, 22.5, 19.4, 13.9; MS (*m/z*): 355 (M^+); HRMS *m/z* (EI) calcd for $C_{19}H_{33}NO_5$ (M^+): 355.2344, found: 355.2358.

Methyl [(2*R*)-4-oxo-2-pentylpyrrolidin-2-yl]butanone (47). To a stirred solution of **46** (640.0 mg, 1.80 mmol) in CH_2Cl_2 (18.00 mL) was added $ZnBr_2$ (812 mg, 3.60 mmol) at rt, and the resulting mixture was stirred overnight at the same temperature. After removal of insoluble materials by filtration through a pad of Celite, the filtrate was treated with saturated aqueous $NaHCO_3$ solution, and then extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane:AcOEt (4:1 v/v) afforded the ester (**47**); $[\alpha]_D^{22}$ +3.7 (*c* 1.1, $CHCl_3$); IR (thin film): 3471, 3141, 2955, 2871, 1766, 1715, 1621, 1457, 1440, 1375, 1278, 1178 cm^{-1}; ^{1}H NMR δ: 3.69 (s, 3H), 3.34 (d, J = 1.2 Hz, 2H), 2.34 (t, J =

7.0 Hz, 2H), 2.19 (s, 2H), 1.82-1.41 (m, 7H), 1.37-1.18 (m, 6H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR δ: 218.3, 173.7, 62.2, 53.2, 51.6, 49.3, 37.9, 37.2, 34.1, 32.3, 23.9, 22.6, 19.6, 14.0; MS (*m/z*): 255 (M^+); HRMS *m/z* (EI) calcd for $C_{14}H_{25}NO_3$ (M^+): 255.1834, found: 255.1851}, which, without further purification, was used in the next step.

(8a*R*)-8a-Pentyltetrahydroindazolidine-2,5(1*H*,3*H*)-dione (48). A solution of **47** obtained above in toluene (15.0 mL) was heated at reflux for 10 h. Removal of the solvent leave a residue, which was purified by column chromatography on silica gel. Elution with AcOEt gave **48** (338 mg, 86%) as colorless solid; mp 50-52 °C; $[\alpha]_D^{23}$ -131.1 (*c* 1.0, $CHCl_3$); IR (thin film): 2955, 2933, 2860, 1763, 1644, 1456, 1409, 1181, 1149 cm^{-1}; ^{1}H NMR δ: 4.34 (d, *J* = 17.0 Hz, 1H), 3.67 (d, *J* = 17.0 Hz, 1H), 2.75 (dt, *J* = 4.4, 18.6 Hz, 1H), 2.67 (d, *J* = 17.5 Hz, 1H), 2.64 (dd, *J* = 8.9, 18.6 Hz, 1H), 2.47 (d, *J* = 17.5 Hz, 1H), 2.24 (dt, *J* = 3.4, 13.6 Hz, 1H), 1.96-1.89 (m, 2H), 1.77-1.68 (m, 2H), 1.60-1.53 (m, 1H), 1.37-1.14 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR: δ 208.3, 171.1, 64.2, 51.5, 30.4, 37.5, 31.8, 31.5, 30.4, 24.0, 22.4, 16.5, 13.9; MS (*m/z*): 223 (M^+); HRMS *m/z* (EI) calcd for $C_{13}H_{21}NO_2$ (M^+): 223.1572, found: 223.1557. Anal calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.79; H, 9.30; N, 6.18.

(2*RS*,8a*R*)-2-Hydroxy-8a-pentylhexahydroindolidin-5(1*H*)-one (49). Toa stirred solution of **48** (150 mg, 0.67 mmol) in THF (7.00 mL) were added SmI_2 (0.2 M in THF, 16.8 mL, 3.4 mmol) and H_2O (30 μL, 1.7 mmol) at 0 °C, and the resulting mixture was stirred for 5 h at the same temperature. The mixture was treated with saturated aqueous $NaHCO_3$ solution and Et_2O, and the whole mixture was stirred for 10 min. After removal of insoluble materials by filtration through a pad of Celite, the filtrate was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with AcOEt:MeOH (10:1 v/v) afforded the recovered starting material (**48**) (33 mg, 22%) and the inseparable mixture of alcohols (**49**) (93 mg, 61%) as a colorless oil; IR (thin film): 3380, 2953, 2931, 1614, 1461, 1410, 1115, 1049 cm^{-1}; ^{1}H NMR δ: 4.55-4.45 (m, 1H), 4.22-3.27 (m, 3H), 2.47-1.95 (m, 5H), 1.89-1.39 (m, 5H), 1.36-1.12 (m, 6H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR δ: 169.4, 168.9, 68.3, 68.0, 64.4, 64.3, 53.5, 52.8, 46.5, 46.3, 37.1, 36.2, 32.11, 32.09, 31.75, 31.71, 30.0, 29.8, 24.6, 24.3, 22.6, 22.5, 17.02, 16.97, 14.03, 13.98; MS (*m/z*): 225 (M^+); HRMS *m/z* (EI) calcd for $C_{13}H_{23}NO_2$ (M^+): 225.1729, found: 225.1715.

(-)-Adalinine (1). To a stirred solution of the ester (**46**) (200.0 mg, 0.56 mmol) in CH_2Cl_2 (6.00 mL) was added $ZnBr_2$ (254 mg, 1.12 mmol) at rt, and the resulting mixture was stirred overnight at the same temperature. After removal of insoluble materials by filtration through a pad of Celite, the filtrate was treated with saturated aqueous $NaHCO_3$ solution, and then extracted with $CHCl_3$. The extract was washed

with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which, without further purification, was used in the next step. The residue obtained above was dissolved into THF (6.0 mL). To this solution was added SmI_2 (0.2 M in THF, 14.0 mL, 2.8 mmol) and H_2O (25 μL, 1.4 mmol) at 0 °C, and the mixture was stirred for 30 min at the same temperature. The mixture was treated with saturated aqueous $NaHCO_3$ solution and Et_2O, and the whole mixture was stirred for 10 min. After removal of insoluble materials by filtration through a pad of Celite, the filtrate was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was dissolved into toluene (6.0 mL), and heated at reflux for 10 h. Removal of the solvent leave a residue, which was subjected to column chromatography on silica gel. Elution with AcOEt:MeOH (10:1 v/v) afforded adalinine (**1**) (17 mg, 16% from **46**) together with **48** (48 mg, 38%). The spectroscopic data including its optical rotaion were comparable to those reported; $[\alpha]_D^{22}$ -24.2 (*c* 1.5, CH_2Cl_2); IR (thin film): 3380, 3284, 3208, 3073, 2953, 2932, 2870, 1709, 1658, 1456, 1406, 1364, 1334, 1175, 1152, 957, 843, 726 cm^{-1}; ^1H NMR δ: 6.66 (br s, 1H), 2.71 (d, *J* = 17.8 Hz, 1H), 2.64 (d, *J* = 17.8 Hz, 1H), 2.35-2.23 (m, 2H), 2.14 (s, 3H), 1.85-1.52 (m, 6H), 1.32-1.11 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ: 207.3, 171.5, 56.2, 51.3, 39.3, 32.0, 31.8, 31.4, 31.3, 23.9, 22.5, 17.2, 14.0; MS (*m/z*): 225 (M^+); HRMS *m/z* (EI) calcd for $C_{13}H_{23}NO_2$ (M^+): 225.1729, found: 225.1738.

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