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CHIRAL SYNTHESIS OF (+)-FEBRIFUGINE AND (-)-ISOFEBRIFUGINE BY MEANS OF SAMARIUM DIIODIDE-PROMOTED CARBON-NITROGEN BOND CLEAVAGE REACTION†

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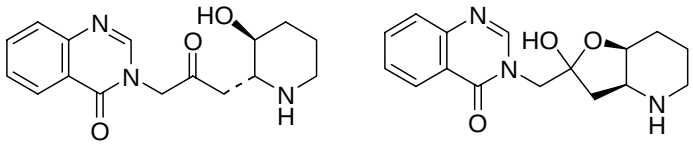
Abstract – (+)-Febrifugine, a potential anti-malarial piperidine alkaloid, was synthesized from (4*S*)-hydroxyproline methyl ester, stereoselectively, where a samarium diiodide-promoted carbon-nitrogen bond cleavage reaction was involved as a key reaction. A stereocontrolled formal synthesis of (-)-isofebrifugine was also described.

Febrifugine (**1**) and isofebrifugine (**2**) were isolated from the roots of *Dichroa febrifuga* Lour. (Chinese Name: Cháng Shan) in 1947, [1] and are recognized as active principles against malaria.[2] Structures including the absolute stereochemistries of those alkaloids were unambiguously established by their syntheses in 1999.[3]



1. Febrifugine **2.** Isofebrifugine

Figure 1. The structures of (+)-febrifugine and (+)-isofebrifugine.

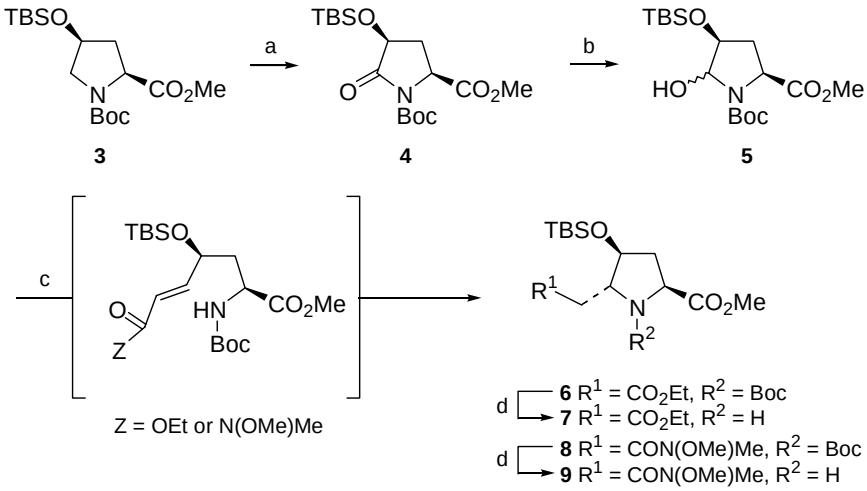
Since these alkaloids exhibit the attractive biological activity, a number of their racemic and chiral syntheses have been established.[4]

Recently, we have developed a novel carbon-nitrogen bond cleavage reaction of α-amino carbonyl compounds by using samarium diiodide as a one electron reducing agent,[5] and have applied the methodology to the synthesis of biologically active natural products.[6] As part of our continuing exploration of the samarium diiodide-promoted carbon-nitrogen bond cleavage reaction, we are interested in the synthesis of potential anti-malarial piperidine alkaloids, febrifugine and isofebrifugine.

Our synthesis of (+)-febrifugine starts from the stereoselective preparation of 4-hydroxy-5-alkyl-L-prolinate, as follows.

Oxidation of methyl *N*-Boc-(4*S*)-*tert*-butyldimethylsilyloxy-L-prolinate (**3**) with ruthenium tetroxide

according to the literature gave the lactam (**4**).[7] In order to synthesize (+)-febrifugine, a stereoselective introduction of an alkyl side chain at the 5-position of **4** with the 2,5-*trans*-stereochemistry would be required. Although a number of strategies have been developed for stereoselective introduction of an alkyl side chain at the 5-position of pyroglutamic acid ester,[8] some of them were found to have a limitation, in terms of nucleophilic species, conversion yield, reaction conditions, and stereoselectivity. Among the various reaction conditions attempted, we could find that a tandem Horner-Emmons-Michael reaction[9] gave the best results for introducing the desired alkyl side chain, in terms of yield and stereoselectivity. Thus, the lactam (**4**) was reduced with lithium triethylborohydride to give the aminal (**5**), which without purification, was treated with triethylphosphonoacetate in the presence of sodium hydride to afford the diester (**6**) in 62% from **4**. Although the diester (**6**) was obtained as a mixture of the amide rotamers, the stereochemistry at the 5-position was assumed to be *R*-configuration based on the analysis of the NMR spectral data. To determine the stereoselectivity of this reaction, the *N*-Boc group of **6** was removed by treatment with trifluoroacetic acid to give the amine (**7**) as the sole product. The spectroscopic data of **7** clearly indicated that a tandem Horner-Emmons-Michael reaction proceeded, stereoselectively, and the stereochemistry at the 5-position of **6** would be controlled during the intramolecular Michael addition of the nitrogen to the α,β-unsaturated ester, generated by the Horner-Emmons reaction, where the addition of the nitrogen might occur from the sterically less hindered side of the substrate.[9b] As the difficulties were mentioned for the selective reduction of the ethyl ester to manipulate the side chain prior to the reduction of the methyl ester, we attempted to prepare a more versatile precursor for further modification of the side chain.



Scheme 1. *Reagents and conditions*: (a) RuO_2 (cat), $NaIO_4$, AcOEt/H_2O, rt (86%); (b) $LiBEt_3H$, THF, -78°C; (c) $(EtO)_2P(O)CH_2CO_2Et$ or $(EtO)_2P(O)CH_2CON(OMe)Me$, NaH, THF, rt (**6**: 62% from **4**, **8**: 83% from **4**); (d) TFA, CH_2Cl_2, 0°C ~ rt (**7**: 53%, **9**: 56%).

Treatment of **5** with diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate in the presence of sodium hydride provided the amide (**8**) in 83% from **4**. The configuration at the 5-position of **8** was assumed to be *R* based on the analyses of NOE experiments, and was unambiguously determined by the X-Ray crystallographic analysis of the corresponding NH compound (**9**).

Since we could achieve the introduction of the side chain at the 5-position with the desired stereochemistry, we focused our attention on further utilization of the amide (**8**) in the synthesis of

(+)-febrifugine. Treatment of the amide (**8**) with methylmagnesium bromide gave the ketone (**10**), as the sole product, in 88% yield, which was further converted into the olefin (**11**) by methylenation with the Wittig reagent in 43% yield.

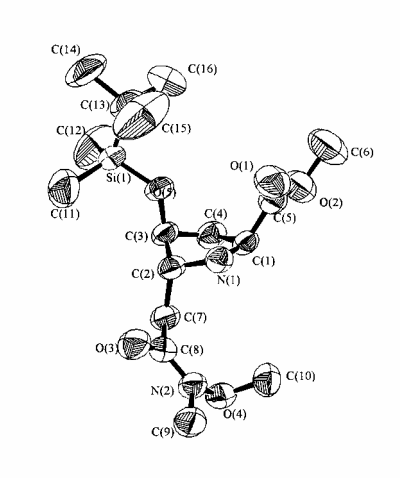
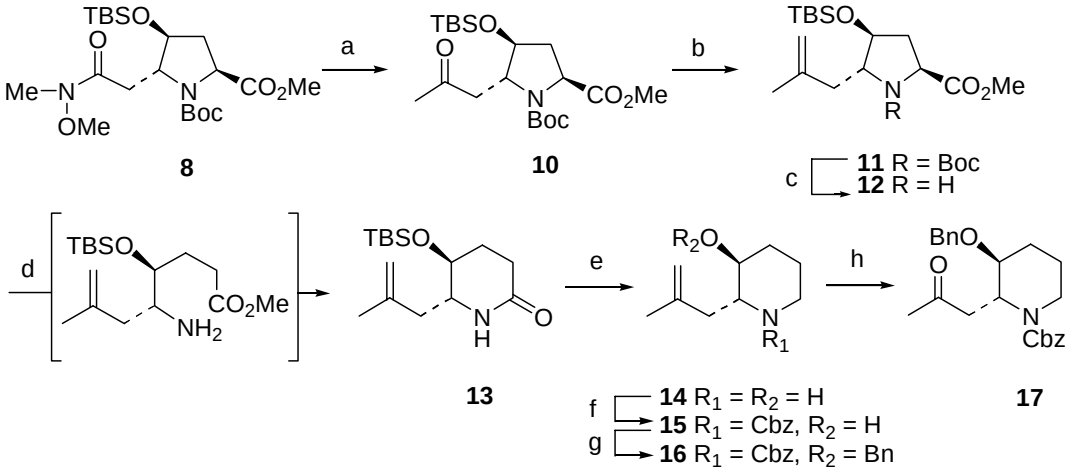


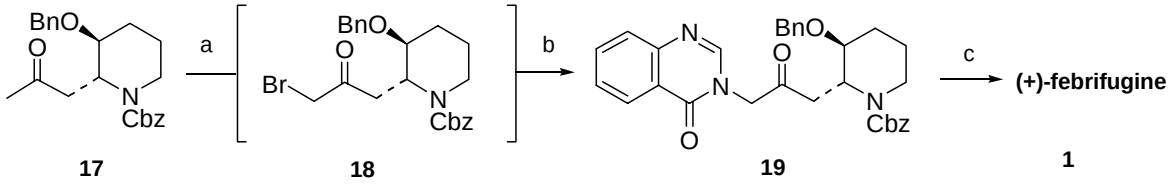
Figure 2. ORTEP Drawing of the compound (**9**).

The olefin (**11**) was also synthesized by treatment of **10** with Tebbe's reagent[10] in an improved yield (81%). After selective removal of the Boc group of **11** with zinc bromide, the resulting amine (**12**) was subjected to the key reductive deamination reaction by using samarium diiodide in the presence of methanol as the proton source to give the δ-lactam (**13**) arising from a recyclization of the carbon-nitrogen bond cleavage product, in 90% yield. Lithium aluminum hydride reduction of **13**, followed by treatment of the resulting hydroxy-amine (**14**) with CbzCl afforded the carbamate (**15**), where deprotection of the silyl group was observed during the reduction of the amide function. Protection of the secondary hydroxy group of **15** with benzyl bromide in the presence of sodium hydride gave the benzyl ether (**16**), which, on ozonolysis, followed by the usual reductive work-up with methyl sulfide, furnished the methyl ketone (**17**) in 83% yield from **15**.



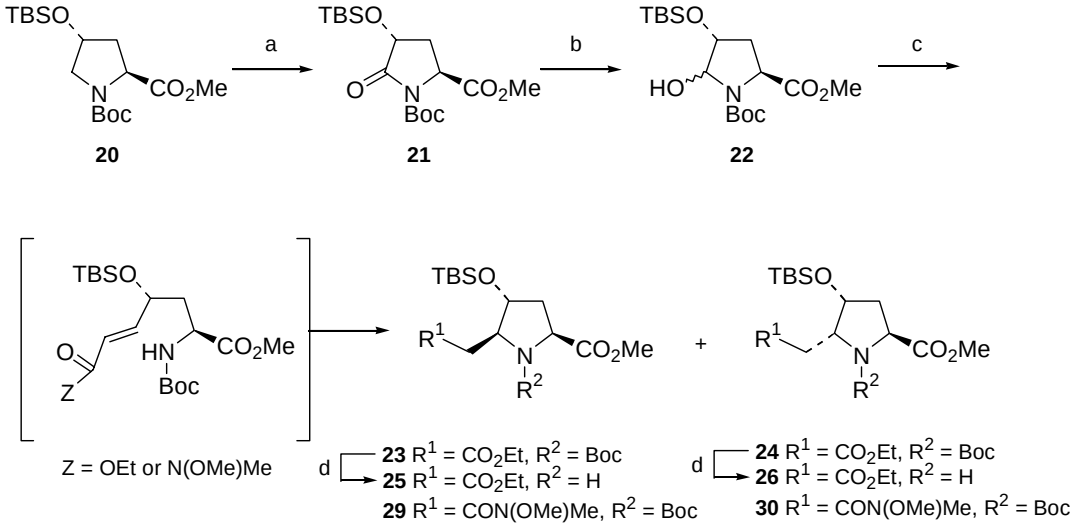
Scheme 2. *Reagents and conditions*: (a) MeMgBr, THF, 0°C (88%); (b) Tebbe's reagent, THF, -40°C ~ rt (81%); (c) $ZnBr_2$, CH_2Cl_2, rt; (d) SmI_2, THF-HMPA, MeOH, 0°C ~ rt (90% from **11**); (e) $LiAlH_4$, THF, 65°C; (f) CbzCl, TEA, DMAP, CH_2Cl_2, rt (95% from **13**); (g) BnBr, NaH, DMF, 0°C (90%); (h) O_3, MeOH, -78°C then Me_2S (92%).

Bromination of **17** was achieved by treatment with trimethylsilyl triflate and subsequently with *N*-bromosuccinimide to give the bromo ketone (**18**), which, without purification, was further coupled with 4-hydroxyquinazoline in the presence of potassium hydride in DMF to provide the protected febrifugine (**19**).



Scheme 3. *Reagents and conditions*: (a) i. TMSOTf, DIPEA, CH_2Cl_2, rt; ii. NBS, rt; (b) 4-hydroxyquinazoline, KH, DMF, 70°C (57% from **17**); (c) 6N HCl, reflux (92%).

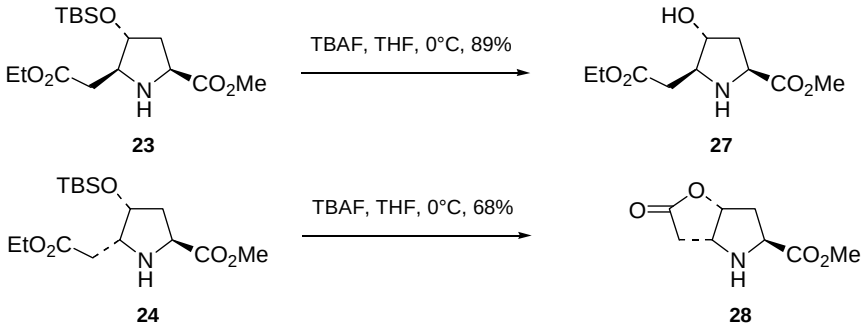
Finally, deprotection of **19** with 6N hydrochloric acid furnished (+)-febrifugine (**1**) in 92% yield. The spectroscopic data of the synthesized compound including the specific optical rotation were identical with those reported in the literatures, mp 139-140 °C; $[\alpha]_D$ +16.0° (*c* 0.4, MeOH) {lit.,[1b] mp 139-140 °C; lit.,[4b] mp 138-139 °C; lit.,[1c] $[\alpha]_D$ +13.0° (*c* 0.65, MeOH)}. Thus, we could develop a novel synthetic pathway to (+)-febrifugine by employing samarium diiodide-promoted reductive deamination, as a key reaction. Since this strategy seems to be applicable to the construction of functionalized piperidine rings in optically active forms, we next attempt the stereoselective synthesis of (-)-isofebrifugine, an antipodal form of the natural product, due to the accessibility of a starting material.



Scheme 4. *Reagents and conditions*: (a) RuO_2 (cat), $NaIO_4$, AcOEt/H_2O, rt (83%); (b) $LiBEt_3H$, THF, -78°C; (c) $(EtO)_2P(O)CH_2CO_2Et$ or $(EtO)_2P(O)CH_2CON(OMe)Me$, NaH, THF, rt (**29**: 5.5% from **21**, **30**: 60% from **21**); (d) TFA, CH_2Cl_2, 0°C ~ rt (**25**: 26% from **21**, **26**: 51% from **21**).

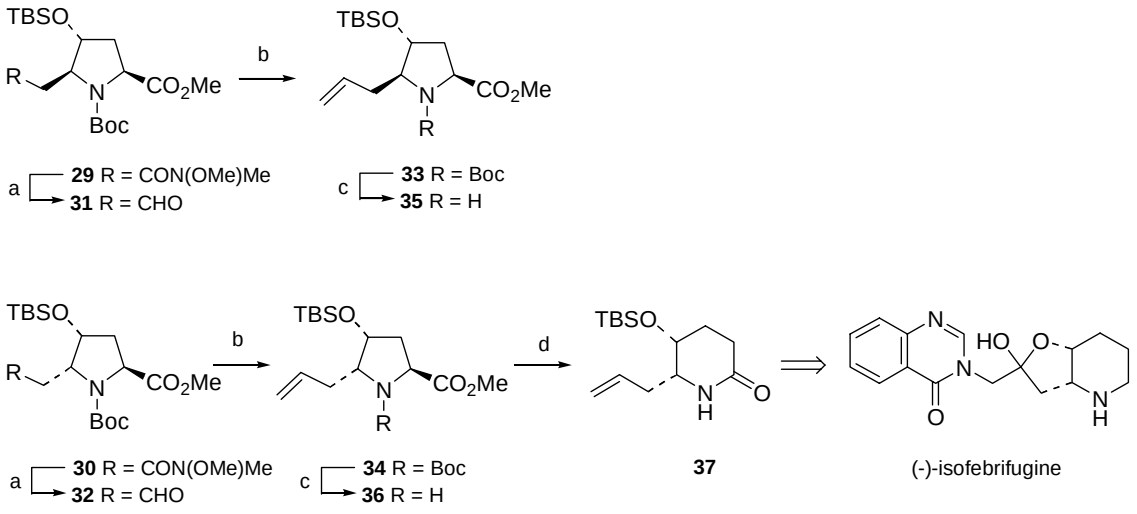
For the synthesis of (-)-isofebrifugine, an introduction of an alkyl side chain at the 5-position of 4-hydroxypyroglutamate would be required with the relative stereochemistry of 2,5-*trans*- and 4,5-*cis*-relationships.

Thus, a commercially available (4*R*)-hydroxy-L-proline was converted into the known *N*-Boc methyl ester (**20**),[7] which on oxidation with ruthenium tetroxide, gave the lactam (**21**) in 83% yield. Reduction of the lactam (**21**) with lithium triethylborohydride as described above, afforded the aminal (**22**). A tandem Horner-Emmons-Michael reaction of **22** with triethyl phosphonoacetate and sodium hydride in DMF gave an inseparable mixture of diastereomers (**23** and **24**), which, on deprotection of the *N*-Boc group with trifluoroacetic acid gave separable two compounds (**25** and **26**) in 77% yield, in a ratio of *ca*. 1 : 2. The structures of these compounds (**25** and **26**) were determined by treatment with tetrabutylammonium fluoride to furnish the alcohol (**27**) and the lactone (**28**), respectively.



Scheme 5. Structure determination of the compounds (**23** and **24**).

When a tandem Horner-Emmons-Michael reaction of **22** was carried out by using diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate as the Wittig reagent, the ratio of the products (**29** and **30**) was improved to *ca.* 1 : 11, where the desired compound (**30**) was found to be the major product. After separation by silica gel column chromatography, those amides (**29** and **30**) were converted into the secondary amines, respectively, as follows. Diisobutylaluminum hydride reduction of the amides (**29** and **30**), followed by methylenation of the resulting aldehydes (**31** and **32**) with methyltriphenylphosphonium bromide and *n*-butyllithium, provided the olefins (**33** and **34**).



Scheme 6. *Reagents and conditions*: (a) DIBAL, THF, -78°C; (b) $Ph_3P^+MeBr^-$, *n*-BuLi, THF, -78°C ~ rt (**33**: 25% from **29**, **34**: 60% from **30**); (c) $ZnBr_2$, CH_2Cl_2; (d) SmI_2, THF-HMPA, MeOH, 0°C ~ rt (71% from **34**).

Selective removal of the *N*-Boc groups of **33** and **34** was achieved by treatment with zinc bromide as described above to give the amines (**35** and **36**), respectively. The stereochemistries of **35** and **36** were determined based on the NMR spectral analysis, and the observed NOEs were depicted in Figure 3.[11]

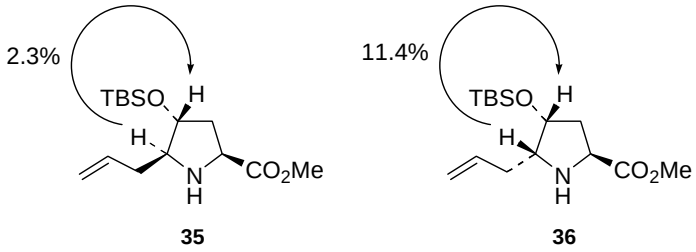


Figure 3. NOE Assignments of the compounds (**35** and **36**).

With the desired compound (**36**) in hands, we attempted its conversion into the corresponding δ-lactam by means of samarium diiodide-promoted reductive deamination reaction. Treatment of **36** with samarium diiodide in the presence of methanol as the proton source in THF-HMPA afforded the desired δ-lactam (**37**) in 71% yield. Again, spectroscopic data of **37** were identical with those reported in the literature[4m] except for the sign of optical rotation, {$[\alpha]_D$ +4.6° (*c* 0.2, $CHCl_3$); lit.,[4m] $[\alpha]_D$ -4.5° (*c* 1.05, $CHCl_3$)}. Since *ent*-**37** was already transformed into (+)-isofebrifugine,[4h] this synthesis constitutes the formal synthesis of (-)-isofebrifugine.

In summary, we have established novel chiral syntheses of (+)-febrifugine and (-)-isofebrifugine. Although the synthesis of isofebrifugine gave the antipodal form of the natural product, we believe that the strategy developed here should provide a useful tool for finding new anti-malarial drugs.

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), or JEOL LA-500 (^{1}H-NMR: 500 MHz, ^{13}C-NMR: 125 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.

(3*S*,5*S*)-1-*tert*-Butoxycarbonyl-3-*tert*-butyldimethylsilyloxy-5-methoxycarbonylpyrrolidin-2-one (**4**)**:** To a stirred suspension of RuO_4 [prepared from RuO_2 hydrate (0.74 g, 5.57 mmol) and $NaIO_4$ (14.9 g, 69.6 mmol) in H_2O (245 mL)] was added a solution of the prolinate (**3)** (10.0 g, 27.9 mmol) in AcOEt (123 mL), and the resulting mixture was stirred at ambient temperature for overnight. After removal of insoluble materials by filtration through Celite pad, the filtrate was extracted with AcOEt. 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:hexane (1:4) afforded the

lactam (**4**) (8.93 g, 86%) as a colorless oil; $[\alpha]_D$ -30.7° (*c* 1.00, $CHCl_3$) ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.45 (t, *J* = 7.4 Hz, 1H), 4.26 (t, *J* = 7.4 Hz, 1H), 3.75 (s, 3H), 2.55 (dt, *J* = 7.4, 13.0 Hz, 1H), 1.97 (dt, *J* = 7.4, 13.0 Hz, 1H), 1.48 (s, 9H), 0.87 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); IR (thin film): 2960, 2930, 2860, 1800, 1760, 1720, 1320, 1150, 970, 840, 780 cm^{-1}; CIMS (*m/z*): 374 (M^++1); HRMS calcd for $C_{17}H_{32}NO_6Si$ (M^++1): 374.1999, found 374.1971.

Methyl (4*S*,5*R*)-4-*tert*-butyldimethylsilyloxy-5-ethoxycarbonylmethyl-L-prolinate (**7**)**:** To a stirred solution of **4** (200 mg, 0.54 mmol) in THF (4 mL) was added $LiBEt_3H$ (1.0 M in THF, 0.65 mL, 0.65 mmol) at -78 °C, and the resulting mixture was stirred for further 30 min at the same temperature. To this mixture were added saturated $NaHCO_3$ solution and 30% H_2O_2 solution (3 drops) at 0 °C. After stirring for 20 min, the mixture was extracted with Et_2O, and the ethereal layer was dried over Na_2SO_4. Evaporation of the solvent gave the aminal (**5**), which, without purification, was dissolved in THF (2.1 mL). This solution was added to a solution of the Wittig reagent [prepared from NaH (65-75% in oil, 26 mg, 0.65 mmol) and triethyl phosphonoacetate (0.13 mL, 0.65 mmol) in THF (1.4 mL)], and the whole was stirred at rt for overnight. After treatment with saturated NH_4Cl solution, the mixture was extracted with AcOEt, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography using AcOEt:hexane (1:4) as an eluent to furnish the ester (**6**) (145 mg, 62%) as a colorless oil. To a stirred solution of **6** (50 mg, 0.11 mmol) in CH_2Cl_2 (1.1 mL) was added TFA (87 μL, 1.11 mmol) at 0 °C, and the mixture was gradually warmed up to rt and stirred for further 18 h. The organic layer was washed with saturated $NaHCO_3$ solution, and dried over Na_2SO_4. Evaporation of the solvent gave the amine (**7**) (20.5 mg, 53%), as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, assigned by ^{1}H-^{1}H correlation experiments): δ 4.15 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.92 (dt, *J* = 4.6, 5.5 Hz, 1H, 4-H), 3.79 (dd, *J* = 4.6, 8.9 Hz, 1H, 2-H), 3.72 (s, 3H, OCH_3), 3.45 (dt, *J* = 4.6, 8.5 Hz, 1H, 5-H), 2.46 (dt, *J* = 5.2, 15.6 Hz, 1H, $COCH_2$), 2.33 (ddd, *J* = 5.5, 8.9, 13.4 Hz, 1H, 3-H), 2.29 (dd, *J* = 8.5, 15.6 Hz, 1H, $COCH_2$), 1.98 (dt, *J* = 4.6, 13.1 Hz, 1H, 3-H), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 0.85 (s, 9H, *t*-Bu), 0.05 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.8, -4.7, 14.2, 17.8, 25.6, 37.6, 39.5, 52.1, 57.6, 60.5, 62.0, 75.5, 171.9, 175.4; IR (thin film): 3360, 2950, 2930, 2860, 1780, 1250, 1180, 835, 780 cm^{-1}; EIMS (*m/z*): 345 (M^+); HRMS calcd for $C_{16}H_{31}NO_5Si$ 345.1971, found 345.1992.

Methyl (4*S*,5*R*)-1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-5-[(*N*-methoxy-*N*-methylcarbonyl)methyl]-L-prolinate (**8**)**:** To a stirred solution of **4** (0.23 g, 0.61 mmol) in THF (4.8 mL) was added $LiBEt_3H$ (1.0 M in THF, 0.73 mL, 0.73 mmol) at -78 °C, and the resulting mixture was stirred for further 30 min at the same temperature. To this mixture were added saturated $NaHCO_3$ solution and 30% H_2O_2 solution (3 drops) at 0 °C. After stirring for 20 min, the mixture was extracted with Et_2O, and the ethereal layer was dried over Na_2SO_4. Evaporation of the solvent gave the aminal (**5**), which, without purification, was dissolved in THF (2.3 mL). This solution was added to a solution of the Wittig reagent [prepared from NaH (65-75% in oil, 29 mg, 0.73 mmol) and diethyl (*N*-methoxy-*N*-methylcarbamoyl-methyl)phosphonate (0.15 mL, 0.73 mmol) in THF (1.6 mL)], and the whole was stirred at rt for overnight. After treatment with saturated NH_4Cl solution, the mixture was extracted with AcOEt, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography using AcOEt:hexane (1:4) as an eluent to furnish the

amide (**8**) (232 mg, 83%) as colorless powder; mp 73-75 °C, $[\alpha]_D$ -38.3° (*c* 0.40, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.02-4.52 (m, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 3.22 (s, 3H), 2.91-3.28 (m, 1H), 2.02-2.42 (m, 3H), 1.42 (and rotamer at 1.49) (s, 9H), 0.83 (and rotamer at 0.84) (s, 9H), 0.07 (and rotamer at 0.09) (s, 3H), 0.03 (and rotamer at 0.04) (s, 3H); IR (KBr): 2930, 2860, 1750, 1680, 1675, 1400, 1085 cm^{-1}; CIMS (*m/z*): 461 (M^++1); HRMS calcd for $C_{21}H_{41}N_2O_7Si$ (M^++1) 461.2683, found 461.2693.

Methyl (4*S*,5*R*)-4-*tert*-butyldimethylsilyloxy-5-[(*N*-methoxy-*N*-methylcarbonyl)methyl]-L-prolinate (**9**)**:** To a stirred solution of **8** (50 mg, 0.11 mmol) in CH_2Cl_2 (1.1 mL) was added TFA (84 μL, 1.07 mmol) at 0 °C, and the mixture was gradually warmed up to rt and stirred for further 18 h. The organic layer was washed with saturated $NaHCO_3$ solution, and dried over Na_2SO_4. Evaporation of the solvent gave the amine (**9**) (21.9 mg, 56%), as a colorless solid. A part of the amine (**9**) was crystallized from hexane to give colorless needles**;** mp 89-91 °C; $[\alpha]_D$ +22.9° (*c* 0.21, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.97 (dt, *J* = 4.6, 4.6 Hz, 1H), 3.82 (d, *J* = 4.6, 8.9 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.47 (dt, *J* = 4.6, 8.7 Hz, 1H), 3.16 (s, 3H), 2.53 (dd, *J* = 4.6, 15.8 Hz, 1H), 2.44 (dd, *J* = 8.7, 15.8 Hz, 1H), 2.33 (ddd, *J* = 4.6, 8.9, 14.1 Hz, 1H), 1.97 (dt, *J* = 4.6, 14.1 Hz, 1H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ -5.3, -5.2, 17.4, 25.2, 36.3, 37.1, 51.7, 57.2, 60.7, 61.6, 75.1, 172.1, 174.7; IR (KBr): 3460, 2960, 2920, 2860, 1730, 1345, 1215, 1105, 1070, 775 cm^{-1}; CIMS (*m/z*): 361 (M^++1); HRMS calcd for $C_{16}H_{33}N_2O_5Si$ (M^++1) 361.2158, found 361.2149.

Crystal data for **9**: $C_{16}H_{32}N_2O_5Si$, *M*=360.52, monoclinic, space group *P2$_1$*, *a*=6.7052(5), *b*=7.6518(7), *c*=20.608(2) Å, β=91.043(7)°, *V*=1057.2(2) Å^3, *Z*=2, D_{calcd}=1.129 g/cm^3. The data were collected at a temperature of 25±1°C using the ω scan technique to a maximum 2θ values of 136.6°. Of the 5762 reflections that were collected, 2073 were unique (R_{int}=0.036); equivalent reflections were merged. The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied. The structure was solved using SIR92. *R*=0.045, *Rw*=0.039.

Methyl (4*S*,5*R*)-1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-5-(2-oxopropyl)-L-prolinate (**10**)**:** To a stirred solution of the amide (**8**) (5.1 g, 11.1 mmol) in THF (110 mL) was added MeMgBr (0.93 M in THF, 23.8 mL, 22.2 mmol) at 0 °C, and the resulting solution was stirred for further 30 min at the same temperature. After treatment with saturated NH_4Cl solution, the whole 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 was subjected to column chromatography on silica gel. Elution with AcOEt:hexane (1:4) gave the ketone (**10**) (4.0 g, 88%) as colorless powders; mp 65-58 °C; $[\alpha]_D$ -30.7° (*c* 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.33 (and rotamer at 4.43), (dd, *J* = 1.3, 9.0 Hz, 1H), 3.96-4.14 (m, 2H), 3.68 (and rotamer at 3.67) (s, 3H), 3.15 (and rotamer at 2.97) (dd, *J* = 4.5, 16.5 Hz, 1H), 2.18-2.33 (m, 2H), 2.16 (s, 3H), 2.01-2.18 (m, 1H), 1.41(and rotamer at 1.48) (s, 9H), 0.83 (and rotamer at 0.84) (s, 9H), 0.02 (and rotamer at 0.08) (s, 6H); IR (KBr): 2950, 2930, 2860, 1760, 1735, 1700, 1295, 1090, 735 cm^{-1}; CIMS (*m/z*): 416 (M^++1); HRMS calcd for $C_{20}H_{38}NO_6Si$ (M^++1) 416.2468, found 416.2463.

Methyl (4*S*,5*R*)-1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-5-(2-methylprop-2-en-1-yl)-L-prolinate (**11**)**:** To a stirred solution of the ketone (**10**) (1.66 g, 4.01 mmol) in THF (36 mL) was added Tebbe's reagent (0.5 M in THF, 8.0 mL, 1.01 mmol) at -40 °C, and the whole was stirred at the same temperature for further 30 min, and then for 2 h at rt. After cooling to -78 °C, 1 M NaOH solution (6.3 mL) was added to this solution, and the resulting mixture was filtered through Celite pad to remove

insoluble materials. 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 AcOEt:hexane (1:4) afforded the olefin (**11**) (1.33 g, 81%) as a colorless solid; mp 35-38 °C; $[\alpha]_D$ -23.5° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.81 (and rotamer at 4.82) (br s, 1H), 4.69 (and rotamer at 4.70) (br s, 1H), 4.41 (and rotamer at 4.46) (br d, *J* = 4.9 Hz, 1H), 4.08 (and rotamer at 4.10) (br d, *J* = 2.1 Hz, 1H), 3.91 (and rotamer at 3.75) (br dd, *J* = 1.3, 6.1 Hz, 1H), 3.67 (and rotamer at 3.66) (s, 3H), 2.68 (and rotamer at 2.52) (br d, *J* = 7.3 Hz, 1H), 2.31 (and rotamer at 2.26) (ddd, *J* = 2.1, 4.9, 7.0 Hz, 1H), 2.08 (br d, *J* = 7.0 Hz, 1H), 1.81 (and rotamer at 1.78) (s, 3H), 1.70-1.77 (m, 1H), 1.41 (and rotamer at 1.50) (s, 9H), 0.81 (and rotamer at 0.82) (s, 9H), -0.01 (br s, 3H), -0.03 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): major rotamer; δ -5.0, -4.9, 17.7, 22.3, 25.5, 28.3, 37.5, 40.5, 51.7, 58.9, 65.2, 73.7, 79.6, 113.1, 143.0, 153.5, 172.8 ; minor rotamer; δ -4.9, -4.8, 17.8, 22.1, 25.5, 28.5, 36.3, 41.8, 51.8, 58.7, 65.0, 74.7, 79.9, 113.6, 142.6, 154.2, 171.8; IR (KBr): 2950, 2930, 2860, 1765, 1700, 1390, 1080, 840, 775 cm^{-1}; CIMS (*m/z*): 414 (M^++1); *Anal*. Calcd for $C_{21}H_{39}N_2O_5Si$: C, 60.98; H, 9.50; N, 3.39. Found: C, 60.83; H, 9.33; N, 3.47.

(5*S*,6*R*)-5-*tert*-Butyldimethylsilyloxy-6-(2-methylprop-2-en-1-yl)piperidin-2-one (**13**)**:** To a stirred suspension of $ZnBr_2$ (1.33 g, 5.93 mmol) in CH_2Cl_2 (10 mL) was added a solution of the olefin (**11**) (1.22 mg, 2.96 mmol) in CH_2Cl_2 (20 mL), and the resulting mixture was stirred for overnight at rt. After removal of insoluble materials by filtration through Celite pad, the filtrate was treated with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave the amine (**12**) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, assigned by ^{1}H-^{1}H correlation experiments): δ 4.79 (br s, 1H, =CH_2), 4.75 (br s, 1H, =CH_2), 3.87 (dt, *J* = 4.3, 5.8 Hz, 1H, 4-H), 3.78 (dd, *J* = 4.3, 9.1 Hz, 1H, 2-H), 3.71(s, 3H, OCH_3), 3.20 (ddd, *J* = 4.3, 5.8, 8.9 Hz, 1H, 5-H), 2.35 (ddd, *J* = 5.8, 9.1, 13.5 Hz, 1H, 3-H), 2.15 (dd, *J* = 5.8, 13.5 Hz, 1H, =C-CH_2), 1.91-1.99 (m, 2H, H-3, =C-CH_2), 1.74 (s, 3H, =C-CH_3), 0.84 (s, 9H, *t*-Bu), 0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, assigned by ^{1}H-^{13}C correlation experiments): δ -4.9 ($SiCH_3$), -4.7 ($SiCH_3$), 17.8 (Si*C*Me_3), 22.4 (=C-*C*H_3), 25.6 (3C, *t*-Bu), 37.9 (C-3), 43.1 (=C-*C*H_2), 52.0 (OCH_3), 57.5 (C-2), 63.2 (C-5), 75.8 (C-4), 112.0 (=CH_2), 143.3 (=C), 175.7 (C=O); IR (thin film): 3360, 2950, 2930, 2900, 2860, 1740, 1650, 840, 775 cm^{-1}; EIMS (*m/z*): 313 (M^+); HRMS calcd for $C_{16}H_{31}NO_3Si$ 313.2073, found 313.2076. The amine obtained was used without further purification in the next step.

To a stirred solution of the amine (**12**) in THF (10 mL) was added a solution of SmI_2 (0.2 M in THF, 38.3 mL, 7.67 mmol) containing HMPA (1.3 mL, 7.67 mmol) and MeOH (155 μL, 3.84 mmol) at 0 °C. The solution was gradually warmed up to rt, and stirred for further 2 h at the same temperature. To this solution were added excess of saturated $NaHCO_3$ and Et_2O, and the whole was stirred for 30 min. After removal of insoluble materials by filtration through Celite pad, the filtrate was extracted with AcOEt , and 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 AcOEt:hexane (5:1) gave the δ-lactam (**13**) (678 mg, 90%) as a colorless oil; $[\alpha]_D$ +12.0° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, assigned by ^{1}H-^{1}H correlation experiments): δ 5.62 (br s, 1H, NH), 4.93 (s, 1H, =CH_2), 4.80 (s, 1H, =CH_2), 3.59 (ddd, *J* = 3.6, 6.9, 10.0 Hz, 1H, 5-H), 3.26 (ddd, *J* = 3.0, 6.9, 10.4 Hz, 1H, 6-H), 2.47-2.55 (m, 2H, 3-H and =C-CH_2), 2.34 (ddd, *J* = 6.4, 10.0, 18.0 Hz, 1H, 3-H), 1.77-1.86 (m, 1H, 4-H), 1.90 (dd,

J = 10.4, 13.7 Hz, 1H, =C-CH_2), 1.93-1.99 (m, 1H, 4-H), 1.72 (s, 3H, =C-CH_3), 0.89 (s, 9H, *t*-Bu), 0.08 (s, 6H, 2×$SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, assigned by ^{1}H-^{13}C correlation experiments): δ -4.8 ($SiCH_3$), -4.2 ($SiCH_3$), 17.9 (Si*C*Me_3), 21.7 (=C-*C*H_3), 25.6 (3C, *t*-Bu), 28.7 (C-3), 28.8 (C-4), 42.7 (=C-*C*H_2), 55.9 (C-6), 69.9 (C-5), 114.9 (=CH_2), 140.8 (=C), 170.9 (C=O); IR (thin film): 3220, 2960, 2930, 2860, 1670, 1090, 840, 770 cm^{-1}; EIMS (*m/z*): 283 (M^+); *Anal*. Calcd for $C_{15}H_{29}NO_2Si$: C, 63.55; H, 10.31; N, 4.94. Found: C, 63.51; H, 10.32; N, 4.97.

(2*R*,3*S*)-3-Benzyloxy-1-benzyloxycarbonyl-2-(2-methylprop-2-en-1-yl)piperidine (**16**)**:** To a stirred solution of the lactam (**13**) (200 mg, 0.71 mmol) in THF (8.4 mL) was added $LiAlH_4$ (161 mg, 4.24 mmol) at rt, and the resulting mixture was heated at 65 °C for 3 h. The mixture was diluted with THF, and 1 M NaOH solution were carefully added to this mixture at 0 °C. After removal of insoluble materials by filtration through Celite pad, the filtrate was dried over Na_2SO_4. Evaporation of the solvent gave the amine (**14**); ^{1}H NMR (500 MHz, $CDCl_3$, assigned by ^{1}H-^{1}H correlation experiments): δ 4.86 (br s, 1H, =CH_2), 4.82 (br s, 1H, =CH_2), 3.26 (ddd, *J* = 4.5, 8.6, 10.7 Hz, 1H, 3-H), 2.98 (br d, *J* = 11.6 Hz, 1H, 6-H), 2.64 (dd, *J* = 3.4, 13.5 Hz, 1H, =C-CH_2), 2.53 (dt, *J* = 2.8, 11.6 Hz, 1H, 6-H), 2.43 (ddd, *J* = 3.4, 8.6, 10.1 Hz, 1H, 2-H), 2.03-2.08 (m, 1H, 4-H), 2.00 (dd, *J* = 10.1, 13.5 Hz, 1H, =C-CH_2), 1.76 (s, 3H, =C-CH_3), 1.68-1.74 (m, 3H, H-5, NH, OH), 1.49-1.61 (m, 1H, 5-H), 1.33 (ddt, *J* = 4.5, 10.4, 12.3 Hz, 1H, 4-H); CIMS (*m/z*): 156 (M^++1); HRMS calcd for $C_9H_{18}NO$ (M^++1) 156.1388, found 156.1366, which, without further purification, was used in the next step.

To a stirred solution of the amine (**14**) in CH_2Cl_2 (3.5 mL) were added CbzCl (0.12 mL, 0.85 mmol), TEA (0.12 mL, 0.85 mmol) and DMAP (8.6 mg, 0.07 mmol) at 0 °C, and the whole was stirred for overnight at ambient temperature. After treatment with saturated NH_4Cl solution, the mixture was extracted with CH_2Cl_2. 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 AcOEt:hexane (2:1) afforded the carbamate (**15**) (195 mg, 95%), as a colorless oil. To a stirred solution of the carbamate (**15**) (78.0 mg, 0.27 mmol) in DMF (1 mL) were added NaH (65-75% in oil, 16.0 mg, 0.40 mmol) and BnBr (0.05 mL, 0.40 mmol) at 0 °C, and the mixture was stirred for further 4 h. After treatment with saturated NH_4Cl solution, the mixture was extracted with AcOEt, and 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 AcOEt:hexane (1:9) afforded the benzyl ether (**16**) (92 mg, 90%), as a colorless oil; $[\alpha]_D$ -41.9° (*c* 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.15-7.40 (m, 10H), 4.35-5.21 (m, 7H), 3.95-4.21 (m, 1H), 3.38-3.51 (m, 1H), 2.80-3.00 (m, 1H), 1.08-2.41 (m, 9H); IR (thin film): 1950, 2860, 1695, 1500, 1425, 1260, 700 cm^{-1}; CIMS (*m/z*) 380 (M^++1); *Anal*. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found: C, 76.16; H, 7.91; N, 3.69.

(2*R*,3*S*)-3-Benzyloxy-1-benzyloxycarbonyl-2-(2-oxopropyl)piperidine (**17**)**:** The stream of ozone was bubbled through a stirred solution of the olefin (**16**) (225 mg, 0.59 mmol) in MeOH (20 mL) at -78 °C until disappearance of the starting material on TLC. The reaction mixture was flushed with argon and treated with Me_2S (0.45 mL, 5.95 mmol). The resulting mixture was allowed to warm to rt and stirred for further 18 h at the same temperature. After removal of the solvent, the residue was subjected to column chromatography on silica gel. Elution with AcOEt:hexane (1:9) afforded the methyl ketone (**17**) (209 mg, 92%) as a colorless oil; $[\alpha]_D$ -32.8° (*c* 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.25-7.32 (m, 10H),

4.90-5.20 (m, 3H), 4.41-4.77 (m, 2H), 4.11 (br s, 1H), 3.44 (br s, 1H), 2.75-2.95 (m, 1H), 2.52-2.74 (m, 2H), 2.14 (br s, 3H), 1.76-2.00 (m, 2H), 1.66-1.74 (m, 1H), 1.32-1.48 (m, 1H); IR (thin film): 2945, 2860, 1720, 1695, 1425, 1260, 700 cm^{-1}; EIMS (*m/z*): 381 (M^+); *Anal*. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.18; H, 7.24; N, 3.78.

(2*R*,3*S*)-3-Benzyloxy-1-benzyloxycarbonyl-2-[2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)propyl]piperidine (**19**)**:** To a stirred solution of the methyl ketone (**17**) (100 mg, 0.26 mmol) in CH_2Cl_2 (0.9 mL) were added DIPEA (55 μL, 0.31 mmol) and TMSOTf (61 μL, 0.34 mmol) at ambient temperature, and the resulting mixture was stirred for 20 min at the same temperature. To this solution was added NBS (57 mg, 0.31 mmol) at room temperature, and the solution was stirred for further 1 h at the same temperature. After treatment with 10% $Na_2S_2O_3$ solution, the mixture was extracted with AcOEt. The extract was washed with saturated $NaHCO_3$ solution, and dried over Na_2SO_4. Evaporation of the solvent gave the bromo ketone (**18**), which, without further purification, was used in the next step.

A solution of the bromo ketone (**18**) in DMF (1.0 mL) was added a solution of 4-hydroxyquinazoline (96 mg, 0.66 mmol) in DMF (1.5 mL) in the presence of KH (21 mg, 0.53 mmol) at 0 °C, and the mixture was stirred for 30 min at the same temperature and then for 10 h at 70 °C. The mixture was treated with saturated NH_4Cl solution, and extracted with Et_2O. 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 AcOEt:hexane (4:1) afforded the protected febrifugine (**19**) (78 mg, 57%), whose spectroscopic data were identical with those reported; $[\alpha]_D$ -36.0° (*c* 0.51, $CHCl_3$); {lit.,[4g] $[\alpha]_D$ -22.0° (*c* 1.00, $CHCl_3$)}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.26 (br d, *J* = 7.7 Hz, 1H), 7.69-7.92 (m, 3H), 7.51 (ddd, *J* = 1.6, 6.6, 8.1 Hz, 1H), 7.17-7.40 (m, 10H), 5.17 (d, *J* = 12.4 Hz, 1H), 5.09 (d, *J* = 12.4 Hz, 1H), 4.99 (br t, *J* = 6.7 Hz, 1H), 4.85 (br s, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.04 (br s, 1H), 3.51 (br s, 1H), 2.97 (br s, 1H), 2.86 (dd, *J* = 8.6, 14.7 Hz, 1H), 2.77 (dd, *J* = 6.3, 14.8 Hz, 1H), 1.90 (br d, *J* = 11.2 Hz, 2H), 1.53-1.79 (m, 2H), 1.38-1.51 (m, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 19.2, 24.1, 39.4, 40.7, 53.7, 67.2, 70.2, 73.5, 77.2, 121.6, 126.5, 127.1, 127.4, 127.5, 127.6, 127.8, 128.2, 128.3, 134.3, 136.4, 138.2, 146.3, 148.1, 156.1, 160.7, 199.9; IR (thin film): 2940, 2860, 1730, 1680, 1615, 1475, 1425, 1360, 1260, 1090, 700 cm^{-1}; EIMS (*m/z*): 525 (M^+); HRMS calcd for $C_{31}H_{31}N_3O_5$ 525.2263, found 525.2280.

(+)-Febrifugine (**1**)**:** A solution of **19** (119 mg, 0.23 mmol) in 6N HCl (17.1 mL) was heated at reflux for 26 h. The solution was basified with K_2CO_3 to pH 9, and extracted with $CHCl_3$. The organic layer was washed with brine and dried over K_2CO_3. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with ammonia saturated $CHCl_3$:MeOH (9:1) afforded febrifugine (**1**) (63 mg, 92%), whose spectroscopic data were identical with those reported; mp 139-140 °C (lit.,[1b] mp 139-140 °C); $[\alpha]_D$ +16.0° (*c* 0.40, MeOH) {lit.,[1c] $[\alpha]_D$ +13.0° (*c* 0.65, MeOH)}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.28 (br s, *J* = 7.2 Hz, 1H), 7.89 (s, 1H), 7.68-7.82 (m, 2H), 7.51 (dt, *J* = 1.6, 8.1 Hz, 1H), 4.89 (d, *J* = 17.3 Hz, 1H), 4.82 (d, *J* = 17.3 Hz, 1H), 3.30 (dt, *J* = 4.6, 9.0 Hz, 1H), 3.12 (dd, *J* = 4.6, 15.8 Hz, 1H), 2.97 (br d, *J* = 11.9 Hz, 1H), 2.87 (ddd, *J* = 4.6, 7.4, 15.8 Hz, 1H), 2.65 (dd, *J* = 7.4, 15.8 Hz, 1H), 2.58 (dt, *J* = 3.0, 12.2 Hz, 1H), 1.98-2.15 (m, 1H), 1.29-1.81 (m, 3H); IR (thin film): 3360, 2930, 2850, 1725, 1670, 1615, 1475, 1370, 1325, 775 cm^{-1}; EIMS (*m/z*): 301 (M^+); HRMS calcd for $C_{16}H_{19}N_3O_3$ 301.1426, found 301.1398.

(3*R*,5*S*)-1-*tert*-Butoxycarbonyl-3-*tert*-butyldimethylsilyloxy-5-methoxycarbonylpyrrolidin-2-one (**21**)**:** The lactam (**21**) (8.64 g, 83%) was synthesized from the silyl ether (**20**) (10.0 g, 27.9 mmol) by the same procedure as described for the preparation of **4**. The spectroscopic data of **21** were identical with those reported in the literature.[7] ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.57 (dd, *J* = 1.6, 9.7 Hz, 1H), 4.41 (dd, *J* = 8.2, 10.0 Hz, 1H), 3.78 (s, 3H), 2.36 (ddd, *J* = 1.6, 8.2, 13.3 Hz, 1H), 2.19 (dt, *J* = 10.0, 13.3 Hz, 1H), 1.49 (s, 9H), 0.88 (s, 9H), 0.16 (s, 3H), 0.09 (s, 3H).

Methyl (4*R*,5*S*)-4-*tert*-butyldimethylsilyloxy-5-ethoxycarbonylmethyl-L-prolinate (**25**) **and methyl (4*R*,5*R*)-4-*tert*-butyldimethylsilyloxy-5-ethoxycarbonylmethyl-L-prolinate** (**26**)**:** The reduction of the amide (**21**) (200 mg, 0.54 mmol) in THF (4.3 mL) with $LiBEt_3H$ (1.0 M in THF, 0.64 mL, 0.64 mmol) was carried out by the same procedure as described for the preparation of **5** to give the aminal (**22**), which, without purification, was dissolved in DMF (2.1 mL). This solution was added to a solution of the Wittig reagent [prepared from NaH (65-75% in oil, 26 mg, 0.65 mmol) and triethyl phosphonoacetate (0.13 mL, 0.64 mmol) in DMF (1.4 mL)], and the whole was stirred at rt for overnight. After treatment with saturated NH_4Cl solution, the mixture was extracted with AcOEt, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a mixture of the crude diesters (**23** and **24**), which were dissolved into CH_2Cl_2 (14.4 mL). To this solution was added TFA (1.11 mL, 14.4 mmol) at 0 °C, and the resulting mixture was stirred for further 3.5 h at rt. The mixture was washed with saturated $NaHCO_3$ solution, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography using AcOEt:hexane (1:2) as an eluent to furnish the amine (**25**) (128 mg, 26%) as a colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.09 (q, *J* = 7.1 Hz, 2H), 3.95 (dd, *J* = 7.1, 8.7 Hz, 1H), 3.86 (dt, *J* = 4.8, 7.1 Hz, 1H), 3.67 (s, 3H), 3.23 (dt, *J* = 4.8, 8.7 Hz, 1H), 2.54 (dd, *J* = 4.8, 16.1 Hz, 1H), 2.35 (dd, *J* = 8.7, 16.1 Hz, 1H), 2.08 (dt, *J* = 7.1, 13.0 Hz, 1H), 1.92 (ddd, *J* = 4.8, 8.7, 13.0 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.82 (s, 9H), 0.01 (s, 6H). Further elution with the same solvent system afforded the amine (**26**) (257 mg, 51%) as a colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.27 (dt, *J* = 2.3, 4.3 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.95 (t, *J* = 7.9 Hz, 1H), 3.66 (s, 3H), 3.51 (dt, *J* = 4.3, 7.1 Hz, 1H), 2.48 (d, *J* = 7.1 Hz, 1H), 2.03 (ddd, *J* = 2.3, 7.9, 11.0 Hz, 1H), 1.96 (ddd, *J* = 4.3, 7.9, 11.0 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.82 (s, 9H), 0.01 (s, 6H).

Methyl (4*R*,5*S*)-5-ethoxycarbonylmethyl-4-hydroxy-L-prolinate (**27**)**:** To a stirred solution of **25** (300 mg, 0.67 mmol) in THF (9.9 mL) was added TBAF (1.0 M in THF, 0.67 mL, 0.67 mmol) at 0 °C, and the mixture was stirred for 1.5 h at rt. After dilution with AcOEt and H_2O, 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 was purified by column chromatography on silica gel. Elution with AcOEt:hexane (1:1) afforded the alcohol (**27**) (199 mg, 89%) as a colorless solid; ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.17 (q, *J* = 7.2 Hz, 2H), 3.94–4.08 (m, 2H), 3.73 (s, 3H), 3.25-3.34 (m 1H), 2.09-2.31 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 1H); IR (thin film): 3500, 2960, 2360, 2340, 1730, 1190, 1020 cm^{-1}; EIMS (*m/z*): 231 (M^+); HRMS calcd for $C_{10}H_{17}NO_5$ 231.1106, found 231.1123.

Methyl (3a*R*,5*S*,6a*R*)-2-oxohexahydrofuro[3,2-*b*]pyrrole-5-carboxylate (**28**)**:** Treatment of the amine (**26**) (50 mg, 0.14 mmol) in THF (2.1 mL) with TBAF (1.0 M in THF, 0.14 mL, 0.14 mmol), followed by purification by column chromatography on silica gel using AcOEt:hexane (9:1), by the same procedure as described above provided the lactone (**28**) (16.6 mg, 68%) as a colorless solid; ^{1}H NMR (270 MHz,

$CDCl_3$): δ 4.90-5.04 (m, 1H), 4.00-4.16 (m, 1H), 3.84-3.96 (m, 1H), 3.68 (s, 3H), 2.70 (dd, *J* = 6.9, 18.1 Hz, 1H), 2.36-2.57 (m, 2H), 1.91-2.12 (m, 1H); IR (thin film): 2930, 2360, 2340, 1770, 1735, 1635, 1180, 670 cm^{-1}; EIMS (*m/z*): 185 (M^+); HRMS calcd for $C_8H_{11}NO_4$ 185.0688, found 185.0670.

Methyl (4*R*,5*S*)-1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-5-[(*N*-methoxy-*N*-methylcarbonyl)methyl]-L-prolinate (**29**) **and methyl (4*R*,5*R*)-1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-5-[(*N*-methoxy-*N*-methylcarbonyl)methyl]-L-prolinate** (**30**)**:** The reduction of the amide (**21**) (200 mg, 0.54 mmol) in THF (4.3 mL) with $LiBEt_3H$ (1.0 M in THF, 0.64 mL, 0.64 mmol) was carried out by the same procedure as described for the preparation of **5** to give the aminal (**22**), which, without purification, was dissolved in THF (2.1 mL). This solution was added to a solution of the Wittig reagent [prepared from NaH (65-75% in oil, 31 mg, 0.64 mmol) and diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate (0.13 mL, 0.64 mmol)] in THF (1.4 mL). After the similar work-up and purification as described for the preparation of **8**, the amide (**29**) (13.4 mg, 5.5%) was obtained as the first eluent; $[\alpha]_D$ -20.1° (*c* 0.5, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 4.21-4.49 (m, 2H), 4.04-4.20 (m, 1H), 3.71 (and rotamer at 3.68) (s, 3H), 3.70 (and rotamer at 3.73) (s, 3H), 3.17 (s, 3H), 2.85-3.12 (m, 1H), 2.85-3.00 (m, 1H), 1.80-2.20 (m, 2H), 1.36 (and rotamer at 1.39) (s, 9H), 0.84 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); IR (thin film): 2960, 2930, 2860, 1760, 1700, 1670, 1390, 1260, 1090, 940, 840, 780 cm^{-1}; CIMS (*m/z*): 461 (M^++1); HRMS calcd for $C_{21}H_{41}N_2O_7Si$ (M^++1) 461.2683, found 461.2696. Further elution with the same solvent system afforded the amide (**30**) (146 mg, 60%); $[\alpha]_D$ -32.2° (*c* 1.05, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 4.44-4.57 (m, 2H), 4.18-4.25 (m, 1H), 3.66 (and rotamer at 3.67) (s, 3H), 3.62 (s, 3H), 3.07 (and rotamer at 3.09) (s, 3H), 2.41-2.86 (m, 2H), 1.90-2.21 (m, 2H), 1.32 (and rotamer at 1.38) (s, 9H), 0.80 (and rotamer at 0.79) (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H); CIMS (*m/z*): 461 (M^++1); HRMS calcd for $C_{21}H_{41}N_2O_7Si$ (M^++1) 461.2683, found 461.2689.

Methyl (4*R*,5*S*)-5-allyl-1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-L-prolinate (**33**)**:** To a stirred solution of the amide (**29**) (200 mg, 0.43 mmol) in THF (18 mL) was added DIBAL (0.95 M in hexane, 0.92 mL, 0.87 mmol) at -78 °C, and the mixture was stirred for 30 min at the same temperature. After treatment with saturated NH_4Cl solution, the mixture was filtered through Celite pad to remove insoluble materials. The filtrate was extracted with AcOEt. The extract was dried over Na_2SO_4. Evaporation of the solvent gave a crude aldehyde (**31**), which, without further purification, was used in the next reaction. A solution of the aldehyde in THF (3.5 mL) was added to the Wittig reagent [prepared from methyltriphenylphosphonium bromide (250 mg, 0.70 mmol) and *n*-BuLi (1.58 M in hexane, 0.36 mL, 0.56 mmol) in THF (7 mL)] at 0 °C, and the resulting mixture was gradually warmed up to rt and stirred for overnight at the same temperature. The mixture was treated with saturated NH_4Cl solution, and extracted with AcOEt. The extract was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using AcOEt:hexane (1:6) as an eluent to give the allyl derivative (**33**) (43.6 mg, 25%) as a colorless oil; $[\alpha]_D$ -31.8° (*c* 0.20, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 5.71-5.90 (m, 1H), 4.98-5.10 (m, 2H), 4.25-4.45 (m, 1H), 4.04-4.13 (m, 1H), 3.69 (and rotamer at 3.70) (s, 3H), 3.57-3.82 (m, 1H), 2.35-2.67 (m, 1H), 1.92-2.15 (m, 3H), 1.37 (and rotamer at 1.42) (s, 9H), 0.81 (s, 9H), 0.00 (br s, 6H); IR (thin film): 2960, 2930, 2360, 1760, 1700, 1640, 1390, 1370, 1260, 840 cm^{-1}; CIMS (*m/z*): 400 (M^++1); HRMS calcd for $C_{20}H_{38}NO_5Si$ (M^++1) 400.2519, found 400.2529.

Methyl (4*R*,5*S*)-5-allyl-4-*tert*-butyldimethylsilyloxy-L-prolinate (**35**)**:** To a stirred suspension of $ZnBr_2$ (49 mg, 0.22 mmol) in CH_2Cl_2 (0.36 mL) was added a solution of the allyl derivative (**33**) (43.6 mg, 0.11 mmol) in CH_2Cl_2 (0.73 mL), and the resulting mixture was stirred for overnight at rt. After removal of insoluble materials by filtration through Celite pad, the filtrate was treated with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a crude α-amino ester (**35**) as a pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79-5.87 (m, 1H), 5.05-5.17 (m, 2H), 3.96 (t, *J* = 8.0 Hz, 1H), 3.93 (dt, *J* = 4.8, 7.5 Hz, 1H), 3.73 (s, 3H), 2.98 (dt, *J* = 5.2, 7.5 Hz, 1H), 2.10-2.18 (m, 1H), 1.99-2.40 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); IR (thin film): 2960, 2930, 2860, 1740, 1640, 1440, 1260, 1210, 1100, 840, 775 cm^{-1}; CIMS (*m/z*): 300 (M^++1); HRMS calcd for $C_{15}H_{30}NO_3Si$ (M^++1) 300.1995, found 300.2001.

Methyl (4*R*,5*R*)-5-allyl-1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-L-prolinate (**34**)**:** Reduction of the amide (**30**) (1.50 g, 3.26 mmol) with DIBAL (0.95 M in hexane, 10.4 mL, 9.78 mmol) was carried out by the same procedure as described for the preparation of **31** to give the aldehyde (**32**), which, without further purification, was subjected to the Wittig reaction using methyltriphenylphosphonium bromide (1.75 g, 4.89 mmol) and *n*-BuLi (1.6 M in hexane, 3.06 mL, 4.89 mmol) to provide the allyl compound (**34**) (778 mg, 60%) as a colorless oil, after purification by column chromatography on silica gel using AcOEt:hexane (1:6) as an eluent; $[\alpha]_D$ -20.5° (c 1.01, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.71-5.95 (m, 1H), 4.88-5.07 (m, 2H), 4.37-4.52 (m, 1H), 4.10-4.23 (m, 1H), 4.00-4.09 (and rotamer at 3.89-3.99) (m, 1H), 3.68 (and rotamer at 3.69) (s, 3H), 2.37-2.60 (m, 1H), 1.86-2.34 (m, 3H), 1.35 (and rotamer at 1.43) (s, 9H), 0.86 (br s, 9H), 0.03 (br s, 9H); IR (thin film): 2960, 2930, 1750, 1704, 1390, 880, 840, 780 cm^{-1}; CIMS (*m/z*): 400 (M^++1); HRMS calcd for $C_{20}H_{38}NO_5Si$ (M^++1) 400.2519, found 400.2547.

Methyl (4*R*,5*R*)-5-allyl-4-*tert*-butyldimethylsilyloxy-L-prolinate (**36**)**:** Selective deprotection of the *N*-Boc group of **34** (300 mg, 0.75 mmol) was carried out by the same procedure as for the preparation of **35** using $ZnBr_2$ (338 mg, 1.50 mmol) to give a crude α-amino ester (**36**) as a pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, assigned by ^{1}H-^{1}H correlation experiments): δ 5.76-5.86 (m, 1H, =CH), 5.00-5.11 (m, 2H, $=CH_2$), 4.18-4.23 (m, 1H, 4-H), 4.00 (br t, *J* = 4.3 Hz, 1H, 2-H), 3.70 (s, 3H, OCH_3), 3.11 (dt, *J* = 3.4, 7.0 Hz, 1H, 5-H), 2.01 (ddd, *J* = 4.3, 8.3, 13.5 Hz, 1H, 3-H), 1.94 (br s, 1H), 2.19-2.32 (m, 2H, $=C-CH_2$), 2.11 (ddd, *J* = 1.9, 8.3, 13.5 Hz, 1H, 3-H), 0.88 (s, 9H, *t*-Bu), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, assigned by ^{1}H-^{13}C correlation experiments): δ -4.8 ($SiCH_3$), -4.4 ($SiCH_3$), 18.0 (Si*C*Me$_3$), 25.8 (3C, *t*-Bu), 34.1 (=C-*C*H_2), 39.8 (C-3), 52.1 (OCH_3), 57.6 (C-2), 63.4 (C-5), 73.3 (C-4), 116.4 ($=CH_2$), 136.0 (=C), 175.8 (C=O); IR (thin film): 3350, 2955, 2930, 2860, 1740, 1255, 835, 775 cm^{-1}; CIMS (*m/z*): 300 (M^++1); HRMS calcd for $C_{15}H_{30}NO_3Si$ (M^++1) 300.1995, found 300.2006. This compound was used without further purification in the next reaction.

(5*R*,6*R*)-5-*tert*-Butyldimethylsilyloxy-6-(prop-2-en-1-yl)piperidin-2-one (**37**)**:** Reductive deamination of the α-amino ester (**36**) obtained above was carried out by the same procedure as described for the preparation of **13** using SmI_2 (0.2 M in THF, 10.8 mL, 2.15 mmol) to furnish the δ-lactam (**37**) (145 mg, 71%) as a colorless solid; mp 66-67 °C (lit.,[4m] mp 67-68 °C); $[\alpha]_D$ +4.6° (*c* 0.20, $CHCl_3$) {lit.,[4m] $[\alpha]_D$ -4.5° (*c* 1.05, $CHCl_3$)}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.76 (br s, 1H), 5.59-5.74 (m, 1H), 5.08-5.20 (m, 2H), 3.90-3.99 (m, 1H), 3.31 (ddd, *J* = 3.1, 4.1, 9.2 Hz, 1H), 2.51 (ddd, *J* = 6.2, 12.0, 18.3 Hz, 1H), 2.24-2.37

(m, 2H), 2.07-2.23 (m, 1H), 1.71-1.85 (m, 1H), 1.87-1.99 (m, 1H), 0.85 (s, 9H), 0.04 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ -5.1, -4.5, 17.9, 25.6, 26.2, 27.9, 36.7, 56.3, 65.7, 119.2, 133.5, 171.4; IR (thin film): 3240, 2960, 2930, 2860, 1670, 1400, 1330, 1255, 835, 775 cm^{-1}; CIMS (*m/z*): 270 (M^++1); HRMS calcd for $C_{14}H_{28}NO_2Si$ (M^++1) 270.1889, found 270.1881. The spectroscopic data were identical with those reported in the literature except for the sign of optical rotation.

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REFERENCES AND NOTE

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1. (a) J. B. Koepfli, J. F. Mead, and J. A. Brockman, Jr., *J. Am. Chem. Soc.*, 1947, **69**, 1837. (b) J. B. Koepfli, J. F. Mead, and J. A. Brockman, Jr., *J. Am. Chem. Soc*., 1949, **71**, 1048. (c) K. Murata, F. Takeno, S. Fushiya, and Y. Oshima, *J. Nat. Prod.*, 1998, **61**, 729.
2. (a) C. S. Jang, F. Y. Fu, C. Y. Wang, K. C. Huang, G. Lu, and T. C. Thou, *Science*, 1946, **103**, 59. (b) T. –Q. Chou, F. Y. Fu, and Y. S. Kao, *J. Am. Chem. Soc*., 1948, **70**, 1765. (c) A. K. Frederick, Jr., C. F. Spencer, and K. Folkers, *J. Am. Chem. Soc*., 1948, **70**, 2091. (c) Y. Takaya, H. Tasaka, T. Chiba, K. Uwai, M. Tanitsu, H. –S. Kim, Y. Wataya, M. Miura, M. Takeshita, and Y. Oshima, *J. Med. Chem.*, 1999, **42**, 3163. (d) H. Kikuchi, H. Tasaka, S. Hirai, Y. Takaya, Y. Iwabuchi, H. Ooi, S. Hatakeyama, H. –S. Kim, Y. Wataya, and Y. Oshima, *J. Med. Chem*., 2002, **45**, 2563. (e) S. Hirai, H. Kikuchi, H. –S. Kim, K. Begum, Y. Wataya, H. Tasaka, Y. Miyazawa, K. Yamamoto, and Y. Oshima, *J. Med. Chem*., 2003, **46**, 4351.
3. S. Kobayashi, M. Ueno, R. Suzuki, and H. Ishitani, *Tetrahedron Lett.*, 1999, **40**, 2175.
4. For recent syntheses of febrifugine and/or isofebrifugine, see: (a) L. E. Burgess, E. K. M. Gross, and J. Jurka, *Tetrahedron Lett.*, 1996, **37**, 3255. (b) S. Kobayashi, M. Ueno, R. Suzuki, H. Ishitani, H. –S. Kim, and Y. Wataya, *J. Org. Chem.*, 1999, **64**, 6833. (c) Y. Takeuchi, H. Abe, and T. Harayama, *Chem. Pharm. Bull.*, 1999, **47**, 905. (d) Y. Takeuchi, M. Hattori, H. Abe, and T. Harayama, *Synthesis*, 1999, 1814. (e) Y. Takeuchi, K. Azuma, M. Takakura, H. Abe, and T. Harayama, *Chem. Commun.*, 2000, 1643. (f) O. Okitsu, R. Suzuki, and S. Kobayashi, *Synlett*, 2000, 989. (g) T. Taniguchi and K. Ogasawara, *Org. Lett.*, 2000, **2**, 3193. (h) Y. Takeuchi, K. Azuma, K. Takakura, H. Abe, H. –S. Kim, Y. Wataya, and T. Harayama, *Tetrahedron*, 2001, **57**, 1213. (i) H. Ooi, A. Urushibara, T. Esumi, Y. Iwabuchi, and S. Hatakeyama, *Org. Lett*., 2001, **3**, 953. (j) M. Sugiura and S. Kobayashi, *Org. Lett*., 2001, **3**, 477. (k) M. Sugiura, H. Hagio, R. Hirabayashi, and S. Kobayashi, *J. Org. Chem.*, 2001, **66**, 809. (l) M. Sugiura, H. Hagio, R. Hirabayashi, and S. Kobayashi, *J. Am. Chem. Soc*., 2001, **123**, 12510. (m) P. –Q. Huang, B. –G. Wei, and Y. –P. Ruan, *Synlett*, 2003, 1663.
5. T. Honda and F. Ishikawa, *Chem. Commun.*, 1999, 1065.
6. (a) T. Honda and M. Kimura, *Org. Lett.*, 2000, **2**, 3925. (b) T. Honda, R. Takahashi, and H. Namiki, *J. Org. Chem.*, 2005, **70**, 499.

7. X. Zhang, A. C. Schmitt, and W. Jiang, *Tetrahedron Lett.*, 2001, **42**, 5335.
8. C. Nájera and M. Yus, *Tetrahedron: Asymmetry*, 1999, **10**, 2245 and references cited therein.
9. (a) I. Collado, J. Ezquerra, J. J. Vaquero, and C. Pedregal, *Tetrahedron Lett.*, 1994, **35**, 8037. (b) J. Mulzer, F. Schülzchen, and J. –W. Bats, *Tetrahedron*, 2000, **56**, 4289.
10. F. N. Tebbe, G. W. Parshall, and G. S. Reddy, *J. Am. Chem. Soc.*, 1978, **100**, 3611.
11. Similar NOE correlations were reported in the literature. See: I. Collado, J. Ezquerra, and C. Pedregal, *J. Org. Chem.*, 1995, **60**, 5011.