Synthesis of (±)-Stemonamide by the Application of Oxidative Coupling Reactions of Stannyl Compounds with Silyl Enol Ethers

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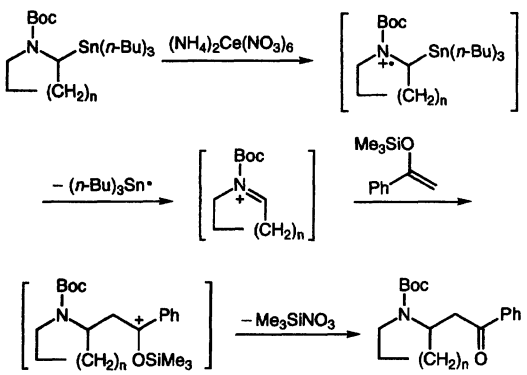
A tricyclic *Stemona* alkaloid, (±)-stemonamide, can be synthesized by applying the oxidative coupling reactions of stannyl compounds with silyl enol ethers to construct the carbon skeleton.

For the purpose of developing carbon–carbon bond forming reactions by using cation radical species, we have studied the generation of cation radicals from some stannyl compounds by the oxidation with metallic oxidants and their cleavage to carbocations or carbon radicals. For example, the oxidation of α-stannyl sulfides and *N*-(1-stannylalkyl) amides and carbamates generates their cation radicals, which are cleaved into carbocations of sulfides, amides, and carbamates by the elimination of the stannyl radical (Scheme 1).[1] In addition, α-stannyl alkanoates are oxidized to generate the corresponding α-radicals of alkanoates and stannyl cation (Scheme 2).[2] Cations or radical intermediates generated in this way are utilized in the carbon–carbon bond forming reactions; they react with various olefinic compounds, such as silyl enol ethers.

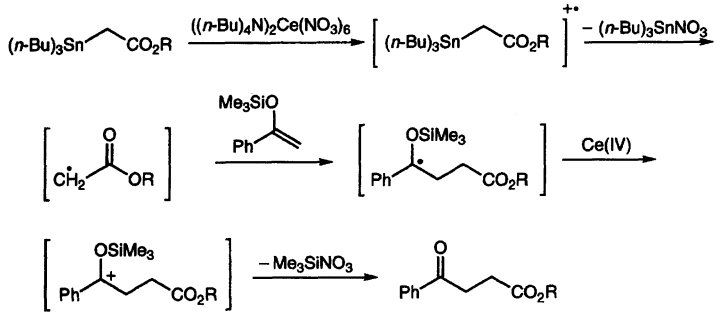


Scheme 1.

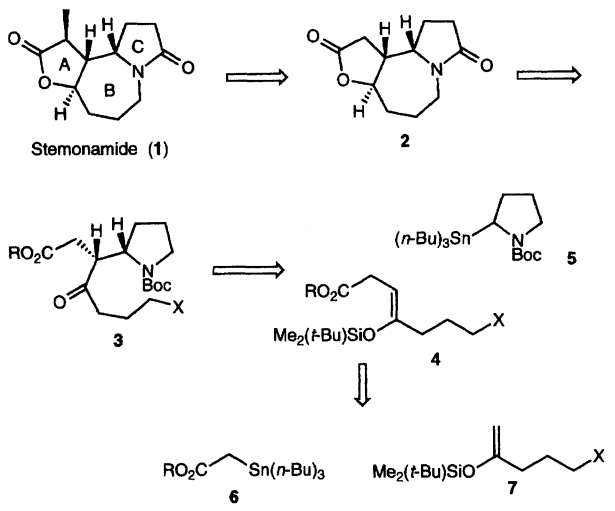
(−)-Stemonamide (**1**), isolated by Lin et al. from roots and rhizomes of *Stemona* (*Stemonaceae*), has been used as an anticough agent and an insecticide in traditional medicines of China and Japan.[3] Recently, Williams et al. reported the first total synthesis of this *stemona* alkaloid.[4] In this paper, we would like to report a total synthesis of (±)-stemonamide by applying the above-mentioned oxidative coupling reactions of the stannyl compounds with silyl enol ethers for the construction of the carbon framework. The retrosynthetic analysis is outlined in Scheme 3. The methyl group could be introduced stereoselectively from the convex side of a tricyclic intermediate **2**. The intermediate **2** would be prepared from a pyrrolidine derivative **3**, which could be constructed from three fragments: 2-(tributylstannyl)pyrrolidine **5**, 2-(tributylstannyl)acetate **6**, and a silyl enol ether **7**. According to this analysis, the carbon framework of stemonamide **1**, except the methyl group, would be prepared by applying our oxidative coupling of three components, **5**, **6**, and **7**.

Results and Discussion

Prior to the attempt to synthesize stemonamide (**1**) itself, some key steps for the synthesis, particularly for construction of a pyrroloazepinone (B–C ring), were examined by using model compounds. Coupling of the 2-stannylpyrrolidine derivative and a silyl ether was tried using a silyl enol ether **9** derived from an acetylenic ketone **8**.[5] The silyl enol ether **9** was reacted with 1-(*t*-butoxycarbonyl)-2-

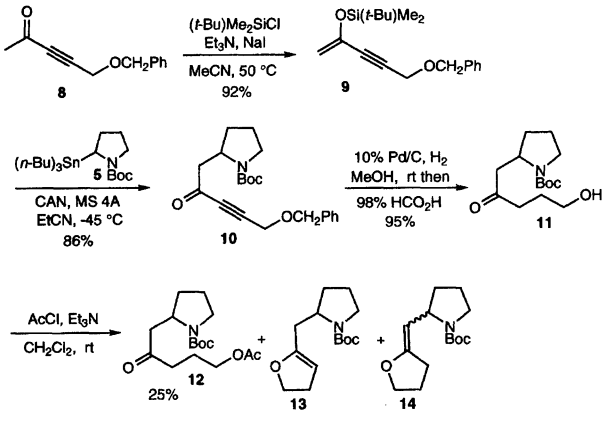


Scheme 2.



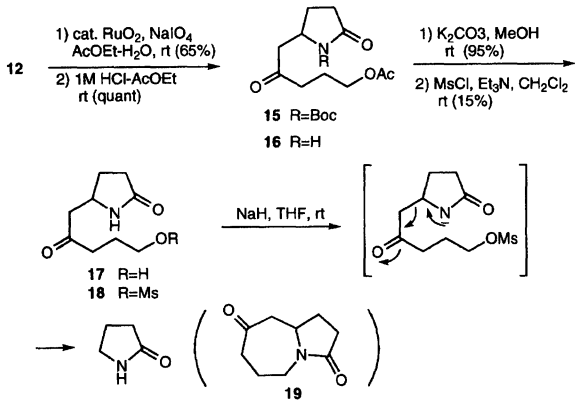
Scheme 3.

(tributylstannnyl)pyrrolidine (**5**) in the presence of ammonium hexanitratocerate(IV) (CAN) and Molecular Sieves 4A (MS 4A), as previously reported.[1] The reaction proceeded smoothly to afford an adduct **10** in 86% yield. The acetylenic moiety of the adduct **10** was reduced by catalytic hydrogenation, and the benzyl group was removed by successive addition of formic acid to the reaction mixture.[6] To convert the pyrrolidinering of **11** to a pyrrolidone moiety, a hydroxyl group of the alcohol **11** was protected by acetylation with acetyl chloride and triethylamine. The desired acetate **12** was, however, isolated in only 25% yield and hydrofuran derivatives **13** and **14** were obtained as by-products in 50% total yield (Eq. 1). Thus the acetylation of the hydroxyl group was considerably disturbed.



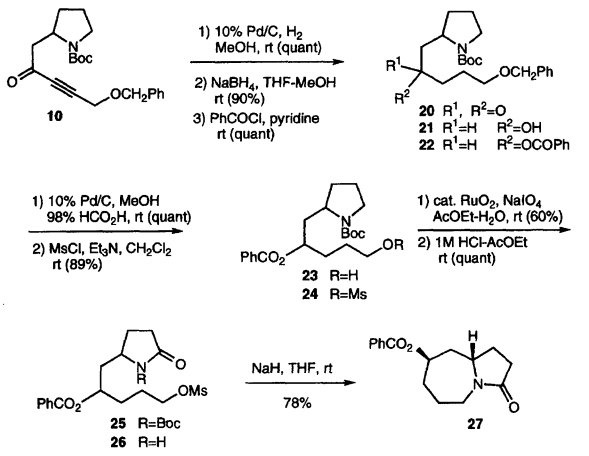
(1)

Oxidation of the pyrrolidine moiety of **12** to a pyrrolidone **16** was carried out smoothly by treatment with a catalytic amount of ruthenium dioxide and excess amounts of $NaIO_4$ in AcOEt–H_2O.[7] Removal of the Boc group with HCl–AcOEt at room temperature and removal of the acetyl group with K_2CO_3–MeOH gave a keto alcohol **17**. To study the cyclization of **17** into a pyrroloazepinedione **19**, mesylation of hydroxyl group of **17** was examined. The existence of the carbonyl group in the side chain, however, makes the reaction troublesome; hydrofuran derivatives, such as **13** and **14**, were formed as major products and the desired mesylate **18** was obtained in poor (15%) yield. In addition, trial of the cyclization of **18** with NaH led to cleavage of the side chain of the pyrrolidone **18** to give 2-pyrrolidone without the formation of a pyrroloazepinone **19** (Eq. 2).



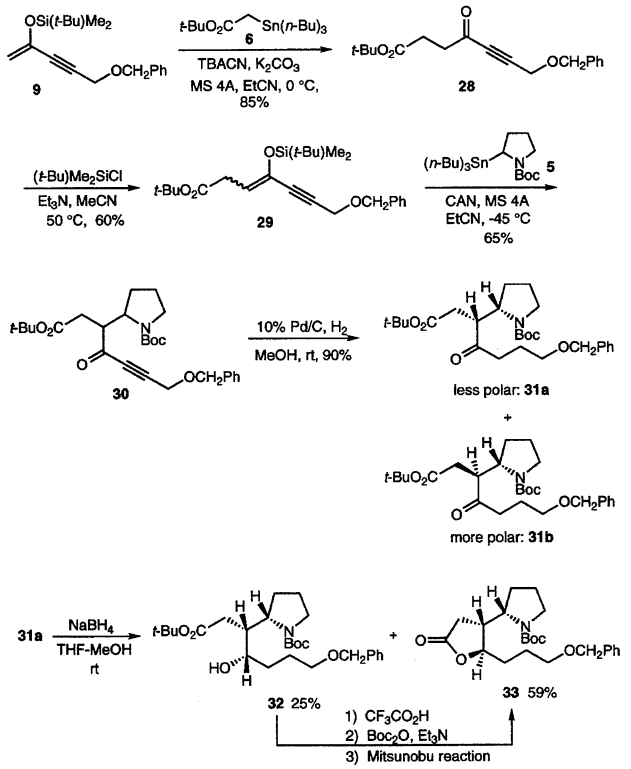
(2)

Since the keto alcohol intermediates **11** and **17** tended to cyclize to the hydrofuran derivatives and the cleavage of the side chain of **18** occurred in the base treatment of the keto pyrrolidone **18**, the carbonyl group was reduced prior to the removal of the benzyl group of **10**. After reduction of the alkynyl group of the coupling product **10**, the carbonyl group was reduced with $NaBH_4$ to afford alcohols **21** in 90% yield as a 81 : 19 diastereomer mixture, which could be separated by silica-gel column chromatography. The hydroxyl group of the major isomer was esterified with benzoyl chloride in pyridine at room temperature; debenzylation followed by mesylation gave a mesylate **24**. Catalytic RuO_4 oxidation of the mesylate **24** to a pyrrolidone **25** and deprotection of the Boc group produced a pyrrolidone **26**. Treatment of **26** with excess NaH in THF under high-dilution conditions afforded a desired cyclized product **27** in 78% yield (Eq. 3). The configuration of the pyrroloazepinone **27** was determined by 2D-NOESY experiment, in which NOE was observed between a methine proton of the pyrrolidone ring and the *ortho* protons of the benzoyl group. This suggests that the benzoyloxy group and the methine proton of the pyrrolidone ring are *cis*-oriented.



(3)

Taking into account the results of the model study, total synthesis of stemonamide was investigated as follows. For the introduction of an acetate unit which corresponds to the A ring of stemonamide, a coupling reaction of a 2-stannylacetate and the silyl enol ether **9** was examined. The oxidative radical addition reaction proceeded in good yield by treatment of a mixture of the silyl enol ether **9** and *t*-butyl 2-(tributylstannyl)acetate **6** with tetrabutylammonium nitratocerate(IV) (TBACN)[8] in the presence of K_2CO_3, giving an acetylenic keto ester **28** in good yield.[2] The adduct **28** was converted to a silyl enol ether **29** (*E*:*Z*=1:1) with *t*-butyldimethylsilyl chloride and triethylamine in acetonitrile. Oxidation of the stannnyl pyrrolidine **5** with CAN in the presence of the silyl enol ether **29** yielded an addition product **30** in 65% yield as a diastereomer mixture, which could not be separated by chromatography. At this stage, all the carbon units of stemonamide except a methyl group were arranged by the 4-step manipulations from the starting material **8**.



(4)

Hydrogenation of the acetylenic moiety of the adduct **30** led to a separable diastereomer mixture **31** in 90% yield (less polar isomer : more polar one=4 : 1). Although the stereochemistry of these isomers **31** was not clearly confirmed at this stage, a subsequent elaboration of the less polar major isomer **31a** to (±)-**1** definitely assigned their configurations as shown in Eq. 4. This stereoselectively is explained by considering transition states of the addition reaction of the silyl enol ether **29** to the acyliminium ion. The addition of the silyl enol ether **29** to the dihydropyrrolium intermediate generated from **5** seemed to proceed preferentially through the transition state **A**, because the steric repulsion between the alkoxycarbonylmethyl group and the methylene group

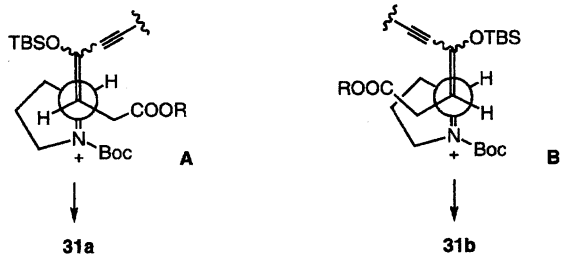


Fig. 1.

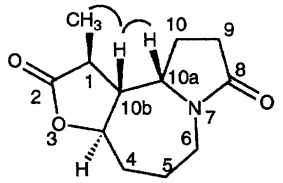
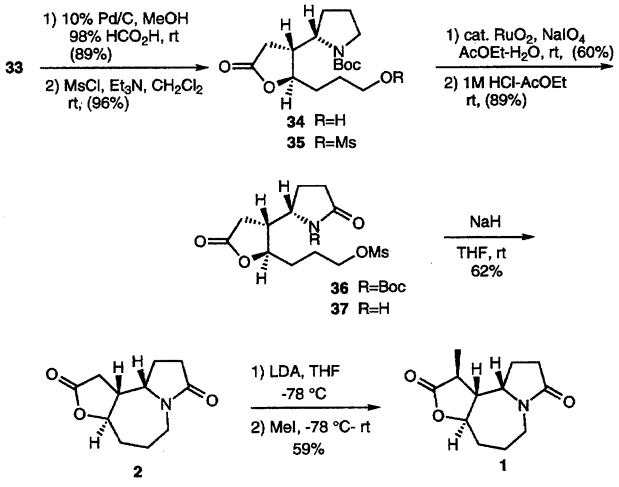


Fig. 2.

of the pyrrolidine makes the transition state **B** unfavorable (Fig. 1). The more polar diastereomer **31b** was found to be isomerized to a 1 : 1 mixture of **31a** and **31b** by epimerization with DBU. Thus the undesired isomer **31b** could be readily converted to the key synthetic intermediate **31a**.

Reduction of the carbonyl group of the major isomer **31a** with $NaBH_4$ gave an alcohol **32** and a lactone **33** in 25 and 59% yield, respectively (Eq. 4). Since the alcohol **32** could be transformed to the lactone **33** by successive treatment with CF_3CO_2H and Boc_2O and Et_3N, followed by the Mitsunobu reaction, the products **32** and **33** are diastereomers each other due to the chiral center generated by the carbonyl reduction. Though the stereochemistry of **32** and **33** could not be confirmed, the configuration of two methine protons of the lactone ring in **33** was expected to be *trans*. The steric repulsion between the Boc–pyrrolidine moiety and the benzyloxypropyl chain would prevent the other isomer **32** from cyclizing into a γ-lactone in which these substituents situate in *cis* relationship. This stereochemical assignment was confirmed by the achievement of the synthesis of stemonamide.



(5)

The transformation of the lactone **33** to a pyrroloazepinone derivative **2** was performed by following the synthetic pro-

cedures of the model compound **27**. Deprotection of the benzyl group and successive mesylation gave a mesylate **35**. RuO_4 oxidation and deprotection of the Boc group with 1 M HCl–AcOEt[9] produced a precursor **37** for cyclization (1 M=1 mol dm^{-3}). The tricyclic system was constructed by treatment of **37** with NaH in THF, giving a cyclized product **2** in 62% yield under high-dilution conditions. The last step, methylation of the lactone unit, proceeded stereoselectively to furnish (±)-stemonamide (**1**) by treatment of **2** with LDA and methyl iodide (Eq. 5). The configuration of (±)-**1** was assigned by 2D-NOESY experiment, in which NOE was observed between a methine proton on C10b and methyl protons, and between a C10b-methine proton and a methine proton of the pyrrolidone ring (Fig. 2). ^1H and ^{13}C NMR spectra of (±)-**1** are identical to those reported for the natural[3] and the synthetic ones.[4] Thus, synthesis of (±)-stemonamide was accomplished in a total of 12 steps.

Experimental

General. IR spectra were measured with a Nihon Bunko FT/IR 5300 spectrometer. ^1H NMR spectra (400 MHz) were recorded on a JEOL JNM-400 spectrometer with $CHCl_3$ (δ=7.24) as an internal standard. ^{13}C NMR spectra (100 MHz) were recorded on a JEOL JNM-400 spectrometer with $CDCl_3$ (δ=77.00) as an internal standard. In the ^{13}C NMR spectra, the rotameric resonance is placed in parentheses after the first resonance. High-resolution mass spectra were recorded on a JEOL JMS-SX102A mass spectrometer operating at 70 eV. Melting points were recorded on a Yanaco MP-500 and are uncorrected.

Acetonitrile and propiononitrile were distilled first from P_2O_5, then from CaH_2, and dried over Molecular Sieves 4A (MS 4A). MeOH was distilled from magnesium methoxide and dried over MS 3A. Triethylamine and pyridine were freshly distilled from CaH_2. Tetrahydrofuran (THF) was freshly distilled from sodium diphenylketyl. CAN (Kanto Chemical Co., Inc., guaranteed grade) and K_2CO_3 (Kanto Chemical Co., Inc., guaranteed grade) were dried under a vacuum at 80 °C before use. TBACN was prepared by a known method.[8] 1-(*t*-Butoxycarbonyl)-2-(tributylstannyl)-pyrrolidine (**5**) was prepared by the method of Beak and Lee.[10] 5-Benzyloxy-3-pentyn-2-one (**8**)[5] and *t*-butyl 2-(tributylstannyl)-acetate (**6**)[11] were prepared according to literature methods. The reactions were monitored by thin-layer chromatography (TLC) using pre-coated silica gel plates (Merck Kieselgel 60 F-254 Art. 5715). Silica-gel column chromatography was carried out with Merck Kieselgel 60 Art. 7734. Preparative TLC was performed on silica gel (Wakogel B-5F). All reactions were performed under an argon atmosphere, unless otherwise noted.

Preparation of 5-Benzyloxy-2-(*t*-butyldimethylsiloxy)-1-penten-3-yne (9). To an acetonitrile (700 ml) solution of 5-benzyloxy-3-pentyn-2-one (**8**) (17.4 g, 92.7 mmol), which was prepared according to a literature method,[5] was added triethylamine (20.7 ml, 148 mmol), NaI (20.8 g, 139 mmol), and *t*-butyldimethylsilyl chloride (21.0 g, 139 mmol). After the solution was stirred for 8 h at 50 °C, the reaction mixture was poured into ice-cold water and the organic materials were extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane : ethyl acetate=10 : 1, v/v) to afford silyl enol ether **9** (25.8 g, 92%) as a colorless oil. **9**: IR (neat) 2957, 2932, 2225, 1607, 1283 cm^{-1}; ^1H NMR δ=0.22 (6H, s), 0.95 (9H, s), 4.29 (2H, s), 4.61 (2H, s), 4.72 (2H, s), 7.30—7.37 (5H, m). Found: C, 71.25; H, 8.60%. Calcd for $C_{18}H_{26}O_2Si$: C, 71.47; H, 8.66%.

Preparation of 2-(5-Benzyloxy-2-oxo-3-pentynyl)-1-(*t*-butoxycarbonyl)pyrrolidine (10). To an EtCN (700 ml) solution of CAN (51.0 g, 93.2 mmol) was added MS 4A (50 g). Then, a solution of 1-(*t*-butoxycarbonyl)-2-(tributylstannyl)pyrrolidine (**5**) (21.5 g, 46.6 mmol) and silyl enol ether **9** (14.1 g, 46.6 mmol) in EtCN (50 ml) was added over 0.5 h at −45 °C. After stirring for 2 h, saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture, and the mixture was filtered through Celite. Organic materials were extracted with CH_2Cl_2, and the combined extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane : ethyl acetate=4 : 1, v/v) to give the adduct **10** (14.3 g, 86%) as a colorless oil. **10**: IR (neat) 2975, 2214, 1693, 1395, 1169 cm^{-1}; ^1H NMR δ=1.46 (9H, s), 1.68 (1H, br), 1.82—1.87 (2H, m), 2.04—2.17 (1H, m), 2.62 (1H, br), 3.03—3.06 (1H, br), 3.34 (2H, br), 4.25 (1H, br), 4.33 (2H, s), 4.62 (2H, s), 7.30—7.39 (5H, m); ^{13}C NMR δ=(22.74, 23.49), 28.41, (30.51, 31.37), (46.02, 46.44), (49.33, 50.34), 53.24, 56.87, (71.99, 72.08), (79.29, 79.78), 85.41, (87.75, 88.12), 127.44, 128.04, 128.44, 136.64, (154.03, 154.18), (185.25, 185.34). Found: C, 70.34; H, 7.38; N, 3.94%. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92%.

Preparation of 1-(*t*-Butoxycarbonyl)-2-(5-hydroxy-2-oxopentyl)pyrrolidine (11). A solution of **10** (3.00 g, 8.39 mmol) in MeOH (150 ml) was hydrogenated in the presence of 10% Pd/C (600 mg) at 1 atm for 3 h. Then 98% HCO_2H (6.00 ml) was added to the reaction mixture. This mixture was then stirred at room temperature for 18 h. After filtration of the catalyst, the filtrate was concentrated in vacuo. To the residue was added AcOEt (500 ml) and the organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate and brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by column chromatography (hexane : ethyl acetate=1 : 1, v/v) to give the alcohol **11** (2.16 g, 95%) as a colorless oil. **11**: IR (neat) 3432, 2975, 1667, 1480 cm^{-1}; ^1H NMR δ=1.45 (9H, s), 1.63—1.83 (5H, m), 2.03—2.10 (1H, m), 2.42—2.46 (1H, m), 2.56—2.66 (2H, m), 2.94 (1H, dd, J=15.6, 4.4 Hz), 3.32—3.34 (2H, m), 3.65 (2H, d, J=5.4 Hz), 4.19 (1H, br); ^{13}C NMR δ=(22.77, 23.51), 26.32, 28.46, (31.19, 31.45), (39.18, 40.08), (46.08, 46.48), 47.59, (53.35, 53.81), (61.58, 61.99), 79.45, (154.27, 154.51), 209.72. Found: C, 61.82; H, 9.07; N, 4.96%. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16%.

Preparation of 2-(5-Acetoxy-2-oxopentyl)-1-(*t*-butoxycarbonyl)pyrrolidine (12). To a CH_2Cl_2 solution (100 ml) of **11** (2.10 g, 7.74 mmol) was added triethylamine (1.80 ml, 12.6 mmol) and acetyl chloride (0.77 ml, 10.9 mmol). After the mixture was stirred for 5 h at room temperature, triethylamine (1.80 ml, 12.6 mmol) and acetyl chloride (0.77 ml, 10.9 mmol) was added to the reaction mixture again. After the mixture was stirred for an additional 8 h, the reaction was quenched with water, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate=3 : 1, v/v) to afford the acetate **12** (606 mg, 25%) as a colorless oil. **12**: IR (neat) 2975, 1740, 1703, 1694, 1397 cm^{-1}; ^1H NMR δ=1.44 (9H, s), 1.61—1.66 (1H, m), 1.77—1.84 (2H, m), 1.89 (2H, qui, J=6.8 Hz), 2.03 (3H, s), 2.00—2.10 (1H, m), 2.33—2.50 (3H, m), 2.88—3.09 (1H, m), 3.30 (2H, br), 4.05 (2H, t, J=6.4 Hz), 4.11 (1H, br). HR-FABMS Found: *m/z* 314.1896. Calcd for $C_{16}H_{28}NO_5$: $M+H^+$, 314.1967.

Preparation of 5-(5-Acetoxy-2-oxopentyl)-1-(*t*-butoxycarbonyl)-2-pyrrolidone (15). To a solution of $NaIO_4$ (4.95 g, 23.2 mmol) in H_2O (30 ml) was added RuO_2 (50 mg). The mixture was vigorously stirred at room temperature and then a solution of **12** (0.60 g, 1.91 mmol) in AcOEt (30 ml) was added to the mixture. After stirring for 4 h, the aqueous layer was extracted with AcOEt. To the combined extracts was added *i*-PrOH (5 ml) and the catalyst was filtrated. The filtrate was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane : ethyl acetate=1 : 1, v/v) to give the pyrrolidone **15** (0.41 g, 65%) as a colorless oil. **15**: IR (neat) 2978, 1784, 1748, 1715, 1312 cm^{-1}; ^1H NMR δ=1.53 (9H, s), 1.74 (1H, ddt, J=14.2, 9.3, 2.4 Hz), 1.92 (2H, qui, J=7.3 Hz), 2.05 (3H, s), 2.21—2.31 (1H, m), 2.42—2.58 (4H, m), 2.63 (1H, dd, J=17.1, 10.3 Hz), 3.04 (1H, dd, J=17.1, 2.4 Hz), 4.06 (1H, dt, J=13.7, 7.3 Hz), 4.09 (1H, dt, J=13.7, 7.3 Hz), 4.54 (1H, ddt, J=10.3, 8.3, 2.4 Hz). HR-FABMS Found: *m/z* 328.1764. Calcd for $C_{16}H_{26}NO_6$: M+H$^+$, 328.1760.

Preparation of 5-(5-Acetoxy-2-oxopentyl)-2-pyrrolidone (16). To a solution of 1 M HCl–AcOEt (10 ml) was added **15** (390 mg, 1.19 mmol) in AcOEt (2 ml). After the reaction mixture was stirred for 5 h at room temperature, the solvent was evaporated. The crude product was purified by column chromatography (CH_2Cl_2 : EtOH= 15 : 1, v/v) to give the pyrrolidone **16** (270 mg, quant) as a colorless oil. **16**: IR (neat) 2957, 1730, 1710, 1682 cm^{-1}; ^1H NMR δ= 1.80—1.89 (1H, m), 1.92 (2H, qui, J=6.8 Hz), 2.05 (3H, s), 2.30—2.37 (3H, m), 2.50 (2H, t, J=6.8 Hz), 2.58 (1H, dd, J=18.1, 9.8 Hz), 2.75 (1H, dd, J=18.1, 3.4 Hz), 4.00—4.05 (1H, m), 4.07 (2H, t, J=6.8 Hz), 6.19 (1H, s). HRMS Found: *m/z* 227.1136. Calcd for $C_{11}H_{17}NO_4$: M, 227.1158.

Preparation of 5-(5-Methylsulfonyloxy-2-oxopentyl)-2-pyrrolidone (18). To a solution of acetate **16** (250 mg, 1.10 mmol) in MeOH (5 ml) was added K_2CO_3 (304 mg, 2.20 mmol). After the mixture was stirred for 5 h at room temperature, the reaction was quenched with 5% aqueous citric acid, and organic materials were extracted with AcOEt. The combined organic extracts were washed with H_2O and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude alcohol **17** (194 mg, 95%) as a colorless oil. This compound was used in the next reaction without purification. **17**: IR (neat) 3430, 1731, 1689, 1263, 1154 cm^{-1}; ^1H NMR δ=1.81—1.90 (1H, m), 1.96 (2H, qui, J=6.8 Hz), 2.25—2.33 (3H, m), 2.53 (2H, t, J=6.8 Hz), 2.59 (1H, dd, J=18.1, 9.7 Hz), 2.77 (1H, dd, J=18.1, 3.5 Hz), 3.58 (2H, br), 3.66 (2H, t, J=6.8 Hz), 6.05 (1H, br). To a solution of the alcohol **17** (190 mg, 1.03 mmol) in CH_2Cl_2 (10 ml) was added triethylamine (0.20 ml, 1.44 mmol) and methanesulfonyl chloride (0.08 ml, 1.03 mmol). After the mixture was stirred for 7 h at room temperature, triethylamine (0.20 ml, 1.44 mmol) and methanesulfonyl chloride (0.08 ml, 1.03 mmol) was added to the reaction mixture again. After the mixture was stirred for an additional 10 h, the reaction was quenched with H_2O, and the organic materials were extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the crude product was purified by column chromatography (CH_2Cl_2 : EtOH=15 : 1, v/v) to give the mesylate **18** (40.5 mg, 15%) as a colorless oil. **18**: IR (neat) 2950, 1713, 1680 cm^{-1}; ^1H NMR δ=1.80—1.89 (1H, m), 1.94 (2H, qui, J=6.8 Hz), 2.31—2.39 (3H, m), 2.51 (2H, t, J=6.8 Hz), 2.57 (1H, dd, J=18.1, 9.8 Hz), 2.75 (1H, dd, J=18.1, 3.4 Hz), 3.01 (3H, s), 4.00—4.05 (1H, m), 4.09 (2H, t, J=6.8 Hz), 6.19 (1H, s). HRMS Found: *m/z* 263.0830. Calcd for $C_{10}H_{17}NO_5S$: M, 263.0827.

Preparation of 2-(5-Benzyloxy-2-oxopentyl)-1-(*t*-butoxycarbonyl)pyrrolidine (20). A solution of **10** (3.01 g, 8.67 mmol) in MeOH (200 ml) was hydrogenated in the presence of 10% Pd/C (600 mg) at 1 atm for 5 h. After filtration of the catalyst, the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (hexane : ethyl acetate=4 : 1, v/v) to give the ketone **20** (3.13 g, quant) as a colorless oil. **20**: IR (neat) 2973, 2876, 1694, 1397, 1171 cm^{-1}; ^1H NMR δ=1.45 (9H, s), 1.58—1.63 (1H, m), 1.77—1.84 (2H, m), 1.88 (2H, qui, J=6.8 Hz), 1.98—2.08 (1H, m), 2.38 (1H, dd, J=15.6, 9.8 Hz), 2.53 (2H, t, J=6.8 Hz), 2.88—3.10 (1H, br), 3.31 (2H, br), 3.47 (2H, t, J=6.4 Hz), 4.13 (1H, br), 4.47 (2H, s), 7.27—7.36 (5H, m); ^{13}C NMR δ=(22.78, 23.53), 23.69, 28.48, (30.80, 31.43), (39.71, 40.00), (46.04, 46.50), (46.92, 47.67), (53.37, 53.79), (69.17, 69.50), (72.81, 72.99), (79.14, 79.47), 127.34, 127.62, 128.33, 138.34, 154.25, (209.08, 209.20). Found: C, 69.71; H, 8.47; N, 3.89%. Calcd for $C_{21}H_{31}NO_4$: C, 69.78; H, 8.64; N, 3.87%.

Preparation of 2-(5-Benzyloxy-2-hydroxypentyl)-1-(*t*-butoxycarbonyl)pyrrolidine (21). To a solution of ketone **20** (4.10 g, 11.3 mmol) in THF (30 ml) was added $NaBH_4$ (430 mg, 11.3 mmol) and MeOH (30 ml). After stirring for 2 h at room temperature, the solvent was removed under reduced pressure. To the residue was added H_2O (50 ml) and the pH of the solution was adjusted to pH 4 by the addition of 10% aqueous solution of citric acid. Organic materials were extracted with AcOEt, and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was concentrated in vacuo and the residue was purified by column chromatography (hexane : ethyl acetate=2 : 1, v/v) to give the less polar alcohol **21** (0.70 g, 17%) and the more polar alcohol **21** (3.00 g, 73%) both as a colorless oil.

Less polar **21**: IR (neat) 3420, 2973, 1672, 1478, 1454, 1171 cm^{-1}; ^1H NMR δ=1.46 (9H, s), 1.50—2.01 (10H, m), 3.33—3.42 (2H, m), 3.48—3.53 (2H, m), 3.70 (1H, br), 3.98 (1H, br), 4.51 (2H, s), 7.27—7.34 (5H, m); ^{13}C NMR δ=23.67, 26.10, 28.50, 32.09, 34.65, 43.77, (46.15, 46.32), (55.30, 55.48), (70.01, 70.13), 70.34, (72.79, 72.97), 79.50, 127.44, 127.56, 128.25, 138.41, (155.34, 155.37). HRMS Found: *m/z* 363.2372. Calcd for $C_{21}H_{33}NO_4$: M, 363.2410.

More polar **21**: IR (neat) 3426, 2973, 1672, 1477, 1454, 1171 cm^{-1}; ^1H NMR δ=1.46 (9H, s), 1.50—2.00 (10H, m), 3.32—3.40 (2H, m), 3.48—3.53 (2H, m), 3.67 (1H, br), 3.98 (1H, br), 4.51 (2H, s), 7.27—7.34 (5H, m); ^{13}C NMR δ=23.67, 26.09, 28.46, 32.09, 34.65, 43.66, (46.15, 46.31), (55.38, 55.48), (70.00, 70.12), 70.34, (72.79, 72.98), 79.49, 127.44, 127.57, 128.26, 138.41, (155.35, 155.38). Found: C, 68.56; H, 8.85; N, 3.90%. Calcd for $C_{21}H_{33}NO_4$: C, 68.26; H, 9.15; N, 3.85%.

Preparation of 2-[2-Benzoyloxy-5-(benzyloxy)pentyl]-1-(*t*-butoxycarbonyl)pyrrolidine (22). To a solution of the more polar alcohol **21** (3.00 g, 8.25 mmol) in pyridine (40 ml) was added benzoyl chloride (1.15 ml, 9.90 mmol). After being stirred for 5 h at room temperature, the reaction mixture was diluted with AcOEt (300 ml) and washed with aqueous solution of 10% citric acid, H_2O, and brine, dried over anhydrous Na_2SO_4. The solvent was concentrated in vacuo and the residue was purified by column chromatography (hexane : ethyl acetate=5 : 1, v/v) to give the benzoate **22** (3.86 g, quant) as a colorless oil. **22**: IR (neat) 3416, 1702, 1694, 1453 cm^{-1}; ^1H NMR δ=1.46 (9H, s), 1.54—1.59 (1H, m), 1.66—1.82 (7H, m), 1.97 (1H, br), 2.20—2.40 (1H, m), 3.31—3.37 (2H, m), 3.49 (2H, t, J=6.3 Hz), 3.80—3.91 (1H, br), 4.45 (2H, s), 5.21—5.23 (1H, br), 7.28—7.35 (5H, m), 7.43 (2H, t, J=7.8 Hz), 7.54—7.56 (1H, m), 8.06 (2H, br); ^{13}C NMR δ=(22.77, 23.54), 25.45, 28.37, (29.91, 30.35), (31.37, 31.72), (37.85, 38.92), (45.84, 46.31), 53.90, 69.70, (71.99, 72.25), 72.70, (78.68, 78.94),

127.31, 127.42, 128.12, 128.28, 129.45, 130.13, 132.72, 138.25, 154.18, 166.04. Found: C, 71.67; H, 7.72; N, 3.05%. Calcd for $C_{28}H_{37}NO_5$: C, 71.92; H, 7.98; N, 3.00%.

Preparation of 2-(2-Benzoyloxy-5-hydroxypentyl)-1-(*t*-butoxycarbonyl)pyrrolidine (23). To a solution of **22** (3.50 g, 7.49 mmol) in MeOH (100 ml) was added 98% HCO_2H (8 ml) in the presence of 10% Pd/C (1.00 g). After stirring for 2 h at room temperature, the catalyst was filtrated and the filtrate was concentrated in vacuo. To the residue was added AcOEt (500 ml) and the organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate and brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by column chromatography (hexane : ethyl acetate=2 : 1, v/v) to give the alcohol **23** (2.82 g, quant) as a colorless oil. **23**: IR (neat) 3436, 2973, 1705, 1693 cm^{-1}; ^1H NMR δ=1.46 (9H, s), 1.59—1.81 (8H, m), 1.98—2.00 (1H, m), 2.14—2.23 (1H, m), 2.77 (1H, br s), 3.34 (2H, br), 3.61—3.70 (2H, m), 3.81—4.00 (1H, m), 5.24 (1H, br s), 7.43 (2H, t, J=7.8 Hz), 7.55 (1H, br), and 8.05 (2H, d, J=7.8 Hz); ^{13}C NMR δ=(22.69, 23.36), 27.99, 28.26, (29.82, 31.34), 30.24, 38.78, (45.78, 46.13), (53.70, 53.88), (60.91, 61.73), (71.81, 72.01), 79.09, 128.08, 129.34, (129.93, 130.13), (132.65, 132.76), (154.19, 154.60), 166.14. Found: C, 66.52; H, 8.09; N, 3.66%. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71%.

Preparation of 2-[2-Benzoyloxy-5-(methylsulfonyloxy)pentyl]-1-(*t*-butoxycarbonyl)pyrrolidine (24). To a solution of **23** (2.70 g, 7.15 mmol) in CH_2Cl_2 (60 ml) was added triethylamine (1.53 ml, 11 mmol) and methanesulfonyl chloride (0.77 ml, 10 mmol). After this solution was stirred for 6 h at room temperature, the reaction was quenched with H_2O, and the organic materials were extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography (hexane : ethyl acetate=2 : 1, v/v) to give the mesylate **24** (2.90 g, 89%) as a colorless oil. **24**: IR (neat) 3488, 2972, 1705, 1682 cm^{-1}; ^1H NMR δ=1.45 (9H, s), 1.57—1.67 (1H, m), 1.80—1.84 (7H, m), 2.00 (1H, br), 2.25—2.38 (1H, m), 3.00 (3H, s), 3.32—3.40 (2H, m), 3.80—3.95 (1H, m), 4.26 (2H, br s), 5.25 (1H, br s), 7.45 (2H, t, J=7.8 Hz), 7.58 (1H, br), 8.06 (2H, br). HR-FABMS Found: *m/z* 456.2134. Calcd for $C_{22}H_{34}NO_7S$: M+H$^+$, 456.2056.

Preparation of 5-[2-Benzoyloxy-5-(methylsulfonyloxy)pentyl]-1-(*t*-butoxycarbonyl)-2-pyrrolidone (25). Treatment of the pyrrolidine **24** (2.80 g, 6.14 mmol) in the same manner as described for compound **15** gave the pyrrolidone **25** (1.73 g, 60%) as a colorless caramel. **25**: IR (KBr) 3455, 1779, 1715, 1453 cm^{-1}; ^1H NMR δ=1.50 (9H, s), 1.74 (1H, ddd, J=13.2, 10.7, 2.4 Hz), 1.82—1.90 (4H, m), 1.94 (1H, ddt, J=13.2, 8.8, 2.4 Hz), 2.11—2.22 (1H, m), 2.35 (1H, ddd, J=13.2, 10.7, 2.4 Hz), 2.44 (1H, ddd, J=18.1, 9.3, 2.4 Hz), 2.58 (1H, ddd, J=18.1, 10.7, 9.3 Hz), 3.01 (3H, s), 4.20 (1H, ddt, J=10.7, 8.8, 2.4 Hz), 4.24—4.32 (2H, m), 5.31—5.35 (1H, m), 7.47 (2H, td, J=8.3, 2.0 Hz), 7.60 (1H, td, J=8.3, 2.0 Hz), 8.05 (2H, dd, J=8.3, 2.0 Hz); ^{13}C NMR δ=22.06, 24.95, 27.82, 30.81, 30.95, 37.13, 38.03, 54.73, 69.10, 70.29, 82.74, 128.32, 129.41, 129.47, 133.20, 149.44, 166.10, 173.93. Found: C, 56.46; H, 6.73; N, 3.07%. Calcd for $C_{22}H_{31}NO_8S$: C, 56.28; H, 6.65; N, 2.98%.

Preparation of 5-[2-Benzoyloxy-5-(methylsulfonyloxy)pentyl]-2-pyrrolidone (26). Treatment of the Boc-compound **25** (1.70 g, 3.62 mmol) in the same manner as described for compound **16** gave the pyrrolidone **26** (1.33 g, quant) as a colorless crystals. **26**: Mp 114 °C (hexane–AcOEt); IR (KBr) 3459, 2969, 1713, 1686, 1354 cm^{-1}; ^1H NMR δ=1.75—1.89 (6H, m), 2.05 (1H, ddd, J=15.6, 9.3, 6.3 Hz), 2.29—2.38 (3H, m), 3.01 (3H, s), 3.70—3.76 (1H, m), 4.23—4.30 (2H, m), 5.28—5.31 (1H, m), 6.07 (1H, s), 7.47 (2H, t, J=8.3 Hz), 7.60 (1H, td, J=8.3, 1.5 Hz), 8.03 (2H, dd, J=8.3, 1.5 Hz); ^{13}C NMR δ=24.92, 27.39, 30.02, 30.77, 37.26, 41.27, 51.58, 69.19, 71.06, 128.50, 129.35, 129.51, 133.31, 166.03, 178.24. Found: C, 55.55; H, 6.30; N, 4.09%. Calcd for $C_{17}H_{23}NO_6S$: C, 55.27; H, 6.28; N, 3.79%.

Preparation of (5*R,7*R**)-5-Benzoyloxy-1-azabicyclo[5.3.0]decan-10-one (27).** To a solution of **26** (1.10 g, 2.98 mmol) in THF (250 ml) was added 60% NaH (1.19 g, 29.8 mmol), and the reaction mixture was stirred for 6 h at room temperature. The reaction mixture was poured into ice-cold 5% aqueous solution of citric acid (100 ml) and the organic materials were extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (CH_2Cl_2 : EtOH=15 : 1, v/v) to afford the product **27** (0.63 g, 78%) as a colorless oil. **27**: IR (neat) 2943, 1713, 1661, 1451, 1424 cm^{-1}; ^1H NMR δ=1.71—1.86 (2H, m), 1.89—2.02 (3H, m), 2.09—2.14 (1H, m), 2.16—2.27 (2H, m), 2.39 (1H, dt, J=16.6, 9.3 Hz), 2.47 (1H, ddd, J=16.6, 9.3, 4.4, Hz), 3.27 (1H, ddd, J=14.2, 8.3, 2.4 Hz), 3.70 (1H, ddd, J=14.2, 7.3, 3.4 Hz), 4.05 (1H, dq, J=14.6, 7.3 Hz), 5.31 (1H, tt, J=6.8, 2.4 Hz), 7.46 (2H, td, J=8.3, 1.5 Hz), 7.59 (1H, tt, J=8.3, 1.5 Hz), 8.04 (2H, dd, J=8.3, 1.5 Hz); ^{13}C NMR δ=22.03, 26.10, 30.68, 34.37, 40.35, 42.42, 53.70, 70.56, 128.35, 129.40, 130.24, 133.02, 165.44, 174.70. Found: C, 70.30; H, 7.24; N, 5.00%. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12%.

Preparation of *t*-Butyl 7-Benzyloxy-4-oxo-5-heptynoate (28). To a propiononitrile (600 ml) solution of TBACN (99.7 g, 100 mmol), K_2CO_3 (27.6 g, 200 mmol) and MS 4A (50 g) was added dropwise a propiononitrile (100 ml) solution of the silyl enol ether **9** (12.1 g, 40 mmol) and *t*-butyl 2-(tributylstannyl)acetate (**6**) (20.3 g, 50 mmol) at 0 °C. After stirring for 2 h, saturated aqueous sodium hydrogencarbonate was added to the reaction mixture and the mixture was then filtrated through Celite. Organic materials were extracted with CH_2Cl_2, and the combined extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane : AcOEt=6 : 1, v/v) to afford the product **28** (10.3 g, 85%) as a colorless oil. **28**: IR (neat) 2978, 2216, 1730, 1682, 1368 cm^{-1}; ^1H NMR δ=1.45 (9H, s), 2.58 (2H, t, J=6.8 Hz), 2.87 (2H, t, J=6.8 Hz), 4.34 (2H, s), 4.62 (2H, s), 7.29—7.36 (5H, m); ^{13}C NMR δ=27.88, 28.98, 39.97, 56.79, 71.97, 80.77, 84.88, 87.94, 127.71, 127.99, 128.39, 136.64, 170.98, 185.01. Found: C, 71.24; H, 7.28%. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33%.

Preparation of *t*-Butyl 7-Benzyloxy-4-(*t*-butyldimethylsilyoxy)-3-hepten-5-ynoate (29). Treatment of the ketone **28** (10.0 g, 33.1 mmol) in the same manner as described for compound **9** gave the silyl enol ether **29** (8.27 g, 60%) as a colorless oil. **29**: IR (neat) 2957, 2932, 2224, 1732, 1636, 1368, 1312, 1256, 1150 cm^{-1}; ^1H NMR δ=0.21, 0.24 (6H, 2s), 0.95, 0.96 (9H, 2s), 1.45 (9H, s), 3.10 (1H, d, J=7.3 Hz), 3.14 (1H, d, J=7.8 Hz), 4.29, 4.34 (2H, 2s), 4.60, 4.62 (2H, 2s), 5.28 (0.5H, t, J=7.3 Hz), 5.42 (0.5H, t, J=7.8 Hz), 7.29—7.38 (5H, m). Found: C, 69.04; H, 8.51%. Calcd for $C_{24}H_{36}O_4Si$: C, 69.19; H, 8.71%.

Preparation of 2-[6-Benzyloxy-1-[(*t*-butoxycarbonyl)methyl]-2-oxo-3-pentynyl]-1-(*t*-butoxycarbonyl)pyrrolidine (30). Treatment of the silyl enol ether **29** (5.29 g, 12.7 mmol) and stannnyl pyrrolidine **5** (5.85 g, 12.7 mmol) in the same manner as described for compound **10** gave the adduct **30** (3.68 g, 65%) as a colorless oil. **30**: IR (neat) 2976, 2934, 2213, 1730, 1694, 1478, 1252 cm^{-1}; ^1H NMR δ=1.43, 1.45, 1.46, 1.49 (18H, 4s), 1.78—1.97 (4H, m), 2.33—2.40 (1H, m), 2.73—2.83 (1H, m), 3.23—

3.25 (1H, m), 3.36—3.56 (2H, m), 4.12—4.15 (1H, m), 4.34 (2H, s), 4.61 (2H, s), 7.28—7.38 (5H, m); ^{13}C NMR δ=(22.89, 23.71), 27.97, 28.43, (33.90, 34.22), (46.68, 46.95), (52.40, 52.59), (53.26, 53.46), (56.94, 57.03), (58.22, 58.57), (71.90, 72.01, 72.25), (79.52, 80.24), (80.93, 81.10), 85.39, (88.72, 89.45), 127.91, 128.04, 128.46, 136.73, (154.34, 154.89), (170.56, 170.64, 170.80), (187.86, 188.21). Found: C, 68.50; H, 7.73; N, 3.02%. Calcd for $C_{27}H_{37}NO_6$: C, 68.77; H, 7.91; N, 2.97%.

Preparation of 2-[6-Benzyloxy-1-[(*t*-butoxycarbonyl)methyl]-2-oxopentyl]-1-(*t*-butoxycarbonyl)pyrrolidine (31). Treatment of the alkynyl pyrrolidine **30** (3.60 g, 7.63 mmol) in the same manner as described for compound **20** gave the products (3.27 g, 90%, **31a** : **31b**=4 : 1).

Less polar isomer **31a**: Colorless oil; IR (neat) 2976, 2932, 1730, 1696, 1480, 1454, 1393, 1256 cm^{-1}; ^{1}H NMR δ=1.39 (9H, s), 1.46, 1.50 (9H, 2br s), 1.69 (2H, br), 1.82—1.94 (4H, m), 2.23—2.27 (1H, m), 2.53—2.58 (1H, m), 2.66—2.72 (2H, m), 3.12 (1H, br), 3.36 (1H, br), 3.46 (2H, t, J=6.3 Hz), 3.69 (1H, br), 3.93 (1H, br s), 4.48 (2H, s), 7.24—7.35 (5H, m); ^{13}C NMR δ=(22.94, 23.76), 23.53, (26.60, 28.22), 27.97, 28.43, 35.32, 41.10, (46.44, 46.99), (48.42, 49.95), (58.97, 59.13), (69.21, 69.45), 72.78, (79.58, 80.04), (80.62, 80.73), 127.42, 127.59, 128.26, 138.47, (154.85, 154.91), 171.13, (211.87, 212.17). Found: C, 68.01; H, 8.41; N, 2.98%. Calcd for $C_{27}H_{41}NO_6$: C, 68.18; H, 8.69; N, 2.94%.

More polar isomer **31b**: Colorless oil; IR (neat) 2975, 2876, 1730, 1699, 1478, 1256 cm^{-1}; ^{1}H NMR δ=1.39 (9H, s), 1.48, 1.50 (9H, 2s), 1.63—1.81 (4H, m), 1.91 (2H, qui, J=6.3 Hz), 2.13 (1H, dd, J=16.6, 2.9 Hz), 2.64 (2H, br), 2.70 (1H, dd, J=16.6, 10.7 Hz), 3.23—3.27 (1H, m), 3.35—3.58 (1H, m), 3.46 (2H, t, J=6.3 Hz), 3.74 (1H, br), 4.08 (1H, br), 4.45, 4.49 (2H, 2d, J=11.7 Hz), 7.28—7.35 (5H, m); ^{13}C NMR δ=23.49, (23.78, 24.20), (26.21, 27.00), 27.93, 28.37, (30.81, 31.46), 39.05, (47.04, 47.26), (49.82, 50.56), (56.55, 56.70), 69.12, 72.74, (79.49, 80.05), 80.49, 127.40, 127.55, 128.23, 138.39, (154.30, 154.52), 171.46, (209.97, 210.43). HRMS Found: *m/z* 475.2958. Calcd for $C_{27}H_{41}NO_6$: M, 475.2934.

Reduction of the Keto Pyrrolidine 31a. Treatment of the keto pyrrolidone **31a** (2.20 g, 4.63 mmol) in the same manner as described for compound **21** gave the products **32** (0.55 g, 25%) and **33** (1.10 g, 59%).

32: Colorless oil; IR (neat) 3447, 2975, 1726, 1692, 1480, 1454, 1391 cm^{-1}; ^{1}H NMR δ=1.43 (9H, s), 1.46 (9H, s), 1.72—2.01 (9H, m), 2.11—2.35 (2H, m), 3.13 (1H, br s), 3.43 (1H, br s), 3.51 (2H, t, J=6.3 Hz), 3.63—3.70 (1H, br), 3.95—4.11 (1H, br), 4.42 (1H, br), 4.52 (2H, s), 7.27—7.36 (5H, m); ^{13}C NMR δ=(23.42, 23.71), (26.40, 26.58), 27.78, 28.15, 31.67, 32.10, (44.16, 45.53), (46.17, 46.72), (47.12, 47.37), (55.66, 57.21), (58.49, 59.39), (70.01, 70.09), (72.19, 72.52), 79.29, 79.67, 127.15, 127.29, 127.97, 138.10, (155.86, 156.02), 172.52. HRMS Found: *m/z* 477.3090. Calcd for $C_{27}H_{43}NO_6$: M, 477.3047.

33: Colorless oil; IR (neat) 2973, 1777, 1700, 1391, 1169 cm^{-1}; ^{1}H NMR δ=1.45 (9H, s), 1.61—1.81 (8H, m), 1.91—2.03 (1H, m), 2.41—2.45 (1H, m), 2.59 (1H, dd, J=17.6, 9.3 Hz), 3.23 (1H, dt, J=11.2, 6.8 Hz), 3.47—3.54 (3H, m), 3.97 (1H, br), 4.34 (1H, br), 4.49 (2H, s), 7.28—7.37 (5H, m); ^{13}C NMR δ=(22.19, 23.20), 24.89, 25.21, 25.72, 27.60, 30.55, 31.15, 43.08, 57.01, 68.83, 71.97, (78.68, 79.98), 81.33, 126.67, 126.76, 127.53, 137.84, (154.07, 154.45), 175.32. Found: C, 68.22; H, 8.16; N, 3.55%. Calcd for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24; N, 3.47%.

Preparation of (3*R,4*R**)-3-[(2*S**)-1-(*t*-Butoxycarbonyl)-pyrrolidin-2-yl]-4-(3-hydroxypropyl)-4-butanolide (34).** Treatment of the pyrrolidine **33** (1.01 g, 2.50 mmol) in the same manner as described for compound **23** gave the hydroxy pyrrolidine **34** (0.70 g, 89%) as a colorless oil. **34**: IR (neat) 3459, 2973, 1775, 1690, 1395, 1169 cm^{-1}; ^{1}H NMR δ=1.46 (9H, s), 1.63—1.93 (8H, m), 2.04—2.19 (1H, m), 2.40—2.54 (2H, m), 2.65 (1H, br), 3.25—3.33 (1H, m), 3.47—3.56 (1H, m), 3.67 (2H, br s), 3.91—4.15 (1H, br), 4.38 (1H, br); ^{13}C NMR δ=23.98, 28.13, 28.32, 29.10, 29.67, 31.32, 46.53, 48.12, 56.19, 60.49, 80.31, 81.48, 155.95, 176.12. HRMS Found: *m/z* 313.1875. Calcd for $C_{16}H_{27}NO_5$: M, 313.1889.

Preparation of (3*R,4*R**)-3-[(2*S**)-1-(*t*-Butoxycarbonyl)-pyrrolidin-2-yl]-4-[3-(methylsulfonyloxy)propyl]-4-butanolide (35).** Treatment of the hydroxy pyrrolidine **34** (650 mg, 2.07 mmol) in the same manner as described for compound **24** gave the mesylate **35** (780 mg, 96%) as a colorless caramel. **35**: IR (KBr) 2975, 1773, 1684, 1354, 1173 cm^{-1}; ^{1}H NMR δ=1.46 (9H, s), 1.53—1.97 (8H, m), 2.00—2.10 (1H, m), 2.42—2.50 (1H, br), 2.55—2.65 (1H, br), 3.02 (3H, s), 3.24—3.31 (1H, m), 3.54 (1H, br), 4.13 (1H, br), 4.24—4.36 (3H, m). HRMS Found: *m/z* 391.1680. Calcd for $C_{17}H_{29}NO_7S$: M, 391.1665.

Preparation of (3*R,4*R**)-3-[(2*S**)-1-(*t*-Butoxycarbonyl)-5-oxopyrrolidin-2-yl]-4-[3-(methylsulfonyloxy)propyl]-4-butanolide (36).** Treatment of the pyrrolidine **35** (730 mg, 1.87 mmol) in the same manner as described for compound **25** gave the pyrrolidone **36** (455 mg, 60%) as a colorless oil. **36**: IR (neat) 2978, 1779, 1752, 1715, 1454 cm^{-1}; ^{1}H NMR δ=1.55 (9H, s), 1.73—2.00 (5H, m), 2.25 (1H, ddd, J=19.1, 13.7, 9.8 Hz), 2.41 (1H, dd, J=18.1, 7.3 Hz), 2.50—2.64 (2H, m), 2.70 (1H, dd, J=18.1, 9.3 Hz), 2.79—2.86 (1H, m), 3.04 (3H, s), 4.22—4.39 (4H, m); ^{13}C NMR δ=20.25, 25.28, 27.82, 30.60, 31.24, 31.37, 37.28, 43.52, 57.08, 68.61, 80.29, 84.02, 150.26, 173.51, 174.82. HRMS Found: *m/z* 405.1461. Calcd for $C_{17}H_{27}NO_8S$: M, 405.1457.

Preparation of (3*R,4*R**)-4-[3-(Methylsulfonyloxy)propyl]-3-[(2*S**)-5-oxopyrrolidin-2-yl]-4-butanolide (37).** Treatment of the Boc-compound **36** (200 mg, 0.49 mmol) in the same manner as described for compound **26** gave the pyrrolidone **37** (133 mg, 89%) as a colorless caramel. **37**: IR (KBr) 2978, 1769, 1688, 1348 cm^{-1}; ^{1}H NMR δ=1.68—1.79 (2H, m), 1.89—2.05 (3H, m), 2.26—2.40 (4H, m), 2.49 (1H, dd, J=17.6, 8.3 Hz), 2.67 (1H, dd, J=17.6, 9.3 Hz), 3.04 (3H, s), 3.81—3.89 (1H, m), 4.27 (1H, dt, J=11.2, 5.4 Hz), 4.31—4.37 (2H, m), 7.69 (1H, s); ^{13}C NMR δ=24.97, 25.37, 30.02, 30.06, 30.91, 37.33, 45.80, 54.49, 69.12, 80.79, 175.15, 179.12. HR-FABMS Found: *m/z* 306.1025. Calcd for $C_{12}H_{20}NO_6S$: M+H$^+$, 306.1011.

Preparation of (3a*R,10a*S**,10b*R**)-Octahydro-2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepin-2,8(1*H*)-dione (2).** Treatment of the pyrrolidone **37** (50 mg, 0.16 mmol) in the same manner as described for compound **27** gave the product **2** (21 mg, 62%) as a colorless caramel. **2**: IR (KBr) 2934, 1771, 1651, 1462 cm^{-1}; ^{1}H NMR δ=1.52—1.60 (2H, m), 1.73 (1H, qui, J=10.7 Hz), 1.84—1.90 (1H, m), 2.05—2.12 (1H, m), 2.36—2.45 (4H, m), 2.51 (1H, dd, J=17.1, 8.8 Hz), 2.64 (1H, dd, J=17.1, 12.7 Hz), 2.65—2.76 (1H, m), 4.00 (1H, dt, J=10.7, 6.4 Hz), 4.11—4.16 (1H, m), 4.30 (1H, dt, J=2.9, 10.3 Hz); ^{13}C NMR δ=22.54, 25.37, 30.48, 30.90, 34.50, 40.08, 44.76, 55.95, 79.71, 174.02, 174.70. HRMS Found: *m/z* 209.1015. Calcd for $C_{11}H_{15}NO_3$: M, 209.1052.

Preparation of Stemonamide (1). To a solution of diisopropylamine (10 mg, 0.10 mmol) in THF (1.0 ml) was added *n*-BuLi (63 µl of a 1.6 M hexane solution, 0.10 mmol) at −78 °C, and the mixture was stirred for 30 min. A THF solution (0.5 ml) of **2** (19 mg, 92 µmol) was added to the above solution at −78 °C. After stirring for 1 h, a THF solution (0.5 ml) of methyl iodide (10 µl, 0.16 mmol) was added. The reaction mixture was stirred from −78 °C to r.t. for 17 h. The reaction was quenched with saturated aqueous solution of NH_4Cl and organic materials were extracted

with AcOEt. The combined extracts were washed with brine, and dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by preparative TLC (CH_2Cl_2 : EtOH=15 : 1, v/v) to give **1** (12 mg, 59%) as a colorless caramel. **1**: IR (KBr) 2937, 1771, 1668, 1455, 1326 cm^{-1}; ^1H NMR δ=1.30 (3H, d, J=6.8 Hz), 1.46—1.56 (2H, m), 1.73 (1H, qui, J=10.7 Hz), 1.83—1.90 (1H, m), 2.07—2.13 (1H, m), 2.36—2.45 (4H, m), 2.60 (1H, dq, J=12.4, 6.8 Hz), 2.65—2.76 (1H, m), 4.01 (1H, dt, J=10.7, 6.4 Hz), 4.11—4.17 (1H, m), 4.26 (1H, dt, J=2.9, 10.3 Hz); ^{13}C NMR δ=13.89, 22.49, 25.49, 30.63, 34.83, 37.22, 40.04, 52.66, 55.85, 77.45, 174.02, 177.23. HRMS Found: m/z 223.1212. Calcd for $C_{12}H_{17}NO_3$: M, 223.1208.

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