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Total synthesis of (±)-stemonamide, (±)-isostemonamide, (±)-stemonamine, and (±)-isostemonamine using a radical cascade

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A total synthesis of (±)-stemonamide and (±)-isostemonamide has been achieved by using a radical cascade that involves two *endo*-selective cyclizations. (±)-Stemonamine and (±)-isostemonamine are synthesized by chemoselective reduction of (±)-stemonamide and (±)-isostemonamide, respectively.

1. Introduction

Stemona alkaloids such as (−)-stemonamide (**1**) and (−)-isostemonamide (**2**) and their reduced compounds, (±)-stemonamine (**3**) and (±)-isostemonamine (**4**), were isolated from the roots of *Stemona japonica*, which have been used in Chinese and Japanese folk medicine as cough medicines and insecticides.[1,2] Their tetracyclic structure including contiguous spirocyclic quaternary centers provides attractive target molecules for total synthesis.[3,4] We wish to report herein a total synthesis of (±)-stemonamide (**1**) and (±)-isostemonamide (**2**) using a radical cascade as the key step and the synthesis of (±)-stemonamine (**3**) and (±)-isostemonamine (**4**) by chemoselective reduction of (±)-**1** and (±)-**2**, respectively (Fig. 1).[5]

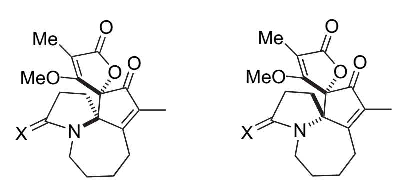
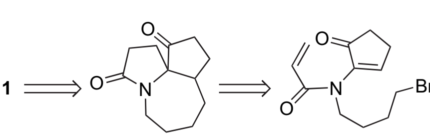


Figure 1. Stemonamide and related alkaloids.



Scheme 1. Retrosynthetic analysis.

2. Results and discussion

2.1. Synthesis of (±)-stemonamide (1) and (±)-isostemonamide (2) using radical cascade involving two *endo*-selective cyclizations

Our strategy for the synthesis of (±)-stemonamide (**1**) is shown in Scheme 1. Compound (±)-**1** was envisaged to arise from tricyclic compound **5**, which, in turn, was obtained by a Bu_3SnH-mediated radical cascade of **6** involving two *endo*-selective cyclizations.

Synthesis of **6** was begun by condensation of 1,2-cyclopentanedione and 4-(*tert*-butyldimethylsilyloxy)butylamine followed by acylation of the resulting imine with acryloyl chloride in the presence of *N*,*N*-diethylaniline to give enamide **7** (Scheme 2). After removal of the TBS group of **7**, mesylation of alcohol **8** followed by bromination of the resultant mesylate with lithium bromide afforded the radical precursor **6**.

When a boiling solution of enamide **6** in toluene was treated with Bu_3SnH in the presence of 1,1′-azobiscyclohexanecarbonitrile (ACN), a mixture of almost equal amounts of tricyclic compound **10**

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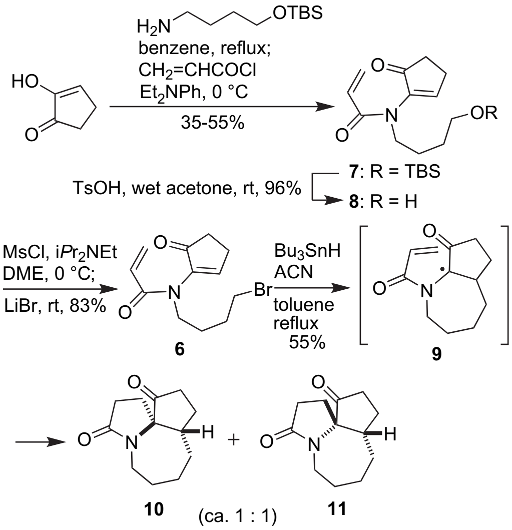
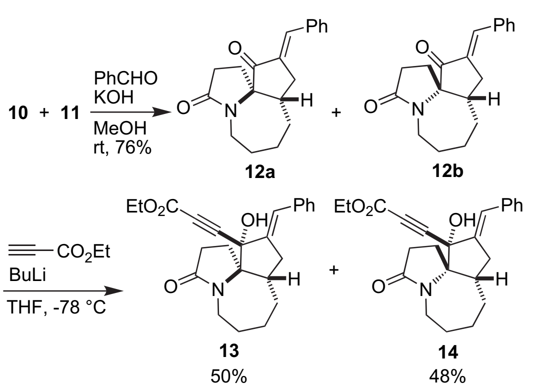


Scheme 2. Synthesis and radical cyclization of **6**.

and its stereoisomer **11** was obtained in 55% total yield (Scheme 2). Formation of **10** and **11** may be best explained by a radical cascade that involves a 7-*endo*-selective cyclization of an alkyl radical onto the alkenic bond of enamide[6] followed by a 5-*endo* cyclization of the resulting α-amidoyl radical **9**.[7]

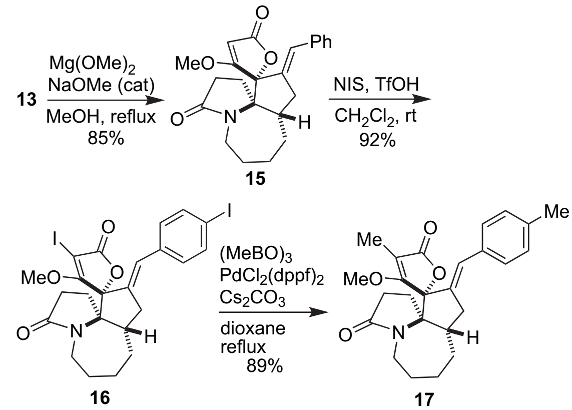
The mixture of compounds **10** and **11** was then subjected to aldol reaction with benzaldehyde to give an inseparable mixture of α,β-unsaturated ketones **12a**,**b** in 76% yield (Scheme 3). A subsequent addition reaction of **12a**,**b** with lithium ethyl propiolate afforded the adducts **13** and **14** in 50% and 48% isolated yields, respectively. X-ray crystallographic analysis of **13** and **14** confirmed their structures, indicating that the phenyl groups of the mixture **12a**,**b** have stereochemistries as depicted in Scheme 3.[8] Formation of **13** and **14** might be a result of an attack of lithium ethyl propiolate on the convex faces of **12a**,**b**, respectively.



Scheme 3. Synthesis of **13** and **14**.

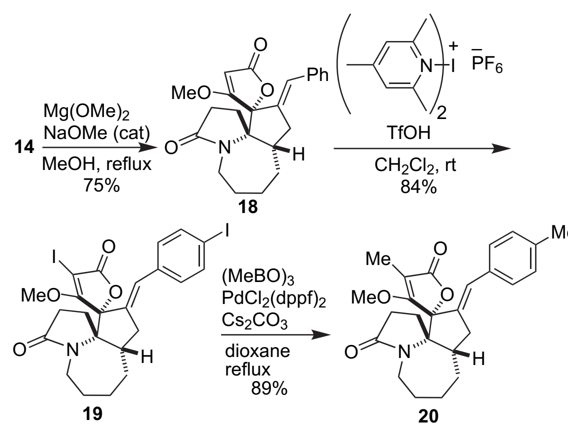
Treatment of the adduct **13** with magnesium methoxide in boiling MeOH[9] afforded methyl tetronate (β-methoxy-α,β-unsaturated lactone) **15** in 85% yield (Scheme 4). α-Methylation of the α,β-unsaturated bond of this tetronate with LDA/methyl iodide[10] giving a compound such as **17** failed, and hence an alternative method of α-methylation was examined. Iodination of **15** with *N*-iodosuccinimide (NIS) in the presence of trifluoromethanesulfonic acid (TfOH) gave iodide **16**. Treatment of compound **16** with trimethylboroxine in the presence of $PdCl_2(dppf)_2$ (Suzuki–Miyaura coupling)[11] afforded methylated compound **17** in high yield (Scheme 4).

Similarly, iodination of compound **18**, prepared from **14** with magnesium methoxide, by bis(trimethylpyridine)iodonium



Scheme 4. Synthesis of **17**.

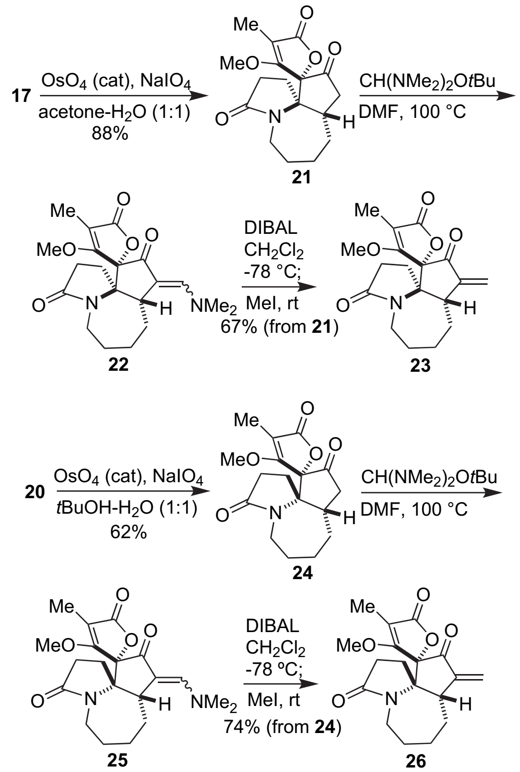
hexafluorophosphate in the presence of TfOH[12] gave **19**. Iodination of NIS/TfOH gave an unsatisfactory result. Suzuki–Miyaura coupling of **19** with trimethylboroxine/$PdCl_2(dppf)_2$ afforded compound **20** (Scheme 5) in 89% yield.



Scheme 5. Synthesis of **20**.

Oxidative cleavage of alkenes **17** with $OsO_4/NaIO_4$ afforded ketone **21** in 88% yield (Scheme 6). α-Methylenation of ketone **21** with Eschenmoser's salt[13] in the presence of various bases such as KH or LDA afforded the unsaturated ketone **23** in poor yield. Similar α-methylenation using paraformaldehyde/*N*-methylanilinium trifluoroacetate[14] also gave an unsatisfactory result. We therefore examined another route to **23**. Treatment of ketone **21** with *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent)[15] gave enaminone **22**, whose reduction with DIBAL[16] followed by methylation with MeI afforded α-methylenated ketone **23** in 67% yield (Scheme 6). Similarly, compound **20** was converted to **26** in good yield.

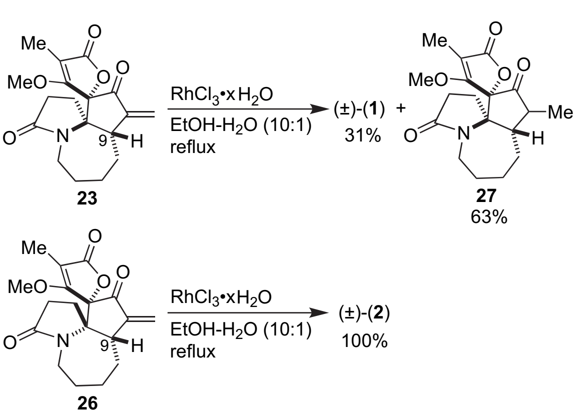
Finally, $RhCl_3$-mediated isomerization of the double bond[17] of *exo*-methylene ketone **23** gave (±)-stemonamide (**1**) (mp 232–233 °C, lit.[3] mp 240–241 °C) along with **27** in 31% and 63% yields, respectively. Spectral data of (±)-**1** were in accord with those of natural (−)-**1**, kindly provided by Professor Ye. ^{1}H NMR spectra of the unexpected compound **27** showed it to be a single stereoisomer. It is presumed that an attack of $RhCl_3$ on the same side (β-face) of 9-H of **23** brings about isomerization of the double bond to give (±)-**1**, whereas, when $RhCl_3$ attacks the opposite side (α-face) of 9-H, and reduction of the double bond with $RhCl_3$ takes place to give **27**. Therefore, the methyl group of **27** seemed to have a β-orientation. On the other hand, $RhCl_3$ attacked the same side (β-face) of 9-H of **26** to afford (±)-isostemonamide (**2**) (mp 223–224 °C, lit.[3] mp 225–227 °C) quantitatively. Spectral data of (±)-**2** were in accord with those of natural (−)-**2** (Scheme 7).



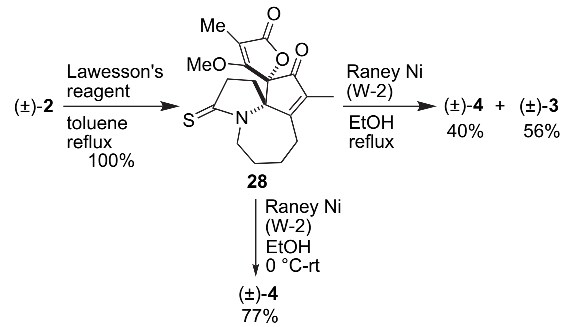
Scheme 6. Synthesis of **23** and **26**.

2.2. Synthesis of (±)-stemonamine (3) and (±)-isostemonamine (4) from (±)-stemonamide (1) and (±)-isostemonamide (2)

We next examined a conversion of (±)-(**1**) or (±)-(**2**) to (±)-stemonamine (**3**) or (±)-isostemonamine (**4**) by reduction of the corresponding lactam carbonyl group. *p*-Methoxyphenylthionophosphine sulfide dimer (Lawesson's reagent)[18] is known to convert the lactam carbonyl groups into the corresponding thiocarbonyl derivatives selectively even in the presence of ketone and lactone groups.[19] Therefore, we examined reduction of the thiocarbonyl group of lactam, prepared from (±)-(**1**) or (±)-**2**, with Raney nickel. We were delighted to find that treatment of (±)-(**2**), obtained in large quantities, with Lawesson's reagent afforded the desired thiocarbonyl lactam **28** quantitatively. A subsequent reduction of **28** with Raney nickel (W-2) in refluxing EtOH provided, in 40% yield, (±)-isostemonamine (**3**), the spectral data of which were in accord with those of a natural one (Scheme 8).

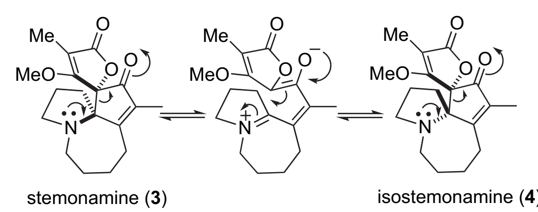


Scheme 7. Synthesis of (±)-**1** and (±)-**2**.



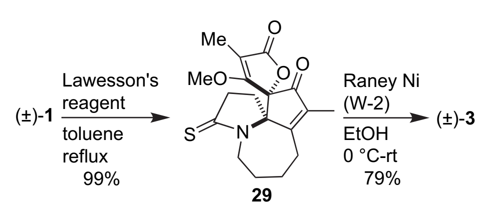
Scheme 8. Synthesis of (±)-**4** and (±)-**3**.

Surprisingly, the same reduction of **28** also afforded, in 56% yield, the unexpected (±)-stemonamine (**3**), the spectral data of which were in accord with those of a natural one. This result might indicate that (±)-stemonamine (**3**) and (±)-isostemonamine (**4**) can easily interconvert to each other. This phenomenon is identical with the fact that natural stemonamine (**3**) and isostemonamine (**4**) are isolated as racemate forms.[2a] We assumed that a cleavage of the spirocyclic ring as depicted in Scheme 9 might result in an isomerization between (±)-**3** and (±)-**4**, since they have β-amino carbonyl and vinylogous β-amino carbonyl moieties.



Scheme 9. Equilibrium between **3** and **4**.

We soon found, however, that such isomerization did not occur at a low temperature. When compound **28** was treated with Raney nickel in EtOH at 0 °C, (±)-**4** was obtained in 77% yield. Similarly, treatment of (±)-stemonamide (**1**) with Lawesson's reagent afforded, in 98% yield, (±)-**29**, whose reduction with Raney nickel at 0 °C gave (±)-stemonamine (**3**) in 79% yield (Scheme 10).



Scheme 10. Synthesis of (±)-**3**.

3. Conclusions

We achieved a total synthesis of (±)-stemonamide (**1**) and (±)-isostemonamine (**2**) by using a radical cascade involving two *endo*-selective cyclizations as the key step. The present synthesis clearly demonstrates the usefulness of the radical cascade process for the synthesis of nitrogen-containing polycyclic compounds. We also performed the synthesis of (±)-stemonamine (**3**) and (±)-isostemonamine (**4**) by reduction of the thiocarbonyl lactams **29** and **28**, prepared from (±)-(**1**) and (±)-(**2**), respectively, with Raney nickel.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrophotometer for solutions in $CHCl_3$. ^1H NMR and ^{13}C NMR spectra were measured on a JEOL EX 500 (500 MHz) or a JEOL JNM-EX 270 (270 MHz) spectrometer. Chemical shifts (δ) quoted are relative to tetramethylsilane. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX-102A mass spectrometer. Column chromatography was carried out on silica gel 60 N (Kanto Kagaku Co., Ltd., spherical, neutral, 63–210 μm) or on alumina 90 (Merck, neutral, 63–200 μm) under pressure.

4.2. *N*-[4-(*tert*-Butyldimethylsilyloxy)butyl]-*N*-(5-oxocyclopentenyl)acrylamide (7)

A mixture of 1,2-cyclopentanedione[20] (10 g, 102 mmol) and 4-(*tert*-butyldimethylsilyloxy)butylamine[21] (20.8 g, 102 mmol) in benzene (350 mL) was heated under reflux with azeotropic removal of water for 2 h. After cooling at 0 °C, acryloyl chloride (11.1 g, 122 mmol) and *N*,*N*-diethylaniline (22.8 g, 153 mmol) were added dropwise and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed successively with a saturated aqueous solution of $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 3:1) to give **7** (12.0–19.2 g, 35–56%) as a pale yellow oil: IR ($CHCl_3$) ν 1720, 1655, 1620 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.87 (9H, s), 1.49–1.61 (4H, m), 2.51–2.55 (2H, m), 2.70–2.75 (2H, m), 3.59 (2H, t, *J*=6.1 Hz), 3.65 (2H, t, *J*=7.1 Hz), 5.60 (1H, dd, *J*=10.2, 2.0 Hz), 6.16 (1H, dd, *J*=10.2, 6.1 Hz), 6.35 (1H, dd, *J*=16.8, 2.0 Hz), 7.46 (1H, t, *J*=2.8 Hz); ^{13}C NMR (67.8 MHz) δ −5.3, 18.3, 24.6, 25.9, 29.8, 33.7, 46.9, 62.6, 128.0, 128.2, 144.6, 157.3, 165.4, 203.8; HRMS calcd for $C_{18}H_{31}NO_3Si$ 337.2073, found 337.2073.

4.3. *N*-(4-Bromobutyl)-*N*-(5-oxocyclopentenyl)acrylamide (6)

To a solution of **8** (4.90 g, 22.0 mmol) and diisopropylethylamine (4.82 g, 37.3 mmol) in DME (140 mL) was added dropwise methanesulfonyl chloride (3.77 g, 32.9 mmol) at 0 °C, and the mixture was further stirred at room temperature for 1.5 h. LiBr (9.54 g, 110 mmol) was added, and the mixture was further stirred at room temperature for 8 h. The reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **6** (5.21 g, 83%) as a colorless oil; ^1H NMR and ^{13}C NMR spectra of **6** showed it to be a mixture of two rotamers: IR ($CHCl_3$) ν 1720, 1660, 1620 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.66 (2H, tt, *J*=7.4, 7.1 Hz), 1.87 (2H, tt, *J*=7.4, 6.4 Hz), 2.55–2.58 (2H, m), 2.74–2.79 (2H, m), 3.43 (2H×17/20, t, *J*=6.4 Hz), 3.55 (2H×3/20, t, *J*=6.4 Hz), 3.68 (2H, t, *J*=7.1 Hz), 5.62 (1H, dd, *J*=10.1, 1.6 Hz), 6.15 (1H, dd, *J*=16.8, 10.1 Hz), 6.36 (1H, dd, *J*=16.8, 1.6 Hz), 7.50 (1H, t, *J*=2.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.6, 26.6, 29.5, 33.5, 33.6, 44.6, 45.9, 128.0, 128.2, 144.3, 157.6, 165.5, 203.8. Anal. Calcd for $C_{12}H_{16}BrNO_2$: C, 50.37; H, 5.64; N, 4.89. Found: C, 50.77; H, 5.84; N, 4.96.

4.4. A mixture of 10 and 11

To a boiling solution of **6** (1.00 g, 3.50 mmol) in toluene (350 mL) was added dropwise a solution of Bu_3SnH (1.53 g, 5.24 mmol) and ACN (1,1-azobiscyclohexanecarbonitrile) (171 mg, 0.699 mmol) in toluene (100 mL) over 5 h by employing a syringe-pump technique, and the mixture was further heated at reflux for 1 h. After evaporation of the solvent, the residue was chromatographed on silica gel containing KF (10% w/w)[22] (hexane/AcOEt, 1:2) to give a mixture of **10** and **11** (399 mg, 55%) as colorless solids: IR ($CHCl_3$) ν 1750, 1680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.31–1.43 (1H, m), 1.50–2.07 (9H, m), 2.15–2.06 (6H, m), 4.04 (1/2H, d, *J*=14.6 Hz), 4.12 (1/2H, d, *J*=14.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 23.1, 23.9, 24.2, 25.5, 27.58, 27.63, 28.0, 28.6, 29.4, 30.1, 30.7, 34.3, 34.7, 39.6, 40.3, 44.6, 46.9, 73.3, 74.2, 175.4, 176.0, 212.4. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.34; H, 8.50; N, 6.88.

4.5. A mixture of 12a and 12b

To a solution of the mixture of **10** and **11** (399 mg, 1.93 mmol) in MeOH (7 mL) containing 10% KOH was added benzaldehyde (225 mg, 2.12 mmol). After stirring for 24 h, the reaction mixture was poured into a saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give a mixture of **12a** and **12b** (433 mg, 76%, ca. 1:1 mixture of diastereoisomers) as a pale yellow amorphous solid: IR ($CHCl_3$) ν 1720, 1680, 1630 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39–1.97 (8H, m), 2.03–2.13 (1H, m), 2.25–2.34 (1H, m), 2.45–2.68 [(2+1/2)H, m], 2.73 (1/2H, td, *J*=14.6, 3.7 Hz), 3.00 (1/2H, dd, *J*=15.9, 6.7 Hz), 3.12 (1/2H, ddd, *J*=17.7, 8.5, 3.1 Hz), 4.04–4.07 (1/2H, m), 4.20 (1/2H, td, *J*=10.4, 4.3 Hz), 7.27–7.58 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.9, 25.1, 25.3, 26.6, 27.7, 28.9, 29.4, 29.5, 30.0, 30.4, 30.8, 32.0, 39.47, 39.51, 42.8, 44.8, 73.9, 74.3, 128.78, 128.84, 129.8, 130.0, 130.4, 130.9, 132.1, 132.9, 134.6, 134.8, 134.9, 136.0, 175.4, 176.3, 202.3, 206.3; HRMS calcd for $C_{19}H_{21}NO_2$ 295.1572, found 295.1572.

4.6. Esters 13 and 14

To solution of ethyl propiolate (232 mg, 2.34 mmol) in THF (5 mL) was added dropwise 1.6 M solution of *n*-butyllithium in hexane (1.46 mL, 2.34 mmol) at −78 °C and the mixture was stirred at the same temperature for 30 min. To this solution was added dropwise a solution of the mixture of **12a** and **12b** (230 mg, 0.778 mmol) in THF (5 mL) and the mixture was stirred at −78 °C for 20 min. The reaction mixture was quenched with a saturated NH_4Cl solution at −78 °C and then extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/EtOAc, 1:1). The first eluent gave **13** (151 mg, 50%) as colorless crystals, mp 209–211 °C (EtOAc/MeOH): IR ($CHCl_3$) ν 1705, 1675 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.29 (3H, t, *J*=7.1 Hz), 1.40–1.50 (3H, m), 1.72–1.84 (4H, m), 2.06–2.40 (3H, m), 2.67–2.92 (3H, m), 3.24 (1H, dd, *J*=14.3, 10.2 Hz), 4.17–4.26 (1H, m), 4.22 (2H, q, *J*=7.1 Hz), 5.87 (1H, br), 6.87 (1H, t-like), 7.21–7.40 (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.0, 24.0, 25.7, 28.4, 30.3, 30.5, 31.7, 41.2, 42.2, 62.0, 76.2, 77.6, 79.3, 87.5, 127.2, 127.3, 128.4, 128.7, 136.8, 140.5, 153.2, 178.3. Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.29; H, 7.00; N, 3.55. The second eluent gave **14** (149 mg, 48%) as colorless crystals, mp 190.5–192 °C (EtOAc/MeOH): IR ($CHCl_3$) ν 1705, 1675 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.21–1.35 (1H, m), 1.30 (3H, t, *J*=7.1 Hz), 1.55–1.70 (4H, m), 1.83–2.06 (2H, m), 2.23–2.32 (2H, m), 2.62–2.92 (5H, m), 3.90 (1H, d, *J*=14.3 Hz), 4.01 (1H, br), 4.23 (2H, q, *J*=7.1 Hz), 6.79 (1H, t-like), 7.26–7.31 (1H, m), 7.37–7.39 (4H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.0, 22.1, 25.1, 28.2, 28.4, 29.4, 30.3, 41.4, 62.2, 76.4, 79.0, 81.0, 86.7, 123.6, 123.7, 127.4, 128.5, 129.0, 136.2, 142.1, 153.3, 176.3. Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.30; H, 6.99; N, 3.57.

4.7. Methyl tetronate 15

To a solution of **13** (159 mg, 0.400 mmol) in MeOH (2 mL) was added 6–10% solution of magnesium methoxide in MeOH (1.5 mL), and the mixture was heated at reflux for 10 h. Sodium methoxide (4.3 mg, 0.0800 mmol) was added and the mixture was heated under reflux for 2 days. The reaction mixture was cooled to room temperature and poured into a saturated NH_4Cl solution and then extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/EtOAc, 1:2) to give **15** (129 mg, 85%) as colorless crystals, mp 247–248 °C (EtOAc/CH_2Cl_2): IR ($CHCl_3$) ν 1760, 1680, 1630 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35–1.41 (2H, m), 1.50–1.57 (1H, m), 1.71–1.80 (3H, m), 1.96 (1H, q, J=11.6 Hz), 2.20–2.27 (2H, m), 2.49 (1H, t, J=13.4 Hz), 2.69 (1H, t, J=12.2 Hz), 2.80–2.99 (3H, m), 3.87 (3H, s), 4.07 (1H, d, J=14.0 Hz), 5.12 (1H, s), 6.37 (1H, s), 7.35–7.39 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.2, 26.1, 28.2, 30.0, 30.1, 32.2, 40.1, 41.2, 59.6, 75.0, 89.3, 94.4, 127.8, 127.9, 128.5, 128.7, 135.6, 135.8, 171.0, 177.9, 181.5; HRMS calcd for $C_{23}H_{25}NO_4$ 379.1784, found 379.1772.

4.8. α-Iodo methyl tetronate 16

To a solution of **15** (200 mg, 0.527 mmol) and *N*-iodosuccinimide (356 mg, 1.581 mmol) in CH_2Cl_2 (7 mL) was added dropwise trifluoromethanesulfonic acid (277 mg, 1.85 mmol) at 0 °C, and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 and washed successively with a saturated $Na_2S_2O_3$ solution and brine. After the organic layer was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel (hexane/EtOAc, 1:2) to give **16** (306 mg, 92%) as colorless crystals, mp 234–237 °C (dec) (EtOAc/CH_2Cl_2): IR ($CHCl_3$) ν 1755, 1685, 1615 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.33–1.58 (3H, m), 1.73–1.83 (3H, m), 1.89–2.05 (1H, m), 2.13–2.29 (2H, m), 2.44 (1H, ddd, J=16.2, 13.2, 3.0 Hz), 2.66–2.87 (3H, m), 2.92–3.03 (1H, m), 4.11 (1H, d, J=13.4 Hz), 4.42 (3H, s), 6.28 (1H, t-like), 7.09 (2H, d, J=8.4 Hz), 7.69 (2H, d, J=8.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 25.1, 26.1, 28.2, 29.8, 30.0, 32.1, 40.3, 41.2, 47.2, 60.3, 75.3, 93.6, 96.6, 127.3, 130.4, 135.0, 136.9, 137.6, 169.5, 177.9, 178.1; HRMS calcd for $C_{23}H_{23}NO_4I_2$ 630.9717, found 630.9716.

4.9. α-Methyl methyl tetronate 17

A mixture of **16** (190 mg, 0.301 mmol), trimethylboroxine (126 mg, 0.903 mmol), $PdCl_2(dppf)_2$ (13 mg, 15.1 μmol), and Cs_2CO_3 (516 mg, 1.51 mmol) in dioxane (10 mL) was heated at reflux for 5 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/EtOAc, 1:2) to give **17** (109 mg, 89%) as colorless crystals, mp 215–216 °C (hexane/EtOAc/CH_2Cl_2): IR ($CHCl_3$) ν 1750, 1680, 1665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.39–1.77 (3H, m), 1.80–1.87 (3H, m), 1.90–2.00 (1H, m), 2.06 (3H, s), 2.16–2.26 (2H, m), 2.35 (3H, s), 2.44 (1H, ddd, J=16.3, 13.2, 3.1 Hz), 2.72–3.04 (4H, m), 4.08 (1H, d, J=14.3 Hz), 4.09 (3H, s), 6.28 (1H, t-like), 7.16 (2H, d, J=8.2 Hz), 7.24 (2H, d, J=8.2 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 9.03, 21.2, 25.2, 26.1, 28.3, 29.9, 30.2, 32.2, 40.1, 41.2, 59.3, 75.0, 93.1, 97.8, 127.1, 128.6, 129.2, 133.2, 135.3, 137.6, 172.9, 173.8, 178.1; HRMS calcd for $C_{25}H_{29}NO_4$ 407.2097, found 407.2102.

4.10. α-Iodo methyl tetronate 19

To a solution of **18** (100 mg, 0.264 mmol) and bis(2,4,6-trimethylpyridine)iodonium hexafluorophosphate (488 mg, 0.949 mmol) in CH_2Cl_2 (10 mL) was added dropwise trifluoromethanesulfonic acid (139 mg, 0.924 mmol) at 0 °C, and the mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 and washed successively with a saturated $Na_2S_2O_3$ solution and brine. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel (EtOAc) to give **19** (139 mg, 84%) as colorless crystals, mp 205–208 °C (dec) (EtOAc/CH_2Cl_2): IR ($CHCl_3$) ν 1770, 1680, 1620 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.26–1.35 (1H, m), 1.51–1.68 (4H, m), 1.84–1.97 (3H, m), 2.24–2.47 (3H, m), 2.74–3.05 (3H, m), 3.95 (1H, d, J=14.7 Hz), 4.44 (3H, s), 6.40 (1H, t-like), 7.10 (2H, d, J=8.4 Hz), 7.72 (2H, d, J=8.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 22.0, 25.1, 28.0, 28.9, 29.4, 29.9, 40.9, 43.0, 43.9, 60.4, 74.7, 93.6, 96.2, 123.7, 130.7, 135.0, 137.7, 138.3, 169.7, 174.0, 180.6; HRMS calcd for $C_{23}H_{23}NO_4I_2$ 630.9717, found 630.9728.

4.11. Ketone 21

To a solution of **17** (100 mg, 0.245 mmol) and sodium metaperiodate (2.60 g, 12.3 mmol) in acetone (10 mL) and water (10 mL) was added 4% OsO_4 solution (five drops), and the mixture was stirred at room temperature for 30 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:2) to give **21** (68.5 mg, 88%) as colorless crystals, mp 260–269 °C (dec) (EtOAc/CH_2Cl_2): IR ($CHCl_3$) ν 1780, 1685, 1620 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.24–1.67 (3H, m), 1.78–1.85 (3H, m), 2.00–2.12 (2H, m), 2.03 (3H, s), 2.21–2.37 (2H, m), 2.60 (1H, dd, J=18.6, 7.7 Hz), 2.68–2.90 (2H, m), 3.20 (1H, dt, J=17.1, 8.7 Hz), 4.11 (3H, s), 4.14 (1H, d, J=12.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 9.1, 24.7, 26.0, 27.9, 29.6, 30.0, 38.0, 40.0, 40.3, 59.6, 73.5, 91.4, 100.1, 167.9, 177.4, 206.0; HRMS calcd for $C_{17}H_{21}NO_5$ 319.1420, found 319.1416.

4.12. α,β-Unsaturated ketone 23

A mixture of **21** (25 mg, 78.3 μmol) and *tert*-butoxybis(dimethylamino)methane (45.8 mg, 0.263 mmol) in DMF (1 mL) was heated at 100 °C for 1.5 h. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure to give **22**. To a solution of the crude **22** in CH_2Cl_2 (2 mL) was added dropwise 0.94 M solution of diisobutylaluminum hydride in hexane (0.14 mL, 0.132 mmol) at −78 °C, and the mixture was further stirred at −78 °C for 10 min and at room temperature for 30 min. To the solution was added methyl iodide (125 mg, 0.878 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with a saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue chromatographed on silica gel (EtOAc) to give **23** (17.3 mg, 67%) as colorless crystals, mp 230–231 °C (EtOAc/CH_2Cl_2): IR ($CHCl_3$) ν 1765, 1750, 1685, 1665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43–1.58 (3H, m), 1.82–1.96 (4H, m), 2.03–2.12 (1H, m), 2.05 (3H, s), 2.24 (1H, dd, J=16.8, 9.3 Hz), 2.77 (1H, ddd, J=11.7, 8.3, 3.2 Hz), 2.88 (1H, ddd, J=13.9, 10.2, 2.2 Hz), 3.75–3.78 (1H, m), 4.11 (3H, s), 4.18 (1H, d, J=14.9 Hz), 5.43 (1H, d, J=3.2 Hz), 6.27 (1H, d, J=3.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.2, 22.2, 26.2, 27.1, 29.2, 30.2, 40.1, 44.8, 59.6, 72.4, 90.6, 100.3, 118.6, 142.6, 168.0, 172.6, 177.5, 195.6; HRMS calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1421.

4.13. (±)-Stemonamide (1) and (±)-dihydrostemonamide (27)

A mixture of **23** (50 mg, 0.151 mmol) and rhodium(III) chloride hydrate (30 mg, 0.453 mmol) in EtOH/H_2O (10:1) (3 mL) was heated at reflux for 4 h. The reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (hexane/AcOEt, 1:2). The first eluent gave **27** (30.8 mg, 62%) as a colorless solid, mp 237–238 °C (EtOAc/CH_2Cl_2): IR ($CHCl_3$) ν 1770, 1685, 1665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (3H, d, *J*=7.3 Hz), 1.26–1.70 (4H, m), 1.80–1.91 (2H, m), 1.98–2.12 (2H, m), 2.03 (3H, s), 2.20–2.28 (2H, m), 2.69–2.80 (2H, m), 2.85 (1H, t, *J*=12.2 Hz), 4.09 (3H, s), 4.14 (1H, d, *J*=13.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.2, 12.6, 23.3, 26.8, 28.4, 29.7, 30.2, 40.3, 44.7, 45.9, 59.7, 72.7, 90.8, 100.3, 168.3, 172.8, 177.5, 209.0; HRMS calcd for $C_{18}H_{23}NO_5$ 333.1576, found 333.1572. The second eluent gave (±)-**1** (15.2 mg, 31%) as colorless crystals, mp 232–233 °C (EtOAc/CH_2Cl_2): IR ($CHCl_3$) ν 1765, 1725, 1685, 1665, 1640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22–1.46 (2H, m), 1.83 (1H, d, *J*=14.0 Hz), 1.87 (3H, s), 1.95 (1H, td, *J*=12.8, 8.9 Hz), 2.02 (3H, s), 2.04–2.18 (2H, m), 2.30 (1H, dd, *J*=16.5, 8.5 Hz), 2.38 (1H, dd, *J*=12.8, 7.3 Hz), 2.61 (1H, ddd, *J*=16.7, 12.0, 7.9 Hz), 2.62 (1H, t, *J*=12.8 Hz), 3.00 (1H, dd, *J*=12.2, 4.9 Hz), 4.00 (3H, s), 4.19 (1H, d, *J*=14.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.4, 9.1, 27.3, 27.4, 29.8, 30.1, 31.8, 41.2, 59.1, 74.5, 90.0, 99.6, 136.9, 168.7, 170.9, 172.9, 175.7, 196.5; HRMS calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1415. ^1H and ^{13}C NMR spectral data of (±)-**1** were in accord with those of the natural and Kende's synthetic stemonamide.

4.14. (±)-Isostemonamide (2)

A mixture of **26** (3.0 mg, 9.05 μmol) and rhodium(III) chloride hydrate (0.4 mg, 1.81 μmol) in EtOH/H_2O (10:1) (0.5 mL) was heated at reflux for 30 min. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (EtOAc) to give (±)-**2** (3.0 mg, 100%) as colorless crystals, mp 223–224 °C (EtOAc/CH_2Cl_2): IR ($CHCl_3$) ν 1765, 1720, 1690, 1665, 1645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25–1.45 (2H, m), 1.78 (1H, dd, *J*=14.5, 3.7 Hz), 1.86 (3H, s), 1.92 (1H, td, *J*=13.2, 9.3 Hz), 2.07 (3H, s), 2.10–2.15 (2H, m), 2.27 (1H, ddd, *J*=16.6, 12.2, 7.6 Hz), 2.35 (1H, dd, *J*=16.6, 9.3 Hz), 2.61 (1H, dd, *J*=13.4, 7.3 Hz), 2.95 (1H, dd, *J*=12.7, 6.6 Hz), 3.00 (1H, t, *J*=19.7 Hz), 4.15 (3H, s), 4.17 (1H, d, *J*=15.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.3, 9.3, 26.9, 27.7, 28.0, 29.4, 29.8, 42.4, 59.9, 73.5, 86.5, 102.9, 136.6, 168.7, 171.7, 172.6, 174.6, 196.9; HRMS calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1417. ^1H and ^{13}C NMR spectral data were in accord with those of the natural and Kende's synthetic isostemonamide.

4.15. Isostemonamide thiocarbonyl lactam 28

Lawesson's reagent (8.1 mg, 19.9 μmol) was added to a solution of (±)-**2** (12 mg, 33.2 μmol) in toluene (1.5 mL), and the mixture was heated at reflux for 1 h. After removal of solvent, the residue was chromatographed on silica gel (hexane/EtOAc, 1:1) to give **28** (12.7 mg, 100%) as a colorless solid, mp 204–206 °C (dec) (EtOAc/CH_2Cl_2): IR ($CHCl_3$) ν 1765, 1725, 1665, 1645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36–1.45 (1H, m), 1.63–1.72 (1H, m), 1.77–1.81 (1H, m), 1.89 (3H, s), 2.01–2.17 (3H, m), 2.07 (3H, s), 2.70 (1H, dd, *J*=13.4, 6.7 Hz), 2.76–2.83 (1H, m), 2.95 (1H, t, *J*=13.4, 5.5 Hz), 3.04 (1H, dd, *J*=17.1, 8.5 Hz), 3.21 (1H, t, *J*=13.4 Hz), 4.16 (3H, s), 4.79 (1H, d, *J*=12.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.4, 9.3, 26.8, 27.2, 28.0, 29.5, 29.7, 42.7, 47.6, 59.9, 79.6, 85.4, 102.6, 137.6, 168.8, 170.9, 171.4, 196.3; HRMS calcd for $C_{18}H_{21}NO_4S$ 347.1191, found 347.1191.

4.16. Treatment of 28 with Raney nickel in EtOH at reflux: stemonamine (3) and isostemonamine (4)

A mixture of **28** (12 mg, 33.2 μmol) and Raney Ni (W-2) (ca. 5 g) in EtOH (2 mL) was heated at reflux for 1.5 h. The reaction mixture was filtered, the filtrate was concentrated, and the residue was chromatographed on silica gel (hexane/EtOAc, 3:1→1:1). The first eluent gave (±)-isostemonamine (**4**) (4.0 mg, 40%) as colorless crystals, mp 148–149 °C (Et_2O): IR ($CHCl_3$) ν 1750, 1710, 1660, 1630 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.13–1.22 (1H, m), 1.37–1.41 (1H, m), 1.49–1.59 (1H, m), 1.67–1.82 (4H, m), 1.76 (3H, s), 2.01–2.06 (1H, m), 2.08 (3H, s), 2.37 (1H, dd, *J*=12.9, 5.9 Hz), 2.83–2.87 (2H, m), 3.10 (1H, dd, *J*=16.6, 12.2 Hz), 3.17–3.22 (2H, m), 4.13 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.0, 9.3, 24.2, 24.3, 27.3, 27.8, 35.6, 49.1, 50.9, 59.3, 75.3, 89.2, 102.3, 134.5, 169.5, 173.5, 176.4, 199.0; HRMS calcd for $C_{18}H_{23}NO_4$ 317.1627, found 317.1628. The second eluent gave (±)-stemonamine (**3**) (5.7 mg, 56%) as colorless crystals, mp 159–160 °C (Et_2O): IR ($CHCl_3$) ν 1750, 1710, 1665, 1630 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.18–1.27 (1H, m), 1.40–1.43 (1H, m), 1.73–1.91 (5H, m), 1.77 (3H, s), 2.02 (3H, s), 2.11 (1H, td, *J*=12.8, 1.8 Hz), 2.16 (1H, dd, *J*=11.0, 4.9 Hz), 2.81 (1H, t, *J*=7.3 Hz), 2.89 (1H, dd, *J*=12.8, 6.1 Hz), 3.04 (1H, dd, *J*=15.3, 14.6 Hz), 3.11–3.16 (2H, m), 3.97 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.2, 9.1, 24.5, 24.8, 26.9, 28.2, 39.0, 48.9, 51.4, 58.6, 76.5, 91.8, 97.5, 135.1, 171.8, 174.8, 175.0, 198.7; HRMS calcd for $C_{18}H_{23}NO_4$ 317.1627, found 317.1626. ^1H and ^{13}C NMR spectral data were in accord with those of the natural stemonamine and isostemonamine.

4.17. Treatment of 28 with Raney nickel in EtOH at low temperature

Compound **28** (10 mg, 28.7 μmol) was treated with excess Raney Ni (W-2) in EtOH (3 mL) at 0 °C for 1.5 h and at room temperature for 0.5 h. The reaction mixture was filtered and the filtrate was concentrated and chromatographed on silica gel (hexane/EtOAc, 2:1) to give **4** (6.7 mg, 77%) as colorless crystals.

4.18. Stemonamide thiocarbonyl lactam 29

A mixture of (±)-**1** (3.0 mg, 9.05 μmol) and Lawesson's reagent (2.3 mg, 5.43 μmol) in toluene (0.5 mL) was heated at reflux for 1 h. After the reaction mixture was cooled to room temperature, solvent was removed under reduced pressure. The residue was chromatographed on silica gel (hexane/EtOAc, 1:1) to give **29** (3.1 mg, 99%) as a colorless solid, mp 175–176 °C (EtOAc/CH_2Cl_2): IR ($CHCl_3$) ν 1770, 1725, 1665, 1640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.38–1.47 (1H, m), 1.62–1.70 (1H, m), 1.81–1.84 (1H, m), 1.91 (3H, s), 2.03 (3H, s), 2.08–2.20 (3H, m), 2.52 (1H, dt, *J*=12.8, 4.0 Hz), 2.97–3.01 (3H, m), 3.18 (1H, t, *J*=12.8 Hz), 4.02 (3H, s), 4.83 (1H, dd, *J*=9.8, 4.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.5, 9.1, 27.1, 27.6, 27.8, 32.8, 42.9, 46.6, 59.4, 81.2, 88.2, 99.9, 138.4, 168.7, 169.2, 172.6, 196.1; HRMS calcd for $C_{18}H_{21}NO_4S$ 347.1191, found 347.1120.

4.19. Treatment of 29 with Raney nickel in EtOH at low temperature

A mixture of **29** (10 mg, 28.7 μmol) and excess Raney Ni (W-2) in EtOH (3 mL) was stirred at 0 °C for 1.5 h and at room temperature for 0.5 h. The reaction mixture was filtered, the filtrate was concentrated, and the residue was chromatographed on silica gel (hexane/EtOAc, 1:1) to give **3** (6.9 mg, 79%) as colorless crystals.

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Supplementary data

Experimental procedures and compound characterization data for compounds **8**, **18**, **20**, **24**, and **26**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.091.

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