Tetrahedron 65 (2009) 5716–5719

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of (±)-13-epineostenine

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ARTICLE INFO

Article history:
Received 11 March 2009
Received in revised form 5 May 2009
Accepted 8 May 2009
Available online 18 May 2009

ABSTRACT

An efficient total synthesis of (±)-13-epineostenine (**2**) has been achieved in 15 steps and 17% overall yield. This approach involved the key alkylation/Michael additions of the central 1,4-cyclohexanedione monoethylene acetal and all of the stereocenters on central cyclohexane moiety were generated in highly stereoselectivity.

1. Introduction

The plant *Stemona* has been used for the treatment of respiratory diseases and as insecticides in China and other East Asia countries for centuries. *Stemona* alkaloids provide attractive targets for total synthesis due to their intriguing structures and the range of associated biological activities.[1] According to their structural features, the *Stemona* alkaloids are classified into six groups, named with the simplest member,[1a] among which the stenine group has stood out as the particularly challenging targets to synthetic chemists. Neostenine (**1**), a member of stenine group (Fig. 1), was isolated by Lin et al. in 2003 from *Stemona tuberose*, which has antitussive activity comparable to that of codeine.[2] The difficulties of its synthesis mainly lie in their fully substituted central cyclohexane ring, tricyclic core with an additional fused lactone ring, and seven contiguous stereogenic centers.

Racemic and enantioselective total synthesis of stenine has been reported several times from 1990s.[3,4] While, neostenine (**1**) has attracted more interest to synthetic organic chemists due to its biological activities. In 2008, Aubé et al. first reported the total synthesis of (±)-neostenine (**1**) and (±)-13-epineostenine (**2**),[4] and nearly simultaneously Booker-Milburn et al. also reported an alternative total synthesis of (±)-neostenine (**1**).[5]

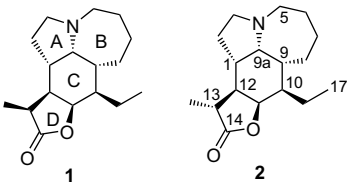


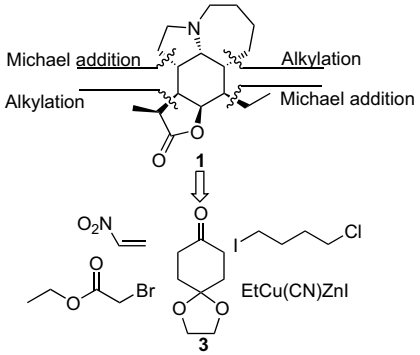
Figure 1. Neostenine (**1**) and 13-epineostenine (**2**).

Our group has succeeded in the total synthesis of *Stemona* alkaloid (±)-stemonamine.[6] And also, we have already employed the nitroethylene as a key building block for the synthesis of (±)-γ-lycorane and (±)-crinane.[7] To use this tactic in synthesis of more complex alkaloids, herein we would like to report the total synthesis of (±)-13-epineostenine.

2. Results and discussion

2.1. Retrosynthetic analysis of (±)-neostenine

By looking into the structural feature of neostenine (**1**), we could find its skeleton containing a central full-substituted cyclohexane moiety. Therefore, our synthesis relies on the sequential alkylation/Michael addition to introduce four alkyls at the central cyclohexane ring (Scheme 1). Ring A was formed through an intramolecular reductive amination reaction. Ring B was closed by intramolecular nucleophilic displacement and ring D was formed through lactonization.



Scheme 1. Retrosynthetic analysis of (±)-neostenine.

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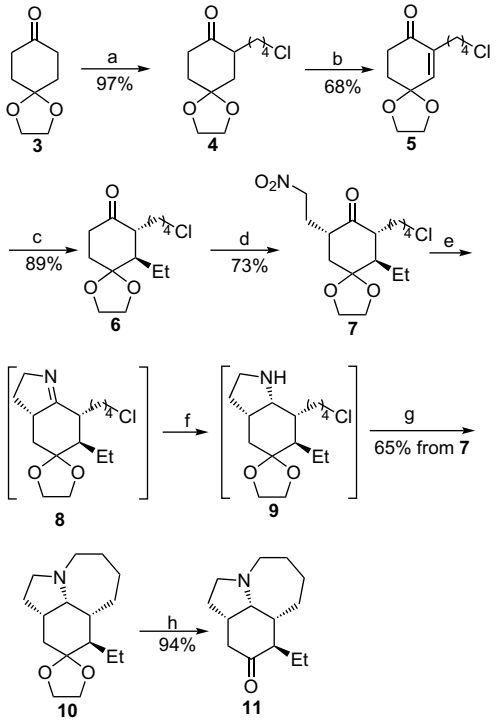
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.05.022

2.2. Synthesis of ABC tricyclic core of (±)-neostenine

Starting from commercially available 1,4-cyclohexanedione monoethylene acetal (**3**), the chloroalkyl side chain was appended by conversion of the starting ketone (**3**) to the dimethylhydrazone, deprotonation with lithium diisopropylamide (LDA), and alkylation with 1-chloro-4-iodobutane. The alkylated hydrazone was then hydrolyzed with acid to give the ketone (**4**). After screening reaction conditions, we found that zero-valent iron,[8] prepared from the reaction of methylmagnesium bromide and ferric chloride, was able to deprotonate ketone (**4**) regiospecifically to give thermodynamic silyl enol ether in the presence of trimethylsilyl chloride. A $Pd(OAc)_2$-catalyzed dehydrosilylation[9] of the resulting silyl enol ether yielded the α,β-unsaturated ketone (**5**) directly. Michael addition of α,β-unsaturated ketone (**5**) with copper reagents,[10] made from ethylzinc iodide by a transmetalation in THF with the soluble salt CuCN·2LiCl, provided ketone (**6**).

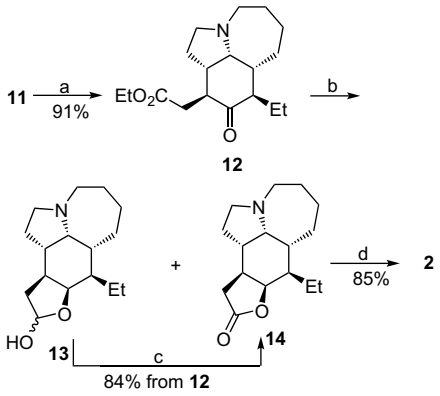
With ketone (**6**) in hand, further Michael reaction was then investigated. As expected, subjection of the kinetics lithium enolates of ketone (**6**) to the nitroethylene gave rise to the desired γ-nitro carbonyl compounds (**7**). The following reductive cyclization of (**7**) with Ni-Raney/H_2 led to the unstable cycloimine (**8**), which was converted to the unstable amine (**9**) by further reduction with $NaBH_3CN$. Direct N-alkylation of **9** under microwave condition gave amine (**10**). Deprotection of the acetal group of **10** with *p*-toluenesulfonic acid (PTS) in acetone completed the synthesis of tricyclic core of (±)-neostenine (Scheme 2).



Scheme 2. Reagents and conditions: (a) (i) NH_2NMe_2, PTS, benzene, reflux; ii) LDA, 1-chloro-4-iodobutane, THF, −78 °C; (iii) AcOH, H_2O, THF; (b) (i) $FeCl_3$, MeMgBr, TMSCl, NEt_3, HMPA, Et_2O; (ii) $Pd(OAc)_2$, benzoquinone, CH_3CN; (c) EtCu(CN)ZnI, TMSCl, THF; (d) LDA,THF −78 °C then nitroethylene; (e) Raney Ni, H_2, EtOH; (f) $NaBH_3CN$, AcOH, THF; (g) MW, CH_3CN, 60 °C; (h) PTS, acetone, reflux.

2.3. Synthesis of (±)-13-epineostenine

Ketone (**11**), which has been reported by Aubé et al.,[11] was regio- and stereospecifically alkylated with ethyl bromoacetate to give ketoester (**12**).[4] Reduction of (**12**) with L-Selectride™ gave an inseparable mixture of lactone (**14**) and diastereomeric lactols (**13**). Initial attempts to oxidate diastereomeric lactols (**13**) to lactone (**14**) with TPAP according to the Aubé's method failed.[4] A screen of oxidant revealed that PCC oxidation of the mixture could give the lactone (**14**). Alkylation with LiHMDS and methyl iodide from the more accessible β-face provided the (±)-13-epineostenine (Scheme 3).[4]



Scheme 3. Reagents and conditions: (a) LiHMDS, THF, HMPA, −78 °C then ethyl bromoacetate; (b) $CeCl_3$, L-Selectride, THF; (c) PCC, silica gel, CH_2Cl_2; (d) LiHMDS, THF, −78 °C then MeI.

According to the Booker-Milburn's tactic,[5a] we then investigated epimerization via an enolization/protonation sequence from the β-face to give (±)-neostenine (**1**), but failed.

3. Experimental section

3.1. General

For product purification by flash column chromatography, silica gel (200–300 mesh) and light petroleum ether (bp 60–90 °C) are used. All solvents were purified and dried by standard techniques and distilled prior to use unless otherwise noted. All organic extracts were dried over anhydrous Na_2SO_4. ^1H and ^{13}C NMR spectra were taken on a Varian Mercury 400 MHz or Bruker AVANCE III 400 MHz spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. The MS data were obtained with EI (70 eV) and the HRMS data were determined on a Bruker Daltonics APEXII 47e FT-ICR spectrometer.

3.2. 2-(4-Chlorobutyl)-1,4-cyclohexanedione-4-monoethylene acetal 4

To a solution of 1,4-cyclohexanedione monoethylene acetal **3** (2.0 g, 12.8 mmol) in benzene (10 mL) was added 1,1-dimethylhydrazine (2.0 mL, 26.1 mmol) dropwise and then PTS (110 mg, 0.6 mmol) was added. The reaction mixture was heated to reflux temperature and removed of water for 6 h. Then quenched with saturated $NaHCO_3$ and extracted with $CHCl_3$ (3×100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product dimethylhydrazone.

To a solution of lithium diisopropylamide (LDA) (16.7 mmol, prepared from diisopropylamine (2.5 mL, 17.9 mmol) and *n*-BuLi (8.3 mL, 2.0 M in hexane, 16.7 mmol)) in THF (15 mL) at −78 °C under argon atmosphere was added dropwise a solution of the above obtained crude dimethylhydrazone product in THF (5 mL). After 1 h, 1-chloro-4-iodobutane (2.2 mL, 19.2 mmol) in THF (5 mL) was added dropwise, the reaction mixture was allowed to warm up to room temperature within 2 h, then quenched with saturated NH_4Cl, and extracted with EtOAc (100 mL) and $CHCl_3$ (2×100 mL). The combined organic layers were concentrated under reduced pressure.

A solution of THF (8 mL), H_2O (8 mL), AcOH (12 mL), and NaOAc (4 g) was added to the above crude product at 0 °C and the reaction mixture was stirred for 1 h. And then H_2O (20 mL) and Na_2CO_3 were added until the solution was neutral. The reaction mixture was extracted with EtOAc (3×100 mL). The organics were dried with Na_2SO_4 and concentrated in vacuo. Silica gel chromatography gave the ketone **4** (3.05 g, 12.4 mmol, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.14–1.19 (m, 1H), 1.32–1.39 (m, 2H), 1.60–1.74 (complex, 4H), 1.87–2.06 (complex, 3H), 2.27–2.32 (m, 1H), 2.52–2.60 (m, 2H), 3.44–3.48 (m, 2H), 3.91–4.00 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ=24.1, 28.0, 32.5, 34.5, 38.0, 40.4, 44.7, 46.0, 64.4, 64.6, 107.2, 211.0 ppm. EIMS: *m*/*z* (% intensity)=246 ([M]$^+$, 1), 211 (5), 189 (15), 169 (4), 155 (10), 99 (100). HRMS (ESI) calcd for $C_{12}H_{23}ClNO_3$ [M+NH_4]$^+$: 264.1361; found: 264.1363. IR: ν=1712, 2874, 2926, 3405 cm^{-1}.

3.3. 2-(4-Chlorobutyl)-2-ene-1,4-cyclohexanedione-4-monoethylene acetal 5

To an orange ethereal solution of anhydrous ferric chloride (950 mg, 5.9 mmol) in ether (30 mL) at 0 °C was added slowly an ethereal solution of methylmagnesium bromide (5.8 mL, 17.5 mmol). The resulting slurry was stirred for 1 h at 25 °C before addition of ketone **4** (1.25 g, 5.1 mmol) in ether (20 mL). After 30 min at 25 °C, TMSCl (2.2 mL, 17.5 mmol), NEt_3 (2.5 mL, 18.3 mmol), and HMPA (0.97 mL, 5.6 mmol) were added in that order. After stirring for 15 h at 25 °C, the solution was diluted with ether (200 mL), washed with cold saturated aqueous sodium bicarbonate (4×40 mL), dried with Na_2SO_4, and concentrated under reduced pressure to give a clear oil, which was used without further purification.

To a clear solution of $Pd(OAc)_2$ (570 mg, 2.5 mmol) and *p*-benzoquinone (330 mg, 3.0 mmol) in CH_3CN (15 mL) a solution of the above obtained crude product in CH_3CN (5 mL) was added with stirring under an argon atmosphere at room temperature, and then the mixture was stirred for 24 h. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ and extracted with EtOAc (2×100 mL). The organics were dried with Na_2SO_4 and concentrated in vacuo. Silica gel chromatography gave the α,β-unsaturated ketone **5** (843 mg, 3.5 mmol, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.52 (dt, *J*=15.2, 7.6 Hz, 2H), 1.73 (dt, *J*=14.4, 7.6 Hz, 2H), 2.11–2.18 (complex, 4H), 2.58 (t, *J*=6.8 Hz, 2H), 3.49 (t, *J*=6.8 Hz, 2H), 3.96–4.01 (m, 4H), 6.32 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ=25.1, 28.0, 32.1, 33.0, 35.5, 44.6, 64.8, 104.5, 140.5, 141.3, 198.3 ppm. EIMS: *m*/*z* (% intensity)=244 ([M]$^+$, 2), 216 (48), 209 (21), 181 (41), 153 (100). HRMS (ESI) calcd for $NaC_{12}H_{17}ClO_3$ [M+Na]$^+$: 267.0758; found: 267.0761. IR: ν=1645, 1680, 2888, 2956 cm^{-1}.

3.4. (±)-(2*R*,3*R*)-2-(4-Chlorobutyl)-3-ethyl-1,4-cyclohexanedione-4-monoethylene acetal 6

A solution of α,β-unsaturated ketone **5** (700 mg, 2.9 mmol) and TMSCl (0.78 mL, 6.3 mmol) in THF (10 mL) was slowly added (0.5 h) to the prepared solution of the copper reagent[10] (3.5 mmol) at −78 °C. After 3 h of stirring at −78 °C, the reaction mixture was allowed to warm up to 25 °C overnight and then worked up with saturated NH_4Cl. The mixture was filtered through a short plug of Celite, then the mixture was extracted with EtOAc (200 mL), and washed with 1 N HCl, aqueous saturated $NaHCO_3$, and brine. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue purified by chromatography on silica gel afforded the desired ketone **6** (700 mg, 2.6 mmol, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.95 (t, *J*=7.2 Hz, 3H), 1.20–1.29 (m, 1H), 1.36–1.44 (m, 2H), 1.65–1.83 (complex, 7H), 2.00–2.07 (m, 1H), 2.37–2.42 (m, 2H), 2.53–2.59 (m, 1H), 3.52 (t, *J*=6.8 Hz, 2H), 3.94–4.05 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ=12.5, 22.2, 24.8, 29.0, 32.1, 32.6, 36.9, 44.8, 48.9, 52.3, 64.4, 64.6, 109.7, 212.8 ppm. EIMS: *m*/*z* (% intensity)=274 ([M]$^+$, 1), 245 (3), 217 (2), 183 (7), 127 (3), 114 (3), 99 (100). HRMS (ESI) calcd for $C_{14}H_{27}ClNO_3$ [M+NH_4]$^+$: 292.1674; found: 292.1681. IR: ν=1711, 2881, 2959 cm^{-1}.

3.5. (±)-(2*R*,3*R*,6*S*)-2-(4-Chlorobutyl)-3-ethyl-6-(2-nitroethyl)-1,4-cyclohexanedione-4-monoethylene acetal 7

To a solution of lithium diisopropylamide (LDA) (4.0 mmol, prepared from diisopropylamine (0.67 mL, 4.7 mmol) and *n*-BuLi (2.0 mL, 2.0 M in hexane, 4.0 mmol)) in THF (15 mL) at −78 °C under argon atmosphere was added dropwise a solution of ketone **6** (1.0 g, 3.6 mmol) in THF (5 mL). The mixture was stirred at −78 °C for 30 min. A solution of nitroethylene (293 mg, 4.0 mmol) in THF (1.5 mL) was added dropwise over a 3 min interval. The reaction mixture was stirred for an additional 5 min at −78 °C and then allowed to warm to room temperature within 30 min. The reaction was quenched by addition of a large excess of an aqueous solution of NaH_2PO_4 (pH ca. 4). The aqueous solution was extracted with EtOAc (2×50 mL) and $CHCl_3$ (3×50 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue through column chromatography on silica gel afforded the desired γ-nitro ketone **7** (924 mg, 2.7 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.97 (t, *J*=7.2 Hz, 3H), 1.31–1.34 (m, 1H), 1.44–1.66 (complex, 6H), 1.74–1.80 (complex, 3H), 1.86–1.91 (m, 1H), 2.10 (dd, *J*=12.8, 5.6 Hz, 1H), 2.31–2.37 (m, 1H), 2.53 (dd, *J*=12.4, 8.4 Hz, 1H), 2.76–2.77 (m, 1H), 3.53 (t, *J*=6.8 Hz, 2H), 4.02–4.09 (m, 4H), 4.40–4.51 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ=12.5, 20.1, 24.7, 25.3, 27.0, 32.9, 41.1, 43.4, 44.8, 50.0, 50.9, 64.9, 65.0, 109.4, 211.0 ppm. EIMS: *m*/*z* (% intensity)=347 ([M]$^+$, 0.2), 318 (0.4), 301 (1.4), 289 (1.2), 256 (1.1), 172 (100). HRMS (ESI) calcd for $C_{16}H_{30}ClN_2O_5$ [M+NH_4]$^+$: 365.1838; found: 365.1844. IR: ν=1552, 1710, 2884, 2959 cm^{-1}.

3.6. (±)-(5*S*,7a*S*,10*R*,10a*R*)-10-Ethyl-decahydroazepino-[3,2,1-hi]indol-9(5*H*)-one ethylene acetal 10

A mixture of **7** (710 mg, 2.0 mmol) and Raney nickel (710 mg of wet catalyst washed with ethanol prior to use) in dry ethanol (5 mL) was hydrogenated at 50 psi of H_2 in parr apparatus for 3 h. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was directly used in the next reaction because the cycloimine **8** was very unstable to air.

To an ice-cold solution of the above residue in glacial acetic acid (1 mL) and THF (4 mL) was added $NaBH_3CN$ (387 mg, 6.1 mmol). After 1 h, 1 N NaOH was added slowly until the solution was neutral. And then the mixture was extracted with $CHCl_3$ (4×50 mL). The combined extracts were washed with brine (25 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue purified by chromatography on basic alumina ($CHCl_3$/CH_3OH/Et_3N 30:1:1) quickly afforded the crude product amine **9**, which was used without further purification.

A solution of the above obtained crude product amine **9** in CH_3CN (10 mL) was heated with MW at 60 °C for 1 h. The reaction was quenched by addition of 1 N NaOH and then the mixture was extracted with $CHCl_3$ (4×40 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue purified by chromatography on silica gel afforded the desired amine **10** (352 mg, 1.3 mmol, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.94 (t, *J*=7.6 Hz, 3H), 1.28–1.34 (m, 1H), 1.38–1.71 (complex, 10H), 1.85–1.96 (complex, 3H), 2.25–2.31 (td, *J*=12.4, 6 Hz, 1H), 2.39–2.52 (complex, 3H), 2.93 (dd, *J*=12, 4 Hz, 1H), 3.28 (dd, *J*=18.4, 8 Hz, 1H), 3.87–3.97 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.4, 18.3, 22.1, 29.5, 30.0, 30.1, 37.1, 38.8, 39.6, 44.7, 56.2, 58.2, 64.3, 64.4, 70.1, 112.1 ppm. EIMS: *m*/*z* (% intensity)=265 ([M]$^+$, 55), 264 ([M−H]$^+$,

59), 220 (100). HRMS (ESI) calcd for $C_{16}H_{28}NO_2$ $[M+H]^+$: 266.2115; found: 266.2123. IR: ν=1666, 2407, 2780, 2876, 2931 cm^{-1}.

3.7. (±)-(5*S*,7a*S*,10*R*,10a*R*)-10-Ethyl-decahydroazepino-[3,2,1-hi]indol-9(5*H*)-one 11

To a solution of amine **10** (274 mg, 1.03 mmol) in acetone (5 mL) was added PTS (196 mg, 1.14 mmol). The reaction mixture was then heated to reflux temperature for 3 h. The reaction was basified by addition of 1 N NaOH, acetone was removed under reduced pressure, and then the mixture was extracted with $CHCl_3$ (4×40 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue purified by chromatography on silica gel afforded the desired ketone **11** (215 mg, 0.97 mmol, 94% yield). ^1H NMR (400 MHz, $CDCl_3$) δ=0.76 (t, J=7.2 Hz, 3H), 1.28–1.38 (m, 2H), 1.42–1.52 (m, 2H), 1.54–1.61 (m, 1H), 1.71–1.82 (complex, 3H), 1.91–2.03 (complex, 3H), 2.24 (dd, J=12, 4 Hz, 2H), 2.28–2.43 (m, 3H), 2.65–2.69 (m, 1H), 2.95 (dd, J=10.4, 4.4 Hz, 1H), 3.00–3.08 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ=9.5, 19.0, 23.2, 30.6, 31.5, 31.6, 36.5, 37.0, 42.4, 50.5, 56.0, 57.6, 65.3, 215.1 ppm. EIMS: m/z (% intensity)=221 ($[M]^+$, 100), 220 ($[M-H]^+$, 83), 206 (59), 192 (56), 178 (59). HRMS (ESI) calcd for $C_{14}H_{24}NO$ $[M+H]^+$: 222.1852; found: 222.1857. IR: ν=1702, 2798, 2852, 2928, 2961 cm^{-1}.

3.8. (±)-Ethyl-2-((5*R*,7a*S*,8*S*,10*R*,10a*R*)-10-ethyl-dodecahydro-9-oxoazepino[3,2,1-hi]indol-8-yl)acetate 12

To a solution of ketone **11** (172 mg, 0.78 mmol) in THF (10.0 mL) and HMPA (0.41 mL, 2.33 mmol) at −78 °C was added LiHMDS (1.9 mL, 1.0 M in THF, 1.9 mmol). The reaction was stirred for 2 h at −78 °C and then ethyl bromoacetate (0.43 mL, 3.9 mmol) was added neat. The cooling bath was removed and the reaction mixture was stirred for 3 h, then quenched with saturated NH_4Cl, and extracted with EtOAc (2×20 mL) and $CHCl_3$ (2×20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel to yield the ketoester **12** (217 mg, 0.71 mmol, 91% yield). ^1H NMR (400 MHz, $CDCl_3$) δ=0.84 (t, J=7.2 Hz, 3H), 1.21 (t, J=7.2 Hz, 3H), 1.49–1.56 (complex, 4H), 1.62–1.78 (complex, 4H), 1.90–1.97 (m, 2H), 2.17–2.18 (m, 1H), 2.24 (dd, J=12.4, 4 Hz, 1H), 2.40–2.47 (m, 1H), 2.48–2.55 (m, 1H), 2.56–2.64 (complex, 3H), 2.91–2.98 (m, 2H), 3.30–3.32 (m, 2H), 4.09 (q, J=7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ=11.7, 14.1, 18.6, 21.8, 28.8, 29.2, 29.3, 33.1, 42.9, 47.2, 48.3, 50.9, 55.9, 56.0, 60.3, 69.6, 172.4, 213.0 ppm. EIMS: m/z (% intensity)=307 ($[M]^+$, 100), 306 ($[M-H]^+$, 91), 292 (29), 278 (40), 264 (53), 262 (57), 250 (27), 234 (94), 220 (34), 218 (36). HRMS (ESI) calcd for $C_{18}H_{30}NO_3$ $[M+H]^+$: 308.2220; found: 308.2213. IR: ν=1710, 1735, 2801, 2872, 2929 cm^{-1}.

3.9. (±)-13-Demethylneostenine 14

Anhydrous cerium trichloride (52 mg, 0.21 mmol) was added to the solution of the ketoester **12** (43 mg, 0.14 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h and L-Selectride™ solution (0.30 mL, 1.0 M in THF, 0.30 mmol) was then added. The reaction was stirred for 15 h, slowly warming to room temperature. The reaction mixture was filtered through a short plug of Celite and the solvent removed in vacuo. The residue was purified by silica chromatography to give a mixture of two diastereomeric lactols **13** and a small amount of lactone **14**, which was used without further purification.

The mixture of the above lactone **14** and lactols **13** were dissolved in CH_2Cl_2 (4 mL) and then silica gel (100 mg) and PCC (95 mg, 0.42 mmol) were added sequentially. The reaction was stirred for 3 h, then filtered through a short plug of Celite, and the solvent removed in vacuo. The residue was purified by silica chromatography to give lactone **14** (31 mg, 0.12 mmol, 84% yield). ^1H NMR (400 MHz, $CDCl_3$) δ=0.99 (t, J=7.2 Hz, 3H), 1.34–1.57 (complex, 4H), 1.63–1.91 (complex, 9H), 2.03–2.10 (m, 1H), 2.31 (dd, J=17.2, 3.2 Hz, 1H), 2.44–2.50 (m, 1H), 2.64 (br s, 1H), 2.71 (dd, J=17.2, 4 Hz, 1H), 2.97 (br s, 1H), 3.18 (br s, 1H), 4.73 (dd, J=6, 2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ=11.3, 20.7, 22.1, 29.1, 29.8, 34.5, 36.8, 37.4, 38.3, 41.0, 55.7, 56.8, 68.3, 80.4, 177.1 ppm. EIMS: m/z (% intensity)=263 ($[M]^+$, 38), 262 ($[M-H]^+$, 100), 234 (23), 220 (19), 204 (17), 192 (23). HRMS (ESI) calcd for $C_{16}H_{26}NO_2$ $[M+H]^+$: 264.1958; found: 264.1962.

3.10. (±)-13-Epineostenine 2

A solution of lactone **14** (18 mg, 0.07 mmol) in THF (1.5 mL) was cooled to −78 °C, a solution of LiHMDS (0.20 mL, 1.0 M in THF, 0.20 mmol) was added, and the reaction mixture was stirred at −78 °C for 1.5 h. Methyl iodide (43 μL, 0.68 mmol) was added neat and the reaction was warmed to room temperature. The reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with $CHCl_3$ (4×15 mL). The organic layers were dried with Na_2SO_4 and concentrated in vacuo. Silica gel chromatography gave (±)-13-epineostenine **2** (16 mg, 0.06 mmol, 85% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ=0.99 (t, J=7.2 Hz, 3H), 1.29–1.38 (complex, 5H), 1.52–1.65 (complex, 4H), 1.69–1.75 (complex, 3H), 1.79–1.85 (m, 2H), 2.31–2.45 (complex, 5H), 2.82 (dd, J=9.2, 4.8 Hz, 1H), 3.03 (dd, J=12.4, 4.8 Hz, 1H), 3.13 (t, J=7.2 Hz, 1H), 4.86 (dd, J=8, 4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ=11.4, 15.4, 19.9, 22.9, 29.7, 31.2, 31.3, 35.0, 38.9, 39.4, 41.5, 42.7, 56.0, 57.7, 65.6, 77.4, 179.8 ppm.[4] EIMS: m/z (% intensity)=277 ($[M]^+$, 40), 276 ($[M-H]^+$, 100), 262 (4), 248 (20), 233 (19). HRMS (ESI) calcd for $C_{17}H_{28}NO_2$ $[M+H]^+$: 278.2115; found: 278.2111. IR: ν=1768, 2796, 2876, 2929 cm^{-1}.

Acknowledgements

We gratefully acknowledge financial support from the NSFC (No. 20621091, 20672048 and 20732002) and the '111' program of Chinese Education Ministry.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.022.

References and notes

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