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Total Synthesis of (±)-Parvineostemonine

Zhi-Hua Chen, Jin-Miao Tian, Zhi-Min Chen, and Yong-Qiang Tu*[a]

Roots and rhizomes of the stemonaceous plant have long been used for the treatment of respiratory diseases and as domestic insecticides in traditional folk medicine of East Asia.[1] So far, over 130 structurally diverse *Stemona* alkaloids have been isolated from the monocotyledonous family Stemonaceae.[2] These *Stemona* alkaloids have fascinating architectures and potential biological activities, which have provoked broad interests in their total synthesis.[3–5] Among the *Stemona* alkaloids, parvineostemonine (**1a**), isolated from *Stemona parviflora* by Ye and co-workers in 2003,[6] is a unique molecule which differs from the typical *Stemona* alkaloids such as **1b**–**1e** (Figure 1). Parvineostemonine features a spirotetracyclic structure with a two-carbon bridge between C-3 and C-9 of the common pyrrolo[1,2-*a*]azepine (ring A and B) of the *Stemona* alkaloids. The piperidine moiety (ring C) contains five contiguous stereogenic carbons, wherein the oxa-quaternary carbon (C-11) is part of a spirobutenolide ring (ring D). Recently, Hsung and co-workers described a skeletal synthetic study toward parvineostemonine that features a highly stereoselective [4+3] cycloaddition.[7] However, the total synthesis of parvineostemonine has not been achieved to date. Herein, we report an approach for the first total synthesis of (±)-parvineostemonine.

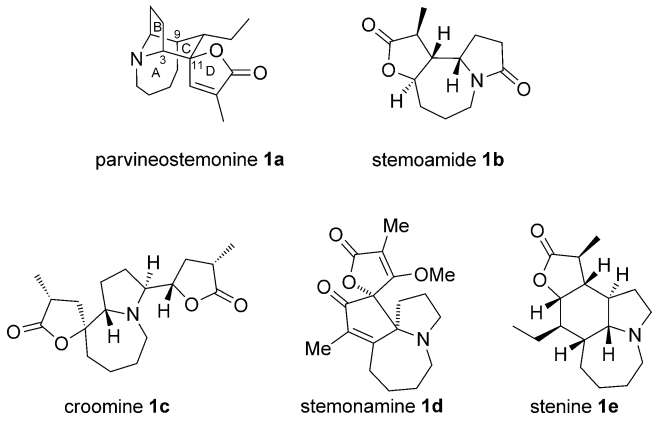
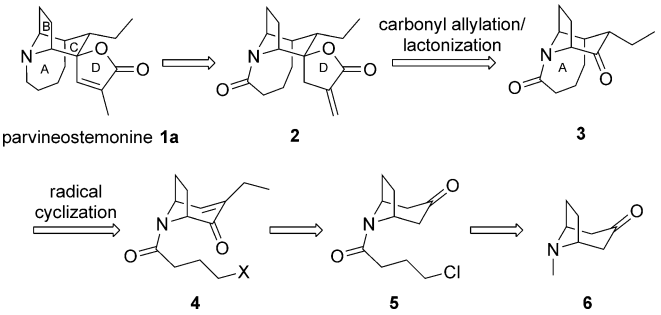


Figure 1. Parvineostemonine (**1a**) and some selected examples of typical *Stemona* alkaloids.

From a structural point of view, we found that **1a** has the same aza-bicyclo[3.2.1]octane unit (ring B and C) as tropinone. Thus, our synthesis of **1a** would focus on the formation of ring A and D from this commercially available material. A retrosynthetic analysis of **1a** is shown in Scheme 1.



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

We envisioned that **1a** could be obtained by isomerization of an exocyclic double bond and reduction of the lactam carbonyl of **2**, the lactone ring D of which could be conveniently constructed by a stereoselective carbonyl allylation/lactonization of tricyclic compound **3**. We further expected that ring A in compound **3** might be formed by a key radical-mediated 7-*exo*-trig cyclization from halide precursor **4**, which could be derived from **5** through several transformations, including oxidation and cross-coupling reactions. We anticipated that amide **5** could be easily obtained in large-scale through a one-pot demethylation and acylation manipulations of inexpensive tropinone **6**.

According to the above-described plan, we commenced our synthesis from the preparation of the known ammonium salt **7**,[8] as depicted in Scheme 2. Demethylation of tropinone **6** with 1-chloroethyl chloroformate afforded the crude ammonium salt **7**, which was directly treated with 4-chlorobutyryl chloride to afford amide **5** in 96% yield. Initial attempts to obtain the α-diketone **9** directly from **5** with SeO_2 in refluxing 1,4-dioxane[9] led to the decomposition of starting material. Thus, an alternative approach involving hydroxylation of **5** and subsequent oxidation was then employed. Treatment of **5** with KOH/$PhI(OAc)_2$[10] followed by

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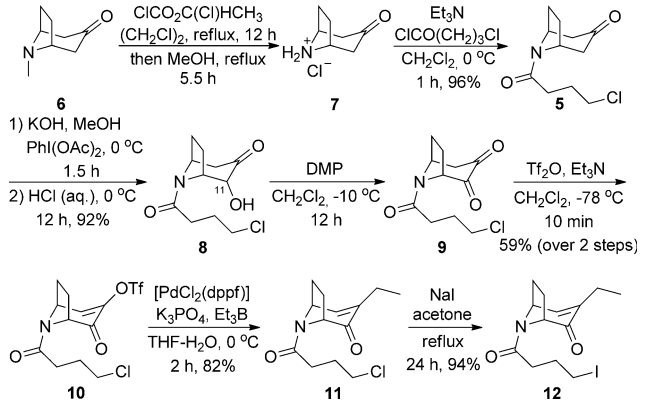
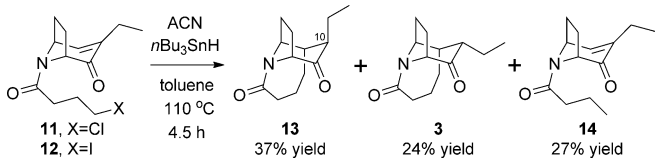


Scheme 2. Synthesis of compound **4**.

a one-pot hydrolyzation with hydrochloric acid provided α-hydroxy ketone **8** as a single diastereoisomer. As the hydroxy moiety in **8** would be oxidized to form a ketone, we did not determine the relative configuration of the newly formed stereocenter at the C-11 position. Swern oxidation[11] of **8** did not afford α-diketone **9** and instead afforded a complex mixture of products. The successful oxidation of **8** was carried out by using Dess–Martin periodinane (DMP),[12] thus furnishing α-diketone **9**, which was labile on silica-gel column chromatography. Therefore, the crude product **9** was immediately treated with triflic anhydride in CH_2Cl_2 at −78 °C to afford enone **10** in 59 % yield over two steps. The introduction of an ethyl moiety was accomplished by using a Suzuki cross-coupling reaction[13] of **10**, which was treated with Et_3B in the presence of [$PdCl_2$(dppf)] (dppf = diphenylphosphinoferrocene) to give radical cyclization precursor **11** in 82 % yield. Given that the corresponding iodo precursor would probably have a higher reactivity in the radical reaction, we also prepared iodide **12** from **11** by a Finkelstein reaction with NaI in refluxing acetone.[14]

Next, the key radical-mediated 7-*exo*-trig cyclization to access tricyclic skeleton **3** was investigated (Scheme 3).



Scheme 3. Key radical-mediated 7-*exo*-trig cyclization.

Treatment of **11** or **12** with SmI_2[15] in tetrahydrofuran (THF) at 0 °C to 66 °C did not produce the cyclization product. By examining the general azobisisobutyronitrile (AIBN)/nBu$_3$SnH reaction conditions,[16] we found that the use of chlorinate **11** did not result in radical cyclization. However, iodide **12** could be converted into the desired tricyclic skeleton **3** along with its epimer **13** and the reduced product **14** under the same reaction conditions. Further studies showed that both the initiator and reaction temperature are crucial for the success of this radical cyclization, and performing the reaction with 1,1′-azobis(cyclohexanecarbonitrile) (ACN) as an initiator[17] in refluxing toluene gave the best results. The two epimers **13** and **3** were readily separated by silica-gel column chromatography. The relative configuration of **13** was assigned by X-ray analysis (Figure 2),[18] and this showed that its stereochemistry at the

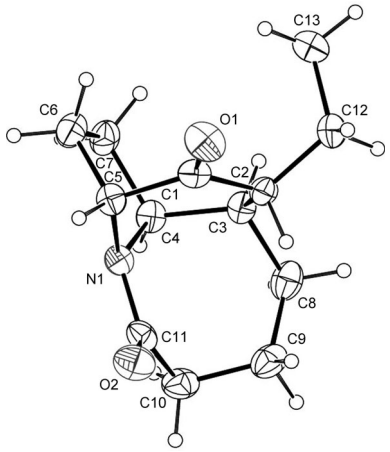
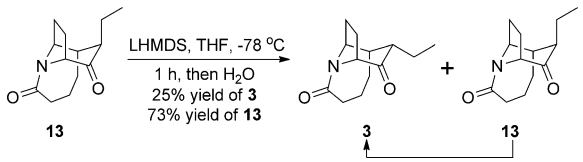


Figure 2. X-ray structure of the tricyclic compound **13**. Ellipsoids set at 30 % probability.[18]

C-10 position was not in agreement with that of parvineostemonine (**1a**). To convert epimer **13** into the requisite compound **3**, we investigated the adjustment of the stereochemistry at the C-10 position in **13** by an enolization/protonation sequence[19] from the β face. A variety of bases such as lithium hexamethyldisilazane (LHMDS), NaHMDS, KHMDS, lithium diisopropylamide (LDA), and *t*BuOK and proton sources such as H_2O, phenol, and 2,6-di-*tert*-butyl-4-methylphenol were employed. However, in all cases a mixture of **3** and **13** were obtained in an approximate ratio of 1:3 (Scheme 4). Ultimately, tricycle **3** was obtained in 40 % yield after subjecting **13** to epimerization for two times.



Scheme 4. Epimerization of **13**.

Having successfully established the cagelike skeleton **3**, we turned our attention to the stereoselective construction of lactone ring D. As shown in Scheme 5, the key carbonyl allylation/lactonization[20] was achieved by treatment of **3** with ethyl (2-bromomethyl)acrylate[21] and zinc powder in refluxing THF, and this provided **2** as a single diastereoisomer in 78 % yield. On the basis of molecular model studies, we assumed that the zinc nucleophile formed in situ would attack the carbonyl carbon (C-11) in **3** from the less sterical-

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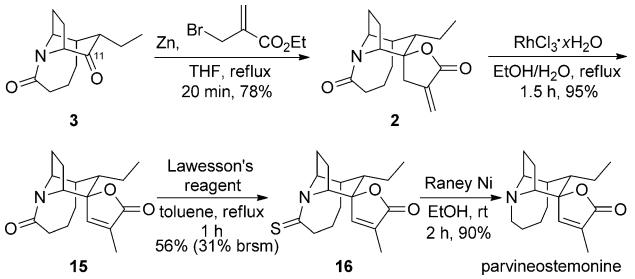

Scheme 5. Synthesis of (±)-parvineostemonine.

ly hindered α face, which might account for the observed high diastereoselectivity. Then, $RhCl_3$-mediated isomerization of the exocyclic double bond[22] of lactone **2** afforded **15** in high yield. With **15** in hand, we attempted to selectively reduce the lactam carbonyl without affecting the unsaturated lactone moiety in **15**. Unfortunately, direct reduction of the lactam using our previously reported one-pot protocol ($MeOTf/CH_2Cl_2$; $NaBH_3CN/EtOH$)[5e,h] resulted in recovery of **15**. Therefore, an alternative method was performed that involved formation of thioamide **16,** which was then subsequently reduced. The reaction of **15** with P_4S_{10}/HMDO[23] (hexamethyldisiloxane) in refluxing toluene gave an undesired dithiocarbonyl product.[24] Replacement of P_4S_{10} with 2 equivalents of Lawesson's reagent[25] in refluxing toluene only resulted in a trace amount of thioamide **16**. However, to our delight, by increasing the amount of Lawesson's reagent to 8 equivalents and keeping the reaction time to 1 hour enhanced the yield of thioamide **16** to 56% along with recovery of starting material **15** in 31% yield. It should be noted that prolonging the reaction time led to complete consumption of **15**, whilst affording a significant amount of dithiocarbonyl byproduct. Finally, reduction of **16** using W-2 Raney Ni[26] in EtOH gave (±)-parvineostemonine (**1a**), the NMR spectra of which were identical to those of the natural product.[27]

In summary, the first total synthesis of (±)-parvineostemonine (**1a**) has been achieved in 11 steps with an overall yield of 9.1% from commercially available tropinone **6**. Key transformations include a radical-mediated 7-*exo*-trig cyclization to construct the tricyclic cagelike skeleton **3** and a stereoselective carbonyl allylation/lactonization to form the spirobutenolide ring D.

Experimental Section

*Ketones (**3**)*

A solution of nBu$_3$SnH (394 μL, 1.465 mmol) and ACN (47.6 mg, 0.195 mmol) in anhydrous toluene (8 mL) was added dropwise to a boiling solution of **12** (338.3 mg, 0.975 mmol) in anhydrous toluene (30 mL) under argon over 3.5 h by employing a syringe-pump technique, and the mixture was further heated at reflux for 1 h. After cooling the solution was evaporated and the residue was purified by silica-gel chromatography (EtOAc/petroleum ether, 7:13–1:1) to give **13** (79.1 mg, 37%) as a white solid and **3** (51.7 mg, 24%) as a light yellow oil. Compound **13**: m.p. 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.65–4.63 (d, J = 6.4 Hz, 1H), 4.20–4.17 (d, J = 8.4 Hz, 1H), 2.83–2.76 (dt, J = 12.8, 2.4 Hz, 1H), 2.46–2.37 (m, 2H), 2.15–2.10 (dd, J = 11.2, 5.6 Hz, 1H), 1.97–1.80 (m, 6H), 1.71–1.68 (m, 1H), 1.62–1.55 (m, 2H), 1.51–1.43 (m, 1H), 0.89–0.86 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.4, 175.3, 64.6, 58.2, 46.1, 43.3, 36.2, 32.9, 30.0, 28.0, 22.1, 19.2, 11.3 ppm; IR (neat): $\tilde{\nu}$ = 2920, 1718, 1653, 1460 cm^{-1}; MS (EI): m/z: 221, 193, 165, 150, 123, 85, 69; HRMS (ESI): m/z: calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$: 222.1489; found 222.1487. Compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68–4.66 (d, J = 7.6 Hz, 1H), 4.30–4.28 (d, J = 7.2 Hz, 1H), 2.80–2.73 (ddd, J = 14.4, 7.2, 7.2 Hz, 1H), 2.48–2.36 (m, 4H), 2.24–2.14 (m, 1H), 2.03–1.84 (m, 3H), 1.78–1.60 (m, 3H), 1.46–1.38 (m, 1H), 1.26–1.16 (m, 1H), 0.90–0.86 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.7, 173.5, 64.9, 57.6, 47.3, 44.3, 35.3, 27.9, 26.6, 26.3, 19.2, 17.2, 11.8 ppm; IR (neat): $\tilde{\nu}$ = 2925, 1723, 1660, 1460 cm^{-1}; MS (EI): m/z: 221, 193, 164, 137, 113, 97, 67; HRMS (ESI): m/z: calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$: 222.1489; found 222.1487.

*Lactone (**2**)*

Zinc powder (254.2 mg, 3.887 mmol) was added to a solution of ketone **3** (85.9 mg, 0.389 mmol) in anhydrous THF (5 mL) under argon. The solution was heated, and when reflux started, a solution of ethyl (2-bromomethyl)acrylate (112.5 mg, 0.583 mmol) in anhydrous THF (2 mL) was added dropwise over 5 min. After stirring for an additional 15 min, the resultant mixture was cooled to room temperature, quenched with water (100 μL), and concentrated under vacuum. The residue was purified by silica-gel chromatography (EtOAc/acetone, 4:1) to afford **2** (87.3 mg, 78%) as a white amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.23–6.22 (t, J = 2.8 Hz, 1H), 5.62–5.61 (t, J = 2.4 Hz, 1H), 4.61–4.60 (d, J = 7.2 Hz, 1H), 4.28–4.26 (d, J = 7.6 Hz, 1H), 2.83–2.67 (m, 3H), 2.31–2.18 (m, 3H), 2.15–1.99 (m, 3H), 1.95–1.92 (m, 1H), 1.78–1.65 (m, 4H), 1.41–1.33 (m, 1H), 1.32–1.23 (m, 1H), 0.90–0.86 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 169.1, 134.4, 122.2, 86.9, 62.6, 57.6, 43.2, 37.9, 35.9, 35.8, 27.6, 25.5, 24.1, 19.4, 16.7, 11.5 ppm; IR (neat): $\tilde{\nu}$ = 2958, 2922, 1751, 1633, 1458 cm^{-1}; MS (EI): m/z: 289, 253, 211, 169, 141, 113, 99, 71; HRMS (ESI): m/z: calcd for $C_{17}H_{24}NO_3$ $[M+H]^+$: 290.1751; found 290.1750.

*Thioamide (**16**)*

Lawesson's reagent (543.1 mg, 1.343 mmol) was added to a solution of **15** (48.5 mg, 0.168 mmol) in anhydrous toluene (10 mL) under argon and the solution was heated at reflux for 1 h. After cooling the solvent was evaporated and the residue was purified by silica-gel chromatography ($MeOH/CH_2Cl_2$, 1:200–2:98) to afford **16** (28.7 mg, 56%) as a light yellow amorphous solid and recovered starting material **15** (14.8 mg, 31%). Thioamide **16**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.84–6.83 (d, J = 1.8 Hz, 1H), 4.96–4.95 (d, J = 7.8 Hz, 1H), 4.53–4.52 (d, J = 7.2 Hz, 1H), 3.35–3.33 (m, 1H), 3.17–3.12 (m, 1H), 2.35–2.28 (m, 1H), 2.21–2.17 (m, 1H), 2.04–1.98 (m, 3H), 1.94–1.93 (d, J = 1.2 Hz, 3H), 1.92–1.90 (d, J = 9.0 Hz, 2H), 1.72–1.61 (m, 2H), 1.32–1.27 (m, 1H), 1.08–1.01 (m, 1H), 0.89–0.84 (m, 1H), 0.83–0.80 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 202.2, 172.0, 148.0, 132.9, 92.4, 67.0, 60.4, 45.3, 39.3, 37.5, 26.8, 24.4, 23.7, 20.2, 16.1, 11.4, 10.8 ppm; IR (neat): $\tilde{\nu}$ = 2926, 1715, 1459, 1374, 1240, 1047 cm^{-1}; MS (EI): m/z: 305, 265, 223, 181, 149, 113, 85; HRMS (ESI): m/z: calcd for $C_{17}H_{24}NO_2S$ $[M+H]^+$: 306.1522; found 306.1522.

*Parvineostemonine (**1a**)*

Raney Ni W-2 (excess) was added to a solution of **16** (28.7 mg, 0.094 mmol) in anhydrous EtOH (10 mL) under argon at room temperature. After stirring for 2 h, the solvent was evaporated and the residue was purified by silica-gel chromatography ($MeOH/CH_2Cl_2$, 1:19) to afford (±)-parvineostemonine (**1a**) (23.3 mg, 90%) as a white amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88–6.87 (d, J = 1.6 Hz, 1H), 3.73–3.72 (d, J = 6.8 Hz, 1H), 3.66–3.59 (dt, J = 12.8, 3.6 Hz, 1H), 3.15–3.11 (ddd, J = 12.0, 3.2, 3.2 Hz, 1H), 2.99–2.97 (d, J = 6.8 Hz, 1H), 2.10–1.94 (m, 4H), 1.92–1.91 (d, J = 1.2 Hz, 3H), 1.89–1.81 (m, 3H), 1.78–1.64 (m, 3H), 1.58–1.52 (m, 1H), 1.39–1.23 (m, 2H), 1.04–0.98 (m, 1H), 0.82–0.78 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0,

152.8, 130.6, 89.4, 66.0, 56.9, 46.5, 38.2, 37.9, 28.2, 28.1, 27.1, 26.9, 24.0, 17.1, 11.7, 10.6 ppm; IR (neat): $\tilde{\nu}$ = 2923, 1747, 997, 731 cm^{-1}; MS (EI): *m*/*z*: 275, 246, 178, 137, 122, 109, 95, 69; HRMS (ESI): *m*/*z*: calcd for $C_{17}H_{26}NO_2$ $[M+H]^+$: 276.1958; found 276.1965.

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Keywords: allylation · parvineostemonine · radicals · *stemona* alkaloids · total synthesis

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