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Total synthesis of (−)-vallesamidine

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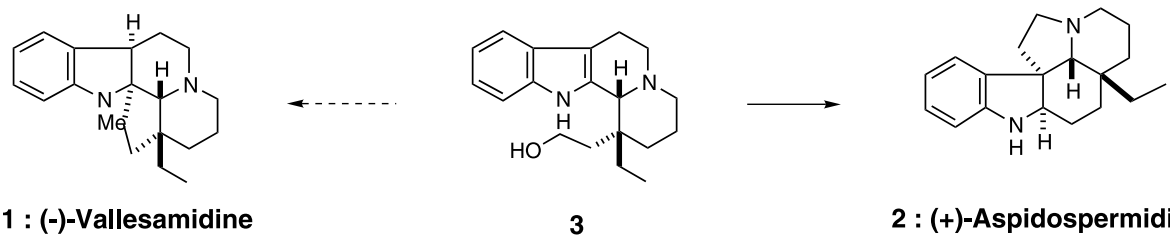
Abstract—A new synthetic method of (−)-vallesamidine, including a unique 2,2,3-trialkylindoline skeleton, is developed by reductive radical cyclization reaction from the 2,3-dialkylindole derivative, which has been known to be an intermediate for the synthesis of aspidospermidine.

Vallesamidine **1** was isolated from *Vallesia dichotoma* in 1965 and its structure and absolute configuration were determined by Djerassii in 1968.[1] The defined structure shows a unique and abnormal indole alkaloid including 2,2,3-trialkylindoline skeleton, which differs from (+)-aspidospermidine **2**, a typical indole alkaloids, having 2,3,3-trialkylindoline chromophore (Scheme 1). The stereochemistry of vallesamidine at C-5 and C-19 is identical to that of aspidospermidine, suggesting that these two alkaloids are possibly biosynthesized from the same intermediate. A great amount of research has been reported on the synthesis of 2,3,3-trialkylated indoline alkaloids such as aspidosperma and strychnos families,[2] but little research has been carried out on the 2,2,3-trialkylated indoline alkaloid.[3]

In 1990, Heathcock reported the first total synthesis of (±)-vallesamidine via newly developed methodology wherein the indolenine skeleton is formed in the late stage of its synthesis.[4] In his paper, it is noted that alkylation at C-2 of a 2,3-disubstituted indole **3** is not generally useful, because of the propensity of the resulting cation to rearrange to the more stable 2,3,3-trialkylindolenium ion. Harley–Mason[5] and Fuji[6] have succeeded in the synthesis of the aspidosperidine skeleton from **3**, being used as a key intermediate, in the cyclization which includes the interesting rearrangement as mentioned above.

On the other hand, Levy's first synthesis of vallesamidine from tabersonine was achieved by treatment with Zn powder in acetic acid.[7] It has been proposed that 2,2,3-trialkylindoline intermediate **6** is included in the equilibrium reaction mixture, in addition to 2,3,3-trialkylindoline **4** and quebrachamine chromophore **5** (Scheme 2). In this way, enanthiomeric (+)-vallesamidine was obtained in 24% yield.

Because of the above discussion, we have investigated a new synthetic approach to vallesamidine wherein the reductive radical cyclization of the known 2,3-dialkylindole derivative **3** provides the 2,2,3-trialkylindoline skeleton. Although many novel ring systems and natural products have been synthesized by radical reactions, a small amount of research has been devoted to the synthesis of indoline alkaloids.[8] In this communication, we report a successful synthesis of (−)-vallesamidine **1** by the following line (Scheme 3).



Scheme 1.

Keywords: radical reaction; cyclization; indole; asymmetric synthesis.

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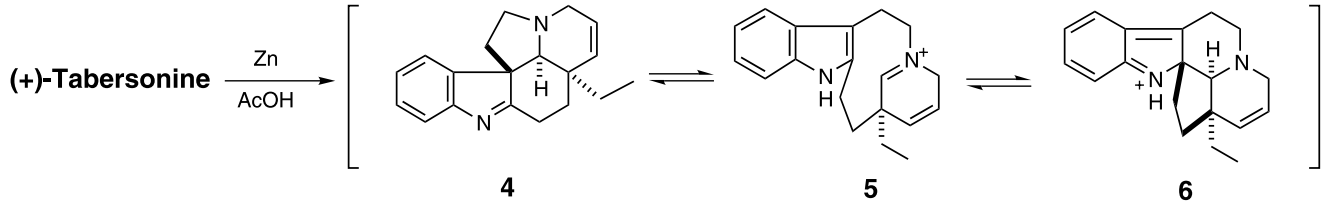
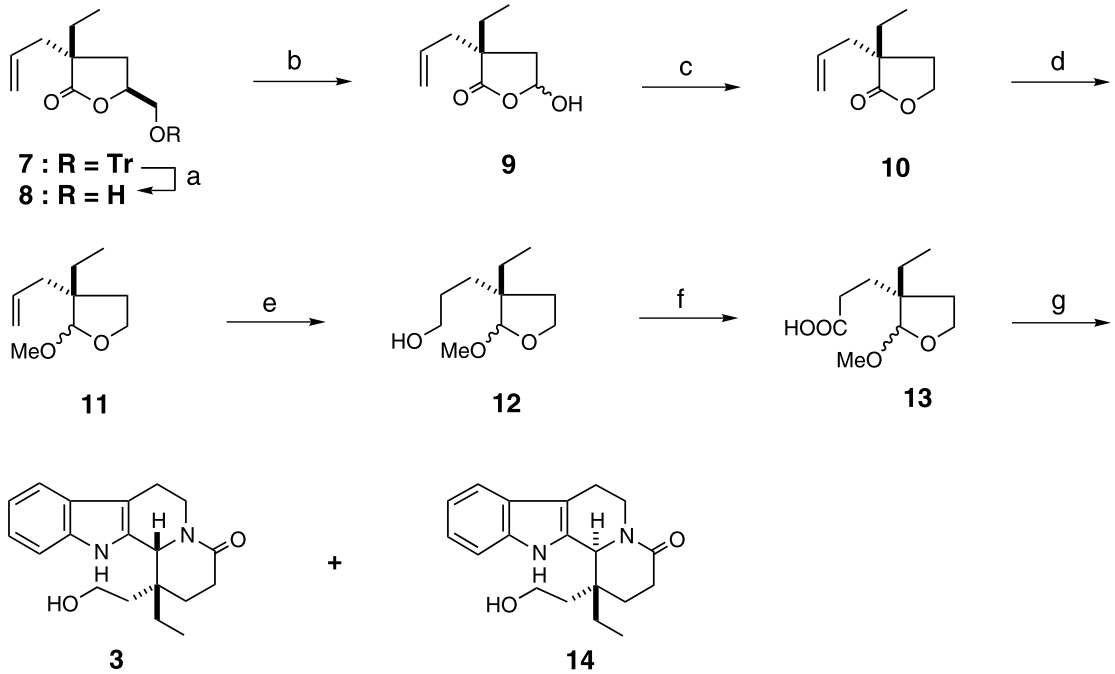


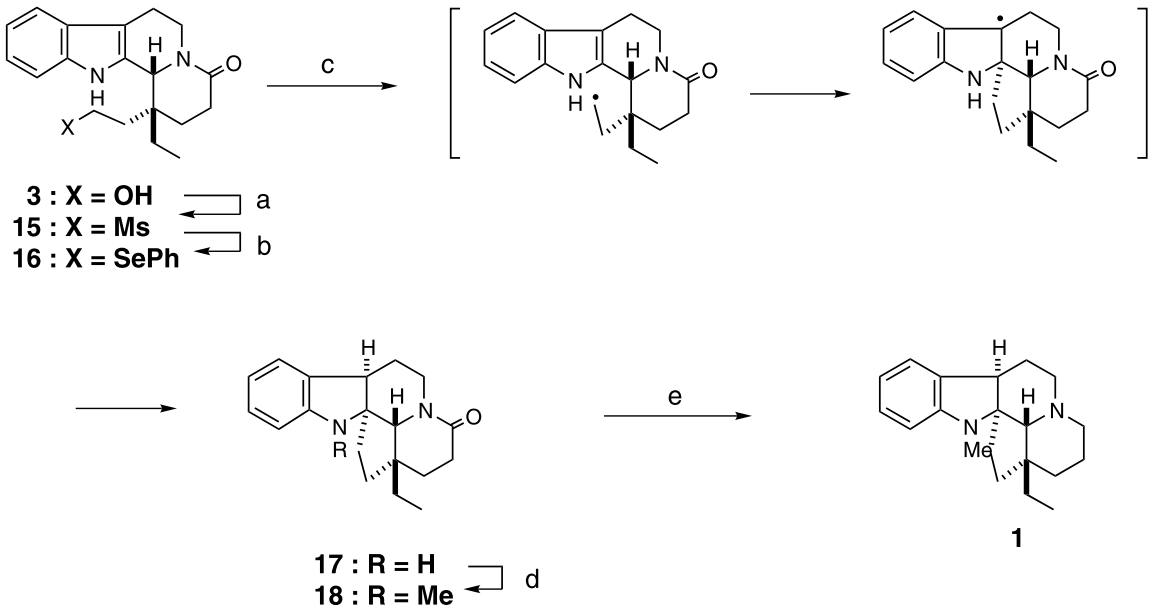
Scheme 2.



Scheme 3. *Reagents and conditions*: (a) 80% AcOH, 80°C, 1 h; (b) (i) 4N-NaOH, dioxane, 100°C, 1 h; (ii) CO_2; (iii) aq. $NaIO_4$, rt, 3 h; (iv) 1N HCl; (c) $NaBH_4$, MeOH, rt, 1 h; (ii) 4N HCl-MeOH, 70°C, 1 h; (d) (i) (1) DIBAL-H, Et_2O, −78°C, 1 h; (ii) $CH(OMe)_3$, *p*-TsOH, MeOH, 80°C, 2 h; (e) (i) 9-BBN, THF, rt, overnight; (ii) 30% H_2O_2, aq. NaOH, THF, rt, 1 h; (f) (i) SO_3-Py, DMSO, TEA, CH_2Cl_2, rt, 30 min; (ii) $NaClO_2$, *t*-BuOH, aq. NaH_2PO_4, $Me_2C{=}CHMe$, rt, 1 h; (g) tryptamine, AcOH, 140°C, 6 days.

The synthesis of the chiral key intermediate **3** was started from **7**, which was obtained from the double alkylation of (*S*)-γ-trityloxymethyl-γ-butyrolactone by using the method reported by Koga.[9] De-tritylation of **7** afforded an alcohol **8** in 93.6% yield, which was hydrolyzed with 4N-KOH in dioxane followed by neutralization with CO_2. The resulting mixture was oxidized with sodium periodate to give hemiacetal **9** in 95.2% yield. Reduction of **9** with sodium borohydride in methanol gave γ-lactones **10** (92.4%). The lactone was then converted to methylacetal **11** by reduction with diisobutylaluminum hydride at −78°C, followed by treatment with methylorthoformate and *p*-toluenesulfonic acid in methanol, in 83.6% yield in two steps. Transformation of the double bond in **11** into primary alcohol **12** was performed by following successive reactions of hydroboration with 9-BBN in THF and oxidation with hydrogenperoxide in alkali in 82.6% yield. The alcohol **12** was further oxidized to carboxylic acid **13** (95.0% yield) in the usual way. Finally, heating the carboxylic acid **13** with triptamine in AcOH for 6 days gave a tetracyclic indole lactam derivatives,[6] which was then hydrolyzed by 20% NaOH in MeOH, to afford the desired alcohol with a diastereomeric mixture (1:1). The mixture was easily separated on TLC, to give **3** (31.2% yield), corresponding to the natural form and its epimer **14**. The stereochemistry of each product was characterized by comparison with ^{1}H NMR spectra[10] of the authentic samples. Our next approach from **3** to **1** is outlined in Scheme 4.

The primary hydroxy group in the side chain of **3** was converted into mesylate by using MsCl–DMAP in pyridine at 0°C in 92% yield. The resulting mesylate **15** was treated with diphenydiselenide and $NaBH_4$ in EtOH at room temperature, giving the desired selenide **16** in 50% yield together with *N*-alkylated product[11] (13.0% yield, eburnamonine chromophore). Treatment of the selenide **16** with a mixture of *n*-Bu_3SnH and AIBN in toluene at 100°C gave a single product in 91% yield, the structure of which was assumed to be pentacyclic compound **17**[12] based on a following physical data; in ^{1}H NMR (δ): the signal at 4.77 ppm (1H, s) of **16** moved to 3.28 ppm (1H, s); in ^{13}C NMR (δ) : two SP^2 carbon signals which appeared at 126–136 ppm corresponding to α- and β-carbon in the indole ring of **16** disappeared and in



Scheme 4. *Reagents and conditions*: (a) MsCl, DMAP, pyridine, 0°C, 2 h; (b) $(PhSe)_2$, $NaBH_4$, EtOH, 0°C→rt, 3 h; (c) *n*-Bu_3SnH, AIBN, toluene, 100°C, 0.5 h; (d) HCHO, $NaBH_3CN$, CH_3CN, then AcOH, rt, 1 h; (e) LAH, THF, 70°C, 0.5 h.

place of these signals, two new signals were observed at 44.6 ppm (-CH-) and 76.3 ppm (quaternary carbon). *N*-Methylation of **17** with the mixture of HCHO–$NaBH_3CN$–AcOH in acetonitrile gave **18** in 87% yield.

Finally, reduction of lactam **18** was completed by using LAH in THF under refluxing temperature, providing (−)-vallesamidine **1** in 82% yield. The structure of the synthetic material was confirmed by comparison with the physical data reported by Heathcock.

In summary, we have developed a new strategy for preparation of the 2,2,3-trialkylindoline skeleton via reductive radical cyclization reaction, which successfully transformed into vallesamidine. This methodology may also be applicable for the synthesis of 2,3,3-trialkylindoline derivatives. Application of this methodology to the other indole alkaloids is now in progress.

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10. Compound **3**: mp 264–268°C decomp.; $[\alpha]_D^{25}$ +188.1° (*c* 0.15, CH_3OH); ^1H NMR (600 MHz, DMSO-d_6): δ 1.01–1.07 (1H, m), 1.06 (3H, t, $J=7.3$ Hz), 1.39 (1H, ddd, $J=13.9$, 10.3, 5.9 Hz), 1.54 (1H, dt, $J=13.2$, 5.1 Hz), 1.76 (1H, dq, $J=14.6$, 7.3 Hz), 1.87 (1H, ddd, $J=13.2$, 10.3, 7.3 Hz), 1.96 (1H, dq, $J=14.6$, 7.3 Hz), 2.32–2.40 (2H, m), 2.52–2.60 (1H, m), 2.60–2.68 (1H, m), 2.68–2.74 (1H, m), 3.22 (1H, td, $J=10.3$, 5.9 Hz), 3.30 (1H, td, $J=10.3$, 5.5 Hz), 4.83 (1H, s), 4.87–4.93 (1H, m), 6.98 (1H, t, $J=7.3$ Hz), 7.06 (1H, t, $J=7.3$ Hz), 7.41 (1H, d, $J=7.3$ Hz), 7.45 (1H, d, $J=7.3$ Hz), 10.30 (1H, br s).
Compound **14**: mp 123–127°C; $[\alpha]_D^{25}$ −141.2° (*c* 0.24, CH_3OH); ^1H NMR (600 MHz, DMSO-d_6): δ 0.74 (3H, t, $J=7.3$ Hz), 1.21 (1H, dq, $J=14.7$, 7.3 Hz), 1.29 (1H, dq, 14.7, 7.3 Hz), 1.52 (1H, ddd, $J=13.2$, 6.6, 3.7 Hz), 1.79 (1H, dt, $J=15.4$, 5.9 Hz), 1.94–2.02 (1H, m), 2.05 (1H, ddd, $J=15.4$, 8.1, 5.9 Hz), 2.24 (1H, ddd, $J=17.6$, 11.0, 6.6 Hz), 2.38 (1H, ddd, $J=17.6$, 6.6, 3.7 Hz), 2.51–2.59 (1H, m), 2.62 (1H, td, $J=11.7$, 2.2 Hz), (1H, dt, $J=13.9$, 2.2 Hz), 3.71–3.80 (1H. br m), 3.82–3.90 (1H, br m), 4.87–4.93 (1H, m), 5.03 (1H, br s), 5.06 (1H, s), 6.98 (1H, t, $J=7.3$ Hz), 7.06 (1H, t, $J=7.3$ Hz), 7.41 (1H, d, $J=7.3$ Hz), 7.43 (1H, d, $J=7.3$ Hz), 10.29 (1H, br s).
11. ^1H NMR (600 MHz, $CDCl_3$): δ 1.01 (3H, t, $J=7.3$ Hz), 1.46–1.60 (3H, m), 2.03–2.12 (2H, m), 2.13–2.18 (1H, m), 2.26 (1H, ddd, $J=17.6$, 5.1, 1.5 Hz), 2.45 (1H, ddd, $J=17.6$, 13.2, 6.6 Hz), 2.70 (1H, dd, $J=15.0$, 4.8 Hz), 3.04 (1H, td, 12.5, 4.8 Hz), 3.07–3.14 (1H, m), 3.69 (1H, td, $J=12.5$, 4.8 Hz), 4.23 (1H, ddd, $J=11.7$, 5.9, 1.5 Hz),

4.37 (1H, s), 4.96 (1H, dd, $J=12.5$, 5.9 Hz), 7.13 (1H, t, $J=8.1$ Hz), 7.20 (1H, t, $J=8.1$ Hz), 7.29 (1H, d, $J=8.1$ Hz), 7.47 (1H, d, $J=8.1$ Hz).

12. Compound **17**: mp 194–195°C; $[\alpha]_D^{25}$ +26.58° (*c* 0.23, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 0.96 (3H, t, $J=7.3$ Hz), 1.63–1.96 (9H, m), 1.96–2.03 (1H, m), 2.27 (1H, ddd, 17.2, 10.6, 5.1 Hz), 2.38 (1H, dt, 17.2, 4.8 Hz), 2.75 (1H, ddd, $J=12.8$, 8.1, 4.8 Hz), 3.15 (1H, t, $J=5.9$ Hz), 3.28 (1H, s), 4.34 (1H, dt, $J=12.8$, 6.6 Hz), 6.63 (1H, d $J=7.3$ Hz), 6.78 (1H, t, $J=7.3$ Hz), 7.06 (1H, t, $J=7.3$ Hz), 7.17 (1H, 7.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 9.1 (CH_3), 24.6 (CH_2), 28.8 (CH_2), 29.1 (CH_2), 35.2 (CH_2), 36.2 (CH_2), 36.5 (CH_2), 40.1 (CH_2), 43.6 (C), 44.6 (CH), 69.7 (CH), 76.3 (C), 109.7 (CH), 119.4 (CH), 123.5 (CH), 127.9 (CH), 130.8 (C), 149.1 (C), 171.0 (C).