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A FIRST TOTAL SYNTHESIS OF MONTANINE-TYPE AMARYLLIDACEAE ALKALOIDS, (±)-COCCININE, (±)-MONTANINE, AND (±)-PANCRACINE

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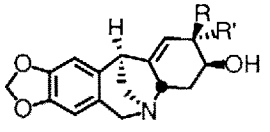
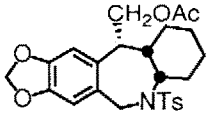
Abstract: Montanine-type Amaryllidaceae alkaloids, (±)-coccinine (**1**), (±)-montanine (**2**), and (±)-pancracine (**3**) were synthesized starting from (±)-1,2-*cis*-2-(3,4-methylenedioxybenzoyl)cyclohex-4-enecarboxylic acid (**6**) via (±)-2,3-*cis*-3-benzyloxy-2-hydroxy-4a,11a-*cis*-11,11a-syn-5,11-methano-8,9-methylenedioxymorphanthridine (**7**) as a key compound.

Although many studies on synthesis of Amaryllidaceae alkaloids[1] are reported, montanine-type Amaryllidaceae alkaloids have not been synthesized so far. Recently, we reported that reductive cyclization[2] of (±)-11-acetoxymethyl-5-tosylmorphanthidine (**4**) with vitride® in boiling toluene gives 5,11-methanomorphanthridine (**5**) in good yield, which is a basic skeleton of montanine-type alkaloids.[3] In the present communication we describe a first total synthesis of (±)-coccinine (**1**), (±)-montanine (**2**), and (±)-pancracine (**3**).



Coccinine (**1**) R=OMe, R'=H
Montanine (**2**) R=H, R'=OMe
Pancracine(**3**) R=H, R'=OH



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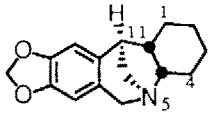


5,11-Methanomorphanthridine (**5**)

A potential key compound (**7**) was synthesized as follows. Reaction of 1,2-*cis*-cyclohex-4-enedicarbxylic anhydride with 3,4-methylenedioxyphenylmagnesium bromide in THF gave the corresponding keto acid (**6**)[4] (m.p. 150-152°C; 96%), which was converted to tosylamide (**8**)[3] (m.p. 150°C; 67%) in the similar manner as reported previously.[2] *Cis*-dihydroxylation of **8** with OsO_4 (catalytic amount) in the presence of N-methylmorphorine N-oxide (NMO)[5] in dioxane-H_2O (4:1) afforded, after acetylation, a separable diastereomeric mixture of β-isomer (**9**)[4] (m.p. 254-256°C; 93%) and α-isomer (**10**)[4] (m.p. 230-231°C; 5%). Reaction of **9** in the similar manner as reported previously[2] gave 2,3-diacetoxy-11-acetoxymethyl-5-tosylmorphanthridine (**11**)[4](m.p. 168.5°C; 83%). Hydrolysis of **11** followed by protection of vicinal hydroxyl groups with benzaldehyde dimethyl acetal gave a benzylidene tosylamide (**12**)[4] (m.p. 235-237°C; 83%). Reductive cyclization of **12** with vitride® in xylene produced the corresponding 5,11-methanomorphanthridine (**13**)[4] (m.p.

177°C; 91%), stereochemistry of which was confirmed by X-ray crystallographic analysis[6] (Fig. 1). Reduction of **13** with diisobutylaluminum hydride (DIBAH)[7] in toluene afforded, after silica gel column chromatography, desired 2-hydroxy product (**7**)[4] (m.p. 161-162°C; 75%) and a regioisomer (**14**)[4] (m.p.123-124°C; 22%), respectively.

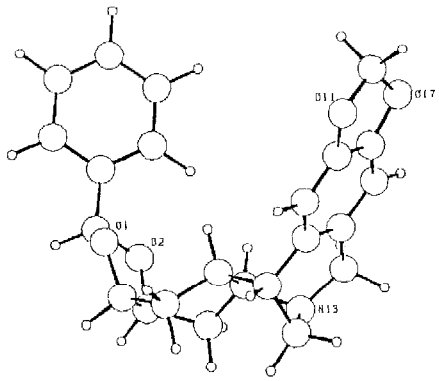


Fig. 1. The molecular structure of **13**.

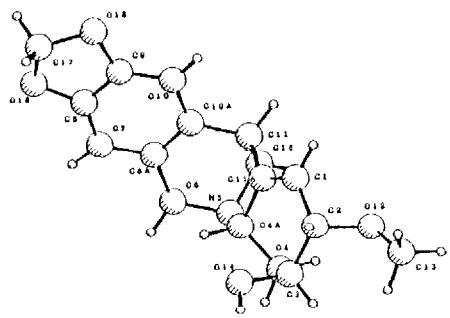


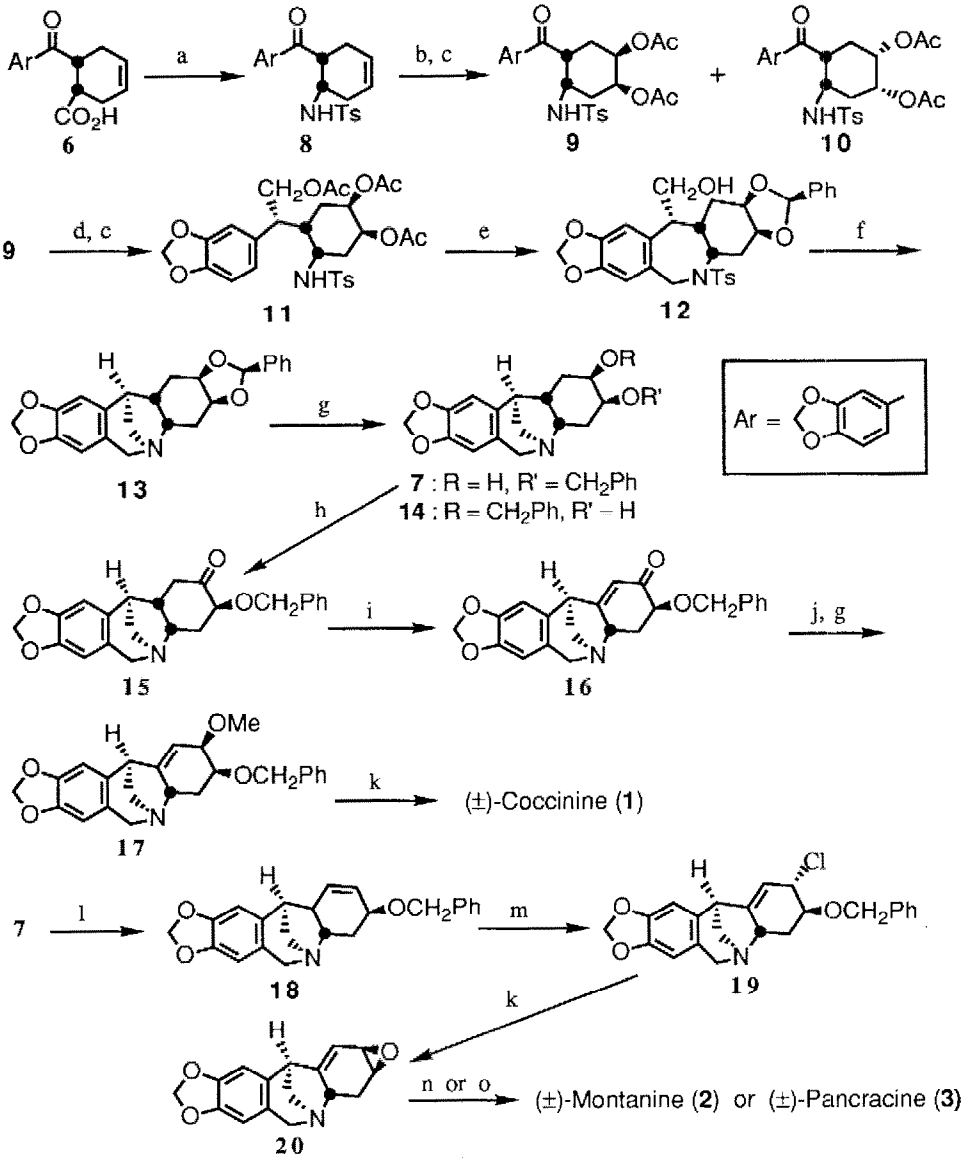
Fig. 2. The molecular structure of **2**.

Conversion of **7** to montanine-type alkaloids required introduction of a double bond and methoxyl group. Therefore, **7** was oxidized with Jones reagent to give 5,11-methanomorphanthridin-2-one (**15**)[4] (oil; 50%). After unfruitful attempts to introduce a double bond to 1(11a) positions in **15**, reaction of **15** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in the presence of disodium hydrogen phosphate in refluxing dioxane afforded an enone (**16**)[4] (oil; 26%). Ketalization of **16** with methyl orthoformate followed by DIBAH reduction[7] produced exclusively (±)-O-benzylcoccinine (**17**)[4] (m.p.117°C; 25% from **16**). Finally, debenzylation of **17** with trimethylsilyl iodide (TMS-I)[8] in $CHCl_3$ afforded (±)-coccinine (**1**)[4] (m.p. 71-73°C; 87%), mass spectrum of which was identical with that reported in a literature.[9]

Next, synthesis of (±)-montanine (**2**) and (±)-pancracine (**3**) was performed starting from the same key compound (**7**). Namely, **7** was converted to olefin (**18**)[4] (oil; 70%) via mesylate[4] (m.p. 200°C). Although attempts to epoxidize **18** were unsuccessful, phenylselenenylation[10] of **18** with phenylselenenyl chloride (PhSeCl) in MeOH under ultrasonication[11] followed by oxidation afforded unexpectedly allylic chloride (**19**)[4] (oil; 82%), which was debenzylated with TMS-I[8] in $CHCl_3$ to produce epoxide (**20**)[4,12] (m.p. 144°C; 87%). Treatment of **20** with $BF_3{\cdot}OEt_2$ in MeOH gave readily (±)-montanine (**2**)[4] (m.p. 200-201°C; 94%), mass spectrum of which was identical with that reported in a literature.[9] Furthermore, stereostructure of (±)-**2** was confirmed by X-ray crystallographic analysis[13] (Fig. 2).

On the other hand, treatment of **20** with aqueous sulfuric acid in THF provided (±)-pancracine (**3**)[4] (m.p. > 280°C; 87%). ^{1}H-NMR spectrum of (±)-pancracine diacetate (m.p. 152°C) was identical with that reported in a literature.[14]

Thus, a first total synthesis of montanine-type Amaryllidaceae alkaloids, (±)-coccinine (**1**), (±)-montanine (**2**), and (±)-pancracine (**3**) was accomplished by development of reductive cyclization.



a) $ClCO_2Et$, Et_3N, $CHCl_3$; NaN_3, H_2O; *t*-BuOH; TFA, $CHCl_3$; TsCl, Et_3N: b) OsO_4 (cat.), NMO, dioxane-H_2O(4:1): c) Ac_2O, C_5H_5N: d) *t*-BuOK, PPh_3MeBr, THF; BH_3, THF; NaOH, H_2O_2, H_2O: e) CH_2O, Ac_2O, $MeSO_3H$, $Cl(CH_2)_2Cl$; NaOMe, MeOH; $PhCH(OMe)_2$, TsOH, $CHCl_3$: f) vitride®, xylene: g) DIBAH, toluene: h) Jones reagent, acetone-H_2O: i) DDQ, Na_2HPO_4, dioxane: j) $CH(OMe)_3$, TsOH, MeOH: k) TMS-I, $CHCl_3$: l) MsCl, Et_3N, CH_2Cl_2; *t*-BuOK, DMSO: m) PhSeCl, MeOH, ultrasound; $NaIO_4$, H_2O: n) $BF_3{\cdot}OEt_2$, MeOH: o) H_2SO_4, H_2O, THF

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References and Notes

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4. All new compounds gave satisfactory chemical and ^{1}H-NMR and mass spectral analyses.
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6. Crystallographic data for (±)-**13**: $C_{23}H_{23}NO_4$ (M.w.=377.4), clear colorless prism, monoclinic, space group *P2₁/c*, monoclinic, *Z*=4, *a*=10.473(6), *b*=19.156(10), *c*=9.868(6)Å, β=107.62(6)°, *V*=1887Å^3, *Dx*=1.329 g·cm^{-3}, *R*=0.053.
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10. It is noteworthy that reaction of **18** with PhSeCl even in MeOH gives PhSeCl / olefin adduct.
11. Reaction of **18** with PhSeCl in MeOH was accelerated under ultrasonication. A review on ultrasonication in organic synthesis. Lindley, L.; Mason, T. J. *Chem. Soc. Rev.* **1987**, *16*, 273.
12. Debenzylation of **18** with BF_3·OEt_2 and Me_2S[15] in CH_2Cl_2 gave allylic alcohol[4] (m.p. 229-230°C; 41 %), phenylselenenylation of which followed by oxidation afforded epoxide (**20**)(41%) accompanied with chloroallylic alcohol[4] (oil; 21%). This finding suggests generation of allylic chlorohydrin in the course of reaction.
13. Crystallographic data for (±)-**2**: $C_{17}H_{19}NO_4$ (M.w.= 301.3), colorless plates, orthorhombic, space group *Pbca*, *Z*=8, *a*=15.444(9), *b*=17.863(10), *c*=11.034(7) Å, *V*= 3044 Å^3, *Dx*=1.315 g·cm^{-3}, *R*= 0.0657.
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