Approaches to the Total Synthesis of Montanine-type Alkaloids: a First Synthesis of (±)-4a,11a-*cis*-11,11a-*anti*-5,11-Methanomorphanthridine and its *trans*-Isomer

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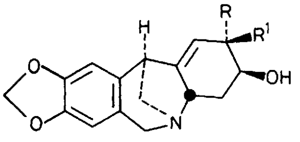
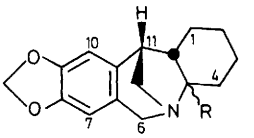
The title compounds (**3**) and (**4**) were synthesised by reductive cyclisation of *cis*- and *trans*-11-hydroxymethyl-*N*-tosylmorphanthridines (**15**) and (**16**) derived from *cis*- and *trans*-nitrocyclohexane derivatives (**5**) and (**6**) with sodium bis(2-methoxyethoxy)aluminium hydride in boiling toluene.

Montanine-type alkaloids, montanine (**1**)[1] and coccinine (**2**),[1] constitute a group of *Amaryllidaceae* alkaloids.[2] The structure possesses a unique 5,11-methanomorphanthridine skeleton; however, there is only one report[3] on synthetic approaches to them so far, in which synthesis of the basic skeleton is unsuccessful. We report a first synthesis of the title compounds (**3**) and (**4**) starting from methyl *cis*- and *trans*-2-nitrocyclohexyl-(3,4-methylenedioxyphenyl)acetates (**5**) and (**6**).

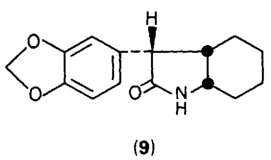
Reaction of 1-nitrocyclohexene[4] with methyl 3,4-methylenedioxyphenylacetate[5] under basic conditions [lithium diisopropylamide (LDA), tetrahydrofuran (THF), −78 °C, 0.5 h] gave *cis*-nitro ester (**5**) (m.p. 125—126 °C) and *trans*-nitro ester (**6**) (m.p. 99—100 °C) in a ratio of 5.8 : 1 (87%) by chromatographic separation.† Structures of (**5**) and (**6**) were determined by the ^{1}H NMR spectra, showing a multiplet ($W_{1/2}$ 8 Hz) of one proton for the =$CHNO_2$ group at δ 4.19 and



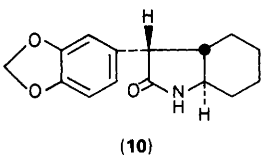
(**1**) R = OMe, R^1 = H
(**2**) R = H, R^1 = OMe



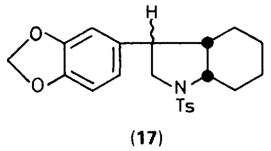
(**3**) R = β-H
(**4**) R = α-H



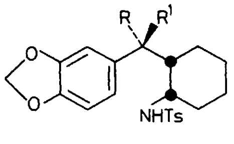
(**9**)



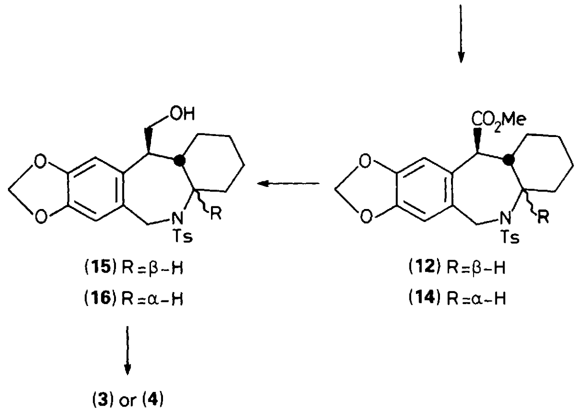
(**10**)



(**17**)



(**18**) R = H, R^1 = CH_2OH
(**19**) R = CH_2OH, R^1 = H



Scheme 1

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† All new compounds gave satisfactory chemical and mass and ^{1}H NMR spectral analyses.

double triplets (J 4.3, 10 Hz) of one proton for the =$CHNO_2$ group at δ 4.19, respectively. Furthermore, the former (**5**) was deduced to be a diastereoisomeric mixture of *cis*-nitro esters on the basis of the ^1H NMR spectral data and chemical evidence.‡ Reduction (Raney Ni, H_2, THF, room temp.) of (**5**) gave two kinds of amino esters (**7**) and (**11**),† each of which was heated at 120 °C to afford a lactam (**9**) (m.p. 186—187 °C; 95%) or lactam (**10**) (oil; 96%).† Conversion [i, BH_3, THF; ii, HCl (6 M); iii, $ClCO_2Et$, Et_3N, $CHCl_3$; 43%] of (**9**) to 1-ethoxycarbonyloctahydroindoline (m.p. 115—116 °C) proceeded smoothly giving a ^1H NMR spectrum which was identical to that of the authentic sample.[3] On the other hand, the lactam (**10**) was found to be identical to a lactam derived from (**6**) by comparison of each ^1H NMR spectral datum. Therefore, the relationship between amino and alkyl groups in (**7**) was determined to be *cis*, while that in (**11**) was determined to be *trans*. Compound (**11**) should be formed by partial epimerization and reduction of a nitro group.

The *cis*-amino ester (**7**) was tosylated in the usual manner [p-TsCl (Ts = $OSO_2C_6H_4Me$), 4-DMAP (4-*N,N*-dimethylaminopyridine), CH_2Cl_2, room temp.] to afford (**8**) (m.p. 221—222 °C; 96%), whose cyclisation[6] (paraformaldehyde, Ac_2O, $MeSO_3H$, $ClCH_2CH_2Cl$, 0 °C, 0.5 h) gave (**12**) (m.p. 168 °C; 97%).† Similarly, *trans*-amino ester (**11**) gave (**14**) (m.p. 161—162 °C; 83% overall yield) through (**13**)† (m.p. 158—159 °C) (Scheme 1).

After fruitless attempts for synthesis of (**3**) and (**4**), their construction was achieved as follows; reduction ($LiAlH_4$, THF) of (**12**) and (**14**) afforded (**15**) (m.p. 159—160 °C; 95%) and (**16**) (m.p. 148—149 °C; 82%), which were treated with sodium bis(2-methoxyethoxy)aluminium hydride (SMEAH)[7]§ in boiling toluene to yield (**3**) [m.p. 96—97 °C; 42%; m/z 257 (M^+), 175 (base peak)] and (**4**) [m.p. 143—145 °C; 75%; m/z 257 (M^+), 175 (base peak)].† The presence of a base peak (m/z 175)[8] in the mass spectra supported the structures of (**3**) and (**4**) well.

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9 O. Hoshino and M. Ishizaki, unpublished results.

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‡ This fact was well supported by the following results. Reduction ($LiAlH_4$, THF) followed by tosylation (p-TsCl, Et_3N, $CHCl_3$) of (**5**) gave (**17**) (oil, 8.5%), (**18**) (m.p. 133.5—134 °C; 12.2%), and (**19**) (m.p. 184 °C; 17.8%). Compounds (**18**) and (**19**) were found to be identical with an authentic sample derived from (**8**) and with another authentic sample,[9] by comparison of each spectral datum.

§ It is noteworthy that treatment of (**15**) or (**16**) with SMEAH gives rise to a cyclised product.