Synthesis of an Antitumour Alkaloid Sinococuline from Sinomenine

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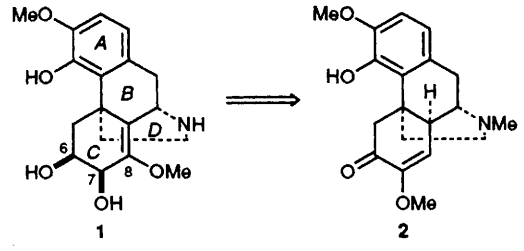
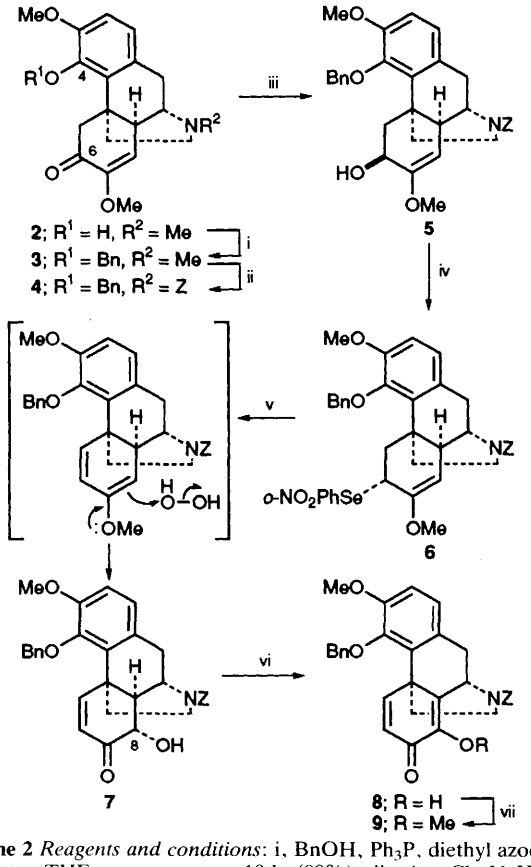
An antitumour morphinane alkaloid sinococuline **1** is synthesised from sinomenine **2** in an efficient manner.

Sinococuline **1** is a morphinane alkaloid isolated from the roots of the plant *Cocculus trilobus*[1] and shows promising antitumour activity against animal tumour models. However, the quantity of **1** in the plant is variable and its high polar and noncrystallizable property makes isolation/purification difficult. These difficulties have hampered further preclinical studies of **1** as an anticancer agent. To develop an alternative route to **1**, we have undertaken a programme to synthesise **1** from sinomenine **2**. It was envisaged that **2** would be a suitable precursor for **1** since **2** possesses a morphinane skeleton with the same substituents on ring *A* and is readily available from the roots of *Sinomenium acutum* (Scheme 1).

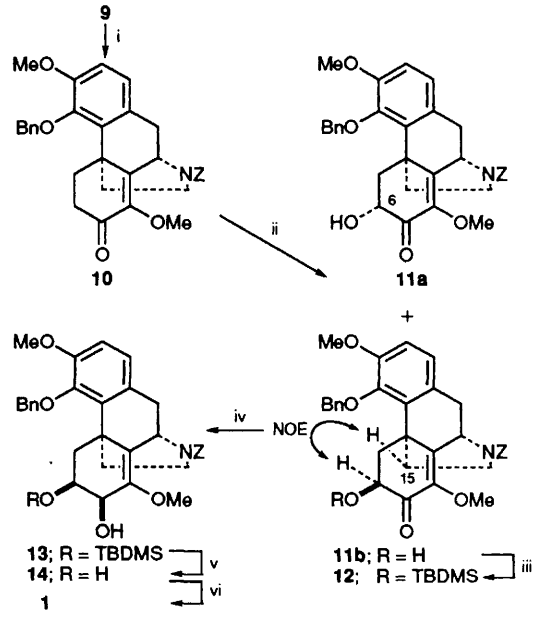


Scheme 1



Scheme 2 *Reagents and conditions*: i, BnOH, Ph_3P, diethyl azodicarboxylate, THF, room temp., 10 h (89%); ii, Acc-Cl, $NaHCO_3$, CH_2ClCH_2Cl, reflux, 2 h; MeOH, reflux, 1 h; ZOSu, $NaHCO_3$, room temp., 0.5 h (98%); iii, $Li(Bu^s)_3BH$, THF, −78 °C, 3 h (91%); iv, *o*-$NO_2PhSeCN$, Bu_3^nP, THF, room temp., 4 h (96%); v, (aq) H_2O_2, THF, room temp., 21 h (89%); vi, $(COCl)_2$, Me_2SO, CH_2Cl_2, −78 °C; Et_3N (89%); vii, *p*-TsOMe, K_2CO_3, acetone, reflux, 15 h (97%)

The C-4 phenolic hydroxy group of **2** was protected as benzyl (Bn) ether **3** (89% yield) through the Mitsunobu's procedure[2] (Scheme 2).† **3** was subjected to *N*-demethylation using 1-chloroethyl chloroformate (Ace-Cl)[3] and $NaHCO_3$ to afford the *N*-(1-chloroethoxycarbonyl)intermediate, which was decomposed by refluxing in MeOH, and the resultant secondary amine was protected by the benzyloxycarbonyl (Z) group using *O*-benzyloxycarbonyl-*N*-hydroxysuccinimide (ZOSu) to give **4** in 98% yield from **3**. Compound **4** was reduced stereospecifically with the sterically hindered L-Selectride [$Li(Bu^s)_3BH$] in THF to give *quasi*-axial C-6β-alcohol **5** in 91% yield.‡ Selenylation[4] of **5** with *o*-$NO_2PhSeCN$ and Bu_3^nP proceeded with inversion of the stereogenic centre to afford C-6α-selenate **6** in 96% yield. Hydrogen peroxide oxidation of **6** did not give the expected diene (shown in the parentheses in Scheme 2) but gave the further oxidized C-8α-hydroxy derivative **7** instead in 89% yield. **7** was subjected to Swern oxidation[5] to provide diosphenol **8** (89% yield), which on treatment with methyl toluene-*p*-sulfonate (*p*-TsOMe) and potassium carbonate gave the methyl ether **9** in 97% yield by exclusive *O*-methylation. Catalytic hydrogenation of **9** using $(Ph_3P)_3RhCl$ in benzene effected selective reduction of C-5–C-6 olefin to afford the desired enone **10** in 97% yield (Scheme 3). Introduction of the C-6-hydroxy group in **10** was achieved by enolate oxidation. Reaction of the lithium, sodium or potassium enolate of **10** with racemic oxidizing agents [*e.g.* (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine)[6]] afforded undesired C-6α-alcohol **11a** predominently due to attack of the reagents from the less hindered α-side. However, a combination of potassium bis(trimethylsilyl)amide (2 equiv.) and (−)-(2*S*, 8a*R*)-(camphorsulfonyl)-



Scheme 3 *Reagents and conditions*: i, $H_2(Ph_3P)_3RhCl$, benzene, room temp., 3 d (97%); ii, potassium bis(trimethylsilyl)amide, (−)-(2*S*, 8a*R*)-(camphorsulfonyl)oxaziridine, THF, −78 °C, 1 h (**11a**, 17%; **11b**, 50%; recovered **10**, 23%); iii, TBDMSCl, imidazole, DMF, room temp., 24 h; iv, $LiBEt_3H$, THF, −78 °C, 3 h; v, cat. *p*-TsOH·H_2O, THF–H_2O (3 : 1), room temp., 4 d (70% from **11b**); vi, $Pd(OH)_2$ on C, cyclohexene–EtOH (1 : 1), reflux, 4.5 h (95%)

oxaziridine[7] (2.5 equiv.) in THF at −78 °C gave C-6β-alcohol **11b** and **11a** in 50 and 17% yields, respectively; 23% of **10** was recovered. The stereochemistry of C-6-hydroxy group in **11b** was confirmed by the observation of NOESYPH[8] correlations between the hydrogen atoms at C-6 and C-15α. Reduction of C-7 carbonyl in **11b** with various reducing agent (*e.g.* L-Selectride, $NaBH_4$ in the presence/absence of $CeCl_3$, Bu^i_2AlH, *etc.*) did not proceed in a stereoselective manner. The problem was circumvented by introduction of a bulky *tert*-butyldimethylsilyl (TBDMS) group on adjacent C-6β=hydroxy group. Super-Hydride ($LiBEt_3H$) reduction of TBDMS ether **12** afforded the desired C-7β-alcohol **13** favourably in a ratio of 25 : 1, and successive treatment of **13** with a catalytic amount of toluene-*p*-sulfonic acid in THF–H_2O (3 : 1) gave the diol **14** in 70% yield from **11**. **14** was treated with Pearlman's palladium catalyst in refluxing cyclohexene–EtOH (1 : 1) to give sinococuline **1** in 95% yield. The product thus obtained was found to be identical in all respects (400 MHz ^1H NMR, 100 MHz ^{13}C NMR, optical rotation§ and MS) with **1** isolated from the plant. This work constitutes the first synthesis of sinococuline since (+)-sinomenine has been synthesised from thebaine.[9]

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Footnotes

† All new compounds were fully characterized by spectroscopic methods, elemental composition being established by high-resolution mass measurement and/or combustion analysis.

‡ The configuration of C-6 hydroxy group in **5** is important. Oxidation of C-6β selenate prepared in the same manner from the C-6α epimer of **5** also gave **7** but in low (18%) yield.

§ Synthesised **1**: $[\alpha]_D^{25}$ −135.9 (*c* 0.11, MeOH); natural **1**: $[\alpha]_D^{25}$ −137.4 (*c* 0.12, MeOH).

References

1 H. Itokawa, S. Tsuruoka, K. Takeya, N. Mori, T. Sonobe, S. Kosemura and T. Hamanaka, *Chem. Pharm. Bull.*, 1987, **35**, 1660.
2 O. Mitsunobu, *Synthesis*, 1981, 1.
3 R. A. Olofson, J. T. Martz, J.-P. Senet, M. Piteau and T. Malfroot, *J. Org. Chem.*, 1984, **49**, 2081.
4 P. A. Grieco, S. Gilman and M. Nishizawa, *J. Org., Chem.*, 1976, **41**, 1485.
5 A. J. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.
6 F. A. Davis, L. C. Vishwakarma, J. M. Billmers and J. Finn, *J. Org. Chem.*, 1984, **49**, 3241.
7 F. A. Davis, M. S. Haque, T. G. Ulatowski and J. C. Towson, *J. Org. Chem.*, 1986, **51**, 2402; F. A. Davis, T. G. Ulatowski and M. S. Haque, *J. Org. Chem.*, 1987, **52**, 5288.
8 G. Bodenhauser, H. Koger and R. R. Ernst, *J. Magn. Reson.*, 1984, **58**, 379.
9 K. Okabe, K. Hayashi and Y. Sawa, *Jpn. J. Pharm. Chem.*, 1968, **39**, 267.