# 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*<sup>1</sup> 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).

ŅH

'NR<sup>2</sup>

'nΖ

OH

H

Scheme 1

Ð

ÔH

OMe 2; R<sup>1</sup> = H, R<sup>2</sup> = Me

3; R<sup>1</sup> = Bn, R<sup>2</sup> = Me = 4; R<sup>1</sup> = Bn, R<sup>2</sup> = Z

OMe

MeO

HO

MeO

BnO

HC

MeO

BnC

o-NO<sub>2</sub>PhSe

H

OMe

ÒМө

5

н

ÓMe

2

ŅМө

NZ

NZ



The C-4 phenolic hydroxy group of 2 was protected as benzyl (Bn) ether 3 (89% yield) through the Mitsunobu's procedure<sup>2</sup> (Scheme 2).  $\dagger$  3 was subjected to *N*-demethylation using 1-chloroethyl chloroformate (Ace-Cl)<sup>3</sup> and NaHCO<sub>3</sub> 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) using O-benzyloxycarbonyl-N-hydroxysuccinimide group (ZOSu) to give 4 in 98% yield from 3. Compound 4 was reduced stereospecifically with the sterically hindered L-Selectride [Li(Bu<sup>s</sup>)<sub>3</sub>BH] in THF to give quasi-axial C-6β-alcohol 5 in 91% yield.<sup>‡</sup> Selenylation<sup>4</sup> of 5 with *o*-NO<sub>2</sub>PhSeCN and Bun<sub>3</sub>P proceeded with inversion of the stereogenic centre to afford C-6 $\alpha$ -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-8a-hydroxy derivative 7 instead in 89% yield. 7 was subjected to Swern oxidation<sup>5</sup> 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<sub>3</sub>P)<sub>3</sub>RhCl 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.  $(\pm)$ -trans-2-(phenylsulfonyl)-3-phenyloxaziridine)<sup>6</sup>] afforded undesired C-6a-alcohol 11a predominently due to attack of the reagents from the less hindered  $\alpha$ -side. However, a combination of potassium bis(trimethylsilyl)amide (2 equiv.) and (-)-(2S, 8aR)-(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<sub>3</sub>H, THF, -78 °C, 3 h; v, cat. *p*-TsOH-H<sub>2</sub>O, THF-H<sub>2</sub>O (3:1), room temp., 4 d (70% from 11b); vi, Pd(OH)<sub>2</sub> on C, cyclohexene–EtOH (1:1), reflux, 4.5 h (95%)

MeC

HC

MeC

R<sup>1</sup>O

BoC

oxaziridine7 (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<sup>8</sup> correlations between the hydrogen atoms at C-6 and C-15 $\alpha$ . Reduction of C-7 carbonyl in 11b with various reducing agent (e.g. L-Selectride, NaBH<sub>4</sub> in the presence/absence of CeCl<sub>3</sub>, Bu<sup>i</sup><sub>2</sub>AlH, 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<sub>3</sub>H) reduction of TBDMS ether 12 afforded the desired C-7 $\beta$ -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 <sup>1</sup>H NMR, 100 MHz <sup>13</sup>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

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

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