Selenium-Mediated Synthesis of Tetrahydroisoquinoline Ring Systems: Application to the Preparation of 6-Deoxy-2,3-Di-*O*-benzyl Lycoricidine

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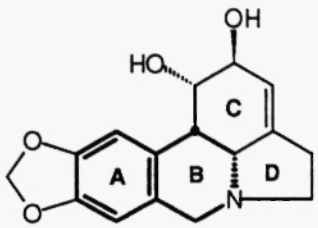
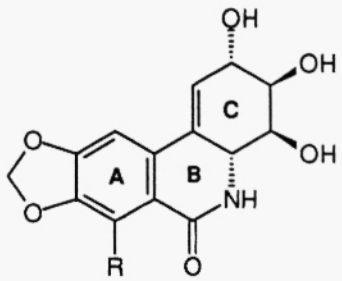
Abstract : A strategy for the synthesis of the tetrahydroisoquinoline skeleton and its application to the synthesis of a protected derivative of 6-deoxy-lycoricidine are described. The key step of this sequence is the selenium mediated B ring closure and subsequent selenoxide elimination to restore the C ring double bond.

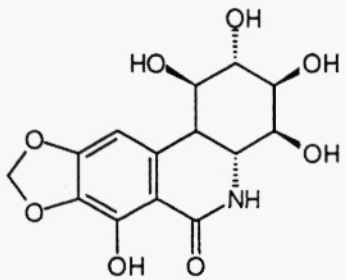
Tetrahydroisoquinolines are the basic skeleton of a number of natural products including alkaloids (1). Several representatives of this class of compounds, isolated from plants of the genus Amaryllidaceae, have in common a unique tetrahydroisoquinoline nucleus (in bold in compound **1**) flanked by another ring with oxygenated substituents (2). Such compounds show interesting antitumor activities (3) in particular those having a highly hydroxylated C ring like lycorine **1**, (4), lycoricidine **2a** (5), narciclasine **2b** (6), or pancratistatin **3** (7).



1 Lycorine



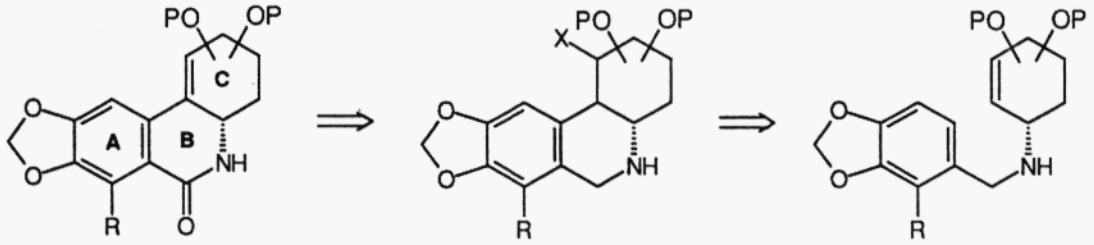
2a R = H Lycoricidine
2b R = OH Narciclasine



3 Pancratistatin

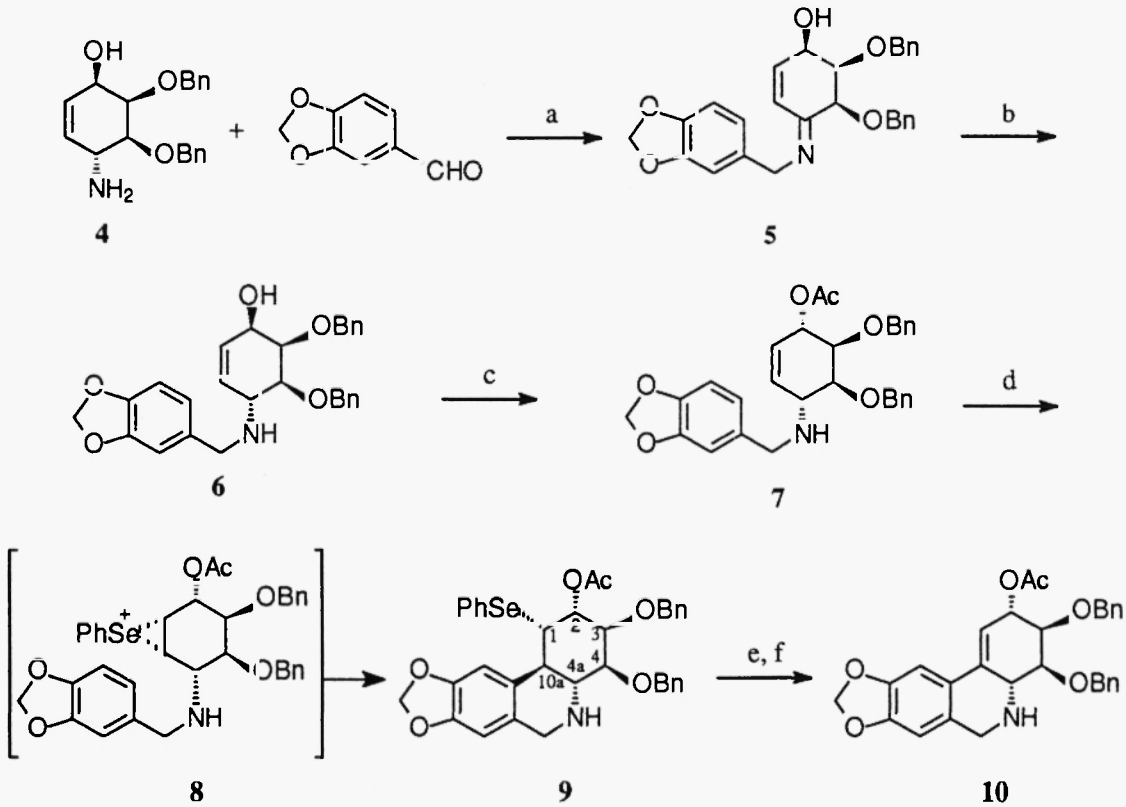
A route to these alkaloids should be devised by formation of the tetrahydroisoquinoline ring system according to the retrosynthetic analysis described in Scheme 1. Several approaches for the construction of the tetrahydroisoquinoline nucleus have been described in the past. Most of the methods of formation of the B-ring are based on the Pomeranz-Fritsch reaction and its variants which require harsh

conditions such as strong acidic medium (1). The reaction conditions are often incompatible with functionalized molecules. Other approaches are based on Friedel-Crafts type reactions (2). Formation of the B-ring of lycoricidine and congeners using the Heck reaction (8), or photocyclisation of enamides (9) have also been reported (10).



Scheme 1

In an effort to open a new route to such heterocycles, we have explored an alternative route using milder conditions and we describe here the synthesis of a protected 6-deoxy lycoricidine derivative. Our route is based on episelenonium ion chemistry. These intermediates have been shown to undergo subsequent electrophilic substitution (11), and have also proved to be attractive for the synthesis of oxazolines derivatives (12).



Scheme 2: Reagents: a) MeOH, rt; b) $NaBH_3CN$, MeOH, 60 % 2 steps; c) PPh_3, AcOH, DEAD, THF, 83%; d) NPSP, $SnCl_4$, CH_2Cl_2, 66 %; e) MCPBA, CH_2Cl_2; f) CH_2Cl_2, reflux, 54% 2 steps

The starting point of this synthesis is the enantiopure aminocyclitol **4** already prepared in our group (13). Amine **4** was condensed with commercially available piperonal to yield an intermediate imine **5** which was reduced *in situ* to the secondary amine **6** (60 %) by sodium cyanoborohydride. Protection of the hydroxyl at C-2 and establishment of the correct stereochemistry of the natural alkaloids was then performed. Thus Mitsunobu acetylation (14), using triphenylphosphine, acetic acid and diethyl azido dicarboxylate (DEAD) in THF gave **7**, with net inversion of configuration at C-2, in 83 % yield. The next key step was the closure of B-ring. Treatment of olefin **7** with N-phenylselenophtalimide (NPSP) in dichloromethane at low temperature in the presence of tin (IV) chloride (12), gave a salt, assumed to be the expected episelenonium ion **8** which smoothly underwent an intramolecular electrophilic substitution at room temperature to yield the selenide **9** (66%) where the phenylselenyl and the aromatic groups were in a *trans* relationship as seen from the large coupling constant between H-1 and H-10a (15). The absolute configuration was tentatively assigned on the basis of a *cis* relationship between H-1 and H-2 (4.5 Hz). This was in agreement with an attack of the double bond π-electrons *anti* to the bulky benzyl protecting groups at O-3 and O-4, one of these group being in an axial or pseudo axial orientation. Moreover complexation of the Lewis acid, associated with the phenylselenyl ion, with the NH group should also orientate attack of the reagent *cis* to the NH group. The remainder of the synthesis consisted in reestablishment of the double bond by transformation of selenide **9** into the corresponding selenoxide by treatment with metachloroperbenzoic acid (MCPBA) (16). Simple heating in dichloromethane afforded the 6-deoxy-2,3-di-O-benzyl lycoricidine **10** in 54 % overall yield (17).

In conclusion, the use of episelenonium chemistry allows the synthesis of the tetrahydroisoquinoline core structure in good yields. This method is compatible with the presence of ester and ether protecting groups. It opens the way to the enantiospecific synthesis of alkaloids of the lycorine series. Studies along these lines are currently in progress in our groups.

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(15) Typical procedure for the preparation of **9** : NPSP (335 mg, 1.1 mmol) was suspended in dry dichloromethane. The solution was cooled to -65°C under nitrogen and $SnCl_4$ (130 µl, 1.1mmol) was added dropwise. After 5 minutes, amine **7** (473mg, 1 mmole) in dichloromethane was added and stirring was continued for 24 h at room temperature. The resulting mixture was diluted with dichloromethane and washed with aqueous $NaHCO_3$ and water. The organic layer was dried over $MgSO_4$ and the solvent evaporated. The crude residue was chromatographed on silica gel using hexane/ethyl acetate mixture (4:3), to give **9**, 415 mg, 66%; R_f = 0.3; m.p 129°C; $[\alpha]_D$ - 41.7 (c, 0.3, $CHCl_3$); I.R. ν_{max} = 3220, 1740 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ : 2.31 (s, 3 H, $COCH_3$); 3.21 (d, 1 H, $J_{NH,4a}$ 11.5 Hz, NH); 3.30 (dd, 1 H, $J_{1,10a}$ 10, $J_{1,2}$ 2 Hz, H-1); 3.58 (m, 1 H, H-4a); 3.62 (m, 1 H, H-4); 3.75 (d, 1 H, J 16 Hz, NCH_2-Ph); 4.05 (m, 2 H, H-3 + H-10a); 4.32 (d, 1 H, J 11 Hz, CH_2-Ph); 4.51 (d, 1H, J 11 Hz, CH_2-Ph); 4.71 (d, 1H, J 11 Hz, CH_2-Ph); 4.89 (d, 1 H, J 11 Hz, NCH_2-Ph); 4.98 (dd, 1 H, $J_{2,3}$ 4.5 Hz, H-2); 5.88 (d, 1 H, J 1Hz, -O-CH_2-O-); 5.93 (d, 1 H, -O-CH_2-O-); 6.57 (s, 1 H, Ar); 6.64 (s, 1 H, Ar); 7.2-7.6 (m, 15 H, Ar). Anal. Calc for $C_{36}H_{35}NO_6Se$: C, 65.9, H, 5.4; N, 2.1; Found: C, 65.95, H, 5.86; N, 2.66

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(17) Analytical data of **10**: R_f = 0.28 (H/A, 1/1); $[\alpha]_D$ + 21.5 (c, 0.2, $CHCl_3$) ; I.R. ν_{max} = 3400, 1650 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ : 2.5 (s, 3 H, $COCH_3$); 2.80 (broad s, 1 H, NH); 3.20 (d, 1 H, J 16 Hz, NCH_2-Ph); 3.67 (d, 1 H, $J_{2,3}$ 10 Hz, H-3); 4.33 (m, 2 H, H-4a, H-4); 4.61 (d, 1 H, J 11 Hz, CH_2-Ph); 4.68 (d, 1 H, J 11 Hz, CH_2-Ph); 4.78 (d, 1H, J 11 Hz, CH_2-Ph); 5.13 (m, 2 H, H-2 + CH_2Ph); 5.30 (d, 1 H, J 16 Hz, NCH_2-Ph); 5.61 (m, 1 H, H-1); 5.92 (s, 2 H, -O-CH_2-O-); 6.67 (s, 1 H, Ar); 6.80 (s, 1 H, Ar); 7.2-7.4 (10 H, Ar); Anal. Calc for $C_{30}H_{29}NO_6$: C, 72.1, H, 5.9; N, 2.8; Found: C, 71.79, H, 6.02; N, 2.93.

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