BIOMIMETIC SYNTHESIS OF (-)-DEOXYRHEXIFOLINE, (-)-TECOSTIDINE, AND (-)-ACTINIDINE

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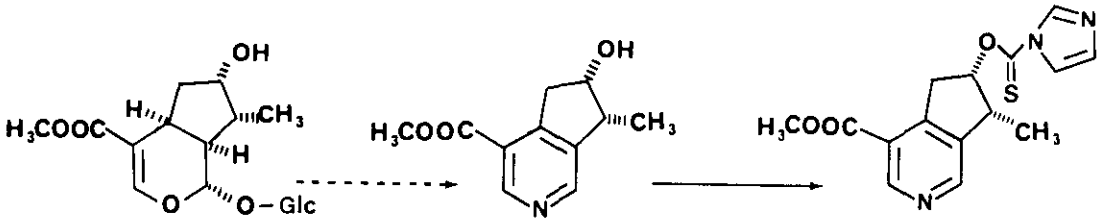
Abstract - The title monoterpene pyridine alkaloids were synthesized by transformations of the iridoid glycoside loganin.

Deoxyrhexifoline (1) is a monoterpene pyridine alkaloid recently isolated from *Castilleja rhexifolia* (Scrophulariaceae),[2] whose absolute configuration could not be determined due to the very small amount of isolated material.[3] (S)-(-)-Tecostidine (2) has been isolated from *Tecoma stans* (Bignoniaceae)[4] and its absolute configuration was deduced from the synthesis of its R-(+)-enantiomer.[5] (S)-(-)-Actinidine (3) occurs naturally in various species of Actinidiaceae[6,7] and Valerianaceae.[8-10] It has been reported as a powerful feline attractant.[11] The synthesis of its racemate has been described[12,13] and that of its (R)-(+)-isomer permitted to ensure its absolute configuration.[14,15] Its natural (S)-(-)-form has been prepared from nepetalinic acid[6] and from iridodial.[16] We wish to describe here a simple chiral pool synthesis of the (S)-(-)-forms of these three pyridine alkaloids, using commercially available loganin as starting material.

We have previously reported[17] that hydrolysis of loganin (4) by β-glucosidase followed by amination of the resulting aglycone by gaseous NH_3 led in almost quantitative yield to an equimolecular mixture of tetrahydrocantleyine and cantleyine (5), readily separable by column chromatography. Considering a polyfunctional compound such as cantleyine, the radical deoxygenation[18] of the alcoholic function at C-7 seemed the most suitable method to obtain readily deoxyrhexifoline. Consequently, cantleyine (5) was converted into its thioimidazolide (6) in 46% yield by treatment with N,N'-thiocarbonyldiimidazole.[19,20]

Radical deoxygenation by tributyltin hydride[19,20] of 6 led to (S)-(-)-deoxyrhexifoline (1) in 78% yield. Borohydride reduction of (S)-(-)-deoxyrhexifoline (1) afforded (S)-(-)-tecostidine (2) in 30% yield. Acetylation of 2 led to the corresponding acetate (7) in 70% yield. Finally, catalytic hydrogenolysis of 7 permitted to obtain (S)-(-)-actinidine (3)[6,21] in 93% yield.



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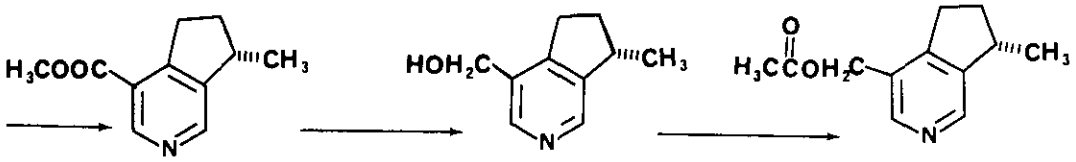

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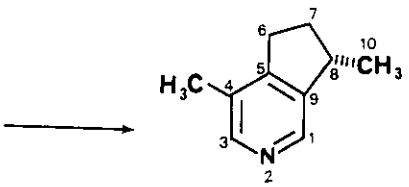

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EXPERIMENTAL

Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Spectra were recorded on the following apparatus : uv, Unicam SP 800; ms, Nermag R-10-10C in desorption-chemical ionisation (reagent gas : NH_3); ^{1}H-nmr, Bruker HX 270 (270 MHz). Chemical shifts are reported in δ value (ppm) relative to TMS as internal standard. The following abbreviations are used : s = singlet, d = doublet, q = quartet, m = multiplet. Column chromatography was carried out on silica gel 60H Merck.

7-O-Thiocarbonylimidazoylcantleyine (6) : To a solution of cantleyine (5) (100 mg, 0.48 mmol) in CH_2Cl_2 (10 ml), was added N,N'-thiocarbonyldiimidazole (500 mg, 2.80 mmol). The mixture was heated under reflux with stirring for 3 h. Evaporation of the solvent followed by column chromatography (solvent: CH_2Cl_2-MeOH, 95:5) gave 6 as a foam (70 mg, 46%), $[\alpha]_D^{20}$ -24° (c 0.2, $CHCl_3$); uv: λ_{max} (MeOH): 270 nm; ms (dci): 318 $(M+H)^+$, 190; ^{1}H-nmr ($CDCl_3$): 9.12 (1H, s, H-3), 8.66 (1H, s, H-1), 8.26 (1H, s, H-2'), 7.51 (1H, d, J=3Hz, H-5'), 7.02 (1H, d, J=3Hz, H-4'), 6.28 (1H, ddd, J=7Hz, J'=5Hz, J"=3Hz, H-7), 4.00 (3H, s, $COOCH_3$), 3.73 (3H, m, H-6a, H-6b, H-8), 1.51 (3H, d, J=8Hz, CH_3-10). Anal. Calcd for $C_{15}H_{15}N_3O_3S$: C, 56.7; H, 4.76; N, 13.24. Found: C, 56.61; H, 4.68; N, 13.18.

(S)-(-)-Deoxyrhexifoline (1) : To a solution of 6 (70 mg, 0.22 mmol) and azabisisobutyronitrile (40 mg, 0.29 mmol) in toluene (10 ml), was added dropwise tributyltin hydride (0.6 ml) in toluene (10 ml). The mixture was then heated under reflux under Ar for 15 min. Evaporation of the solvent followed by purification by column chromatography (solvent: CH_2Cl_2-MeOH 99:1) yielded 1 as a foam (33 mg, 78%), $[\alpha]_D^{20}$ -18° (c 0.3, $CHCl_3$); uv: λ_{max} (MeOH): 270 nm; ms (dci): 192 $(M+H)^+$; ^{1}H-nmr ($CDCl_3$): 8.99 (1H, s, H-3), 8.54 (1H, s, H-1), 3.94 (3H, s, $COOCH_3$), 3.40 (1H, ddd, J=18Hz, J'=8Hz, J"=4Hz, H-6a), 3.31 (1H, dqd, J=8Hz, J'=7Hz, J"=1Hz, H-8), 3.14 (1H, ddd, J=18Hz, J'=8Hz, J"=3Hz, H-6b), 2.40 (1H, m, H-7b), 1.68 (1H, m, H-7a), 1.35 (3H, d, J=7Hz, CH_3-10); spectral data identical with those of the natural coumpound.

(S)-(-)-Tecostidine (2) : Sodium borohydride (600 mg, 15.8 mmol) was added to a stirred solution of 1 (287 mg, 1.50 mmol) in MeOH at 0°C. After 12 h, the

reaction mixture was neutralized by addition of Amberlite IRC 50 H^+ ion exchange resin. The solvent was removed under reduced pressure. Column chromatography (solvent: CH_2Cl_2-MeOH 95:5) of the residue afforded 2 as a foam (74 mg, 30%), $[\alpha]_D^{20}$ -6° (c 0.5, $CHCl_3$); uv: λ_{max} (MeOH): 260, 269 nm; ms (dci): 164 $(M+H)^+$; ^{1}H-nmr ($CDCl_3$): 8.36 (2H, br.s, H-1, H-3), 4.72 (2H, s, CH_2OH), 3.30 (1H, qdd, J=7Hz, J'=6Hz, J"=1Hz, H-8), 3.02 (1H, ddd, J=17Hz, J'=9Hz, J"=4Hz, H-6a), 2.91 (1H, ddd, J=17Hz, J'=9Hz, J"=1Hz, H-6b), 2.38 (1H, m, H-7b), 1.69 (1H, m, H-7a), 1.34 (3H, d, J=7Hz, CH_3-10).

(S)-(-)-Acetyltecostidine (7) : Acetic anhydride (2 ml, 21 mmol) was added to a solution of 2 (42 mg, 0.25 mmol) in pyridine (2 ml) and the mixture was left at 25°C for 48 h. Removal of the solvent followed by column chromatography (solvent: hexanes-EtOAc 50:50) afforded 7 as a foam (37 mg, 70%), $[\alpha]^{20}$-5° (c 0.3, $CHCl_3$); uv: λ_{max} (MeOH): 260 nm; ms (dci): 206 $(M+H)^+$, 191, 150, 130; ^{1}H-nmr ($CDCl_3$): 8.40 (1H, s, H-3), 8.37 (1H, s, H-1), 5.12 (2H, s, CH_2OAc), 3.30 (1H, qdd, J=7Hz, J'=6Hz, J"=1Hz, H-8), 3.00 (1H, ddd, J=16Hz, J'=8Hz, J"=4Hz, H-6a), 2.88 (1H, dd, J=16Hz, J'=9Hz, H-6b), 2.38 (1H, m, H-7b), 2.11 (3H, s, OAc), 1.67 (1H, m, H-7a), 1.35 (3H, d, J=7Hz, CH_3-10). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.12; H, 7.31; N, 6.87.

(S)-(-)-Actinidine (3) : A solution of 7 (30 mg, 0.15 mmol) in AcOH (2 ml) containing 10% Pd-C (30 mg) was submitted to hydrogenolysis (H_2, 1 atm.) at 25°C for 2h. After filtration over celite, evaporation of the solvent under reduced pressure afforded 3 as a foam (20 mg, 93%), $[\alpha]_D^{20}$ -7° (c 0.1, $CHCl_3$); spectral data identical with those previously published.[6,21]

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