

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

Yvonne Ranarivelo,¹ Françoise Hotellier, Alexios-Léandros Skaltsounis,
and François Tillequin*

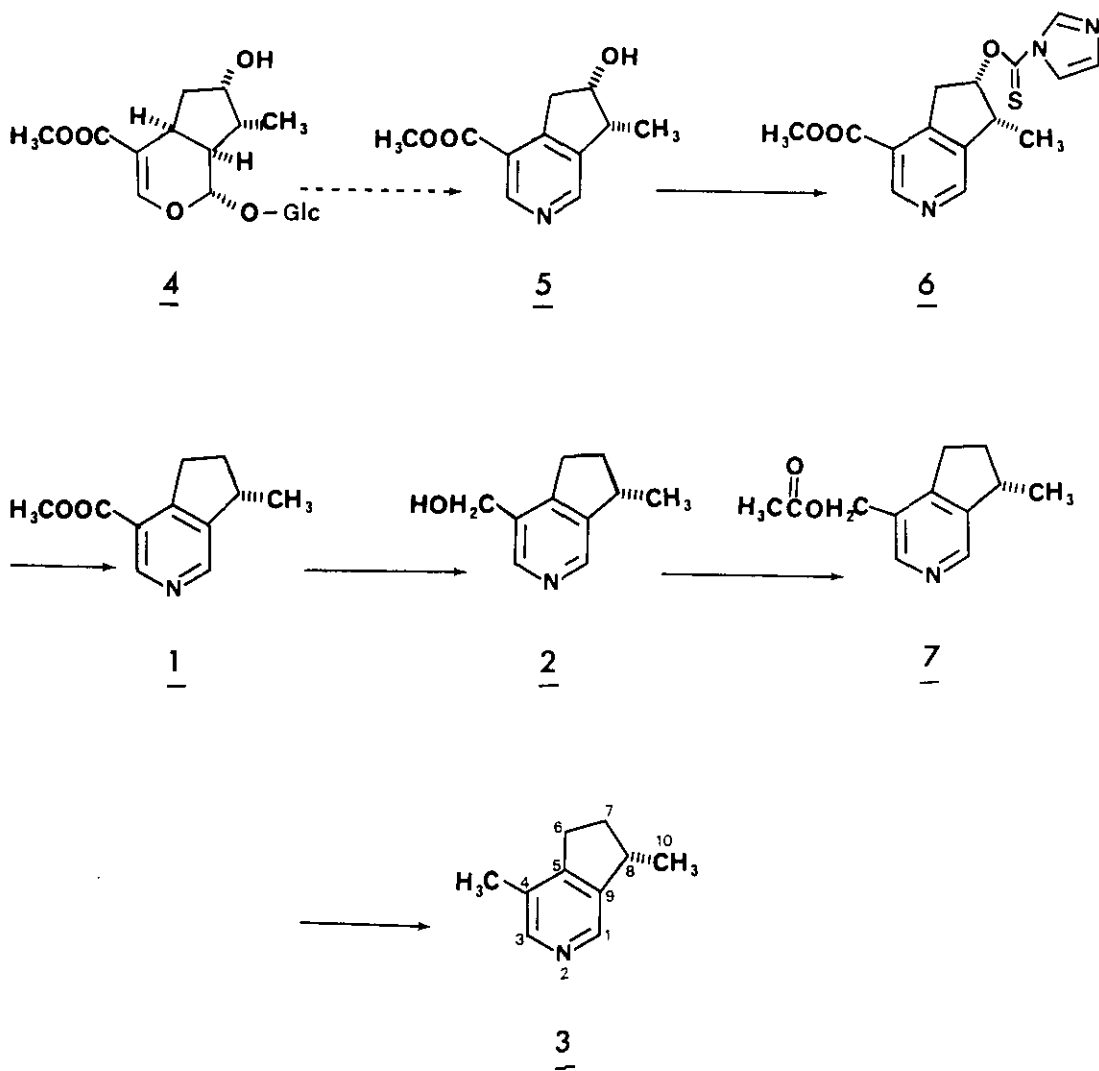
Département de Pharmacognosie de l'Université René Descartes, U.R.A. au
C.N.R.S. n° 1310, Faculté des Sciences Pharmaceutiques et Biologiques,
4, Avenue de l'Observatoire, F - 75006 Paris, France

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)-(-)-Tecos-
tidine (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 Vale-
rianaceae.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 acid⁶ 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 reported¹⁷ 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 tetrahydrocantlyne and
cantlyne (5), readily separable by column chromatography. Considering a poly-
functional compound such as cantleyne, the radical deoxygenation¹⁸ of the
alcoholic function at C-7 seemed the most suitable method to obtain readily
deoxyrhexifoline. Consequently, cantleyne (5) was converted into its thioimida-
zolid (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.



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); ^1H -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-Thiocarbonylimidazolcantlyne (6) : To a solution of cantleyine (5) (100 mg, 0.48 mmol) in CH_2Cl_2 (10 ml), was added $\text{N,N}'$ -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%), $(\alpha)_D^{20} -24^\circ$ (c 0.2, CHCl_3); uv: λ_{max} (MeOH): 270 nm; ms (dci): 318 ($\text{M}+\text{H}^+$), 190; ^1H -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, $J=3\text{Hz}$, H-5'), 7.02 (1H, d, $J=3\text{Hz}$, H-4'), 6.28 (1H, ddd, $J=7\text{Hz}$, $J'=5\text{Hz}$, $J''=3\text{Hz}$, H-7), 4.00 (3H, s, COOCH_3), 3.73 (3H, m, H-6a, H-6b, H-8), 1.51 (3H, d, $J=8\text{Hz}$, CH_3 -10). Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3\text{S}$: 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 azabis-isobutyronitrile (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%), $(\alpha)_D^{20} -18^\circ$ (c 0.3, CHCl_3); uv: λ_{max} (MeOH): 270 nm; ms (dci): 192 ($\text{M}+\text{H}^+$); ^1H -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, $J=18\text{Hz}$, $J'=8\text{Hz}$, $J''=4\text{Hz}$, H-6a), 3.31 (1H, dqd, $J=8\text{Hz}$, $J'=7\text{Hz}$, $J''=1\text{Hz}$, H-8), 3.14 (1H, ddd, $J=18\text{Hz}$, $J'=8\text{Hz}$, $J''=3\text{Hz}$, H-6b), 2.40 (1H, m, H-7b), 1.68 (1H, m, H-7a), 1.35 (3H, d, $J=7\text{Hz}$, CH_3 -10); spectral data identical with those of the natural compound.

(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: CH₂Cl₂-MeOH 95:5) of the residue afforded 2 as a foam (74 mg, 30%), [α]_D²⁰ -6° (c 0.5, CHCl₃); uv: λ_{\max} (MeOH): 260, 269 nm; ms (dci): 164 (M+H)⁺; ¹H-nmr (CDCl₃): 8.36 (2H, br.s, H-1, H-3), 4.72 (2H, s, CH₂OH), 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, CH₃-10).

(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%), [α]_D²⁰ -5° (c 0.3, CHCl₃); uv: λ_{\max} (MeOH): 260 nm; ms (dci): 206 (M+H)⁺, 191, 150, 130; ¹H-nmr (CDCl₃): 8.40 (1H, s, H-3), 8.37 (1H, s, H-1), 5.12 (2H, s, CH₂OAc), 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, CH₃-10). Anal. Calcd for C₁₂H₁₅N₂O₂: 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 (H₂, 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%), [α]_D²⁰ -7° (c 0.1, CHCl₃); spectral data identical with those previously published.^{6,21}

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