

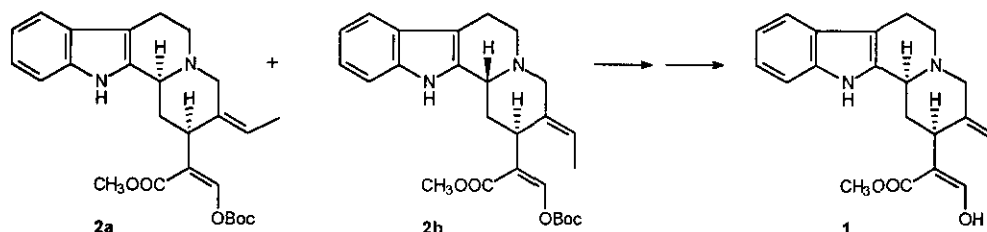
SYNTHESIS OF ($\pm$)-CATHENAMINE AND ($\pm$)-19-EPI-CATHENAMINE, ISOLATED AS THEIR C-21 α -CYANO DERIVATIVES

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Abstract - A short synthetic route from the easily accessible *O*-Boc-*Z*-geissoschizine (**2a**) to ($\pm$)-catenamine (**3**) and ($\pm$)-19-epicatenamine (**4**) is presented. Both compounds, which are important biogenetic intermediates in the formation of heteroyohimbine alkaloids, were isolated as their synthetic equivalents, ($\pm$)-21 α -cyanotetrahydroalstonine (**5**) and ($\pm$)-21 α -cyano-19-epiajmalicine (**6**), respectively.

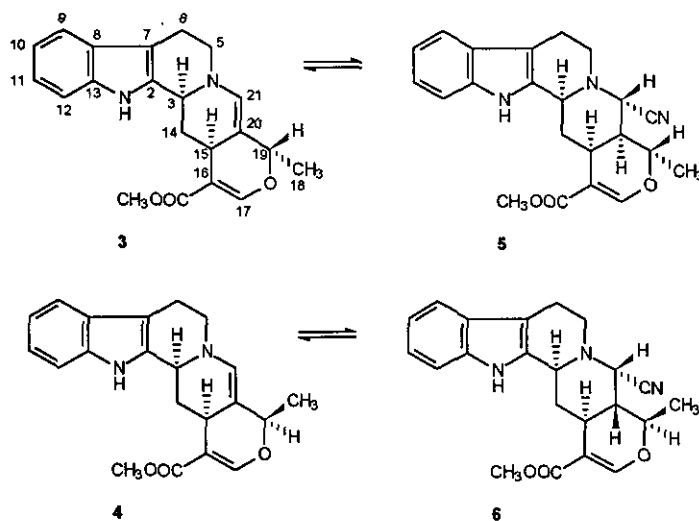
We recently presented a short synthetic route to ($\pm$)-geissoschizine (**1**) from the easily accessible mixture (~9:1) of *O*-Boc-*Z*-geissoschizine (**2a**) and *O*-Boc-3-*epi-E*-geissoschizine (**2b**) (Scheme 1).¹



Scheme 1.

We have now used *O*-Boc-*Z*-geissoschizine (**2a**) in the preparation of catenamine (**3**) and 19-epicatenamine (**4**), which are important biogenetic intermediates for heteroyohimbine alkaloids.²⁻⁹ The relatively reactive

($\pm$)-cathenamine (3) and ($\pm$)-19-epicathenamine (4) were isolated as their 21 α -cyano derivatives, ($\pm$)-21 α -cyanotetrahydroalstonine (5) and ($\pm$)-21 α -cyano-19-epiajmalicine (6), respectively, from which compounds (3) and (4) can subsequently be regenerated (Scheme 2).²



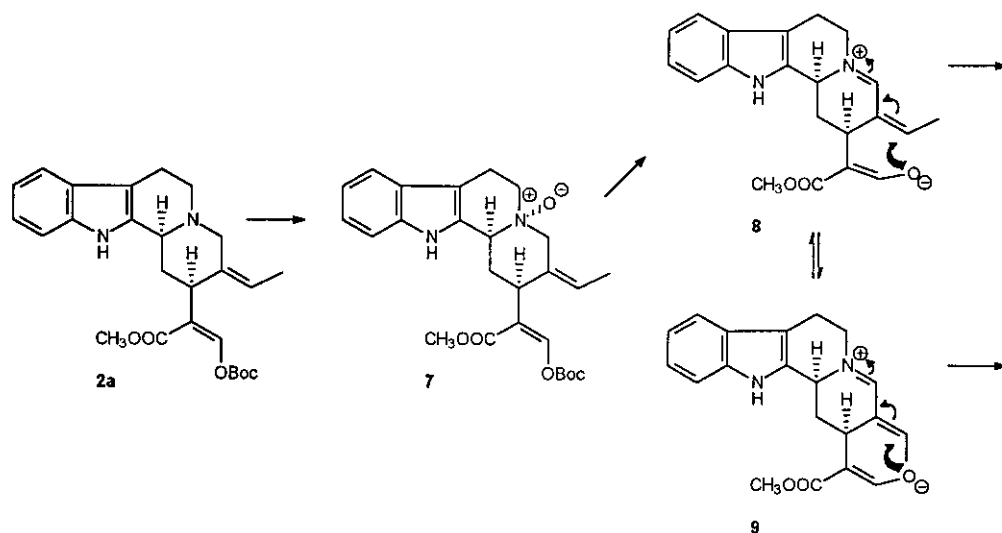
Scheme 2.

RESULTS AND DISCUSSION

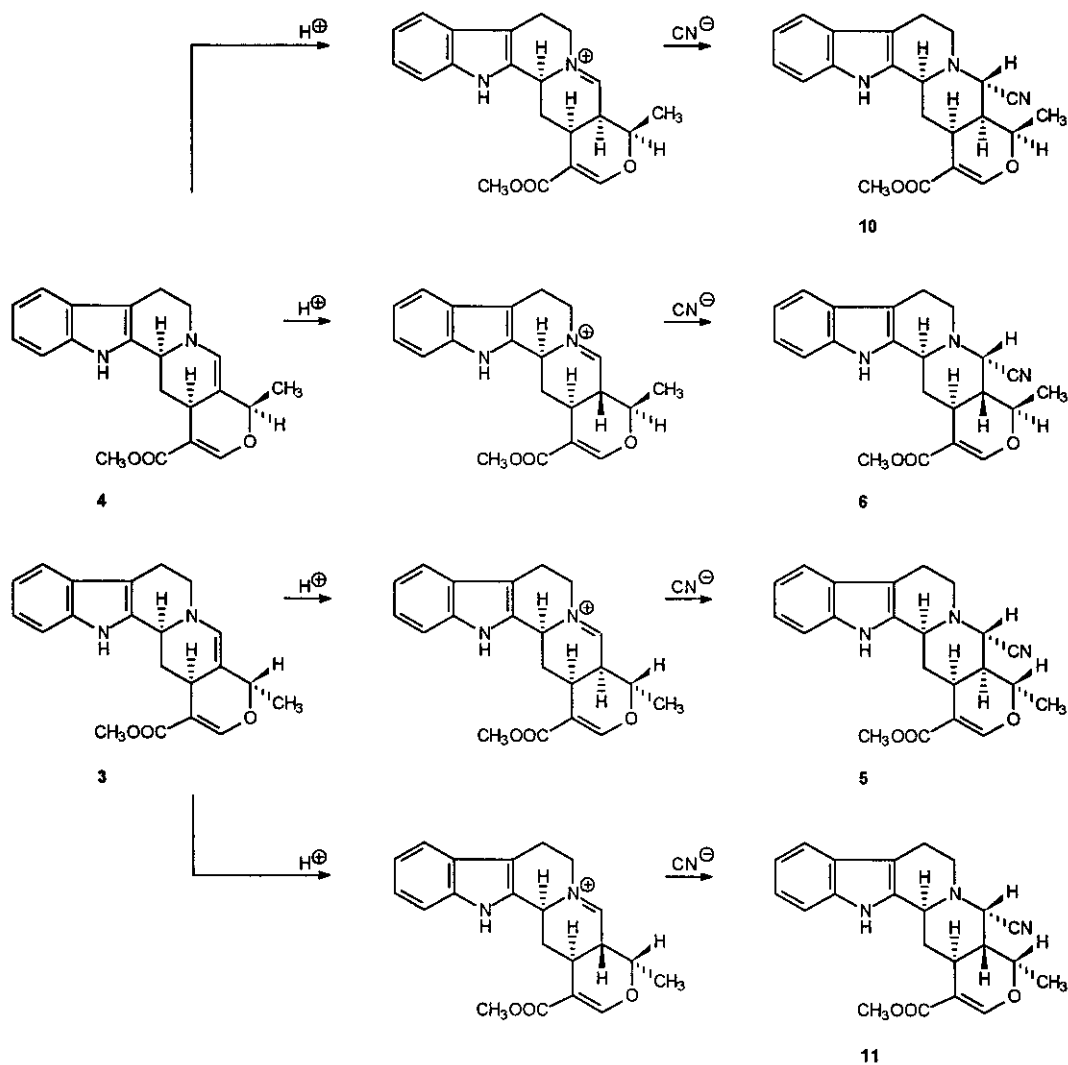
Oxidation of carefully purified *O*-Boc-*Z*-geissoschizine (2a) with *m*-chloroperbenzoic acid afforded the corresponding *cis*-*N_b*-oxide (7).¹ Treatment of compound (7) with trifluoroacetic anhydride (TFAA; Polonovski-Potier reaction), followed by KCN trapping under carefully controlled conditions (*vide infra*),¹⁰⁻¹³ yielded ($\pm$)-21 α -cyanotetrahydroalstonine (5) and ($\pm$)-21 α -cyano-19-epiajmalicine (6) (Scheme 3).

Mechanistically, the formation of a 21 α -cyanoheteroyohimbine structure can be described as the formation of $\Delta^{4(21)}$ iminium ion followed by *O*-Boc

cleavage [intermediate (8)], Michael addition, protonation, and cyano trapping. The stereochemical conditions are such that the Michael addition can take place only from the β -face [when the racemic intermediates are presented as in formulae (8) and (9)]. In the case of a *Z*-ethylidene side-chain [intermediate (8)] this means H-19 α stereochemistry, and after cyano trapping 21 α -cyano-19-epiajmalicine (6) [and/or 21 α -cyanorauniticine (10)]. For the formation of the corresponding compounds possessing the H-19 β stereochemistry, i.e. 21 α -cyanotetrahydroalstonine (5) [and/or 21 α -cyanoajmalicine (11)], the ethylidene side-chain must possess the *E*-configuration. Since 21 α -cyanotetrahydroalstonine (5) was found among the reaction products [(5)/(6); 3/1], partial isomerization of the *Z*-ethylidene side-chain to the *E*-ethylidene side-chain [intermediate (9)] must have taken place before the cyclization (Scheme 3).



Scheme 3 (continues next page).



Scheme 3 (contd).

The spectral data of compounds (**5**) and (**6**) (*vide infra*), support the presented structures. Especially, the ^{13}C -NMR spectra (Figure 1), compared with earlier results,¹⁴⁻¹⁸ are in good agreement with the proposed structures.

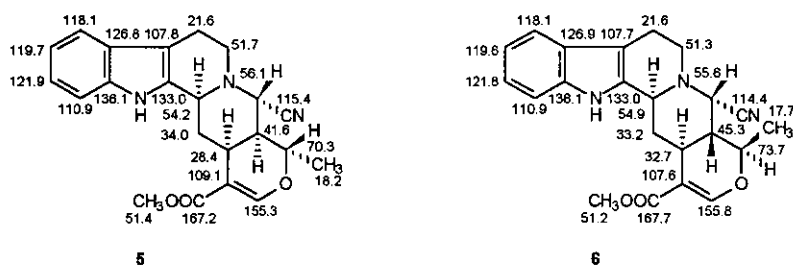


Figure 1. ^{13}C -NMR spectral data of compounds (5) and (6).

CONCLUSIONS

An easy method is now available for the preparation of ($\pm$)-cathenamine (3) and ($\pm$)-19-epicathenamine (4), isolable as their synthetic equivalents, ($\pm$)-21 α -cyanotetrahydroalstonine (5) and ($\pm$)-21 α -cyano-19-epialjmalicine (6).

For an alternative strategy for the preparation of ($\pm$)-cathenamine (3), see Ref. 19.

EXPERIMENTAL

IR spectra were recorded with a Perkin-Elmer 700 spectrophotometer in CHCl_3 . IR absorption bands are given in reciprocal centimetres (cm^{-1}). ^1H - and ^{13}C -NMR spectra were measured in CDCl_3 with a Varian Unity-400 NMR spectrometer working at 399.952 MHz (^1H -NMR) and 100.577 MHz (^{13}C -NMR). Chemical shifts are given in ppm by reference to TMS (^1H -NMR; $\delta_{\text{H}}=0.0$ ppm) and CDCl_3 (^{13}C -NMR; $\delta_{\text{C}}=77.0$ ppm). Signal assignments were confirmed by APT experiments. Abbreviations s, d, t, q, m, and br are used to designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. For the ^{13}C -NMR data, see Figure 1. Mass spectrometry (EIMS and HRMS) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of (±)-21 α -cyanotetrahydroalstonine (5) and (±)-21 α -cyano-19-epiajmalicine (6). Compound (7) (237 mg, 0.51 mmol) was dissolved in CH₂Cl₂ (10 mL) and the mixture cooled to -15°C (Ar atm). Freshly distilled trifluoroacetic anhydride (TFAA) (0.18 mL, 1.28 mmol) was added under stirring during 5 min. Stirring was continued for 2 h at 0°C (ice-bath). KCN (98 mg, 1.50 mmol), predissolved in H₂O (4 mL), was added and the pH of the mixture was adjusted to 5 (ACONa). Stirring was continued for 1.5 h at rt. Na₂CO₃ solution (10%) was added until the pH of the mixture was 10. Stirring was continued for 10 min and the phases were separated. After normal work-up compounds (5) and (6) were purified by repeated TLC (silica gel, CH₂Cl₂/MeOH; 99/1).

(±)-21 α -Cyanotetrahydroalstonine (5). Yield: 28 mg (15%). mp: 232-233°C (EtOH) [lit.,² 231-232°C (MeOH) for (-)-5]. IR: 2250 (s, CN), 1690 (br s, C=O). ¹H-NMR²⁰: 1.42 (3H, d, J_{18,19}=6 Hz, H-18), 1.54 (1H, ddd, J_{3,14 β} =12 Hz, J_{14 α ,14 β} =14 Hz, J_{14 β ,15 β} =12 Hz, H-14 β), 1.98 (1H, ddd, J_{15,20}=4 Hz, J_{19,20}=10 Hz, J_{20,21 β} =2 Hz, H-20), 2.57 (1H, ddd, J_{3,14 α} =4 Hz, J_{14 α ,14 β} =14 Hz, J_{14 α ,15}=4 Hz, H-14 α), 3.15 (1H, ddd, J_{14 α ,15}=4 Hz, J_{14 β ,15}=12 Hz, J_{15,20}=4 Hz, H-15), 3.77 (3H, s, COOCH₃), 4.01 (1H, br d, J_{3,14 β} =12 Hz, H-3), 4.16 (1H, d, J_{20,21 β} =2 Hz, H-21 β), 4.43 (1H, qd, J_{18,19}=6 Hz, J_{19,20}=10 Hz, H-19), 7.09 (1H, dd, J_{9,10}=7 Hz, J_{10,11}=7 Hz, H-10), 7.15 (1H, dd, J_{10,11}=7 Hz, J_{11,12}=7 Hz, H-11), 7.30 (1H, d, J_{11,12}=7 Hz, H-12), 7.46 (1H, d, J_{9,10}=7 Hz, H-9), 7.54 (1H, s, H-17), 7.80 (1H, br s, NH). ¹³C-NMR, see Figure 1. MS: 377 (M⁺, 100%), 350, 335, 249, 224, 209, 170, 169, 156. HRMS: Calcd for C₂₂H₂₃N₃O₃ 377.1739. Found: 377.1755. Anal. Calcd for C₂₂H₂₃N₃O₃: C, 70.01; H, 6.14; N, 11.13. Found C, 69.82; H, 6.18; N, 10.96.

(±)-21 α -Cyano-19-epiajmalicine (6). Yield: 9 mg (5%). Amorphous [lit.,³ 260°C (EtOH) for (+)-6]. IR: 2250 (s, CN), 1710 (br s, C=O). ¹H-NMR: 1.28 (1H, ddd, J_{3,14 β} =7 Hz, J_{14 α ,14 β} =12 Hz, J_{14 β ,15}=12 Hz, H-14 β), 1.45 (3H, d, J=6

Hz, H-18), 1.95 (1H, ddd, $J_{15,20}=11$ Hz, $J_{19,20}=11$ Hz, $J_{20,21}=4$ Hz, H-20), 3.06 (1H, br dd, $J_{14\beta,15}=11$ Hz, $J_{15,20}=11$ Hz, H-15), 3.21 (1H, ddd, $J_{3,14\alpha}=3$ Hz, $J_{14\alpha,14\beta}=12$ Hz, $J_{14\alpha,15}=3$ Hz, H-14 α), 3.75 (3H, s, COOCH₃), 3.90 (1H, dd, $J_{3,14\alpha}=3$ Hz, $J_{3,14\beta}=7$ Hz, H-3), 4.06 (1H, qd, $J_{18,19}=6$ Hz, $J_{19,20}=11$ Hz, H-19), 4.13 (1H, d, $J_{20,21\beta}=4$ Hz, H-21 β), 7.10 (1H, dd, $J_{9,10}=7$ Hz, H-10), 7.16 (1H, dd, $J_{10,11}=7$ Hz, $J_{11,12}=7$ Hz, H-11), 7.32 (1H, d, $J_{11,12}=7$ Hz, H-12), 7.47 (1H, d, $J_{9,10}=7$ Hz, H-9), 7.57 (1H, s, H-17), 7.96 (1H, br s, NH). ¹³C-NMR data, see Figure 1. MS: 377 (M⁺, 100%), 350, 335, 249, 224, 209, 170, 169, 156. HRMS: Calcd for C₂₂H₂₃N₃O₃: 377.1739. Found: 377.1735. Anal. Calcd for C₂₂H₂₃N₃O₃: C, 70.01; H, 6.14; N, 11.13. Found C, 69.80; H, 6.22; N, 10.86.

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 20. Note! Some earlier reported ^1H -NMR shifts for compound (5),² especially those of H-17 and H-18, have been rectified.

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