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

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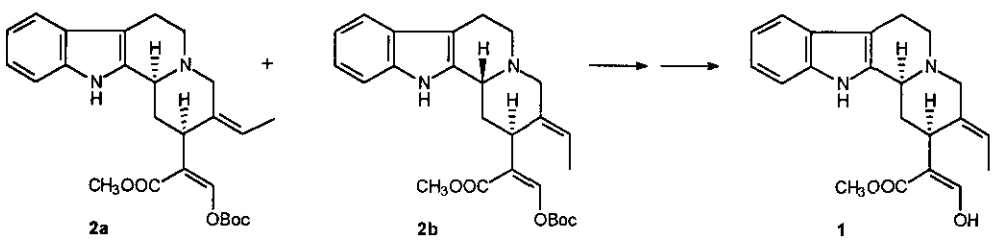
Abstract - A short synthetic route from the easily accessible *O*-Boc-*Z*-geissoschizine (**2a**) to (±)-cathenamine (**3**) and (±)-19-epicathenamine (**4**) is presented. Both compounds, which are important biogenetic intermediates in the formation of heteroyohimbine alkaloids, were isolated as their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

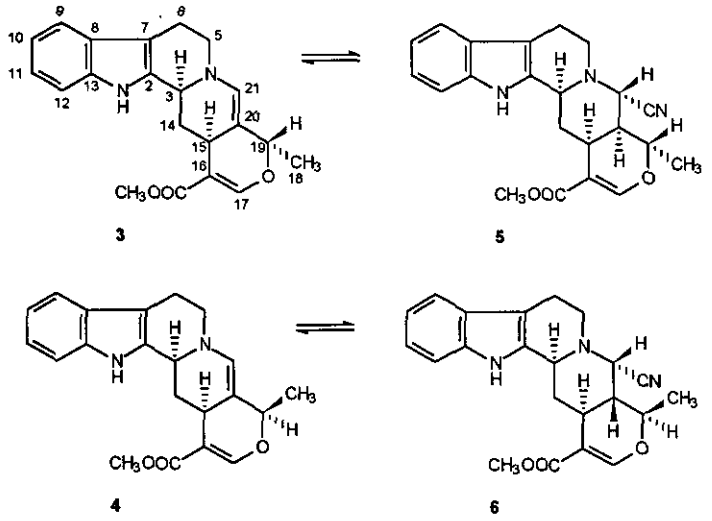
We recently presented a short synthetic route to (±)-geissoschizine (**1**) from the easily accessible mixture (~9:1) of *O*-Boc-*Z*-geissoschizine (**2a**) and *O*-Boc-3-epi-*E*-geissoschizine (**2b**) (Scheme 1).[1]



Scheme 1.

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

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



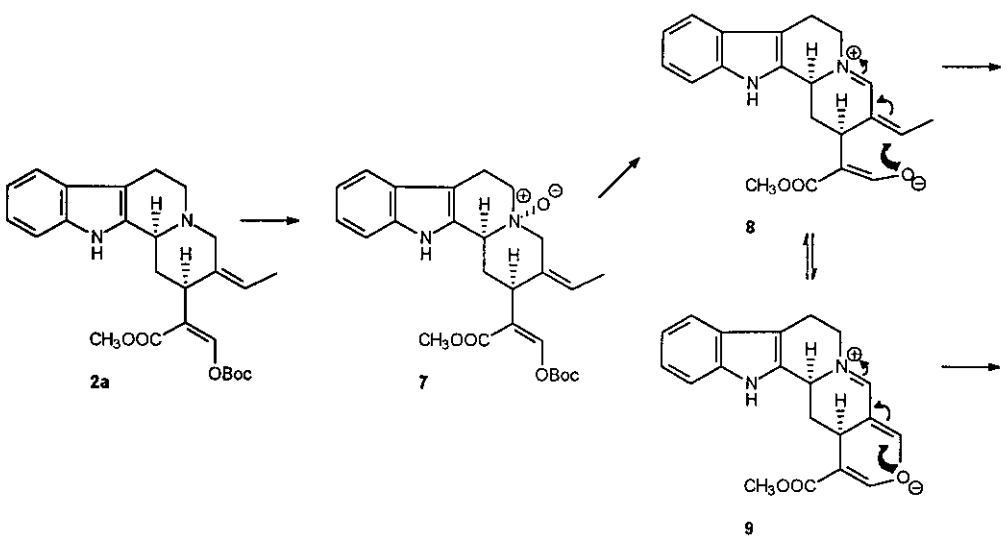
Scheme 2.

RESULTS AND DISCUSSION

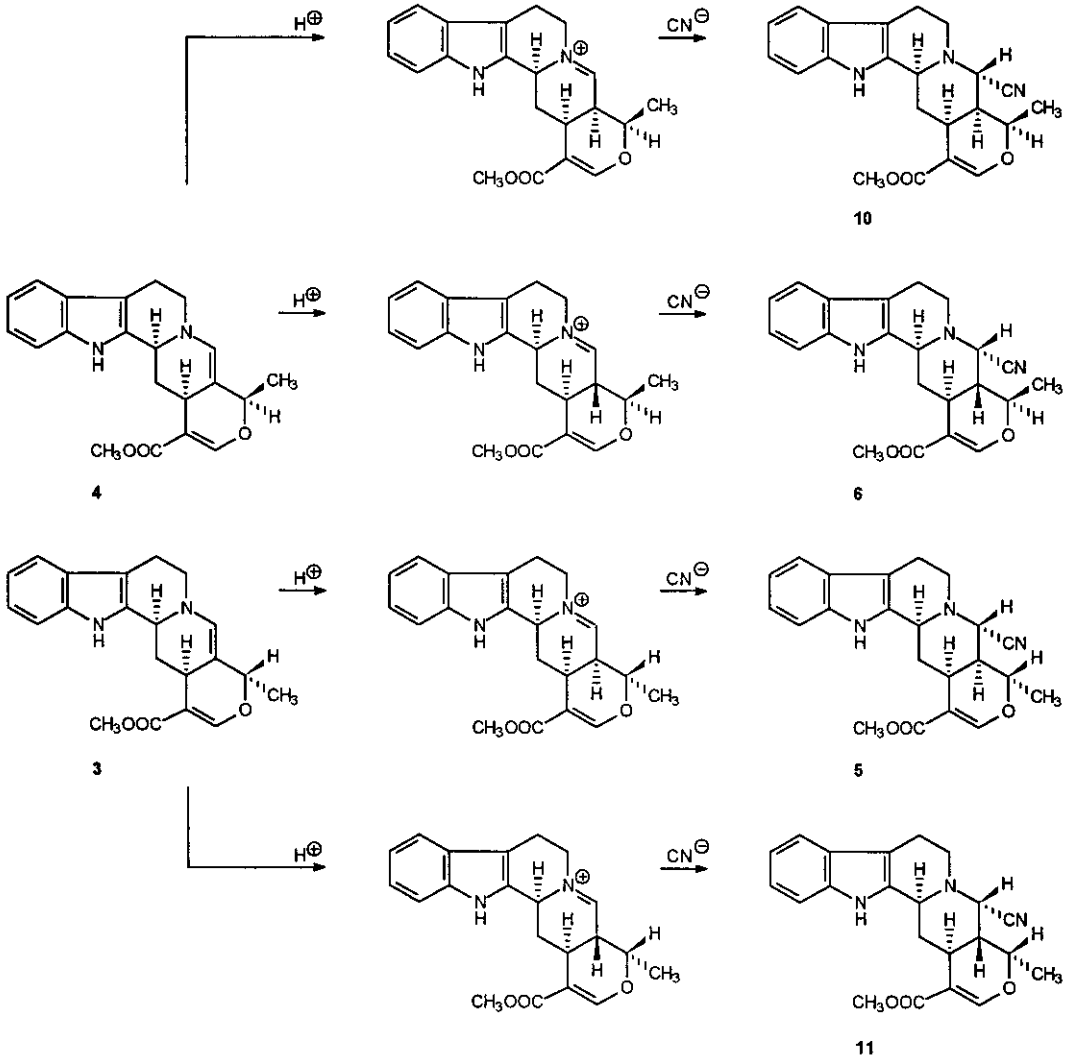
Oxidation of carefully purified *O*-Boc-*Z*-geissoschizine (**2a**) with *m*-chloroperbenzoic acid afforded the corresponding *cis*-N_b-oxide (**7**).[1] Treatment of compound (**7**) with trifluoroacetic anhydride (TFAA; Polonovski-Potier reaction), followed by KCN trapping under carefully controlled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

Mechanistically, the formation of a 21α-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-19α stereochemistry, and after cyano trapping 21α-cyano-19-epiajmalicine (**6**) [and/or 21α-cyanorauniticine (**10**)]. For the formation of the corresponding compounds possessing the H-19β stereochemistry, *i.e.* 21α-cyanotetrahydroalstonine (**5**) [and/or 21α-cyanoajmalicine (**11**)], the ethylidene side-chain must possess the *E*-configuration. Since 21α-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).

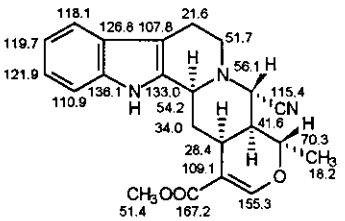


Scheme 3 (continues next page).



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.



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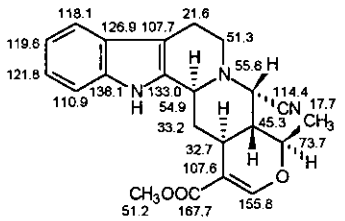

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Figure 1. ^{13}C-NMR spectral data of compounds (**5**) and (**6**).

CONCLUSIONS

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

For an alternative strategy for the preparation of (±)-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}). ^{1}H- and ^{13}C-NMR spectra were measured in $CDCl_3$ with a Varian Unity-400 NMR spectrometer working at 399.952 MHz (^{1}H-NMR) and 100.577 MHz (^{13}C-NMR). Chemical shifts are given in ppm by reference to TMS (^{1}H-NMR; δ_H=0.0 ppm) and $CDCl_3$ (^{13}C-NMR; δ_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 (±)-21α-cyanotetrahydroalstonine (5) and (±)-21α-cyano-19-epiajmalicine (6). Compound (7) (237 mg, 0.51 mmol) was dissolved in CH_2Cl_2 (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 H_2O (4 mL), was added and the pH of the mixture was adjusted to 5 (AcONa). Stirring was continued for 1.5 h at rt. Na_2CO_3 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, CH_2Cl_2/MeOH; 99/1).

(±)-21α-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). ^{1}H-NMR[20]: 1.42 (3H, d, $J_{18,19}$=6 Hz, H-18), 1.54 (1H, ddd, $J_{3,14\beta}$=12 Hz, $J_{14\alpha,14\beta}$=14 Hz, $J_{14\beta,15\beta}$=12 Hz, H-14β), 1.98 (1H, ddd, $J_{15,20}$=4 Hz, $J_{19,20}$=10 Hz, $J_{20,21\beta}$=2 Hz, H-20), 2.57 (1H, ddd, $J_{3,14\alpha}$=4 Hz, $J_{14\alpha,14\beta}$=14 Hz, $J_{14\alpha,15}$=4 Hz, H-14α), 3.15 (1H, ddd, $J_{14\alpha,15}$=4 Hz, $J_{14\beta,15}$=12 Hz, $J_{15,20}$=4 Hz, H-15), 3.77 (3H, s, $COOCH_3$), 4.01 (1H, br d, $J_{3,14\beta}$=12 Hz, H-3), 4.16 (1H, d, $J_{20,21\beta}$=2 Hz, H-21β), 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). ^{13}C-NMR, see Figure 1. MS: 377 (M^+, 100%), 350, 335, 249, 224, 209, 170, 169, 156. HRMS: Calcd for $C_{22}H_{23}N_3O_3$ 377.1739. Found: 377.1755. Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found C, 69.82; H, 6.18; N, 10.96.

(±)-21α-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). ^{1}H-NMR: 1.28 (1H, ddd, $J_{3,14\beta}$=7 Hz, $J_{14\alpha,14\beta}$=12 Hz, $J_{14\beta,15}$=12 Hz, H-14β), 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, $J_{3,14\alpha}$=3Hz, $J_{14\alpha,14\beta}$=12 Hz, $J_{14\alpha,15}$=3 Hz, H-14α), 3.75 (3H, s, $COOCH_3$), 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-21β), 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). ^{13}C-NMR data, see Figure 1. MS: 377 (M^+, 100%), 350, 335, 249, 224, 209, 170, 169, 156. HRMS: Calcd for $C_{22}H_{23}N_3O_3$: 377.1739. Found: 377.1735. Anal. Calcd for $C_{22}H_{23}N_3O_3$: 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 ^{1}H-NMR shifts for compound (**5**),[2] especially those of H-17 and H-18, have been rectified.

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