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SHORT STEREOSELECTIVE SYNTHESIS OF dl-ALLOYOHIMBANE AND dl-EPIALLOYOHIMBANE.

MAURI LOUNASMAA* AND REIJA JOKELA

Laboratory for Organic and Bioorganic Chemistry,
Technical University of Helsinki, SF-02150 Espoo, Finland

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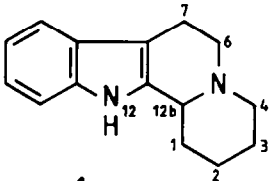
Abstract - A short and stereoselective synthesis for both dl-alloyohimbane and dl-epialloyohimbane using one and the same starting compound is presented.

We recently developed a new synthetic method[1-3] which permits the preparation of 1-, 2- and 3-monosubstituted 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine 1 derivatives possessing the C(12b)H-C(1)H, C(12b)H-C(2)H and C(12b)H-C(3)H relationship, respectively, cis or trans at will. We have now explored the applicability of our method[1-3], for the preparation of dl-alloyohimbane 2 and dl-epialloyohimbane 3, which formally are 2,3-



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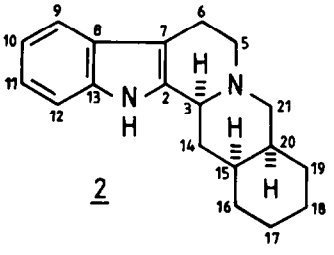

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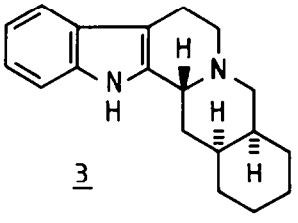

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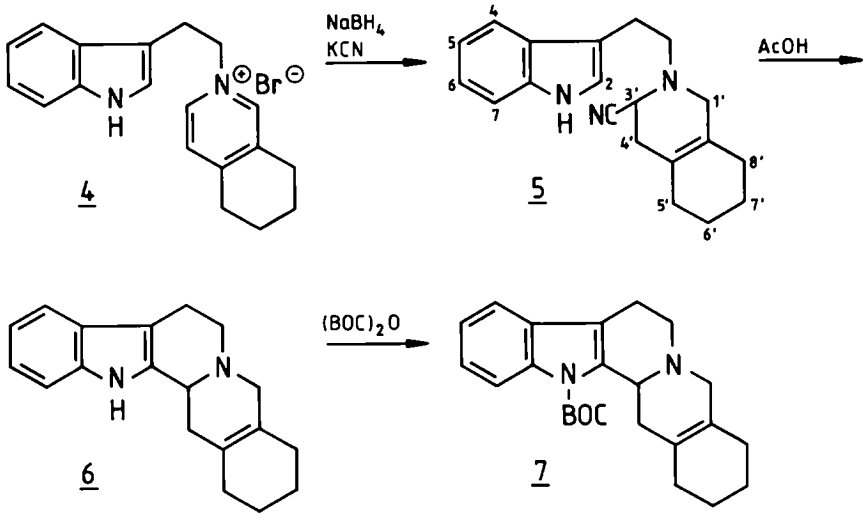
disubstituted 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine derivatives possessing the C(12b)H-C(2)H, C(12b)H-C(3)H cis, cis and trans, trans relationships, respectively [corresponding to the C(3)H-C(15)H, C(3)-C(20)H cis, cis and trans, trans relationships in the biogenetic numbering[4] used in the present paper for the yohimbane skeleton[5]].

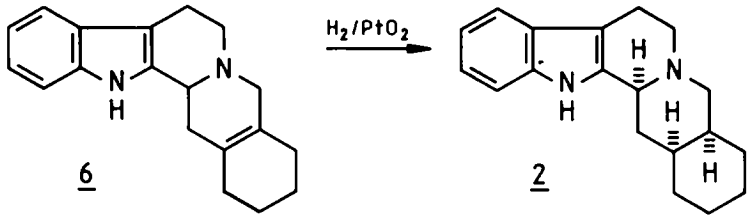
RESULTS AND DISCUSSION

Alkylation of 5,6,7,8-tetrahydroisoquinoline[6] with tryptophyl bromide[7] yielded the tetrahydroisoquinolinium salt 4, which by $NaBH_4$ reduction and cyanide trapping[8-11] afforded the α-aminonitrile 5. Acid-induced cyclization of 5 yielded compound 6. A part of compound 6 was transformed to the corresponding BOC-protected compound 7 using di-t-butyl dicarbonate [$(BOC)_2O$] (Scheme 1).[12-14]



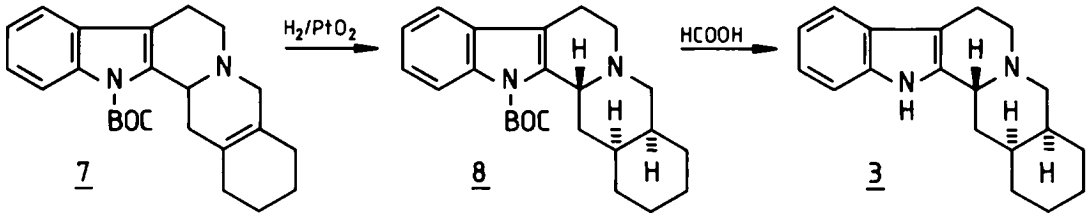
Scheme 1

Catalytic hydrogenation (PtO_2) of compound 6 led exclusively to dl-alloyohimbane 2 (Scheme 2).



Scheme 2

By contrast, catalytic hydrogenation (PtO_2) of compound 7 afforded the BOC-protected dl-epialloyohimbane 8, from which dl-epialloyohimbane 3 was obtained by acid (HCOOH) treatment (Scheme 3).



Scheme 3

^{13}C NMR data, which are in full agreement with the presented structures, are given in Fig. 1.

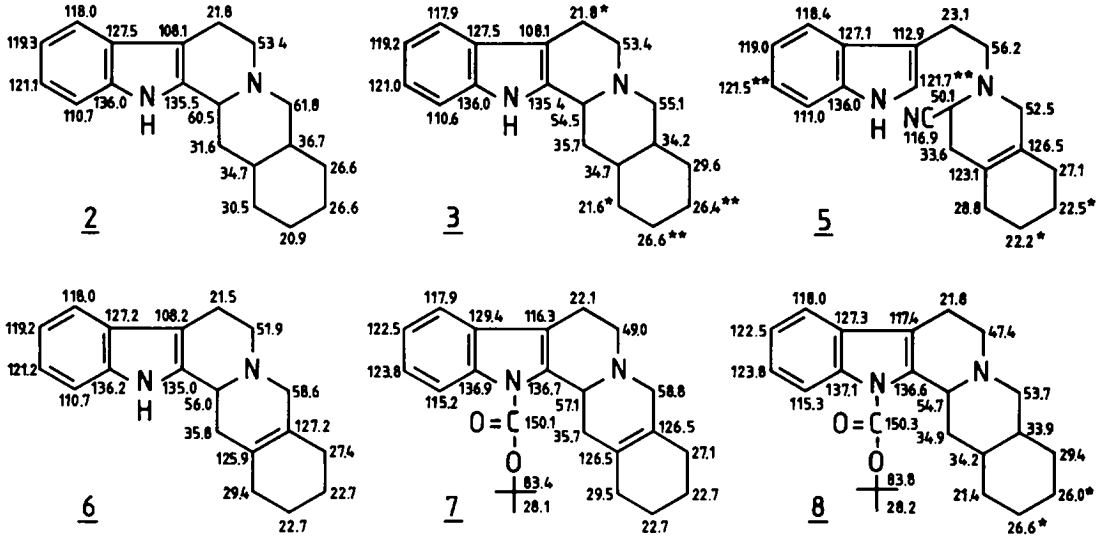


Fig. 1

CONCLUSIONS

The present results show, that our recently developed method[1-3] can be successfully applied to a short and stereoselective synthesis of both dl-alloyohimbane 2 and dl-epialloyohimbane 3 using one and the same starting compound. The present results confirm the generality of our method.[1-3]

Interesting applications of the method in the reserpine series can be expected.

EXPERIMENTAL

IR spectra were recorded with a Perkin-Elmer 700 spectrometer, using liquid film between NaCl crystals. IR absorption bands are expressed in reciprocal centimetres (cm^{-1}) using polystyrene calibration. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^{1}H NMR) and 15.04 MHz (^{13}C NMR). Chemical shift data are given in ppm downfield from TMS. Abbreviations s, d, t, m and br are used to designate singlet, doublet, triplet, multiplet and broad, respectively. For ^{13}C NMR data see Fig. 1. Mass spectrometry was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compound 5

Hydrochloric acid (6N, 4 ml) was added dropwise to a stirred cooled (0°C) solution of KCN (3.20 g, 49.23 mmol) in H_2O (3 ml) and layered with Et_2O (20 ml). MeOH (5 ml) and the corresponding pyridinium salt 4 (3.00 g, 8.40 mmol) (prepared from tryptophyl bromide[7] and commercial 5,6,7,8-tetrahydroisoquinoline[6]) were added, after which $NaBH_4$ (0.35 g, 9.26 mmol) was added during 0.5 h keeping the solution at 0°C. Stirring was continued for 4 h at rt. The ethereal layer was separated and the aqueous layer was extracted several times with ether. The combined ethereal layers were dried over Na_2SO_4 and evaporated to yield nitrile 5, which was used without purification in the next step.

Y. 2.44 g (95%). Amorphous material.

IR: 3430 (NH), 2240 (CN).

^1H NMR: 3.92 (1H, m, H-3'), 6.89 (1H, d, J=2.4 Hz, H-2), 7.19-7.65 (4H, m, H-4, 5, 6, 7), 8.06 (1H, br s, -NH).

MS: 305 (M^+), 278, 175, 161, 144 (100%), 130; exact mass: 305.1883 (calc. for $C_{20}H_{23}N_3$: 305.1892).

Preparation of compound 6

Compound 5 (2.56 g, 8.39 mmol) was dissolved in 50% AcOH (200 ml) and stirred (rt) for 68 h. After evaporation and neutralization (2N Na_2CO_3) the solution was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. The product was purified by column chromatography (alumina, CH_2Cl_2) to yield compound 6.

Y. 1.28 g (55%). Amorphous material.

IR: 3430 (NH).

^1H NMR: 7.01-7.54 (4H, m, arom. H), 7.74 (1H, br s, -NH).

MS: 278 (M^+), 277, 170 (100%), 169; exact mass: 278.1800 (calc. for $C_{19}H_{22}N_2$: 278.1783).

Preparation of compound 2

Compound 6 (0.20 g, 0.72 mmol) in MeOH (8 ml) was hydrogenated (PtO_2) for 120 h. Purification of the crude product (TLC, silica, CH_2Cl_2/MeOH, 9/1) afforded pure compound 2.

Y. 0.14 g (70%). Mp. 146-147°C (MeOH) (lit. Mp. 145-147°C[16], 143.5 -144°C[17], 145-148°C[18]).

IR: 3430 (NH), 2830 and 2780 (Bohlmann bands).

^1H NMR: 3.23 (1H, m, H-3), 6.99-7.53 (4H, m, arom. H), 7.89 (1H, br s, -NH).

MS: 280 (M^+), 279 (100%), 170, 169; exact mass: 280.1933 (calc. for $C_{19}H_{24}N_2$: 280.1939).

Preparation of compound 7

50% NaOH (10 ml) was added to compound 6 (0.30 g, 1.08 mmol) in toluene (10 ml), and then tetrabutylammonium hydrogen sulphate (96 mg). The two-phase system was stirred under argon for 5 min. Di-t-butyl dicarbonate [$(BOC)_2O$] (0.48 mg, 2.18 mmol) in toluene (2 ml) was added during 10 min and stirring was continued for another 10 min. The organic layer was separated and the aqueous layer was washed several times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography (alumina, CH_2Cl_2) to yield pure compound 7.

Y. 0.31 g (75%). Viscous oil.

IR: 1730 (C=O).

^1H NMR: 1.65 (9H, s, $-C(CH_3)_3$), 4.03 (1H, br d, H-3), 7.12-7.41 (3H, m, H-9, 10, 11), 8.08 (1H, m, H-12).

MS: 378 (M^+), 322, 321 (100%), 214, 170, 169; exact mass: 278.2344 (calc. for $C_{24}H_{30}N_2O_2$: 378.2307).

Preparation of compound 8

Catalytic hydrogenation (PtO_2) of compound 7 (0.30 g, 0.79 mmol) in MeOH (10 ml) for 24 h afforded crude product 8, which was purified by column chromatography (alumina, CH_2Cl_2).

Y. 45 mg (15%).[19] Viscous oil.

IR: 1730 (C=O).

^1H NMR: 1.67 (9H, s, $-C(CH_3)_3$), 4.42 (1H, m, H-3), 7.13-7.48 (3H, m, H-9, 10, 11), 7.96 (1H, m, H-12).

MS: 380 (M^+), 323 (100%), 279, 169; exact mass: 380.2434 (calc. for $C_{24}H_{32}N_2O_2$: 380.2467).

Preparation of compound 3

Compound 8 (42 mg, 0.11 mmol) was stirred in HCOOH (2 ml) for 70 h (rt, Ar atm). After evaporation and neutralization (10% Na_2CO_3) the solution was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated to yield compound 3.

Y. 30 mg (95%). Mp. 186-187°C (MeOH) (lit. Mp. 188-189°C[16], 185-186°C[17], 186°C[20]).

IR: 3380 (NH).

^1H NMR: 3.62 (1H, m, H-3), 7.03-7.53 (4H, m, H-9, 10, 11, 12), 7.98 (1H, br s, -NH).

MS: 280 (M^+), 279 (100%), 170, 169; exact mass: 280.1931 (calc. for $C_{19}H_{24}N_2$: 280.1939).

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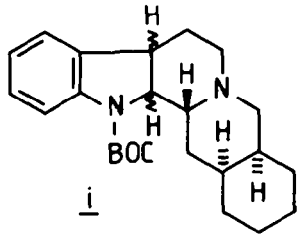
19. About 30% of the starting material (compound 7) was recovered. Moreover, a partial overreduction of compound 7, leading to compound(s) i, (M^+ at m/z 382) could not be avoided. If the used

reaction time (24 h) was exceeded, the overreduction became more pronounced.



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