Tetrahedron Vol. 45, No. 23, pp. 7449 to 7458, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

STEREOSELECTIVE SYNTHESIS OF dl-18,19-DIHYDROANTIRHINE AND dl-3-EPI-18,19-DIHYDROANTIRHINE

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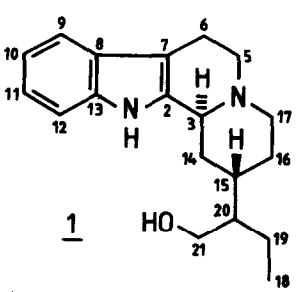
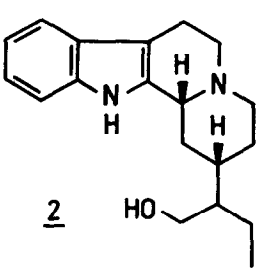
(*Received in UK* 10 *August* 1989)

Abstract - A rapid and stereoselective synthesis for both dl-18,19-dihydroantirhine and dl-3-epi-18,19-dihydroantirhine using one and the same starting compound is described.

We recently developed a method[1] which permits choosing at will the C(12b)H-C(2)H relationship [corresponding to the C(3)H-C(15)H relationship when the biogenetic numbering[2] of the indole alkaloids is used] in the preparation of 2-substituted 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines with high degree of stereoselectivity using one and the same starting compound.

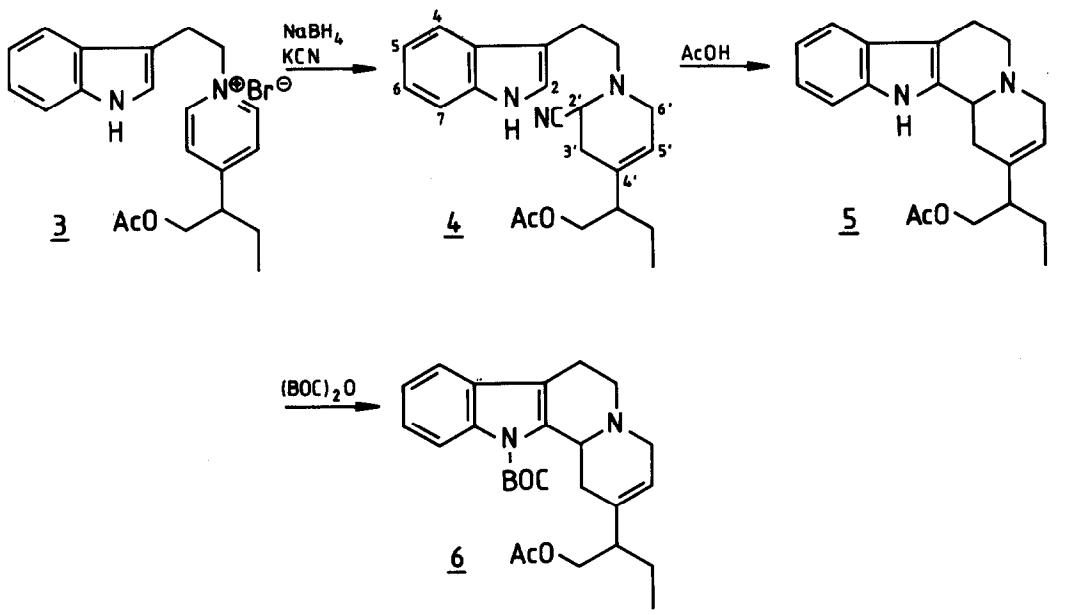




Our method seemed to be ideally suited for a rapid and stereoselective synthesis of both dl-18,19-dihydroantirhine 1 [C(3)H-C(15)H trans relationship] and dl-3-epi-18,19-dihydroantirhine 2 [C(3)H-C(15)H cis relationship] (biogenetic numbering[2]), which are dihydro derivatives of the known indole alkaloids antirhine[3] and 3-epiantirhine[4], respectively. In the present paper we describe the results obtained.

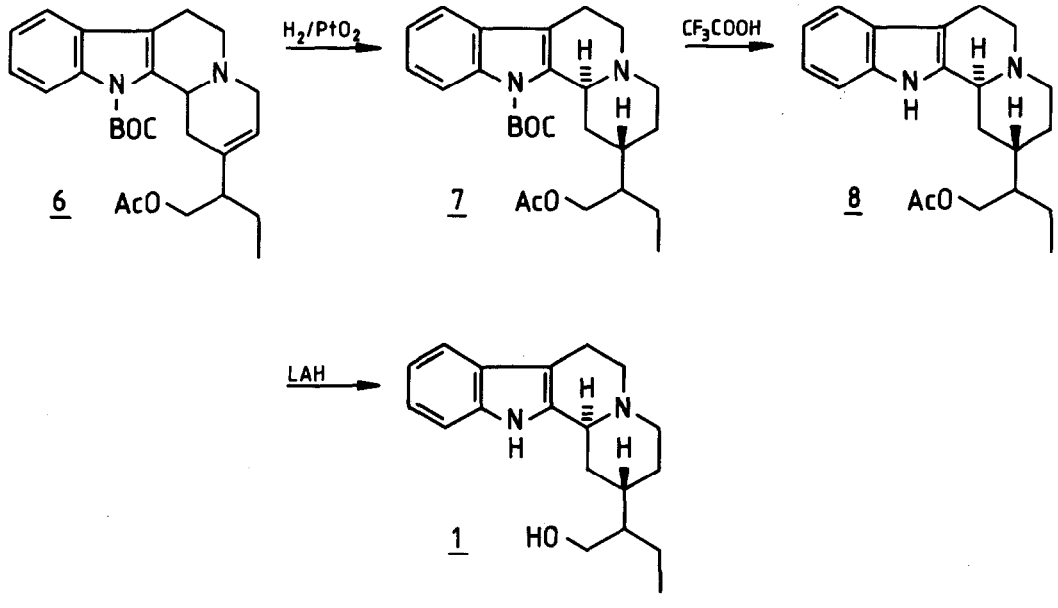
RESULTS AND DISCUSSION

Transformation of 2-(4'-pyridyl)butanol[5] to the corresponding acetate followed by alkylation with tryptophyl bromide[6] yielded the known[7] pyridinium salt 3, which by $NaBH_4$ reduction and cyanide trapping[1,8-11] was transformed to α-aminonitrile 4. Treatment of 4 with AcOH yielded compound 5 .[12-14] A part of compound 5 was transformed to the corresponding BOC-protected compound 6 using di-t-butyl dicarbonate [$(BOC)_2O$] (Scheme 1).[11,15,16]



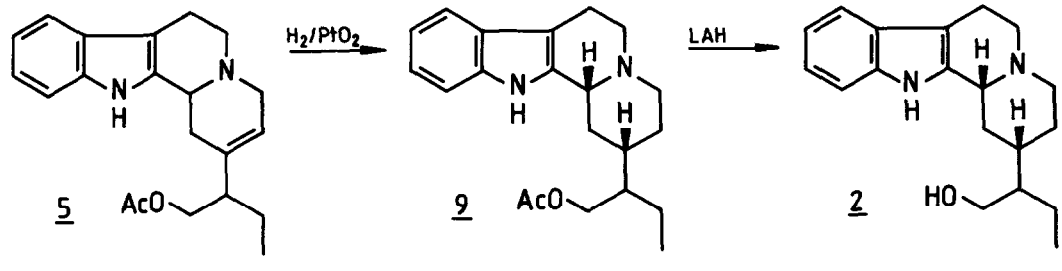
Scheme 1

Catalytic hydrogenation (PtO_2) of the BOC-protected compound 6 led to compound 7 [C(3)H-C(15)H trans relationship], which by acid induced cleavage (CF_3COOH) of the BOC group afforded compound 8. Treatment of 8 with LAH yielded dl-18,19-dihydroantirhine 1 (Scheme 2).



Scheme 2

By contrast, catalytic hydrogenation (PtO_2) of compound 5 led to compound 9 [C(3)H-C(15)H cis relationship], which by LAH treatment afforded dl-3-epi-18,19-dihydroantirhine 2 (Scheme 3).[7,17,18]



Scheme 3

^{13}C NMR data of all the compounds formed are given in Fig. 1.

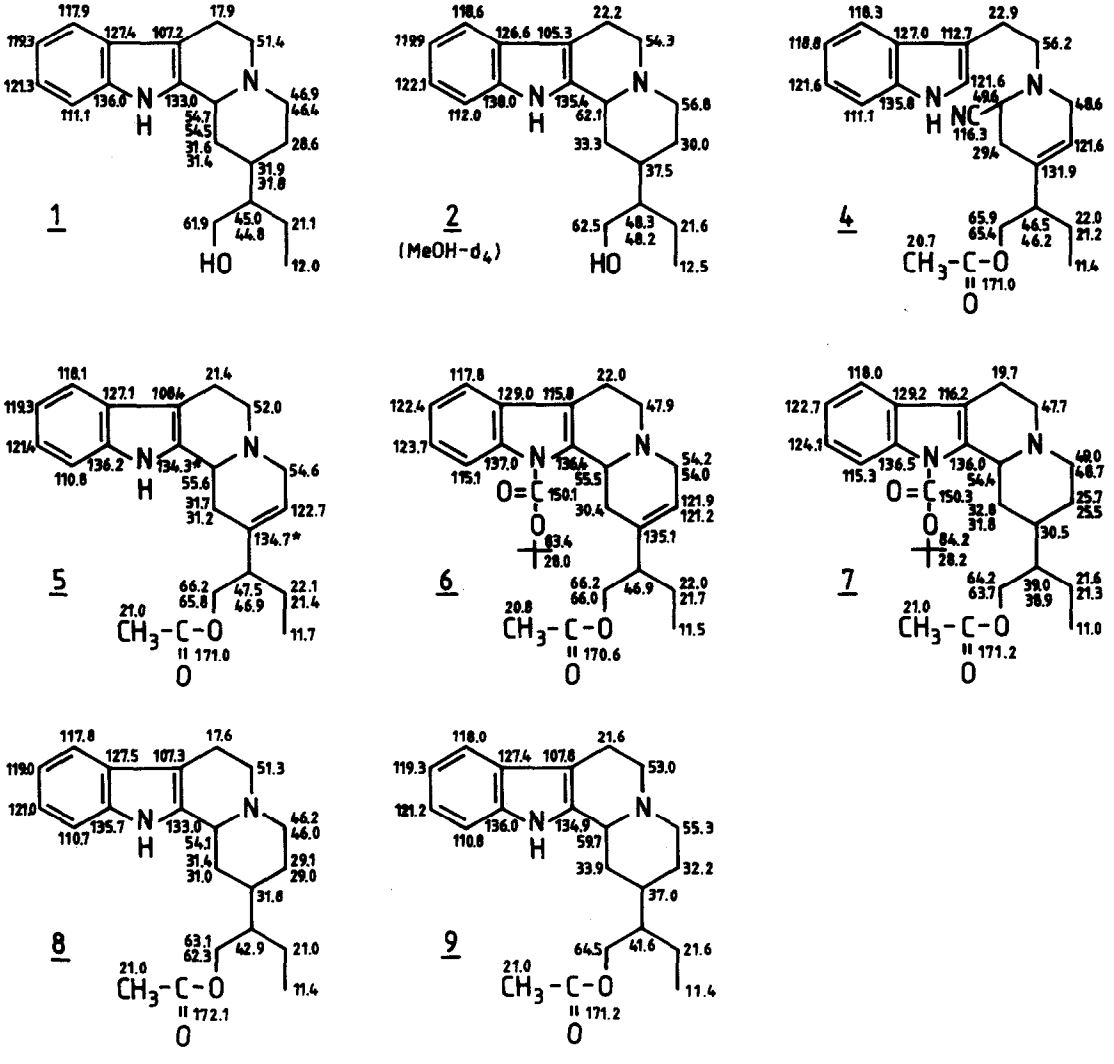
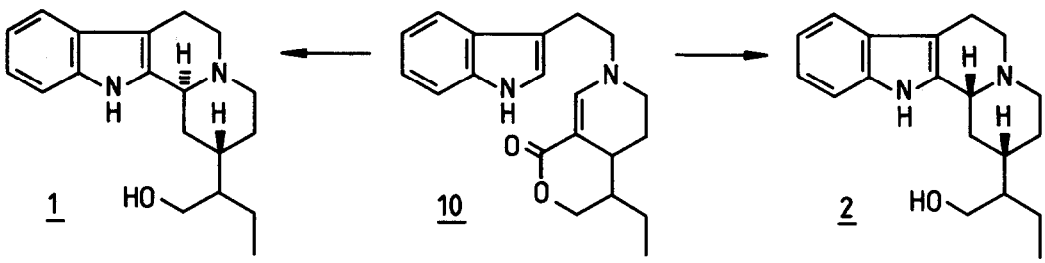


Fig. 1

Comparison of the chemical shifts found for compounds 1, 2, 5, 6, 7, 8 and 9 with those of antirhine and 3-epiantirhine,[4] taking into account the conformational considerations presented in connection with the corresponding t-butyl analogues,[1] gives clear evidence of the

stereostructures depicted in the formulae. The "double signals" found for several carbons in 1, 2, 5, 6, 7, and 8 are in agreement that the samples consist of mixtures of C(20) epimers (See also the ^1H NMR spectra of compounds 5 and 6).

In connection with the present work we have reexamined the old claim of Wenkert et al.[19] that alkaline hydrolysis (followed by decarboxylation and cyclization) of tetrahydropyridine 10 leads to dl-18,19-dihydroantirhine 1 (Scheme 4).



Scheme 4

Repetition of the alkaline hydrolysis of tetrahydropyridine 10[20], led to a reaction mixture where the only clearly detectable dihydroantirhine was dl-3-epi-18,19-dihydroantirhine 2 [= dl-15-epi-18,19-dihydroantirhine, provided that both samples consist of equimolar mixtures of C(20) epimers (vide supra)] (Scheme 4). The presence of dl-18,19-dihydroantirhine 1, if any, must be in trace amounts (cf. Ref. 7).

CONCLUSIONS

The presented results show clearly, that our recently developed method[1] can successfully be applied to a rapid and stereoselective synthesis of both dl-18,19-dihydroantirhine 1 and dl-3-epi-18,19-dihydroantirhine 2.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 700 spectrometer, using liquid film between NaCl crystals. IR absorption bands are expressed in reciprocal centimetres (cm^{-1}) using polystyrene calibration. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (if not otherwise stated) on a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^1H NMR) and 15.04 MHz (^{13}C NMR). Chemical shift data are given in ppm downfield from TMS. Abbreviations s, d, t, m, br and def are used to designate singlet, doublet, triplet, multiplet, broad and deformed, respectively. For ^{13}C NMR data see Fig. 1. Mass spectrometry was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compound 4

Hydrochloric acid (6N, 4 ml) was added dropwise to a stirred cooled solution (0°C) of KCN (3.11 g, 47.85 mmol) in H_2O (3.0 ml) and layered with Et_2O (20 ml). MeOH (5 ml), the corresponding pyridinium salt 3 (3.47 g, 8.32 mmol) prepared from tryptophyl bromide[6] and the acetylated 2-(4'-pyridyl)butanol[5] were added, after which $NaBH_4$ (0.350 g, 9.26 mmol) was added during 0.5 h (0°C). Stirring was continued for 1.5 h at rt. The ethereal layer was separated and the aqueous layer was extracted several times with Et_2O. The combined organic layers were dried over Na_2SO_4 and evaporated to yield compound 4, which was used without purification in the next step.

Y. 95% (crude[21]). Viscous oil.

IR: 3400 (NH), 2220 (CN), 1730 (C=O).

^1H NMR: 0.82 (3H, t, J=6.0 Hz, $-CH_3$), 2.00 and 2.02 (3H, two s, -OAc), 3.92 (1H, m, H-2'), 5.46 (1H, br s, H-5'), 6.90 (1H, d, J < 1 Hz, H-2), 7.16-7.63 (4H, m, H-4, 5, 6, 7), 8.46 (1H, br s, -NH).

MS: 365 (M^+), 338, 305, 250, 235, 175, 144 (100%), 130; exact mass: 365.2062 (calc. for $C_{22}H_{27}N_3O_2$: 365.2103).

Preparation of compound 5

Compound 4 (1.90 g, 5.21 mmol) was stirred with 50% acetic acid (200 ml) for 72 h (rt, Ar-atm). After evaporation and neutralization with 2N Na_2CO_3 the solution was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography (alumina, CH_2Cl_2).[22]

Y. 30%. Amorphous material.

IR: 3400 (NH), 1710 (C=O).

^1H NMR: 0.81 (3H, t, J=6.0 Hz, $-CH_3$), 1.98 and 2.00 (3H, two s, -OAc),

5.50 (1H,br s, H-16), 7.12-7.53 (4H, m, H-9, 10, 11, 12), 8.51 (1H, br s, -NH).
MS: 338 (M^+), 337, 223, 170 (100%), 169; exact mass: 338.1998 (calc. for $C_{21}H_{26}N_2O_2$: 338.1990).

Preparation of compound 6
To compound 5 (0.34 g, 1.01 mmol) in toluene (8 ml) were added 50% NaOH (5 ml) and tetrabutylammonium hydrogen sulphate (90 mg). The two-phase system was stirred under argon for 5 min. Di-t-butyl dicarbonate (0.44 g, 2 equiv.) in toluene (2 ml) was added during 10 min and stirring was continued for 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 over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography (alumina, CH_2Cl_2).
Y. 75%. Viscous oil.
IR: 1730 (C=O).
^1H NMR: 0.88 (3H, t, J=6.5 Hz, $-CH_3$), 1.66 (9H, s, $-C(CH_3)_3$), 2.01 and 2.03 (3H, two s, -OAc), 4.09 (1H, m, H-3), 5.56 (1H, br s, H-16), 7.13-7.50 (3H, m, H-9, 10, 11), 8.04 (1H, m, H-12).
MS: 438 (M^+), 382, 381, 337, 214 (100%), 170, 169; exact mass: 438.2539 (calc. for $C_{26}H_{34}N_2O_4$: 438.2519).

Preparation of compound 7
Catalytic hydrogenation (PtO_2) of compound 6 (0.15 g, 0.34 mmol) in MeOH (7 ml) for 24 h afforded compound 7.
Y. 80%. Viscous oil.
IR: 1730 (C=O).
^1H NMR: 0.91 (3H, t, J=6.0 Hz, $-CH_3$), 1.66 (9H, s, $-C(CH_3)_3$), 2.02 (3H, s, -OAc), 7.15-7.50 (3H, m, H-9, 10, 11), 7.96 (1H, m, H-12).
MS: 440 (M^+), 384, 383 (100%), 339, 269; exact mass: 440.2675 (calc. for $C_{26}H_{36}N_2O_4$: 440.2675).

Preparation of compound 8
Trifluoroacetic acid (0.3 ml) was added during 15 min to a cooled solution (0°C) of compound 7 (0.14 g, 0.32 mmol) in CH_2Cl_2 (0.6 ml). Stirring was continued (rt) for 3 h until all of the starting compound had disappeared (TLC). The mixture was neutralized with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2. The crude product 8 was purified by flash chromatography (alumina, CH_2Cl_2/MeOH; 97/3).
Y. 60%. Amorphous material (lit.[7] amorphous material).

IR: 3400 (NH), 1730 (C=O).
^{1}H NMR: 0.91 (3H, def, -CH_3), 2.02 (3H, s, -OAc), 4.17 (1H, m, H-3), 6.99-7.51 (4H, m, H-9, 10, 11, 12), 8.37 (1H, br s, -NH).
MS: 340 (M^+, 100%), 339, 225, 197, 184, 170, 169; exact mass: 340.2148 (calc. for $C_{21}H_{28}N_2O_2$: 340.2151).

Preparation of compound 1
LAH reduction of compound 8 (60 mg, 0.18 mmol) in abs. THF for 2.5 h (rt, Ar-atm) afforded crude product 1, which was purified by TLC (silica, CH_2Cl_2/MeOH; 9/1).
Y. 35%. Amorphous material (lit.[7] amorphous material).
IR: 3420 (NH), 3270 (OH).
^{1}H NMR: 0.93 (3H, def, -CH_3), 4.29 (1H, m, H-3), 7.00-7.54 (4H, m, H-9, 10, 11, 12), 8.80 (1H, br s, -NH).
MS: 298 (M^+), 297 (100%), 225, 197, 184, 170, 169; exact mass: 298.2025 (calc. for $C_{19}H_{26}N_2O$: 298.2041).

Preparation of compound 9
Catalytic hydrogenation (PtO_2) of compound 5 (0.33 g, 0.98 mmol) in MeOH (10 ml) for 40 h afforded compound 9.
Y. 35%. Mp. 133-135°C (n-hexane) (lit.[18] 142-143°C).
IR: 3400 (NH), 2840 and 2780 (Bohlmann bands), 1730 (C=O).
^{1}H NMR: 0.92 (3H, def, -CH_3), 2.06 (3H, s, -OAc), 7.00-7.54 (4H, m, H-9, 10, 11, 12), 8.03 (1H, br s, -NH).
MS: 340 (M^+, 100%), 339, 225, 197, 184, 170, 169; exact mass: 340.2128 (calc. for $C_{21}H_{28}N_2O_2$: 340.2151).

Preparation of compound 2
LAH reduction of compound 9 (0.15 g, 0.44 mmol) in abs. THF for 3 h (rt, Ar-atm) afforded crude product 2, which was purified by TLC (silica, CH_2Cl_2/MeOH; 9/1).
Y. 50%. Mp. 197-199°C (MeOH) (lit.[18] 196.8-197.8°C).
IR: 3320 (OH), 2840 and 2780 (Bohlmann bands).
^{1}H NMR: 0.89 (3H, def, -CH_3), 7.05-7.56 (4H, m, H-9, 10, 11, 12), 8.01 (1H, br s, -NH).
MS: 298 (M^+), 297 (100%), 225, 197, 184, 170, 169; exact mass: 298.2048 (calc. for $C_{19}H_{26}N_2O$: 298.2041).

Alkaline treatment of tetrahydropyridine 10
Alkaline hydrolysis (followed by decarboxylation and cyclization) of 60 mg of tetrahydropyridine 10[20] using 15 ml of 10% KOH (24 h, 60 °C, Ar-atm)

led to a reaction mixture where the only clearly detectable dihydroantirhine, purified by TLC (alumina, EtOAc/MeOH; 4/1), was dl-3-epi-18,19-dihydroantirhine 2.

Y. 25%.

Analytical data were identical with those described above for compound 2.

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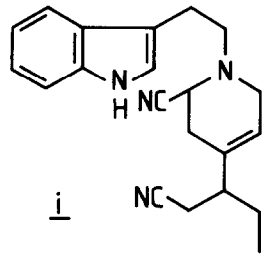
21. A weak second molecular peak at m/z 332 suggested the presence of compound i in the crude product 4.



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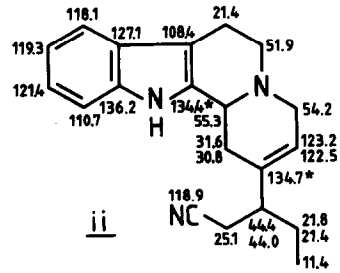
22. The isolation of small amounts of compound ii (M^+ at m/z 305) in connection with the purification of compound 5 was in agreement with the detection of compound i in the crude product 4 (cf. Note 21).



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