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NOVEL APPLICATIONS OF THE MODIFIED POLONOVSKI REACTION - IX[1]
A NEW ROUTE TO WENKERT'S ENAMINE

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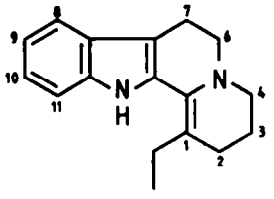
Abstract - A practical synthetic entry to Wenkert's enamine 1 employing the modified Polonovski reaction is described. Complete ^{13}C NMR spectral data of 1 is presented. Conformational analysis of the intermediate 1-hydroxy- and 1-ethyl-1-hydroxy-indoloquinolizidines 20a, 20b, 21a and 21b based on simple but reliable ^{13}C NMR spectral correlations is presented.

INTRODUCTION

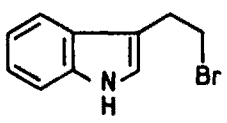
Wenkert's enamine 1 is a key intermediate for the preparation of several clinically useful antihypertensive eburnane alkaloids.[2-4] Several methods for the preparation of this compound have been described in the literature.[3-8] Our research activity being focused on the preparation of therapeutically important indole alkaloid derivatives[1,9] we wanted to test the feasibility of applying the modified Polonovski reaction[10-12] in the preparation of this intermediate.



1

Application of the modified Polonovski reaction in the synthesis of the enamine 1 has once been described in the literature.[4] The synthesis starts from tryptophyl bromide 2 and 3-ethyl pyridine and gives 1 in four steps. However, the

synthesis suffers from two drawbacks, causing low overall yield. First, the tetrahydropyridine 4 is obtained in a lowish 66 % yield by $NaBH_4$ reduction of the pyridinium salt 3. The product is obtained as a 9:1 mixture with its double bond isomer 5, contaminated by a small amount (about 4 %) of the fully reduced piperidine derivative 6.[13] Obviously, the desired hydride addition at the 2-position of the pyridinium salt 3 is accompanied with some addition at the 6- and 4-positions giving rise to 5 and 6, respectively. Secondly, trifluoroacetic anhydride (TFAA) treatment of the N-oxide, obtained by H_2O_2-oxidation of 4, gave the tetracyclic indoloquinolizidine 7 in 30 % yield.



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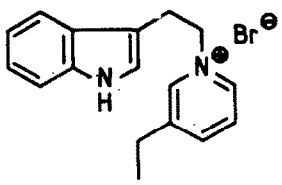

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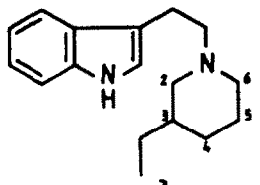
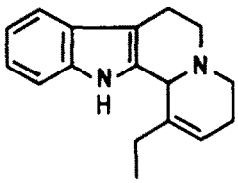


4 Δ^3
5 Δ^4
6



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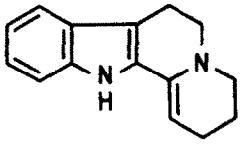
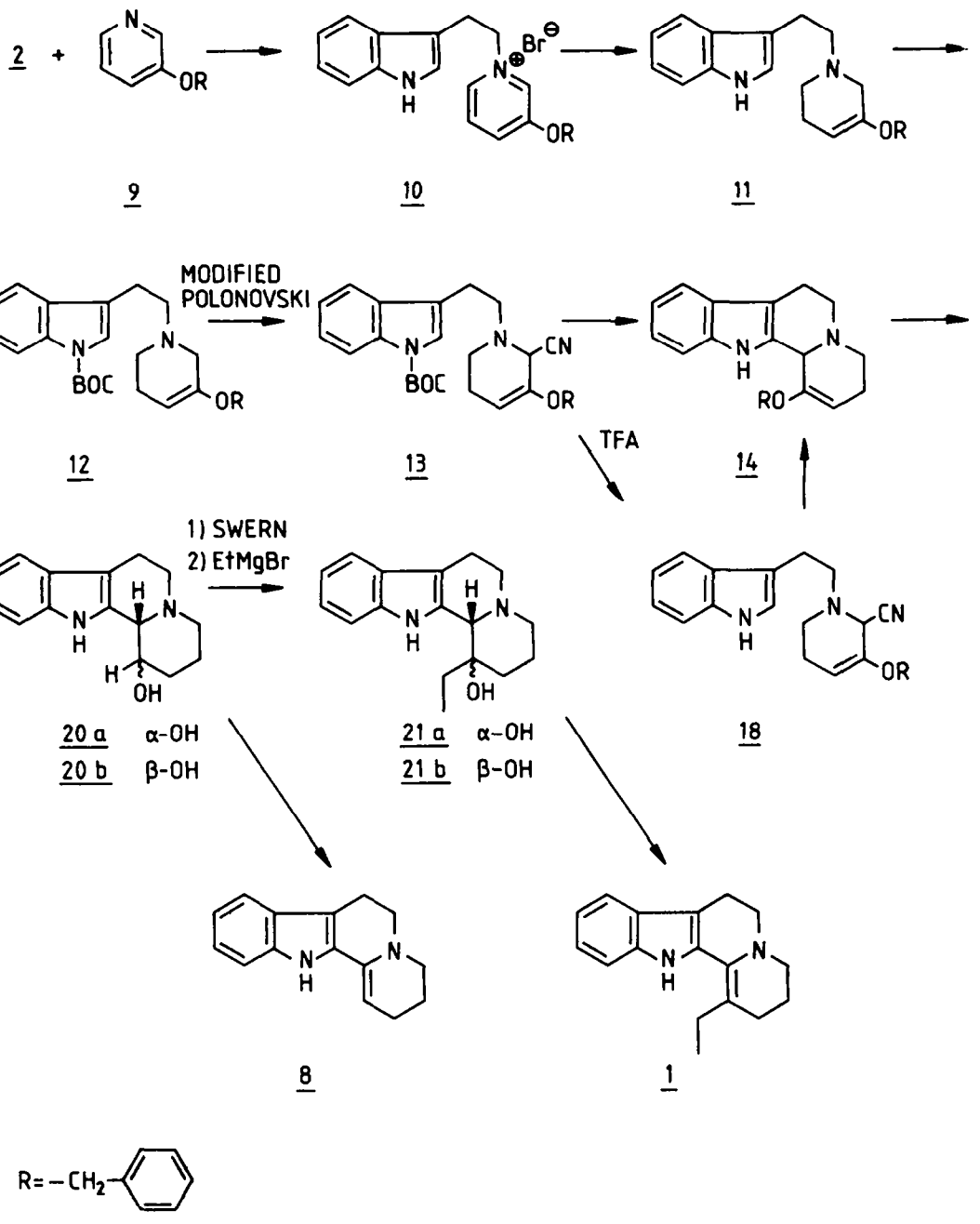


8

We thought that the regiochemistry in the hydride reduction could better be controlled by proper choice of the substituent at the 3-position of the pyridine ring. A benzyloxy substituent seemed most attracting. We reasoned that the electron donating nature of the substituent would disfavor hydride addition at the 4-position, and would also provide a convenient handle for the introduction of the ethyl side chain at a later stage in the synthesis. The enol ether would function as a masked ketone which after debenzylation should allow introduction of the ethyl appendage *via* Grignard reaction. Dehydration would finally furnish the target compound 1.

The yield in the modified Polonovski reaction can be greatly improved by protecting the indole nitrogen with a suitable electron withdrawing group.[13,14] The *t*-butoxycarbonyl (BOC) group seems to suit ideally for this purpose as it is sufficiently base stable to survive basic aqueous work-ups, and it is acid labile enough to be cleaved with HCl/MeOH or trifluoroacetic acid (TFA) in CH_2Cl_2. Based on the latter feature we hoped that the deprotection and cyclisation operat-


2
OR
9
Br
10
11
MODIFIED
POLONOVSKI
BOC
12
CN
13
TFA
RO
14
1) SWERN
2) EtMgBr
OH
20 a α-OH
20 b β-OH
21 a α-OH
21 b β-OH
18
8
1
R= -CH2-

SCHEME 1

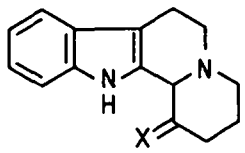
ions can be performed in one step.

During the course of our studies, we needed reference data to establish the identity of the desired product. After a literature search, we discovered that although the enamine 1 has been widely used in alkaloid syntheses (*vide supra*), several of its physical data, particularly the highly informative ^{13}C NMR ones, were still missing. In connection with the present work, we decided to determine the missing data both for the enamine 1 and its desethyl analogue 8.

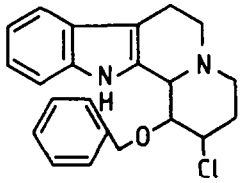
RESULTS AND DISCUSSION

Our approach to 1 is presented in Scheme 1. The early stages of the synthesis proceeded uneventfully. Reaction of tryptophyl bromide 2 with 3-benzyloxy pyridine 9[15] gave the salt 10[16] in 99% yield. As expected, sodium borohydride reduction of 10 in ethanol afforded the enol ether 11[16] in excellent yield with less than 5 % of the regioisomeric olefin as evidenced by TLC and NMR. The indole N was then protected with the BOC group using the method of Grehn and Ragnarsson[17] (BOC_2O, DMAP, CH_2Cl_2, rt) to give the carbamate 12 in 90 % yield after flash chromatography.[18] In the next step, the carbamate 12 was subjected to the modified Polonovski reaction conditions, followed by cyanide trapping, to furnish the α-aminonitrile 13 quantitatively.

We then attempted to achieve BOC cleavage and cyclisation in one step by using $AgBF_4$ in THF to generate the iminium ion, followed by stirring in HCl/MeOH to effect the cyclisation to the indoloquinolizidine 14. The only product isolated by column chromatography on alumina was the dimethyl ketal 15. Its structure was evident from its MS, ^1H and ^{13}C NMR spectra. In the mass spectrum, the product showed a molecular ion at m/z 286. In the NMR spectra, anticipated signals due to the benzyl enol ether and BOC moieties were absent. Further, the ^1H NMR spectrum revealed the presence of a dimethyl ketal (3H singlets at δ 3.03 and 3.31 ppm). Correspondingly, from the ^{13}CNMR spectrum, the signals at δ 48.1 and 49.2 ppm (quartets on SFORD) were detectable, as were also those due to the quaternary C-1 (δ 100.5 ppm) and the tertiary C-12b (δ 62.9 ppm). These data confirmed the structure as 15. For practical purposes, however, the yield was unacceptably low.



15 X = $(OMe)_2$
19 X = O



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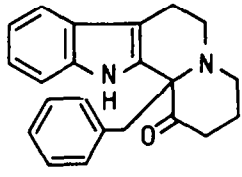


17

We next tried to circumvent this problem by generating the iminium ion directly from the enol ether 12 via Polonovski reaction, and then treating it, without cyanide trapping, with anhydrous diethyl ether saturated with HCl. The major reaction in this case was addition of hydrogen chloride on the enol ether double bond giving the diastereomeric products 16 in 43 % yield after flash chromatography on silica. The mass spectra of these isomers exhibited characteristic M+2 isotope peaks along with base peaks at m/z 331 (M-35) and other spectral data corresponding to the structure 16.[19] A minor compound (6 % yield), isolated in earlier fractions showed some interesting spectral features. An IR absorption at 1700 cm^{-1} and a signal at δ 212.9 ppm (singlet in SFORD) in the ^{13}C NMR spectrum suggested that a keto group is present. That the benzyl group was still present but had migrated to C_{12b} was proven by the appearance a singlet at δ 71.6 ppm. These facts together with other spectral data confirmed the structure as 17.[20] The product is surprisingly stable for an α-aminoketone, obviously because enolisation towards the nitrogen is prevented by the absence of H-12b.

These interesting but unfruitful results forced us to abandon this "one-pot deprotection-cyclisation" approach and assume a more conventional one. Thus, the BOC protecting group was first cleaved with TFA in CH_2Cl_2 at rt to give the α-aminonitrile 18 in 95 % yield. This was then cyclised without purification in 50 % aqueous AcOH to the tetracyclic enol ether 14 in 65 % yield after preparative HPLC. The overall yield from tryptophyl bromide was 55 %.

All attempts to convert the enol ether 14 to the ketone 19 failed, however, probably due to the highly unstable nature of the α-amino ketone 19. We reasoned that this problem could be avoided by reducing the enol ether 14 to alcohol oxidation level (20a and 20b). These diastereomeric alcohols could then be re-oxidised to the ketone 19 and treated immediately with ethyl magnesium bromide to give the tertiary alcohols 21 from which the desired enamine 1 could be obtained via dehydration.

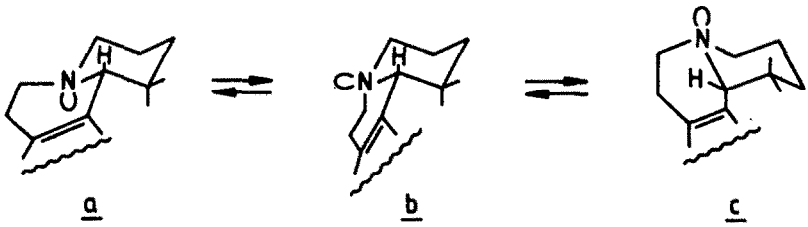
First we had to prepare the starting alcohols. This was achieved by catalytic transfer hydrogenolysis[21] over Pd/C in methanol using ammonium formate as the hydrogen source. A 1:2 mixture of the known[22] alcohols 20a and 20b was obtained in 88 % combined yield. Using the Ireland one-pot modification of the Swern oxidation/Grignard addition,[23,24] the mixture of alcohols 20 was converted to a 4:1 mixture of the alcohols 21a and 21b in 56% combined yield (65% based on recovered 20b) employing an excess of ethyl magnesium bromide. These alcohols have previously been described by Danieli et al.[8b,8c] They obtained 21b in 92 % yield by $NaBH_4$ reduction of the corresponding iminium salt. The other diastereomer, 21a, which is the major one in our synthesis, was obtained in 10 % yield by dissolving metal reduction of the same starting material.[23,24] Our synthesis of the alcohols 21 can thus be regarded as complementary to that of the Italian group.

The stage was now set for the final dehydration of the alcohols 21 to the target compound. Owing to the lability of the free enamine 1, we felt that dehydration should be performed under strongly acidic conditions, whence the enamine would be protonated to the more stable iminium ion as soon as it is formed. Preliminary attempts with conc. H_2SO_4 were not very promising, however, yielding

only unconverted starting material along with varying amounts of unidentified polar products. The mass spectra of the crude reaction mixtures showed that only traces of 1 could have been present. In the model series, refluxing 20 in neat TFA[27] for 17 hours gave 8 in almost quantitative yield. Finally, similar TFA treatment of the alcohols 21 gave the enamine 1 quantitatively. No double bond isomers could be detected by TLC or spectroscopic means. A major feature in the mass spectrum of this latter compound is the abundance of the m/z 237 peak (M-15, 100%) which, along with the molecular ion at m/z 252, is the only prominent peak. The model compound 8 was useful in assigning the ^{13}C NMR spectrum of 1.[28,29] The ethyl group shows a deshielding α-effect and a shielding β-effect, as expected, C-1 appearing at δ 113.5 ppm and C-12b at δ 130.2 (or 131.5) ppm compared to the values of the desthyl analogue 8 at δ 94.9 and 136.7 ppm, respectively.

CONFORMATIONAL ANALYSIS OF COMPOUNDS 20a, 20b, 21a AND 21b

The 1-*mono*- and 1,1-disubstituted 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]-quinolizine systems can exist in six conformations (two configurations) with equilibration by nitrogen inversion and cis-decalin type ring interconversion (Scheme 2). Ring C is assumed to be in the half chair conformation, and only the chair forms of ring D are considered. The stereochemical assigments for 20a, 20b[22] and 21a[8] have been proposed earlier, and that of 21b was determined by ^{13}C NMR spectral analysis as shown below.



a b c

SCHEME 2

The chemical shift of C-7 reflects the contribution of different conformations to the equilibrium, mainly due to the interaction of C-7 with C-4.[30,31] Taking the C-7 shift values δ 21.8 (a) ppm and δ 16.8 (b) ppm as a basis, the present conformational equilibrium can be estimated (the contribution of conformer b is considered negligible). Correlation of shift values δ 20.6 and 19.5 ppm, found for the signals of C-7 in compounds 20a and 21a, with the above values indicates that the contributions of conformer c is approximately 24 % and 46 %, respectively. The value δ 21.6 ppm found for C-7 for both compounds 20b and 21b indicates that they exist almost totally in conformation a.

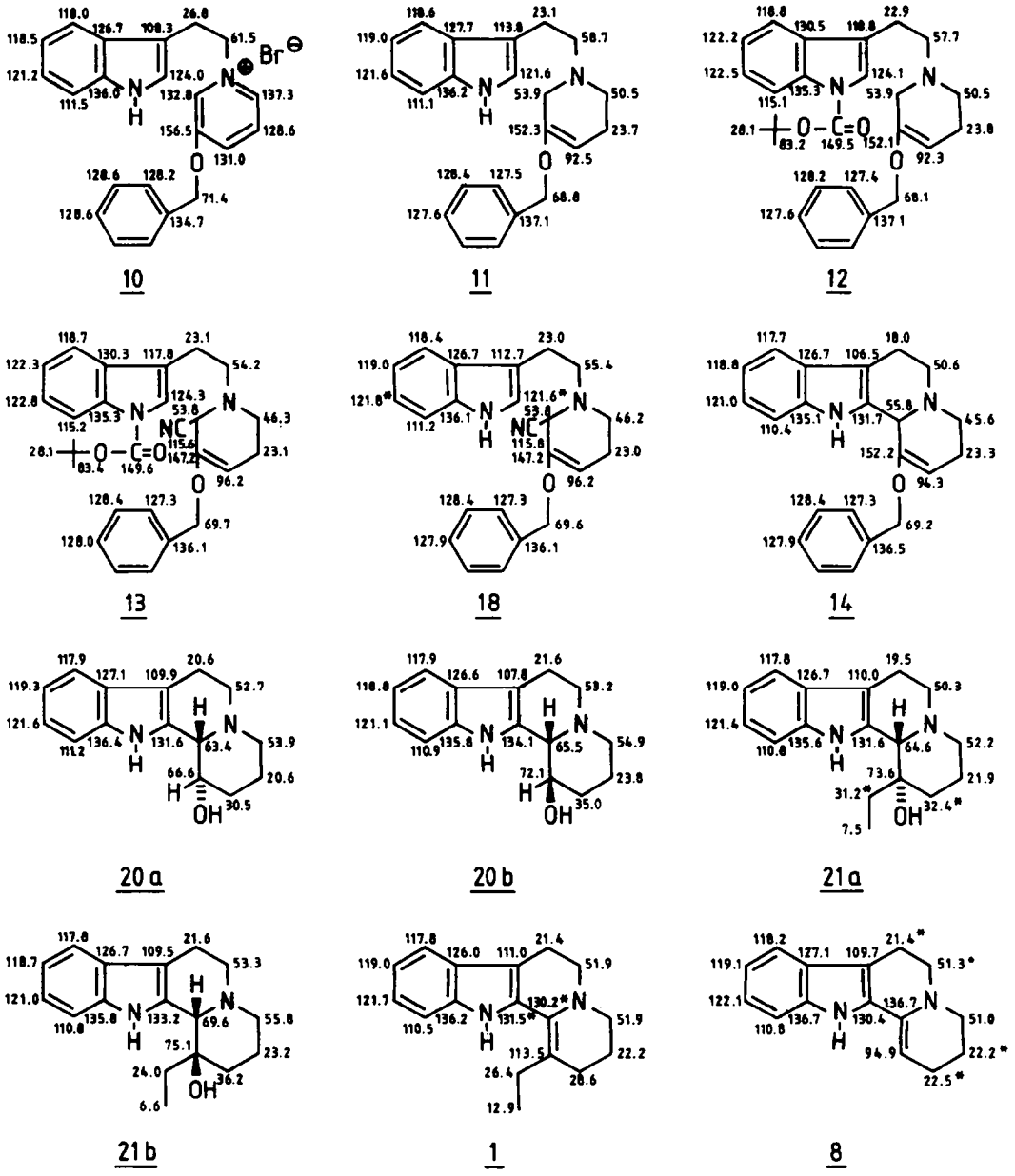
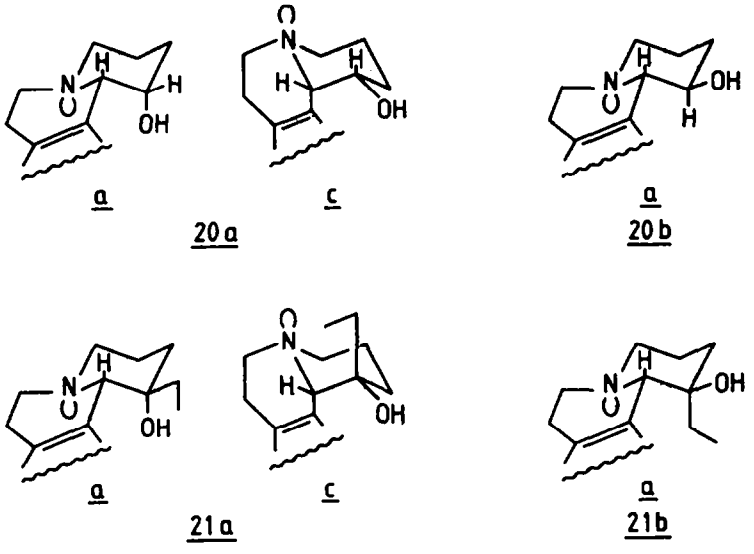


Fig. 1.

The predominance of conformation a in compounds 20b and 21b is also supported by ^{1}H NMR spectroscopy. The presence of the H-12b signal upfield from δ 3.4 ppm (observed, δ 3.07 and 3.24 ppm, respectively) is characteristic of conformation a (trans-quinolizidine juncture).[32] Owing to the diamagnetic displacement effect of the electron pair of the basic nitrogen, which effects the H-12b in conformation c, the H-12b signals of 20a and 21a appear at lower field (δ 3.50 and 3.72 ppm, respectively), in agreement with the proposed structures. Moreover, the relatively strong intensities of the Bohlmann bands in the IR spectra of compounds 20a, 20b and 21b and their weakness in the case of 21a are in agreement with the conclusions presented.



These results are in agreement with earlier results from our laboratory.[29] Compound 21b predominately assumes conformation a to avoid steric interactions between an equatorial ethyl group and the indolic part and for the same reason the conformational equilibrium of compound 21a is shifted towards conformation c. The hydroxyl group is sterically less demanding, and thus exists mostly axially in compound 20a and almost exclusively equatorially in 20b. In the latter case, hydrogen bonding with indole N probably plays a major role in the conformational equilibrium.

CONCLUSIONS

Wenkert's enamine 1 and its desethyl analogue 8 have been obtained in 24 % and 48 % overall yields, respectively. For the first time, the title compound has been fully characterised by spectroscopic means including its ^{13}C NMR data. Conformational analysis of indoloquinolizidines 20a, 20b, 21a and 21b based on simple ^{13}C NMR spectral data reveals the importance of steric interactions bet-

ween the 1-substituents and the indole nitrogen in determining the position of the conformational equilibrium.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 700 Spectrophotometer using liquid film between NaCl crystals. IR absorption bands are reported in reciprocal centimeters (cm^{-1}) using polystyrene calibration. Only bands yielding structural information are reported. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise specified. Tetramethylsilane (TMS) was used as internal standard (δ = 0.00 ppm). The spectra were recorded on a Jeol JNM-FX 60 spectrophotometer working at 59.8 MHz (for ^1H) and 15.04 MHz (for ^{13}C). The ^{13}C NMR data is presented in Figure 1. Chemical shift data are given in ppm downfield from TMS, where s, d, t, q and m designate singlet, doublet, triplet, quartet and multiplet, respectively. Coupling constants J are given in Hz. Mass spectrometry and high resolution mass spectrometry (HRMS) were performed on a Jeol DX 303/DA 5000 instrument.

Tetrahydrofuran (THF) was distilled from $LiAlH_4$ prior to use, CH_2Cl_2 was dried by distillation from CaH_2 and diethyl ether was dried using sodium wire. Other solvents and reagents were used without further purification.

For column chromatography, Silica Woelm TSC, and for flash chromatography[18], Silica gel 60 Merck 9385 were used. TLC plates were coated with Silica gel 60 $PF_{254+366}$ from Merck. Dragendorff-Munier reagent was used to locate reaction components.

Pyridinium salt 10. 3-Benzyloxypyridine 9[19] (2.56 g, 13.8 mmol) was dissolved in 28 mL of anhydrous ether. Tryptophyl bromide 1 (3.10 g, 13.8 mmol) was added in 10 mL of dry ether and the solution was stirred under a stream of nitrogen at 90 °C. After 3 hr and 15 min, the residue was allowed to cool to rt. The resulting yellow glass was triturated several times with dry ether affording 5.62 g (99 %) 10 as a white powder. mp. 134-140 °C. ^1H NMR δ 3.44 (2H, m), 4.95 (2H, m, N^+-CH_2), 5.30 (2H, br s, OCH_2), 7.0-7.5 (10 H, m, aromatic H), 8.0-8.3 (4H, m), 8.67 (1H, d, 5 Hz), 9.07 (1H, br s, pyridine H-2), 11.11 (1H, br s, NH).

Enol ether 11. To a stirred solution of the salt 10 (5.62 g, 13.7 mmol) in 100 mL EtOH at 0 °C under argon, sodium borohydride (1.04 g, 27.4 mmol) was added in portions over a period of 20 min. Stirring was continued for another 90 min at rt. Then, water (50 mL) was added to the mixture and the solution was concentrated under reduced pressure. The resulting mixture was extracted with methylene chloride (6 x 50 mL), the combined extracts were washed with brine (2 x 50 mL) and water (50 mL), dried over Na_2SO_4 and concentrated to give 4.54 g (13.7 mmol, 100 %) of 11 as a yellow solid. mp 104-109 °C. IR 1680 (C=C-O). ^1H NMR δ 2.3-2.9 (8H, m), 3.16 (2H, m), 4.73 (3H, br s, OCH_2 and =CH), 6.88 (1H, d, 2 Hz, indole H-2), 7.0-7.7 (9H, m, aromatic H), 8.41 (1H, br s, NH). MS m/z 332 (M^+), 202, 143, 130, 91 (100 %). HRMS found 332.1907, calc. for $C_{22}H_{24}N_2O$ 332.1889.

Protection of the indolic nitrogen - 12. Enol ether 11 (7.02 g, 21.1 mmol) was dissolved in 50 mL CH_2Cl_2 at rt. To the stirred solution under argon atmosphere, 4-dimethylaminopyridine (237 mg, 2.1 mmol) was added, followed by di-tert-butyl dicarbonate ($(BOC)_2O$) (5.53 g, 25.3 mmol) in 10 mL CH_2Cl_2. After 3 hr, the solvent was evaporated and the residue was purified by flash chromatography[17] over silica gel (CH_2Cl_2:MeOH:TEA, 100:1:0.3) to give pure 12 (8.2 g, 19.0 mmol, 90 %) as a viscous oil. IR 1730 (C=O), 1680 (C=C-O). ^1H NMR δ 1.65 (9H, s, CH_3), 2.3-2.9 (8H, m), 3.13 (2H, m), 4.74 (3H, br s, OCH_2 and =CH), 7.2-7.6 (9H, m, aromatic H), 8.11 (1H, d, 8 Hz). MS m/z 432 (M^+), 417, 341, 241, 220, 202, 142, 130, 91. HRMS found 432.2415, calc. for $C_{27}H_{32}N_2O_3$ 432.2413.

Aminonitrile 13. m-Chloroperbenzoic acid (90 %, 929 mg, 4.84 mmol) in 15 mL dry CH_2Cl_2 was added over a few minutes to a 0 °C stirred solution of 12 (1.905 g, 4.40 mmol) in 18 mL dry CH_2Cl_2 under argon. Stirring was continued at 0 °C for 1 hr, the solution was then cooled to -13 °C and trifluoroacetic anhydride (1.40 mL, 10.57 mmol) was added dropwise over a period of 15 min. Stirring was continued at this temperature for 1 hr and at rt for 15 min. Potassium cyanide (574 mg, 8.80 mmol) in water (4.7 mL) was then added and the pH adjusted to 5 by the addition of solid NaOAc. The two phase mixture was stirred vigorously for 30 min, basified with 10 % aq Na_2CO_3 and extracted with CH_2Cl_2 (5 x 25 mL). The combined extracts were washed with water (2 x 25 mL), dried over Na_2SO_4 and concentrated to give practically quantitative yield of 13 of sufficient purity to be used in the next step. IR 2250 (CN), 1730 (C=O), 1690 (C=C-O). ^1H NMR δ 1.66 (9H, s, CH_3), 2.1-3.1 (8H, m), 4.24 (1H, br s, CH-CN), 4.78 (2H, m, OCH_2), 4.89 (1H, m, =CH), 7.1-7.6 (9H, m, aromatic H), 8.16 (1H, d, 9 Hz). MS m/z 457 (M^+), 202, 143, 130, 91. HRMS found 457.2363, calc. for $C_{28}H_{31}N_3O_3$ 457.2365.

Nitrile 18. Trifluoroacetic acid (1.8 mL) was added dropwise to a cooled (0 °C) stirred solution of 13 (918 mg, 2.01 mmol) in 18 mL dry CH_2Cl_2 under argon. Stirring was continued for 15 min at 0 °C and then at rt until TLC showed disappearance of the starting material (6 hr). The solution was poured into

cold aq $NaHCO_3$ (30 mL). Then $CHCl_3$ (30 mL) and 1M aq K_2CO_3 were added, the phases were separated, and the aq phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4) and concentrated to give 680 mg (95 %) crude 18. IR 2260 (CN), 1675 (C=C-O). ^1H NMR δ 2.1-3.1 (8H, m), 4.23 (1H, br s, CH-CN), 4.75 (2H, br s, OCH_2), 4.84 (1H, m, =CH), 6.93 (1H, s, indole H-2), 7.0-7.6 (9H, m, aromatic H), 8.48 (1H, br s, NH). MS m/z 357 (M^+), 330, 239, 202, 143, 130, 91 (100 %). HRMS found 357.1835, calc. for $C_{23}H_{23}N_3O$ 357.1841.

Enolether 14. A mixture of the nitrile 6 (545 mg, 1.525 mmol) and 160 mL 50 % aq AcOH was stirred at rt overnight. The reaction mixture was then carefully basified with aq ammonia at 0 °C and extracted with CH_2Cl_2 (5 x 40 mL). The crude product was purified by HPLC (Waters 500A, EtOAc:hexane:TEA, 50:50:0.2, normal phase) to give 327 mg (65 %) pure 14 as an amorphous solid. IR 1675 (C=C-O). ^1H NMR δ 2.15-3.3 (8H, m), 4.56 (1H, br s, H-12b), 4.72 (2H, br s, OCH_2), 4.80 (1H, m, =CH), 7.0-7.5 (9H, m, aromatic H), 8.40 (1H, br s, NH). MS m/z 330 (M^+), 239 (100 %), 91. HRMS found 330.1745, calc. for $C_{22}H_{22}N_2O$ 330.1732.

Preparation of alcohols 20a and 20b. Enol ether 14 (467 mg, 1.41 mmol) was dissolved in 14.5 mL MeOH and the solution was degassed by passing N_2 through it. 10 % Pd/C (467 mg, 100 wt%) and ammonium formate (891 mg, 14.1 mmol) were added and the mixture was vigorously refluxed for 1h, filtered hot and evaporated. The residue was partitioned between 10% aq Na_2CO_3 (10 mL) and CH_2Cl_2 and the aq layer was extracted with two more 20 mL portions of CH_2Cl_2. Drying over Na_2SO_4, filtration and evaporation gave 300 mg (88 %) of a roughly 1:2 mixture of alcohols 20a and 20b which was used without further purification in the next step. Analytical samples were obtained by preparative TLC (CH_2Cl_2:MeOH, 95:5).
20a (minor isomer) amorph. IR 3250 (OH), 2830, 2780, 2720 (Bohlmann bands). ^1H NMR δ 1.5-3.1 (11H, m), 3.50 (1H, m, H-12b), 4.18 (1H, m, H-1), 7.0-7.55 (4H, m), 8.31 (1H, br s, NH). MS m/z 242 (M^+, 100 %), 241, 225, 197, 185, 169. HRMS found 242.1413, calc. for $C_{15}H_{18}N_2O$ 242.1419.
20b (major isomer) amorph. IR 3350 (OH), 2830, 2770 (Bohlmann bands). ^1H NMR δ 1.5-3.1 (11H, m), 3.07 (1H, d, 9 Hz, H-12b), 3.70 (1H, m, H-1), 7.0-7.55 (4H, m), 9.09 (1H, br s, NH). MS m/z 242 (M^+), 241, 224, 197, 185, 169 (100 %). HRMS found 242.1418, calc. for $C_{15}H_{18}N_2O$ 242.1419.

Preparation of the alcohols 21a and 21b. Dimethyl sulfoxide (53 µL, 0.75 mmol) was added dropwise to a cooled (-78 °C) stirred solution of oxalyl chloride (59 µL, 0.69 mmol) in 2 mL dry THF under argon. The solution was allowed to warm to -35 °C where it was stirred for 3 min, and then recooled to -78 °C. A mixture of the alcohols 20a and 20b (151 mg, 0.62 mmol) in 1.5 mL THF was added over a period of 10 min. The yellow mixture was allowed to warm to -35 °C and stirring was continued for 15 min. Triethylamine (0.43 mL, 3.1 mmol) was added dropwise and the reaction mixture was then stirred at rt for 5 min. After recooling to -78 °C ethyl magnesium bromide (2 M in THF, 3.1 mL, 6.2 mmol) was added dropwise and the mixture was stirred for 90 min during which time the temperature was allowed to rise to -25 °C. The mixture was again cooled to -78 °C and was then carefully treated with 0.85 mL EtOH and 1.7 mL sat aq NH_4Cl. The cooling bath was removed and the warmed reaction mixture was poured into 60 mL of saturated aq NH_4Cl and extracted with diethyl ether and ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered and concentrated to give the crude product, which was purified by flash chromatography (cyclohexane:$CHCl_3$:diethylamine, 30:25:5) to give 94 mg (56 %) of alcohols 21a and 21b as a 4:1 mixture. Later fractions gave 21 mg starting alcohols 20a and 20b.
21a (major isomer), amorph. IR 2840, 2780 (Bohlmann bands). ^1H NMR δ 1.05 (3H, t, 7.4 Hz, CH_3), 1.55-2.15 (6H, m), 2.4-3.3 (7H, m), 3.72 (1H, br s, H-12b), 7.0-7.54 (4H, m), 8.54 (1H, br s, NH). MS m/z 270 (M^+), 171 (100 %). HRMS found 270.1732, calc. for $C_{17}H_{22}N_2O$ 270.1732.
21b (minor isomer), amorph. IR 2830, 2780 (Bohlmann bands). ^1H NMR δ 0.80 (3H, t, 7 Hz, CH_3), 1.4-3.1 (13H, m), 3.24 (1H, s, H-12b), 7.0-7.5 (4H, m), 8.95 (1H, br s, NH). MS m/z 270 (M^+), 171 (100 %). HRMS found 270.1729, calc. for $C_{17}H_{22}N_2O$ 270.1732.

Preparation of the enamine 1. The purified alcohol mixture 21a and 21b (94 mg, 0.35 mmol) was dissolved in 10 mL TFA and refluxed under argon for 24 hrs. The solvent was evaporated and the residue was stirred with 2 mL CH_2Cl_2 and 4 mL 2% aq NaOH for 10 min. The organic layer was separated, and the aq phase extracted with CH_2Cl_2. The combined organic phases were dried (Na_2CO_3), filtered and evaporated to give 80 mg (90 %) 1. IR 1670 (C=C-N). ^1H NMR δ 1.24 (3H, t, 7.6 Hz, CH_3), 1.94-2.5 (6H, m), 3.0 (6H, m), 7.0-7.55 (4H, m, aromatic H), 8.09 (1H, br s, NH). MS m/z 252 (M^+), 237 (100 %). HRMS found 252.1625, calc. for $C_{17}H_{20}N_2$ 252.1626. The enamine 1 proved to be identical with Wenkert's enamine prepared by a method described earlier.[7]

Preparation of the enamine 8. The crude mixture of alcohols 20a and 20b (41 mg, 0.17 mmol) was dissolved in 2 mL TFA and the solution was refluxed under argon for 17 hrs. Work-up as in the case of 1 gave enamine 8 in practically quantitative yield. IR 1640 (C=C-N). ^1H NMR δ 2.11 (4H, m), 2.96 (6H, m), 4.90 (1H, m, =CH), 7.0-7.5 (4H, m), 7.96 (1H, br s, NH). MS m/z 224 (M^+), 223 (100 %). HRMS 224.1316, calc. for $C_{15}H_{16}N_2$ 224.1313.

Ketal 15. Aminonitrile 13 (274 mg, 0.60 mmol) was dissolved in 10 mL dry THF, and the solution was stirred under argon at rt. Silver tetrafluoroborate (134 mg, 0.69 mmol) was added to the solution and the resulting black suspension was stirred for 2 hr. The solvent was evaporated and 70 mL methanol saturated with HCl(g) was added. The resulting suspension was stirred for 2 days at rt un-

der argon. The mixture was neutralized with solid $NaHCO_3$, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (120 mL), washed with 8% aq $NaHCO_3$ (30 mL) and water (30 mL), dried (Na_2SO_4) and concentrated to give 198 mg of crude **15** as a dark brown solid. The crude product was purified column chromatographically (Alumina, 1:1 hexane:CH_2Cl_2) yielding 44.1 mg (26 %) pure **15**. ^1H NMR 3.03 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 3.71 (1H, br s, H-12b), 6.9-7.6 (4H, m), 8.41 (1H, br s, NH). ^{13}C NMR 48.1 (q, OCH_3), 49.2 (q, OCH_3), 62.9 (d, C-12b), 100.5 (s, C-1). MS m/z 286 (M^+), 271 (100 %). HRMS found 286.1683, calc. for $C_{17}H_{22}N_2O_2$ 286.1681.

Preparation of the chlorides 16. m-Chloroperbenzoic acid (90 %, 241 mg, 1.26 mmol) in 3 mL dry CH_2Cl_2 was added to a cooled (0 °C) stirred solution of **12** (494 mg, 1.14 mmol) in 5 mL dry CH_2Cl_2. After stirring at 0 °C for 1 hr, the solution was cooled to -15 °C, and trifluoroacetic anhydride (0.39 mL, 2.74 mmol) was added dropwise over 15 min. Stirring was continued for another 1 hr during which time the temperature was allowed to rise to 0 °C. The solvents were evaporated, and the residue dissolved in 10 mL dry CH_2Cl_2. Diethyl ether (25 mL) saturated with HCl(g) was added and the solution stirred overnight. After evporation of the solvents and aqueous work up, 424 mg crude product was obtained. Purification by flash chromatography gave 22 mg (6 %) of the ketone **17** and 179 mg (43 %) of the chlorides **16** as a 4:1 mixture of diastereomers.
17, amorph. IR 1700 (C=O), ^1H NMR 1.4-3.4 (12H, m), 7.0-7.5 (9H, m, aromatic H), 8.65 (1H, br s, NH). ^{13}C NMR 71.6 (s, C-12b), 212.9 (s, C-1). MS m/z 330 (M^+), 239 (100 %). HRMS found 330.1724, calc. for $C_{22}H_{22}N_2O$ 330.1732.
16 ^{13}C NMR : major isomer: 56.9 (d), 57.5 (d), 70.7 (t, OCH_2), 79.1 (d, C-1). minor isomer: 56.7 (d), 57.2 (d), 74.3 (t, OCH_2), 81.1 (d, C-1). MS (both isomers) 368 ($M+2^+$), 366 (M^+), 331 (100 %), 277, 275. HRMS found 366.1514, calc. for $C_{22}H_{23}ClN_2O$ 366.1499.

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