PREPARATION OF ENANTIOMERICALLY PURE DECAHYDRO-6H-ISOQUINO[2,1-g]-[1,6]NAPHTHYRIDINES UTILIZING THE OPENSHAW-WHITTAKER HEXAHYDROBENZO-[a]QUINOLIZINONE RESOLUTION.

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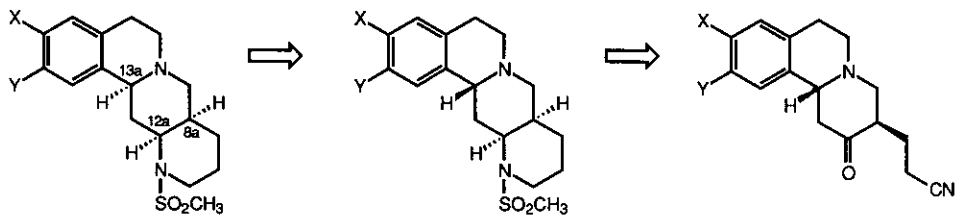
Abstract - The (8aR,12aS,13aS)-decahydro-6H-isoquino[2,1-g][1,6]-naphthyridine sulfonamides 1a,b were prepared from (+)-(3R,11bS)-3-cyanoethylhexahydrobenzo[a]quinolizinones 3a,b. These key intermediates were obtained by resolution of (±)-3a,b with (+)-camphorsulfonic acid in ethyl acetate according to the conditions used in the Openshaw-Whittaker synthesis of (-)-emetine.

The (8aR,12aS,13aS)-12-methylsulfonyldecahydro-6H-isoquino[2,1-g][1,6]-naphthyridines 1a and 1b are potent and selective α_2-adrenoceptor antagonists.[1] Our interest in further pharmacological evaluation of these agents prompted us to develop an efficient process for their preparation on a multi-gram scale. The previous synthesis of 1a,[1] which involved chromatographic separation of diastereomeric optically active α-methylbenzyl-amine ureas, was not deemed practical for this purpose. The retrosynthetic analysis depicted in Scheme 1[2] led us to consider the 3-cyanoethylhexahydro-benzo[a]quinolizinones 3a,b as key intermediates provided they could be efficiently obtained in enantiomerically pure form. This paper describes the realization of this sequence which provides two additional examples of the Openshaw-Whittaker resolution originally used in the synthesis of (-)-emetine.[3]

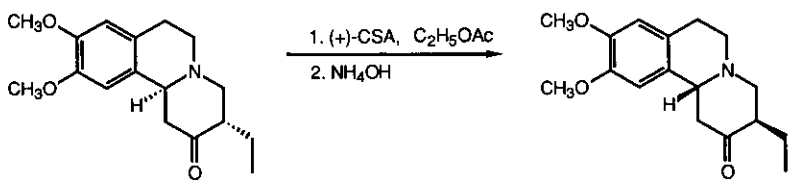
Scheme 1



1a: X = OCH_3, Y = H **2a,b** **3a,b**
1b: X, Y = OCH_2O

In that classical synthesis, the racemic 3-ethylhexahydrobenzo[a]quinolizinone **4** was treated with (+)-10-camphorsulfonic acid ((+)-CSA) in hot ethyl acetate to afford an 81% yield of the (+)-CSA salt of enantiomer (+)-**4**.[3] This process involves precipitation of the less soluble (+)-CSA salt with concurrent racemization of the other enantiomer which remains in solution. This was probably the first example of what was termed a "second order asymmetric transformation"[3] since two asymmetric centers were simultaneously inverted. Other examples of this type of resolution, in which advantage is taken of disparate solubilities of epimerizable substrates, have been reported.[4]

Scheme 2

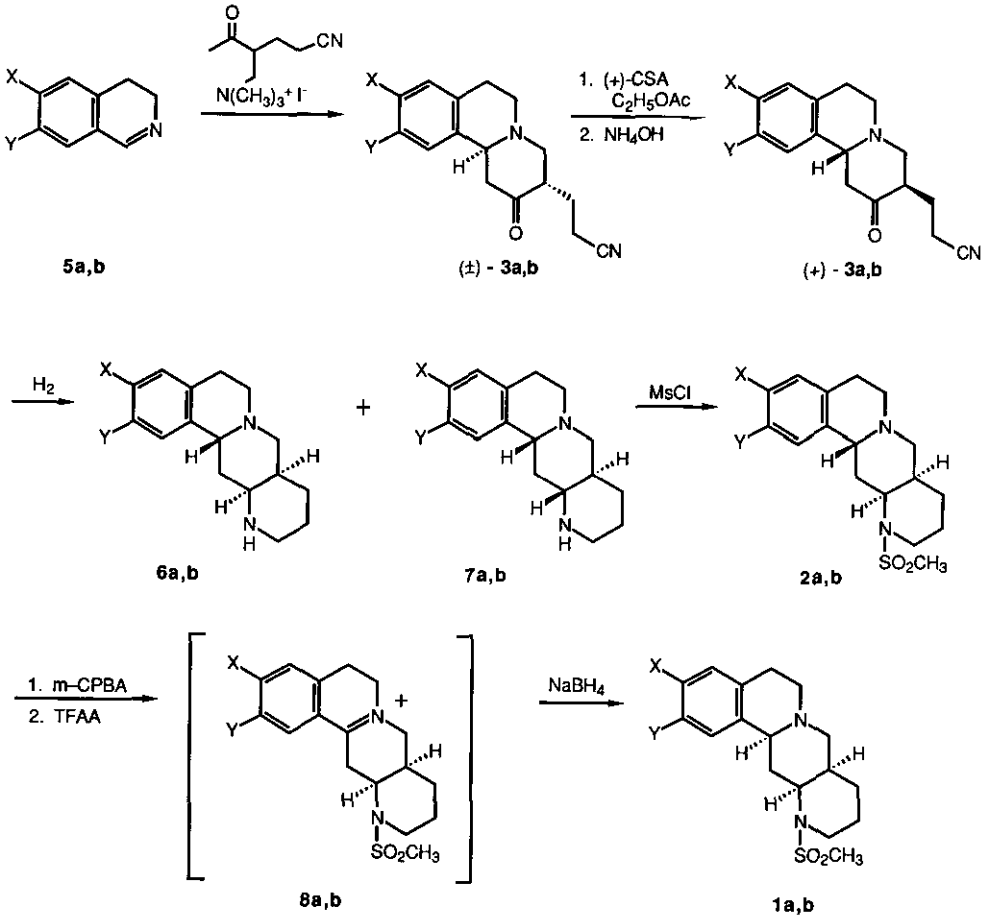


(±) - **4** (+) - **4** (80% yield)

The racemic 3-cyanoethylhexahydrobenzo[a]quinolizinones **3a** and **3b**[5] were prepared in 74% and 56% yield, respectively, as previously described by condensation of trimethyl-(2-acetyl-4-cyanobutyl)ammonium iodide[6,7] with dihydroisoquinolines **5a,b** (Scheme 3). Resolution of **3a** was carried out essentially as described for resolution of **4**.[3] Thus, a solution of

(±)-3a (1 equiv.) and (+)-CSA (1.05 equiv.) in ethyl acetate was seeded with an enriched sample of the (+)-CSA salt of (+)-3a (experimental section) and heated under reflux for 24-48 h. Filtration afforded the (+)-CSA salt of (+)-3a in 55-72% yield. Additional product could be obtained by similar processing of the filtrate to afford yields of greater than 80%. After conversion to the base, the enantiomeric purity of the (+)-3a so obtained was determined to be >99% (>98% ee) by chiral hplc and $Eu(hfc)_3$ nmr analysis.

Scheme 3



a: X = OCH_3, Y = H
b: X, Y = OCH_2O

Resolution of 3b proceeded in a somewhat different, and more efficient, fashion. Addition of (+)-CSA (1.05 equiv.) to a hot ethyl acetate solution of (±)-3b (1 equiv.) caused rapid precipitation of the (+)-CSA salt of (±)-3b. When this heterogeneous mixture was heated and stirred for 24 h, the precipitate was transformed into the pure (+)-CSA salt of (+)-3b which was obtained in 90% yield after filtration. The (+)-3b obtained from this salt was also of high optical purity (> 98% ee) by hplc and nmr analysis.

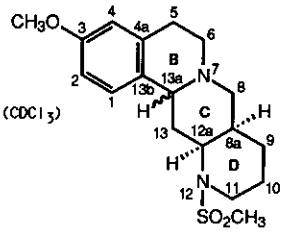
Szantay and co-workers had previously reported that transfer hydrogenation (10% Pd-C, formic acid) of (±)-3b afforded (±)-6b and (±)-7b in yields of 14% and 23%, respectively.[8] We found that the yields of the desired cis-anti products 6a,b were considerably higher under catalytic hydrogenation conditions. Hydrogenation of (+)-3a in THF-ethanol with 5% Rh-Al_2O_3 as catalyst afforded 6a in 61% yield. The undesired stereoisomer 7a was obtained in 12% yield and could be separated by chromatography. A similar yield (63%) of 6b was obtained by reduction of (+)-3b in the same solvent mixture with 5% Rh-C as catalyst.

Mesylation of 6a,b afforded methylsulfonamides 2a,b which were found to be virtually devoid of pharmacological activity. Epimerization to the pharmacologically active isomers 1a,b was effected by stereospecific reduction of iminium ions 8a,b which were generated by the modified Polonovski reaction.[9] A similar strategy was recently used in the interconversion of the alkaloids antirhine and epi-3-antirhine[10] and has its origins in early work on Rauwolfia alkaloids.[11,12] In the present case, conversion of 2a,b to 1a,b was carried out in a one-pot sequence involving oxidation of 2a,b with m-CPBA in dichloromethane followed by addition of trifluoroacetic anhydride to generate iminium ions 8a,b. After evaporation of solvents and addition of ethanol, sodium borohydride reduction stereospecifically afforded 1a,b in overall yields of 50-60%.

^{1}H and ^{13}C nmr data for diastereomers 1a and 2a are presented in Table 1. The ^{1}H nmr data for 1a are consistent with a chair-chair conformation for rings C and D (axial-axial and axial-equitorial couplings for H-13a and H-12a). Bohlmann bands in the ir spectrum of 1a are indicative of a trans B/C ring fusion.[13] Both of these points have been confirmed by single crystal X-ray analysis of the hydrochloride salt of 1a.[14] On the other hand, the B/C ring fusion in 2a appears to be cis. Evidence for this is the absence of Bohlmann bands in the ir spectrum and the lack of an axial-axial coupling for H-13a. The most significant difference in the ^{13}C nmr spectrum of 1a and 2a is an 11 ppm upfield shift of C-8 in 2a which can be explained by increased γ-gauche interactions.[15] It is of interest to note that amine 6a appears to have a trans B/C ring fusion (Bohlmann bands and axial-axial coupling of 10.8 Hz for H-13a) as has been reported for 6b.[8] The reason for this change in B/C ring conformation upon conversion to the sulfonamide is not clear. However, the cis B/C ring fusion observed for 2a is consistent with a similar ring fusion in the related epi-α-yohimbine series.[16]

The absolute stereochemistry of 1a was previously established by X-ray analysis[1] and this served as the basis for the assignment of the absolute stereochemistry of (+)-3a and (+)-3b, as well as of 6a,b and 2a,b. Thus, the Openshaw-Whittaker resolution of (±)-3a,b with (+)-CSA affords enantiomers of the same stereochemical series as in the original resolution of (+)-4.[3]

Table I. ^{1}H (500 MHz) and ^{13}C (125.5 MHz) nmr data for Ia and 2a ($CDCl_3$)



1a: 13a αH
2a: 13a βH

Position	^{1}H Chemical Shift (multiplicity, coupling constant)		^{13}C Chemical Shift (multiplicity)	
	Ia	**2a**	**Ia**	**2a**
1	7.07 (d, 8.6 Hz)	7.25 (d, 8.6 Hz)	125.71 (d)	126.70 (d)
2	6.72 (dd, 8.6, 2.7 Hz)	6.80 (dd, 8.6, 2.8 Hz)	112.06 (d)	112.36 (d)
3			157.8 (s)	158.03 (s)
4	6.62 (d, 2.7 Hz)	6.62 (d, 2.8 Hz)	113.40 (d)	114.22 (d)
4a			135.90 (s)	135.87 (s)
5	2.64 (dd, 16.5, 3.5 Hz) 3.10 (m)	2.50 (m) 3.04 (m)	29.93 (t)	24.58 (t)
6	2.40 (ddd, 11.7, 11.7, 3.5 Hz) 2.85 (dd, 11.7, 5.8 Hz)	3.08 (m) 3.10 (m)	52.10 (t)	50.92 (t)
8	2.55 (dd, 11.7, 3.4 Hz) 2.77 (dd, 11.7, 1.7 Hz)	2.52 (m) 2.90 (dd, 11.7, 4 Hz)	61.01 (t)	51.13 (t)
8a	1.90 (m)	1.80 (m)	35.62 (d)	35.55 (d)
9	1.58 (m) 2.08 (m)	1.58 (m) 2.08 (m)	23.96 (t)	24.49 (t)
10	1.54 (m) 1.72 (m)	1.52 (m) 1.78 (m)	25.44 (t)	24.83 (t)
11	2.94 (ddd, 13, 13, 3 Hz) 3.65 (m)	3.24 (m) 3.42 (m)	40.20 (t)	42.05 (t)
12a	4.18 (dd, 11.6, 3, 3 Hz)	3.80 (m)	53.86 (d)	50.64 (d)
13	1.97 (ddd, 11.6, 11.6, 11.6 Hz) 2.18 (ddd, 11.6, 3, 3 Hz)	2.16 (ddd, 13.6, 4, 4 Hz) 2.64 (ddd, 13.6, 13.6, 4 Hz)	30.67 (t)	27.53 (t)
13a	3.14 (dd, 11.6, 3 Hz)	4.16 (dd, 4, 2 Hz)	61.59 (d)	56.63 (d)
13b			129.71 (s)	127.47 (s)
OCH_3	3.77 (s)	3.78 (s)	55.20 (q)	55.18 (q)
SO_2CH_3	2.92 (s)	2.85 (s)	40.55 (q)	39.17 (q)

EXPERIMENTAL

Silica gel chromatography was performed using 70-230 mesh (Merck) silica gel. Medium pressure (flash) chromatography was performed using 230-400 mesh Merck Kieselgel. Melting points are uncorrected. ^{1}H and ^{13}C nmr spectra were measured on a Bruker WM 300 and a Bruker AM 500 spectrometer in $CDCl_3$ solution referenced to internal tetramethylsilane. Proton assignments were confirmed by ^{1}H-^{1}H homonuclear shift correlation experiments and ^{1}H-^{13}C heteronuclear shift correlation was used to assign the protonated carbons in the ^{13}C nmr spectra.

Trimethyl-(2-acetyl-4-cyanobutyl)ammonium iodide.

A mixture of 5-oxohexanenitrile (167 g, 1.5 mol), chlorotrimethylsilane (227 ml, 1.8 mol), triethylamine (390 ml, 2.8 mol), and N,N-dimethylformamide (600 ml) was heated under reflux for 72 h.[17] The cooled mixture was diluted with 1.2 l of pentane and washed (carefully) with 1.5 l of ice-cold saturated sodium bicarbonate solution. The organic layer was washed twice with water, dried over Na_2SO_4, and evaporated. Distillation at ca. 30 mm Hg afforded 205 g (75%) of a mixture of silyl enol ethers, bp 150-160 °C. ^{1}H Nmr analysis indicated a 83:17 ratio of trisubstituted (multiplet at δ 4.0-4.5) to disubstituted isomer (singlet at δ 3.86). To a solution of this material (147 g, 0.8 mol) in 750 ml of CH_2Cl_2 was added N,N-dimethylmethyleneimmonium chloride (75 g, 0.8 mol). After stirring for 3 h a clear solution resulted. Saturated sodium bicarbonate solution (500 ml) was carefully added followed by NH_4OH to make the aqueous layer strongly basic. The layers were separated and the aqueous was extracted with CH_2Cl_2. The combined CH_2Cl_2 extract was evaporated to a liquid residue which was dissolved in 1 l of ether. Iodomethane (60 ml, 0.96 mol) was added. The gummy precipitate solidified after remaining overnight at room temperature and filtration afforded 155 g (63%) of the product. This material, which contained ca. 10% of the isomeric adduct, was used directly in the next step.

(±)-3-[9-Methoxy-2-oxo-1,3,4,6,7,11bα-hexahydro-2H-benzo[a]quinolizinyl-(3α)]propionitrile (±)-3a).

A solution of 6-methoxy-3,4-dihydroisoquinoline (5a, 69.6 g, 0.43 mol) and methiodide salt from above (134 g, 0.43 mol) in 350 ml of MeOH was heated under reflux for 5 h. The mixture was refrigerated for 14 h and filtered to afford 83.4 g (68%) of analytically pure (±)-3a. An additional 7 g was obtained after refrigeration of the filtrate overnight (total yield 74%), mp 135-136 °C; ^{1}H nmr ($CDCl_3$) δ 1.55 (1H, m, H-2'), 2.15 (1H, m, H-2'), 2.46 (1H, dd, J = 11.6, 11 Hz, H-4_{ax}), 2.50-2.58 (3H, m, CH_2CN, H-1_{ax}), 2.62 (1H, m, H-6), 2.80 (1H, m, H-7), 2.84 (1H, m, H-3), 2.90 (1H, dd, J = 13.7, 3.1 Hz, H-1_{eq}), 3.15 (2H, m, H-6,7), 3.28 (1H, dd, J = 11.4, 6.1 Hz, H-4_{eq}), 3.56 (1H, dd, J = 12, 3.1 Hz, H-11b), 3.78 (3H, s, OMe), 6.68 (1H, d, J = 2.6 Hz, H-8), 6.76 (1H, dd, J = 8.5, 2.6 Hz, H-10), 6.98 (1H, d, J = 8.5 Hz, H-11). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.63; H, 7.04; N, 9.74.

(±)-3-[9,10-Methylenedioxy-2-oxo-1,3,4,6,7,11bα-hexahydro-2H-benzo[a]-quinolizinyl-(3α)]-propionitrile ((±)-3b).

This material was obtained in 56% yield according to the procedure described for (±)-3a, mp 152-153 °C (lit.[5] mp: 154-155 °C).

(3R,11bS)-(+)-3-(9-Methoxy-2-oxo-1,3,4,6,7,11b-hexahydro-2H-benzo[a]-quinolizinyl)propionitrile ((+)-3a).

Seed crystals used below were obtained by adding 25 ml of ether to a solution of (±)-3 (1.0 g, 3.5 mmol) and (+)-10-camphorsulfonic acid (0.8 g, 3.5 mmol) in 25 ml of acetone. After 48 h at room temperature the mixture was filtered to afford 1.27 g of white solid. A small amount of this material was added to a hot solution of (±)-3 (1.0 g, 3.5 mmol) and (+)-CSA (0.8 g, 3.5 mmol) and the resulting mixture, from which a solid gradually separated, was heated under reflux for 16 h. The cooled mixture was filtered to afford 1.4 g solid. This was dissolved in water, basified with NH_4OH, and filtered. The $[\alpha]_D^{25}$ of the resultant solid (+ 21.5°, c 1.5, $CHCl_3$) indicated a slight enrichment in (+)-3a.

To a solution of (±)-3a (5.7 g, 20 mmol) in 50 ml of hot ethyl acetate was added (+)-CSA (4.9 g, 21 mmol). The clear solution was heated at reflux and seeded with ca. 50 mg of the enriched base from above. Reflux was maintained and after 0.5 h a precipitate began to appear. After 48 h under reflux the mixture was allowed to stand at room temperature for 1 h. The precipitate was filtered off and washed with ethyl acetate to afford 7.4 g (72%) of the (+)-CSA salt of (+)-3a, mp 169-170 °C; $[\alpha]_D^{25}$ + 37.5° (c 1, H_2O). Anal. Calcd for $C_{27}H_{36}N_2O_6S$: C, 62.76; H, 7.02; N, 5.42. Found: C, 62.62; H, 7.05; N, 5.23. An additional 10% yield could be obtained by seeding the filtrate and additional reflux.

The (+)-CSA salt of (+)-3a (120 g, 0.23 mol) was dissolved in 5 l of water, cooled in an ice bath, and 70 ml of NH_4OH was added. Filtration afforded 63 g (96%) of (+)-3a after drying under vacuum at 50 °C, mp 116-117 °C, $[\alpha]_D^{25}$ + 122.6° (c 1.2, $CHCl_3$). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.47; H, 7.13; N, 9.78. Enantiomeric purity of (+)-3a was determined by 300 MHz ^1H nmr spectroscopy in $CDCl_3$ using the chiral shift reagent $Eu(hfc)_3$. The largest LIS (lanthanide induced shift) separation was on the H-11 resonance (δ 6.98) where a shift difference of 23 Hz was observed between the two enantiomers at a molar ratio of 0.6:1, $Eu(hfc)_3$ to (±)-3. Under this protocol, (+)-3a was found to be enantiomerically pure within the limits of detection (ca. 1-2%). Analysis on a chiral AGP hplc column (pH 7 phosphate buffer, 5% IPA, 0.3 mL/min) indicated ca 1% of the other enantiomer (98% ee). Retention times were 8.6 and 11.3 min for (-)-3 and (+)-3, respectively.

(3R,11bS)-(+)-3-(9,10-Methylenedioxy-2-oxo-1,3,4,6,7,11b-hexahydro-2H-benzo[a]-quinolizinyl)propionitrile ((+)-3b.

Seed crystals were obtained by adding (+)-CSA (0.24 g, 1.05 mmol) to a refluxing solution of (±)-3b (0.3 g, 1 mmol) in 8 ml of ethyl acetate. After 12 h at reflux, the mixture was cooled and filtered to afford 0.5 g of solid, $[\alpha]_D^{25}$ + 12° (c 0.6, H_2O).

A solution of (±)-3b (124 g, 0.42 mol) in 3.5 l of ethyl acetate was heated to reflux, cooled slightly, and (+)-CSA (102 g, 0.44 mol) and ca 0.1 g of seed crystals from above were added. A great deal of solid formed almost at once. The mixture was heated under reflux for 48 h and then allowed to cool to room temperature. Filtration afforded 198 g (90%) of the (+)-CSA salt of (+)-3b, mp 198-199 °C; $[\alpha]_D^{25}$ + 50.4° (c 0.9, H_2O). Anal. Calcd for $C_{27}H_{34}N_2O_7S$: C, 61.11; H, 6.46; N, 5.28. Found: C, 60.93; H, 6.51; N, 5.16. This material was dissolved in 5 l of water, cooled in an ice bath, and basified with NH_4OH. Filtration gave 110 g (88% overall) of (+)-3b after drying under vacuum at 50 °C; $[\alpha]_D^{25}$ + 134.5° (c 1.5, $CHCl_3$). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.25; H, 6.13; N, 9.45. ^1H Nmr analysis with Eu(hfc)$_3$ indicated that (+)-3b was enantiomerically pure within limits of detection (ca. 1-2%). Analysis was based on the methylenedioxy protons where a LIS difference of 5.1 Hz was observed at a molar ratio of 1:10 substrate to Eu(hfc)$_3$.

(8a*R*,12a*S*,13a*R*)-(+)- and (8a*R*,12a*R*,13a*R*)-(+)-5,8,8a,9,10,11,12,12a,13,13a-Decahydro-3-methoxy-6*H*-isoquino[2,1-*g*][1,6]naphthyridine (6a and 7a).

A mixture of (+)-3a (2.5 g, 8.8 mmol) and 5% Rh-Al_2O_3 (1 g) in 50 ml of THF and 50 ml of ethanol was hydrogenated at 60 psi for 36 h. The catalyst was removed by filtration and solvents were removed en vacuo. Tlc analysis (20% MeOH-CH_2Cl_2, 1% NH_4OH) showed a major product (6a) at R_f 0.6 and a minor product (7a) at R_f 0.4. Chromatography on silica gel (12% MeOH-CH_2Cl_2-1% NH_4OH) afforded 1.46 g (61%) of 6a as an oil which slowly crystallized, mp 110-112 °C; $[\alpha]_D^{25}$ + 101.5° (c 0.4, $CHCl_3$); ^1H nmr ($CDCl_3$) δ 1.44 (1H, m), 1.65 (3H, m), 1.75 (1H, m), 2.08 (1H, m), 2.20 (1H, ddd, *J* = 2.5,2.5,13.8 Hz), 2.58 (1H, dd J= 11.5, 4.2 Hz), 2.60-2.80 (3H, m), 2.94 (2H, m) 3.15 (3H, m), 3.52 (1H, broad d, J = 10.8 Hz, H-13a), 3.76 (3H, s) 6.60 (1H, d, J = 2.6 Hz, H-4), 6.68 (1H, dd, J = 8.6, 2.6 Hz, H-2), 7.06 (1H, d, J= 8.6 Hz, H-1); ir ($CHCl_3$) 2820 cm^{-1} (Bohlmann bands). A dihydrochloride salt was prepared from ethanol-ether, mp 285-287 °C. Anal. Calcd for $C_{17}H_{24}N_2O.2HCl$: C, 59.13; H, 7.59; N, 8.11. Found: C, 58.85; H, 7.76; N, 7.88.

Further elution afforded 0.3 g (12%) of isomer 7a, mp 148-150 °C; $[\alpha]_D^{25}$ + 105° (c 0.8, $CHCl_3$); ir ($CHCl_3$) 2810, 2760 cm^{-1} (Bohlmann bands). A dihydrochloride salt was prepared from ethanol-ether, mp 285-287 °C. Anal. Calcd for $C_{17}H_{24}N_2O \cdot 2$ HCl: C, 59.13; H, 7.59; N, 8.11. Found: C, 58.85; H, 7.76; N, 7.88.

(8a*R*,12a*S*,13a*R*)-(+)-5,8,8a,9,10,11,12,12a,13,13a-Decahydro-2,3-methylenedioxy-6H-isoquino[2,1-*g*][1,6]naphthyridine (6b).

Hydrogenation of (+)-3b (58 g, 0.2 mol) with 5% Rh-C (20 g) in 750 ml of THF and 750 ml of ethanol as described for 6a afforded 35 g (63%) of 6b after chromatographic purification, oil: $[\alpha]_D^{25}$ + 119.4° (c 1.8, $CHCl_3$); ^1H nmr ($CDCl_3$) δ 3.48 (1H, broad d, J = 11.4 Hz, H-13a), 5.87 (2H, s), 6.52 (1H, s), 6.62 (1H, s).

(8a*R*,12a*S*,13a*R*)-(+)-5,8,8a,9,10,11,12,12a,13,13a-Decahydro-3-methoxy-12-methylsulfonyl-6H-isoquino[2,1-*g*][1,6]naphthyridine (2a).

A solution of 6a (18 g, 66 mmol) in 200 ml of CH_2Cl_2 containing 10 ml of triethylamine was cooled in an ice bath and methanesulfonyl chloride (5.8 ml, 75 mmol) was added. The mixture was allowed to warm to room temperature over 3 h and was then concentrated en vacuo. The residue was partitioned between dilute HCl and ethyl acetate. The aqueous layer was basified with NH_4OH and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried (Na_4SO_2) and evaporated to a solid residue that extract was crystallized from CH_2Cl_2-ether to afford 21 g (91%) of 2a, mp 140-142 °C; $[\alpha]_D^{25}$ + 17.6° (c 0.4, $CHCl_3$). Anal. Calcd for $C_{18}H_{26}N_2O_3S$: C, 61.68; H, 7.48; N, 7.99. Found: C, 61.58; H, 7.52; N, 7.84.

(8a*R*,12a*S*,13a*R*)-(+)-5,8,8a,9,10,11,12,12a,13,13a-Decahydro-2,3-methylenedioxy-12-methylsulfonyl-6H-isoquino[2,1-*g*][1,6]naphthyridine (2b).

Mesylation of 6b as described above afforded 2b (95% yield), mp 219-220 °C (EtOH); $[\alpha]_D^{25}$ + 45.3° (c 1.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.32; H, 6.64; N, 7.69. Found: C, 59.59; H, 6.64; N, 7.50.

(8a*R*,12a*S*,13a*S*)-(-)-5,8,8a,9,10,11,12,12a,13,13a-Decahydro-3-methoxy-12-methylsulfonyl-6*H*-isoquino[2,1-*g*][1,6]naphthyridine (1a).

A solution of 2a (3.5 g, 10 mmol) in 50 ml of chloroform was cooled in an ice bath and *m*-chloroperoxybenzoic acid (ca. 85%, 2.6 g, 13 mmol) was added. The mixture was stirred in the bath for 1 h and trifluoroacetic acid (6 ml, 78 mmol) was added. After 3 h at room temperature the mixture was concentrated en vacuo and 30 ml of ethanol was added. The resulting solution was cooled to -20 °C and 15% NaOH was added until the pH was ca. 8 (litmus paper). Sodium borohydride (1.9 g, 50 mmol) was added in small portions until the imminium ion (R_f 0.6, 20% MeOH-CH_2Cl_2-1% NH_4OH) was no longer evident by tlc *analysis. The mixture was diluted with water and extracted with* CH_2Cl_2. The CH_2Cl_2 was evaporated and the residue was purified by medium pressure chromatography (60% ethyl acetate-hexane) to afford 2.1 g (60%) of 1a which was identical to material previously prepared by a different route[1], mp 165-166 °C; $[\alpha]_D^{25}$ - 54.2° (c 1.1, $CHCl_3$); ir ($CHCl_3$) 2820, 2760 cm^{-1} (Bohlmann bands). Anal. Calcd for $C_{18}H_{26}N_2O_3S$: C, 61.68; H, 7.48; N, 7.99. Found: C, 61.55; H, 7.51; N, 8.01.

(8a*R*,12a*S*,13a*S*)-(-)-5,8,8a,9,10,11,12,12a,13,13a-Decahydro-2,3-methylenedioxy-12-methylsulfonyl-6*H*-isoquino[2,1-*g*][1,6]naphthyridine (1b).

This was prepared in 50% overall yield from 6b according to the procedure described for the preparation of 1a, mp 113-115 °C; $[\alpha]_D^{25}$ - 84.4°; (c 1.05, $CHCl_3$). A hydrochloride salt was prepared from ethanol-ether, mp 263-265 °C; $[\alpha]_D^{25}$ - 17° (c 0.9, MeOH). Anal. Calcd for $C_{18}H_{24}N_2O_4S \cdot HCl$: C, 53.92; H, 6.29; N, 6.99. Found: C, 53.63; H, 6.41; N, 6.86.

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