Stereospecific Synthesis of the (3aα,11α,12aα)-Decahydrobenzo[*a*]pyrrolo[3,2-*g*]quinolizine Ring System

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A stereospecific synthesis of racemic (3aα,11bα,12aβ)-1,2,3,3a,4,6,7,11b,12,12a-decahydro-9-methoxy-1-(methylsulfonyl)benzo[α]pyrrolo[3,2-*g*]quinolizine (**2**) is reported. Cyclocondensation of lithiated pyrrolecarboxamide **5** and dihydroisoquinoline **6** afforded the key tetracyclic intermediate **7**. Hydrogenation of **7** gave the 3aα,11bα,12aα-isomer **9** which was subsequently converted to **2**.

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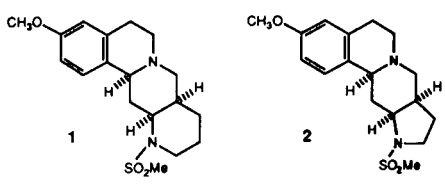
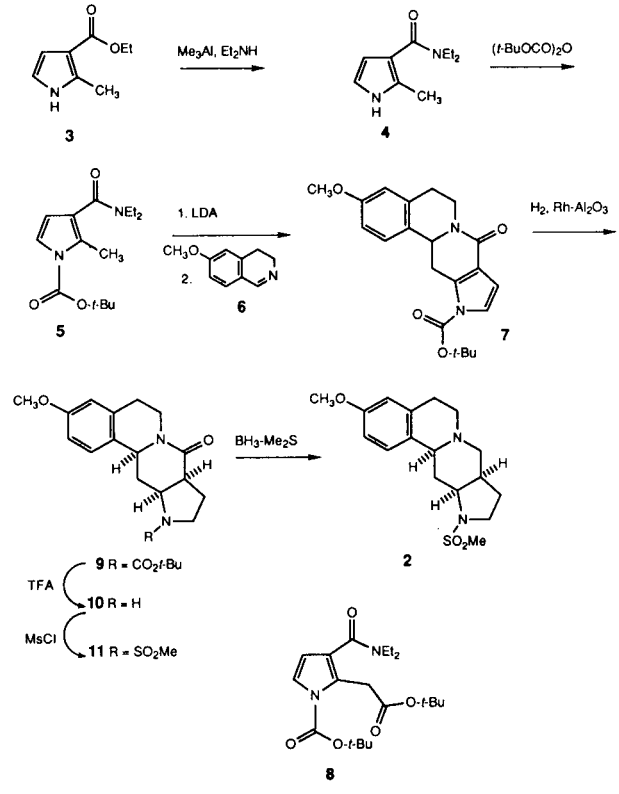
We have previously reported the synthesis and pharmacological characterization of the decahydroisoquino[2,1-*g*]-naphthyridine sulfonamide **1** [1,2]. This compound, which bears some structural resemblance to the natural product rauwolscine, is a potent and selective *alpha*-two adrenoceptor antagonist and is currently undergoing clinical evaluation. Our continuing interest in the structure-activity relationships of *alpha*-two antagonists [3] prompted us to prepare the D-ring seco analogue **2**. In this note we report a stereospecific synthesis of the racemate of this compound.

Entry into the desired tetracyclic ring system involved a variation of previously exploited toluamide-imine cyclocondensation methodology [1,4]. Ethyl 2-methylpyrrole-3-carboxylate (**3**) [5] was converted in two steps to the 1-*tert*-butoxycarbonyl (BOC) protected pyrrole diethylamide **5**. Treatment of **5** with lithium diisopropylamide afforded the lithio derivative which was treated with 3,4-dihydro-6-methoxyisoquinoline (**6**) to afford the key cyclocondensation product **7** in 55% yield. The modest yield of **7** was due in part to the propensity of the lithio derivative of **5** to undergo intermolecular acylation as evidenced by the formation of compound **8** in 15% yield (along with a corresponding amount of deacylated starting pyrrole carboxamide **4**). Nonetheless, the yield of **7** was considered acceptable in light of the ready accessibility of starting materials **5** and **6** and the convergent, single-step nature of the route.

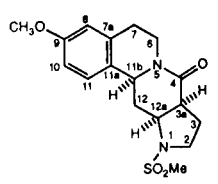
By analogy with our previous experience in the catalytic hydrogenation of the pyridone progenitor of **1** [1], it was anticipated that reduction of **7** would lead to the *cis-syn* stereoisomer **9** as the major product. However, it was somewhat surprising that hydrogenation of **7** (5% rhodium-alumina, ethanol, 40 psi) [6] afforded **9** as the sole product. There is no apparent reason for the stereospecificity of this hydrogenation. Both an examination of molecular models and computer modeling indicate that **7** is a relatively flat molecule and that the *tert*-butoxycarbonyl group lies predominantly within the plane of the pyrrole (D) ring. However, the *tert*-butoxycarbonyl group is implicated as an important factor since hydrogenation of the corresponding *N*-benzyl pyrrole derivative afforded a mixture of diastereomers [7].





The stereochemistry of **9** was assigned by detailed ^{1}H nmr spectral analysis of the derived methylsulfonamide (**11**) obtained by standard deprotection (trifluoroacetic acid) to **10** and subsequent mesylation. The spectrum of **11** was easier to analyze since **9** appeared to exist as a mixture of *tert*-butoxycarbonyl rotamers. Particularly diagnostic features of the ^{1}H nmr spectrum of **11** (Table 1) were the observed *trans*-diaxial couplings between H-12 (axial)

Table 1. ^{1}H nmr data for **11**



proton	chemical shift (δ)	multiplicity	coupling constant (Hz)
H-2	3.26	ddd	6.34, 7.99, 10.21
H-2	3.52	ddd	1.79, 7.80, 7.99
H-3	2.13	dddd	7.80, 10.21, 11.73, 12.92
H-3	2.55	dddd	1.79, 6.34, 7.99, 12.92
H-3a	3.08	ddd	7.99, 8.55, 11.73
H-6 (ax)	2.92	m	
H-6 (eq)	4.69	m	
H-7 (ax)	2.72	m	
H-7 (eq)	2.90	m	
H-8	6.67	d	2.62
H-10	6.80	dd	2.62, 8.67
H-11	7.13	d	8.67
H-11b	4.63	dd	2.80, 11.60
H-12 (ax)	1.64	ddd	11.60, 11.87, 13.56
H-12 (eq)	2.81	ddd	2.80, 4.96, 13.56
H-12a	4.11	ddd	4.96, 8.55, 11.87
SO_2CH_3	2.89	s	
OCH_3	3.79	s	

[a]Determined at 500 MHz in deuteriochloroform

Table 2. Nuclear Overhauser Effect data for **11**[a]

proton irradiated	observed nOe
H-11b	H-11, H-12a, H-6 (ax), H-12 (eq)
H-12a	H-11b, H-3a, H-12 (eq)
H-3a	H-12a, H-3

[a]Determined at 300 MHz in deuteriochloroform

and H-12a and between H-3a and H-3 (pseudo-axial). Neither of these couplings would be anticipated for the alternative *cis*-C,D ring diastereomer. Further confirmation of the stereochemical assignments was obtained by nuclear Overhauser experiments (Table 2) which demonstrated the *cis*-relationships of the three bridgehead protons (H-11b, H-12a, and H-3a).

Reduction of lactam **11** with borane-methylsulfide complex furnished the target compound **2**. As was previously established for homolog **1**, the C-ring of **2** appears to be in a chair conformation [*trans*-diaxial coupling between H-12a and H-12 (axial)] and the B-C ring juncture is *trans* (Bohlmann bands in the ir spectrum). Thus, the reduction of **11** proceeded without change in stereochemistry.

The affinity of **2** for *alpha*-two adrenoceptors of rat cerebral cortex was measured by displacement of [^{3}H]yohimbine and a p*K*i value of 8.5 was determined (compared to a p*K*i of 9.1 for racemic **1**). The high *alpha*-two adrenoceptor affinity of **2** is further confirmation that this compound belongs to the same stereochemical series as homolog **1**. On the basis of results obtained on diastereomers of **1**, the alternative (*cis-anti*) isomer would be expected to have lower affinity by 2-3 log orders [1].

In conclusion, we have achieved a short and convergent synthesis of the decahydrobenzo[*a*]pyrrolo[3,2-*g*]quinolizine ring system. This synthesis is further evidence of the utility of tolyl lithio derivatives in the preparation of heterocycles.

EXPERIMENTAL

Silica gel chromatography was performed under medium pressure using 230-400 mesh Merck Kieselgel. Melting points are uncorrected. Microanalyses were performed by the Syntex Analytical Department. Pmr and cmr spectra were measured on a Bruker WM 300 and AM 500 spectrometer in deuteriochloroform 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 cmr spectra.

N,N-Diethyl-2-methylpyrrole-3-carboxamide (**4**).

A solution of diethylamine (26 ml, 0.25 mole) in 500 ml of toluene was cooled in an ice bath and a solution of trimethylaluminum in toluene (125 ml of 2 *M*, 0.25 mole) was slowly added. The resulting mixture was stirred at room temperature for 1 hour and ethyl 2-methylpyrrole-3-carboxylate (**3** [5]) (30.6 g, 0.2 mole) was then added. The solution was heated at reflux for 24 hours, cooled, and cold dilute hydrochloric acid was added until the aqueous layer was acidic. The toluene layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried (sodium sulfate) and evaporated. Crystallization of the residue from ethyl acetate afforded 20.0 g (56%) of *N,N*-diethyl-2-methylpyrrole-3-carboxamide, mp 120-121°; ir: (potassium bromide) λ 3200 (NH), 1590 (C = O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.18 (t, 6H, J = 7.1 Hz), 2.15 (s, 3H), 3.48 (q, 4H, J = 7.1 Hz), 6.10 (dd, 1H, J = 2.7, 2.7 Hz), 6.45 (dd, 1H, J = 2.7, 2.7 Hz), 9.45 (br s, 1H, NH).

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.55. Found: C, 66.41; H, 9.01; N, 15.63.

N,N-Diethyl-1-(*tert*-butoxycarbonyl)-2-methylpyrrole-3-carboxamide (**5**).

A solution of amide **4** (25.5 g, 0.14 mole) and di-*tert*-butyl dicarbonate (32.7 g, 0.15 mole) in 250 ml of acetonitrile was stirred at room temperature for 4 hours. The solution was concentrated *in vacuo*, water was added, and the mixture was extracted with ethyl acetate. The ethyl acetate was washed with water and brine, dried (sodium sulfate), and evaporated. Purification by silica gel chromatography (40% ethyl acetate-hexane) afforded 39.0 g (98%) of **5** as a thick oil; ir (neat film): γ 1745, 1626 (C = O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.03 (t, 6H, J = 7.0 Hz), 1.53 (s, 9H), 2.38 (s, 3H), 3.36 (q, 4H, J = 7.0 Hz), 6.03 (d, 1H, J = 2.9 Hz), 7.08 (d, 1H, J = 2.9 Hz).

Anal. Calcd. for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: 64.16; H, 8.82; N, 10.16.

1-(*tert*-Butoxycarbonyl)-1,4,6,7,11b,12-hexahydro-9-methoxybenzo[*a*]pyrrolo[3,2-*g*]quinolizine (**7**).

A solution of *n*-butyllithium in hexane (12.5 ml, 1.6 *M*, 20 mmoles) was added to a −70° solution of diisopropylamine (2.8 ml, 20 mmoles). A solution of pyrrole **5** (4.2 g, 15 mmoles) in 7 ml of tetrahydrofuran was added and the resulting yellow solution was stirred at −70° for 3 minutes. A solution of 3,4-dihydro-6-methoxyisoquinoline (**6**) (2.9 g, 18 mmoles) in 5 ml of tetrahydrofuran was added. The resulting dark solution was stirred for 30 minutes at −70° and was then allowed to warm to −30° over a

30 minute period. Water (100 ml) was added and the mixture was extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, water, and brine, dried (sodium sulfate), and evaporated. Medium pressure chromatography of the residue afforded 3.04 g (55%) of **7** as a white crystalline solid, mp 121-122°; ir (potassium bromide): γ 1747, 1651 (C = O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.62 (s, 9H), 2.75-3.00 (m, 4H), 3.81 (s, 3H), 3.88 (dd, 1H, J = 4.9, 17.2 Hz), 4.82 (m, 1H), 4.95 (dd, 1H, J = 4.9, 13.6 Hz), 6.62 (d, 1H, J = 3.4 Hz), 6.72 (d, 1H, J = 2.6 Hz), 6.82 (dd, 1H, J = 2.6, 8.7 Hz), 7.18 (m, 2H); ms: (electron impact) m/z 368 (molecular ion), 312, 267, 162.

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.56; N, 7.61. Found: C, 68.27; H, 6.60; N, 7.57.

N,N-Diethyl-1-(*tert*)-butoxycarbonyl)-2-(*tert*-butoxycarbonyl)methylpyrrole-3-carboxamide (**8**).

This compound was obtained in 14% yield as a less polar component from the chromatographic purification of **7**, mp 94-95°; ir (potassium bromide); γ 1750, 1726, 1620 (C = O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.16 (br t, 6H), 1.43 (s, 9H), 1.57 (s, 9H), 3.45 (br q, 4H), 3.90 (s, 2H), 6.14 (d, 1H, J = 3.4 Hz), 7.20 (d, 1H, J = 3.4 Hz).

Anal. Calcd. for $C_{20}H_{32}N_2O_5$: C, 63.14; H, 8.48; N, 7.36. Found: C, 63.02; H, 8.29; N, 7.28.

3aα,11bα,12aα)-1,2,3,3a,4,6,7,11b,12,12a-Decahydro-9-methoxy-4-oxobenzo[*a*]pyrrolo[3,2-*g*]quinolizine (**10**).

A mixture of **7** (15.0 g, 40.8 mmoles) and 3.5 g of 5% rhodium on alumina in 200 ml of ethanol was hydrogenated at 40 psi for 4 hours. The mixture was filtered and evaporated to 15.2 g (100%) of the 1-(*tert*-butoxycarbonyl) derivative **9** as an oil. Tlc analysis showed a single spot at R_f 0.6 (ethyl acetate). This material was dissolved in 100 ml of dichloromethane and trifluoroacetic acid (15 ml) was added. The resulting solution was stirred at room temperature for 12 hours, diluted with additional dichloromethane, and carefully washed with cold aqueous ammonium hydroxide. The basic aqueous layer was extracted twice with dichloromethane and the combined extracts were dried (sodium sulfate) and evaporated. Tlc analysis showed a single spot at R_f 0.3 (10% methanol-dichloromethane, 0.1% ammonium hydroxide). Purification by medium pressure chromatography (same solvent as tlc) afforded 7.8 g (70%) of **10**, mp 98-99°; ir (potassium bromide): γ 3400 (NH), 1632 (C = O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.52 (m, 1H), 2.10 (m, 1H), 2.34 (m, 1H), 2.50 (m, 1H), 2.72 (m, 1H), 2.80-3.10 (m, 6H, includes NH), 3.74 (m, 1H), 3.80 (s, 3H), 4.64 (br d, 1H, H-11b), 4.72 (m, 1H), 6.68 (d, 1H, J = 2.7 Hz), 6.80 (dd, 1H, J = 2.7, 8.6 Hz), 7.10 (d, 1H, J = 8.6 Hz).

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.38; H, 7.34; N, 9.99.

(3aα,11bα,12aα)-1,2,3,3a,4,6,7,11b,12,12a-Decahydro-9-methoxy-1-(methylsulfonyl)-4-oxobenzo[*a*]pyrrolo[3,2-*g*]quinolizine (**11**).

Methanesulfonyl chloride (1.15 g, 10.0 mmoles) was added to a solution of **10** (2.04 g, 7.5 mmoles) in 50 ml of dichloromethane and 2 ml of triethylamine and the resulting solution was stirred for 1 hour. The mixture was washed with water, dilute hydrochloric acid, and brine, dried (sodium sulfate) and evaporated. Purification by medium pressure chromatography (10% methanol-ethyl acetate) afforded 2.23 g (85%) of **11** as a white solid, mp 220-221°; ir (potassium bromide): γ 1628 (C = O), 1330 cm^{-1}; cmr (deuteriochloroform): δ 29.21 and 21.29 (2t, C-7 and C-12), 35.81 (s, SO_2CH_3), 37.92 (t, C-3), 39.25 (t, C-6), 44.12 (d, C-3a), 47.19 (t, C-2), 53.80 (d, C-12a), 55.29 (s, OCH_3), 55.78 (d, C-11b), 112.99 and 113.45 (2d, C-8 and C-10), 126.78 (d, C-11), 127.48 (s, C-11a), 136.23 (s, C-7a), 158.33 (s, C-9), 168.62 (s, C-4).

Anal. Calcd. for $C_{17}H_{22}N_2O_4S$: C, 58.26; H, 6.33; N, 8.00. Found: C, 58.16; H, 6.33; N, 7.98.

(3aα,11bα,12aα)-1,2,3,3a,4,6,7,11b,12,12a-Decahydro-9-methoxy-1-(methylsulfonyl)benzo[*a*]pyrrolo[3,2-*g*]quinolizine (**2**).

Borane-methylsulfide complex (2 ml, 1.6 g, 21 mmoles) was added to a solution of **11** (2.00 g, 5.7 mmoles) in 150 ml of tetrahydrofuran. The resulting solution was heated under reflux for 3 hours, cooled in an ice bath, and 5 ml of water followed by 5 ml of concentrated hydrochloric acid were carefully added. The mixture was heated under reflux for 45 minutes and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water and the aqueous (acidic) layer was separated, made basic with ammonium hydroxide, and extracted with dichloromethane. The dichloromethane extract was evaporated and purification of the residue by medium pressure chromatography (ethyl acetate) afforded 1.6 g (83%) of **2** as a white solid, mp 182-183°; ir (potassium bromide): γ 2820, 2760 (Bohlmann bands), 1360, 1150 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.55 [ddd, 1H, J = 11.4, 11.4, 12.8 Hz, H-12 (ax)], 1.94 (m, 1H), 2.24-2.70 (m, 8H), 2.86 (s, 3H), 3.05 (m, 2H), 3.34 (m, 1H), 3.45 (m, 1H), 3.77 (s, 3H), 3.96 (ddd, 1H, J = 6.6, 6.6, 11.0 Hz, H-12a), 6.62 (d, 1H, J = 2.7 Hz), 6.72 (dd, 1H, J = 2.7, 8.7 Hz), 7.10 (d, 1H, J = 8.7 Hz).

Anal. Calcd. for $C_{17}H_{24}N_2O_3S$: C, 60.68; H, 7.19; N, 8.33. Found: C, 60.40; H, 7.15; N, 8.24.

The hydrochloride salt of **2** crystallized from ethanolic hydrogen chloride upon addition of ethyl ether, mp 253-254°.

Anal. Calcd. for $C_{17}H_{25}ClN_2O_3S$: C, 54.75; H, 6.76; N, 7.51. Found: C, 54.72; H, 6.84; N, 7.42.

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[7] R. D. Clark and D. B. Repke, unpublished results. It was also found that the *N*-benzyl group was reduced to cyclohexylmethyl, thereby precluding removal of the *N*-protecting group.