

The Structure of McN-5652

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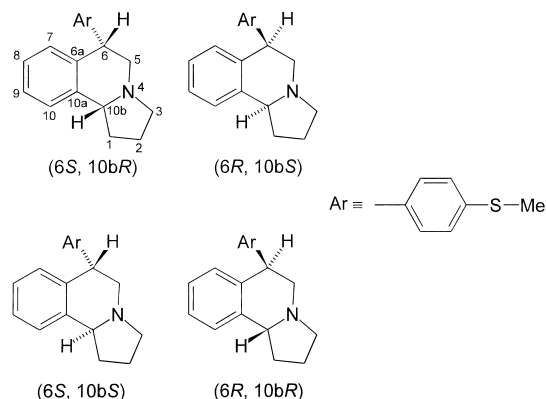
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Abstract—The configuration of the diastereoisomers of 6-(4-methylthiophenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline **1** (McN-5652) is determined and unequivocally assigned by NMR spectroscopy (NOE measurements) and an X-ray structural analysis of the *trans* diastereoisomer. The enantiomers of *cis*-**1** are separated by preparative HPLC on a chiral phase. One of the enantiomers of *cis*-**1** represents the precursor for imaging the serotonin 5-HT transporter with positron emission tomography (PET). © 2001 Elsevier Science Ltd. All rights reserved.

Introduction

McN-5652-Z is a highly potent serotonin 5-HT transporter uptake blocker. Its [¹¹CH₃] derivative allows the visualization and evaluation of the serotonergic transporter density by the method of positron emission tomography (PET).^{1–4} These studies might reveal what damage is caused to the brain by drug (MDMA, e.g., Ecstasy) abuse and whether the damaged brain can regenerate after the drug abuse is stopped. The chemical name of this compound is 6-(4-methylthiophenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (**1**). Due to the fact that this compound possesses two centres of asymmetry there are four stereoisomers (6*S*, 10*bR*)-**1**, (6*R*, 10*bS*)-**1**, (6*S*, 10*bS*)-**1** and (6*R*, 10*bR*)-**1** (Scheme 1). Regarding the position of the hydrogen atoms at C-6 and C-10b the two enantiomeric pairs should be called ‘*cis*’ or ‘*trans*’. Because it is known that these four isomers possess different *K_i* values for the serotonin 5-HT transporter uptake inhibition,^{3–7} it is important to characterize their chemical configuration correctly. Although a lot of work has been performed

on these compounds there is still a lack of information about the correct stereochemistry of the individual isomers. The information that can be found in the literature is misleading and contradictory,^{5,6} that is a *cis*-stereoisomer can be found in a scheme but in the text it is called *trans*.⁶ Furthermore, to the best of our knowledge, there has never been an unequivocal proof of the correct identification of any isomer.



Scheme 1. The four stereoisomers of **1**: two *cis*-enantiomers (top) and two *trans*-enantiomers (bottom).

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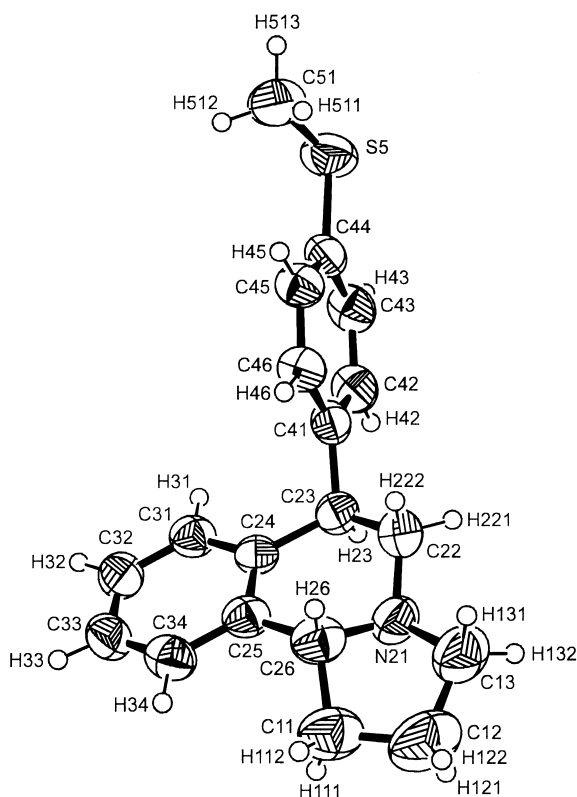


Figure 3. ORTEP view of the X-ray diffraction structure of racemic *trans*-1 [only the (6*R*, 10*bR*)-enantiomer is shown] with atom numbering. Thermal ellipsoids are drawn at the 50% probability level.

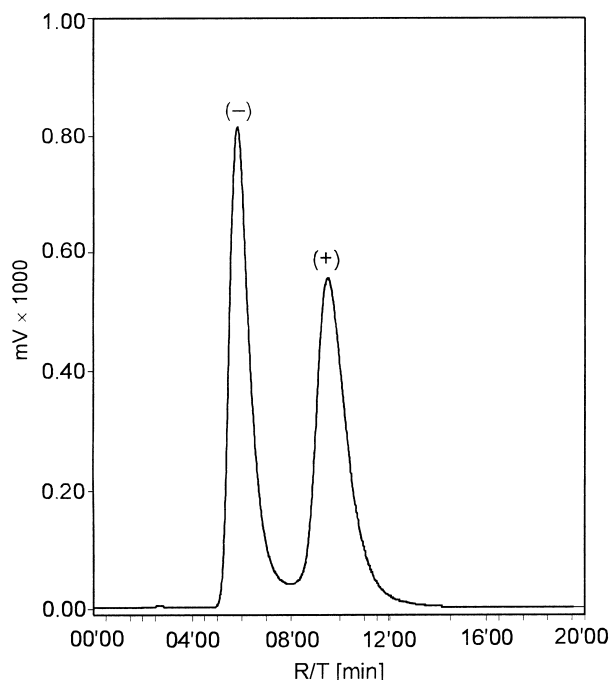


Figure 4. HPLC separation of the two enantiomers of *cis*-1.

Nevertheless, we did not know, whether the *cis*- or the *trans*-diastereoisomer was the more potent serotonin uptake blocker. Comparison with an authentic sample of the most active isomer proved, however, that it was identical with our *cis*-diastereoisomer. In order to find out which of the two *cis*-enantiomers was the previously described (+)-enantiomer,⁵ we had to separate and compare them with an authentic sample of the (+)-McN-5652-Z enantiomer.⁸ Therefore, we developed a separation on a chiral column. The chiralpak[®] AD material [amylose tris(3,5-dimethylphenyl)carbamate] showed very good separation of the (+)/(-)-enantiomers. A representative chromatogram of the separation of the *cis*-enantiomers is given in Figure 4. The (-)-enantiomer was eluted first as compared with the reference sample.

Since **1** is a compound of high physiological activity we have, finally, performed a 3-D QSAR calculation based on our X-ray structural data using the HyperChem[®] software.⁹ The calculated data are compiled in Table 1.

Experimental

General procedures

Melting points were determined by the use of an Electrothermal apparatus (values are corrected). IR spectra were measured with an ATI Mattson Genesis spectrometer. NMR spectra were recorded with Bruker AMX 400 and DRX 500 spectrometers. Chemical shifts (ppm) are related to Me₄Si (¹H and ¹³C). Coupling constants *J* are given in Hz. Multiplicity abbreviations: multiplet (m), singlet (s), doublet (d). Standard correlation techniques were used for assignments. Mass spectra were measured on Varian CH 7 (EI, 70 eV) and VG Analytical 70-250 S (HRMS) apparatus. TLC was carried out on E. Merck PF₂₅₄ foils (detection: UV light, EtOH–H₂SO₄ spray/200 °C), and column chromatography on E. Merck Kieselgel 60 (70–230 mesh). Solvents were purified and dried according to standard laboratory procedures.¹⁰ The purity of the separated diastereoisomers was analyzed with HPLC on nucleosil 100 3 C18, 125×3 mm. The mobile phase was 50% acetonitrile/50% water with 0.02 mol ammonium formate.

The preparative separation of the (+)/(-)-enantiomers was performed on a 250×10 mm column packed with chiralpak[®] AD 25 μm. The mobile phase was 97% *n*-hexane/3% 2-propanol/0.05% triethylamine.

Table 1. Theoretical QSAR parameters for *trans*-1

Partial charge	Net charge = 0.00 e
Surface area (approx.)	428.20 Å ²
Surface area (grid)	508.27 Å ²
Volume	850.66 Å ³
Hydration energy	−1.04 kcal mol ^{−1}
LogP	1.44
Refractivity	100.02 Å ³
Polarizability	35.74 Å ³
Mass	295.44 amu

Table 2. Crystal data and structure refinement for *trans*-1^a

Diffractometer	KappaCCD Nonius
Molecular formula	C ₁₉ H ₂₁ NS
Molecular weight (g mol ⁻¹)	295.43
Temperature (K)	293(2)
Wavelength (Å)	0.7107, MoK _α , graphite monochromated
Scan mode	Rotation Φ
Crystal system	Monoclinic
Space group	P2 ₁ /c
Unit cell dimensions	<i>a</i> = 17.278(1) Å <i>b</i> = 5.661(1) Å <i>c</i> = 25.069(1) Å <i>α</i> = <i>γ</i> = 90° <i>β</i> = 138.39(1)°
Volume (Å ³)	1628.3(3)
Z (molecules per cell)	4
D _{calc} (g cm ⁻³)	1.205
Absorption coefficient (mm ⁻¹)	0.192
<i>F</i> (000)	632
Crystal size (mm)	0.39 × 0.35 × 0.32
θ Range for data collection (°)	1.63–25.02
Index ranges	0 ≤ <i>h</i> ≤ 20; 0 ≤ <i>k</i> ≤ 6; -29 ≤ <i>l</i> ≤ 19
Reflections collected	7579
Independent reflections	2810
Reflections with <i>I</i> ≥ 2σ(<i>I</i>)	2218
Refinement method	Full-matrix-block least-squares on <i>F</i> ²
Function minimized	$\sum w(F_o^2 - F_c^2)^2$, $w = 1/[\sigma^2(F_o^2) + (0.1160P)^2 + 0.7813P]$, where $P = (F_o^2 + 2F_c^2)/3$
H-Atom refinement	Geom. and difmap
Data/restraints/parameters	2810/0/245
Goodness-of-fit on <i>F</i> ²	1.050
Final <i>R</i> indices [<i>I</i> ≥ 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0556, <i>wR</i> ₂ = 0.1556
<i>R</i> Indices (all data)	<i>R</i> ₁ = 0.0773, <i>wR</i> ₂ = 0.2012
Largest difference peak and hole (e Å ⁻³)	0.248 and -0.336

^aFull crystallographic details, excluding structure features, have been deposited with the Cambridge Crystallographic Data Centre. These data may be obtained, on request, from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Tel.: +44-1223-336408; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk (deposition number CCDC-142696).

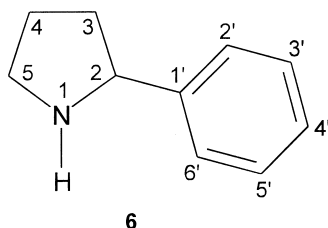
Table 3. Selected bond lengths (pm), bond angles (°) and torsion angles (°) of *trans*-1

S(5)–C(44)	176.3 (3)	C(23)–C(24)–C(25)	121.6 (2)
S(5)–C(51)	176.5 (4)	C(24)–C(25)–C(26)	119.4 (3)
N(21)–C(13)	145.4 (4)	C(24)–C(25)–C(34)	119.3 (3)
N(21)–C(22)	144.5 (4)	C(11)–C(26)–C(25)	119.2 (3)
N(21)–C(26)	145.2 (5)	C(23)–C(41)–C(42)	121.5 (2)
C(11)–C(12)	151.2 (7)	C(22)–N(21)–C(13)–C(12)	165.4 (4)
C(11)–C(26)	152.9 (5)	C(26)–N(21)–C(13)–C(12)	42.8 (4)
C(12)–C(13)	151.9 (7)	C(13)–N(21)–C(22)–C(23)	172.5 (3)
C(22)–C(23)	152.5 (4)	C(26)–N(21)–C(22)–C(23)	–68.5 (4)
C(23)–C(24)	152.5 (4)	C(13)–N(21)–C(26)–C(11)	–46.2 (3)
C(24)–C(25)	139.9 (4)	C(22)–N(21)–C(26)–C(11)	–172.1 (3)
C(25)–C(26)	150.5 (4)	C(13)–N(21)–C(26)–C(25)	–174.1 (3)
C(23)–C(41)	151.2 (4)	C(22)–N(21)–C(26)–C(25)	60.0 (3)
C(41)–C(42)	138.4 (4)	C(11)–C(12)–C(13)–N(21)	–22.4 (5)
C(44)–S(5)–C(51)	105.14 (17)	C(12)–C(11)–C(26)–N(21)	30.3 (4)
C(13)–N(21)–C(22)	116.1 (3)	N(21)–C(22)–C(23)–C(24)	40.9 (4)
C(13)–N(21)–C(26)	104.4 (3)	N(21)–C(22)–C(23)–C(41)	169.9 (3)
C(22)–N(21)–C(26)	111.1 (3)	C(24)–C(25)–C(26)–N(21)	–26.5 (4)
N(21)–C(13)–C(12)	102.3 (3)	C(26)–C(11)–C(12)–C(13)	–4.7 (5)
N(21)–C(22)–C(23)	109.6 (2)	C(12)–C(11)–C(26)–C(25)	152.3 (4)
N(21)–C(26)–C(25)	110.3 (3)	C(22)–C(23)–C(24)–C(25)	–10.1 (4)
N(21)–C(26)–C(11)	102.3 (3)	C(41)–C(23)–C(24)–C(25)	–137.4 (2)
C(12)–C(11)–C(26)	103.4 (4)	C(22)–C(23)–C(41)–C(42)	113.2 (3)
C(11)–C(12)–C(13)	106.3 (3)	C(24)–C(23)–C(41)–C(42)	–118.8 (3)
C(22)–C(23)–C(24)	112.2 (3)	C(23)–C(24)–C(25)–C(26)	3.0 (4)
C(22)–C(23)–C(41)	111.0 (2)	C(24)–C(25)–C(26)–C(11)	–144.5 (4)
C(24)–C(23)–C(41)	114.1 (2)		

X-ray structure analysis. The crystal data and a summary of experimental details for racemic *trans*-**1** are given in Table 2. Cell parameters were determined by least-squares refinement of the angular settings of 159 centred reflections with $\Theta = 9\text{--}25^\circ$. The structure was solved by direct methods using the SIR-97 program,¹¹ and refined by full-matrix-block least-squares on F^2 using all data and the SHELXL-97 program.¹² Hydrogen positions were obtained in the mixed mode. Selected bond lengths and angles are given in Table 3.

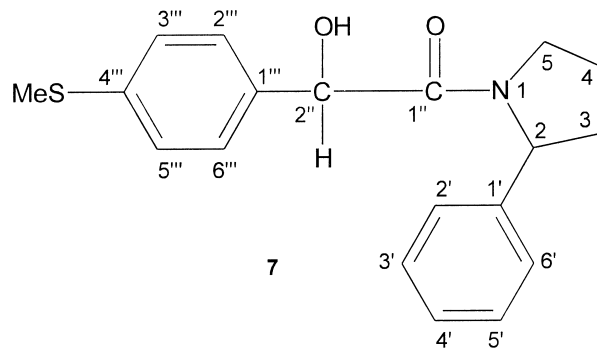
2-Hydroxy-2-(4-methylthiophenyl)ethanoic acid (3). The crude product obtained according to the literature⁶ was treated with 1 N NaOH and the resulting sodium salt of **3** was filtered and washed intensively with diethyl ether. Then aq HCl (20%) was added and the solution was extracted with diethyl ether. After drying with MgSO_4 and evaporation of the solvent racemic **3** was isolated as a pale yellow solid, mp. 132°C ($138\text{--}140^\circ\text{C}$).⁶ Yield: 98%. ^1H NMR (400 M Hz, acetone- d_6): δ 10.27 (bs, 1H, COOH), 7.43 (ddd, 2H, H_{ar} , $J = 8.6, 2.0, 2.0$), 7.25 (ddd, 2H, H_{ar} , $J = 8.7, 2.1, 2.1$), 5.21 (s, 1H, CH(OH)), 2.46 (s, 3H, SMe). ^{13}C NMR (101 M Hz, acetone- d_6): δ = 207.5 (acetone), 175.0 (C_q , COOH), 139.9 (C_q), 137.8 (C_q), 128.6 (2 CH), 127.3 (2 CH), 73.5 (CH, CH(OH)), 30.4 (acetone), 15.9 (CH_3 , SMe). IR (KBr): ν = 3439, 3053, 2925, 2638, 1708, 1597, 1493, 1433, 1408, 1381, 1349, 1321, 1286, 1255, 1231, 1195, 1185, 1093, 1073, 1013, 946, 919, 891, 858, 813, 759, 726, 688, 651, 576, 494, 435 cm^{-1} . MS (FAB): m/z (%) 199 (37, $\text{M}^+ + 1$), 198 (100, M^+), 181 (97, $\text{M}^+ + 1 - \text{H}_2\text{O}$). $\text{C}_9\text{H}_{10}\text{O}_3\text{S}$ (198.2): calcd C 54.53, H 5.08, S 16.18; found C 54.74, H 5.02, S 16.29.

2-Phenyl- Δ^1 -pyrroline (5). Purification of the crude product was accomplished by distillation in vacuo to yield the pure pyrroline which crystallized on standing. ^1H NMR (400 M Hz, CDCl_3): δ 7.86–7.81 (m, 2H, 2'-H, 6'-H), 7.43–7.36 (m, 3H, 3'-H, 4'-H, 5'-H), 4.06 (tt, 2H, 5a-H, 5b-H, $J = 7.4, 2.0$), 2.93 (tt, 2H, 3a-H, 3b-H, $J = 8.2, 2.0$), 2.02 (m, 2H, $\text{H}_a\text{-H}$, 4b-H). ^{13}C NMR (101 M Hz, CDCl_3): δ 173.3 (C_q , C2), 134.6 (C_q , C1'), 130.3 (CH, C2', C6'), 128.4 (CH, C3', C5'), 127.6 (CH, C4'), 61.5 (CH_2 , C5), 34.9 (CH_2 , C3), 22.7 (CH_2 , C4).

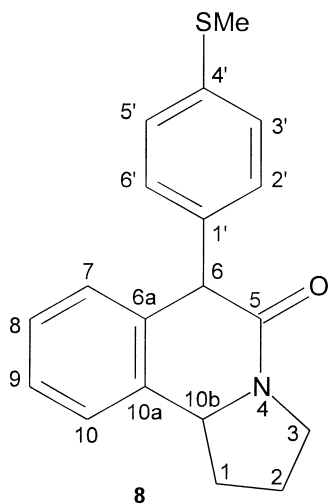


2-Phenylpyrrolidine (6). ^1H NMR (400 M Hz, CDCl_3): δ 7.42–7.19 (m, 5H, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H), 4.12 (dd, 1H, 2-H, $J = 7.7, 7.7$), 3.20 (ddd, 1H, 5a-H, $J = 10.2, 7.7, 5.4$), 3.01 (ddd, 1H, 5b-H, $J = 10.2, 8.3, 6.7$), 2.26 (br s, 1H, NH), 2.23–1.62 (m, 4H, 3a-H, 3b-H, 4a-H, 4b-H). ^{13}C NMR (101 M Hz, CDCl_3): δ 138.8 (C_q , C1') 129.1, 128.7, 127.2 (2:2:1, each CH, C2', C3', C4', C5', C6'),

70.5 (CH, C2), 55.4 (CH_2 , C5), 33.4 (CH_2 , C3), 24.7 (CH_2 , C4).



1-[2-Hydroxy-2-(4-methylthiophenyl)]ethanoyl-2-phenylpyrrolidine (7). Deviating from Maryanoff's procedure,⁶ a catalytic amount of 4-toluenesulphonic acid was added to the reaction mixture. After filtration through silica gel the product crystallized from ethyl acetate as a colourless solid, mp. 135°C . The mother liquor was concentrated and again filtered through silica gel. According to the ^1H NMR spectrum the ratio of the two diastereoisomers (total yield 83%) was 2.7:1. Major diastereoisomer: ^1H NMR (400 M Hz, CDCl_3): δ 7.35–7.21 (m, 7H, 3'-H, 4'-H, 5'-H, 2''-H, 3'''-H, 5'''-H, 6'''-H), 7.16–7.13 (m, 2H, 2'-H, 6'-H), 5.21 (dd, 1H, 2-H, $J = 8.1, 2.5$), 5.13 (s, 1H, 2'-H), 4.12 (bs, 1H, OH), 3.83 (ddd, 1H, 5a-H, $J = 10.1, 8.1, 3.4$), 3.07 (ddd, 1H, 5b-H, $J = 10.0, 9.0, 7.1$), 2.48 (s, 3H, SMe), 2.17–2.08 (m, 1H, 3a-H), 2.00–1.70 (m, 3H, 3b-H, 4a-H, 4b-H). ^{13}C NMR (101 M Hz, CDCl_3): δ 170.6 (C_q , C1''), 142.2 (C_q , C1'), 139.2, 135.4 (each C_q , C1''', C4'''), 128.5, 128.3, 127.0, 126.8 (2:2:1:2, each CH, C3', C4', C5', C2''', C3''', C5''', C6'''), 125.3 (CH, C2', C6'), 72.4 (CH, C2''), 61.9 (CH, C2), 46.8 (CH_2 , C5), 33.6 (CH_2 , C3), 23.4 (CH_2 , C4), 15.56 (S-CH $_3$). Minor diastereoisomer: ^1H NMR (400 M Hz, CDCl_3): δ 7.02 (dddd, 1H, 4'-H, $J = 7.2, 7.2, 1.3, 1.3$), 6.96 (dddd, 2H, 3'-H, 5'-H, $J = 7.2, 7.2, 0.8, 0.8$), 6.78 (ddd, 2H, 3'''-H, 5'''-H or 2'''-H, 6'''-H, $J = 8.5, 1.9, 1.9$), 6.74 (ddd, 2H, 3'''-H, 5'''-H or 2'''-H, 6'''-H, $J = 8.5, 1.9, 1.9$), 6.62 (dddd, 2H, 2'-H, 6'-H, $J = 7.2, 1.6, 1.6, 1.6$), 5.09 (d, 1H, 2-H, $J = 7.5$), 5.04 (s, 1H, 2'-H), 4.12 (bs, 1H, OH), 3.83 (ddd, 1H, 5a-H, $J = 12.2, 10.0, 7.6$), 3.69 (ddd, 1H, 5b-H, $J = 12.5, 8.7, 2.3$), 2.33 (s, 3H, SMe), 2.31–2.22 (m, 1H, 3a-H), 2.00–1.70 (m, 3H, 3b-H, 4a-H, 4b-H). ^{13}C NMR (101 M Hz, CDCl_3): δ = 171.9 (C_q , C1''), 141.2 (C_q , C1'), 138.0, 135.3 (each C_q , C1''', C4'''), 128.1, 128.0, 126.43, 126.38 (2:2:1:2, each CH, C3', C4', C5', C2''', C3''', C5''', C6'''), 125.1 (CH, C2', C6'), 72.2 (CH, C2''), 61.2 (CH, C2), 47.6 (CH_2 , C5), 35.9 (CH_2 , C3), 20.5 (CH_2 , C4), 15.78 (S-CH $_3$). Diastereoisomeric mixture: IR (KBr): ν = 3400, 3254, 3081, 3063, 3028, 2979, 2946, 2922, 2882, 1827 (s), 1581, 1493, 1441, 1357, 1339, 1317, 1285, 1244, 1198, 1185, 1161, 1112, 1072, 1044, 1027, 1016, 992, 965, 955, 926, 898, 870, 850, 824, 803, 791, 772, 754, 700, 662, 629, 597, 563, 548, 532, 491, 463 cm^{-1} . MS (FAB): m/z (%) 328 (100, $\text{M}^+ + 1$), 310 (34, $\text{M}^+ + 1 - \text{H}_2\text{O}$). $\text{C}_{19}\text{H}_{21}\text{NO}_2\text{S}$ (327.4): calcd C 69.69, H 6.46, N 4.28, S 9.79; found C 69.40, H 6.50, N 4.21, S 10.13.



6-(4-Methylthiophenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline-5-one (8). According to a modified literature synthesis¹³ the amide **7** was cyclodehydrated with concd H₂SO₄ in a trifluoroacetic acid (TFA) medium. After stirring overnight at room temperature the reaction mixture was quenched by addition of water and extracted with CH₂Cl₂. The organic layer was washed with water and brine, dried (MgSO₄) and concentrated to give **8** as a brown syrup. Yield: 92%. Diastereoisomeric mixture: ¹H NMR (400 M Hz): δ 7.42–7.02 (m, 8H, 7-H, 8-H, 9-H, 10-H and 2'-H, 3'-H, 5'-H, 6'-H), 4.89 (s, 1H, 6-H), 4.53 (dd, 1H, 10b-H, *J*=6.3, 9.1), 3.66–3.51 (m, 2H, 3a-H, 3b-H), 2.64–2.59 (m, 1H, 1a-H), 2.42 (s, 3H, MeS), 2.14–2.09 (m, 1H, 2a-H), 1.98–1.88 (m, 2H, 1b-H, 2b-H). ¹³C NMR (101 M Hz, CDCl₃): δ 169.0 (C_q, C5), 137.7, 137.3, 135.9, 135.2 (each C_q, C6a, C10a, C1', C4'), 131.9, 128.9, 128.6, 128.2, 127.9, 127.3, 124.8 (each CH, C7, C8, C9, C10 and C2', C3', C5', C6'), 59.4 (CH, C10b), 54.0 (CH, C6), 45.8 (CH₂, C3), 32.1 (CH₂, C1), 23.4 (CH₂, C2), 16.3 (SMe). IR: ν=3435, 2972, 2949, 2920, 2879, 1647 (s, CO), 1491(s), 1439, 1404, 1344, 1317, 1304, 1236, 1198, 1161, 1093, 1016, 910, 812, 758, 731, 685 cm⁻¹.

6-(4-Methylthiophenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (1). This was obtained as described in ref 6. The diastereoisomers were separated by column chromatography with ethyl acetate as mobile phase. The pair of *trans*-enantiomers was eluted first (*R_f*=0.20, ethyl acetate) and crystallized as a pale brown solid, mp. 79–81 °C. The pair of *cis*-enantiomers followed (*R_f*=0.07, ethyl acetate) and was isolated as a brown syrup. The ratio of the diastereoisomers *trans/cis* was 5:1.

trans-**1**: ¹H NMR (500 M Hz, CDCl₃): δ 7.22–7.19 (m, 2H, H_{ar}), 7.19–7.15 (m, 1H, H_{ar}), 7.13–7.11 (m, 1H, H_{ar}), 7.10–7.08 (m, 2H, H_{ar}), 7.08–7.04 (m, 1H, H_{ar}), 6.83 (ddd, 1H, H-2', *J*=7.8, 0.9, 0.9), 4.35 (dd, 1H, 6-H, *J*=10.6, 6.4), 3.65 (dd, 1H, 10b-H, *J*=7.7, 7.7), 3.43 (dd, 1H, 5a-H, *J*=11.8, 6.4), 3.15 (ddd, 1H, 3a-H, *J*=9.0, 7.8, 4.2), 2.69 (dd, 1H, 5b-H, *J*=11.3, 11.3), 2.57 (ddd, 1H, 3b-H, *J*=8.3, 8.3, 8.3), 2.47 (s, 3H, SMe), 2.49–2.42 (m, 1H, 1b-H), 2.00–1.87 (m, 2H, 2a-H, 2b-

H), 1.86–1.77 (m, 1H, 1a-H). ¹³C NMR (101 M Hz, CDCl₃): δ 141.2, 139.0, 137.5, 136.4 (each C_q, C6a, C10a, C1', C4'), 129.7 (CH, C2', C6' or C3', C5'), 129.1 (CH, C7 or C10), 127.0 (CH, C2', C6' or C3', C5'), 126.3 (CH, C8, C9), 125.3 (CH, C7 or C10), 63.8 (CH, C10b), 57.9 (CH₂, C5), 53.0 (CH₂, C3), 44.6 (CH, C6), 30.7 (CH₂, C1), 22.1 (CH₂, C2), 16.0 (CH₃, SMe). IR (KBr): ν=3064, 3035, 3022, 2968, 2924, 2914, 2881, 2870, 2781, 2740, 2725, 2673, 1597, 1491(s), 1448, 1431, 1408, 1371, 1346, 1327, 1284, 1261, 1234, 1215, 1203, 1180, 1163, 1134, 1109, 1092, 1061, 1036, 1016, 976, 953, 918, 868, 820, 785, 752, 721, 648, 633, 609, 584, 552, 480, 444 cm⁻¹. C₁₉H₂₁NS (295.4): calcd C 77.24, H 7.16, N 4.74, S 10.85; found C 77.14, H 7.36, N 4.26, S 10.69.

cis-**1**: ¹H NMR (500 M Hz, CDCl₃): δ 7.19–7.12 (m, 6H), 7.09–7.05 (m, 1H), 6.88 (ddd, 1H, 2'-H, *J*=7.7, 1.0, 1.0), 4.17 (dd, 1H, 6-H, *J*=5.3, 5.3), 3.61 (dd, 1H, 10b-H, *J*=9.6, 6.9), 3.01 (dd, 1H, 5a-H or 5b-H, *J*=11.1, 5.6), 2.95 (ddd, 1H, 3a-H or 3b-H, *J*=10.2, 8.2, 3.1), 2.91 (dd, 1H, 5a-H or 5b-H, *J*=11.0, 5.1), 2.69 (ddd, 1H, 3a-H or 3b-H, *J*=8.9, 8.9, 8.9), 2.45 (s, 3H, MeS), 2.40–2.34 (m, 1H, 1-H or 2-H), 2.04–1.94 (m, 1H, 1-H or 2-H), 1.91–1.80 (m, 2H, 1-H or 2-H). ¹³C NMR (101 M Hz, CDCl₃): δ 143.1, 138.7, 137.2, 135.9 (each C_q, C6a, C10a, C1', C4'), 129.4, 129.3, 126.7, 126.2, 126.1, 125.8 (2:1:2:1:1:1, each CH, C7, C8, C9, C10, C2', C3', C5', C6'), 63.6 (CH, C10b), 56.1 (CH₂, C5), 54.3 (CH₂, C3), 45.6 (CH, C6), 30.5 (CH₂, C1), 22.3 (CH₂, C2), 16.1 (CH₃, SMe). IR (KBr): ν=3070, 3060, 3018, 2964, 2939, 2922, 2873, 2785, 2731, 1651, 1601, 1491(s), 1448, 1439, 1404, 1375, 1348, 1323, 1292, 1215, 1163, 1132, 1117, 1092, 1016, 966, 823, 752 cm⁻¹.

(+)-McN-5652-Z. As mentioned above we separated the two *cis*-enantiomers of **1** on a 250×10 mm column packed with chiralpak[®] AD 25μm. The mobile phase was 97% *n*-hexane/3% 2-propanol/0.05% triethylamine. The flow rate was 4.7 mL min⁻¹. The capacity factors were 1.12 for the (–)-enantiomer and 2.99 for the (+)-enantiomer.

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