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ORIGINAL PAPER

(*S*)-(−)-α-Methylbenzylamine as chiral auxiliary in the synthesis of (+)-lortalamine

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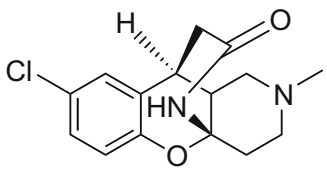
Abstract (+)-Lortalamine was synthesised using (*S*)-(−)-α-methylbenzylamine as a chiral auxiliary. The stereochemistry of an intermediate compound was established on the basis of X-ray crystallography, allowing unambiguous assignment of the absolute configuration.

Keywords Drug research · Tetracyclic antidepressants · Relative stereochemistry · Heterocycles · X-ray structure determination

Introduction

Considering the growing number of people suffering from depressive illnesses, the development of efficient antidepressants seems to be a very important target for the pharmaceutical industry. The search for possible lead compounds with desired activity, which has been based mainly on the monoamine theory of depression, has led in recent decades to the discovery of several promising candidates [1–4]. Among them, the tetracyclic compound (1*R**,9*R**,10*S**)-6-chloro-12-methyl-2-oxa-12,15-diazatetracyclo[7.5.3.$0^{1,10}$.$0^{3,8}$]heptadeca-3,5,7-trien-16-one (**1**) has been developed and introduced as a relatively safe antidepressant and antipsychotic drug (lortalamine, LM 1404) [1, 2].



(+)-**1**

As a result of the presence of the rigid multi-ring system, two stable enantiomers of lortalamine (**1**) are possible. Interestingly, to date there are no reports of a stereoselective preparation of non-racemic **1**. The asymmetric synthesis of pharmacologically valuable compounds using readily available chiral inductors is one of the leading tasks in synthetic organic chemistry, since it is well documented that enantiomers usually exhibit different biological activity and metabolic profiles. In this context, we decided to use (*S*)-(−)-α-methylbenzylamine (**2**), which is widely known as an effective chiral adjuvant [5, 6] and whose utility has also been proven in our laboratory [7].

Results and discussion

It is known that the racemic hexahydrobezopyrano[3,2-c] pyridine ring system can be prepared in a two-step procedure from ethyl coumarin-3-carboxylate and 1-methyl-4-piperidone [1, 2]. Since *N*-[(*S*)-α-methylbenzyl]-4-piperidone (**3**) can easily be obtained from commercially available and relatively inexpensive compound **2** without loss of

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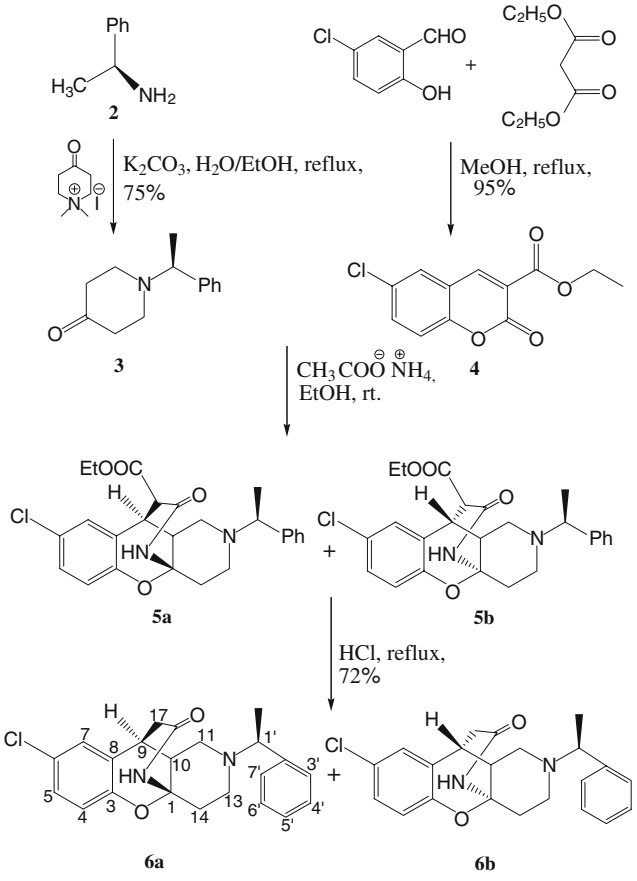
enantiomeric purity, we considered it as an interesting chiral building block for the stereoselective synthesis of lortalamine (**1**). Compound **3** was synthesised according to the protocol described by Kuehne et al. [8]. Another component, 5-chloro-3-carboxyethylcoumarin (**4**), can be prepared in nearly quantitative yield in a Knoevenagel-type condensation as proposed by Horning and Dimmig [9]. Compounds **3** and **4** suspended in absolute ethanol underwent a condensation reaction in the presence of ammonium acetate. The resulting *β*-ketoesters **5a** and **5b** were not stable enough for spectroscopic characterisation, but their presence can be assumed considering previous syntheses of other lortalamine analogues [10]. We have already shown that, in the preparation of *des*-chlorolortalamine and 4-chlorolortalamine, *β*-ketoesters were stable enough to allow purification and characterisation [10]. In the case of the synthesis of racemic lortalamine, according to Briet et al. [1, 2], the condensation was followed directly by acid-catalysed hydrolysis without purification of the intermediates. The diastereoisomers **6a** and **6b** (Scheme 1) were formed in 72% total yield and could be easily separated via column chromatography on silica gel (**6a** was the less polar isomer). HPLC analysis showed the diastereomeric ratio to be 49:51.

In the case of diastereomer **6b**, we were able to obtain a monocrystal suitable for X-ray structure analysis, which proved unambiguously the stereochemistry of this compound (Fig. 1). The characteristic feature of this crystal structure is the hydrogen bonding N–H···O network formed by the N–H and C=O groups of one of the lortalamine rings of adjacent molecules. These form a system of anti-parallel hydrogen-bonded polar chains, where the chains pass in the *a*-direction. The crystal was a weak diffractor, which resulted in a low number of observed data points [976 data points with $I > 2\sigma(I)$] and hence higher *R* and *wR* factors. This might be interpreted as the result of thermal motion, especially visible in an *N*-substituent region.

The chiral auxiliary was then removed from compound **6a** by hydrogenation with a Pd/C catalyst to give the enantiopure **7a** (Scheme 2), which was isolated in the form of a hydrochloride in 61% yield. The hydrochloride salt was both more prone to efficient purification by crystallisation and more stable than the free amine. The amine **7a** was then *N*-methylated to give (+)-lortalamine ((+)-**1**). The purity of this compound was proven by HPLC analysis on a chiral stationary phase.

Although we have already observed that the use of (*R*)-(+)-1-(1-naphthyl)ethylamine in a similar reaction sequence leading to lortalamine analogues gave considerably better diastereoselectivity (up to 84:16) [10], we found that, in the present sequence, the diastereoselectivity increase (if any) was overshadowed by unfavourable chromatographic properties of the isomers that precluded their effective separation. Therefore, it seems that the use of (*S*)-(−)-α-methylbenzylamine (**2**) was the optimal choice.



Scheme 1

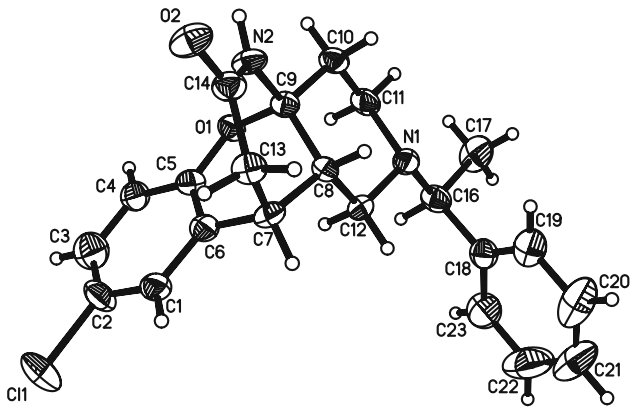
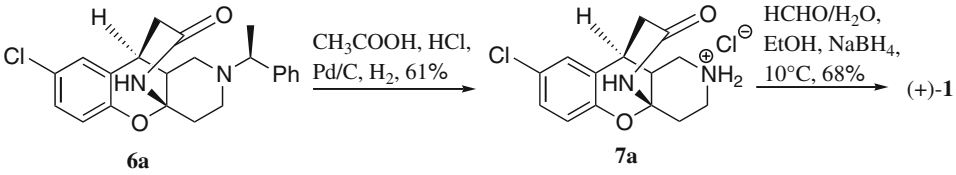


Fig. 1 Conformation of **6b** and the numbering scheme. The non-hydrogen atoms are shown as 30% probability ellipsoids

Scheme 2



Experimental

The NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz for ^{1}H NMR and at 125 for ^{13}C NMR with TMS as an internal standard. Mass spectra were collected with an AMD 604 apparatus; high-resolution mass spectra were acquired using LSIMS (positive ion mode), GC/MS was performed on a HP 6890 with an HP 5973 mass detector (oven 280°C, injection 300°C, detector 300°C). A ChiraDex β-Dex120 30 m/0.25 mm Supelco column was used for analytical enantiomer separations. Optical rotation was measured on a Perkin-Elmer 247 MC polarimeter. TLC analysis was performed on Merck 60 silica gel glass plates and visualised using iodine vapour. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (230–400, Merck). HPLC analyses were performed on a Knauer apparatus (model 64) with Eurochrom 2000 software using 4 mm × 250 mm silica (5 μm) column model Li-Chrosorb Si-60 (Knauer) with a gradient ratio of dichloromethane/methanol. Melting points were determined on a Boetius hot-plate microscope.

X-ray data were collected applying a Kuma KM4 κ-axis single crystal diffractometer and the characteristic MoKα radiation. These data were used consecutively to solve and then refine the crystal structure using SHELXS97 and SHELXL97 programs [11, 12].

*(1R,9R,10S)-6-Chloro-12-[(1′S)-phenyl-ethyl]-2-oxa-12,15-diazatetracyclo[7.5.3.0^{1,10}.0^{3,8}]heptadeca-3,5,7-trien-16-one (**6a**, $C_{22}H_{23}ClN_2O_2$) and (1S,9S,10R)-6-chloro-12-[(1′S)-phenyl-ethyl]-2-oxa-12,15-diazatetracyclo [7.5.3.0^{1,10}.0^{3,8}]heptadeca-3,5,7-trien-16-one (**6b**, $C_{22}H_{23}ClN_2O_2$)*

A suspension containing 2.20 g *N*-[(*S*)-α-methylbenzyl]-4-piperidone (**3**) (10.84 mmol), 2.70 g 5-chloro-3-carboethoxycoumarin (**4**) (10.84 mmol) and 4.17 g ammonium acetate (54.18 mmol) in 7 cm^3 absolute ethyl alcohol was stirred for 72 h at room temperature. After evaporation of the solvent, 5 cm^3 concentrated hydrochloric acid was added and the mixture was heated at reflux for 45 min. The volatiles were then evaporated and the residue (3.0 g) was purified by column chromatography on silica gel using 3% (v/v) methanol/chloroform mixture as eluent. The mixture was then subjected to a column chromatography on silica gel using 1% (v/v) methanol/chloroform mixture as an eluent (TLC, silica plates, $CHCl_3$:MeOH = 19:1, R_f = 0.50 for **6a** and R_f = 0.45 for **6b**). The pure diastereomers **6a** and **6b** were obtained in 35% and 37% yield, respectively. The crystals of **6b**, suitable for an X-ray analysis were obtained by a slow evaporation from a chloroform/diethyl ether mixture.

6a: M.p.: 122–128 °C (from $CHCl_3$/Et_2O); ^{1}H NMR ($CDCl_3$): δ = 7.34 − 7.29 and 7.25 − 7.22 (m, 5H, H-3'–H-7'), 7.12 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.5 Hz, H-5), 7.03 (d, 1H, J = 2.5 Hz, H-7), 6.73 (d, 1H, J = 8.5 Hz, H-4), 6.57 (br.s, 1H, NH), 3.46 (apparent q, 1H, J = 4.0 Hz, H-1'), 2.94-2.88 (br.m, 1H, H-9), 2.89-2.88 (br.d, 1H, H-11), 2.78 (dd_{AB}, 1H, J_1 = 17.3 Hz, J_2 = 5.5 Hz, H-17), 2.79-2.72 (br.m, 1H, H-10), 2.57 (dd_{AB}, 1H, J_1 = 17.3 Hz, J_2 = 1.5 Hz, H-17), 2.30–2.38 (br.m, 2H, H-13), 2.00 − 1.91 (br.m, 2H, H-11, H-14), 1.86 (br.t, 1H, J = 11.0 Hz, H-14), 1.32 (br.d, 3H, J = 4.0 Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 170.7, 148.5, 128.7, 128.7, 128.4, 127.3, 127.0, 126.4, 124.8, 118.8, 81.6, 64.1, 48.6, 47.2, 41.9, 37.6, 36.2, 32.8, 18.7 ppm; ES (+): *m*/*z* (%) = 383 (100), 385 (40); $[\alpha]_D^{22} = -29.3°$ cm^3 g^{-1} dm^{-1} (*c* 1.2, $CHCl_3$).

6b: M.p.: 165–170 °C (from $CHCl_3$/Et_2O); ^{1}H NMR ($CDCl_3$): δ = 7.30–7.21 (m, 5H, H-3'–H-7'), 7.11 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.5 Hz, H-5), 6.96 (d, 1H, J = 2.5 Hz, H-7), 6.82 (br.s, 1H, NH), 6.72 (d, 1H, J = 8.5 Hz, H-4), 3.36 (q, 1H, J = 6.0 Hz, H-1′), 3.08 (br.d, 1H, J = 5.5 Hz, H-11), 2.76–2.74 (br.m, 1H, H-9), 2.72 (dd_{AB}, 1H, J_1 = 19.0 Hz, J_2 = 5.0 Hz, H-17), 2.60–2.58 (br.m, 1H, H-10), 2.51 (dd_{AB}, 1H, J_1 = 19.0 Hz, J_2 = 4.0 Hz, H-17), 2.36–2.24 (m, 2H, H-13), 2.11–1.96 (br.m, 2H, H-11, H-14), 1.72 (br.t, 1H, J = 11.2 Hz, H-14), 1.30 (d, 3H, J = 6.0 Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 170.9, 148.4, 128.6, 128.4, 128.4, 127.2, 127.0, 127.2, 126.2, 124.8, 118.7, 81.6, 64.4, 50.8, 45.3, 41.89, 37.5 36.3, 32.5, 19.9 ppm; $[\alpha]_D^{22} = -98°$ cm^3 g^{-1} dm^{-1} (*c* 1.2, $CHCl_3$).

After mounting and centring a crystal of dimensions 0.3 × 0.26 × 0.2 mm^3, the unit cell was found and data were collected. Crystallographic data: orthorhombic crystal, $P2_12_12_1$ space group, a = 7.3850(15), b = 9.2730(19), c = 33.589(7) Å, α = β = γ = 90°, V = 2300.2(8) Å^3, Z = 4, $F(000)$ = 808, μ(MoKα) = 0.183 mm^{-1}, T = 293(2) K, 4,139 reflections [976 with $I > 2\sigma(I)$], R = 0.0896. The detailed structural data had been deposited with the Cambridge Structural Data Centre under the number CCDC 225585.

*(1R,9R,10S)-6-Chloro-2-oxa-12,15-diazatetracyclo [7.5.3.0^{1,10}.0^{3,8}]heptadeca-3,5,7-trien-16-one hydrochloride (**7a**, $C_{14}H_{16}Cl_2N_2O_2$)*

To a solution containing 220 mg of the diastereomer **6a** (0.58 mmol) in 30 cm^3 freshly distilled acetic acid, 1.3 cm^3 conc. hydrochloric acid and 100 mg 10% Pd/C were added. The flask was then filled with hydrogen under a pressure of ca. 1.5 atm; hydrogenation proceeded for 80 h at 50 °C with vigorous stirring. The suspension was then filtered through a thin layer of Celite. [CAUTION: Activated hydrogenation catalysts are highly pyrophoric and have to be handled with special care!] The solvent was removed in vacuo and the residue was purified *via* column chromatography on silica gel with 7% (v/v) MeOH in $CHCl_3$ to give 110 mg (61%) of the amine **7a** hydrochloride as white crystals (TLC, silica plates, $CHCl_3$:MeOH = 17:3, $R_f = 0.4$). M.p.: > 220 °C (decomposition, from $CHCl_3$/MeOH); ^{1}H NMR (DMSO-d_6): $\delta = 9.81$ (s, 1H, HCl), 9.55 (br.s, 1H, NH), 8.84 (s, 1H, NH), 7.34 (d, 1H, J = 2.5 Hz, H-7), 7.25 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.5 Hz, H-5), 6.90 (d, 1H, J = 9.0 Hz, H-4), 3.30 (br.d, 2H, H-13), 3.15–3.13 (br.m, 1H, H-10), 2.95 (m, 1H, H-11), 2.80 (dd_{AB}, 1H, J_1 = 17.3 Hz, J_2 = 5.0 Hz, H-17), 2.68 (br.m, 1H, J = 10.0 Hz, H-14), 2.40 (d_{AB}, 1H, J = 17.0 Hz, H-17), 2.35-2.27 (br.m, 2H, H-9, H-11), 2.14 (m, H-14) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.5$, 148.0, 129.2, 128.4, 125.2, 124.8, 118.8, 80.1, 48.4, 42.1, 41.4, 32.9, 31.4, 30.8 ppm; $[\alpha]_D^{22} = +63.5°$ cm^3 g^{-1} dm^{-1} (c 1.2, MeOH);

*(+)-Lortalamine ((+)-**1**, $C_{15}H_{17}ClN_2O_2$)*

(+)-Lortalamine ((+)-**1**, $C_{15}H_{17}ClN_2O_2$)Hydrochloride **7a** (110 mg, 0.35 mmol) was basified with a 15% solution of NaOH, and extracted with CH_2Cl_2 (3x5 cm^3). The solution was dried over $MgSO_4$, and the solvent was removed in vacuo. A volume of 0.15 cm^3 37% (w/v) formalin and 5 cm^3 EtOH were added, followed by a portionwise addition of 200 mg (5.26 mmol) $NaBH_4$ at 10 °C. After 48 h of stirring at room temperature, the solvents were removed in vacuo and 20 cm^3 brine was added. The product was extracted with CH_2Cl_2 (3x5 cm^3). After drying over $MgSO_4$, the solvent was removed, and the residue was purified by column chromatography on silica gel using 2% (v/v) MeOH:$CHCl_3$ to give 68 mg (68%) of crystalline solid (TLC, silica plates, $CHCl_3$:MeOH = 23:2, $R_f = 0.65$). M.p.: 212–216 °C (from $CHCl_3$); ^{1}H NMR (DMSO-d_6): $\delta = 8.61$ (s, 1H, NH), 7.27 (d, 1H, J = 1.95 Hz, H-7), 7.19 (dd, 1H, J_1 = 8.79 Hz, J_2 = 1.95 Hz, H-5), 6.83 (d, 1H, J = 8.79 Hz, H-4), 2.94 (m, 1H, H-9), 2.76 (dd_{AB}, 1H, J_1 = 17.6 Hz, J_2 = 4.9 Hz, H-17), 2.73–2.69 (br.m, 1H, H-13), 2.64 (dd, 1H, J_1 = 10.7 Hz, J_2 = 3.9 Hz, H-11), 2.32 (ddd, 1H, J_1 = 13.7 Hz, J_2 = 4.0 Hz, J_3 = 2.0 Hz, H-14), 2.29 (dd_{AB}, 1H, J_1 = 17.6 Hz, J_2 = 2.0 Hz, H-17), 2.14 (s, 3H, CH_3), 2.11–2.07 (m, 2H, H-11, H-13), 1.78 (td, 1H, J_1 = 13.7 Hz, J_2 = 4.0 Hz, H-14), 1.55 (t, 1H, J = 10.7 Hz, H-10) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.9$, 148.7, 128.8, 127.9, 126.2, 124.4, 118.4, 81.4, 54.2, 50.5, 45.3, 41.8, 36.0, 35.0, 31.6 ppm; $[\alpha]_D^{22} = +39.3°$ cm^3 g^{-1} dm^{-1} (c 1.2, MeOH); LSIMS (+): m/z (%) = 315 $[M + Na]^+$ (25), 293 $[M + H]^+$ (25), 269 (30), 258 (30), 199 (30) 106 (100), 93 (25).

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