Short Communication

Resolution of 1-Methyl-2-propynylamine via Chromatographic Separation of its Diastereomeric *O*-Methylmandelic Amides

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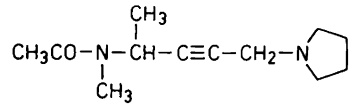
Racemic *N*-methyl-*N*-(1-methyl-4-pyrrolidino-2-butynyl)acetamide (**1**)[1] has been reported to act as a presynaptic muscarinic antagonist and a postsynaptic muscarinic agonist in certain rat brain regions.[2,3] Such a selectivity profile has not previously been reported, and **1** may have clinical potential in the treatment of senile cognitive decline.[2,4] Only two reports have appeared on the pharmacology of the enantiomers of **1**.[5,6] This is probably due to the poor accessibility of the key synthetic intermediates (*R*- and (*S*)-1-methyl-2-propynylamine (**2**): (±)-**2** has been resolved by fractional crystallization of the diastereomeric bromocamphorsulfonates[7] or tartrates,[7,8] but the yields were poor and an attempt to prepare (*R*)- and (*S*)-**2** by asymmetric synthesis resulted in low enantiomeric purities.[9] We now report a more effective procedure for the preparation of (*R*)- and (*S*)-**2** which is based on separation by flash chromatography[10] of the diastereomeric *O*-methylmandelic amides of (±)-**2**, followed by cleavage of the amide function by a mild two-step procedure.[11–13]

Acylation of (±)-**2** with (*R*)-*O*-methylmandeloyl chloride gave a mixture of diastereomeric amides which was separated chromatographically to afford **3** (99.7 % de) and **4** (99.5 % de), in 63 and 60 % yield, respectively. To hydrolyze the two diastereomeric amides, we followed the mild



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procedure reported by Grehn *et al.*[12,13] Compounds **3** and **4** were acylated with di-*tert*-butyl dicarbonate. These reactions were sluggish and required a ten-fold excess of reagent to go to completion in 100 h; it is known that the rate of this reaction is decreased by substituents in the vicinity of the nitrogen.[11,12] The *O*-methylmandelic acid moiety was removed by treatment with 1,1,3,3-tetramethylguanidine in methanol[13] to give partially racemized methyl *O*-methylmandelate[§] and the carbamates (*R*)-and (*S*)-**5**. Finally, the carbamates were converted into (*R*)- and (*S*)-**2** by treatment with trifluoroacetic acid. Compounds (*R*)- and (*S*)-**2** were conveniently isolated as the oxalates in overall yields of 42 %. The enantiomeric excess of (*R*)- (99.6 % ee) and (*S*)-**2** (99.2 % ee), as determined by GLC analysis of reacylated [(*R*)-*O*-methylmandeloyl chloride]

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[§]Attempts to separate chromatographically the diastereomers formed from (±)-**1** and (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (Mosher's acid chloride), a non-enolizable acid residue, were unsuccessful.

(*R*)- and (*S*)-**2**, was almost identical to the diastereomeric excess of **3** and **4**. Thus, no significant racemization or epimerization occurred during the preparation of the diastereomeric amides. Comparison of the optical rotations of the acetamides of (*R*)- and (*S*)-**2** [(*R*)- and (*S*)-**6**, respectively] with those previously reported[5] indicates that the enantiomeric purities obtained in the present investigation are at least as high as those obtained by fractional crystallization of diastereomeric tartrates.

The cost of *O*-methylmandelic acid and the fact that partially racemized ester/acid is recovered prohibits the use of the present method on a large scale. However, it provides convenient access to gram amounts of (*R*)- and (*S*)-**2** with high enantiomeric purities.

Experimental

Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. IR spectra were recorded on a Perkin-Elmer 157G spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Jeol FX 90Q spectrometer, using TMS as reference. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Capillary-GLC analyses were performed at 135 °C, helium flow rate 2 ml min^{-1} on a Carlo-Erba 6000 instrument equipped with an FID-40 flame ionization detector and a Milton Roy CI-10B integrator, using an SE 52 column (25 m). TLC was carried out on aluminum plates pre-coated with silica gel 60 F_{254} (0.2 mm; E. Merck). Elemental analyses were performed by *Mikro Kemi AB*, Uppsala, Sweden.

N-*[(*R*)-1-Methyl-2-propynyl]-(*R*)-O-methylmandelic amide* (**3**) *and* N-*[(S)-1-methyl-2-propynyl]-(*R*)-O-methylmandelic amide* (**4**). A solution of (*R*)-*O*-methylmandelic acid (6.29 g, 37.9 mmol) and $SOCl_2$ (155 ml) was stirred for 24 h at room temperature under nitrogen. Excess $SOCl_2$ was evaporated at 35 °C under reduced pressure [removal of the excess $SOCl_2$ by distillation at normal pressure was deleterious owing to decomposition of the (*R*)-*O*-methylmandeloyl chloride]. The residue was dissolved in dichloromethane (130 ml), and a mixture of (±)-**2** · HCl[7] (3.07 g, 29.1 mmol), water (25 ml) and 1 M sodium hydroxide (58 ml) was added. The mixture was stirred for 24 h at room temperature and an additional portion of dichloromethane (125 ml) was added. The organic layer was washed with 2.5 M hydrochloric acid (3×175 ml) and with saturated aqueous sodium bicarbonate (4×235 ml), dried (magnesium sulfate), filtered, and concentrated. The diastereomeric amides were separated by repeated flash chromatography[10] (column size: 200×30 mm; elution rate: about 50 ml min^{-1}) on silica gel (120 g) with ether/light petroleum (1:1) as eluent. The selection of this eluent system was based on TLC experiments using a variety of solvents and solvent mixtures.

3: Yield, 2.00 g (63 %, 99.7 % de); in addition, 0.47 g of a less pure fraction (79.8 % de) was obtained. GLC-retention time 34.5 min; R_f[TLC, ether/light petroleum (1:1)] 0.38; m.p. 103–104 °C, Ref. 8 104–105 °C; $[\alpha]_D^{22}$ −9.6° (*c* 0.7, C_2H_5OH), Ref. 8 $[\alpha]_D^{22}$ −9.6° (*c* 0.8, C_2H_5OH); ^1H NMR data were in accordance with those previously reported.[8] ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 22.17 (C1−Me), 36.41 (C1), 57.20 (O−Me), 70.48 (benzylic CH), 83.57 (C3), 83.97 (C2), 126.96, 128.35, 128.37 and 136.75 (aromatic carbons), 169.46 (C=O).

4: Yield, 1.91 g (60 %, 99.5 % de); in addition, 0.15 g of a less pure fraction (94.8 % de) was obtained. GLC-retention time 36.5 min; R_f[TLC, ether/light petroleum (1:1)] 0.30; m.p. 87.5–88 °C, Ref. 8 87–88 °C; $[\alpha]_D^{22}$ −180° (*c* 0.57, C_2H_5OH), Ref. 8 $[\alpha]_D^{22}$ −186.5° (*c* 0.6, C_2H_5OH); ^1H NMR data were in accordance with those previously reported.[8] ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 22.33 (C1−Me), 36.38 (C1), 57.07 (O−Me), 70.54 (benzylic CH), 83.57 (C2), 83.85 (C3), 127.18, 128.57 and 136.63 (aromatic carbons), 169.30 (C=O).

*(S)-*tert*-Butyl-1-methyl-2-propynylcarbamate* [(*S*)-**5**]. Di-*tert*-butyl dicarbonate (19.0 g, 87 mmol) and 4-(dimethylamino)pyridine (1.30 g, 10.6 mmol) were added to a stirred solution of **4** (1.85 g, 8.7 mmol) in dry acetonitrile (35 ml) under nitrogen at room temperature. Additional portions of di-*tert*-butyl dicarbonate (1.3 g, 14.2 mmol) and 4-(dimethylamino)pyridine (0.35 g, 2.9 mmol) were added after 24 h. The reaction mixture was stirred for another 24 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ether (350 ml) and 1 M

aqueous sodium hydrogen sulfate (75 ml). The organic layer was extracted with additional portions of 1 M aqueous sodium hydrogen sulfate (5×75 ml), followed by extraction with sodium bicarbonate (5×75 ml) and with saturated aqueous sodium chloride (3×75 ml). The ether layer was dried (magnesium sulfate), filtered, and concentrated. The resulting crude *N-tert*-butoxycarbonyl-*N*-[(*S*)-1-methyl-2-propynyl]-(*R*)-*O*-methylmandelic amide was dissolved in methanol (10 ml) and a solution of 1,1,3,3-tetramethylguanidine (1.2 g, 10.4 mmol) in methanol (2 ml) was added. The reaction mixture was stirred at room temperature for 1.5 h. The methanol was evaporated and the residue was partitioned between ether (350 ml) and 1 M aqueous sodium hydrogen sulfate (75 ml). The ether layer was then treated as above. Purification on a silica column with ether/light petroleum (1:3) as eluent gave 2.04 g of a colourless solid product consisting of (*S*)-**5** and di-*tert*-butyl dicarbonate in a 55:45 ratio (^{1}H NMR analysis), and 1.11 g of partially racemized methyl *O*-methyl mandelate [R_f(TLC) 0.4; $[\alpha]_D^{22}$ −57.1° (*c* 1.2, acetone); Ref. 14 $[\alpha]_D^{24}$ −89.1° (*c* 1.1, acetone)]. In preparative runs, crude (*S*)-**5** was used directly in the next step. An analytical sample of (*S*)-**5** was obtained by repeated recrystallization from *n*-hexane. R_f(TLC) 0.52; m.p. 85–86.5 °C; $[\alpha]_D^{22}$ −96.3° (*c* 0.06, CH_3OH). ^{1}H NMR (89.55 MHz, $CDCl_3$): δ 4.85–4.30 (m, 2H, N*H* and C*H*), 2.26 (d, 1H, ≡C*H*, *J* = 2.2 Hz), 1.45 [s, 9H, C(CH_3)$_3$], 1.41 (d, 3H, CH_3). Anal. $C_9H_{15}NO_2$: C, H, N.

In one experiment, use of only a catalytic amount of 1,1,3,3-tetramethylguanidine in the above reaction also resulted in recovery of partially racemized methyl *O*-methyl mandelate.

(S)-1-Methyl-2-propynylamine [(*S*)-**2**]. Trifluoroacetic acid (7.5 ml) was added dropwise to a solution of crude (*S*)-**5** (2.00 g; 6.5 mmol) in dichloromethane (15 ml) kept at 0 °C under nitrogen. The reaction mixture was allowed to reach room temperature. The hydrolysis was complete after 1 h (TLC), and 2 M hydrochloric acid (100 ml) and ether (60 ml) were added. The aqueous layer was washed with ether (2×60 ml) and then basified with 5 M sodium hydroxide to pH 11–12. Repeated extraction with ether, drying (potassium carbonate), and filtration, afforded an ethereal solution of (*S*)-**2**. The addition of ethereal oxalic acid led to formation of the corresponding oxalate as a white precipitate. The yield of the dried oxalate of (*S*)-**2** was 970 mg (42 % based on racemic **2** · HCl). M.p. 158–159.5 °C (from methanol/ether); $[\alpha]_D^{22}$ −12.4° (*c* 0.63, CH_3OH); Anal. $C_6H_9NO_4$: C, H, N. The ^{1}H NMR spectrum was indistinguishable from that of racemic **2** · $(CO_2H)_2$. An analytical sample of the (−)-tartrate of (*S*)-**2** was prepared for comparative purposes. M.p. 143–144.5 °C, Ref. 8 153.5–155 °C; $[\alpha]_D^{22}$ −28.4° (*c* 0.8, H_2O), Ref. 8 $[\alpha]_D^{22}$ −24.1° (*c* 1.3, H_2O); Anal. $C_8H_{13}NO_6$ · 3/4 H_2O: C, H, N. Lindquist *et al.*[8] reported $C_8H_{13}NO_6$ · 1/2 H_2O.

(R)-1-Methyl-2-propynylamine [(*R*)-**2**]. The compound (*R*)-**2** $(CO_2H)_2$ was prepared from **3** (1.95 g, 9.0 mmol) by the same method. The intermediate (*R*)-*tert*-butyl 1-methyl-2-propynylcarbamate [(*R*)-**5**] had m.p. 86–87 °C and $[\alpha]_D^{22}$ +94° (*c* 0.05, CH_3OH). Isolated methyl *O*-methylmandelate had $[\alpha]_D^{22}$ −22.1° (*c* 1.0, acetone). (*R*)-**2** · $(CO_2H)_2$: Yield 970 mg [42 % based on (±)-**2** · HCl]; m.p. 155–157 °C; $[\alpha]_D^{22}$ +10.5° (*c* 0.6, CH_3OH); Anal. $C_6H_9NO_4$: C, H, N. The ^{1}H NMR spectrum was indistinguishable from that of racemic **2** · $(CO_2H)_2$. An analytical sample of the (+)-tartrate of (*R*)-**2** was prepared for comparative purposes. M.p. 142–143 °C, Ref. 8 151.5–154 °C; $[\alpha]_D^{22}$ +26.6° (*c* 0.6, H_2O), Ref. 8 $[\alpha]_D^{22}$ + 24.4° (*c* 1.1, H_2O). Anal. $C_8H_{13}NO_6$ · 3/4 H_2O: C, H, N. Lindquist *et al.*[8] reported $C_8H_{13}NO_6$ · 1/2 H_2O.

(S)-N-(1-Methyl-2-propynyl)acetamide [(*S*)-**6**]. Compound (*S*)-**2** (396 mg, 5.73 mmol) was acetylated by a previously reported procedure.[1] The resulting crude (*S*)-**6** was chromatographed on a silica column with $CHCl_3/CH_3OH$ (9:1) as eluent. Yield, 630 mg (98 %); R_f(TLC) 0.46; m.p. 88–89 °C, Ref. 5 85–87 °C; $[\alpha]_D^{22}$ −134.7° (*c* 0.5, C_2H_5OH), −135.8° (*c* 1.6, C_2H_5OH), Ref. 5 $[\alpha]_D^{22}$ −130.8° (*c* 0.6–1.6, C_2H_5OH).

(R)-N-(1-Methyl-2-propynyl)acetamide [(*R*)-**6**]. Compound (*R*)-**2** (391 mg, 5.66 mmol) was acetylated by the same procedure as for the (*S*)-enantiomer. Yield, 570 mg (91 %); m.p. 86–87 °C, Ref. 5 86–87 °C; $[\alpha]_D^{22}$ +139.1° (*c* 0.6, C_2H_5OH), +135.1° (*c* 1.3, C_2H_5OH), Ref. 5 $[\alpha]_D^{22}$ +133.6° (*c* 0.6–1.6, C_2H_5OH).

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