Resolution and Absolute Configuration of 1,2,3,5,6,10bβ-Hexahydro-6α-phenylpyrrolo[2,1-*a*]isoquinoline (McN-4612-Z). A Problem of Determination of the Enantiomeric Purity for a Tertiary Amine

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Received January 28, 1985

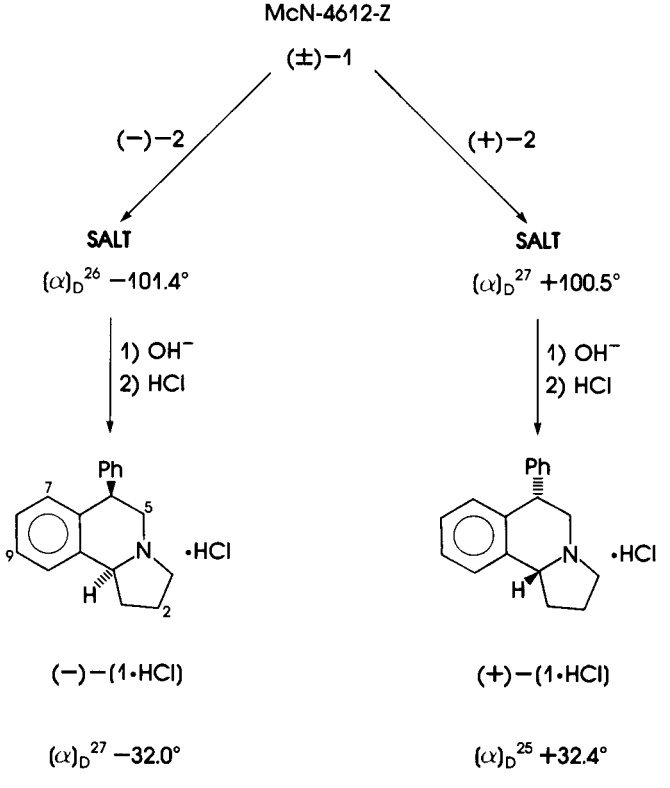
Details for the resolution of 1,2,3,5,6,10bβ-hexahydro-6α-phenylpyrrolo[2,1-*a*]isoquinoline (**1**), a potent antidepressant-like compound, into its enantiomers with di-*p*-toluoyltartaric acid (**2**) are reported. Enantiomerically-enriched *R*-(+)-2-phenylpyrrolidine was transformed into enantiomerically-enriched **1** to determine enantiomeric purity and absolute stereochemistry for the resolved amines **1**. Thus, we ascertain that samples of (+)- and (−)-**1** with an enantiomeric purity of ≥99% were prepared, and that bioactive (+)-**1** possesses the 6*S*,10b*R* absolute configuration. The enantiomeric purity of ≥99% was confirmed by 360-MHz ^{1}H nmr examination of 1:1 diastereomeric salts formed from **1** or (−)-**1** and (+)-Mosher's acid (MTPA). The maximal optical rotation reported (ref 8) for (+)-**3** (100% o.p.) was shown to correspond to 100% e.e.

J. Heterocyclic Chem., **22**, 911 (1985).

We have been investigating a series of hexahydropyrrolo[2,1-*a*]isoquinoline compounds as potential antidepressant agents [1]. *Trans* (6α,10bβ) derivatives, such as prototype **1**, were found to be very potent inhibitors of uptake of the important central neurotransmitters norepinephrine, dopamine and serotonin into nerve cells. The intense biological activity impressed us with the necessity of testing for enantioselectivity within the series. Consequently, we have resolved the enantiomers of **1** with di-*p*-toluoyltartaric acid, **2**, thereby discovering that the biological activity resides exclusively in the (+)-enantiomer [1]. Details for this difficult resolution are presented herein.

Since **1** is a tertiary amine without auxiliary sites for derivatization, methods for determining enantiomeric purity are somewhat limited. After exploring methods involving chiral hplc columns and chiral nmr shift reagents/solvents to little avail (*vide infra*), we found a little used nmr procedure that worked very well: high-field ^{1}H nmr spectroscopy of diastereomeric salts derived from (+)-*R*-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(+)-Mosher's acid; (+)-MTPA]. Additionally, we performed an enantiospecific synthesis of (+)-**1** from (+)-*R*-2-phenylpyrrolidine, establishing the 6*S*,10b*R* absolute configuration for the bioactive enantiomer (Scheme I), and providing an independent assessment of enantiomeric purity.

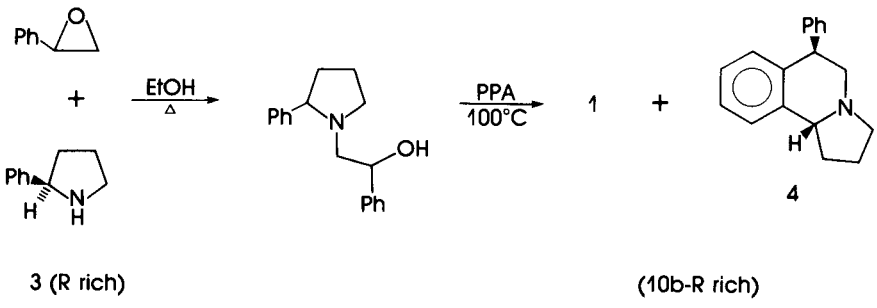
Scheme I



Resolution.

Racemic amine **1** was resolved *via* 1:1 salts formed with di-*p*-toluoyltartaric acid (**2**). Diastereomeric salts from (+)-acid **2** were separated by a series of fractional crystallizations first from acetone, then methylene chloride/hexanes (2:1), and ultimately methanol, until a constant optical rotation was attained (−101.4°). Melting point constancy was not a satisfactory criterion owing to decomposition of the melt. Enrichment in the opposite direction could only be taken as far as 2:1 or 3:1; attempts to proceed beyond this point resulted in noncrystalline, enriched salt that could not be fractionated further. Thus, combined residues were converted into diastereomeric salts of (−)-acid **2**, which were fractionated in a similar manner to constant rotation (+100.5°). The resolved amines were then obtained as hydrochloride salts with optical rotations of −32.0° and +32.4° (Scheme I).

Scheme II



Enantiomeric Purity and Absolute Configuration.

Attempts were made to quantitate the degree of resolution by nmr methods. Proton nmr analyses (90 MHz) of a 1:1 mixture of the diastereomeric salts in Scheme I, or of **1** in the presence of chiral europium shift reagents or solvating agents [2], were not useful, being hampered by a lack of sharp signals for protons in the vicinity of the nitrogen atom. Carbon-13 nmr (15.1 MHz) examination of these diastereomeric salts or of chiral shift-reagent complexes of **1** was also fruitless. Eventually, we were able to analyze the enantiomers of **1** very effectively *via* 360 MHz ^{1}H nmr examination of diastereomeric salts formed between **1** or (−)-**1** and (+)-Mosher's acid [(+)-MTPA] in benzene-d_6 (Figure 1) [3,4]. One proton on C_3 and one on C_5 were nicely doubled in a spectrum of the 1:1 complex derived from (±)-**1**. The pairs of resonances for H_{5e} integrated in a 1:1 ratio, as did the pairs for H_3. Thus, the sample of (−)-**1** was ≥99% enantiomerically pure by this criterion. The general applicability of the (+)-MTPA method for determining enantiomeric purity of amines (especially tertiary amines) will be the subject of a future paper [4].

Analysis of **1** on a covalent or ionic Pirkle hplc column offered no positive results [5]. However we were able to separate (±)-**1** into two peaks with a column of (+)-poly(tritylmethacrylate) on silica gel [Chiralpak OT(+)] [6]. Elution with methanol did not give baseline separation due to peak trailing, but addition of a small amount of triethylamine rectified this situation. So with ethanol/triethylamine, 2000:1, the peaks were completely distinct. Unfortunately, the baseline was too unstable under these conditions, introducing an unusually larger error (10-20%) into the integration measurements. Thus, the determination of enantiomeric purity by this method could be no better than 90%.

We sought to determine the absolute configuration for (+)- and (−)-**1** by asymmetric synthesis of one of the enantiomers from a known chiral educt. As an offshoot, this process would also afford another means for gauging enantiomeric purity. Although our original synthesis of **1** was based on an acyliminium-ion cyclization process [7], we subsequently employed routes starting with 2-phenylpyrrolidine (**3**) in order to prepare various analogues [1]. For-

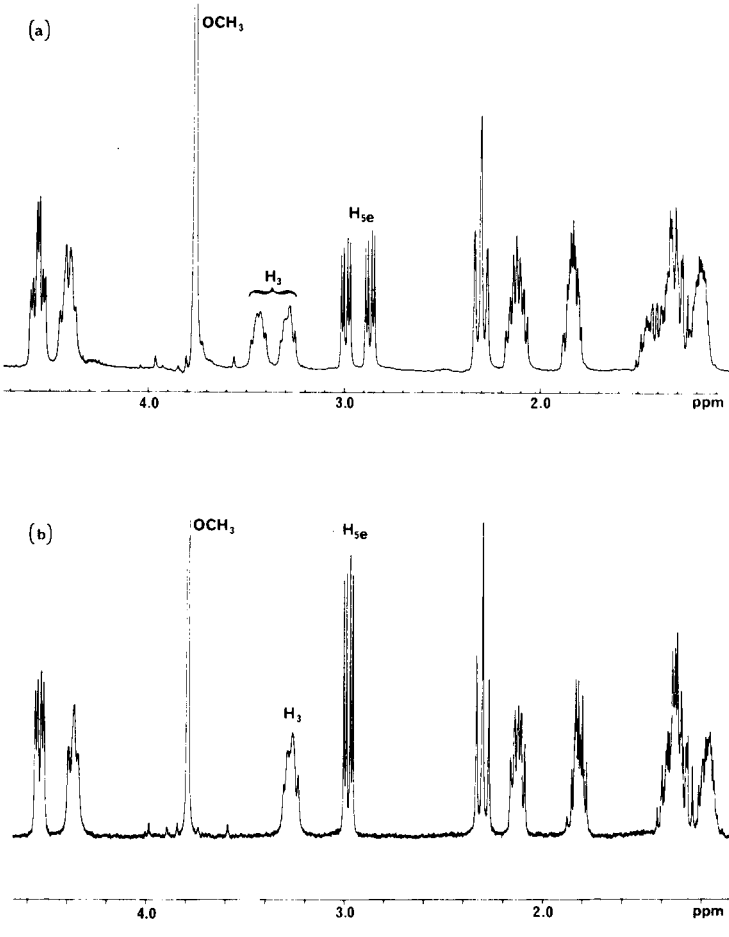


Figure 1. 360 MHz ^{1}H nmr spectra in perdeuteriobenzene (*ca.* 0.01 *M*) of (+)-*R*-α-methoxy-α-(trifluoromethyl)-phenylacetic acid [(+)-Mosher's acid; (+)-MTPA] and (a) (±)-**1**; (b) (−)-**1** from its diastereomeric salt with (+)-**2**, $[\alpha]_D^{26}$ −101.4°. There is a 1:1 ratio between the amine substrate and Mosher's acid. Minimum detection limits by electronic integration of H_3 or H_{5e} were determined to be 1%.

tunately for the current intention, 2-phenylpyrrolidine had not only been resolved already, but its absolute configuration had also been established [8]. Several recrystallizations of the (+)-tartaric acid salt of **3** furnished a sample of amine (+34.3°) that was 75% optically pure by comparison with the literature rotation for (allegedly) 100% enantiomerically pure material (+32.5°) [8]. Enriched (+)-**3** was condensed with styrene oxide and the intermediate amino alcohols were cyclized in polyphosphoric acid (PPA) (Scheme I). Amines **1** and **4**, produced in an unfavorable 1:4 ratio, were separated by column chromatography. The hydrochloride salt of this enriched **1** had an optical rotation of +23.9°, which corresponds to 74% of the value (+32.4°) observed for the hydrochloride salt of resolved **1** that came from the salt of (−)-**2** with a rotation of +100.5°. Thus, assuming that the optically purity (75%) of the enriched (+)-**3** is identical to enantiomeric purity (*i.e.* that the literature rotation for **3** relates to 100% enantiomeric purity), the resolution of **1** had reached ≥99% completion.

For purposes of thoroughness, we checked for whether the maximal rotation reported for resolved 2-phenylpyrrolidine corresponds to 100% enantiomeric purity. α-Naphthoyl derivatives of racemic **3** were separable by hplc on a covalent Pirkle column [5], but satisfactory baseline separation was not achieved, preventing accurate quantitation. Amide diastereomers from derivatization of (±)-**3** with (+)-Mosher's acid [3a], although not adequately analyzable by gc, were nicely separated by tlc [9] and hplc (silica). Analysis by hplc of the Mosher's amides derived from enriched (+)-**3** (+26.2°, 81% o.p.) gave a 91:9 ratio of diastereomers (82% e.e.), indicating that the maximum reported [8] rotation corresponds to 100% e.e.

(+)-2-Phenylpyrrolidine is known to possess the *R* configuration through a lengthy correlation with (+)-*R*-glyceraldehyde [8,10]. Therefore, (+)-[**1**·HCl], and (+)-**1**, possess the 6*S*,10b*R* absolute stereochemistry (no sign reversal between the hydrochloride salt and the free base).

Since biological testing of the enantiomers of **1** (hydrochloride salts) revealed that activity resides virtually exclusively in the (+)-isomer [1], resolved (+)-**3** (92% e.e.) has proved useful in the synthesis of the active enantiomers of analogues in this series. With this in mind, we briefly explored acquiring highly enriched (+)-**3** *via* asymmetric reduction of 2-phenyl-1-pyrroline; however, initial attempts have met with limited success. For example, reduction of 2-phenyl-1-pyrroline at 25° with 2.5 equivalents of sodium tri(*N*-benzyloxycarbonyl-(−)-prolinoxy)borohydride, a reagent that gives high enantioselectivity with a variety of imines [11], produced (±)-**3** with a low e.e. of 15%.

EXPERIMENTAL

General Information and Procedures.

Proton nmr spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard, unless otherwise indicated. The nmr abbreviations used are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet, br = broad. The ir spectra were obtained on a Perkin-Elmer 282 spectrophotometer in potassium bromide (pellets). The hplc analyses were performed on silica columns on a Waters Associates analytical instrument equipped with a uv detector (254 nm) and a Hewlett-Packard Model 3390A Integrator. Pirkle Type 1-A ionic and covalent phenylglycine hplc columns were purchased from Regis Chemical Co., Morton Grove, IL. The chiralpak OT(+) column was purchased from Daicel Industries, Ltd., Tokyo, Japan. Melting points are corrected. Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Chemical microanalyses were determined by Atlantic Microlab, Inc., Atlanta, GA.

Resolution of (±)-1.

Chromatographed (silica gel) amine (±)-**1** (29.9 g, 0.120 mole, >99% diastereomerically pure by glc) was dissolved in 1600 ml of reagent grade acetone. Di-*p*-toluoyl-*d*-tartaric acid (46.0 g, 0.119 mole, 97% assay) was dissolved in 1600 ml of acetone. The two solutions were filtered and combined in a 4-l vessel. (A small aliquot was removed to measure the optical rotation for a 1:1 mixture of diastereomeric salts, which was $[\alpha]_D$ −75°). On standing at 24° for 3 hours, fine needles began to separate. After the mixture stood for 2 days, it was cooled to 15° and the supernate was carefully decanted. The solid aggregate was dispersed in 200 ml of cold acetone and filtered (14.0 g, $[\alpha]_D$ −64°). The acetone solutions were combined and cooled at 5° to give 4.68 g of additional solid ($[\alpha]_D$ − 80°). The solution was concentrated *in vacuo* to 20% of original volume (*ca.* 750 ml) and let stand for 24 hours at 24° to give 12.30 g of off-white solid ($[\alpha]_D$ −88°). A second crop of 8.15 g ($[\alpha]_D$ −78°) was obtained after another 24 hours; slow concentration of the supernate to 100 ml gave 2.5 g of solid ($[\alpha]_D$ −85°). Evaporation to dryness afforded 30 g of noncrystalline residue. The two solids with $[\alpha]_D$ −80° and −78° were recrystallized together (13 g) from 200 ml of methylene chloride/hexane (2:1) at 5° to give 3.8 g of off-white solid ($[\alpha]_D$ −89°); the supernate was evaporated to give 10.5 g of solid residue ($[\alpha]_D$ −67°).

The 30 g residue was partitioned between aqueous sodium hydroxide (1 *N*) and ethyl acetate. The organic layer was rinsed with 2% aqueous sodium carbonate, dried (sodium sulfate), and concentrated to dryness (10.9 g). The free amine was distilled by kugelrohr to give 9.8 g of pale yellow liquid (hydrochloride salt: $[\alpha]_D$ +6°; slightly enriched in (+)-**1**). The oil (0.038 mole) in 150 ml of acetone was combined with 14.6 g of di-*p*-toluoyl-*l*-tartaric acid in 150 ml of acetone. Solid (9.8 g) separated at 24° ($[\alpha]_D$ +95°) and cooling at 5° provided 9.5 g of solid ($[\alpha]_D$ +63°). The latter material was partitioned between methylene chloride and 3 *N* sodium hydroxide to afford 3.2 g of viscous free base, after kugelrohr distillation. This amine in 50 ml of acetone was treated with 4.9 g of di-*p*-toluoyl-*d*-tartaric acid in 50 ml of acetone, depositing 7.5 g of solid ($[\alpha]_D$ −87°) on standing at 24°.

The four fractions with $[\alpha]_D$ between −85° and −89° were recrystallized en masse (*ca.* 26 g) from 350 ml of methylene chloride/hexane (2:1) as follows. The material was boiled in 200 ml of methylene chloride for 15 minutes and filtered. The recovered solid was reboiled in 100 ml of fresh methylene chloride for 10 minutes and filtered. The combined extracts were concentrated to *ca.* 230 ml, filtered, and diluted with *ca.* 120 ml of warm hexane. The undissolved solid weighed 6.0 g ($[\alpha]_D$ −96°). The solution deposited 6.85 g of solid ($[\alpha]_D$ −99°), after 16 hours at 24°. Cooling to 5° gave a second crop of 6.90 g ($[\alpha]_D$ −98°). The solids with $[\alpha]_D$ between −96° and −99° were collectively (20 g) recrystallized from 200 ml of methanol to give 14.7 g of bright white solid, $[\alpha]_D^{24}$ −101.6° (c 0.198, methanol), mp 151.5-153° (39% yield); ir: ν max 1722, 1612, 1265 and 1103 cm^{-1}; ^1H nmr (deuteriochloroform/dimethylsulfoxide-d_6, 4/1): δ 7.95 (d, 4H, J = 9 Hz), 5.88 (s, 2H, CHO), 4.7-4.5 (m, H_{10b}), 4.38 (dd, H_6, J = 4.5, 11 Hz), 2.38 (s, CH_3). One-half of this salt (7.5 g) was converted to free base, which was distilled by kugelrohr to give 3.4 g of white solid. The solid was dissolved in dry ether, filtered, and treated with ethereal

hydrogen chloride, affording 3.05 g of bright white powder, mp 237-240° (turned tan), $[\alpha]_D^{26}$ −32.2° (c 0.258, methanol). Diastereomeric salt from a separate independent resolution, with mp 153-153.5° dec; $[\alpha]_D^{26}$ −101.4° (c 0.244, methanol), gave hydrochloride salt with mp 230-238°, $[\alpha]_D^{27}$ −32.0° (c 0.294, methanol) [12]. The optical rotation of distilled free base [(−)-**1**] from the hydrochloride salt with mp 230-238°: $[\alpha]_D^{21}$ −77.0° (c 0.334, methanol); ir: ν max 2370, 1487, 1445, 1020 and 760 cm^{-1}; ^1H nmr: δ 5.0-4.65 (m, H_6 and H_{10b}), 4.0 (ddd, H_3), 3.62 (dd, H_5, J = 4.5, 12 Hz). The two samples with $[\alpha]_D$ −64° and −67° were combined (*ca.* 25 g) and converted to free base (8.0 g distilled). This amine in 150 ml of acetone was treated with 12.0 g of di-*p*-toluoyl-*l*-tartaric acid in 150 ml of acetone. After cooling to 5°, 16.4 g of solid was obtained ($[\alpha]_D$ +92°). Concentration to 200 ml supplied 4.0 g of solid ($[\alpha]_D$ +63°).

The samples with $[\alpha]_D$ +92° and +95° were recrystallized together (*ca.* 26 g) from 350 ml of methylene chloride/hexane (2:1) as described above. Undissolved solid weighed 15.3 g ($[\alpha]_D$ +92°). The solution was cooled to 5° and 8.4 g of solid was collected ($[\alpha]_D$ +97°). Recrystallization of the 15.3-g fraction from methanol gave 10.5 g of white solid ($[\alpha]_D$ +100.5°). The two fractions with $[\alpha]_D$ +100.5° and +97° were recrystallized together (19 g) from methanol to furnish 14.2 g of solid ($[\alpha]_D$ +100°, mp 150-152°, dec), which was recrystallized again (methanol), giving 11.2 g of white needles, $[\alpha]_D$ +100.6° (c 0.301, methanol), mp 152.5-154° dec (30% yield); ir ν max 1720, 1608, 1262 and 1100 cm^{-1}; ^1H nmr (deuteriochloroform/dimethylsulfoxide-d_6, 4/1): δ 7.95 (d, 4H, J = 9 Hz), 5.87 (s, 2H, CHO), 4.7-4.5 (m, H_{10b}), 4.38 (dd, H_6, J = 4.5, 11 Hz), 2.38 (s, CH_3). This salt (9.0 g) was converted to free base (distilled), then to a hydrochloride salt (3.60 g), mp 232-239° (turned amber), $[\alpha]_D^{26}$ +31.3° (c 0.262, methanol). Diastereomeric salt from another resolution with mp 145-146.5° dec, $[\alpha]_D^{27}$ +100.5° (c 0.170, methanol) gave hydrochloride salt with mp 232-242° (turned amber), $[\alpha]_D^{25}$ +32.4° (c 0.247, methanol) [12]; ir: ν max 2544, 1495, 1028 and 767 cm^{-1}; ^1H nmr:δ 6.78 (br d, H_7), 5.0-4.65 (m, H_6 and H_{10b}), 3.63 (dd, H_5, J = 4.5, 11.0 Hz).

Resolution of (±)-2-Phenylpyrrolidine (**3**).

2-Phenylpyrrolidine (10.0 g, 0.068 mole) and L-(+)-tartaric acid (10.2 g, 0.068 mole) were combined in 50 ml of absolute ethanol and allowed to crystallize slowly at ambient temperature. The recovered salt (14.25 g) was recrystallized four times from ethanol to give highly enriched *R*-(+)-**3**•(+)-tartrate (2.5 g), mp 131-134°. This salt was partitioned between methylene chloride and dilute aqueous sodium hydroxide and the organic layer was washed with water, dried (potassium carbonate), and evaporated to give *R*-(+)-**3** (1.20 g, 75% e.e.), $[\alpha]_D^{23}$ +24.3° (c 0.30, methanol).

Validation of Enantiomeric Purity For *R*-(+)-**3**.

Enriched (+)-**3** (50 mg, $[\alpha]_D$ +26.2°, 81% o.p.) was dissolved in 1 ml of dry methylene chloride. With stirring, (+)-*R*-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [3a] (200 mg) in 1 ml of dry methylene chloride was added and the solution was stirred for 1 hour. Analysis by tlc indicated complete reaction of the (±)-**3**. The methylene chloride solution was washed once with water, dilute aqueous sodium hydroxide, 1 *N* hydrochloride, and saturated sodium chloride; then dried (potassium carbonate) and evaporated to give an oil (200 mg). Analytical hplc analysis of this material (silica column, 1% 2-propanol in hexane) revealed a 91:9 ratio of the diastereomeric amides, indicative of 82% e.e. for the (+)-**3** used.

(+)-6*S*,10b*R*-1,2,3,5,6,10bβ-Hexahydro-6α-phenylpyrrolo[2,1-*a*]isoquinoline Hydrochloride, (+)-[**1**•HCl].

R-(+)-2-phenylpyrrolidine **3** (1.10 g, 7.5 mmoles, 75% e.e.) and styrene oxide (0.90 g, 7.5 mmoles) were combined in 10 ml of absolute ethanol and refluxed for 16 hours. The solution was evaporated to an oil, which was combined with PPA (11 g) and heated at 100° for 1 hour. The reaction was cooled, diluted with ice water, basified with 40% aqueous potassium hydroxide (*p*H > 11) under cooling, and extracted with methylene chloride. The organic layer was washed with water, dried (potassium carbonate), and evaporated to an oil (1.20 g, 64%, **4**/**1** = 4.3). The mixture was separated by column chromatography (silica gel, ethyl acetate/methanol, 10:1) to give enantiomerically-enriched, individual samples of **4** and **1**. The hydrochloride salt of this sample of **1**, prepared with ethereal hydrochloride, was obtained as a white powdery solid (60 mg), $[\alpha]_D^{24}$ +23.9° (c 0.293, methanol).

Acknowledgement.

We thank Martin Mutter for nmr spectral data and Joan Rogers for some optical rotation measurements. We also thank Frank Villani, Jr., Dr. David McClure, and Professor Harry S. Mosher (Stanford University) for helpful discussions regarding nmr of (+)-MTPA salts.

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[12] Satisfactory elemental analyses were obtained for the diastereomeric salts [Calcd. for $C_{18}H_{19}N{\cdot}C_{20}H_{18}O_8$: C, 71.81; H, 5.87; Found: for (+)-salt: C, 72.12; H, 6.06 and for (−)-salt: C, 71.65; H, 5.89], and for the hydrochloride salts [Calcd. for $C_{18}H_{19}N{\cdot}HCl$: C, 75.64; H, 6.70; Cl, 12.40. Found: for (+)-salt: C, 75.62; H, 7.06; Cl, 12.42. and for (−)-salt: C, 75.61; H, 7.05; Cl, 12.41].