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ASYMMETRIC SYNTHESIS AND ABSOLUTE STEREOCHEMISTRY OF LY248686

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Summary: Reduction of 3-(dialkylamino)-1-aryl-1-propanones with a 2:1 complex of [(2*R*,3*S*-(+)-4--dimethylamino-1,2-diphenyl-3-methyl-2-butanol] (**8**) and lithium aluminum hydride (LAH) provided the corresponding 1,3-aminoalcohols in high ee's (80-88%). This process was developed and applied to the synthesis of LY248686 (**1**), a potent inhibitor of serotonin (5HT) and norepinephrine (NE) uptake. Absolute configurations have been established by single crystal x-ray analysis.

Recently, reports from Robertson and Wong have shown that a series of 3-(1-naphthoxy)-3-arylpropanamines are potent inhibitors of the serotonin and norepinephrine uptake carriers[1]. Such compounds could augment the utility of existing investigational drugs and might find application for the treatment of depression, obesity, and alcoholism[2]. Among various analogs, thiophene **1** (LY248686) exhibited promising activity. Selection of this candidate for preclinical development necessitated the preparation of kilogram amounts of optically pure **1**. We delineate herein an efficient, enantioselective synthesis of **1** in about 60% overall yield from 2-acetylthiophene (**2**) via a four-stage sequence of: Mannich reaction (**2** into **3**); asymmetric reduction (**3** into **5**); alkylation with 1-fluoronaphthalene (**5** into **6**); and N-methyl dealkylation (**6** into **1**) with final isolation as the oxalate salt **7** and/or maleate salt **7a** of LY248686 (See Scheme).

Crucial to the development of this synthesis of **1** was our observation that reduction of some requisite Mannich bases with the kinetically-formed Yamaguchi-Mosher-Pohland (YMP) complex ($LiAlH_4$ + 2 equiv **9**) gave the corresponding aminoalcohol with unexpectedly high ee's (Table)[3]. The absolute stereochemistry of **1** has not been previously established[1a] and the outcome of the reduction of the Mannich bases (e.g. **3**) with YMP complexes (from **8** or **9**[5b]) not recorded. The stereochemistry has now been determined. Reduction of the free base of **3** with "$LiAl(9)_2H_2$" in ether[3a-c] (Table) at -78 °C and treatment of the resultant carbinolamine with hydrobromic acid afforded **5**. The stereochemistry of **5** was shown to be *R* by single crystal x-ray analysis[4] (Figure).

Subjecting pure **5** to the reaction sequence as depicted in the Scheme gave the *antipode* of LY248686. Therefore the stereochemistry of LY248686 is *S* and the reduction stereochemistry of **3** with the YMP complex corresponds to a number of reported cases[3d].

Within this present work, reductions utilizing **8** were of importance to our concerns since this auxiliary was available in large quantities[5a] on a low-cost basis[5c]. For successful development of this reduction several difficulties associated with the use of "complexed-LAH" were avoided. Notable among these are: (a). *Purification* - When desired, highly efficient upgrades in the ee of **4** were accomplished in a very simple manner[6a]. However, alcohol **4** of 85% ee could be utilized and

SCHEME

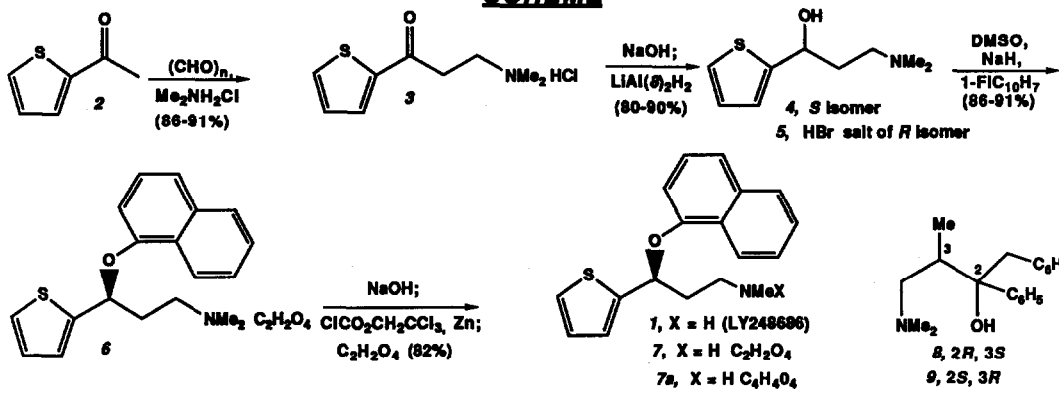
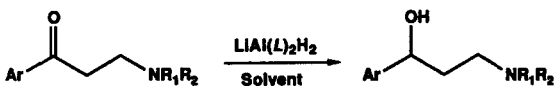
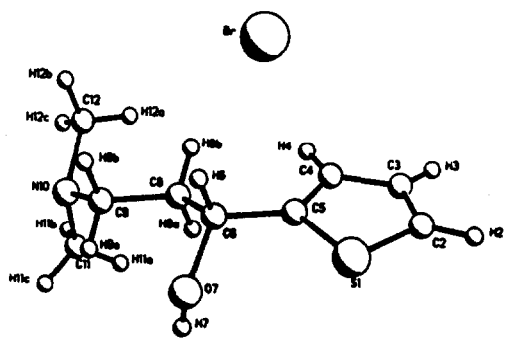


TABLE (REDUCTION OF MANNICH BASES)



Ar =	R_1 = R_2 =	equiv. LAH *L* (equiv.)	Solvent (M/L, *L*)	% ee (Configuration)
2-Thiophenyl	CH_3, CH_3	1.1 *9* (2.5)	ether (0.21)	85-88 (R)
2-Thiophenyl	CH_3, $CH_2C_6H_5$	1.1 *9* (2.3)	toluene (0.23)	84 (R)
Phenyl	CH_3, CH_3	1.1 *9* (2.5)	toluene (0.20)	80-88 (R)
2-Thiophenyl	CH_3, CH_3	1.1 *8* (2.4)	toluene (0.18)	80-88 (S)

FIGURE



Computer-generated plot of the hydrobromide salt of compound *5* from reaction of $LiAl(9)_2H_2$ with *3*.

typically provided **1** of >98% ee after subsequent crystallizations. (b) *Separations* - Simple extraction served to separate **8** from **4**. (c) *Recycle* - Pure **8** was recovered by simply cooling the extraction solution.[7] (d) *Safety* - Toluene was used as reaction solvent in place of diethyl ether[8]. (e) *Scale* - Large-scale, cryogenic reductions (>1 Kg) have been run in the continuous mode[9].

Preparation of the "*ent*-YMP" complex *for this work* was accomplished by the addition of dry **8** (15.6 g/180 ml toluene) to LAH·$(THF)_2$ (25.1 mL, 1M in toluene) at -25 °C to -30 °C in <10 min. This insoluble complex was cooled immediately to <-70 °C and a dry solution of the amine (from neutralization of 5.00 g of *3*[10] with 4.90 ml of 5N NaOH in 80 ml toluene) was then added (<-65 °C, <10 min). After 16 h at -70 °C , the mixture was quenched by cautious addition of saturated sodium sulfate, filtered, washed with hot THF, and concentrated *in vacuo*. Pure **4** was isolated[6b] by addition of hexane (25 ml), extraction into 1:1 methanol water (6×25 ml), concentration, and filtration (80-90% yield, ee = 85-88%). Alkylation was accomplished by reaction of **4** (350g) with 60% sodium hydride (1.0 equiv in DMSO, 3.4 mL/g, 25 °C, 25 min) and then with 1-fluoronaphthalene (1.2 equiv, 45-50

°C, 48-72 h) after which excess reactants were removed by acidification (pH = 3) and hexane extraction. Extraction of the free base (methylene chloride, pH = 12) and salt formation with oxalic acid afforded 86-91% of pure **6**. Dealkylation[1a] was accomplished via neutralization of **6** (242.9 g in toluene with 2N sodium hydroxide) and sequential treatment of the dried toluene solution with 30 g of Proton Sponge®[11a], 2,2,2-trichloroethylchloroformate (290 mL, 75-80 °C for 1 h)[11b], methanol (105 mL for quench), triethylamine (355 mL, 30 min, 25 °C), and hydrochloric acid (2.25 L). Concentration of the toluene layer and treatment with active zinc dust (408 g) in 2.5% formic acid in dimethylformamide (4.1 L) afforded **1** (in solution) after routine extractive work-up involving concentrated ammonium hydroxide (pH = 11) and ethyl acetate (8 L). Isolation and purification of **7** was accomplished by treatment of **1** with oxalic acid (1 equiv) in ethyl acetate (82% overall from **6**). The maleate **7a** was prepared in a like manner by reaction of **1** with maleic acid[1a].

Acknowledgements

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References and Notes

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4. Compound **5** crystallized from ethanol in the monoclinic space group $P2_1$ having the dimensions a = 5.950(1) Å, b =15.756(2) Å, c = 6.512(1) Å, B = 105.144 deg. and a calculated density of 1.50 g cm^{-3}. A total of 928 reflections with 2θ less than 116.0° were measured on an automated four-circle diffractometer using monochromatic copper radiation. The structure was solved using the direct methods routine SOLV of the SHELXTL program library (see Sheldrick, G. M. *Shelxtl*, Rev 4, Instrument Corporation, **1983**) and was refined by the least squares method with anistropic temperature factors for all atoms except hydrogen. All hydrogen atoms, except the HBr salt

hydrogen, were included with isotropic temperature factors at calculated positions. The final R-factor was 0.059 for 817 unique observed reflections.

5. a) Carbinolamine **9** has been referred to as "Darvon alcohol" at various points in the literature. This use of the Darvon® trademark has not been authorized by Eli Lilly and Company. b) This material is sold by Aldrich Chem. Co. under the trademark Chirald®. c) Industrially, **9** is obtained by classical resolution from the corresponding *d,l* mixture with (-)-camphorsulfonic acid *in ethanol.* Purified **8** is efficiently recovered from the mother liquors of **9** by resolution with the same acid *in acetone.* For this work **8** was obtained from Eli Lilly Industries, Mayaguez, Puerto Rico. See Pohland, A.; Sullivan, H. R. *J. Am. Chem. Soc.* **1955**, *77*, 3400.

6. a) For example, isolated **4** (99% chemical purity, 86 % ee, 12.18 g) is stirred in methanol-water (112 mL of 1:1 v/v) for 30-60 min at 25 °C. Filtration and drying affords **4** (10.98 g, 92 %ee). b) All crystallized intermediates of the reaction Scheme exhibited satisfactory ^{1}H NMR, ^{13}C NMR, IR, UV, MS, titration, and combustion analysis data. MP's (°C); **3** = 174-76; **4** = 78-80; **5** = 108-10; **6** = 151-152; **7** = 149-50; **7a** = 129-130; **1** = oil; $[\alpha]_D$ (C=1, MeOH) **4** = -7.6°; **5** = +20°; **6** = +109°; **7** = +84°; **7a** = +94°; **1** (oil) = +117°. c) Chiral assays were performed on free amines by 300 MHz ^{1}H NMR analysis in the presence of (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TAE) in $CDCl_3$ (observe N-methyls - see Pirkle, W. H.; Hauske. J. R. *J. Org. Chem.* **1977**, *14*, 2436) and by direct chiral HPLC assay on a Chiralcel® OD column using 0.2% diethylamine in 10% isopropanol-hexane at 230 or 254 nm at 1.00 mL/min., R_t = min: **4** = 6.1; **5** = 6.4; **6** = 4.7; **6-*R*** = 5.5; **1** = 10.9; **1-*R*** = 15.0. See Bopp, R. J.; Kennedy, J. H.; Jensen, E. C.; Maloney, A. Presented at the Eastern Anal. Symposium, Sept. 13-18, 1987; Abstract #425. Bopp, R. J.; Kennedy, J. H. *LC-GC*, **1988**, *6*, 6.

7. Typically in a reduction employing 248 g of **8**, the dried hexane layer is concentrated to 900 ml, cooled to -20 °C, and filtered. Concentration of the filtrate to 300 ml, re-cooling and filtration provides a second crop (total recovery = 84%).

8. Spills of LAH·$(THF)_2$ in toluene do not easily ignite.see *Lithium Aluminium Hydride*, 1987; Lithium Division of Chemetal. VHS-NTSC Video (englisch), Kinax Film- und Videoproduktion, Kopierwerk, Wilhelm Ax KG, Am Zwingel 6340 Dillenburg, Postfach 1542.

9. Because of the nature of the reagent, ee's fall to about 75% in 22-L equipment. However unpublished results of Louis Hibbard and Randy Hawley from this lab show that high ee's are maintained when the reaction is conducted through a 500 ml Zipperclave® reactor at < -70 °C.

10. Prepared in 86-91% yield (directly crystallized) by reaction of **2** with dimethylamine hydrochloride (0.83 Kg|Kg **2**) and paraformaldehyde (0.36 Kg|Kg **2**) using 12 N hydrochloric acid (16ml/Kg **2**) in ethanol (2.45 L/Kg **2** reflux 20-24 h). Plastino, E.; Loprieno, N.; Bugian, A.; Tenerini, J. Ital. Patent 637 371, 1962. *Chem. Abstr.* **1964**, *60*, 479c.

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12. The third entry of the Table was isolated in 94% yield and represents a candidate for the synthesis of *R*- or *S*-fluoxetine. For recent enantioselective syntheses of fluoxetine see Srebnik, M.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1988**, *53*, 2916. Gao, Y.; Sharpless, K. B. *J. Org. Chem.*, **1988**, *53*, 4081 Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.*,**1989**, *30*, 5207.

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