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Communications to the Editor

Substrate Modification Approach to Achieve Efficient Resolution: Didesmethylcitalopram: A Key Intermediate for Escitalopram[#]

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Abstract:

Research work presented here describes an approach to achieve the enantiopure escitalopram (1) via didesmethyl escitalopram (4), which is easily resolvable compared to citalopram (1a) through diastereomeric salt crystallization. The resolved intermediate (didesmethylcitalopram) was subsequently used for the preparation of the desired drug. This simple modification of the substrate makes a remarkable difference in the chemical resolution process. The first resolution of didesmethylcitalopram (±)-4 to furnish (+)-4, a novel key intermediate to assemble escitalopram (1) was achieved via diastereomeric salt resolution using (−)-di-*p*-toluoyltartaric acid (DPTTA). The resolution conditions were optimized; a key feature of this process is the addition of specific quantity of water at a specific temperature to the reaction mixture.

Introduction

Enantiopure compounds can generally be synthesized either by asymmetric synthesis or resolution techniques. Despite its image as a "low-tech method" resolution via diastereomeric salt crystallization is of interest for the production of enantiomerically pure compounds at industrial scale, having the advantage of relative simplicity and requiring only standard production equipment. Successful formation and separation of diastereomeric salts depend upon the presence of a suitable chiral handle on the substrate, chiral resolving agents, and a solvent system that can easily separate the diastereomeric pair. Traditionally, resolving agents are screened or modified when a substrate of interest is very difficult to resolve due to its structural limitations or poor solubility differences between diastereomeric pairs.[1] Modification of the substrate, however, is seldom practiced. The solubility difference between a diastereomeric pair can be achieved by modifying the substrate, provided that the modified substrate, after resolution, should be easily converted to the desired product by simple chemical transformations at the end. Herein we report a case study wherein modification of racemic citalopram (**1a**) enabled us to achieve an efficient resolution of didesmethylcitalopram (±)-**4** (Figure 2), a potential intermediate for escitalopram (**1**) in a novel, economic, and plant-friendly way. Escitalopram (**1**), the *S*-enantiomer of citalopram (**1a**), a highly selective serotonin reuptake inhibitor (SSRI) antidepressant, developed for the treatment of depression and anxiety disorders and sold on the market as Lexapro. Preclinical studies have demonstrated that the therapeutic activity of citalopram (**1a**) resides in escitalopram and the *R*-citalopram is approximately 30-fold less potent than escitalopram[2] (**1**). Lundbeck[3a] accomplished the first synthesis of **1** in two different approaches employing diol intermediate **2a** to assemble the required stereochemistry of **1**. To date, to have a stereocontrolled access to **1**, various synthetic methods have been exploited with different intermediates (Figure 1). The published approaches are summarized below:

(a) HPLC separation or fractional crystallization of diastereomeric esters of diol **2a**;[3a] (b) resolution of diol intermediate **2a** by diastereomeric salt formation with (+)-di-*p*-toluoyltartaric acid (DPTTA);[3a] (c) chromatographic separation[3b] of enantiomers of citalopram (**1a**), bromocitalopram (**1b**), diol intermediates **2a** and **2b** using chiral stationary phase; (d) diastereomeric salt resolution[3c] of bromocitalopram (**1b**); (e) resolution of bromomonoester intermediate **3b** by diastereomeric salt crystallization;[3d] (f) enzymatic resolution of diol intermediate **2a**, monoester **3a**, and their related analogues;[3e] and (g) enzymatic resolution[3f] of diol intermediate **2a**. Most of the above-reported procedures have limitations in terms of scalability and reaction yields. Herein we report a new and economic process for large-scale synthesis

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(1) (a) Bolchi, C.; Pallavicini, M.; Fumagalli, L.; Marchini, N.; Moroni, B.; Rusconi, C.; Valoti, E. *Tetrahedron: Asymmetry* **2005**, *16*, 1639. (b) Kobayashi, Y.; Kurasawa, T.; Kinbara, K.; Saigo, K. *J. Org. Chem.* **2004**, *69*, 7436. (c) Marchini, N.; Bombieri, G.; Artali, R.; Bolchi, C.; Pallavicini, M.; Valoti, E. *Tetrahedron: Asymmetry* **2005**, *16*, 2099. (d) Pallavicini, M.; Bolchi, C.; Fumagalli, L.; Valoti, E.; Villa, L. *Tetrahedron: Asymmetry* **2002**, *13*, 2277.

(2) Burke, W. J. *Expert Opin. Invest. Drugs* **2002**, *11*(10), 1477.

(3) (a) Klaus, P. B.; Jens P. U.S. Patent 4,943,590, 1990. (b) Bech, S. M.; Nielsen, O.; Petersen, H.; Ahmadian, H.; Pedersen, H.; Brosen, P.; Geiser, F.; Lee, J.; Cox, G.; Dapremont, O.; Suteu, C.; Assenza, S.; Hariharan, S.; Nair, U. WO Patent 006449A1, 2003. (c) Ahmadian, H.; Petersen, H. WO Patent 051861A1, 2003. (d) Tse, H. L. A. WO Patent 087081A1, 2003. (e) Taoka, N.; Kato, T.; Yamamoto, S.; Yoshida, T.; Takeda, T.; Ueda, Y.; Petersen, H.; Dancer, R.; Ahmadian, H.; Lyngsolars, O. WO Patent 014821A1, 2004. (f) Cotticelli, G.; Rocchietti, S.; Terreni, M.; Pregnolato, M.; Salvetti, R. WO Patent 098018A1, 2005.

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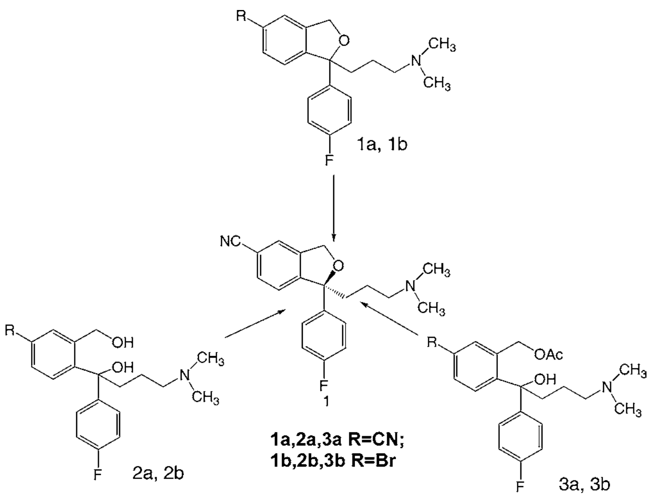


Figure 1. **Reported approaches.**

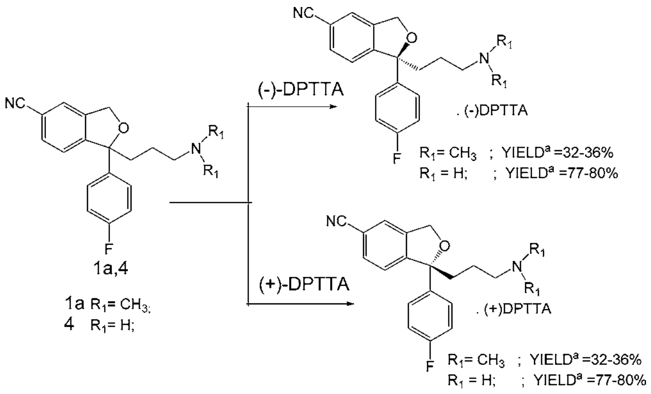


Figure 2. **Resolution of 1a and 4 with both antipodes of DPTTA. *a*: Yields were calculated relative to the theoretical amount, which is half of the starting racemate.**

of escitalopram through diastereomeric salt resolution of a modified substrate, didesmethylcitalopram (**4**).

Results and Discussions

Prompted by the ready accessibility of citalopram (**1a)**, initially we focused on development of a diastereomeric salt resolution process for **1a**. Of the many resoluting agents screened, use of (−)-DPTTA, though found to be useful,[4] in our hands proved to be unsatisfactory for an industrial-scale application due to low yields and multiple crystallizations. Believing that the minor structural modifications of the substrate **1a** could exhibit a better resolvability, we ventured to study the resolution of the primary amine (±)-**4**, and this led to an efficient, scalable, and economic synthesis of escitalopram (**1**) (Figure 2).

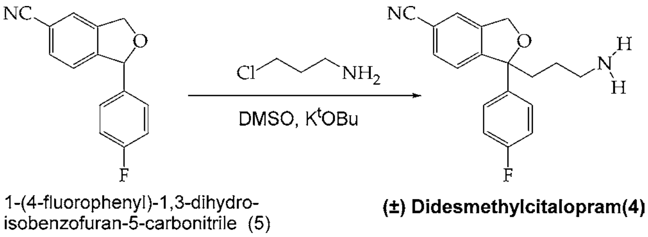
Our interest in the preparation and resolution of (±)-**4** was aroused by (i) encouraging results disclosed in preceding reports[3a−f] and (ii) its potential importance as a key intermediate. After several unsuccessful synthetic approaches we established an optimum procedure to access (±)-(**4**) by C-alkylation of 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**5**) with 3-chloropropylamine in the presence of base (Scheme 1).[5]

Table 1. **Resolution of (±)-4 with (−)-DPTTA in various solvents**

entry	solvent	yield[a] (%)	chiral purity[b] (%) (+)-**4**·(−)-DPTTA	chiral purity[b] (%) (−)-**4**·(−)-DPTTA
1	methanol	52.5	50.7	49.29
2	acetone	52.5	82.0	17.97
3	acetonitrile	95.0	50.8	49.2
4	ACN/H_2O (10:2)	84.5	73.4	26.4
5	ACN/H_2O (10:3)	83.0	91.1	8.9
6	ACN/H_2O (10:4)	55.2	86.9	13.1
7	ACN/H_2O (10:10)	72.5	60.0	40
8	ACN/MeOH (10:3)	42.2	76.6	23.4
9	MeOH/H_2O	43.0	83.0	17

[a] Relative to theoretical amount, i.e., half of starting material. [b] Chiral purity of liberated precipitate.

Scheme 1



With (±)-**4** in hand, we evaluated a number of enantiomerically pure acids (e.g., tartaric acid, di-*p*-toluoyltartaric acid, dibenzoyl tartaric acid, and camphorsulphonic acid), using various organic solvents such as methanol, acetonitrile, ethylacetate, acetone, dichloromethane, and chloroform for their ability to resolve (±)-**4**. Among those tested, the antipodes of DPTTA were found to be an excellent choice for diastereomeric salt formation in acetonitrile, methanol, and acetone. It is common to apply the opposite enantiomer of the resolving agent to obtain the desired stereoisomer of the target substrate;[6] hence, we opted for (−)-DPTTA as the resolving agent for diastereomeric resolution of (±)-**4**. Screening of different solvents and solvent mixtures for the separation of diastereomers (+)-**4**·(−)-DPTTA and (−)-**4**·(−)-DPTTA led to the finding that the specific combination of acetonitrile/water was an excellent choice for separation of (+)-**4**·(−)-DPTTA (white crystalline solid) during the screening process, and the results are shown in Table 1. These results suggest that water plays an important role for the separation of diastereomers.

In order to improve the resolution efficiency, a systematic optimization study was taken up using acetonitrile/water solvent combinations to study the parameters, namely the quantity of water and the mode and temperature of the water addition. The study revealed that the amount of water used and the temperature of the water addition have significant impact on chiral purity and yield of the product.

An optimized experimental procedure is as follows: A mixture of (−)-DPTTA and acetonitrile was stirred at room temperature until a clear solution was obtained; then a

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(4) Klaus, P. B. reported that the attempts to resolve citalopram by diastereomeric salt crystallization have not been sucessful.[3a]

(5) Sundaram, V.; Mathad, V. T.; Elati, R. R. C.; Kolla, N.; Vankawala, P. J.; Govindan, S.; Chalamala, S.; Gangula, S. WO Patent 047274, 2005.

(6) Kozma, D. CRC *Handbook of Optical Resolutions via Diastereomeric Salt Formation*; CRC Press: Boca Raton, 2002.

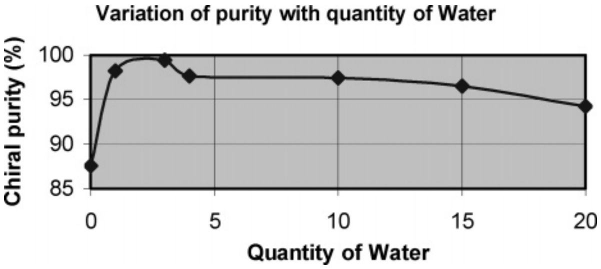

Figure 3. **Variation of purity with quantity of water.**

Table 2. **Solubility data of (+)-4·(−)-DPTTA and (−)-4·(−)-DPTTA diastereomers in acetonitrile/water at different temperatures (mg/mL)**

entry	compound	ACN/H_2O	0 °C	26 °C	45 °C	58 °C
1	(+)-**4**·(−)-DPTTA	10:1	5.2	10.5	11.5	18.5
2	(−)-**4**·(−)-DPTTA	10:1	12.1	90.5	125	260
3	(+)-**4**·(−)-DPTTA	10:3	4.3	10	12.5	21.8
4	(−)-**4**·(−)-DPTTA	10:3	16.12	111	200	500
5	(+)-**4**·(−)-DPTTA	10:5	3.3	8.3	11.1	20
6	(−)-**4**·(−)-DPTTA	10:5	8.3	74	200	312.5

solution of compound (±)-**4** in acetonitrile was added, and the mixture was stirred for 10−15 min. To the white precipitate was slowly added water, maintaining the temperature at 55−60 °C; the suspension was stirred for 45−60 min at 55−60 °C. After cooling the mass between 0 and 5 °C for 1.0−1.5 h, the temperature was raised to 25−35 °C, and the mixture was stirred for 45 min. This temperature-cycling process was repeated two more times, and the resulting solid was filtered at 0−5 °C. Before undertaking the optimization study, samples of individual diastereomers (+)-**4**·(−)-DPTTA and (−)-**4**·(−)-DPTTA were prepared in order to determine the solubility in different combinations of acetonitrile/water at different temperatures. The results of the solubility studies are listed in Table 2.

The experimental results of the optimization study are well in agreement with the solubility data. In this experimental study[7] 10 times the acetonitrile quantity is kept constant. Experiments carried out with 3 times the water quantity represented good enantiomeric purity. A steady decrease in purity was noticed with an increase in water greater than 3 times, and this is due to the poor solubility of (−)-**4**·(−)-DPTTA (Figure 3, Table 2).

A difference in the tendency to crystallize (−)-**4**·(−)-DPTTA in competition with (+)-**4**·(−)-DPTTA is observed in experiments carried out with addition of water at different temperatures. On one hand, addition of water between 55 and 60 °C resulted in a solid suspension and produced superior yields and chiral purities of the desired isomer upon subsequent cooling, indicating the complete solubility of the undesired diastereomer in the solvent mixture. On the other hand, addition of water above 62 °C resulted in a homogeneous clear solution; the resulting solid, after crystallization, produced low purities and yields, indicating the solubility of both the diastereomer and crystallization of the undesired diastereomer along with the desired isomer upon subsequent cooling. Finally, escitalopram (**1**) is produced by the methylation of the chiral intermediate (+)-**4** following Elschwier−Clarke methylation[8] using formic acid and formaldehyde. Thus, a simple and new synthesis for **1** through diastereomeric salt resolution of *S*-didesmethylcitalopram has been achieved. The spectroscopic data of our process samples **4** and **1** were well in agreement with those reported previously.[9]

Conclusions

In summary a new and efficient method for the preparation of *S*-didesmethylcitalopram (+)-**4** was developed by simple crystallization of (±)-**4**·(−)-DPTTA salt. This process was used for the preparation of enantiomerically pure escitalopram (**1**) in an economic route. Current efforts are focused on the resolution of desmethylcitalopram to study the effect of structural modification of the substrate on resolution efficiency. The results will be reported in due course.

Experimental Section

General. All commercially available reagents and solvents were used as received. The ^{1}H NMR spectra were measured on a Varian Gemini 200 MHz FT NMR spectrometer and/or 400 MHz FT NMR Varian Mercury plus spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on HP-5989a LC−MS spectrometer.

***S*-(+)-1-(3-Amino-propyl)-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile(−)di-*p*-toluoyltartrate (*S*-(+)-4·(−)-DPTTA).** A mixture of (−)-DPTTA monohydrate (136 g, 0.33 mol) and acetonitrile (500 mL) was stirred at room temperature for 5 min, then a solution of compound (±)-**4** (100 g, 0.33 mol) in acetonitrile (500 mL) added in a period of 15 min, and the mixture stirred for 10−15 min. To the resultant white precipitate was slowly added water (300 mL) at 55−60 °C, and the suspension was stirred for 45−60 min at 55−60 °C. After cooling the flask to 0−5 °C for 1.0−1.5 h, the temperature was raised to 25−35 °C, and the mixture was stirred for 45 min. This temperature cycling process was repeated for two more times, and the resulting solid was filtered at 0−5 °C. The filtered cake was washed with acetonitrile (200 mL) and dried at 60−65 °C to afford 92.5 g of (+)-**4**·(−)-DPTTA. Yield (%): 80 (calculated relative to theoretical which is half of the starting racemate) $[\alpha]_D = -76.81$ (*c* 1, methanol); chiral purity:[10] 99.0% ee; mp: 178−179 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.3−1.5 (m, 2H), 2.25 (m, 2H), 2.35 (s, 6H), 2.75 (t, $J = 8.0,7.6$ Hz, 2H), 5.19 (q, $J = 2.8$ Hz, 2H), 5.6 (s, 2H), 7.15 (t, $J = 8.8$ Hz, 2H), 7.27 (d, 4H), 7.75 (d, 2H), 7.8 (d, 4H); IR (KBr, cm^{-1}): 3439, 3177, 2947, 2228 (−C≡N), 1717 (−C=O), 1612, 1509, 1269, 834, and 762; MS (APCI) *m*/*z* 297 ($M^+ + 1$).

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[7] For this experimental study (+)-**4** of 85% chiral purity is employed.

[8] Icke, R. N.; Wisegarvu, B. B.; Alles, G. A. *Organic Synthesis*; CV(3)723.

[9] Rock, M.; Ahmadian, H. WO Patent 43525A2, 2001.

[10] Enantiopurity of (+)-**4** was estimated by chiral HPLC analysis with Chiralcel ADH, 5.0 μm, 250 × 4.6 mm; mobile phase: *n*-hexane, ethanol, diethylamine, and propionic acid in the ratio of 85:15:0.2:2.0 (v/v); 0.8 mL/min; 240 nm.

***S*-(+)-1-(3-Dimethylamino-propyl)-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile oxalate.** To a suspension of *S*-(+)-didesmethyl citalopram (+)-**4** (40 g, 0.135 mol) in water (400.0 mL) were added 37% aqueous formaldehyde (35.5 mL, 0.472 mol) and formic acid (18.mL g, 0.472 mol). The mixture was stirred at reflux temperature for 4−5 h. After reaction completion by TLC, the resulting clear solution was washed with toluene (2 × 100.0 mL), the pH of the resulting aqueous layer was adjusted to below 2 using concentrated HCl (15.0 mL) and washed with MTBE (2 × 100.0 mL). The obtained aqueous layer is alkalinized with concentrated NaOH (7.0 mL), and then the whole was extracted into toluene (3 × 250.0 mL). The final organic phase was washed with water (2 × 250.0 mL) and then concentrated under vacuum. The oxalate salt was obtained from the residue by precipitation using EtOAc (100 mL) as a solvent. Yield 44.7 g, 80%; mp 148.4 °C; $[\alpha]_D$ +12.0 (*c* 1.0, methanol).

^{1}H NMR (200 MHz, DMSO-d_6): δ 1.25−1.3 (m, 2H), 2.25 (t, 2H), 2.63 (s, 6H), 2.97 (t, 2H), 5.2 (q, 2H), 7.16 (t, 2H), 7.58 (dd, 1H), 7.6 (dd, 1H), 7.74 (d, 1H), 7.79 (d, 1H), 7.8 (s, 1H); ^{13}C NMR: δ 19.04, 36.97, 42 (2C), 56.42, 71.15, 90.36, 110.6, 115.2 (2C), 118.7, 123.1, 125.7, 127 (2C), 132.1, 139.8, 140.0, 148.8, 162.5, 164.9 (2C); MS (ES) = 325 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{23}N_2FO_5$: C, 63.76; H, 5.55; N, 6.76. Found: C, 63.2; H, 5.77; N, 6.73.

***S*-(+)-1-(3-Dimethylamino-propyl)-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile (*S*-(+)-1·(−)-DPTTA).** A mixture of compound **1a** (25 g, 0.077 mol) and acetonitrile (125 mL) was stirred at room temperature for 5 min, and then a solution of (−)-DPTTA monohydrate (31.4 g, 0.077 mol) in acetonitrile (125 mL) was added and the mixture stirred for 10−15 min. To the resultant white precipitate was added methanol (20 mL) slowly at 70−75 °C, and the resulting clear solution was slowly cooled to room temperature. After cooling the flask to 0−5 °C for 1.0−1.5 h, the resulting solid was filtered. The recrystallization with acetonitrile/methanol was repeated for two more times, and the resulting solid was filtered. The filtered cake was washed with acetonitrile (20 mL) and dried at 60−65 °C to afford 9.8 g of **1**. (−)-DPTTA. Yield (%): 36 (calculated relative to theoretical which is half of the starting racemate); $[\alpha]_D$ for free base = 10.8 (*c* 1, methanol); chiral purity:[11] 98.4%; ^{1}H NMR for free base (200 MHz, DMSO-d_6): δ 1.25−1.3 (m, 2H), 2.25 (t, J = 8.0 Hz, 2H), 2.63 (s, 6H), 2.97 (t, J = 8.0 Hz, 2H), 5.2 (q, J = 13.6 Hz, 2H,), 7.16 (t, J = 8.8 Hz, 2H), 7.58 (dd, J = 5.4 Hz, 2.0, 1H), 7.6 (dd, J = 5.4, 2.0 Hz, 1H), 7.74 (d, 1H), 7.79 (d, 1H), 7.8 (s, 1H); MS (APCI) *m*/*z* 325 ($M^+ + 1$).

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[11] Enantiopurity of **1** was estimated by chiral HPLC analysis with Chiralcel ODH, 250 × 4.6 mm, 5 μm; mobile phase: 2-propanol, *n*-hexane, and diethylamine in the ratio of 50:950:2.0 (v/v); 0.8 mL/min; 240 nm.