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# Response to Dancer's Comments on Our Article "Substrate Modification Approach to Achieve Efficient Resolution: Didesmethylcitalopram: A Key Intermediate for Escitalopram" [*Org. Process Res. Dev.* 2007, *11*, 289−292]

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**Abstract:**

**Recently, we published a synthesis of escitalopram (S-1) consisting of the resolution of didesmethylcitalopram (3) and subsequent methylation of *S*-didesmethylcitalopram (S-3) (*Org. Process Res. Dev.* 2007, *11*, 289−292). Some of our observations regarding citalopram resolution and C-alkylation of a benzofuran analogue (2) to produce didesmethylcitalopram (3) were disputed by Dr. Dancer of H. Lundbeck (preceding article). A detailed response to his comments regarding stabilization of the 3-chloroproylamine free base by dilution with certain solvents, its storage and handling, optimized experimental conditions for C-alkylation to prepare didesmethylcitalopram, and a corrected process for citalopram resolution are included.**

## Introduction

Our recent article[1] published in *Org. Process Res. Dev.* described a three-step synthesis of escitalopram (***S*-1**) consisting of: (i) alkylation of 1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile (**2**) to produce didesmethylcitalopram (**3**), (ii) diastereomeric salt resolution of didesmethylcitalopram (**3**) using (−)-di-*p*-toluoyltartaric acid (−)-DPTTA as the chiral acid, and (iii) Eschweiler−Clarke methylation of *S*-didesmethylcitalopram (***S*-3**) using formic acid and formaldehyde to form escitalopram (***S*-1**) (Scheme 1). Unfortunately, the synthesis of escitalopram (***S*-1**) via the diastereomeric salt resolution of citalopram (**1**) with DPTTA as a chiral acid was not feasible at industrial scale as disclosed due to poor yields, low purities, and a lengthy process. Since citalopram (**1**) was an unfavorable substrate to achieve efficient resolution, our efforts were redirected towards the synthesis of didesmethylcitalopram (**3**) whose subsequent successful resolution enabled us to achieve the synthesis of escitalopram (***S*-1**). In summary, our manuscript concerned the substrate modification approach that offered a better molecule for resolution as compared to citalopram (**1**) itself.

After publication of our article,[1] Dancer and Lopez De Diego have published observations[2] concerning the nonreproducibility of (a) the resolution of citalopram (**1**) in the manner detailed in our article and (b) the method for the C-alkylation step cited in our patent.[3]

***Table 1.*** **Chiral purities of the precipitate and solids obtained from concentration of the filtrate**

| | precipitated solid | | solid from filtrate | |
|---|---|---|---|---|
| isolation | *S*-isomer (%) | *R*-isomer (%) | *S*-isomer (%) | *R*-isomer (%) |
| first isolation | 45.73 | 54.25 | 59.33 | 40.67 |
| second isolation | 48.23 | 51.77 | 83.33 | 16.67 |
| third isolation | 57.56 | 42.44 | 96.38 | 3.62 |

## Results and Discussion

We agree with the findings of Dancer and Lopez De Diego[2] wherein the resolution of citalopram with (−)-DPTTA as the chiral resolving agent is not feasible in the manner cited in our article, but we disagree that resolution of citalopram (**1**) is not possible by other means. The desired isomer, *S*-citalopram, was isolated from the mother liquor after repeated resolutions as discussed in the Introduction. With respect to the process for C-alkylation for the preparation of didesmethylcitalopram (**3**), we disagree with their conclusions, and our response is discussed in this section, Results and Discussion.

**Resolution of Citalopram.** We appreciate the efforts made by Dancer and Lopez De Diego regarding the evaluation of our results for citalopram resolution.[1] We agree with them to the extent that the diastereomeric salt of *S*-citalopram cannot be crystallized by reaction with DPTTA; however, we discovered that harvesting *S*-citalopram salt from the filtrate of the salt mixture was feasible. This was conducted by producing a solution of citalopram and (+)-DPTTA monohydrate in methanolic acetonitrile at 70−75 °C and gradually cooling to 25−30 °C. Following a hold period, the precipitated solid was removed by filtration, and the resulting filtrate was concentrated to obtain a solid. The chiral purities of filtered solid and filtrate-derived residue were 54.25:45.73 and 40.67:59.33 for the *R*- and *S*-isomers, respectively. The residue was hydrolyzed with 10% aqueous sodium hydroxide solution, and following workup in toluene, the free base was attained. This was subjected to the above process twice more to produce ***S*-(+)-1-(+)**-DPTTA salt from the filtrate in 96.4% chiral purity[4] (Table 1) in 11.0% overall yield. This finding is in agreement with example 11 cited in our patent.[3] During the preparation of our article, we inadvertently missed incorporating a few words in the text, e.g.

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(1) Elati, C. R.; Kolla, N.; Vankawala, P. J.; Gangula, S.; Chalamala, S.; Sundaram, V.; Bhattacharya, A.; Vurimidi, H.; Mathad, V. T. *Org. Process Res. Dev.* **2007**, *11*, 289–292.

(2) Dancer, R. J.; Lopez de Diego, H. *Org. Process Res. Dev.* **2008**, *13*, 23–33.

(3) Sundaram, V.; Mathad, V. T.; Elati, R. R. C.; Kolla, N.; Vankawala, P. J.; Govindan, S.; Chalamala, S.; Gangula, S. WO Patent 047274; *Chem. Abstr.* **2005**, *142*, 481937.

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


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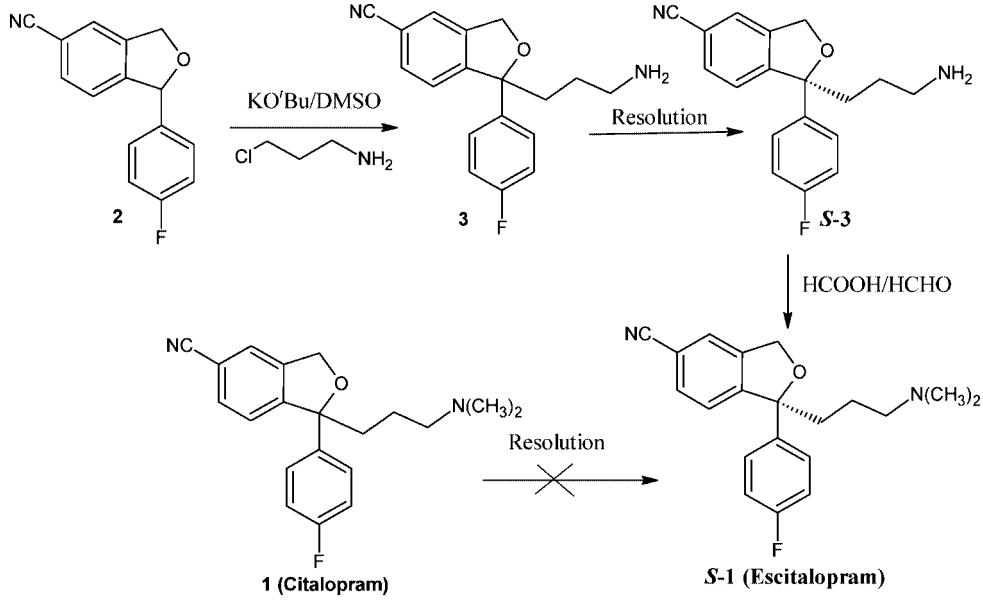
***Scheme 1.*** **Synthesis of escitalopram via preparation and resolution of didesmethylcitalopram**




"repetitive diastereomeric salt formation of the product collected from the concentration of the filtrate", which led to the nonreproducibility of the example cited in our article. The chiral acid we listed: (−)-DPTTA should have been (+)-DPTTA. We sincerely apologize for this unintentional error.

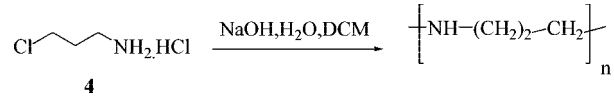
**C-Alkylation of the Benzofuran Analogue.** We did not discuss the synthesis of didesmethylcitalopram (**3**) in detail in our previous publication as our intention was to focus on the resolution.[1] The findings of Dancer and Lopez De Diego[2] with respect to C-alkylation are based solely on the presumption that the free base of chloropropylamine is unstable, which is further based on the disclosure in the literature[5] that the "separation of 3-chloropropylamine and 2-chloropropylamine by distillation appeared hopeless, because of the instability of the chloropropylamines." It is evident that the separation of 3-chloropropylamine and 2-chloropropylamine is difficult but not the collection or extraction of 3-chloropropylamine free base from commercially available 3-chloropropylamine hydrochloride.

In example 1 of our patent,[3] the alkylation was performed in DMSO, using 3-chloropropylamine free base (3-CPA free base) obtained by free basing 3-chloropropylamine hydrochloride (3-CPA HCl). In all three examples in our patent, we have specifically mentioned that the rapid addition of 3-chloropropyl amine to the carbanion of the benzofuran derivative (**2**) is crucial to the success of the alkylation. Any delay in adding 3-chloropropyl amine would lead to the failure of intended C-alkylation. In example 2,[3] the alkylation was performed in acetone. It is known that carbonyl compounds under basic conditions often undergo condensation reactions. In comparison to example 1, this transformation was not as smooth and did result in a low yield.[3] Not much discussion was devoted to this particular example as our aim was to isolate the desired product instead of the aldol product.

In example 13,[3] 3-CPA HCl was free based in a biphasic medium of water and toluene using sodium hydroxide as a base in order to obtain 3-CPA free base. The organic layer was separated and added directly to the reaction mass containing the precursor of didesmethylcitalopram (**3**). This successful alkylation procedure is based on the following study which was not discussed in that article.

(5) Kharasch, M. S.; Fuchs, C. F. *J. Org. Chem.* **1945**, *10*, 159–169.

***Scheme 2.*** **Self polymerization of 3-chloropropylamine**




**4**

***Table 2.*** **Stability study results of 3-CPA free base in different solvents**

| entry | storage conditions[a] | temp (°C) | time for polymerization[b] (h) |
|---|---|---|---|
| 1 | 3-CPA + DMSO | 0−5 | ∼36.0 |
| 2 | 3-CPA + DCM | 0−5 | ∼36.0 |
| 3 | 3-CPA[c] | 0−5 | ∼18.0 |
| 4 | 3-CPA + DMSO | 25−30 | ∼12.0 |
| 5 | 3-CPA + DCM | 25−30 | ∼12.0 |
| 6 | 3-CPA[c] | 25−30 | ∼8.0 |
| 7 | 3-CPA + DCM + DMSO | 0−5 | ∼24.0 |
| 8 | 3-CPA + DCM | 30−35 | ∼5.0 |
| 9 | 3-CPA[c] | 40−45 | ∼0.25 |
| 10 | 3-CPA + toluene | 25−30 | ∼72.0 |
| 11 | 3-CPA + MTBE | 25−30 | ∼2.0 |
| 12 | 3-CPA + 1,4-dioxane | 25−30 | ∼2.0 |

[a] 1.0 g of 3-CPA free base/10 mL of respective solvent. [b] Polymer is confirmed based on the appearance of a precipitate. [c] 3-CPA was obtained after the complete distillation of dichloromethane.

During the process development of C-alkylation, handling and storing 3-CPA free base was a major challenge as it is unstable. Storing 3-CPA for >8 h resulted in the slow appearance of insoluble solids and white vapor, which could be due to self-polymerization of 3-chloropropylamine (Scheme 2).

In an attempt to circumvent this problem, we designed a protocol to study and establish the stability of 3-CPA free base in different solvents at different temperature conditions (Table 2). Factors which were important to improve the robustness of 3-CPA free base were solvent dilution and temperature. While 3-CPA free base polymerized at 25−45 °C in the absence of solvent, 3-CPA free base extracted into DCM, MTBE, or

toluene were relatively stable. Hence, 3-CPA free base diluted in a nonpolar aprotic solvent such as toluene ameliorated the self-polymerization reaction, and hence, its use for C-alkylation reaction was successful.

In light of these results, 3-CPA free base was extracted into either toluene or dichloromethane, and this solution was used directly for the C-alkylation step. We found that the direct addition of a solution of 3-CPA free base in dichloromethane to the benzofuran anion resulted predominantly in the formation of an unknown impurity (Table 3, entry 2). In contrast, addition of a solution of 3-CPA in toluene to a solution of the benzofuran analogue (**2**) in DMSO/KO$^t$Bu led to clean alkylation and furnished didesmethylcitalopram (**3**) in 69% yield. The reaction conditions in terms of addition temperature, addition time of 3-CPA, reaction time, and mole ratio of 3-CPA were studied and led to our optimized reaction conditions described as example 13 in our patent.

Several examples from laboratory and pilot-plant preparations of didesmethylcitalopram (**3**) are depicted in Table 4. The results of these experiments represent the successful synthesis of **3**, and hence we can completely rule out the perception[2] that we utilized the hydrochloride salt of 3-chloropropyl amine, as under these conditions the hydrochloride salt would be highly insoluble in toluene.

## Conclusions

We conclude the following: (a) the resolution of citalopram (**1**) is feasible, and the nonreproducibility of the example cited in our article was due to an inadvertent error during the compilation of our manuscript; (b) we stand by our findings on the C-alkylation step: 3-CPA hydrochloride salt was hydrolyzed in a mixture of toluene−water−sodium hydroxide, and 3-CPA free base was extracted into toluene for a successful subsequent C-alkylation if conducted in a rapid manner; and (c) 3-CPA free base diluted in toluene is sufficiently stable for these purposes.

## Experimental Section

**Preparation of *S*-(+)-1-(3-Dimethylamino-propyl)-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile [*S*-(+)-1-(+)-DPTTA].** *First Isolation.* To a stirred solution of **1** (50 g, 0.154 mol) in acetonitrile (250 mL) was added a (+)-DPTTA monohydrate (62.8 g, 0.14 mol) solution in acetonitrile (250 mL) and was stirred for 60 min at room temperature. The mixture was slowly heated to 70−75 °C, and methanol (40 mL) was added to obtain a clear solution at 70−75 °C. The resulting clear solution was slowly cooled to 25−30 °C and stirred for 1.5 −2.0 h. The precipitated solid was separated by filtration, and the resulting filtrate was distilled off completely to obtain a thick residue (23.0 g). The enantiomer ratios of filtered solid (70.0 g) and residue (23.0 g) obtained through stripping the filtrates were found to be 45.73:54.25 and 59.33:40.67 for the *S* and *R* isomers, respectively. The resulting residue (23 g) was free based with 10% aqueous NaOH solution (230 mL), and the free base was extracted into toluene (2 × 230 mL). The combined organic layers were dried over sodium sulfate and concentrated to afford 15.0 g of free base.

***Table 3.*** **Extraction of 3-CPA free base from 3-CPA HCl and its subsequent use for the preparation of 3**

| | | | | HPLC purity[6] | |
|---|---|---|---|---|---|
| entry | solvent for extraction | 3-CPA addition mode[a] | yield of **3** (%) | **3** (%) | 2.84 RRT impurity |
| 1 | DCM | A | 50 | 87.19 | 0.07 |
| 2 | DCM | B | *b* | 6.46 | 80.06 |
| 3 | no solvent | C | *c* | − | − |
| 4 | toluene | D | 69 | 92.68 | ND |

[a] A = 3-CPA extracted into DCM, concentrated and diluted with DMSO. B = 3-CPA extracted in DCM and directly added to reaction mass. C = Direct addition of 3-chloropropylamine hydrochloride to the reaction by dissolving it in DMSO. D = 3-CPA extracted in toluene and directly added to reaction. [b] No attempts for isolation were made, as an impurity formed. [c] No product formed.

***Table 4.*** **Results of experiments carried out under final experimental conditions for the preparation of 3**

| entry | **2** (g) | mole ratio of 3-CPA | solvent for extraction | KO$^t$Bu (equiv) | yield % of **3** | HPLC purity[6] of **3** |
|---|---|---|---|---|---|---|
| 1 | 200 | 1.75 | toluene | 1.5 | 71.0 | 91.6 |
| 2 | 500 | 1.75 | toluene | 1.5 | 72.0 | 94.3 |
| 3 | 6000 | 1.75 | toluene | 1.5 | 67.0 | 92.1 |

*Second Isolation.* To a solution of free base **1** obtained above (15.0 g, 0.046 mol) in acetonitrile (75.0 mL) was added the (+)-DPTTA monohydrate (18.7 g, 0.046 mol) solution in acetonitrile (75.0 mL) and was stirred for 60 min at room temperature. The mixture was slowly heated to 70−75 °C at which point methanol (12.0 mL) was added to obtain a clear solution. The resulting clear solution was slowly cooled to 25−30 °C and stirred for 1.5−2.0 h. The precipitated solid was separated by filtration, and the resulting filtrate was distilled off completely to obtain a thick residue. The resulting residue (12.0 g) was hydrolyzed with 10% aqueous NaOH solution (120 mL), and free base was extracted into toluene (2 × 120 mL). The combined organic layers were dried over sodium sulfate and concentrated to afford 5.0 g of free base.

*Third Isolation.* To a solution of the above free base **1** (5.0 g, 0.015 mol) in acetonitrile (25.0 mL) was added the (+)-DPTTA monohydrate (6.06 g, 0.015 mol) solution in acetonitrile (25.0 mL) and was stirred for 60 min at room temperature. The mixture was slowly heated to 70−75 °C at which point methanol (4.0 mL) was added to obtain a clear solution. The resulting clear solution was slowly cooled to 25−30 °C and stirred for 1.5−2.0 h. The precipitated solid was separated by filtration, and the resulting filtrate was concentrated to afford 6.0 g of ***S*-(+)-1-(+)-**DPTTA salt. Yield (%): 11.0 (calculated relative to theoretical which is half of the starting racemate); chiral purity:[4] 96.4%.

**Preparation of 1-(3-Aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carbonitrile (3).** *(a) Preparation of 3-Chloropropan-1-amine Solution in Toluene.* A mixture of aqueous NaOH solution (182 g in 1100 mL of water), 3-CPA hydrochloride (470 g, 3.61 mol), and toluene (2750 mL) were stirred for 10−15 min, and the organic layer was separated. The resulting aqueous layer was re-extracted twice with toluene (2 × 1100 mL) to ensure the complete extraction of 3-CPA

free base (TLC). The combined organic layers were used as such in the alkylation step as soon as possible.

*(b) Coupling.* Dimethylsulfoxide (2500 mL) and potassium-*tert*-butoxide (355 g, 3.16 mol) were heated at 65−70 °C for 60 min, and a solution of **2** (500 g, 2.09 mol) in DMSO (1500 mL) was added to the flask over 10−15 min at 30−35 °C. To the resulting purple colored solution was added in over 10 min the solution of 3-CPA free base in toluene prepared above, and the resulting mixture was maintained at 40−45 °C for 1 h. The reaction mixture was cooled to 25−35 °C and slowly quenched into cold water (5.0 L) at 10−15 °C. The organic layer was separated, and the resulting aqueous layer was extracted with toluene (3 × 1100 mL). The combined organic layers were extracted with aqueous HCl solution (240 mL of concentrated HCl in 5000 mL of water) and washed with toluene (4 × 2500 mL). The pH of the aqueous layer was adjusted to 10.5 with aqueous NaOH solution (150 mL), and the mixture was extracted with toluene (3 × 2500 mL). The resulting toluene layer was washed with hot water (3 × 1500 mL) and concentrated to obtain 447.0 g of **3**.

Yield: 72%; HPLC purity:[6] 94.3%; $^1$H NMR (400 MHz, DMSO-$d_6$) of (−)-DPTTA salt of (±)-**3**: $\delta$ 1.31−1.44 (m, 2H), 2.18−2.34 (m, 2H), 2.34 (s, 6H), 2.72 (t, $J$ = 7.6 2H), 5.12 (q, $J$ = 3.2, 2H), 5.59 (s, 2H), 7.14 (t, $J$ = 8.8, 21H), 7.26 (d, $J$ = 8.0, 4H), 7.56 (d, 2H), 7.71−7.81 (m, 4H); MS (APCI) $m/z$ 297 ($M^+ + 1$).

(6) Purity of **3** was estimated by HPLC analysis with Inertsil ODS 3V, 250 mm × 4.6 mm, 5 $\mu$; mobile phase A: mixture of buffer and acetonitrile in the ratio of 800:200; mobile phase B: mixture of acetonitrile and buffer in the ratio of 700:300; run time: 60 min, 240 nm. Buffer preparation: to 1000 mL of water was added 0.5 mL of phosphoric acid, and the pH was adjusted to 3.5 with triethylamine.

**Gradient profile**

| | time (min) | flow | A (%) | B (%) |
|---|---|---|---|---|
| 1 | 0.01 | 1.0 | 100 | 0.0 |
| 2 | 5.00 | 1.0 | 90 | 10.0 |
| 3 | 10.00 | 1.0 | 90 | 10.0 |
| 4 | 15.00 | 1.0 | 80 | 20.0 |
| 5 | 20.00 | 1.0 | 70 | 30.0 |
| 6 | 25.00 | 1.0 | 50 | 50.0 |
| 7 | 30.00 | 1.0 | 40 | 60.0 |
| 8 | 35.00 | 1.0 | 30 | 70.0 |
| 9 | 40.00 | 1.0 | 20 | 80.0 |
| 10 | 45.00 | 1.0 | 20 | 80.0 |
| 11 | 50.00 | 1.0 | 100 | 0.0 |
| 12 | 60.00 | 1.0 | 100 | 0.0 |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