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Response to the Comments by Elati et al. in Response to Our Article Examining One of Their Previous Articles

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Abstract:

This reply highlights and discusses what we observe as internal inconsistencies in the data and analysis presented by Elati and coauthors in conjunction with their resolution protocols, as well as inconsistencies between their original manuscript, the associated patent, and the response to our disputing manuscript. We address also their comments concerning their alkylation procedures.

Introduction

In our article "Attempted Resolution of Citalopram using (−)-*O*,*O*′-Di-*p*-toluoyl-(*R*,*R*)-Tartaric Acid, and Reflections on an Alkylation Reaction; Comment on an Article by Elati et al."[1] we drew attention to our inability to repeat the resolution of citalopram reported by Elati et al.[2] using (−)-*O*,*O*′-di-*p*-toluoyl-(*R*,*R*)-tartaric acid (DTT; Elati et al. use the abbreviation "DPTTA"). In addition, we expressed concern over their procedure to produce the most important intermediate in their article, didesmethylcitalopram. It should be noted here that there was no experimental detail given for this reaction in the article, but only a reference to a patent application[3] by essentially the same authors.

Elati et al. have been invited to comment on our article,[4] and we thank them for their clarifications and expansions. However, we would like to point out what we believe are a number of inconsistencies in their article, their patent application, and their reply letter, in addition to what we believe are some errors in matters of fact. Some are inconsistencies between documents, and some are internal inconsistencies. This discussion has been separated into two sections: (a) Resolutions (including the revised procedure for the resolution of citalopram by Elati et al. and also of their resolution of didesmethylcitalopram) and (b) Comments regarding their alkylation reactions and the stability of 3-chloropropyl amine (CPA).

Resolutions

Resolution of Citalopram Using DTT. First, we appreciate the clear comment by Elati et al. that "resolution of citalopram with (−)-DPTTA as the chiral resolving agent is not feasible in the manner cited in our article"[4] (Note: in the article it was clearly stated in a number of places that the (−)-isomer of DTT is used). However, they then describe a different resolution protocol, derived from (but not identical to) an example in their patent application. This procedure involves crystallisation of racemic citalopram with (+)-DTT, leading to mother liquors slightly enriched with the salt of (*S*)-citalopram. Elati et al. then reported that successive repetitive crystallisations with (+)-DTT, taking the mother liquors each time, led to essentially pure (*S*)-citalopram. Elati et al. then stated in their letter that it is this latter procedure ("back-to-front" resolution) that should have been in the article, and that a minor omission in the text led to this confusion. We will now address the matters raised here in the following order: (a) the level of changes to the original manuscript necessary in order to incorporate this new experiment, (b) a discussion of the procedure referred to in the patent application, (c) a discussion of the currently described procedure (letter), along with mention of some of its internal inconsistencies, and (d) our efforts to repeat this last procedure.

(a) Rewording. We revisit the wording of the original article by Elati et al.[2] in order to discuss the level of changes required to the original manuscript in order to accommodate their revised procedure. Although Elati et al. imply that only a few small changes in the wording of their original article are required to this end, our interpretation is that a much deeper and thorough rewriting of certain sections would be required. We begin with the first mention of the resolution of citalopram (we have placed their footnote in brackets for clarity): "Of the many resoluting agents screened, use of (−)-DPTTA, though found to be useful (Klaus, P.B. reported that the attempts to resolve citalopram by diasteromeric salt crystallization have not been successful [Klaus, P. B.; Jens P. U.S. Patent 4,943,590, 1990]), in our hands proved to be unsatisfactory for an industrial-scale application due to low yields and multiple crystallisations." In the Experimental Section a yield of 36% is reported (relative to theoretical maximum, i.e. 50% of starting material; in other words a yield of 18% relative to starting racemic citalopram). We believe that the text and experimental detail are in good agreement with each other, as they both describe processes which can be used to *obtain* a *useful* quantity of escitalopram (18% yield overall, 98.4% "chiral purity") but which are unsuited to production (by means of comparison, the patent example gives no yield for the final purified compound, and the current version of this procedure described in the letter of Elati et al. gives an overall yield of 5.5%, "chiral purity" 96.8%). Note also that both the

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(1) Dancer, R. J.; De Diego, H. L. *Org. Process Res. Dev.* **2009**, *13*, 23.

(2) 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.

(3) Sundaram, V.; Mathad, V. T.; Venkavala, P. J.; Elati, C. R.; Kolla, N.; Govindan, S.; Chalamala, S. R.; Gangula, S. (Dr. Reddy's Laboratories, Inc.). Preparation of Escitalopram. WO2005/047274 A1, 2005;CAN 2005:451372

(4) Elati, C. R.; Kolla, N.; H.; Mathad, V. T. *Org. Process Res. Dev.* **2009**, *13*, 34.

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text and the footnote specify crystallisations, with no mention of the use of mother liquors.

To quote from the Experimental Section: "...the resulting solid was filtered. The recrystallisation with acetonitrile/methanol was repeated for two more times, and the resulting solid was filtered. The filter cake was washed with acetonitrile (20 mL) and dried... to afford 9.8 g of **1**·(−)-DPTTA."[2] All of the manipulations here refer clearly to the solids isolated by filtration, and not the mother liquors, and the yields and purities quoted differ significantly from those in the example provided in their letter. On the basis of this information, it is our belief that in order to accommodate the changes proposed in the letter of Elati et al., no simple incorporation of additional text to the existing article would be sufficient. Certain sections would need to be more deeply rewritten, and the experimental for this procedure would need to be completely replaced. It is also worthy to note that the authors published a correction to *precisely the same Experimental Section* approximately 6 months after publication of the original article.[5] Precisely the same wording of the Experimental Section (as quoted above) was also used in the correction.

(b) Patent Application Example. The "back-to-front" resolution procedure given in the patent example is identical to that described in the letter by Elati et al. (i.e., the same quantities of materials, the same ratio between citalopram and DTT, and the same ratios between citalopram, acetonitrile, and methanol (10 volumes acetonitrile and 0.8 volumes methanol)). However, the results reported differ. The patent example reports that *two* crystallisations were required in order to reach a "chiral purity" of 98.89%, whereas the letter example reports that *three* crystallisations were required to obtain a "chiral purity" of 96.8% (using the same ratios between reactants, reagents, and solvents for each individual crystallisation. In addition, whilst the patent example reports a yield of 12.0 g (free base) for the first step, the letter example reports a yield of 15.0 g (free base) from the first step. Unfortunately, other comparisons are not possible, as the patent example only reports a yield for the first step (no purity), and only purity for the second step (no yield).

We would like to point out a curiosity in the workup of the patent example. The mother liquor after filtration contains citalopram isomers and DTT (a diacid) in a 1:1 ratio. After the first crystallisation, 12 g (37 mmol) citalopram is isolated after freeing the base with sodium hydroxide (1.6 g in 100 mL; 40 mmol). This means that 1.08 equiv of sodium hydroxide was used for the neutralisation of a monoamine salt of a *diacid*. It would be expected that over 2 equiv would be required for such a neutralisation, and indeed in our hands it was found that, after the addition of the specified amount of sodium hydroxide, essentially no citalopram was extracted into the toluene phase. In our hands, a small excess over 2 equiv was required (typically, 2.2−2.5 equiv).

Finally, it may be of interest to observe that in the first priority application for this patent application, only the "normal" resolution of citalopram was claimed (using a variety of different chiral acids). It therefore follows that the chronology of resolution procedures for citalopram claimed or otherwise reported by Elati et al. runs as follows: "normal" (priority application, Nov 2003), "back-to-front" (final patent application, Nov 2004),[3] "normal" (article, Jan 2007),[2] "normal" (correction, Jun 2007),[5] "back-to-front" (letter, Sep 2008).[4]

(c) Letter Example. As previously stated, this procedure is essentially the same as that used in the patent application, but the results were not (patent required 2 crystallisations to exceed *S*:*R* 96:4; letter required 3; after 2 crystallisations the ratio *S*:*R* was 83.33:16.67, despite the fact that the procedures described are identical). Therefore, although the letter procedure can be derived from the patent procedure, it is not in agreement with the patent procedure, contrary to the statement of Elati et al.[4] As also mentioned previously, a comparison of yields for pure escitalopram between the letter and the patent application is not possible, since there are no yields for the purified escitalopram in the patent application.

However, we would like to focus on a portion of a mass balance analysis of the reported products of the letter procedure. For each cycle of the crystallisation process, the starting mass and the *S*:*R* ratio of the free base is reported, along with the *S*:*R* ratios of the filtered solids and the residues after evaporation. From those values it was possible to back-calculate some of the reported values in order to perform a cross-check. We present here two inconsistencies found in this manner. The first was found at the end of the First Isolation. It was stated that the mass of the DTT salt isolated from the mother liquor was 23 g (32 mmol). However, after the salt was neutralised, they obtained a yield of 15 g (46 mmol) of the free base. In other words, from *32 mmol salt*, they obtained *46 mmol free base*. Another more serious inconsistency can be found in the crucial Third Isolation. The starting material is quoted as having a mass (free base) of 5 g, and an *S*:*R* ratio of 83.33:16.67, giving masses of *S*-citalopram and *R*-citalopram (as the free base) of 4.17 and 0.83 g respectively. In a similar manner, it can be calculated from the quoted mass of salt isolated from the mother liquor (6 g, equivalent to 2.74 g free base) with an *S*:*R* ratio of 96.38:3.62, that the masses of *S*-citalopram and *R*-citalopram (as the free base) in the final product were 2.64 and 0.099 g, respectively. Therefore, it follows that the masses of *S*-citalopram and *R*-citalopram (as the free base) in the *precipitated solid* were 1.53 and 0.73 g, respectively. This gives an *S*:*R* ratio of 67.7:32.3, which is significantly different from the reported ratio 57.56:42.44.

(d) Our Results. We repeated the resolution procedure described in the letter of Elati et al. using the same quantities of starting materials, the same solvent mixtures, and the same ratios between citalopram mixtures and DTT, acetonitrile, and methanol. Our yields from the mother liquors were somewhat lower (10.9 g vs 15.0, and 3.9 g vs 5 g) and purities somewhat higher (*S*%: 64.4 vs 59.3, and 88.3 vs 83.3) than those reported by Elati et al. for the first and second isolations. However, when we attempted to repeat the third isolation, we obtained *no* precipitate whatsoever (in contrast to Elati et al., who obtained 6 g of a DDT salt from the mother liquor, and therefore must have obtained approximately 5 g precipitated salt). One possible explanation for this discrepancy could be that, whilst Elati et al. began with a sample with an *S*:*R* ratio of 83.3:16.7, our sample had an *S*:*R* ratio of 88.3:11.7, and subsequent differences

(5) 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*, 780.

in solubilities could have led to the observed differences in results. We therefore prepared a 5 g sample containing citalopram isomers in the ratio *S*:*R* 83.9:16.1, and then used precisely the same procedure as reported by Elati et al. under "Third Isolation". After the prescribed 2 h at 25−30 °C, virtually no precipitate was observed (only cloudiness). The mixture was then seeded with a citalopram·DTT salt from a previous step (*S*:*R* of seed material 45:55), and allowed to stir for a further 1 h. The mixture was filtered, and the mother liquor was evaporated to give the final salt (10.13 g, *S*:*R* 87.6:12.4; cf. Elati et al. 6.0 g, *S*:*R* 96.4:3.6).

We consider it interesting and instructive that the greatest deviation in our results from those of Elati et al., are for the critical final crystallisation, where the data of Elati et al. are internally inconsistent.

Resolutions of Didesmethylcitalopram using DTT. In their reply letter,[4] Elati et al. state that their intention was to focus on the resolution of didesmethylcitalopram. Since the submission of our article, we have also begun examine this resolution. In the article by Elati et al.[2] a "chiral purity" after a single crystallisation of 99.0% is claimed. In our hands, such a high purity has never been obtainable. We have found that typical *S*:*R* ratios obtained are around 84:16 (equivalent to ee 68%). On closer inspection of the article by Elati et al. we observed an oddity in their Figure 3.[2] This figure is a graph of "Chiral purity (%)" vs quantity of water in the acetonitrile used for the crystallisation. It shows that the starting purity (no water) of 85% rises to approximately 100% when water is approximately 2, thereafter steadily declining. We believe that the casual reader would assume that these experiments were performed on racemic material. However, this is not the case. There is a note in the article to say that the material used for this set of experiments was didesmethylcitalopram with "85% chiral purity". This note is not in Figure 3, and nor in the body of the text describing the figure. Instead, this information is only found in a footnote to the body of the text.

We found the use of such enantiomerically enriched material for a screening experiment for the resolution of a *racemic* mixture to be unusual and worrying. The thermodynamic properties (solubilities, *S*/*R* compositions of precipitates) of such an enantiomerically enriched material will necessarily be different to that of the racemate, and therefore results (such as purity or yield) from such a screen will be meaningless when applied to the racemate. Our physicochemical characterisation of this system is not yet complete, but it is already clear from our existing results that this is a case of a *partial solid solution*. For a detailed description of what this entails we recommend to the reader an excellent article by Coquerel's group (in particular his discussion of Figure 4).[6] However, in summary, it means that despite a reasonable difference in solubilities of the diasteromeric salts, it is nonetheless impossible to obtain pure material from the first crystallisation. Multiple crystallisations are necessary, and to quote from Coquerel's group, "Unfortunately, in this case, as the excess in salt A tends to 100%, the yield tends to 0%."

(6) Marchand, P.; Lefèbvre, L.; Querniard, F.; Cardinaël, P.; Perez, G.; Counioux, J.-J.; Coquerel, G. *Tetrahedron Asymmetry* **2004**, *15*, 2455–2465.

Alkylations. Alkylation reactions on heteroatoms where CPA is added as the HCl salt, with *in situ* neutralisation have been widely reported in the literature,[7] although reported C-alkylation is somewhat rarer.[8] Furthermore, it is conceivable that with an appropriate procedure for the neutralisation/isolation and use of the free base, alkylation with the free base could be effective. However, our concerns in our original article[1] were in part based upon the fact that Elati et al. in their article[2] did not give any experimental details for this reaction, but instead refer to their patent application. Furthermore, in this patent application, two of the examples require the isolation of the free base with no discussion of how the base is to be isolated (and in addition, one of these two examples is unworkable). Finally, the third example reported neither yield nor purity.

In this context, we respond to the claim in the letter[4] of Elati et al. that (use of italics is ours) "the findings of Dancer and Lopez De Diego 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[9] that the 'separation of 3-chloropropylamine and 2-chloropropylamine by distillation appeared hopeless, because of the instability of the chloropropylamines.' " We believe that this assertion is simply incorrect. Our concerns are based upon the following considerations:

1. Despite the fact that this alkylation reaction was a critical step in their synthesis, an Experimental Section for this procedure has never before been described in the nonpatent chemical literature.
2. We were surprised that the authors did not decide to publish this information in *Org. Process Res. Dev.* (OPRD), given OPRD's emphasis on solid, robust chemistry.
3. The authors referred instead to a patent application written by essentially the same authors. In the patent application there are three examples of this alkylation. Two of the procedures employed solutions of CPA derived from neat CPA, and the third employed a solution of CPA in toluene.
4. CPA as the free base is unstable. This is strongly implied by the fact that a Scifinder search failed to find a preparation of the free base, nor any physical properties of the free base. Furthermore, the reference we cited[9] gives evidence that CPA is much less stable than *N*,*N*-dialkylated derivatives.
5. Despite the fact that Elati et al.[2] employed solutions derived from CPA free base, we were surprised that they had not included details of this important isolation.
6. The second example of the alkylation in the patent application employed acetone as solvent, and a yield of 64% was claimed. *Bretherick's Handbook of Reactive Chemicals*, 6th ed.[10] cites the reaction of potassium *tert*-butoxide with acetone as hazardous, and in our

(7) For an early example, see: Turk, S. D.; Louthan, R. P.; Cobb, R. L.; Bresson, C. R. *J. Org. Chem.* **1962**, 2846–2853.

(8) See, for example: (a) Adger, B. M.; Mastrocola, A. R. (Smith Kline & French Laboratories Limited). Synthesis of 2-Pyridylalkylamines. U.S. 4,526,974, 1985,CAN 100:68182. (b) Cooper, D. G.; Durant, G. J.; Ganellin, C. R.; Ife, R. J.; Meeson, M. L.; Sach, G. S. *Farmaco* **1991**, *46*, 3–19.

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

(10) Urben, P. G., Ed.; Pitt, M. J., Compiler; *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Butterworth-Heinemann (Reed Elsevier plc group): Oxford, 1999; Vol. 1, pp 430, 551.

hands the procedure gave no yield of the required compound, nor the characteristic deep red colour of the phthalane anion. Instead, a quantity of white solid (a mixture of aldol products) was observed after a vigorous/violent reaction.

7. The final example of the alkylation in the patent application gave no yields or purities and so was therefore of very little use.

We will now examine how these points were affected by the reply of Elati et al.[4]

1. No change.
2. Elati et al.[4] stated that their intention was to focus on the resolution step. Nonetheless, we find it surprising that Elati et al.[2,4] chose not to publish their optimum procedure in OPRD, especially since (a) no useful procedure had been published by them elsewhere, (b) the following dimethylation step *was* included in the article, and (c) they chose to publish their procedure for the resolution of citalopram (which they have now in essence withdrawn).
3. No change.
4. (a) Elati et al. confirmed that CPA is unstable as the free base[4] and did not give any physical properties for the free base (apart from some quoted stabilities; we refer again to these figures below). (b) They claimed in their reply letter that the article we quoted suggested simply that distillation of CPA is difficult, not the isolation or handling. They then later state that, in their hands, "handling and storing 3-CPA free base was a major challenge as it is unstable". The article we quoted is a clear *comparison* of the stabilities of CPA and the *N*,*N*-diethyl derivatives (the latter has a quoted boiling point and published preparations, the former does not). (c) Elati et al. state that (our use of italics) "While 3-CPA freebase polymerized at 25−45 °C in the absence of solvent, 3-CPA extracted into DCM, MTBE, or toluene were *relatively stable*." However, in their table of stability of CPA free base under different conditions, the relative stabilities of different solutions (10% w/v) at 25−30 °C are given in the following order (numbers in brackets denote time required for decomposition): toluene (72 h), DMSO (12 h), DCM (12 h), neat (8 h), MTBE (2 h), 1,4-dioxane (2 h). In other words, the text states that an MTBE solution is more stable than the isolated free base, yet the reported data show the opposite.
5. Elati et al. in their letter state[4] that neat CPA was obtained by the complete distillation of DCM from a DCM solution. However, they have still not provided a procedure for this distillation.
6. We were somewhat suprised that Elati et al.[4] continue to claim that the alkylation reaction in acetone using potassium *tert*-butoxide can be performed successfully, and in their quoted yield of 64%. In their letter they state that (our comments in square brackets; the reference numbers refer to their references, not ours) "In example 2[2] the alkylation was performed in acetone. It is known that carbonyl compounds under basic conditions often undergo condensation reaction. In comparison to example 1 [performed in DMSO, quoted yield 80 %], this transformation was not as smooth and did result in a low yield [yield of 64 % is quoted].[2] Much discussion was not devoted to this particular example as our aim was to isolate the desired product instead of the aldol product." (a) As noted previously, the mixture of potassium *tert*-butoxide and acetone is known to be hazardous. (b) We have performed two alkylation reactions using methyl iodide as the alkylating agent instead of CPA, one using DMSO as solvent, and the other using acetone as solvent, both on the same scales as reported by Sundaram et al. in their patent application.[3] The only difference in the procedure was that the methyl iodide was added neat instead of a very concentrated solution. Where DMSO was used as solvent, addition of methyl iodide to the reaction mixture at 25 °C gave an immediate transformation of the deep red/purple anion colour to a transparent yellow colour, with an immediate rise in temperature to around 65 °C. The reaction was finished almost instantaneously, and workup gave an almost quantitative yield of the methylated phthalane. Where acetone was used as solvent, there was none of the characteristic anion colour present. On addition of methyl iodide, there was essentially no temperature increase, and even after 24 h there was no sign of methylation products by HPLC (principally starting phthalane, plus a number of small impurities). This indicates that alkylation is impossible in this system, regardless of the alkylating agent used.
7. In their letter of reply, Elati et al.[4] gave yields and purities for their third alkylation procedure. However, they also make the statement "hence we can completely rule out Dancer's perception that we utilized the hydrochloride salt of 3-chloropropyl amine, as under these conditions the hydrochloride salt would be highly insoluble in toluene." The first step of their alkylation procedure as stated in their patent application is the neutralisation of CPA·HCl using a mixture of toluene and sodium hydroxide solution. However, in the patent application it is clearly stated that the *free base* of CPA is treated with toluene and sodium hydroxide, not the salt. In our article we noted that this was likely to be an error in the patent application, and indeed Elati et al. have incorporated our suggested correction into the Experimental Section in their letter of reply. So in that context it is therefore surprising that they "completely rule out" an alteration that they have themselves made later on in their own letter.

Summary

We summarise our comments in point form, divided up into (a) crystallisation issues and (b) alkylation issues:

(a) Crystallisation Issues.

In the letter by Elati et al.[4] they state that all mention of a "normal" resolution in their article was a mistake; a simple error arising from the fact that they had "not incorporated a few words in the text" of their original article and that a different, "back-to-front" resolution from their patent application should have been published instead. We find it difficult to see how a simple addition of words to the text could support such a change.

Although Elati et al.[4] claim that the procedures for the "back-to-front" resolutions in their letter and patent

application are in agreement, they differ significantly in terms of purity after the second crystallisation. Furthermore, the data that Elati et al.[4] report in their letter for the final recrystallisation are internally inconsistent in a mass-balance analysis.

We have been unable to repeat the "back-to-front" resolution procedure described by Elati et al. in their letter.[4] Furthermore, we consider it noteworthy that the point where our results most strongly disagreed with those of Elati et al. was at the final critical crystallisation, where the data of Elati et al. were internally inconsistent.

Preliminary data from our physicochemical characterisation of the resolution of didesmethylcitalopram are in clear disagreement with the results reported by Elati et al.[2] This doubt is reinforced by an oddity in the manner they have reported the results of some of their optimisation reactions in their original article.

(b) Alkylation Issues.

Despite the data on the stability of CPA in their letter,[4] Elati et al. have still not produced details as to how to isolate CPA.

The article quoted in our article compares the *relative* stability of CPA and a tertiary CPA analogue. It is therefore of relevance when discussing the isolability of CPA. Again, Scifinder™ reports no preparation of CPA as the free base, but reports numerous preparations of *N*,*N*-diethyl-CPA. Elati et al.[4] agree that CPA is unstable as the free base, but quote data supporting the stability of certain solutions of CPA. However, their statements and data contain a number of internal inconsistencies and contradictions.

Despite the continuing claims of Elati et al.[2,4] to the contrary, Example 2 from their patent application[3] (alkylation in acetone) is completely unworkable.

Experimental Section

General Methods. Acetonitrile (HPLC grade) and methanol (Anhydroscan) were purchased from LAB-Scan and were used without purification. DTT (both monohydrate and anhydrous) were purchased and were used without further purification. Chiral HPLC analyses were performed using a Chiralcel OD column (4.6 mm i.d., 250 mm) using a mixture of heptane/ethanol/diethylamine (98.4:1.5:0.1) as eluent. A flow rate of 1 mL/min was used at 30 °C with UV detection at 240 nm. Nonchiral HPLC analyses of reaction mixtures were performed using a Lichrosphere 100 RP-8e (5 μm) column (4 mm i.d., 250 mm) using a 50:50 (v/v) mixture of acetonitrile/water buffered to pH 3 with a triethylammonium phosphate buffer as mobile phase. A flow rate of 1 mL/min was used, with UV detection at 220 nm. NMR spectra were acquired on a Bruker Avance AV-500 spectrometer operating at 500.13 MHz for ^{1}H spectra and 125.77 MHz for ^{13}C spectra. Selected NMR spectra are available in Supporting Information.

Attempted Resolution of Citalopram Using (+)-DTT after Elati et al.[4] To a solution/suspension of citalopram (50.0 g, 154 mmol) in acetonitrile (250 mL) at 27 °C was added a solution of (+)-DTT·H_2O (62.8 g, 155 mmol) in acetonitrile (250 mL) and the mixture was stirred at 27 °C for 60 min.The resultant slurry was heated to 75 °C and methanol (40 mL) was added to give a clear solution. The solution was cooled to 27 °C over 1 h and kept at this temperature for 1.75 h. The resulting precipitate was filtered under vacuum and dried overnight at 60 °C under vacuum to give a yield of 84.60 g (119.0 mmol; *S*:*R* 45.0:55.0). The mother liquor was evaporated to dryness (26.0 g, 36.6 mmol). This residue was basified with NaOH (10% w/v 260 mL) at 27 °C for 10 min and extracted with toluene (2 × 260 mL). The combined organic phases were dried over anhydrous sodium sulfate (11 g) and evaporated to dryness under vacuum to give an oil (10.92 g, 33.7 mmol; *S*:*R* 64.4:35.6).

This procedure was repeated using this oil (10.92 g, 33.7 mmol; *S*:*R* 64.4:35.6) in acetonitrile (55 mL) and (+)-DTT·H_2O (13.6 g, 33.6 mmol) in acetonitrile (55 mL). This gave a precipitate (14.00 g, 19.7 mmol; *S*:*R* 52.4:47.6) and a residue from the mother liquors (9.82 g, 13.8 mmol) This residue was basified to give the free base (3.92 g, 12.1 mmol; *S*:*R* 88.3:11.7).

This procedure was repeated using this oil (3.92 g, 12.1 mmol; *S*:*R* 88.3:11.7) in acetonitrile (20 mL) and (+)-DTT·H_2O (4.9 g, 12.1 mmol) in acetonitrile (20 mL). However, on this occasion no precipitate was observed.

A solution was prepared containing citalopram enanantiomers (5.0 g, 15.4 mmol; *S*:*R* 83.9:16.1) in acetonitrile (25 mL), and the above procedure was repeated using (+)-DTT·$1H_2O$ (6.06 g, 15.4 mmol) in acetonitrile (25 mL). After the usual cooling/stirring was completed, only cloudiness was observed without any significant precipitation. The solution was then seeded with some of the precipitate from the first part of this experimental (approximately 30 mg; *S*:*R* 45.0:55.0). After stirring for a further 1 h a precipitate had formed. The precipitate was removed by filtration and dried under vacuum to give a solid (1.0 g, 1.41 mmol; *S*:*R* 56.3:43.7), and evaporation of the mother liquors gave a residue as a salt (10.13 g, 14.25 mmol; *S*:*R* 87.6:12.4).

Resolution of Didesmethylcitalopram Using (−)-DTT after Elati et al.[2] A mixture of (−)-DTT (6.5 g, 17.0 mmol) and acetonitrile (25 mL) was stirred for 5 min. To this mixture was added a solution of didesmethylcitalopram (5.0 g, 17.0 mmol) in acetonitrile (25 mL) over 15 min at 27 °C. The slurry was warmed to 55−60 °C and water (15 mL) was added dropwise. After a further 50 min the solution was cooled to 0 °C for 1 h, followed by stirring at 27 °C for a further 45 min. This warming/cooling cycle was repeated two more times, and the resulting solid was filtered at 0−5 °C, washed with cold acetonitrile (10 mL), and dried under vacuum (60 °C) to give didesmethylcitalopram.(−)-DTT as a solid (4.15 g, 5.85 mmol; *S*:*R* 84:16)

Alkylation of Cyanophthalane with Methyl Iodide in DMSO Using the Method of Sundaram et al.[3] A solution of potassium *tert*-butoxide (7.5 g, 67 mmol) and DMSO (40 mL) was warmed to 60−65 °C for 10 min. The solution was allowed to cool to 25−30 °C, and a solution of cyanophthalane (10.0 g, 41.8 mmol) in DMSO (35 mL) was added dropwise over 10 min, and the resulting intense deep red/purple solution was

stirred for a further 20 min at that temperature. A water bath was then added for cooling (25 °C), neat methyl iodide (17.8 g, 125 mmol) was added in one portion, and the temperature rose rapidly to approximately 65 °C; the solution almost immediately lost the previous deep colour and instead gained an orange colour. After 10 min, cold water (200 mL) and toluene (100 mL) were added. The organic phase was separated, and the aqueous phase was washed further with toluene (2 × 200 mL). The combined toluene phases were evaporated to give the methylated phthalane as an oil (10.9 g, purity (HPLC) 94.3%).

Alkylation of Cyanophthalane with Methyl Iodide in Acetone Using the Method of Sundaram et al.[3] To acetone (40 mL) at reflux (56 °C) was added potassium *tert*-butoxide (7.5 g, 67 mmol). A vigorous/violent reaction ensued, and the temperature rose to approximately 63 °C, with concomitant formation of a large amount of white solids. The solution/slurry was allowed to cool to 25−30 °C, and a solution of cyanophthalane (10.0 g, 41.8 mmol) in acetone (35 mL) was added dropwise over 10 min, and the resulting solution was stirred for a further 20 min at that temperature. Apart from a large amount of a white precipitate, no colour was observed in the solution/slurry. A water bath was then added for cooling (25 °C), neat methyl iodide (17.8 g, 125 mmol) was added in one portion, and the temperature rose slowly to approximately 30 °C. After 10 min, analysis by HPLC indicated that the mixture contained mostly starting cyanophthalane, plus a number of small impurities. The mixture was stirred overnight at 25 °C, and thereafter at 40−45 °C for 1 h. HPLC indicated that the composition of the reaction mixture was essentially unchanged. The reaction mixture was then discarded.

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Supporting Information Available

^{1}H NMR spectrum of the crude product from the alkylation of cyanophthalide with methyl iodide in DMSO; HPLC chromatograms comparing reaction mixtures in the alkylation reaction using DMSO or acetone as solvent. This material is available free of charge via the Internet at http://pubs.acs.org.

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