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Communication

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Process Development of Citalopram/Escitalopram Oxalate: Isolation and Synthesis of Novel Impurities

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Supporting Information

ABSTRACT: During process optimization of Escitalopram oxalate novel impurities, **6** and **7** were observed, which were isolated and characterized, and the proposed structure was confirmed by chemical synthesis. Investigation of the cause of impurities formation improved the yield and purity of the drug product during the bulk API synthesis.

INTRODUCTION

Citalopram (**1**; see Figure 1) belongs to the class of SSRIs (selective serotonin reuptake inhibitors or serotonin-specific

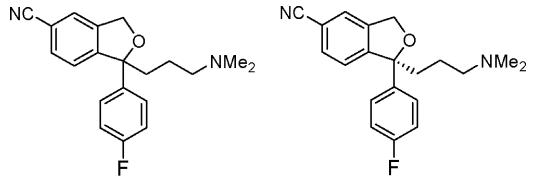

Figure 1.

reuptake inhibitors) and is a well-known antidepressant drug. It is primarily used for the treatment of major depressive and general anxiety disorders in adults; it has the highest rate of efficacy and acceptability among adults for the acute phase treatment of major depression.[1] Citalopram (**1**) is sold as the racemate; however, the (*S*)-(+) enantiomer, known as Escitalopram (**2**), inhibits serotonin uptake 2 orders of magnitude better than the other enantiomer. Since its (**1**) development in 1989, it has been used in more than 65 countries, with a total estimated worldwide exposure of 8 million persons. Its use is extensive, and safety is well established.[1−5]

Several processes were reported for the preparation of Citalopram (**1**)[6a−g] and Escitalopram (**2**)[7a,b] but the most preferable and convenient route for synthesis of Escitalopram is preparation of the cyano-diol intermediate (**3**) starting from 5-cyanophthalide by double Grignard addition followed by cyclization via labile esters such as mesylate or tosylate resulting in the final product (Scheme 1).

During the process development of Citalopram/Escitalopram Oxalate (using either racemic cyano-diol or chiral cyano-diol resolved with *p*-DTTA) while performing the final cyclization reaction using $MsCl/Et_3N$, a new impurity other than the impurities listed in the US Pharmacopeia was observed in the range of 0.1−0.5% in routine HPLC analysis of the crude free base. LCMS data indicated the M^+ to be 307. To improve the process and quality of the product, identification and characterization of the impurities in the drug product[8] is very important and is a regulatory requirement. This report describes the isolation, identification, detailed mechanistic study, and synthesis of this novel process Impurity-**6** as well as a recent USP listed Impurity-**7** of Citalopram/Escitalopram oxalate.[9]

RESULT AND DISCUSSION

Even though it was difficult, we could isolate a small sample of Impurity-**6** by prep HPLC from the combined and enriched mother liquors from a few batches after oxalate salt formation. This was just enough to characterize and confirm the assigned structure by ^1H NMR, ^{13}C NMR, and mass spectral analysis. After deep and careful analysis, we suggested/predicted an unusual 8-membered cyclic compound (**6**) having a quaternary nitrogen atom as part of the ring (Figure 2).

As per our prediction, we envisaged the formation of a mixture of the two olefinic intermediates (**4** and **5**), namely the *E* and *Z* isomers, via dehydration of the tertiary -OH (in the form of -OMs elimination). Because of the geometry of the *Z*-olefin (**5**), the $-NMe_2$ group will come within attacking distance of the primary -OMs, which would result in an intramolecular cyclization and would provide the new cyclic structure (**6**). However, the *E* isomer will be in a disfavored position for a similar internal attack to replace the primary -OMs group and, hence, would not give compound **6**. Instead, the $-NMe_2$ group of another molecule of Citalopram/Escitalopram would possibly attack and replace the -OMs group, resulting in a dimeric structure (**7**, Figure 2). With these thoughts, we tried to observe the formation of Impurity-**7** in the crude Citalopram free base as well as in the mother liquors, and fortunately, we could track Impurity-**7** in the other side of the HPLC diagram (Citalopram at the nonpolar side; Impurity-**7** at the polar side) in a very low percentage, as confirmed by LCMS (M^+: 631). Despite our efforts, we were unable to isolate a sufficient quantity of Impurity-**7** for complete characterization and analytical need. It is worth mentioning that, during the course

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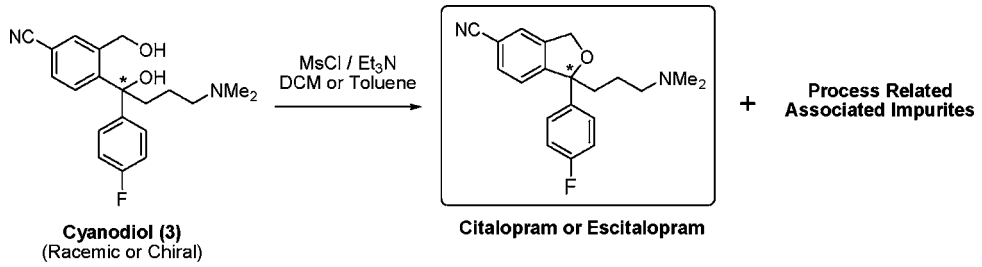
Scheme 1



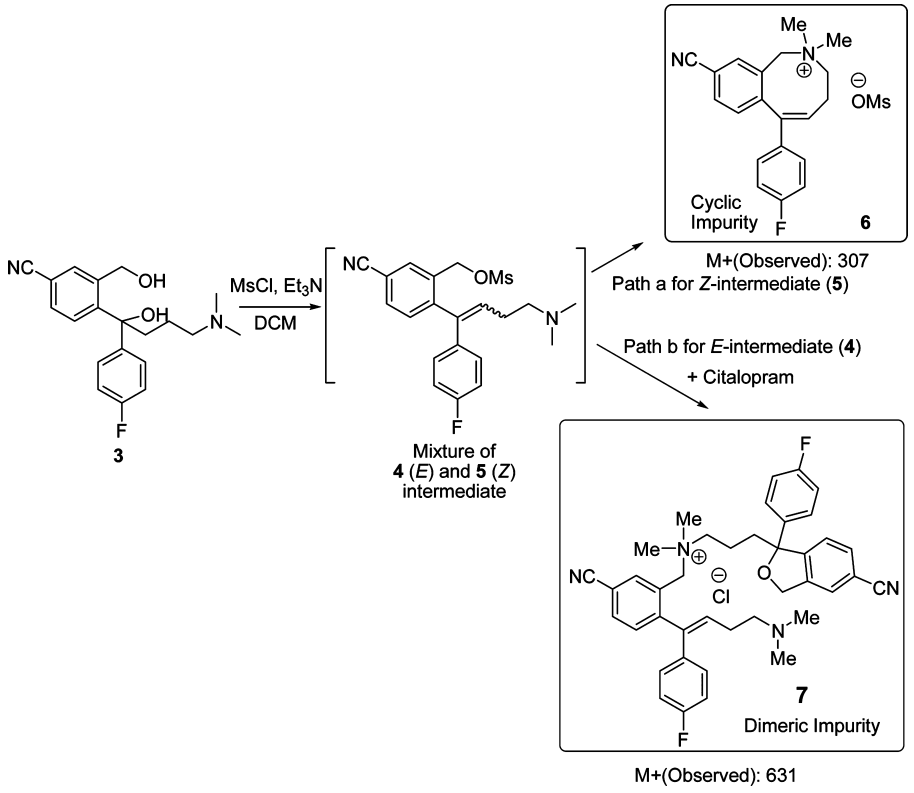
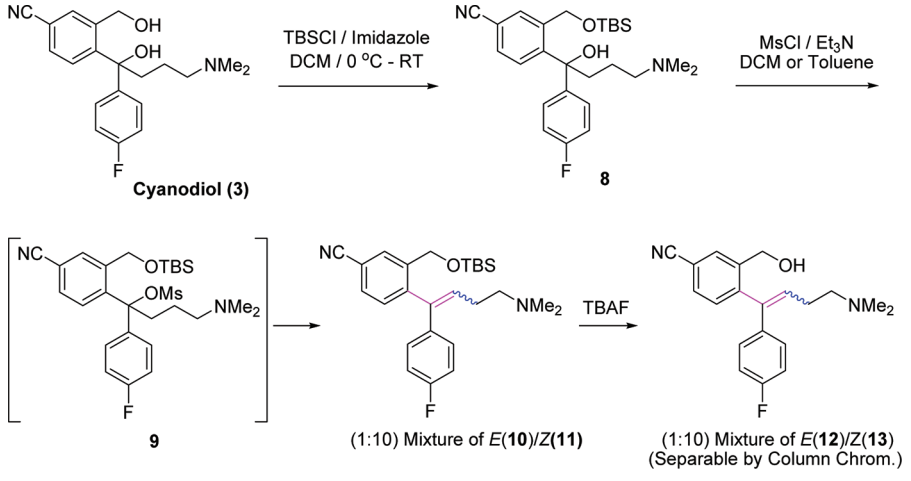


Figure 2.

Scheme 2



of this work, the US Pharmacopeia[9] added this new dimeric Impurity-**7** to their existing list of impurities but surprisingly did not mention the cyclic Impurity-**6** which seems to be forming in comparably higher percent during the manufacturing process. Also, no details on any of these impurities are available/reported in the literature. Hence, we intended to

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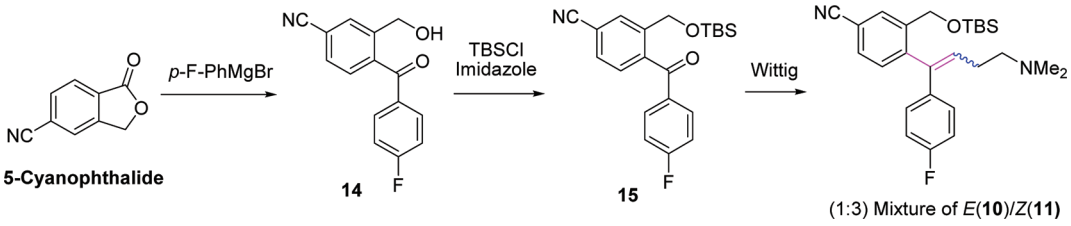
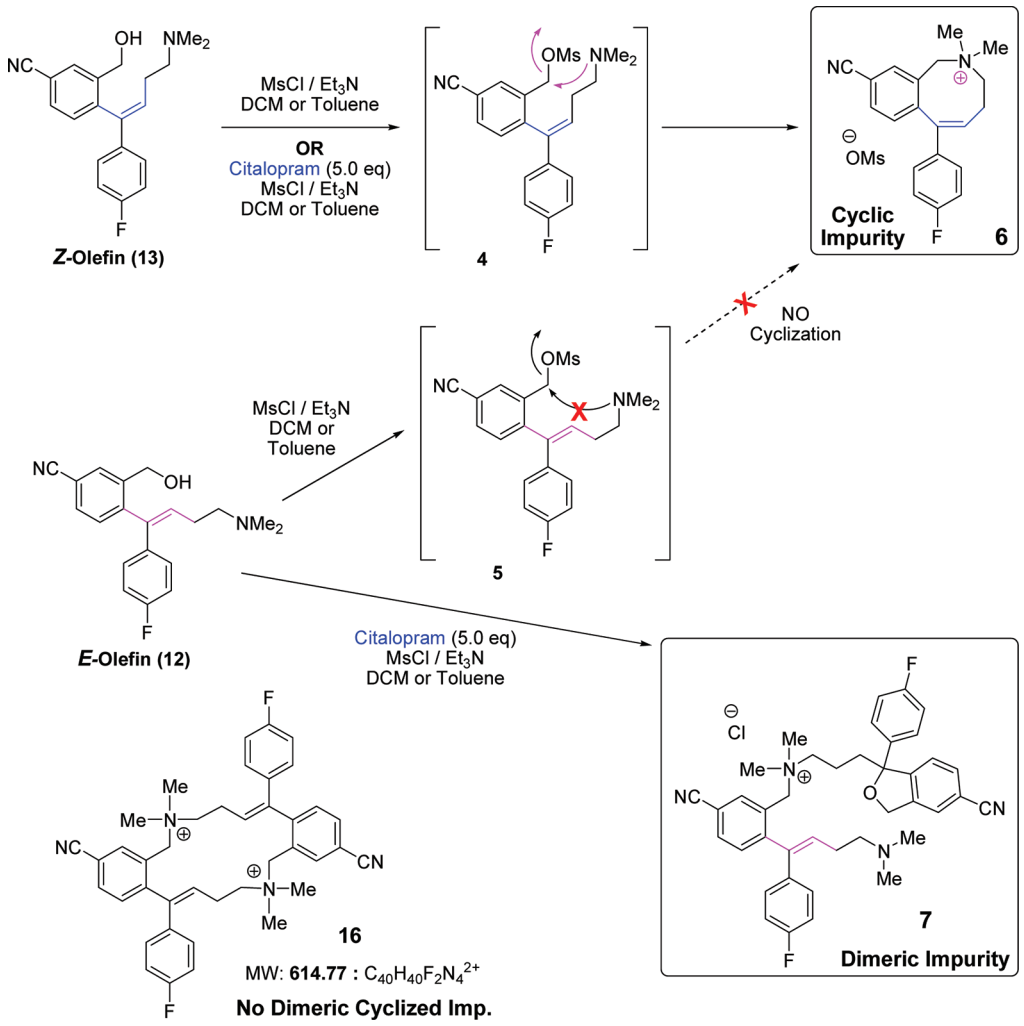
Scheme 3



Scheme 4



formally synthesize both these impurities, which not only will undoubtedly confirm the structures of the impurity but also will provide sufficient quantities to satisfy the analytical need under regulatory requirements. Moreover, this will also help in the mechanistic aspect of the formation of these two impurities. Accordingly, we planned our synthetic approach to arrive at olefinic intermediates (**12** and **13**). The easiest thing for us to do was to eliminate the tertiary -OH of Cyanodiol (**3**) and examine the outcome with respect to *E* and *Z* double bond formation. The primary -OH of diol-**3** was protected as its TBS ether using reported conditions (protection of primary -OH was needed before dehydration using MsCl/Et_3N; otherwise, Citalopram will be the major product). Subsequent dehydration of the tertiary -OH of **8** using MsCl/Et_3N was effected under ambient temperature to afford a mixture of *E* and *Z* isomers (**10** and **11** with a 1:10 ratio) which when further treated with TBAF for -OTBS deprotection yielded a mixture of **12** and **13** (Scheme 2).

As an alternative to obtain a sufficient quantity of *E* isomer, we also explored the Wittig route to give the desired olefinic intermediates as depicted in Scheme 3. Accordingly, *p*-fluorophenyl Grignard addition to 5-cyanophthalide afforded ketone **14** after workup. The primary hydroxyl group of **14** was protected as its TBS ether, and the resulting intermediate was subjected to Wittig reaction using [3-(dimethylamino)propyl]-phosphonium bromide hydrobromide and NaH as base, which afforded an inseparable mixture of *E* and *Z* (**10** and **11**) in a 1:3 ratio in favor of the *Z* isomer. The TBS group of **10** and **11** (as a mixture) was removed under mild conditions using TBAF to furnish the desired free alcohol. Fortunately, after the TBS

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deprotection, the olefinic intermediates **12** and **13** were marginally separable on TLC, and by careful column chromatography we could isolate a reasonable quantity of both the isomers (*E* and *Z*), which allowed us to move forward and complete our synthetic targets.

Finally, both these intermediates were separately treated with MsCl/Et_3N in DCM or toluene, upon which the *Z* isomer cyclized at 0 °C to provide the target compound (**6**) in very good yield within 30 min, whereas the *E* isomer, despite complete conversion to the mesylate, did not give any cyclized product at 0 °C or after prolonged stirring at room temperature. The starting alcohol was recovered after basic aqueous workup. Raising the temperature also proved to be futile to effect the cyclization (Scheme 4).

In another set of experiments, both these intermediates (**12** and **13**) along with excess Citalopram were treated with MsCl/Et_3N at 0 °C separately. Here, in the case of the *E* isomer, we could observe slow formation of Impurity-7, which was easily isolated by column chromatography. In the case of the *Z* isomer, within 30 min, exclusive formation of the cyclized impurity was observed (Scheme 4) with no dimeric Impurity-7, suggesting that, if positioned well, the attack by the internal -NMe_2 group is much more favored than that of the -NMe_2 group of another molecule (intermolecular attack is less favored). No dimeric cyclized impurity such as (**16**) was observed in any of the experiments.

We felt, owing to the very small size of the sulfonating reagent (MsCl), the tertiary -OH group is undergoing sulfonation, albeit in low yield. If a larger size (hindered) sulfonating reagent such as (TsCl) is used instead of MsCl, these impurity formations can be completely avoided. Indeed, when we tried the cyclization of diol (**3**) with TsCl/Et_3N in DCM or toluene, the formation of these impurities was not at all observed. Currently, this process is under evaluation for commercial manufacturing of Citalopram/Escitalopram (using the chiral cyanodiol resolved with *p*-DTTA) in our organization.

CONCLUSION

In conclusion, during the systematic study of the manufacturing process of Citalopram/Escitalopram, two process related impurities were isolated and characterized, and their structures were confirmed by chemical synthesis. Detailed investigation revealed the course of their formation; this helped to improve the yield and purity of the drug molecule during the bulk synthesis. We believe this will be immensely useful for process chemists working in this direction.

EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufacturers. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian 400 MR spectrometer in $CDCl_3$ and DMSO-d_6, and mass spectra were determined on an API-2000LCMS mass spectrometer from Applied Biosystems. Elemental Analysis was done with a VarioEL III instrument.

Preparation of 4-(4-Fluorobenzoyl)-3-(hydroxymethyl)benzonitrile (14). To a suspension of magnesium turnings (2.25 g, 92.0 mmol) in dry THF (10 mL) was added a solution of 1-bromo-4-fluorobenzene (13.2 g, 75.0 mmol) in dry THF (35 mL) at reflux temperature slowly under nitrogen atmosphere. The reaction mixture was allowed to cool at rt slowly over a period of 30 min. The THF solution of the resulting Grignard reagent was added dropwise to a THF solution of 5-cyanophthalide (10.0 g, 63.0 mmol) under nitrogen atmosphere at 0 °C and stirred for 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched by the addition of 20% ammonium chloride solution (100 mL) at 0 °C. Product was extracted with ethyl acetate (50 mL × 2). The combined ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to yield **14** (11.2 g, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 2.86 (t, J = 6.0 Hz, 1H), 4.67 (d, J = 6.0 Hz, 2H), 7.15−7.21 (m, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.69 (dd, J = 7.8 Hz, 1.5 Hz, 1H), 7.80−7.85 (m, 2H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 62.4, 114.7, 115.9, 116.1, 117.8, 123.9, 125.3, 129.5, 130.6, 132.7, 132.8, 132.9, 140.9, 142.1, 165.0, 167.5, 195.4. ESI-Mass: For $C_{15}H_{10}FNO_2$, (M + H)/z: 256.25. Found: (M + H)/z: 256.0. A small sample was purified by preparative TLC for elemental analysis. Anal. for $C_{15}H_{10}FNO_2$, Calcd C, 70.58; H, 3.95; N, 5.49. Found: C, 70.48; H, 3.88; N, 5.45.

Preparation of Compound 4-(4-Fluorobenzoyl)-3-(*tert*-butyldimethylsiloxymethyl)benzonitrile (15). To a solution of compound **14** (8.0 g, 31.0 mmol) in DCM (40 mL) were added imidazole (4.2 g, 62.0 mmol) and TBDMSCl (5.9 g, 39.0 mmol), respectively, portionwise at 10−15 °C, and the reaction mixture was allowed to stir for 30 min. The reaction was monitored by TLC. The reaction mixture was quenched by the addition of water. The reaction mixture was extracted with DCM (50 mL × 2). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude residue, which was purified by silica gel column chromatography using ethyl acetate and hexane (1:19) to yield **15** (9.7 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 0.00 (s, 6H), 0.83 (s, 9H), 4.8 (s, 2H), 7.13−7.2 (m, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.63 (dd, J = 7.8 Hz, 1.4 Hz, 1H), 7.77−7.81 (m, 2H), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): −5.7, 18.2, 25.7, 62.1, 114.1, 115.8, 116.0, 118.2, 128.5, 130.1, 131.0, 132.7, 132.8, 140.3, 142.3, 164.9, 167.4, 194.9. ESI-Mass: For $C_{21}H_{24}FNO_2Si$, (M + H)/z: 370.52. Found: (M + H)/z: 370.2. Anal. for $C_{21}H_{24}FNO_2Si$, Calcd C, 68.26; H, 6.55; N, 3.79. Found: C, 68.23; H, 6.53; N, 3.82.

Preparation of Intermediate 4-(*E*/*Z*)-4-(Dimethylamino)-1-(4-fluorophenyl)but-1-enyl-3-(hydroxymethyl)-benzonitrile (12 and 13). To a THF solution of [3-(dimethylamino)propyl]phosphonium bromide hydrobromide (21.70 g, 43.0 mmol) was added sodium hydride (4.0 g, 100 mmol, 60% dispersion in mineral oil) portionwise at 5 °C under nitrogen atmosphere, and the reaction mixture was allowed to stir for 30 min. The reaction mixture was heated to 60 °C for 3 h; a deep orange colored solution of Wittig ylide was obtained. The reaction mixture was cooled to 25 °C. To this a solution of compound **15** (9.0 g, 24 mmol, in 15 mL of THF) was added, and the reaction mixture was heated to 60 °C and stirred overnight. After completion of the reaction, it was quenched by the addition of cooled water and extracted with ethyl acetate (30 mL × 2). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to yield **10**/**11** (as a crude residue). The crude reaction mixture was dissolved in THF, 1.0 M TBAF solution (70 mL) was added to it, and the reaction mixture was stirred for 2 h. The reaction mixture was concentrated to leave a crude residue. The *E* and *Z* isomers (**12**/**13**) were purified by silica gel column chromatography using methanol and chloroform (1:99) as

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eluent. ***E*-isomer (12) (1.3 g, 16.5%):** ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 2.08 (s, 6H), 2.36−2.44 (m, 2H), 2.50−2.54 (m, 2H), 4.63 (s, 2H), 5.73 (t, J = 7.1 Hz, 1H), 6.98−7.03 (m, 3H), 7.12−7.17 (m, 2H), 7.46 (dd, J = 7.9 Hz, 1.6 Hz, 1H), 7.65 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 27.0, 44.5, 58.6, 62.9, 110.5, 115.0, 115.2, 118.7, 130.7, 130.7, 130.9, 131.0, 131.7, 133.1, 134.7, 134.7, 138.4, 141.4, 148.3, 160.6, 163.1. ESI-Mass: For $C_{20}H_{21}FN_2O$, (M + H)/z: 325.4. Found: (M + H)/z: 325.3. A small sample was further purified by preparative TLC for elemental analysis. Anal. for $C_{20}H_{21}FN_2O$, Calcd C, 74.05; H, 6.53; N, 8.64. Found: C, 74.1; H, 6.49; N, 8.32. ***Z*-isomer (13) (4.1 g, 51.8%):** ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 2.01 (s, 6H), 2.06−2.17 (m, 2H), 2.25−2.30 (m, 1H), 2.44−2.51 (m, 1H), 4.22 (d, J = 12.6 Hz, 1H), 4.38 (d, J = 12.6 Hz, 1H), 5.17 (bs, 1H), 6.21 (dd, J = 7.0 Hz, 8.6 Hz, 1H), 6.93−6.98 (m, 2H), 7.10−7.13 (m, 2H), 7.27 (d, J = 8.9 Hz, 1H), 7.64 (dd, J = 8.9 Hz, 1.5 Hz, 1H), 7.81 (d, J = 1.5 Hz, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 27.9, 45.3, 58.8, 61.3, 111.7, 115.2, 115.4, 118.6, 127.4, 127.5, 128.6, 130.8, 130.9, 132.3, 135.8, 135.8, 138.6, 141.7, 142.6, 160.9, 163.3. ESI-Mass: For $C_{20}H_{21}FN_2O$, (M + H)/z: 325.4. Found: (M + H)/z: 325.2. A small sample was further purified by preparative TLC for elemental analysis. Anal. for $C_{20}H_{21}FN_2O$: C, 74.05; H, 6.53; N,8.64. Found: C, 73.97; H, 6.55; N, 8.67.

Alternative Preparation of Intermediates 12 and 13. *Preparation of 4-(4-(Dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl)-3-(tert-butyldimethylsiloxymethyl)-benzonitrile (**8**).* To a solution of diol **3** (10 g, 29.0 mmol) in DCM (60 mL) were added imidazole (4.0 g, 59.0 mmol) and TBDMSCl (5.5 g, 36.0 mmol) portionwise at 10−15 °C, respectively. The reaction mixture was stirred for 30 min at 10−15 °C and quenched by adding water (40 mL). Layers were separated, and the organic layer was washed with water (50 mL × 2). DCM was distilled out completely, and product was washed with hexane (50 mL) to get desired O-TBDMS protected **8** (10.9 g, 82%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): −0.16 (s, 3H), −0.12 (s, 3H), 0.8 (s, 9H), 1.5−1.6 (m, 2H), 2.14−2.2 (m, 7H), 2.3−3.0 (m, 1H), 2.34−2.39 (m, 1H), 2.49−2.55 (m, 1H), 4.40 (d, J = 15.5 Hz, 1H), 4.83 (d, J = 15.5 Hz, 1H), 6.91−6.96 (m, 2H), 7.24−7.28 (m, 2H), 7.53−7.60 (m, 2H), 7.97 (s, 1H), 8.9 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): −5.7, −5.6, 18.2, 22.3, 25.8, 43.3, 44.7, 59.9, 62.4, 110.7, 114.4, 114.7, 119.3, 126.5, 127.6, 127.7, 129.3, 131.2, 142.6, 142.6, 143.1, 148.3, 160.3, 162.7; ESI-Mass: For $C_{26}H_{37}FN_2O_2Si$, (M + H)/z: 457.68. Found: (M + H)/z: 457.4. Anal. for $C_{26}H_{37}FN_2O_2Si$: Calcd C, 68.38; H, 8.17; N, 6.13. Found: C, 68.32; H, 8.13; N, 6.19.

*Preparation of Intermediate 4-(E/Z)-4-(Dimethylamino)-1-(4-fluorophenyl)but-1-enyl)-3-(hydroxymethyl)benzonitrile (**12** and **13**).* To a solution of **8** (10 g, 22.0 mmol) in DCM (50 mL) were added triethyl amine (3.3 g, 33.0 mmol) and methane sulfonyl chloride (2.6 g, 23.0 mmol) respectively at 0−5 °C. After complete addition, the reaction mixture was warmed at 25 °C and stirred for 1 h. Reaction was quenched by adding water (50 mL), layers were separated, and the organic layer was dried over anhydrous sodium sulfate and solvent was distilled out completely. The crude reaction mixture was dissolved in THF, 1.0 M TBAF solution (70 mL) was added to it, and the reaction mixture was stirred for 2 h. Reaction mixture was concentrated to leave a crude residue. E and Z isomer (**12**/**13**) were purified by silica gel column chromatography using methanol and chloroform (1:99) as eluent.

Preparation of Cyclic Impurity-6 [(*Z*)-6-(4-Fluorophenyl)-1,2,3,4-tetrahydro-2,2-dimethylbenzo(c)azoline-9-carbonitrile Mesylate]. To a solution of Z-intermediate (**13**) (3.2 g, 10.0 mmol) in DCM (15 mL) were added triethyl amine (1.2 g, 12.0 mmol) and methane sulfonylchloride (1.3 g, 11.0 mmol) respectively at 20 to 25 °C. After complete addition, the reaction mixture was stirred for 10 min followed by addition of saturated sodium bicarbonate solution (50 mL). After the biphasic mixture was stirred for 30 min, the layers were separated and the aqueous layer was washed with DCM (20 mL). Water was distilled out completely, and the remaining residue was stirred with acetone (25 mL) and filtered. The filtrate was concentrated to yield Impurity-**6** (2.4 g 60%). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.0 (s, 3H), 2.1−2.2 (m, 1H), 2.7−2.8 (m, 1H), 3.5−3.5 (m, 4H), 3.9 (s, 3H), 3.9−4.0 (m, 1H), 4.4 (d, J = 12.9 Hz, 1H), 5.6 (d, J = 12.9 Hz, 1H), 6.4 (t, J = 7.8 Hz, 1H), 7.0−7.1 (m, 4H), 7.2−7.3 (m, 1H), 7.7 (dd, J = 8.1, 0.6 Hz, 1H), 8.9 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ δ ppm): 23.4, 39.6, 48.7, 56.5, 62.5, 63.5, 112.1, 115.4, 115.6, 117.8, 128.6, 129.5, 129.5, 130.0, 131.4, 133.2, 136.4, 138.6, 139.7, 145.8, 161.3, 163.8. ESI-Mass: For $C_{20}H_{21}FN_2$ (M^+)/z: 307.40. Found: (M^+)/z: 307.2. Anal. for $C_{20}H_{21}FN_2{\cdot}CH_3O_3S$: Calcd C, 62.66; H, 6.01; N,6.96. Found: C, 62.60; H, 5.99; N, 7.13.

Preparation of Impurity-7. To a solution of E-intermediate **12** (1.0 g, 15.3 mmol) in DCM (5.0 mL) were added triethyl amine (0.4 g, 3.8 mmol), Citalopram free base (5.0 g, 49.0 mmol), and methane sulfonyl chloride (0.4 g, 3.4 mmol) respectively at 20 to 25 °C. After complete of addition, the reaction mixture was stirred for 24 h at reflux temperature. Solvent was distilled out, and Impurity-7 was isolated by HPLC preparative column chromatography using potassium phosphate as buffer and a Phenomenex Luna C18 column to yield 0.8 g (45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.5−1.4 (m, 4H), 2.2 (m, 2H), 2.5 (s, 6H), 2.7 (s, 3H), 2.7 (s, 3H), 3.2 (m, 4H), 4.0 (bs, 2H), 5.2 (ABq, J = 13.5 Hz, 2 H), 5.8 (t, J = 3.1 Hz, 1H), 7.5 (m, 5H), 7.6−7.5 (m, 3H), 7.7 (d, J = 7.8 Hz, 2H), 7.8 (d, J = 8.6 Hz, 1H), 7.8 (s, 1H), 8.0 (s, 1H), 8.1 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 17.4, 24.7, 29.0, 36.6, 42.2, 49.3, 49.4, 55.6, 62.9, 64.7, 71.1, 90.1, 110.8, 111.3, 115.4, 115.7, 116.0, 118.0, 118.7, 123.0, 125.8, 126.8, 126.9, 127.1, 128.8, 130.9, 131.0, 131.5, 132.1, 133.5, 133.7, 134.3, 138.0, 140.0, 140.0, 148.7, 150.3, 160.2, 160.4, 162.6, 162.8. ESI-Mass: For $C_{40}H_{42}F_2N_4O$ (M^+)/z 631.80. Found: (M^+)/z 631.3.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data of selected intermediates and final compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Dorell, K.; Cohen, M. A.; Huprikar, S. S.; Gorman, J. M.; Jones, M. *Psychosomatics* **2005**, *46*, 91−93.
(2) Parker, N. G.; Brown, C. S. *Ann. Pharmacother.* **2000**, *34*, 761−771.
(3) Brosen, K.; Naranja, C. A. *Eur. Neuropsychopharmacol.* **2001**, *11*, 275−283.
(4) Baldwin, D.; Johnson, F. N. *Rev. Contemp. Pharmacother.* **1995**, *6*, 315−325.
(5) Keller, M. B. *J. Clin. Psychiatry* **2000**, *61*, 896−908.
(6) (a) Boegesoe, K. P.; Toft, A. S. US 4,136,193, 1979. (b) Boegesoe, K. P. US 4,650,884, 1987. (c) Boegesoe, K. P.; Lyngby; Jaegerspris, J. P.; US 4,943,590, 1990. (d) Petersen, H.; Boegesoe, K. P.; Sommer, M. B. US 6,291,689 B1, 2001. (e) Babu, N. A.; Vuddamari, S. G.; Laxman, G. S.; Manjunath, S. G.; Kulkarni, A. K. WO 2005/077927 A1, 2005. (f) Greenhood, A. K.; McHattie, D.; Rechka, J. A.; Hedger, P. C. M.; Gamble, M. P. US 7,002,025 B2, 2006. (g) Humble, R. E.; Christensen, T. V.; Rock, M. H.; Nielsen, O.; Petersen, H.; Dancer, R. US 7,112,686 B2, 2006.
(7) (a) Sommer, M. B.; Nielsen, O.; Petersen, H.; Ahmadian, H.; Pedersen, H.; Brosen, P.; Geiser, F.; Lee, J.; Cox, G.; Dapremont, O.; Suten, C.; Assenza, S. P.; Hariharan, S.; Nair, U. US 2011/0065938 A1, 2011. (b) Giridhar, T.; Srinivasulu, G.; Rao, K. S. US 2011/0092719 A1, 2011.
(8) (a) ICH Guidelines, Q3A (R), Impurities in New Drug Substances, The quality guidelines for Active Pharmaceutical Ingredients related to impurities according to the International Conference of Horminization. February 2002. (b) ICH Guidelines, Q3B (R) Impurities in New Drug Products, The quality guidelines for Active Pharmaceutical Ingredients related to impurities according to the International Conference of Horminization. February 2002. (c) International Conferences on Harmonizations, Impurities guidelines for residual solvents. Q3(c), Federal Register, 1997, *62* (247), 67377.
(9) USP Pending monograph Draft 1 for Citalopram Oral Solution.