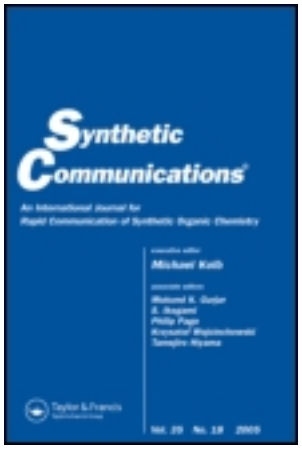

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Acid-Catalyzed Ether Rearrangement: Total Synthesis of Isomimosifoliol and (±)-Dihydromimosifoliol

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ACID-CATALYZED ETHER REARRANGEMENT: TOTAL SYNTHESIS OF ISOMIMOSIFOLIOL AND (±)-DIHYDROMIMOSIFOLIOL

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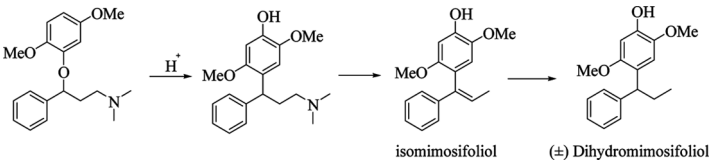
GRAPHICAL ABSTRACT



Abstract *An acid-catalyzed rearrangement of benzyl phenyl ethers to diphenylmethane derivatives, followed by salt formation and Hofmann elimination, is a simple method for the syntheses of isomimosifoliol and dihydromimosifoliol.*

Keywords Benzyl phenyl ethers; ether rearrangement; Hofmann elimination; tetraalkylammonium salts

INTRODUCTION

(+)-Mimosifoliol **(1)** was recently isolated by Wall et al.[1] from the root of *Aeschynomene mimosifolia* Vatke (Leguminosae) along with (+)-mimosifolenone **(2)**. Mimosifoliol **(1)** demonstrated weak activity in a DNA strand scission assay. A concentration of 25 μg/ml of **1** was approximately equal in activity to 0.1 μg/ml of bleomycin sulfate. Despite its activity in the assay, (+)-mimosifoliol **(1)** proved to be inactive against several human cancer cell lines. We herein report a total synthesis of isomimosifoliol in a new route developed by our group.

We have recently observed a novel acid-catalyzed rearrangement on ethers during the investigation of duloxetine[2] as shown in Scheme 1.

Using this novel rearrangement as a key step, we have synthesized tolterodine in good yields[3] as shown in Scheme 2.

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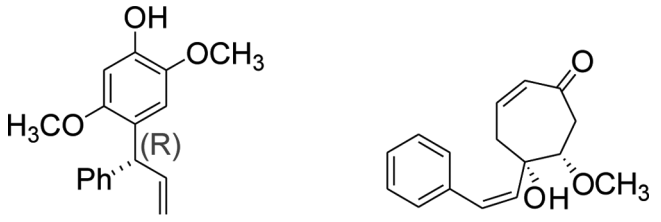
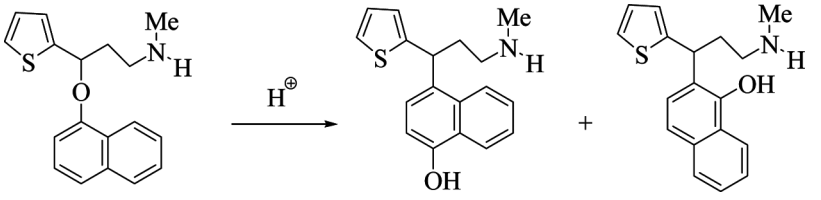
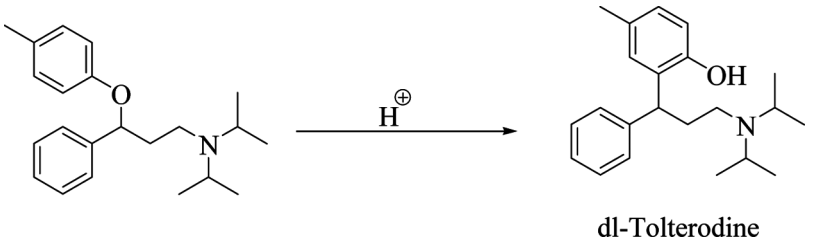


(+)-Mimosifoliol, **1** (+)-Mimosifolenone, **2**

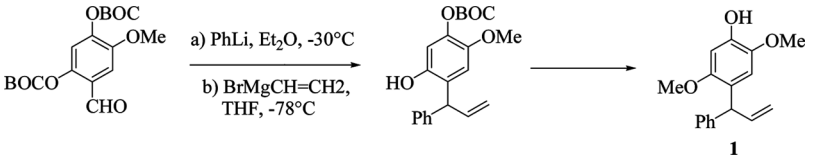


Scheme 1. Novel ether rearrangement in duloxetine.



dl-Tolterodine

Scheme 2. Key rearrangement step in tolterodine.

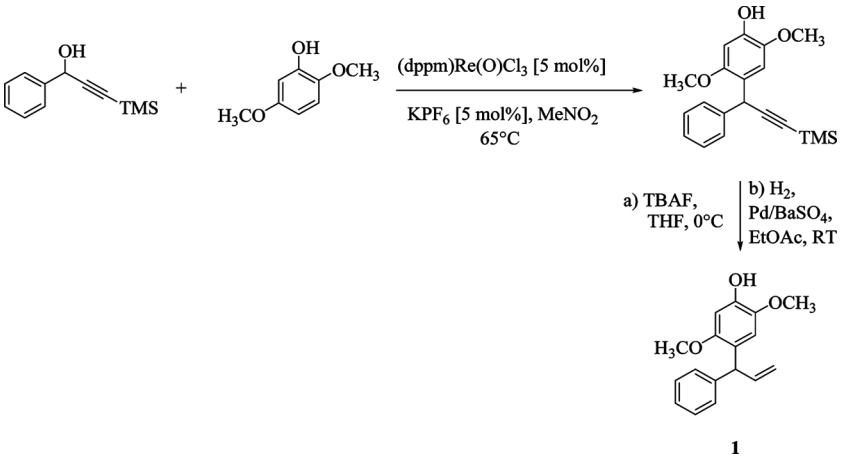


1

Scheme 3. Pettus strategy.

The first synthesis of mimosifoliol by Pettus used o-quinone methide intermediate strategy with protection and deportation of the phenolic group[4] as shown in Scheme 3.

The second synthesis by Toste et al. utilized rhenium-catalyzed aromatic propargylation as a key step without protection of phenols[5] as shown in Scheme 4.



Scheme 4. Toste methodology.

RESULTS AND DISCUSSION

In our quest to develop a general methodology for derivatives and analogs of mimosifoliol **(1),** we adopted our recent acid-catalyzed rearrangement method[2] as shown in Scheme 1.

Mannich adduct of acetophenone was reduced with sodium borohydride to give alcohol **(3)**. Alcohol was reacted with 2,5-dimethoxy fluorobenzene to give an ether product **(4)**. The ether **(4)** was rearranged in perchloric acid to give phenols **5a** and **5b**. The compounds **4**, **5a**, and **5b** were characterized by their spectral data and microelemental analysis. Compounds **5a** and **5b** were reacted with methyl iodide to give quaternary salts **6a** and **6b** as shown in Scheme 5.

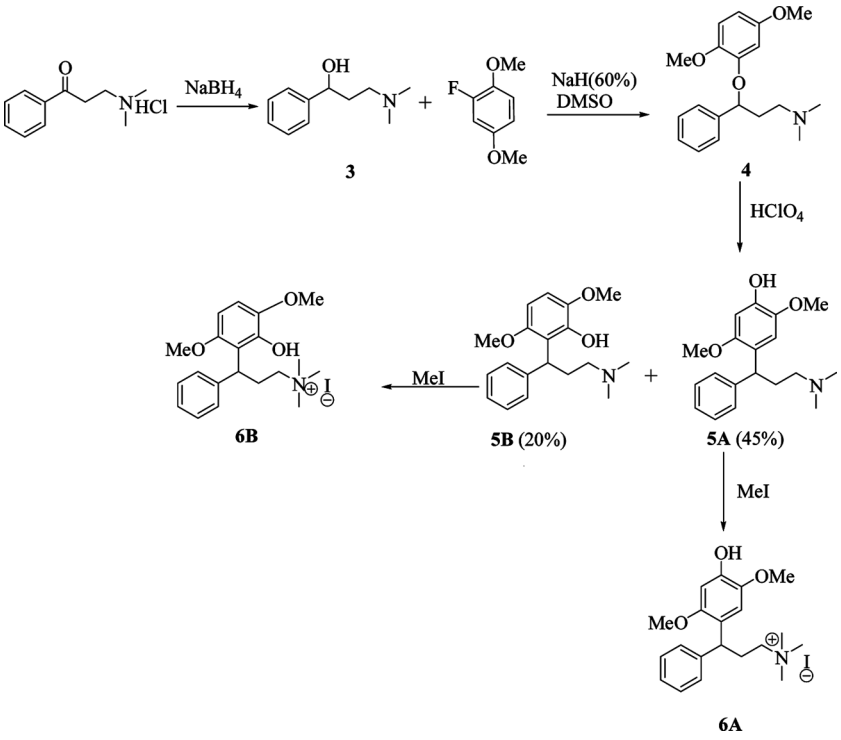
The salt **(6a)** was characterized by its characteristic spectral data. The quaternary salt was subjected to Hofmann elimination conditions to get mimosifoliol **(1)** as shown in Scheme 6.

During Hofmann elimination with butyl lithium, it was observed that along with a minor dl-mimosifoliol, a major isomimosifoliol **(7)** was also formed. Isomimosifoliol **(7)** was characterized thoroughly and also converted into (±)-dihydromimosifoliol **(8)** by hydrogenation. Both compounds were characterized by spectral data and microelemental analysis.

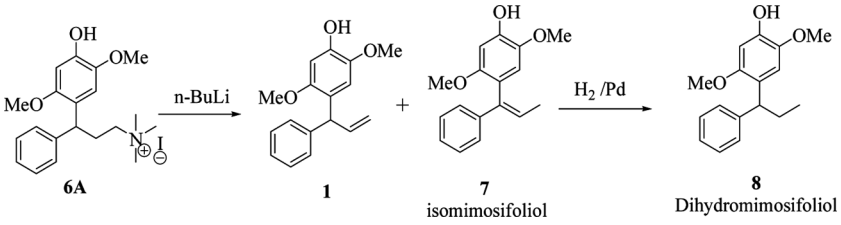
During the rearrangement of ether **(4)**, the *o*-isomer **(5b)** was also formed (20%) along with the *p*-isomer **(5a)** (45%). The product **5b** was reacted with methyl iodide and the formed salt **6b** was subjected to Hofmann elimination under 1,8-diazabicyclo [5.4.0]under-7-ese (DBU)/toluene-isopropyl alcohol (IPA) reflux conditions to give 5,8-dimethoxy-4-phenyl-chroman (or dl-cyclomimosifoliol) **(9)** as shown in Scheme 7, which has been characterized thoroughly.

EXPERIMENTAL

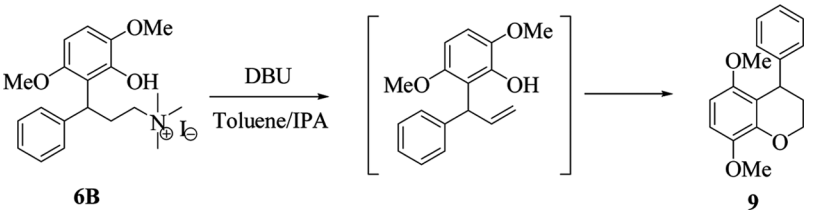
^{1}H and ^{13}C NMR spectra were recorded using a Bruker 400 spectrophotometer (400 and 100 MHz respectively) with tetramethylsilane (TMS) as internal standard.



Scheme 5. Preparation of diphenyl quaternary ammonium derivatives **6a** and **6b**.



Scheme 6. Hofmann elimination product of **6a**.



Scheme 7. Hofmann elimination product of **6b**.

Infrared (IR) spectra were recorded on a Perkin-Elmer spectrophotometer as KBr pellets or neat. Analytical thin-layer chromatography (TLC) was conducted on E-Merck 60F254 aluminum-backed silica-gel plates (0.2 mm). Developed plates were visualized using ultraviolet (UV) light or iodine chamber. High-performance liquid chromatographic (HPLC) spectra were recorded on a Shimadzu 2010 instrument.

Preparation of 3-Dimethylamino-1-phenyl-propan-1-ol (3)

3-Dimethylamino-1-phenyl propan-1-one hydrochloride (70.0 g, 0.328 mol) was dissolved in methanol (350.0 mL) and cooled to 10–15 °C. Sodium borohydride solution [12.48 g, 0.329 mol (sodium borohydride dissolved in 130.0 mL of 10% aqueous NaOH solution)] was added over 30 min and the reaction mass was stirred for 3 h. Reaction progress was monitored by TLC, and after completion of the reaction, solvent was evaporated under vacuum below 60 °C to get the crude alcohol. The crude product was dissolved in ethyl acetate and washed with water (2 × 500.0 mL). The organic layer was dried over anhydrous sodium sulfate, and concentration of solvent under vacuum gave a colorless liquid (54.0 g, yield: 92%).

IR (neat, cm^{-1}): 3747, 3350, 2824, 1463, 515; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (m, 4H), 7.24 (t, 1H, $J = 7.08$ Hz), 5.26 (s, 1H), 4.94 (q, 1H, $J = 4.12$ Hz), 2.63 (m, 1H), 2.43 (m, 1H), 2.29 (s, 6H), 1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.09, 128.09, 126.76, 125.49, 75.49, 58.24, 45.23, 34.55; ESI-MS (+Ve mode): m/z (%) = 181.03 [M + 2]; Purity by HPLC: 99.92%.

Preparation of [3-(2,5-Dimethoxy-phenoxy)3-phenylpropyl]dimethylamine (4)

Sodium hydride (15.64 g, 60%, 0.391 mol) was added to a solution of 3-dimethylamino-1-phenyl propan-1-ol (50.0 g, 0.279 mol) in dimethyl sulfoxide (250.0 mL) and stirred for 30 min at rt. 2,5-Dimethoxy-1-fluorobenzene (52.34 g, 0.335 mol) was added to the reaction mass, heated to 135–140 °C, and stirred for 4 h. Reaction progress was monitored by TLC, and after completion of the reaction, the mass was cooled to rt. Water (300.0 mL) was added, and the product was extracted into toluene (2 × 250.0 mL). The toluene layer was washed with saturated brine solution (2 × 100.0 mL) followed by water (100.0 mL). The toluene layer was dried over anhydrous sodium sulfate and concentrated under vacuum at <70 °C to get the crude product (87.5 g). The obtained crude was dissolved in ethyl acetate (200.0 mL) and 30.0 g of 85% *o*-phosphoric acid was added drop wise at (25–30 °C). After the addition, the reaction mixture was stirred for 30 min, cooled to 10–15 °C, and stirred for 1 h. The slurry was then filtered and the solids were washed with 50.0 mL of cold ethyl acetate (10–15 °C). The solid was stirred in a mixture of 50.0 mL dichloromethane and 100.0 mL of water at 25–30 °C, and 90.0 mL of 30% aqueous ammonium hydroxide solution was added. The reaction mixture was stirred for 10 min at 25–30 °C, and the layers were separated. The organic layer was washed with water (50.0 mL × 2) and dried over anhydrous sodium sulfate. The solution was concentrated at 35–40 °C to get solid material (55.0 g, yield: 63%).

IR (KBr, cm^{-1}): 3433, 2946, 1690, 1878, 1609, 1509, 1460, 1231, 1162, 762; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, 2H, $J = 7.3$ Hz), 7.31 (t, 2H, $J = 7.3$ Hz),

7.25 (t, 2H, $J = 7.22$ Hz), 6.78 (d, 1H, $J = 8.7$ Hz), 6.39 (d, 1H, $J = 2.7$ Hz), 6.35 (dd, 1H, $J_1 = 8.6$, $J_2 = 2.8$ Hz), 5.24 (t, 1H, $J = 5.6$ Hz), 3.83 (s, 3H), 3.50 (s, 3H), 2.46 (t, 2H, $J = 7.2$ Hz), 2.30 (m, 1H), 2.23 (s, 6H), 2.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.93, 148.66, 144.32, 141.72, 128.42, 127.47, 126.03, 113.27, 104.26, 104.15, 56.93, 55.75, 55.32, 45.39, 36.40; ESI-MS (+Ve mode): m/z (%) = 316.3 [M + 1]; DSC: 57.62 °C; Purity by HPLC: 99.95%. Anal. calcd. for $C_{19}H_{25}NO_3$ (315.40): C, 72.35; H, 7.99; N, 4.44. Found: C, 72.0961; H, 7.8667; N, 4.7088.

Preparation of 4-(3-Dimethylamino-1-phenyl-propyl)2,5-dimethoxy-phenol (5)

To a solution of [3-(2,5-dimethoxy-phenoxy)3-phenyl-propyl]-dimethylamine **4** (60.0 g, 0.19 mol) in dichloromethane (400.0 mL) was added 100.0 mL of perchloric acid (71–73%) at 0–5 °C. The reaction mixture was stirred for 3 h at 0–5 °C, and the reaction progress was monitored by TLC. After the staring material disappeared ice water was added to the reaction mixture and basified (pH 9–10) with aqueous ammonium hydroxide solution. The reaction mixture was stirred for 30 min, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 100.0 mL). Combined organic layers were washed with water (2 × 100.0 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated at 40 °C to get 40.0 g of crude material. The crude product mixture was separated using column chromatography. Three compounds, *para*-isomer (**5a**, 45%), *ortho*-isomer **(5b**, 22%), and 2,5-dimethoxy phenol (5.0 g, 10%), were isolated and characterized as follows.

***Para*-isomer (5a).** IR (KBr, cm^{-1}): 2830, 2477, 1587, 1466, 1199, 1041, 787; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 1H), 7.26 (m, 5H), 6.72 (s, 1H), 6.50 (s, 1H), 4.35 (t, 1H, $J = 7.6$ Hz), 3.77 (s, 3H), 3.69 (s, 3H), 2.27 (m, 2H), 2.19 (s, 6H), 2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.43, 144.98, 144.75, 140.67, 128.09, 127.77, 125.70, 123.67, 111.03, 99.94, 45.21, 40.90, 32.69; ESI-MS (+Ve mode): m/z (%) = 316.30 [M + 1]; DSC: 139.03 °C; Purity by HPLC: >99%. Anal. calcd. for $C_{19}H_{25}NO_3$ (315.40): C, 72.35; H, 7.99; N, 4.44. Found: C, 71.9882; H, 8.2287; N, 4.9499.

***Ortho*-isomer (5b).** IR (KBr, cm^{-1}): 2936, 2860, 2775, 1597, 1480, 1359, 1244, 1151, 1094, 701; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.0 (s, 1H), 7.26 (m, 5H), 6.70 (d, 1H, $J = 8.7$ Hz), 6.26 (d, 1H, $J = 7.8$ Hz), 4.55 (t, 1H, $J = 9.0$ Hz), 3.86 (s, 3H), 3.20 (s, 3H), 2.43 (m, 4H), 2.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.43, 144.97, 144.67, 140.60, 128.09, 127.77, 125.69, 123.74, 111.00, 99.86, 58.16, 56.47, 56.02, 45.35, 40.90, 32.75; ESI-MS (+Ve mode): m/z (%) = 316.30 [M + 1]; DSC: 118.31 °C; Purity by HPLC: >95%. Anal. calcd. for $C_{19}H_{25}NO_3$ (315.40): C, 72.35; H, 7.99; N, 4.44. Found: C, 72.1818; H, 8.1739; N, 4.6845.

Quaternary Salt Preparation of 4-(3-Dimethylamino-1-phenyl-propyl)-2,5-dimethoxy-phenol with Methyl Iodide (6a)

To a solution of 4-(3-dimethylamino-1-phenyl-propyl)-2,5-dimethoxy-phenol **5a** (8.0 g, 0.025 mol) in dichloromethane (100.0 mL) was added methyl iodide (4.50 g, 0.0317 mol). The reaction mixture was stirred for 1 h at rt, and the reaction

progress was monitored by TLC. After the disappearance of starting material, the salt was filtered from the reaction mixture, and the cake was washed with dichloromethane (20.0 mL) to get a white compound (10.62 g, yield: 92%).

IR (KBr) (cm^{-1}): 3231, 1521, 1452, 1209, 730, 481; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H), 7.33 (m, 4H), 7.17 (t, 1H, $J = 7.1$ Hz), 6.94 (s, 1H), 6.45 (s, 1H), 4.22 (t, 1H, $J = 7.6$ Hz), 3.72 (s, 3H), 3.64 (s, 3H), 3.18 (m, 2H), 3.0 (s, 9H), 2.5 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.29, 146.36, 144.49, 141.91, 128.69, 127.90, 126.48, 121.03, 113.21, 101.15, 64.96, 57.34, 56.52, 52.61, 27.39; ESI-MS (+Ve mode): m/z (%) = 330.02 [M − I]. Melting point: 262.2–263.5 °C.

Preparation of Isomimosifoliol (7)

The quaternary salt **6a** (6.0 g, 0.013 mol) was suspended in tetrahydrofuran (THF), and the reaction mass was cooled to 0–5 °C. n-Butyl lithium in hexane (1.6 M, 36.0 mL) was added over a period of 15 min at 0–5 °C, and slowly the reaction mixture temperature was raised to 25–30 °C over a period of 1 h. It was stirred for 1 h at rt, and the reaction progress was monitored by TLC. After the starting material disappeared, ice water was added to the reaction mixture. The product was extracted with ethyl acetate (4 × 25.0 mL) and dried over anhydrous sodium sulfate. The combined organic layer was concentrated at 60 °C to get a light yellow material (4.0 g).

GC-MS of crude sample shows 31% of mimosifoliol **1** and **35%** of isomimosifoliol **7**.

Pure product was isolated from the crude mixture by column chromatography eluting with hexane and ethyl acetate (9:1) and recrystallized two times with methylenechloride and hexane mixture as solvent to get pure isomimosifoliol **7**. (We could not isolate mimosifoliol in pure form; it always was mixture of **1** and **7**).

IR (KBr, cm^{-1}): 3519, 2938, 2914, 2840, 2025, 1630, 1598, 1509, 1416, 1296, 1216, 1037, 655; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (m, 5H), 6.66 (s, 1H), 6.58 (s, 1H), 6.29 (q, 1H, $J = 6.8$ Hz), 5.65 (s, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 1.68 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.81, 145.39, 142.14, 140.31, 138.30, 127.95, 126.38, 126.10, 124.93, 119.38, 113.95, 99.84, 56.53, 56.25, 15.63; ESI-MS (+Ve mode): m/z (%) = 271.32 [M + 1]; melting point: 101.2–104.4 °C; GC-MS: 99.28%. Anal. calcd. for $C_{17}H_{18}O_3$ (270.32): C, 75.53; H, 6.71. Found: C, 75.6458; H, 6.8322.

Preparation of Dihydromimosifoliol (8)

To a solution of isomimosifoliol **7** (75.0 mg, 0.277 mmol) in methanol was added 5% Pd/C (wet, 10.0 mg) in an autoclave. It was hydrogenated at 50 psi for 2 h at 35–40 °C. The reaction progress was monitored by TLC. After the starting material disappeared, the reaction mass was cooled to rt, filtered through a celite bed, and concentrated under vacuum at <60 °C to get the crude product. The product was separated by column chromatography and after bulb-to-bulb distillation gave an off-white solid (47.5 mg, yield: 63%).

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