Concise Total Synthesis of Antiarrhythmic Drug Dronedarone *via* a Conjugate Addition Followed Intramolecular Heck Cyclization

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Abstract

A concise, scalable, and an efficient total synthesis for dronedarone (**2**) was described using conjugate addition followed by intramolecular Heck cyclization. The other key reaction includes selective reduction the of nitro functionality and addition of lithiated terminal alkyne to the aldehyde. The overall yield of this approach is 44% in 6 steps.

Keywords

Total synthesis; dronedarone; antiarrhythmic drug; conjugate addition; intramolecular Heck cyclization; C-C bond formation

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and is an irregular heartbeat disease that can lead to heart stroke, blood clots, heart failure, and other major heart-related complications.[1] In 2016, the Global Burden of Disease project estimated there are at least 46.3 million people suffering with AF worldwide, with a 3-fold increase over the past 50 years.[2] Untreated AF doubles the risk of major heart-related deaths and is associated with a 5-fold increased risk of heart stroke. Amiodarone (**1**)[3] (Figure 1) is an effective multichannel blocker and is the drug of choice to treat AF. Amiodarone (**1**) is a widely used class III anti-arrhythmic drug that effectively blocks aberrant electrical signals in the heart that cause irregular heartbeat. amiodarone is an iodine-rich benzofuran derivative, and it contains approximately 37% iodine by weight. Each 200 mg Amiodarone capsule contains approximately 75 mg of organic iodine, 8-17 % of which is free iodine: more than 100-times excess iodine that is required for normal daily function. The regular use of amiodarone causes several diseases, such as thyroid dysfunction pulmonary fibrosis and liver related disease, and can accumulate in adipose tissues, liver, muscle, and lung tissue for up to 100 days.[4] Dronedarone (**2**) is a modified structural analog with electrophysiologic similarities to

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amiodarone (**1**) and is developed by Sanofi Pharma. Unlike amiodarone, the benzofuranyl ring of dronedarone (**2**) is not iodinated, while an additional sulfonamide modification on benzofuran significantly decreases half-life and lipophilicity, resulting in drastically lowered tissue accumulation. The minimal side effects of dronedarone as a potent multi-channel blocker led to U.S. FDA approval in 2009 for atrial fibrillation.

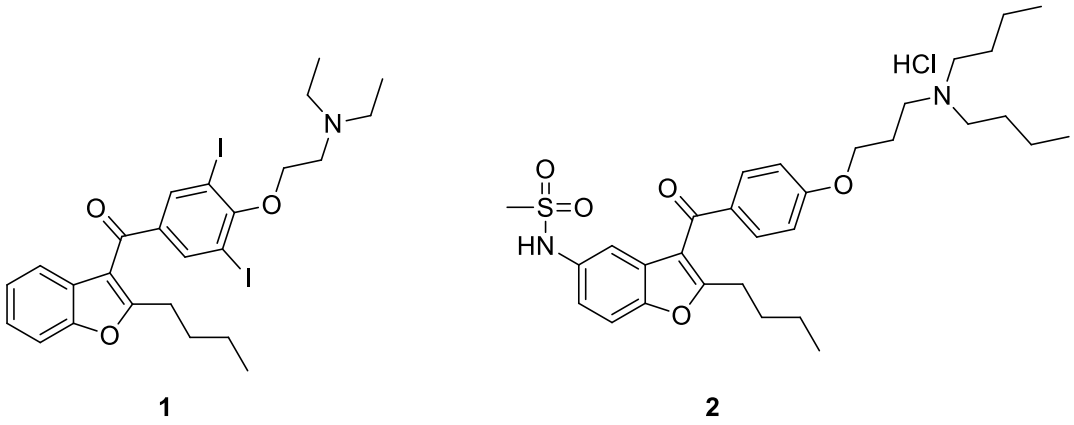


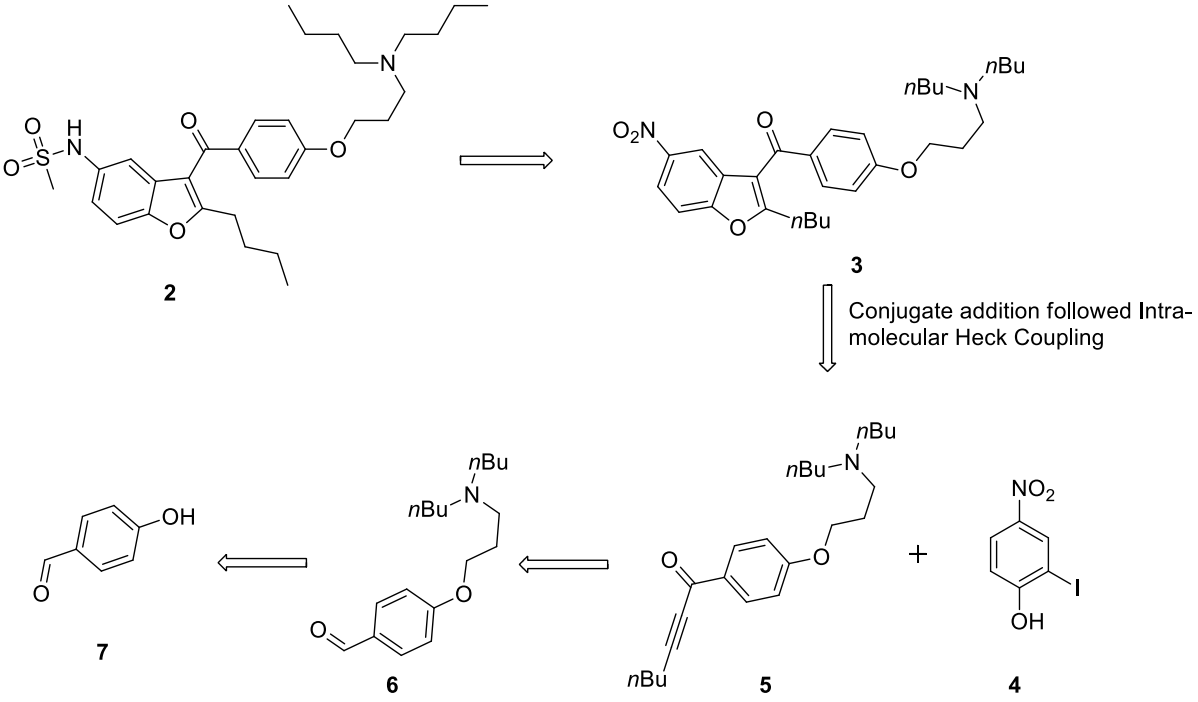
Figure 1: Antiarrhythmic agents' amiodarone (**1**) and dronedarone (**2**)

The first total synthesis of dronedarone was reported in 1993 by Gubin *et al.* [5] Several synthetic routes for total synthesis of dronedarone have since been reported using diverse methods. [6] As a part of our work on the total synthesis of biologically active natural products,[7] herein we reported a novel and efficient total synthesis of dronedarone based on a conjugate addition followed by an intramolecular Heck Coupling reaction strategy.

Results and Discussion

Retrosynthetic Analysis of 2

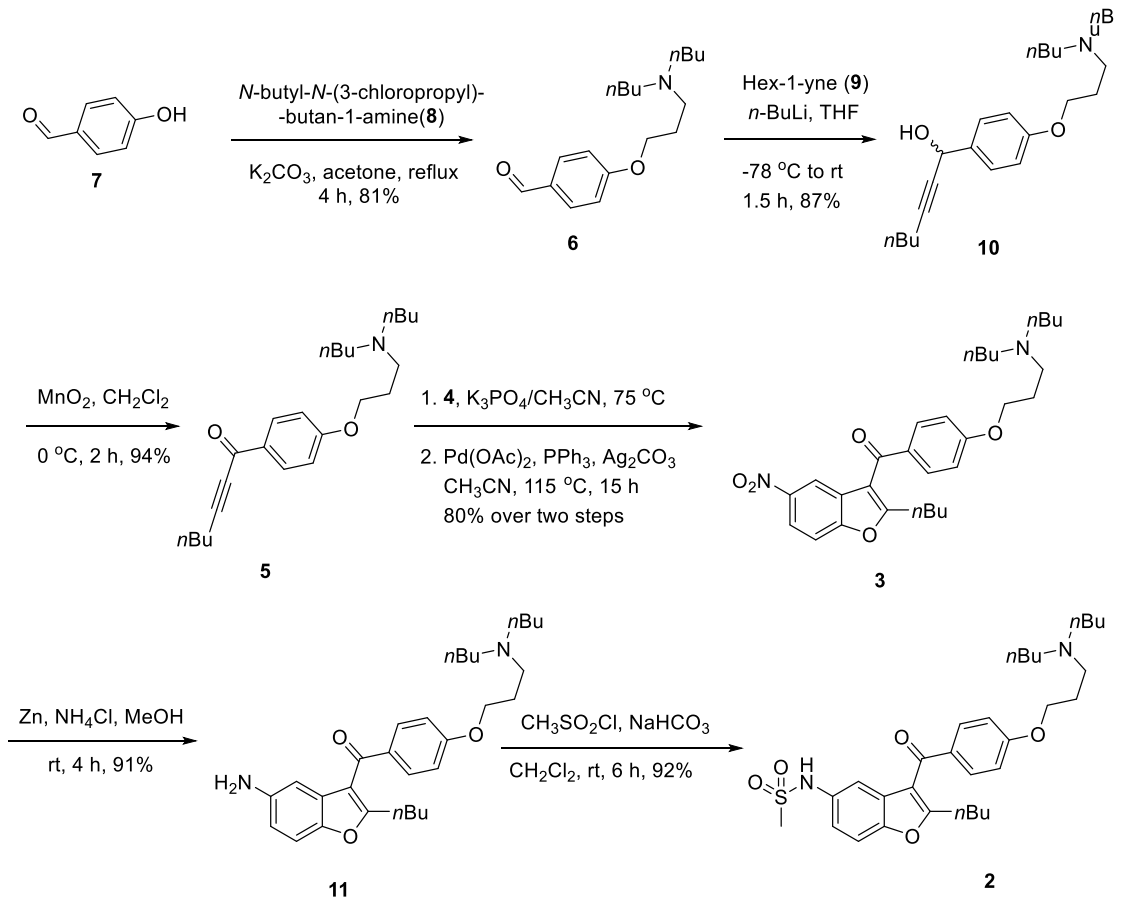
The retrosynthetic analysis of the dronedarone is outlined in Scheme 1. The target molecule dronedarone (**2**) would be generated by late-stage sulfonamide formation and reduction from **3**, which could be anticipated from two intermediates **4** and **5** using conjugate addition followed by intramolecular Heck cross-coupling. The advanced intermediate **5** could be synthesized from intermediate **6**, which was obtained from 4-hydroxybenzaldehyde **7**.



Scheme 1. Retrosynthetic analysis of dronedarone (**2**)

***Synthesis of* 2**

As depicted in the Scheme 2, the target molecule was synthesized from 4-hydroxy benzaldehyde **7,** which was treated with commercially available *N*-butyl-*N*-(3-chloropropyl)butan-1-amine (**8**) and K_2CO_3 under reflux to access aldehyde **6**. The compound **6** was treated with lithiated terminal alkyne **9** to provide racemic alcohol **10** in 87% yield, which was then oxidized to the ketone by treatment with MnO_2 in DCM, providing compound **5** in 94% yield. Having sufficient amounts of key fragments **4** and **5** in hand, the stage was set for the crucial coupling reaction.[8] The conjugate addition of 2-Iodo-4-nitrophenol **4** to the ynone **5** in the presence of potassium phosphate in acetonitrile at 75 ^{o}C, followed by intramolecular Heck reaction provided the benzofuran derivative **3** in 80% over two steps. The nitro group on benzofuran was selectively reduced to the corresponding amine using zinc and ammonium chloride in methanol, providing compound **11** in 91% yield. [9] Finally, exclusive mesylation was performed using sodium bicarbonate and methane sulfonyl chloride in DCM at room temperature for 6 h to provide dronedarone (**2)** in 92% yield. The analytical and spectral (^{1}H and ^{13}C NMR) data of synthesized compound **2** are in agreement with the reported data.[6]



Scheme 2. Total Synthesis of dronedarone (**2**)

Conclusions

In summary, we have achieved the total synthesis of dronedarone (**2**) in an efficient, eco-friendly manner using an industrially viable mode starting from commercially available 4-hydroxy benzaldehyde and economically cheaper reagents. The protocol offers an operationally simple approach, featuring mild conditions, protecting-group-free synthesis and superior yield when compared to earlier methods. The highlight of our synthetic strategy is the conjugate addition of an *o*-iodophenol derivative followed by intramolecular-Heck coupling with ynones yielding the desired core in a single step. The present strategy proceeds in good to excellent yield

Experimental

General details: All reactions are performed under inert atmosphere. The apparatus perfectly cleaned, and oven dried before the use. All the anhydrous solvents such as acetone, CH_3CN, MeOH, CH_2Cl_2 and all the other solvents are brought from Fisher Scientific or Sigma Aldrich and directly used without further purification. The anhydrous THF was distilled over Na and

benzophenone. The silica gel (100-200 mesh) for column chromatography was perched from Merck & Co. The proton and carbon NMR were recorded using 400MHz Bruker Avance II and 500 MHz Brucker Apex II instrument with TMS as internal solvent. The HRMS spectrum was recorded using ESI-HRMS instrument. The chemical shifts are in ppm and coupling constants are reported in hertz (Hz) and the following abbreviations s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

4-(3-(Dibutylamino)propoxy)benzaldehyde (6): K_2CO_3 (5.37 g, 39.0 mmol) was added to stirred solution of 4-hydroxybenzaldehyde (1.6 g, 13.65 mmol) and N-butyl-N-(3-chloropropyl) butan-1-amine (**8**) (4.0 g, 19.51 mmol) in acetone (80 mL) at room temperature. The resultant mixture was stirred under reflux for 4h. After completion of the reaction (The progress of the reaction was monitored by TLC), the rection mixture was brought to room temperature and the solids were filtered up. The filtrate was evaporated, and the crude product was purified by silica gel column chromatography (ethyl acetate/ hexane = 1:30) to give compound **6** (4.6 g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 4.11 (t, *J* = 6.3 Hz, 2H), 2.59 (t, *J* = 6.9 Hz, 2H), 2.42(t, *J* = 7.3 Hz, 4H), 1.94 (quint, *J* = 13.3, 6.6 Hz, 2H), 1.44-1.37 (m, 4H), 1.33-1.24 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 164.0, 131.6, 129.5, 114.5, 66.3, 53.7, 50.0, 29.0, 26.7, 20.4, 13.8; HRMS (ESI) calcd for $C_{18}H_{30}O_2N$ $[M + H]^+$: 292.2260; found: 292.2271.

1-(4-(3-(Dibutylamino)propoxy)phenyl)hept-2-yn-1-ol (10): *n*-Butyl lithium was added to a stirred solution of 1-hexyne (**9**) (1.3 mL, 11.16 mmol) in anhydrous THF (40 mL) at -78 ^{o}C. After 20 min, the reaction mixture was allowed to stir at room temperature for 1 h. The reaction mixture was then cooled -78 ^{o}C and aldehyde (**6**) (2.5 g, 8.59 mmol) was added. The resulting mixture was slowly brought into room temperature and allowed to stir for additional 1h then quenched with saturated NH_4Cl. The mixture was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were washed with brine solution, then dried over Na_2SO_4. The solvent was removed under vacuum and purified by silica gel column chromatography (ethyl acetate/ hexane = 2:30) to give desired alcohol (**10**) (2.8 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.39 (t, *J* = 1.8 Hz, 1H), 3.99 (t, *J* = 6.4 Hz, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 2.40 (t, *J* = 7.3 Hz, 4H), 2.27 (dt, *J* = 7.0, 2.1 Hz, 2H), 1.89 (quint, *J* = 6.4 Hz, 2H), 1.57-1.48 (m, 2H), 1.47-1.36 (m, 6H), 1.34-1.23 (m, 4H), 0.94-0.87 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 133.8, 127.8, 114.1, 86.7, 80.4, 66.2, 63.9, 53.6, 50.2, 30.6, 28.7, 26.5, 21.8, 20.6, 18.4, 13.9, 13.4; HRMS (ESI) calcd for $C_{24}H_{40}O_2N$ $[M + H]^+$ 374.3044; found: 374.3053.

1-(4-(3-(Dibutylamino)propoxy)phenyl)hept-2-yn-1-one (5): MnO_2 (6.3 g, 72.38 mmol was added to a stirred solution of the alcohol (**10**) (2.7 g, 7.23 mmol) in DCM (60 mL) at room temperature. The resulting solution was stirred for 2 h, after completion of the reaction (the progress of the reaction was monitored by TLC) the reaction mixture was filtered through celite. The solvent was removed under vacuum and the crude residue was purified by silica gel column chromatography give to desired ketone as a colourless oil (**5**) (2.5 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 2.49 (t, *J* = 7.1 Hz, 2H), 2.41 (t, *J* = 7.3 Hz, 4H), 1.92 (quintet, *J* = 13.3, 6.4 Hz, 2H), 1.70-1.61 (m, 2H), 1.55-1.46 (m, 2H), 1.45-1.35 (m, 4H), 1.34- 1.23 (m, 6H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 163.8, 131.7, 130.0, 114.0, 95.6, 79.5, 66.4, 53.8, 50.1, 29.8, 29.2, 26.8, 21.9, 20.6, 18.7, 13.9, 13.4; HRMS (ESI) calcd for for $C_{24}H_{38}O_2N$ $[M + H]^+$: 372.2887; found: 372.2897.

(2-Butyl-5-nitrobenzofuran-3-yl)(4-(3-(dibutylamino)propoxy)phenyl)methanone (3) : K_3PO_3 (572 mg, 2.7 mmol) was added to a stirred solution of o-iodonitrophenol (715 mg, 2.7 mmol) and activated alkyne (**5**) (1.0 g, 2.7 mmol) in CH_3CN (10 mL). The resultant mixture was stirred at 75 ^{o}C until the reaction reached to completion. After completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to give crude product. The crude product was used for next step without further purification. The crude product was (2.7 mmol)), PPh_3 (70 mg, 0.27 mmol), Ag_2CO_3 (740 mg, 2.7 mmol), in CH_3CN (15 mL) was stirred at 115 ^{o}C for 15 h under inert atmosphere. After completion (the progress of the reaction was monitored by TLC), the mixture was brought into room temperature and diluted with water (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum to give crude product. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexane = 1:1) to give compound **3** (1.0 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.34 (d, *J* = 2.1 Hz, 1H), 8.22 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.9 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.12 (t, *J* = 6.2 Hz, 2H), 2.92 (t, *J* = 7.6 Hz, 2H), 2.60 (t, *J* = 7.0 Hz, 2H), 2.42 (t, *J* = 7.2 Hz, 4H), 1.95 (quint, *J* = 13.1, 6.5 Hz, 2H), 1.76 (quint, *J* = 15.2, 7.6 Hz, 2H), 1.46- 1.24 (m, 10H), 0.93-0.86 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 189.0, 167.0, 163.6, 156.2, 144.5, 131.6, 130.6, 127.9, 120.1, 117.6, 117.3, 114.4, 111.3, 66.6, 53.9, 50.3, 29.9, 29.3, 27.9, 27.0, 22.3, 20.6, 14.0, 13.6; ESI-HRMS m/z calcd. for $C_{30}H_{41}O_5N_2$ $[M + H]^+$: 509.2985; found: 509.3010.

(5-amino-2-butylbenzofuran-3-yl)(4-(3(dibutylamino)propoxy)phenyl)methanone (11): Added saturated ammonium chloride (408 mg, 7.7 mmol) slowly to a stirred solution of nitroarene 700 mg, 1.37 mmol) and zinc dust (1.37 g, 208 mmol) in MeOH (20 mL). The resultant mixture was stirred for 30 min. After completion (the progress of the reaction was monitored by TLC), the reaction mixture was quenched with saturated Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (3 ×15 mL). The combined organics were dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum to give crude product. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexane = 2:1) to give compound **11** (600 mg, 91%) as a colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.9 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 2.1 Hz, 1H), 6.62 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.54 (br s, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.59 (t, *J* = 6.9 Hz, 2H), 2.42 (t, *J* = 7.3 Hz, 4H), 1.94 (quint, *J* = 13.4, 6.6 Hz, 2H), 1.75-1.28 (m, 2H), 1.45-1.38 (m, 4H), 1.37-1.24 (m, 6H), 0.91-0.85 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 164.9, 162.8, 148.0, 142.5, 131.5, 131.5, 127.9, 116.4, 114.0, 112.9, 111.0, 106.1, 66.4, 53.9, 50.2, 30.0, 29.3, 27.8, 27.0, 22.2, 20.6, 14.0, 13.6; ESI-HRMS m/z calcd. for $C_{30}H_{43}O_3N_2$ $[M + H]^+$: 479.3240; found: 479.3268.

N-(2-Butyl-3-(4-(3-(dibutylamino)propoxy)benzoyl)benzofuran-5-yl)methanesulfonamide (2): Sodium bicarbonate (140 mg, 1.67 mmol) was added to a stirred solution of the compound **11** (500 mg, 1.046 mmol) in dichloromethane (10 mL) and methane sulfonyl chloride (119 mg, 1.046 mmol) was added at 35 ^{o}C. The resultant solution was stirred under reflux for 6 h, After completion (the progress of the reaction was monitored by TLC), the reaction mixture was quenched with water (10 mL). The mixture was extracted with DCM (20 x 3) and dried over Na_2SO_4. The solvent was removed under vacuum to give crude product and n-hexane (100 mL) was added to the crude product and stirred at 25 ^{o}C for overnight to afford the title compound 2 (530 mg, 92%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.9 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.28-7.23 (m, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 4.10 (t, *J* = 6.4 Hz, 2H), 2.92 (s, 3H), 2.87 (t, *J* = 7.6 Hz, 2H), 2.59 (t, *J* = 6.9 Hz, 2H), 2.42 (t, *J* = 7.3 Hz, 4H), 1.94 (quint, *J* = 13.4, 6.6 Hz, 2H), 1.71 (m, 2H), 1.45-1.38 (m, 4H), 1.37-1.24 (m, 6H), 0.91-0.85 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 165.4, 163.1, 151.6, 132.7, 131.6, 131.1, 128.0, 120.1, 116.6, 115.4, 114.1, 111.5, 66.4, 53.7, 50.1, 38.7, 29.9, 29.0, 27.9, 27.7, 22.1, 20.5, 14.0, 13.5; ESI-HRMS m/z calcd. for $C_{31}H_{45}O_2N_2S$ $[M + H]^+$: 557.3020; found: 557.3043.

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Supplementary Materials: ^{1}H and ^{13}C NMR spectra of unknown compounds.

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