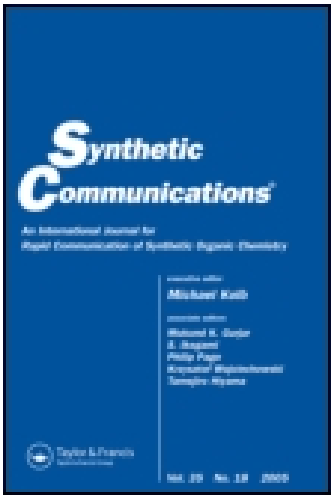

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Efficient Arndt-Eistert Synthesis of Selective 5-HT_7 Receptor Antagonist SB-269970

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Efficient Arndt–Eistert Synthesis of Selective 5-HT$_7$ Receptor Antagonist SB-269970

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Abstract: This contribution describes a novel Arndt–Eistert approach for the efficient synthesis of the potent and selective 5-HT$_7$-antagonist, (*R*)-3-(2-(2-(4-methylpiperidin-1-yl)-ethyl)pyrrolidine-1-sulfonyl)phenol (SB-269970), from D-proline. The synthesis was carried out in 10 steps with an overall yield of 23%.

Keywords: Arndt–Eistert homologation, D-proline, selective 5-HT$_7$ receptor antagonist

Development of selective antagonists against human receptors is a widely used strategy in medicinal chemistry to obtain a desired pharmacological response. Drug targets such as the human serotonin (5-HT) receptor,[1] of which seven distinct types are currently known, are still not fully understood and continue to attract attention among neurophysiologists and medicinal chemists. Recently, Lovell and coworkers[2] reported that SB-269970 (**9**) was a highly potent and selective antagonist against the human 5-HT$_7$ receptor,[3] and since then, numerous important scientific contributions have found SB-269970 to have an effect on anxiety and to act as an antidepressant.[4–6]

Although certain steps in the original synthesis of SB-269970 (**9**) have been published,[2] no full protocol is currently available in the scientific or patent literature.[7] We here report an efficient, novel, and complete synthesis of homochiral SB-269970 with full experimental details in the

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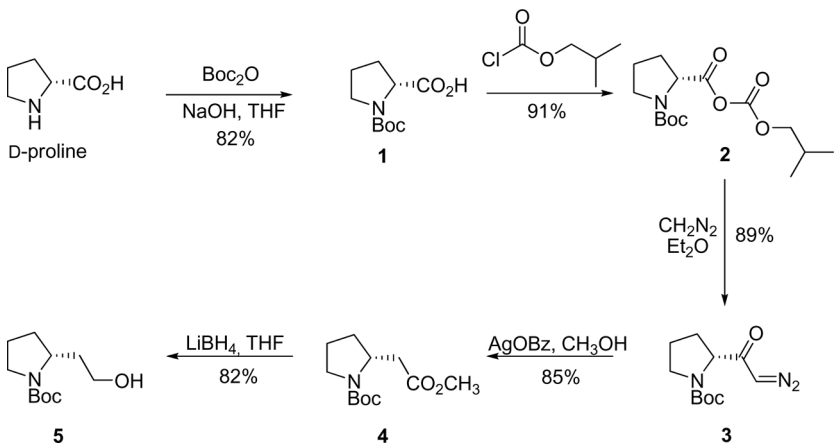
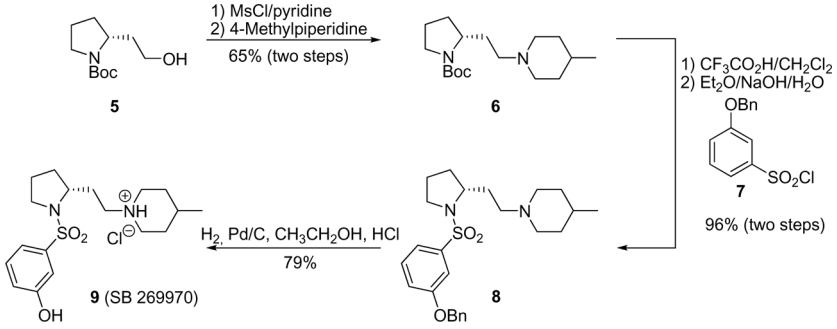
hope that this will lead to further investigations of the physiological effects exerted by this promising drug on the human 5-HT_7 receptor.

We set out to prepare SB-269970 (**9**) using an Arndt–Eistert route from commercially available D-proline. Because of the well-known ring-opening reaction associated with Wolff rearrangement of proline sulfonamides,[8] we decided to introduce a *tert*-butyl carbamate (Boc) as a temporary nitrogen protecting group and prepare the sulfonamide function late in the synthetic sequence. D-Proline was Boc-protected and reacted with isobutyl chloroformate in the presence of triethylamine to give **2**, in 82% and 91% yields (Scheme 1). The mixed anhydride (**2**) was treated with diazomethane to give diazoketone (**3**) (89%),[9] which subsequently underwent silver benzoate–promoted Wolff rearrangement[10] in methanol to give methyl ester **4** in 85% yield.[9] The ester function was next reduced with lithium borohydride in tetrahydrofuran (THF) to give primary alcohol **5** in 82% yield (Scheme 2).[11]

We noticed some discrepancies in the literature, such as specific optical rotation values for this known Boc-homoprolinol (**5**). Despite it being well accepted that Arndt–Eistert synthesis leads to complete retention of stereochemistry,[10,12] partial erosion of stereochemical purity could in principle have occurred prior to the Wolff rearrangement step, and a rigorous investigation of the enantiofidelity up to this point was accordingly undertaken. The high-performance liquid chromatography (HPLC) traces of racemic Boc-homoprolinol [(±)**5**] made through the same synthetic sequence and that of (*R*)-**5** prepared from D-proline led us to the conclusion that no racemization had occurred.



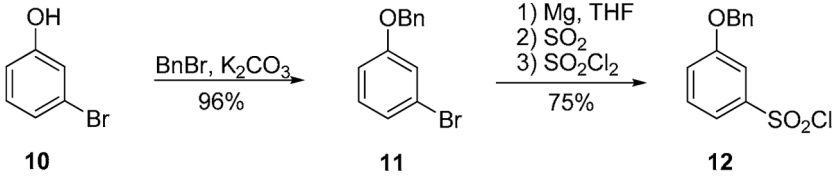
Scheme 1. Synthesis of Boc-homoprolinol from proline.



Scheme 2. Synthesis of SB 269970-HCl salt from Boc-homoprolinol.

The primary alcohol (**5**) underwent reaction with methanesulfonyl chloride in pyridine followed by substitution with 4-methyl piperidine in acetonitrile to give tertiary amine **6** in an overall yield of 65%.[2] The carbamate protecting group was removed by treatment by trifluoroacetic acid treatment, and the amine function reacted with the appropriate benzyl-protected arylsulfonyl chloride (**7**, Scheme 3). This gave sulfonamide **8** in near quantitative yield over two steps. The benzyl group was finally removed by hydrogenolysis at 1 bar over a Pd-C catalyst to give SB 269970 (**9**).[2]

3-Benzyloxy benzenesulfonyl chloride (**7**) was made according to a slight modification of a protocol by Pandya and coworkers.[13] First, 3-bromophenol (**10**, Scheme 3) was reacted with benzyl bromide in acetone in the presence of potassium carbonate to give 3-benzyloxy bromobenzene (**11**) in quantitative yield. This was then added to magnesium turnings in THF to give the corresponding Grignard reagent. For this particular bromide, it was essential for reaction success to heat the solution for only 15 min and not the full hour as suggested by Pandya et al.[13] Further reaction with sulfur dioxide and later oxidation by sulfuryl chloride gave the arylsulfonyl chloride (**12**, Scheme 3).



Scheme 3. Synthesis of sulfonyl chloride **12**.

In conclusion, we have demonstrated that the 5-HT_7 receptor antagonist SB 269970 (**9**) could be prepared efficiently in enantiopure form from D-proline using an Arndt–Eistert approach. The synthetic sequence gave an overall yield of 23% over 10 steps and can be used for gram-scale preparation of SB 269970 for antidepressive and anti-anxiety tests in animal models.

EXPERIMENTAL

All glassware used for reactions under nitrogen was dried in the oven (~120°C). Anhydrous solvents were dried by standard procedures.[14] Thin-layer chromatography (TLC) was performed on silica-coated aluminium sheets (Merck 60 F_{254}). They were visualized in ultraviolet (UV) light or by staining with ninhydrin, $KMnO_4$, or anisaldehyde.

Flash chromatography was done using Fluka silica gel 60 (230–400 mesh) as stationary phase.

NMR spectra were recorded on a Varian Mercury 400 spectrometer. Optical rotation was measured at 293 K on a PE-314 polarimeter with the unit $deg \cdot cm^2/g$, and concentrations were reported in g/100 mL. Melting points were measured on a Büchi B-540 instrument and are uncorrected. Mass spectra (MS) were recorded at a Micromass LC-TOF instrument using electrospray ionization (ESI). D-Proline ($[\alpha]_D$ 74.4 (*c* 4.0, H_2O), $[\alpha]_D$ 75.4 (*c* 1.0, CH_3OH)) was purchased from FluoroChem and used without purification. 3-Bromophenol was purchased from Sigma-Aldrich.

(*R*)-(1-*tert*-Butoxycarbonyl)proline (1)

Di-*tert*-butyl dicarbonate (20.9 g, 0.096 mol) was added to a solution of D-proline (10.0 g, 0.087 mol) in THF (60 mL) and a 2 M solution of aqueous sodium hydroxide (60 mL). The reaction mixture was stirred at room temperature overnight. The THF was then evaporated, and the resulting mixture was washed with diethyl ether. The aqueous phase was acidified to pH ~2–3 by addition of an aqueous solution of 1% hydrochloric acid and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give the Boc-protected proline (15.3 g, 82%) as white crystals. Further purification was not necessary. Mp 132.6–135.2°C; lit. 133–134°C.[15] R_f 0.67 (EtOAc/CH_3COOH 95:5). $[\alpha]_D$ 46.6 (*c* 1.0, CH_3OH); lit. $[\alpha]_D$ 63.6 (*c* 1.0, acetic acid).[15] ^1H NMR ($CDCl_3$, 400 MHz) δ 9.56 (bs, 0.5H), 4.38–4.32 (m, 0.5H), 4.28–4.21 (m, 0.5H),

3.61–3.30 (m, 2H), 2.38–2.21 (m, 1H), 2.12–1.83 (m, 3H), 1.48, 1.42 (9H, appearing as two singlets). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.1, 176.1, 156.3, 154.3, 81.4, 80.6, 59.4, 59.2, 47.2, 46.6, 31.0, 29.0, 28.6, 28.5, 24.5, 23.9. Double signals in H and C NMR are seen because of the presence of rotamers. HRMS(ES): calcd. for $C_{10}H_{17}NO_4Na$ 238.1055; found 238.1051.

(*R*)-2-Isobutoxycarbonyloxycarbonyl-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (2)

Triethylamine (9.8 mL, 0.072 mol) and isobutylchloroformate (3.3 mL, 0.026 mol) were added to a solution of Boc-proline (**1**) (5.0 g, 0.024 mol) in dry CH_2Cl_2 (40 mL) at 0°C. The reaction mixture was stirred under nitrogen at 0°C for 2 h before dilution with CH_2Cl_2. The organic layer was washed twice with a 1% hydrochloric acid, three times with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to give anhydride **2** (6.7 g, 91%) as a colorless oil. No further purification was necessary. R_f 0.59 (petrol/EtOAc 5:1). $[\alpha]_D$ 37.9 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.41–4.35 (m, 0.5H), 4.31–4.26 (m, 0.5H), 4.08–4.01 (m, 2H), 3.61–3.35 (m, 2H), 2.35–2.23 (m, 1H), 2.18–1.85 (m, 4H), 1.45, 1.43 (9H, appearing as two singlets), 0.96 (d, 6H, *J* 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 153.6, 149.2, 80.9, 76.0, 59.3, 46.6, 30.8, 29.7, 28.3, 23.9, 18.9. Double signals in ^{1}H NMR are seen because of the presence of rotamers.

(*R*)-*tert*-Butyl 2-(2-diazoacetyl)pyrrolidine-1-carboxylate (3)

Caution: This reaction was carried out behind a blast shield in a darkened fume hood using Clearfit® glassware. Diazald (21.4 g) in diethylether (140 mL) was added via an addition funnel over 30 min to a magnetically stirred, oil bath–heated (70°C), 250-mL, round-bottomed flask containing potassium hydroxide (KOH) (6 g, 0.11 mol), H_2O (20 mL), and diethylene glycol monoethyl ether (35 mL). The evaporating yellow ethereal diazomethane solution was condensed and put into a receiving, ice bath–cooled (0°C), 250-mL, round-bottomed flask containing anhydride **2** (3.33 g, 10.6 mmol) in dry diethylether (55 mL). After the addition of the 140-mL Diazald in diethylether, diethylether (30 mL) was added via the addition funnel to drive out the remaining diazomethane, which could be seen by the distillate turning colorless. The receiving flask was then allowed to warm to room temperature and left to stir for another 3 h. The reaction mixture was then flushed with nitrogen for 30 min and afterward heated to 43°C for 30 min to concentrate the reaction

mixture, which was then transferred to a regular round-bottomed flask and evaporated to dryness under reduced pressure. The material was purified by flash chromatography (petrol/EtOAc 3:1) to give diazoketone **3** (2.25 g, 89%) as a yellow oil. R_f 0.38 (petrol/EtOAc 2:1). $[\alpha]_D$ 119.3 (*c* 1.0, $CHCl_3$). Lit. $[\alpha]_D$ −118 (*c* 1.0, CH_3OH) for antipode.[9] NMR data was in accordance with those previously reported for the antipode.[9] HRMS(ES): calcd. for $C_{11}H_{17}N_3O_3Na$ 262.1168; found: 262.1168.

(*R*)-1-*tert*-Butoxycarbonyl-2-carbomethoxymethylpyrrolidine (4)

A solution of silver benzoate (210 mg, 0.92 mmol) in Et_3N (4 mL, 28 mmol) was added to a stirred solution of diazoketone **3** (2.20 g, 9.2 mmol) in CH_3OH (37 mL, 0.92 mol) at 0°C. The reaction mixture was stirred overnight in the dark under an atmosphere of nitrogen and allowed to reach room temperature. The solvent was then evaporated under reduced pressure, and the residue was taken up in ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Filtration and concentration gave a black oil, which was purified by flash chromatography (petrol/EtOAc 10:1) to give methylester **4** (1.90 g, 85%) as a colorless oil. R_f 0.6 (petrol/EtOAc 3:1). $[\alpha]_D$ 32.1 (*c* 1.0, $CHCl_3$). $[\alpha]_D$ 39.8 (*c* 1.0, CH_3OH). Lit. −43.2 (*c* 1.0, CH_3OH) for antipode.[9] NMR spectra were identical with those previously reported for the antipode.[9] HRMS(ES): calcd. for $C_{12}H_{21}NO_4Na$ 266.1368; found:266.1360.

(*R*)-*tert*-Butyl 2-(2-Hydroxyethyl)pyrrolidine-1-carboxylate (5)

Lithium borohydride (440 mg, 20 mmol) was added to a stirred solution of methylester **4** (1.63 g, 6.7 mmol) in dry THF (18 mL). The reaction mixture was stirred at 50°C under nitrogen for 3 h before cooling to ambient temperature and was diluted with H_2O and ethyl acetate. The aqueous layer was acidified to pH ~2–3 by addition of 3% hydrochloric acid. The organic phase was then washed twice with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by flash chromatography (petrol/EtOAc 3:1) to give **5** (1.18 g, 82%) as a colorless oil. R_f 0.26 (petrol/EtOAc 2:1). $[\alpha]_D$ −16.5 (*c* 1.0, benzene); $[\alpha]_D$ 6.9 (*c* 1.0, $CHCl_3$); lit. $[\alpha]_D$ −57.6 (*c* 1.0, benzene) for antipode.[16] $[\alpha]_D$ −13.8 (*c* 1.1, $CHCl_3$) for antipode.[17] ^1H NMR ($CDCl_3$, 400 MHz) δ 4.15–4.08 (m, 1H), 3.63–3.52 (m, 2H), 3.42–3.25 (m, 3H), 2.04–1.82 (m, 3H), 1.72–1.56 (m, 2H), 1.46 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.6, 79.9, 59.2, 53.6, 46.5, 38.5, 31.3, 28.5, 23.6. The NMR data were largely in accordance with previously reported data for the antipode.[18] HRMS(ES): calcd. for $C_{11}H_{21}NO_3Na$: 238.1419; found:238.1423.

To prove that no racemization had occurred, HPLC analysis of primary alcohol (*R*)**5** and (±)**5** was carried out as follows: 10 μL of sample [**5** or (±)**5,** 5 mg/mL in *i*PrOH/hexane] was analyzed (λ 202.2 nm) on an AD28 HPLC column (eluent: *i*PrOH/hexane 5:95, flow: 1 mL/min). *t*[(*R*)**5**] 14.6 min. only; *t*[(±)**5**] 10.4 and 15.1 min.

(*R*)-2-[2-(4-Methyl-piperidine-1-yl)-ethyl]-pyrrolidine-1-carboxylic acid *tert*-Butyl Ester (6)

Alcohol **5** (1.00 g, 4.6 mmol) was dissolved in dry pyridine (20 mL). Methanesulfonyl chloride (0.50 mL, 6.0 mmol) was added to the solution at 0°C, and the reaction mixture was stirred under nitrogen and at 0°C for 2 h before being diluted with CH_2Cl_2 and washed with H_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to give the crude mesylate. This was dissolved in dry acetonitrile (5 mL) containing 4-methylpiperidine (1.1 mL, 9.2 mmol). The mixture was stirred at room temperature and overnight and then heated to 50°C for 90 min to obtain full conversion. The acetonitrile was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 and washed twice with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, and removal of the solvent gave a yellow oil, which was purified by flash chromatography (petrol/EtOAc/Et_3N 49.5:49.5:1) to give amine **6** (0.90 g, 65%) as a colorless oil. R_f 0.49 (petrol/EtOAc/Et_3N 49.5:49.5:1). $[\alpha]_D$ 30.5 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 3.85–3.72 (m, 1H), 3.46–3.28 (m, 2H), 2.95–2.87 (m, 2H), 2.40–2.25 (m, 2H), 2.10–1.55 (m, 10H), 1.44 (s, 9H), 1.39–1.15 (m, 3H), 0.89 (d, 3H, *J* 6.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 79.2, 56.2, 55.9, 54.3, 46.4, 34.3, 32.1, 31.6, 30.9, 28.7, 23.9, 22.0. HRMS(ES): calcd. for $C_{17}H_{32}N_2O_2Na$ 319.2364; found 319.2354.

(*R*)-1-(2-(1-(3-(Benzyloxy)phenylsulfonyl)pyrrolidin-2-yl)ethyl)-4-methylpiperidine (8)

Boc-protected tertiary amine **6** (560 mg, 1.89 mmol) was dissolved in CH_2Cl_2/trifluoroacetic acid (1:1, 10 mL) and stirred under nitrogen and at ambient temperature for 30 min. The solvents were evaporated under reduced pressure, and the remaining salt was dissolved in aqueous NaOH (2 M, 10 mL) at 0°C. To this solution was added freshly prepared

3-(benzyloxy)benzene-1-sulfonyl chloride (**7**) (1.01 g, 3.6 mmol) in diethylether (12 mL). The biphasic mixture was vigorously stirred at 0°C and during the night allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2 and made acidic by adding an aqueous solution of 3% hydrochloric acid. The water phase was removed, and the organic phase was washed three times with a sodium carbonate solution. It was dried over $MgSO_4$, and the solvent was removed. The residue was dissolved in CH_2Cl_2 and was again washed with sodium carbonate three times and dried. Removal of the solvent gave the title compound (806 mg, 96%) as a light pink oil without the need for further purification. R_f 0.67 (petrol/EtOAc/Et_3N 65.3:32.7:2). $[\alpha]_D$ 68.8 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45–7.31 (m, 8H), 7.21–7.15 (m, 1H), 5.13 (s, 2H), 3.66–3.57 (m, 1H), 3.38–3.31 (m, 1H), 3.15–3.06 (m, 1H), 3.01–2.86 (m, 2H), 2.49–2.30 (m, 2H), 2.11–1.85 (m, 3H), 1.81–1.18 (m, 10H), 0.91 (d, 3H, *J* 6.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.0, 138.9, 136.4, 130.3, 128.9, 128.4, 127.7, 120.2, 120.0, 113.5, 70.5, 59.2, 55.8, 54.2, 49.1, 34.4, 33.7, 31.1, 24.2, 22.1. HRMS(ES): calcd. for $C_{25}H_{34}N_2O_3SH$ 443.2368; found 443.2363. The ^1H NMR data were similar with those previously reported.[2]

(*R*)-3-(2-(2-(4-Methylpiperidin-1-yl)ethyl)pyrrolidin-1-ylsulfonyl)phenol Hydrochloric Salt (SB 269970) (9)

A solution of sulfonamide **8** (1.00 g, 2.3 mmol) in ethanol (30 mL) and concentrated hydrochloric acid (1.0 mL) was hydrogenated over palladium on charcoal (10%, 180 mg) at room temperature for 72 h. During the course of the reaction, more palladium catalyst was added twice. The reaction mixture was filtered through celite with methanol and concentrated. The residue was dissolved in hot methanol and filtered. Removal of the solvent gave a solid, which was purified by flash chromatography ($CHCl_3/CH_3OH$ 9:1) to give SB 269970 (0.69 g, 79%) as a fine white powder. R_f 0.38 ($CHCl_3/CH_3OH$ 9:1). $[\alpha]_D$ 35.2 (*c* 1.0, DMSO). ^1H NMR (DMSO-d_6, 400 MHz) δ 10.3 (s, 1H), 10.1 (b s, 1H), 7.47 (t, 1H, *J* 7.6 Hz), 7.32–7.24 (m, 2H), 7.14 (dd, 1H, *J* 1.6 Hz, *J* 8.4 Hz), 3.77–3.67 (m, 1H), 3.54–3.40 (m, 2H), 3.35–3.29 (m, 1H), 3.26–2.81 (m, 6H), 2.14–1.88 (m, 4H), 1.70–1.41 (m, 6H), 0.96 (d, 3H, *J* 6.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 158.4, 137.7, 130.8, 120.6, 118.0, 114.2, 58.2, 53.5, 52.1, 48.8, 30.9, 30.5, 29.7, 28.4, 23.7, 21.4. ^1H NMR data were similar to those previously reported.[2] HRMS(ES) calcd. for $C_{18}H_{28}N_2O_3SH$ 353.1899; found 353.1893.

1-(Benzyloxy)-3-bromobenzene (11)

K_2CO_3 (16 g, 116 mmol) and benzyl bromide (7.55 mL, 63.6 mmol) were added to a solution of 3-bromophenol (10.0 g, 57.8 mmol) in dry acetone (60 mL). The reaction mixture was refluxed for 2 h before the solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and H_2O. The aqueous phase was further extracted three times with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a solid. The product was recrystallized from petrol, and the mother liquor was purified by flash chromatography (petrol → petrol/CH_2Cl_2 95:5) to give the desired product (combined yield: 16.9 g, 96%). Mp. 60.9–61.5 (petrol); lit.: 61–62°C.[18] R_f 0.41 (petrol/CH_2Cl_2 95:5). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44–7.32 (m, 5H), 7.17–7.09 (m, 3H), 6.93–6.90 (m, 1H), 5.05 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.8, 136.6, 130.8, 128.9, 128.4, 127.7, 124.3, 123.0, 118.4, 114.1, 70.4. NMR data were similar to those previously reported.[19]

3-(Benzyloxy)benzene-1-sulfonyl Chloride (7)

Magnesium turnings (896 mg, 37 mmol) in dry THF (10 mL) were activated with addition of dibromoethane (0.5 mL) before benzylated bromophenol (**11**) (4.85 g, 18.4 mmol) in dry THF (20 mL) was added at such a rate that the solution was kept at a gentle reflux. The reaction mixture was further refluxed for 15 min before it was cooled to −40°C. Sulfur dioxide was bobbled through the solution for 5 min, and the solution was additionally stirred for 15 min at −40°C before SO_2Cl_2 (1.5 mL, 18.4 mmol) was added and the cold bath was removed. The solution was allowed to reach ambient temperature and stirred for an additional 15 min. The reaction mixture was then poured into an ice water/Et_2O mixture. The layers were separated, and the aqueous phase was extracted three times with Et_2O. The combined ethereal layers were then washed with aqueous saturated $NaHCO_3$ solution until pH ∼7, dried over $MgSO_4$, and concentrated. Flash column chromatography on silica (petrol/CH_2Cl_2 5:1) afforded sulfonyl chloride **7** (3.89 g, 75%) as light yellow crystals. R_f 0.25 (petrol/CH_2Cl_2 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68–7.29 (m, 9H), 5.15 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 145.5, 135.7, 130.9, 129.0, 128.8, 127.9, 122.7, 119.6, 112.6, 71.0. HRMS(ES): calcd. for $C_{13}H_{11}{}^{35}ClO_3SNa$ 305.0015; found 305.0013.

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