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Optically Active 1-Deuterio-1-phenylethane – Preparation and Proof of Enantiopurity

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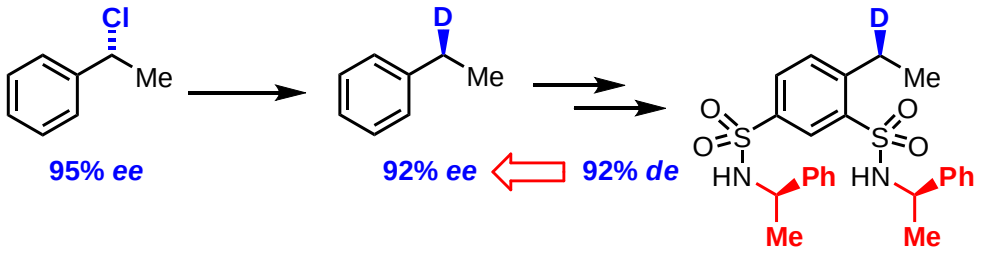
Abstract: Enantiopure (*S*)-(1-^{2}H)ethylbenzene was prepared in two steps from optically active (*S*)-1-phenylethanol *via* (*R*)-(1-chloroethyl)benzene (two inversions of configuration). Since the value for the specific rotation [α] is very low for the enantiomers of (1-^{2}H)ethylbenzene, the enantiopurity of the synthetic product could not be determined with certainty by polarimetry. Therefore, bissulfonamides were prepared by twofold chlorosulfonation (*para* and *ortho*) of (*S*)-(1-^{2}H)ethylbenzene and subsequent amidation with (*R*)- and (*S*)-α-phenethylamine. For both diastereoisomers, the (*R*,*R*,*S*)- and the (*S*,*S*,*S*)-sulfonamides, 92% *de* was determined by ^{1}H NMR spectroscopy. Therefore, it could be concluded, that (*S*)-(1-^{2}H)ethylbenzene had been obtained with 92% *ee*.

Key Topic: Stereospecific deuteration

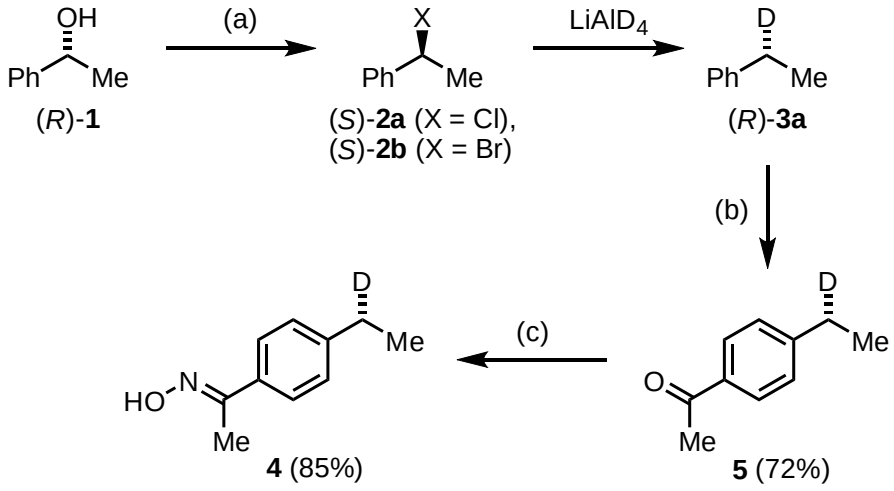
Graphical Abstract: Optically active (*S*)-(1-^{2}H)ethylbenzene was prepared from (*S*)-1-phenylethanol *via* the chloro compound. Its optical purity was determined by NMR spectroscopy after derivatization to a sulfonamide with (*R*)-α-phenethylamine.



Keywords: chirality, deuteration, hydrocarbons, NMR spectroscopy, sulfonamides

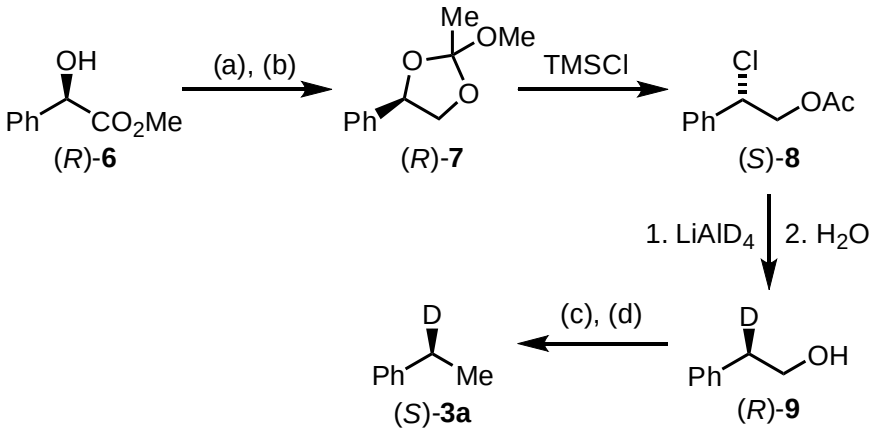
Introduction

Optically active 1-deuterio-1-phenylethane [(1-^{2}H)ethylbenzene, **3a**] was used in several mechanistic studies on the stereoselective α-hydroxylation of ethylbenzene (**3b**) by either chiral metal complexes[1] or microorganisms like fungi.[2] The title compound **3a** was first prepared by Eliel in 1949 by reduction of α-chloroethylbenzene (**2a**) with $LiAlD_4$ (Scheme 1).[3] The author started from (*R*)-1-phenylethanol (**1**), which was first converted with $SOCl_2$ to (*S*)-(–)-**2a**, before reduction with $LiAlD_4$ furnished hydrocarbon (*R*)-(–)-**3a** (Scheme 1). Interestingly, the only tool for determination of enantiopurity was at that time measurement of the specific rotation (α^{25}_{D} = –0.51°, neat, l = 2 dm). After Friedel-Crafts acetylation the respective ketone was transformed to its crystalline oxime, which showed after multiple recrystallizations no change of its specific rotation. Therefore, quantitative enantiopurity also for the starting material **3a** was assumed. It was furthermore assumed, that both of the two steps proceeded with inversion of configuration, thus, overall retention of configuration was proposed. The latter assumption was actually based on investigations by Trevoy and Brown.[4] The latest report (in the year 2010) on the preparation of both enantiomers of compound **3a** also started from phenylethanols **1**, but went *via* the respective bromo compounds **2b** as intermediate products.[5] Both enantiomers of intermediate product **2b** were obtained with 86% *ee*. Also in this publication it was assumed, that the compounds **3a** had "the same *ee* values, since the configuration cannot be changed during deuteration".



Scheme 1. Literature known preparation of optically active (1-^{2}H)ethylbenzene (**3a**) from 1-phenylethanol (**1**) and further derivatization to crystalline oxime **4**. Reagents: (a) $SOCl_2$ for X = Cl or $POBr_3$ for X = Br; (b) AcCl, $AlCl_3$; (c) NaOAc, HO-NH_2 · HCl.

The second route to enantiopure compound **3a** was published by Elsenbaumer and Mosher in 1979,[6] who started from methyl (*R*)-mandelate (**6**), which was first transformed with one inversion of configuration to chloroester **8** *via* the orthoester **7** (this compound was an optically active mixture of two epimers at the orthoester moiety, Scheme 2). Three further steps including another inversion gave hydrocarbon (*S*)-(+)-**3a**. The key advantage of this route is that it proceeds *via* the primary alcohol **9**, which was recrystallized after transformation into its 3,5-dinitrobenzoate. Therefore, quantitative enantiopurity of compound **9** was assumed. For this reason, this method is actually referred to by most authors who subsequently used either (*R*)-(–)-**3a** or (*S*)-(+)-**3a** in their investigations, although herein the determination of enantiopurity also relied on the optical rotation (α^{20}_D = +0.71°, neat, l = 1 dm).



Scheme 2. Modified preparation of optically active (1-^{2}H)ethylbenzene (**3a**) from methyl mandelate (**6**). Reagents: (a) $LiAlH_4$, (b) $MeC(OMe)_3$, (c) TosCl, pyridine, (d)

$LiAlH_4$.

To the best of our knowledge, the only determination of the optical purity of compound **3a** by a method different from optical rotation was published by Flood *et al.*,[7] who used (*R*)-**3a** [with 80% *ee* according to $[\alpha]^{20}_D$ = –0.65° (neat)] as intermediate product for the preparation of 8-(α-deuterioethyl)quinoline. The enantiopurity of this final product was determined to be 40% *ee* using an optically active, paramagnetic NMR shift reagent.

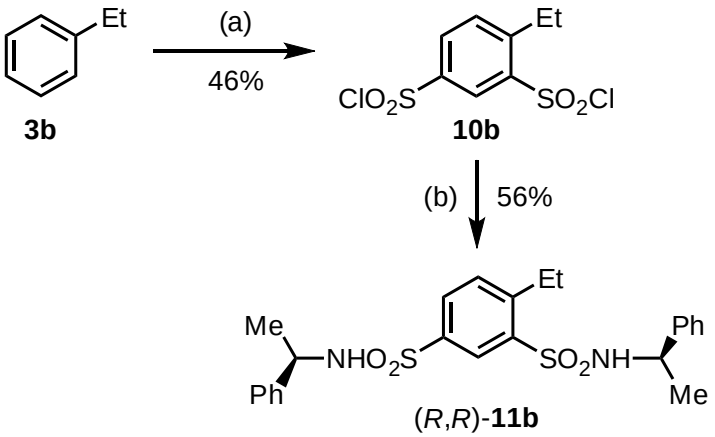
Elucidation of the stereochemistry of hydrocarbon-transforming enzyme reactions could provide valuable insights into the reaction mechanism as previously demonstrated for anaerobic transformation of *n*-hexane.[8] It has been shown, that the denitrifying betaproteobacterium *Aromatoleum aromaticum* EbN1 employs an intriguing Mo-containing, multisubunit enzyme (ethylbenzene dehydrogenase) to anaerobically (in the absence of O_2) hydroxylate the methylene carbon atom of ethylbenzene.[9] Furthermore, stereospecific formation of (*S*)-1-phenylethanol by ethylbenzene dehydrogenase has been demonstrated.[10]

Current perception of the reaction mechanism involves the formation of an intermediate carbocation.[11] However, it is unclear whether the reaction proceeds with retention, inversion or racemization at the methylene group of ethylbenzene. In particular, racemization would hint at the occurrence of a free carbenium ion in the transition state. We envisioned enantiopure (1-^{2}H)ethylbenzene (**3a**) to be a perfect substrate for investigations aiming at discriminating these mechanistic possibilities.

Anyhow, after a literature survey we had doubts on the enantiopurity of (*R*)-**3a** and (*S*)-**3a** as reported in the literature so far, since the determination of optical rotations is known to be often associated with large errors, in particular, if the absolute values are relatively low, like it is the case for compounds **3a**.[6] Furthermore, standard cuvettes require an amount of at least 7 mL of sample volume and, so far, the optical rotation was determined in a neat sample. Therefore, the objective of this study is the development of a reliable method to establish the enantiopurity based on NMR spectroscopy of diastereoisomeric derivatives.

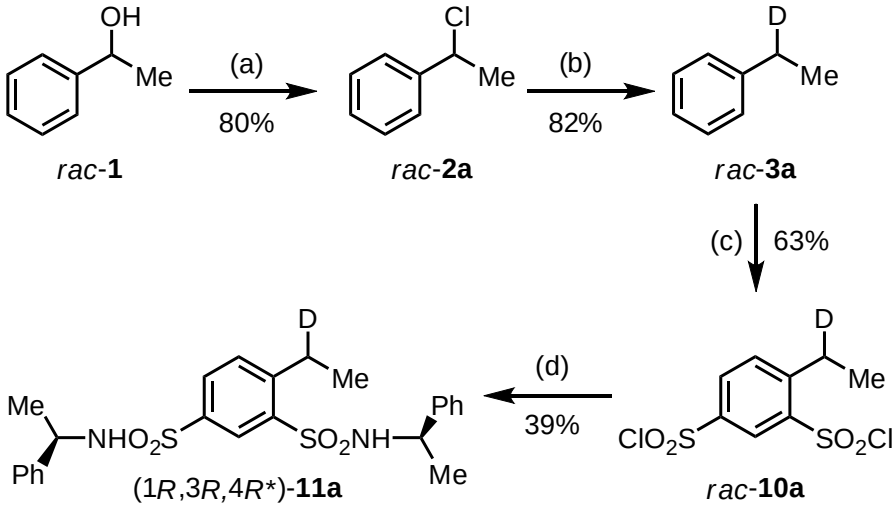
Results and Discussion

A chiral derivative of ethylbenzene (**3b**) would be the ideal tool for measuring the enantiopurity of (1-^{2}H)ethylbenzene (**3a**), e.g. by ^{1}H NMR spectroscopy. After some unsuccessful experimentation with Friedel-Crafts acylation reactions with optically active acid chlorides we decided to prepare the sulfonylchloride from ethylbenzene and react it with optically active amines. Indeed, the 4-ethylbenzenesulfonylchloride could be obtained with chlorosulfonic acid (full conversion within 3 h at ambient temperature) and it was subsequently converted with α-phenethylamine. However, since the *para*-product was formed, the methylene protons, although formally diastereotopic, appear still as a quartet in the proton NMR spectrum. For this reason, we aimed at double chlorosulfonation of ethylbenzene (**3b**) although due to the deactivating effect of the first (*para*) sulfonyl group, the second, *ortho*-substitution required rather harsh conditions (150°C for 19 h) and the yield was low (46% of compound **10b**, Scheme 3). The pains and drawbacks of double and threefold sulfonations of benzene derivatives have been experienced in the literature.[12] Anyhow, compound **10b** was converted with two equiv. of (*R*)-α-phenethylamine in the presence of pyridine to furnish bis-sulfonamide **11b** in 56% yield. Upon inspection of the ^{1}H NMR spectrum the diastereotopic methylene protons indeed appeared as the AM-part of an AMX_3 spin system with sufficient baseline resolution (Figure 1A, $\Delta\delta$ = 0.12 ppm).



Scheme 3. Twofold chlorosulfonation of ethylbenzene (**3b**) and conversion to bis-sulfonamide **11b**. Reagents and conditions: (a) 6 equiv. $ClSO_3H$, –78→23°C, 3 h; 150°C, 19 h; (b) 2.4 equiv. (*R*)-$PhCH(NH_2)Me$, 4 equiv. pyridine, CH_2Cl_2, 40°C, 20 h.

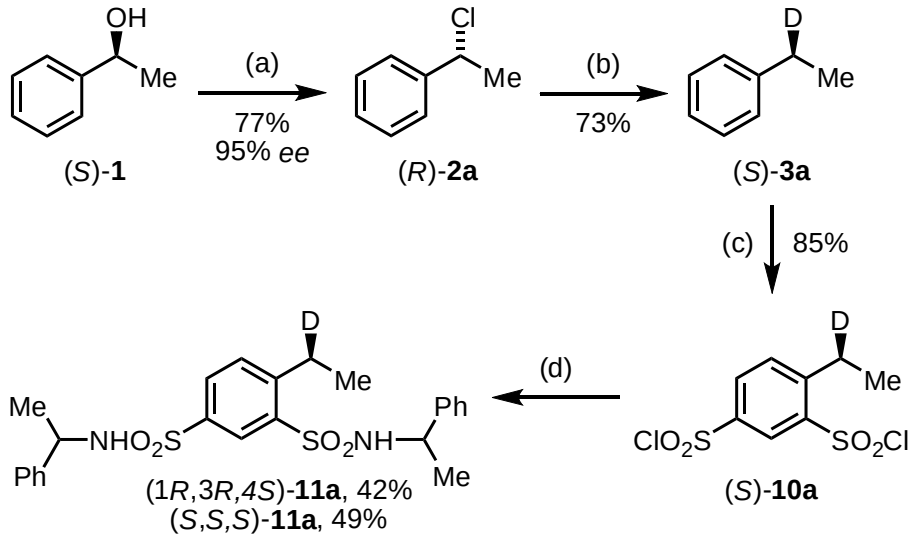
We then turned to the preparation of bis-sulfonamide **11a** from racemic (1-^{2}H)ethylbenzene (**3a**) and, therefore, started with racemic alcohol **1**, which was converted to chloro compound **2a** (Scheme 4). This intermediate was investigated by GLC on a chiral phase and, fortunately, baseline resolution of both enantiomers of compound **2a** was achieved. It was then reduced with $LiAlD_4$ under formation of racemic hydrocarbon **3a**. The latter material was further transformed using the conditions established before into bis-sulfonamide **11a**, which was obtained according to ^{1}H NMR spectroscopy as a mixture of two diastereoisomers (ratio 1 : 1). In particular, the protons at the CHD α-carbon atom were detected as two distinguished multiplets, one for each diastereoisomer, which appear as quartets broadened by the $^2J(^1H,^2H)$ coupling at δ = 2.83 and 2.90 ppm (Figure 1B).



Scheme 4. Preparation of racemic (1-^{2}H)ethylbenzene (**3a**) and conversion to bis-sulfonamide **11a** (two diastereoisomers, *dr* 1:1). Reagents and conditions: (a) 1.1 equiv. $SOCl_2$, Et_2O, 23°C, 20 min; (b) 2.0 equiv. $LiAlD_4$, THF, 75°C, 20 h; (c) 6 equiv. $ClSO_3H$, CH_2Cl_2, –78→23°C, 3 h; 95°C, 16 h; (d) 3.0 equiv. (*R*)-PhCH(NH_2)Me, 3.2 equiv. pyridine, CH_2Cl_2, 40°C, 20 h.

With this preliminary result in the racemic series we turned to the preparation of enantiopure hydrocarbon **3a** and therefore started with (*S*)-phenylethanol (**1**) (Scheme 5). For the preparation of optically active (1-chloroethyl)benzene (**2a**) we relied on a recent report by Huy *et al.*, who developed excellent reaction conditions for the stereoselective nucleophilic displacement of a secondary alcohol function to the respective chloro compound with inversion of configuration.[13] Compound (*R*)-**2a** could be obtained with 77% yield and 95% *ee*, as was established by GLC on a chiral phase. Reduction with $LiAlD_4$ gave the title compound (*S*)-**3a**. The optical rotation was mea-

sured in pentane solution (c = 1 g L^{-1}) to be zero, which actually points out the problems associated with the determination of enantiopurity by this method. Anyhow, further transformation to bis-sulfonamide (1*R*,3*R*,4*S*)-**11a** with (*R*)-phenethylamine gave a material, which was a single diastereoisomer according to ^{1}H NMR spectroscopy (Figure 1C). Only minor residual signals of the diastereoisomer are observed at 2.83 ppm. In order to access this other diastereoisomer **11a** for comparative NMR investigations, we also prepared compound (*S*,*S*,*S*)-**11a** from (*S*)-phenethylamine. Figure 1D shows its ^{1}H NMR spectrum. Now only residual signals at 2.90 ppm are observed. Since the integration of the respective multiplets could not be executed with high accuracy, we have acquired proton decoupled ^{1}H NMR spectra of all four isomers by irradiation of the methyl protons at 1.2 ppm. Figures 2A–2D show the respective spectra. For the protio-compound (*R*,*R*)-**11b** an AB-system with ^2J = 15 Hz was obtained (Figure 2A). The epimeric mixture of (1*R*,3*R*,4*R**)-**11a** shows two singlets at 2.90 and 2.84 ppm with equal integrals (Figure 2B). Finally, the spectra of the two diastereomerically and optically pure isomers (1*R*,3*R*,4*S*)-**11a** (Figure 2C) and (*S*,S,*S*)-**11a** (Figure 2D) show the same singlets with of course significantly different integrals (1.00 *vs*. 0.04 and 0.04 *vs*. 1.00, resp.). From this ratio the enantiopurity of compound (*S*)-**3a** was determined to be 92% *ee*. Please remind that the optical rotation of this material was determined to be zero (at c = 1 g L^{-1} in pentane).



Scheme 5. Preparation of optically active (1-^{2}H)ethylbenzene (**3a**) and conversion to bis-sulfonamide **11a** (two diastereoisomers). Reagents and conditions: (a) 1.5 equiv. PhCOCl, 0.2 equiv. 1-formylpyrrolidine, 23°C, 24 h; (b) 2.0 equiv. $LiAlD_4$, THF, 75°C, 20 h; (c) 6 equiv. $ClSO_3H$, –78→23°C, 3 h; 95°C, 16 h; (d) 3.0 equiv. (*R*)-PhCH(NH_2)Me or (*S*)-PhCH(NH_2)Me, 3.2 equiv. pyridine, CH_2Cl_2, 40°C, 20 h.

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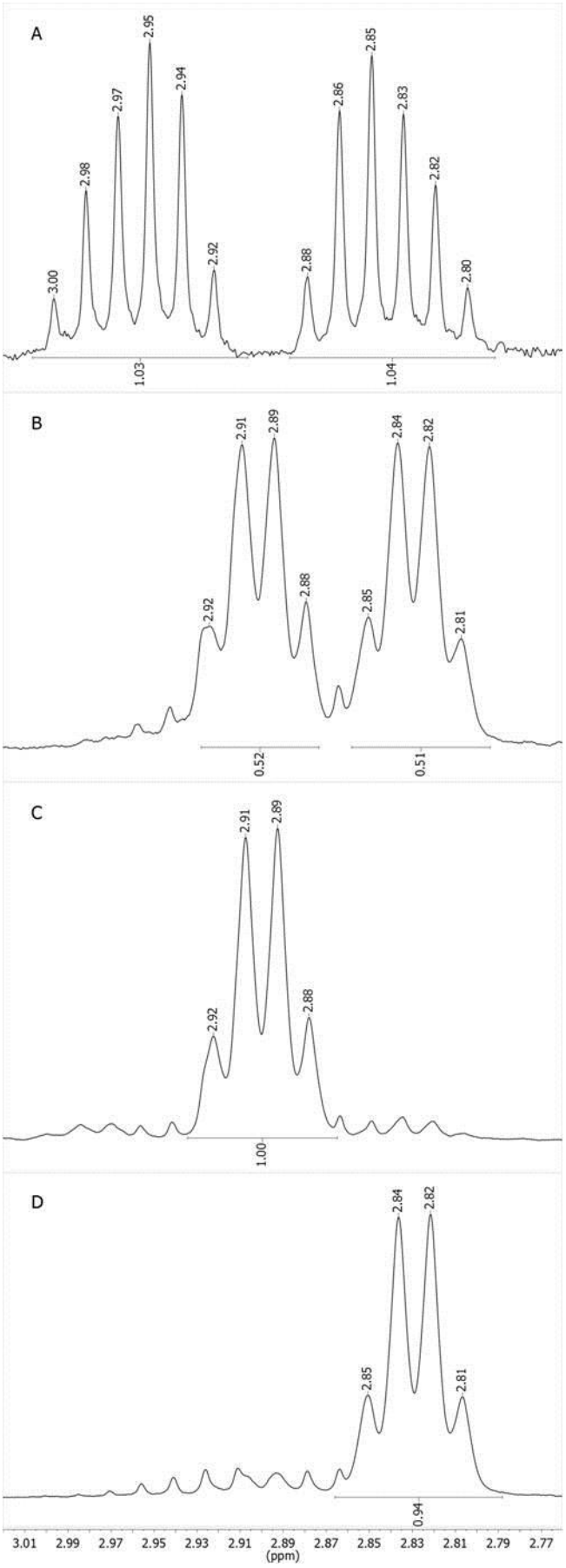

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Figure 1. Methylene region of the ^{1}H NMR-spectra (500 MHz, $CDCl_3$) of compounds (*R*,*R*)-**11b** (A), (1*R*,3*R*,4*R**)-**11a** (B), (1*R*,3*R*,4*S*)-**11a** (C) and (*S*,*S*,*S*)-**11a** (D).

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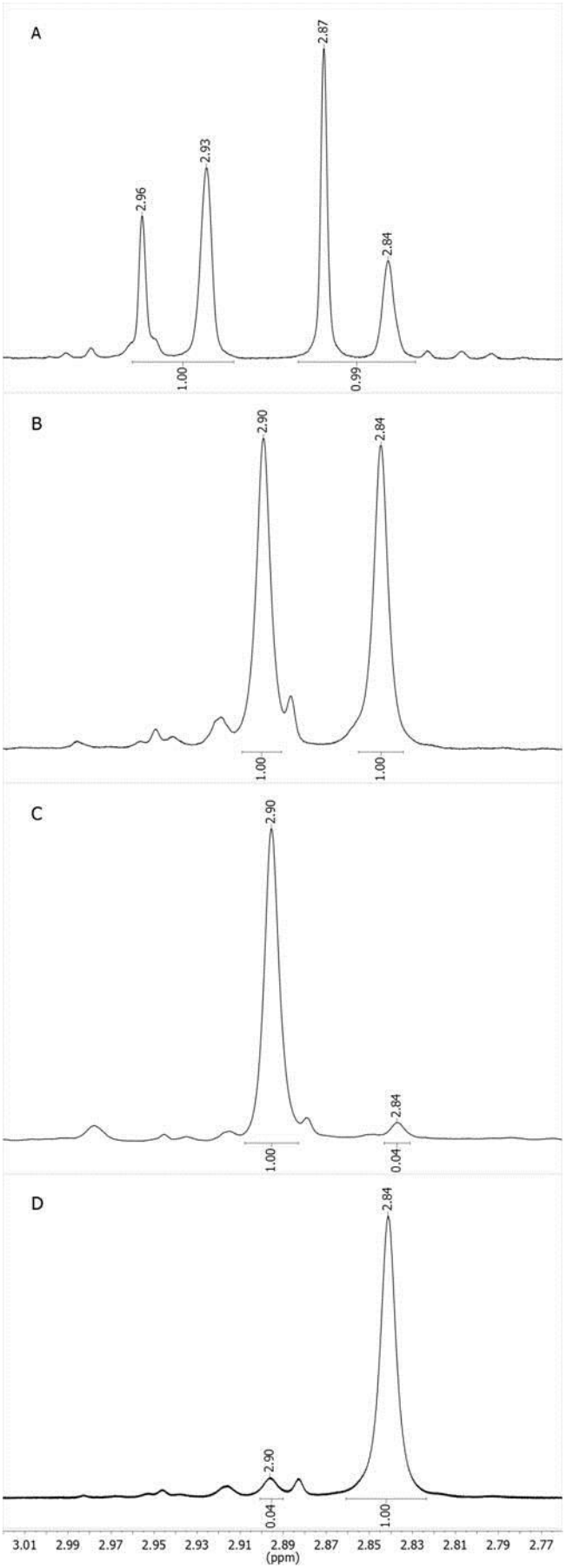

Figure 2. Methylene region of the ^{1}H NMR-spectra (500 MHz, $CDCl_3$) with proton de-

coupling by irradiation of the methyl group at 1.2 ppm of compounds (*R*,*R*)-**11b** (A), (1*R*,3*R*,4*R**)-**11a** (B), (1*R*,3*R*,4*S*)-**11a** (C) and (*S*,*S*,*S*)-**11a** (D).

Conclusion

Optically active (1-^{2}H)ethylbenzene (**3a**) was reported to be a useful substrate for mechanistic investigations in metal catalysis and bioorganic chemistry. It's preparation from optically active 1-phenylethanol (**1**) by twofold nucleophilic displacement *via* α-chloro- or bromoethylbenzene (**2a** or **2b**) was reported before in the literature. However, the determination of the enantiopurity of the title compound **3a** was so far relying on the optical rotation. This methodology is generally associated with relatively large uncertainty. Even worse in this case is the very low [α] for compound **3a** with the necessity to obtain the value of α in a neat sample, i.e. without dilution by solvent. Since we were aiming to prepare compound **3a** in optically pure form for mechanistic investigations, we report herein a method for the determination of enantiopurity by NMR-spectroscopy of a derivative with additional stereocenters. First of all, we followed a recently published protocol[13] for the stereospecific preparation of α-chloroethylbenzene (*R*)-**2a** from (*S*)-1-phenylethanol (**1**) (77% yield). Enantiopurity of compound **2a** was determined by GLC on a chiral phase to be 95% *ee*. We then submitted this intermediate product **2a** to S_N2 reaction with $LiAlD_4$ and indeed obtained title compound (*S*)-**3a** in 73% yield, however, no optical rotation could be detected in pentane solution. We then submitted this product to twofold chlorosulfonation with $ClSO_3H$ (85% yield) and converted this intermediate with (*R*)- and (*S*)-α-phenethylamine and obtained two diastereoisomeric bissulfonamides (1*R*,3*R*,4*S*)- and (*S*,*S*,*S*)-**11a**. The diastereomeric ratio of both compounds was determined by ^{1}H NMR spectroscopy to be 25:1 in both cases (i.e. 92% *de*), therefore, it could be concluded, that (1-^{2}H)ethylbenzene (*S*)-**3a** had an enantiopurity of 92% *ee*. Consequently, the nucleophilic substitution from chloro compound **2a** (95% *ee*) to product **3a** (92% *ee*) was proceeding with almost full inversion of configuration.

Experimental Section

General. All synthetic transformations were performed under inert conditions (nitrogen atmosphere, exclusion of air and moisture). Preparative column chromatography was carried out using Merck SiO_2 (35–70 µm, type 60 A) with hexanes, *n*-pentane, *tert*-butylmethylether (MTBE), and diethyl ether as eluents. TLC was performed on aluminum plates coated with SiO_2 F_{254}. ^1H, ^2H and ^{13}C NMR spectra were recorded on Bruker Avance DRX 500 and 300 instruments. Multiplicities of carbon signals were determined with DEPT experiments. HRMS spectra of products were obtained with Waters Q-TOF Premier (ESI) or Thermo Scientific DFS (EI) spectrometers. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a diamond ATR unit. Optical rotations were determined with a with a Perkin Elmer polarimeter 343. GLC analyses were performed on a Focus GC (Thermo-Fisher) on a chiral Lipodex E capillary column (Macherey-Nagel, 25 m, 0.25 mm) with H_2 as carrier gas. All starting materials were commercially available.

***rac*-(1-Chloroethyl)benzene (*rac*-2a).** At 0°C (ice-water bath), $SOCl_2$ (13.2 mmol, 1.57 g, 1.1 eq) was added to a solution of 1-phenylethanol (*rac*-**1**) (12.0 mmol, 1.47 g, 1.0 eq) in abs. Et_2O (6 mL) and the mixture was stirred at ambient temperature for 20 min. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine (each 10 mL), dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was chromatographed (SiO_2, *n*-pentane, R_f = 0.50) to yield compound *rac*-**2a** (1.35 g, 9.60 mmol, 80%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.86 (d, *J* = 6.9 Hz, 3H), 5.11 (q, *J* = 6.9 Hz, 1H), 7.28–7.40 (m, 3H), 7.40–7.46 (m, 2H) ppm. All other data were in accordance with the literature.[13] GLC (Lipodex E, 5 min at 50°C, then 1 K min^{-1} to 90°C, then 10 K min^{-1} to 180°C): t_R(*R*) = 37.51 min, t_R(*S*) = 40.52 min. C_8H_9Cl (140.61 g mol^{-1}).

(*R*)-(1-Chloroethyl)benzene [(*R*)-2a]. Following the procedure of Huy *et al.*,[13] benzoyl chloride (30.0 mmol, 4.22 g, 1.5 eq) was added at 0°C (ice-water bath) to a solution of 1-phenylethanol (*S*)-**1** (20.0 mmol, 2.44 g, 1.0 eq) and 1-formylpyrrolidine (4.0 mmol, 0.40 g, 0.2 eq) over a period of 5 min and the mixture was stirred for 2 h at 0°C and finally for 24 h at ambient temperature. Ethanolamine (40.0 mmol, 2.44 g, 2.0 eq) was added at ambient temperature and the mixture was stirred for 30 min at

ambient temperature. It was then diluted with Et_2O (60 mL), and at 0°C (ice-water bath), saturated aqueous $NaHCO_3$ (20 mL) and water (10 mL) were added and the mixture was stirred for 5 min at 0°C. The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and the solvent was evaporated (40°C, 100 mbar, 2 min). The residue was chromatographed (21.1 g SiO_2, *n*-pentane/Et_2O 200:1, R_f = 0.66) to yield compound (*R*)-**2a** (2.16 g, 15.4 mmol, 77%, 95% *ee*) as a colorless oil. All data were in accordance with the racemate. GLC (Lipodex E, 5 min at 50°C, then 1 K min^{-1} to 90°C, then 10 K min^{-1} to 180°C): t_R(*R*) = 37.34 min (major), t_R(*S*) = 40.91 min (minor), 95% *ee*. $[\alpha]_D^{20}$ = +113.15° (CH_2Cl_2, 0.9 g L^{-1}). {lit.[13] $[\alpha]_D^{20}$ = +108.0 ($CDCl_3$, 8.8 g L^{-1}). C_8H_9Cl (140.61 g mol^{-1}).

***rac*-(1-^{2}H)Ethylbenzene (*rac*-3a).** At 0°C (ice-water bath), $LiAlD_4$ (5.3 mmol, 0.22 g, 2.0 eq) was added to a solution of *rac*-**2a** (2.6 mmol, 0.37 g, 1.0 eq) in abs. THF (20 mL) and the mixture was stirred for 20 h at 75°C. At 0°C (ice-water bath), it was diluted with ice-cold water (10 mL) and extracted with *n*-pentane (3 × 10 mL). The combined organic layers were washed with phosphoric acid (85%), water, saturated aqueous $NaHCO_3$ solution, again water and brine (each 30 mL), dried over $MgSO_4$, filtered and the solvent was evaporated (50°C, 950 mbar) to yield *rac*-**3a** (0.23 g, 2.15 mmol, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (dt, *J* = 7.6 Hz, *J* = 1.1 Hz, 3H), 2.67 (qt, *J* = 7.6 Hz, *J* = 2.0 Hz, 1H), 7.16–7.26 (m, 3H), 7.27–7.36 (m, 2H) ppm. ^{2}H NMR (77 MHz, $CDCl_3$): δ = 2.74 (s, 1D) ppm. All other data were in accordance with the literature.[5] C_8H_9D (107.07 g mol^{-1}).

(*S*)-(1-^{2}H)Ethylbenzene [(*S*)-3a]. Following the procedure for *rac*-**3a**, the product (*S*)-**3a** (1.19 g, 11.1 mmol, 73%) was obtained as a colorless oil from (*R*)-**2a** (2.15 g, 15.3 mmol) and $LiAlD_4$ (1.28 g, 30.5 mmol). All data were in accordance with the racemate. $[\alpha]_D^{20}$ = ±0.00° (*n*-pentane, 1.0 g L^{-1}). C_8H_9D (107.07 g mol^{-1}).

4-Ethyl-1,3-benzenedisulfonyldichloride (10b). At –78°C (cooling with dry ice-acetone), $ClSO_3H$ (56.5 mmol, 6.58 g, 6.0 eq) was added to ethylbenzene (**3b**) (9.40 mmol, 1.00 g, 1.0 eq) and the mixture was stirred for 3 h at 0°C, then 3 h at ambient temperature and finally for 19 h at 150°C. It was diluted with CH_2Cl_2 (10 ml) and washed with ice-cold water (3 × 10 mL). The organic layer was dried over $MgSO_4$,

filtered and concentrated by evaporation to yield 4-ethyl-1,3-benzenedisulfonyldichloride (**10b**) (1.32 g, 4.35 mmol, 46%) as a dark-yellow oil, which was used further without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.5 Hz, 3H), 3.33 (q, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 1H), 8.28 (dd, *J* = 8.3 Hz, *J* = 2.0 Hz, 1H), 8.71 (d, *J* = 2.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.66 (CH_3), 26.27 (CH_2), 127.64 (CH), 132.63 (CH), 133.40 (CH), 142.58 (C), 143.67 (C), 151.94 (C) ppm. IR (ATR): nu(tilde) = 3095 (w), 3069 (w), 2972 (w), 2939 (w), 1381 (vs), 1172 (vs), 699 (m), 657 (s), 610 (m), 586 (m), 577 (vs) cm^{-1}. HRMS (ESI, neg. mode): calcd. 300.9168 (for $C_8H_7Cl_2O_4S_2^-$); found 300.9171 [M – H$^+$]. $C_8H_8Cl_2O_4S_2$ (303.17 g mol^{-1}).

(*R*,*R*)-4-Ethyl-1,3-benzenedisulfonic acid bis(1-phenylethyl)amide [(*R*,*R*)-11b]. (*R*)-(+)-1-Phenylethylamine (3.96 mmol, 480 mg, 2.4 eq) and pyridine (6.60 mmol, 522 mg, 4.0 eq) were added to a solution of compound **10b** (1.65 mmol, 500 mg, 1.0 eq) in CH_2Cl_2 (5 mL) at 0°C (ice-water bath). After stirring the mixture at 40°C for 20 h it was cooled to ambient temperature and diluted with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine (each 5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was chromatographed (SiO_2, hexanes/MTBE 1:2, R_f = 0.50) to yield compound (*R*,*R*)-**11b** (438 mg, 0.93 mmol, 56%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.5 Hz, 3H), 1.43 (d, *J* = 6.9 Hz, 3H), 1.46 (d, *J* = 6.9 Hz, 3H), 2.85 (dq, *J* = 14.9 Hz, *J* = 7.5 Hz, 1H), 2.96 (dq, *J* = 14.9 Hz, *J* = 7.5 Hz, 1H), 4.41–4.53 (m, 2H), 4.74 (d, *J* = 7.2 Hz, 1H), 4.76 (d, *J* = 7.1 Hz, 1H), 6.95–7.05 (m, 4H), 7.09–7.20 (m, 7H), 7.63 (dd, *J* = 8.1 Hz, *J* = 2.0 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.75 (CH_3), 23.57 (CH_3), 23.65 (CH_3), 25.91 (CH_2), 53.93 (CH), 53.96 (CH), 126.02 (2 CH), 126.10 (2 CH),127.63 (CH), 127.73 (CH), 128.07 (CH), 128.54 (2 CH), 128.62 (2 CH), 130.42 (CH), 130.83 (CH), 138.61 (C), 139.10 (C), 141.26 (2 C), 147.46 (C) ppm. IR (ATR): nu(tilde) = 3277 (br), 2973 (w), 2929 (w), 1454 (m), 1425 (m), 1320 (s), 1147 (vs), 1104 (s), 1083 (s), 1018 (m), 961 (s), 873 (m), 842 (m), 762 (s), 698 (vs), 668 (s), 610 (s), 588 (vs) cm^{-1}. HRMS (ESI, pos. mode): calcd. 495.1383 (for $C_{24}H_{28}N_2NaO_4S_2^+$); found 495.1384 [M + Na$^+$]. $[\alpha]_D^{20}$ = +60.7° (CH_2Cl_2, 1 g L^{-1}). $C_{24}H_{28}N_2O_4S_2$ (472.62 g mol^{-1}).

***rac*-4-(1-^{2}H)Ethyl-1,3-benzenedisulfonyldichloride (*rac*-10a).** At –78°C (cooling with dry ice-acetone), $ClSO_3H$ (10.3 mmol, 1.20 g, 6.0 eq) dissolved in abs. CH_2Cl_2 (1 mL) was added to a solution of (1-^{2}H)ethylbenzene (*rac*-**3a**) (1.72 mmol, 184 mg, 1.0 eq) in abs. CH_2Cl_2 (2 mL) and the mixture was stirred for 3 h. During that time the mixture was allowed to warm up to 0°C and finally it was stirred for 16 h at 95°C. It was then diluted with CH_2Cl_2 (5 ml) and overlaid with ice-cold water (5 mL). Without mixing them, the layers were separated and aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and after filtration concentrated by evaporation to yield 4-(1-^{2}H)ethyl-1,3-benzenedisulfonyldichloride (*rac*-**10a**) (0.33 g, 1.1 mmol, 63%) as a dark-red oil which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (d, *J* = 7.4 Hz, 3H), 3.30 (qt, *J* = 7.4 Hz, *J* = 2.1 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 8.29 (dd, *J* = 8.3 Hz, *J* = 2.0 Hz, 1H), 8.69 (d, *J* = 2.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.57 (CH_3), 25.95 (t, *J* = 20.0 Hz, CHD), 127.57 (CH), 132.64 (CH), 133.47 (CH), 142.49 (C), 143.58 (C), 151.94 (C) ppm. IR (ATR): nu(tilde) = 3090 (w), 3075 (w), 2997 (w), 2979 (w), 2941 (w), 1375 (s), 1168 (s), 1100 (m), 1051 (m), 1026 (m), 831 (m), 696 (m), 676 (m), 653 (m), 606 (m), 572 (s), 560 (vs) cm^{-1}. HRMS (EI): calcd. 302.9298 (for $C_8H_7Cl_2DO_4S_2^+$); found 302.9304 [M^+]. $C_8H_7DCl_2O_4S_2$ (304.17 g mol^{-1}).

(1*R*,3*R*,4*R)-4-(1-^{2}H)Ethyl-1,3-benzenedisulfonic acid bis(1-phenylethyl)amide [(1*R*,2*R*,4*R**)-11a].** Following the procedure for (*R*,*R*)-**11b**, the product (1*R*,3*R*,4*R**)-**11a** (0.20 g, 0.42 mmol, 39%) was obtained from *rac*-**10a** (1.07 mmol, 325 mg), (*R*)-(+)-1-phenylethylamine (3.21 mmol, 388 mg) and pyridine (3.42 mmol, 270 mg) after chromatography (SiO_2, hexanes/MTBE 3:2, R_f = 0.22) as a colorless solid, mp. 55–70°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 7.6 Hz, 3H), 1.42 (d, *J* = 6.9 Hz, 3H), 1.45 (d, *J* = 6.9 Hz, 3H), 2.83 (q, *J* = 7.4 Hz, 0.5H), 2.90 (q, *J* = 7.4 Hz, 0.5H), 4.45–4.51 (m, 2H), 5.07 (d, *J* = 7.2 Hz, 1H), 5.17 (d, *J* = 7.3 Hz, 1H), 7.02–7.06 (m, 4H), 7.10–7.16 (m, 7H), 7.61 (dd, *J* = 8.1 Hz, *J* = 1.7 Hz, 1H), 8.11–8.14 (m, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.66 (CH_3), 23.56 (CH_3), 23.64 (CH_3), 25.62 (t, *J* = 19.6 Hz, CHD), 53.95 (CH), 53.98 (CH), 126.04 (2 CH), 126.12 (2 CH), 127.64 (CH), 127.74 (CH), 128.08 (CH), 128.56 (2 CH), 128.64 (2 CH), 130.44 (CH), 130.88 (CH), 138.73 (C), 139.24 (C), 141.35 (2 C), 147.49 (C) ppm. ^{2}H NMR (77 MHz, $CDCl_3$): δ = 2.93 (s, 1D) ppm. IR (ATR): nu(tilde) = 3277 (br), 3065 (w), 3029 (w), 2976 (w), 2936 (w), 1320 (s), 1151 (vs), 1118 (m), 1104 (s), 1083 (s), 1062 (m),

1018 (m), 962 (s), 910 (m), 875 (m), 762 (m), 698 (vs), 666 (s), 609 (s), 594 (s) cm^{-1}. HRMS (ESI, pos. mode): calcd. 480.1708 (for $C_{24}H_{27}DLiN_2O_4S_2^+$); found 480.1703 [M + Li^+]. $[\alpha]_D^{20}$ = +98.33° (CH_2Cl_2, 1 g L^{-1}). $C_{24}H_{27}DN_2O_4S_2$ (473.62 g mol^{-1}).

(*S*)-4-(1-^{2}H)Ethyl-1,3-benzenedisulfonyldichloride [(*S*)-10a]. Following the procedure for *rac*-**10a**, the product (*S*)-**10a** (0.63 g, 2.07 mmol, 85%) was obtained as a dark-red oil from (*S*)-**3a** (0.26 g, 2.44 mmol) and $ClSO_3H$ (1.70 g, 14.6 mmol). All data were in accordance with the racemate. $[\alpha]_D^{20}$ = +0.07° (CH_2Cl_2, 1.09 g L^{-1}). $C_8H_7DCl_2O_4S_2$ (304.17 g mol^{-1}).

(1*R*,3*R*,4*S*)-4-(1-^{2}H)Ethyl-1,3-benzenedisulfonic acid bis(1-phenylethyl)amide [(1*R*,3*R*,4*S*)-11a]. Following the procedure for (*R*,*R*)-**11b**, the product (1*R*,3*R*,4*S*)-**11a** (0.39 g, 0.82 mmol, 42%) was obtained from (*S*)-**10a** (1.97 mmol, 600 mg), (*R*)-(+)-1-phenylethylamine (5.92 mmol, 717 mg) and pyridine (6.30 mmol, 498 mg) after chromatography (SiO_2, hexanes/MTBE 2:3, R_f = 0.57) as a colorless solid. mp. 57–65°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 7.4 Hz, 3H), 1.42 (d, *J* = 6.9 Hz, 3H), 1.45 (d, *J* = 6.9 Hz, 3H), 2.90 (q, *J* = 7.4 Hz, 1H), 4.45–4.52 (m, 2H), 5.12 (d, *J* = 7.3 Hz, 1H), 5.23 (d, *J* = 7.4 Hz, 1H), 7.02–7.06 (m, 4H), 7.10–7.16 (m, 7H), 7.61 (dd, *J* = 8.1 Hz, *J* = 2.0 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.69 (CH_3), 23.56 (CH_3), 23.64 (CH_3), 25.61 (t, *J* = 20.1 Hz, CHD), 53.92 (CH), 53.96 (CH), 126.02 (2 CH), 126.10 (2 CH),127.62 (CH), 127.71 (CH), 128.06 (CH), 128.53 (2 CH), 128.61 (2 CH), 130.42 (CH), 130.86 (CH), 138.62 (C), 139.12 (C), 141.28 (C), 141.49 (2 C), 147.44 (C) ppm. ^{2}H NMR (77 MHz, $CDCl_3$): δ = 2.91 (s, 1D) ppm. IR (ATR): nu(tilde) = 3280 (br), 2979 (w), 2931 (w), 2886 (w), 1457 (m), 1428 (m), 1321 (s), 1153 (vs), 1106 (s), 1085 (s), 1063 (m), 1020 (m), 964 (s), 876 (m), 764 (m), 700 (vs), 669 (s), 590 (s) 560 (vs) cm^{-1}. HRMS (EI): calcd. 473.2548 (for $C_{24}H_{27}DN_2O_4S_2^+$); found 473.1544 [M^+]. $[\alpha]_D^{20}$ = +116.67° (CH_2Cl_2, 1.0 g L^{-1}). $C_{24}H_{27}DN_2O_4S_2$ (473.62 g mol^{-1}).

(*S*,*S*,*S*)-4-(1-^{2}H)Ethyl-1,3-benzenedisulfonic acid bis(1-phenylethyl)amide [(*S*,*S*,*S*)-11a]. Following the procedure for (*R*,*R*)-**11b**, the product (*S*,*S*,*S*)-**11a** (0.30 g, 0.63 mmol, 49%) was obtained from (*S*)-**10a** (1.3 mmol, 0.39 mg), (*S*)-(–)-1-phenylethylamine (3.83 mmol, 464 mg) and pyridine (3.83 mmol, 303 mg) after chromatography (SiO_2, hexanes/MTBE 2:3, R_f = 0.48) as a colorless solid, mp. 51–76°C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 7.4 Hz, 3H), 1.42 (d, *J* = 6.9 Hz, 3H), 1.45 (d, *J* = 6.9 Hz, 3H), 2.83 (q, *J* = 7.4 Hz, 1H), 4.45–4.51 (m, 2H), 5.10 (d, *J* = 7.3 Hz, 1H), 5.21 (d, *J* = 7.4 Hz, 1H), 7.01–7.05 (m, 4H), 7.10–7.17 (m, 7H), 7.62 (dd, *J* = 8.1 Hz, *J* = 2.0 Hz, 1H), 8.12 (d, *J* = 2.0 Hz, 1H) ppm. $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ = 14.69 (CH_3), 23.57 (CH_3), 23.65 (CH_3), 25.62 (t, *J* = 19.5 Hz, CHD), 53.93 (CH), 53.96 (CH), 126.02 (2 CH), 126.10 (2 CH),127.63 (CH), 127.72 (CH), 128.07 (CH), 128.53 (2 CH), 128.62 (2 CH), 130.42 (CH), 130.86 (CH), 138.62 (C), 139.11 (C), 141.27 (2 C), 147.45 (C) ppm. ^{2}H NMR (77 MHz, $CDCl_3$): δ = 2.96 (s, 1D) ppm. IR (ATR): nu(tilde) = 3294 (br), 2974 (w), 2931 (w), 2886 (w), 1457 (m), 1428 (m), 1321 (s), 1153 (vs), 1106 (s), 1085 (s), 1063 (m), 1020 (m), 964 (s), 876 (m), 764 (m), 700 (vs), 669 (s), 590 (s) 560 (vs) cm^{-1}. HRMS (ESI, pos. mode): calcd. 496.1445 (for $C_{24}H_{27}DN_2NaO_4S_2^+$); found 496.1443 [M + Na^+]. $[\alpha]_D^{20}$ = –91.67° (CH_2Cl_2, 1.0 g L^{-1}). $C_{24}H_{27}DN_2O_4S_2$ (473.62 g mol^{-1}).

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