Diastereoselective Hydrolysis of α,γ-Substituted γ-Sultones in the Asymmetric Synthesis of γ-Hydroxy Sulfonates

Dieter Enders,* Wacharee Harnying, Gerhard Raabe

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule, Professor-Pirlet-Str. 1, 52074 Aachen, Germany
Fax +49(241)8092127; E-mail: Enders@rwth-aachen.de

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Abstract: The hydrolysis of enantiopure α,γ-substituted γ-sultones with water under mild conditions leads to α,γ-substituted γ-hydroxy methyl sulfonates in very good yields and excellent diastereo- and enantiomeric excesses (de, ee ≥ 98%). The reaction proceeds via a S_N2 mechanism with inversion of configuration at the attacked γ-carbon atom whose absolute configuration was established by X-ray crystallography.

Key words: sultones, sulfonates, asymmetric synthesis, hydrolysis, ring-opening

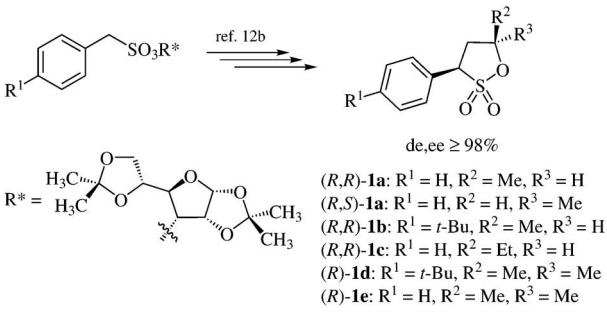
Derivatives of sulfonic acids are important constituents of living organisms.[1] However, in many cases nothing is known about their physiological properties. To get further insight into their mode of action a stereoselective access to these derivatives is desirable and compulsory for physiological tests. In our ongoing research concerning the chemistry of sultones we have now developed an efficient diastereo- and enantioselective approach to one class of these derivatives, the title γ-hydroxy sulfonates. Hitherto, only a few synthetic routes for the asymmetric synthesis of these interesting compounds have been described. Traynor et al. reported the facile synthesis of β-hydroxy sulfonates from optically active terpene epoxides by nucleophilic oxirane opening with sodium sulfite.[2] The asymmetric synthesis of β-hydroxy sulfonates by BINAP/Ru-catalyzed hydogenation of β-keto sulfonates has been described by Noyori, Kitamura et al.[3] There have been a few reports on the synthesis of the marine natural product, D-cysteinolic acid (2-amino-3-hydroxy-propanesulfonic acid), either starting from protected α-amino acids[4] or via ring-opening of chiral aziridines with sodium bisulfite.[5] Our synthetic strategy for γ-hydroxy sulfonates focused on the hydrolysis of enantio- and diastereomerically pure γ-sultones.

Sultones are valuable heterocyclic intermediates which can react with a variety of nucleophiles cleaving the carbon-oxygen bond to introduce an alkylsulfonic acid functionality and they also offer novel possibilities for stereoselective transformations.[6] Several reports have been devoted to the hydrolysis of aliphatic sultones. Bordwell et al. have studied the effects of methyl substituents on the hydrolysis rates of γ-sultone derivatives bearing either no, one or two substituents in the γ-position (primary, secondary and tertiary γ-sultones) in 2.8% dioxane leading to the conclusion that these sultones were hydrolyzed predominantly by an unimolecular mechanism.[7] Mori et al. demonstrated that the hydrolysis of propanesultone in $H_2{}^{18}O$ in a strong alkaline medium (pH > 12) led to 86% C–O fission and 14% S–O fission corresponding to unimolecular and bimolecular mechanisms, respectively.[8] The hydrolysis of sultones can lead to hydroxy alkanesulfonates by a substitution or to alkenesulfonates by an elimination reaction. Nilsson found that the ratio of elimination to substitution products increases by going from primary to secondary and tertiary γ-sultones.[9] Kaiser and Püschel have reported the hydrolysis of long chain tertiary γ-sultones giving 67% yield of γ-hydroxy sulfonate and 33% yield of unsaturated products consisting of 30% of the 3-alkenesulfonate and only 3% of the Δ^2-isomer.[10]

To the best of our knowledge, neither an asymmetric strategy nor the diastereoselectivity of the hydrolysis of γ-sultones has been investigated so far.

We have recently reported efficient asymmetric electrophilic α-substitutions of benzylsulfonates bearing 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose as a chiral auxiliary with various alkyl halides and nitroolefins.[11] Moreover, we have extended this methodology using allylic halides as electrophiles for the diastereo- and enantioselective synthesis of α,γ-substituted γ-sultones in good yields.[12]

We now wish to describe the successful application of these enantiopure γ-sultones **1** (Scheme 1) to the asymmetric synthesis of γ-hydroxy sulfonates by hydrolysis with water under mild conditions, the diastereoselectivity of this ring-opening and thus the mechanism of the sultone hydrolysis.



Scheme 1 Asymmetric synthesis of the enantiopure γ-sultones **1a–e**

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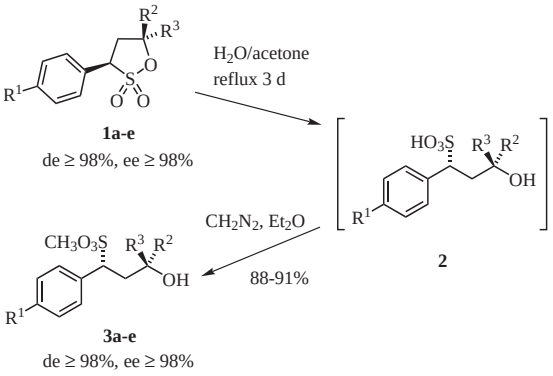
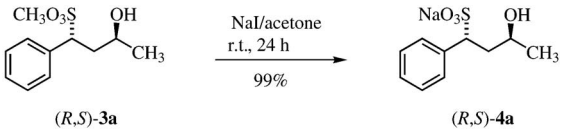
As shown in Scheme 2, refluxing of diastereo- and enantiomerically pure γ-sultones **1** in a solution of H_2O–acetone (1:2) for 3 days led to the corresponding sulfonic acids **2**. In order to obtain the final product in a more accessible form, the sulfonic acids **2** were directly converted into the corresponding methyl sulfonates **3** with diazomethane. The γ-hydroxy methyl sulfonates **3** were obtained in very good yields (88–91%) and excellent diastereo- and enantiomeric excesses (de, ee ≥ 98%, Table 1). The ee values of the products, in the case of (*R*,*S*)-**3a** and (*R*)-**3d**, were determined by HPLC analysis using a chiral stationary phase by comparison with the racemate and showed that the ring-opening of these sultones with water under such conditions proceeds without epimerization at the α-position of the sulfonyl group. The hydrolysis of the secondary γ-sultones **1a–c** gave only the substitution products **3a–c** and no elimination products could be detected from the crude product. However, a small amount of unsaturated sulfonate could be observed from the reactions of tertiary γ-sultones **1d** and **1e**.



Scheme 2 Hydrolysis of the enantiopure γ-sultones **1** to form the corresponding γ-hydroxy methyl sulfonates **3**

The hydrolysis of the epimeric sultones (*R*,*R*)-**1a** and (*R*,*S*)-**1a** gave one single diastereomer, (*R*,*S*)-**3a** and (*R*,*R*)-**3a**, respectively, whose ^{1}H NMR spectra apparently were different from each other. Since both diastereomers obtained differ from each other and due to the excellent diastereoselectivity of the reaction, it would be reasonable to assume that the reaction proceeds via a bimolecular nucleophilic substitution with inversion of configuration at the attacked γ-position of the γ-sultones rather than via a unimolecular reaction, which should result in an γ-epimeric mixture. In addition, the absolute configuration of (*R*,*S*)-**3a** was determined by X-ray crystallography of the corresponding sodium sulfonate.[13–15]

The γ-hydroxy sodium sulfonate **4a** could be obtained by cleaving the methyl group of (*R*,*S*)-**3a** with NaI in acetone at room temperature (Scheme 3). The X-ray diffraction study of compound **4a** established unambiguously that the absolute configuration of the stereogenic center at γ-position is *S* (Figure 1). The configuration of the γ-hydroxy methyl sulfonates **3b** and **3c** is also expected to be (1*R*,3*S*) based on the assumption of an uniform reaction mechanism operating in all substitutions.



Scheme 3 Cleavage of γ-hydroxy methyl sulfonate (*R*,*S*)-**3a** to form the γ-hydroxy sodium sulfonate (*R*,*S*)-**4a**

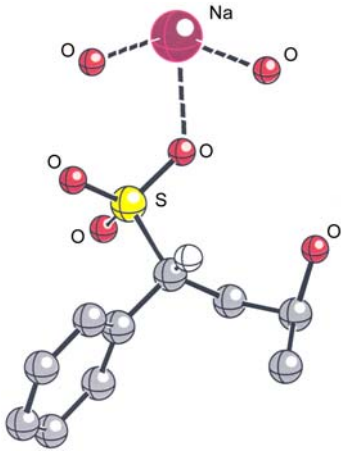


Figure 1 X-ray crystal structure of (*R*,*S*)-**4a**

Table 1 Hydrolysis of the Enantiopure Sultones **1** Affording the γ-Hydroxy Methyl Sulfonates **3**

3	R^1	R^2	R^3	Yield (%)	de (%)[a]	ee (%)[b]
(*R*,*S*)-**3a**	H	Me	H	89	≥ 98	≥ 98
(*R*,*R*)-**3a**	H	H	Me	91	≥ 98	≥ 98[c]
(*R*,*S*)-**3b**	*t*-Bu	Me	H	90	≥ 98	≥ 98[c]
(*R*,*S*)-**3c**	H	Et	H	88	≥ 98	≥ 98[c]
(*R*)-**3d**	*t*-Bu	Me	Me	88	–	≥ 98
(*R*)-**3e**	H	Me	Me	89	–	≥ 98[c]

[a] Determined by ^{1}H NMR and HPLC.
[b] Determined by HPLC using a chiral stationary phase.
c Based on the ee values of the enantiopure sultones.

In summary, we have developed a facile asymmetric synthesis of α,γ-substituted γ-hydroxy sulfonates in very good yields and excellent diastereo- and enantiomeric excesses (de, ee ≥ 98%) by ring-opening of enantiopure γ-sultones with water under mild conditions. The inversion of configuration at the attacked γ-position leads to the conclusion that the reported hydrolysis proceeds via a S_N2 mechanism.

Preparative column chromatography: Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). Analytical TLC: silica gel 60 F254 plates from Merck, Darmstadt. Optical rotation values were measured on a Perkin–Elmer P241 polarimeter. Microanalyses were obtained with a Vario EL element analyzer. Mass spectra were acquired on a Finnigan SSQ7000 (CI 100 eV; EI 70 eV) spectrometer. IR spectra were taken on a Perkin-Elmer FT/IR 1760. ^{1}H and ^{13}C NMR spectra were recorded on Gemini 300 or Varian Inova 400 and all measurements were performed with tetramethylsilane as internal standard. Melting points were determined on a Tottoli melting point apparatus and are uncorrected.

Preparation of α,γ-Substituted γ-Hydroxy Methyl Sulfonates 3a–e; General Procedure

The enantiopure sultone **1** (0.25 mmol) was dissolved in a H_2O-acetone solution (5:10 mL). The solution was heated at reflux for 3 d until disappearance of the starting material (TLC monitoring). After removal of acetone under reduced pressure, EtOH (10 mL) was added. The resulting colorless ethanolic solution was treated with an etheral solution of diazomethane until the yellow color persisted. The solvent was evaporated under reduced pressure and the aqueous residue was extracted with Et_2O. The combined organic layers were washed with brine and dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, Et_2O–*n*-pentane) to give the product **2**.

Methyl (1*R*,3*S*)-3-Hydroxy-1-phenylbutane-1-sulfonate [(*R*,*S*)-3a]

≥According to the general procedure, the solution of the enantiopure sultone (*R*,*R*)-**1a** (110 mg, 0.5 mmol) in acetone–H_2O (10:5 mL) was refluxed for 3 d. The crude product consisting of only one diastereomer was purified by column chromatography (SiO_2, Et_2O–*n*-pentane, 1:1) to give (*R*,*S*)-**3a** as a colorless solid (112 mg, 89%); de ≥ 98% (NMR); ee ≥ 98% (HPLC, Daicel OD, *n*-heptane–*i*-PrOH, 9:1); mp 63 ºC; $[\alpha]_D^{26}$ +38.85 (*c* 1.0, $CHCl_3$).

IR (KBr): 3483 (vs), 3033 (w), 2970 (m), 2931 (m), 1498 (w), 1463 (m), 1405 (m), 1346 (s), 1321 (s), 1323 (w), 1168 (vs), 1129 (m), 1076 (m), 968 (vs), 830 (m), 768 (m), 733 (m), 700 (m), 630 (m), 596 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 6.3 Hz, 3 H, CHC*H*$_3$), 1.92 (br s, 1 H, OH), 2.19 (ddd, *J* = 14.3, 8.5, 6.7 Hz, 1 H, C*H*H), 2.54 (ddd, *J* = 14.3, 7.4, 4.7 Hz, 1 H, CH*H*), 3.60 (s, 3 H, SO_3CH_3), 4.07 (m, 1 H, C*H*OH), 4.53 (t, *J* = 7.1 Hz, 1 H, $CH_2CHSO_3CH_3$), 7.36–7.46 (m, 5 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3 (CH_3), 39.9 (CH_2), 57.0 (SO_3CH_3), 63.7 ($CHSO_3$), 65.1 (CHOH), 128.8, 129.0, 129.2 (Ar*C*H), 133.2 (Ar*C*).

MS (EI, 70 eV): *m*/*z* (%) = 244 (0.2) [M$^+$], 200 (1), 149 (8), 105 (100), 91 (4), 77 (5), 65 (1), 51 (3), 45 (22).

Anal. Calcd for $C_{11}H_{16}O_4S$ (244.31): C, 54.08; H, 6.60. Found: C, 54.21; H, 6.74.

Methyl (1*R*,3*R*)-3-Hydroxy-1-phenylbutane-1-sulfonate [(*R*,*R*)-3a]

According to the general procedure, the solution of the enantiopure sultone (*R*,*S*)-**1a** (21 mg, 0.1 mmol) in acetone–H_2O (10:5 mL) was refluxed for 3 d. The crude product consisting of only one diastereomer was purified by column chromatography (SiO_2, Et_2O–*n*-pentane, 1:1) to give (*R*,*R*)-**3a** as a colorless solid (22 mg, 91%); de ≥ 98% (NMR); ee ≥ 98% (based on the *ee* value of the sultone); mp 127 ºC; $[\alpha]_D^{24}$ –2.7 (*c* 1.1, $CHCl_3$).

IR (KBr): 3062 (m), 3033 (m), 2997 (m), 2955 (m), 2931 (m), 2896 (m), 1500 (m), 1457 (m), 1349 (s), 1238 (w), 1170 (s), 1143 (s), 1075 (s), 987 (s), 924 (w), 833 (s), 778 (m), 722 (m), 699 (m), 623 (m), 589 (s), 506 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 6.2 Hz, 3 H, CHC*H*$_3$), 1.46 (br s, 1 H, OH), 2.33 (m, 2 H, CH_2), 3.47 (m, 1 H, C*H*OH), 3.68 (s, 3 H, SO_3CH_3), 4.63 (dd, *J* = 10.9, 4.2 Hz, 1 H, $CH_2CHSO_3CH_3$), 7.37–7.48 (m, 5 H, Ar*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4 (CH_3), 38.9 (CH_2), 56.7 (SO_3CH_3), 63.8 ($CHSO_3$), 64.2 (CHOH), 129.0, 129.2, 129.7 (Ar*C*H), 131.9 (Ar*C*).

MS (CI, 100 eV, CH_4): *m*/*z* (%) = 245 (1) [M$^+$ + 1], 183 (1), 163 (2), 149 (6), 131 (11), 123 (5), 105 (100), 91 (1), 77 (7).

Methyl (1*R*,3*S*)-1-(4-*tert*-Butylphenyl)-3-hydroxybutane-1-sulfonate [(*R*,*S*)-3b]

According to the general procedure, the solution of the enantiopure sultone (*R*,*R*)-**1b** (81 mg, 0.3 mmol) in acetone–H_2O (10:5 mL) was refluxed for 3 d. The crude product consisting of only one diastereomer was purified by column chromatography (SiO_2, Et_2O–*n*-pentane, 1:1) to give (*R*,*S*)-**3b** as a colorless solid (82 mg, 90%); de ≥ 98% (NMR); ee ≥ 98% (based on the ee value of the sultone); mp 68 ºC; $[\alpha]_D^{29}$ +37.4 (*c* 1.3, $CHCl_3$).

IR ($CHCl_3$): 3291 (m), 2966 (s), 2877 (m), 1517 (m), 1464 (m), 1354 (vs), 1169 (vs), 1089 (m), 994 (vs), 947 (m), 859 (m), 848 (m), 758 (s), 603 (s), 584 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.3 Hz, 3 H, CHC*H*$_3$), 1.31 [s, 9 H, C(CH_3)$_3$], 1.87 (br s, 1 H, OH), 2.18 (ddd, *J* = 14.6, 8.5, 6.9 Hz, 1 H, C*H*H), 2.52 (ddd, *J* = 14.6, 7.4, 4.7 Hz, 1 H, CH*H*), 3.61 (s, 3 H, SO_3CH_3), 4.06 (m, 1 H, C*H*OH), 4.50 (t, *J* = 7.1 Hz, 1 H, $CH_2CHSO_3CH_3$), 7.35, 7.40 [each d (AB system), *J* = 8.5 Hz, 2 H, Ar*H*].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3 (CH_3), 31.2 [C(*C*H_3)$_3$], 34.6 [*C*(CH_3)$_3$], 40.0 (CH_2), 56.9 (SO_3CH_3), 63.4 ($CHSO_3$), 65.1 (CHOH), 125.7, 128.8 (Ar*C*H), 129.9, 152.1 (Ar*C*).

MS (EI, 70 eV): *m*/*z* (%) = 300 (1) [M$^+$], 285 (1), 253 (2), 205 (12), 189 (4), 161 (100), 145 (12), 131 (3), 117 (6), 105 (9), 91 (4), 57 (60).

Anal. Calcd for $C_{15}H_{24}O_4S$ (300.42): C, 59.97; H, 8.05. Found: C, 59.57; H, 7.77.

Methyl (1*R*,3*S*)-3-Hydroxy-1-phenylpentane-1-sulfonate [(*R*,*S*)-3c]

According to the general procedure, the solution of the enantiopure sultone (*R*,*R*)-**1c** (36 mg, 0.16 mmol) in acetone–H_2O (10:5 mL) was refluxed for 3 d. The crude product consisting of only one diastereomer was purified by column chromatography (SiO_2, Et_2O–*n*-pentane, 1:1) to give (*R*,*S*)-**3c** as a colorless solid (36 mg, 88%); de ≥ 98% (NMR); ee ≥ 98% (based on the ee value of the sultone); mp 51 ºC; $[\alpha]_D^{30}$ +40.2 (*c* 1.0, $CHCl_3$).

IR (KBr): 3488 (vs), 3062 (w), 3034 (w), 2960 (m), 2931 (m), 1497 (w), 1456 (m), 1411 (m), 1338 (s), 1163 (s), 1114 (m), 1077 (m), 997 (vs), 834 (m), 786 (m), 729 (m), 700 (m), 632 (m), 586 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.43 (m, 2 H, $CHCH_2CH_3$), 1.84 (br s, 1 H, OH), 2.11 (ddd, *J* = 14.6, 8.9, 6.2 Hz, 1 H, C*H*H), 2.59 (ddd, *J* = 14.6, 7.9, 4.2 Hz, 1 H, CH*H*), 3.59 (s, 3 H, SO_3CH_3), 3.88 (m, 1 H, C*H*OH), 4.58 (dd, *J* = 7.9, 6.2 Hz, 1 H, $CH_2CHSO_3CH_3$), 7.36–7.47 (m, 5 H, Ar*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.7 (CH_3), 30.2 (CH_2CH_3), 38.3 (CH_2), 57.1 (SO_3CH_3), 63.8 ($CHSO_3$), 70.4 (CHOH), 128.9, 129.1, 129.4 (Ar*C*H), 133.8 (Ar*C*).

MS (EI, 70 eV): *m*/*z* (%) = 258 (0.2) [M^+], 200 (1), 162 (10), 133 (9), 105 (100), 91 (3), 59 (23).

Anal. Calcd for $C_{12}H_{18}O_4S$ (258.34): C, 55.79; H, 7.02. Found: C, 55.82; H, 7.05.

Methyl (1*R*)-1-(4-*tert*-Butylphenyl)-3-hydroxy-3-methylbutane-1-sulfonate [(*R*)-3d]

According to the general procedure, the solution of the enantiopure sultone (*R*)-**1d** (61 mg, 0.2 mmol) in acetone–H_2O (10:5 mL) was refluxed for 3 d. The crude product was purified by column chromatography (SiO_2, Et_2O–*n*-pentane, 1:1) to give (*R*)-**3d** as a colorless solid (60 mg, 88%); ee ≥ 98% (HPLC, Chiralpak AD, *n*-heptane/*i*-PrOH, 9:1); mp 113 ºC; $[\alpha]_D^{28}$ +21.6 (*c* 1.0, $CHCl_3$).

IR (KBr): 3347 (s), 2966 (s), 2871 (m), 1515 (m), 1464 (m), 1350 (vs), 1269 (m), 1235 (m), 1164 (vs), 980 (vs), 909 (m), 855 (m), 781 (m), 603 (s), 576 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03, 1.28 (each s, 3 H, CH_3), 1.31 [s, 9 H, $C(CH_3)_3$], 1.62 (br s, 1 H, OH), 2.39 (dd, *J* = 14.6, 9.3 Hz, 1 H, C*H*H), 2.57 (dd, *J* = 14.6, 2.5 Hz, 1 H, CH*H*), 3.64 (s, 3 H, SO_3CH_3), 4.57 (dd, *J* = 9.1, 2.5 Hz, 1 H, $CH_2CHSO_3CH_3$), 7.40 (s, 4 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.0, 30.7 (CH_3), 31.2 [$C(CH_3)_3$], 34.6 [$C(CH_3)_3$], 42.9 (CH_2), 56.9 (SO_3CH_3), 63.1 ($CHSO_3$), 70.2 (COH), 125.7, 129.2 (Ar*C*H), 130.3, 152.1 (Ar*C*).

MS (EI, 70 eV): *m*/*z* (%) = 314 (2) [M^+], 296 (1), 281 (1), 219 (3), 203 (6), 185 (1), 161 (100), 145 (11), 131 (2), 117 (4), 105 (2), 91 (2), 59 (50).

Anal. Calcd for $C_{16}H_{26}O_4S$ (314.45): C, 61.12; H, 8.33. Found: C, 60.82; H, 8.36.

Methyl (1*R*)-3-Hydroxy-3-methyl-1-phenylbutane-1-sulfonate [(*R*)-3e]

According to the general procedure, the solution of the enantiopure sultone (*R*)-**1e** (59 mg, 0.25 mmol) in acetone–H_2O (10:5 mL) was refluxed for 3 d. The crude product was purified by column chromatography (SiO_2, Et_2O–*n*-pentane, 1:1) to give (*R*)-**3e** as a colorless solid (60 mg, 89%); ee ≥ 98% (based on the ee value of the sultone); mp 71.5 ºC; $[\alpha]_D^{26}$ +16.8 (*c* 1.0, $CHCl_3$).

IR (KBr): 3513 (vs), 3035 (w), 2970 (m), 2934 (m), 1498 (m), 1458 (m), 1401 (m), 1342 (vs), 1295 (m), 1233 (s), 1161 (vs), 1084 (m), 983 (vs), 834 (m), 795 (m), 700 (m), 625 (m), 540 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.65 (br s, 1 H, OH), 2.39 (dd, *J* = 14.6, 9.4 Hz, 1 H, C*H*H), 2.58 (dd, *J* = 14.6, 2.5 Hz, 1 H, CH*H*), 3.63 (s, 3 H, SO_3CH_3), 4.61 (dd, *J* = 9.4, 2.5 Hz, 1 H, $CH_2CHSO_3CH_3$), 7.36–7.44 (m, 3 H, Ar*H*), 7.45–7.51 (m, 2 H, Ar*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.9 (CH_3), 31.0 (CH_3), 42.9 (CH_2), 57.1 (SO_3CH_3), 63.5 ($CHSO_3$), 70.3 (COH), 129.0, 129.1, 129.9 (Ar*C*H), 133.9 (Ar*C*).

MS (EI, 70 eV): *m*/*z* (%) = 258 (0.3) [M^+], 243 (1), 200 (2), 162 (6), 147 (8), 105 (48), 91 (3), 79 (5), 59 (100).

Anal. Calcd for $C_{12}H_{18}O_4S$ (258.34): C, 55.79; H, 7.02. Found: C, 56.06; H, 7.19.

Sodium (1*R*,3*S*)-3-Hydroxy-1-phenylbutane-1-sulfonate [(*R*,*S*)-4a]

The γ-hydroxy methyl sulfonate (*R*,*S*)-**3a** (118 mg, 0.48 mmol) was dissolved in acetone (20 mL) and NaI (80 mg, 0.53 mmol) was added. The reaction mixture was allowed to stir at r.t. for 24 h. The solvent was evaporated under reduced pressure and the crude product was purified by recrystallization from EtOH–Et_2O to give (*R*,*S*)-**4a** as a colorless solid (120 mg, 99%); de, ee ≥ 98% (based on the de, ee value of (*R*,*S*)-**3a**); mp 245 ºC; $[\alpha]_D^{24}$ +10.6 (*c* 1.1, MeOH).

IR (KBr): 3402 (vs), 3061 (w), 3032 (w), 2972 (m), 1639 (m), 1496 (w), 1455 (m), 1407 (m), 1385 (m), 1295 (m), 1244 (s), 1210 (vs), 1170 (vs), 1129 (m), 1091 (m), 1051 (vs), 948 (m), 825 (m), 751 (m), 703 (s), 672 (m), 587 (m) cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 1.16 (d, *J* = 6.2 Hz, 3 H, $CHCH_3$), 2.31 (ddd, *J* = 13.6, 9.4, 5.9 Hz, 1 H, C*H*H), 2.41 (ddd, *J* = 13.6, 7.7, 5.4 Hz, 1 H, CH*H*), 3.69 (dq, *J* = 13.6, 6.2 Hz, 1 H, C*H*OH), 4.00 (dd, *J* = 9.4, 5.4 Hz, 1 H, CH_2CHSO_3), 7.24–7.36 (m, 3 H, Ar*H*), 7.44–7.50 (m, 2 H, Ar*H*).

^{13}C NMR (75 MHz, CD_3OD): δ = 20.6 (CH_3), 40.1 (CH_2), 62.8 ($CHSO_3$), 64.6 (CHOH), 126.4, 127.2, 128.6 (Ar*C*H), 137.0 (Ar*C*).

MS (ESI): *m*/*z* (%) = 229 (100) [$C_{10}H_{13}SO_4^-$].

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(13) **X-ray Crystallographic Study of 4a**: The compound ($C_{10}H_{16}O_{5.5}SNa$: M_r = 279.29) crystallizes in monoclinic space group *C*2 (Nr. 5) with cell dimensions of *a* = 14.019(3), *b* = 5.6250(11), *c* = 17.061(3) Å, and β = 110.097(3)°. A cell volume of V = 1263.4(4) Å^3 and *Z* = 4 result in a calculated density of ρ_{calcd} = 1.468 gcm^{-3}. 16500 reflections have been collected in the ω mode at T = 298 K on an Bruker SMART APEX CCD diffractometer employing MoK_α-radiation (λ = 0.71073 Å). Data collection covered the range –18 ≤ h ≤ 18, –7 ≤ k ≤ 7, and –22 ≤ l ≤ 22 up to θ_{max} = 28.29°; absorption correction with SADABS (μ = 0.301mm^{-1}). The structure has been solved by direct methods as implemented in the Xtal3.7 suite of crystallographic routines[14] where GENSIN has been used to generate the structure-invariant relationships and GENTAN for the general tangent phasing procedure. 1682 observed reflections [I>2σ(I)] have been included in the final full-matrix least-squares refinement on F involving 159 parameters and converging at $R(R_w)$ = 0.031 (0.041, *w* = 1/[σ^2(F) + 0.0004F^2]), S = 1.454, and a residual electron density of –0.17/0.33 eÅ^{-3}. The absolute configuration has been determined using Flack's method and a data set collected using CuK_α radiation. X_{abs} = –0.022(55)[15] for the structure shown in Figure 1. The hydrogen positions have been calculated in idealized positions. Their *U*s have been fixed at 1.5 times *U* of the relevant heavy atom, and no hydrogen parameters have been refined. The asymmetric unit contains 1.5 water molecules which explains deviations between the crystallographic and chemical formulae and densities. The crystal structure of **4a** has been deposited as supplementary publication no. CCDC 227543 at the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk, or http//www.ccdc.cam.ac.uk).

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