A Highly Efficient Asymmetric Synthesis of Homotaurine Derivatives via Diastereoselective Ring-Opening of \( \gamma \)-Sultones

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Abstract: A highly efficient asymmetric synthesis of \( \alpha, \gamma \)-substituted \( \gamma \)-amino sulfonates via diastereoselective ring-opening of enantiopure \( \alpha, \gamma \)-substituted \( \gamma \)-sultones with inversion of configuration at the attacked \( \gamma \)-carbon is described. In the key step sodium azide is used as the nucleophilic nitrogen source. Secondary and tertiary \( \gamma \)-amino sulfonates were synthesized in very good yields and excellent diastere- and enantiomeric excesses (de, ee \( \geq 98\% \)).

Key words: amino sulfonates, sultones, asymmetric synthesis, ring-opening, azide

Derivatives of sulfonic acids are important constituents in mammals and are involved in various physiological processes. The best known are 2-aminothanesulfonic acid (taurine, TA) and related compounds. Homotaurine (HTA, 3-aminopropanesulfonic acid) is a structural analogue of \( \gamma \)-aminobutyric acid (GABA), which is of great importance as a specific inhibitor of impulse transmission in the central nervous system (CNS). It has been reported that homotaurine has more potent inhibitory effects than taurine. In addition, it increases the synthesis of dopamine in the brain, and shows antinociceptive activity. The medication acamprosate (calcium acetylhomotaurine) has been available in Europe for the treatment of alcohol dependence since 1989. However, in many cases the physiological role of these sulfonic acid derivatives remain unclear. To get a further insight into their mode of action, a stereoselective access to these derivatives is desirable and compulsory for further physiological tests.

Several reports have been devoted to the asymmetric synthesis of \( \beta \)-amino sulfonates, whereas the literature concerning optically active \( \gamma \)-amino sulfonates is scarce. Interestingly, Prager and co-workers have synthesized 3-amino-2-(4-chlorophenyl)propanesulfonic acid (saclofen) and 3-amino-2-(4-chlorophenyl)-2-hydroxypropanesulfonic acid (hydroxysaclofen) whose racemates exhibited activity as specific antagonists of GABA at the GABA\(_B\) receptors. Moreover, they reported the synthesis and biological tests of both enantiomers of hydroxysaclofen. (\(R\))-(-)-Hydroxysaclofen was completely inactive, whereas (\(S\))- (+)-hydroxysaclofen was a potent and specific antagonist with an activity 2 to 3 times that of the racemate.

On the other hand, aminooalkanesulfonic acid derivatives can provide interesting applications in the field of peptide mimetics. Over the past several years, the syntheses of \( \alpha \)-, \( \beta \)-, and vinylogous sulfono peptides have drawn great attention. Therefore, it is of importance to develop asymmetric approaches to amino sulfonic acid derivatives as building blocks for the synthesis of sulfono peptides.

Recently, an efficient asymmetric synthesis of \( \beta \)-amino sulfonates viaaza-Michael addition of the enantiopure hydrazines SAMP or RAMBO to \( \alpha, \beta \)-unsaturated sulfonates in the presence of a Lewis acid as catalyst has been described by our group. In our ongoing research concerning the chemistry of sulfonates with the purpose to develop an efficient asymmetric route to pharmacologically interesting sulfonic acid derivatives, we envisioned to gain access to \( \gamma \)-amino sulfonates via ring-opening reaction of diastereo- and enantiopure \( \gamma \)-sultones.

In previous communications and a full paper, we have described efficient asymmetric electrophilic \( \alpha \)-substitutions of benzyl sulfonates bearing 1,2,5,6-di-O-isopropylidene-\( \alpha \)-D-allofuranose as a chiral auxiliary with various alkyl halides and nitroalkenes. In subsequent investigations, we have shown the extension of this methodology using allylic halides as electrophiles in the diastereo- and enantioselective synthesis of the \( \alpha, \gamma \)-substituted \( \gamma \)-sultones 1 (Scheme 1). Moreover, in our synthesis of optically active \( \alpha, \gamma \)-substituted \( \gamma \)-alkoxy and \( \gamma \)-hydroxy sulfonates from these sultones, we have explored that the ring-opening reaction of these \( \gamma \)-sultones proceeded via a \( \text{Sn}2\) mechanism with an inversion of configuration at the attacked \( \gamma \)-carbon.

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We now wish to describe herein the successful application of these enantiopure \( \gamma \)-sultones to the asymmetric synthesis of a very important class of sulfonic acid derivatives, namely homotaurine and its derivatives.

In fact, there have been many reports on the ring-opening of sultones with amines to introduce the amino group.\(^{17,18}\) However, sultones bearing a stereogenic center at the \( \alpha \)-position of the sulfonyl group would probably undergo epimerization at this center. To circumvent this problem, we planned an indirect synthetic strategy using sodium azide as a reagent in the ring-opening reaction of sultones.

We assumed that using the azide ion (a strong nucleophile but weakly basic synthetic equivalent of the amino group) should allow an epimerization-free ring-opening of sultones. After this, the amino group would be obtained by a mild reduction of the azido group. To yield the desired \( \gamma \)-amino sulfonates, the sulfonic acid group would have to be protected appropriately in order to warrant its stability under the reduction conditions.

As expected, the ring-opening of the sultone \( (R,R)\)-1a with an excess of sodium azide could be performed smoothly in DMF under anhydrous conditions. The reaction was complete after stirring at 60 °C for 2 hours yielding the corresponding sodium sulfonate 2a, which could be directly converted to its isopropyl sulfonate in a two-step sequence. Protonation with methanolic HCl and subsequent treatment with triisopropyl orthoformate in refluxing CH\(_2\)Cl\(_2\) provided the desired \( \gamma \)-azido isopropyl sulfonate \( (R,S)\)-4a in 96% overall yield (Scheme 2).

This three-step sequence showed to be general in scope, providing a range of substituted \( \gamma \)-azido isopropyl sulfonates derived from secondary and tertiary \( \gamma \)-sultones as summarized in Table 1. The \( \gamma \)-azido isopropyl sulfonates \( (R,S)\)-4a-d were obtained in excellent yields (96–98%) as well as diastereoi- and enantiomeric excesses (de, ee ≥98%). In the cases of tertiary \( \gamma \)-sultones \( (R)\)-1e and \( (R)\)-1f, the products arising from the ring-opening reaction, namely \( (R)\)-4e and \( (R)\)-4f, respectively, could be isolated in acceptable yields along with the major by-products β-\( \gamma \)- and \( \gamma \)-\( \delta \)-unsaturated sulfonates arising from elimination reactions.

The ring-opening of the enantiopure sultones \( (R,R)\)-1a-d proceeded with very high degree of diastereoselectivity to give the corresponding \( \gamma \)-azido sulfonates \( (R,S)\)-4a-d as a single isomer, respectively. To get more insight into these ring-opening reactions, we also investigated the reaction of the (racemic) \( \gamma \)-epimeric sulfone \( (R,S)\)-1a, i.e. \( \text{trans-1a}\). As expected, the \( \gamma \)-azido isopropyl sulfonate \( \text{rac-syn-4a}\) was obtained as a single isomer. Both diastereomers obtained clearly differed from each other as shown by their \( ^1H \) NMR spectra in Figure 1.

### Table 1 Synthesis of the \( \gamma \)-Azido Isopropyl Sulfonates 4 from the Enantiopure Sultones 1

<table>
<thead>
<tr>
<th>Product 4</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>Yield (%)</th>
<th>de (%)(^a)</th>
<th>ee (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( (R,S))-4a</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>96</td>
<td>≥98</td>
<td>≥98</td>
</tr>
<tr>
<td>( (R,S))-4b</td>
<td>( t)-Bu</td>
<td>Me</td>
<td>H</td>
<td>97</td>
<td>≥98</td>
<td>≥98</td>
</tr>
<tr>
<td>( (R,S))-4c</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>97</td>
<td>≥98</td>
<td>≥98</td>
</tr>
<tr>
<td>( (R,S))-4d</td>
<td>( t)-Bu</td>
<td>Et</td>
<td>H</td>
<td>98</td>
<td>≥98</td>
<td>≥98</td>
</tr>
<tr>
<td>( R)-4e</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>77</td>
<td>-</td>
<td>≥98(^c)</td>
</tr>
<tr>
<td>( R)-4f</td>
<td>( t)-Bu</td>
<td>Me</td>
<td>Me</td>
<td>74</td>
<td>-</td>
<td>≥98(^c)</td>
</tr>
</tbody>
</table>

\(^a\) Determined by \( ^1H \) NMR and HPLC.  
\(^b\) Based on the ee-values of the enantiopure sultones.  
\(^c\) Determined by HPLC using a chiral stationary phase.
Therefore, it is reasonable to assume that the reactions proceed via a bimolecular nucleophilic substitution with inversion of configuration at the attacked γ-carbon atom rather than via a unimolecular reaction, which should result in an epimeric mixture. The absolute configurations of the γ-azido isopropyl sulfonates 4a-d are assigned to be (1R,3S) based on the assumption of a uniform reaction mechanism operating in all the substitutions.

The conversion of the azido group into a N-Boc-protected amino group was finally carried out in a one-pot procedure according to a reported method21 by using Pd/C-catalyzed hydrogenation in the presence of (Boc)2O (Scheme 3). The N-Boc-protected γ-amino sulfonates 5 were obtained in very good yields and excellent diastereomeric purity. On the other hand, the Boc group could be deprotected using NaI in refluxing acetone for 2 days leading to the corresponding enantiopure sultones. Moreover, it seems to be of special interest that both protecting groups in (R,S)-5a can be cleaved independently without epimerization as illustrated in Scheme 4.

The isopropyl group was deprotected using NaI in refluxing acetone for 2 days leading to the corresponding sodium sulfonate (R,S)-6 in 91% yield and in acceptable purity. On the other hand, the Boc group could be depro-

Table 2 Transformation of the γ-Azido Sulfonates 4 to the N-Boc-Protected γ-Amino Sulfonates 5

<table>
<thead>
<tr>
<th>Product 5</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
<th>de (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R,S)-5a</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>91</td>
<td>≥98</td>
<td>≥98</td>
</tr>
<tr>
<td>(R,S)-5b</td>
<td>t-Bu</td>
<td>Me</td>
<td>H</td>
<td>90</td>
<td>≥98</td>
<td>≥98</td>
</tr>
<tr>
<td>(R,S)-5c</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>86</td>
<td>≥98</td>
<td>≥98</td>
</tr>
<tr>
<td>(R,S)-5d</td>
<td>t-Bu</td>
<td>Et</td>
<td>H</td>
<td>80</td>
<td>≥98</td>
<td>≥98</td>
</tr>
<tr>
<td>(R)-5e</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>79</td>
<td>–</td>
<td>2≥98&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>(R)-5f</td>
<td>t-Bu</td>
<td>Me</td>
<td>Me</td>
<td>81</td>
<td>–</td>
<td>≥98</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR and HPLC.

<sup>b</sup> Based on the ee-values of the enantiopure sultones.

<sup>c</sup> Determined by HPLC using a chiral stationary phase.

Scheme 3 Transformation of the γ-azido sulfonates 4 to the N-Boc-protected γ-amino sulfonates 5. Reagents and conditions: a) H₂, Pd/C, (Boc)₂O, EtOAc, r.t., 18–22 h.

Scheme 4 Selective deprotection of the γ-amino sulfonates (R,S)-5a. Reagents and conditions: a) NaI, acetone, reflux, 2 d; b) i. 30% TFA–CH₂Cl₂, r.t., 30 min, ii. CbzCl, K₂CO₃, CH₂Cl₂/H₂O, r.t., 15 h.
tected selectively with TFA in CH₂Cl₂ at room temperature. The resultant amine was not isolated but directly protected withCb₂Cl to give the carbamate (R,S)-7 in an excellent yield of 96%.

The free γ-amino sulfonic acid could be easily synthesized from the γ-sultone in a three step sequence as depicted in Scheme 5. Ring-opening of the sultone (R,R)-1a with sodium azide was followed by protonation of the resulting sodium sulfonate with an excess of methanolic HCl. The resultant γ-azido sulfonic acid was directly reduced employing Pd/C-catalyzed hydrogenation to give the free γ-amino sulfonic acid (R,S)-8 in 92% overall yield.

To establish the conversion of the enantiopure sultones (R,R)-1 to the corresponding γ-azido sulfonates (R,S)-4 had occurred with an inversion of configuration, the γ-sultone (R,R)-1a was converted into the known N-acetylamino (S)-11 via the intermediate γ-azido sulfonate (R,S)-2a as depicted in Scheme 6.

After opening of the sultone (R,R)-1a with sodium azide, the sodium sulfonate (R,S)-2a was converted into the γ-azido sulfonyle chloride 9 with phosphene at room temperature. It is noteworthy that we observed a severe loss of stereochemical integrity at the α-position of the sulfonyle group in the product 9 under these conditions. After removal of the polar impurity by filtration through a short column of silica gel, the γ-azido sulfonyle chloride 9 was hydrogenated in the presence of Pd/C as a catalyst. In this fashion, the azido group was reduced with a concomitant reductive cleavage of the sulfonyle group leading to the primary amine 10, which was directly used for the acetylation step by treatment with acetic acid anhydride in CH₂Cl₂ in the presence of triethylamine. The desired N-acetylamino 11 was obtained in 70% overall yield. Its absolute configuration was established to be S by comparison of its optical rotation with the value reported in the literature ([α]₂⁰ = −34.1 (c = 0.65, EtOH), Lit.²⁵ [α]₁²⁶ = −35.2 (c = 0.7, EtOH)).

In summary, we have developed an efficient asymmetric access to N-Boc-protected γ-amino isopropyl sulfonates in a simple four-step sequence starting from diastereomeric and enantiopure γ-sultones. The diastereoselective ring-opening of γ-sultones with sodium azide proceeds via a S₈,2 mechanism with an inversion of configuration at the attacked carbon atom. The following steps, a protonation of the resultant sodium sulfonates, a protection of the sulfonic acids as their isopropyl sulfonates and finally a conversion of the azido group into a N-Boc-protected amino group afforded the title compounds in very good yields and excellent diastereo- and enantiomeric excesses (de, ee ≥98%). In addition, we have shown a selective removal of either the isopropyl or the Boc protecting groups without epimerization.

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. 1H and 13C NMR spectra were recorded on a Gemini 300 or a Varian Inova 400 and all measurements were performed with tetramethylsilane as an internal standard. Mass spectra were acquired on a Finnigan SSQ 7000 spectrometer (CI 100 eV; EI 70 eV). High-resolution mass spectra were recorded with a Finnigan MAT 95 spectrometer. Microanalyses were obtained with a Vario EL element analyzer. Melting points were determined on a Tottoli melting point apparatus and are uncorrected.

α,γ-Substituted γ-Azido Isopropyl Sulfonates 4a–f; General Procedure 1 (GP 1)
A mixture of the enantiopure sultone 1 (0.5 mmol), NaN₃ (2.5 mmol) and NH₄Cl (1.1 mmol) in anhyd DMF (5 mL) was heated at 60 °C under argon for 2 h. DMF was removed under vacuum and the resulting sodium sulfonate 2 was treated with an excess of methanolic HCl. After removal of MeOH under vacuum, the solid was triturated with CH₂Cl₂ for 30 min and filtered twice. The combined CH₂Cl₂ fractions were evaporated under reduced pressure to give the sulfonic acid 3. A solution of the crude sulfonic acid and triisopropyl orthoformate (5 mmol) in CH₂Cl₂ (5 mL) was refluxed for 2 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (SiO₂, Et₂O–n-pentane) to give the γ-azido isopropyl sulfonate 4.
Isopropyl (1H, C9.2 mmol) in CH2Cl2 (10 mL) was refluxed for 2 h. The crude product was purified by column chromatography (SiO2, EtO-n-pentane) to give the N-Boc-protected γ-amino sulfonate 5a-

Isopropyl (1H, C9.2 mmol) in CH2Cl2 (10 mL) was refluxed for 2 h. The crude product was purified by column chromatography (SiO2, EtO-n-pentane). IR (film): 2983 (m), 2937 (m), 2111 (s), 1497 (w), 1456 (m), 1348 (m), 1266 (m), 1170 (s), 1087 (m), 983 (m), 778 (m), 700 (m), 562 (m). 1H NMR (300 MHz, CDCl3): δ = 1.10 [d, J = 6.4 Hz, 3 H, SOCH2CH2CH2CH3], 1.27 [d, J = 6.7 Hz, 3 H, CH2CH2CH3], 1.31 [d, J = 6.2 Hz, 3 H, SOCH2CH2CH2CH3], 2.21 (dd, J = 7.4, 8.2, 14.4 Hz, 1 H, CH2CH2CH2CH3], 3.70 (m, 1 H, CHN3), 4.32 (t, J = 7.0 Hz, 1 H, ArCHSO3), 4.64 (sept, J = 6.2 Hz, 1 H, CH2CH2CH3), 7.39 (m, 5 H, ArH). 13C NMR (75 MHz, CDCl3): δ = 22.5, 23.3, 37.3 (CH3), 55.3 (CH3), 64.6 (CHSO3), 78.4 (SO2CH2), 128.9, 129.2, 129.3 (CH2), 133.0 (Caram). 

MS (Cl, 100 eV, methane): m/e (%) = 298 (10) [M+1], 255 (12), 228 (32), 213 (9), 174 (4), 146 (100), 131 (16), 105 (6).

Anal. Calcd for C16H26ClN2O3S: C, 52.5; H, 6.44; N, 14.13. Found: C, 53.0; H, 6.54; N, 14.22.

Isopropyl (1R,3S)-3-Azido-1-(4-tert-butylphenyl)butanesulfonate [(R,S)-4b]

According to GP 1, a mixture of the enantiopure sultone (R,R)-1b (61 mg, 0.22 mmol), NaCN (80 mg, 1.25 mmol) and NH4Cl (30 mg, 0.55 mmol) in anhyd DMF (3 mL) was heated at 60 °C under argon for 2 h. The resulting sodium sulfonate was first treated with methanolic HCl (3 mL). After removal of MeOH, a solution of the crude sulfamic acid and triisopropyl orthoformate (1.0 mL, 6 mmol) in CH2Cl2 (5 mL) was refluxed for 2 h. The crude product was purified by column chromatography (SiO2, EtO-n-pentane). IR (KBr): 2968 (m), 2934 (m), 2129 (s), 1459 (m), 1351 (s), 1266 (s), 1108 (m), 907 (s), 777 (m), 702 (m), 589 (m), 562 (m). 1H NMR (300 MHz, CDCl3): δ = 1.00 (t, J = 7.4 Hz, 3 H, CH3CH2), 1.10, 1.30 [two d, J = 6.2 Hz, 6 H, SO(CH2CH3)2], 1.43–1.63 (m, 6 H, 2 CH2CH2CH3), 2.15 (dd, J = 6.9, 8.7, 14.6 Hz, 1 H, CHCH2CH3), 2.60 (dd, J = 5.2, 6.9, 14.6 Hz, 1 H, CHCH2CH3), 3.54 (m, 1 H, CHN3), 4.34 (t, J = 7.0 Hz, 1 H, ArCHSO3), 4.64 (sept, J = 6.2 Hz, 1 H, CH2CH2CH3), 7.35–7.44 (m, 5 H, ArH).

13C NMR (75 MHz, CDCl3): δ ≥ 122.5, 22.3 [CH2(CH3)2SO3], 37.3 (CH3), 55.3 (CH3), 64.6 (CHSO3), 78.4 (SO2CH2), 128.9, 129.2, 129.3 (CH2), 133.0 (Caram).

MS (CI, 100 eV, methane): m/e (%) = 312 (2) [M+1], 270 (2), 242 (26), 227 (6), 188 (3), 160 (100), 145 (31), 131 (44), 118 (6), 105 (11), 91 (3).

Anal. Calcd for C16H26ClN2O3S: C, 54.00; H, 6.80; N, 13.49. Found: C, 54.05; H, 6.72; N, 13.41.

Isopropyl (1R,3S)-3-Azido-1-(4-tert-butylphenyl)pentanesulfonate [(R,S)-4d]

According to GP 1, a mixture of the enantiopure sultone (R,R)-1d (100 mg, 0.35 mmol) and NaCN (120 mg, 1.75 mmol) and NH4Cl (41 mg, 0.77 mmol) in anhyd DMF (4 mL) was heated at 60 °C under argon for 2 h. The resulting sodium sulfonate was first treated with methanolic HCl (3 N, 5 mL). After removal of MeOH, a solution of the crude sulfamic acid and triisopropyl orthoformate (0.6 mL, 3 mmol) in CH2Cl2 (5 mL) was refluxed for 2 h. The crude product was purified by column chromatography (SiO2, EtO-n-pentane, 1:19) to give [(R,S)-4d] as a colorless liquid (128 mg, 98%); de ≥ 98% (NMR); ee ≥ 98% (based on the ee-value of the sultone); [α]D26 + 246.6 (c = 1.2, CHCl3).

IR (film): 2966 (s), 2857 (m), 2100 (s), 1513 (m), 1464 (m), 1345 (s), 1270 (m), 1169 (s), 1096 (m), 914 (s), 883 (m), 756 (m), 608 (s) cm-1.

1H NMR (400 MHz, CDCl3): δ = 0.99 (t, J = 7.4 Hz, 3 H, CH3CH2), 1.09 (d, J = 6.3 Hz, 3 H, SO(CH2CH3)2), 1.31 [d, J = 6.3 Hz, 3 H, SO(CH2CH3)2], 1.31 [s, 9 H, CH(CH3)2], 2.21 (dt, J = 7.8, 14.3 Hz, 1 H, CHCH2CH3), 2.50 (dt, J = 6.6, 14.3 Hz, 1 H, CHCH2CH3), 3.70 (m, 1 H, CHN3), 4.32 (t, J = 7.2 Hz, 1 H, ArCHSO3), 4.64 (sept, J = 6.2 Hz, 1 H, CH2CH2CH3), 7.31, 7.40 [two d (AB system), J = 8.4 Hz, 4 H, ArH].
Isopropyl (1R,3S)-3-Azido-3-methyl-1-phenylbutanesulfonate ([R,S]-5a)

According to GP 2, a mixture of the γ-azido sulfonate (R,S)-4a (45 mg, 0.15 mmol) and Boc₂O (0.05 mL, 0.2 mmol) in EtOAc (5 mL) containing a catalytic amount of 10% Pd/C was stirred under a H₂ atmosphere for 18 h at rt. The crude product was purified by flash column chromatography (SiO₂, Et₂O–n-pentane, 1:3) to give (R,S)-5a as a colorless solid (51 mg, 91%); de 98% (NMR and HPLC); ee ≥ 98% (HPLC, Chiral OD, n-heptane–iPrOH, 95:5); mp 88 °C; [α]D 30 +4.4 (c = 1.1, CHCl₃).

IR (CHCl₃): 3389 (m), 2979 (m), 2934 (m), 1702 (s), 1511 (m), 1455 (m), 1364 (m), 1247 (m), 1169 (s), 1059 (m), 913 (s), 883 (s), 757 (s), 699 (cm⁻¹).

1H NMR (400 MHz, CDCl₃): δ = 1.10 (d, J = 6.9 Hz, 3 H, CH₂CH₃), 1.12, 1.30 [two d (J = 1.0, CH₂CH₃), 2.38 (dd, J = 10.2, 14.3 Hz, 1 H, CH(CH₃)₂), 2.57 (dd, J = 1.9, 14.3 Hz, 1 H, CH₂CH₃), 4.28 (dd, J = 1.9, 10.2 Hz, 1 H, ArCH₂SO₂), 4.56 (sept, J = 6.3 Hz, 1 H, (CH₃)₂CHSO₂), 7.35–7.41 (m, 3 H, ArH), 7.43–7.47 (m, 2 H, ArH).

13C NMR (100 MHz, CDCl₃): δ = 22.6, 23.6, 26.4, 27.2 (CH₃), 41.3 (CH₂), 60.9 (CN), 64.6 (CHSO₂), 78.4 (SO₂CH₃), 128.9, 129.1, 129.8 (CH₃CH₂), 133.6 (CH₃O).

MS (EI, 70 eV): m/z (%) = 371 (0.1, [M⁺]), 315 (12), 271 (5), 229 (12), 192 (37), 174 (9), 144 (40), 131 (15), 104 (15), 88 (100), 70 (57). Anal. Calcd for C₆H₉NO₃S: C, 58.20; H, 7.87; N, 11.37. Found: C, 58.66; H, 7.55; N, 3.75.

Isopropyl (1R,3S)-3-tert-Butoxycarbonyl-1-phenylbutanesulfonate ([R,S]-5b)

According to GP 2, a mixture of the γ-azido sulfonate (R,S)-4b (57 mg, 0.16 mmol) and Boc₂O (0.05 mL, 0.23 mmol) in EtOAc (5 mL) containing a catalytic amount of 10% Pd/C was stirred under a H₂ atmosphere for 20 h at rt. The crude product was purified by flash column chromatography (SiO₂, Et₂O–n-pentane, 1:3) to give (R,S)-5b as a colorless viscous liquid (62 mg, 90%); de 98% (NMR); ee ≥ 98% (based on the ee-value of the sulfone); [α]D 30 +6.8 (c = 1.0, CHCl₃).

IR (film): 3389 (m), 2979 (m), 2934 (m), 1702 (s), 1511 (m), 1455 (m), 1364 (m), 1247 (m), 1169 (s), 1059 (m), 913 (s), 883 (s), 757 (s), 699 (cm⁻¹).

1H NMR (400 MHz, CDCl₃): δ = 1.10 (d, J = 6.9 Hz, 3 H, CH₂CH₃), 1.12, 1.30 [two d (J = 1.0, CH₂CH₃), 2.38 (dd, J = 10.2, 14.3 Hz, 1 H, CH(CH₃)₂), 2.57 (dd, J = 1.9, 14.3 Hz, 1 H, CH₂CH₃), 4.28 (dd, J = 1.9, 10.2 Hz, 1 H, ArCH₂SO₂), 4.56 (sept, J = 6.3 Hz, 1 H, (CH₃)₂CHSO₂), 7.35–7.41 (m, 3 H, ArH), 7.43–7.47 (m, 2 H, ArH).

13C NMR (100 MHz, CDCl₃): δ = 20.3 (CH₃), 22.5, 23.3 (CH₂SO₂), 28.3 (CH₂Cl), 36.7 (CH₂), 44.8 (CHN), 65.4 (CHSO₂), 78.0 (SO₂CH₃), 83.8 (CH₃O).

Isopropyl (1R,3S)-3-tert-Butyloxycarbonylazoni-1-phenylpentanesulfonate [(R,S)-5c]

According to GP 2, a mixture of the \( \gamma \)-azido sulfonate (R,S)-4c (64 mg, 0.2 mol), and Boc\(_2\)O (0.05 mL, 0.23 mmol) in EtOAc (5 mL) containing a catalytic amount of 10\% Pd/C was stirred under a H\(_2\) atmosphere for 20 h at r.t. The crude product was purified by flash column chromatography (SiO\(_2\), EtO\(_2\)-n-pentane, 1:4) to give (R,S)-5c as a colorless solid (68 mg, 86\%); de \( > 99\% \) (NMR); ee \( > 98\% \) (based on the ee-value of the sultone); mp 68 °C; \([\alpha]_D^{25} +5.2 \quad (c = 0.8, \text{CHCl}_3).

IR (KBr): 3394 (s), 2970 (m), 2932 (m), 1686 (s), 1522 (s), 1455 (m), 1349 (s), 1276 (m), 1245 (m), 1173 (s), 1095 (m), 875 (s), 807 (m), 796 (m), 698 (m), 632 (m), 560 (m) cm\(^{-1}\).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 98.0 \) (CH, \( \text{CH}_2\)), 22.3, 23.3 [(CH\(_3\))\(_3\)C], 27.4 (CH\(_3\)), 28.3 (CH\(_3\)CH\(_3\)), 35.2 (CH\(_3\)), 50.6 (CHN), 65.4 (CHSO\(_3\)), 77.9 (SO\(_3\))CH\(_3\)), 79.0 [(CH\(_2\))\(_3\)], 128.6, 128.7, 129.3 (CH\(_3\)SO\(_3\)), 131.7 (C\(_{\text{Ar}}\)), 155.0 (CO\(_2\)).

MS (CI, 100 eV, methane): \( m/z \% = 386 \) (\([M+1]^-\)), 356 (6), 330 (11), 316 (7), 288 (100), 272 (8), 256 (7), 244 (37), 206 (64), 188 (6), 158 (12), 145 (5), 132 (6), 102 (30).

Anal. Calc'd for C\(_{19}\)H\(_{31}\)NO\(_5\)S: C, 59.54; H, 8.11; N, 3.75. Found: C, 59.48; H, 8.11; N, 3.63. 

Isopropyl (1R,3S)-3-tert-Butyloxycarbonylazoni-1-(4-butylylphenyl)pentanesulfonate [(R,S)-5d]

According to GP 2, a mixture of the \( \gamma \)-azido sulfonate (R,S)-4d (70 mg, 0.2 mol) and Boc\(_2\)O (0.05 mL, 0.23 mmol) in EtOAc (5 mL) containing a catalytic amount of 10\% Pd/C was stirred under a H\(_2\) atmosphere for 19 h at r.t. The crude product was purified by flash column chromatography (SiO\(_2\), EtO\(_2\)-n-pentane, 1:4) to give (R,S)-5d as a colorless solid (67 mg, 80\%); de \( > 99\% \) (NMR); ee \( > 98\% \) (based on the ee-value of the sultone); mp 67 mg, 80\%; de \( > 99\% \) (NMR); ee \( > 98\% \) (based on the ee-value of the sultone); mp 68 °C; \([\alpha]_D^{25} +5.2 \quad (c = 0.8, \text{CHCl}_3).

IR (KBr): 3394 (s), 2970 (m), 2932 (m), 1686 (s), 1522 (s), 1455 (m), 1349 (s), 1276 (m), 1245 (m), 1173 (s), 1095 (m), 915 (s), 875 (s), 807 (m), 776 (m), 698 (m), 632 (m), 560 (m) cm\(^{-1}\).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 98.0 \) (CH, \( \text{CH}_2\)), 22.3, 23.3 [(CH\(_3\))\(_3\)C], 27.4 (CH\(_3\)), 28.3 (CH\(_3\)CH\(_3\)), 35.2 (CH\(_3\)), 50.6 (CHN), 65.4 (CHSO\(_3\)), 77.9 (SO\(_3\))CH\(_3\)), 79.0 [(CH\(_2\))\(_3\)], 128.7, 128.6, 129.3 (CH\(_3\)SO\(_3\)), 131.7 (C\(_{\text{Ar}}\)), 155.0 (CO\(_2\)).

MS (CI, 100 eV, methane): \( m/z \% = 386 \) (\([M+1]^-\)), 356 (6), 330 (11), 316 (7), 288 (100), 272 (8), 256 (7), 244 (37), 206 (64), 188 (6), 158 (12), 145 (5), 132 (6), 102 (30).

Anal. Calc'd for C\(_{19}\)H\(_{31}\)NO\(_5\)S: C, 59.54; H, 8.11; N, 3.75. Found: C, 59.48; H, 8.11; N, 3.63.
Anal. Calcd for C_{10}H_{15}NO_{3}S: C, 52.38; H, 6.59; N, 6.11. Found: C, 52.09; H, 6.88; N, 5.92; IR (KBr): 2931, 2869, 2832, 1775, 1710, 1662, 1619, 1560, 1507, 1458, 1382, 1327, 1252, 1178, 1132, 1084, 1030, 909, 828, 755, 733, 698, 662 cm\(^{-1}\).

(5)-N-Acetyl-4-phenyl-2-butanoylamine ([S]-11)

A mixture of the enantiopure sultone ([R]-1a) (75 mg, 0.354 mmol), NaN\(_3\) (115 mg, 1.77 mmol) and NH\(_2\)Cl (42 mg, 0.78 mmol) in anhyd DMF (3 mL) was heated at 60 °C under argon for 2 h. DMF was removed under vacuum almost completely and the remaining sodium sulfonate ([R]-2a) in a small amount of DMF (about 0.2 mL) was suspended in anhyd CH\(_2\)Cl\(_2\) (5 mL). A solution of 20% COCl\(_2\) in toluene (0.5 mL) was added dropwise at 0 °C and the mixture was stirred at r.t. for 1 h. The mixture was then filtered and the solid was triturated with CH\(_2\)Cl\(_2\) and refiltered. The combined CH\(_2\)Cl\(_2\) fractions were evaporated under reduced pressure and the crude product was purified again through a short-path silica gel column in order to remove the polar impurities. The solvent was removed to give the sulfonyl chloride 9, which was used in the next step without further purification. A solution of the crude \(\gamma\)-azido sulfonyl chloride 9 in MeOH (10 mL) containing a catalytic amount of 10% Pd/C was stirred under H\(_2\) at r.t. The catalyst was removed by filtration off through a pad of Celite and washed with H\(_2\)O. The filtrate was evaporated under reduced pressure. The resulting solid was washed with Et\(_2\)O providing the desired product ([S]-8) as a colorless solid (210 mg, 92%); de \(\geq98\%\) (based on the ee-value of sultone); mp >300 °C; \([\alpha]_{D}^{26} = 35.2\) (c = 0.7, EtOH).

IR (KBr): 3307 (s), 2966 (s), 1632 (m), 1453 (m), 1398 (m), 1240 (s), 1195 (s), 1157 (s), 1038 (s), 785 (m), 701 (s), 651 (s), 591 (m), 523 (m) cm\(^{-1}\).

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1H NMR (300 MHz, CDCl3): δ = 1.17 (d, J = 6.6 Hz, 3 H, CH3), 1.75 (m, 2 H, CH2CH3), 1.93 (s, 3 H, CO2CH3), 2.65 (t, J = 8.0 Hz, 2 H, PhCH2), 4.05 (m, 1 H, CHNH), 7.14–7.22 (m, 3 H, ArH), 7.24–7.32 (m, 2 H, ArH).

13C NMR (75 MHz, CDCl3): δ = 21.1 (CH3), 23.5 (CH3), 32.5 (CH3), 38.6 (CH2), 45.3 (CHN), 125.9, 128.3, 128.4 (CHarom), 141.8 (C aromatic), 169.5 (C=O).

MS (EI, 70 eV): m/z (%) = 191 (52, [M]+), 132 (22), 117 (51), 87 (100), 72 (23), 58 (13).

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References


