Asymmetric Synthesis of β-Amino-cyclohexyl Sulfonates via aza Michael Addition

Dieter Enders,* Stefan Wallert

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

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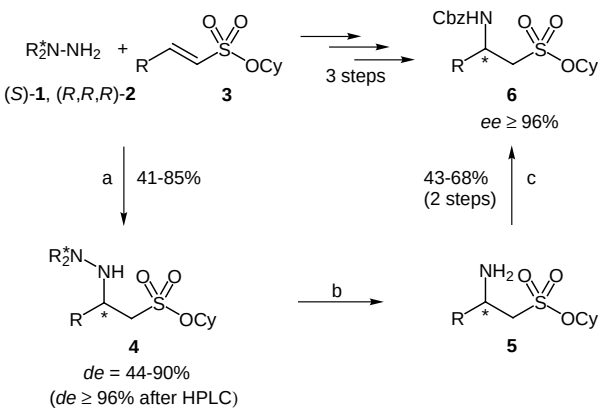
Abstract: The Lewis acid catalyzed asymmetric synthesis of β-amino-cyclohexyl sulfonates via aza-Michael addition is reported. As key step the addition of (*S*)-1-amino-2-methoxymethyl-pyrrolidine (SAMP) or (*R*,*R*,*R*)-2-amino-3-methoxymethyl-2-azabicyclo[3.3.0]-octane (RAMBO) to alkenyl-cyclohexyl sulfonates is applied, to give β-hydrazino sulfonates in moderate to good yields and diastereomeric excesses (yield = 41–85%, *de* = 55–90%). The epimers are separated by preparative HPLC, followed by reductive N–N bond cleavage with BH_3·THF and protection of the resulting amines with CbzCl to afford *N*Cbz-protected-β-amino-cyclohexyl sulfonates in moderate to good yields (38–68%, 2 steps) and enantiomeric excesses (*ee*) of ≥96%.

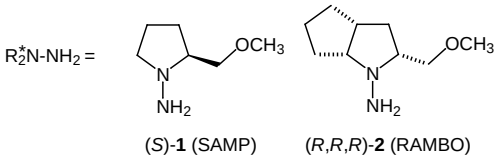
Key words: asymmetric synthesis, Michael addition, sulfonates, hydrazines, Lewis acid

The synthesis of unnatural amino acids is still of great importance, since these compounds can be utilized for example in the preparation of new peptides with a high potential for biological activities. In recent years 2-substituted taurines were used in the synthesis of β-amino sulfonopeptides.[1] White et al. designed β-sulfonopeptides as inhibitors of D-alanyl-D-alanine transpeptidases containing a taurine instead of a penultimate amino acid.[2] Furthermore, Liskamp et al. synthesized oligopeptido sulfonamides on solid phase in order to analyze their three-dimensional structure and biological activity.[3]

In addition to the peptides, the β-amino-sulfonates themselves are of great interest. The best known β-amino-sulfonic acid is taurine, but there are also other interesting derivatives like 2-amino-2-phenylethanesulfonic acid[4] as a potential $GABA_B$ receptor antagonist or flavocristamide[5] A and B, which have inhibitory activity against DNA polymerase α.

The Michael reaction can provide an efficient access to the desired taurine derivatives. The first published aza-Michael addition to alkenyl-sulfonates is dated to 1970, when Dumaitre et al. reacted primary and secondary amines with ethene-sulfonates.[6] During the following years, considerable attention towards the aza-Michael addition to alkenyl-sulfonates[7] has been shown, but to our knowledge enantioselective 1,4-additions with enantiopure nitrogen-nucleophiles have not been described.





Scheme *Reagents and conditions*: a) $ZnBr_2$ (0.2 equiv), MeOH, add **3**, add (*S*)-**1** or (*R*,*R*,*R*)-**2** (3.0 equiv), r.t., 7–14 d. b) BH_3·THF (10 equiv, 1.0 M in THF), THF, reflux, 5 h; r.t., add MeOH, reflux, 1 h. c) CbzCl (3.0 equiv), Na_2CO_3 (6.0 equiv), CH_2Cl_2–H_2O (4:1), reflux, 1–3 d.

We now wish to report the 1,4-addition of (*S*)-1-amino-2-methoxymethyl-pyrrolidine (SAMP, (*S*)-**1**)[8] to (*E*)-alkenyl-cyclohexyl sulfonates **3**. As shown in the Scheme, (*S*)-**1** could be added to **3** in the presence of catalytic amounts of zinc bromide ($ZnBr_2$) in moderate to good yields and moderate diastereomeric excesses (Table 1). After work up, the epimers could be separated by preparative HPLC to yield virtually diastereomerically pure β-hydrazino-cyclohexyl sulfonates **4**. The absolute configuration was determined by NMR spectroscopy (NOE-experiments).[9]

Further investigations led us to (*R*,*R*,*R*)-2-amino-3-methoxymethyl-2-azabicyclo[3.3.0]octane [RAMBO, (*R*,*R*,*R*)-**2**], which was used as a chiral auxiliary in the aza-Michael addition to alkenyl-sulfones.[10] The enantiomer SAMBO was first synthesized by Martens et al.[11] Starting from (*R*,*R*,*R*)-2-azabicyclo[3.3.0]octane-3-carboxylic acid benzyl ester, a side product in the synthesis of the ACE-inhibitors ramipril of the former Hoechst AG,[12] (*R*,*R*,*R*)-**2** was produced in a 5 step synthesis. The use of RAMBO instead of SAMP had a significant effect on the diastereomeric excesses, which increased from *de* =

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Table 1 Aza-Michael Addition of SAMP [(*S*)-**1**] to 1-(*E*)-Alkenyl-Cyclohexyl Sulfonates **3**

4	R	Yield (%)	*de*[a] (%)
(*R*,*S*)–**4a**	Me	78	44 (≥ 96)
(*R*,*S*)–**4b**	Et	74	55 (≥ 96)
(*R*,*S*)–**4c**	*n*-Pr	73	58 (≥ 96)
(*R*,*S*)–**4d**	*i*-Pr	41	80 (≥ 96)
(*R*,*S*)–**4e**	$Ph(CH_2)_2$	66	60 (≥ 96)

[a] Determined by ^{13}C NMR spectroscopy; in brackets: after HPLC on chiral stationary phase (Daicel AD).

50–60% up to *de* = 80–90% (Table 2). As in the case of SAMP, the epimers **4** could be separated by preparative HPLC and the configuration of the new stereogenic center was determined by NMR-spectroscopy (NOE-experiments).[9]

Table 2 Aza-Michael Addition of RAMBO [(*R*,*R*,*R*)-**2**] to 1-(*E*)-Alkenyl Cyclohexyl Sulfonates **3**

4	R	Yield (%)	*de*[a] (%)
(*S*,*R*,*R*,*R*)–**4f**	Me	77	64 (≥ 96)
(*S*,*R*,*R*,*R*)–**4g**	Et	85	77 (≥ 96)
(*S*,*R*,*R*,*R*)–**4h**	*n*-Pr	62	82 (≥ 96)
(*S*,*R*,*R*,*R*)–**4i**	*i*-Pr	44	90 (≥ 96)
(*S*,*R*,*R*,*R*)–**4j**	$Ph(CH_2)_2$	63	78 (≥ 96)
(*S*,*R*,*R*,*R*)–**4k**	*n*-Bu	65	80 (≥ 96)

[a] Determined by ^{13}C NMR spectroscopy, in brackets: after HPLC on chiral stationary phase (Daicel AD).

In the following step the chiral auxiliary of **4** was removed by a racemization free reductive N–N bond cleavage utilizing BH_3·THF.[13] The resulting crude amines **5** were not purified, but directly protected with CbzCl to yield *N*-Cbz-protected-β-amino-cyclohexyl sulfonates **6** in moderate to good yields and high enantiomeric excesses (Table 3).

In summary, we have developed a novel method for the asymmetric synthesis of β-amino-cyclohexyl sulfonates. The reaction sequence starts with an aza-Michael-addition of SAMP or RAMBO to 1-*(E)*-alkenyl cyclohexyl sulfonates, followed by N–N-bond cleavage of the generated hydrazines utilizing BH_3·THF and Cbz protection of the resulting amines.[14–16]

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Table 3 Synthesis of *N*-Cbz-Protected Amines **6**.

6	R	Yield[a] (%)	*ee*[b] (%)
(*R*)–**6a**	Me	68	≥ 96
(*R*)–**6b**	Et	53	≥ 96
(*R*)–**6c**	*n*-Pr	43	≥ 96
(*R*)–**6d**	*i*-Pr	52	≥ 96
(*R*)–**6e**	$Ph(CH_2)_2$	53	≥ 96
(*S*)–**6a**	Me	56	≥ 96
(*S*)–**6b**	Et	53	≥ 96
(*S*)–**6c**	*n*-Pr	38	≥ 96
(*S*)–**6d**	*i*-Pr	57	≥ 96
(*S*)–**6e**	$Ph(CH_2)_2$	56	≥ 96
(*S*)–**6f**	*n*-Bu	63	≥ 96

[a] Over 2 steps.
[b] Determined by HPLC on chiral stationary phase (Daicel AD).

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(9) (*R*,*S*)-**4d**: NOE's were observed between: C*H*N↔NCH_2, C*H*C$H_{3\,(a)}$↔CH_2CH_3, C*H*-Cy↔CH_2SO_2. (*S*,*R*,*R*,*R*)-**4j**: NOE's were observed between: C*H*CH_3↔CH_2CH_3, CHC$H_{3\,(a)}$↔CH_2CH_3, C*H*-Cy↔N*H*, C*H*NH↔NCHCH_2CH_2.

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(14) General procedure for the preparation of compounds **4**–**6**.
Synthesis of β-hydrazino-cyclohexyl sulfonates **4a**–**k**:
$ZnBr_2$ (0.2 equiv) was dissolved in dry MeOH (1 mL/mmol **3**) under argon atmosphere. The sulfonate **3** was added to the mixture and the solution was stirred for 10 min at room temperature. Then 3 equiv (*S*)-**1** or (*R*,*R*,*R*)-**2** was added and the reaction mixture was stirred for 7–14 d at room temperature. The solution was poured into a mixture of *n*-pentane and diethyl ether (2:1, 30 mL/mmol **3**) to precipitate the Lewis acid. After filtration through Celite® the crude product was purified by column chromatography (SiO_2, *n*-pentane–diethyl ether) to afford **4** as colorless oils.
Synthesis of β-amino-cyclohexyl sulfonates **5**:
The β-hydrazino-sulfonates **4a**–**k** were dissolved in dry THF (10 mL/mmol **4**) under argon atmosphere. BH_3·THF (10 equiv, 1.0 M in THF) was added and the reaction mixture was refluxed for 5 h. After cooling to r.t. the solution was slowly quenched with MeOH (3 mL/mmol **4**). The solvents were carefully evaporated and the mixture was treated again with MeOH (30 mL/mmol **4**). The solution was refluxed for 30 min after which the solvent was removed under reduced pressure and the crude amines were used in the next reaction step without further purification.
Synthesis of Cbz-protected amines **6**:
The crude product **5** was dissolved in a mixture of CH_2Cl_2 and H_2O (4:1, 10 mL/mmol **4**). Na_2CO_3 (6 equiv) and CbzCl (3 equiv) were added at r.t. The reaction mixture was refluxed for 1–3 d. After separation of the organic layer the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 solution and brine. After drying over $MgSO_4$ the solvent was evaporated and the products were purified by column chromatography (SiO_2, *n*-pentane–Et_2O) to afford **6** as colorless solids.
(15) Selected analytical and spectroscopic data of compounds **4** and **6**. Analytical data of compound (*S*,*R*,*R*,*R*)-**4h**: $[\alpha]_D^{24}$ = +17.7 (1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.9 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3); 1.1–2.1 (m, 22 H, $CH_2CH_2CH_2$, $CH_2CH_2CH_3$, $CHCH_2CH$, CH_2-Cy), 2.4 (q, *J* = 8.79 Hz, 1 H, NCHC*H*), 2.7 (sex, *J* = 5.40 Hz, 1 H, NC*H*CH_2O), 3.1 (dd, *J* = 14.3, 5.5 Hz, 2 H, NC*H*CH, CH*H*SO_2), 3.3 (m, 2 H, C*H*HSO_2, CH*H*OCH_3), 3.3 (s, 3 H, OCH_3), 3.5 (m, 2 H, C*H*$HOCH_3$, C*H*NH), 4.7 (sep, *J* = 4.3 Hz, 1 H, C*H*-Cy); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.60, 18.61, 23.84, 24.50, 25.23, 33.16, 33.42, 33.89, 35.10, 35.72, 38.93, 54.01, 55.00, 59.23, 68.81, 75.58, 75.91, 81.24; MS (EI) *m/z* 402, 320, 277, 276, 275, 169, 67; IR ($CHCl_3$): 3260, 2938, 2863, 2371, 1649, 1451, 1348, 1265, 1240, 1195, 1168, 1119, 1033, 1004, 937, 870, 833, 792, 737, 702, 643, 603, 564, 531, 490, 463 cm^{-1}; Anal. Calcd. for: $C_{20}H_{38}N_2O_4S$: C, 59.70; H, 9.45; N, 6.97. Found: C, 59.50; H, 9.64; N, 7.16.
Analytical data of compound (*R*,*S*)-**4e**: $[\alpha]_D^{24}$ = –55.7 (1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.1–2.1 (m, 16 H, $NCH_2CH_2CH_2$, CH_2-Cy, CH_2CH_2Ar), 2.3 (q, *J* = 8.70 Hz, 1 H, CH*H*N), 2.6–2.8 (m, 3 H, OCH_2CHN, CH_2CH_2Ar), 2.9 (s, 1 H, N*H*), 3.1 (dd, *J* = 14.56, 4.12 Hz, 1 H, CH*H*SO_2), 3.2 (dd, *J* = 14.43, 7.50 Hz, 1 H, C*H*HSO_2), 3.3 (s, 3 H, OCH_3), 3.3–3.5 (m, 3 H, C*H*NH, CH*H*O, C*H*HN), 3.5 (dd, *J* = 9.06, 4.12 Hz, 1 H, C*H*HO), 4.7 (sep, *J* = 4.3 Hz, 1 H, C*H*-Cy), 7.2–7.3 (m, 5 H, C*H*-Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.24, 23.69, 25.07, 26.39, 31.45, 32.95, 33.02, 34.53, 54.36, 54.43, 57.16, 59.26, 66.15, 75.04, 81.39, 126.14, 128.59, 128.62, 141.90; MS (EI) *m/z* 424, 342, 299, 298, 297, 129, 91, 70; IR ($CHCl_3$): 3639, 3281, 3085, 3061, 3026, 2937, 2862, 2312, 1947, 1805, 1724, 1603, 1583, 1496, 1454, 1344, 1265, 1169, 1118, 1031, 1003, 935, 870, 829, 747, 700, 644, 595, 533, 489, 457 cm^{-1}; Anal. Calcd. for: $C_{22}H_{36}N_2O_4S$: C, 62.26; H, 8.49; N, 6.60. Found: C, 62.33; H, 8.80; N, 6.69.
Analytical data of compound (*R*,*S*)-**6k**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.9 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.2–2.0 (m, 14 H, CH_2-Cy, $CH_2CH_2CH_3$), 3.3 (dd, *J* = 14.43, 4.21 Hz, 1 H, CH*H*SO_2), 3.4 (dd, *J* = 14.42, 5.60 Hz, 1 H, C*H*HSO_2), 4.1 (m, 1 H, C*H*NH), 4.7 (sep, *J* = 4.12 Hz, 1 H, C*H*–Cy), 5.1 (s, 2 H, OCH_2), 5.2 (s, 1 H, N*H*), 7.3–7.4 (m, 5 H, *H*-Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.71, 25.06, 32.51, 32.94, 32.99, 35.29, 47.78, 55.12, 67.16, 82.05, 126.47, 128.34, 128.48, 128.82, 128.67, 136.53, 140.86, 155.89; IR (KBr): 3854, 3839, 3751, 3676, 3362, 3030, 2936, 2863, 2344, 1691, 1533, 1498, 1454, 1409, 1384, 1328, 1294, 1247, 1214, 1170, 1127, 1049, 1010, 930, 905, 874, 832, 776, 742, 728, 699, 614, 585, 559, 528, 493, 458 cm^{-1}; Anal. Calcd. for: $C_{24}H_{31}NO_5S$: C, 64.72; H, 7.00; N, 3.15. Found: C, 64.63; H, 7.44; N, 3.06.
(16) All new compounds showed suitable spectroscopic data (NMR, MS, IR) and correct elemental analyses.