A General Route to the Synthesis of N-Protected 1-Substituted and 1,2-Disubstituted Taurines

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Abstract: *N*-Benzyloxycarbonyl protected α-substituted and α,β-disubstituted taurines were synthesized from olefins and epoxides via *N*-benzyloxycarbonylamino alcohol thioacetates as key intermediates. They are important sulfur analogues of naturally occurring amino acids and building blocks for the synthesis of α-substituted and α,β-disubstituted β-sulfonopeptides.

Key words: amino acid, aminoalkanesulfonic acid, epoxide, olefin, synthesis

There is a growing interest in the structural modification of natural peptides to overcome the limitations associated with their development as therapeutically useful agents, and to gain information on the nature and mechanism of the peptide-receptor interactions.[1–3] The phosphonamidate, phosphonate and sulfonamide-linked peptides are very important modified peptides and are recognized to be able to mimic transition-state analogues of hydrolysis of ester and amide bonds because of their tetrahedrally structural properties. During the last decade aminoalkylphosphonic acid and aminoalkanesulfonic acid derivatives, and phosphonopeptides and sulfonopeptides have been used as enzyme inhibitors and haptens in the development of catalytic antibodies.[4–7] Sulfonopeptides are more stable under both mildly acidic and basic conditions compared to phosphonopeptides and will be used more widely. β-Aminoalkanesulfonic acids are very important sulfur analogues of naturally occurring amino acids for the synthesis of sulfonopeptides because α-aminoalkanesulfonic acids and their derivatives are unstable.[8] There are three types of structural analogues of naturally occurring amino acids for β-aminoalkanesulfonic acids, which include 1-substituted taurines, 2-substituted taurines, and 1,2-disubstituted taurines (Figure 1). 2-Substituted taurines have been synthesized effectively from β-amino primary alcohols,[9–18] which were easily obtained by reduction of natural amino acids, from β-amino secondary alcohols[19,20] via sulfite displacement of their methanesulfonates,[9–12] peroxy acid oxidation of their thioacetates,[13–17,21] and sulfite ring-opening of aziridines.[18] But little attention has been paid to the synthesis of 1-substituted and 1,2-disubstituted taurines[15,21,22] and their sulfonopeptides.[21,23,24] To synthesize structurally diverse sulfonopeptides, it is very important to develop an effective and general method for the preparation of 1-substituted and 1,2-disubstituted taurines. Herein we describe a general route to 1-substituted and 1,2-disubstituted taurines from olefins and epoxides.

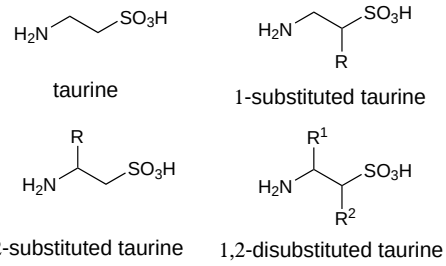

Figure 1

Taurine and substituted taurines

As part of a program to synthesize structurally diverse sulfur analogues of naturally occurring amino acids, we sought to prepare 1-substituted and 1,2-disubstituted taurines. 1,2-Amino secondary alcohols are important key intermediates for synthesizing 1-substituted taurines. They could be prepared from available terminal olefins or 1,2-epoxyalkanes. Although alkenes could be converted to 1,2-N-protected amino alcohols directly via Sharpless aminohydroxylation, terminal alkenes generally yield a mixture of 1,2-N-protected amino primary/secondary alcohols in most cases.[25] Recently there was a report on the preparation of useful levels of 1,2-N-protected amino secondary alcohols in high regioselectivity, however, the alkenes used were limited to styrenes.[26] Thus, we planned to prepare 1,2-amino secondary alcohols via ammonia ring opening of epoxides, which could be synthesized from terminal alkenes. Firstly, terminal olefin styrene (**1a**) was converted to styrene oxide (**3a**) using Oxone and 1,3-dichloroacetone in 63% yield.[27] The yield is not satisfactory and a large quantity of Oxone was necessary. Finally, terminal olefins styrene (**1a**) and hex-1-ene (**1b**) were converted conveniently to corresponding bromohydrins **2a**,**b** with NBS in water,[28] which were treated with ammonia to yield aminohydrins **4a**,**b** directly via epoxide intermediates **3a**,**b**, followed by reaction with benzyl chloroformate to afford benzyl *N*-(2-hydroxyalkyl)carbamates **5a**,**b**. The 1,2-epoxyalkanes **3c**–**e** were treated with ammonia, followed by reaction with benzyl chloro-

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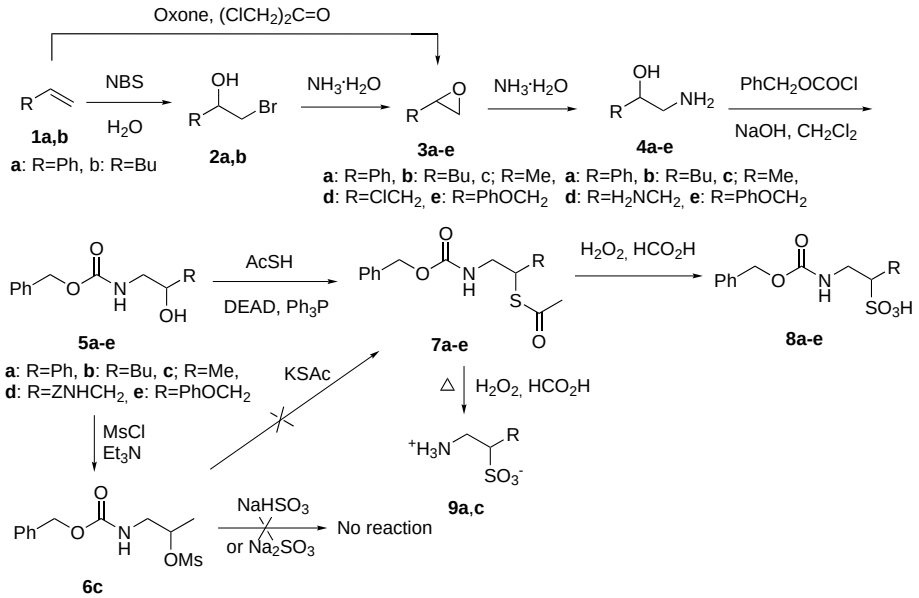
formate to afford carbamates **5c**–**e**. In the case of epoxide **3d**, the chloro group was also converted to (benzyloxycarbonyl)amino group at the same time.

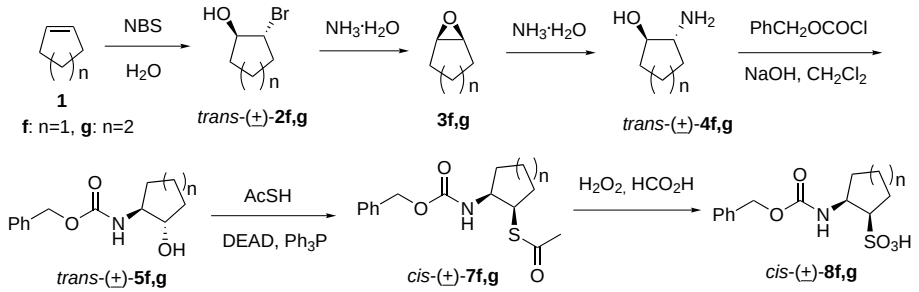
When we investigated the mechanism of transformation of β-amino alcohol methanesulfonate hydrochlorides into sodium β-amino alkanesulfonates with sodium sulfite, we found that β-amino alcohol methanesulfonates favor the formation of aziridines via intramolecular amino substitution by participation of a neighboring group and then undergo a ring-opening reaction through sulfite attack at the less steric carbon atom in the aziridine ring.[18] We presumed first that the nucleophilicity of the amino group of β-amino alcohol methanesulfonates could be reduced if it is protected with a carbamate group and 1-substituted taurines could be prepared from N-protected β-amino secondary alcohol methanesulfonates. Thus, 1-(benzyloxycarbonyl)aminopropan-2-ol methanesulfonate (**6c**) was prepared first from carbamate **5c** via methanesulfonation with methanesulfonyl chloride. Although 2-(benzyloxycarbonyl)aminopropan-1-ol methanesulfonate reacted with sodium bisulfite or sodium sulfite smoothly to yield 2-(benzyloxycarbonyl)aminopropane-1-sulfonic acid in good yield,[9–12] methanesulfonate **6c** did not react with sodium bisulfite or sodium sulfite under a variety of reaction conditions, which included sodium bisulfite or sodium sulfite in a mixture of ethanol and water, in DMF or DMSO, or in a biphase mixture of dichloromethane and water with the phase-transfer catalyst TEBA, etc. (Scheme 1). This indicates that the nucleophilicity of bisulfite and sulfite is not strong enough to attack the secondary alcohol methanesulfonate possibly because there is more steric hindrance here than a primary alcohol methanesulfonate.

An alternative method to prepare aminoalkanesulfonic acids is the oxidation of aminoalkyl mercaptans, their disulfides or their thioacetates.[13–17] The hydroxy carbamates **5a**–**e** were esterified with thiolacetic acid, DEAD (diethyl azodicarboxylate), and triphenylphosphine under Mitsunobu conditions to give (benzyloxycarbonyl)aminoalkyl thioacetates **7a**–**e**.[13–15] Although vicinal *N*-acylamino alcohols afford oxazoline or oxazole derivatives usually as main byproducts or desired products under the Mitsunobu conditions,[29–32] no oxazoline derivative was found in the present reaction mixture due to the difficult enolization of the carbamates and the existence of a strong nucleophilic thioacetate anion in the reaction medium. The preparation of thioacetates **7c** was also attempted from the reaction of methanesulfonate **6c** and potassium thioacetate in DMF at room temperature and heating conditions. However, no desired product was obtained although 2-(benzyloxycarbonyl)aminoalkan-1-ol methanesulfonate can undergo a substitution reaction smoothly with potassium or cesium thioacetate.[10,15–17] The difference was presumed to be due to the more steric hindrance of a secondary alcohol methansulfonate. The thioacetates **7a**–**e** were oxidized with performic acid, generated in situ by mixing formic acid and hydrogen peroxide, to produce desired N-protected 1-substituted taurines **8a**–**e** after mixing the crude product with silica gel, evaporation at room temperature, and silica gel chromatographic separation. If direct removal of solvent and excess performic acid by evaporation under reduced pressure at above 50 °C was carried out, free 1-substituted taurines **9a**,**c** were obtained directly (Scheme 1).

In a similar manner, two cyclic aminoalkanesulfonic acids **8f**,**g**, a type of 1,2-disubstituted taurines, were also prepared from cyclopentene (**1f**) and cyclohexene (**1g**), respectively. Bromohydrination of **1f**,**g** gave *trans*-2-bromocycloalkanols *trans*-**2f**,**g**. During treatment with ammonia *trans*-2-bromocycloalkanols *trans*-**2f**,**g** were converted first to *meso*-1,2-epoxycycloalkanes **3f**,**g** as in-



Scheme 1 Synthesis of 1-substituted taurines



Scheme 2 Synthesis of 1,2-disubstituted taurines

termediates, which further underwent a ring-opening reaction followed by N-protection with benzyl chloroformate to give *trans*-2-(benzyloxycarbonyl)aminocycloalkanols *trans*-**5f**,**g**. The alcohols *trans*-**5f**,**g** were converted to the corresponding thioacetates *cis*-**7f**,**g** by Mitsunobu reaction,[13–15] in which Walden conversion occurred completely. The thioacetates *cis*-**7f**,**g** were subsequenetly oxidized with performic acid to afford *cis*-2-(benzyloxycarbonyl)aminocycloalkanesulfonic acids *cis*-**8f**,**g** in good yields (Scheme 2). The cyclic aminoalkanesulfonic acids could be considered as a type of sulfur mimetics of proline.

In summary, 1-substituted and 1,2-disubstituted (cyclic) taurines were prepared from olefins and epoxides by employing N-protected 2-aminoalkan-1-ol thioacetates as key intermediates. They are important sulfur analogues of naturally occurring amino acids and building blocks for synthesis of α-substituted and α,β-disubstituted β-sulfonopeptides and other substituted 2-aminoethanesulfonic acid containing compounds.

Melting points were measured on a Yanaco MP-500 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 (200 MHz) or Mercury Plus 300 (300 MHz) spectrometer in $CDCl_3$ with TMS as an internal standard or in DMSO-d_6. Mass spectra were obtained on a VG-ZAB-HS mass spectrometer or a Bruker ESQUIRE-LC^{TM} ESI ion trap spectrometer. CHN analyses were recorded on an Elementar Vario EL analyzer. The analytical data of all known compounds are identical to those reported earlier in the literature.[25–27]

THF was refluxed over sodium and distilled prior to use. Et_3N was refluxed over NaOH and distilled prior to use.The petroleum ether used had a bp range 60–90 °C.

Vicinal Bromohydrins 2; General Procedure

Alkene **1** (10 mmol) and NBS (1.78 g, 10 mmol) were added to H_2O (4 mL). The resulting suspension was stirred for 1 to 48 h depending on alkene (monitoring by TLC). After the reaction was over, the mixture was separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with aq 10% $NaHSO_3$ (2 × 15 mL) to remove excess NBS and Br_2 (***Caution!*** it is advisable to use a big separatory funnel due to Br_2 vapors) and dried (Na_2SO_4). After concentration, the residue was distilled to afford the bromohydrin as a colorless oil.

2-Bromo-1-phenylethanol (2a)

Colorless liquid; yield: 72%; bp 140–160 °C/6 mmHg (Lit.[28] bp 120–123 °C/5 mmHg).

1-Bromohexan-2-ol (2b)

Colorless liquid; yield: 82%; bp 100–104 °C/6 mmHg (Lit.[33] colorless liquid).

***trans*-2-Bromocyclopentanol (2f)**

Colorless liquid; yield: 64%; bp 105–130 °C/25 mmHg (Lit.[34] colorless liquid).

***trans*-2-Bromocyclohexanol (2g)**

Colorless liquid; yield: 54%; bp 70–76 °C/6 mmHg (Lit.[28] bp 73–75 °C/5 mmHg).

Vicinal Benzyloxycarbonylamino Alcohols 5; General Procedure

To 26–28% aq ammonia (or a mixture with some EtOH for water-insoluble bromohydrin, 500 mL) was added rapidly a solution of bromohydrin **2** or epoxide **3** (25 mmol) in EtOH (15 mL) under stirring at r.t. After stirring for 12–24 h, the resulting mixture was concentrated (for bromohydrins, the resulting mixtures were neutralized with aq 1 N NaOH to convert NH_4Br into NaBr and NH_3, so that NH_3 could be removed during concentration) to afford a residue (about 10–20 mL) under reduced pressure below 80 °C (below 40 °C for 1-aminopropan-2-ol).[35] The residue was added to a mixture of aq 1 N NaOH (25 mL) and CH_2Cl_2 (25 mL). To the solution was added dropwise a 50% (wt) solution of benzyl chloroformate in toluene (8.53 g, 25 mmol) under vigorous stirring over 10 min at –5 to 5 °C in an ice-salt bath. The resulting solution was allowed to warm to r.t., and stirred overnight. After separation, the aqueous phase was extracted with CH_2Cl_2 (15 mL) and the combined organic layers were washed with H_2O (2 × 10 mL), brine (10 mL), and dried ($MgSO_4$). After removal of solvent, a colorless crystalline or an oily product was obtained, which could be purified by crystallization from petroleum ether–EtOAc. For the preparation of dicarbamate **5d**, 50 mmol of NaOH and benzyl chloroformate were used.[36]

Benzyl *N*-(2-Hydroxy-2-phenylethyl)carbamate (5a)

Colorless crystals; yield: 62%; mp 120–121 °C (Lit.[25] mp 114–115 °C).

Benzyl *N*-(2-Hydroxyhexyl)carbamate (5b)

Colorless needles; yield: 84%; mp 60.5–61 °C; R_f 0.40 (petroleum ether–EtOAc, 2:1, silica gel plate).

IR (KBr): 3400 and 3346 (NH, OH), 1701 cm^{-1} (C=O).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35 (s, 5 H, C_6H_5), 5.26 (br s, 1 H, NH), 5.10 (s, 2 H, OCH_2), 3.68 (m, 1 H, CH), 3.38 (ddd, *J* = 3.0, 6.4, 13.8 Hz, 1 H, NC*H*H), 3.05 (ddd, *J* = 5.2, 7.8, 13.8 Hz, 1 H, NCH*H*), 2.31 (s, 1 H, OH), 1.41–1.33 (m, 6 H, 3 × CH_2), 0.90 (t, *J* = 6.2 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.93, 136.22, 128.23, 127.84, 127.79, 70.77, 66.51, 46.74, 34.07, 27.42, 22.40, 13.78.

MS (EI): *m*/*z* (%) = 251 (M^+, 1.6), 165 (M^+ – BuCHO, 18), 150 (M^+ – $PhCH_2O_2CNH$, 2.7), 108 ($PhCH_2OH^+$, 17), 91 ($PhCH_2^+$, 100).

Anal. Calcd for $C_{14}H_{21}NO_3$ (251.32): C, 66.91; H, 8.42; N, 5.57. Found: C, 66.69; H, 8.69; N, 5.65.

Benzyl *N*-(2-Hydroxypropyl)carbamate (5c)
Colorless oil; yield: 77% (based on 1- aminopropan-2-ol) (Lit.[37] mp 31–32 °C).

Dibenzyl *N*,*N*′-1,3-(2-Hydroxypropylene)dicarbamate (5d)
Colorless crystals; yield: 73%; mp 127.5–128.5 °C (Lit.[38] mp 122–123 °C).

Benzyl *N*-(2-Hydroxy-3-phenoxypropyl)carbamate (5e)
Colorless crystals; yield: 86%; mp 77.5–78 °C; R_f 0.20 (petroleum ether–EtOAc, 2:1, silica gel plate).

IR (KBr): 3356 (NH, OH), 1703 cm^{-1} (C=O).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–6.82 (m, 10 H, 2 × C_6H_5), 5.53 (t, *J* = 6.6 Hz, 1 H, NH), 5.06 (s, 2 H, OCH_2), 4.04 (m, 1 H, CH), 3.89 (m, 2 H, OCH_2), 3.46 (ddd, *J* = 3.9, 6.6, 14.1 Hz, 1 H, NC*H*H), 3.29 (ddd, *J* = 5.7, 6.6, 14.1 Hz, 1 H, NCH*H*), 3.23 (s, 1 H, OH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.20, 157.17, 136.19, 129.39, 128.38, 128.03, 127.94, 121.09, 114.39, 69.37, 69.29, 66.81, 43.69.

MS (EI): *m*/*z* (%) = 301 (M^+, 0.87), 208 (M^+ – PhO, 9.0), 192 (M^+ – H_2O – $PhCH_2$, 23), 108 ($PhCH_2OH^+$, 7.7), 107 ($PhCH_2O^+$, 9.8), 91 ($PhCH_2^+$, 100).

Anal. Calcd for $C_{17}H_{19}NO_4$ (301.34): C, 67.76; H, 6.36; N, 4.65. Found: C, 67.59; H, 6.49; N, 4.75.

***trans*-Benzyl *N*-(2-Hydroxycyclopentyl)carbamate (5f)**
Colorless crystals; yield: 60%; mp 61.5–62 °C (Lit.[39] mp 57–59 °C).

***trans*-Benzyl *N*-(2-Hydroxycyclohexyl)carbamate (5g)**
Colorless needles; yield: 78%; mp 109.5–110 °C (Lit.[40] mp 115–116 °C).

1-(Benzyloxycarbonyl)aminopropan-2-ol Methanesulfonate (6c)
To an ice-cooled solution of **5c** (0.65 g, 3.1 mmol) and Et_3N (0.35 g, 3.4 mmol) in CH_2Cl_2 (10 mL) was added a solution of MsCl (0.39 g, 3.4 mmol) in CH_2Cl_2 (10 mL) dropwise over 0.5 h. The mixture was evaporated in vacuo, and the residue was treated with EtOAc and H_2O. The separated organic layer was washed with 5% aq $NaHCO_3$ and brine, and dried (Na_2SO_4). The solvent was removed in vacuo to give a colorless oil; yield: 98%.

IR (KBr): 3389 (NH), 2939 (C–H), 1718 (C=O), 1252 (SO_2), 1176 cm^{-1} (SO_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 5 H, C_6H_5), 5.38 (br s, 1 H, NH), 5.10 (s, 2 H, OCH_2), 4.84 (ddq, *J* = 3.3, 6.3, 6.6 Hz, 1 H, CH), 3.47 (ddd, *J* = 3.3, 6.2, 15.0 Hz, 1 H, NC*H*H), 3.27 (ddd, *J* = 6.3, 7.2, 15.0 Hz, 1 H, NCH*H*), 2.92 (s, 3 H, CH_3SO_3), 1.38 (d, *J* = 6.6 Hz, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 156.42, 136.19, 128.44, 128.12, 128.05, 78.19, 66.83, 45.83, 38.06, 18.44.

ESI-MS: *m*/*z* (%) = 287 (MH^+, 10), 310 (MNa^+, 100).

Anal. Calcd for $C_{12}H_{17}NO_5S$ (287.33): C, 50.16; H, 5.96; N, 4.87. Found: C, 50.30; H, 5.79; N, 5.03.

1-Substituted 2-(Benzyloxycarbonyl)aminoethyl Thioacetates and 1-Substituted 2-(Benzyloxycarbonyl)aminocycloalkyl Thioacetates 7; General procedure
Diethyl azodicarboxylate (1.74 g, 10 mmol) in anhyd THF (6 mL) was added to an efficiently stirred solution of Ph_3P (2.62 g, 10 mmol) in anhyd THF (12 mL) at –10 °C. The mixture was stirred at for 0.5 h at –10 °C. A white precipitate appeared. The Cbz-amino alcohol **5** (5 mmol) and thiolacetic acid (0.76 g, 10 mmol) in THF (12 mL) were added dropwise over 30 min and the mixture was stirred for 1 h at –10 °C and for 20 h at r.t.. The resulting mixture was concentrated in reduced pressure. The triphenylphosphine oxide crystallized out upon addition of EtOAc–petroleum ether. The combined filtrates were concentrated in vacuo and subjected to silica gel column chromatographic separation with a mixture of petroleum ether and Et_2O (8:1) as an eluent to give the thioacetate **7**.

2-(Benzyloxycarbonyl)amino-1-phenylethyl Thioacetate (7a)
Colorless crystals, yield: 63%; mp 75–76 °C; R_f 0.30 (petroleum ether–Et_2O, 3:1, silica gel plate).

IR (KBr): 3342 (NH), 1718 (C=O), 1696 cm^{-1} (C=O).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.29 (m, 10 H, 2 × C_6H_5), 5.08 (s, 2 H, OCH_2), 4.96 (s, 1 H, NH), 4.72 (t, *J* = 7.5 Hz, 1 H, CH), 3.68 (dd, *J* = 6.9, 7.5 Hz, 2 H, NCH_2), 2.30 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 194.27, 156.09, 138.46, 136.38, 128.77, 128.64, 128.38, 127.98, 127.84, 127.79, 66.69, 47.81, 45.55, 30.34.

MS (EI): *m*/*z* (%): 329 (M^+, 1.2), 286 (M^+ – Ac, 15), 254 (M^+ – AcS, 2.4), 253 (M^+ – AcSH, 8.6), 238 (M^+ – $PhCH_2$, 20), 108 ($PhCH_2OH^+$, 5.9), 91 ($PhCH_2^+$, 100).

Anal. Calcd for $C_{18}H_{19}NO_3S$ (329.41): C, 65.63; H, 5.81; N, 4.25. Found: C, 65.51; H, 5.69; N, 4.05.

1-(Benzyloxycarbonyl)aminomethylpentyl Thioacetate (7b)
Yellowish oil; yield: 37%; R_f 0.25 (petroleum ether–Et_2O, 5:1, silica gel plate).

IR (KBr): 3344 (NH), 1718 (C=O), 1695 cm^{-1} (C=O)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.31 (m, 5 H, C_6H_5), 5.13 (br s, 1 H, NH), 5.09 (s, 2 H, OCH_2), 3.58 (dddd, *J* = 5.1, 5.1, 7.2, 7.2 Hz, 1 H, CH), 3.46 (ddd, *J* = 5.1, 5.1, 14.1 Hz, 1 H, NC*H*H), 3.31 (ddd, *J* = 7.2, 7.2, 14.1 Hz, 1 H, NCH*H*), 2.29 (s, 3 H, $COCH_3$), 1.65–1.44 (m, 2 H,CH_2), 1.41–1.26 (m, 4 H, 2 × CH_2), 0.88 (t, *J* = 6.6 Hz, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 195.77, 156.35, 136.42, 128.35, 127.96, 127.87, 66.58, 44.99, 44.88, 31.29, 30.63, 28.86, 22.26, 13.77.

MS (EI): *m*/*z* (%) = 309 (M^+, 0.81), 266 (M^+ – Ac, 0.78), 233 (M^+ – AcSH, 10), 108 ($PhCH_2OH^+$, 8.0), 91 ($PhCH_2^+$, 100).

Anal. Calcd for $C_{16}H_{23}NO_3S$ (309.42): C, 62.11; H, 7.49; N, 4.53. Found: C, 61.89; H, 7.39; N, 4.45.

2-(Benzyloxycarbonyl)amino-1-methylethyl Thioacetate (7c)
Yellowish oil; yield: 51%; R_f 0.25 (petroleum ether–Et_2O, 1:1, silica gel plate).

IR (KBr): 3344 (NH), 1721 (C=O), 1692 cm^{-1} (C=O).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5 H, C_6H_5), 5.10 (s, 2 H, OCH_2), 5.02 (br s, 1 H, NH), 3.66 (ddq, *J* = 6.3, 6.9, 6.9 Hz, 1 H, CH), 3.43 (ddd, *J* = 5.7, 6.3, 13.9 Hz, 1 H, NC*H*H), 3.31 (ddd, *J* = 6.9, 6.9, 13.9 Hz, 1 H, NCH*H*), 2.30 (s, 3 H, $COCH_3$), 1.30 (d, *J* = 6.9 Hz, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 195.69, 156.41, 136.35, 128.45, 128.07, 127.98, 66.73, 46.08, 39.72, 30.68, 18.06.

MS (EI): *m*/*z* (%) = 267 (M^+, 1.1), 224 (M^+ – Ac, 1.2), 191 (M^+ – AcSH, 9.3), 108 ($PhCH_2OH^+$, 13.7), 107 ($PhCH_2O^+$, 8.2), 91 ($PhCH_2^+$, 100).

Anal. Calcd for $C_{13}H_{17}NO_3S$ (267.35): C, 58.40; H, 6.41; N, 5.24. Found: C, 58.61; H, 6.29; N, 5.09.

2-(Benzyloxycarbonyl)amino-1-(benzyloxycarbonyl)aminomethylethyl Thioacetate (7d)

Yellowish solid; directly used for oxidation without further purification.

2-[(Benzyloxycarbonyl)amino]-1-phenoxymethylethyl Thioacetate (7e)

Colorless crystals; yield: 55%; mp 101.5–102.5 °C; R_f 0.20 (petroleum ether–EtOAc, 9:1, silica gel plate).

IR (KBr): 3355 (NH), 1695 (C=O), 1693 cm^{-1} (C=O).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.29–6.84 (m, 10 H, 2 × C_6H_5), 5.39 (dd, *J* = 5.7, 6.3, 1 H, NH), 5.09 (s, 2 H, OCH_2), 4.12 (dd, *J* = 5.1, 6.4 Hz, 1 H, PhOC*H*H), 4.01 (m, 1 H, H in PhOCH*H*), 3.99 (m, 1 H, CH), 3.63 (ddd, *J* = 5.7, 5.7, 14.1 Hz, 1 H, NC*H*H), 3.50 (ddd, *J* = 6.3, 6.3, 14.1 Hz, 1 H, NCH*H*), 2.67 (s, 3 H, $COCH_3$).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 194.64, 157.96, 156.24, 136.25, 129.28, 128.23, 127.84, 127.73, 121.08, 114.36, 67.87, 66.51, 43.47, 41.95, 30.41.

MS (EI): *m*/*z* = 359 (M^+, 0.35), 284 (M^+ – AcS, 15), 266 (M^+ – PhO, 5.2), 224 (M^+ – $PhCH_2O_2C$, 14), 91 ($PhCH_2^+$, 100).

Anal. Calcd for $C_{19}H_{21}NO_4S$ (359.44): C, 63.49; H, 5.89; N, 3.90. Found: C, 63.51; H, 5.69; N, 4.05.

***cis*-2-[(Benzyloxycarbonyl)amino]cyclopentyl Thioacetate (7f)**

Colorless crystals; yield: 65%; mp 66–66.5 °C; R_f 0.20 (petroleum ether–Et_2O, 8:1, silica gel plate).

IR (KBr): 3342 (NH), 1711 (C=O), 1695 cm^{-1} (C=O).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 5 H, C_6H_5), 5.09 (s, 2 H, OCH_2), 4.86 (br s, 1 H, NH), 4.25 (m, 1 H, SCH), 3.97 (m, 1 H, NCH), 2.29 (s, 3 H, CH_3), 2.21–1.98 (m, 2 H, CH_2), 1.81–1.58 (m, 3 H, CH_2), 1.56–1.41 (m, 1 H, CH*H*).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.05, 155.78, 136.48, 128.45, 128.09, 128.04, 66.73, 54.31, 47.20, 31.06, 30.71, 30.53, 20.99.

MS (EI): *m*/*z* = 293 (M^+, 0.49), 217 (M^+ – AcS, 13), 108 ($PhCH_2OH^+$, 5.3), 91 ($PhCH_2^+$, 100).

Anal. Calcd for $C_{15}H_{19}NO_3S$ (293.38): C, 61.41; H, 6.53; N, 4.77. Found: C, 61.31; H, 6.39; N, 4.95.

***cis*-2-[(Benzyloxycarbonyl)amino]cyclohexyl Thioacetate (7g)**

Colorless needles; yield: 38%; mp 105.5–106 °C; R_f 0.40 (petroleum ether–Et_2O, 5:1, silica gel plate).

IR (KBr): 3335 (NH), 1716 (C=O), 1697 cm^{-1} (C=O).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 5 H, C_6H_5), 5.08 (s, 2 H, OCH_2), 4.98 (d, *J* = 7.8 Hz, 1 H, NH), 4.07 (dt, *J* = 4.0, 4.0 Hz, 1 H, SCH), 3.91 (m, 1 H, NCH), 2.31 (s, 3 H, $COCH_3$), 1.83–1.71 (m, 3 H, CH_2), 1.71–1.61 (m, 1 H, CH*H*), 1.61–1.49 (m, 1 H, CH*H*), 1.49–1.26 (m, 3 H, CH_2).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 194.26, 155.40, 136.38, 128.36, 128.05, 127.96, 66.58, 51.09, 46.51, 30.95, 30.82, 30.20, 23.59, 22.30.

MS (EI): *m*/*z* = 307 (M^+, 0.85), 264 (M^+ – Ac, 0.90), 231 (M^+ – AcSH, 10), 216 (M^+ – $PhCH_2$, 19.8), 108 ($PhCH_2OH^+$, 6.1), 91 ($PhCH_2^+$, 100).

Anal. Calcd for $C_{16}H_{21}NO_3S$ (307.41): C, 62.51; H, 6.89; N, 4.56. Found: C, 62.51; H, 6.69; N, 4.65.

1-Substituted 2-(Benzyloxycarbonyl)aminoethanesulfonic Acids and 2-(Benzyloxycarbonyl)aminocycloalkanesulfonic Acids 8; General Procedure

To a performic acid solution, prepared by mixing and stirring 30% H_2O_2 (1.2 mL) and 88% HCO_2H (12 mL) at r.t. for 1 h and cooled in an ice bath, was added the appropriate thioacetate derivative **7** (2 mmol) in 88% HCO_2H (2.7 mL) dropwise, keeping the temperature at 0 °C. After stirring the mixture for an additional 2 h at 0 °C and for 20 h at r.t., the resulting mixture was mixed with silica gel and evaporated to dryness at r.t. The residue was separated on a silica gel column with a mixture of $CHCl_3$ and MeOH (20:1 to 10:1) and MeOH as eluents to give pure **8**.

2-(Benzyloxycarbonyl)amino-1-phenylethanesulfonic Acid (8a)

Colorless crystals; yield: 91%; mp 192–194 °C; R_f 0.40 ($CHCl_3$–MeOH, 4:1, silica gel plate).

IR (KBr): 3413 (br, NH and SOH), 1698 (C=O), 1222 (SO_2), 1172 cm^{-1} (SO_2).

^1H NMR (200 MHz, DMSO-d_6): δ = 7.36–7.22 (m, 10 H, ArH), 6.99 (s, 1 H, NH), 4.92 (s, 2 H, OCH_2), 3.78 (dd, *J* = 8.6, 14.6 Hz, 1 H, CH), 3.64 (m, 2 H, NCH_2).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 155.79, 137.48, 137.22, 129.48, 128.33, 127.66, 127.45, 127.40, 126.47, 65.05, 64.42, 42.55.

MS (ESI, negative ion): *m*/*z* = 334 $(M – H)^-$.

Anal. Calcd for $C_{16}H_{17}NO_5S$ (335.38): C, 57.30; H, 5.11; N, 4.18. Found: C, 57.52; H, 5.29; N, 4.06.

2-(Benzyloxycarbonyl)amino-1-butylethanesulfonic Acid (8b)

Colorless crystals; yield: 83%; mp >360 °C; R_f 0.60 ($CHCl_3$–MeOH, 4:1, silica gel plate).

IR (KBr): 3382 and 3291 (br, NH and SOH), 1692 (C=O), 1230 (SO_2), 1168 cm^{-1} (SO_2).

^1H NMR (200 MHz, DMSO-d_6): δ = 7.32 (s, 5 H, C_6H_5), 6.85 (br s, 1 H, NH), 5.00 (s, 2 H, OCH_2), 3.29 (t, *J* = 5.4 Hz, 2 H, NCH_2), 2.42 (tt, *J* = 5.4, 7.6 Hz, 1 H, CH), 1.31–1.20 (m, 6 H, 3 × CH_2), 0.82 (t, *J* = 6.6 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 155.90, 137.27, 128.38, 127.81, 127.67, 65.30, 58.23, 40.92, 29.00, 27.39, 22.33, 13.87.

MS (ESI, negative ion): *m*/*z* = 314 $(M – H)^-$.

Anal. Calcd for $C_{14}H_{21}NO_5S$ (315.39): C, 53.32; H, 6.71; N, 4.44. Found: C, 53.51; H, 6.89; N, 4.70.

2-(Benzyloxycarbonyl)amino-1-methylethanesulfonic Acid (8c)

Colorless crystals; yield: 90%; mp >360 °C; R_f 0.50 ($CHCl_3$–MeOH, 4:1, silica gel plate).

IR (KBr): 3362 (br, NH and SOH), 1701 (C=O), 1215 (SO_2), 1170 cm^{-1} (SO_2).

^1H NMR (300 MHz, DMSO-d_6): δ = 7.33 (s, 5 H, C_6H_5), 7.04 (s, 1 H, NH), 4.99 (s, 2 H, OCH_2), 3.40–3.28 (m, 1 H, NCH*H*), 3.08 (ddd, *J* = 7.5, 7.5, 12.9 Hz, 1 H, NC*H*H), 2.57 (m, 1 H, CH), 1.06 (d, *J* = 6.9 Hz, 3 H, CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 156.11, 137.30, 128.47, 127.88, 127.80, 65.33, 53.66, 42.77, 13.80.

MS (ESI, negative ion): *m*/*z* = 272 $(M – H)^-$.

Anal. Calcd for $C_{11}H_{15}NO_5S$ (273.31): C, 48.34; H, 5.53; N, 5.12. Found: C, 48.50; H, 5.79; N, 5.00.

2-(Benzyloxycarbonyl)amino-1-(benzyloxycarbonyl)aminomethylethanesulfonic Acid (8d)
Colorless crystals; yield: 41% {based on 1,3-di[(benzyloxycarbonyl)amino]propan-2-ol}; mp 255–256 °C; R_f 0.40 ($CHCl_3$–MeOH, 4:1, silica gel plate).

IR (KBr): 3376 and 3260 (br, NH and SOH), 1699 (C=O), 1240 (SO_2), 1176 cm^{-1} (SO_2).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.33 (s, 10 H, 2 × C_6H_5), 6.96 (br s, 2 H, 2 × NH), 5.00 (s, 4 H, 2 × OCH_2), 3.25 (m, 4 H, 2 × NCH_2), 2.59 (quintet, *J* = 6.0 Hz, 1 H, CH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 155.93, 137.17, 128.46, 127.87, 127.78, 65.44, 58.04, 37.67.

MS (ESI, negative ion): *m*/*z* = 421 $(M – H)^-$.

Anal. Calcd for $C_{19}H_{22}N_2O_7S$ (422.45): C, 54.02; H, 5.25; N, 6.63. Found: C, 53.96; H, 5.03; N, 6.69.

2-(Benzyloxycarbonyl)amino-1-phenoxymethylethanesulfonic Acid 8e
Colorless crystals; yield: 91%; mp 251–253 °C; R_f 0.30 ($CHCl_3$–MeOH, 4:1, silica gel plate).

IR (KBr): 3441 (br, NH and SOH), 1700 (C=O), 1239 (SO_2), 1200 cm^{-1} (SO_2).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.29–6.87 (m, 10 H, ArH), 6.25 (br s, 1 H, NH), 4.99 (s, 2 H, OCH_2), 4.38 (d, *J* = 8.4 Hz, 1 H, PhOC*H*H), 4.00 (dd, *J* = 8.4, 9.2 Hz, 1 H, PhOCH*H*), 3.52 (m, 2 H, NCH_2), 3.05 (m, 1 H, CH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 158.52, 156.00, 137.25, 129.67, 128.50, 127.91, 127.78, 120.85, 114.75, 66.25, 65.55, 57.95, 39.92.

MS (ESI, negative ion): *m*/*z* = 364 $(M – H)^-$.

Anal. Calcd for $C_{17}H_{19}NO_6S$ (365.40): C, 55.88; H, 5.24; N, 3.83. Found: C, 56.01; H, 5.01; N, 3.97.

***cis*-2-(Benzyloxycarbonyl)aminocyclopentanesulfonic Acid (8f)**
Colorless crystals; yield: 91%; mp 173–176 °C; R_f 0.60 ($CHCl_3$–MeOH, 6:1, silica gel plate).

IR (KBr): 3413 (br, NH and SOH), 1694 (C=O), 1212 (SO_2), 1181 cm^{-1} (SO_2).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.41 (s, br, 1 H, NH), 7.33 (s, 5 H, ArH), 4.97 (s, 2 H, CH_2O), 3.78 (m, 1 H, CHN), 2.93 (m, 1 H, CHS), 1.92–1.74 (m, 3 H, CH_2), 1.67 (m, 2 H, CH_2), 1.49 (m, 1 H, H in CH*H*).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 157.45, 137.10, 128.40, 128.31, 127.87, 65.22, 59.53, 53.49, 31.50, 26.12, 21.04.

MS (ESI, negative ion): *m*/*z* = 298 $(M – H)^-$.

Anal. Calcd for $C_{13}H_{17}NO_5S$ (299.34): C, 52.16; H, 5.72; N, 4.68. Found: C, 51.97; H, 5.99; N, 4.82.

***cis*-2-(Benzyloxycarbonyl)aminocyclohexanesulfonic Acid (8g)**
Colorless crystals; yield: 91%; mp 181–182 °C; R_f 0.60 ($CHCl_3$–MeOH, 4:1, silica gel plate).

IR (KBr): 3426 (br, NH and SOH), 1693 (C=O), 1202 (SO_2), 1175 cm^{-1} (SO_2).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.42–7.20 (m, 5 H, ArH), 6.92 (br s, 1 H, NH), 5.01 (d, *J* = 12.6 Hz, 1 H, H in CH_2O), 4.94 (d, *J* = 12.6 Hz, 1 H, H in CH_2O), 3.83 (m, 1 H, CHN), 2.56 (m, 1 H, CHS), 2.18 (m, 1 H, CH*H*), 1.83–1.60 (m, 3 H, CH_2), 1.50–1.16 (m, 4 H, 2 × CH_2).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 155.64, 137.18, 128.45, 128.39, 127.84, 65.20, 58.05, 48.35, 39.78, 28.59, 23.62, 20.51.

MS (ESI, negative ion): *m*/*z* = 312 $(M – H)^-$.

Anal. Calcd for $C_{14}H_{21}NO_5S$ (313.37): C, 53.66; H, 6.11; N, 4.47. Found: C, 53.42; H, 6.00; N, 4.18.

1-Substituted 2-Aminoethanesulfonic Acids 9; General Procedure
To a performic acid solution, prepared by mixing and stirring 30% H_2O_2 (1.2 mL) and 88% HCO_2H (12 mL) for 1 h at r.t. and cooled in an ice bath, was added the corresponding thioacetate derivative **7** (2 mmol) in 88% HCO_2H (2.7 mL) dropwise. The resulting mixture was refluxed and stirred overnight. After removal of solvent, the residue was crystallized from MeOH to give pure **9**.

2-Amino-1-phenylethanesulfonic Acid (9a)
Colorless crystals; yield: 90%; mp 281–282 °C (Lit.[22] mp 283–286 °C).

2-Amino-1-methylethanesulfonic Acid (9c)
Colorless crystals; yield: 83%; mp >360 °C (Lit.[22] mp 379 °C).

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References

(1) Liskamp, R. M. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 633.
(2) Burgess, K.; Linthicum, D. S.; Shin, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 907.
(3) de Bont, D. B. A.; Dijkstra, G. D. H.; den Hartog, J. A. J.; Liskamp, R. M. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3035; and references cited therein.
(4) Pollack, S. J.; Hsiun, P.; Schultz, P. G. *J. Am. Chem. Soc.* **1989**, *111*, 5961.
(5) Morgan, B. P.; Scholtz, J. M.; Ballinger, M. D.; Zipkin, I. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 297.
(6) Xu, J. X.; Yu, L. *Chin. J. Synth. Chem. (Hecheng Huaxue)* **1999**, *7*, 153; *Chem. Abstr.* **1999**, *131*, 257590g.
(7) Xu, J. X.; Fu, N. Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1223; and references cited therein.
(8) Xu, J. X. *Chin. J. Org. Chem.* **2003**, *23*, 1; *Chem. Abstr.* **2003**, *138*, 338419e.
(9) Higashiura, H.; Morino, H.; Matsuura, H.; Toyomaki, Y.; Ienaga, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1479.
(10) Gude, M.; Piarulli, U.; Potenza, D.; Salom, B.; Gennari, C. *Tetrahedron Lett.* **1996**, *37*, 8589.
(11) Braghiroli, D.; Di Bella, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2145.
(12) Braghiroli, D.; Avallone, R.; Di Bella, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2209.
(13) Higashiura, K.; Ienaga, K. *J. Org. Chem.* **1992**, *57*, 764.
(14) Moree, W. J.; van der Marel, G. A.; Liskamp, R. M. J. *Tetrahedron Lett.* **1992**, *33*, 6389.
(15) Moree, W. J.; van der Marel, G. A.; Liskamp, R. M. J. *J. Org. Chem.* **1995**, *60*, 5157.
(16) Monnee, M. C. F.; Marijne, M. F.; Brouwer, A. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **2000**, *41*, 7991.
(17) Brouwer, A. J.; Monnee, M. C. F.; Liskamp, R. M. J. *Synthesis* **2000**, 1579.
(18) Xu, J. X. *Tetrahedron: Asymmetry* **2002**, *13*, 1129.
(19) Braghiroli, D.; Mussati, E.; Di Bella, M.; Saladini, M. *Tetrahedron: Asymmetry* **1996**, *7*, 831.

(20) Braghiroli, D.; Di Bella, M. *Tetrahedron Lett.* **1996**, *37*, 7319.
(21) Lowik, D. W. P. M.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2000**, 1219.
(22) Gold, M. H.; Skebelsky, M.; Lang, G. *J. Org. Chem.* **1951**, *16*, 1500.
(23) Moree, W. J.; van Gent, L. C.; van der Marel, G. A.; Liskamp, R. M. J. *Tetrahedron* **1993**, *49*, 1133.
(24) Carson, K. G.; Schwender, C. F.; Shroff, H. N.; Cochran, N. A.; Gallant, D. L.; Briskin, M. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 711.
(25) Herranz, E.; Biller, S. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1978**, *100*, 3596.
(26) Nesterenko, V.; Byers, J. T.; Hergenrother, P. J. *Org. Lett.* **2003**, *5*, 281.
(27) Ma, Y. *Heteroatom Chem.* **2002**, *13*, 310.
(28) Guss, C. O.; Rosenthal, R. *J. Am. Chem. Soc.* **1955**, *77*, 2549.
(29) Roush, D. M.; Patel, M. M. *Synth. Commun.* **1985**, *15*, 675.
(30) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267.
(31) Wang, F. J.; Hauske, J. R. *Tetrahedron Lett.* **1997**, *38*, 6529.
(32) Jiao, P.; Xu, J. X.; Zhang, Q. H.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 3081.
(33) Kotsuki, H.; Shimanouchi, T.; Ohshima, R.; Fujiwara, S. *Tetrahedron* **1998**, *54*, 2709.
(34) Gupta, A. K.; Kazlauskas, R. J. *Tetrahedron: Asymmetry* **1993**, *4*, 879.
(35) Levene, P. A.; Walti, A. *J. Biol. Chem.* **1927**, *71*, 461.
(36) Benalil, A.; Carboni, B.; Vaultier, M. *Tetrahedron* **1991**, *47*, 8177.
(37) Muramatsu, T.; Hara, I. *Bull. Soc. Chim. Fr.* **1971**, 3338.
(38) Jones, D. S.; Srinivasan, A.; Kasina, S.; Fritzberg, A. R.; Wilkening, D. W. *J. Org. Chem.* **1989**, *54*, 1940.
(39) Maestro, A.; Astorga, C.; G otor, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3153.
(40) Hoenig, H.; Seufer-Wasserthal, P. *Synthesis* **1990**, 1137.