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Versatile Synthesis of Free and *N*-Benzyloxycarbonyl-Protected 2,2-Disubstituted Taurines

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An effective and versatile method was developed to synthesize *N*-benzyloxycarbonyl-protected and free 2,2-disubstituted taurines. Several novel 2,2-disubstituted taurines, including aliphatic/aromatic and cyclic/acyclic derivatives, were obtained, which demonstrates the generality of this method.

Introduction

Taurine and substituted taurines are not only very important sulfur analogues of naturally occurring aminocarboxylic acids, but they are also one class of important naturally occurring amino acids. They have been found in many mammalian tissues and are involved in various physiological processes.[1,2] In contrast, their derivatives, especially sulfonopeptides, have been widely used as enzyme inhibitors and haptens in the development of catalytic antibodies during the last two decades because of their tetrahedral structure.[2–6]

Recently, α,α-disubstituted amino acids have been widely used as building blocks to prepare peptidomimetics for peptide-like drug discovery with better biological stability.[7–10] As sulfur analogues of naturally occurring amino acids, some *gem*-disubstituted aminoalkanesulfonic acids,[11–13] a series of 1,1-disubstituted taurines,[11] and a few 2,2-disubstituted taurines[12,13] and *vic*-disubstituted taurines[14–17] have been synthesized to date. For the investigation of biological activities and structure–activity relationships, the discovery of peptidomimetic drug, and the synthesis of sulfonopeptides, we wish to develop efficient methods to prepare structurally diverse substituted taurines. Although we recently reported an efficient method to synthesize 2,2-dialkyl-substituted taurines from 2,2-disubstituted aziridines,[14] the preparation of aryl 2,2-disubstituted taurines proved futile, as such *N*-acetyl aryl taurines decomposed when heated at reflux in aqueous hydrochloric acid in the deacetylation step. Herein, we present a method of good generality for the synthesis of various *N*-benzyloxycarbonyl-protected and free 2,2-disubstituted taurines from ketones.

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Results and Discussion

As part of our ongoing program to synthesize structurally diverse substituted taurines, we prepared 1-monosubstituted and 1,1- and 1,2-disubstituted taurines effectively from simple starting materials, such as alkenes, epoxides, ketones;[11,15,16,18] 2-monosubstituted, and 1,2- and 2,2-disubstituted taurines from various aziridines.[14,19]

2-Amino-2-methylpropanesulfonic acid, the simplest 2,2-disubstituted taurine, has been synthesized from 2-methylalanine,[12] acetone cyanohydrin,[12] and 2,2-dimethyl-β-sultam.[13] We also prepared 2,2-dialkyl-substituted taurines efficiently from 2,2-dialkyl-substituted aziridines. However, when the method was extended to prepare aromatic 2,2-disubstituted taurines, monoaryl 2,2-disubstituted taurines were obtained in very low yields and no 2,2-diaryl taurine was afforded due to complex decomposition in the deacetylation step. We therefore hoped to develop a general and versatile method for the synthesis of structurally diverse free and *N*-benzyloxycarbonyl-protected 2,2-disubstituted taurines from commercially available ketones.

At first, acetophenone (**1a**) was selected as a model to prepare the 2,2-disubstituted taurine 2-amino-2-phenylpropanesulfonic acid as well as its *N*-benzyloxycarbonyl derivative. Cyanoamination of acetophenone afforded 2-amino-2-phenylproponitrile (**2a**), which was hydrolyzed in hydrochloric acid to give 2-phenylalanine (**3a**).[20] To simplify the

separation of the desired amino acid from the inorganic salt ammonium chloride, 2-phenylanaline (**3a**) was protected directly with benzyl chloroformate to yield *N*-benzyloxycarbonyl-2-phenylanaline (Z-**3a**), which was easily extracted with ethyl acetate from the aqueous solution. This is a convenient method to separate amino acids from an aqueous solution after the Strecker synthesis. However, the sodium borohydride–iodine reduction of *N*-benzyloxycarbonyl-2-phenylanaline (Z-**3a**) afforded 2-amino-2-phenylpropanol (**4a**) instead of the corresponding 2-*N*-benzyloxycarbonylamino-2-phenylpropanol (**5a**). The protecting group was removed during the reduction. Similar results were also observed in the reduction of 1-benzyloxycarbonylamino-1-cyclohexanecarboxylic acid (Z-**3e**), whereas the reduction of Z-**3e** with sodium borohydride furnished benzyl *N*-cyclohexylcarbamate. Decarboxylation occurred during the reduction.

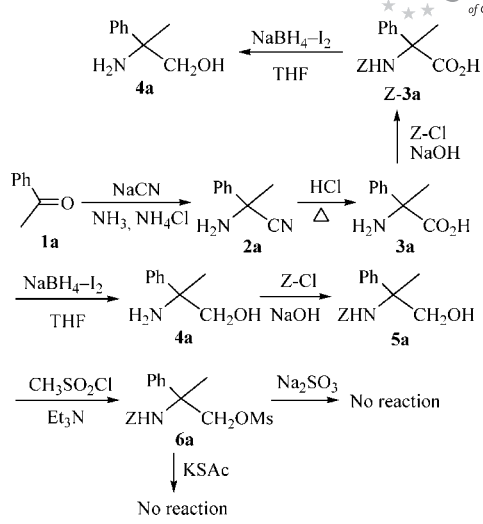
Alternatively, 2-phenylanaline (**3a**) was first purified through recrystallization from ethanol, then reduced with sodium borohydride–iodine to afford 2-amino-2-phenyl-1-propanol (**4a**),[21] which was directly treated with benzyl chloroformate to give rise to *N*-protected amino alcohol **5a** in a good overall yield of 82%. Amino alcohol **4a** was not separated, as either distillation or silica gel chromatography would impair the overall yields owing to its high boiling point and strong polarity.

Because sodium sulfite or bisulfite displacement of the amino alcohol methanesulfonate is the most efficient method to synthesize 2-substituted taurines,[22] we converted *N*-protected amino alcohol **5a** into its methanesulfonate (**6a**) with methanesulfonic chloride.[15] Unfortunately, sodium sulfite/bisulfite displacement was unsuccessful possibly due to the steric hindrance around the methanesulfonate group. Furthermore, methanesulfonate **6a** cannot react with potassium thioacetate to prepare corresponding amino alcohol thioacetate **7a** (Scheme 1). Consequently, alcohol **5a** was converted into thioacetate **7a** by the Mitsunobu reaction with thiolacetic acid, DEAD (diethyl azodicarboxylate), and triphenylphosphane.[15]

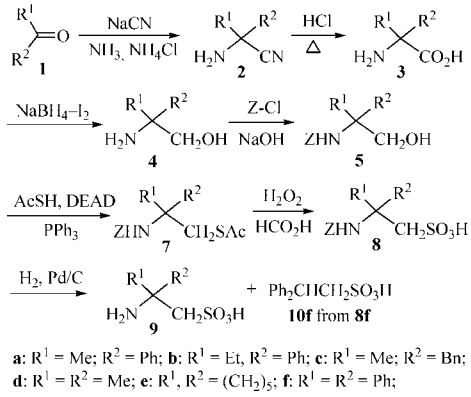
Finally, thioacetate **7a** was oxidized in performic acid to afford 2-(benzyloxycarbonyl)amino-2-phenylpropanesulfonic acid (**8a**) in good yield. After the oxidation was complete, formaldehyde was added into the reaction mixture to eliminate the excess amount of oxidant, because aromatic 2,2-disubstituted taurines are unstable under the oxidizing conditions (Scheme 2).

Free 2-amino-2-phenylpropanesulfonic acid (**9a**) was obtained in excellent yield by hydrogenolysis in methanol under an atmosphere of hydrogen in the presence of palladium on carbon powder (Scheme 2).[15] The time of hydrogenolysis should be carefully controlled to avoid further *N*-benzylic cleavage.

After successful synthesis of 2-amino-2-phenylpropanesulfonic acid (**8a**) and its *N*-benzyloxycarbonyl derivative **9a** from acetophenone, a series of commercially available ketones **1** were converted into α,α-disubstituted α-amino acids **3** by Strecker amino acid synthesis. 2,2-Diphenylglycine (**3f**) was prepared from sodium hydroxide hydrolysis of 5,5-diphenylhydantoin,[23] which was synthesized from benzil and urea.[24] After reduction with sodium borohydride–iodine and subsequent *N*-acylation with benzyl chloroformate, *N*-benzyloxycarbonyl-protected 2,2-disubstituted vicinal amino alcohols **5** were obtained in good yields. Protected amino alcohols **5** were further converted into corresponding thioacetates **7** in acceptable-to-satisfactory yields by Mitsunobu reaction with thiolacetic acid. 2,2-Diphenyl glycinol (**6f**) gave corresponding thioacetate **7f** in a low yield of 17% because of more bulky steric hindrance around its hydroxy group. Thioacetates **7** were dissolved in formic acid and oxidized with performic acid to afford *N*-benzyloxycarbonyl protected 2,2-disubstituted taurines **8**.[14,15] *N*-Benzyloxycarbonyl-2,2-diphenyltaurine (**8f**) is quite unstable in performic acid and partly decomposes to 2,2-diphenyltaurine (**9f**). Free 2,2-disubstituted taurines **9** were obtained in good-to-excellent yields after palladium-catalyzed hydrogenolysis in methanol (Scheme 2). For *N*-protected 2,2-diphenyltaurine (**8f**), the corresponding desired free 2,2-diphenyl taurine was also obtained in high yield through careful time control: prolonged hydrogenolysis could result in *N*-benzylic cleavage, which would



Scheme 1. Attempt to synthesize *N*-Z-protected 2,2-disubstituted taurines.



Scheme 2. General route for the synthesis of *N*-Z-protected and free 2,2-disubstituted taurines.

give rise to 2,2-diphenylethanesulfonic acid (**10f**) as a by-product; this was confirmed by an authentic sample synthesized from 2,2-diphenylethyl thioacetate (**11**) by performic acid oxidation.[25] In this way, a series of *N*-benzyloxycarbonyl protected and free 2,2-disubstituted taurines, including aliphatic/aromatic and cyclic/acyclic derivatives, were efficiently synthesized.

Conclusions

Aliphatic and aromatic, cyclic and acyclic, and free and *N*-benzyloxycarbonyl-protected 2,2-disubstituted taurines were synthesized from ketones by Strecker amino acid synthesis, reduction with sodium borohydride–iodine, protection with benzyl chloroformate, Mitsunobu thioacetylation with thiolacetic acid, oxidation with performic acid, and subsequent hydrogenolysis in the presence of palladium on carbon powder. This route could serve as a general approach to structurally diverse 2,2-disubstituted taurines.

Experimental Section

General Remarks: Melting points were measured with a Yanaco MP-500 melting point apparatus, which was calibrated with eight standard samples with melting points in the range from 50 to 250 °C. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian Mercury 200 (200 MHz) or Varian Mercury Plus 300 (300 MHz) spectrometer in $CDCl_3$ with TMS as an internal standard, in D_2O, or in [D_6]DMSO. Mass spectra were obtained with a Bruker ESQUIRE~LC ESI ion trap mass spectrometer. HRMS data was obtained with an Agilent LC/MSD TOF mass spectrometer. IR spectra were determined with a Nicolet AVATAR 330 FTIR spectrometer. C, H, and N analyses were recorded with an Elementar Vario EL analyzer. Amino nitriles **2a**–**e** were prepared from ketones **1a**–**e** in acceptable-to-good yields according to a literature method.[26] Amino acids **3a**–**e** were prepared from amino nitriles **2a**–**e** in acceptable-to-good yields according to a modified literature method.[20] Amino acid **3f** was prepared from 5,5-diphenylhydantoin,[23] which was obtained from benzil and urea in good yield.[24] The analytical data of all known compounds are identical to those reported in the literature.

General Procedure for the Preparation of Amino Acids 3: Amino acids **3a**–**e** were prepared from amino nitriles **2a**–**e** by a modified literature method.[20] A 250-mL round-bottomed flask equipped with a magnetic stirring bar was charged with ketone **1** (150 mmol), NH_4Cl (9.20 g, 172 mmol), ammonia (20 mL, 270 mmol), ethanol (45 mL), and water (38 mL). After the mixture was dissolved into a clear solution, NaCN (8.50 g, 173 mmol) was added, and the flask was quickly sealed with a rubber stopper. The mixture was stirred for 3 d (for **2a** and **2b**, the mixture was heated cautiously to 65 °C and stirred for 8 h; for **2c**, 1.0 g of benzyltriethylammonium chloride was added), which resulted in a colorless-to-dark-brown solution, which was cooled to room temperature, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with water to remove the remaining NaCN, dried with anhydrous sodium sulfate, and concentrated under reduced pressure to afford a residue amino nitrile **2**, which was used directly in the next step without purification. The flask containing amino nitrile **2** was equipped with a magnetic stirring bar and a condenser, and cooled in an ice–water bath. Hydrochloric acid (150 mL, precooled in an ice–water bath) was poured into the flask through the top of the condenser. The resulting mixture was stirred overnight, diluted with water (150 mL), and heated at reflux for 3 h. The azeotrope of remaining ketone **1**, HCl, and water was distilled off. The aqueous phase was extracted with CH_2Cl_2 (20 mL). The aqueous solution was evaporated under vacuum to give a colorless-to-brown residue, which was dissolved in warm water (50 mL) and then neutralized by sodium hydroxide to reach pH 3–4. To the solution was added ethanol (or a mixture of ethanol and ether) as quickly as possible. After standing overnight, the white solid that precipitated from the solution was collected with a Buchner funnel. The solid was purified by recrystallization from a mixture of ethanol and water (or ether) to give pure colorless crystals **3**.

General Procedure for the Preparation of *N*-Benzyloxycarbonyl Protected Amino Alcohols 5: To a 100-mL round-bottomed flask charged with amino acid **3** (10 mmol), $NaBH_4$ (0.95 g, 25 mmol), and anhydrous THF (30 mL) was added dropwise a solution of iodine (2.54 g, 10 mmol) in anhydrous THF (7 mL) through a pressure-equalizing addition funnel equipped with a $CaCl_2$ desiccating tube whilst keeping the temperature at 0 °C. When the addition was complete and the evolution of hydrogen gas ceased, the mixture was stirred and heated at reflux for 20 h and then cooled to room temperature. The reaction was cautiously quenched with methanol to produce a clear solution. The mixture was stirred for 30 min, and the solution was concentrated under vacuum to give a white paste, which was then dissolved in 20% aqueous KOH and stirred overnight. The mixture was diluted with water and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was dried with Na_2SO_4, and the solvent was removed thoroughly under vacuum to give an oily or crystalline product amino alcohol **4**, which was used directly in the next step. A 100-mL three-necked round-bottomed flask containing amino alcohol **4** (about 10 mmol) in CH_2Cl_2 (50 mL) was equipped with a magnetic stirring bar and two pressure-equalizing addition funnels containing aqueous NaOH (0.39 g, 9.8 mmol in 20 mL water) and a solution of 50 wt.-% CbzCl in toluene (3.41 g, 10 mmol, diluted with 10 mL of CH_2Cl_2), respectively. In a –10 °C ice–salt bath, the aqueous NaOH and CbzCl solutions were added dropwise simultaneously over 1 h. The reaction mixture was stirred vigorously throughout the addition. After the addition, the ice–salt bath was warmed to room temperature and vigorous stirring was continued for 15 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phase was dried with anhydrous $MgSO_4$, concentrated under vacuum, and purified by recrystallization or silica gel column chromatography to afford *N*-benzyloxycarbonylamino alcohol **6** as colorless crystals or oil.

Benzyl *N*-(2-Hydroxy-1-methyl-1-phenyl)ethylcarbamate (5a): Colorless crystals, m.p. 57–58.5 °C, overall yield 82% from amino acid **3a**. R_f = 0.23 [petroleum ether (60–90 °C)/ethyl acetate, 3:1; silica gel plate]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.15 (m, 10 H, ArH), 5.81 (br. s, 1 H, NH), 5.00 (s, 2 H, CH_2O), 3.66 (d, J = 10.8 Hz, 1 H in CH_2), 3.59 (s, 1 H, OH), 3.47 (d, J = 10.8 Hz, 1 H in CH_2), 1.57 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.7, 142.9, 136.2, 128.3, 127.9, 126.9, 125.3, 70.5, 66.4, 59.5, 23.1 ppm. IR: $\tilde{\nu}$ = 3292.0 (br., NH & OH), 1701.2 (C=O) cm^{-1}. MS (ESI): m/z = 308 [M + Na]$^+$. $C_{17}H_{19}NO_3$ (285.34): calcd. C 71.56, H 6.71, N 4.91; found C 71.46, H 6.93, N 4.86.

Benzyl *N*-(1-Hydroxymethyl-1-phenyl)propylcarbamate (5b): Colorless crystals, m.p. 87.5–88.5 °C, overall yield 93% from amino acid **3b**. R_f = 0.24 [petroleum ether (60–90 °C)/ethyl acetate, 3:1; silica gel plate]. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.21 (m, 10 H, ArH), 5.52 (s, 1 H, NH), 5.06 (s, 2 H, CH_2O), 3.98 (d, J = 11.4 Hz,

1 H in OCH_2), 3.84 (d, J = 11.4 Hz, 1 H in OCH_2), 3.70 (br. s, 1 H, OH), 1.96 (m, CH_2), 0.76 (d, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 156.2, 141.9, 136.2, 128.5, 128.4, 128.1, 127.0, 125.9, 68.3, 66.7, 63.2, 29.8, 7.7 ppm. IR: $\tilde{\nu}$ = 3264.4 (br., NH & OH), 1688.9 (C=O) cm^{-1}. MS (ESI): m/z = 322 $[M + Na]^+$. $C_{18}H_{21}NO_3$ (299.36): calcd. C 72.22, H 7.07, N 4.68; found C 71.96, H 7.12, N 4.51.

Benzyl *N*-(1-Benzyl-2-hydroxy-1-methyl)ethylcarbamate (5c): Colorless crystals, m.p. 77–78 °C, overall yield 98% from amino acid **3c**. R_f = 0.23 [petroleum ether (60–90 °C)/ethyl acetate, 3:1; silica gel plate]. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5 H, ArH), 7.30–7.20 (m, 3 H, ArH), 7.19–7.09 (m, 2 H, ArH), 5.14 (d, J = 12 Hz, 1 H in CH_2O), 5.05 (d, J = 12 Hz, 1 H in CH_2O), 4.84 (br. s, 1 H, NH), 3.68 (s, 2 H, CH_2), 3.58 (br. s, 1 H, OH), 3.11 (d, J = 13.6 Hz, 1 H in CH_2), 2.82 (d, J = 13.6 Hz, 1 H in CH_2), 1.11 (s, 3 H, CH_3) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 156.2, 136.7, 136.4, 130.6, 128.6, 128.2, 126.6, 68.8, 66.6, 57.3, 41.1, 22.6 ppm. IR: $\tilde{\nu}$ = 3228.2 (br., NH & OH), 1667.5 (C=O) cm^{-1}. MS (ESI): m/z = 322 $[M + Na]^+$. $C_{18}H_{21}NO_3$ (299.36): calcd. C 72.22, H 7.07, N 4.68; found C 72.26, H 7.07, N 4.60.

Benzyl *N*-(2-Hydroxy-1,1-dimethyl)ethylcarbamate (5d):[27] Colorless oil, overall yield 86% from amino acid **3d**. R_f = 0.25 [petroleum ether (60–90 °C)/ethyl acetate, 3:1; silica gel plate]. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 5 H, ArH), 5.14 (br. s, 1 H, NH), 5.04 (s, 2 H, CH_2O), 3.73 (br. s, 1 H, OH), 3.56 (s, 2 H, CH_2), 1.26 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 156.0, 136.2, 128.4, 128.02, 127.96, 70.0, 66.4, 54.3, 24.2 ppm.

Benzyl *N*-[(1-Hydroxymethyl)cyclohexyl]carbamate (5e): Colorless crystals, m.p. 90–90.5 °C, overall yield 90% from amino acid **3e**. R_f = 0.22 [petroleum ether (60–90 °C)/ethyl acetate, 3:1; silica gel plate]. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5 H, ArH), 5.06 (s, 2 H, CH_2O), 4.89 (br. s, 1 H, NH), 3.79 (br. s, 1 H, OH), 3.67 (s, 2 H, CH_2), 1.82 (m, 2 H in 2 CH_2), 1.55–1.30 (m, 2 H in 2 CH_2 & 6 H in 3 CH_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 156.1, 136.2, 128.5, 128.1, 128.0, 69.1, 66.6, 56.4, 31.9, 25.5, 21.3 ppm. IR: $\tilde{\nu}$ = 3456.8 (NH), 3285.9 (OH), 1703.4 (C=O) cm^{-1}. MS (ESI): m/z = 286 $[M + Na]^+$. $C_{15}H_{21}NO_3$ (263.33): calcd. C 68.42, H 8.04, N 5.32; found C 68.43, H 7.86, N 5.24.

Benzyl *N*-(2-Hydroxy-1,1-diphenyl)ethylcarbamate (5f): Colorless crystals, m.p. 133–135 °C, overall yield 72% from amino acid **3f**. R_f = 0.34 [petroleum ether (60–90 °C)/ethyl acetate, 3:1; silica gel plate]. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.50–7.21 (m, 15 H, ArH), 5.84 (s, 1 H, NH), 5.09 (s, 2 H, CH_2O), 4.38 (s, 2 H, CH_2), 4.29 (br. s, 1 H, OH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 156.5, 142.0, 135.9; 128.53, 128.47, 128.3, 128.2, 127.7, 127.3, 69.8, 67.2, 66.6 ppm. IR: $\tilde{\nu}$ = 3216.6 (br., NH & OH), 1687.9 (C=O) cm^{-1}. MS (ESI): m/z = 370 $[M + Na]^+$. $C_{22}H_{21}NO_3$ (347.41): calcd. C 76.06, H 6.09, N 4.03; found C 75.78, H 6.04, N 4.22.

2-(Benzyloxycarbonyl)amino-2-phenylpropyl Methanesulfonate (6a): To an ice-cooled solution of **5a** (0.790 g, 2.77 mmol) and triethylamine (0.312 g, 3.1 mmol) in dichloromethane (15 mL) was added a solution of MsCl (0.382 g, 3.33 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% aqueous $NaHCO_3$ and brine and dried with Na_2SO_4. After removal of the solvent, the residue was recrystallized from petroleum ether (60–90 °C)/ethyl acetate to give colorless crystals of **6a** in 91% yield. M.p. 106.5–107.5 °C. R_f = 0.27 [petroleum ether (60–90 °C)/ethyl acetate, 3:1; silica gel plate]. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.23 (m, 10 H, ArH), 5.54 (s, 1 H, NH), 5.03 (s, 2 H, CH_2O), 4.64 (d, J = 9.0 Hz, 1 H in CH_2), 4.43 (d, J = 9.0 Hz, 1 H in CH_2), 2.72 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.4, 141.4, 136.1, 128.4, 128.2, 127.7, 127.4, 124.9, 72.9, 66.1, 57.2, 36.3, 24.1 ppm. IR: $\tilde{\nu}$ = 3399.8 (NH), 1724.4 (C=O), 1264.5 (SO_2), 1179.7 (SO_2) cm^{-1}. MS (ESI): m/z = 386 $[M + Na]^+$. $C_{18}H_{21}NO_5S$ (363.43): calcd. C 59.49, H 5.82, N 3.85; found C 59.50, H 5.78, N 3.80.

General Procedure for Synthesis of 2-Substituted-2-(Benzyloxycarbonyl)aminoalkyl Thioacetates 7: To an efficiently stirred solution of triphenylphosphane (2.62 g, 10 mmol) in anhydrous THF (12 mL) was added dropwise a solution of diethyl azodicarboxylate (DEAD, 1.74 g, 10 mmol) in anhydrous THF (6 mL) at –10 °C over 15 min. The resulting mixture was stirred at –10 °C for another 0.5 h. A white precipitate appeared. A solution of Cbz-amino alcohol **5** (5 mmol) and thiolacetic acid (0.76 g, 10 mmol) in anhydrous THF (12 mL) was added dropwise over 30 min, and the reaction mixture was stirred for an additional 2 h at –10 °C to give a clear-orange solution. Further stirring at room temperature turned the solution from orange to yellow, indicating the reaction was complete. After concentrated under reduced pressure, triphenylphosphane oxide was crystallized upon the addition of a mixture of ethyl acetate and petroleum ether (60–90 °C). After filtration, the combined filtrates were concentrated in vacuo and subjected to silica gel column chromatography [petroleum ether (60–90 °C)/ethyl acetate, 8:1] to afford colorless thioacetate **7**. For alcohol **6f**, triphenylphosphane (3.28 g, 12.5 mmol), diethyl azodicarboxylate (2.18 g, 12.5 mmol), and thiolacetic acid (0.95 g, 12.5 mmol) were added.

2-(Benzyloxycarbonyl)amino-2-phenylpropyl Thioacetate (7a): Colorless crystals, m.p. 66–68 °C, yield 67%. R_f = 0.32 [petroleum ether (60–90 °C)/ethyl acetate, 6:1; silica gel plate]. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.44–7.22 (m, 10 H, ArH), 5.56 (s, 1 H, NH), 5.03 (s, 2 H, CH_2O), 3.58 (d, J = 14.0 Hz, 1 H in CH_2), 3.40 (d, J = 14.0 Hz, 1 H in CH_2), 2.34 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 196.2, 154.7, 144.4, 136.5, 128.5, 128.4, 128.0, 127.2, 125.1, 66.2, 58.2, 40.4, 30.3, 25.6 ppm. IR: $\tilde{\nu}$ = 3330.0 (NH), 1686.3 (C=O) cm^{-1}. MS (ESI): m/z = 366 $[M + Na]^+$. $C_{19}H_{21}NO_3S$ (343.44): calcd. C 66.45, H 6.16, N 4.08; found C 66.16, H 6.20, N 4.02.

2-(Benzyloxycarbonyl)amino-2-phenylbutyl Thioacetate (7b): Colorless crystals, m.p. 53.5–55 °C, yield 60%. R_f = 0.31 [petroleum ether (60–90 °C)/ethyl acetate, 6:1; silica gel plate]. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.45–7.20 (m, 10 H, ArH), 5.24 (s, 1 H, NH), 5.06 (s, 2 H, CH_2O), 3.88 (d, J = 13.4 Hz, 1 H in CH_2), 3.72 (d, J = 13.4 Hz, 1 H in CH_2), 2.31 (s, 3 H, CH_3), 2.02 (m, 2 H, CH_2), 0.71 (t, J = 7.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 195.4, 155.6, 142.4, 136.5, 128.5, 128.3, 128.1, 127.1, 125.6, 66.5, 61.4, 37.0, 31.8, 30.5, 24.9, 7.9 ppm. IR: $\tilde{\nu}$ = 3333.7 (NH), 1707.1 (C=O), 1692.1 (C=O) cm^{-1}. MS (ESI): m/z = 380 $[M + Na]^+$. $C_{20}H_{23}NO_3S$ (357.47): calcd. C 67.20, H 6.49, N 3.92; found C 66.88, H 6.40, N 3.86.

2-(Benzyloxycarbonyl)amino-2-methyl-3-phenylpropyl Thioacetate (7c): Colorless crystals, m.p. 42.5–43.5 °C, yield 45%. R_f = 0.40 [petroleum ether (60–90 °C)/ethyl acetate, 6:1; silica gel plate]. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 5 H, ArH), 7.28–7.20 (m, 3 H, ArH), 7.09–7.02 (m, 2 H, ArH), 5.14 (d, J = 12.5 Hz, 1 H in CH_2O), 5.04 (d, J = 12.5 Hz, 1 H in CH_2O), 4.74 (s, 1 H, NH), 3.51 (d, J = 13.8 Hz, 1 H in CH_2), 3.27 (d, J = 13.4 Hz, 1 H in CH_2), 3.23 (d, J = 13.8 Hz, 1 H in CH_2), 2.83 (d, J = 13.4 Hz, 1 H in CH_2), 2.33 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 195.6, 154.7, 136.64, 136.57, 130.5, 128.5, 128.2, 128.11, 128.07, 126.6, 66.1, 55.9, 43.1, 37.7, 30.4, 23.5 ppm. IR: $\tilde{\nu}$ = 3351.9 (NH), 1717 (C=O), 1692.0 (C=O) cm^{-1}. MS (ESI):

m/*z* = 380 [M + Na]$^+$. $C_{20}H_{23}NO_3S$ (357.47): calcd. C 67.20, H 6.49, N 3.92; found C 67.08, H 6.48, N 3.82.

2-(Benzyloxycarbonyl)amino-2-methylpropyl Thioacetate (7d): Light yellowish oil, yield 57%. R_f = 0.40 [petroleum ether (60–90 °C)/ethyl acetate, 6:1; silica gel plate]. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34 (m, 5 H, ArH), 5.05 (s, 2 H, CH_2O), 4.93 (br. s, 1 H, NH), 3.30 (s, 2 H, CH_2), 2.34 (s, 3 H, CH_3), 1.34 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 195.6, 154.6, 136.5, 128.41, 128.40, 128.0, 66.1, 53.0, 38.7, 30.5, 26.3 ppm. IR: $\tilde{\nu}$ = 3353.8 (NH), 1695.0 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 304 [M + Na]$^+$. HRMS: calcd. for $C_{14}H_{19}NNaO_3S$ 304.0977; found 304.0981.

[1-(Benzyloxycarbonyl)aminocyclohexyl]methyl Thioacetate (7e): Light yellowish oil (used directly with a little impurity), yield 68%. R_f = 0.45 [petroleum ether (60–90 °C)/ethyl acetate, 6:1; silica gel plate]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 5 H, ArH), 5.07 (s, 2 H, CH_2O), 4.63 (s, 1 H, NH), 3.41 (s, 2 H, CH_2), 2.33 (s, 3 H, CH_3), 1.98 (m, 2 H in 2 CH_2), 1.55 (m, 2 H in 2 CH_2), 1.47–1.40 (m, 4 H, 2 CH_2), 1.26 (m, 2 H, CH_2) ppm. MS (ESI): *m*/*z* = 344 [M + Na]$^+$. HRMS: calcd. for $C_{17}H_{23}NNaO_3S$ 344.1296; found 344.1294.

2-(Benzyloxycarbonyl)amino-2,2-diphenylethyl Thioacetate (7f): Colorless crystals, m.p. 106–107 °C, yield 17%. R_f = 0.38 [petroleum ether (60–90 °C)/ethyl acetate, 6:1; silica gel plate]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.18 (m, 15 H, ArH), 5.90 (s, 1 H, NH), 5.02 (s, 2 H, CH_2O), 4.19 (s, 2 H, CH_2), 2.23 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 195.0, 154.9, 143.3, 136.4, 128.4, 128.3, 128.1, 127.4, 126.7, 66.7, 64.2, 39.0, 30.4 ppm. IR: $\tilde{\nu}$ = 3313.6 (NH), 1692.5 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 428 [M + Na]$^+$. $C_{24}H_{23}NO_3S$ (405.51): calcd. C 71.09, H 5.72, N 3.45; found C 70.81, H 5.72, N 3.36.

General Procedure for the Preparation of *N*-Benzyloxycarbonyl-2,2-disubstituted Taurines 8: To a performic acid solution, prepared by mixing and stirring 30% H_2O_2 (1.2 mL) and 88% HCO_2H (12 mL) at room temperature for 1 h and cooled in an ice bath, was added thioacetate **7** (2 mmol) in 88% HCO_2H (2.7 mL) dropwise, keeping the temperature at 0 °C. The reaction was stirred at 0 °C for an additional 2 h and then quenched by the addition of 36% formaldehyde (10 mL). The resulting solution, along with the ice bath, was warmed to room temperature over 2 h. Stirring was continued until performic acid was removed completely (tested with KI–starch paper). Then, the solution was poured into a Petri dish containing silica gel. The mixture was air dried at room temperature for 24–48 h. The residue was separated on a silica gel column (chloroform/methanol, 8:1) to afford colorless crystals of **8**. For thioacetate **7f**, silica gel column chromatography separation afforded *N*-Cbz taurine **8f** in 66% yield and taurine **9f** in 31% yield.

2-(Benzyloxycarbonyl)amino-2-phenylpropanesulfonic Acid (8a): Colorless crystals, m.p. 114–115.5 °C (dec.), yield 85%. R_f = 0.38 (chloroform/methanol, 4:1; silica gel plate). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.30 (br. s, 1 H, NH), 7.40–7.13 (m, 10 H, ArH), 4.92 (s, 2 H, CH_2O), 2.68 (s, 2 H, CH_2), 1.86 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 154.1, 147.0, 137.3, 128.4, 128.0, 127.8, 127.6, 126.0, 125.0, 64.8, 62.3, 56.0, 22.8 ppm. IR: $\tilde{\nu}$ = 3294.3 (br., NH & OH), 1694.5 (C=O), 1224.6 (SO_2), 1181.5 (SO_2) cm^{-1}. MS (ESI): *m*/*z* = 348 [M – H]$^-$. HRMS: calcd. for $C_{17}H_{19}NNaO_5S$ 372.0876; found 372.0875.

2-(Benzyloxycarbonyl)amino-2-phenylbutanesulfonic Acid (8b): Colorless crystals, m.p. 130.5–132 °C (dec.), yield 93%. R_f = 0.38 (chloroform/methanol, 4:1; silica gel plate). ^{1}H NMR (200 MHz, [D$_6$]-DMSO): δ = 7.88 (br. s, 1 H, NH), 7.33 (s, 5 H, Ph), 7.25 (s, 5 H, Ph), 4.96 (s, 2 H, CH_2O), 3.11 (s, 2 H, CH_2), 2.37 (m, 1 H in CH_2), 1.98 (m, 1 H in CH_2), 0.76 (br. s, 3 H, CH_3) ppm. ^{13}C NMR (50.3 MHz, [D$_6$]DMSO): δ = 154.4, 145.4, 137.6, 130.8, 128.4, 127.8, 127.5, 125.9, 125.8, 64.8, 59.2, 56.7, 31.3, 8.7 ppm. IR: $\tilde{\nu}$ = 3351.5 (br., NH & OH), 1680.1 (C=O), 1248.5 (SO_2), 1170.2 (SO_2) cm^{-1}. MS (ESI): *m*/*z* = 362 [M – H]$^-$. HRMS: calcd. for $C_{18}H_{21}NNaO_5S$ 386.1032; found 386.1036.

2-(Benzyloxycarbonyl)amino-2-methyl-3-phenylpropanesulfonic Acid (8c): Colorless crystals, m.p. 102–105 °C (dec.), yield 88%. R_f = 0.41 (chloroform/methanol, 4:1; silica gel plate). ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.59 (br. s, 1 H, NH), 7.37 (s, 5 H, ArH), 7.21–7.06 (m, 5 H, ArH), 5.09 (d, *J* = 12.4 Hz, 1 H in CH_2O), 4.96 (d, *J* = 12.4 Hz, 1 H in CH_2O), 3.47 (d, *J* = 13.0 Hz, 1 H in CH_2), 2.80 (d, *J* = 13.0 Hz, 1 H in CH_2), 2.54 (s, 2 H, CH_2), 1.43 (s, 3 H, CH_3) ppm. ^{13}C NMR (50.3 MHz, [D$_6$]DMSO): δ = 154.5, 137.9, 137.6, 130.83, 130.80, 128.5, 127.9, 126.2, 64.7, 56.7, 42.4, 53.8, 23.8 ppm. IR: $\tilde{\nu}$ = 3357.8 (br., NH & OH), 1283.3 (SO_2), 1180.8 (SO_2) cm^{-1}. MS (ESI): *m*/*z* = 364 [M + H]$^+$. HRMS: calcd. for $C_{18}H_{22}NO_5S$ [M + H] 364.1213; found 364.1219.

2-(Benzyloxycarbonyl)amino-2-methylpropanesulfonic Acid (8d): Colorless crystals, m.p. 98.5–100.5 °C (dec.), yield 84%. R_f = 0.37 (chloroform/methanol, 4:1; silica gel plate). ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.60 (br. s, 1 H, NH), 7.33 (s, 5 H, ArH), 4.94 (s, 2 H, CH_2O), 2.68 (s, 2 H, CH_2), 1.37 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (50.3 MHz, [D$_6$]DMSO): δ = 154.6, 137.5, 128.6, 128.0, 64.8, 60.5, 51.1, 26.3 ppm. IR: $\tilde{\nu}$ = 3338.6 (br., NH & OH), 1688.5 (C=O), 1215.5 (SO_2), 1119.7 (SO_2) cm^{-1}. MS (ESI): *m*/*z* = 310 [M + Na]$^+$. HRMS: calcd. for $C_{12}H_{17}NNaO_5S$ 310.0719; found 310.0720.

[1-(Benzyloxycarbonyl)aminocyclohexyl]methanesulfonic Acid (8e): Colorless crystals, m.p. 135–138 °C (dec.), yield 79%. R_f = 0.41 (chloroform/methanol, 4:1; silica gel plate). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.30 (s, 5 H, Ph), 7.21 (br. s, 1 H, NH), 4.94 (s, 2 H, CH_2O), 2.81 (s, 2 H, CH_2), 2.16 (m, 2 H in 2 CH_2), 1.72 (m, 2 H in 2 CH_2), 1.50–1.20 (m, 6 H, 3CH_2) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 154.3, 137.5, 128.3, 127.62, 127.58, 64.5, 55.9, 53.7, 32.6, 25.1, 21.9 ppm. IR: $\tilde{\nu}$ = 3335.2 (br., NH & OH), 1688.2 (C=O), 1210.9 (SO_2), 1177.3 (SO_2) cm^{-1}. MS (ESI): *m*/*z* = 350 [M + Na]$^+$. HRMS: calcd. for $C_{15}H_{21}NNaO_5S$ 350.1019; found 350.1019.

2-(Benzyloxycarbonyl)amino-2,2-diphenylethanesulfonic Acid (8f): Colorless crystals, m.p. 82.5–85 °C (dec.), yield 66%. R_f = 0.45 (chloroform/methanol, 4:1; silica gel plate). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.65 (br. s, 1 H, NH), 7.36–7.18 (m, 15 H, ArH), 4.92 (s, 2 H, CH_2O), 3.47 (s, 2 H, CH_2) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 154.5, 143.1, 137.3, 128.40, 128.37, 127.7, 127.6, 127.3, 126.3, 65.0, 62.9, 60.9 ppm. IR: $\tilde{\nu}$ = 3363.5 (br., NH & OH), 1684.4 (C=O), 1217.8 (SO_2), 1176.5 (SO_2) cm^{-1}. MS (ESI): *m*/*z* = 434 [M + Na]$^+$. HRMS: calcd. for $C_{22}H_{21}NNaO_5S$ 434.1032; found 434.1038.

General Procedure for the Synthesis of 2,2-Disubstituted Taurines 9 (Hydrogenolysis): Taurine **8** (0.50 mmol) was dissolved in methanol (5 mL), and 10% Pd on carbon powder (20 mg) was added. The suspension was stirred under an atmosphere of hydrogen at room temperature overnight (1 h for **8f**). Methanol (20 mL) was added to dissolve the precipitated product. The catalyst was removed by hot filtration and was washed with methanol (2 × 5 mL). Evaporation of the solvent afforded taurine **9** as colorless crystals.

2-Amino-2-phenylpropanesulfonic Acid (9a): Colorless crystals, m.p. 236–238 °C, yield 98%. R_f = 0.20 (chloroform/methanol, 4:1; silica gel plate). ^{1}H NMR (200 MHz, D_2O): δ = 7.33–7.11 (m, 5 H, ArH), 3.26 (d, *J* = 14.4 Hz, 1 H in CH_2), 3.15 (d, *J* = 14.4 Hz, 1 H in

CH_2), 1.38 (s, 3 H, CH_3) ppm. ^{13}C NMR (50.3 MHz, D_2O, DMSO as internal standard): δ = 147.4, 130.4, 128.9, 127.1, 64.4, 55.7, 31.1 ppm. IR: $\tilde{\nu}$ = 3373.4 (br., NH & OH), 1246.1 (SO_2), 1196.4 (SO_2) cm^{-1}. MS (ESI): *m*/*z* = 216 $[M + H]^+$. HRMS: calcd. for $C_9H_{14}NO_3S$ [M + H] 216.0688; found 216.0691.

2-Amino-2-phenylbutanesulfonic Acid (9b): Colorless crystals, m.p. 253–255 °C, yield 99%. R_f = 0.26 (chloroform/methanol, 4:1; silica gel plate). ^1H NMR (300 MHz, D_2O): δ = 7.42–7.20 (m, 5 H, ArH), 3.57 (d, *J* = 15.6 Hz, 1 H in CH_2), 3.50 (d, *J* = 15.6 Hz, 1 H in CH_2), 2.26–2.02 (m, 2 H, CH_2), 0.67 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, D_2O, DMSO as internal standard): δ = 139.0, 131.5, 131.0, 127.5, 63.3, 59.3, 34.3, 9.1 ppm. IR: $\tilde{\nu}$ = 3425.0 (br., NH & OH), 1169.8 (SO_2) cm^{-1}. MS (ESI): *m*/*z* = 230 $[M + H]^+$. HRMS: calcd. for $C_{10}H_{16}NO_3S$ [M + H] 230.0845; found 230.0848.

2-Amino-2-benzylpropanesulfonic Acid (9c): Colorless crystals, m.p. 197–199 °C, yield 90%. R_f = 0.22 (chloroform/methanol, 4:1; silica gel plate). ^1H NMR (200 MHz, D_2O): δ = 7.30–7.05 (m, 5 H, ArH), 2.94 (s, 2 H, CH_2), 2.77 (s, 2 H, CH_2), 1.16 (s, 3 H, CH_3) ppm. ^{13}C NMR (50.3 MHz, D_2O, DMSO as internal standard): δ = 137.4, 133.0, 130.6, 129.3, 60.5, 54.8, 47.7, 26.1 ppm. IR: $\tilde{\nu}$ = 3469.9 (br., NH & OH), 1169.9 (SO_2) cm^{-1}. MS (ESI): *m*/*z* = 230 $[M + H]^+$. HRMS: calcd. for $C_{10}H_{16}NO_3S$ [M + H] 230.0845; found 230.0849.

2-Amino-2-methylpropanesulfonic Acid (9d): Colorless crystals, m.p. 325 °C (dec.) [ref.[14] 325 °C (dec.)], yield 99%. R_f = 0.08 (chloroform/methanol, 4:1; silica gel plate). ^1H NMR (200 MHz, D_2O): δ = 3.02 (s, 2 H, CH_2), 1.29 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (50.3 MHz, D_2O, DMSO as internal standard): δ = 59.7, 54.0, 27.1 ppm.

(1-Amino-1-cyclohexane)methanesulfonic Acid (9e): Colorless crystals, m.p. 331 °C (dec.) [ref.[14] 331 °C (dec.)], yield 87%. R_f = 0.15 (chloroform/methanol, 4:1; silica gel plate). ^1H NMR (200 MHz, D_2O): δ = 3.13 (s, 2 H, CH_2), 1.88–1.73 (m, 2 H in 2 CH_2), 1.57–1.10 (m, 8 H, 2 CH_2 & 2 H in 2 CH_2) ppm. ^{13}C NMR (50.3 MHz, D_2O, DMSO as internal standard): δ = 57.0, 55.5, 35.4, 25.8, 22.7 ppm.

2-Amino-2,2-diphenylethanesulfonic Acid (9f): Colorless crystals, m.p. 239–242.5 °C (dec), yield 31% from **7f**; yield 87% from **8f**. R_f = 0.26 (chloroform/methanol, 4:1; silica gel plate). ^1H NMR (200 MHz, D_2O): δ = 7.28–6.92 (m, 10 H, Ph), 3.77 (s, 2 H, CH_2) ppm. ^{13}C NMR (75.5 MHz, D_2O, DMSO as internal standard): δ = 147.1, 130.4, 129.3, 128.4, 62.2, 61.8 ppm. IR: $\tilde{\nu}$ = 3424.1 (br., NH & OH), 1178.8 (SO_2) cm^{-1}. MS (ESI): *m*/*z* = 300 $[M + Na]^+$. HRMS: calcd. for $C_{14}H_{15}NNaO_3S$ [M + Na] 300.0664; found 300.0667.

2,2-Diphenylethanesulfonic Acid (10f):[25] Colorless crystals, m.p. 93–95 °C. R_f = 0.25 (chloroform/methanol, 4:1; silica gel plate). ^1H NMR (300 MHz, D_2O): δ = 7.25–7.04 (m, 10 H, Ph), 4.36 (t, *J* = 7.0 Hz, 1 H, CH), 3.56 (d, *J* = 7.0 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75.5 MHz, D_2O, DMSO as internal standard): δ = 145.4, 130.8, 129.4, 128.7, 57.4, 49.3 ppm. IR: $\tilde{\nu}$ = 3373.0 (br., OH), 1171.3 (SO_2) cm^{-1}. MS (ESI): *m*/*z* = 261 $[M - H]^-$.

2,2-Diphenylethyl Thioacetate(11f):[25] Colorless crystals, m.p. 100.5–101.5 °C. R_f = 0.48 [petroleum ether (60–90 °C)/ethyl acetate, 20:1; silica gel plate]. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 10 H, Ph), 4.17 (t, *J* = 8.1 Hz, 1 H, CH), 3.57 (d, *J* = 8.1 Hz, 2 H, CH_2), 2.27 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 195.5, 142.7, 128.5, 127.9, 126.7, 50.6, 34.4, 30.6 ppm. IR: $\tilde{\nu}$ = 1678.2 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 257 $[M + H]^+$.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **5**, **6a**, **7**–**9**, **10f**, and **11**.

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