A Convenient Synthesis of Cis and Trans 4-*tert*-Butoxycarbonyl-Substituted Cyclohexylglycine

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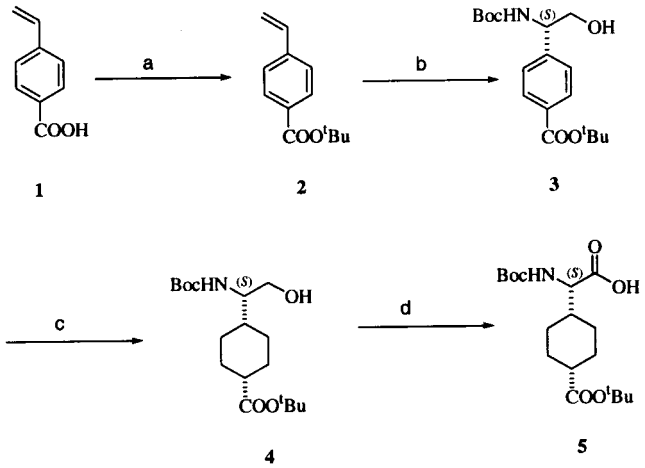
Abstract: A novel synthesis of cis and trans substituted 4-*tert*-butoxycarbonyl cyclohexylglycines via asymmetric aminohydroxylation of vinyl styrene followed by reduction of the aromatic ring and subsequent oxidation is reported.

The nonproteinogenic amino acid cyclohexylglycine is widely found in various natural products and pharmaceutical intermediates.[1] The incorporation of these amino acids into the peptide inhibitors renders resistance from peptidases and proteinases and thereby imparts pharmacological stability to molecules.[2] In the course of our ongoing program to identify pharmaceutically active targets, we required large quantities of cis and trans substituted 4-*tert*-butoxycarboxyl substituted cyclohexylglycine. The paucity of methods for asymmetric synthesis of substituted cyclohexylglycine led us to develop a general synthesis for this class of compounds.

As outlined in Scheme 1, synthesis of *cis*-4-*tert*-butoxycarbonyl-substituted cyclohexylglycine was initiated from 4-vinylbenzoic acid **1**. The acid **1** was protected as the *tert*-butyl ester by refluxing it with dimethylformamide di-*tert*-butyl acetal in benzene to form **2** in 66% yield.[3] Other methods involving strong acid and isobutene or *tert*-butyl alcohol for the formation of the *tert*-butyl ester failed or resulted largely in polymeric mixtures with very low yields of **2**. The amino hydroxylation of the styrene derivative **2** was carried out according to the procedure reported by Reddy and Sharpless.[4] Thus, treatment of the styrene **2** with ^{t}BuOC(O)NH$_2$, ^{t}BuOCl, and catalytic amounts of (DHQ)$_2$Phal and K_2OsO_4·2H$_2$O formed the alcohol **3** in 50−70%. Various attempts to assess the enantiomeric purity of **3** using chiral HPLC were unsuccessful with the current protecting groups. Thus, **3** was converted to methyl (*S*)-4-[1-[[(benzyloxycarbonyl]amino]-2-hydroxyethyl]benzoate, and the ee of the alcohol was determined using HPLC with a chiracel-AD column to be >97% after single recrystallization.[5] The aromatic ring of the amino alcohol **3** was reduced using Rh/C[6] and hydrogen to yield **4** as a single diastereomer.

Scheme 1[a]



[a] Reagents and conditions: (a) HCNMe$_2$(O^{t}Bu)$_2$, benzene reflux 66%; (b) ^{t}BuOC(O)NH$_2$, K_2OsO_4, (DHQ)$_2$Phal, ^{t}BuOCl, PrOH−H$_2$O, 70%; (c) Rh/C, H$_2$, CH$_3$OH, 100%; (d) RuCl$_3$, H$_5$IO$_6$, H$_2$O/CH$_3$CN, CCl$_4$, 66%.

The stereochemistry of the product **4** was assigned using ^{1}H NMR coupling constant analysis. (Figure 1).

As shown in Figure 1, the coupling constants of the hydrogen attached to C(α) [indicated as H$_1$] with the adjacent equatorial and axial hydrogens (indicated as H$_2$ and H$_3$) were identified. If the stereochemistry of the *tert*-butoxycarbonyl group was trans with respect to the amino alcohol, both substituents would occupy equatorial positions. Then the trans isomer would have $J_{H1,2} = 5-7$ Hz, and $J_{H1,3} \sim 10-11$ Hz, whereas the cis isomer should generate two small couplings of $J_{H1,2} \sim 5-7$ Hz and $J_{H1,3} \sim 5-7$ Hz. Similarly, the coupling constant $J_{C1-H2,3}$ was observed in the proton-coupled ^{13}C NMR spectrum. In the case of the trans isomer, $J_{C1-H2,3}$ should have a large 5−8 Hz coupling and four small couplings $J \sim 2$ Hz and the cis should have three large $J_{C1-H2,3}$ couplings in the order of 5−8 Hz and two small 2 Hz couplings.[7] Analysis

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(5) Racemic material for the enantiomeric excess determination was obtained by epoxidation of methyl 4-vinylbenzoate, followed by acid-catalyzed opening of the resulting epoxide with azide and subsequent reduction and *N*-Cbz protection. Enantiomeric excess was determined using Chiracel-AD column (hexanes/isopropyl alcohol 4: 1), flow = 1 mL/min, t_R = 7.26 min (*S*-isomer) and 12.91 min (*R*-isomer): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.89 (d, 2 H, J = 8.7 Hz), 7.83 (d, 1 H, J = 8.4 Hz), 7.44 (d, 2 H, J = 9.0 Hz), 7.34 (bs, 4 H), 5.04−4.93 (m, 3 H), 4.65 (bq, 1 H, J = 8.1 Hz), 3.83 (s, 3 H), 3.53−3.50 (m, 2 H).

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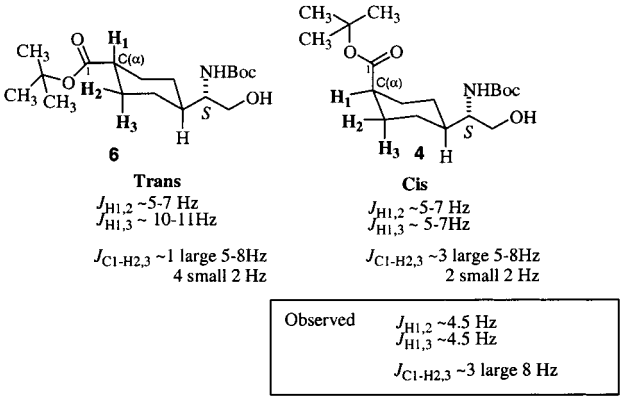

Figure 1.

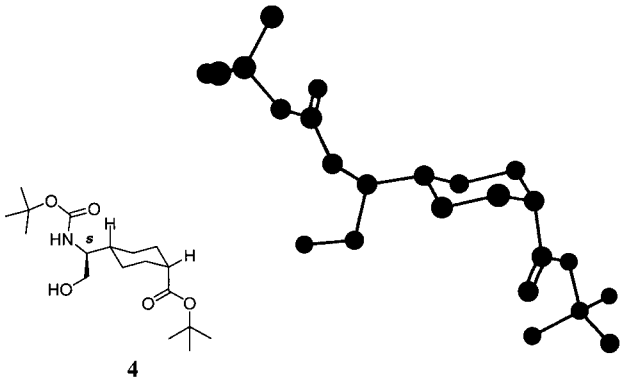

Figure 2. Ball and stick representation of X-ray structure of the reduction product **4**.

of the NMR spectra of **4** clearly indicated exclusive formation of the cis isomer, which had the following coupling pattern: $J_{H1,2} \sim 4.5$ Hz, $J_{H1,3} \sim 4.5$ Hz, and $J_{C1-H2,3} \sim 8$ Hz.

To further confirm our analysis, a single-crystal X-ray of the reduction product **4** was obtained. As shown in Figure 2, the ball-and-stick representation of the X-ray structure of **4** clearly indicated that hydrogenation of **3** exclusively generated the cis product with the cyclohexane ring adopting a chair conformation and the *tert*-butylcarboxyl group occupying an axial position**.** The completion of the synthesis of protected *cis*-4-*tert*-butoxycarbonyl-substituted cyclohexylglycine (**5**) was accomplished by oxidation of the alcohol to the corresponding acid using $RuCl_3$ and $HIO_5 \cdot 2H_2O$ in 66% yield.[8]

Having synthesized the cis isomer, we now needed an efficient synthesis of the trans isomer. The isomerization of the cis isomer to the trans isomer by treatment of base seemed facile because the *tert*-butoxycarboxyl group would prefer an equatorial position (Figure 3). Initial attempts to epimerize **4** under thermodynamic conditions using mild bases proved futile. To our surprise, the epimerization was difficult and only the cis isomer was isolated under various conditions. The list of the different bases used and the yields obtained are shown in Table 1.

As shown in the Table 1, the attempted isomerization of the cis isomer **4** with mild base was unsuccessful. However, treatment of **4** with 8 equiv of LDA at −78 °C

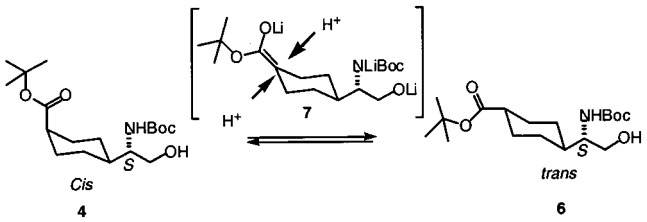

Figure 3.

Table 1[a]

entry	base/conditions	% yield	trans/cis ratio
1	K_2CO_3, CH_3OH, 24 h rt.	80	0:1
2	K^{t}BuO, 4 equiv, reflux 12 h	0	decomposition
3	DBU reflux	100	0:1
4	phospazene[9] P_4 base, −78 °C, 30 min	100	0:1
5	LDA, 8.0 equiv, −78→ 0 °C, 1 h	40	1:1
6	LDA, 2.5 equiv, −78 °C→ 0 °C, 1 h	33	0:1
7	LDA, 8.0 equiv, −78 °C, 2 h	81	1:1.2

[a] The cis/trans ratio was determined by integration of H_1 in the ^{1}H NMR spectra. The hydrogen in the cis isomer appears at δ 2.5 ppm whereas the hydrogen in the trans isomer is at δ 1.8 ppm.

and quenching with methanol resulted in the formation of an inseparable cis/trans mixture in a ratio 1:1.2. All attempts to separate the mixture using chromatographic techniques proved futile. Fortunately, the treatment of the mixture of isomers with hexane resulted in the preferential precipitation of the cis isomer **4**. This method allowed isolation of the pure cis and trans isomers. Repetition of the isomerization process followed by preferential precipitation of the cis isomer from hexane allowed total conversion of the cis to the trans compound **6**. The stereochemistry of the trans isomer **6** was once again established using coupling constant analysis as described above.[7] The observed couplings were $J_{H1,2} =$ 12 Hz and $J_{C1-H2,3} = 6.8$ Hz (doublet of quartet). The amino alcohol **6** was oxidized using $RuCl_3$ and $HIO_4 \cdot 2H_2O$ to produce the trans acid. The crude acid obtained by this method was used directly for further incorporation into peptide targets. To enable efficient characterization of the acid, it was converted to the methyl ester by treatment with TMS-diazomethane,[10] and the methyl ester was further crystallized from hexanes at −30 °C. This method allowed for routine synthesis of gram quantities of substituted cyclohexylglycines.

In summary, the synthesis of nonproteinogenic amino acid *cis*-4-*tert*-butoxycarbonyl-substituted cyclohexylglycines using aminohydroxylation of styrene has been reported. A method for the isomerization of the cis isomer using LDA and separation of the cis and trans mixture by precipitation using hexane has also been established, which allows for routine synthesis of multigram quantities of the amino acid. This method is versatile and can be applied for the synthesis of other analogues of cyclohexylglycine, a very useful nonnatural amino acid.

Experimental Section

General Methods. All glassware were dried in an oven at 150 °C prior to use. Dry solvents were purchased from Aldrich

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or Acros and used without further purification. Other solvents or reagents were used as acquired except when otherwise noted. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel plates available from Analtech. Column chromatography was performed using Merck silica gel 60 (particle size 0.040−0.055 mm, 230−400 mesh). Visualization was accomplished with UV light or by staining with a basic $KMnO_4$ solution, methanolic H_2SO_4, or Vaughn's reagent. NMR spectra were recorded in $CDCl_3$ unless otherwise noted in either 300 or 400 MHz (^{1}H NMR) or 75 or 100 MHz (^{13}C NMR).

1,1-Dimethylethyl 4-Ethenylbenzoate[11] (2). A solution of vinyl benzoic acid **1** (10 g, 68 mmol) in dry benzene (150 mL) was treated with dimethylformamide di-*tert*-butyl acetal (69 g, 340 mmol, 5.0 equiv) and heated at reflux for 4 h. The reaction mixture was concentrated in vacuo and diluted with aq NaOH (1 M, 300 mL). The aqueous mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were extracted with aq NaOH (1 M, 100 mL), H_2O (2 × 100 mL), brine (1 × 100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was distilled under reduced pressure (1 mmHg) to obtain **2** as a colorless oil: 9.2 g (66%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, 2 H, J = 5.7 Hz), 7.43 (d, 2 H, J = 8.4 Hz), 6.74 (dd, 1 H, J = 10.8, 6.6 Hz), 5.85 (d, 1 H, J = 17 Hz), 5.35 (d, 1 H, J = 10.2 Hz), 1.60 (s, 9 H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 165.4, 141.3, 136.0, 131.1, 129.8, 125.8, 116.0, 80.8, 28.1.

***(S)*-1,1-Dimethylethyl 4-[1-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxyethyl]benzoate (3).** A solution of *tert*-butyl carbamate (5.96 g, 50.9 mmol) in 1-PrOH (68 mL) was treated with aq NaOH (128 mL, 0.41 M) and *tert*-butyl hypochlorite (5.5 g, 50.9 mmol) and stirred at room temperature for 20 m. The reaction mixture was cooled to 0 °C, and $(DHQ)_2$Phal (780 mg, 1.00 mmol) in 1-PrOH (64 mL) was added. A solution of *tert*-butyl 4-vinylbenzoate **2** in 1-PrOH (119 mL) was added followed by $K_2OsO_4{\cdot}2H_2O$ (248 mg, 0.7 mmol). The reaction mixture was stirred at 0 °C for 12 h. The green reaction mixture was concentrated in vacuo, and the residue was diluted with H_2O (300 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were extracted with aq HCl (200 mL) and brine (100 mL), dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by chromatography (SiO_2, Hex/EtOAc, 2:1) to yield **3** as a colorless solid (3.7 g, 70%): $[\alpha]_D$ = 33.4 (c = 0.68, $CHCl_3$, 25 °C); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.90 (d, 2 H, J = 6.3 Hz), 7.40 (d, 2 H, J = 6.0 Hz), 7.14 (bd, 1 H, J = 5.7 Hz), 4.88 (bm, 1 H), 3.69−3.65 (m, 2 H) 1.58 (s, 9 H), 1.42 (s, 9 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 169.7, 160.5, 149.8, 134.5, 132.9, 130.4, 84.7, 82.9, 68.7, 60.7, 31.3, 30.9; MS (FAB) m/z relative intensity 675 ([2M + 1]$^+$, 15), 338 ([M + 1]$^+$, 15), 282 (65), 225 (50), 165 (100); HRMS m/z calcd for $C_{18}H_{28}NO_5$ (M + 1): 338.1967, found 338.1967.

1,1-Dimethylethyl 4-[(1*S*)-1-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxyethyl]cyclohexaneacetate (4). A solution of the ester **3** (1.0 g, 2.96 mmol) in CH_3OH (20 mL) was treated with Rh/C (10% w/w 100 mg) and hydrogenated (60 psi) for 3 d. The reaction mixture was filtered through a plug of Celite, and the residue was concentrated in vacuo to yield **4**. The crude product was purified by chromatography (SiO_2, Hex/EtOAc 4:1) to yield the cis compound **4** (830 mg, 83%) which was further purified by crystallization from hexanes: $[\alpha]_D$ = −20.0 (c = 0.87, $CHCl_3$, 25 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.59−3.55 (m, 2 H), 3.50−3.46 (m, 1 H), 2.32−2.29 (m, 1 H), 2.13−2.03 (m, 2 H), 1.42 (s, 9 H), 1.36 (s, 9 H), 1.47−1.26 (m, 7 H); ^{13}C NMR (C_6H_6/CD_3OD, 100 MHz) δ 174.4, 157.0, 79.6, 78.9, 63.0, 56.1, 40.9, 37.8, 28.4, 28.0, 26.9, 26.5, 25.5; MS (FAB) m/z relative intensity 687 ([2M + 1]$^+$, 5), 344 ([M + 1]$^+$, 20), 232 (40), 188 (100), 107 (13); HRMS calcd for $C_{18}H_{34}NO_5$ (M + 1): 343.2437, Found: 344.2444. Anal. Calcd for $C_{18}H_{33}NO_5$: C 64.07, H 8.07, N 4.15. Found: C 64.32, H 8.21, N 4.32.

1,1-Dimethylethyl 4-[(1*S*)-1-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-(hydroxyethyl)cyclohexaneacetate (6). A solution of amino alcohol **4** (3.3 g, 11.08 mmol) in dry THF (200 mL) was cooled to −78 °C (internal temperature −68 °C) and was treated with LDA (44 mL, 2 M solution in heptanes, 88 mmol). The reaction mixture was stirred at −78 °C for 2 h and quenched with CH_3OH (20 mL). The reaction mixture was treated with aq HCl (150 mL, 1 M) and extracted with ether (3 × 100 mL). The combined ether layers were extracted with brine (50 mL), dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography (SiO_2, Hex/EtOAc 4:1). The isolated mixture was crystallized from boiling hexanes. The solid separating out from the mother liquor was predominantly cis stereoisomer, whereas concentration of the mother liquor gave the enriched trans isomer. The above sequence was repeated twice to obtain 2.7 g of the trans compound and 600 mg of cis and trans mixture: $[\alpha]_D$ = −1.48 (c = 0.68, $CHCl_3$, 25 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.76 (d, 1 H, J = 8.8 Hz), 3.67−3.60 (m, 2 H), 3.42 (bs, 1 H), 2.5 (bs, 1 H), 2.47−2.06 (m, 1 H), 1.99−1.96 (bd, 2 H), 1.83 (bt, 2 H), 1.44 (s, 18 H), 1.44−1.05 (m, 4H) 1.05−1.02 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3, 156.6, 79.8, 63.6, 57.0, 44.1, 38.3, 37.7, 28.9, 28.6, 28.4, 28.1, 26.6, 26.1. MS (FAB) m/z relative intensity: 344 [(M + 1)$^+$,70], 342 (10), 288 (100), 244 (60); HRMS calcd for $C_{18}H_{34}NO_5$ 344.2437, found: 344.2444.

***cis*-4-[(1,1-Dimethylethoxy)carbonyl]-(*S*)-α-[[(1,1-dimethylethoxy)carbonyl]amino]cyclohexaneacetic Acid (5).** A solution of alcohol **4** (2.6 g, 7.6 mmol) in CH_3CN (150 mL) and CCl_4 (150 mL) was treated with H_2O (22 mL), cooled to 0 °C, and treated with periodic acid (7.05 g, 30.92 mmol, 4.0 equiv) and $RuCl_3{\cdot}3H_2O$ (60 mg, 0.3 mmol, 4 mol %). The reaction mixture was stirred at 0 °C for 3 h and concentrated in vacuo. The residue was diluted with water (150 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were filtered through a plug of Celite and extracted with H_2O (100 mL) and aqueous NaOH (1 M, 3 × 100 mL). The combined aqueous layers were acidified with HCl (6 M, pH ∼1) and extracted with EtOAc (3 × 100 mL). The ethyl acetate layers were pooled, extracted with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to yield acid **5** (1.8 g, 66%) used for further couplings without purification: MS (FAB) m/z relative intensity 380 ([M + Na]$^+$, 30) 358 ([M + 1]$^+$, 5), 302 (20), 258(20), 246 (100), 202 (70), 200 (20) The amino acid was characterized as the methyl ester obtained by the treatment of the acid with TMS-diazomethane in benzene/methanol (5:1 v/v): $[\alpha]_D$ = 17.7 (c = 1.06, $CHCl_3$, 25 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.01 (d, 1 H, J = 9.0 Hz), 4.24 (dd, 1 H, J = 5.7, 3.3 Hz), 3.72 (s, 3 H), 2.50−2.47 (m, 1 H), 2.12−2.08 (bm, 2 H), 1.73 (bs, 1 H), 1.56−1.23 (m, 6 H), 1.45 (s, 9 H), 1.43 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 172.8, 155.4, 85.7, 80.0, 79.7, 57.5, 52.0, 40.2, 39.8, 28.3, 28.1, 26.8, 26.6, 25.7, 24.4; MS (FAB) m/z, relative intensity: 394 [(M + Na)$^+$, 93), 372 [(M + 1)$^+$, 38), 316 (25), 260 (100), 216 (84). Anal. Calcd for $C_{19}H_{33}NO_6$: C 61.43, H 8.95, N 3.77. Found: C 61.32, H 8.73, N 3.64.

***trans*-4-[(1,1-Dimethylethoxy)carbonyl] (*S*)-α-[[(1,1-Dimethylethoxy)carbonyl]amino]cyclohexaneacetic Acid.** The desired trans acid was prepared from **6** in 55% yield according to the oxidation procedure mentioned for the synthesis of acid **5**. MS (FAB) m/z relative intensity 380 ([M + Na]$^+$, 30) 358 ([M + 1]$^+$, 5), 302 (20), 258(20), 246 (100), 202 (70), 200 (20); HRMS calcd for $C_{18}H_{32}NO_6$ (M + 1)$^+$: 358.2230, found: 358.2237. The crude mixture was converted to the methyl ester by the treatment of TMS-diazomethane: $[\alpha]_D$ = 12 (c = 0.39, $CHCl_3$, 25 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.03 (d, 1 H, J = 9.0 Hz), 4.24 (dd, 1 H, J = 4.5, 4.5 Hz), 3.74 (s, 3 H), 2.10 (tt, 1 H, J = 8.4 Hz), 2.06−1.90 (bm, 2 H), 1.77−1.60 (bm, 3 H), 1.40−1.02 (m, 2 H), 1.44 (s, 9 H), 1.43 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.0, 172.7, 155.5, 79.9, 57.8, 52.2, 43.8, 40.4, 28.4, 28.3, 28.1, 27.1; MS (FAB) 394 [(M + Na)$^+$, 80], 372 [(M + 1)$^+$, 20], 316 (30), 260 (100), 216 (84), 156 (34); HRMS calcd for $C_{19}H_{34}NO_6$ (M + H)$^+$ 372.2386; found 372.2388.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for cyclohexylglycines and synthetic intermediates **2**, **3**, **4**, and X-ray stucture data of **4** are available free of charge via the Internet at http://www.pubs.acs.org.

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