Communications to the Editor

# Practical, Scalable, Enantioselective Synthesis of (2*R*,3*R*)-*N*-Boc-2-amino-3-cyclohexyl-3-hydroxypropanoic Acid

Mònica Alonso,[†] Ferran Santacana,[†] Llorenç Rafecas,[‡] and Antoni Riera*,[†]

Unitat de Recerca en Síntesi Asimètrica (URSA-PCB), Parc Científic de Barcelona and Departament de Química Orgànica, Universitat de Barcelona, and Enantia, S.L. Parc Científic de Barcelona, C/Josep Samitier, 1-5, 08028-Barcelona, Spain

Abstract:

An enantioselective synthesis of (2*R*,3*R*)-2-(*tert*-butoxycarbonyl)amino-3-cyclohexyl-3-hydroxypropanoic acid has been described starting from enantiomerically enriched ethyl 3-cyclohexyl-2,3-dihydroxypropanoate, easily available by Sharpless asymmetric dihydroxylation. The key reaction is the direct preparation of a sulfate by diol treatment with sulfuryl chloride, thus avoiding ruthenium-catalyzed sulfite oxidation.

β-Hydroxy-α-amino acids are constituents of many biologically active natural products and medicinally important compounds.[1–4] Since both the relative and absolute stereochemistry of their chiral centres is crucial for their biological activity, many stereoselective syntheses of this type of nonproteinogenic amino acids have been reported up to now.[2–5] Among these compounds, (2*R*,3*R*)-2-amino-3-hydroxy-3-cyclohexylpropanoic acid **1** is particularly relevant since it is a key component in the antiinflammatory and HIV antagonist drug ONO-4128 **2**.[6] Although some enantioselective syntheses of this particular amino acid have been described to date,[7] a practical, reliable, and scalable stereoselective synthesis of this important amino acid would be of great interest.
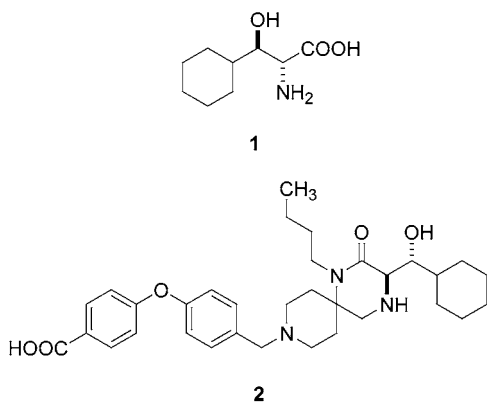

During the past decade we have been involved in a project devoted to the asymmetric synthesis of biologically active amino acids.[8] In the present case, we envisaged that the asymmetric Sharpless dihydroxylation of the unsaturated ester **3** to give the enantiomerically enriched diol **4** would be a good procedure to establish the stereochemistry of both centres, since absolute configuration would be controlled by the ligand, and the nucleophilic introduction of the amino function with inversion of configuration would afford the required *erythro* relative esterechemistry. For this general

(1) *Amino Acids, Peptides and Proteins; Special Periodical Reports*; Royal Society of Chemistry: London, 1968-1995; Vols. 1−28.

(2) Selected synthesis of β-hydroxy amino acids based on aldol reactions: (a) MacMillan, J. B.; Molinski, T. F. *Org. Lett.* **2002**, *4*, 1883−1886. (b) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K.; *Angew. Chem., Int. Ed.* **2002**, *41*, 4542−4544. (c) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843−3846. (d) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405−6406.

(3) Selected syntheses of β-hydroxy amino acids based on Sharpless epoxidation: (a) Nagamitzu, T.; Sunazuka, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A.; Smith, A. B., III. *J. Am. Chem. Soc.* **1996**, *118*, 3584−3590. (b) Rao, A. V. R.; Dhar, T. G. M.; Bose, D. S.; Chakraborty, T. K.; Gurjar, M. K. *Tetrahedron* **1989**, *45*, 7361−7370.

(4) Selected syntheses of β-hydroxy amino acids based on catalytic non-aldol reactions: (a) Amador, M.; Ariza, X.; Garcia, J.; Sevilla, S. *Org. Lett.* **2002**, *4*, 4511−4514. (b) Shao, H.; Goodman, M. *J. Org. Chem.* **1996**, *61*, 2582−2583. (c) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1989**, *30*, 6637−6640. (d) Schmidt, U.; Respondek, M.; Lieberknecht, A.; Werner, J.; Fischer, P. *Synthesis* **1989**, 256−261.

(5) Selected syntheses of β-hydroxy amino acids based on dynamic kinetic resolution. (a) Makino, K.; Goto, T.; Hiroki, Y.; Hamada, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 882−882. (b) Genet, J. P.; Pinel, C.; Mallart, S.; Juge, S.; Thorimbert, S.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1991**, *2*, 555−567. (c) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134−9135.

(6) (a) Takaoka, Y.; Okamoto, M.; Genba, Y. (Ono Pharmaceutical Co., Japan). WO 026874, 2004. (b) Takaoka, Y.; Nishizawa, R.; Shibayama, S.; Sagawa, K.; Matsuo, M. (Ono Pharmaceutical Co., Japan). WO 26873, 2004. (c) Imawaka, H.; Shibayama, S.; Takaoka, Y. (Ono Pharmaceutical Co., Japan). WO 035074, 2004. (d) Habashita, H.; Hamano, S.; Shibayama, S.; Takaoka, Y. (Ono Pharmaceutical Co., Japan). WO 074770, 2002. (e) Mitsuya, H.; Maeda, K.; Shibayama, S.; Takaoka, Y. (Ono Pharmaceutical Co., Japan). WO 074769, 2002.

(7) (a) Ikeo, T. (Nippon Kayaku Kabushiki Kaisha, Japan). WO 024934, 2004. (b) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5553−5562.

(8) See inter alia: (a) Poch, M.; Alcón, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1993**, *34*, 7781−7784. (b) Pastó, M.; Castejón, P.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1996**, *61*, 6033−6037. (c) Castejón, P.; Moyano, A.; Pericàs, M. A.; Riera, A. *Chem. Eur. J.* **1996**, *2*, 1001−1006. (d) Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 8425−8431. (e) Medina, E.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 8574−8578. (f) Medina, E.; Moyano, A.; Pericàs, M. A.; Riera, A. *Helv. Chim. Acta* **2000**, *83*, 972−988. (g) Martín, R.; Islas, G.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **2001**, *57*, 6367−6374.

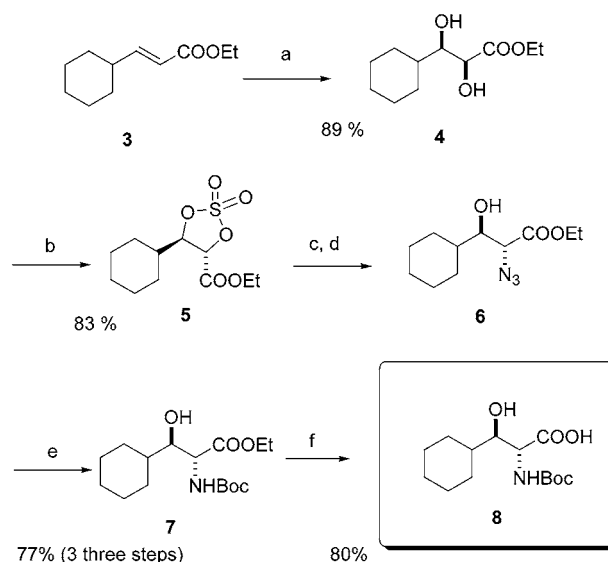* To whom correspondence should be addressed. E-mail: ariera@pcb.ub.es.
† Unitat de Recerca en Síntesi Asimètrica (URSA-PCB), Parc Científic de Barcelona and Departament de Química Orgànica, Universitat de Barcelona.
‡ Enantia, S.L. Parc Científic de Barcelona.

sequence, Sharpless developed a general methodology[9] that involves the following steps: (a) reaction of a vicinal diol with thionyl chloride to give a cyclic sulfite, (b) oxidation to sulfate with periodate and a catalytic amount of Ru-containing compound, and (c) reaction with a nucleophile, which in the synthesis of a hydroxy amino acid would be azide. However, this sequence has the usual drawbacks associated with the use of ruthenium: difficult workup and generation of heavy metal residues. Somewhat surprisingly, the direct transformation of diols into sulfates using sulfuryl chloride has been scarcely described in the literature, probably because in most cases the reaction conditions lead to a complex mixture of compounds. The few reports using this reagent[10,11] claimed that only cyclic or electron-deficient substrates give good yields. We describe here the preparation of sulfate **5** from unsaturated amino ester **3** by an advantageous procedure based on Sharpless asymmetric dihydroxylation and sulfuryl chloride treatment, (not involving sulfite/sulfate oxidation), and the transformation of **5** into (2R,3R)-2-(*tert*-butoxycarbonyl)amino-3-hydroxy-3-cyclohexylpropanoic acid, **8**, a useful precursor of pharmacologically important drugs such as ONO-4128, **2**.
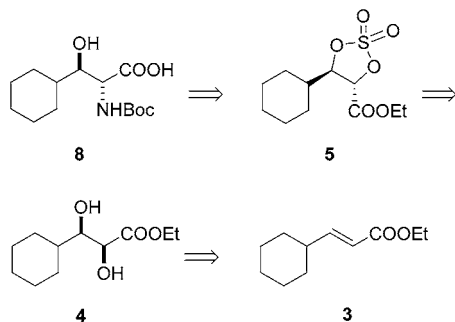
Submitting the known[12] unsaturated ester **3** to the standard Sharpless asymmetric dihydroxylation[13] afforded the enantiomerically enriched diol **4** uneventfully. The preparation of the sulfate was initially attempted in methylene chloride in the presence of triethylamine under the typical conditions.[10] However at −78 °C the main product was the bis-chlorosulfate **9**. By increasing the temperature up to 0 °C

(9) (a) Sharpless, K. B.; Gao, Y. (Massachusetts Institute of Technology, U.S.A.). U.S. Patent 5,321,143, 1994. (b) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538−7539.

(10) (a) Rinner, U.; Siengalewicz, P.; Hudlicky, T. *Org. Lett.* **2002**, *4*, 115−117. (b) Tai, V. W.-F.; Imperiali, B. *Tetrahedron Lett.* **1998**, *39*, 7215−7218, (c) Liu, P.; Vandewalle, M. *Tetrahedron Lett.* **1993**, *34*, 3625−3628. (d) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2732−2735. (e) Seimbille, Y.; Ali, H.; van Lier, J. E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 657−663. (f) Seimbille, Y.; Bénard, F.; van Lier, J. E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2275−2281. (g) Vanhessche, K. P. M.; Sharpless, K. B. *Chem. Eur. J.* **1997**, *3*, 517−522.

(11) (a) Fuentes, J.; Angulo, M.; Pradera, M. A. *J. Org. Chem.* **2002**, *67*, 2577−2587. (b) Tewson, T. J. *J. Org. Chem.* **1983**, *48*, 3507−3510.

(12) (a) Shabtai, J.; Ney-Igner, E.; Pines, H. *J. Org. Chem.* **1981**, *46*, 3795−3802. (b) Borne, R. F.; Forrester, M. L.; Waters, I. W. *J. Med. Chem.* **1977**, *20*, 771−776.

(13) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771. (b) Sharpless, K. B.; Beller, M.; Blackburn, B.; Kawanami, Y.; Kwong, H. L.; Ogino, Y.; Shibata, T.; Ukita, T.; Wang, L. WO 922067, 1992.

Scheme 1[a]

[a] Reagents and conditions: (a) K$_3$Fe(CN)$_6$, (DHQD)$_2$PHAL, 0.4% mol K$_2$OsO$_2$(OH)$_2$, CH$_3$SO$_2$NH$_2$ (76% yield). (b) SO$_2$Cl$_2$, NEt$_3$, AcOEt, 0 °C (93% yield). (c) NaN$_3$, acetone:H$_2$O (5:1) 0 °C, 2 h. (d) H$_2$SO$_4$, 20% Et$_2$O (1:1) o.n. (e) Pd/C, AcOEt, H$_2$, Boc$_2$O (77% three steps). (f) KOH, THF (80% yield).

the reaction took place in very low yields. An extensive set of solvents (toluene, isopropyl acetate, methyl isopropyl ketone) and temperatures was then tested, but in most cases the yields were disappointingly low. Attempted purification of the sulfate by chromatography gave the rearranged ketone **10** as the main product of the reaction. Performing the reaction in ethyl acetate, at −78 °C, also led to **9** as the major product. Nevertheless, the slow addition of sulfuryl chloride into a diluted solution of diol **4** and triethylamine in ethyl acetate at 0 °C[11] afforded a clean reaction crude that, after work up, gave sulfate **5** in 93% yield. It is worth noting that, to the best of our knowledge, this is the first acyclic diol without electron-deficient substituents that has been converted into sulfate by direct treatment with sulfuryl chloride.
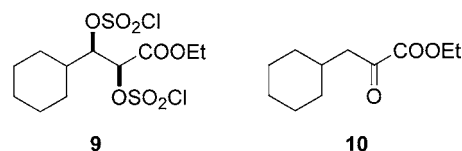
With sulfate **5** in hand, the transformation into the *N*-Boc derivative **7** took place in 77% yield by regioselective ring-opening with sodium azide, followed by hydrogenation over Pd/C and in situ protection with Boc$_2$O. The previously unknown ethyl *N*-Boc-2-amino-3-cyclohexyl-3-hydroxy ester (**7**) was hydrolyzed under basic conditions to afford the desired protected amino acid **8**. During the entire sequence all intermediates were either isolated pure from the reaction or purified by crystallization. Consequently, no chromatographic separations were necessary. The final product was obtained in very high chemical and optical purity (99% ee as determined by chiral HPLC). In summary, we have developed a practical and completely stereoselective syn-

thesis of (2*R*,3*R*)-2-(*tert*-butoxycarbonyl)-amino-3-hydroxy-3-cyclohexylpropanoic acid, **8**, using the Sharpless asymmetric dihydroxylation as a source of chirality. The process has been done on multigram scale without any chromatographic purification. The key step of the synthesis is the preparation of sulfate **5** from enantiomerically enriched diol **4** using sulfuryl chloride in ethyl acetate, instead of the usual conditions that involve sulfite/sulfate oxidation with ruthenium reagents.

Experimental Section

General. Optical rotations were measured at room temperature (concentration in g/100 mL). ^{1}H NMR spectra were obtained at 400 MHz (s = singlet, d = doublet, t = triplet, dt = double triplet, m = multiplet, and b = broad) ^{13}C NMR spectra were obtained at 75 MHz. ^{1}H chemical shifts are quoted relative to TMS and ^{13}C shifts relative to solvent signals. 3-Cyclohexylacrylic acid ethyl ester, **2**, was prepared according to the literature procedures.[12]

Ethyl (2*S*, 3*R*)-2,3-Dihydroxy-3-cyclohexylpropanoate 4. To a mixture of (DHQD)$_2$PHAL (800 mg, 1.03 mmol), K$_3$Fe(CN)$_6$ (101.5 g, 308 mmol), K$_2$CO$_3$ (42.6 g, 308 mmol) in H$_2$O: ^{t}BuOH (1:1, 1000 mL) cooled to 0 °C was added K$_2$OsO$_4$(OH)$_4$ (158 mg, 0.411 mmol) followed by methanesulfonamide (9.8 g, 102.8 mmol). After stirring 10 min at 0 °C, 3-cyclohexylacrylic acid ethyl ester (**2**) (18.7 g, 102.8 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 18 h and then quenched with sodium sulfite (154 g). Stirring was continued for 1 h at room temperature and the solution extracted with CH$_2$Cl$_2$ (3 × 300 mL). The organic layer was washed with KOH 2 N, dried over MgSO$_4$, and evaporated to give **4**. Crystallization in heptane afforded 17.0 g of **4** as a white solid (76% yield). Mp 75.5−76.0 °C. [α]$_D$ +12.5 (*c* 1.0, CHCl$_3$). IR: 3461(b), 2924, 2851, 1737, 1448, 1261 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): 4.29 (q, 2H), 3.55 (t, 1H), 3.05 (s broad, 1H), 2.04 (d broad, 1H), 1.55−1.86 (m, 4H), 1.32 (t, 3H), 0.9−1.27 (m, 6H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): 174.4 (CO), 77.0 (CH), 71.0 (CH), 62.2 (CH$_2$), 40.5 (CH), 31.3 (CH), 29.4 (CH$_2$), 29.2 (CH$_2$), 26.4 (CH$_2$), 26.0 (CH$_2$), 14.3 (CH$_3$) ppm.

(4*S*,5*R*)-4-Ethoxycarbonyl-5-cyclohexyl-1,3,2-dioxathiolane-2,2-dioxide 5. To a solution of diol **4** (14.3 g, 66 mmol) in dry AcOEt (2600 mL) was added NEt$_3$ (110.4 mL, 792 mmol). The reaction mixture was cooled to 0 °C under stirring, and SO$_2$Cl$_2$ (26.5 mL, 330 mmol) was added dropwise. After 2 h of stirring at this temperature, the reaction mixture was extracted with water (3 × 800 mL) and NaCl (2 × 500 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated to give an oil. The crude was crystallized in hexane to give 17.1 g of sulfate **5** as a white solid (93% yield). Mp 84.5−85.0 °C. [α]$_D$ +71.07 (*c* 1.0, CHCl$_3$). IR: 2933, 2858, 1767, 1745, 1397, 1210 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): 4.96 (d, 1H, *J* = 6.4 Hz), 4.79 (t, 1H, *J* = 6.4 Hz), 4.35 (q, 2H), 1.70−2.00 (m, 5H), 1.36 (t, 3H), 1.00−1.30 (m, 6H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): 165.6 (CO), 87.6 (CH), 78.0 (CH), 63.4 (CH$_2$), 40.4

(CH), 28.2 (CH$_2$), 27.5 (CH$_2$), 25.9 (CH$_2$), 25.5 (CH$_2$), 25.2 (CH$_2$), 14.1 (CH$_3$) ppm. Anal. Calcd for C$_{11}$H$_{18}$O$_6$S: C, 47.47; H, 6.52; S, 11.52. Found: C, 47.30; H, 6.56; S, 11.69.

Ethyl (2*R*, 3*R*)-2-Azido-3-hydroxy-3-cyclohexylpropanoate 6. Cyclic sulfate **5** (5.18 g, 18.6 mmol) was dissolved in a mixture of acetone:water (5:1, 150 mL) and cooled to 0 °C. NaN$_3$ (2.42 g, 37.2 mmol) was added, and the stirring was continued for 3 h. The solvent was evaporated, and the crude was dissolved in Et$_2$O (90 mL) and 20% H$_2$SO$_4$ (90 mL). After stirring overnight, excess NaHCO$_3$ was added to the reaction mixture. The aqueous layer was extracted with Et$_2$O (3 × 250 mL), and the combined organic extracts were dried (MgSO$_4$). The solvent was concentrated, and the solution (ca. 50−100 mL) was directly used in the next step. A small sample was evaporated to dryness for characterization to give azide **6** as an oil. IR: 3488 (b), 2927, 2853, 2109, 1737, 1449, 1261, 1192, 1024 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): 4.30 (q, 2H), 3.95 (d, 1H, *J* = 6 Hz), 3.70 (t, 1H, *J* = 6 Hz), 2.63 (b, 1H), 1.90−1.50 (m, 5H), 1.34 (t, 3H), 1.00−1.30 (m, 6H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): 169.7 (CO), 76.1 (CH), 63.5 (CH$_2$), 62.2 (CH), 40.1 (CH), 29.6 (CH$_2$), 27.2 (CH$_2$), 26.3 (CH$_2$), 26.2 (CH$_2$), 26.0 (CH$_2$), 14.3 (CH$_3$) ppm.

Ethyl (2*R*,3*R*)-2-(*tert*-Butoxycarbonyl)amino-3-hydroxy-3-cyclohexylpropanoate 7. A solution of crude azide **6** and Boc$_2$O (5.3 g, 24.2 mmol) in ethyl acetate (30 mL) was added to a stirred suspension of 10% Pd/C (448 mg) in ethyl acetate (60 mL) under hydrogen. The mixture was stirred under hydrogen until the starting material could not be detected by TLC (20 h). Then, the suspension was filtered through Celite, washing with ethyl acetate. Solvent was evaporated at reduced pressure to give crude **7** as an oil. Crystallization in heptane gave 4.5 g of **7** as a white solid (77% yield from sulfate **5**). Mp 76−78 °C. [α]$_D$ −15.6 (*c* 1.0, CHCl$_3$). IR: 3440 (b), 2978, 2925, 2852, 1717, 1502, 1163 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): 5.50 (bd, 1H, *J* = 6.8 Hz), 4.43 (bd, 1H, *J* = 4.8 Hz), 4.15−4.27 (m, 2H), 3.50 (bd, 1H, *J* = 5.2 Hz), 2.56 (b, 1H), 1.93 (bd, 1H, *J* = 12 Hz), 1.80−1.60 (m, 4H), 1.45 (s, 9H), 1.28 (t, 3H), 0.9−1.3 (m, 6H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): 171.4 (CO), 146.9 (CO), 85.3 (CH), 77. 9 (C), 61.6 (CH$_2$), 56.0 (CH), 40.9 (CH), 29.2 (CH$_2$), 29.1 (CH$_2$), 28.4 (CH$_3$), 26.3 (CH$_2$), 26.0 (CH$_2$), 25.9 (CH$_2$), 14.9 (CH$_3$) ppm. Anal. Calcd for C$_{16}$H$_{29}$NO$_5$: C, 60.93; H, 9.27; N, 4.44. Found: C, 60.80; H, 9.52; N, 4.42.

(2*R*,3*R*)-2-(*tert*-Butoxycarbonyl)amino-3-hydroxy-3-cyclohexylpropanoic Acid 8. To a stirred solution of **7** (2.5 g, 7.9 mmol) in THF, a KOH aqueous solution (0.9 g, 15.8 mmol in 60 mL) was added. After 2 h, no starting material was detected by TLC. The mixture was concentrated under vacuum, cooled to 0 °C, acidified with 0.1 M HCl, and filtered to afford 1.8 g of **8** as a white solid (80% yield). Mp 142.5−143 °C. [α]$_D$ −15.2 (*c* 1.0, CHCl$_3$). IR: 3442 (b), 3319 (b), 2926, 2852, 1692, 1512, 1366, 1166 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): 6.41 (broad, 1H), 5.64 (broad, 1H), 4.47 (s broad, 1H), 3.54 (s broad, 1H), 2.01 (d broad, 1H), 1.80−1.60 (m, 4H), 1.46 (s, 9H), 0.9−1.30 (m, 6H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): 174.5 (CO), 156.3 (CO),

80. 8 (C), 78.1 (CH), 55.8 (CH), 40.4 (CH), 29.4 (CH$_2$), 29.0 (CH$_2$), 28.4 (CH$_3$), 26.4 (CH$_2$), 26.0 (CH$_2$), 25.9 (CH$_2$) ppm. Optical purity: amino acid **8** was converted into its methyl ester which was analyzed by HPLC (Chiralcel OD, hexane:2-propanol, 98:2; 0.5 mL/min, $\lambda = 220$ nm; t_R (2*R*,3*R* isomer) = 28.0 min, t_R (2*S*,3*S* isomer) = 31.1 min) showing an enantiomeric purity of 99% ee.