First Stereocontrolled Synthesis of (S)-Cleonin and Related Cyclopropyl-Substituted Amino Acids.

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Supporting Information

^{1}H, ^{13}C and ^{19}F NMR spectra were acquired on a Varian VXR 300 spectrometer. Deuterated solvents used were $CDCl_3$ or [d_6]-dmso. Chemical shifts are given in ppm relative to TMS. Abbreviations used in the description of spectra are: bs (broad singlet), s, singlet, m, multiplet. Micro-analytical data were obtained on a Perkin-Elmer 240D elemental analyzer. Reversed-phase high performance liquid chromatography was performed on a LC-18-DB (5 x 150 mm). Eluent detection was monitored by UV absorbance at 220 nm. The linear elution gradient was 20 to 60% B in 25 min at 1.5 mL /min (A = 0.05% TFA in H_20, B = 0.05% TFA in MeCN).

(*4 R*)-**3-Carbobenzyloxy-2,2-dimethyl-4-(1-hydroxycyclopropyl)-oxazolidine** (**3)**
To a cooled (0°C) solution of oxazolidine **2** (1.5 g, 5.1 mmol) and $Ti(OiPr)_4$ (0.7 g, 2.5 mmol) in anhydrous Et_2O (15 mL) under nitrogen and magnetic stirring, a solution of freshly prepared EtMgBr (4.2 mL of a 3 M solution in Et_20, 12.6 mmol) was slowly added. The mixture was stirred at room temperature overnight, and the reaction subsequently quenched with a saturated solution of NH_4Cl. The organic layer was separated, the aqueous solution extracted three times with Et_2O and the organic fraction collected and dried. Evaporation of the solvent and flash chromatography on silica gel (EtOAc: hexane 2 :1) gave the pure compound **3** (0.93 g, 64%) as an oil; δ_H 0.51-0.96 (m, 4H), 1.50 (s, 3H), 1.60 (s, 3H), 3.78 (bs, 1H), 4.04 (m, 2H), 4.56 (m, 1H), 5.15 (m, 2H), 7.30-7.40 (m, 5H). δ_C 10.9, 11.7, 26.4, 26.9, 49.1, 59.6, 67.8, 70.2, 87.6, 127.2, 127.9, 128.1, 139.9, 155.7. Calcd. for $C_{16}H_{21}O_4$; C 65.96, H 7.27, N 4.81. Found C, 65.07; H, 7.17; N, 4.70.

1-((1*S*)-1-(Benzyloxycarbonylamino)-2-hydroxyethyl)-1-hydroxycyclopropane (**5)**. To a solution of **3** (0.9 g, 3.0 mmol) in 100 mL of MeOH, PPTS (1.0 g, 4 mmol) was added in small portions and the mixture stirred at rt for 8 h. The solvent was evaporated under vacuum to 1/3 of the original volume and EtOAc (150 mL) was added followed by water. The organic layer was separated, washed with a 5% $NaHCO_3$ solution, and with brine. After drying and evaporation of the solvent, column chromatography on silica gel (EtOAc : hexane 3 : 1) gave compound **5** (0.64 g 85%) as a pale yellow oil. δ_H 0.56-0.91 (m, 4H), 2.70 (bs, 2H), 4.04-4.31 (m, 3H), 5.15 (bs, 2H), 6.05 (bs, 1H7, 7.30-7.40 (m, 5H). δ_C 10.6, 11.4, 56.0, 60.0, 68.1, 70.1, 127.3, 127.6, 129.1, 140.1, 159.7.

(*S*)-N-Carbobenzyloxycleonin (6). To a solution of **4** (100 mg, 0.39 mmol) dissolved in anhydrous DMF (5 mL), PDC (2.4 mmol) was added and the mixture stirred at rt for 12 h. The solution was

cooled to 0°C and a 1M solution of HCl was added untill the mixture reaches pH 3 . The solution was saturated with NaCl and extracted three times with CH_2Cl_2. After drying, the dark solution is passed through a short column filled with 10 g of silica gel and 5 g of Na_2SO_3. The column was eluted with MeOH and the eluted solvent was collected, dried over Na_2SO_4 and evaporated to dryness to give **6** (79 mg, 75%) as a solid. m.p.196-198 °C (dec). δ_H 0.66-0.98 (m, 4H), 2.90 (bs, 1H), 4.48 (bs, 1H), 5.11 (s, 2H), 5.98 (bs, 1H), 7.30-7.46 (m, 5H), 10.31 (s, 1H). δ_C 11.4 (2C), 53.8, 61.78, 70.4, 127.3, 127.7, 129.8, 139.0, 157.7, 177.0.

(S)-Cleonin (7). Compound **6** (70 mg, 0.27 mmol) was deprotected in *i*-PrOH (5 mL) in the presence of Pd/C 10% (5 mg) and $HCOONH_4$ (15 mg) in a microwave oven as described in ref. 11 of the text. After filtration and evaporation of the solvent a solid was immediately formed. The residue was dried under vacuum and washed several times with EtOAc and Et_2O, filtered and dried under vacuum to give 38 mg (85%) of (S)-cleonin. M.p. 245-248 °C (dec) (lit ref 5 m.p. of the racemate 255-258 °C (dec.).δ_H (d_6-dmso) 0.60-0.89 (m, 4H), 3.20 (bs, 5H exchangeable protons) 4.48 (s, 1H). δ_C (d_6-dmso) 13.24; 13.88, 55.8, 63.0 179.7.

4-(2-Butyl-1-hydroxy-cyclopropyl)-1-carbobenzyloxy-2,2-dimethyl-oxazolidine (9). To a solution of **2** (1.0 g, 3.43 mmol) in anhydrous THF (20 mL) containing $ClTi(OiPr)_3$ (0.89 g, 3.43 mmol) and 1-hexene (0.32 g, 3.77 mmol), cyclohexylMgBr (3.5 mL of a 1M solution in Et_2O) was slowly added during 2 h. The mixture was stirred at rt and the reaction quenched with a saturated solution of NH_4Cl. The organic layer was separated and dried. After evaporation of the solvent, column chromatography on silica gel (EtOAc : hexane 1 : 1) gave compound **9** (0.78 g 65%) as a pale yellow oil. Exclusively the signals of the major isomer are reported: δ_H 0.56-0.90 (m, 3H), 1.00 (m, 3H), 1.20-1.60 (m, 6H),1.30 and 1.35 (s, 6H), 3.20 (bs, 1H), 4.00-4.40 (m, 3H), 5.10 (s, 2H), 7.20-7.40 (m, 5H). Calcd for $C_{20}H_{29}N0_4$; C 69.14, H 8.41, N 4.03. Found C 69.10, H 8.17, N 4.16.

Benzyloxycarbonylamino-(2-butyl-1-hydroxy-cyclopropyl)acetic Acid (10). Exclusively the signals of the major isomer are reported δ_H 0.56-0.90 (m, 3H), 1.05 (m, 3H), 1.20-1.60 (m, 6H), 3.20 (bs, 1H), 4.20 (bs, 1H), 5.16 (s, 2H), 5.90 (bs, 1H), 7.20-7.40 (m, 5H), 11.37 (bs, 1H). Calcd for $C_{17}H_{23}N0_5$; C 63.45, H 7.21, N 4.36. Found C 63.10, H 7.17, N 4.26.

Benzyloxycarbonylamino-{2-[3-(*tert*-butyl-dimethyl-silyloxy)-propyl]-1-hydroxy-cyclopropyl}-acetic Acid (11). Exclusively the signals of the major isomer are reported δ_H 0.20 (s 6H), 0.56-0.95 (m, 3H), 1.40 (s, 9H), 1.30-1.80 (m, 4H), 3.20 (bs, 1H), 3.65 (m, 2H), 4.35 (bs, 1H), 5.10 (s, 2H),

6.05 (bs, 1H), 7.20-7.40 (m, 5H), 10.95 (s, 1H). Calcd for $C_{22}H_{35}NO_6Si$; C, 60.38, H 8.06, N 3.20. Found C, 60.08, H 8.00, N 3.11.

Benzyloxycarbonylamino-{2-[3-phenylpropyl]-1-hydroxy-cyclopropyl}-acetic Acid (12). Exclusively the signals of the major isomer are reported δ_H 0.50-0.96 (m, 3H), 1.76 (m, 2H), 2.25 (m, 2H), 3.20 (bs, 1H), 4.30 (bs, 1H), 5.16 (s, 2H), 5.95 (bs, 1H), 7.20-7.50 (m, 10H), 10.65 (s, 1H). Calcd for $C_{21}H_{23}N0_5$; C, 68.28, H 6.28, N 3.79. Found C 68.08, H 6.18, N 3.57.