Stereoselective Synthesis of L-2-(Carboxycyclopropyl)glycines via Stereocontrolled 1,3-Dipolar Cycloadditions of Diazomethane on *Z*- and *E*-3,4-L-Didehydroglutamates OBO Esters

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Introduction

Due to the importance of metabotropic glutamate receptor (mGluR) and the crucial role of L-glutamate (L-Glu) as the major excitatory neurotransmitter in the mammalian central nervous system, the search for new structures with activity as agonists or antagonists is very intense. Several structural analogues of L-glutamic acid have been synthesized and found to be more specific agonists than L-Glu which not only activates mGluRs but also the ionotropic glutamate receptors.[1−3] Some conformationally constrained analogues of L-Glu recognize and bind to the various types of glutamate receptors in exclusive or preferential manner. Among them, the 2,3-[4] and 3,4-methano derivatives of L-Glu are most prominent;[5] the latter compounds are also referred to as carboxycyclopropylglycines (CCGs). The four isomeric **CCG-I**−**CCG-IV** were found to be agonists for either the *N*-methyl-D-aspartic acid (NMDA) or the metabotropic L-glutamate receptor.[6] The neurophysiological assays suggested that the extended conformer of L-Glu, which is equivalent to **CCG-I** and **-II**, activates the metabotropic L-Glu receptor and that the NMDA receptor is activated by the folded conformer of L-Glu, which is equivalent to **CCG-III** and **-IV**.[6] Interestingly, both amino acids **CCG-I** and **-III** were also isolated as natural products by Fowden from the green fruits of *Aesculus parviflora* and *Blighia sapida*,[7] and **CCG-I** was found in the fruits of *Blighia unijugata*.[8] These compounds are also of interest as useful synthetic intermediates[9] and as conformationally restricted analogues in peptide mimetics.[10]

CCG-I−**CCG-IV** (Figure 1) were first synthesized as diastereomeric mixtures by Ohfune et al. by cyclopropanation of chiral olefinic precursors through palladium-catalyzed cycloaddition of diazomethane.[6] Later, other enantioselective syntheses of CCG derivatives were described on the basis of cyclopropanation of chiral precursors by means of rhodium-catalyzed cycloaddition of diazomethane[11] or by using sulfoxonium ylides.[12]

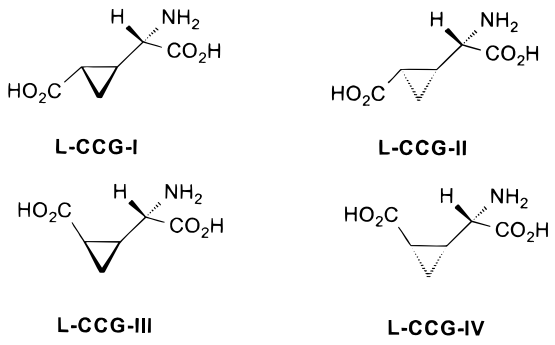

Figure 1.

One of our laboratories has previously investigated the 1,3-dipolar cycloaddition of diazomethane to chiral amino enoates followed by photolysis of the resultant pyrazolines as a convenient protocol to prepare enantiopure cyclopropane amino acids with high stereoselectivity.[4,13] The bulky 4-methyl-2,6,7-trioxabicyclo[2.2.2] ortho (OBO) ester function has been shown to be a useful protecting group of carboxylic acids for preventing epimerization at the α-carbon and to induce good diastereoselectivities in the transformations performed on serine aldehyde or threonine ketone equivalents, i.e. carbonyl addition reactions,[14] reductions of ketones to secondary alcohols,[15,16] and substitution reactions,[17] leading to a wide range of amino acids.

In this paper we describe a concise and stereoselective syntheses of **CCG-I** and **CCG-III** based on the highly

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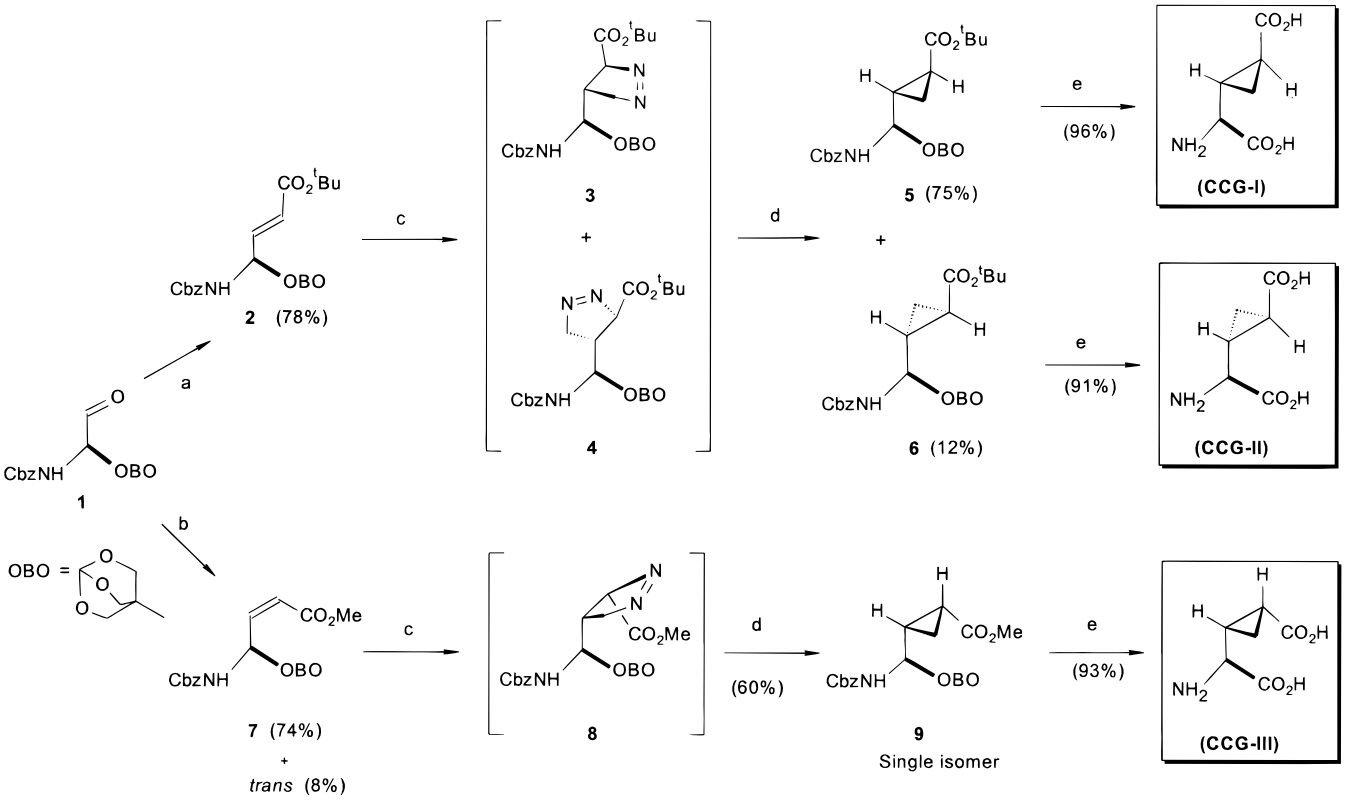
Scheme 1[a]



[a] Reaction conditions: (a) $(Ph)_3P{=}CH_2CO_2{}^tBu$, CH_2Cl_2, 15 min; (b) $(CF_3CH_2O)_2P(O)CHCO_2Me$, NaH, THF, −78 °C, 45 min; (c) CH_2N_2, Et_2O, 1 h; (d) hν, CH_2Cl_2 (or acetonitrile), benzophenone, −45 °C, 1 h; (e) 6 N HCl, 90 °C, 5 h.

efficient stereochemical control of the 1,3-dipolar cycloaddition of diazomethane provided by the presence of the OBO function on the chiral *E*- or *Z*-3,4-L-didehydroglutamate used as substrates.

Results and Discussion

Preparation of the *E*-3,4-L-didehydroglutamate **2** was performed as described previously[14] for the Fmoc derivative by the olefination of the Cbz-L-Ser-aldehyde-OBO **1** with Wittig−Horner reagent[15] (Scheme 1). Optically pure **2** was obtained after chromatography and no *Z*-isomer was detected by NMR. Addition of etheral diazomethane to **2** gave a mixture of pyrazoline **3** and **4** in excellent yields but proved to be too unstable to be separated by chromatography. Thus, the mixture of pyrazoline **3** and **4** was subjected to optimized photolysis conditions to give a 86% yield of a 6:1 mixture of *syn*- and *anti-trans*-cylopropane derivatives **5** and **6**, as determined by NMR analysis. The use of acetonitrile as solvent was critical as the usual solvent, CH_2Cl_2, led to partial ring opening of the OBO ester. Pure diastereomers **5** and **6** were obtained after by flash chromatography and recrystallization.

The *Z*-3,4-L-didehydroglutamate **7** was obtained from the OBO serine aldehyde **1** by olefination with $Na(CF_3CH_2O)_2P{=}CHCO_2Et$ as 9:1 mixture of *Z*:*E* isomer (Scheme 1) which were separated by flash chromatography. Addition of etheral diazomethane to **7** gave the corresponding pyrazoline **8** exclusively. The pyrazoline **8** is even more unstable than **3** and **4**. In fact when the crude pyrazoline **8** was irradiated under the same conditions used for **3** and **4**, large amount of cycloreversion product (didehydroglutamate **5**) was obtained and little of the desired cyclopropane could be isolated. Various conditions for the photolysis reaction were then examined. Lower temperatures or change of photosensitizer to acetone gave similar results. We eventually found that increasing the amount of benzophenone to 30 mol % gave good yields (60% for both steps) of *cis*-cyclopropane **9**. Removal of the methyl or *tert*-butyl ester, the OBO, and Cbz protecting groups from the fully protected cyclopropanes **5**, **6**, and **9** was achieved in a single step by acid hydrolysis (6 N HCl, 90 °C, 5 h). After evaporation, the crude amino acids were treated with propylene oxide, filtered through a reverse phase cartridge and recrystallized from H_2O/EtOH to give **CCG-I**, **-II** and **-III** in their pure form in 91−96% yields. The stereochemistry of **CCG-I**, **-II** and **-III** and their precursors was determined by comparison of the NMR and optical rotation of CCGs of each isomers reported by Ohfune et al.[6]

The observed syn π-facial diastereoselectivity in the cycloaddition reactions can be rationalized by consideration of the active conformers for dehydroglutamates **2** and **7**. Figure 2 shows the conformers **2A** and **2B** leading to the same *syn*-pyrazoline **3** from *Z*-precursor **2**, through the preferential attack of diazomethane to the less hindered face of the double bond. On the contrary, conformer **2C** leads to the anti adduct **4** which is the minor isomer. Thus the diastereoselection observed can be explained on the basis of the serious steric congestion in **2C**. The exclusive production of *syn*-pyrazoline **8** from *Z*-didehydroglutamate **7** can be explained in a similar manner. The facial stereoselectivity can, in part, be explained by the allylic 1−3 strain arguments.[18] Notable is the effectiveness of the bulky OBO group to achieve

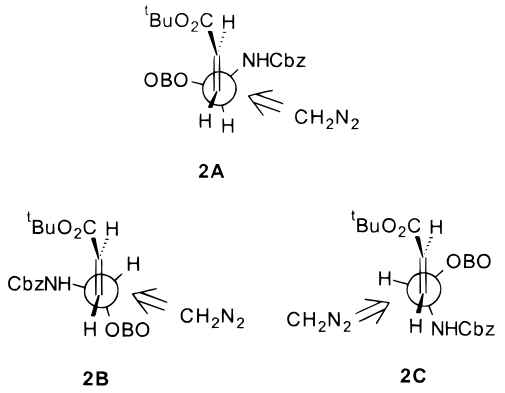


Figure 2.

these highly diastereoselective cycloadditions of diazomethane. The OBO substituent is much better than the chiral dioxolane ring used as the selectivity-directing group in the reactions on related substrates.[13b]

Conclusion

In summary, we described a very efficient method for the stereoselective synthesis of two of the carboxycyclopropylglycines **CGC-I** or **-III**. The major advantages of this new approach for the preparation of CCGs are the ease of preparation of the starting enoates; the high diastereoselectivity in the diazomethane cycloaddtion induced by the OBO ester; and the minimal manipulation necessary to convert the cyclopropane intermediates to the deprotected cyclopropyl amino acids, which is effected by the simultaneous removal of the protecting groups. As part of our joint program, we are currently examining the cycloaddition of other dipoles to more substituted 3,4-didehydroglutamate OBO derivatives. We also envisage carrying out theoretical calculations of the ground and transition states involved in these reactions to rationalize their stereochemical outcome. Results of these studies will be published in due course.

Experimental Section

General. All chemicals were purchased from Aldrich, Fluka, or Sigma and used directly. CH_2Cl_2 was distilled from CaH_2, and THF from Na/benzophenone. Melting point are uncorrected. Mass spectra were determined at a ionizing voltage of 70 eV. Most reactions were carried out under dry argon in glassware dried overnight at 120 °C or flame-dried before use. TLC was carried out on Merck aluminum-backed silica gel 60 F254, with visualization by UV or 5% $(NH_4)_6MoO_{24}$/0.2% $Ce(SO_4)_2$/5% H_2SO_4 or ninhydrin solution (2% in EtOH). TLC solvent systems commonly used are A, 5:1 CH_2Cl_2/EtOAc; B, 10:1 CH_2Cl_2/EtOAc; C, 3:1 CH_3OH/EtOAc; and D, 10:1 CH_3OH/EtOAc. Column chromatography was done on a silica gel (230−400 mesh) column. IR spectra were recorded in the 4000−625 cm^{-1} range. Optical rotations were measured on a digital polarimeter using a cuvette of 0.5 cm in length. Elemental analyses were performed by MHW laboratories in Phoenix, AZ, or by Institut de Química Bio-Orgànica de Barcelona, Spain.

***N*-Cbz-(O-tBu)-*E*-2,3-L-dehydroglutamate OBO Ester (2).** Cbz-L-Ser OBO[13] ester **1** (500 mg, 1.55 mmol) and $Ph_3P{=}CHCO_2$-tBu (700 mg, 1.86 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) under nitrogen and stirred for 15 min at room temperature. The solution was then washed with 3% NH_4Cl (2 × 20 mL), dried ($MgSO_4$), and evaporated to dryness. The yellowish oil was purified by flash chromatography (silica gel, 3:2 EtOAc/hexane with 1% Et_3N) to give a white solid that was recrystallized from EtOAc and hexane to yield 510 mg of **2** (78%). Mp: 147−148 °C. $[\alpha]^{25}_D = -24.0$ ($c = 1.00$, AcOEt). IR (KBr): 3312, 2974, 2935, 2885, 1722, 1704, 1686 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 0.78 (s, 3H), 1.45 (s 9H), 3.88 (s, 6 H), 4.52 (dd, $J = 8.0$, 5.1 Hz, 1H), 5.10 (br m, 3H), 5.88 (dd, $J = 16.1$, 1.4 Hz, 1H), 6.85 (dd, $J = 16.1$, 5.1 Hz, 1H), 7.33 (br m., 5 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 14.24, 28.07, 30.73, 55.96, 66.05, 72.84, 80.41, 107.71, 124.51, 128.12, 128.48, 136.27, 141.62, 155.90, 165.43. Anal. Calcd for $C_{22}H_{29}NO_7$: C, 62.99; H, 6.97; N; 3.34. Found: C, 62.98; H, 6.94; N, 3.41.

***N*-Cbz-(O-Me)-*Z*-2,3-L-dehydroglutamate OBO Ester (7).** A dispersion of NaH 60% in oil (124 mg, 3.1 mmol) was added to THF (2 mL) in a round-bottom flask under nitrogen. $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ (0.98 g, 650 μL, 3.1 mmol) was added and the mixture cooled to −78 °C. In another flask Cbz-L-Ser OBO ester **1** (400 mg, 1.2 mmol) was dissolved in THF (5 mL) under nitrogen and cooled to −78 °C. This solution was transferred to the first flask and was stirred at this temperature for 45 min. The solution is then poured in 2:1 CH_2Cl_2/5% NH_4Cl and extracted with EtOAc. The organic layer was separated, washed with 10% NaCl, dried ($MgSO_4$), filtered, and evaporated to dryness. The resulting oil was purified by flash column chromatography (silica gel, 1:3 EtOAc/hexane with 1% Et_3N) to give the *Z*-2,3-L-dehydroglutamate **7** (438 mg, 74%) and the corresponding *E* isomer (38 mg, 8%) both as oils for a combined yield of 82%. **Data for 7**: $[\alpha]^{25}_D = -47.5$ ($c = 0.80$, AcOEt). IR (film): 3352, 2951, 2882, 1728, 1659 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): 0.73 (s, 3H), 3.68 (s, 3H), 3.85 (s, 6 H), 5.04 (s, 1H), 5.28 (m, 1H), 5.68 (t, $J = 8.7$, 8.7 Hz, 1H), 5.84−6.01 (br m, 2H), 7.28, (br m, 5 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 14.07, 30.51, 51.21, 551.69, 66.60, 72.70, 107.74, 122.27, 127.82, 127.95, 128.23, 136.27, 141.20, 155.29, 165.66. Anal. Calcd for $C_{22}H_{29}NO_7$: C, 62.99; H, 6.97; N, 3.34. Found: C, 63.12; H, 7.05; N, 3.13.

***N*-Cbz-(O-tBu)-*trans*-2-(carboxycyclopropyl)glycine OBO Ester (5).** Excess ethereal solution of diazomethane (ca. 15 equiv) was distilled onto a solution of *E*-2,3-L-dehydroglutamate **2** (1.00 g, 2.38 mmol) dissolved in ether (30 mL) at 0 °C. The resulting solution was protected from light and stirred at room temperature for 1 h. Anhydrous $CaCl_2$ (1.0 g) was then added to destroy the excess diazomethane and, after filtration, evaporated under vacuum to give an oil. The mixture of pyrazolines **3** and **4** obtained was very unstable (purification attempts by chromatography or crystallization gave decomposition products) and was used without purification. The mixture of pyrazolines **3** and **4** and benzophenone (50 mg, 0.27 mmol) was dissolved in acetonitrile (500 mL) and transferred into a Pyrex reactor under nitrogen atmosphere, cooled at −45 °C and irradiated with a 125 W medium-pressure mercury-lamp for 10 min. The solvent was removed under vacuum and the crude was purified by flash chromatography (silica gel, 1:1 EtOAc:hexane, with 1% of triethylamine), to give 903 mg (2.08 mmol, 87% yield) of a mixture of the two possible isomers in a ratio 6:1 as determined by NMR analysis. Recrystallization (EtOAc/pentane) provided 600 mg (58%) of the major isomer **5** in a pure form. Mp: 145−145.5 °C. $[\alpha]^{25}_D = +38.0$ ($c = 2.00$, EtOAc). IR (KBr): 3380, 2974, 2932,1730, 1522 cm^{-1}. ^1H NMR (250 MHz) ($CDCl_3$) 0.77 (s, 3H), 0.83 (m, 1 H), 1.09 (m, 1 H), 1.39 (br m, 10H), 1.55 (m, 1 H), 3.48 (m, 1 H), 3.87 (s, 6 H), 5.00 (d, $J = 10.2$ Hz, 1 H), 5.07, (d, $J = 10.2$ Hz, 1 H), 7.32 (br s, 5H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 13.68, 14.32, 17.95, 22.22, 28.12, 30.62, 56.68, 66.80, 72.70, 79.94, 108.33, 127.97 (2 × C), 128.14, 136.52, 156.29, 173.28. Anal. Calcd for $C_{23}H_{31}NO_7$: C, 63.73; H, 7.21; N, 3.23. Found: C, 63.77; H, 7.21; N, 3.32. Additional recrystallization gave a small quantity of the minor diastereomer **6** in a pure form. Mp 115−117 °C (AcOEt/hexane). $[\alpha]^{25}_D = -45.5$ ($c = 1.00$, EtOAc). IR (KBr): 3387, 2972, 2930, 2881, 1726 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): 0.78 (s, 3H), 0.83 (m, 1 H), 0.96 (m, 1 H), 1.41 (s, 9H), 1.42 (m, 10H), 1.58 (m, 1 H), 3.61 (dd, $J = 10.2$, 6.6 Hz, 1H), 3.86 (s, 6H), 5.07 (br m, 1H), 7.33 (m, 5 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 10.85, 14.24, 15.74, 21.53, 28.06, 30.56, 56.03, 66.82, 72.65, 79.88, 108.26, 127.99, 128.41, 136.23, 155.85, 173.20. Anal. Calcd for $C_{23}H_{31}NO_7$: C, 63.73; H, 7.21; N, 3.23. Found: C, 63.52; H, 7.34; N, 3.58.

***N*-Cbz-(O-Me)-*Z*-2-(carbocyclopropyl)glycine OBO ester (9)** was synthesized as for **6**, with *Z*-dehydroglutamate **7** (162 mg, 0.4 mmols), except the reaction was completed in 2 h. The irradiation of the resulting pyralozine **8** was performed in

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the presence of a larger concentration of benzophenone (24 mg, 30 mol % instead of 10 mol %). Under these conditions, the *cis*-cyclopropane **9** was isolated after flash column chromatography (1:1 EtOAc:hexane) as a white solid (101 mg, 0.3 mmol, 60%). Mp 90−92 °C (AcOEt/hexane). $[\alpha]^{25}_D = +14.0$ ($c = 2.00$, AcOEt). IR (KBr): 3600−3300 (br), 2953, 2881, 1724, 1727 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): 0.77 (s, 3H), 1.10 (m, 1 H), 1.33 (m, 1 H), 1.45 (m, 1H), 1.64 (m, 1 H), 3.56 (s, 3H), 3.86 (s, 6H), 3.95 (m, 1 H), 5.03 (br m, 2H), 5.23 (d, NH, $J = 9.5$ Hz), 7.31 (Br m, 5 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 12.74, 14.36, 19.24, 22.21, 30.63, 51.82, 53.59, 66.47, 72.68, 108.88, 127.78, 127.96, 128.31, 136.87, 155.66, 172.92. Anal. Calcd for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.19; H, 6.58; N, 3.71.

General Procedure for the Removal of the Protecting Groups. The suitable amount of the fully protected product was introduced in a round-bottom flask followed by the addition of 6 M HCl. The solution was stirred at 90 °C for 5 h. The solvent was then evaporated to dryness and the resulting crude amino acid was dissolved in EtOH. Propylene oxide was added until cloudiness appears. After sedimentation the precipitate was filtered, dissolved in water, and eluted through a reverse phase C-18 cartridge. After removal the water under vacuum, the solid was recrystallized from H_2O/EtOH.

Deprotection of 5: (2*S*,1*S*′,2*S*′)-2-(carboxycyclopropyl)-glycine (CCG-I). The protected cyclopropane derivative **5** (200 mg, 0.5 mmol) was dissolved in 6 M HCl (10 mL). The reaction yielded (2*S*,1′*S*,2′*S*)-2-(carboxycyclopropyl)glycine, **CCG-I** (70 mg, 0.4 mmol, 96%). Mp: 243−245 °C dec (lit. 243−247 °C dec). $[\alpha]^{25}_D = +101.3$ ($c = 0.50$, H_2O) (lit. +102, $c = 0.5$, H_2O). ^1H NMR (D_2O, 250 MHz): 1.19 (ddd, $J = 8.4, 5.9, 5.1$ Hz, 1H), 1.30 (ddd, $J = 9.5, 5.1, 5.1$ Hz, 1 H), 1.62−1.77 (br m, 2 H), 3.20 (d, $J = 10.2$ Hz, 1H). ^{13}C NMR (D_2O, 62.5 MHz): 15.10, 20.13, 23.37, 58.33, 173.65, 178.53.

Deprotection of 6: (2*S*,1′*R*,2′*R*)-2-(Carboxycyclopropyl)-glycine, CCG-II. The protected cyclopropane **6** (77 mg, 0.2 mmol) was treated as described above with 6 M HCl (4 mL). The reaction yielded (2*S*,1′*R*,2′*R*)-2-(carboxycyclopropyl)glycine, **CCG-II** (25 mg, 0.2 mmol, 90%). Mp: 253−256 °C dec (lit. 255−258 °C dec). $[\alpha]^{25}_D = -20.3$ ($c = 1.50$, H_2O) (lit. −20.2, $c = 0.5$, H_2O). ^1H NMR (D_2O, 250 MHz): 1.04 (ddd, $J = 8.8, 5.7, 5.0$ Hz, 1H), 1.22 (ddd, $J = 9.1, 5.1, 5.0$ Hz, 1H), 1.70−1.82 (br m, 2H), 3.35 (d, $J = 9.1$ Hz, 1H). ^{13}C NMR (D_2O, 62.5 MHz): 14.81, 21.14, 24.42, 59.15, 174.28, 177.94.

Deprotection of 9: (2*S*,1′*S*,2′*R*)-2-(Carboxycyclopropyl)-glycine, CCG-III. The protected *cis*-cyclopropane **9** (100 mg, 0.2 mmol) was treated as described above with 6 M HCl (5 mL). The reaction yielded (2*S*,1′*S*,2′*R*)-2-(carboxycyclopropyl)glycine, **CCG-III** (37 mg, 0.2 mmol, 93%). Mp: 190−193 °C dec (lit. 192−197 °C dec). $[\alpha]^{25}_D = +20.4$ ($c = 1.50$, H_2O) (lit. +20.8, $c = 0.5$, H_2O). ^1H NMR (D_2O, 250 MHz): 1.24 (ddd, $J = 6.8, 5.7, 5.0$ Hz, 1H), 1.37 (ddd, $J = 9.3, 9.1, 5.0$ Hz, 1H), 1.59 (m, 1H), 1.85 (ddd, $J = 9.1, 7.7, 5.7$ Hz, 1H), 3.86 (d, $J = 10.8$ Hz, 1H). ^{13}C NMR (D_2O, 62.5 MHz): 16.91, 19.94, 24.76, 60.01, 175.15, 178.61.

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