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Enantioselective Synthesis of 2-(3'-Alkyl-2'-Carboxy Cyclopropyl)Glycines

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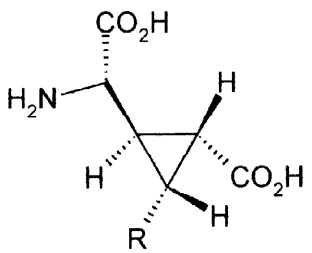
Abstract

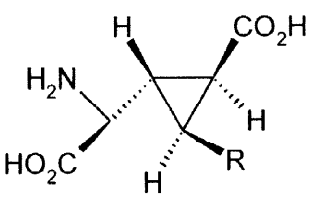
New conformationally restricted glutamate analogues 2-(3`-alkyl-2`-carboxycyclopropyl)glycines (**1a-c** and **2a-c**) were enantioselectively prepared by the addition-elimination reaction of the chiral lithium bislactim ether anion of **3** to racemic 4-alkyl-4-bromobut-2-enoates.

1. Introduction

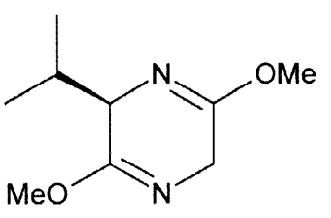
The cyclopropane subunit is found in a number of natural and unnatural substrates which have attracted attention due to their interesting biological effects.[1] Introduction of the cyclopropane moiety into biologically active substances has been recognized as an important chemical modification owing to its conformational rigidity and potential chemical reactivity.[2] In particular, conformationally restricted analogues of glutamic acid having the cyclopropane moiety have been shown to be useful pharmacological probes for the investigation of excitatory amino acids (EAA) glutamate



1a-c



2a-c



3

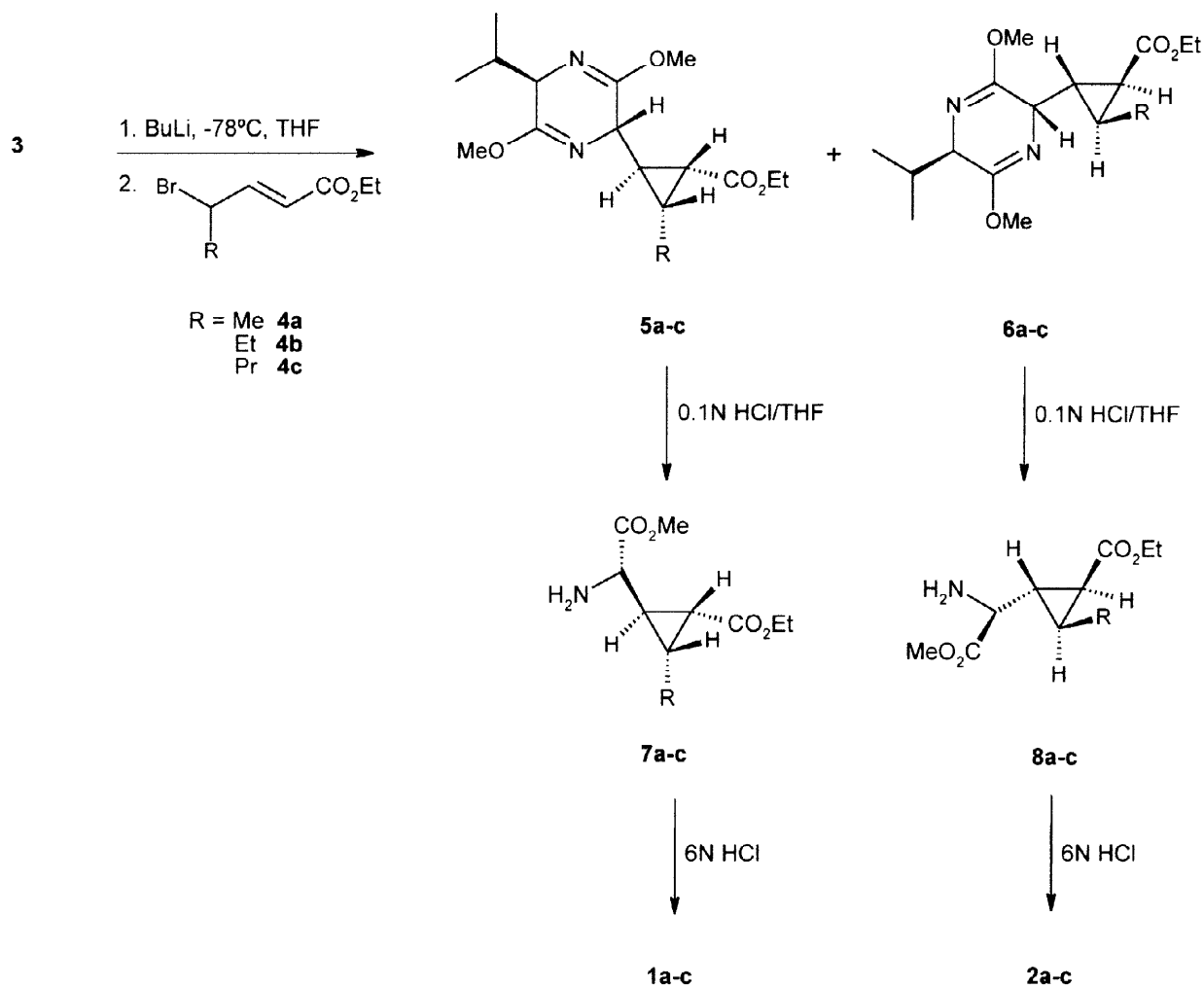
Scheme 1

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00333-6

receptors (R=H, Scheme 1).[3] Thus, the stereochemistry and substitution pattern of 2-carboxycyclopropyl glycines (CCGs) each play a key role in activating or deactivating different glutamate receptor subtypes.[4]

2. Results and discussion

The alkylation of lithiated bis-lactim ethers, in particular the (2*R*)-(-)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (**3**) developed by Schollkopf and collaborators,[5] is widely used in the asymmetric synthesis of amino acids. The diastereoselectivity of the reaction is very high, irrespective of the nature of the electrophile, yielding the product which results from attack at the less sterically hindered face (trans to the isopropyl).[6] Thus, the conjugate addition of metallated bis-lactim ethers to unsaturated esters,[7] ketones[8] and nitro compounds[9] provides a valuable protocol for preparing non-proteinogenic amino acids with diastereomeric excesses greater than 98%.



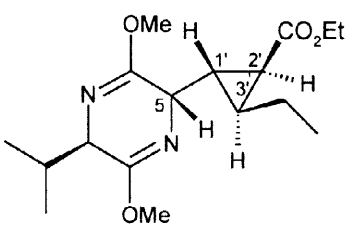
Scheme 2

Alternatively, the addition of racemic *N*-(diphenylmethylene) glycinate enolates to 4-bromobut-2-enoate followed by intramolecular displacement of bromine to yield cyclopropanes has been described by Joucla.[10]

As part of our ongoing effort in the EAA field, we report here, for the first time, the enantioselective synthesis of 2-(3'-alkyl-2'-carboxycyclopropyl-1'-yl) glycines (**1a-c** and **2a-c**, Scheme 1) by an asymmetric intramolecular ring-closure reaction, which *controlled four stereogenic centres*. A combination of two reactions provides the strategy for the synthesis of desired **1a-c** and **2a-c**. The first one involves the anionic Michael addition reaction of the commercially available chiral **3** to racemic 4-alkyl-4-bromobut-2-enoates.[11] Subsequent enolate displacement of the bromine led to the formation of the cyclopropane (Scheme 2).

The lithiated bislactim ether of **3** was obtained by treatment of **3** with butyllithium at -78°C. Then, the addition of 4-alkyl-4-bromobut-2-enoates (**4a-c**) at the same temperature led to a 1:1 mixture of the corresponding diastereoisomers **5a-c** and **6a-c**.

Pure diastereoisomers were separated by column chromatography. Both diastereoisomers have the same relative configuration at the three centres of the cyclopropane ring, and have the same absolute configuration at C-5 (*S*). The stereochemical determination relied upon nOe difference experiments and the relative sizes of vicinal coupling constants. For example, in one of the isomers (**6b**) when H-3' is irradiated an nOe of 4.7% is observed at H-2'. Similarly, an nOe effect is observed between H-1' and the methylene of the ethyl substituent on C-2' confirming the *cis* arrangement of these groups. The absolute stereochemistry for both diastereomers was *tentatively* assigned based on the biological activity observed for the final aminoacids **2a-c** which exhibited activity as metabotropic EAA receptor agonists (the counterparts **1a-c** did not have any activity).[12] This is only compatible with literature precedent assuming the 5*S*,1'*S*,2'*S* absolute configuration for **2a-c**.[3,4]



6b

The hydrolysis of the adducts **5a-c** and **6a-c** with two equivalents of 0.1N HCl at room temperature for 24 h afforded the enantiomerically pure amino acid alkyl esters **7a-c** and **8a-c** along with methyl L-valine ester which is readily removed *in vacuo*.[5,7,8,9]

The enantiomeric purity of diastereoisomers **7a-c** and **8a-c** was established by ^{1}H-NMR using Eu(hfc)$_3$ as shift reagent, using the methyl singlets for chiral analysis.

Final hydrolysis of **7a-c** and **8a-c** was accomplished by heating with 6N HCl and yielded the hydrochloride salts of amino acids **1a-c** and **2a-c** which, after treatment with propylene oxide gave rise to the corresponding zwitterions.

Therefore, we have achieved the enantioselective synthesis of 2-(3'-alkyl-2'-carboxycyclopropyl) glycines as new conformationally restricted glutamate analogues.

3. Experimental

All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. THF was distilled from sodium benzophenone ketyl prior to use. All reactions were performed under a positive pressure of argon. ^{1}H-NMR and ^{13}C-NMR data were recorded on a Bruker AC-200P (200 MHz and 400 MHz). IR spectra were obtained on Nicolet 510 P-FT (film and KBr). Melting points were determined on a Büchi apparatus and are not corrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Universidad Complutense Analytical Centre (Facultad de Farmacia) Madrid.

(2*R*,5*S*,1'*R*,2'*R*,3'*R*/2*R*,5*S*,1'*S*,2'*S*,3'*S*)-2,5-dihydro-2-isopropyl-5-(2'-ethoxycarbonyl 3'-alkylcyclopropyl)-3,6-dimethoxypyrazine.

General procedure. A solution of (2*R*)-(-)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (1 mmol) in THF (1.5 mL) under a dry nitrogen atmosphere was cooled to -78°C. A 1.6M solution of *n*-butyllithium in hexane (1.5 mmol) was injected slowly into the reaction mixture and stirring was continued at -78°C for 30 min. Then the γ-bromo α,γ-unsaturated ester (1.5 mmol) dissolved in THF (1.5 mL) was injected into the solution at -78°C and the mixture maintained at this temperature for 2-3h and then hydrolysed with water and extracted with dichloromethane (3x25 mL). The combined organic layers were dried over anhidrous magnesium sulphate and evaporated under reduced pressure to give an oil which was purified by chromatography (hex/EtOAc: 15/1) to give the following compounds:

(2*R*,5*S*,1'*R*,2'*R*,3'*R*)-2,5-dihydro-2-isopropyl-5-(2'-ethoxycarbonyl-3'-methyl cyclopropyl)-3,6-dimethoxypyrazine (5a)

Yield: 19%. Oil. $[\alpha]_D$= -23.5 (c=0.68, $CHCl_3$); ^{1}H-NMR (200 MHz. $CDCl_3$): 0.69 (d, *J* 6.8 Hz, 3H), 1.04 (d, *J* 6.8 Hz, 3H), 1.14 (m, 3H), 1.27 (t, *J* 7.2 Hz, 3H), 1.64 (m, 1H), 1.91 (m, 1H), 2.07 (m, 1H), 2.22 (d sext, *J* 3.4, 6.8 Hz, 1H), 3.63 (s, 3H), 3.73 (s, 3H), 3.92 (t, *J* 3.7 Hz, 1H), 4.05 (t, *J* 3.7 Hz, 1H) and 4.16 ppm (q, *J* 7.2 Hz, 2H); ^{13}C-NMR (50MHz, $CDCl_3$): 11.45, 14.40, 16.71, 17.82, 18.98, 21.70, 30.16, 31.96, 52.46, 52.59, 53.25, 60.19, 60.80, 163.47, 164.76 and 172.59 ppm; IR (oil, ν): 1728 and 1695 cm^{-1} (C=O and C=N); HRMS (EI): M^+ found 310.1899. $C_{16}H_{26}N_2O_4$ requires 310.1892.

(2*R*,5*S*,1'*S*,2'*S*,3'*S*)-2,5-dihydro-2-isopropyl-5-(2'-ethoxycarbonyl-3'-methyl cyclopropyl)-3,6-dimethoxypyrazine (6a)

Yield: 20%. Oil. $[\alpha]_D$= +37.38 (c=1.95, $CHCl_3$); ^{1}H-NMR (300 MHz. $CDCl_3$): 0.69 (d, *J*=7.1 Hz, 3H), 1.03 (d, *J* 7.1 Hz, 3H), 1.22 (d, *J* 7.0 Hz, 3H), 1.24 (t, *J* 7.2 Hz, 3H), 1.48 (dd, *J* 5.1, 9.2 Hz, 1H), 1.69 (m, 1H), 1.82 (m, 1H), 2.24 (m, 1H), 3.63 (s, 3H), 3.71 (s, 3H), 3.92 (t, *J* 3.6 Hz, 1H), 4.01 (dd, *J* 3.6, 5.1 Hz, 1H) and 4.11 ppm (q, *J* 7.2 Hz, 2H); ^{13}C-NMR (50MHz, $CDCl_3$): 11.46, 14.32, 16.64, 18.97, 19.09, 21.01, 30.89, 31.86, 52.41, 52.63, 53.73, 60.12, 60.70, 163.26, 169.69 and 172.31 ppm; IR (oil, ν): 1726, 1703 and 1693 cm^{-1} (C=O and C=N); HRMS (EI): M^+ found 310.1889. $C_{16}H_{26}N_2O_4$ requires 310.1892.

2*R*,5*S*,1'*R*,2'*R*,3'*R*)-2,5-dihydro-2-isopropyl-5-(2'-ethoxycarbonyl-3'-ethyl cyclopropyl)-3,6-dimethoxypyrazine (5b)

Yield: 23%. Oil. $[\alpha]_D$= -17.62 (c=0.91, $CHCl_3$); ^{1}H-NMR (200 MHz. $CDCl_3$): 0.68 (d, *J* 6.9 Hz, 3H), 0.86 (t, *J* 7.3 Hz, 3H), 1.03 (d, *J* 6.9 Hz, 3H), 1.27 (t, *J* 7.2 Hz, 3H), 1.5 (qt, *J* 7.2 Hz, 2H), 1.90 (dd, *J* 5.0, 11.4 Hz, 1H), 2.09 (dd, *J* 4.3, 9.1 Hz, 1H), 2.22 (d sext, *J* 3.5, 6.9 Hz, 1H), 3.64 (s, 3H), 3.70 (s, 3H), 3.93 (t, *J* 3.5 Hz, 1H), 4.07 (t, *J* 4.3 Hz, 1H) and 4.15 ppm (q, *J* 7.2 Hz, 2H); ^{13}C-NMR (50MHz, $CDCl_3$): 13.56, 14.27, 16.56, 18.89, 19.41, 21.36, 25.31, 29.35, 31.67, 52.41, 53.20, 60.10, 60.68, 163.32, 164.67 and 172.56 ppm; IR (oil, ν): 1728 and 1693 cm^{-1} (C=O and C=N); HRMS (EI): M^+ found 324.2040. $C_{17}H_{28}N_2O_4$ requires 324.2049.

(2*R*,5*S*,1'*S*,2'*S*,3'*S*)-2,5-dihydro-2-isopropyl-5-(2'-ethoxycarbonyl-3'-ethyl cyclopropyl)-3,6-dimethoxypyrazine (6b)

Yield: 22%. Oil. $[\alpha]_D$= +37.10 (c=1.0, $CHCl_3$); ^{1}H-NMR (200 MHz. $CDCl_3$): 0.68 (d, *J* 6.9 Hz, 3H), 0.92 (t, *J* 6.9 Hz, 3H), 1.04 (d, *J* 6.9 Hz, 3H), 1.25 (t, *J* 7.2 Hz, 3H), 1.53 (m, 4H), 1.84 (dd, *J* 5.0, 10.9 Hz, 1H), 2.25 (d sext, *J* 3.4, 6.8 Hz, 1H), 3.64 (s, 3H), 3.71 (s, 3H), 3.93 (t, *J* 3.4 Hz, 1H), 3.98 (t, *J* 5.0 Hz, 1H) and 4.11 ppm (q, *J* 7.2 Hz, 2H); ^{13}C-NMR (50MHz, $CDCl_3$): 13.64, 14.21, 16.49, 18.92, 19.68, 20.77, 26.67, 32.20, 31.66, 52.33, 52.42, 54.22, 60.04, 60.54, 163.10, 164.50 and 172.29 ppm; IR (oil, ν): 1726 and 1697 cm^{-1} (C=O and C=N); HRMS (EI): M^+ found 324.2052. $C_{17}H_{28}N_2O_4$ requires 324.2049.

(2*R*,5*S*,1'*R*,2'*R*,3'*R*)-2,5-dihydro-2-isopropyl-5-(2'-ethoxycarbonyl-3'-propyl cyclopropyl)-3,6-dimethoxypyrazine (5c)

Yield: 17%. Oil. $[\alpha]_D$= -5.29 (c=1.03, $CHCl_3$); ^{1}H-NMR (200 MHz. $CDCl_3$): 0.69 (d, *J* 6.8 Hz, 3H), 0.86 (t, *J* 7.2 Hz, 3H), 1.03 (d, *J* 6.8 Hz, 3H), 1.45 (t, *J* 6.8 Hz, 3H), 1.2-1.5 (m, 4H), 1.92 (m, 1H), 2.08 (dd, *J* 4.8, 9.1 Hz, 1H), 2.23 (d sext, *J* 3.4, 6.8 Hz, 1H), 3.64 (s, 3H), 3.72 (s, 3H), 3.93 (t, *J* 3.4 Hz, 1H), 4.07 (t, *J* 4.8 Hz, 1H) and 4.15 ppm (q, *J* 6.8 Hz, 2H); ^{13}C-NMR (50MHz, $CDCl_3$): 13.66, 14.32, 16.59, 18.93, 21.34, 22.47, 23.45, 28.11, 29.31, 31.90, 52.42, 53.28, 60.14, 60.69, 163.22, 164.67 and 172.64 ppm; IR (oil, ν): 1728 and 1697 cm^{-1} (C=O and C=N); HRMS (EI): M^+ found 338.2210. $C_{18}H_{30}N_2O_4$ requires 338.2205.

(2*R*,5*S*,1'*S*,2'*S*,3'*S*)-2,5-dihydro-2-isopropyl-5-(2'-ethoxycarbonyl-3'-propyl cyclopropyl)-3,6-dimethoxypyrazine (6c)

Yield: 21%. Oil. $[\alpha]_D$= +36.38 (c=1.01, $CHCl_3$); ^{1}H-NMR (200 MHz. $CDCl_3$): 0.66 (d, *J* 6.8 Hz, 3H), 0.91 (t, *J* 7.0 Hz, 3H), 1.06 (d, *J* 6.8 Hz, 3H), 1.24 (t, *J* 7.1 Hz, 3H), 1.2-1.7 (m, 6H), 1.83 (dd, *J* 4.9, 10.6 Hz, 1H), 2.24 (d sext, *J* 3.1, 6.8 Hz, 1H), 3.54 (s, 3H), 3.77 (s, 3H), 3.90 (m, 2H) and 4.10 ppm (q, *J* 7.1 Hz, 1H); ^{13}C-NMR (50MHz, $CDCl_3$): 13.88, 14.24, 16.36, 16.53, 19.04, 20.83, 22.51, 24.95, 28.37, 30.14, 31.46, 52.28, 52.48, 57.75, 60.56, 161.32, 164.76 and 172.38 ppm; IR (oil, ν): 1728 and 1699 cm^{-1} (C=O and C=N); HRMS (EI): M^+ found 338.2200. $C_{18}H_{30}N_2O_4$ requires 338.2205.

2.-Synthesis of (2*S*,1'*R*,2'*R*,3'*R*/2*S*,1'*S*,2'*S*,3'*S*)-2-(2'-ethoxycarbonyl-3'-alkyl cyclopropyl) glycine

General Procedure: 0.1N HCl (2 mmol, 20 mL) was added to a solution of above dihydropyrazine (1 mmol) in THF (10 mL) and stirring continued for 24h at room temperature. The mixture was extracted with ether which was discarded. The water layer was saturated with sodium chloride, ether was added and the solution brought to pH 8-10 with concentrated ammonia. The ether layer was separated and the water layer extracted four times with ether. The combined ether layers were dried over anhydrous sodium sulphate and evaporated under reduced pressure to give the desired compounds.

(2*S*,1'*R*,2'*R*,3'*R*)-2-(2'-ethoxycarbonyl-3'-methylcyclopropyl)glycine (7a)

Yield: 62%. Oil. $[\alpha]_D$= +56.6 (c=1.1, $CHCl_3$); ^{1}H-NMR (200 MHz. $CDCl_3$): 1.19 (d, *J* 6.0 Hz, 3H), 1.26 (t, *J* 7.0 Hz, 3H), 1.34 (m, 1H), 1.60 (dd, *J* 5.0, 13.1 Hz, 1H), 1.74 (br s, 2H), 1.83 (dd, *J* 5.0, 9.0 Hz, 1H), 3.22 (d, *J* 7.0 Hz, 1H), 3.74 (s, 3H) and 4.11 ppm (q, *J* 7.1 Hz, 2H); ^{13}C-NMR (50MHz, $CDCl_3$): 11.65, 14.27, 19.94, 23.29, 31.16, 52.14, 53.33, 60.34, 171.62 and 174.77 ppm; IR (oil, ν): 3381, 3323 (NH) and 1732 cm^{-1} (C=O); HRMS (EI): M^+ found 215.1150. $C_{10}H_{17}NO_4$ requires 215.1158.

(2*S*,1'*S*,2'*S*,3'*S*)-2-(2'-ethoxycarbonyl-3'-methylcyclopropyl)glycine (8a)

Yield: 57%. Oil. $[\alpha]_D$= +26.9 (c=1.0, $CHCl_3$); ^{1}H-NMR (200 MHz. $CDCl_3$): 1.19 (d, *J* 5.9 Hz, 3H), 1.27 (t, *J* 7.2 Hz, 3H), 1.40-1.7 (m, 5H), 3.10 (d, *J* 7.2 Hz, 1H), 3.76 (s, 3H) and 4.13 ppm (q, *J* 7.2 Hz, 2H); ^{13}C-NMR (50MHz, $CDCl_3$): 11.41, 14.28, 20.83, 23.44, 31.91, 52.24, 56.11, 60.43, 171.66 and 174.76 ppm; IR (oil, ν): 3383, 3325 (NH), 1724 and 1738 cm^{-1} (C=O); HRMS (EI): M^+ found 215.1164. $C_{10}H_{17}NO_4$ requires 215.1158.

(2*S*,1'*R*,2'*R*,3'*R*)-2-(2'-ethoxycarbonyl-3'-ethylcyclopropyl)glycine (7b)

Yield: 85%. Oil. $[\alpha]_D$= +20.27 (c=1.1, $CHCl_3$); ^{1}H-NMR (200 MHz. $CDCl_3$): 0.92 (t, *J* 7.4 Hz, 3H), 1.26 (t, *J* 7.1 Hz, 3H), 1.53 (dd, *J* 5.8, 7.2 Hz, 1H), 1.66 (m, 1H), 1.71 (br s, 2H), 1.86 (dd, *J* 5.8, 9.2 Hz, 1H), 3.25 (d, *J* 7.4 Hz, 1H), 3.74 (s, 3H) and 4.13 ppm (q, *J* 7.1 Hz, 2H); ^{13}C-NMR(50MHz, $CDCl_3$): 13.55, 14.14, 19.53, 22.73, 27.28, 30.28, 52.02, 54.91, 60.25, 171.66 and 174.69 ppm; IR (oil, ν): 3382, 3321 (NH), 1736 and 1724 cm^{-1} (C=O); HRMS (EI): M^+ found 229.1310. $C_{11}H_{19}NO_4$ requires 229.1314.

(2*S*,1'*S*,2'*S*,3'*S*)-2-(2'-ethoxycarbonyl-3'-ethylcyclopropyl)glycine (8b)

Yield: quant. Oil. $[\alpha]_D$= +40.1 (c=1.0, $CHCl_3$). ^{1}H-NMR (200 MHz. $CDCl_3$): 0.91 (t, *J* 7.2 Hz, 3H), 1.26 (t, *J* 7.2 Hz, 3H), 1.3-1.64 (m, 4H), 1.65 (br s, 2H), 1.75 (dd, *J* 3.9, 8.8 Hz, 1H), 3.04 (d, *J* 7.1 Hz, 1H), 3.75 (s, 3H) and 4.13 ppm (q, *J* 7.2 Hz, 2H); ^{13}C-NMR (50MHz, $CDCl_3$): 13.43, 14.16, 19.53, 23.34, 28.42, 31.32, 51.98, 56.46, 60.35, 171.63 and 174.68 ppm; IR (oil, ν): 3383, 3319 (NH), 1736 and 1724 cm^{-1} (C=O); HRMS (EI): M^+ found 229.1318. $C_{11}H_{19}NO_4$ requires 229.1314.

(2*S*,1'*R*,2'*R*,3'*R*)-2-(2'-ethoxycarbonyl-3'-propylcyclopropyl)glycine (7c)

Yield: 61%. Oil. $[\alpha]_D$= +18.8 (c=1.0, $CHCl_3$); ^{1}H-NMR (200 MHz. $CDCl_3$): 0.89 (t, *J* 7.0 Hz, 3H), 1.26 (t, *J* 7.1 Hz, 3H), 1.2-1.7 (m, 6H), 1.86 (dd, *J* 4.9, 9.1 Hz, 1H), 2.85 (br s, 2H), 3.28 (d, *J* 7.0 Hz, 1H), 3.75 (s, 3H) and 4.15 ppm (q, *J* 7.1 Hz, 2H); ^{13}C-NMR (50MHz, $CDCl_3$): 13.68, 14.23, 22.53, 22.94, 25.61, 28.29, 29.97, 52.21, 55.04, 60.39, 171.75 and 174.45 ppm; IR (oil, ν): 3377 (NH), 1738 and 1728 cm^{-1} (C=O); HRMS (EI): M^+ found 243.1474. $C_{12}H_{21}NO_4$ requires 243.1470.

(2*S*,1'*S*,2'*S*,3'*S*)-2-(2'-ethoxycarbonyl-3'-propylcyclopropyl)glycine (8c)

Yield: 84%. Oil. $[\alpha]_D$= +29.19 (c=1.4, $CHCl_3$); ^{1}H-NMR (200 MHz. $CDCl_3$): 0.90 (t, *J* 7.2 Hz, 3H), 1.26 (t, *J* 7.1 Hz, 3H), 1.3-2.0 (m, 9H), 3.05 (d, *J* 7.8 Hz, 1H), 3.75 (s, 3H) and 4.12 ppm (q, *J* 7.1 Hz, 2H); ^{13}C-NMR (50MHz, $CDCl_3$): 13.67, 14.19, 2.32, 23.32, 26.56, 28.22, 31.25, 52.03, 56.45, 60.39, 171.71 and 174.69 ppm; IR (oil, ν): 3379, 3323 (NH), 1740 and 1728 cm^{-1} (C=O); HRMS (EI): M^+ found 243.1464. $C_{12}H_{21}NO_4$ requires 243.1470.

Synthesis of (2*S*,1'*R*,2'*R*,3'*R*/2*S*,1'*S*,2'*S*,3'*S*)-2-(2'-carboxy-3'-alkyl cyclopropyl)glycine

General procedure: The (*S*)-α-aminoacid diester (1 mmol) was refluxed in 6N HCl (5 mL) for 2h. The solvent was evaporated and the residue dissolved in absolute ethanol (5 mL). To this solution, methyloxirane (2 mL) was added, the mixture was refluxed for 15 min., and then

cooled to 0°C. The precipitated product was isolated by suction (In some cases it was found necessary to wash with ether in order to recover solid).

(2*S*,1'*R*,2'*R*,3'*R*)-2-(2'-carboxy-3'-methylcyclopropyl)glycine (1a)

Yield: 73%. m.p.>150°C (dec.); $[\alpha]_D$= -26.7 (c=0.42, H_2O); ^{1}H-NMR (200 MHz. D_2O): 0.93 (d, *J* 5.5 Hz, 3H), 1.37 (m, 2H), 1.79 (dd, *J* 5.5, 9.0 Hz, 1H) and 3.15 ppm (d, *J* 9.0 Hz, 1H); ^{13}C-NMR (50MHz, D_2O): 11.15, 21.67, 25.41 , 27.86, 57.01, 172.79 and 175.43 ppm; IR (KBr, ν): 3600-2200 (CO_2H), 3431 (NH), 1697 and 1630 cm^{-1} (C=O). Anal. calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.85; H, 6.65; N, 8.39.

(2*S*,1'*S*,2'*S*,3'*S*)-2-(2'-carboxy-3'-methylcyclopropyl)glycine (2a)

Yield: 68%. m.p.>151°C (dec.); $[\alpha]_D$= +31.5 (c=0.25, H_2O); ^{1}H-NMR (200 MHz. D_2O): 0.93 (d, *J* 5.8 Hz, 3H), 1.39 (m, 2H), 1.66 (dd, *J* 4.7, 9.5 Hz, 1H) and 3.03 ppm (d, *J* 9.5 Hz, 1H); ^{13}C-NMR (50MHz, D_2O): 11.16, 22.10, 25.32, 28.12, 57.66, 172.40 and 176.09 ppm; IR (KBr, ν): 3600-2700 (CO_2H), 3437 (NH) and 1630 cm^{-1} (C=O). Anal. calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.80; H, 6.70; N, 8.39.

(2*S*,1'*R*,2'*R*,3'*R*)-2-(2'-carboxy-3'-ethylcyclopropyl)glycine (1b)

Yield: 54%. m.p.>152°C (dec.); $[\alpha]_D$= +24.4 (c=0.31, H_2O); ^{1}H-NMR (200 MHz. D_2O): 0.67 (m, 3H), 1.31 (m, 4H), 1.76 (m, 1H) and 3.14 ppm (d, *J* 8.9 Hz, 1H); ^{13}C-NMR (50MHz, D_2O): 12.83, 19.89, 24.92, 26.89, 29.16, 56.95, 172.74 and 175.75 ppm; IR (KBr, ν): 3600-2700 (CO_2H), 3429 (NH), 1697 and 1628 cm^{-1} (C=O). Anal. calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.63; H, 6.75; N, 7.49.

(2*S*,1'*S*,2'*S*,3'*S*)-2-(2'-carboxy-3'-ethylcyclopropyl)glycine (2b)

Yield: 90%. m.p.>194°C (dec.); $[\alpha]_D$= +37.98 (c=0.30, H_2O); ^{1}H-NMR (200 MHz. D_2O): 0.67 (t, *J* 7.0 Hz, 3H), 1.35 (m, 4H), 1.69 (dd, *J* 7.0, 13.8 Hz, 1H) and 3.0 ppm (d, *J* 9.1 Hz, 1H); ^{13}C-NMR (50MHz, D_2O): 12.72, 19.82, 24.57, 27.66, 29.79, 57.54, 172.83 and 175.83 ppm; IR (KBr, ν): 3700-2700 (CO_2H), 3433 (NH), 1678 and 1616 cm^{-1} (C=O). Anal. calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.63; H, 6.80; N, 7.78.

(2*S*,1'*R*,2'*R*,3'*R*)-2-(2'-carboxy-3'-propylcyclopropyl)glycine (1c)

Yield: 63%. m.p.>138°C (dec.); $[\alpha]_D$= +28.39 (c=0.28, H_2O); ^{1}H-NMR (200 MHz. D_2O): 0.63 (t, *J* 6.2 Hz, 3H), 1.0-1.5 (m, 6H), 1.74 (dd, *J* 5.1, 8.8 Hz, 1H) and 3.16 ppm (d, *J* 8.8 Hz, 1H); ^{13}C- NMR (50MHz, D_2O): 13.29, 21.99, 25.05, 26.73, 27.42, 28.51, 56.91, 172.99 and 176.15 ppm; IR (KBr, ν): 3600-2300 (CO_2H), 3433 (NH), 1684 and 1630 cm^{-1} (C=O). Anal. calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.73; H, 7.75; N, 7.20.

(2*S*,1'*S*,2'*S*,3'*S*)-2-(2'-carboxy-3'-propylcyclopropyl)glycine (2c)

Yield: 78%. m.p.>190°C (dec.); $[\alpha]_D$= +41.04 (c=0.26, H_2O); ^{1}H-NMR (200 MHz. D_2O): 0.68 (m, 3H), 1.29 (m, 6H), 1.67 (m, 1H) and 2.99 ppm (d, *J* 9.6 Hz, 1H); ^{13}C-NMR (50MHz, D_2O): 13.27, 21.87, 25.12, 27.43, 27.77, 28.44, 57.85, 173.28 and 176.65 ppm; IR (KBr, ν): 3700-2300 (CO_2H), 3441 (NH), 1670 and 1628 cm^{-1} (C=O). Anal. calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.83; H, 7.81; N, 7.20.

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[11]Horner-Emmons reaction of the corresponding racemic α-bromo aldehyde with diethylphosphonoacetate gave the corresponding **4a-c.**

[12] Unpublished results.