Tetrahedron Vol. 48, No. 6, pp. 1123-1130, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00
Pergamon Press plc

SYNTHESIS OF ASYMMETRIC (E)-α-[2-PHENYL(ETHYL)CYCLOPROPYL]GLYCINES FROM SERINE BY DIASTEREOSELECTIVE DIBROMOCYCLOPROPANATION

Mª Pilar de Frutos, Mª Dolores Fernández, E. Fernández-Alvarez, and Manuel Bernabé*

Instituto de Química Orgánica, CSIC, Juan de la Cierva 3, 28006-Madrid (Spain)

(*Received in UK 27 November* 1991)

Abstract: An asymmetric synthesis of (E)-α-(2-phenylcyclopropyl)glycines and also of a homolog of allocoronamic acid, namely (E)-α-(2-ethylcyclopropyl)glycine, is reported. The key step is the dibromocyclopropanation of tert-butyl (E,4R)- or (E,4S)-2,2-dimethyl-4-(2'-phenylvinyl)- and -(2'-ethylvinyl)-3-oxazolidinecarboxylates, easily prepared from L- or D-serine. This reaction gives good diastereomeric ratios of dibromocyclopropanes. The major compounds were transformed, in three steps, in the corresponding cyclopropylaminoacids.

Introduction

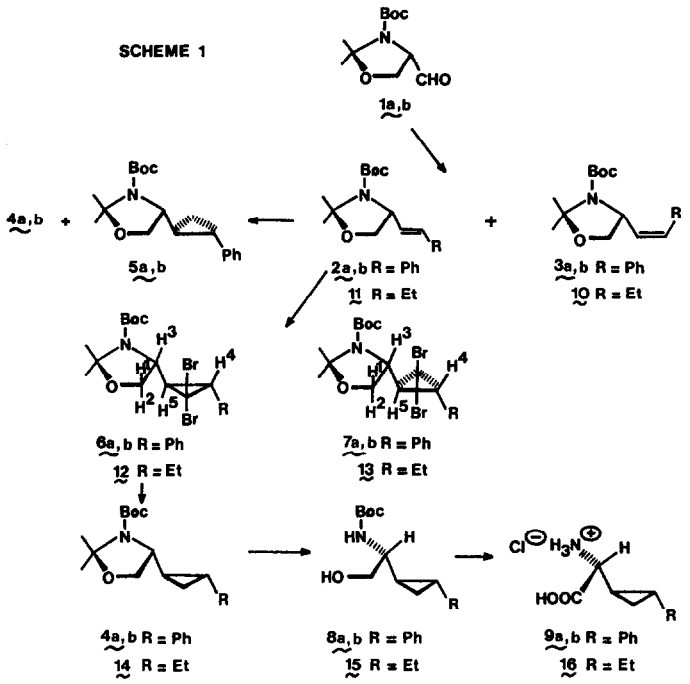
Continuous attention is being paid to the synthesis of cyclopropaneaminoacids,[1] especially that of 1-aminocyclopropanecarboxylic acids[2] and α-cyclopropylglycines,[3] because of their biological properties.[3,4] Most of the comparatively fewer papers published on these last compounds deal with the synthesis of α-(methylenecyclopropyl)glycine[3a,f] and α-(2-carboxycyclopropyl)-glycine.[3c-e]

Taking into account the strict stereostructural requisites of biological receptors, which have been emphasized for α-(2-carboxycyclopropyl)glycine, a NMDA receptor agonist[3c,e], general enantioselective methods to obtain cyclopropaneaminoacids are still lacking. We have described the asymmetric synthesis of 1-amino-2-phenylcyclopropanecarboxylic acids,[5] and we report now on the asymmetric synthesis of their homologs, namely α-(2-phenylcyclopropyl)glycines,[6] and α-(2-ethylcyclopropyl)glycine, conformationally restricted analogs of homophenylalanine and homoallocoronamic acid, for enzymatic studies,[4b,c] using either enantiomer of serine as starting material.

Results and discussion

S-Serine was transformed in four steps, in 65 % overall yield, into the oxazolidine aldehyde **1a**, which have been shown to be 95 % enantiomerically pure.[7] The Wittig reaction of this aldehyde with the non-stabilized ylide derived from benzyltriphenylphosphonium bromide gave a 75 : 25 mixture of E and Z alkenes **2a** (J_{vinyl} = 15.8 Hz) and **3a** (J = 11.7 Hz), (Scheme 1) which were easily separated by flash chromatography.

SCHEME 1



For the cyclopropanation of **2a** we first tried the Simmons-Smith reaction, for which several examples of diastereoselective addition to chiral substrates have been published.[8] In our case we obtained a mixture of two diastereomeric cyclopropanes **4a** and **5a** in 50 % yield and 75 : 25 diastereomeric ratio, but these compounds refused to be separated by either chromatographic means or fractional crystallisation.

As an alternative we studied the addition of dihalocarbene to compound **2a**. Few examples of diastereoselective synthesis, using addition of dihalocarbenes to chiral alkenes, have been described.[9] Dibromocarbene was generated by the phase-transfer catalytic technique[10] and reaction with **2a** gave 87 % of a mixture of two bromides (85 : 15), flash chromatography of which led to straightforward isolation of **6a** and **7a**.

The major compound **6a** was easily converted into cyclopropane **4a** (97 %) by reduction with 2 molar equivalents of tributyltin hydride. This two-step sequence for cyclopropanation turned out to be the method of choice because of higher overall yields, better diastereoselectivity, and facile separation of diastereoisomers.

Attempts to achieve cyclopropanation of the Z-olefine **3a** by either Simmons-Smith reaction or addition of dibromocarbene were unfruitful.

Acid-catalysed cleavage of the oxazolidine moiety produced the alcohol **8a** which was treated with Jones' reagent to deliver α-(2-phenylcyclopropyl)glycine in 81 % yield.

An analogous sequence was used, starting from R-serine, in order to accomplish the synthesis of the enantiomeric α-(2-phenylcyclopropyl)glycine (compounds **b** in Scheme 1).

Obviously, the achiral centre of the cyclopropylglycine is D when L-serine is used as starting material and vice versa.

We then try to extend this sequence to the more appealing homologous derivative of allocoronamic acid. Thus, aldehyde **1a** was made to react with the ylide derived from propyltriphenylphosphonium bromide to produce 63 % of a 25 : 75 mixture of compounds **11** and **10** respectively, which were isolated by flash chromatography.

In this case, neither compound reacted with the Simmons-Smith reagent. However, compound **11**, treated under phase transfer conditions with CH_2Br_2, gave derivatives **12** and **13** (75 : 25). As compound **10** slowly reacted (7 days) with CH_2Br_2 giving also a similar mixture **12**: **13**, it seems clear that an isomerization reaction Z ⟶ E took place in the first place, dibromocarbene being exclusively added to the last isomer. Consequently, we treated directly the 25 : 75 mixture of **11** and **10** under the same conditions, obtaining similar results after 4 days reaction, and making evident that the rate-determining step was the isomerization reaction.

Clean isomerization **10** ⇌ **11** (and also **3** ⇌ **2**) was achieved in a few hours by refluxing compound **10** with N-bromosuccinimide in benzene, to produce a 50 : 50 mixture of both alkenes. This mixture was treated with CH_2Br_2, giving analogous results as above, in 2 days. Flash chromatography of the mixture of bromocyclopropanes led to isolation of compounds **12** (33 %) and **13** (12 %). Reduction of the major compound with tributyltin hydride gave 80 % of compound **14**, from which aminoacid **16** was obtained by hydrolisis and Jones' oxidation of the resulting carbamate **15**.

Table I. Relevant data for compounds **1-16**

Compound		m.p. (°C)	$[\alpha]_D$ (°) [a]
1a	4S		-80 (c 1.0)
1b	4R		+95 (c 1.2)
2a	E, 4R	79-80	-50 (c 2.0)
2b	E, 4S	79-81	+46 (c 1.5)
3a	Z, 4R	72-74	+41 (c 1.2)
3b	Z, 4S	73-75	-35 (c 1.0)
4a	4R,1'R,2'R	67-69	-108 (c 0.8)
4b	4S,1'S,2'S	60-63	+100 (c 1.0)
6a	4R,1'R,3'R	103-105	-26 (c 2.0)
6b	4S,1'S,3'S	100-102	+25 (c 1.6)
7a	4R,1'S,3'S	92-94	-3 (c 0.8)
7b	4S,1'R,3'R	96-98	+2 (c 0.9)
9a	2R,1'R,2'R	215-218 [b]	-76 (c 0.2) [c]
9b	2S,1'S,2'S	210-213 [b]	+71 (c 0.4) [c]
10	Z, 4R	-	+34 (c 3.5)
11	E, 4R	-	+6 (c 0.7)
12	4R,1'R,3'S	63-69	-14 (c 0.8)
13	4R,1'S,3'R	78-81	-10 (c 0.5)
16	2R,1'S,3'R	240-245 [b]	-48 (c 0.3) [c]

[a] Measured in Cl_3CH; [b] m.p. with decomposition; [c] Measured in H_2O.

Table II

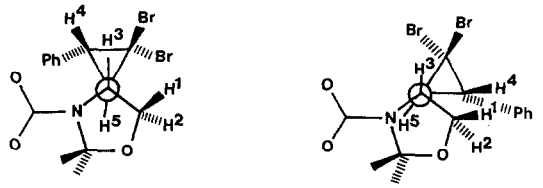
Relevant ^{1}H-NMR data for dibromocyclopropyl compounds **6a** and **7a**

	Compound **6a**	Compound **7a**
H-1	3.89	3.61
H-2	4.06	3.67
H-3	3.94	4.10
H-4	3.36	2.47
H-5	2.23	2.37
J_{35}	8.8	4.1

Table I gathers relevant structural and physical data of all the compounds synthesized.

Structural analyses were carried out for compounds **6a** and **7a**, on the basis of 1D and 2D ^{1}H-NMR spectral data (Table II). The large coupling constant of 8.8 Hz indicates

a dihedral angle about 170° between protons H-3 and H-5 in compound **6a**, while the value of the coupling for analogous protons in **7a** ($J_{35} = 4.1$) suggests a dihedral angle in the neighbourhood of 140°. On the other hand, comparison of the chemical shifts of protons H-1 to H-5 in both compounds reveals shieldings of 0.4 - 0.3 ppm in H-1 and H-2 and a strong shielding of H-4 (0.9 ppm) in compound **7a**. These shifts are consistent with geometries such as those depicted in Fig. 1, with **6a** holding a configuration 4R,1'R,3'R and **7a** a configuration 4R,1'S, 2'S. Those assigned structures are supported by 1D NOE and 2D NOESY experiments. Thus, irradiation of H-4 in the major compound **6a** induced a 7% increase on H-3, not detected in **7a**. Moreover, in addition to the expected connections for the oxazolidine moiety, cross signals H-3/H-4 and H-2/H-5 are observed in the NOESY spectrum of **6a**, while in that of **7a**, cross-peaks H-2/H-4 and H-3/H-5 can be seen, indicating the close proximity of H-4 to H-2 in the last derivative.



6a (4R,1'R,3'R) **7a** (4R,1'S,3'S)

FIG. 1

Irradiation of H-4 in compound **12** induced a 6% increment of H-3, as in the case of **6a**. Overlapping of protons in **12** and **13** precluded NOESY experiments on these derivatives.

Acknowledgments.- This research was supported by the Dirección General de Política Científica (Grant FAR 88-0194/1). We thank to Ministerio de Educación y Ciencia for scholarships (to M.D.F. and M.P.F.).

EXPERIMENTAL SECTION

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel (Merck, Kiesegel 60, F 254). Column chromatography separation were effected on silica gel (Merck, Kieselgel 60, 230-400 mesh) under pressure (flash chromatography). Infrared spectra were measured with a Perkin-Elmer 681 spectrometer for KBr pellets. Observed rotations at the Na-D line were obtained at 20 °C using a Perkin-Elmer 141 polarimeter. ^{1}H-NMR spectra were recorded on a Varian XL-300 spectrometer, for solutions in hexadeuteriobencene, at 70 °C unless otherwise stated. 2D-NOESY experiments were effected in the phase-sensitive mode by using the pulse sequence 90°-t_1-t_m-90°-acq, with mixing times of 2.1 s for **6a** and 2.6 for **7a**.

Synthesis of the alkenes. General Procedure: To a suspension of the corresponding triphenylphosphonium bromide (30 mmol) in hexane (50 mL) 1.6 M n-butyllithium in hexane (19 mL, 30 mmol) was added dropwise. After stirring for 30 minutes, a solution of the respective aldehyde **1**[7] (**a** or **b**) (6.7 g, 30 mmol) in hexane (30 mL) was added and the stirring was continued for 2 h. After addition of water (30 mL) the organic layer was separated and the aqueous mixture was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude

product was flash chromatographed by eluting with (10:1) hexane-EtOAc, giving the following alkenes.

***tert*-Butyl (E) and (Z)-2,2-dimethyl-4-(2'-phenylvinyl)-3-oxazolidinecarboxylates (2) and (3).** From benzyltriphenylphosphonium bromide (13 g, 30 mmol) and the corresponding aldehyde **1a** or **1b** were prepared 4.65 (52%, Rf = 0.5) of the E-alkene **2** (**a** or **b**) and 1.55 g (17.5%, Rf = 0.4) of the respective Z-alkene **3** (**a** or **b**). These compounds were recrystallized from hexane. Compounds **2a** or **2b**: IR(KBr): 1700, 1380 cm^{-1}; ^{1}H-NMR: δ 7.3 - 7.0 (m, 5H, arom), 6.53 (d, 1H, =CH-Ph, J = 15.8 Hz), 6.12 (dd, 1H, =CH, J = 15.8 and 7.8 Hz), 4.3 (br s, 1H, oxazolidine), 3.79 (dd, 1H, oxazolidine, J = 8.8 and 6.2 Hz), 3.57 (dd, 1H, oxazolidine, J = 8.8 and 2.6 Hz), 1.77 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.40 (s, 9H, ^{t}Bu). Anal. Calcd. for $C_{18}H_{25}NO_3$: C, 71.29; H, 8.25; N, 4.62. Found: C, 70.99; H, 8.28; N, 4.43. Compounds **3a** or **3b**: IR (KBr): 1700, 1380 cm^{-1}; ^{1}H-NMR: δ 7.2 - 7.1 (m, 5H, arom), 6.37 (d, 1H, =CH-Ph, J = 11.7 Hz), 5.69 (dd, 1H, =CH, J = 11.7 and 9.2 Hz), 4.8 (br s, 1H, oxazolidine), 3.81 (dd, 1H, oxazolidine, J = 8.5 and 6.6 Hz), 3.61 (dd, 1H, oxazolidine, J = 8.5 and 3.4 Hz), 1.73 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.34 (s, 9H, ^{t}Bu). Anal. Calcd. for $C_{18}H_{25}NO_3$: C, 71.29; H, 8.25; N, 4.62. Found: C, 71.40; H, 8.56; N, 4.70.

***tert*-Butyl (Z) and (E)-2,2-dimethyl-4-(1'-butenyl)-3-oxazolidinecarboxylates (10) and (11).** From propyltriphenylphosphonium bromide (11.5 g, 30 mmol) 2.8 g (48%, Rf = 0.35) of the Z-alkene (**10**) and 0.9 g (15%, Rf = 0.30) of the E-alkene (**11**) were obtained as colorless oils. Compound **10**: IR (neat): 1700 cm^{-1}; ^{1}H-NMR: δ 5.45 - 5.3 (m, 2H, 2 =CH), 4.52 (br, s, 1H, oxazolidine), 3.77 (dd, 1H, oxazolidine, J = 8.5 and 6.2 Hz), 3.47 (dd, 1H, oxazolidine, J = 8.6 and 3.2 Hz), 2.15 - 1.9 (m, 2H, CH_2), 1.68 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.41 (s, 9H, ^{t}Bu), 0.89 (t, 3H, CH_3 - CH_2, J = 7.5). Anal. Calcd. for $C_{14}H_{25}NO_3$: C, 65.88; H, 9.80; N, 5.49. Found: C, 65.49; H, 10.02; N, 5.15. Compound **11**: IR (neat): 1700 cm^{-1}; ^{1}H-NMR: δ 5.6-5.5 (m, 1H, =CH), 5.42 (dd, 1H, =CH, J = 1.54 and 7.3 Hz), 4.16 (br s, 1H, oxazolidine), 3.73 (dd, 1H, oxazolidine, J = 8.7 and 6.2 Hz), 3.51 (dd, 1H, oxazolidine, J = 8.7 and 2.7 Hz), 1.91 (dc, 2H, CH_2, J = 7.6 and 6.3 Hz), 1.71 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.42 (s, 9H, ^{t}Bu), 0.89 (t, 3H, CH_3-CH_2, J = 7.6). Anal. Calcd. for $C_{14}H_{25}NO_3$: C, 65.88; H, 9.80; N, 5.49. Found: C, 65.30; H, 10.10; N, 5.32.

Isomerization of the Z-alkenes (3 and 10): A suspension of the corresponding alkene, N-bromosuccinimide (5%) and barium carbonate (10%) in benzene was refluxed for 8 hours. The mixture was cooled to 0 °C, filtered and the solvent was removed in vacuo to give a mixture of the Z and E alkenes in the proportion indicated in each case.

***tert*-Butyl (Z)-2,2-dimethyl-4-(2'-phenylvinyl)-3-oxazolidinecarboxylate (3).** Quantativative yield, proportion Z : E = 40 : 60.

***tert*-Butyl (Z)-2,2-dimethyl-4-(1'-butenyl)-3-oxazolidinecarboxylate (10).** Quantitative yield, proportion Z : E = 50 : 50.

Cyclopropanation of 2a: To a solution of the oxazolidine **2a** (0.12 g, 0.4 mmol) in dry diethyl ether (20 mL), 1M diethylzinc in hexane (1 mL) was added at 0 °C. Methylene iodide (0.18 mL, 2 mmol) was then added dropwise and the mixture was vigorously stirred and allowed to rise to room temperature and further refluxed for 5 h. The reaction mixture was poured into cold aqueous ammonium chloride (10 mL) and the product was extracted with diethyl ether (3 x 10 mL), the combined organic extracts were washed with aqueous sodium thiosulfate and brine, dried over sodium sulfate and concentrated in vacuo. The crude product was flash chromatographed on silica gel by eluting with (10:1) hexane-EtOAc, affording 60 mg (50% yield) of a mixture (75:25) of the cyclopropanes **4a** + **5a** as a white solid. Attempted separation by chromatographic means and also by fractional crystallization failed.

***tert*-Butyl (E)-4-(2',2'-dibromo-3'-phenylcyclopropyl)-2,2-dimethyl-3-oxazolidinecarboxylates (6) and (7).** General Procedure: A mixture of the corresponding alkene **2** (**a** or **b**) (2 g, 7 mmol), bromoform (3.7 g, 15 mmol), benzene (5 mL), 50% aqueous sodium hydroxide (12 mL, 150 mmol), benzyltriethylammonium chloride (0.1 g, 0.4 mmol) and ethanol (0.1 mL) were stirred vigorously at room temperature for 2 days. The suspension was diluted with water (25 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give an oil, flash chromatography of which (10:1 hexane-EtOAc) afforded the respective dibromocyclopropanes **6**

(**a** or **b**) (2.5 g, 74%, Rf = 0.5) and **7** (**a** or **b**) (0.4 g, 13%, Rf = 0.4). In each case both compounds were recrystallized from hexane. Compounds **6a** or **6b**: IR (KBr): 1700, 1380 cm^{-1}; ^{1}H-NMR: δ 7.2 - 7.0 (m, 5H, arom), 4.06 (d, 1H, oxazolidine, J = 8.5 Hz), 3.94 (br s, 1H, oxazolidine), 3.89 (dd, 1H, oxazolidine, J = 8.5 and 5.4 Hz), 3.36 (br, s, 1H, cyclopropane), 2.23 (dd, 1H, cyclopropane, J = 8.8 and 8.8. Hz), 1.72 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.27 (s, 9H, ^{t}Bu). Anal. Calcd. for $C_{19}H_{25}NO_3Br_2$: C, 48.20; H, 5.28; N, 2.96; Br, 33.40. Found: C, 48.09; H, 5.35; N, 2.91; Br, 33.51. Compounds **7a** or **7b**: IR (KBr): 1710, 1380 cm^{-1}; ^{1}H-NMR: δ 7.2 - 7.0 (m, 5H, arom), 4.1 (br s, 1H, oxazolidine), 3.67 (dd, 1H, oxazolidine, J = 9.4 and 2.1 Hz), 3.61 (dd, 1H, oxazolidine, J = 9.4 and 5.5 Hz), 2.47 (d, 1H, cyclopropane, J = 9.1 Hz), 2.37 (dd, 1H, cyclopropane, J = 9.1 and 4.1 Hz), 1.67 (s, 3H, CH_3), 1.57 (s, 9H, ^{t}Bu), 1.55, s, 3H, CH_3). Anal. Calcd. for $C_{19}H_{25}NO_3Br_2$: C, 48.20; H, 5.28; N, 2.96; Br, 33.40. Found: C, 48.32; H, 5.37; N, 2.75; Br, 33.15.

***tert*-Butyl (E)-4-(2',2'-dibromo-3'-ethylcyclopropyl)-2,2-dimethyl-3-oxazolidinecarboxylates (12) and (13).** To a solution of a 50:50 mixture of the alkenes **10** and **11** (1.8 g, 7. mmol), bromoform (3.7 g, 15 mmol) and benzyltriethylammonium chloride (0.1 g, 0.4 mmol) in dry benzene powdered potassium hydroxyde (8.4 g, 0.15 mmol) was added portionwise and the suspension was stirred vigorously at room temperature for 2 days. The solid was filtered through celite and a new batch of bromoform and powdered KOH was added to the solution; the stirring was maintained for 2 additional days, the mixture was then filtered through celite and the organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give an oil which was flash chromatographed (10:1 hexane-EtOAc) affording the dibromocyclopropanes **12** (1 g, 33%, Rf = 0.50) and **13** (0.36 g, 12%, Rf = 0.58) and unreacted E-alkene (**11**) (0.36 g, 20%, Rf = 0.30). Similar results were obtained if the neat Z-alkene (**10**) was used and the reaction was stirred for 7 days. Compound **12**: IR (KBr): 1700 cm^{-1}; ^{1}H-NMR (DMSO, 90 °C): δ 4.11 (dd, 1H, oxazolidine, J = 9.0 and 5.4 Hz), 3.89 (dd, 1H, oxazolidine, J = 9.0 and 1.0 Hz), 3.73 (m, 1H, oxazolidine, J = 9.5, 5.4 and 1.0), 1.8 (m, 1H, cyclopropane), 1.65 - 1.35 (m, 2H, CH_2), 1.54 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.43 (s, 9H, ^{t}Bu), 1.38 (m, 1H, cyclopropane), 1.01 (t, 3H, CH_3-CH_2, J = 7.3 Hz), Anal. Calcd. for $C_{15}H_{25}NO_3Br_2$: C, 42.35; H, 5.88; N, 3.29; Br, 37.18. Found: C, 42.55; H, 5.97; N, 3.15; Br, 37.32. Compound **13**: IR (KBr); 1700 cm^{-1}; ^{1}H-NMR (DMSO, 80 °C): δ 4.14 (dd, 1H, oxazolidine, J = 8.9 and 5.4 Hz), 3.96 (dd, 1H, oxazolidine, J = 8.9 and 1.4 Hz), 3.72 (m, 1H, oxazolidine, J = 9.3, 5.4 and 1.4), 1.93 (m, 1H, cyclopropane), 1.90 - 1.70 (m, 2H, CH_2), 1.56 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.42 (s, 9H, ^{t}Bu), 1.40 (m, 1H, cyclopropane), 1.07 (t, 3H, CH_3-CH_2, J = 7.3 Hz). Anal. Calcd. for $C_{15}H_{25}NO_3Br_2$: C, 42.35; H, 5.88; N, 3.29; Br, 37.18. Found: C, 42.35; H, 5.88; N, 3.29; Br, 37.18.

Reduction of dibromocyclopropanes 6 and 12: General Procedure: Tributyltinhydride (0.63 mL, 2.5 mmol) was added under argon atmosphere to a stirred solution of the proper dibromocyclopropane (1 mmol) in hexane (10 mL). The reaction mixture was then heated under reflux for 6 h. The organic layer was washed with saturated aqueous solution of ammonium chloride (20 mL), the aqueous layer was extracted with hexane (2 x 25 mL) and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The product was purified via flash chromatography, by eluting first with hexane and then with (10:1) hexane-EtOAc. Thus, the following cyclopropanes were obtained:

***tert*-Butyl (E)-4-(2'-phenylcycloproyl)-2,2-dimethyl-3-oxazolidinecarboxylates (4).** From the corresponding dibromocyclopropane **6** (**a** or **b**) (0.5 g, 1 mmol) the compounds **4a** or **4b** respectively (0.32 g, 97%) were prepared: IR (KBr): 1700, 1390 cm^{-1}; ^{1}H-NMR: δ 7.28 - 7.24 (m, 5H, arom), 3.80 (dd, 1H, oxazolidine, J = 8.6 and 5.5 Hz), 3.73 (dd, 1H, oxazolidine, J = 8.6 and 1.4 Hz), 3.62 (br s, 1H, oxazolidine), 2.45 (br s, 1H, cyclopropane) 1.80 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.56 (s, 9H, ^{t}Bu), 1.5 (m, 1H, cyclopropane), 0.86 - 0.73 (m, 2H, cyclopropane). Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.92; H, 8.52; N, 4.42. Found: C, 71.59; H, 8.69; N, 3.88.

***tert*-Butyl (E)-4-(2'-ethylcyclopropyl)-2,2-dimethyl-3-oxazolidinecarboxylate (14).** From compound **12** (0.2 g, 0.47 mmol) 0.1 g (80%) of the cyclopropane **14** were obtained: IR (KBr): 1710 cm^{-1}; ^{1}H-NMR:(DMSO, 80 °C): δ 3.85 (dd, 1H, oxazolidine, J = 8.7 and 5.9 Hz), 3.65 (dd, 1H, oxazolidine, J = 8.6 and 1.2 Hz), 3.40 (m, 1H, oxazolidine, J = 8.7, 8.6 and 1.2), 1.52 (s, 3H, CH_3), 1.43 (s, 9H, ^{t}Bu), 1.40 (s, 3H, CH_3), 1.4 - 1.3 (m, 2H, CH_2), 0.92 (m, 1H, cyclopropane), J = 8.4, 4.9, and 4.4 Hz), 0.88 (t, 3H, CH_3 -CH_2, J = 7.5 Hz), 0.73 (m, 1H, cyclopropane, J = 8.6,

8.5, 4.5, and 4.4 Hz), 0.30 (m, 1H, cyclopropane, J = 8.4, 4.8 and 4.5 Hz), 0.17 (m, 1H, cyclopropane, J = 8.5, 4.9, and 4.8 Hz).

Hydrolysis of the oxazolidine: General Procedure: A solution of the respective oxazolidine (1 mmol) and p-toluenesulfonic acid monohydrated (15 mg, 0.08 mmol) in methanol (5 mL) was stirred for 5 h, sodium acetate (15 mg) was then added and the stirring was continued for 30 min. The mixture was concentrated in vacuo and filtered through silica gel by eluting with (1 : 1) hexane-EtOAc and the solvent was removed in vacuo. In this manner were prepared the carbamates **8** (**a** and **b**) and **15**.

***tert*-Butyl (E)-|2-hydroxy-1-(2'-phenylcyclopropyl)|-*N*-ethylcarbamates (8).** The respective oxazolidine **4** (**a** or **b**) (0.24 g, 0.76 mmol) was transformed in the alcohol **8a** or **8b** (0.21 g, quantitative yield): ^{1}H-NMR: δ 7.3 - 7.0 (m, 5H, arom), 4.9 (br s, 1H, NH), 3.80 (dd, 1H, CH-O, J = 10.7 and 3.5), 3.70 (dd, 1H, CH-O, J = 10.7 and 6.0), 3.2 (br s, 1H, CH-N), 2.7 (br s, 1H, exchanged with D_2O, OH), 2.0 (m, 1H, cyclopropane), 1.44 (s, 9H, ^{t}Bu), 1.2 (m, 1H, cyclopropane), 1.0 (m, 2H, cyclopropane).

***tert*-Butyl (E)-|2-hydroxy-1-(2'-ethylcyclopropyl)|-*N*-ethylcarbamate (15).** From the oxazolidine **14** (80 mg, 0.3 mmol), 65 mg (95 %) of the carbamate **15** were obtained: ^{1}H-NMR: δ 4.75 (d, 1H, NH, J = 7.5 Hz), 3.76 (dd, 1H, CH-O), J = 11.0 and 3.4 Hz), 3.63 (dd, 1H, CH-O, J = 8.6 and 1.2 Hz), 2.97 (m, 1H, CH-N, J = 9.2, 7.5, 6.3 and 3.4 Hz), 2.7 (br s, 1H, exchanged with D_2O), 1.45 (s, 9H, ^{t}Bu), 1.1 - 1.4 (m, 2H, CH_2), 0.95 (t, 3H, CH_3-CH_2, J = 7.3 Hz), 0.77 (m, 1H, cyclopropane, J = 8.5, 5.0, and 4.4 Hz), 0.57 (m, 1H, cyclopropane, J = 9.4, 8.6, 4.7, and 4.4. Hz), 0.43 (m, 1H, cyclopropane, J = 8.5, 5.0, and 4.7 Hz), 0.33 (m, 1H, cyclopropane, J = 8.6, 5.0, and 5.0 Hz).

Jones' oxidation: General Procedure: To a stirred ice-cold solution of the appropriate alcohol (1 mmol) in acetone (2.8 mL), a mixture of chromic anhydride (0.2 g, 2 mmol), sulfuric acid (0.17 mL), water (0.48 mL) and acetone (2.1 mL), was added. The mixture was allowed to come to room temperature and stirred for 2 h. Isopropanol (3.3 mL) was added and, after ten minutes of stirring, the mixture was filtered through celite that was washed several times with anhydrous EtOAc. The extracts were evaporated in vacuo to give an oil which was treated with 6N HCl (1 mL), stirred for 30 minutes, filtered through cotton and concentrated in vacuo to give the respective hydrochloride as a white solid which was recrystallized from etanol/diethyl ether.

(E)-α-(2-phenylcyclopropyl)glycine hydrochlorides (9): Yield 81 %: Compounds **9a** or **9b**: IR (KBr): 3600-3200, 1750, 1600, 1500 cm^{-1}; ^{1}H-NMR (D_2O, 30 °C): δ 7-1 - 7.3 (m, 5H, arom), 3.48 (d, 1H, CO-CH-N, J = 9.7 Hz), 2.09 (q, 1H, cyclopropane, J = 9.7, 5.1 and 4.8 Hz), 1.46 (sep, 1H, cyclopropane, J = 9.7, 9.4, 5.4 and 4.8 Hz), 1.25 (dt, 1H, cyclopropane, J = 9.4, 5.4 and 5.1 Hz), 1.16 (dt, 1H, cyclopropane, J = 9.7, 5.4 and 5.4 Hz), ^{13}C-NMR (D_2O, 30 °C): δ 142.47, 130.09, 127.70, 127.25, 59.28, 24.06, 22.93, 15.90. Mass spectrum, m/e 191 (M^+ - HCl), 146 (191 - CO_2H), 129 ($|Ph\text{-}C_4H_4|^+$), 117 ($|Ph\text{-}C_3H_4|^+$).

(E)-α-(2-ethylcyclopropyl)glycine hydrochloride (16): Yield 76 %: IR (KBr): 3500-2600, 1750 cm^{-1}; ^{1}H-NMR (D_2O, 30 °C): δ 3.37 (d, 1H, CO-CH-N, J = 9.4 Hz), 1.4 - 1.1 (m, 2H, CH_2), 1.0 - 0.8 (m, 2H, cyclopropane), 0.89 (t, 3H, CH_3-CH_2, J = 7.1 Hz), 0.75 (m, 1H, cyclopropane), 0.6 (m, 1H, cyclopropane), ^{13}C-NMR (D_2O, 30 °C): 58.71, 26.72, 20.89, 19.36, 13.80, 12.10. Anal. Calcd. for $C_7H_{13}ClNO_2$: C, 47.06; H, 7.28; N, 7.84. Found: C, 46.54; H, 7.52; N, 7.46.

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