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Wittig Olefination of Methyl *(1S,2R)*-1-Benzamido-2-formylcyclopropanecarboxylate. A Powerful Tool for the Synthesis of New Conformationally Constrained Cyclopropyl Amino Acids.

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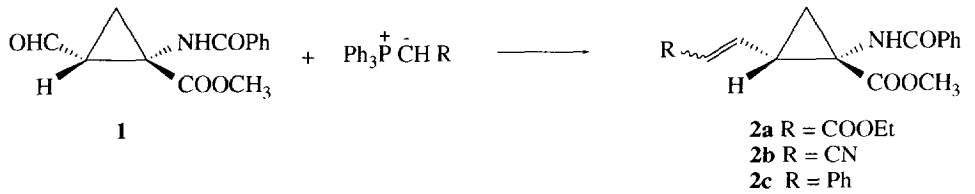
Abstract: The behaviour of methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate with stabilised and semi-stabilised ylids has been tested in order to evaluate its synthetic utility in the synthesis of cyclopropyl amino acids by Wittig olefination. Wittig adducts were further elaborated to obtain the corresponding cyclopropyl amino acids in high yields and enantiomerically pure form.

With the dramatic increase in the development of peptide-based pharmaceuticals, enantioenriched 2,3-methanoamino acids have played an important role in the design and synthesis of conformationally constrained peptidomimetics.[1] Peptide analogues from 2,3-methanoamino acids are relatively rigid compounds due to the bond stretching imposed by the cyclopropyl moiety and the unsaturated character of this molecular fragment, which hinders rotation around the Cα-CO bond owing to *pseudoconjugation*. These conformational restrictions give rise to important changes in peptide conformations,[2] modulating the ability of cyclopropyl analogues to interact with the active site of an enzyme or bio-receptor. Moreover, the presence of the cyclopropyl moiety also alters the reactivity of the peptidomimetic, increasing its stability in comparison with that of the parent-peptide towards enzymatic hydrolysis[3] and incorporating a reactive centre capable of capturing nucleophiles and electrophiles; consequently, some cyclopropyl analogues can act as suicide inhibitors.[4] In this way, introduction of these methanologues into peptides provides a virtually unlimited means of manipulating their properties and, as a consequence, their bioactivities. Research progress in this area has been minimal, however, and this is mainly due to the inaccessibility of optically pure compounds. Only a few of them occur naturally, their large scale isolation being inconvenient, and very few efficient selective syntheses have been developed.[5] Consequently, efficient asymmetric syntheses of these compounds are both timely and important.

Wittig olefination has been recognised as one of the most useful routes to the creation of C-C bonds; its effectiveness and general applicability changed the course of olefin synthesis for all time. Recently, we have developed an efficient and practical route to methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate **1** based on stereoselective methylene insertion on the exocyclic double bond of the chiral oxazolone derived from *D*-glyceraldehyde as the key step.[6] This substrate can be a useful key intermediate in the synthesis of enantiomerically pure cyclopropyl amino acids since it possesses a formyl group in a suitable position of the cyclopropyl ring, which can be easily transformed into several functional groups, giving access to a wide variety

of valuable compounds. In this sense, reduction of the carbonyl group allowed us to obtain (-)-*(1S,2R)*-allonorcoronamic acid,[7] and its Wittig olefination with a non-stabilised ylid afforded a direct precursor of (-)-*(1S,2R)*-allocoronamic acid.[8]

In view of this, and in connection with our studies on the asymmetric synthesis of amino acids from readily available and cheap starting materials, we were interested in studying the behaviour of methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate **1** in Wittig olefination reactions with stabilised and semi-stabilised ylids in order to develop a general synthetic approach to new cyclopropyl amino acids.



1

2a R = COOEt
2b R = CN
2c R = Ph

Scheme 1

First, we tested the reaction of methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate **1** with carbethoxymethylentriphenylphosphorane under different conditions: a) treatment of carbethoxymethyltriphenylphosphonium chloride with an aqueous solution of sodium hydroxide and reaction of the carbonyl compound with the isolated ylid, b) treatment of the carbethoxymethyltriphenylphosphonium chloride with sodium methoxide in an organic solvent to generate the ylid and addition of the carbonyl compound to the reaction mixture and c) generation of the ylid *in situ* by treatment of the carbethoxymethyltriphenylphosphonium chloride with an excess of propylene oxide in the presence of the carbonyl compound. In all cases the desired compound **2a** was obtained in high yield as a mixture of diastereoisomeric alkenes with a high preference for the alkene of *(E)*-configuration.

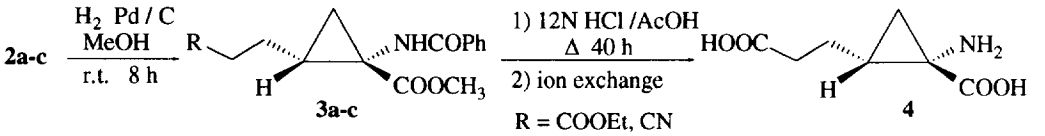
Table 1. Reaction of compound **1** with triphenylphosphoranes.

Ylid	Reaction conditions	Temp.	Time	Yield	*(Z):(E)*[a]
$Ph_3PCHCOOEt$	$NaOH/H_2O$	r.t.	60 m	94	6:94
$Ph_3PCHCOOEt$	MeONa/benzene	r.t.	15 m	95	22:78
$Ph_3PCHCOOEt$	propylene oxide	r.t.	90 m	89	13:87
Ph_3PCHCN	MeONa/benzene	r.t.	15 m	94	57:43
Ph_3PCHCN	propylene oxide	r.t.	90 m	87	42:58
Ph_3PCHPh	KHMDS/toluene	0 °C	20 m	89	23:77

[a] Determined by integration of the ^{1}H-NMR spectra of the reaction mixture

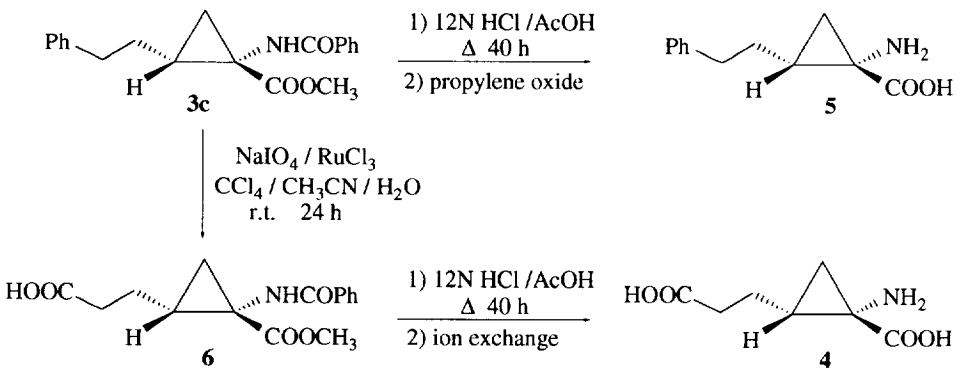
The reaction of compound **1** with cyanomethylentriphenylphosphorane according to b) and c) afforded the desired methyl *(1S,2S)*-1-benzamido-2-(-2-cyanovinyl)cyclopropanecarboxylate **2b** also in high yield but, in this case, an almost equimolecular mixture of diastereomeric alkenes was obtained. Finally, we tried the same

reaction conditions with benzyltriphenylphosphonium chloride and we observed a decrease in both the yield and the reaction rate, so Wittig olefination was carried out by generating the ylid by treatment of the phosphonium salt with a strong base, potassium bis(trimethyldisilyl)amide, previously to the addition of the carbonyl compound and, under these conditions, we obtained an 89% yield of a *Z/E* mixture of methyl *(1S,2S)*-1-benzamido-2-(α-styryl)cyclopropanecarboxylate **2c** in which the *E* olefin was the major component. The best results for these reactions are collected in Table 1.



Scheme 2

With **2a-c** in hand, elaboration to cyclopropyl amino acids was then attempted. The first step of the synthesis involved the hydrogenation of the double bond in the presence of the cyclopropane unit, which can be troublesome since substituted cyclopropanes can be easily cleaved under catalytic hydrogenation conditions. However, hydrogenation of compounds **2a-c** at room temperature and atmospheric pressure in the presence of palladium on charcoal cleanly afforded the corresponding saturated compounds **3a-c** in nearly quantitative yield and without hydrogenolysis of the cyclopropane ring to any extent. Hydrolysis of compounds **3a** and **3c** with 12N hydrochloric acid in acetic acid under reflux conditions gave the desired cyclopropyl amino acids **4** and **5** in enantiomerically pure form as their hydrochloride salts. In the case of **3b**, hydrolysis under the same conditions occurred with concomitant hydrolysis of the cyano group and we obtained again *(1S,2R)*-1-amino-2-(2-carboxyethyl)cyclopropanecarboxylic acid **4**. From these compounds, free amino acids were obtained in nearly quantitative yield by ion exchange chromatography or treatment with an excess of propylene oxide followed by elution through a sep-pak C_{18} cartridge.



Scheme 3

It is worth noting that compound **3c** can also act as a precursor to *(1S,2R)*-1-amino-2-(2-carboxyethyl)cyclopropanecarboxylic acid **4** as the phenyl group present in the side chain can be easily transformed into a carboxy group. Due to the special interest in this compound, we tested this transformation and we found that oxidative breaking of the aromatic ring under Sharpless conditions,[9] cleanly afforded

(1S,2R)-1-amino-2-(2-carboxyethyl)cyclopropanecarboxylic acid **6**, from which the free amino acid **4** could be obtained in two steps, acidic hydrolysis with 12N hydrochloric acid in acetic acid under reflux conditions followed by ion exchange chromatography.

From these results and those we previously reported,[8] we can conclude that methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate **1** is an adequate substrate in the Wittig reaction with stabilised, semi-stabilised and non-stabilised ylids, proving their versatility in the synthesis of the side chain of new cyclopropyl amino acids. We have proved its usefulness by accomplishing the synthesis of *(1S,2R)*-1-amino-2-(2-carboxyethyl)cyclopropanecarboxylic acid **4**, a conformationally constrained analogue of α-aminoadipic acid, a known selective antagonist[10] of the excitatory amino acid *N*-methyl-*D*-aspartic acid, and *(1S,2R)*-1-amino-2-(α-phenethyl)cyclopropanecarboxylic acid **5**, in high overall yields (about 90%) from compound **1**.

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EXPERIMENTAL

Apparatus: Melting points were determined using a Büchi 510 capillary melting point apparatus and are uncorrected. Specific rotations were recorded using a Perkin-Elmer 241-C polarimeter with a thermally-jacketed 10 cm cell at 25°C. IR spectra were obtained on a Perkin-Elmer 1600 FTIR infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuteriochloroform or deuterated water and referenced with respect to the residual solvent signal on a Varian Unity 300 or a Bruker AMX300 spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00 ppm), and coupling constants *(J)* are measured in Hertz. Elemental analyses were performed on a Perkin-Elmer 200 C,H,N,S elemental analyser.

Chemicals: Solvents were dried prior to use. All reagents were purchased from the Aldrich Chemical Co. and used as received. Methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate **1**[8] and carbethoxymethylenetriphenylphosphorane[11] were prepared following the method described in the literature. TLC was performed on precoated silica-gel plates which were visualised using UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Flash column chromatography was undertaken on silica gel (Kiesegel 60).

General procedures for the Wittig olefination of methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate 1.

Method A: A mixture of methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate **1** (247 mg, 1 mmol) and carbethoxytriphenylphosphorane (696 mg, 2 mmol) in benzene (30 ml) was stirred at room temperature for 60 min. The reaction mixture was washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to afford a crude which was purified by flash chromatography on a silica gel column (eluent hexane/ethyl acetate 4/6) to afford 298 mg (94% yield) of methyl *(1S,2S)*-1-benzamido-2-(2-carbethoxyvinyl)cyclopropanecarboxylate **2a** as a 6:94 mixture of *Z* and *E* alkenes which was used as such in the following step.

Method B: Sodium methoxide (108 mg, 2 mmol) was added to a solution of the corresponding triphenylphosphonium chloride (2 mmol) in benzene (30 ml) at room temperature. After stirring for 10 min at room temperature, methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate **1** (247 mg, 1 mmol) was added and the solution was stirred at room temperature for an additional 15 min. The reaction mixture was

washed with water and evaporated *in vacuo*. Purification of the residue by flash chromatography on a silica gel column (eluent hexane/ethyl acetate 4/6) afforded the corresponding Wittig adducts as *Z/E* mixtures of alkenes which were used as such in the following step.

Method C: The corresponding triphenylphosphonium chloride (2 mmol) was added to a solution of methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate **1** (247 mg, 1 mmol) in propylene oxide (30 ml) at room temperature. After stirring for 90 min at room temperature, the solvent was evaporated *in vacuo* and the residue dissolved in dichloromethane. The organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to afford a crude which was purified by flash chromatography on a silica gel column (eluent hexane/ethyl acetate 4/6) to afford Wittig adducts as *Z/E* mixtures of alkenes which were used as such in the following step.

Method D: Benzyltriphenylphosphonium chloride (1.28 g, 3.3 mmol), previously dried in a vacuum oven overnight, (5 mmHg at 50 °C), and dry toluene (20 ml) were added under nitrogen to a flame-dried flask. Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 6 ml, 3 mmol) was added dropwise by syringe at room temperature. The resulting solution was stirred for 30 min at room temperature, the reaction mixture was cooled to 0 °C and a solution of methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate **1** (617 mg, 2.5 mmol) in dry THF (15 ml) was added. The ice bath was removed, the solution was warmed to room temperature and then stirred for 20 min. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in ethyl acetate (60 ml), washed with water, dried with anhydrous magnesium sulphate and concentrated *in vacuo* to afford a crude oil. Purification of the residue by flash chromatography on a silica gel column (eluent hexane/ethyl acetate 4/6) afforded 713 mg (89% yield) of methyl *(1S,2S)*-1-benzamido-2-(α-styryl)cyclopropanecarboxylate **2c** as a 23:77 mixture of *Z* and *E* alkenes which was used as such in the following step.

Methyl *Z/E (1S,2S)*-1-benzamido-2-(2-carbethoxyvinyl)cyclopropanecarboxylate 2a.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found C, 64.47; H, 5.96; N, 4.32.

Spectroscopical data for *Z*-alkene ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, 3H, J = 7.2 Hz), 1.50 (dd, 1H, J = 7.2 Hz, J = - 5.4 Hz), 2.25 (dd, 1H, J = 9.4 Hz, J = - 5.4 Hz), 3.71 (s, 3H), 3.76 (ddd, 1H, J = 9.9 Hz, J = 9.4 Hz, J = 7.2 Hz), 4.19 (q, 2H, J = 7.2 Hz), 5.79 (dd, 1H, J = 11.7 Hz, J = 9.9 Hz), 5.94 (d, 1H, J = 11.7 Hz), 6.54 (brs, 1H), 7.40-7.55 (m, 3H), 7.75-7.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 24.5, 27.3, 40.6, 52.9, 60.3, 122.8, 127.1, 128.7, 132.1, 133.7, 144.3, 166.1, 168.5, 171.4.

Spectroscopical data for *E*-alkene ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 3H, J = 7.2 Hz), 1.54 (dd, 1H, J = 7.2 Hz, J = - 5.7 Hz), 2.14 (dd, 1H, J = 9.3 Hz, J = - 5.7 Hz), 2.61 (ddd, 1H, J = 9.6 Hz, J = 9.3 Hz, J = 7.2 Hz), 3.70 (s, 3H), 4.14 (q, 2H, J = 7.2 Hz), 6.04 (d, 1H, J = 15.6 Hz), 6.60 (d, 1H, J = 15.6 Hz, J = 9.6 Hz), 6.65 (brs, 1H), 7.37-7.56 (m, 3H), 7.73-7.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 23.9, 30.0, 40.5, 53.0, 60.4, 123.9, 127.1, 128.7, 132.1, 133.7, 143.9, 165.8, 168.7, 171.3.

Methyl *Z/E (1S,2S)*-1-benzamido-2-(2-cyanovinyl)cyclopropanecarboxylate 2b.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found C, 66.78; H, 5.17; N, 10.25.

Spectroscopical data for *Z*-alkene ^1H NMR ($CDCl_3$, 300 MHz) δ 1.62 (dd, 1H, J = 6.9 Hz, J = - 6.0 Hz), 2.16 (dd, 1H, J = 9.6 Hz, J = - 6.0 Hz), 3.02 (ddd, 1H, J = 10.2 Hz, J = 9.6 Hz, J = 6.9 Hz), 3.71 (s, 3H), 5.39 (d, 1H, J = 11.1 Hz), 6.11 (dd, 1H, J = 11.1 Hz, J = 10.2 Hz), 6.81 (brs, 1H), 7.38-7.56 (m, 3H), 7.75-7.80 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.4, 29.3, 40.9, 53.1, 100.9, 116.0, 127.1, 128.7, 132.3, 133.2, 150.0, 168.6, 170.6.

Spectroscopical data for *E*-alkene ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (dd, 1H, J = 6.9 Hz, J = - 6.0 Hz), 2.06 (dd, 1H, J = 9.3 Hz, J = - 6.0 Hz), 2.68 (ddd, 1H, J = 9.6 Hz, J = 9.3 Hz, J = 6.9 Hz), 3.69 (s, 3H), 5.50 (d, 1H, J = 16.2 Hz), 6.34 (dd, 1H, J = 16.2 Hz, J = 9.6 Hz), 6.84 (brs, 1H), 7.39-7.56 (m, 3H), 7.75-7.80 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.3, 30.5, 40.9, 53.1, 101.4, 117.0, 127.2, 128.7, 132.3, 133.1, 150.8, 168.7, 170.8.

Methyl *Z/E (1S,2S)*-1-benzamido-2-(α-styryl)cyclopropanecarboxylate 2c.
Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found C, 74.86; H, 5.89; N, 4.29.
Spectroscopical data for *Z*-alkene ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (dd, 1H, J = 7.5 Hz, J = - 5.3 Hz), 2.18 (dd, 1H, J = 9.6 Hz, J = - 5.3 Hz), 2.85 (ddd, 1H, J = 9.6 Hz, J = 8.7 Hz, J = 7.5 Hz), 3.70 (s, 3H), 5.36 (dd, 1H, J = 11.7, J = 8.7 Hz), 6.56 (brs, 1H), 6.66 (d, 1H, J = 11.7 Hz), 7.22-7.54 (m, 8H), 7.74-7.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.9, 27.8, 39.6, 52.8, 126.7, 127.1, 127.4, 128.5, 128.6, 128.7, 131.9, 133.7, 133.9, 136.5, 168.4, 171.9.
Spectroscopical data for *E*-alkene ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52 (dd, 1H, J = 7.5 Hz, J = - 5.7 Hz), 2.17 (dd, 1H, J = 9.3 Hz, J = - 5.7 Hz), 2.61 (ddd, 1H, J = 9.3 Hz, J = 8.4 Hz, J = 7.5 Hz), 3.70 (s, 3H), 5.94 (dd, 1H, J = 15.9 Hz, J = 8.4 Hz), 6.63 (d, 1H, J = 15.9 Hz), 6.65 (brs, 1H), 7.18-7.52 (m, 8H), 7.72-7.77 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.3, 31.3, 39.4, 52.7, 124.8, 126.1, 127.1, 127.7, 128.6, 128.6, 131.8, 133.9, 134.0, 136.6, 168.5, 172.0.

Methyl *(1S,2R)*-1-benzamido-2-(2-carbethoxyethyl)cyclopropanecarboxylate 3a. A solution of methyl *Z/E (1S,2S)*-1-benzamido-2-(2-carbethoxyvinyl)cyclopropanecarboxylate **2a** (317 mg, 1 mmol) in methanol (15 ml) was hydrogenated at atmospheric pressure in the presence of 10 % palladium on charcoal (20 mg) for 8 h. After completion, the catalyst was separated by filtration and the solvent was evaporated *in vacuo*. Purification of the residue by flash chromatography on a silica gel column (eluent hexane/ethyl acetate 1/1) afforded 308 mg (97% yield) of methyl *(1S,2R)*-1-benzamido-2-(2-carbethoxyethyl)cyclopropanecarboxylate **3a** as an oil. $[\alpha]_D$ = 39.4 (c = 1 in $CHCl_3$); IR 3331, 1732, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00 (dd, 1H, J = 7.5 Hz, J = - 5.1 Hz), 1.25 (t, 3H, J = 7.2 Hz), 1.58-1.68 (m, 1H), 1.70-1.84 (m ,1H), 1.86-1.98 (m, 2H), 2.44-2.63 (m, 2H), 3.65 (s, 3H), 4.16 (q, 2H, J = 7.2 Hz), 7.40-7.54 (m, 3H), 7.88 (brs, 1H), 7.90-7.95 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 28.3, 33.8, 37.5, 52.5, 61.0, 77.2, 127.2, 128.5, 131.6, 134.0, 168.5, 173.0, 174.6. Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found C, 64.11; H, 6.66; N, 4.28.

Methyl *(1S,2R)*-1-benzamido-2-(2-cyanoethyl)cyclopropanecarboxylate 3b. A solution of methyl *Z/E (1S,2S)*-1-benzamido-2-(2-cyanovinyl)cyclopropanecarboxylate **2b** (270 mg, 1 mmol) in methanol (15 ml) was hydrogenated at atmospheric pressure in the presence of 10 % palladium on charcoal (25 mg) for 8 h. After completion, the catalyst was separated by filtration and the solvent was evaporated *in vacuo* to afford 271 mg (100% yield) of methyl *(1S,2R)*-1-benzamido-2-(2-cyanoyethyl)cyclopropanecarboxylate **3b** as an oil. $[\alpha]_D$ = - 9.8 (c = 0.4 in $CHCl_3$); IR 3332, 2246, 1732, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.11 (dd, 1H, J = 7.2 Hz, J = - 5.3 Hz), 1.74-1.86 (m, 2H), 1.86-2.05 (m, 2H), 2.55 (t, 2H, J = 6.8 Hz), 3.69 (s, 3H), 6.70 (brs, 1H), 7.40-7.47 (m, 2H), 7.49-7.56 (m, 1H), 7.78-7.82 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.1, 22.1, 24.7, 26.9, 38.1, 52.8, 119.9, 127.1, 128.7, 132.1, 133.5, 169.0, 172.2. Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N,10.29. Found C, 66.05; H, 6.01; N, 10.37.

Methyl *(1S,2R)*-1-benzamido-2-(α-phenethyl)cyclopropanecarboxylate 3c. A solution of methyl *Z/E (1S,2S)*-1-benzamido-2-(α-styryl)cyclopropanecarboxylate **2c** (642 mg, 2 mmol) in methanol (20 ml) was hydrogenated at atmospheric pressure in the presence of 10 % palladium on charcoal (40 mg) for 8 h. After completion, the catalyst was separated by filtration and the solvent was evaporated *in vacuo* to afford 644 mg (100% yield) of methyl *(1S,2R)*-1-benzamido-2-(α-phenethyl)cyclopropanecarboxylate **3c** as a white solid. Mp 113 °C, $[\alpha]_D$ = + 4.9 (c = 1 in $CHCl_3$); IR 3300, 1726, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00 (dd, 1H, J = 6.2 Hz, J = - 4.1 Hz), 1.68-2.03 (m, 4H), 2.76 (ddd, 1H, J = -13.5 Hz, J = 9.0 Hz, J = 6.3 Hz), 2.85-2.94 (m, 1H), 3.69 (s, 3H), 5.69 (brs, 1H), 7.22-7.63 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.8, 28.4, 30.2, 35.5, 37.8, 52.4, 126.3, 127.1, 128.3, 128.6, 128.7, 131.6, 133.9, 141.5, 168.7, 172.9. Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.30; H, 6.55; N,4.33. Found C, 74.39; H, 6.48; N, 4.40.

***(1S,2R)*-1-Amino-2-(2-carboxyethyl)cyclopropanecarboxylic acid 4.** 12 N HCl (15 ml) was added to a solution of methyl *(1S,2R)*-1-benzamido-2-(2-carbethoxyethyl)cyclopropanecarboxylate **3a** (222 mg, 0.7 mmol), methyl *(1S,2R)*-1-benzamido-2-(2-cyanoethyl)cyclopropanecarboxylate **3b** (190 mg, 0.7 mmol) or methyl *(1S,2R)*-1-benzamido-2-(2-carboxyethyl)cyclopropanecarboxylate **6** (204 mg, 0.7 mmol) in glacial acetic acid (15 ml) and the mixture was refluxed for 40 h. After completion, the solvent was evaporated *in vacuo* and the residue dissolved in water. The solution was extracted with chloroform to eliminate the benzoic acid and the aqueous layer was evaporated *in vacuo*. The hydrochloride salt was dissolved in distilled water and eluted by ion exchange chromatography (Dowex 50x8-200, acidic form) with 2M ammonium hydroxide as an eluent. Evaporation of the eluate containing the free amino acid, identified by the ninhydrin test, afforded *(1S,2R)*-1-amino-2-(2-carboxyethyl)cyclopropanecarboxylic acid **4** in nearly quantitative yield. Mp 170 °C (decomp.), $[\alpha]_D$ = - 58.8 (c = 0.4 in H_2O); IR 3500-2300, 1652, 1607 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 0.85 (dd, 1H, J = 6.4 Hz, J = - 5.9 Hz), 1.35 (dd, 1H, J = 9.1 Hz, J = - 5.9 Hz), 1.45-1.72 (m, 3H), 2.25-2.35 (m, 2H). ^{13}C NMR (D_2O, 75 MHz) δ 16.3, 22.2, 22.3, 34.8, 38.1, 174.2, 180.4. Anal. Calcd. for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found C, 48.67; H, 6.35; N, 7.99.

***(1S,2R)*-1-Amino-2-(α-phenethyl)cyclopropanecarboxylic acid 5.** 12 N HCl (10 ml) was added to a solution of methyl *(1S,2R)*-1-benzamido-2-(α-phenethyl)cyclopropanecarboxylate **3c** (258 mg, 0.8 mmol) in glacial acetic acid (10 ml) and the mixture was refluxed for 40 h. After completion, the solvent was evaporated *in vacuo* and the residue dissolved in water. The solution was extracted with chloroform to eliminate the benzoic acid and the aqueous layer was evaporated *in vacuo*. Anhydrous ethanol (10 ml) and a large excess of propylene oxide (3 ml) were added to the residue and the mixture was refluxed for 30 min. After removal of the ethanol, the white residue was dissolved in distilled water (6 ml) and eluted through a C_{18} reverse-phase Sep-pak cartridge. Removal of water afforded *(1S,2R)*-1-amino-2-(α-phenethyl)cyclopropanecarboxylic acid **5** as a white solid in nearly quantitative yield. Mp 196 °C (decomp.), $[\alpha]_D$ = - 8.9 (c = 0.9 in DMSO); IR 3500-2300, 1597, 1561 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 0.73 (dd, 1H, J = 7.4 Hz, J = - 6.0 Hz), 1.30 (dd, 1H, J = 9.5 Hz, J = - 6.0 Hz), 1.46-1.57 (m, 1H), 1.59-1.74 (m, 2H), 2.70 (t, 2H, J = 7.2 Hz), 7.15-7.28 (m, 5H). ^{13}C NMR (D_2O, 75 MHz) δ 19.9, 25.8, 31.3, 36.8, 42.1, 128.6, 130.9, 131.0, 143.9, 177.8. Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found C, 70.30; H, 7.29; N, 6.89.

Methyl *(1S,2R)*-1-benzamido-2-(2-carboxyethyl)cyclopropanecarboxylate 6. Methyl *(1S,2R)*-1-benzamido-2-(α-phenethyl)cyclopropanecarboxylate **3c** (323 mg, 1 mmol) and $NaIO_4$ (3.85 g, 18 mmol) were dissolved in 2:2:3 carbon tetrachloride-acetonitrile-water (20 ml). The biphasic solution was then treated with

$RuCl_3 \cdot H_2O$ (5 mg, 0.022 mmol) and, after being vigorously stirred for 24h at room temperature, dichloromethane (20 ml) was added. The organic phase was separated and the aqueous phase extracted with dichloromethane (3 x 30 ml). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo,* and the residue was purified by flash chromatography on a silica gel column (eluent hexane/ethyl acetate 4/6 to 0/10) to afford 206 mg (71% yield) of methyl *(1S,2R)*-1-benzamido-2-(2-carboxyethyl)cyclopropanecarboxylate **6** as a white solid. Mp 146 °C, $[\alpha]_D$ = - 2.4 (c = 0.5 in CH_3OH); IR 3306, 3500-2500, 1740, 1714, 1656 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (dd, 1H, J = 7.1 Hz, J = - 5.1 Hz), 1.68-1.92 (m, 4H), 2.50-2.66 (m, 2H), 3.66 (s, 3H), 7.40-7.55 (m, 3H), 7.64 (brs, 1H), 7.84-7.90 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.5, 22.8, 28.0, 33.2, 37.9, 52.7, 127.2, 128.6, 131.8, 133.8, 169.0, 172.9, 177.8. Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found C, 61.96; H, 5.81; N, 4.73.

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