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Stereospecific Synthesis of *trans*-2,3-Diaryl Substituted 1-Aminocyclopropanecarboxylic Acid Derivatives

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ABSTRACT

The stereospecific syntheses of trans-2,3-diaryl-1-aminocyclopropanecarboxylic acid derivatives are reported. The key step is a

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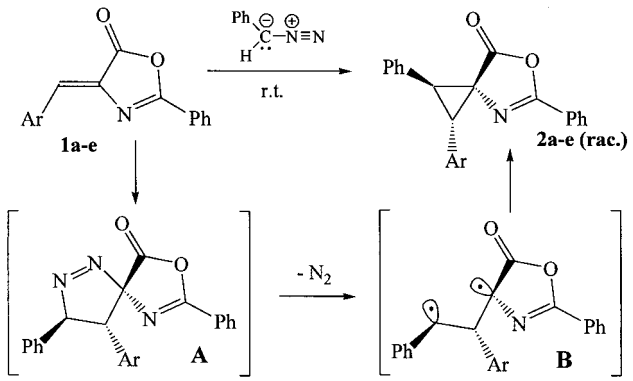
1,3-dipolar cycloaddition of phenyldiazomethane to (*Z*)-2-phenyl-4-arylidene-5(4H)-oxazolones, followed by the extrusion of nitrogen in situ.

Key Words: Stereospecific syntheses; *trans*-2,3-Diaryl-1-amino-cyclopropanecarboxylic acid; Phenyldiazomethane; Oxazolones; 1,3-Dipolar cycloaddition.

Since the first report on the isolation[1] and identification of 1-aminocyclopropanecarboxylic acid as an intermediate in the biosynthesis of ethylene in higher plants,[2] the synthesis of this compound and its derivatives (ACCs) has been, and currently still is the subject of numerous synthetic efforts.[3] This interest stems from their diverse documented biological activities, and their potential use in the synthesis of conformationally constrained peptides. The constrained peptide analogues are of great value in structure-function relationship studies aimed at elucidating the biologically active conformations. ACCs constitute a special class of side-chain conformationally constrained residues. The rigid cyclopropane ring forces the substituents to adopt a well-defined orientation with respect to the peptide backbone; if a β-substituent is present on the cyclopropyl ring, the possibility of choosing the *cis* (β-substituent to respect nitrogen atom) or trans stereoisomer allows the evaluation of the substituent effect on the interaction between the drug and receptor site.[4]

Among the considerable numbers of ACCs synthesized, most were 2-substituted or 2,2-disubstituted-1-aminocyclopropanecarboxylic amino acids,[5] with some reports on 2,3-disubstituted ACCs,[6] only several stereoselective syntheses of 2,3-diaryl ACCs have been reported.[4b,4d] In the previous report, we described the stereoselective synthesis of trans-2,3-diphenyl-1-aminocyclopropanecarboxylic acid.[6a] In a continuation of our studies on the selective synthesis of ACCs,[5l,6a] we wish to report now the stereospecific synthesis of trans-2,3-diaryl-1-aminocyclopropanecarboxylic acid derivatives. The key step is a 1,3-dipolar cycloaddition of phenyldiazomethane to (*Z*)-2-phenyl-4-arylidene-5(4H)-oxazolones **1**, followed by the extrusion of N_2 in situ (Sch. 1).

(*Z*)-2-Phenyl-4-arylidene-5(4H)-oxazolones **1**, readily obtained (yield vary from 60% to 79%) by condensation of hippuric acid and aromatic aldehydes following the classical Erlenmeyer procedure employed by Buck and Ide,[7] reacted with phenyldiazomethane in toluene at room temperature for 8–48 h to give pure *t*-1-(4-methoxyphenyl)-*c*-2, *t*-5-diphenyl-4-aza-6-oxaspiro[2.4]hept-4-en-*r*-7-one **2**, in 78%–91% yields after



a-d, Ar = *p*-X-C_6H_4: X=H, X=CH_3O, X =Cl, X=NO_2; **e**, Ar = 2-furyl

Scheme 1.

recrystallization from ethyl acetate/hexane. In the course of the room temperature addition of a toluene solution of phenyldiazomethane to (*Z*)-2-phenyl-4-arylidene-5(4H)-oxazolones **1**, a slow evolution of gas was observed. Presumably the reaction proceeds through a 3 + 2 cycloaddition to form a spiro-pyrazoline **A** which immediately losses nitrogen to form the biradical **B**. In contrast, when diazomethane is used in these kinds of cycloadditions, the subsequent pyrazolines are stable and can be isolated. They can only be converted to cyclopropanes by heating at ~100°C or by photolysis.[3] Apparently in the case of spiro-pyrazoline **A**, the 3-phenyl substituent and 5-spirocycle either destabilizes the pyrazoline sterically or lowers the energy of the presumed diradical intermediate **B** so that the nitrogen extrusion takes place at room temperature. This is in agreement with the studies of Overberger and Anselme[8] who showed that the addition of phenyl substituent to a pyrazoline reduced the activation energy for nitrogen loss by over 20 kcal/mol resulting in a 500-fold increase in the rate of cycloproprane formation.

All new compounds (**2**, **3**, **4**) gave satisfactory spectroscopic and analytical data. GC-MS of the crude reaction mixtures showed the presence of only one diastereomer of the spirocyclopropanes **2a–2e**, indicating that the cycloaddition is diastereoselective and that no loss of stereochemistry occurs in subsequent formation of the diradical **B**.[9] ^{1}H NMR analysis of **2** revealed there are two cyclopropyl-H signals at δ 3.77–3.81 (d) and 3.91–4.03 (d) in compounds **2a–2e** and the coupling constants between the two cyclopropane protons of are quite high

($J = 9.0$, 9.5). This is not definitive evidence for the trans relation of the aryl group as the range for vicinal cyclopropane couplings is $J_{cis} = 7$–13, $J_{trans} = 4$–9.[10] The trans relationship of the aryl substituents was confirmed by single crystal X-ray studies of **2b**. The crystal structure (Fig. 1) showed the two aryl groups in a trans relationship with the *p*-methoxyphenyl group being cis to the spiro-nitrogen substituent.

Spirocyclopropane derivatives **2** were readily converted into the corresponding benzamido methyl esters **3** in nearly quantitative yields by treatment with absolute methanol containing catalytic amounts of sodium methoxide. Hydrolysis of esters **3** with hydrochloric acid/acetic acid furnished the corresponding 2,3-diaryl-1-aminocyclopropanecarboxylic acid hydrochlorides **4** in 57–67% yields (Sch. 2).

^{1}H NMR analysis of **3** revealed there are two cyclopropyl-H signals at δ 3.70–3.93 (d) and 3.44–3.69 (d) in compounds **3a–3e**, likewise for compounds **4a–4c**, 3.47–3.53 (d) and 3.14–3.21 (d). The vicinal cyclopropane coupling constants for esters **3a–3e** and amino acids **4a–4c** remain close to the values for the starting spirocyclopropanes ($J = 8.5$, 9.0) sug-

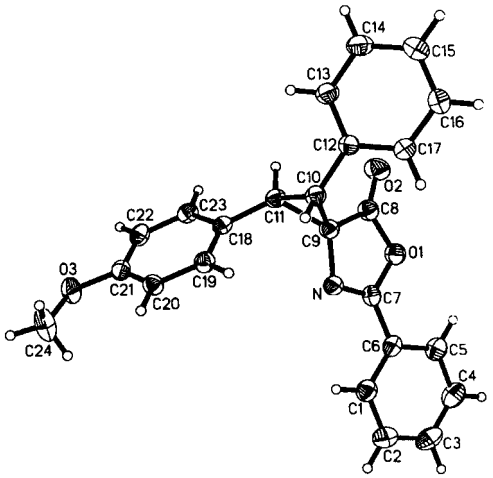
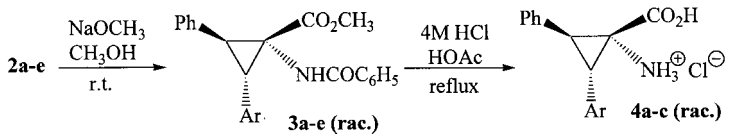


Figure 1. X-ray crystal structure of **2b**.



Scheme 2.

gesting the trans relationship of the aryl groups is maintained in **3** and **4**, this is in accordance with our previous report.[6a] In fact, the trans stereochemistry of **3a** had been confirmed by X-ray diffraction analysis.[6a]

In conclusion, we developed a stereospecific synthesis methodology of the highly constrained trans-2,3-diaryl-1-aminocyclopropanecarboxylic acid derivatives. This methodology has significant advantages: common available materials, mild reaction conditions, simple operations, high yields and above all the high stereoselectivity. Additional synthesis of highly constrained ACCs and their incorporation into model peptides is currently under investigation and will be reported elsewhere.

EXPERIMENTAL

All reagents were obtained from commercial suppliers. All solvents and liquid reagents were purified by standard procedures, and solvents were freshly distilled prior to use. (*Z*)-2-Phenyl-4-arylidene-5(4H)-oxazolones (**1a–e**), *p*-toluenesulfonylhydrazide and benzaldehyde tosylhydrazone were prepared as previously described.[11] Melting points were determined on a WRS-IA apparatus without correction. All elemental analyses were performed by Carlo Erba model 1106 analyzer. ^{1}H spectra were recorded on a Varian INOVA 500 MHz spectrometer in $CDCl_3$ or in DMSO-d_6. Infrared spectra were recorded on a Nicolet ESP 360 FT-IR spectrometer as KBr pellets. GC-MS spectra were measured at 70 eV (EI).

Synthesis of Phenyldiazomethane[12]

To a 500 mL two-neck flask was added benzaldehyde tosylhydrazone (7.0 g, 25 mmol) and toluene (100 mL), then to this solution was added triethylbenzylammonium chloride (TEBAC, 1.4 g, 6.25 mmol) and 15% NaOH (100 mL). The mixture was heated under stirring for 2 h. Cooled, the organic phase was washed by water.

Syntheses of 2a–e

To a mixture of **1a–1e** (10 mmol) in toluene (50 mL) was added a solution of phenyldiazomethane in toluene dropwise over 1 h. The mixture was stirred at room temperature for another 8–48 h, the progress of the reaction was monitored by TLC (9/1, hexane/ethyl acetate). After

the reaction was finished, excess of phenyldiazomethane was decomposed by addition of glacial acetic acid. The solution was dried over $MgSO_4$, filtered and the solvent was removed in vacuo to provide a yellow solid. The crude products were recrystallized from ethyl acetate/hexane to afford pure **2a–2e**, the yields vary from 78% to 91%.

2a. White solid, yield 87%, m.p. 134–135°C, R_f (hexane/ethyl acetate 4/1, v/v) 0.57. IR (KBr, ν, cm^{-1}): 1800 (C=O), 1634 (C=N), 695 (Ar-H). ^{1}H NMR ($CDCl_3$, δ, ppm): 8.0–7.3 (m, 15H, ArH), 3.97 (d, J = 9.5 Hz, 1H, cyclopropyl), 3.78 (d, J = 9.0 Hz, 1H, cyclopropyl). Anal. calcd. for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.12; H, 5.23; N, 4.16.

2b. White solid, yield 91%, m.p. 144–145°C, R_f (hexane/ethyl acetate 4/1) 0.46. IR (KBr, ν, cm^{-1}): 1796 (C=O), 1633 (C=N), 695 (Ar-H). ^{1}H NMR ($CDCl_3$, δ, ppm): 8.0–6.9 (m, 14H, ArH), 3.93 (d, J = 9.5 Hz, 1H, cyclopropyl), 3.82 (s, 3H, CH_3O), 3.75 (d, J = 9.5 Hz, 1H, cyclopropyl). Anal. calcd. for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 78.20; H, 5.30; N, 3.83.

The single crystal growth was carried out from a saturated solution of **2b** in ethyl acetate after standing overnight in the refrigerator. X-ray crystallographic analysis was performed with a Siemens P4 four-circle diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073 Å). Crystal data of compound **2b:** $C_{24}H_{19}NO_3$, $0.54 \times 0.50 \times 0.44\,mm^3$, M_f = 369.40, monoclinic, Space group $P2_1/n$, a = 11.3462 (2) Å, b = 10.464 (2) Å, c = 16.557 (3) Å, $\alpha = 90^\circ$, $\beta = 105.52\ (1)^\circ$, $\gamma = 90^\circ$, V = 1894.0 (6) $Å^3$, Z = 4, Dc = 1.295 $Mg\,m^{-3}$, μ (MoKα) = 0.086 mm^{-1}, F (000) = 776. T = 292K; 3528 reflections were independent and unique, $I > 2\sigma$ (I), and 22 with $2.56^\circ < \theta < 14.96^\circ$ were used for the solution of the structure. $R_1 = 0.0367$, $wR_2 = 0.0836$.

X-ray data for the compound **2b** has been deposited at the Cambridge Crystallographic Data Center. Copies of the data may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax: (+) 44 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

2c. White solid, yield 85%, m.p. 132–133°C, R_f (hexane/ethyl acetate 4/1) 0.60. IR (KBr, ν, cm^{-1}): 1803 (C=O), 1631 (C=N), 693 (Ar-H). ^{1}H NMR ($CDCl_3$, δ, ppm): 8.0–7.3 (m, 14H, ArH), 3.91 (d, J = 9.5 Hz, 1H, cyclopropyl), 3.73 (d, J = 9.0 Hz, 1H, cyclopropyl). Anal. calcd. for $C_{23}H_{16}NO_2Cl$: C, 73.90; H, 4.31; N, 3.75. Found: C, 74.02; H, 4.34; N, 3.78.

2d. Pale yellow solid, yield 89%, m.p. 181–182°C, R_f (hexane/ethyl acetate 4/1) 0.52. IR (KBr, ν, cm^{-1}): 1804 (C=O), 1638 (C=N), 696 (Ar-H). ^{1}H NMR ($CDCl_3$, δ, ppm): 8.3–7.3 (m, 14H, ArH), 3.98 (d, J = 9.5 Hz, 1H, cyclopropyl), 3.81 (d, J = 9.0 Hz, 1H, cyclopropyl).

Anal. calcd. for $C_{23}H_{16}N_2O_4$: C, 71.87; H, 4.20; N, 7.29. Found: C, 71.72; H, 4.31; N, 7.39.

2e. White solid, yield 78%, m.p. 155 156°C, R_f (hexane/ethyl acetate 4/1) 0.55. IR (KBr, ν, cm^{-1}): 1803 (C=O), 1628 (C=N), 694 (Ar-H). ^1H NMR ($CDCl_3$, δ, ppm): 8.0–6.4 (m, 13H, ArH), 4.03 (d, $J = 9.0$ Hz, 1H, cyclopropyl), 3.77 (d, $J = 9.0$ Hz, 1H, cyclopropyl). Anal. calcd. for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.59; N, 4.25. Found: C, 76.51; H, 4.66; N, 4.30.

Syntheses of 3a–e

To a flask containing 40 mL of absolute methanol was added a little piece of sodium, then to this solution was added 5 mmol of **2a–e** under stirring, the mixture was stirred for another 30 min (monitored by TLC, hexane/ethyl acetate 3/1). After the reaction was finished, the methanol was removed in vacuo. The solid was dissolved in ethyl acetate, then washed by water, brine, dried over $MgSO_4$ overnight. Filtered, the solvent was removed in vacuo to provide a white solid of **3a–e**.

3a. Yield 97%, m.p. 216–217°C, R_f (hexane/ethyl acetate 3/1) 0.28. IR (KBr, ν, cm^{-1}): 3239 (N-H), 1732 (C=O), 1645 (C=O), 697 (Ar-H). ^1H NMR (DMSO-d^6, δ, ppm): 9.07 (s, 1H, N-H), 7.7–7.1 (m, 15H, Ar-H), 3.74 (d, $J = 9.0$ Hz, 1H, cyclopropyl), 3.53 (d, $J = 8.5$ Hz, 1H, cyclopropyl), 3.33 (s, 3H, CO_2CH_3). Anal. calcd. for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.55; H, 5.78; N, 3.82.

3b. Yield 99%, m.p. 169–171°C, R_f (hexane/ethyl acetate 3/1) 0.20. IR (KBr, ν, cm^{-1}): 3274 (N-H), 1738 (C=O), 1634 (C=O), 697 (Ar-H). ^1H NMR ($CDCl_3$, δ, ppm): 7.7–6.9 (m, 14H, Ar-H), 6.15 (s, 1H, N-H), 3.83 (s, 3H, OCH_3), 3.71 (d, $J = 9.0$ Hz, 1H, cyclopropyl), 3.48 (s, 3H, OCH_3), 3.44 (d, $J = 9.0$ Hz, 1H, cyclopropyl). Anal. calcd. for $C_{25}H_{23}NO_4$: C, 74.49; H, 5.77; N, 3.49. Found: C, 74.45; H, 5.80; N, 3.53.

3c. Yield 98%, m.p. 183°C, R_f (hexane/ethyl acetate 3/1) 0.29. IR (KBr, ν, cm^{-1}): 3237 (N-H), 1739 (C=O), 1632 (C=O), 698 (Ar-H). ^1H NMR ($CDCl_3$, δ, ppm): 7.6–7.3 (m, 14H, Ar-H), 6.20 (s, 1H, N-H), 3.74 (d, $J = 8.5$ Hz, 1H, cyclopropyl), 3.48 (s, 3H, OCH_3), 3.46 (d, $J = 9.0$ Hz, 1H, cyclopropyl). Anal. calcd. for $C_{24}H_{20}NO_3Cl$: C, 71.02; H, 4.97; N, 3.45. Found: C, 70.92; H, 5.01; N, 3.49.

3d. Yield 92%, m.p. 209°C, R_f (hexane/ethyl acetate 3/1) 0.18. IR (KBr, ν, cm^{-1}): 3249 (N-H), 1741 (C=O), 1634 (C=O), 700 (Ar-H). ^1H NMR (DMSO-d^6, δ, ppm): 9.28 (s, 1H, N-H), 8.1–7.3 (m, 14H, Ar-H), 3.93 (d, $J = 8.5$ Hz, 1H, cyclopropyl), 3.69 (d, $J = 8.5$ Hz, 1H, cyclopropyl), 3.35 (s, 3H, OCH_3). Anal. calcd. for $C_{24}H_{20}N_2O_5$: C, 69.22 ; H, 4.84; N, 6.73. Found: C, 69.31; H, 4.80; N, 6.81.

3e. Yield 94%, m.p. 212–213°C, R_f (hexane/ethyl acetate 3/1) 0.28. IR (KBr, ν, cm^{-1}): 3253 (N-H), 1737 (C=O), 1645 (C=O), 696 (Ar-H). ^{1}H NMR (DMSO-d^6, δ, ppm): 9.14 (s, 1H, N-H), 7.7–6.2 (m, 13H, Ar-H), 3.70 (d, $J = 8.5$ Hz, 1H, cyclopropyl), 3.47 (d, $J = 9.0$ Hz, 1H, cyclopropyl), 3.33 (s, 3H, OCH_3). Anal. calcd. for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.21; H, 5.36; N, 3.92.

Syntheses of 4a–c

To a flask containing glacial acetic acid (25 mL) and 4 M HCl (25 mL) was added 1 mmol of **3a–3c** under stirring, the mixture was heated under reflux for 24 h. The liquid was evaporated in vacuo, the white residue was dissolved in 0.5 M HCl (40 mL), then washed with $CHCl_3$ (3×15 mL), the water phase was filtered and the water removed in vacuo. Recrystallization from hot water furnished the products **4a–4c** as white solids.

4a. M.p. 204–205°C, yield 57%. IR (KBr, ν, cm^{-1}): 3001 (br, OH), 1773 (C=O), 1595 (NH_3), 1505 (C=O), 1445 (NH_3), 698 (Ar-H). ^{1}H NMR (DMSO-d^6, δ, ppm): 7.5–7.2 (m, 10H, Ar-H), 3.54 (d, $J = 8.5$ Hz, 1H, cyclopropyl), 3.21 (d, $J = 9.0$ Hz, 1H, cyclopropyl). Anal. calcd. for $C_{16}H_{16}NO_2Cl$: C, 66.32; H, 5.57; N, 4.83. Found: C, 66.41; H, 5.51; N, 4.87.

4b. M.p. 180–182°C, yield 67%. IR (KBr, ν, cm^{-1}): 2936 (br, OH), 1727 (C=O), 1610 (NH_3), 1515 (C=O), 1448 (NH_3), 699 (Ar-H). ^{1}H NMR (DMSO-d^6, δ, ppm): 7.4–6.9 (m, 9H, Ar-H), 3.76 (s, 3H, OCH_3), 3.47 (d, $J = 8.5$ Hz, 1H, cyclopropyl), 3.14 (d, $J = 9.0$ Hz, 1H, cyclopropyl). Anal. calcd. for $C_{17}H_{18}NO_3Cl$: C, 63.85; H, 5.67; N, 4.38. Found: C, 63.72; H, 5.73; N, 4.44.

4c. M.p. 216°C, yield 60%. IR (KBr, ν, cm^{-1}): 3001 (br, OH), 1737 (C=O), 1600 (NH_3), 1503 (C=O), 1441 (NH_3), 699 (Ar-H). ^{1}H NMR (DMSO-d^6, δ, ppm): 7.5–7.2 (m, 9H, Ar-H), 3.53 (d, $J = 8.5$ Hz, 1H, cyclopropyl), 3.20 (d, $J = 8.5$ Hz, 1H, cyclopropyl). Anal. calcd. for $C_{16}H_{15}NO_2Cl_2$: C, 59.28; H, 4.66; N, 4.32. Found: C, 59.38; H, 4.58; N, 4.39.

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REFERENCES

1. Burroughs, L.F. 1-Aminocyclopropane-1-carboxylic acid: a new amino acid in perry pears and cider apples. Nature **1957**, *179*, 360–361.
2. Adams, D.O.; Yang, S.F. Ethylene biosynthesis: Identification of 1-aminocyclopropane-1-carboxylic acid as an intermediate in the conversion of methionine to ethylene. Proc. Natl. Acad. Sci. USA **1979**, *76* (1), 170–174.
3. For recent reviews on ACCs, see: (a) Salaun, J. Cyclopropane derivatives and their diverse biological activities. Top. Curr. Chem. **2000**, *207*, 1–67; (b) Cativiela, C.; Diaz-de-Viellgas, M.D. Stereoselective synthesis of quaternary α-amino acids. Part 2: cyclic compounds. Tetrahedron: Asymmetry **2000**, *11* (3), 645–732; (c) Salaun, J.; Baird, M.S. Biologically active cyclopropanes and cyclopropenes. Curr. Med. Chem. **1995**, *2* (1), 511–542; (d) Burgess, K.; Ho, K.-K.; Moye-Sherman, D. Asymmetric syntheses of 2,3-methanoamino acids. Synlett **1994**, *8*, 575–583.
4. For some researches about ACCs were used in conformationally constrained peptides, see: (a) Jimenez, A.I.; Cativiela, C.; Marraud, M. A γ-turn induced by a highly constrained cyclopropane analog of phenylalanine (c3diPhe) in the solid state. Tetrahedron Lett. **2000**, *41* (28), 5353–5356; (b) Moye-Sherman, D.; Jin, S.; Li, S.; Welch, M.B.; Reibenspies, J.; Burgess, K. Cyclopropane amino acids that mimic two χ^1-conformations of phenylalanine. Chem. Eur. J. **1999**, *5* (9), 2730–2739; (c) Jimenez, A.I.; Cativiela, C.; Aubry, A.; Marraud, M. β-Turn preferences induced by 2,3-methanophenylalanine chirality. J. Am. Chem. Soc. **1998**, *120* (37), 9452–9459; (d) Moye-Sherman, D.; Jin, S.; Ham, I.; Burgess, K. Conformational preferences of RNase A C-peptide derivatives containing a highly constrained analog of phenylalanine. J. Am. Chem. Soc. **1998**, *120* (37), 9435–9443; (e) Lim, D.; Burgess, K. Spirocyclic peptidomimetics featuring 2,3-methanoamino acids. J. Am. Chem. Soc. **1997**, *119* (41), 9632–9640; (f) Jimenez, A.I.; Vandersse, R.; Marraud, M.; Aubry, A.; Cativiela, C. Folding types of dipeptides containing the diastereoisomeric cyclopropanic analogs of phenylalanine. Tetra. Lett. **1997**, *38* (43), 7559–7562; (g) Burgess, K.; Ke, C.-Y. On the conformational bias of F((2R,3S)-cyclo-M)RFa induced by the *cis*-2,3-methanomethionine residue. J. Org. Chem. **1996**, *61* (24), 8627–8631; (h) Burgess, K.; Ho, K.-K.; Pal, B. Comparison of the effects of (2S,3S)-2,3-methanomethionine, (2R,3R)-2,3-methanomethionine, and (2R,3R)-2,3-methanophenylalanine on the

conformations of small peptides. J. Am. Chem. Soc. **1995**, *117* (13), 3808–3819; (i) Burgess, K.; Ho, K.-K.; Pettitt, B.M. J. Am. Chem. Soc. Conformational effects of substituting methionine with (2S,3S)-2,3-methanomethionine in Phe-Met-Arg-Phe-NH_2. **1995**, *117* (1), 54–65; (j) Balaji, V.N.; Ramnarayan, K.; Chan, M.-F.; Rao, S. Conformational studies on model peptides with 1-aminocyclopropane-1-carboxylic acid residues. Pep. Res. **1994**, *7* (2), 60–71; (k) Burgess, K.; Ho, K.-K.; Pettitt, B.M. A γ-turn structure induced by 2S,3S-2,3-methanomethionine. J. Am. Chem. Soc. **1994**, *116* (2), 799–800; (l) Mapelli, C.; Newton, M.G.; Ringold, C.E.; Stammer, C.H. Cyclopropane amino acid ester dipeptide sweeteners. Int. J. Peptide Protein Res. **1987**, *30* (4), 498–510.

5. For some selected recent examples about the synthesis of 2-substituted or 2,2-disubstituted ACCs, see: (a) Abellan, T.; Mancheno, B.; Najera, C.; Sansano, J.M. Asymmetric synthesis of α-amino acids from α,β-(*Z*)-didehydroamino acid derivatives with 1,2,3,6-tetra-hydropyrazin-2-one structure. Tetrahedron **2001**, *57* (30), 6627–6640; (b) Clerici, F.; Gelmi, M.L.; Pocar, D.; Pilati, T. Masked constrained cysteines: diastereoselective and enantioselective synthesis of 1-amino-2-mercaptocyclo-propanecarboxylic acid derivatives. Tetrahedron: Asymmetry **2001**, *12* (19), 2663–2669; (c) Salgado, A.; Huybrechts, T.; Eeckhaut, A.; Van der Eycken, J.; Szakonyi, Z.; Fulop, F.; Tkachev, A.; De Kimpe, N. Synthesis of (1S)-1-amino-2,2-dimethylcyclopropane-1-carboxylic acid via PLE mediated hydrolysis of *bis*(2,2,2-trifluoroethyl)-2,2-dimethylcyclopropane-1,1-dicarboxylate. Tetrahedron **2001**, *57* (14), 2781–2786; (d) Debache, A.; Collet, S.; Bauchat, P.; Danion, D.; Euzenat, L.; Hercouet, A.; Carboni, B. Belokon's Ni(II) complex as a chiral masked glycine for the diastereoselective synthesis of 2-substituted 1-aminocyclo-propane carboxylic acids. Tetrahedron: Asymmetry **2001**, *12* (5), 761–764; (e) Racouchot, S.; Ollivier, J.; Salaun, J. Titanium-mediated diastereoselective formation of (*Z*)-1-(1-alkenyl)-2-substituted-cyclopropyl esters efficient precursors of (*Z*)-2,3-methanoamino acids. Synlett **2000**, *12*, 1729–1732; (f) Abellan, T.; Chinchilla, R.; Galindo, N.; Najera, C.; Sansano, J.M. New oxazinone and pyrazinone derivatives as chiral reagents for the asymmetric synthesis of α-amino acids. J. Heterocyclic Chem. **2000**, *37* (3), 467–479; (g) Katagiri, T.; Irie, M.; Minoru, U.K. Syntheses of optically active trifluoro-norcoronamic acids. Org. Lett. **2000**, *2* (16), 2423–2425; (h) Donkor, I.O.; Zheng, X.; Han, J.; Miller, D.D. Asymmetric synthesis of

2,3-methanoleucine stereoisomers from common intermediates. Chirality **2000**, *12*, 551–557; (i) Chinchilla, R.; Falvello, L.R.; Galindo, N.; Najera, C. New chiral didehydroamino acid derivatives from a cyclic glycine template with 3,6-dihydro-2H-1,4-oxazin-2-one structure: applications to the asymmetric synthesis of nonproteinogenic α-amino acids. J. Org. Chem. **2000**, *65* (10), 3034–3041; (j) Kordes, M.; Winsel, H.; de Meijere, A. Cyclopropyl building blocks for organic synthesis 58; A new short access to amino acids incorporating an aminocyclopropyl moiety from *N*,*N*-dibenzylcarboxamides. Eur. J. Org. Chem. **2000**, *18*, 3235–3245; (k) Kozyrkov, Y.; Pukin, A.; Kulinkovich, O.; Ollivier, J.; Salaun, J. A convenient approach to substituted 1-(1-alkenyl)cyclopropanols: a new preparation of 2,3-methano amino acids. Tetrahedron Lett. **2000**, *41* (33), 6399–6402; (l) Dorizon, P.; Su, G.; Ludvig, G.; Nikitina, L.; Paugam, R.; Ollivier, J.; Salaun, J. Stereoselective synthesis of highly functionalized cyclopropanes. Application to the asymmetric synthesis of (1S,2S)-2,3-methanoamino acids. J. Org. Chem. **1999**, *64* (13), 4712–4724.

6. (a) Jimenez, A.I.; Lopez, P.; Laureano, O.; Cativiela, C. Facile synthesis and highly efficient resolution of a constrained cyclopropane analogue of phenylalanine. Tetrahedron **2001**, *57* (28), 6019–6026; (b) Anisimova, N.A.; Deiko, L.I.; Berkova, G.A. Synthesis of 1-aminocyclopropane-1,2-dicarboxylic acid derivatives. Russ. J. Org. Chem. **1999**, *35*, 155–156; (c) Koskinen, A.M.P.; Munoz, L. Intramolecular cyclopropanation: stereospecific synthesis of (*E*)- and (*Z*)-1-amino-cyclopropane-1-carboxylic acids. J. Org. Chem. **1993**, *58* (4), 879–886; (d) Lalitha, N.; Bhalerao, U.T.; Iyengar, D.S. Stereospecific synthesis of *gem*-diphenylcyclopropanecarboxamides: aminolysis of spiro cyclopropano lactones by acetonitrile and triethylamine. J. Org. Chem. **1992**, *57* (24), 6684–6686; (e) Zhu, Y.F.; Yamazaki, T.; Tsang, J.W.; Lok, S.; Goodman, M. Synthesis and taste properties of L-aspartylmethylated 1-aminocyclopropanecarboxylic acid methyl esters. J. Org. Chem. **1992**, *57* (4), 1074–1081. (f) Lalitha, N.; Iyengar, D.S.; Bhalerao, U.T. Cyclopropanation of 2-ylidene-oxazol-5-one with diphenyldiazomethane. Stereospecific synthesis of novel *gem*-diphenylcyclopropyl amino acid derivatives. J. Org. Chem. **1989**, *54* (7), 1771–1773; (g) Schollkopf, U.; Hupfeld, B.; Gull, R. Angew. Chem. Int. Ed. Engl. Simple synthesis of 1-aminocyclopropanecarboxylic acids from *tert*-butyl isocyanoacetate and epoxides. Synthesis of 5,6-dihydro-4-H-1,3-oxazine-4-carboxylic acid esters. **1986**, *25* (8), 754–755.

7. Buck, J.S.; Ide, W.S. *Organic Synthesis*; Blatt, A.H., Ed.; Wiley: New York, 1943; Collect. Vol. II, 55–57.
8. Overberger, C.G.; Anselme, J.-P. Azo compounds. *XLIII*. Five-membered cyclic azo compounds. Their stereospecific decomposition. J. Am. Chem. Soc. **1964**, *86* (4), 658–660.
9. (a) Arai, S.; Nakayama, K.; Hatano, K.; Shioiri, T. Stereoselective synthesis of cyclopropane rings under phase-transfer-catalyzed conditions. J. Org. Chem. **1998**, *63* (25), 9572–9575; (b) Overberger, C.G.; Anselme, J.-P.; Hall, J.R. Azo compounds. XLII. Dipole moments and spectral data. J. Am. Chem. Soc. **1963**, *85* (18), 2752–2754; (c) Overberger, C.G.; Anselme, J.-P. A five-membered ring azo compound. A stereoselective decomposition. J. Am. Chem. Soc. **1962**, *84* (5), 869–870.
10. Silverstein, R.M.; Webster, F.X. *Spectrometric Identification of Organic Compounds*, 6th Ed.; John Wiley & Sons, Inc.: New York, 1998; Chapter 4, 212.
11. (a) Vogel, A.I. *Vogel's Textbook of Practical Organic Chemistry*, 5th Ed.; Longman: London, 1989; 1156; (b) Albert, A.; Boyer, R. J. Chem. Soc. **1949**, 1148–1152; (c) Farnum, D.G. Preparation of aryldiazoalkanes by the Bamford-Stevens reaction. J. Org. Chem. **1963**, *28* (3), 870–872.
12. Wulfman, D.S.; Yousefian, S.; White, J.M. Metal salt-catalyzed carbenoids. XIX. The synthesis of aryldiazomethanes. Synth. Commun. **1988**, *18* (18), 2349–2352.

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