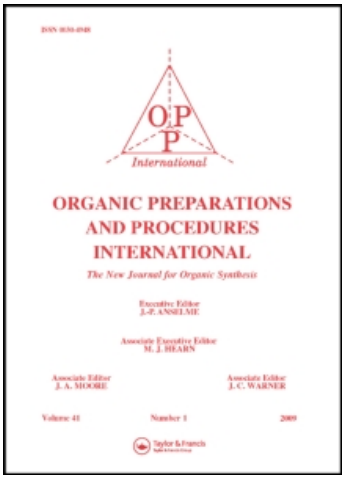

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Chengxue Pan[a]; Guifa Su[a]; Jiangke Qin[a]
[a] College of Chemistry & Chemical Engineering, Guangxi Normal University, Guilin, PR CHINA

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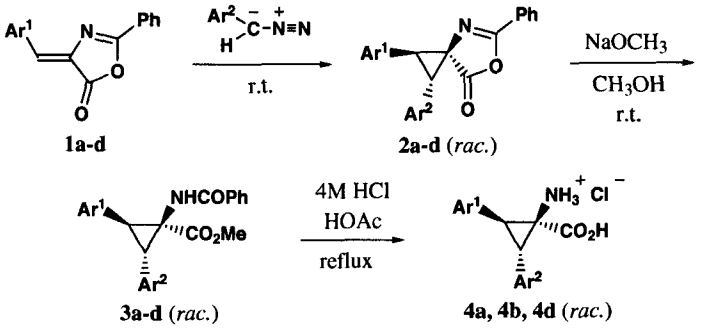
DIASTEREOSPECIFIC SYNTHESIS OF *trans*-2,3-DIARYL-1-AMINOCYCLOPROPANECARBOXYLIC ACIDS

Chengxue Pan, Guifa Su* and Jiangke Qin

College of Chemistry & Chemical Engineering
Guangxi Normal University, Guilin 541004, P. R. CHINA
e-mail: gfsu@sina.com and edward_su75@163.com

1-Aminocyclopropanecarboxylic acid and its derivatives (*Accs*) have been extensively used as mechanistic probes and enzyme inhibitors as well as in the design and synthesis of conformationally constrained peptidomimetics. The constrained peptide analogues from *Accs* are relatively rigid and capable of capturing nucleophiles and electrophiles, which entails important changes in their reactivity and conformation.[1] Much synthetic effort has been devoted to achieving stereoselective and efficient syntheses of cyclopropane amino acids.[1-3] Recently, we reported that 1,3-dipolar cycloaddition of phenyldiazomethane to (Z)-2-phenyl-4-arylidene-5(*4H*)-oxazolones to the stereospecific formation of *trans*-2,3-diaryl-4-aza-5-phenyl-6-oxaspiro-[2.4]hept-4-en-7-one.[1] These results prompted us to investigate the addition of aryldiazomethanes to substrate **1a-1d**; apart from stereoselective aspects, the spiro compounds formed should be of interest as precursors for the synthesis of *trans*-2,3-diaryl-1-aminocyclopropanecarboxylic acid derivatives and we now report our results in detail (*Scheme 1*).[4]

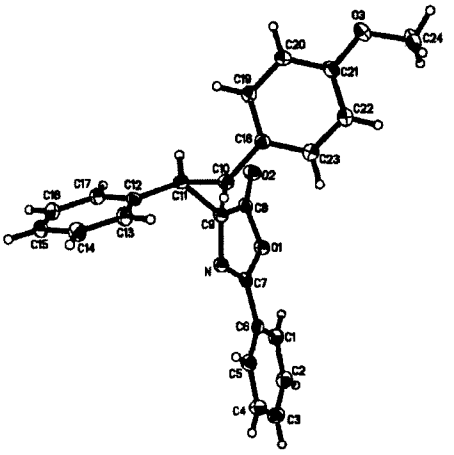


Ar^1 = *p*-X-C_6H_4: **a** X = Cl; **b,d** X = H; **c** X = CH_3O
Ar^2 = *p*-X-C_6H_4: **a,b** X = Cl; **c,d** X = CH_3O

Synthesis of the *Accs*

Scheme 1

The key step is a 1,3-dipolar cycloaddition of aryldiazomethanes to (*Z*)-2-phenyl-4-arylidene-5(*4H*)-oxazolones (**1a-1d**) with slow evolution of nitrogen. GC-MS of the crude reaction mixtures showed the presence of only one diasteromer (spirocyclopropanes **2a-2d**). In view of these results, it was assumed that 3+2 cycloaddition occurred with the formation of spiropyrazolines which immediately extruded nitrogen to generate a biradical; rapid ring-closure of the biradical which should be faster than rotation around the C-C bond, thus leads to the formation of cyclopropane in stereospecific fashion.[1] This is in agreement with Ortuño's studies on photodenitrogenation of 1-pyrazoline;[5] their theoretical calculation results also supported this conclusion.[6]

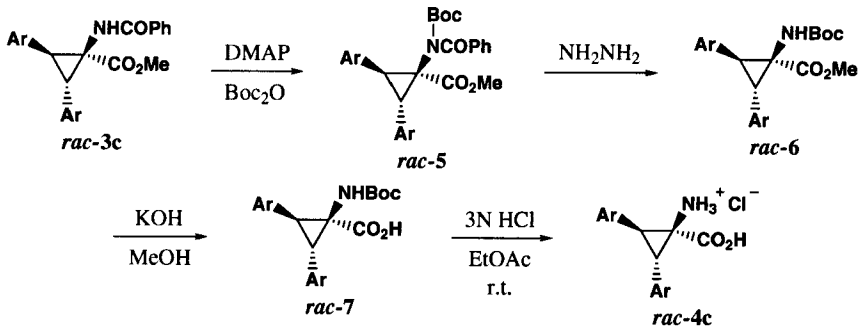


X-ray Crystal Structure of 2d

Fig. 1

Comparison of its crystal structure with that reported in *ref. 1*, showed that their structures are nearly the same, the only difference being the relative position of the *p*-methoxyphenyl group relative to the spiro-nitrogen substituent; in compound **2d**, the two aryl groups are in a *trans* relationship with the *p*-methoxyphenyl group *trans* to the spiro-nitrogen substituent; in the single crystal reported in *ref. 1*, the *p*-methoxyphenyl group is *cis* to the spiro-nitrogen substituent. This fact means that by using different (*Z*)-2-phenyl-4-arylidene-5(*4H*)- oxazolones to react with the various aryldiazomethanes, different *trans*-2,3-diarylaminocyclo- propanecarboxylic acid derivatives possessing the same substituents but bearing different specific configurations may be prepared.

Compounds **2a-2d** were readily converted into the corresponding methyl esters (**3a-3d**) in nearly quantitative yields by treatment with absolute methanol containing catalytic amounts of sodium methoxide. Removal of the protecting groups in *rac*-**3a**, **3b**, **3d** was performed by refluxing in hydrochloric acid/acetic acid and provided **4a**, **4b** and **4d** (46-68% yields). However, when the same procedure was attempted to prepare **4c**, after 10 h. reflux the reaction mixture turned dark grey, to finally give a dark sticky liquid, presumably because the cyclopropane moiety of **4c** is unstable under these harsh experimental conditions. Fortunately, the desired product was obtained by the milder procedure developed by Jimenez *et al.*[3c] (*Scheme 2*).



Ar = 4-MeO-C_6H_4, Boc = ^{t}BuOOC-, DMAP: 4-(dimethylamino)pyridine

Synthesis of 4c

Scheme 2

The benzamido group in *rac*-**3c** was acylated with Boc_2O in the presence of a catalytic amount of 4-(dimethylamino)pyridine, then the imide *rac*-**5** was debenzoylated by treatment with hydrazine monohydrate to afford *rac*-**6**; saponification of *rac*-**6** with a methanolic solution of KOH led to the desired N-*Boc* amino acid *rac*-**7**. Finally, *rac*-**7** was treated with a saturated solution of hydrogen chloride in the anhydrous ethyl acetate to provide the desired amino acid hydrochloride **4c**.

In summary, this synthetic strategy significantly extends the range of stereospecific synthesis of the highly constrained *trans*-2,3-diaryl *Acc* derivatives. By using different oxazolones and aryldiazomethanes, we were able to synthesize different *trans*-2,3-diaryl-1-aminocyclopropanecarboxylic acid derivatives possessing specified configurations.

EXPERIMENTAL SECTION

All reagents were obtained from commercial suppliers. All solvents and liquid reagents were dried and purified before use according to standard procedures. **1a-1d** were prepared according to literature procedures.[7] Melting points were determined on a WRS-IA apparatus and are uncorrected. Microanalyses were performed by Carlo Erba model 1106 analyzer. ^{1}H NMR spectra were recorded on a Varian INOVA 500 MHz spectrometer in $CDCl_3$ or in DMSO-d_6 with TMS as internal standard. Infrared spectra were recorded as KBr pellets on a Nicolet ESP 360 FT-IR spectrometer. GC-MS spectra were recorded under electron impact at 70 eV.

Preparation of 2a-d. General Procedure[1].- To a mixture of **1a-1d** (10 mmol) in toluene (50 mL) was added dropwise a solution of aryldiazomethane[8] (about 25 mmol) in toluene (100 mL) over 1 h. The mixture was stirred at room temperature for another 8-48 h, and the progress of the reaction was monitored by TLC (hexane/ethyl acetate 4/1, v/v). After the reaction was complete, excess of aryldiazomethane was decomposed by addition of a small quantity of silica gel H. The solution was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to provide a yellow solid. The crude products were dissolved in ethyl acetate (50-80 mL) and decolored with charcoal (2-3 g), then recrystallized from ethyl acetate/petroleum ether (1/1) to afford pure **2a-2d** as white solids; the yields vary from 82-90%.

Compound 2a: Yield 82%, mp. 136-137°C, R_f (hexane/ethyl acetate 4/1, v/v) 0.67. IR (KBr): 1809 (C=O), 1627 (C=N), 1598, 1577, 1493, 1449 (Ar-H), 1223 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.9 (m, 2H, ArH), 7.6-7.3 (m, 11H, ArH), 3.85 (d, J = 9.5 Hz, 1H, cyclopropyl), 3.67 (d, J = 9.5 Hz, 1H, cyclopropyl).

Anal. Calcd for $C_{23}H_{15}Cl_2NO_2$: C, 67.66; H, 3.70; N, 3.43. Found: C, 67.59; H, 3.75; N, 3.49

Compound 2b: Yield 82%, mp. 121-122°C, R_f (hexane/ethyl acetate 4/1, v/v) 0.61. IR (KBr): 1804 (C=O), 1630 (C=N), 1600, 1576, 1494, 1449 (Ar-H), 1223 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.94 (m, 2H, ArH), 7.5-7.3 (m, 12H, ArH), 3.90 (d, J = 9.5 Hz, 1H, cyclopropyl), 3.72 (d, J = 9.5 Hz, 1H, cyclopropyl).

Anal. Calcd for $C_{23}H_{16}ClNO_2$: C, 73.90; H, 4.31; N, 3.75. Found: C, 73.74; H, 4.23; N, 3.80

Compound 2c: Yield 85%, mp. 131-133°C, R_f (hexane/ethyl acetate 4/1, v/v) 0.45. IR (KBr): 1806 (C=O), 1629 (C=N), 1577, 1517, 1448 (Ar-H), 1247 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.9 (m, 2H, ArH), 7.5-7.3 (m, 7H, ArH), 6.9 (m, 4H, ArH), 3.88 (d, J = 9.5 Hz, 1H, cyclopropyl), 3.81 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.71 (d, J = 9.5 Hz, 1H, cyclopropyl).

Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 75.25; H, 5.19; N, 3.57

Compound 2d: Yield 90%, mp. 159-162°C, R_f (hexane/ethyl acetate 4/1, v/v) 0.53. IR (KBr): 1806 (C=O), 1628 (C=N), 1610, 1577, 1518, 1449 (Ar-H), 1258 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.9 (m, 2H, ArH), 7.5-7.3 (m, 10H, ArH), 6.9 (m, 2H, ArH) 3.93 (d, J = 9.5 Hz, 1H, cyclopropyl), 3.81 (s, 3H, OMe), 3.74 (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, 77.94; H, 5.27; N, 3.85

The single crystal was grown by the slow evaporation from a saturated solution of **2d** in DMF. X-ray crystallographic analysis was performed with a Siemens P4 four-circle diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073Å). Crystal data of compound **2d**: $C_{24}H_{19}NO_3$, 0.58 x 0.48 x 0.36 mm^3, M_f = 369.40, orthorhombic, space group $P2_12_12_1$, a = 5.387(1) Å, b = 10.049 (2) Å, c = 34.540 (11) Å, V = 1869.8 (8) $Å^3$, Z = 4, Dc = 1.312 Mg m^{-3}, μ (MoKα) = 0.087 mm^{-1}, F (000) = 776. T = 291(2)K; 2557 reflections were independent and unique (R_{int} = 0.0108), I >2σ (I), and 1777 with 1.18° < θ < 27.49° were used for the solution of the structure. R_1 = 0.0371, wR_2 = 0.0771. $\Delta\rho_{max}$ = 0.115e $Å^{-3}$, $\Delta\rho_{min}$ = -0.118e $Å.^{-3}$

Preparation of 3a-d. General Procedure.- 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-d** under stirring; the mixture was stirred for another 30 min (monitored by TLC, hexane/ethyl acetate 2/1, v/v). After the reaction was finished, about 20 mL of methanol was removed *in vacuo,* and then 80 mL of water was added, filtered. The solid was washed with water (3 x 20 mL), recrystallized from methanol to afford a white solid of **3a-d**. The yields nearly are quantitative.

Compound 3a: mp. 175-177°C, R_f (hexane/ethyl acetate 2/1, v/v) 0.52. IR (KBr): 3307 (N-H), 1736 (C=O, ester), 1645 (C=O, amide), 1601, 1579, 1526, 1494, 1438 (Ar-H), 1259 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.6-7.3 (m, 13H, ArH), 6.18 (s, 1H, N-H), 3.68 (d, J = 9.0 Hz, 1H, cyclopropyl), 3.51 (s, 3H, CO_2Me), 3.41 (d, J = 9.0 Hz, 1H, cyclopropyl).

Anal. Calcd for $C_{24}H_{19}Cl_2NO_3$: C, 65.47; H, 4.35; N, 3.18. Found: C, 65.39; H, 4.29; N, 3.25

Compound 3b: mp. 135-136°C, R_f(hexane/ethyl acetate 2/1, v/v) 0.41. IR (KBr): 3438, 3243 (N-H), 1730 (C=O, ester), 1648 (C=O, amide), 1600, 1533, 1495, 1435 (Ar-H), 1264 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.6-7.3 (m, 14H, ArH), 6.12 (s, 1H, N-H), 3.71 (d, J = 9.0 Hz, 1H, cyclopropyl), 3.52 (s, 3H, CO_2Me), 3.45 (d, J = 9.0 Hz, 1H, cyclopropyl).

Anal. Calcd for $C_{24}H_{20}ClNO_3$: C, 71.02; H, 4.97; N, 3.45. Found: C, 70.89; H, 5.06; N, 3.50

Compound 3c: mp. 156-158°C, R_f(hexane/ethyl acetate 2/1, v/v) 0.22. IR (KBr): 3318, 3234 (N-H), 1734 (C=O, ester), 1635 (C=O, amide), 1580, 1516, 1488 (Ar-H), 1255 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.6-7.3(m, 9H, ArH), 6.9 (m , 4H, ArH), 6.16 (s, 1H, N-H), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.67 (d, J = 9.0 Hz, 1H, cyclopropyl), 3.50 (s, 3H, CO_2Me), 3.37 (d, J = 9.0 Hz, 1H, cyclopropyl).

Anal. Calcd for $C_{26}H_{25}NO_5$: C, 72.37; H, 5.84; N, 3.25. Found: C, 72.36; H, 5.76; N, 3.29

Compound 3d: mp. 216-217°C, R_f(hexane/ethyl acetate 2/1, v/v) 0.35. IR (KBr): 3443, 3254 (N-H), 1726 (C=O, ester), 1648 (C=O, amide), 1608, 1578, 1515 (Ar-H), 1240 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.6-7.3m, 12H, ArH), 6.9 (m, 2H, ArH), 6.12 (s, 1H, N-H), 3.81 (s, 3H, OMe), 3.74 (d, J = 9.0 Hz, 1H, cyclopropyl), 3.51 (s, 3H, CO_2Me), 3.45 (d, J = 9.0 Hz, 1H, cyclopropyl).

Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 74.86; H, 5.69; N, 3.48

Preparation of 4a, 4b and 4d. General procedure[1].- To a flask containing glacial acetic acid (25 mL) and 4 M HCl (25 mL) was added 1 mmol of **3a**, **3b** and **3d** under stirring, the reaction mixture was refluxed for 24 hrs. The solvent was evaporated *in vacuo*, the resulting solid was dissolved in 0.5 M HCl (40 mL), and then washed with $CHCl_3$ (3 x 15 mL), the water layer was filtered and the water was removed *in vacuo*. Recrystallization from hot water furnished the products **4a**, **4b**, and **4d** as white solids.

Compound 4a: Yield 68%, mp. 182-184°C, IR (KBr): 3260-2250 (O-H and NH_3^+ stretching), 1728 (C=O), 1495 (NH_3^+, symmetrical bending), 836 (aromatic, 1,4-di-substituted) cm^{-1}. ^1H NMR (DMSO-d^6): δ 7.6-7.4 (m, 2H, ArH), 7.4 (m, 6H, ArH), 3.67 (d, J = 9.0 Hz, 1H, cyclopropyl), 3.45 (d, J = 9.0 Hz, 1H, cyclopropyl).

Anal. Calcd for $C_{16}H_{14}Cl_3NO_2$: C, 53.58; H, 3.93; N, 3.91. Found: C, 53.70; H, 4.00; N, 3.99.

Compound 4b: Yield 56%, mp. 181-183°C, IR (KBr): 3250-2250 (O-H and NH_3^+ stretching), 1724 (C=O), 1507, 1495 (NH_3^+, symmetrical bending), 835 (aromatic, 1,4- disubstituted) cm^{-1}. ^1H NMR (DMSO-d^6): δ 7.5-7.3 (m, 9H, ArH), 3.57 (d, J = 9.0 Hz, 1H, cyclopropyl), 3.28 (d, J = 9.0 Hz, 1H, cyclopropyl).

Anal. Calcd. for $C_{16}H_{15}Cl_2NO_2$: C, 59.28; H, 4.66; N, 4.32. Found: C, 59.26; H, 4.58; N, 4.46

Preparation of 4c.- A saturated solution of hydrogen chloride in anhydrous ethyl acetate (6 mL, prepared by bubbling dry HCl into the anhydrous EtOAc for 30 min) was added to **7** (0.35 g, 1 mmol) and the mixture was stirred at room temperature for 50 min. After removal of the solvent *in vacuo*, 15 mL of water was added and the mixture was set in the refrigerator for 5 h. The precipitated white solid was collected, washed with chloroform (2 x 3 mL) and dried to furnish a white solid **4c** (0.33 g, 96%).

Compound 4c: Yield 67% (based on **3c**), mp. 194-195°C (decompose), IR (KBr): 3200-2250 (O-H and NH_3^+ stretching), 1613 (NH_3^+, anti-symmetrical bending), 1580 (COO^- anti-symmetric stretching), 1517 (NH_3^+, symmetrical bending), 1392 (COO symmetric stretching), 1245(C-O), 843 (aromatic, 1,4-disubstituted) cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.28 (d, J = 8.5 Hz, 2H, ArH), 7.19 (d, J = 8.5 Hz, 2H, ArH), 6.88 (d, J = 8.5 Hz, 2H, ArH), 6.82 (d, J = 8.5 Hz, 2H, ArH), 3.74 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.27 (d, J = 9.0 Hz, 1H, cyclopropyl), 2.82 (d, J = 9.0 Hz, 1H, cyclopropyl).

Anal. Calcd for $C_{18}H_{20}ClNO_4$: C, 61.80; H, 5.76; N, 4.04. Found: C, 61.67; H, 5.66; N, 4.15

Compound 4d: Yield 46%, mp. 178-180°C (decomposition), IR (KBr): 3500-2250 (O-H and NH_3^+ stretching), 1733 (C=O), 1613 (NH_3^+, anti-symmetrical bending), 1583 (COO^- anti-symmetric stretching), 1517 (NH_3^+, symmetrical bending), 1251 (C-O), 834, 700 (aromatic) cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.5-7.4 (m, 5H, ArH), 7.30 (d, J = 8.6 Hz, 2H, ArH), 6.91 (d, J = 8.6 Hz, 2H, ArH), 3.75 (s, 3H, OMe), 3.66 (d, J = 9.0 Hz, 1H, cyclopropyl), 3.34 (d, J = 9.0 Hz, 1H, cyclopropyl).

Anal. Calcd for $C_{16}H_{15}Cl_2NO_2$: C, 53.58; H, 3.93; N, 3.91. Found: C, 53.64; H, 4.00; N, 4.02

Preparation of 4c (*see Scheme 2*).

Preparation of 5.- To a solution of *rac*-**3c** (0.806 g, 1.87 mmol) in THF (5 mL) were added 4-(dimethylamino)pyridine (DMAP, 0.15 g, 1.23 mmol) and di-*tert*-butyl-dicarbonate (0.6 g, 2.74 mmol). The mixture was stirred at room temperature for 48 h. At this time, another portion of di-*tert*-butyl-dicarbonate (0.2 g, 0.92 mmol) was added and the mixture was stirred for another 24 h. The solvent was removed *in vacuo*, the resultant residue was purified by column chromatography (eluent: hexane/ethyl acetate 4/1) to afford colorless crystals **5** (0.81 g, 81%), mp. 141-142°C, R_f (hexane/ethyl acetate 4/1, v/v) 0.36. IR (KBr): 1735 (C=O, ester), 1680 (C=O, amide) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.6-6.9 (m, 13H, ArH), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.70 (d, J = 9.0 Hz, 1H, cyclopropyl), 3.43 (s, 3H, CO_2Me), 3.40 (d, J = 9.0 Hz, 1H, cyclopropyl), 0.95 (s, 9H).

Anal. Calcd for $C_{31}H_{33}NO_7$: C, 70.04; H, 6.26; N, 2.63. Found: C, 69.96; H, 6.36; N, 2.58

Preparation of 6.- To a solution of **5** (0.7 g, 1.32 mmol) in THF-MeOH (10 mL, 1/1) was added hydrazine monohydrate (0.2 g, 4 mmol) under stirring, the mixture was stirred for 60 h at room temperature. The solvent was removed *in vacuo*, then a mixture of hexane and diethyl ether (15 mL, 2/1) was added. Shaking, then standing, white solid precipitated after 20 min later, filtered, the solid was washed with hexane/ether (25 mL, 2/1). The combined filtrate was concentrated *in vacuo*, the residue was purified by column chromatography (hexane/ethyl acetate 2/1) to afford a white solid **6** (0.51 g, 91%), mp. 112-113°C, R_f (hexane/ethyl acetate 4/1, v/v) 0.23. IR (KBr): 3360 (N-H), 1720, 1710 (C=O, ester) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.5-7.0 (m, 8H, ArH), 4.73 (bs, 1H, N-H), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.50 (d, J = 9.0 Hz, 1H, cyclopropyl), 3.47 (s, 3H, CO_2Me), 3.20 (d, J = 9.0 Hz, 1H, cyclopropyl), 1.38 (s, 9H).

Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.56; H, 6.69; N, 3.29

Preparation of 7.- To a 50 mL of flask was added **6** (0.5 g, 1.2 mmol) and 2 N solution of KOH in methanol (10 mL), the mixture was stirred for 80 h at room temperature. After evaporation of methanol, the remaining residue was dissolved in water (10 mL). Neutralization with 5% aqueous $KHSO_4$ to pH 6, resulted in the precipitation of the desired product, after standing 3 h, the white solid was collected, washed with water (3 x 5 mL) and dried to afford a white solid **7** (0.47 g, 95%), mp. 173-174°C. IR (KBr): 3400-2350 (O-H and N-H), 1708, 1650 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.5-7.0 (m, 8H, ArH), 4.77 (bs, 1H, N-H), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.67 (d, J = 9.0 Hz, 1H, cyclopropyl), 3.22 (d, J = 9.0 Hz, 1H, cyclopropyl), 1.38 (s, 9H).

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.98; H, 6.43; N, 3.32

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