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A Straightforward Synthesis of (-)-(*1S,2R*)-Allonorcoronamic Acid Using *D*-Mannitol as the Chiral Source

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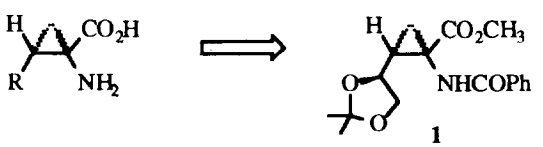
Abstract: *(-)-(1S,2R)-Allonorcoronamic acid was synthesized in its enantiomerically pure form from methyl (1S,2R)-1-benzamido-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropanecarboxylate, which is easily obtained by methylene insertion on the chiral azlactone derived from 1,2-O-isopropylidene-D-glyceraldehyde .*

1-Aminocyclopropanecarboxylic acid (ACC) is an unusual amino acid found in the extracts of pears and other fruits[1] which has been shown to be an intermediate in the biosynthesis of ethylene, a plant growth regulator, in higher plants,[2] and as a result active research directed towards the synthesis of this compound and its alkylated analogs has been developed during recent years.[3] This interest stems from their potential to act as plant growth and fruit ripening[4] regulators.

Enantioenriched 2,3-methanoamino acids have also been extensively used as mechanistic probes and enzyme inhibitors[5] as well as in the design and synthesis of conformationally constrained peptidomimetics.[6] Peptide analogs from 2,3-methanoamino acids are relatively rigid and capable of capturing nucleophiles and electrophiles, which entails important changes in their reactivity and conformation. In this way, incorporation of these methanologs 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.[7] Consequently, efficient asymmetric syntheses of these compounds are both timely and important.



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We have recently reported[8,9] a simple and convenient route to methyl *(1S,2R)*-1-benzamido-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropanecarboxylate **1** from the easily accessible *(Z)*-azlactone derived from

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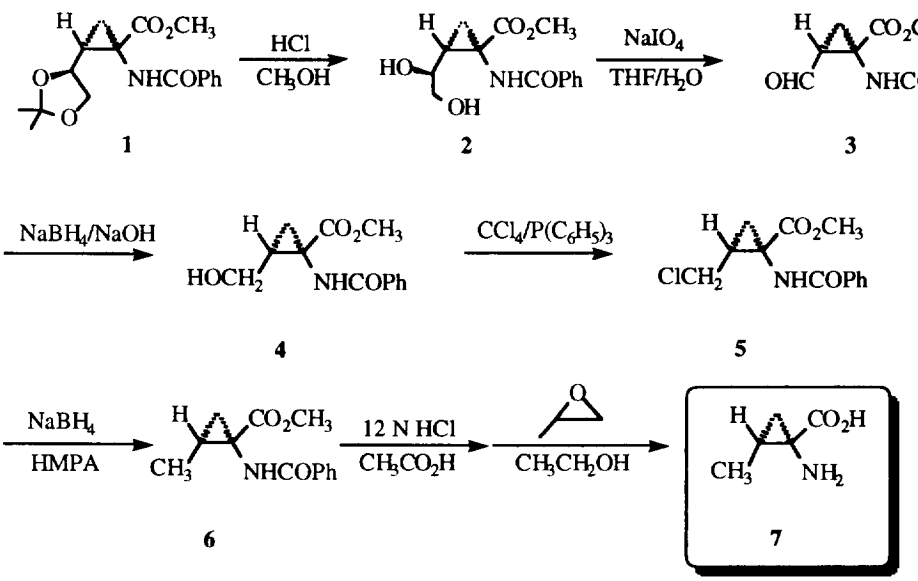
"in memoriam" to Prof. F. Serratosa

1,2-O-isopropylidene-*D*-glyceraldehyde, which can be used as a useful chiral intermediate in the synthesis of enantiomerically pure 2,3-methanoamino acids, as it has been shown in the preparation of *(1S,2R)*-allocoronamic acid.[10]

In this paper we wish to report the conversion of the intermediate **1** into *(1S,2R)*-allonorcoronamic acid, a substrate and the strongest known competitive inhibitor of the ethylene-forming enzyme in some plants.[5d] To develop an efficient route to the target molecule we first converted compound **1** into the corresponding 2-formylderivative **3** by hydrolysis with 3 N hydrochloric acid in methanol followed by oxidative cleavage by treatment with a slight excess of sodium periodate at room temperature using tetrahydrofuran as solvent, as we have previously described.[10]

The next step involved the transformation of the formyl group into a methyl group, which in our case has not been trivial since the reduction of the tosylhydrazone derived from compound **3** was not achieved under any tested conditions, i.e. treatment with sodium borohydride,[11] sodium triacetoxyborohydride,[12] sodium cyanoborohydride,[13] and bis(benzoyloxy)borane[14] according to literature described procedures. We tested next the reduction with sodium borohydride of the more easily reducible[15] 2,4,6-triisopropylbenzenesulphonylhydrazone derived from the aldehyde **3**, but unfortunately the reaction also failed.



Scheme 1

Finally, we developed an alternative three-step route that allowed us to convert the 2-formyl derivative into the 2-methylderivative in 90 % overall yield. Compound **3** was reduced to methyl 1-benzamido-2-hydroxymethylcyclopropanecarboxylate **4** in 96 % yield, by reaction with sodium borohydride in an alkaline medium. The corresponding chloro derivative was then easily obtained in quantitative yield by treatment of the alcohol with carbon tetrachloride in the presence of triphenylphosphine.

The following step of the synthesis was the reduction of the halide in the presence of the cyclopropane unit, which can be troublesome since substituted cyclopropanes can be easily cleaved under catalytic

hydrogenation conditions. In our experiment, the catalytic procedure using a palladised barium sulphate catalyst afforded the desired methyl 1-benzamido-2-methyl-cyclopropanecarboxylate **6** in 85 % yield. Alternatively, reduction of the halide with sodium borohydride in HMPA cleanly afforded methyl 1-benzamido-2-methyl-cyclopropanecarboxylate **6** in higher yield, 95 %.

Hydrolysis of compound **6** with 12 N hydrochloric acid in acetic acid under reflux conditions gave enantiomerically pure *(1S,2R)*-allonorcoronamic acid hydrochloride. From this compound, the free amino acid **7** was obtained in nearly quantitative yield by refluxing the salt in ethanol with excess propylene oxide followed by purification by eluting an aqueous solution of the free amino acid through a Sep-pak C_{18} cartridge. The specific rotation of **7** is in agreement with the values previously reported[16] and confirms the structure of **7** as well as its enantiomeric purity.

Further studies on the asymmetric synthesis of enantiomerically pure 2-substituted-1-aminocyclopropanecarboxylic acids from this easily available chiral synthon are in progress and will be published in due course.

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EXPERIMENTAL

Apparatus: ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Unity 300 MHz spectrometer in deuteriochloroform, deuterated dimethylsulphoxide or deuterium oxide using the solvent signal as the internal standard, chemical shifts are expressed in ppm. IR spectra were recorded on a Perkin-Elmer 1600 FTIR infrared spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241-C polarimeter at 25°C. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Elemental analyses were made on a Perkin-Elmer 2400 C, H, N, S elemental analyser.

Chemicals: All the reactions were carried out under argon with magnetic stirring. Solvents were dried prior to use. Methyl *(1S,2R)*-1-benzamido-2-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropanecarboxylate **1** was prepared following the method described in the literature.[10] TLC was performed on Merck precoated silica-gel plates which were visualised using UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Medium Pressure chromatography was performed using 230-400 mesh (Merck) silica-gel. Sep-Pak C_{18} (reverse phase) cartridges were purchased from Waters.

Methyl *(1S,2R)*-1-benzamido-2-[*(S)*-1,2-dihydroxyethyl]cyclopropanecarboxylate **2**

3 N Hydrochloric acid (1.2 ml) was added to a solution of methyl *(1S,2R)*-1-benzamido-2-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropanecarboxylate **3** (3.2 g, 10 mmol) in methanol (150 ml) at room temperature and the mixture was stirred for 24 h. After completion, the solution was concentrated *in vacuo* to afford methyl *(1S,2R)*-1-benzamido-2-[*(S)*-1,2-dihydroxyethyl]cyclopropanecarboxylate **2** as a white solid in nearly quantitative yield.

M.p. 151 °C; $[\alpha]_D$ = - 36.8 (c = 0.25 in CH_3OH); IR 3450, 3350, 1717, 1653 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.24 (dd, 1H, J = 7.6 Hz, J = - 4.8 Hz), 1.54 (dd, 1H, J = 9.6 Hz, J = - 4.8 Hz), 1.73-1.82 (m, 1H), 3.18-3.26 (m, 1H), 3.44-3.48 (m, 2H), 3.57 (s, 3H), 4.76 (d, 1H, J = 5.3 Hz), 5.00 (t, 1H, J = 4.5 Hz),

7.42-7.50 (m, 2H), 7.50-7.58 (m, 1H), 7.78-7.82 (m, 2H), 8.76 (brs, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.2, 30.5, 37.4, 52.2, 65.9, 70.0, 127.2, 128.4, 131.6, 133.8, 167.2, 172.3. Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14 N, 5.01. Found C, 60.17; H, 6.23; N, 4.87.

Methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate **3**

A suspension of sodium periodate (2.32 g, 10.8 mmol) in water (4 ml) was added dropwise to a stirred solution of methyl *(1S,2R)*-1-benzamido-2-[*(S)*-1,2-dihydroxyethyl]cyclopropanecarboxylate **2** (2.8 g, 10 mmol) in THF (200 ml). The mixture was then stirred at room temperature for 6 h and the resultant suspension was filtered. The organic solvent was evaporated and the residue was dissolved in dichloromethane (100 ml), washed with water, dried with anhydrous magnesium sulphate and concentrated *in vacuo* to afford a yellow oil. Purification of the residue by flash chromatography on a silica gel column (eluent ethyl acetate/dichloromethane 6/4) afforded 2 g (85 % yield) of pure methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate **3** as a pale yellow solid.

M.p.105-108 °C; $[\alpha]_D$ = - 158 (c = 1 in $CHCl_3$); IR 3326, 1703, 1649 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.91 (dd, 1H, J = 8.9 Hz, J = - 5.4 Hz), 1.97 (dd, 1H, J = 7.2 Hz, J = - 5.4 Hz), 3.15 (m, 1H, J = 8.9 Hz, J = 7.2 Hz, J = 2.7 Hz), 3.73 (s, 3H), 6.74 (brs, 1H), 7.38-7.44 (m, 2H), 7.47-7.53 (m, 1H), 7.71-7.74 (m, 2H), 9.58 (d, 1H, J = 2.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.3, 35.7, 41.4, 53.2, 127.1, 128.6, 132.1, 133.2, 168.8, 170.0, 194.9. Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found C, 63.01; H, 5.42; N, 5.77.

Methyl *(1S,2R)*-1-benzamido-2-hydroxymethylcyclopropanecarboxylate **4**

A solution of sodium borohydride (28 mg, 0.7 mmol) in 0.2 M sodium hydroxide (0.4 ml) was added dropwise to a solution of methyl *(1S,2R)*-1-benzamido-2-formylcyclopropanecarboxylate **3** (494 mg, 2 mmol) in methanol (40 ml) and the solution was then stirred at room temperature for 30 min. The solvent was evaporated and the residue was dissolved in dichloromethane (60 ml), washed with water, dried with anhydrous magnesium sulphate and concentrated *in vacuo* to afford a pale yellow oil which is used in the following step without further work-up. Purification of the residue by flash chromatography on a silica gel column (eluent ethyl acetate) afforded 480 mg (96 % yield) of pure methyl *(1S,2R)*-1-benzamido-2-hydroxymethylcyclopropanecarboxylate **4** as a colourless oil.

Oil; $[\alpha]_D$ = - 58.4 (c = 1 in $CHCl_3$); IR 3322, 1731, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (dd, 1H, J = 7.8 Hz, J = - 5.1 Hz), 1.69 (dd, 1H, J = 9.7 Hz, J = - 5.1 Hz), 2.42 (m, 1H, J = 9.7 Hz, J = 7.8 Hz, J = 3.4 Hz, J = 10.3 Hz), 3.12 (ddd, 1H, J = 1.6 Hz, J = 10.3 Hz, J = - 12.4 Hz), 3.54 (dd, 1H, J = 1.6 Hz, J = 10.8 Hz), 3.69 (s, 3H), 4.02 (ddd, 1H, J = 3.4 Hz, J = 10.8 Hz, J = - 12.4 Hz), 6.72 (brs, 1H), 7.38-7.48 (m, 2H), 7.50-7.58 (m, 1H), 7.78-7.82 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 30.8, 37.9, 52.7, 61.5, 127.3, 128.6, 132.2, 133.1, 170.7, 172.0. Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found C, 62.81; H, 5.92; N, 5.77.

Methyl *(1S,2R)*-1-benzamido-2-chloromethylcyclopropanecarboxylate **5**

A solution of methyl *(1S,2R)*-1-benzamido-2-hydroxymethylcyclopropanecarboxylate **4** (498 mg, 2 mmol) and triphenylphosphine (786 mg, 3 mmol) in carbon tetrachloride (50 ml) was stirred under reflux conditions for 32 h. The solvent was evaporated and the residue was purified by flash chromatography on a silica gel column

(eluent hexane/ethyl acetate 3/7) to afford 520 mg (98 % yield) of methyl *(1S,2R)*-1-benzamido-2-chloromethylcyclopropanecarboxylate **5** as a white solid.

M.p.123 °C; $[\alpha]_D$ = + 93 (c = 1 in $CHCl_3$); IR 3280, 1731, 1653 cm^{-1}; H NMR ($CDCl_3$, 300 MHz) δ 1.35 (dd, 1H, J = 7.2 Hz, J = - 5.7 Hz), 2.03 (dd, 1H, J = 9.3 Hz, J = - 5.7 Hz), 2.28 (m, 1H, J = 9.9 Hz, J = 6.3 Hz, J = 7.2 Hz, J = 9.3 Hz), 3.48 (dd, 1H, J = - 11.7 Hz, J = 9.9 Hz), 3.69 (s, 3H), 3.89 (dd, 1H, J = - 11.7 Hz, J = 6.3 Hz), 6.91 (brs, 1H), 7.40-7.48 (m, 2H), 7.50-7.56 (m, 1H), 7.78-7.82 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.7, 29.2, 38.5, 44.7, 52.8, 127.1, 128.7, 132.1, 133.5, 168.8, 171.7. Anal. Calcd. for $C_{13}H_{14}ClNO_3$: C, 58.33; H, 5.27; N, 5.23; Cl, 13.24. Found C, 58.45; H, 5.44; N, 5.37; Cl, 13.01.

Methyl *(1S,2R)*-1-benzamido-2-methylcyclopropanecarboxylate **6**

METHOD A: A solution of methyl *(1S,2R)*-1-benzamido-2-chloromethylcyclopropanecarboxylate **5** (267 mg, 1 mmol) in methanol (10 ml) was shaken in a hydrogen atmosphere at 30 °C and in the presence of 5 % palladised barium sulphate (600 mg) for 36 h. After completion, the reaction mixture was filtered and evaporated in *vacuo* . Purification of the residue by flash chromatography on a silica gel column (eluent hexane/ethyl acetate 1/1) afforded 200 mg (86 % yield) of pure methyl *(1S,2R)*-1-benzamido-2-methylcyclopropanecarboxylate **6** as a white solid.

METHOD B: A solution of methyl *(1S,2R)*-1-benzamido-2-chloromethylcyclopropanecarboxylate **5** (267 mg, 1 mmol) and sodium borohydride (114 mg, 3 mmol) in HMPA (10 ml) was heated for 6 h at 70 °C, after completion, the solution was diluted with water and extracted with ethyl acetate (3 x 10 ml). The organic phases were combined and washed with water (3 x 10 ml), dried over anhydrous magnesium sulphate, filtered, and concentrated in *vacuo*. Purification of the residue by flash chromatography on a silica gel column (eluent hexane/ethyl acetate 1/1) afforded 220 mg (95 % yield) of pure methyl *(1S,2R)*-1-benzamido-2-methylcyclopropanecarboxylate **6** as a white solid.

M.p.145-146 °C; $[\alpha]_D$ = - 20.9 (c = 0.70 in $CHCl_3$); IR 3318, 1726, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (dd, 1H, J = 7.2 Hz, J = - 4.9 Hz), 1.21 (d, 3H, J = 6.3 Hz), 1.79 (dd, 1H, J = 9.6 Hz, J = - 4.9 Hz), 1.84-1.98 (m, 1H), 3.67 (s, 3H), 6.47 (brs, 1H), 7.38-7.46 (m, 2H), 7.46-7.54 (m, 1H), 7.74-7.82 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.2, 23.1, 24.0, 37.8, 52.5, 127.0, 128.6, 131.8, 134.1, 168.7, 173.0. Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found C, 65.12; H, 6.42; N, 5.83.

(1S,2R)-Allonorcoronamic acid **7**

12 N Hydrochloric acid (10 ml) was added to a solution of compound **6** (186 mg, 0.8 mmol) in glacial acetic acid (10 ml) and the mixture was refluxed for 24 h. The solution was extracted with chloroform and the aqueous layer was evaporated *in vacuo*. Anhydrous ethanol (10 ml) and a large excess of propylene oxide (4 ml) was added to the crystalline residue was added 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. After removal of water allonorcoronamic acid was obtained as a white solid in nearly quantitative yield.

M.p. 215 °C dec. ; $[\alpha]_D$ = - 69.7 (c = 0.38 in H_2O) (Lit.,[16] $[\alpha]_D$ = - 69 (c = 0.3 in H_2O); ^1H NMR (D_2O, 300 MHz) δ 0.77 (dd, 1H, J = 7.2 Hz, J = - 6.3 Hz), 1.08 (d, 3H, J = 6.6 Hz), 1.32 (dd, 1H J = 9.6 Hz, J = - 6.3 Hz), 1.48-1.58 (m, 2H). ^{13}C NMR (D_2O-$CO(CD_3)_2$, 75 MHz) δ 11.5, 18.1, 18.9, 39.7, 175.8.

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