Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 1, pp. 177-182, 1995

0957-4166/95 $9.50+0.00

0957-4166(94)00373-4

A Simple Synthesis of (-)-*(1S,2R)*-Allocoronamic Acid in its Enantiomerically Pure Form

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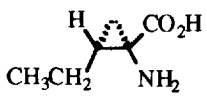
Abstract: *(-)-(1S,2R)-Allocoronamic acid was synthesized in its enantiomerically pure form by starting from the chiral azlactone derived from 1,2-O-isopropylidene-D-glyceraldehyde in an overall yield of 37 %.*

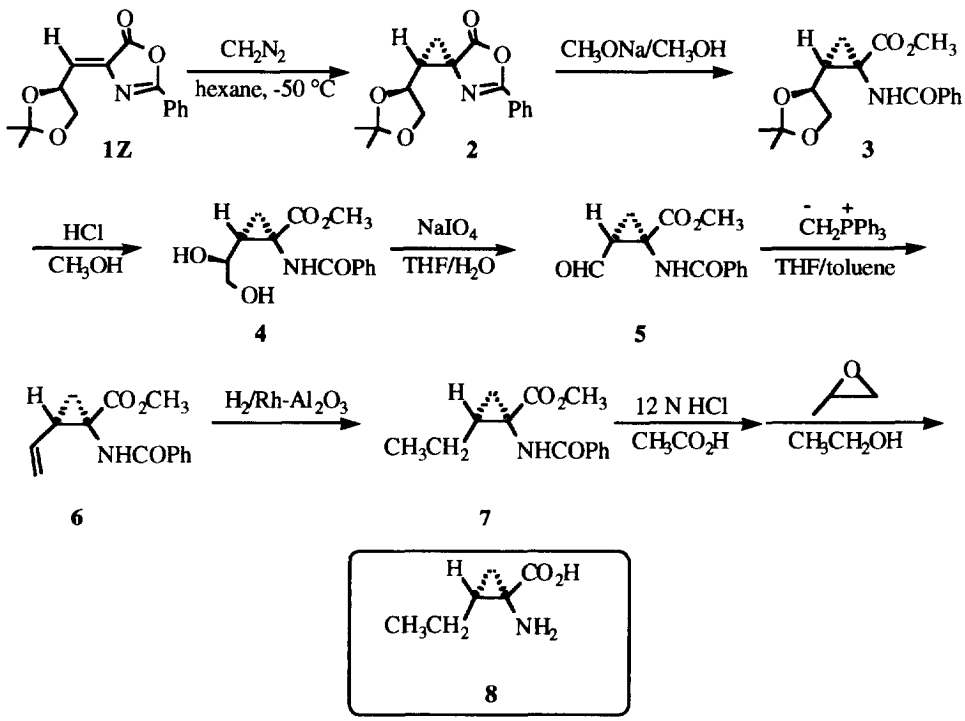
Since the first report[1] on the isolation and identification of 1-aminocyclopropanecarboxylic acid (ACC) as an intermediate in the biosynthesis of ethylene in higher plants,[2] the synthesis of this compound and its derivatives has attracted special interest.[3] Of particular interest is the development of substrates that may induce an inhibition of the ethylene production, thus allowing potential control of the ripening process. In this context, extensive efforts have been directed towards the synthesis of ACC analogues monosubstituted in the cyclopropane ring in order to conserve the α-amino acid moiety. Among 2-substituted cyclopropanecarboxylic acids, allocoronamic acid is one of the amino acids that can be processed by plant tissues and promises the possibility of the control of enzymatic processes for plant growth and fruit ripening.[4]



allocoronamic acid

Although several approaches to the preparation of allocoronamic acid have been described, most of them have been the result of a resolution of racemic mixtures,[5] and only a few asymmetric syntheses of this compound have been published.[6] Very recently Ortuño *et al.*[7] have described a highly efficient synthesis of an intermediate in the synthesis of allocoronamic acid based on asymmetric cyclopropanation of a chiral α,β-didehydroamino acid derivative obtained from *D*-mannitol. We now report a new enantioselective synthesis of (-)-*(1S,2R)*-allocoronamic acid based on the asymmetric cyclopropanation of the chiral *(Z)*-azlactone derived from 1,2-O-isopropylidene-*D*-glyceraldehyde.

As we have communicated previously,[8] the reaction of the *Z* isomer of the chiral azlactone derived from 1,2-O-isopropylidene-*D*-glyceraldehyde **1Z** with diazomethane afforded a separable mixture of spirocompounds. *Cis/trans* selectivity and diastereofacial selectivity was dependent on the solvent and reaction temperature used, and the best results were obtained in hexane at -50 °C. In these conditions the major compound **2** was obtained with a *cis/trans* ratio of 83/17 and a *cis* diastereofacial selectivity of 88/12. From the reaction mixture the diastereomerically pure compound **2** was isolated in 73 % yield by Medium Pressure Chromatography eluting with hexane/ethyl acetate : 4/1. This compound is a valuable chiral synthon for the synthesis of *(1S,2R)*-allocoronamic acid (Scheme 1).



Scheme 1

Methanolysis of compound **2** with sodium methoxide in methanol at room temperature for 0.5 h afforded compound **3** in nearly quantitative yield. A single crystal X-ray[7] analysis of this compound showed a *(1S,2R)* configuration. Treatment of **3** with 3 N hydrochloric acid in methanol afforded compound **4** also in nearly quantitative yield. The 1,2-diol **4** was subjected to oxidative cleavage by treatment with a slight excess of sodium periodate at room temperature using tetrahydrofuran as solvent, and the expected formyl derivative **5** was obtained in 85 % yield. Aldehyde **5** was converted to methyl 1-benzamido-2-vinylcyclopropanecarboxylate **6** in 70 % yield, by methylenation with triphenylphosphonium methylide in toluene/tetrahydrofuran from 0 °C to room temperature.

The next step of the synthesis involved the reduction of the vinyl substituent 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, hydrogenation of compound **6** in the presence of a catalytic amount of 10 % palladium on activated carbon afforded the desired methyl 1-benzamido-2-ethyl-cyclopropanecarboxylate **7** as the major product, although it was contaminated with 20 % of easily removable hydrogenolysis by-products. As an alternative, diimine generated *in situ* from potassium azadicarboxylate and acetic acid was employed as the reducing agent, but after 24 h only unreacted starting material was recovered. We therefore investigated other hydrogenation catalysts and temperature conditions, and the best results were obtained using 5 % rhodium on alumina at room temperature; with this catalyst we obtained the desired compound contaminated with only 5 % of hydrogenolysis by-products. Analytically pure compound **7** was easily isolated in 87 % yield by flash chromatography eluting with hexane/ethyl acetate : 3/2 and its hydrolysis with 12 N hydrochloric acid in acetic acid under reflux conditions gave enantiomerically pure *(1S,2R)*-allocoronamic acid hydrochloride. From this compound, the free amino acid **8** 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 **8** is in agreement with the values previously reported[6] and confirms the structure of **8** 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.

Acknowledgement: This work was supported by the Dirección General de Investigación Científica y Técnica, project number PB91-0696. Ana I. Jiménez would like to express her gratitude to the Diputación General de Aragón for a grant.

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 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 Ar with magnetic stirring. Solvents were dried prior to use. *N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine, potassium bis(trimethylsilyl)amide (0.5 M in toluene), methyltriphenylphosphonium bromide and 5 % rhodium on alumina were purchased from Aldrich Chemical Co. Oxazolone **1Z** was prepared following the method described in the literature.[9] 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.

(1S,2R)- 2[*(S)*-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-spiro-{4'[2'-phenyl-5'(4'H)-oxazolone]}cyclopropane **2.**
CAUTION! Diazomethane is a very harmful and hazardous reagent and must be handled with caution. A solution of diazomethane (22 mmol) in hexane (generated from *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine) was added to a solution of *Z*-2-phenyl-4-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4H)-oxazolone **1Z** (4 g, 15 mmol) in hexane (300 ml) in a stoppered flask, which was protected from light, at - 50 °C for about 10 min until completion (TLC, hexane/ethyl acetate = 9:1). The solution was treated with anhydrous $CaCl_2$ to destroy the excess diazomethane and after filtration was concentrated *in vacuo* to afford a mixture of cycloaddition products in nearly quantitative yield. After medium pressure chromatography on silica gel using hexane-ethyl acetate 8/2 *(1S,2R)*-2-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-yl]-1-spiro-{4'[2'-phenyl-5'(4'H)-oxazolone]}cyclo_ propane **2** was isolated in 73 % yield.
M.p. 132 °C; $[\alpha]_D$ = - 15.8 (c = 1 in $CHCl_3$); IR 1816, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 3H), 1.45 (s, 3H), 1.98 (dd, 1H, J = 9.5 Hz, J = - 4.1 Hz), 2.01 (dd, 1H, J = 8.7 Hz, J = - 4.1 Hz), 2.19 (m, 1H, J = 9.5 Hz, J = 9.4 Hz, J = 8.7 Hz), 3.61 (dd, 1H, J = 8.2 Hz, J = 6.4 Hz), 4.04 (dd, 1H, J = 8.2 Hz, J = 6.1 Hz), 4.17 (m, 1H, J = 9.4 Hz, J = 6.4 Hz, J = 6.1 Hz), 7.42-7.48 (m, 2H), 7.52-7.58 (m, 1H), 7.92-7.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.4, 25.7, 26.8, 34.3, 50.8, 69.0, 76.3, 109.6, 126.0, 127.4, 128.8, 132.6, 162.4, 177.5. Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found C, 66.98; H, 5.82; N, 4.96.

Methyl *(1S,2R)*-1-benzamido-2-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropanecarboxylate **3**
A suspension of the spirooxazolone **2** (2.9 g, 10 mmol) in a solution of sodium methoxide (0.02 g) in absolute methanol (80 ml) was stirred at room temperature for 30 min. After completion, the solution was concentrated *in vacuo* and the residue was dissolved in chloroform, washed with water, dried with anhydrous magnesium sulphate and concentrated *in vacuo* to afford methyl *(1S,2R)*-1-benzamido-2-[*(S)*-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropanecarboxylate **3** in nearly quantitative yield.
M.p. 153 °C; $[\alpha]_D$ = - 80.3 (c = 1 in $CHCl_3$); IR 3340, 1732, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (s, 3H), 1.31 (dd, 1H, J = 7.7 Hz, J = - 5.3 Hz), 1.43 (s, 3H), 1.73 (dd, 1H, J = 9.6 Hz, J = - 5.3 Hz), 2.18 (m, 1H, J = 9.6 Hz, J = 7.7 Hz, J = 7.4 Hz), 3.70 (s, 3H), 3.86 (m, 1H, J = 7.7 Hz, J = 6.2 Hz, J = 6.1 Hz), 3.94 (dd, 1H, J = 8.5 Hz, J = 6.1 Hz), 4.08 (dd, 1H, J = 8.5 Hz, J = 6.2 Hz), 6.56 (brs, 1H), 7.40-7.46 (m, 2H), 7.48-7.56 (m, 1H), 7.74-7.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.9, 25.5, 26.8, 30.0, 37.9, 52.8, 69.8, 75.2, 109.0, 127.1, 128.7, 132.0, 133.7, 168.6, 171.8. Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.38. Found C, 64.02; H, 6.71; N, 4.29.

Methyl *(1S,2R)*-1-benzamido-2-[*(S)*-1,2-dihydroxyethyl]cyclopropanecarboxylate **4**
3 N Hydrochloric acid (12 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 **4** 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}; ^1H 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 **5**

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 **4** (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 **5** 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,2S)*-1-benzamido-2-vinylcyclopropanecarboxylate **6**

Methyltriphenylphosphonium bromide (1.1 g, 3 mmol), previously dried in a vacuum oven overnight, (5 mm Hg 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 at room temperature by syringe. 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 **5** (0.5 g, 2 mmol) in dry THF (10 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 (40 ml), washed with water, dried with anhydrous magnesium sulphate and concentrated *in vacuo* to afford a brown oil. Purification of the residue by flash chromatography on a silica gel column (eluent hexane/ethyl acetate 6/4) afforded 340 mg (70 % yield) of methyl *(1S,2S)*-1-benzamido-2-vinylcyclopropanecarboxylate **6** as a white solid.

M.p. 125 °C; $[\alpha]_D$ = - 1.44 (c = 1.25 in $CHCl_3$); IR 3290, 1721, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (dd, 1H, J = 7.5 Hz, J = - 5.6 Hz), 2.05 (dd, 1H, J = 9.3 Hz, J = - 5.6 Hz), 2.43-2.52 (m, 1H, J = 9.3 Hz, J = 7.8 Hz, J = 7.5 Hz), 3.69 (s, 3H), 5.21 (dd, 1H, J = 10.2 Hz, J = - 1.5 Hz), 5.29 (dd, 1H, J = 17.4 Hz, J = - 1.5 Hz), 5.59 (m, 1H, J = 17.4 Hz, J = 10.2 Hz, J = 7.8 Hz), 6.49 (brs, 1H), 7.38-7.44 (m, 2H), 7.47-7.53 (m, 1H), 7.74-7.77 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7, 31.2, 38.8, 52.7, 118.9, 127.0, 128.6, 131.9, 133.2, 133.9, 168.4, 172.0. Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found C, 68.54; H, 6.24; N, 5.79.

Methyl *(1S,2R)*-1-benzamido-2-ethylcyclopropanecarboxylate **7**

A solution of methyl *(1S,2S)*-1-benzamido-2-vinylcyclopropanecarboxylate **6** (245 mg, 1 mmol) in methanol (10 ml) was hydrogenated at atmospheric pressure in the presence of 5 % rhodium on alumina (20 mg) for 3 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 6/4) afforded 215 mg (87 % yield) of methyl *(1S,2R)*-1-benzamido-2-ethylcyclopropanecarboxylate **7** as a white solid.
M.p. 119 °C; $[\alpha]_D$ = - 1.42 (c = 3.5 in $CHCl_3$); IR 3060, 1720, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94-1.02 (m, 1H), 1.05 (t, 3H, J = 7.2 Hz), 1.23-1.36 (m, 1H), 1.65-1.76 (m, 1H), 1.77-1.84 (m, 2H), 3.67 (s, 3H), 6.44 (brs, 1H), 7.40-7.45 (m, 2H), 7.48-7.54 (m, 1H), 7.74-7.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 21.7, 22.9, 30.2, 37.9, 52.5, 127.0, 128.6, 131.8, 134.2, 168.7, 173.0. Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found C, 67.92; H, 6.81; N, 5.53.

(1S,2R)-Allocoronamic acid **8**
To a solution of compound **7** (200 mg, 0.8 mmol) in glacial acetic acid (10 ml) was added 12 N HCl (10 ml) and the mixture was refluxed for 16 h. The solution was extracted with chloroform and the aqueous layer was evaporated *in vacuo*. To the crystalline residue was added anhydrous ethanol (10 ml) and a large excess of propylene oxide (4 ml) 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 which, after removal of water, gave allocoronamic acid as a white solid in nearly quantitative yield.
M.p. 185-187 °C dec.(Lit ,[6d] m.p. 183 dec) ; $[\alpha]_D$ = - 60 (c = 0.4 in H_2O) (Lit.,[6b] $[\alpha]_D$ = - 52 (c = 1.83 in H_2O); ^1H NMR (D_2O, 300 MHz) δ 0.73-0.78 (m, 1H), 0.89 (t, 3H, J = 7.2 Hz), 1.15-1.32 (m, 2H), 1.41-1.49 (m, 2H). ^{13}C NMR (D_2O-$CO(CD_3)_2$, 75 MHz) δ 12.8, 17.7, 20.6, 25.7, 39.8, 175.9.

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(*Received in UK* 20 *September* 1994)