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Stereoselective Synthesis of Enantiopure Cyclopropane Didehydroamino Acid Derivatives: (-)-(Z)-2-Benzyloxycarbonylamino-4,5-cyclopropane-2-hexenodioic Acid Dimethyl Ester

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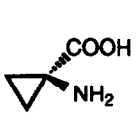
Abstract: *The title amino acid derivative has been synthesized stereoselectively in 40% overall yield from 5-tert-butyldiphenylsilyloxymethyl-2(5H)-furanone used as a chiral precursor.*

Cyclopropane amino acids and derivatives are products of increasing interest due to their manifold biological activities and the variety of known structures for natural or designed compounds. The most classical cyclopropane amino acids are included in the ACC family, among them the parent ACC, **1**, and (+)-*allo*-coronamic acid, **2**, with important roles in the secondary metabolism of plants.[1]



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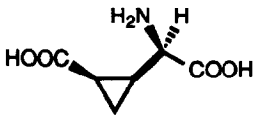

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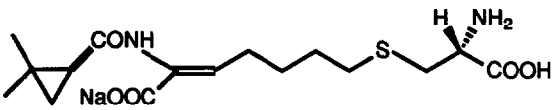

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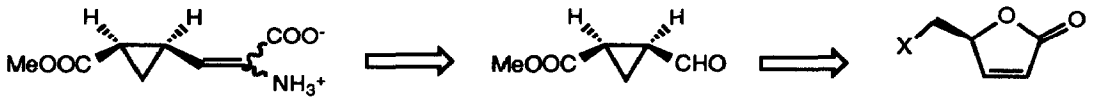
There is another class of compound that contains the amino and the carboxyl groups not directly linked to the cyclopropane ring. Such is the case of molecule **3**, considered as a cyclopropyl analog of D-glutamic acid (D-CGA), being a potent and selective NMDA receptor ligand.[2] On the other hand, α,β-didehydro amino acids possess a double bond conjugated to the carbonyl and are susceptible to nucleophilic additions or cycloaddition

reactions.[1,3] Finally, there are molecules such as cilastatin, **4**, a known reversible enzyme inhibitor, in which a conjugated double bond and a cyclopropane unit are joined.[4]

In our research program towards the asymmetric synthesis of unusual amino acids[5] we have envisaged target molecule **5a** as a simple model of cyclopropane didehydroamino acid (Scheme 1). Retrosynthetic analysis relates this compound with cyclopropyl aldehyde **6** as a key intermediate, in which the absolute configuration of the two stereogenic centers has been controlled. The geometry of the double bond will depend on the stereoselectivity involved in a Wittig-type condensation allowing the introduction of the conjugate amino acid function.



5a **6** X = OH, **7**

OTs, **7a**

I, **7b**

Scheme 1

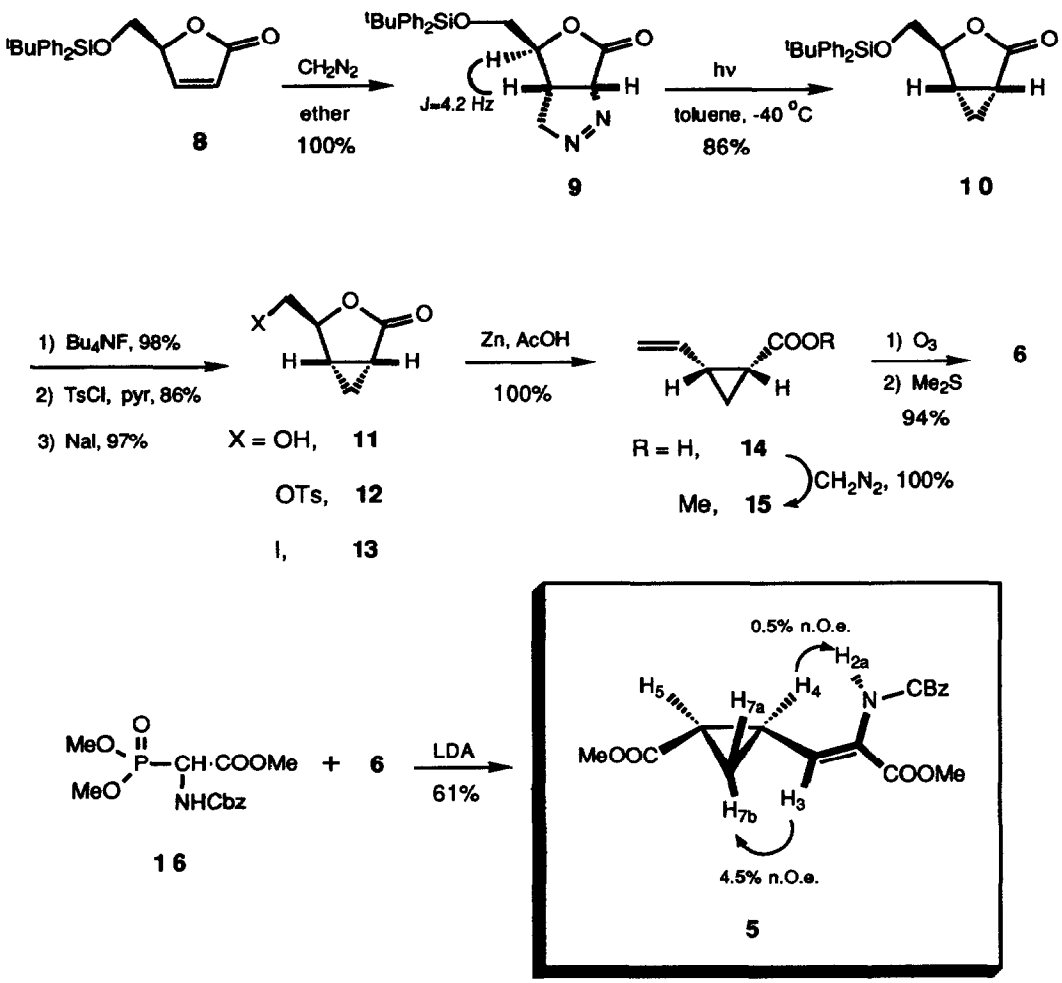
In this paper we describe the highly stereoselective synthesis of compound **5** (Scheme 2), the stereocontrolled cyclopropanation of a chiral furanone being the key step.

Two main methods have been used to prepare cyclopropyl derivatives from furanones. One of them, deals with the photochemically mediated addition of alcohols to chiral 5-substituted 2(5*H*)-furanones.[6] The most common protocol, however, is the 1,3-dipolar cycloaddition of diazoalkanes followed by photo-induced decomposition of the pyrazoline initially formed. Feringa[7] reported very recently a detailed study on this cycloadditions performed on 5-alkoxyfuranones. *Anti*-attack of the dipole occurs preferentially, the ratio of stereoisomers being dependent on the reaction conditions.

In connection with the synthesis of umbelactone (5-hydroxymethyl-4-methyl-2(5*H*)-furanone), we published several years ago the reaction of hydroxy-methylfuranone **7** and its *O*-benzyl derivative with diazomethane to giving the corresponding pyrazolines as unstable oils that could not be purified and that were used in the next step without further investigation.[8] Later, Hanessian[9] described the stereoselective and efficient reaction of the alkylsilyloxyfuranone **8**[10] (Scheme 2) with diazomethane affording crystalline pyrazoline **9**, that was established to be the stereoisomer shown, although no rationalisation was given in that work. In fact, this stereochemistry is characterised by the coupling constant value of 4.2 Hz for the protons marked in Scheme 2 for **9**, according with the values found for similar protons in other bicyclic systems derived from furanones.[10]

Encouraged by this result, we proceeded to prepare **9**. Its photochemical decomposition was performed as a toluene solution contained in a Pyrex reactor by irradiation with a 400 W medium-pressure mercury-lamp, at -40 °C for 1 h. The new cyclopropyl derivative **10** was thus obtained in 86% yield as a solid, m.p. 110-112 °C, $[\alpha]_D$ -163.[11] Solvent and temperature are crucial to obtain good yields of **10** and to prevent the formation of the olefinic insertion product.

The silyl ether was removed by treatment of **10** with Bu_4NF at room temperature for 5 minutes, giving alcohol **11**, m.p. 54-55 °C, $[\alpha]_D$ +63 (98% yield).



Scheme 2

The direct conversion of alcohol **11** into aldehyde **6** was attempted by using $Pb(OAc)_4$ in refluxing benzene-methanol.[12] A mixture of **6** (*ca* 10%), the methoxyfuranone derived from reaction of **6** with methanol, and starting **11** (all of them identified from the ^1H NMR spectrum) was obtained. These products could not be isolated by column chromatography and reaction of the mixture with phosphonate **16**[13] afforded a condensation product in very low yield, among other unidentified substances. Thereby, we tried the oxidation of **11** with sodium periodate in the presence on 2N H_2SO_4,[14] recovering in this case the unaltered starting product.

In view of these results, aldehyde **6** was intended to be synthesized through ozonolysis of the vinyl derivative **15** (Scheme 2), which preparation was achieved as follows. Alcohol **11** was reacted with tosyl chloride in pyridine and the resulting tosylate **12** was subsequently converted into the iodide **13**, solid m.p. 68-70 °C, $[\alpha]_D$ +86, in 83% yield from **11**. At this stage and regarding to shorten the synthetic sequence, we tried the cyclopropanation of tosyloxy- and iodomethyl butenolides **7a** and **7b**[15] (Scheme 1), respectively. In these

cases, however, results were not satisfactory by-products being obtained from elimination of p-TsOH or HI favoured by the acidity of the allylic proton in those molecules.

Vinyl acid **14** was synthesized quantitatively by reductive β-elimination.[16] Thus, treatment of **13** with Zn in glacial acetic acid afforded **14** which was converted into the methyl ester **15** by reaction with diazomethane. The vinyl group in **15** was ozonolyzed to provide the key cyclopropyl aldehyde **6** as a volatile liquid, $[\alpha]_D$ +94 in 94%.

The last synthetic step consisted in the condensation of aldehyde **6** with phosphonate **16**,[13] by using LDA as a base, to give the target molecule **5** as a single (*Z*) stereoisomer, in 61% yield. This compound is an oil, $[\alpha]_D$ -73, whose geometry was established on the basis of differential n.O.e. experiments. Thus, 0.5% differential n.O.e. was observed on H_{2a} when H_4,H_5 (chemical shifts for these protons are very close)[11] were irradiated. Furthermore, significant n.O.e. values were found on H_7, but not on H_{2a}, when H_3 was selectively irradiated. In addition n.O.e. produced between H_3 and H_{7b} suggests a conformation around C_3-C_4 as represented in Scheme 2, in which these protons are close.

Therefore, in this way the amino acid derivative **5** was synthesized stereoselectively in 40% overall yield from the chiral precursor **8**. The synthesis of other related products is the object of active investigatons in our laboratory.

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11. All new products were characterized by their physical constants and spectral data and products **5**, **10-13** gave correct microanalyses. Selected spectral description for compounds **5** and **6** follows. Compound **6**: IR (film) 3400 (broad), 1736 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.20 ((m, 1H), 1.50 (m, 1H), 1.90-2.10 (m, 2H), 3.68 (s, 3 H), 9.30 (d, J=6.5 Hz, 1H). Compound **5**: IR (film) 1721, 1651 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.20 (m, H_{7a}/H_{7b}), 1.40 (m, H_{7b}/H_{7a}), 2.09-2.20 (m, H_4 and H_5), 3.68 (s, CH_3O), 3.72 (s, CH_3O, 5.12 (s, CH_2-Ph), 6.29 (broad s, H_{2a}), 6.70 (d, J=10.3 Hz, H_3), 7.47 (m, Ph); 60-MHz ^{13}C NMR ($CDCl_3$) δ 15.81, 20.44, 21.86, 51.95, 52.39, 67.36, 126.20, 128.14, 128.21, 128.47, 137.45, 135.90, 154.19, 164.72, 172.04.
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