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Highly Efficient and Stereocontrolled Synthetic Route to Enantiopure ACC Derivatives. Synthesis of (+)-*N*-Benzyloxycarbonyl-γ,δ-dehydro-*allo*-Coronamic Acid Methyl Ester

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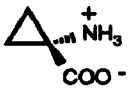
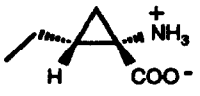
Abstract: *Highly diastereoselective cyclopropanation of a chiral α,β-dehydroamino acid derivative, obtained from D-mannitol, leads to a single isomer which has been transformed into the title compound in 65% overall yield. This product can be a useful intermediate in the synthesis of enantiopure ACC derivatives.*

Conformationally restricted amino acids constitute a wide family of naturally occurring or synthetic compounds of growing interest due to their biological properties. Among them, 1-aminocyclopropane-1-carboxylic acid (ACC) derivatives are prominent. For instance, the parent compound (ACC) was isolated from several fruits,[1] and coronamic acid was isolated from the hydrolysis of coronatine, a plant toxine.[2] Also ACC[3] and other molecules such as *allo*-coronamic acid,[4] play important roles in biosynthetic pathways. Furthermore, this pool of amino acids is important because of their potential use as biosynthetic and mechanistic probes, and in conformationally constrained peptides.[5]



ACC

coronamic acid



allo -coronamic acid

Although several synthetic approaches to this class of products are published,[5] only few methods have been reported for the synthesis of optically active cyclopropane amino acids. Most of them use asymmetric cyclopropanation of chirally derivatized dehydro amino acids,[6] or the very recently described cyclopropanation of an intrinsecally chiral azlactone.[7] In many of these cases, only a moderate diastereoselectivity was accomplished and, consistently, mixtures of stereoisomers were produced.

We describe herein a new and efficient synthetic route to enantiopure ACC compounds starting from the chiral dehydro amino acid derivative **1**. This product is easily prepared in multigramme scale according to the procedure reported by Schmidt.[8] Thus, reaction between (*S*)-glyceraldehyde acetonide and the anion of methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphinyl)-acetate, formed by using *t*-BuOK as a base, gives **1** as the major geometric isomer in 80% yield.

Cyclopropanation of **1** was achieved through highly diastereoselective 1,3-dipolar cycloaddition of diazomethane to afford quantitatively the corresponding pirazoline, **2**, as a single isomer (Scheme 1). Compound **2** in toluene solution, contained in a Pyrex reactor, was decomposed by irradiation with a 125 W middle-pressure mercury-lamp, at -78 °C for 5 hours. In this way, cyclopropane **3** was obtained in 80% yield accompanied with some insertion olefin **3a** (ca 5%). Ratio of **3a** was incremented when photochemical reaction was performed at room temperature. Product **3** is a dense oil whose isomeric homogeneity was verified by 100-MHz ^{13}C NMR.[9] Reaction between **3** and methanol in the presence of diluted HCl afforded diol **4** in 100% yield. This molecule was converted into the vinyl cyclopropane **6** by using the Corey-Hopkins method to obtain olefins from 1,2-diols *via* a thiocarbonate derivative as intermediate.[10] Compound **4** was reacted with thiocarbonyldiimidazole (TCDI) in refluxing THF, instead of thiphosgene/DMAP as in the original protocol,[10] giving the thiocarbonate **5** as a solid, m.p. 108-110 °C, $[\alpha]_D$ -72.3, in 90% yield. X-Ray analysis of a single crystal allowed to assign unequivocally (1*S*,2*R*) absolute configuration to the two stereogenic centers in the cyclopropane ring, as shown in Fig 1.

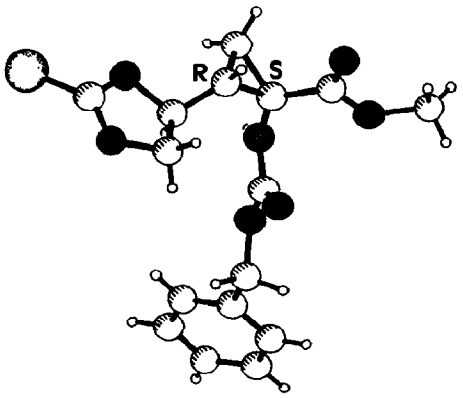
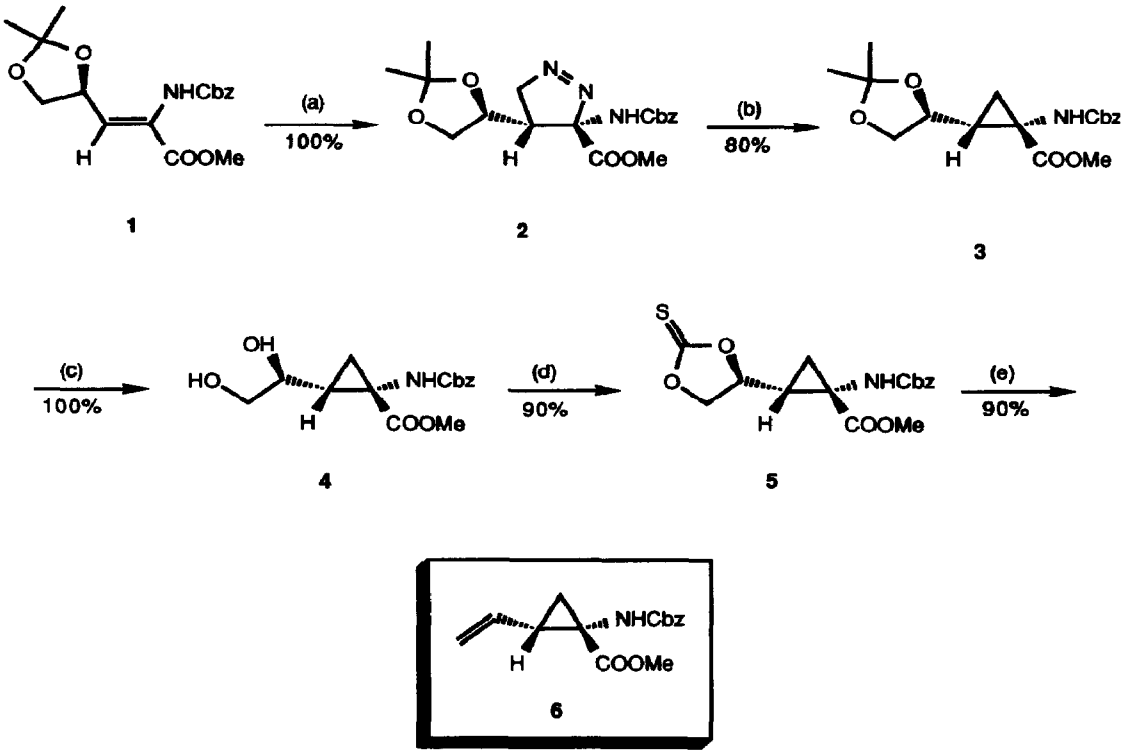
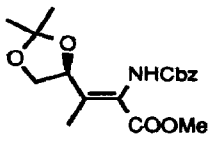


Fig 1. *Structure of compound **5** as determined by X-ray structural analysis. The atomic coordinates and thermal parameters for structure **5** are available on request from the Director of the Cambridge Crystallographic Data Center. Any request should be accompanied by a full literature citation of this paper .*

Thiocarbonate **5** was treated with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (DMPDAP) giving (+)-*N*-benzyloxycarbonyl-γ,δ-dehydro-*allo*-coronamic acid methyl ester, **6** (90% yield) as a solid, m.p. 61-62 °C, $[\alpha]_D$ +155.8, which was obtained in 65% overall yield from **1**.

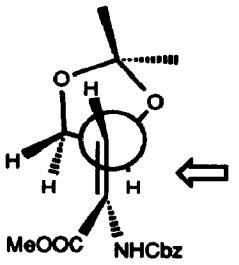




Reagents. *(a): CH_2N_2, ether, r.t. 12 h. (b): hν, Pyrex, toluene, -78 °C, 5 h. (c): MeOH, 5% HCl, r.t., 2.5 h. (d): TCDI, THF, reflux, 6 h. (e): DMPDAP, THF, 50 °C, 20 h.*

Scheme 1

The chirality of the cyclopropane ring and the high diastereoselection in the cycloaddition step can be explained by the preferential attack of diazomethane on the less hindered *re* face of the double bond of **1**, by considering a preferred conformation such as represented in next page. Nevertheless, the stereochemical outcome of 1,3-dipolar or Diels-Alder cycloadditions is not always well rationalized by regarding only the ground state of reactants,[11] being necessary the determination of associated energies and geometries of the TS's leading to the possible stereoisomers. A detailed experimental and theoretical study of this cycloaddition and related processes is being carried out by our group.



re - attack to yield (1S, 2R)-

cyclopropane derivative

The cyclopropane derivative **6** is a branching point from which divergent synthetic routes leading to a variety of cyclopropane amino acids can be derived. Effectively, simple transformations of the double bond should allow the introduction of new functional groups or chain elongation.

Therefore, the methodology reported herein proves to be useful in the synthesis of enantio pure ACC derivatives in high yields from easily available materials. Preparation of other interesting compounds is under active investigation in our laboratory.

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