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Enantioselective Total Syntheses of (-)-*allo*-Coronamic Acid, (-)-(*Z*)-2,3-Methanohomoserine, and (2*S*,3*R*)-Cbz-cyclo-Asp-OMe

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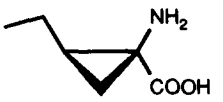
Abstract. *The title amino acids have been synthesized in 45, 47, and 63% overall yields, respectively, from enantiopure aminopentenoates, easily available from D-glyceraldehyde as a source of chirality, following divergent pathways from similar diols as common key intermediate compounds.*

Cyclopropane amino acids (ACC derivatives) are an important class of unusual amino acids whose synthesis and biological properties have been reviewed by several authors,[1] being the object of attention for many research groups. Nevertheless, there is a lack of methods that display efficiency, stereocontrol, and versatility and thus provide easy synthetic access to a variety of ACC derivatives in high yields, using simple protocols from common available precursors.

We reported recently the highly stereoselective cyclopropanation of the chiral didehydroamino acid derivative **4** to yield cyclopropane **6** as the only diastereoisomer with an unambiguous absolute configuration, as well as its transformation into the vinylcyclopropane **10** *via* diol **8** (Schemes 1 and 2).[2]

In this communication we describe the enantioselective syntheses of (-)-*allo*-coronamic acid **1**, (-)-(*Z*)-2,3-methanohomoserine **2**, and (2*S*,3*R*)-Cbz-cycloAsp-OMe (*N*-benzyloxycarbonyl-cyclopropane-aspartic acid methyl ester) **3** from the similar diols **8** or **9**, as on illustration of the scope provided by our methodology.

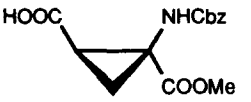


(-)-*allo*-Coronamic Acid

1

(-)-(*Z*)-2,3-Methanohomoserine

2



(2*S*,3*R*)-Cbz-cyclo-Asp-OMe

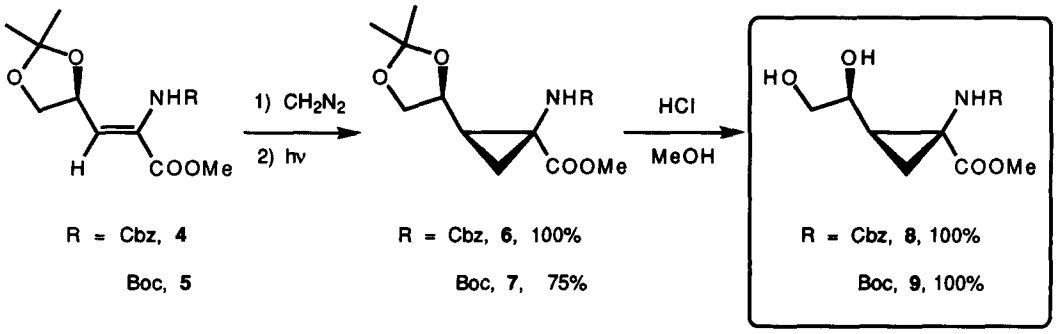
3

The target molecules chosen as synthetic goals are interesting for different reasons. Thus, *allo*-coronamic acid is a substrate for 1-butene biosynthesis in plants.[3] (*Z*)-2,3-Methanohomoserine is an analogue of the precursor to the plant growth hormone ethylene, and has been implicated in the generation of

antibodies.[4] Moreover, it has been functionalized to *allo*-coronamic acid[5] and carnosadine,[6] and, in addition, a derivative of (+)-**3** has been oxidized to Boc-Z-cyclo-Asp-O*t*-Bu.[1c]

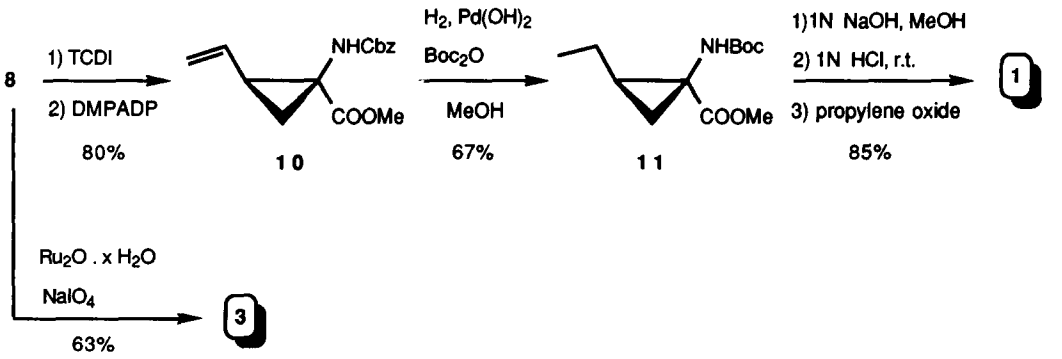
The amino pentenoates **4** and **5** are easily prepared on a multigramme scale by reaction of D-glyceraldehyde acetonide[8] with the potassium anion of methyl 2-benzyloxycarbonylamino or 2-*t*-butyloxy-carbonylamino-2-(dimethoxyphosphynyl)-acetate to afford **4** or **5**, respectively, in 80-85% yields, according to the procedure described by Schmidt *et al.*[9] The major isomer **4** could be easily purified by column chromatography whereas **5** remained contaminated by the (*E*)-isomer (*c.a.* 5%).

Cyclopropanation was accomplished in a stereospecific manner through the 1,3-dipolar cycloaddition of diazomethane to **4** or **5** followed by photochemical decomposition of the corresponding intermediate pyrazolines (Scheme 1). In this way, cyclopropane **6** was obtained quantitatively,[10] and the new compound **7** was produced in 75% yield once derivatives from (*E*)-olefin, among other byproducts, were eliminated by recrystallization.[11]



Scheme 1

Deprotection of the diol by the action of 5%HCl in MeOH at room temperature afforded diols **8** and **9**, respectively, in a quantitative manner. These products differ in the protection of the amino group and constitute the branching point in the divergent synthetic pathways leading to **1**, **2**, and **3**, respectively.

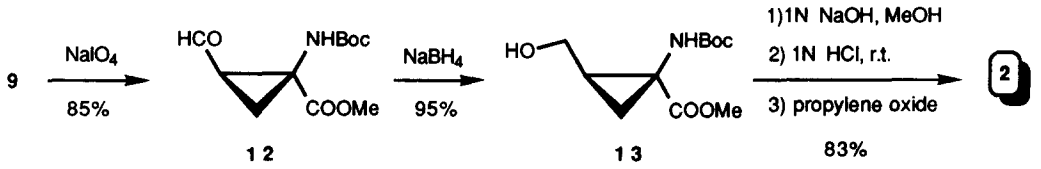


Scheme 2

The synthesis of (-)-*allo*-coronamic acid **1** was achieved as follows (Scheme 2). Reductive elimination from **8** gave **10** in 80% yield, as described in our previous work.[2] The preparation of a similar vinylcyclopropane has recently been published by Cativiela *et al.*[12] in connection with the synthesis of **1**, using a chiral azlactone derivative as a substrate to cyclopropanation. Hydrogenation of the vinyl group could not be satisfactorily realized by using palladium on charcoal as catalyst, as also stated by those authors.[12] Nevertheless, in our case hydrogenation of **10** in the presence of $Pd(OH)_2$ and Boc_2O furnished the saturated *N*-Boc derivative **11** in 67% yield. Boc is more convenient than Cbz protection since it can be removed in milder acid conditions. Thus, saponification of the methyl ester was carried out with methanolic 1N NaOH. Hydrolysis of the carbamate and purification of the resultant amino acid was achieved with 1N HCl at room temperature for 24 h, followed by treatment with excess propylene oxide, and subsequent elution of the aqueous solution through a commercial C_{18}-reverse phase cartridge. In this way, the free amino acid **1** was obtained in 45% overall yield from **4**, this being the highest yield reported for the enantioselective synthesis of *allo*-coronamic acid from an easily available precursor.[5,13]

On the other hand, oxidative cleavage of the diol **8** by using catalytic Ru_2O. x H_2O in the presence of sodium periodate, at room temperature for 2 hours, afforded new (2*S*,3*R*)-Cbz-cyclo-Asp-OMe **3** in 63% overall yield from **4**. This protein amino acid surrogate is suitably protected for incorporation into peptidomimetics.

The synthesis of methanohomoserine **2** was efficiently realized from diol **9** according to the sequence of Scheme 3. Aldehyde **12** was obtained in 85% yield by treatment of **9** with sodium periodate in a THF-H_2O solution, at 0 C for five minutes. Reduction of **12** with sodium borohydride in methanol at 0 C for ten minutes produced alcohol **13**,[4] that was converted into the free amino acid **2** following the same protocol described above for **1**. This synthetic route leads to **2** in 47% overall yield, being the shortest and most efficient synthesis described up to present for this amino acid.[4,14]



Scheme 3

In conclusion, three different types of 2,3-methanoamino acids have efficiently been synthesized from common precursors, by means of selective transformations of functional groups. The synthesis of ACC derivatives bearing an ethyl, a carboxyl or a hydroxymethyl group proves the versatility of the methodology described herein. The synthesis of other interesting related products is being carried out in our laboratory and will be reported in the near future.

Acknowledgements. J. M. J. and J. R. thanks the Direció General de Universitats for respective predoctoral fellowships. Financial support from Dirección General de Investigación Científica y Técnica (DGICYT) through the project PB91-0502, and from Comissionat per Universitatas i Recerca de la Generalitat de Catalunya (GRQ93-2070), is gratefully acknowledged.

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8. D-glyceraldeyde acetonide is easily prepared from cheap and commercially available D-mannitol, according to: Mann, J.; Partlett, N. K.; Thomas, A. *J. Chem. Res.* (S) **1987**, 369, and references therein.
9. (a) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53. (b) Schmidt, U.; Lieberknecht, A.; Kazmaier, U.; Griesser, H.; Jung, G.; Metzger, J. *Synthesis*, **1991**, 49.
10. Photochemical decomposition of the pyrazolines was initially performed as a toluene solution contained in a Pyrex reactor by irradiation with a 125 W medium-pressure mercury-lamp, at -78 C for 1 h, acording to the original method described in ref 2. Applying this procedure, a percentage(5-12%) of insertion olefin always accompanied the resultant cyclopropanes. Later, we realized that production of by-products was avoided and, consequently, yield in cyclopropanes was improved by performing the irradiation on a dichloromethane solution in the presence of 0.1 eq of benzophenone as a photosensitizer.
11. All new products were fully characterized by their physical constants and spectral data, and gave satisfactory microanalysis. Some selected data for the most representative compounds synthesized follow.

    Diol 8: Crystals (from ethyl acetate-pentane), m.p. 74-76 C; $[\alpha]_D$ -40.0 (c 1.25, chloroform). *Diol 9:* Crystals (from ethyl acetate-pentane), m.p. 131-132 C; $[\alpha]_D$ -54.6 (c 1.08, chloroform). *allo-Coronamic acid 1:* Crystals (from water-acetone), m.p. 182-186 C dec; $[\alpha]_D$ -58.0 (c 1.00, water) [Lit ref 12: m.p. 185-187 C dec, $[\alpha]_D$ -60 (c 0.4, water); ref 13a: $[\alpha]_D$ -52 (c 1.83, water)]. *(Z)-2,3-Methanohomoserine 2:* Crystals (from water-ethanol), m.p. 220 C dec; $[\alpha]_D$ -70.3 (c 0.18, water) [Lit ref 4: m.p. 240 C dec, $[\alpha]_D$ -74.5 (c 0.18, water); ref 14: m.p. 232-234 C dec, $[\alpha]_D$ -71.6 (c 1.04, water)]. *N-Boc-2:* Crystals (from ethyl acetate-pentane), m.p. 157 C (dec), $[\alpha]_D$ -37.8 (c 0.45, methanol) [Lit ref 4: m.p. 148 C (dec), $[\alpha]_D$ -38.0 (c 2.55, methanol)]. *(2S,3R)-Cbz-cyclo-Asp-OMe 3:* Crystals (from ethyl acetate-pentane), m.p. 118-119 C; $[\alpha]_D$ -112.0 (c 1.25, chloroform).
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