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Enantiospecific synthesis of norcoronamic acids

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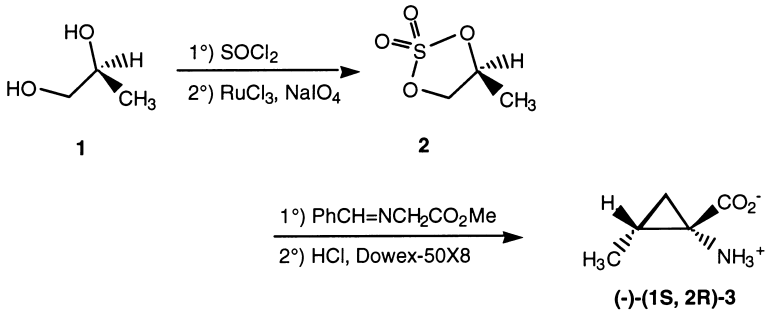
Abstract

The synthesis of enantiomerically pure norcoronamic acids, starting from enantiomerically pure 1,2-propanediols, is described.

1-Aminocyclopropanecarboxylic acids (ACC derivatives) are currently attracting attention, because of their conformationally constrained structure, providing them with particularly interesting biological properties.[1] In this area, allonorcoronamic and norcoronamic acids provide a significant challenge to synthetic chemists, due to the difficulty in controlling the stereochemistry around the cyclopropane ring. We have recently reported[2] the synthesis of (−)-(1*S*,2*R*) allonorcoronamic acid **3**, *via* condensation of cyclic sulfate **2** on a Schiff base (Scheme 1).



Scheme 1.

Asymmetric syntheses of norcoronamic acids have also been reported,[3–6] but several of these suffer from unresolved mixtures and moderate diastereoisomeric excess. We now report a new and expedient enantiospecific synthesis of optically active norcoronamic acid **4**, one that can provide multigram quantities of enantiomerically pure material (Scheme 2).

The synthesis of cyclic sulfate **2** from (*S*)-(+)-1,2-propanediol **1** was achieved in 95% overall yield by the one pot procedure previously reported.[2] The next step involved the condensation of **2** with dimethyl

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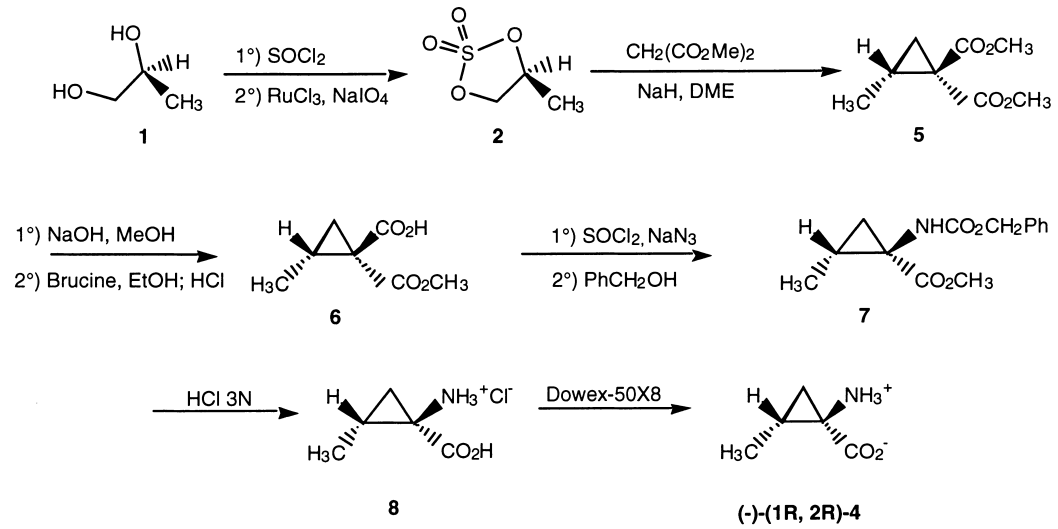

Scheme 2.

malonate in DME at room temperature in the presence of two equivalents of sodium hydride, to give the alkylated diester **5** in nearly quantitative yield. In order to realize the aminoacid synthesis, selective differentiation of the two carboxylate functions had to be done.

Regioselective saponification of racemic **5** to give the racemic monoacid ester **6** has been described by Baldwin.[7] In our hands, the same conditions applied to optically active diester **5** gave monoester **6** with 90% diastereoisomeric excess. To overcome this problem, we used a two step procedure. In the first step, the diester was treated in methanol with one equivalent of sodium hydroxide. In the second step, the brucine salt of the monoacid was recrystallized from ethanol. In these conditions the monoester **6** was obtained, after acidification, with 99.5% diastereoisomeric excess and 72% overall yield. Curtius rearrangement of the cyclopropane carboxylic acid **6** and subsequent in situ reaction of the intermediate isocyanate with benzyl alcohol, gave quantitatively the N-CBZ protected aminoacid ester **7**.

Hydrolysis of carbamate **7** with 3 N HCl at reflux (12 h) led, after treatment with ion-exchange resin (Dowex-50X8), to free (1*R*,2*R*)-1-amino-2-methylcyclopropane carboxylic acid **4** ((−)-(E)-norcoronamic acid). The specific rotation of **4** is in agreement with the value previously reported.[6] The availability of both enantiomers of 1,2-propanediol allows the unambiguous preparation of either the *l* or *d* forms of (E)-norcoronamic acid. The methodology described herein, complements the existing approaches to this class of aminoacids.

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