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ASYMMETRIC SYNTHESIS OF CIS AND TRANS 2-METHYL AND 2-ETHYL 1-AMINO CYCLOPROPANECARBOXYLIC ACIDS

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Summary : A new four step asymmetric synthesis of 2-methyl and 2-ethyl 1-amino cyclopropane carboxylic acids resulted from the cycloaddition of diazomethane to the corresponding chirally derivatized dehydro-aminoacid.

For some years 1-amino cyclopropanecarboxylic acid (ACC) and derivatives have attracted interest due to their biological activity[1], particularly in the hope of controlling enzymatic processes of plant growth and fruit ripening. We wanted to obtain coronamic acid 8b, a constituent of coronatin which is a vivotoxin inducing chlorosis of the leaves of italian rye-grass[2], and the isomeric allo-coronamic acid 7b which is converted into 1-butene by plant tissues[3]. This paper reports a simple approach to the asymmetric synthesis of 2-methyl and 2-ethyl ACC derivatives.

Most of the optically pure diastereoisomers of ACC derivatives result from the resolution of racemic mixtures [3-9]. The first asymmetric synthesis was achieved by Pirrung et al[9] applying Schollkopf's procedure[10-11] to two optically active 1,2-dibromopropanes and ethyl isocyanoacetate; (1R,2S) and (1S,2R)-2-methyl ACC are thus obtained with respectively 91 and 82 ee%. (1R,2S) and (1S,2R) 2-hydroxymethyl ACC are prepared in optically pure form respectively by Pirrung et al[12] from optically active epichlorhydrin and dimethyl malonate and Husson et al[1b,13] from the (-) N-cyanomethyl-4-phenyl-oxazolidine synthon; according to the same procedure, Marco[14] reported the synthesis of (-) (1S,2R) allo-coronamic acid 7b, but the enantiomeric excess (about 20%) and the overall yield (1%) were poor. Lastly Bernabe et al[15] reported the preparation of (+) and (-) 2-phenyl ACC by reaction of diazomethane on chirally derivatized 4-benzylidene-oxazolones.

A simpler method for preparing chiral cyclopropanic aminoacids should result from the cycloaddition of diazoalkanes to a chirally derivatized dehydro aminoacid.

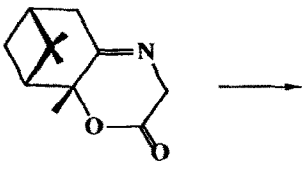
The starting material 1 has already been prepared in our laboratory[16] by esterification of Boc-glycine with (1R,2R,5R)-2-hydroxy 3-pinanone, deprotection of the amine function followed by a spontaneous cyclisation. 1,2-Addition of the corresponding enolate to acetaldehyde and propionaldehyde in the usual conditions[16] (THF, t-BuOK, -78°C) afforded in 85% yield respectively compounds 3a (mp = 68°C) and 3b (oil) resulting from the spontaneous dehydration of the intermediate aldols. On the contrary, reaction with acetone under the same conditions, gave the tertiary alcohol 2 (oil), but the yield was less than 10%. NMR spectra (recorded in $CDCl_3$) of 3a and 3b showed that only the Z configuration was present; this is ascertained from the comparison of the chemical shifts of the ethylenic methyl group in 3a (2.02ppm), 3c (2.04 and 2.33ppm) and 3d (2.23ppm) and also of the ethylenic proton in 3a (6.72ppm) and 3b (6.55ppm).

During reaction of compound 3a with a solution of diazomethane at 0°C, we observed the formation of a precipitate, difficult to isolate due to its instability, but the NMR spectrum showed that only one pyrazoline derivative was formed. The cycloaddition reaction was therefore at the same time regioselective (as already observed in similar cases[5,15-21]) and stereoselective. Cis addition on the starting Z ethylenic compound will afford either the 3R,4R or the 3S,4S configuration for the pyrazoline moiety of 4a; assignment of a 3R,4R configuration resulted from the configuration assignment of the derived amino cyclopropanic carboxylic acids 7a and 8a. The precipitate rapidly dissolved in the reaction medium and after evaporation of the solvent, we obtained an oil containing a mixture of four products separable by column chromatography on silica gel[22] (solvent : ether/hexane 1/1) respectively the starting material 3a (17%), the ethylenic compound 3c (30%) and the two cyclopropane derivatives 5a (34.5%, mp = 101°C, $[\alpha]_D$ -272 c = 5 CH_2Cl_2) and 6a (8.5%, mp = 132°C, $[\alpha]_D$ -192 c = 5 CH_2Cl_2).

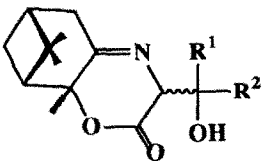
Each compound 5a and 6a was then hydrolysed by a HCl water-THF solution to afford with a 30% yield respectively 7a and 8a; (-)(1S,2R) and (-)(1R,2R) structures resulted from comparing their specific rotations, respectively -75 and -45 , with those reported by Baldwin[8] (respectively -69 and -42) and Pirrung[9] (-67 .4 with 82% ee) and measured in the same conditions.

Treatment of 3b with an excess of an etheral solution of diazomethane at 0°C afforded in 46% yield the pyrazoline derivative 4b (mp = 124°C), the homogeneity of which was checked by NMR. We also recovered the starting product 3b (36%) and the ethylenic compound 3d (oil, yield = 18%), which NMR spectrum showed the same Z configuration as 3b. Heating a solution of 4b in toluene for 3hr afforded an oil containing the ethylenic compound 3d (30%) which was isolated by chromatography on silica gel, and a mixture (70%) of two compounds that we were not able to separate. Examination of this last mixture by mass spectrometry and NMR showed the presence of the two diastereoisomers 5b and 6b. Indeed nitrogen extrusion from the diastereoisomerically pure pyrazoline 4b could proceed, as above, with partial inversion of the configuration of the spiro asymmetric carbon.

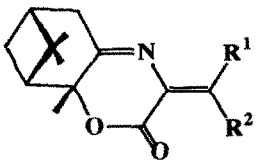
Hydrolysis of the mixture with a 2N HCl water-THF solution at room temperature



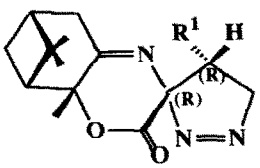
1 (*1R,2R,5R*)



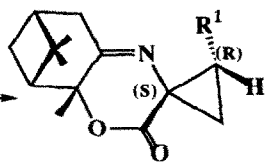
2 $R^1=R^2=CH_3$



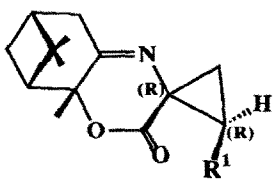
3a $R^1=CH_3$ $R^2=H$
3b $R^2=C_2H_5$ $R^2=H$
3c $R^1=R^2=CH_3$
3d $R^1=C_2H_5$ $R^2=CH_3$



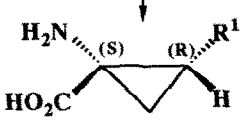
4a $R^1=CH_3$
4b $R^1=C_2H_5$



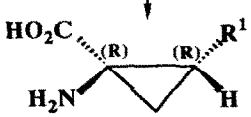
5a $R^1=CH_3$
5b $R^1=C_2H_5$



6a $R^1=CH_3$
6b $R^1=C_2H_5$



7a $R^1=CH_3$
7b Allocoronamic acid
$R^1=C_2H_5$



8a $R^1=CH_3$
8b Coronamic acid
$R^1=C_2H_5$

for 3 days afforded in an only 25% yield a mixture (mp = 205°C) of two aminoacids : coronamic acid 8b and allo-coronamic acid 7b (other products could not be identified).

The specific rotation value (-52 , c = 1.83, H_2O) proved that the major compound was the (-)(1S,2R) allo-coronamic acid ($[\alpha]_D$ -68·4[6], c = 1.67, H_2O); the $[\alpha]_D$ of (-) coronamic acid is much smaller[7] (-14·2, c = 1.67, H_2O). This result allowed us to assign the (-)(1R,2R) configuration to the minor coronamic acid[23]. Indeed in the two aminoacids, the asymmetric carbon located in position 2 must have the same absolute configuration; thus we could determine the composition of the aminoacid mixture : 70% of (-)(1S,2R) allo-coronamic acid 7b and 30% of (-)(1R,2R) coronamic acid 8b.

When the same reactions were carried out from (1S,2S,5S) 2-hydroxy 3-pinanone in place of the (1R,2R,5R) diastereoisomer, we obtained (+)(1R,2S) and (+)(1S,2S) cyclopropanic aminoacid derivatives.

In summary this four step sequence from an easily available starting chiral auxiliary is a very simple method to afford enantiomerically pure 2-methyl ACC.

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