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Synthesis of Enantiomerically Pure 2-Alkyl 1-Amino Cyclopropane-1-Carboxylic Acid

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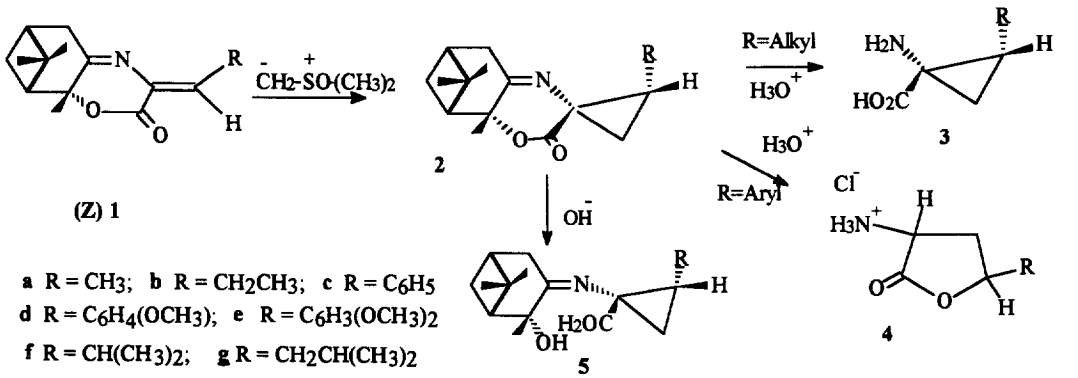
Abstract : Asymmetric synthesis of 1-amino 2-alkyl cyclopropane carboxylic acids using (1R,2R,5R)-2-hydroxy pinan-3-one as the chiral auxiliary and Corey's ylide as reagent is described.

1-Aminocyclopropane 1-carboxylic acid (ACC) and its substituted derivatives constitute an important class of amino acids because of their biological activity and their use in conformationally restricted peptides[1].

We previously described an asymmetric synthesis of 2-methyl and 2-ethyl ACC by the cycloaddition of diazomethane to chirally derivatized dehydroamino acids[2]. The condensation of the selected chiral auxiliary (1R,2R,5R)-2-hydroxy pinan-3-one with glycine led to a rigid 1,4-oxazinone, and subsequent 1,2-addition of the corresponding enolate to acetaldehyde or propionaldehyde afforded the corresponding dehydroamino acid derivatives. Treatment with diazomethane provided, beside a small amount of methylated compound, a Δ-1-pyrazoline ring resulting from a regio and stereoselective addition on the less hindered face opposite to the gem dimethyl bridge[2]. Unfortunately, during the subsequent nitrogen extrusion to form the cyclopropane ring, a partial inversion of the configuration of the spiro carbon occurred with formation of two diastereoisomeric cyclopropanic derivatives.

In order to avoid this drawback, we explored the replacement of diazomethane by Corey's ylide, the dimethyl sulfoxonium methylide (DMSY)[3] which, through a Michael addition[4], might give directly the cyclopropane derivatives. Since the rigid 1,4-oxazinone derivatives **1** afforded only one stereoisomeric pyrazoline when treated with diazomethane, it can be assumed that the same stereoselectivity must be observed when using Corey's ylide.



a R = CH_3; **b** R = CH_2CH_3; **c** R = C_6H_5
d R = $C_6H_4(OCH_3)$; **e** R = $C_6H_3(OCH_3)_2$
f R = $CH(CH_3)_2$; **g** R = $CH_2CH(CH_3)_2$

The 1,2-addition of the oxazinone enolate of (1R,2R,5R)-2-hydroxy pinan-3-one[2,5] to alkyl or aryl aldehydes and spontaneous dehydration of the intermediate alcohol give directly the alkene derivatives **1** except in the cases of isobutyraldehyde and benzaldehyde for which a small amount of the corresponding alcohol was also isolated. The alcohol was easily isolated by chromatography and can be converted in

quantitative yield into the corresponding alkenes by the use of DAST[6]. The derivatives **1a-e**, were isolated as single Z stereoisomers in 55 to 70% yield[2,5]. In the cases of the more hindered aldehydes, isobutyraldehyde and isovaleraldehyde, both Z and E alkene derivatives were formed in 80/20 and 87/13 ratios respectively, the Z form being always predominant. Each isomer can be isolated in pure form by chromatography. Treatment at 0°C of Z isomers **1a-g** with one molar equivalent of DMSY[4a,7] afforded in each case, as determined by NMR analysis[2], only one cyclopropyl derivative **2**[8,9] in 45 to 95% yield. Corey's ylide attacked the less shielded face opposite to the gem dimethyl group, and DMSO removal with formation of the spirocyclic adduct occurred prior to bond rotation[4a]. The same reaction when applied to the E isomers led to a mixture of two diastereoisomeric cyclopropane derivatives (55 / 45) that we were unable to separate.

Each cyclopropane derivative **2a-g** was then hydrolysed with a 6N HCl water-THF solution (70°C, 3h). For alkyl cyclopropanic compounds **2a**, **2b**, **2f** and **2g**, the expected free amino acids **3**[10] were isolated after propylene oxide treatment in 25 to 40% yield. Comparison of the melting points and the specific rotations of compounds **3** with those already reported[3b,11] confirms a cis orientation of the amine and the alkyl group. Unfortunately, acid hydrolysis of aryl cyclopropanic derivatives **2c**, **2d** and **2e** afforded racemic α-amino lactones **4**[9] in 28 to 45% yield with no trace of cyclopropanic acid. A protonation of the cyclopropane ring probably occurs giving rise to a stabilized benzylic cation followed by a lactone cyclisation. A comparable result has been described during acid hydrolysis of aryl oxazolones[12]. Another possibility of oxazinone ring cleavage was basic hydrolysis of **2** which led to the corresponding compound **5**[9] but subsequent acidic hydrolysis caused cleavage of the cyclopropane ring.

In conclusion, 2-hydroxy pinan-3-one is a very efficient chiral auxiliary for derivatization of dehydroamino acids which, when used with Corey's ylide, affords enantiomerically pure alkyl ACC derivatives. Unfortunately, for aryl compounds its use is limited by the final cleavage conditions which involve a side reaction.

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8 **mp 2a** 102°C, **2b** 104°C, **2c** 127°C, **2d** 160°C, **2e** 128°C, **2f** 109°C, **2g** 107°C $[\alpha]_D$ **2a** -275 (c=2, CH_2Cl_2), **2b** -217 (c=2, CH_2Cl_2), **2c** -440 (c=2, CH_2Cl_2), **2d** -536 (c=2, CH_2Cl_2), **2e** -485(c=2, CH_2Cl_2), **2f** - 163 (c=2, CH_2Cl_2), **2g** -197 (c=2,CH_2Cl_2);

9 All new compounds were characterized by 250Hz NMR and MS which are consistent with the assigned structures.

10 **mp 3a** 216°C, **3b** 180°C, **3f** 220°C, **3g** 194°C (dec); $[\alpha]_D$ **3a** (1S, 2R) -75 (c=0.5, H_20), **3b** (1S, 2R) -65 (c=1, H_20), **3f** (1S, 2S) -38 (c=0.6, H_20), **3g** (1S, 2R) -75(c=1, H_20).

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