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STEREOSELECTIVE INTRAMOLECULAR MICHAEL ADDITION INDUCED BY A THERMOLABILE GROUP : SYNTHESIS OF OPTICALLY ACTIVE FIVE-MEMBERED OXYGEN-CONTAINING RINGS.

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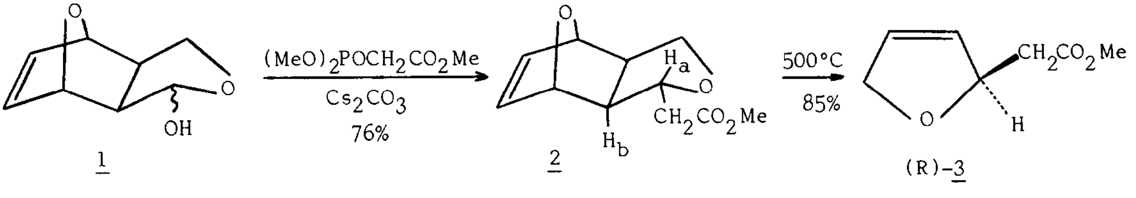
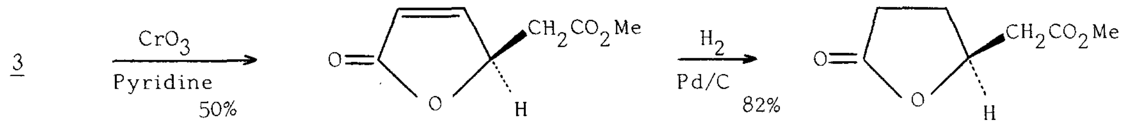
Abstract : A tandem Wittig-Michael reaction allows the stereoselective formation of the tricyclic compound 2 from the chiral lactol 1. A retro Diels-Alder reaction leads to the dihydrofuran 3 of high enantiomeric purity.

Chiral di- and tetrahydrofuran-type rings are structural features of many natural products[1] and furthermore are useful intermediates for the synthesis of a variety of natural acyclic compounds[2]. In connection with our work related to stereoselective reactions induced by a thermolabile group[3], we wish to report a simple synthesis and some transformations of optically active 2-methoxycarbonylmethyl-2,5-dihydrofuran.

The starting point of our synthesis is the lactol 1 obtained by reduction of the corresponding lactone easily prepared in optically active form [4]. It was anticipated that, due to the steric bulk of the oxanorbornenyl group, tandem Wittig-Michael reactions would give rise stereoselectively to the most stable tricyclic compound 2 where the methoxycarbonylmethyl substituent is in an exo position[5]. A simple retro Diels-Alder reaction would then afford an optically active dihydrofuran.



Effectively optically active lactol 1 (5 mmol) reacted with methyl dimethoxyphosphonoacetate (6 mmol) in the presence of cesium carbonate (THF, 60°, 24 h) to give directly compound 2, $[\alpha]_D^{20} = -6°$ (c = 1, $CHCl_3$) as a unique diastereoisomer (de $>$98% as shown by ^1H NMR : for example Hb appeared as a unique doublet of doublet, J = 5.3 and 8.1 Hz) of high enantiomeric purity (ee$>$ 95%)[6]. The most probable exo configuration of the methoxycarbonylmethyl group could not be assigned at this stage on the basis of spectroscopic data [7]. Flash thermolysis of 2 (1 mmol) at 500°C led with an excellent yield to 2-methoxycarbonylmethyl-2,5-dihydrofuran 3, $[\alpha]_D^{20} = -76°$ (c = 1, $CHCl_3$), ee= 94%. In order to determine the absolute configuration of the 2-position and thus to confirm the stereochemistry of the transformation 1 $\longrightarrow$ 2, the compound 3 was oxidized with Collins reagent to the corresponding butenolide 4, $[\alpha]_D^{20}$ = -78° (c = 1, $CHCl_3$), ee = 95%.



(R)-4 (S)-5

Butenolide 4 has been recently described as a mildly cytotoxic compound isolated from the marine sponge Xestospongia sp. [8] The (R) configuration tentatively assigned to the asymetric center of the natural product, $[\alpha]_D^{20}$ = +80° (c = 0.27, $CHCl_3$) on the basis of an empirical correlation is the opposite of the configuration we had assumed for 2. We then looked for more reliable arguments and found that hydrogenation of 4 led to (S)-(+)-γ-methoxycarbonylmethylbutanolide 5, $[\alpha]_D^{20}$ = +39° (c = 1, EtOH). The absolute configuration of 5 was assigned by comparison of the signs of optical rotation of our product and of the known (S)-5 [9a], $[\alpha]_D^{20}$ = +29° (c = 0.4, EtOH) and (R)-5[9b], $[\alpha]_D^{25}$ = -36° (c = 1, EtOH). This result confirms the (R) configuration of the dihydrofuran 3 and the butenolide 4, and the exo position of the methoxycarbonylmethyl group in 2. It also shows that, in contrast with the reported assignment, the natural product 4 possesses an (S) configuration.

Further uses of the optically active dihydrofuran 3 for the synthesis of natural products are currently under investigation.

References and notes

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3. For previous examples see a) R. Bloch and J. Abecassis, Tetrahedron Lett. 1983, 24, 1247 ; b) R. Bloch and L. Gilbert, Tetrahedron Lett. 1986, 27, 3511 and 1987, 28, 423.
4. a) R. Bloch, E. Guibé-Jampel and C. Girard, Tetrahedron Lett. 1985, 26, 4087 ; b) T. Ferrari and P. Vogel, Tetrahedron Lett. 1986, 27, 5507.
5. Such reactions have been used for the preparation of furanosyl C-glycosides but always led to a mixture of diastereomers : H. Ohrui, G.H. Jones, J.G. Moffatt, M.L. Maddox, A.T. Christensen and S.K. Byram, J. Am. Chem. Soc. 1975, 97, 4602.
6. Satisfactory spectroscopic data and microanalytical data were obtained for new compounds. The enantiomeric excesses were estimated in all cases by ^1H NMR in the presence of the chiral shift reagent, $Eu(hfc)_3$. In all cases for a ratio $Eu(hfc)_3$/ester = 0.1, the signals due to the ester methyl groups of the racemic compounds appeared as two well separated singlets.
7. Due to the conformational mobility of the tetrahydrofuran rings, the value of the coupling constant J_{HaHb} = 5.3 Hz is not useful to assign the stereochemistry of the methoxycarbonylmethyl group in 2.
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