A SIMPLE ENANTIOSELECTIVE INVERSION IN CHIRAL 2-OXABICYCLO[3.3.0]OCTA-6-EN-3-ONE, A KEY INTERMEDIATE FOR CHIRAL PROSTAGLANDIN SYNTHESES

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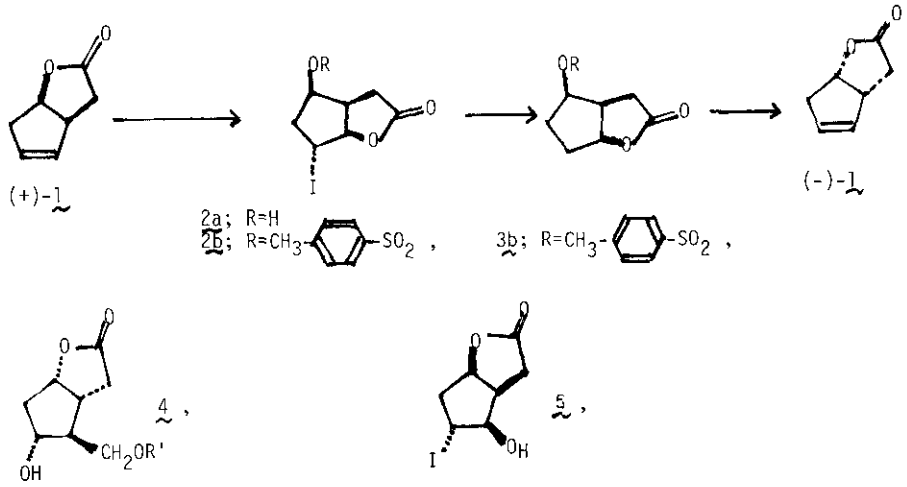
Abstract - A simple and effective inversion of (1R,5S)-2-oxabicyclo[3.3.0]octa-6-en-3-one into its enantiomer was described.

(1S,5R)-2-Oxabicyclo[3.3.0]octa-6-en-3-one ((-)-1) has been recognized as the most fundamental chiral intermediate for the syntheses [1,2,3] of natural and related prostaglandins, especially after success in the regio- and stereospecific conversion[4] of 1 into 4, the Corey lactone[5], which has the same stereochemistry of the four substituents on the cyclopentane ring as natural prostaglandins.

Much efforts to prepare (-)-1 opened the several methods which include the direct chemical [1c] or biochemical[6] resolution of racemic modification, assymmetric synthesis[7] and the chemical conversion from chemically[8] or biochemically[9] resolved meso-compound derivatives or from the other chiral compound[10]. Among these methods, the direct chemical resolution of (±)-1 seems to be the most effective and attractive one unless the accompanying (+)-1, the by-product with the undesirable configuration, is produced.

We wish to describe here a simple and effective conversion of (+)-1 into (-)-1, the key intermediate with the same configuration as natural prostaglandins.



Saponification of (+)-1, mp 46°C, $[\alpha]_D^{20}$ +104.6°(c=1.2, $CHCl_3$)[13], in aqueous solution of sodium hydroxide (1.1 eq.) followed by acidification to pH 5.0 with 5N-acetic acid [12] at 24°C and iodolactonization with potassium triiodide at 24-26°C gave the iodolactone, (-)-2a[11], mp 58°C, $[\alpha]_D^{20}$-48.9° (c=0.98, $CHCl_3$), in a 94.3% yield. One recrystallization from ethyl acetate-n-hexane afforded optically pure (-)-2a, mp 60°C, $[\alpha]_D^{24}$ -51.2° (c=2.06, $CHCl_3$).

Successive treatment of (-)-2a with tosyl chloride in pyridine at 20-25°C for 66 hr yielded the tosylate, (+)-2b[11], an oil, $[\alpha]_D^{20}$ + 40.7° (c=0.95, $CHCl_3$), in an 87.5% yield.

Deiodination of (+)-2b with tributyltinhydride (1.2 eq.) in ethyl acetate at reflux for 2 hr afforded the tosyllactone, (+)-3b[11], an oil, $[\alpha]_D^{20}$ +16.6° (c=0.93, $CHCl_3$), in an 84.3% yield.

On heating (+)-3b in hexamethylphosphoramide at 121-129°C for 8 hr, the olefin-lactone, (-)-1, mp 46°C, $[\alpha]_D^{20}$ -104.2° (c=1.01, $CHCl_3$), was obtained in a 58.6% yield[11].

Although the reaction conditions have not been optimized, addition of bases to the detosylation reaction mixtures decreased the chemical yield of the products. It should be also noted that the ease of enantiomeric inversion of chiral 1 adds further to its practical usefulness as a starting material for the synthesis of chiral prostanoids.

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11) Satisfactory analytical and spectral data were obtained for this compound.

12) Under the alkali conditions (pH 9.2), a mixture of 2a and 5 (15:85) was obtained.

13) (+)-Ephedrine was used as the resolving agent.

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