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ENANTIOSELECTIVE SYNTHESIS OF (+)-(S)-β-ANGELICA LACTONE FROM L-TARTARIC ACID

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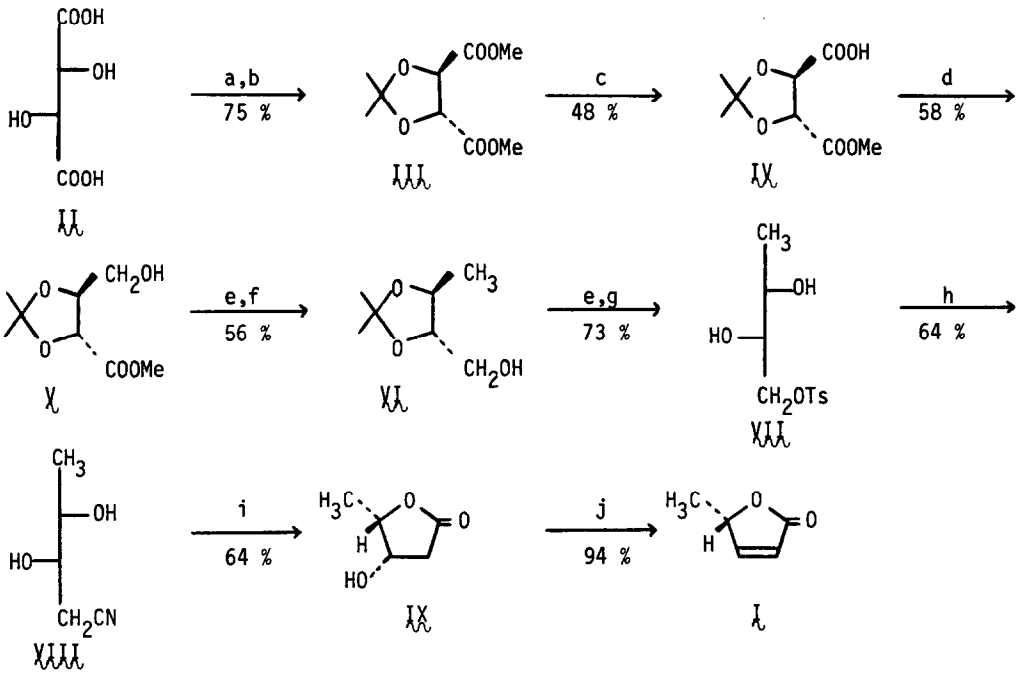
Summary .- The first synthesis of (+)-(S)-β-angelica lactone, from L-tartaric acid as chiral starting material, is reported.

A large number of natural products have the γ-lactone moiety in their structural constitution and, for this reason, β-angelica lactone has been proved to be an interesting synthon for the preparation of such substances[1]. Since we have already described a method to synthesize the levo enantiomer from D-ribonolactone[2], we decided to explore a convenient route to obtain (+)-(S)-β-angelica lactone, I, a compound not previously described. The cheap and readily available (+)-L-tartaric acid, II, was chosen as the chiral starting material.

The synthetic sequence is depicted in the Scheme. The key step is the monosaponification of the diester acetonide III[3], followed by chemoselective reduction of the carboxyl group in the resultant hemiester acetonide IV[3] upon the action of the complex BH_3-THF[4] (0.4 M in THF), leading to the hydroxyester V in 21 % overall yield from II. In the last reaction, the use of reducing agent solutions in concentrations higher than 1.5 M was not compatible with the presence of the ketal protecting group, giving V in low yields as well as by-products resulting from molecular rearrangements. Tosylation of V and subsequent reduction with $LiAlH_4$ gave directly the alcohol VI. At this stage, transformation of one of the two carboxyl groups of the L-tartaric acid molecule into a methyl group had been achieved. Tosylation of VI and subsequent acidic methanolysis gave the new dihydroxytosylate VII, m.p. 82-83°, $\{\alpha\}_D^{20}$=-1.97° (c=0.4 $CHCl_3$). The carbon chain was then extended by reaction with sodium cyanide in DMSO, affording the nitrile VIII as a viscous oil, $\{\alpha\}_D^{20}$=-0.66° (c=2.1, $CHCl_3$); deprotection of the glycol was carried out before the displacement of the tosyloxy group by cyanide to prevent the steric hindrance of the gem-dimethyl substitution in the dioxolane ring hindering the attack of the nucleophile[5]. Treatment of VIII with methanolic hydrogen chloride afforded 2,5-dideoxy-L-xylono-γ-lactone, IX, which was then reacted with 1.2 eq. of MsCl and 2 eq. of Et_3N in CH_2Cl_2 as solvent[6]. Elimination of methanesulfonic acid from the mesylate formed in situ, led to introduction of a conjugate double bond, leading to formation of (+)-(S)-β-angelica lactone, I, as a liquid, b.p. 98-100° (oven)/15 torr, $\{\alpha\}_D^{20}$=+93.8°(c=0.5, $CHCl_3$) (Lit.[2] $\{\alpha\}_D^{20}$=-95.9°(c=0.7, $CHCl_3$) for the enantiomer).

The synthetic pathway presented in this work provides a useful methodology for preparation of I from a very simple chiral starting material, through conventional transformations of functional groups.



a: $MeOH/H_2SO_4/CH_2Cl_2$, reflux; b: 2,2-dimethoxypropane, acetone, p-TsOH, reflux; c: KOH (1eq), MeOH, rt, 1 hr; d: BH_3-THF (0.4 M), 0°, 8.5 hr; e: TsCl, pyr; f: $LiAlH_4$, ether; g: Lewatit S-100 resin, MeOH, reflux; h: NaCN, DMSO, rt; i: i) HCl sat MeOH, reflux, 2 hr, ii) H_2O, rt, overnight, then reflux 30 min; j: MsCl, Et_3N, CH_2Cl_2, 0°, 1 hr.

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Notes and references

1. J. Cardellach, J. Font and R. M. Ortuño, Tetrahedron Lett. 26, 2815 (1985). The authors apologize for an error in the configuration assigned to (-)-β-angelica lactone in that paper. This configuration must be (R), as can be easily deduced from the scheme there represented.
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