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ASYMMETRIC SYNTHESIS OF POLYHYDROXYLATED NATURAL PRODUCTS
I. EFFICIENT PREPARATION OF L-ARABINITOL

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Abstract : A new approach to sugar synthesis is demonstrated through the synthesis of L-arabinitol. Reduction of allylic β-ketosulfoxides followed by hydroxylation of the double bond in the resulting allylic β-ketosulfoxides are the two important asymmetric steps involved in the process.

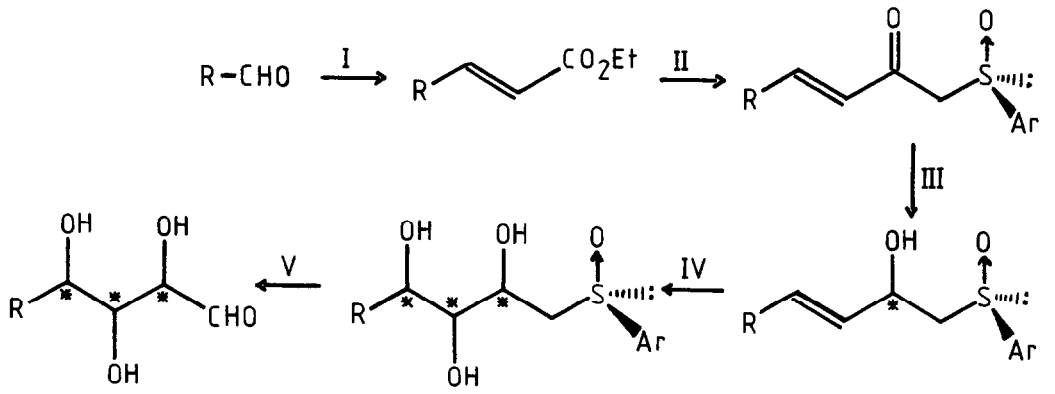
Recently, Sharpless and Masamune[1,2] reported the synthesis of polyhydroxylated natural products and particularly simple monosaccharides. Their approach basically consisted of the repetitive addition of a two carbon unit on a proper starting aldehyde, creating two chiral hydroxymethylene centers in each cycle of the sequence as a result of the very efficient Sharpless asymmetric epoxidation.

We would like to report in this paper another methodology to obtain optically pure polyhydroxylated natural products. This methodology consists of two asymmetric steps : the stereospecific reduction of β-ketosulfoxides and the stereospecific hydroxylation of allylic β-hydroxysulfoxides, two reactions we recently described[3-6].

The overall process is described in Scheme 1.

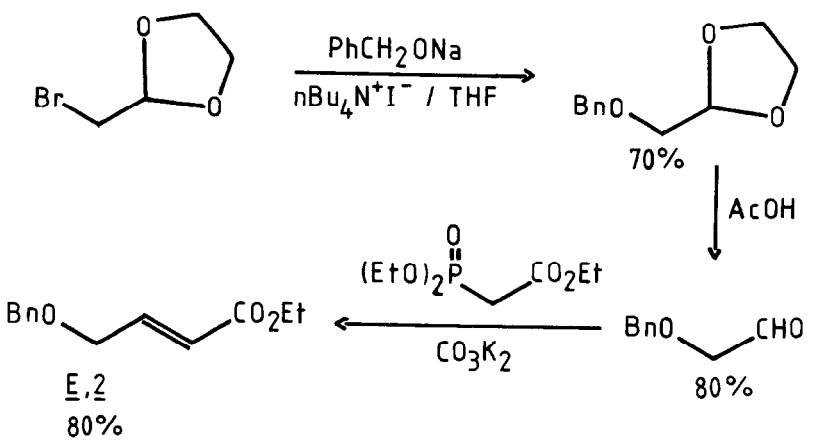
The basic set of transformations involves the preparation of an α,β-unsaturated ester (step I), its transformation to allylic β-ketosulfoxide (step II, the pure E isomer is always obtained whatever the configuration of the ester), reduction of the ketosulfoxide (step III, both diastereoisomers can be obtained from the same configuration at sulfur according the nature of the reducing agent[3]), hydroxylation of the double bond with a catalytic amount of osmium tetroxide (step IV) and Pummerer rearrangement (step V).

The overall process leads to the formation of three adjacent chiral hydroxylic centers.



Scheme 1

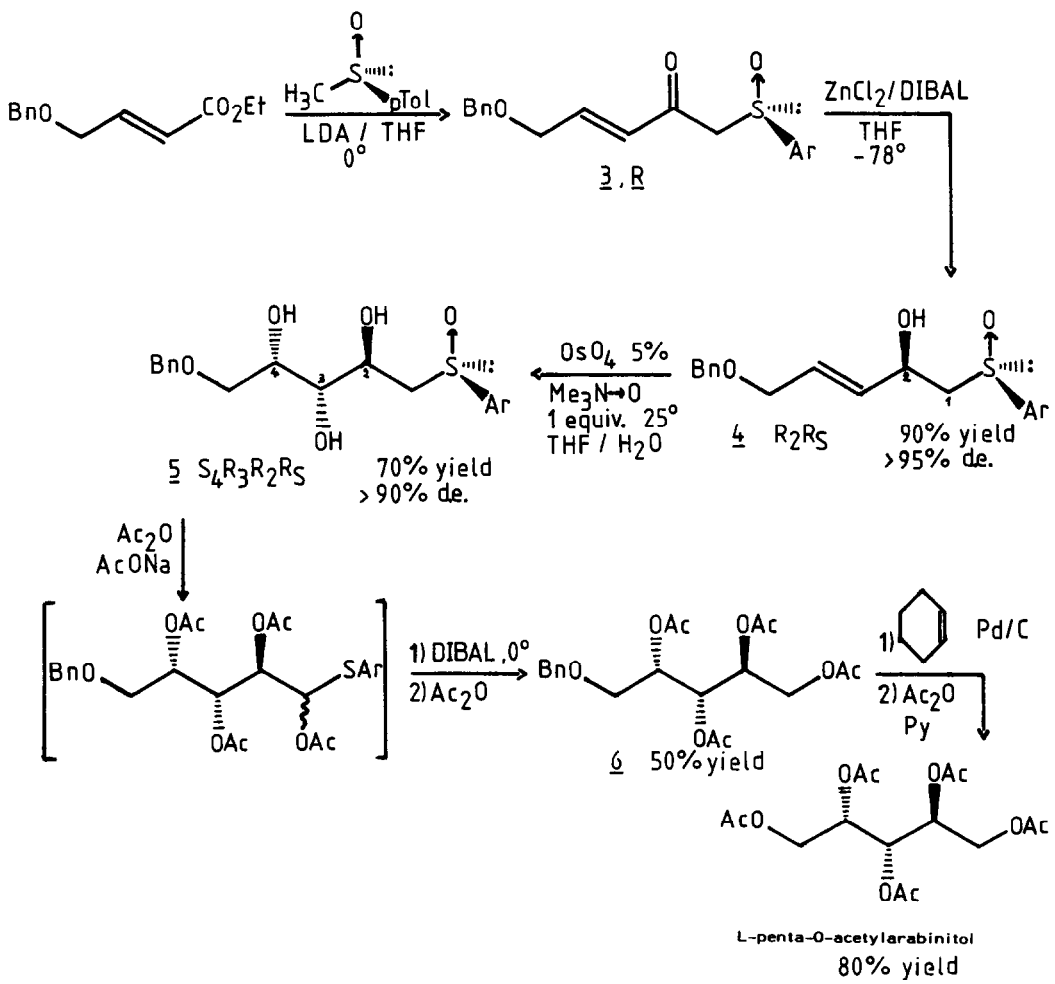
The α,β-unsaturated ester 2 required for the synthesis of L-arabinitol was readily prepared from the commercially available 2-bromomethyl-1,3-dioxolane by the following sequence : benzylation, acetal hydrolysis and Wittig reaction in conditions giving only the E isomer[7]. (Scheme 2)



Scheme 2

The ester 2 was then condensed with the carbanion of R(+) methyl-p-tolylsulfoxide at 0° (in order to avoid Michael addition[4] which occurs significantly at -78°) giving the unsaturated E β-ketosulfoxide 3,R (60% yield). The reduction of the keto group was performed with $ZnCl_2$/DIBAL[3] in order to get the R_2Rs diastereoisomer 4 (90% yield, 200MHz NMR : non equivalence of CH_2 α to sulfur : $\Delta\nu$ = 40.5Hz[8]. Oxidation of the double bond with a catalytic amount of OsO_4 and 1 equiv.of trimethylamino N-oxide (in order to avoid oxidation of sulfoxide to sulfone) gave in 70% yield the triol 5 in the configuration $S_4R_3R_2R_S$ [5,6] (only this diastereoisomer could be detected by NMR, d.e. ≈ 90%[9]).

Pummemer rearrangement in acetic anhydride of the sulfoxide 5, followed by reduction at 0° of the intermediate and final acetylation yielded the tetraacetate 6 in 50% overall yield from 5. Finally, debenzylation and acetylation gave L-penta-O-acetyl arabinitol[10] in 80% yield : $[\alpha]_D$ -37° ($CHCl_3$, c=1.5) (Lit.[11] -38°).



A pleasant quality of this methodology is the possibility to obtain natural pentoses in the D configuration only by changing the configuration of the starting sulfoxide.

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8) The other diastereoisomer S_2R_s was obtained by reduction with DIBAL ; the non-equivalence for the CH_2 α to the sulfoxide is in this case much larger $\Delta\nu$ = 70.9Hz, which is consistent with R_sS_2 configuration[3-4].
9) Osmylation in the same conditions of diastereoisomer 4,S_2R_s yielded in 70% yield and 50% d.e. the sulfoxide triol $R_4S_3S_2R_s$, a result consistent with previous studies[5,6].

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