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SYNTHESIS OF (3R,4R)-1,5-HEXADIEN-3,4-DIOL AND ITS UNSYMMETRICAL DERIVATIVES : APPLICATION TO (R)-(+)-α-LIPOIC ACID *

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Summary *(3R,4R)-1,5-Hexadien-3,4-diol and its unsymmetrical derivatives were prepared starting from D-mannitol and their utility in the synthesis of (R)-(+)-α-lipoic acid has been explored.*

The utility of 1,5-hexadien-3,4-diol (1,2-divinylglycol) as a versatile intermediate in natural product chemistry has been well appreciated because of the presence of C_2 symmetry in its molecule[1-4]*. The ease with which one of the vinylic groups in 1*[5] *could be functionalised at the expense of the other indeed led to the synthesis of various naturally occurring compounds.*[2] *It was realised that optically active 1 could prove to be a valuable synthon for the preparation of such molecules in optically active forms. Herein we report a convenient route to (R,R)-1,2-divinylglycol (1) and some of its unsymmetrical derivatives.*

The strategy reported here utilises readily available[6] *1,2;5,6-di-O-isopropylidene-D-mannitol (2) as starting material and takes advantage of C_2 symmetry present in the mannitol molecule. Accordingly, 2 was treated with benzoyl chloride - pyridine mixture at room temperature for 3 h to afford* 3,4-dibenzoate *3 (90%). Hydrolysis of the isopropylidene groups in 3 was achieved with 50% aqueous acetic acid on boiling water bath for 3 h to give the tetrol which on treatment with methanesulphonyl chloride - pyridine yielded the tetramesylate (4). Reaction of 4 with sodium iodide and zinc dust in refluxing N,N'-dimethylformamide for 2 h followed by debenzoylation with sodium methoxide gave (3R,4R)-1,2-divinylglycol (1) (40%).*

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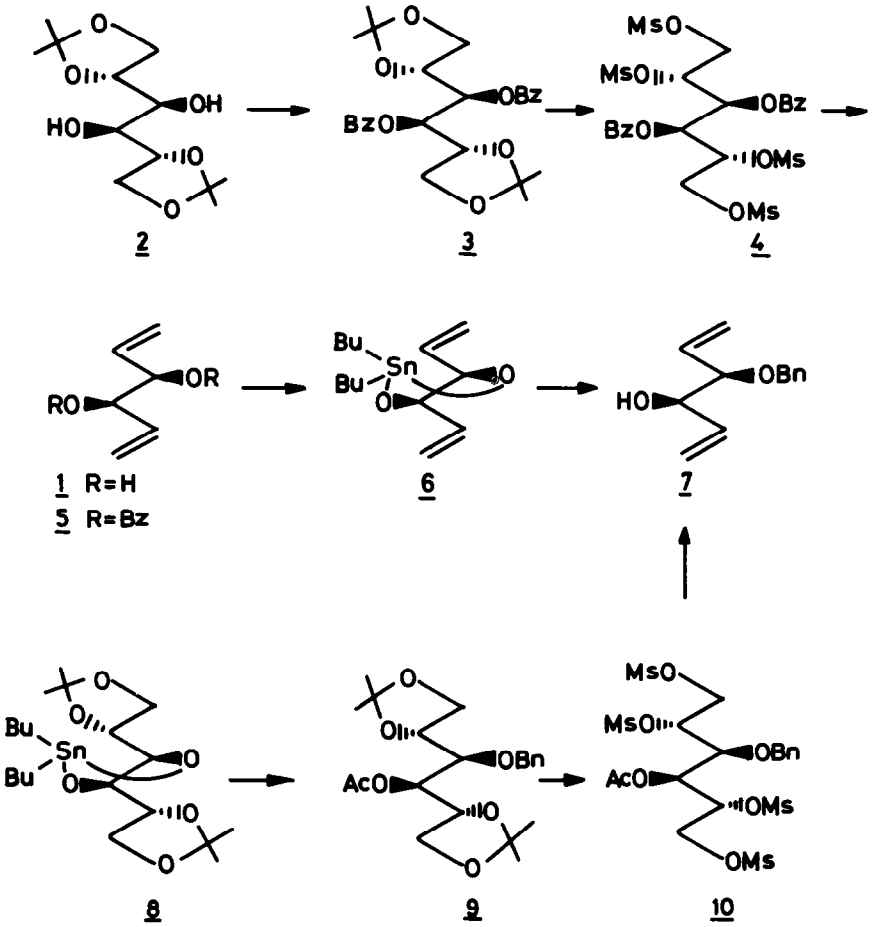
* *RRL Communication No. 2001*

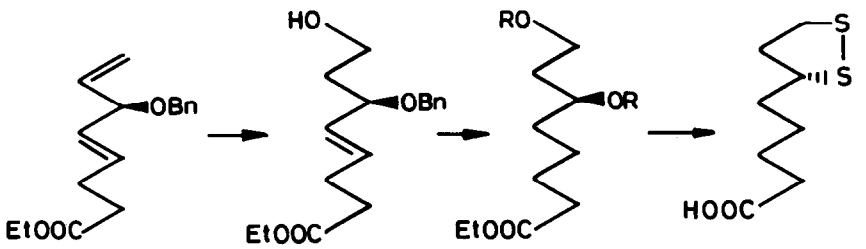
Scheme - 1



The ready availability of optically active 1 by this method prompted us to explore its transformation into (R)-(+)-α-lipoic acid, a cofactor in biochemical decarboxylation[7] of α-keto acids. (R,R)-1 was treated with dibutyltin oxide[8] in refluxing toluene and then the resulting tin-derivative 6 was treated with 1.2 eq. of benzyl bromide in DMF at 100° to afford mono-benzyl ether 7 (77%).

In an alternative but direct approach towards 7, 2 was first converted into dibutyltin derivative 8 which, with 1.2 eq. of benzyl bromide in DMF afforded the mono-benzyl ether. The latter product was acetylated with acetic anhydride - pyridine to give 9. Hydrolysis of 9 followed by mesylation gave 10 which on treatment with sodium iodide and zinc dust in DMF and deacetylation with sodium methoxide afforded 7 (40%). (Scheme 1).

Scheme - 2



11 12 13 R = H 14 R = Ms 15

The Claisen-ester rearrangement[9] of 7 with excess of triethylorthoacetate and catalytic amount of propionic acid at 145° gave the diene-ester 11 (81%). Selective hydroboration-oxidation of the terminal double-bond was achieved with 9-BBN and the resulting product 12 (80%) was hydrogenated with palladised charcoal at normal pressure and room temperature to afford the diol 13 (76%). Transformation of 13 into (R)-(+)- α -lipoic acid was effected by the procedure of Golding et al.[10] according to which the diol 13 was first converted to the dimesylate 14. Reaction of 14 with sodium sulfide-sulfur in DMF at 90° and hydrolysis afforded (R)-15 whose ^{1}H-n.m.r. spectrum and $[\alpha]_D$ values were comparable with the reported data.[11-13] (Scheme 2).

Further utility of (R,R)-1 in the synthesis of other natural products is being explored.

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