

The Enantiospecific Synthesis of Dihydromevinolin from L-Glutamic Acid

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An enantiospecific synthesis of the diol (**3**), a compound which has previously been converted into dihydromevinolin, is reported.

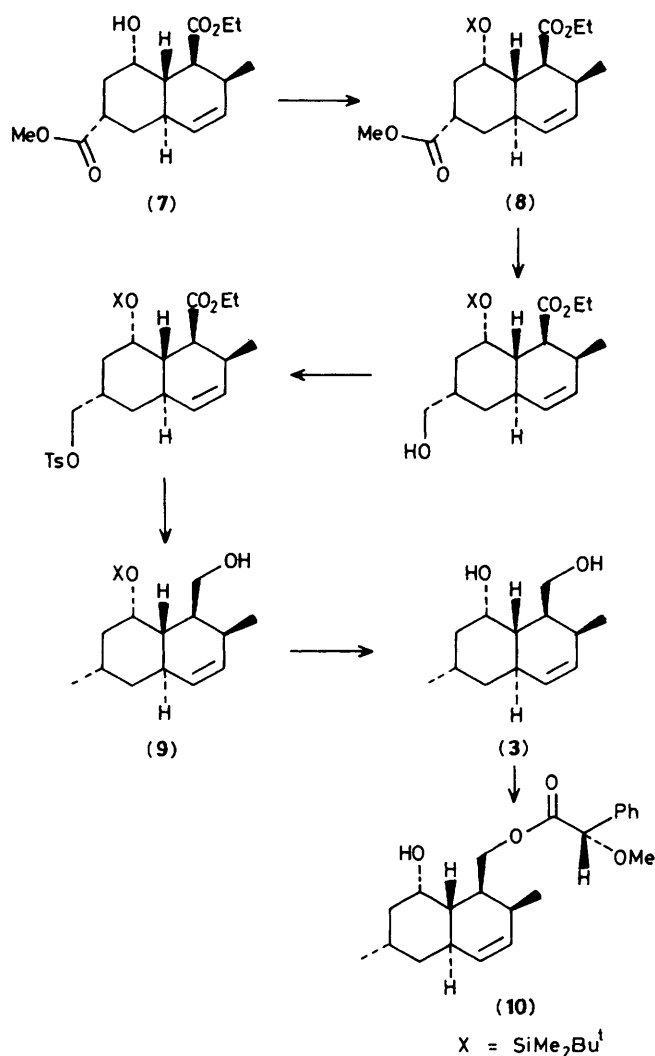
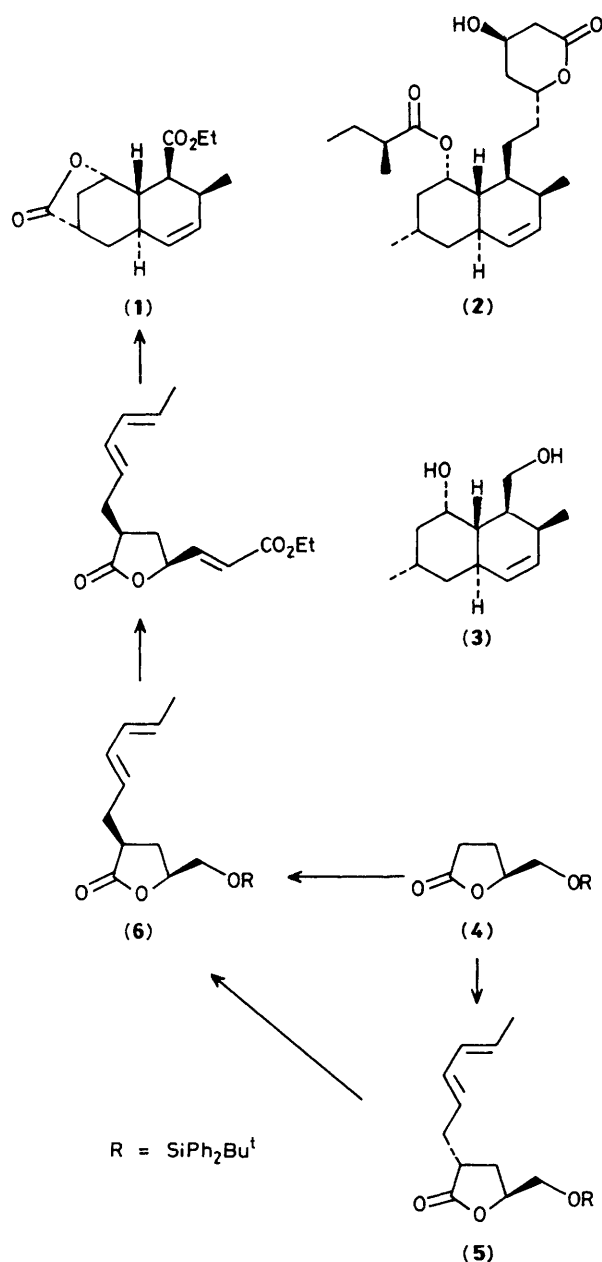
The mevinic acids are a series of fungal metabolites which have attracted a great deal of interest¹ owing to their ability to lower blood cholesterol levels in both test animals and humans.² Recently we reported³ the synthesis of lactone (**1**), a potential intermediate in the synthesis of one member of this series, dihydromevinolin (**2**). In this communication we report improvements to the synthesis of (**1**) and its efficient conversion into (**3**), a compound which has previously been used in the synthesis of dihydromevinolin.^{4†}

For the synthesis of (**1**) we reported that lactone (**4**; R = SiMe₂Bu^t) could be alkylated to give (**5**; R = SiMe₂Bu^t) and (**6**; R = SiMe₂Bu^t) in a ratio of 14:1. The desired *cis* compound (**6**; R = SiMe₂Bu^t) was then obtained by enolate formation and kinetic protonation. The two drawbacks with this approach were that it required two steps and the ratio of *cis* to *trans* isomers obtained was not particularly high. We now report that by changing the protecting group R from SiMe₂Bu^t to SiPh₂Bu^t we can carry out this conversion in one

pot and improve the ratio of *cis*:*trans* isomers from 1.5:1 to 4.5:1.

Treatment of lactone (**4**; R = SiPh₂Bu^t) with sodium hexamethyldisilazide and 1-bromohexa-2,4-diene followed by lithium hexamethyldisilazide and *t*-butyl bromide (as the proton source) gave (**6**; R = SiPh₂Bu^t) in 65% yield together with *ca.* 14% of the *trans* compound (**5**; R = SiPh₂Bu^t). Deprotection, Swern-Wittig, and Diels-Alder cyclisation then gave lactone (**1**). Reaction of (**1**) with sodium methoxide in tetrahydrofuran (THF) gave the ring opened methyl ester (**7**) in almost quantitative yield. Protection of the secondary alcohol in (**7**) proved troublesome owing to the ease with which (**7**) ring closed to form (**1**). However, protection could be achieved by using *t*-butyldimethylsilyl trifluoromethanesulphonate and lutidine⁵ which gave silyl ether (**8**) in 90% yield. The ethyl ester in (**8**) is extremely hindered, hence selective reduction of the methyl ester could be easily achieved using lithium triethylborohydride. Tosylation of the primary alcohol, followed by treatment with excess lithium triethylborohydride in THF at reflux, reduced the tosylate to a methyl

† All new compounds gave satisfactory elemental analyses.



In conclusion we have described a short (9 steps), efficient [30% overall yield from (4)], enantiospecific synthesis of a diol (3), a compound which has previously been transformed into dihydromevinolin.

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group and the ethyl ester to an alcohol. The overall yield for the conversion of (8) to (9) was 80% and no column chromatography was required.

Deprotection of (9) gave the diol (3) $\{[\alpha]_D + 152^\circ$ (c 0.98, $\text{CHCl}_3\}$ whose high-field ^1H n.m.r. spectrum was identical to that reported⁴ for the racemic material. In Heathcock's synthesis⁴ of dihydromevinolin, the diol (3) was resolved[‡] via its O-methylmandelate ester (10). Compound (3) was therefore converted to (10) and the optical rotation compared with the value obtained for the resolved material $\{[\alpha]_D + 138^\circ$ (c 1.24, $\text{CHCl}_3\}$; lit.⁴ $[\alpha]_D + 130^\circ$ (c 1.24, $\text{CHCl}_3\}$. The comparison clearly shows that (3), obtained above, does have the correct absolute stereochemistry and is of high optical purity.

[‡] (S)-(+)-O-Methylmandelic acid was used.