The Enantiospecific Synthesis of Dihydromevinolin from L-Glutamic Acid

Alan H. Davidson,[a]* Andrew J. Jones,[a] Chris D. Floyd,[b] Christopher Lewis,[a] and Peter L. Myers[b]

[a] *Department of Applied Chemistry, UWIST, P.O. Box 13, Cardiff CF1 3XF, U.K.*
[b] *G. D. Searle Research Ltd., High Wycombe HP12 4HL, U.K.*

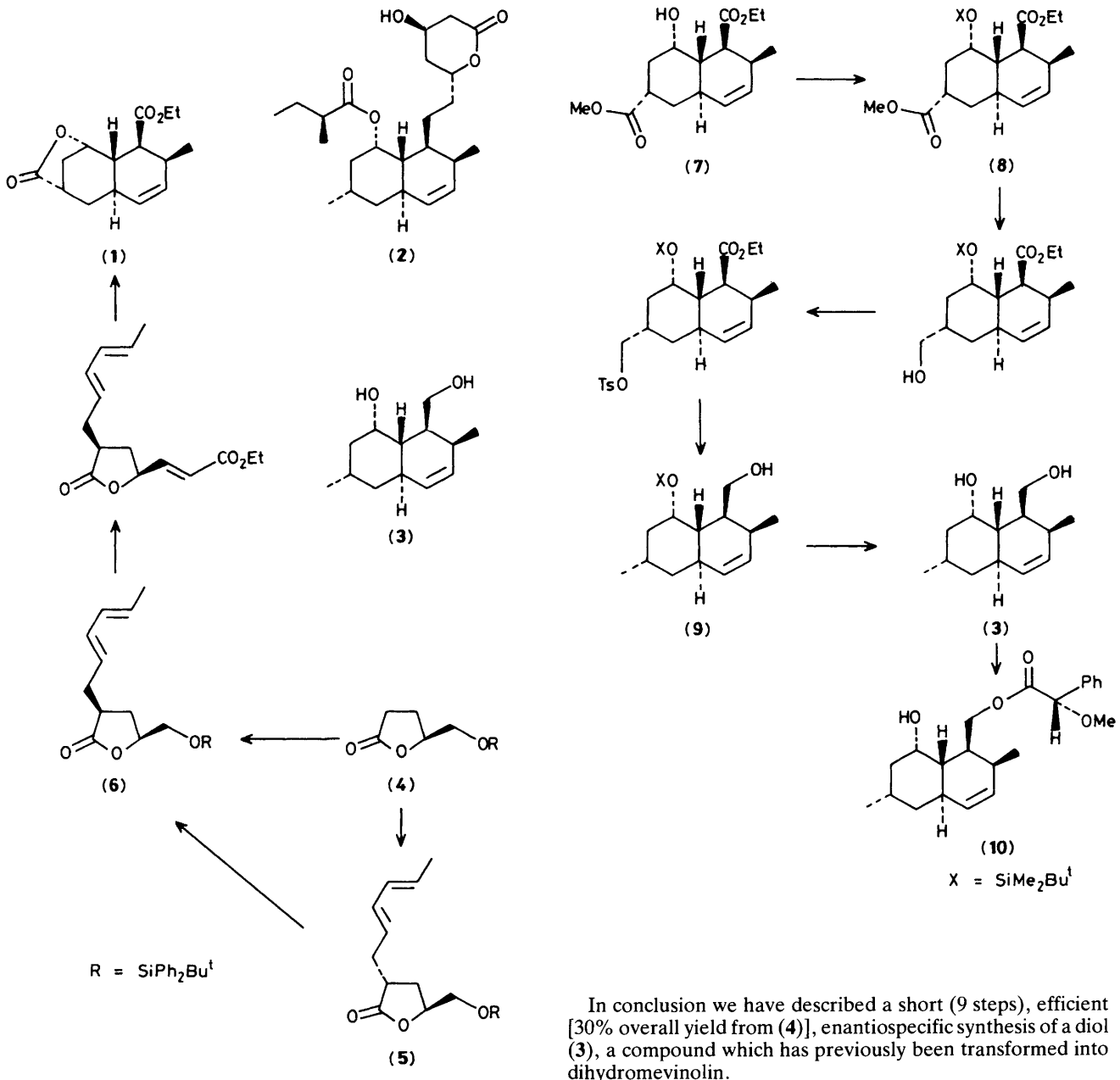
An enantiospecific synthesis of the diol (**3**), a compound which has previously been converted into dihydromevinolin, is reported.

The mevinic acids are a series of fungal metabolites which have attracted a great deal of interest[1] owing to their ability to lower blood cholesterol levels in both test animals and humans.[2] Recently we reported[3] 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 = $SiMe_2Bu^t$) could be alkylated to give (**5**; R = $SiMe_2Bu^t$) and (**6**; R = $SiMe_2Bu^t$) in a ratio of 14:1. The desired *cis* compound (**6**; R = $SiMe_2Bu^t$) 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 $SiMe_2Bu^t$ to $SiPh_2Bu^t$ 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 = $SiPh_2Bu^t$) with sodium hexamethyldisilazide and 1-bromohexa-2,4-diene followed by lithium hexamethyldisilazide and t-butyl bromide (as the proton source) gave (**6**; R = $SiPh_2Bu^t$) in 65% yield together with *ca.* 14% of the *trans* compound (**5**; R = $SiPh_2Bu^t$). 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 lutidine[5] 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.



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° (*c* 0.98, $CHCl_3$)} whose high-field ^1H n.m.r. spectrum was identical to that reported[4] for the racemic material. In Heathcock's synthesis[4] 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° (*c* 1.24, $CHCl_3$); lit.[4] $[\alpha]_D$ + 130° (*c* 1.24, $CHCl_3$)}. 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.

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.

We thank the S.E.R.C. and G. D. Searle for a Co-operative Research Grant (C. N. L.) and CASE award (A. J. J.), and British Bio-technology for additional funding.

Received, 29th July 1987; Com. 1101

References

1 C. H. Heathcock and T. Rosen, *Tetrahedron*, 1986, **42**, 4909.
2 A. Endo, *Trends Biochem. Sci.*, 1981, **6**, 10; A. Endo, *Methods Enzymol.*, Sect. D, 1981, **72**, 684; T. J. Bach and H. K. Lichtenthaler, *Z. Naturforsch., Teil. C*, 1983, **38**, 212.
3 A. H. Davidson, C. D. Floyd, A. J. Jones, and P. L. Myers, *J. Chem. Soc., Chem. Commun.*, 1985, 1662.
4 C. H. Heathcock and S. J. Hecker, *J. Am. Chem. Soc.*, 1986, **108**, 4586.
5 E. J. Corey, H. Cho, C. Rucker, and D. H. Hua, *Tetrahedron Lett.*, 1981, **22**, 3455.