THE CONFIGURATIONS OF (-)-2,3,3-TRIMETHYL-2-HYDROXYBUTANOIC ACID, Me₃CC(Me)(OH)CO₂H, (-)-3,3,4-TRIMETHYL-3-HYDROXY-1-PENTYNE AND (-)-3-t-BUTYL-3-METHYL-1-CHLOROALLENE

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Abstract: The configurations of the title compounds are reassigned, based on stereoselective syntheses of the hydroxyacid and corresponding glycol and application of Cram's, Prelog's and Sharpless' rules.

In the late 1970's we developed a highly enantioselective (asymmetric) synthesis¹ based on a chiral oxathiane² as chiral auxiliary. The method was subsequently³ applied to the synthesis of tertiary α -hydroxyacids as shown in Scheme 1. In the original three cases studied³ and in all subsequent applications⁴ we found that the configuration of the product could be correctly



Scheme 1

predicted based on Cram's chelate rule⁵ assuming that the chelating atom was the oxygen of the oxathiane ring. Thus if R has precedence over R' in the Cahn-Ingold-Prelog sequence rules, the configuration of the product shown in Scheme 1 is \underline{S} .

There was one apparent exception.⁶ Application of the method to the case where $R = (CH_3)_3 C$ and $R' = CH_3$ gave the levorotatory acid which should thus have the <u>S</u> configuration (A).⁷ However, the <u>S</u> configuration had previously been assigned⁸ to the dextrorotatory enantiomer on the basis of Prelog's rule⁹ by an enantioselective synthesis following the route shown in Scheme 2. This case is of particular importance, since acid A has been configurationally correlated with (-)-3,3,4-trimethyl-3-hydroxy-l-pentyne (cf. Scheme 3) by oxidation of the latter; the levorotatory propargylic alcohol, in turn, has been correlated⁸ (Scheme 3) with $(-)-3-\underline{t}-butyl-3-methyl-l-chloroallene, the first allene whose absolute configuration was thus (purportedly) determined.$



Scheme 2



Scheme 3

While there was the possibility that Gram's chelate rule might have failed in the case of the bulky ketone precursor (Scheme 1, R = t-butyl), we contemplated the alternative possibility that the earlier work⁸ had miscarried because of occurrence of kinetic resolution in the saponification of the menthyl ester depicted in Scheme 2. Prelog⁹ had observed such kinetic resolution in his original work; if saponification is incomplete and if the minor diastereomeric menthyl ester adduct is saponified faster than the major one, the configuration deduced from the rotation of the saponification product may be false. In the present case, the probability of such an occurrence seemed enhanced because a) the yield achieved in the original saponification⁸ was low and b) the specific rotation of the acid so obtained was low (<1°). We therefore reduced the menthyl ester to the glycol corresponding to the acid (Scheme 2); this reaction is nearly quantitative (and can thus not lead to kinetic resolution) and the rotation of the glycol is much higher than that of the acid. The (S)-glycol obtained from the menthyl ester has the same (-) rotation as the glycol obtained by reduction of the (presumably) (S)-acid obtained by the oxathiane route (A, Scheme 1) via the corresponding (dextrorotatory) methyl ester. Moreover the same dextrorotatory methyl ester was obtained by esterification of the acid obtained by the menthyl ester route (Scheme 2) (its specific rotation is considerably larger than that of the acid).

Finally we repeated the saponification of the menthyl ester shown in Scheme 2 with a reaction time of 91 hr. This produced the acid in 83% yield and it was levorotatory. Thus the rotations of all three products of the two reaction schemes (1 and 2) agree: the <u>S</u> configuration must be assigned to the (-)-acid, the (-)-glycol and the (+)-methyl ester. It follows that the opposite (<u>R</u>) configuration must now be assigned to the levorotatory pentyne¹⁰ shown in Scheme 3 (since its oxidation yields the dextrorotatory acid) as well as to the levorotatory allene obtained from it, provided the configurational correlation made by Landor⁸ for the thionyl chloride reaction is correct, which, in the light of later work,^{11,12} is virtually certain.

While the above work was in process, Baldwin¹³ provided yet another piece of evidence the the <u>S</u> configuration of the levorotatory glycol shown in Scheme 2 by preparing it via Sharpless oxidation¹⁴ (followed by hydride reduction) of the 2-<u>t</u>-butylallyl alcohol, $(CH_3)_3C-C(CH_2OH)=CH_2$ using (+)-diisopropyl tartrate as the chiral auxiliary. Cram's, Prelog's and Sharpless' rules thus agree in the assignment of the configurations mentioned above.

The above configurational assignment was completed in 1982 and was submitted as a communication to the editor at that time but was rejected on the referee's advice who said that it rested on empirical rules of kinetic reactivity which might be wrong. While there is a finite chance of any such rule being wrong (say, pessimistically, 10%), the chances of all three rules being wrong would, with this assumption, be no more than 0.1%. Of course, the problem could be resolved unequivocally by an X-ray structure analysis of compound A (Scheme 1); unfortunately this compound, though solid, is not suitable for crystallography and, so far, we have not been able to prepare a derivative which is.

In the light of recent, fairly intensive work on the configuration of allenes,¹⁵ the misassignment of the configuration of the chloroallene shown in Scheme 3 has caused a certain amount of confusion.¹⁶ It is therefore fortunate that a paper has finally appeared¹² in which - on the basis of mechanistic analogies - the configuration of the compounds shown in Scheme 3 has been set straight, five years after we attempted to do so. We must point out, however, that the speculations¹² as to why Prelog's rule failed in the case of the menthyl ester shown in Scheme 3 are misplaced: Prelog's rule, in fact, is perfectly valid in this case!

Acknowledgement. This work was supported by NSF grant CHE-7828118.

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(Received in USA 14 May 1987)

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