A New Synthesis of Chiral Acetic Acid

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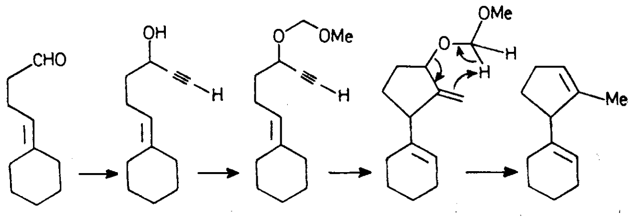
Summary Pyrolysis of the doubly-labelled chiral ether (**7**) leads to the formation of a product containing a chiral methyl group of predictable configuration, thus providing a new method for the generation of chiral acetic acid.

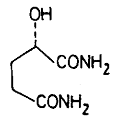
Specimens of chiral acetic acid with a given configuration have been prepared so far by two routes. One of these relies on the chemical resolution of a doubly-labelled racemic intermediate,[1] while the second rests in part upon enzymic manipulation of substrates;[2] in both syntheses at least one of the labels is introduced as a hydride ion. We now report a different preparation of chiral acetic acid.

The key reaction of the new synthesis was first investigated with the racemic form of the propargylic ether (**3**), available from (**1**)[3] by its conversion to the propargylic alcohol (**2**) and treatment of the latter with chloromethyl methyl ether in *NN*-diethylaniline. Pyrolysis of (**3**) in a sealed tube at 260 °C for 2·5 h gave methyl formate and, in 80% isolated yield, a doubly-unsaturated bicyclic hydrocarbon $C_{12}H_{18}$, which on the basis of its spectral data [*inter alia* ^{1}H n.m.r. signals at δ 1·6 (3H), 3·0 (1H) and 5·4 (2H)] was assigned structure (**5**). A similar overall transformation resulting in the production of a known hydrocarbon was observed with the corresponding ether from dehydrolinaloöl. When the pyrolysis of (**3**) was monitored by n.m.r. spectroscopy it was found that the disappearance of the acetylenic hydrogen was much faster than the appearance of methyl formate, and transient signals could be observed at δ 4·5—4·9 (multiplets), 5·0 and 5·2. This is in keeping with the intermediary presence of (**4**) in the reaction. Accordingly, formation of the product (**5**) can be described as the outcome of two successive symmetry-allowed thermal processes, an ene reaction, (**3**) → (**4**), followed by a reductive elimination [*cf.* arrows in (**4**)]†

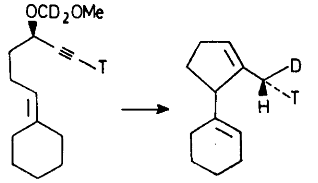
The optically active intermediate required for the new synthesis was obtained in the following way. Esterification of racemic (**2**) with (*R*)-*N*-phthaloyl-β-leucine, available by the Arndt-Eistert reaction of the lower homologue, was accomplished by the method of Brewster and Ciotti.[4] Fractional crystallization of the mixture in toluene–pentane gave one of the diastereomeric esters, m.p. 96 °C, $[\alpha]_D^{25}$ $+32°$ (*c* 0·6, EtOH), shown to be pure by its n.m.r. spectrum. Hydrolysis of this ester gave an optically active form of (**2**) with $[\alpha]_D^{25}$ $-21°$ (*c* 0·2, EtOH). The antipodal compound was prepared in a similar way using the (*S*)-form of the resolving agent. The (*S*)-configuration of the (+)-propargylic alcohol was established by converting its acetate through ozonolysis, oxidation with hydrogen peroxide, esterification, and ammonolysis to the known[5] (*S*)-diamide (**6**), m.p. 187 °C, $[\alpha]_D^{25}$ $-35°$ (*c* 0·5, H_2O).



(1) (2) (3) (4) (5)



(6)



(7) (8)

A sample containing the optically pure doubly-labelled species (**7**) was obtained by treatment of the (*R*)-(−)-alcohol with chloromethyl methyl ether fully deuteriated in the methylene group[6] and subsequent exchange of the acetylenic hydrogen with tritiated water to which a trace

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† Additional examples illustrating the general value of the reductive elimination step have been studied by T. Scholl and Q. Branca and will be reported elsewhere.

amount of n-butyl-lithium had been added. Pyrolysis of this material gave the doubly-labelled hydrocarbon (**8**) in which the sense of the chirality of the methyl group is dictated by the absolute configuration of the starting material (**7**) and by the strict geometrical requirements imposed upon the two transition states that lead to its formation. Kuhn-Roth oxidation of (**8**) took place with negligible exchange and gave a sample of chiral acetic acid which was admixed with a ^{14}C-standard as an internal reference. When subjected to the previously described [1,2] configurational assay, this sample gave a specimen of (*S*)-malate which retained 77% of its tritium content upon equilibration with fumarase. This result verifies the predicted (*R*)-configuration of the methyl group in (**8**) and indicates a high degree of optical purity.[7]

As the two labels are introduced from water in a very late step of the reaction sequence, and as both enantiomers of the unlabelled intermediate (**2**) can be made available in reasonable quantities, the synthesis described herein seems particularly apt for the preparation of samples of chiral acetic acid possessing a desired configuration as well as a high specific activity.

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