

# The Absolute Configuration of 4-(Trichloromethyl)oxetan-2-one; A Case of Double Anchimeric Assistance with Inversion

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It has been shown that the absolute configuration of the oxetan-2-one (**1**) is opposite to that of its hydrolysis product, *S*-(-)-malic acid (**3**).

4-(Trichloromethyl)oxetan-2-one (**1**) is a key intermediate in the synthesis of both enantiomers of malic acid (**3**)<sup>1</sup> (Scheme 1). Its primary acid-hydrolysis product, 4,4,4-trichloro-3-hydroxybutanoic acid (**2**) has been prepared and resolved as its optical isomers.<sup>2</sup> The enantiomer of (**2**) having an  $[\alpha]_{546}^{20}$  value of 26.1 (*c* 1, acetone) was hydrolysed by McKenzie<sup>2</sup> to yield *S*-(-)-malic acid (**3**),  $[\alpha]_{\text{D}}^{20} -28.6$  (*c* 5.5, pyridine).

Although the simplicity of this hydrolytic transformation might tempt us to assign the *S*-configuration to the trichlorohydroxy acid (**2**), and by further extrapolation to the starting oxetan-2-one (**1**), this leads to the wrong answer.

We have found that direct reduction of the oxetanone (**1**),  $[\alpha]_{578}^{20} -15.6$  (*c* 1, cyclohexane) leads to the trichlorodiols (**4**),  $[\alpha]_{578}^{20} 53.4$  (*c* 1, EtOH) which can, by catalytic hydrogenolysis, be converted into butane-1,3-diol (**5**),  $[\alpha]_{\text{D}}^{20} 30.1$  (*c* 3, EtOH), whose absolute configuration is known to be *S*.<sup>3,4</sup> Furthermore, acid ethanolsis of the same oxetan-2-one, followed by catalytic hydrogenolysis, gives ethyl 3-hydroxybutanoate (**7**),  $[\alpha]_{\text{D}}^{20} 44.4$  (*c* 1.3,  $\text{CHCl}_3$ ), whose absolute configuration is known to be *S*.<sup>4,5</sup>

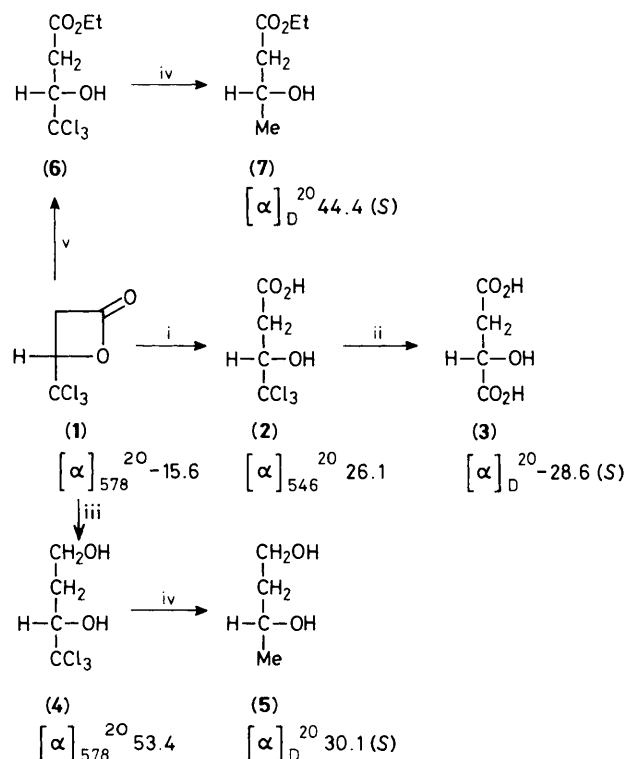
Applying priority rules to the different substituents on the chiral carbon atoms in the above two examples, one must conclude that, if no inversion has taken place during reactions leading to (**5**) or (**7**), the starting oxetan-2-one must have had the *R* configuration.

These findings are in apparent contradiction with the fact that the oxetan-2-one yields *S*-(-)-malic acid (**3**) upon hydrolysis and must therefore have the *S* configuration. We have to conclude that inversion has taken place somewhere along the reaction path leading to (**5**) and (**7**) or that leading to (**3**). Since complete inversion at a chiral carbon bearing a hydroxy group during  $\text{LiAlH}_4$  reduction, acid ethanolsis, and acid hydrolysis of the oxetan-2-one, or during catalytic hydrogenolysis seems unlikely, we conclude that inversion has taken place during the basic hydrolysis of compound (**2**), leading to malic acid. For this inversion process we propose a double anchimeric assistance mechanism (Scheme 2).

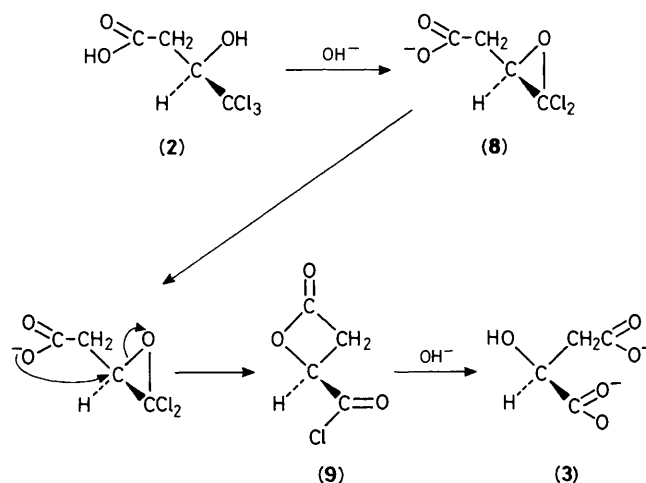
Treatment of (**2**) with aqueous base leads, after formation of the carboxylate anion, to the epoxide (**8**), with liberation of HCl. Thus, with the anchimeric assistance of the hydroxy group, one of the chlorine atoms is expelled from the molecule. The dichloroepoxide (**8**) is then ring opened by intramolecular backside attack of the carboxylate anion. This second case of anchimeric assistance leads to complete inversion at the chiral centre. The newly formed oxetanone (**9**) is hydrolysed further to malic acid, without involvement of the chiral centre.

The formation of dichloroepoxides from trichloromethyl alcohols upon treatment with base is of course well documented in the literature.<sup>6</sup> In the case of 1,1,1,3,3,3-hexachloropropan-2-ol, the epoxide is a stable compound and can be isolated in 74% yield.<sup>7</sup> However, since basic hydrolysis of chiral trichloromethyl alcohols, *via* dichloroepoxides, usually leads to considerable racemization,<sup>8</sup> this mechanism was rejected by us earlier.

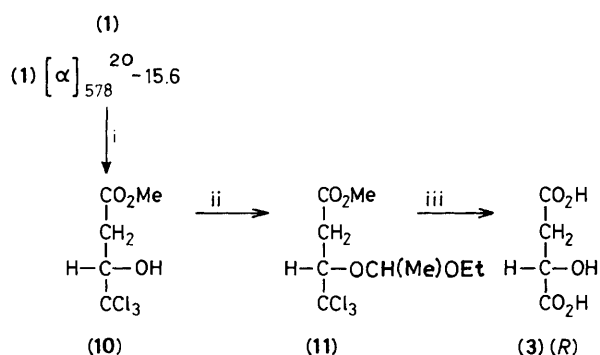
The importance of the OH group in the hydrolysis of acid



Scheme 1. i, 4 M HCl, reflux; ii, NaOH (5 equiv.),  $\text{H}_2\text{O}$ , room temp.; iii,  $\text{LiAlH}_4$ , tetrahydrofuran, 0 °C; iv, Pd/C, MeOH,  $\text{K}_2\text{CO}_3$ ,  $\text{H}_2$ , 3 atm.; v, HCl, EtOH, reflux. No absolute stereochemistry is implied.



Scheme 2



**Scheme 3.** i, MeOH, HCl, reflux; ii, CF<sub>3</sub>CO<sub>2</sub>H, ethyl vinyl ether, reflux; iii, 10% NaOH, reflux, 48 h.

(2) is shown by comparison of the reaction sequence in Scheme 3 with the conversion (1)→(2)→(3), Scheme 1. Mild hydrolysis of acid (2) (5 equiv. NaOH, H<sub>2</sub>O, room temperature), prepared from oxetan-2-one [ $\alpha$ ]<sub>578</sub><sup>20</sup> -15.6 leads to *S*-(-)-malic acid in excellent yield (85–90%). Methanolysis of the same oxetan-2-one to the methyl ester (10), protection of the free hydroxy group with ethyl vinyl ether to give (11), and subsequent hydrolysis under much more drastic conditions (48 h reflux, 10% NaOH) leads, after initial hydrolysis of the methyl ester, to the predominant formation of the *R*-(+)-malic acid (3) (*R*), among other products.

The results presented above force us to propose a double anchimeric assistance mechanism,<sup>9</sup> to account for the complete inversion at the chiral centre. Moreover we have to conclude that the 4-(trichloromethyl)oxetan-2-one [ $\alpha$ ]<sub>578</sub><sup>20</sup> -15.6, to which we initially<sup>1</sup> assigned the *S* configuration, has the *R* configuration.

Received, 23rd May 1984; Com. 721

## References

- H. Wynberg and E. G. J. Staring, *J. Am. Chem. Soc.*, 1982, **104**, 166.
- A. McKenzie, H. J. Plenderleith, and N. Walker, *J. Chem. Soc.*, 1923, **123**, 2875; A. McKenzie and H. J. Plenderleith, *ibid.*, p. 1090.
- H. Gerlach, K. Oertle, and A. Thalmann, *Helv. Chim. Acta*, 1976, **59**, 755.
- E. Hungerbühler, D. Seebach, and D. Wasmuth, *Helv. Chim. Acta*, 1981, **64**, 1467.
- K. Mori and H. Watanabe, *Tetrahedron*, 1984, **40**, 299; K. Mori, *ibid.*, 1981, **37**, 1341.
- W. Reeve, *Synthesis*, 1971, 131; W. Reeve and C. W. Woods, *J. Am. Chem. Soc.*, 1960, **82**, 4062; J. T. Lai, *J. Org. Chem.*, 1980, **45**, 754; J. T. Lai, *Synthesis*, 1982, 72.
- O. Neunhoeffer and A. Spange, *Liebigs Ann. Chem.*, 1960, **632**, 22.
- R. J. Bianchi, Dissertation, University of Maryland, 1967.
- A net retention of stereochemistry in the hydrolysis of chiral trichloromethyl alcohols has been proposed: J. P. Benner, G. B. Gill, S. J. Parrott, and B. Wallace, *J. Chem. Soc., Perkin Trans. 2*, 1984, 331.