Stereospecificity in Radical Carbon–Carbon Bond Formation Reactions Based on Tartaric Acid

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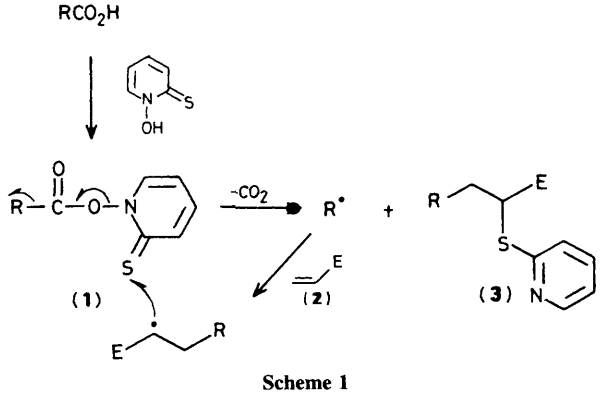
Radical decarboxylative addition to activated alkenes, using the thiohydroxamic ester method, of a suitably protected derivative of (+)-L-tartaric acid leads to overall substitution of the carboxy group with essentially complete retention of configuration.

Tartaric acid has always held a prominent position in the chemist's ever expanding list of chiral starting materials. It is cheap and readily available in both enantiomeric forms. In addition, tartaric acid possesses a two-fold axis of symmetry which causes all the functional groups to exist as homotopic pairs. This simplifying feature permeates its chemistry.

So far, the elaboration of tartaric acid has relied almost exclusively on ionic reactions[1] with radical processes playing only a small part if at all. Given the ease of formation of carbon–carbon bonds[2] using radical addition such reactions would hold considerable synthetic promise if they could be applied to tartaric acid with acceptable stereoselectivity.

Over the past few years we have demonstrated the utility of *N*-hydroxy-2-thiopyridone esters (**1**) as mild and convenient sources of carbon radicals.[3] The latter are easily captured by electron-poor alkenes (**2**) to give, ultimately, compounds of



Scheme 1

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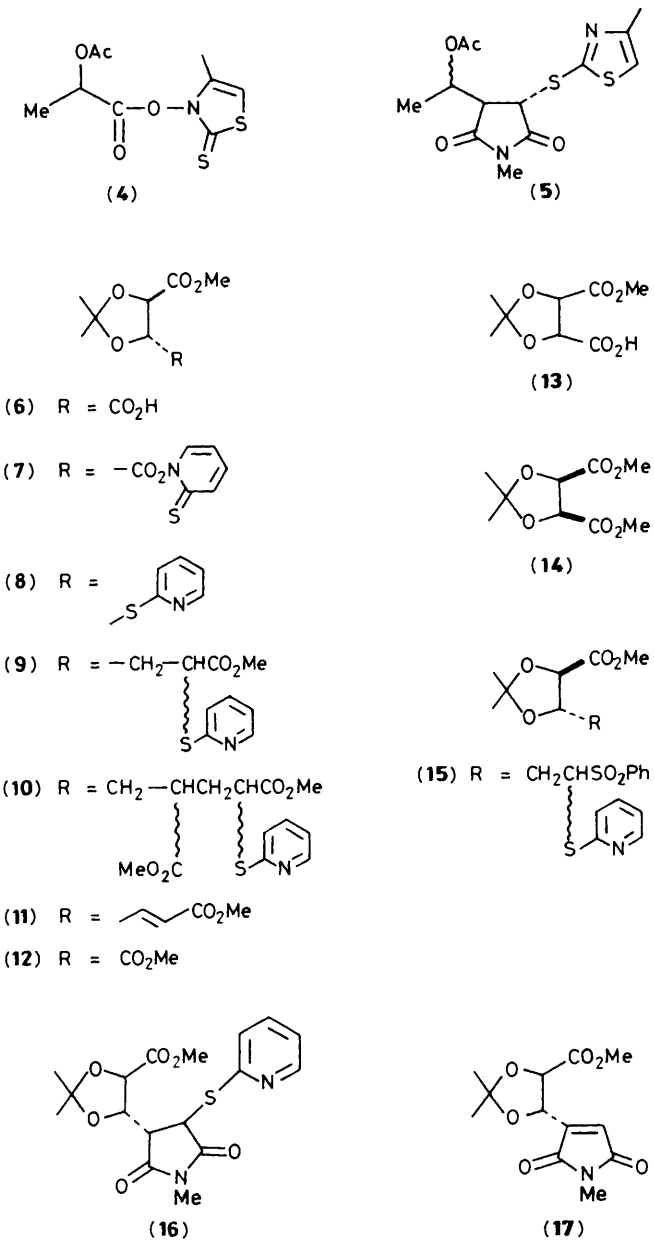

Scheme 2

structure (**3**) as outlined in Scheme 1. As far as the carboxylic acid is concerned, the overall process may be termed as a radical decarboxylative addition.

Applications of this reaction to an open chain derivative of tartaric acid appeared fraught with difficulties from the outset. Apart from problems of β-elimination, the decarboxylation step would lead to a trivalent carbon with irretrievable loss of chirality. This aspect of radical chemistry is well precedented. We have had occasion to observe it ourselves in many instances. For example, heating of the (+)-L-lactic acid derivative (**4**) in the presence of *N*-methylmaleimide gave adduct (**5**) (87%) with complete racemisation. In the case of tartaric acid it was also unlikely that asymmetric induction by the other chiral centre would be sufficient to ensure good stereoselectivity.

To conserve all the stereochemical imprint in tartaric acid, the use of a cyclic derivative such as the known isopropylidene *R,R*-monoester (**6**)[5] seems much more promising. Not only is β-elimination more difficult in this case but also one of the faces of the dioxolane ring is encumbered by the methyl ester. The approach of the radical trap will therefore take place preferentially from the opposite side resulting in an overall retention of configuration (Scheme 2).

The preparation of ester (**7**) was achieved through the mixed anhydride method using isobutyl chloroformate.[6] Irradiation of (**7**) with a tungsten lamp in the absence of the radical trap gave sulphide (**8**) in 78% ($[\alpha]_2^{25}$ −214°, *c* 0.96, $CDCl_3$) as the only isomer detectable by n.m.r. spectroscopy. Although the *trans* relationship follows from the above stereochemical argument, the coupling constant of the ring hydrogens (5 Hz) does not allow an unambiguous conclusion to be drawn.[7] A more rigorous proof for the *trans* addition was obtained by a careful study of the methyl acrylate adduct (**9**).

This compound was obtained in 70% yield by irradiating (**7**) in the presence of methyl acrylate, as a mixture of diastereoisomers with respect to the newly created terminal asymmetric centre. Small amounts of the double addition product (**10**) (6%) and sulphide (**8**) (2%) were also isolated. Oxidation of the sulphide group in (**9**) to the sulphoxide by *m*-chloroperbenzoic acid followed by thermolysis in boiling toluene furnished cleanly the *trans* alkene (**11**) ($[\alpha]_D^{25}$ −35.4°, *c* 2.21, $CHCl_3$). Cleavage of the double bond with RuO_2–$NaIO_4$ in acetone–water and methylation with diazomethane gave (**12**) {$[\alpha]_D^{25}$ −58°, *c* 0.86, MeOH, b.p. 85 °C (0.15 mmHg)}, identical in all respects with an authentic sample {$[\alpha]_D^{25}$ −58.7°, *c* 0.81, MeOH, b.p. 85 °C (0.15 mmHg) lit.,[9] $[\alpha]_D^{25}$ −53.1°}. The retention of configuration during addition is thus confirmed. Although none of the *meso* isomer (**14**) could be detected by n.m.r. spectroscopy following the degradation sequence, careful h.p.l.c. analysis‡ of the crude degradation product (**12**) indicated nevertheless the presence of about 4% of (**14**) again by comparison with an authentic specimen.

An identical sequence of reactions performed this time on the racemic monoester (**13**), derived from the *meso* (**14**) by partial saponification, gave racemic (**12**), indicating essentially complete inversion of configuration in this case. Again h.p.l.c.‡ analysis of the crude degradation product of the racemic (**12**) showed the presence of about 4% of the *meso* diester (**14**).

The *trans* substitution of the dioxolane ring is thus firmly established. The stereoselectivity of the process is sufficiently high (*ca.* 25 : 1) for most practical purposes but could undoubtedly be improved, if necessary, by replacing either the methyl ester or the dioxolane ring with a bulkier one.

We have briefly examined two other alkenes: phenyl vinyl sulphone and *N*-methylmaleimide, which gave respectively adducts (**15**) and (**16**) in 70 and 93% yield. Both were mixtures of diastereoisomers as the stereochemistry of the asymmetric centres created beyond the dioxolane ring cannot be controlled. In the case of (**16**), we can safely assume however that the pyridyl sulphide and the dioxolane ring are *trans* to each other. Heating (**16**) with copper powder caused a smooth elimination of the pyridyl sulphide group to give the alkene (**17**) which distilled as formed.[8] The n.m.r. spectrum again indicated the presence of only one isomer.

Although we have modified only one of the carboxylic groups originally present in tartaric acid, the second could, in principle, also be transformed using the same procedure.

‡ The details of this part of the work will be published elsewhere. All new compounds have been characterised by spectral measurements and by microanalysis.

This time, the group introduced in the first decarboxylation should control the stereochemistry of the second substitution. An overall double retention can thus be confidently predicted.

These preliminary results are particularly encouraging. They reflect the mildness and efficiency of the decarboxylation reaction and give a glimpse of the possibilities for enantioselective syntheses from tartaric acid and related substances using modern radical chemistry.

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