

Stereoselective Radical Reactions of Some Tartaric and Glyceric Acid Derivatives

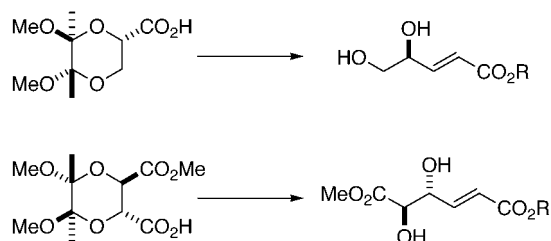
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ABSTRACT

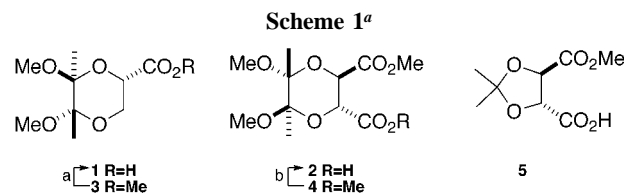


Free radicals generated by the decarboxylation of dimethoxydioxanecarboxylic acids derived from L-(+)-tartaric acid and L-glyceric acid added to some maleimides and acrylates with high stereoselectivity. This method provides easy access to some chiral building blocks.

Mixed anhydrides derived from aliphatic or alicyclic carboxylic acids and a suitable thiohydroxamic acid undergo a smooth free radical mediated decarboxylation leading to sulfides.^{1–3} The experimental conditions are mild enough to allow the application to substrates with labile functional groups. Furthermore, the inclusion of external radical traps into the system leads to a variety of synthetically useful extensions⁴ to the basic process.

Barton has previously applied his thiohydroxamic acid mixed anhydride technology to radical carbon–carbon bond

forming reactions, using the isopropylidene acetal of the monomethyl ester of tartaric acid **5** (Scheme 1).^{2,5} The 2,3-



^a (a) KOH 2 M/MeOH, rt, 92%; (b) KOH (0.2 M, 1.05 equiv), MeOH/THF (1:4), 0 °C/rt, 96%.

dimethoxybutane-2,3-dioxy acetals of glyceric acid **1** as well as the 2,3-dimethoxybutane-2,3-dioxy acetal monomethyl ester of tartaric acid **2** are readily available in isomerically

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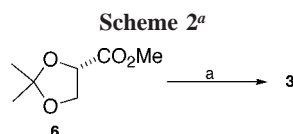
(3) Barton, D. H. R.; Gateau-Olesker, A.; Gero, S. D.; Lacher, B.; Tachdjian, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1987**, 1790–1792.

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pure form. They contain additional stereocenters which could control the conformation of the molecule and influence the stereochemical outcome of radical reactions. Free radicals derived from the tartaric acid derivative **2** by decarboxylation contain three stereocenters, one directly associated with the initial natural product and the other two indirectly associated. Likewise, free radicals, similarly derived from glyceric acid derivative **1**, only contains two stereocenters and these are both indirectly associated. Free radicals generated on a carbon atom adjacent to an oxygen atom in a six membered ring should be comparable to those generated at the anomeric position of sugars. It has been shown that an anomeric effect exists for free radical coupling reactions during the formation of C-glycosides,⁶ and an explanation has been proposed⁷ which links the stereoselectivity of these reactions to molecular conformation. We predicted that trapping of the free radicals derived from dioxanes **1** and **2**, using radical C–C bond forming traps, would result in the formation of a new axial substituent. If this held true then for the tartaric acid derivative, the stereochemistry at the stereogenic center in the tartrate skeleton should be the opposite to that formed during similar reactions of the isopropylidene acetal **5**.

The isopropylidene acetal of glyceric acid **6** was readily available from L-serine.⁸ A transacetalization reaction (Scheme 2) with 2,2,3,3-tetramethoxybutane (TMB) furnished methyl



^a (a) TMB, MeOH, *p*-TsOH, (CH₃O)₃CH, reflux, 98%.

ester **3** (98% yield), and after hydrolysis, acid **1** was produced in 92% yield. The tartrate monoacid **2** was also prepared by a controlled hydrolysis reaction of the diester **4**⁹ (Scheme 1). To show that no epimerization had occurred during these processes, samples of the freshly prepared acids were esterified with diazomethane and the original esters recovered unchanged.

On comparing the ¹H NMR spectra of ester **3** with that of acid **1**, differences in the coupling constants of the dd of H-1 were notable. Thus, in the methyl ester this signal had *J* = 11.1 Hz and *J* = 3.9 Hz, corresponding clearly to axial–axial and axial–equatorial interactions between H-1 and the H-2s. These constants correlated well with a chair conformation where the ester group was equatorial (Figure 1). However, in the case of acid **1**, the respective coupling

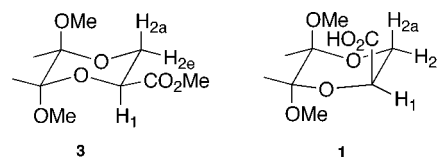
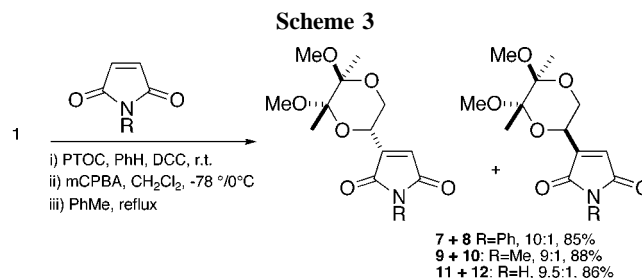


Figure 1.

constants were 8.3 and 6.8 Hz. Thus we concluded that this compound had adopted a distorted boat conformation, as indicated in Figure 1, placing the carboxylic acid group in a pseudoaxial position and H-1 eclipsed by one of the H-2, giving rise to the coupling constants observed. Acid **2** existed exclusively in the chair form as was evident from a typical axial–axial coupling constant (9.9 Hz).

From these two acids **1** and **2** the pyridinethione oxycarbonyl (PTOC) mixed anhydrides were formed at rt using DCC as coupling agent. Unusually, the addition of DMAP was found to be detrimental to the formation of the mixed anhydride. Subsequent decarboxylation in ambient light at rt produced the corresponding free radicals which were readily captured by good Michael acceptors such as maleimides and acrylate esters.

Glyceric acid derivative **1** afforded efficiently the addition compounds as mixtures of diastereoisomers. Oxidation of the sulfur atom with mCPBA at low temperatures and thermal elimination of the sulfenic acid in refluxing toluene (Scheme 3, Figure 2) afforded the substituted maleimides **7**,



9, and **11** and their isomers **8**, **10**, and **12**. The selectivity of the radical reaction was determined (NMR) and was found to be good (Scheme 3). As for the acid **1**, the coupling

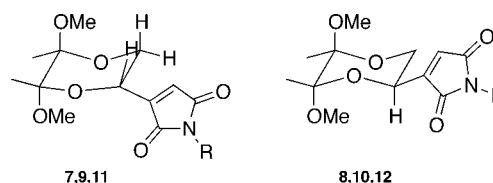


Figure 2.

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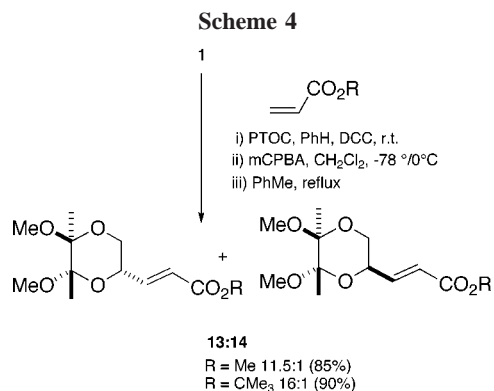
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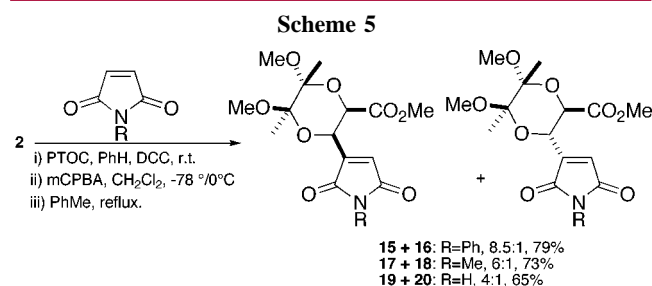
constants in the proton NMR spectra of **7**, **9**, and **11** showed that these compounds also presented the distorted boat conformation. Their isomers **8**, **10**, and **12** had a normal chair conformation, with typical values for the vicinal coupling constants. The nature of the *N*-substituent had little effect upon the stereoselectivity.

Using acrylates as radical traps (Scheme 4), slightly better selectivities were obtained (**13** and **14**), which improved with

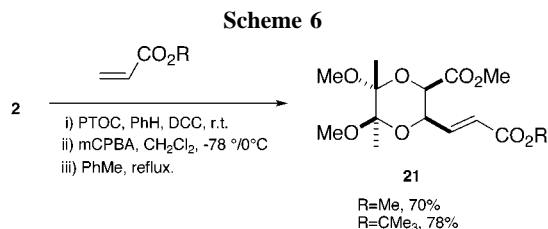


the bulkier *tert*-butyl ester. Contrary to the conformation observed with the maleimide substituents, both isomers **13** and **14** attained a chair conformation, possibly because of the less bulky nature of the acrylate moiety, even with large ester groups attached.

The thiohydroxamic anhydrides produced from tartaric acid derivative **2** (Schemes 5 and 6) reacted with maleimides



to form mainly the *cis* adducts **15**, **17**, and **19**, the stereochemistry of which was easily deduced from the vicinal coupling constants of the proton NMR spectrum and by



comparison with that of the *trans* isomers **16**, **18**, and **20**. It is of interest to note that the *cis/trans* selectivity for the addition decreased in the order *N*-phenylmaleimide > *N*-methylmaleimide > maleimide and is probably a function of the bulkyness of the *N*-substituent. Also different from the outcome of the glyceric acid experiments was the conformation of the products, with both isomers existing in the chair conformation. The trapping of free radicals derived from **2** with methyl acrylate afforded exclusively the *cis* product **21** (Scheme 6). The major isomer obtained by Barton and co-workers retained the original tartrate relative configuration, i.e., the *trans* isomer,² whereas in this study the major products were the *cis* isomers.

A more rigorous proof of the stereochemistry of the main products was obtained by oxidative cleavage of the double bond of the acrylate function of the addition products from both glyceric and tartaric acid derivatives (**13**:**14**, R = Me and **21**, R = Me, respectively) employing NaIO₄ and catalytic RuCl₃ (Schemes 7 and 8, Figure 3). From a mixture of **13**

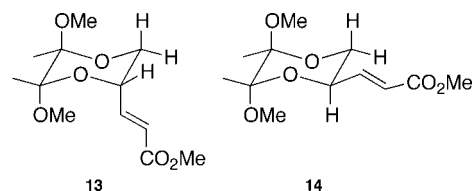
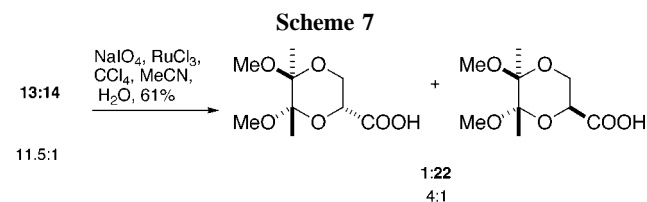


Figure 3. Conformations of compounds **13** and **14** as determined by NMR.

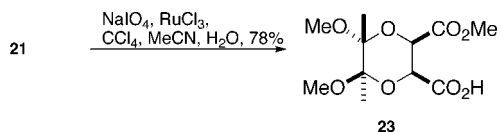
and **14** (11.5:1), a mixture of the acids **22** and **1** (4:1) (Scheme 7) was obtained, from which two conclusions could



be made: first, the major isomer from the addition reaction was probably the one with the *cis* configuration, and second, that during the oxidation, epimerization occurred, probably at the aldehyde stage of the two-step process. Barton et al. confirmed the stereochemistry of their products using the same oxidation followed by esterification of the acid formed. No epimerization was reported in this case, and no epimerization was observed when the ruthenium oxidation reaction was employed to form acid **23** from acrylate **21** (R = Me) (Scheme 8). The ¹H NMR spectrum of the acidic product clearly indicated that *cis* compound **23** had been formed and not *trans* acid **2** from which we had started.

Ozonolysis of a mixture of acrylates **13** and **14** followed by immediate reduction (NaBH₄) afforded the corresponding

Scheme 8



primary alcohols, with the major isomer having an NMR spectrum in accord with an axial hydroxymethyl group and isomeric with the alcohol produced by DIBAL-H reduction of starting ester **3**.

Deprotection of the acetal **15** and a mixture of **13** + **14** using TFA afforded, after chromatography, the diols **24**, $[\alpha]_{\text{D}}^{20} -38$ ($c = 0.4$, CH_2Cl_2), and **25**, $[\alpha]_{\text{D}}^{20} -7.3$ ($c = 2.62$, CH_2Cl_2) (4:1 *E:Z*),¹⁰ in good (94–99%) yield (Figure 4).

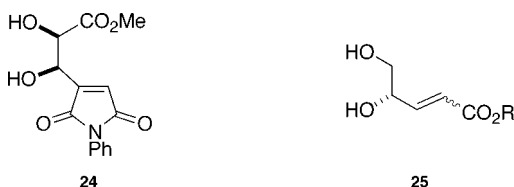


Figure 4.

In conclusion, using 2,3-dimethoxybutane-2,3-dioxy protected tartaric and glyceric acid derivatives it is possible to perform mild and stereoselectively efficient radical addition reactions. The stereoselectivity is possibly linked to an anomeric effect. In general, the major product is that predicted for an active anomeric effect. The conformation

of the radical intermediate is difficult to predict, but the products indicate that they may mimic to some extent the conformation of the starting acid. They are probably more flexible with less intramolecular interactions which could induce conformational preferences other than the chair form. The additions of the glyceric acid derived dioxane radical to acrylate are less selective than those of tartaric acid which has an adjacent carboxyl group. The effect of this group is seen where the additions to bulky maleimides are not as stereoselective as those involving the glycerate. This indicates that the stereoselectivity is probably not controlled exclusively by the conformational anomeric effect or a simple stereochemical preference.

The products obtained offer possibilities as useful intermediates for enantioselective syntheses. Furthermore, with the tartaric acid derived dioxane, it is possible to produce optically pure intermediates with the stereochemistry obtainable by manipulation of a carboxyl group of *meso*-tartaric acid.

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Supporting Information Available: NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) Although not verified, we concluded that compound **24** was probably enantiomerically pure whereas starting from a 11.5:1 mixture of **13** and **14**, compound **25** should have an ee of about 85%. For compound **25**, it was evident from both the ^{13}C and ^1H NMR spectra that the *E* and *Z* diastereoisomers were formed. The *Z* isomer had not lactonized.