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Resolution of a citric acid derivative: synthesis of (*R*)-(−)-homocitric acid-γ-lactone

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Abstract: Both the (*R*) and (*S*) enantiomers of the citric acid derivative **1** have been obtained in ≥90% ee *via* resolution of the racemate by fractional crystallisation of the (*S*) and (*R*)-α-methylbenzylamine salts respectively. The stereochemistry of (*R*)-**1** has been assigned by its conversion to (*R*)-(−)-homocitric acid utilising an Arndt–Eistert homologation followed by acid catalysed deprotection. © 1997 Elsevier Science Ltd

As part of a program on the use of citric acid in the synthesis of natural products and designed compounds we required access to both enantiomers of a suitably protected derivative.[1] Herein we report on a simple procedure which delivers multigram quantities of (*R*) and (*S*)-**1** (Figure 1). (*R*)-**1** was subsequently converted to (−)-homocitric acid-γ-lactone **8**.[2]

Our requirement for both enantiomers of a citric acid derivative suggested that a resolution strategy would be appropriate. We settled on derivative **1** which had the two prochiral carboxyl groups of citric acid differentiated as a methyl ester and an acid.[3]

Compound **1** was prepared by a modification of the procedure of Nau *et al.*[4] Thus dry pyrolysis of citric acid with paraformaldehyde at 156°C initially leads to melting then resolidification of the melt. Crude ^{1}H NMR showed this solid to be an approximately 1:1 mixture of citric acid and **2**, from which a 40–42% yield of **2** was obtained by crystallisation from water.[5] It was found that if DMSO (3 ml/10 g citric acid) was added then solidification was prevented at 156°C. On cooling, a solid was obtained which on crystallisation from water afforded a much improved 67% yield of **2**. Treatment of a suspension of **2** in $CHCl_3$ with $POCl_3$ according to the literature procedure afforded the corresponding glutaric anhydride **3** (85%) which smoothly ring opened in refluxing MeOH to afford **1** in quantitative yield as a colourless solid (m.p. 126–127°C diethyl ether) (Scheme 1).[6]

After some experimentation it was found that **1** could be resolved by treatment with α-methylbenzylamine (both enantiomers are readily available) to form a separable mixture of diastereoisomeric salts.[7] We have carried out this resolution on scales between 1 and 50 g. Typically **1** was dissolved in EtOH (10 ml/g at R.T.) and treated with (*S*)-α-methylbenzylamine. On standing, needle crystals separated (*ca.* 40%) which were shown by ^{1}H NMR to be present as a 5–7:1 mixture of diastereoisomers. A second crystallisation from hot EtOH (70°C)[8] produced a ≥95:5 mixture of

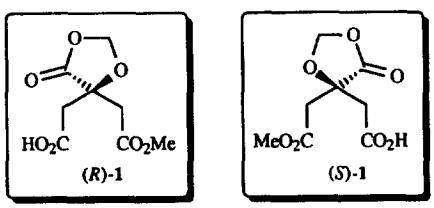

Figure 1.

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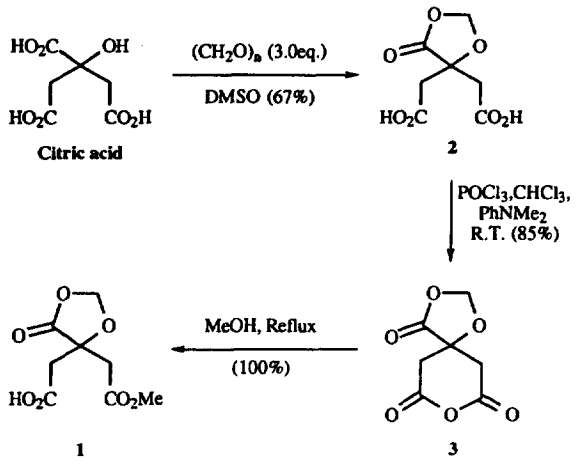
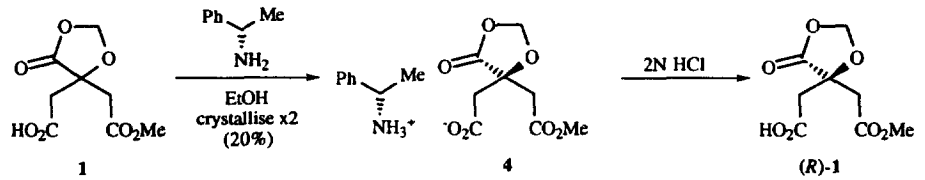


Scheme 1.

diastereoisomers in *ca.* 20% overall yield from which (*R*)-**1** could be recovered by washing the salt with 2 N HCl (Scheme 2). Due to the poor crystallinity of the (*S,S*) diastereoisomer, (*S*)-**1** was obtained by acid washing the mother liquor (2 N HCl) then repeating the above procedure with (*R*)-α-methylbenzylamine to give, after a single crystallisation and subsequent acid wash, (*S*)-**1** (20%, ≥90% ee).[9]

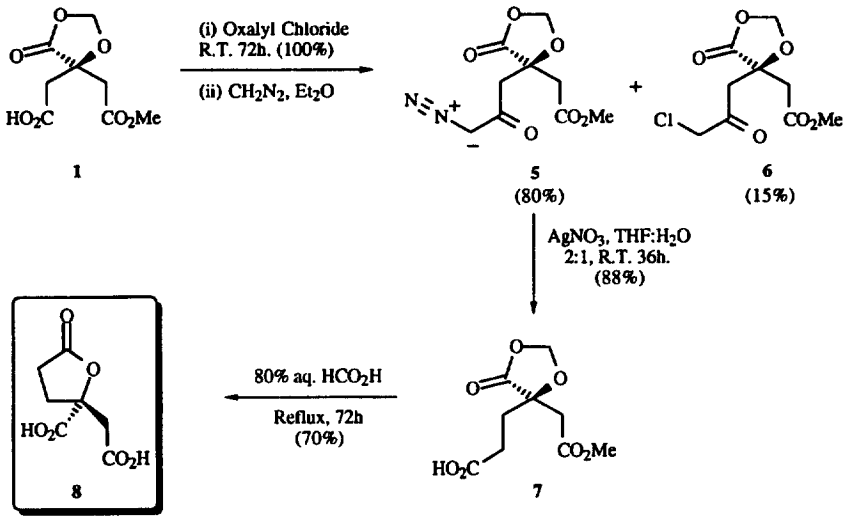


Scheme 2.

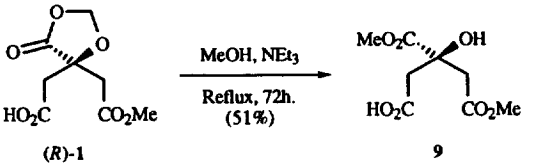
To determine the absolute stereochemistry of **1** and to demonstrate the utility of these compounds we undertook a synthesis of (−)-homocitric acid-γ-lactone **8**. (−)-Homocitric acid is a metabolite on the lysine biosynthetic pathway in yeast and certain fungi and has been isolated as its γ-lactone **8**.[2] The first synthesis of the natural antipode of **8** was described recently by Rodriguez and Biellmann.[10]

The required one carbon extension of (*R*)-**1** was achieved by an Arndt–Eistert homologation (Scheme 3). Thus treatment of (*R*)-**1** with neat oxalyl chloride afforded the corresponding acid chloride which was treated directly with excess diazomethane to afford mainly the diazoketone **5** accompanied by 15% of the α-chloroketone **6**. The sequence was completed by a Wolff rearrangement in THF:H_2O mediated by silver nitrate to give the carboxylic acid **7** (70% overall yield from **1**).[11] Deprotection was effected by refluxing **7** with 80% aqueous formic acid for 72 hours to give (−)-homocitric acid-γ-lactone **8** (70%). Measurement of the specific rotation ($[\alpha]_D$ −50.0 (*c* 0.35 in H_2O); lit. $[\alpha]_D$ −50.5 (*c* 0.33 in H_2O)[2a]) showed the absolute stereochemistry of **8** and thus **1** to be (*R*) and that the sample is of high enantiomeric excess.

Confirmation of the absolute stereochemistry of (*R*)-**1** was obtained on its conversion to **9** by refluxing in MeOH in the presence of an equivalent of triethylamine (Scheme 4),[12] the specific rotation of (*R*)-**9** being found to be +4.0 (*c* 1.00 in MeOH) in agreement with Bergeron.[1]



Scheme 3.



Scheme 4.

Conclusions

In conclusion we have successfully resolved a derivative of citric acid on a 50 g scale and demonstrated its use in synthesis by carrying out a preparation of (−)-homocitric acid-γ-lactone. Further applications of these and other chiral citric acid derivatives are current objectives.

Acknowledgements

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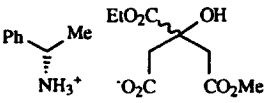
7. The (*S*)- and (*R*)-α-methylbenzylamines used in these resolutions were purchased from Avocado Research Chemicals Ltd. and were found to have the following specific rotations: (*S*)- $[\alpha]_D$ −39.4 (neat); (*R*)- $[\alpha]_D$ +38.3 (neat). lit. $[\alpha]_D$ +39.2 to +39.7 (neat) for (*R*)-α-methylbenzylamine, Ingersoll, A. W. *Organic Synthesis, Col. Vol. II* **1943**, 506.

8. A small amount of ring opening to give the ethyl ester **10** was found to accompany this treatment but **10** remained in the mother liquor.



10

9. Basification of the aqueous layer with sodium hydroxide allows the recovery and recycling of the α-methylbenzylamine.
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