COMMUNICATION

Preparation of desymmetrised *meso*-tartrate derivatives—synthesis and utility of (*R*′,*R*′,*R*,*S*)-2,3-butane diacetal protected dimethyl tartrate

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The synthesis of 2,3-butane diacetal protected dimethyl tartrate (*R*′,*R*′,*R*,*S*)-1 using a chiral memory protocol and its utility for the preparation of desymmetrised *meso*-tartrate derivatives through selective transesterification and aminolysis of the spatially different carboxylate termini is described.

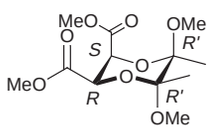
The desymmetrisation of *meso*-compounds still remains one of the most attractive methods for the production of asymmetric materials.[1] Although this area of synthesis has been dominated for many years by the use of enzymatic techniques, chemical methods for the analogous transformations are becoming increasingly important.

One particular area where this has become apparent in recent years is in the desymmetrisation of *meso*-1,2- and *meso*-1,3-diol compounds. The chemical methods available for this process fall into two general categories. One relies on the stereoselective acylation of the enantiotopic hydroxy termini using either asymmetric acylating reagents[2] or achiral acylating agents in conjunction with chiral amine bases.[3] The other pivots on the stereoselective cleavage of a preformed acetal using either chiral Lewis acids[4] or the chirality present in the initial carbonyl compound[5] to discriminate the enantiotopic or diastereotopic acetal carbon–oxygen single bonds respectively.

Here, we wish to describe a new chemical approach for the desymmetrisation of *meso*-1,2-tartrate esters through stereoselective discrimination of the spatially different carboxylate termini by virtue of the embedded chirality within an attached 2,3-butane diacetal (BDA) protecting group.

In the previous paper we described the use of (*R*,*R*)- and (*S*,*S*)-tartaric acid derived 2,3-butane diacetal protected butane tetrols as effective building blocks for the efficient and highly diastereoselective synthesis of polyol compounds. In this work the BDA moiety features not only as a *protecting group*[6] but also as a *stereodirecting group* for the addition of carbon centred nucleophiles to aldehyde termini. It was clear to us that if one of the stereogenic centres of the C_2 symmetric (*R*,*R*)-tartrate functionality could be cleanly inverted, then the residual chirality of the conformationally rigid (*R*,*R*)-configured BDA backbone would necessarily place the two carboxylate functions in different steric environments. More specifically, the methyl ester attached to the new *S* stereogenic centre of the tartrate would adopt an axial position whereas that of the *R* stereogenic centre would remain conveniently placed in an equatorial site. Early work by Barton effectively illustrated the inherent rate differences in the hydrolysis of equatorial over axial carboxylic esters[7] and it was on the basis of this that we believed that **1**[8] would constitute an effective precursor to numerous terminally differentiated enantiopure (*R*,*S*)-tartaric acid derivatives (Fig. 1).

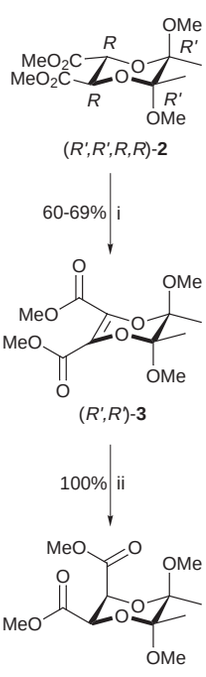
The two step synthesis of **1** commenced from the readily prepared (*R*′,*R*′,*R*,*R*)-2,3-butane diacetal protected dimethyl tartrate **2** described in the previous paper. Oxidation of this material *via* double deprotonation with LDA in THF at −78 °C and treatment of the resulting dianion with one equivalent of iodine afforded the maleate derivative **3**, in good yield (60–69%)



(*R*′,*R*′,*R*,*S*)-**1**

Fig. 1

and on multigram scales after a single recrystallisation of the crude material. Stereospecific reduction of maleate **3** in methanol with hydrogen (80 bar) over rhodium on alumina (20% by mass) for 5 days at room temperature gave the crystalline product **1** in quantitative yield (Scheme 1).

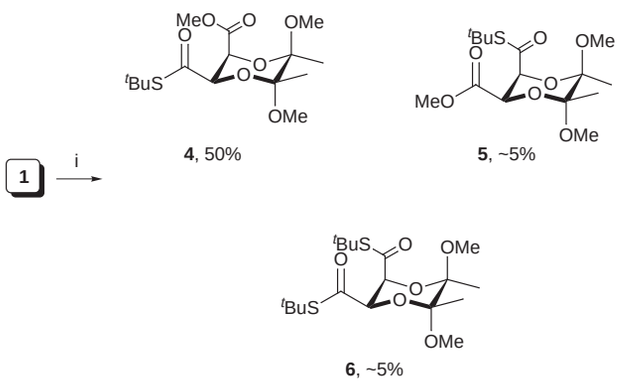


Scheme 1 *Reagents and conditions*: i, LDA (2.0 equiv.), THF, −78 °C, 30 min then I_2 (1.0 equiv.); ii, H_2 (80 bar), Rh–Al_2O_3 (20%), MeOH, 5 days.

Clearly, this efficient synthetic procedure relies on a chiral memory protocol where the natural chirality of the tartaric acid derivative fixes the chirality of the BDA backbone which, after the two step inversion process, renders the resulting *meso*-dimethyl tartrate desymmetrised.

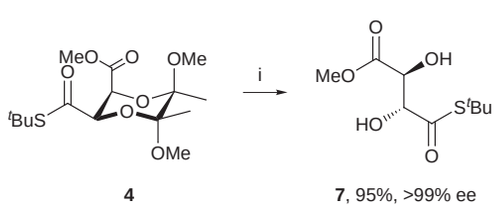
In order to assess the utility of *meso*-dimethyl tartrate **1**, we investigated the possibility of terminal differentiation using a selection of *S*-, *O*- and *N*-centred nucleophiles. This process allows us to learn about the inherent rate differences between axial and equatorial ester attack and secondly provide material for the subsequent deprotection reactions.

In the first example studied, treatment of **1** with an excess of dimethylaluminium *tert*-butyl thiolate (4 equiv.) at room temperature in toluene for 24 hours afforded, after aqueous work up and flash chromatography, the equatorial mono *tert*-butyl thiolate **4** in 50% yield alongside a small quantity (10%) of the unreacted starting material **1**. Additionally, ~5% of the axial mono-*tert*-butyl thiolate **5** and ~5% of the di-*tert*-butyl thiolate **6** were identified within the reaction mixture. Assuming that the majority of di-*tert*-butyl thiolate **6** formation is a result of a second attack on the axial mono-*tert*-butyl thiolate **5**, then the inherent reactivity difference between equatorial and axial carboxylate groups is ~5 : 1 (Scheme 2).



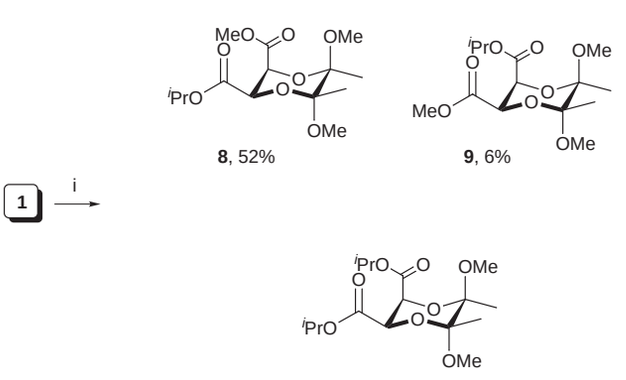
Scheme 2 *Reagents and conditions*: i, $Me_2AlS'Bu$ (4 equiv.), toluene, RT, 24 h.

Deprotection of **4** with the standard conditions for BDA removal, namely addition of a 90% trifluoroacetic acid solution for five minutes at room temperature followed by removal of volatiles *in vacuo*, afforded enantiopure (*R,S*)-tartaric acid derivative **7** in 95% yield (Scheme 3).



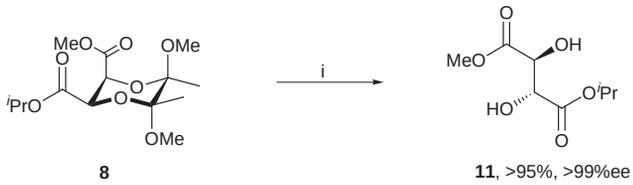
Scheme 3 *Reagents and conditions*: i, TFA (90%), RT, 5 min.

Selective transesterification of **1** using titanium tetraisopropoxide (0.2 equiv.) in propan-2-ol at 70 °C was also successful. Under these conditions after seventy two hours the reaction was ~70% complete and purification by column chromatography afforded the mono equatorial isopropyl ester **8** in 52% yield, the mono axial isopropyl ester **9** in 6% yield and the diisopropyl ester **10** in 8% yield (Scheme 4).



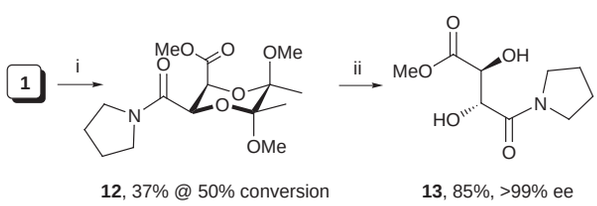
Scheme 4 *Reagents and conditions*: i, $Ti(O^iPr)_4$ (0.2 equiv.), ^{i}PrOH, 70 °C, 72 h.

Clearly the rate difference between equatorial and axial attack was only modest (~4 : 1), however, separation of the reaction products was easy and removal of the BDA group from **8** using the standard conditions afforded enantiopure (*R,S*)-tartaric acid derivative **11** in >95% yield (Scheme 5).



Scheme 5 *Reagents and conditions*: i, TFA (90%), RT, 5 min.

Finally, selective aminolysis was also possible. Treatment of (*R′*,*R′*,*R*,*S*)-2,3-butane diacetal protected dimethyl tartrate **1** with an excess of pyrrolidine dimethylaluminium amide (4 equiv.) in toluene at room temperature for 3 days resulted in a clean yet sluggish conversion to the mono equatorial pyrrolidine amide. Purification by column chromatography afforded **12** in 37% yield and the unreacted starting material in 50% yield. Although the chemical yield of this unoptimised aminolysis was only moderate, no evidence for axial attack was observed in the reaction. Deprotection of **12** using the standard conditions afforded enantiopure (*R,S*)-tartaric acid derivative **13** in 85% yield (Scheme 6).



Scheme 6 *Reagents and conditions*: i, $Me_2AlN(CH_2CH_2)_2$ (4 equiv.), toluene, RT, 72 h; ii, TFA (90%), RT, 5 min.

In summary, using a chiral memory protocol the synthesis of (*R′*,*R′*,*R*,*S*)-2,3-butane diacetal protected dimethyl tartrate **1** was achieved and its preliminary use in the production of enantiopure (*R*,*S*)-tartrate derivatives was investigated.

These studies should be taken in context with the accompanying papers which describe additional new approaches towards stereoselective polyol assembly.

Acknowledgements

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