COMMUNICATION

A general and efficient procedure for the preparation of enantiopure *anti*-1,2-diols—synthesis and utility of (*R′*,*R′*,*S*,*R*)-2,3-butane diacetal protected butane tetrol

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The synthesis and utility of 2,3-butane diacetal protected butane tetrol (*R′*,*R′*,*R*,*S*)-2 for the general and efficient production of enantiopure *anti*-1,2-diols through selective silylation, alkylation and acetalisation of the spatially different hydroxy termini is described.

Methods for the efficient *asymmetric* synthesis of *anti*-1,2-diols are few in number despite the prevalence of this structural motif in biologically important and naturally occurring compounds such as annonaceous acetogenins, polyketides, pyrrolidines, sugars and many others.

The more notable methods for their synthesis include catalytic asymmetric dihydroxylation of *Z*-alkenes,[1] catalytic asymmetric Mukaiyama aldol reactions of glycolate derivatives,[2] asymmetric alkoxy allylations of aldehydes[3] and enzymatic desymmetrisation of 2,3-protected *meso*-butane-1,2,3,4-tetrol derivatives.[4] Typically these methods suffer from low stereodifferentiation leading to products with poor ee's, are restricted to a limited range of glycolate protecting groups and/or aldehydes compatible with the catalytic system or, as in the case of any enzymatic desymmetrisation, can be severely limited by substrate specificity.

Clearly, the need for the development of new and general methods for the effective asymmetric synthesis of *anti*-1,2-diols is of considerable importance. In the previous paper we described the use of (*R′*,*R′*,*R*,*S*)-2,3-butane diacetal (BDA) protected dimethyl tartrate **1**[5] as a new building block for the preparation of terminally differentiated enantiopure (*R*,*S*)-tartaric acid derivatives. This work highlighted that the BDA functionality can operate not only as a protecting group for 1,2 diols[6] but also as an effective chiral auxiliary for stereodifferentiation.

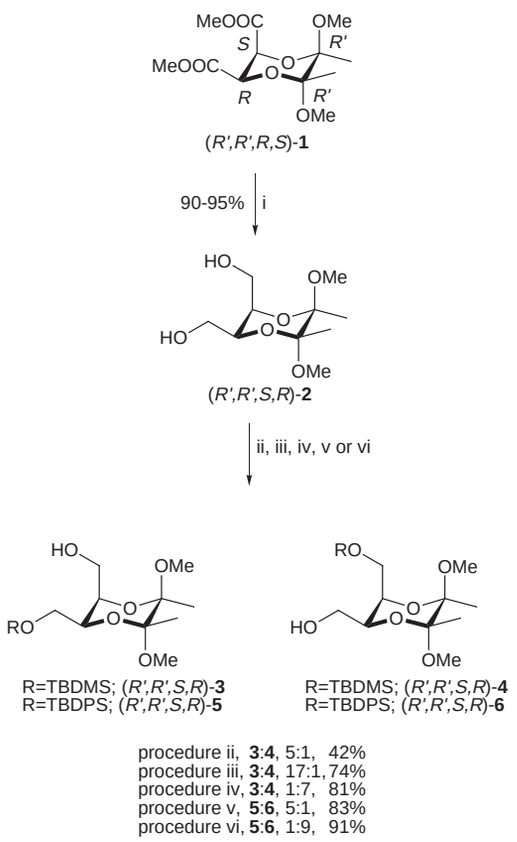
Limited to the preparation of desymmetrised *meso*-tartaric acid derivatives, it was clear that exhaustive reduction of both ester functionalities in (*R′*,*R′*,*R*,*S*)-2,3-butane diacetal protected dimethyl tartrate **1**, would produce (*R′*,*R′*,*S*,*R*)-2,3-butane diacetal protected butane tetrol **2**—effectively a desymmetrised *meso*-butanetetrol and thus potential precursor to any *anti*-1,2-diol. With the results of the previous paper in mind it was apparent that the chirality embedded within the diacetal backbone of **2**, should allow effective differentiation of the primary alcohol termini by placing them in different spatial environments. Exploitation of this asymmetry through selective derivatisation would then result in a desymmetrised *meso*-butane tetrol suitable for synthetic elaboration.

Here we wish to report our preliminary observations in the use of (*R′*,*R′*,*S*,*R*)-2,3-butane diacetal protected butane tetrol **2** for the potential synthesis of any *anti*-1,2-diol product.

When (*R′*,*R′*,*R*,*S*)-2,3-butane diacetal protected dimethyl tartrate **1** was treated with excess lithium aluminium hydride (1.1 equiv.) in diethyl ether at 0 °C to room temperature over one hour, the diol **2** was obtained as a highly crystalline solid in yields of 90–95% (Scheme 1). This reaction could be performed on multigram quantities to provide the key precursor which was then studied in the terminal alcohol differentiation reactions towards silylation, alkylation and acetalisation.

In the first of these studies, diol **2** was treated with *tert*-butyldimethylsilyl chloride (1.0 equiv.) and imidazole (1.5 equiv.) in dimethylformamide at room temperature for 2 hours. On work-up, inspection of the crude ^{1}H NMR spectrum revealed that both monosilylated products **3** and **4** had been formed, but with a significant bias towards the silyl ether of the equatorial alcohol (**3**:**4**; 5:1). Purification by flash column chromatography allowed separation of the two diastereoisomers which were isolated in a combined yield of 42%. When the reaction was repeated using tetrahydrofuran as solvent the selectivity of the reaction increased (**3**:**4**; 17:1) and the products were isolated in 74% yield.

Selective monosilylation with the more bulky *tert*-butyl diphenylchlorosilane was also possible. Following the best conditions described above, treatment of **2** with *tert*-butyldiphenylchlorosilane (1.0 equiv.) and imidazole in tetrahydrofuran at room temperature afforded **5** and **6** in the ratio of 5:1 and in a combined yield of 83% after column chromatography. Again, the preference towards equatorial alcohol silylation was maintained under these conditions.

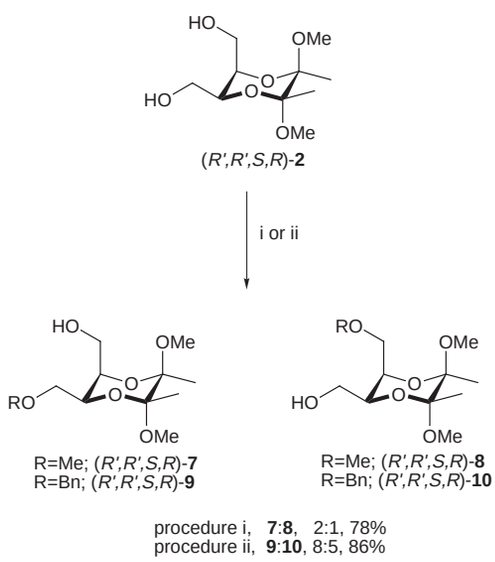


Scheme 1 *Reagents and conditions*: i, $LiAlH_4$ (1.1 equiv.), Et_2O, 0 °C, 1 h; ii, imidazole (1.5 equiv.), TBDMSCl (1.0 equiv.), DMF, RT, 2 h; iii, imidazole (1.5 equiv.), TBDMSCl (1.0 equiv.), THF, RT, 2 h; iv, NaH (1.0 equiv.), THF, RT then TBDMSCl (1.0 equiv.), 2 h; v, imidazole (1.5 equiv.), TBDPSCl (1.0 equiv.), THF, RT, 2 h; vi, NaH (1 equiv.), THF, RT then TBDPSCl (1.0 equiv.), 2 h.

Interestingly, when silylation was performed by prior deprotonation with NaH (1.0 equiv.) in tetrahydrofuran[7] at room temperature followed by addition of *tert*-butyldimethylsilyl chloride and stirring for 1 hour, *the stereochemical bias in the reaction was reversed*. Inspection of the crude ^{1}H NMR spectrum revealed that both monosilylated products **3** and **4** had been formed, but in this case a significant bias towards the silyl ether of the axial alcohol (**4**:**3**; 7:1) was observed. Purification allowed separation of **3** and **4** which were isolated in 81% combined yield. Similarly, when the more bulky *tert*-butyldiphenylchlorosilane was used as the electrophile under these anionic conditions, a strong preference towards axial silylation (**6**:**5**; 9:1, 91%) was again observed (Scheme 1).

These initial results constitute an attractive starting point for *anti*-1,2-diol synthesis. The ability to choose protection at either axial or equatorial hydroxy termini in **2** translates, after further skeletal elaboration, to having the ability to select either enantiomer (*R*,*S* or *S*,*R*) of a given *anti*-1,2-diol. We believe that the predominance for equatorial silylation with imidazole as the base is simply a result of the higher accessibility of the equatorial hydroxy functionality towards electrophilic silicon as compared to its axial counterpart. Whereas, the predominance for axial silylation when using sodium hydride is probably a consequence of an energetic bias favouring the axial alkoxide through stabilising intramolecular ligation of the sodium counterion.[8] Such a stabilisation is not possible when the alkoxide resides in the equatorial position.

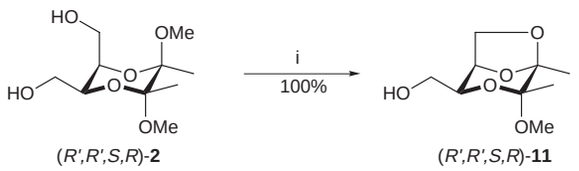
In contrast to the silylation results, only minimal selectivities in the analogous base mediated monoalkylation of (*R′*,*R′*,*S*,*R*)-2,3-butane diacetal protected butane tetrol were observed favouring the products of *equatorial* attack. For example, treatment of **2** with sodium hydride at room temperature followed by addition of iodomethane lead to the formation of **7** and **8** in the ratio of 2:1 and in 78% combined yield. Similarly when benzyl bromide was used as the electrophile **9** and **10** were produced in 86% combined yield and in the ratio of 8:5 respectively (Scheme 2).



Scheme 2 *Reagents and conditions*: i, NaH (1.0 equiv.), THF, RT then MeI, overnight; ii, NaH (1.0 equiv.), THF, RT then BnBr, overnight.

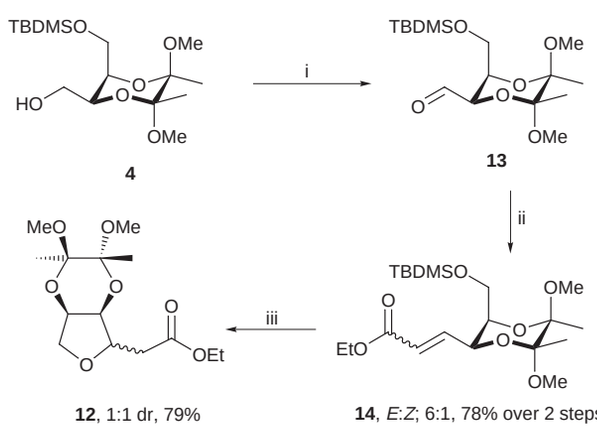
The bias towards equatorial ether formation with iodomethane and benzyl bromide is probably a result of alkoxide equilibration prior to alkylation of the more accessible equatorial sodium alkoxide. Clearly, alkoxide quenching with the more reactive silyl halides is faster than alkoxide equilibration.

A unique mode of selective mono protection of the axial hydroxy functionality was also possible through a type of acetal exchange with the dimethoxybutane diacetal backbone. Thus, treatment of (*R′*,*R′*,*S*,*R*)-2,3-butane diacetal protected butane tetrol **2** with a catalytic quantity of Amberlyst 15 in dichloromethane at room temperature for 2 hours afforded a quantitative yield of alcohol **11** in which the BDA is acting as a novel triol protecting group (Scheme 3).



Scheme 3 *Reagents and conditions*: i, Amberlyst® A15, CH_2Cl_2, 2 h.

To highlight the utility of **2** for the general synthesis of *anti*-1,2-diols, the highly crystalline mono *tert*-butyldimethylsilyl ether **4** was efficiently transformed into the BDA protected (*R*,*S*)-2,3-dihydroxylated furan derivative **12** in a three step process. Thus, oxidation of **4** using the Swern[9] oxidation conditions afforded the crude equatorial aldehyde which was subsequently treated with ethoxycarbonylmethylenetriphenylphosphorane in dichloromethane at room temperature. On work-up, the α,β-unsaturated ester **14** was obtained as a mixture of geometrical isomers (*E*:*Z*; 6:1) in a combined yield of 78% over 2 steps. Treatment of **14** with tetrabutylammonium fluoride (3 equiv.) in tetrahydrofuran at room temperature resulted in a tandem deprotection–Michael addition of the axial hydroxy group to form furan **12** as a 1:1 mixture of epimers in 79% yield (Scheme 4).



Scheme 4 *Reagents and conditions*: i, $(COCl)_2$ (1.3 equiv.), DMSO (2.6 equiv.), CH_2Cl_2, −78 °C then Et_3N (3.5 equiv.), −78 °C–RT over 30 min; ii, $EtO_2CCHPPh_3$ (1.0 equiv.), CH_2Cl_2, RT overnight; iii, TBAF (3 equiv.), THF, RT.

In summary, we have described the synthesis and utility of (*R′*,*R′*,*S*,*R*)-2,3-butane diacetal protected butane tetrol **2** for the general and efficient production of enantiopure *anti*-1,2-diols through selective silylation, alkylation and acetalisation of the spatially different hydroxy termini. This and the previous two communications combine to form a powerful, new stereoselective approach to diol and polylol production which we believe should find numerous applications in synthesis.

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Notes and references

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