COMMUNICATION

New building blocks for efficient and highly diastereoselective polyol production—synthesis and utility of (*R′*,*R′*,*S*,*S*) and (*S′*,*S′*,*R*,*R*)-2,3-butane diacetal protected butane tetrol derivatives

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Received (in Cambridge) 6th April 1999, Accepted 17th May 1999

The efficient synthesis of aldehydes derived from 2,3-butane diacetal protected butane tetrols (*S′*,*S′*,*R*,*R*)-5 and (*R′*,*R′*,*S*,*S*)-6 and their utility in the controlled synthesis of polyhydroxylated materials through highly diastereoselective Lewis acid mediated addition reactions of allyltributylstannane and silyl enol ether nucleophiles is described.

The abundance of polyhydroxylated natural products, ranging from relatively simple sugars to more structurally complex macrolide and polyketide materials which exhibit a broad range of biological properties, continues to stimulate the development of new methods for their stereoselective synthesis. While numerous methods for their preparation have appeared in the literature, by far the most popular approach, especially for low molecular weight targets, is the stereoselective addition of a carbon centred nucleophile to a suitably protected hydroxy aldehyde substrate derived from cheap enantiopure starting materials. Clearly, the utility of this type of approach pivots on the nature and role of the hydroxy protecting group during the carbon–carbon bond forming reaction and has resulted in extensive investigation.[1]

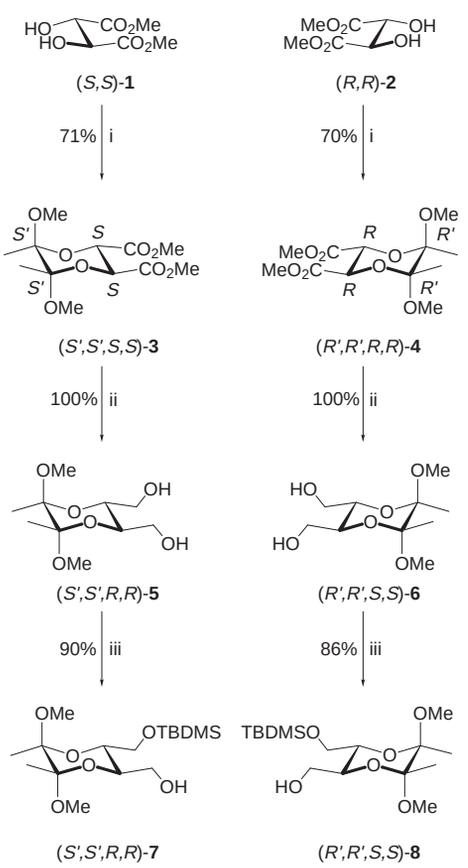
As a result of our interest in the synthesis of complex polyhydroxylated natural products we have recently adopted this strategy and studied the use of tartrate derived building blocks for the purpose of efficient stereoselective polyol production. More specifically, our interest has focused on additions to aldehydes derived from 2,3-butane diacetal (BDA) protected butane tetrols. The butane diacetal (BDA)[2] and 1,2-cyclohexane diacetal (CDA)[3] protecting groups for diol, and in some cases triol substrates, were introduced by our group some years ago. Not only did these 1,2-diacetal motifs introduce a new and general mode of vicinal diol protection, but also allowed selective 1,2-diequatorial hydroxy protection in carbohydrates[4] as a result of the rigid chair conformation combined with double anomeric stabilization.

With this in mind we believed that under the appropriate conditions, addition of various carbon centred nucleophiles to terminal aldehydes derived from 2,3-butane diacetal (BDA) protected butane tetrols would proceed with high stereoselectivity by virtue of the chirality embedded within the rigid BDA backbone. Additionally, the removal of the BDA moiety is trivial and invariably high yielding, thus making the overall sequence very attractive for stereoselective polyol production.

Here we report the initial results of studies into the stereoselective synthesis of polyol materials using aldehydes derived from 2,3-butane diacetal (BDA) protected butane tetrols through Lewis acid mediated stereoselective addition reactions.

For any asymmetric building block to be synthetically useful it is necessary that it is readily available in multigram quantities and in both enantiomeric forms. In this work dimethyl tartrates (*S*,*S*)-**1** and (*R*,*R*)-**2** were reacted directly with butane-2,3-dione at reflux in methanol with a catalytic quantity of camphorsulfonic acid, following our previously reported protocol, to give the corresponding BDA protected dimethyl tartrate (*S′*,*S′*,*S*,*S*)-**3** and its enantiomer (*R′*,*R′*,*R*,*R*)-**4** in 71 and 70% yields, respectively. These protected derivatives could be readily prepared in greater than 100 g quantities from the parent dimethyl tartrates. Both **3** and **4** have been prepared previously from tartrate esters using acetal exchange from butanedione acetals.[5] These compounds have also been converted to novel phosphine ligands and other ligating diols[6] for potential application in asymmetric synthesis.[7] For this work, **3** and **4** were reduced with lithium aluminium hydride to give the corresponding diols **5** and **6** in essentially quantitative yields.

With multigram quantities of diols **5** and **6** in hand an efficient terminal differentiation through suitable monoprotection was essential in order to give useful synthetic



Scheme 1 *Reagents and conditions*: i, $CH_3COCOCH_3$ (1.2 equiv.), CSA (0.1 equiv.), $CH(OCH_3)_3$ (3.0 equiv.), CH_3OH, reflux, 14 h; ii, $LiAlH_4$ (1.1 equiv.), THF, 0 °C to RT, 0.5 h; iii, NaH (1 equiv.), THF, RT then TBDMSCl (1 equiv.), 2 h.

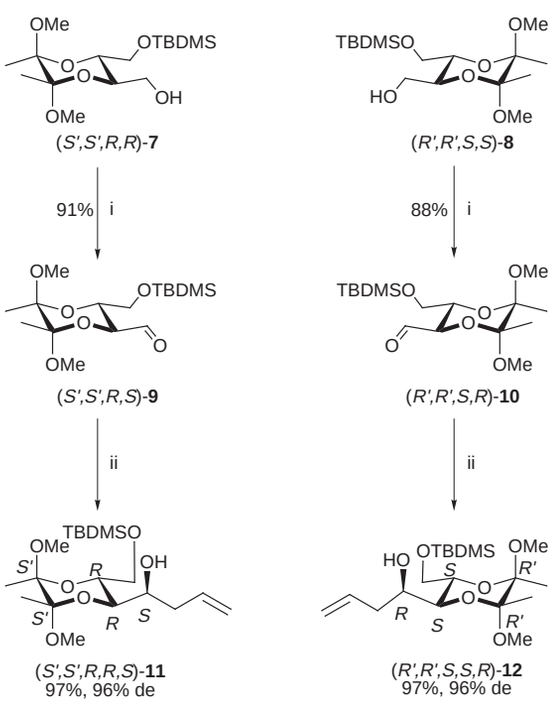
building blocks. This was indeed possible through monosilylation using NaH (1 equiv.) in THF at 0 °C followed by addition of TBDMSCl (1 equiv.) and afforded the highly crystalline monosilylated[8] products **7** and **8** in 90% and 86% yields, respectively (Scheme 1).

Standard Swern oxidation[9] of the residual alcohol to the desired enantiomeric aldehydes **9** and **10** occurred smoothly and in good yield in both cases. These materials were stable for days at room temperature and their enantiopurity (>99% ee) was confirmed by reduction to the parent alcohols **7** and **8** and derivatisation with (*R*)- and (*S*)-Mosher's acid chlorides.

To investigate the utility of the key aldehydes **9** and **10** as building blocks for general polyol production their behaviour towards certain carbon centred nucleophiles was investigated. From the outset we chose to mediate the reactions with Lewis acids. This mode was adopted as we believed chelation from the carbonyl group to the adjacent oxygen atom would be strong as a result of the conformational rigidity of the BDA backbone and should therefore give rise to high levels of stereocontrol.

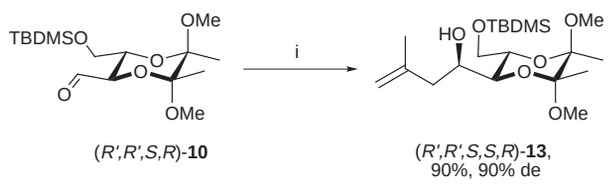
In the first addition reaction studied, **9** was treated with allyltributylstannane (3 equiv.) and lithium perchlorate[10] (3 equiv.) in diethyl ether at 0 °C to room temperature overnight and on work up gave a 98 : 2 mixture of diastereoisomeric products. Chromatographic purification afforded the diastereomerically pure homoallylic alcohol **11** in 97% yield. Derivatisation of **11** with (*R*)- and (*S*)-Mosher's acid chlorides allowed unambiguous assignment[11] of the newly formed stereogenic centre as *S* and indicated that the stereochemistry of the major product was the result of chelation control during the addition reaction.

This excellent stereocontrol combined with the near quantitative yield of separable diastereoisomeric products in the allylation reaction was very pleasing and confirmed the initial proposals. Unsurprisingly, when the identical reaction conditions were applied to the enantiomeric aldehyde **10** the enantiomeric homoallylic alcohol product **12** was formed with identical diastereoselectivity and similar chemical yield. In this case the stereochemistry of the newly formed stereocentre was determined as *R* (Scheme 2).



Scheme 2 *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, $Bu_3SnCH_2CHCH_2$ (3 equiv.), $LiClO_4$ (3 equiv.), Et_2O, 0 °C to RT, overnight.

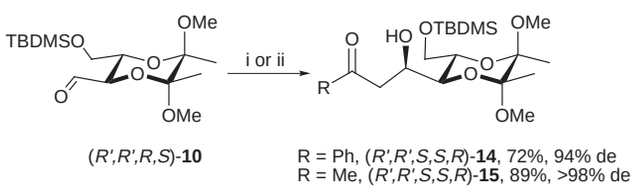
In a similar fashion to the above, treatment of aldehyde **10** with (methylallyl)tributylstannane (3 equiv.) and lithium perchlorate (3 equiv.) in diethyl ether at 0 °C to room temperature overnight gave a 95 : 5 mixture of diastereoisomeric products. Although the observed diastereoselectivity had decreased slightly in this example, the diastereoisomeric products were again easily separated by silica gel chromatography and the yield of the major homomethylallylic alcohol product **13** was excellent (90%). Again, the stereochemistry of the new hydroxy stereogenic centre was determined unambiguously as *R* by derivatisation with (*R*) and (*S*)-Mosher's acid chlorides and was consistent with addition occurring through chelation control (Scheme 3).



Scheme 3 *Reagents and conditions*: i, $Bu_3SnCH_2C(CH_3)CH_2$ (3 equiv.), $LiClO_4$ (3 equiv.), Et_2O, 0 °C to RT overnight.

Paralleling the allylstannane reactions, treatment of aldehyde **10** with silyl enol ether nucleophiles in the presence of Lewis acids also resulted in highly efficient and diastereoselective Mukaiyama aldol reactions. For example, pre-complexation of aldehyde **10** with magnesium bromide (3 equiv.) at room temperature in diethyl ether, followed by cooling to 0 °C and treatment with an excess of 1-phenyl-1-trimethylsilyloxyethene led to the formation of the aldol product **14** in good yield (72%) and with high diastereoselectivity (97 : 3 dr). The sense of the asymmetric induction could again be rationalised by addition *via* chelation control.

Similarly, an 89% yield of the diastereomerically pure Mukaiyama aldol product **15** was obtained when aldehyde **10** was treated with 2-trimethylsilyloxypropene (3 equiv.) in diethyl ether at 0 °C in the presence of magnesium bromide–diethyl ether. Interestingly in this case, the reaction diastereoselectivity had increased to >99 : 1 (Scheme 4).



Scheme 4 *Reagents and conditions*: i, $MgBr_2$ (3 equiv.), Et_2O, RT to 0 °C then 1-phenyl-1-trimethylsilyloxyethene (4 equiv.), 0 °C, 30 min; ii, $MgBr_2$ (3 equiv.), Et_2O, RT to 0 °C then 2-trimethylsilyloxypropene (4 equiv.), 0 °C, 30 min.

The initial results described above clearly show the synthetic potential of the enantiomeric aldehydes **9** and **10** as building blocks for the stereocontrolled synthesis of polyol materials. The key aldehydes are efficiently prepared in enantiopure form on multigram scales from the parent BDA protected dimethyl tartrate (*S′*,*S′*,*S*,*S*)-**3** and its enantiomer (*R′*,*R′*,*R*,*R*)-**4**. Subsequent addition reactions of a range of allyltributylstannane nucleophiles and trimethylsilyl enol ethers to **9** and **10** in the presence of certain Lewis acids occur efficiently and with excellent diastereoselectivity at temperatures above 0 °C. The sense of the asymmetric induction in every case studied was consistent with addition occurring *via* chelation control.

We believe that these preliminary results described above together with the following papers open up new opportunities for stereoselective polyol production.

Acknowledgements

We thank the EPSRC (to DJD, ACF and DJR), Rhône Poulenc Rorer (to DJR), Zeneca Agrochemicals (to ACF), the Novartis Studentship (to JSB), the Novartis Research Fellowship (to

SVL) and Pfizer Inc., Groton, U.S.A. for further financial support.

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Communication 9/02734C