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Directed and undirected asymmetric dihydroxylation reactions: application in the synthesis of a *C*-linked analogue of allolactose

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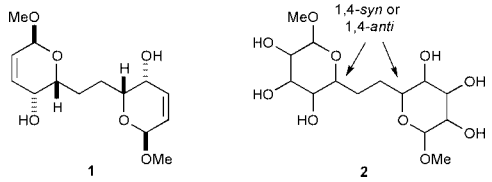
The complex OsO_4·(*S*,*S*)-1,2-diphenyl-*N*,*N*′-bis(2,4,6-trimethylbenzyl)ethane-1,2-diamine is an effective reagent for the desymmetrisation of *meso*-1,2-bis(3,6-dihydro-2*H*-pyran-2-yl)ethanes by asymmetric dihydroxylation; this process, whose sense of diastereoselectivity depends on substitution and stereochemistry, has been exploited in the synthesis of a *C*-linked analogue of allolactose.

Previously, we have described methods for the synthesis of some stereoisomeric *C*-linked disaccharide mimetics.[1] A key feature of our approach was that diastereomeric mimetics could be prepared by minor variation of a general reaction sequence. For example, complementary undirected[2] and directed[3] dihydroxylation reactions were exploited in the two-directional elaboration of diols (such as C_2-symmetric **1**) to give products of general stucture **2** with 1,4-syn stereochemistry. In order to

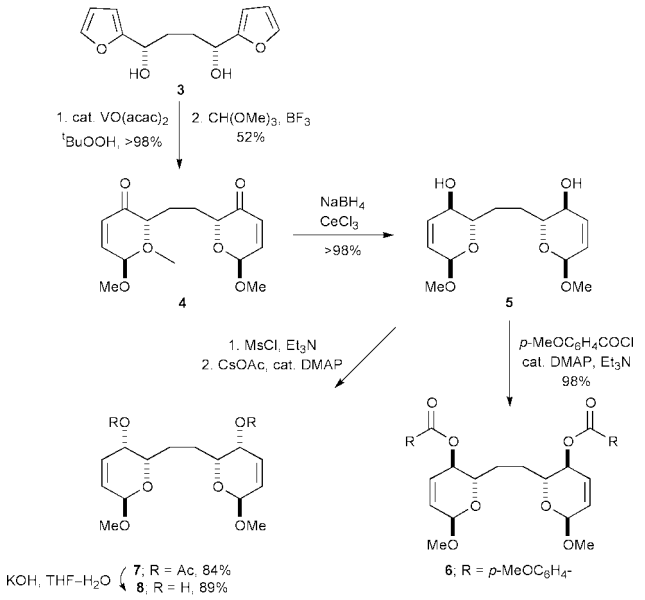


synthesise the mimetics with the opposite 1,4-stereochemical relationship, an efficient method for the desymmetrisation[4] of the *meso* difuryl diol[1] **3** or one of its derivatives would be required.

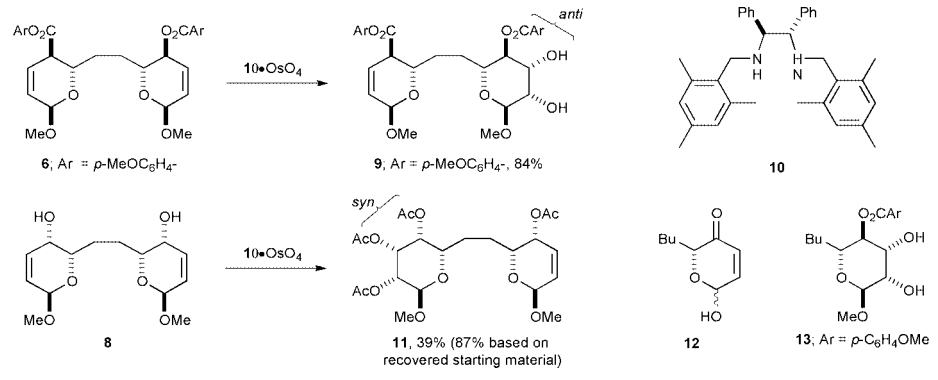
Oxidative ring expansion of the furan rings of the diol **3** using $VO(acac)_2$–^{t}BuOOH, and acetalisation, gave the dipyranone **4** as a 75 : 25 mixture of *meso* and unsymmetrical anomers, from which the required *meso* diastereoisomer was crystallised in 52% yield (Scheme 1). Reduction of **4** under Luche's conditions gave the diol **5** in > 98% yield, which was converted into the *p*-methoxybenzoyl diester **6**. The diastereoisomeric diol **8** was synthesised by hydrolysis of the diacetate **7** obtained by inversion of the dimesylate derived from **5**.

Treatment of **6** with OsO_4·**10** at −20 °C lead to complete consumption of the starting material and gave the desymmetrised diol **9**† as a single diastereoisomer in 84% yield with 60% ee (Scheme 2). Dihydroxylation occurred *anti*[2] to the pseudo-equatorial allylic *p*-methoxybenzoyloxy group. Previously, prochiral cyclic dienes have been desymmetrised using AD-mix β, with dihydroxylation occurring on the outside of their bicyclic structure.[6] This natural diastereoselectivity could be reversed by delivery of OsO_4·**10** to the double bond: dihydroxylation of **8** was highly *syn* selective, and gave, after peracetylation, the tetraacetate **11** with 93% ee (87% yield based on recovered starting material). We believe that diastereoselectivity stems from hydrogen bonding of the reagent to the pseudoaxial hydroxy group,[3] and that this reaction is the first example of a directed asymmetric dihydroxylation.

As a prelude to the diastereoselective functionalisation of the remaining double bond of **9**, we studied the functionalisation of the allylic *p*-methoxybenzoate **15** using iodine and silver benzoate in dry carbon tetrachloride (Scheme 3).[7] In view of the



Scheme 1



Scheme 2

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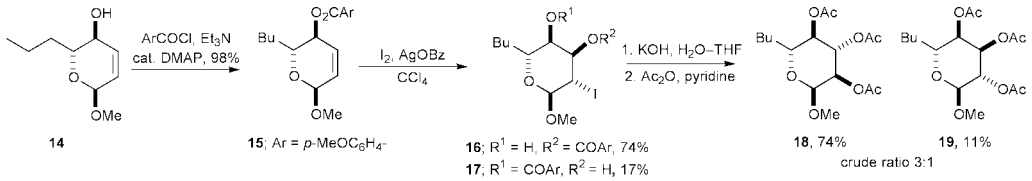
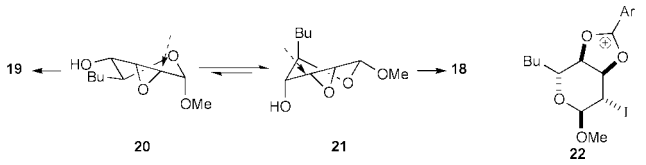


Scheme 3



Scheme 4

rigorously dry reaction conditions of these reactions, the *syn* stereospecificity of this process (**15** → **16**, **17**) and the absence of benzoate from the products are remarkable. Presumably, participation[8] of the *p*-methoxybenzoyloxy group gave the dioxonium ion **22** which was stable to the reaction conditions; subsequent hydrolysis of this intermediate, presumably on aqueous work-up, gave the observed *syn* hydroxy *p*-methoxybenzoates **16** and **17**. In general, *syn* hydroxyesters are only obtained when Prévost reactions are conducted in the presence of water because, under these conditions, the intermediate dioxonium is hydrolysed *in situ*.[9]

Treatment of the iodoesters **16**–**17** (4:1 mixture of regioisomers) with potassium hydroxide in water–THF, followed by peracetylation, gave a 3:1 diastereomeric mixture of the triacetates **18** and **19**. Presumably, **16** and **17** were converted into the same epoxide which was opened by hydroxide ion.‡ *trans*-Diaxial opening[11] of the major conformer (**20** → **19**, Scheme 4) requires opening at the site which is β to the two oxygens of the acetal;[12] consequently, reaction *via* the conformer **21** (→ **18**)—that is, away from the two β oxygens[12]—is competitive with, and in fact dominates over, this process.

In a similar vein, treatment of the desymmetrised compound **23** with iodine and silver benzoate in dry carbon tetrachloride, followed by treatment with aqueous potassium hydroxide solution, gave the *C*-linked disaccharide mimetic *ent*-**25** (Scheme 5); peracetylation gave the hexaacetate **24** in 64% yield over 3 steps. The *C*-linked allolactose mimetic **25**, in which C-6 of the galactose ring has been replaced by a methoxy group, could clearly have been prepared by the same synthetic methods using the enantiomeric diamine ligand in the key desymmetrisation step. It has been suggested that stable analogues of allolactose, the intracellular inducer of the lactose (*lac*) operon, may also exert negative control over gene expression.[13]

Our synthesis of the *C*-linked disaccharide mimetic *ent*-**25** is unusual in that neither ring derives directly from a sugar, though Vogel has reported the use of a non-carbohydrate based template to introduce one of the sugar rings to some *C*-linked disaccharides.[14] Key steps in our synthesis include the desymmetrisation of a highly functionalised *meso* di-DHP using an asymmetric dihydroxylation reaction, and the use of a *p*-methoxybenzoate ester to control the stereospecificity of a Prévost reaction.

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Notes and references

† The absolute configuration of **9** was deduced by comparing the 500 MHz ^{1}H NMR spectra of its (*R*)- and (*S*)-Mosher diesters with those of the diol **13**, which was derived from the pyranone[5] (2*R*)-**12**.

‡ For the hydrolysis of similar epoxides, see ref. 10.

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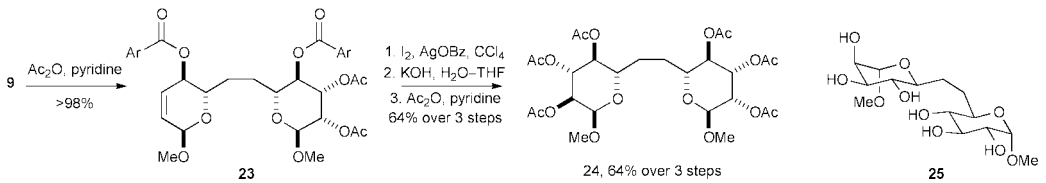

Scheme 5