Stereoselective synthesis of protected L- and D-dideoxy sugars and analogues via Prins cyclisations†

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A de novo approach for the rapid construction of orthogonally protected L- and D-dideoxy sugars and analogues is described. A novel and robust silicon-acetal undergoes Prins cyclisations with a series of homoallylic alcohols in high yield and excellent stereocontrol. Modified Tamao–Fleming oxidation of the resulting silyl tetrahydropyrans gives direct access to deoxyglycoside analogues and the approach was showcased in the synthesis of protected L-oliose, a component of the anticancer agent aclacinomycin A.

Introduction

Deoxyglycosides are important components of a wide variety of natural products isolated from plants, fungi and bacteria including compounds exhibiting anticaner and antibiotic activities. Some have proved effective for use in the clinic (e.g. the antibiotic vancomycin and the anthracycline antibiotic altromycin B) or as lead compounds to pharmaceuticals. In addition, deoxyglycans are also prevalent in bacterial membrane glycoproteins, thus being a viable target for drug discovery and vaccine development.†

The ability to fully understand and exploit the glycobiology of rare deoxysugars and analogues is hindered by the challenges of isolating pure materials in reasonable quantities from natural sources. In addition, synthetic approaches from naturally-abundant carbohydrates often require lengthy synthetic routes which make rare sugars very expensive.† An alternative and potentially more versatile approach is the de novo asymmetric synthesis of deoxy sugars. An ideal synthetic strategy would be efficient, robust and readily adapted for the construction of a series of deoxysugars and derivatives. To this end, we have developed a new approach for the enantioselective synthesis of differentially-protected L- and D-deoxyglycosides and analogues via Prins cyclisations and its utility exemplified by the synthesis of 2,4- and 2,6-dideoxyglycosides including protected L-oliose.

Prins cyclisations involve acid-mediated reactions of homoallylic alcohols I (or derivatives thereof) to form an oxy-carbenium ion I which cyclises via carbocation II and is subsequently trapped by a nucleophile, giving tetrahydropyrans 2 with excellent stereocontrol (Scheme 1).† Reddy, Yadav and co-workers have used sugar derivatives as substrates in Prins cyclisations.† Success of our proposed approach to deoxyglycosides relied upon use of a suitable electrophile bearing a hydroxyl surrogate (X in Scheme 1) which would need to be both stable to the acidic conditions required for the cyclisation and would readily be converted to a suitable functional group (e.g. acetate 3) for use in glycosylation reactions. An orthoformate was considered as the electrophile to directly introduce a 1-O-alkyl side-chain, but these have rarely been used in Prins cyclisations and are limited to substrates in which the reaction proceeds via a tertiary carbocation.†

Results and discussion

A trialkylsilane was considered a suitable hydroxyl surrogate as, following cyclisation, a Tamao–Fleming oxidation would lead to the required acetol. Whilst dimethylphenylsilanes have been widely used,† Hosomi and co-workers reported the benzylidimethylsilyl group (BDMS) as an attractive alternative that is readily oxidised to alcohols.† An important criterion for our synthetic strategy was that the electrophile should be stable and readily prepared on a synthetically valuable scale. Thus, novel silyl acetol 5 was prepared in two steps and 76% overall yield via treatment of 2-lithio-1,3-dithiane with benzylidimethylsilyl chloride (BDMSCl) to give dithiane 4 followed by mercuric-

Scheme 1 Proposed synthetic approach to deoxysugars.
mediated deprotection in ethanol (Scheme 2). The reaction was conducted on a multigram scale and the acetal is stable with no apparent decomposition after 6 months on the bench.

Initially, the key Prins cyclisation was optimised using the known (R)-homoallylic alcohol 6 prepared from dihydrocinnamaldehyde via a Norakami crotyl transfer reaction. Several methods have been reported for the introduction of oxygen nucleophiles, and in this case treatment of alcohol 6 and acetal 5 with trifluoroacetic acid (TFA) at 0 °C, then hydrolysis of the resultant ester gave alcohol 7 in 97% yield (Scheme 3). A single diastereomer was isolated in which all four substituents were equatorial.

Our ultimate targets, 2,6- and 2,4-dideoxy sugars, lack a substituent at C-2 and their synthesis requires a substrate with a terminal alkene. Hence (R)-homoallylic alcohol 8 (prepared via a Brown allylation) was treated with acetal 5 under the optimised reaction conditions to give alcohol 9 in 93% yield. It is known that the mechanism of Prins cyclisations is not simple and, depending on the nature of the substrate and reaction conditions, competing processes may occur. To ensure that there was no loss of stereochemical integrity during the cyclisation, the enantiopurity (97.5 : 2.5 e.r.) of 9 was confirmed by chiral SFC.

An alternative synthetic approach to the silyl tetrahydropyrans was to incorporate the silyl moiety into the alkene coupling partner which on reaction with an aldehyde would enable the facile introduction of a range of side-chains at C-5 of the target deoxysugars (Scheme 4). Several methods were investigated for the synthesis of α-stylyl homoallylic alcohol 10 via acid-mediated allylation of acetal 5 (e.g. in the presence of InCl₃, AgNO₃, SnCl₄) but none of the required product was isolated. In contrast, when silyl acetal 5 was treated with allytributylstannane and LiBF₄ in wet acetonitrile, alcohol 10 was isolated in 61% yield. The TFA mediated reaction of 10 with either acetaldehyde or 3-benzoxypyropanal followed by hydrolysis of the resultant ester gave silyltetrahydropyrans 11 and 12 in 89% and 82% yields, respectively, from acetal 5. By varying the reaction conditions the analogous acetates 13 and 14 were readily prepared. Further studies are ongoing to investigate the enantioselective allylation of acetal 5.

The second stage of our synthetic strategy required oxidation of the benzylidemethylsilyl group; Trost and Donohoe have reported the use of tetrabutylammonium fluoride (TBAF) followed by hydrogen peroxide for similar transformations. Following detailed investigations we established suitable conditions for the successful oxidation of silane 7 (Scheme 5). It was evident that two steps are involved. First addition of TBAF converted silane 7 to silanol 15 which could be isolated and characterised.

However, it was not necessary to isolate 15 as it was converted in situ to hemiacetal 16 via a urea hydrogen peroxide oxidation and then directly acetylated to give 17 in 73% yield from silane 7. It proved vital to keep the temperature of the fluoride activation step in the range 0–5 °C, as at higher temperatures disiloxanes were formed from the condensation of two silanols, which were only slowly oxidised under the reaction conditions.

To confirm that the oxidation/acetylation protocol was compatible with different protecting groups commonly used in carbohydrate chemistry, the secondary alcohols in 7 and 9 were converted to acetates (18 and 19) and benzyl ethers (20 and 21) in high yields using standard reaction conditions (Scheme 6). Oxidation of each silane gave the corresponding anomic acetates (17, 22–24) in 64–80% isolated yield.

Next the optimised cyclisation/oxidation/acetylation strategy was applied to the preparation of protected 2,4-dideoxyglycosides (Scheme 7). Homoallylic alcohol 26 was prepared in 88% overall yield from (5)-glycidol via protection of the alcohol as silyl ether 25 and ring opening of the oxirane with...
vinylmagnesium bromide and CuCN. Treatment of 26 with silyl acetate 5 and TESOTf in acetic acid gave silyl tetrahydropyran 27 in 65% yield which was readily converted to triacetate 28 as a 1:2 mixture of anomers using the oxidation/acetylation protocol. Interestingly, treatment of the mixture of homoalyl alcohol 26 and acetal 5 with TFA, our standard cyclisation conditions, gave none of the expected product, instead the analogous ethyl ether 29 was isolated. Some deoxysugars indeed have ethers at C-3, for example, D-oleandrose is a component of the highly potent and selective anticancer agent digitoxin (Fig. 1).25

Next we turned our attention to the synthesis of protected 2,6-dideoxyglycosides. Initial studies revealed that whilst homoallylic alcohol 35 was readily prepared via Brown allylation of allyl ethyl ether, reaction of 35 with silyl acetate 5 under our standard TFA conditions gave the 5-membered ring aldehyde 36 in 46% yield (Scheme 9). Aldehyde 36 is likely to be formed via a Prins-pinacol reaction involving oxonia-Cope rearrangement of vinylcarbenium ion III to enol ether IV followed by cyclisation to tetrahydropyran V and finally O-alkyl cleavage to generate the carbonyl group.26 Hence to favour formation of a tetrahydropyran over a tetrahydropyran we reasoned that an electron withdrawing group rather than an ether was required and a carbamate protecting group was selected.27 Thus an asymmetric synthesis of homoalyl alcohol 40 was required which could be readily adapted for both the L- or D-protected 2,6-dideoxy sugars since, for example, L-oliose is a component of aclarubicin, clinically used for the treatment of acute leukaemias, whilst D-oliose is present in the antitumour drugs mithramycin and chromocyclomycin, as well as the HIV-inhibitor durhamycin A.28

Singh and Guiry reported that Sharpless asymmetric epoxidation (SAE) of divinylcarbinol, followed by Mitsunobu inversion of the resulting alcohol gives epoxide 37 (Scheme 10).29 Importantly, choice of (−)-DIPT or (+)-DIPT in the SAE step allows access to the D- and L-series, respectively. Protection of alcohol 37 with N,N-diisopropylcarbamoyl chloride gave a mixture of chlorohydrin 38 and the required epoxide 39. Chlorohydrin 38 was readily converted to 39 by treatment with NaOH in THF at room temperature within a matter of minutes. Reductive ring opening of the oxirane with DIBALH gave monoprotected syn allylic diol 40 which cyclised with acetel 5 to give the required tetrahydropyran 41 with an equatorial C-3 alcohol.

![Scheme 7](image_url) Preparation of 2,4-dideoxyglycosides 31 and 34.

![Scheme 8](image_url) Synthesis of protected 2,4-dideoxyglycosides 31 and 34.

![Scheme 9](image_url) Cyclisation to tetrahydropyran 36 and nOe correlations.

![Scheme 10](image_url) Enantioselective synthesis of protected L-oliose 42.
and the axial C-4 protected hydroxyl. Finally oxidation of silane 41 gave protected l-olivose 42 in 77% yield as a 1:1 mixture of anomers. The methodology could be extended to the synthesis of l-olivose via protected alcohol 44 which was prepared from epoxide 43 using the same conditions as for assembly of the diastereomer 40 (Scheme 11). Interestingly, reaction of 44 with acetal 5 under the standard conditions gave a mixture of products due to migration of the carbamoyl group but on reduction of the mixture with LiAlH₄, diol 45 was isolated in 57% yield. It is possible that neighbouring group participation by the carbamoyl group traps the intermediate carbocation in the Prins cyclisation giving II and resulting in migration of the carbamyl group but this has not been proven.

Conclusions

In conclusion, a de novo approach for the rapid construction of a series of orthogonally protected l- and d-2,6-dideoxysugars and analogues is described from simple starting materials. A stable acetal 5 was prepared in two high yielding steps and used in a series of acid-mediated Prins cyclisations with different homoallylic alcohols to give the corresponding tetrahydropyrans in good yield and excellent diastereoselectivity. These reactions are readily performed on gram scales. A modified Tamao–Fleming oxidation/acetylation protocol gave the target 2,4-dideoxy sugars with an acetyl group at the anomeric position. Extending the utility of the new methodology to the synthesis of 2,6-dideoxysugars revealed the importance of the choice of protecting group to avoid formation of tetrahydrofurans. The enantioselective synthesis of protected l-olivose is described using N,N-diisopropylcarbomoyl as a protecting group. Silane 41 has potential value for the synthesis of other 2,6-dideoxysugars for example methylation of the free hydroxyl group will lead to protected l-digiosine while Mitsunobu inversion will give l-boivinose derivatives and subsequent methylation to l-sarmentose and these investigations are ongoing in our laboratories.

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Notes and references


3 Recently some elegant strategies have been reported for the synthesis of 2,4-dideoxysugars starting from readily available carbohydrates, e.g. M. Emmadi and S. S. Kulkarni, Org. Biomol. Chem., 2013, 11, 3098–3102.


9 Prins cyclisations have been used to assemble tetrahydropyrans with a hydroxymethyl side-chain which then can be oxidatively cleaved to give lactones, see for example, J. S. Yadav, M. S. Reddy and A. R. Prasad, Tetrahedron Lett., 2005, 46, 2133–2136.


31 Carbamates have been used to good effect in intramolecular Samurai cyclisations, B. Leroy and I. E. Markó, Tetrahedron Lett., 2001, 42, 8685–8688.


