

Synthesis of amino-sugars using the directed dihydroxylation reaction

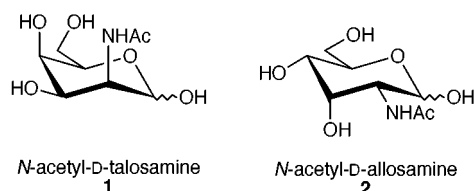
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The synthesis of protected forms of two amino-sugars, talosamine **1** and allosamine **2**, is described; the *syn, syn* stereochemistry at C-2, C-3 and C-4 was controlled by the use of a hydrogen-bonding directed dihydroxylation reaction using stoichiometric and catalytic OsO₄; proof of the relative stereochemistry of the allosamine series was obtained through an X-ray crystal structure of a protected derivative.

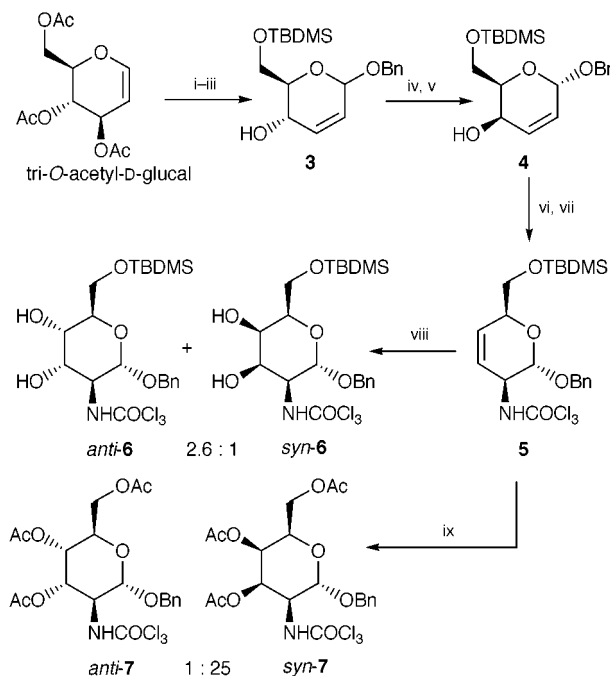
2-Amino-sugars are the key constituents of a variety of naturally occurring polysaccharides. We are interested in the synthesis of two of the rarer amino-sugars, talosamine and allosamine: *N*-acetyltalosamine has been isolated from both bovine and ovine cartilage,¹ whilst *N*-acetylallosamine is the repeat unit in the sugar portion of allosamidin² (which is an interesting chitinase inhibitor).



We have recently described that combination of OsO₄ with an amine (usually TMEDA) produces a reagent which dihydroxylates allylic amides: efficient hydrogen bonding between the oxidant and the allylic amide means that the stereoselectivity observed is contra-steric and therefore opposite to that obtained under standard oxidation conditions.³ Examination of talosamine and allosamine reveals that they both have *syn, syn* stereochemistry at C2–C4 and so are ideally configured for synthesis *via* our chemistry.

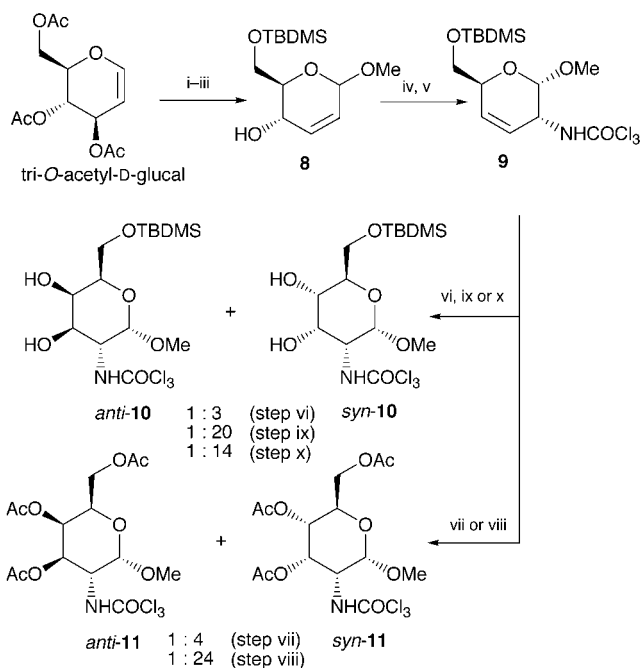
Our synthesis of *N*-acetyl talosamine began with tri-*O*-acetyl-D-glucal, which was converted into the allylic trichloroacetamide **5** using standard chemistry (Scheme 1).⁴ Compounds **3**, **4** and **5** are formed as mixtures of anomers (9:1) and the major one was separated and is shown for clarity. The dihydroxylation of **5** was then examined under a variety of conditions to investigate ways of forming the *syn, syn* isomer which corresponds to the talosamine series. As can be observed from Scheme 1, oxidation under standard Upjohn conditions (step viii) gave predominantly the *syn, anti* isomer (this corresponds to the allose series of amino sugars) as expected. However, use of OsO₄ and TMEDA at low temperature was successful in completely reversing the facial bias of this molecule and provides the *syn, syn* isomer with complete stereoselectivity (as measured by ¹H NMR spectroscopy, step ix) and excellent yield. The relative stereochemistry of the adducts shown in Scheme 1 was proven by correlation to a compound of known configuration (*vide infra*). Note that the products from the stoichiometric and catalytic oxidations are slightly different; the acidic work-up used with stoichiometric OsO₄ removes the TBDMS group at C-6; the resulting triol was then peracetylated with Ac₂O in order to expedite isolation.

We then turned our attention to allosamine **2** and proceeded to prepare allylic amide **9** by a process analogous to that described earlier (Scheme 2).^{5†} The modified conditions reported by Isobe and co-workers were crucial to success in the Overman rearrangement.⁶ The oxidation of **9** (again the major anomer was isolated and is shown for clarity) proved to be most interesting. In this case the standard Upjohn reaction was moderately *syn* selective for the allosamine isomer (step vi). Unfortunately the addition of TMEDA to OsO₄ only marginally improved the *syn* selectivity of the oxidation, (step vii). Occasionally, our attempts to use TMEDA/OsO₄ for directing the dihydroxylation reaction have been frustrated by either electrostatic or steric repulsion between the substrate and the oxidant.⁷ In such cases we have found that addition of a monodentate amine (quinuclidine is best) to OsO₄ can give better *syn* stereoselectivity *via* a hydrogen bonding process; this was indeed the case (step viii), and the selectivity attainable was now high enough to be synthetically useful. The reagent formed during this reaction is not as effective a hydrogen bond acceptor as OsO₄/TMEDA but can give higher levels of *syn* stereoselectivity, presumably as a consequence of its reduced steric bulk. One of the advantages of using a monodentate amine promoter in the dihydroxylation reaction is that the process can be made catalytic in osmium by using the amine as its



Scheme 1 Reagents and conditions: i, BnOH (1.1 equiv.), BF₃·OEt₂ (0.1 equiv.), CH₂Cl₂, –20 °C room temp., 1 h, 98%; ii, K₂CO₃ (0.5 equiv.), MeOH–H₂O (4:1), room temp., 1 h, 93%; iii, TBDMSCl (1.1 equiv.), Et₃N (2.2 equiv.), CH₂Cl₂, room temp., 24 h, 74%; iv, PPh₃ (4.0 equiv.), PhCO₂H (4.0 equiv.), DEAD (4.0 equiv.), THF, 0 °C, 2 h, 88%; v, NaOMe (0.5 equiv.), MeOH, room temp., 86%; vi, DBU (1.2 equiv.) CCl₃CN (1.3 equiv.), CH₂Cl₂, –20 °C–room temp., 97%; vii, xylene, cat. K₂CO₃, Δ, 18 h, 93%; viii, NMO (1.5 equiv.), cat. OsO₄, acetone–H₂O (4:1), room temp., 77%; ix, TMEDA (1.05 equiv.), OsO₄ (1.05 equiv.), CH₂Cl₂, –78 °C–room temp., then MeOH–HCl, then Ac₂O, 89%.

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Scheme 2 Reagents and conditions: i, MeOH (1.1 equiv.), $\text{BF}_3 \cdot \text{OEt}_2$ (0.5 equiv.), toluene, -20°C –room temp., 1 h, 89%; ii, K_2CO_3 (0.5 equiv.), MeOH– H_2O (4:1), room temp., 1 h, 92%; iii, TBDMSCl (1.1 equiv.), Et_3N (2.2 equiv.), CH_2Cl_2 , room temp., 24 h, 91%; iv, DBU (1.2 equiv.), CCl_3CN (1.3 equiv.), CH_2Cl_2 , -20°C –room temp., 98%; v, Ph_2O , cat. K_2CO_3 , 195°C , 3 h, 64%; vi, NMO (1.5 equiv.), cat. OsO_4 , acetone– H_2O (4:1), room temp., 75%; vii, TMEDA (1.05 equiv.), OsO_4 (1.05 equiv.), CH_2Cl_2 , -78°C –room temp., then MeOH–HCl, then Ac_2O , 90%; ix, quinuclidine *N*-oxide (2.0 equiv.), cat. OsO_4 , CH_2Cl_2 , room temp., 80%; x, $\text{Me}_3\text{NO} \cdot 2\text{H}_2\text{O}$ (1.5 equiv.), cat. OsO_4 , CH_2Cl_2 , room temp., 87%.

corresponding *N*-oxide (with sufficient water added to allow the catalytic cycle to turn over). So, the use of quinuclidine *N*-oxide (2 equiv.)⁸ and catalytic OsO_4 (5 mol%) with approximately 4 equiv. of water, also gave an excellent level of *syn* stereoselectivity (step ix). This novel oxidising system gave better stereoselectivity than that observed by using trimethylamine *N*-oxide as a reoxidant (step x).⁹

The relative stereochemistry of the allosamine series of compounds was proven by an X-ray crystal structure on the benzylidene protected derivative **12** (Fig. 1).[§]

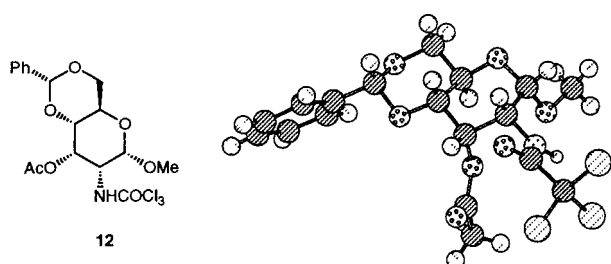
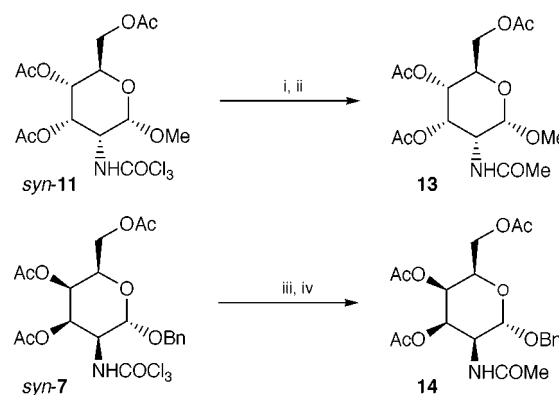


Fig. 1 X-Ray structure of **12**.

As amino-sugars frequently occur in nature as their *N*-acetyl derivatives, we removed the trichloroacetyl group and added an acetyl functionality. This was accomplished readily in a two stage, one pot process (Scheme 3).[¶] Compound **14** prepared by this route is known in the literature¹⁰ and displayed characteristics identical to those previously reported (^1H NMR, $[\alpha]_D$); this correlation proves the stereochemistry of the talosamine series described in Scheme 1.

To conclude, we have prepared protected forms of two naturally occurring and rare amino-sugars, talosamine and allosamine: both compounds are available in high yield and with excellent levels of stereoselectivity. These derivatives are ideally configured for further elaboration into polysaccharides and work is continuing in this direction. Moreover, we have



Scheme 3 Reagents and conditions: i, NaOH, EtOH, 10 min; ii, Ac_2O , cat. DMAP, pyridine, 24 h, 82%; iii, NaOH, EtOH, 10 min; iv, Ac_2O , cat. DMAP, pyridine, 24 h, 86%.

introduced a novel oxidising system, using quinuclidine *N*-oxide, which is capable of dihydroxylating certain allylic amides with hydrogen-bonding control^{||} and which uses catalytic OsO_4 .

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Notes and references

[‡] A similar strategy has been adopted previously for the synthesis of allosamine. However, the reported route is troubled by both a low yielding Overman rearrangement (30%) and oxidation with RuO_4 (50%).

[§] Crystal data for $\text{C}_{18}\text{H}_{20}\text{NO}_7\text{Cl}_3$ **12**: $M = 468.70$, orthorhombic, $a = 12.862(7)$, $b = 27.763(6)$, $c = 6.007(4)$ Å, $T = 296$ K, space group $P2_12_12_1$ (no. 19), $Z = 4$, $\mu(\text{Cu-K}\alpha) = 4.225$ mm $^{-1}$, 2179 independent reflections which were used in all calculations. The final $wR(F^2)$ was 0.1554 (all data). $R(F)$ was 0.0499 using 1703 reflections with $I > 2\sigma(I)$. The structure was solved using direct methods and developed using difference Fourier techniques, then refined by full matrix least-squares on F^2 . CCDC 182/1357.

[¶] Selected data for **13**: $[\alpha]_D +69$ (c 5.33, EtOH); δ_{H} (300 MHz; CDCl_3) 5.83 (d, 1H, J 9.3), 5.51 (dd, 1H, J 3.0, 3.5), 4.97 (dd, 1H, J 3.0, 10.2), 4.68 (d, 1H, J 4.4), 4.48 (ddd, 1H, J 3.5, 4.4, 9.3), 4.30–4.15 (m, 3H), 3.42 (s, 3H), 2.16 (s, 3H), 2.09 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H); δ_{C} (75 MHz; CDCl_3) 170.6, 170.4, 169.2, 169.0, 97.6, 68.3, 66.0, 63.0, 62.1, 55.7, 47.4, 23.0, 20.9, 20.6, 20.4. For **14**: $[\alpha]_D +72$ (c 0.80, CHCl_3); δ_{H} (300 MHz; CDCl_3) 6.39 (d, 1H, J 9.6), 5.40 (m, 1H), 5.34 (dd, 1H, J 3.5, 4.5), 4.91 (d, 1H, J 1.1), 4.68 (d, 1H, J 11.6), 4.54 (d, 1H, J 11.6), 4.48 (ddd, 1H, J 9.6, 4.7, 1.1, 1.1), 4.27 (ddd, 1H, J 7.1, 6.2, 1.3), 4.12 (ABX, 2H, J_{AB} 11.1, J_{AX} 6.2, J_{BX} 7.1), 2.18 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H); δ_{C} (75 MHz; CDCl_3) 170.3, 169.4, 169.4, 168.9, 136.2, 128.5, 128.1, 128.0, 99.1, 69.8, 67.7, 66.5, 64.7, 61.7, 48.5, 23.4, 20.6, 20.5.

^{||} Oxidation of **5** with quinuclidine *N*-oxide under the conditions described in Scheme 2 gave a 1:1 mixture of stereoisomers. However, other allylic amides do give *syn* selective results using this oxidant; details will be reported in due course.

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