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Trichloro-oxazolines as Activated Donors for Aminosugar Coupling

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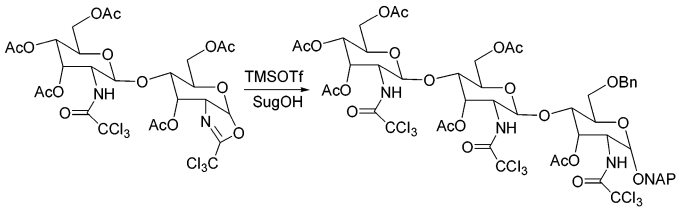
ABSTRACT

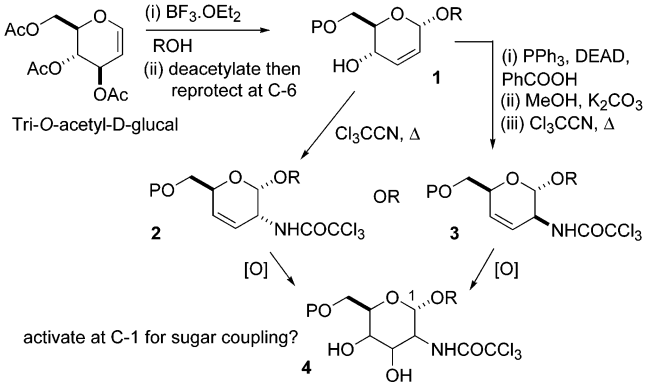


Starting from tri-*O*-acetyl-D-glucal, a combination of the Overman rearrangement and subsequent dihydroxylation produces a range of aminosugars. These can be activated by formation of the corresponding trichloro-oxazolines, which are excellent glycosyl donors as they form disaccharides with good (trans) stereoselectivity under mild conditions. Propagation of these trichloro-oxazolines gave trisaccharides that can then be dehalogenated under a variety of conditions.

2-Amino-2-deoxy sugars are widely distributed throughout Nature occurring as key constituents of many glycoproteins and glycolipids.[1] They are also essential components of various other natural products such as the antibiotics streptothricin, streptomycin, and adriamycin.[2] As a consequence, there is considerable interest in new strategies for the synthesis of such molecules, especially 2-amino-2-deoxy oligosaccharides.

Recently, we disclosed a strategy for accessing a range of 2-amino-2-deoxy sugars that was based upon Ferrier glycosidation (tri-*O*-acetyl-D-glucal → **1**),[3] Overman rearrangement (**1** → **2**/**3**), and subsequent dihydroxylation, Scheme 1.[4] While the stereochemistry at C-4 in structure **1** is initially

Scheme 1



set as shown, it could also be readily inverted by a Mitsunobu reaction.[4] As the Overman rearrangement is stereospecific, this meant that we could fully control the stereochemistry at C-2 in trichloroacetamides **2** and **3** and gain access to many allosamine and talosamine derivatives not readily accessible by other methods.

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(1) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167.
(2) See: *Carbohydrates Structure and Biology*; Lehmann, L.; Thieme: Stuttgart, 1998.
(3) Ferrier, R. J. *J. Chem. Soc. C* **1964**, 5443. For a recent reference, see: Das, S. K.; Reddy, K. A.; Abbineni, C.; Roy, J.; Rao, K. V. L. N.; Sachwani, R. H.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 4507.
(4) Donohoe, T. J.; Blades, K.; Helliwell, M. *Chem. Commun.* **1999**, 1733. See Supporting Information.

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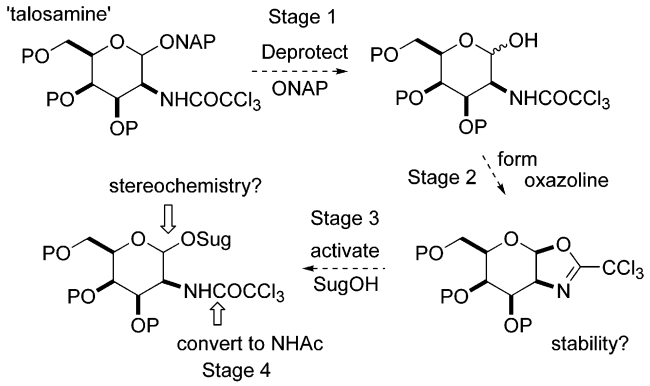
To ascertain whether compounds of general structure **4** might prove to be useful for oligosaccharide synthesis, we recently investigated ways of converting them into a range of trichloro-oxazoline glycosyl donors so that we could study subsequent coupling with glycosyl acceptors.

It should be noted that the use of trichloroacetamide-protected aminosugars as glycosyl donors was originally established by Jacquinet,[5] but that there are only two sugar-derived trichloro-oxazolines reported in the literature (derived from glucosamine[5] and galactosamine[6]). Furthermore, the formation of C-2 mannose-configured trichloro-oxazolines was unknown. Coupling reactions of isolated trichloro-oxazoline donors are rare, and only the glucosamine derivative, prepared from the anomeric *O*-acetate by Jacquinet, had been subjected to a handful of glycosylations.[5,7]

Herein, we now report success in our endeavor, having successfully accomplished the synthesis of several rare disaccharide derivatives containing allosamine and talosamine substructures.

Our general strategy for preparing the appropriate trichloro-oxazoline donors from **1** exploited a β-naphthylmethyl[8] as the *O*(1) protecting group and used the Overman/dihydroxylation tactic to fashion the appropriately *O*-hydroxylated amino sugar; for example, see talosamine, Scheme 2. Next,

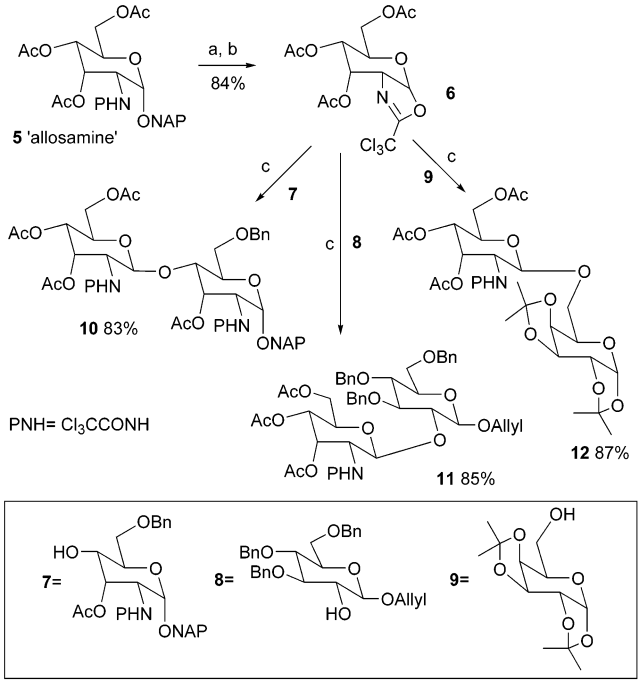
Scheme 2



we detached the naphthylmethyl group from the protected product with DDQ (stage 1, Scheme 2). Oxazoline formation was then effected by activation of the anomeric hydroxyl group (stage 2). Thereafter, the trichloro-oxazoline was coupled with a glycosyl acceptor after activation with TMSOTf (stage 3). Finally, we converted the trichloro-acetamide unit into a *N*-acetyl group (since this is the naturally occurring derivative of most C-2 aminosugars).

Initially, we chose the allosamine-derived sugar **5** as an example on which to test our synthetic plans, Scheme 3. This

Scheme 3[a]



[a] Reagents and conditions: (a) DDQ, H_2O, CH_2Cl_2; (b) Ms_2O, MeCN, Et_3N; (c) SugOH (1−1.2 equiv), TMSOTf (20 mol %), −30 to −10 °C, CH_2Cl_2.

was prepared via the previously published route (see Scheme 1), which involves a directed dihydroxylation reaction using catalytic osmium tetroxide.[4] Removal of the NAP group was straightforward using DDQ,[9] and we then chose methanesulfonic anhydride (Ms_2O) as a mild and effective reagent for oxazoline formation **6**. The trichloro-oxazoline **6** was stable at room temperature for 1−2 days and for longer periods in the freezer.

Next we investigated the glycosylation of **6** using three sugar acceptors chosen to provide useful challenges. The acceptors were **7** (protected allosamine),[10] **8** (protected glucose),[11] and **9** (galactose diisopropylidene acetal). Pleasingly, donor **6** glycosylated easily with the three acceptors (1−1.2 equiv) at temperatures between −30 and −10 °C using catalytic TMSOTf as an activator.[12,5] In each case, a single disaccharide product **10**−**12** was isolated from the reaction mixture in 83−87% yield.

Clearly, trichloro-oxazolines are promising derivatives for glycosyl coupling because the halo groups increase the reactivity of the donor relative to a methyl-substituted oxazoline (which can require vigorous conditions for coupling).[13] The enhanced reactivity of a trichloro-oxazoline

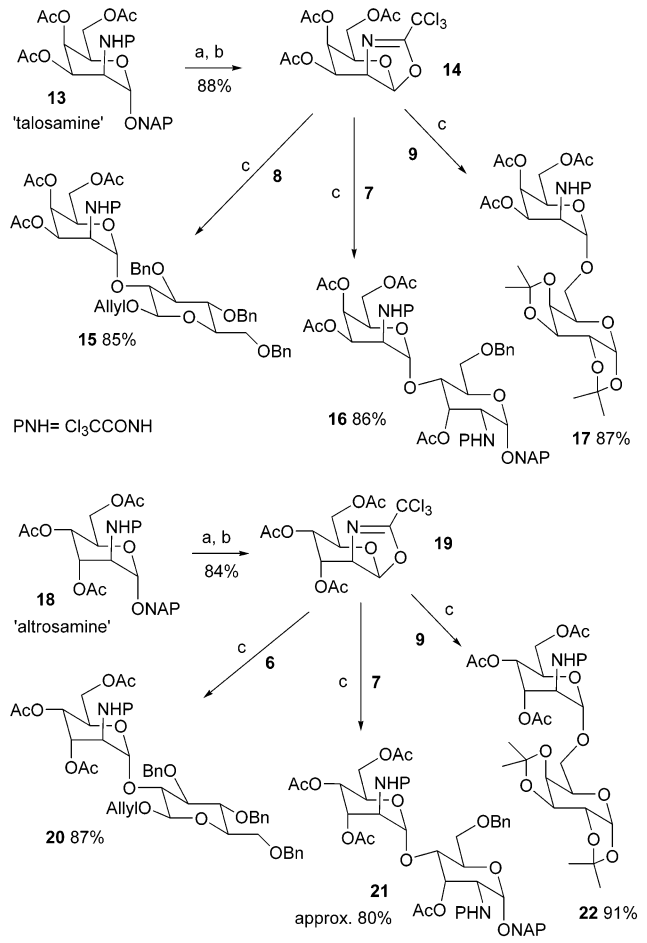
(5) Blatter, G.; Beau, J.-M.; Jacquinet, J.-C. *Carbohydr. Res.* **1994**, *260*, 189.
(6) Bartek, J.; Müller, K. *Carbohydr. Res.* **1998**, *308*, 259. Bélot, F.; Jacquinet, J.-C. *Carbohydr. Res.* **2000**, *325*, 93.
(7) Sherman, A. A.; Olga, N. Y.; Mironov, Y. V.; Sukhova, E. V.; Shashkov, A. S.; Menshov, V. M.; Nifantiev, N. E. *Carbohydr. Res.* **2001**, *336*, 13.
(8) Sarkar, A. K.; Rostand, K. S.; Jain, R. K.; Matta, K. L.; Esko, J. D. *J. Biol. Chem.* **1997**, *272*, 25608. Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63*, 4172.
(9) Xia, J.; Abbas, S. A.; Locke, R. D.; Piskork, C. F.; Alderfer, J. L.; Matta, K. L. *Tetrahedron Lett.* **2000**, *41*, 169.
(10) See Supporting Information.
(11) Bundle, D. R.; Purse, B. W.; Nitz, M.; *Org. Lett.* **2000**, *2*, 2939.

activating group can be explained by analogy to the anomeric trichloroacetimidates introduced by Schmidt.[14]

The configuration at the newly formed anomeric center was proven to be β by $^1J_{CH}$ coupling constants that are particularly diagnostic of the stereochemistry at C-1.[15] In this case, the large ^3J coupling between C1−H and C2−H (**10**−**12**, ^3J 7−7.6 Hz, trans diaxial) is also indicative of the stereochemistry indicated. The outcome from coupling is consistent with an S_N2-like reaction between glycosyl donor and (activated) glycosyl acceptor

Next, we examined the effect of changing the configuration at C-2, by preparing and then glycosylating two donors derived from talosamine and altrosamine, Scheme 4 (**13** and

Scheme 4[a]



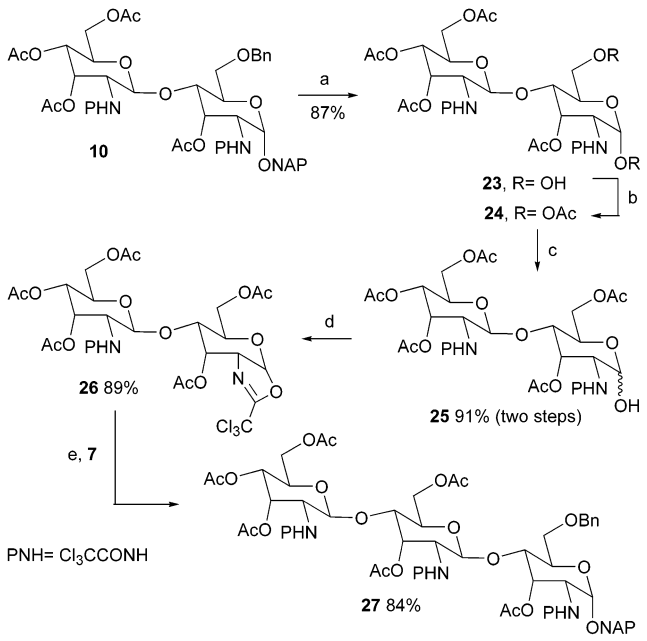
[a] Reagents and conditions: (a) DDQ, H_2O, CH_2Cl_2; (b) Ms_2O, MeCN, Et_3N; (c) SugOH (1−1.2 equiv), TMSOTf (20 mol %), −30 to −10 °C, CH_2Cl_2.

18 were both prepared by using the general chemistry in Scheme 1[4]). In these cases, an S_N2 displacement on the trichloro-oxazolines would yield the α-linked disaccharides.

As predicted, the glycosylation of **14** and **19** took place readily at low temperature and again they each gave a single disaccharide product in 85−91% yield. For each disaccharide that was prepared, the $^1J_{CH}$ coupling constant showed that the configuration at the new anomeric center was α.[16] Extensive NOE experiments also helped to confirm the structures as shown, and in most cases NOESY cross-peaks between the two sugar rings established the connectivity of the disaccharides. Although compound **21** could be isolated from the glycosylation reaction, it was contaminated (≤10%) with a byproduct of unknown composition.

To further extend this methodology, we investigated the propagation of trichloro-oxazolines to make trisaccharide-derived aminosugars, Scheme 5. The disaccharide **10** was

Scheme 5[a]



[a] Reagents and conditions: (a) DDQ, H_2O, CH_2Cl_2; (b) Ac_2O, py, DMAP; (c) $NH_2NH_2{\cdot}CH_3CO_2H$, DMF; (d) Ms_2O, MeCN, Et_3N; (e) **7** (1.1 equiv), TMSOTf (20 mol %), −10 °C, CH_2Cl_2.

chosen for deprotection, formation of a trichloro-oxazoline, and subsequent glycosylation. It is important to note that the β-configured dimer of allosamine **10** is the disaccharide portion of the natural product allosamidin (a potent inhibitor of chitin synthase)[17] and so this sequence will also define a possible synthetic route to allosamidin whereby the aglycone could be attached (via **26**) to this sugar portion in subsequent synthetic studies.

This methodology worked as planned, and selective deprotection of **10** with DDQ gave the diol **23**, which was

(12) $BF_3{\cdot}OEt_2$ can also be used as an activator, although the couplings are slower.

(13) See: Shrader, W. D.; Imperiali, B. *Tetrahedron Lett.* **1996**, *37*, 599. Wittmann, V.; Lennartz, D. *Eur. J. Org. Chem.* **2002**, *8*, 1363.

(14) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.

(15) $^1J_{CH}$ (Hz) **10** (C1, 176; C1′, 167); **11** (C1, 157; C1′, 162); **12** (C1, 178; C1′, 167) numbering from the reducing end first. Block, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.

(16) $^1J_{CH}$ (Hz) **15** (C1, 159; C1′, 179); **16** (C1, 177; C1′, 176); **17** (C1, 181; C1′, 176); **20** (C1, 157; C1′, 172); **21** (C1, 177; C1′, 173); **22** (C1, 182; C1′, 170) numbering from the reducing end first.

(17) Sakuda, S.; Isogai, A.; Matsumoto, S.; Susuki, A.; Koeski, K.; *Tetrahedron Lett.* **1986**, *27*, 2475.

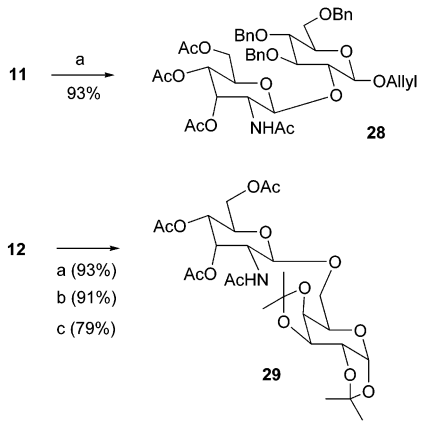
subsequently peracetylated (**24**) before the anomeric OAc was cleaved by reaction with hydrazine acetate to give **25**.[18] Subsequent formation of trichloro-oxazoline **26** occurred smoothly, as did stereoselective formation of trisaccharide **27** with acceptor **7**, Scheme 5.[19]

Finally, for this methodology to be useful, access to a variety of conditions for conversion of the trichloroacetyl group into the naturally occurring *N*-acetyl derivative is required.

Originally, Jacquinet reported radical-based chemistry (Bu_3SnH) to remove the three chlorines from a trichloroacetamide, and we also found this method to be effective with the saccharides that we had prepared, Scheme 6.[5] If one is to use this methodology in a synthetic sequence, then ideally there should be plenty of alternative methods for accomplishing the interconversion of a TCA group into its parent acetamide. To this end, we investigated a range of different methods for reducing **12** and found that, in addition to tin hydride, hydrogenolysis[20] (55 psi) and cleavage with NaOH (followed by reacetylation)[3] were also viable conditions, Scheme 6.

To conclude, we have defined a new protecting group (ONAP) arrangement for oligosaccharide synthesis that is introduced via the Ferrier rearrangement and compatible with subsequent Overman rearrangement and a dihydroxylation sequence. By using DDQ to deprotect the ONAP group, we were able to prepare trichloro-oxazolines from rare amino sugars and then investigated the glycosylation of these activated derivatives. Both possible configurations at C-2 are compatible with this sequence and give high stereoselectivity for the trans arrangement at C1−C2. Moreover, we have shown that the substituted oxazolines can be elaborated to form trisaccharides and finally that there are a variety of different methods for the reduction of the TCA group to an acetamide.

Scheme 6[a]



[a] Reagents and conditions: (a) Bu_3SnH, AIBN, Δ; (b) H_2, Pd-C, MeOH, 55 psi; (c) NaOH, EtOH, then Ac_2O, py, DMAP.

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Supporting Information Available: Full experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydr. Res.* **1975**, *39*, 368.

(19) $^1J_{CH}$ (Hz) **27** (C1, 177; C1′, 163; C1″, 162) numbering from the reducing end first.

(20) Armstrong, P. L.; Coull, I. C.; Hewson, A. T.; Slater, M. J. *Tetrahedron Lett.* **1995**, *36*, 4311.