Ethyl 2-acetamido-4,6-di-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glycopyranoside as a versatile GlcNAc donor†

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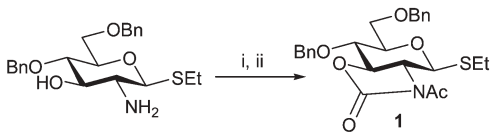
The title donor, ethyl 2-acetamido-4,6-di-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glycopyranoside, is shown to be an excellent glycosyl donor giving immediate and efficient access to variant GlcNAc-containing oligosaccharides.

Glucosamine is a most common monosaccharide residue in natural polysaccharides of animal, plant and microbial origin. Almost always it is present as its 2-acetamido derivative. Hence, from a synthetic point of view, a 2-acetamido type of donor is desirable to minimise protecting group manipulations. Unfortunately, donors of this type suffer from drawbacks mainly due to competing oxazoline formation. Obviously, the participating properties of the *N*-acetate are also a problem if an α-linkage is desired. To circumvent these problems, various protective groups for the amino group have been developed and used in glycosyl donors.[1] However, although effective during coupling reactions, all these groups have to be removed and substituted with an acetyl group at some time during the synthesis; reactions which are not always high-yielding. An alternative approach is to substitute the hydrogen on the acetamide group with another protective group, thus inhibiting oxazoline formation. The *N*,*N*-diacetate, where the removal of the second acetate is trivial and high-yielding, was tried by Schmidt.[2] However, the coupling yields with *N*,*N*-diacetates as donors are generally not too high, and so this methodology is not frequently used. We reasoned that other protective groups might be a better choice, and became especially interested in cyclic groups linking the 2-*N* and the 3-*O* of the donor moiety. Several attempts to introduce TIPDS-, isopropylidene-, BDA- or diacid groups were made without success. The formation of the *trans*-fused cyclic carbamate, on the other hand, worked nicely. This protection mode was described as a non-participating group as early as 1969 by Gross *et al.*,[3] and Kerns *et al.*[4] have reported on 2-*N*,3-*O*-carbamates as glycosyl donors. A high α-selectivity was obtained, when a carbamate protected thiophenylglycoside was used together with phenylsulfenyl triflate as promoter at low temperature. Also, recently Crich *et al.*[5] utilized the carbamate not in glycosyl donors, but in efficient glycosyl acceptors. The standard conditions employed for the introduction of the carbamate group are the use of 4-nitrophenyl chloroformate, producing a mixture of the desired compound and uncyclised material that is converted to the fully protected material in an additional step. We were able to improve this sequence by adapting a protocol with triphosgene as reagent which was originally described for the formation of isocyanates from amines (Scheme 1).[6] This procedure yielded the cyclic carbamate in almost quantitative yield and in excellent purity even without chromatography. Since our interest was in β-linked GlcNAc-containing target structures, the nitrogen was acetylated and the resulting *N*-acetyl-oxazolidinone thioglycoside donor **1** tried in coupling reactions with various acceptors. As desired, the donor showed complete β-selectivity using NIS and a catalytic amount of AgOTf as promoter system at ambient temperature. Both with a steroid alcohol and with primary and secondary carbohydrate acceptors the isolated yields of glycosylation product were excellent (Table 1). A bit surprisingly and by serendipity, similar high yields of α-coupling product could be reproducibly obtained using a larger quantity (0.4 equiv.) of AgOTf in the couplings, perhaps due to *in situ* anomerisation. Recently Crich *et al.*,[7] when attempting reductive benzylidene openings of a β-thioglycoside, also noted a tendency of these 2,3-oxazolidinone derivatives to rapidly anomerise to the α-anomer. Thus, depending on the amount of promoter added either the α- or the β-glycoside can be efficiently produced in the coupling reactions. In our hands (*i.e.* using 4,6-di-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside as donor together with cholesterol as acceptor and the NIS/AgOTf (cat.) promoter system at ambient temperature) also the non-acetylated donor afforded the β-product in contrast to the earlier published work.[4] Although surprisingly there are precedents in the literature of glucosamine donors without a 2-participating group giving β-selectivity in glycosylations.[8,9]

Another attractive aspect of the *N*-acetylated compounds was found when deprotection was attempted. Normally cyclic carbonates are quite base stable; however, when the *N*-acetyloxazolidinone was treated with sodium methoxide under mild conditions, the carbonate was removed smoothly to produce the desired *N*-acetamido compound.

In conclusion, a most effective glucosamine donor **1** has been developed, which contains a number of attractive features. As shown by others, similar derivatives are most efficient acceptors for glycosylation in the 4-position,[5] making a smooth entry into LacNAc derivatives. The donor gives very high yields of



i. triphosgene, CH_2Cl_2/$NaHCO_3$(sat), 98 %;
ii. diisopropylethylamine, AcCl, CH_2Cl_2, 91 %.

Scheme 1 Preparation of ethyl 2-acetamido-4,6-di-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside **1**.

† Electronic supplementary information (ESI) available: experimental details and spectroscopic data. See http://www.rsc.org/suppdata/cc/b5/b503651h/

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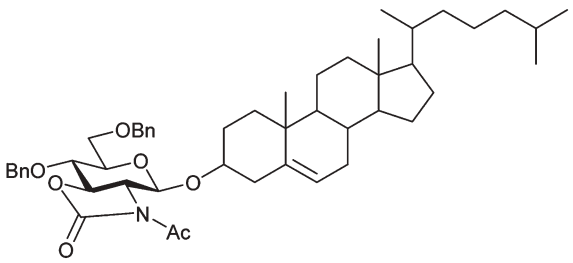
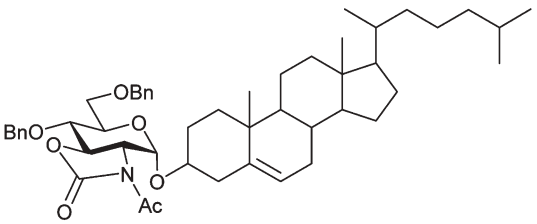
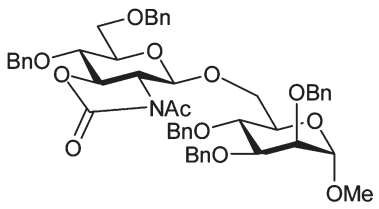
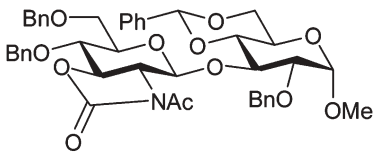
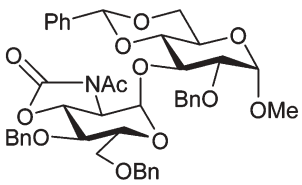
Table 1 Stereoselective coupling reactions[a] using the carbamate protected donor **1** and different acceptors

Entry	Acceptor	Product	H-1(^{1}H) δ [ppm]/ J [Hz]	Yield (%)
1	Cholesterol		5.12/*6.6*	91
2			5.83/*2.7*	89
3	Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside		5.00/*6.4*	90
4	Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside		5.68/*7.1*	94
5			6.31/*2.7*	91

[a] All coupling reactions were carried out in dry CH_2Cl_2 (molecular sieves 4 Å) at ambient temperature using a slight excess of donor **1** (1.2–1.5 equiv.) and the NIS/AgOTf promoter system.

glycosylation products, and the stereochemical outcome of the reaction can be determined simply by choosing more or less acidic coupling conditions giving entry to both α- and β-linked GlcNAc oligosaccharides. Mild methoxide treatment produces directly GlcNAc derivatives with a free 3-OH, thus allowing synthesis of LacNAc type II compounds or Lewis x and y type structures.

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Notes and references

1 J. Banoub, P. Boullanger and D. Lafont, *Chem. Rev.*, 1992, **92**, 1167.
2 J. C. Castro-Palomino and R. R. Schmidt, *Tetrahedron Lett.*, 1995, **36**, 6871.
3 K. Miyai and P. H. Gross, *J. Org. Chem.*, 1969, **34**, 1638.

4 K. Benakli, C. Zha and R. J. Kerns, *J. Am. Chem. Soc.*, 2001, **123**, 9461; R. J. Kerns, C. Zha, K. Benakli and Y.-Z. Lian, *Tetrahedron Lett.*, 2003, **44**, 8069.
5 D. Crich and A. U. Vinod, *Org. Lett.*, 2003, **5**, 1297.
6 Y. Ichikawa, Y. Matsukawa, T. Nishiyama and M. Isobe, *Eur. J. Org. Chem.*, 2004, 586.
7 D. Crich and A. U. Vinod, *J. Org. Chem.*, 2005, **70**, 1291.
8 T. Kaneko, K. Takahashi and M. Hirama, *Heterocycles*, 1998, **47**, 91.
9 H. Jiao and O. Hindsgaul, *Angew. Chem., Int. Ed.*, 1999, **38**, 346.

