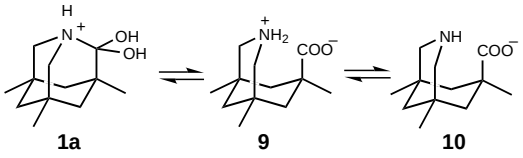
carboxylate carbon atoms of zwitterion **9** and anion **10** [Eq. (1)]. However, at pH 3.30 there is no absorption in this



1a **9** **10** (1)

region, but a new peak at $\delta = 106.3$. This signal can be assigned with some confidence to the orthoamide carbon atom of the hydrate **1a**[11] of the conjugate acid of the twisted amide **1**: The very similarly substituted carbon atom of N-methylated **7** (which has been fully characterized) absorbs at $\delta = 111$ in $CDCl_3$.

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[8] Relevant known structures: A. Greenberg, C. A. Venanzi, *J. Am. Chem. Soc.* **1993**, *115*, 6951-6957.

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[11] Protonated hydrates such as **1a**, high-energy intermediates in the acid-catalyzed hydrolysis of normal amides, are formed with particular ease from twisted amides[12] and derive further stabilization from the adamantane framework in our system.

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Amidoglycosylation of Polymer-Bound Glycals: A Complete Solid-Phase Synthesis of the Oligosaccharide Domain of the Lewis^b Blood Group Determinant**

Changsheng Zheng, Peter H. Seeberger, and Samuel J. Danishefsky*

Blood group determinants are a class of cell surface glycoconjugates that are involved in a variety of functions such as cell – cell adhesion, control of cell growth and differentiation, and immune response.[1] Docking of viral and bacterial pathogens is also often initiated through binding of cell surface carbohydrates.[2] In this regard the Lewis^b blood group antigen (Le^b) is of particular interest, as it has been identified as a mediator for the binding of *Helicobacter pylori* to human gastric epithelium.[3] Clinical studies have identified *H. pylori* as a causative agent in gastric and duadenal ulcers.[4] Antimicrobial treatments are currently the means of combatting infection.[5] Since bacterial attachment is a prerequisite to infection,[6] small-molecule lookalikes of the Le^b antennary structure may serve as therapeutic alternatives to broad-spectrum antibiotics.

Although many carbohydrate antigens of the A, B, H, and Lewis families has been synthesized in solution phase, synthetic access has often been laborious and time-consuming.[6] A particularly desirable goal would be the development of generally applicable methods for the rapid assembly of oligosaccharides with a long-term view toward automation. Our laboratory has been investigating an approach in which glycals are key building blocks for the synthesis of oligosaccharides and glycoconjugates.[7] This approach has also proven to be amenable to the synthesis of complex structures on solid supports.[7]

Our solution-phase synthesis of glycosides of 2-deoxy-2-acetylamidoglucose (GlcNac) and -galactose (GalNAc) takes

[*] Prof. Dr. S. J. Danishefsky, Dr. C. Zheng, Dr. P. H. Seeberger
Laboratory for Bioorganic Chemistry
Sloan-Kettering Institute for Cancer Research
Box 106, 1275 York Avenue, New York, NY 10021 (USA)
Fax: (+1) 212-772-8691
E-mail: c-kandell@ski.mskcc.org

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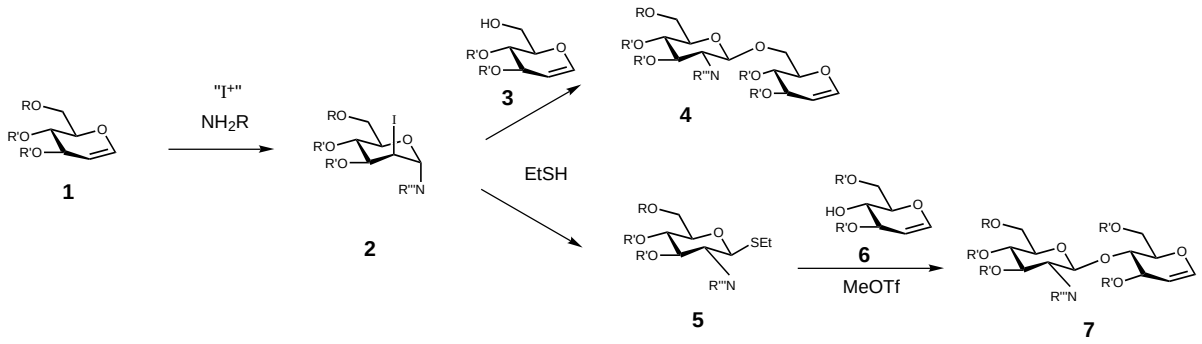


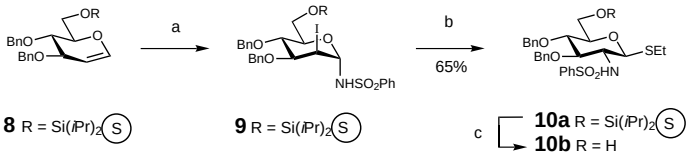
Scheme 1. Conversion of solid support bound glycals into thiodonors for amidoglycosylation. R = protecting group or solid support; R′, R″, R‴ = protecting groups; Tf = triflate.

advantage of sulfonamidoglycosylation. This sequence starts with the addition of a halonium arenesulfonamide to a glycal such as **1** to afford **2** (Scheme 1). The latter reacts with glycal acceptor **3** to afford **4**. The C2-α-sulfonamide group can be converted into a C2-α-acetamido function by any of several protocols.[8]

Our previous approaches towards the solid-phase synthesis of blood group determinants underscored a serious shortcoming in our polymer-based methodological arsenal. The glycal assembly method permitted rapid and concise access to β-glucosidic and β-galactosidic linkages where C2 carries a protected oxy group.[9] The solution-phase protocol of sulfonamidoglycosylation did not translate to the solid phase since silver ion catalysis is apparently needed in the direct coupling step. We had to take recourse to solution-phase azaglycosylation for the construction of *N*-acetylaminoglycosidic linkages prevalent in biologically important blood group determinants, as well as gangliosides.[10] Needless to say, protocols allowing for the efficient formation of these β-2-aminoglucosidic linkages in solid-phase syntheses would greatly facilitate the synthetic entry to a variety of biologically important targets.

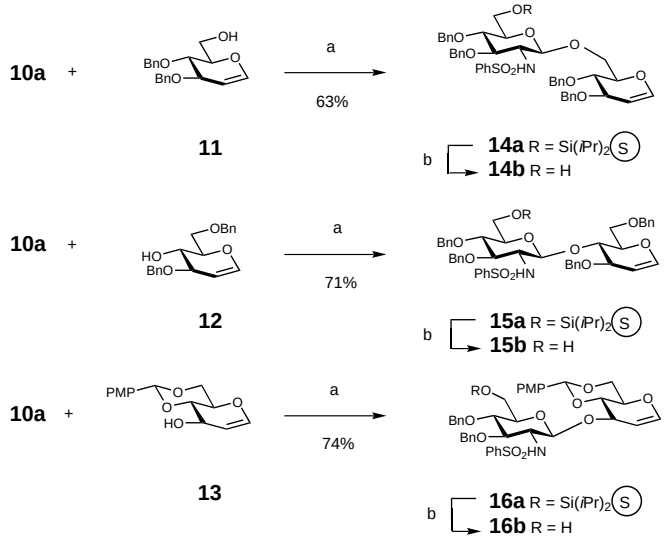
The strategy for success borrowed from a refinement in sulfonamidoglycosylation first demonstrated in solution phase. We found that such direct couplings with encumbered acceptors tended to fail or to occur in poor yield. The modification was developed for transformations with hindered or otherwise weakly reactive acceptors in a projected direct rearrangement – coupling sequence with a 2-β-iodo-1-α-arenesulfonamide donor. Our procedure required prior conversion of **2** to **5** through reaction with ethanethiolate. At this point system **5** serves as an effective donor with a hindered glycal acceptor of type **6** under promotion by methyl trifluoromethanesulfonate (triflate).

We therefore wondered about the transferability of this two-stage sulfonamidoglycosylation methodology to the solid phase. Herein we report the feasibility of converting support-bound glycals into ethylsulfanyl 2-amidoglucosyl donors. These donors were subsequently employed in the construction of β(1,3)-, β(1,4)-, and β(1,6)-2-aminoglucosidic linkages using glycal acceptors. This methodological advance paved the way to the solid-support synthesis of the Lewis^b pentasaccharide glycal. Polymer-supported glucal **8**[8] was treated with iodonium *sym*-collidine perchlorate to form iodosulfonamide **9** as an intermediate (Scheme 2). Rearrangement – displacement through the agency of ethanethiolate yielded the protected ethylsulfanyl glycosyl donor **10** (65%).



Scheme 2. Synthesis of polymer-bound ethylsulfanyl 2-amidoglucosyl donor **10**. a) $I(coll)_2ClO_4$, $PhSO_2NH_2$, CH_2Cl_2, 0°C; b) LHMDS/EtSH, DMF, $-40 \rightarrow 0$°C; c) TBAF/AcOH, THF, 40°C, 18 h. Bn = Benzyl, Ⓢ = polystyrene, coll = *sym*-collidine (2,4,6-trimethylpyridine), LHMDS = lithium bis(trimethylsilyl)amide, TBAF = tetrabutylammonium fluoride.

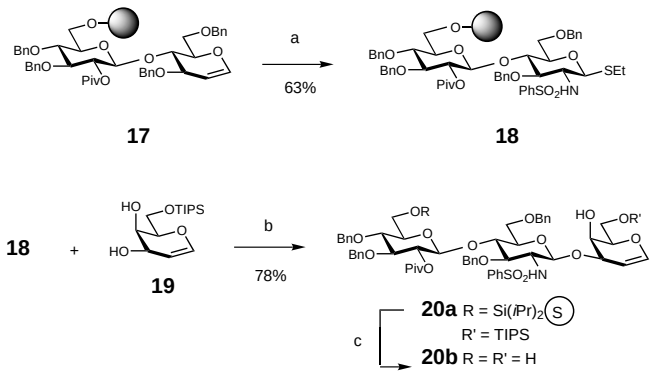
Recently, we have shown that support-bound thioglycosides bearing a protected hydroxyl functionality in the C2 position can be efficiently coupled to glycal acceptors by activation with methyl triflate as a thiophile.[11] One equivalent of the nonnucleophilic base di-*tert*-butylpyridine (DTBP) was added to stabilize the glycal linkage during the coupling experiments. These reaction conditions also proved successful in the case of the ethylsulfanyl 2-amidoglucosyl donors: the formation of β-2-aminoglucosyl (1,4)-linked disaccharide **15a** and β-2-aminoglucosyl (1,3)-linked disaccharide **16a** proceeded in over 70% yield (Scheme 3). The β-2-aminoglucosyl (1,6)-linked disaccharide **20a** was formed in lower yields; this result



Scheme 3. Synthesis of disaccharides with a polymer-bound ethylsulfanyl 2-aminoglucosyl donor. a) MeOTf, DTBP, molecular sieves (4 Å), CH_2Cl_2, $0° \rightarrow 20$°C, 8 h; b) TBAF/AcOH, THF, 40°C, 18 h. PMP = 4-methoxyphenyl.

was not unexpected based on the findings of the study in the C2-oxy series.

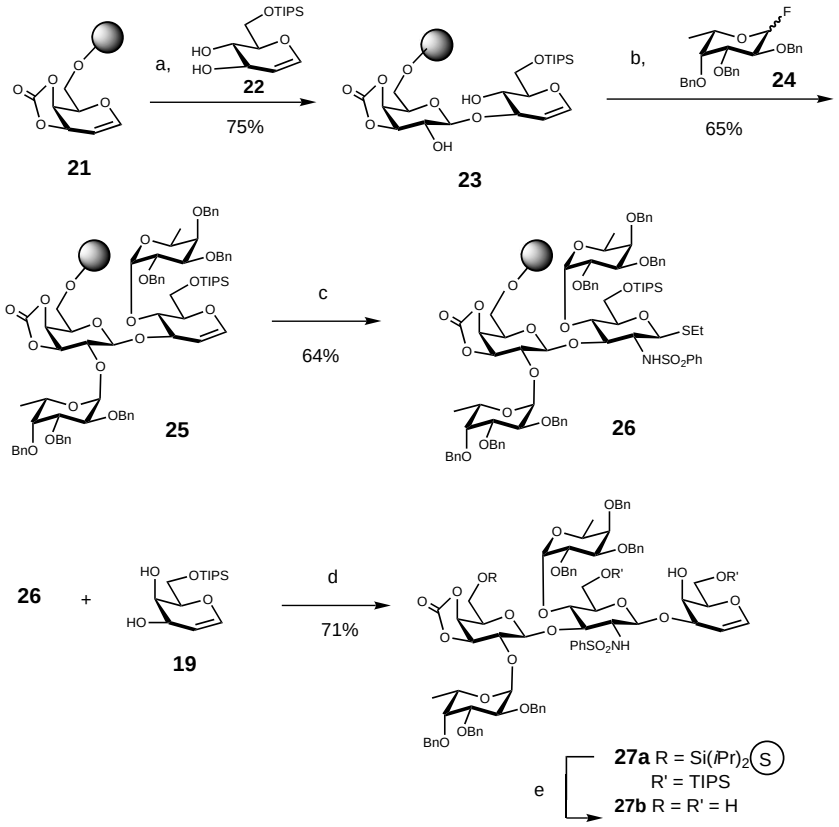
Good coupling yields and excellent selectivities were also obtained in the fashioning of a β-2-aminoglucosyl (1,3) linkage between the support-bound disaccharide donor **18a** and galactal acceptor **19** presenting two exposed hydroxyl functions. Trisaccharide **20a** was formed in 78% yield as the only isomer. (Scheme 4).



Scheme 4. Synthesis of a trisaccharide with polymer-bound ethylsulfanyl 2-aminoglycosyl donor. a) 1. $I(coll)_2ClO_4$, $PhSO_2NH_2$, CH_2Cl_2, 0°C; 2. LHMDS/EtSH, DMF, $-40 \rightarrow 0$°C; b) MeOTf, DTBP, molecular sieves (4 Å), CH_2Cl_2, $0 \rightarrow 20$°C, 8 h; c) TBAF/AcOH, THF, 40°C, 18 h. ● = polymer. TIPS = triisopropylsilyl.

After an efficient coupling protocol for the synthesis of β-2-amidoglucosidic linkages had been established, this methodology was applied to the synthesis of the Lewis[b] pentasaccharide glycal (Scheme 5). Our earlier synthesis failed at the stage of sulfonamidoglycosylation.[12] The tetrasaccharide glycal **25** had to be cleaved from the polymeric carrier and further elaborated by solution-based methods to form the Le[b] oligosaccharide domain in bioconjugatable form. Expanding now on these earlier advances, we converted branched tetrasaccharide **25**[12] into the ethylsulfanyl donor **26**. Coupling to galactal acceptor **19** yielded 71% of the desired pentasaccharide **27a** (Scheme 5). Retrieval of the pentasaccharide was accomplished with tetrabutylammonium fluoride to afford **27b** in 20% overall yield.

A major advance in solid-support oligosaccharide synthesis by the glycal assembly approach has now been achieved. A novel protocol for the conversion of support-bound glycals into ethylsulfanyl 2-amidoglycosyl donors has been developed. Coupling of these glycosyl donors was shown to proceed in good yields in the construction of a variety of different glycosidic linkages. This methodological advance together with other recent methodological progress has brought about a vast expansion of the arsenal of glycosidic linkages accessible by the glycal assembly approach where the donor moiety is linked to the solid support. The range of biologically important oligosaccharides and glycopeptides now accessible by solid-support synthesis is accordingly amplified. This fact was exemplified by preparation of the previously elusive Lewis[b] pentasaccharide glycal. The challenge of solid-support synthesis of blood group determinants, gangliosides, and carbohydrate tumor-associated antigens of increasing complexity is becoming eminently "doable".



Scheme 5. Solid-phase synthesis of the pentasaccharide glycal of the Lewis[b] blood group determinant. a) 1. DMDO, CH_2Cl_2; 2. **19**, $ZnCl_2$, THF; b) $Sn(OTf)_2$, DTBP, molecular sieves (4 Å), THF/toluene (1/4); c) 1. $I(coll)_2ClO_4$, $PhSO_2NH_2$, CH_2Cl_2, 0°C; 2. LHMDS/EtSH, DMF, $-40 \rightarrow 0$°C; d) MeOTf, DTBP, molecular sieves (4 Å), CH_2Cl_2, $0 \rightarrow 20$°C, 8 h; e) TBAF/AcOH, THF, 40°C, 18 h. DMDO = dimethyldioxirane.

Experimental Section

General procedure for the synthesis of polymer-bound ethylsulfanyl 2-amidoglucosyl donors: Polymer-bound glycal (loading: 0.6 mmol g^{-1}) was suspended in anhydrous CH_2Cl_2 under N_2 and cooled to 0°C. Benzenesulfonamide (8 equiv) and $I(coll)_2ClO_4$ (5.5 equiv) were added. The mixture was stirred at 0°C for 6 h and quenched with saturated $Na_2S_2O_3$ solution. The polymer was filtered and washed with water, acetone, DMSO, acetone, THF, and CH_2Cl_2. The iodosulfonamide intermediate was suspended in anhydrous DMF and cooled to -40°C. Ethanethiol (20 equiv) and LHMDS (8 equiv of a 1.0 M solution in THF) were added sequentially. The suspension was gradually warmed up to 0°C over 3 h and stirred for 5 h. The reaction mixture was quenched with saturated NH_4Cl, filtered, and washed with water, acetone, DMSO, acetone, and THF.

General procedure for the coupling of polymer-bound ethylsulfanyl 2-amidoglucosyl donors with glycal acceptors: Polymer-bound ethylsulfanyl 2-amidoglucoside and activated 4 Å molecular sieves (2 mg per 1 mg of polymer) were suspended in anhydrous CH_2Cl_2 under N_2 and cooled to 0°C. Di-*tert*-butylpyridine (20 equiv) was added and the

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mixture was stirred for 30 min. Methyl triflate (20 equiv) was added dropwise, and the reaction mixture was warmed gradually to room temperature and stirred for 5 h. Triethylamine (60 equiv) was added and the reaction mixture stirred for 15 min. The polymer was filtered and suspended in acetone in order to remove the molecular sieves. The polymer was further washed with DMSO, acetone, CH_2Cl_2, and THF.

Analytical samples of the intermediates and the final product were cleaved from the solid support following published procedures[12] and were purified by flash column chromatography.

10b: ^{1}H NMR ($CDCl_3$): $\delta = 7.89$ (d, $J = 7.3$ Hz, 2 H, SO_2Ph), 7.46 (m, 1 H, SO_2Ph), 7.38 (m, 2 H, SO_2Ph), 7.34 – 7.18 (m, 10 H, Bn), 4.77 – 4.67 (m, 3 H), 4.64 (d, $J = 8.2$ Hz, 1 H), 4.59 (d, $J = 11$ Hz, 1 H), 3.84 – 3.78 (m, 1 H), 3.72 – 3.65 (m, 1 H), 3.63 – 3.57 (m, 2 H), 3.56 – 3.48 (m, 1 H), 3.45 – 3.39 (m, 1 H), 2.53 (q, $J = 7.6$ Hz, 2 H, SCH_2CH_3), 1.91 (m, 1 H), 1.14 (t, $J = 7.6$ Hz, 3 H, SCH_2CH_3); Positive-ion electrospray (ES) MS: *m/z*: 566.2 ($[M]^+ + Na^+$); Negative-ion ES MS: 578.2 ($[M]^- + Cl^-$).

27b: ^{1}H NMR ($CDCl_3$): $\delta = 7.86$ (m, 2 H), 7.68 – 7.56 (m, 3 H), 7.50 – 7.17 (m, 65 H), 6.24 (d, $J = 6.0$ Hz, 1 H), 5.29 – 5.25 (m, 1 H), 5.20 – 5.14 (m, 1 H), 5.11 – 4.99 (m, 7 H), 4.89 – 4.42 (m, 34 H), 4.37 – 4.28 (m, 3 H), 4.12 – 3.94 (m, 7 H), 4.00 – 3.82 (m, 8 H), 3.79 – 3.53 (m, 21 H), 1.11 – 1.04 (dd, $J = 6.3$, 6.2 Hz, 6 H); Positive-ion ES MS: 1490.5 ($[M]^+ + Na^+$); Negative-ion ES MS: 1466.7 ($[M]^- - H^+$).

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The Total Synthesis of Eleutherobin: A Surprise Ending**

Xiao-Tao Chen, Bishan Zhou, Samit K. Bhattacharya, Clare E. Gutteridge, Thomas R. R. Pettus, and Samuel J. Danishefsky*

In memory of John K. Stille

The "eleuthesides" comprise[1] a family of marine-derived natural products that exhibit cytotoxic activity.[1, 2] Most intriguing of these is eleutherobin (**1**),[3] which has a modality of action and a potency to warrant its inclusion with paclitaxel, the epothilones, and discodermolide as actual or potential anticancer agents of mechanistic commonality. The first total synthesis of eleutherobin (as well as that of sarcodictyin A) was recently disclosed by Nicolaou et al.[4]

Our own efforts pursuant to the synthesis of the eleuthesides were recently described.[5] The most advanced compound in our synthesis was the ketone **2**. We viewed this compound as a platform structure through which naturally occurring eleuthesides could be reached, and a large number of analogues could be fashioned. We turned to the synthesis of eleutherobin (**1**) from **2** (Scheme 1). The conventional approach to this kind of problem would be to develop a method to convert **2** into a suitable glycosyl acceptor (**3**) by overall addition of a C_1 fragment to carbon 3. We would also synthesize a glycosyl donor (cf. suitably activated arabinosyl donor **4**). Classical glycosylation could eventually lead to **1**. In this simple formulation, we do not yet address the question of the order of introduction of the sugar and the urocanic acid appendages.

It seemed possible that one-carbon homologation of enol triflate **5**[6] could serve as a possible route to reach acceptor **3**. In the event, ketone **2** was converted into **5** by deprotonation and enol triflation. We shall return to this compound shortly.

While the matter of the relative configurations of the aglycone and carbohydrate sectors of eleutherobin had not yet been proven to our satisfaction,[7] we began with the assumption that the compound is derived from D-arabinose.[4] Following peracetylation and introduction of an ethylthiol group at the anomeric carbon of D-arabinose, compound **6** became available (Scheme 2). Hydrolysis of the three acetate

[*] Prof. S. J. Danishefsky,[+] X.-T. Chen, B. Zhou, Dr. S. K. Bhattacharya, Dr. C. E. Gutteridge, Dr. T. R. R. Pettus
Department of Chemistry, Columbia University
Havemeyer Hall, New York, NY 10027 (USA)

[+] Other address:
Laboratory for Bioorganic Chemistry,
The Sloan-Kettering Institute for Cancer Research
1275 York Avenue, New York, NY 10021 (USA)
Fax: (+1) 212-772-8691
E-mail: c-kandell@ski.mskcc.org

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