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Stereoselective Synthesis of the Disaccharide Unit of Incednine

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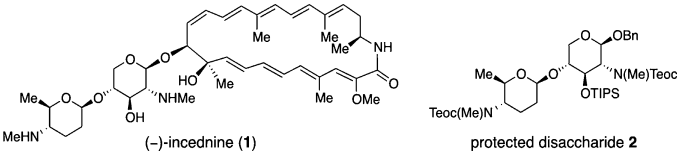
ABSTRACT



A stereoselective synthesis of a fully protected version of the disaccharide unit (2) of incednine (1) is described. The synthesis of 2 proceeds in 4.7% overall yield from commercially available allyl α-D-galactopyranoside over the longest linear sequence.

The structure determination of incednine (**1**), isolated from *Streptomyces* sp. ML694-90F3 using a cell-based chemical-genetic screen targeting inhibitors of the oncoprotein Bcl-xL, was reported in 2008.[1] It was reported in this initial publication that incednine induced apoptosis in Bcl-xL-overexpressing cells, thereby sensitizing these otherwise resistant cells to chemotherapeutic treatment. Unlike most existing Bcl-xL inhibitors, which recognize surface binding pockets on this protein, incednine neither disrupted the binding of Bcl-xL to the pro-apoptotic Bcl-2 family of proteins nor decreased expression levels of this oncoprotein.[1,2] These data suggest that the mechanism of action of incednine is distinct from that of existing Bcl-xL inhibitors. Further studies are necessary to determine the biological target(s) of this compound.[3]

The intriguing biological properties of incednine define it to be an important target for chemical synthesis and further biological studies. While a total synthesis of incednine has not yet been reported, syntheses of the aglycon and of the disaccharide unit have been described.[4] We describe here our synthesis of the incednine disaccharide **2** in fully protected form.

Our strategy for the synthesis of disaccharide **2** is summarized in Figure 1. We envisaged that the diamine precursor **3** could be obtained from a tandem azide reduction and alcohol deoxygenation sequence carried out on thiocarbonate **4**. Intermediate **4** originates from disaccharide **5**, which is the product of a β-selective glycosylation reaction between the glycosyl donor **6** and acceptor **7**.

The synthesis of thioglycoside donor **6** originated from the known azido sugar **9**, which was prepared in nine steps (23% overall yield) from commercially available allyl α-D-galactopyranoside (**8**) according to a literature procedure (Scheme 1).[5] Removal of the 1,2-propylidene acetal was accomplished by treatment of **9** with aqueous trifluoroacetic acid. Subsequent treatment of the crude diol with acetic anhydride in pyridine provided diacetate **10** in 90% yield for the two steps. Conversion of **10** to the

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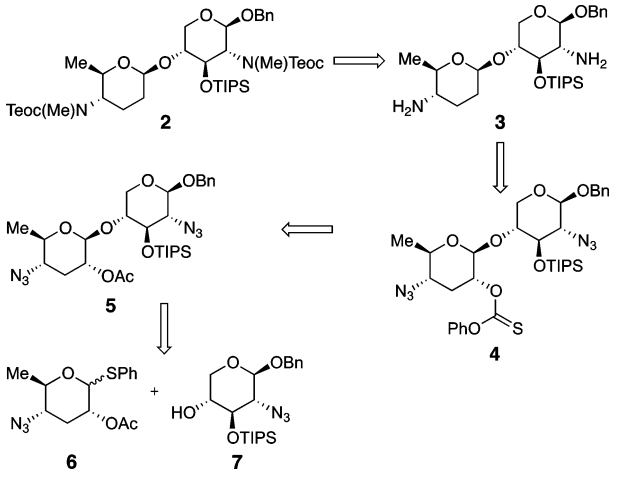
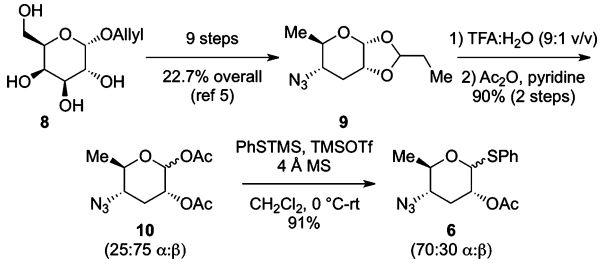


Figure 1. Retrosynthetic analysis of disaccharide **2**.

thioglycoside **6** proceeded smoothly upon treatment with phenylthiotrimethylsilane (PhSTMS) in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), which provided **6** in 91% yield as an inconsequential 70:30 α:*β* mixture of anomers.

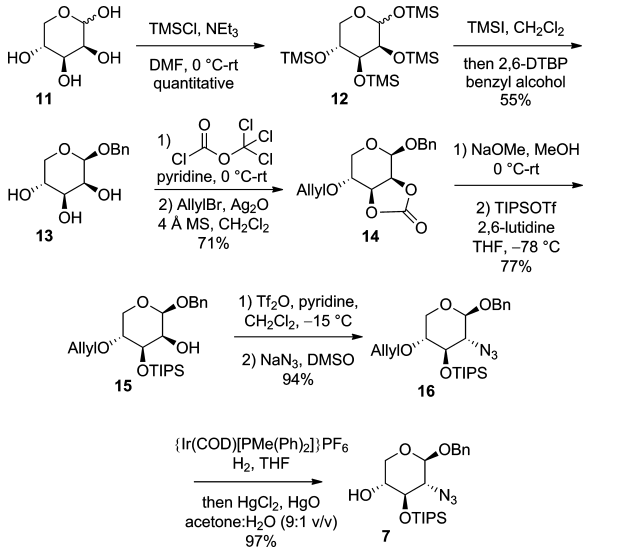
Scheme 1. Synthesis of Thioglycoside Donor **6**



We focused next on the synthesis of glycosyl acceptor **7** (Scheme 2). Persilylation of commercially available D-lyxose (**11**) in the presence of triethylamine produced **12** in essentially quantitative yield. Treatment of **12** first with iodotrimethylsilane, followed by benzyl alcohol and 2,6-di-*tert*-butylpyridine (2,6-DTBP), and finally with MeOH provided the benzyl glycoside **13** in 55% yield as a single anomer after chromatographic purification.[6] Selective protection of the *cis* 2,3-diol unit of **13** was best achieved by using trichloromethyl chloroformate in pyridine. Subsequent *O*-allylation of the remaining C(4)-hydroxyl group with allyl bromide in the presence of silver(I) oxide furnished carbonate **14** in 71% yield for the two operations. Removal of the 2,3-*O*-carbonate by treatment of **14** with NaOMe in MeOH followed by selective silylation of the equatorial C(3)-hydroxyl group with triisopropylsilyl trifluormethanesulfonate (TIPS-OTf) at −78 °C provided alcohol **15** in

(6) This procedure is known to produce α-glycosides with high selectivity: Uchiyama, T.; Hindsgaul, O. *Synlett* **1996**, 499.

Scheme 2. Synthesis of Glycosyl Acceptor **7**



77% yield over the two steps. Installation of the azide function at C(2) by conversion of **15** to the corresponding triflate and displacement using NaN_3 in DMSO proceeded smoothly to give the C(2)-equatorial azide **16** in 94% yield.

With the required functionalities in place, only removal of the allyl group remained for completion of the synthesis of the targeted glycosyl acceptor **7**. Attempts to achieve this transformation by treatment of **16** with $PdCl_2$, NaOAc, and AcOH[7] were low yielding, and treatment of **16** with sodium borohydride and iodine led only to decomposition.[8] Gratifyingly, a two-step deallylation protocol involving, first, isomerization of the allyl group to the propenyl ether using catalytic amounts of the iridium catalyst Ir(COD)-$[PMePh_2]PF_6$, followed by hydrolysis of the propenyl ether with mercury(II) chloride and mercury(II) oxide in aqueous acetone, provided the glycosyl acceptor **7** in 97% yield.[9,10]

The coupling of the two protected monosaccharide units is summarized in Scheme 3. Treatment of thioglycoside **6** with *N*-iodosuccinimide (1.2 equiv) in the presence of trimethylsilyl trifluoromethanesulfonate (0.15 equiv) and acceptor **7** (1.1 equiv) at −78 °C provided disaccharide **5** in 82% yield and with excellent *β*:α selectivity (97:3).

Two key transformations then remained to complete the synthesis of the fully protected disaccharide **2**: deoxygenation of C(2′) of the forosamine unit [deriving from **6**] and reduction of the azide functionalities present in both monosaccharide units. Previous experience with this sequence of transformations suggested that these two operations could

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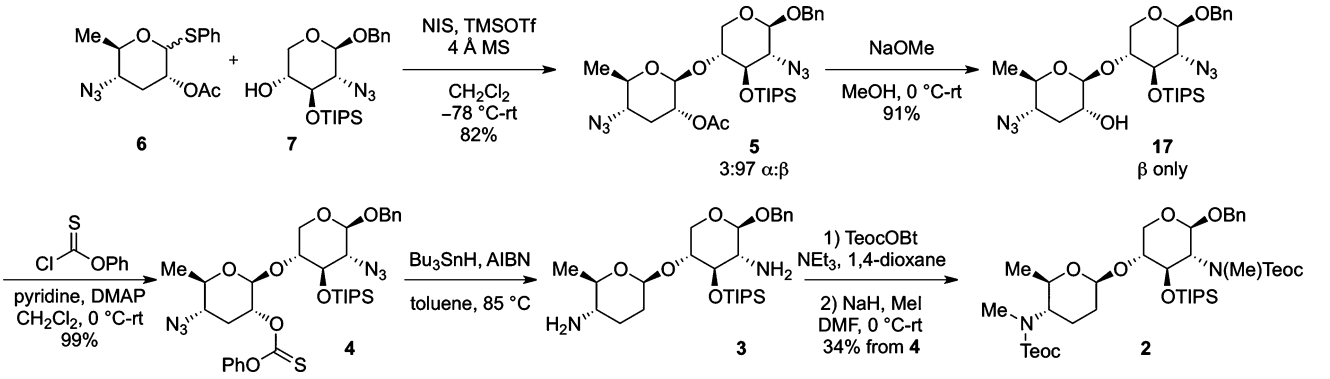
Scheme 3. Synthesis of Disaccharide **2**



be performed concomitantly, and indeed, this proved to be the case.[11]

Saponification of the C(2′)−OAc unit of **5** by treatment with sodium methoxide in methanol proceeded smoothly to give alcohol **17** (Scheme 3). The very minor amounts of undesired α-disaccharide formed in the glycosylation reaction were removed at this stage by silica gel chromatography. Alcohol **17** was then acylated with phenyl chlorothionoformate to furnish **4** (99% yield), the substrate for the tandem deoxygenation−azide reduction step. Treatment of azidothiocarbonate **4** with excess tributyltin hydride and catalytic amounts of AIBN in toluene at 85 °C effected reduction of the thiocarbonate and azide functionalities.[12] After filtration of the reaction mixture through a short pad of silica gel, diamine **3** was obtained contaminated with small amounts of tin-containing byproducts. This mixture was used directly in the final transformations without additional purification. Thus, treatment of the diamine intermediate with TeocOBt and Et_3N and subsequent bis-*N*-methylation of the two carbamates by treatment with NaH and MeI in DMF provided the targeted disaccharide **2** in 34% yield for the final three operations. At this point it should be noted that, although HRMS and IR confirmed the structure of **2**, the presence of carbamate bond rotamers complicated the ^1H and ^{13}C NMR spectra. Poor resolution was observed in ^1H and ^{13}C NMR experiments performed at room temperature in a variety of solvents (chloroform-*d*, benzene-d_6, DMSO-d_6), but acceptable NMR data were obtained when samples of **2** were heated in DMSO-d_6 at 80 °C. As further structural proof, a small sample of **2** was treated with TBAF and the deprotected disaccharide benzyl glycoside was characterized completely (see Supporting Information).

In summary, our synthesis of the fully protected disaccharide unit (**2**) of incednine proceeded in 4.7% overall yield from commercially available allyl α-D-galactopyranoside (18 steps, longest linear sequence). Our efforts toward the synthesis of the incednine aglycon, and the synthesis of incednine itself, will be reported in due course.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.