ORGANIC LETTERS

2013
Vol. 15, No. 1
62–64

Stereoselective Synthesis of the Disaccharide Unit of Incednine

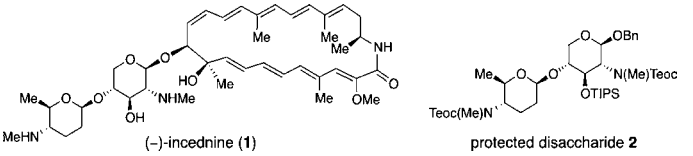
Jason R. Abbott and William R. Roush*

Department of Chemistry, The Scripps Research Institute—Florida, 130 Scripps Way Jupiter, Florida 33458, United States

roush@scripps.edu

Received November 9, 2012

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

(1) Futamura, Y.; Sawa, R.; Umezawa, Y.; Igarashi, M.; Nakamura, H.; Hasegawa, K.; Yamasaki, M.; Tashiro, E.; Takahashi, Y.; Akamatsu, Y.; Imoto, M. *J. Am. Chem. Soc.* **2008**, *130*, 1822.

(2) (a) Reed, J. C. *Curr. Opin. Oncol.* **1999**, *11*, 68. (b) Adams, J. M.; Cory, S. *Oncogene* **2007**, *26*, 1324. (c) Wang, J.-L.; Liu, D.; Zhang, Z.-J.; Shan, S.; Han, X.; Srinivasula, S. M.; Croce, C. M.; Alnemri, E. S.; Huang, Z. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7124. (d) Oltersdorf, T.; Elmore, S. W.; Shoemaker, A. R.; Armstrong, R. C.; Augeri, D. J.; Belli, B. A.; Bruncko, M.; Deckwerth, T. L.; Dinges, J.; Hajduk, P. J.; Joseph, M. K.; Kitada, S.; Korsmeyer, S. J.; Kunzer, A. R.; Letai, A.; Li, C.; Mitten, M. J.; Nettesheim, D. G.; Ng, S.; Nimmer, P. M.; O'Connor, J. M.; Oleksijew, A.; Petros, A. M.; Reed, J. C.; Shen, W.; Tahir, S. K.; Thompson, C. B.; Tomaselli, K. J.; Wang, B.; Wendt, M. D.; Zhang, H.; Fesik, S. W.; Rosenberg, S. H. *Nature* **2005**, *435*, 677. (e) Shoemaker, A. R.; Oleksijew, A.; Bauch, J.; Belli, B. A.; Borre, T.; Bruncko, M.; Deckwirth, T.; Frost, D. J.; Jarvis, K.; Joseph, M. K.; Marsh, K.; McClellan, W.; Nellans, H.; Ng, S.; Nimmer, P.; O'Connor, J. M.; Oltersdorf, T.; Qing, W.; Shen, W.; Stavropoulos, J.; Tahir, S. K.; Wang, B.; Warner, R.; Zhang, H.; Fesik, S. W.; Rosenberg, S. H.; Elmore, S. W. *Cancer Res.* **2006**, *66*, 8731.

(3) Kobayashi, H.; Harada, H.; Nakamura, M.; Futamura, Y.; Ito, A.; Yoshida, M.; Iemura, S.-i.; Shin-ya, K.; Doi, T.; Takahashi, T.; Natsume, T.; Imoto, M.; Sakakibara, Y. *BMC Chem. Biol.* **2012**, *12*, 2.

(4) (a) Ohtani, T.; Tsukamoto, S.; Kanda, H.; Misawa, K.; Urakawa, Y.; Fujimaki, T.; Imoto, M.; Takahashi, Y.; Takahashi, D.; Toshima, K. *Org. Lett.* **2010**, *12*, 5068. (b) Ohtani, T.; Sakai, S.; Takada, A.; Takahashi, D.; Toshima, K. *Org. Lett.* **2011**, *13*, 6126.

(5) Tietze, L. F.; Böhnke, N.; Brasche, G. *ARKIVOC* **2007**, 12.

10.1021/ol303093z
Published on Web 12/18/2012

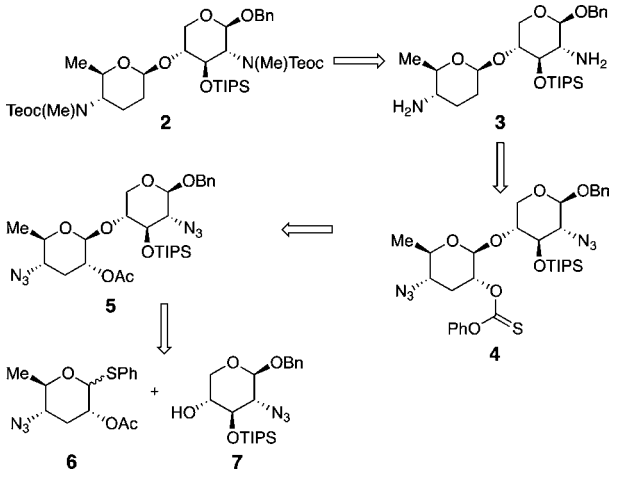
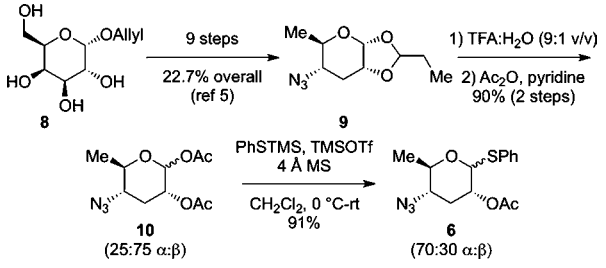


Figure 1. Retrosynthetic analysis of disaccharide **2**.

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.

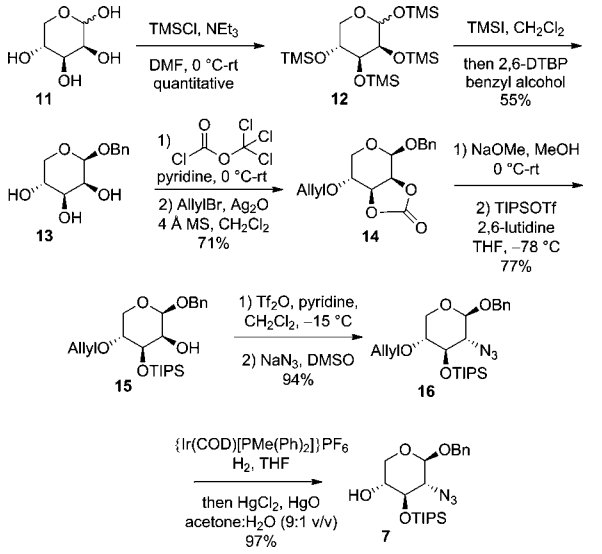
Scheme 1. Synthesis of Thioglycoside Donor **6**



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

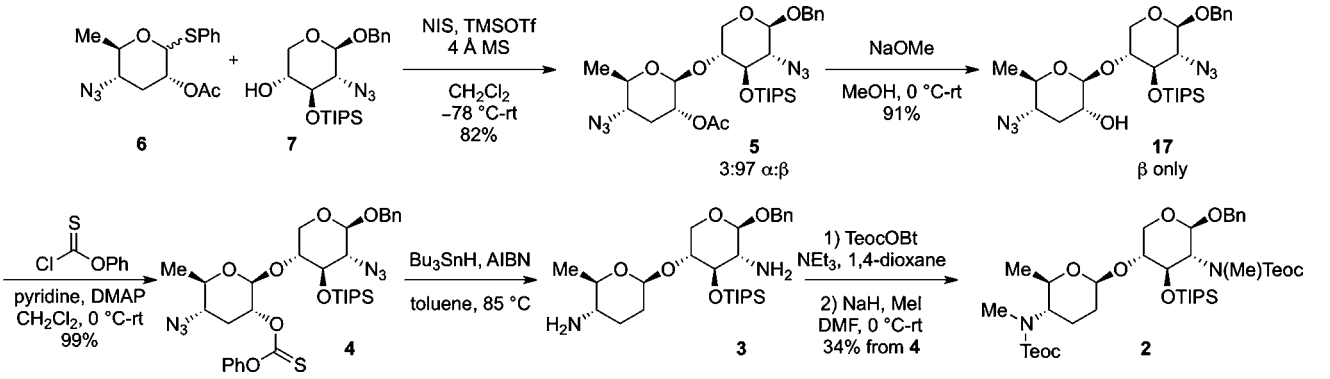
(7) (a) Ogawa, T.; Horisaki, T. *Carbohydr. Res.* **1983**, *123*, C1. (b) Smith, A. B., III; Rivero, R. A.; Hale, K. J.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113*, 2092. (c) Lohman, G. J. S.; Seeberger, P. H. *J. Org. Chem.* **2004**, *69*, 4081.

(8) Thomas, R. M.; Mohan, G. H.; Iyengar, D. S. *Tetrahedron Lett.* **1997**, *38*, 4721.

(9) Gigg, R.; Warren, C. D. *J. Chem. Soc. C* **1968**, 1903.

(10) Oltvoort, J. J.; Van Boeckel, C. A. A.; De Koning, J. H.; Van Boom, J. H. *Synthesis* **1981**, 305.

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.

Acknowledgment. Financial support provided by the National Institutes of Health (GM038436) is gratefully acknowledged. J.R.A. also thanks Eli Lilly for a graduate fellowship.

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.

(11) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11955.

(12) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585.

The authors declare no competing financial interest.