HHS Public Access

Author manuscript

Bioorg Med Chem Lett. Author manuscript; available in PMC 2018 June 15.

Published in final edited form as:

Bioorg Med Chem Lett. 2017 June 15; 27(12): 2752–2756. doi:10.1016/j.bmcl.2017.04.065.

Design, Synthesis and Biological Evaluation of Fucose-Truncated Monosaccharide Analogues of Ipomoeassin F

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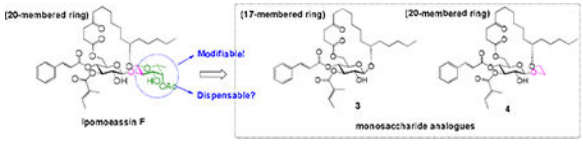
Abstract

Ipomoeassin F is a plant-derived macrocyclic glycolipid with single-digit nanomolar IC_{50} values against cancer cell growth. In previous structure–activity relationship studies, we have demonstrated that certain modifications around the fucoside moiety did not cause significant cytotoxicity loss. To further elucidate the effect of the fucoside moiety on the biological activity, we describe here the design and synthesis of several fucose-truncated monosaccharide analogues of ipomoeassin F. Subsequent biological evaluation strongly suggests that the 6-membered ring of the fucoside moiety is essential to the overall conformation of the molecule, thereby influencing bioactivity.

Graphical abstract



Keywords

Resin glycosides; Ipomoeassin F; Monosaccharide analogues; Macrolide; Cytotoxicity

Resin glycosides are amphipathic secondary metabolites unique to the morning glory family, *Convolvulaceae*. Their broad bioactivities, such as anticancer, antibacterial, biosurfactant, ionophoretic, purgative and plant growth controlling activities, have attracted more and more attention from phytochemists and pharmaceutical chemists. The common macrolide structure of resin glycosides contains a hydrophobic C-l 1 hydroxylated fatty acid aglycone and a hydrophilic oligosaccharide. The latter usually comprises two to six sugar units, part

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Notes: The authors report no conflicts of interest.

Supplementary Data: Supplementary data associated with this article can be found, in the online version, at *link*.

or entire portion of which forms the ring structure with the fatty acid.[1] Although monosaccharide cyclic glycolipids have been isolated from other families of plants, no resin glycosides containing a single carbohydrate moiety have been reported to date.

Ipomoeassins are a family of resin glycosides containing an embedded disaccharide. They were discovered by Kingston's group in 2005 and 2007.[2] Whereas most resin glycosides showed micromolar cytotoxicity, several members of the ipomoeassin family exhibited low to single-digit nanomolar IC_{50} values against several cancer cell lines. Moreover, the naturally most abundant member of the family, ipomoeassin A, was screened against the NCI-60 tumor cell lines and its cytotoxicity profile is well distinguished from those of other anticancer agents in the database.[3] Therefore, the ipomoeassins quickly inspired synthetic chemists to tackle their total syntheses. In particular, ipomoeassin F (Table 1) has been an attractive synthetic target due to its highest potency.[4,5]

Recently, we developed new efficient gram-scale syntheses of ipomoeassin F and conducted its most systematic structure-activity relationship (SAR) studies to date.[6–8] During the studies, we found that two α,β-unsaturated esters in the (3-D-glucoside moiety, that is, cinnamate and tiglate (Table 1), are the most critical to the cytotoxicity of ipomoeassin F. On the other hand, modifications of the (3-D-fucoside moiety,[7] i.e. removal of the acetyl group from 4-OH-Fuc*p* (analogue 1, Table 1) or introduction of an acetyl group to 3-OH-Fuc*p* (analogue 2, Table 1), did not cause a dramatic cytotoxicity loss for the five tested cancer cell lines (2-23 fold loss for 1 and 2-14 fold loss for 2, respectively). The IC_{50} values of both 1 and 2 are largely still below 150 nM. Therefore, the contribution of the whole fucoside moiety to the cytotoxicity is of great interest. In addition, given the high price of D-fucose ($427/5g, Sigma-Aldrich), relatively potent monosaccharide analogues (IC_{50} < 0.5 μM) of ipomoeassin F without the fucoside moiety would significantly decrease the production cost and also shorten the synthetic route, thereby benefiting future ipomoeassin research in drug discovery and chemical biology.

In our earlier studies, we proved that some peripheral modifications of the fucoside moiety could be well withstood (analogues **1** and **2**, Table 1). To further elucidate function of the fucoside moiety, analogue **3** (Figure 1) was first designed, in which the entire fucoside moiety is removed. This analogue also changes the ring size from 20-membered ring in ipomoeassin F to 17-membered ring. Because ring size may have a great impact on biological activity, we also designed analogue **4** (Figure 1) in which the fucoside moiety is partially truncated; therefore, **4** maintains the same ring size as ipomoeassin F. Using both analogues **3** and **4**, we hope to address the question of whether the fucoside ring is dispensable or not.

The two monosaccharide analogues **3** and **4** can be straightforwardly synthesized by using the same strategy we developed for the total synthesis of ipomoeassin F (Scheme 1).[6] From the diene intermediate **6a**/**b**, ring-closing metathesis (RCM) and hydrogenation were still adopted to construct the saturated ring structure in **5a**/**b**, to which cinnamate could be introduced, followed by removal of the TBS group, to give the desired monosaccharide analogues **3** and **4**. To control the β-linkage in **6a**/**b**, the glucosyl donor **7**[6] with Alloc as the neighboring participation group was chosen to couple with the alcohol acceptor **8a**/**b**. After

that, replacement of the Alloc group with TBS, followed by removal of isopropylidene and then chemoselective esterification with 4-oxo-8-nonenoic acid **9**,[9] would lead to the key diene intermediate **6a**/**b** as the RCM precursor. Synthesis of the acceptor **8b** could be achieved by alkylation of alcohol **8a**[4] with bromoacetic acid, followed by the esterification and reduction procedure.

The synthesis of **8b** is outlined in Scheme 2. Alkylation of the other acceptor **8a**[4] with bromoacetic acid in the presence of NaH afforded acid **10** in moderate yield. Direct reduction of acid **10** using $LiAlH_4$ was not successful. Then we converted acid **10** to ethyl ester **11** first, followed by reduction with $LiAlH_4$ to give **8b** in 62% overall yield over two steps.

The glucosyl donor **7** was synthesized by following the route we developed previously. With both glucosyl donor and two acceptors in hand, the RCM precursor **6a/b** was synthesized as shown in Scheme 3. Schmidt glycosylation of **7** with acceptor **8a/b** promoted by TMSOTf in cold CH_2Cl_2 gave β-linked glycoside **12a** in 62% yield or **12b** in 46% yield. Alloc group was then selectively removed in the presence of CH_3COONH_4, $Pd[P(C_6H_5)_3]_4$, and $NaBH_4$ in excellent yield to give alcohol **13a**/**b** within 4 min.[10] Alcohol **13a**/**b** was then treated with *tert*-butyldimethylsilyl triflate (TBSOTf) in the presence of 2,6-lutidine to give silyl ether **14a** in 84% yield or **14b** in 97% yield. Removal of isopropylidene using camphorsulfonic acid (CSA) in MeOH afforded diol **15a**/**b** without any problem. The subsequent chemoselective Steglich esterification of diol **15a**/**b** with 4-oxo-8-nonenoic acid **9**[9] to give diene **6a/b** as the key RCM precursor.

RCM of **6a**/**b** using Hoveyda-Grubbs catalyst (II)[11] (10 mol%) under refluxing in CH_2Cl_2, followed by hydrogenation of the resulting alkene isomers over Wilkinson's catalyst, constructed the desired ring structure (76% for **5a** and 62% for **5b**) over two steps (Scheme 4). Cinnamate ester was then introduced to **5a**/**b** through Mukaiyama esterification to afford the fully protected compound 1**6a**/**b** in high yield. In the last step, removal of TBS using TBAF in cold THF/MeOH was first tried on substrate **16a**. Unfortunately, instead of forming the desired monosaccharide analogue **3**, the acyl-migrated compound **17** was obtained as the major product (42% yield) along with **18** as the minor product (29% yield). The structures of compounds **17** and **18** were supported by ^1H, ^{13}C, COSY and HMBC NMRs (see the Supporting Information). Treatment of 1**6a**/**b** with TBAF and acetic acid in THF/MeOH finally delivered the desired monosaccharide analogues in good yield (79% for **3** and 77% for **4**). The structures of compounds **3** and **4** were confirmed by ^1H, ^{13}C, COSY and HMBC NMRs. Key correlations in COSY and HMBC are illustrated in Figure 2.

Using the fluorescent alarmarBlue or colorimetric MTT assay, the cytotoxicity of monosaccharide analogues **3** and **4**, together with the unexpected analogue **17**, was evaluated against two breast cancer cell lines (MDA-MB-231 and MCF7) using ipomoeassin F as the positive control and vehicle-treated cells as the negative control. Compared to ipomoeassin F, all the three analogues showed no appreciable or very weak inhibition of cell growth at 10 μM (Figure 3), demonstrating that the fucoside moiety is indispensable for the cytotoxicity of the ipomoeassins.

In summary, we report here the synthesis and biological evaluation of three monosaccharide analogues of ipomoeassin F, **3**, **4**, and **17**, consisting of a truncated carbohydrate core. The fucoside moiety was completely or partially removed from the disaccharide portion of the original natural product. Evaluation of these compounds against two breast cancer cell lines unambiguously revealed the vital role of the pyranose ring of the fucoside moiety in the biological activity of ipomoeassin F, very likely through conformational control. Further studies of using other economical carbohydrate building blocks to replace expensive D-fucose are planned to consolidate and enrich the SAR data while improving the production efficiency. In this regard, D-galactose is the most attractive to us (Figure 4). The small 6-OH-Gal*p* may provide an anchor point for introduction of new functional moieties to better biological activities and/or facilitate the discovery of molecular targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was primarily supported by the startup funds from the University of Arkansas and also in part by Grant Number P30GM103450 and R15GM116032 from the National Institute of General Medical Sciences of the National Institutes of Health (NIH) and by the seed money from the Arkansas Biosciences Institute (ABI). MH is currently the recipient of a Distinguished Doctoral Fellowship from the University of Arkansas. CM was the recipient of the Student Undergraduate Research Fellowship (SURF) from the Arkansas Department of Higher Education.

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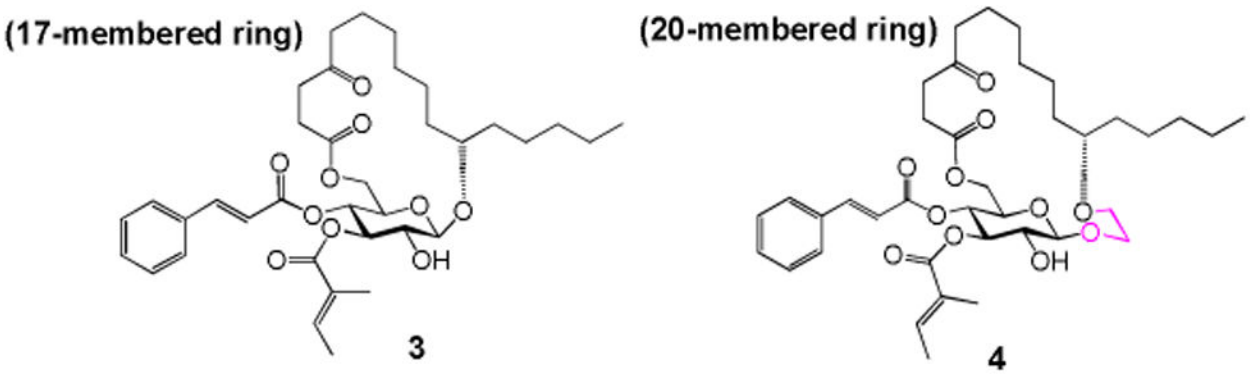
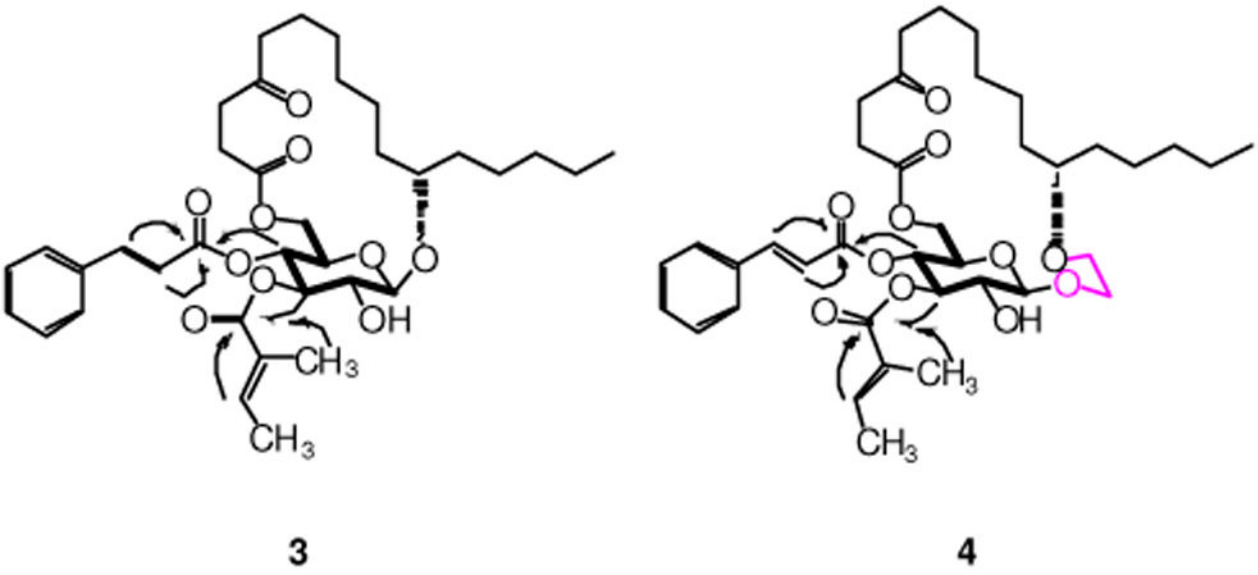


Figure 1.
Design of the monosaccharide analogues **3** and **4**.



3 4

Figure 2.
Key COSY (bold) and HMBC (arrows) correlations in **3** and **4**.

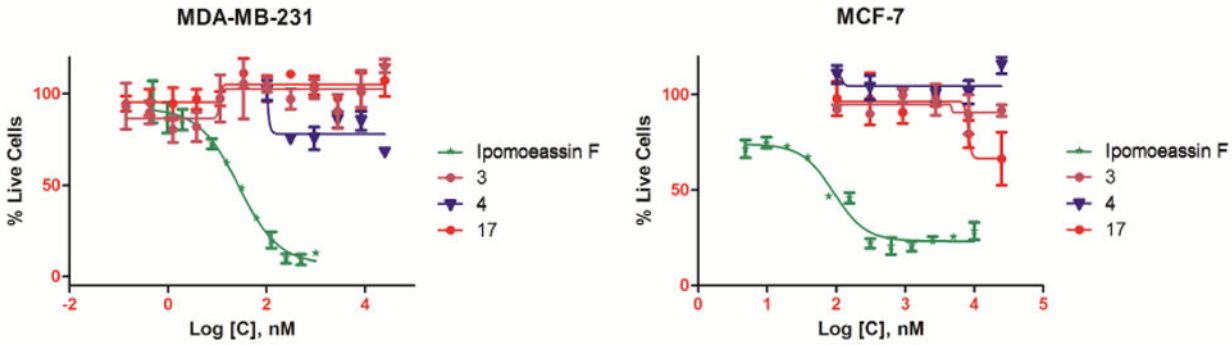


Figure 3.

IC_{50} curves of ipomoeassin F and analogues **3**, **4** and **17** against the MDA-MB-231 and MCF-7 cell line.

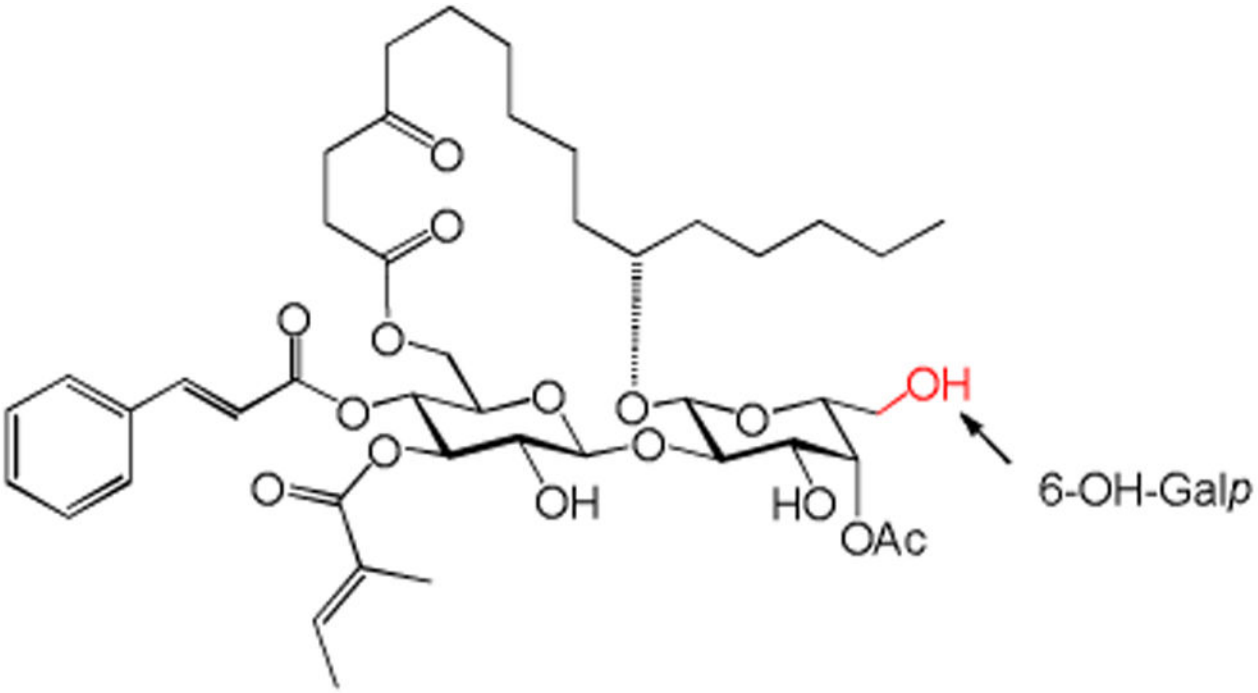
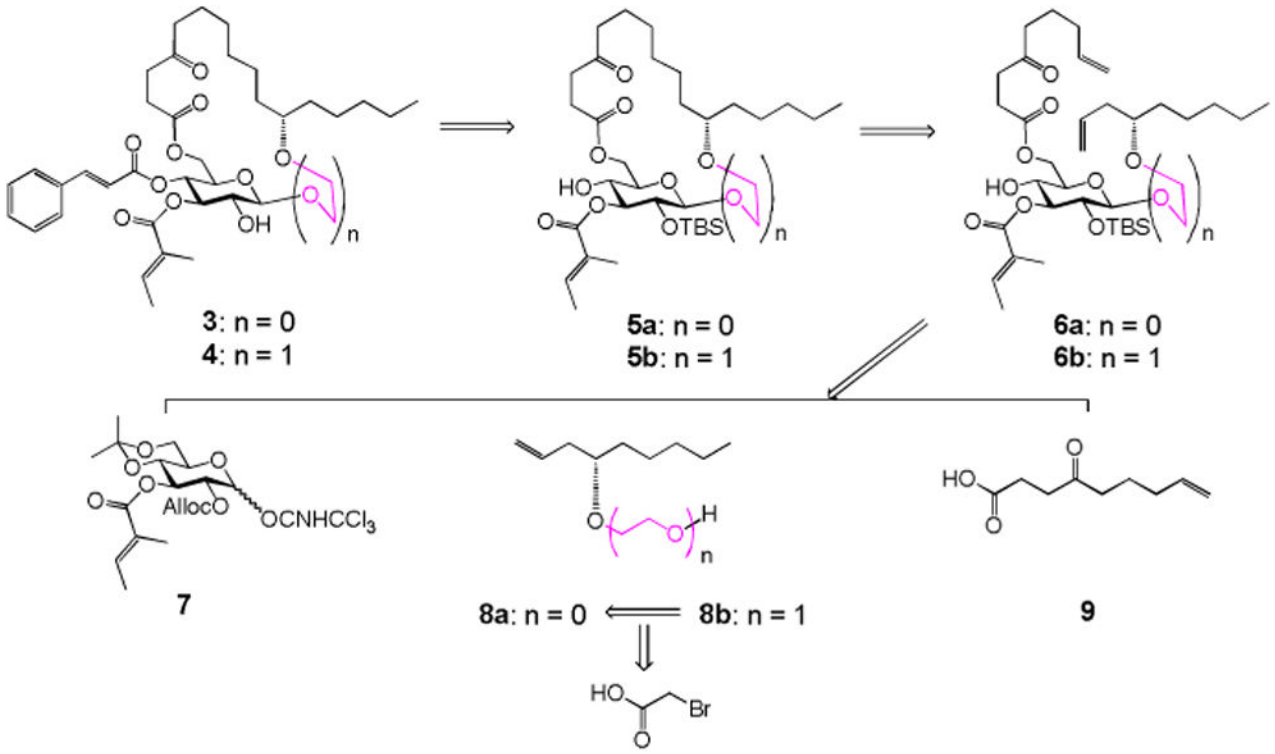
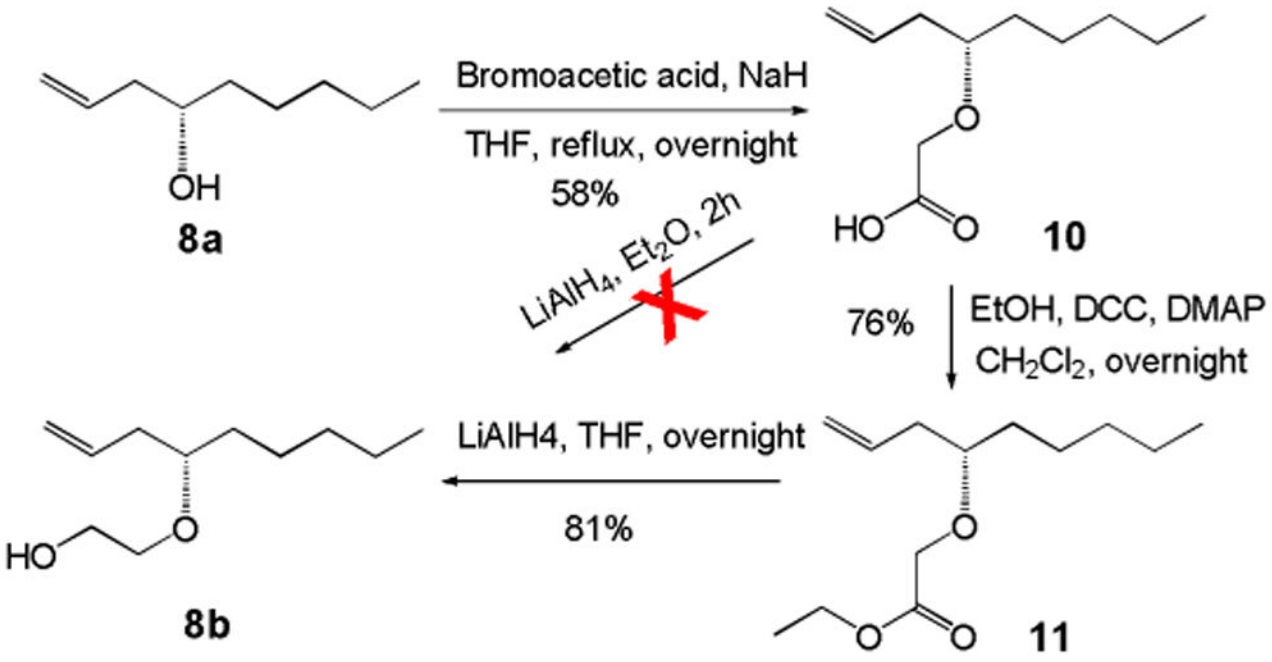


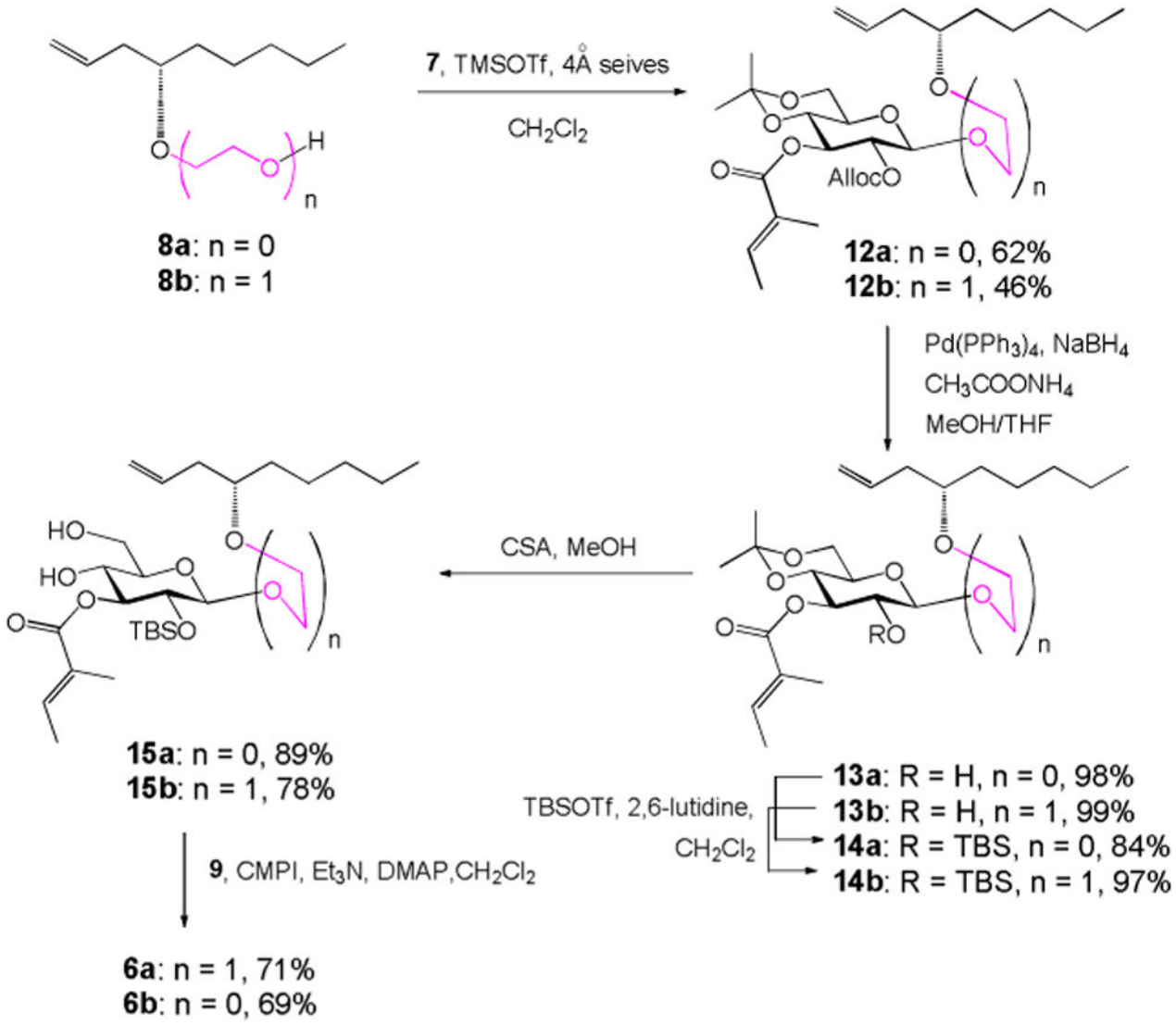
Figure 4.
D-galactose-containing analogue of ipomoeassin **F**.



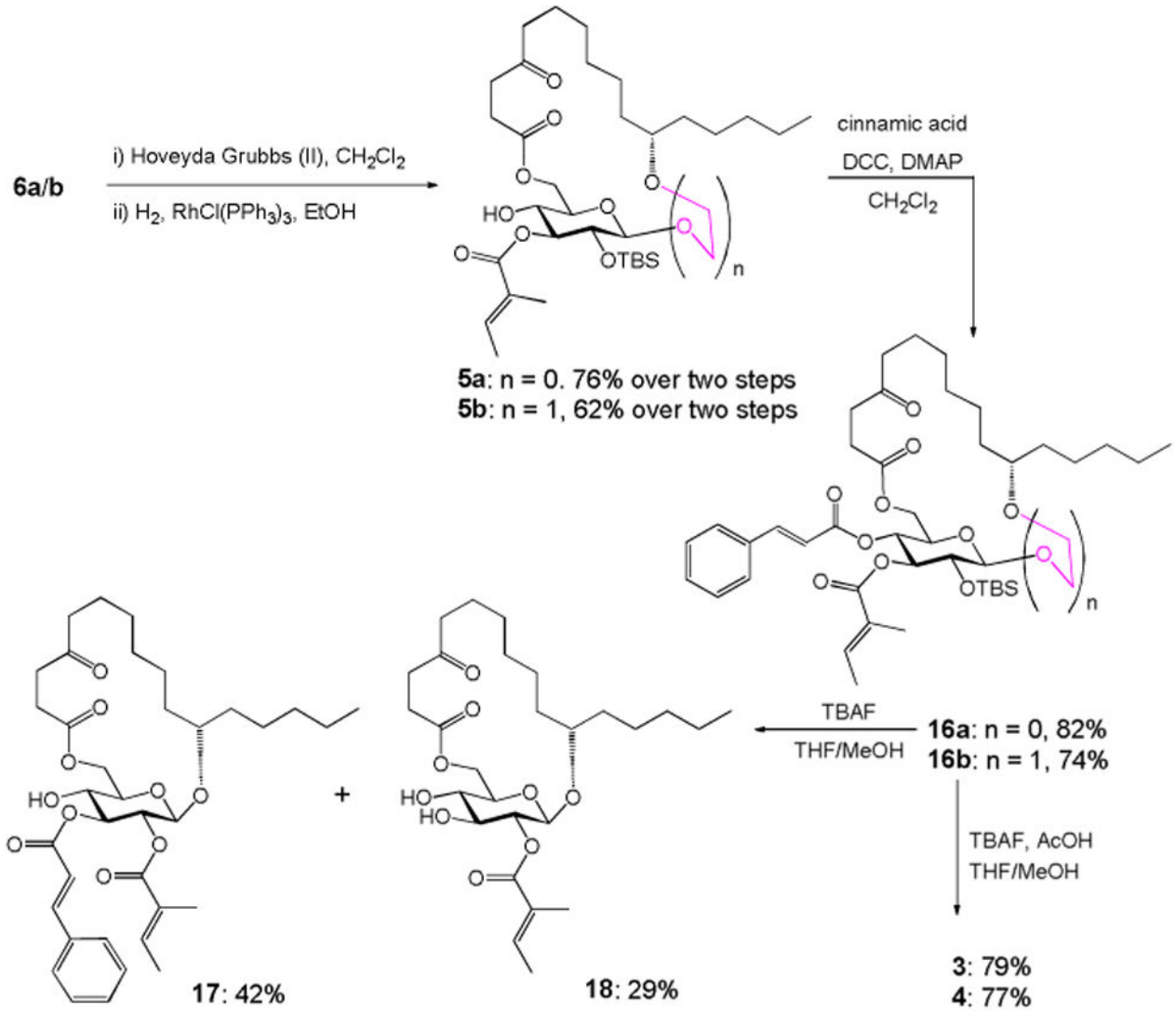
Scheme 1.
Retrosynthesis of the monosaccharide analogues **3** and **4**.



Scheme 2.
Synthesis of the acceptor **8b**.



Scheme 3.
Synthesis of diene **6a/b**.



Scheme 4.
Synthesis of monosaccharide analogues **3** and **4**.

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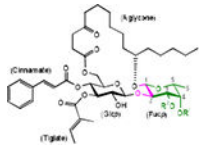
Table 1

Structures and IC_{50} Values of Ipomoeassin F and Its Analogues

	Compounds	structure		IC_{50}(nM)				
		R^1	R^2	MDA-MB-231	MCF7	HeLa	U937	Jurkat
	ipomoeassin F	Ac	H	6.5	43.7	16.4	5.4	6.1
	1	H	H	131	86.7	133	72.5	139
	2	Ac	Ac	16.5	216	138	79.8	82.6