# Total Synthesis and Biological Evaluation of Ipomoeassin F and Its Unnatural 11*R*-Epimer

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S *Supporting Information*
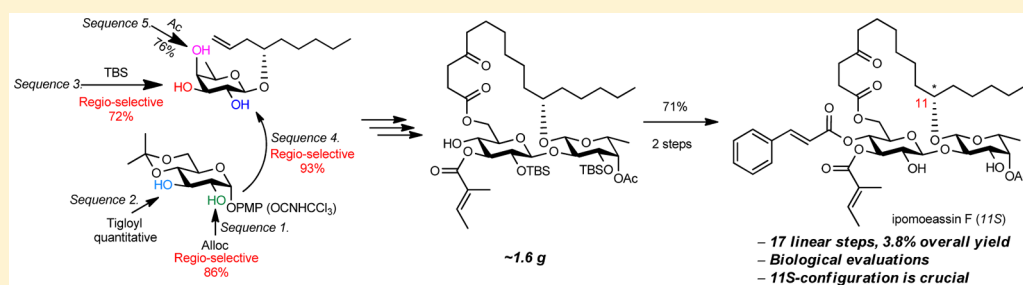
ABSTRACT: Ipomoeassin F, a macrolide glycoresin containing an embedded disaccharide, possesses potent in vitro antitumor activity with an unknown mechanism of function. It inhibits tumor cell growth with single-digit nanomolar IC_{50} values, superior to many clinical chemotherapeutic drugs. To facilitate translation of its bioactivity into protein function for drug development, we report here a new synthesis for the gram-scale production of ipomoeassin F (3.8% over 17 linear steps) from commercially available starting materials. The conformation-controlled subtle reactivity differences of the hydroxyl groups in carbohydrates were utilized to quickly construct the disaccharide core, which, along with judicial selection of protecting groups, made the current synthesis very efficient. The same strategy was also applied to the smooth preparation of the 11*R*-epimer of ipomoeassin F for the first time. Cytotoxicity assays demonstrated the crucial role of the natural 11*S* configuration. In addition, cell cycle analyses and apoptosis assays on ipomoeassin F and/or its epimer were conducted. This work has laid a solid foundation for understanding the medicinal potential of the ipomoeassin family of glycolipids in the future.

■ INTRODUCTION

Resin glycosides (also called glycoresins) are a large collection of amphiphilic glycolipids consisting of a differently acylated oligosaccharide glycosylated with a mono- or dihydroxy C_{14} or C_{16} fatty acid.[1,2] The latter is usually folded back to form a macrolactone ring of various sizes spanning two or more sugar units. Resin glycosides are primarily isolated from the morning glory family (Convolvulaceae) of plants that have been extensively used as traditional herbal medicines for many diseases. Because of their unique macrocyclic architectures with embedded carbohydrates and a broad spectrum of biological activities, resin glycosides have attracted considerable attention from the synthetic community, but not much beyond.[3−5]

In 2005 and 2007, a new family of glycoresins, ipomoeassins A−F (Table 1), was isolated from the leaves of *Ipomoea squamosa* in the Suriname rainforest.[6,7] These newly discovered natural glycoconjugates quickly inspired synthetic chemists to tackle their total syntheses[8] because two members of the family, ipomoeassins D and F, exhibited exceptionally potent cytotoxicity with single-digit nanomolar IC_{50} values against several cancer cell lines (Table 1). More importantly, in the NCI 60-cell line screen, the naturally most abundant member of the family, ipomoeassin A, showed strong and selective

growth inhibition of different cancer cells, and its pattern of activity was clearly distinguished from other known anticancer agents based on a COMPARE analysis.[9] Therefore, it suggests that the ipomoeassins have novel molecular targets and can serve as promising new leads for developing a new class of antineoplastic agents.

With the long-term goal of utilizing underexploited natural glycoconjugates to study biological systems for drug development, our laboratory became enamored with the ipomoeassin family of glycolipids for both chemical and biological reasons. Chemically, it is still necessary to develop more scalable and flexible syntheses of the ipomoeassins and their analogues to offer solutions to the scarce availability. From a biological vantage point, we are interested in biological assessment of those chemical entities resulting from such efforts, which would open the door to understanding the mechanism of action of the ipomoeassins and may eventually lead to new therapeutic and/or preventative interventions. Ipomoeassin F was selected as a representative compound in this venture because it showed the highest activity in the family.

**Table 1. Structures and IC$_{50}$ Values of Ipomoeassin A–F**

	Structure			IC$_{50}$ (nM)						
Ipomoeassin	R^1	R^2	n	HeLa	L-929	A2780	U937	HT-29	MDA-MB-435	H522-T1
A	H	Ac	1	64	77.8	500	20.2	46.1	42.6	108.9
B	H	H	1	2500		400	134	396	2700	1070
C	OH	Ac	1	1500	>1000	2900				
D	OAc	Ac	1	32	135	35	7.9	11.8	19.9	23.2
E	OAc	H	1	4300	>1000	3300	163	393	1633	967
F	H	Ac	3		7.4	36	2.6	4.2	9.4	12.9

To date, two total syntheses of ipomoeassin F have been achieved independently by Postema[10] and Fürstner.[11] Given its favorable reactivity profile and high flexibility, RCM[12,13] was adopted by both groups for the formation of the 20-membered macrolactone ring. RCM has demonstrated great success for the syntheses of many resin glycosides;[4,5] however, incompatibility between two unsaturated ester groups (cinnamate and tiglate at 4-O-Glc$p$ (glucosylpyranoside) and 3-O-Glc$p$, respectively) and common hydrogenation conditions presented a substantial challenge in protecting group maneuver for the ipomoeassin F syntheses. To solve this problem, the Fürstner group found that trisubstituted alkenes can well survive hydrogenation catalyzed by Wilkinson's catalyst; therefore, they elegantly designed the key intermediate 1 (Chart 1) with a

Chart 1. Key Intermediates in the Previous Total Syntheses of Ipomoeassin F (Fürstner and Postema)
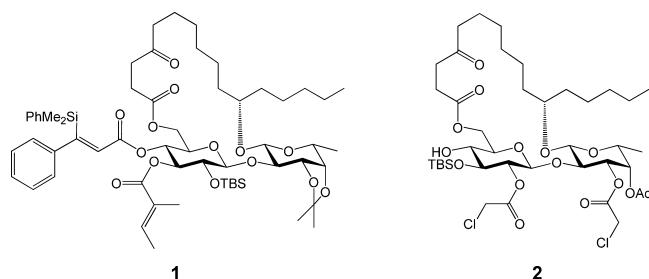
C-silylated cinnammic acid ester and achieved the total synthesis of ipomoeassin F in ~1.0% overall yield.[11] By contrast, Postema and co-workers decided to go through the orthogonally protected intermediate 2 (Chart 1), thereby postponing the assembly of both cinnamate and tiglate to a later stage after RCM and hydrogenation. Intermediate 2 offers great flexibility for synthesizing ipomoeassin F analogues. Unfortunately, the total yield for this route is only ~0.4%.[10]

Because of the critical role of the disaccharide core, the sequence for the installation of its peripheral ester functional groups, in particular the cinnamate moiety, is crucial to the overall efficiency for synthesizing ipomoeassin F. In addition, we were attracted by this sole aromatic functionality of cinnamate for two other reasons. First, cinnamoyl-containing compounds classified as phenylpropanoids have received significant attention in medicinal research as antitumor agents.[14] Second, we hypothesized that the disubstituted α,β-unsaturated Michael system in the cinnamate group could be a covalent protein modifier through 1,4-nucleophilic addition.[15] In order to conduct efficient SAR studies to clarify the role of the cinnamic ester in the future, it is essential to introduce this moiety as late as possible. Based on this principle, this full

account traces the evolution of our studies that enabled the scalable synthesis and biological evaluation of ipomoeassin F and its 11R-epimer.

RESULTS AND DISCUSSION

Strategic Considerations. Because of the high efficiency of RCM in making macrocycles, we decided to continue to incorporate it in our strategy (Scheme 1). However, the

Scheme 1. Retrosynthesis of Ipomoeassin F
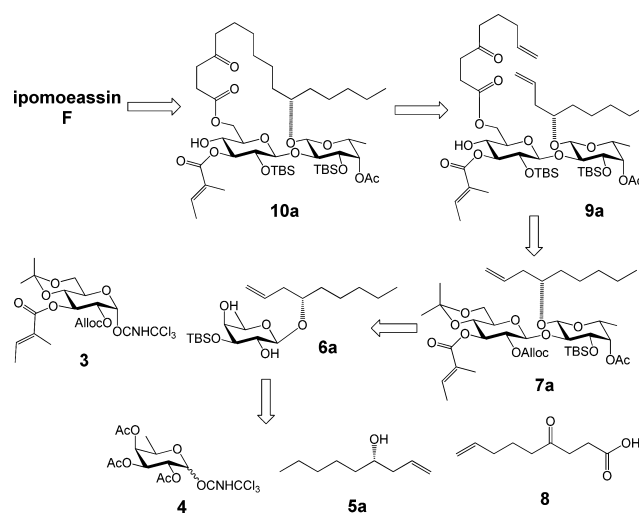
requirement for hydrogenation after RCM along with the presence of a variety of ester moieties in ipomoeassin F makes the choice of protecting groups very limited because of orthogonality issues. Thus, TBS groups were selected, and a new diene intermediate 9a with minimal transient protections was designed. Using 9a, the introduction of the cinnamate moiety could be postponed right after RCM and hydrogenation (intermediate 10a), which would lead to ipomoeassin F after the removal of TBS. To make the synthesis even more challenging, the β-(1→2) linkage further limits the choice of the protecting group on 2-O-Glc$p$ to those with the neighboring group participation effect. Therefore, the monosaccharide building blocks, 3 and 6a, were proposed. In the glucosyl donor 3, tiglate was introduced in an early stage to minimize the number of protection and deprotection steps. The requirement of a participating group for β-glycosylation, which is also orthogonal to esters, made us opt for the allyloxycarbonyl (Alloc) group as a transient protection because its mild deprotection conditions could be well tolerated by many functional groups.[16] To prepare 3, the reactivity

Scheme 2. Regioselective Acylation at 2-OH and 3-OH of β-D-Glucoside (13) and α-D-Glucoside (18) and Synthesis of Glucosyl Donor 3
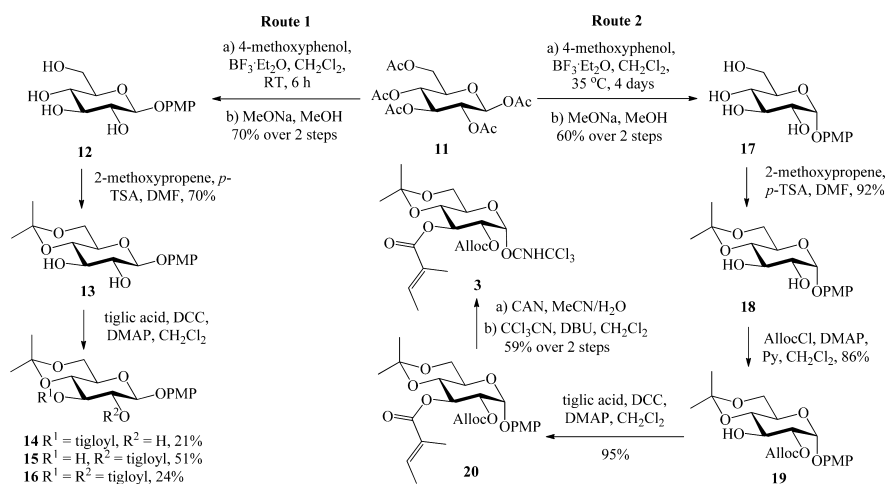
difference between 2-OH-Glcp and 3-OH-Glcp was investigated and exploited.[17] Similarly, by exploiting the reactivity differences of the hydroxyl groups in a pyranose ring,[17] the fucosyl acceptor **6a** was designed with minimal protection steps from fucosyl donor **4**[18] and chiral alcohol **5a**.[11] The regioselective TBS protection on 3-OH-Fucp (fucosylpyranoside), followed by the regioselective glycosylation on the equatorial 2-OH-Fucp in **6a** and then acetylation on the 4-OH-Fucp, afforded the disaccharide **7a**, which led to the diene intermediate **9a** after replacement of Alloc with TBS, followed by deisopropylidenation and consequent chemoselective esterification of 6-OH-Glcp with 4-oxo-8-nonenoic acid **8**.[19]

To the best of our knowledge, the stereochemistry for the fatty acid carbon that is connected to the carbohydrate core of a natural resin glycoside through the glycosydic bond is exclusively the *S* configuration. In ipomoeassin F, we believe that this sole stereogenic center of the aglycon has great influence on the overall conformation of the molecule, only second to the sugar core. Although it is a reasonable assumption that the naturally occurring *S* configuration would be preferred for biological activities, no experimental evidence has been documented in the literature as yet. Therefore, we also include the 11*R*-epimer of ipomoeassin F in our studies by using the same strategy.

Synthesis of Glucosyl Donor 3. The synthesis commenced with the preparation of D-glucosyl donor **3** (Scheme 2). For esterification, it has been found that the 3-OH is more active than 2-OH in the case of β-D-glucopyranoside.[17] Therefore, we first tried to introduce tiglate to the 3-O position of *p*-methoxyphenyl (PMP)-β-D-glucopyranoside (**13**)[20,21] utilizing Steglich esterification.[22] Unexpectedly, we obtained a mixture of products in which 2-O-tiglate was the major product in a ratio of 2.4:1 for 2-O-tiglate versus 3-O-tiglate. Because it has also been found that regioselective esterification favored 2-OH in an α-glucopyranoside,[17] we next explored the selectivity for installing Alloc on the 2-OH of α-glucopyranoside **18**, which was obtained through isopropylidenation of *p*-methoxylphenyl α-D-glucopyranoside **17**.[23] To our delight, we got exclusive selectivity on the 2-O-Glcp position with a yield of 86% when treated with AllocCl at low temperature (Scheme 2, route 2). The resulting compound **19** was subsequently acylated with tiglic acid to give an excellent yield of glucosyl donor precursor **20** (95%). Cleavage of the 4-

methoxyphenyl group in **20** with CAN, followed by the reaction with trichloroacetonitrile and DBU,[24] gave the trichloroacetimidate donor **3** in 59% yield over two steps.

Synthesis of Fucoside Acceptor 6a/b. The synthetic route for fucoside acceptor **6a/b** is outlined in Scheme 3. The

**Scheme 3. Preparation of Fucoside Acceptor 6**
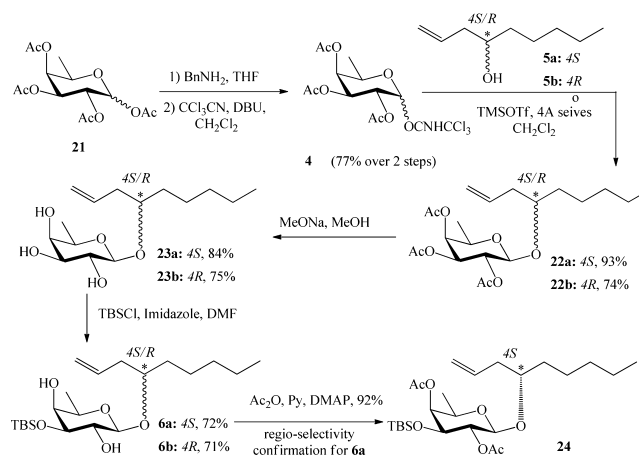
known fucosyl donor **4**[18] was prepared in 77% yield from compound **21**[25] using a two-step sequence involving selective removal of anomeric acetate followed by trichloroacetimidate formation. Glycosylation of fucosyl donor **4** with (*S*)- or (*R*)-4-hydroxy-1-nonene (**5a**[11] or **5b**) was accomplished by using TMSOTf as the catalyst in the presence of 4 Å molecular sieves, which then underwent global deacetylation to give triol **23a**[10] or **23b** in good to excellent yield over two steps. In the literature,[17] it has been established that in the galacto configuration the reactivity order for the secondary hydroxyl groups is 3-OH > 2-OH > 4-OH. The 3-OH is most nucleophilic because of the hydrogen bonding with axial 4-OH. Therefore, we applied this rationale to 6-deoxy galactopyranose (D-fucose) to selectively protect 3-OH. Thankfully, regioselective silylation on 3-OH of the triol **23a/b** with TBSCl provided the diol product in good yield (72% for **6a** and 71% for **6b**). The regioselectivity was confirmed by acetylation of **6a** to give **24** (92%). Both ¹H and COSY NMR spectra of **24** showed the signals for *H-2* and *H-4* moving

downfield, while a doublet of doublet peak stays at δ 3.78 ppm with $J_{2,3}$ = 9.6 and $J_{3,4}$ = 3.6 Hz for H-3 when compared to that of **6a**. This single-step regioselective silylation without using any other protecting groups significantly improved the overall efficiency of our synthesis.

Synthesis of Diene Intermediate 9a/b. With the glucosyl donor **3** and the fucoside acceptor **6a/b** in hand, the diene **9a/b** was prepared efficiently as outlined in Scheme 4. The

Scheme 4. Synthesis of Diene 9a/b
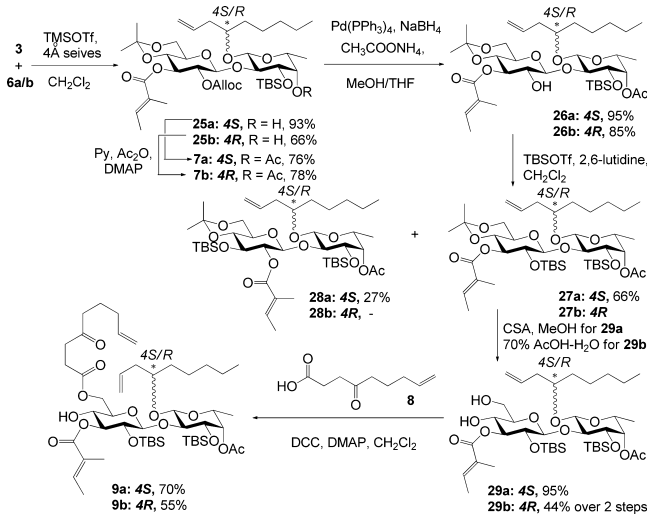
regioselective Schmidt glycosylation[24] of acceptor **6a/b** and donor **3** in dichloromethane at −60 °C in the presence of TMSOTf, followed by acetylation of the remaining hydroxyl group, showed excellent regio- and stereoselectivity, giving exclusively β-(1 → 2)-linked disaccharide **7a** in 71% yield or **7b** in 51% yield over two steps. The configuration of the glycosyl bond and the regioselectivity of the coupling reaction were confirmed by the ^1H, COSY, and HSQC NMR spectra. Using **7a** as the example, although the signal for H-1-Glc$p$ overlapped with the signals for the terminal alkenes of the Alloc and the lipophilic tether, the coupling constant for H-2-Glc$p$ (J = 9.6, 8.0 Hz) indicates the β-linkage; a signal at 3.90 ppm (dd, 1H, $J_{1,2}$ = 9.2, 8.0 Hz, 2-H-Fuc$p$) and a signal at 5.00 ppm (m, 1H, H-4-Fuc$p$, 4-O-Fuc$p$ acetylated) confirmed the (1 → 2)-linkage of the disaccharide. The subsequent selective removal of the Alloc group was achieved in the presence of CH_3COONH_4, $Pd[P(C_6H_5)_3]_4$, and $NaBH_4$ in 95% yield within 4 min.[16] The treatment of the resulting alcohol with TBSOTf and 2,6-lutidine afforded the desired silyl ether **27a** as the major product (66%) and also a byproduct **28a**, in which the tigloyl group in glucose migrated from 3-O-Glc$p$ to 2-O-Glc$p$ and the TBS group was introduced to the 3-O-Glc$p$ position. The structure of each isomer was confirmed by the ^1H, ^{13}C, COSY, and HMBC NMR spectra (Figure 1). The separation of **27b** from **28b** was not possible. The removal of the isopropylidene group using camphor-10-sulfonic acid (CSA) followed by the chemoselective esterification of 6-OH-Glc$p$ with 4-oxo-8-nonenoic acid **8**[19] in the presence of DCC and DMAP gave diene as the RCM precursor (70% for **9a** and 55% for **9b**) over two steps.

Total Synthesis of Ipomoeassin F and its 11R-Epimer. Treatment of the diene **9a/b** with Hoveyda−Grubbs catalyst (II)[26,27] (10 mol %) furnished macrolide **a/b** as a mixture of E/Z isomers, which was subjected to hydrogenation over
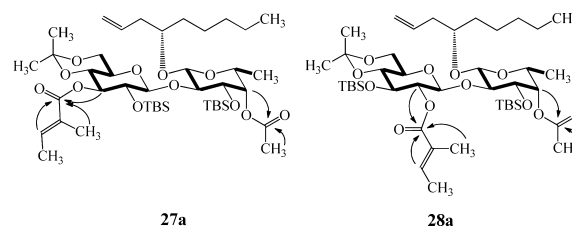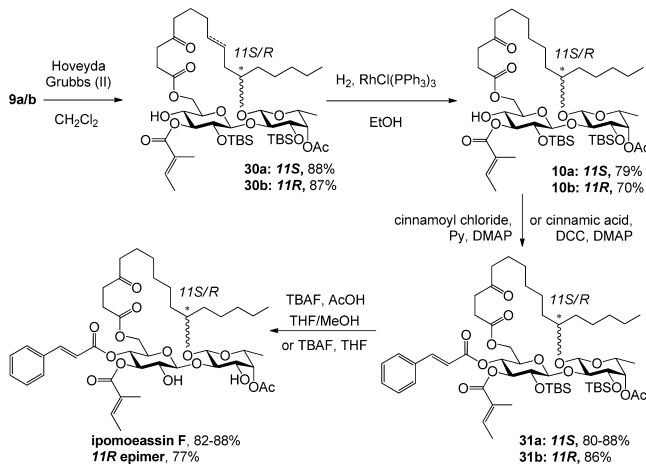

Figure 1. Key COSY (bold) and HMBC (arrows) correlations in **27a** and **28a**.

Wilkinson's catalyst to give **10a/b** as the major product (79%) (Scheme 5). In the penultimate step, the cinnamate

Scheme 5. Completion of the Total Synthesis

moiety was introduced in 80% yield by reacting **10a/b** with cinnamoyl chloride in a pyridine solution promoted by DMAP. We also tried to use Steglich esterification to introduce the cinnamate moiety and found that increasing concentration of the reactants could further improve the synthesis up to 88% yield in 12 h for **10a**. The final removal of the TBS groups was achieved by treating **31a** either with TBAF and AcOH at room temperature to give ipomoeassin F in 88% yield or with TBAF alone at low temperature to give ipomoeassin F in 82% yield. Its ^1H and ^{13}C NMR spectra are consistent with the published literature data.[7,10,11] Thus, ipomoeassin F was synthesized in 3.8% overall yield over 17 steps of the longest linear sequence from commercially available starting materials **11** and **21**, which is more efficient (9- and 4-fold) than the previously reported two syntheses (ca. 0.4%[10] and 1.0%[11] overall yield, respectively, calculated based on the noncommercially available starting materials). In our route, three highly regioselective reactions were developed: (a) selective allyloxycarbonylation of the 2-OH-Glc$p$ in diol **18**; (b) selective silylation of the 3-OH-Fuc$p$ in triol **23a**; and (c) selective glycosylation of 2-OH-Fuc$p$ in diol **6a**. To our delight, all of them were accomplished in good to excellent yield (86%, 72% and 93%, respectively). Using this route, ipomoeassin F can be synthesized on a gram scale since the key intermediate **10a** was prepared on a scale of 1.6 g. Similarly, the 11R-epimer of ipomoeassin F was prepared from **31b**.

Cytotoxicity of Ipomoeassin F. By using the MTT (3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) colorimetric assay[28] with Taxol as the positive control, the cytotoxicity of ipomoeassin F obtained through our total

Table 2. Cell Cytotoxicity (IC_{50} nM)^{a,b} of Ipm F^c and Taxol

	MDA-MB-231	MCF7	HeLa	U937	Jurkat	MCF-10A	NIH/3T3
Ipm F[10,11]	d			2.6^e			
Ipm F	6.5	43.7	16.4	5.4	6.1	5.4	16.8
Epimer	240.2	830.7	440.2	190.1	325.1	159.2	1370.5
Taxol	5.1	11.0	1.6	2.7	2.8	41.0	344.0

^{a}Three-day treatment. ^{b}The data were obtained from at least two independent experiments, and the standard errors are within 20%. ^{c}Ipm = ipomoeassin. ^{d}"−" = not tested. ^{e}Four-to-five-day treatment.

synthesis was evaluated against a small panel of cell lines, including five human tumor cell lines, one immortalized normal human mammary epithelial cell line (MCF-10A), and one immortalized normal mouse embryo fibroblast cell line (NIH/3T3). The U937 human leukemic monocyte lymphoma cell line was selected for comparison with the literature-reported cytotoxicity data.[10,11] All of the other cell lines, especially the two nontumor cell lines, were screened for the first time. The results presented in Table 2 illustrate the concentrations required for 50% cell death (IC_{50} values) when compared to the vehicle-treated negative control. The IC_{50} values for ipomoeassin F range from 5.4 nM to 43.7 nM, close to Taxol, whereas the 11R-epimer is significantly (20−80-fold) less active. In particular, the IC_{50} value (5.4 nM) for U937 cells is comparable to the literature-reported value (2.6 nM),[10,11] which further confirms the success of our synthesis. The 2-fold difference could be explained by the longer treatment time in the literature conditions. In addition, ipomoeassin F exhibited markedly different toxicity (~8-fold) against two cancer cell lines (U937 and MCF7), suggesting that the cytotoxicity of ipomoeassin F is selective. Although Taxol had lower IC_{50} values, the cell viability curves showed that ipomoeassin F could inhibit cell growth to a 20−30% greater extent than Taxol at concentrations over 100 nM. One representative example is shown in Figure 2. Unfortunately, no selectivity between tumor and nontumor cell lines was observed for ipomeassin F.
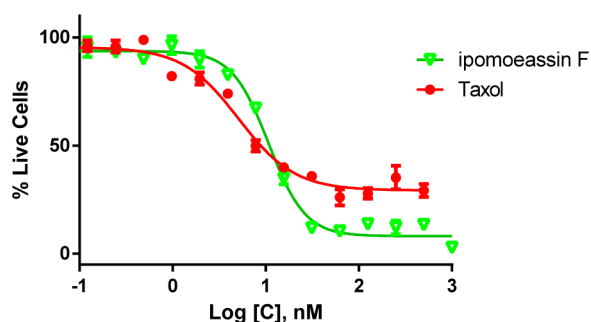

Figure 2. Cytotoxic effect of synthetic ipomoeassin F and Taxol on MDA-MB-231 cells.

Ipomoeassin F Induces G1 Cell Cycle Arrest. To date, very little is known about the functional mechanism of the ipomoeassins. The only related biological studies that have been performed are cell cycle analyses.[11] The published data showed that a 24-h treatment with the ipomoeassins led to the G1 arrest of mouse L-929 fibroblast cells, accompanied by a decreased cell number in the G2/M phase. The continued (48 h) exposure caused a significant number of sub-G1 cells and apoptosis. To explore the potential mechanism of action of ipomoeassin F in human cells, U937 cells were treated with

ipomoeassin F (90 nM) for 48 h and then the cell cycle was analyzed by flow cytometry after the cells were stained with propidium iodide (PI). Consistent with the previous report, the ipomoeassin F treatment resulted in significant G1 arrest (~25%, Figure 3A,B), which was accompanied by a decreased cell population in both S and G2/M phase. In particular, the cell population in the G2/M phase was reduced by ~21%.
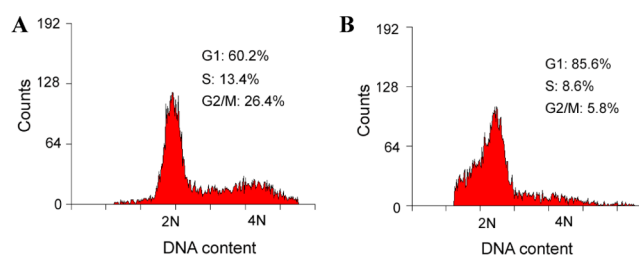

Figure 3. Ipomoeassin F induces G1 arrest in U937 cells. Human U937 cells were (A) mock treated or (B) treated with ipomoeassin F (90 nM). After 48 h, the cells were harvested, stained with propidium iodide (PI), and analyzed by flow cytometry.

Ipomoeassin F Induces Apoptosis. To determine whether ipomoeassin F may kill cancer cells through apoptosis, the U937 cells treated with ipomoeassin F (90 nM) for 48 h were stained with both propidium iodide (PI) and FITC-conjugated annexin V and then analyzed by flow cytometry.[29] The results demonstrated that the ipomoeassin F treatment induced a substantial increase in cell apoptosis: the percentage of apoptotic cells increased from 13.2% (3.99% + 9.17%, Figure 4A) in control cells to 33.6% (16.13% + 17.46%, Figure 4B) in the ipomoeassin F treated cells.
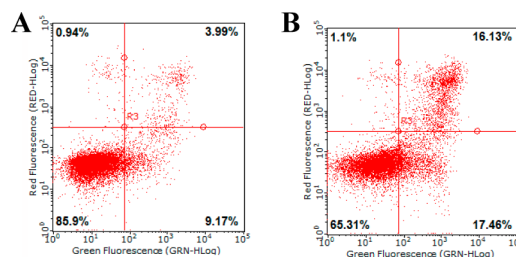

Figure 4. Ipomoeassin F induces apoptosis in U937 cells. Human U937 cells were (A) mock treated or (B) treated with ipomoeassin F (90 nM). After 48 h, the cells were harvested, stained with PI and FITC-conjugated annexin V, and analyzed by flow cytometry.

To confirm the results obtained from the annexin V staining experiment, human MDA-MB-231 breast cancer cells were also treated with ipomoeassin F, followed by a DNA fragmentation assay. DNA fragmentation is an indicator of late apoptosis. Consistent with the flow cytometry results, it is clear that the treatment of MDA-MB-231 cells with ipomoeassin F (lane 3,

Figure 5) at a concentration of IC$_{90}$ (100 nM) resulted in smaller DNA fragments that were also present for the positive

1 2 3 4

Figure 5. Ipomoeassin F induces DNA fragmentation in MDA-MB-231 cells: lane 1, marker; lane 2, nontreated; lane 3, 100 nM ipomoeassin F; lane 4, 750 nM staurosporine (positive control).

control (lane 4, staurosporine, Figure 5), but not in nontreated cells (lane 2, Figure 5).

■ CONCLUSIONS

In conclusion, by meticulous examination of subtle reactivity differences among various hydroxyl groups and careful selection of protecting groups, we introduced the peripheral ester functional groups to the disaccharide core in such a desired sequence that a much more efficient total synthesis of ipomoeassin F (3.8% overall yield for 17 linear steps) from commercially available starting materials was accomplished. In our route, three highly regioselective reactions were developed: (a) selective allyloxycarbonylation of the 2-OH-Glc$p$ in diol **18**; (b) selective silylation of the 3-OH-Fuc$p$ in triol **23a/b**; and (c) selective glycosylation of 2-OH-Fuc$p$ in diol **6a/b**. To our delight, all of them were accomplished in good to excellent yield. The synthesis can be easily scaled up to gram-scale. This new route secured a meaningful material supply and enabled several biological assessments for this scarce natural resin glycoside. Using the same synthetic strategy, the 11R-epimer of ipomoeassin F was prepared for the first time. The cytotoxicity screens of both compounds undoubtedly demonstrate that the 11S configuration is crucial for the cytotoxicity of ipomoeassin F. For the first time, we also confirmed that in human cells ipomoeassin F can arrest cell cycle in the G1 phase and induce remarkable apoptosis.

■ EXPERIMENTAL SECTION

General Methods. Reactions were carried out in oven-dried glassware. All reagents were purchased from commercial sources and were used without further purification unless noted. Unless stated otherwise, all reactions were carried out under a nitrogen atmosphere and monitored by TLC using silica gel GF$_{254}$ plates with detection by charring with 5% (v/v) H$_2$SO$_4$ in EtOH or by visualizing in UV light (254 nm). Column chromatography was performed on silica gel (230−450 mesh). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). ^{1}H NMR spectra were obtained in deuteriochloroform (CDCl$_3$) with chloroform (CHCl$_3$, δ = 7.27 for ^{1}H) as an internal reference. ^{13}C NMR spectra were proton decoupled and were performed in CDCl$_3$ with CHCl$_3$ (δ = 77.0 for ^{13}C) as an internal reference. Chemical shifts are reported in ppm (δ). Data are presented in the form: chemical shift (multiplicity, coupling constants, and integration). ^{1}H data are reported as though they were first order. The errors between the coupling constants for two coupled protons

were less than 0.5 Hz, and the average number was reported. Proton assignments, when made, were done so with the aid of COSY NMR spectra. For some compounds, HSQC and HMBC NMR were also applied to assign the proton signals. Optical rotations were measured at 25 ± 1 °C for solutions in a 1.0 dm cell. IR spectra were recorded on an FT-IR spectrometer. HRMS were obtained by electrospray ionization (ESI) or matrix-assisted laser desorption/ionization (MALDI) technique in positive mode. The type of the mass analyzer is FTMS. The purity (>95%) of the obtained ipomoeassin F and its 11R-epimer was determined by HPLC analysis equipped with a C18 column (150 mm × 4.6 mm, 5 μm) measured at 280 nm. The mobile phase was a MeCN/H$_2$O mixture. The tested compounds were at least 95% pure.

Chemistry: Synthetic Procedures and Analytical Data. *p-Methoxyphenyl 3-O-Tigloyl-4,6-O-isopropylidene-β-D-glucopyranoside (14).* Compound **13** was synthesized from penta-O-acetyl-β-D-glucopyranose (**11**) through three steps with an overall yield of 49% following the procedure reported in the literature.[21] DCC (850 mg, 4.12 mmol) was added in one portion to a cold (0 °C) solution of compound **13** (1120 mg, 3.43 mmol), tiglic acid (412 mg, 4.12 mmol), and 4-(dimethylamino)pyridine (41.9 mg, 0.343 mmol) in CH$_2$Cl$_2$ (50 mL). The reaction was allowed to warm to ambient temperature and stirred overnight. At this point, TLC (silica, 1:2 EtOAc−hexanes) showed the reaction was complete. The precipitate formed was filtered through a pad of Celite using CH$_2$Cl$_2$ (10 mL) as the eluent, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica, EtOAc−hexanes, 1:6 → 1:1) to give **14** (298 mg, 21%), **15** (720 mg, 51%), and **16** (410 mg, 24%) as white amorphous solids.

*Compound **14**:* [α]$^{25}_D$ −64.1 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.03−6.97 (m, 2H, 2 × ArH), 6.98−6.91 (m, 1H, MeCHC(Me)C═O), 6.85−6.80 (m, 2H, 2 × ArH), 5.12 (t, J = 9.6 Hz, 1H, H-3), 4.93 (d, J = 7.6 Hz, 1H, H-1), 3.98 (dd, J = 10.8, 5.2 Hz, 1H, H-6), 3.85−3.75 (m, 6H, H-2, H-4, H-6, −OCH$_3$), 3.48−3.41 (m, 1H, H-5), 3.21 (d, J = 3.6 Hz, 1H, OH), 1.90−1.80 (m, 6H, CH_3CHC(CH_3)C═O), 1.48 (s, 3H, (CH_3)$_2$C), 1.39 (s, 3H, (CH_3)$_2$C); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.6, 155.6, 150.9, 138.7, 128.1, 118.68 (×2), 114.52 (×2), 102.9, 99.7, 74.8, 73.6, 71.1, 67.4, 62.1, 55.6, 28.9, 18.9, 14.5, 12.1.

*Compound **15**:* [α]$^{25}_D$ −57.3 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.99−6.89 (m, 3H, MeCHC(Me)C═O, 2 × ArH), 6.84−6.77 (m, 2H, 2 × ArH), 5.15 (dd, J = 9.2, 8.0 Hz, 1H, H-2), 4.99 (d, J = 7.6 Hz, 1H, H-1), 3.99 (dd, J = 10.8, 5.6 Hz, 1H, H-6), 3.90−3.80 (m, 2H, H-3, H-6), 3.78−3.72 (m, 4H, H-4, −OCH$_3$), 3.43−3.35 (m, 1H, H-5), 2.89 (br, 1H, OH), 1.90−1.78 (m, 6H, CH_3CHC(CH_3)C═O), 1.55 (s, 3H, (CH_3)$_2$C), 1.46 (s, 3H, (CH_3)$_2$C); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.7, 155.6, 151.1, 138.9, 127.9, 118.72 (×2), 114.48 (×2), 101.1, 99.9, 74.8, 73.5, 73.0, 67.2, 61.9, 55.6, 28.9, 19.0, 14.5, 12.2.

*Compound **16**:* [α]$^{25}_D$ +8.2 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.96−6.88 (m, 2H, 2 × ArH), 6.86−6.76 (m, 4H, 2 × ArH, 2 × MeCHC(Me)C═O), 5.38−5.27 (m, 2H, H-2, H-3), 5.10−5.00 (d, J = 7.2 Hz, 1H, H-1), 4.00 (dd, J = 11.2, 5.6 Hz, 1H, H-6), 3.94−3.80 (m, 2H, H-4, H-6), 3.76 (s, 3H, −OCH$_3$), 3.54−3.46 (m, 1H, H-5), 1.82−1.73 (m, 12H, 2 × CH_3CHC(CH_3)C═O), 1.49 (s, 3H, (CH_3)$_2$C), 1.39 (s, 3H, (CH_3)$_2$C); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.1, 166.5, 155.6, 151.1, 138.3, 138.0, 128.0, 127.8, 118.8 (×2), 114.5 (×2), 101.2, 99.7, 72.1, 72.0, 71.4, 67.6, 62.1, 55.6, 28.9, 18.9, 14.4, 14.4, 12.1, 12.1.

p-Methoxyphenyl 4,6-O-Isopropylidene-α-D-glucopyranoside (18). To a cold (0 °C) solution of the penta-O-acetyl-β-D-glucopyranose **11** (70.0 g, 179 mmol) and p-methoxyphenol (33.4 g, 269 mmol) in dry CH$_2$Cl$_2$ (800 mL) was added boron trifluoride diethyl etherate (111 mL, 897 mmol) over 30 min. The mixture was then heated to 35 °C and agitated for 4 days, at the end of which time TLC (EtOAc−hexanes, 1:2) indicated that the reaction was complete. The reaction mixture was poured onto crushed ice, and the excess boron trifluoride diethyl etherate was neutralized by the careful addition of saturated aqueous NaHCO$_3$ solution. The organic layer was washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo to

provide a yellowish syrup. The syrup was dried under high vacuum for 2 h before being dissolved in MeOH (500 mL). Sodium methoxide (2 g) was added to the reaction mixture and then stirred at room temperature for 2 h. The residue was purified by column chromatography (silica, EtOAc−MeOH, 1:20 → 1:5) to afford *p*-methoxyphenyl *α*-D-glucopyranoside **17**[23] (30.8 g, 60% over two steps) as a white solid. To a solution of compound **17** (28.8 g, 101 mmol) in DMF (200 mL) containing TsOH·H$_2$O (0.38 g, 2.0 mmol) was added 2-methoxypropene (11.6 mL, 121 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 6 h at room temperature until completion (EtOAc−hexanes, 2:1). The reaction was quenched with Et$_3$N (0.5 mL) and then diluted with EtOAc (400 mL) and washed with water (400 mL × 3) and brine (100 mL). The aqueous layer was extracted with EtOAc (400 mL × 2). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica, EtOAc−hexanes, 1:1 → 2:1) to give compound **18** (30.2 g, 92%) as a white foam: $[\alpha]^{25}_D$ +124.7 (*c* 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) *δ* 7.02−6.96 (m, 2H, 2 × Ar*H*), 6.84−6.79 (m, 2H, 2 × Ar*H*), 5.41 (d, *J* = 3.6 Hz, 1H, H-1), 4.00 (td, *J* = 9.2, 2.0 Hz, 1H), 3.88−3.66 (m, 7H, H-2, H-5, 2 × H-6, -OC*H*$_3$), 3.61 (t, *J* = 8.8 Hz, 1H), 3.45−3.40 (m, 1H, O*H*), 3.00−2.92 (m, 1H, O*H*), 1.52 (s, 3H, (C*H*$_3$)$_2$C), 1.44 (s, 3H, (C*H*$_3$)$_2$C); ^{13}C NMR (100 MHz, CDCl$_3$) *δ* 155.4, 150.2, 118.4 (×2), 114.6 (×2), 99.8, 98.6, 73.4, 72.8, 71.9, 64.0, 62.1, 55.6, 29.0, 19.1; IR (film) *ν* = 3397, 2994, 2938, 1654, 1508, 1504, 1206, 1043, 847; HRMS (ESI) *m/z* calcd for C$_{16}$H$_{22}$NaO$_7$ [M + Na]$^+$ 349.1263, found 349.1260.

p-Methoxyphenyl 2-O-(Allyloxycarbonyl)-4,6-O-isopropylidene-*α*-D-glucopyranoside (19). Compound **18** (20.4 g, 62.5 mmol) was dissolved in CH$_2$Cl$_2$ (300 mL) containing pyridine (20 mL, 250 mmol) and DMAP (0.76 g, 6.3 mmol), then under an N$_2$ atmosphere, allyl chloroformate (7.3 mL68.8 mmol) in CH$_2$Cl$_2$ (50 mL) was added dropwise to the solution at −35 °C in 30 min. The reaction mixture was allowed to gradually warm to 0 °C in 30 min, at the end of which time TLC (silica, 1:2 EtOAc−hexanes) showed it was complete. The reaction mixture was then quenched with MeOH (0.5 mL) and washed with 1 M HCl (200 mL), saturated aqueous NaHCO$_3$ (100 mL), and brine (100 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (200 mL). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica, EtOAc−hexanes, 1:4 → 1:3) to give compound **19** (22.1 g, 86%) as a white foam: $[\alpha]^{25}_D$ +153.2 (*c* 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) *δ* 7.01−6.94 (m, 2H, 2 × Ar*H*), 6.85−6.77 (m, 2H, 2 × Ar*H*), 5.96−5.85 (m, 1H, CH$_2$=CHCH$_2$−), 5.65 (d, *J* = 3.6 Hz, 1H, H-1), 5.38−5.22 (m, 2H, C*H*$_2$=CHCH$_2$−), 4.72 (dd, *J* = 9.6, 3.6 Hz, 1H, H-2), 4.66−4.59 (m, 2H, CH$_2$=CHC*H*$_2$−), 4.26 (t, *J* = 9.2 Hz, 1H, H-3), 3.92−3.81 (m, 2H, H-5, H-6), 3.81−3.74 (m, 4H, H-6, −OC*H*$_3$), 3.75−3.64 (m, 1H, H-4), 3.04 (br, 1H, O*H*), 1.54 (s, 3H, (C*H*$_3$)$_2$C), 1.45 (s, 3H, (C*H*$_3$)$_2$C); ^{13}C NMR (100 MHz, CDCl$_3$) *δ* 155.3, 154.4, 150.3, 131.1, 119.2, 118.2 (×2), 114.5 (×2), 100.0, 95.8, 76.7, 73.7, 68.97, 68.8, 63.7, 62.1, 55.6, 28.9, 19.1. IR (film) *ν* = 3462, 2994, 2941, 1744, 1508, 1205, 1024; HRMS (ESI) *m/z* calcd for C$_{20}$H$_{26}$NaO$_9$ [M + Na]$^+$ 433.1475, found 433.1466.

p-Methoxyphenyl 2-O-(Allyloxycarbonyl)-3-O-tigloyl-4,6-O-iso-propylidene-*α*-D-glucopyranoside (20). DCC (8.60 g, 41.7 mmol) was added in one portion to a 0 °C CH$_2$Cl$_2$ (100 mL) solution of **19** (11.4 g, 27.8 mmol), tiglic acid (4.17 g, 41.7 mmol), and 4-(dimethylamino)pyridine (0.34 g, 2.78 mmol). The reaction was allowed to warm to ambient temperature and stirred overnight. At this point, TLC (silica, 1:2 EtOAc−hexanes) showed the reaction was complete. The reaction was diluted with ether (100 mL) and hexanes (50 mL), stirred for 20 min, and then filtered through a pad of Celite using ether (50 mL) as the eluent, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica, EtOAc−hexanes, 1:6 → 1:5) to give **20** (13.1 g, 95%) as a colorless syrup: $[\alpha]^{25}_D$ +127.9 (*c* 1 CHCl$_3$); ^{1}H NMR (400 MHz, MeOD) *δ* 7.05−6.99 (m, 2H, 2 × Ar*H*), 6.93−6.83 (m, 3H, MeCHC(Me)C=O, 2 × Ar*H*), 5.94−5.75 (m, 1H, CH$_2$= CHCH$_2$−), 5.67 (d, *J* = 3.6 Hz, 1H, H-1), 5.57 (t, *J* = 10.0 Hz, 1H, H-

3), 5.29−5.15 (m, 2H, C*H*$_2$=CHCH$_2$−), 4.97 (dd, *J* = 10.0, 3.6 Hz, 1H, H-4), 4.65−4.51 (m, 2H, CH$_2$=CHC*H*$_2$−), 4.01−3.79 (m, 4H, H-4, H-5, 2 × H-6), 3.75 (s, 3H, −OC*H*$_3$), 3.75 (d, *J* = 4.7 Hz, 3H), 1.86−1.78 (m, 6H, C*H*$_3$CHC(C*H*$_3$)-C=O), 1.50 (s, 3H, (C*H*$_3$)$_2$C), 1.34 (s, 3H, (C*H*$_3$)$_2$C); ^{13}C NMR (100 MHz, MeOD) *δ* 168.4, 157.0, 155.6, 151.7, 139.6, 132.8, 129.2, 119.4 (×2), 118.9, 115.7 (×2), 101.2, 97.7, 75.9, 73.1, 70.8, 69.8, 65.7, 63.1, 56.0, 29.3, 19.4, 14.5, 12.2; IR (film) *ν* = 2994, 2940, 1747, 1718, 1653, 1510, 1277, 1247, 1211, 1042; HRMS (ESI) *m/z* calcd for C$_{25}$H$_{32}$NaO$_{10}$ [M + Na]$^+$ 515.1893, found 515.1891.

2-O-[(Allyloxy)carbonyl]-3-O-tigloyl-4,6-O-isopropylidene-*α*-D-glucopyranosyl Trichloroacetimidate (3). To a solution of compound **20** (10.9 g, 22.1 mmol) in acetonitrile (120 mL) and water (30 mL) was added a solution of CAN (24.3 g, 44.3 mmol) in water (30 mL) over 5 min at −10 °C. The mixture was stirred for 15 min at the same temperature, at the end of which time TLC (silica, 1:2 EtOAc−hexanes) indicated that the reaction was complete. The reaction was quenched with saturated aqueous NaHCO$_3$ and extracted with EtOAc (400 mL × 2). The combined organic phase was dried over Na$_2$SO$_4$ and concentrated. The obtained residue was purified by column chromatography (silica, EtOAc−hexanes, 1:4 → 1:2) to afford the desired hemiacetal. To a solution of the obtained hemiacetal in CH$_2$Cl$_2$ (100 mL) were added trichloroacetonitrile (8.9 mL, 88 mmol) and DBU (0.33 mL, 2.2 mmol). The mixture was stirred overnight at room temperature and then was concentrated. The residue was purified by column chromatography (silica, EtOAc−hexanes, 1:5 → 1:3) to afford the glucosyl donor **3** (6.93 g, 59% over two steps) as a colorless syrup: $[\alpha]^{25}_D$ +59.6 (*c* 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) *δ* 8.65 (s, 1H, CN*H*CCl$_3$), 6.90−6.83 (m, 1H, MeC*H*C-(Me)C=O), 6.57 (d, *J* = 4.0 Hz, 1H, H-1), 5.93−5.76 (m, 1H, CH$_2$=C*H*CH$_2$−), 5.61 (t, *J* = 9.6 Hz, 1H, H-3), 5.36−5.17 (m, 2H, C*H*$_2$=CHCH$_2$−), 5.03 (dd, *J* = 9.6, 4.0 Hz, 1H, H-2), 4.65−4.54 (m, 2H, CH$_2$=CHC*H*$_2$−), 4.05−3.72 (m, 4H, H-2, H-4, H-5, 2 × H-6), 1.90−1.76 (m, 6H, C*H*$_3$CHC(C*H*$_3$)C=O), 1.49 (s, 3H, (C*H*$_3$)$_2$C), 1.41 (s, 3H, (C*H*$_3$)$_2$C); ^{13}C NMR (100 MHz, CDCl$_3$) *δ* 166.6, 161.2, 154.2, 138.0, 131.1, 128.0, 118.8, 100.0, 93.6, 74.0, 71.7, 69.07, 68.97, 66.2, 62.0, 28.8, 18.9, 14.4, 12.1.

1-Nonen-4S/R-yl 2,3,4-Tri-O-acetyl-*β*-D-fucopyranoside (22a/b). Fucosyl donor **4**[18] was synthesized from tetra-O-acetyl-D-fucopyranose through two steps with an overall yield of 77% following the procedure reported in literature. (*S*)-4-Hydroxy-1-nonene (**5a**)[11] and (*R*)-4-hydroxy-1-nonene (**5b**)[30] were synthesized from (*S*)-(+)-epichlorohydrin and (*R*)-(−)-epichlorohydrin through three steps with overall yields of 68% and 58%, respectively.

Compound 22a. A mixture of acceptor **5a** (3.21 g, 22.5 mmol), donor **4** (9.80 g, 22.5 mmol), and 4 Å molecular sieves (5 g) in anhydrous, redistilled CH$_2$Cl$_2$ (200 mL) was stirred under an N$_2$ atmosphere for 30 min and then cooled to −10 °C. TMSOTf (408 *μ*L, 2.3 mmol) was added to the mixture, and then the reaction mixture was allowed to gradually warm to ambient temperature with the cold bath in place and was stirred for 1 h. TLC (silica, 1:3 EtOAc−hexanes) indicated that the reaction was complete. The reaction mixture was quenched with Et$_3$N (320 *μ*L) and filtrated. The filtrate was evaporated in vacuo to give a residue, which was purified by silica gel column chromatography (silica, EtOAc−hexanes, 1:7 → 1:5) to give compound **22a** (8.68 g, 93%) as a yellowish syrup: $[\alpha]^{25}_D$ −9.9 (*c* 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) *δ* 5.81−5.71 (m, 1H, CH$_2$= CHCH$_2$−), 5.23−5.11 (m, 2H, H-4-Fuc*p*, H-2-Fuc*p*), 5.09−4.94 (m, 3H, H-3-Fuc*p*, CH$_2$=CHCH$_2$−), 4.47 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 3.80−3.73 (m, 1H, H-5-Fuc*p*), 3.65−3.58 (m, 1H, −C*H*$_2$CHCH$_2$−), 2.25−2.20 (m, 2H), 2.16 (s, 3H, CH$_3$C=O), 2.02 (s, 3H, CH$_3$C=O), 1.98 (s, 3H, CH$_3$C=O), 1.62−1.44 (m, 2H), 1.38−1.21 (m, 6H), 1.20 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) *δ* 170.8, 170.3, 169.4, 134.4, 117.0, 100.5, 80.2, 71.5, 70.3, 69.3, 68.9, 38.4, 34.4, 31.7, 24.6, 22.5, 20.9, 20.7, 20.6, 16.1, 14.0. The ^{1}H, ^{13}C NMR data were in accordance with the literature.[10]

Compound 22b. Compound **22b** (2.80 g, 74%) was prepared by coupling of acceptor **5b** (1.32 g, 9.3 mmol) with donor **4** (4.28 g, 9.8 mmol) under the same conditions as described for the synthesis of **22a** by coupling of **5a** with **4**: $[\alpha]^{25}_D$ +9.7 (*c* 1 CHCl$_3$); ^{1}H NMR (400

MHz, CDCl$_3$) δ 5.88–5.75 (m, 1H, CH$_2$=CHCH$_2$–), 5.25–5.13 (m, 2H, H-4-Fuc$p$, H-2-Fuc$p$), 5.09–4.96 (m, 3H, H-3-Fuc$p$, CH$_2$=CHCH$_2$–), 4.49 (d, J = 7.6 Hz, 1H, H-1-Fuc$p$), 3.84–3.74 (m, 1H, H-5-Fuc$p$), 3.65–3.56 (m, 1H, –CH$_2$CHCH$_2$–), 2.51–2.27 (m, 2H), 2.18 (s, 3H, CH$_3$C=O), 2.04 (s, 3H, CH$_3$C=O), 1.99 (s, 3H, CH$_3$C=O), 1.50–1.40 (m, 2H), 1.40–1.23 (m, 6H), 1.24 (d, J = 6.4 Hz, 3H, H-6-Fuc$p$), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.8, 170.3, 169.4, 134.7, 116.9, 101.2, 81.0, 71.5, 70.3, 69.3, 69.0, 39.7, 33.5, 31.9, 24.7, 22.6, 20.8, 20.7, 20.7, 16.1, 14.0. IR (film) ν = 2936, 2856, 1755, 1600, 1368, 1254, 1229, 1078; HRMS (ESI) m/z calcd for C$_{21}$H$_{34}$NaO$_8$ [M + Na]$^+$ 437.2151, found 437.2148.

1-Nonen-4S-yl β-D-Fucopyranoside (23a). MeONa (224 mg, 4.15 mmol) was added in one portion to a solution of **22a** (8.60 g, 20.7 mmol) in MeOH (200 mL) at room temperature. The reaction mixture was stirred at room temperature overnight. TLC (silica, 3:1 EtOAc–hexanes) showed the reaction was complete. Neutralization of the reaction mixture was accomplished with acidic ion-exchange resin (Amberlite IR-120 (H+), Alfa Aesar), and the organic phase was concentrated in vacuo. The residue was purified by column chromatography (silica, EtOAc–hexanes, 3:1 → 5:1) to give triol **23a** (5.05 g, 84%) as a colorless syrup: [α]$^{25}_D$ –21.2 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.91–5.78 (m, 1H, CH$_2$=CHCH$_2$–), 5.20–5.02 (m, 2H, CH$_2$=CHCH$_2$–), 4.24 (d, J = 7.6 Hz, 1H, H-1-Fuc$p$), 3.74–3.53 (m, 5H, H-2-Fuc$p$, H-3-Fuc$p$, H-4-Fuc$p$, H-5-Fuc$p$, –CH$_2$CHCH$_2$–), 3.36 (d, J = 4.8 Hz, 1H, OH), 2.97 (br, 1H, OH), 2.73 (d, J = 5.6 Hz, 1H, OH), 2.40–2.22 (m, 2H), 1.67–1.48 (m, 2H), 1.42–1.21 (m, 9H), 0.89 (d, J = 6.8 Hz, 3H, H-6-Fuc$p$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.0, 117.5, 102.3, 79.2, 73.9, 72.1, 71.6, 70.5, 38.6, 34.7, 31.8, 24.8, 22.6, 16.3, 14.1. The ^{1}H, ^{13}C NMR data were in accordance with the literature.[10]

1-Nonen-4R-yl β-D-Fucopyranoside (23b). Compound **23b** (1.37 g, 73%, colorless syrup) was prepared by treating **22b** (2.69 g, 6.49 mmol) with MeONa (80 mg, 1.48 mmol) under the same conditions as described for the synthesis of **23a**: [α]$^{25}_D$ +2.0 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.91–5.78 (m, 1H, CH$_2$=CHCH$_2$–), 5.11–4.99 (m, 2H, CH$_2$=CHCH$_2$–), 4.25 (d, J = 7.6 Hz, 1H, H-1-Fuc$p$), 3.76–3.54 (m, 5H, H-2-Fuc$p$, H-3-Fuc$p$, H-4-Fuc$p$, H-5-Fuc$p$, –CH$_2$CHCH$_2$–), 3.90 (br 1H, OH), 3.41 (br, 1H, OH), 3.24 (br, 1H, OH), 2.46–2.30 (m, 2H), 1.57–1.48 (m, 2H), 1.45–1.21 (m, 9H), 0.89 (d, J = 6.8 Hz, 3H, H-6-Fuc$p$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.0, 116.8, 102.6, 79.7, 73.9, 71.7, 71.6, 70.5, 39.6, 33.5, 31.9, 24.8, 22.6, 16.4, 14.0; IR (film) ν = 3381, 2928, 2859, 1639, 1070, 995, 912, 756; HRMS (ESI) m/z calcd for C$_{15}$H$_{28}$NaO$_5$ [M + Na]$^+$ 311.1834, found 311.1830.

1-Nonen-4S-yl 3-O-(tert-Butyldimethylsilyl)-β-D-fucopyranoside (6a). To a cold (0 °C) solution of triol **23a** (5.05 g, 17.5 mmol) and 1H-imidazole (3.58 g, 52.5 mmol) in DMF (100 mL) was added tert-butyldimethylsilyl chloride (3.70 g, 24.5 mmol). The reaction was stirred at 0 °C for 30 min and then was allowed to warm to ambient temperature and stirred for a further 2 h. At this point, TLC (silica, 1:9 EtOAc–hexanes) showed the reaction was complete. The reaction mixture was diluted with ether (500 mL) and washed with water (3 × 150 mL) and brine (100 mL). The aqueous layer was extracted with ether (200 mL). The combined organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:30 → 1:20) to afford compound **6a** (5.05 g, 72%) as a colorless syrup: [α]$^{25}_D$ –6.9 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.91–5.74 (m, 1H, CH$_2$=CHCH$_2$–), 5.14–4.98 (m, 2H, CH$_2$=CHCH$_2$–), 4.20 (d, J = 7.8 Hz, 1H, H-1-Fuc$p$), 3.73–3.65 (m, 1H, –CH$_2$CHCH$_2$–), 3.63 (dd, J = 9.2, 3.6 Hz, 1H, H-3-Fuc$p$), 3.59–3.48 (m, 3H, H-2-Fuc$p$, H-4-Fuc$p$, H-5-Fuc$p$), 2.62 (br, 1H, OH), 2.38–2.21 (m, 2H), 2.17 (d, J = 1.6 Hz, 1H, OH), 1.67–1.47 (m, 2H), 1.39–1.22 (m, 9H), 0.96–0.84 (m, 12H), 0.15 (s, 3H, CH$_3$Si), 0.13 (s, 3H, CH$_3$Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.1, 117.4, 102.2, 78.9, 74.9, 72.1, 72.1, 70.0, 38.5, 34.7, 31.8, 25.8(3), 24.7, 22.6, 18.1, 16.4, 14.1, –4.4, –5.0; IR (film) ν = 3537, 2930, 2857, 1655, 1109, 1066, 997, 910, 839, 781; HRMS (ESI) m/z calcd for C$_{21}$H$_{42}$NaO$_5$Si [M + Na]$^+$ 425.2699, found 425.2696.

1-Nonen-4R-yl 3-O-(tert-Butyldimethylsilyl)-β-D-fucopyranoside (6b). Compound **6b** (0.36 g, 71%, colorless syrup) was prepared by treating **23b** (0.36 g, 1.2 mmol) with 1H-imidazole (0.24 g, 3.5 mmol) under the same conditions as described for the synthesis of **6a**: [α]$^{25}_D$ +7.8 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.91–5.74 (m, 1H, CH$_2$=CHCH$_2$–), 5.14–4.98 (m, 2H, CH$_2$=CHCH$_2$–), 4.20 (d, J = 7.8 Hz, 1H, H-1-Fuc$p$), 3.73–3.65 (m, 1H, –CH$_2$CHCH$_2$–), 3.63 (dd, J = 9.2, 3.6 Hz, 1H, H-3-Fuc$p$), 3.59–3.48 (m, 3H, H-2-Fuc$p$, H-4-Fuc$p$, H-5-Fuc$p$), 2.62 (br, 1H, OH), 2.38–2.21 (m, 2H), 2.17 (d, J = 1.6 Hz, 1H, OH), 1.67–1.47 (m, 2H), 1.39–1.22 (m, 9H), 0.96–0.84 (m, 12H), 0.15 (s, 3H, CH$_3$Si), 0.13 (s, 3H, CH$_3$Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.1, 117.4, 102.2, 78.9, 74.9, 72.1, 72.1, 70.0, 38.5, 34.7, 31.8, 25.8 (×3), 24.7, 22.6, 18.1, 16.4, 14.1, –4.4, –5.0; IR (film) ν = 3379, 2930, 2856, 1653, 1074, 997, 800, 760; HRMS (ESI) m/z calcd for C$_{21}$H$_{42}$NaO$_5$Si [M + Na]$^+$ 425.2699, found 425.2693.

1-Nonen-4S-yl 2,4-Di-O-acetyl-3-O-(tert-butyldimethylsilyl)-β-D-fucopyranoside (24). To a solution of compound **6a** (10 mg, 0.025 mmol) and DMAP (1 mg) in pyridine (1 mL) was added acetic anhydride (100 μL). The reaction mixture was stirred at room temperature overnight, at the end of which time TLC (silica, 1:6 EtOAc–hexanes) indicated that the reaction was complete. The mixture was concentrated under diminished pressure and then coevaporated with toluene (2 × 3 mL) to give the crude product. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:10) to afford compound **24** (11 mg, 92%) as a colorless syrup: [α]$^{25}_D$ –1.1 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.84–5.69 (m, 1H, CH$_2$=CHCH$_2$–), 5.11–4.99 (m, 4H, CH$_2$=CHCH$_2$–, H-2-Fuc$p$, H-4-Fuc$p$), 4.36 (d, J = 8.0 Hz, 1H, H-1-Fuc$p$), 3.78 (dd, J = 9.6, 3.6 Hz, 1H, H-3-Fuc$p$), 3.70–3.63 (m, 1H, H-5-Fuc$p$), 3.62–3.55 (m, 1H, –CH$_2$CHCH$_2$–), 2.28–2.18 (m, 2H), 2.15 (s, 3H, CH$_3$C=O), 2.05 (s, 3H, CH$_3$C=O), 1.65–1.21 (m, 8H), 1.18 (d, J = 6.4 Hz, 3H, H-6-Fuc$p$), 0.88 (t, J = 6.8 Hz, 3H), 0.83 (s, 9H), 0.07 (s, 3H, CH$_3$Si), 0.06 (s, 3H, CH$_3$Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.9, 169.2, 134.7, 116.9, 100.6, 79.9, 72.9, 72.3, 71.5, 69.0, 38.4, 34.4, 31.8, 25.4 (×3), 24.7, 22.6, 21.3, 20.9, 17.8, 16.3, 14.1, –4.8, –5.1; IR (film) ν = 2928, 2855, 1744, 1371, 1231, 1119, 1063, 837, 781.

Disaccharide 25a. A mixture of acceptor **6a** (4.30 g, 10.7 mmol), donor **3** (6.24 g, 11.7 mmol), and 4 Å molecular sieves (5 g) in anhydrous, redistilled CH$_2$Cl$_2$ (300 mL) was stirred under an N$_2$ atmosphere for 30 min and then cooled to –60 °C. TMSOTf (193 μL, 1.07 mmol) was added to the mixture. The reaction mixture was then allowed to gradually warm to –20 °C over 2 h, at the end of which time TLC (silica, 1:6 EtOAc–hexanes) showed it was complete. The reaction mixture was quenched with Et$_3$N (150 μL) and filtrated. The filtrate was evaporated in vacuo to give a residue, which was purified by silica gel column chromatography (silica, EtOAc–hexanes, 1:20 → 1:10) to give compound **25a** (7.62 g, 93%) as a colorless syrup: [α]$^{25}_D$ –17.2 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.86–6.81 (m, 1H, MeCH=C(Me)C=O), 6.05–5.92 (m, 1H, CH$_2$=CHCH$_2$–), 5.90–5.78 (m, 1H, CH$_2$=CHCH$_2$–), 5.33–5.00 (m, 6H, 2 × CH$_2$=CHCH$_2$–, H-3-Glu$p$, H-1-Glu$p$), 4.71 (dd, J = 9.6, 8.0 Hz, 1H, H-2-Glu$p$), 4.65–4.45 (m, 2H, CH$_2$=CHCH$_2$O–), 4.29 (d, J = 7.6 Hz, 1H, H-1-Fuc$p$), 3.97 (dd, J = 11.2, 5.6 Hz, 1H, H-6-Glu$p$), 3.85–3.68 (m, 4H, H-2-Fuc$p$, H-3-Fuc$p$, H-4-Glu$p$, H-6-Glu$p$), 3.68–3.59 (m, 1H), 3.55–3.45 (m, 2H), 3.30 (m, 1H, H-5-Glu$p$), 2.38 (br, 1H, OH), 2.29 (t, J = 6.8 Hz, 2H), 1.87–1.72 (m, 6H, CH_3CHC(CH_3)C=O), 1.56–1.47 (m, 2H), 1.45 (s, 3H), 1.42–1.18 (m, 12H), 1.02–0.83 (m, 12H), 0.17 (s, 3H, CH$_3$Si), 0.10 (s, 3H, CH$_3$Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 166.9, 154.2, 137.9, 135.6, 131.4, 128.0, 118.4, 116.3, 100.7, 99.6, 99.6, 79.3, 77.2, 76.1, 75.6, 72.4, 72.3, 71.7, 69.5, 68.4, 67.2, 62.1, 38.3, 34.3, 31.9, 28.9, 25.9 (×3), 24.6, 22.6, 18.8, 18.0, 16.4, 14.4, 14.1, 12.1, –4.6 (×2); IR (film) ν = 3561, 2932, 2859, 1757, 1721, 1655, 1263, 1070, 980, 908, 835, 779. HRMS (ESI) m/z calcd for C$_{39}$H$_{66}$NaO$_{13}$Si [M + Na]$^+$ 793.4170, found 793.4169.

Disaccharide 25b. **25b** (0.51 g, 66%, colorless syrup) was prepared by coupling of acceptor **6b** (0.45 g, 1.1 mmol) with donor **3** (0.54 g, 1.0 mmol) under the same conditions as described for the synthesis of **25a** by coupling of **6a** with **3**. [α]$^{25}_D$ –3.9 (c 1 CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.89–6.79 (m, 1H, Me–CH=C(Me)-C=O), 5.85–

5.79 (m, 2H, 2 x C*H*$_2$=CH-CH$_2$−), 5.34−4.99 (m, 6H, 2 × C*H*$_2$=CH−CH$_2$−, H-3-Glu*p*, H-1-Glu*p*), 4.72 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2-Glu*p*), 4.62−4.49 (m, 2H, CH$_2$=CH−C*H*$_2$−O−), 4.28 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 3.97(dd, *J* = 11.2, 5.6 Hz, 1H, H-6-Glu*p*), 3.86−3.67 (m, 4H, H-2-Fuc*p*, H-3-Fuc*p*, H-4-Glu*p*, H-6-Glu*p*), 3.68−3.59 (m, 1H), 3.56−3.47 (m, 2H), 3.31 (m, 1H, H-5-Glu*p*), 2.37 (br, 1H, O*H*), 2.36 (t, *J* = 6.8 Hz, 2H), 1.83−1.75 (m, 6H, C*H*$_3$-CH−C(C*H*$_3$)-C=O), 1.55−1.46 (m, 2H), 1.46 (s, 3H), 1.41−1.20 (m, 12H), 1.00−0.82 (m, 12H), 0.18 (s, 3H, C*H*$_3$Si), 0.11 (s, 3H, C*H*$_3$Si). ^{13}C NMR (100 MHz, CDCl$_3$) δ 166.9, 154.2, 137.9, 135.2, 131.4, 128.1, 118.3, 116.5, 101.1, 99.6, 99.6, 79.9, 77.2, 75.8, 75.7, 72.4, 72.3, 71.8, 69.5, 68.4, 67.2, 62.2, 39.4, 33.5, 32.3, 28.9, 25.9 (×3), 24.7, 22.9, 18.8, 18.0, 16.5, 14.4, 14.0, 12.1, −4.6 (×2). IR (film) ν = 3356, 2932, 2860, 1759, 1724, 1651, 1269, 1096, 839, 760. HRMS (ESI) *m/z* calcd for C$_{39}$H$_{66}$NaO$_{13}$Si [M + Na]$^+$ 793.4170, found 793.4167.

Disaccharide 7a. To a cold (0 °C) solution of compound **25a** (7.60 g, 9.86 mmol) and DMAP (120 mg, 0.99 mmol) in pyridine (20 mL) was added acetic anhydride (10 mL). The reaction mixture was heated to 60 °C and stirred for a further 24 h, at the end of which time TLC (silica, 1:6 EtOAc−hexanes) indicated that the reaction was complete. The mixture was concentrated under diminished pressure and then coevaporated with toluene (2 × 20 mL) gave the crude product. The residue was purified by column chromatography (silica, EtOAc−hexanes, 1:20 → 1:10) to afford compound **7a** (6.12 g, 76%) as a colorless syrup; recovered **25a** (0.60g, 8%, ^{1}H NMR, 400 MHz). [α]$^{25}_D$ −11.1 (*c* 1 CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.89−6.80 (m, 1H, Me−C*H*=C(Me)-C=O), 6.10−5.96 (m, 1H, CH$_2$=C*H*-CH$_2$−), 5.89−5.73 (m, 1H, CH$_2$=C*H*-CH$_2$−), 5.35−5.03 (m, 6H, 2 × C*H*$_2$=CH−CH$_2$−, H-3-Glu*p*, H-1-Glu*p*), 5.00 (m, 1H, H-4-Fuc*p*), 4.75 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2-Glu*p*), 4.62−4.46 (m, 2H, CH$_2$=CH−C*H*$_2$−O−), 4.31 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 4.02 (dd, *J* = 10.8, 5.2 Hz, 1H, H-6-Glu*p*), 3.90 (dd, *J* = 9.2, 8.0 Hz, 1H, H-2-Fuc*p*), 3.82−3.70 (m, 3H, H-3-Fuc*p*, H-4-Glu*p*, H-6-Glu*p*), 3.68−3.57 (m, 2H), 3.33 (m, 1H, H-5-Glu*p*), 2.34 (br, 2H), 2.12 (s, 3H, C*H*$_3$-C=O), 1.84−1.74 (m, 6H, C*H*$_3$-CH−C(C*H*$_3$)-C=O), 1.62−1.48 (m, 2H), 1.46 (s, 3H, (C*H*$_3$)$_2$C), 1.40−1.22 (m, 9H), 1.13 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.94−0.83 (m, 12H), 0.12 (s, 3H, C*H*$_3$Si), 0.09 (s, 3H, C*H*$_3$Si). ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.8, 166.8, 154.2, 137.9, 135.6, 131.4, 128.0, 118.3, 116.2, 101.3, 99.6, 99.5, 80.5, 77.1, 75.5, 73.5, 73.4, 72.3, 71.8, 68.9, 68.4, 67.3, 62.2, 38.4, 34.3, 31.8, 28.9, 25.8 (×3), 24.6, 22.6, 20.9, 18.9, 17.7, 16.5, 14.4, 14.1, 12.1, −4.3, −4.9; IR (film) ν = 2932, 2859, 1759, 1744, 1653, 1649, 1253, 1069, 839, 758; HRMS (ESI) *m/z* calcd for C$_{41}$H$_{68}$NaO$_{14}$Si [M + Na]$^+$ 835.4276, found 835.4270.

Disaccharide 7b. Compound **7b** (321 mg, 78%, colorless syrup) was prepared by treating **25b** (392 mg, 0.51 mmol) with acetic anhydride (1 mL) and DMAP (6.2 mg, 0.051 mmol) in pyridine (3 mL) under the same conditions as described for the synthesis of **7a**: [α]$^{25}_D$ −0.6 (*c* 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.89−6.80 (m, 1H, Me−C*H*=C(Me)C=O), 5.91−5.78 (m, 2H, 2 × C*H*$_2$=CHCH$_2$−), 5.33−5.02 (m, 6H, 2 × C*H*$_2$=CHCH$_2$−, H-3-Glu*p*, H-1-Glu*p*), 5.00 (m, 1H, H-4-Fuc*p*), 4.74 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2-Glu*p*), 4.62−4.47 (m, 2H, CH$_2$=CHCH$_2$O−), 4.30 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 4.01 (dd, *J* = 10.8, 5.2 Hz, 1H, H-6-Glu*p*), 3.92 (dd, *J* = 9.2, 8.0 Hz, 1H, H-2-Fuc*p*), 3.80−3.67 (m, 3H, H-3-Fuc*p*, H-4-Glu*p*, H-6-Glu*p*), 3.66−3.57 (m 2H), 3.31 (m, 1H, H-5-Glu*p*), 2.35 (br, 2H), 2.11 (s, 3H, C*H*$_3$C=O), 1.82−1.72 (m, 6H, C*H*$_3$CHC(C*H*$_3$)-C=O), 1.62−1.48 (m, 2H), 1.43 (s, 3H, (C*H*$_3$)$_2$C), 1.41−1.25 (m, 9H), 1.13 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.98−0.82 (m, 12H), 0.12 (s, 3H, C*H*$_3$Si), 0.09 (s, 3H, C*H*$_3$Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.8, 166.8, 154.3, 137.9, 135.0, 131.4, 128.0, 118.3, 116.7, 101.6, 99.6, 99.5, 81.0, 77.1, 75.2, 73.5, 73.4, 72.2, 72.0, 68.9, 68.4, 67.2, 62.3, 39.4, 33.7, 32.3, 28.9, 25.8 (×3), 24.9, 22.9, 20.9, 18.8, 17.7, 16.6, 14.4, 14.2, 12.0, −4.2, −5.0; IR (film) ν = 2932, 2859, 1759, 1655, 1269, 1115, 1096, 839, 760; HRMS (ESI) *m/z* calcd for C$_{41}$H$_{68}$NaO$_{14}$Si [M + Na]$^+$ 835.4276, found 835.4273.

Disaccharide 26a. To a cooled (−10 °C) solution of compound **7a** (5.52 g, 6.79 mmol) in 1:1 MeOH−THF (160 mL) was added CH$_3$COONH$_4$ (5.23 g, 67.9 mmol). With vigorous stirring, NaBH$_4$ (51 mg, 1.4 mmol), Pd[P(C$_6$H$_5$)$_3$]$_4$ (314 mg, 0.27 mmol), and

NaBH$_4$[16,31−33] (462 mg, 12.2 mmol) were added in three portions immediately one after another. Four minutes after the addition of the second portion of NaBH$_4$, TLC (EtOAc−hexanes, 1:6) indicated that the reaction was complete. The reaction mixture was concentrated under diminished pressure, the residue was dissolved in CH$_2$Cl$_2$ (200 mL) and washed with water (100 mL), and then the organic layer was dried over Na$_2$SO$_4$. Evaporation and purification by column chromatography (silica, EtOAc−hexanes, 1:10) afforded compound **26a** (4.71 g, 95%) as a colorless syrup: [α]$^{25}_D$ −8.6 (*c* 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.90−6.81 (m, 1H, MeC*H*=C(Me)C=O), 5.92−5.79 (m, 1H, CH$_2$=CHCH$_2$−), 5.16 (t, *J* = 9.6 Hz, 1H, H-3-Glu*p*), 5.11−5.00 (m, 3H, C*H*$_2$=CHCH$_2$−, H-4-Fuc*p*), 4.72 (d, *J* = 8.0 Hz, 1H, H-1-Glu*p*), 4.39 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 3.98−3.85 (m, 2H, H-6-Glu*p*, H-2-Fuc*p*), 3.82−3.74 (m, 2H, H-6-Glu*p*, H-3-Fuc*p*), 3.73−3.65 (m, 2H, H-4-Glu*p*), 3.64−3.56 (m, 1H, H-5-Fuc*p*), 3.55−3.46 (m, 2H, H-2-Glu*p*, O*H*), 3.42−3.37 (m, 1H, H-5-Glu*p*), 2.37−2.24 (m, 2H), 2.10 (s, 3H, C*H*$_3$C=O), 1.88−1.74 (m, 6H, C*H*$_3$CHC(C*H*$_3$)C=O), 1.60−1.49 (m, 2H), 1.45 (s, 3H, (C*H*$_3$)$_2$C), 1.40−1.21 (m, 9H), 1.13 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.91−0.83 (m, 12H), 0.17 (s, 3H, C*H*$_3$Si), 0.14 (s, 3H, C*H*$_3$Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.8, 167.5, 137.3, 134.6, 128.4, 116.9, 104.6, 101.4, 99.6, 79.1, 79.0, 75.4, 72.8, 72.7, 72.6, 71.6, 68.8, 68.3, 62.2, 38.1, 34.0, 31.8, 28.9, 25.8 (×3), 24.3, 22.6, 20.9, 18.9, 17.8, 16.4, 14.3, 14.0, 12.1, −4.5, −4.6; IR (film) ν = 3447, 2930, 2859, 1744, 1719, 1653, 1252, 1233, 1066, 837, 754; HRMS (ESI) *m/z* calcd for C$_{37}$H$_{64}$NaO$_{12}$Si [M + Na]$^+$ 751.4065, found 751.4060.

Disaccharide 26b. Compound **26b** (343 mg, 85%, colorless syrup) was prepared by treating **7b** (450 mg, 0.55 mmol) with CH$_3$COONH$_4$ (427 mg, 5.53 mmol), Pd[P(C$_6$H$_5$)$_3$]$_4$ (26 mg, 0.02 mmol), and NaBH$_4$ (31 mg, 0.82 mmol) in 1:1 MeOH−THF (15 mL) under the same conditions as described for the synthesis of **26a**: [α]$^{25}_D$ −1.5 (*c* 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.90−6.80 (m, 1H, Me−C*H*=C(Me)C=O), 5.93−5.79 (m, 1H, CH$_2$=CHCH$_2$−), 5.15 (t, *J* = 9.6 Hz, 1H, H-3-Glu*p*), 5.10−5.00 (m, 3H, CH$_2$=CHCH$_2$−, H-4-Fuc*p*), 4.70 (d, *J* = 8.0 Hz, 1H, H-1-Glu*p*), 4.39 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 3.99−3.85 (m, 2H, H-6-Glu*p*, H-2-Fuc*p*), 3.83−3.72 (m, 2H, H-6-Glu*p*, H-3-Fuc*p*), 3.72−3.69 (m, 2H, H-4-Glu*p*), 3.62−3.58 (m, 1H, H-5-Fuc*p*), 3.57−3.43 (m, 2H, H-2-Glu*p*, O*H*), 3.40−3.35 (m, 1H, H-5-Glu*p*), 2.49−2.30 (m, 2H), 2.10 (s, 3H, C*H*$_3$C=O), 1.90−1.73 (m, 6H, C*H*$_3$CHC(C*H*$_3$)C=O), 1.60−1.50 (m, 2H), 1.46 (s, 3H, (C*H*$_3$)$_2$C), 1.41−1.21 (m, 9H), 1.15 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.94−0.80 (m, 12H), 0.18 (s, 3H, C*H*$_3$Si), 0.15 (s, 3H, C*H*$_3$Si); ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.9, 167.6, 137.4, 134.6, 128.4, 117.0, 104.5, 101.5, 99.6, 79.5, 78.8, 75.4, 72.8, 72.8, 72.7, 71.7, 68.8, 68.3, 62.3, 38.7, 32.9, 32.1, 29.0, 25.8 (×3), 24.7, 22.6, 20.9, 18.9, 17.8, 16.5, 14.4, 14.1, 12.1, −4.5, −4.5; HRMS (ESI) *m/z* calcd for C$_{37}$H$_{64}$NaO$_{12}$Si [M + Na]$^+$ 751.4065, found 751.4058.

Disaccharide 27a. TBSOTf (5.94 mL, 25.8 mmol) was added to a solution of compound **26a** (4.71 g, 6.46 mmol) and 2,6-lutidine (7.48 mL, 64.6 mmol) in distilled CH$_2$Cl$_2$ (100 mL) at 0 °C. The reaction was allowed to warm to ambient temperature and stirred for 24 h. At this point, TLC (silica, 1:6 EtOAc−hexanes) showed the reaction was complete. Evaporation of the solvent followed by purification of the residue by flash chromatography (silica, EtOAc−hexanes, 1:20 → 1:10) gave compound **27a** (3.61 g, 66%) as a colorless syrup and **28a** (1.45 g, 27%) as a white foam.

27a: [α]$^{25}_D$ −7.8 (*c* 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.88−6.75 (m, 1H, MeC*H*=C(Me)C=O), 6.16−5.99 (m, 1H, CH$_2$=CHCH$_2$−), 5.15−5.02 (m, 3H, H-3-Glu*p*, CH$_2$=CHCH$_2$−), 4.99−4.92 (m, 2H, H-1-Glu*p*, H-4-Fuc*p*), 4.32 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 4.03 (dd, *J* = 9.2, 7.6 Hz, 1H, H-2-Fuc*p*), 3.95 (dd, *J* = 10.8, 5.2 Hz, 1H, H-6-Glu*p*), 3.85 (dd, *J* = 9.2, 4.0 Hz, 1H, H-3-Fuc*p*), 3.71 (t, *J* = 10.4 Hz, 1H, H-6-Glu*p*), 3.67−3.58 (m, 2H, H-5-Fuc*p*, −C*H*$_2$CHCH$_2$−), 3.57−3.50 (m, 2H, H-2-Glu*p*, H-4-Glu*p*), 3.30−3.21 (m, 1H, H-5-Glu*p*), 2.32 (t, *J* = 6.4 Hz, 2H), 2.11 (s, 3H, C*H*$_3$C=O), 1.82−1.75 (m, 6H, C*H*$_3$CHC(C*H*$_3$)C=O), 1.66−1.45 (m, 2H), 1.41 (s, 3H, (C*H*$_3$)$_2$C), 1.39−1.22 (m, 9H), 1.12 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.91−0.83 (m, 12H), 0.78 (s, 9H), 0.14 (s, 3H, C*H*$_3$Si), 0.09 (s, 3H, C*H*$_3$Si), 0.08 (s, 3H, C*H*$_3$Si), −0.01 (s, 3H, C*H*$_3$Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.9, 166.8, 136.9, 135.9,

128.7, 116.1, 101.0, 100.5, 99.3, 80.6, 74.9, 74.3, 74.2, 73.8, 73.3, 72.5, 68.8, 66.9, 62.5, 38.5, 34.3, 31.8, 28.9, 25.8 (×3), 25.8 (×3), 24.5, 22.6, 21.0, 18.8, 18.1, 17.6, 16.7, 14.3, 14.0, 12.1, −3.2, −4.0, −4.3, −5.3; IR (film) ν = 2930, 2859, 1743, 1728, 1653, 1200, 1066, 835, 777; HRMS (ESI) m/z calcd for $C_{43}H_{78}NaO_{12}Si_2$ [M + Na]$^+$ 865.4930, found 865.4929.

28a: $[\alpha]^{25}_D$ −19.3 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.92−6.75 (m, 1H, MeCH=C(Me)C=O), 6.09−5.93 (m, 1H, CH$_2$=CHCH_2−), 5.15−5.03 (m, 2H, CH_2=CHCH$_2$−), 5.02 (d, J = 7.6 Hz, 1H, H-1-Glu$p$), 4.98−4.91 (m, 2H, H-2-Glu$p$, H-4-Fuc$p$), 4.32 (d, J = 7.6 Hz, 1H, H-1-Fuc$p$), 3.95 (dd, J = 10.8, 5.2 Hz, 1H, H-6-Glu$p$), 3.86 (dd, J = 9.2, 7.6 Hz, 1H, H-2-Fuc$p$), 3.77 (t, J = 10.4 Hz, 1H, H-6-Glu$p$), 3.72 (d, J = 9.6, 3.6 Hz, 1H, H-3-Fuc$p$), 3.72−3.63 (m, 2H, H-5-Fuc$p$, −CH$_2$CHCH$_2$−), 3.61−3.51 (m, 2H, H-3-Glu$p$, H-4-Glu$p$), 3.25−3.16 (m, 1H, H-5-Glu$p$), 2.36 (t, J = 6.4 Hz, 2H), 2.09 (s, 3H, CH_3C=O), 1.85−1.76 (m, 6H, CH_3CHC(CH_3)C=O), 1.61−1.50 (m, 2H), 1.47 (s, 3H, (CH_3)$_2$C), 1.40 (s, 3H, (CH_3)$_2$C), 1.38−1.21 (m, 6H), 1.11 (d, J = 6.4 Hz, 3H, H-6-Fuc$p$), 0.88 (t, J = 6.8 Hz, 3H), 0.85 (s, 9H), 0.79 (s, 9H), 0.07 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si), −0.04 (s, 3H, CH_3Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.8, 166.0, 137.5, 135.5, 128.6, 116.4, 101.3, 99.7, 99.3, 80.0, 75.7, 75.3, 73.9, 73.8, 73.6, 73.4, 68.8, 67.2, 62.4, 38.3, 34.2, 31.9, 29.0, 25.8 (×3), 25.6 (×3), 24.6, 22.6, 20.9, 18.9, 18.1, 17.8, 16.5, 14.2, 14.1, 12.3, −4.2, −4.5, −4.6, −5.1; IR (film) ν = 2930, 2857, 1744, 1728, 1653, 1246, 1066, 835, 777.

Disaccharide 27b. Compound **27b** (298 mg crude product) was prepared by treating **26b** (343 mg, 0.47 mmol) with TBSOTf (0.43 mL, 1.9 mmol) and 2,6-lutidine (0.55 mL, 4.7 mmol) in distilled CH$_2$Cl$_2$ (5 mL) under the same conditions as described for the synthesis of **27a**. Attempts to obtain pure **27b** using column chromatography (silica, EtOAc−hexanes) were not successful. The crude product was used in the next step to obtain **29b**.

Diol 29a. CSA (199 mg, 0.86 mmol) was added in one portion to a solution of **27a** (3.61 g, 4.28 mmol) in MeOH (100 mL) at room temperature. The reaction mixture was stirred for 3 h, at which point TLC (silica, 1:3 EtOAc−hexanes) showed it was complete. The reaction was quenched with Et$_3$N (240 μL, 1.72 mmol) and concentrated. The residue was purified by column chromatography (silica, EtOAc−hexanes, 1:3 → 1:2) to give compound **29a** (3.26 g, 95%) as a white foam: $[\alpha]^{25}_D$ +19.1 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.00−6.85 (m, 1H, MeCH=C(Me)C=O), 6.07−5.94 (m, 1H, CH$_2$=CHCH_2−), 5.16−5.02 (m, 2H, CH_2=CHCH$_2$−), 5.01−4.88 (m, 3H, H-1-Glu$p$, H-3-Glu$p$, H-4-Fuc$p$), 4.31 (d, J = 7.6 Hz, 1H, H-1-Fuc$p$), 4.06 (t, J = 8.4 Hz, 1H, H-2-Fuc$p$), 3.91 (dd, J = 12.0, 3.6 Hz, 1H, H-6-Glu$p$), 3.85 (dd, J = 9.2, 3.6 Hz, 1H, H-3-Fuc$p$), 3.78 (dd, J = 12.0, 4.4 Hz, 1H, H-6-Glu$p$), 3.70−3.59 (m, 3H, H-4-Glu$p$, H-5-Fuc$p$, −CH$_2$CHCH$_2$−), 3.58−3.52 (m, 1H, H-2-Glu$p$), 3.41−3.33 (m, 1H, H-5-Glu$p$), 235−2.29 (m, 4H), 2.14 (s, 3H, CH_3C=O), 1.88−1.77 (m, 6H, CH_3CHC(CH_3)C=O), 1.69−1.50 (m, 2H), 1.43−1.21 (m, 6H), 1.14 (d, J = 6.4 Hz, 3H, H-6-Fuc$p$), 0.92−0.82 (m, 12H), 0.80 (s, 9H), 0.15 (s, 3H, CH_3Si), 0.11 (s, 6H, 2 × CH_3Si), 0.06 (d, J = 11.9 Hz, 3H, CH_3Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.9, 169.2, 138.7, 135.4, 128.2, 116.5, 101.2, 100.0, 80.7, 79.2, 75.2, 74.4, 73.8, 73.5, 73.3, 70.7, 68.9, 62.2, 38.5, 34.3, 31.8, 25.9 (×3), 25.8 (×3), 24.6, 22.6, 21.1, 18.1, 17.6, 16.7, 14.5, 14.1, 12.1, −3.0, −3.9, −4.2, −5.3; IR (film) ν = 3446, 2930, 2857, 1740, 1718, 1653, 1256, 1076, 839, 762; HRMS (ESI) m/z calcd for $C_{40}H_{74}NaO_{12}Si_2$ [M + Na]$^+$ 825.4617, found 825.4614.

Diol 29b. Compound **27b** (298 mg, crude product) was dissolved in a 70% solution of acetic acid and water (10 mL). The reaction mixture was stirred at 70 °C for 1 h, at which point TLC (silica, 1:3 EtOAc−hexanes) showed it was complete. The reaction was concentrated and then coevaporated with toluene (3 × 5 mL). The residue was purified by column chromatography (silica, EtOAc−hexanes, 1:3 → 1:2) and gave compound **29b** (165 mg, 44% over two steps) as a white foam: $[\alpha]^{25}_D$ +15.4 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.96−6.85 (m, 1H, Me−CH=C(Me)C=O), 5.90−5.79 (m, 1H, CH$_2$=CHCH_2−), 5.11−5.01 (m, 2H, CH_2=CHCH$_2$−), 5.01−4.90 (m, 3H, H-1-Glu$p$, H-3-Glu$p$, H-4-Fuc$p$), 4.31 (d, J = 7.6 Hz, 1H, H-1-Fuc$p$), 4.08 (t, J = 8.4 Hz, 1H, H-2-Fuc$p$),

3.88 (dd, J = 12.0, 3.6 Hz, 1H, H-6-Glu$p$), 3.85 (dd, J = 9.2, 3.6 Hz, 1H, H-3-Fuc$p$), 3.77 (dd, J = 12.0, 4.4 Hz, 1H, H-6-Glu$p$), 3.69−3.56 (m, 3H, H-4-Glu$p$, H-5-Fuc$p$, −CH$_2$CHCH$_2$−), 3.55−3.49 (m, 1H, H-2-Glu$p$), 3.40−3.31 (m, 1H, H-5-Glu$p$), 2.50−2.28 (m, 4H), 2.13 (s, 3H, CH_3C=O), 1.88−1.78 (m, 6H, CH_3CHC(CH_3)C=O), 1.60−1.46 (m, 2H), 1.40−1.22 (m, 6H), 1.14 (d, J = 6.4 Hz, 3H, H-6-Fuc$p$), 0.97−0.83 (m, 12H), 0.80 (s, 9H), 0.15 (s, 3H, CH_3Si), 0.11 (s, 6H, 2 × CH_3Si), 0.05 (d, J = 11.9 Hz, 3H, CH_3Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.9, 169.1, 138.6, 134.8 128.2, 116.9, 101.6, 100.0, 81.5, 79.2, 75.3, 74.4, 73.9, 73.4, 73.3, 70.8, 68.8, 62.1, 39.6, 33.9 32.1, 25.8 (×3), 25.8 (×3), 25.3, 22.7, 21.0, 18.1, 17.6, 16.7, 14.4, 14.0, 12.0, −3.0, −3.9, −4.2, −5.2.

Diene 9a. DCC (853 mg, 4.14 mmol) was added in one portion to a 0 °C CH$_2$Cl$_2$ (200 mL) solution of **29a** (3.02 g, 3.76 mmol), 4-oxonon-8-eneoic acid **8**,[19] (703 mg, 4.14 mmol) and 4-(dimethylamino)pyridine (46 mg, 0.38 mmol). The reaction was allowed to warm to ambient temperature and stirred overnight. At this point, TLC (silica, 1:3 EtOAc−hexanes) showed the reaction was complete. The reaction mixture was diluted with ether (100 mL) and hexanes (40 mL), stirred for 20 min, and then filtered through a pad of Celite using ether (50 mL) as the eluent, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica, EtOAc−hexanes, 1:6) to give diene **9a** (2.51 g, 70%) as a colorless syrup: $[\alpha]^{25}_D$ +9.2 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.97−6.90 (m, 1H, Me−CHC(Me)C=O), 6.24−6.04 (m, 1H, CH$_2$=CHCH_2−), 5.82−5.70 (m, 1H, CH$_2$=CHCH_2−), 5.20−4.88 (m, 7H, 2 × CH$_2$=CHCH$_2$−, H-1-Glu$p$, H-3-Glu$p$, H-4-Fuc$p$), 4.43 (dd, J = 12.0, 4.4 Hz, 1H, H-6-Glu$p$), 4.37 (d, J = 8.0 Hz, 1H, H-1-Fuc$p$), 4.34−4.28 (dd, J = 12.0, 2.0 Hz, 1H, H-6-Glu$p$), 4.06 (t, J = 9.2, 7.6 Hz, 1H, H-2-Fuc$p$), 3.89 (dd, J = 9.2, 3.6 Hz, 1H, H-3-Fuc$p$), 3.68−3.47 (m, 4H, H-2-Glu$p$, H-4-Glu$p$, H-5-Fuc$p$, −CH$_2$CHCH$_2$−), 3.46−3.39 (m, 1H, H-5-Glu$p$), 2.94 (d, J = 4.8 Hz, 1H, OH), 2.87−2.49 (m, 4H), 2.49−2.42 (m, 2H), 2.31 (t, J = 6.0 Hz, 2H), 2.13 (s, 3H, CH_3C=O), 2.09−2.00 (m, 2H), 1.88−1.77 (m, 6H, CH_3CHC(CH_3)C=O), 1.74−1.47 (m, 4H), 1.42−1.19 (m, 6H), 1.14 (d, J = 6.4 Hz, 3H, H-6-Fuc$p$), 0.92−0.82 (m, 12H), 0.80 (s, 9H), 0.13 (s, 3H, CH_3Si), 0.08 (s, 6H, 2 × CH_3Si), 0.02 (s, 3H, CH_3Si); ^{13}C NMR (101 MHz, CDCl$_3$) δ 208.6, 173.2, 170.9, 168.9, 138.5, 137.8, 136.1, 128.2, 116.2, 115.3, 100.8, 99.9, 80.8, 78.6, 74.1, 74.0, 73.8, 73.7, 73.4, 70.1, 68.9, 63.3, 41.8, 38.6, 37.1, 34.4, 33.0, 31.9, 27.7, 25.8 (×3), 25.8 (×3), 24.5, 22.7, 22.6, 21.0, 18.1, 17.6, 16.7, 14.4, 14.1, 12.0, −3.2, −4.0, −4.3, −5.3; IR (film) ν = 3482, 2930, 2857, 1736, 1717, 1653, 1641, 1257, 1074, 839, 762; HRMS (ESI) m/z calcd for $C_{49}H_{86}NaO_{14}Si_2$ [M + Na]$^+$ 977.5454, found 977.5444.

Diene 9b. Compound **9b** (110 mg, 55%, colorless syrup) was prepared by treating **29b** (176 mg, 0.22 mmol) with 4-oxonon-8-eneoic acid **8**[19] (41.0 mg, 0.241 mmol) and 4-(dimethylamino)-pyridine (2.5 mg, 0.022 mmol) in distilled CH$_2$Cl$_2$ (10 mL) under the same conditions as described for the synthesis of **9a**: $[\alpha]^{25}_D$ +4.2 (c 1 CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.00−6.89 (m, 1H, MeCHC(Me)C=O), 5.95−5.69 (m, 2H, 2 × CH$_2$=CHCH$_2$−), 5.12−4.89 (m, 7H, 2 × CH$_2$=CHCH$_2$−, H-1-Glu$p$, H-3-Glu$p$, H-4-Fuc$p$), 4.41 (dd, J = 12.0, 4.4 Hz, 1H, H-6-Glu$p$), 4.39 (d, J = 8.0 Hz, 1H, H-1-Fuc$p$), 4.35−4.33 (dd, J = 12.0, 2.0 Hz, 1H, H-6-Glu$p$), 4.08 (t, J = 9.2, 7.6 Hz, 1H, H-2-Fuc$p$), 3.90 (dd, J = 9.2, 3.6 Hz, 1H, H-3-Fuc$p$), 3.70−3.49 (m, 4H, H-2-Glu$p$, H-4-Glu$p$, H-5-Fuc$p$, −CH$_2$CHCH$_2$−), 3.48−3.40 (m, 1H, H-5-Glu$p$), 2.94 (d, J = 4.8 Hz, 1H, OH), 2.82−2.55 (m, 4H), 2.52−2.41 (m, 2H), 2.38 (t, J = 6.0 Hz, 2H), 2.13 (s, 3H, CH_3C=O), 2.11−2.01 (m, 2H), 1.89−1.77 (m, 6H, CH_3CHC(CH_3)C=O), 1.76−1.65 (m, 4H), 1.42−1.21 (m, 6H), 1.14 (d, J = 6.4 Hz, 3H, H-6-Fuc$p$), 0.97−0.85 (m, 12H), 0.80 (s, 9H), 0.15 (s, 3H, CH_3Si), 0.11 (s, 6H, 2 × CH_3Si), 0.04 (s, 3H, CH_3Si); ^{13}C NMR (75 MHz, CDCl$_3$) δ 208.7, 173.1, 171.0, 169.1, 138.7, 137.9, 135.0, 128.2, 116.9, 115.3, 101.1, 100.0, 81.0, 79.0, 74.3, 73.9, 73.8, 73.4, 70.4, 68.8, 63.6, 41.8, 39.6, 37.1, 33.8, 33.0, 32.3, 27.7, 25.8 (×3), 25.8 (×3), 25.3, 22.9, 22.7, 21.1, 18.1, 17.6, 16.7, 14.5, 14.3, 12.0, −3.1, −3.9, −4.2, −5.1.

RCM/Hydrogenation Product 10a. To a solution of diene **9a** (2.25 g, 2.36 mmol) in CH$_2$Cl$_2$ (500 mL) was added Hoveyda−Grubbs second generation catalyst[26,27] (148 mg, 0.24 mmol) in one portion at

room temperature. The reaction mixture was refluxed for 4 h. At this point, TLC (silica, 1:2 EtOAc−hexanes) showed the reaction was complete. The reaction was cooled to ambient temperature and then concentrated. Flash chromatography (silica, EtOAc−hexanes, 1:4 → 1:2) gave isomer **30a** (1.92 g, 88%) as a white foam which was not fully characterized. To a solution of **30a** (715 mg, 0.771 mmol) in EtOH (4 mL) was added Wilkinson's catalyst (143 mg, 0.154 mmol) in one portion at room temperature. The reaction was then stirred under an atmosphere of hydrogen (1 atm) overnight. At this point, TLC (silica, 1:2 EtOAc−hexanes) showed the reaction was complete. The reaction mixture was filtered through a pad of Celite using EtOAc (5 mL) as the eluent and the resulting filtrate concentrated. Flash chromatography (silica, EtOAc−hexanes, 1:5 → 1:3) gave **10a** (565 mg, 79%) as a colorless syrup: $[\alpha]^{25}_D$ +17.3 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.98−6.90 (m, 1H, MeCHC(Me)C=O), 5.08−4.92 (m, 3H, H-1-Glu*p*, H-3-Glu*p*, H-4-Fuc*p*), 4.75 (m, 1H, H-6-Glu*p*), 4.38 (br, 1H, H-1-Fuc*p*), 4.04−4.34 (m, 2H, H-6-Glu*p*, H-2-Fuc*p*), 3.99−3.89 (m, 1H, H-3-Fuc*p*), 3.73−3.65 (m, 1H, H-5-Fuc*p*), 3.57 (br, 1H, H-5-Glu*p*), 3.51−3.33 (m, 3H, H-2-Glu*p*, H-4-Glu*p*, −CH$_2$CHCH$_2$−), 3.13−3.06 (m, 1H, OH), 3.01−2.84 (m, 1H), 2.75−2.56 (m, 3H), 2.52−2.41 (m, 1H), 2.36−2.24 (m, 1H), 2.11 (s, 3H, CH$_3$C=O), 1.87−1.80 (m, 6H, CH$_3$CHC(CH$_3$)C=O), 1.78−1.49 (m, 6H), 1.47−1.20 (m, 12H), 1.13 (d, J = 6.4 Hz, 3H, H-6-Fuc*p*), 0.91−0.84 (m, 12H), 0.82 (s, 9H), 0.16 (s, 3H, CH$_3$Si), 0.11 (s, 3H, CH$_3$Si), 0.10 (s, 3H, CH$_3$Si), 0.01 (s, 3H, CH$_3$Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 210.3, 172.4, 170.9, 168.0, 137.8, 128.5, 100.7, 100.2, 78.0, 74.5, 74.0, 73.9, 73.7, 69.0, 68.7, 63.3, 41.8, 37.1, 34.9, 33.5, 32.0, 29.6, 29.1, 28.5, 28.3, 25.9, 25.8 (×6), 25.2, 24.5, 23.4, 22.6, 20.9, 18.0, 17.6, 16.6, 14.4, 14.0, 12.0, −3.3, −4.0, −4.3, −5.1; IR (film) ν = 3476, 2928, 2857, 1740, 1717, 1246, 1070, 837, 777; HRMS (ESI) *m/z* calcd for C$_{47}$H$_{84}$NaO$_{14}$Si$_2$ [M + Na]$^+$ 951.5297, found 951.5288.

RCM/Hydrogenation Product 10b. Compound **30b** (93 mg, 87%, white foam) was prepared by treating **9b** (110 mg, 0.12 mmol) with Hoveyda−Grubbs second generation catalyst[26,27] (7.2 mg, 0.011 mmol) in distilled CH$_2$Cl$_2$ (40 mL) under the same conditions as described for the synthesis of **30a**. Compound **10b** (36.1 mg, 70%, colorless syrup) was prepared by treating **30b** (51.4 mg, 0.055 mmol) with Wilkinson's catalyst (22 mg, 0.024 mmol) in EtOH (2 mL) under the same conditions as described for the synthesis of **10a**: $[\alpha]^{25}_D$ +18.0 (c 1 CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.00−6.89 (m, 1H, MeCHC(Me)C=O), 5.03−4.85 (m, 3H, H-1-Glu*p*, H-3-Glu*p*, H-4-Fuc*p*), 4.51 (m, 1H, H-6-Glu*p*), 4.47 (br, 1H, H-1-Fuc*p*), 4.35−4.21 (m, 2H, H-6-Glu*p*, H-2-Fuc*p*), 3.99−3.89 (m, 1H, H-3-Fuc*p*), 3.72−3.61 (m, 1H, H-5-Fuc*p*), 3.59 (br, 1H, H-5-Glu*p*), 3.51−3.40 (m, 3H, H-2-Glu*p*, H-4-Glu*p*, −CH$_2$CHCH$_2$−), 3.08−2.95 (m, 1H, OH), 2.95−2.89 (m, 1H), 2.78−2.60 (m, 3H), 2.60−2.48 (m, 1H), 2.38−2.27 (m, 1H), 2.12 (s, 3H, CH$_3$C=O), 1.89−1.78 (m, 6H, CH$_3$CHC(CH$_3$)C=O), 1.75−1.51 (m, 6H), 1.49−1.21 (m, 12H), 1.12 (d, J = 6.4 Hz, 3H, H-6-Fuc*p*), 0.95−0.86 (m, 12H), 0.79 (s, 9H), 0.16 (s, 3H, CH$_3$Si), 0.12 (s, 3H, CH$_3$Si), 0.11 (s, 3H, CH$_3$Si), 0.05 (s, 3H, CH$_3$Si); ^{13}C NMR (75 MHz, CDCl$_3$) δ 210.1, 172.5, 170.9, 169.4, 138.9, 128.1, 99.8, 100.2, 79.4, 74.3, 74.1, 73.8, 73.5, 61.1, 68.7, 63.8, 41.7, 37.2, 33.3, 32.8, 32.3, 28.8, 27.0, 26.7, 26.0, 25.9 (×6), 24.9, 23.0, 22.7, 22.6, 21.1, 18.1, 17.7, 16.6, 14.5, 14.2, 12.0, −3.3, −3.9, −4.3, −5.2.

Compound 31a. Method 1. To a cold (0 °C) solution of compound **10a** (47.4 mg, 0.051 mmol) and DMAP (12.5 mg, 0.102 mmol) in pyridine (3 mL) was added cinnamoyl chloride (34.0 mg, 0.204 mmol). The reaction mixture was allowed to warm to ambient temperature and stirred for 24 h. At the end of this time, TLC (silica, 1:2 EtOAc−hexanes) indicated that the reaction was complete. The reaction was quenched with MeOH (20 μL) diluted with CH$_2$Cl$_2$ (20 mL), washed with 1 M HCl (20 mL) and saturated aqueous NaHCO$_3$ (20 mL), and dried (Na$_2$SO$_4$). The solvent was evaporated under vacuum, and the residue was purified by column chromatography (silica, EtOAc−hexanes, 1:6) to afford compound **31a** (43 mg, 80%) as a white foam.

Method 2. Cinnamic acid (14.3 mg, 0.097 mmol) was added in one portion to a solution of compound **10a** (60 mg, 0.065 mmol), DCC (20.0 mg, 0.097 mmol), and DMAP (1.6 mg, 0.013 mmol) in CH$_2$Cl$_2$

(2 mL). The reaction mixture was stirred at room temperature overnight. At this point, TLC (silica, 1:3 EtOAc−hexanes) showed the reaction was complete. The reaction mixture was diluted with ether (2 mL) and hexanes (1 mL), stirred for 20 min, and then filtered through a pad of Celite using ether (3 mL) as the eluent and the filtrate concentrated in vacuo. The residue was purified by column chromatography (silica, EtOAc−hexanes, 1:4) to give compound **31a** (60.2 mg, 88%) as a colorless syrup. **31a**: $[\alpha]^{25}_D$ −40.6 (c 1 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63 (d, J = 16.0 Hz, 1H, PhCH=C−), 7.55−7.46 (m, 2H, 2 × ArH), 7.41−7.33 (m, 3H, 3 × ArH), 6.87−6.72 (m, 1H, MeCHC(Me)C=O), 6.35 (d, J = 16.0 Hz, 1H, PhCH=CH−), 5.25 (t, J = 9.2 Hz, 1H, H-3-Glu*p*), 5.13−4.95 (m, 3H, H-1-Glu*p*, H-4-Fuc*p*), 4.61 (br, 1H, H-1-Fuc*p*), 4.30−4.22 (m, 1H, H-6-Glu*p*), 4.21−4.14 (m, 1H, H-6-Glu*p*), 4.10−4.01 (m, 1H, H-3-Fuc*p*), 4.00−3.91 (m, 1H, H-2-Fuc*p*), 3.80−3.66 (m, 3H, H-5-Glu*p*, H-5-Fuc*p*, −CH$_2$CHCH$_2$−), 3.60 (dd, J = 8.8, 7.6 Hz, 1H, H-2-Glu*p*), 2.84−2.70 (m, 2H), 2.65−2.34 (m, 4H), 2.13 (s, 3H, CH$_3$C=O), 1.80−1.61 (m, 9H), 1.60−1.49 (m, 3H), 1.47−1.20 (m, 12H), 1.13 (d, J = 6.4 Hz, 3H, H-6-Fuc*p*), 0.94−0.84 (m, 12H), 0.81 (s, 9H), 0.20 (s, 3H, CH$_3$Si), 0.12 (s, 3H, CH$_3$Si), 0.11 (s, 3H, CH$_3$Si), 0.01 (s, 3H, CH$_3$Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 209.1, 172.0, 171.0, 166.9, 165.6, 146.0, 138.0, 134.1, 130.5, 128.8 (×2), 128.2 (×2), 128.1, 116.8, 99.8, 99.8, 75.2, 73.9, 73.8, 71.2, 69.7, 68.8, 41.7, 36.9, 34.3, 32.0, 28.5, 27.9, 27.4, 25.8 (×3), 25.7 (×3), 24.5, 24.4, 23.3, 22.6, 21.0, 18.0, 17.8, 16.5, 14.4, 14.1, 12.0, −3.7, −3.9, −4.5, −5.2; IR (film) ν = 2928, 2857, 1736, 1719, 1638, 1248, 1067, 837, 777; HRMS (MALDI) *m/z* calcd for C$_{56}$H$_{90}$NaO$_{15}$Si$_2$ [M + Na]$^+$ 1081.5716, found 1081.5717.

Compound 31b. Compound **31b** (27.5 mg, 86%, white foam) was prepared by treating **10b** (28.1 mg, 0.030 mmol) with DMAP (9.0 mg, 0.060 mmol) and cinnamoyl chloride (20.1 mg, 0.120 mmol) in pyridine (2 mL) under the same conditions as described for the synthesis of **31a** (method 1): $[\alpha]^{25}_D$ −1.8 (c 0.5 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (d, J = 16.0 Hz, 1H, PhCH=C−), 7.54−7.47 (m, 2H, 2 × ArH), 7.44−7.35 (m, 3H, 3 × ArH), 6.85−6.75 (m, 1H, MeCHC(Me)C=O), 6.33 (d, J = 16.0 Hz, 1H, PhCH=CH−), 5.25 (t, J = 9.2 Hz, 1H, H-3-Glu*p*), 5.09−4.93 (m, 3H, H-1-Glu*p*, H-4-Fuc*p*), 4.51 (br, 1H, H-1-Fuc*p*), 4.34−4.27 (m, 1H, H-6-Glu*p*), 4.20−4.11 (m, 1H, H-6-Glu*p*), 4.06−4.00 (m, 1H, H-3-Fuc*p*), 3.99−3.92 (m, 1H, H-2-Fuc*p*), 3.78−3.70 (m, 3H, H-5-Glu*p*, H-5-Fuc*p*, −CH$_2$CHCH$_2$−), 3.66 (dd, J = 8.8, 7.6 Hz, 1H, H-2-Glu*p*), 3.01−2.70 (m, 2H), 2.78−2.46 (m, 4H), 2.12 (s, 3H, CH$_3$C=O), 1.76−1.70 (m, 9H), 1.70−1.55 (m, 3H), 1.46−1.22 (m, 12H), 1.12 (d, J = 6.4 Hz, 3H, H-6-Fuc*p*), 0.99−0.84 (m, 12H), 0.80 (s, 9H), 0.20 (s, 3H, CH$_3$Si), 0.13 (s, 3H, CH$_3$Si), 0.12 (s, 3H, CH$_3$Si), 0.03 (s, 3H, CH$_3$Si); ^{13}C NMR (100 MHz, CDCl$_3$) δ 210.1, 172.1, 170.9, 167.0, 165.8, 146.3, 138.0, 134.1, 130.6, 128.9 (×2), 128.3 (×2), 128.2, 116.7, 100.1, 100.0, 75.0, 74.0, 73.8, 71.6, 70.1, 68.6, 41.7, 37.1, 33.8, 31.9, 28.8, 27.9, 27.4, 25.9 (×3), 25.8 (×3), 24.9, 24.7, 23.0, 22.7, 21.1, 18.1, 17.7, 16.6, 14.4, 14.1, 11.9, −3.5, −3.9, −4.3, −5.3.

Ipomoeassin F.[7,10,11] Method 1. To a solution of **31a** (34 mg, 0.032 mmol) in THF (3 mL) and MeOH (1 mL) were added AcOH (367 μL, 6.42 mmol) and TBAF (1 M solution in THF, 3.21 mL, 3.21 mmol) at 0 °C. The reaction was allowed to warm to ambient temperature and stirred for 48 h. At this point, TLC (silica, 1:1 EtOAc−hexanes) showed the reaction was complete. The reaction mixture was diluted with Et$_2$O (30 mL) and washed with 1 M HCl (15 mL), saturated aqueous NaHCO$_3$ (15 mL), and brine (15 mL). The aqueous layer was extracted with Et$_2$O (30 mL). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica, EtOAc−hexanes, 1:2 → 1:1) to give ipomoeassin F (23.3 mg, 88%) as a white film.

Method 2. To a solution of **31a** (58 mg, 0.055 mmol) in THF (4 mL) was added TBAF (1 M solution in THF, 0.27 mL, 0.27 mmol) at −10 °C. The reaction mixture was stirred at the same temperature for 4 h at which point TLC (silica, 1:1 EtOAc−hexanes) showed the reaction was complete. The reaction mixture was diluted with Et$_2$O (40 mL) and washed with 1 M HCl (20 mL), saturated NaHCO$_3$ (20 mL), and brine (10 mL). The aqueous layer was extracted with Et$_2$O

(40 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica, EtOAc−hexanes, 1:2 → 1:1) to give compound ipomoeassin F (37.3 mg, 82%) as a white foam: $[\alpha]^{25}_D$ −62.4 (c 0.5 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 16.0 Hz, 1H, PhC*H*=C−), 7.53−7.47 (m, 2H, 2 × Ar*H*), 7.43−7.34 (m, 3H, 3 × Ar*H*), 6.93−6.85 (m, 1H, MeC*H*C(Me)C=O), 6.35 (d, J = 16.0 Hz, 1H, PhCH=C*H*−), 5.32 (t, J = 9.6 Hz, 1H, H-4-Glu*p*), 5.18−5.10 (m, 2H, H-3-Glu*p*, H-4-Fuc*p*), 4.62 (d, J = 8.0 Hz, 1H, H-1-Glu*p*), 4.58 (br, 1H, O*H*), 4.47 (dd, J = 12.4, 3.6 Hz, 1H, H-6-Glu*p*), 4.41 (d, J = 7.6 Hz, 1H, H-1-Fuc*p*), 4.15 (dd, J = 12.4, 2.4 Hz, 1H, H-6-Glu*p*), 3.96−3.87 (m, 2H, O*H*, H-3-Fuc*p*), 3.80−3.74 (m, 1H, H-5-Glu*p*), 3.73−3.57 (m, 4H, H-2-Glu*p*, H-2-Fuc*p*, H-5-Fuc*p*, −CH₂CHCH₂−), 2.85−2.38 (m, 6H), 2.18 (s, 3H, C*H₃*C=O), 1.80−1.72 (m, 6H, C*H₃*CHC(C*H₃*)C=O), 1.71−1.61 (m, 2H), 1.58−1.46 (m, 4H), 1.41−1.21 (m, 12H), 1.20 (t, J = 6.4 Hz, 3H, H-6-Fuc*p*), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 171.8, 171.7, 168.8, 165.4, 146.1, 139.8, 134.0, 130.6, 128.9 (×2), 128.3 (×2), 127.5, 116.7, 105.7, 100.2, 82.8, 79.7, 75.8, 73.9, 72.7, 72.6, 72.4, 68.8, 67.4, 61.8, 41.8, 37.6, 34.3, 33.1, 31.9, 29.1, 29.0, 28.3, 24.7, 24.5, 23.5, 22.6, 20.9, 16.3, 14.6, 14.1, 12.0; HRMS (MALDI) m/z calcd for $C_{44}H_{62}NaO_{15}$ $[M + Na]^+$ 853.3986, found 853.3984. The ^1H, ^{13}C NMR data were in accordance with the literature.[11] HPLC (96.7%; $MeCN/H_2O$ 1:9, 0−5 min; increase to 9:1 over 20 min, 5−25 min; 9:1, 25−35 min; finally return to 1:9 in 1 min, 35−36 min; 1 mL/ min, t_R = 30.4 min).

11R-Epimer. 11R-Epimer (12.0 mg, 77%, white foam) was prepared by treating **31b** (20.0 mg, 0.019 mmol) with TBAF (1 M solution in THF, 0.11 mL, 0.113 mmol) in THF (2 mL) under the same conditions as described for the synthesis of ipomoeassin F (method 2): $[\alpha]^{25}_D$ −17.0 (c 1.0 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 16.0 Hz, 1H, PhC*H*=C−), 7.55−7.48 (m, 2H, 2 × Ar*H*), 7.43−7.35 (m, 3H, 3 × Ar*H*), 6.93−6.84 (m, 1H, MeC*H*C(Me)C=O), 6.38 (d, J = 16.0 Hz, 1H, PhCH= C*H*−), 5.23 (t, J = 9.6 Hz, 1H, H-4-Glu*p*), 5.20−5.16 (m, 2H, H-3-Glu*p*, H-4-Fuc*p*), 4.67 (d, J = 8.0 Hz, 1H, H-1-Glu*p*), 4.22 (br, 1H, O*H*), 4.49 (dd, J = 12.4, 3.6 Hz, 1H, H-6-Glu*p*), 4.46 (d, J = 7.6 Hz, 1H, H-1-Fuc*p*), 4.16 (dd, J = 12.4, 2.4 Hz, 1H, H-6-Glu*p*), 3.95−3.86 (m, 2H, O*H*, H-3-Fuc*p*), 3.85−3.81 (m, 1H, H-5-Glu*p*), 3.81−3.66 (m, 4H, H-2-Glu*p*, H-2-Fuc*p*, H-5-Fuc*p*, −CH₂CHCH₂−), 3.00−2.91 (m, 1H), 2.75−2.42 (m, 5H) 2.20 (s, 3H, C*H₃*C=O), 1.80−1.75 (m, 6H, C*H₃*CH−C(C*H₃*)C=O), 1.75−1.70 (m, 2H), 1.70−1.52 (m, 4H), 1.51−1.20 (m, 12H), 1.19 (t, J = 6.4 Hz, 3H, H-6-Fuc*p*), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 171.8, 171.5, 168.2, 165.6, 146.2, 139.1, 134.0, 130.7, 129.0 (×2), 128.3 (×2), 127.8, 116.7, 103.1, 98.0, 78.5, 77.5, 76.0, 74.6, 72.7, 72.2, 71.8, 69.2, 68.6, 62.5, 42.0, 37.4, 33.2, 32.6, 32.1, 29.7, 28.8, 28.1, 27.4, 24.7, 23.5, 23.1, 22.6, 21.0, 16.3, 14.5, 14.1, 12.0; IR (film) ν = 3422, 2930, 2859, 1736, 1717, 1653, 1636, 1248, 1155, 1072; HRMS (ESI) m/z calcd for $C_{44}H_{62}NaO_{15}$ $[M + Na]^+$ 853.3986, found 853.3986; HPLC (95.3%; $MeCN/H_2O$ 3:1; 1 mL/min, t_R = 17.1 min).

Biology. *MTT Cytotoxicity Assay.* Ipomoeassin F and its analogues were tested for cytotoxicity by using the MTT assay. The compounds were dissolved in DMSO to make drug stocks. The stock solutions were diluted with a DMEM or RPMI medium (according to the cell type) to make fresh working solutions at varying concentrations right before each test. Experiments were done in triplicate. First, 100 μL of cell suspension at a density of 50000 cells/mL was seeded in a 96-well plate (5,000 cells/well), which was incubated at 37 °C in 5% CO_2 for 24 h. Subsequently, the cells were treated with a compound at various concentrations in a total volume of 200 μL/well for 72 h. After 72 h, the media were discarded, and 200 μL of fresh medium containing 10% of MTT stock solution (5 mg/mL) was added to each well. The plate was then incubated at 37 °C in 5% CO_2 for another 3 h. Next, 180 μL of the medium was discarded from each well. The formed formazan crystals were dissolved with 180 μL of DMSO. An absorbance of formazan was detected by a microplate reader (BioTek Synergy H1) at 570 nm with 650 nm as the reference wavelength. The percentage of viability compared to the negative control (DMSO-treated cells) was determined. The GraphPad Prism 6 software was

used to make a plot of % viability versus sample concentration and to calculate the concentration at which a compound exhibited 50% cytotoxicity (IC_{50}).

Cell Cycle. Cell cycle analysis was performed with flow cytometry. Briefly, ipomoeassin F in DMSO was added to the exponentially growing U937 cells (cultured in RPMI-1640 medium with 10% fetal bovine serum) at a final concentration of 90 nM. For control, the cells were treated with an equivalent amount of DMSO. After 48 h of incubation of the cells with ipomoeassin F (or DMSO for control) at 37 °C in a CO_2 incubator, the cells were harvested, washed twice with PBS, and fixed with 70% ice-cold ethanol at 4 °C overnight. The fixed cells were washed twice with PBS and incubated with 100 μg/mL of DNase-free RNase in PBS at 37 °C for 30 min. The cells were then stained with PI at a final concentration of 50 μg/mL, and the stained cells were kept at 4 °C before analysis. The fluorescence of the cells was measured with flow cytometry (Guava easyCyte HT system; EMD Millipore, Billerica, MA). Ten thousand events were recorded for each measurement. The cell cycle data were analyzed with software WinMDI (Version 2.8).

Cell Apoptosis Analysis. Cell apoptosis was analyzed by flow cytometry using annexin V-CF488A conjugate according to the procedures described by the manufacturer (Biotium, Hayward, CA). Briefly, U937 cells were treated with ipomoeassin F or DMSO as described for the cell cycle analysis. Forty-eight hours after treatment, the cells were harvested, washed twice with PBS, and resuspended in a binding buffer (10 mM Hepes, pH 7.4, 140 mM NaCl, and 2.5 mM $CaCl_2$) at a concentration of 2×10^6 cells/mL. An aliquot of 100 μL of the resuspended cells was incubated with annexin V-CF488 conjugate at a final concentration of 0.25 μg/mL at room temperature for 15 min in the dark, followed by addition of 400 μL of the binding buffer to each sample. The cells were further stained with PI at a final concentration of 0.5 μg/mL and immediately analyzed by flow cytometry (Guava easyCyte HT system; EMD Millipore, Billerica, MA). The apoptosis data were analyzed with software GuavaSoft 2.6.

DNA Fragmentation Analysis. DNA fragmentation was used to determine apoptosis induction by observing biochemical changes of DNA in cells. In brief, 1 mL of cells were cultured in each well of a 6-well tissue culture plate at the density of 1×10^6 cell/mL for 24 h, and then treated with 1 mL of Ipomoeassin F at the final concentration of its IC_{90} (100 nM in the total volume of 2 mL). Staurosporine (1 μM) was used as the positive control. After 72 h, the cells were collected and washed with PBS. Then the cell suspension was transferred to a 1.5 mL microcentrifuge tube and centrifuged at 300 × g for 5 min to collect the cell pellet. The DNA in the cell pellet was extracted using AccuPrep Genomic DNA Extraction Kit from Bioneer (cataloge No. K-3032) and 2 μg of DNA was analyzed by electrophoresis on 1.8%w/ v agarose gel containing 0.75%w/v ethidium bromide. Gel electrophoresis was run at 250 V for 1 min to push the DNA inside Agarose gel followed by 23 V for an additional 4 h to separate DNA fragments. The images were acquired with the Molecular Imager ChemiDoc XRS System using the software Quantity One (Bio-Rad, Hercules, CA).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01765.

> ^1H and ^{13}C NMR spectra of all synthesized compounds (COSY, HSQC, HMBC NMR, and HRMS for representative compounds) (PDF)

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Notes

The authors declare no competing financial interest.

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