Supporting Information for:

Ring-Expansion Leads to A More Potent Analogue of Ipomoeassin F

Guanghui Zong,[a,†] Zhijian Hu,[b,†] Kwabena Baffour Duah,[c] Lauren E. Andrews,[c] Jianhong Zhou,[d] Sarah O'Keefe,[e] Lucas Whisenhunt,[f] Joong Sup Shim,[g] Yuchun Du,[d] Stephen High,[e] and Wei Q. Shi[c,*]

[a] Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States

[b] Angion Biomedica Corp., 51 Charles Lindbergh Blvd, Uniondale, NY 11553, USA

[c] Department of Chemistry, Ball State University, Muncie, Indiana 47306, USA

[d] Department of Biological Sciences, University of Arkansas, Fayetteville, Arkansas 72701, USA

[e] School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, M13 9PT, United Kingdom.

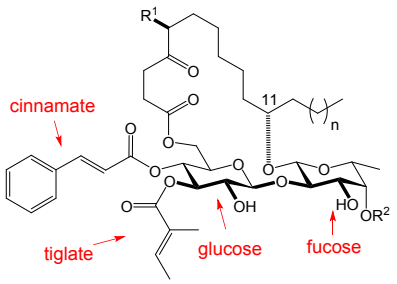
[f] Thermo Fisher Scientific, 6173 E. Old Marion Hwy., Florence, SC 29501, USA

[g] Faculty of Health Sciences, University of Macau, Avenida da Universidade, 999078, Taipa, Macau SAR, China

† Equal contribution as first-author

* Corresponding author, E-mail: wqshi@bsu.edu.

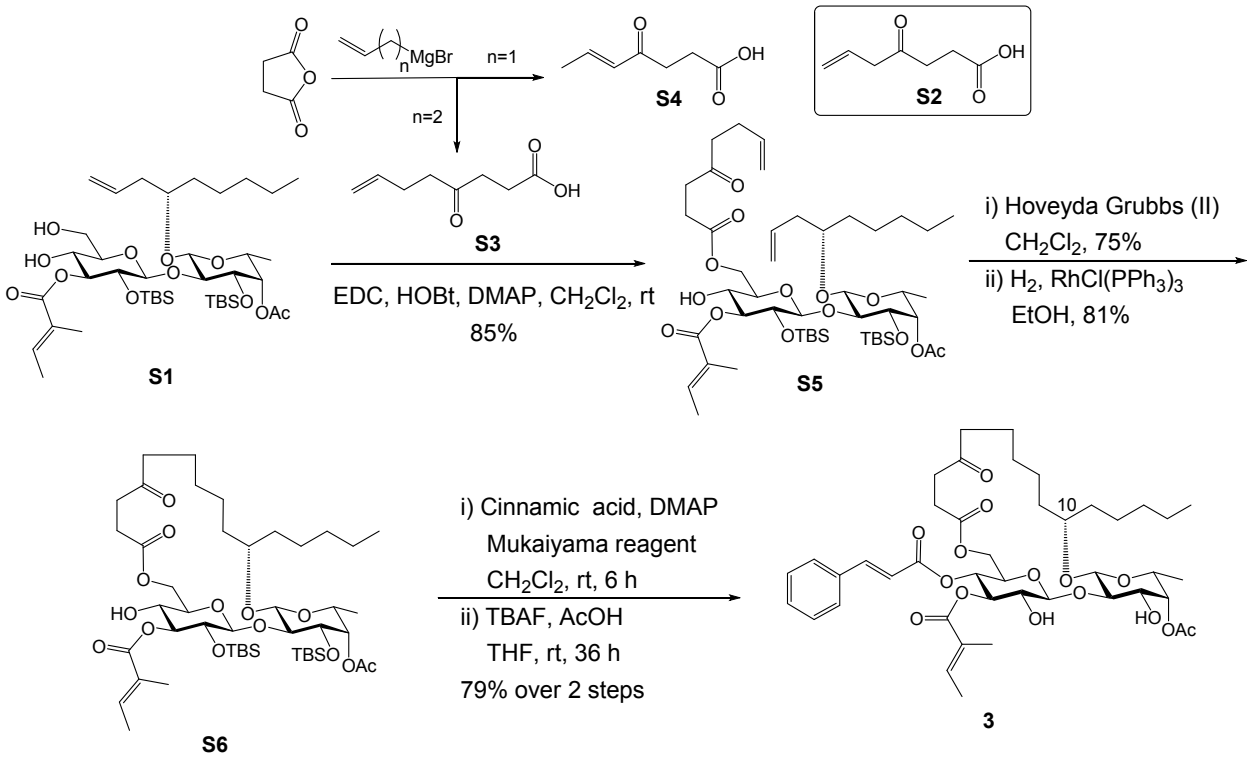
Table of Contents



Ipomoeassin	Structure		
	R^1	R^2	n
A	H	Ac	1
B	H	H	1
C	OH	Ac	1
D	OAc	Ac	1
E	OAc	H	1
F	H	Ac	3

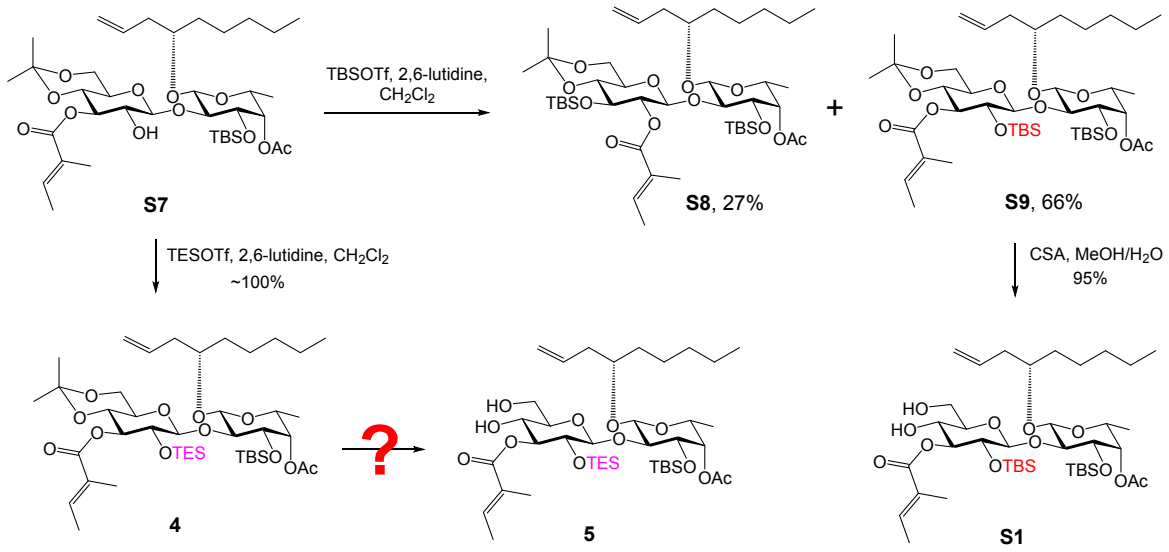
Figure S1. Structures of ipomoeassins A–F.

Scheme S1. Synthesis of 19-Membered Ring Analogue 3.



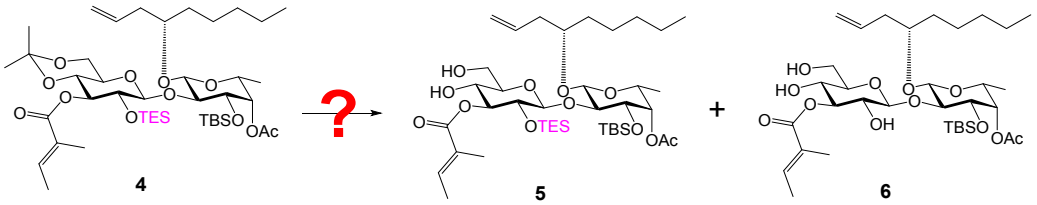
Initially, we thought that the 18-membered ring analogue **1** could be easily obtained by coupling **S1** with 4-oxo-6-heptenoic acid **S2**. After a literature search, however, we realized that the reaction of succinic anhydride with allylmagnesium bromide would cause alkene migration, leading to (*E*)-4-oxo-5-heptenoic acid **S4** (see the inset, Scheme S1) due to the acidic α-Hs of the carbonyl group and higher stability of internal vs. terminal alkenes. This was confirmed by our initial attempts. Therefore, we revised our plan to synthesize the 19-membered ring analogue **3** (Figure 1) instead. As expected, 4-oxo-7-octenoic acid **S3** was successfully prepared from succinic anhydride and 3-butenylmagnesium bromide. EDC-mediated esterification installed the acid **S3** onto the primary alcohol in **S1** to generate the diene **S5** in good yield. Subsequent ring-closing metathesis (RCM), followed by chemo-selective hydrogenation catalyzed by Wilkinson's catalyst, successfully produced the 19-membered ring alcohol precursor **S6**. After cinnamic acid was introduced to 4-OH-Glc*p* (glucopyranose), both TBS protecting groups were removed by tetra-*n*-butylammonium fluoride (TBAF) buffered with acetic acid to deliver the final 19-membered ring analogue **3**.

Scheme S2. Syntheses of Diol Intermediates S1 and 5.



Although the desired TBS-protected compound **S9** was the major product, a significant amount of by-product **S8,** with tiglate migration from 3-*O*-Glc*p* (glucopyranose) to 2-*O*-Glc*p,* was also generated (~27%). More importantly, given the very small polarity difference between **S8** and **S9**, purification of **S9** by column chromatography was time-consuming and labor-intensive. To overcome these two shortcomings, we first explored switching the 2-OH-Glc*p* protecting group of **4** from TBS to TES, envisioning that the comparatively reduced steric bulk of the TES group would encounter less steric hindrance from the existing bulky 3-*O*-Fuc*p* (fucosepyranose) TBS group and, hence, be more efficiently incorporated than TBS. Encouragingly, we saw an almost quantitative transformation of **S7** to **4** when TESOTf, in place of TBSOTf, was employed as the silylation reagent.

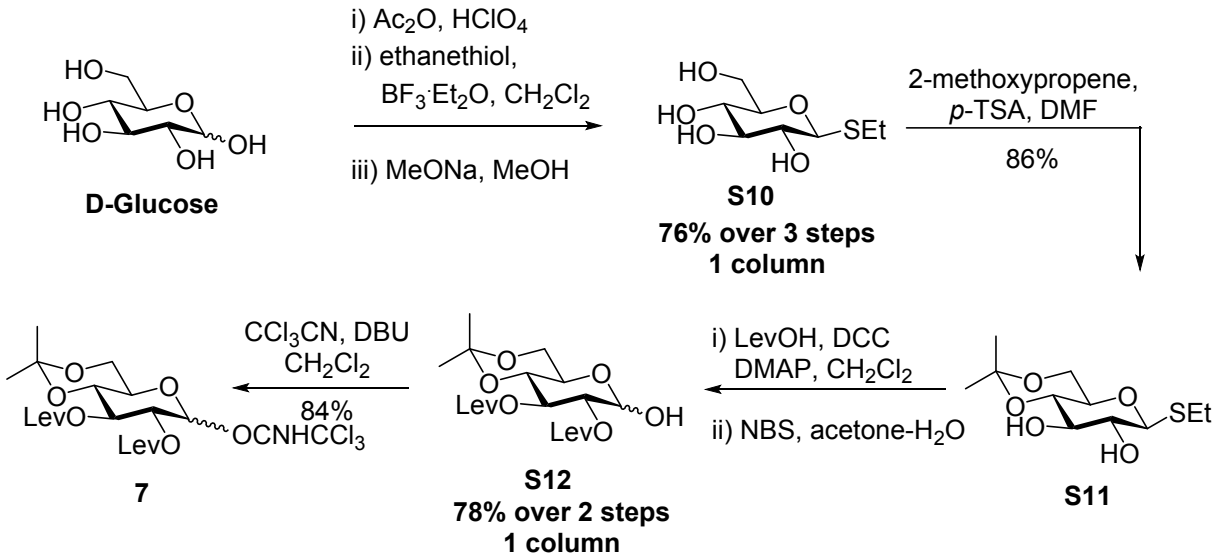
Table S1. Optimization of Chemoselective Removal of Isopropylidene.[a]



Entry	Acid		Solvent	Time	Products[b]		
	Name	Equivalents			**4**	**5**	**6**
1	CSA	0.2	$MeOH/CH_2Cl_2$ *v*/*v*, 1/1	6 h	~20%	~70%	~10%
2	AcOH	3/1, v/v	H_2O	1.5 h	none	70-80%	20-30%
3	AcOH	50	MeOH	84 h	~10%	60-70%	20-30%
4	AcOH	50	CH_2Cl_2	72 h	100%	none	none

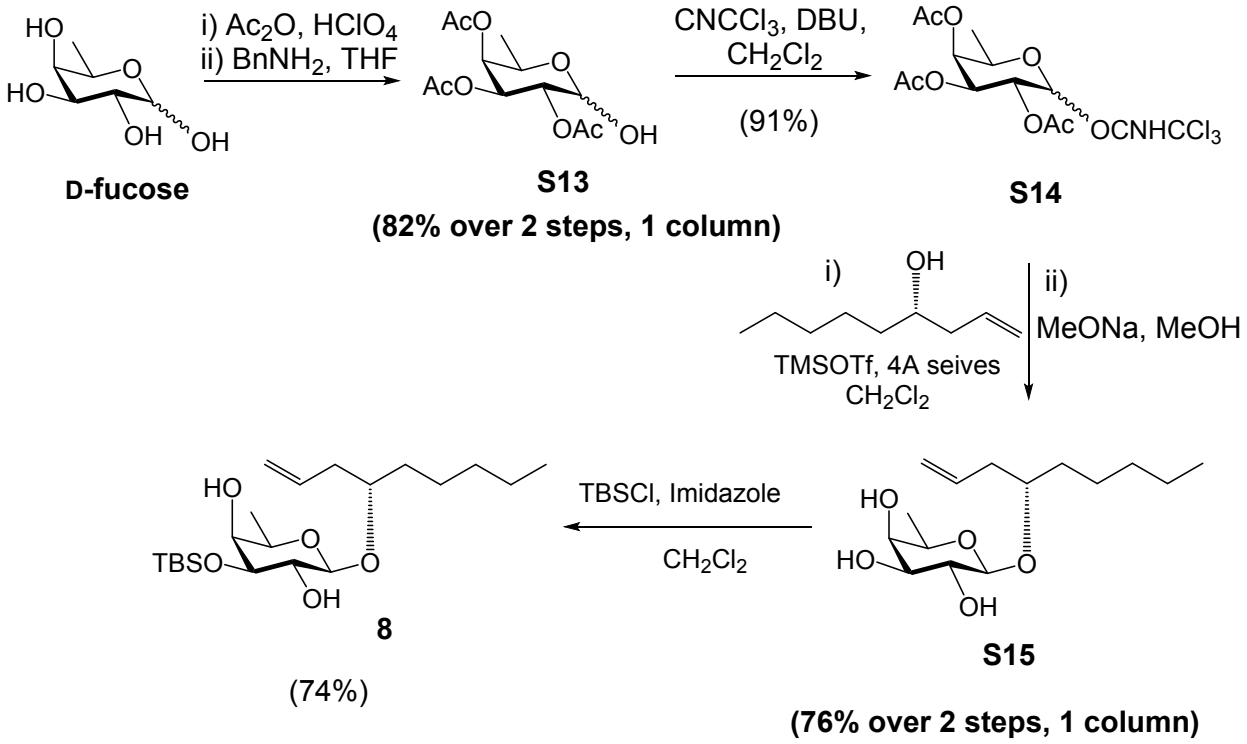
[a] Reaction conditions: 50 mg of **4** in 1 mL solvent. The reactions were all carried out at room temperature.
[b] The ratios were determined by ^1H NMR analyses of the crude reaction mixture.

Scheme S3. Synthesis of glucosyl donor 7.



7 steps, 4 columns, 42.8% overall yield

Scheme S4. Synthesis of fucosyl acceptor 8.



6 steps, 4 columns, 42.0% overall yield