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Total Synthesis of Ipomoeassin F

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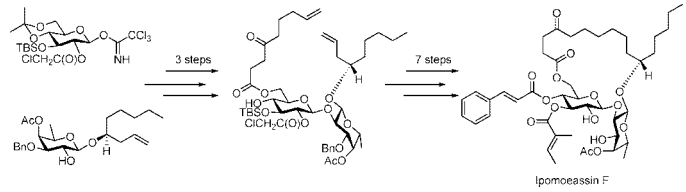
ABSTRACT



The first total synthesis of ipomoeassin F was carried out using a convergent approach that relied upon the use of Schmidt glycosidation technology for the coupling of two suitably protected monosaccharide fragments. After two steps, ring-closing metathesis was used to form the macrocyclic ring, and seven more steps then furnished ipomoeassin F. In vitro inhibitory activity against a four-panel cell line showed low nanomolar inhibitory activity.

The ipomoeassins are a structurally unique family of compounds recently isolated from *Ipomoea* sp. in Suriname by the Kingston group that showed cytotoxicity toward the A2780 ovarian cancer cell line.[1] *Ipomoea* sp., commonly known as morning glory, has about 650 species distributed worldwide with over 300 species found in the Americas alone. Many of these plants contain glycoside resins that are comprised of a few sugars with either single or multiple long-chain fatty acid(s). Members of the morning glory family have been long known to possess laxative and puragative properties[2] as well as displaying a range of other biological effects. For example, these glycosidic resins have been used as crop protectants in Mexico as they inhibit the growth of invasive weeds.[3] *Ipomoea squamosa* has shown activity against *Mycobacterium tuberculosis*,[4] while triclorin A, isolated from *Ipomoea tricolor* displays activity against cultured P-388 and human breast cancer cells[3] as well as antifungal activity.[5]

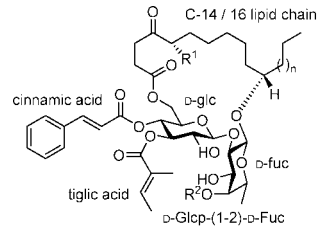


Figure 1. Ipomoeassin natural products.

The ipomoeassin natural products (Figure 1) possess several interesting structural features. The presence of oxygenation on the linking acid chain and the shorter tail at

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(1) Cao, S.; Guza, R. C.; Wisse, J. H.; Miller, J. S.; Evans, R.; Kingston, D. G. I. *J. Nat. Prod.* **2005**, *68*, 487–492.
(2) Pereda-Miranda, R.; Bah, M. *Curr. Top. Med. Chem.* **2003**, *3*, 111–131.
(3) Pereda-Miranda, R.; Mata, R.; Anaya, A. L.; Wickramaratne, D. B. M.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **1993**, *56*, 571–582.
(4) Barnes, C. C.; Smalley, M. K.; Manfredi, K. P.; Kindscher, K.; Loring, H.; Sheeley, D. M. *J. Nat. Prod.* **2003**, *66*, 1457–1462.
(5) Castelli, M. V.; Cortes, J. C.; Escalante, A. M.; Bah, M.; Pereda-Miranda, R.; Ribas, J. C.; Zacchino, S. A. *Planta Med.* **2002**, *68*, 739–742.

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the fucoside anomeric center are both uncommon relative to other glycoside resins. The cinnamate and tiglate functions are somewhat rare in related compounds since the reduced or hydrated forms of the tiglate (2-methylbutyrate or 3-hydroxy-2-methylbutyric acid) are the more commonly encountered motifs.[6]

The ipomoeassin natural products consist of a fucose- and glucose-derived (1→2)-β-disaccharide joined at *O*-1′ and *O*-6″ by a 14-carbon seco acid chain. Ipomoeassins A and B are differentiated from ipomoeassin C, D, and E by the presence of a free or acetylated hydroxyl group at *C*-5 on the lipid chain. Ipomoeassins A, C, and D differ from B and E in the sense that they have *O*-4′ acetylated.

The published cell growth inhibitory activity for these compounds against the A2780 OVCAR cell line was in the range of 35−1900 nM with ipomoeassin D being the most potent of the series.[1] Recently, a new member of the family, ipomoeassin F,[7] bearing striking similarity to ipomoeassin A was isolated by the same group. Ipomoeassin F (**1f**) boasted superior potency in our in-house cell growth inhibitory assays compared to the other members of the ipomoessin family (**1a**−**e**) (Table 1).[8]

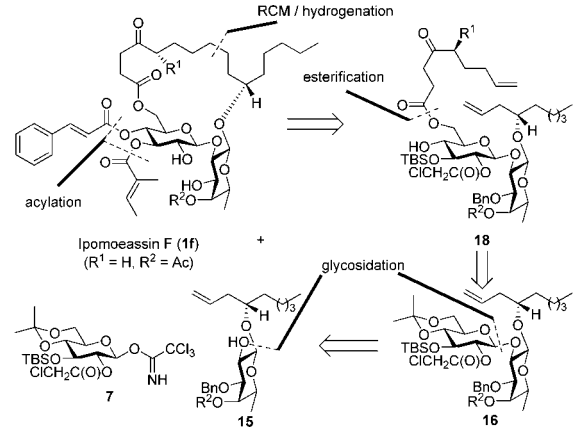
Table 1. Cell Growth Inhibitory Data for Natural Ipomoeassin A, B, D, E, and F (nM)[a]

	HT-29	MDA-MB-435	H522-T1	U937
Ipomoeassin A	46.1	42.6	108.9	20.2
Ipomoeassin B	396	2700	1070	134
Ipomoeassin D	11.8	19.9	23.2	7.9
Ipomoeassin E	393	1633	967	163
Ipomoeassin F	4.2	9.4	12.9	2.6

[a] Values averaged over two experiments.

Given the number of varied acyl-based groups contained within ipomoeassin F, a strategy based upon ring closing metathesis (RCM) with the *O*-6″ acyl chain and the *O*-4′ acetate in place followed by a late stage *O*-3″ and *O*-4″ acylation was chosen as a possible approach to the target molecule (Scheme 1). This is contrasted by an approach based upon macrolactonization[9] that would necessitate a higher degree of orthogonal hydroxyl protection. We chose to employ the α-chloroacetate group ($ClCH_2C(O)$) to protect the sole two free hydroxyl groups of ipomoeassin F that would be liberated in the last step of the synthesis under suitably mild conditions.[10] We anticipated that a TBS group would serve well to block *O*-3″ while simultaneously

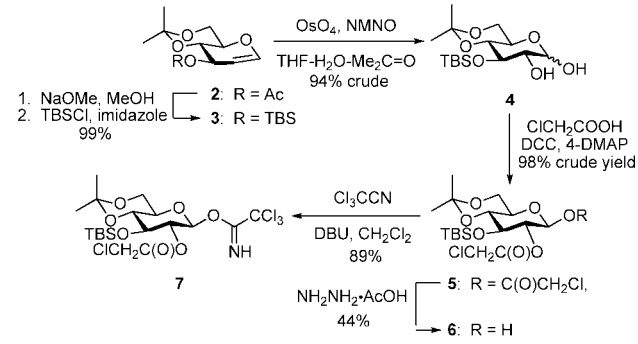
Scheme 1. Retrosynthetic Analysis for Ipomoeassin F



shielding *O*-4″ from unwanted derivatization thus reducing the number of required protecting groups. On the fucoside sugar, the *O*-4′ hydroxyl would be acetylated thereby necessitating preservation of this function for the entire synthesis. Upon completion of this work, a communication outlining the total synthesis of total ipomoeassin B and E, the least potent compounds of the group, appeared.[11] These workers relied upon an elegant ring-closing metathesis (RCM) approach[12] in their synthetic strategy.

Our synthesis begins with the preparation of the two required monosaccharide fragments, *gluco* donor **7** and fucoside acceptor **15**. The acetate on the known glucal[13] **2** was exchanged for a TBS group in excellent yield, and subsequent dihydroxylation (OsO_4, NMNO, 94%)[14] gave a mixture of anomers **4** followed by dichloroacetylation to give **5** (Scheme 2). The β-isomer, which was fully characterized,[15]

Scheme 2. Synthesis of Glucosyl Donor **7**



was found to be the major product (2.3:1, ^{1}H NMR). Selective removal of the anomeric acyl group with hydrazine acetate[16] gave compound **6**, and this was followed by a high-yielding installation of the trichloroacetimidate group to furnish the Schmidt donor[17] **7** in 86% yield as a yellow crystalline solid.

The required fucoside was prepared by condensation of the known fucosyl bromide **8**[18] with chiral alcohol **9**[19] to

(6) See for example: Hernández-Carlos, B.; Bye, R.; Pereda-Miranda, R. *J. Nat. Prod.* **1999**, *62*, 1096–1100.

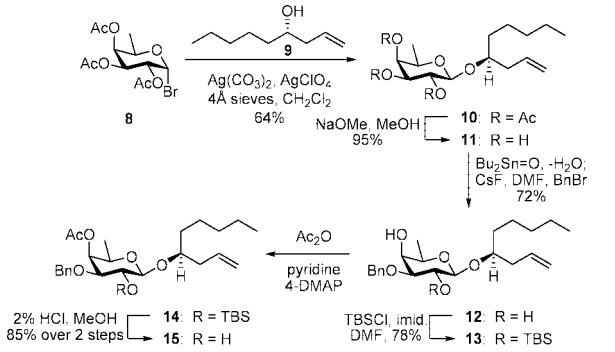
(7) Cao, S.; Norris, A.; Wisse, J. H.; Miller, J. S.; Evans, R.; Kingston, D. G. I. *Nat. Prod Res.* **2007**, *21*, 872–876.

(8) We thank Professor Kingston for supplying these compounds to us.

(9) (a) Larson, D. P.; Heathcock, C. H. *J. Org. Chem.* **1997**, *62*, 8406–8418. (b) Lu, S.-F.; O'yang, Q.; Guo, Z.-W.; Yu, B.; Hui, Y.-Z. *J. Org. Chem.* **1997**, *62*, 8400–8405. (c) Brito-Arias, M.; Pereda-Miranda, R.; Heathcock, C. H. *J. Org. Chem.* **2004**, *69*, 4567–4570.

(10) Greene, T. W.; Wuts, P. G. W. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

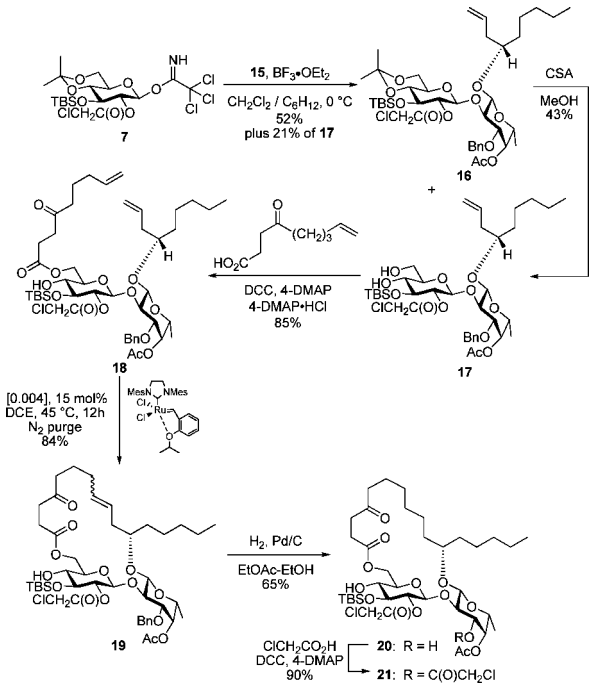
Scheme 3. Synthesis of Fucoside Acceptor **15**



give **10** as a single isomer in 64% yield (Scheme 3). Global deacetylation furnished triol **11**, and stannylidene-mediated equatorial benzylation[20] brought the sequence as far as **12**. Selective silylation (TBSCl, imidazole, DMF) of the equatorial hydroxyl group[21] gave **13** in 78% yield. Acetylation then delivered **14**, and the sequence was completed by acid-mediated deprotection of the TBS group to produce **15** in 85% yield over two steps along with 8% of diol **12**.

Optimized coupling conditions called for the use of a 1.5:1 ratio of **7** and **15** and 0.5 equiv of boron trifluoride etherate to furnish a 52% yield (87% based on recovered starting material) of the target β-disaccharide **16** along with **17**, the product in which the acetonide was lost in 21% yield (Scheme 4).

Scheme 4. Disaccharide Coupling and Macrocycle Formation



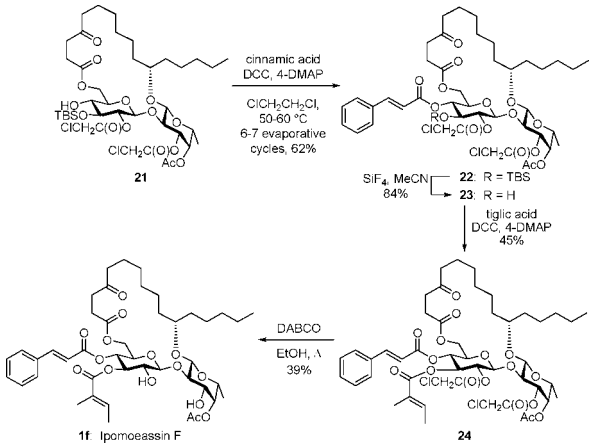
To complete the conversion of **16** to **17**, the acetonide was removed in 43% yield (67% based on recovered starting material) with CSA in methanol. Selective DCC-mediated acylation with 4-nonone-8-enoic acid[22] of the primary *O*-6″ alcohol (**17**→**18**, 85%, Scheme 4) gave the precursor to ring-closing metathesis. RCM proceeded best[23] with 15 mol % of Hoveyda−Grubbs catalyst[24] added portion-wise in 1,2-dichloroethane (45 °C for 3 h at 0.05 M dilution) to provide **19** in 84% yield as a mixture of isomers that were not separated but were directly subjected to hydrogenation (H_2, Pd/C, EtOAc−EtOH) to first saturate the mixture of olefins (as shown by TLC, silica, 30% EtOAc−hexanes) and then reductively cleave the *O*-3′ benzyl group to deliver **20**. Selective chloroacetylation of the *O*-3′ hydroxyl group then gave **21** (Scheme 4).

The TBS group at *O*-3″ hindered the *O*-4″ hydroxyl to a greater extent than initially anticipated, and the cinnamoyl group could only be installed by heating a DCC-mediated coupling reaction in 1,2-dichloroethane under evaporative conditions. After several iterations of solvent evaporation and replacement, a 62% yield of **22** was obtained (75% based on recovered starting material). A high-yielding removal of the TBS group was effected with SiF_4[25] to give an 84% yield of alcohol **23** (Scheme 5). Tigloylation (tiglic acid, DCC, 4-DMAP, 4-DMAP•HCl) gave the fully blocked precursor to ipomoeassin F **24**, and removal of the α-chloroacetates by employing an excess of DABCO in hot ethanol[26] furnished the natural product ipomoeassin F (**1f**) in 39% yield after purification by flash chromatography and HPLC.

The synthetic material obtained was identical to a natural sample of ipomoeassin F kindly provided by Professor

(11) Fürstner, A.; Nagano, T. *J. Am. Chem. Soc.* **2007**, *129*, 1906–1907.
(12) In fact, Fürstner was the first to employ a RCM approach to these types of compounds, see: (a) Fürstner, A.; Muller, T. *J. Org. Chem.* **1998**, *63*, 424–425. (b) Fürstner, A.; Muller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814–7821. (c) Fürstner, A.; Jeanjean, F.; Razon, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2097–2101.
(13) RajanBabu, T. V. *J. Org. Chem.* **1985**, *50*, 3642–3644.
(14) Crich, D.; Lim, L. B. *J. Chem. Soc., Perkin Trans. 1* **1991**, *9*, 2209–2214.
(15) All new compounds were fully characterized by ^{1}H, ^{13}C, and COSY NMR, high-resolution mass spectroscopy, FT-IR, and optical rotation. HPLC and GC methods were employed when deemed appropriate.
(16) Fürstner, A.; Jeanjean, F.; Razon, P.; Wirtz, C.; Mynott, R. *Chem.−Eur. J.* **2003**, *9*, 307–319.
(17) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123.
(18) Adelhorst, K.; Whitesides, G. M. *Carbohydr. Res.* **1993**, *242*, 69–76.
(19) Chiral alcohol **9** was prepared in >99% ee by addition of a vinyl cuprate to optically pure 1,2-epoxyheptane. The latter was readily available through the use of Jacobsen chiral epoxidation technology: Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.
(20) See, for example: Kanie, O.; Takeda, T.; Ogihara, Y. *Carbohydr. Res.* **1989**, *190*, 53–64.
(21) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
(22) The γ-keto-acid was prepared by copper-mediated addition of the Grignard reagent derived from 5-bromo-1-pentene to succinic anhydride, see: L'hommet, G.; Freville, S.; Thuy, V.; Petit, H.; Celerier, J. P. *Synth. Commun.* **1996**, *26*, 3897–3901.
(23) In a closely related system, it was found that both the first- and second-generation Grubbs catalysts mediated the ring closure, but catalyst loadings of up to 50 and 35 mol %, respectively, were needed to push the reactions to completion making purification somewhat problematic.
(24) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
(25) Corey, E. J.; Yi, K. Y. *Tetrahedron Lett.* **1992**, *33*, 2289–2290.
(26) Lefeber, D. J.; Kamerling, J. P.; Vliegenthart, J. F. G. *Org. Lett.* **2000**, *2*, 701–703.

Scheme 5. Completion of the Synthesis of Ipomoeassin F



Kingston[7] as shown by HPLC, ^{1}H and ^{13}C NMR, and optical rotation.[27] The in vitro cell growth inhibitory activity (Table 2) also correlated well with that from the natural material.

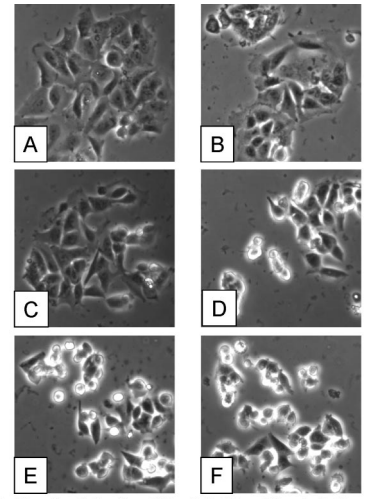
Table 2. Comparison of Cell Growth Inhibitory Data for Natural and Synthetic Ipomoeassin F (nM)[a]

	HT-29	MDA-MB-435	H522-T1	U937
Ipomoeassin F	4.2	9.4	12.9	2.6
Ipomoeassin F (synthetic)	1.4	4.3	2.7	1.1

[a] Values averaged over two experiments.

The data show that the synthetic ipomoeassin F was slightly more potent than the natural material, exhibiting single digit nanomolar potency or less against the four cell lines tested.

The effect of ipomoeassin F on tumor cells was further examined by phase contrast microscopy. As shown in Figure 2, ipomoeassin F induced cell death of H522-T1 lung cancer cells which was preceded by rounding up of the cells.[28]



A: untreated, B: 3 nM, C: 10 nM, D: 30 nM, E: 100 nM, F: 300 nM

Figure 2. Phase contrast microscopy of Ipomoeassin F treated H522-T1 cells.

The described synthetic route to ipomoeassin F is flexible and should allow access to a variety of analogues as other members of the ipomoeassin family.[29]

Acknowledgment. The authors would like to thank Yuan (John) Wang (ERI) for supplying copious amounts of glycal **2**, Jian DelVecchio and Michael Alaimo (ERI) for analytical support, Ted Suh, Keith Wilcoxen, and Brian Gallagher (ERI) for helpful chemistry discussions, Lynn Hawkins and Keith Wilcoxen (ERI) for help in proof reading the mansuscript, Melvin Yu and Bruce Littlefield (ERI) for their support of this project, and Professor David Kingston (Virginia Polytechnic Institute) for supplying several natural ipomoeassins.

Supporting Information Available: Experimental procedures for **1f**, **3**−**7**, and **10**−**24**. Copies of ^{1}H and ^{13}C NMR spectra for compounds **1f**, **3**−**7**, **10**−**18**, and **20**−**24** along with HPLC data for **1f** (synthetic and natural) along with copies of COSY NMR spectra for compounds **7**−**18** and **20**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) See Supporting Information.

(28) Rounding up of cells is commonly associated with loss of cell−matrix adhesions and detachment of cells from the matrix. See, for example: Hajdo-Milasinovic, A.; Ellenbroek, S. I. J.; van Es, S.; van der Vaart, B.; Collard, J. G. *J. Cell. Sci.* **2007**, *120*, 555–566.

(29) By making the appropriate changes to the top chain and the fucoside fragment, access to all current members of the ipomoeassin family should be possible using the current synthetic strategy.