Ipomoeassins A−E, Cytotoxic Macrocyclic Glycoresins from the Leaves of *Ipomoea squamosa* from the Suriname Rainforest[1]

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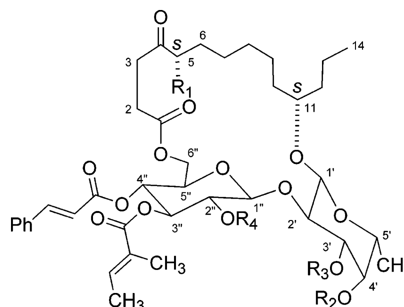
The new glycoresins, ipomoeassins A−E (**1**−**5**), have been isolated from the leaves of *Ipomoea squamosa*. The structures were elucidated by spectroscopic analyses and chemical transformations. The absolute configurations of C-5 (ipomoeassins **3**−**5**) and C-11 (ipomoeassins **1** and **2**) were determined by their derivatives with (*R*)- and (*S*)-MPA. All the isolates were active in the A2780 human ovarian cancer cell line assay, and **4** showed the highest activity with an IC_{50} value of 35 nM.

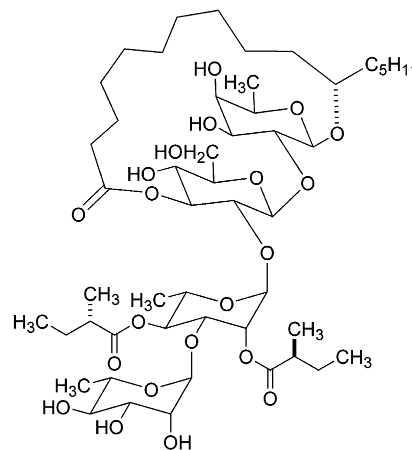
About 650 species of morning glories (*Ipomoea* sp., family Convolvulaceae) are distributed across the world's tropical and subtropical regions, and more than 300 species come from the Americas alone. *Ipomoea batatas* (L.) Lam. is the common sweet potato. Most species of *Ipomoea* are vines, a small group of neotropical species are small trees, but most have characteristic funnel-shaped flowers that open in early morning and last a single day. The genus *Ipomoea* has afforded glycoresins that are usually composed of a few sugars and one or more long-chain fatty acid(s),[2−9] and the purgative properties of some *Ipomoea* sp. are due to the presence of glycolipids in their resins.[2,5] It has been reported that *Ipomoea leptophylla* showed activity against *Mycobacterium tuberculosis*.[8] *Ipomoea squamosa* Choisy is a vine that is widespread in the neotropics. The constituents of morning glories have been recently reviewed.[10]

The pharmaceutical partner in our International Cooperative Biodiversity Group (ICBG) in Suriname, Bristol-Myers Squibb Pharmaceutical Research Institute (BMS), obtained an isolate (BMS-247181) from an *Ipomoea* sp. from Suriname that exhibited potent *in vitro* activity toward the M109 lung cancer cell line. The compound was identified as a resin glycoside, and a tentative structure was proposed, although the stereochemistry was not determined. BMS-247181 had a maximum UV absorption at 280 nm and a molecular mass of approximately 900 Daltons. A preliminary *in vivo* experiment indicated that it had a narrow therapeutic window, and work on the extract at BMS was subsequently discontinued.

BMS withdrew from the Suriname ICBG in 2002, and it was subsequently decided to reinvestigate the cytotoxic constituents of *Ipomoea* sp. from Suriname, in the expectation that they might contain additional resin glycosides with potentially improved properties as compared with BMS-247181. The original extract from which BMS-24718 had been isolated was no longer available, but eight *Ipomoea* extracts were available from the National Cancer Institute and two *Ipomoea* extracts were available in-house, including one (E940631) that was a re-collection of the original plant that had furnished the extract provided to BMS. Analysis of all 10 extracts was carried out by LC-MS, using 280 nm as a monitoring wavelength and 800−1000 Da as a scanning range, and E940631 was chosen as the starting material since its LC-MS chromatogram showed peaks that had the same UV pattern and similar MW(s) to BMS-247181. E940631 had an IC_{50} value of 8.0 μg/mL against the A2780 ovarian cancer cell line.



1 $R_1 = R_3 = R_4 = H$; $R_2 = Ac$;
2 $R_1 = R_2 = R_3 = R_4 = H$
3 $R_1 = OH$; $R_2 = Ac$; $R_3 = R_4 = H$
4 $R_1 = OAc$; $R_2 = Ac$; $R_3 = R_4 = H$
5 $R_1 = OAc$; $R_2 = R_3 = R_4 = H$
6 $R_1 = H$; $R_2 = R_3 = R_4 = Ac$
7 $R_1 = OAc$; $R_2 = R_3 = R_4 = Ac$



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Results and Discussion

Fractionation of E940631 was carried out by flash chromatography on a C18 column followed by HPLC on

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Table 1. ^{1}H NMR Data (δ) for Compounds **1−5**

no.	**1**	**2**	**3**	**4**	**5**
2	2.40 ddd (17.4, 9.4, 3.4)	2.38 ddd (17.4, 9.4, 3.4)	2.65 ddd (17.9, 9.1, 4.2)	2.57 ddd (18.1, 9.2, 2.8)	2.55 ddd (18.1, 9.2, 2.8)
	2.14 ddd (17.4, 7.7, 3.5)	2.13 ddd (17.4, 7.7, 3.5)	1.80 ddd (17.9, 7.8, 4.4)	2.38 ddd (18.1, 7.8, 3.4)	2.34 ddd (18.1, 7.8, 3.4)
3	2.65 ddd (16.1, 7.7, 3.4)	2.62 ddd (16.1, 7.7, 3.4)	3.01 ddd (16.4, 9.1, 4.4)	2.83 ddd (16.3, 9.2, 3.4)	2.81 ddd (16.3, 9.2, 3.4)
	2.52 ddd (16.1, 9.4, 3.5)	2.50 ddd (16.1, 9.4, 3.5)	2.21 ddd (16.4, 7.8, 4.2)	2.43 ddd (16.3, 7.8, 2.8)	2.39 ddd (16.3, 7.8, 2.8)
5	2.07 t (6.0)	2.07 t (6.2)	3.96 m	5.05 dd (6.2, 3.9)	5.04 dd (6.2, 3.9)
6	1.56 m, 1.65 m	1.56 m, 1.65 m	1.80 m	1.75 m, 1.95 m	1.75 m, 1.95 m
7	1.32 m	1.31 m	1.45 m	1.50 m	1.50 m
8	1.34 m	1.29 m	1.35 m	1.30 m	1.30 m
9	1.35 m, 1.55 m	1.35 m, 1.51 m	1.45 m	1.50 m	1.50 m
10	1.54 m, 1.72 m	1.52 m, 1.70 m	1.50 m, 1.70 m	1.50 m, 1.70 m	1.50 m, 1.70 m
11	3.72[a] m	3.71 m	3.66[c] m	3.70 m	3.71 m
12	1.54 m, 1.65 m	1.53 m, 1.61 m	1.65 m	1.55 m, 1.65 m	1.55 m, 1.65 m
13	1.55 m	1.57 m	1.55 m	1.55 m	1.55 m
14	0.95 t (7.1)	0.96 t (7.1)	0.96 t (6.9)	0.95 t (7.1)	0.97 t (6.9)
1′	4.40 d (7.7)	4.38 d (7.6)	4.32 d (7.6)	4.29 d (7.6)	4.28 d (7.6)
2′	3.96[b] dd (9.5, 7.7)	3.88 dd (9.5, 7.6)	3.90 dd (9.7, 7.6)	3.88 dd (9.5, 7.6)	3.80[e] dd (9.5, 7.6)
3′	3.72[a] dd (9.5, 3.7)	3.65 dd (9.5, 3.3)	3.66[c] dd (9.7, 3.4)	3.62 dd (9.5, 3.7)	3.55 dd (9.5, 3.7)
4′	5.15 dd (3.7, 0.5)	3.53 br s	5.12 br d (3.4)	5.09 br d (3.7)	3.44 br s
5′	3.10 qd (6.4, 0.5)	3.11 br q (6.4)	3.11 br q (6.4)	3.06 br q (6.4)	3.02 br q (6.4)
6′	1.10 d (6.4)	1.29 d (6.4)	1.09 d (6.4)	1.08 d (6.4)	1.25 d (6.4)
1″	4.52 d (7.9)	4.59 d (7.8)	4.54 d (7.8)	4.51[d] d (7.8)	4.50[f] d (7.8)
2″	3.91[b] dd (9.7, 7.9)	3.95 dd (9.7, 7.8)	3.83 dd (9.7, 7.8)	3.79 dd (9.7, 7.8)	3.81[e] dd (9.7, 7.8)
3″	5.39 t (9.7)	5.50 t (9.7)	5.41 t (9.7)	5.39 t (9.7)	5.38 t (9.7)
4″	5.69 t (9.7)	5.72 t (9.7)	5.72 t (9.7)	5.69 t (9.7)	5.70 t (9.7)
5″	3.24 ddd (9.7, 3.2, 1.6)	3.44 br d (9.7)	3.26 br d (9.7)	3.29 br d (9.7)	3.36 br d (9.7)
6″	4.66 dd (12.6, 3.2)	4.66 dd (12.6, 2.1)	4.37 dd (12.4, 1.6)	4.51[d] br d (11.5)	4.51[f] dd (11.0, 2.0)
	4.11 dd (12.6, 1.6)	4.16 br d (12.6)	4.26 dd (12.4, 0.9)	4.19 br d (11.5)	4.20 br d (11.0)
AA-2[g]	1.82 s		1.84 s	1.82 s	
AA-2′				1.70 s	1.67 br s
TA-3[h]	6.95 m	6.95 m	6.95 m	6.95 m	6.95 m
TA-4	1.23 d (7.1)	1.27 (7.1)	1.27 d (7.1)	1.26 d (7.1)	1.25 d (7.1)
TA-5	1.68 br s	1.72 br s	1.71 br s	1.70 br s	1.67 br s
CA-2[i]	6.39 d (15.9)	6.40 d (16.1)	6.38 d (16.0)	6.37 d (15.8)	6.40 d (16.1)
CA-3	7.81 d (15.9)	7.81 d (16.1)	7.81 d (16.0)	7.81 d (15.8)	7.81 d (16.1)
CA-5	6.89−7.07	6.88−7.07	6.88−7.03	6.88−7.03	6.88−7.03
CA-6	6.89−7.07	6.88−7.07	6.88−7.03	6.88−7.03	6.88−7.03
CA-7	6.89−7.07	6.88−7.07	6.88−7.03	6.88−7.03	6.88−7.03

[a−f] Interchangeable. [g] AA = acetoyl. [h] TA = tigloyl. [i] CA = cinnamoyl.

C18 and then phenyl columns. Five cytotoxic compounds (**1**−**5**) were isolated and were designated ipomoeassins A−E. Ipomoeassin D (**4**) showed particularly potent inhibition of the A2780 human ovarian cancer cell line with an IC_{50} value of 35 nM.

Ipomoeassin A (**1**) was obtained as a colorless oil, whose molecular formula was determined to be $C_{42}H_{58}O_{15}$ from the positive ion HRESIMS. Its ^{1}H NMR (Table 1), ^{13}C NMR (Table 2), COSY, TOCSY, and ROESY data suggested the presence of glucose (fragment A1) and fucose (fragment B1) components (Figure 1). The olefinic proton at δ_H 6.95 (1H, m, H-TA-3, TA-tiglic acid), showing HMBC correlations with both δ_C 12.1 (C-TA-5) and δ_C 168.5 (C-TA-1), had a COSY correlation with the signal at δ_H 1.23 (3H, d, J = 7.1 Hz, H-TA-4). This suggested the presence of a 2-methylbut-2-enoyl moiety (fragment A2). The *E* stereochemistry of the double bond in fragment A2 was unequivocally assigned based on the ROESY correlations between the signal at δ_H 1.23 and the signals at δ_H 6.95 and 1.68. The deshielding of proton TA-3 due to the anisotropy of the carbonyl (C-TA-1) was also a proof for the *E* stereochemistry of the tigloyl residue.

A pair of *trans*-coupled olefinic protons at δ_H 7.81 (1H, d, J = 15.9 Hz) and 6.39 (1H, d, J = 15.9 Hz) and a multiplet due to five protons at δ_H 6.89−7.07 suggested the presence of a 3-phenylprop-2-enoyl moiety (CA = cinnamic acid, fragment A3). This was confirmed by the HMBC correlations between δ_H 7.81 and δ_C 134.5 (C-CA-4) and 128.5 (C-CA-5). The methyl singlet at δ_H 1.82 (3H, s) showed an HMBC correlation with the carbonyl at δ_C 171.0 (C-AA-1, AA = acetic acid), suggesting the presence of an acetyl moiety (fragment B2). The ^{1}H NMR spectrum of **1** also exhibited signals for two methylenes at δ_H 2.65 (H-3a) and 2.52 (H-3b) and at 2.40 (H-2a) and 2.14 (H-2b). These two methylenes were flanked by two carbonyls and displayed one spin system (fragment C1) in the TOCSY spectrum. The methyl triplet at δ_H 0.95 (3H, t, J = 7.1 Hz, H-14), the methylene triplet at δ_H 2.07 (2H, t, J = 6.0 Hz, H-5), the oxygenated methine at δ_H 3.72 (1H, m, H-11), and the other seven methylenes, all of which were parts of another spin system (fragment C2), were separated from fragment C1 by the carbonyl group at C-4 (δ_C 208.4), since C-4 showed HMBC correlations with H-2, H-3, and H-5.

The HMBC (Figure 2) experiment also provided evidence for the location of the ester substituents. The methyl group at δ_H 1.82 (H-AA-2) and H-4′ (δ_H 5.15, H-F-4, F = fucose) both correlated with the carbonyl at δ_C 171.0 (C-AA-1) in the HMBC spectrum. The carbonyl group at δ_C 168.5 was assigned to carbon TA-1 on the basis of its HMBC correlations with H-3″ (δ_H 5.39, H-G-3, G = glucose), proton TA-5 (δ_H 1.68), and proton TA-3 (δ_H 6.95); these correlations established the acylation position of the tigloyl group as 3″ (C-G-3). ^{13}C−^{1}H long-range cross-peaks were observed between the carbonyl group at δ_C 165.6 (C-CA-1) and H-4″ (δ_H 5.69, H-G-4), proton CA-2 (δ_H 6.39), and proton CA-3 (δ_H 7.81), which confirmed the presence of the cinnamoyl moiety at the 4″-position (C-G-4). The site of lactonization (δ_C 171.5, C-1) was determined to be at C-6″ (C-G-6) of the glucose by the observed ^{2}J coupling with H_2-2 (δ_H 2.40 and 2.14) and ^{3}J couplings with H_2-3 (δ_H 2.65 and 2.52) and H_2-6″ (δ_H 4.66, 4.11, H_2-G-6).

Table 2. ^{13}C NMR Data (δ) for Compounds **1**−**5**

no.[a]	1	2	3	4	5
1	171.5	171.5	171.6	171.3	171.4
2	37.3[b]	37.4	33.0	34.0[l]	34.0[r]
3	29.7[c]	29.5[f]	28.3	28.3	28.3
4	208.4	208.3	210.7	205.7	205.8
5	41.6	41.5	76.3[i]	78.4[m]	78.2[s]
6	23.8	23.6	32.7	30.3[m]	30.3[t]
7	28.7	28.6	22.7	24.0	24.0
8	29.4[c]	29.3[f]	29.9	30.6[n]	30.5[t]
9	25.5	25.4	25.1	25.2	25.2
1	34.3	34.3	34.1	34.0[l]	34.0[r]
11	79.0	78.8	78.8	78.5[m]	78.5[s]
12	37.6[b]	37.4	37.6	37.7	37.7
13	18.7	18.8	18.8	18.9	18.9
14	14.4[d]	14.3[g]	14.4[j]	14.4[o]	14.4[u]
1′	100.8	100.6	100.7	100.6	100.5
2′	84.0	83.7	83.7	83.9	84.2
3′	72.7[e]	74.2[h]	72.7[k]	72.8[p]	74.0
4′	72.9[e]	71.6	72.6[k]	72.7[p]	71.6
5′	69.0	70.2	68.9	68.9	70.0
6′	14.1[d]	14.0[g]	14.1[j]	14.1[o]	14.1[u]
1″	106.6	106.4	106.4	106.6	106.7
2″	74.8	74.6[h]	74.7	75.0	74.9
3″	6.4	76.3	76.4[i]	76.6	76.6
4″	67.8	67.8	67.9	67.6	67.7
5″	73.0[e]	73.0	72.8[k]	72.9[p]	72.9
6″	61.5	61.4	61.6	61.2	61.2
AA-1	171.0		171.0	170.9	
AA-2	20.5		20.5	20.4[q]	
AA-1′				169.8	169.8
AA-2′				20.3[q]	20.3
TA-1	168.5	168.5	168.5	168.8	168.9
TA-2	128.0	128.0	128.0	128.0	128.0
TA-3	139.2	139.1	139.3	139.4	139.6
TA-4	16.6	16.6	16.5	16.5	16.6
TA-5	12.1	12.0	12.1	12.0	12.0
CA-1	165.6	165.5	165.4	165.5	165.5
CA-2	117.6	117.6	117.5	117.6	117.5
CA-3	146.1	146.0	146.2	146.2	146.2
CA-4	134.5	134.4	134.4	134.4	134.4
CA-5	128.5	128.4	128.5	128.4	128.3
CA-6	128.9	128.8	128.9	128.8	128.5
CA-7	130.4	130.3	130.4	130.4	130.4

[a] AA = acetyl; TA = tigloyl; CA = cinnamoyl. [b−u] Interchangeable.

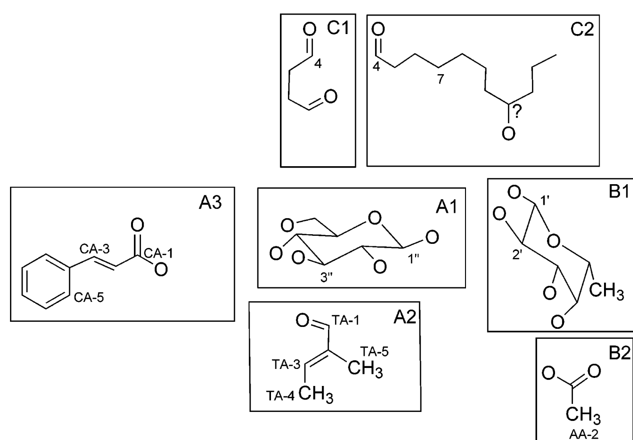


Figure 1. Fragments of **1** based on 2D NMR data.

In the HMBC spectrum of **1**, H-1″ (δ_H 4.52, H-G-1, G = glucose) showed a ^3J correlation with C-2′ (δ_C 84.0, C−F-2, F = fucose), which established the connectivity between fucose and glucose. A $^3J_{CH}$ interaction between H-1′ (δ_H 4.40, H-F-1) and the oxygenated carbon (δ_C 79.0, C-11) on fragment C2 was observed. Both H_3-14 and H-11 showed HMBC (J_{CH} = 5 Hz) correlations with C-12 and C-13, which

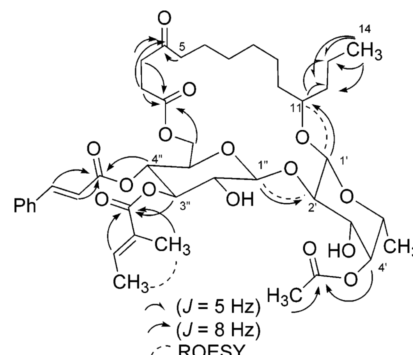
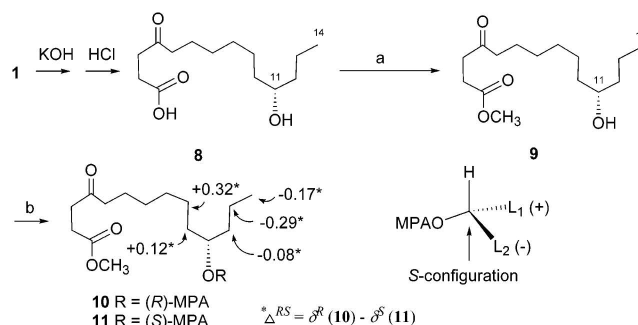


Figure 2. Key HMBC and ROSEY correlations of **1**.

Scheme 1[a]



[a] Key: (a) CH_2N_2; (b) (*R*)-MPA or (*S*)-MPA, EDCI, DMAP, CH_2Cl_2, rt, 12 h.

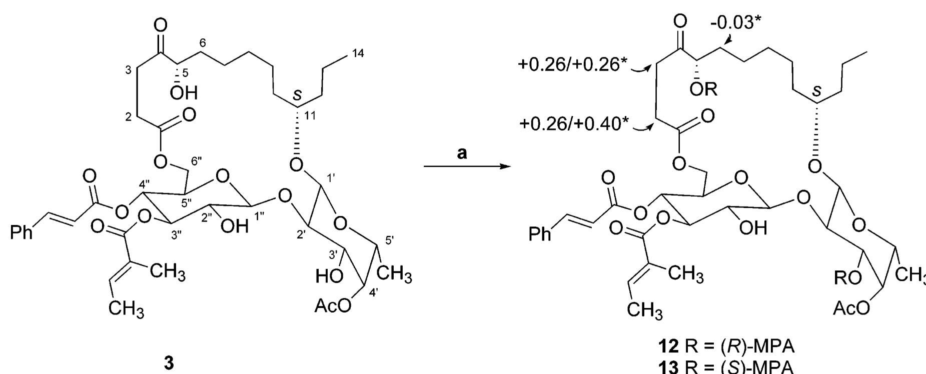
meant that the oxygenated methine had to be located at position 11. These correlations established the structure of **1**.

To determine the stereochemistry at the 11-position, **1** was hydrolyzed first with base and then with acid to yield 11-hydroxy-4-oxo-tetradecanoic acid (**8**). The long-chain fatty acid (**8**) was reacted with excess diazomethane to furnish 11-hydroxy-4-oxo-tetradecanoic acid methyl ester (**9**). Compound **9** was converted to the two Mosher esters **10** and **11** with (*R*)- and (*S*)-methoxyphenylacetic acid (MPA), using the EDCI/DMAP coupling conditions.[11] The resulting 11-MPA esters **10** and **11** were subjected to NMR analysis. The chemical shift differences $\Delta\delta^{RS}$ were significant (Scheme 1), which made it possible to conclude that **1** had the *S*-configuration at C-11. The sugars were determined as D-glucose and D-fucose by hydrolysis and determination of the sign of rotation of the isolated carbohydrates. This conclusion was supported by MM2 calculations, which indicated that only the diastereomer with both D-sugars would give the relatively strong ROESY correlations between H-11 and H-F-1 and between H-F-2 and H-G-1 that were exhibited in the spectrum of **1**.

Ipomoeassin B (**2**) was also obtained as a colorless oil, and the molecular formula $C_{40}H_{56}O_{14}$ was determined by HRFABMS and ^{13}C NMR. A careful analysis of its UV, IR, MS, 1D NMR (Tables 1 and 2), and 2D NMR data resulted in the conclusion that the structure of **2** was similar to that of **1**. It was hypothesized that the only difference between these two compounds was the presence of a hydroxyl group, rather than an acetoxyl group, located at the 4′-position in **2**. This was confirmed by the acetylation of both **1** and **2** to the same product **6**. The detailed assignments of the ^{1}H NMR and ^{13}C NMR signals were performed by COSY, TOCSY, ROESY, HMQC, and HMBC experiments. Accordingly, the structure of **2** was established as shown.

Ipomoeassin C (**3**) was isolated as a colorless oil, and its molecular formula was established as $C_{42}H_{58}O_{16}$ by

Scheme 2[a]



[a] Key: (a) (*R*)-MPA or (*S*)-MPA, EDCI, DMAP, CH_2Cl_2, rt, 12 h. *$\Delta d^{RS} = d^R(\mathbf{12}) - d^S(\mathbf{13})$.

HRFABMS. The ^{1}H NMR (Table 1), ^{13}C NMR (Table 2), COSY, TOCSY, and ROESY data of **3** also showed the presence a fucose, a glucose, a tiglic acid, a cinnamic acid, an acetic acid, and a long-chain fatty acid. These spectra indicated that **3** was also closely related to **1**, but contained a resonance for a secondary alcohol (δ_H 3.96/δ_C 76.3 ppm) instead of a methylene group of **1** (δ_H 2.07/δ_C 41.6 ppm). On the basis of its COSY, TOCSY, ROESY, HMQC, and HMBC spectra, **3** was determined to be the 5-hydroxy derivative of **1**. The absolute stereochemistry of the 5-position of **3** was also determined as *S* by analysis of the ^{1}H NMR spectra of the Mosher esters **12** and **13** (Scheme 2). The stereochemistry at the 11-position and of the fucose and glucose moieties could not be determined experimentally because of the limited sample size. It is probable however that these stereochemistries are the same as those of ipomoeassin A (**1**) because the compounds almost certainly share the same biosynthetic pathway. Compound **3** exhibited the same positive direction of optical rotation as **1**, which supported the above assumption. The structure of ipomoeassin C is thus assigned as **3**.

The molecular formula of ipomoeassin D (**4**) was established as $C_{44}H_{60}O_{17}$ by HRFABMS. The ^{1}H NMR and ^{13}C NMR spectra of **4** were very similar to those of **3** (Tables 1 and 2). The major difference between **3** and **4** was the presence of an extra acetate group (C=O: δ_C 169.8; CH_3: δ_H 1.70/δ_C 20.3) at the 5-position in **4**, which resulted in chemical shift changes in the ^{1}H NMR spectra for H-5 from δ_H 3.96 (**3**) to δ_H 5.05 (**4**), and in the ^{13}C NMR spectrum for C-5 from δ_C 76.3 (**3**) to δ_C 78.4 (**4**). The structure and stereochemistry of **4** were confirmed by acetylation of both **3** and **4** separately to produce the same acetylated derivative, **7**, thus confirming that both **3** and **4** have the *S*-configuration at the 5-position.

Ipomoeassin E (**5**) was also obtained as a colorless oil, and its molecular formula of $C_{42}H_{58}O_{16}$ was determined by HRFABMS and ^{13}C NMR. The ^{1}H NMR spectrum of **5** was similar to that of **3**, with the only difference being the position of substitution of the acetyl group. In the HMBC spectrum of **5**, H-2, H-3, and H-5 correlated to C-4, and both H-5 (δ_H 5.04, dd, J = 6.2, 3.9 Hz) and H-AA-2′ (δ_H 1.67, s) showed HMBC correlations to the carbonyl group at δ_C 169.8 (C-AA-1′), which suggested that the acetoxyl group was located at C-5 in **5** instead of C-4′ as in **3**. The detailed assignments of the ^{1}H NMR and ^{13}C NMR signals were performed by COSY, TOCSY, ROESY, HSQC, and HMBC experiments. Acetylation of **5** gave **7**, which confirmed the structure of ipomoeassin E (**5**) and indicated that it had the same stereochemistry as **3** and **4** at the 5-position.

Table 3. Cytotoxicities of Compounds **1**−**7**[a]

	1	2	3	4	5	6	7
IC_{50} (μM)	0.5	0.4	2.9	0.035	3.3	15.8	19.1

[a] Concentration of each compound that inhibited 50% (IC_{50}) of the growth of the A2780 human ovarian cell line according to the procedure described.[12] Actinomycin D (IC_{50} 0.8−2.4 nM) was the positive control.

All the ipomoeassins showed cytotoxicity toward the A2780 ovarian cancer cell line.[12] Ipomoeassins A−C and E (**1**−**3** and **5**) were moderately active, with IC_{50} values ranging from 0.5 to 3.3 μM (Table 3). Interestingly, ipomoeassin D (**4**), which differs from ipomoeassin C (**3**) only by an acetyl group, is almost 2 orders of magnitude more cytotoxic than **3**, with an IC_{50} value of 35 nM. The fully acetylated compounds **6** and **7** were significantly less active than the ipomoeassins, with IC_{50} values of 15.8 and 19.1 μM. All this suggests that relatively minor structural variations may make significant differences to cytotoxicity and possibly other activities also, and warrants further investigation of these compounds.

A recent paper describes the X-ray crystal structure of tricolorin A (**14**), a related compound isolated from *I. tricolor*,[13] and proposes that this structure supports the hypothesis that the cytotoxic activity of compounds of this class is due to their ability to form pores in cell membranes. Although this is certainly possible, this hypothesis does not fully explain why our closely similar compounds show such different cytotoxicities; our work thus raises the possibility that other mechanisms of action are involved.

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. IR and UV spectra were measured on MIDAC M-series FTIR and Shimadzu UV-1201 spectrophotometers, respectively. NMR spectra were obtained on a JEOL Eclipse 500 or a Unity 400 spectrometer in C_6D_6 or $CDCl_3$. Mass spectra were obtained on a JEOL JMS-HX-110 instrument, in the positive ion mode. The chemical shifts are given in δ (ppm), and coupling constants are reported in Hz. A Horizon flash chromatograph from BioTage Inc. was used for flash column chromatography. HPLC was performed on a Shimadzu LC-10AT instrument with a semipreparative C18 or Phenyl Varian Dynamax column (5 μm, 250 × 10 mm) and a preparative C18 Varian Dynamax column (8 μm, 250 × 21.4 mm). A Finnigan LTQ LC/MS^n with a C18 Hypersil column (5 μm, 100 × 2.1 mm) was used for crude sample analysis.

Cytotoxicity Bioassays. Cytotoxicity measurements were performed at Virginia Polytechnic Institute and State University against the A2780 ovarian cancer cell line as previously

described. The A2780 cell line is a drug-sensitive ovarian cancer cell line.

Plant Material. Leaves of *Ipomoea squamosa* Choisy (Convolvulaceae) were collected in Sipaliwini, Suriname, in 1994, on the south side of Kuruni Island, on a riverbank east of the trail from camp to a canoe landing on the south branch of the Kuruni River around the island, ca. 30 airline km east of its confluence on the Corantijn River at 180 m in elevation. Collection was made by Randall Evans, George Lewis, Edgar Klass, and Marlan Wegman on November 25, 1994, and the sample was designated Evans 2000. Voucher specimens have been deposited in the National Herbarium of Suriname and at the Missouri Botanical Garden. The plant material was extracted at Bedrijf Geneesmiddelen Voorziening Suriname with EtOAc to give extract E940631.

Isolation. The crude extract (10 g, IC_{50} 8.0 μg/mL) of E940631 was separated using Biotage's Horizon high-performance flash chromatograph over C18 using MeCN/H_2O (75:25, 420 mL) and then 100% MeOH (210 mL), furnishing 30 tubes (21 mL/tube). Based on Si-gel TLC (DCM/MeOH, 20:1), these 30 tubes were combined into five fractions (I−V), of which fraction III (800 mg) was found to be the most active (IC_{50} 0.2 μg/mL). Five peaks were collected from fraction III using HPLC chromatography over C18 using 75% MeCN/H_2O, and ipomoeassin A (**1**, 60 mg, t_R 26 min), ipomoeassin B (**2**, 6 mg, t_R 16 min), and ipomoeassin E (**5**, 5 mg, t_R 14 min) were isolated as pure components. Ipomoeassins C and D (collected from C18 HPLC eluting with 75% MeCN/H_2O, t_R 10 and 23 min, respectively) were further purified on normal-phase (DCM/MeOH, 20:1) TLC (**3**, 4 mg, R_f 0.3) and reversed-phase (MeCN/H_2O, 92:8) phenyl HPLC (**4**, 7 mg, t_R 18 min).

Ipomoeassin A (1): colorless oil; $[\alpha]^{25}_D$ −36° (*c* 0.2, EtOH); IR (film) ν_{max} 3414, 2928, 2858, 1721, 1636, 1450, 1380, 1250, 1152, 1134, 1071; UV (EtOH) λ_{max} (log ϵ) 280 (3.90) nm; ^1H NMR (500 MHz, C_6D_6) and ^{13}C NMR (125 MHz, C_6D_6) data, see Tables 1 and 2, respectively; HRESIMS *m/z* 803.3854 (calcd for $C_{42}H_{59}O_{15}$, 803.3854).

Ipomoeassin B (2): colorless oil; $[\alpha]^{25}_D$ −39° (*c* 0.3, EtOH); IR (film) ν_{max} 3400, 2929, 2853, 1743, 1717, 1630, 1449, 1370, 1315, 1266, 1248, 1155, 1137, 1071; UV (EtOH) λ_{max} (log ϵ) 280 (4.04) nm; ^1H NMR (500 MHz, C_6D_6) and ^{13}C NMR (125 MHz, C_6D_6) data, see Tables 1 and 2, respectively; HRESIMS *m/z* 761.3729 (calcd for $C_{40}H_{57}O_{14}$ 761.3748).

Ipomoeassin C (3): colorless oil; $[\alpha]^{25}_D$ −29° (*c* 0.4, EtOH); IR (film) ν_{max} 3400, 2930, 2855, 1721, 1637, 1450, 1380, 1249, 1154, 1074; UV (EtOH) λ_{max} (log ϵ) 280 (3.80) nm; ^1H NMR (500 MHz, C_6D_6) and ^{13}C NMR (125 MHz, C_6D_6) data, see Tables 1 and 2, respectively; HRESIMS *m/z* 819.3806 (calcd for $C_{42}H_{59}O_{16}$ 819.3803).

Ipomoeassin D (4): colorless oil; $[\alpha]^{25}_D$ −35° (*c* 0.2, EtOH); IR (film) ν_{max} 3409, 2933, 2864, 1723, 1636, 1450, 1374, 1239, 1154, 1072; UV (EtOH) λ_{max} (log ϵ) 280 (4.29) nm; ^1H NMR (500 MHz, C_6D_6) and ^{13}C NMR (125 MHz, C_6D_6) data, see Tables 1 and 2, respectively; HRESIMS *m/z* 861.3909 (calcd for $C_{44}H_{61}O_{17}$, 861.3909).

Ipomoeassin E (5): colorless oil; $[\alpha]^{25}_D$ −24° (*c* 0.2, EtOH); IR (film) ν_{max} 3400, 2930, 2855, 1721, 1637, 1449, 1370, 1308, 1249, 1154, 1071; UV (EtOH) λ_{max} (log ϵ) 280 (4.06) nm; ^1H NMR (500 MHz, C_6D_6) and ^{13}C NMR (125 MHz, C_6D_6) data, see Tables 1 and 2, respectively; HRESIMS *m/z* 819.3784 (calcd for $C_{42}H_{59}O_{16}$ 819.3803).

Preparation of Derivatives 6 and 7. Ipomoeassins A−E (**1**−**5**, 1 mg each) were independently acetylated with Ac_2O/pyridine (1:1). Compounds **1** and **2** yielded **6**, while ipomoeassins C−E (**3**−**5**) gave **7**. Derivatives **6** (1.0 and 1.1 mg from **1** and **2**, respectively, t_R 17 min) and **7** (1.1, 1.0 and 1.1 mg from **3**, **4**, and **5**, respectively, t_R 19 min) were purified by C18 HPLC [Varian Dynamax column (8 μm, 250 × 21.4 mm), 2 mL/min, 85% MeOH/H_2O]. In each case the identities of the acetylated products were confirmed by comparison of ^1H NMR data, optical rotations, MS, and HPLC retention times.

3′,2″-*O*-Diacetylipomoeassin A (6): colorless oil; $[\alpha]^{25}_D$ −26° (*c* 0.1, EtOH); ^1H NMR (500 MHz, C_6D_6) δ_H 7.78 (1H, d, *J* = 16.1 Hz, H-CA-3), 6.88−7.02 [6H, m, H-TA-3,CA-5(×2),6-(×2),7], 6.36 (1H, d, *J* = 16.1 Hz, H-CA-2), 5.71 (1H, t, *J* = 9.7 Hz, H-3″ or 4″), 5.63 (1H, t, *J* = 9.7 Hz, H-4″ or 3″), 5.45 (1H, dd, *J* = 9.7, 8.0 Hz, H-2″), 5.31 (1H, d, *J* = 3.5 Hz, H-4′), 5.15 (1H, dd, *J* = 10.2, 3.5 Hz, H-3′), 4.96 (1H, d, *J* = 8.0 Hz, H-1″), 4.53 (1H, dd, *J* = 12.6, 3.0 Hz, H-6″), 4.30 (1H, d, *J* = 7.6 Hz, H-1′), 4.12 (1H, dd, *J* = 10.2, 7.6 Hz, H-2′), 4.02 (1H, dd, *J* = 12.6, 2.3 Hz, H-6″), 3.59 (1H, m, H-11), 3.15 (1H, br d, *J* = 9.7 Hz, H-5″), 3.07 (1H, br q, *J* = 6.5 Hz, H-5′), 2.70 and 2.21 (2H, m, H_2-3), 2.70 and 2.52 (2H, m, H_2-2), 2.09 (1H, m, H-5), 2.03 (3H, s, Ac), 1.91 (3H, s, Ac), 1.74 (3H, br s, H_3-TA-5), 1.71 (3H, s, Ac), 1.30−1.80 (15H, m, H-5 and H_2-6,7,8,9,10,12,13), 1.21 (3H, dd, *J* = 7.1, 1.2 Hz, H_3-TA-4), 0.96 (3H, d, *J* = 6.5 Hz, H_3-6″), 0.87 (3H, t, *J* = 7.1 Hz, H_3-14); HRESIMS *m/z* 887.4108 (calcd for $C_{46}H_{63}O_{17}$ 887.4065).

5,3′,2″-*O*-Triacetylipomoeassin C (7): colorless oil; $[\alpha]^{25}_D$ −30° (*c* 0.1, EtOH); ^1H NMR (500 MHz, C_6D_6) δ_H 7.77 (1H, d, *J* = 16.1 Hz, H-CA-3), 6.88−7.02 [6H, m, H-TA-3,CA-5(×2),6-(×2),7], 6.35 (1H, d, *J* = 16.1 Hz, H-CA-2), 5.66 (1H, t, *J* = 9.7 Hz, H-3″ or 4″), 5.61 (1H, t, *J* = 9.7 Hz, H-4″ or 3″), 5.35 (1H, dd, *J* = 9.7, 8.0 Hz, H-2″), 5.28 (1H, dd, *J* = 3.7, 1.4 Hz, H-4′), 5.15 (1H, dd, *J* = 9.5, 4.4 Hz, H-5), 5.10 (1H, dd, *J* = 10.1, 3.4 Hz, H-3′), 4.94 (1H, d, *J* = 8.0 Hz, H-1″), 4.49 (1H, dd, *J* = 12.4, 3.0 Hz, H-6″), 4.22 (1H, d, *J* = 7.8 Hz, H-1′), 4.07 (1H, dd, *J* = 10.1, 8.0 Hz, H-2′), 4.02 (1H, dd, *J* = 12.4, 1.8 Hz, H-6″), 3.59 (1H, m, H-11), 3.16 (1H, br d, *J* = 9.7 Hz, H-5″), 3.02 (1H, br q, *J* = 6.5 Hz, H-5′), 2.92 and 2.50 (2H, m, H_2-3), 2.63 and 2.58 (2H, m, H_2-2), 2.09 (1H, m, H-5), 2.01 (3H, s, Ac), 1.89 (3H, s, Ac), 1.88 (3H, s, Ac), 1.72 (3H, br s, H_3-TA-5), 1.70 (3H, s, Ac), 1.30−1.80 (14H, m, H_2-6,7,8,9,10,12,13), 1.23 (3H, dd, *J* = 7.1, 1.2 Hz, H_3-TA-4), 0.95 (3H, d, *J* = 6.4 Hz, H_3-6″), 0.88 (3H, t, *J* = 7.1 Hz, H_3-14); HRESIMS *m/z* 945.4141 (calcd for $C_{48}H_{65}O_{19}$ 945.4120).

Hydrolysis of 1. Approximately 40 mg of **1** was dissolved in 4 mL of freshly distilled THF and 6 mL of 1.0 M NaOH. The solution was refluxed for 3 h. The reaction was cooled to room temperature and acidified to pH 4 with 2.0 N HCl. This solution was extracted three times with 10 mL aliquots of ether. The ether extracts were combined and evaporated to dryness. A GC/CI-MS analysis identified two acids, cinnamic acid and 2-methylbut-2-enoic acid. To verify the identities, standard samples of the two acids were purchased and treated as above.

The aqueous-THF layer from the initial base hydrolysis was evaporated to dryness and dissolved in 4 mL of fresh THF containing 4 mL of 2.0 N HCl. The sample was refluxed for 4 h. The reaction was cooled to room temperature and extracted three times with 10 mL aliquots of ether. 11-Hydroxy-4-oxo-tetradecanoic acid (**8**, 5 mg) was deduced to be the major component in the ether extract on the basis of a main peak on C18 HPLC (MeOH/H_2O, 70:30; t_R 17 min) and its HRESIMS (*m/z* 259.1907, calcd for $C_{14}H_{27}O_4$, 259.1909). 11-Hydroxy-4-oxo-tetradecanoic acid (**8**, 4.0 mg) was reacted with excess diazomethane to furnish 11-hydroxy-4-oxo-tetradecanoic acid methyl ester (**9**, 4 mg).

Sugar Analysis of 1. The aqueous layer was neutralized with 1 M NaOH and extracted with n-BuOH (3 × 4 mL). The n-BuOH extract was evaporated to afford about 10 mg of a mixture of monosaccharides, which was subjected to TLC [$CHCl_3$/MeOH/H_2O (6:4:1): R_f 0.4 (D-glucose); 0.6 (D-fucose)][4] and HPLC [Varian Dynamax NH_2, 5 μm, 250 × 10 mm, 2 mL/min; 70% MeCN/H_2O; light scattering detector (Dedex 75, Sedere); D-glucose 1 mg, t_R = 19 min; D-fucose 1 mg, t_R = 14.6 min] analysis. The absolute configurations of the sugars were determined by their rotations. Glucose had $[\alpha]^{19}_D$ +114° (*c* 0.1, H_2O), and fucose had $[\alpha]^{19}_D$ +116° (*c* 0.09, H_2O). An aliquot of the hydrolysis mixture was derived with Sigma Sil-A for 35 min at 70 °C. GC-MS analysis[4] [Varian GC column, VF-5MS; 30 m × 0.32 mm (i.d.); film thickness 0.25 mm; 80−280 °C at 80 °C/min; injection temperature 200 °C] allowed the identification of the following TMS-sugars by coelution with authentic samples: penta-TMS-glucose, t_R = 16.3 min; tetra-TMS-fucose, t_R = 13.2 min.

11-Hydroxy-4-oxo-tetradecanoic acid (8): colorless oil; $[\alpha]^{25}_D$ −25° (*c* 0.1, EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ_H 3.60 (1H, m, H-11), 2.73 (2H, m, H-3), 2.64 (2H, m, H-2), 2.45 (2H, t, *J* = 7.3 Hz, H-5), 1.60 (2H, m, H-6), 1.30−1.48 (12H, m, H_2-

7-H_2-10, H_2-12 and H_2-13), 0.93 (3H, t, $J = 7.0$ Hz, H-14); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 209.5 (C-4), 175.8 (C-1), 71.7 (C-11), 42.6 (C-5), 39.6 (C-12), 37.3 (C-10), 37.0 (C-2), 29.7 (C-8), 29.3 (C-7), 29.0 (C-3), 25.3 (C-9), 23.6 (C-6), 18.8 (C-13), 14.1 (C-14); HRESIMS *m/z* 259.1907 (calcd for $C_{14}H_{27}O_4$, 259.1909).

11-Hydroxy-4-oxo-tetradecanoic acid methyl ester (9): colorless oil; $[\alpha]^{25}_D$ $-4°$ (*c* 0.1, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.67 (3H, s, OMe), 3.59 (1H, m, H-11), 2.71 (2H, t, $J = 6.3$ Hz, H-3), 2.59 (2H, t, $J = 6.3$ Hz, H-2), 2.45 (2H, t, $J = 7.3$ Hz, H-5), 1.59 (2H, m, H-6), 1.30−1.48 (12H, m, H_2-7−H_2-10, H_2-12 and H_2-13), 0.92 (3H, t, $J = 7.2$ Hz, H-14); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 209.2 (C-4), 173.3 (C-1), 71.7 (C-11), 51.7 (OMe), 42.7 (C-5), 39.5 (C-12), 37.5 (C-10), 36.8 (C-2), 29.4 (C-8), 29.0 (C-7), 27.6 (C-3), 25.4 (C-9), 23.5 (C-6), 18.7 (C-13), 13.9 (C-14); HRESIMS *m/z* 273.2066 (calcd for $C_{15}H_{29}O_4$, 273.2066).

Mosher Esters 10 and 11. To a solution of (*R*)-MPA (6.0 mg) and DMAP (5.0 mg) in CH_2Cl_2 (0.5 mL) was added 11-hydroxy-4-oxo-tetradecanoic acid methyl ester (**9**, 1 mg) in CH_2Cl_2 (0.5 mL), followed by EDCI (5.0 mg), and the resulting solution was stirred for 12 h. EtOAc was then added to quench the reaction and the solution concentrated. The resulting residue was purified on C18 HPLC, eluting with MeOH/H_2O, 85:15, to give **10** (1.5 mg, 97%, t_R 12 min). Treatment of **9** with (*S*)-MPA by the same procedure as described above, and eluting with MeOH/H_2O, 80:20, yielded **11** (1.2 mg, 78%, t_R 17 min).

11-(*R*-MPA)-4-oxo-tetradecanoic acid methyl ester (10): colorless oil; $[\alpha]^{25}_D$ $-13°$ (*c* 0.1, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.44 (2H, m), 7.35 (3H, m), 4.90 (1H, m, H-11), 4.73 (1H, s), 3.67 (3H, s, 1-OMe), 3.42 (3H, s, OMe), 2.72 (2H, t, $J = 6.4$ Hz, H-3), 2.59 (2H, t, $J = 6.4$ Hz, H-2), 2.43 (2H, t, $J = 7.3$ Hz, H-5), 1.49 (2H, m, H_2-10), 1.38 (2H, m, H_2-12), 1.15−1.30 (6H, m, H_2-6−H_2-8), 1.23 (2H, m, H_2-9), 0.98 (2H, m, H_2-13), 0.71 (3H, t, $J = 7.4$ Hz, H_3-14); HRESIMS *m/z* 421.2574 (calcd for $C_{24}H_{37}O_6$ 421.2590).

11-(*S*-MPA)-4-oxo-tetradecanoic acid methyl ester (11): colorless oil; $[\alpha]^{25}_D$ $-2°$ (*c* 0.1, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.44 (2H, m), 7.35 (3H, m), 4.91 (1H, m, H-11), 4.72 (1H, s), 3.67 (3H, s, 1-OMe), 3.41 (3H, s, OMe), 2.71 (2H, t, $J = 6.4$ Hz, H-3), 2.59 (2H, t, $J = 6.4$ Hz, H-2), 2.38 (2H, t, $J = 7.3$ Hz, H-5), 1.46 (2H, m, H_2-12), 1.37 (2H, m, H_2-10), 1.27 (2H, m, H_2-13), 1.00−1.10 and 1.00−1.10 (6H, m, H_2-6-H_2-8), 0.91 (2H, m, H_2-9), 0.88 (3H, t, $J = 7.4$ Hz, H_3-14); HRESIMS *m/z* 421.2607 (calcd for $C_{24}H_{37}O_6$ 421.2590).

Mosher Esters 12 and 13. To a solution of (*R*)-MPA (6.0 mg) and DMAP (5.0 mg) in CH_2Cl_2 (0.5 mL) was added **3** (1 mg) in CH_2Cl_2 (0.5 mL), followed by EDCI (5.0 mg), and the resulting solution was stirred for 12 h. EtOAc was then added to quench the reaction and the solution concentrated. The resulting residue was purified on C18 HPLC, eluting with MeCN/H_2O, 85:15, to give **12** (1.3 mg, 95%, t_R 17 min). Treatment of **3** with (*S*)-MPA by the same procedure described above yielded **13** (1 mg, 75%, t_R 18.5 min).

5-(*R*-MPA)-ipomoeassin C (12): colorless oil; $[\alpha]^{25}_D$ $-8°$ (*c* 0.1, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.64 (1H, d, $J = 16.0$ Hz, H-CA-3), 7.30−7.55 (15H, m), 6.86 (1H, m, H-TA-3), 6.36 (1H, d, $J = 16.0$ Hz, H-CA-2), 5.25 (3H, m, H-3″,4″,4′), 5.06 (1H, dd, $J = 6.2$, 4.2 Hz, H-5), 4.78 (1H, dd, $J = 10.3$, 3.4 Hz, H-3′), 4.90 (1H, s), 4.78 (1H, s), 4.61 (1H, d, $J = 7.8$ Hz, H-1″), 4.42 (1H, d, $J = 7.8$ Hz, H-1′), 4.37 (1H, dd, $J = 12.2$, 3.2 Hz, H-6″), 4.15 (1H, dd, $J = 12.2$, 3.0 Hz, H-6″), 3.99 (1H, dd, $J = 10.3$, 7.8 Hz, H-2′), 3.72 (2H, m, H-5′,5″), 3.65 (1H, m, H-11), 3.50 (1H, m, H-2″), 3.44 (3H, s, OMe), 3.31 (3H, s, OMe), 2.82 and 2.69 (2H, m, H_2-3), 2.69 and 2.53 (2H, m, H_2-2), 1.97 (3H, s, Ac), 1.77 (3H, br s, H_3-TA-5), 1.75 (1H, m, H_2-7), 1.71 (3H, dd, $J = 7.2$, 1.2 Hz, H_3-TA-4), 1.69 (1H, m, H_2-6), 1.20−1.90 (10H, m, H_2-8,9,10,12,13), 1.13 (3H, d, $J = 6.5$ Hz, H_3-6″), 0.90 (3H, t, $J = 7.1$ Hz, H_3-14); HRESIMS *m/z* 1115.4899 (calcd for $C_{60}H_{75}O_{20}$ 1115.4852).

5-(*S*-MPA)-ipomoeassin C (13): colorless oil; $[\alpha]^{25}_D$ $-4°$ (*c* 0.1, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.61 (1H, d, $J = 16.0$ Hz, H-CA-3), 7.30−7.55 (15H, m), 6.87 (1H, m, H-TA-3), 6.34 (1H, d, $J = 16.0$ Hz, H-CA-2), 5.25 (1H, t, $J = 9.9$ Hz, H-3″), 5.21 (1H, d, $J = 5.0$ Hz, H-4′), 5.16 (1H, t, $J = 9.9$ Hz, H-4″), 5.09 (1H, dd, $J = 6.6$, 3.4 Hz, H-5), 5.00 (1H, dd, $J = 11.5$, 5.0 Hz, H-3′), 4.89 (1H, s), 4.76 (1H, s), 4.59 (1H, d, $J = 7.8$ Hz, H-1″), 4.44 (2H, m, H-1′,6″), 4.00 (2H, m, H-2′,6″), 3.71 (2H, m, H-5′,5″), 3.62 (1H, dd, $J = 12.2$, 3.0 Hz, H-5″), 3.48 (3H, s, OMe), 3.37 (1H, m, H-2″), 3.34 (3H, s, OMe), 2.56 and 2.43 (2H, m, H_2-3), 2.43 and 2.13 (2H, m, H_2-2), 1.93 (3H, s, Ac), 1.81 (3H, br s, H_3-TA-5), 1.79 (1H, m, H_2-7), 1.73 (3H, d, $J = 7.2$ Hz, H_3-TA-4), 1.72 (1H, m, H_2-6), 1.20−1.90 (10H, m, H_2-8,9,10,12,13), 1.10 (3H, d, $J = 6.5$ Hz, H_3-6′), 0.90 (3H, t, $J = 7.4$ Hz, H_3-14); HRESIMS *m/z* 1115.4852 (calcd for $C_{60}H_{75}O_{20}$ 1115.4852).

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Supporting Information Available: ^{1}H NMR spectra of **1**−**5** and **10**−**13**. These materials are available free of charge via the Internet at http://pubs.acs.org.

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