Limonoids from *Swietenia macrophylla* and *S. aubrevilleana*

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An investigation of the seeds of *Swietenia macrophylla* and *S. aubrevilleana* (Meliaceae) is reported. Three new compounds, augustineolide (**1**) and 3β,6-dihydroxydihydrocarapin (**2**) from *S. macrophylla* and 6-acetoxyhumilinolide C (**3**) from *S. aubrevilleana* were isolated and characterized along with fifteen known compounds. Four of the compounds were subjected to an antifeedant bioassay on the final instar larvae of *Spodoptera frugiperda*. The antifeedant activity was comparable to that of bicyclononanolides previously tested.[13]

The isolation of thirty six limonoids from the seeds of *S. mahagoni*[1,2] collected in Medan, Indonesia and the interesting bioactivity reported for these compounds prompted us to reinvestigate the local *Swietenia* species.[3] Of the four known *Swietenia* species, viz. *S. aubrevilleana, S. humilis, S. macrophylla*, and *S. mahagoni*, only *S. humilis* does not occur in Trinidad. *S. aubrevilleana* is the only species that has not been previously investigated. *S. aubrevilleana* is a hybrid of *S. mahagoni* and *S. macrophylla*.[4] It is distributed throughout the West Indies and is also found in the Far East, Taiwan, and Indonesia.[4] We report here on the investigation of the seeds of *S. macrophylla* King and *S. aubrevilleana* Stehle and Cusin collected on the grounds of the St. Augustine campus, University of the West Indies (UWI), Trinidad, West Indies.

Fifteen limonoids were isolated from *S. macrophylla*: 7-deacetoxy-7-oxogedunin,[5] andirobin,[5] and thirteen bicyclononanolides. Eleven of the latter were the known compounds swietenine, proceranolide, swietenolide, 6-*O*-acetylswietenolide, 3,6-*O*,*O*-diacetylswietenolide, khayasin T, and swietemahonins E−G all recently reported from *S. mahagoni*,[1,2] 2-hydroxyswietenine,[6] and 6-deoxyswietenine (febrifugin).[7] In addition we report the new compounds augustineolide (**1**) and 3β,6-dihydroxydihydrocarapin (**2**).

Six of the compounds identified above together with deacetylgedunin,[8] 6-hydroxymethylangolensate,[9] and a new compound 6-acetoxyhumilinolide C (**3**) were identified from *S. aubrevilleana*.

All of the known compounds were identified by detailed analysis of their respective high resolution ^{1}H and ^{13}C NMR spectra including COSY, HETCOR, and HMBC correlations.

Results and Discussion

Augustineolide (**1**), $C_{38}H_{48}O_{14}$ (HREIMS), showed hydroxyl (3500 cm^{-1}), carbonyl (1735−1720 cm^{-1}), and furan (880 cm^{-1}) absorption maxima in the IR spectrum. The ^{1}H and ^{13}C NMR spectra gave signals that were similar to those of swietenolide (**4**)[1] including the fully substituted olefinic resonances at δ_C 134.0 and 139.1 due to C-8 and C-14, respectively.

Compound **1**, however, was much more highly substituted than swietenolide and showed three additional carbonyl resonances (δ_C 166.7, 169.4, and 174.0) due to tiglate, acetate and isobutanoate moieties, and these were placed at C-3, C-15, and C-30, respectively. The signal at δ_C 166.7 showed HMBC correlations to H-3 (δ_H 5.01), δ_C 169.4 to H-15 (δ_H 6.57), and δ_C 174.0 to H-30 (δ_H 5.72).The carbinol protons at C-3 and C-30 were both singlets which implied that C-2 was fully substituted, and also bore a hydroxyl functionality which resonated at δ_C 78.9 and showed $^2J_{CH}$ correlations to both H-3 (δ_H 5.01) and H-30 (δ_H 5.72). The detailed bond connectivities and assignments of all the ^{1}H and ^{13}C NMR signals were obtained from the HMQC, COSY, and HMBC data.

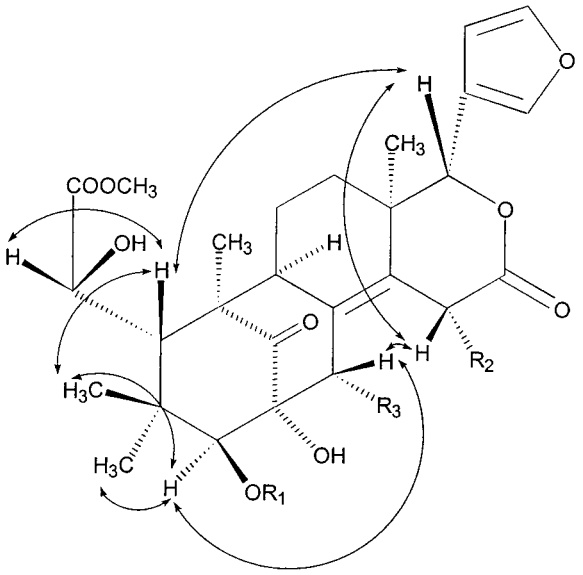

Figure 1. Major NOESY correlations of augustineolide (**1**).

The relative stereochemistry at C-2, C-3, C-5, C-6, and C-17 and at the ring junctions were assumed from biogenetic analogy with swietenolide (**4**). The NOESY data (Figure 1) is consistent with these assignments and also confirms the stereochemistry at the new asymmetric centers, C-15 and C-30.

3β,6-Dihydroxydihydrocarapin (**2**) was isolated as a white amorphous solid. The molecular formula, $C_{27}H_{34}O_8$, was obtained from the HREIMS data. The IR spectrum showed hydroxyl (3480 cm^{-1}), carbonyl (1720 cm^{-1}), and

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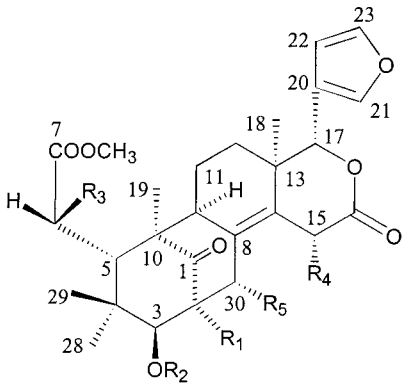
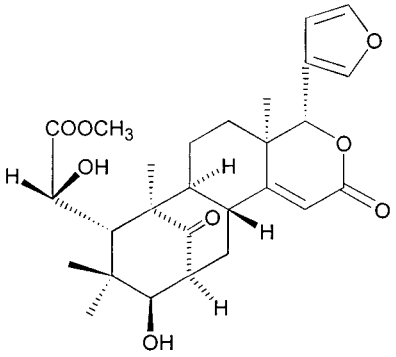
Chart 1

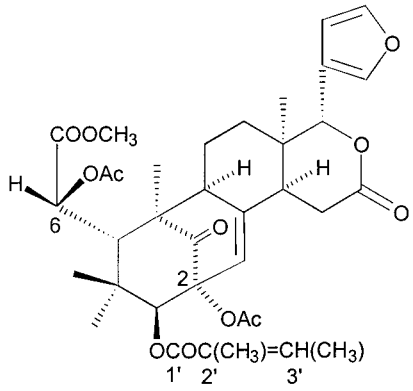


1	R_1 = OH	R_2 = Tg	R_3 = OH	R_4 = OAc	R_5 = 4' 5' $OCOCH(CH_3)_2$
4	R_1 = H	R_2 = H	R_3 = OH	R_4 = H	R_5 = H
5	R_1 = H	R_2 = H	R_3 = OAc	R_4 = H	R_5 = H
6	R_1 = H	R_2 = Ac	R_3 = OAc	R_4 = H	R_5 = H

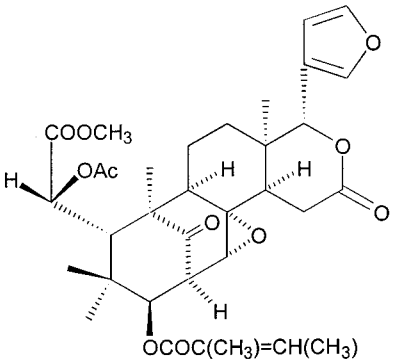
1' 2' 3'
Tg = $COC(CH_3)=CH(CH_3)$



2



3



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furan (880 cm^{-1}) absorption maxima. The UV spectrum (MeOH) λ_{max} (log ϵ) 213 (4.16) nm was consistent with an a, β-unsaturated δ-lactone.

The NMR data of **2** indicated a bicyclononanolide structure. A trisubstituted olefin was present (HETCOR) at Δ,[14,15] confirming the α,β-unsaturated δ-lactone inferred from the UV and IR spectra. The proton on C-15 (δ 5.84, d, J = 2.5 Hz) showed $^2J_{CH}$ bond connectivity with C-16 (δ_C 164.9) and $^3J_{CH}$ correlation with C-13 (δ_C 38.2). Three oxymethine proton signals were present at δ_H 3.66, 4.62, and 5.10. The resonance at δ_H 5.10 was characteristic of H-17 in the limonoids and was confirmed by COSY coupling to H-21 (δ_H 7.48, dd, J = 1.8, 0.8 Hz). The other two signals were due to protons on hydroxyl bearing carbon atoms and were placed at C-3 and C-6. Both H-3 (δ_H 3.66, d, J = 10.0 Hz) and H-5 (δ_H 3.32, br s) showed $^3J_{CH}$ connectivities to the gem-dimethyl carbons C-28 and C-29 and H-6 (δ_H 4.62, br s) showed COSY coupling to H-5.

The stereochemistry of **2** was assigned by biogenetic analogy and by relating **2** to 3β-acetoxydihydrocarapin.[10] COSY coupling of H-8 (δ_H 3.23 m) to H-15 (δ_H 5.84, d, J = 2.5 Hz) and its NOESY correlation to H-5 (δ_H 3.32, br s) further confirmed the β-orientation of H-8.

The new compound (**3**) from *S. aubrevilleana*, $C_{36}H_{44}O_{12}$ (HREIMS), showed carbonyl (1770−1720 cm^{-1}) and furan (880 cm^{-1}) absorption maxima in the IR spectrum. The ^1H and ^{13}C NMR spectra of **3** revealed its close resemblance to humilinolides C and D.[11] From HMBC data, C-5 was readily identified (δ_C 44.7) and it showed connectivities to the C-28 and C-29 methyl protons (δ_H 1.27 and δ_H 0.91) as well as to H-3 (δ_H 5.43, s) and H-6 (δ_H 5.59, br s). The corresponding proton, H-5 (δ_H 3.62, br s) showed COSY correlation with H-6.

The characteristic olefinic proton on the C-8/C-30 double bond (δ_H 5.36, t, J = 1.5 Hz) showed $^3J_{CH}$ and $^2J_{CH}$ correlation to C-1 (δ_C 206.9) and C-2 (δ_C 85.0), respectively. In addition, H-3 correlated to C-2 as well as to the carbonyl of the tiglate moiety attached to C-3. The complete structure is revealed as 6-acetoxyhumilinolide C (**3**) (Chart 1).

In our continuing appraisal of limonoids as antifeedant agents four of the compounds, swietenolide (**4**), 6-*O*-acetylswietenolide (**5**), 3,6-*O*,*O*-diacetylswietenolide (**6**), and swietemahonin F (**7**) were subjected to a bioassay on the final instar larvae of *Spodoptera frugiperda*[12,13] at concentrations of 1000 ppm. The results showed antifeedant activity comparable (Table 1) to each other and to ruageanins A and

Table 1. Antifeedant Activity of Compounds Bioassayed with *S. frugiperda* (Final Instar Larvae)[12,13]

compound	AI[a] ± SEM
swietenolide (**4**)[2]	94.1 ± 2.90
6-*O*-acetylswietenolide (**5**)[1]	72.2 ± 19.60
3,6-*O*,*O*-diacetylswietenolide (**6**)[1]	72.0 ± 9.38
swietemahonin F (**7**)[2]	70.2 ± 8.90

[a] AI represents the antifeedant index calculated from AI = $[(C - T)/(C + T)] \times 100$. *C* and *T* represent the amount eaten by the larvae of the control and treatment disks, respectively (Wilcoxin's matched pairs test, $p < 0.05$).

B,[13] two bicyclononanolides which were obtained previously from *Ruagea glabra*.

Experimental Section

General Experimental Procedures. These are as described in the literature.[13]

Plant Material. The fruits of *S. macrophylla* and *S. aubrevilleana* were collected in February, 1993, at (UWI), Trinidad. Voucher specimens of *S. aubrevilleana* (33272) and *S. macrophylla* (33274) are deposited at the National Herbarium of Trinidad and Tobago.

Extraction and Isolation of *S. macrophylla*. The dried ground seeds of *S. macrophylla* (3.0 kg) were extracted with acetone (20 L) to give an acetone extract (1.0 kg). This was washed with petroleum ether (60−80 °C) and triturated with EtOAc to yield a brown gum on evaporation of the solvent (215 g).

In an initial investigation, a portion of the EOAc extract (15.0 g) was subjected to silica gel column chromatography using $CHCl_3$ with increasing amounts of EtOAc. Fractions were combined on the basis of their TLC profiles to give nineteen fractions in order of increasing polarity. Further PTLC purification of selected fractions using varying concentrations of petroleum ether−EtOAc as solvent gave swietemahonin F (**7**, 70 mg, mp 279−81 °C), 7-deacetoxy-7-oxogedunin (250 mg, mp 264−66 °C), 6-deoxyswietenine (10 mg, oil), 3,6-*O*,*O*-diacetylswietenolide (**6**, 41 mg, mp 223−25 °C), swietenine (46 mg, mp 275−76 °C), proceranolide (15 mg, oil), 6-*O*-acetylswietenolide (**5**, 20 mg, mp 262−64 °C), 2-hydroxyswietenine (18 mg, mp 217−19 °C), swietenolide (**4**, 10 mg, mp173−74 °C), and 3*β*,6-dihydroxydihydrocarapin (**2**, 9 mg, amorphous solid). Swietemahonin G (21 mg, mp 136−38 °C) was obtained from a fraction following PTLC with petroleum ether−$CHCl_3$−MeOH (9:40:1, ×2).

From a second column chromatography of the crude EtOAc extract (72.0 g) four additional compounds were obtained from two selected early fractions. One fraction on further column chromatography followed by PTLC yielded khayasin T (46 mg, colorless gum, CH_2Cl_2−EtOAc, 49:1, ×2), andirobin (49 mg, yellow oil, CH_2Cl_2−EtOAc, 49:1, ×2), and swietemahonin E (118 mg, mp 242−50 °C, hexanes−EtOAc, 3:2, ×2). The other fraction, on repeated PTLC yielded augustineolide (**1**, 10 mg, colorless oil, CH_2Cl_2−MeOH, 70:1, ×4; CH_2Cl_2−EtOAc, 5:1).

Extraction and Isolation of *S. aubrevilleana*. The dried ground seeds (3.5 kg) were subjected to an extraction scheme similar to that used for *S. macrophylla*. The final petroleum ether-insoluble, EtOAc-soluble extract of the seeds (49.6 g) was subjected to silica gel column chromatography with a $CHCl_3$−EtOAc solvent mixture and the fractions combined on the basis of their TLC profiles to give seventeen fractions.

Further purification of these fractions by column chromatography and PTLC gave 3*β*,6-dihydroxydihydrocarapin, swietenolide, 6-*O*-acetylswietenolide, 3,6-*O*,*O*-diacetylswietenolide, and 7-deacetoxy-7-oxogedunin from fractions of similar polarity as for *S. macrophylla*. The material eluted from the column with $CHCl_3$−EtOAc (95:1) yielded from selected fractions, (i) 6-hydroxymethylangolensate (30 mg, mp 248−50 °C) by further column chromatography (hexane−acetone, 4:1) and PTLC (hexanes−EtOAc, 2:1, ×6); (ii) 6-acetoxyhumilinolide C (**3**, 197 mg, mp 206−08 °C) by column chromatography (benzene−MeOH, 25:1); and (iii) deacetylgedunin (200 mg, mp 275−77 °C by column chromatography (hexane−acetone, 4:1).

Augustineolide (1): colorless oil; $[\alpha]^{25}_D$ −8.3° (*c* 0.12, $CHCl_3$); IR (thin film) ν_{max} 3500, 1735, 1720, 1500, 880 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.56 (1H, m, H-21), 7.44 (1H, t, J = 2.3 Hz, H-23), 6.77 (1H, dq, J = 7.0, 1.6 Hz, H-3′), 6.57 (1H, d, J = 2.5 Hz, H-15), 6.44 (1H, dd, J = 2.3, 1.2 Hz, H-22), 5.72 (1H, s, H-30), 5.58 (1H, s, H-17), 5.01 (1H, s, H-3), 4.60 (1H, br s, H-6), 3.86 (3H, s, OCH_3), 3.41 (1H, br s, H-5), 2.46 (1H, m, H-9), 2.46 (1H, sept, J = 7.0 Hz, H-5′), 2.04 (3H, s, OCOCH_3), 2.01 (3H, br s, CH_3-2′), 1.96 (1H, m, H-11), 1.82 (1H, m, H-11), 1.79 (1H, m, H-12), 1.79 (3H, dd, J = 7.0, 1.6 Hz, CH_3-3′), 1.57 (3H, s, CH_3-19), 1.19 (1H, m, H-12), 1.14, 1.08 (2 × 3H, d, J = 7.0 Hz, 2 × CH_3-5′), 1.05 (3H, s, CH_3-18), 1.04 (3H, s, CH_3-28), 0.83 (3H, s, CH_3-29); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.6 (C-1), 175.0 (C-7), 174.0 (C-4′), 169.4 (O*C*OCH$_3$), 167.7 (C-16), 166.7 (C-1′), 143.3 (C-23), 141.6 (C-21), 139.1 (C-14), 136.4 (C-3′), 134.0 (C-8), 131.3 (C-2′), 120.5 (C-20), 109.7 (C-22), 86.5 (C-3), 80.4 (C-17), 78.9 (C-2), 73.8 (C-30), 73.2 (C-6), 64.5 (C-15), 53.4 (O*C*H$_3$), 52.3 (C-10), 49.0 (C-9), 45.8 (C-5), 40.2 (C-4), 39.2 (C-13), 33.9 (C-5′), 29.1 (C-12), 23.3 (*C*H$_3$-29), 22.3 (*C*H$_3$-28), 21.3 (OCO*C*H$_3$), 19.2, 18.5 (2 × *C*H$_3$-5′), 18.5 (C-11), 17.9 (*C*H$_3$-19), 17.5 (*C*H$_3$-18), 14.4 (*C*H$_3$-3′), 12.8 (*C*H$_3$-2′); EIMS *m*/*z* 728 $[M]^+$ (3), 668 (2), 632 (13), 605 (5), 580 (6), 532 (8), 502 (15), 480 (6), 445 (6), 411 (22), 374 (13), 321 (12), 293 (6), 259 (25), 223 (27), 201 (10), 153 (22), 83 (100); HREIMS *m*/*z* 728.3021 (calcd for $C_{38}H_{48}O_{14}$, 728.3044).

3*β*,6-Dihydroxydihydrocarapin (2): amorphous solid; $[\alpha]^{25}_D$ +39.2° (*c* 0.18, MeOH); UV (MeOH) λ_{max} (log ϵ) 213 (4.16) nm; IR (thin film) ν_{max} 3480, 1720, 1520, 880 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48 (1H, dd, J = 1.8, 0.8 Hz, H-21), 7.39 (1H, t, J = 1.8 Hz, H-23), 6.43 (1H, dd, J = 1.8, 0.8 Hz, H-22), 5.84 (1H, d, J = 2.5 Hz, H-15), 5.10 (1H, br s, H-17), 4.62 (1H, br s, H-6), 3.90 (3H, s, OCH_3), 3.66 (1H, d, J = 10.0 Hz, H-3), 3.32 (1H, br s, H-5), 3.23 (1H, m, H-8), 3.01 (1H, ddd, J = 10.0, 5.4, 1.8 Hz, H-2), 2.83 (1H, ddd, J = 14.5, 5.5, 2.5 Hz, H-30), 1.83 (2H, m, H-11), 1.81 (1H, m, H-9), 1.59 (1H, m, H-30), 1.54 (1H, m, H-12), 1.40 (1H, m, H-12), 1.37 (3H, s, CH_3-19), 1.06 (3H, s, CH_3-18), 1.02 (3H, s, CH_3-28), 0.97 (3H, s, CH_3-29); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 219.9 (C-1), 176.4 (C-7), 171.0 (C-14), 164.9 (C-16), 143.0 (C-23), 141.2 (C-21), 120.1 (C-20), 112.8 (C-15), 109.9 (C-22), 81.2 (C-17), 78.9 (C-3), 73.7 (C-6), 53.4 (O*C*H$_3$), 51.5 (C-10), 49.6 (C-9), 48.0 (C-2), 43.5 (C-5), 39.8 (C-4), 38.2 (C-13), 35.2 (C-8), 34.7 (C-30), 26.7 (C-12), 24.1 (*C*H$_3$-29), 22.9 (*C*H$_3$-28), 18.6 (C-11), 18.2 (*C*H$_3$-18), 17.3 (*C*H$_3$-19); EIMS *m*/*z* 486 $[M]^+$ (14), 429 (6), 396 (28), 390 (100), 362 (11), 344 (7), 329 (6), 301 (56), 283 (40), 273 (37), 269 (23), 255 (54), 241 (15), 227 (21), 207 (9), 175 (6), 137 (82), 119 (44), 105 (25), 91 (28), 79 (16); HREIMS *m*/*z* 487.2330 $[M+H]^+$ (calcd for $C_{27}H_{35}O_8$, 487.2332).

6-Acetoxyhumilinolide C (3): colorless needles (MeOH): mp 206−208 °C; $[\alpha]^{25}_D$ −114.3° (*c* 0.35, MeOH); IR (Nujol) ν_{max} 1770−1720 (broad), 880 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69 (1H, s, H-21), 7.45 (1H, t, J = 1.5 Hz, H-23), 6.89 (1H, dq, J = 7.0, 1.5 Hz, H-3′), 6.44 (1H, dd, J = 1.6, 1.0 Hz, H-22), 5.63 (1H, s, H-17), 5.59 (1H, br s, H-6), 5.43 (1H, s, H-3), 5.36 (1H, t, J = 1.5 Hz, H-30), 3.71 (3H, s, OCH_3), 3.62 (1H, br s, H-5), 2.86 (2H, m, H-15), 2.31 (1H, m, H-9), 2.31 (1H, m, H-14), 2.18 (1H, m, H-11), 2.18 (3H, s, OCOCH_3-6), 2.14 (3H, s, OCOCH_3-2), 1.83 (3H, s, CH_3- 3′), 1.81 (1H, m, H-11), 1.77 (3H, dd, J = 7.0, 1.6 Hz, CH_3-2′), 1.76 (1H, m, H-12), 1.45 (1H, m, H-12), 1.27 (3H, s, CH_3-28), 1.26 (3H, s, CH_3-19), 1.06 (3H, s, CH_3-18), 0.91 (3H, s, CH_3-29); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.9 (C-1), 171.0 (C-7), 169.7 (O*C*OCH$_3$-6), 169.0 (O*C*OCH$_3$-2), 168.6 (C-16), 166.3 (C-1′), 143.1 (C-23), 141.3 (C-21), 139.6 (C-3′), 137.0 (C-8), 127.3 (C-2′), 126.0 (C-30), 120.8 (C-20), 109.4 (C-22), 85.0 (C-2), 80.3 (C-3), 76.9 (C-17), 72.5 (C-6), 56.9 (C-9), 53.3 (O*C*H$_3$), 50.4 (C-10), 45.1 (C-14), 44.7 (C-5), 41.1 (C-4), 36.7 (C-13), 34.4 (C-12), 29.6 (C-15), 23.4 (*C*H$_3$-28), 22.3 (*C*H$_3$-29), 21.6 (*C*H$_3$-18), 21.5 (OCO*C*H$_3$-2), 21.0 (OCO*C*H$_3$-6), 21.0 (C-11), 15.5 (*C*H$_3$-19), 14.7 (*C*H$_3$-2′), 11.9 (*C*H$_3$-3′); EIMS *m*/*z* 668 $[M]^+$ (6), 626 (53), 569 (8), 526 (7), 484 (18), 451 (4), 409 (5), 379 (6), 339 (5), 269 (3), 191 (10), 155 (8), 134 (15), 83 (100); HREIMS *m*/*z* 668.2831 (calcd for $C_{36}H_{44}O_{12}$, 668.2833).

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