Five New Withanolides from *Tacca plantaginea*

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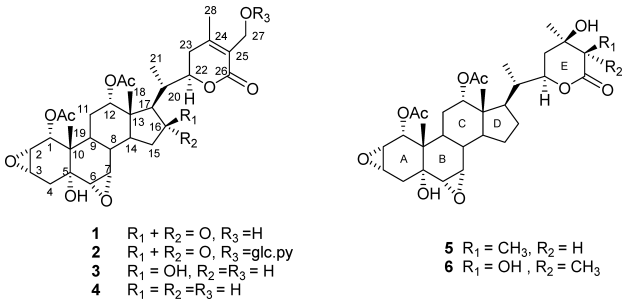
Five new withanolides named plantagiolides A—E (1, 3—6), together with a known withanolide glucoside, chantriolide A (2) were isolated from the whole plants of *Tacca plantaginea* (HANCE). Their structures were elucidated by means of spectroscopic methods including extensive 1D and 2D-NMR techniques.

Key words *Tacca plantaginea*; plantagiolide A; plantagiolide B; plantagiolide C; plantagiolide D; plantagiolide E

Taccaeae, a small family, includes Tacca and Schizacapsa genus and is predominately distributed in the tropical region of Asia, the Pacific Islands, and Australia.[1)] Taccalonolides,[2—4)] anthocyanins,[5)] diarylheptanoids and diarylheptanoid glucosides,[6)] steroidal sapogenins and steroidal glycosides such as C-27 steroidal saponins, C-28 sterol glucosides and withanolide glucosides[7—15)] have been isolated from some Tacca species.

Tacca plantaginea (HANCE) is a perennial plant that grows in southeastern China. Its rhizomes is a folk medicine used as analgesic, antipyretic, anti-inflammatory agents and for the treatment of incised wounds.[16)] Chen and co-workers have reported the isolation and purification of the highly oxygenated taccalonolides from the rhizomes of *T. plantaginea*.[17—21)] Taccalonolides A and E were claimed to be important for initiation of paclitaxel-like microtubule bundling; therefore, they represent the first plantderived microtubule-stabilising agents to be identified since paclitaxel and the first natural steroids to show microtuble-stabilizing activity.[22)] Previously, we have reported two new steroidal saponins from this whole plant.[23)] Further chemical investigation on the $CHCl_3$ soluble part of the EtOH extracts of this plant resulted in the isolation of five new withanolides, named plantagiolides A—E (**1**, **3**—**6**). The known chantriolide A (**2**) was separated from the AcOEt soluble part. The structures of the five new compounds were determined by analysis of their spectral data, especially two dimensional (2D) NMR spectra. Herein, we reported the isolation and structural elucidation of those compounds.

Plantagiolide A (**1**) was obtained as colorless needles. Its molecular formula of $C_{32}H_{42}O_{11}$ was established by the positive high-resolution electrospray ionization mass spectrum (HR-ESI-MS) ($[M+Na]^+$, *m*/*z* 625.2623) and ^{13}C-NMR spectrum (Table 2), a molecular formula corresponding to 12 degrees of unsaturation. A careful comparison the ^1H- and ^{13}C-NMR data of **1** with those of the aglycone of chantriolide A (**2**),[13)] it was obvious that compound **1** was the aglycone of chantriolide A (**2**) and the stereochemistry of compound **1** was same as that of the aglycone of chantriolide A (**2**). Accordingly, the structure of **1** was elucidated as (20*S*,22*R*)-1α,12α-diacetoxy-2α,3α;6α,7α-diepoxy-5α,27-dihydroxy-16-oxowith-24-enolide, named plantagiolide A, which was firstly obtained as natural compound.



1 $R_1 + R_2 = O$, $R_3 = H$
2 $R_1 + R_2 = O$, R_3 = glc.py
3 $R_1 = OH$, $R_2 = R_3 = H$
4 $R_1 = R_2 = R_3 = H$

5 $R_1 = CH_3$, $R_2 = H$
6 $R_1 = OH$, $R_2 = CH_3$

Plantagiolide B (**3**), a white amorphous powder, showed a molecular ion peak at *m*/*z* 605 $[M+H]^+$ in its positive fast atom bombardment mass spectrometry (FAB-MS), consistent with a molecular formula $C_{32}H_{44}O_{11}$ (11 degrees of unsaturations), as confirmed by its (HR)-ESI-MS ($[M+Na]^+$, *m*/*z* 627.2776) and ^{13}C-NMR spectrum. By step-by-step comparison of the ^1H- and ^{13}C-NMR spectral features of **3** with those of **1**, the other signals of **3** were similar to those of **1** except for the disappearance of a carbonyl group and the presence of a hydroxyl group located at C-16 (δ 70.6) and an oxygenated methine (δ 4.34) in compound **3**. Therefore, it was supposed that the carbonyl group at C-16 was protonated to hydroxyl group in compound **3**, which was confirmed by the mass difference of *m*/*z*=2 and the heteronuclear multiple bond correlation (HMBC) spectrum. In the HMBC spectrum of **2**, the correlations of H-14 (δ 2.54, dd, *J*=8.0, 10.0 Hz), H_α-15 (δ 2.50, m), H_β-15 (δ 1.40, m), H-17 (δ 1.64, m), and H-20 (δ 2.36, m) with C-16 (δ 70.6, d) were observed. The relative configuration of the hydroxyl group in C-16 was determined by ROESY experiment (Fig. 1). The H-16 signal showed ROESY correlations with H-14 and H-17 suggesting a α-orientation of H-16. On the basis of above evidence, the structure of **3** was established as (20*S*,22*R*)-1α,12α-diacetoxy-2α,3α;6α,7α-diepoxy-5α,16β,27-trihydroxywith-24-enolide, named plantagiolide B, which was the aglycone of chantriolide B.[13)]

Plantagiolide C (**4**) was isolated as colorless needles. The (HR)-ESI-MS of **3** displayed a $[M+Na]^+$ peak at *m*/*z* 611.2835, corresponding to the empirical molecular formula of $C_{32}H_{44}O_{10}$, which was also deduced by analysis of its ^{13}C-NMR and DEPT spectral data. The mass spectrum indicated that compound **4** was 14 mass units less than compound **1**. The ^1H- and ^{13}C-NMR spectral data of **4** were close to those of **1**. The only significant differences included the absence

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Table 1. ^{1}H-NMR Data for Compounds **1**, **3**—**6** (δ in ppm; J in Hz)

H	**1**[a,d]	**3**[a,e]	**4**[a,d]	**5**[c,e]	**6**[b,e]
1	4.65 (d, 5.5)	4.62 (d, 5.2)	4.54 (d, 4.8)	4.47 (d, 5.2)	4.86 (d, 5.2)
2	3.75 (dd, 4.0, 4.5)	3.73 (dd, 4,0, 4.6)	3.65 (br s)	3.56 (dd, 4.1, 4.6)	3.89 (dd, 4.2, 4.3)
3	3.45 (br s)	3.55 (dd, 1.6, 3.3)	3.48 (br s)	3.41 (br d, 3.0)	3.64 (br s)
4α	2.43 (d, 16.0)	2.41 (m)	2.31 (d, 15.6)	2.21 (d, 15.6)	2.36 (m)
4β	2.10 (m)	2.05 (m)	2.00 (m)	1.94 (d, 6.1)	2.20 (m)
6	2.90 (d, 3.0)	2.85 (d, 3.5)	2.77 (d, 2.6)	2.70 (d, 3.4)	3.02 (d, 3.4)
7	3.09 (br s)	3.12 (br s)	3.04 (br s)	2.97 (br s)	3.14 (br s)
8	1.96 (m)	1.83 (m)	1.69 (m)	1.63 (m)	1.71 (m)
9	2.23 (m)	2.04 (m)	1.91 (m)	1.85 (m)	2.36 (m)
11α	1.64 (dd, 3.5, 14.5)	1.56 (m)	1.50 (m)	1.73 (m)	1.67 (m)
11β	1.61 (m)	1.50 (m)	1.44 (m)	1.27 (m)	1.33 (m)
12	5.00 (br s)	4.95 (br s)	4.89 (br s)	4.80 (br s)	5.01 (br s)
14	2.54 (dd, 8.0, 10.0)	1.96 (m)	1.93 (m)	1.84 (m)	2.07 (m)
15α	2.49 (d, 8.5)	2.50 (m)	1.82 (m)	1.72 (m)	1.82 (m)
15β	2.04 (m)	1.40 (m)	1.26 (dd, 3.4, 7.9)	1.17 (m)	1.25 (m)
16α	—	4.34 (m)	1.69 (m)	1.44 (m)	1.69 (m)
16β	—	—	1.35 (m)	1.27 (m)	1.24 (m)
17	2.53 (m)	1.64 (m)	1.67 (m)	1.55 (d, 9.1)	1.83 (m)
18	1.01 (s)	1.05 (s)	0.74 (s)	0.64 (s)	0.69 (s)
19	0.85 (s)	0.81 (s)	0.74 (s)	0.65 (s)	0.81 (s)
20	2.36 (m)	2.48 (m)	1.86 (m)	1.81 (m)	2.05 (m)
21	0.95 (d, 7.0)	0.92 (d, 6.9)	0.80 (d, 6.4)	0.70 (d, 6.9)	1.11 (d, 6.5)
22	4.97 (m)	4.65 (m)	4.36 (m)	4.57 (dt, 3.1, 6.3, 12.0)	5.14 (br d, 12.0)
23α	2.34 (m)	2.49 (m)	2.37 (m)	1.58 (m)	2.80 (br s)
23β	2.14 (m)	2.13 (d, 2.8)	2.33 (m)	1.44 (m)	1.82 (m)
25	—	—	—	2.13 (d, 7.1)	—
27a	4.37 (ABd, 12.5)	4.38 (ABd, 12.2)	4.32 (ABd, 12.6)	1.12 (d, 7.1)	2.05 (s)
27b	4.32 (ABd, 12.5)	4.31 (ABd, 12.2)	4.26 (ABd, 12.6)	—	—
28	2.06 (s)	2.06 (s)	1.99 (s)	1.17 (s)	1.82 (s)
OAc	2.03 (s)	2.01 (s)	1.91 (s)	1.86 (s)	2.03 (s)
	2.14 (s)	2.07 (s)	2.00 (s)	1.92 (s)	2.15 (s)

a) Measured in $CDCl_3$. *b*) Measured in C_5D_5N. *c*) Measured in $CDCl_3$ and CD_3OD. *d*) Recorded in 500 MHz. *e*) Recorded in 400 MHz.

of a carbonyl group and the upfield shift of H-17 (δ −0.86 ppm), which was reasonable to assume that **4** is the reduction of 16-carbonyl to methylene derivative of **1**. In the heteronuclear multiple bond correlation (HMBC) spectrum, long-long correlations between H-14 (δ 1.93, m), H-17 (δ 1.67, m), H-20 (δ 1.86, m) and C-16 (δ 26.3, t) were observed, which affirmed the above assumption. Thus, plantagiolide D (**3**) was assigned to be (20*S*,22*R*)-1α,12α-diacetoxy-2α,3α;6α,7α-diepoxy-5α,27-dihydroxy-with-24-enolide.

Plantagiolide D (**5**), obtained as colorless needles, possesses a molecular formula of $C_{32}H_{46}O_{10}$ (10 degrees of unsaturation) as determined by its (HR)-ESI-MS ($[M+Na]^+$, m/z 613.2988) and ^{13}C-NMR spectrum. The comparison of the spectral data with those of **4** revealed that the hydrogen and carbon atom chemical shift values for the rings of A—D in **5** are in good agreement with those of **4** except for the disappearance of carbon–carbon double bond and a hydroxymethyl group and the existence of one additional oxygenated quaternary carbons (δ 68.7) and an additional methyl in E-ring. The the heteronuclear multiple bond correlation (HMBC) of H-22 (δ 4.57, dt, J=3.1, 6.3, 12.0 Hz), H-25 (δ 2.13, d, J=7.1 Hz), Me-27 (δ 1.12, d, J=7.1 Hz), and Me-28 (δ 1.17, s) with C-24 (δ 68.7, s) indicated that the additional hydroxyl group was attached to C-24 in compound **5**. The doublet at δ 0.70 (d, J=6.9 Hz) suggested that C-21 is a secondary methyl having the usual α-orientation,[24] which confirmed the large between H-17 and H-20 (d, J=9.1 Hz) and the ROESY correlation of H-20/Me-18 and Me-21/H-12. The identical ^{13}C-NMR chemical shifts of δ-lactone moiety of **5** with those of philadelphicalactone B[25] indicated that **5** had the same structure, including stereochemistry, as that of philadelphicalactone B, which Me-27 was β-eq and Me-28 was α-eq and was confirmed *via* a ROESY experiment. The correlation of H-22 with Me-28, H-25 with Me-28 could be clearly observed from the spectrum, suggesting that the hydroxyl groups located at C-24 and the Me-27 were both in β-orientation. Therefore, the structure of **5** concluded to be (20*S*,2*R*,24*R*,25*R*)-1α,12α-diacetoxy-2α,3α;6α,7α-diepoxy-5α,24β-dihydroxy-withanolide, and designated plantagiolide D.

Plantagiolide E (**6**) was obtained as colorless needles. The molecular formula, $C_{32}H_{46}O_{11}$, was deduced from the positive high-resolution electrospray ionization mass spectrum (HR-ESI-MS) ($[M+Na]^+$ m/z 629.2952) and NMR spectra (Table 2). The comparison of the NMR spectral data with those of **5** showed that the chemical shifts of the rings of A—D in **6** are highly comparable with those of **5**. The differences were the disappearance of a doublet of Me-27 and the presence of a singlet of Me-27 and the existence of one additional oxygenated quaternary carbons (δ 75.5) in E-ring. These observations strongly implied that compound **5** was the 25-hydroxy derivative of **6**. Three groups of HMBC correlations were observed to established the structural features of **5**: H_2-23 (δ 1.82/2.80, m) showed cross peaks with C-24 (δ 72.8, s), C-25 (δ 75.7, s); Me-27 (δ 2.05, s) correlated with C-24 (δ 72.8, s), C-25 (δ 75.7, s); and Me-28 (δ 1.82, s) correlated with C-24 (δ 72.8, s), C-25 (δ 75.7, s). The above observations suggested that the another hydroxyl

Table 2. ^{13}C-NMR Data for Compounds **1**, **3**—**6** (δ in ppm)

Carbon	**1**[a,d]	**3**[a,e]	**4**[a,d]	**5**[c,d]	**6**[b,e]
1	71.3 d	71.6 d	71.5 d	71.5 d	72.8 d
2	50.8 d	51.0 d	50.9 d	50.8 d	52.1 d
3	54.9 d	55.0 d	54.9 d	54.8 d	56.0 d
4	32.3 t	32.5 t	32.4 t	32.1 t	33.5 t
5	69.8 s	69.9 s	69.7 s	69.8 s	70.8 s
6	56.2 d	56.2 d	56.0 d	55.8 d	57.1 d
7	53.5 d	53.9 d	53.9 d	54.0 d	54.8 d
8	34.8 d	35.6 d	35.8 d	35.6 d	36.6 d
9	28.1 d	28.1 d	27.8 d	27.7 d	28.9 d
10	39.8 s	39.8 s	39.6 s	39.4 s	40.7 s
11	23.9 t	24.1 t	24.4 t	25.9 t	25.1 t
12	73.6 d	75.4 d	75.1 d	75.2 d	76.2 d
13	46.2 s	46.0 s	45.8 s	45.6 s	46.5 s
14	39.5 d	42.5 d	44.1 d	44.0 d	45.3 d
15	37.1 t	35.4 t	22.5 t	22.3 t	23.2 t
16	215.1 s	70.6 d	26.3 t	24.2 t	26.8 t
17	56.0 d	49.5 d	43.3 d	43.1 d	44.1 d
18	14.1 q	13.1 q	12.2 q	11.7 q	12.5 q
19	16.1 q	16.2 q	16.1 q	15.8 q	16.6 q
20	34.4 d	33.0 d	37.9 d	38.0 d	39.6 d
21	13.1 q	12.1 q	11.9 q	11.3 q	12.5 q
22	77.0 d	79.0 d	78.3 d	77.9 d	79.3 d
23	31.6 t	31.2 t	29.4 t	35.2 t	31.6 t
24	152.8 s	153.2 s	152.8 s	68.7 s	72.8 s
25	125.7 s	125.7 s	125.6 s	45.9 d	75.7 s
26	166.3 s	166.6 s	166.5 s	175.0 s	176.4 s
27	56.8 t	57.0 t	57.0 t	8.7 q	19.2 q
28	20.1 q	20.1 q	20.1 q	27.2 q	24.2 q
OAc	170.0 s	169.9 s	169.8 s	170.1 s	171.1 s
	170.1 s	170.1 s	169.9 s	170.3 s	171.1 s
	19.8 q	20.2 q	19.9 q	19.8 q	20.8 q
	21.2 q	21.3 q	21.2 q	20.8 q	21.5 q

a) Measured in $CDCl_3$. *b*) Measured in C_5D_5N. *c*) Measured in $CDCl_3$ and CD_3OD. *d*) Recorded in 125 MHz. *e*) Recorded in 100 MHz.

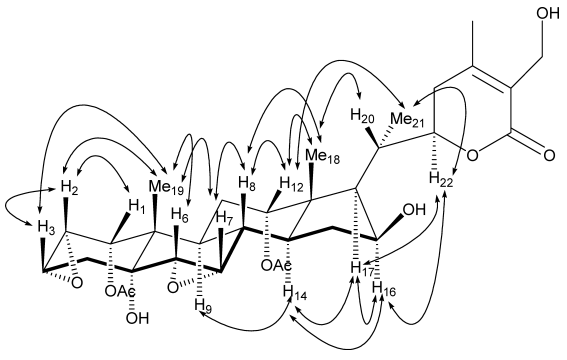

Fig. 1. Significant ROESY Correlations of Plantagiolide B (**2**)

group should connect with C-25. The ROESY cross-peaks of H-22/Me-27, H-22/Me-28 established the Me-27 was α-ax and Me-28 was in α-eq, as drawn. Accordingly, the structure of plantagiolide E (**6**) concluded to be (20*S*,22*R*,24*R*,25*R*)-1α,12α-diacetoxy-2α,3α;6α,7α-diepoxy-5α,24β,25β-trihydroxy-withanolide.

The five new withanolides **1**—**6** obtained from this plant were tested for *in vitro* cytotoxicity against Eca-109, SPC-A-1, BGC-823, AGS, K562 cells. However, all of them were noncytotoxic.

Experimental

General Procedures Melting points were recorded on an XRC-1 micro melting point apparatus and are uncorrected. Optical rotations were measured in a JASCO DIP-370 digital polarimeter. UV spectra were measured using a Shimadzu UV-2401PC spectrophotometer. IR spectra were obtained on a Bio-Rad FTS-135 infrared spectrophotometer with KBr pellets. FAB mass spectrum were obtained on a VG Auto spec-3000 spectrometer and high-resolution ESI mass spectrum were recorded on an API Qstar Pulsar instrument. 1D and 2D NMR experiments were performed on Bruker AM-400 and DRX-500 instruments with TMS as internal standard. Chemical shifts (δ) were expressed in ppm with reference to the solvent signals. Column chromatography was performed on silica gel (200—300 mesh, Qingdao Marine Chemical Inc., Qingdao, People's Republic of China) or on silica gel H (10—40 μm, Qingdao Marine Chemical Inc.) and Lichroprep Rp-18 (43—63 μm, Merck). Fractions were monitored by TLC and spots were visualized by heating silica gel plates sprayed with 10% H_2SO_4 in EtOH.

Plant Material The whole plant *Tacca plantaginea* were collected in Guilin, Guangxi Zhuang Autonomous Region, People's Republic of China, in August 1999, and identified by professor De-Ding Tao (Kunming Institute of Botany, the Chinese Academy of Sciences).

Extraction and Isolation The powdered air-dried plant of *T. plantaginea* (30 kg) were exhaustively extracted three times with 95% EtOH under reflux. After evaporated, the resulting residue (1.5 kg) was extracted with $CHCl_3$ and *n*-butanol, successively. The $CHCl_3$ layer (700 g) was subjected to silica gel column chromatography eluting with a petroleum ether–AcOEt gradient (1 : 0, 10 : 1, 5 : 1, 7 : 3, 1 : 1) to give five fractions 1—5. Fraction 4 (150 g) was repeatedly chromatographed over silica gel ($CHCl_3$/H_2O) and RP-18 (MeOH/H_2O) to afforded **1** (70 mg), **3** (33 mg), **4** (25 mg), **5** (120 mg), and **6** (11 mg). The EtOAc layer (50 g) was repeatedly chromatographed on silica gel column, eluting with a $CHCl_3$–MeOH gradient (9 : 1) to give compound **2** (120 mg).

Plantagiolide A (**1**): Colorless needles from chloroform. mp 246—247 °C. $[\alpha]_D^{26}$ +11.1° (c=3.3, $CHCl_3$). UV λ_{max} ($CHCl_3$) nm (log ε): 241 (3.96). IR (KBr) ν_{max} cm^{-1}: 3480, 2978, 2938, 1736, 1706, 1651, 1466, 1421, 1380, 1246, 1027. ^{1}H-NMR ($CDCl_3$, 500 MHz) and ^{13}C-NMR ($CDCl_3$, 125 MHz) see Tables 1 and 2. Positive FAB-MS *m*/*z*: 603 $[M+H]^+$, 543 $[M-CH_3COOH]^+$, 525 $[M-CH_3COOH-H_2O]^+$, 483 $[M-2\times CH_3COOH]^+$, 465 $[M-2\times CH_3COOH-H_2O]^+$, 447 $[M-2\times CH_3COOH-2\times H_2O]^+$. Positive HR-ESI-MS *m*/*z*: 625.2623 $[M+Na]^+$ (Calcd for $C_{32}H_{42}O_{11}Na$, 625.2624).

Plantagiolide B (**3**): White amorphous powder. mp 253—255 °C. $[\alpha]_D^{26}$ +65.2° (c=2.6, $CHCl_3$). UV λ_{max} ($CHCl_3$) nm (log ε): 241 (3.90). IR (KBr) ν_{max} cm^{-1}: 3443, 2927, 1734, 1635, 1379, 1250, 1031. ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 400 MHz) see Tables 1 and 2. Positive FAB-MS *m*/*z*: 605 $[M+H]^+$. Positive HR-ESI-MS *m*/*z*: 627.2776 $[M+Na]^+$ (Calcd for $C_{32}H_{44}O_{11}Na$, 627.2781).

Plantagiolide C (**4**): Colorless needles from chloroform. mp 208—210 °C. $[\alpha]_D^{26}$ +93.5° (c=4.2, $CHCl_3$). UV λ_{max} ($CHCl_3$) nm (log ε): 240 (3.88). IR (KBr) ν_{max} cm^{-1}: 3448, 2944, 1732, 1705, 1641, 1397, 1381, 1252, 1030. ^{1}H-NMR ($CDCl_3$, 500 MHz) and ^{13}C-NMR ($CDCl_3$, 125 MHz) see Tables 1 and 2. Positive FAB-MS *m*/*z*: 589 $[M+H]^+$. Positive HR-ESI-MS *m*/*z*: 611.2835 $[M+Na]^+$ (Calcd for $C_{32}H_{44}O_{10}Na$, 611.2832).

Plantagiolide D (**5**): Colorless needles from chloroform–methanol. mp 237—239 °C. $[\alpha]_D^{26}$ +66.1° (c=13.6, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3497, 2982, 1739, 1690, 1400, 1382, 1261, 1239. ^{1}H-NMR ($CDCl_3$–CD_3OD, 400 MHz) and ^{13}C-NMR ($CDCl_3$–CD_3OD, 100 MHz) see Tables 1 and 2. Positive FAB-MS *m*/*z*: 591 $[M+H]^+$, 573 $[M+H-H_2O]^+$, 531 $[M+H-CH_3COOH]^+$, 513 $[M+H-H_2O-CH_3COOH]^+$, 495 $[M+H-2\times H_2O-CH_3COOH]^+$, 471 $[M+H-2\times CH_3COOH]^+$. Positive HR-ESI-MS *m*/*z*: 613.3005 $[M+Na]^+$ (Calcd for $C_{32}H_{46}O_{10}Na$, 613.2988).

Plantagiolide E (**6**): Colorless needles from methanol. mp 328—330 °C. $[\alpha]_D^{26}$ +198.5° (c=2.7, pyridine). IR (KBr) ν_{max} cm^{-1}: 3479, 3456, 2944, 1736, 1693, 1381, 1257, 1030. ^{1}H-NMR (pyridine-d_5, 400 MHz) and ^{13}C-NMR (pyridine-d_5, 100 MHz) see Tables 1 and 2. Positive FAB-MS *m*/*z*: 607 $[M+H]^+$. Positive HR-ESI-MS *m*/*z*: 629.2952 $[M+Na]^+$ (Calcd for $C_{32}H_{46}O_{11}Na$, 629.2937).

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