# Four *ent*-Kaurane-Type Diterpenoids from *Croton tonkinensis* Gagnep.

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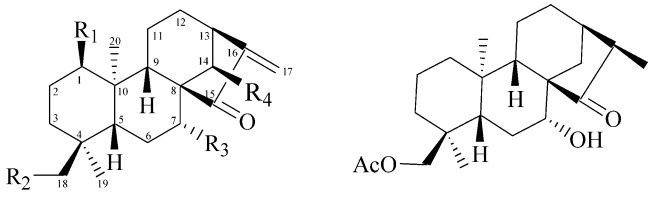
**From the leaves of the endemic Vietnamese medicinal plant *Croton tonkinensis* Gagnep. (Euphorbiaceae) the four new *ent*-kaurane-type diterpenoids *ent*-1α,14α-diacetoxy-7β-hydroxykaur-16-en-15-one (1), *ent*-1α,7β-diacetoxy-14α-hydroxykaur-16-en-15-one (2), *ent*-18-acetoxy-14α-hydroxykaur-16-en-15-one (3), and *ent*-(16*S*)-18-acetoxy-7β-hydroxykauran-15-one (4) were isolated. Their structures were elucidated by spectroscopic analyses.**

**Key words** *Croton tonkinensis*; Euphorbiaceae; *ent*-kaurane; diterpenoid

*Croton tonkinensis* Gagnep. (Euphorbiaceae), commonly known as *Kho sam cho la* in Vietnamese, is a small plant indigenous to Northern Vietnam. In Vietnamese traditional medicine the species is used as remedies for gastric and duodenal ulcers and many other diseases.[1)] Recently, the antiinflammatory and cancer chemopreventive activity of *C. tonkinensis* extracts were discovered through its ability to inhibit the activation of the transcription factor nuclear factor kappa B (NF-κB), and the activity is assumed to be correlated with the *ent*-kaurane diterpenoid constituents.[2)] The presence of kaurane diterpenoids in the *Croton* species is very uncommon, although so far the *ent*-kauranes have been found in many plants of the genus *Rabdosia* (Labitae).[3)] Therefore further phytochemical study on the *ent*-kaurane diterpenoids accumulated in *C. tonkinensis* is necessary. Other constituents were also isolated from this plant including phytosterols, long-chain alkyl alcohols, and flavonoid glucosides.[4)] In the continuation of our study, this paper deals with the isolation and structural elucidation of the four new *ent*-kaurane-type diterpenoids **1**—**4** (Fig. 1).

Compound **1** was isolated as an amorphous powder and its elemental composition was determined to be $C_{24}H_{34}O_6$ by the $[M+Na]^+$ peak at *m*/*z* 441.6 in the positive-ion electrospray ionization mass spectrometry (ESI-MS) and $[M+Na]^+$ peak at *m*/*z* 441.2243 in the positive-ion high-resolution (HR)-FAB-MS. The IR spectrum indicated the presence of a hydroxy (3558 $cm^{-1}$), an ester (1728 $cm^{-1}$) and a conjugated ketone (1648 $cm^{-1}$). The $^1$H- (Table 1) and $^{13}$C-NMR (Table 2) signals of **1** were found to be similar to those of *ent*-1α-acetoxy-7β,14α-dihydroxykaur-16-en-15-one (**5**),[2)] which was isolated from the same extract, except for the presence of an additional acetyl signal ($\delta_H$: 1.97, s; $\delta_C$: 170.6, 21.4). The $^1$H- and $^{13}$C-NMR chemical shifts of two oxygenated methine groups at C-1 ($\delta_H$: 4.86, br s; $\delta_C$: 72.7, d) and C-7 ($\delta_H$: 4.19, dt; $\delta_C$: 72.9, d) in **1** remained almost the same as in **5**: ($\delta_H$: 4.84, br s; $\delta_C$: 72.8, d) and ($\delta_H$: 4.38, dd; $\delta_C$: 74.5, d),[2)] respectively, suggesting the location of an additional acetyl group at C-14. The signals displayed a downfield shift for the 14-oxymethine ($\delta_H$: 6.01, $\Delta\delta$+1.12 ppm; $\delta_C$: 76.1, $\Delta\delta$+1.3 ppm) when compared with those of **5**, and the heteronuclear multiple bond correlation (HMBC) correlations (Fig. 2) of this methine proton with C-9 ($\delta_C$: 48.1), C-12 ($\delta_C$: 32.3), C-15 ($\delta_C$: 206.5), C-16 ($\delta_C$: 146.0), and the acetyl carbonyl carbon ($\delta_C$: 170.6) confirmed this assignment. On the basis of the NOE correlations between H-1 and H-20, H-14 and H-20, and H-7 and H-5 and H-9 in the nuclear Overhauser enhancement and exchange spectroscopy (NOESY) spectrum of **1** (Fig. 2) the acetoxyl groups at C-1 and C-14 were assigned to occupy an *ent*-α-orientation, and the hydroxyl group at C-7 an *ent*-β-orientation. Thus the structure of **1** was determined to be *ent*-1α,14α-diacetoxy-7β-hydroxykaur-16-en-15-one. Full assignments of the $^1$H- and $^{13}$C-NMR signals of **1** were established by the detailed analysis of the $^1$H–$^1$H correlated spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC), HMBC, and NOESY spectra.

The positive-ion HR-FAB-MS of compound **2** showed a quasimolecular ion peak ($[M+Na]^+$) at *m*/*z* 441.2243, consistent with the molecular weight of **1**. Comparison of the $^1$H- (Table 1) and $^{13}$C-NMR (Table 2) data of **2** with those of **1** revealed very close agreement, showing the presence of a 20-carbon skeleton of an *ent*-kaurane diterpenoid together with two secondary acetoxyl groups. The main differences




| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **1** | OAc | H | OH | OAc |
| **2** | OAc | H | OAc | OH |
| **3** | H | OAc | H | OH |
| **5** | OAc | H | OH | OH |
| **6** | H | OAc | OH | OH |

Fig. 1. Chemical Structures of *ent*-Kaurane-Type Diterpenoids

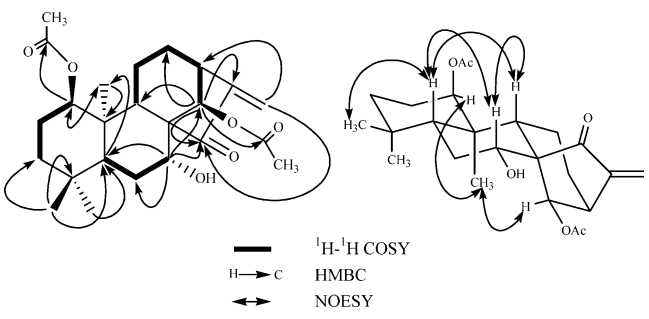



Fig. 2. $^1$H–$^1$H COSY, HMBC, and NOESY Correlations of **1**

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Table 1. $^1$H-NMR Spectroscopic Data of Compounds **1**—**4** ($\delta$ in ppm, 500 MHz, $CDCl_3$)

| H | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| 1 | 4.86 br s | 4.86 br s | 0.79 ddd (13.1, 12.8, 3.9) | 0.72 ddd (13.7, 12.2, 3.9) |
| | | | 1.76 dt (12.8, 2.6) | 1.74 dt (12.2, 3.7) |
| 2 | 1.63 m | 1.63[a] | 1.43[a] | 1.49 dquint. (14.2, 3.7) |
| | 1.95[a] | 1.98[a] | 1.63[a] | 1.65[a] |
| 3 | 1.46[a] | 1.23[a] | 1.34[a] | 1.34[a] |
| | 1.50[a] | 1.25[a] | 1.40[a] | 1.37 br d (12.4) |
| 5 | 1.42 dd (12.3, 2.1)[b] | 1.59[a] | 1.28[a] | 1.25 dd (11.7, 1.6) |
| 6 | 1.81[a] | 1.67 q (12.4) | 1.43[a] | 1.40 q (11.7) |
| | 1.92 ddd (11.7, 4.6, 2.1) | 2.08 br dd (12.4, 3.9) | 1.63[a] | 1.65[a] |
| 7 | 4.19 dt (11.9, 4.6) | 5.45 dd (12.4, 3.9) | 1.64[a] | 3.91 dd (11.7, 4.4) |
| | | | 1.94 m | |
| 9 | 1.82[a] | 1.83[a] | 1.46[a] | 1.08 br d (8.7) |
| 11 | 1.30 m | 1.30[a] | 1.32[a] | 1.46[a] |
| | 1.50[a] | 1.50[a] | 1.54 m | 1.62[a] |
| 12 | 1.82[a] | 1.79[a] | 1.82[a] | 1.65[a] |
| | 2.13 m | 2.0[a] | 2.04 m | 1.76[a] |
| 13 | 3.08 br s | 3.12 br s | 3.06 br s | 2.5 m |
| 14 | 6.01 s | 4.89 s | 4.56 s | 1.98 dd (11.9, 4.4) |
| | | | | 2.09 br d (11.9) |
| 16 | | | | 2.23 quint. (7.1) |
| 17 | 5.41 s | 5.42 s | 5.35 s | 1.10 d (7.1) |
| | 6.18 s | 6.17 s | 6.11 s | |
| 18 | 0.95 s | 0.97 s | 3.66 d (11.2) | 3.64 d (11.0) |
| | | | 3.86 d (11.2) | 3.86 d (11.0) |
| 19 | 0.90 s | 0.87 s | 0.83 s | 0.83 s |
| 20 | 1.27 s | 1.16 s | 1.07 s | 1.12 s |
| 1-OAc | 1.99 s | 2.01 s | | |
| 7-OAc | | 2.02 s | | |
| 14-OAc | 1.97 s | | | |
| 18-OAc | | | 2.09 s | 2.08 s |
| 14-OH | | 4.00 s | | |

*a*) Overlapping signals. *b*) Coupling constants (*J* in Hz) are given in parentheses.

Table 2. $^{13}$C-NMR Spectroscopic Data of Compounds **1**—**4** ($\delta$ in ppm, $CDCl_3$)

| C | 1[a] | 2[a] | 3[b] | 4[b] |
|---|---|---|---|---|
| 1 | 72.7 | 72.7 | 39.1 | 38.7 |
| 2 | 22.7 | 22.6 | 17.8 | 17.5 |
| 3 | 35.0 | 34.9 | 35.5 | 35.5 |
| 4 | 32.9 | 33.0 | 36.5 | 36.4 |
| 5 | 47.6 | 46.9 | 49.2 | 46.5 |
| 6 | 27.3 | 25.0 | 17.8 | 28.3 |
| 7 | 72.9 | 75.9 | 25.0 | 71.3 |
| 8 | 61.6 | 60.9 | 58.8 | 58.4 |
| 9 | 48.1 | 46.99 | 54.9 | 51.8 |
| 10 | 43.0 | 42.3 | 39.9 | 39.2 |
| 11 | 16.6 | 16.6 | 18.15 | 17.8 |
| 12 | 32.3 | 31.0 | 32.3 | 25.3 |
| 13 | 44.2 | 45.7 | 46.5 | 34.4 |
| 14 | 76.1 | 74.3 | 73.6 | 28.4 |
| 15 | 206.5 | 205.0 | 208.8 | 224.8 |
| 16 | 146.0 | 146.7 | 146.9 | 48.4 |
| 17 | 117.7 | 118.3 | 117.2 | 9.98 |
| 18 | 33.2 | 32.99 | 72.6 | 72.3 |
| 19 | 21.4 | 21.2 | 17.5 | 17.48 |
| 20 | 18.6 | 18.5 | 18.2 | 18.2 |
| 1-OAc | 21.2 | 21.2 | | |
| | 170.1 | 170.1 | | |
| 7-OAc | | 21.2 | | |
| | | 168.1 | | |
| 14-OAc | 21.4 | | | |
| | 170.6 | | | |
| 18-OAc | | | 21.1 | 21.1 |
| | | | 171.3 | 171.2 |

*a*) Measured at 150 MHz. *b*) Measured at 100 MHz.

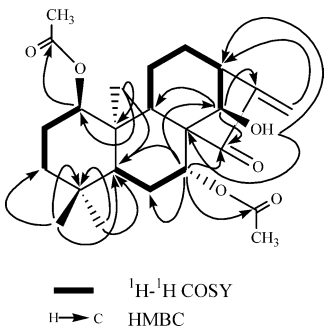


Fig. 3. $^1$H–$^1$H COSY and HMBC Correlations of **2**

were displayed in the signal of 7-methine bearing an acetoxyl group which shifted downfield ($\delta_H$: 5.45, $\Delta\delta$+1.26, $\delta_C$: 75.9, $\Delta\delta$+3.0), and in the signal of 14-methine bearing a hydroxyl group which now shifted upfield to be of almost the same values ($\delta_H$: 4.89, $\Delta\delta$ −1.12, $\delta_C$: 74.3, $\Delta\delta$ −1.8) as those of **5**,[2] while the signals for the 1-oxymethine and the acetyl group at C-1 remained unchanged. In addition, the 14-OH signal appeared as a sharp singlet ($\delta_H$: 4.00) as would be expected from the intramolecular hydrogen bond from 14-OH to the oxygen atom of the acetoxyl group at C-7.[5] The HMBC correlations (Fig. 3) between H-7 ($\delta_H$: 5.45) and the acetyl carbonyl carbon ($\delta_C$: 168.1), and between 14-OH ($\delta_H$: 4.00, s) and C-8 ($\delta_C$: 60.9) and C-13 ($\delta_C$: 45.7) confirmed the presence of the 7-OAc and 14-OH groups. In the NOESY spectrum of **2**, NOEs were observed between H-1 and H-20; H-7 and H-5, H-9; and H-14 and H-6$\alpha$ ($\delta_H$: 1.67), H-12$\alpha$

($\delta_H$: 2.0), indicating that the stereochemistry of **2** is the same as that of **1**. Thus compound **2** was determined to be *ent*-1$\alpha$,7$\beta$-diacetoxy-14$\alpha$-hydroxykaur-16-en-15-one.

The *ent*-$\alpha$-orientation of the 1-acetoxyl groups in compounds **1** and **2** is unusual among the *Rabdosia ent*-kaurane-type diterpenoids that naturally occur as *ent*-1$\beta$ substituted. In various recent publications on *Rabdosia* species only maoecrystal I and rabdolongin A were isolated as *ent*-1$\alpha$-hydroxy kaurane derivatives.[3)]

Compound **3** was determined to be a 7-dehydroxy derivative of compound **6** previously isolated and structurally characterized by us from the same extract.[2)] The $^1$H- (Table 1) and $^{13}$C-NMR (Table 2) data of **3** were in close agreement of those of **6**, but the disappearance of the 7-hydroxyl group was seen [$\delta_C$: 25.0 (C-7) in **3** instead of $\delta_C$: 74.4 (C-7) in **6**]. The 14-methine bearing a hydroxyl group appeared at $\delta_H$ 4.56 (s), $\delta_C$ 73.6 (d); these chemical shifts resulted from the loss of the *ent*-7$\beta$-hydroxyl group and were close to those reported for 7-dehydroxy 14-hydroxy *ent*-kaurane derivatives.[5,6)] The NOESY correlations between H-14 and H-20 and H-12$\alpha$ ($\delta_C$: 2.04) confirmed the *ent*-14$\alpha$-hydroxy stereochemistry. Thus compound **3** was determined to be *ent*-18-acetoxy-14$\alpha$-hydroxykaur-16-en-15-one.

The similarity in the NMR data and the coexistence of compound **4** with the *ent*-kauranes **1**—**3**, **5**, and **6** grouped **4** in the family of *ent*-kaurane-type ditepenoids. The molecular formula of **4** was analyzed for $C_{22}H_{34}O_4$ using negative-ion HR-FAB-MS. The $^1$H-NMR spectrum of **4** showed a three-proton signal ($\delta_H$: 1.10, d, $J$=7.1 Hz; $\delta_C$: 9.98, q) coupled with a methine proton at $\delta_H$ 2.23 (quint., $J$=7.1 Hz) typical of a secondary methyl group. The ketone carbonyl signal assigned to C-15 ($\delta_C$: 224.8, s) which shifted downfield was indicative of the saturation of the C-16/C-17 double bond in the *ent*-kaurane skeleton.[6—9)] The acetyl group ($\delta_H$: 2.08; $\delta_C$: 171.2, 21.1) and the hydroxyl group were placed at C-18 ($\delta_H$: 3.64, 3.86; $\delta_C$: 72.3) and at C-7 ($\delta_H$: 3.91; $\delta_C$: 71.3), respectively, and the stereochemistry of the 17-$CH_3$ was suggested to be *ent*-$\alpha$ (16*R*) as a result of the $^1$H- and $^{13}$C-NMR comparison with those of the previously reported *ent*-(16*S*)-kauran-15-one structures.[6—9)] Moreover, the NOEs observed in the NOESY spectrum of **4** between H-16 and H-13, H-14$\beta$ ($\delta_H$: 2.09); H-20 and H-14$\alpha$ ($\delta_H$: 1.98); and H-17 and H-12$\beta$ ($\delta_H$: 1.76) and between H-7 and H-5 supported the *ent*-$\beta$- and *ent*-$\alpha$-orientations of the hydroxyl group at C-7 and 17-methyl group, respectively. The circular dichroism (CD) spectrum of **4** showed first negative (306 nm), second positive (273 nm), and third negative (208 nm) Cotton effects characteristic of the *ent*-(16*S*)-kauran-15-ones.[6,10)] Thus the absolute structure of **4** was established to be *ent*-(16*S*)-18-acetoxy-7$\beta$-hydroxykauran-15-one.

To confirm the absolute configuration of compounds **1**—**3** the CD spectra were measured. The first negative, second negative, and third negative Cotton effects (see Experimental) observed in **1**—**3** were the same as those of *ent*-11$\alpha$-acetoxy-7$\beta$,14$\alpha$-dihydroxy-16-kauren-15-one.[6)] Together with the consideration of the cooccurrence of compound **4**, **1**—**3** were unambiguously assigned to the *ent*-kaurane diterpenoids.

There was a possibility that compounds **1** and **2** might be artifacts arising from the *trans*-esterification reactions of compound **5** present in the same extract with ethyl acetate used in the solvent systems during the silica gel column chromatographic processes. To verify the hypothesis, an original MeOH extract sample was tested using analytical HPLC, alone and coinjected with compounds **1** and **2**. The increase in peak heights corresponding to the retention times of pure **1** and **2** provided evidence for the natural origins of compounds **1** and **2**. Compounds **3** and **4** were also detected in the MeOH extract upon analytical HPLC coinjections and thus were confirmed to be naturally occurring in the plant.

## Experimental

**General Procedure** Melting points were determined on a Yanagimoto micromelting point apparatus without correction. Optical rotations were measured on a Union Giken PM-101 digital polarimeter at 15 °C. FT-IR spectra were recorded on a Horiba FT-710 spectrophotometer. $^1$H-NMR (500 MHz) spectra were obtained on a JEOL JNM-ECP 500 spectrometer, $^{13}$C-NMR (150, 100 MHz) spectra were obtained on a Bruker DMX 600 and a JEOL JNM $\alpha$-400 NMR spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard. ESI-MS was measured for compound **1** on a Finigan Navigator mass spectrometer. Negative-ion and positive-ion HR-FAB-MS were measured on a JEOL SX-102 mass spectrometer with PEG-400 and PEG-600, respectively, as the calibration matrix. CD spectra were obtained on a JASCO J-720 spectropolarimeter. HPLC was carried out with JASCO PU-1580 pump and UV-2075 Plus detector (set at 210 nm) on YMC ODS columns (150×4.6 mm i.d. in analytical and 150×20 mm i.d. in preparative scales) at the corresponding flow rates of 0.5 and 5 ml/min. Silica gel 60 (0.063—0.200 mm, Merck) and reverse-phase octadecyl silica (ODS) gel (YMC) were used for open column chromatography. TLC was carried out on Merck precoated TLC sheets (silica gel 60 $F_{254}$), and detected by spraying with 10% $H_2SO_4$ in 50% EtOH, followed by heating on a hot plate at 200 °C.

**Plant Material** The air-dried leaves of *C. tonkinensis* were collected in the suburbs of Hanoi, Vietnam, and identified by Professor Vu Van Chuyen (Hanoi College of Pharmacy, Hanoi, Vietnam) in September 2003. A voucher specimen (No. DHD 2002-5) was deposited in the Herbarium of the Hanoi College of Pharmacy.

**Extraction and Isolation** The powdered air-dried leaves of *C. tonkinensis* were extracted with MeOH and fractionated with solvents of increasing polarity as described in the previous paper.[2)] The combined *n*-hexane- and $CH_2Cl_2$-soluble fractions (59.2 g) were chromatographed on a silica gel column using *n*-hexane, *n*-hexane–EtOAc (6 : 1, 3 : 1, 1 : 1), and EtOAc as solvent systems to give five fractions. Fraction 4 (9.5 g) eluted with *n*-hexane–EtOAc (1 : 1) was subjected to silica gel column chromatography (*n*-hexane–EtOAc, 2 : 1) to obtain six fractions. Fractionation of half of fraction 4 (1.56 g) by preparative HPLC using MeOH–$H_2O$ (7 : 3) gave compounds **1** (24.6 mg), **2** (27.9 mg), and **3** (5.0 mg), while separation of fraction 5 (1.93 g) on an ODS column (MeOH–$H_2O$, 7 : 3, 9 : 1) followed by purification with preparative HPLC (MeOH–$H_2O$, 4 : 1) afforded compound **4** (51.0 mg).

*ent*-1$\alpha$,14$\alpha$-Diacetoxy-7$\beta$-hydroxykaur-16-en-15-one (**1**): White amorphous powder. $[\alpha]_D^{15}$ −16° ($c$=0.10, MeOH). IR $\nu_{max}$ (film) cm$^{-1}$: 3558, 2952, 2871, 1728, 1648, 1369, 1240, 1090, 1033, 735. CD (MeOH): $\Delta\varepsilon$ (nm): −0.25 (333), −6.68 (239), −2.53 (208) ($c$=2.87×10$^{-4}$ M). $^1$H- and $^{13}$C-NMR: see Tables 1 and 2. Positive-ion ESI-MS: $m/z$ 441.6 $[M+Na]^+$. Positive-ion HR-FAB-MS: $m/z$ 441.2243 $[M+Na]^+$ (Calcd for $C_{24}H_{34}O_6Na$: 441.2253).

*ent*-1$\alpha$,7$\beta$-Diacetoxy-14$\alpha$-hydroxykaur-16-en-15-one (**2**): White amorphous powder. $[\alpha]_D^{15}$ −22° ($c$=0.10, MeOH). IR $\nu_{max}$ (film) cm$^{-1}$: 3558, 2951, 2871, 1730, 1649, 1451, 1369, 1240, 1091, 1033, 734. CD (MeOH): $\Delta\varepsilon$ (nm): −0.25 (334), −6.77 (239), −2.07 (206) ($c$=3.11×10$^{-4}$ M). $^1$H- and $^{13}$C-NMR: see Tables 1 and 2. Positive-ion HR-FAB-MS: $m/z$ 441.2243 $[M+Na]^+$ (Calcd for $C_{24}H_{34}O_6Na$: 441.2253).

*ent*-18-Acetoxy-14$\alpha$-hydroxykaur-16-en-15-one (**3**): White amorphous powder. $[\alpha]_D^{15}$ −30° ($c$=0.30, MeOH). IR $\nu_{max}$ (film) cm$^{-1}$: 3448, 2932, 2868, 1732, 1648, 1455, 1381, 1242, 1065, 1041, 926, 738. CD (MeOH): $\Delta\varepsilon$ (nm): −0.35 (341), −2.59 (245), −4.48 (207) ($c$=5.56×10$^{-4}$ M). $^1$H- and $^{13}$C-NMR: see Tables 1 and 2. Negative-ion HR-FAB-MS: $m/z$ 359.2245 $[M-H]^-$ (Calcd for $C_{22}H_{31}O_4$: 359.2222).

*ent*-(16*S*)-18-Acetoxy-7$\beta$-hydroxykaur-15-one (**4**): Colorless needles, mp 175—176 °C. $[\alpha]_D^{15}$ −18° ($c$=0.10, MeOH); IR $\nu_{max}$ (film) cm$^{-1}$: 3494, 2931, 2868, 1735, 1719, 1457, 1374, 1244, 1044, 991, 934, 740. CD (MeOH): $\Delta\varepsilon$ (nm): −0.83 (306), +0.09 (273), −1.38 (208) ($c$=2.76×10$^{-4}$ M). $^1$H- and $^{13}$C-NMR: see Tables 1 and 2. Negative-ion HR-FAB-MS: $m/z$ 361.2354 $[M-H]^-$ (Calcd for $C_{22}H_{33}O_4$: 361.2379).

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