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ANNONACEOUS ACETOGENINS OF THE SEEDS FROM *ANNONA MURICATA*

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Muricatenol (**1**) is a new C₃₇ non-THF ring acetogenin with four hydroxyls and one isolated double bond in the long aliphatic chain. 2,4-*cis*-Gigantetrocinone (**2**) and 2,4-*trans*-gigantetrocinone (**3**) have been isolated as their acetates by preparative TLC. 2,4-*trans*-Isoannonacin-10-one (**4**) and 2,4-*trans*-isoannonacin (**5**) have been isolated as only 2,4-*trans*-form for the first time (no *cis*-form). Also four known acetogenins, gigantetrocin-A (**6**), gigantetrocin-B (**7**), anomontacin (**8**), gigantetronenin (**9**) and a mixture of *N*-fatty acyl tryptamines have been isolated (**10**). Their structures have been established on the basis of spectral analyses. The CHCl₃ fraction of the seeds showed strong antitumor activities.

Keywords: *Annona muricata*; Annonaceae; Acetogenins; Muricatenol; 2,4-*cis*-gigantetrocinone; 2,4-*trans*-gigantetrocinone; 2,4-*trans*-isoannonacin-10-one; 2,4-*trans*-isoannonacin; Antitumor activities

INTRODUCTION

Annonaceous acetogenins (polyketides) are a group of extensively investigated natural compounds possessing antitumor, antiparasitic and pesticidal activities. Over 350 acetogenins have been isolated and most of them have one to three tetrahydrofuran (THF) rings, several hydroxyls and

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a terminal γ -lactone ring. As part of our investigation of the title species, we have reported four new C_{35} acetogenins: muricatalin [1], muricatalicin [2], annonacin B [3], murihexol [4] and four known compounds: annonacin, annonacin A, annonacin-10-one [3] and donhexocin [4]. Now we wish to report the isolation of a new C_{37} non-THF acetogenin: muricatenol (**1**), as well as 2,4-*cis*-gigantetrocinone (**2**), 2,4-*trans*-gigantetrocinone (**3**), 2,4-*trans*-isoannonacin-10-one (**4**), 2,4-*trans*-isoannonacin (**5**) (**4**, **5** are only 2,4-*trans* form, not a mixture of 2,4-*cis* and *trans* form), gigantetrocin A (**6**), gigantetrocin B (**7**), anomontacin (**8**), gigantetronenin (**9**) and a mixture of *N*-fatty acyl tryptamies (**10**). The $CHCl_3$ fraction of the seeds showed strong antitumor activities.

RESULTS AND DISCUSSION

Muricatenol (**1**) was isolated as white crystals, mp 50–53°C. The molecular formula was established to be $C_{37}H_{68}O_6$ from the HRFAB-MS (m/z 609.4993 $[M+H]^+$, calcd. 609.5076). It showed IR absorption bands at 3400 (OH) and 1745 cm^{-1} (C=O), 1H NMR signals at δ 7.19 (1H, *d*, $J=1.4$ Hz), 5.07 (1H, *qd*, $J=7.0, 1.4$ Hz) and 1.44 (3H, *d*, $J=7.0$ Hz) and ^{13}C NMR signals at δ 174.60 (C=O), 151.88, 131.05 (C=O), 78.02 (C—O) and 19.11 (CH_3). These data supported the presence of an α,β -unsaturated γ -methyl γ -lactone moiety in an annonacin-type acetogenin [5]. Compound **1** exhibited five carbon signals of (C—O) bonds in the ^{13}C NMR spectrum and five proton signals of (H—C—O) bonds in the 1H NMR spectrum. These included the signals of the lactone moiety at δ 78.02 and δ 5.07, four signals of hydroxylated methines at δ 69.93, 71.84, 74.18 and 74.48, δ 3.85 (1H), 3.59 (1H) and 3.43 (2H) respectively. The non-equivalent signals of H-3a and H-3b at δ 2.41 (1H, *ddt*, $J=14.0, 8.0, 1.4$ Hz) and 2.54 (1H, *ddt*, $J=14.0, 4.4, 1.4$ Hz) in 1H NMR suggested the presence of C_4 —OH [5]. Lack of signals in the δ 79.00–82.00 region of ^{13}C NMR strongly indicated the absence of any THF ring in the molecule. 1H NMR signals at δ 5.42 (1H, *dt*, $J=11.0, 7.0$ Hz), 5.37 (1H, *dt*, $J=11.0, 7.0$ Hz) and ^{13}C NMR signals at δ 131.05, 128.84 supported the presence of an isolated double bond in **1** (Tab. I). The diagnostic EI fragment ions in the mass spectrum and HRMS analyses showed that the hydroxyls were located at C-10 (241 \rightarrow 223 \rightarrow 205), C-18 (337 \rightarrow 319 \rightarrow 301) and (271 \rightarrow 253 \rightarrow 235) and the isolated double bond was between them. 1H NMR signals at δ 3.43 (2H, *m*) and ^{13}C NMR signals at δ 74.18, 74.48 showed the presence of

TABLE I ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectral data for muricataenol (**1**) in CDCl_3

| C/H | ^{13}C | ^1H (J in Hz) |
|------------------|-----------------|----------------------------------|
| 1 | 174.60 | — |
| 2 | 131.05 | — |
| 3a | 33.11 | 2.41 <i>ddt</i> (15.0, 8.0, 1.4) |
| 3b | — | 2.54 <i>ddt</i> (15.0, 4.4, 1.4) |
| 4 | 69.93 | 3.85 <i>m</i> |
| 10 | 71.84 | 3.59 <i>m</i> |
| 14 | 131.01 | 5.42 <i>dt</i> (11.0, 7.0) |
| 15 | 128.84 | 5.37 <i>dt</i> (11.0, 7.0) |
| 18 | 74.48 | 3.43 <i>m</i> |
| 19 | 74.18 | 3.43 <i>m</i> |
| 34 | 14.12 | 0.88 <i>t</i> (7.0) |
| 35 | 151.88 | 7.19 <i>d</i> (1.4) |
| 36 | 78.02 | 5.07 <i>qd</i> (7.0, 1.4) |
| 37 | 19.11 | 1.44 <i>d</i> (7.0) |
| $\text{CH}_2^\#$ | 22–37 | 1.26–1.65 <i>m</i> |

$^\#$ These included signals of carbons and protons at C-5 to C-9, C-11 to C-13, C-16 to C-17, and C-20 to C-33.

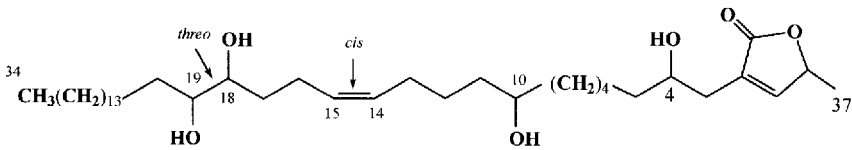
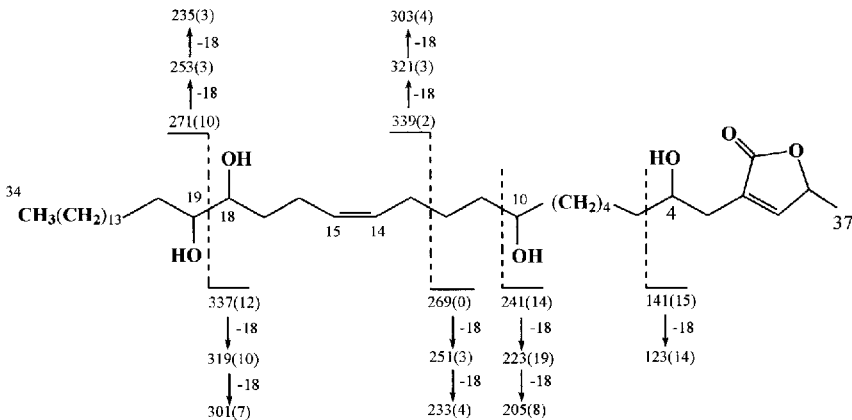
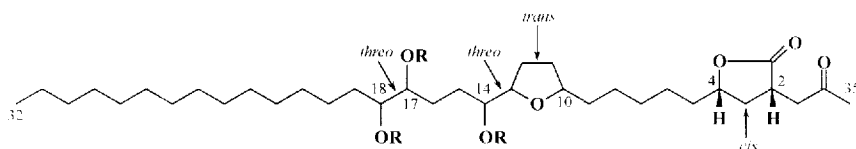
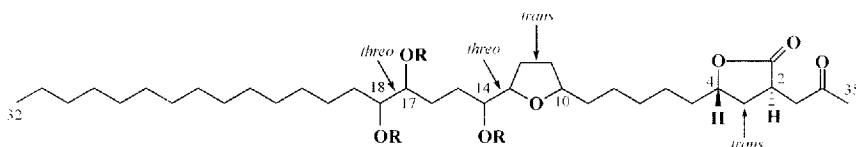
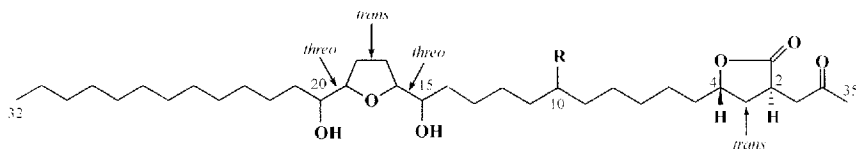
FIGURE 1 Structure of muricataenol (**1**).FIGURE 2 Diagnostic fragment ions of muricataenol (**1**).

TABLE II High resolution mass spectral data and elemental compositions of muricataenol (**1**)

| <i>m/z</i> of ions | Compositions | |
|--------------------|--|--|
| | C-17/18 | |
| 337.2379 | C ₂₀ H ₃₃ O ₄ | |
| 319.2270 | C ₂₀ H ₃₁ O ₃ | |
| 301.2162 | C ₂₀ H ₂₉ O ₂ | |
| | C-10/11 | |
| 241.1444 | C ₁₃ H ₂₁ O ₄ | |
| 223.1331 | C ₁₃ H ₁₉ O ₃ | |
| 205.1227 | C ₁₃ H ₁₇ O ₂ | |

FIGURE 3 Structures of 2,4-*cis*-gigantetrocinone (**2**, *R* = H and its acetate **2a**, *R* = Ac).FIGURE 4 Structures of 2,4-*trans*-gigantetrocinone (**3**, *R* = H) and its acetate (**3a**, *R* = Ac).FIGURE 5 Structures of **4**, **5**. *R* = O: 2,4-*trans*-isoannonacin-10-one (**4**), *R* = OH, 2,4-*trans*-isoannonacin (**5**).

vicinal hydroxyls in **1** [4]. According to the HRMS data, they should be located at C-18/C-19. The ¹³C NMR and ¹H NMR signals at δ 74.48, 74.18 and δ 3.43 (2H) indicated the vicinal diol at C-18/C-19 must be in *threo* configuration. The diagnostic ions in the EI-MS spectrum suggested that the double bond should be located at C-14/C-15 (339 → 321 → 303 and 269 → 251 → 233, double bonds often had β-homolysis). The ¹H NMR signals at δ 5.42 (1H, *dt*, *J* = 11.0, 7.0 Hz) and 5.37 (1H, *dt*, *J* = 11.0), indicated that the double bond at C-14/C-15 must be in the *cis* form

TABLE III ^{13}C (125 MHz) and ^1H (500 MHz) NMR spectral data of 2,4-*cis/trans*-gigantetrocinone (**2**)[†] and ^1H (300 MHz) NMR spectral data of their acetates in CDCl_3

| C/H | 2 | 3 | 2 | 3 | 2a | 3a |
|--------------------|--------|--------|--------------------------|--------------------------|---------------------|---------------------|
| 1 | 178.26 | 178.79 | — | — | — | — |
| 2 | 43.73 | 44.20 | 3.02 m | 2.99 m | 3.05 dd (12.0, 3.3) | 3.02 dd (9.5, 3.3) |
| 3a | 33–36 | 33–36 | 1.48 m | 1.99 m | 1.48 m | 1.99 m |
| 3b | — | — | 2.58 m | 2.23 m | 2.58 m | 2.24 m |
| 4 | 79.27 | 78.83 | 4.39 m | 4.55 m | 4.38 m | 4.53 m |
| 10 | 79.19 | 79.19 | 3.88 m | 3.88 m | 3.86 m | 3.86 m |
| 13 | 81.78 | 81.78 | 3.81 ddd (7.5, 7.0, 6.5) | 3.81 ddd (7.5, 7.0, 6.5) | 3.94 m | 3.94 m |
| 14 | 74.23* | 74.34* | 3.42 m | 3.42 m | 4.84 m | 4.84 m |
| 17 | 74.41* | 74.52* | 3.42 m | 3.42 m | 4.98 m | 4.97 m |
| 18 | 74.52* | 74.73* | 3.42 m | 3.42 m | 4.98 m | 4.97 m |
| 32 | 14.10 | 14.10 | 0.88 t (6.8) | 0.88 t | 0.88 t (6.8) | 0.88 t (6.8) |
| 33a | 25–37 | 25–37 | 2.64 dd (16.0, 8.8) | 2.68 dd (16.5, 9.2) | 2.64 dd (18.0, 7.8) | 2.67 dd (18.0, 9.3) |
| 33b | — | — | 3.10 dd (16.0, 3.5) | 3.05 dd (9.2, 5.6) | 3.14 dd (18.0, 3.3) | 3.07 dd (8.8, 3.3) |
| 34 | 205.59 | 205.59 | — | 2.20 s | — | — |
| 35 | 22.65 | 22.65 | — | — | 2.20 s | 2.20 s |
| OAc | — | — | — | — | 2.078 s (3H) | 2.076 s (3H) |
| $\text{CH}_2^{\#}$ | 22–37 | 22–37 | 1.26–1.65 m | 1.26–1.65 m | 2.083 s (6H) | 2.083 s (6H) |
| | | | | | 1.26–1.65 m | 1.26–1.65 m |

* Signals may be interchangeable.

[†] These included signals of carbons and protons at C-5 to C-9, C-11 to C-12, C-15 to C-16 and C-19 to C-31.

TABLE IV ^{13}C (125 MHz) and ^1H (500 MHz) NMR spectral data of 2,4-*trans*-isoannonacin-10-one (4), 2,4-*trans*-isoannonacin (5) and ^1H (300 MHz) NMR spectral data of their acetates in CDCl_3

| C/H | 4 | 5 | 4 | 5 | 4a | 5a |
|--------------------|---------|---------|---------------------|---------------------|---------------------|---------------------|
| 1 | 178.75 | 178.80 | — | — | — | — |
| 2 | 44.17 | 44.20 | 3.06 m | 3.06 m | 3.06 m | 3.07 m |
| 3a | 33–36 | 33–36 | 2.22 m | 2.22 m | 2.22 m | 2.23 m |
| 3b | — | — | 1.99 m | 1.99 m | 1.95 m | 1.96 m |
| 4 | 78.72 | 78.84 | 4.54 m | 4.55 m | 4.54 m | 4.54 m |
| 9 | 42.48 c | 22–38 | 2.41 t (6.5) c | 1.24–1.99 | 2.39 t (7.4) | 1.24–1.99 |
| 10 | 211.05 | 71.66 | — | 3.59 brs | — | 4.85 m |
| 11 | 42.68 c | 22–38 | 2.39 t (7.5) c | 1.24–1.99 | 2.39 t (7.4) | 1.24–1.99 |
| 15 | 73.72 d | 73.95 d | 3.41 m | 3.41 m | 4.85 m | 4.85 m |
| 16 | 82.55 e | 83.61 e | 3.79 m | 3.80 m | 3.79 m | 3.97 m |
| 19 | 82.66 e | 82.67 e | 3.79 m | 3.80 m | 3.97 m | 3.97 m |
| 20 | 74.01 d | 74.02 d | 3.41 m | 3.41 m | 4.85 m | 4.85 m |
| 32 | 14.08 | 14.09 | 0.88 t (6.8) | 0.88 t (7.3) | 0.88 t (6.6) | 0.88 t (6.8) |
| 33a | 220.36 | 22–36 | 2.68 dd (19.0, 9.5) | 2.68 dd (21.0, 9.8) | 2.68 dd (18.8, 9.5) | 2.67 dd (18.9, 9.3) |
| 33b | — | — | 3.01 m | 3.02 m | 3.01 m | 3.01 m |
| 34 | 205.51 | 205.54 | — | — | — | — |
| 35 | 22–36 | 22–36 | 2.20 s | 2.20 s | 2.20 s | 2.20 s |
| OAc | — | — | — | — | 2.07 s (6H) | 2.04 s (3H) |
| $\text{CH}_2^{\#}$ | 22–37 | 22–37 | 1.26–1.65 m | 1.26–1.65 m | 1.26–1.65 m | 1.26–1.65 m |

c, d, e: Signals may be interchangeable.

[#] These included signals of carbons and protons at C-5 to C-8, C-12 to C-14, C-17 to C-18 and C-21 to C-31.

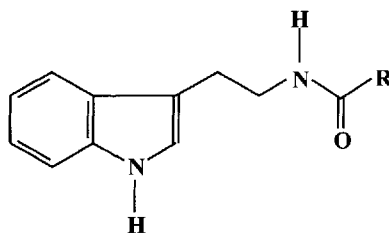


FIGURE 6 Structures of *N*-fatty acyl tryptamines (**10**). $R = C_{19}H_{39}$, $C_{21}H_{43}$, $C_{23}H_{47}$, $C_{24}H_{49}$, $C_{25}H_{51}$, $C_{27}H_{55}$.

(Fig. 2, Tab. II). From all these data, **1** was established to have four hydroxyls, located at C-4, C-10, C-18 and C-19 respectively and the one isolated double bond located at C-14/C-15. **1** is a new compound and named muricatenol.

Gigantetrocinones (**2** and **3**) have been reported as a mixture of *cis* and *trans* isoacetogenins [6] (Figs. 3 and 4), we isolated their acetates by preparative TLC: the pure acetates of 2,4-*cis*-gigantetrocinone (**2a**) and 2,4-*trans*-gigantetrocinone (**3a**) for the first time. 1H and ^{13}C NMR data of **2**, **3**, **2a** and **3a** are in Table III.

Isoannonacin-10-one and isoannonacin have been isolated as 2,4-*cis/trans* mixture [7]. We got only their pure 2,4-*trans* form: 2,4-*trans*-isoannonacin-10-one (**4**) and 2,4-*trans*-isoannonacin (**5**) by ordinary isolation processes (Fig. 5, Tab. IV).

Four known acetogenins have been isolated: gigantetrocin-A (**6**), gigantetrocin-B (**7**), annomontacin (**8**), gigantetronenin (**9**).

A series of *N*-fatty tryptamines [8] have been isolated from *Annona reticulata*, we isolated a similar mixture of six compounds (**10**) from *A. muricata* as shown in Figure 6.

Bioactivity test of the $CHCl_3$ fraction showed antitumor activities, ED_{50} ($\mu g/ml$): KB (nasopharyngeal carcinoma): 9.9; HCT-8 (colon adenocarcinoma): < 0.1 ; Bel (hepatoma cell lines): < 0.1 and A-549 (human lung carcinoma): < 0.1 .

EXPERIMENTAL SECTION

General Experimental Procedures

Melting points were determined on a FISHER-JOHNS melting point apparatus and are uncorrected. The IR spectra were recorded on a

Perkin-Elmer 983G IR spectrometer. NMR spectra were run on a INOVA 500 (500 MHz for ^1H and 125 MHz for ^{13}C) spectrometer. FAB-MS were taken on a Autospec-UltimaETOF instrument. EIMS on a VG ZAB-2f instrument. TLC was performed on silica gel GF and gel H (5–7 μm). Separation and purification were performed by column chromatography on silica gel (120–180 mesh). HPLC were performed on a WATERS-600 HPLC apparatus. The column is PHENOMENEX HYPER 8 μm , (C18120A, 250 \times 10.0 mm, 8 μm).

Plant Material

The seeds of *Annona muricata* L. were collected in August, 1996 from Hainan Island, The People's Republic of China. A voucher specimen was identified by Prof. W. Y. Lian and deposited in the Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing.

Extraction and Isolation

Powdered seeds (4.2 Kg) were exhaustively defatted with hexane and percolated with 95% EtOH at room temperature to give brown extract (420 g), which was partitioned between H_2O and CHCl_3 giving a CHCl_3 soluble extract (320 g). Further purification of this fraction was taken by repeated chromatography over silica gel (gradients of CHCl_3 –MeOH and hexane–EtOAc–MeOH) and gave **2/3** (35 mg), **4** (20 mg), **5** (20 mg) and **10** (20 mg). **1** (7 mg), **6** (15 mg), **7** (15 mg), **8** (15 mg) and **9** (14 mg) were prepared by HPLC/MeOH– H_2O (80:20). Acetylation of **2**, **3**, **4** and **5** were carried out with Ac_2O –pyridine and yielded **2a/3a**, **4a** and **5a** respectively. **2a** and **3a** were separated by preparative TLC/ CHCl_3 –MeOH (95:5).

Muricatenol (1)

White powder, mp 50–51°C. IR $\nu_{\text{max}}^{\text{KBr}}$ (cm^{-1}): 3400, 1745. HRFAB-MS: m/z 609.4993 $[\text{M}+\text{H}]^+$ (Calcd. 609.5076), EIMS and HREIMS: Figure 2 and Table II, ^1H and ^{13}C NMR: Table I.

2,4-cis-Gigantetrocinone (2) and 2,4-trans-gigantetrocinone (3)

White crystals, mp 69–70°C. FAB-MS: m/z 597 $[\text{M}+\text{H}]^+$, EIMS: m/z (%) 369 (11), 351 (19), 333 (17), 281 (67), 257 (1), 239 (30), 221 (7), 197 (7), 141 (7). ^1H and ^{13}C NMR of **2**, **3**; ^1H NMR of their acetates **2a**, **3a**: Table III.

2,4-trans-Isoannonacin-10-one (4)

White crystals, mp 106–107°C. FAB-MS: m/z 617 $[M+Na]^+$, EIMS: m/z (%) 377 (12), 359 (26), 325 (33), 307 (54), 289 (62), 239 (23), 221 (53), 199 (7), 181 (7), 169 (8), 141 (12), 1H and ^{13}C NMR: Table IV.

2,4-trans-Isoannonacin (5)

White crystals, mp 93–94°C. FAB-MS: m/z 596 $[M]^+$, EIMS: m/z (%) 379 (7), 361 (39), 327 (1), 309 (100), 291 (52), 241 (18), 223 (5), 199 (2), 181 (2), 169 (3), 141 (5), 1H and ^{13}C NMR: Table IV.

Gigantetrocin-A (6)

White crystals, mp 67–70°C. FAB-MS: m/z 620 $[M+Na+H]^+$, EIMS: m/z (%) 351 (10), 333 (13), 315 (7), 281 (42), 263 (9), 239 (25), 221 (10), 197 (9), 141 (7), 123 (11). NMR data were identical with Ref. [9].

Gigantetrocin-B (7)

White crystals, mp 67–70°C. FAB-MS: m/z 620 $[M+Na+H]^+$, EIMS: m/z (%) 351 (10), 333 (13), 315 (7), 281 (42), 263 (9), 239 (25), 221 (10), 197 (9), 141 (7), 123 (11). NMR data were identical with Ref. [9].

Annonamontacin (8)

White crystals, mp 64–66°C. EIMS: m/z (%) 592 $[M]^+$, 425 (1), 407 (3), 389 (19), 371 (16), 355 (12), 337 (100), 319 (60), 301 (15), 269 (14), 251 (8), 241 (16), 223 (26), 205 (15), 199 (4), 181 (6), 141 (20), 123 (20). NMR data were identical with Ref. [10].

Gigantetronenin (9)

White crystals, mp 45–47°. FAB-MS: m/z 623 $[M+H]^+$, EIMS: m/z (%) 369 (2), 351 (38), 339 (1), 333 (24), 321 (10), 315 (12), 311(3), 303 (3), 293 (3), 283 (9), 275 (3), 265 (2), 253 (4), 247 (2), 239 (100), 235 (5), 221 (13), 209 (3), 141 (12), 123 (18). NMR data were identical with Ref. [11].

N-Fatty Acyl Tryptamines (10)

Yellow crystals mp 114–116°C. FAB-MS: m/z 566 (M_1^+ , $R = C_{27}H_{55}$), 538 (M_2^+ , $R = C_{25}H_{51}$), 524 (M_3^+ , $R = C_{24}H_{49}$), 510 (M_4^+ , $R = C_{23}H_{47}$),

482 (M_5^+ , $R = C_{21}H_{43}$), 454 (M_6^+ , $R = C_{19}H_{39}$), EI-MS: m/z (%) 396 (7), 382 (3), 368 (18), 354 (2), 143 (100), 130 (14). 1H and ^{13}C NMR data were identical with Ref. [8].

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