New Furanoid and *seco*-Labdanoid Diterpenes from *Leonurus persicus*

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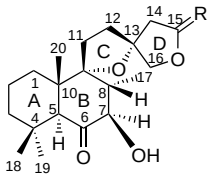
Six new labdane diterpenoids, leopersin C (**1**), 15-*epi*-leopersin C (**2**), leopersin D (**3**), leopersin E (**4**), leopersin F (**5**), and 7-*epi*-leopersin F (**6**) were isolated from the aerial parts of *Leonurus persicus*. Their structures were elucidated by extensive use of 1D and 2D homonuclear and heteronuclear shift-correlated ^{1}H−^{13}C-NMR spectroscopic methods. Leopersin C (**1**) and 15-*epi*-leopersin C (**2**) were obtained as a C-15 epimeric mixture, and their structures were elucidated on this basis.

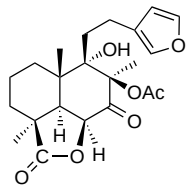
The genus *Leonurus* (Lamiaceae) comprises more than 20 species, of which five grow in Turkey.[1] In a continuation of our phytochemical investigations into *Leonurus* species[2] found in the Turkish flora, we recently reported the isolation and structure elucidation of some labdane diterpenes from the aerial parts of *Leonurus persicus* Boiss.[3] This was the first extensive phytochemical study on this plant. In the present paper, six further new furanoid and *seco*-labdanoid diterpenes from the same source are described.

Results and Discussion

The petroleum ether extract of the air-dried and powdered aerial parts of *Leonurus persicus* was subjected to repeated chromatography to yield six new labdane-derived diterpenes, **1**−**6**.



1 R = H_α, OH_β
2 R = H_β, OH_α
3 R = O



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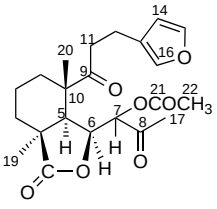
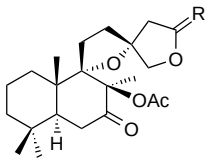


5, 6

Compound **1/2** was isolated as an inseparable mixture (1:1) of two isomers, which were deduced to have the molecular formula $C_{20}H_{32}O_5$ as determined by accurate mass measurement. Its ^{13}C-NMR spectrum showed the presence of resonances for one carbon−oxygen double bond but no further sp^2- or sp-hybridized carbon atoms; thus, **1/2** must be tetracyclic. The IR spectrum of **1/2** had absorption bands typical for hydroxyl (3420 cm^{-1}) and keto (1710 cm^{-1}) functionalities. The ^{1}H- and ^{13}C-NMR spectra contained duplicate resonances attributable to 3 × tertiary methyl (δ_H 0.84, 0.86; 0.96, 0.97; 1.26, 1.27, all s; δ_C 19.7 × 2; 22.1, 22.2; 32.4 × 2, all q) and one secondary methyl (δ_H 1.11 and 1.15, both d, J = 6.5 Hz; δ_C 13.1, 13.3, both q) groups, 7 × CH_2, 4 × CH, two of which are oxygen-bearing (δ_C 77.4 × 2 d, and 99.0 × 2 d), and 5 × C atoms, including a carbonyl (δ_C 211.5 and 212.0, both s) function. These data indicated **1/2** to be closely related to the mixture of leopersin B (**7**) and 15-*epi*-leopersin B (**8**), which was previously isolated from the same plant.[3] Detailed investigation of 2D shift-correlated ^{1}H−^{1}H COSY90, ^{1}H-^{13}C NMR HMQC (J = 150 Hz), and HMBC (J = 8.3 Hz) spectra of **1/2** showed these compounds to be identical in rings A, C, and D. The major differences between **1/2** and **7/8** were the absence of an acetoxyl function and the presence of a secondary hydroxyl group in ring B of **1/2**. Thus, H_3-17 (δ 1.11 and 1.15; d, J = 6.5 Hz) coupled to H-8 (δ 1.88), which further coupled to an oxymethine proton (H-7, δ 3.83 and 3.87, both ddd, J = 1.0, 3.4, 10.8 Hz), and suggested that the hydroxyl group resides at C-7. This deduction was supported by HMBC correlations from C-7 and C-8 to O*H*-7 (δ 3.71, d, J = 3.4 Hz), which also coupled to H-7. In turn, H-7 long-range coupled to H-5 (δ 2.60 and 2.73, both d, J = 1.0 Hz). Long-range ^{1}H−^{13}C couplings observed in the HMBC spectrum between C-6 and H-5, H-7, O*H*-7, and H-8 clearly positioned the free keto function at C-6. All other data (see Tables 1 and 2) were consistent with the presence of a secondary hydroxyl group at C-15 and, hence, the source of the epimerism, as was the case for **7/8**.



7 R = H_α, OH_β
8 R = H_β, OH_α

The relative stereochemistry of centers C-5, C-7, C-8, C-9, C-10, and C-13 in **1/2** were assigned on the basis

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Table 1. ^{1}H-NMR Data of **1-6** ($CDCl_3$, 300 MHz, δ, J Hz)

proton	**1/2**[a]	**3**	**4**	**5**	**6**
1	1.48−1.56[b]	1.48[b]	1.45[b]	1.30−2.13[b]	1.26−2.21[b]
2	1.59[b]	1.59[b]	1.53[b]	1.51[b]	1.37−1.60[b]
3	1.08−1.35[b]	1.06−1.37[b]	1.33−2.21[b]	1.30−1.48[b]	1.26−1.43[b]
5	2.60 (d, 1.0)/2.73 (d, 1.0)	2.67 (s)	2.98 (d, 6.4)	3.29 (d, 9.0)	3.00 (d, 9.2)
6			4.99 (d, 6.4)	4.54 (dd, 2.5, 9.0)	4.82 (dd, 1.5, 9.2)
7	3.83 (ddd, 1.0, 3.4, 10.8)/ 3.87 (ddd, 1.0, 3.4, 10.8)	3.81 (dd, 3.6, 11.1)		5.20 (d, 2.5)	5.13 (d, 1.5)
8	1.88[b]	1.88[b]			
11	1.80−2.15[b]	1.90−2.19[b]	1.82−2.15[b]	2.75[b]	2.73[b]
12	2.00−2.20/2.28[b]	2.12−2.24[b]	2.60[b]	2.80[b]	2.68−2.84[b]
14	2.11−2.40[b]	2.60−3.00 (d, 17.0)	6.27 (dd, 0.9, 1.7)	6.28 (dd, 0.9, 1.7)	6.25 (dd, 0.8, 1.7)
15	5.47 (m)/5.63 (d, 5.2)		7.38 (t, 1.7)	7.34 (t, 1.7)	7.34 (t, 1.7)
16	3.74 (d, 8.9), 4.29 (d, 8.9)/ 4.02 (d, 8.9), 4.09 (d, 8.9)	4.26−4.45 (d, 9.1)	7.25 (m)	7.25 (dd, 0.9, 1.7)	7.23 (dd, 0.8, 1.7)
17	1.11 (d, 6.5)/1.15 (d, 6.5)	1.14 (d, 6.5)	1.93 (s)	2.28 (s)	2.22 (s)
18	1.26/1.27 (s)	1.28 (s)			
19	0.96/0.97 (s)	0.98 (s)	1.31 (s)	1.14 (s)	1.13 (s)
20	0.84/0.86 (s)	0.87 (s)	0.72 (s)	1.04 (s)	1.01 (s)
22			2.14 (s)	2.24 (s)	2.29 (s)
O*H*[c]	3.71 (d, 3.4) (O*H*-7) 3.46 (d, 8.2) 2.78 (br. s)	3.69 (d, 3.6) (O*H*-7)			

[a] Signal pairs are given together, separated by "/". [b] Multiplicity of the signals are unclear due to overlapping. [c] Signals exchange upon the addition of D_2O.

Table 2. ^{13}C-NMR Data of **1**−**6** ($CDCl_3$, 75.5 MHz, ppm)

carbon	**1/2**[a]	**3**	**4**	**5**	**6**
1	32.3/32.7 (t)[b]	32.5 (t)	30.1 (t)	28.9 (t)	30.1 (t)
2	18.2/18.3 (t)	18.2 (t)	17.8 (t)	17.6 (t)	18.2 (t)
3	42.4 × 2 (t)	42.3 (t)	29.0 (t)	30.7 (t)	31.2 (t)
4	32.4 × 2 (s)	32.4 (s)	41.5 (s)	42.7 (s)	42.8 (t)
5	57.0/57.2 (d)	56.9 (d)	45.6 (d)	44.7 (d)	43.5 (d)
6	211.5/212.0 (s)	211.2 (s)	76.0 (d)	77.3 (d)	76.9 (d)
7	77.4 × 2 (d)	77.3 (d)	200.5 (s)	79.2 (d)	78.3 (d)
8	46.8/47.0 (d)	46.6 (d)	90.3 (s)	204.5 (s)	204.9 (s)
9	92.1/93.4 (s)	93.7 (s)	84.6 (s)	211.3 (s)	211.1 (s)
10	48.2/48.3 (s)	48.2 (s)	42.1 (s)	47.9 (s)	48.1 (s)
11	29.1/29.5 (t)	29.1 (t)	32.6 (t)	19.2 (t)	19.1 (t)
12	35.9/38.8 (t)	37.8 (t)	20.0 (t)	37.1 (t)	36.8 (t)
13	90.7/91.0 (s)	86.9 (s)	124.6 (s)	123.6 (s)	123.6 (s)
14	46.4/47.9 (t)	42.7 (t)	110.5 (d)	110.9 (d)	110.8 (d)
15	99.0 × 2 (d)	174.1 (s)	143.4 (d)	142.9 (d)	143.0 (d)
16	76.9/78.4 (t)	78.3 (t)	138.6 (d)	139.3 (d)	139.3 (d)
17	13.1/13.3 (q)	13.2 (q)	22.0 (q)	28.5 (q)	27.0 (q)
18	22.1/22.2 (q)	22.2 (q)	179.6 (s)	179.9 (s)	179.8 (s)
19	32.4 × 2 (q)	32.3 (q)	26.6 (q)	22.3 (q)	22.3 (q)
20	19.7 × 2 (q)	19.6 (q)	17.1 (q)	24.6 (q)	24.4 (q)
21			168.9 (s)	170.1 (s)	170.3 (s)
22			22.3 (q)	20.8 (q)	20.7 (q)

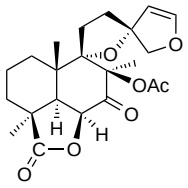
[a] Signal pairs are given together separated by "/". [b] Multiplicity by DEPT.

of NOE interactions and interproton coupling patterns. The observation of cross peaks in the NOESY spectrum between H-5/H-7, H-5/H_3-19, H-7/H_3-17, and H_3-17/H-5 indicated that they were all on the same face of the molecule (α), while interactions between H-8/H_3-20, H_2-11/H_3-20, and H_3-18/H_3-20 revealed that these were on the opposite face (β). It was also evident from 10.8-Hz coupling between H-7 and H-8 that these two protons have a trans-diaxial relationship. These interactions also fix the two six-membered rings into chair conformations. Additional NOE interactions between H_3-17 and H_2-16 supported the relative configuration at C-13 to be as shown in **1/2**. The trivial names of leopersin C and 15-*epi*-leopersin C are proposed for compounds **1** and **2**, respectively.

Compound **3** had the molecular formula $C_{20}H_{30}O_5$, by HREIMS and ^{13}C-NMR spectroscopy. A close comparison of the ^{1}H- and ^{13}C-NMR data of **3** with those of **1/2** suggested that these molecules are very similar, particularly from C-1 to C-12. The only significant differences were attributable to the presence of a lactone carbonyl function in **3**, as determined by IR and ^{1}H- and ^{13}C-NMR data. Absence of the ^{1}H-NMR resonances associated with C-15, the secondary alcohol function found in **1/2**, suggested that the keto function resides at this position and, hence, generates a γ-lactone in **3**. On the basis of the ^{1}H−^{1}H and ^{1}H−^{13}C (J = 150 Hz) 2D NMR COSY measurements, it was possible to assign the doublets at δ 2.60 and 3.00 (J = 17.0 Hz) to H_2-14 and δ 4.26 and 4.45 (J = 9.1 Hz) to H_2-16. The NOESY spectrum of **3** further revealed an interaction between H_3-17 and H_2-16, supporting this deduction. Stereochemically, compound **3** was determined to be the same as **1/2**, in a relative sense, at all corresponding centers, on the basis of NOE data and interproton coupling patterns. For this compound, the trivial name of leopersin D is proposed.

Mass spectrometry indicated that compound **4** had the molecular formula $C_{22}H_{28}O_7$. Of the implied nine degrees of unsaturation, five were accounted for by multiple bonds, two were carbon−carbon double bonds and three carbon−oxygen double bonds, indicating that compound **4** was a tetracyclic molecule. Its IR spectrum had adsorptions characteristic of hydroxyl (3520 cm^{-1}), γ-lactone (1785 cm^{-1}), ester (1750 and 1240 cm^{-1}), and keto (1730 cm^{-1}) functionalities. The ^{1}H- and ^{13}C-NMR data contained resonances associated with an ester (δ_C 179.6 s), 3 × tertiary methyl groups (3H each, δ_H 0.72, 1.31, 1.93, all s; δ_C 17.1, 22.0, 26.6, all q), 5 × CH_2 and 5 × CH groups including two carbon−carbon double bonds (δ_C 110.5 d, 124.6 s, 138.6 d, 143.4 d), as well as 7 × C atoms, including a carbonyl (δ_C 200.5 s) and an acetoxyl (δ_H 2.14 s; δ_C 22.3 q; 168.9 s) function. Closer examination of these data revealed them to be very similar to those of (−)-leosibiricin (**9**)[3] and consistent with the occurrence of only a β-mono-substituted furan ring [two α-furan protons with resonances at δ 7.25 (m, H-16) and δ 7.38 (t, J = 1.7 Hz, H-15) and one β-furan proton with a resonance at δ 6.27 (dd, J = 0.9, 1.8 Hz, H-14)] in **4**, instead of the α,α,α,α-tetrasubstituted tetrahydro- and β,β-disubstituted dihydrofuran rings

found in compound **9**. This transformation required cleavage of the 9-13-epoxide to generate the 9-OH (84.6 ppm, s), followed by elimination of H at C-16, a known elimination rearrangement for prefuranic diterpenes.[3,4] The relative stereochemistry at the six chiral centers within **4** was proposed from the data contained in a NOESY NMR spectrum of **4**. Diagnostic NOEs observed between H-5/H-6, H-5/H_3-17, H-5/H_3-19, H-6/H_3-17, H-6/H_3-19, and H_3-17/H_3-19, as well as between H_2-11/H_3-20 and H_3-20/H_3-OCOCH$_3$, indicated **4** to have the same relative stereochemistry as (−)-leosibiricin (**9**) at all corresponding centers. For compound **4**,[5] a probable artifact of isolation, the trivial name of leopersin E is proposed.



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Compound **5** was found to have the molecular formula $C_{22}H_{28}O_7$ by a combination of mass spectrometry and ^{13}C-NMR spectroscopy. These data also indicated that **5** was a tricyclic molecule containing four carbon−oxygen double bonds and two carbon−carbon bonds. Its IR spectrum showed the presence of furanoid (3145, 1500, 875 cm^{-1}), γ-lactone (1770 cm^{-1}), ester (1730 cm^{-1}), and keto (1715 cm^{-1}) functionalities. Its ^{1}H- and ^{13}C-NMR spectra contained resonances for two tertiary methyl groups (δ_H 1.04 s, 1.14 s; δ_C 22.3 q, 24.6 q) and a methyl group adjacent to a carbonyl group (δ_H 2.28 s; δ_C 28.5 q, carbonyl 204.5 s), an acetate (δ_H 2.24 s; δ_C 20.8 q, 170.1 s), a γ-lactone (δ_C 179.9 s), a keto functionality (δ_C 211.3 s), 5 × CH_2, 6 × CH, three of which were attributed to a β-substituted furan, and three quaternary carbons. Comparison of the ^{1}H- and ^{13}C-NMR data of **5** with those of **4** indicated that these two compounds were similar. Apparent differences were the presence of an additional COCH$_3$ and keto groups and the absence of one ring in **5**. From the ^{1}H−^{1}H COSY spectrum, it was evident that H-5 (δ 3.29, d, J = 9.0 Hz) coupled to H-6 (δ 4.54 dd, J = 2.5, 9.0 Hz), which further coupled to another CH group assigned as H-7 (δ 5.20, d, J = 2.5 Hz). Long-range ^{1}H−^{13}C correlations observed between C-8 (204.5 ppm, s), H_3-17, and H-7 and between C-21 (170.1 ppm, s) and H-7 allowed both the COCH$_3$ and the acetate function to be positioned at C-7. The remaining keto group was attributed to C-9 (211.3 ppm, s) on the basis of cross peaks observed in the HMBC spectrum between C-9 and H_2-1, H-5, H_2-11, H_2-12, and H_3-20, indicating **5** to be an 8,9-*seco*-labdane. All further structural assignments were substantiated by the results contained in the 2D shift-correlated ^{1}H−^{1}H COSY90, ^{1}H−^{13}C NMR HMQC (J = 150 Hz), and HMBC (J = 8.3 Hz) spectra of **5**.

It was possible to assign relative stereochemistry to four of the five chiral centers within **5** from the results of a 2D NOESY measurement. Thus, NOE cross peaks observed between H_3-20 and H-5, H-6, and H-7 and between H_3-19 and H-5 clearly indicated that centers C-4, C-5, C-6, and C-10 had the relative configurations as shown in **5**. For C-7 no stereochemical assignment could be made inasmuch as it is apparently freely rotating. Leopersin F is proposed as the trivial name for **5**.

Compound **6**, by HREIMS and ^{13}C-NMR spectroscopy, had the same molecular formula as **5**, $C_{22}H_{28}O_7$. Close comparison of its ^{1}H- and ^{13}C-NMR data with those of **5** revealed these two compounds to be almost identical. Consideration of these data showed that there were only very minor differences between these two molecules in the region around C-5 to C-7: C-5 [δ_H 3.00 (d, J = 9.2 Hz), δ_C 43.5 (d) for **6**, δ_H 3.29 (d, J = 9.0 Hz), δ_C 44.7 (d) for **5**]; C-6 [δ_H 4.82 (dd, J = 1.5, 9.2 Hz), δ_C 76.9 (d) for **6**, δ_H 4.54 (dd, J = 2.5, 9.0 Hz) δ_C 77.3 (d) for **5**]; and C-7 [δ_H 5.13 (d, J = 1.5 Hz), δ_C 78.3 (d) for **6**, δ_H 5.20 (d, J = 2.5 Hz), δ_C 79.2 (d) for **5**]. In all other respects, the molecules had virtually identical spectral properties. Because the NOESY spectrum of **6** showed no significant stereochemical differences between **5** and **6** at C-4, C-5, and C-6 and because $J_{6,7}$ in **5** is 2.5 Hz and in **6** is 1.5 Hz, it was concluded that **6** was the C-7 epimer of **5** and, hence, was 7-*epi*-leopersin F. Since a structure very similar to **5** and **6** was obtained by a weak acid treatment of leocardin,[7] an epimeric mixture isolated from *Leonurus cardiaca*, it is possible that **5** and **6** may also be artifacts of isolation and not natural products in their own right.

Experimental Section

General Experimental Procedures. See Tasdemir *et al.*[3] for general procedures.

Plant Material. *Leonurus persicus* Boiss. was collected in early Aug 1992 from Tekman province of Erzurum, East Anatolia, Turkey. Voucher specimens are deposited in the Herbarium of Pharmacognosy Department, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey (voucher number HUEF 92111).

Extraction and Isolation. The extraction and preliminary fractionation procedures for *Leonurus persicus* have been reported.[3] A 2-g sample of combined VLC fractions 8 and 9 was refractionated by VLC over Si gel, employing hexane−$CHCl_3$−MeOH (175:95:5 to 0:30:70) mixtures. TLC and ^{1}H-NMR investigations of these fractions indicated that fractions 1−5 (combined) and 6 were of further interest. Fraction 6 was chromatographed by normal-phase HPLC with $CHCl_3$−MeOH−hexane (95:5:270) to give 13 fractions. Of these, fraction 7 was separated by RP-HPLC with CH_3CN−i-PrOH−H_2O (7:1:10) to give **1/2**.

Leopersin C and 15-*epi*-leopersin C (1/2): colorless oil (14.6 mg, 0.0016%); IR ν max (film) 3420, 2980, 1710, 1465, 1270, 1065 cm^{-1}; EIMS m/z (rel int) [M]$^+$ 352 (<1), 334 (7), 319 (1), 316 (1), 199 (100), 193 (19), 181 (16), 123 (24), 109 (17), 95 (22), 82 (47), 81 (30); HREIMS 352.2259 (calcd for $C_{20}H_{32}O_5$ 352.2251); ^{1}H-NMR, see Table 1; ^{13}C-NMR, see Table 2.

Normal-phase HPLC separation (LiChrosorb Si60, 5 μm) of combined fractions 1−5 (see above) with $CHCl_3$−MeOH−hexane (95:5:270) as eluent yielded 10 fractions. Of these fractions, one (fraction 5) was rechromatographed using the same column but with hexane−Me_2CO−MeOH (81:20:2) as eluent to give 10 further fractions, of which fractions 5, 7, and 9 were further purified. Repeated purification of fraction 5 by RP-HPLC with CH_3CN−i-PrOH-H_2O (7:1:6.5) yielded **3**.

Leopersin D (3): white amorphous powder (3 mg, 0.0003%); $[\alpha]^{20}_D$ +26.3° (c 0.18, $CHCl_3$); IR ν max (film)

3500, 2980, 1790, 1715, 1370, 1045, 1030 cm^{-1}; EIMS *m/z* (rel int) $[M]^+$ 350 (11), 332 (22), 317 (8), 208 (33), 198 (16), 197 (100), 151 (17), 149 (13), 123 (15), 109 (28), 83 (17), 81 (19); HREIMS 350.2095 (calcd for $C_{20}H_{30}O_5$ 350.2094); ^{1}H-NMR, see Table 1; ^{13}C-NMR, see Table 2.

Normal-phase HPLC separation of fraction 9 (155 mg) with hexane−EtOAc (76:24) as eluent afforded compound **4**.

Leopersin E (4): white amorphous powder (65 mg, 0.007%); $[\alpha]^{20}_D$ +44.3° (*c* 0.24, $CHCl_3$); IR *ν* max (film) 3520, 2935, 1785, 1750, 1730, 1505, 1240, 1045, 875 cm^{-1}; EIMS *m/z* (rel int) $[M]^+$ 404 (11), 344 (6), 282 (4), 239 (6), 221 (15), 193 (52), 175 (10), 123 (14), 109 (65), 95 (35), 81 (39); HREIMS 404.1845 (calcd for $C_{22}H_{28}O_7$ 404.1836); ^{1}H-NMR, see Table 1; ^{13}C-NMR, see Table 2.

Fraction 7 (81.3 mg) was separated by RP-HPLC (Spherisorb ODS II, 250 × 8 mm, 5 μm) using CH_3CN−i-PrOH−H_2O (7:1:6.4) as eluent to afford 10 fractions. Further separation of combined fractions 1−4 with CH_3CN−i-PrOH-H_2O (7:1:8.1) gave **5** and **6**.

Leopersin F (5): white amorphous powder (10 mg, 0.001%); $[\alpha]^{20}_D$ −7.2° (*c* 0.58, $CHCl_3$); IR *ν* max (film) 3145, 2930, 1770, 1730, 1715, 1500, 1235, 1050, 875 cm^{-1}; EIMS *m/z* (rel int) $[M + H]^+$ 405 (2), $[M]^+$ 404 (8), 344 (<1), 282 (12), 239 (4), 193 (20), 151 (29), 137 (27), 123 (23), 109 (47), 95 (45), 81 (71), 43 (100); HREIMS 404.1794 (calcd for $C_{22}H_{28}O_7$ 404.1836); ^{1}H-NMR, see Table 1; ^{13}C-NMR, see Table 2.

7-*epi*-Leopersin F (6): colorless oil (4 mg, 0.0004%); $[\alpha]^{20}_D$ −19.2° (*c* 0.3, $CHCl_3$); IR *ν* max (film) 3145, 2930, 1780, 1750, 1710, 1500, 1230, 1045, 875 cm^{-1}; EIMS *m/z* (rel int) $[M + H]^+$ 405 (5), $[M]^+$ 404 (21), 344 (2), 282 (8), 239 (5), 193 (25), 151 (26), 137 (20), 123 (44), 109 (36), 95 (49), 81 (66), 43 (100); HREIMS 404.1845 (calcd for $C_{22}H_{28}O_7$ 404.1836); ^{1}H-NMR see Table 1; ^{13}C-NMR, see Table 2.

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References and Notes

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