SESQUITERPENE ESTERS FROM MAYTENUS CHUBUTENSIS

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Abstract - From the aerial part of Maytenus chubutensis Speg. six new dihydro-β-agarofuran skeleton sesquiterpenes were isolated and identified by spectroscopy, chemical reactions and selective hydrolysis. Absolute configurations were established by cd methods.

In the course of a programme of phytochemical research into Celastraceae used in folk medicine or elsewhere, we earlier reported the isolation and structure determination of new metabolites with antibiotic[1] and cytostatic[2] activity. These bioactive metabolites are methylene quinone triterpenes and were obtained from the roots of various Celastraceae. When the dihydro-β-agarofuran skeleton sesquiterpenes isolated from these species[3-7] were assayed, however, they showed no antibiotic activity.[8] As species of Celastraceae used as insecticide[9] contain sesquiterpenes, we are now studying the antifeedant activity[10] of a wide range of sesquiterpenes.

This paper gives an account of the results of a study of the extract of the aerial part of Maytenus chubutensis Speg.,[11] an Andean species from Chile which was chosen because the Artemia salina[12] test for bioactivity showed a LC_{50}>1000. The new metabolites **1**-**6** were isolated and their structures were determined from spectral data, chemical correlations and selective hydrolysis. The absolute configuration of the compounds was established from the cd data of the natural ketone, **5**, and **12**, the benzoyl derivative of natural **3**. This is of particular

interest as the literature on the dihydro-β-agarofuran sesquiterpenes has at times been unclear because of uncertainty[13-15] about the absolute configurations.

Compound **1** was isolated as a crystalline substance; hrms gave the molecular formula, $C_{32}H_{40}O_{13}$, and fragments at m/z 105 and 42 suggested the presence of a benzoate and acetate in the molecule. This was confirmed by the ^1H nmr spectrum where five aromatic protons were observed between δ 8.10 and 7.35 and acetate methyls at δ 1.46, 2.07, 2.10, 2.20 and 2.26, and by the ^{13}C nmr spectrum in which carbons appeared at δ 128.57(2), 128.65, 130.31(2), 133.89 and 164.76, and 20.45, 21.31 and 21.41(3). The

	R_1	R_2	R_3	R_4	R_5	R_6	R_7
1	OAc	OAc	OAc	H	OAc	OBz	OAc
2	OAc	OAc	OAc	H	OAc	OBz	OH
3	OAc	OAc	OAc	H	OH	OBz	OAc
4	OAc	OAc	OAc	H	OH	OBz	OH
5	OAc	OAc	OAc	=O	=O	OBz	OAc
6	OAc	OAc	OAc	=O	=O	OBz	OH
7	OH	OAc	OAc	H	OH	OBz	OH
8	OH	OAc	OH	H	OH	OBz	OH
9	OH	OH	OAc	H	OH	OBz	OH
10	OH	OH	OH	H	OH	OBz	OAc
11	OH	OH	OAc	H	OH	OH	OH
12	OAc	OAc	OAc	H	OBz	OBz	OAc
13	OH	OH	H	H	OH	OH	OH

Table 1: ^{13}C nmr Data

	1	**2**[a]	**3**	**4**
C-1	74.11	73.76	74.56	74.27
C-2	71.75	70.15	71.73	72.06
C-3	31.18	31.20	29.85	29.65
C-4	32.90	33.21	32.94	33.15
C-5	89.91	89.78	89.98	89.94
C-6	69.32	71.79*	69.46	69.76
C-7	53.27	53.70	55.85	56.33
C-8	75.05*	76.54	75.62*	74.96*
C-9	77.16*	75.25*	75.98*	75.41*
C-10	52.79	52.83	52.75	54.39
C-11	81.63	81.95	81.72	81.76
C-12	30.42	30.84	30.67	30.95
C-13	25.92	25.83	25.95	25.70
C-14	17.05	17.69	17.23	17.63
C-15	65.69	64.81	65.51	63.26

δ values based on DEPT experiments and correlations.
a Values obtained from ^1H-^{13}C two-dimensional nmr correlations.
* Interchangeable values, most probably as shown.

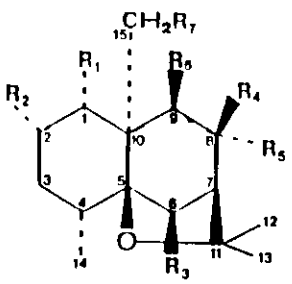


Table 2. ^{1}H nmr Shifts in δ, J in Hz. Solvent $CDCl_3$

	H-1	H-2	H-3	H-6	H-7	H-8	H-9	H-15	OAc-1	OAc-2	OAc-6	OAc-8	OAc-15
1	5.70d (3.7)	5.58m	1.75dd (2.7,15.0)	6.38br s	2.36d (2.9)	5.27d (2.9)	5.51s	5.10-4.52d$_{AB}$ (12.8)	1.46	2.07	2.20	2.10	2.26
2	5.73d (3.7)	5.58m	1.82dd (2.7,15.0)	5.90br s	2.52d (2.9)	5.30d (2.9)	5.87s	4.74-3.98d$_{AB}$ (12.8)	1.51	2.07	2.20	2.08	
3	5.72d (3.7)	5.60m	1.80dd (2.7,15.0)	6.43br s	2.37d (2.9)	4.25d (2.9)	5.31s	5.04-4.58d$_{AB}$ (12.8)	1.48	2.07	2.12		2.26
4	5.67d (3.7)	5.57m*	1.80dd (2.7,15.0)	6.37br s	2.42d (2.9)	4.25d (2.9)	5.57s*	4.51-4.27d$_{AB}$ (11.7)	1.54	2.05	2.12		
5	5.62d (3.7)	5.58m	1.80*	6.49br s	3.00s		5.87s	5.18-4.42d$_{AB}$ (12.8)	1.49	2.08	2.14		2.19
6	5.59d (3.3)	5.36m	1.85dd (2.7,15.0)	6.66br s	3.15s		5.88s	4.50-4.28d$_{AB}$ (12.3)	1.55	2.06	2.14		
7	4.67d (3.7)	5.43m		5.95br s	2.45d (2.9)	4.42d (2.9)	5.71s	4.10d (12.5)		2.07	2.09		
8	4.69d (3.7)	5.65m	*	4.32s	2.37d (2.9)	4.52d (2.9)	5.80s	4.80-4.10d$_{AB}$ (12.8)		2.07			
9	4.46d (3.7)	4.22m	1.90dd (2.7, 15.0)	5.90s	2.42d (2.9)	4.42d (2.9)	5.69s	4.78-4.14d$_{AB}$ (12.8)			2.09		
10	4.54d (3.6)	4.28m		4.07s	2.39d (3.3)	4.43d (3.1)	6.07s	5.23-4.89d$_{AB}$ (12.0)					2.09
11	4.41d (3.7)	4.26*		5.72s	2.25d (2.9)	4.37d (2.9)	4.26*	4.64-4.00d$_{AB}$ (11.5)			2.06		
12	5.70d (3.7)	5.60m		6.47br s	2.50d (2.9)	5.37d (2.9)	5.77s	5.14-4.60d$_{AB}$ (12.3)	1.48	2.00	2.05		2.17

* partially overlapping another signal.

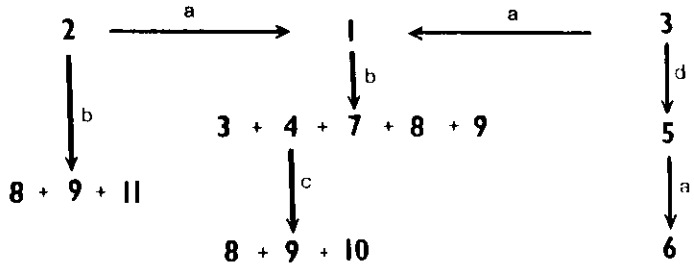
anomalous highfield shift of one of the methyls (1.46) only occurs when the methyl faces a benzoate and the shift itself is characteristic of 1α being found facing 9β or vice versa;[16] double resonance experiments and study of the coupling constants[17] identified the substitution positions as 1α,2α,6β,8α,9β and 15, indicating a basic pentahydroxydihydroagarofuran (**13**) 6β-hydroxy derivative skeleton.[17] The relative positions of the benzoate and the acetates remained to be solved. The hydrolysis of **1** with 0.1 M $NaHCO_3$ gave compounds **3**, **4**, **7**, **8** and **9** (see ^1H and ^{13}C nmr data) which showed the benzoate at 9β: nOe difference experiments confirmed this relative configuration, irradiation of the 14-Me showing a clear nOe effect on the H-6 and one of the H-15 protons and a less intense effect on H-9.

Product **3** proved to be a derivative of **1** deacetylated at C-8. In ^1H nmr (see Table) the proton geminal to the acetate on C-8 shifted from δ 5.27 in **1** to δ 4.25 in **3** while the signal for an acetate methyl disappeared. Product **4** is a bisdeacetyl derivative of **1**, having lost the acetates at C-8 and C-15 (see Table 2). Compound **7** is a trideacetyl derivative with acetate loss at C-1, C-8 and C-15. Products **8** and **9** proved to be tetradeacetyl derivatives of **1** with the acetates missing from C-1, C-8, C-15 and C-6 in **8** and C-1, C-8, C-15 and C-2 in **9**. Obviously the hydrolysis products **3** and **4** are identical to the natural compounds.

In order to determine the absolute configuration of the above compounds, product **3** was studied by the dibenzoate chirality method, an extension of the circular dichroism exciton chirality method.[18,19] The necessary dibenzoate derivative, **12**, was obtained by treating compound **3** with benzoyl chloride in pyridine, followed by hplc purification. The ^1H nmr spectrum of **12** showed a single resonance for H-9 ($J_{8,9}=0$), making the dihedral angle between the two benzoate chromophores approximately 150°. The compound was therefore eminently suitable for cd study. The cd spectrum showed a split cd curve with extrema at right wavelengths, i.e., the first Cotton effect was located at 237 nm ($\Delta\epsilon=-19.3$) and the second at 217 nm ($\Delta\epsilon=+1.8$). The weakish second Cotton effect can be attributed to negative overlaying background ellipticity.[18,19] As the cd Cotton effects show the benzoate chirality, the absolute configuration of **12** can be established. A cd study of product **5**, showing a positive Cotton effect for the

n→π* transition of the keto group[5,20] at 290 nm ($\Delta\epsilon$=+3.6), supported the same absolute configuration as that ascribed to compound **12** when the cd dibenzoate method was applied.

The other products could be correlated with **1** either directly or indirectly (see Figure 1).



a) Ac_2O/Py; b) 0.1M $NaHCO_3$; c) 17.5% HCl; d) Jones reagent.

The compounds **1**-**6** are natural products.

Figure 1

EXPERIMENTAL

The mp is uncorrected. Ir spectra were taken on a PE 681 spectrophotometer and ^1H and ^{13}C nmr on a Bruker WP-200 SY in $CDCl_3$ (200 and 50 MHz, respectively) (TMS as internal reference); optical rotations were measured on a Perkin-Elmer 241 automatic polarimeter; mass spectra were recorded on a VG Micromass LTD-ZAB-2F and/or on an HP 5930A at 70 eV; uv spectra were run on a Perkin-Elmer Model 550-SE and cd spectra on a Jasco-J-600 spectropolarimeter. Prior to measurement of the cd spectra, compounds **12** and **5** were purified by hplc (μ-Porasil, 10μ, 0.8 x 30 cm, 2ml/min, λ254 nm, EtOAc-hexane 3:7). The concentrations of the cd samples (MeCN) were ascertained from the uv spectra, using the values of 15300 and 27000 for the mono- and dibenzoate,[19] respectively.

Plant Collection The plant was gathered in January, 1987 in the Septima region in Talca province, Chile and a voucher specimen is on file with the Facultad de Ciencias, Universidad de Chile, Santiago.

Extraction and Isolation The aerial part of the plant (2 kg) was extracted with EtOH (10,000 ml) at room temperature for 1 week. The extract thus obtained was concentrated at reduced pressure at 40°C and part (44 g) of the resulting extract (378 g) was chromatographed on Sephadex LH-20. Sesquiterpene-containing fractions (20.1 g) were obtained with hexane-$CHCl_3$-MeOH (2:1:1) as solvent and were repeatedly chromatographed on silica gel with hexane-EtOAc mixtures of

increasing polarity as eluents and then were re-chromatographed with the solvents shown. The following products were isolated: **1** (54 mg) (hexane–EtOAc 3:1); **2** (56 mg) (hexane–EtOAc 1:1); **3** (33 mg) (C_6H_6–Et_2O 3:2); **4** (50 mg) (C_6H_6–EtOAc 2:3); **5** (15 mg) (C_6H_6–EtOAc 2:1) and **6** (8 mg) ($CHCl_3$–C_6H_6–MeOH 95:4:1).

1: mp, 135–140° C (EtOAc); $[\alpha]_D^{20}$ = 7.7° (c 0.52, $CHCl_3$); ir ν_{max} ($CHCl_3$) cm^{-1}: 3000, 1730, 1365, 1275, 1240, 1095, 710; ^1H nmr δ: 1.16 (3H, d, J=7.4 Hz), 1.43 (3H, s), 1.56 (3H, s), 7.49 (3H, m), 8.00 (2H, m); ^{13}C nmr: see Table 1; uv λ_{max} (EtOH) nm: 234, 276, 287; ms, m/z: 632 (M^+) (1), 617 (3), 590 (40), 572 (4), 548 (2), 530 (3), 512 (1), 497 (2), 488 (2), 470 (2), 437 (3), 408 (2), 348 (3), 306 (4), 288 (6), 105 (100), calcd for $C_{32}H_{40}O_{13}$, 632.2436, found, 632.2452.

Partial Hydrolysis of **1** **1** (47 mg), dissolved in EtOH (4 ml), was treated with 0.1 M $NaHCO_3$ (3 ml) at 50° C for 45 min, the excess solvent was eliminated under reduced pressure, and the residue was poured onto water and extracted with EtOAc to give a mixture which was separated by preparative tlc with C_6H_6–EtOAc (2:3) as eluent to give products identical to the natural substances **3** (5 mg) and **4** (4 mg) and three other deacetyl derivatives, **7** (1 mg), **8** (5 mg) and **9** (6.8 mg).

2 was isolated as an oil; $[\alpha]_D^{20}$ = −20.6° (c 1.79, $CHCl_3$); ir ν_{max} ($CHCl_3$) cm^{-1}: 3560, 3000, 1730, 1360, 1270, 1230, 1090, 710; ^1H nmr δ: 1.17 (3H, d, J=7.4 Hz), 1.40 (3H, s), 1.53 (3H, s), 7.47 (3H, m), 8.00 (2H, m); ^{13}C nmr: see Table 1; uv λ_{max} (EtOH) nm: 234, 276, 285; ms, m/z: 590 (M^+) (2), 548 (4), 530 (2), 515 (1), 488 (1), 470 (2), 468 (3), 426 (1), 423 (4), 348 (2), 288 (4), 237 (5), 105 (100), calcd for $C_{30}H_{38}O_{12}$, 590.2332, found, 590.2347.

2 (3 mg) was dissolved in Py (4 drops) with Ac_2O (2 drops) at room temperature for 24 h. EtOH (3 ml) and C_6H_6 (3 ml) were then added and the mixture was taken to dryness under reduced pressure. Purification by column chromatography on silica gel with hexane–EtOAc (3:2) as eluent gave a product identical to **1** (2 mg).

Partial Hydrolysis of **2** **2** (12.5 mg), dissolved in MeOH (2 ml), was treated with 0.2 M $NaHCO_3$ (0.8 ml) at room temperature for 7 days, the excess solvent was eliminated under reduced pressure, and the residue was poured onto water and extracted with EtOAc. This hydrolysed mixture was separated by preparative tlc with C_6H_6–EtOAc (1:9) as eluent to give the deacetyl derivatives **8** (2 mg) and **9** (1.3 mg) and the debenzoyl derivative **11** (1 mg).

3 was isolated as an oil; $[\alpha]_D^{20}$ – insufficient material available, as the

product was used up in hydrolysis; ir ν_{max} ($CHCl_3$) cm^{-1}: 3580, 3020, 2920, 1730, 1365, 1270, 1245, 1090, 710; ^1H nmr δ: 1.18 (3H, d, J=7 Hz), 1.42 (3H, s), 1.44 (3H, s), 7.48 (3H, m), 8.03 (2H, m); ^{13}C nmr: see Table 1; uv λ_{max} (EtOH) nm: 233, 274, 285; ms, m/z: 590 (M^+) (1), 575 (2), 548 (8), 530 (1), 488 (8), 408 (17), 351 (5), 306 (5), 261 (6), 243 (15), 231 (9), 105 (100), calcd for $C_{29}H_{35}O_{12}$, [M^+-15], 575.2196, found, 575.2162.

Treatment of **3** with Benzoyl Chloride Benzoyl chloride (100 μl) was applied to a solution of **3** (1.0 mg, 1.69 μmol) in dry pyridine (1 ml) with DMAP as catalyst and the resulting solution was stirred for 14 h at 60° C. The reaction mixture was quenched with a few drops of MeOH and the excess solvent was removed under reduced pressure in the presence of n-heptane. The residue was then spotted on preparative tlc (hexane-EtOAc 7:3) to give the desired dibenzoate **12** (0.9 mg).

Acetylation of **3** Product **3** (5 mg) was acetylated as for **2** (Ac_2O and Py) at room temperature for 24 h and purified by column chromatography on silica gel with hexane-EtOAc (4:1) as eluent to give a product (1 mg) identical to **1**.

Oxidation of **3** **3** (4 mg) was dissolved in acetone (2 ml) and treated with Jones reagent (1 drop) for 1 h at room temperature. The reaction was halted by the addition of isopropanol and the mixture was taken to dryness first with MeOH and thereafter with C_6H_6, then filtered over fluorosil *in vacuo* and washed with Et_2O to give **5** (2 mg) as sole product.

4 was isolated as an oil; $[\alpha]_D^{20}$ = 17.2° (c 0.53, $CHCl_3$); ir ν_{max} ($CHCl_3$) cm^{-1}: 3600, 3450, 3000, 2920, 2840, 1730, 1360, 1265, 1245, 1090, 710; ^1H nmr δ: 1.26 (3H, d, J=7.5 Hz), 1.44 (6H, s), 7.48 (3H, m), 8.03 (2H, m); ^{13}C nmr: see Table 1; uv λ_{max} (EtOH) nm: 234, 278, 285; ms, m/z: 548 (M^+) (3), 533 (2), 488 (9), 473 (1), 428 (2), 384 (2), 366 (10), 291 (5), 261 (2), 201 (5), 105 (100), calcd for $C_{28}H_{36}O_{11}$, 548.2231, found, 548.2244.

Acetylation of **4** **4** (6.6mg) was acetylated in the same way as **2** (Ac_2O and Py) at room temperature for 24 h and then subjected to preparative tlc in C_6H_6-MeOH (9:1), giving **1** (2 mg) and **3** (4 mg).

Hydrolysis of **4** **4** (30 mg) was dissolved in dioxan (4 ml), 17.5% HCl (4 ml) was added and the mixture was heated at 60°C for 3 h. The reaction was halted by pouring onto water and the mixture was extracted with EtOAc and subjected to preparative tlc with C_6H_6-EtOAc (3:7) as eluent to give **8** (3 mg), **9** (6 mg)and **10** (3 mg).

5 was isolated as an oil and purified by hplc with hexane-EtOAc (7:3) as solvent (retention time = 20 min); $[\alpha]_D^{20}$ = 17.4° (c 0.46, $CHCl_3$); ir ν_{max} ($CHCl_3$) cm^{-1}: 2920, 1740, 1365, 1260, 1235, 1085, 710; ^1H nmr δ: 1.00 (3H, d, J=7.5 Hz), 1.47 (3H, s), 1.52 (3H, s), 7.47 (3H, m), 8.00 (2H, m); uv λ_{max} (EtOH) nm: 235, 278, 287; uv λ_{max} (MeCN) nm: 280 (850), 275 (1000), 231 (15300); cd (MeCN) λ_{ext} nm: 310 ($\Delta\epsilon$=+1.7), 300 ($\Delta\epsilon$=+3.3), 290 ($\Delta\epsilon$=+3.6), 246 ($\Delta\epsilon$=-0.8), 227 ($\Delta\epsilon$=+1.7); ms, m/z: 588 (M^+) (1), 573 (1), 546 (1), 528 (1), 500 (30), 468 (2), 466 (7), 458 (3), 382 (1), 353 (1), 105 (100), calcd for $C_{30}H_{36}O_{12}$, 588.2286, found, 588.2246.

6 was obtained as an oil; $[\alpha]_D^{20}$ = 10.0° (c 0.27, $CHCl_3$); ir ν_{max} ($CHCl_3$) cm^{-1}: 2920, 1730, 1365, 1235, 1095, 710; ^1H nmr δ: 1.33 (3H, d, J=7.5 Hz), 1.49 (3H, s), 1.51 (3H, s), 7.52 (3H, m), 8.00 (2H, m); ms, m/z: 531 (M^+-15) (1), 504 (1), 458 (36), 444 (3), 416 (2), 413 (2), 383 (1), 338 (1), 279 (5), 105 (100), calcd for $C_{28}H_{34}O_{11}$, 546.2089, found, 546.2095.

Acetylation of **6** When **6** (8 mg) was acetylated as described above for 6 days at room temperature, and then purified by preparative tlc using C_6H_6-EtOAc (4:1) as eluent, a substance (3.5 mg) identical to the natural compound **5** was obtained.

7 was isolated as an oil; the optical rotations were not taken as **7** was sent in its entirety for biological assaying; ir ν_{max} ($CHCl_3$) cm^{-1}: 3680, 3585, 3020, 2920, 2840, 1720, 1365, 1270, 1240, 1090, 710; ^1H nmr δ: 1.00 (3H, d, J=7.5 Hz), 1.43 (3H, s), 1.46 (3H, s), 7.64 (3H, m), 8.02 (2H, m); uv λ_{max} (EtOH) nm: 232, 275, 284; ms, m/z: 488 (M^+-18) (2), 464 (1), 446 (2), 428 (2), 404 (1), 386 (1), 342 (1), 324 (2), 264 (4), 234 (2), 216 (2), 105 (100), calcd for $C_{24}H_{37}O_7$, [M^+-42], 464.1966, found, 464.2006.

8: $[\alpha]_D^{20}$ = 1.8° (c 1.00, $CHCl_3$); ^1H nmr δ: 1.14 (3H, d, J=7.4 Hz), 1.39 (3H, s), 1.56 (3H, s), 7.45 (3H, m), 8.08 (2H, m); ms, m/z: 446 (M^+-18) (1), 415 (3), 401 (1), 341 (1), 309 (2), 281 (7), 105 (100), calcd for $C_{23}H_{27}O_7$, [M^+-49], 415.1742, found, 415.1749.

9: $[\alpha]_D^{20}$ = -20.5° (c 0.83, $CHCl_3$); ^1H nmr δ: 1.23 (3H, d, J=7.4 Hz), 1.42 (6H, s), 7.50 (3H, m), 8.00 (2H, m); ms, m/z: 446 [M^+-18] (1), 386 (3), 371 (1), 339 (3), 297 (5), 281 (3), 264 (7), 105 (100), calcd for $C_{24}H_{30}O_6$ [M^+-18], 446.1902, found, 446.1921.

10: $[\alpha]_D^{20}$ = 0° (c 0.18, $CHCl_3$); ^1H nmr δ: 1.39 (3H, s), 1.53 (3H, s), 7.46 (3H, m), 8.12 (2H, m); ms, m/z: 446 (M^+-18) (2), 404 (4), 386 (4), 371 (2), 341 (2), 339 (3), 311 (4), 105 (100), calcd for $C_{24}H_{30}O_6$, [M^+-18], 446.1968, found

446.1954.

11: the optical activity was not measured as all this substance was used up in a biological assay; ^{1}H nmr δ: 1.36 (3H, s), 1.51 (3H, s); ms, m/z: 345 (M^+-15) (5), 318 (1), 313 (3), 311 (16), 300 (4), 285 (3), 283 (7), 255 (8), calcd for $C_{16}H_{25}O_6$, [M^+-15], 345.1707, found 345.1628.

12 was purified by hplc with hexane-EtOAc (7:3) (retention time = 15 min); the optical activity was not measured as this substance was sent for biological assaying; ^{1}H nmr δ: 1.22 (3H, d, J=7.5 Hz), 1.40 (6H, s), 7.24, 8.25 (10H, m); uv λ_{max} (MeCN): 230; cd λ_{ext} (MeCN) nm: 237 ($\Delta\epsilon$=-19.3), 217 ($\Delta\epsilon$=+1.8); ms, m/z: 652 (M^+-42) (5), 634 (1), 592 (1), 530 (1), 470 (1), 410 (2), 337 (6), 105 (100), calcd for $C_{35}H_{40}O_{12}$, [M^+-42], 652.2698, found 652.2609.

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