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Cryptoporic and isocryptoporic acids from the fungal cultures of *Polyporus arcularius* and *P. ciliatus*

Gabriela M. Cabrera[a,*], M. Julia Roberti[a], Jorge E. Wright[b], Alicia M. Seldes[a]

[a]*Depto de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, Pab. II, (1428) Buenos Aires, Argentina*

[b]*Depto de Biología and PRHIDEB-CONICET, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, Pab. II, (1428) Buenos Aires, Argentina*

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Abstract

In a chemical study of several fungal cultures of *Polyporus*, a methyl ester of cryptoporic H was isolated from *P. ciliatus,* together with cryptoporic acid H and 5-hydroxymethylfuran-3-carboxylic acid. Furthermore, two additional compounds, named isocryptoporic acids H and I, were isolated from *P. arcularius*. These isocryptoporic acids are isomers of the cryptoporic acids with drimenol instead of albicanol as the terpenoid fragment; their structural elucidation was determined by application of spectroscopic methods. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Polyporus; Polyporales; Basidiomycete, Drimane sesquiterpenoids

1. Introduction

Polyporus species are basidiomycetes belonging to the Polyporales, which are wood-rotting fungi. They grow on living trees or dead wood, and possess exoenzymes that can degrade cellulose and lignin. Many of them, fruiting bodies collected from host trees or grown on liquid cultures, have been chemically investigated and yielded alkaloids and quinones (Gill and Steglich, 1987), linear compounds (Birkinshaw et al., 1952), alkaloids (Cavill et al., 1953), pyrones (Ali et al., 1996) and terpenoids (Tai et al., 1995). Some of these compounds were isolated by bioassay-guided fractionation via monitoring their antibacterial and/or immunomodulatory activities.

P. arcularius has been previously chemically investigated (Fleck et al., 1996) yielding isodrimenediol, drimenediol and related sesquiterpenes. In the course of our studies on bioactive and new components from fungi (Cabrera and Seldes, 1997; Levy et al., 2000), new and known drimane terpenoids were isolated and identified from the fungal cultures of *Polyporus arcularius* and *P. ciliatus*. Different species of this genus were also examined, in order to correlate chemotaxonomic profiles with recent enzymatic and morphologic studies (Borges da Silva, 2001).

2. Results and discussion

Strains of *P. arcularius*, *P. ciliatus*, *P. philippinensis*, *P. guianensis* and *P. tenuiculus* were grown on a malt extract broth for two weeks and filtered. The filtrates were extracted with EtOAc to give crude extracts, which were analyzed by TLC, bioassays and by ^{1}H NMR spectroscopy. The culture media extracts of *P. arcularius* and *P. ciliatus* showed major polar compounds, as evidenced by ^{1}NMR spectral analysis, with acidic characteristics as observed by TLC. The extracts corresponding to the other strains did not show any appreciable secondary metabolite production by ^{1}H NMR and TLC. Based on these results, *P. arcularius* and *P. ciliatus* were cultured on a larger scale. Both extracts were subjected to HPLC yielding compounds **1** and **2** from *P. arcularius* and **3**, **4** and **5** from *P. ciliatus*.

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[*] Corresponding author. Tel./fax: +5411-4576-3346.
E-mail address: gabyc@qo.fcen.uba.ar (G.M. Cabrera).

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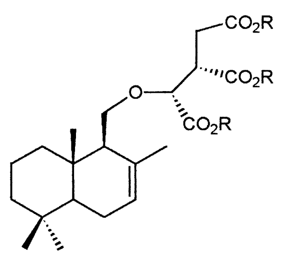
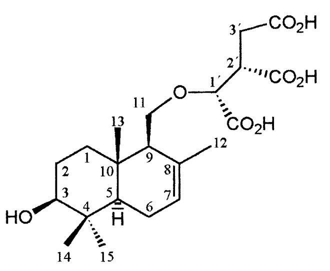


1 R=H
1a R=CH$_3$



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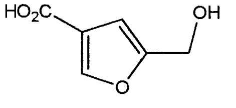

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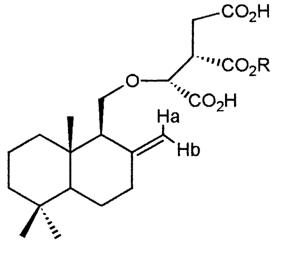
3a R=CH$_3$



4 R=H
5 R=CH$_3$

The molecular formula of compound **1** was $C_{21}H_{32}O_7$, as determined by HRFABMS. Full structural assignments were made by interpretation of the 2D NMR spectra, including COSY, RCT, HETCOR, COLOC and NOESY. The ^1H NMR spectrum showed three quaternary methyls at δ 0.81, 0.86 and 0.89, a broad singlet at 5.45 ppm characteristic of a double bond, a methyl group at δ 1.74 attached to a double bond and six signals between 2.5 and 4.1 ppm, indicative of the presence of heteroatoms in the molecule. The ^{13}C NMR spectrum revealed the presence of a double bond with carbon chemical shifts at δ 123.2 and 134.3, two carbons attached to oxygen, at δ 70.3 (CH_2) and δ 79.6 (CH), and three carbonyl carbons at δ 173.7, 174.2 and 175.0. COSY and RCT spectra allowed the identification of the partial structures—CH_2–CH_2–CH_2–C–CH_3, CH–CH_2–CH=C(CH_3)–CH–CH_2–O and O–CH–CH–CH_2–. The structure of **1** was finally established by the detailed analysis of the COLOC spectrum. This experiment exhibited strong correlations between the methyl at δ 0.89 with the carbon at δ 33.6, the methyl at δ 0.86 with the carbons at δ 50.6, 42.8 and 22.2, and the methyl at δ 0.81 with the carbons at δ 55.4, 40.0 and 36.3, respectively. These correlations established a drimenol substructure as part of compound **1**. The above 2D experiments thus permitted the identification of an isocitrate subunit, which was connected to the drimenol portion via an ether linkage between C-11 and C-1′. All the spectroscopic data of the sesquiterpene were in accordance with those of drimenol (De Bernardi et al., 1980) supporting the relative stereochemistry of the sesquiterpenoid portion of the molecule.

In order to determine the absolute configuration of the molecule, a permethylated ester derivative **1a** was prepared and compared by ^1H NMR spectral analysis to the four diastereomeric cryptoporic acids recently synthesised (Tori et al., 2000). Compound **1a** had ^1H NMR signals corresponding to H-1′, H-2′ and 2H-3′ at δ 4.07, 3.45, 2.82 and 2.57 respectively, suggesting the absolute stereochemistry of either 1′*S*2′*R* or 1′*R*2′*S*. On the basis of the optical rotations of compound **1**, drimenol and isocitric acid, and by comparison with cryptoporic acid H (Hirotani et al., 1991), the 1′*R*2′*S* stereochemistry was deduced for compound **1**. From these data the structure of **1**, named isocrytoporic acid H, was established as 3-carboxy-2-(2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-1-ylmethoxy)-pentanedioic acid. [The name isocryptoporic is proposed based on the isomeric relationship between compound **1** and cryptoporic acid H where a drimenol instead of an albicanol moiety is present in the molecule.]

Compound **2**, $C_{21}H_{32}O_8$ by HRFABMS, had, as evidenced by ^1H and ^{13}C NMR spectral analyses, a similar pattern to compound **1**, i.e. a double bond proton resonance at δ 5.44, the characteristic signals of the isocitric moiety at δ 4.08 (*d*, 4.6 Hz), 3.33 (*m*), 2.74 (*dd*, 17.0 and 9.8 Hz) and 2.54 (*dd*, 17.0 and 4.8 Hz), a vinyl methyl at δ 1.73, as well as a new signal at 3.18 (*dd*, 11.2 and 4.8 Hz). The ^{13}C NMR spectrum exhibited also an additional methine carbon at δ 79.7 indicating the presence of a hydroxyl group in the molecule. Again the COSY spectrum allowed us to obtain partial structures which were connected by correlations observed in the COLOC experiment, identifying 3-hydroxydrimenol as the sesquiterpene portion of the molecule. COLOC and NOESY spectra showed correlations of H-11 protons with C-1′ and H-1′ respectively. Fig. 1 shows the most structurally relevant correlations observed. The absolute stereochemistry of **2** was assumed to be the same than compound **1**. For the above mentioned reasons, the structure of **2** was established as 3-carboxy-2-(6-hydroxy-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-1-ylmethoxy)-pentanedioic acid. Compound **2**

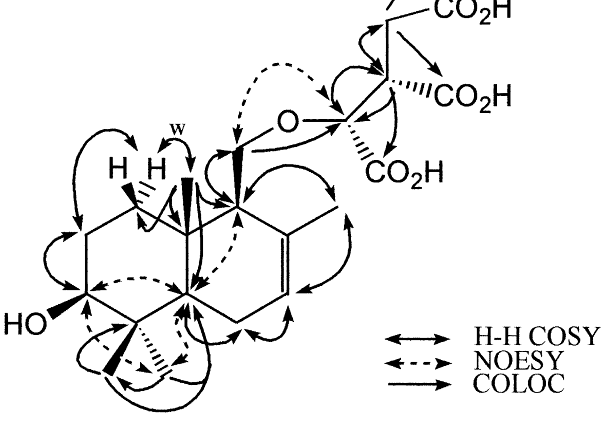


Fig. 1. 2D NMR important correlations observed for compound **2**.

was named isocryptoporic acid I by analogy with cryptoporic acid I.

Compound **3**, $C_6H_6O_4$ by HREIMS, had a simple ^1H NMR spectrum with just three signals at δ 7.94 (1H), 6.49 (1H) and 4.40 (2H), whereas ^{13}C NMR spectrum showed six carbon resonances, one carbonyl at δ 176.9, four aromatic carbons and a methylene group attached to oxygen. The chemical shifts were consistent with the presence of a furan ring bearing carboxyl and hydroxymethyl substituents. The small coupling (0.5 Hz) between the hydroxymethyl protons and the furan proton at 6.49 ppm suggested that they were on adjacent carbons. The furan protons lacked further coupling and were clearly not vicinal. To confirm this assumption compound **3** was methylated to yield **3a** and a NOESY experiment was carried out. A correlation between the *O*-methyl group and the signal at δ 7.55 confirmed the proposed structure for compound **3** as 5-hydroxymethylfuran-3-carboxylic acid. This compound has not been previously isolated as a natural product, but has been reported as a synthetic intermediate (Pevzner et al., 1999; Ionin, B.I., personal communication).

The ^1H and ^{13}C NMR spectra of compound **5** resembled that of cryptoporic acid H (Hirotani et al., 1991) except for the appearance of a methyl ester group (^1H: δ 3.64 s, ^{13}C: δ 52.5) and the upfield shift of one of the carbonyl groups in the ^{13}C NMR spectrum. The upfield shifted carbonyl seemed to be 5′ by comparison of the ^{13}C NMR spectra of **5** and crytoporic H. COSY, TOCSY and ROESY spectra confirmed the proposed structure and the HMBC spectrum allowed us to determine the position of the additional methyl group. Fig. 2 shows the important correlations in the isocitric moiety observed in the HMBC experiment. These data and the similar optical rotation of compound **5** and cryptoporic acid H allowed us to establish the structure as 2″-*O*-methyl cryptoporic acid H.

Compound **4** was identified as cryptoporic acid H by comparison of spectroscopic data (^1H and ^{13}C NMR spectra, FABMS) and optical rotation (Hirotani et al., 1991).

The extracts of *P. philippinensis*, *P. guianensis* and *P. tenuiculus* were analyzed by TLC and ^1H NMR and compared with the isolated compounds. In all cases compounds **1**–**5** were absent, even at trace levels. Remarkably, the above mentioned strains showed very poor productivity of secondary metabolites. In conclusion, only two of the studied strains produce drimane derivatives, *P. arcularius* and *P. ciliatus*. It is noteworthy that these strains belong to the same phenotypic group in phenograms based on morphological data, while the others belong to different groups (Borges da Silva, 2001). None of the isolated compounds exhibited antibiotic or antifungal activity in vitro.

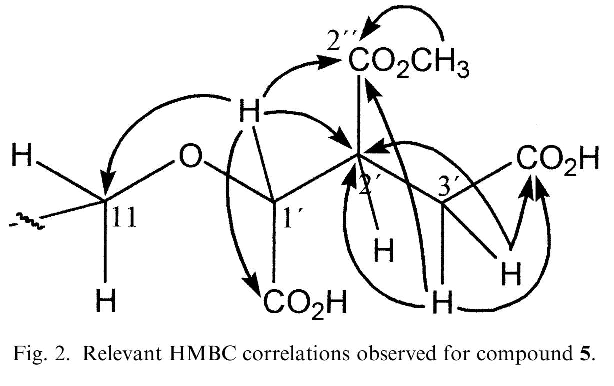


Fig. 2. Relevant HMBC correlations observed for compound **5**.

Drimane sesquiterpenoids have been isolated from the basidiomycetes *P. arcularius* (Fleck at al., 1996) and *Lactarius uvidus* (De Bernardi et al., 1980; Garlaschelli et al., 1994), *Roseoformes subflexibilis* (Nozoe et al., 1993), *Haploporus odorus* (Morita et al., 1995) and *Cryptoporus volvatus* (Hashimoto et al., 1987, 1989; Hirotani et al., 1991; Asakawa et al., 1992). However, in all the above cases the sesquiterpenoid portion of the drimane-isocitric ethers is albicanol (Hirotani et al., 1991; Asakawa et al., 1992; Nozoe et al., 1993; Morita et al., 1995). This is the first report on the isolation of drimenol derivatives of this class, for which the name isocryptoporic acid is given.

3. Experimental

3.1. General

FTIR spectra were recorded on a Nicolet Magna-IR 550. The UV spectra were recorded on a Hewlett Packard 8451 A diode array spectrophotometer, whereas optical rotations employed a Perkin Elmer polarimeter 343. NMR spectra were acquired on a Bruker AM-500 instrument at 500.13 MHz for ^1H and at 125.13 MHz for ^{13}C NMR, respectively. The NMR spectra of compound **5**, however, were determined at the Instituto Nacional de Tecnología Industrial (INTI, Bs As, Argentina) using a Bruker Advance DPX 400 instrument. FAB-MS were obtained on a ZAB-SEQ (BEqQ) instrument (VG Analytical, Manchester, UK), whereas HR–FABMS were recorded at the Washington University Resource for Biomedical and Bio-organic Mass Spectrometry.

3.2. Fermentation

P. arcularius Batsch. ex Fr. (Cult. BAFC 109), *P. philippinensis* (Cult. BAFC 368), *P. ciliatus* (Cult. BAFC 2308), *P. guianensis* (Cult. BAFC 2793), *P. tennuiculus* (Cult. BAFC 162) were supplied by one of us [Dr. J.E. Wright] from the BAFC Culture Collection (FCEN-UBA, CONICET). An agar slant of each fungus was used to inoculate two 250 ml Erlenmeyer flasks containing 75 ml of malt extract medium composed of malt extract 30 g and peptone 5 g per liter. Fermentation was carried out at 25 °C for 15 days under static conditions. *P. arcularius* and *P. ciliatus* were further cultivated seeding 2×4 l and 1×4 l Erlenmeyer flasks respectively containing 1 l of culture media with the above one week precultured media. Final pH was 4.4 (*P. arcularius*) and 5.0 (*P. ciliatus*).

3.3. Extraction and isolation

Fermentation broths of *P. arcularius* and *P. ciliatus* were filtered and the filtrates were partitioned with EtOAc. The extracts were subjected to HPLC (C_{18}, 25×2 cm, MeOH–H_2O 8:2, 6 ml/min, UV 215 nm, RI) yielding compounds **1** (51 mg) and **2** (37 mg) from *P. arcularius* and **3**, **4** (2.5 mg) and **5** (2.9 mg) from *P. ciliatus*. Compound **2** was purified by the same technique (C_{18}, MeOH–H_2O 7:3, 6 ml/min, UV 215 nm) and compound **3** was purified by prep. TLC on silica gel using EtOAc as elution solvent (Rf 0.5) (17 mg). Compounds **1a** and **3a** were prepared by treatment of the corresponding compounds **1** and **3** with CH_2N_2 in Et_2O.

3.4. Antibiotic assay

Antibiotic activity was determined by the agar diffusion method using 100 μg of sample/disk against *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 25923 and *Escherichia coli* ATCC 25922*, Candida albicans* ATCC 18804 and *Cladosporium cucumerinum* as test organisms. All compounds were inactive.

3.5. Compound *1*

Oil. $\alpha_D = +24°$ (MeOH; *c* 0.41). HRFAB$^+$MS (glycerol Na), *m*/*z* [M+2Na-H]$^+$, found 441.1854, calc. for $C_{21}H_{31}O_7Na_2$ 441.1866. FAB$^+$MS (glycerol) *m*/*z* (rel. int.): 419 [M+Na]$^+$ (30), 205 (35). UV (MeOH) λ_{max} nm (log ε) 242 (3.17), 204 (3.48). FTIR (KBr) ν_{max} cm^{-1}: 3422 (OH), 3223 (OH), 2924 (CH), 1737 (CO), 1720 (CO). ^{1}H and ^{13}C NMR: Tables 1 and 2. *Compound **1a***. ^{1}H NMR ($CDCl_3$): 5.45 (*br s*, H-7), 4.07 (*d*, 4.9 Hz, H-1′), 3.80 (*dd*, 9.6 and 6.0 Hz, H-11a), 3.75 (*s*, OCH_3), 3.69 (*s*, OCH_3), 3.68 (*s*, OCH_3), 3.45 (*dt*, 9.4 and 4.9 Hz, H-2′), 3.41 (*dd*, 9.6 and 2.7 Hz, H-11b), 2.82 (*dd*, 17.1 and 9.4 Hz, H-3′a), 2.57 (*dd*, 17.1 and 4.9 Hz, H-3′b), 1.71 (*s*, H-12), 0.88 (*s*, H-14), 0.85 (*s*, H-15), 0.80 (*s*, H-13).

3.6. Compound *2*

Oil. $\alpha_D = +17°$ (MeOH; *c* 0.39). HRFAB$^+$MS (glycerol Na), *m*/*z* [M+2Na-H]$^+$, found 457.1808, calc. for $C_{21}H_{31}O_8Na_2$ 457.1815. FAB$^+$MS (glycerol) *m*/*z* (rel. int.): 435 [M+Na]$^+$ (45), 223 (85), 207 (100). UV (MeOH) λ_{max} nm (log ε) 244 (3.34), 206 (3.37). FTIR (KBr) ν_{max} cm^{-1}: 3451 (OH), 3210 (OH), 2945 (CH), 1740 br (CO), 1719 (CO). For ^{1}H and ^{13}C NMR spectra, see Tables 1 and 2.

Table 1
^{13}C NMR spectroscopic data for compounds **1** ($CDCl_3$–CD_3OD 20%) and **2**, **4** and **5** (CD_3OD)

C	**1**	**2**	**4**	**5**
1	40.0	38.9	40.4	40.4
2	19.3	28.1	20.3	20.3
3	42.8	79.7	43.2	43.2
4	33.4	39.8	34.4	34.4
5	50.6	51.0	56.5	56.5
6	24.2	24.4	25.1	25.1
7	123.2	123.6	38.7	38.7
8	134.3	134.7	148.4	148.4
9	55.4	56.2	56.9	56.9
10	36.3	36.8	39.8	39.8
11	70.3	70.5	69.1	69.1
12	22.1	22.1	108.6	108.5
13	14.8	15.0	15.8	15.8
14	22.2	15.9	22.2	22.2
15	33.6	28.7	34.1	34.1
1′	79.6	80.2	79.7	79.7
2′	45.2	45.8	45.7	45.8
3′	32.8	33.2	33.0	33.1
4′	173.7	173.9	174.2	174.0
5′	174.2	174.4	174.5	173.3
6′	175.0	175.4	175.5	175.2
O*C*H_3				52.5

Table 2
^{1}H NMR spectroscopic data for compounds **1**, **2** and **5** (CD_3OD)

H		**1**	**2**		**5**
1	α	1.10 *m*	1.23 *dt* (4.6,13.3)		1.18 *m*
	β	1.98 *m*	2.02 *dt* (13.3, 3.4)		1.72 *m*
2	α	1.46 *m*	1.58–1.66 *m*		1.48 *dqn* (13.8, 3.6)
	β	1.55 *m*			1.60 *tq* (3.3, 13.8)
3	α	1.20 *m*	3.18 *dd* (11.2, 4.8)		1.22 *m*
	β	1.42 *m*			1.40 *br d* (13.2)
5		1.20 *m*	1.19 *dd* (10.3, 6.2)		1.16 *dd* (12.9, 2.4)
6		1.87–1.97 *m*	1.90–2.05 *m*	α	1.72 *m*
				β	1.34 *dq* (4.4, 12.9)
7		5.45 *bs*	5.44 *bs*	α	2.05 *dt* (4.8, 13.0)
				β	2.38 *ddd* (13.0, 4.4, 2.4)
9		1.95 *m*	1.91 *m*		1.96 *br d* (8.1)
11		3.50 *dd* (10.0, 2.8)	3.49 *dd* (9.8, 3.0)		3.55 *dd* (10.0, 3.9)
		3.80 *dd* (10.0, 6.4)	3.82 *dd* (9.8, 6.0)		3.91 *dd* (10.0, 8.1)
12		1.74 *bs*	1.73 *bs*	a	4.76 *d* (1.5)
				b	4.82 *d* (1.5)
13		0.81 *s*	0.84 *s*		0.75 *s*
14		0.89 *s*	0.84 *s*		0.83 *s*
15		0.86 *s*	0.95 *s*		0.88 *s*
1′		4.11 *d* (4.7)	4.08 *d* (4.6)		4.07 d (4.8)
2′		3.39 *bdd* (13.9, 4.7)	3.33 *m*		3.32 *m*
3′		2.58 *dd* (17.1, 4.7)	2.54 *dd* (17.0, 4.8)		2.54 *dd* (17.1, 4.9)
		2.80 *dd* (17.1, 9.6)	2.74 *dd* (17.0, 9.8)		2.72 *dd* (17.1, 9.6)
OC*H*$_3$					3.64 *s*

3.7. Compound *3*

Colorless needles (MeOH). Pf. 153–154 °C. HREIMS M$^{+\bullet}$ *m*/*z*, found 142.0273, calc. for $C_6H_6O_4$ 142.0266. EI MS (70 eV): 142 (M$^{+\bullet}$, 100), 113 (79), 97 (18), 85 (38), 69 (95). UV (MeOH) λ_{max} nm (log ε): 269 (3.78), 217 (3.98). FTIR (KBr) ν_{max} cm^{-1}: 3401 (OH), 2923 (CH), 2859 (CH), 1656 (CO), 1639 (CO), 1610 (CO), 870. ^{1}H NMR (CD_3OD): 7.94 (*s*, H-2), 6.49 (*br t*, 0.5 Hz, H-4), 4.40 (*br d*, 0.5 Hz, H-7). ^{13}C NMR (CD_3OD): 176.9 (C-6), 170.4 (C-5), 147.4 (C-3), 141.0 (C-2), 110.8 (C-4), 61.2 (C-7). Compound **3a**. ^{1}H NMR ($CDCl_3$): 7.55 (*s*, H-2), 6.52 (*br t*, 0.6 Hz, H-4), 4.48 (*br d*, 0.6 Hz, H-7), 3.76 (*s*, OCH_3).

3.8. *Compound* **5**

Oil. $\alpha_D = +32°$ (CH_3OH; *c* 0.23). HRFAB–MS (glycerol), *m*/*z* [M–H]$^-$, found 409.2234, calc. for $C_{22}H_{33}O_7$ 409.2226. FAB–MS (glycerol) *m*/*z* (rel. int.): 409 [M–H]$^-$ (100). UV (MeOH) λ_{max} nm (log ε): 202 (3.89), 228 *sh* (3.33). FTIR (KBr) ν_{max} cm^{-1} 3429 (OH), 3202 (OH), 2931 (CH), 1740 *br* (CO). For ^{1}H and ^{13}C NMR spectra, see Tables 1 and 2.

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