New Cembranoids from the Hainan Soft Coral *Sarcophyton glaucum*

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From the soft bodied coral *Sarcophyton glaucum* collected from the South China Sea two new cembranoids, (7*R*,8*S*)-dihydroxydeepoxy-*ent*-sarcophine (**1**) and secosarcophinolide (**2**), together with one known related compound, *ent*-sarcophine (**3**), were isolated. The structures of the new compounds were determined by extensive analysis of their spectroscopic data and chemical correlation. The absolute configuration of **1** was determined by chemical correlation with **3** and by comparison of its optical rotation value with that of its corresponding enantiomer, (7*S*,8*R*)-dihydroxydeepoxysarcophine (**5**).

Introduction. – Soft corals are marine invertebrates possessing a vast range of terpenoid metabolites. These terpenoids, mainly cembranoids, represent the animal's main chemical defence tools against their natural predators [1][2]. In addition, cembranoids also exhibit a wide range of biological activities including neuroprotective, antimicrobial, and antitumor properties [3][4]. The soft corals of the genus *Sarcophyton* (family Alcyoniidae) are one of the most abundant coral reef animals with high cembranoid content. Recently, several species of *Sarcophyton* collected off the Sanya coast, Hainan Province, P. R. China, were chemically investigated, and a series of novel cembranoids and biscembranoids were isolated and structurally characterized by our group [5–8]. In our continuing search for biologically active and structurally unique compounds from Hainan marine organisms [9–12], we have collected *Sarcophyton glaucum* QUOY & GAIMARD and chemically investigated it. *S. glaucum* is frequently encountered in the South China Sea. In the course of this study, two new cembranoids, (7*R*,8*S*)-dihydroxydeepoxy-*ent*-sarcophine (**1**)[2]) and secosarcophinolide (**2**), along with a known one, *ent*-sarcophine (**3**) [13], were isolated from the Et_2O-soluble portion of the Me_2CO extract of the animal. Interestingly, like the situation between **3** and sarcophine (**4**) [14–16], the new compound **1** is the enantiomer of (7*S*,8*R*)-dihydroxydeepoxysarcophine (**5**)[2]) that was previously isolated from the Taiwan soft coral *S. trocheliophorum* [17] and also obtained from the acid-catalyzed transannular reaction of sarcophine (**4**) [16]. The new cembranoid **2** containing a rare butyl ester group at C(16) was discovered for the first time in nature. In the present article, we describe the isolation and structural elucidation of the new compounds **1** and **2**.

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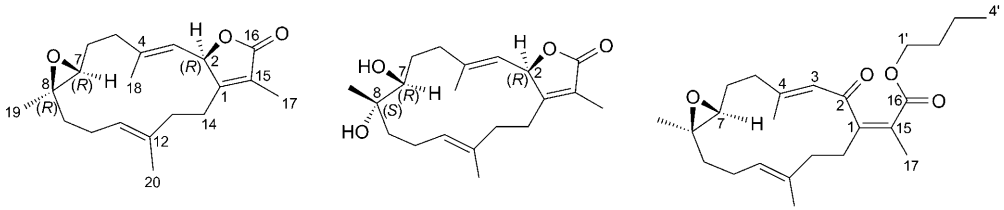
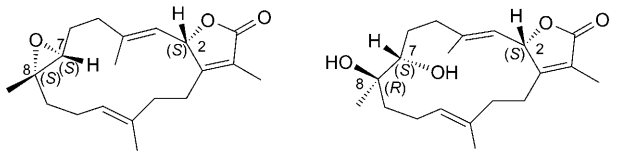
[1]) The authors contributed equally to this work.
[2]) Arbitrary numbering. For systematic names, see *Exper. Part*.



3[2]) **1**[2]) **2**[2])



4[2]) **5**[2])

Results and Discussion. – Freshly collected specimens of *S. glaucum* were immediately put at $-20°$, and kept frozen prior to extraction. The Et_2O-soluble portion from Me_2CO extract was repeatedly chromatographed over silica gel, *Sephadex LH-20* gel, and RP-HPLC to afford three cembranoids, *ent*-sarcophine (**3**), (7*R*,8*S*)-dihydroxydeepoxy-*ent*-sarcophine (**1**)[2]) and secosarcophinolide (**2**). The structure of the known compound **3** was determined as *ent*-sarcophine by extensive analysis of its 2D-NMR spectra and by careful comparison of its spectroscopic data with those reported in the literature [13–16]. X-Ray diffraction analysis (*Fig. 1*) on a single crystal of **3** unambiguously confirmed this conclusion. It may be worth to point out that no X-ray structure of *ent*-sarcophine has been previously reported. The absolute configuration of **3** was established by comparison of the optical rotation and CD data with those of previously isolated and identified *ent*-sarcophine and sarcophine (**4**). In fact,

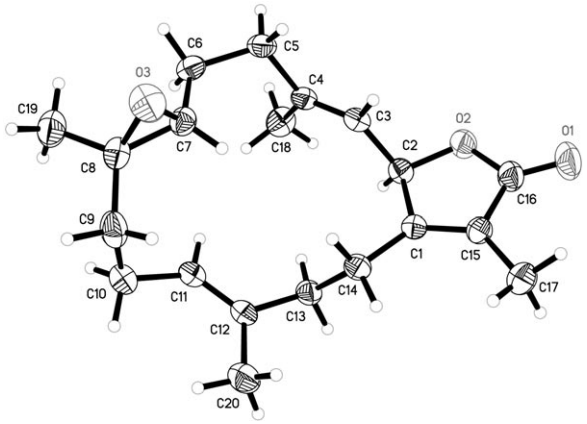


Fig. 1. *Perspective drawing of the X-ray structure of compound* **3**

the sign of the $[\alpha]_D^{25}$ value of **3** ($[\alpha]_D^{25} = -80.0$ ($c = 0.35$, $CHCl_3$)) is the same as the one of the published data of *ent*-sarcophine ($[\alpha]_D^{25} = -161.5$ ($c = 0.11$, $CHCl_3$)) [13], and opposite to the one of sarcophine ($[\alpha]_D^{25} = +92.0$ ($c = 1.0$, $CHCl_3$)) [14–16].

Compound **1**, (7*R*,8*S*)-dihydroxyepoxy-*ent*-sarcophine[2]), a colorless oil, had the molecular formula $C_{20}H_{30}O_4$ according to the HR-ESI-MS (positive ion-mode) ($[M + Na]^+$ at *m/z* 357.2037; calc. 357.2042), 18 mass units more than that of co-occurring *ent*-sarcophine (**3**). Careful comparison of the ^{1}H- and ^{13}C-NMR data of **1** and **3** revealed that they only differ from each other by a trisubstituted epoxy functionality in **3** *vs.* the presence of two OH groups (δ(H) 3.49 (*d*, $J = 11.4$, H–C(7); δ(C) 72.8, C(7), 75.4, C(8))[2]) in **1**. Detailed analysis of ^{1}H,^{1}H-COSY, HMQC, and HMBC spectra allowed the unambiguous assignment of the structure of **1** as an 7,8-epoxy ring-opened derivative of **3**.

A literature survey revealed that the ^{1}H- and ^{13}C-NMR data of **1** (*Table*) were identical to those of (7*S*,8*R*)-dihydroxydeepoxysarcophine (**5**)[2]) [16][17]. In fact, the only difference between **1** and **5** is the optical rotation sign ($[\alpha]_D^{25} = -118.7$ ($c = 0.38$, $CHCl_3$) for **1**, and $[\alpha]_D^{25} = +104.6$ ($c = 0.26$, $CHCl_3$) for **5**), indicating that they are enantiomers. Moreover, the CD spectra for **1** and *ent*-sarcophine (**3**) are nearly congruent (*Fig. 2*) suggesting the same (*R*)-configuration of the γ-C-atom of butenolide ring at C(2) [18][19]. Consequently, (*R*)- and (*S*)-configurations could be respectively assigned for C(7) and C(8). *Czarkie et al.* had reported a conversion of sarcophine (**4**) to (7*S*,8*R*)-dihydroxydeepoxysarcophine (**5**) by treating **4** with diluted H_2SO_4 [16]. To confirm the assigned absolute configurations for C(7) and C(8) of **1**, the chemical reaction to convert *ent*-sarcophine (**3**) to **1** was carried out. Refluxing **3** in 2% H_2SO_4/Me_2CO for 30 min at 60° afforded the expected epoxy ring opened product **1**, which was identical in all aspects to the model compound **5**, except for sign of the $[\alpha]_D$ value.

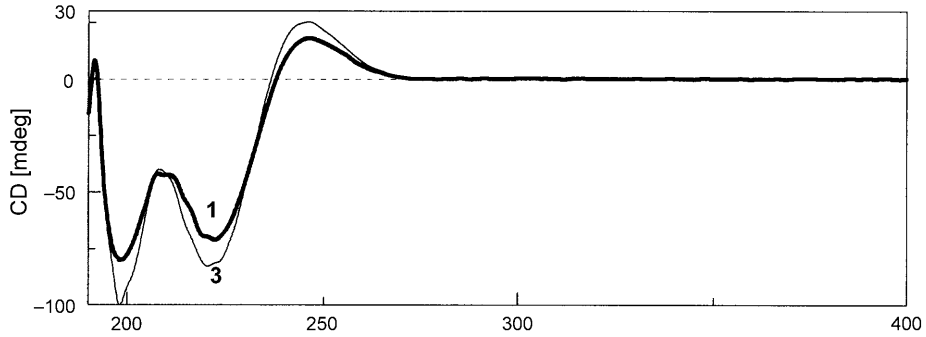


Fig. 2. *CD Curves of compounds* **3** *and* **1**

Secosarcophinolide (**2**) was isolated as an optically inactive colorless oil. The HR-ESI-MS revealed a *quasi*-molecular-ion peak at *m/z* 411.2501 ($[M + Na]^+$; calc. 411.2511), consistent with a molecular formula of $C_{24}H_{36}O_4$. The strong IR bands at 1714, 1672, and 1614 cm^{-1} indicated the presence of two conjugated CO groups in the molecule, which was supported by the observation of a strong UV absorption at 252 nm ($\log\varepsilon$ 3.62). The identical cembrane skeleton of **2** compared to **3** and **1** was immediately

Table. *^{1}H- and ^{13}C-NMR Data for* **2** *and* **1** *and ^{13}C-NMR Data for* **3**[a])[2]). In $CDCl_3$; δ in ppm, J in Hz.

	2		**1**		**3**
	δ(H)	δ(C)[b])	δ(H)	δ(C)[b])	δ(C)[b])
C(1)	–	151.0 (*s*)	–	162.7 (*s*)	162.1 (*s*)
C(2) or H–C(2)	–	196.7 (*s*)	5.58 (*dq*, *J* = 10.3, 1.3)	79.1 (*s*)	78.7 (*d*)
H–C(3)	5.92 (*s*)	123.8 (*d*)	4.95 (*d*, *J* = 10.3)	120.9 (*d*)	120.6 (*d*)
C(4)	–	155.8 (*s*)	–	143.9 (*s*)	144.0 (*s*)
H_a–C(5)	2.35–2.37 (*m*)	37.6 (*t*)	2.44 (*ddd*, *J*= 12.8, 12.4, 3.3)	35.5 (*t*)	37.4 (*t*)
H_b–C(5)	2.34–2.36 (*m*)		2.13–2.15 (*m*)		
H_a–C(6)	1.94–1.96 (*m*)	24.9 (*t*)	1.83–1.85 (*m*)	26.7 (*t*)	25.2 (*t*)
H_b–C(6)	1.67–1.69 (*m*)		1.54–1.56 (*m*)		
H–C(7)	2.71 (*dd*, *J* = 7.0, 3.6)	62.0 (*d*)	3.49 (*d*, *J* = 11.4)	72.8 (*d*)	61.4 (*d*)
C(8)	–	60.5 (*s*)	–	75.4 (*s*)	59.9 (*s*)
H_a–C(9)	1.97–1.99 (*m*)	37.2 (*t*)	1.80–1.82 (*m*)	37.1 (*t*)	39.0 (*t*)
H_b–C(9)	1.41–1.43 (*m*)		1.72–1.74 (*m*)		
H_a–C(10)	2.09–2.11 (*m*)	22.7 (*t*)	2.20–2.22 (*m*)	22.7 (*t*)	23.3 (*t*)
H_b–C(10)	1.99–2.01 (*m*)		2.17–2.19 (*m*)		
H–C(11)	4.98 (*dd*, *J* = 5.7, 5.6)	125.9 (*d*)	4.99 (*dd*, *J* = 9.4, 3.5)	125.2 (*d*)	124.9 (*d*)
C(12)	–	134.3 (*s*)	–	134.8 (*s*)	135.5 (*s*)
H_a–C(13)	2.13–2.15 (*m*)	36.6 (*t*)	2.05–2.07 (*m*)	36.5 (*t*)	36.3 (*t*)
H_b–C(13)	2.12–2.14 (*m*)		1.99–2.01 (*m*)		
H_a–C(14)	2.64–2.66 (*m*)	29.3 (*t*)	2.71–2.73 (*m*)	26.8 (*t*)	27.5 (*t*)
H_b–C(14)	2.54–2.56 (*m*)		2.10–2.12 (*m*)		
C(15)	–	127.8 (*s*)	–	122.8 (*s*)	122.9 (*s*)
C(16)	–	168.8 (*s*)	–	175.6 (*s*)	174.7 (*s*)
Me(17)	1.94 (*s*)	15.1 (*q*)	1.80 (br. *s*)	8.9 (*q*)	9.0 (*q*)
Me(18)	2.21 (*s*)	19.6 (*q*)	1.90 (*s*)	16.5 (*q*)	16.1 (*q*)
Me(19)	1.27 (*s*)	17.4 (*q*)	1.18 (*s*)	24.2 (*q*)	17.1 (*q*)
Me(20)	1.55 (*s*)	15.5 (*q*)	1.68 (*s*)	15.4 (*q*)	15.4 (*q*)
H_a–C(1′)	4.08–4.10 (*m*)	65.1 (*t*)	–	–	–
H_b–C(1′)	3.98–4.00 (*m*)		–	–	–
CH_2(2′)	1.54–1.56 (*m*)	30.3 (*t*)	–	–	–
CH_2(3′)	1.33–1.35 (*m*)	19.1 (*t*)	–	–	–
Me–C(4′)	0.89 (*t*, *J* = 7.3)	13.7 (*q*)	–	–	–

[a]) Assignments made by DEPT, ^{1}H,^{1}H-COSY, HMQC, and HMBC experiments. [b]) Multiplicities from DEPT sequence.

inferred from the 2D-NMR data, mainly ^{1}H,^{1}H-COSY, HMQC, and HMBC measurements (*Fig. 3*). In fact, the NMR data of **2** were strongly reminiscent of those of *ent*-sarcophine (**3**). Careful comparison of the ^{13}C-NMR data (*Table*) of **2** and **3** revealed clear evidences for the presence of one trisubstituted epoxy ring (δ(C) 62.0, C(7), 60.5, C(8))[2]), and two trisubstituted C=C bonds (δ(C) 123.8, C(3), and 155.8, C(4); δ(C) 125.9, C(11), and 134.3, C(12)), in analogy to **3**. The most significant difference observed in the ^{13}C-NMR spectrum of **2** is that the characteristic ^{13}C-NMR signal due to the γ-C-atom (δ(C) 78.7, C(2)) of the butenolide ring of **3** was absent, and meanwhile, a downfield signal resonating at δ(C) (196.7, C(2)) and four C-atom signals attributable to a Bu group (δ(C) 65.1 C(1′), 30.3 C(2′), 19.1 C(3′), 13.7 C(4′)) was observed in the spectrum of **2**. In addition, the ^{13}C-NMR chemical shifts of C(3), C(4),

C(15), and C(17) were significantly shifted downfield, while those of C(1) and C(16) were shifted upfield, with respect to those of **3**. These differences could only be rationalized by the oxidative cleavage/opening of the butenolide ring in **3** and a subsequent formation of a Bu ester at C(16) as shown in the formula of **2**. A series of distinct HMBC correlations between $CH_2(1')$ (δ(H) 3.98–4.00, *m*; 4.08–4.10, *m*) and C(16) (δ(C) 168.8); between Me(18) (δ(H) 2.21, *s*) and C(2) (δ(C) 196.7), C(3) (δ(C) 123.8), C(4) (δ(C) 155.8), and C(5) (δ(C) 37.6); between $CH_2(14)$ (δ(H) 2.54–2.56, *m*; 2.64–2.66, *m*) and C(1) (δ(C) 151.0), C(2) (δ(C) 196.7), and C(15) (δ(C) 127.8); and between Me(17) (δ(H) 1.94, *s*) and C(1) (δ(C) 151.0), C(2) (δ(C) 196.7), C(15) (δ(C) 127.8), and C(16) (δ(C) 168.8) (*Fig. 3*) led to unambiguously assign the structure of **2**. The $[\alpha]_D$ value of **2** ($[\alpha]_D^{25} = 0$ ($c = 0.05$, $CHCl_3$)) suggested that **2** is a racemate. It should be pointed out that BuOH was not used during the isolation process. This fact allowed us to rule out the possibility that **2** is an artifact. To the best of our knowledge, this is the first report of a cembranoid possessing a butyl ester group in the molecule.

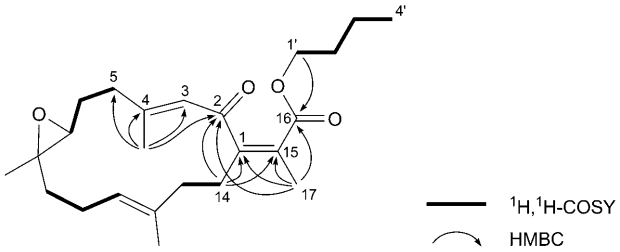


Fig. 3. *Selected 2D-NMR correlations of compound* **2**

Sarcophine (**4**) is a well known compound that is widely present in the soft corals of the genus *Sarcophyton*. Its cancer chemopreventive properties have been extensively investigated [20–23]. The promising antitumor activities of **4** stimulate our interests to test if (7*R*,8*S*)-dihydroxydeepoxy-*ent*-sarcophine (**1**)[2]) and *ent*-sarcophine (**3**) are also cytotoxic. However, compounds **1**–**3** were inactive at concentrations up to 20 μg/ml against the growth of several tumor cell lines, including murine lymphocytic leukaemia (P388), human promyelocytic leukemia (HL-60), and human lung adenocarcinoma (A549).

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Experimental Part

General. Column chromatography (CC): commercial silica gel (SiO_2; *Qing Dao Hai Yang Chemical Group Co.*, 200–300 and 400–600 mesh) or *Sephadex LH-20* (*Amersham Biosciences*). TLC: precoated silica gel plates (*Yan Tai Zi Fu Chemical Group Co.*, *G60*, *F-254*). Reversed-phase HPLC: *Agilent 1100* series liquid chromatograph using a *VWD G1314A* detector at 210 nm, and a semi-prep. *ZORBAX ODS* (5 μm, 9.4 × 250 mm) column (*Agilent*) was employed for the purification. M.p.: *X-4* digital micro-melting point apparatus; uncorrected. Optical rotation: *Perkin-Elmer polarimeter 341* at the Na D-line, cell length 100 mm. CD Spectra: *Jasco J-810* spectropolarimeter; λ_{extr} ($\Delta\varepsilon$) in nm. UV Spectra: *756 CRT*

spectrophotometer (Shanghai, China); λ_{max} (log ε) in nm. IR Spectra: *Nicolet-Magna FT-IR 750* spectrometer, ν_{max} in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker DRX-400* (400 MHz for ^1H and 100 MHz for ^{13}C); chemical shift δ in ppm, with the solvent signal in $CDCl_3$ (δ(H) 7.26, δ(C) 77.0) as an internal standard, coupling constant J in Hz; assignments supported by ^1H,^1H-COSY, HSQC, HMBC, and ROESY experiments. ESI-MS and HR-ESI-MS: *Q-TOF Micro* (*Waters*) LC-MS/MS mass spectrometer, in m/z.

Animal Material. The soft coral *S. glaucum* was collected off the coast of Lingshui Bay, Hainan Province, P. R. China, in December 2004, at a depth of -20 m and identified by Prof. *R.-L. Zhou* of South China Sea Institute of Oceanology, Chinese Academy of Sciences. A voucher specimen (LS-181) is available for inspection at Shanghai Institute of Materia Medica, CAS.

Extraction and Isolation. The frozen animals (550 g dried weight) were cut into pieces and extracted exhaustively with acetone at r.t. (3×1.5 l). The org. extract was evaporated to give a residue (10.5 g), which was partitioned between Et_2O (3×300 ml) and H_2O (300 ml). The Et_2O soln. was concentrated under reduced pressure to give a dark green residue (3.1 g), which was fractionated by gradient SiO_2 CC (0–100% acetone in petroleum ether (PE)), yielding 10 fractions. *Frs. 6–8* showed interesting red TLC spots after spraying with H_2SO_4. *Fr. 6* was firstly subjected to a SiO_2 CC (400–600 mesh, PE/Et_2O 85:15), and then RP-HPLC (MeOH/H_2O (75:25), 2.0 ml/min) to give compound **2** (5.4 mg; t_R 15.4 min). *Fr. 7* gave compound **3** (92.5 mg) after CC on SiO_2 (400–600 mesh, PE/Et_2O 85:15). *Fr. 8* was purified by SiO_2 CC (400–600 mesh, PE/acetone 90:10), followed by CC on *Sephadex LH-20* ($CHCl_3$) to yield compound **1** (12.1 mg).

ent-*Sarcophine* (= *(1a*R,*4*E,*10a*R,*11*E,*14a*R*)-2,3,6,7,10a,13,14,14a-Octahydro-1a,5,8,12-tetramethyloxireno[9,10]cyclotetradeca[1,2-*b*]furan-9(1a*H*)-one*; **3**). Colorless crystals (PE/Et_2O). M.p. 132–133°. $[\alpha]_D^{25} = -80.0$ ($c = 0.35$, $CHCl_3$). CD ($c = 4.87 \times 10^{-3}$, MeOH): 246 (+25.25), 221 (−82.74), 208 (−40.22), 198 (−99.98). ^{13}C-NMR: *Table.*

Conversion of **3** *into* **1**. Compound **3** (13.9 mg) was stirred for 30 min in a soln. of Me_2CO (5 ml) and aq. 2% H_2SO_4 (1 ml) at 60°. The reaction progress was monitored by TLC analysis on SiO_2, eluted with PE/acetone (7:3; R_f 0.85, **3**; R_f 0.55, **1**). The mixture was concentrated under reduced pressure to afford a yellow oil (14.5 mg), which was subjected to SiO_2 CC using increasing amounts of acetone in PE (95:5 to 90:10) to yield the major product **1** (8.3 mg).

*(7*R,*8*S*)-Dihydroxydeepoxy*-ent-*sarcophine* (= *(6*E,*10*S,*11*R,*14*E,*15a*R*)-5,8,9,10,11,12,13,15a-Octahydro-10,11-dihydroxy-3,6,10,14-tetramethylcyclotetradeca[*b*]furan-2(4*H*)-one*; **1**). Colorless oil. $[\alpha]_D^{25} = -118.7$ ($c = 0.38$, $CHCl_3$). CD ($c = 3.14 \times 10^{-3}$, MeOH): 246 (+18.09), 222 (−71.07), 208 (−42.00), 198 (−80.03). UV (MeOH): 247 (2.88), 275 (2.68). IR (KBr): 3431, 2926, 2854, 1738, 1637, 1458, 1103. ^1H- and ^{13}C-NMR: *Table.* ESI-MS: 357.2 (100, $[M+Na]^+$). HR-ESI-MS: 357.2037 ($[M+Na]^+$, $C_{20}H_{30}NaO_4^+$; calc. 357.2042).

Secosarcophinolide (= *Butyl (2*Z*)-2-[(1*R,*4*E,*10*E,*14*R*)-4,10,14-Trimethyl-6-oxo-15-oxabicyclo[12.1.0]pentadeca-4,10-dien-7-ylidene]propanoate*; **2**). Colorless oil. $[\alpha]_D^{25} = 0$ ($c = 0.05$, $CHCl_3$). UV (MeOH): 252 (3.62). IR (liquid film): 3411, 2925, 2854, 1714, 1672, 1614, 1456, 1238, 1120, 760. ^1H- and ^{13}C-NMR: *Table.* ESI-MS: 411.4 (100, $[M+Na]^+$). HR-ESI-MS: 411.2501 ($[M+Na]^+$, $C_{24}H_{36}NaO_4^+$; calc. 411.2511).

Crystallographic Data of **3**. Colorless crystals, $C_{20}H_{28}O_3$, $M_r = 316.42$, orthorhombic, crystal size $0.397 \times 0.385 \times 0.216$ mm, space group $P2(1)2(1)2(1)$; $a = 10.7482(9)$, $b = 12.4152(10)$, $c = 13.7621(12)$ Å, $\alpha = \beta = \gamma = 90.0°$, $V = 1836.4(3)$ Å^3, $Z = 4$, $D_{calc} = 1.144$ mg/m^3, $F_{000} = 688$, 10905 collected reflections, 2284 unique reflections ($R_{int} = 0.0595$), final R indices [$I > 2\sigma(I)$] $R_1 = 0.0412$, $wR_2 = 0.0883$, R indices (all data) $R_1 = 0.0604$, $wR_2 = 0.0953$, and goodness of fit = 0.925. The X-ray measurements were made on a *Bruker SMART APEX CCD* X-ray diffractometer with graphite-monochromated MoK_α ($\lambda = 0.71073$ Å) radiation at 293(2) K. The structure was solved by direct methods (SHELXS-97) and refined with full-matrix least-squares on F^2 (SHELXL-97). The non-H-atoms were refined anisotropically. All H-atoms were located in a difference *Fourier* map, but they were introduced in calc. positions and treated as riding on their parent atoms (C–H = 0.93–0.97 Å, O–H = 0.82 Å, and $U_{iso}(H) = 1.2\,U_{eq}(C)$ and $1.51\,U_{eq}(C, O)$). Crystallographic data for the structure of **3** has been deposited with the *Cambridge Crystallographic Data Center* with the deposition No. CCDC-682303. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/conts/retrieving.html.

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