138. A Novel, Degraded Polyketidic Lactone, Leptosphaerolide, and Its Likely Diketone Precursor, Leptosphaerodione. Isolation from Cultures of the Marine Ascomycete *Leptosphaeria oraemaris* (LINDER)[1])

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Acetone extraction of cultures of the marine ascomycete *Leptosphaeria oraemaris* (LINDER) on cornmeal disk gave the novel polyketide derivative leptosphaerolide (= (+)-7-[(1*E*)-1,3-dimethylpent-1-enyl]-10-hydroxy-3-methoxybenzo[1,2-*b*:5,4-*c*']dipyran-2(9*H*)-one; (+)-**8**) besides the *o*-dihydroquinone 3-[(1*E*)-1,3-dimethylpent-1-enyl]-8,10-dihydroxy-7-methoxy-8-(2-oxopropyl)-1*H*-naphtho[2,3-*c*]pyran-9(8*H*)-one (**1**) as a 10:9 mixture of epimers. *retro*-Aldol reaction of **1** gave leptosphaerodione (= (−)-3-[(1*E*)-1,3-dimethylpent-1-enyl]-10-hydroxy-7-methoxy-1*H*-naphtho[2,3-*c*]pyran-8,9(8*H*)-dione; (−)-**6**) which was also present in small amounts in the extracts and which gave **1** on reaction with acetone. It is thus likely that **1** is an artefact of the extraction by acetone. Biogenetically (+)-**8** might derive from (−)-**6** *via* an unusual oxidation with loss of CO_2.

1. Introduction. – In contrast with the wealth of studies devoted to natural products from terrestrial fungi [1], marine fungi have been scarcely investigated from this viewpoint [2]. The lignicolous marine ascomycete *Leptosphaeria oraemaris* (LINDER), which belongs to the Loculoascomycetes, Pleosporales, is one of the few exceptions; it was found to produce in culture both the antifungal sesquiterpene culmorin, previously isolated from the terrestrial ascomycetes *Fusarium culmorin* and *Fusarium graminearum* (Pyrenomycetes, Hypocreales) [3], and the 2-aminohexose leptosphaerin [4].

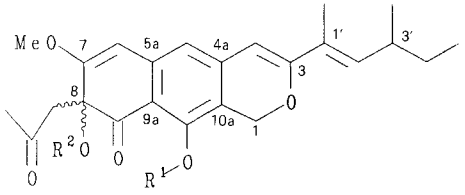
We report here that *L. oraemaris* (LINDER), collected in the bay of Naples, produces in liquid culture on cornmeal disk a novel lactone, leptosphaerolide ((+)-**8**), besides its likely dione precursor, trapped as *o*-dihydroquinone **1** during the extraction with acetone.

2. Results and Discussion. – 2.1. o-*Dihydroquinone* **1**. The most abundant component of the isolated mixture was epimer mixture **1**[2]) (10:9) whose structure was deduced from its spectra and its transformation to derivatives **2**–**5**.

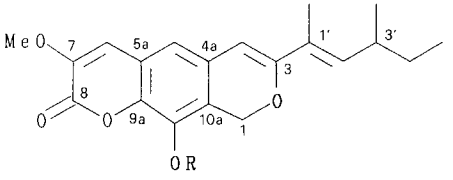
High-resolution MS of **1** indicate the composition $C_{21}H_{22}O_5$ for the base peak; its formation from the molecular ion (*m*/*z* 412) by loss of an acetone unit is suggested by the signals for a CH_2COCH_3 unit in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum (*Table*) reveals 24 C-atoms which bear 26 H-atoms; therefore, the remaining 2H must be O-bound, and are a phenolic and an alcoholic proton on the basis of ^{1}H-NMR data (*Exper. Part*). The (*E*)-dimethylpentenyl side chain is supported by 1D and COSY data, while differential NOE experiments suggest its linkage to C(3). The remaining H-atoms are isolated systems. This, ^1J and ^nJ ^{1}H,^{13}C-COSY (*Table*), and the data of the acetylation products **2**–**4** fully support structure **1**. An additional feature is H-bonding between the

[1]) Presented in part by *A.G.* at the 'Giornate di Chimica delle Sostanze Naturali' meeting, Maratea (Potenza), on June 3, 1991.

[2]) For all compounds discussed here, systematic numbering is only used for retrieval purposes (see *Exper. Part* and *Summary*); all experimental data are given in terms of the arbitrary numbering indicated at the structural formulas.



1 $R^1 = R^2 = H$ (10:9 epimer mixture)
2 $R^1 = H$, $R^2 = Ac$
3 $R^1 = R^2 = Ac$
4 $R^1 = Ac$, $R^2 = H$
5 $R^1 = Me_3Si(CH_2)_2OCH_2$, $R^2 = H$
(10:9 epimer mixture)



(+)-**8** R = H
(+)-**9** R = Me

phenolic H-atom and C(9)=O, which is suggested by both a sharp ^{1}H-NMR signal at δ 12.0 and failure of etherification of **1** with CH_2N_2, MeI/K_2CO_3, or Me_2SO_4/K_2CO_3.

Doubling of the ^{1}H-NMR signals of **1** for 2 H–C(1), Me–C(3′), and 3 H–C(5′) (*Exper. Part*) is compatible with either slow conformational motions or the presence of two diastereoisomers. Raising of the temperature did not result in any signal broadening, while a gradual shift, accompanied by the merging of the above signals, was observed. That this must be the result of a complex dependence of the chemical shift on the temperature was established by experiments with the chiral shift reagent [Yb(tfc)$_3$] (tfc = tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]). While **1** proved unsuitable to this purpose owing to a general signal broadening, derivative **5**, at a ratio [[Yb(tfc)$_3$]]/[**5**] = 0.2, showed separate signals, integrating for 10:9, for *Me*COCH$_2$, MeO, and H–C(6) of the two diastereoisomers.

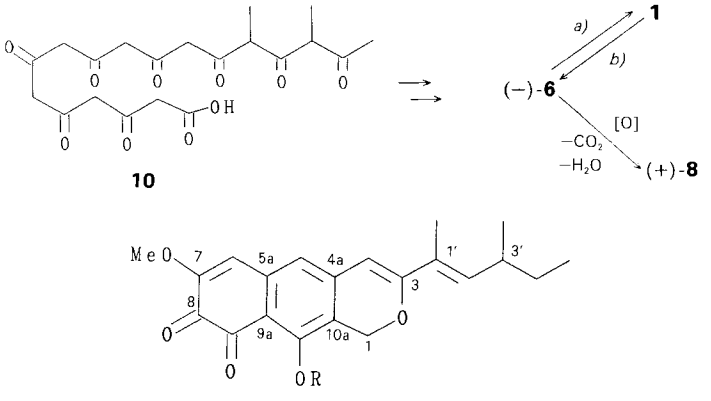
Table. *^{13}C-NMR Data, and Correlated ^{1}H, for* o*-Dihydroquinone* **1** *and Leptosphaerolide* ((+)-**8**) *in* $CDCl_3$

C-Atom	**1**		(+)-**8**[2])	
	δ(C)	correlated ^{1}H	δ(C)	correlated ^{1}H
C(1)	62.95 (*t*)		62.97 (*t*)	
C(3)	160.11 (*s*)	2 H–C(1), H–C(4), Me–C(1′), H–C(2′)	155.85 (*s*)	Me–C(1′)
C(4)	100.43 (*d*)	H–C(5)	99.82 (*d*)	H–C(5)
C(4a)	142.85 (*s*)	H–C(4), H–C(5)	130.21 (*s*)	2 H–C(1)
C(5)	113.63 (*d*)	H–C(4), H–C(6)	111.74 (*d*)	H–C(4), H–C(6)
C(5a)	138.64 (*s*)	H–C(5)	119.00 (*s*)	
C(6)	97.62 (*d*)	H–C(5)	113.18 (*d*)	H–C(5)
C(7)	158.66 (*s*)	H–C(6), MeO, MeCOC*H*$_2$	144.36 (*s*)	MeO
C(8)	73.54 (*s*)	MeCOC*H*$_2$, H–C(6)	156.77 (*s*)	H–C(6)
C(9)	199.86 (*s*)	MeCOC*H*$_2$		
C(9a)	108.14 (*s*)	H–C(5), H–C(6), OH–C(10)	136.09 (*s*)	H–C(5), H–C(6)
C(10)	158.14 (*s*)	OH–C(10)	137.90 (*s*)	2 H–C(1)
C(10a)	111.09 (*s*)	H–C(4), H–C(5), OH–C(10)	115.30 (*s*)	2H–C(1), H–C(4), H–C(5)
C(1′)	126.69 (*s*)	H–C(4), Me–C(1′)	126.94 (*s*)	Me–C(1′)
C(2′)	139.39 (*d*)	Me–C(1′), Me–C(3′)	136.84 (*d*)	
C(3′)	34.74 (*d*)	Me–C(3′)	34.58 (*d*)	
C(4′)	30.16 (*t*)	Me–C(3′)	30.29 (*t*)	
C(5′)	12.03 (*q*)		12.07 (*q*)	
MeCO*C*H$_2$	50.72 (*t*)	*Me*COCH$_2$		
Me*C*OCH$_2$	206.37 (*s*)	*Me*COC*H*$_2$		
*Me*COCH$_2$	31.15 (*q*)			
Me–C(1′)	12.90 (*q*)	H–C(2′)	12.90 (*q*)	
Me–C(3′)	20.31 (*q*)	H–C(2′)	20.53 (*q*)	
MeO	55.69 (*q*)		56.39 (*q*)	

Regrettably, our attempts at determining the absolute configuration at C(3′) of **1** failed. In fact, unlike the case of sclerotionin, which was found to loose the olefinic side chain as a dienoic acid (the equivalent of the C(3)–C(5′) side chain of **1** with C(3) as a carboxylic group) in basic media [5], mixture **1** gave only tars under such conditions.

On the treatment of mixture **1** with $ClCH_2O(CH_2)_2SiMe_4$ and base, we obtained not only the protected phenol **5** but also the protected diketonic phenol **7** which must be formed in a base-induced *retro*-aldol condensation of **1** with loss of the 2-oxopropyl chain. The isolation of **7** allowed the attribution of spurious signals in the sample of **1** from the culture medium to the parent (–)-**6** (see *Exper. Part*). In agreement, when **1** was left for 14 h at room temperature in $CHCl_3$ solution containing a catalytic amount of $(i\text{-}Pr)_2EtN$, diketone (–)-**6**, which we call leptosphaerodione, was isolated in > 35% yield (*Scheme*). In this connection, it is worth mentioning that a C(11)–C(12) side-chain-hydrogenated form of leptosphaerodione was isolated by AcOEt extraction from the air-dried mycelium obtained from cultures of *Leptosphaeria obiones* [6].

Scheme



a) $(CH_3)_2CO$, $(i\text{-}Pr)_2EtN$.
b) $CHCl_3$, $(i\text{-}Pr)_2EtN$.

(–)-**6** R = H
(+)-**7** $Me_3Si(CH_2)_2OCH_2$

2.2. *Leptosphaerolide* (+)-**8**. Another component isolated from the culture medium, leptosphaerolide ((+)-**8**), showed ^{1}H-NMR signals suggesting the same upper portion of the molecule and the fused phenol and dihydropyran moieties of the epimers **1**. In the ^{13}C-NMR spectrum of (+)-**8** (*Table*), the signals of the $MeCOCH_2$–C(8)–C(9) portion of **1** is replaced by a lactone group which resonates at the same frequency as in coumarin. This suggests structure (+)-**8**, which finds further support in differential NOE and ^{1}H,^{13}C-COSY experiments, as well as in the HR-MS for the molecular ion (*Exper. Part* and *Table*). In accordance, (+)-**8** could be methylated to (+)-**9**.

2.3. *The Biogenesis*. A hypothetical nonaketide **10** could undergo intramolecular condensation, followed by oxidations and reductions to give leptosphaerodione ((–)-**6**; see *Scheme*). The latter might undergo oxidation with loss of CO_2 to give an intermediate phenolic carboxylic acid which undergoes lactonization to leptosphaerolide ((+)-**8**). To our knowledge, the closest chemical analogy to the suggested biogenetic conversion of

(−)-**6** to (+)-**8** is the formation of 2,4-dinitrobenzoic acid and 2,4-dinitrophenol on treatment of 2,2′,4,4′-tetranitrobenzil with alkaline H_2O_2 [7][3]).

Less likely is the alternative view that **1** is derived from intramolecular condensations of a polyalkylated polyketide bearing a ketonic C_3 chain at C(8), which might have a 3-ketobutyrate origin as with ochrephilone [8]. This would involve an intermediate phenol undergoing stereorandom [9] oxidation to an *o*-dihydroquinone from which (+)-**8** would arise *via* (−)-**6**. Easy addition of acetone to (−)-**6** in the presence of a tertiary amine to give, albeit accompanied by another product which could not be characterized due to the small amounts, *o*-dihydroquinone **1** (*Scheme*), seem to rule out this alternative route.

In any event, no one of the metabolites previously isolated from *L. oraemaris* [3] [4] was found in our culture. This may be either due to a different strain of *L. oraemaris* or to different culture medium and conditions.

We thank Mr. *L. Zuppiroli* for recording high-resolution MS and Mr. *A. Sterni* for low-resolution MS. The work in Trento was financially supported by both *MPI* (Progetti di Interesse Nazionale) and *CNR*, Roma.

Experimental Part

1. *General.* All evaporations were carried out at reduced pressure. Yields for chemical reactions are given on reacted substrate. TLC: *Merck* silica gel *60 PF_{254}*. Flash chromatography (FC): *Merck* silica gel *Si60*, 20–50 μm. Reversed-phase FC: *Merck-LiChrosorb RP18* (20–50 μm). Reversed-phase HPLC (25 × 1 cm columns): *Merck-LiChrosorb RP18* (7 μm). Polarimetric data: *JASCO-DP-181* polarimeter. UV (λ_{max} in nm, ε in $mol^{-1}l\,cm^{-1}$): *Perkin-Elmer Lambda 3* spectrophotometer. NMR: *Varian-XL-300* at 75.43 (^{13}C) and 299.94 MHz (^1H); δ's (ppm) rel. to internal Me_4Si (= 0 ppm) and *J*'s in Hz; multiplicities and C and H assignments from DEPT [10], $^1H,^1H$-COSY [11], and $^1H,^{13}C$-COSY [12]. EI-MS (*m/z* (%)): home-built quadrupole mass spectrometer based on the *ELFS-4-162-8 Extranuclear* quadrupole [13] (low resolution) or *VG 70-70* (high resolution).

2. *Collection and Isolation. L. oraemaries* (LINDER) was isolated from the stem of the plant *Arundo donax* which grows near the mouth of Sarno river, bay of Naples, and was cultured in liquid medium (5 l) on cornmeal disk (*Cornmeal*). The whole culture was lyophilized and the residue (143 g) extracted first with acetone and then with EtOH. The combined extracts were evaporated to give 9 g of a residue which was subjected to reversed-phase FC (gradient elution with H_2O/MeOH). The fraction eluted with H_2O/MeOH 1:9 was evaporated to give 0.30 g of a residue which was subjected to FC with hexane/AcOEt 1:1 followed by reversed-phase HPLC with MeOH/H_2O 4:1 (8 ml min^{-1}, λ = 254 nm) to give 0.018 g of the epimeric mixture **1**, t_R 7.3 min, and 3.6 mg of leptosphaerolide ((+)-**8**), t_R 9.7 min. On standing, and more quickly in a basic medium, **1** decomposed giving the less polar (−)-**6** which was separated by TLC with hexane/AcOEt 1:1, R_f 0.75.

3. *3-[(1E)-1,3-Dimethylpent-1-enyl]-8,10-dihydroxy-7-methoxy-8-(2-oxopropyl)-1H-naphtho[2,3-c]pyran-9(8H)-one* (**1**). Mixture (10:9) of optically active epimers. Yellow semisolid which also contains *ca.* 10% of (−)-**6**. $[\alpha]_D$ = −0.36 (0.13M, MeOH). UV/VIS (MeOH): 228 (12800), 243 (13900), 262 (16700), 392 (15300). UV/VIS (with added NaOH): 278 (12300), 426 (6200), 522 (7200). ^1H-NMR ($CDCl_3$; signals for minor epimer, when emerging, in brackets; for (−)-**6**, see below): 5.19, 5.12 [5.17, 5.14] (*AB*, *J*(*AB*) = 13.2 [13.1], 2 H–C(1)); 5.83 (*s*, H–C(4)); 6.30 (*s*, H–C(5)); 5.60 (*s*, H–C(6)); 6.14 (br. *d*, *J*(2′,3′) = 9.9, *J*(2′,Me–C(1′)) = 1.2, H–C(2′)); 2.43 (*m*, H–C(3′)); 1.40 (*m*, 2 H–C(4′)); 0.858 [0.855] (*t*, *J*(5′,4′) = 7.0, 3 H–C(5′)); 3.11 (br. *s*, $MeCOCH_2$); 2.16 (*s*, $MeCOCH_2$); 1.85 (*d*, *J*(Me–C(1′),2′) = 1.2, Me–C(1′)); 0.999 [0.996] (*d*, *J*(Me–C(3′),3′) = 6.9, Me–C(3′)); 3.76 (*s*, MeO); 12.0 (*s*, OH–C(10)); differential NOE: 5.83 → 8% on 6.30 and 4% on 1.85; 6.30 → 9% on 5.83 and 8% on 5.60; 5.60 → 12% on 6.30 and 4% on 3.76; 3.11 → 2% on 2.16 and 0.5% on 3.76; 2.16 → 3% on 3.11; 2.43 → 2% on 1.85; 1.4 → 3% on 6.14; 3.76 → 13% on 5.60. MS: 412 (12, M^+), 394 (1), 355 (36), 354 (100, [*M* − acetone]$^+$), 339

[3]) We thank a referee for pointing out that the analogy may be poor, however, as leptosphaerodione ((−)-**6**) lacks electron-withdrawing groups. Unfortunately, when we became aware of the work in [7], no leptosphaerodione was any more available for alkaline H_2O_2 treatment.

(1, $[354 - CH_3]^+$), 336 (8, $[354 - 18]^+$), 325 (8, $[354 - 29]^+$), 310 (4, $[354 - 29 - 15]^+$), 307 (12, $[354 - 29 - 18]^+$). HR-MS: 354.1474 ($C_{21}H_{22}O_5$, calc. 354.1467).

4. *Acetylation of* **1**. To **1** (1.5 mg, 0.0036 mmol) were added Ac_2O (50 µl) and pyridine (0.5 ml) and stirred for 12 h at −5° and then for 5 h at r.t. Prep. TLC with hexane/AcOEt 2:1 led to compounds **2** (R_f 0.8; 0.5 mg, 38%), **3** (R_f 0.7; 0.5 mg, 35%), and **4** (R_f 0.4; 0.2 mg, 15%).

3-[(1E)-1,3-Dimethylpent-1-enyl]-8,9-dihydro-10-hydroxy-7-methoxy-9-oxo-8-(2-oxopropyl)-1H-naphtho[2,3-c]pyran-8-yl Acetate (**2**): ^{1}H-NMR ($CDCl_3$): 5.18, 5.16 (*AB*, *J*(*AB*) = 13.0, 2 H–C(1)); 5.83 (*s*, H–C(4)); 6.33 (*s*, H–C(5)); 5.72 (*s*, H–C(6)); 6.12 (br. *d*, *J*(2′,Me–C(1′)) = 1.5, *J*(2′,3′) = 9.9, H–C(2′)); 2.42 (*m*, H–C(3′)); 1.40 (*m*, 2 H–C(4′)); 0.86 (*t*, *J*(5′,4′) = 7.4, 3 H–C(5′)); 3.13, 2.94 (*AB*, *J*(*AB*) = 14.1, $MeCOCH_2$); 2.22 (*s*, $MeCOCH_2$); 1.86 (*d*, *J*(Me–C(1′),2′) = 1.5, Me–C(1′)); 1.01 (*d*, *J*(Me–C(3′),3′) = 6.6, Me–C(3′)); 3.70 (*s*, MeO); 2.14 (*s*, Ac); 11.90 (*s*, OH). MS: 454 (5, $M^{+\cdot}$), 410 (7), 409 (5), 396 (6), 304 (6), 367 (14), 351 (49), 43 (100).

3-[(1E)-1,3-Dimethylpent-1-enyl]-8,9-dihydro-7-methoxy-9-oxo-8-(2-oxopropyl)-1H-naphtho[2,3-c]pyran-8,10-diyl Diacetate (**3**): ^{1}H-NMR ($CDCl_3$): 5.04 (*m*, 2 H–C(1)); 5.91 (*s*, H–C(4)); 6.68 (*s*, H–C(5)); 5.71 (*s*, H–C(6)); 6.09 (br. *d*, *J*(2′,Me–C(1′)) = 1.3, *J*(2′,3′) = 9.7, H–C(2′)); 2.42 (*m*, H–C(3′)); 1.40 (*m*, 2 H–C(4′)); 0.86 (*t*, *J*(5′,4′) = 7.5, 3 H–C(5′)); 2.98, 2.78 (*AB*, *J*(*AB*) = 13.8, $MeCOCH_2$); 2.22 (*s*, $MeCOCH_2$); 1.86 (*d*, *J*(Me–C(1′),2′) = 1.3, Me–C(1′)); 1.00 (*d*, *J*(Me–C(3′),3′) = 6.6, Me–C(3′)); 3.68 (*s*, MeO); 2.14 (*s*, AcO–C(8)); 2.36 (*s*, AcO–C(10)). MS: 496 (4, $M^{+\cdot}$), 454 (9), 452 (1), 436 (3), 422 (10), 412 (13), 411 (11), 369 (41), 43 (100).

3-[(1E)-1,3-Dimethylpent-2-enyl]-8,9-dihydro-8-hydroxy-7-methoxy-9-oxo-8-(2-oxopropyl)-1H-naphtho[2,3-c]pyran-10-yl Acetate (**4**): ^{1}H-NMR ($CDCl_3$): 5.03 (br. *s*, 2 H–C(1)); 5.92 (*s*, H–C(4)); 6.64 (*s*, H–C(5)); 5.56 (*s*, H–C(6)); 6.10 (br. *d*, *J*(2′,Me–C(1′)) = 1.2, *J*(2′,3′) = 9.8, H–C(2′)); 2.42 (*m*, H–C(3′)); 1.4 (*m*, 2 H–C(4′)); 0.86 (*t*, *J*(5′,4′) = 7.3, 3 H–C(5′)); 2.86, 2.79 (*AB*, *J*(*AB*) = 14.0, $MeCOCH_2$); 2.22 (*s*, $MeCOCH_2$); 1.86 (*d*, *J*(Me–C(1′),2′) = 1.2, Me–C(1′)); 1.00 (*d*, *J*(Me–C(3′),3′) = 6.7, Me–C(3′)); 3.77 (*s*, MeO); 2.37 (*s*, Ac). MS: 454 (13, $M^{+\cdot}$), 422 (9), 412 (1), 396 (22), 380 (19), 378 (10), 354 (52), 43 (100).

5. *(−)-3-[(1E)-1,3-Dimethylpent-1-enyl]-10-hydroxy-7-methoxy-1H-naphtho[2,3-c]pyran-8,9(8H)-dione* ((−)-**6**). Deep-red solid. $[\alpha]_D^{20} = -53.3$ (*c* = 0.02[4], MeOH). UV/VIS (MeOH): 240 (22900), 302 (20000), 480 (10700). ^{1}H-NMR ($CDCl_3$): 5.20, 5.17 (*AB*, *J*(*AB*) = 13.5, 2 H–C(1)); 5.87 (*s*, H–C(4)); 6.43 (*s*, H–C(5)); 6.30 (*s*, H–C(6)); 6.23 (*dq*, *J*(2′,3′) = 9.9, *J*(2′,Me–C(1′)) = 1.2, H–C(2′)); 2.45 (*m*, H–C(3′)); 1.41 (*m*, 2 H–C(4′)); 0.87 (*t*, *J*(5′,4′) = 7.0, 3 H–C(5′)); 1.88 (*d*, *J*(Me–C(1′),2′) = 1.2, Me–C(1′)); 1.02 (*d*, *J*(Me–C(3′),3′) = 6.8, Me–C(3′)); 3.83 (*s*, MeO); 12.38 (*s*, OH); differential NOE: 5.87 → 7% on 6.43 and 3% on 1.88; 6.30 → 3% on 3.83 and 10% on 6.43; 6.43 → 7% on 6.30 and 7% on 5.87. MS: 354 (75, $M^{+\cdot}$), 336 (7), 321 (3), 273 (57), 43 (100).

6. *Treatment of* **1** *with [2-(Trimethylsilyl)ethoxy]methyl Chloride*. To epimer mixture **1** (0.006 g, 0.015 mmol) were added $Me_3Si(CH_2)_2OCH_2Cl$ (4 µl, 0.022 mmol) and $(i\text{-}Pr)_2EtN$ (0.02 mmol) in 1 ml of dry CH_2Cl_2. The mixture was stirred for 14 h at r.t. and then evaporated, and the residue was subjected to TLC with hexane/AcOEt 3:1. The higher red band gave **7** (0.8 mg), while the lower yellow band gave **5** (4.1 mg).

3-[(1E)-1,3-Dimethylpent-1-enyl]-8-hydroxy-7-methoxy-8-(2-oxopropyl)-10-{[2-(trimethylsilyl)ethoxy]methoxy}-1H-naphtho[2,3-c]pyran-9(8H)-one (**5**): UV/VIS (MeOH): 258 (15400), 294 (10300), 377 (13400). ^{1}H-NMR ($CDCl_3$; signals for minor epimer, when emerging, within brackets): 5.22, 5.20 [5.21, 5.18] (*AB*, *J*(*AB*) = 13.5, 2 H–C(1)); 5.88 (*s*, H–C(4)); 6.53 (*s*, H–C(5)); 5.53 (*s*, H–C(6)); 6.13 (*dq*, *J*(2′,3′) = 9.9, *J*(2′,Me–C(1′)) = 1.2, H–C(2′)); 2.44 (*m*, H–C(3′)); 1.38 (*m*, 2 H–C(4′)); 0.86 (*t*, *J*(5′,4′) = 7.0, 3 H–C(5′)); 2.94, 2.76 (*AB*, *J*(*AB*) = 13.5, $MeCOCH_2$); 2.24 (*s*, $MeCOCH_2$); 1.86 (*d*, *J*(Me–C(1′),2′) = 1.2, Me–C(1′)); 1.00 (*d*, *J*(Me–C(3′),3′) = 6.6, Me–C(3′)); 3.78 (*s*, MeO); 1.6 (br. *s*, OH); 5.13, 5.10 (*AB*, *J*(*AB*) = 7.5, OCH_2O); 3.83, 1.00 (A_2X_2, OCH_2CH_2Si); 0.03 (*s*, $SiMe_3$). ^{13}C-NMR ($CDCl_3$): 64.12 (*t*, C(1)); 159.58 (*s*, C(3) or C(7)); 100.20 (*d*, C(4)); 141.01 (*s*, C(4a) or C(5a)); 117.49 (*d*, C(5)); 140.11 (*s*, C(5a) or C(4a)); 96.91 (*d*, C(6)); 159.10 (*s*, C(7) or C(3)); C(8) not detected; 197.05 (*s*, C(9)); 119.31 (*s*, C(9a)); 154.05 (*s*, C(10)); 115.22 (*s*, C(10a)); 126.58 (*s*, C(1′)); 138.91 (*d*, C(2′)); 34.71 (*d*, C(3′)); 30.19 (*t*, C(4′)); 12.05 (*q*, C(5′)); 52.08 (*t*, $MeCOCH_2$); 205.97 (*s*, $MeCOCH_2$); 32.02 (*q*, $MeCOCH_2$); 12.93 (*q*, *Me*–C(1′)); 20.37 (*q*, *Me*–C(3′)); 55.83 (*q*, MeO); 99.31 (*t*, OCH_2O); 67.54 (*t*, OCH_2CH_2Si); 18.21 (*t*, OCH_2CH_2Si); −1.41 (*q*, $SiMe_3$). MS: 542 (5, $M^{+\cdot}$), 513 (1), 499 (2), 452 (9), 428 (14), 412 (19), 411 (20), 354 (44), 101 (15), 73 (100).

3-[(1E)-1,3-Dimethylpent-1-enyl]-7-methoxy-10-{[2-(trimethylsilyl)ethoxy]methoxy}-1H-naphtho[2,3-c]-pyran-8,9(8H)-dione ((+)-**7**): $[\alpha]_D^{20} = +32.0$ (*c* = 0.02, MeOH). UV/VIS (MeOH): 240 (10900), 300 (7800), 447 (5300). ^{1}H-NMR ($CDCl_3$): 5.23, 5.19 (*AB*, *J*(*AB*) = 13.6, 2 H–C(1)); 5.90 (*s*, H–C(4)); 6.63 (*s*, H–C(5)); 6.34 (*s*, H–C(6)); 6.19 (*dq*, *J*(2′,3′) = 9.9, *J*(2′,Me–C(1′)) = 1.2, H–C(2′)); 2.45 (*m*, H–C(3′)); 1.42 (*m*, 2 H–C(4′)); 0.87 (*t*,

[4]) This is the highest concentration allowed by the high absorption of this substanee in the VIS region.

$J(5',4') = 6.9$, 3 H–C(5')); 1.88 (*d*, J(Me–C(1'),2') = 1.2, Me–C(1')); 1.01 (*d*, J(Me–C(3'),3') = 6.7, Me–C(3')); 3.83 (*s*, MeO); 5.13 (*s*, OCH_2O); 3.84, 1.00 (A_2X_2, OCH_2CH_2Si); 0.03 (*s*, $SiMe_3$). MS: 484 (1, M^+), 456 (2), 428 (15), 413 (16), 411 (14), 354 (35), 73 (100).

7. *Leptosphaerolide* (= *(+)-7-[(1E)-Dimethylpent-1-enyl]-10-hydroxy-3-methoxybenzo[1,2-b:5,4-c']dipyran-2(9H)-one;* (+)-**8**). Yellow semisolid. $[\alpha]_D^{20} = +39.0$ (589), +45.8 (546; $c = 0.13$, MeOH). UV/VIS (MeOH): 228 (9800), 244 (9500), 301 (22750). UV/VIS (with added NaOH): 238 (12500), 314 (21600). ^{1}H-NMR[2]) ($CDCl_3$): 5.23, 5.21 (br. *AB*, $J(AB) = 13.6$, J(1,5) small, 2 H–C(1)); 5.90 (br. *s*, J(4,12) and J(4,5) small, H–C(4)); 6.61 (br. *s*, J(5,4), J(5,1), and J(5,6) small, H–C(5)); 6.78 (br. *s*, J(6,5) and J(6,MeO) small, H–C(6)); 6.04 (br. *dq*, J(2',Me–C(1') = 1.2, $J(2',3') = 9.6$, J(2',4) small, H–C(2')); 2.43 (*m*, H–C(3')); 1.40 (*m*, 2 H–C(4')); 0.86 (*t*, $J(5',4') = 7.5$, 3 H–C(5')); 1.86 (*d*, J(Me–C(1'),2') = 1.2, Me–C(1')); 1.01 (*d*, J(Me–C(3'),3') = 6.6, Me–C(3')); 3.92 (br. *s*, J(MeO,6) small, MeO); differential NOE: 5.90 → 13% on 6.61 and 5% on 1.86; 6.61 → 12% on 5.90 and 6% on 6.78; 6.78 → 8% on 6.61 and 4% on 3.92; 1.86 → 5% on 2.43 and 14% on 5.90. MS: 342 (97, M^+), 327 (9), 313 (23), 285 (24), 273 (100), 257 (37). HR-MS: 342.1463 ($C_{20}H_{22}O_5$, calc. 342.1467), 273.0749 ($C_{15}H_{13}O_5$, calc. 273.0763).

8. *Methylation of (+)-***8**. Leptosphaerolide ((+)-**8**; 3.6 mg) was treated with excess CH_2N_2 in Et_2O for 13 h at r.t. to give 2.9 mg of *leptosphaerolide methyl ether* (= *7-[(1E)-dimethylpent-1-enyl]-3,10-dimethoxybenzo[1,2-b:5,4-c']dipyran-2(9H)-one;* (+)-**9**): ^{1}H-NMR[2]) ($CDCl_3$): 5.20, 5.18 (*AB*, $J(AB) = 13.8$, 2 H–C(1)); 5.92 (br. *s*, H–C(4)); 6.76 (br. *s*, H–C(5), H–C(6)); 6.04 (br. *dq*, J(2',Me–C(1')) = 1.4, $J(2',3') = 9.8$, H–C(2')); 2.42 (*m*, H–C(3')); 1.40 (*m*, 2 H–C(4')); 0.86 (*t*, $J(5',4') = 7.5$, 3 H–C(5')); 1.87 (*d*, J(Me–C(1'),2') = 1.4, Me–C(1')); 1.00 (*d*, J(Me–C(3'),3') = 6.6, Me–C(3')); 3.91 (*s*, MeO–C(7)); 4.01 (*s*, MeO–C(10)); differential NOE: 6.76 → 15% on 5.92 and 4% on 3.91; 3.91 → 15% on 6.76; 5.19 → 2% on 4.01. ^{13}C-NMR[2]) ($(CD_3)_2CO$): 63.83 (*t*, C(1)); 156.26 (*s*, C(3)); 100.91 (*s*, C(4)); 130.45 (*s*, C(4a)); 116.65 (*d*, C(5)); 121.67 (*s*, C(5a)); 113.74 (*d*, C(6)); 145.38 (*s*, C(7)); 148.91 (*s*, C(8)); 142.56 (*s*, C(9a) or C(10)); 142.05 (*s*, C(10) or C(9a)); 122.18 (*s*, C(10a)); 127.65 (*s*, C(1')); 136.72 (*d*, C(2')); 35.07 (*d*, C(3')); 30.94 (*t*, C(4')); 12.25 (*q*, C(5')); 12.97 (*q*, *Me*–C(1')); 20.78 (*q*, *Me*–C(3')); 56.56 (*q*, *Me*O–C(7)); 61.85 (*q*, *Me*O–C(10)). MS: 356 (93, M^+), 341 (16), 327 (29), 299 (27), 287 (100), 155 (60), 149 (75).

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