Synthetic Studies on Kinamycin Antibiotics: Synthesis of a Trioxygenated Benz[*f*]indenone and its *Diels–Alder* Reaction to a Kinamycin Skeleton

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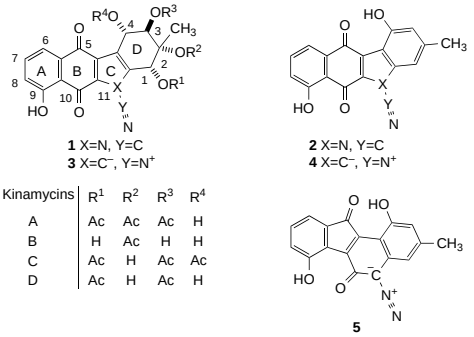
A benzo[*b*]fluorene skeleton such as **10**, a basic four-ring system in the revised diazo structures **3** of kinamycin antibiotics, was synthesized by *Diels-Alder* reaction between dienophile 4,7,8-trioxygenated 1*H*-benz[*f*]inden-1-one **11** and *Danishefsky*-type diene **7**. The indenone **11** was prepared by deoxygenation of 2,3-dihydro-1*H*-benz[*f*]inden-1-one **12** with the inexpensive 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) after modification of the known protocol. Indenone **12** in turn was obtained from naphthalene-1,5-diol (**14**) *via* an intramolecular *Friedel-Crafts* cyclization of naphthalene-2-propanoic acid **13** as a key step.

1. Introduction. – Kinamycin antibiotics [1], strongly active against gram-positive bacteria, were isolated from *Streptomyces murayamaensis* [2] and established to be composed of a 6-6-5-6 ring system with a highly oxygenated cyclohexene moiety (D ring) [3]. However, there has been some confusion regarding their structures as mentioned in our previous papers [4]; *i.e.*, benzo[*b*]carbazolequinone-derived cyanamides **1** and **2** had been first characterized as the basic structures of kinamycins [3] and prekinamycin [5] (a biosynthetic precursor of kinamycins [6]), respectively; however, these structures were revised to diazobenzo[*b*]fluorenediones **3** and **4** after reexamination of X-ray crystallographic analysis and synthesis of an *N*-cyanamide structure proposed for prekinamycin [7]. Furthermore, a quite recent investigation [8] indicated that an isomeric benzo[*a*]fluorene **5** could be a more reasonable structure for prekinamycin than **4** and, accordingly, it was proposed that compounds **4** and **5** should be newly named as isoprekinamycin and prekinamycin, respectively. Thus, synthetic approaches to kinamycin derivatives with the revised diazobenzo[*b*]fluorene skeleton are necessary for their structural establishment.

We had started to synthesize benzo[*b*]fluorene skeletons before the further revision [8] of the prekinamycin structure and achieved in a model study the stereoselective preparation of the diazofluorene **9** with a 3,4,5,6-tetraoxygenated cyclohexene-ring moiety and the correct relative configuration (*cis*,*trans*,*trans* for the OH groups) of the kinamycin skeleton [4]. In this synthesis, the *Diels–Alder* reaction of 4-(benzyloxy)-1*H*-inden-1-one (**6**) with *Danishefsky*-type diene **7** [9] had been used for the ring-system construction such as that of **8** (*Scheme 1*).

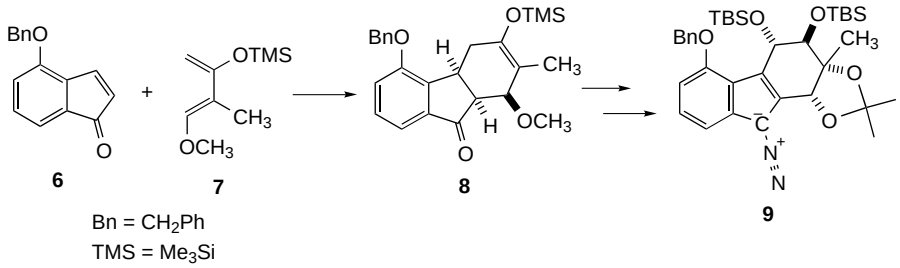
We now report the synthesis of a trioxygenated 1*H*-benz[*f*]inden-1-one **11** by dehydrogenation of the corresponding indanone **12**, which was independently prepared from naphthalene-1,5-diol (**14**) by an improved synthetic method. The dehydrogenation of **12** was achieved with 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX), and the *Diels–Alder* reaction of the resulting **11** with **7** led to the benzo[*b*]fluorene derivative **10**, which contains the basic ring system of the revised structures **3** of the kinamycin antibiotics.



Kinamycins	R^1	R^2	R^3	R^4
A	Ac	Ac	Ac	H
B	H	Ac	H	H
C	Ac	H	Ac	Ac
D	Ac	H	Ac	H

Figure. *Proposed structures of kinamycins and related compounds.* The locants in the *Formulae* **1** and **3** refer to **3** (X=C) only.

Scheme 1. *Synthesis of a Model Compound* **9** *Reflecting the Desired Correct Configurations*

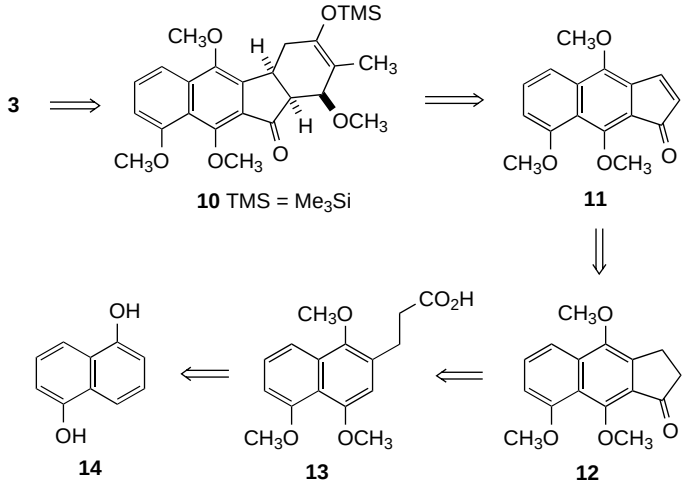


2. Results and Discussion. – Based on our model study [4], a trioxygenated benz[*f*]indenone **11** should be a synthetic unit in the *Diels-Alder* reaction for the construction of the kinamycin ring systems **3** with a benzo[*b*]fluorenone skeleton as shown in *Scheme 2*. Benz[*f*]indanone **12**, a synthetic precursor for **11**, has already been synthesized from a 3-bromojuglone derivative (3-bromo-5-methoxy-1,4-naphthoquinone), which was prepared from naphthalene-1,5-diol (**14**) in six steps (methylation, formylation, *Baeyer–Villiger* oxidation, hydrolysis, bromination, and oxidation) [10]; metal-exchange cyclization of the corresponding 3-bromonaphthalene-2-propanoic acid yielded **12** [11]. However, we independently planned the synthesis of **12** *via* an intramolecular *Friedel-Crafts* reaction (IFCR) of naphthalenepropanoic acid **13**, derived from **14**, as a more practical and convenient methodology.

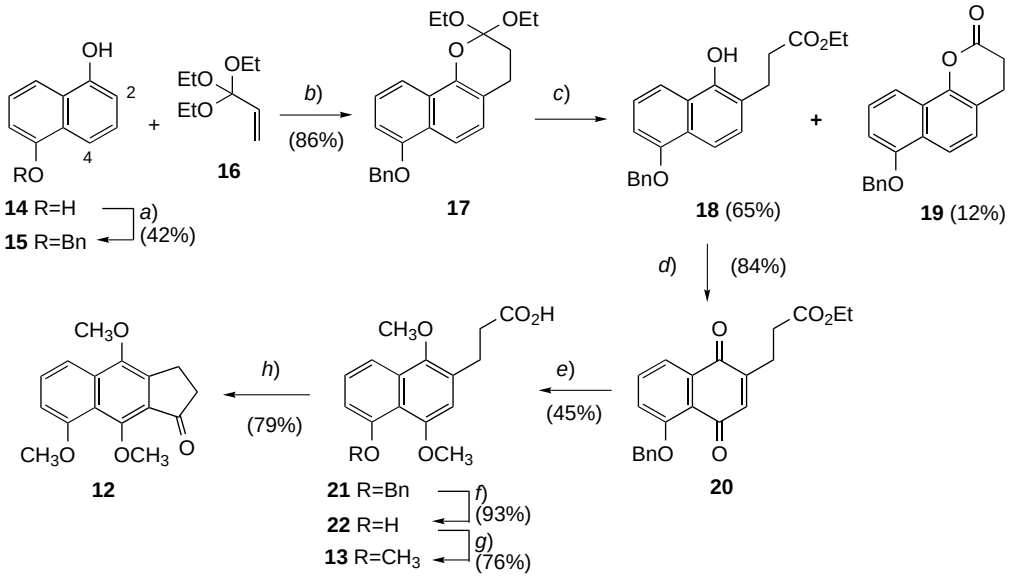
At first, we examined direct introduction of a C_3 unit at the 2 position of the naphthalene skeleton for the preparation of naphthalenepropanoic acid **13** as a substrate of IFCR after differentiation of the symmetrical OH groups of **14** by selective benzylation (*Scheme 3*). Treatment of **14** with 1 equiv. of benzyl bromide in the presence of 2 equiv. of NaH gave as expected a monobenzylated product **15** in 42% yield[1]). Treatment of **15** with triethyl orthoacrylate (**16**) [13] in the presence of pivalic

[1]) During our studies, the stepwise procedure for the synthesis of **15** was reported (diacetylation, partial hydrolysis, benzylation, and hydrolysis) [12]. The overall yield was 35%.

Scheme 2. *Retrosynthetic Analysis of Kinamycins* **3**



Scheme 3. *Preparation of Benz[*f*]indanone* **12** *by Cyclization of Naphthalenepropanoic Acid* **13** via *Diethoxychromane* **17**.



a) Benzyl bromide (1.0 equiv.); NaH (2.2 equiv.), DMF, 0°, 3 h. *b*) Pivalic acid (Me_3CCOOH) (0.5 equiv.), toluene, 120° (bath temp.), 1 h. *c*) 10% HCl soln., Et_2O, r.t., 5 h. *d*) *Fremy*'s salt (4.4 equiv.), 0.16M aq. KH_2PO_4, DMF, r.t., 20 h. *e*) 1) $SnCl_2 \cdot 2\,H_2O$ (3.5 equiv.), conc. HCl soln. (8.3 equiv.), EtOH, 50°, 1.5 h; 2) dimethyl sulfate (15 equiv.), 50% KOH soln. (48 equiv.), 65° (bath temp.), 1 h. *f*) H_2, 1% PdCl soln. in dil. HCl soln., charcoal, EtOH, r.t., 2 h. *g*) Dimethyl sulfate (4.4 equiv.), 15% NaOH soln. (4.7 equiv.), r.t., 5 h. *h*) P_2O_5 (3.3 equiv.), $MeSO_3H$ (40 equiv.), r.t., 2 h

acid followed by *Claisen* rearrangement [14] without purification afforded diethoxychromane **17**. Acid hydrolysis of **17** furnished a ring-opened product **18** in 65% yield, together with a minor amount of dihydrocoumarin **19** (12%).

Oxidation of **18** to a naphthoquinone derivative was examined for the introduction of an O-function at the 4 position. It is known that *Fremy*'s salt is a selective and mild reagent for the preparation of *p*-quinone derivatives even sensitive to steric factors [15]. Treatment of **18** with *Fremy*'s salt and dimethylformamide (DMF) as a solvent was successfully achieved to give a dioxonaphthalenepropanoic acid **20**[2]). Reduction of the quinone moiety in **20** with tin(II) chloride ($SnCl_2$) under acidic conditions [16] followed by methylation in a strong basic medium [17] gave 5-(benzyloxy)-1,4-dimethoxynaphthalene-2-propanoic acid **21**. Trials for cyclization of **21** to an indanone skeleton even under basic conditions ($POCl_3/K_2CO_3$ in MeCN) [18] resulted in the formation of complex mixtures, suggesting that the benzyloxy group in **21** was unstable. Then, the benzyl function was replaced by a Me group by the conventional method (hydrogenation ($\rightarrow$ **22**) and methylation) to give 1,4,5-trimethoxynaphthalene-2-propanoic acid (**13**). The IFCR of **13** with $P_2O_5/MeSO_3H$[3]) successfully provided the expected trimethoxybenz[*f*]indanone **12** in 79% yield, with concomitant production of the corresponding 9-*O*-demethylated indanone in 9% yield.

Thus, although **12** could be prepared from naphthalene-1,5-diol (**14**) in eight steps (*Scheme 3*), this pathway should be improved for the following reasons: 1) low yield in the selective benzylation of **14** (step *a*), 2) unstability of orthoacrylate **16** (step *b*), 3) difficult separation of naphthalenepropanoate **18** from dihydrocoumarin **19** produced as a by-product (step *c*), and 4) unnecessary replacement of the benzyl group by a methyl group (steps *f* and *g*). In addition, the total yield (5%) was lower than that of the reported method (17% from 1,5-dimethoxynaphthalene) [10][11].

Therefore, we next tried an alternative preparation of naphthalenepropanoic acid **13** from **14** by stepwise introduction of the propanoic acid unit as shown in *Scheme 4*. Diacetate **23**, obtained by nonselective acetylation of **14**, was subjected to oxidative bromination with *N*-bromosuccinimide (NBS) in aqueous AcOH to smoothly give 2-bromo-5-*O*-acetyljuglone (**24**) [20]. After replacement of the acetyl function of **24** by the Me group, reduction of **26** with $SnCl_2$ followed by methylation under nonaqueous conditions [21] afforded 2-bromo-1,4,5-trimethoxynaphthalene (**27**). Successive treatment of **27** with butyllithium and DMF gave the corresponding naphthaldehyde **28** in high yield. The *Knoevenagel* reaction of **28** with malonic acid under sonication [22] followed by catalytic hydrogenation provided the intended naphthalenepropanoic acid **13** in nearly quantitative yield. The overall yield of **12** from **14** in this synthetic route could be estimated to be 37% considering the 79% yield of the IFCR **13** $\rightarrow$ **12** (see *Scheme 3*). Thus, successful improvement of the preparation of benz[*f*]indanone **12** from naphthalene-1,5-diol (**14**) was achieved.

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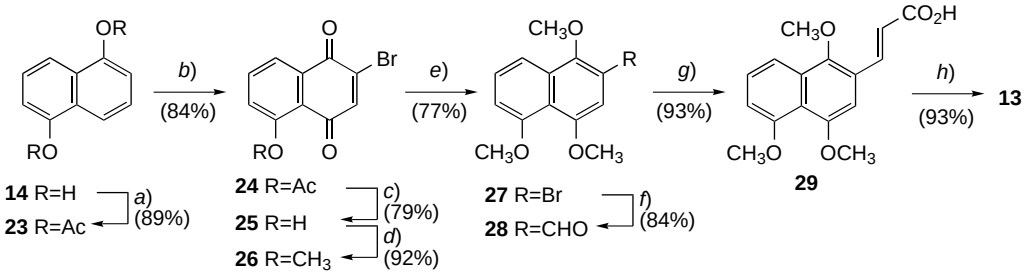
[2]) The yield of **20** was 39% when MeOH was used as a solvent because of reduced solubility of the starting **18** in the solvent.

[3]) Prof. *K. Shishido* (Tokushima University, Japan) kindly informed us about this reagent [19]. Improved yield was observed when P_2O_5 was completely dissolved in $MeSO_3H$ under heating before the reaction. The yield of **12** was decreased to 34% in case of incomplete dissolution.

Scheme 4. *Modification of the Synthetic Route to Naphthalenepropanoic Acid* **13**



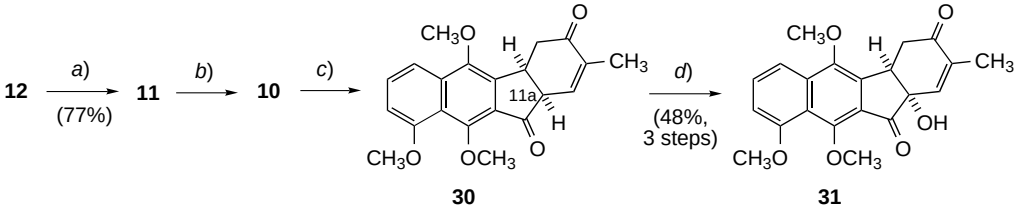
a) Ac_2O (3.0 equiv.), pyridine (9.0 equiv.), r.t., 1 h. *b*) NBS (4.6 equiv.), AcOH/H_2O 1:1, 60°, 1 h. *c*) 1.5M H_2SO_4 (4.8 equiv.), EtOH, reflux, 2 h. *d*) Ag_2O (1.6 equiv.), MeI (3.3 equiv.), CH_2Cl_2, r.t., 2 days. *e*) 1) $SnCl_2 \cdot 2H_2O$ (3.4 equiv.), conc. HCl soln. (8.4 equiv.), EtOH, 50°, 1 h; 2) NaH (3.0 equiv.), MeI (3.0 equiv.), DMF, r.t., 21.5 h. *f*) 1) BuLi (1.1 equiv.), THF, −78°, 2 h; 2) DMF (2.0 equiv.), THF, −78°, 1 h. *g*) Malonic acid (2.0 equiv.), pyridine (5.7 equiv.), piperidine (0.2 equiv.), sonication, 30°, 21.5 h. *h*) H_2, 5% Pd/C, EtOH, r.t., 21 h.

In our model synthesis of a fluorenone skeleton [4], *Saegusa*'s method [23] with a stoichiometric amount of an expensive palladium acetate had been employed in the dehydrogenation of indanone to indenone. Recently, *Nicolaou et al.* [24] reported the effective oxidation of ketones to enone substrates with IBX, suggesting the possible role of IBX as an inexpensive reagent in our oxidation step of benz[*f*]indanone **12**. We first examined the IBX oxidation of **12** to **11** with some modification (4 equiv. of IBX, or at 85°) of the reported method (2 equiv. of IBX in DMSO/toluene 1:2 or DMSO/fluorobenzene 1:2 at 65°) [24]. However, ineffective conversion (**12**/**11** 1:*ca* 0.7) was observed in each case. Replacement of an aromatic solvent in the mixed solvent system by (trifluoromethyl)benzene or anisole resulted in no improvement of the production of the indenone **11**, whereas a promising result was achieved with 4 equiv. of IBX in DMSO/chlorobenzene even if the reaction was incomplete (**12**/**11** 1:2.2).

Thus, treatment of **12** with IBX (4 equiv.) in DMSO/chlorobenzene at 65° for longer time (48 h) successfully afforded the corresponding dehydro product **11** in 77% yield with recovery of **12** in 6% yield. The benz[*f*]indenone **11** was subjected to thermal *Diels–Alder* reaction with *Danishefsky*-type diene **7** under reflux in benzene according to our model study [4]; however, ineffective cycloaddition was observed. Use of other solvents with higher boiling point such as toluene, xylene, or diethylaniline resulted in no improvement. On the other hand, the *Diels-Alder* reaction in CH_2Cl_2 in the presence of a catalytic amount of $ZnCl_2$ at −15° smoothly gave an adduct **10**. Treatment of **10** with camphorsulfonic acid (CSA) followed by air-oxidation of the resulting enone **30** in the presence of KF without purification provided a γ-hydroxyenone **31** in 48% overall yield from **11**: spectral data showed that **31** possessed a benzo[*b*]fluorene skeleton such as in the revised structures of kinamycin antibiotics with O-functions in appropriate positions at the *AB* ring.

3. Conclusions. – In summary, we have succeeded in improving the synthesis of benz[*f*]indanone **12** from naphthalene-1,5-diol (**14**) by the IFCR of naphthalenepropanoic acid **13** as a key step and dehydrogenation of **12** with inexpensive IBX to the

Scheme 5. *Oxidation of Benz[*f*]indanone* **12** *and Construction of the Kinamycin Skeleton*



a) IBX (4.0 equiv.), DMSO/PhCl 1:2, 65°, 48 h. *b*) **7** (2.4 equiv.), $ZnCl_2$ (0.1 equiv.), CH_2Cl_2, −15°, 1.5 h. *c*) CSA (0.2 equiv.), CH_2Cl_2, 0°, 1.5 h. *d*) KF (0.1 equiv.), DMSO, air, r.t., 1.5 h.

corresponding benz[*f*]indenone **11**. Furthermore, a benzo[*b*]fluorenone skeleton, a basic ring system in the revised structures of kinamycin antibiotics, could be smoothly provided by the $ZnCl_2$-catalyzed *Diels–Alder* reaction of **11** and *Danishefsky*-type diene **7**. Currently our efforts continues to complete the total synthesis of kinamycins.

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Experimental Part

General. CH_2Cl_2 was distilled from P_2O_5 before use and DMF from CaH_2. NBS was recrystallized from H_2O before use. $ZnCl_2$ was dried with a heat gun under vacuum before use. Org. extracts were dried ($MgSO_4$) before evaporation. M.p.: micro melting-point hot stage (*Yanagimoto*); uncorrected. IR Spectra: *Jasco FT/IR-300E* spectrophotometer; in cm^{-1}. ^{1}H-NMR Spectra: *Jeol JNM-GSX400A* (400 MHz) or *-GSX500A* (500 MHz) spectrometer; $CDCl_3$ soln.; δ in ppm rel. to $SiMe_4$ (0.00 ppm) as internal standard, *J* in Hz. ^{13}C-NMR Spectra: *Jeol-JNM-ECP600* (150 MHz) spectrometer; $CDCl_3$ soln.; middle resonance of $CDCl_3$ (77.0 ppm) as internal standard. EI-MS: *Jeol Automass* or *Jeol GC-mate* with direct inlet or a *Hewlett-Packard 5890-II* gas chromatograph and *5971A* mass-selective detector with GC-MS. HR-FAB-MS: *JMS-HX110* with *m*-nitrobenzyl alcohol as matrix. Column chromatography (CC): silica gel (*Fuji Silysia FL100D*).

5-(Benzyloxy)naphthalen-1-ol (**15**). A mixture of **14** (101 mg, 0.63 mmol) and NaH (60%; 55 mg, 1.38 mmol) in DMF (1.0 ml) was stirred at 0° for 30 min under Ar, and then a soln. of benzyl bromide (111 mg, 0.647 mmol) in DMF (1.0 ml) was added at 0°. The mixture was stirred at 0° for 3 h and extracted with AcOEt after acidification with 10% HCl soln. (pH 1). The org. soln. was successively washed with H_2O and brine and evaporated. Purification of the residue by CC (hexane/AcOEt 10:1) gave **15** (67 mg, 42%). Yellow prisms. M.p. 135–138° ([12]: 136–138°). ^{1}H-NMR (500 MHz): 5.25 (*s*, PhCH_2O); 5.40 (br. *s*, OH); 6.86 (*dd*, *J* = 7.3, 1.0, H–C(2)); 6.92 (*d*, *J* = 7.6, H–C(6)); 7.29–7.43 (*m*, 5 H); 7.53 (*d*, *J* = 7.3, H–C(2′), H–C(6′)); 7.76 (*d*, *J* = 8.5, H–C(8)); 7.94 (*d*, *J* = 8.5, H–C(4)). EI-MS: 251 (13, $[M+1]^+$), 91 (100).

*7-(Benzyloxy)-2,2-diethoxy-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran* (**17**). A soln. of **15** (443 mg, 1.77 mmol) and pivalic acid (91.2 mg, 0.893 mmol) in toluene (6.0 ml) was successively added to a soln. of **16** (624 mg, 3.58 mmol) in toluene (6.0 ml) at r.t., and the mixture was stirred at 120° (bath temp.) for 1 h. After cooling, the mixture was diluted with Et_2O and washed with 10% NaOH soln., H_2O, and brine and evaporated. Purification of the residue by CC (hexane/AcOEt 20:1) gave **17** (573 mg, 86%). Colorless prisms. M.p. 95–97°. ^{1}H-NMR (500 MHz): 1.20 (*t*, *J* = 7.2, 2 *Me*CH_2O); 2.20 (*t*, *J* = 6.9, CH_2–C(3)); 2.98 (*t*, *J* = 6.9, CH_2–C(4)); 3.70–3.76, 3.80–3.87 (each *m*, 2 MeCH_2); 5.24 (*s*, PhCH_2O); 6.87 (*d*, *J* = 7.6, H–C(8)); 7.17 (*d*, *J* = 7.6, H–C(5)); 7.32–7.36 (*m*, 2 H); 7.42 (*dd*, *J* = 7.6, 7.6, H–C(3′), H–C(5′)); 7.52 (*d*, *J* = 7.6, H–C(2′), H–C(6′)); 7.82 (*d*, *J* = 7.9, H–C(10)); 7.88 (*d*, *J* = 8.5, H–C(6)). EI-MS: 378 (97, M^+), 333 (42), 287 (40), 213 (100).

Ethyl 5-(Benzyloxy)-1-hydroxynaphthalene-2-propanoate (**18**) *and 7-(Benzyloxy)-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran-2-one* (**19**). A soln. of **17** (332 mg, 0.877 mmol) in Et_2O (30 ml) containing 10% aq. HCl soln. (5.0 ml) was stirred at r.t. for 5 h. The aq. soln. was extracted with Et_2O and the combined org. phase washed with H_2O,sat. $NaHCO_3$ soln., H_2O, and brine and evaporated. Purification of the residue by CC (hexane/AcOEt 10:1) gave less-polar **18** (199 mg, 65%) and more-polar **19** (36 mg, 12%).

Data of **18**: Yellow prisms. M.p. 49–52°. IR (nujol): 3279, 1700. ^{1}H-NMR (500 MHz): 1.22 (t, J = 7.2, *Me*CH$_2$); 2.80 (t, J = 5.7, CH$_2$(α)); 3.03 (t, J = 5.7, CH$_2$(β)); 4.14 (q, J = 7.2, MeC*H*$_2$O); 5.23 (s, PhC*H*$_2$O); 6.87 (d, J = 7.6, H–C(6)); 7.16 (d, J = 8.5, H–C(3)); 7.33–7.37 (m, H–C(7), H–C(4′)); 7.41 (dd, J = 7.3, 7.3, H–C(3′), H–C(5′)); 7.51 (d, J = 7.3, H–C(2′),H–C(6′)); 7.86 (d, J = 7.6, H–C(8)); 7.91 (d, J = 8.5, H–C(4)); 8.29 (s, OH). EI-MS: 305 (3, [M + 1]$^+$), 304 (17, M^+), 91 (100).

Data of **19**: Colorless prisms. M.p. 114–116°. IR (nujol): 1752. ^{1}H-NMR (400 MHz): 2.90 (t, J = 7.0, CH$_2$(3)); 3.15 (t, J = 7.0, CH$_2$(4)); 5.26 (s, PhC*H*$_2$O); 6.94 (d, J = 8.2, H–C(8)); 7.24 (d, J = 8.5, H–C(5)); 7.52 (d, J = 7.2, H–C(2′), H–C(6′)); 7.82 (d, J = 8.5, H–C(6)); 8.10 (d, J = 8.2, H–C(10)).

Ethyl 5-(Benzyloxy)-1,4-dihydro-1,4-dioxonaphthalene-2-propanoate (**20**). A soln. of *Fremy*'s salt (1.79 g, 6.35 mmol) in H$_2$O (200 ml) and 0.16M aq. KH$_2$PO$_4$ (60 ml) was added to a soln. of **18** (507 mg, 1.45 mmol) in DMF (80 ml) at r.t. After stirring at r.t. for 20 h, the mixture was extracted with AcOEt. The org. soln. was washed with H$_2$O and brine and evaporated. Recrystallization of the residue from cyclohexane gave **20** (404 mg, 77%). The mother liquor was evaporated and purified by CC (hexane/AcOEt 10:1) to give additional **20** (39 mg, 7%). Yellow prisms. M.p. 107–108°. IR (nujol): 1721, 1655. ^{1}H-NMR (400 MHz): 1.25 (t, J = 7.2, *Me*CH$_2$); 2.62 (t, J = 7.3, CH$_2$(α)); 2.86 (t, J = 7.3, CH$_2$(β)); 4.14 (q, J = 7.2, MeC*H*$_2$O); 5.30 (s, PhC*H*$_2$O); 6.72 (s, H–C(3)); 7.32 (m, H–C(6), H–C(7)); 7.41 (dd, J = 7.6, 7.6, H–C(3′), H–C(5′)); 7.56 (d, J = 7.6, H–C(2′), H–C(6′)); 7.62 (dd, J = 7.6, 7.6, H–C(4′)); 7.76 (d, J = 7.7, H–C(8)). EI-MS: 365 (6, [M + 1]$^+$), 364 (27, M^+), 91 (100).

5-(Benzyloxy)-1,4-dimethoxynaphthalene-2-propanoic Acid (**21**). A suspension of SnCl$_2$·2 H$_2$O (1.11 g, 4.91 mmol) in conc. HCl soln. (1.10 ml, 13.2 mmol) was added to a soln. of **20** (495 mg, 1.36 mmol) in EtOH (8.5 ml), and the mixture was stirred at 50° for 1 h. After cooling, the mixture was extracted with Et$_2$O after addition of ice-water (20 ml). The org. soln. was washed with H$_2$O and brine and evaporated. Me$_2$SO$_4$ (2.0 ml, 21.1 mmol) and 50% KOH soln. (7.6 ml, 67.7 mmol) was added to the residue under ice-cooling, and the mixture was stirred at 65° (bath temp.) for 27 h. After further addition of Me$_2$SO$_4$ (0.7 ml, 7.4 mmol) and 50% KOH soln. (2.0 ml, 17.8 mmol), the mixture was stirred at 65° (bath temp.) for 19.5 h and cooled. Then 10% HCl soln. was added (pH 1) and the mixture extracted with Et$_2$O. The org. soln. was washed with H$_2$O and brine and evaporated: **21** (223 mg, 45%), which was recrystallized from cyclohexane/benzene 1:1. Pale brown needles. M.p. 69–70°. IR (nujol): 1710. ^{1}H-NMR (500 MHz): 2.77 (t, J = 7.9, CH$_2$(α)); 3.12 (t, J = 7.9, CH$_2$(β)); 3.87, 3.91 (2s, 2 MeO); 5.20 (s, PhC*H*$_2$O); 6.68 (s, H–C(3)); 6.93 (d, J = 7.6, H–C(6)); 7.33 (dd, J = 7.6, 7.6, H–C(4′)); 7.39–7.43 (m, H–C(7), H–C(3′), H–C(5′)); 7.59 (dd, J = 7.6, H–C(2′), H–C(6′)); 7.67 (d, J = 7.6, H–C(8)). EI-MS: 366 (100, M^+). Anal. calc. for C$_{22}$H$_{22}$O$_5$: C 72.12, H 6.05; found: C 71.89, H 6.27.

1,4-Dimethoxy-5-hydroxynaphthalene-2-propanoic Acid (**22**). A mixture of **21** (298 mg, 0.82 mmol), charcoal (116 mg), and 1% PdCl$_2$ soln. in 10% HCl soln. (1.30 ml, 0.073 mmol as PdCl$_2$) in EtOH (6.0 ml) was stirred at r.t. for 2 h under H$_2$. After removal of the insoluble materials by filtration through a *Celite* pad, the filtrate was evaporated. The residue was diluted with AcOEt, washed with H$_2$O and brine, and evaporated. Purification of the residue by CC (CHCl$_3$/MeOH 50:1) gave **22** (207 mg, 93%), which was recrystallized from EtOH. Colorless prisms. M.p. 142–143°. IR (nujol): 3370, 1708. ^{1}H-NMR (400 MHz): 2.76 (t, J = 7.9, CH$_2$(α)); 3.10 (t, J = 7.9, CH$_2$(β)); 3.87, 4.03 (2s, 2 MeO); 6.61 (s, H–C(3)); 6.87 (dd, J = 8.0, 1.2, H–C(6)); 7.39 (dd, J = 8.0, 8.0, H–C(7)); 7.51 (dd, J = 8.0, 1.2, H–C(8)); 9.32 (s, OH). EI-MS: 276 (18, M^+), 215 (21), 167 (38), 149 (100). Anal. calc. for C$_{15}$H$_{16}$O$_5$: C 65.21, H 5.84; found: C 65.10, H 5.92.

1,4,5-Trimethoxynaphthalene-2-propanoic Acid (**13**). A mixture of **22** (931 mg, 3.37 mmol) and Me$_2$SO$_4$ (0.86 ml, 4.16 mmol) in 15% NaOH soln. (3.7 ml, 14.0 mmol) was stirred at 0° for 30 min and then at r.t. for 5.5 h. During this reaction, Me$_2$SO$_4$ (0.20 ml, 2.11 mmol) and 15% NaOH soln. (0.5 ml, 1.87 mmol) were added to keep the mixture weakly basic. After addition of 40% NaOH soln. (0.42 ml, 4.20 mmol) the mixture was refluxed for 1.5 h, cooled to r.t., acidified with 10% HCl soln. (pH 1), and extracted with CHCl$_3$. The org. soln. was washed with H$_2$O and brine and evaporated. Recrystallization of the residue from benzene gave **13** (753 mg, 76%). Pale brown prisms. M.p. 122–123°. IR (nujol): 1689. ^{1}H-NMR (400 MHz): 2.77 (t, J = 7.9, CH$_2$(β)); 3.11 (2 H, t, J = 7.9, CH$_2$(α)); 3.87, 3.93, 3.97 (3s, 3 MeO); 6.67 (s, H–C(3)); 6.85 (d, J = 8.2, H–C(6)); 7.41 (dd, J = 8.2, 8.2, H–C(7)); 7.48 (dd, J = 8.2, 1.0, H–C(8)). EI-MS: 290 (51, M^+), 229 (76), 84 (100). Anal. calc. for C$_{15}$H$_{16}$O$_5$: C 66.19, H 6.25; found: C 66.04, H 6.31.

*2,3-Dihydro-4,8,9-trimethoxy-1*H*-benz[f]inden-1-one* (**12**). A mixture of P$_2$O$_5$ (1.59 g, 11.2 mmol) and MeSO$_3$H (9.0 ml, 137 mmol) was stirred at 50° for 3 h under Ar. After addition of **13** (1.00 g, 3.45 mmol) at r.t., the mixture was stirred at r.t. for 2 h, poured into ice-water, and extracted with CHCl$_3$. The org. soln. was washed with H$_2$O and brine and evaporated. Purification of the residue by CC (benzene/AcOEt 10:1) gave **12** (741 mg, 79%). Pale green prisms. M.p. 149–151° ([14]: 154–155°). IR (nujol): 1707. ^{1}H-NMR (400 MHz): 2.76 (t, J = 6.8, CH$_2$(2)); 3.23 (t, J = 6.8, CH$_2$(3)); 3.97, 4.00, 4.01 (3s, 3 MeO); 6.87 (d, J = 8.2, H–C(7)); 7.41 (dd, J = 8.2,

8.2, H–C(6)); 7.48 (*dd*, *J* = 8.2, 0.9, H–C(5)). EI-MS: 272 (100, M^+). Anal. calc. for $C_{16}H_{16}O_4$: C 70.57, H 5.92; found: C 70.29, H 5.97.

Naphthalene-1,5-diol Diacetate (**23**). A mixture of **14** (48.8 g, 305 mmol), Ac_2O (86.0 ml, 911 mmol), and pyridine (220 ml, 2.72 mol) was stirred at r.t. for 1 h, poured into H_2O, and extracted with AcOEt. The org. soln. was washed with H_2O, sat. $CuSO_4$ soln., H_2O, and brine, and evaporated: **14** (66.3 g, 89%), which was recrystallized from benzene. Colorless prisms. M.p. 162–164° ([12]: 158–159°). IR (nujol): 1757. ^{1}H-NMR (400 MHz): 2.47 (*s*, 2 Ac); 7.29 (*dd*, *J* = 7.7, 0.9, H–C(4), H–C(8)); 7.50 (*dd*, *J* = 7.7, 7.7, H–C(3), H–C(7)); 7.78 (*dd*, *J* = 7.7, 0.9, H–C(2), H–C(6)). EI-MS: 244 (10, M^+), 160 (100).

5-Acetoxy-2-bromonaphthalene-1,4-dione (**24**). A soln. of NBS (167 mg, 0.936 mmol) in AcOH (2.3 ml) and H_2O (5.2 ml) was added to a soln. of **23** (50 mg, 0.21 mmol) in AcOH (2.3 ml) at 50°. The mixture was stirred at 50° for 1.5 h, poured into H_2O, and extracted with $CHCl_3$. The org. soln. was washed with H_2O, sat. $NaHCO_3$ soln., H_2O, and brine and evaporated. Recrystallization of the residue from EtOH gave **24** (48 mg, 84%). Orange needles. M.p. 150–155° ([20]: 154.5–156°). IR (nujol): 1773, 1678. ^{1}H-NMR (400 MHz): 2.44 (*s*, Ac); 7.39 (*s*, H–C(3)); 7.42 (*dd*, *J* = 7.9, 1.3, H–C(6)); 7.78 (*dd*, *J* = 7.9, 7.9, H–C(7)); 8.15 (*dd*, *J* = 7.9, 1.3, H–C(8)). EI-MS: 280 (2, $[M-{}^{81}Br]^+$), 278 (0.2, $[M-{}^{79}Br]^+$), 254 (40), 84 (100).

2-Bromo-5-hydroxynaphthalene-1,4-dione (**25**). A mixture of **24** (501 mg, 1.70 mmol) in EtOH (17.8 ml) and 1.5M H_2SO_4 (5.6 ml, 8.10 mmol) was refluxed for 2.5 h with stirring and extracted with AcOEt. The org. soln. was washed with H_2O and brine and evaporated. Purification of the residue by CC (hexane/AcOEt 15 : 1) gave **25** (340 mg, 79%). Yellow prisms. M.p. 125–129° ([25]: 135–136°). IR (nujol): 3095, 1676, 1636. ^{1}H-NMR (400 MHz): 7.32 (*dd*, *J* = 7.7, 1.1, H–C(8)); 7.50 (*s*, H–C(3)); 7.65 (*dd*, *J* = 7.7, 7.7, H–C(7)); 7.74 (*dd*, *J* = 7.7, 1.1, H–C(6)); 11.78 (*s*, OH). EI-MS: 254 (3, $[M-{}^{81}Br]^+$), 278 (3, $[M-{}^{79}Br]^+$), 149 (100).

2-Bromo-5-methoxynaphthalene-1,4-dione (**26**). A mixture of **25** (35.4 g, 140 mmol), MeI (19.2 ml, 308 mmol), and Ag_2O [26] (35.6 g, 154 mmol) in CH_2Cl_2 (1000 ml) was stirred at r.t. for 1 day. After further addition of Ag_2O (17.8 g, 76.9 mmol) and MeI (9.5 ml, 153 mmol), the mixture was stirred at r.t. for 1 day. Insoluble materials were filtered off and washed with $CHCl_3$. The filtrate and the washings were combined and evaporated. Recrystallization of the residue from EtOH gave **26** (27.6 g, 74%). Purification of the mother liquor by CC (hexane/AcOEt 3 : 1) after evaporation afforded additional **26** (6.63 g, 18%). Red prisms. M.p. 118–120° ([25]: 131–133°). IR (nujol): 1676, 1649. ^{1}H-NMR (400 MHz): 4.02 (*s*, MeO); 7.35 (*d*, *J* = 8.2, H–C(8)); 7.41 (*s*, H–C(3)); 7.70 (*dd*, *J* = 8.2, 8.2, H–C(7)); 7.74 (*d*, *J* = 8.2, H–C(6)). EI-MS: 268 (79, $[M-{}^{81}Br]^+$), 266 (76, $[M-{}^{79}Br]^+$), 129 (100).

2-Bromo-1,4,5-trimethoxynaphthalene (**27**). A suspension of $SnCl_2 \cdot 2\,H_2O$ (3.95 g, 17.0 mmol) in conc. HCl soln. (4.17 ml, 42.2 mmol) was added to a suspension of **25** (1.34 g, 5.00 mmol) in EtOH (54.0 ml). The mixture was stirred at 50° for 40 min, poured into ice-water (20 ml) and extracted with Et_2O. The org. soln. was washed with H_2O and brine and evaporated. A soln. of the residual brown solid (1.71 g) in DMF (20 ml) was added to a suspension of NaH (60%; 603 mg, 15.1 mmol; washed with dry hexane before use) in DMF (20 ml) at 0°, and the mixture was stirred at 0° for 2 h. After addition of a soln. of MeI (0.93 ml, 14.9 mmol) in DMF (10 ml), the mixture was stirred at r.t. for 21.5 h, poured into H_2O, and extracted with $CHCl_3$. The org. soln. was washed with H_2O and brine and evaporated. Purification of the residue by CC (hexane/AcOEt 10 : 1) gave **27** (1.14 g, 77%). Pale yellow prisms. M.p. 115–116.5° ([25]: 115–117°). ^{1}H-NMR (400 MHz): 3.92, 3.94, 3.97 (3*s*, 3 MeO), 6.90 (*d*, *J* = 8.0, H–C(8)); 6.91 (*s*, H–C(3)); 7.44 (*dd*, *J* = 8.0, 8.0, H–C(7)); 7.69 (*dd*, *J* = 8.0, 1.0, H–C(6)). EI-MS: 298 (57, $[M-{}^{81}Br]^+$), 296 (58, $[M-{}^{79}Br]^+$), 281 (100).

1,4,5-Trimethoxynaphthalene-2-carbaldehyde (**28**). At −70°, 1.48M BuLi in hexane (48.0 ml, 71.0 mmol) was added to a soln. of **27** (19.2 g, 64.5 mmol) in THF (190 ml) under Ar, and the mixture was stirred at −70° for 1 h. After slow addition of DMF (10 ml, 129 mmol) during 1 h, the mixture was stirred at −70° for 30 min, quenched with sat. NH_4Cl soln. (100 ml) and extracted with AcOEt. The org. soln. was washed with H_2O and brine and evaporated. Purification of the residue by CC (hexane/AcOEt 5 : 1) gave **28** (13.3 g, 84%). Pale yellow prisms. M.p. 75–78°. IR (nujol): 1675. ^{1}H-NMR (400 MHz): 3.99, 4.00, 4.07 (3*s*, 3 MeO), 7.06 (*d*, *J* = 8.2, H–C(8)); 7.13 (*s*, H–C(3)); 7.52 (*dd*, *J* = 8.2, 8.2, H–C(7)); 7.84 (*d*, *J* = 8.2, H–C(6)); 10.56 (*s*, CHO). EI-MS: 246 (28, M^+), 231 (20), 102 (100). Anal. calc. for $C_{14}H_{14}O_4$: C 68.28, H 5.73; found: C 68.43, H 5.70.

*(2*E*)-3-(1,4,5-Trimethoxynaphthalen-2-yl)prop-2-enoic Acid* (**29**). A mixture of **28** (6.35 g, 25.8 mmol), malonic acid (5.37 g, 51.6 mmol), pyridine (11.9 ml, 147 mmol), and piperidine (0.51 ml, 5.16 mmol) was sonicated at r.t. for 8.3 h. After acidification with 10% HCl soln. (pH 1), precipitates were collected by filtration, washed with H_2O, and dried to give yellow needles (7.51 g). The filtrate was extracted with AcOEt. The org. soln. was washed with H_2O and brine and evaporated to give a yellow solid (1.20 g). The solids were combined and recrystallized from EtOH to give **29** (6.91 g, 93%). Yellow needles. M.p. 171–173°. IR (nujol): 1676, 1593. ^{1}H-NMR (400 MHz): 3.93, 3.99, 4.00 (3*s*, 3 MeO); 6.54 (*dd*, *J* = 16.0, 1.4, CH=*CH*COOH); 6.92 (*s*, H–C(3));

6.97 (*d*, *J* = 8.2, H–C(8)); 7.47 (*dd*, *J* = 8.2, 8.2, H–C(7)); 7.76 (*d*, *J* = 8.2, H–C(6)); 8.27 (*dd*, *J* = 16.0, 1.4, C*H*=CHCOOH). EI-MS: 288 (100, M^+). Anal. calc. for $C_{16}H_{16}O_5$: C 66.66, H 5.59; found: C 66.76, H 5.68.

Catalytic Hydrogenation of **29**: *1,4,5-Trimethoxynaphthalene-2-propanoic Acid* (**13**). A suspension of 5% Pd/C (1.12 g) in EtOH (330 ml) was stirred at r.t. for 1 h under H_2, and then **29** (11.2 g, 38.8 mmol) was added. The mixture was vigorously stirred under the same conditions for 21 h, and insoluble materials were filtered through a *Celite* pad. Evaporation of the filtrate followed by recrystallization from EtOH gave **13** (10.47 g, 93%). Colorless prisms. M.p. 122–123°. Data identical with those of the sample obtained from **22**.

*4,8,9-Trimethoxy-1*H-*benz[*f*]inden-1-one* (**11**). A mixture of **12** (2.00 g, 7.35 mmol) and IBX (95%; 8.67 g, 29.4 mmol) in DMSO (37 ml) and chlorobenzene (73 ml) was stirred at 65° (bath temp.) for 43.5 h under Ar and diluted with AcOEt (200 ml). Insoluble materials were filtered off, and the filtrate was washed with sat. $NaHCO_3$ soln., H_2O, and brine and evaporated. Purification by CC (benzene/AcOEt 10:1) gave **11** (1.50 g, 76%). Yellow prisms. M.p. 105–108°. IR (nujol): 1700. ^{1}H-NMR (400 MHz): 3.97, 4.01, 4.07 (3*s*, 3 MeO); 6.05 (*d*, *J* = 5.9, H–C(2)); 6.94 (*d*, *J* = 8.0, H–C(7)); 7.47 (*dd*, *J* = 8.0, 8.0, H–C(6)); 7.69 (*dd*, *J* = 8.0, 1.1, H–C(5)); 7.87 (*d*, *J* = 5.9, H–C(3)). EI-MS: 270 (74, M^+), 241 (77), 84 (100). Anal. calc. for $C_{16}H_{14}O_4$: C 71.10, H 5.22; found: C 71.17, H 5.22.

*(±)-(1*R*,4a*S*,11a*S*)-1,4,4a,11a-Tetrahydro-1,5,10-trimethoxy-2-methyl-3-[(trimethylsilyl)oxy]-11*H-*benzo[*b*]fluoren-11-one* (**10**). A suspension of **11** (152 mg, 0.56 mmol) and **7** (254 mg, 1.36 mmol) in CH_2Cl_2 (1.0 ml) containing $ZnCl_2$ (8.2 mg, 0.062 mmol) was stirred at −15° for 1 h, poured into H_2O (2.0 ml), and extracted with $CHCl_2$. The org. soln. was washed with H_2O and brine and evaporated: **10** (456 mg). Pale yellow prisms, which were used in the next step without further purificaton.

*(±)-(4a*S*,11a*R*)-4,4a,11,11a-Tetrahydro-5,9,10-trimethoxy-2-methyl-3*H-*benzo[*b*]fluorene-3,11-dione* (**30**). A soln. of crude **10** (456 mg) and CSA (27 mg, 0.12 mmol) in CH_2Cl_2 (1.0 ml) was stirred at 0° for 2 h, quenched with sat. $NaHCO_3$ soln. (4.0 ml), and extracted with $CHCl_3$. The org. soln. was washed with H_2O and brine and evaporated: **30** (320 mg). Red oil, which was used in the next step without further purification.

*(±)-(4a*S*,11a*S*)-3,4,4a,11a-Tetrahydro-11a-hydroxy-5,9,10-trimethoxy-2-methyl-3*H-*benzo[*b*]fluorene-3,11-dione* (**31**). A mixture of crude **30** (320 mg) and KF (3.9 mg, 0.067 mmol) in DMSO (1.5 ml) was stirred at r.t. for 2 h under air, poured into H_2O (6 ml), and extracted with AcOEt. The org. soln. was washed with H_2O and brine and evaporated. Purification of the residue by CC (benzene/AcOEt 3:1) gave **31** (100 mg,48% over 3 steps). Red oil. IR ($CHCl_3$): 3520, 1707, 1677. ^{1}H-NMR (400 MHz): 1.72 (*d*, *J* = 1.3, Me–C(2)); 3.14 (*dd*, *J* = 16.5, 6.8, 1 H, CH_2(4)); 3.44 (br. *s*, OH–C(11a), exchangeable); 3.46 (*dd*, *J* = 16.5, 2.7, 1 H, CH_2(4)); 3.91, 4.00, 4.01 (3*s*, 3 MeO); 6.26 (*t*-like, *J* = 1.3, H–C(1)); 6.91 (*d*, *J* = 8.1, H–C(6)); 7.56 (*dd*, *J* = 8.1, 8.1, H–C(7)); 7.71 (*d*, *J* = 8.1, H–C(8)). ^{13}C-NMR (150 MHz): 15.9; 35.8; 41.7; 56.3; 61.2; 63.2; 78.2; 106.9; 114.6; 121.4; 121.5; 130.3; 133.1; 136.6; 138.8; 148.9; 155.1; 159.3; 168.8; 201.0. HR-FAB-MS: 368.1251 ($C_{21}H_{20}O_6^+$; calc. 368.1260).

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