Syntheses of Prekinamycin and a Tetracyclic Quinone from Common Synthetic Intermediates

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Towards total synthesis of a series of kinamycin and related antibiotics *via* common synthetic intermediates, total synthesis of prekinamycin was achieved *via Suzuki* coupling of naphthaleneboronic acid and bromobenzene derivative, intramolecular *Friedel–Crafts* reaction of 2-(naphthalen-2-yl)benzoic acid, and diazotization in ten steps from 3,5-dimethylphenol. Synthetic studies towards kinamycin antibiotics was also examined, and the tetracyclic quinone core for kinamycins was synthesized. Palladium-catalyzed site-selective hydroxylation of a benzoic acid derivative with the *AB-D* ring part was successfully applied to the selective *D*-ring functionalizations.

Introduction. – Kinamycin antibiotics [1] were isolated from culture broth of *Streptomyces murayamaensis* by *Ōmura* and co-workers [2], and they possess antiviral activity towards *Gram*-positive bacteria as well as antitumor activity [2b][2]). The structure was at first determined as *N*-cyanobenzo[*b*]carbazoloquinone **1** (*cf. Fig. 1*) [4]. Later, the so called 'prekinamycin' was isolated from the same bacterium by *Seaton* and *Gould* [5], which was identified as **2**, with an aromatized *D* ring of **1**. Reinvestigation of spectroscopic data [6], the isolation of other metabolites [7], and synthetic studies of kinamycins [8–10] including our work [11] resulted in the revision of the structures: *i*) Kinamycins are not cyanamides **1** but diazo alkanes **3**. *ii*) The structure of so-called 'prekinamycin' isolated by *Seaton* and *Gould* (*vide infra*) was revised as, temporarily, diazobenzo[*b*]fluorene **4** [6a][6b] and, finally, diazobenzo[*a*]fluorene **5**, renamed as isoprekinamycin [6c]. *iii*) The compound with the structure **4** was isolated as a metabolite produced by *S. murayamensis* mutant MC2 [7] and finally named as prekinamycin [6c]. Recent progress on the isolation [12] and synthetic studies [13] of the antitumor antibiotic lomaiviticin A (**6**), a dimerized diazobenzo[*b*]fluorene, confirms the importance of this class of natural products.

We have continued efforts for synthetic studies towards polyketide antibiotics such as kinamycins (**3**) [11][14] and jadomycin A (**7**) [15] (*Fig. 1*). Next, we planned the total synthesis of these antibiotics including prekinamycin (**4**) *via* common synthetic intermediates. We herein report the total synthesis of prekinamycin (**4**) and a tetracyclic quinone towards kinamycins, **3**.

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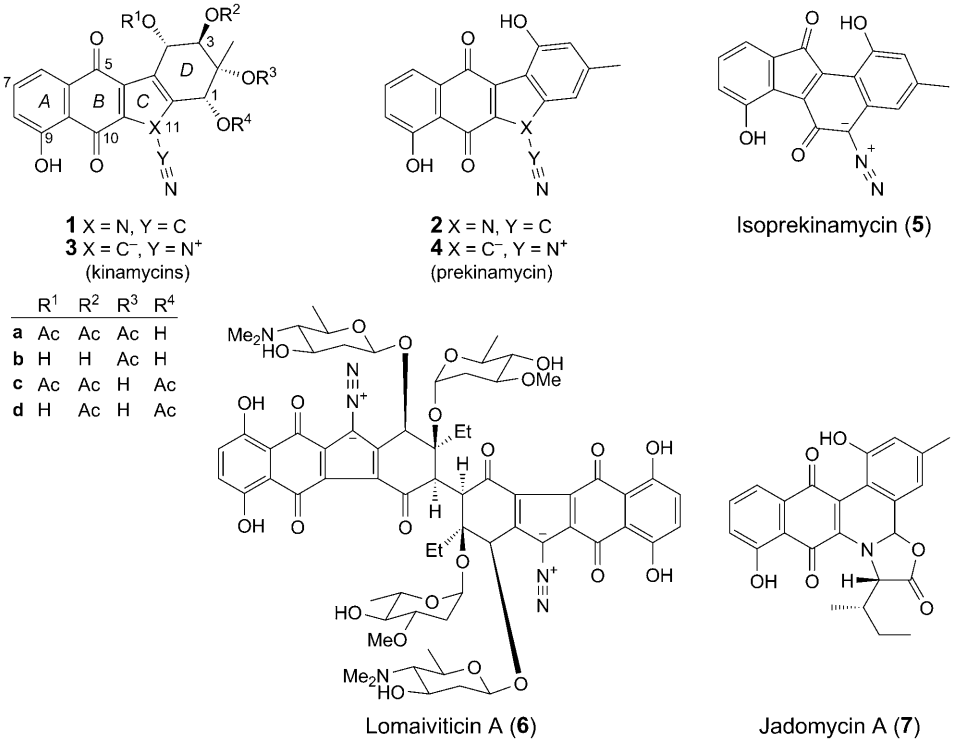
[2]) For examples of recent studies on cytotoxicity of kinamycins and related compounds, see [3].



	R^1	R^2	R^3	R^4
a	Ac	Ac	Ac	H
b	H	H	Ac	H
c	Ac	Ac	H	Ac
d	H	Ac	H	Ac

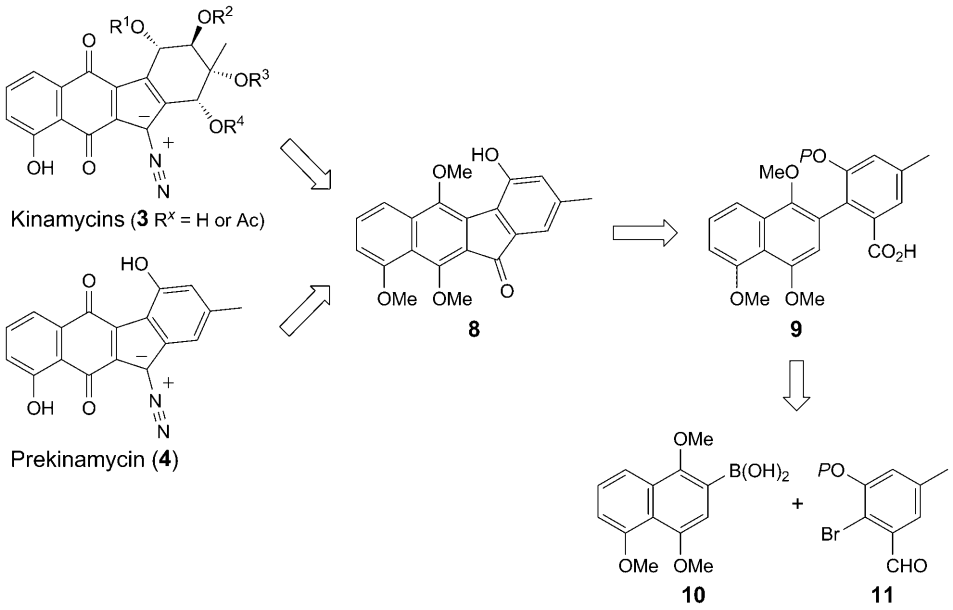
Fig. 1. *Structures of kinamycin and the related antibiotics*

Results and Discussion. – We considered benzofluorenone **8** or 2-(naphthalen-2-yl)benzoic acid **9**[3]) as the common synthetic intermediates, accessible by *Suzuki* coupling of oxygenated naphthalene-2-boronic acid **10** and bromobenzene **11** with a more labile protecting group (*P*) than the Me group on the phenolic OH group on ring *D* for selective functionalization (*Scheme 1*). We started the synthesis of these intermediates according to a modified procedure reported by *Koyama* and *Kamikawa* [16b].

At first, the (*tert*-butyl)(dimethyl)silyl (TBS) group was chosen as the protecting group of phenol OH on ring *D*. One of the benzylic Me groups of the TBS ether **12b** derived from 3,5-dimethylphenol (**12a**) was brominated by *N*-bromosuccinimide (NBS) in the presence of catalytic amount of azobis[isobutyronitrile] (AIBN) in refluxing cyclohexane (*Scheme 2*). Benzyl bromide **13b** was treated with 2-nitropropane and NaH under *Hass–Bender* condition [17] to afford aldehyde **14b** [18]. Site-selective lithiation–bromination *via* aminal **15b** from aldehyde **14b** and lithium amide, prepared from *N*,*N*,*N*′-trimethylethylenediamine and BuLi, gave the desired bromo derivative **16b** only in 9% yield. Expecting a more rigid chelation toward lithium cation like **15c′**, the protecting group was changed from TBS to the methoxymethyl (MOM) group.

[3]) For similar intermediates employed for the syntheses of gilvocarcin aglycon and stealthin derivatives, respectively, see [16].

Scheme 1. *Retrosynthetic Analysis of Kinamycins* (**3**) *and Prekinamycin* (**4**)



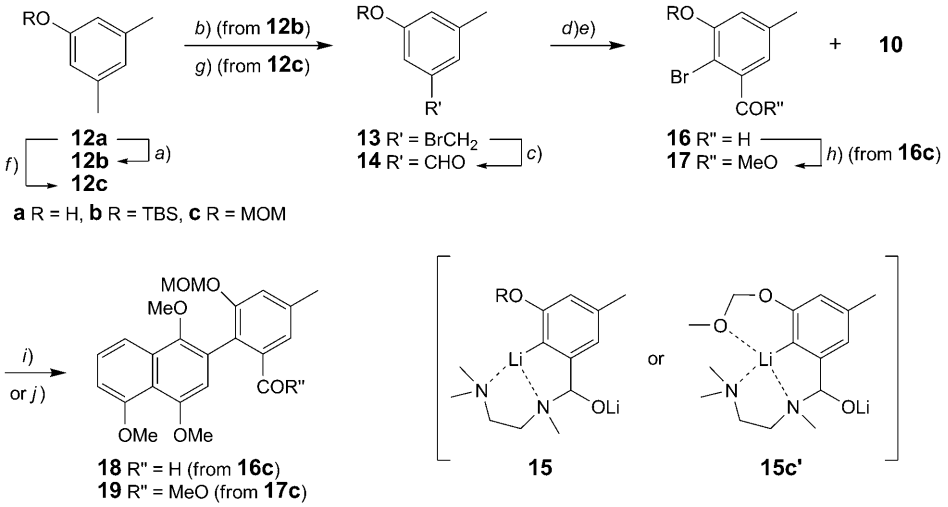
Thus, the MOM-protected aldehyde **14c**, prepared in a similar manner as **14b**, *via* MOM ether **12c** was subjected to the same bromination condition, and the desired **16c** was obtained in improved yield (58%). Methyl ester **17c** was prepared as an alternative substrate for *Suzuki* coupling by oxidation of aldehyde **16c** with I_2 in the presence of KOH in MeOH [19]. *Suzuki* coupling reaction with naphthalene-2-boronic acid **10** [16] and bromo-benzaldehyde **16c** in 1,2-dimethoxyethane (DME) for the conjunction of *AB* and *D* ring parts gave the desired 2-(naphthalen-2-yl)benzaldehyde **18** in 97% yield. However, application of ester **17c** for this reaction failed: only a trace amount of the desired ester **19** was obtained. The yield of **19** could not be improved even by using another solvent system such as benzene/EtOH [16a] instead of DME (*Scheme 2*).

Next, oxidation of aldehyde **18c** to ester **19** and carboxylic acid **20** was attempted. No reaction occurred with I_2/KOH in MeOH [19]. Quinone ketal **21**[4]) and the corresponding epoxide **22** (*Fig. 2*) were generated instead of the desired **20** with $NaClO_2$ [20]. Only the system $NaOH/H_2O_2$ [16b] gave the desired carboxylic acid **20**. Attempts of intramolecular *Friedel–Crafts* reaction (IFCR) of **20** in a one-pot procedure with $(CF_3CO)_2O$ [8a] or $POCl_3/K_2CO_3$ [21] led to complex mixtures. Conversion of acid **20** to acid chloride **23** with $(COCl)_2$ in CH_2Cl_2 at room temperature, followed by IFCR with $SnCl_4$ [16b], gave the key MOM-deprotected benzo[*b*]fluorenone **8** only in 4% yield (*Scheme 3*). Preparation of acid chloride **23** in MeCN instead of CH_2Cl_2 as a solvent at higher temperature (80°) and application of $AlCl_3$ as a *Lewis* acid for IFCR improved the yield of **8** up to 81%[5]). Demethylation of **8** with BBr_3 gave

[4]) For similar oxidation reaction with ceric ammonium nitrate (CAN), see [16a].

[5]) Yields of IFCR with other *Lewis* acids: $TiCl_4$, 33%; $SnCl_4$, 67%.

Scheme 2. *Synthesis of 2-(Naphthalen-2-yl)benzaldehyde* **18**



a) TBSCl, 1*H*-imidazole, DMF, r.t., 1.5 h; 98%. *b*) NBS, AIBN, cyclohexane, reflux, 1 h; 88%. *c*) NaH, 2-nitropropane, DMF, 0°, 2 h; 85% for **14b** from **13b**, and 58% for **14c** from **12c**. *d*) 1. *N,N,N′*-Trimethylethylenediamine, BuLi, THF, −65°, 30 min, then **14**, −65°, 45 min; 2. BuLi, −20°, 10–30 h. *e*) $BrCF_2CF_2Br$, r.t., 1.5 h; 9% for **16b**, 58% for **16c**. *f*) MOMCl, NaH, DMF, r.t., 4 h; 84%. *g*) NBS, benzoyl peroxide, CCl_4, reflux, 1 h. *h*) I_2, KOH, MeOH, r.t., 4 h; 92%. *i*) $Pd(PPh_3)_4$, 2M aq. Na_2CO_3, DME, 90°, 48 h; 97% for **18**, trace for **19**. *j*) $Pd(PPh_3)_4$, 2M aq. Na_2CO_3, benzene/EtOH 1:1, reflux, 48 h; 10% for **19** from **17c**.

tetraol **24**, to which $TsNHNH_2$ was added to afford hydrazone **25**. Oxidation of the hydrazone and hydroquinone part of **25** by *Fetizon*'s reagent (Ag_2CO_3 on *Celite*®) [22] gave prekinamycin (**4**) in 47% yield in three steps from **8** (*Scheme 3*). In this study, we have achieved the total synthesis of prekinamycin (**4**) in 7% yield in ten steps from 3,5-dimethylphenol (**12a**).

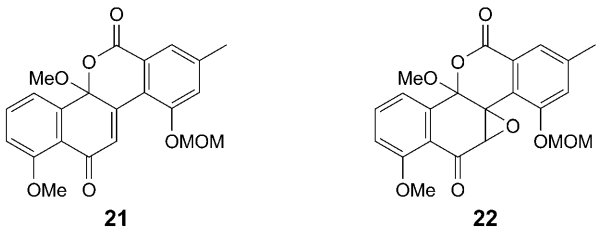
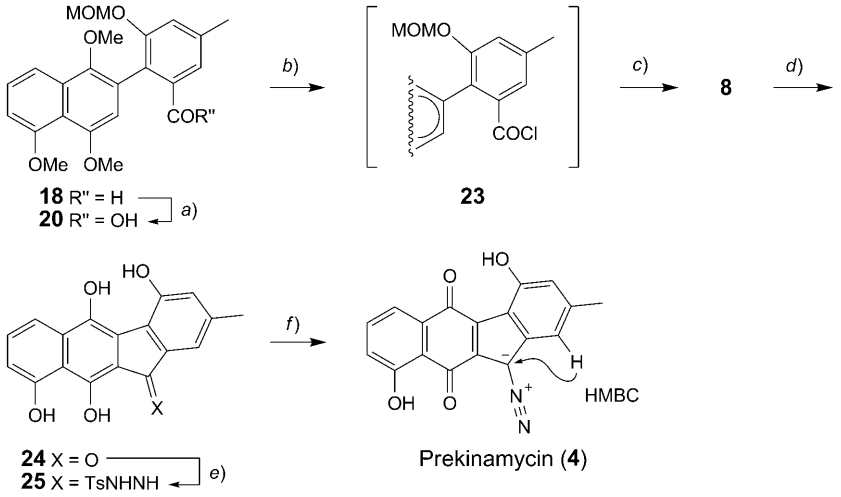


Fig. 2. *Structures of products of $NaClO_2$ oxidation of aldehyde* **18**

Neither the ^{13}C-NMR chemical shift of the diazo alkane C-atom, nor the molecular-ion peak in the mass spectrum of prekinamycin (**4**) were reported in the precedent examples of isolation [7] and total syntheses [9]. Our attempt to detect the ^{13}C-NMR

Scheme 3. *Synthesis of Prekinamycin* (**4**)



a) 15% NaOH, 30% H_2O_2, MeOH, 120°, 1 h; 80%. *b*) $(COCl)_2$, MeCN, 80°, 10 min. *c*) $AlCl_3$, CH_2Cl_2, r.t., 2.5 h; 81%. *d*) BBr_3, CH_2Cl_2, −40°, 24 h. *e*) $TsNHNH_2$, 1M HCl, EtOH, 90°, 2 h. *f*) *Fetizon*'s reagent, Et_3N, MeCN, r.t., 30 min; 47% in 3 steps.

signal failed probably because of the low solubility of **4** in $CDCl_3$, C_6D_6, and (D_6)acetone, and the low sensitivity of quaternary diazo alkane C-atom. Application of HMBC technique resulted in the detection of a cross-peak from 6.85 ppm in ^{1}H-NMR (H–C(4)) to *ca.* 70.5 ppm in ^{13}C-NMR[6]), which implies that the signal derived from diazo alkane C-atom of prekinamycin (**4**) could be observed at *ca.* 70.5 ppm[7]). On the other hand, the molecular-ion peak was not detected in EI- or FAB-MS of **4**, but the application of negative-ion-mode ESI-MS led to the observation of the molecular-ion peak of **4** (*m/z* 317.0576; calc. for $C_{18}H_9N_2O_4$: 317.0562).

Next, we proceeded to synthetic studies towards kinamycins including phenol oxidation of *D* ring of **8** to quinone **28**, followed by stereoselective introduction of the O-functionality (*Scheme 4*)[8]). Iodosobenzene bis(trifluoroacetate) (PIFA) [26] oxidation of **8** in MeCN/H_2O led to *B*-ring oxidation to give the undesired quinone **29** in 11% yield, whereas the reaction in MeOH gave quinone ketal **30** in 72% yield. The position of ketal C-atom in **30** was identified as C(11) by HMBC correlation with H–C(10). On the other hand, ceric ammonium nitrate (CAN) oxidation of **8** led to the desired **28** and undesired quinone **29**, each in low yield (13–22%). Trials for oxidation of **8** to **28** and the corresponding alcohol **31** to **32**, expecting the increase of electron

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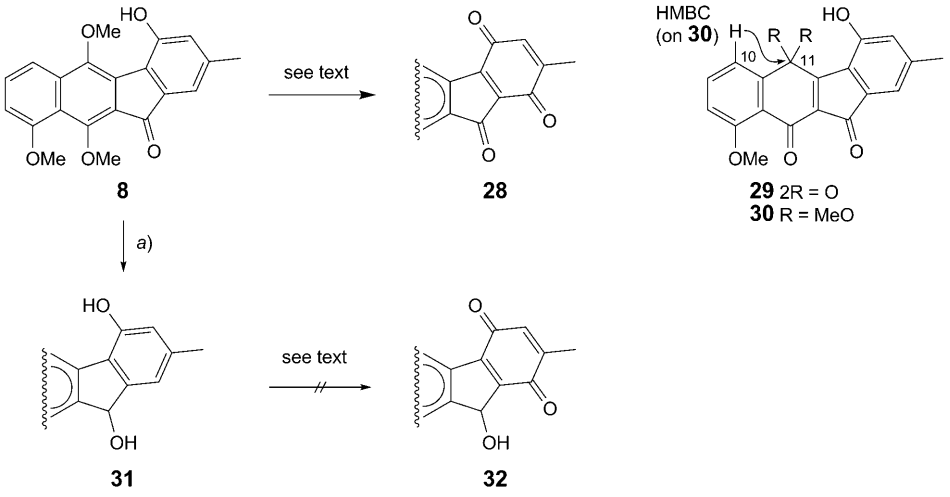
6) A similar correlation on a long-range heteronuclear COSY experiment of kinamycin D was reported: see [23]; see also [6b].

7) ^{13}C-NMR Chemical shifts of diazo alkane C-atom of 1,7-*O*-diacetylprekinamycin and 1,7-*O*-dimethylprekinamycin-11-^{13}C were reported as 70.53 (in CD_2Cl_2) [9a] and 69.99 ppm (in $CDCl_3$) [24], respectively.

8) When we started this research, stereoselective introduction of the O-functionality towards naphthoquinone derivatives to model *D* ring core of kinamycin F was reported; see [25].

Scheme 4. *Trials for Oxidation of* D *Rings of* **8** *and* **31**

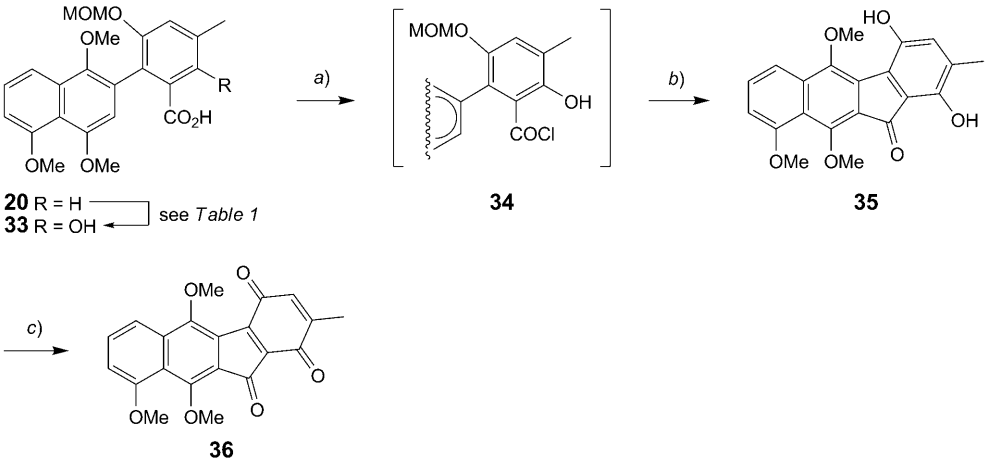


a) $NaBH_4$, $CeCl_3 \cdot 7\ H_2O$, EtOH, r.t., 5 h; 99%.

density on *D* ring, with *Fremy*'s salt (potassium nitrosodisulfonate; $K_2NO(SO_3)_2$) [27] or salcomine/O_2 system [28] were unsuccessful.

Consequently, transformation of carboxylic acid **20** was investigated (*Scheme 5*). Palladium-catalyzed *ortho*-selective hydroxylation of benzoic acid derivatives reported by *Zhang* and *Yu* [29] was applied for the site-selective introduction of the O-functionality of *D* ring in **20** (*Table*). In the first trial based on the reported procedure (catalytic amount of $Pd(OAc)_2$, stoichiometric amount of AcOK, and *p*-benzoquinone

Scheme 5. *Synthesis of Quinone* **36**



a) $(COCl)_2$, MeCN, 80°, 10 min. *b*) $FeCl_3$, CH_2Cl_2, THF, r.t., 90 min; 73% from **33**. *c*) Ag_2O, $MgSO_4$, THF, O_2, r.t., 7 h; 91%.

Table. *Pd-Catalyzed Hydroxylation of Carboxylic Acid* **20**[a])

Entry	PdX_2	Base	BQ [equiv.]	Temp. [°]	Time	**33** [%]
1	$Pd(OAc)_2$	AcOK	1.2	115	2 d	0
2	$Pd(OAc)_2$	AcOK	1.2	150	2 d	4
3	$Pd(OAc)_2$	AcOCs	1.2	150	1.5 d	33
4	$Pd(OAc)_2$	AcOCs	2.3	150	15 h	38
5[b])	$Pd(OAc)_2$	AcOCs	2.3	150	15 h	49
6[b])	$Pd(OAc)_2$	AcOCs	2.3	140	20 h	57
7[b])	$Pd(O_2CCF_3)_2$	AcOCs	2.3	140	20 h	62

[a]) PdX_2 (11 mmol-%), base (2.4 equiv.), BQ (*p*-Benzoquinone) in DMA under O_2 atmosphere was applied unless otherwise noted. [b]) O_2 was introduced *via* bubbling.

(BQ) in *N*,*N*-dimethylacetamide (DMA) at 115° under O_2 atmosphere) [29], phenol **33** could not be obtained (*Entry 1*). An experiment at elevated temperature, 150°, gave the desired **33** in 4% yield (*Entry 2*). Use of AcOCs as a base instead of AcOK (*Entry 3*), increase of equivalent of BQ (*Entry 4*), and introduction of O_2 gas *via* bubbling (*Entry 5*) led to improved yields. No reaction was observed, when air was bubbled through the mixture instead of O_2. Observing the generation of trace amount of by-products such as decarboxylated product at 150°, the same reaction was examined at 140° to afford **33** in 57% yield (*Entry 6*). Finally, application of palladium bis(trifluoroacetate) ($Pd(O_2CCF_3)_2$) instead of $Pd(OAc)_2$ gave the best yield (62%) among our trials (*Entry 7*).

Following IFCR of carboxylic acid **33** *via* acid chloride **34** with $SnCl_4$ gave the desired fluorenone **35** in 51% yield from **33**. The yield was improved with $FeCl_3$ to 73%. Successful oxidation of the hydroquinone part of **35** with Ag_2O under O_2 [30] afforded tetracyclic quinone **36** in 91% yield.

Conclusions. – Towards the total synthesis of a series of kinamycins and related antibiotics, we have completed the total synthesis of prekinamycin (**4**) from 3,5-dimethylphenol (**12a**) *via* fluorenone **8** in ten steps, including *Suzuki* coupling of naphthalene-2-boronic acid and bromobenzene derivative, intramolecular *Friedel–Crafts* reaction of 2-(naphthalen-2-yl)benzoic acid, and diazotization. In synthetic studies towards kinamycins from the common synthetic intermediate **8**, selective phenol oxidation on *D* ring failed. Pd-Catalyzed *ortho*-selective hydroxylation of benzoic acid **20**, followed by IFCR-oxidation sequence, gave the desired quinone **36**. Trials for stereoselective introduction of the O-functionalities of quinone **36** and completion of the total synthesis of kinamycins are now in progress.

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Experimental Part

General. Anh. CH_2Cl_2 and DMF were used as purchased from *Kanto Chemical*, and anh. THF was used as purchased from *Wako Chemical*. TLC: *Merck Art 5715 DC-Fertigplatten Kieselgel 60* F_{254}.

Column chromatography (CC): *Kanto Chemical* silica gel *60 spherical*. M.p.: *Yanagimoto MPSI* melting point apparatus; uncorrected. IR Spectra: Attenuated Total Reflectance (ATR) system on a *JASCO FT/IR-300E* spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *JEOL JNM-ECP-400*, *JNM-ECA-600*, and *JNM-ECP-600* instruments; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *JEOL JNM MS-GCMATE* for EI-MS, *JEOL JNM HX-110* for HR-FAB-MS, and *JEOL AccuTOF* and *Thermo Scientific Exactive* system for HR-ESI-MS, resp.; in *m/z* (rel. %).

(1,4,5-Trimethoxynaphthalen-2-yl)boronic Acid (**10**). BuLi (1.59M; 0.95 ml, 1.51 mmol) was added to a soln. of 2-bromo-1,4,5-trimethoxynaphthalene (300 mg, 1.01 mmol) in THF (3 ml) at $-78°$, and the mixture was stirred at $-78°$ for 1 h. $(i\text{-}PrO)_3B$ (0.46 ml, 2.99 mmol) was added, and the mixture was stirred at $-78°$ for 15 min and at r.t. for 1 h. H_2O (10 ml) and 5% HCl (10 ml) were added, and the mixture was extracted with CH_2Cl_2 (3×10 ml). The combined org. layers were washed with H_2O (2×10 ml) and brine (1×10 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt 10:1) to give **10** (215 mg, 81%). Colorless needles. ^1H-NMR (400 MHz): 3.95 (*s*, 3 H); 3.99 (*s*, 3 H); 4.00 (*s*, 3 H); 6.51 (br. *s*, 2 H); 6.95 (*d*, *J* = 7.8, 1 H); 7.17 (*s*, 1 H); 7.45 (*dd*, *J* = 8.3, 7.8, 1 H); 7.67 (*dd*, *J* = 8.3, 1.0, 1 H).

*1-{[(*tert*-Butyl)(dimethyl)sily]oxy}-3,5-dimethylbenzene* (**12b**). A mixture of **12a** (4.63 g, 37.9 mmol), 1*H*-imidazole (8.01 g, 118 mmol), and TBSCl (6.80 g, 45.1 mmol) in DMF (4.5 ml) was stirred at r.t. for 1.5 h. AcOEt (75 ml) was added, and the mixture was washed with H_2O (10×10 ml) and brine (1×10 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane) to give **12b** (8.75 g, 98%). Colorless oil. IR: no characteristic absorption. ^1H-NMR (400 MHz): 0.20 (*s*, 6 H); 1.00 (*s*, 9 H); 2.27 (*s*, 6 H); 6.48 (*s*, 2 H); 6.61 (*s*, 1 H). ^{13}C-NMR (100 MHz): −4.4; 18.2; 21.3; 25.7; 117.8; 123.0; 139.0; 155.5. HR-EI-MS: 236.1608 (M^+, $C_{14}H_{24}OSi^+$; calc. 236.1596).

*1-(Bromomethyl)-3-{[(*tert*-butyl)(dimethyl)sily]oxy}-5-methylbenzene* (**13b**). A mixture of **12b** (8.75 g, 37.0 mmol), NBS (7.63 g, 42.9 mmol), and AIBN (365 mg, 2.22 mmol) in cyclohexane (135 ml) was refluxed for 1 h. The reaction vessel was shielded from light with covering with alminium foil. After cooling, the mixture was filtered, and and the precipitate was washed with cyclohexane. The mixture was washed with H_2O (1×70 ml) and brine (1×70 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane) to give **13b** (10.3 g, 88%). Colorless oil. IR: no characteristic absorption. ^1H-NMR (400 MHz): 0.20 (*s*, 6 H); 0.99 (*s*, 9 H); 2.29 (*s*, 3 H); 4.40 (*s*, 2 H); 6.59 (*s*, 1 H); 6.68 (*s*, 1 H); 6.80 (*s*, 1 H). ^{13}C-NMR (100 MHz): −4.4; 18.1; 21.3; 25.6; 33.6; 117.7; 121.0; 122.8; 138.7; 139.8; 155.7. HR-EI-MS: 316.0707 (M^+, $C_{14}H_{23}{}^{81}BrOSi^+$; calc. 316.0681).

*3-{[(*tert*-Butyl)(dimethyl)sily]oxy}-5-methylbenzaldehyde* (**14b**). A mixture of NaH (60%, 41 mg, 1.70 mmol), washed with hexane (3×4 ml), and a soln. of 2-nitropropane (0.30 ml, 3.40 mmol) in DMF (6 ml) was stirred at 0° for 15 min. Compound **13b** (536 mg, 1.70 mmol) was added, and the mixture was stirred at 0° for 2 h. H_2O (20 ml) was added, and the aq. layer was neutralized with 10% HCl. The mixture was extracted with AcOEt (25 ml). The org. layer was washed with H_2O (10×10 ml) and brine (1×10 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt 10:1) to give **14b** (339 mg, 85%). Yellow oil. IR: 1701. ^1H-NMR (400 MHz): 0.22 (*s*, 6 H); 1.00 (*s*, 9 H); 2.38 (*s*, 3 H); 6.93 (*s*, 1 H); 7.13 (*s*, 1 H); 7.29 (*s*, 1 H); 9.91 (*s*, 9 H). ^{13}C-NMR (100 MHz): −4.5; 18.2; 21.3; 25.6; 177.2; 124.2; 127.2; 137.8; 140.3; 156.2; 192.2.

*2-Bromo-3-{[(*tert*-butyl)(dimethyl)sily]oxy}-5-methylbenzaldehyde* (**16b**). BuLi (1.40M; 0.50 ml, 0.71 mmol) was added to a soln. of *N,N,N′*-trimethylethylenediamine (0.10 ml, 0.77 mmol) in THF (0.15 ml) at −65°, and the mixture was stirred at −65° for 30 min. Compound **14b** (161 mg, 0.64 mmol) in THF (1.0 ml) was added at −65°, and the mixture was stirred at −65° for 45 min. BuLi (1.40M; 1.35 ml, 1.92 mmol) was added at −65°, and the mixture was stirred at −20° for 10 h. $BrCF_2CF_2Br$ (0.40 ml, 3.33 mmol) was added, and the mixture was stirred at r.t. for 1.5 h. H_2O (5 ml) was added, and the mixture was evaporated *in vacuo*. The residue was diluted with 10% HCl (5 ml) and extracted with CH_2Cl_2 (3×5 ml). The combined org. layers were washed with H_2O (1×5 ml) and brine (1×5 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt 20:1) to give **16b** (19 mg, 9%). Colorless needles. M.p. 112–116°. IR: 1668. ^1H-NMR (400 MHz): 0.41 (*s*, 6 H); 0.99 (*s*, 9 H); 2.32 (*s*, 3 H); 6.77 (*s*, 1 H); 7.40 (*s*, 1 H); 10.30 (*s*, 1 H). ^{13}C-NMR (100 MHz): −0.09; 18.4; 20.9; 27.1; 121.1; 121.2; 121.7; 141.3; 144.4; 161.5; 194.6.

1-(Methoxymethoxy)-3,5-dimethylbenzene (**12c**). MOMCl (0.93 ml, 12.3 mmol) was added to a mixture of NaH (60%, 654 mg, 16.4 mmol), washed with hexane (3 × 10 ml), and **12a** (1.00 g, 8.18 mmol) in DMF (6 ml) at 0°, and the mixture was stirred at r.t. for 4 h. Ice-H_2O (20 ml) was added, and the mixture was extracted with hexane (1 × 25 ml). The org. layer was washed with H_2O (10 × 10 ml) and brine (1 × 10 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt 100:1 to 10:1) to give **12c** (1.14 g, 84%). Colorless oil. IR: no characteristic absorbtion. ^{1}H-NMR (400 MHz): 2.29 (*s*, 6 H); 3.47 (*s*, 3 H); 5.15 (*s*, 2 H); 6.66 (*s*, 1 H); 6.67 (*s*, 2 H). ^{13}C-NMR (100 MHz): 21.4; 55.9; 94.3; 113.9; 123.6; 139.2; 157.2. HR-EI-MS: 166.0998 (M^+, $C_{10}H_{14}O_2^+$; calc. 166.0994).

3-(Methoxymethoxy)-5-methylbenzaldehyde (**14c**). A mixture of **12c** (100 mg, 0.60 mmol), NBS (118 mg, 0.66 mmol), and benzoyl peroxide (15 mg, 0.06 mmol) in CCl_4 (10 ml) was refluxed for 1 h. After cooling, the mixture was filtered, and the precipitate was washed with CCl_4. The filtrate and the washing were combined and washed with H_2O (1 × 5 ml) and brine (1 × 5 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residual crude **13c** was used in the next step without further purification. A mixture of NaH (60%, 36 mg, 0.90 mmol), washed with hexane (3 × 5 ml), and 2-nitropropane (0.11 ml, 1.20 mmol) in DMF (6 ml) was stirred at 0° for 15 min. A soln. of crude **13c** (*vide infra*) in DMF (1 ml) was added, and the mixture was stirred at r.t. for 2 h. Ice-H_2O (5 ml) was added, and the aq. layer was neutralized with 10% HCl. The mixture was extracted with hexane (25 ml). The org. layer was washed with H_2O (3 × 10 ml) and brine (1 × 10 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt 25:1 to 10:1) to give **14c** (63 mg, 58%; 2 steps). Yellow oil. IR: 1698. ^{1}H-NMR (400 MHz): 2.41 (*s*, 3 H); 3.49 (*s*, 3 H); 5.22 (*s*, 2 H); 7.12 (br. *s*, 1 H); 7.35 (br. *s*, 2 H); 9.93 (*s*, 1 H). ^{13}C-NMR (100 MHz): 21.2; 56.1; 94.3; 113.4; 123.4; 124.4; 137.7; 140.5; 157.6; 192.2. HR-EI-MS: 180.0786 (M^+, $C_{10}H_{12}O_3^+$; calc. 180.0786).

2-Bromo-3-(methoxymethoxy)-5-methylbenzaldehyde (**16c**). BuLi (1.57M; 11.4 ml, 17.8 mmol) was added to a soln. of *N*,*N*,*N*′-trimethylethylenediamine (2.50 ml, 19.5 mmol) in THF (2 ml) at −65°, and the mixture was stirred at −65° for 30 min. A soln. of **14c** (2.92 g, 16.2 mmol) in THF (30 ml) was added at −65°, and the mixture was stirred at −65° for 45 min. BuLi (1.57M; 31.0 ml, 48.7 mmol) was added at −65°, and the mixture was stirred at −20° for 30 h. $BrCF_2CF_2Br$ (10.0 ml, 84.3 mmol) was added, and the mixture was stirred at r.t. for 1.5 h. H_2O (10 ml) was added, and the mixture was evaporated *in vacuo*. The residue was diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined org. layers were washed with H_2O (1 × 10 ml) and brine (1 × 10 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt 20:1) to give **16c** (2.45 g, 58%). Colorless needles. M.p. 50–51° (hexane). IR: 1682. ^{1}H-NMR (400 MHz): 2.35 (*s*, 3 H); 3.54 (*s*, 3 H); 5.28 (*s*, 2 H); 7.21 (*s*, 1 H); 7.37 (*s*, 1 H); 10.37 (*s*, 1 H). ^{13}C-NMR (100 MHz): 21.0; 56.4; 95.1; 114.7; 122.0; 123.1; 134.1; 138.6; 153.8; 192.0. FAB-MS: 261 ($[M(^{81}Br)+H]^+$), 259 ($[M(^{79}Br)+H]^+$). Anal. calc. for $C_{10}H_{11}BrO_3$ (259.10): C 46.36, H 4.28; found: C 46.39, H 4.02.

Methyl 2-Bromo-3-(methoxymethoxy)-5-methylbenzoate (**17c**). To a soln. of **16c** (100 mg, 0.39 mmol) in MeOH (3 ml), a soln. of KOH (85%, 56 mg, 0.85 mmol) in MeOH (3 ml) was added at 0°. A soln. of I_2 (127 mg, 0.50 mmol) in MeOH (3 ml) was added, and the mixture was stirred at 0° for 1 h and at r.t. for 4 h. H_2O (5 ml) and sat. aq. $Na_2S_2O_3$ (5 ml) were added, and the mixture was evaporated *in vacuo*. The residue was extracted with $CHCl_3$ (1 × 10 ml). The org. layer was washed with H_2O (1 × 5 ml) and brine (1 × 5 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt 25:1 to 10:1) to give **17c** (102 mg, 92%). Colorless oil. IR: 1730. ^{1}H-NMR (400 MHz): 2.33 (*s*, 3 H); 3.52 (*s*, 3 H); 3.92 (*s*, 3 H); 5.25 (*s*, 2 H); 7.08 (br. *s*, 1 H); 7.16 (br. *s*, 1 H). ^{13}C-NMR (100 MHz): 21.1; 52.5; 56.4; 95.1; 108.8; 119.2; 124.3; 134.2; 138.4; 154.1; 167.2. HR-EI-MS: 288.0025 (M^+, $C_{11}H_{13}{}^{79}BrO_4^+$; calc. 287.9997).

3-(Methoxymethoxy)-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde (**18**). A mixture of **10** (50 mg, 0.19 mmol), **16c** (50 mg, 0.19 mmol), $Pd(PPh_3)_4$ (6 mg, 5.5 mmol) in DME (3 ml), and 2M aq. Na_2CO_3 (0.12 ml, 0.24 mmol) was heated at 90° for 2 d. After cooling, the mixture was diluted with H_2O (3 ml), and the org. layer was separated. The aq. layer was extracted with CH_2Cl_2 (3 × 10 ml). The combined org. layers were washed with H_2O (2 × 5 ml) and brine (1 × 5 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt 10:1 to 3:1) to give **18** (73 mg, 97%). Colorless prisms. M.p. 163–164° (AcOEt). IR: 1684. ^{1}H-NMR (400 MHz): 2.48 (*s*, 3 H); 3.33 (*s*, 3 H); 3.46 (*s*, 3 H); 3.92 (*s*, 3 H); 4.01 (*s*, 3 H); 5.10 (*d*, J = 8.4, 1 H); 5.13 (*d*, J = 8.4, 1 H); 6.72 (*s*, 1 H);

6.94 (*d*, *J* = 7.1, 1 H); 7.31 (br. *s*, 1 H); 7.46 (*t*, *J* = 8.2, 1 H); 7.57 (br. *s*, 1 H); 7.76 (*d*, *J* = 8.4, 1 H); 9.72 (*s*, 1 H). ^{13}C-NMR (100 MHz): 21.6; 56.1; 56.5; 56.8; 60.8; 94.8; 107.1; 109.5; 115.1; 118.3; 120.8; 121.2; 122.2; 126.9; 129.0; 131.2; 134.7; 139.4; 147.7; 152.7; 154.7; 157.3; 192.6. FAB-MS: 419 ([*M* + Na]$^+$), 396 (M^+). Anal. calc. for $C_{23}H_{24}O_6$ (396.43): C 69.68, H 6.10; found: C 69.56, H 6.06.

Methyl 3-(Methoxymethoxy)-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzoate (**19**). A mixture of **10** (265 mg, 1.01 mmol), **17c** (292 mg, 1.01 mmol), $Pd(PPh_3)_4$ (10 mg, 8.3 mmol) in benzene/EtOH (10 : 1, 5.0 ml), and 2M Na_2CO_3 (0.6 ml, 1.20 mmol) was heated at 90° for 2 d. After cooling, the mixture was diluted with H_2O (10 ml), and the org. layer was separated. The aq. layer was extracted with CH_2Cl_2 (3 × 20 ml). The combined org. layers were washed with H_2O (3 × 10 ml) and brine (1 × 10 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC ($CHCl_3$) and prep. TLC ($CHCl_3$) to give **19** (43 mg, 10%). Yellow oil. IR: 1726. ^{1}H-NMR (400 MHz): 2.45 (*s*, 3 H); 3.27 (*s*, 3 H); 3.50 (*s*, 3 H); 3.52 (*d*, 3 H); 3.90 (*s*, 3 H); 4.00 (*s*, 3 H); 5.00 (*d*, *J* = 7.0, 1 H); 5.09 (*d*, *J* = 7.0, 1 H); 6.66 (*s*, 1 H); 6.89 (*d*, *J* = 7.0, 1 H); 7.20 (br. *s*, 1 H); 7.41 (diffused *t*, *J* = 8.1, 1 H); 7.41 (br. *s*, 1 H); 7.75 (*dd*, *J* = 8.4, 0.9, 1 H). ^{13}C-NMR (100 MHz): 21.4; 51.9; 56.0; 56.4; 56.9; 60.8; 94.9; 106.3; 109.3; 115.2; 117.8; 119.5; 123.9; 125.7; 126.0; 126.3; 131.2; 132.8; 138.9; 147.0; 152.4; 154.8; 157.2; 168.5. HR-EI-MS: 426.1680 (M^+, $C_{24}H_{26}O_7^+$; calc. 426.1679).

*1,4b-Dimethoxy-10-(methoxymethoxy)-8-methyl-4b*H*-dibenzo[*c,h*]chromene-6,12-dione* (=*1,4b-Dimethoxy-10-(methoxymethoxy)-8-methyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6,12(4b*H*)-dione*; **21**) and *7,10b-Dimethoxy-4-(methoxymethoxy)-2-methyl-5a*H*,12*H*-dibenzo[*c,h*]oxireno[*e*]chromene-6,12(10b*H*)-dione* (=*7,10b-Dimethoxy-4-(methoxymethoxy)-2-methyl-5a*H*,12*H*-oxireno[2,3]naphtho[1,2-*c*][2]benzopyran-6,12(10b*H*)-dione*; **22**). To a suspension of **18** (50 mg, 0.13 mmol) in MeCN (1.5 ml), a soln. of $NaH_2PO_4 \cdot 2\,H_2O$ (5 mg, 0.30 mmol) in H_2O (1 ml) and 30% H_2O_2 (0.015 ml, 0.13 mmol) were added successively. After cooling to 0°, a soln. of $NaClO_2$ (16 mg, 0.14 mmol) in H_2O (1 ml) was added, and the mixture was stirred at r.t. for 12 h. After cooling to 0°, 10% HCl (3 ml) was added, and MeCN was evaporated *in vacuo*. The residue was extracted with AcOEt (3 × 10 ml). The combined org. layers were washed with H_2O (1 × 5 ml) and brine (1 × 5 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt 5 : 1 to 3 : 1) to give **21** as yellow needles (30 mg, 59%) and **22** as red needles (3 mg, 6%).

Data of **21**. IR: 1741, 1657. ^{1}H-NMR (400 MHz): 2.46 (*s*, 3 H); 2.90 (*s*, 3 H); 3.53 (*s*, 3 H); 4.01 (*s*, 3 H); 5.34 (*d*, *J* = 7.0, 1 H); 5.40 (*d*, *J* = 7.0, 1 H); 7.13 (*dd*, *J* = 8.2, 1.3, 1 H); 7.36 (br. *s*, 1 H); 7.42 (*s*, 1 H); 7.64 (*dd*, *J* = 7.9, 1.3, 1 H); 7.69 (*t*, *J* = 8.0, 1 H); 7.76 (br. *s*, 1 H). ^{13}C-NMR (100 MHz): 21.9; 51.7; 56.3; 56.6; 94.6; 96.5; 113.3; 118.2; 119.5; 121.0; 124.3; 125.5; 132.1; 134.8; 137.7; 139.9; 142.6; 155.5; 159.6; 162.8; 183.6. LR-EI-MS: 396 (11, M^+), 351 (10, [M − MOM]$^+$), 320 (24), 135 (36), 91 (69), 59 (100).

Data of **22**. IR: 1740, 1680. ^{1}H-NMR (400 MHz): 2.44 (*s*, 3 H); 3.04 (*s*, 3 H); 3.52 (*s*, 3 H); 3.95 (*s*, 3 H); 5.24 (*d*, *J* = 7.0, 1 H); 5.29 (*d*, *J* = 7.0, 1 H); 5.39 (*s*, 1 H); 7.15 (*dd*, *J* = 7.5, 1.8, 1 H); 7.30 (*s*, 1 H); 7.65 (*t*, *J* = 7.5, 1 H); 7.67 (*dd*, *J* = 7.5, 1.8, 1 H); 7.82 (br. *s*, 1 H). ^{13}C-NMR (100 MHz): 21.6; 51.5; 56.3; 56.7; 57.1; 59.7; 94.8; 101.2; 113.7; 116.6; 117.7; 118.8; 121.8; 125.0; 128.3; 133.8; 136.1; 142.0; 155.8; 158.6; 162.1; 192.7. HR-EI-MS: 412.1149 (M^+, $C_{22}H_{20}O_8^+$; calc. 412.1158).

3-(Methoxymethoxy)-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzoic Acid (**20**). To a soln. of **18** (302 mg, 0.76 mmol) in MeOH (10 ml), a mixture of 15% NaOH (10 ml, 37.5 mmol) and 30% H_2O_2 (6.4 ml, 56.4 mmol) was added at 60°, and the mixture was stirred at 120° for 30 min. A mixture of 15% NaOH (10 ml, 37.5 mmol) and 30% H_2O_2 (6.4 ml, 56.4 mmol) was added, and the mixture was refluxed for 1 h. After cooling, MeOH was removed by evaporation. The residue was washed with $CHCl_3$ (4 × 10 ml) to recover **18**. The aq. layer was acidified with 10% HCl to pH 4 and extracted with $CHCl_3$ (4 × 10 ml). The combined org. layers were washed with H_2O (1 × 5 ml) and brine (1 × 5 ml), dried ($MgSO_4$), and evaporated *in vacuo* to give crude **20** (182 mg, 58%). For the recovery of **18**, the $CHCl_3$ washings were combined, washed with H_2O (1 × 5 ml) and brine (1 × 5 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The recovered crude **18** was directly subjected to similar reaction conditions (15% NaOH (10 ml), 30% H_2O_2 (6.4 ml) at 120° for 1 h) to give crude **20** (122 mg, 39%). The combined crude **20** was recrystallized from toluene to give **20** (251 mg, 80%). Pale yellow needles. M.p. 164–167°. IR: 3200, 1716. ^{1}H-NMR (400 MHz): 2.44 (*s*, 3 H); 3.27 (*s*, 3 H); 3.54 (*s*, 3 H); 3.87 (*s*, 3 H); 3.99 (*s*, 3 H); 5.00 (*d*, *J* = 7.2, 1 H); 5.08 (*d*, *J* = 7.2, 1 H); 6.63 (*s*, 1 H); 6.90 (*d*, *J* = 7.2, 1 H); 7.22 (br. *s*, 1 H); 7.42 (*t*, *J* = 8.2, 1 H); 7.46 (br. *s*, 1 H); 7.72 (*d*, *J* = 8.4, 1 H). ^{13}C-NMR (100 MHz): 21.4; 56.0; 56.4; 56.8; 60.9; 94.8; 106.5;

109.5; 115.2; 118.0; 120.1; 124.6; 125.6; 126.3; 126.4; 131.2; 131.5; 139.0; 146.8; 152.5; 154.9; 157.2; 171.8. HR-ESI-MS: 413.1586 ($[M+H]^+$, $C_{23}H_{25}O_7^+$; calc. 413.1600); 435.1401 ($[M+Na]^+$, $C_{23}H_{24}NaO_7^+$; calc. 435.1420). Anal. calc. for $C_{23}H_{24}O_7$ (412.43): C 66.98, H 5.87; found: C 66.72, H 5.75.

*4-Hydroxy-5,9,10-trimethoxy-2-methyl-11*H*-benzo[*b*]fluoren-11-one* (**8**). $(COCl)_2$ (0.02 ml, 0.23 mmol) was added to a soln. of **20** (15 mg, 0.037 mmol) in MeCN (1 ml), and the mixture was stirred at 80° for 10 min. The solvent was evaporated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (1 ml). $AlCl_3$ (49 mg, 0.36 mmol) was added, and the mixture was stirred at r.t. for 2.5 h. Sat. aq. $NaHCO_3$ (2.0 ml) was added, and the mixture was stirred for 5 min. $MgSO_4$ was added and then filtered. The precipitate was washed with AcOEt (3 × 10 ml). The org. layers were combined and evaporated *in vacuo*. The residue was purified by CC (CH_2Cl_2/MeOH 100:1) to give **8** (11 mg, 81%). Yellow needles. M.p. 232–234° (hexane/CH_2Cl_2). IR: 3240, 1700. ^{1}H-NMR (400 MHz): 2.37 (*s*, 3 H); 4.01 (*s*, 3 H); 4.02 (*s*, 3 H); 4.06 (*s*, 3 H); 6.91 (*s*, 1 H); 6.91 (*dd*, *J* = 7.3, 1.5, 1 H); 7.16 (*s*, 1 H); 7.54 (*dd*, *J* = 8.4, 7.3, 1 H); 7.57 (*dd*, *J* = 8.4, 1.5, 1 H); 9.43 (*s*, 1 H). ^{13}C-NMR (100 MHz): 21.3; 56.4; 62.8; 63.9; 108.2; 114.7; 117.1; 121.7; 122.2; 122.9; 123.4; 128.5; 130.5; 134.8; 138.0; 142.4; 142.8; 152.1; 156.2; 159.9; 189.8. HR-ESI-MS: 351.1219 ($[M+H]^+$, $C_{21}H_{19}O_5^+$; calc. 351.1232), 373.1037 ($[M+Na]^+$, $C_{21}H_{18}NaO_5^+$; calc. 373.1052).

Prekinamycin (=*11-Diazonio-10,11-dihydro-4,9-dihydroxy-2-methyl-5,10-dioxo-5*H*-benzo[*b*]fluoren-11-ide*; **4**). BBr_3 (1M soln. in CH_2Cl_2, 0.18 ml, 0.18 mmol) was added to a soln. of **8** (11 mg, 0.032 mmol) in CH_2Cl_2 (1 ml) at −40°, and the mixture was stirred at −40° for 24 h. MeOH (2 ml) was added, and the solvent was evaporated *in vacuo*. The residue was dissolved in EtOH (1 ml), and a soln. of $TsNHNH_2$ (60 mg, 0.32 mmol) in EtOH (3 ml) and 1M HCl (one drop) were added. The mixture was stirred at 90° for 2 h. The solvent was evaporated *in vacuo*. The residue was suspended in acetone (2 ml), and Et_3N (0.5 ml, 0.5 mmol), and *Fetizon*'s reagent (273 mg) were added. The mixture was vigorously stirred at r.t. for 30 min. The solvent was evaporated *in vacuo*. CH_2Cl_2 (5 ml) was added and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by CC (hexane/CH_2Cl_2 1:1), followed by washing with acetone, to give **4** (5 mg, 47%). Black-purple needles. M.p. > 300°. IR: 2119, 1607. ^{1}H-NMR (400 MHz): 2.44 (*s*, 3 H); 6.72 (*s*, 1 H); 6.85 (*s*, 1 H); 7.24–7.26 (*m*, 1 H); 7.61 (*t*, *J* = 7.6, 1 H); 7.79 (*d*, *J* = 8.4, 1 H); 11.06 (*s*, 1 H); 12.15 (*s*, 1 H). ^{13}C-NMR (150 MHz): 22.0; 110.3; 114.0; 115.6; 117.5; 120.7; 125.2; 128.2; 131.6; 133.5; 135.7; 136.3; 141.8; 154.5; 162.2; 181.2; 184.7. HR-ESI-MS: 317.0576 ($[M-H]^-$, $C_{18}H_9N_2O_4^-$; calc. 317.0562).

*4-Hydroxy-9-methoxy-2-methyl-5*H*-benzo[*b*]fluorene-5,10,11-trione* (**29**). Iodosobenzene bis(trifluoroacetate) (PIFA; 14 mg, 0.031 mmol) was added to a suspension of **8** (19 mg, 0.029 mmol) in MeCN/H_2O 2:1 (1 ml) at r.t., and the mixture was stirred at r.t. for 50 min. Sat. aq. $NaHCO_3$ (5 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The combined org. layers were washed with brine (1 × 5 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt 4:1 to 1:1) and prep. TLC (CH_2Cl_2) gave **29** (1 mg, 11%). Purple needles. M.p. 195–200° (dec.). IR: 3096, 1716, 1645, 1590. ^{1}H-NMR (400 MHz): 2.37 (*s*, 3 H); 4.02 (*s*, 3 H); 6.92 (*s*, 1 H); 7.11 (*s*, 1 H); 7.46 (*dd*, *J* = 8.4, 1.1, 1 H); 7.74 (*dd*, *J* = 8.4, 7.5, 1 H); 7.90 (*dd*, *J* = 7.5, 1.1, 1 H). ^{13}C-NMR (100 MHz): 29.7; 56.7; 116.3; 119.6; 120.3; 121.2; 125.7; 127.6; 130.9; 132.3; 134.1; 134.7; 147.2; 154.1; 154.6; 160.3; 179.6; 187.8; 191.9. HR-EI-MS: 320.0664 (M^+, $C_{19}H_{12}O_5^+$; calc. 320.0685).

*4-Hydroxy-5,5,9-trimethoxy-2-methyl-5*H*-benzo[*b*]fluorene-10,11-dione* (**30**). PIFA (26 mg, 0.060 mmol) was added to a suspension of **8** (10 mg, 0.030 mmol) in MeOH (5 ml) at r.t., and the mixture was stirred at r.t. for 30 min. MeOH was evaporated *in vacuo*, and the residue was washed with $CHCl_3$ (3 × 10 ml). The combined org. layers were washed with H_2O (3 × 10 ml) and brine (3 × 10 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by prep. TLC (CH_2Cl_2) to give **30** (8 mg, 72%). Orange needles. M.p. 216–218°. IR: 1721, 1654. ^{1}H-NMR (400 MHz): 2.37 (*s*, 3 H); 3.11 (*s*, 6 H); 3.99 (*s*, 3 H); 6.89 (*s*, 1 H); 7.09 (*s*, 1 H); 7.14 (*d*, *J* = 8.4, 1 H); 7.41 (*d*, *J* = 7.7, 1 H); 7.69 (diffused *t*, *J* = 8.1, 1 H); 8.58 (*s*, 1 H). ^{13}C-NMR (150 MHz): 21.7; 52.4 × 2; 56.3; 97.3; 114.4; 117.0; 118.4; 118.7; 122.9; 124.8; 128.5; 132.9; 134.8; 138.5; 146.5; 153.1; 160.8; 164.2; 178.5; 190.9. HR-EI-MS: 366.1091 (M^+, $C_{21}H_{18}O_6^+$; calc. 366.1103).

*5,9,10-Trimethoxy-2-methyl-11*H*-benzo[*b*]fluorene-4,11-diol* (**31**). $CeCl_3 \cdot 7\,H_2O$ (12 mg, 0.033 mmol) and $NaBH_4$ (1.3 mg, 0.034 mmol) were added to a suspension of **8** (11 mg, 0.030 mmol) in EtOH (1 ml) at −40°, and the mixture was stirred at 0° for 1 h and at r.t. for 5 h. Sat. aq. NH_4Cl soln. (1 ml) was added, and EtOH was removed by evaporation *in vacuo*. The residue was extracted with

$CHCl_3$ (3×5 ml). The combined org. layers were washed with brine (3×5 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by short-passed CC (hexane/AcOEt 1:1) to give **31** (10 mg, 99%). Colorless needles. M.p. 185°. IR: 3474, 3249. ^{1}H-NMR (400 MHz): 2.38 (*s*, 3 H); 3.13 (br. *s*, 1 H); 3.98 (*s*, 3 H); 3.98 (*s*, 3 H); 4.00 (*s*, 3 H); 5.94 (*s*, 1 H); 6.77 (*s*, 1 H); 6.87 (*d*, $J = 7.9$, 1 H); 7.03 (*s*, 1 H); 7.44 (*t*, $J = 8.2$, 1 H); 7.63 (*d*, $J = 8.4$, 1 H); 9.53 (*s*, 1 H). ^{13}C-NMR (100 MHz): 21.5; 56.0; 62.5; 63.8; 73.0; 106.2; 114.6; 117.5; 117.8; 120.0; 120.3; 127.1; 128.8; 131.9; 134.1; 141.9; 142.7; 146.6; 150.8; 152.1; 156.6. HR-EI-MS: 352.1305 (M^+, $C_{21}H_{20}O_5^+$; calc. 352.1311).

2-Hydroxy-5-(methoxymethoxy)-3-methyl-6-(1,4,5-trimethoxynaphthalen-2-yl)benzoic Acid (**33**) A mixture of **20** (54 mg, 0.13 mmol), $Pd(O_2CCF_3)_2$ (4.5 mg, 0.014 mmol), benzoquinone (32 mg, 0.30 mmol), and AcOCs (59 mg, 0.29 mmol) in *N*,*N*-dimethylacetamide (3 ml) was stirred at 140° (bath temp.) for 20 h with bubling of O_2. The solvent was evaporated *in vacuo*, and the residue was diluted with AcOEt (10 ml) and sonicated. The precipitate was filtered off, and the filtrate was washed with brine (3×10 ml) and extracted with sat. aq. $NaHCO_3$ (3×10 ml). The aq. layers were combined, acidified with 10% HCl to pH 7, and extracted with $CHCl_3$ (3×20 ml). The combined org. layers were washed with brine (3×10 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC (hexane/AcOEt 1:1) to give **33** (35 mg, 62%). Yellow needles. M.p. 70–72°. IR: 3170, 1659. ^{1}H-NMR (400 MHz): 2.33 (*s*, 3 H); 3.18 (*s*, 3 H); 3.55 (*s*, 3 H); 3.86 (*s*, 3 H); 3.97 (*s*, 3 H); 4.82 (*d*, $J = 6.7$, 1 H); 4.92 (*d*, $J = 6.7$, 1 H); 6.60 (*s*, 1 H); 6.87 (*d*, $J = 7.7$, 1 H); 7.28 (*s*, 1 H); 7.39 (*t*, $J = 8.1$, 1 H); 7.67 (*d*, $J = 8.2$, 1 H). ^{13}C-NMR (100 MHz): 16.3; 56.0; 56.3; 56.9; 60.9; 96.1; 106.6; 109.3; 110.9; 115.1; 117.9; 126.1; 126.3; 126.5; 127.3; 127.8; 131.2; 146.5; 146.8; 152.5; 156.4; 157.0; 173.3. HR-EI-MS: 428.1456 (M^+, $C_{23}H_{24}O_8^+$; calc. 428.1471).

*1,4-Dihydroxy-5,9,10-trimethoxy-2-methyl-11*H*-benzo[*b*]fluoren-11-one* (**35**). $(COCl)_2$ (0.2 ml, 2.33 mmol) was added to a soln. of **33** (50 mg, 0.12 mmol) in MeCN (3 ml) at 80°, and the mixture was stirred at the same temp. for 10 min. After cooling, the solvent was evaporated *in vacuo*, and the residue was diluted with CH_2Cl_2 (10 ml). A soln. of $FeCl_3$ (192 mg, 1.18 mmol) in THF (10 ml) was added, and the mixture was stirred at r.t. for 90 min. Sat. aq. $NaHCO_3$ soln. (5 ml) was added, and the mixture was stirred for 5 min. $MgSO_4$ was added, and the mixture was extracted with AcOEt (3×20 ml). The solvent was evaporated *in vacuo*, and the residue was purified by CC (hexane/AcOEt 1:1) to give **35** (31 mg, 73%). Red needles. M.p. 233°. IR: 3274, 1662. ^{1}H-NMR (400 MHz): 2.23 (*s*, 3 H); 4.00 (*s*, 3 H); 4.01 (*s*, 3 H); 4.06 (*s*, 3 H); 6.85 (*s*, 1 H); 6.91 (*d*, $J = 7.3$, 1 H); 7.53 (*t*, $J = 8.2$, 1 H); 7.56 (*d*, $J = 6.8$, 1 H); 8.82 (*s*, 1 H); 9.18 (*s*, 1 H). ^{13}C-NMR (100 MHz): 14.8; 56.4; 62.9; 63.9; 108.1; 114.7; 119.1; 119.4; 121.4; 122.4; 127.1; 128.1; 130.58; 130.59; 134.7; 143.6; 145.1; 150.8; 156.2; 159.9; 192.8. HR-EI-MS: 366.1098 (M^+, $C_{21}H_{18}O_6^+$; calc. 366.1103).

*5,9,10-Trimethoxy-2-methyl-1*H*-benzo[*b*]fluorene-1,4,11-trione* (**36**). A mixture of **35** (18 mg, 0.048 mmol), Ag_2O (105 mg, 0.46 mmol), and $MgSO_4$ (48 mg, 0.40 mmol) in THF (5 ml) was stirred at r.t. for 20 h under O_2. The solvent was evaporated *in vacuo*. The residue was diluted with AcOEt (10 ml), and the precipitate was filtered through a pad of *Celite*®. The filtrate was evaporated *in vacuo*, and the residue was purified by short-passed CC (hexane/AcOEt 1:1) to give **36** (16 mg, 91%). Purple needles. M.p. 218–220°. IR: 1697. ^{1}H-NMR (400 MHz): 2.12 (*d*, $J = 1.6$, 3 H); 3.99 (*s*, 3 H); 4.01 (*s*, 3 H); 4.08 (*s*, 3 H); 6.74 (*q*, $J = 1.6$, 1 H); 7.05 (*d*, $J = 8.2$, 1 H); 7.59 (*t*, $J = 8.1$, 1 H); 7.81 (*dd*, $J = 8.3$, 1.0, 1 H). ^{13}C-NMR (100 MHz): 15.2; 56.6; 62.9; 64.5; 111.1; 117.7; 118.3; 122.3; 123.6; 130.8; 131.2; 134.3; 136.5; 145.9; 151.2; 151.6; 157.2; 160.4; 183.7; 184.5; 187.4. HR-ESI-MS: 387.0842 ($[M + Na]^+$, $C_{21}H_{16}NaO_6^+$; calc. 387.0845).

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