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Synthetic studies on kinamycin antibiotics: elaboration of a highly oxygenated D ring

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Abstract—The synthesis of the model compound of kinamycin antibiotics, which possesses correct relative configurations at C1–C4 on the D ring, is reported in detail. The key steps involved a Diels–Alder reaction of indenone (**12**) and a Danishefsky-type diene (**13**), and stereoselective construction of a tetraoxygenated D ring. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Kinamycins were isolated from the culture broth of *Streptomyces murayamaensis* sp. nov. Hata et Ohtani by Omura et al.[1] in 1970.[2] These antibiotics are strongly active against gram-positive bacteria but less against gram-negative ones. The structures had been characterized as benzo[*b*]carbazoloquinone *N*-cyanamides (**1**) with a highly oxygen-functionalized D ring by spectroscopic means, chemical reactions[3] and X-ray crystallographic analysis.[4] On biosynthetic studies for kinamycins, Gould et al.[5] reported the isolation of dehydrorabelomycin (**3**) and prekinamycin (now called isoprekinamycin[6]) from *S. murayamaensis* as minor metabolites, the former between which was shown to be a precursor by the incorporation of deuterated **3** into kinamycins. The latter metabolite was also supposed to be a precursor, and the same benzo[*b*]carbazoloquinone skeleton as **1** was proposed for its structure such as **4** by the resemblance of the spectral data to those of kinamycins.[7]

Problems still remained for the determination of the substituent pattern at 11 position[8] (atoms X and Y in **1**). The reported data of ^{13}C NMR (δ_C 78.5 ppm)[9] for *N*-cyanamide structures of kinamycins poorly agreed with those of *N*-cyanoindoloquinones (δ_C 104.7 ppm for **6**, 103.6 ppm for **7**).[10] Furthermore, the compound **4** was synthesized by Echavarren et al.,[11] however, it was not identical with so-called prekinamycin isolated by Gould et al.[5] Thus, in 1994, Gould et al.[12] revised the *N*-cyanamide structures (**1** for kinamycins, **4** for so-called prekinamycin) to diazonium ones (**2** for kinamycins, **8** for so-called prekinamycin) by the re-examination of X-ray crystallographic analysis of (+)-α-methylbutyrate of kinamycin D. At the same time, Dmitrienko et al.[13] independently reported the revision of the structures of kinamycins and so-called prekinamycin based on an alternative synthesis of a compound **5**, and finally reached to the same conclusion that Gould et al. proposed.

However, in spite of the accepted structures **2** for kinamycins, Gould has doubted the diazonium structure **8** for so-called prekinamycin due to some discrepancies between a synthetic compound **8** and so-called prekinamycin.[14] Quite recently, Proteau, Gould and Dmitrienko et al.[6] revised the structure of so-called prekinamycin from benzo[*b*]fluorene skeleton **8** to benzo[*a*]fluorene one **9** based on precise examination of spectral data of a model compound with the latter skeleton. Further, they proposed to name so-called prekinamycin isolated by Gould et al. as isoprekinamycin and a compound with the formula **8** as prekinamycin, respectively.

Thus, there have been some confusion on structures of kinamycin derivatives. Therefore, it should be important to determine the structure of kinamycins by the synthesis of the compounds with the structure **2**. We first planned the stereoselective synthesis of a model compound **10** as shown in Scheme 1, in which Diels–Alder reaction between indenone **12** and Danishefsky diene **13** was involved as a key step for the elaboration of a highly oxygenated cyclohexene ring.[15] In this paper, we in detail report the first successful construction of a 3,4,5,6-tetraoxygenated cyclohexene ring with a correct relative configuration (*cis*,*trans*,*trans*) in kinamycin skeletons (Fig. 1).[16]

Keywords: kinamycins; antibiotics; Diels–Alder reaction; indenone; stereoselective dihydroxylation.

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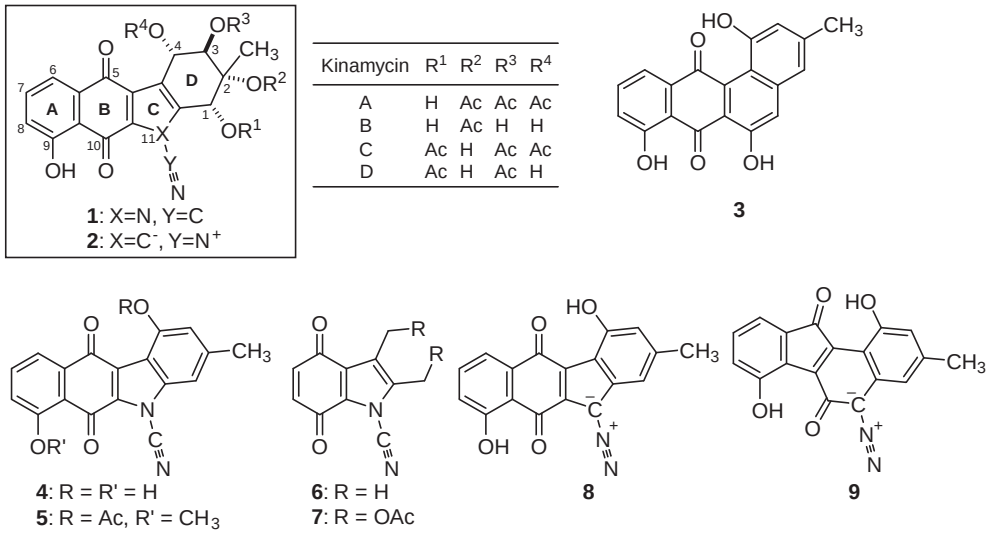
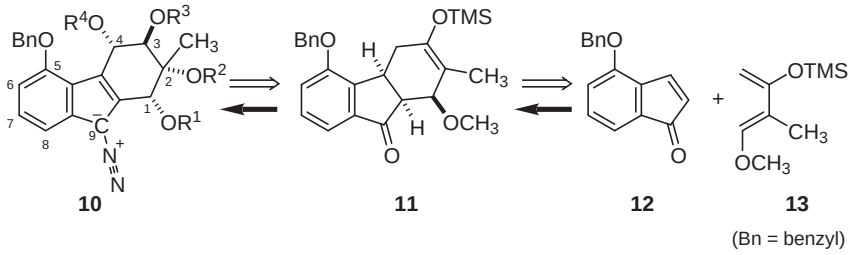


Figure 1. Proposed structures of kinamycins (**1**, **2**) and related compounds (**3**–**9**).



Scheme 1. Retrosynthesis of **10**.

2. Results and discussion

Indenone **12** was prepared from indanone **14**[17] by dehydrosilylation of the corresponding silyl enol ether **15**[18] in palladium acetate [$Pd(OAc)_2$]-*p*-benzoquinone system.[19] Trials for the preparation of **12** with other procedures, such as dehydrobromination of α-bromoketone and thermal decompositions of α-sulfoxides, resulted in formation of complex mixtures. Diels–Alder reaction of **12** and diene **13**[20] by refluxing in benzene proceeded smoothly to afford *endo* adduct **11**. The relative configuration of **11** was determined by NOE enhancements (Fig. 2). Trial for the

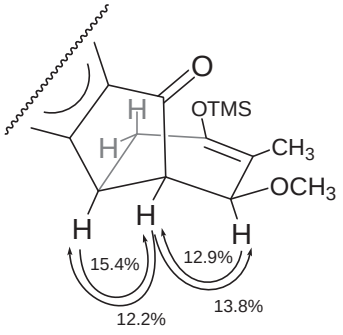
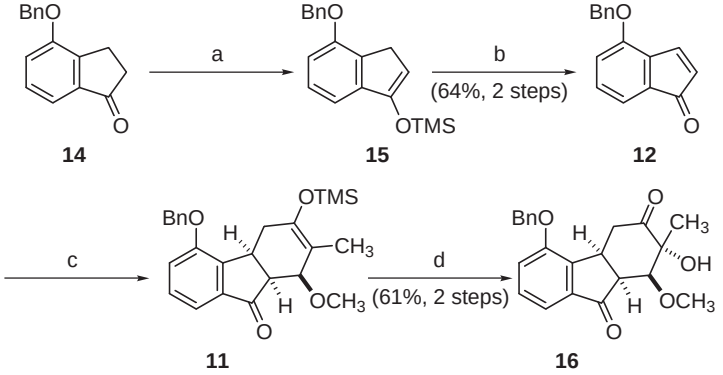


Figure 2. Selected NOE enhancements of **11**.



Scheme 2. Synthesis of α-hydroxyketone **16**. (a) TMSCl, Et_3N, DMF, 60°C, 16 h; (b) $Pd(OAc)_2$, *p*-benzoquinone, CH_3CN, rt, 5 h; (c) **13**, benzene, reflux, 2 h; (d) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 0°C, 3 h, and then rt, 5 h.

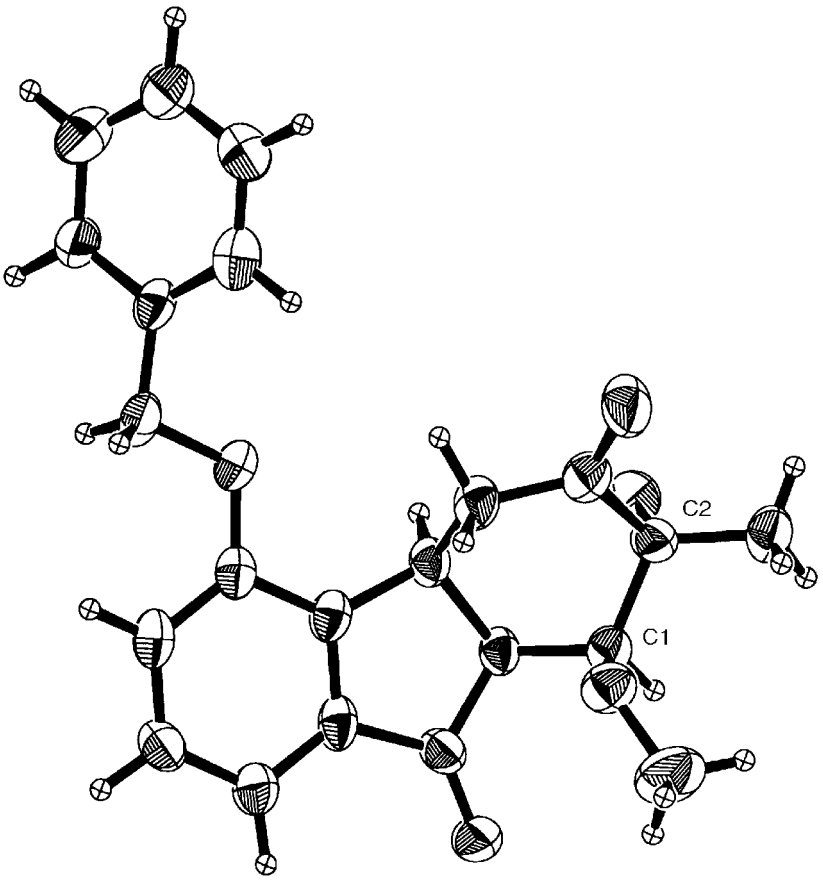
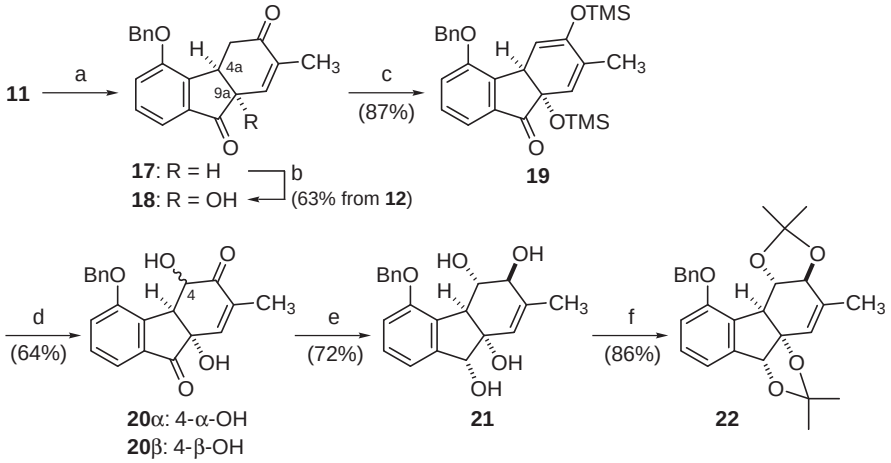


Figure 3. X-Ray crystallography of **16**.



Scheme 3. Synthesis of diketal **22**. (a) CSA, CH_2Cl_2, 0°C, 10 min; (b) O_2 (1 atm), KF, DMSO, rt, 2 h; (c) TMSOTf, Et_3N, CH_2Cl_2, 0°C, 10 min; (d) (i) OsO_4, NMO, THF–H_2O (20:1), 0°C, 1 h, and then rt, 12 h; (ii) 10% HCl, CH_3OH, rt, 2 min; (e) DIBAL–H, THF, −78°C, 1 h; (f) 2-methoxypropene, CSA, DMF, rt, 2 h.

diastereoselective epoxidation of **11** with *m*-chloroperbenzoic acid (*m*-CPBA) for introduction of an oxygen function into the C2 position[21] gave α-hydroxyketone **16**. However, X-ray crystallographic analysis[22] showed that the oxidation occurred at the convex face to produce an undesired *trans* system between C1–C2 positions (Scheme 2, Fig. 3).

Desilylation of **11** under an acidic condition gave enone **17**. A doubly activated position at C9a in **17** was found to be easily oxygenated by molecular oxygen (O_2). Thus, treatment of **17** in dimethylsulfoxide (DMSO) under O_2 atmosphere in the presence of potassium fluoride (KF)[23] afforded γ-hydroxyenone **18** in 63% yield from **12**. The position of the hydroxy group introduced in **18** was determined by the observation of a cross peak between H-4a (δ_H 3.92 ppm) and C-9a (δ_C 78.5 ppm) in the HMBC experiments. The enone **18** was converted to the corresponding silyl dienol ether **19**, which was hydroxylated by a catalytic amount of osmium tetroxide (OsO_4) in the presence of

N-methylmorpholine *N*-oxide (NMO) followed by acidic work-up to afford a 5:1 mixture of 1,3-diols **20**α and **20**β. The mixture was subjected to the reduction with diisobutylaluminum hydride (DIBAL-H) in tetrahydrofuran (THF) at −78°C followed by recrystallization from ethanol to give tetrol **21** derived from a major component. A desired stereochemical relationship at C3 and C4 of **21** was confirmed by NOE experiments of the corresponding diketal **22** (Scheme 3, Fig. 4).

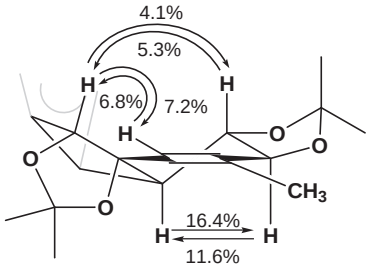
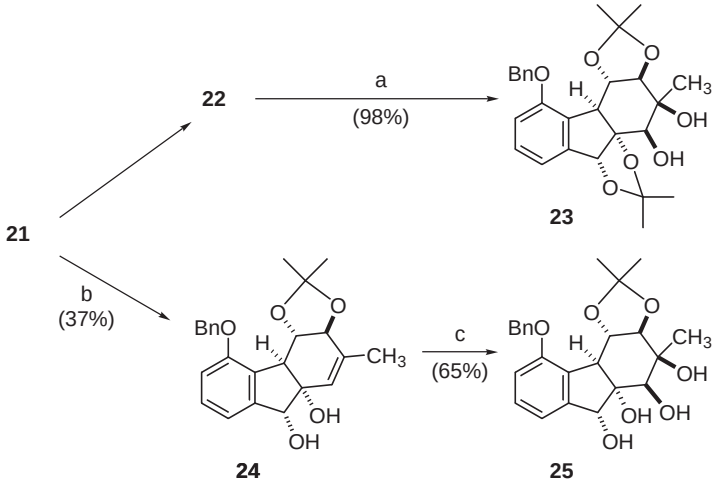


Figure 4. Selected NOE enhancements of **22**.

Kishi et al.[24] have proposed that dihydroxylation in allyl ether functions with OsO_4 is generally controlled by configuration at the allylic position. This could not be simply



Scheme 4. Synthesis of diol **23** and tetrol **25**. (a) OsO_4, NMO, THF–H_2O (8:1), 0°C, 1 h, and then rt, 24 h; (b) 2-methoxypropene, CSA, DMF, rt, 2 h; (c) OsO_4, NMO, THF–H_2O (20:1), rt, 18 h.

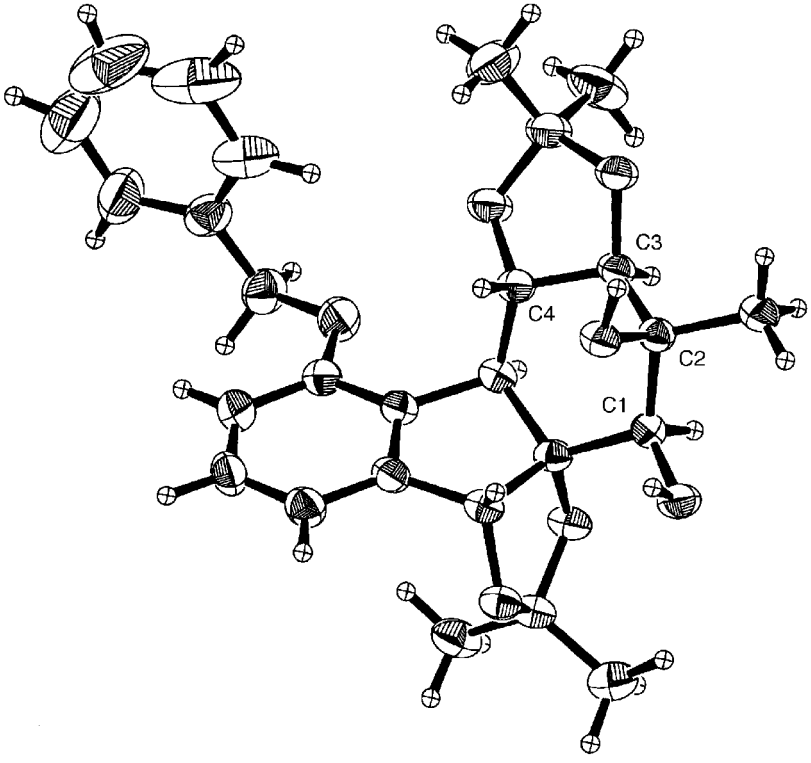
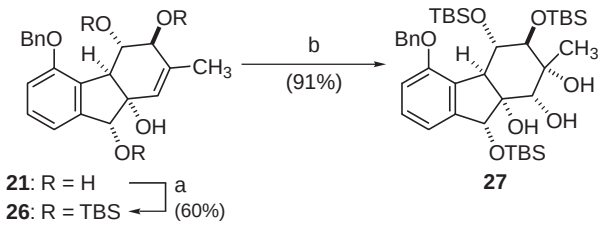


Figure 5. X-Ray crystallography of **23**.



Scheme 5. Synthesis of triol **27**. (a) TBSCl, imidazole, DMF, rt, 5 h, and then 50°C, 2.5 h; (b) OsO_4, pyridine, 0°C, 1 h, and then rt, 24 h.

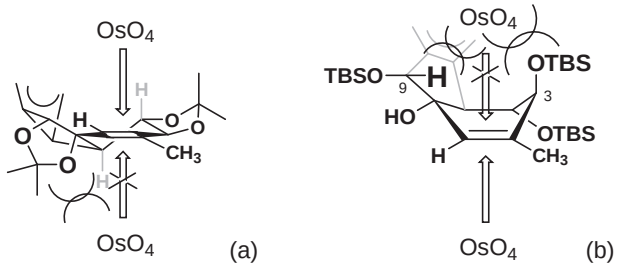


Figure 6. Proposed mechanisms for dihydroxylation of **22** (a) and **26** (b).

applied to the diastereoselectivity in dihydroxylation of **22** with OsO_4 because of the presence of two allylic alcohol units (C3 and C9a) in **22**, however, we expected the dihydroxylation from the convex face, as in the case of **11**, to produce a pentaoxygenated cyclohexane ring with correct *cis*,*trans*,*trans*configuration at C1 to C4. Treatment of **22** with OsO_4-NMO system gave diol **23**, the undesired stereochemistry of which was shown by X-ray crystallography (Fig. 5). The same diastereoselectivity was also observed even in the dihydroxylation of a less hindered monoketal **24** (Scheme 4).[25,26] These dihydroxylations from concave sites may be caused by the significant shield of convex sites by a C9a–O bond in more planer conformation due to a ketal bridge between C3–C4 as shown in Fig. 6a.

Alternation of a protecting group from a cyclic functionality to an acyclic and a bulky one, such as *tert*-butyldimethylsilyl (TBS) group, was expected to greatly change a conformation. Protection of tetrol **21** with *tert*-butylchlorodimethylsilane (TBSCl) gave tri-TBS ether **26**. Whereas large coupling constants among H-3, H-4 and H-4a ($J_{3,4}$=8.3 Hz, $J_{4,4a}$=11.6 Hz) were observed in diketal **22**, in which oxygen functions at C3 and C4 should be fixed in diequatorial positions due to a ketal ring formation, a small coupling constant (J=3.7 Hz) between H-3 and H-4 and no coupling between H-4 and H-4a in **26** indicated

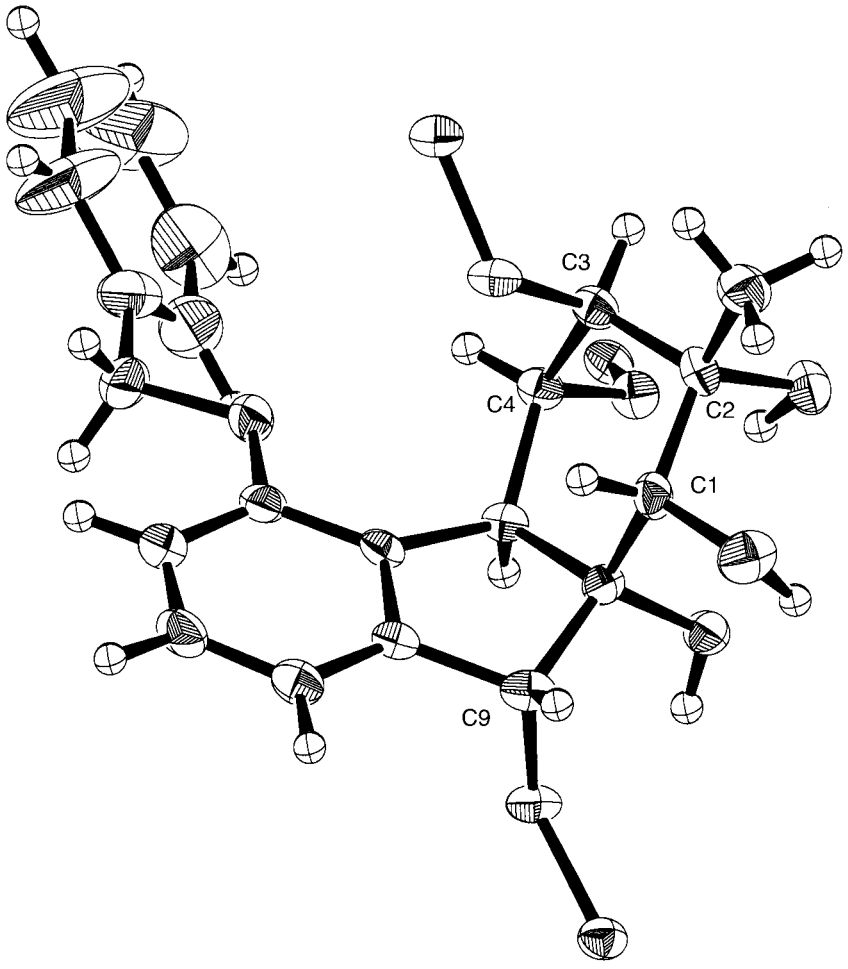
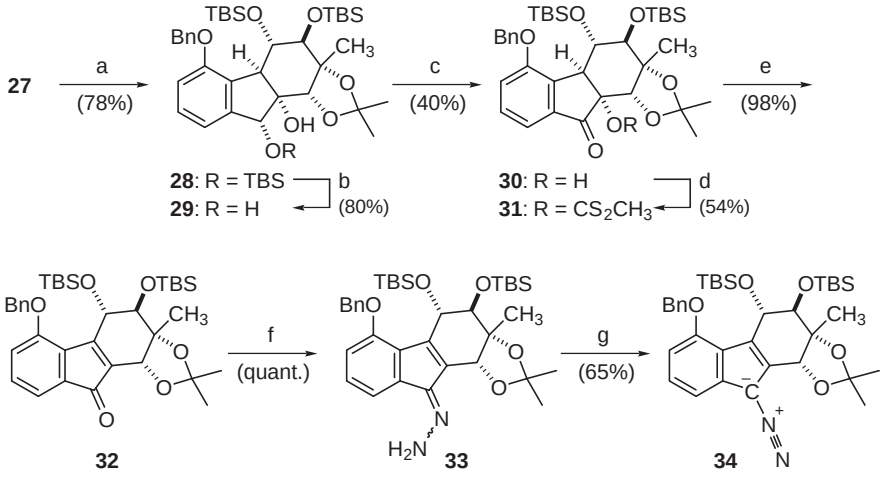


Figure 7. X-Ray crystallography of **27**. Alkyl groups on TBS were omitted for clarity.

diaxial orientation of the OTBS groups at C3 and C4. In this situation, the concave face of **26** would be severely shielded by an axial C3-OTBS group and C9-H in the boat-like conformation (Fig. 6b). Thus, treatment of tri-TBS ether **26** with stoichiometric amount[27] of OsO_4 in pyridine afforded triol **27** with a desired relative configuration,[28] which was confirmed by the X-ray crystallography (Scheme 5, Fig. 7).

Selective ketal formation between C1– and C2–OH of triol **27** followed by partial desilylation with an equimolar amount of tetrabutylammonium fluoride (TBAF) afforded diol **29** as only one isomer. The structure of **29** was determined by the X-ray crystallography (Fig. 8). Oxidation of **29** with pyridinium dichromate (PDC) gave α-hydroxyketone **30**, which was converted to the corresponding xanthate **31** by treatment with carbon disulfide (CS_2) and iodomethane (CH_3I). Pyrolysis of **31** under vacuum smoothly proceeded to yield a tetrahydrofluorenone system **32**. The enone **32**



Scheme 6. Synthesis of diazo compound **34**. (a) 2,2-dimethoxypropane–acetone (5:1), *p*-TsOH·H_2O, 60°C, 19 h; (b) TBAF, THF, 0°C, 15 min; (c) PDC, CH_2Cl_2, rt, 24 h; (d) (i) NaH, THF, rt, 1 h, (ii) CS_2, rt, 1 h, (iii) CH_3I, rt, 1.5 h; (e) 300°C, 20 mmHg (Kugelrohr), 20 min; (f) NH_2NH_2·H_2O, EtOH, reflux, 3 h; (g) Ag_2O, Et_2O, then KOH in CH_3OH, 0°C, 1 h, and then rt, 2 h.

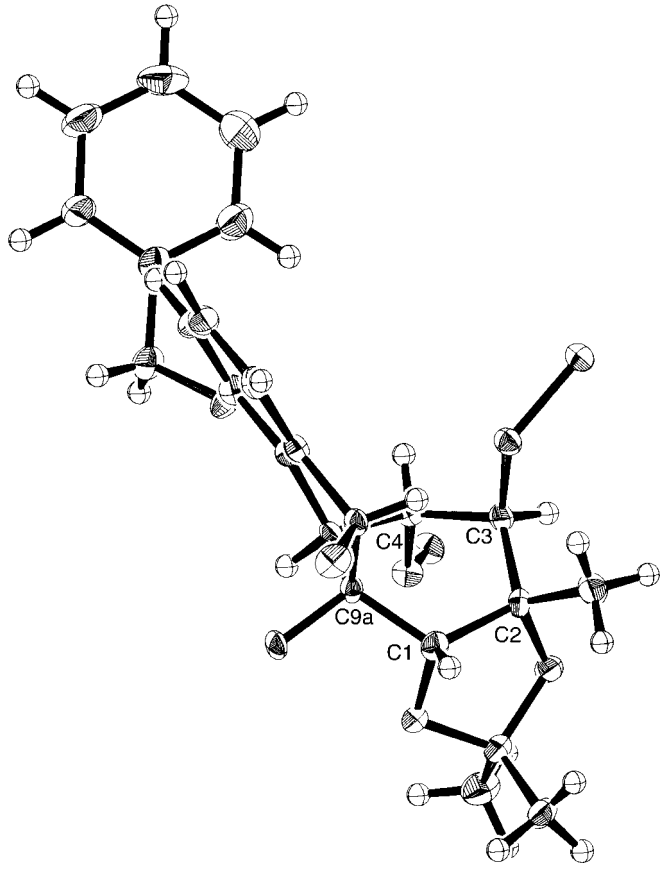


Figure 8. X-Ray crystallography of **29**. Alkyl groups on TBS were omitted for clarity.

was treated with hydrazine hydrate in ethanol to afford hydrazone **33** as (*E*)- and (*Z*)-isomers at a ratio of ca. 1:1, which were easily isomerized each other to give ca. 1:1 mixtures. Conversion of a ca. 1:1 mixture of **33** to a diazo system was successfully achieved with silver (I) oxide (Ag_2O) in the presence of potassium hydroxide (KOH)[29] to give a desired 9-diazotetrahydrofluorene **34** with correct stereochemistries at C1–C4 (Scheme 6). The absorption at 2067 cm^{-1} in the IR spectrum and the resonance at 66.1 ppm in the ^{13}C NMR of **34** are in the range for those of the typical diazo compounds.[30]

3. Conclusions

In conclusion, we have succeeded in elaboration of highly oxygenated D ring with correct stereochemistries for kinamycin skeletons. Currently our efforts continue to improve ineffective steps and to complete the enantioselective total synthesis of kinamycins.

4. Experimental

4.1. General

All melting points were measured on a micro melting-point hot stage (Yanagimoto) and uncorrected. IR spectra were recorded on a JASCO FT/IR-300E spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ on JEOL JNM-GSX400A (400 MHz), -GSX500A (500 MHz) or -ECP600 (600 MHz), using tetramethysilane (0.00 ppm) or residual chloroform ($CHCl_3$) (7.26 ppm) as an internal standard unless stated otherwise. ^{13}C NMR spectra were recorded on JEOL JNM-GSX500A (125 MHz) or -ECP600 (150 MHz), using the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. EIMS were recorded on a JEOL Automass with direct inlet or a Hewlett Packerd 5890 Series II Gas Chromatograph and 5971A Mass Selective Detector with GC-MS. FABMS were recorded on a JMS-HX110 with *m*-nitrobenzyl alcohol as a matrix. Silica gel (Fuji Silysia FL100D) was used for column chromatography. Dichloromethane (CH_2Cl_2) was distilled from phosphorus pentoxide (P_2O_5) before use. Chlorotrimethylsilane (TMSCl), *N*,*N*-dimethylformamide (DMF) and acetonitrile (CH_3CN) were distilled from calcium hydride (CaH_2). $Pd(OAc)_2$ was purified according to the reported procedure.[31] *p*-Benzoquinone was recrystallized from benzene. Organic extract was dried over Na_2SO_4 before evaporation.

4.1.1. 7-Benzyloxy-3-trimethylsilyloxyindene (15). A mixture of 4-benzyloxy-1-indanone (4.00 g, 16.8 mmol), TMSCl (3.20 mL, 25.2 mmol) and triethylamine (5.36 mL, 38.4 mmol) in DMF (40 mL) was stirred at 60°C for 16 h under N_2. After addition of saturated $NaHCO_3$ aq (100 mL), the whole was extracted with *n*-hexane (3×50 mL). The combined organic layer was successively washed with cold 5% HCl (1×30 mL), saturated $NaHCO_3$ aq (1×30 mL), H_2O (1×30 mL) and brine (1×30 mL), and evaporated to give **15** as an orange oil (5.41 g), which was used to the next step without further purification. IR ν ($CHCl_3$, cm^{-1}): 1610, 1580. ^1H NMR (500 MHz) δ: 0.30 (9H, s, TMS), 3.28 (2H, d, J=2.4 Hz, 1-H_2), 5.16 (2H, s, PhCH_2O), 5.44 (1H, t, J=2.4 Hz, 2-H), 6.81 (1H, d, J=8.1 Hz, 6-H), 7.03 (1H, d, J=7.3 Hz, 4-H), 7.25 (1H, dif. t, J=7.5 Hz, 5-H), 7.32 (1H, d, J=7.4 Hz, 4′-H), 7.39 (2H, t, J=7.4 Hz, 3′-, 5′-H), 7.45 (1H, d, J=7.4 Hz, 2′-, 6′-H).

4.1.2. 4-Benzyloxy-1-indenone (12). A solution of **15** (5.41 g, 17.4 mmol) in CH_3CN (20 mL) was added to a solution of $Pd(OAc)_2$ (1.88 g, 8.39 mmol) and *p*-benzoquinone (907 mg, 8.39 mmol) in CH_3CN (60 mL) under nitrogen (N_2) and the mixture was stirred at room temperature (rt) for 2 h. After further addition of $Pd(OAc)_2$ (950 mg, 4.23 mmol), the mixture was stirred at rt for 3 h. AcOEt (80 mL) was added and precipitates were filtered off through Celite pad. Evaporation of the AcOEt solution followed by purification by column chromatography (*n*-hexane–AcOEt=30:1) gave **12** as an orange oil (2.54 g, 64% in 2 steps). IR ν ($CHCl_3$, cm^{-1}): 1700, 1615, 1600. ^1H NMR (500 MHz) δ: 5.14 (2H, s, PhCH_2O), 5.78 (1H, d, J=5.8 Hz, 2-H), 6.99 (1H, d, J=8.6 Hz, 5-H), 7.09 (1H, d, J=7.0 Hz, 7-H), 7.19 (1H, dd, J=8.6, 7.0 Hz, 6-H), 7.30–7.45 (5H, m, Ar–H), 7.80 (1H, d, J=5.8 Hz, 3–H). EIMS *m*/*z*: 236 (M^+, 8.3%), 91 (100%).

4.1.3. (±)-(1*S*,4a*S*,9a*S*)-5-Benzyloxy-1-methoxy-2-methyl-1,4,4a,9a-tetrahydro-3-trimethylsilyloxy-9-fluorenone (11). A solution of **12** (2.12 g, 8.97 mmol) and **13** (4.01 g, 21.5 mmol) in dry benzene (20 mL) was refluxed for 2 h under argon (Ar) and the solvent was evaporated. The excess of **13** was distilled off under reduced pressure (110°C, 20 mmHg) to give **11** (3.92 g) as an orange oil, which was used to the next step without further purification. IR ν (neat, cm^{-1}): 1717, 1676. ^1H NMR (500 MHz) δ: 0.14 (9H, s, TMS), 1.77 (3H, d, J=2.5 Hz, 2-CH_3), 2.55 (1H, ddd, J=14.9, 10.8, 2.5 Hz, 4-H), 2.85 (1H, dd, J=14.9, 7.8 Hz, 4-H), 2.91 (1H, dd, J=8.8, 4.6 Hz, 9a-H), 3.10 (3H, s, OCH_3), 3.71 (1H, br ddd, J=10.8, 8.8, 7.6 Hz, 4a-H), 4.38 (1H, d, J=4.6 Hz, 1-H), 5.10, 5.13 (each 1H, d, J=11.2 Hz, PhCH_2O), 7.10 (1H, d, J=7.8 Hz, 6-H), 7.31–7.46 (7H, m, 7-, 8-, Ar–H).

4.1.4. (±)-(1*S*,2*R*,4a*S*,9a*S*)-5-Benzyloxy-1,2,3,4,4a,9a-hexahydro-2-hydroxy-1-methoxy-2-methyl-3,9-fluorenedione (16). A solution of *m*-CPBA (80%, 78 mg, 0.36 mmol) in CH_2Cl_2 (0.5 mL) was added to a suspension of **11** (153 mg, 0.36 mmol) and Na_2HPO_4 (81 mg, 0.57 mmol) in CH_2Cl_2 (1 mL) and the mixture was stirred at 0°C for 3 h and then at rt for 5 h. After addition of 10% Na_2SO_3 aq (5 mL), the whole was extracted with AcOEt (3×10 mL). The combined organic layer was washed with H_2O (1×10 mL) and brine (1×10 mL) and evaporated. Purification of the residue by column chromatography (*n*-hexane–AcOEt=1:1) gave **16** as colorless needles (78 mg, 61%, 2 steps from **12**), mp 180–183°C, which were recrystallized from ethanol. IR ν (Nujol, cm^{-1}): 3377, 1721, 1687. ^1H NMR (500 MHz) δ: 1.42 (3H, s, CH_3), 2.31 (1H, br s, OH), 2.77 (1H, dd, J=14.6, 12.6 Hz, 4-H), 3.30 (1H, dd, J=14.6, 6.0 Hz, 4-H), 3.32 (1H, dd, J=8.2, 4.4 Hz, 9a-H), 3.42 (3H, s, OCH_3), 3.88 (1H, ddd, J=12.6, 8.2, 6.0 Hz, 4a-H), 4.14 (1H, d, J=4.4 Hz, 1-H), 5.15, 5.18 (each 1H, d, J=12.2 Hz, PhCH_2O), 7.11 (1H, dd, J=8.0, 0.9 Hz, 6-H), 7.31–7.47 (7H, m, 7-, 8-, Ar–H). EIMS *m*/*z*: 366 (M^+,

3.6%), 91 (100%). Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C,72.07; H, 6.17.

4.1.5. (±)-(4a*S*,9a*S*)-5-Benzyloxy-2-methyl-3,4,4a,9a-tetrahydro-3,9-fluorenedione (17). Camphorsulfonic acid (CSA) (431 mg, 1.85 mmol) was added to a solution of **11** (3.92 g, 9.28 mmol) in CH_2Cl_2 (40 mL) in one portion at 0°C and the mixture was stirred at 0°C for 10 min. After addition of saturated $NaHCO_3$ aq (20 mL), the aqueous layer was separated and extracted with AcOEt (2×50 mL). The combined organic layer was washed with H_2O (1×20 mL) and brine (1×20 mL) and evaporated to give crude **17** as an orange oil (3.34 g), which was used to the next step without further purification. IR ν (neat, cm^{-1}): 1710, 1680. ^1H NMR (500 MHz) δ: 1.83 (3H, s, 2-CH_3), 2.61 (1H, dd, J=16.2, 9.2 Hz, 4-H), 3.10 (1H, dd, J=16.2, 7.3 Hz, 4-H), 3.56 (1H, m, 9a-H), 4.18 (1H, ddd, J=9.2, 7.3, 7.3 Hz, 4a-H), 5.15, 5.20 (each 1H, d, J=11.6 Hz, PhCH_2O), 6.85 (1H, dd, J=4.6, 1.9 Hz, 1-H), 7.15 (1H, d, J=6.9, 2.0 Hz, 6-H), 7.30 (7H, m, 7-, 8-, Ar–H). ^{13}C NMR (125 MHz) δ: 16.2 (CH_3), 35.0 (C4a), 40.3 (C4), 49.5 (C9a), 70.3 (OCH_2Ph), 116.4 (C6), 117.4 (C8), 127.4 (C2′, C6′), 128.3 (C4′), 128.8 (C3′, C5′), 130.0 (C7), 136.0, 136.1, 136.4, 138.2 (C1), 144.5 (C2), 156.1 (C5), 198.0 (C=O), 202.5 (C=O). EIMS m/z: 318 (M^+, 100%), 91 (94%).

4.1.6. (±)-(4a*R*,9a*R*)-6-Benzyloxy-9a-hydroxy-2-methyl-3,4,4a,9a-tetrahydro-3,9-fluorenedione (18). A solution of crude **17** (3.04 g, 9.55 mmol) and KF (553 mg, 9.52 mmol) in DMSO (30 mL) was stirred at rt for 2 h under O_2. AcOEt (300 mL) was added and the whole was washed by H_2O (100 mL). The aqueous layer was extracted with AcOEt (2×100 mL). The combined organic layer was washed with H_2O (1×100 mL) and brine (1×100 mL) and evaporated. Purification of the residue by column chromatography (*n*-hexane–AcOEt=10:1–3:1) gave **18** as colorless prisms (1.72 g, 63%, 3 steps from **12**), mp 128.5–129.5°C, which were recrystallized from ethanol. IR ν (Nujol, cm^{-1}): 3464, 1726, 1657. ^1H NMR (400 MHz) δ: 1.76 (3H, d, J=1.5 Hz, 2-CH_3), 3.02 (1H, dd, J=16.5, 7.3 Hz, 4-H), 3.15 (1H, br, OH, exchangeable), 3.62 (1H, dd, J=16.5, 3.0 Hz, 4-H), 3.92 (1H, ddd, J=7.3, 3.0, 1.5 Hz, 4a-H), 5.14, 5.18 (each 1H, d, J=11.5 Hz, PhCH_2O), 6.28 (1H, dif. t, J=1.5 Hz, 1-H), 7.18 (1H, m, 6-H), 7.35–7.50 (7H, m, 7-, 8-, Ar–H). EIMS m/z: 334 (M^+, 4.3%), 91 (100%). Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.39; H, 5.27.

4.1.7. (±)-(4a*R*,9a*R*)-5-Benzyloxy-4a,9a-dihydro-2-methyl-3,9a-bis(trimethylsilyloxy)-9-fluorenone (19). Trimethylsilyl trifluoromethanesulfonate (0.63 mL, 3.24 mmol) was added to a solution of **18** (495 mg, 1.48 mmol) and triethylamine (0.50 mL, 3.59 mmol) in CH_2Cl_2 (5 mL) at 0°C. After 10 min, saturated $NaHCO_3$ aq (10 mL) was added. The aqueous layer was separated and extracted with AcOEt (2×20 mL). The combined organic layer was washed with H_2O (1×10 mL) and brine (1×10 mL) and evaporated. Purification of the residue by column chromatography (*n*-hexane–AcOEt=10:1) gave **19** as yellow prisms (616 mg, 87%), mp 122–124°C. IR ν ($CHCl_3$, cm^{-1}): 1720. ^1H NMR (400 MHz) δ: 0.10, 0.15 (each 9H, s, 2×TMS), 1.74 (3H, d, J=1.2 Hz, 2-CH_3), 3.99 (1H, d, J=6.1 Hz, 4a-H), 5.14, 5.17 (each 1H, d, J=12.2 Hz, PhCH_2O), 5.50 (1H, br s, 1-H), 5.67 (1H, d, J=6.1 Hz, 4-H), 7.15 (1H, d, J=8.0 Hz, 6-H), 7.26–7.48 (7H, m, 7-, 8-, Ar–H).

4.1.8. Dihydroxylation of the dienol 19 followed by desilylation. OsO_4 (17.8 mg, 7.0×10^{-2} mmol) was added to a suspension of **19** (671 mg, 1.40 mmol) and NMO (97%, 237 mg, 1.96 mmol) in THF–H_2O (20:1, 7 mL) at 0°C. After stirring at 0°C for 1 h and then at rt for 12 h, the mixture was concentrated to ca. 1 mL and partitioned with AcOEt (50 mL) and 10% Na_2SO_3 aq (50 mL). The aqueous layer was extracted with AcOEt (2×50 mL). The combined organic layer was washed with 10% Na_2SO_3 aq (1×50 mL), H_2O (1×50 mL) and brine (1×50 mL) and evaporated. The residue was dissolved in methanol (10 mL) and 10% HCl (0.5 mL) was added at rt. After 2 min, saturated $NaHCO_3$ aq (50 mL) was added and the whole was extracted with AcOEt (3×30 mL). The combined organic layer was washed with H_2O (1×30 mL) and brine (1×30 mL) and evaporated. Purification of the residue by column chromatography (*n*-hexane–AcOEt=5:1–1:1) gave a ca. 5:1 mixture of **20**α and **20**β as colorless prisms (314 mg, 64%), which were used to the next step without separation.

4.1.9. (±)-(4*S*,4a*S*,9a*S*)-5-Benzyloxy-4,9a-dihydroxy-2-methyl-3,4,4a,9a-tetrahydro-3,9-fluorenedione (20α). A part of the mixture was recrystallized from AcOEt to give **20**α as colorless prisms, mp 140–142°C. IR ν (Nujol, cm^{-1}): 3376, 1702. ^1H NMR (500 MHz) δ: 1.91 (3H, d, J=1.2 Hz, 2-CH_3), 2.91 (1H, br s, 9a-OH, exchangeable), 3.52 (1H, d, J=3.7 Hz, 4-OH, exchangeable), 3.96 (1H, d, J=7.6 Hz, 4a-H), 4.50 (1H, dd, J=7.6, 3.7 Hz, 4-H), 5.17, 5.23 (each 1H, d, J=11.6 Hz, PhCH_2O), 6.61 (1H, s, 1-H), 7.23–7.50 (8H, m, Ar–H). EIMS m/z: 350 (M^+, 0.3%), 91 (100%). Anal. Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 72.05; H, 5.31.

4.1.10. (±)-(4*R*,4a*S*,9a*S*)-5-Benzyloxy-4,9a-dihydroxy-2-methyl-3,4,4a,9a-tetrahydro-3,9-fluorenedione (20β). Recrystallization of the mother liquor from CH_2Cl_2 gave **20**β as colorless prisms, mp 188–191°C. IR ν (Nujol, cm^{-1}): 3430, 3360, 1705, 1665. ^1H NMR (400 MHz) δ: 1.73 (3H, d, J=1.5 Hz, 2-CH_3), 3.22 (1H, br s, 9a-OH, exchangeable), 4.00 (1H, dd, J=5.1, 1.7 Hz, 4a-H), 4.61 (1H, d, J=11.5 Hz, 4-OH, exchangeable), 5.06 (1H, dd, J=11.5, 5.1 Hz, 4-H), 5.18, 5.22 (each 1H, d, J=11.0 Hz, PhCH_2O), 6.08 (1H, dq, J=1.5, 1.5 Hz, 1-H), 7.23–7.50 (8H, m, Ar–H). EIMS m/z: 350 (M^+, 1.3%), 332 (2.9%), 91 (100%). Anal. Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 71.79; H, 5.17.

4.1.11. (±)-(3*S*,4*S*,4a*S*,9*R*,9a*S*)-5-Benzyloxy-2-methyl-3,4,4a,9a-tetrahydro-3,4,9,9a-fluorenetetrol (21). DIBAL-H (1.0 M in hexane, 0.13 mL, 0.13 mmol) was added to a solution of a ca. 5:1 mixture of **20**α and **20**β (22 mg, 6.3×10^{-2} mmol) in THF (0.5 mL) at −78°C. After stirring at −78°C for 1 h, 10% HCl (3 mL) was added and the whole was extracted with AcOEt (3×5 mL). The combined organic layer was washed with H_2O (1×10 mL) and brine (1×10 mL) and evaporated. Recrystallization of the residue from ethanol gave **21** as colorless needles (16 mg, 72%), mp 208.5–210.5°C. IR ν (Nujol, cm^{-1}): 3430, 3371, 1592. ^1H

NMR (500 MHz, $CDCl_3$–CD_3OD) δ: 1.86 (3H, s, 2-CH_3), 3.47 (1H, d, J=11.3 Hz, 4a-H), 3.52 (1H, dd, J=11.3, 7.3 Hz, 4-H), 4.26 (1H, d, J=7.3 Hz, 3-H), 4.99 (1H, s, 9-H), 5.10, 5.17 (each 1H, d, J=11.3 Hz, PhCH_2O), 5.62 (1H, s, 1-H), 6.92 (1H, d, J=8.2 Hz, 6-H), 7.07 (1H, d, J=7.3 Hz, 8-H), 7.30 (1H, dif. t, J=7.5 Hz, 7-H), 7.32–7.42 (5H, m, Ar–H). FABMS m/z: 335 [$(MH)^+$]. Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 70.99; H, 6.06.

4.1.12. (±)-(3*S*,4*S*,4a*S*,9*R*,9a*S*)-5-Benzyloxy-3,4;9,9a-bis-(dimethylmethylenedioxy)-2-methyl-3,4,4a,9a-tetrahydrofluorene (22). A solution of 2-methoxypropene (95%, 0.10 mL, 0.99 mmol) in DMF (0.60 mL) was prepared. **21** (22 mg, 5.9×10^{-2} mmol) and CSA (2 mg, 8.6×10^{-3} mmol) were added to a part of the DMF solution (0.30 mL) and the mixture was stirred at rt for 2 h. After addition of AcOEt (20 mL), the whole was washed with saturated $NaHCO_3$ aq (1×15 mL). The aqueous layer was extracted with AcOEt (2×10 mL). The combined organic layer was washed with H_2O (1×10 mL) and brine (1×10 mL) and evaporated. Recrystallization of the residue from *n*-hexane gave **22** as colorless needles (22 mg, 86%), mp 151–155°C. IR ν (Nujol, cm^{-1}): 1592. ^{1}H NMR (400 MHz) δ: 0.84, 1.36, 1.48, 1.53 (each 3H, s, 4×CH_3), 1.93 (3H, dd, J=1.2, 1.2 Hz, 2-CH_3), 3.27 (1H, dd, J=11.6, 8.3 Hz, 4-H), 3.91 (1H, d, J=11.6 Hz, 4a-H), 4.39 (1H, dq, J=8.3, 1.2 Hz, 3-H), 5.09, 5.19 (each 1H, d, J=11.9 Hz, PhCH_2O), 5.40 (1H, s, 9-H), 5.49 (1H, dq, J=1.2, 1.2 Hz, 1-H), 6.89 (1H, d, J=8.3 Hz, 6-H), 7.04 (1H, d, J=7.3 Hz, 8-H), 7.27–7.47 (4H, m, 7-, 3′-, 4′-, 5′-H), 7.62 (2H, d, J=7.3 Hz, 2′-, 6′-H). EIMS m/z: 435 [$(M+1)^+$, 0.2%], 434 (M^+, 0.3%), 91 (100%). Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.63; H, 6.96. Found: C, 74.84; H, 7.00.

4.1.13. (±)-(1*R*,2*S*,3*R*,4*R*,4a*S*,9*R*,9a*R*)-5-Benzyloxy-3,4;9,9a-bis(dimethylmethylenedioxy)-2-methyl-1,2,3,4,4a,9a-hexahydro-1,2-fluorenediol (23). OsO_4 (1.2 mg, 4.8×10^{-3} mmol) was added to a mixture of **22** (16 mg, 3.7×10^{-2} mmol) and NMO (97%, 6 mg, 5.0×10^{-2} mmol) in THF–H_2O (8:1, 0.5 mL) at 0°C. After stirring at 0°C for 1 h and then at rt for 24 h, AcOEt (10 mL) was added and the whole was washed with 10% Na_2SO_3 aq (1×10 mL). The aqueous layer was extracted with AcOEt (2×10 mL). The combined organic layer was washed with H_2O (1×10 mL) and brine (1×10 mL) and evaporated. Recrystallization of the residue from CH_2Cl_2–*n*-hexane gave **23** as colorless prisms (17 mg, 98%), mp 178–183°C. IR ν (Nujol, cm^{-1}): 3530, 3412. ^{1}H NMR (500 MHz) δ: 0.92, 1.31 (each 3H, s, 2×CH_3), 1.50 (9H, s, 3×CH_3), 2.37 (1H, s, 2-OH, exchangeable), 2.87 (1H, d, J=5.8 Hz, 1-OH, exchangeable), 3.63 (1H, d, J=9.8 Hz, 3- or 4a-H), 3.68 (1H, d, J=10.4 Hz, 3- or 4a-H), 3.78 (1H, d, J=5.8 Hz, 1-H), 3.79 (1H, dd, J=10.4, 9.8 Hz, 4-H), 5.10, 5.13 (each 1H, d, J=11.6 Hz, PhCH_2O), 5.70 (1H, s, 9-H), 6.87 (1H, d, J=8.2 Hz, 6-H), 7.06 (1H, d, J=7.3 Hz, 8-H), 7.23–7.30 (2H, m, 7-, 4′-H), 7.34 (2H, dif. t, J=7.7 Hz, 3′-, 5′-H), 7.57 (2H, dif. d, J=7.0 Hz, 2′-, 6′-H). EIMS m/z: 469 [$(M+1)^+$, 0.1%], 468 (M^+, 0.2%), 91 (100%). Anal. Calcd for $C_{27}H_{32}O_7$: C, 69.21; H, 6.88. Found: C, 68.81; H, 6.86.

4.1.14. (±)-(3*S*,4*S*,4a*S*,9*R*,9a*S*)-5-Benzyloxy-3,4-dimethylmethylenedioxy-2-methyl-3,4,4a,9a-tetrahydro-9,9a-fluorenediol (24). A solution of 2-methoxypropene (95%, 0.10 mL, 0.99 mmol) in DMF (1 mL) was prepared. A part of the solution (0.5 mL) was added to a solution of **21** (83 mg, 0.24 mmol) and CSA (2.6 mg, 1.1×10^{-2} mmol) in DMF (3 mL) at rt. After stirring at rt for 2 h, saturated $NaHCO_3$ aq (10 mL) was added and the whole was extracted with AcOEt (3×20 mL). The combined organic layer was washed with H_2O (1×10 mL) and brine (1×10 mL) and evaporated. Purification of the residue by column chromatography (*n*-hexane–AcOEt=3:1–2:1) gave crystalline product (65 mg),[32] which was recrystallized from AcOEt to give **24** (34 mg, 37%) as colorless needles, mp 191–193°C, in addition to diketal **22** (23 mg, 22%). IR ν (Nujol, cm^{-1}): 3288, 1590. ^{1}H NMR (500 MHz) δ: 1.38, 1.54, 1.93 (each 3H, s, 3×CH_3), 2.35 (1H, br s, 9a-OH, exchangeable), 2.76 (1H, d, J=9.8 Hz, 9-OH, exchangeable), 3.45 (1H, dd, J=11.9, 8.6 Hz, 4-H), 3.71 (1H, d, J=11.9 Hz, 4-H), 4.40 (1H, br d, J=8.6 Hz, 3-H), 5.02 (1H, d, J=9.2 Hz, 9-H), 5.06, 5.20 (each 1H, d, J=11.9 Hz, PhCH_2O), 5.57 (1H, br s, 1-H), 6.88 (1H, d, J=8.2 Hz, 6-H), 7.04 (1H, d, J=7.7 Hz, 8-H), 7.28 (2H, m, 7-, 4′-H), 7.36 (2H, d, J=7.3, 7.3 Hz, 3′-, 5′-H), 7.60 (2H, dif. d, J=7.3 Hz, 2′-, 6′-H). Anal. Calcd for $C_{24}H_{26}O_5$: C, 73.08; H, 6.64. Found: C, 72.74; H, 6.48.

4.1.15. (±)-(1*S*,2*S*,3*S*,4*S*,4a*S*,9*S*,9a*S*)-5-Benzyloxy-3,4-dimethylmethylenedioxy-2-methyl-3,4,4a,9a-tetrahydro-1,2,9,9a-fluorenetetrol (25). OsO_4 (1 mg, 3.9×10^{-3} mmol) was added to a mixture of **24** (11 mg, 2.8×10^{-2} mmol) and NMO (97%, 4.3 mg, 3.6×10^{-2} mmol) in THF–H_2O (20:1, 0.2 mL) at 0°C. After stirring at rt for 6 h, NMO (97%, 4.3 mg, 3.6×10^{-2} mmol) and OsO_4 (1 mg, 3.9×10^{-3} mmol) were added. After stirring at rt for 12 h, AcOEt (10 mL) was added and the whole was washed with 10% Na_2SO_3 aq (1×10 mL). The aqueous layer was extracted with AcOEt (2×10 mL). The combined organic layer was washed with 10% Na_2SO_3 aq (1×10 mL), H_2O (1×20 mL) and brine (1×20 mL) and evaporated. Recrystallization of the residue from AcOEt–CH_2Cl_2 gave **25** as colorless needles (8 mg, 65% as 1/2 hydrate), mp 191–193°C. IR ν (Nujol, cm^{-1}): 3411, 3298. ^{1}H NMR (500 MHz) δ: 1.37, 1.51, 1.52 (each 3H, s, 3×CH_3), 2.10 (1H, br s, OH), 2.91 (1H, d, J=6.8 Hz, 1-OH, exchangeable), 3.52 (1H, s, 9a-OH, exchangeable), 3.53 (1H, d, J=10.8 Hz, 3- or 4a-H), 3.56 (1H, d, J=9.6 Hz, 3- or 4a-H), 3.76 (1H, dd, J=10.8, 9.6 Hz, 4-H), 3.88 (1H, d, J=6.8 Hz, 1-H), 5.07, 5.17 (each 1H, d, J=12.4 Hz, PhCH_2O), 5.69 (1H, d, J=4.4 Hz, 9-H), 6.85 (1H, d, J=8.4 Hz, 6-H), 7.03 (1H, d, J=7.2 Hz, 8-H), 7.24–7.26 (4H, m, 7-, 3′-, 4′-, 5′-H), 7.57 (2H, dif. d, J=7.2 Hz, 2′-, 6′-H). Anal. Calcd for $C_{24}H_{28}O_7\cdot1/2\ H_2O$: C, 65.89; H, 6.68. Found: C, 66.07; H, 6.72.

4.1.16. (±)-(3*R*,4*S*,4a*S*,9*R*,9a*S*)-5-Benzyloxy-2-methyl-3,4,4a,9a-tetrahydro-3,4,9-tris(*tert*-butyldimethylsilyloxy)-9a-fluorenol (26). A mixture of **21** (93.5 mg, 0.26 mmol), TBSCl (199 mg, 1.32 mmol) and imidazole (126 mg, 1.85 mmol) in DMF (2 mL) was stirred at rt for 5 h and then at 50°C for 2.5 h under Ar. After addition of AcOEt (30 mL), the whole was washed with cold 5% HCl (2×10 mL), H_2O (1×20 mL) and brine (1×20 mL), and evaporated. Purification of the residue by column chromatography (*n*-hexane–AcOEt=30:1–20:1) gave **26** as a colorless oil (109 mg, 60%), IR ν (neat, cm^{-1}): 3511, 1595. ^{1}H NMR (500 MHz) δ: −0.26 (3H, s, CH_3), −0.05 (6H, s,

2×CH_3), −0.04, 0.18, 0.21 (each 3H, s, 3×CH_3), 0.53, 0.82, 0.98 (each 9H, s, 3×^{t}Bu), 1.83 (3H, d, J=1.5 Hz, 2-CH_3), 3.46 (1H, s, 4a-H), 3.81 (1H, d, J=3.7 Hz, 3-H), 3.96 (1H, br, 9a-OH), 4.40 (1H, d, J=3.7 Hz, 4-H), 5.13 (1H, d, J=12.5 Hz, PhCH_2O), 5.16 (1H, s, 9-H), 5.17 (1H, d, J=12.5 Hz, PhCH_2O), 5.86 (1H, br s, 1-H), 6.67 (1H, d, J=8.2 Hz, 6-H), 6.73 (1H, d, J=7.6 Hz, 8-H), 7.07 (1H, dd, J=8.2, 7.6 Hz, 7-H), 7.30 (1H, dif. t, J=7.0 Hz, 4′-H), 7.35 (2H, dif. t, J=7.0 Hz, 3′-, 5′-H), 7.40 (2H, dif. d, J=7.4 Hz, 2′-, 6′-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.2, −5.12, −5.06, −4.7, −4.4, −4.2, 17.6, 17.8, 18.1, 22.5, 25.3, 25.7, 25.8, 56.8, 69.7, 71.5, 73.2, 76.3, 85.5, 111.0, 116.8, 127.4, 127.8, 128.3, 128.6, 130.1, 132.6, 134.8, 137.3, 143.8, 155.3. HRFABMS *m/z*: 735.3673 (Calcd for $C_{39}H_{64}O_5Si_3K$: 735.3699).

4.1.17. (±)-(1*S*,2*S*,3*R*,4*S*,4a*R*,9*S*,9a*S*)-5-Benzyloxy-1,2,3,4,4a,9a-hexahydro-2-methyl-3,4,9-tris(*tert*-butyldimethylsilyloxy)-1,2,9a-fluorenetriol (27). OsO_4 (32 mg, 0.13 mmol) was added to a solution of **26** (80 mg, 0.11 mmol) in pyridine (1 mL) at 0°C. After stirring at 0°C for 1 h and then at rt for 24 h, $NaHSO_3$ aq (119 mg, 1.14 mmol in 0.2 mL) was added and the whole was extracted with AcOEt (3×15 mL). The combined organic layer was washed with saturated $NaHCO_3$ aq (1×10 mL), H_2O (1×10 mL) and brine (1×10 mL) and evaporated. Purification of the residue by column chromatography (*n*-hexane–AcOEt=20:1) gave **27** (73 mg, 91%) as colorless prisms, mp 132–133.5°C, which were recrystallized from ethanol. IR ν (Nujol, cm^{-1}): 3567, 3504. ^{1}H NMR (400 MHz) δ: −0.13, −0.11 (each 3H, s, 2×CH_3), 0.02 (9H, s, 3×CH_3), 0.21 (3H, s, CH_3), 0.50, 0.86, 0.88 (each 9H, s, 3×^{t}Bu), 1.19 (3H, s, 2-CH_3), 2.90 (1H, br, OH, exchangeable), 3.25 (1H, s, OH, exchangeable), 3.33 (1H, br s, 1-H), 3.65 (1H, br s, 4a-H), 3.68 (1H, d, J=2.9 Hz, 3-H), 4.36 (1H, s, OH, exchangeable), 4.99 (1H, d, J=10.6 Hz, PhCH_2O), 5.00 (1H, s, 9-H), 5.05 (1H, d, J=10.6 Hz, PhCH_2O), 5.07 (1H, dd, J=2.9 Hz, 1.2 Hz, 4-H), 6.79 (1H, d, J=8.4 Hz, 6-H), 6.92 (1H, d, J=7.5 Hz, 8-H), 7.11 (1H, dif. t, J=7.9 Hz, 7-H), 7.34–7.36 (3H, m, 2′-, 4′-, 6′-H), 7.43–7.44 (2H, m, 3′-, 5′-H). FABMS *m/z*: 753 [$(MNa)^+$]. Anal. Calcd for $C_{39}H_{66}O_7Si_3$: C, 64.06; H, 9.10. Found: C, 64.17; H, 9.20.

4.1.18. (±)-(1*R*,2*R*,3*R*,4*S*,4a*S*,9*R*,9a*R*)-5-Benzyloxy-1,2-dimethylethylenedioxy-1,2,3,4,4a,9a-hexahydro-2-methyl-3,4,9-tris(*tert*-butyldimethylsilyloxy)-9a-fluorenol (28). A mixture of **27** (77 mg, 0.11 mmol), 2,2-dimethoxypropane (0.8 mL, 6.5 mmol), acetone (0.2 mL, 2.72 mmol) and *p*-toluenesulfonic acid hydrate (0.5 mg, 2.6×10^{-3} mmol) was stirred at 60°C for 19 h. $NaHCO_3$ powder (10 mg, 0.12 mmol) was added and the mixture was stirred at rt for 30 min and evaporated. Purification of the residue by preparative TLC (*n*-hexane–AcOEt=10:1) gave **28** as a colorless oil (64 mg, 78%). IR ν ($CHCl_3$, cm^{-1}): 3493. ^{1}H NMR (500 MHz) δ: −0.29, 0.00 (each 3H, s, CH_3), 0.11 (6H, s, 2×CH_3), 0.26, 0.28 (each 3H, s, 2×CH_3), 0.67, 0.91, 0.97 (each 9H, s, 3×^{t}Bu), 1.46 (3H, s, ketal CH_3), 1.50 (3H, s, 2-CH_3), 1.60 (3H, s, ketal CH_3), 3.63 (1H, d, J=3.1 Hz, 3-H), 3.70 [2H (1H with D_2O), br s, 4a-H, OH], 4.14 (1H, s, 1-H), 4.29 (1H, br d, J=3.1 Hz, 4-H), 5.18, 5.21 (each 1H, d, J=14.6 Hz, PhCH_2O), 5.24 (1H, s, 9-H), 6.61 (1H, d, J=8.3 Hz, 6-H), 6.75 (1H, d, J=7.7 Hz, 8-H), 7.03 (1H, dd, J=8.3, 7.7 Hz, 7-H), 7.26–7.37 (5H, m, Ar–H). ^{13}C NMR (125 MHz) δ: −5.1, −4.8, −4.4, −3.6, −3.4, −2.8, 17.8, 18.1, 18.5, 25.7, 25.8, 25.9, 26.5, 26.8, 28.4, 52.0, 69.8, 75.0, 76.0, 78.7, 78.8, 81.5, 81.9, 107.6, 111.8, 117.1, 126.7, 127.6, 128.4, 128.6, 131.3, 137.5, 143.1, 155.6. HRFABMS *m/z*: 793.4266 (Calcd for $C_{42}H_{70}O_7Si_3Na$: 793.4327).

4.1.19. (±)-(1*R*,2*R*,3*S*,4*S*,4a*S*,9*R*,9a*S*)-5-Benzyloxy-3,4-bis(*tert*-butyldimethylsilyloxy)-1,2-dimethylmethylenedioxy-1,2,3,4,4a,9a-hexahydro-2-methyl-9,9a-fluorenediol (29). TBAF (1 M in THF, 0.11 mL, 0.11 mmol) was added to a solution of **28** (28 mg, 3.6×10^{-2} mmol) in THF (0.5 mL) at 0°C under Ar. After stirring at 0°C for 15 min, H_2O (10 mL) and brine (5 mL) was added and the whole was extracted with AcOEt (3×20 mL). The combined organic layer was washed with H_2O (1×10 mL) and brine (1×10 mL) and evaporated. Purification of the residue by column chromatography (*n*-hexane–AcOEt=8:1) gave **29** as colorless needles (19 mg, 80%), mp 133–134°C, which were recrystallized from *n*-hexane. IR ν ($CHCl_3$, cm^{-1}): 3568, 1593. ^{1}H NMR (500 MHz) δ: −0.31, 0.00 (each 3H, s, 2×CH_3), 0.10 (6H, s, 2×CH_3), 0.56 (9H, br s, ^{t}Bu), 0.89 (9H, s, ^{t}Bu), 1.46, 1.50, 1.56 (each 3H, s, 3×CH_3), 3.01, 3.10 (each 1H, br, 2×OH, exchangeable), 3.56 (1H, s, 4a-H), 3.63 (1H, d, J=2.8 Hz, 3-H), 4.26 (1H, br s, 4-H), 4.34 (1H, s, 1-H), 5.08 (1H, br s, 9-H), 5.18, 5.21 (each 1H, d, J=15.2 Hz, PhCH_2O), 6.64 (1H, d, J=8.3 Hz, 6-H), 6.94 (1H, d, J=7.7 Hz, 8-H), 7.06 (1H, dif. t, J=8.0 Hz, 7-H), 7.26–7.47 (5H, m, Ar–H). FABMS *m/z*: 679 [$(MNa)^+$], 657 [$(MH)^+$]. Anal. Calcd for $C_{36}H_{56}O_7Si_2$: C, 65.81; H, 8.59. Found: C, 65.57; H, 8.36.

4.1.20. (±)-(1*R*,2*R*,3*S*,4*S*,4a*S*,9a*R*)-5-Benzyloxy-1,2-dimethylmethylenedioxy-1,2,3,4,4a,9a-hexahydro-9a-hydroxy-2-methyl-9-fluorenone (30). PDC (98%, 335 mg, 0.87 mmol) was added to a solution of **29** (195 mg, 0.30 mmol) in CH_2Cl_2 (5 mL) at 0°C. After stirring at rt for 24 h, the mixture was diluted with diethyl ether (Et_2O) (20 mL). The precipitates were filtered off through Celite pad and washed with Et_2O. The filtrate and the washings were combined and evaporated. Purification of the residue by column chromatography (*n*-hexane–AcOEt=20:1) gave **30** as colorless prisms (78 mg, 40%), mp 121.5–123.5°C, which were recrystallized from Et_2O–*n*-hexane. IR ν (KBr, cm^{-1}): 3420, 1730. ^{1}H NMR (500 MHz) δ: −0.46, −0.06, 0.10, 0.12 (each 3H, s, 4×CH_3), 0.53, 0.90 (each 9H, s, 2×^{t}Bu), 1.37, 1.50, 1.57 (each 3H, s, 3×CH_3), 3.06 (1H, br, OH, exchangeable), 3.61 (1H, s, 3-H), 4.34 (1H, d, J=3.4 Hz, 4-H), 4.64 (1H, s, 1-H), 5.25, 5.28 (each 1H, d, J=14.1 Hz, PhCH_2O), 6.99 (1H, d, J=8.0 Hz, 6-H), 7.19 (1H, dd, J=8.0 Hz, 7-H), 7.29–7.50 (6H, m, 8-, Ar–H). FABMS *m/z*: 655 [$(MH)^+$]. Anal. Calcd for $C_{36}H_{54}O_7Si_2$: C, 66.02; H, 8.31. Found: C, 66.16; H, 8.34.

4.1.21. (±)-(1*S*,2*R*,3*R*,4*S*,4a*S*,9a*R*)-*O*-[5-Benzyloxy-3,4-bis(*tert*-butyldimethylsilyloxy)-1,2-dimethylmethylenedioxy-1,2,3,4,4a,9a-hexahydro-2-methyl-9-oxo-9a-fluorenyl]-*S*-methyl dithiocarbonate (31). Solutions of CS_2 (0.10 mL, 1.66 mmol) in THF (1 mL) and of CH_3I (0.10 mL, 1.61 mmol) in THF (1 mL) were prepared. A solution of **30** (33 mg, 5.0×10^{-2} mmol) in THF (1.5 mL) was added to a suspension of NaH (60%, 10 mg,

0.25 mmol) in THF (0.5 mL) at 0°C and the whole was stirred at 0°C for 1 h. A part of the CS_2 solution (0.16 mL, 0.24 mmol) was added at 0°C. After stirring at 0° C for 1 h, a part of the CH_3I solution (0.16 mL, 0.23 mmol) was added at 0°C. After stirring at 0°C for 1.5 h, saturated NH_4Cl aq (10 mL) was added and the whole was extracted with AcOEt (3×10 mL). The combined organic layer was washed with H_2O (1×10 mL) and brine (1×10 mL) and evaporated. Purification of the residue by preparative TLC (*n*-hexane–AcOEt=20:1) gave **31** as a yellow oil (20 mg, 54%). IR ν ($CHCl_3$, cm^{-1}): 1726. ^1H NMR (500 MHz) δ: −0.11, −0.07, −0.03, 0.03 (each 3H, s, 4×CH_3), 0.71 (9H, br s, ^{t}Bu), 0.85 (9H, s, ^{t}Bu), 1.39, 1.54, 1.56 (each 3H, s, 3×CH_3), 2.50 (3H, s, SCH_3), 3.86 (1H, d, *J*=3.7 Hz, 3-H), 4.46 (1H, s, 4a-H), 4.56 (1H, s, 1-H), 4.80 (1H, dd, *J*=3.7 Hz, 1.8 Hz, 4-H), 5.14, 5.19 (each 1H, d, *J*=11.9 Hz, PhCH_2O), 7.10 (1H, d, *J*=8.0 Hz, 6-H), 7.19 (1H, dif. t, *J*=8.0 Hz, 7-H), 7.34–7.39 (6H, m, 8-, Ar–H). ^{13}C NMR (125 MHz) δ: −4.8, −4.5, −4.34, −4.25, 18.1, 19.2, 23.8, 26.0, 26.1, 26.7, 27.4, 47.9, 70.6, 73.4, 79.5, 80.8, 82.1, 89.8, 109.2, 116.6, 118.1, 128.1, 128.5, 128.8, 129.5, 135.8, 136.9, 138.4, 155.8, 197.6, 211.2. HRFABMS *m/z*: 745.3124 (Calcd for $C_{38}H_{57}O_7S_2Si_2$: 745.3117).

4.1.22. (±)-(1*R*,2*R*,3*R*,4*S*)-5-Benzyloxy-3,4-bis(*tert*-butyldimethylsilyloxy)-1,2-dimethylmethylenedioxy-2-methyl-1,2,3,4-tetrahydro-9-fluorenone (32). 31 (17 mg, 2.3×10^{-2} mmol) in Kugelrohr apparatus was heated at 300°C for 20 min under vacuum (20 mmHg) to leave **32** as a yellow oil (14 mg, 96%). IR ν ($CHCl_3$, cm^{-1}): 1708. ^1H NMR (500 MHz) δ: −0.06, 0.06 (each 3H, s, 2×CH_3), 0.12 (6H, s, 2×CH_3), 0.71, 0.85 (each 9H, s, 2×^{t}Bu), 1.32, 1.42, 1.45 (each 3H, s, 3×CH_3), 4.03 (1H, d, *J*=2.5 Hz, 3-H), 4.63 (1H, s, 1-H), 4.91 (1H, d, *J*=2.5 Hz, 4-H), 5.16, 5.20 (each 1H, d, *J*=12.8 Hz, PhCH_2O), 6.92 (1H, m, 6-H), 7.11–7.13 (2H, m, 7-, 8-H), 7.34–7.36 (5H, m, Ar–H). ^{13}C NMR (125 MHz) δ: −4.7, −4.5, −3.9, −3.3, 17.9, 18.3, 25.0, 25.8, 25.9, 29.0, 29.9, 69.3, 70.9, 73.3, 75.5, 81.5, 111.3, 115.9, 119.5, 127.3, 128.2, 128.75, 128.80, 129.9, 130.7, 133.8, 136.3, 152.6, 155.9, 196.8. HRFABMS *m/z*: 659.3198 (Calcd for $C_{36}H_{52}O_6Si_2Na$: 659.3200).

4.1.23. (±)-(1*R*,2*R*,3*R*,4*S*)-5-Benzyloxy-3,4-bis(*tert*-butyldimethylsilyloxy)-1,2-dimethylmethylenedioxy-2-methyl-1,2,3,4-tetrahydro-9-fluorenohydrazone (33). Hydrazine hydrate (25 mg, 0.50 mmol) was added to a solution of **32** (6.8 mg, 1.1×10^{-2} mmol) in ethanol (1 mL). After refluxing for 3 h, the solvent was evaporated. Purification of the residue by preparative TLC (*n*-hexane–AcOEt = 5:1) gave **33**[33] as geometrical isomers (less polar one: a yellow oil, 3.3 mg; more polar one: a yellow oil, 3.9 mg, totally in quant.). Less polar isomer: R_f: 0.56 (*n*-hexane–AcOEt=5:1). IR ν (neat, cm^{-1}): 3440, 3300, 3210. ^1H NMR (500 MHz) δ: −0.07, 0.02, 0.11, 0.12 (each 3H, s, 4×CH_3), 0.80, 0.81 (each 9H, s, 2×^{t}Bu), 1.28, 1.46, 1.47 (each 3H, s, 3×CH_3), 4.06 (1H, d, *J*=2.8 Hz, 3-H), 4.87 (1H, s, 1-H), 5.14 (1H, d, *J*=2.8 Hz, 4-H), 5.16, 5.22 (each 1H, d, *J*=13.1 Hz, PhCH_2O), 6.72 (1H, d, *J*=8.3 Hz, 6-H), 7.08 (1H, dif. t, *J*=8.0 Hz, 7-H), 7.26–7.39 (6H, m, 8-, Ar–H). More polar isomer: R_f: 0.11 (*n*-hexane–AcOEt=5:1). IR ν (neat, cm^{-1}): 3400, 3303, 3230. ^1H NMR (500 MHz) δ: −0.02, 0.02 (each 3H, s, 2×CH_3), 0.12 (6H, s, 2×CH_3), 0.815, 0.822 (each 9H, s, 2×^{t}Bu), 1.31, 1.42, 1.47 (each 3H, s, 3×CH_3), 4.09 (1H, d, *J*=3.0 Hz, 3-H), 4.86 (1H, s, 1-H), 5.06 (1H, d, *J*=3.0 Hz, 4-H), 5.22 (2H, s, PhCH_2O), 6.61 (2H, br, NH_2), 6.82 (1H, d, *J*=8.5 Hz, 6-H), 7.12 (1H, dif. t, *J*=8.5 Hz, 7-H), 7.28–7.40 (6H, m, 8-, Ar–H).

4.1.24. (±)-(1*R*,2*R*,3*R*,4*S*)-5-Benzyloxy-3,4-bis(*tert*-butyldimethylsilyloxy)-1,2-dimethylmethylenedioxy-9-diazo-2-methyl-1,2,3,4-tetrahydrofluorene (34). Ag_2O (2.5 mg, 1.1×10^{-2} mmol) was added to a suspension of **33** (2.5 mg, 3.8×10^{-3} mmol) and Na_2SO_4 (10 mg) in dry Et_2O (0.5 mL) at 0°C. After stirring at 0°C for 30 min, 0.3% KOH in CH_3OH (0.2 mL) was added. After stirring at 0°C for 1 h and then at rt for 2 h, Et_2O (2 mL) was added. The precipitates were filtered off through Celite pad and washed with Et_2O. The filtrate and the washings were combined and evaporated. Purification of the residue by preparative TLC (*n*-hexane–AcOEt=10:1) gave **34** as a colorless oil (1.6 mg, 65%). IR ν ($CHCl_3$, cm^{-1}): 2067. ^1H NMR (600 MHz) δ: −0.10, 0.01, 0.11, 0.12 (each 3H, s, 4×CH_3), 0.79, 0.81 (each 9H, s, 2×^{t}Bu), 1.14, 1.46, 1.48 (each 3H, s, 3×CH_3), 4.08 (1H, d, *J*=2.8 Hz, 3-H), 4.93 (1H, s, 1-H), 5.16 (1H, d, *J*=2.8 Hz, 4-H), 5.17, 5.25 (each 1H, d, *J*=14.0 Hz, PhCH_2O), 6.63 (1H, dd, *J*=6.6, 2.2 Hz, 8-H), 7.03–7.06 (2H, m, 6-, 7-H), 7.30 (1H, dif. t, *J*=7.0 Hz, 4′-H), 7.34 (2H, dif. t, *J*=7.4 Hz, 3′-, 5′-H), 7.39 (2H, dif. d, *J*=6.9 Hz, 2′-, 6′-H). ^{13}C NMR (150 MHz) δ: −4.58, −4.57, −3.8, −3.6, 18.0, 18.3, 25.3, 25.9, 25.9, 28.7, 29.7, 30.0, 66.1, 69.0, 69.9, 76.2, 82.1, 106.8, 111.5, 111.7, 122.3, 124.0, 124.4, 127.8, 128.3, 128.6, 137.3, 154.5. HRFABMS *m/z*: 648.3395 (Calcd for $C_{36}H_{52}N_2O_5Si_5$: 648.3415).

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26. The hydroxy-directed dihydroxylation of cyclic allylic alcohols giving *cis*,*cis*-triols was reported: Donohoe, T. J.; Moore, P. R.; Waring, M. J. *Tetrahedron Lett.* **1997**, *38*, 5027–5030.
27. Use of OsO_4–NMO system resulted in recovery of **26**.
28. The diastereoselectivities of **27** was 90%.
29. Moss, R. A.; Funk, J. D. *J. Chem. Soc. (C)* **1967**, 2026–2027.
30. Diazoindene showed an absorption maximum at 2068 cm^{-1} due to the diazo function in the IR spectrum (Rewicki, D.; Tuchscherer, C. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 44–45) and a signal attributable to the carbon bonded to the diazo group at 67.1 ppm in the ^{13}C NMR spectrum (Duthaler, R. O.; Förster H. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1978**, *100*, 4974–4979).
31. Ohrai, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11737–11748.
32. The product was composed of **24** and an isomeric monoketal in a ratio of ca. 10:1.
33. HRFABMS of the ca. 1:1 mixture, *m*/*z*: 651.3607 (Calcd for $C_{36}H_{55}N_2O_2Si_2$: 651.3650).