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General Synthesis Route to Benanomicin-Pradimicin Antibiotics

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Dedicated to the memory of Professor Tsuguo Mizuochi

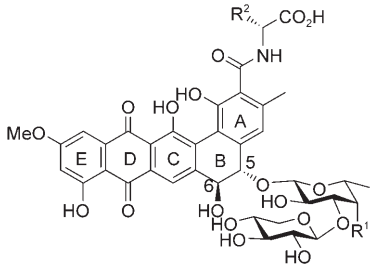
Abstract: A general approach to the regio- and stereoselective total synthesis of the benanomicin-pradimicin antibiotics (BpAs) is described. Construction of the aglycon has been achieved by 1) the diastereoselective ring-opening of a biaryl lactone by using (*R*)-valinol as a chiral nucleophile and 2) the stereocontrolled semi-pinacol cyclization of the aldehyde acetal by using SmI_2 in the presence of $BF_3{\cdot}OEt_2$ and a proton source to afford the ABCD tetracyclic monoprotected diol. This strategy enabled us to control the two stereogenic sites in the B ring (C-5 and C-6) and the regioselective introduction of the carbohydrate moiety. The ABCD tetracycle could serve as an ideal platform for the divergent access to various BpAs. The amino acid (D-alanine) was introduced onto the ABCD tetracycle. Glycosylation was promoted by the combination of Cp_2HfCl_2 and AgOTf (1:2 ratio). Construction of the E ring followed by deprotection completed the first total synthesis of benanomicin A (**2a**), benanomicin B (**2b**), and pradimicin A (**1a**). The route is flexible enough to allow the synthesis of other congeners differing in their amino acid and carbohydrate moieties.

Keywords: antibiotics · benanomicin · natural products · pradimicin · total synthesis

Introduction

The benanomicin-pradimicin antibiotics (BpAs) were isolated from the culture of the *Actinomyces* species in 1988 by two independent groups.[1] To date, more than 20 congeners have been identified (Figure 1) that share a unique structure, which consists of a benzo[*a*]naphthacene core with different amino acid and disaccharide moieties. Their potent antifungal and anti-HIV activities are attributed to Ca^{2+}-mediated specific binding to the mannose-rich oligosaccharides presented on fungi or virus surfaces, and therefore, they are called "lectin-mimics".[2]

Because of these intriguing biological properties as well as their structural novelty, the synthetic community,[3] which includes our group,[4–7] has focused considerable attention on the BpAs. This paper will detail our efforts towards the synthesis of BpAs with particular emphasis on the new strat-



	R^1	R^2
pradimicin A (**1a**)	N(Me)H	Me
pradimicin B (**1b**)[a]	N(Me)H	Me
pradimicin D (**1c**)	N(Me)H	H
pradimicin E (**1d**)	NH_2	H

[a] Sugar moiety of **1b** is shown below.

	R^1	R^2
pradimicin FA-1 (**1e**)	N(Me)H	CH_2OH
pradimicin FA-2 (**1f**)	NH_2	CH_2OH
benanomicin A (**2a**)	OH	Me
benanomicin B (**2b**) (= pradimicin C)	NH_2	Me
BMY–28864 (**2c**)[b]	NMe_2	CH_2OH

[b] Unnatural product.

Figure 1. Structures of the benanomicin-pradimicin antibiotics.

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egies and tactics developed during the course of this synthetic study.

In planning the total synthesis of the BpAs, three problems were considered: 1) The construction of the densely functionalized pentacyclic chromophore, 2) the control of the diol stereochemistry in the B ring, and 3) the regioselective introduction of the sugar moiety.

Results and Discussion

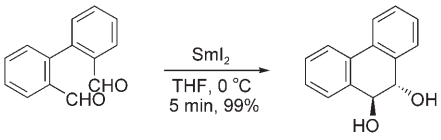
Strategic considerations

Pseudo-symmetry problem: The major challenge in this whole synthetic venture was the regio- and stereochemical control of the vicinal diol at C-5 and C-6 with pseudo-symmetry. To highlight the essence of the problem, Scheme 1 shows a hypothetical route based on the asymmetric epoxidation of benzo[*a*]naphthacene core **A** (Step 1) followed by hydrolytic epoxide cleavage (Step 2). Even if Step 1 occurred with high enantiofacial selectivity, Step 2 must occur regioselectively to obtain the enantiopure diol. This would not be straightforward because the two ends of the epoxide have similar reactivities, both are benzylic and there is little difference in the sterics in the vicinity of the epoxide moiety. In addition, even if this pseudo-C_s-symmetry problem were somehow managed, one must confront the pseudo-C_2 symmetry of the resulting diol, which would raise the problem of regioselective installation of the carbohydrate moiety (Step 3) that would once again not be a trivial issue.

Stereochemical clues from model studies: With these issues in mind, we became interested in another possible route to the stereogenic diol motif, that is, the pinacol cyclization of a biaryl dialdehyde (Scheme 2). The problems of diastereo- and enantiocontrol need to be addressed for this particular approach to be valid.

Scheme 2. Pinacol cyclization strategy.

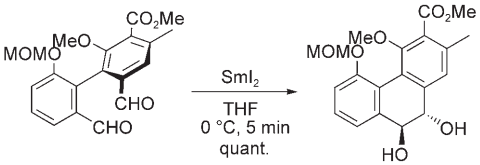
To our delight, initial attempts to solve the diastereocontrol problem immediately gave positive results.[5] Reaction of biaryl dialdehyde **3**[8] with SmI_2[9] cleanly afforded *trans*-diol **4**[10] as the sole product [Eq. (1)]. Consistently high yields and *trans* selectivity were attained in the intramolecular pinacol coupling reaction of various biaryl dialdehydes by using various reducing agents (cf. Sm, V, Ti).[5] In particular, SmI_2 gave excellent *trans* selectivity.



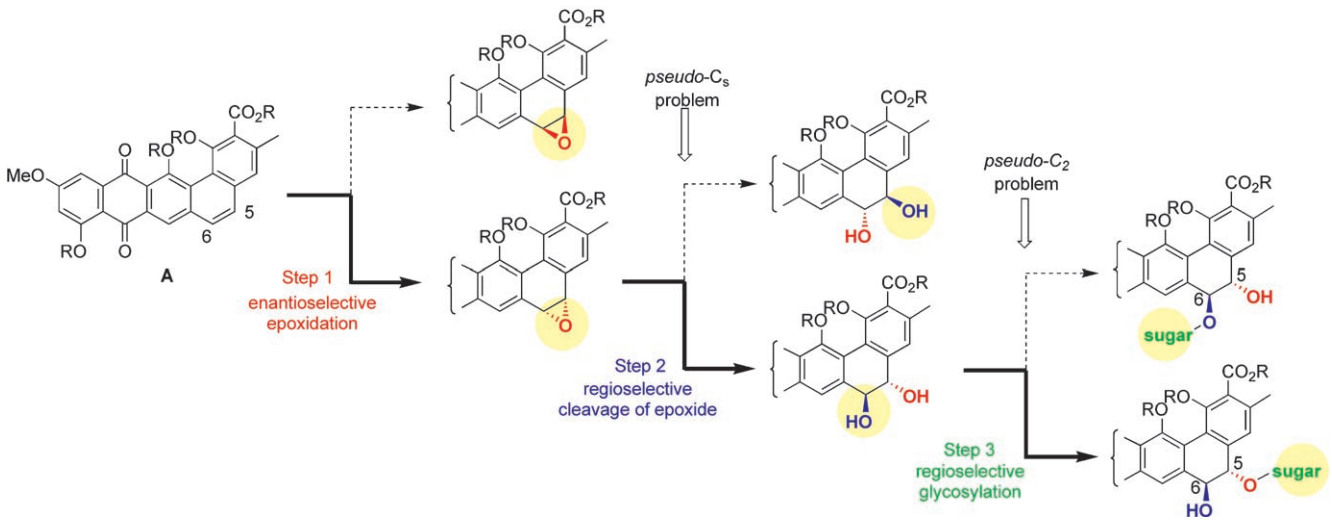
3 **4**

single diastereomer (1)

The clue to enantiocontrol was obtained when pinacol cyclization was applied to chiral, nonracemic biaryl dialdehyde **5**. For example, reaction of (*M*)-**5** with SmI_2 gave a quantitative yield of the *trans*-diol (*S*,*S*)-**6** [Eq. (2)]. Thus, the axial stereochemistry in **5** was completely transmitted into the stereogenicities of *trans*-diol **6**.[11]

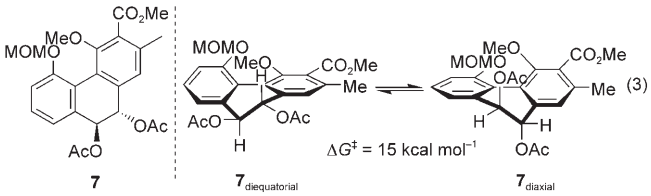


(*M*)-**5**; >99% *ee* (*S*,*S*)-**6**; >99% *ee* (2)



Scheme 1. Hypothetical route to BpAs based on a three-step protocol.

Additional information: During the structure determination of diol **6**, we discovered an interesting fact concerning its axial stereochemistry. Diacetate **7**, which was derived from diol **6**, has a low barrier (ca. 15 kcal mol^{-1}) for conformational flipping, as estimated by variable-temperature NMR spectroscopy [Eq. (3)].[5] The ratio of $\mathbf{7}_{diequatorial}$ and $\mathbf{7}_{diaxial}$ at −40 °C was about 1:1.



This observation was in line with the pioneering work of Mislow and Harvey who reported that the flipping barrier of tethered biaryl **B** ($\Delta G^{\ddagger}$ = 24.1 kcal mol^{-1}) is much lower than that of the nontethered counterpart **C** ($\Delta H^{\ddagger}$ = 50.8 kcal mol^{-1}, calculated; Figure 2).[12a] In general, a two-atom bridge renders the biaryl configurationally labile, allowing the interconversion of **B** and *ent*-**B**, in sharp contrast to the behavior of nontethered biaryl **C**.

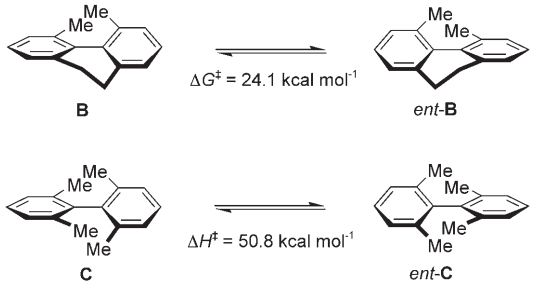


Figure 2. Properties of biaryl compounds.

Such properties of tethered biaryls (configurationally labile) and tetra-*ortho*-substituted biaryls (configurationally inert) inspired us to envision a three-step strategy for a stereocontrolled access to the key tetrol structure **H** embedded in the target molecules (Figure 3): 1) Biaryl lactone **E**, even if it is sterically encumbered, would be available by taking advantage of intramolecular C–C bond formation in the ester precursor **D** (Step 1),[13] 2) chiral biaryl dialdehyde **F** would be obtained by the Bringmann-type asymmetric cleavage of the configurationally labile lactone **E**[14] by employing a chiral, nonracemic reagent (Step 2), and 3) dihydrophenanthrenetetrol **G** could be constructed by stereospecific pinacol cyclization of enantioenriched biaryl dialdehyde **F** (Step 3).

This strategy takes advantage of the stereochemical lability of lactone **E** to drive the enantioselective ring-opening completely to a single enantiomer of **F**, which subsequently undergoes stereospecific pinacol coupling to *trans*-diol **G**.

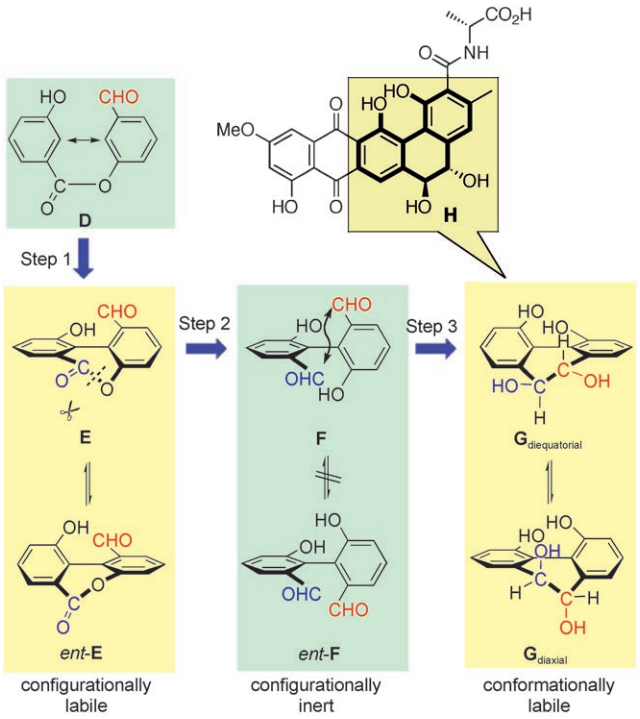


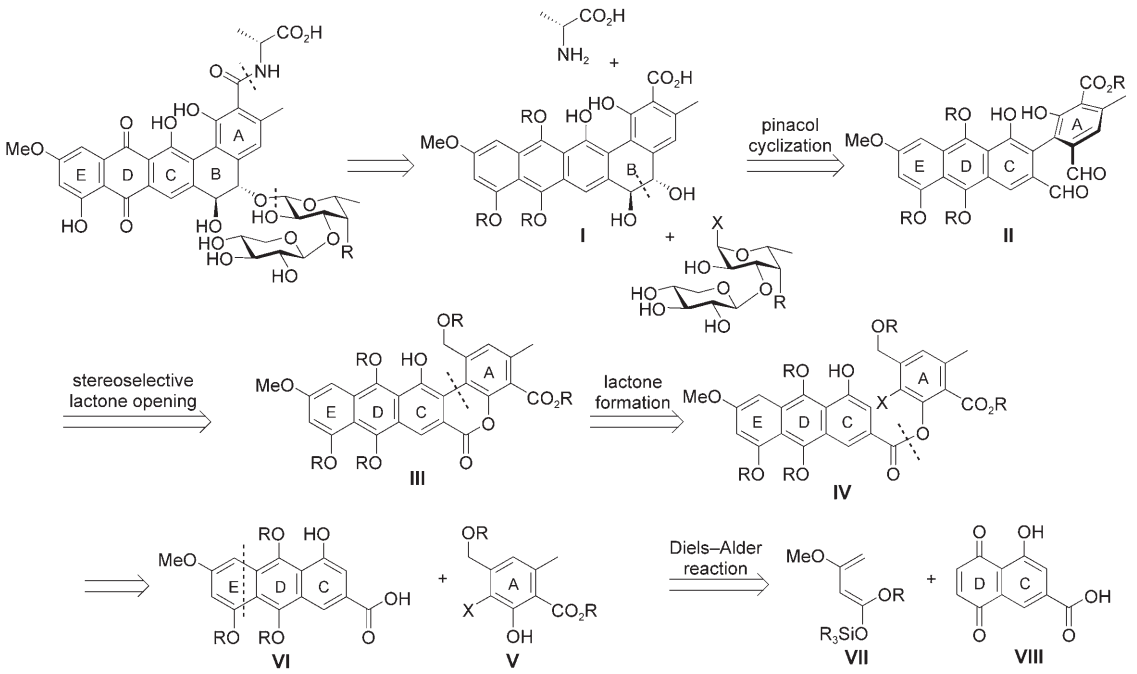
Figure 3. Three-step strategy for the construction of the tetrol substructure.

Although the axial stereochemistry, set inertly during the formation of **F** from **E**, becomes labile again in **G**, the stereochemical interplay between the stereochemistry of the diol and the biaryl axis results in the preservation of stereochemical information.[10a,12]

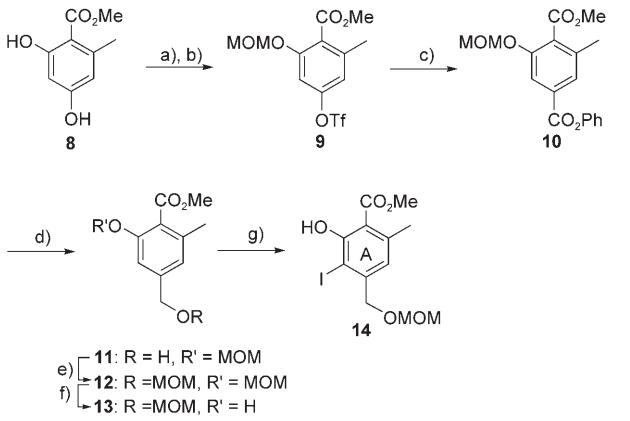
Retrosynthetic analysis: Scheme 3 shows our retrosynthetic analysis of the BpAs, which starts with the fragmentation of the target into three moieties, a sugar, an amino acid, and aglycon **I**. By assuming that the B ring would be constructed by the pinacol cyclization reaction, the enantiopure biaryl dialdehyde **II** was set as the precursor, which could in principle be available by the asymmetric ring-opening reaction of lactone **III** pioneered by Bringmann and co-workers.[14] To cope with the sterically encumbered biaryl bond formation between the anthracene and the A ring segment, we envisioned an intramolecular biaryl C–C bond formation (cf. Figure 3).[13] Ester **IV** could be further dissected into anthracene **VI** and the orsellinic acid derivative **V**. Anthracene **VI** would be constructed by the Diels–Alder reaction of naphthoquinone **VIII** with diene **VII**.[15]

First-generation total synthesis

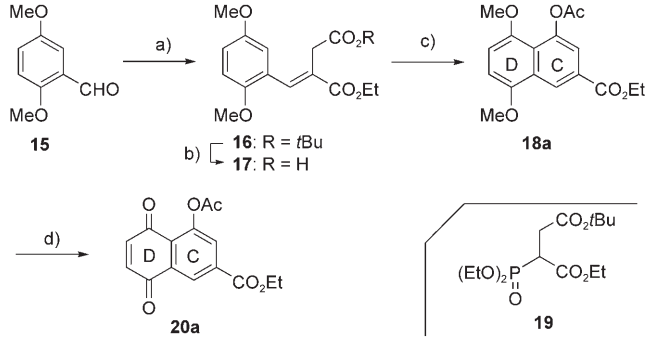
Initial approach to the aglycon: Based on these analyses, A-ring segment **14** was synthesized from the known orsellinic acid derivative **8** (Scheme 4).[16] Phenol **8** was converted into triflate **9** by selective triflation of the phenol *para* to a methoxycarbonyl group followed by protection of the remaining phenol as a methoxymethyl (MOM) ether. Carbonyla-



Scheme 3. Retrosynthetic analysis.



Scheme 4. Preparation of the A-ring segment (unless otherwise noted, the reactions were performed at ambient temperatures). Reagents and conditions: a) $PhNTf_2$, K_2CO_3, acetone, 24 h, 70%; b) MOMCl, iPr_2NEt, CH_2Cl_2, 5.5 h, quant; c) $Pd(OAc)_2$, DPPF, CO, PhOH, DMF, 60→80 °C, 3 h, quant; d) $LiBH_4$, THF, 24 h, 98%; e) MOMCl, iPr_2NEt, CH_2Cl_2, 3 h, 88%; f) CF_3CO_2H, CH_2Cl_2, 0 °C, 3 h, 99%; g) $BnMe_3N^+ICl_2^-$, $NaHCO_3$, MeOH, CH_2Cl_2, 0 °C, 10 h, 83%. Tf = trifluoromethanesulfonyl, DPPF = diphenylphosphinoferrocene.



Scheme 5. Preparation of the CD-ring segment (unless otherwise noted, the reactions were performed at ambient temperatures). Reagents and conditions: a) **19**, LiCl, DBU, CH_3CN, 20 h, 77% (E/Z = 20:1); b) CF_3CO_2H, H_2O, 3.5 h, 90%; c) NaOAc, Ac_2O, 140 °C, 30 min, 99%; d) $Ce(NH_4)_2(NO_2)_6$, CH_3CN, H_2O, 0 °C, 10 min, quant. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

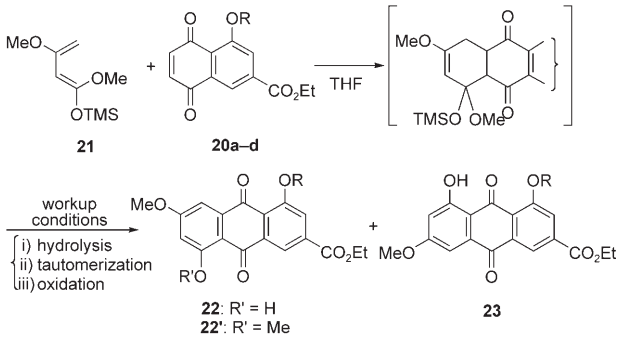
tion of triflate **9** in the presence of phenol afforded phenyl ester **10**.[17] Selective reduction of the phenyl ester in **10** was cleanly achieved with $LiBH_4$ without affecting the methyl ester moiety to give alcohol **11**, which was protected as bis-MOM ether **12**. Acid treatment of **12** gave selective removal of the MOM protecting group of the phenol to give **13** and its iodination by using $BnMe_3N^+ICl_2^-$ gave iodophenol **14**.[18]

Synthesis of the CDE-ring segment started with commercially available aldehyde **15** (Scheme 5). Wittig–Horner reaction of **15** with phosphonate **19**[19] gave the corresponding unsaturated ester, the *tert*-butyl ester of which was selectively hydrolyzed under acidic conditions to give unsaturated acid **17**.[20] Treatment of **17** with acetic anhydride in the presence of sodium acetate afforded naphthalene **18a**,[20,21] which corresponds to the CD-ring system.

To annulate the E ring, naphthalene **18a** was oxidized to the corresponding naphthoquinone **20a** in preparation for a Diels–Alder reaction with siloxydiene **21** (Table 1).[15] Because the regioselectivity of the Diels–Alder reaction of 1,4-naphthoquinones is highly sensitive to the substitution pattern, we tested four related quinones **20a–d** with different protecting groups (R) for comparison purposes.

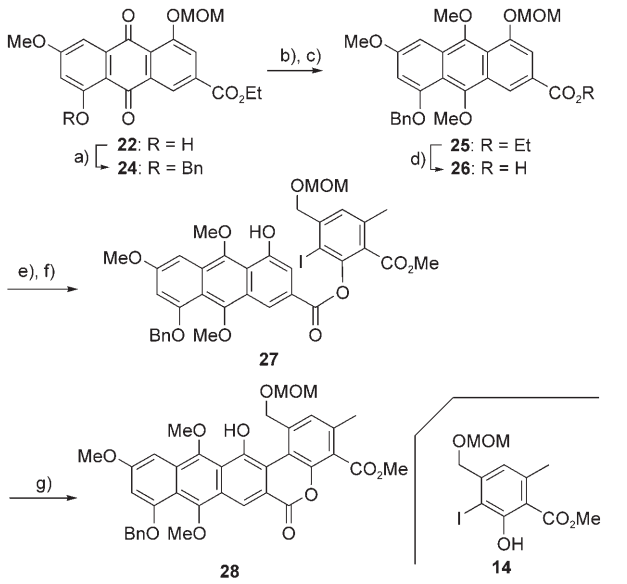
The reactions were conducted by adding diene **21** to a solution of quinone **20a–d** in THF at 0 °C. After stirring for

Table 1. Diels–Alder reactions of quinone **20a–d**.



Entry	Substrate	R	Hydrolysis conditions[a]	**22**:**22′**:**23**	Yield[b] [%]
1	**20a**	Ac	SiO_2	2:0:1	34
2	**20b**	MOM	SiO_2	4:3:1	40
3	**20c**	Me	SiO_2	34:1:0	59
4	**20d**	H	SiO_2	0:0:1	49
5	**20b**	MOM	nBu_4NF	1:0:0	84

[a] In THF at 0 °C, 7 h. [b] Combined yield of **22**, **22′**, and **23**.



Scheme 6. Preparation of biaryl lactone **28** (unless otherwise noted, the reactions were performed at ambient temperatures). Reagents and conditions: a) Cs_2CO_3, BnBr, DMF, 7.5 h, 89%; b) $Na_2S_2O_4$, cat. nBu_4NBr, THF, 30 min; c) Me_2SO_4, 50% aq. KOH, 1 h, 98% (2 steps); d) 5 M aq. KOH, EtOH, reflux, 1.5 h, 91%; e) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, 3 h, then **14**, DMAP, 0.5 h, 94%; f) CF_3CO_2H, CH_2Cl_2, 2 h, 87%; g) $Pd(OCOCF_3)_2$, $P(tBu)_3$, PPh_3, $tBuCO_2Na$, DMA, 110 °C, 25 min, 64%. Bn = benzyl, TMS = trimethylsilyl, DMAP = 4-dimethylaminopyridine, DMA = *N*,*N*-dimethylacetamide.

7 h at room temperature, acidic silica gel was added to hydrolyze the silyl acetal. The resulting ketone underwent tautomerization and spontaneous air-oxidation to afford a varied mixture of desired anthraquinone **22**, undesired methyl ether **22′**, and undesired regioisomer **23** (entries 1–3). When **20d** was used as the substrate, only undesired regioisomer **23** was obtained (entry 4).[22]

For ease later in the synthesis (for deprotection of the R group in **22** in the palladium-mediated cyclization reaction, cf. Scheme 6) and to optimize the regioselectivity of the Diels–Alder reaction, we decided to employ MOM ether **20b** as the substrate for the synthesis. The remaining problems in this context were the low yield and the presence of another mode of acetal cleavage that produces methyl ether **22′**. TLC analysis suggested that the cycloaddition step proceeded without a problem and it seemed that the low yield stemmed from the workup conditions: 1) The hydrolysis of the silyl acetal, 2) the tautomerization step to the hydroquinone, and 3) the oxidation step.

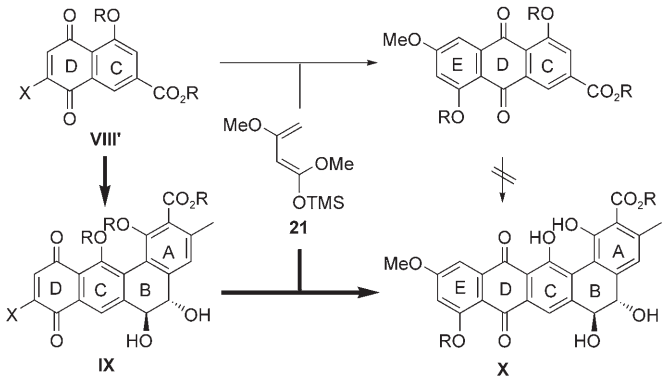
Extensive optimization studies revealed a protocol that would achieve smooth conversion to desired anthraquinone **22** with complete regioselectivity (entry 5). Thus, upon treatment of the crude cycloadduct with nBu_4NF under air in THF, the color changed from yellow to purple, and after several minutes, the color returned to light yellow, which gave the anthraquinone **22** in a yield of 84%.

Anthraquinone **22**, thus obtained, was converted into anthracene **26** because the quinone moiety would be incompatible with the reductive conditions of the pinacol cyclization reaction (Scheme 6). After protection of the phenol in **22**, the resulting benzyl ether **24** was subjected to reductive dimethylation to afford anthracene **25**, which was hydrolyzed to give carboxylic acid **26**.

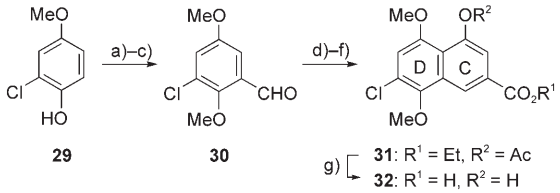
With A-ring segment **14** and CDE-ring segment **26** in hand, their combination was attempted. After esterification of **14** and **26** by using 2,4,6-trichlorobenzoyl chloride,[23,24] the resulting ester was treated with CF_3CO_2H to detach the MOM group to give ester **27** in high yield. Because ester **27** turned out to be rather labile, easily undergoing color change upon exposure to air and/or light, it was immediately subjected to the palladium-mediated cyclization reaction.[13] After careful optimization, we were able to obtain lactone **28** in a yield of 64% by using $Pd(OCOCF_3)_2$. Unfortunately, handling of this advanced intermediate **28** was even more difficult, particularly in terms of its air-sensitivity, and therefore, we decided to abandon this synthetic route.

Successful pathway to aglycon: Recognizing the instability of anthracene derivatives, we decided to postpone the construction of the E ring until a later stage of the synthesis (Scheme 7). To secure the regioselectivity of the Diels–Alder reaction with siloxydiene **21**, we planned to introduce a chlorine atom (X = Cl) into the CD-ring precursor **VIII′** en route to the ABCD-ring segment **IX**.

Chloronaphthalene **32**, the CD-ring intermediate,[4a] was synthesized from the known compound **29**[25] (Scheme 8). Regioselective hydroxymethylation of **29** under Casiraghi conditions,[26] followed by methylation of the phenol, and MnO_2 oxidation of the benzylic alcohol afforded benzaldehyde **30**. The same sequence of reactions, which was already described for the conversion of **15** into **18** (see Scheme 5), was applied to aldehyde **30** to give naphthalene **31** in an overall yield of 76%. Hydrolysis of ester **31** gave carboxylic acid **32** in a yield of 87%.

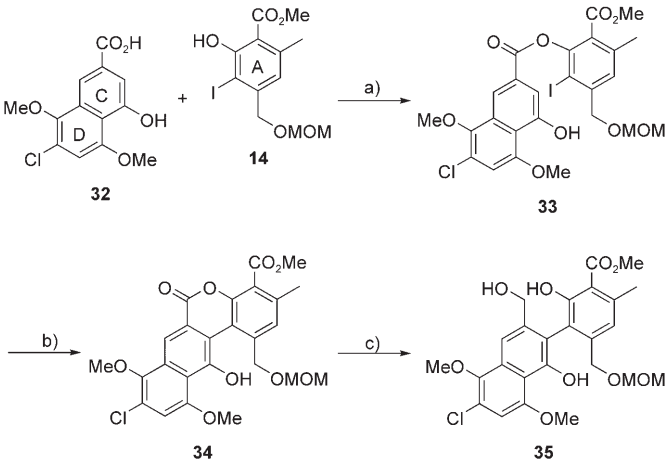


Scheme 7. Naphthalene route.



Scheme 8. Preparation of the CD-ring segment (unless otherwise noted, the reactions were performed at ambient temperatures). Reagents and conditions: a) $(HCHO)_n$, Me_2AlCl, CH_2Cl_2, 5 h, 93%; b) Me_2SO_4, K_2CO_3, acetone, reflux, 13 h, 91%; c) MnO_2, CH_2Cl_2, 40°C, 17 h, 90%; d) NaH, **19**, THF, 0°C→RT, 1 h; e) CF_3CO_2H, H_2O, 40 min; f) NaOAc, Ac_2O, reflux, 1 h, 76% (3 steps); g) 3M aq. NaOH, THF, EtOH, 70°C, 1 h, 87%.

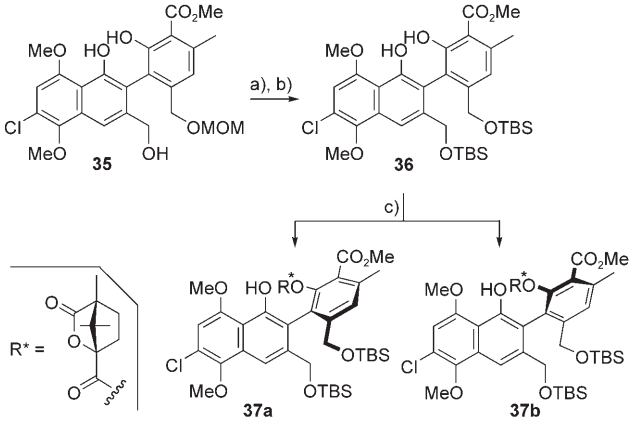
Joining the A-ring segment **14** and the CD-ring segment **32** was achieved by using a water-soluble carbodiimide (EDCI: 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride) to give ester **33**, which was ready for biaryl bond formation (Scheme 9). After considerable optimization, the palladium-catalyzed cyclization of ester **33** proceeded smoothly in the presence of sodium pivalate to give tetracycle **34**.[13] However, the product **34** turned out to be highly



Scheme 9. Preparation of triol **35**. Reagents and conditions: a) EDCI, DMAP, CH_2Cl_2, RT, 3 h, 78%; b) $Pd(OAc)_2$, PPh_3, $tBuCO_2Na$, DMA, 110°C, 1.5 h; c) $NaBH_4$, THF, MeOH, −40°C, 3 h, 86% (2 steps).

prone to hydrolysis during purification by silica gel column chromatography. Lactone **34**, which was once obtained in a small amount, was stable as a crystalline material. In spite of various attempts to improve the workup procedure, we were unable to find a suitable protocol for the high-yielding formation of **34**. At this juncture, we opted to reduce the crude product of **34** with $NaBH_4$ to obtain alcohol **35** in a yield of 86%. Thus, at this stage, the opportunity for the planned asymmetric lactone-opening was lost and we decided to resort to optical resolution as an alternative means of obtaining the requisite biaryl enantiomer.

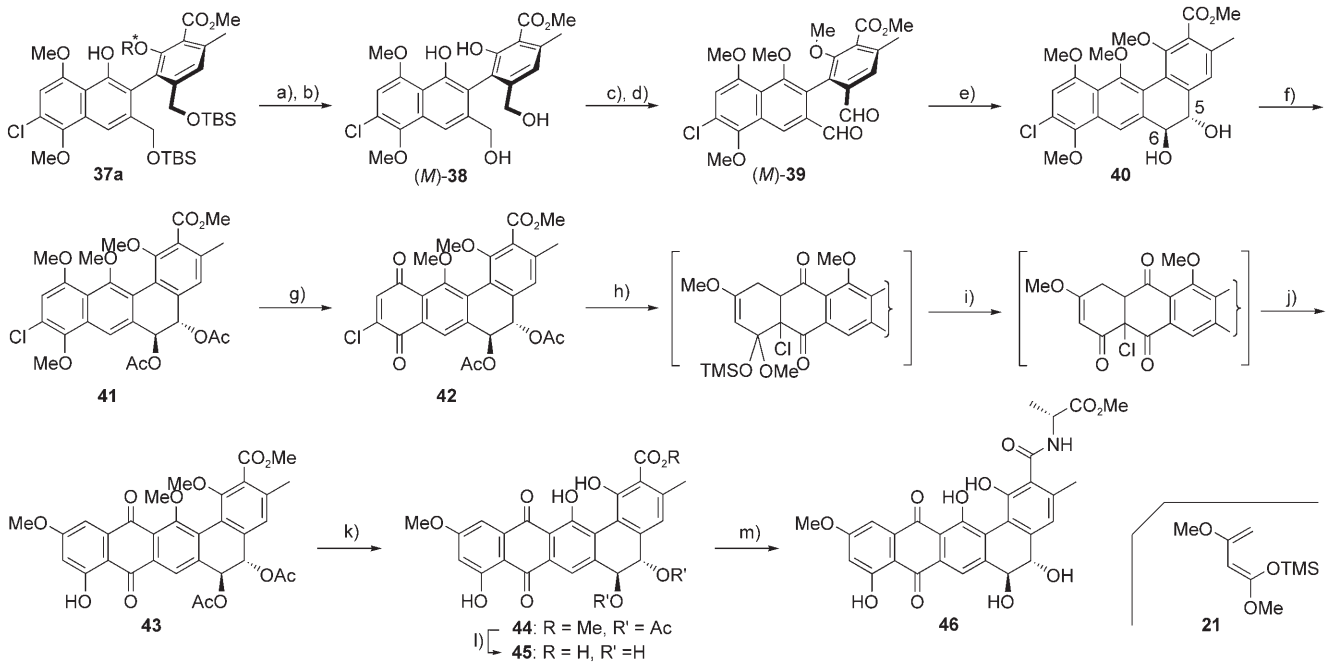
Scheme 10 shows the optical resolution protocol. After detachment of the MOM group in **35**, the benzyl alcohol



Scheme 10. Optical resolution protocol. Reagents and conditions: a) 6M aq. HCl, DME, 3 h, 50°C, 93%; b) TBSCl, imidazole, DMF, RT, 25 min, 84%; c) (1*S*,4*R*)-(−)-camphanoyl chloride, DMAP, pyridine, RT, 20 h; separation by silica gel column chromatography (see text), 38%. DME = 1,2-dimethoxyethane, TBS = *tert*-butyldimethylsilyl.

moieties in the resulting tetrol were protected by TBS groups to give bis-phenol **36**, which was treated with (−)-(1*S*,4*R*)-camphanoyl chloride. Esterification occurred selectively at the phenol *ortho* to the methoxycarbonyl in the A ring to give a diastereomeric mixture of monoesters **37a** and **37b**. Column chromatography (SiO_2, hexane/EtOAc = 7:3) allowed separation of these diastereomers, which gave the more polar isomer **37a** (R_f = 0.34, hexane/EtOAc = 7:3; 38%) and the less polar isomer **37b** (R_f = 0.42, hexane/EtOAc = 7:3; 40%), respectively. Isomer **37a** possessed the requisite *M* configuration.[27]

The requisite diastereomer **37a** was then converted in two steps into enantiopure tetrol (*M*)-**38** (Scheme 11). After protection of the phenols in (*M*)-**38** as methyl ethers, the remaining benzyl alcohols were oxidized to afford enantiomerically pure biaryl dialdehyde (*M*)-**39**.[28] Upon treatment of (*M*)-**39** with SmI_2 (0°C, THF, 10 min), the pinacol cyclization reaction proceeded smoothly to afford *trans*-diol **40** as a single product in quantitative yield with high stereoselectivity (>99% enantiomeric excess (*ee*)), as shown by HPLC analysis.[29] The circular dichroism (CD) measurement revealed an absolute configuration of 5*S*,6*S* for *trans*-diol



Scheme 11. Synthesis of benanomicinone methyl ester (unless otherwise noted, the reactions were performed at ambient temperatures). Reagents and conditions: a) HF, CH_3CN, 0 °C→RT, 45 min, 97%; b) K_2CO_3, MeOH, 19 h, quant; c) MeI, K_2CO_3, acetone, 40 °C, 11 h, 91%; d) MnO_2, CH_2Cl_2, 26 h, 79%; e) SmI_2, THF, 0 °C, 10 min, quant; f) Ac_2O, pyridine, DMAP, 20 min, 98%; g) $Ce(NH_4)_2(NO_3)_6$, CH_3CN, H_2O, 0 °C, 10 min, quant; h) diene **21**, THF, 0 °C→RT, 2 h; i) SiO_2, 12 h; j) K_2CO_3, THF, CH_2Cl_2, 2.5 h, 90% (3 steps); k) BCl_3, CH_2Cl_2, −10 °C, 30 min, 99%; l) 2 M aq. NaOH, 70 °C, 2.5 h; m) D-alanine methyl ester·HCl, BOP, Et_3N, DMF, 1.5 h, 80% (2 steps).

40.[10] Pleasingly, the axial stereochemistry in **39** was completely transmitted into the stereogenicities of *trans*-diol **40**.

For elaborating tetracycle **40** into the pentacyclic full carbon skeleton, the two hydroxy groups were protected as diacetate **41**. Reaction of **41** with $Ce(NH_4)_2(NO_3)_6$ (CAN) effected the selective oxidation of the D ring to afford a quantitative yield of chloroquinone **42**, which was then subjected to the Diels–Alder reaction with siloxydiene **21** to annulate the E ring.[15]

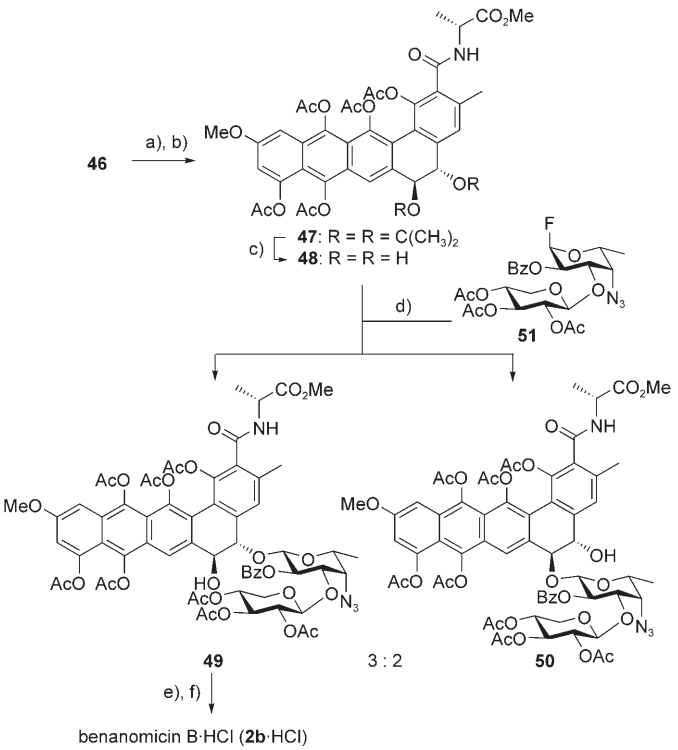
We were pleased to find that the following optimized protocol enabled the formation of pentacycle **43** in high yield. This method for E-ring annulation turned out to be highly reliable and was repeatedly employed in the later syntheses (cf. Scheme 17, Scheme 19, and Scheme 20).

A solution of siloxydiene **21** in THF was added to a solution of **42** in THF at 0 °C and stirring was continued until the consumption of the starting material was complete (TLC assay, 2 h). The resulting silyl acetal was selectively hydrolyzed by treatment with acidic silica gel. Elimination of HCl was achieved with K_2CO_3 to give naphthacenequinone **43** in a yield of 90% from **42**. Note that the chloro group played two roles: 1) To direct the regioselective cycloaddition and 2) to facilitate the aromatization.

Having pentacycle **43** in hand, selective removal of the methyl ethers proximal to the carbonyl groups was readily achieved with BCl_3 to give ester **44**, which was saponified to give carboxylic acid **45**. Compounds **44**–**46** were scarcely soluble in solvents other than water, DMF, and/or DMSO, presumably owing to the presence of the quinone moiety, the handling of **45** was especially difficult.

Condensation of acid **45** with D-alanine methyl ester was effected by using benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP) in DMF, which gave benanomicinone methyl ester (**46**) in a yield of 80% from **45**, which was identical to an authentic specimen.[30]

Glycosylation study—towards the formation of benanomicin B: With aglycon **46** in hand, the stage was set for the final installation of the carbohydrate moiety. Considering the potential problems expected from the presence of the quinone functionality (e.g., deactivation of the Lewis acid used for the glycosylation,[31] poor solubility), we chose to reduce the oxidation level of the aglycon moiety (Scheme 12). According to the procedure of Oki and co-workers, conversion of anthraquinone **46** into the corresponding anthraquinone diacetate **48** was carried out.[2g] After protection of the 1,2-diol in **46** as an acetonide, the resulting product was subjected to reductive acetylation (acetic anhydride, zinc powder, pyridine) to afford anthracene **47**, in which all of the phenols as well as two hydroquinone phenoxides, reductively generated in situ, were fully acetylated. Again, careful handling was required to cope with the sensitive nature of the anthracene derivative to light and oxygen after the quinone functionality of **46** had been reduced. Careful removal of the acetonide and purification afforded pentacycle **48** in a yield of 68% (three steps), which was ready for glycosylation.



Scheme 12. Glycosylation study and synthesis of benanomicin B (unless otherwise noted, the reactions were performed at ambient temperatures). Reagents and conditions: a) $CH_2{=}C(OCH_3)CH_3$, TsOH·H_2O, DMF, 18 h; b) Ac_2O, Zn, pyridine, 10 h, 73% (2 steps); c) TsOH·H_2O, CH_3CN, H_2O, 2 h, 93%; d) fluoride **51**, $Cp_2HfCl_2/AgClO_4$ (1:2), MS4A, CH_2Cl_2, −12 °C, 25 min, 44% (**49**/**50** = 3:2); e) H_2, Pd/C, 1 M aq. HCl, MeOH, 6 h; f) 1 M aq. NaOH, MeOH, 2 h, then 2 M aq. HCl, 68% (2 steps). Ts = *p*-toluenesulfonyl.

Benanomicin B (**2b**) was selected as the initial target. In accordance with the results of model studies on the glycosidation of glycosyl fluoride **51**, Cp_2HfCl_2 and $AgClO_4$ (1:2 ratio) were used in combination as promoters.[32,33] A suspension of Cp_2HfCl_2 and $AgClO_4$ in the presence of molecular sieves (MS4A) in CH_2Cl_2 was stirred at room temperature for 10 min and chilled to −78 °C. A CH_2Cl_2 solution of glycosyl fluoride **51** and diol **48** was added to this mixture. Reaction at −12 °C for 25 min afforded two regioisomeric β-glycosides **49** and **50** in yields of 26 and 18%, respectively (Scheme 12). Extensive NMR studies, which included HMBC and HMQC analyses, showed that **49** was the necessary regioisomer for the total synthesis.[34] Although unfortunate, the poor regioselectivity at this stage was not surprising if one took into consideration the approximate C_2 symmetry of the diol.

In any event, the final stage of the total synthesis was examined. After reduction of the azide in **49** by hydrogenolysis in the presence of aqueous HCl, treatment with 1 M aqueous NaOH accomplished the detachment of all of the acyl groups and hydrolysis of the methyl ester. The reaction mixture was acidified with 2 M aqueous HCl (pH 3.5) to afford the final product, benanomicin B hydrochloride (**2b**·HCl), as a red solid. As the ^1H NMR spectrum proved highly dependent on the pH, the concentration, and the temperature, identification of **2b** was not an easy issue. However, its identification was finally achieved by the measurement of a ^1H NMR spectrum of a sample that contained a mixture of synthetic and authentic **2b** at a low pH (ca. 3.5).[35]

Second-generation total synthesis

Improved strategies for the regio- and stereocontrolled total synthesis of BpAs: In the total synthesis described above, two issues remained unsolved (Figure 4): 1) The axially

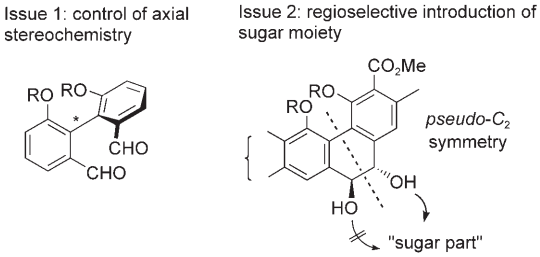


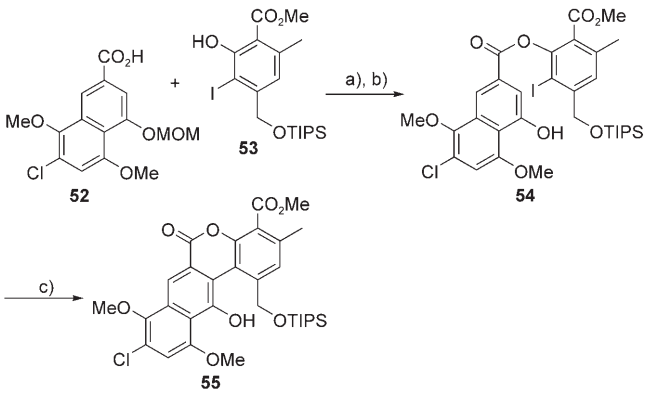
Figure 4. The two remaining tasks for the fully-controlled total synthesis.

chiral biaryl dialdehyde (*M*)-**39** was only obtained by tedious optical resolution, which inevitably produced the useless enantiomer (*P*)-**39** and 2) the sugar moiety was introduced with poor regioselectivity, originating from the approximate C_2-symmetric structure. Seeking a fully controlled total synthesis, we next addressed these two problems.[4b]

Control of axial stereochemistry: Our original plan to tackle the first problem, that is, the control of axial stereochemistry, involved using the Bringmann-type asymmetric ring-opening of the biaryl lactone.[14] This strategy was, however, hampered by the difficulty in preparing the related lactone **34** as a result of its high lability to hydrolysis during silica gel chromatography (cf. Scheme 9). Thus, the prerequisite was the preparation of the lactone itself, which had seemed hopeless in the early phase of our investigation.

Fortunately, however, the following protocol enabled us to achieve this goal (Scheme 13). After Yamaguchi esterification of carboxylic acid **52** with the A-ring segment **53** (TIPS was used as the protecting group of the benzyl alcohol (TIPS: triisopropylsilyl)), the MOM protecting group of the resulting ester was removed by CF_3CO_2H to afford the ester **54**, which was subjected to the palladium-catalyzed cyclization reaction. Again, lactone product **55** was highly labile to hydrolysis during purification by silica gel chromatography. However, addition of water to the reaction mixture at 0 °C effected the precipitation of lactone **55** as fine needles that were collected by filtration. The overall yield from **52** was 59% in three steps.[34]

Prior to asymmetric ring-opening, we observed the dynamic behavior of lactone **55** by using variable-temperature



Scheme 13. Preparation of biaryl lactone **55**. Reagents and conditions: a) 2,4,6-Trichlorobenzoyl chloride, Et_3N, DMAP, toluene, RT, 20 min, 99%; b) CF_3CO_2H, CH_2Cl_2, RT, 3.5 h, 99%; c) $Pd(OAc)_2$, PPh_3, *t*Bu-CO_2Na, DMA, 110°C, 20 min, 60%.

^{1}H NMR analysis of lactone **55** (Figure 5). At −15°C, a singlet was observed at 4.95 ppm, which could be assigned to the benzyl protons. Upon cooling, the peak broadened and finally started to split at −75°C (coalescence temperature) and two peaks appeared upon further cooling (−95°C).

The estimated barrier for the conformational interchange was $\Delta G^{\neq} = 9.8\ \mathrm{kcal\,mol^{-1}}$, which indicated an extremely facile interconversion between enantiomers (*P*)-**55** and (*M*)-**55**.

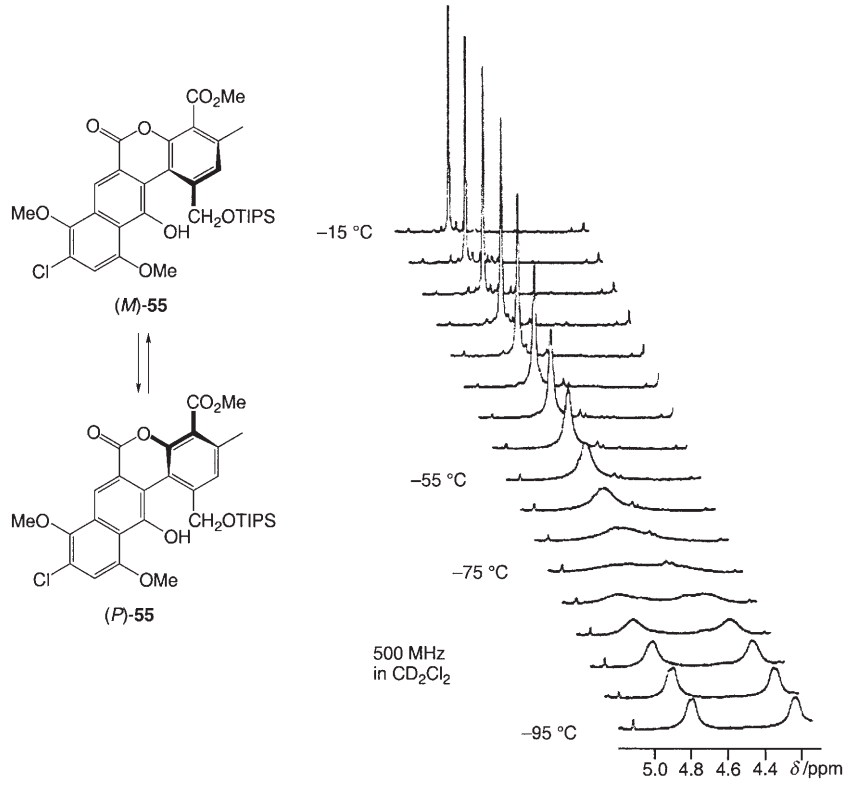
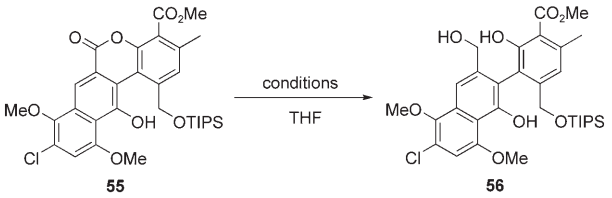


Figure 5. Variable-temperature ^{1}H NMR spectra of **55**.

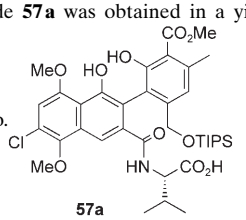
With the requisite lactone **55** in hand, asymmetric ring-opening was examined (Table 2). For the enantioselective ring-opening of **55**, we first applied borane reduction catalyzed by a chiral oxazaborolidine which, unfortunately, gave poor enantioselectivity (entry 1). The enantioselectivities were also disappointing in reactions carried out with $LiBH_4$ or $NaBH_4$ in the presence of various stoichiometric chiral modifiers, such as *N*,*N*-dibenzoylcysteine (entries 2 and 3)[36] and diethyl L-tartrate (entries 4 and 5).[37] However, an unexpected but important pointer was obtained when L-valine was employed (entry 6).[38] Although the result from the reaction itself was again poor (8% yield, 2% *ee*), the formation of a sizable amount of a polar by-product was noted which was identified as amide **57a**, that is, the direct addition product of L-valine. Importantly, amide **57a** was highly enriched in one of the diastereomers (90:10 diastereomeric ratio).

Table 2. Enantioselective biaryl lactone ring-opening.



Entry	Reductant	Chiral modifier	Yield [%]	*ee* [%]	Recovery [%]
1	$BH_3{\cdot}SMe_2$	$B(OMe)_3$, (*R*)-α,α-diphenyl-pyrrolidine-2-methanol	80	10	–
2	$LiBH_4$	*N*,*N*-dibenzoylcysteine	17	–	42
3	$NaBH_4$	*N*,*N*-dibenzoylcysteine	57	5	–
4	$LiBH_4$	diethyl L-tartrate	–[a]	–	–
5	$NaBH_4$	diethyl L-tartrate	40	0	40
6	$NaBH_4$	L-valine	8[b]	2	–

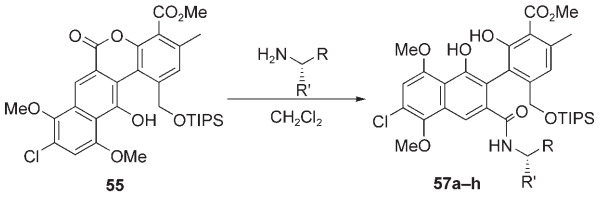
[a] No reaction. [b] Amide **57a** was obtained in a yield of 54% with a 90:10 diastereomeric ratio.



With the poor enantioselectivities in mind, we pursued the diastereoselective ring-opening of **55** by

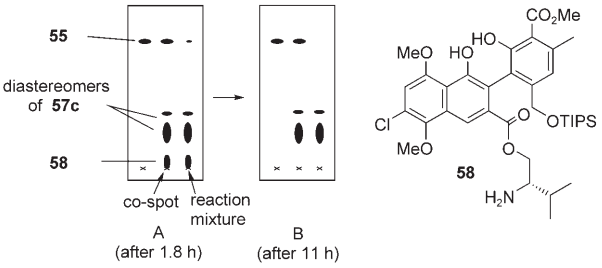
using various stoichiometric chiral nucleophiles (Table 3). Of course, the first choice was L-valine in the absence of $NaBH_4$. However, no reaction occurred, presumably as a result of the insolubility of the amino acid in less polar organic solvents such as CH_2Cl_2 (entry 1). When L-valine ethyl ester was used as a "soluble nucleophile", a slow reaction proceeded, which gave the ring-opened product in a yield of 51%, albeit with poor stereoselectivity (entry 2).

Table 3. Diastereoselective biaryl lactone ring-opening.



Entry	R	R′	Ratio[a]	Temperature[b] [°C]	Time [h]	Product	Yield [%]
1	CO_2H	*i*Pr	–	RT	–	–	–[c]
2	CO_2Et	*i*Pr	70:30	RT	120	**57b**	51
3	CH_2OH	*i*Pr	90:10	RT	1.8	**57c**	72[d]
4	CH_2OH	*i*Pr	86:14	RT	11	**57c**	88
5	CH_2OMe	*i*Pr	50:50	0	720	**57d**	82
6	CH_2OH	*i*Pr	91:9	0	43	**57c**	90
7	CH_2OH	*t*Bu	85:15	0	37	**57e**	92
8	CH_2OH	Bn	86:14	0	56	**57f**	79
9	CH_2OH	Me	76:24	0	15	**57g**	79
10	CH(Ph)OH[e]	Me	45:55	0	48	**57h**	79

[a] The ratio was determined by ^1H NMR analysis. [b] RT = room temperature. [c] No reaction. [d] Ester **58** was obtained in a yield of 14% (3:2 d.r.). [e] (−)-Norephedrine was employed.



A breakthrough came with the use of an amino alcohol; treatment of lactone **55** with (*S*)-valinol at room temperature for 1.8 h gave amide **57c** in a yield of 72% in a diastereomeric ratio (d.r.) of 90:10 (entry 3). Although the result was adequate, the material balance was low. TLC inspection (TLC A, Table 3) showed three new polar spots (R_f = 0.38, 0.25, and < 0.1, hexane/EtOAc = 1:1), the first two spots correspond to the minor/major diastereomers of amide **57c** and the most polar product corresponds to a small amount (14%) of the *O*-addition product **58** formed with a low diastereomeric ratio (3:2).

In contrast, when the reaction was prolonged (11 h), ester **58** disappeared (see TLC B, Table 3) and only amide **57c** was obtained in an improved yield (88%) with a slightly lower diastereomeric ratio (84:16, entry 4). We ascribed this phenomenon to the in situ conversion of ester **58** into amide **57c**.

Indeed, such an *N,O* acyl rearrangement happens without mutation of the axial stereochemistry. Upon retreatment with valinol, isolated ester **58** (d.r. 3:2) was converted into amide **57c** in a yield of 86% (d.r. 3:2).[39] Thus, albeit a minor path, the competing *O*-addition process, which gave ester **58**, serves as an indirect supplier of amide **57c**, although with a lower diastereomeric ratio.

To eliminate this stereodeteriorating *O*-addition pathway, the *O*-methylated valinol derivative was used. However, a very slow and nonselective ring-opening was observed, after one month amide **57d** was obtained in a yield of 82% with a 1:1 diastereomeric ratio (entry 5). Thus, the hydroxy group in the amino alcohol is essential for the smooth progress of the reaction and for high diastereoselection.

Fortunately, optimization experiments showed that the reaction temperature was decisive. The reaction at 0°C for 43 h gave the best result to afford a yield of 90% of amide **57c** in a diastereomeric ratio of 91:9 (entry 6). The *O*-addition pathway seemed to be less pronounced under these conditions.

Hoping for further enhancement of the diastereoselectivity, other amino alcohols, such as *tert*-leucinol, phenylalaninol, alaninol, and norephedrine, were also examined, but their use only resulted in lower selectivities (entries 7–10).

In summary, (*S*)-valinol turned out to be the best chiral nucleophile for this diastereoselective biaryl lactone ring-opening process. The structure of the major isomer of **57c** was unambiguously established by single-crystal X-ray analysis. After separation of the diastereomers of **57c** by column chromatography (silica gel, hexane/EtOAc = 1:2), the major isomer of **57c** gave single crystals suitable for X-ray analysis (Figure 6).[40] The biaryl axis was revealed to have the *P* configuration, which was the wrong stereochemistry for our synthetic purposes (cf. Scheme 11).

Thus, (*R*)-valinol was proven to be the right enantiomer for establishing the requisite *M* configuration in the biaryl intermediate in the total synthesis (see Scheme 15).

Discrimination of the 1,2-diol moiety: To address the pivotal issue of diol discrimination at the B ring, we planned a semi-pinacol cyclization (Scheme 14). The hope was that

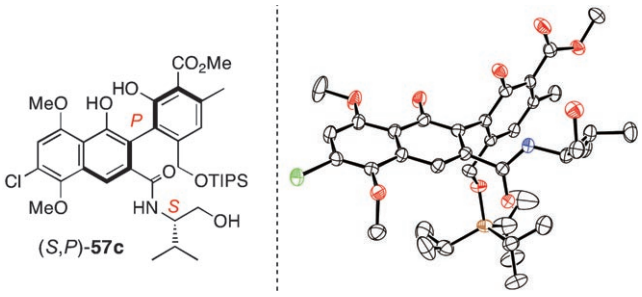
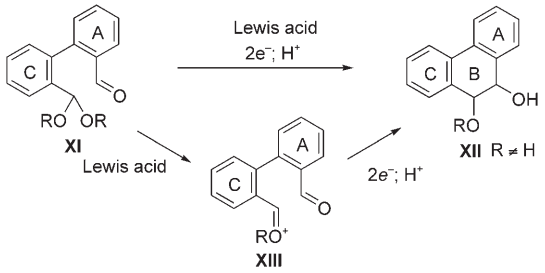
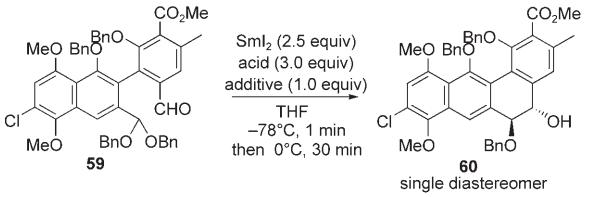


Figure 6. X-ray structure of the major isomer of **57c**. Hydrogen atoms have been omitted for clarity.



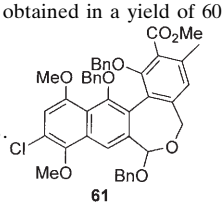
Scheme 14. Semi-pinacol cyclization strategy.

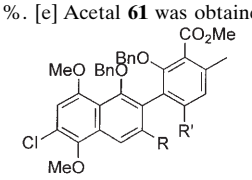
Table 4. Attempts at the semi-pinacol cyclization reaction.



Entry	Acid	Additive	Yield [%]	Entry	Acid	Additive	Yield [%]
1	$BF_3{\cdot}OEt_2$	–	–[a]	6	$TiCl_4$	–	–[b]
2	$BF_3{\cdot}OEt_2$	H_2O	85	7	$TiCl_4$	H_2O	32[d]
3	$BF_3{\cdot}OEt_2$	MeOH	95	8	TfOH	–	–
4	TMSOTf	–	–[b]	9	TfOH	H_2O	29[e]
5	TMSOTf	H_2O	71[c]				

[a] The yield of **60** fluctuated, varying between 0 and 70%, and sizable amounts of by-products were produced. [b] Many unidentified by-products were produced. [c] Acetal **61** was obtained in a yield of 21%. [d] Dialdehyde **64** was obtained in a yield of 60%. [e] Acetal **61** was obtained in a yield of 41%.





62: R = CH_2OBn, R' = CHO
63: R = CH_2OBn, R' = CH_2OH
64: R = R' = CHO

mono-masked diol **XII** would be accessible from the acetal aldehyde **XI** by activation with an acid (e.g., Lewis acid) and a net two-electron reduction. If the strategy proved to be viable then the product would be ideally suited to regioselective installation of the sugar moiety.[6] Of course, we expected that a careful choice of the reaction conditions would be necessary because the timing between the generation of the oxocarbenium intermediate (**XI**→**XIII**) and net two-electron reduction (**XIII**→**XII**) would be critical.

With this scenario in mind, we began extensive modeling studies[6] by using acetal aldehyde **59** as the substrate (Table 4). The first attempt proceeded smoothly by treatment of (±)-**59** with SmI_2[9] in the presence of $BF_3{\cdot}OEt_2$.[41] Thus, SmI_2 in THF (0.1 M) was added to a solution of (±)-**59** and $BF_3{\cdot}OEt_2$ in degassed THF at −78 °C. Stirring at 0 °C for 30 min afforded cyclized product **60** in a yield of 70% in a fully *trans*-selective manner. However, this key reaction turned out to be capricious because all of the subsequent attempts suffered from poor reproducibility; the yields fluctuated widely in the range of 0 to 70% with concomitant formation of varying amounts of by-products (e.g., cyclic acetal **61**, aldehyde **62**, alcohol **63**, and/or dialdehyde **64**), even with slight changes in the reaction parameters (entry 1).

After numerous unfruitful experiments, we finally found that the presence of a suitable proton source was the key to securing reproducibility. In the presence of H_2O, the reaction occurred cleanly to give semi-pinacol **60** in a yield of 85% (entry 2) and methanol proved to be even more effective (entry 3).

As the need for a proton source for the facile formation of **60** is clearly evident from entries 2 and 3, other acids were also examined in the absence/presence of a proton source. In all cases (entries 4–9), compound **60** was only formed when H_2O was added to the reaction (entries 5, 7, and 9), otherwise a complex mixture was produced (entries 4, 6, and 8). When TMSOTf was employed with H_2O, compound **60** was formed in a yield of 71% along with acetal **61** (entry 5). In the case of a combination of $TiCl_4$ and H_2O, the yield of **60** decreased to 32% and was accompanied by the formation of dialdehyde **64** (entry 7). TfOH was also used as a Brønsted acid in the presence of H_2O. The yield of **60** was 29% with **61** was also formed in a yield of 41% (entry 9).

In summary, $BF_3{\cdot}OEt_2$ turned out to be the best acid for the semi-pinacol cyclization reaction.

To gain a further insight into this transformation, the reaction was monitored by time-resolved IR spectroscopy (Figure 7). Thus, in a solution of **59** in THF at −78 °C, absorptions were observed that are characteristic of the C=O stretching of the methoxycarbonyl (1732 cm^{-1}) and formyl groups (1698 cm^{-1}). Amazingly, these signals persisted at −78 °C even after the addition of $BF_3{\cdot}OEt_2$, MeOH, and SmI_2 (Time A).

However, when the reaction temperature was raised to 0 °C (Time B), the absorption at 1698 cm^{-1} disappeared with the emergence of a strong absorption at 1572 cm^{-1} which could be assigned to the stretching vibration of a ketyl radical ($^{\bullet}C\text{-}O^{-}$) species.[42]

This observation suggested that the one-electron reduction of the formyl group to form the ketyl radical species is the initial step, though the precise mechanism still remains uncertain.

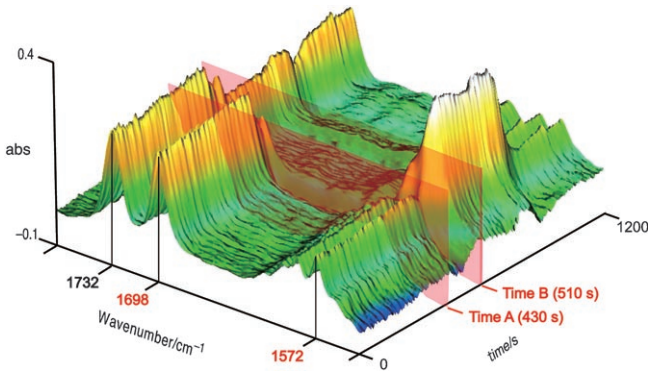
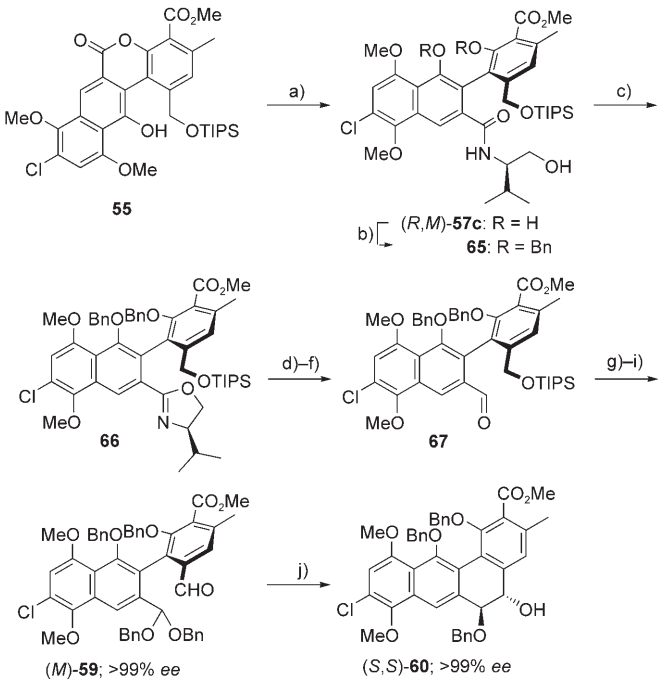


Figure 7. Time-resolved IR monitoring (React-IR) of the semi-pinacol reaction of **59**.

*Preparation of enantiopure tetracycle (S,S)-**60***: After establishing these two stereoselective processes, that is, the lactone ring-opening of biaryl lactone with valinol and the semi-pinacol cyclization of acetal aldehyde **59**, we applied these to the preparative-scale synthesis of chiral, nonracemic **60** (Scheme 15). We were pleased to find that asymmetric ring-opening was viable for the gram-scale reaction, and lactone **55** (2.0 g), upon treatment with (*R*)-valinol (0 °C, 43 h), afforded a combined yield of 90 % of amide **57c** with a diastereoselectivity of 91:9. The desired diastereomer **57c** with *R*,*M* configurations was isolated as yellow crystals (1.9 g) by silica gel column chromatography and recrystallization.



Scheme 15. Preparation of tetracycle (*S*,*S*)-**60** (unless otherwise noted, the reactions were performed at ambient temperatures). Reagents and conditions: a) (*R*)-Valinol, CH_2Cl_2, 0 °C, 43 h, 90 % (*M*/*P* = 91:9); b) BnBr, Cs_2CO_3, DMF, 0 °C, 1 h, 97 %; c) PPh_3, I_2, imidazole, CH_2Cl_2, 20 min, quant; d) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 1 h; e) L-Selectride, 0 °C, 20 min; f) SiO_2, 17 h, 96 % (3 steps); g) BnOTMS, cat. TMSOTf, toluene, −78→−15 °C, 4 h, quant; h) nBu_4NF, THF, 1 h, 0 °C, quant; i) MnO_2, CH_2Cl_2, 15 h, 99 %; j) $BF_3{\cdot}OEt_2$, SmI_2, MeOH, THF, −78→0 °C, 30 min, 95 %. L-Selectride = lithium tri-*sec*-butylborohydride.

After the selective benzylation of the two phenolic hydroxy groups in the amide (*R*,*M*)-**57c**, the hydroxy amide moiety in the resulting bis-benzyl ether **65** was cyclized (PPh_3, I_2, imidazole), which gave oxazoline **66** in quantitative yield. After *N*-methylation of **66**, the activated C=N bond underwent facile reduction with L-Selectride, and the resulting *N*,*O*-acetal was hydrolyzed by exposure to silica gel to give aldehyde **67** in a yield of 96 %.[43] Conversion of **67** into the corresponding dibenzyl acetal,[44] followed by detachment of the silyl protection, and MnO_2 oxidation afforded the enantiopure acetal aldehyde (*M*)-**59**, which was ready for the key cyclization reaction.[45]

SmI_2 (2.5 equiv) was added to a solution of (*M*)-**59** in the presence of $BF_3{\cdot}OEt_2$ (3.0 equiv) and MeOH (1.0 equiv) in THF at −78 °C. The temperature was immediately raised to 0 °C and the stirring was continued for 30 min to give (*S*,*S*)-**60** in a yield of 95 %. Importantly, this semi-pinacol cyclization reaction also allowed the specific transmission of the axial stereochemistry, as shown by HPLC analyses on a chiral stationary phase (Figure 8).[46]

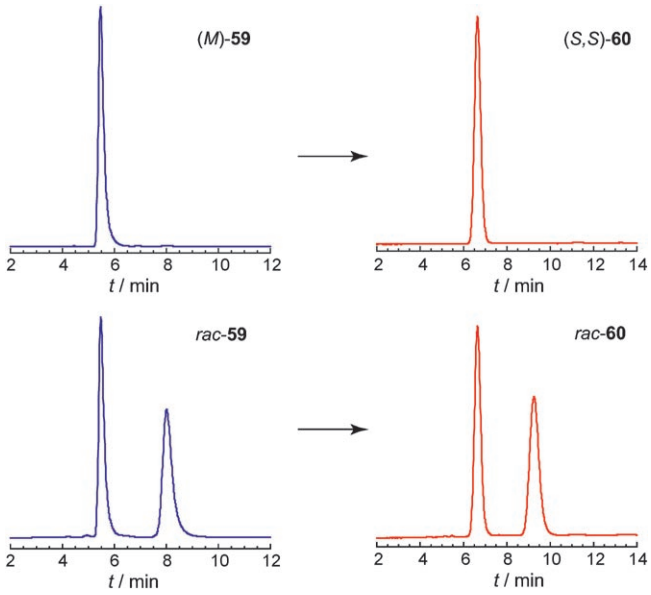


Figure 8. HPLC analyses of the semi-pinacol cyclization reaction. HPLC conditions: for (*M*)-**59** and *rac*-**59**, Chiralpak AD-H (0.46 × 25 cm) column, 25 °C, UV detection at 254 nm, flow rate: 1.0 mL min^{-1}, eluent: hexane/*i*PrOH 9:1; for (*S*,*S*)-**60** and *rac*-**60**: Chiralpak AD-H (0.46 × 25 cm) column, 25 °C, UV detection at 300 nm, flow rate: 1.0 mL min^{-1}, eluent: hexane/EtOH 9:1.

Divergent approach to BpAs: Enantiopure tetracycle (*S*,*S*)-**60**, thus obtained, could serve as an ideal platform for the divergent access to various natural/unnatural congeners of BpAs. Figure 9 represents the three branching points for the divergency: 1) introduction of the amino acid moiety, 2) glycosylation with a disaccharide derivative, and 3) construction of the E ring by Diels–Alder reaction with a diene. To demonstrate such divergency, we report herein the total syn-

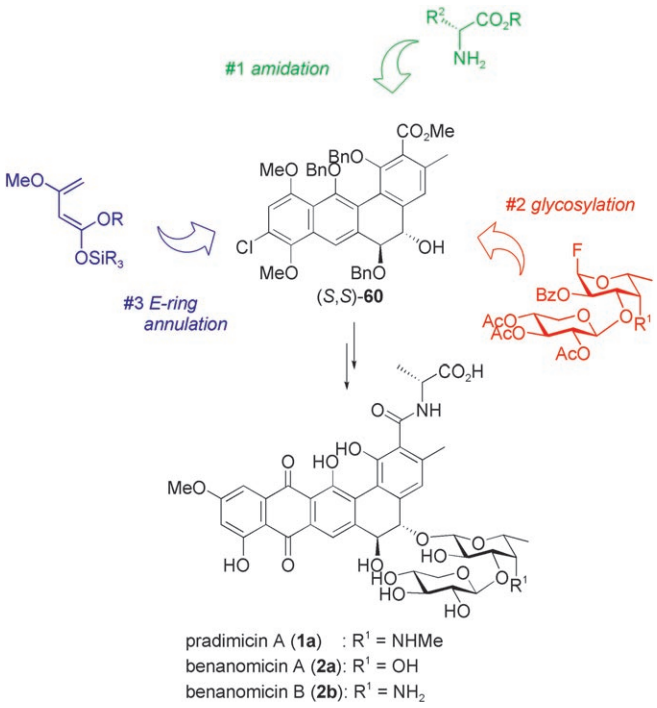
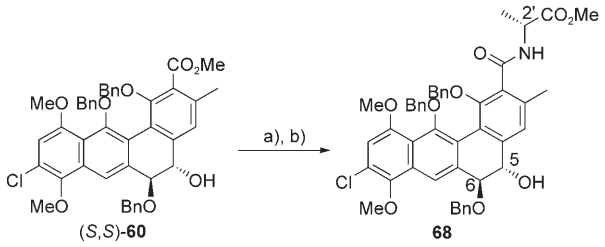


Figure 9. Divergent access to various BpAs.

thesis of three natural BpAs, that is, benanomicin B (**2b**), pradimicin A (**1a**), and benanomicin A (**2a**). These three BpAs share D-alanine as the amino acid, but differ in their disaccharide moieties. Among the possibilities in assembling these three modules, we chose to form the amide bond first, then perform the glycosylation reaction, and finally the synthesis was completed by E-ring annulation. This choice has the advantage of reserving the generation of the quinone functionality until the latest stage because we knew that quinones might pose problems associated with chemical transformations and poor solubility (cf. Scheme 11).

Scheme 16 shows the installation of the amino acid, the methyl ester of D-alanine. Tetracycle (*S*,*S*)-**60** was hydrolyzed under basic conditions to afford the corresponding carboxylic acid. This saponification reaction proceeded only under harsh basic conditions that nonetheless did not cause aromatization. The resulting carboxylic acid was condensed with the methyl ester of D-alanine by using BOP to give the



Scheme 16. Installation of the amino acid moiety into (*S*,*S*)-**60**. Reagents and conditions: a) 5 M aq. KOH, EtOH, sealed tube, 100 °C, 3 h; b) BOP, Et_3N, D-alanine methyl ester·HCl, DMF, RT, 1 h, 84 % (2 steps).

amide **68** in excellent yield whose structure was unambiguously established by single-crystal X-ray analysis (Figure 10).[47]

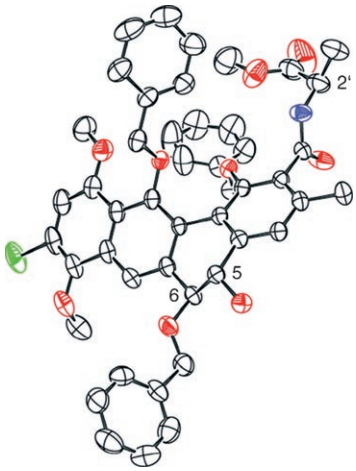


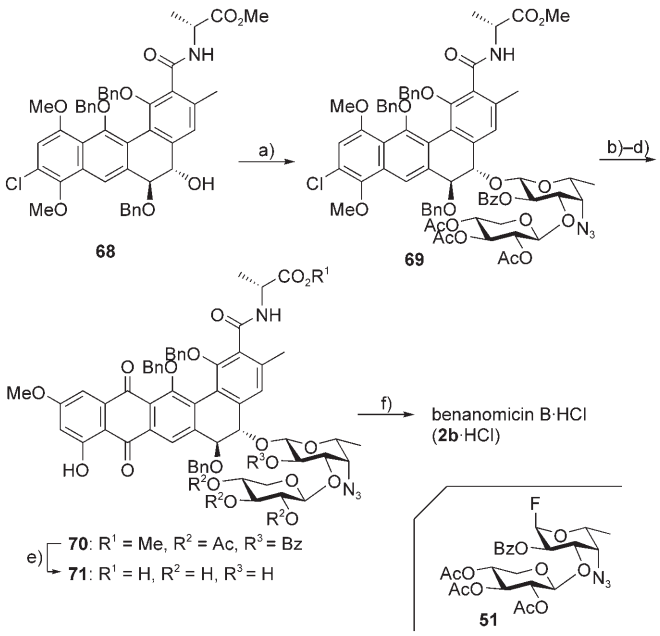
Figure 10. X-ray structure of amide **68**. Hydrogen atoms have been omitted for clarity.

Amide **68** served as a key intermediate for the divergent synthesis of the three natural products **2b**, **1a**, and **2a**, prepared by installing three different disaccharides followed by E-ring annulation.

Benanomicin B (2b): The first target was benanomicin B (**2b**), which has a primary amine in the sugar moiety. Glycosyl fluoride **51** was used as the glycosyl donor (cf. Scheme 12) because it has an azide that can be converted into the corresponding primary amine at the appropriate time (Scheme 17).

The glycosylation process was initially attempted by using a combination of Cp_2HfCl_2 and $AgClO_4$ (1:2 ratio). Although this procedure had previously given the best result,[33] it only induced the decomposition of **68** at the reaction temperature of −36 °C.[48] After careful reinvestigation of the protocol (Ag salt, molarity, and temperature), optimal conditions were found: Treatment of fluoride **51** and alcohol **68** with a 1:2 ratio of Cp_2HfCl_2 and AgOTf (instead of $AgClO_4$) in the presence of MS4A at −36 °C for 11 h gave β-glycoside **69** in a yield of 72 % along with its α anomer in a yield of 9 %. After separation, β anomer **69** was oxidized with CAN and the resulting unstable chloroquinone was immediately subjected to a Diels–Alder reaction with siloxydiene **21**.[15] The previously described protocol (see Scheme 11, **42**→**43**) worked well to afford pentacycle **70** in a fully regiocontrolled manner (74 % overall yield in three steps).

The next stage was the removal of the protecting groups in **70**, which was rather difficult as a result of the high polarity and the poor solubility of the partially deprotected intermediates in organic solvents. Careful optimization showed that the removal of the four acyl protecting groups and saponification of the methyl ester was possible by treatment



Scheme 17. Synthesis of benanomicin B (unless otherwise noted, the reactions were performed at ambient temperatures). Reagents and conditions: a) Fluoride **51**, Cp_2HfCl_2/AgOTf (1:2), MS4A, CH_2Cl_2, −36 °C, 11 h, 9% for the α anomer, 72% for the β anomer; b) CAN, H_2O, CH_3CN, 20 min; c) diene **21**, THF, 20 min, then SiO_2, 8 h; d) K_2CO_3, CH_2Cl_2, THF, 40 °C, 3 h, 74% (3 steps); e) 2 M aq. NaOH, MeOH, 8.5 h; f) H_2, Pd/C, 1 M aq. HCl, MeOH, DMF, 2 h, then 2 M aq. HCl, 53% (2 steps), for purification see text.

with 2 M aqueous NaOH (room temperature, 8.5 h), which gave compound **71**. Although the acyl protecting groups were removed fairly rapidly (2.5 h), hydrolysis of the methyl ester required a longer time (8.5 h).

The final stage of the synthesis required the removal of the three benzyl protecting groups and conversion of the azide into the primary amine, which could be achieved under catalytic hydrogenation conditions. This stage was again troublesome owing to the poor solubility of the partially deprotected intermediates and also to catalyst deactivation by the resulting amino group. After considerable screening of the reaction conditions, an appropriate choice of solvent and additives allowed us to achieve the total synthesis: Treatment of **71** with 5% Pd/C in MeOH and DMF (3:1)[49] in the presence of dilute aqueous HCl[50] effected the desired conversion. During the filtration of the catalyst in air through Hyfro Super-Cel, the color of the filtrate changed from orange to purple, which suggested the transformation of the in situ formed hydroquinone back to the quinone.

The filtrate was purified by successive column chromatography on Cosmosil (C18, $CH_3CN/H_2O = 3:7$, phosphate buffer pH 3) and then on Sephadex LH-20 (DMF) to afford benanomicin B as a DMF solvate that was dissolved in MeOH and the pH adjusted to 3.5 by the addition of 2 M aqueous HCl. After removal of the solvent, the residue was dissolved in a small amount of DMSO to which $CHCl_3$ was added. The resulting red precipitate was collected by filtration to afford benanomicin B hydrochloride (**2b**·HCl), which was identical to an authentic specimen (m.p. 213–215 °C, $[\alpha]_D^{22} = +360$ ($c = 0.0501$ in H_2O); lit.:[1a] m.p. > 220 °C, $[\alpha]_D^{30} = +353$ ($c = 0.05$ in H_2O)).

*Pradimicin A (**1a**)*: The second target was pradimicin A (**1a**), the most abundant congener of the pradimicins. This compound possesses an *N*-monomethylamino group instead of the primary amino group in **2b**. Because the direct conversion of a primary amine into the corresponding monoalkylamine is often hampered by bis-alkylation,[51] indirect routes are often employed, such as temporary protection, alkylation, and deprotection.

However, we have developed a method for the selective conversion of an azide into the corresponding *N*-monomethylamino group without forming the bis-methylation product [Eq. (4)].[7] Trimethylphosphine reacts with an azide to form the corresponding iminophosphorane,[52] which undergoes aza-Wittig reaction with $(HCHO)_n$ to form the corresponding imine. In situ reduction of this imine with $NaBH_4$ affords the requisite *N*-monomethylamine.

$$R{-}N_3 \xrightarrow{PMe_3} R{-}N{=}PMe_3 \xrightarrow{(HCHO)_n} R{-}N{=}CH_2 \xrightarrow{H^-} R{-}\underset{H}{\overset{CH_3}{N}} \qquad (4)$$

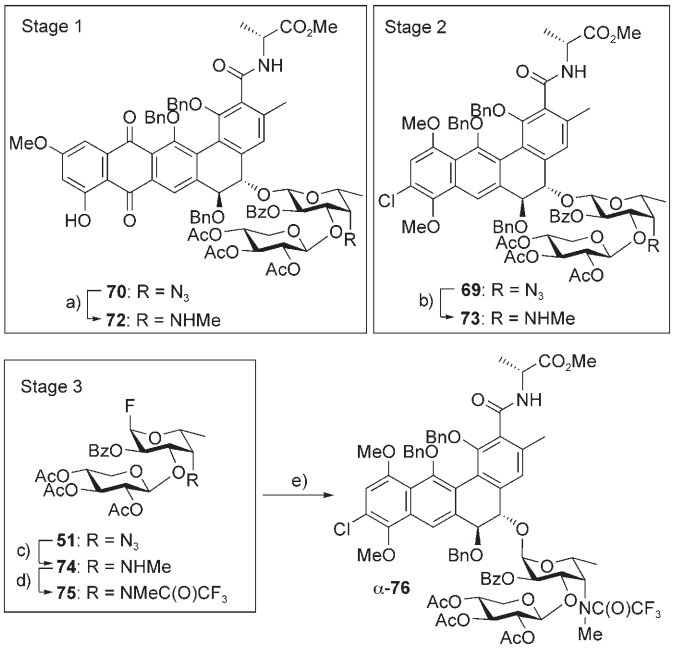
By adapting this synthetic protocol, the azide-containing intermediates used for the synthesis of **2b** could be utilized for the synthesis of **1a**. In terms of the timing of the transformation ($-N_3 \rightarrow -NHMe$), there were three optional stages (Scheme 18),[53] stage 1: advanced intermediate **70**; stage 2: tetracyclic glycoside **69**; stage 3: glycosyl donor **51**.

We examined these three possibilities and stage 2 turned out to be the best choice, as described below. stage 1 proved to be inappropriate because the attempted conversion of **70** only produced an intractable mixture of multiple products, presumably owing to side reactions at the quinone functionality.

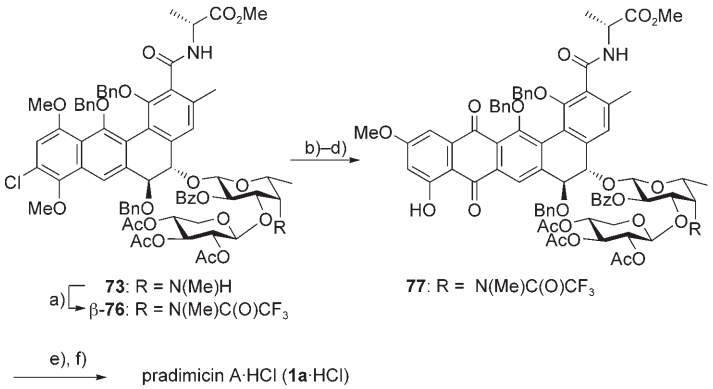
On the other hand, stage 3 revealed a different problem. Azide sugar **51** was successfully converted into monomethylamine **74** and subsequently to trifluoroacetylated glycosyl fluoride **75**. However, glycosidation of **75** with acceptor **68** gave exclusively the undesired α-glycoside **76** owing to the remote participation of the trifluoroacetamido group.[54]

Fortunately, stage 2 was a viable one: Glycoside **69** in CH_2Cl_2 was successively treated with Me_3P, $(HCHO)_n$, and $NaBH_4$ to give monomethylamine **73** in a yield of 75% (see Scheme 18), which was successfully converted into the target **1a** (see below).

Scheme 19 illustrates the final stages en route to target **1a**. The amino group in **73** was masked with a trifluoroacetyl group to give β-**76** in a yield of 90%. After oxidation of β-**76** with CAN, construction of the E ring was achieved by the standard protocol (see Scheme 11) to give pentacycle **77** in a yield of 75% (three steps). After hydrogenolysis of **77** to detach the three benzyl groups, final removal of the five acyl groups (including a trifluoroacetyl group) and hydroly-



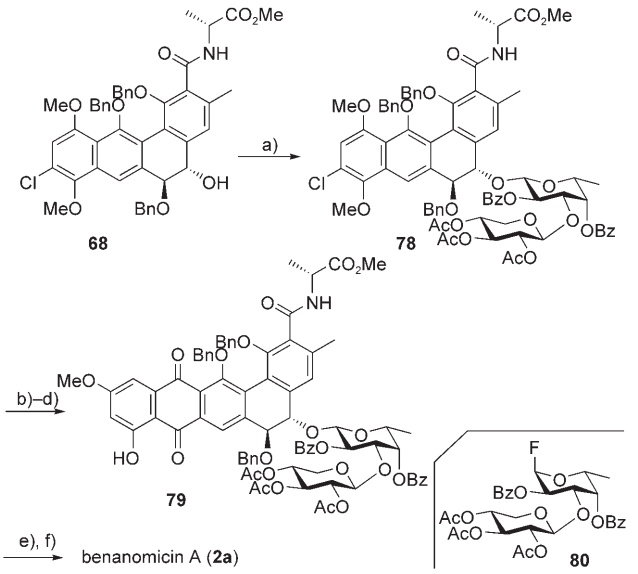
Scheme 18. Three optional stages for the conversion of azide into the *N*-monomethylamine derivative (unless otherwise noted, the reactions were performed at ambient temperatures). Reagents and conditions: a) Me_3P, 1.5 h, $(HCHO)_n$, CH_2Cl_2, 15.5 h, $NaB(CN)H_3$, MeOH, 0 °C, 10 min, 60 % (contaminated with unidentified by-products); b) Me_3P, 1.5 h, $(HCHO)_n$, CH_2Cl_2, 11 h, $NaBH_4$, MeOH, 0 °C, 10 min, 75 %; c) Me_3P, 1.5 h, $(HCHO)_n$, CH_2Cl_2, 13 h, $NaBH_4$, MeOH, 0 °C, 10 min, 78 %; d) $(CF_3CO)_2O$, pyridine, CH_2Cl_2, 0 °C, 30 min, 91 %; e) amide **68**, Cp_2HfCl_2/AgOTf (1:2), MS4A, CH_2Cl_2, −25 °C, 11 h, 93 %.



Scheme 19. Synthesis of pradimicin A (unless otherwise noted, the reactions were performed at ambient temperatures). Reagents and conditions: a) $(CF_3CO)_2O$, pyridine, CH_2Cl_2, 20 min, 0 °C, 90 %; b) CAN, H_2O, CH_3CN, 20 min; c) diene **21**, THF, 20 min then SiO_2, 14 h; d) K_2CO_3, CH_2Cl_2, THF, 2 h, 40 °C, 75 % (3 steps); e) H_2, Pd/C, MeOH, DMF, 30 min; f) 0.5 M aq. NaOH, 24 h, then 2 M aq. HCl, 61 % (2 steps), for purification, see text.

sis of the methyl ester were achieved by treatment with 0.5 M aqueous NaOH without MeOH (cf. Scheme 17).[55] After acidification with 2 M aqueous HCl (pH 3.5), the filtrate was purified by successive column chromatography on Cosmosil (C18, $CH_3CN/H_2O = 3:7$, phosphate buffer pH 3) and Sephadex LH-20 (DMF) to afford pradimicin A as a DMF solvate that was dissolved in MeOH and the pH was adjusted to 3.5 by the addition of 2 M aqueous HCl. The reprecipitation protocol described above (see above) gave a red powder of pradimicin A hydrochloride (**1a**·HCl) in a yield of 61 %[56] which was identical to an authentic sample (m.p. 194–197 °C, $[\alpha]_D^{26} = +280$ ($c = 0.0100$ in 1.00 M aq. HCl); lit.:[1d] m.p. 193–195 °C, $[\alpha]_D^{30} = +287$ ($c = 0.01$ in 1.0 M aq. HCl)).

*Benanomicin A (**2a**)*: The last target was benanomicin A (**2a**), which has a neutral sugar (Scheme 20). Fluoride **80**



Scheme 20. Synthesis of benanomicin A (unless otherwise noted, the reactions were performed at ambient temperatures). Reagents and conditions: a) **80**, Cp_2HfCl_2/AgOTf (1:2), MS4A, CH_2Cl_2, −30 °C, 17 h, 7 % for the α anomer and 74 % for the β anomer; b) CAN, H_2O, CH_3CN, 20 min; c) diene **21**, THF, 30 min then SiO_2, 14 h; d) K_2CO_3, CH_2Cl_2, THF, 40 °C, 2 h, 66 % (3 steps); e) H_2, Pd/C, MeOH, DMF, 50 min; f) 0.5 M aq. NaOH, 15 h, then 1 M aq. HCl, 68 % (2 steps).

was used as the glycosyl donor.[57] The glycosidation reaction was initially attempted under exactly the same conditions as those used for the synthesis of **69**. Unexpectedly, however, the reactivity of this neutral glycosyl fluoride **80** was lower than that of the azide-containing glycosyl donor **51**, and therefore, no reaction occurred at −36 °C. Fortunately, a subtle difference in the reaction temperature proved decisive and the reaction proceeded smoothly at −30 °C. Fluoride **80** and alcohol **68** were treated with Cp_2HfCl_2 and AgOTf (1:2 ratio) in the presence of MS4A in CH_2Cl_2 at −78 °C and stirred at −30 °C for 17 h to give β-glycoside **78** (74 %) along with its α anomer (7 %). After isolation and oxidation of β-**78** by CAN, the resulting unstable chloroquinone was immediately subjected to the previously described E-ring annulation protocol (see Scheme 11) to give pentacycle **79** in a fully regiocontrolled manner (66 % yield over three steps). After hydrogenolysis of **79** in a mixed solvent

(MeOH/DMF = 3:1) for 50 min,[49] removal of the five acyl groups and hydrolysis of the methyl ester were achieved by treatment with 0.5 M aqueous NaOH for 15 h. After acidification with 2 M aqueous HCl (pH 3.5), the residue was purified by successive column chromatography on Diaion HP-20 (H_2O/MeOH = 1:0 to 0:1, gradient elution) and Sephadex LH-20 (DMF). After removal of the DMF, the residue was dissolved in a small amount of DMSO to which $CHCl_3$ was added. The resulting precipitates were collected by filtration to afford benanomicin A (**2a**) as a red powder (68% yield). The synthetic sample showed spectroscopic properties identical to those of the natural product (m.p. 242–244 °C (decomp); lit.:[1b] m.p. > 220 °C).

Conclusion

A general synthetic route to benanomicin-pradimicin antibiotics has been developed that is based on three significant findings: 1) Diastereoselective biaryl lactone ring-opening, 2) correlation of the biaryl educt configuration to pinacol product stereochemistry, and 3) semi-pinacol cyclization for the discrimination of the diol moiety in the B ring. By using this synthetic strategy, it should be possible to synthesize various natural/unnatural BpA congeners.

Experimental Section

General methods: All experiments involving air- and moisture-sensitive compounds were conducted under an atmosphere of dry argon. Dichloromethane was successively distilled from P_2O_5 and CaH_2 and stored over 4 Å molecular sieves. For TLC analyses, Merck precoated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) were used. For flash column chromatography, silica gel 60N (Spherical, neutral, 23–210 μm) from Kanto Chemicals was used. Preparative TLC (PTLC) was performed on Merck silica gel 60 PF_{254} (Art 7747). Melting point (m.p.) determinations were performed by using a Yanako MP-S3 or MP-500 instrument and are uncorrected; ^1H and ^{13}C NMR spectra were recorded by using a JEOL JNM EX-270 (270 MHz), a JNM AL-400 (400 MHz), a JNM lambda-400 (400 MHz), or a Bruker DRX-500 (500 MHz) spectrometer in the solvent indicated; chemical shifts (δ) are given in ppm relative to tetramethylsilane and coupling constants (J) are reported in Hz. Multiplicities are described by the following abbreviations s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad. Infrared (IR) spectra were recorded by using a Jasco IR-Report-100 or a Perkin–Elmer Spectrum 100 spectrometer. Attenuated total reflectance Fourier-transform infrared (ATR-FTIR) spectra were recorded by using a Perkin–Elmer 1600 FTIR spectrometer. In situ IR spectra were recorded by using a REMSPEC mid-IR fiber-Optic probe with an MCT detector. Ten scans were acquired per spectrum at a resolution of 4 cm^{-1} by using the Time Base software package (Perkin–Elmer). Optical rotations ($[\alpha]_D$) were measured by using a Jasco DIP-1000 polarimeter. UV spectra were recorded by using a Hitachi 300 spectrometer. CD spectra were recorded by using a Jasco J500C spectropolarimeter. High-performance liquid chromatography (HPLC) analyses were performed by using a Jasco 880PU instrument with UV detection at 254 or 300 nm. Low-resolution mass spectra (LRMS) were obtained with a Shimadzu Kratos Kompact MALDI IIS spectrometer. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-700 spectrometer. Elementary analyses were performed on a Perkin–Elmer series II 2004 instrument. X-ray crystallographic data were recorded with a Rigaku RAXIS-RAPID diffractometer at the Tokyo Institute of Technology X-ray Laboratory.

First-generation total synthesis

Methyl 2-hydroxy-6-methyl-4-(trifluoromethylsulfonyloxy)benzoate: K_2CO_3 (4.55 g, 24.7 mmol) and $PhNTf_2$ (5.88 g, 16.5 mmol) were added to a solution of **8** (3.00 g, 16.5 mmol) in acetone (30 mL) at 0 °C. After stirring for 24 h at room temperature, the reaction mixture was filtered through a Celite pad (washed with methanol). The filtrate was concentrated in vacuo, the mixture was diluted with H_2O, and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Mg_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel, hexane/EtOAc = 95:5 to 80:20, gradient elution) gave the undesired regioisomer methyl 4-hydroxy-2-methyl-6-(trifluoromethylsulfonyloxy)benzoate as a white crystalline solid (1.09 g, 21%) and somewhat impure methyl 2-hydroxy-6-methyl-4-(trifluoromethylsulfonyloxy)-benzoate contaminated with PhNHTf, which was further purified by washing with saturated aqueous K_2CO_3, followed by extraction with EtOAc to afford a pure form of methyl 2-hydroxy-6-methyl-4-(trifluoromethylsulfonyloxy)benzoate as a white amorphous solid (3.63 g, 70%). M.p. 52–53 °C (Et_2O); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.58 (s, 3H), 3.99 (s, 3H), 6.65 (d, J = 2.6 Hz, 1H), 6.78 (d, J = 2.6 Hz, 1H), 11.6 ppm (s, 1H; OH); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 24.2, 52.6, 108.4, 115.4, 118.6 (q, $^1J_{C,F}$ = 317 Hz), 128.6, 114.5, 152.4, 164.4, 171.2 ppm; IR (film): $\tilde{\nu}$ = 3090, 3050, 2990, 2970, 1660, 1610, 1590, 1510, 1460, 1440, 1410, 1380, 1350, 1310, 1270, 1240, 1220, 1200, 1140, 1130, 1060, 1040, 970, 950, 880, 850, 810, 770 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_9F_3O_6S$: C 38.22, H 2.89, S 10.20; found: C 38.03, H 2.90, S 10.11. Methyl 4-hydroxy-2-methyl-6-(trifluoromethylsulfonyloxy)benzoate: M.p. 88–89 °C (hexane and Et_2O); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 3.93 (s, 3H), 5.77 (s, 1H; OH), 6.65 (d, J = 2.4 Hz, 1H), 6.71 ppm (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 52.7, 107.1, 117.6, 118.2, 118.4 (q, $^1J_{C,F}$ = 318 Hz), 141.9, 148.1, 158.2, 166.2 ppm; IR (KBr): $\tilde{\nu}$ = 3380, 2950, 1700, 1610, 1570, 1490, 1450, 1410, 1300, 1240, 1210, 1120, 1100, 1040, 970, 940, 850, 810, 780, 760, 700, 680 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_9F_3O_6S$ (314.24): C 38.22, H 2.89, S 10.20; found: C 38.25, H 3.02, S 10.05.

*Methyl 2-methoxymethoxy-6-methyl-4-(trifluoromethylsulfonyloxy)benzoate (**9**)*: iPr$_2$NEt (33 mL, 0.191 mol) and a solution of MOMCl (11.6 mL, 0.152 mol) in CH_2Cl_2 (80 mL) were added over 1 h to a solution of methyl 2-hydroxy-6-methyl-4-(trifluoromethylsulfonyloxy)benzoate (40.0 g, 0.127 mol) in CH_2Cl_2 (100 mL) at 0 °C. After the reaction mixture had been stirred for 5.5 h at RT, the reaction was stopped by adding pH 7 phosphate buffer and then the mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with 2 M aq. HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. After adding Et_2O and hexane to the residue, the precipitate was collected by filtration to afford **9** (1st crop: 25.1 g, 55%; 2nd crop: 10.7 g, 23%) as a white solid. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 86:14) to afford **9** (9.83 g, 22%, total yield: quant) as a white solid. M.p. 41–42 °C (hexane and Et_2O); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3H), 3.47 (s, 3H), 3.93 (s, 3H), 5.18 (s, 2H), 6.79 (d, J = 2.0 Hz, 1H), 6.95 ppm (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 19.4, 52.4, 56.3, 94.9, 106.1, 115.9, 118.9 (q, $^1J_{C,F}$ = 319 Hz), 124.8, 138.7, 150.0, 155.1, 167.2 ppm; IR (neat): $\tilde{\nu}$ = 3460, 3100, 2960, 2830, 2080, 1970, 1730, 1590, 1480, 1430, 1280, 1210, 1140, 1050, 1000, 970, 930, 860, 840, 760 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{13}O_7F_3S$: C 40.23, H 3.66, S 8.95; found: C 40.16, H 3.73, S 8.90.

*1-Methyl 4-phenyl 2-methoxymethoxy-6-methylterephthalate (**10**)*: A mixture of **9** (2.37 g, 6.62 mmol), $Pd(OAc)_2$ (75.6 mg, 0.337 mmol), 1,1′-bis(diphenylphosphino)ferrocene (181 mg, 0.326 mmol), Et_3N (2.11 g, 20.9 mmol), and PhOH (3.04 g, 32.3 mmol) in DMF (13 mL) was bubbled with CO gas for 10 min. The reaction mixture was stirred for 1.5 h at 60 °C and then for 1.5 h at 80 °C. After cooling to RT, the reaction mixture was diluted with water and extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 84:16) to afford **10** as a white solid (2.18 g, quant). M.p. 71.5–72.0 °C (hexane and EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.49 (s, 3H), 3.95 (s, 3H), 5.25 (s, 2H), 7.27 (t,

J=7.8 Hz, 1H), 7.27 (d, J=7.8 Hz, 2H), 7.43 (t, J=7.8 Hz, 2H), 7.72 (s, 1H), 7.77 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.2, 52.4, 56.4, 94.7, 113.5, 121.7, 125.3, 126.0, 129.5, 129.6, 131.2, 136.9, 150.8, 153.9, 164.5, 167.8 ppm; IR (KBr): $\tilde{\nu}$=2950, 2830, 1730, 1590, 1490, 1430, 1400, 1320, 1300, 1270, 1200, 1160, 1120, 1100, 1080, 1050, 1000, 940, 930, 840, 790, 760, 730 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{18}O_6$: C 65.45, H 5.49; found: C 65.41, H 5.57.

*Methyl 4-hydroxymethyl-2-methoxymethoxy-6-methylbenzoate (**11**)*: $LiBH_4$ (1.62 g, 74.5 mmol) was added to a solution of **10** (24.6 g, 74.5 mmol) in THF (260 mL) at 0°C. The reaction temperature was allowed to rise to RT and the mixture was stirred for 24 h. The reaction was stopped by adding AcOH and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc=1:1) to afford **11** as a colorless oil (17.5 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.28 (s, 3H), 2.31 (t, J=6.0 Hz, 1H; OH), 3.45 (s, 3H), 3.91 (s, 3H), 4.61 (d, J=6.0 Hz, 2H), 5.16 (s, 2H), 6.83 (s, 1H), 6.96 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.3, 52.2, 56.2, 64.7, 94.6, 110.4, 121.7, 123.8, 136.8, 143.7, 154.1, 168.7 ppm; IR (film): $\tilde{\nu}$=3430, 2950, 2830, 1740, 1720, 1610, 1580, 1440, 1400, 1360, 1280, 1210, 1190, 1150, 1090, 1050, 1000, 930, 850, 820, 780, 750 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{16}O_5$: C 59.99, H 6.71; found: C 59.87, H 6.94.

*Methyl 2-methoxymethoxy-4-(methoxymethoxy)methyl-6-methylbenzoate (**12**)*: iPr$_2$NEt (17.0 mL, 97.2 mmol) and MOMCl (7.2 mL, 95 mmol) were added to a solution of **11** (7.82 g, 32.5 mmol) in CH_2Cl_2 (65 mL) at 0°C. The reaction mixture was allowed to warm to RT and stirred for 3 h. The reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with 2M aq. HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc=8:2) to afford **12** as a colorless oil (8.11 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.29 (s, 3H), 3.41 (s, 3H), 3.47 (s, 3H), 3.91 (s, 3H), 4.54 (s, 2H), 4.69 (s, 2H), 5.18 (s, 2H), 6.86 (brs, 1H), 6.98 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.3, 52.1, 55.4, 56.2, 68.7, 94.7, 95.7, 111.4, 122.7, 124.1, 136.7, 140.5, 154.1, 168.6 ppm; IR (neat): $\tilde{\nu}$=3620, 2950, 2830, 2070, 1970, 1900, 1730, 1620, 1580, 1560, 1440, 1400, 1370, 1320, 1270, 1210, 1190, 1150, 1090, 1050, 1010, 950, 920, 850, 820 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{20}O_6$: C 59.14, H 7.09; found: C 58.92, H 7.26.

*Methyl 2-hydroxy-4-(methoxymethoxy)methyl-6-methylbenzoate (**13**)*: Trifluoroacetic acid (1.2 mL, 16 mmol) was added to a solution of **12** (1.45 g, 5.09 mmol) in CH_2Cl_2 (25 mL) at 0°C. After stirring for 3 h, the reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc=9:1) to afford phenol **13** as a colorless oil (1.22 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.54 (s, 3H), 3.41 (s, 3H), 3.95 (s, 3H), 4.52 (s, 2H), 4.71 (s, 2H), 6.70 (s, 1H), 6.84 (s, 1H), 11.33 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.1, 52.1, 55.5, 68.2, 95.9, 111.3, 114.1, 121.7, 141.5, 144.8, 163.1, 172.1 ppm; IR (neat): $\tilde{\nu}$=2950, 2890, 1730, 1660, 1620, 1570, 1440, 1420, 1380, 1360, 1320, 1260, 1210, 1150, 1100, 1050, 1010, 990, 940, 920, 850, 810, 750 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{16}O_5$: C 59.99, H 6.71; found: C 59.97, H 6.79.

*Methyl 2-hydroxy-3-iodo-4-(methoxymethoxy)methyl-6-methylbenzoate (**14**)*: $NaHCO_3$ (5.23 g, 62.7 mmol) and $BnMe_3N^+ICl_2^-$ (10.8 mL, 30.9 mmol) were added to a solution of **13** (7.48 g, 31.1 mmol) in CH_2Cl_2/MeOH (5:2, 310 mL) at 0°C. The reaction mixture was stirred for 10 h at 0°C. The reaction was stopped by adding 10% aqueous $Na_2S_2O_3$ and the mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with 10% aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by recrystallization from EtOH to afford **14** as a white solid (1st crop: 8.00 g, 70%; 2nd crop: 0.75 g, 6.5%; 3rd crop: 0.75 g, 6.5%; total yield: 83%). M.p. 67.5–68.0°C (EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.54 (s, 3H), 3.45 (s, 3H), 3.99 (s, 3H), 4.59 (s, 2H), 4.79 (s, 2H), 6.94 (s, 1H), 12.36 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.9, 52.6, 55.7, 73.4, 85.6, 96.4, 111.3, 122.6, 141.5, 147.1, 160.9, 171.8 ppm; IR (KBr): $\tilde{\nu}$=2960, 2890, 1660, 1600, 1540, 1450, 1390, 1370, 1350, 1290, 1250, 1200, 1150, 1110, 1060, 1000, 960, 940, 910, 860, 810, 770, 710 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{15}O_5I$: C 39.36, H 4.13; found: C 39.47, H 4.34.

*4-tert-Butyl 1-ethyl 2-(2,5-dimethoxybenzylidene)succinate (**16**)*: Phosphonate **19** (4.90 g, 14.5 mmol) in CH_3CN (15 mL), DBU (2.20 g, 1.44 mmol), and 2,5-dimethoxybenzaldehyde (2.00 g, 12.0 mmol) were added to a suspension of LiCl (0.827 g, 19.6 mmol) in CH_3CN (90 mL) at RT and the reaction mixture was stirred for 44 h. The reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/Et_2O/$CHCl_3$=14:3:3) to afford the E (3.12 g, 73%) and Z isomers (156 mg, 3.7%) of **16** as yellow oils.

16 (E isomer): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.32 (t, J=7.1 Hz, 3H), 1.42 (s, 9H), 3.39 (s, 2H), 3.73 (s, 3H), 3.77 (s, 3H), 4.25 (q, J=7.1 Hz, 2H), 6.81 (d, J=9.0 Hz, 1H), 6.85 (dd, J=2.7, 9.0 Hz, 1H), 6.89 (d, J=2.7 Hz, 1H), 7.91 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2, 27.9, 35.3, 55.6, 55.9, 60.8, 80.7, 111.6, 114.8, 115.5, 124.7, 126.9, 137.4, 151.7, 153.1, 167.3, 170.5 ppm; IR (neat): $\tilde{\nu}$=2730, 2725, 1720, 1710, 1640, 1580, 1500, 1460 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{26}O_6$: C 65.13, H 7.48; found: C 65.43, H 7.50.

16 (Z isomer): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.08 (t, J=7.1 Hz, 3H), 1.44 (s, 9H), 3.38 (s, 2H), 3.73 (s, 3H), 3.75 (s, 3H), 4.09 (q, J=7.1 Hz, 2H), 6.74–6.81 (m, 3H), 6.86 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 28.0, 42.0, 55.7, 56.0, 60.4, 81.0, 111.4, 114.4, 115.6, 125.8, 128.0, 134.5, 151.2, 152.9, 167.7, 170.0 ppm; IR (neat): $\tilde{\nu}$=2730, 2725, 1720, 1490, 1220 1160 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{26}O_6$: C 65.13, H 7.48; found: C 65.43, H 7.74.

*3-(2,5-dimethoxybenzylidene)succinic acid monoethyl ester (**17**)*: Trifluoroacetic acid (5.2 mL) was added to a solution of (*E*)-**16** (2.99 g, 8.55 mmol) in water (0.58 mL). After stirring for 3.5 h, volatile materials were removed by azeotropic distillation with toluene (×3). The resulting solid was filtered to afford **17** as a white powder (2.13 g, 85%). The filtrate was purified by flash column chromatography (silica gel, hexane/EtOAc=1:1 then MeOH/$CHCl_3$=1:9) to afford **17** as a white solid (0.14 g, 5%; total yield: 90%). ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.35 (t, J=7.1 Hz, 3H), 3.51 (s, 2H), 3.77 (s, 3H), 3.80 (s, 3H), 4.31 (q, J=7.1 Hz, 2H), 6.82–6.82 (m, 3H), 7.99 (s, 1H), 10.6 ppm (s, 1H).

*Ethyl 4-acetoxy-5,8-dimethoxy-2-naphthoate (**18a**)*: NaOAc (0.800 g, 9.75 mmol) was added to a solution of **17** (2.10 g, 7.13 mmol) in acetic anhydride (11.5 mL) at RT and the reaction mixture was stirred for 30 min at 140°C. After cooling to RT, the resulting precipitate was collected by filtration to afford **18a** as a white powder (1.99 g, 88%). The filtrate was concentrated in vacuo. The residue was azeotroped with toluene (×2) to remove volatile materials and recrystallized (hexane/EtOAc) to afford **18a** (0.162 g, 7%). The mother liquor was extracted with EtOAc (×3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc=7:3) to afford **18a** as a white solid (0.0937 g, 11%; total yield: 99%). ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.43 (t, J=7.1 Hz, 3H), 2.38 (s, 3H), 3.89 (s, 3H), 3.97 (s, 3H), 4.42 (q, J=7.1 Hz, 2H), 6.77 (d, J=8.6 Hz, 1H), 6.87 (d, J=8.6 Hz, 1H), 7.69 (d, J=1.7 Hz, 1H), 8.90 ppm (d, J=1.7 Hz, 1H).

*Ethyl 4-hydroxy-5,8-dimethoxy-2-naphthoate (**18d**)*: K_2CO_3 (56.8 g, 0.411 mol) was added to a solution of **18a** (26.3 g, 0.0826 mol) in EtOH (410 mL) at RT. After stirring for 1 h at 70°C, the reaction was extracted with EtOAc (×3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by recrystallization (hexane/EtOAc) to afford **18d** as a white powder (20.1 g, 89%). The mother liquor was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=65:35) to afford **18d** as a white powder (2.03 g, 9%; total yield: 98%). M.p. 120.0–120.2°C (hexane and EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.43 (t, J=7.2 Hz, 3H), 3.97 (s, 3H), 4.03 (s, 3H), 4.41 (q, J=7.2 Hz, 2H), 6.69 (d, J=8.4 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 7.49 (d, J=1.2 Hz, 1H), 8.46 (d, J=1.2 Hz, 1H), 9.49 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.4, 55.7, 56.3, 61.0, 103.5, 105.7, 110.5, 115.7,

117.5, 127.4, 128.8, 149.5, 150.9, 154.4, 166.5 ppm; IR (KBr): $\tilde{\nu}$ = 3370, 1710, 1620, 1520, 1450, 1390, 1290, 1250, 1230, 1110, 1050, 1030, 810, 770 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{16}O_5$: C 65.21, H 5.84; found: C 65.33, H 5.90.

*Ethyl 5,8-dimethoxy-4-methoxymethoxy-2-naphthoate (**18b**)*: Compound **18d** (20.9 g, 0.0766 mmol) and MOMCl (9.33 g, 0.116 mol) were added to a suspension of NaH (60% dispersion in mineral oil, washed with hexane (4.02 g, 0.100 mol)) in DMF (240 mL) at 0°C. After stirring for 20 min, the reaction was stopped by adding water and the mixture was extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. After adding Et_2O and hexane to the residue, the precipitate was collected by filtration to afford **18b** as a white solid (23.8 g, 99%). M.p. 78.7–79.2°C (hexane and EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, J = 7.2 Hz, 3H), 3.62 (s, 3H), 3.92 (s, 3H), 3.98 (s, 3H), 4.43 (q, J = 7.2 Hz, 2H), 5.41 (s, 2H), 6.78 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H), 8.70 ppm (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 55.8, 56.6, 57.3, 61.1, 96.7, 104.6, 109.5, 112.8, 119.4, 121.4, 127.5, 127.9, 150.2, 150.4, 153.6, 166.4 ppm; IR (KBr): $\tilde{\nu}$ = 2980, 1710, 1600, 1520, 1470, 1380, 1280, 1150, 1090, 1040, 920, 800, 760, 730, 720, 660 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{20}O_6$: C 63.74, H 6.29; found: C 63.53, H 6.45.

*Ethyl 8-methoxymethoxy-1,4-naphthoquinone-6-carboxylate (**20b**)*: A solution of CAN (20.1 g, 36.6 mmol) in water (63 mL) was added to a solution of **18b** (5.80 g, 18.3 mmol) in CH_3CN (183 mL) at 0°C. After stirring for 10 min, the reaction was stopped by adding water, the precipitate was collected by filtration, and washed with Et_2O. After adding water and stirring for 10 min, precipitate was collected by filtration to afford **20b** (4.36 g, 83%) as a yellow solid. The filtrate was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The precipitate was collected by filtration and washed with Et_2O to afford **20b** as a yellow solid (0.683 g, 13%; total yield: 96%). M.p. 107–108°C (hexane and EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, J = 7.2 Hz, 3H), 3.56 (s, 3H), 4.45 (q, J = 7.2 Hz, 2H), 5.42 (s, 2H), 6.92 (d, J = 10.4 Hz, 1H), 6.90 (d, J = 10.4 Hz, 1H), 8.16 (d, J = 1.6 Hz, 1H), 8.41 ppm (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 56.8, 62.0, 95.1, 122.4, 123.0, 134.0, 135.9, 137.0, 140.7, 157.0, 164.5, 183.5, 184.1 ppm; IR (KBr): $\tilde{\nu}$ = 3680 3630, 1720, 1660, 1610, 1600, 1560, 1550, 1430, 1370, 1340, 1320, 1270, 1210, 1170, 1110, 1090, 1000, 920, 880, 850, 770 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{14}O_6$: C 62.06, H 4.86; found: C 61.84, H 4.95.

*Ethyl 8-hydroxy-6-methoxy-4-methoxymethoxy-9,10-anthraquinone-2-carboxylate (**22b**)*: Diene **21** (3.47 g, 10.5 mmol) was added to a solution of **20b** (2.50 g, 8.73 mmol) in THF (87 mL) at 0°C. After stirring the reaction mixture for 7 h at −78°C, nBu$_4$NF (1.0 M in THF, 13 mL, 13 mmol) was added and the mixture bubbled with O_2 for 5 min at RT. The mixture was poured into water (150 mL) and stirred for 15 min. The resulting precipitate was collected by filtration to afford **22b** as a yellow solid (2.11 g, 84%). M.p. 195.0–195.4°C (hexane and EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, J = 7.2 Hz, 3H), 3.59 (s, 3H), 3.94 (s, 3H), 4.46 (q, J = 7.2 Hz, 2H), 5.45 (s, 2H), 6.69 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 8.16 (d, J = 1.5 Hz, 1H), 8.62 (d, J = 1.5 Hz, 1H), 12.71 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 56.0, 56.9, 62.1, 95.2, 106.0, 107.7, 110.2, 121.3, 122.5, 124.8, 136.0, 136.1, 136.4, 158.0, 164.7, 165.1, 166.7, 181.2, 185.5 ppm; IR (KBr): $\tilde{\nu}$ = 2380, 2360, 1730, 1680, 1650, 1630, 1590, 1560, 1430, 1400, 1300, 1260, 1150, 1010, 960, 930, 820 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{18}O_8$: C 62.17, H 4.70; found: C 62.11, H 4.78.

*Ethyl 8-benzyloxy-6-methoxy-4-methoxymethoxy-9,10-anthraquinone-2-carboxylate (**24**)*: Cs_2CO_3 (4.29 g, 13.2 mmol) and BnBr (1.44 mL, 11.6 mmol) were added to a solution of anthraquinone **22b** (2.02 g, 5.27 mmol) in DMF (150 mL) at 0°C. After stirring for 7.5 h at RT, the reaction was stopped by adding water and the mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The precipitate was collected by filtration and washed with Et_2O to afford **24** as a yellow powder (2.23 g, 89%). M.p. 179–180°C (hexane and EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 (t, J = 7.0 Hz, 3H), 3.59 (s, 3H), 3.92 (s, 3H), 4.43 (q, J = 7.0 Hz, 2H), 5.27 (s, 2H), 5.43 (s, 2H), 6.78 (s, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.38 (s, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.61 (d, J = 7.6 Hz, 2H), 8.07 (s, 1H), 8.61 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 55.8, 56.7, 61.8, 71.0, 95.3, 103.7, 105.7, 115.8, 120.9, 121.8, 124.3, 126.8, 127.9, 128.7, 136.00, 136.01, 137.6, 139.0, 157.1, 161.0, 164.8, 165.0, 179.9, 182.3 ppm; IR (KBr): $\tilde{\nu}$ = 2460, 1710, 1670, 1650, 1600, 1560, 1460, 1390, 1310, 1240, 1150, 1110, 1030, 970, 930, 760 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{24}O_8$: C 68.06, H 5.08; found: C 67.96, H 5.31.

*Ethyl 8-benzyloxy-6,9,10-trimethoxy-4-(methoxymethoxy)anthracene-2-carboxylate (**25**)*: A solution of $Na_2S_2O_4$ (5.14 g, 29.4 mmoL) in degassed water (112 mL) was added to a suspension of anthraquinone **24** (1.40 g, 2.94 mmol) and nBu$_4$NBr (237 mg, 0.735 mmol) in degassed THF (50 mL). After stirring for 30 min at RT, 50% aqueous KOH (9 mL) was added to the mixture, which was stirred for 30 min. After adding Me_2SO_4 (0.735 mL, 7.35 mmoL) and stirring for 1 h, the reaction was stopped by adding water and *N,N*-dimethyl-1,3-propanediamine (2 mL) at 0°C and the organic layer was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 75:25) to afford **25** as a yellow amorphous solid (1.46 g, 98%). M.p. 144.5–145.4°C (hexane and EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, J = 7.2 Hz, 3H), 3.66 (s, 3H), 3.87 (s, 3H), 3.98 (s, 3H), 4.00 (s, 3H), 4.44 (q, J = 7.2 Hz, 2H), 5.24 (s, 2H), 5.43 (s, 2H), 6.63 (d, J = 1.6 Hz, 1H), 7.26 (d, J = 1.6 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.57 (d, J = 1.4 Hz, 1H), 7.62 (d, J = 7.5 Hz, 2H), 8.81 ppm (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 55.8, 57.1, 61.4, 62.9, 64.6, 71.7, 92.5, 96.6, 101.4, 109.3, 116.6, 120.8, 122.0, 126.2, 126.3, 128.1, 128.5, 129.0, 131.4, 137.0, 146.7, 151.8, 153.1, 157.2, 158.9, 167.1 ppm; IR (KBr): $\tilde{\nu}$ = 2940, 1700, 1620, 1540, 1410, 1360, 1310, 1260, 1220, 1150, 1110, 1060, 990, 830, 770, 750, 700 cm^{-1}; elemental analysis calcd (%) for $C_{29}H_{30}O_8$: C 68.76, H 5.77; found: C 68.46, H 5.98.

*8-Benzyloxy-6,9,10-trimethoxy-4-(methoxymethoxy)anthracene-2-carboxylic acid (**26**)*: A 5 M aq. KOH solution (133 mL) was added to a suspension of anthracene **25** (1.30 g, 2.57 mmoL) in EtOH (186 mL) and stirred for 1.5 h under reflux conditions. After cooling to RT, the reaction mixture was diluted with water and washed with Et_2O (×3). The aqueous layer was acidified with 2 M aq. HCl and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The precipitate was collected by filtration and washed with Et_2O to afford **26** as a yellow powder (1.12 g, 91%). M.p. 198–199°C (hexane and EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66 (s, 3H), 3.88 (s, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 5.26 (s, 2H), 5.44 (s, 2H), 6.64 (d, J = 1.7 Hz, 1H), 7.27 (d, J = 1.7 Hz, 1H), 7.38 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.3 Hz, 2H), 7.58 (s, 1H), 7.63 (d, J = 7.3 Hz, 2H), 8.93 (s, 1H) ppm; IR (KBr): $\tilde{\nu}$ = 2370, 2340, 1680, 1640, 1560, 1460, 1420, 1360, 1330, 1250, 1160, 1060, 1030, 1000, 830 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{26}O_8$: C 67.77, H 5.48; found: C 68.07, H 5.30. This title compound was carried on to the subsequent experiment without further characterization.

2-Iodo-6-methoxycarbonyl-3-(methoxymethoxy)methyl-5-methylphenyl 8-benzyloxy-6,9,10-trimethoxy-4-(methoxymethoxy)anthracene-2-carboxylate: Et_3N (140 mg, 1.38 mmol) and 2,4,6-trichlorobenzoyl chloride (459 mg, 1.88 mmol) were added to a solution of carboxylic acid **26** (600 mg, 1.25 mmol) in toluene (10 mL) at RT. After stirring for 3 h at RT, iodophenol **14** (689 mg, 1.88 mmol) and DMAP (460 mg, 3.77 mmol) was added to the reaction mixture and then stirred for 30 min. The reaction was stopped by adding water and the mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 70:30) to afford the title compound as a yellow amorphous solid (974 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 3.45 (s, 3H), 3.67 (s, 3H), 3.71 (s, 3H), 3.90 (s, 3H), 4.00 (s, 3H), 4.03 (s, 3H), 4.64 (s, 2H), 4.80 (s, 2H), 5.26 (s, 2H), 5.46 (s, 2H), 6.65 (d, J = 2.2 Hz, 1H), 7.28 (d, J = 2.2 Hz, 1H), 7.32 (s, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H), 7.62 (d, J = 7.4 Hz, 1H), 7.64 (d, J = 1.4 Hz, 1H), 9.05 ppm (d, J = 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.0, 52.3, 55.4, 55.7, 56.8, 62.6, 64.3, 71.3, 73.0, 91.9, 92.1, 96.2, 96.3, 101.0, 108.7, 116.3, 120.6, 123.4, 124.1, 125.7, 126.6, 127.3, 127.6, 127.8, 128.1, 128.6, 131.5, 136.4, 138.5,

144.0, 146.4, 149.3, 151.8, 152.9, 156.9, 163.8, 166.0 ppm; IR (KBr): $\tilde{\nu}$ = 2930, 1740, 1690, 1650, 1620, 1560, 1540, 1450, 1410, 1360, 1260, 1210, 1170, 1060, 980 cm^{-1}; elemental analysis calcd (%) for $C_{39}H_{39}O_{12}I$: C 56.67, H 4.63; found: C 56.46, H 4.63.

*2-Iodo-6-methoxycarbonyl-3-(methoxymethoxy)methyl-5-methylphenyl 8-benzyloxy-4-hydroxy-6,9,10-trimethoxyanthracene-2-carboxylate (**27**)*: Trifluoroacetic acid (133 mg, 1.17 mmol) was added to a degassed solution of 2-iodo-6-(methoxycarbonyl)-3-(methoxymethoxy)methyl-5-methylphenyl 8-(benzyloxy)-6,9,10-trimethoxy-4-(methoxymethoxy)anthracene-2-carboxylate (320 mg, 0.387 mmol) in CH_2Cl_2 (6 mL) at 0 °C. After stirring for 2 h at RT, the reaction was stopped by adding saturated aqueous $NaHCO_3$ and water, and then the mixture was extracted with CH_2Cl_2 (× 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, benzene/EtOAc = 9:1) to afford **27** as a yellow solid (264 mg, 87 %). M.p. 187–188 °C (hexane and EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3H), 3.45 (s, 3H), 3.70 (s, 3H), 3.90 (s, 3H), 4.01 (s, 3H), 4.10 (s, 3H), 4.63 (s, 2H), 4.80 (s, 2H), 5.26 (s, 2H), 6.63 (d, J = 2.2 Hz, 1H), 7.01 (d, J = 2.2 Hz, 1H), 7.32 (s, 1H), 7.38 (t, J = 7.3 Hz, 1H), 7.45 (dd, J = 7.3, 7.6 Hz, 2H), 7.53 (d, J = 1.5 Hz, 1H), 7.62 (d, J = 7.6 Hz, 2H), 8.85 (d, J = 1.5 Hz, 1H), 9.81 ppm (s, 1H; OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.0, 52.4, 55.5, 55.7, 63.2, 64.3, 71.4, 73.1, 90.7, 91.9, 96.3, 100.9, 107.8, 116.4, 118.6, 120.2, 125.3, 125.6, 126.6, 127.7, 127.8, 128.2, 128.7, 128.9, 136.2, 138.6, 144.0, 145.4, 149.4, 152.8, 153.1, 157.3, 159.1, 163.9, 166.1 ppm; IR (KBr): $\tilde{\nu}$ = 3320, 2950, 1740, 1650, 1620, 1560, 1540, 1450, 1410, 1370, 1260, 1190, 1060, 960, 820, 740, 700 cm^{-1}; elemental analysis calcd (%) for $C_{37}H_{35}O_{11}I$: C 56.79, H 4.51; found: C 56.76, H 4.56.

*Methyl 9-benzyloxy-14-hydroxy-8,11,13-trimethoxy-1-(methoxymethoxy)-methyl-3-methyl-6-oxo-6H-anthra[2,3-c]benzopyran-4-carboxylate (**28**)*: PPh_3 (41.4 mg, 0.158 mmol) and **27** (99.8 mg, 0.128 mmol) were added to a suspension of $Pd(OCOCF_3)_2$ (99.8 mg, 0.128 mmol), sodium pivalate (44.6 mg, 0.359 mmol), and P(t-Bu)$_3$ (35 μL, 0.15 mmol) in DMA (12.8 mL). After stirring at 110 °C for 25 min, the reaction mixture was cooled to 0 °C. The reaction was stopped by adding water and saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (× 3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was azeotropically distiled with benzene (100 mL) and purified by flash column chromatography (silica gel, benzene/EtOAc = 9:1) to afford **28** as a red amorphous solid (53.6 mg, 64 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 3.22 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 4.05 (s, 3H), 4.53 (s, 2H), 4.78 (s, 2H), 5.19 (s, 2H), 6.57 (d, J = 1.7 Hz, 1H), 6.94 (d, J = 1.7 Hz, 1H), 7.33 (t, J = 7.3 Hz, 1H), 7.38(s, 1H), 7.40 (t, J = 7.3 Hz, 2H), 7.55 (d, J = 7.3 Hz, 2H), 8.84 (s, 1H), 10.73 ppm (s, 1H; OH).

2-Chloro-6-hydroxymethyl-4-methoxyphenol: Me_2AlCl (1.0 M toluene solution, 24.4 mL, 0.263 mol) and $(HCHO)_n$ (8.67 g, 0.263 mol) were added to a solution of 2-chloro-4-methoxyphenol (**29**) (27.7 g, 0.175 mol) in CH_2Cl_2 (500 mL) at 0 °C. After the addition was complete, the ice bath was removed and the reaction mixture was stirred for 5 h. The reaction was stopped by adding 2 M aq. HCl at 0 °C and the mixture was extracted with EtOAc (× 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. After adding Et_2O and hexane to the residue, the precipitate was collected by filtration to afford 2-chloro-6-hydroxymethyl-4-methoxyphenol as a white crystalline solid (25.9 g, 89 %). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 6:4) to afford 2-chloro-6-hydroxymethyl-4-methoxyphenol as a white solid (4.94 g, 4 %; total yield: 93 %). M.p. 70–72 °C (hexane and EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51 (t, J = 5.3 Hz, 1H; OH), 3.75 (s, 3H), 4.73 (d, J = 5.3 Hz, 2H), 6.26 (br s, 1H; OH), 6.70 (d, J = 3.0 Hz, 1H), 6.82 ppm (d, J = 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.9, 62.7, 113.2, 113.6, 120.4, 128.0, 144.1, 153.1 ppm; IR (neat): $\tilde{\nu}$ = 3510, 3250, 2930, 2840, 1590, 1480, 1450, 1430, 1380, 1350, 1320, 1290, 1240, 1190, 1170, 1130, 1050, 1040, 980, 930, 860, 830, 790 cm^{-1}; elemental analysis calcd (%) for $C_8H_9O_3Cl$: C 50.94, H 4.81; found: C 50.77, H 4.95.

3-Chloro-2,5-dimethoxybenzyl alcohol: K_2CO_3 (68.1 g, 492 mmol) and Me_2SO_4 (15.0 mL, 158 mmol) were added to a solution of 2-chloro-6-hydroxymethyl-4-methoxyphenol (18.6 g, 98.6 mmol) in acetone (400 mL) at RT. The reaction mixture was heated at reflux for 13 h. After cooling to 0 °C, Et_3N (150 mL) was added and the stirring was continued for 1 h. The resulting suspension was filtered through a Celite pad (washed with EtOAc) and the volatile materials were removed in vacuo. The resulting mixture was diluted with EtOAc and water, and the mixture was extracted with EtOAc (× 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Recrystallization from benzene afforded 3-chloro-2,5-(dimethoxyphenyl)methanol as colorless needles (1st crop: 11.0 g, 55 %; 2nd crop: 4.57 g, 23 %). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7:3) to afford 3-chloro-2,5-dimethoxyphenylmethanol as a white solid (2.50 g, 13 %; total yield: 91 %). M.p. 54–55 °C (benzene); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (t, J = 3.9 Hz, 1H; OH), 3.77 (s, 3H), 3.83 (s, 3H), 4.69 (d, J = 3.9 Hz, 2H), 6.84 (d, J = 2.9 Hz, 1H), 6.85 ppm (d, J = 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7, 61.1, 61.2, 112.8, 114.7, 127.9, 136.2, 147.4, 156.0 ppm; IR (neat): $\tilde{\nu}$ = 3420, 2940, 2840, 1600, 1570, 1480, 1430, 1360, 1310, 1270, 1230, 1180, 1120, 1050, 1000, 950, 860, 760 cm^{-1}; elemental analysis calcd (%) for $C_9H_{11}O_3Cl$: C 53.35, H 5.47; found: C 53.46, H 5.49.

*3-Chloro-2,5-dimethoxybenzaldehyde (**30**)*: MnO_2 (33.4 g, 384 mmol) was added to a solution of 3-chloro-2,5-(dimethoxyphenyl)methanol (15.5 g, 76.5 mmol) in CH_2Cl_2 (260 mL) at RT and the reaction mixture was warmed to 40 °C and stirred. After about every 1 h, MnO_2 (ca. 5 g) was added seven times and then the suspension was stirred further 10 h. The reaction mixture was filtered through a Celite pad (washed with EtOAc) and concentrated in vacuo. Recrystallization from benzene afforded aldehyde **30** as colorless needles (1st crop: 7.92 g, 52 %; 2nd crop: 1.27 g, 8 %; 3rd crop: 2.85 g. 19 %). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 9:1) to afford **30** as a white solid (1.72 g, 11 %; total yield: 90 %). M.p. 69–70 °C (benzene); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3H), 3.95 (s, 3H), 7.21 (d, J = 3.0 Hz, 1H), 7.23 (d, J = 3.0 Hz, 1H), 10.25 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 63.5, 109.4, 123.6, 129.4, 130.6, 153.4, 156.1, 188.9 ppm; IR (KBr): $\tilde{\nu}$ = 3080, 3020, 2970, 2940, 2870, 2840, 2750, 1690, 1610, 1470, 1420, 1390, 1330, 1260, 1230, 1210, 1110, 1050, 990, 870, 850, 770 cm^{-1}; elemental analysis calcd (%) for $C_9H_9O_3Cl$: C 53.88, H 4.52; found: C 53.72, H 4.65.

*Ethyl 4-acetoxy-7-chloro-5,8-dimethoxy-2-naphthoate (**31**)*: *tert*-Butyl 3-ethoxycarbonyl-3-diethoxyphosphorylpropionate (**19**) (1.80 g, 5.32 mmol) in THF (10 mL) was added to a suspension of NaH (60 % dispersion in mineral oil, washed with hexane (209 mg, 5.22 mmol)) in THF (10 mL) at 0 °C and the reaction mixture was stirred for 2 h. A solution of **30** (955 mg, 4.76 mmol) in THF (10 mL) was added at 0 °C. The reaction mixture was warmed to RT and the stirring was continued for 1 h. The reaction was stopped by adding water and the mixture was extracted with EtOAc (× 3). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting mixture was dissolved in trifluoroacetic acid/water (9:1, 34 mL) and the reaction mixture was stirred for 40 min at RT. After adding toluene, azeotropic evaporation was performed three times. NaOAc (3.45 g, 42.0 mmol) and Ac_2O (47.0 mL, 499 mmol) were added to this crude material at RT. The reaction mixture was heated at reflux for 1 h. After cooling to RT, the reaction was stopped by adding water and then the mixture was extracted with EtOAc (× 3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 77:23) to afford **31** as a pale yellow solid (1.24 g, 76 %). M.p. 104–105 °C (hexane and EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, J = 7.3 Hz, 3H), 2.38 (s, 3H), 3.92 (s, 3H), 3.99 (s, 3H), 6.88 (s, 1H), 4.44 (q, J = 7.3 Hz, 2H), 7.68 (d, J = 1.7 Hz, 1H), 8.71 ppm (d, J = 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 20.8, 56.6, 61.5, 61.8, 109.9, 119.5, 120.8, 123.0, 124.2, 129.3, 131.0, 146.5, 147.0, 151.6, 165.5, 170.7 ppm; IR (KBr): $\tilde{\nu}$ = 3411, 2984, 2942, 2846, 1770, 1760, 1715, 1593, 1478, 1459, 1424, 1387, 1366, 1333, 1271, 1232, 1214, 1160, 1130, 1117, 1029, 939, 914, 872, 840, 814 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{17}O_3Cl$: C 57.88, H 4.86; found: C 57.66, H 4.98.

*7-Chloro-4-hydroxy-5,8-dimethoxy-2-naphthoic acid (**32**)*: A 3M aq. NaOH solution of (23.0 mL) was added to a suspension of **31** (2.60 g, 7.35 mmol) in THF/EtOH (1:1) (30 mL) and the reaction mixture was heated at 70°C for 1 h. After cooling to RT, the aqueous layer was washed with Et_2O (×2). The aqueous phase was acidified with 2M aq. HCl. The precipitates were collected by filtration to afford **32** as a white powder (1.81 g, 87%). M.p. >250°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.86 (s, 3H), 3.99 (s, 3H), 7.06 (s, 1H), 7.27 (d, J=1.4 Hz, 1H), 8.06 (d, J=1.4 Hz, 1H), 9.65 (s, 1H; OH), 13.0–13.4 ppm (br, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=56.9, 61.2, 107.7, 110.3, 114.3, 116.5, 123.0, 130.2, 130.7, 145.7, 152.9, 155.1, 167.0 ppm; IR (KBr): $\tilde{\nu}$=3380, 2940, 2640, 1680, 1630, 1600, 1510, 1470, 1430, 1380, 1340, 1310, 1280, 1240, 1210, 1120, 1090, 1020, 940, 820, 800, 770 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{11}O_5Cl$: C 55.24, H 3.92; found: C 55.24, H 4.15.

*2-Iodo-6-methoxycarbonyl-3-(methoxymethoxy)methyl-5-methylphenyl 7-chloro-4-hydroxy-5,8-dimethoxy-2-naphthoate (**33**)*: 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI) (196 mg, 0.981 mmol) and DMAP (125 mg, 1.02 mmol) were added to a mixed suspension of acid **32** (252 mg, 0.892 mmol) and phenol **14** (651 mg, 1.78 mmol) in CH_2Cl_2 (9 mL) at RT. After stirring for 3 h, the reaction was stopped by adding water. The mixture was extracted with EtOAc (×3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc=7:3) to afford **33** as a yellow solid (438 mg, 78%). M.p. 174.5–175.2°C (hexane and EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.45 (s, 3H), 3.45 (s, 3H), 3.70 (s, 3H), 4.00 (s, 3H), 4.09 (s, 3H), 4.63 (s, 2H), 4.81 (s, 2H), 6.88 (s, 1H), 7.33 (s, 1H), 7.63 (s, 1H), 8.50 (s, 1H), 9.32 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.1, 52.4, 55.7, 56.8, 61.7, 73.0, 91.7, 96.2, 108.2, 111.1, 116.8, 117.1, 123.6, 126.4, 128.0, 129.0, 130.9, 138.7, 144.2, 147.5, 149.2, 152.4, 155.4, 163.6, 165.9 ppm; IR (KBr): $\tilde{\nu}$=3390, 2950, 2890, 2850, 1740, 1600, 1520, 1450, 1390, 1340, 1280, 1200, 1180, 1150, 1120, 1070, 1060, 1040, 990, 950, 920, 880, 800, 750 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{24}O_9Cl$: C 47.60, H 3.83; found: C 47.62, H 4.03. Starting material **14** was also recovered (359 mg, 55%).

*Methyl (±)-3-(6-chloro-1-hydroxy-3-hydroxymethyl-5,8-dimethoxynaphthalen-2-yl)-2-hydroxy-4-(methoxymethoxy)methyl-6-methylbenzoate (**35**)*: A suspension of ester **33** (307 mg, 0.486 mmol), $Pd(OAc)_2$ (33.3 mg, 0.148 mmol, 30 mol%), PPh_3 (81.1 mg, 0.309 mmol), and sodium pivalate (187 mg, 1.50 mmol) in DMA (33 mL) was heated at 110°C for 1.5 h. After cooling to RT, the resulting dark brown suspension was filtered through a Celite pad (washed with EtOAc). The filtrate was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. $NaBH_4$ (29.2 mg, 0.772 mmol) was added to a solution of this crude material, which included **34**, in THF/MeOH (20:1) (17 mL) at −40°C. After stirring for 3 h, the reaction was stopped by adding five drops of AcOH at that temperature. After warming to RT, water was added and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, benzene/EtOAc=85:15) to afford (±)-**35** as a yellow solid (211 mg, 86%).

34: M.p. 218.5–219.3°C (hexane and Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.44 (s, 3H), 3.31 (s, 3H), 3.98 (s, 3H), 4.03 (s, 3H), 4.15 (s, 3H), 4.58 (s, 2H), 4.72 (s, 2H), 6.94 (s, 1H), 7.43 (s, 1H), 8.57 (s, 1H), 10.16 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.6, 52.7, 55.5, 57.1, 61.8, 68.9, 96.2, 109.0, 113.7, 114.3, 116.4, 116.7, 121.2, 123.5, 124.3, 126.0, 129.9, 136.6, 138.9, 146.8, 147.6, 151.4, 152.2, 160.4, 167.0 ppm; IR (KBr): $\tilde{\nu}$=3310, 2950, 1740, 1720, 1610, 1600, 1460, 1440, 1390, 1360, 1330, 1260, 1200, 1150, 1090, 1050, 1040, 1010, 950, 920, 840, 810, 760, 710 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{23}O_9Cl$: C 59.71, H 4.61; found: C 59.65, H 4.57.

(±)-**35**: M.p. 142.5–143.3°C (hexane and EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.64 (s, 3H), 2.72 (t, J=6.3 Hz, 1H; OH), 3.13 (s, 3H), 3.979 (s, 3H), 3.981 (s, 3H), 4.00 (s, 3H), 4.27 (d, J=12.2 Hz, 1H), 4.34 (d, J=12.2 Hz, 1H), 4.42 (d, J=6.6 Hz, 1H), 4.46 (d, J=6.3 Hz, 2H), 4.53 (d, J=6.6 Hz, 1H), 6.74 (s, 1H), 7.03 (s, 1H), 7.80 (s, 1H), 9.45 (s, 1H; OH), 11.77 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.3, 52.4, 55.3, 56.6, 61.3, 64.1, 67.4, 96.2, 105.9, 111.9, 113.1, 114.0, 117.2, 121.3, 122.8, 123.3, 131.3, 141.2, 141.4, 143.7, 146.6, 151.3, 152.5, 159.9, 172.4 ppm; IR (KBr): $\tilde{\nu}$=3390, 2940, 1660, 1620, 1600, 1450, 1380, 1360, 1290, 1260, 1200, 1150, 1110, 1050, 1010, 970, 950, 820 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{27}O_9Cl$: C 59.23, H 5.37; found: C 59.14, H 5.50.

*Methyl (±)-3-(6-chloro-1-hydroxy-3-hydroxymethyl-5,8-dimethoxynaphthalen-2-yl)-2-hydroxy-4-hydroxymethyl-6-methylbenzoate (**38**)*: A 6M aq. HCl solution (7 mL) was added to a solution of (±)-**35** (516 mg, 1.02 mmol) in DME (10 mL) at RT and the reaction mixture was heated at 50°C for 3 h. After the mixture had cooled to RT, water was added and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc=45:55) to afford (±)-**38** as a white solid (440 mg, 93%). M.p. 117–120°C (hexane and EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.64 (s, 3H), 2.35–2.70 (br, 2H; OH), 3.98 (s, 3H), 3.99 (s, 3H), 4.01 (s, 3H), 4.32 (s, 2H), 4.45 (d, J=12.0 Hz, 1H), 4.50 (d, J=12.0 Hz, 1H), 6.76 (s, 1H), 7.04 (s, 1H), 7.79 (s, 1H), 9.54 (s, 1H; OH), 11.76 ppm (s, 1H; OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ=24.2, 52.3, 56.6, 61.3, 63.4, 64.2, 106.2, 111.9, 113.4, 114.1, 117.5, 121.0, 123.0, 123.8, 131.1, 140.8, 141.7, 146.3, 146.7, 151.3, 152.4, 160.6, 172.4 ppm; IR (neat): $\tilde{\nu}$=3390, 2940, 1650, 1620, 1600, 1450, 1390, 1360, 1300, 1260, 1200, 1130, 1110, 1070, 1040, 1000, 980, 820, 750 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{23}O_8Cl$: C 59.68, H 5.01; found: C 59.76, H 5.31.

*Methyl (±)-4-(tert-butyldimethylsiloxy)methyl-3-[3-(tert-butyldimethylsiloxy)methyl-6-chloro-1-hydroxy-5,8-dimethoxynaphthalen-2-yl]-2-hydroxy-6-methylbenzoate (**36**)*: Imidazole (211 mg, 3.10 mmol) and *tert*-butylchlorodimethylsilane (355 mg, 2.36 mmol) were added to a solution of (±)-**38** (358 mg, 0.774 mmol) in DMF (5 mL) at RT. After stirring for 25 min, the reaction was stopped by adding water and the mixture was extracted with Et_2O (×3). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc=85:15) to afford (±)-**36** as a white solid (451 mg, 84%). M.p. 162.5–163.4°C (hexane and EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ=−0.05 (s, 3H), −0.04 (s, 3H), 0.01 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 0.95 (s, 9H), 2.64 (s, 3H), 3.97 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 4.27 (d, J=15.0 Hz, 1H), 4.40 (d, J=16.0 Hz, 1H), 4.49 (d, J=15.0 Hz, 1H), 4.59 (d, J=16.0 Hz, 1H), 6.71 (s, 1H), 7.11 (s, 1H), 7.90 (s, 1H), 9.36 (s, 1H; OH), 11.55 ppm (s, 1H; OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.49, −5.43, −5.40, −5.38, 18.3 (2C), 24.5, 25.9, 52.1, 56.5, 61.1, 62.5, 62.9, 105.3, 110.0, 110.9, 113.5, 115.5, 118.7, 120.9, 122.4, 130.9, 140.9, 141.8, 146.5, 147.1, 150.8, 152.7, 159.6, 172.5 ppm; IR (neat): $\tilde{\nu}$=3400, 2960, 2860, 1740, 1660, 1610, 1500, 1460, 1390, 1360, 1290, 1260, 1200, 1120, 1060, 1020, 1010, 990, 960, 950, 840, 780 cm^{-1}; elemental analysis calcd (%) for $C_{35}H_{51}O_8ClSi_2$: C 60.80, H 7.43; found: C 60.57, H 7.62.

*Camphanoyl esters **37a** and **37b***: (1*S*)-(−)-Camphanic chloride (235 mg, 1.08 mmol) and DMAP (18.0 mg, 0.147 mmol) were added to a solution of (±)-**36** (497 mg, 0.719 mmol) in pyridine (3.6 mL) at RT and the reaction mixture was stirred for 20 h. The reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with 2M aq. HCl (×2), saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc=8:2) to afford the less polar ester **37b** as a white solid (250 mg, 40%) and a more polar mixture that included **37a**. The mixture was further purified by column chromatography (benzene/EtOAc=6:4) to afford the more polar ester **37a** (237 mg, 38%).

37a: R_f=0.34 (hexane/EtOAc=7:3); m.p. 97.0–98.0°C (hexane and EtOAc); $[\alpha]_D^{22}$=−60.3 (c=0.975 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=−0.07 (brs, 6H), 0.03 (s, 3H), 0.05 (s, 3H), 0.40 (s, 3H), 0.64 (s, 3H), 0.86 (s, 9H), 0.93 (s, 3H), 0.96 (s, 9H), 1.40–1.72 (m, 3H), 1.90–2.02 (m, 1H), 2.51 (s, 3H), 3.85 (s, 3H), 3.92 (s, 3H), 4.01 (s, 3H), 4.33 (d, J=14.2 Hz, 1H), 4.35 (d, J=15.4 Hz, 1H), 4.44 (d, J=14.2 Hz, 1H), 4.57 (d, J=15.4 Hz, 1H), 6.73 (s, 1H), 7.48 (s, 1H), 7.87 (s, 1H), 9.30 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−5.53, −5.47, −5.45, −5.3, 9.5, 15.6, 15.9, 18.2, 18.3, 20.8, 25.9 (2C), 28.7, 30.6, 52.3, 53.7, 54.7, 56.7, 61.0, 62.3, 62.5, 90.8, 105.5, 110.2, 113.3, 114.1, 123.0, 124.4, 125.2, 127.2, 130.9,

138.0, 141.9, 144.1, 145.7, 146.3, 151.6, 152.5, 165.0, 166.8, 177.8 ppm; IR (neat): $\tilde{\nu}$ = 3380, 2950, 2860, 1790, 1730, 1620, 1600, 1500, 1460, 1390, 1360, 1320, 1260, 1210, 1170, 1120, 1060, 1020, 990, 950, 840 cm^{-1}; elemental analysis calcd (%) for $C_{45}H_{63}O_{11}ClSi_2$: C 62.01, H 7.29; found: C 61.77, H 7.55.

37b: R_f = 0.42 (hexane/EtOAc = 7:3); $[\alpha]_D^{24}$ = +58.2 (c = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = −0.07 (s, 3H), −0.06 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.24 (s, 3H), 0.61 (s, 3H), 0.86 (s, 9H), 0.92 (s, 3H), 0.96 (s, 9H), 1.45–1.56 (m, 1H), 1.63–1.76 (m, 2H), 1.96–2.05 (m, 1H), 2.51 (s, 3H), 3.85 (s, 3H), 3.93 (s, 3H), 4.00 (s, 3H), 4.33 (d, J = 14.4 Hz, 1H), 4.35 (d, J = 15.1 Hz, 1H), 4.45 (d, J = 14.4 Hz, 1H), 4.57 (d, J = 15.1 Hz, 1H), 6.71 (s, 1H), 7.48 (s, 1H), 7.87 (s, 1H), 9.29 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.44, −5.40, −5.37, −5.2, 9.6, 15.4, 16.0, 18.28, 18.34, 20.8, 25.7, 25.9, 28.7, 30.8, 52.2, 53.6, 54.7, 56.7, 61.0, 62.3, 62.4, 90.6, 105.4, 110.0, 113.2, 113.9, 122.9, 124.4, 124.9, 127.0, 130.8, 138.0, 141.7, 143.9, 145.8, 146.0, 151.6, 152.5, 165.0, 166.6, 177.7 ppm; IR (neat): $\tilde{\nu}$ = 3380, 3020, 2960, 2930, 2860, 1790, 1730, 1620, 1600, 1500, 1460, 1390, 1360, 1320, 1260, 1210, 1100, 1060, 1030, 990, 950, 840, 760 cm^{-1}; elemental analysis calcd (%) for $C_{45}H_{63}O_{11}ClSi_2$: C 62.01, H 7.29; found: C 61.73, H 7.39.

*Tetrol (M)-**38***: Two drops of 40% aqueous HF were added to a solution of **37a** (237 mg, 0.272 mmol) in CH_3CN (3 mL) at 0 °C. The reaction mixture was gradually warmed to RT and stirred for 45 min. The reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 35:65) to afford the triol derivative of **37a** as a white solid (170 mg, 97%). M.p. 242–243 °C; $[\alpha]_D^{26}$ = −108 (c = 1.07 in $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): δ = 0.26 (s, 3H), 0.67 (s, 3H), 0.92 (s, 3H), 1.42–1.78 (m, 3H), 1.95–2.08 (m, 1H), 2.48 (s, 3H), 2.70–3.15 (br, 2H; OH), 3.86 (s, 3H), 3.92 (s, 3H), 4.01 (s, 3H), 4.29 (d, J = 12.5 Hz, 1H), 4.34 (d, J = 12.5 Hz, 1H), 4.42 (d, J = 12.5 Hz, 1H), 4.49 (d, J = 12.5 Hz, 1H), 6.76 (s, 1H), 7.44 (s, 1H), 7.55 (s, 1H), 9.47 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.5, 15.4, 16.0, 20.4, 28.7, 30.8, 52.4, 53.7, 54.7, 56.8, 61.3, 62.8, 63.1, 90.6, 106.2, 113.2, 113.7, 115.8, 123.4, 126.1, 126.4, 129.7, 131.1, 138.4, 141.1, 143.8, 145.8, 146.4, 152.1, 152.3, 165.2, 166.6, 177.6 ppm; IR (neat): $\tilde{\nu}$ = 3380, 2960, 2880, 1770, 1730, 1620, 1600, 1510, 1460, 1390, 1360, 1320, 1260, 1210, 1170, 1130, 1100, 1060, 1040, 990, 940, 870, 810, 800 cm^{-1}; elemental analysis calcd (%) for $C_{33}H_{35}O_{11}Cl$: C 61.63, H 5.49; found: C 61.35, H 5.69.

K_2CO_3 (367 mg, 2.66 mmol) was added to a solution of the triol derivative of **37a** (170 mg, 0.264 mmol) in MeOH (3 mL). After stirring for 19 h at RT, the reaction was stopped by adding 2 M aq. HCl and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 4:6) to afford tetrol (*M*)-**38** as a white solid (122 mg, quant). $[\alpha]_D^{28}$ = −52.7 (c = 1.07 in $CHCl_3$); m.p. 117–119 °C (hexane and EtOAc).

*Dialdehyde (M)-**39***: K_2CO_3 (235 mg, 1.70 mmol) and MeI (0.11 mL, 1.77 mmol) were added to a solution of (*M*)-**38** (78.6 mg, 0.170 mmol) in acetone (3.4 mL) at RT. The reaction mixture was warmed to 40 °C and stirred for 11 h. The reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with 2 M aq. HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (benzene/EtOAc = 1:1) to afford the dimethyl ether derivative of (*M*)-**38** as a white solid (75.8 mg, 91%). M.p. 171.5–172.3 °C; $[\alpha]_D^{27}$ = −106 (c = 1.10 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 3.01 (brs, 1H; OH), 3.23 (brs, 1H; OH), 3.44 (s, 3H), 3.53 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 3.99 (s, 3H), 4.23 (brs, 2H), 4.37 (d, J = 12.4 Hz, 1H), 4.45 (d, J = 12.4 Hz, 1H), 6.81 (s, 1H), 7.22 (s, 1H), 8.04 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 52.3, 56.6, 61.4 (2C), 61.8, 63.2, 63.7, 107.7, 118.5, 119.4, 123.5, 126.2, 126.6, 127.0, 127.5, 131.8, 137.1, 139.9, 142.5, 145.6, 152.7, 153.8, 154.5, 168.7 ppm; IR (neat): $\tilde{\nu}$ = 3390, 3010, 2940, 2840, 1730, 1590, 1570, 1460, 1390, 1340, 1290, 1200, 1140, 1100, 1050, 960, 920, 890, 800, 750 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{27}O_8Cl$: C 61.16, H 5.54; found: C 61.25, H 5.61.

MnO_2 (62.0 mg, 0.713 mmol) was added to a solution of the dimethyl ether derivative of (*M*)-**38** (71.3 mg, 0.145 mmol) in CH_2Cl_2 (3 mL) at RT and the reaction mixture was stirred for 26 h. The reaction was monitored by TLC and MnO_2 (62.0 mg, 0.713 mmol) was added about every 4 h. When the reaction was completed, the mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by PTLC (benzene/EtOAc = 6:4) to afford dialdehyde **39** as a yellow oil (55.4 mg, 79%). $[\alpha]_D^{27}$ = +16.7 (c = 1.08 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3H), 3.36 (s, 3H), 3.46 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 4.06 (s, 3H), 6.99 (s, 1H), 7.71 (s, 1H), 8.59 (s, 1H), 9.74 (s, 1H), 9.88 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 52.6, 56.8, 61.4, 61.5, 61.9, 110.8, 122.0, 122.2 (2C), 123.4, 125.0, 125.5, 128.0, 131.4, 133.4, 133.6, 135.9, 137.5, 146.9, 152.8, 155.2, 167.7, 190.8, 190.9 ppm; IR (neat): $\tilde{\nu}$ = 3380, 3020, 2940, 2840, 2750, 2000, 1740, 1700, 1600, 1570, 1460, 1390, 1360, 1340, 1280, 1240, 1210, 1190, 1140, 1100, 1080, 1050, 1000, 970, 930, 810, 750 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{23}O_8Cl$: C 61.67, H 4.76; found: C 61.77, H 5.02.

The enantiomeric purity of **39** was assessed by HPLC analysis (DAICEL CHIRALCEL OD-H (0.46 cm φ × 25 cm), hexane/*i*PrOH = 9:1, flow rate = 0.7 mL min^{-1}, t_R = 18.3 min for the *M* isomer, 26.4 min for the *P* isomer).

*Diol **40***: SmI_2 (0.1 M THF solution, 3.5 mL, 0.35 mmol) was added to a solution of (*M*)-**39** (68.5 mg, 0141 mmol) in THF (3.0 mL) at 0 °C. After stirring for 10 min at 0 °C, the reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were successively washed with 2 M aq. HCl, water, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (benzene/EtOAc = 50:50) to afford **40** as a yellow solid (68.9 mg, quant). M.p. 225–226 °C (decomp); $[\alpha]_D^{26}$ = −282 (c = 1.08 in $CHCl_3$), $[\alpha]_D^{27}$ = −215 (c = 1.11 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.11–3.36 (br, 2H; OH), 3.39 (s, 3H), 3.42 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 4.36–4.56 (br, 2H), 6.79 (s, 1H), 7.30 (brs, 1H), 8.06 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 52.3, 56.5, 61.3, 61.5, 62.3, 73.8, 74.0, 107.4, 111.6, 119.2, 119.4, 120.0, 120.3, 123.8, 128.4, 131.3, 136.5, 137.7, 140.7, 145.3, 153.6, 154.8, 155.1, 169.1 ppm; IR (neat): $\tilde{\nu}$ = 3453, 3009, 2936, 2837, 1728, 1619, 1589, 1574, 1454, 1421, 1343, 1285, 1216, 1120, 1096, 1044, 1002, 969, 926, 892, 816, 798, 755 cm^{-1}; UV (MeOH): λ_{max} = 357 (ε = 8500), 339 (7800), 323 (9500), 309 (10000), 278 (34000), 270 (34000), 229 nm (34000 $M^{-1}cm^{-1}$); CD (MeOH): λ_{ext} = 354 ($\Delta\varepsilon$ = −2.8), 321 (−8.0), 278 (+14), 246 (−32), 224.5 nm (+35 $M^{-1}cm^{-1}$); elemental analysis calcd (%) for $C_{25}H_{25}O_8Cl$: C 61.42, H 5.15; found: C 61.25, H 5.35.

The enantiomeric purity of **40** was assessed by HPLC analysis (DAICEL CHIRALCEL OD-H (0.46 cm φ × 25 cm), hexane/*i*PrOH = 9:1, flow rate = 1.0 mL min^{-1}, t_R = 10.9 min for the *R*,*R* isomer, 15.0 min for the *S*,*S* isomer).

*Diacetate **41***: Ac_2O (0.050 mL, 0.53 mmol) and a catalytic amount of DMAP were added to a solution of **40** (63.5 mg, 0.131 mmol) in pyridine (2.6 mL) at RT. After stirring for 20 min, the reaction was stopped by adding water and the mixture was extracted with EtOAc (×2). The combined organic extracts were successively washed with 1 M aq. HCl, water, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (benzene/EtOAc = 85:15) to afford **41** as a white amorphous solid (72.9 mg, 98%). M.p. 98–100 °C; $[\alpha]_D^{26}$ = +106 (c = 1.15 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$ at 300 K): δ = 1.70–2.45 (br, 6H), 2.37 (s, 3H), 3.43 (s, 3H), 3.46 (s, 3H), 3.94 (s, 3H), 3.98 (brs, 6H), 5.58–6.20 (br, 2H), 6.84 (brs, 1H), 7.05–7.30 (br, 1H), 7.55–8.15 ppm (br, 1H); ^{1}H NMR (400 MHz, [D_6]DMSO, at 333 K): δ = 1.80–2.20 (br, 6H), 2.28 (s, 3H), 3.321 (s, 3H), 3.324 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 5.91 (d, J = 7.1 Hz, 1H), 6.00 (d, J = 7.1 Hz, 1H), 7.02 (s, 1H), 7.06–7.14 (br, 1H), 7.60–7.92 ppm (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 20.2, 20.3, 51.8, 56.8, 60.4, 60.9, 61.2, 70.1, 70.3, 108.5, 119.5, 120.4, 123.1, 129.0, 130.0, 132.3, 135.3, 135.4, 144.7, 153.1, 155.0, 155.1, 167.5, 169.3 ppm (signals for four sp^2 carbon atoms were not detected presumably owing to peak-broadening ascribed to the slow conformational interconversion, diaxial⇔diequatorial); IR

(neat): $\tilde{\nu}$ = 3010, 2940, 2840, 1760, 1730, 1620, 1580, 1460, 1370, 1340, 1290, 1220, 1140, 1100, 1030, 970, 940, 920, 900, 890, 850, 810, 760 cm^{-1}; elemental analysis calcd (%) for $C_{29}H_{29}O_{10}Cl$: C 60.79, H 5.10; found: C 60.69, H 5.38.

Quinone ***42***: A solution of CAN (299 mg, 0.545 mmol) in water (2 mL) was added to a solution of **41** (126 mg, 0.220 mmol) in CH_3CN (3 mL) at 0 °C. After stirring for 10 min at 0 °C, the reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 4:6) to afford **42** as a yellow solid (120 mg, quant). M.p. 187–188 °C; $[\alpha]_D^{25} = +98.9$ ($c = 1.04$ in $CHCl_3$); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 333 K): δ = 1.92–2.26 (br, 6H), 2.30 (s, 3H), 3.39 (s, 3H), 3.49 (s, 3H), 3.89 (s, 3H), 5.94 (d, J = 7.3 Hz, 1H), 6.00 (d, J = 7.3 Hz, 1H), 7.06–7.20 (br, 1H), 7.36 (s, 1H), 7.77–7.94 pppm (br, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 18.5, 20.17, 20.22, 52.0, 60.9, 61.5, 69.6 (br, 2C), 78.9, 119.0 (br), 120.7, 123.6 (br), 128.8, 131.2, 132.2, 135.2 (br), 137.4, 137.5, 138.8 (br), 142.4, 155.2, 157.9, 167.1, 169.3 (2C), 177.0, 180.7 ppm; IR (neat): $\tilde{\nu}$ = 3470, 3020, 2930, 2850, 1740, 1680, 1660, 1610, 1580, 1460, 1370, 1300, 1260, 1230, 1140, 1080, 1040, 980, 940, 900, 860, 750 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{23}O_{10}Cl$: C 59.73, H 4.27; found: C 59.49, H 4.48.

Anthraquinone ***43***: A solution of siloxydiene **21** (94.5 mg, 0.467 mmol) in THF (2 mL) was added to a solution of **42** (120 mg, 0.220 mmol) in THF (3 mL) at 0 °C. Immediately, the ice bath was removed and the reaction mixture was stirred for 2 h at RT. Acidic SiO_2 (pH 6) (8 g) was added to the reaction mixture and the solvent removed in vacuo. After standing for 12 h, the SiO_2 was placed on a Celite pad, washed with EtOAc, and then the filtrate was concentrated in vacuo. K_2CO_3 (348 mg, 2.52 mmol) was added to the solution of this crude material in THF/CH_2Cl_2 (1:3) (10 mL) at RT. After stirring for 1.5 h, K_2CO_3 (324 mg, 2.34 mmol) was added to the reaction mixture and stirred for a further 1 h. The reaction was stopped by adding 1 M aq. HCl and the mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. After adding Et_2O to the residue, the precipitate was collected by filtration to afford quinone **43** as a yellow powder (101 mg, 76%). The filtrate was concentrated in vacuo and the residue was purified by PTLC ($CHCl_3$/MeOH = 95:5) to afford **43** as a yellow solid (18.8 mg, 14%; total yield: 90%). M.p. > 220 °C; $[\alpha]_D^{26} = +76.8$ ($c = 0.800$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70–2.37 (br, 6H), 2.38 (s, 3H), 3.51 (s, 3H), 3.64 (s, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 5.90–6.16 (br, 2H), 6.68 (d, J = 2.5 Hz, 1H), 6.80–7.30 (br, 1H), 7.34 (d, J = 2.5 Hz, 1H), 7.80–8.40 (br, 1H), 12.71 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$, 323 K): δ = 19.4, 20.8, 29.7, 52.4, 56.1, 61.8, 62.2, 70.7 (br), 106.1, 107.6, 110.6, 126.3 (br), 129.8 (br), 131.7 (br), 135.0, 135.6 (br), 136.8, 138.3, 139.9 (br), 156.3, 159.5, 165.1, 166.8, 168.2, 169.8, 181.1, 185.7 ppm (signals for four sp^2 carbon atoms were not detected presumably owing to peak-broadening ascribed to the slow conformational interconversion, diaxial⇔diequatorial); IR (KBr): $\tilde{\nu}$ = 3450, 3020, 2950, 1740, 1680, 1630, 1610, 1590, 1440, 1370, 1310, 1260, 1230, 1160, 1120, 1070, 1040, 970, 750 cm^{-1}; elemental analysis calcd (%) for $C_{32}H_{28}O_{12}$: C 63.57, H 4.67; found: C 63.37, H 4.86.

Phenol ***44***: BCl_3 (1.0 M in hexane, 0.50 mL, 0.50 mmol) was added to a solution of **43** (31.9 mg, 52.8 μmol) in CH_2Cl_2 (2 mL) at −10 °C. The reaction mixture was stirred for 30 min and then the reaction was stopped by adding saturated aqueous $NaHCO_3$. After adding 1 M aq. HCl, the mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. After adding Et_2O to the residue, the precipitate was collected by filtration to afford quinone **44** as an orange powder (28.1 mg, 92%). The filtrate was concentrated in vacuo and the residue was purified by PTLC ($CHCl_3$/MeOH = 97:3) to afford **44** as a red powder (2.0 mg, 7%; total yield: 99%). M.p. > 220 °C; $[\alpha]_D^{31} = +127$ ($c = 0.500$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 323 K): δ = 2.08 (s, 3H), 2.13 (s, 3H), 2.48 (s, 3H), 3.94 (s, 3H), 3.99 (s, 3H), 5.99 (d, J = 7.8 Hz, 1H), 6.05 (d, J = 7.8 Hz, 1H), 6.72 (d, J = 2.5 Hz, 1H), 6.85 (s, 1H), 7.40 (d, J = 2.5 Hz, 1H), 7.90 (s, 1H), 10.18 (brs, 1H; OH), 12.78 (s, 1H; OH), 14.27 ppm (brs, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$, 323 K): δ = 20.8, 21.7, 52.3, 56.2, 70.6, 70.8, 107.5, 108.5, 110.7, 116.2, 116.8, 118.2 (br), 121.0 (br), 127.3, 132.5, 134.5, 136.8, 140.9, 142.4, 156.0, 158.2, 165.8, 166.6, 169.7, 169.8, 170.2, 185.0, 188.7 ppm (signals for four sp^2 carbon atoms were not detected presumably owing to the peak-broadening ascribed to the slow conformational interconversion, diaxial⇔diequatorial); IR (KBr): $\tilde{\nu}$ = 2950, 1760, 1660, 1610, 1490, 1450, 1420, 1370, 1350, 1290, 1260, 1230, 1180, 1160, 1120, 1080, 1030, 970, 920, 810, 750 cm^{-1}; elemental analysis calcd (%) for $C_{30}H_{24}O_{12}$: C 62.50, H 4.20; found: C 62.80, H 4.47.

*Benanomicinone methyl ester (****46****)*: A suspension of **44** (9.9 mg, 17 μmol) in 2 M aq. NaOH (5 mL) was heated at 70 °C for 2.5 h. After cooling to RT, the reaction mixture was acidified with 2 M aq. HCl. The precipitates were collected by filtration to afford crude material of carboxylic acid **45** as a deep-red powder (8.5 mg). D-Ala-OMe•HCl (12.4 mg, 88.8 μmol), BOP (112 mg, 25.3 μmol), and Et_3N (17 μL, 120 μmol) were added to a solution of crude **45** (8.5 mg) in DMF (0.4 mL) at RT. After stirring for 1.5 h, the reaction was stopped by adding 2 M aq. HCl and the reaction mixture was diluted with EtOAc. After separating the two layers, the organic layer was washed with 2 M aq. HCl and brine, dried (Na_2SO_4), and concentrated in vacuo. After adding Et_2O to the residue, the precipitate was collected by filtration to afford **46** as a red powder (6.1 mg, 63%). The filtrate was concentrated in vacuo and the residue was purified by column chromatography ($CHCl_3$/MeOH = 93:7) to afford **46** (2.8 mg, 17%; total yield: 80%).

45: M.p. > 230 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 313 K): δ = 2.48 (s, 3H), 3.94 (s, 3H), 4.25 (d, J = 10.5 Hz, 1H), 4.32 (d, J = 10.5 Hz, 1H), 6.90 (d, J = 2.3 Hz, 1H), 7.08 (s, 1H), 7.27 (d, J = 2.3 Hz, 1H), 8.08 (s, 1H), 12.86 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 313 K): δ = 21.7, 56.3, 71.6, 72.2, 106.6, 107.4, 110.1, 114.3, 115.1, 115.4, 117.8, 118.1, 125.7, 131.4, 134.6, 139.7, 143.6, 149.4, 155.7, 157.7, 164.6, 165.9, 171.4, 185.3, 187.0 ppm; IR (KBr): $\tilde{\nu}$ = 3396, 2930, 2850, 1715, 1605, 1488, 1446, 1386, 1296, 1255, 1188, 1162, 1119, 1083, 1064, 1033, 983, 967, 822 cm^{-1}.

46: M.p. > 230 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 313 K): δ = 1.32 (d, J = 7.3 Hz, 3H), 2.32 (s, 3H), 3.67 (s, 3H), 3.91 (s, 3H), 4.23 (d, J = 10.0 Hz, 1H), 4.25 (d, J = 10.0 Hz, 1H), 4.46 (qd, J = 6.7, 7.3 Hz, 1H), 5.95 (brs, 1H; OH), 6.15 (brs, 1H; OH), 6.86 (d, J = 2.4 Hz, 1H), 7.07 (s, 1H), 7.19 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H), 8.46 (brs, 1H), 8.68 (d, J = 6.7 Hz, 1H; NH), 12.81 (s, 1H; OH), 13.84 ppm (brs, 1H; OH); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 313 K): δ = 16.7, 19.0, 47.8, 51.7, 56.4, 71.4, 72.3, 106.8, 107.6, 110.0, 113.7, 115.3, 115.6, 117.5, 125.8, 127.1, 131.2, 134.2, 137.4, 141.0, 149.9, 150.8, 156.6, 164.8, 165.9, 173.0, 185.1, 187.4 ppm (signals for four sp^2 carbon atoms were not detected presumably owing to peak-broadening ascribed to the slow conformational interconversion, diaxial⇔diequatorial); IR (neat): $\tilde{\nu}$ = 3490, 3250, 1740, 1640, 1600, 1450, 1430, 1400, 1380, 1340, 1290, 1240, 1210, 1160, 1140, 1110, 1080, 1070, 1030, 1000, 980, 960, 920, 900, 880, 840, 810, 800, 790 cm^{-1}; elemental analysis calcd (%) for $C_{29}H_{25}NO_{11}$: C 61.81, H 4.47, N 2.49; found: C 61.51, H 4.71, N 2.29.

Benzo[a]naphthacene ***48***: 2-Methoxypropene (264 mg, 3.65 mmol) and TsOH•H_2O (21.5 mg, 0.113 mmol) were added to a solution of **46** (205 mg, 0.364 mmol) in DMF (3 mL) at RT. After stirring 18 h at RT, the reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with water (×3) and brine, dried (Na_2SO_4), and concentrated in vacuo. Ac_2O (0.8 mL) and zinc powder (40 mg, 0.764 mmol) were added to the solution of this crude material in pyridine (6 mL) at RT. After stirring for 10 h at this temperature, the reaction was stopped by adding MeOH and the mixture was extracted with EtOAc (×3). The combined organic extracts were successively washed with 2 M aq. HCl (×3), water (×1), saturated aqueous $NaHCO_3$ (×1), and brine (×2), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (benzene/acetone = 75:25) to afford pentacycle **47** as a yellow solid (218 mg, 73%, two steps) contaminated with a trace amount of impurity (< 1%, ^{1}H NMR) arising from the air sensitivity of this compound. This material was employed in the next experiment without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (d, J = 7.1 Hz, 3H), 1.60 (s, 3H), 1.63 (s, 3H), 2.17 (s, 3H), 2.28 (s, 3H), 2.44 (s, 3H), 2.46 (s, 3H), 2.57 (s, 3H), 2.60 (s, 3H), 3.78 (s, 3H), 3.93 (s, 3H), 4.54 (d, J = 10.7 Hz, 1H), 4.60 (d, J =

10.7 Hz, 1H), 4.79 (qd, J=7.1, 7.8 Hz, 1H), 6.25 (d, J=7.8 Hz, 1H; NH), 6.93 (d, J=2.4 Hz, 1H), 7.09 (d, J=2.4 Hz, 1H), 7.29 (s, 1H), 7.86 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.3, 19.1, 20.7, 21.06, 21.14, 21.2, 27.28, 27.31, 48.0, 52.6, 55.5, 79.2, 79.7, 96.8, 112.5, 115.4, 116.0, 116.7, 120.8, 122.3, 124.6, 127.8, 131.0, 133.3, 138.1, 138.5, 138.7, 139.3, 141.3, 143.8, 146.2, 150.7, 157.5, 166.1, 168.3, 168.7, 169.0, 169.2, 169.8, 172.6 ppm.

TsOH·H_2O (36.5 mg, 0.192 mmol) was added to a solution of **47** (63.6 mg, 0.0780 mmol) in CH_3CN/H_2O (4:1) (3 mL) at RT. After stirring for 2 h at RT, the reaction was stopped by adding water, the mixture was extracted with EtOAc (×2), and washed with saturated aqueous $NaHCO_3$ and water. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (benzene/acetone=1:1) to afford **48** as a yellow solid (56.5 mg, 93%). M.p. 190–191 °C (hexane and EtOAc); ^{1}H NMR (400 MHz, [D$_6$]acetone): δ=1.46 (d, J=7.2 Hz, 3H), 2.21 (s, 3H), 2.31 (s, 3H), 2.44 (s, 3H), 2.46 (s, 3H), 2.61 (s, 3H), 2.71 (s, 3H), 3.76 (s, 3H), 3.99 (s, 3H), 4.36 (dd, J=4.8, 10.8 Hz, 1H), 4.44 (ddd, J=0.8 4.4, 10.8 Hz, 1H), 4.68 (qd, J=7.2, 7.2 Hz, 1H), 5.13(br s, 1H; OH), 5.26 (d, J=4.8 Hz, 1H; OH), 7.05 (d, J=0.8 Hz, 1H), 7.27 (s, 1H), 7.55 (s, 1H), 7.62 (d, J=7.2 Hz, 1H; NH), 8.25 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]acetone): δ=17.6, 19.3, 20.7, 21.0, 21.16, 21.21, 21.3, 48.9, 52.3, 56.1, 73.6, 74.2, 97.2, 115.2, 116.5, 117.4, 120.9, 121.6, 123.9, 124.3, 125.3, 128.5, 132.2, 138.2, 138.4, 138.8, 140.2, 141.2, 142.5, 144.5, 147.7, 158.5, 166.8, 168.9, 169.1, 169.8, 169.9, 170.1, 173.5 ppm; IR (ATR): $\tilde{\nu}$=3490, 3340, 2940, 2860, 1760, 1640, 1530, 1450, 1430, 1420, 1360, 1240, 1180, 1120, 1020, 880 cm^{-1}; elemental analysis calcd (%) for $C_{39}H_{37}NO_{16}$: C 60.39, H 4.81, N 1.81; found: C 60.61, H 5.01, N 1.72.

β-*Glycosides* ***49*** *and* ***50***: MS4A (300 mg) was placed in a two-necked round-bottomed flask and flame dried. The promoter was prepared in situ by stirring a mixture of Cp_2HfCl_2 (31.5 mg, 0.0830 mmol) and $AgClO_4$ (32.0 mg, 0.154 mmol) in CH_2Cl_2 (1.0 mL) for 10 min at RT. A solution of **48** (20.3 mg, 0.0261 mmol) and glycosyl fluoride **51** (28.3 mg, 0.0530 mmol) in CH_2Cl_2 (3.0 mL) was added to this suspension at −78 °C. The reaction mixture was warmed to −12 °C, stirred for 25 min, and the reaction was stopped by adding saturated aqueous $NaHCO_3$. The mixture was filtered through a Celite pad and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (acetone/benzene=3:7) to afford β-glycoside **49** as a yellow amorphous solid (9.1 mg, 27%) and its regioisomeric β-glycoside **50** also as a yellow amorphous solid (5.1 mg, 17%).

49: M.p. 198.2–199.1 °C; $[\alpha]_D^{25}$=−75.2 (c=0.874 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.34 (d, J=6.3 Hz, 3H), 1.44 (d, J=7.2 Hz, 3H), 1.62 (s, 3H), 1.97 (s, 3H), 2.01 (s, 3H), 2.11 (s, 3H), 2.26 (s, 3H), 2.42 (s, 6H), 2.49 (s, 3H), 2.57 (s, 3H), 3.33 (dd, J=9.3, 11.6 Hz, 1H), 3.66–3.72 (m, 1H), 3.78 (s, 3H), 3.89 (dd, J=0.8, 3.6 Hz, 1H), 3.92 (s, 3H), 4.08 (dd, J=3.6, 10.0 Hz, 1H), 4.14 (dd, J=5.2, 11.6 Hz, 1H), 4.49 (br d, 11.2 Hz, 1H), 4.66 (d, J=7.2 Hz, 1H), 4.77 (qd, J=7.2, 7.7 Hz, 1H), 4.9016 (dd, J=7.2, 9.2 Hz, 1H), 4.9025 (d, J=8.2 Hz, 1H), 4.94 (ddd, J=5.2, 9.1, 9.3 Hz, 1H), 5.05 (dd, J=9.1, 9.2 Hz, 1H), 5.68 (dd, J=8.2, 10.0 Hz, 1H), 6.16 (d, J=7.7 Hz, 1H; NH), 6.91 (d, J=2.3 Hz, 1H), 7.05 (s, 1H), 7.50–7.67 (m, 4H), 7.98 (s, 1H), 8.08–8.13 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=17.2, 18.2, 19.3, 19.9, 20.6, 20.7 (2C), 20.98, 21.03, 21.1, 21.2, 48.0, 52.5, 55.5, 62.4, 65.6, 68.9, 69.7, 71.0, 71.3, 71.6, 72.8, 80.3, 81.7, 96.7, 102.2, 102.3, 114.8, 115.9, 116.5, 119.9, 120.3, 121.9, 124.5, 125.6, 127.8, 128.9, 129.2, 129.7, 131.1, 133.8, 134.6, 137.8, 138.1, 139.2, 139.5, 140.4, 143.1, 146.3, 157.5, 164.7, 166.2, 168.5, 168.6–169.3 (3C), 169.1, 169.6, 169.8, 170.2, 172.6; IR (ATR): $\tilde{\nu}$=3488, 3369, 2941, 2111, 1742, 1667, 1638, 1520, 1450, 1433, 1361, 1247, 1175, 1116, 1025, 876, 713 cm^{-1}; elemental analysis calcd (%) for $C_{63}H_{64}N_4O_{27}$: C 57.80, H 4.93, N 4.28; found: C 57.60, H 5.21, N 4.05.

50: M.p. 191.5–192.5 °C; $[\alpha]_D^{26}$=−192 (c=0.705 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.32 (br s, 3H), 1.45 (d, J=7.2 Hz, 3H), 1.66 (s, 3H), 1.97 (s, 3H), 2.01 (s, 3H), 2.16 (s, 3H), 2.20 (s, 3H), 2.39 (s, 3H), 2.49 (s, 3H), 2.56 (s, 3H), 2.77 (s, 3H), 3.32 (dd, J=10.0, 11.2 Hz, 1H), 3.68 (br s, 1H), 3.77 (s, 3H), 3.91 (s, 3H), 3.94 (d, J=3.6 Hz, 1H), 4.10 (dd, J=3.6, 10.0 Hz, 1H), 4.13 (dd, J=6.7, 11.2 Hz, 1H), 4.41–4.52 (m, 2H), 4.64 (d, J=7.4 Hz, 1H), 4.77 (qd, J=7.2, 7.5 Hz, 1H), 4.86 (d, J=8.1 Hz, 1H), 4.93 (dd, J=7.4, 9.2 Hz, 1H), 4.95 (ddd, J=6.7, 9.2, 10.0 Hz, 1H), 5.06 (dd, J=9.2, 9.2 Hz, 1H), 5.70 (br s, 1H), 6.22 (d, J=7.5 Hz, 1H; NH), 6.92 (s, 1H), 7.03 (s, 1H), 7.38 (s, 1H), 7.53 (dd, J=7.4, 7.8 Hz, 2H), 7.65 (t, J=7.4 Hz, 1H), 8.09 (d, J=7.8 Hz, 2H), 8.22 ppm (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=17.2, 18.3 (2C), 19.2, 19.7, 20.0, 20.6, 20.7, 20.8, 21.0, 21.1, 21.2, 48.0, 52.5, 55.4, 62.6, 65.9, 69.0, 69.5, 71.1, 71.2, 71.7, 72.4, 72.8, 80.4, 96.6, 102.4, 103.0, 115.8, 116.7, 117.1, 119.9, 120.6, 121.6, 123.9, 124.6, 127.8, 129.0, 129.6, 131.0, 133.4, 133.9, 137.6, 137.9, 139.9, 140.0, 140.5, 143.2, 146.5, 157.4, 164.6, 166.1, 168.1, 168.9 (br), 169.0, 169.2, 169.7, 169.8, 170.0, 170.2, 172.7 ppm (signals for four sp^2 carbon atoms were not detected presumably owing to peak-broadening ascribed to the slow conformational interconversion, diaxial⇔diequatorial); IR (ATR): $\tilde{\nu}$=3528, 3376, 2941, 2109, 1741, 1667, 1638, 1513, 1432, 1361, 1247, 1184, 1113, 1025, 876, 712 cm^{-1}; elemental analysis calcd (%) for $C_{63}H_{64}N_4O_{27}$: C 57.80, H 4.93, N 4.28; found: C 58.01, H 5.17, N 4.01.

*Benanomicin B hydrochloride (****2b****·HCl)*: A 2 M aq. HCl solution (100 μL) and 5% Pd/C (30 mg) were added to a solution of **49** (37.0 mg, 0.0283 mmol) in MeOH (5.0 mL). After stirring under H_2 (1 atm) at RT for 6 h, the reaction mixture was filtered though a Celite pad (washed with MeOH) and the filtrate was concentrated in vacuo. A 1 M aq. NaOH solution (5 mL) was added to a solution of this crude material (36.0 mg) in MeOH (5.0 mL). After stirring for 2 h, the reaction was stopped by adding 2 M aq. HCl (ca. 3.0 mL) and the mixture concentrated in vacuo (azeotropic evaporation ×5). The residue was purified by Sephadex LH-20 (DMF) to afford a dimethyformamide solvate of benanomicin B which was dissolved in MeOH and then 2 M aq. HCl was added until pH 3.5. After removal of the volatile material in vacuo, the residue was dissolved in DMSO (0.05 mL) and $CHCl_3$ (ca. 6.0 mL) was added. The precipitate was collected by filtration to afford benanomicin B hydrochloride (16.7 mg, 68%67% given in legend to Scheme 12.) as a red amorphous powder. M.p. 213–215 °C (decomp) (lit.:[1b] >220 °C (decomp)); $[\alpha]_D^{22}$=+353 (c=0.0501 in H_2O) (lit.:[1b] +360 (c=0.05, H_2O)); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 313 K): δ=1.18 (d, J=6.5 Hz, 3H), 1.34 (d, J=7.3 Hz, 3H), 2.33 (s, 3H), 3.07 (dd, J=10.7, 10.9 Hz, 1H), 3.16–3.18 (m, 3H), 3.29–3.34 (m, 1H), 3.39–3.44 (m, 1H), 3.60 (br, 1H), 3.72 (dd, J=5.3, 11.3 Hz, 1H), 3.83 (br q, J=6.5, 1H), 3.91–3.94 (m, 1H), 3.95 (s, 3H), 4.42 (dq, J=7.1, 7.3 Hz, 1H), 4.53–4.56 (m, 2H), 4.58–4.65 (m, 1H), 4.74 (d, J=7.6 Hz, 1H), 6.94 (d, J=2.4 Hz, 1H), 7.23 (br s, 1H), 7.31 (d, J=2.4 Hz, 1H), 8.06 (s, 1H), 8.43 (d, J=7.1 Hz, 1H), 12.8 ppm (s, 1H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 313 K): δ=16.3, 16.9, 19.1, 47.6, 54.2, 56.4, 65.7, 66.9, 69.4, 69.7, 73.3, 75.9, 77.4, 80.9, 104.0, 104.5, 106.9, 107.6, 110.1, 113.7, 115.6, 125.7, 127.5, 131.3, 134.3, 137.3, 137.8, 147.9, 151.0, 156.9, 164.7, 166.0, 166.8, 173.9, 185.0, 187.5 ppm; IR (KBr): $\tilde{\nu}$=3360, 1730, 1610, 1300, 1160, 1080, 1040 cm^{-1}; LRMS (MALDI-TOF, DHBA matrix): m/z: calcd for $C_{39}H_{42}O_{18}N_2Na$ ([M+Na]$^+$): 849.2; found: 849.2; HRMS (FAB): m/z: calcd for $C_{39}H_{43}O_{18}N_2$ ([M+H]$^+$): 827.2511; found: 827.2506.

Second-generation synthesis

Methyl 2-methoxymethoxy-6-methyl-4-[(triisopropylsiloxy)methyl]benzoate: Imidazole (17.3 g, 0.254 mol) and triisopropylsilyl chloride (28.2 mL, 0.133 mol) were added to a solution of **11** (30.5 g, 0.127 mol) in DMF (130 mL) at 0 °C. After stirring for 2 h at RT, the reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc=4:1 to 3:1, gradient elution) to afford methyl 2-methoxymethoxy-6-methyl-4-[(triisopropylsiloxy)methyl]benzoate as a colorless oil (50.5 g, quant). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.05–1.25 (m, 21H), 2.29 (s, 3H), 3.46 (s, 3H), 3.90 (s, 3H), 4.79 (s, 2H), 5.16 (s, 2H), 6.83 (s, 1H), 7.04 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.1, 18.1, 19.5, 52.1, 56.0, 64.5, 94.7, 109.6, 120.4, 123.0, 136.2, 144.4, 154.1, 168.6 ppm; IR (neat): $\tilde{\nu}$=3000, 2890, 2870, 1730, 1610, 1590, 1460, 1440, 1270, 1160, 1110, 1090, 1050, 1000, 930, 880, 810 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{36}O_5Si$: C 63.60, H 9.15; found: C 63.50, H 9.08.

Methyl 2-hydroxy-6-methyl-4-[(triisopropylsiloxy)methyl]benzoate: Trifluoroacetic acid (8.8 mL, 0.12 mol) was added to a solution of methyl 2-methoxymethoxy-6-methyl-4-[(triisopropylsiloxy)methyl]benzoate (30.4 g, 76.5 mmol) in CH_2Cl_2 (300 mL) at 0 °C. After stirring for 3.5 h at 0 °C and then for 2.5 h at RT, the reaction was stopped by adding saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. After adding Et_2O and hexane to the residue, the precipitate was collected by filtration to afford methyl 2-hydroxy-6-methyl-4-[(triisopropylsiloxy)methyl]benzoate (1st crop: 22.8 g, 85 %; 2nd crop: 1.50 g, 5.5 %) as a white solid. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 95:5) to afford methyl 2-hydroxy-6-methyl-4-[(triisopropylsiloxy)methyl]benzoate as a white solid (1.40 g, 5.2 %; total yield: 96 %). M.p. 56.5–57.2 °C (hexane and Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06–1.27 (m, 21H), 2.53 (s, 3H), 3.95 (s, 3H), 4.76 (s, 2H), 6.67 (s, 1H), 6.87 (s, 1H), 11.37 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 18.1, 24.3, 52.0, 64.3, 110.5, 112.2, 119.9, 141.0, 148.6, 163.0, 172.1; IR (ATR): $\tilde{\nu}$ = 2950, 2890, 2860, 1660, 1630, 1580, 1450, 1420, 1370, 1320, 1280, 1220, 1160, 1110, 1060, 1010, 990, 950, 880, 850, 800 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{32}O_4Si$: C 64.73, H 9.15; found: C 64.93, H 9.39.

*Methyl 2-hydroxy-3-iodo-6-methyl-4-[(triisopropylsiloxy)methyl]benzoate (**53**)*: $NaHCO_3$ (2.39 g, 28.4 mmol), $BnMe_3N^+ICl_2^-$ (4.99 g, 14.3 mmol), and MeOH (35 mL) were added to a solution of methyl 2-hydroxy-6-methyl-4-[(triisopropylsiloxy)methyl]benzoate (5.00 g, 14.2 mmol) in CH_2Cl_2 (90 mL). After stirring for 4 h at RT, the reaction was stopped by adding aqueous $Na_2S_2O_3$ and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was passed through a silica gel column (hexane/EtOAc = 95:5) to afford somewhat impure **53** with trace amounts of by-products. The mixture was further purified by washing with MeOH to give a pure form of **53** as a white amorphous solid (5.77 g, 85 %). The filtrate was concentrated in vacuo and the residue was further purified by flash column chromatography (silica gel, hexane/benzene = 1:1) to afford an additional product of **53** as a white amorphous solid (0.650 g, 9.6 %; total yield: 95 %). M.p. 33.9–34.1 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06–1.24 (m, 21H), 2.53 (s, 3H), 3.96 (s, 3H), 4.68 (s, 2H), 7.05 (s, 1H), 12.3 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 18.1, 24.2, 52.5, 70.0, 83.4, 110.8, 121.6, 141.2, 149.9, 160.4, 171.8 ppm; IR (KBr): $\tilde{\nu}$ = 2940, 2890, 2870, 1660, 1600, 1540, 1470, 1450, 1390, 1360, 1340, 1280, 1240, 1200, 1180, 1120, 1060, 980, 950, 880, 820 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{31}IO_4Si$: C 47.70, H 6.53; found: C 47.70, H 6.56.

Ethyl 7-chloro-4-hydroxy-5,8-dimethoxy-2-naphthoate: K_2CO_3 (33.9 g, 0.245 mol) was added to a solution of **31** (28.8 g, 81.7 mmol) in EtOH (350 mL) at RT. The reaction mixture was warmed to 60 °C and heated at this temperature with stirring for 1.5 h. After cooling to 0 °C, the reaction mixture was diluted with water and then the reaction was stopped by adding 6 M aq. HCl. The mixture was filtered through a Celite pad (washed with EtOAc) and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. After adding Et_2O and hexane to the residue, the precipitate was collected by filtration to afford the title compound as a white crystalline solid (22.2 g, 88 %). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7:3) to afford further ethyl 7-chloro-4-hydroxy-5,8-dimethoxy-2-naphthoate as a white crystalline solid (2.84 g, 11 %; total yield: 99 %). M.p. 130–131 °C (hexane and EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, J = 7.1 Hz, 3H), 3.97 (s, 3H), 4.06 (s, 3H), 4.43 (q, J = 7.1 Hz, 2H), 6.82 (s, 1H), 7.49 (d, J = 1.7 Hz, 1H), 8.29 (d, J = 1.7 Hz, 1H), 9.22 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 56.7, 61.3, 61.5, 107.6, 110.9, 115.5, 116.6, 123.2, 130.6, 130.8, 147.4, 152.3, 155.0, 166.3 ppm; IR (KBr): $\tilde{\nu}$ = 3560, 3100, 3030, 2990, 2950, 2900, 2850, 1720, 1600, 1520, 1460, 1390, 1340, 1310, 1270, 1230, 1210, 1160, 1120, 1090, 1030, 1020, 970, 940, 870, 840, 810, 770 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{15}O_5Cl$: C 57.98, H 4.87; found: C 58.0, H 5.03.

Ethyl 7-chloro-5,8-dimethoxy-4-methoxymethoxy-2-naphthoate: 7-Chloro-4-hydroxy-5,8-dimethoxy-2-naphthoate (25.7 g, 82.8 mmol) and MOMCl (9.43 mL, 0.124 mmol) were added to a suspension of NaH (55 % dispersion in mineral oil, washed with hexane (4.69 g, 0.108 mol)) in DMF (830 mL) at 0 °C. After stirring for 1 h, the reaction was stopped by adding water and the resulting mixture was extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. After adding Et_2O and hexane to the residue, the precipitate was collected by filtration to afford the title compound as a white powder (1st crop: 14.8 g, 51 %; 2nd crop: 8.94 g, 30 %; 3rd crop: 4.39 g, 15 %; 4th crop: 1.17 g, 4 %; total yield: quant). M.p. 119.7–120.0 °C (hexane and EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, J = 8.1 Hz, 3H), 3.60 (s, 3H), 3.95 (s, 3H), 3.98 (s, 3H), 4.44 (q, J = 8.1 Hz, 2H), 5.31 (s, 2H), 6.88 (s, 1H), 7.62 (d, J = 1.6 Hz, 1H), 8.49 ppm (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 56.6, 56.7, 61.3, 61.6, 96.4, 109.6, 112.0, 118.8, 120.1, 123.9, 129.3, 131.3, 146.3, 153.4, 154.5, 166.2 ppm; IR (KBr): $\tilde{\nu}$ = 3120, 3070, 2980, 2830, 1730, 1590, 1510, 1460, 1390, 1330, 1270, 1230, 1180, 1150, 1140, 1050, 1030, 930, 820, 770 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{19}O_6Cl$: C 57.55, H 5.40; found: C 57.35, H 5.55.

*7-Chloro-5,8-dimethoxy-4-methoxymethoxy-2-naphthoic acid (**52**)*: A 6 M aq. NaOH solution (330 mL) was added to a suspension of ethyl 7-chloro-5,8-dimethoxy-4-methoxymethoxy-2-naphthoate (35.0 g, 98.5 mmol) in THF (450 mL) and EtOH (180 mL) and the reaction mixture was heated at 70 °C for 1 h. After cooling to RT, the reaction mixture was diluted with water and then the aqueous layer was washed with Et_2O (×3). The aqueous phase was acidified with 6 M aq. HCl. The crystalline precipitates were collected by filtration and dried to afford **52** as a white powder (32.1 g, quant). M.p. 192–193 °C (Et_2O and EtOAc); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.32 (s, 3H), 3.87 (s, 3H), 3.99 (s, 3H), 5.29 (s, 2H), 7.08 (s, 1H), 7.53 (d, J = 1.5 Hz, 1H), 8.28 (d, J = 1.5 Hz, 1H), 13.3 ppm (br s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 56.0, 56.7, 61.3, 95.7, 109.3, 111.1, 117.3, 119.1, 123.4, 129.8, 130.5, 145.2, 153.4, 154.6, 166.8 ppm; IR (ATR): $\tilde{\nu}$ = 2960, 2930, 2910, 2840, 1640, 2540, 1700, 1590, 1510, 1460, 1440, 1370, 1330, 1280, 1230, 1160, 1130, 1090, 1030, 990, 970, 920, 910, 890, 800, 770, 710 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{15}O_6Cl$: C 55.14, H 4.63; found: C 54.91, H 4.86.

2-Iodo-6-methoxycarbonyl-5-methyl-3-[(triisopropylsiloxy)methyl]phenyl 7-chloro-5,8-dimethoxy-4-methoxymethoxy-2-naphthoate: Et_3N (8.45 mL, 60.6 mmol) and 2,4,6-trichlorobenzoyl chloride (9.47 mL, 60.6 mmol) were added to a solution of carboxylic acid **52** (18.0 g, 55.1 mmol) in toluene (540 mL) at RT. After stirring for 3 h at RT, iodophenol **53** (27.7 g, 57.9 mmol) and DMAP (10.2 g, 82.7 mmol) were added to the reaction mixture which was then stirred for 20 min. The reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. After adding Et_2O and hexane to the residue, the precipitate was collected by filtration to afford the title compound as a yellow solid (40.1 g, 95 %). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 9:1 to 7:3, gradient elution) to afford further 2-iodo-6-methoxycarbonyl-5-methyl-3-(triisopropylsiloxymethyl)phenyl 7-chloro-5,8-dimethoxy-4-methoxymethoxy-2-naphthoate as a yellow solid (1.67 g, 4 %; total yield: 99 %). M.p. 156–157 °C (hexane and Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08–1.28 (m, 21H), 2.47 (s, 3H), 3.62 (s, 3H), 3.70 (s, 3H), 3.97 (s, 3H), 4.00 (s, 3H), 4.75 (s, 2H), 5.34 (s, 2H), 6.93 (s, 1H), 7.46 (s, 1H), 7.75 (s, 1H), 8.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 18.1, 20.4, 52.3, 56.7, 56.8, 61.7, 69.7, 89.6, 96.4, 110.2, 112.0, 120.0, 120.5, 124.2, 125.6, 126.9, 127.7, 131.3, 138.5, 146.3, 146.8, 148.5, 153.4, 154.8, 163.4, 166.0 ppm; IR (KBr): $\tilde{\nu}$ = 2940, 2890, 2860, 1730, 1590, 1460, 1370, 1340, 1260, 1190, 1150, 1120, 1080, 1020, 980, 920, 880, 820, 800, 750 cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{44}ClO_9Si$: C 51.88, H 5.63; found: C 52.08, H 5.64.

*2-Iodo-6-methoxycarbonyl-5-methyl-3-[(triisopropylsiloxy)methyl]phenyl 7-chloro-4-hydroxy-5,8-dimethoxy-2-naphthoate (**54**)*: Trifluoroacetic acid (9.4 mL, 0.122 mol) was added to a solution of 2-iodo-6-methoxycarbonyl-5-methyl-3-[(triisopropylsiloxy)methyl]phenyl 7-chloro-5,8-dimethoxy-4-methoxymethoxy-2-naphthoate (32.0 g, 40.7 mmol) in CH_2Cl_2 (410 mL)

at 0 °C. After stirring for 3.5 h at RT, the reaction was stopped by adding saturated aqueous $NaHCO_3$ and water, and then the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. After adding Et_2O and hexane to the residue, the precipitate was collected by filtration to afford phenol **54** as a white crystalline (21.2 g; 70 %). The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 4:1) to afford crude material that included **54**. Addition of Et_2O and hexane allowed the formation of a precipitate that was collected by filtration to afford **54** as a white solid (1st crop; 4.39 g, 15 %; 2nd crop; 4.32 g, 14 %; total yield: 99 %). M.p. 139.5–140.0 °C (hexane and Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09–1.30 (m, 21H), 2.46 (s, 3H), 3.70 (s, 3H), 4.00 (s, 3H), 4.08 (s, 3H), 4.75 (s, 2H), 6.87 (s, 1H), 7.45 (s, 1H), 7.63 (s, 1H), 8.50 (s, 1H), 9.30 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 18.1, 20.4, 52.3, 56.8, 61.6, 69.7, 89.6, 108.1, 111.0, 116.7, 117.0, 123.5, 125.6, 126.9, 129.0, 130.8, 138.5, 146.8, 147.3, 148.6, 152.2, 155.2, 163.5, 166.0 ppm; IR (KBr): $\tilde{\nu}$ = 3394, 2943, 2866, 1736, 1603, 1514, 1448, 1387, 1340, 1265, 1205, 1151, 1119, 1078, 1026, 978, 951, 922, 883, 845, 820, 798, 756 cm^{-1}; elemental analysis calcd (%) for $C_{32}H_{40}ClO_8Si$: C 51.72, H 5.43; found: C 51.44, H 5.31.

*Biaryl lactone **55***: A suspension of ester **54** (1.50 g, 2.02 mmol), $Pd(OAc)_2$ (136 mg, 0.604 mmol), PPh_3 (317 mg, 1.21 mmol), and sodium pivalate (751 mg, 6.05 mmol) in DMA (100 mL) was heated at 110 °C for 20 min. After cooling the mixture to 0 °C, the reaction was stopped by adding water. The crystalline precipitates were collected by filtration and washed with Et_2O. The resulting powder was dissolved in CH_2Cl_2 and filtered through a Celite pad. The filtrate was concentrated in vacuo to afford **55** as yellow solid (747 mg, 60 %). M.p. 233.5–234.2 °C (CH_2Cl_2 and hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91–1.08 (m, 21H), 2.45 (s, 3H), 4.01 (s, 3H), 4.02 (s, 3H), 4.14 (s, 3H), 4.93 (s, 2H), 6.96 (s, 1H), 7.51 (s, 1H), 8.61 (s, 1H), 10.2 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.9, 17.9, 19.6, 52.6, 57.1, 61.9, 65.1, 109.1, 113.0, 114.8, 116.3, 116.8, 120.9, 123.6, 124.1, 125.6, 129.9, 136.5, 142.2, 146.8, 147.8, 151.4, 152.1, 160.5, 167.2 ppm; IR (KBr): $\tilde{\nu}$ = 3310, 2960, 2860, 1750, 1610, 1460, 1390, 1330, 1260, 1210, 1150, 1090, 1060, 1040, 950, 880, 830, 810 cm^{-1}; elemental analysis calcd (%) for $C_{32}H_{39}ClO_8Si$: C 62.48, H 6.39; found: C 62.21, H 6.26; HRMS (FAB): m/z: calcd for $C_{32}H_{40}O_8ClSi$ ([M+H]$^+$): 615.2181; found: 615.2199.

*Amide alcohol **57c***: (*R*)-Valinol (0.875 g, 8.48 mmol) was added to a solution of **55** (2.01 g, 3.27 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After stirring for 43 h at 0 °C, the reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 4:6) to afford a diastereomeric mixture of **57c** as a yellow solid (2.11 g, 90 %, *R*,*M*:*R*,*P* = 10:1). Recrystallization from hexane/EtOAc gave pure (*R*,*M*)-**57c** (1.85 g, 79 %) as a yellow powder. The filtrate was concentrated in vacuo and the residue was further purified by PTLC (hexane/EtOAc = 4:6) to afford (*R*,*M*)-**57c** (0.0622 g, 2.6 %, total yield: 82 %) as a yellow powder and (*R*,*P*)-**57c** (0.187 g, 8 %) as a yellow amorphous solid.

(*R*,*M*)-**57c**: M.p. 184–185 °C (hexane and EtOAc); $[\alpha]_D^{25}$ = +58.0 (c = 0.994 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.63 (d, J = 6.8 Hz, 3H), 0.67 (d, J = 6.8 Hz, 3H), 0.78–1.12 (m, 21H), 1.59 (dsept, J = 6.8, 6.8 Hz, 1H), 2.47 (t, J = 5.6 Hz, 1H; OH), 2.62 (s, 3H), 3.50–3.55 (m, 2H), 3.61–3.72 (m, 1H), 3.96 (s, 3H), 3.99 (s, 3H), 4.01 (s, 3H), 4.44 (d, J = 14.4 Hz, 1H), 4.58 (d, J = 14.4 Hz, 1H), 6.35 (d, J = 8.0 Hz, 1H; NH), 6.79 (s, 1H), 7.18 (s, 1H), 7.99 (s, 1H), 9.55 (s, 1H; OH), 11.76 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 18.0, 18.4, 18.9, 24.4, 28.9, 52.3, 56.7, 57.9, 61.5, 63.1, 64.1, 106.9, 111.1, 113.6, 114.5, 114.8, 119.7, 121.5, 123.2, 130.6, 138.0, 141.3, 146.9, 147.3, 151.5, 152.2, 159.4, 169.2, 172.2 ppm; IR (KBr): $\tilde{\nu}$ = 3360, 2940, 2890, 2870, 1660, 1620, 1600, 1520, 1460, 1400, 1360, 1290, 1270, 1200, 1180, 1130, 1110, 1040, 1000, 950, 880, 810 cm^{-1}; elemental analysis calcd (%) for $C_{37}H_{52}ClNO_9Si$: C 61.86, H 7.30, N 1.95; found: C 62.14, H 7.45, N 1.86; HRMS (FAB): m/z: calcd for $C_{37}H_{53}O_9NClSi$ ([M+H]$^+$): 718.3179; found: 718.3164.

(*R*,*P*)-**57c**: $[\alpha]_D^{27}$ = −26.8 (c = 1.09 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.92–1.08 (m, 21H), 1.54–1.62 (m, 1H), 1.92 (brs, 1H; OH), 2.64 (s, 3H), 3.12–3.29 (m, 2H), 3.68–3.73 (m, 1H), 3.97 (s, 3H), 3.99 (s, 3H), 4.01 (s, 3H), 4.42 (d, J = 15.2 Hz, 1H), 4.55 (d, J = 15.2 Hz, 1H), 6.35 (d, J = 8.8 Hz, 1H; NH), 6.80 (s, 1H), 7.23 (s, 1H), 7.95 (s, 1H), 9.56 (s, 1H; OH), 11.83 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 17.9, 18.2, 19.3, 24.4, 28.7, 52.3, 56.7, 57.6, 61.4, 62.8, 63.8, 106.8, 110.8, 113.0, 114.3, 114.7, 119.5, 121.4, 123.2, 130.6, 138.1, 141.3, 146.8, 147.7, 151.6, 152.2, 159.1, 169.1, 172.4 ppm; IR (neat): $\tilde{\nu}$ = 3380, 2960, 2940, 2870, 1660, 1610, 1600, 1520, 1450, 1410, 1360, 1290, 1260, 1200, 1130, 1100, 1040, 990, 950, 880, 810, 750 cm^{-1}; elemental analysis calcd (%) for $C_{37}H_{52}ClNO_9Si$: C 61.86, H 7.30, N 1.95; found: C 61.58, H 7.20, N 1.67; HRMS (FAB): m/z: calcd for $C_{37}H_{53}O_9NClSi$ ([M+H]$^+$): 718.3179; found: 718.3184.

*Benzyl ether (R,M)-**65***: BnBr (0.59 mL, 4.93 mmol) and Cs_2CO_3 (2.66 g, 8.15 mmol) were added to a solution of (*R*,*M*)-**57c** (1.48 g, 2.06 mmol) in DMF (15 mL) at 0 °C. After stirring for 1 h, the reaction was stopped by adding water and *N*,*N*-dimethylpropanediamine (0.5 mL), and the mixture was extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 65:35) to afford (*R*,*M*)-**65** as a yellow oil (1.79 g, 97 %). $[\alpha]_D^{27}$ = −80.7 (c = 0.976 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69 (d, J = 6.8 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H), 0.88–1.05 (m, 21H), 1.64–1.70 (m, 1H), 2.41 (s, 3H), 2.62 (brs, 1H; OH), 3.40–3.50 (m, 2H), 3.59–3.63 (m, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 4.00 (s, 3H), 4.59–4.77 (m, 6H), 6.23 (d, J = 6.8 Hz, 1H; NH), 6.85 (s, 1H), 6.96–7.00 (m, 4H), 7.10–7.11 (m, 3H), 7.25–7.26 (m, 3H), 7.32 (s, 1H), 8.47 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 17.87, 17.93, 18.8, 19.0, 19.6, 28.9, 52.3, 56.4, 58.5, 61.7, 63.7, 63.8, 75.8, 75.9, 109.0, 119.8, 120.9, 123.9, 124.0, 125.1, 126.2, 127.2, 127.3, 127.4, 127.5, 127.8, 128.0, 131.2, 136.6, 136.9, 137.1, 137.5, 143.0, 146.1, 152.5, 152.7, 153.6, 168.2, 168.3 ppm; IR (neat): $\tilde{\nu}$ = 3420, 2940, 2870, 1730, 1660, 1600, 1570, 1520, 1460, 1340, 1280, 1060, 1040, 740, 700 cm^{-1}; elemental analysis calcd (%) for $C_{51}H_{64}ClNO_9Si$: C 68.17, H 7.18, N 1.56; found: C 68.17, H 7.33, N 1.36; HRMS (FAB): m/z: calcd for $C_{51}H_{65}O_9NClSi$ ([M+H]$^+$): 898.4117; found: 898.4126.

*Oxazoline (R,M)-**66***: I_2 (1.17 g, 4.62 mmol) was added to a solution of (*R*,*M*)-**65** (2.06 g, 2.30 mmol), imidazole (390 mg, 5.73 mmol), and PPh_3 (1.53 g, 5.83 mmol) in CH_2Cl_2 (80 mL). After stirring for 20 min, the reaction was stopped by adding saturated aqueous $Na_2S_2O_3$ and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/Et_2O/$CHCl_3$ = 70:15:15) to afford oxazoline (*R*,*M*)-**66** as a yellow oil (2.02 g, quant). $[\alpha]_D^{28}$ = −58.6 (c = 1.06 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, J = 6.8 Hz, 3H), 0.76 (d, J = 6.8 Hz, 3H), 0.93–1.05 (m, 21H), 1.52–1.56 (m, 1H), 2.39 (s, 3H), 3.72 (s, 3H), 3.76 (s, 3H), 3.80–3.87 (m, 2H), 3.99 (s, 3H), 4.18–4.25 (m, 1H), 4.54 (d, 14.4 Hz, 1H), 4.58 (d, 14.4 Hz, 1H), 4.59 (d, J = 11.2 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H) 4.69 (d, J = 11.2 Hz, 1H), 4.73 (d, J = 10.0 Hz, 1H), 6.83–6.85 (m, 3H), 6.96–7.05 (m, 5H), 7.17–7.24 (m, 3H), 7.34 (s, 1H), 8.44 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 18.0, 18.6, 18.9, 19.8, 33.3, 51.9, 56.6, 61.3, 63.1, 70.2, 73.5, 75.6, 75.9, 109.1, 120.0, 121.4, 122.6, 123.5, 126.0, 126.3, 126.7, 127.0, 127.1, 127.2, 127.7, 127.9, 128.0, 128.5, 130.7, 135.5, 137.6, 137.7, 143.8, 145.9, 152.7, 153.3, 153.6, 161.8, 169.1 ppm; IR (neat): $\tilde{\nu}$ = 2940, 2870, 1730, 1660, 1600, 1570, 1450, 1400, 1370, 1340, 1280, 1230, 1140, 1100, 1060, 1040, 950, 880, 810, 750, 700 cm^{-1}; elemental analysis calcd (%) for $C_{51}H_{62}ClNO_8Si$: C 69.56, H 7.10, N 1.59; found: C 69.66, H 7.37, N 1.53; HRMS (FAB): m/z: calcd for $C_{51}H_{63}O_8NClSi$ ([M+H]$^+$): 880.4011; found: 880.4003.

*Aldehyde (M)-**67***: 2,6-Di-*tert*-butylpyridine (325 μL, 1.48 mmol) and MeOTf (160 μL, 1.46 mmol) were added to a solution of (*R*,*M*)-**66** (434 mg, 0.493 mmol) in CH_2Cl_2 (4.5 mL) at RT. The reaction mixture was stirred for 1 h at RT before L-Selectride (1.0 M in THF, 1.97 mL, 1.97 mmol) was added at 0 °C and the mixture was then stirred for an additional 20 min at 0 °C. The reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in

vacuo. Acidic silica gel (5 g, pH 6, Kanto Chemical) was added to the residue and organic solvents were removed by evaporation. After kept standing for 17 h, the SiO_2 was placed on a glass filter and washed with EtOAc, and then the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7:3) to afford aldehyde (*M*)-**67** as a yellow powder (379 mg, 96%). M.p. 144–145°C (hexane and EtOAc); $[\alpha]_D^{29} = -92.2$ ($c = 1.07$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.76$–1.01 (m, 21H), 2.46 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 4.03 (s, 3H), 4.40 (d, $J = 13.2$ Hz, 1H), 4.57 (d, $J = 10.8$ Hz, 1H), 4.62 (d, $J = 13.2$ Hz, 1H), 4.65 (d, $J = 10.8$ Hz, 1H), 4.72 (s, 2H), 6.81–6.85 (m, 2H), 6.95 (s, 1H), 7.01–7.12 (m, 6H), 7.26–7.30 (m, 2H), 7.38 (s, 1H), 8.57 (s, 1H), 9.82 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.9$, 17.9, 19.8, 52.2, 56.6, 61.9, 63.5, 75.8, 76.2, 110.5, 119.4, 123.0, 123.2, 124.1, 124.8, 127.1, 127.2, 127.4, 127.48, 127.51, 127.8, 127.9, 128.1, 130.9, 133.5, 136.7, 137.2, 137.3, 143.3, 147.0, 152.7, 153.7, 153.9, 168.5, 191.4 ppm; IR (KBr): $\tilde{\nu} = 2950$, 2940, 2860, 1730, 1700, 1600, 1570, 1460, 1400, 1360, 1340, 1280, 1210, 1100, 1060, 990, 970, 940, 910, 880, 810, 740, 700 cm^{-1}; elemental analysis calcd (%) for $C_{46}H_{53}ClO_8Si$: C 69.28, H 6.70; found: C 69.09, H 6.95; HRMS (FAB): m/*z*: calcd for $C_{46}H_{54}O_8ClSi$ ($[M+H]^+$): 797.3277; found: 797.3257.

*Acetal aldehyde (M)-**59***: Benzyloxytrimethylsilane (3.5 mL, 18 mmol) was added to a solution of (*M*)-**67** (2.13 g, 2.67 mmol) in toluene (21 mL) at RT. TMSOTf (5.7 mg, 0.026 mmol) was added to the reaction mixture at −78°C and stirred for 4 h at −15°C. The reaction was stopped by adding Et_3N (0.1 mL) and saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 95:5 to 80:20, gradient elution) to afford the acetal derivative of (*M*)-**67** as a white amorphous solid (2.66 g, quant). $[\alpha]_D^{29} = -64.2$ ($c = 1.22$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$–1.02 (m, 21H), 2.43 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 3.96 (s, 3H), 4.24 (d, $J = 11.6$ Hz, 1H), 4.30–4.42 (m, 4H), 4.57 (d, $J = 10.4$ Hz, 1H), 4.67–4.74 (m, 3H), 4.79 (d, $J = 10.4$ Hz, 1H), 5.52 (s, 1H), 6.75 (d, $J = 7.2$ Hz, 2H), 6.82 (s, 1H), 7.09 (m, 7H), 7.20–7.26 (m, 11H), 7.39 (s, 1H), 8.42 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.0$, 18.0, 20.0, 52.0, 56.6, 61.5, 62.8, 68.6, 68.7, 75.5, 75.6, 99.4, 108.4, 116.3, 120.4, 123.2, 123.7, 124.3, 126.4, 126.7, 127.1, 127.2, 127.26, 127.29, 127.4, 127.5, 127.78, 127.80, 127.85, 127.87, 128.1 (2C), 131.2, 136.3, 137.2, 137.3, 137.7, 137.8, 137.9, 144.2, 146.0, 152.7, 152.79, 152.80, 168.8 ppm; IR (neat): $\tilde{\nu} = 3430$, 2940, 1730, 1650, 1600, 1570, 1500, 1450, 1410, 1340, 1280, 1220, 1190, 1120, 1060, 1000, 910, 880, 810, 740, 700 cm^{-1}; elemental analysis calcd (%) for $C_{60}H_{67}ClO_9Si$: C 72.37, H 6.78; found: C 72.20, H 6.83.

nBu_4NF (1.0 M in THF, 1.28 mL, 1.28 mmol) was added to a solution of the acetal (1.07 g, 1.01 mmol) in THF (10 mL) at 0°C. After stirring for 1 h at 0°C, the reaction was stopped by adding water and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7:3) to afford the acetal alcohol derivative of (*M*)-**67** as a white amorphous solid (0.898 g, quant). $[\alpha]_D^{30} = -111$ ($c = 0.924$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.42$ (s, 3H), 2.45 (t, $J = 6.6$, OH), 3.77 (s, 3H), 3.82 (s, 3H), 3.97 (s, 3H), 4.15 (d, $J = 11.2$ Hz, 1H), 4.15–4.26 (m, 2H), 4.34 (d, $J = 11.2$ Hz, 1H), 4.11 (s, 2H), 4.50 (d, $J = 10.0$ Hz, 1H), 4.63 (d, $J = 10.0$ Hz, 1H), 4.72 (d, $J = 10.0$ Hz, 1H), 4.76 (d, $J = 10.0$ Hz, 1H), 5.59 (s, 1H), 6.77 (d, $J = 7.6$ Hz, 2H), 6.85 (s, 1H), 6.97–7.29 (m, 19H), 8.44 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.6$, 52.2, 56.4, 61.5, 63.5, 68.3, 69.4, 75.7, 75.8, 99.4, 108.3, 116.5, 120.1, 123.6, 125.9, 126.8, 126.9, 127.48, 127.50, 127.57, 127.59 (2C), 127.63, 127.7, 127.8, 128.0, 128.1, 128.16, 128.20, 128.3, 131.2, 136.7, 136.8 (2C), 137.2, 137.4, 137.6, 143.5, 145.9, 152.57, 152.59, 152.7, 168.5 ppm; IR (neat): $\tilde{\nu} = 3500$, 3090, 3060, 3030, 3010, 2950, 2930, 2870, 1730, 1600, 1590, 1570, 1500, 1450, 1440, 1400, 1370, 1340, 1280, 1220, 1200, 1140, 1100, 1050, 1030, 910, 810, 750, 740, 700 cm^{-1}; elemental analysis calcd (%) for $C_{51}H_{47}ClO_9$: C 72.98, H 5.64; found: C 72.92, H 5.85.

MnO_2 (8.67 g, 99.6 mmol) was added to a solution of the acetal alcohol derivative of (*M*)-**67** (4.18 g, 4.98 mmol) in CH_2Cl_2 (100 mL). After stirring for 15 h at RT, the reaction mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo to afford analytically pure (*M*)-**59** (4.11 g, 99%) as a white amorphous solid. $[\alpha]_D^{30} = -59.1$ ($c = 1.07$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.38$ (s, 3H), 3.71 (s, 3H), 3.85 (s, 3H), 3.98 (s, 3H) 4.27 (d, $J = 11.6$ Hz, 1H), 4.35 (d, 11.6 Hz, 1H), 4.41 (s, 2H), 4.54 (d, $J = 10.4$ Hz, 1H), 4.60 (d, $J = 10.4$ Hz, 1H), 4.68 (d, $J = 10.4$ Hz, 1H), 4.76 (d, $J = 10.4$ Hz, 1H), 5.49 (s, 1H), 6.76 (d, $J = 7.6$ Hz, 2H), 6.83 (s, 1H), 6.91–6.95 (m, 2H), 6.95–6.99 (m, 2H), 7.04 (t, $J = 7.6$ Hz, 2H), 7.09–7.13 (m, 1H), 7.16–7.32 (m, 11H), 7.48 (s, 1H), 8.45 (s, 1H), 9.66 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.4$, 52.4, 56.3, 61.5, 68.1, 69.1, 75.6, 76.2, 99.0, 108.3, 116.5, 119.9, 124.0, 124.1, 124.5, 126.9, 127.3, 127.4, 127.5, 127.69, 127.72, 127.9, 127.96, 128.05, 128.1, 128.2, 130.6, 131.5, 133.6, 133.8, 136.0, 136.4, 136.6, 136.7, 137.3, 137.35, 137.42, 145.9, 152.6, 153.40, 153.45, 167.7, 191.0 ppm; IR (KBr): $\tilde{\nu} = 3030$, 3000, 2950, 2930, 2870, 2840, 1730, 1700, 1590, 1570, 1500, 1450, 1340, 1280, 1220, 1100, 1040, 910, 850, 810, 740, 700 cm^{-1}; elemental analysis calcd (%) for $C_{51}H_{45}ClO_9$: C 73.15, H 5.42; found: C 73.44, H 5.62; HRMS (FAB): m/*z*: calcd for $C_{51}H_{46}O_9Cl$ ($[M+H]^+$): m/*z*: 837.2831; found: 837.2803.

The enantiomeric purity of (*M*)-**59** was assessed by HPLC analysis (DAICEL CHIRALPAK AD-H (0.46 cm $\varphi \times 25$ cm), hexane/*i*PrOH = 9:1, flow rate = 1.0 mL min^{-1}, $t_R = 5.4$ min for the *M* isomer, 8.0 min for the *P* isomer).

*Tetracycle (S,S)-**60***: $BF_3{\cdot}OEt_2$ (21.5 μL, 0.174 mmol) and a solution of MeOH (0.57 M in THF, 100 μL, 0.057 mmol) were added to a solution of (*M*)-**59** (48.4 mg, 0.0578 mmol) in THF (3.0 mL) at −78°C. Samarium diiodide (0.1 M in THF, 1.5 mL, 0.15 mmol) was added to the mixture at −78°C and the reaction temperature was immediately raised to 0°C. After stirring for 30 min at 0°C, the reaction was stopped by adding 5% aqueous K_2CO_3 and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 7:3 and benzene/EtOAc = 8:2) to afford tetracycle (*S,S*)-**60** as a white amorphous solid (40.2 mg, 95%).

Experimental procedure for the preparative-scale synthesis of (*S,S*)-**60**: $BF_3{\cdot}OEt_2$ (88 μL, 0.72 mmol) and MeOH (19 μL, 0.0567 mmol) was added to a solution of (*M*)-**59** (200 mg, 0.239 mmol) in THF (12 mL) at −78°C. Samarium diiodide (0.1 M in THF, 1.5 mL, 0.15 mmol) was added to the reaction mixture at −78°C and the reaction temperature was immediately raised to −30°C. The reaction temperature was then gradually raised from −30°C to −15°C over 30 min. The reaction was stopped by adding 5% aqueous K_2CO_3 and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (benzene/EtOAc = 9:1) to afford tetracycle (*S,S*)-**60** as a white amorphous solid (155 mg, 89%). Compound (*S,S*)-**60** was formed as a mixture of two conformers: diaxial/diequatorial = 1:3.5). $[\alpha]_D^{29} = -30.8$ ($c = 0.866$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, the minor conformer is indicated by an asterisk): $\delta = 0.42$* (d, $J = 6.5$ Hz, OH), 2.36* (s, 3H), 2.38 (s, 3H), 2.88 (d, $J = 1.8$ Hz, 1H; OH), 3.84* (s, 3H) 3.90 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 3.98 (dd, $J = 1.8$, 10.6 Hz, 1H), 4.00* (s, 3H), 4.01* (s, 3H), 4.05 (d, $J = 10.6$ Hz, 1H), 4.36 (d, $J = 11.4$ Hz, 1H), 4.41* (d, $J = 12.4$ Hz, 1H), 4.476* (d, $J = 12.1$ Hz, 1H), 4.480* (s, 2H), 4.52* (d, $J = 3.3$ Hz, 1H), 4.55* (dd, $J = 3.3$, 6.5 Hz, 1H), 4.59 (d, $J = 12.1$ Hz, 1H), 4.68 (d, $J = 11.2$ Hz, 1H), 4.81 (d, $J = 11.2$ Hz, 1H), 4.89 (d, $J = 11.4$ Hz, 1H), 5.00 (d, $J = 11.2$ Hz, 1H), 5.11* (d, $J = 12.1$ Hz, 1H), 6.75–6.79* (m, 2H), 6.81–6.85 (m, 3H), 6.87* (s, 1H), 6.89* (s, 1H), 6.93* (t, $J = 7.6$ Hz, 2H), 6.96–7.16 (m, 8H), 6.96–7.16* (m, 9H), 7.20–7.27* (m, 2H), 7.24 (s, 1H), 7.36–7.41 (m, 1H), 7.43–7.47 (m, 2H), 7.54–7.58 (m, 2H), 7.72* (s, 1H), 7.92 ppm (s, $J = 1.4$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, the minor conformer is indicated by an asterisk): $\delta = 19.2$*, 19.5, 52.1*, 52.2, 56.4, 56.5*, 61.2, 61.4*, 69.9*, 70.8*, 72.3, 74.9, 76.4, 76.7*, 77.1*, 77.2, 78.0*, 82.4, 107.3, 108.1*, 111.6, 119.5, 120.0, 120.2*, 120.5*, 120.9, 122.5*, 122.6, 122.8*, 123.5, 123.8*, 126.5*, 127.4, 127.48, 127.515, 127.517*, 127.598*, 127.60, 127.7, 127.9, 128.2, 128.36, 128.38, 128.6*, 128.81, 128.83, 129.2, 130.5*, 131.0*, 131.4, 132.5*, 136.09, 136.10*, 136.5, 136.8, 137.0*, 137.4*, 137.6, 137.9*, 138.8*, 139.8, 145.5, 145.6*, 152.2, 153.0, 153.1*, 153.2*, 153.4, 154.9, 168.6*, 169.0 ppm; IR (neat): $\tilde{\nu} = 3480$, 2950, 2870, 1730, 1590, 1570, 1450, 1340, 1280, 1220, 1130, 1100, 1050, 810, 750, 700 cm^{-1};

elemental analysis calcd (%) for $C_{44}H_{39}ClO_8$: C 72.27, H 5.38; found: C 72.27, H 5.50; HRMS (FAB): m/z: calcd for $C_{44}H_{40}O_8Cl$ ($[M+H]^+$): 731.2411; found: 731.2377.

The enantiomeric purity of (*S*,*S*)-**60** was analyzed by HPLC analysis (DAICEL CHIRALPAK AD-H (0.46 cm $\varphi \times 25$ cm), hexane/EtOH = 8:2, flow rate = 1.0 mL min^{-1}, t_R = 6.6 min for the *S*,*S* isomer, 9.3 min for the *R*,*R* isomer; Figure 1).

Amide ***68***: A 5 M aq. KOH solution (10 mL) was added to a solution of (*S*,*S*)-**60** (199 mg, 0.272 mmol) in EtOH (18 mL). The mixture was sealed in a thick-walled glass tube and heated at 100 °C. After stirring for 3 h at 100 °C, the mixture was diluted with Et_2O and the phases were separated. The organic layer was extracted with water (×2). The combined water layers were acidified with 2 M aq. HCl and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in DMF (6 mL), and BOP (172 mg, 0.388 mmol), D-Ala-OMe·HCl (185 mg, 1.33 mmol), and Et_3N (250 μL, 1.79 mmol) were added to the resulting solution. After stirring for 1 h at RT, the reaction was stopped by adding 2 M aq. HCl and then the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 1:1) to afford amide **68** as a white solid (184 mg, 84 %). Mixture of two conformers: diaxial/diequatorial = 1:4.5; m.p. 163.6–164.3 °C (hexane and Et_2O); $[\alpha]_D^{29} = -25.3$ ($c = 0.872$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, the minor conformer is indicated by an asterisk): δ = 0.99* (d, J = 6.2 Hz, 1H; OH), 1.23* (d, J = 7.2 Hz, 3H), 1.39 (d, J = 7.2 Hz, 3H), 2.42* (s, 3H), 2.44 (s, 3H), 2.94 (d, J = 2.3 Hz, 1H; OH), 3.67 (s, 3H), 3.73* (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 3.96* (s, 3H), 3.97 (dd, J = 1.4, 11.4 Hz, 1H; 6-H), 4.00* (s, 3H), 4.24 (d, J = 11.4 Hz, 1H), 4.25 (d, J = 11.4 Hz, 1H; C-5), 4.37* (d, J = 11.6 Hz, 1H), 4.43* (d, J = 12.3 Hz, 1H), 4.45* (d, J = 11.0 Hz, 1H), 4.51* (d, J = 12.3 Hz, 1H), 4.54* (d, J = 11.0 Hz, 1H), 4.578 (d, J = 11.5 Hz, 1H), 4.585* (d, J = 4.3 Hz, 1H; 6-H), 4.66* (dq, J = 7.3, 7.3 Hz, 1H), 4.67 (dq, J = 7.1, 7.1 Hz, 1H), 4.70* (d, J = 4.3 Hz, 1H; 5-H),4.76 (d, J = 11.5 Hz, 1H), 4.82 (d, J = 11.2 Hz, 1H), 4.91 (d, J = 11.4 Hz, 1H), 5.01 (d, J = 11.2 Hz, 1H), 6.06* (d, J = 7.2 Hz, 1H; NH), 6.35 (d, J = 7.2 Hz, NH), 6.82 (s, 1H), 6.87* (s, 1H), 6.92–6.99 (m, 5H), 7.02–7.19 (m, 6H), 7.23–7.30 (m, 1H), 7.37–7.41* (m, 2H), 7.44–7.48 (m, 2H), 7,57–7.59 (m, 2H), 7.93 ppm (d, J = 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, the minor conformer is indicated by an asterisk): δ = 17.8*, 18.1, 19.2*, 19.8, 48.2*, 48.4, 52.25, 52.31*, 56.5, 61.2, 61.4*, 69.9*, 71.1*, 72.4, 74.9, 76.1*, 76.6, 76.8* (overlapped by a signal of $CDCl_3$), 77.2, 78.0*, 82.4, 107.3, 108.1*, 111.7, 119.5, 120.2*, 120.6*, 120.7, 121.0, 122.1*, 122.6, 122.9*, 123.5, 123.8*, 126.9*, 127.39*, 127.43, 127.47, 127.50*, 127.6, 127.7*, 127.8*, 127.88, 127.89*, 128.1*, 128.18, 128.22, 128.37, 128.40*, 128.7, 128.8, 136.3, 136.8, 137.3, 137.5*, 137.6, 137.7*, 137.9*, 138.1, 138.9*, 139.6, 145.47, 145.54*, 152.5, 152.9, 153.2*, 153.3, 153.5*, 154.7*, 167.2*, 167.4, 173.1, 173.2* ppm; IR (neat): $\tilde{\nu}$ = 3420, 3060, 3030, 3000, 2940, 2870, 2840, 2360, 1740, 1660, 1650, 1590, 1570, 1500, 1450, 1340, 1210, 1150, 1130, 1110, 1050, 750, 700 cm^{-1}; elemental analysis calcd (%) for $C_{47}H_{44}ClNO_9$: C 70.36, H 5.53, N 1.75; found: C 70.11, H 5.44, N 1.70; HRMS (FAB): m/z: calcd for $C_{47}H_{45}O_9NCl$ ($[M+H]^+$): 802.2782; found: 802.2809.

Glycoside ***69***: MS4A (320 mg) was placed in a two-necked round-bottomed flask and flame dried. The promoter was prepared in situ by stirring a mixture of Cp_2HfCl_2 (62.8 mg, 0.165 mmol) and AgOTf (84.2 mg, 0.328 mmol) in CH_2Cl_2 (0.8 mL) for 10 min at RT. A solution of **68** (122 mg, 0.152 mmol) and **51** (100 mg, 0.181 mmol) in CH_2Cl_2 (2.8 mL) were added to this suspension at −78 °C. After stirring for 11 h at −36 °C, the reaction was stopped by adding saturated aqueous $NaHCO_3$. The mixture was filtered through a Celite pad and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/Et_2O/CH_3CN = 3:4.5:1.5) to afford β-glycoside **69** as a white amorphous solid (145 mg, 72 %) and α-glycoside **69** also as a white amorphous solid (18.4 mg, 9 %).

β-**69** (a mixture of two conformers: diaxial/diequatorial = 50:50): M.p. 114–116 °C; $[\alpha]_D^{22} = +20.0$ ($c = 0.880$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, without distinction of the two conformers): δ = 1.07 (d, J = 7.2 Hz, 3H), 1.35 (d, J = 7.3 Hz, 3H), 1.362 (d, J = 6.6 Hz, 3H), 1.37 (s, 3H), 1.38 (d, J = 6.6 Hz, 3H), 1.57 (s, 3H), 1.89 (s, 3H), 1.96 (s, 3H), 1.99 (s, 3H), 2.02 (s, 3H), 2.34 (s, 3H), 2.45 (s, 3H), 3.24 (dd, J = 9.1, 11.7 Hz, 1H), 3.35 (dd, J = 9.2, 11.6, 1H), 3.62 (dq, J = 1.3, 6.6 Hz, 1H), 3.65 (s, 3H), 3.70–3.74 (m, 1H), 3.72 (s, 3H), 3.79 (s, 3H), 3.80 (dd, J = 1.3, 3.7 Hz, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 3.88 (dd, J = 1.1, 3.8 Hz, 1H), 3.89 (s, 3H), 3.92 (dd, J = 3.7, 9.9 Hz, 1H), 3.99 (d, J = 11.3 Hz, 1H), 4.04 (dd, J = 1.4, 10.8 Hz, 1H), 4.071 (dd, J = 5.0, 11.7 Hz, 1H), 4.072 (dd, J = 3.8, 10.1 Hz, 1H), 4.16 (dd, J = 5.1, 11.6 Hz, 1H), 4.25 (d, J = 11.3 Hz, 1H), 4.38 (s, 2H), 4.39 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 12.3 Hz, 1H), 4.451 (d, J = 7.1 Hz, 1H), 4.46–4.50 (m, 3H), 4.53 (d, J = 8.0 Hz, 1H), 4.55 (d, J = 10.8 Hz, 1H), 4.58 (dq, J = 7.2, 7.3 Hz, 1H), 4.63 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 3.2 Hz, 1H), 4,655 (qd, J = 7.2, 7.9 Hz, 1H), 4.660 (d, J = 7.3 Hz, 1H), 4.71 (d, J = 12.3 Hz, 1H), 4.73 (dd, J = 7.3, 8.9 Hz, 1H), 4.85 (ddd, J = 5.1, 8.9, 9.1 Hz, 1H), 4.87–4.92 (m, 3H), 4.93 (ddd, J = 5.0, 8.9, 9.2 Hz, 1H), 5.02 (d, J = 3.2 Hz, 1H), 5.03 (dd, J = 8.9, 8.9 Hz, 1H), 5.15 (dd, J = 8.0, 10.1 Hz, 1H), 5.16 (d, J = 7.9 Hz, 1H), 5.54 (d, J = 7.9 Hz, 1H; NH), 5.69 (dd, J = 7.9, 9.9 Hz, 1H), 6.23 (d, J = 7.2 Hz, 1H; NH), 6.65 (s, 1H), 6.76 (s, 1H), 6.80–6.89 (m, 3H), 6.92–6.99 (m, 4H), 7.03–7.16 (m, 5H), 7.17–7.37 (m, 23H), 7.39–7.44 (m, 4H), 7.46 (s, 1H), 7.48–7.54 (m, 1H), 7.81 (d, J = 1.4 Hz, 1H), 7.95–7.99 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, without distinction of the two conformers): δ = 17.29, 17.30, 17.4, 18.1, 19.0, 19.6, 19.8, 19.9, 20.5, 20.60, 20.65, 20.69, 47.9, 48.4, 52.2, 56.47, 56.52, 61.1 (2C), 62.3, 62.4, 65.5, 65.8, 68.9, 69.0, 69.2, 69.4, 69.9, 70.6, 70.8, 70.9, 71.3, 71.5, 71.6, 74.0, 74.3, 74.4, 75.9, 76.50, 76.53, 77.1, 77.2 (overlapped by a signal of $CDCl_3$), 77.4, 79.8, 80.4, 81.5, 97.8, 100.8, 102.1, 102.4, 107.3, 107.9, 112.3, 118.9, 119.6, 120.9, 122.5, 122.8, 123.1, 123.23, 123.25, 127.1, 127.2, 127.3, 127.47, 127.52, 127.54, 127.59, 127.63, 127.67, 127.73, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 128.7, 129.7 (2C), 130.3, 131.2, 132.7, 133.0, 133.3, 136.5, 136.6, 136.9, 137.2, 137.3, 137.5, 137.89, 138.0, 138.2, 138.8, 145.1, 145.5, 152.3, 152.7, 153.3, 153.4, 154.3, 154.4, 163.8, 164.7, 167.4, 168.9, 169.1, 169.70, 169.73, 170.05, 170.14, 172.9, 173.1 ppm; IR (KBr): $\tilde{\nu}$ = 2100, 1760, 1750, 1660, 1590, 1510, 1450, 1370, 1340, 1270, 1220, 1060, 750, 710, 700 cm^{-1}; elemental analysis calcd (%) for $C_{71}H_{71}ClN_4O_{20}$: C 63.84, H 5.36, N 4.19; found: C 63.56, H 5.32, N 3.91.

α-**69** (mixture of two conformers: diaxial/diequatorial = 75:25): M.p. 95–97 °C; $[\alpha]_D^{28} = +111$ ($c = 0.960$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, the minor conformer is indicated by an asterisk): δ = 0.84* (d, J = 6.4 Hz, 3H), 1.05 (d, J = 7.2 Hz, 3H), 1.23 (s, 3H), 1.36* (d, J = 7.2 Hz, 3H), 1.38 (d, J = 6.4 Hz, 3H), 1.48* (s, 3H), 1.62* (s, 3H), 1.89 (s, 3H), 1.98* (s, 3H), 2.01 (s, 3H), 2.07* (s, 3H), 2.29 (s, 3H), 3.24 (dd, J = 9.2, 11.8 Hz, 1H), 3.52* (dd, J = 9.0, 11.8 Hz, 1H), 3.57–3.59 (m, 1H), 3.60 (d, J = 11.3 Hz, 1H), 3.63* (s, 3H), 3.67 (s, 3H), 3.69 (s, 3H), 3.85 (d, J = 11.3 Hz, 1H), 3.87 (dd, J = 1.3, 3.6 Hz, 1H), 3.91–3.96 (m, 1H), 3.96* (s, 3H), 3.99* (s, 3H), 4.05 (dd, J = 5.2, 11.8 Hz, 1H), 4.06 (s, 3H), 4.09 (dd, J = 3.6, 10.2 Hz, 1H), 4.21* (dd, J = 1.3, 11.0 Hz, 1H), 4.21* (d, J = 11.0 Hz, 1H), 4.257 (dd, J = 5.0, 11.8 Hz, 1H), 4.258* (d, J = 11.5 Hz, 1H), 4.35 (d, J = 11.1 Hz, 1H), 4.43* (d, J = 11.4 Hz, 1H), 4.45 (d, J = 12.4 Hz, 1H), 4.45–4.49* (m, 1H), 4.46 (d, J = 11.1 Hz, 1H), 4.48 (d, J = 7.3 Hz, 1H), 4.52 (d, J = 12.4 Hz, 1H), 4.55–4.60* (m, 1H), 4.58 (qd, J = 7.2, 7.9 Hz, 1H), 4.59* (dq, J = 7.0, 7.9 Hz, 1H), 4.71* (d, J = 11.4 Hz, 1H), 4.73 (dd, J = 7.3, 9.1 Hz, 1H), 4.75 (d, J = 3.3 Hz, 1H), 4.76 (d, J = 3.3 Hz, 1H), 4.84* (d, J = 10.6 Hz, 1H), 4.85 (ddd, J = 5.2, 9.2, 9.2 Hz, 1H), 4.88* (d, J = 11.5 Hz, 1H), 4.89–4.94* (m, 2H), 4.90–4.95 (m, 1H), 4.99* (ddd, J = 5.0, 8.6, 9.0 Hz, 1H), 5.03* (d, J = 10.6 Hz, 1H), 5.07 (d, J = 4.0 Hz, 1H), 5.14* (dd, J = 8.6, 9.0 Hz, 1H), 5.18* (d, J = 3.6 Hz, 1H), 5.19 (dd, J = 4.0, 10.1 Hz, 1H), 5.53 (d, J = 7.9 Hz, 1H; NH), 5.56* (dd, J = 3.6, 10.5 Hz, 1H), 6.34* (d, J = 7.0 Hz, 1H; NH), 6.64* (s, 1H), 6.68 (s, 1H), 6.82–6.86 (m, 1H), 6.89–7.05 (m, 4H), 7.07–7.13 (m, 4H), 7.15–7.36 (m, 10H), 7.39–7.66 (m, 2H), 7.81 (s, 1H), 8.01* (d, J = 1.3 Hz, 1H), 8.19–8.23 ppm* (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, without distinction of the two conformers): δ = 16.5, 17.3, 17.4, 18.1, 18.7, 19.0, 19.5, 19.8, 20.55, 20.64, 20.68, 20.75, 47.9, 48.5, 52.2, 52.3, 56.2, 56.5, 61.2, 61.5, 62.3, 62.4, 64.75, 64.85, 66.1, 66.6, 68.95, 69.02, 69.1, 70.0, 70.1, 71.0, 71.1, 71.5, 71.6, 74.6, 75.0, 75.8, 75.9, 76.2, 76.5, 77.21, 77.16 (overlapped by a signal of $CDCl_3$), 77.5, 77.68, 80.0, 93.4, 96.1, 100.9, 101.0, 102.1, 102.3, 107.3, 107.9, 112.1, 119.3, 119.5, 119.8, 120.8, 122.0, 122.3, 122.7, 122.9, 123.6, 126.8, 127.1, 127.2, 127.4, 127.6, 127.68, 127.73, 127.76, 127.80, 127.82,

128.0, 128.1, 128.3, 128.5, 128.6, 128.7, 128.9, 128.99, 129.01, 129.2, 129.3, 130.1, 130.3, 130.5, 131.4, 132.9, 133.0, 133.9, 133.98, 134.0, 136.8, 137.0, 137.1, 137.77, 137.82, 137.84, 137.9, 138.7, 145.3, 145.5, 152.3, 153.0, 153.4, 153.8, 154.6, 164.7, 165.7, 167.2, 167.3, 168.9, 169.0, 169.75, 169.83, 170.0, 170.1, 172.8, 173.0 ppm; IR (KBr): $\tilde{\nu}$ = 3060, 3030, 2940, 2110, 1760, 1660, 1590, 1500, 1450, 1370, 1340, 1270, 1250, 1220, 1160, 1110, 1070, 1050, 950, 900, 880, 820, 750, 740, 710, 700 cm^{-1}; elemental analysis calcd (%) for $C_{71}H_{71}ClN_4O_{20}$: C 63.84, H 5.36, N 4.19; found: C 63.59, H 5.49, N 3.94.

Quinone **70**: A solution of CAN (158 mg, 0.288 mmol) in water (0.32 mL) was added to a solution of glycoside **69** (165 mg, 0.123 mmol) in CH_3CN (0.9 mL) at RT. After stirring for 20 min, water (15 mL) was added to the reaction and a precipitate was formed which was collected by filtration as a red powder (154 mg). The powder was directly added to a solution of diene **21** (250 mg, 0.123 mmol) in THF (2.5 mL) at RT. Mixture allowed to stand for 20 min, acidic silica gel (pH 6, Kanto chemical) was added, and the organic solvent was removed in vacuo. After standing for 8 h, the silica gel was placed on a glass filter and washed with EtOAc. Then the filtrate was concentrated in vacuo. K_2CO_3 (176 mg) was added to the solution of this crude material (227 mg) in THF/CH_2Cl_2 (1:3, 8 mL) at RT. The mixture was heated at 40 °C for 3 h, and the reaction was stopped by adding 2 M aq. HCl and then the mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/Et_2O/CH_3CN = 2:3:1) and HPLC (Cica-reagent, Myghtysil Si60, 250–20 (5 μm), hexane/EtOAc = 1:2, 3.5 mL min^{-1}) to afford quinone **70** as a yellow solid (124 mg, 74 %). Mixture of two conformers: diaxial/diequatorial = 78:22; m.p. 126.0–126.8 °C (hexane and EtOAc); $[\alpha]_D^{20}$ = +111 (*c* = 1.17 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, the minor conformer is indicated by an asterisk): δ = 1.08 (d, *J* = 7.2 Hz, 3H), 1.26 (s, 3H), 1.35* (d, *J* = 6.3 Hz, 3H), 1.37* (d, *J* = 7.2 Hz, 3H), 1.45 (d, *J* = 6.3 Hz, 3H), 1.87 (s, 3H), 1.96* (s, 3H), 1.98 (s, 3H), 2.02* (s, 3H), 2.04* (s, 3H), 2.36 (s, 3H), 2.48* (s, 3H), 3.26 (dd, *J* = 8.9, 11.8 Hz, 1H), 3.36* (dd, *J* = 9.3, 11.6 Hz, 1H), 3.63* (s, 3H), 3.69–3.73 (m, 1H), 3.70–3.74* (m, 1H), 3.75 (s, 3H), 3.85 (dd, *J* = 1.4, 3.9 Hz, 1H), 3.89* (br d, *J* = 4.1 Hz, 1H), 3.91* (dd, *J* = 1.1, 11.0 Hz, 1H), 3.946* (s, 3H), 3.947 (dd, *J* = 3.9, 9.9 Hz, 1H), 4.00 (s, 3H), 4.06* (dd, *J* = 4.1, 9.9 Hz, 1H), 4.08 (dd, *J* = 5.2, 11.8 Hz, 1H), 4.12 (d, *J* = 11.0 Hz, 1H), 4.17* (dd, *J* = 5.2, 11.6 Hz, 1H), 4.30* (d, *J* = 11.2 Hz, 1H), 4.32 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 12.1 Hz, 1H), 4.42* (d, *J* = 11.6 Hz, 1H), 4.441 (d, *J* = 12.1 Hz, 1H), 4.442 (d, *J* = 11.5 Hz, 1H), 4.47* (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 7.3 Hz, 1H), 4.51 (d, *J* = 7.8 Hz, 1H), 4.52* (d, *J* = 11.0 Hz, 1H), 4.55 (qd, *J* = 7.2, 7.9 Hz, 1H), 4.57 (d, *J* = 3.0 Hz, 1H), 4.64* (qd, *J* = 7.2, 7.2 Hz, 1H), 4.65* (d, *J* = 7.3 Hz, 1H), 4.69* (d, *J* = 11.4 Hz, 1H), 4.71 (dd, *J* = 7.3, 8.7 Hz, 1H), 4.77* (d, *J* = 11.6 Hz, 1H), 4.85 (ddd, *J* = 5.2, 8.9, 9.8 Hz, 1H), 4.90 (dd, *J* = 8.7, 8.9 Hz, 1H), 4.91* (dd, *J* = 7.3, 9.0 Hz, 1H), 4.91–4.95* (m, 1H), 4.96 (d, *J* = 3.0 Hz, 1H), 5.03* (dd, 1H; *J* = 9.0, 9.0 Hz, 1H), 5.12* (d, *J* = 8.0 Hz, 1H), 5.14 (d, *J* = 11.0 Hz, 1H), 5.15 (dd, *J* = 7.8, 9.9 Hz, 1H), 5.18* (d, *J* = 11.2 Hz, 1H), 5.37 (d, *J* = 7.9 Hz, 1H; NH), 5.69* (dd, *J* = 8.0, 9.9 Hz, 1H), 6.24* (d, *J* = 7.2 Hz, 1H; NH), 6.69–6.80 (m, 3H), 6.95–7.14 (m, 11H), 7.19–7.40 (m, 7H), 7.51–7.59 (m, 2H), 7.60 (s, 1H), 7.95* (s, 1H), 7.97* (s, 1H), 8.08* (d, *J* = 1.1 Hz, 1H), 12.7 (s, 1H; OH), 12.9 ppm* (s, 1H; OH); ^{13}C NMR (125 MHz, $CDCl_3$, without distinction of the two conformers): δ = 17.25, 17.3, 17.35, 18.0, 19.0, 19.5, 19.9, 20.1, 20.5, 20.60, 20.64, 20.7, 47.8, 48.4, 52.2, 52.3, 56.0, 56.1, 62.4, 62.5, 65.4, 65.7, 68.9, 69.0, 69.4, 69.5, 70.6, 70.8, 70.9, 71.1, 71.2, 71.5, 71.6, 73.2, 74.1, 74.6, 76.7, 76.8 (overlapped by a signal of $CDCl_3$), 77.1, 77.3 (2C, overlapped by a signal of $CDCl_3$), 79.8, 80.3, 80.5, 98.1, 100.6, 102.2, 102.4, 105.8, 106.0, 107.0, 107.3, 110.4, 110.8, 118.2, 120.3, 121.5, 123.1, 123.2, 125.1, 126.1, 127.3, 127.55, 127.58, 127.64, 127.66, 127.8, 127.9, 128.1, 128.26, 128.31, 128.4, 128.49, 128.50, 128.6, 128.67, 128.68, 128.8, 129.0, 129.6, 129.7, 130.2, 132.4, 132.9, 133.1, 133.3, 133.4, 134.4, 135.3, 136.1, 136.3, 136.5, 136.6, 136.7, 137.27, 137.31, 137.4, 137.8, 138.2, 139.1, 139.9, 140.1, 144.1, 152.9, 154.8, 156.5, 158.5, 163.5, 164.6, 164.7, 164.9, 166.51, 166.54, 166.99, 167.02, 168.8, 169.1, 169.70, 169.75, 170.0, 170.1, 172.8, 172.9, 180.5, 181.0, 185.5, 186.0 ppm; IR (KBr): $\tilde{\nu}$ = 2960, 2920, 2850, 2110, 1740, 1670, 1630, 1600, 1580, 1450, 1380, 1310, 1260, 1220, 1100, 1070, 1030, 800, 710 cm^{-1}; elemental analysis calcd (%) for $C_{74}H_{70}N_4O_{22}$: C 65.00, H 5.16, N 4.10; found: C 65.00, H 5.29, N 4.08.

*Benanomicin B hydrochloride (**2b**·HCl)*: A 2 M aq. NaOH solution (0.25 mL) was added to a solution of **70** (59.3 mg, 0.0434 mmol) in MeOH (5.0 mL). After stirring for 8.5 h, the reaction was stopped by adding 2 M aq. HCl (0.55 mL) and the mixture was concentrated in vacuo (azeotropic evaporation ×5). The residue was purified by reversed-phase silica gel column chromatography (Cosmosil: MeOH/H_2O = 9:1) and Sephadex (LH-20: MeOH) to afford the crude product of **71**. A 1 M aq. HCl solution (100 μL) and 5 % Pd/C (82.3 mg) were added to a solution of this crude material (46.5 mg) in MeOH (4.5 mL) and DMF (1.5 mL). After stirring under H_2 (1 atm) at RT for 2 h, the reaction mixture was filtered through a Hyflo Super-Cel pad (washed with DMF) and concentrated in vacuo. The residue was purified by reversed-phase silica gel column chromatography (Cosmosil: CH_3CN/H_2O = 3:7, pH 3) to give red precipitates, which were further purified by Sephadex LH-20 (DMF) (twice) to afford benanomicin B dimethylformamide solvate which was dissolved in MeOH and then 2 M aq. HCl was added to adjust the pH value to 3.5. After removal of the solvent in vacuo, the residue was dissolved in DMSO (0.1 mL), and $CHCl_3$ (6.0 mL) was added. The precipitates were collected by filtration to afford benanomicin B hydrochloride (**2b·HCl**) as a red amorphous powder (19.7 mg, 53 %). M.p. 213–215 °C (decomp) (lit.:[1b] > 220 °C (decomp)); $[\alpha]_D^{22}$ = +353 (*c* = 0.0501, H_2O) (lit.:[1b] +360 (*c* = 0.05, H_2O)); ^{1}H NMR (500 MHz, [D_6]DMSO, 313 K): δ = 1.18 (d, *J* = 6.5 Hz, 3H), 1.34 (d, *J* = 7.3 Hz, 3H), 2.33 (s, 3H), 3.07 (dd, *J* = 10.7, 10.9 Hz, 1H), 3.16–3.18 (m, 3H), 3.29–3.34 (m, 1H), 3.39–3.44 (m, 1H), 3.60 (br, 1H), 3.72 (dd, *J* = 5.3, 11.3 Hz, 1H), 3.83 (br q, *J* = 6.5, 1H), 3.91–3.94 (m, 1H), 3.95 (s, 3H), 4.42 (dq, *J* = 7.1, 7.3 Hz, 1H), 4.53–4.56 (m, 2H), 4.58–4.65 (m, 1H), 4.74 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 7.23 (br s, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 8.06 (s, 1H), 8.43 (d, *J* = 7.1 Hz, 1H), 12.8 ppm (s, 1H); ^{13}C NMR (125 MHz, [D_6]DMSO, 313 K): δ = 16.3, 16.9, 19.1, 47.6, 54.2, 56.4, 65.7, 66.9, 69.4, 69.7, 73.3, 75.9, 77.4, 80.9, 104.0, 104.5, 106.9, 107.6, 110.1, 113.7, 115.6, 125.7, 127.5, 131.3, 134.3, 137.3, 137.8, 147.9, 151.0, 156.9, 164.7, 166.0, 166.8, 173.9, 185.0, 187.5 ppm; IR (KBr): $\tilde{\nu}$ = 3360, 1730, 1610, 1300, 1160, 1080, 1040 cm^{-1}; LRMS (MALDI-TOF, DHBA matrix): m/*z*: calcd for $C_{39}H_{42}O_{18}N_2Na$ ([*M*+Na]$^+$): 849.2; found: 849.2; HRMS (FAB): m/*z*: calcd for $C_{39}H_{43}O_{18}N_2$ ([*M*+H]$^+$): 827.2511; found: 827.2506.

N-*Monomethylamine* **73**: A solution of Me_3P in toluene (0.91 M, 50 μL, 0.048 mmol) was added to a solution of **69** (53.5 mg, 0.0401 mmol) in CH_2Cl_2 (0.67 mL) at 0 °C. After stirring for 1.5 h at RT, $(HCHO)_n$ (6.50 mg, 0.201 mmol) was added. The reaction mixture was stirred for 11 h at RT before treatment with MeOH (0.50 mL) and $NaBH_4$ (10.6 mg, 0.281 mmol) at 0 °C. After stirring for 10 min, the reaction was stopped by adding AcOH and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/Et_2O/CH_3CN/MeOH = 22:55:17:6) to afford *N*-monomethylamine **73** (39.9 mg, 75 %) as a white amorphous solid. Mixture of two conformers: diaxial/diequatorial = 57:43); m.p. 95–97 °C; $[\alpha]_D^{30}$ = +42.6 (*c* = 1.14 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, the minor conformer is indicated by an asterisk): δ = 1.06 (d, *J* = 7.3 Hz, 3H), 1.338* (d, *J* = 6.0 Hz, 3H), 1.342 (s, 3H), 1.36* (d, *J* = 7.3 Hz, 1H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.57* (s, 3H), 1.88 (s, 3H), 1.96* (s, 3H), 1.99 (s, 3H), 2.04* (s, 3H), 2.35 (s, 3H), 2.44* (s, 3H), 2.51 (s, 3H), 2.65* (s, 3H), 2.75 (br d, *J* = 4.3 Hz, 1H), 2.86* (br d, *J* = 4.3 Hz, 1H), 3.24 (dd, *J* = 8.7, 11.8 Hz, 1H), 3.36* (dd, *J* = 8.9, 11.6 Hz, 1H), 3.54–3.60 (m, 1H), 3.65* (s, 3H), 3.67–3.72* (m, 1H), 3.72 (s, 3H), 3.76 (s, 3H), 3.79* (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.91* (s, 3H), 3.94 (d, *J* = 11.3 Hz, 1H), 3.95* (dd, *J* = 4.3, 10.0 Hz, 1H), 4.00* (dd, *J* = 1.3, 10.6 Hz, 1H), 4.06* (dd, *J* = 5.0, 11.6 Hz, 1H), 4.15* (dd, *J* = 5.1, 11.8 Hz, 1H), 4.25 (d, *J* = 11.4 Hz, 1H), 4.38 (s, 2H), 4.39* (d, *J* = 7.0 Hz, 1H), 4.41* (s, 2H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.46* (d, *J* = 11.3 Hz, 1H), 4.47* (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 7.8 Hz, 1H), 4.56* (d, *J* = 10.6 Hz, 1H), 4.57 (dq, *J* = 6.8, 7.3 Hz, 1H), 4.62 (d, *J* = 7.1 Hz, 1H), 4.63* (d, *J* = 11.3 Hz, 1H), 4.66* (dq, *J* = 7.2, 7.3 Hz, 1H), 4.67 (d, *J* = 3.1 Hz, 1H), 4.71 (dd, *J* = 7.1, 8.7 Hz, 1H), 4.72* (d, *J* = 12.0 Hz, 1H), 4.84 (ddd, *J* = 5.1, 8.7, 8.7 Hz, 1H), 4.87 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.88* (dd, *J* = 7.0, 8.9 Hz, 1H), 4.90 (d, *J* = 11.4 Hz, 1H), 4.93* (ddd, *J* = 5.0, 8.9, 8.9 Hz, 1H), 5.00* (dd, *J* = 8.9, 8.9 Hz, 1H), 5.04 (dd, *J* = 7.8, 10.3 Hz, 1H), 5.07 (d, *J* = 3.1 Hz, 1H), 5.16* (d, *J* = 7.6 Hz, 1H), 5.54 (d, *J* = 6.8 Hz, 1H; NH), 5.59* (dd, *J* = 7.6, 10.0 Hz, 1H), 6.24* (d, *J* = 7.2 Hz,

1H; NH), 6.65 (s, 1H), 6.77* (s, 1H), 6.78–6.83 (m, 1H), 6.83–6.87* (m, 1H), 6.90–6.93 (m, 2H), 6.94–6.97* (m, 2H), 7.05–7.37 (m, 16H), 7.34–7.42 (m, 2H), 7.47 (s, 1H), 7.42–7.52* (m, 1H), 7.80* (d, $J=1.3$ Hz, 1H), 7.93–7.97 ppm* (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, without distinction of the two conformers): $\delta=17.2$, 17.4 (2C), 18.1, 19.0, 19.7, 19.8, 19.9, 20.55, 20.61, 20.69, 20.73, 38.1, 38.2, 47.9, 48.4, 52.19, 52.22, 56.4, 56.5, 61.08, 61.10, 62.1, 62.2, 63.9, 64.0, 69.0, 69.1, 69.9, 70.6, 70.8, 71.2, 71.5, 71.6, 71.8, 72.1, 73.7, 74.2, 74.3, 75.9, 76.5, 76.6, 77.3 (overlapped by $CDCl_3$), 80.6, 81.2, 81.6, 97.9, 101.0, 101.8, 102.1, 107.2, 107.8, 112.3, 118.9, 119.5, 120.8, 121.0, 122.5, 122.7, 122.8, 123.1, 123.20, 123.22, 127.05, 127.06, 127.2, 127.3, 127.50, 127.51, 127.56, 127.63, 127.66, 127.3, 127.8, 127.89, 127.94, 128.0, 128.1, 128.3, 128.4, 128.49, 128.52, 128.7, 128.9, 129.6, 129.8, 130.16, 130.23, 131.2, 132.2, 132.6, 133.1, 133.2, 136.6, 136.8, 137.17, 137.22, 137.7, 137.89, 137.93, 138.2, 138.8, 139.0, 145.1, 145.4, 152.2, 152.6, 153.2, 153.3, 154.2, 154.3, 163.9, 165.0, 167.5, 169.2, 169.4, 169.8, 169.9, 169.96, 170.04, 172.9, 173.1 ppm; IR (KBr): $\tilde{\nu}=3640$, 3410, 2940, 2870, 1750, 1660, 1590, 1590, 1500, 1450, 1370, 1340, 1270, 1220, 1110, 1050, 910, 820, 750, 700 cm^{-1}; elemental analysis calcd (%) for $C_{72}H_{75}ClN_2O_{20}$: C 65.32, H 5.71, N 2.12; found: C 65.05, H 5.97, N 1.96.

Trifluoroacetoamide β-***76***: Pyridine (0.1 mL, 1.25 mmol) and trifluoroacetic anhydride (0.01 mL, 0.625 mmol) were added to a solution of **73** (82.7 mg, 0.0625 mmol) in CH_2Cl_2 (0.8 mL) at 0°C. After stirring for 20 min, the reaction was stopped by adding saturated aqueous $NaHCO_3$ and then the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with 2M aq. HCl and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc=4:6) to afford trifluoroacetoamide β-**76** as a white solid (79.9 mg, 90%). Mixture of two conformers: diaxial/diequatorial=57:43); m.p. 110–113°C (Et_2O and hexane); $[\alpha]_D^{30}=+32.2$ ($c=1.13$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, the minor conformer is indicated by an asterisk): $\delta=1.09$ (d, $J=7.2$ Hz, 3H), 1.25* (d, $J=6.4$ Hz, 3H), 1.27 (d, $J=6.4$ Hz, 3H), 1.35* (d, $J=7.2$ Hz, 3H), 1.45 (s, 3H), 1.65* (s, 3H), 1.88 (s, 3H), 1.95* (s, 3H), 1.96 (s, 3H), 2.00* (s, 3H), 2.36 (s, 3H), 2.43* (s, 3H), 3.19 (dd, $J=7.9$, 12.0 Hz, 1H), 3.25 (s, 2H), 3.32* (dd, $J=8.1$, 12.0 Hz, 1H), 3.57* (s, 3H), 3.66* (s, 3H), 3.71 (s, 3H), 3.78* (s, 3H), 3.80–3.84 (m, 1H), 3.82 (s, 3H), 3.85 (s, 3H), 3.90* (s, 3H), 3.93 (dd, $J=5.0$, 12.0 Hz, 1H), 3.93–3.98* (m, 1H), 4.03* (dd, $J=5.3$, 12.0 Hz, 1H), 4.04 (dd, $J=7.3$, 10.3 Hz, 1H), 4.05* (dd, $J=1.5$, 10.7 Hz, 1H), 4.06 (d, $J=11.3$ Hz, 1H), 4.24 (d, $J=11.4$ Hz, 1H), 4.26* (dd, $J=7.2$, 10.3 Hz, 1H), 4.35 (d, $J=6.9$ Hz, 1H), 4.403* (d, $J=12.4$ Hz, 1H), 4.405 (s, 2H), 4.457* (d, $J=10.8$ Hz, 1H), 4.460* (d, $J=12.3$ Hz, 1H), 4.47 (d, $J=11.3$ Hz, 1H), 4.48* (d, $J=12.4$ Hz, 1H), 4.57* (d, $J=10.7$ Hz, 1H), 4.561 (d, $J=8.0$ Hz, 1H), 4.562* (d, $J=6.8$ Hz, 1H), 4.60 (qd, $J=7.2$, 7.8 Hz, 1H), 4.63 (dd, $J=6.9$, 8.8 Hz, 1H), 4.64* (d, $J=10.8$ Hz, 1H), 4.65 (d, $J=3.1$ Hz, 1H), 4.67* (qd, $J=7.2$, 7.3 Hz, 1H), 4.69* (d, $J=12.3$ Hz, 1H), 4.79 (ddd, $J=5.0$, 7.9, 8.5 Hz, 1H), 4.80* (dd, $J=6.8$, 8.4 Hz, 1H), 4.83 (dd, $J=8.5$, 8.8 Hz, 1H), 4.87 (d, $J=11.4$ Hz, 1H), 4.89* (ddd, $J=5.3$, 8.1, 8.4 Hz, 1H), 4.96* (dd, $J=8.4$, 8.4 Hz, 1H), 4.99 (dd, $J=3.1$, 7.3 Hz, 1H), 5.01 (d, $J=3.1$ Hz, 1H), 5.11* (dd, $J=7.2$, 10.3 Hz, 1H), 5.24* (d, $J=8.0$ Hz, 1H), 5.29 (dd, $J=8.0$, 10.3 Hz, 1H), 5.67 (d, $J=7.8$ Hz, 1H; NH), 5.88* (dd, $J=8.0$, 10.3 Hz, 1H), 6.29* (d, $J=7.3$ Hz, 1H; NH), 6.64 (s, 1H), 6.77* (s, 1H), 6.81–6.85 (m, 2H), 6.86–6.90* (m, 1H), 6.91–6.95* (m, 2H), 6.98–7.02* (m, 2H), 7.05–7.18 (m, 7H), 7.18–7.40 (m, 10H), 7.41–7.46 (m, 2H), 7.48 (s, 1H), 7.51–7.56 (m, 1H), 7.81 (d, $J=1.6$ Hz, 1H), 7.95–7.99 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, without distinction of the two conformers): $\delta=16.0$ (2C), 17.5, 18.1, 19.1, 19.8, 20.0, 20.1, 20.5, 20.57, 20.64, 20.7, 34.23, 34.24, 47.9, 48.3, 52.2, 56.2, 56.4, 56.5, 56.6, 61.1, 62.2, 62.4, 68.9, 69.1, 70.3, 70.4, 70.8, 71.0, 71.3, 71.4, 71.5, 72.4, 74.31, 74.34, 74.5, 76.0, 76.4, 76.5, 76.6, 77.1, 77.2, 77.6, 81.4, 98.6, 100.8, 101.4, 101.8, 102.1, 107.4, 108.0, 112.4, 116.7 (q, $^1J_{C,F}=286$ Hz), 116.8 (q, $^1J_{C,F}=286$ Hz), 119.0, 119.6, 120.8, 121.1, 122.8, 122.9, 123.4, 123.5, 127.1, 127.2, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.01, 128.03, 128.2, 128.4, 128.5, 128.7, 128.8, 129.3, 129.7, 130.30, 130.32, 131.2, 132.5, 132.8, 133.0, 133.6, 136.3, 136.7, 136.8, 137.3, 137.4, 137.8, 137.8, 138.0, 138.7, 138.8, 145.2, 145.5, 152.4, 153.0, 153.2, 153.3, 154.35, 154.39, 158.76 (q, $^2J_{C,F}=35$ Hz), 158.83 (q, $^2J_{C,F}=35$ Hz), 164.0, 164.9, 167.30, 167.33, 168.9, 169.1, 169.56, 169.59, 169.9, 170.0, 172.9, 173.1 ppm; IR (KBr): $\tilde{\nu}=3410$, 2940, 1750, 1700, 1660, 1580, 1510, 1460, 1370, 1340, 1250, 1220, 1150, 1070, 900, 820, 750, 700 cm^{-1}; elemental analysis calcd (%) for $C_{74}H_{74}ClF_3N_2O_{21}$: C 62.60, H 5.25, N 1.97; found: C 62.33, H 5.28, N 1.87.

Anthraquinone ***77***: A solution of CAN (77.8 mg, 0.142 mmol) in water (0.18 mL) was added to a solution of β-**76** (96.0 mg, 0.0676 mmol) in CH_3CN (0.53 mL) at 0°C. After stirring for 20 min at RT, the reaction was stopped by adding water. The precipitates were collected by filtration to afford the chloroquinone (71.3 mg) as a red powder. The filtrate was extracted with EtOAc (×3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. A solution of diene **21** (150 mg, 0.744 mmol) in THF (1.4 mL) was added to the combined crude material (99.6 mg) at RT and stirred for 20 min. Acidic silica gel (pH 6, Kanto chemical) was added and the organic solvent was removed in vacuo. After standing for 14 h, the silica gel was placed on a glass filter (washed with $CHCl_3$/MeOH=9:1) and then the filtrate was concentrated in vacuo. K_2CO_3 (251 mg) was added to the solution of this crude material in THF/CH_2Cl_2 (1:3, 6.8 mL) at RT. After stirring for 3 h at 40°C, the reaction was stopped by adding 2M aq. HCl and then the mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/Et_2O/CH_3CN=2:3:1) to afford anthraquinone **77** as a yellow solid (73.9 mg, 75%). Mixture of two conformers: diaxial/diequatorial=75:25; m.p. 123–126°C (Et_2O and hexane); $[\alpha]_D^{30}=+110$ ($c=1.10$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, the minor conformer is indicated by an asterisk): $\delta=1.12$ (d, $J=7.3$ Hz, 3H), 1.25* (d, $J=6.4$ Hz, 3H), 1.35 (d, $J=6.4$ Hz, 3H), 1.366* (d, $J=7.2$ Hz, 3H), 1.371 (s, 3H), 1.64* (s, 3H), 1.85 (s, 3H), 1.95* (s, 3H), 1.96 (s, 3H), 2.00* (s, 3H), 2.38 (s, 3H), 2.47* (s, 3H), 3.22 (dd, $J=8.0$, 12.2 Hz, 1H), 3.27 (s, 3H), 3.32* (dd, $J=8.1$, 12.2 Hz, 1H), 3.56* (s, 3H), 3.69* (s, 3H), 3.75 (s, 3H), 3.88–3.93* (m, 1H), 3.92–3.96 (m, 1H), 3.938 (dd, $J=5.0$, 12.1 Hz, 1H), 3.946* (dd, $J=0.6$, 12.4 Hz, 1H), 3.949* (s, 3H), 4.00 (s, 3H), 4.03* (dd, $J=4.9$, 12.2 Hz, 1H), 4.09 (dd, $J=7.1$, 10.3 Hz, 1H), 4.20 (d, $J=11.1$ Hz, 1H), 4.24* (dd, $J=7.2$, 10.3 Hz, 1H), 4.29* (d, $J=11.2$ Hz, 1H), 4.34 (d, $J=11.5$ Hz, 1H), 4.38 (d, $J=6.8$ Hz, 1H), 4.42 (d, $J=12.1$ Hz, 1H), 4.43* (d, $J=11.7$ Hz, 1H), 4.46 (d, $J=12.1$ Hz, 1H), 4.465 (d, $J=11.5$ Hz, 1H), 4.471* (d, $J=12.1$ Hz, 1H), 4.54* (d, $J=12.4$ Hz, 1H), 4.55 (d, $J=7.9$ Hz, 1H), 4.57 (d, $J=3.3$ Hz, 1H), 4.54–4.59 (m, 1H), 4.61 (dd, $J=6.8$, 8.8 Hz, 1H), 4.61–4.67* (m, 1H), 4.69* (d, $J=12.1$ Hz, 1H), 4.76–4.81 (m, 1H), 4.78–4.82* (m, 3H), 4.82 (dd, $J=8.8$, 8.8 Hz, 1H), 4.89* (ddd, $J=4.9$, 8.1, 8.2 Hz, 1H), 4.95 (d, $J=3.3$ Hz, 1H), 4.96* (dd, $J=8.2$, 9.2 Hz, 1H), 5.04 (dd, $J=3.2$, 7.1 Hz, 1H), 5.11 (d, $J=11.1$ Hz, 1H), 5.10–5.14* (m, 1H), 5.17* (d, $J=11.2$ Hz, 1H), 5.21* (d, $J=7.9$ Hz, 1H) 5.30* (dd, $J=7.9$, 10.3 Hz, 1H), 5.52* (d, $J=7.9$ Hz, 1H; NH), 5.87 (dd, $J=7.9$, 10.3 Hz, 1H), 6.29 (d, $J=7.2$ Hz, 1H; NH), 6.70* (d, $J=2.5$ Hz, 1H), 6.72 (d, $J=2.5$ Hz, 1H), 6.72–6.81 (m, 1H), 6.98–7.18 (m, 10H), 7.20–7.25 (m, 2H), 7.25–7.40 (m, 7H), 7.53–7.62 (m, 1H), 7.62 (s, 1H), 7.96–7.98 (m, 1H), 8.08* (d, $J=0.6$ Hz, 1H), 12.6 (s, 1H; OH), 12.8 ppm (s, 1H; OH); ^{13}C NMR (125 MHz, $CDCl_3$, without distinction of the two conformers): $\delta=16.0$, 16.1, 17.5, 18.0, 19.2, 19.7, 20.0, 20.4, 20.5, 20.57, 20.63, 20.7, 29.7, 34.2, 47.9, 48.4, 52.26, 52.31, 56.06, 56.11, 56.2, 56.6, 62.2, 62.4, 68.9, 69.1, 70.2, 70.4, 71.0, 71.1, 71.16, 71.17, 71.2, 71.4, 71.5, 72.3, 73.4, 74.0, 74.6, 76.4, 76.8, 76.9 (2C), 77.2, 77.3, 80.4, 98.7, 101.3, 101.9, 102.1, 105.8, 106.0, 107.1, 107.4, 110.4, 110.7, 116.6 (q, $^1J_{C,F}=286$ Hz), 118.3, 120.5, 121.7, 122.5, 123.2, 125.2, 126.2, 127.3, 127.4, 127.5, 127.6, 127.68, 127.72, 127.9, 128.05, 128.12, 128.2, 128.3, 128.4, 128.45, 128.48, 128.56, 128.64, 128.8, 129.0, 129.1, 129.7, 130.3, 132.6, 132.8, 133.1, 133.5, 133.7, 134.6, 135.1, 136.0, 136.3, 136.4, 136.5, 136.8, 137.1, 137.2, 138.0, 138.1, 139.2, 139.8, 140.0, 144.0, 153.1, 154.9, 156.5, 158.4, 158.8 (q, $^2J_{C,F}=35$ Hz), 163.7, 164.6, 164.9, 166.6, 166.9, 168.9, 169.1, 169.55, 169.59, 169.9, 170.0, 172.86, 172.90, 180.5, 181.1 ppm; IR (KBr): $\tilde{\nu}=3410$, 2960, 1750, 1700, 1670, 1630, 1610, 1580, 1540, 1500, 1450, 1380, 1320, 1260, 1220, 1150, 1070, 1030, 900 870, 800, 740, 700 cm^{-1}; elemental analysis calcd (%) for $C_{77}H_{73}F_3N_2O_{23}$: C 63.72, H 5.07, N 1.93; found: C 64.00, H 5.21, N 1.76.

*Pradimicin A hydrochloride (****1a****·HCl)*: 5% Pd/C (27.8 mg) was added to a solution of **77** (21.0 mg, 0.0145 mmol) in MeOH (1.6 mL) and DMF (0.5 mL). After stirring under H_2 (1 atm) at RT for 30 min, the reaction mixture was filtered though a Hyflo Super-Cel pad (washed with $CHCl_3$/MeOH=9:1) and concentrated in vacuo. The residue was purified by PTLC ($CHCl_3$/MeOH=9:1) to afford the corresponding tetrol (13.5 mg)

as a red amorphous solid. A 5 M aq. NaOH solution (0.07 mL) was added to the solution of this crude material in H_2O (0.71 mL) at 0 °C. After stirring for 24 h at RT, the reaction was stopped by adding 2 M aq. HCl (pH 3.5) and the mixture concentrated in vacuo. The residue was purified by reversed-phase silica gel column chromatography (Cosmosil: CH_3CN/H_2O = 3:7, pH 3) to give red precipitates that were further purified by Sephadex LH-20 (DMF) to afford pradimicin A (**1a**) dimethylformamide solvate, which was dissolved in MeOH and then 2 M aq. HCl was added until a pH value of 3.5 was obtained. After removal of the solvent in vacuo, the residue was dissolved in DMSO (25 μL) and $CHCl_3$ was added. The precipitates were collected by filtration to afford **1a·HCl** as a red amorphous powder (4.3 mg, 61 %). M.p. 194–197 °C (decomp) (lit.[1d] 193–195 °C (decomp)); $[\alpha]_D^{26} = +280$ ($c = 0.100$ in 0.1 M aq. HCl) (authentic: +287 ($c = 0.100$ in 0.1 M aq. HCl)); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 313 K): $\delta = 1.25$ (d, $J = 6.2$ Hz, 3H), 1.35 (d, $J = 7.0$ Hz, 3H), 2.29 (s, 3H), 2.61 (s, 3H), 3.74 (dd, $J = 5.3$, 11.2 Hz, 1H), 3.84 (q, $J = 6.2$ Hz, 1H), 4.39 (q, $J = 7.0$ Hz, 1H), 4.44 (d, $J = 7.3$ Hz, 1H), 4.46 (d, $J = 10.3$ Hz, 1H), 4.49 (d, $J = 10.3$ Hz, 1H), 4.73 (d, $J = 7.7$ Hz, 1H), 6.71 (d, $J = 2.4$ Hz, 1H), 6.85 (s, 1H), 7.11 (d, $J = 2.4$ Hz, 1H), 7.69 (s, 1H), 8.78 ppm (d, $J = 7.0$ Hz, 1H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 313 K): $\delta = 16.6$, 17.5, 19.7, 36.8, 48.2, 57.0, 63.8, 66.4, 68.0, 70.0, 70.6, 74.1, 76.5, 79.7, 81.5, 104.6, 105.3, 107.5, 108.2, 110.7, 114.4, 116.2, 126.4, 128.2, 131.9, 134.9, 137.9, 138.3, 148.5, 151.7, 157.5, 165.3, 166.6, 167.4, 174.5, 185.6, 188.1 ppm; IR (KBr): $\tilde{\nu} = 3380$, 2980, 2880, 1720, 1610, 1450, 1390, 1330, 1300, 1260, 1200, 1160, 1060, 970, 910, 880, 790, 750, 660, 650 cm^{-1}; LRMS (MALDI-TOF, DHBA matrix): m/z: calcd for $C_{40}H_{44}O_{18}N_2Na$ ([M+Na]$^+$): 863.2; found: 863.1; HRMS (FAB): m/z: calcd for $C_{40}H_{45}O_{18}N_2$ ([M+H]$^+$): 841.2667; found: 841.2679.

Glycoside ***78***: MS4A (537 mg) was placed in a two-necked round-bottomed flask and flame dried. The promoter was prepared in situ by stirring a mixture of Cp_2HfCl_2 (104 mg, 0.274 mmol) and AgOTf (141 mg, 0.548 mmol) in CH_2Cl_2 (1.9 mL) for 10 min at RT. A solution of **68** (200 mg, 0.249 mmol) and **80** (189 mg, 0.299 mmol) in CH_2Cl_2 (4.0 mL) was added to this suspension at −78 °C. After stirring for 17 h at −30 °C, the reaction was stopped by adding saturated aqueous $NaHCO_3$. The mixture was filtered through a Celite pad and extracted with EtOAc (× 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/Et_2O/CH_3CN = 2:3:1) to afford β-glycoside **78** as a white amorphous (261 mg, 74 %), along with some mixed fractions including α-glycoside **78**. Further purification by PTLC (hexane/EtOAc = 1:1) gave pure α-glycoside **78** (26.2 mg, 7.4 %) as a white amorphous solid.

β-**78** (a mixture of two conformers: diaxial/diequatorial = 54:46): M.p. 118–119 °C (Et_2O and hexane); $[\alpha]_D^{24} = +54.0$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, the minor conformer is indicated by an asterisk): $\delta = 1.10$ (d, $J = 7.2$ Hz, 3H), 1.25[7]* (d, $J = 6.4$ Hz, 3H), 1.29 (d, $J = 6.4$ Hz, 3H), 1.340 (s, 3H), 1.341* (d, $J = 7.2$ Hz, 3H), 1.51* (s, 3H), 1.65 (s, 3H), 1.76* (s, 3H), 1.97 (s, 3H), 2.02* (s, 3H), 2.35 (s, 3H), 2.47* (s, 3H), 3.31* (dd, $J = 6.5$, 12.4 Hz, 1H), 3.44* (dd, $J = 6.3$, 12.4 Hz, 3H), 3.65* (s, 3H), 3.71 (s, 3H), 3.78–3.84 (m, 1H), 3.81* (s, 3H), 3.82 (s, 3H), 3.89* (s, 3H), 3.92* (dq, $J = 1.0$, 6.4 Hz, 1H), 3.98 (dd, $J = 3.7$, 10.3 Hz, 1H), 4.03 (dd, $J = 4.3$, 12.4 Hz, 1H), 4.10* (dd, $J = 1.6$, 10.7 Hz, 1H), 4.13 (d, $J = 11.3$ Hz, 1H), 4.16* (dd, $J = 3.6$, 10.1 Hz, 1H), 4.17* (dd, $J = 4.4$, 10.2 Hz, 1H), 4.25* (d, $J = 11.3$ Hz, 1H), 4.41 (s, 2H), 4.42* (d, $J = 11.9$ Hz, 1H), 4.47 (d, $J = 11.8$ Hz, 1H), 4.49* (d, $J = 11.9$ Hz, 1H), 4.50 (d, $J = 11.3$ Hz, 1H), 4.5098 (dd, $J = 7.4$, 7.9 Hz, 1H), 4.510* (d, $J = 12.4$ Hz, 1H), 4.60 (qd, $J = 7.2$, 8.4 Hz, 1H), 4.64* (d, $J = 10.7$ Hz, 1H), 4.650 (d, $J = 11.8$ Hz, 1H), 4.652* (qd, $J = 7.2$, 7.2 Hz, 1H), 4.67–4.70* (m, 1H), 4.68* (d, $J = 7.9$ Hz, 1H), 4.69 (d, $J = 7.9$ Hz, 1H), 4.70–4.73 (m, 1H), 4.71 (d, $J = 3.3$ Hz, 1H), 4.71–4.74* (m, 1H), 4.75* (d, $J = 12.4$ Hz, 1H), 4.76 (dd, $J = 7.1$, 7.4 Hz, 1H), 4.81–4.84* (m, 1H), 4.87* (d, $J = 11.3$ Hz, 1H), 4.90* (dd, $J = 7.2$, 7.6 Hz, 1H), 5.08 (d, $J = 3.3$ Hz, 1H), 5.29* (dd, $J = 7.9$, 10.2 Hz, 1H), 5.30 (d, $J = 7.9$ Hz, 1H), 5.51 (dd, $J = 1.1$, 3.7 Hz, 1H), 5.62* (dd, $J = 1.0$, 4.4 Hz, 1H), 5.63 (d, $J = 8.4$ Hz, 1H), 5.87 (dd, $J = 7.9$, 10.2 Hz, 1H), 6.27* (d, $J = 7.2$ Hz, 1H), 6.65 (s, 1H), 6.77* (s, 1H), 6.82–6.91 (m, 4H), 6.94–7.03 (m, 6H), 7.05–7.46 (m, 12H), 7.48–7.58 (m, 3H), 7.63–7.67* (m, 1H), 7.86* (d, $J = 1.6$ Hz, 1H), 7.97–8.01* (m, 1H), 8.01–8.05 (m, 1H), 8.21–8.25 ppm* (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, without distinction of the two conformers): $\delta = 16.38$, 16.42, 17.5, 18.1, 19.0, 19.6, 19.8, 20.0, 20.2, 20.4, 20.7, 20.8, 47.9, 48.4, 52.2, 56.4, 56.5, 61.08, 61.10, 61.4, 61.5, 68.7, 68.8, 69.5, 69.7, 69.9 (2C), 70.1, 70.18, 70.22, 71.4, 72.2, 72.8, 73.2, 74.37, 74.43, 75.4, 76.0, 76.47, 76.50, 77.0 (overlapped by a signal of $CDCl_3$), 77.1, 77.3, 77.6, 78.0, 81.3, 98.1, 100.9, 101.0, 101.4, 107.3, 107.9, 112.5, 119.1, 119.6, 120.9, 121.1, 122.4, 122.97, 123.04, 123.29, 123.31, 127.0, 127.1, 127.25, 127.31, 127.4, 127.55, 127.64, 127.65, 127.72, 127.81, 127.82, 127.9, 127.98, 128.00, 128.1, 128.3, 128.40, 128.44, 128.5, 128.57, 128.62, 128.7, 128.8, 129.5, 129.6, 129.7, 129.8, 130.07, 130.13, 130.3, 131.2, 132.4, 132.7, 133.0, 133.2, 133.3, 133.4, 136.5, 136.8, 136.9, 137.3, 137.4, 137.7, 137.87, 137.91, 138.2, 138.8, 139.1, 145.2, 145.5, 152.4, 152.8, 153.26, 153.33, 154.3, 154.4, 164.0, 164.9, 166.15, 166.24, 167.39, 167.41, 168.5, 168.7, 169.6, 169.69, 169.72, 169.8, 172.9, 173.1 ppm; IR (KBr): $\tilde{\nu} = 2940$, 1730, 1660, 1590, 1570, 1560, 1510, 1460, 1370, 1340, 1270, 1220, 1160, 1110, 1100, 1070, 1030, 910, 810, 740, 710 cm^{-1}; elemental analysis calcd (%) for $C_{78}H_{76}ClNO_{22}$: C 66.21, H 5.41, N 0.99; found: C 65.99, H 5.43, N 0.78.

α-**78** (a mixture of two conformers: diaxial/diequatorial = 82:18): M.p. 105–107 °C (Et_2O and hexane); $[\alpha]_D^{23} = +143$ ($c = 0.990$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, the minor conformer is indicated by an asterisk): $\delta = 0.78$* (d, $J = 6.6$ Hz, 3H), 1.06 (d, $J = 7.2$ Hz, 3H), 1.25 (s, 3H), 1.26 (d, $J = 6.6$ Hz, 3H), 1.36* (d, $J = 7.2$ Hz, 3H), 1.55* (s, 3H), 1.657 (s, 3H), 1.662* (s, 3H), 1.69* (s, 3H), 1.99 (s, 3H), 2.07* (s, 3H), 2.31 (s, 3H), 3.33 (dd, $J = 6.2$, 12.5 Hz, 1H), 3.62* (dd, $J = 5.7$, 12.8 Hz, 1H), 3.63* (s, 3H), 3.68 (s, 3H), 3.697 (s, 3H), 3.698 (d, $J = 11.2$ Hz, 1H), 3.93 (d, $J = 11.2$ Hz, 1H), 3.95* (s, 3H), 4.00* (s, 3H), 4.05 (dd, $J = 4.1$, 12.5 Hz, 1H), 4.068 (s, 3H), 4.070 (br q, $J = 6.6$ Hz, 1H), 4.17* (dd, $J = 0.9$, 11.2 Hz, 1H), 4.19 (dd, $J = 3.5$, 10.3 Hz, 1H), 4.27* (d, $J = 11.3$ Hz, 1H), 4.28* (dd, $J = 4.5$, 12.8 Hz, 1H), 4.30* (d, $J = 11.2$ Hz, 1H), 4.40 (d, $J = 11.0$ Hz, 1H), 4.46* (d, $J = 11.4$ Hz, 1H), 4.48 (d, $J = 12.3$ Hz, 1H), 4.493 (d, $J = 11.0$ Hz, 1H), 4.50 (dd, $J = 5.5$, 7.5 Hz, 1H), 4.54 (d, $J = 5.5$ Hz, 1H), 4.55 (d, $J = 12.3$ Hz, 1H), 4.55 (d, $J = 12.3$ Hz, 1H), 4.57–4.63* (m, 2H), 4.60 (qd, $J = 7.2$, 7.9 Hz, 1H), 4.69–4.74* (m, 3H), 4.70–4.75 (m, 1H), 4.78 (dd, $J = 7.5$, 7.5 Hz, 1H), 4.82 (s, 2H), 4.83–4.87* (m, H), 4.90* (d, $J = 11.1$ Hz, 1H), 4.93* (d, $J = 11.3$ Hz, 1H), 4.96* (dd, $J = 6.7$, 6.7 Hz, 1H), 5.01* (d, $J = 4.9$ Hz, 1H), 5.05* (d, $J = 11.1$ Hz, 1H), 5.22 (d, $J = 4.0$ Hz, 1H), 5.33* (dd, $J = 1.0$, 3.0 Hz, 1H), 5.34 (dd, $J = 4.0$, 10.3 Hz, 1H), 5.36* (d, $J = 3.6$ Hz, 1H), 5.54 (dd, $J = 1.0$, 4.6 Hz, 1H), 5.58 (d, $J = 7.9$ Hz, 1H), 5.74* (dd, $J = 3.6$, 10.7 Hz, 1H), 6.34* (d, $J = 7.1$ Hz, 1H), 6.68 (s, 1H), 6.74* (s, 1H), 6.83* (s, 1H), 6.87–7.00 (m, 3H), 7.02–7.08 (m, 1H), 7.09–7.14 (m, 2H), 7.16–7.36 (m, 8H), 7.42–7.65 (m, 5H), 7.84 (s, 1H), 8.04* (d, $J = 1.0$ Hz, 1H), 8.04–8.15 (m, 2H), 8.20–8.23 ppm* (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, without distinction of the two conformers): $\delta = 15.6$, 16.4, 17.5, 18.1, 18.8, 19.1, 19.6, 20.0, 20.25, 20.32, 20.8, 20.9, 47.9, 48.5, 52.20, 52.24, 56.2, 56.5, 61.1, 61.2, 61.3, 61.4, 65.7, 65.8, 68.6, 68.8, 69.4, 69.5, 69.7, 70.09 (2C), 70.14, 71.0, 73.3, 73.46, 73.49, 73.9, 75.0, 75.2, 75.8, 75.9, 76.3, 76.7, 77.2, 77.3 (overlapped by a signal of $CDCl_3$), 80.1, 93.4, 96.1, 100.9, 101.0, 107.3, 107.9, 112.1, 119.4, 119.6, 119.9, 120.7, 122.0, 122.3, 122.8, 122.9, 123.6, 123.7, 126.8, 127.0, 127.2, 127.4, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.46, 128.47, 128.52, 128.6, 128.8, 128.9, 129.0, 129.16, 129.24, 129.6, 129.77, 129.80, 130.0, 130.09, 130.13, 130.4, 130.5, 131.4, 132.9, 133.0, 133.18, 133.23, 133.3, 133.9, 134.0, 134.3, 137.1, 137.2, 137.3, 137.79, 137.80, 137.82, 137.83, 138.7, 138.9, 145.4, 145.5, 152.3, 153.0 (2C), 153.4, 153.8, 154.7, 165.0, 166.0, 166.11, 166.14, 167.2, 167.3, 168.5, 168.6, 169.692, 169.694, 169.73, 169.8, 172.8, 173.0 ppm; IR (neat): $\tilde{\nu} = 3400$, 2930, 1760, 1740, 1720, 1660, 1600, 1580, 1570, 1550, 1500, 1450, 1360, 1340, 1260, 1240, 1220, 1160, 1100, 1070, 1050, 900, 810, 720, 710 cm^{-1}; elemental analysis calcd (%) for $C_{78}H_{76}ClNO_{22}$: C 66.21, H 5.41, N 0.99; found: C 65.97, H 5.18, N 0.69.

Anthraquinone ***79***: A solution of CAN (85.9 mg, 0.157 mmol) in water (0.19 mL) was added to a solution of **78** (106 mg, 0.0746 mmol) in CH_3CN (0.57 mL) at 0 °C. After stirring for 20 min at RT, a further solution of CAN (22.5 mg, 0.0411 mmol) in water (0.05 mL) was added and the reaction mixture was stirred for a further 10 min. The reaction was stopped by adding water and then the precipitates were collected by filtration to afford the chloroquinone as a red powder (79.7 mg). The filtrate was extracted with EtOAc (×3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. A solution of diene **21** (166 mg, 0.821 mmol) in THF (1.5 mL) was added to

a solution of the combined crude material (110 mg) at RT. After stirring for 30 min, the reaction was stopped by adding acidic silica gel and concentrated in vacuo. After standing for 14 h, the silica gel was placed on a glass filter, washed with EtOAc, and then the filtrate was concentrated in vacuo. K_2CO_3 (276 mg) was added to the solution of this crude material in CH_2Cl_2 (5.7 mL) and THF (1.9 mL) at RT. After stirring for 2 h at 40 °C, the reaction was stopped by adding 2 M aq. HCl and then the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/Et_2O/CH_3CN = 40:45:15 and $CHCl_3$/EtOAc = 8:2) to afford **79** as a yellow solid (71.7 mg, 66 %). Mixture of two conformers: diaxial/diequatorial = 75:25; m.p. 124–125 °C (Et_2O and hexane); $[\alpha]_D^{26} = +137$ ($c = 0.985$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, the minor conformer is indicated by an asterisk): $\delta =$ 1.13 (d, $J = 7.2$ Hz, 3H), 1.255* (d, $J = 7.3$ Hz, 3H), 1.259 (s, 3H), 1.35 (d, $J = 7.3$ Hz, 3H), 1.361* (d, $J = 7.2$ Hz, 3H), 1.51* (s, 3H), 1.63 (s, 3H), 1.77* (s, 3H), 1.97 (s, 3H), 2.02* (s, 3H), 2.35 (s, 3H), 2.49* (s, 3H), 3.33 (dd, $J = 6.3$, 12.4 Hz, 1H), 3.44* (dd, $J = 6.3$, 12.3 Hz, 1H), 3.68* (s, 3H), 3.75 (s, 3H), 3.88–3.93 (m, 1H), 3.89–3.94* (m, 1H), 3.94* (s, 3H), 3.97* (dd, $J = 1.0$, 11.0 Hz, 1H), 4.00 (s, 3H), 4.02 (dd, $J = 3.6$, 10.1 Hz, 1H), 4.05 (dd, $J = 4.3$, 12.4 Hz, 1H), 4.14* (dd, $J = 3.5$, 10.1 Hz, 1H), 4.16* (dd, $J = 4.3$, 12.3 Hz, 1H), 4.292* (d, $J = 11.1$ Hz, 1H), 4.293 (d, $J = 11.1$ Hz, 1H), 4.34 (d, $J = 11.5$ Hz, 1H), 4.43 (d, $J = 12.1$ Hz, 1H), 4.44* (d, $J = 11.7$ Hz, 1H), 4.466 (d, $J = 12.1$ Hz, 1H), 4.468 (dd, $J = 5.7$, 7.5 Hz, 1H), 4.470 (d, $J = 11.5$ Hz, 1H), 4.52* (d, $J = 12.1$ Hz, 1H), 4.55 (d, $J = 5.7$ Hz, 1H), 4.58 (qd, $J = 7.2$, 7.9 Hz, 1H), 4.605* (d, $J = 11.0$ Hz, 1H), 4.607 (d, $J = 3.0$ Hz, 1H), 4.64* (dq, $J = 7.2$, 7.3 Hz, 1H), 4.67 (d, $J = 8.0$ Hz, 1H), 4.66–4.76* (m, 3H), 4.68–4.72 (m, 1H), 4.75 (dd, $J = 7.5$, 7.5 Hz, 1H), 4.79* (d, $J = 11.7$ Hz, 1H), 4.83* (ddd, $J = 4.3$, 7.4, 12.3 Hz, 1H), 4.90* (dd, $J = 7.4$, 7.4 Hz, 1H), 5.00 (d, $J = 3.0$ Hz, 1H), 5.17* (d, $J = 11.1$ Hz, 1H), 5.20 (d, $J = 11.1$ Hz, 1H), 5.26* (d, $J = 8.0$ Hz, 1H), 5.28 (dd, $J = 8.0$, 10.1 Hz, 1H), 5.46 (d, $J = 7.9$ Hz, 1H; NH), 5.54 (d, $J = 3.6$ Hz, 1H), 5.62* (d, $J = 3.5$ Hz, 1H), 5.87* (dd, $J = 8.0$, 10.1 Hz, 1H), 6.27* (d, $J = 7.2$ Hz, 1H; NH), 6.69–6.87 (m, 2H), 6.98–7.17 (m, 9H), 7.18–7.43 (m, 1H), 7.43–7.69 (m, 4H), 7.56–8.02 (m, 2H), 8.12* (d, $J = 1.0$ Hz, 1H), 8.25 (d, $J = 7.2$ Hz, 1H), 12.7 (s, 1H; OH), 12.9 ppm* (s, 1H; OH); ^{13}C NMR (125 MHz, $CDCl_3$, without distinction of the two conformers): $\delta =$ 16.40, 16.42, 17.5, 18.0, 19.1, 19.5, 19.8, 20.2, 20.30, 20.34, 20.7, 20.8, 47.9, 48.4, 52.2, 52.3, 56.0, 56.1, 61.4, 61.5, 68.7, 68.8, 69.5, 69.7, 70.07, 70.11, 70.2, 70.3, 71.10, 71.11, 71.4, 72.1, 72.8, 73.1, 73.8, 74.4, 74.6, 76.9, 77.2, 77.26, 77.30 (overlapped by a signal of $CDCl_3$), 77.4, 77.5, 80.2, 98.5, 100.7, 101.1, 101.4, 105.8, 106.0, 107.1, 107.4, 110.4, 110.7, 118.3, 120.5, 121.7, 123.3, 125.2, 126.1, 127.3, 127.4, 127.5, 127.59, 127.61, 127.7, 127.8, 128.0, 128.1, 128.2, 128.31, 128.33, 128.4, 128.5, 128.6, 128.7, 128.9, 129.0, 129.5, 129.7, 129.8, 130.00, 130.1, 132.4, 132.89, 132.94, 133.2, 133.38, 133.43, 133.5, 134.5, 135.3, 136.1, 136.4, 136.5, 136.6, 136.8, 137.2, 137.3, 137.4, 138.0, 138.5, 139.1, 139.9, 140.0, 144.2, 153.0, 154.9, 156.6, 158.6, 163.7, 164.6, 164.89, 164.91, 166.1, 166.2, 166.50, 166.52, 167.0, 168.4, 168.7, 169.6, 169.7, 169.8, 172.86, 172.92, 180.6, 181.1, 185.5, 185.9 ppm; IR (neat): $\tilde{\nu} =$ 3400, 2940, 1730, 1660, 1620, 1600, 1580, 1540, 1500, 1450, 1360, 1310, 1300, 1260, 1220, 1160, 1100, 1060, 1020, 910, 880, 720, 700 cm^{-1}; elemental analysis calcd (%) for $C_{81}H_{75}NO_{24}$: C 67.26, H 5.23, N 0.97; found: C 67.19, H 5.12, N 0.80.

*Benanomicin A (**2a**)*: 5 % Pd/C (39.7 mg) was added to a solution of **79** (30.0 mg, 0.0207 mmol) in MeOH (2.25 mL) and DMF (0.75 mL). After stirring under H_2 (1 atm) at RT for 50 min, the reaction mixture was filtered though a Hyflo Super-Cel pad (washed with $CHCl_3$/MeOH = 9:1) and concentrated in vacuo. The residue was purified by PTLC ($CHCl_3$/MeOH = 95:5) to afford the corresponding tetrol (20.4 mg) as a red amorphous solid. A 5 M aq. NaOH solution (0.23 mL) was added to the solution of this crude material in H_2O (2.3 mL) at 0 °C. After stirring for 15 h at RT, the reaction was stopped by adding 2 M aq. HCl (pH 3.5) and the mixture concentrated in vacuo. The residue was purified by Diaion HP-20 (H_2O/MeOH = 1:0 to 0:1, gradient elution) to give red precipitates which were further purified by Sephadex LH-20 (DMF) (twice) to afford a red amorphous solid. The product was dissolved in DMSO (40 μL) and then $CHCl_3$ was added. The precipitate was collected by filtration and dried in vacuo at 50 °C for 2 days to afford benanomicin A as a red amorphous powder (11.6 mg, 68 %). M.p. 242–244 °C (decomp) (lit.:[1b] > 220 °C); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 313 K): $\delta = 1.03$ (d, $J =$ 6.3 Hz, 3H), 1.36 (d, $J = 7.3$ Hz, 3H), 2.32 (s, 3H), 2.91–3.38 (m, 6H), 3.27 (s, 3H), 3.60 (dd, $J = 5.2$, 11.3 Hz, 1H), 3.96 (s, 3H), 4.06 (dd, $J = 7.1$, 9.6 Hz, 1H), 4.44 (d, $J = 7.1$ Hz, 1H), 4.45 (q, $J = 6.7$ Hz, 1H), 4.55 (d, $J =$ 10.0 Hz, 1H), 4.63 (d, $J = 10.0$ Hz, 1H), 4.72 (d, $J = 7.7$ Hz, 1H), 4.78 (dd, $J = 2.9$, 7.0 Hz, 1H), 6.91 (d, $J = 2.5$ Hz, 1H), 7.11 (br, 1H), 7.32 (d, $J =$ 2.5 Hz, 1H), 7.94 (br, 1H), 8.11 (br, 1H), 8.18 (br, 1H), 12.82 ppm (s, 1H); ^{13}C NMR (500 MHz, [D$_6$]DMSO, 313 K): $\delta = 16.3$, 16.9, 19.1, 47.7, 56.4, 65.6, 69.5, 70.1, 70.4, 71.9, 70.4, 71.9, 73.7, 76.1, 81.6, 83.0, 104.5, 105.3, 106.9, 107.6, 110.1, 113.6, 115.6, 125.6, 127.5, 131.3, 134.3, 137.4, 138.1, 147.9, 151.1, 156.9, 164.7, 166.0, 166.9, 173.0, 174.0, 185.0, 187.5) ppm (signals for four sp^2 carbon atoms were not detected presumably owing to peak-broadening ascribed to the slow conformational interconversion, diaxial→diequatorial; IR (KBr): $\tilde{\nu} =$ 3420, 2980, 2940, 1720, 1620, 1520, 1450, 1390, 1340, 1300, 1260, 1210, 1190, 1160, 1130, 1070, 1050, 1000, 980, 900, 860, 800, 750, 660 cm^{-1}; LRMS (MALDI-TOF, DHBA matrix): m/z: calcd for $C_{39}H_{41}O_{19}NNa$ ([M+Na]$^+$): 850.2; found: 850.2; HRMS (FAB): m/z: calcd for $C_{39}H_{41}O_{19}NNa$ ([M+Na]$^+$): 850.2170; found: 850.2162.

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[28] The enantiomeric purity of the biaryl dialdehyde **39** was assessed by HPLC analysis (DAICEL CHIRALCEL OD-H (0.46 cm $\varphi\times25$ cm), hexane/*i*PrOH = 9:1, flow rate = 0.7 mL min^{-1}, t_R = 18.2 min for the *M* isomer, 26.4 min for the *P* isomer).

[29] The enantiomeric purity of diol **40** was assessed by HPLC analysis (DAICEL CHIRALCEL OD-H (0.46 cm $\varphi\times25$ cm), hexane/*i*PrOH = 9:1, flow rate = 1.0 mL min^{-1}, t_R = 10.9 min for the *R*,*R* isomer, 15.0 min for *S*,*S* isomer).

[30] The same conversion was applied to the racemate of **38**. Sample **46**, thus obtained, showed additional ^{1}H NMR peaks that could be assigned to the 5,6-bis-epimer (relative to the D-alanine moiety).

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[39] Acyl rearrangement was very slow in the absence of valinol.

[40] The relative axial stereochemistry was determined by X-ray crystallographic analysis. CCDC-262629 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[46] The enantiomeric purity of **60** was analyzed by HPLC analysis [DAICEL CHIRALPAK AD-H (0.46 cm $\varphi \times 25$ cm), hexane/EtOH = 8:2, flow rate = 1.0 mL min^{-1}, t_R = 6.6 min for the *S*,*S* isomer, 9.3 min for the *R*,*R* isomer].
[47] The relative stereochemistry of the two stereogenic centers at the B ring was determined by X-ray crystallographic analysis. CCDC-622146 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[48] The lowest temperature for activation of the glycosyl fluoride was −36 °C, and **68** underwent decomposition with an excess of Cp_2HfCl_2 (e.g., 1.2 equiv) and $AgClO_4$ (e.g., 2.4 equiv).
[49] DMF was necessary for the completion of this step as the intermediates were insoluble in MeOH. When only DMF was used as the solvent, the reaction did not go to completion.
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[57] For the preparation of glycosyl donor **80**, see the Supporting Information.

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