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Actinorhodins

Synthetic Studies on Actinorhodin and γ-Actinorhodin: Synthesis of Deoxyactinorhodin and Deoxy-γ-actinorhodin/Crisamicin A Isomer

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Abstract: A strategy based on bidirectional Dötz benzannulation and the oxa-Pictet–Spengler reaction toward the synthesis of actinorhodin and γ-actinorhodin has been explored. This work has resulted in the synthesis of deoxyactinorhodin and deoxy-γ-actinorhodin. The latter is a regioisomer of crisamicin A (which has 10,10′-dihydroxy groups).

Introduction

The soil-dwelling bacteria *Streptomyces coelicolor*[1–3] produces a red pigment that shows litmuslike properties, bright blue in alkaline and red in acid media. The red pigment structure was assigned by means of extensive chemical degradation[4] and mass spectrometry[5] to be the dimeric pyranonaphthoquinone known as actinorhodin **1** (Figure 1). The other congeners of **1** have been isolated from the same culture of bacteria[6,7] including γ-actinorhodin **2**. ^{1}H and ^{13}C NMR spectroscopic studies[5,7] showed that **1** and **2** are dimeric with two similar halves joined in a symmetrical C8–C8′ linkage. The dihydropyran ring contains a quasi-axial methyl group at C1, which is *trans* to an equatorial acetic acid side chain at C3 that is able to participate in γ-lactone formation thorough a quinone–methide intermediate. The absolute configuration of stereogenic centers of **1** (1*R*,1′*R*,3*S*,3′*S*) were confirmed by comparison of the optical rotary dispersion (ORD) curves of triacid (obtained from the oxidative degradation of actinorhodin diethyl ester with alkaline H_2O_2) with that of (+)-(*S*)-lactic acid.[4b,c] Actinorhodin **1** shows activity against the *Staphylococcus aureus*[2] bacteria found in the human respiratory tract and on the skin. Crisamicin A (**3**) was isolated from *Micromonospora purpureochromogenes*[8] and shows activity against B16 murine melanoma cells, herpes simplex, and vesicular stomatitis viruses.[9] A closely related compound GTRI-BB (**4**)[10] has shown very promising anticancer activities, such as renal (ACHN; $IC_{50}=0.08\ \mu g\,mL^{-1}$), colon (SW 620; $IC_{50}=0.11\ \mu g\,mL^{-1}$), and melanoma (UACC 62; $IC_{50}=0.08\ \mu g\,mL^{-1}$). The inhibitory effect is much higher than adriamycin (a commercial anticancer drug). This indicates that a structure–activity relationship (SAR) study might enhance the cytotoxic efficacy of these compounds. Whereas the syntheses of monomeric pyranonaphthoquinones and hemi-**1** and **2** are well documented,[11] the total synthesis of **1** and **2** is yet to be achieved. The first synthetic attempt toward *ent*-**1** was reported by Laatsch[12] from a degradation product of the antibacterial metabolite α-naphthocyclinone. Brimble and co-workers[13] have reported the synthesis of analogues of **1** and **3**. A racemic synthesis of crisamicin A (**3**) was elegantly achieved by Wang and co-workers[14] by homocoupling of monomer units. In our efforts toward the synthesis of pyranonapthoquinones and related compounds,[11g–m,15] we observed that the sequence of Dötz benzannulation[16] and oxa-Pictet–Spengler[17] reaction enables the rapid construction of the pyranonaphthoquinone framework. Recently we adopted a bidirectional strategy for the synthesis of (+)-demethoxycardinalin 3.[15] Herein we wish to

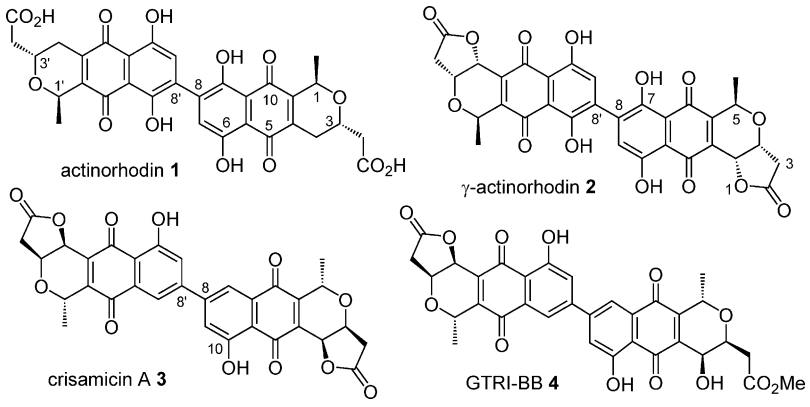

Figure 1. Some dimeric pyranonaphthoquinones.

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report our bidirectional synthetic studies on the dimeric pyrananaphthoquinones **1** and **2** based on Dötz benzannulation and oxa-Pictet–Spengler reactions.

Results and Discussion

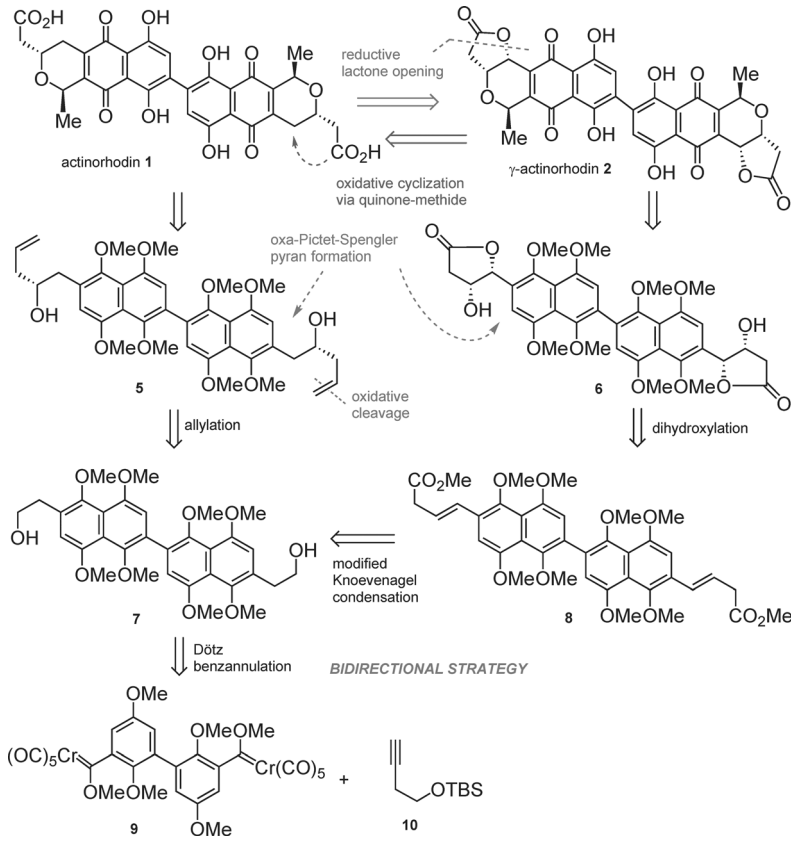
Our bidirectional retrosynthetic strategy is depicted in Scheme 1. Both **1** and **2** could be traced to the common intermediate diol **7**. Actinorhodin **1** can be traced from **7** through a sequence of allylation, pyran formation, and terminal double-bond cleavage. A modified Knoevenagel condensation on the aldehyde from **7** would lead to ester **8**. Subsequent dihydroxylation and pyran formation would give **2**. By biomimicking the viability of **1** to **2** conversion chemically (oxidative cyclization) and vice versa (reductive lactone opening), we could adopt either a route to **1** or **2** and their interconversion. The interconversion, although unknown for the dimeric compounds, is quite feasible for the monomeric molecules.[11k,18] Diol **7** seemed easily possible through the Dötz benzannulation of dimeric Fischer carbene **9** with alkyne **10**.

To synthesize dimeric Fischer carbene **9**, we needed the requisite dibromobiaryl compound **11a** (Scheme 2). Commercially available 4-methoxyphenol was converted to **11a** in two steps.[19] The biaryl phenol **11a** was methylated to **12** (94%; Scheme 2). Fischer carbene **9** was prepared from **12** and condensed with alkyne **10** in a bidirectional Dötz benzannulation reaction to afford **13** (70%). The protection of phenolic OH (**14**, 86%) and subsequent *tert*-butyldimethylsilyl(TBS) removal gave dimeric diol **7** in good yields (93%). Further 2-iodoxybenzoic acid (IBX) oxidation gave the dialdehyde in moderate yield (60%). The oxidation conditions by Piancatelli et al.[20] with a catalytic amount of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) in the presence of [bis(acetoxy)iodo]benzene delivered the dialdehyde in good yield, and subsequent allylation gave **5** in 85% yield from **7**. The oxa-Pictet–Spengler reaction has worked well to construct the pyran ring for the monomeric molecules.[11g,h,k–m,15] However, under similar conditions, compound **5** failed to provide pyran **15**. We employed various Lewis acids such as $BF_3{\cdot}OEt_2$, $TiCl_4$, trimethylsilyl trifluoromethanesulfonate (TMSOTf), and $ZnCl_2$, or changed solvents and temperature conditions, but with no success. We believe the highly oxygenated aryl ring has the Lewis acid coordinated to the methoxy groups. Carrying out the reaction by bubbling dry HCl gas[15] through a solution of **5** in ether as well as acetaldehyde dimethylacetal also failed to yield the pyran product **15**.

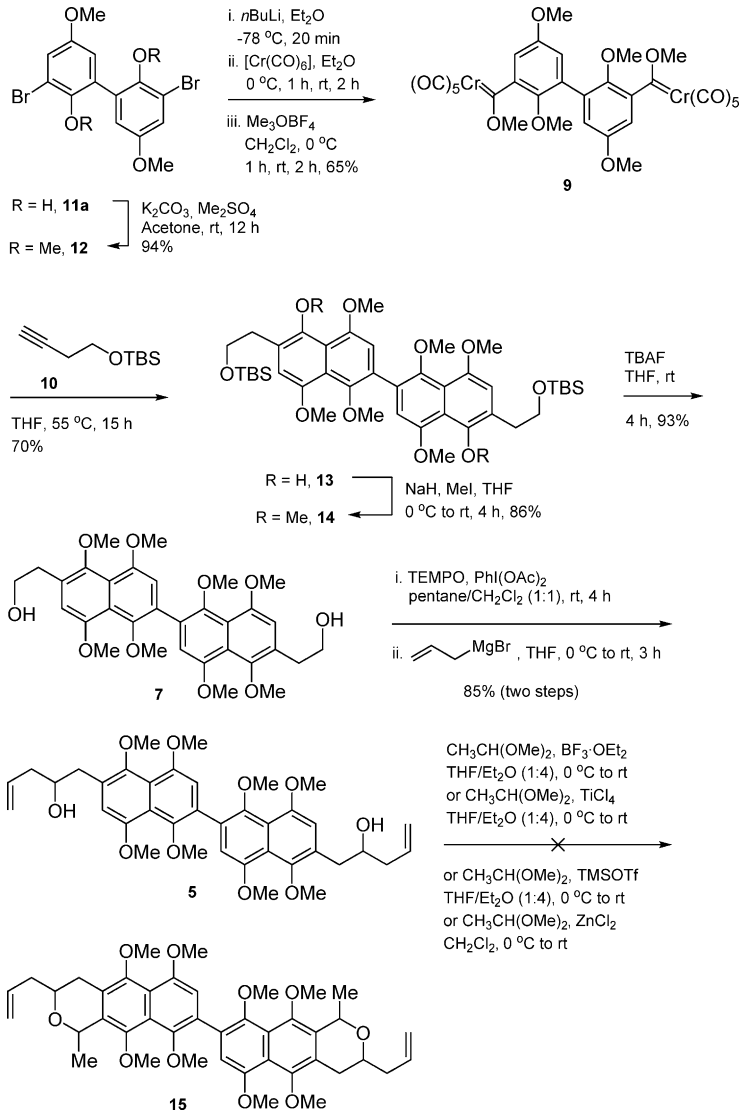
We next planned to use a different alkyne **17** (Scheme 3) in Dötz benzannulation to deliver **16**. The latter through an oxa-Pictet-Spengler reaction would lead to **1** and then to **2**.

The Dötz benzannulation of **9** with alkyne **17**[21] delivered bisnaphthol **18** in 52% yield (Scheme 4). The protection of phenolic OH (**19**, 88%) and subsequent TBS removal gave diol **16** in excellent yield (96%). The oxa-Pictet–Spengler reaction on **16** delivered the inseparable mixture of *syn*/*anti*-pyran products **20**. This mixture was subjected to cerium(IV) ammonium nitrate (CAN) oxidation. However, it gave a complex mixture. We also tried other conditions using Ag_2O, phenyliodine bis(trifluoroacetate) (PIFA), and CrO_3. In all cases either the starting material decomposed or it delivered regioisomeric and differently oxidized inseparable quinone mixtures, which could be due to multiple 1,4-dimethoxy aryl units present and/or possible quinone isomerizations.

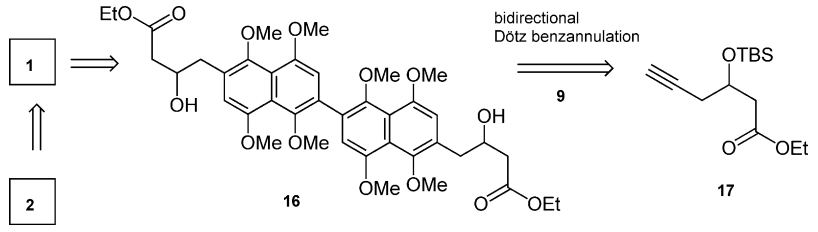
As illustrated in Scheme 1, we moved our attention toward γ-actinorhodin **2** synthesis as this in turn can be converted into **1** through reductive lactone opening. The reaction of dialdehyde from **7** with half ester of malonic acid under decarboxylative deconjugative Knoevenagel condensation[22] delivered the mixture (63%) of desired β,γ-unsaturated ester **8** along with a trace amount of α,β-unsaturated isomer (Scheme 5). Upon dihydroxylation[23] the mixture gave the bis-γ-lactones **6** (70%) as a single diastereomer (*ee* not determined). Lactone **6** has the



Scheme 1. Retrosynthesis of actinorhodin **1** and γ-actinorhodin **2**.



Scheme 2. Attempted synthesis of compound **15**.

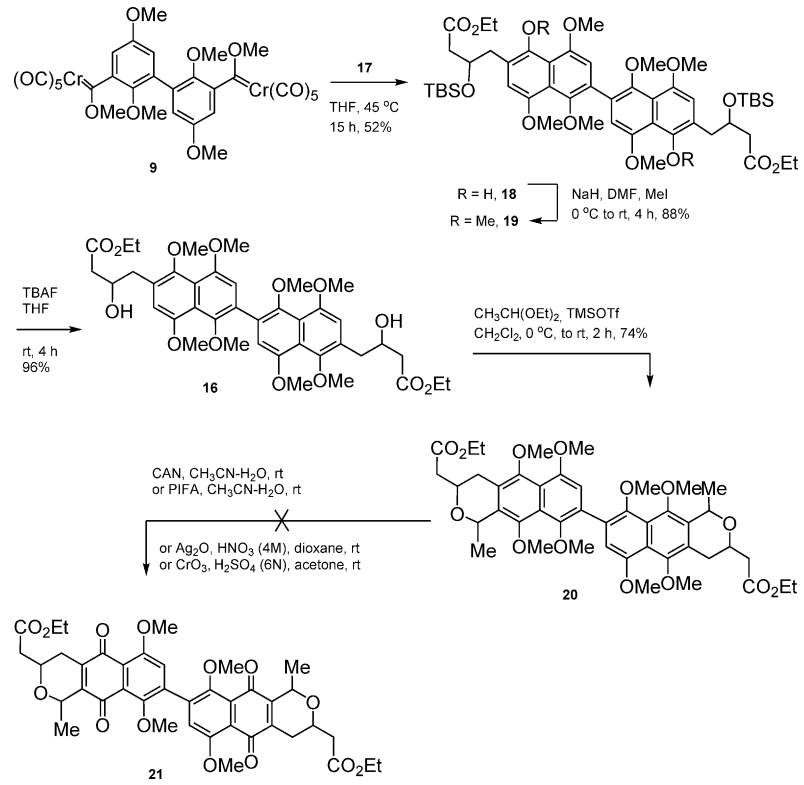


Scheme 3. Revised plan for **1** and **2**.

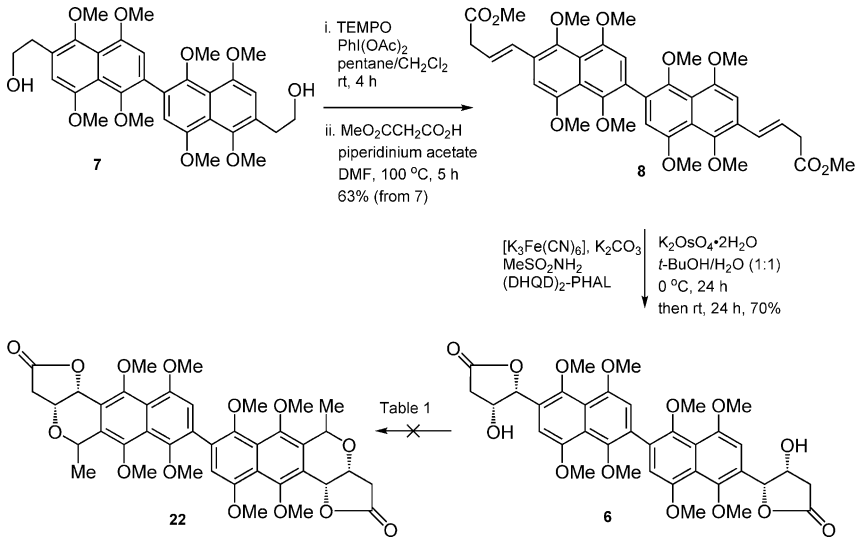
desired skeletal structure for **2**, minus the pyran rings. All attempts to construct the pyran ring on compound **6** using various Lewis acids similar to that used on compound **5** by means of oxa-Pictet–Spengler reaction failed to deliver product **22** (Table 1). In most cases, decomposition of **6** was observed. We also attempted the oxa-Pictet–Spengler reaction in a preheated (80 °C) mixture of $BF_3{\cdot}OEt_2$ (10 equiv) in trifluoroacetic acid (TFA) solvent and then addition of **6** (in THF) followed by $(CH_3O)_2CHCH_3$ (6.0 equiv). These conditions worked well to directly deliver the *anti*-pyran product in our arizonin C1 synthesis.[11m] However, compound **6** decomposed under these conditions (Table 1, entry 7).

We next considered lowering the number of methoxy groups on the biaryl system with the aim of investigating both the oxa-Pictet–Spengler reaction and the difficulty associated with quinone formation. Although this means analogue synthesis, the envisioned targets would have the skeletal structures of **1** and **2** with the quinone, pyran, and lactone installed. The freshly prepared Fischer carbene **23**[15] on bidirectional Dötz benzannulation reaction with alkyne **10** gave **24** (66%; Scheme 6). The protection of phenolic OH (**25**, 86%) and subsequent TBS removal afforded **26** in good yield (93%). The oxidation of **26** to dialdehyde and modified Knoevenagel condensation delivered the mixture (63%) of desired β,γ-unsaturated ester **27** along with trace amounts of α,β-unsaturated isomer. Upon dihydroxylation the mixture gave the bis-γ-lactone **28** in 70% yield as a single diastereomer (*ee* not determined). Unfortunately, all our attempts to construct the pyran ring on **28** using various Lewis acids (similar to that used in Table 1 for bis-lactone **6**) failed to deliver pyran **29**. It is surprising that on monomer molecules these reactions worked well in our laboratory.[11k]

We further considered the bidirectional Dötz benzannulation of Fischer carbene **23** with alkyne **17**. This reaction gave bisnaphthol **30** in 63% yield (Scheme 7). The protection of free phenolic OH to **31** (88%) and subsequent TBS removal afforded **32** in excellent yields (96%). The oxa-Pictet–Spengler reaction of **32** using $BF_3{\cdot}OEt_2$ gave a complex mixture, whereas the same reaction catalyzed by TMSOTf to our delight afforded the inseparable mixture of pyran diastereomers **33** (81%). The mixture was subjected to CAN oxidation to provide separable quinones **34** and **35** (one pyran ring with *syn*-methyl and the other *anti* to the C3 substituent) in 62 and 18% isolated yields, respectively.[24] The separated quinone **34** on treatment with $AlCl_3$ gave compound **36** (79%). The undesired **35** was converted into **36** by treatment with $AlCl_3$ and then H_2SO_4-mediated epimerization. Compound **36** represents the diethyl ester of deoxyactinorhodin with pyran and quinone installed. Various bases were screened for the hydrolysis of ester **36** to liberate the diacid. However, the acid isolation failed in our hands. Hence the crude acid was stirred in an open flask in MeOH to deliver **37** through a quinone–methide intermediate[18] in 34% isolated



Scheme 4. Attempted synthesis of **21** using alkyne **17**.



Scheme 5. Attempted synthesis of pyranolactone **22**.

yield. Thus the biomimetic conversion of acid to lactone through the quinone–methide intermediate known for monomeric molecules worked well for the diacid here. This completed the synthesis of deoxy-γ-actinorhodin **37**, which is also an isomer of crisamicin A with differently placed hydroxyl groups (see crisamicin A; Figure 1).

Conclusion

We have efficiently utilized the bidirectional approach through Dötz benzannulation and oxa-Pictet–Spengler reaction to achieve the synthesis of deoxyactinorhodin and deoxy-γ-actinorhodin. The latter is an isomer of crisamicin A. Efforts are still underway in our laboratory to achieve target molecules **1** and **2**.

Experimental Section

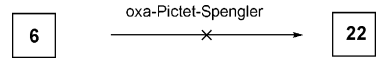
General information

Flasks were oven- or flame-dried and cooled in a desiccator. Dry reactions were carried out under an atmosphere of Ar or N_2. Solvents and reagents were purified by standard methods. Thin-layer chromatography was performed using EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by using a UV lamp. ^1H and ^{13}C NMR spectra were recorded at 400 or 500 and 100 or 125 MHz, respectively, and chemical shifts are based on the TMS peak at $\delta = 0.00$ ppm for proton NMR spectroscopy and the $CDCl_3$ peak at $\delta = 77.00$ ppm (t) for carbon NMR spectroscopy. IR samples were prepared by evaporation from $CHCl_3$ on CsBr plates. High-resolution mass spectra were obtained using positive electrospray ionization.

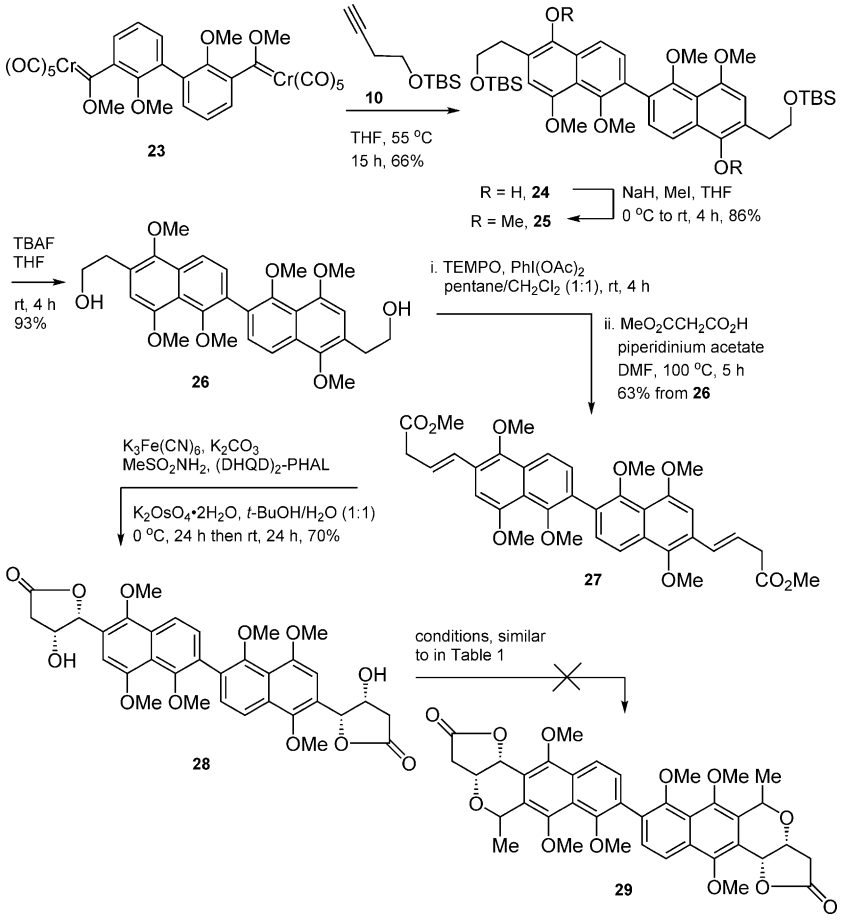
Synthesis

3,3′-Dibromo-2,2′,5,5′-tetramethoxybiphenyl (12): Anhydrous K_2CO_3 (2.05 g, 14.85 mmol, 3.0 equiv) was added to a stirred solution of **11a** (2.0 g, 4.95 mmol) in dry acetone (40 mL) and stirred at room temperature for 10 min. Dimethylsulfate (1.56 g, 12.4 mmol, 2.5 equiv) was added, and the reaction mixture was stirred for 12 h at the same temperature. It was then quenched with water (20 mL), and acetone was evaporated at reduced pressure. EtOAc (40 mL) was added, and the separated aqueous layer was extracted with EtOAc (2×40 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (19:1 to 9:1) as eluent to afford **12** (2.01 g, 94%) as a colorless solid. M.p. 99–100 °C; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 3.53$ (s, 6H), 3.79 (s, 6H),

Table 1. The oxa-Pictet–Spengler reaction of bislactone **6**.



Entry	Reaction conditions	Results
1	$(CH_3O)_2CHCH_3$ (4.0 equiv), $BF_3{\cdot}OEt_2$ (4.0 equiv), CH_2Cl_2, 0 °C to RT, 12 h	decomposed
2	$(CH_3O)_2CHCH_3$ (4.0 equiv), $BF_3{\cdot}OEt_2$ (6.0 equiv), THF/Et_2O (1:4), 0 °C to RT, 36 h	decomposed
3	$(CH_3O)_2CHCH_3$ (3.0 equiv), $BF_3{\cdot}OEt_2$ (4.0 equiv), THF/Et_2O (1:4), 0 °C, 24 h	decomposed
4	$(CH_3O)_2CHCH_3$ (4.0 equiv), TMSOTf (4.0 equiv), CH_2Cl_2, 0 °C to RT, 12 h	complex mixture
5	$(CH_3O)_2CHCH_3$ (4.0 equiv), $TiCl_4$ (4.0 equiv), CH_2Cl_2, 0 °C to RT, 10 h	complex mixture
6	$(CH_3O)_2CHCH_3$ (6.0 equiv), HCl gas, Et_2O, RT, 12 h	decomposed
7	preheated mixture of $BF_3{\cdot}OEt_2$ (10.0 equiv) in TFA, then addition of **6** and $(CH_3O)_2CHCH_3$ (6.0 equiv), 1 min	decomposed



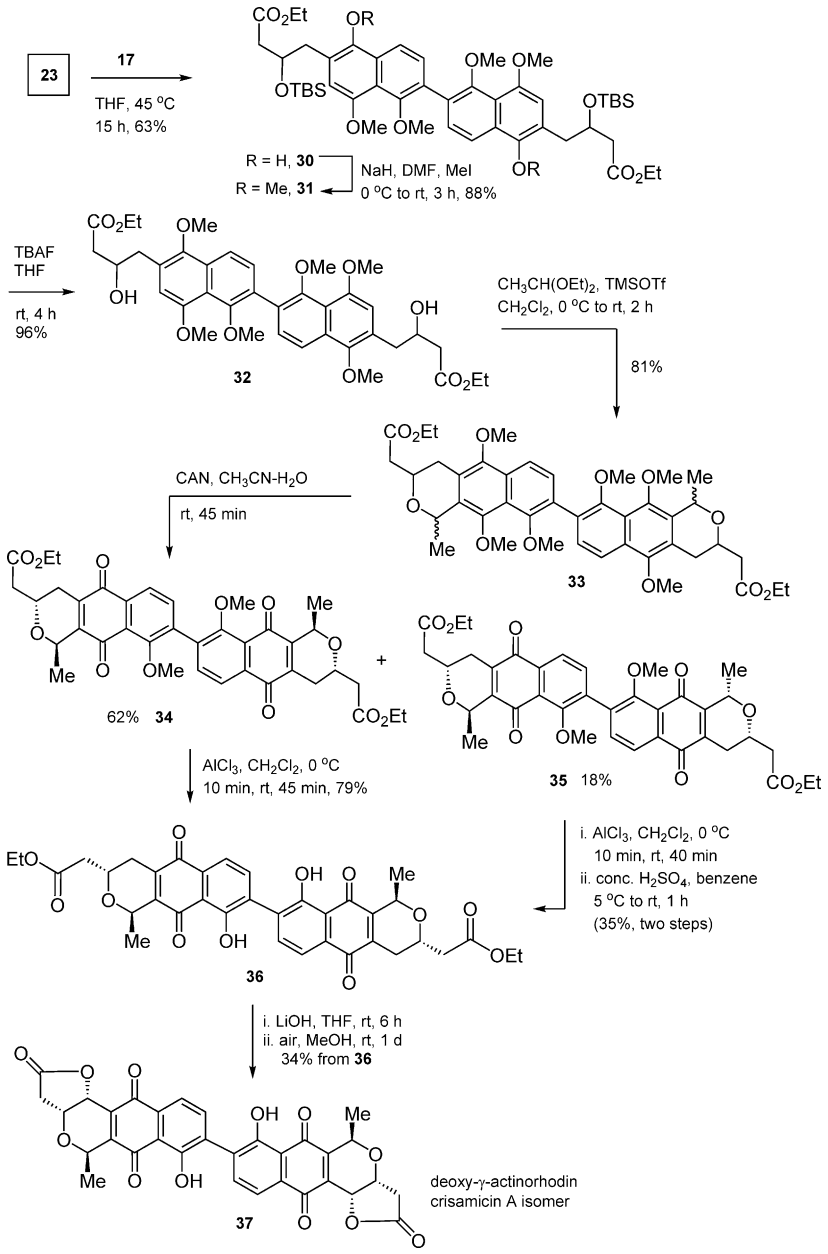
Scheme 6. Attempted synthesis of pyranolactone **29**.

6.84 (d, $J=3.0$ Hz, 2H), 7.14 ppm (d, $J=3.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=55.8$, 60.9, 115.9, 117.7, 118.3, 133.0, 148.3, 155.5 ppm; IR (KBr): $\tilde{\nu}=3072$, 3001, 2941, 2835, 1600, 1567, 1480, 1443, 1424, 1407, 1333, 1285, 1224, 1179, 1123, 1038, 1002, 949, 869, 855, 846, 807, 780, 770, 733, 720, 677, 625, 607 cm^{-1}; HRMS: *m/z* calcd for $[C_{16}H_{16}O_4Br_2+H]^+$: 430.9494; found: 430.9492.

Fischer carbene (9): *n*BuLi (3.2 mL, 5.1 mmol, 2.2 equiv, 1.6 M solution in hexane) was added to a solution of **12** (1.0 g, 2.31 mmol) in dry Et_2O (25 mL) at −78 °C, and the reaction mixture was stirred for 20 min. It was then transferred to a suspension of $[Cr(CO)_6]$ (1.12 g, 5.1 mmol, 2.2 equiv) in dry Et_2O (25 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then at room temperature for 2 h. Et_2O was evaporated and the residue was dissolved in dry CH_2Cl_2 (30 mL). Me_3OBF_4 (1.03 g, 6.93 mmol, 3.0 equiv) was added to this solution in one portion at 0 °C, and the reaction mixture was stirred for 1 h. It was warmed to room temperature and stirred for 2 h. The red reaction mixture was concentrated, and the residue was purified by silica gel column chromatography using petroleum ether/CH_2Cl_2 (9:1 to 3:1) as eluent to give **9** (1.12 g, 65%) as a red solid. This was immediately used in the next step.

6,6′-Bis[2-(*tert*-butyldimethylsilyloxy)ethyl]-1,1′,4,4′,8,8′-hexamethoxy-2,2′-binaphthyl-5,5′-diol (13): Alkyne **10** (1.11 g, 6.04 mmol, 4.0 equiv) in dry and degassed THF (5 mL) was added to a solution of freshly prepared Fischer carbene **9** (1.12 g, 1.51 mmol) in dry and degassed THF (15 mL). The reaction mixture was heated at 55 °C for 15 h and then allowed to cool to room temperature. It was then exposed to air and stirred for 1 h. THF was removed, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to afford **13** (0.83 g, 70%) as an orange solid. M.p. 146–147 °C; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta=$ 0.04 (s, 12H), 0.90 (s, 18H), 3.00 (t, $J=7.1$ Hz, 4H), 3.51 (s, 6H), 3.90 (t, $J=7.4$ Hz, 4H), 3.94 (s, 6H), 4.02 (s, 6H), 6.86 (s, 2H), 7.03 (s, 2H), 9.60 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.3$, 18.4, 26.0, 34.3, 56.8, 57.1, 61.3, 62.8, 109.0, 112.7, 116.9, 120.3, 121.2, 127.4, 145.9, 148.1, 148.2, 151.2 ppm; IR (KBr): $\tilde{\nu}=3384$, 2953, 2929, 2856, 1655, 1615, 1519, 1465, 1450, 1419, 1385, 1253, 1221, 1076, 1007, 927, 837, 777, 667 cm^{-1}; HRMS: *m/z* calcd for $[C_{42}H_{62}O_{10}Si_2+H]^+$: 783.3960; found: 783.3959.

[1,1′,4,4′,5,5′,8,8′-Octamethoxy-(2,2′-binaphthalene)-6,6′-diyl]bis-(ethane-2,1-diyl)bis(oxy)bis(*tert*-butyldimethylsilane) (14): NaH (0.046 g, 1.92 mmol, 3.0 equiv) was added to a solution of **13** (0.50 g, 0.64 mmol) in dry THF (15 mL) at 0 °C and was stirred for 30 min. MeI (0.16 mL, 2.56 mmol, 4.0 equiv) was added, and the reaction mixture was stirred for 4 h at room temperature. Ice-cooled water was added, and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated.



Scheme 7. Synthesis of deoxyactinorhodin and deoxy-γ-actinorhodin/crisamicin A isomer.

The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 3:2) as eluent to give **14** (0.445 g, 86%) as a yellow solid. M.p. 116–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 0.06$ (s, 12H), 0.91 (s, 18H), 3.04 (t, $J =$ 7.1 Hz, 4H), 3.53 (s, 6H), 3.81 (s, 6H), 3.94 (t, $J = 7.2$ Hz, 4H), 3.95 (s, 6H), 3.96 (s, 6H), 6.85 (s, 2H), 7.07 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.3$, 18.4, 26.0, 34.1, 56.7, 56.8, 61.5, 62.5, 63.9, 110.2, 110.9, 122.1, 122.5, 128.6, 129.0, 147.5, 148.0, 151.0, 152.2 ppm; IR (KBr): $\tilde{\nu} = 2954$, 2930, 2857, 1591, 1491, 1462, 1435, 1365, 1344, 1320, 1279, 1240, 1192, 1153, 1084, 1063, 1045, 989, 937, 833, 774, 739, 672 cm^{-1}; HRMS: *m/z* calcd for $[C_{44}H_{66}O_{10}Si_2+H]^+$: 811.4273; found: 811.4281.

2,2′-(1,1′,4,4′,5,5′,8,8′-Octamethoxy-2,2′-binaphthyl-6,6′-diyl)diethanol (7): Tetra-*n*-butylammonium fluoride (TBAF; 0.87 mL, 0.865 mmol, 2.5 equiv, 1 M solution in THF) was added to a solution of **14** (0.28 g, 0.346 mmol) in dry THF (15 mL) at room temperature, and the mixture was stirred for 4 h. It was then quenched with water (5 mL) and stirred for 30 min. THF was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:1 to 1:1) as eluent to give **7** (0.187 g, 93%) as a yellow solid. M.p. 213–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 2.09$ (s, 2H; OH), 3.08 (t, $J = 6.4$ Hz, 4H), 3.54 (s, 6H), 3.83 (s, 6H), 3.96 (s, 6H), 3.97 (s, 6H), 3.97 (t, $J = 6.4$ Hz, 4H), 6.79 (s, 2H), 7.08 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.1$, 56.8, 56.9, 61.7, 62.4, 63.5, 109.7, 111.1, 122.3, 122.6, 128.7, 128.8, 147.6, 148.0, 151.1, 152.7 ppm; IR (KBr): $\tilde{\nu} = 3512$, 2925, 2874, 2831, 1596, 1492, 1452, 1368, 1347, 1243, 1197, 1147, 1079, 1058, 1021, 989, 834, 741, 678 cm^{-1}; HRMS: *m/z* calcd for $[C_{32}H_{38}O_{10}+H]^+$: 583.2543; found: 583.2540.

1,1′-(1,1′,4,4′,5,5′,8,8′-Octamethoxy-2,2′-binaphthyl-6,6′-diyl)dipent-4-en-2-ol (5): $PhI(OAc)_2$ (0.139 g, 0.43 mmol, 2.5 equiv) and TEMPO (5.5 mg, 0.035 mmol, 0.2 equiv) were added to a solution of **7** (0.10 g, 0.172 mmol) in pentane/CH_2Cl_2 (1:1, 8.0 mL) at room temperature. The resulting mixture was stirred for 4 h at the same temperature. It was then diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (4×10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine, dried (Na_2SO_4), and concentrated. The dialdehyde (99.3 mg) obtained was immediately used in the next step.

Allyl magnesium bromide (0.22 mL, 0.43 mmol, 2.5 equiv, 2 M solution in THF) was added to a stirred solution of the above dialdehyde (99.3 mg) in dry THF (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous NH_4Cl (2 mL). The aqueous layer was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1 to 1:1) as eluent to afford **5** (97 mg, 85% from **7**) as a yellow solid. M.p. 168–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta =$ 2.30–2.44 (m, 4H), 2.92 (dd, $J = 13.5$, 8.1 Hz, 2H), 3.03 (dd, $J = 13.5$, 4.2 Hz, 2H), 3.55 (s, 6H), 3.82 (s, 6H), 3.96 (s, 6H), 3.97 (s, 6H),

4.06–4.09 (m, 2H), 5.16–5.22 (m, 4H), 5.88–5.98 (m, 2H), 6.79 (s, 2H), 7.09 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.1, 41.8, 56.7, 56.8, 61.5, 62.2, 71.6, 110.0, 111.2, 117.8, 122.3, 122.5, 128.5, 128.8, 135.0, 147.5, 147.9, 151.0, 152.5 ppm; IR (KBr): $\tilde{\nu}$ = 3454, 3073, 2930, 2836, 1638, 1602, 1495, 1455, 1385, 1365, 1347, 1243, 1195, 1109, 1080, 1049, 1021, 990, 913, 874, 825, 745, 618 cm^{-1}; HRMS: *m/z* calcd for $[C_{38}H_{46}O_{10}+H]^+$: 663.3169; found: 663.3172.

Diethyl 4,4′-[5,5′-dihydroxy-1,1′,4,4′,8,8′-hexamethoxy-(2,2′-binaphthalene)-6,6′-diyl]bis(3-*tert*-butyldimethylsilyloxy)butanoate (18): Alkyne **17** (0.73 g, 2.7 mmol, 4.0 equiv) in dry and degassed THF (5 mL) was added to a solution of freshly prepared Fischer carbene **9** (0.5 g, 0.673 mmol) in dry and degassed THF (10 mL). The reaction mixture was heated at 45 °C for 15 h and then allowed to cool to room temperature. It was exposed to air and stirred for 1 h. THF was removed under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to afford **18** (0.353 g, 52%) as an orange solid. M.p. 173–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.03 (s, 6H), 0.07 (s, 6H), 0.88 (s, 18H), 1.24 (t, *J* = 7.1 Hz, 6H), 2.44–2.52 (m, 4H), 2.86 (dd, *J* = 13.0, 7.4 Hz, 2H), 3.10 (dd, *J* = 13.0, 5.6 Hz, 2H), 3.52 (s, 6H), 3.94 (s, 6H), 4.03 (s, 6H), 4.06–4.13 (m, 4H), 4.57–4.62 (m, 2H), 6.80 (s, 2H), 7.03 (s, 2H), 9.60 ppm (s, 2H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.1, −4.6, 14.2, 17.9, 25.8, 39.0, 42.4, 56.8, 57.2, 60.2, 61.3, 69.2, 109.1, 113.1, 116.9, 119.4, 121.4, 127.6, 146.3, 148.1, 148.2, 151.2, 172.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3391, 2954, 2930, 2856, 1732, 1612, 1463, 1449, 1412, 1366, 1311, 1251, 1229, 1197, 1149, 1076, 1045, 1005, 962, 838, 812, 667 cm^{-1}; HRMS: *m/z* calcd for $[C_{50}H_{74}O_{14}Si_2+Na]^+$: 977.4509; found: 977.4509.

Diethyl 4,4′-[1,1′,4,4′,5,5′,8,8′-octamethoxy-(2,2′-binaphthalene)-6,6′-diyl]bis(3-*tert*-butyldimethylsilyloxy)butanoate (19): NaH (24 mg, 1.0 mmol, 3.0 equiv) was added to a solution of **18** (0.32 g, 0.335 mmol) in dry DMF (10 mL) at 0 °C and stirred for 30 min. Then MeI (0.1 mL, 1.6 mmol, 4.8 equiv) was added, and the reaction mixture was stirred for 4 h at room temperature. Ice-cooled water was added, and the mixture was extracted with EtOAc (3× 20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 3:2) as eluent to give **19** (0.29 g, 88%) as a yellow solid. M.p. 139–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.01 (s, 6H), 0.06 (s, 6H), 0.87 (s, 18H), 1.23 (t, *J* = 7.1 Hz, 6H), 2.47 (d, *J* = 6.3 Hz, 4H), 2.92 (dd, *J* = 13.0, 7.3 Hz, 2H), 3.11 (dd, *J* = 13.0, 5.9 Hz, 2H), 3.52 (s, 6H), 3.80 (s, 6H), 3.95 (s, 6H), 3.96 (s, 6H), 4.05–4.13 (m, 4H), 4.53–4.60 (m, 2H), 6.80 (s, 2H), 7.07 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.1, −4.7, 14.1, 17.9, 25.7, 38.9, 42.3, 56.6, 56.8, 60.2, 61.5, 62.2, 69.9, 110.5, 111.0, 122.2, 122.5, 127.9, 128.6, 147.5, 148.2, 151.0, 152.1, 171.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 2955, 2930, 2856, 1734, 1595, 1494, 1464, 1367, 1326, 1248, 1216, 1198, 1148, 1081, 962, 838, 667 cm^{-1}; HRMS: *m/z* calcd for $[C_{52}H_{78}O_{14}Si_2+Na]^+$: 1005.4822; found: 1005.4822.

Diethyl 4,4′[1,1′,4,4′,5,5′,8,8′-octamethoxy-(2,2′-binaphthalene)-6,6′-diyl]bis(3-hydroxybutanoate) (16): TBAF (0.64 mL, 0.64 mmol, 2.5 equiv, 1 M solution in THF) was added to a solution of **19** (0.25 g, 0.254 mmol) in dry THF (10 mL) at room temperature, and the mixture was stirred for 4 h. It was then quenched with water (5 mL) and stirred for 30 min. THF was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (3× 15 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:1 to 1:1) as eluent to give **16** (0.184 g, 96%) as a yellow solid. M.p. 201–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.24 (t, *J* = 7.1 Hz, 6H), 2.49–2.60 (m, 4H), 2.98–3.07 (m, 4H), 3.12 (s, 2H; OH), 3.53 (s, 6H), 3.79 (s, 6H), 3.94 (s, 6H), 3.95 (s, 6H), 4.14 (q, *J* = 7.4 Hz, 4H), 4.40–4.46 (m, 2H), 6.79 (s, 2H), 7.07 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 37.4, 40.9, 56.6, 56.8, 60.5, 61.5, 62.1, 68.8, 109.8, 111.1, 122.3, 122.4, 127.6, 128.8, 147.5, 147.9, 150.9, 152.4, 172.7 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3445, 2930, 2838, 1729, 1595, 1465, 1368, 1245, 1193, 1155, 1079, 1057, 993, 842, 669 cm^{-1}; HRMS: *m/z* calcd for $[C_{40}H_{50}O_{14}+Na]^+$: 777.3093; found: 777.3093.

Diethyl 2,2′-(5,5′,6,6′,9,9′,10,10′-octamethoxy-1,1′-dimethyl-3,3′,4,4′-tetrahydro-1*H*,1′*H*-8,8′-dibenzo[*g*]isochromene-3,3′-diyl)-diacetate (20): Acetaldehyde diethylacetal (0.06 mL, 0.424 mmol, 4.0 equiv) and TMSOTf (0.06 mL, 0.318 mmol, 3.0 equiv) were added to a solution of **16** (0.080 g, 0.106 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. It was then quenched with saturated aqueous $NaHCO_3$ (5 mL), and the solution was extracted with CH_2Cl_2 (3× 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to afford **20** (0.063 g, 74%, colorless oil) as an inseparable mixture of diastereomers. The ^{1}H NMR spectra showed a mixture of diastereomers with conclusive and characteristic peaks for pyran methyl, C1 proton, and ester ethyl groups. The entire structure was confirmed by HRMS: *m/z* calcd for $[C_{44}H_{54}O_{14}+Na]^+$: 829.3407; found: 829.3412.

(3*E*,3′*E*)-Dimethyl 4,4′-(1,1′,4,4′,5,5′,8,8′-octamethoxy-2,2′-binaphthyl-6,6′-diyl)dibut-3-enoate (8): $PhI(OAc)_2$ (0.139 g, 0.43 mmol, 2.5 equiv) and TEMPO (5.5 mg, 0.035 mmol, 0.2 equiv) were added sequentially to a solution of **7** (0.10 g, 0.172 mmol) in pentane/CH_2Cl_2 (1:1, 8 mL) at room temperature. The resulting mixture was stirred for 4 h at room temperature. It was then diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $Na_2S_2O_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine, dried (Na_2SO_4), and concentrated. The crude dialdehyde (0.099 g) obtained was immediately used in the next step.

The above crude dialdehyde (0.099 g) in DMF (4 mL) was added to a solution of piperidinium acetate (1.0 mg, 0.007 mmol, 4.0 mol%) in DMF (1.4 mL). A solution of monomethyl malonate (0.082 g, 0.69 mmol, 4.0 equiv) in DMF (0.6 mL) was added, and the reaction mixture was stirred at 100 °C for 5 h. It was then allowed to cool to room temperature and diluted with EtOAc/H_2O (1:1, 20 mL). The layers were separated, and the aqueous layer was saturated with NaCl and extracted with EtOAc (4×10 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1 to 1:1) as eluent to afford **8** and its α,β-unsaturated isomer in minor amount (0.075 g, 63% over two steps) as a yellow solid. M.p. 177–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.39 (dd, *J* = 7.1, 1.4 Hz, 4H), 3.54 (s, 6H), 3.76 (s, 6H), 3.79 (s, 6H), 3.96 (s, 6H), 4.01 (s, 6H), 6.39 (dt, *J* = 16.0, 7.2 Hz, 2H), 7.04 (s, 2H), 7.08 (dt, *J* = 16.1, 1.4 Hz, 2H), 7.09 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.5, 51.8, 56.5, 56.8, 61.5, 62.6, 103.9, 111.4, 122.3, 122.5, 122.7, 126.4, 127.9, 129.3, 147.46 147.5, 151.6, 152.6, 172.1 ppm; IR (KBr): $\tilde{\nu}$ = 3002, 2922, 2833, 1742, 1624, 1588, 1460, 1432, 1410, 1372, 1344, 1284, 1244, 1199, 1165, 1081, 1060, 989, 969, 840, 818, 765, 753 cm^{-1}; HRMS: *m/z* calcd for $[C_{38}H_{42}O_{12}+H]^+$: 691.2755; found: 691.2749.

(4*R*,4′*R*,5*R*,5′*R*)-5,5′-(1,1′,4,4′,5,5′,8,8′-Octamethoxy-2,2′-binaphthyl-6,6′-diyl)bis(4-hydroxydihydrofuran-2(3*H*)-one) (6): A mixture of $K_3[Fe(CN)_6]$ (0.342 g, 1.04 mmol, 8.0 equiv), K_2CO_3 (0.144 g, 1.04 mmol, 8.0 equiv), $MeSO_2NH_2$ (0.037 g, 0.39 mmol, 3.0 equiv),

$NaHCO_3$ (0.087 g, 1.04 mmol, 8.0 equiv), hydroquinidine 1,4-phthalazinediyl diether ($(DHQD)_2$-PHAL) (10 mg, 0.013 mmol, 10 mol%), and $K_2OsO_4 \cdot 2H_2O$ (1.5 mg, 3.9 μmol, 3 mol%) in *t*BuOH (2 mL) and water (5 mL) was stirred for 5 min at room temperature and then cooled to 0 °C. A solution of the β,γ-unsaturated ester **8** (0.09 g, 0.13 mmol) in *t*BuOH (3 mL) was added to this mixture. The reaction mixture was stirred at 0 °C for 24 h and at room temperature for 24 h. It was then quenched with solid Na_2SO_3 (0.164 g) and stirred for 30 min. The solution was extracted with EtOAc (5× 10 mL), and the combined organic layers were washed with 1 M KOH (3 mL), water (5 mL), and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:2 to 1:3) as eluent to afford **6** (0.063 g, 70%) as a yellow solid. M.p. 290 °C (decomp); $[\alpha]_D^{25} = +10.5$ ($c = 0.44$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 2.78$ (d, $J = 17.7$ Hz, 2H), 3.00 (dd, $J = 17.8$, 5.5 Hz, 2H), 3.53 (s, 6H), 3.84 (s, 6H), 3.94 (s, 6H), 4.01 (s, 6H), 4.95–4.97 (m, 2H), 5.93 (d, $J = 3.5$ Hz, 2H), 7.03 (s, 2H), 7.11 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 38.2, 56.5, 56.7, 61.6, 62.5, 69.7, 82.2, 104.9, 110.8, 121.7, 123.2, 123.7, 129.5, 146.2, 147.6, 150.9, 153.2, 175.6 ppm; IR ($CHCl_3$): $\tilde{\nu} =$ 3472, 2929, 2850, 1776, 1595, 1506, 1468, 1452, 1371, 1309, 1242, 1196, 1159, 1114, 1079, 1055, 1032, 905, 843, 797, 701 cm^{-1}; HRMS: *m/z* calcd for $[C_{36}H_{38}O_{14}+Na]^+$: 717.2154; found: 717.2159.

6,6′-Bis[2-(*tert*-butyldimethylsilyloxy)ethyl]-1,1′,8,8′-tetramethoxy-2,2′-binaphthyl-5,5′-diol (24): Alkyne **10** (1.30 g, 7.04 mmol, 4.0 equiv) in dry and degassed THF (5 mL) was added to a solution of freshly prepared Fischer carbene **23**[15] (1.2 g, 1.76 mmol) in dry and degassed THF (15 mL). The reaction mixture was heated at 55 °C for 15 h and then allowed to cool to room temperature. It was exposed to air and stirred for 1 h. THF was removed under reduced pressure and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to afford **24** (0.84 g, 66%) as an orange solid. M.p. 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 0.11$ (s, 12H), 0.95 (s, 18H), 3.02 (t, $J = 4.8$ Hz, 4H), 3.56 (s, 6H), 3.94 (s, 6H), 4.04 (t, $J =$ 4.9 Hz, 4H), 6.60 (s, 2H), 7.61 (d, $J = 8.7$ Hz, 2H), 8.11 (d, $J = 8.7$ Hz, 2H), 8.52 ppm (s, 2H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.6$, 18.3, 25.8, 35.8, 57.1, 61.5, 65.9, 110.1, 117.9, 119.7, 120.4, 128.6, 129.4, 129.8, 145.5, 149.5, 153.2 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3277$, 2954, 2931, 2858, 1661, 1626, 1600, 1464, 1353, 1316, 1257, 1218, 1138, 1098, 1063, 1039, 1008, 939, 925, 856, 837, 777, 667 cm^{-1}; HRMS: *m/z* calcd for $[C_{40}H_{58}O_8Si_2+H]^+$: 723.3743; found: 723.3744.

(1,1′,5,5′,8,8′-Hexamethoxy-2,2′-binaphthalene-6,6′-diyl)bis-(ethane-2,1-diyl)bis(oxy)bis(*tert*-butyldimethylsilane) (25): NaH (0.045 g, 1.87 mmol, 3.0 equiv) was added to a solution of **24** (0.45 g, 0.622 mmol) in dry THF (15 mL) at 0 °C and stirred for 30 min. Then MeI (0.16 mL, 2.5 mmol, 4.0 equiv) was added, and the reaction mixture was stirred for 4 h at room temperature. Ice-cooled water was added, and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 3:2) as eluent to give **25** (0.402 g, 86%) as a yellow solid. M.p. 121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta =$ 0.06 (s, 12H), 0.91 (s, 18H), 3.05 (t, $J = 7.0$ Hz, 4H), 3.56 (s, 6H), 3.92 (s, 6H), 3.95 (t, $J = 7.3$ Hz, 4H), 3.98 (s, 6H), 6.78 (s, 2H), 7.65 (d, $J =$ 8.7 Hz, 2H), 7.85 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.3$, 18.4, 26.0, 33.9, 56.4, 61.6, 62.1, 63.7, 108.4, 117.3, 120.4, 127.4, 129.0, 130.6, 131.0, 147.6, 152.4, 154.0 ppm; IR ($CHCl_3$): $\tilde{\nu} =$ 2954, 2931, 2857, 1619, 1598, 1570, 1463, 1380, 1360, 1342, 1245, 1100, 1045, 1010, 921, 837, 775, 667 cm^{-1}; HRMS: *m/z* calcd for $[C_{42}H_{62}O_8Si_2+Na]^+$: 773.3875; found: 773.3876.

2,2′-(1,1′,5,5′,8,8′-Hexamethoxy-2,2′-binaphthalene-6,6′-diyl)bis-(ethan-1-ol) (26): TBAF (1.2 mL, 1.2 mmol, 2.5 equiv, 1 M solution in THF) was added to a solution of **25** (0.35 g, 0.47 mmol) in dry THF (15 mL) at room temperature, and the mixture was stirred for 4 h. It was then quenched with water (5 mL) and stirred for 30 min. THF was removed under reduced pressure and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:1 to 1:1) as eluent to give **26** (0.227 g, 93%) as a yellow solid. M.p. 196–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 2.11$ (s, 2H; OH), 3.08 (t, $J = 6.4$ Hz, 4H), 3.56 (s, 6H), 3.92 (s, 6H), 3.97 (t, $J = 6.4$ Hz, 4H), 3.98 (s, 6H), 6.72 (s, 2H), 7.65 (d, $J = 8.7$ Hz, 2H), 7.85 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 33.8$, 56.4, 61.6, 61.9, 63.2, 107.9, 117.3, 120.5, 127.1, 129.1, 130.7, 131.0, 147.7, 152.8, 154.1 ppm; IR ($CHCl_3$): $\tilde{\nu} =$ 3431, 2934, 2840, 1619, 1598, 1570, 1453, 1380, 1359, 1341, 1244, 1135, 1099, 1045, 1016, 843 cm^{-1}; HRMS: *m/z* calcd for $[C_{30}H_{34}O_8+Na]^+$: 545.2146; found: 545.2146.

(3*E*,3′*E*)-Dimethyl 4,4′-(1,1′,5,5′,8,8′-hexamethoxy-2,2′-binaphthalene-6,6′-diyl)bis(but-3-enoate) (27): $PhI(OAc)_2$ (0.31 g, 0.96 mmol, 2.5 equiv) and TEMPO (0.012 g, 0.077 mmol, 0.2 equiv) were added sequentially to a solution of **26** (0.2 g, 0.383 mmol) in pentane/CH_2Cl_2 (1:1, 14 mL) at room temperature. The resulting mixture was stirred for 4 h at room temperature and then diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $Na_2S_2O_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine, dried (Na_2SO_4), and concentrated. The crude dialdehyde (0.197 g) obtained was immediately used in the next step.

The crude dialdehyde (0.197 g) in DMF (7 mL) was added to a solution of piperidinium acetate (2.2 mg, 0.0153 mmol, 4.0 mol%) in DMF (2 mL). A solution of monomethyl malonate (0.180 g, 1.53 mmol, 4.0 equiv) in DMF (0.6 mL) was added, and the reaction mixture was stirred at 100 °C for 5 h. It was then allowed to cool to room temperature and diluted with EtOAc/H_2O (1:1, 20 mL). The layers were separated and the aqueous layer was saturated with NaCl and extracted with EtOAc (4×10 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1 to 1:1) as eluent to afford **27** and its α,β-unsaturated isomer in a minor amount (0.152 g, 63% over two steps) as a yellow solid. M.p. 183–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 3.39$ (d, $J = 7.2$ Hz, 4H), 3.56 (s, 6H), 3.76 (s, 6H), 3.90 (s, 6H), 4.02 (s, 6H), 6.43 (dt, $J = 15.8$, 7.2 Hz, 2H), 6.97 (s, 2H), 7.00 (d, $J = 16.0$ Hz, 2H), 7.65 (d, $J = 8.7$ Hz, 2H), 7.89 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.6$, 52.0, 56.4, 61.7, 62.4, 102.6, 117.7, 121.2, 122.7, 124.9, 127.7, 129.7, 130.8, 131.3, 147.2, 152.8, 154.1, 172.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 2933$, 2843, 1738, 1589, 1450, 1383, 1347, 1243, 1167, 1099, 1054, 1018, 976, 798 cm^{-1}; HRMS: *m/z* calcd for $[C_{36}H_{38}O_{10}+Na]^+$: 653.2357; found: 653.2357.

(4*R*,4′*R*,5*R*,5′*R*)-5,5′-(1,1′,5,5′,8,8′-Hexamethoxy-2,2′-binaphthalene-6,6′-diyl)bis(4-hydroxydihydrofuran-2(3*H*)-one) (28): A mixture of $K_3[Fe(CN)_6]$ (0.543 g, 1.65 mmol, 8.0 equiv), K_2CO_3 (0.228 g, 1.65 mmol, 8.0 equiv), $MeSO_2NH_2$ (0.059 g, 0.62 mmol, 3.0 equiv), $NaHCO_3$ (0.136 g, 1.62 mmol, 8.0 equiv), $(DHQD)_2$-PHAL (8.0 mg, 0.0103 mmol, 5 mol%), and $K_2OsO_4 \cdot 2H_2O$ (1.5 mg, 0.0041 mmol, 2 mol%) in *t*BuOH (2 mL) and water (5 mL) was stirred for 5 min and cooled to 0 °C. A solution of the β,γ-unsaturated ester **27** (0.130 g, 0.206 mmol) in *t*BuOH (3 mL) was added to this mixture. The reaction mixture was stirred at 0 °C for 24 h and at room temperature for 24 h. It was then quenched with solid Na_2SO_3 (0.20 g)

and stirred for 30 min. The solution was extracted with EtOAc (5× 10 mL), and the combined organic layers were washed sequentially with 1 M KOH (4 mL), water (5 mL), and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:2 to 1:3) as eluent to afford **28** (0.092 g, 70%) as a yellow solid. M.p. 247–248 °C; $[\alpha]_D^{25} = -16.3$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 2.77$ (d, $J = 17.6$ Hz, 2H), 2.98 (dd, $J = 17.7$, 5.4 Hz, 2H), 3.55 (s, 6H), 3.95 (s, 6H), 4.00 (s, 6H), 4.89 (t, $J = 4.3$ Hz, 2H), 5.91 (d, $J = 3.5$ Hz, 2H), 6.96 (s, 2H), 7.68 (d, $J = 8.6$ Hz, 2H), 7.82 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.3$, 56.4, 61.7, 62.2, 69.8, 81.8, 103.8, 117.2, 121.6, 122.4, 129.9, 130.4, 131.0, 146.1, 153.2, 154.2, 175.6 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3457$, 3007, 2935, 2847, 1778, 1621, 1599, 1572, 1454, 1383, 1339, 1231, 1198, 1157, 1099, 1079, 1060, 1029, 982, 906, 868, 800, 701 cm^{-1}; HRMS: *m/z* calcd for $[C_{34}H_{34}O_{12}+H]^+$: 635.2123; found: 635.2122.

Diethyl 4,4′-(5,5′-dihydroxy-1,1′,8,8′-tetramethoxy-2,2′-binaphthyl-6,6′-diyl)bis(3-*tert*-butyldimethylsilyloxy)butanoate (30): Alkyne **17** (1.19 g, 4.4 mmol, 3.0 equiv) in dry and degassed THF (5 mL) was added to a solution of freshly prepared Fischer carbene **23** (1.0 g, 1.466 mmol) in dry and degassed THF (15 mL). The reaction mixture was stirred at 45 °C for 15 h and then allowed to cool to room temperature. It was then exposed to air and stirred for 1 h. THF was removed under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) to afford **30** (0.826 g, 63%) as a pale yellow solid. M.p. 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta =$ 0.09 (s, 6H), 0.13 (s, 6H), 0.95 (s, 18H), 1.28 (t, $J = 7.1$ Hz, 6H), 2.47–2.58 (m, 4H), 3.02 (dd, $J = 14.7$, 5.8 Hz, 2H), 3.23 (dd, $J = 14.7$, 3.0 Hz, 2H), 3.55 (s, 6H), 3.92 (s, 6H), 4.18 (q, $J = 7.1$ Hz, 4H), 4.53–4.59 (m, 2H), 6.53 (s, 2H), 7.63. (d, $J = 8.7$ Hz, 2H), 8.10 (d, $J =$ 8.7 Hz, 2H), 8.21 ppm (s, 2H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ −5.03, −5.01, 14.1, 18.0, 25.7, 39.1, 40.5, 56.9, 60.7, 61.5, 70.9, 110.5, 116.2, 117.8, 120.5, 128.4, 129.4, 129.8, 145.2, 149.4, 153.2, 171.6 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3305$, 2955, 2932, 2858, 1735, 1662, 1626, 1600, 1578, 1464, 1375, 1349, 1315, 1257, 1194, 1146, 1097, 1041, 1008, 961, 839, 812, 778, 703 cm^{-1}; HRMS: *m/z* calcd for $[C_{48}H_{70}O_{12}Si_2+K]^+$: 933.4043; found: 933.4048.

Diethyl 4,4′-(1,1′,5,5′,8,8′-hexamethoxy-2,2′-binaphthyl-6,6′-diyl)bis(3-*tert*-butyldimethylsilyloxy)butanoate (31): NaH (0.054 g, 2.23 mmol, 2.5 equiv) was added to a solution of **30** (0.80 g, 0.893 mmol) in dry DMF (15 mL) at 0 °C and stirred for 30 min. Then MeI (0.25 mL, 4.02 mmol, 4.5 equiv) was added, and the reaction mixture was stirred for 3 h at room temperature. Ice-cooled water was added, and the mixture was extracted with EtOAc (3× 20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 3:2) as eluent to give **31** (0.726 g, 88%) as a colorless solid. M.p. 139–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 0.00$ (s, 6H), 0.06 (s, 6H), 0.87 (s, 18H), 1.24 (t, $J = 7.1$ Hz, 6H), 2.49 (d, $J = 6.1$ Hz, 4H), 2.93 (dd, $J = 13.1$, 7.1 Hz, 2H), 3.10 (dd, $J = 13.1$, 5.9 Hz, 2H), 3.55 (s, 6H), 3.90 (s, 6H), 3.98 (s, 6H), 4.06–4.15 (m, 4H), 4.52–4.58 (m, 2H), 6.73 (s, 2H), 7.66. (d, $J = 8.7$ Hz, 2H), 7.84 ppm (d, $J =$ 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.1$, −4.7, 14.2, 18.0, 25.7, 38.6, 42.3, 56.4, 60.3, 61.6, 61.7, 69.9, 108.8, 117.3, 120.5, 126.5, 129.0, 130.6, 131.0, 148.0, 152.4, 154.0, 171.8 ppm; IR ($CHCl_3$): $\tilde{\nu} = 2954$, 2931, 2856, 1737, 1662, 1619, 1600, 1570, 1464, 1381, 1341, 1312, 1251, 1204, 1147, 1099, 1071, 985, 961, 910, 837, 812, 777, 735 cm^{-1}; HRMS: *m/z* calcd for $[C_{50}H_{74}O_{12}Si_2+K]^+$: 961.4356; found: 961.4354.

Diethyl 4,4′-(1,1′,5,5′,8,8′-hexamethoxy-2,2′-binaphthyl-6,6′-diyl)bis(3-hydroxybutanoate) (32): TBAF (2.0 mL, 2.0 mmol, 2.6 equiv, 1 M solution in THF) was added to a solution of **31** (0.71 g, 0.769 mmol) in dry THF (15 mL) at room temperature, and the mixture was stirred for 4 h. It was then quenched with water (5 mL) and stirred for 30 min. THF was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1 to 1:3) to give **32** (0.512 g, 96%) as a colorless solid. M.p. 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.27$ (t, $J = 7.1$ Hz, 6H), 2.51–2.62 (m, 4H), 2.99–3.10 (m, 4H) 3.36 (d, $J = 3.8$ Hz, 2H; OH), 3.56 (s, 6H), 3.91 (s, 6H), 3.98 (s, 6H), 4.17 (q, $J = 7.1$ Hz, 4H), 4.40–4.46 (m, 2H), 6.73 (s, 2H), 7.65 (d, $J = 8.7$ Hz, 2H), 7.84 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$, 37.2, 40.8, 56.3, 60.6, 61.6, 61.8, 68.8, 108.1, 117.3, 120.7, 126.1, 129.2, 130.7, 130.9, 147.7, 152.7, 154.1, 172.8 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3486$, 2984, 2935, 2842, 1732, 1622, 1599, 1569, 1455, 1380, 1338, 1246, 1193, 1145, 1099, 1048, 1013, 980, 857, 829, 798, 667 cm^{-1}; HRMS: *m/z* calcd for $[C_{38}H_{46}O_{12}+Na]^+$: 717.2881; found: 717.2885.

Diethyl 2,2′-(5,5′,9,9′,10,10′-hexamethoxy-1,1′-dimethyl-3,3′,4,4′-tetrahydro-1*H*;1′*H*-8,8′-dibenzo[*g*]isochromene-3,3′-diyl)diacetate (33): Acetaldehyde diethylacetal (0.082 mL, 0.576 mmol, 4.0 equiv) and TMSOTf (0.078 mL, 0.432 mmol, 3.0 equiv) were added to a solution of **32** (0.10 g, 0.144 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. It was then quenched with saturated aqueous $NaHCO_3$ (5 mL), and the solution was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) to afford an inseparable mixture of diastereomers **33** (0.087 g, 81%). The mixture was used for the next reaction immediately.

Diethyl 2,2-(9,′9′-dimethoxy-1,1′-dimethyl-5,5′,10,10′-tetraoxo-3,3′,4,4′,-5,5′,10,10′-octahydro-1*H*,1′*H*-[8,8′-dibenzo[*g*]isochromene]-3,3′-diyl)diacetate (34) and diethyl 2,2′-(9,9′-dimethoxy-1,1′-dimethyl-5,5′,10,10′-tetraoxo-3,3′,4,4′,-5,5′,10,10′-octahydro-1*H*,1′*H*-[8,8′-dibenzo[*g*]isochromene]-3,3′-diyl]diacetate (35): A solution of ceric(IV) ammonium nitrate (0.235 g, 0.428 mmol, 4.0 equiv) in water (5 mL) was added to a stirred solution of **33** (0.080 g, 0.107 mmol) in CH_3CN (5 mL). The reaction mixture was stirred at room temperature for 45 min. It was then diluted with EtOAc (15 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (3×15 mL), and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 7:3) as eluent to give **34** (45.6 mg, 62%) and **35** (13.3 mg, 18%) as yellow solids. For **34**: M.p. 165–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta =$ 1.31 (t, $J = 7.2$ Hz, 6H), 1.57 (d, $J = 6.8$ Hz, 6H), 2.38 (ddd, $J = 18.9$, 10.5, 2.0 Hz, 2H), 2.61–2.69 (m, 4H), 2.81 (dd, $J = 18.9$, 3.1 Hz, 2H), 3.63 (s, 6H), 4.16–4.27 (m, 4H), 4.32–4.39 (m, 2H), 5.06 (q, $J =$ 6.8 Hz, 2H), 7.69 (d, $J = 7.9$ Hz, 2H), 8.00 ppm (d, $J = 7.9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 19.3, 27.5, 40.7, 60.8, 61.9, 63.5, 67.5, 122.4, 124.5, 133.9, 136.3, 138.6, 139.6, 147.9, 157.8, 170.6, 182.3, 183.4 ppm; IR ($CHCl_3$): $\tilde{\nu} = 2980$, 2933, 2854, 1738, 1659, 1635, 1558, 1462, 1402, 1373, 1312, 1268, 1205, 1160, 1127, 1093, 1075, 1032, 990, 952, 855, 825, 666 cm^{-1}; HRMS: *m/z* calcd for $[C_{38}H_{38}O_{12}+Na]^+$: 709.2255; found: 709.2253. For **35**: ^{1}H NMR spectroscopy indicated one pyran ring with a *syn* C1 methyl with a C3 side chain and another pyran ring with *anti* placement of the groups. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.25$–1.35 (m, 6H), 1.52 (d, $J = 6.6$ Hz, 3H), 1.53 (d, $J = 6.7$ Hz, 3H), 2.28–2.41 (m, 2H), 2.60–2.89 (m, 6H), 3.618 (s, 3H), 3.62 (s, 3H), 3.89–3.99 (m, 1H), 4.15–

4.24 (m, 4H), 4.30–4.38 (m, 1H), 4.85–4.95 (m, 1H), 5.01–5.09 (m, 1H), 7.62–7.71 (m, 2H), 7.95–8.03 ppm (m, 2H); HRMS: *m/z* calcd for $[C_{38}H_{38}O_{12}+Na]^+$: 709.2255; found: 709.2259.

Diethyl 2,2′-(9,9′-dihydroxy-1,1′-dimethyl-5,5′,10,10′-tetraoxo-3,3′,4,4′,-5,5′,10,10′-octahydro-1*H*;1′*H*-[8,8′-dibenzo[*g*]isochromene]-3,3′-diyl)diacetate (36): $AlCl_3$ (29 mg, 0.22 mmol, 5.0 equiv) was added to a solution of **34** (30 mg, 0.044 mmol) in dry CH_2Cl_2 (15 mL) in portions at 0 °C, and the reaction mixture was stirred for 10 min. The ice bath was removed and stirring continued at room temperature for 45 min. It was then quenched with water (5 mL) and the solution extracted with CH_2Cl_2 (5×15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (4:1 to 4:3) as eluent to provide **36** (22.7 mg, 79%) as a yellow solid. M.p. 175–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta=1.30$ (t, $J=7.1$ Hz, 6H), 1.58 (d, $J=6.8$ Hz, 6H), 2.36 (ddd, $J=19.2$, 10.5, 1.9 Hz, 2H), 2.61–2.73 (m, 4H), 2.85 (dd, $J=19.2$, 3.3 Hz, 2H), 4.17–4.25 (m, 4H), 4.32–4.38 (m, 2H), 5.02 (q, $J=6.3$ Hz, 2H), 7.65–7.78 (m, 4H), 12.53 ppm (s, 2H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.2$, 19.4, 27.9, 40.7, 60.8, 63.4, 67.2, 114.9, 118.6, 131.7, 137.7, 142.5, 146.5, 159.3, 170.6, 182.7, 188.7 ppm; IR ($CHCl_3$): $\tilde{\nu}=3460$, 2976, 2918, 2850, 1738, 1661, 1640, 1607, 1471, 1415, 1341, 1270, 1158, 1116, 1078, 1032, 860, 792 cm^{-1}; HRMS: *m/z* calcd for $[C_{36}H_{34}O_{12}+Na]^+$: 681.1942; found: 681.1942.

Synthesis of 36 from 35 through demethylation with $AlCl_3$- and H_2SO_4-mediated epimerization: $AlCl_3$ (11.5 mg, 0.086 mmol, 5.0 equiv) was added to a solution of **35** (11.8 mg, 0.0172 mmol) in dry CH_2Cl_2 (15 mL) in one portion at 0 °C, and the reaction mixture was stirred for 10 min. The ice bath was removed and stirring continued at room temperature for 40 min. It was then quenched with water (5 mL), and the solution was extracted with CH_2Cl_2 (5× 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1 to 4:3) as eluent to provide the demethylated compound (9 mg). Concentrated H_2SO_4 (1 mL) was added to a stirred solution of this in benzene (3 mL) at 5 °C. The resulting mixture was stirred at room temperature for 1 h. Brine solution (5 mL) was added, and the reaction mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1 to 4:3) as eluent to give **36** (4.1 mg, 35%, two steps) as a yellow solid. The spectroscopic data were the same as before.

7,7′-Dihydroxy-5,5′-dimethyl-3,3a,3′,3′a-tetrahydro-2*H*,2′*H*-(8,8′-dibenzo[*g*]furo[3,2-*c*]isochromene)-2,2′,6,6′,11,11′-(5*H*,5′*H*,11b*H*,11′b*H*)-hexanone (37): A solution of LiOH (2 mg) in H_2O (0.5 mL) was added to a solution of **36** (15 mg, 0.0023 mmol) in THF (0.5 mL) at 0 °C and stirred for 12 h. HCl (2 N, 0.2 mL) was added, and the solution was filtered through a pad of Celite. The filtrate was concentrated, and the residue was dissolved in MeOH (0.5 mL) and stirred in an open vial for one day at room temperature. It was then concentrated, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluent to give **37** (4.6 mg, 34% from **36**) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta=1.59$ (d, $J=6.8$ Hz, 6H), 2.72 (d, $J=17.7$ Hz, 2H), 3.00 (dd, $J=17.8$, 5.2 Hz, 2H), 4.71 (dd, $J=5.1$, 3.0 Hz, 2H), 5.12 (q, $J=6.8$ Hz, 2H), 5.28 (d, $J=3.0$ Hz, 2H), 7.75–7.82 (m, 4H), 12.35 ppm (s, 2H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=18.6$, 36.9, 66.2, 66.4, 68.5, 115.0, 119.2, 131.4, 135.3, 138.55, 138.6, 149.9, 159.6, 173.9, 181.2, 188.3 ppm; IR ($CHCl_3$): $\tilde{\nu}=3435$, 2923, 2853, 1789, 1652, 1621, 1454, 1423, 1328, 1271, 1243, 1204, 1162, 1085, 1039, 909, 869, 788, 686 cm^{-1}; HRMS: *m/z* calcd for $[C_{32}H_{22}O_{12}+H]^+$: 599.1184; found: 599.1172.

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