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Synthetic Studies towards Radicicol through Biomimetic Macrolactonization and Transannular Aromatization Reactions

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Studies towards the total synthesis of the natural product radicicol are described that employ a late-stage esterification and aromatization by trapping a ketene intermediate. The subsequent biomimetic aromatization of the resultant triketo ester gave highly functionalized resorcylates. Two distinct methods were examined that trap the ketene intermediate through either an intermolecular or intramolecular process. In the first approach, the synthesis of the resorcylate was followed by a ring-closing metathesis, which gave the macrolactone and protected precursors to monocillin I. In the second approach, an intramolecular ketene trapping was examined as an alternative to close the macrocycle and form the resorcylate macrolactone. These studies showcased a wide range of sensitive functional groups that tolerated the aromatization reaction conditions, which started from the corresponding dioxinone precursors.

Introduction

Radicicol (**2**), first isolated in 1953 from *Monicillium nordinii*,[1] is a member of the large family of natural products named resorcylic acid lactones, each of which contains a 6-alkyl-2,4-dihydroxybenzoic acid or β-resorcylate unit that is fused to a macrocyclic lactone ring (see Figure 1). Many such resorcylates exhibit a wide array of biological activities.[2] For this reason, along with their interesting and often complex structures, this class of compounds has inspired many research groups to undertake their total syntheses.[2a]

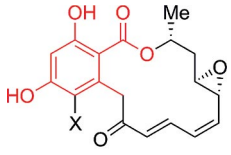
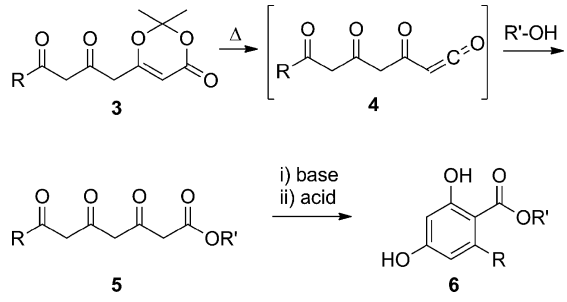


Figure 1. Radicicol (**2**) with β-resorcylate unit shown in red.

Radicicol was initially shown to have mildly sedative and antibiotic activities.[1,3] In the 1990s, it selectively inhibited Hsp90 (IC_{50} of 20 nM), a molecular chaperone, thereby preventing the proliferation of cancer cells to become a promising anticancer hit structure.[4] The three groups of Lett,[5] Danishefsky,[6] and Winssinger[7] have previously reported syntheses of radicicol, each of which functionalized a preformed resorcylate core followed by a macrocyclization step. Lett utilized a Mitsunobu reaction, whereas both Danishefsky and Wissinger utilized a ring-closing alkene metathesis reaction. These routes towards radicicol have inherent problems, such as difficulty preventing the formation of isocoumarin side products. More importantly, the previous syntheses of radicicol are not readily adaptable to the syntheses of its analogues. Although radicicol (**2**) shows activity in vitro, it does not show activity in vivo, which makes its analogues attractive targets, with their potential to retain the anticancer activity and improve upon the pharmacokinetic properties.[8] Herein, we describe two routes towards the total synthesis of radicicol (**2**) from diketo-dioxinone precursors that proceed through either the intermolecular or intramolecular trapping of a ketene intermediate followed by biomimetic aromatization reactions (see Scheme 1). This approach was inspired by the earlier work of Harris and Harris on the biomimetic syntheses of resorcylates and of Hyatt on dioxinone thermolysis reactions as



Scheme 1. General synthesis of resorcylates from dioxinone precursors.

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well as the pioneering studies by Boeckman on using the Hyatt approach to macrocyclization reactions.[9]

Our group has extended these studies to the biomimetic syntheses of several complex resorcylate natural products, which also have a diverse range of biological activities.[10] Triketo-ketene **4** was produced from the retro-Diels–Alder fragmentation of diketo-dioxinone **3** and then trapped by the addition of an alcohol to form triketo ester **5**. A subsequent base-catalyzed aldol cyclization and acid-promoted dehydration of the triketo ester gave resorcylate **6**. This versatile method tolerated diverse and sensitive functional groups. Herein, we report that the preparation of resorcylates from dioxinone precursors may be applied to the total synthesis of radicicol (**2**), which contains sensitive functionality, as well as to the syntheses of a number of related resorcylates.

Results and Discussion

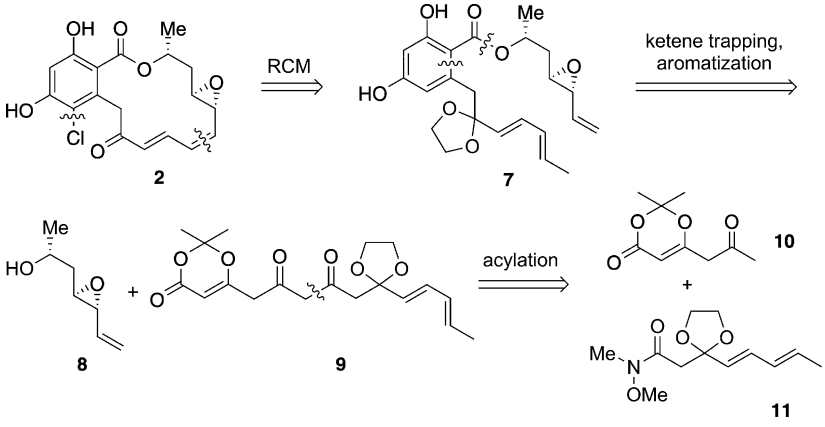
In the first approach, we considered that the resorcylate unit could be constructed by trapping the ketene intermediate from diketo-dioxinone **9** with known alcohol **8**.[6] This highly convergent route would combine the three key fragments, keto-dioxinone **10**,[10d] Weinreb amide **11**, and alcohol **8**. Upon its generation, diketo-dioxinone **9** could be submitted to the retro-Diels–Alder and aromatization reaction to give resorcylate **7**. Macrolactonization could be accomplished through a ring-closing alkene metathesis, which is closely modelled on the Danishefsky synthesis, to yield the (*E*,*Z*) double-bond geometry, as illustrated in the retrosynthetic analysis (see Scheme 2).

Weinreb amide **11** was synthesized in three steps from sorbic acid (**12**, see Scheme 3). The Claisen condensation of the dianion derived from keto-dioxinone **10** with Weinreb amide **11** proceeded in superior yield in the presence of diethylzinc, as previously reported by our group.[11] This reaction gave diketo-dioxinone **9**, which was used immediately in subsequent reactions without characterization because of its high reactivity. The reaction of diketo-dioxinone **9** and alcohol **8**[6] in toluene at reflux proceeded through a retro-Diels–Alder reaction and alcohol trapping. Aromatization of the resultant diketo-dioxinone with cesium acetate followed by treatment with acetic acid and subsequent acetylation of the phenol unit gave the protected resorcylate **13** in a one-pot procedure (68% yield). The subsequent macrocyclization was carried out by using Grubbs–Hoveyda II catalyst (**16**) to provide lactone **14** in a 27% unoptimized yield. Unfortunately, problems arose with the attempted deprotection of ketal **14** under acidic conditions, which resulted in the preferential cleavage of the reactive epoxide ring. However, in spite of this problem, the methods in Scheme 3 represent a concise approach to resorcylate lactones related to radicicol (**2**).

As a consequence of the problems with the attempted deprotection of ketal **14**, we examined the aromatization and macrocyclization steps by using the corresponding silyl-protected alcohol. In this venture, we first focused our attention on the generation of Weinreb amide **18a**. Hydroxyalkylation of the enolate derived from *N*-methoxy-*N*-methylacetamide[12] (**17**) with sorbic aldehyde followed by protection of the alcohol as triisopropylsilyl ether **18a** (see Scheme 4) proceeded in 75% yield. Subsequent *C*-acylation of the dianion derived from keto-dioxinone **10** with amide **18a** gave the required adduct **19a** in 66% yield.

The coheating of diketo-dioxinone **19a** with alcohol **8** and the subsequent aromatization proceeded without difficulty to give the desired resorcylate **20a** in 74% yield by following the same procedure as before. In this instance, it was not possible to protect the phenol groups in the same flask. Nevertheless, acetyl protection was carried out in 98% yield, and the ring-closing metathesis by using the Grubbs–Hoveyda II catalyst (**16**) gave macrocyclic lactone **21a** in 57% yield as a mixture of the two diastereomers (see Scheme 5).

The attempted desilylation of **21a** by using tetrabutylammonium fluoride was unsuccessful, and the starting material was recovered. In contrast, the use of alternative sources of fluoride such as tetrabutylammonium difluorotriphenylsilicate, hexafluorosilicic acid, and pyridinium hydrogen fluoride resulted in the opening of the reactive epoxide ring. We were unable to use basic conditions for the desilylation to avoid the well-known isocoumarin for-



Scheme 2. An intermolecular ketene trapping approach to radicicol (**2**).

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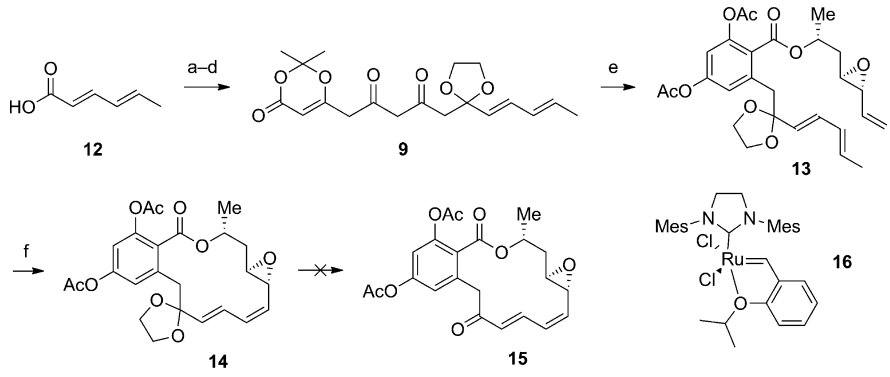
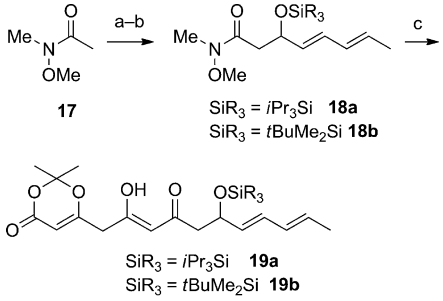


a) i) $(COCl)_2$, CH_2Cl_2, 25 °C; ii) EtOAc, $LiN(SiMe_3)_2$, THF, –78 °C, b) ethylene glycol, *p*TSA·H_2O, triethyl orthoformate, PhMe, 20 mbar, 40 °C, 74%; c) *n*BuLi, NHMe(OMe),HCl, THF, –78 °C to 25 °C, 20%; d) **10**, $LiN(iPr)_2$, Et_2Zn, THF, –78 °C to –10 °C, 63%, e) i) **8**, PhMe, 110 °C, ii) CH_2Cl_2, *i*PrOH, CsOAc, 25 °C; iii) AcOH, iv) THF, Ac_2O, DMAP, 25 °C, 68%; f) i) **16**, CH_2Cl_2, 40–45 °C, ii) DMSO, 25 °C, 27%.

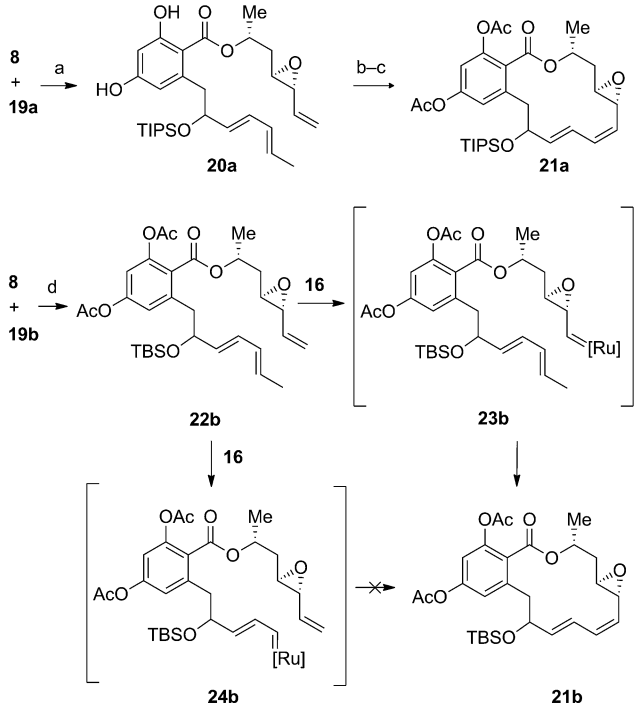
Scheme 3. Synthesis of resorcylate **14** (THF = tetrahydrofuran, *p*TSA = *p*-toluenesulfonic acid, DMAP = 4-(dimethylamino)pyridine, DMSO = dimethyl sulfoxide).



SiR_3 = iPr_3Si **19a**
SiR_3 = $tBuMe_2Si$ **19b**

SiR_3 = iPr_3Si: a) $LiN(iPr)_2$, sorbic aldehyde, THF, –78 °C; b) iPr_3SiCl, 0 °C to 25 °C, 75%; c) **10**, $LiN(iPr)_2$, Et_2Zn, THF, –78 to –10 °C, 66%.
SiR_3 = $tBuMe_2Si$: a) $LiN(iPr)_2$, sorbic aldehyde, THF, –78 °C, 68%; b) $tBuMe_2SiCl$, imidazole, CH_2Cl_2, 25 °C, 83%; c) $LiN(iPr)_2$, THF, –78 to –40 °C, 75%.

Scheme 4. Synthesis of diketo-dioxinones **19a** and **19b**.



a) i) PhMe, 110 °C; ii) CH_2Cl_2, *i*PrOH, CsOAc, 25 °C; iii) AcOH, 25 °C, 74%; b) Ac_2O, DMAP, THF, 25 °C, 98%; c) i) **16**, CH_2Cl_2, 45 °C; ii) DMSO, 25 °C, 57%. d) i) PhMe, 110 °C; ii) Cs_2CO_3, MeOH, 25 °C; iii) AcOH, 25 °C; iv) Ac_2O, DMAP, THF, 25 °C, 42%.

Scheme 5. Synthesis of macrocycle **21a** and attempted synthesis of **21b** (TIPS = triisopropylsilyl, TBS = *tert*-butyldimethylsilyl).

mation.[6] As a consequence of these difficulties, we next investigated *tert*-butyldimethylsilyl-protected analogue **19b**, which was readily synthesized by an equivalent pathway (see Scheme 4).

The ketene trapping and aromatization sequence of dioxinone **19b** and alcohol **8** proceeded smoothly, and subsequent protection of the phenol groups gave resorcylate **22b**. Interestingly, the attempted macrocyclization of triene **22b** through the ring-closing metathesis proceeded in very poor yield (<5% yield), despite varying the catalyst loading, dilution, reaction time, and solvent for this process (see Scheme 5).

Porco reported similar problems with regard to the attempted ring-closing metatheses and proposed that this was possibly the result of the formation of a low reactivity ruthenium complex such as **24b**.[13] To bypass this problem, the use of a tether and metathesis relay strategy was employed to favor the formation of the initial ruthenium complex at the desired terminus. This would be driven by the elimination of cyclopentene before the actual ring-closing could occur. Thus, the Wittig reaction between the known aldehyde **26**[6] and the ylide derived from phosphonium salt **25**[14] along with the subsequent desilylation gave alcohol **27** in 67% yield for the two steps (see Scheme 6). Alcohol **27** and diketo-dioxinone **19b** were converted into the corresponding resorcylate (64% yield) by using the standard procedure. The subsequent acetylation gave resorcylate tetraene **28** in 97% yield. Much to our delight, the alkene relay and ring-closing metathesis by using the Hoveyda–

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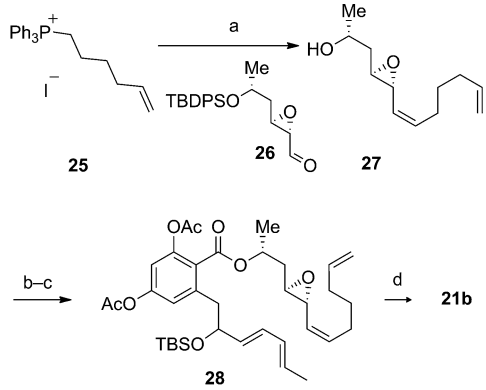
Grubbs II catalyst (**16**) proceeded smoothly at 60 °C to give the resorcylate lactone **21b** (75% yield).



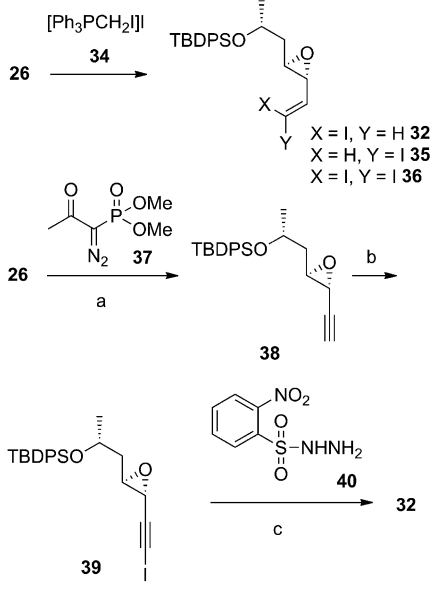
a i) $NaN(SiMe_3)_2$, THF, –10 °C to 25 °C; ii) tBu_4NF, 4 Å molecular sieves, THF, 25 °C, 67%; b) i) **19b**, PhMe, 110 °C; ii) 4 Å molecular sieves, *i*PrOH, CH_2Cl_2, 100 °C, sealed tube, 64%; c) Ac_2O, DMAP, THF, 25 °C, 97%; d) **16**, $ClCH_2CH_2Cl$, 60 °C, sealed tube, 75%.

Scheme 6. Synthesis of tethered alcohol **27** and macrocycle **21b**.

Lactone **21b** also could not be converted into monocillin I (**1**), as the desilylation of ether **21b** proved again to be insurmountably difficult because of the reactivity of the epoxide ring. Against expectations, the *tert*-butyldimethylsilyl protecting group was not sufficiently labile, and its removal was not possible. These results highlight the particularly unstable nature of the conjugated diene-epoxide moiety under multiple deprotection conditions. In contrast, our aromatization reaction proceeded under sufficiently mild conditions, and the epoxide survived intact.

Following these studies, we examined the intramolecular trapping of a triketo-ketene intermediate with an alcohol to form the radicicol (**2**) core. This is illustrated in the retrosynthetic analysis shown in Scheme 7. We considered that fragments **32** and **33** could be linked through a Suzuki coupling reaction followed by an aldol reaction of keto-dioxinone **30**[15] with aldehyde **31**. The early incorporation of chlorine would serve to bypass the known, moderate yield for the chlorination reaction of monocillin I (**1**) to produce radicicol (**2**). The intramolecular trapping of a ketene was first reported by Paquette and has since been successfully incorporated into the generation of resorcylate lactones by the Barrett group.[16]

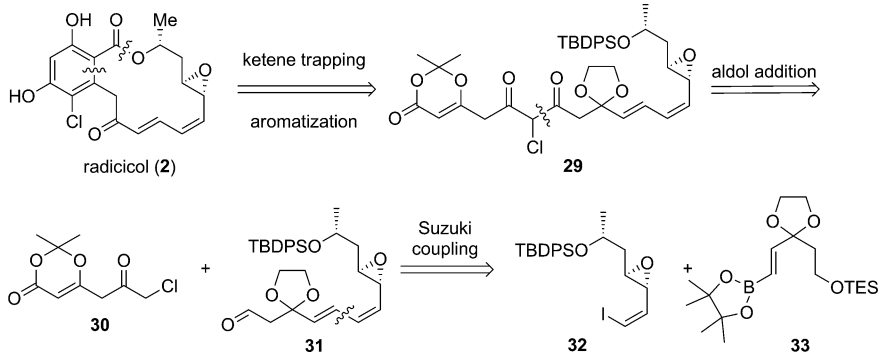
The Wittig reaction of aldehyde **26** with the ylide derived from phosphonium salt **34** under Stork conditions[17] gave the desired *cis*-alkene **32** as an inseparable mixture with *trans*-alkene **35**, an unidentifiable impurity, and diiodo-substituted alkene **36**, a side product which has previously been reported (see Scheme 8).[18] The assignments of these structures were tentatively determined by ^1H NMR spectroscopic analysis of the crude mixture.



a) K_2CO_3, MeOH, 0 °C, 66%; b) *N*-iodosuccinimide, $AgNO_3$, Me_2CO, 25 °C, dark, 98%; c) Et_3N, *i*PrOH/THF, 25 °C, dark, 80%.

Scheme 8. Synthesis of iodo-substituted alkene **32**.

Since we were unable to produce pure *cis*-alkene **32** by this method, an alternative route was used. Aldehyde **26** was converted into alkyne **38** in 66% yield by using the Ohira–Bestmann reagent **37**. The alkyne was readily iodinated to give iodoalkyne **39** in excellent yields with *N*-iodosuccinimide and silver nitrate. This was subsequently reduced to give the desired *cis*-alkene **32** in 78% over the two steps by employing the diimide that was derived from sulfonamide **40** (see Scheme 8).



Scheme 7. Intramolecular approach to radicicol (**2**) (TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl).

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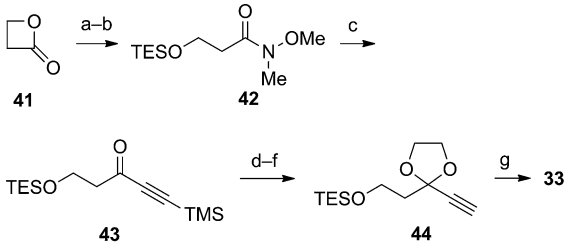
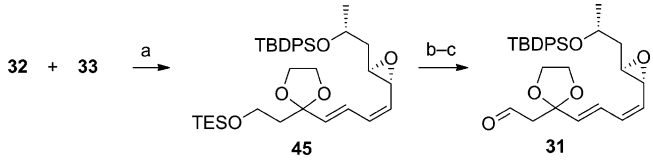
With the iodide component for the Suzuki coupling in hand, our attention turned to synthesis of boronate ester **33** (see Scheme 9). β-Propiolactone (**41**) was treated with *N*,*O*-dimethylhydroxylamine hydrochloride, and the resultant amide was protected by treatment with triethylsilyl chloride to give Weinreb amide **42** in 72% yield over the two steps. This was converted into alkyne **43** by the reaction with ethynyltrimethylsilane and *n*BuLi (94% yield). The unstable alkynone was protected through the reaction with ethylene glycol, trimethyl orthoformate, and a catalytic quantity of 4-toluenesulfonic acid to give its ketal derivative in 68% yield. This reaction also resulted in loss of the triethylsilyl protecting group. The removal of the trimethylsilyl group gave the free alkyne in 83% yield, whereupon the alcohol was reprotected by triethylsilylation in quantitative yield to give ketal-alkyne **44**. Alkyne **44** was converted into boronic ester **33** in 76% yield by treatment with neat pinacol borane at 70 °C for 6 d.



a) HN(OMe)Me·HCl, $AlMe_2Cl$, CH_3CN, 0 to 25 °C, 73%; b) Et_3SiCl, Et_3N, CH_2Cl_2, 0 to 25 °C, 99%; c) ethynyltrimethylsilane, *n*BuLi, Et_2O, –78 to –20 °C, 94%; d) ethylene glycol, *p*-TS·H_2O, $(MeO)_3CH$, PhMe, 25 °C, 68%; e) K_2CO_3, MeOH, 25 °C, 83%; f) Et_3SiCl, Et_3N, CH_2Cl_2, 0 to 25 °C; 100%; g) HB(pin), 70 °C, 76%.

Scheme 9. Generation of pinacol boronic ester **33** (TMS = trimethylsilyl, pin = pinacol).

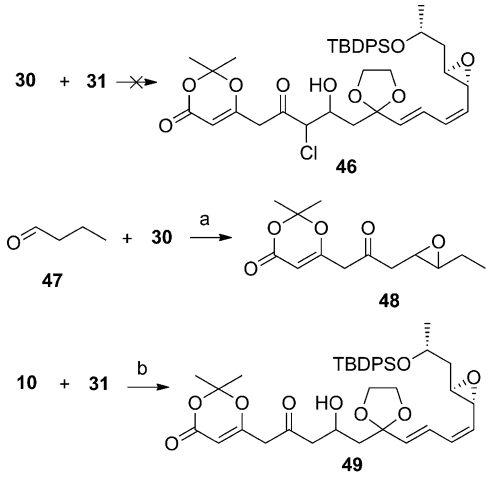
Boronic ester **33** and iodo-substituted alkene **32** successfully underwent a Suzuki coupling by using $Pd(PPh_3)_4$ and aqueous cesium carbonate in THF at 55 °C to furnish (*E*,*Z*)-diene **45** in 71% yield (see Scheme 10). The removal of the triethylsilyl group at 0 °C by treatment with tetrabutylammonium fluoride gave the primary alcohol, which was readily oxidized to give aldehyde **31** in 76% yield for the two steps.



a) $Pd(PPh_3)_4$, Cs_2CO_3, THF, H_2O, 55 °C, 71%; b) *t*BuN_4F, THF, 0 °C, 91%; c) Dess Martin periodinane, CH_2Cl_2, 25 °C, 83%

Scheme 10. Coupling of fragments **32** and **33**.

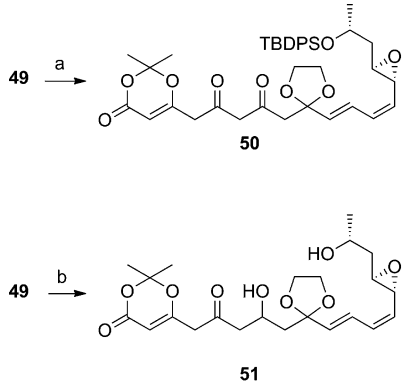
The attempted addition of the dianion that was derived from chloro-substituted keto-dioxinone **30** with aldehyde **31** was not successful (see Scheme 11). The attempted aldol reaction of the dianion derived from **30** with butyraldehyde (**47**) was very slow and ultimately gave epoxide **48**, but in only 19% yield, which showed the impracticality of chlorination at this stage. Fortunately, hydroxyalkylation of the dianion derived from keto-dioxinone **10** with aldehyde **31** was successful and gave the required adduct **49** in 73% yield.



a) *n*BuLi, *i*Pr_2NH, THF, –78 to 25 °C, 19%; b i) *n*-BuLi, *i*Pr_2NH, THF, –78 to -40 °C; ii) formic acid, –40 to 25 °C, 73%.

Scheme 11. Formation of β-hydroxy keto-dioxinone **49**.

The oxidation of alcohol **49** with Dess–Martin periodinane (DMP) gave unstable diketo-dioxinone **50**, which decomposed upon an attempted desilylation. In contrast, the desilylation of keto-dioxinone **49** with tetrabutylammonium fluoride gave the corresponding alcohol **51** in 79% yield (see Scheme 12). We briefly examined the thermolysis of diol-dioxinone **51**, as we expected that ketene trapping to form the macrocyclic lactone would be favored over the eight-membered ring lactone. However, when diol **51** was heated in toluene, only an intractable mixture of products was obtained.



a) DMP, CH_2Cl_2, 25 °C; b) *t*Bu_4NF, 4 Å molecular sieves, THF, 25 °C, 79%.

Scheme 12. Generation of diketo-dioxinone **50** and diol **51**.

Conclusions

Two concise strategies towards the synthesis of radicicol (**2**) and related macrolactones have been investigated. The

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biomimetic intermolecular route provides a simple and functional group tolerant pathway towards the resorcylates and incorporates both the esterification and aromatization steps through a reliable one-pot procedure. It is particularly noteworthy that the protected precursor (i.e., ketal **14**) to monocillin I (**1**) was obtained in 10 steps as its longest linear sequence. Further studies of resorcylate chemistry for use with both total synthesis and medicinal chemistry will be reported in due course.

Experimental Section

General Methods: All reactions were carried out at room temperature in oven-dried glassware under dry N_2 or Ar, unless otherwise stated. The reaction solvents THF and PhMe were distilled over Na/Ph_2CO under N_2, and MeOH, CH_2Cl_2, and Et_3N were distilled over CaH_2 under N_2. H_2O refers to redistilled H_2O. Other solvents and all reagents were obtained from commercial suppliers, and they were used as obtained if the purity was >98%. Flash chromatography was performed with Merck silica gel 60 particle size 40–63 mm (eluents are given in parentheses). Hexanes refer to petroleum spirits with a boiling range of 40–60 °C. Thin layer chromatography was performed on precoated aluminum-backed plates (Merck Kieselgel 60 F254), and the visualization was accomplished under UV light (254 nm) and by staining with aqueous potassium permanganate or vanillin followed by gentle heating with a heat gun. IR spectra were recorded neat. The ^1H and ^{13}C NMR spectroscopic data were recorded at 400 or 500 MHz and at 100 or 125 MHz, respectively. The chemical shifts (δ) are reported in parts per million (ppm) and referenced to the solvent peak (residual $CHCl_3$ for ^1H NMR, δ = 7.26 ppm; $CDCl_3$ for ^{13}C NMR, δ = 77.00 ppm). Coupling constants (J) are reported in Hertz (Hz) to the nearest 0.1 Hz.

Ethyl 2-[(1*E*,3*E*)-Penta-1,3-dienyl]-1,3-dioxolan-2-yl)acetate: Oxalyl chloride (10.3 mL, 120 mmol, 1.2 equiv.) was added dropwise with stirring to a suspension of sorbic acid **12** (11 g, 100 mmol) in CH_2Cl_2 (50 mL). After 16 h, all volatiles were removed in vacuo, and the crude acid chloride was used directly in the following reaction. EtOAc (12 mL, 120 mmol, 1.2 equiv.) was added with stirring to freshly prepared $LiN(SiMe_3)_2$ (220 mmol, 2.2 equiv.) in dry THF (200 mL) at –78 °C. After 30 min, the crude sorbyl chloride (100 mmol, 1.0 equiv.) in THF (20 mL) was added dropwise, and the reaction mixture was stirred at –78 °C for 1 h. Saturated aqueous NH_4Cl (50 mL), brine (50 mL), and Et_2O (500 mL) were added, and the pH of the aqueous layer was adjusted to <3 by the addition of aqueous HCl (2 M). The layers were separated, and the organic layer was washed with brine (100 mL), dried with $MgSO_4$, and filtered. All volatiles were removed in vacuo, and the residue was dissolved in dry PhMe (100 mL). A mixture of $(EtO)_3CH$ (33 mL, 200 mmol, 2.0 equiv.), ethylene glycol (34 mL, 600 mmol), and pTSA·H_2O (1.0 g, 5.30 mmol, 0.05 equiv.), which was kept at 20 mbar and at 40 °C for 1 h, was added with stirring to the PhMe solution of the crude β-keto ester. After 16 h, the reaction mixture was concentrated in vacuo, and the residue was purified by chromatography (hexanes/EtOAc, 20:1 to 5:1) to obtain the title compound (17 g, 74.0 mmol, 74% yield) as a colorless oil that consisted of both the (*Z*) and (*E*) geometric isomers in a ratio of 1:4.0. The NMR spectroscopic data are given for the major (*E*) geometric isomer. IR (neat): $\tilde{\nu}$ = 1734, 1370, 1174, 1097, 1035, 991, 948 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.34 (dd, J = 10.4, 15.3 Hz, 1 H), 6.02 (m, 1 H), 5.80–5.72 (m, 1 H), 5.57 (d, J = 15.3 Hz, 1 H), 4.14 (q, J = 7.1 Hz, 2 H), 4.02–3.87 (m, 4 H), 2.77 (s, 2 H), 1.75 (d, J = 7.1 Hz, 3 H), 1.24 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ = 168.9, 131.7, 131.2, 130.1, 128.5, 106.5, 64.7 (2 C), 60.5, 44.3, 18.1, 14.2 ppm. HRMS [CI+ (chemical ionization)]: calcd. for $C_{12}H_{19}O_4$ $[M + H]^+$ 227.1278; found 227.1285.

***N*-Methoxy-*N*-methyl-2-(2-penta-1,3-dienyl-1,3-dioxolan-2-yl)acetamide (11):** *n*BuLi (1.6 M in hexane, 2.4 mL, 3.80 mmol, 3.0 equiv.) was added to Me(MeO)NH·HCl (180 mg, 1.89 mmol, 1.5 equiv.) in dry THF (25 mL) at –78 °C. The reaction mixture was warmed to room temperature, and ethyl (2-penta-1,3-dienyl-[1,3]dioxolan-2-yl) acetate (290 mg, 1.26 mmol, 1.0 equiv.) was added. The mixture was then stirred for 16 h. Saturated aqueous NH_4Cl (10 mL), brine (10 mL), and EtOAc (75 mL) were added, and the pH of the aqueous layer was adjusted to <3 by the addition of aqueous HCl (2 M). The layers were separated, and the organic layer was washed with brine (10 mL), dried with $MgSO_4$, and filtered. All volatiles were removed in vacuo, and the residue was purified by chromatography (hexanes/EtOAc, 2:1) to provide **11** (61 mg, 0.25 mmol, 20% yield) as a colorless oil that consisted of the (*Z*) and (*E*) geometric isomers in a ratio of 1:3.7. The NMR spectroscopic data are given for the major (*E*) geometric isomer. IR (neat): $\tilde{\nu}$ = 1664, 1438, 1383, 1181, 1117, 1033, 995, 950 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.34 (dd, J = 10.6, 15.3 Hz, 1 H), 6.05 (m, 1 H), 5.75 (m, 1 H), 5.66 (d, J = 15.3 Hz, 1 H), 4.02–3.85 (m, 4 H), 3.68 (s, 3 H), 3.17 (s, 3 H), 2.95 (s, 2 H), 1.74 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ = 169.7, 131.4, 130.7, 130.3, 129.3, 107.1, 64.6 (2 C), 61.2, 40.9, 32.0, 18.2 ppm. HRMS (ESI+): calcd. for $C_{12}H_{19}NNaO_4$ $[M + Na]^+$ 264.1206; found 264.1220.

(2*R*,4*R*,5*R*)-1-Methyl-2-(3-ethenyloxiranyl)ethyl 2,4-Diacetoxy-6-(2-penta-1,3-dienyl-1,3-dioxolan-2-ylmethyl)benzoate (13): Keto-dioxinone **10** (260 mg, 1.40 mmol, 1.0 equiv.) was added to freshly prepared $LiN(iPr)_2$ (3.10 mmol, 2.2 equiv.) in dry THF (30 mL) at –78 °C, and the temperature was increased to –60 °C over 1 h. Et_2Zn (1 M in THF, 2.8 mL, 2.80 mmol, 2.0 equiv.) was added dropwise. After 30 min at –40 °C, *N*-methoxy-*N*-methyl-2-(2-penta-1,3-dienyl-1,3-dioxolan-2-yl)acetamide (**11**, 350 mg, 1.45 mmol, 1.1 equiv.) was added with stirring, and the temperature was kept below –10 °C for 2.5 h. Aqueous citric acid (10% solution, 20 mL) and EtOAc (100 mL) were added, and the layers were separated. The organic layer was washed with brine (10 mL), dried with $MgSO_4$, and filtered. All volatiles were removed in vacuo, and the residue was purified by chromatography (CH_2Cl_2/EtOAc, 5:1) to obtain dioxinone **9** (320 mg, 0.88 mmol, 63% yield) as a pale yellow oil. This compound was too unstable for full characterization and was used in the subsequent reaction immediately upon isolation. Dioxinone **9** (198 mg, 0.54 mmol, 1.0 equiv.) and alcohol **8** (77 mg, 0.600 mmol, 1.1 equiv.) were heated in PhMe (5 mL) at 110 °C for 2 h. After complete consumption of dioxinone **9**, as determined by TLC analysis, CH_2Cl_2 (5 mL), *i*PrOH (5 mL), and CsOAc (500 mg, 2.50 mmol, 5.0 equiv.) were added. The resulting mixture was stirred for 2 h, and then AcOH (3.0 mL, approximately 100 equiv.) was added. After 1 h, the reaction mixture was concentrated in vacuo, and the residue was dissolved in THF (20 mL). Ac_2O (4.0 mL) and DMAP (61 mg) were added. After 30 min, the reaction mixture was concentrated in vacuo, and the residue was purified by chromatography (hexanes/EtOAc, 5:1) to give ester **13** (190 mg, 0.370 mmol, 68% yield) as a colorless oil that consisted of a mixture of (*Z*) and (*E*) geometric isomers in a 1:3.9 ratio. The NMR spectroscopic data are given for the major (*E*) geometric isomer. $[\alpha]_D^{25}$ = –1.4 (c = 0.95, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1771, 1722, 1612, 1369, 1281, 1187, 1135, 1035, 990, 907, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.98 (d, J = 2.1 Hz, 1 H), 6.86 (d, J = 2.1 Hz, 1 H), 6.28 (dd, J = 10.6, 15.2 Hz, 1 H), 6.01 (m, 1 H), 5.57

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(qd, J = 6.7, 13.4 Hz, 1 H), 5.61–5.43 (m, 3 H), 5.34–5.25 (m, 2 H), 3.73–3.66 (m, 2 H), 3.50–3.45 (m, 2 H), 3.36 (d, J = 14.0 Hz, 1 H), 3.20 (d, J = 14.0 Hz, 1 H), 3.12 (dd, J = 2.0, 7.3 Hz, 1 H), 2.95 (td, J = 2.0, 5.9 Hz, 1 H), 2.27 (s, 3 H), 2.25 (s, 3 H), 2.00–1.87 (m, 2 H), 1.76 (d, J = 6.9 Hz, 3 H), 1.43 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ = 168.8, 168.6, 165.1, 151.0, 149.0, 137.3, 135.3, 132.3, 131.4, 130.5, 130.3, 130.1, 123.6, 119.5, 115.0, 108.0, 69.6, 64.9, 64.9, 58.3, 56.7, 41.8, 38.0, 21.1, 21.0, 19.6, 18.2 ppm. HRMS (ESI+): calcd. for $C_{27}H_{32}NaO_9$ [M + Na]$^+$ 523.1939; found 523.1936.

(1a*R*,2*Z*,4*E*,14*R*,15a*R*)-14-Methyl-12-oxo-1a,7,12,14,15,15a-hexahydrospiro{benzo[*c*]oxireno[2,3-*k*][1]oxacyclotetradecine-6,2′-1,3-dioxolane}-9,11-diyl Diacetate (14): Triene **13** (150 mg, 0.300 mmol) was dissolved in CH_2Cl_2 (250 mL), and the solution was heated at reflux for 20 min under N_2. Grubbs–Hoveyda II catalyst (**16**, 56 mg, 0.0900 mmol, 30 mol-%) was added in one portion, and the reaction mixture was kept at 40 to 45 °C for 4 h. DMSO (0.1 mL) was added, and the mixture was stirred overnight. All volatiles were removed in vacuo, and the residue was purified by chromatography (hexanes/EtOAc, 5:1 to 5:2) to obtain macrocycle **14** (37 mg, 80.7 μmol, 27% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, J = 2.2 Hz, 1 H), 6.87 (d, J = 2.2 Hz, 1 H), 6.61 (dd, J = 9.5, 15.9 Hz, 1 H), 6.00 (t, J = 10.2 Hz, 1 H), 5.61 (d, J = 15.9 Hz, 1 H), 5.39 (dd, J = 4.8, 10.9 Hz, 1 H), 5.23 (m, 1 H), 4.10–3.96 (m, 4 H), 3.43 (m, 1 H), 3.42 (d, J = 15.0 Hz, 1 H), 3.16 (d, J = 15.3 Hz, 1 H), 2.99 (m, 1 H), 2.31 (ddd, J = 3.6, 5.6, 15.0 Hz, 1 H), 2.27 (s, 3 H), 2.23 (s, 3 H), 1.68 (ddd, J = 3.5, 7.1, 15.0 Hz, 1 H), 1.51 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ = 168.5, 168.3, 165.2, 151.5, 148.4, 137.3, 132.8 130.9, 129.5, 128.2, 125.0, 121.1, 114.9, 108.7, 69.8, 65.1, 64.6, 55.7, 54.8, 38.2, 36.9, 21.1, 20.9, 19.1 ppm. HRMS (ESI+): calcd. for $C_{24}H_{26}NaO_9$ [M + Na]$^+$ 481.1469; found 481.1475.

(4*E*,6*E*)-*N*-Methoxy-*N*-methyl-3-[(triisopropylsilyl)oxy]octa-4,6-dienamide (18a): Amide **17** (1.0 g, 10.0 mmol, 1.0 equiv.) was added with stirring to freshly prepared LiN(iPr)$_2$ (11.0 mmol, 1.1 equiv.) in dry THF (25 mL) at –78 °C. After 30 min, sorbic aldehyde (0.96 g, 10.0 mmol, 1.0 equiv.) was added in one portion, and after 10 min, the solution was warmed to 0 °C. iPr$_3$SiCl (2.3 mL, 11.0 mmol, 1.1 equiv.) was added at 0 °C, and the mixture was warmed to room temperature overnight. Saturated aqueous NH_4Cl (10 mL), brine (10 mL), and Et_2O (150 mL) were added, and the pH of the aqueous layer was adjusted to <3 by the addition of aqueous HCl (2 M). The layers were separated, and the organic layer was washed with brine (10 mL), dried with $MgSO_4$, and filtered. All volatiles were removed in vacuo, and the residue was purified by chromatography (hexanes/EtOAc, 30:1 to 15:1) to obtain amide **18a** (2.7 g, 7.51 mmol, 75% yield) as a colorless oil that consisted of both the (*Z*) and (*E*) geometric isomers in a 1:8.8 ratio. The NMR spectroscopic data are given for the major (*E*) geometric isomer. IR (neat): $\tilde{\nu}$ = 1665, 1463, 1384, 1085, 1067, 990, 884, 746, 680 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (dd, J = 10.4, 15.2 Hz, 1 H), 6.03–5.95 (m, 1 H), 5.70–5.55 (m, 2 H), 4.80 (q, J = 6.8 Hz, 1 H), 3.67 (s, 3 H), 3.15 (s, 3 H), 2.81 (dd, J = 6.3, 14.5 Hz, 1 H), 2.52 (dd, J = 6.6, 14.5 Hz, 1 H), 1.73 (d, J = 6.9 Hz, 3 H), 1.04 (s, 21 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ = 171.6, 133.3, 130.8, 130.0, 129.5, 70.4, 61.3, 41.3, 31.9, 18.1, 18.0 (6 C), 12.3 (3 C) ppm. HRMS (ESI+): calcd. for $C_{19}H_{37}NNaO_3Si$ [M + Na]$^+$ 378.2435; found 378.2455.

6-{(2*Z*,7*E*,9*E*)-2-Hydroxy-4-oxo-6-[(triisopropylsilyl)oxy]undeca-2,7,9-trien-1-yl}-2,2-dimethyl-4*H*-1,3-dioxin-4-one (19a): Keto-dioxinone **10** (370 mg, 2.01 mmol, 1.0 equiv.) was added to freshly prepared LiN(iPr)$_2$ (4.22 mmol, 2.1 equiv.) in dry THF (40 mL) at –78 °C, and the temperature was increased to –60 °C over 1 h. Et_2Zn (1 M in THF, 4.0 mL, 4.02 mmol, 2.0 equiv.) was added dropwise. After 30 min at –40 °C, Weinreb amide **18a** (710 mg, 2.01 mmol, 1.0 equiv.) was added, and the mixture was stirred for 2.5 h, as the temperature was kept below –10 °C. Saturated aqueous NH_4Cl (10 mL), brine (10 mL), and Et_2O (200 mL) were added, and the pH of the aqueous layer was adjusted to <3 by the addition of aqueous HCl (2 M). The layers were separated, and the organic layer was washed with brine (10 mL), dried with $MgSO_4$, and filtered. All volatiles were removed in vacuo, and the residue was purified by chromatography (hexanes/EtOAc, 15:1) to obtain dioxinone **19a** (650 mg, 1.36 mmol, 66% yield) as a colorless oil that consisted of both the (*Z*) and (*E*) geometric isomers in a 1:5.8 ratio. The NMR spectroscopic data are given for the major (*E*) geometric isomer: IR (thin film): $\tilde{\nu}$ = 2943, 2866, 1735, 1615, 1389, 1376, 1272, 1204, 1015, 985, 883, 680 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.01 (br. s, 1 H), 6.11 (dd, J = 10.4, 15.1 Hz, 1 H), 6.03–5.95 (m, 1 H), 5.72–5.63 (m, 1 H), 5.56–5.47 (m, 1 H), 5.55 (s, 1 H), 5.36 (s, 1 H), 4.66 (q, J = 6.7 Hz, 1 H), 3.19 (s, 2 H), 2.56 (dd, J = 7.0, 13.7 Hz, 1 H), 2.42 (dd, J = 5.9, 13.7 Hz, 1 H), 1.74 (d, J = 6.4 Hz, 3 H), 1.68 (s, 6 H), 1.04–1.02 (m, 21 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ = 189.0, 188.7, 164.9, 160.7, 132.3, 130.6, 130.5, 130.2, 107.1, 101.5, 96.3, 70.9, 47.2, 43.6, 24.92, 24.85, 18.1, 18.0, 12.3 ppm. HRMS (ESI+): calcd. for $C_{26}H_{42}NaO_6Si^+$ [M + Na]$^+$ 501.2643; found 501.2637.

(2*R*,4*R*,5*R*)-1-Methyl-2-(3-ethenyloxiranyl)ethyl 2,4-Dihydroxy-6-(2-triisopropylsilyloxy-hepta-3,5-dienyl)benzoate (20a): Dioxinone **19a** (500 mg, 1.02 mmol, 1.0 equiv.) and alcohol **8** (150 mg, 1.20 mmol, 1.2 equiv.) were heated in PhMe (2.0 mL) at 110 °C for 2 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (5 mL) and iPrOH (5 mL). CsOAc (960 mg, 5.00 mmol, 5.0 equiv.) was added. The mixture was stirred for 2 h, whereupon AcOH (3.0 mL, approximately 50 equiv.) was added. After 12 h, EtOAc (80 mL), water (5 mL), and brine (5 mL) were added, and the layers were separated. The organic layer was washed with brine (4 mL) and dried with $MgSO_4$, and all volatiles were removed in vacuo. The residue was dissolved in PhMe (2 mL), and purification by chromatography (hexanes/Et_2O, 7:1) produced resorcylate **20a** (400 mg, 0.750 mmol, 74% yield) as a colorless oil that consisted of an inseparable mixture of diastereomers [CH-OSi(iPr)$_3$]. IR (thin film): $\tilde{\nu}$ = 3383, 1646, 1619, 1449, 1310, 1257, 1104, 988, 882, 679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = [11.66, 11.53] (s, 1 H), 6.30 (br. s, 2 H), 6.14–5.94 (m, 2 H), 5.70–5.61 (m, 1 H), 5.60–5.37 (m, 5 H), 5.30–5.24 (m, 1 H), 4.50–4.42 (m, 1 H), 3.53–3.32 (m, 1 H), 3.16–3.08 (m, 1 H), 2.96–2.86 (m, 1 H), 2.75–2.67 (m, 1 H), 2.02–1.94 (m, 2 H), 1.78–1.72 (m, 3 H), 1.47–1.42 (m, 3 H), 0.93 (s, 21 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ = [170.7, 170.6], [165.3, 164.9], [159.9, 159.8], [144.0, 143.9], [135.0, 134.8], [133.9, 133.7], 130.8, [130.1, 129.9], [129.5, 129.4], [119.8, 119.7], [113.7, 113.4], [106.0, 105.6], 101.9, [74.2, 74.0], [70.2, 70.1], [58.4, 58.2], [57.0, 56.9], [45.1, 44.7], [38.2, 38.2], [20.1, 20.1], 18.1, [18.0, 18.0] (6 C), 12.50 (3 C) ppm. N.B.: The data in square brackets correspond to the signals for the diastereomers. HRMS (ESI+): calcd. for $C_{30}H_{46}NaO_6Si$ [M + Na]$^+$ 553.2956; found 553.2962.

(2*R*,4*R*,5*R*)-1-Methyl-2-(3-ethenyloxiranyl)ethyl 2,4-Diacetoxy-6-(2-triisopropylsilyloxy-hepta-3,5-dienyl)benzoate: Resorcylate **20a** (290 mg, 0.506 mmol, 1.0 equiv.) was dissolved in THF (15 mL), and Ac_2O (3.0 mL, excess) and DMAP (13 mg, 0.101 mmol, 0.20 equiv.) were added. After 1 h, EtOAc (200 mL), H_2O (20 mL), saturated aqueous $NaHCO_3$ (4 mL), and brine (20 mL) were added, and the layers were separated. The organic layer was washed with brine (2 × 20 mL), dried with $MgSO_4$, and concentrated in vacuo to give (2*R*,4*R*,5*R*)-1-methyl-2-(3-ethenyloxiranyl)ethyl 2,4-

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diacetoxy-6-(2-triisopropylsilyloxy-hepta-3,5-dienyl)benzoate (330 mg, 0.537 mmol, 98% yield) as a colorless oil that consisted of an inseparable mixture of diastereomers [CH-OSi(*i*Pr)$_3$]. The product was used in the ring-closing metathesis step without further purification. IR (thin film): $\tilde{\nu}$ = 1778, 1725, 1613, 1464, 1429, 1369, 1274, 1192, 1137, 1090, 989, 884, 681 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99–6.96 (m, 1 H), 6.87–6.86 (m, 1 H), 6.08–5.93 (m, 2 H), 5.68–5.43 (m, 4 H), 5.33–5.24 (m, 2 H), 4.55–4.44 (m, 1 H), 3.13–3.08 (m, 1 H), 2.96–2.82 (m, 3 H), 2.26 (s, 3 H), 2.24 (s, 3 H), 1.93–1.88 (m, 2 H), 1.76–1.72 (m, 3 H), 1.44–1.39 (m, 3 H), 0.96–0.94 (m, 21 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ = [168.4, 168.4], 165.4, 151.0, 148.5, [139.4, 139.4], 135.2, 133.3, 133.1, 130.8, [130.4, 130.3], 129.6, [124.6, 124.6], [122.5, 122.4], [119.6, 119.5], 114.6, 73.9, 69.9, [58.1, 58.1], 56.6, [43.0, 42.9], [38.0, 38.0], 21.0, 20.9, [19.8, 19.7], 18.1, [18.0, 17.9] (6 C), 12.4 (3 C). N.B.: The data in square brackets correspond to the signals for the diastereomers. HRMS (ESI+): calcd. for $C_{34}H_{50}NaO_8Si$ [M + Na]$^+$ 637.3167; found 637.3164.

(1a*R*,2*Z*,4*E*,14*R*,15a*R*)-14-Methyl-12-oxo-6-[(triisopropylsilyl)oxy]-6,7,12,14,15,15a-hexahydro-1a*H*-benzo[*c*]oxireno[2,3-*k*][1]oxacyclotetradecine-9,11-diyl Diacetate (21a): (2*R*,4*R*,5*R*)-1-Methyl-2-(3-ethenyloxiranyl)ethyl 2,4-diacetoxy-6-(2-triisopropylsilyloxy-hepta-3,5-dienyl)benzoate (120 mg, 0.195 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (250 mL), and the solution was heated at reflux for 20 min under N_2. Grubbs–Hoveyda II catalyst (**16**, 13 mg, 20.7 μmol, 10 mol-%) was added in one portion, and the reaction mixture was kept at 40 to 45 °C for 7 h. DMSO (1 mL) was added, and the mixture was stirred overnight. The solution was washed with H_2O (30 mL) and H_2O/brine (1:1, 30 mL) and then dried with $MgSO_4$. All volatiles were removed in vacuo. The resultant diastereomers **21aI** and **21aII** (65 mg, 0.113 mg, 57% yield) were separated by chromatography (hexanes/EtOAc, 10:1) to obtain **21aI** (30 mg) and **21aII** (35 mg), which were both colorless oils. Data for **21aI**: IR (thin film): $\tilde{\nu}$ = 1777, 1721, 1611, 1464, 1428, 1369, 1282, 1194, 1137, 1084, 915, 884, 681 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 2.2 Hz, 1 H), 6.87 (d, *J* = 2.2 Hz, 1 H), 6.28 (dd, *J* = 9.3, 15.8 Hz, 1 H), 6.02 (m, 1 H), 5.71 (dd, *J* = 5.6, 15.8 Hz, 1 H), 5.34 (dd, *J* = 4.7, 10.8 Hz, 1 H), 5.19 (m, 1 H), 4.81 (q, *J* = 5.7 Hz, 1 H), 3.42 (m, 1 H), 3.33 (dd, *J* = 5.0, 14.8 Hz, 1 H), 3.06 (dd, *J* = 6.9, 14.8 Hz, 1 H), 2.99 (ddd, *J* = 2.5, 3.5, 6.9 Hz, 1 H), 2.37 (ddd, *J* = 3.7, 7.5, 14.9 Hz, 1 H), 2.27 (s, 3 H), 2.25 (s, 3 H), 1.64 (ddd, *J* = 2.9, 7.2, 14.9 Hz, 1 H), 1.50 (d, *J* = 6.3 Hz, 3 H), 1.06 (m, 21 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ = 168.4, 168.4, 165.6, 151.4, 148.8, 139.2, 137.2, 131.4, 127.7, 126.0, 124.5, 120.9, 114.7, 71.9, 70.1, 56.2, 54.5, 40.1, 37.2, 21.1, 20.9, 19.6, 18.0 (6 C), 12.3 (3 C) ppm. HRMS (ESI+): calcd. for $C_{31}H_{45}O_8Si$ [M + H]$^+$ 573.2878; found 573.2873. Data for **21aII**: IR (thin film): $\tilde{\nu}$ = 1775, 1723, 1611, 1464, 1426, 1369, 1277, 1193, 1138, 1087, 910, 883, 683 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 1.8 Hz, 1 H), 6.86 (d, *J* = 2.3 Hz, 1 H), 6.18 (dd, *J* = 7.5, 16.2 Hz, 1 H), 6.04 (m, 1 H), 5.67 (dd, *J* = 3.9, 15.7 Hz, 1 H), 5.17 (dd, *J* = 7.2, 11.1 Hz, 1 H), 5.04 (m, 1 H), 4.63 (m, 1 H), 3.55 (dd, *J* = 1.4, 7.1 Hz, 1 H), 3.41 (dd, *J* = 9.5, 14.5 Hz, 1 H), 3.07 (dd, *J* = 3.6, 14.5 Hz, 1 H), 2.98 (m, 1 H), 2.28 (s, 3 H), 2.26 (s, 3 H), 2.23 (m, 1 H), 1.92 (ddd, *J* = 2.1, 4.3, 15.6 Hz, 1 H), 1.44 (d, *J* = 6.3 Hz, 3 H), 1.11 (m, 21 H) ppm. ^{13}C NMR (100.7 MHz, $CDCl_3$): δ = 168.4, 168.3, 165.1, 151.6, 148.9, 139.9, 135.8, 132.4, 128.3, 124.9, 124.6, 120.6, 114.7, 73.5, 68.2, 56.1, 54.0, 39.0, 35.9, 21.2, 21.0, 19.9, 18.1 (6 C), 12.4 (3 C) ppm. HRMS (ESI+): calcd. for $C_{31}H_{45}O_8Si$ [M + H]$^+$ 573.2878; found 573.2868.

(4*E*,6*E*)-3-Hydroxy-*N*-methoxy-*N*-methylocta-4,6-dienamide: Amide **17** (6.0 g, 50.0 mmol, 1.1 equiv.) in THF (20 mL) was added dropwise with stirring to freshly prepared LiN(*i*Pr)$_2$ (65.0 mmol) in THF (60 mL) at –78 °C. After 1 h, sorbic aldehyde (5.2 mL, 47.5 mmol, 1.0 equiv.) in THF (20 mL) was added dropwise, and the reaction mixture was stirred at –78 °C for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (50 mL), and the mixture was warmed to room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (50 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexanes, 1:3) to give the title amide (6.4 g, 32.1 mmol, 68% yield) as a light brown oil that consisted of both the (*Z*) and (*E*) geometric isomers in a ratio of 1:7.5. The NMR spectroscopic data are given for the major (*E*) geometric isomer. IR (thin film): $\tilde{\nu}$ = 3438, 1651, 1387, 1179, 1108, 987 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.27 (dd, *J* = 15.3, 10.4 Hz, 1 H), 6.05 (ddd, *J* = 14.9, 10.5, 1.4 Hz, 1 H), 5.73 (dq, *J* = 13.4, 6.6 Hz, 1 H), 5.61 (dd, *J* = 15.3, 6.2 Hz, 1 H), 4.67–4.51 (m, 1 H), 3.67 (s, 3 H), 3.18 (s, 3 H), 2.64 (dt, *J* = 16.7, 12.6 Hz, 2 H), 1.80–1.70 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.2, 131.2, 130.8, 130.7, 130.1, 68.5, 61.3, 38.4, 31.8, 18.1 ppm. HRMS (ESI+): calcd. for $C_{10}H_{17}NO_3$ [M + Na]$^+$ 222.1106; found 222.1105.

(4*E*,6*E*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*-methylocta-4,6-dienamide (18b): *t*BuMe$_2$SiCl (1.1 g, 7.33 mmol, 1.1 equiv.) and imidazole (0.5 g, 7.33 mmol, 1.1 equiv.) were added with stirring to (4*E*,6*E*)-3-hydroxy-*N*-methoxy-*N*-methylocta-4,6-dienamide (1.3 g, 6.66 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL). After 16 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with saturated aqueous NH_4Cl (40 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography (Et_2O/hexanes, 1:10 to 1:5) give amide **18b** (1.7 g, 5.53 mmol, 83% yield) as a pale yellow oil that consisted of both the (*Z*) and (*E*) geometric isomers in a ratio of 1:6.8. The NMR spectroscopic data are given for the major (*E*) geometric isomer. IR (thin film): $\tilde{\nu}$ = 1662, 1077, 987, 829, 776 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.17 (dd, *J* = 15.2, 10.4 Hz, 1 H), 6.05–5.98 (m, 1 H), 5.71–5.63 (m, 1 H), 5.57 (dd, *J* = 14.8, 6.4 Hz, 1 H), 4.70 (dd, *J* = 12.8, 6.0 Hz, 1 H), 3.68 (s, 3 H), 3.17 (s, 3 H), 2.84 (dd, *J* = 14.4, 8.0 Hz, 1 H), 2.40 (dd, *J* = 14.4, 5.2 Hz, 1 H), 1.74 (d, *J* = 5.2 Hz, 3 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 189.7, 133.1, 130.8, 129.5, 129.5, 70.3, 61.4, 40.7, 31.9, 25.8 (3 C), 25.6, 18.1, –4.5, –5.0 ppm. HRMS (ESI+): calcd. for $C_{16}H_{31}NO_3Si$ [M + Na]$^+$ 336.1971; found 336.1978.

6-[(2*Z*,7*E*,9*E*)-6-(*tert*-Butyldimethylsilyloxy)-2-hydroxy-4-oxoundeca-2,7,9-trienyl]-2,2-dimethyl-4*H*-1,3-dioxin-4-one (19b): Ketodioxinone **10** (2.1 g, 11.5 mmol, 2.0 equiv.) in dry THF (20 mL) was added with stirring to freshly prepared LiN(*i*Pr)$_2$ (23.0 mmol, 4.0 equiv.) in dry THF (100 mL) at –78 °C, and the mixture was warmed to –40 °C. After 1 h, amide **18b** (1.8 g, 5.74 mmol, 1.0 equiv.) in dry THF (10 mL) was added with stirring at –40 °C. After 2 h, the mixture was acidified to pH = 4 by the addition of 10% aqueous citric acid (approximately 100 mL), and the resulting mixture was warmed to room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexanes, 1:5) to give dioxinone **19b** (1.9 g, 4.31, 75% yield) as a pale yellow oil. IR (thin film): $\tilde{\nu}$ = 1733, 1609, 1376, 1272, 1016, 837 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.12 (dd, *J* = 14.8, 10.4 Hz, 1 H), 5.99 (ddd, *J* = 14.8, 10.4, 1.2 Hz, 1 H), 5.72–5.64 (m, 1 H), 5.55 (s, 1

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H), 5.47 (dd, J = 14.8, 6.8 Hz, 1 H), 5.36 (s, 1 H), 4.53 (dd, J = 13.2, 6.8 Hz, 1 H), 3.19 (s, 2 H), 2.44–2.39 (m, 2 H), 1.76 (d, J = 6.8 Hz, 3 H), 1.68 (s, 6 H), 0.83 (s, 9 H), –0.01 (s, 3 H), –0.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.0, 189.0, 165.0, 160.6, 132.2, 130.5 (2 C), 130.2, 107.1, 101.6, 96.3, 70.6, 46.8, 43.6, 25.7 (3 C), 25.0, 24.8, 18.1 (2 C), –4.4, –5.2 ppm. HRMS (ESI+): calcd. for $C_{23}H_{36}O_6Si$ $[M + Na]^+$ 459.2179; found 459.2193.

5-{(3*E*,5*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]hepta-3,5-dien-1-yl}-4-[({(*R*)-1-[(2*R*,3*R*)-3-ethenyloxiran-2-yl]propan-2-yl}oxy)carbonyl]-1,3-phenylene Diacetate (22b): Dioxinone **19b** (221 mg, 0.504 mmol, 1.3 equiv.) and alcohol **8** (50 mg, 0.390 mmol, 1.0 equiv.) in dry PhMe (5 mL) were heated to reflux for 3 h, and then the reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in MeOH (10 mL), and Cs_2CO_3 (640 mg, 1.95 mmol, 5.0 equiv.) was added. After 3 h, glacial AcOH (2.5 mL) was added, and the mixture was stirred for 2 h. The reaction was quenched by the addition of brine (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2× 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude material was filtered through a plug of silica and then used directly in the next step. The crude (*R*)-1-[(2*R*,3*R*)-3-ethenyloxiran-2-yl]propan-2-yl-2-{(3*E*,5*E*)-2-[(*tert*-butyldimethylsilyl)oxy]hepta-3,5-dien-1-yl}-4,6-dihydroxy benzoate in dry THF (15 mL) was added with stirring to DMAP (4.8 mg, 39.0 μmol, 10 mol-%) and Ac_2O (0.11 mL, 1.17 mmol, 3.0 equiv.) at room temperature, and the mixture was stirred for 2 h. The reaction was quenched by the addition of water (15 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3× 15 mL). The combined organic layers were washed with water (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL), and brine (30 mL) and then dried with $MgSO_4$. The organic phase was concentrated in vacuo, and the residue was purified by chromatography (EtOAc/hexanes, 1:6) to give resorcylate triene **22b** (94 mg, 0.164 mmol 42% yield) as a colorless oil. IR (thin film): $\tilde{\nu}$ = 1774, 1723, 1188, 1136, 837, 778 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95–6.93 (m, 1 H), 6.88–6.87 (m, 1 H), 6.16–6.07 (m, 1 H), 6.04–5.98 (m, 1 H), 5.69–5.63 (m, 1 H), 5.58–5.43 (m, 3 H), 5.34–5.25 (m, 2 H), 4.38–4.28 (m, 1 H), 3.13–3.10 (m, 1 H), 2.96–2.85 (m, 2 H), 2.74–2.68 (m, 1 H), 2.26 (s, 3 H), [2.25, 2.24] (m, 3 H), 1.94–1.89 (m, 2 H), 1.74 (d, J = 6.8 Hz, 3 H), 1.45–1.39 (m, 3 H), 0.79 (s, 9 H), [–0.15, –0.16] (2 s, 3 H), [–0.29, –0.30] (2 s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [168.5, 168.4], 165.4, 151.0, 148.6, [139.8, 139.7], 135.1, [133.2, 133.1], 130.8, [130.0, 130.0], 129.5, 124.4, [122.7, 122.6], [119.6, 119.6], 114.7, 73.3, 70.0, [58.2, 58.1], 56.6, [42.7, 42.7], [38.0, 38.0], 25.8 (6 C), [21.0, 21.0], 19.8, 19.7, [18.1, 18.0], –4.8, –5.4 ppm; N.B.: The data in square brackets correspond to the signals for the diastereomers (CH-OSi*t*BuMe$_2$). HRMS (ESI+): calcd. for $C_{31}H_{44}O_8$-SiNa $[M + Na]^+$ 595.2703; found 595.2693.

(*R*)-1-{(2*R*,3*R*)-3-[(*Z*)-Hepta-1,6-dienyl]oxiran-2-yl}propan-2-ol (27): $NaN(SiMe_3)_2$ (1.0 M in THF, 4.9 mL, 4.90 mmol, 1.8 equiv.) was added dropwise with stirring to phosphonium salt **25** (2.5 g, 5.21 mmol, 1.9 equiv.) in THF (20 mL) at 0 °C. After 30 min, the solution was cooled to –10 °C, and aldehyde **26** (1.0 g, 2.74 mmol, 1.0 equiv.) in THF (10 mL) was added dropwise. The mixture was stirred at –10 °C for 2 h, and the reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3× 10 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude material was filtered through a plug of silica and then used directly in the next step. Molecular sieves (4 Å, 900 mg) and Bu_4NF (1.0 M in THF, 3.0 mL, 3.01 mmol, 1.1 equiv.) were added sequentially with stirring to the crude *tert*-butyl[(*R*)-1-{(2*R*,3*R*)-3-[(*Z*)-hepta-1,6-dienyl]oxiran-2-yl}propan-2-yloxy]diphenylsilane in THF (20 mL). After 2 h, silica gel (400 mg) was added, and the solvent was removed in vacuo. The residue was purified by chromatography to give diene **27** (360 mg, 1.84 mmol, 67% yield) as a colorless oil. $[\alpha]_D^{25}$ = +20.2 (c = 1.0, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 3410, 1457, 1110, 992, 908 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85–5.86 (m, 2 H), 5.06–4.93 (m, 3 H), 4.12–4.04 (m, 1 H), 3.38 (dd, J = 1.6, 8.8 Hz, 1 H), 3.00–2.96 (m, 1 H), 2.30–2.06 (m, 4 H), 1.89–1.83 (m, 1 H), 1.63–1.47 (m, 3 H), 1.24 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 136.7, 126.8, 114.9, 66.5, 58.2, 5.9, 40.8, 33.1, 28.6, 27.0, 23.4 ppm. HRMS (ESI+): calcd. for $C_{12}H_{20}O_2$ $[M + H]^+$ 197.1542; found 197.1542.

(*R*)-1-{(2*R*,3*R*)-3-[(*Z*)-Hepta-1,6-dien-1-yl]oxiran-2-yl}propan-2-yl 4-Acetoxy-2-{(3*E*,5*E*)-2-[(*tert*-butyldimethylsilyl)oxy]hepta-3,5-dien-1-yl}-6-hydroxybenzoate: Diketo-dioxinone **19b** (140 mg, 0.330 mmol, 1.3 equiv.) and alcohol **27** (50 mg, 0.255 mmol, 1.0 equiv.) in PhMe (12 mL) were heated at reflux for 3 h, and the reaction mixture was then cooled to room temperature and concentrated in vacuo. The residue was dissolved in dry CH_2Cl_2 (8 mL) and *i*PrOH (4 mL), and the resulting mixture was heated over molecular sieves (4 Å, 200 mg) in a sealed tube to 100 °C for 16 h. The reaction mixture was cooled to room temperature and filtered through a plug of Celite® (CH_2Cl_2), and the filtrate was concentrated in vacuo. The residue was purified by chromatography (Et_2O/hexanes, 1:9) to give the title resorcylate (89 mg, 0.163 mmol, 64% yield) as a colorless oil. $[\alpha]_D^{25}$ = –26.4 (c = 1.0, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 3327, 1644, 1310, 1254, 1103, 833, 774 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = [11.70 and 11.63] (2 s, 1 H), 6.31–6.30 (m, 1 H), 6.26–6.24 (m, 1 H), 6.21–6.14 (m, 1 H), 6.09–6.02 (m, 1 H), 5.83–5.75 (m, 1 H), 5.72–5.66 (m, 2 H), 5.61–5.56 (m, 1 H), 5.49–5.41 (m, 1 H), 5.26–5.21 (m, 1 H), 5.04–4.96 (m, 3 H), 4.32–4.30 (m, 1 H), 3.51–3.46 (m, 1 H), 3.37–3.34 (m, 1 H), 2.95–2.91 (m, 1 H), [2.82–2.76 and 2.65–2.59] (2 m, 1 H), 2.25–2.07 (m, 4 H), 2.03–1.92 (m, 2 H), 1.76 (d, J = 6.8 Hz, 3 H), 1.52–1.49 (m, 2 H), 1.46 (d, J = 6.4 Hz, 3 H), [0.78 and 0.77] (2 s, 9 H), [–0.19 and –0.20] (2 s, 3 H), [–0.36 and –0.37] (2 s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [170.7, 170.7], [165.4, 165.2], [159.8, 159.7], [144.3, 144.3], 138.3, 136.8, 133.6, 130.9, [139.8, 129.7], 129.4, 126.6, 114.9, [113.8, 113.5], [105.9, 105.5], 101.9, [73.6, 73.4], [70.1, 70.1], 56.7, [53.8, 53.8], [44.9, 44.6], [38.4, 38.2], 33.1, 28.6, 27.0, [25.8 (3 C), 25.8 (3 C)], [20.2, 20.2], [18.1, 18.1], [–4.8, –4.8], [–5.4 –5.4] ppm. N.B.: The data in the square brackets correspond to the signals for the diastereomers (CH-OSi*t*BuMe$_2$), one carbon is missing as a result of overlapping signals. HRMS (ESI+): calcd. for $C_{32}H_{48}O_6SiNa$ $[M + Na]^+$ 579.3118; found 579.3126.

5-{(3*E*,5*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]hepta-3,5-dien-1-yl}-4-{[(*R*)-1-{(2*R*,3*R*)-3-[(*Z*)-hepta-1,6-dien-1-yl]oxiran-2-yl}propan-2-yloxy]carbonyl}-1,3-phenylene Diacetate (28): DMAP (5 mg, 10 mol-%) was added dropwise to (*R*)-1-{(2*R*,3*R*)-3-[(*Z*)-hepta-1,6-dien-1-yl]oxiran-2-yl}propan-2-yl 4-acetoxy-2-{(3*E*,5*E*)-2-[(*tert*-butyldimethylsilyl)oxy]hepta-3,5-dien-1-yl}-6-hydroxybenzoate (210 mg, 0.357 mmol, 1.0 equiv.) in dry THF (40 mL) at 0 °C. Ac_2O (0.18 mL, 1.85 mmol, 5.0 equiv.) was added, and the mixture was stirred for 1 h. The solvent was removed in vacuo, and the residue was immediately purified by chromatography (EtOAc/hexanes, 1:9) to furnish tetraene **28** (230 mg, 0.346 mmol, 97% yield) as a colorless oil. $[\alpha]_D^{25}$ = –22.4 (c = 0.8, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2929, 2856, 1774, 1724, 1187, 1133, 835, 776 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95–6.93 (m, 1 H), 6.88–6.87 (m, 1 H), 6.16–6.07 (m, 1 H), 6.04–5.98 (m, 1 H), 5.85–5.62 (m, 3 H), 5.56–5.49 (m, 1 H), 5.35–5.29 (m, 1 H), 5.05–4.96 (m, 3 H), 4.38–4.29 (m, 1 H), 3.38–

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3.34 (m, 1 H), 2.96–2.94 (m, 1 H), 2.90–2.86 (m, 1 H), 2.74–2.68 (m, 1 H), 2.27 (s, 3 H), 2.25 (s, 3 H), 2.22–2.16 (m, 2 H), 2.10–2.03 (m, 2 H), 1.94–1.89 (m, 2 H), 1.74 (d, J = 6.4 Hz, 3 H), 1.54–1.47 (m, 2 H), 1.45–1.41 (m, 3 H), 0.80 (s, 9 H), –0.13 to –0.16 (m, 3 H), –0.29 to –0.30 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 165.4, 151.0, 148.6, 138.3, [136.8, 136.8], [133.2, 133.1], 130.8, [130.0, 130.0], [129.6, 129.8], 128.6, 126.7, 125.3, 124.4, 122.7, 114.9, 114.7, 73.3, 70.0, 56.3, 53.9, 42.7, [38.2, 38.1], 33.1, 28.6, 27.1, 25.7 (5 C), [21.0, 21.0], [19.8, 19.7], [18.1, 18.0], –4.8, –5.4 ppm; N.B.: The data in square brackets correspond to the signals for the diastereomers (CH-OSi*t*BuMe$_2$). HRMS (ESI+): calcd. for $C_{36}H_{52}O_8Si$ [M + Na]$^+$ 663.3329; found 663.3337.

(1a*R*,2*Z*,4*E*,14*R*,15a*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]-14-methyl-12-oxo-6,7,12,14,15,15a-hexahydro-1a*H*-benzo[*c*]oxireno[2,3-*k*][1]oxacyclotetradecine-9,11-diyl Diacetate (21b): Tetraene **28** (12 mg, 20.0 μmol, 1.0 equiv.) in dry $ClCH_2CH_2Cl$ (10 mL) was heated to 60 °C in a sealed tube. Hoveyda–Grubbs II catalyst (**16**, 2.3 mg, 0.2 mol-%) was added in one portion, and the mixture was heated at 60 °C for 3 h. The solvent was removed in vacuo, and the residue was purified by chromatography (EtOAc/hexanes, 1:9) to give macrocycle **21b** (8 mg, 0.0150 mmol, 75% yield) as a colorless oil that consisted of an inseparable mixture of diastereomers. IR (thin film): $\tilde{\nu}$ = 1776, 1724, 1367, 1258, 1191, 1137, 837 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = [7.13 (d, J = 2.0 Hz, 1 H), 7.07 (d, J = 2.0 Hz, 1 H)], [6.88 (d, J = 2.1 Hz, 1 H), 6.87 (d, J = 2.1 Hz, 1 H)], [6.30–6.25 (m, 1 H), 6.19–6.14 (m, 1 H)], 6.08–6.02 (m, 2 H), [5.68 (dd, J = 12.8, 4.4 Hz, 1 H), 5.61 (ddd, J = 12.4, 2.8, 1.0 Hz, 1 H)], [5.37 (dd, J = 10.8, 4.4 Hz, 1 H)], [5.23–5.19 (m, 1 H)], [5.14 (dd, J = 11.2, 7.6 Hz, 1 H)], [5.02–4.99 (m, 1 H)], [4.68–4.64 (m, 1 H), 4.52–4.48 (m, 1 H)], [3.59–3.57 (m, 1 H), 3.43–3.41 (m, 1 H)], [3.36 (dd, J = 11.2, 7.6 Hz, 1 H), 3.22 (dd, J = 11.6, 4.0 Hz, 1 H)], 3.03–2.98 (m, 4 H), [2.40 (ddd, J = 8.8, 6.0, 2.8 Hz, 1 H), 2.27 (m, 1 H)], 2.29–2.25 (m, 12 H), [1.98–1.94 (m, 1 H), 1.63 (ddd, J = 12.0, 5.6, 2.0 Hz, 1 H)], [1.49 (d, J = 6.4 Hz, 3 H), 1.43 (d, J = 5.2 Hz, 3 H)], [0.96 (s, 9 H), 0.88 (s, 9 H)], [0.17 (s, 3 H), 0.14 (s, 3 H)], [0.04 (s, 3 H), 0.02 (s, 3 H)] ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = [168.4, 168.4], [168.3, 168.2], [165.7, 165.1], [151.7, 151.3], [149.0, 148.8], [139.8, 138.8], [137.1, 135.4], [132.4, 131.3], [128.4, 127.6], [126.2, 125.5], [124.6, 124.6], [121.1, 120.7], [114.8, 114.8], [73.5, 72.3], [70.3, 68.1], [56.3, 56.1], [54.4, 53.6], [40.5, 39.3], [37.4, 35.8], [25.8 (3 C), 25.8 (3 C)], [21.1, 21.1], [21.0, 20.9], [20.0, 19.7], [18.2, 18.1], [–4.6, –4.6], [–4.6, –4.7] ppm. N.B.: The data in square brackets correspond to the signals for the diastereomers (CH-OSi*t*BuMe$_2$). HRMS (ESI+): calcd. for $C_{28}H_{38}O_8SiNa$ [M + Na]$^+$ 553.2234; found 553.2236.

***tert*-Butyl({(*R*)-1-[(2*R*,3*R*)-3-ethynyloxiran-2-yl]propan-2-yl}oxy)-diphenylsilane (38):** K_2CO_3 (2.3 g, 16.6 mmol, 2.3 equiv.) was added to aldehyde **26** (2.7 g, 7.21 mmol, 1.0 equiv.) in MeOH (90 mL) at 0 °C. Dimethyl (1-diazo-2-oxopropyl)phosphonate (**37**, 1.9 mg, 10.1 mmol, 1.4 equiv.) in MeOH (25 mL) was then added slowly, and the reaction mixture was stirred at 0 °C for an additional 3 h. The mixture was diluted with Et_2O (100 mL), and the mixture was washed with saturated aqueous $NaHCO_3$ (150 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine (150 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 50:1) to give acetylene **38** (1.7 g, 4.75 mmol, 66% yield) as a colorless oil. $[\alpha]_D^{25}$ = +30.5 (c = 0.97, CH_2Cl_2). IR (thin film): $\tilde{\nu}$ = 1427, 1380, 1110, 1074, 997, 878, 821, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 4 H), 7.45–7.36 (m, 6 H), 4.06 (app. sextet, J = 6.0 Hz, 1 H), 3.27 (td, J = 5.6, 2.2 Hz, 1 H), 3.03 (dd, J = 2.3, 1.6 Hz, 1 H), 2.32 (d, J = 1.6 Hz, 1 H), 1.74–1.59 (m, 2 H), 1.14 (d, J = 6.2 Hz, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.8 (2 C), 135.8 (2 C), 134.3, 133.9, 129.7, 129.6, 127.7 (2 C), 127.5 (2 C), 80.4, 71.8, 67.2, 57.4, 44.7, 41.1, 27.0 (3 C), 23.2, 19.2 ppm. HRMS (CI+): calcd. for $C_{23}H_{32}NO_2Si$ [M + NH_4]$^+$ 382.2202; found 382.2189.

***tert*-Butyl({(*R*)-1-[(2*R*,3*R*)-3-(iodoethynyl)oxiran-2-yl]propan-2-yl}oxy)diphenylsilane (39):** $AgNO_3$ (160 mg, 0.914 mmol, 0.2 equiv.) was added with stirring to acetylene **38** (1.7 g, 4.57 mmol, 1.0 equiv.) and *N*-iodosuccinimide (1.2 g, 5.48 mmol, 1.2 equiv.) in Me_2CO (40 mL) in the dark. After 1 h, the reaction mixture was quenched by the addition of ice-cold water (40 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 50:1) to give alkynyl iodide **39** (2.2 g, 4.53 mmol, 98% yield) as a yellow oil. $[\alpha]_D^{25}$ = +48.3 (c = 0.77, CH_2Cl_2). IR (thin film): $\tilde{\nu}$ = 1428, 1112, 1025, 822, 740, 702 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 4 H), 7.45–7.42 (m, 2 H), 7.40–7.36 (m, 4 H), 4.05 (app. sextet, J = 6.0 Hz, 1 H), 3.25 (td, J = 5.8, 2.1 Hz, 1 H), 3.11 (d, J = 2.1 Hz, 1 H), 1.73–1.68 (m, 1 H), 1.61–1.56 (m, 1 H), 1.14 (d, J = 6.2 Hz, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.8 (2 C), 135.8 (2 C), 134.2, 133.8, 129.7, 129.6, 127.7 (2 C), 127.5 (2 C), 90.9, 67.2, 57.7, 46.1, 41.1, 27.0 (3 C), 23.2, 19.2, 1.5 ppm. HRMS (ESI+): calcd. for $C_{23}H_{28}IO_2Si$ [M + H]$^+$ 491.0903; found 491.0901.

***tert*-Butyl{[(*R*)-1-{(2*R*,3*R*)-3-[(*Z*)-2-iodoethenyl]oxiran-2-yl}-propan-2-yl]oxy}diphenylsilane (32):** In the dark, sulfonamide **40** (790 g, 3.66 mmol, 1.1 equiv.) was added with stirring to iodoalkyne **39** (1.6 g, 3.32 mmol, 1.0 equiv.) in *i*PrOH/THF (1:1, 40 mL). Subsequently, Et_3N (0.69 mL, 4.98 mmol, 1.5 equiv.) was added with stirring. After 24 h, TLC analysis showed that the reaction had not reached completion, and additional sulfonamide **40** (290 mg, 1.33 mmol, 0.4 equiv.) and Et_3N (0.25 mL, 1.65 mmol, 0.5 equiv.) were added with stirring. After 16 h, the mixture was diluted with Et_2O (50 mL), and the solution was washed with 10% aqueous NaCl (5 × 50 mL). The organic phase was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 100:1) to give alkenyl iodide **32** (1.3 g, 2.66 mmol, 80% yield) as a yellow solid; m.p. 50–52 °C (CH_2Cl_2). $[\alpha]_D^{25}$ = –27.4 (c = 2.19, CH_2Cl_2). IR (thin film): $\tilde{\nu}$ = 1428, 1380, 1272, 1111, 1074, 1040, 1025 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 4 H), 7.45–7.36 (m, 6 H), 6.49 (dd, J = 7.9, 1.0 Hz, 1 H), 5.94 (t, J = 7.8 Hz, 1 H), 4.09 (app. sextet, J = 5.5 Hz, 1 H), 3.32 (ddd, J = 7.7, 2.1, 1.1 Hz, 1 H), 3.08 (dt, J = 5.9, 2.2 Hz, 1 H), 1.83–1.78 (m, 1 H), 1.75–1.69 (m, 1 H), 1.16 (d, J = 6.2 Hz, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.3, 135.8 (2 C), 135.8 (2 C), 134.4, 134.0 129.7, 129.6, 127.7 (2 C), 127.5 (2 C), 84.8, 67.5, 60.1, 56.7, 41.4, 27.0 (3 C), 23.4, 19.2 ppm. HRMS (CI+): calcd. for $C_{23}H_{30}IO_2Si$ [M + H]$^+$ 493.1060; found 493.1048.

3-Hydroxy-*N*-methoxy-*N*-methylpropanamide: The reaction was carried out in triplicate in parallel. Me_2AlCl (1.0 M in hexanes, 200 mL, 200 mmol, 4.0 equiv.) was added with stirring to *N*,*O*-Me-O(Me)NH·HCl (9.8 g, 100 mmol, 2.0 equiv.) in CH_3CN (160 mL) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 1 h. After cooling the mixture to 0 °C, β-propiolactone **41** (3.6 g, 50.0 mmol, 1.0 equiv.) was added, and the solution was warmed to room temperature over 16 h. The reaction was quenched by the addition of aqueous HCl (0.5 M, 400 mL) at 0 °C, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (8 × 150 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated in vacuo. The residue

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was purified by chromatography (EtOAc/MeOH, 99:1) to give the title amide (14 g, 109 mmol, 73% yield) as a colorless oil. IR (thin film): $\tilde{\nu}$ = 3421 (br.), 1638, 1463, 1387, 1179, 1055, 1036, 992 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (app. q, J = 5.0 Hz, 2 H), 3.68 (s, 3 H), 3.18 (s, 3 H), 3.07 (t, J = 6.5 Hz, 1 H), 2.66 (t, J = 4.9 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.8, 61.2, 58.2, 33.8, 31.9 ppm. HRMS (ESI+): calcd. for $C_5H_{12}NO_3$ [M + H]$^+$ 134.0817; found 134.0814.

***N*-Methoxy-*N*-methyl-3-[(triethylsilyl)oxy]propanamide (42):** Et_3SiCl (13 mL, 78.2 mmol, 1.1 equiv.) was added with stirring to 3-hydroxy-*N*-methoxy-*N*-methylpropanamide (9.5 g, 71.1 mmol, 1.0 equiv.) and Et_3N (12 mL, 85.3 mmol, 1.2 equiv.) in CH_2Cl_2 (60 mL) at 0 °C. After 15 min, the ice bath was removed, and the mixture was stirred for 16 h. The mixture was filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$ (300 mL), water (300 mL), and brine (300 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 8:1) to give amide **42** (18 g, 70.5 mmol, 99% yield) as a colorless oil. IR (thin film): $\tilde{\nu}$ = 1665, 1461, 1416, 1383, 1093, 1005 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (t, J = 6.6 Hz, 2 H), 3.70 (s, 3 H), 3.18 (s, 3 H), 2.69 (t, J = 6.6 Hz, 2 H), 0.95 (t, J = 7.9 Hz, 9 H), 0.61 (q, J = 7.9 Hz, 6 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.4, 61.3, 58.9, 35.2, 31.9, 6.6 (3 C), 4.3 (3 C) ppm. HRMS (ESI+): calcd. for $C_{11}H_{26}NO_3Si$ [M + H]$^+$ 248.1682; found 248.1691.

5-[(Triethylsilyl)oxy]-1-(trimethylsilyl)pent-1-yn-3-one (43): *n*BuLi (2.5 M in hexanes, 34 mL, 84.9 mmol, 3.0 equiv.) was added dropwise to ethynyltrimethylsilane (12 mL, 84.9 mmol, 3.0 equiv.) in Et_2O (120 mL) at –78 °C. The mixture was stirred at this temperature for 30 min, and then Weinreb amide **42** (7.0 g, 28.3 mmol, 1.0 equiv.) in Et_2O (70 mL) was added dropwise with stirring. The reaction mixture was warmed to –20 °C and stirred at this temperature for 30 min. It was then quenched by the addition of saturated aqueous NH_4Cl (250 mL). The two phases were separated, and the aqueous phase was extracted with Et_2O (2× 300 mL). The combined organic phases were washed with brine (250 mL), dried with $MgSO_4$, and concentrated in vacuo to give ynone **43** (7.5 g, 26.5 mmol, 94% yield) as an orange oil, which was used immediately upon isolation in the subsequent reaction without further purification. IR (thin film): $\tilde{\nu}$ = 1681, 1252, 1092, 1007, 844 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.98 (t, J = 6.3 Hz, 2 H), 2.78 (t, J = 6.3 Hz, 2 H), 0.95 (t, J = 8.0 Hz, 9 H), 0.60 (q, J = 8.0 Hz, 6 H), 0.24 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.0, 101.9, 98.1, 58.0, 48.3, 6.7 (3 C), 4.3 (3 C), –0.8 (3 C) ppm. HRMS (ESI+): calcd. for $C_{14}H_{29}O_2Si_2$ [M + H]$^+$ 285.1706; found 285.1714.

2-{2-[(Trimethylsilyl)ethynyl]-1,3-dioxolan-2-yl}ethanol: *p*TsOH·H_2O (61 mg, 0.356 mmol, 0.1 equiv.) was added with stirring to ynone **43** (1.0 g, 3.56 mmol, 1.0 equiv.), $CH(OMe)_3$ (3.9 mL, 35.6 mmol, 10 equiv.), and $HOCH_2CH_2OH$ (3.0 mL, 53.4 mmol, 15 equiv.) in PhMe (10 mL). After 16 h, the mixture was washed with saturated aqueous $NaHCO_3$ (100 mL), and the aqueous phase was extracted with Et_2O (3× 100 mL). The combined organic layers were washed with brine (100 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (hexanes/Et_2O, 2:1) to give the title acetylene (520 mg, 2.42 mmol, 68% yield) as a colorless oil. IR (thin film): $\tilde{\nu}$ = 3425 (br.), 1251, 1194, 1107, 1031, 863, 843 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13–4.07 (m, 2 H), 4.06–4.00 (m, 2 H), 3.86 (dt, J = 6.1, 5.4 Hz, 2 H), 2.46 (t, J = 6.1 Hz, 1 H), 2.19 (t, J = 5.5 Hz, 2 H), 0.18 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 102.7, 101.7, 89.6, 64.5 (2 C), 58.6, 41.0, –0.3 (3 C) ppm. HRMS (CI+): calcd. for $C_{10}H_{22}NO_3Si$ [M + NH_4]$^+$ 232.1369; found 232.1367.

2-(2-Ethynyl-1,3-dioxolan-2-yl)ethanol: K_2CO_3 (1.6 g, 11.3 mmol, 1.2 equiv.) was added with stirring to 2-{2-[(trimethylsilyl)ethynyl]-1,3-dioxolan-2-yl}ethanol (2.0 g, 9.38 mmol, 1.0 equiv.) in MeOH (40 mL). After 2 h, water (100 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3× 100 mL). The combined organic phases were washed with brine (100 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (hexanes/Et_2O, 1:1) to give the title acetylene (1.1 g, 7.78 mmol, 83% yield) as a pale yellow oil. IR (thin film): $\tilde{\nu}$ = 3403 (br.), 3278, 1196, 1108, 1066, 1028, 946 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18–4.12 (m, 2 H), 4.09–4.06 (m, 2 H), 3.91 (td, J = 5.8, 5.3 Hz, 2 H), 2.59 (s, 1 H), 2.45 (t, J = 5.6 Hz, 1 H), 2.24 (t, J = 5.5 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 102.6, 80.8, 72.6, 64.6 (2 C), 58.3, 40.9 ppm. HRMS (EI+): calcd. for $C_7H_{10}O_3$ [M]$^+$ 142.0630; found 142.0642.

Triethyl[2-(2-ethynyl-1,3-dioxolan-2-yl)ethoxy]silane (44): Et_3SiCl (1.7 mL, 10.0 mmol, 1.2 equiv.) was added with stirring to 2-(2-ethynyl-1,3-dioxolan-2-yl)ethanol (1.2 g, 8.36 mmol, 1.0 equiv.) and Et_3N (1.5 mL, 10.9 mmol, 1.3 equiv.) in CH_2Cl_2 (12 mL) at 0 °C. After 15 min, the ice bath was removed, and the mixture was stirred for 16 h and then filtered through Celite®. The filtrate was washed with saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 99:1) to give acetylene **44** (2.1 g, 8.36, mmol, 100% yield) as a colorless oil. IR (thin film): $\tilde{\nu}$ = 3308, 1238, 1199, 1144, 1088, 1038, 1004, 976, 944 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.09–4.03 (m, 2 H), 4.02–3.96 (m, 2 H), 3.86 (t, J = 7.9 Hz, 2 H), 2.50 (s, 1 H), 2.21 (t, J = 7.9 Hz, 2 H), 0.96 (t, J = 7.8 Hz, 9 H), 0.61 (q, J = 7.8 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 101.1, 81.1, 72.1, 64.5 (2 C), 58.4, 41.9, 6.7 (3 C), 4.3 (3 C) ppm. HRMS (ESI+): calcd. for $C_{13}H_{25}O_3Si$ [M + H]$^+$ 257.1573; found 257.1582.

(*E*)-Triethyl(2-{2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-ethenyl]-1,3-dioxolan-2-yl}ethoxy)silane (33): Acetylene **44** (1.2 g, 4.76 mmol, 1.0 equiv.) and pinacol borane (6.9 mL, 47.6 mmol, 10 equiv.) were stirred neat at 70 °C for 3 d. After this time, additional pinacol borane (2.3 mL, 15.9 mmol, 3.3 equiv.) was added, and the mixture was stirred for an additional 3 d. The reaction mixture was cooled to room temperature and was then purified by chromatography (hexanes/EtOAc, 10:1 then 5:1) to furnish borane derivative **33** (1.4 g, 3.61 mmol, 76% yield) as a colorless oil. IR (thin film): $\tilde{\nu}$ = 1643, 1459, 1352, 1326, 1207, 1144, 1088, 1045, 1003, 971 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41 (d, J = 18.1 Hz, 1 H), 5.72 (d, J = 18.1 Hz, 1 H), 3.92–3.87 (m, 2 H), 3.86–3.81 (m, 2 H), 3.72 (t, J = 7.6 Hz, 2 H), 2.02 (t, J = 7.7 Hz, 2 H), 1.26 (s, 12 H), 0.94 (t, J = 8.0 Hz, 9 H), 0.58 (q, J = 8.0 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.8, 118.4, 107.9, 83.4 (2 C), 64.5 (2 C), 58.2, 40.7, 24.8 (4 C), 6.8 (3 C), 4.4 (3 C) ppm. HRMS (ESI+): calcd. for $C_{19}H_{38}BO_5Si$ [M + H]$^+$ 385.2582; found 385.2588.

***tert*-Butyldiphenyl{[(*R*)-1-{(2*R*,3*R*)-3-[(1*Z*,3*E*)-4-(2-{2-[(triethylsilyl)oxy]ethyl}-1,3-dioxolan-2-yl)buta-1,3-dien-1-yl]oxiran-2-yl}propan-2-yl]oxy}silane (45):** A degassed solution of pinacol borane **33** (420 mg, 1.09 mmol, 1.4 equiv.) and aqueous Cs_2CO_3 (3.0 M, 6.1 mL, 18.2 mmol, 20 equiv.) in THF (4.1 mL) was added to degassed iodide **32** (390 mg, 0.792 mmol, 1.0 equiv.) and $Pd(PPh_3)_4$ (53 mg, 45.5 μmol, 5 mol-%) in THF (6.5 mL). The resulting mixture was heated to 55 °C for 7 h and then cooled to room temperature, and the aqueous layer was extracted with EtOAc (3× 25 mL). The combined organic layers were washed with brine (25 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 20:1) to give diene **45**

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(350 mg, 0.558 mmol, 71% yield) as an orange oil. $[\alpha]_D^{25}$ = +4.2 (*c* = 1.40, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1428, 1105, 1085, 1044, 1006, 950, 822 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 4 H), 7.45–7.35 (m, 6 H), 6.71 (dd, *J* = 15.1, 11.4 Hz, 1 H), 6.24 (t, *J* = 11.3 Hz, 1 H), 5.69 (d, *J* = 15.1 Hz, 1 H), 5.06 (dd, *J* = 10.0, 10.2 Hz, 1 H), 4.08 (app. sextet, *J* = 6.0 Hz, 1 H), 3.96–3.81 (m, 4 H), 3.76–3.72 (m, 2 H), 3.44 (dd, *J* = 9.2, 1.8 Hz, 1 H), 3.02 (dt, *J* = 5.9, 2.0 Hz, 1 H), 2.07–2.03 (m, 2 H), 1.82–1.68 (m, 2 H), 1.16 (d, *J* = 6.2 Hz, 3 H), 1.06 (s, 9 H), 0.96 (t, *J* = 7.8 Hz, 9 H), 0.60 (q, *J* = 7.8 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.8 (2 C), 135.8 (2 C), 135.6, 134.4, 134.0, 132.9, 129.6, 129.5, 129.3, 127.6 (2 C), 127.5 (2 C), 124.5, 107.8, 67.5, 64.7, 64.4, 58.3, 57.6, 54.0, 41.6, 41.5, 27.0 (3 C), 23.3, 19.2, 6.7 (3 C), 4.4 (3 C) ppm. HRMS (ESI+): calcd. for $C_{36}H_{55}O_5Si_2$ $[M + H]^+$ 623.3588; found 623.3573.

2-{2-[(1*E*,3*Z*)-4-{(2*R*,3*R*)-3-[(*R*)-2-(*tert*-Butyldiphenylsilyloxy)propyl]oxiran-2-yl}buta-1,3-dien-1-yl]-1,3-dioxolan-2-yl}ethanol: Bu_4NF (1.0 M in THF, 0.92 mL, 0.918 mmol, 1.1 equiv.) was added with stirring to diene **45** (520 mg, 0.835 mmol, 1.0 equiv.) in THF (20 mL) at 0 °C. After 30 min, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (25 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3× 25 mL). The combined organic layers were washed with water (25 mL) and brine (25 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 1:1) to give the title alcohol (390 mg, 0.757 mmol, 91% yield) as a colorless, viscous syrup. $[\alpha]_D^{25}$ = –2.0 (*c* = 1.3, CH_2Cl_2). IR (thin film): $\tilde{\nu}$ = 3473 (br.), 1738, 1428, 1111, 1037 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.65 (m, 4 H), 7.44–7.35 (m, 6 H), 6.74 (dd, *J* = 15.1, 12.1 Hz, 1 H), 6.24 (t, *J* = 11.2 Hz, 1 H), 5.67 (d, *J* = 15.1 Hz, 1 H), 5.10 (t, *J* = 10.1 Hz, 1 H), 4.08 (app. sextet, *J* = 6.0 Hz, 1 H), 4.04–3.85 (m, 4 H), 3.77 (td, *J* = 10.9, 5.6 Hz, 2 H), 3.43 (dd, *J* = 9.2, 1.9 Hz, 1 H), 3.03 (td, *J* = 5.9, 2.1 Hz, 1 H), 2.67 (t, *J* = 5.8 Hz, 1 H), 2.04–2.01 (m, 2 H), 1.82–1.68 (m, 2 H), 1.15 (d, *J* = 6.2 Hz, 3 H), 1.05 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.8 (2 C), 135.8 (2 C), 134.8, 134.3, 134.0, 132.6, 129.9, 129.6, 129.6, 127.6 (2 C), 127.5 (2 C), 125.4, 109.3, 67.5, 64.7, 64.4, 58.4, 57.6, 53.9, 41.5, 39.7, 27.0 (3 C), 23.3, 19.2 ppm. HRMS (ESI+): calcd. for $C_{30}H_{40}NaO_5Si$ $[M + Na]^+$ 531.2543; found 531.2531.

2-{2-[(1*E*,3*Z*)-4-{(2*R*,3*R*)-3-[(*R*)-2-(*tert*-Butyldiphenylsilyloxy)propyl]oxiran-2-yl}buta-1,3-dien-1-yl]-1,3-dioxolan-2-yl}acetaldehyde (31): Dess–Martin periodinane (230 mg, 0.538 mmol, 1.2 equiv.) was added with stirring to 2-{2-[(1*E*,3*Z*)-4-{(2*R*,3*R*)-3-[(*R*)-2-(*tert*-butyldiphenylsilyloxy)propyl]oxiran-2-yl}buta-1,3-dien-1-yl]-1,3-dioxolan-2-yl}ethanol (230 mg, 0.448 mmol, 1.0 equiv.) in CH_2Cl_2 (3.0 mL). After 2 h, the mixture was washed with saturated aqueous $NaHCO_3$ (10 mL), and the two phases were separated. The aqueous layer was extracted with Et_2O (3× 10 mL), and the combined organic phases were washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 3:1) to give aldehyde **31** (190 mg, 0.371 mmol, 83% yield) as a colorless, viscous syrup. $[\alpha]_D^{25}$ = +1.6 (*c* = 1.25, CH_2Cl_2). IR (thin film): $\tilde{\nu}$ = 1725, 1473, 1428, 1379, 1199, 1110, 1069, 1038 997, 950 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.73 (t, *J* = 2.7 Hz, 1 H), 7.68–7.66 (m, 4 H), 7.44–7.35 (m, 6 H), 6.79 (dd, *J* = 15.1, 11.8 Hz, 1 H), 6.24 (t, *J* = 11.2 Hz, 1 H), 5.71 (d, *J* = 15.1 Hz, 1 H), 5.13 (t, *J* = 10.0 Hz, 1 H), 4.08 (app. sextet, *J* = 5.7 Hz, 1 H), 4.04–3.90 (m, 4 H), 3.43 (dd, *J* = 9.1, 1.7 Hz, 1 H), 3.03 (dt, *J* = 5.8, 2.0 Hz, 1 H), 2.78 (d, *J* = 2.8 Hz, 2 H), 1.83–1.69 (m, 2 H), 1.16 (d, *J* = 6.2 Hz, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.6, 135.8 (2 C), 135.7 (2 C), 134.3, 134.0, 133.9, 132.2, 130.6, 129.6, 129.6, 127.6 (2 C), 127.5 (2 C), 125.8, 106.5, 67.5, 65.0, 64.7, 57.6, 53.8, 51.0, 41.5, 27.0 (3 C), 23.3, 19.2 ppm. HRMS (ESI+): calcd. for $C_{30}H_{38}NaO_5Si$ $[M + Na]^+$ 529.2386; found 529.2389.

2,2-Dimethyl-6-[2-oxo-2-(3-propyloxiran-2-yl)ethyl]-4*H*-1,3-dioxin-4-one (48): Keto-dioxinone **30** (250 mg, 1.16 mmol, 2.1 equiv.) in THF (1.8 mL) was added to freshly prepared $LiN(iPr)_2$ (2.31 mmol, 4.2 equiv.) in THF (10 mL) at –78 °C, and the solution was warmed to –40 °C over 1 h. The solution was cooled to –78 °C, and *n*PrCHO (**47**, 50 μL, 0.550 mmol, 1.0 equiv.) in THF (1 mL) was added with stirring. The mixture was warmed incrementally to room temperature over 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (15 mL), and the pH was adjusted to 3–4 with 10% aqueous AcOH. The mixture was diluted with Et_2O (10 mL), and the phases were separated. The aqueous layer was extracted with Et_2O (3× 15 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 5:1 to 2:1) to give epoxide **48** (30 mg, 0.107 mmol, 19% yield, pure *trans* isomer) as a yellow oil. IR (thin film): $\tilde{\nu}$ = 1719, 1638, 1390, 1374, 1272, 1253, 1201, 1014, 902 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.33 (s, 1 H), 3.32 (d, *J* = 17.0 Hz, 1 H), 3.25 (d, *J* = 1.9 Hz, 1 H), 3.21 (d, *J* = 17.0 Hz, 1 H), 3.12 (ddd, *J* = 6.3, 4.9, 1.9 Hz, 1 H), 1.69 (s, 6 H), 1.69–1.45 (m, 4 H), 0.97 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.8, 163.8, 1605, 107.3, 97.1, 59.5, 58.0, 41.1, 33.5, 25.1, 24.8, 19.0, 13.7 ppm. HRMS (CI+): calcd. for $C_{13}H_{22}NO_5$ $[M + NH_4]^+$ 272.1498; found 272.1476.

6-(5-{2-[(1*E*,3*Z*)-4-{(2*R*,3*R*)-3-[(*R*)-2-(*tert*-Butyldiphenylsilyloxy)propyl]oxiran-2-yl}buta-1,3-dien-1-yl]-1,3-dioxolan-2-yl}-4-hydroxy-2-oxopentyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (49): Keto-dioxinone **10** (160 mg, 0.860 mmol, 2.1 equiv.) in THF (1.5 mL) was added to freshly prepared $LiN(iPr)_2$ (1.81 mmol, 4.2 equiv.) in THF (7.4 mL) at –78 °C. The solution was warmed to –40 °C over 1 h, and then aldehyde **31** (220 mg, 0.430 mmol, 0.1 equiv.) in THF (0.7 mL) was added with stirring. After an additional 3 h at –40 °C, HCO_2H (0.072 mL, 1.94 mmol) in THF (0.7 mL) was added, and the solution was warmed to room temperature. The organic phase was washed with saturated aqueous NH_4Cl (15 mL), and the aqueous phase was acidified to pH = 3–4 by using 10% aqueous AcOH. The aqueous phase was then extracted EtOAc (2× 15 mL). The combined organic phases were washed with brine (15 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 2:1 and subsequently 1:1) to yield keto-dioxinone **49** (220 mg, 0.318 mmol, 73% yield) as an orange gum that consisted of an inseparable mixture of diastereomers. IR (thin film): $\tilde{\nu}$ = 3490 (br.), 1727, 1638, 1428, 1376, 1273, 1203, 1111, 1016 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 4 H), 7.44–7.34 (m, 6 H), 6.77–6.71 (m, 1 H), 6.23 (t, *J* = 11.3 Hz, 1 H), 5.63 (d, *J* = 15.2 Hz, 1 H), 5.34 (s, 1 H), 5.11 (t, *J* = 10.0 Hz, 1 H), 4.42–4.35 (m, 1 H), 4.08 (app. sextet, *J* = 5.8 Hz, 1 H), 4.03–3.83 (m, 4 H), 3.54 (d, *J* = 5.9 Hz, 1 H), 3.43–3.41 (m, 1 H), 3.41 (s, 2 H), 3.05–3.01 (m, 1 H), 2.69 (ddd, *J* = 15.8, 8.2, 2.5 Hz, 1 H), 2.35 (dd, *J* = 15.8, 4.2 Hz, 1 H), 1.93–1.91 (m, 2 H), 1.81–1.68 (m, 2 H), 1.71 (s, 6 H), 1.15 (d, *J* = 6.2 Hz, 3 H), 1.05 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.4, 164.4, 160.7, 135.8 (2 C), 135.7 (2 C), [134.3, 134.3], 134.0, [132.4, 132.3], 130.1, 129.6, 129.5, 127.6 (2 C), 127.5 (2 C), [125.7, 125.6], 108.6, 107.1, 96.7, 67.4, [64.8, 64.6], [64.3, 64.2], [64.1, 64.1], [57.6, 57.6], [53.8, 53.8], [49.8, 49.7], 48.0, 43.7, 41.5, 26.9 (3 C), 25.0, 24.9, 23.2, 19.1 ppm. N.B.: There is a carbon assignment missing because of overlapping signals, and the ^{13}C NMR data in square

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brackets correspond to signals from epimers. HRMS (ESI+): calcd. for $C_{39}H_{50}O_9NaSi$ $[M + Na]^+$ 713.3122; found 713.3122.

6-(4-Hydroxy-5-{2-[(1*E*,3*Z*)-4-{(2*R*,3*R*)-3-[(*R*)-2-hydroxypropyl]-oxiran-2-yl}buta-1,3-dien-1-yl]-1,3-dioxolan-2-yl}-2-oxopentyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (51): Bu_4NF (1.0 M in THF, 0.28 mL, 0.280 mmol, 2.0 equiv.) was added with stirring to keto-dioxinone **49** (97 mg, 0.140 mmol, 1.0 equiv.) and molecular sieves (4 Å, 100 mg) in THF (3.0 mL). After 40 h, the reaction mixture was filtered, and the filtrate was concentrated in vacuo without heating to leave the crude material. The crude product was dissolved in THF (0.5 mL) and then purified by chromatography (100% EtOAc) to afford keto-dioxinone **51** (50 mg, 0.111 mmol, 79% yield) as a colorless gum that consisted of an inseparable mixture of diastereomers. IR (thin film): $\tilde{\nu}$ = 3475 (br.), 1718, 1634, 1392, 1376, 1274, 1203, 1016 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.78–6.71 (m, 1 H), 6.22 (t, J = 11.3 Hz, 1 H), 5.63 (dd, J = 15.2, 4.8 Hz, 1 H), 5.32 (s, 1 H), 5.14 (dd, J = 10.0, 9.6 Hz, 1 H), 4.39–4.31 (m, 1 H), 4.10–4.05 (m, 1 H), 4.05–3.85 (m, 4 H), 3.59–3.51 (m, 2 H), 3.39 (s, 2 H), 3.04–3.00 (m, 1 H), 2.72–2.65 (m, 1 H), 2.37–2.50 (m, 1 H), 1.92–1.90 (m, 2 H), 1.85 (dt, J = 14.2, 4.4 Hz, 1 H), 1.69 (s, 6 H), 1.69–1.60 (m, 1 H), 1.24 (d, J = 6.3 Hz, 3 H) ppm. N.B.: One OH signal is missing because of overlap. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.3, [164.4, 164.4], 160.7, [134.5, 134.3], 132.5, [129.8, 129.7], [125.7, 125.6], [108.6, 108.5], 107.2, 96.7, 66.2, [64.8, 64.6], 64.3, [64.1, 64.1], 58.3, 53.8, 49.7, 48.0, [43.7, 43.6], 40.7, 25.0, 24.9, 23.4 ppm. N.B.: The ^{13}C NMR data in square brackets correspond to signals from the diastereomers. HRMS (ESI+): calcd. for $C_{23}H_{33}O_9$ $[M + H]^+$ 453.2125; found 413.2146.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR characterization data.

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