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A Unified Strategy for the Syntheses of Angucyclinone Antibiotics: Total Syntheses of Tetrangulol, Kanglemycin M, X-14881-E, and Anhydrolandomycinone

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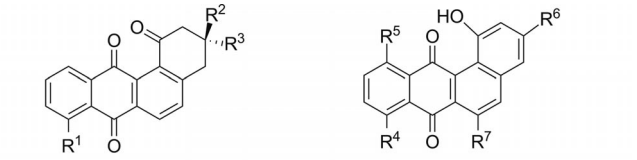
A unified strategy for the syntheses of angucyclinone antibiotics was developed utilizing sequential intramolecular enyne metathesis, Diels–Alder/aromatization, photooxygenation, and one-pot elimination/aromatization reactions. The diversity in this sequence was introduced in the Diels–Alder reaction where a common diene was treated with various appropriately functionalized quinones as the dienophiles to accomplish the total syntheses of tetrangulol, kanglemycin M, X-14881-E, and anhydrolandomycinone in moderate to good overall yields. The requisite diene was synthesized in excellent yield from a known enyne through an intramolecular enyne metathesis. The scope of this flexible and divergent strategy can be extended to the syntheses of similar scaffolds and unnatural aromatic angucyclinones.

Introduction

Angucyclines[1] belong to a relatively new and large group of antibiotic natural products featuring an angularly assembled carbotetracyclic skeleton. These natural products are isolated from the culture broth of different microorganisms. Besides their interesting structural features, they also exhibit widespread biological activities such as antitumor, antifungal, and antiviral properties.[2] This group of antibiotics includes naturally occurring quinones,[3] characterized by an angular tetracyclic framework, which are believed to be biosynthesized from a decaketide derivative.[4] In general, the angucyclines possess a benz[*a*]anthraquinone ring system as a common structural framework. Angucyclines can be classified further into two subgroups depending on the presence or absence of a C-glycoside moiety. Angucyclines in the latter group, without a hydrolyzable sugar moiety, are known as angucyclinones (Figures 1 and 2).

Tetrangomycin and tetrangulol were the first set of angucyclinone antibiotics isolated by Kunstman and Mitscher in 1965 from the species *Streptomyces cyanogenus* S-136.[5] Anhydrolandomycinone and X-14881-E, which are structurally similar to tetrangulol by having angular tetracyclic planar frameworks but differerent C-11 and C-8 functionalities, were isolated from the species *Streptomyces cyanogenus* S-136[6] and *Streptomyces fradiae* strain 34,[7] respectively. Kanglemycin M was isolated from the fermentation broth of *Nocardia mediterranei kanglensis* 1747-64 by Cheng-Hang Sun in 1996.[8]



1: R^1 = OH, R^2 = CH_3, R^3 = H (+)-ochromycinone
2: R^1 = OCH_3, R^2 = CH_3, R^3 = H (+)-rubiginone B_2
3: R^1 = OH, R^2 = CH_2OH, R^3 = H YM-181741
4: R^1 = OH, R^2 = CH_3, R^3 = OH (–)-tetrangomycin
5: R^1 = OCH_3, R^2 = CH_3, R^3 = OH MM-47755
6: R^4 = OH, R^5 = H, R^6 = CH_3, R^7 = H tetrangulol
7: R^4 = OH, R^5 = H, R^6 = CH_2OH, R^7 = H kanglemycin M
8: R^4 = OCH_3, R^5 = H, R^6 = CH_3, R^7 = H X-14881-E
9: R^4 = OH, R^5 = OH, R^6 = CH_3, R^7 = H anhydrolandomycinone
10: R^4 = OH, R^5 = H, R^6 = CH_3, R^7 = OH dehydrorabelomycin

Figure 1. Some examples of angucyclinones.

To date, several synthetic strategies to construct the benzo[*a*]anthraquinone skeleton of angucyclinone have been reported employing Diels–Alder[9,10–14] and Friedel–Crafts reactions,[15] nucleophilic additions,[16] free radical annulations,[17a–17d,17f,17g] rearrangements of cyclobutenones,[17e] and cobalt-mediated [2+2+2] cycloadditions[18] (see Figure 3). Among all of these strategies, the Diels–Alder approach has been widely used to assemble the benzo[*a*]anthraquinone skeleton by using a chiral catalyst, an enantiopure diene, or a chiral dienophile. In view of their promising biological profiles and interesting structural framework, we are interested in the syntheses of angucyclines and their analogues. As a part of our ongoing pro-

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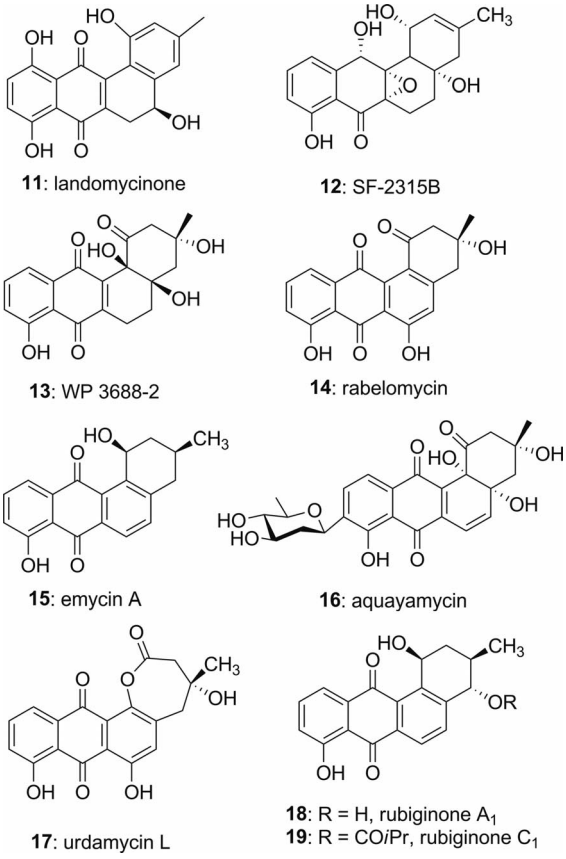


Figure 2. More examples of angucyclinone natural products.

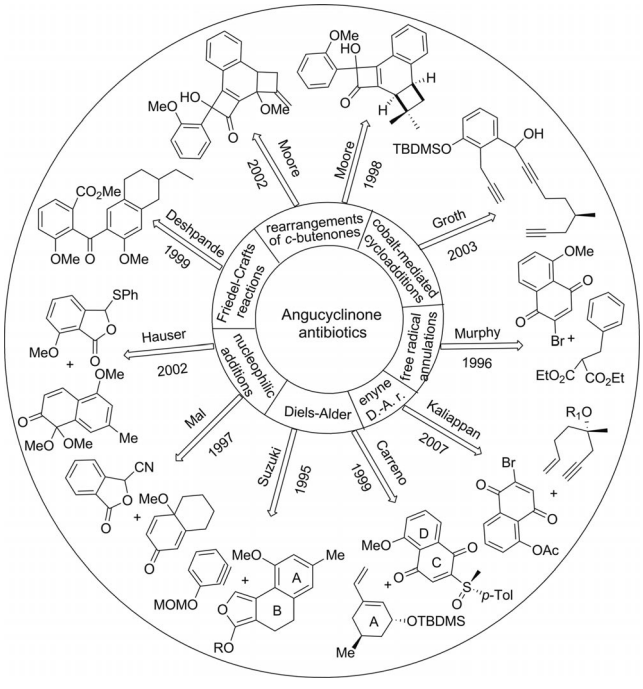
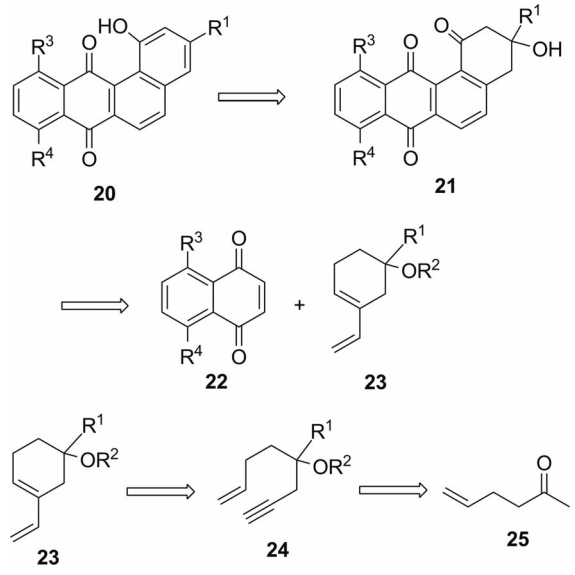


Figure 3. Earlier synthetic strategies to the tetracyclic framework of angucyclinones.

gram to exploit the synthetic utility of sequential enyne metathesis and Diels–Alder reactions (DAR), we developed a unified strategy for the syntheses of angucyclinone natural products. Earlier, we reported the enantioselective syntheses of YM-181741, (+)-ochromycinone, (+)-rubiginone B2, (–)-tetrangomycin, and MM-47755,[19] and, herein, we disclose our unified strategy for the syntheses of tetrangulol, X-14881-E, anhydrolandomycinone, and kanglemycin M.

Results and Discussion

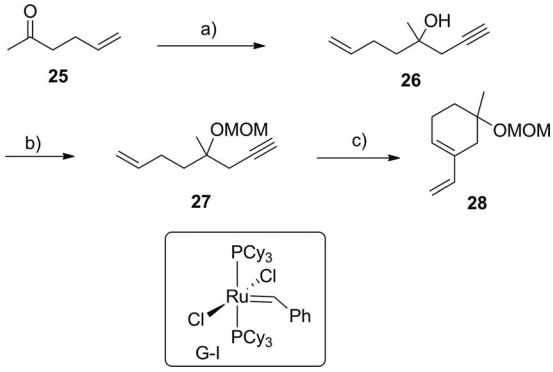
Over the past few years, our group has been actively exploring the intra- and intermolecular enyne metathesis and Diels–Alder reaction sequence, and it has culminated in the syntheses of various sugar-quinone hybrids,[20] *C*-aryl glycosides,[21] and some of angucyclinone natural products[19] (vide supra). In this paper, we describe an application of our strategy to construct the tetracyclic skeleton of angucyclinones by using sequential enyne metathesis, DAR, photooxygenation, and aromatization reactions as the key steps. According to our general retrosynthetic analysis as shown in Scheme 1, we envisaged that the angular tetracyclic planar framework of angucyclinones **20** could be derived from ketone **21** through one-pot elimination and aromatization reactions. We envisioned that the assembly of benzo[*a*]anthraquinone skeleton **21** required a Diels–Alder reaction between common diene **23** and dienophile **22**. Diene **23** originated from enyne **24** through an intramolecular enyne metathesis. Enyne **24** could be traced back to ketone **25**.



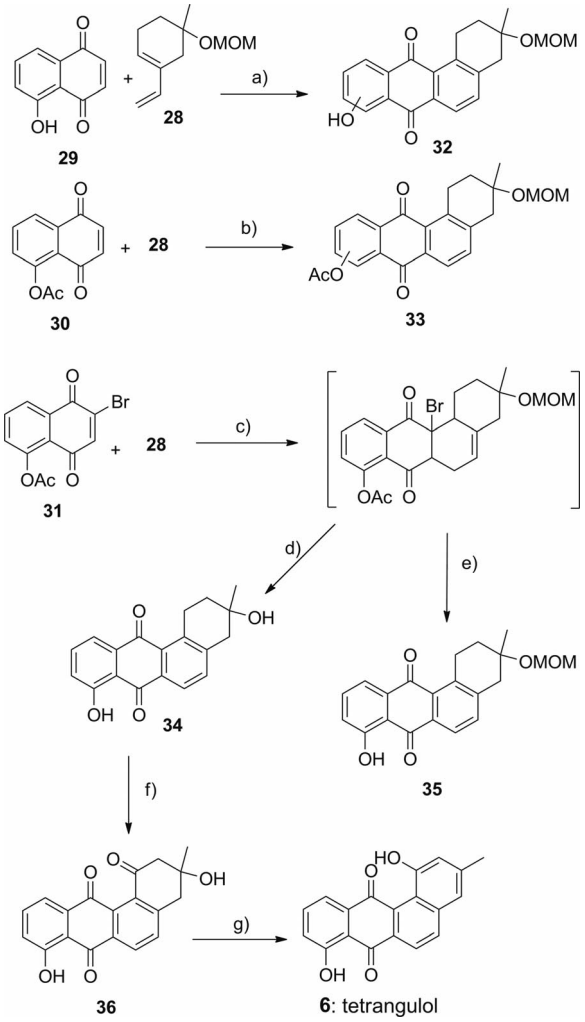
Scheme 1. General retrosynthetic analysis.

Synthesis of Diene 28

The synthesis of requisite diene **28** commenced with the nucleophilic addition of allenylmagnesium bromide to ketone **25** to afford enyne **26**.[22] The hydroxy group was then protected to give MOM ether **27** in 91% yield. Upon the synthesis of **27**, we executed an intramolecular enyne metathesis using Grubbs' first-generation catalyst (G-I)[23] to furnish the desired diene **28** in 90% yield (Scheme 2).



Scheme 2. Synthesis of diene **28**. Reagents and conditions: (a) allenylmagnesium bromide, THF (tetrahydrofuran), –78 °C, 3 h 85%; (b) MOMCl (methoxymethyl chloride), DIPEA (diisopropylethylamine), CH_2Cl_2, 91%; (c) G-I (Cy = cyclohexyl), CH_2Cl_2, reflux, 8 h, 90%.



Scheme 3. Reagents and conditions: (a) (i) toluene, 80 °C to 100 °C, 12 h; (ii) SiO_2, NEt_3, $CHCl_3$, 4 h, 88% for two steps; (b) (i) toluene, 80 °C to 100 °C, 12 h; (ii) SiO_2, NEt_3, $CHCl_3$, 4 h, 74% for two steps; (c) toluene, 80 °C to 100 °C, 12 h; (d) K_2CO_3, MeOH, 71% for two steps; (e) excess amount of K_2CO_3, MeOH, 72%; (f) hν, O_2, benzene, 2 d, 65%; (g) PTSA, benzene, reflux, 2 h, 70%.

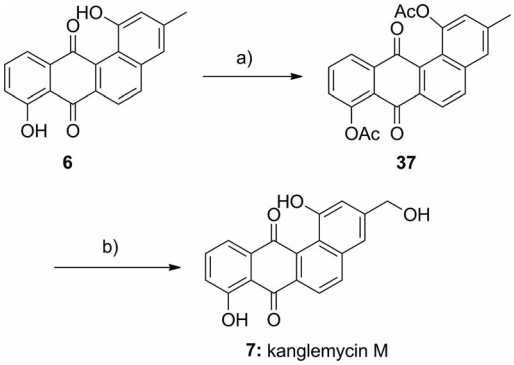
Total Synthesis of Tetrangulol

After synthesizing the required diene in good quantity, the stage was set for investigating the Diels–Alder reaction with an appropriate dienophile. Our first target was tetrangulol (**6**), for which juglone (**29**) was identified as the appropriate dienophile. Accordingly, diene **28** was treated with juglone (**29**) at 80 °C for 12 h to afford a mixture of two regioisomers in a 1:2 ratio in favor of the undesired isomer. When juglone was acetylated and the resultant 5-acetoxynaphthoquinone (**30**) was used as the dienophile, the Diels–Alder reaction led to similar results, and the ratio of two regioisomers did not change significantly. Eventually, 5-acetoxy-2-bromo-1,4-naphthoquinone[24] (**31**) was found to provide the desired regioisomer exclusively (see Scheme 3). The resultant cycloadduct was subsequently aromatized with K_2CO_3 and MeOH occurring with concomitant cleavage of the MOM ether to give compound **34** in 71% for the two steps. The cleavage of the MOM group might be caused by the HBr generated in situ during the reaction. This was supported further by evidence that the MOM group remained intact when the reaction was performed in the presence of an excess amount of K_2CO_3. Subsequently, compound **34** was subjected to photooxygenation[25] (Hg lamp, 125 W, and Philips India) to install the oxygen functionality and afford ketone **36** in 65% yield. Finally, ketone **36** was treated with a catalytic amount of PTSA (*p*-toluenesulfonic acid) to provide tetrangulol (**6**) in 70% yield. The spectroscopic data of synthetic tetrangulol was in good agreement with that of the natural product in all aspects, thus completing the total synthesis of tetrangulol (**6**)[26] in 22% overall yield starting from compound **25**.

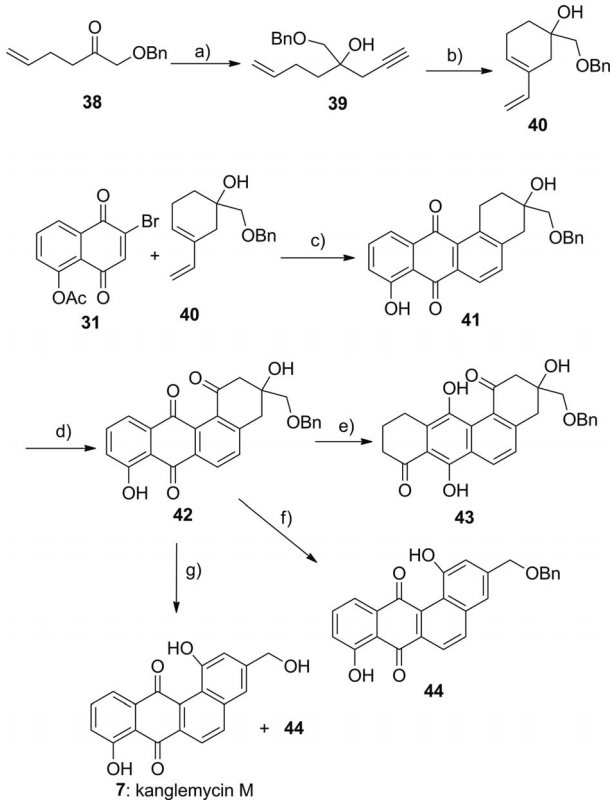
Total Synthesis of Kanglemycin M

Kanglemycin M is structurally similar to tetrangulol and varies only by having a C-3 hydroxy functionality, and, therefore in principle, it could be derived from tetrangulol by benzylic oxidation. However, all of our efforts to execute this transformation were unsuccessful under several conditions {such as SeO_2, dioxane, reflux; NBS (*N*-bromosuccinimide), AIBN [azobis(isobutyronitrile)], CCl_4, reflux; TBAP (tetrabutylammonium perchlorate), Py (pyridine)}. The failure of this reaction is attributed to the presence of free hydroxy groups in tetrangulol. Therefore, the hydroxy groups of tetrangulol were protected as in diacetate **37** in 94% yield. This time, the sequence of bromination and hydrolysis leading to kanglemycin M was successful, but the yield could not be improved to more than 40% (see Scheme 4).

Because of the poor yield and difficulties encountered in transforming tetrangulol into kanglemycin M through a benzylic oxidation, we developed an alternative strategy wherein the requisite hydroxymethyl group is introduced at an early stage of the synthesis. Accordingly, we envisioned that the total synthesis of kanglemycin M could be achieved from diene **40** through a Diels–Alder reaction with quinone **31** (see Scheme 5).



Scheme 4. Reagents and conditions: (a) NaOAc, Ac_2O, 100 °C, 7 h, 94%; (b) (i) NBS, $(PhCO)_2O_2$, CCl_4, reflux, 8 h; (ii) dioxane/H_2O, 24 h, reflux; (iii) NaOH (1 N), MeOH.

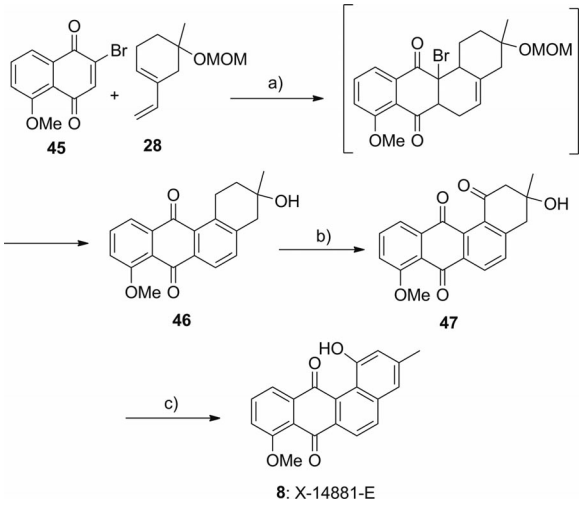


Scheme 5. Reagents and conditions: (a) Allenylmagnesium bromide, THF, –78 °C, 3 h, 88%; (b) G-I, CH_2Cl_2, reflux, 8 h, 78%; (c) (i) toluene, 80 °C to 100 °C, 12 h; (ii) K_2CO_3, MeOH, 75% for two steps; (d) hv, O_2, benzene, 2 d, 75%; (e) Pd/C, H_2, EtOH, room temp., 18 h, 85%; (f) BCl_3 (5 equiv.), CH_2Cl_2, 78 °C to room temp., 12 h, 65%; (g) BCl_3 (15 equiv.), CH_2Cl_2, 0 °C to room temp., 36 h, **7** (57%) and **44** (21%).

Thus, the addition of allenylmagnesium bromide to ketone **38**[27] resulted in the requisite enyne **39**, which upon treatment with G-I, was smoothly transformed into diene **40** in good yield. With substantial quantities of diene **40** in hand, we turned our attention to study the key Diels–Alder reaction. As anticipated, this reaction proceeded smoothly with dienophile **31** to furnish the corresponding cycloadduct which was subsequently aromatized with K_2CO_3 and MeOH to afford compound **41** in 75% yield. The photooxygenation of **41** (Hg lamp, 125 W, and Philips India) under the positive pressure of oxygen afforded ketone **42** in 75% yield. The completion of the kanglemycin M synthesis required the removal of the benzyl group and aromatization. However, removing the benzyl group under hydrogenolysis conditions led to the partial hydrogenation of the phenolic ring with no reaction occurring at the benzyl group to afford **43** in excellent yield. Though the exact reasons for this unusual transformation are unknown, we presume that it may be due to the presence of a phenolic OH group. Nevertheless, this problem was circumvented by carrying out the debenzylation with BCl_3. When BCl_3 (5 equiv.) was used at –78 °C, only aromatized compound **44** was obtained in 65% yield. However, when ketone **42** was treated with 15 equiv. of BCl_3 at 0 °C and warmed to room temp. for 36 h, it was smoothly converted into kanglemycin M (**7**) in 57% yield and **44** in 21% yield. Thus, the total synthesis of kanglemycin M (**7**) was accomplished in 22% overall yield from compound **38**. The spectroscopic data of kanglemycin M were good in agreement with those reported.[8]

Total Synthesis of X-14881-E

After the successful syntheses of tetrangulol and kanglemycin M, we engaged in the synthesis of X-14881-E (**8**) by utilizing the same strategy. The synthesis started with the Diels–Alder reaction of diene **28** with 5-methoxy-2-bromo-1,4-naphthoquinone (**45**) to provide the corresponding cycloadduct which was further subjected to dehydrobromination/aromatization by using K_2CO_3 and MeOH to afford compound **46** in 64% yield, resulting in concomitant removal of the MOM group. Photooxygenation of compound **47** under the positive pressure of oxygen and subsequent aromatization under acidic conditions completed the total synthesis of X-14881-E (**8**) in 74% yield for the two steps (see Scheme 6).[25d,26a,28] The spectroscopic data of the syn-

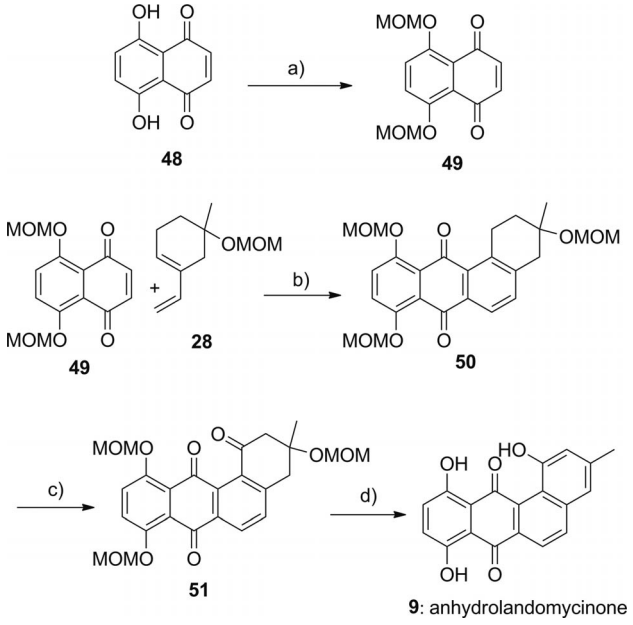


Scheme 6. Reagents and conditions: (a) (i) Toluene, 80 °C to 100 °C, 12 h; (ii) K_2CO_3, MeOH, 64% for two steps; (b) hv, O_2, benzene, 2 d, 73%; (c) PTSA, benzene, reflux, 2 h, 74%.

thetic product matched with those of the natural product, and thus, a short total synthesis of X-14881-E (**8**) was accomplished in 24% overall yield.

Total Synthesis of Anhydrolandomycinone

Following the syntheses of tetrangulol, kanglemycin M, and X-14881-E, we then focused our attention on the synthesis of anhydrolandomycinone (**9**) using our general strategy. Towards this end, we anticipated that the protected dihydroxynaphthoquinone **49** was a better dienophile to provide the cycloadduct in good yield. Accordingly, compound **48** was protected as its MOM ether using MOMCl and DIPEA to afford **49** in 91% yield. Gratifyingly, protected dienophile **49** smoothly underwent a Diels–Alder reaction to furnish the corresponding cycloadduct. On the basis of our earlier experience,[20] we immediately treated the cycloadduct with triethylamine and silica gel to facilitate the air oxidative aromatization without further purification to provide **50** in 64% yield for the two steps. The introduction of the oxygen functionality was achieved through photooxygenation (Hg lamp, 125 W, and Philips India) under the positive pressure of oxygen to afford ketone **51** in 66% yield (see Scheme 7). Finally, aromatization of ketone **51** under acidic conditions using PTSA provided anhydrolandomycinone (**9**) in 70% yield. The spectroscopic data of the synthetic sample matched with those of the natural product, and thus, we completed the total synthesis of anhydrolandomycinone (**9**)[29] in 20% overall yield.



Scheme 7. Reagents and conditions: (a) MOMCl, DIPEA, CH_2Cl_2, 0 °C to room temp. 6 h, 91%; (b) (i) toluene, 80 °C to 100 °C, 12 h; (ii) silica gel, NEt_3, $CHCl_3$, 4 h, 64% for two steps; (c) hν, O_2, benzene, 2 d, 66%; (d) PTSA, benzene, reflux, 2 h, 70%.

Conclusions

In summary, we presented a unified strategy for the syntheses of angular all-aromatic tetracyclic planar molecules by utilizing sequential intramolecular enyne metathesis and Diels–Alder reactions. Using this flexible strategy, we successfully achieved the total syntheses of tetrangulol, kanglemycin M, X-14881-E, and anhydrolandomycinone. Furthermore, our efforts are underway towards extending the scope of this strategy for the syntheses of various natural products with a similar molecular framework such as dehydrorabelomycine and analogues thereof.

Experimental Section

General Methods: Unless and otherwise noted, all starting materials and reagents were obtained from commercial suppliers and used after further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl, and toluene was distilled from sodium. Dichloromethane, hexanes, and pyridine were freshly distilled from calcium hydride. All solvents used for the routine isolation of products and for chromatography were reagent grade and glass distilled. Reaction flasks were dried in an oven at 100 °C for 12 h. Air- and moisture-sensitive reactions were performed under an argon/nitrogen atmosphere. Chromatography was performed using silica gel (100–200 mesh) with the indicated solvents. All reactions were monitored by thin layer chromatography which was performed on 0.25 mm E. Merck silica plates (60F-254) using UV light as the visualizing agent and aqueous phosphomolybdic acid, containing concentrated H_2SO_4, and heat as the developing agents. IR spectra were recorded with Thermo Nicolet Avater 320 FTIR and Nicolete Impact 400 machines. Mass spectra were obtained with a Waters Micromass-Q-Tof micro™ (YA105) spectrometer. ^1H and ^{13}C NMR spectroscopic data were recorded with either Bruker AV 400 MHz or Varian AS 400 MHz spectrometers. The NMR spectroscopic data is presented in the order of chemical shift, multiplicity (s, singlet; br. s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in Hertz (Hz), and number of protons.

General Procedure for DAR Followed by Aromatization: A solution of the dienophile (1.1 mmol) in toluene (15 mL) was treated with a solution of 1,3-diene (1.0 mmol) in toluene (3 mL) at room temperature, and then the mixture was heated at 80 °C for 12 h followed by 100 °C for 2 h. After removing the solvent in vacuo, the crude Diels–Alder adduct was dissolved in MeOH (10 mL), and the resulting solution was treated with solid K_2CO_3 (3 mmol) and stirred in the dark for 12 h. The solvent was removed in vacuo, and the residue was treated with water. The mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. Purification by silica gel column chromatography afforded the tetracycle.

General Procedure for Photooxygenation: A solution of the tetracyclic quinone (1 mmol) in benzene (315 mL) was irradiated with a mercury lamp (125 W, Philips India) under a positive pressure of oxygen for 24 to 36 h. The solvent was removed in vacuo, and the residue was then purified by silica gel flash column chromatography.

General Procedure for A-Ring Aromatization: A solution of the quinone (0.1 mmol) in benzene (5 mL) was treated with a catalytic amount of PTSA, and the reaction mixture was heated to reflux for 2 h. The reaction mixture was cooled to room temp. and quenched with an aqueous $NaHCO_3$ solution. The resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with a brine solution, dried with Na_2SO_4, and evaporated in vacuo. The crude compound was puri-

fied by silica gel flash column chromatography to afford the tetracycle.

4-Methyloct-7-en-1-yn-4-ol (26): A solution of allenylmagnesium bromide (prepared from 6.85 mL, 61.2 mmol of propargyl bromide) in diethyl ether (20 mL) was added to a solution of ketone **25** (2 g, 20.4 mmol) in THF (50 mL) at –78 °C. After stirring for 3 h, the reaction mixture was warmed to room temp. and diluted with an aqueous NH_4Cl solution. The aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4, and then the solvent was evaporated in vacuo. The crude compound was purified by flash column chromatography to afford **26** as colorless liquid (2.4 g, 85%); R_f = 0.4 (ethyl acetate/hexanes, 1:9). IR ($CHCl_3$): $\tilde{\nu}$ = 3307, 3019, 2978, 2400, 1377, 1215, 1112, 916, 759, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.90–5.80 (m, 1 H), 5.06 (dd, J = 17.2, 1.7 Hz, 1 H), 4.98 (dd, J = 11.1, 1.7 Hz, 1 H), 2.38 (t, J = 2.4 Hz, 2 H), 2.19–2.12 (m, 2 H), 2.09 (t, J = 2.4 Hz, 1 H), 1.82 (s, 1 H), 1.75–1.62 (m, 2 H), 1.29 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 114.7, 80.9, 71.7, 71.4, 40.1, 32.6, 28.1, 26.4 ppm. HRMS (ESI): calcd. for $C_9H_{16}O$ $[M + H]^+$ 139.1123; found 139.1120.

5-(Methoxymethoxy)-5-methyloct-1-en-7-yne (27): To a stirred solution of alcohol **26** (2.5 g, 18.0 mmol) and DIPEA (19 mL, 108.5 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added dropwise MOMCl (3 M in toluene, 30 mL, 90 mmol), and the reaction mixture was stirred for 6 h at room temp. The reaction mixture was quenched with water, and the resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The crude compound was purified by flash column chromatography to afford **27** (3 g, 91%) as a colorless liquid; R_f = 0.5 (ethyl acetate/hexanes, 1:9). IR ($CHCl_3$): $\tilde{\nu}$ = 3088, 2929, 1947, 1677, 1643, 1606, 1449, 1375, 1261, 1216, 1119, 1039, 917, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.91–5.77 (m, 1 H), 5.04 (dd, J = 17.0, 1.8 Hz, 1 H), 4.95 (dd, J = 9.6, 1.8 Hz, 1 H), 4.77–4.69 (m, 2 H), 3.39 (s, 3 H), 2.46 (dd, J = 2.6, 0.9 Hz, 2 H), 2.20–2.09 (m, 2 H), 2.01 (t, J = 2.6 Hz, 1 H), 1.88–1.61 (m, 2 H), 1.33 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 114.5, 91.3, 81.2, 76.9, 70.5, 55.7, 38.1, 30.3, 28.0, 23.5 ppm. HRMS (ESI): calcd. for $C_{11}H_{18}O_2$ $[M + Na]^+$ 205.1204; found 205.1198.

5-(Methoxymethoxy)-5-methyl-1-vinylcyclohex-1-ene (28): A solution of enyne **27** (500 mg, 2.74 mmol) in CH_2Cl_2 (60 mL) was treated with G-I (7 mmol-%), and the resulting mixture was then heated to reflux for 8 h. The reaction mixture was cooled to room temp., and DMSO was added (50 equiv. with respect to the catalyst, 5.0 mmol). The mixture was stirred for 6 h to remove the metal impurities. Evaporation of the solvent followed by purification the residue by silica gel flash column chromatography provided 1,3-diene **28** (450 mg, 90%); R_f = 0.5 (ethyl acetate/hexanes, 1:9). IR ($CHCl_3$): $\tilde{\nu}$ = 3079, 3016, 2979, 2932, 2119, 1640, 1452, 1378, 1216, 1144, 1036, 915, 758, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.38 (dd, J = 17.6, 10.5 Hz, 1 H), 5.73 (s, 1 H), 5.08 (d, J = 17.6 Hz, 1 H), 4.91 (d, J = 10.5 Hz, 1 H), 4.78 (d, J = 7.4 Hz, 1 H), 4.72 (d, J = 7.4 Hz, 1 H), 3.35 (s, 3 H), 2.45 (d, J = 17.6 Hz, 1 H), 2.36–2.28 (m, 1 H), 2.17 (d, J = 17.6 Hz, 1 H), 2.13–2.10 (m, 1 H), 1.84–1.78 (m, 1 H), 1.65–1.57 (m, 1 H), 1.30 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.7, 134.1, 128.4, 110.2, 91.0, 74.5, 55.3, 36.1, 33.5, 25.2, 23.8 ppm. HRMS (ESI): calcd. for $C_{11}H_{18}O_2Na$ $[M + Na]^+$ 205.1204; found 205.1208.

Hydroxy-Substituted 3-(Methoxymethoxy)-3-methyl-1,2,3,4-tetrahydrotetraphene-7,12-dione (32): Following the general procedure for the Diels–Alder reaction, a solution of juglone (**29**) (52 mg, 0.30 mmol) and diene **28** (50 mg, 0.27 mmol) in toluene was heated at 80 °C for 12 h and then at 100 °C for 2 h. After the solvent was removed in vacuo, the crude Diels–Alder adduct was dissolved in $CHCl_3$ (2 mL), and the resulting solution was treated with NEt_3 (1 mL) and silica gel (1 g). The mixture was stirred for 4 h to afford tetracycle **32** (85 mg, 88%) in 1:2 ratio as a yellow semisolid; R_f = 0.40 (ethyl acetate/hexanes, 1:2). IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 3016, 2929, 2857, 1669, 1635, 1584, 1369, 1275, 1153, 1079, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.9 (s, 1 H, major isomer), 12.54 (s, 1 H, minor isomer), 8.18 (d, J = 8.0 Hz, 1 H, minor isomer), 8.17 (d, J = 8.0 Hz, 1 H, major isomer), 7.77 (dd, J = 7.8, 1.2 Hz, 1 H, major isomer), 7.74 (dd, J = 7.8, 1.2 Hz, 1 H, minor isomer), 7.67–7.60 (m, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.28 (dd, J = 7.8, 1.2 Hz, 1 H, major isomer), 7.25 (dd, J = 7.8, 1.2 Hz, 1 H, minor isomer), 4.85 (d, J = 7.2 Hz, 1 H), 4.67 (d, J = 7.2 Hz, 1 H), 3.55–3.48 (m, 2 H), 3.19 (s, 3 H), 3.18 (d, J = 17.2 Hz, 1 H), 2.92 (d, J = 17.2 Hz, 1 H), 2.20–2.12 (m, 1 H), 1.86–1.78 (m, 1 H), 1.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.9, 189.0, 185.0, 183.2, 162.5, 161.2, 144.8, 144.2, 140.9, 136.8, 136.2, 135.9, 135.2, 133.7, 133.2, 133.0, 131.0, 130.5, 125.8, 125.2, 124.6, 123.3, 119.5, 118.8, 117.5, 91.2, 72.9, 72.8, 55.4, 43.4, 43.2, 34.1, 34.0, 29.9, 27.0, 26.7, 25.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{21}O_5$ $[M + H]^+$ 353.1389; found 353.1387.

3-(Methoxymethoxy)-3-methyl-7,12-dioxo-1,2,3,4,7,12-hexahydrotetraphenyl Acetate (33): Following the general procedure for the Diels–Alder reaction, a solution of compound **30** (65 mg, 0.30 mmol) and diene **28** (52 mg, 0.27 mmol) afforded a mixture of tetracycle **33** (80 mg, 74%) as a yellow, viscous solid. R_f = 0.30 (ethyl acetate/hexanes, 1:2). IR ($CHCl_3$): $\tilde{\nu}$ = 3016, 2929, 2857, 1772, 1669, 1625, 1594, 1530, 1369, 1275, 1193, 1039, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, J = 8.0 Hz, 1 H), 8.06 (d, J = 7.9 Hz, 1 H), 7.75 (t, J = 7.9 Hz, 1 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.37 (d, J = 7.9 Hz, 1 H), 4.84 (d, J = 7.5 Hz, 1 H), 4.66 (d, J = 7.5 Hz, 2 H), 3.50–3.46 (m, 2 H), 3.18 (s, 3 H), 3.15 (d, J = 17.2 Hz, 1 H), 2.88 (d, J = 17.2 Hz, 1 H), 2.48 (s, 3 H), 2.16–2.10 (m, 1 H), 1.84–1.76 (m, 1 H), 1.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.2, 184.9, 183.3, 182.5, 169.9, 169.8, 149.6, 144.1, 143.6, 139.9, 139.4, 137.1, 135.3, 134.8, 134.7, 134.6, 134.3, 134.0, 132.6, 132.3, 130.2, 129.7, 129.0, 127.0, 125.9, 125.5, 125.1, 125.0, 124.3, 91.1, 73.1, 73.0, 55.4, 43.2, 43.1, 34.1, 34.0, 29.8, 26.5, 26.2, 25.1, 21.5, 21.4 ppm. HRMS (ESI): calcd. for $C_{23}H_{23}O_6$ $[M + H]^+$ 395.1495; found 395.1497.

3,8-Dihydroxy-3-methyl-1,2,3,4-tetrahydrotetraphene-7,12-dione (34): Using the general procedure for the Diels–Alder reaction followed by aromatization, 5-acetoxy-2-bromo-1,4-naphthoquinone (**31**, 355 mg, 1.20 mmol), diene **28** (200 mg, 1.0 mmol), and K_2CO_3 (451 mg, 3.27 mmol) afforded tetracycle **34** which was purified by silica gel flash column chromatography to give a yellow solid (250 mg, 71%). R_f = 0.5 (ethyl acetate/hexanes, 1:1); m.p. 205–206.6 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3348, 2957, 2926, 2852, 1663, 1630, 1454, 1371, 1273, 1249, 1160, 1073, 909, 824, 774, 712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.52 (s, 1 H), 8.19 (d, J = 8.0 Hz, 1 H), 7.74 (dd, J = 8.3, 1.2 Hz, 1 H), 7.65 (t, J = 8.3 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.25 (dd, J = 8.3, 1.2 Hz, 1 H), 3.54 (t, J = 6.8 Hz, 1 H), 2.99 (s, 2 H), 2.07–1.93 (m, 1 H), 1.89–1.82 (m, 1 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.9, 185.0, 162.0, 144.4, 140.3, 136.8, 135.4, 135.2, 133.3, 131.3, 125.3, 123.3, 119.5, 115.7, 68.1, 45.0, 35.9, 28.9, 26.7 ppm. HRMS (ESI): calcd. for $C_{19}H_{17}O_4$ $[M + H]^+$ 309.1127; found 309.1131.

8-Hydroxy-3-(methoxymethoxy)-3-methyl-1,2,3,4-tetrahydrotetraphene-7,12-dione (35): Using the general procedure for the Diels–Alder reaction followed by aromatization, 5-acetoxy-2-bromo-1,4-

naphthoquinone (**31**) (355 mg, 1.2 mmol), diene **28** (200 mg, 1.0 mmol), and K_2CO_3 (1.35 g, 9.81 mmol), afforded tetracycle **35** which was purified by silica gel flash column chromatography (30% ethyl acetate in hexanes) to give a yellow solid (280 mg, 72%). R_f = 0.4 (ethyl acetate/hexanes, 1:2); m.p. 205–206.6 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3390, 3018, 2925, 2852, 1667, 1634, 1581, 1454, 1364, 1290, 1238, 1156, 1072, 1039, 918, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.49 (s, 1 H), 8.12 (d, J = 8.0 Hz, 1 H), 7.69 (dd, J = 7.8, 1.2 Hz, 1 H), 7.61 (t, J = 7.8 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.21 (dd, J = 7.8, 1.2 Hz, 1 H), 4.84 (d, J = 7.5 Hz, 1 H), 4.66 (d, J = 7.5 Hz, 1 H), 3.46 (t, J = 6.8 Hz, 1 H), 3.19 (s, 3 H), 3.17 (d, J = 17.3 Hz, 1 H), 2.89 (d, J = 17.3 Hz, 1 H), 2.17–2.10 (m, 1 H), 1.83–1.76 (m, 1 H), 1.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.9, 184.9, 161.9, 144.7, 140.6, 136.7, 135.2, 135.1, 133.31, 130.9, 125.1, 123.2, 119.4, 115.7, 91.1, 72.9, 55.4, 43.3, 33.9, 26.6, 25.1 ppm. HRMS (ESI): calcd. for $C_{21}H_{21}O_5$ $[M + H]^+$ 353.1389; found 353.1385.

3,8-Dihydroxy-3-methyl-3,4-dihydrotetraphene-1,7,12(2*H*)-trione (36): Following the general procedure for photooxygenation, a solution of tetracycle **34** (100 mg, 0.32 mmol) in benzene (300 mL) was irradiated for 40 h to afford compound **36** (70 mg, 65%) as an orange solid. R_f = 0.3 (ethyl acetate/hexanes, 1:1); m.p. 183–185.8 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3459, 2961, 2923, 2846, 1697, 1666, 1633, 1589, 1454, 1365, 1281, 1219, 1156, 1075, 915, 770 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.18 (s, 1 H), 8.24 (d, J = 8.1 Hz, 1 H), 7.61–7.57 (m, 2 H), 7.49 (d, J = 8.1 Hz, 1 H), 7.23–7.20 (m, 1 H), 3.10 (s, 2 H), 3.05 (d, J = 15.0 Hz, 1 H), 2.94 (d, J = 15.0 Hz, 1 H), 1.55 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 187.9, 183.3, 162.2, 147.8, 137.3, 136.3, 135.4, 133.9, 133.8, 129.5, 123.8, 119.8, 115.5, 72.7, 54.0, 44.2, 30.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{15}O_5$ $[M + H]^+$ 323.0919; found 323.0920.

Tetrangulol (6): Following the general procedure for the A-ring aromatization, a solution of quinone **36** (100 mg, 0.31 mmol) in benzene (20 mL) was treated with a catalytic amount of PTSA, and the reaction mixture was heated to reflux for 2 h to afford compound **6** (66 mg, 70%) as a brown solid. R_f = 0.7 (ethyl acetate/hexanes, 1:10); m.p. 189–191.2 °C. IR (KBr): $\tilde{\nu}$ = 3408, 2924, 2832, 2716, 1599, 1362, 1308, 1296, 1270, 1154, 778 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.25 (s, 1 H), 11.27 (s, 1 H), 8.31 (d, J = 8.6 Hz, 1 H), 8.13 (d, J = 8.6 Hz, 1 H), 7.85 (d, J = 7.6 Hz, 1 H), 7.69 (t, J = 7.6 Hz, 1 H), 7.33 (d, J = 7.6 Hz, 1 H), 7.26 (s, 1 H), 7.14 (d, J = 1.8 Hz, 1 H), 2.49 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9, 188.0, 161.8, 155.4, 142.2, 139.3, 137.9, 137.0, 135.0, 132.6, 124.9, 122.0, 121.5, 121.4, 120.4, 114.8, 21.4 ppm. HRMS (ESI): calcd. for $C_{19}H_{13}O_4$ $[M + H]^+$ 305.0814; found 305.0819.

3-Methyl-7,12-dioxo-7,12-dihydrotetraphene-1,8-diyl Diacetate (37): NaOAc (65 mg, 0.78 mmol) was added to a solution of tetrangulol (**6**) (80 mg, 0.26 mmol) in Ac_2O (10 mL) at room temp. The reaction mixture was heated to 100 °C for 8 h, cooled to room temp., and then diluted with water. The mixture was extracted with diethyl ether (3 × 30 mL), and the solvent was removed in vacuo to give a yellow solid which was purified by silica gel column chromatography to afford compound **37** as a yellow solid (96 mg, 94%). R_f = 0.5 (ethyl acetate/hexanes, 1:1); m.p. 188–190.5 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3012, 2928, 2857, 1772, 1670, 1596, 1450, 1367, 1281, 1195, 1104, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, J = 8.6 Hz, 1 H), 8.02 (d, J = 8.6 Hz, 1 H), 7.96 (d, J = 7.7 Hz, 1 H), 7.78 (t, J = 7.7 Hz, 1 H), 7.56 (s, 1 H), 7.38 (d, J = 7.7 Hz, 1 H), 7.32 (s, 1 H), 2.55 (s, 3 H), 2.50 (s, 3 H), 2.37 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.1, 181.5, 169.7, 169.1, 149.7, 147.3, 140.3, 138.1, 137.9, 135.2, 134.4, 134.0, 133.4, 128.9, 126.1, 125.9, 124.6, 123.9, 122.5, 121.1, 21.7, 21.35, 21.27 ppm. HRMS (ESI): calcd. for $C_{23}H_{17}O_6$ $[M + H]^+$ 389.1025; found 389.1031.

Kanglemycin M (7): To a solution of diacetate **37** (90 mg, 0.23 mmol) dissolved in dry CCl_4 (10 mL) were added NBS (33 mg, 0.18 mmol) and $(PhCO_2)O_2$ (5 mg, 0.02 mmol) at room temp. under a nitrogen atomosphere. The reaction mixture was heated to reflux for 5 h and then cooled to room temp., and the solvent was removed in vacuo. For hydrolysis, the crude residue was dissolved, in dioxane (10 mL)/H_2O (10 mL) and $CaCO_3$ (250 mg), and the mixture was heated at 100 °C for 24 h. The resulting alcohol solution was cooled to room temp. and extracted with EtOAc (3 × 20 mL). The combined organic layers were was dried with anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The crude compound was immediately treated with NaOH (1 N solution, 10 mL) in MeOH (20 mL) for 5 h, and the mixture was neutralized with a dilute solution of HCl. The reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the solvent was removed in vacuo. The crude residue was purified by silica gel column chromatography to give kanglemycin M (**7**, 30 mg, 40%) as a brown solid. R_f = 0.4 (ethyl acetate/hexanes, 1:1); m.p. 143–145 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3455, 3016, 2924, 2853, 1662, 1634, 1454, 1412, 1363, 1289, 1261, 1042, 758 cm^{-1}. ^1H NMR (400 MHz, [D_6]-DMSO): δ = 11.98 (s, 1 H), 10.70 (s, 1 H), 8.24 (d, J = 8.5 Hz, 1 H), 8.12 (d, J = 8.5 Hz, 1 H), 7.77 (t, J = 7.9 Hz, 1 H), 7.57 (d, J = 7.9 Hz, 1 H), 7.46 (s, 1 H), 7.33 (d, J = 7.9 Hz, 1 H), 7.08 (s, 1 H), 5.46 (t, J = 5.4 Hz, 1 H, OH), 4.64 (d, J = 5.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 187.3, 186.1, 160.4, 155.1, 146.1, 138.1, 137.2, 136.0, 135.1, 134.9, 133.1, 123.2, 121.2, 119.2, 119.0, 116.4, 114.9, 113.3, 62.4 ppm. HRMS (ESI): calcd. for $C_{19}H_{13}O_5$ $[M + H]^+$ 321.0763; found 321.0763.

4-(Benzyloxymethyl)oct-7-en-1-yn-4-ol (39): A solution of allenylmagnesium bromide (prepared from 4.1 mL, 36.70 mmol of propargyl bromide) in diethyl ether (20 mL) was added to a solution of ketone **38** (2.5 g, 12.20 mmol) in THF (50 mL) at –78 °C. After stirring for 3 h, the reaction mixture was warmed to room temp. and then diluted with an aqueous NH_4Cl solution. The aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The crude compound was purified by flash column chromatography to afford **39** (2.65 g, 88%) as a colorless liquid; R_f = 0.6 (ethyl acetate/hexanes, 2:8). IR ($CHCl_3$): $\tilde{\nu}$ = 3547, 3302, 3066, 3031, 2920, 2860, 2117, 1640, 1453, 1205, 1098, 997, 914, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 5.88–5.76 (m, 1 H), 5.03 (d, J = 17.2 Hz, 1 H), 4.95 (d, J = 10.2 Hz, 1 H), 4.57 (s, 2 H), 3.52 (d, J = 9.0 Hz, 1 H), 3.41 (d, J = 9.0 Hz, 1 H), 2.49 (d, J = 2.6 Hz, 2 H), 2.41 (s, 1 H), 2.17–2.11 (m, 2 H), 2.01 (t, J = 2.6 Hz, 1 H), 1.74–1.69 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 138.0, 128.6, 128.5, 127.9, 127.8, 114.6, 80.6, 74.4, 73.6, 73.3, 70.9, 35.4, 27.6, 27.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{20}O_2Na$ $[M + Na]^+$ 267.1360; found 267.1361.

1-(Benzyloxymethyl)-3-vinylcyclohex-3-enol (40): A solution of enyne **39** (500 mg, 2.04 mmol) in CH_2Cl_2 (60 mL) was treated with G-I (7 mmol-%), and then the reaction mixture was heated to reflux for 8 h. The mixture was cooled to room temperature, and DMSO (50 equiv. with respect to the catalyst, 5.00 mmol) was added. The mixture was stirred for 6 h to remove the metal impurities. Evaporation of the solvent and purification of the residue by silica gel flash column chromatography provided 1,3-diene **40** (390 mg, 78%). R_f = 0.5 (ethyl acetate/hexanes, 2:8). IR ($CHCl_3$): $\tilde{\nu}$ = 3271, 2924, 2854, 1643, 1453, 1217, 1097, 1027, 989, 899, 762 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5 H), 6.37 (dd, J = 17.5, 10.7 Hz, 1 H), 5.74 (s, 1 H), 5.06 (d, J = 17.5 Hz, 1 H), 4.91 (d, J = 10.7 Hz, 1 H), 4.58 (s, 2 H), 3.40 (s, 2 H), 2.46 (s, 1 H), 2.37–2.29 (m, 1 H), 2.24 (s, 2 H), 2.20–2.08 (m, 1 H), 1.78–

1.62 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.5, 138.2, 133.5, 128.5, 128.4, 127.8, 127.7, 110.7, 76.63, 73.5, 70.4, 33.7, 30.5, 22.9 ppm. HRMS (ESI): calcd. for $C_{16}H_{21}O_2$ $[M + H]^+$ 245.1542; found 245.1548.

3-(Benzyloxymethyl)-3,8-dihydroxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (41): Using the general procedure for the Diels–Alder reaction followed by aromatization, 5-acetoxy-2-bromo-1,4-naphthoquinone (**31**) (355 mg, 1.00 mmol), diene **40** (220 mg, 0.9 mmol), and K_2CO_3 (372 mg, 2.70 mmol) afforded tetracycle compound **41** which was purified by silica gel flash column chromatography to give a yellow solid (280 mg, 75%). R_f = 0.6 (ethyl acetate/hexanes, 1:1); m.p. 113–115.5 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3435, 2923, 2855, 1665, 1635, 1583, 1455, 1368, 1270, 1160, 1093, 1073, 773 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.54 (s, 1 H), 8.18 (d, J = 8.0 Hz, 1 H), 7.74 (dd, J = 7.6, 1.2 Hz, 1 H),7.64 (t, J = 7.6 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.39–7.29 (m, 5 H), 7.25 (dd, J = 8.0, 1.1 Hz, 1 H), 4.61 (s, 2 H), 3.54–3.50 (m, 2 H), 3.48 (s, 2 H), 3.01 (s, 2 H), 2.53 (s, 1 H), 2.07–2.01 (m, 1 H), 1.87–1.82 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.9, 184.9, 161.9, 144.0, 140.7, 138.0, 136.7, 135.3, 133.2, 131.2, 128.7, 128.1, 127.9, 125.2, 123.3, 119.5, 115.7, 76.7, 73.8, 69.6, 40.5, 31.2, 25.9 ppm. HRMS (ESI): calcd. for $C_{26}H_{23}O_5$ $[M + H]^+$ 415.1545; found 415.1542.

3-(Benzyloxymethyl)-3,8-dihydroxy-3,4-dihydrotetraphene-1,7,12(2*H*)-trione (42): Following the general procedure for photooxygenation, a solution of tetracycle compound **41** (250 mg, 0.60 mmol) in benzene (300 mL) was irradiated for 40 h to afford compound **42** (110 mg, 75%) as an orange semisolid; R_f = 0.3 (ethyl acetate/hexanes, 1:1). IR ($CHCl_3$): $\tilde{\nu}$ = 3459, 2925, 2855, 1703, 1673, 1636, 1592, 1455, 1361, 1276, 1217, 1159, 1097, 913, 754 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.26 (s, 1 H), 8.30 (d, J = 8.0 Hz, 1 H), 7.67–7.63 (m, 2 H), 7.54 (d, J = 8.0 Hz, 1 H), 7.39–7.29 (m, 6 H), 4.60 (s, 2 H), 3.52, 3.48 (ABq, $J_{A,B}$ = 3.5 Hz, 2 H), 3.16 (s, 2 H), 3.11, 3.02 (ABq, $J_{A,B}$ = 15.3 Hz, 2 H), 2.82 (br. s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.0, 187.6, 183.1, 162.2, 147.3, 137.5, 137.2, 136.2, 135.9, 135.2, 134.0, 133.7, 129.5, 128.8, 128.3, 128.0, 123.8, 119.8, 115.5, 73.9, 73.8, 49.6, 39.7 ppm. HRMS (ESI): calcd. for $C_{26}H_{21}O_6$ $[M + H]^+$ 429.1338; found 429.1342.

3-(Benzyloxymethyl)-3,7,12-trihydroxy-3,4,10,11-tetrahydrotetraphene-1,8(2*H*,9*H*)-dione (43): To a solution of quinone **42** (80 mg, 0.18 mmol) dissolved in EtOH (10 mL) under a H_2 atomosphere was added a catalytic amount of 10% Pd/C. The reaction mixture was stirred for 18 h. The solid in the reaction mixture was filtered through Celite, and the filtrate was subjected to silica gel column chromatography to afford compound **43** (70 mg, 85%) as a dark red semisolid; R_f = 0.4 (ethyl acetate/hexanes, 1:1). IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 2927, 2252, 1725, 1637, 1495, 1455, 1389, 1354, 1328, 1090, 910, 735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.46 (s, 1 H), 9.43 (s, 1 H), 8.67 (d, J = 8.5 Hz, 1 H), 7.38–7.31 (m, 5 H), 7.24 (d, J = 8.5 Hz, 1 H), 4.59 (s, 2 H), 3.51 (s, 2 H), 3.44, 3.24 (ABq, $J_{A,B}$ = 17.1 Hz, 2 H), 3.11 (t, J = 6.0 Hz, 2 H), 3.08 (s, 2 H), 2.79 (br. s, 1 H), 2.73 (t, J = 6.0 Hz, 2 H), 2.12 (quint, J = 6.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 203.3, 155.7, 149.8, 141.1, 137.5, 132.7, 128.7, 128.6, 128.2, 127.9, 127.6, 127.5, 126.2, 124.0, 112.7, 75.8, 73.8, 72.5, 50.1, 41.9, 38.8, 29.9, 24.5, 22.2 ppm. HRMS (ESI): calcd. for $C_{26}H_{25}O_6$ $[M + H]^+$ 433.1651; found 433.1650.

Kanglemycin M (7): To a solution of quinone **42** (50 mg, 0.12 mmol) dissolved in CH_2Cl_2 (10 mL) under a nitrogen atmosphere at 0 °C was added dropwise a solution of BCl_3 (1 M in CH_2Cl_2, 1.76 mL, 1.76 mmol). The reaction mixture was warmed to room temp., stirred for 36 h, and then diluted with water. The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the solvent was removed in vacuo. The crude residue was purified by silica gel column chromatography to give kanglemycin M (**7**) (21 mg, 57%) as a brown solid along with compound **44** (10 mg, 21%). Data for compound **44**: R_f = 0.7 (ethyl acetate/hexanes, 2:8); m.p. 167–169.5 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 2923, 2852, 1637, 1456, 1418, 1369, 1306, 1259, 1171, 1102, 1017, 750 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.24 (s, 1 H), 11.33 (s, 1 H), 8.30 (d, J = 8.6 Hz, 1 H), 8.23 (d, J = 8.6 Hz, 1 H), 7.87 (d, J = 7.8 Hz, 1 H), 7.70 (t, J = 7.8 Hz, 1 H), 7.50 (s, 1 H), 7.43–7.32 (m, 5 H), 7.29 (s, 1 H), 4.71 (s, 2 H), 4.66 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.6, 187.7, 161.6, 155.6, 142.1, 139.0, 138.2, 137.8, 136.9, 135.3, 134.7, 132.3, 128.5, 127.8, 124.8, 122.0, 121.3, 121.2, 119.5, 117.3, 114.5, 72.6, 70.9 ppm. HRMS (ESI): calcd. for $C_{26}H_{19}O_5$ $[M + H]^+$ 411.1232; found 411.1233.

3-Hydroxy-8-methoxy-3-methyl-1,2,3,4-tetrahydrotetraphene-7,12-dione (46): Using the general procedure for the Diels–Alder reaction followed by aromatization, 5-methoxy-2-bromo-1,4-naphthoquinone (**45**) (80 mg, 0.30 mmol), diene **28** (50 mg, 0.27 mmol), and K_2CO_3 (111 mg, 0.81 mmol) afforded tetracycle **46** which was purified by silica gel flash column chromatography to give a yellow semisolid (250 mg, 64%); R_f = 0.4 (ethyl acetate/hexanes, 1:1). IR ($CHCl_3$): $\tilde{\nu}$ = 3460, 2923, 2851, 1659, 1587, 1467, 1353, 1268, 1107, 1025, 991, 823, 749, 719 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.0 Hz, 1 H), 7.84 (dd, J = 7.7, 1.1 Hz, 1 H), 7.68 (t, J = 7.7 Hz, 1 H), 7.43 (d, J = 7.7 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 1 H), 4.03 (s, 3 H), 3.49 (t, J = 6.2 Hz, 2 H), 2.95 (s, 2 H), 2.00–1.94 (m, 1 H), 1.87–1.80 (m, 1 H), 1.65 (br. s, 1 H), 1.38 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.9, 183.2, 159.8, 142.4, 138.7, 137.7, 135.4, 135.0, 130.3, 125.6, 121.0, 119.9, 117.0, 68.2, 56.7, 44.9, 35.9, 28.8, 26.6 ppm. HRMS (ESI): calcd. for $C_{20}H_{19}O_4$ $[M + H]^+$ 323.1283; found 323.1287.

3-Hydroxy-8-methoxy-3-methyl-3,4-dihydrotetraphene-1,7,12(2*H*)-trione (47): Following the general procedure for photooxygenation, a solution of tetracycle compound **46** (40 mg, 0.12 mmol) in benzene (300 mL) was irradiated for 40 h to afford compound **47** (30 mg, 73%) as an orange solid. R_f = 0.3 (ethyl acetate/hexanes, 1:1); m.p. 144–146.5 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3512, 2928, 1696, 1655, 1590, 1440, 1346, 1304, 1268, 1225, 1116, 1022, 820, 798, 722 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, J = 8.0 Hz, 1 H), 7.76 (dd, J = 8.1, 1.3 Hz, 1 H), 7.70 (t, J = 8.1 Hz, 1 H), 7.52 (d, J = 8.0 Hz, 1 H), 7.30 (dd, J = 8.1, 1.3 Hz, 1 H), 4.03 (s, 3 H), 3.16 (s, 2 H), 3.09 (d, J = 14.8 Hz, 1 H), 2.99 (d, J = 14.8 Hz, 1 H), 1.50 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.4, 184.7, 181.5, 159.7, 147.1, 137.7, 135.4, 135.1, 134.9, 134.4, 133.8, 129.8, 120.6, 119.5, 117.2, 72.1, 56.5, 53.8, 44.1, 29.8 ppm. HRMS (ESI): calcd. for $C_{20}H_{17}O_5$ $[M + H]^+$ 337.1076; found 337.1074.

X-14881-E (8): Following the general procedure for the A-ring aromatization, a solution of quinone **47** (50 mg, 0.14 mmol) in benzene (10 mL) was treated with a catalytic amount of PTSA, and the reaction mixture was heated to reflux for 2 h to afford compound **8** (30 mg, 74%) as a brown solid. R_f = 0.7 (ethyl acetate/hexanes, 1:10); m.p. 185–187.4 °C. IR (KBr): $\tilde{\nu}$ = 3428, 2923, 2851, 2716, 1660, 1586, 1468, 1354, 1316, 1269, 1171, 1035, 1010, 958, 791, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.15 (s, 1 H), 8.28 (d, J = 8.5 Hz, 1 H), 7.93 (dd, J = 7.7, 0.9 Hz, 1 H), 7.73 (t, J = 7.7 Hz, 1 H), 7.35 (d, J = 8.5 Hz, 1 H), 7.24 (br. s, 1 H), 7.12 (d, J = 1.7 Hz, 1 H), 4.07 (s, 3 H), 2.48 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7, 182.2, 159.6, 155.1, 141.2, 138.4, 137.6, 137.3, 136.8, 135.4, 130.7, 122.8, 121.3, 121.0, 119.9, 119.8, 119.2, 118.2, 56.7, 21.3 ppm. HRMS (ESI): calcd. for $C_{20}H_{15}O_4$ $[M + H]^+$ 319.0970; found 319.0963.

5,8-Bis(methoxymethoxy)naphthalene-1,4-dione (49): To a stirred solution of dihydroxyquinone **48** (500 g, 2.63 mmol) and DIPEA (2.75 mL, 15.78 mmol) in CH_2Cl_2 (20 mL) at 0 °C under a nitrogen atmosphere was added dropwise MOMCl (3 M in toluene, 4.38 mL, 13.15 mmol), and the reaction mixture was stirred for 6 h at room temp. The reaction mixture was quenched with water, and the resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and evaporated in vacuo. The crude compound was purified by flash column chromatography to afford **49** as a purple semisolid (670 mg, 91%). R_f = 0.5 (ethyl acetate/hexanes, 1:9). IR ($CHCl_3$): $\tilde{\nu}$ = 2985, 2853, 1663, 1448, 1374, 1242, 1047, 847, 787, 634 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (s, 2 H), 6.78 (s, 2 H), 5.27 (s, 4 H), 3.54 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.7, 152.3, 138.6, 125.3, 122.3, 96.1, 56.7 ppm. HRMS (ESI): calcd. for $C_{14}H_{14}O_6Na$ $[M + Na]^+$ 301.0688; found 301.0685.

3,8,11-Tris(methoxymethoxy)-3-methyl-1,2,3,4-tetrahydrotetraphene-7,12-dione (50): Following the general procedure for the Diels–Alder reaction, a solution of 5,8-bis(methoxymethoxy)naphthalene-1,4-dione (**49**) (168 mg, 0.60 mmol) and diene **28** (100 mg, 0.5 mmol) in toluene was heated at 80 °C for 12 h and then at 100 °C for 2 h. After the solvent was removed in vacuo, the crude Diels–Alder adduct was dissolved in $CHCl_3$ (2 mL), and the resulting solution was treated with NEt_3 (1 mL) and silica gel (1 g). The reaction mixture was stirred for 4 h to afford tetracycle **50** (160 mg, 64%) as a yellow, viscous liquid; R_f = 0.45 (ethyl acetate/hexanes, 1:1). IR ($CHCl_3$): $\tilde{\nu}$ = 3021, 2928, 1645, 1586, 1454, 1316, 1261, 1217, 1025, 759, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.0 Hz, 1 H), 7.47–7.40 (m, 3 H), 7.36 (d, J = 8.0 Hz, 1 H), 5.30 (s, 2 H), 5.29 (s, 2 H), 4.84 (d, J = 7.5 Hz, 1 H), 4.68 (d, J = 7.5 Hz, 2 H), 3.57 (s, 3 H), 3.56 (s, 3 H), 3.22 (s, 3 H), 3.15 (d, J = 17.0 Hz, 1 H), 2.86 (d, J = 17.0 Hz, 1 H), 2.11–2.04 (m, 1 H), 1.82–1.75 (m, 1 H), 1.38 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.5, 184.0, 151.8, 151.5, 142.6, 137.3, 134.3, 134.2, 132.9, 127.4, 125.2, 124.5, 123.8, 96.6, 96.4, 91.2, 73.5, 56.7, 56.6, 55.4, 43.0, 34.0, 25.6, 25.2 ppm. HRMS (ESI): calcd. for $C_{25}H_{28}O_8Na$ $[M + Na]^+$ 479.1682; found 479.1680.

3,8,11-Tris(methoxymethoxy)-3-methyl-3,4-dihydrotetraphene-1,7,12(2*H*)-trione (51): Following the general procedure for photooxygenation, a solution of quinone **50** (150 mg, 0.32 mmol) in benzene (300 mL) was irradiated for 30 h to afford compound **51** (105 mg, 66%) as an orange, viscous liquid; R_f = 0.25 (ethyl acetate/hexanes, 1:1). IR ($CHCl_3$): $\tilde{\nu}$ = 2929, 2857, 1673, 1636, 1572, 1471, 1409, 1321, 1246, 1154, 1082, 1001, 920, 757 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.4 Hz, 1 H), 7.73 (d, J = 7.8 Hz, 1 H), 7.48, 7.40 (ABq, $J_{A,B}$ = 9.2 Hz, 2 H), 5.36, 5.33 (ABq, $J_{A,B}$ = 7.0 Hz, 2 H), 5.30 (s, 2 H), 4.87, 4.48 (ABq, $J_{A,B}$ = 7.8 Hz, 2 H), 3.60 (s, 3 H), 3.55 (s, 3 H), 3.38 (d, J = 15.2 Hz, 1 H), 3.14 (d, J = 2.2 Hz, 1 H), 3.10 (d, J = 2.2 Hz, 1 H), 3.07 (s, 3 H), 2.93 (d, J = 15.2 Hz, 1 H), 1.48 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.7, 185.7, 182.0, 152.0, 150.6, 147.2, 138.7, 134.2, 133.0, 132.9, 129.7, 127.5, 125.1, 123.6, 123.3, 96.3, 96.1, 91.2, 56.7, 55.7, 51.9, 42.6, 25.6 ppm. HRMS (ESI): calcd. for $C_{25}H_{26}O_9Na$ $[M + Na]^+$ 493.1475; found 493.1467.

Anhydrolandomycinone (9): Following the general procedure for aromatization, a solution of compound **51** (100 mg, 0.31 mmol) in benzene (20 mL) was treated with a catalytic amount of PTSA, and the resulting mixture was heated to reflux for 2 h to afford compound **9** (66 mg, 70%) as a purple solid. R_f = 0.7 (ethyl acetate/hexanes, 1:10); m.p. 204–206.5 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3447, 2921, 2851, 1731, 1608, 1585, 1498, 1449, 1414, 1317, 258, 1181, 1143, 786 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 13.02 (s, 1 H), 12.52 (s, 1 H), 11.13 (s, 1 H), 8.36 (d, J = 8.5 Hz, 1 H), 8.17 (d, J = 8.5 Hz, 1 H), 7.36 (d, J = 2.7 Hz, 2 H), 7.31 (s, 1 H), 7.19 (s, 1 H), 2.51 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.1, 186.3, 159.1, 158.3, 155.2, 142.1, 139.3, 138.4, 135.8, 131.7, 130.7, 130.5, 122.0, 121.8, 120.9, 120.2, 113.8, 111.4, 21.4 ppm. HRMS (ESI): calcd. for $C_{19}H_{13}O_5$ $[M + H]^+$ 321.0763; found 321.0753.

Supporting Information (see footnote on the first page of this article): Characterization data including ^1H and ^{13}C NMR spectra for all the compounds.

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