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General Diastereoselective Synthetic Approach toward Isospongian Diterpenes. Synthesis of (−)-Marginatafuran, (−)-Marginatone, and (−)-20-Acetoxymarginatone

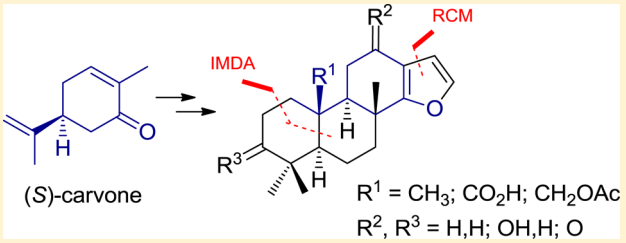
Antonio Gris,[†] Nuria Cabedo,[‡] Ismael Navarro,[†] Ignacio de Alfonso,[†] Consuelo Agulló,[†] and Antonio Abad-Somovilla*[,†]

[†]Departamento de Química Orgánica, Facultad de Química, Universidad de Valencia, Dr Moliner 50, 46100 Burjassot, Valencia, Spain

[‡]Centro de Ecología Química Agrícola, Universidad Politécnica de Valencia, Campus de Vera, Edificio 6C, 46022 Valencia, Spain

Supporting Information

ABSTRACT: This work describes a synthetic approach to the carbocyclic skeleton of isospongian diterpenes that uses the commercially available monoterpene (*S*)-carvone as a C-ring synthon, which is incorporated into the tetracyclic isospongian framework via a C→ABC→ABCD ring annulation strategy using intramolecular Diels−Alder and ring-closing metathesis reactions. This approach has been successfully used to prepare both the title natural isospongians and several nonnatural oxygenated analogues. A preliminary evaluation of the inhibitory activity of the small collection of synthesized isospongians on the mammalian mitochondrial respiratory chain revealed that most were able to inhibit the integrated electron transfer chain (NADH oxidase activity) in the micromolar range.



INTRODUCTION

A remarkable collection of terpenoid compounds has been isolated from different marine organisms, primarily sponges and nudibranchs, over the last three decades.[1,2] Among them is a small group of diterpenic compounds that share the tetracyclic isospongian carbon skeleton **1**,[3] which has a 2,3-fused tetrahydrofuran ring instead of the 3,4-fused tetrahydrofuran ring normally found in the more common spongian diterpenes (**2**) (Figure 1).[4−6]

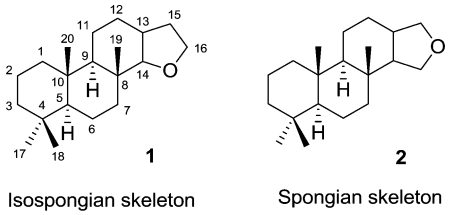


Figure 1.

Marginatafuran (**3**) (Figure 2), the first example of an isospongian-type diterpenoid, was isolated in 1985 from skin extracts of the northwestern Pacific common dorid nudibranch *Cadlina luteomarginata*.[7,8] This is a delicate, shell-less mollusk that primarily feeds on a variety of sponges to obtain selected metabolites that are stored in its dorsal glands and skin as a defense against predator attacks. In fact, this compound was later found in the extract of a sponge belonging to the genus *Aplysilla*, a normal part of this nudibranch's diet.[9] Other examples of these diterpenes are polyrhaphin D (**4**), which was

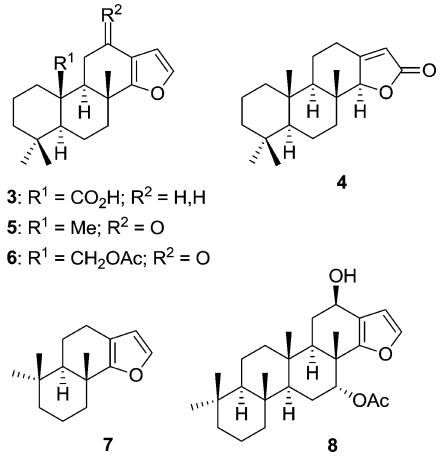


Figure 2.

isolated from the sponge *Aplysilla polyrhaphis*,[10] marginatone (**5**), which was isolated from the sponge *Aplysilla glacialis*,[11] and its derivative 20-acetoxymarginatone (**6**), which was isolated from skin extracts of the nudibranch *Cadlina luteomarginata*.[9]

Isospongian diterpenes are not the only terpene-type compounds of marine origin with an octahydronaphtho[1,2-*b*]furan or octahydronaphtho[1,2-*b*]furan-2-one system forming part of their structure, as a large number of sesquiterpenes and sesterterpenes with these structural characteristics are also

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known, many of which possess diverse biological activities.[1,12,13] Representative examples of these compounds are furanosesquiterpene pallescensin A[14] (**7**) and furanosesterterpene furoscalarol (**8**).[15]

The synthesis of isospongians has been the objective of various research groups, and several syntheses of the isospongian framework have been described. Indeed, the isospongian skeleton was synthesized before the first isolation of a naturally occurring example by Sharma during his studies on the biomimetic cyclization of ambliofuran.[16] Nishizawa[17] and, more recently, Loh[18] have also prepared the furanoisospongian skeleton via biomimetic-like olefin and epoxide-initiated cyclizations, respectively. In the early 1990s, Zoretic used the Mn(III)-mediated oxidative free-radical cyclization of a polyene to prepare a tricyclic system that transformed into an nonnatural isospongian compound after subsequent elaboration of the furan ring.[19] Finally, Ragoussis and co-workers have recently described the first and only synthesis of a natural isospongian, (−)-marginatone (**5**), using the labdane-type diterpene (+)-coronarin E as the starting material and a stereocontrolled, intramolecular electrophilic cyclization as the key synthetic step.[20]

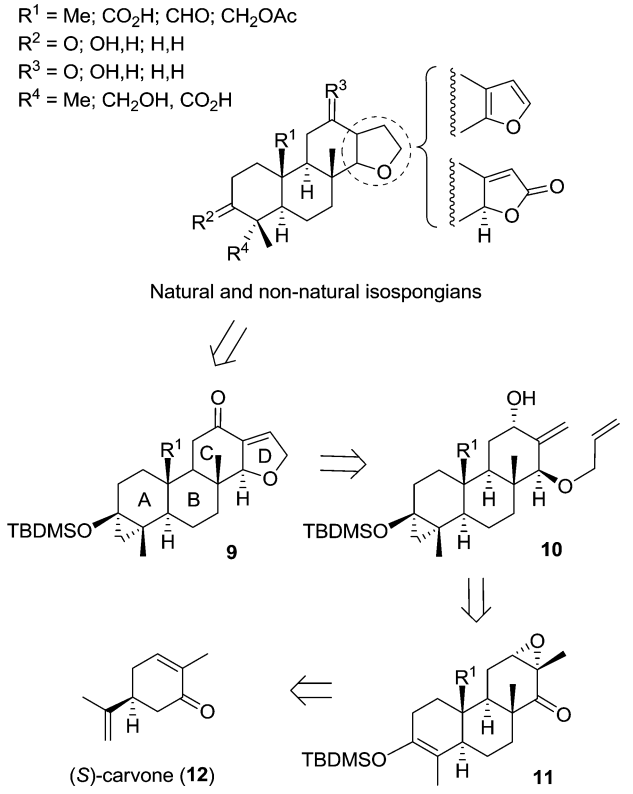
In this paper, we describe a general approach for the synthesis of isospongian diterpenes as a continuation of our previous work on synthesizing spongian diterpenes.[21] The purpose of our work was not only to synthesize the most representative of these natural diterpenes but also to prepare the related nonnatural analogues and create a small collection of isospongian-like compounds with diverse functionalities for biological activity screening. As far as we know, despite the diverse biological activities of the structurally related furanosesquiterpenes and furanosesterterpenes as well as regioisomeric spongian diterpenes,[22] the biological activities of compounds of this type have not yet been investigated.

RESULTS AND DISCUSSION

As the retrosynthetic analysis in Scheme 1 illustrates, we considered compounds such as **9** as good intermediates for the synthesis of these compounds. This key synthetic intermediate possesses adequate functionalities for completing the diterpenoid isospongian framework and introducing a variety of oxygenated groups at various positions, such as those characteristic of natural isospongians. Therefore, the 2,5-dihydrofuran ring can be used to prepare the D-ring of furano- and lactone-isospongians via the dehydrogenation of either the dihydrofuran ring or allylic oxidation, respectively. The oxygenated function at C-12 (diterpene numbering) and the *tert*-butyldimethylsilyloxy cyclopropane ring are convenient for managing not only the functionalization of the C and A rings but also the C-17 position of the isospongian system.[23] The 2,5-dihydrofuran moiety in **9** could be prepared via ring-closing metathesis (RCM) using diolefin **10**, which would be derived from an appropriately substituted *trans-anti-trans*-hydrophenanthrenone system, such as **11**, that could conceivably be prepared in an enantiomerically pure form from (*S*)-(+)-carvone (**12**) using well-established methodology.[24,25] It must be noted that the synthesis of isospongian systems functionalized at the C-20 position, e.g., **3** and **6**, requires that this position is functionalized at the beginning of the synthesis, which could, in principle, be accomplished via the allylic oxidation of the isopropylene group in carvone.

We began our work by using this synthetic strategy to prepare isospongians that were not functionalized at the C-10

Scheme 1. C→ABC→ABCD Approach Used To Prepare Isospongian-Type Diterpenes



angular methyl group, specifically, marginatone (**5**), and several novel nonnatural analogs. The synthesis of these compounds started with the preparation of the required hydrophenanthrenone derivative, **18**, from (*S*)-(+)-carvone (Scheme 2). Therefore, the known dialkylated epoxy carvone **14**, which was obtained from (*S*)-carvone at an overall yield of 68% after two consecutive alkylation reactions using MeI and 3-iodopropanaldehyde diethyl acetal followed by the subsequent stereoselective epoxidation of the enone moiety with alkaline hydrogen peroxide,[26] was transformed into dicarbonyl compound **15** via the acid hydrolysis of the diethyl acetal with pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone. The chemoselective Horner−Wadsworth−Emmons olefination reaction of the aldehyde group in **15** with the sodium salt of 2-(diethoxyphosphoryl)-3-oxobutane (generated in situ from the reaction of the corresponding diethylphosphonate and sodium hydride) in THF at room temperature (rt) stereoselectively produced the (*E*)-enone **16**,[27] which afforded dienol silyl ether **17** via the subsequent TBDMS triflate and Et_3N treatment under standard kinetic conditions with nearly 61% overall yield over the final three steps. Dienol silyl ether **17** underwent a stereoselective intramolecular Diels−Alder (IMDA) reaction at 190−200 °C in toluene over 7 days in the presence of propylene oxide as an acid scavenger to yield Diels−Alder adduct **18** in very high yield after chromatographic purification.

After completing the ABC ring system of the isospongian framework and before preparing the D ring, enol silyl ether **18** was subjected to Simmons−Smith cyclopropanation reaction conditions to cyclopropanate the A-ring double bond, a transformation that was required to form the geminal dimethyl group at C-4 in the target compounds.

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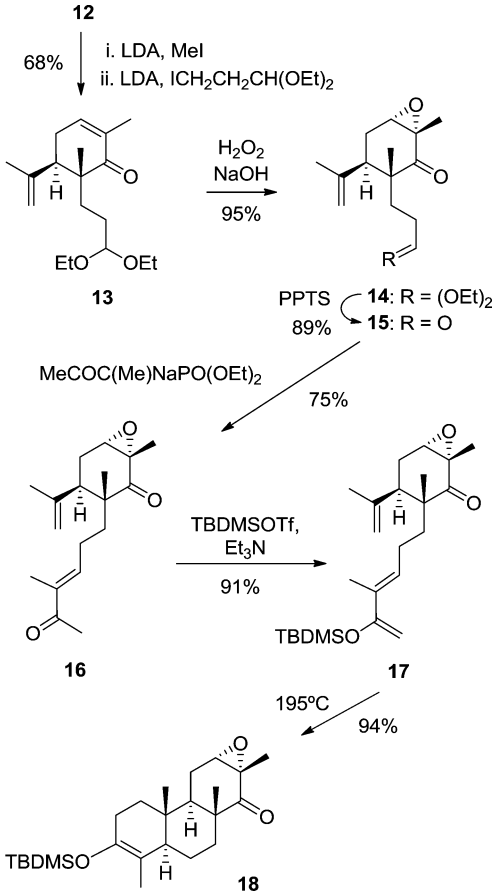
Scheme 2. Synthesis of the Tricyclic ABC System 18

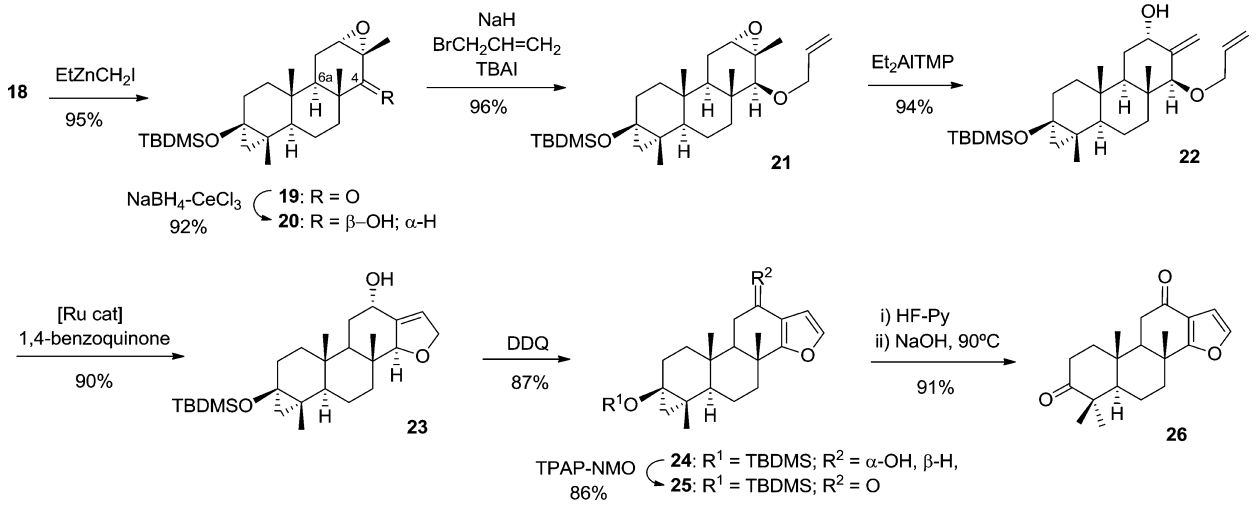


This reaction was more troublesome than initially expected, and a good yield for the cyclopropanated product was only achieved when a large excess of the Furukawa reagent ($EtZnCH_2I$),[28] which was prepared using a 1:1 stoichiometry of Et_2Zn to CH_2I_2,[29] was used in toluene at 0 °C (Scheme 3). The reaction was stereoselective for the less hindered α-side of the double bond under these conditions and afforded cyclopropanated derivative **19** with an excellent yield of 95%.

With compound **19** in hand, we focused on preparing the D ring of the isospongian skeleton. After exploring several possibilities, all of which were based on first opening the methyloxirane moiety in **19** to form an allylic alcohol, we discovered that a good means for achieving this task was via the RCM of a bis-allyl ether such as **22**. First, ketone **19** was stereoselectively reduced under Luche conditions to the equatorial alcohol **20**,[30] which was then allylated using allyl bromide and sodium hydride with a catalytic amount of tetrabutylammonium iodide (TBAI) to yield allyl ether **21**. Subsequent treatment of this compound with *N*,*N*-diethylaluminum tetramethylpiperidide (Et_2AlTMP) in benzene at 0 °C promoted the desired eliminative ring-opening of the epoxide moiety to afford the allylic alcohol **22** in 83% overall yield from ketoepoxide **19**. The first attempt to perform this RCM reaction using Grubbs' second-generation catalyst [(1,3-dimesityl-2-imidazolylidene)(PCy_3)Cl_2Ru=CHPh] in refluxing CH_2Cl_2 resulted in a modest (55−60%) yield of the cyclized product. The low yield was caused partly by competitive homodimerization; however, the primary cause was the isomerization of the allyloxy moiety to an *E*/*Z* mixture of vinyl ethers.[31] These side reactions could be almost entirely suppressed by diluting the reaction mixture (0.02 M in CH_2Cl_2) and adding 20% of 1,4-benzoquinone.[32] Under such conditions, the RCM took less than 1 h under reflux to complete, resulting in a 90% yield of 2,5-dihydrofuran derivative **23** after the chromatographic purification of the crude product.[33]

The dehydrogenation of the dihydrofuran ring in **23** was accomplished using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in anhydrous benzene at rt. The oxidative aromatization of **23** using DDQ provided the desired furan **24** in 87% yield.[34] The hydroxyl group in **24** was oxidized to the corresponding carbonyl group using tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO) in the presence of powdered 4 Å molecular sieves before opening the cyclopropane ring to complete the geminal dimethyl group at C-4. Attempts to open the *tert*-butyldimethylsilyloxy cyclopropane moiety in **25** using PTSA in refluxing $CHCl_3$ under the conditions used to previously open a related system[35] formed a complex mixture of products. This result was attributed to the furan ring being incompatible

Scheme 3. Synthesis of the Isospongian Skeleton



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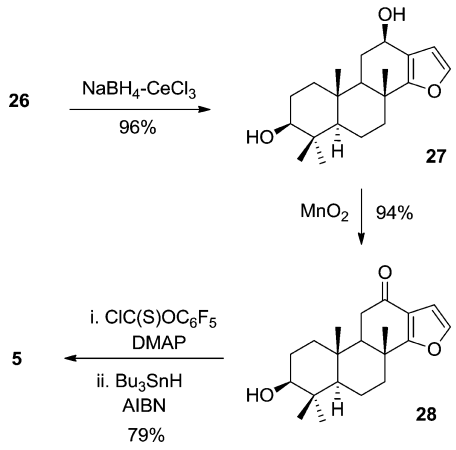
with these conditions. Therefore, an alternative, two-step procedure involving milder conditions was used to achieve this transformation. First, compound **25** was treated with an HF−pyridine complex in acetonitrile at 0 °C to remove the TBDMS protecting group, and the resulting cyclopropanol was subjected to a ring-opening reaction using two equivalents of NaOH in a 4:1 mixture of dioxane−H_2O under reflux in a strictly oxygen-free atmosphere.[36] Under these conditions, the transformation of compound **25** into isospongian-3,12-dione (**26**) was achieved with an excellent overall yield of 91%.

Having completed the isospongian framework, we were ready to make the necessary functional group modifications to form marginatone (**5**) (Scheme 4). This was successfully

Scheme 4. Synthesis of the Isospongian Diterpene (−)-Marginatone (5)



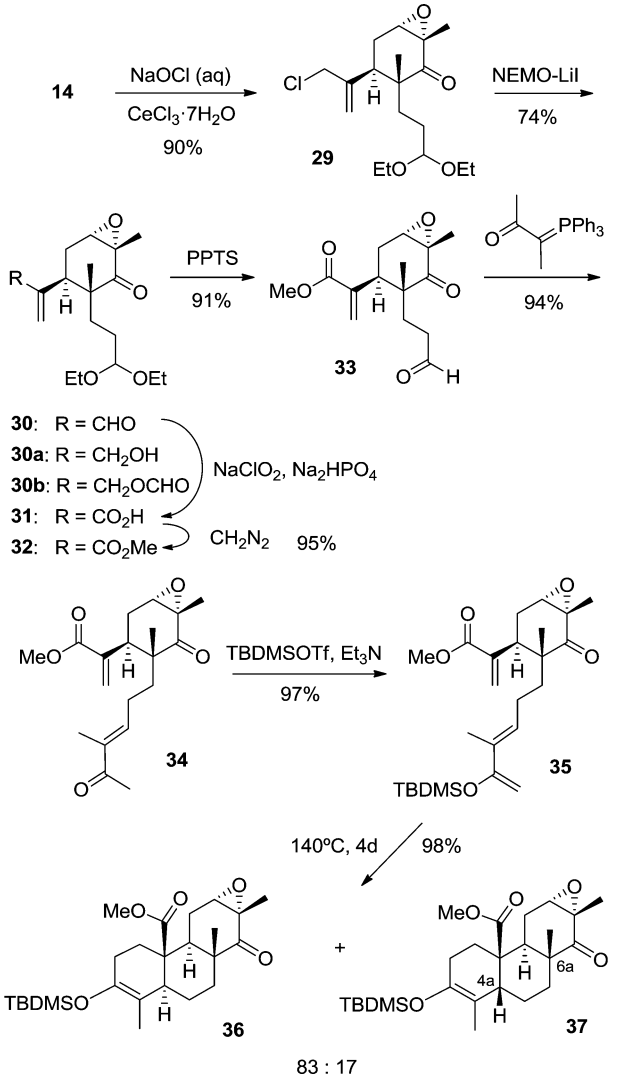
accomplished by taking advantage of the different electronic natures at the C-3 and C-12 positions. First, both of the carbonyl groups in **26** were stereoselectively reduced under Luche conditions to give isospongian-3β,12β-diol (**27**). The hydroxyl group at the C-12 position was then chemoselectively oxidized to form a keto group using activated manganese dioxide in $CHCl_3$ at rt. Both transformations occurred effectively to provide 3β-hydroxyisospongian-12-one (**28**) in 90% yield. Finally, the reduction of the hydroxyl moiety in the C-3 position, which completes the synthesis of the target natural isospongian, was accomplished via a radical deoxygenation of the corresponding thionocarbonate derivative. Therefore, **28** was treated with pentafluorophenyl chlorothioformate in CH_2Cl_2 in the presence of DMAP to yield the *O*-(perfluorophenoxy)carbonothioyl derivative that, when reacted with tributyltin hydride−azoisobutyronitrile in boiling benzene, produced **5**, which had physical and spectroscopic properties consistent with those reported for (−)-marginatone, with a 79% overall yield.[9,11]

Having successfully synthesized marginatone, we attempted to use the same synthetic strategy to prepare isospongian systems functionalized at the angular C-20 position by focusing on the natural isospongians marginatafuran (**3**) and 20-acetoxymarginatone (**6**) as the primary synthetic targets.

The first step to achieving this goal was to prepare a tricyclic system, such as **11** (see Scheme 1), that possessed an adequate functionality in the angular R^1 group to prepare the required C-20 functionalization in the target isospongians.

A carboxylate group was chosen as the most appropriate of the various options available. The preparation of the corresponding tricyclic systems started with the allylic chlorination of the isopropenyl group in compound **14** using sodium hypochlorite in the presence of cerium trichloride heptahydrate as the Lewis acid catalyst in a CH_2Cl_2 and water biphasic system.[37] The reaction proceeded rapidly at 0 °C without any noticeable hydrolysis of the labile diethyl ketal group to form chloride derivative **29** in high yield (Scheme 5).[38]

Scheme 5. Synthesis of the Tricyclic ABC System Functionalized at the Angular Position



This allylic chloride was oxidized to the corresponding α,β-unsaturated aldehyde by treating with *N*-ethylmorpholine *N*-oxide (NEMO)[39] and a catalytic amount of LiI in DMF at 55 °C.[40] This procedure worked more efficiently than those based on Kornblum oxidation[41] (DMSO and $NaHCO_3$ at 90 °C; DMSO−$MeNO_2$ and $AgBF_4$ at rt) and afforded aldehyde **30** in 74% yield along with the corresponding alcohol, **30a** (9%), and formate, **30b** (7%), derivatives,[42] which were further transformed into the aldehyde via either oxidation (TPAP, NMO, 5 Å MS, CH_2Cl_2, rt, 80%) or hydrolysis−oxidation (Na_2CO_3, MeOH, rt, 98% then TPAP, NMO, 5 Å MS, CH_2Cl_2, rt, 78%) reactions, respectively. Next, aldehyde **30** was oxidized to carboxylic acid **31** via the reaction with sodium chlorite in a

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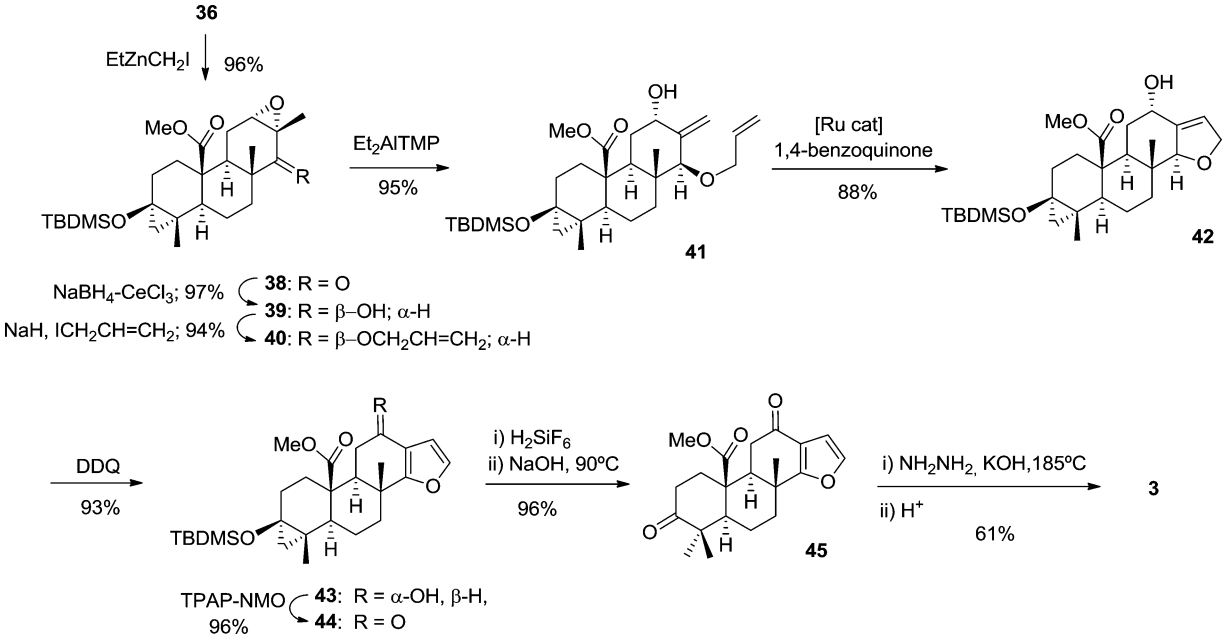
Scheme 6. Synthesis of the Isospongian Diterpene (−)-Marginatafuran (3)



NaH_2PO_4-buffered solution in the presence of 2-methyl-2-butene as a chlorine scavenger and methylated with diazomethane to produce methyl ester **32** in a 95% overall yield for the last two steps.

The remaining steps to form the 1,3,9-decatriene, which was required for the IMDA reaction, from methyl ester **32** involved the hydrolysis of the diethyl ketal moiety to the aldehyde followed by Wittig olefination to generate the methyl *trans*-enone and finally, the formation of the kinetic dienol silyl ether function. Except for the olefination reaction, which was performed using 3-(triphenylphosphoranylidene)butan-2-one as the Wittig reagent,[43,44] the remaining steps were performed under basically identical conditions to those used to transform **13** into **17**. All of the reactions proceeded satisfactorily to produce dienol silyl ether **35** in 86% overall yield for all three steps.

As expected, the IMDA reaction of the α,β-unsaturated ester **35** proceeded under milder conditions and was more rapid than that of **17**; in this case, the IMDA reaction was completed upon heating a solution of **35** in toluene to 140 °C for 4 days. This reaction occurred with a very high yield; however, unlike the results obtained for the related reaction of **17**, it led to an 87:13 mixture of the *trans-anti-trans* and *cis-anti-trans* fused adducts **36** and **37**, respectively.[45] Although the diastereomeric adducts could not be easily separated via conventional column chromatography, the desired major adduct **36** was obtained nearly pure via crystallization from hexanes in a yield of approximately 60%. The minor diastereomeric adduct **37** was obtained for analytical purposes via preparative reversed-phase HPLC of the residue from the crystallized mother liquor, which was an approximately 1:1 mixture of both adducts. The structure and stereochemistry of the two adducts were established via conventional NMR; the *trans-anti-trans* adduct **36** showed the same ^1H and ^{13}C NMR signal patterns as those of **18** except for the expected modifications associated with the different functionalization of the angular position. The *cis-anti-trans* stereochemistry of the minor adduct **37** was inferred from its ^{13}C NMR data and later confirmed via NOE experiments that showed, as expected for the proposed stereochemistry, that the irradiation of both the AB-ring fusion proton H-4a (δ 2.97 ppm) and the axial methyl group at C-6a (δ 0.841 ppm) caused a weak (less than 1%) but significant increase in the intensity of the methyl ester group (δ 3.27 ppm).[46]

Having completed the preparation of the isospongian ABC core system, i.e., compound **36**, we then proceeded to build the furan ring and elaborate the geminal dimethyl group in the A ring. As summarized in Scheme 6, the reaction sequence used to effect these transformations was identical to that previously used for the noncarboxylated tricyclic system **18**, with a few minor modifications. The most noteworthy modification was the change to the reagent used during the TBDMS deprotection step; in this case, we used aqueous hexafluorosilicic acid in MeCN at 4 °C, which not only led to a very smooth hydrolysis of the silyl ether moiety in **43** but also to a nearly quantitative yield for the corresponding cyclopropanol intermediate. Having optimized the reaction conditions for each step, the transformation of Diels–Alder adduct **36** into the C-20-functionalized isospongian **45** was accomplished via this eight-step sequence, which resulted in a 60% overall yield.

The remaining transformations required to complete the synthesis of the target natural isospongians only required an apparently simple manipulation of the functional groups in **45**. Initially, we examined the transformation of this intermediate into marginatafuran (**3**), which required reducing the C-3 and C-12 carbonyl groups to the corresponding methylenes. After evaluating several methods that use relatively mild reaction conditions to produce this reduction,[47] we found that treating **45** with the rather harsh classical Wolff–Kishner reaction conditions (hydrazine and diethylene glycol at 120 °C then potassium hydroxide at 185 °C for 8 h) not only reduced both carbonyl groups to the methylene but also hydrolyzed the ester group at C-20 to produce **3** with a moderate yield of 61%. This synthesized **3** possessed nearly identical physical and spectral properties to those reported for the natural (−)-marginatafuran product.[7]

The synthesis of the last natural isospongian target, compound **6**, from **45** proved to be somewhat more elaborate. As in the synthesis of marginatone (**5**) above, the selective

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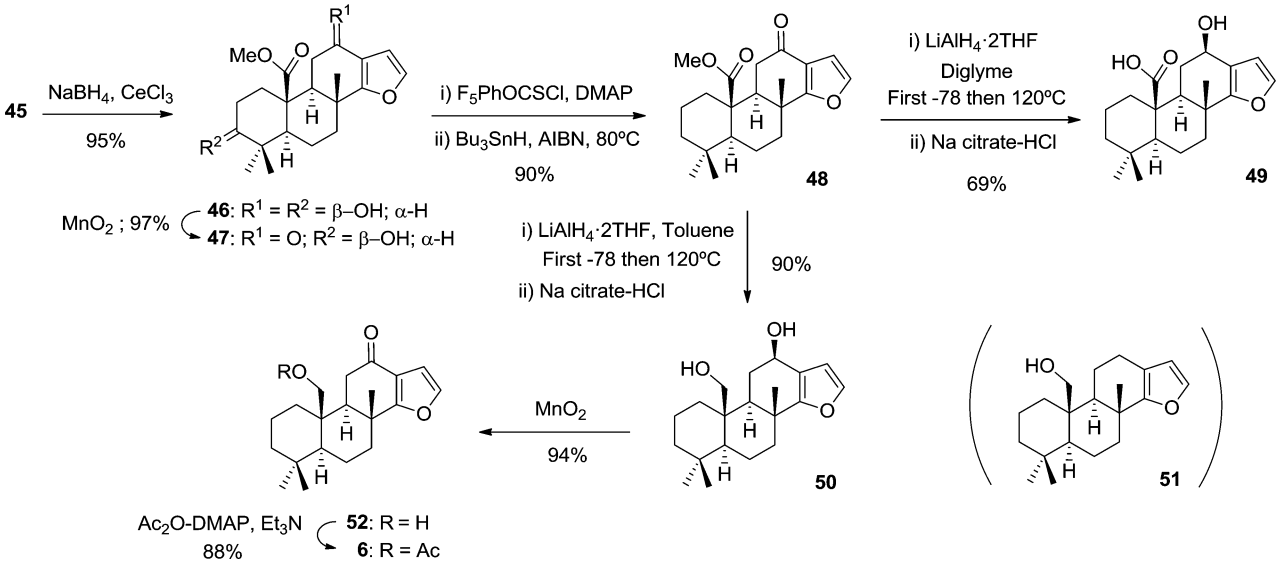
Scheme 7. Synthesis of the Isospongian Diterpene (−-)-20-Acetoxymarginatone (6)



reduction of the C-3 carbonyl group to a methylene was indirectly accomplished through a four-step process (Scheme 7) involving the stereoselective reduction of both carbonyl groups to the corresponding equatorial alcohols, the chemoselective oxidation of the benzylic hydroxyl group to a keto group, and finally, the free-radical reductive deoxygenation of the remaining C-3 hydroxyl after its derivatization to the corresponding thionocarbonate. This four-step reduction of the C-3 carbonyl group to methylene produced keto ester **48** with an overall yield of approximately 83% from the key intermediate, **45**.

The necessary reduction of the hindered C-20 methoxycarbonyl group to a hydroxymethylene group was not easy, and it was necessary to evaluate various reaction conditions to find an appropriate one. The treatment of keto ester **48** with a $LiAlH_4$·2THF complex in THF at low temperature followed by refluxing exclusively reduced the C-12 keto group even after refluxing overnight. Unexpectedly, changing the solvent to bis(2-methoxyethyl) ether (diglyme) and heating to 120 °C for 5 h only led to the reduction of the carbonyl group and the hydrolysis of the methyl ester moiety to produce hydroxy acid **49** (12-hydroxymarginatafuran) in 69% yield as the only identified product after chromatographic purification of the crude product.[48] Finally, we found that changing the solvent from diglyme to toluene and heating at 120 °C for 8 h reduced both the keto and carboxylate groups to give diol **50** in high yield. A byproduct identified as compound **51** was also isolated in small, variable amounts in some of the runs of this reaction.[49,50] It was found after some experimentation that performing the reduction of **48** with an excess of $LiAH_4$·2THF under the reaction conditions specified above but in the presence of 3−4 equiv of 6,7-dihydrobenzofuran-4(5*H*)-one (see the Experimental Section) resulted in no observable formation of compound **51**.

Having successfully prepared **50**, the synthesis of (−)-20-acetoxymarginatone (**6**) was then accomplished using two final, conventional operations. First, the oxidation of the secondary alcohol in **50** with activated MnO_2 to produce hydroxy ketone **52** followed by the acetylation of the primary hydroxyl group to afford **6**, which was spectroscopically identical to that isolated from natural sources.

In addition to the synthetic work, most of the prepared isospongians were assayed for inhibition of the bovine heart mitochondrial respiratory chain as a first evaluation of the potential biological activity of these compounds.[51] Many of the tested compounds were able to inhibit the integrated electron transfer chain, which includes respiratory complexes I, III, and IV (NADH oxidase activity), in the micromolar range with IC_{50} values ranging from 1.04 μM for both marginatone (**5**) and **48** to 9.5 μM for **47** (Table 1). These compounds showed a midrange potency relative to the most potent respiratory chain inhibitors, for example, *Annonaceous* acetogenins such as bullatacin (IC_{50} of 0.8 nM)[52] and the classic inhibitor rotenone (IC_{50} of 5.1 nM),[53] which are considered to be potent antitumor agents. Analysis of the data presented in Table 1 indicates that a lack of oxygenated substituents at the C-3

Table 1. IC_{50} Values of Some Isospongian Diterpenes against Their NADH Oxidase Activity[a]

compd	IC_{50} (μM)
3	2.5 ± 0.4
5	1.04 ± 0.09
6	4.4 ± 1.1
25a[b]	1.8 ± 0.8
26	>10
27	>10
28	>10
45	>10
46	>10
47	9.5 ± 1.1
48	1.04 ± 0.13
49	3.7 ± 1.1
50	1.2 ± 0.3
51	2.49 ± 0.15
51 acetate[c]	1.4 ± 0.9
52	5.4 ± 1. 8

[a]Data are the means ± the SD for three determinations of each compound. [b]Cyclopropanol intermediate derived from the HF-Py treatment of **25** (i.e., **25** with R^1 = H and R^2 = O). [c]Prepared by treating **51** with Ac_2O, DMAP, and Et_3N in CH_2Cl_2.

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position improved the activity against NADH oxidase as a general trend, while the various oxygenated functional groups at C-12 and C-20 did not drastically change the activity even though they may contribute to its modulation.

EXPERIMENTAL SECTION

General Features. See the Supporting Information.

Biological Assay Procedures. Stock solutions (30 mM in absolute EtOH) of the tested compounds were prepared and stored in the dark at −20 °C. Inverted submitochondrial particles (SMP) from beef heart were obtained via Fato's method 52,[54] which involved the ultrasonic disruption of frozen−thawed mitochondria to produce open membrane fragments that lost the permeability barriers to the substrates and stored at −70 °C at 28 mg/mL (protein measured by the Biuret method). The beef heart SMP were transferred to glass test tubes, diluted to 0.5 mg/mL with 250 mM sucrose and 10 mM Tris-HCl buffer, pH 7.4, and treated with 300 μM NADH to activate complex I before starting experiments. Aliquots of the stocks solutions (1 μL) were successively added to 500 μL of the SMP preparations followed by 5 min incubation on ice (ethanol never exceeded 2% of the total volume). After each incubation, an aliquot of the SMP (25 μL) was diluted to 6 μg/mL in 50 mM potassium phosphate buffer (pH 7.4) and 1 mM EDTA in a cuvette at 22 °C in the presence of 75 μM NADH. Immediately, NADH oxidase activity was measured as the aerobic oxidation of NADH. Reaction rates were calculated for each inhibitor (at increasing concentrations) by spectrophotometrically measuring the linear decrease in NADH concentration (λ 340 nm, ε 6.22 mM^{-1} cm^{-1}). The inhibitory concentration (IC_{50}) was taken as the concentration in the assayed cuvette that yielded 50% inhibition of the NADH oxidase activity. Data from individual titrations were used to assess the mean and standard deviation over three assays for each compound.

3-((1*S*,3*R*,4*R*,6*S*)-1,3-Dimethyl-2-oxo-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-3-yl)propanal (15). A solution of ketal **14**[26] (1.64 g, 5.3 mmol) and PPTS (1.33 g, 5.3 mmol) in 4% aqueous acetone (80 mL) was heated at 45 °C for 1.5 h. The mixture was cooled to rt, poured into water, and extracted with EtOAc. The usual workup left a residue that was purified by column chromatography (8:2 hexanes−EtOAc) to afford aldehyde **15** (1.121 g, 89%) as a colorless oil: $[\alpha]^{20}_D$ +80 (*c* 1.2, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 1727s, 1701s, 1639w; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.72 (1H, d, *J* = 1.5 Hz, H-1), 4.94 (1H, br s, H-1″), 4.74 (1H, br s, H′-1″), 3.41 (1H, br s H-6′), 2.77 (1H, dd, *J* = 10.7, 5.3 Hz, H-4′), 2.45 (1H, dddd, *J* = 17.6, 11.0, 5.2, 1.5 Hz, H-2), 2.37 (1H, dddd, *J* = 17.6, 11.0, 5.0, 1.5 Hz, H′-2), 2.20 (2H, m, H-5′), 2.02 (1H, ddd, *J* = 14.0, 11.0, 5.0 Hz, H-3), 1.80 (1H, ddd, *J* = 14.0, 11.0, 5.2 Hz, H′-3), 1.734 (3H, s, Me-$C_{2''}$), 1.408 (3H, s, Me-$C_{1'}$), 1.006 (3H, s, Me-$C_{3'}$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.1 ($C_{2'}$), 201.7 (C_1), 143.7 ($C_{2''}$), 115.7 ($C_{1''}$), 60.8 ($C_{6'}$), 58.2 ($C_{1'}$), 48.9 ($C_{3'}$), 40.5 ($C_{4'}$), 39.3 (C_2), 28.2 (C_3), 26.3 ($C_{5'}$), 23.3 (Me -$C_{2''}$), 20.5 (Me-$C_{3'}$), 16.2 (Me-$C_{1'}$); MS (EI) *m*/*z* 236 (M^+, 4), 221 (13), 208 (15), 207 (13), 193 (26), 179 (31), 137 (62), 123 (54), 109 (53), 107 (53), 85 (63), 81 (100), 67 (60); HRMS *m*/*z* calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1369.

(1*S*,3*R*,4*R*,6*S*)-1,3-Dimethyl-3-((*E*)-4-methyl-5-oxohex-3-en-1-yl)-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-one (16). Diethyl 2-oxobutane-3-phosphonate (1.30 g, 1.15 mL, 6.3 mmol) was added to a stirred slurry of prewashed NaH (60% dispersion oil; 199 mg, 5.0 mmol) in THF (21 mL) at 0 °C dropwise using a syringe. After hydrogen evolution had ceased, the mixture was warmed to rt and stirred for 10 min. The resulting mixture was cooled to 0 °C, and a solution of aldehyde **15** (1.12 g, 4.7 mmol) in THF (27 mL) was added. After being stirred at rt for 30 min, the mixture was quenched with saturated aqueous NH_4Cl and poured into water. Extraction with CH_2Cl_2 followed by the usual workup afforded an oil, which was purified by column chromatography (9:1 hexanes−Et_2O) to yield (*E*)-olefin **16** (1.03 g, 75%): $[\alpha]^{25}_D$ −51 (*c* 1.0, $CHCl_3$), IR ν_{max}/cm^{-1} (NaCl) 1670s, 1667s, 1643s; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.53 (1H, ddd, *J* = 7.2, 7.2, 1.1 Hz, H-3′), 4.96 (1H, t, *J* = 1.4 Hz, H-1″), 4.78 (1H, br s, H′-1″), 3.42 (1H, t, *J* = 2.0 Hz, H-6), 2.90 (1H, dd, *J* = 10.8, 5.0 Hz, H-4), 2.282 (3H, s, Me-$C_{5'}$), 2.27 (1H, m, H-2′), 2.26 (1H, ddd, *J* = 15.2, 4.9, 2.7 Hz, H-5α), 2.16 (1H, ddd, *J* = 15.2, 10.8, 1.6 Hz, H-5β), 2.04 (1H, m, H′-2′), 1.84 (1H, ddd, *J* = 13.6, 12.1, 4.5 Hz, H-1′), 1.764 (3H, s, Me-$C_{2''}$), 1.746 (3H, s, Me-$C_{4'}$), 1.60 (1H, ddd, *J* = 13.6, 11.8, 5.1 Hz, H′-1′), 1.420 (3H, s, Me-C_1), 0.999 (3H, s, Me-C_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.8 ($C_{5'}$), 209.6 (C_2), 144.0 ($C_{2''}$), 143.0 ($C_{3'}$), 137.7 ($C_{4'}$), 115.5 ($C_{1''}$), 60.9 (C_6), 58.5 (C_1), 49.6 (C_3), 40.5 (C_4), 35.5 ($C_{1'}$), 26.4 (C_5), 25.4 (Me-$C_{5'}$), 24.4 ($C_{2'}$), 23.3 (Me-$C_{2''}$), 21.0 (Me-C_3), 16.3 (Me-C_1), 11.1 (Me-$C_{4'}$); MS (EI) *m*/*z* 290 (M^+, 1.7), 218 (11), 180 (58), 165 (51), 164 (30), 163 (52), 137 (74), 112 (83), 111 (100); HRMS *m*/*z* calcd for $C_{18}H_{26}O_3$ 290.1882, found 290.1862.

(1*S*,3*R*,4*R*,6*S*)-3-((*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-methylhexa-3,5-dien-1-yl)-1,3-dimethyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-one (17). A solution of enone **16** (520 mg, 1.79 mmol) in CH_2Cl_2 (18 mL) was cooled to −78 °C and sequentially treated with Et_3N (0.75 mL, 5.37 mmol) and TBDMSOTf (0.53 mL, 2.32 mmol). After 1 h at −78 °C, the reaction mixture was quenched with 5% $NaHCO_3$ solution, poured into water, and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried, and concentrated. Purification of the obtained residue by column chromatography (9:1 hexanes−Et_2O with 0.2% of Et_3N) afforded silyl enol ether **17** (653 mg, 91%) as a colorless oil: $[\alpha]^{20}_D$ +35 (*c* 0.75, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 1701s, 1633w, 1590 m; ^{1}H NMR (C_6D_6), 300 MHz) δ 6.30 (1H, br dd, *J* = 7.4, 7.4 Hz, H-3′), 4.81 and 4.60 (1H each, each br s, 2 × H-1″), 4.48 and 4.37 (1H each, each s, 2 × H-6′), 2.90 (1H, dd, *J* = 11.1, 4.6 Hz, H-4), 2.78 (1H, dd, *J* = 2.5, 1.6 Hz, H-6), 2.26 (1H, m, H-2′), 1.97 (1H, ddd, *J* = 15.7, 13.4, 5.1 Hz, H′-2′), 1.83 (1H, m, H-5), 1.775 (3H, s, Me-$C_{4'}$), 1.65 (1H, ddd, *J* = 13.5, 11.1, 5.5 Hz, H-1′), 1.55 (1H, ddd, *J* = 12.7, 11.2, 2.3 Hz, H′-5), 1.504 (3H, s, Me-$C_{2''}$), 1.48 (1H, m, H′-1′), 1.340 (3H, s, Me-C_1), 1.022 (9H, s, Me_3CSi), 0.820 (3H, s, Me-C_3), 0.173 (6H, s, 2 × MeSi); ^{13}C NMR (C_6D_6, 75 MHz) δ 209.1 (C_2), 158.0 ($C_{5'}$), 144.7 ($C_{2''}$), 131.8 ($C_{4'}$), 131.8 ($C_{3'}$), 115.1 ($C_{1''}$), 91.3 ($C_{6'}$), 60.7 (C_6), 58.6 (C_1), 49.7 (C_3), 41.0 (C_4), 37.2 ($C_{1'}$), 26.5 (C_5), 26.1 (Me_3CSi), 23.9 ($C_{2'}$), 23.4 (Me-$C_{2''}$), 21.2 (Me-C_3), 18.5 (Me_3CSi), 16.5 (Me-C_1), 13.4 (Me-$C_{4'}$), −4.5 (2 × MeSi); MS (EI) *m*/*z* 404 (M^+,20), 389 (4), 347 (2), 250 (4), 226 (19), 225 (100), 223 (15), 197 (16), 168 (52); HRMS *m*/*z* calcd for $C_{24}H_{40}O_3Si$ 404.2747, found 404.2757.

(4a*R*,6a*R*,7a*S*,8a*S*,9a*R*,9b*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-4,6a,7a,9b-tetramethyl-1,4a,5,6,6a,7a,8a,9,9a,9b-decahydrophenanthro[2,3-*b*]oxiren-7(2*H*)-one (18). A small crystal of BHT was added to a solution of triene **17** (470.5 mg, 1.16 mmol) in toluene (13 mL) that had been placed in a previously silylated and dried ampule. After rigorously degassing using the freeze−thaw method, the mixture was cooled under N_2 before adding a drop of propylene oxide and sealing the ampule under vacuum. After the mixture was heated to 195 °C for 7 days, the solvent was eliminated on a rotary evaporator, and the crude product was purified by column chromatography (95:5 hexanes−EtOAc) to yield Diels−Alder adduct **18** as a white solid (444.5 mg, 94%): mp 165−168 °C (from hexanes); $[\alpha]^{20}_D$ −28 (*c* 0.5 $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 1711s, 1675 m; ^{1}H NMR (C_6D_6, 300 MHz) δ 2.86 (1H, br t, *J* = 2.0 Hz, H-8a), 2.05−1.86 (4H, m, 2 × H-2, H-6, H-9), 1.60−1.50 (3H, m, H′-6, H-5, H-4a), 1.581 (3H, s, Me-C_4), 1.50−1.30 (3H, m, H-9a, H′-9, H-1), 1.385 (3H, s, Me-C_{7a}), 1.033 (9H, s, Me_3CSi), 0.98 (1H, m, H′-5), 0.83 (1H, ddd, *J* = 11.7, 11.7, 7.5 Hz, H′-1), 0.757 (3H, s, Me-C_{6a}), 0.651 (3H, s, Me-C_{9b}), 0.130 (6H, s, 2 × MeSi); ^{13}C NMR (C_6D_6, 75 MHz) δ 207.2 (C_7), 142.3 (C_3), 112.3 (C_4), 59.3 (C_{8a}), 56.4 (C_{7a}), 47.9 (C_{4a}), 45.9 (C_{6a}), 40.4 (C_{9a}), 35.7 (C_{9b}), 35.3 (C_1), 33.9 (C_6), 27.8 (C_2), 26.1 (Me_3CSi), 21.7 (C_9), 20.5 (C_5), 18.4 (Me_3CSi), 18.1 (Me-C_{6a}), 17.0 (Me-C_{7a}), 13.6 (Me-C_{9b}), 12.9 (Me-C_4), −3.4 and −3.6 (2 × MeSi); MS (EI) *m*/*z* 404 (M^+, 100), 389 (43), 347 (10), 237 (7), 211 (6), 185 (6), 173 (7), 171 (8), 159 (9); HRMS *m*/*z* calcd for $C_{24}H_{40}O_3Si$ 404.2747, found 404.2744.

(1a*S*,1b*R*,3a*R*,4a*S*,5a*S*,6a*R*,6b*S*,8a*R*)-8a-((*tert*-Butyldimethylsilyl)oxy)-1a,3a,4a,6b-tetramethyldodecahydro-1*H*-cyclopropa[7,8]phenanthro[2,3-*b*]oxiren-4(1a*H*)-one (19). CH_2I_2 (408 μL, 5.1 mmol) was added dropwise to a stirred solution

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of diethylzinc in hexane (0.85 M, 6 mL, 5.1 mmol) at 0 °C under N_2. After 5 min, a solution of *tert*-butyldimethyl silyl enol ether **18** (258 mg, 0.638 mmol) in dry toluene (3.9 mL) was added via cannula at 0 °C, and the mixture was stirred for 2 h. The mixture was diluted with Et_2O (2−3 mL), quenched by the addition of a saturated NH_4Cl solution, and extracted with Et_2O. The organic extracts were successively washed with 10% $Na_2S_2O_3$ solution, water, and brine before drying and concentrating to yield a solid. Chromatography (10:0 → 9:1 hexanes−EtOAc) afforded the cyclopropanated compound **19** (248 mg, 95%) as a white solid: mp 168−169 °C (from MeOH−hexanes); $[\alpha]^{25}_D$ −9 (*c* 1.0, $CHCl_3$), IR ν_{max}/cm^{-1} (KBr) 1706s, 1660w; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.34 (1H, br s, H-5a), 2.24 (1H, ddd, *J* = 15.3, 3.0, 3.0 Hz, H-6α), 2.09 (1H, ddd, *J* = 13.7, 6.2, 1.5 Hz, H-8α), 1.97−1.73 (4H, m, H-8β, H-6β, H-3, H-2), 1.66 (1H, ddd, *J* = 13.3, 7.1, 1.5 Hz, H-7β), 1.50−1.33 (2H, m, H′-3, H′-2), 1.403 (3H, s, Me-C_{4a}), 1.26 (1H, dd, *J* = 12.7, 3.7 Hz, H-6a), 1.064 (3H, s, Me-C_{3a}), 1.029 (3H, s, Me-C_{1a}), 0.893 (3H, s, Me-C_{6b}), 0.852 (9H, s, Me_3CSi), 0.78 (1H, dd, *J* = 12.5, 2.7 Hz, H-1b), 0.57 (1H, ddd, *J* = 13.3, 13.3, 6.2 Hz, H-7α), 0.51 (1H, dd, *J* = 5.3, 1.0 Hz, H-1β), 0.22 (1H, d, *J* = 5.3 Hz, H-1α), 0.101 and 0.041 (3H each, each s, 2 × MeSi); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.1 (C_4), 59.6 (C_{5a}), 58.2 (C_{8a}), 56.3 (C_{4a}), 53.6 (C_{1b}), 45.8 (C_{3a}), 39.5 (C_{6a}), 35.4 (C_{6b}), 35.2 (C_7), 33.2 (C_3), 28.9 (C_8), 28.8 (C_1), 25.8 (Me_3CSi), 21.9 (C_{1a}), 21.5 (C_6), 21.4 (C_2), 17.9 (Me_3CSi), 17.7 (Me-C_{3a}), 16.7 (Me-C_{4a}), 15.5 (Me-C_{1a}), 13.4 (Me-C_{6b}), −3.8 and −3.1 (2 × MeSi); MS (EI) *m*/*z* 418 (M^+, 82), 403 (34), 389 (9), 361 (100), 345 (13), 333 (9), 211 (58); HRMS *m*/*z* calcd for $C_{25}H_{42}O_3Si$ 418.2903, found 418.2860.

(1a*S*,1b*R*,3a*R*,4*S*,4a*R*,5a*S*,6a*R*,6b*R*,8a*R*)-8a-((*tert*-Butyldimethylsilyl)oxy)-1a,3a,4a,6b-tetramethyltetradecahydro-1*H*-cyclopropa[7,8]phenanthro[2,3-*b*]oxiren-4-ol (20). $CeCl_3{\cdot}7H_2O$ (146 mg, 0.0.39 mmol) was added to a solution of epoxy ketone **19** (164 mg, 0.39 mmol) in MeOH (9.4 mL) and CH_2Cl_2 (2.8 mL). This mixture was stirred at rt until the cerium salt completely dissolved and then cooled to −30 °C. $NaBH_4$ (29.5 mg, 0.78 mmol) was then added slowly in small portions while the reaction was monitored by TLC (8:2 hexanes−EtOAc). Upon the completion (ca. 30 min), the reaction was quenched with acetone (0.4 mL), diluted with water, and extracted with CH_2Cl_2. The usual workup followed by chromatographic purification (8:2 hexanes−EtOAc) afforded epoxy alcohol **20** (152 mg, 92%) as a white solid: mp 205−206 °C (from benzene−hexanes); $[\alpha]^{25}_D$ +35 (*c* 0.96, $CHCl_3$), IR ν_{max}/cm^{-1} (KBr) 3256 m, 3054w, 1253s, 1055s, 998s, 832s, 780s; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.20 (1H, d, *J* = 5.1 Hz, H-4), 3.08 (1H, br s, H-5a), 2.10−1.97 (2H, m, H-8, H-6), 1.93−1.81 (2H, m, H′-8, H-3), 1.73−1.58 (3H, m, H-7β, H′-6, H-2α), 1.40 (1H, ddd, *J* = 13.1, 13.1, 3.1 Hz, H-2β), 1.312 (3H, s, Me-C_{4a}), 1.027 (3H, s, Me-C_{1a}), 0.96 (1H, m, H-3α), 0.880 (3H, s, Me-C_{6b}), 0.851 (9H, s, Me_3CSi), 0.851 (3H, s, Me-C_{3a}), 0.77 (1H, dd, *J* = 13.0, 3.7 Hz, H-1b), 0.73 (1H, dd, *J* = 12.5, 4.5 Hz, H-6a), 0.53 (1H, ddd, *J* = 13.2, 13.2, 6.1 Hz, H-7α), 0.49 (1H, dd, *J* = 5.2, 1.0 Hz, H-1β), 0.22 (1H d, *J* = 5.2 Hz, H-1α), 0.097 and 0.040 (3H each, each s, 2 × MeSi); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 81.1 (C_4), 61.1 (C_{5a}), 59.7 (C_{4a}), 58.4 (C_{8a}), 54.1 (C_{1b}), 43.3 (C_{6a}), 38.5 (C_3), 36.9 (C_{3a}), 35.2 (C_7), 34.8 (C_{6b}), 29.0 (C_8), 28.7 (C_1), 25.8 (Me_3CSi), 22.3 (C_6), 22.0 (C_{1a}), 21.8 (C_2), 19.7 (Me-C_{4a}), 17.9 (Me_3CSi), 15.6 (Me-C_{1a}), 13.0 (Me-C_{6b}), 12.9 (Me-C_{3a}), −3.0 and −3.8 (2 × MeSi); MS (EI) *m*/*z* 420 (M^+, 8), 405 (4), 402 (3), 363 (23), 345 (7), 253 (4), 211 (100); HRMS *m*/*z* calcd for $C_{25}H_{44}O_3Si$ 420.3060, found 420.3023.

(1a*S*,1b*R*,3a*R*,4*S*,4a*S*,5a*S*,6a*R*,6b*R*,8a*R*)-4-(Allyloxy)-1a,3a,4a,6b-tetramethyltetradecahydro-1*H*-cyclopropa[7,8]-phenanthro[2,3-*b*]oxiren-8a-yl)oxy)(*tert*-butyl)dimethylsilane (21). A solution of epoxy alcohol **20** (130 mg, 0.30 mmol) and TBAI (22.5 mg, 0.07 mmol) in dry THF (5.3 mL) was slowly added to a stirred suspension of sodium hydride (184 mg of 60% dispersion in oil, 4.6 mmol, prewashed with pentane) in THF (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 30 min before addition of allyl bromide (282 mg, 203 μL 2.32 mmol) and heating to 50 °C. After being stirred for 24 h at this temperature, the reaction mixture was cooled in an ice bath, and the excess sodium hydride was quenched with water. After being stirred for a few minutes, the mixture was extracted with CH_2Cl_2 and worked up. Chromatographic purification of the residue after evaporating the solvent (9:1 hexanes−EtOAc) yielded allyl epoxide **21** (137 mg, 96%) as a white solid: mp 133−134 °C (from MeOH−pentane); $[\alpha]^{25}_D$ +20 (*c* 0.9, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3048w, 2930s, 2858s,, 835s, 774s; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.92 (1H, dddd, *J* = 17.2, 10.4, 5.5, 5.5 Hz, H-2′), 5.28 (1H, dq, *J* = 12.7, 1.6 Hz, H-3′), 5.15 (1H, dq, *J* = 10.4, 1.3 Hz, H′-3′), 4.20 (1H, dddd, *J* = 12.7, 5.3, 1.4, 1.4 Hz, H-1′), 3.98 (1H, dddd, *J* = 12.7, 5.7, 1.3, 1.3 Hz, H′-1′), 3.05 (1H, br s, H-5a), 2.80 (1H, s, H-4), 2.06 (1H, ddd, *J* = 13.7, 6.3, 1.5 Hz, H-8α), 2.03−1.91 (2H, m, H-7, H-3β), 1.87 (1H, ddd, *J* = 13.7, 13.3, 7.0 Hz, H-8β), 1.70−1.57 (3H, m, H′-7, H-6, H-2α), 1.35 (1H, ddd, *J* = 13.1, 13.1, 2.9 Hz, H-2β), 1.305 (3H, s, Me-C_{4a}), 1.024 (3H, s, Me-C_{1a}), 0.91 (1H, m, H-3α), 0.883 (3H, s, Me-C_{6b}), 0.851 (9H, s, Me_3−C-Si), 0.833 (3H, s, Me-C_{3a}), 0.77 (1H, dd, *J* = 13.1, 3.0 Hz, H-1b), 0.70 (1H, dd, *J* = 12.8, 4.8 Hz, H-6a), 0.51 (1H, ddd, *J* = 13.3, 13.3, 6.1 Hz, H′-6), 0.48 (1H, dd, *J* = 5.1, 1.0 Hz, H-1β), 0.21 (1H, d, *J* = 5.1 Hz, H-1α), 0.097 and 0.041 (3H each, each s, 2 × Me-Si); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.8 ($C_{2'}$), 116.5 ($C_{3'}$), 89.0 (C_4), 74.5 ($C_{1'}$), 61.2 (C_{5a}), 60.1 (C_{4a}), 58.5 (C_{8a}), 54.3 (C_{1b}), 43.9 (C_{6a}), 38.5 (C_3), 37.5 (C_{3a}), 35.2 (C_7), 34.9 (C_{6b}), 29.0 (C_8), 28.7 (C_1), 25.8 (Me_3CSi), 22.3 (C_2), 22.1 (C_{1a}), 21.8 (C_6), 19.9 (Me-C_{4a}), 17.9 (Me_3CSi), 15.6 (Me-C_{1a}), 13.6 (Me-C_{6b}), 13.0 (Me-C_{3a}), −3.0 and −3.8 (2 × MeSi); MS (EI) *m*/*z* 460 (M^+, 26), 445 (7), 419 (7), 403 (54), 211 (100); HRMS *m*/*z* calcd for $C_{28}H_{48}O_3Si$ 460.3373, found 460.3374.

(1a*S*,1b*R*,3a*R*,4*S*,6*S*,7a*R*,7b*R*,9a*R*)-4-(Allyloxy)-9a-((*tert*-butyldimethylsilyl)oxy)-1a,3a,7b-trimethyl-5-methylenetetradecahydro-1*H*-cyclopropa[*a*]phenanthren-6-ol (22). BuLi (1.39 M in hexane, 0.92 mL, 1.27 mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.247 mL, 1.46 mmol) in dry benzene (1.4 mL) at 0 °C. After 10 min, the reaction mixture was treated with Et_2AlCl (1.8 M in toluene, 0.76 mL, 1.27 mmol) and stirred for an additional 30 min at the same temperature. Then, a solution of epoxide **21** (147 mg, 0.32 mmol) in benzene (0.5 mL) was added to the mixture and stirred at 0 °C for 30 min before being quenched with 5% $NaHCO_3$ and extracted with EtO_2. The combined organic phases were worked up as usual, and the residue obtained after evaporation of the solvent was purified by column chromatography (9:1 → 8:2 hexanes−EtOAc) to afford allyl alcohol **22** (138 mg, 94%) as an amorphous solid: $[\alpha]^{20}_D$ +32 (*c* 0.62, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3360 m, 1654w, 1588w, 835s; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.91 (1H, dddd, *J* = 17.2, 10.6, 5.8, 5.3 Hz, H-2′), 5.26 (1H, dq, *J* = 17.2, 1.6 Hz, H-3′), 5.13 (1H, dq, *J* = 10.6, 1.3 Hz, H′-3′), 4.97 (2H, m, 2 × H-1″), 4.46 (1H, m, H-4), 4.07 (1H, dddd, *J* = 12.8, 5.3, 1.5, 1.5 Hz, H-1′), 3.87 (1H, dddd, *J* = 12.8, 5.8, 1.3, 1.3 Hz, H′-1′), 3.63 (1H, br s, H-6), 2.08 (1H, ddd, *J* = 13.6, 7.5, 1.4 Hz, H-9α), 1.99 (1H, ddd, *J* = 13.0, 3.2, 3.2 Hz, H-3β), 1.92 (1H, m, H-9β), 1.75−1.63 (2H, m, H-2α, H-8β), 1.74 (1H, dddd, *J* = 19.5, 14.0, 2.5, 2.5 Hz, H-7β), 1.57−1.42 (2H, m, H-7α, H-2β), 1.33 (1H, dd, *J* = 14.0, 2.5 Hz, H-7a), 1.13 (1H, ddd, *J* = 13.0, 13.0, 3.2 Hz, H-3α), 1.031 (3H, s, Me-C_{1a}), 0.88 (1H, dd, *J* = 13.0, 3.5 Hz, H-1b), 0.854 (9H, s, Me_3CSi), 0.790 and 0.785 (3H each, each s, Me-C_{7b} and Me-C_{3a}), 0.62 (1H, ddd, *J* = 13.1, 13.1, 6.4 Hz, H-8α), 0.51 (1H, dd, *J* = 5.1, 1.2 Hz, H-1β), 0.23 (1H, d, *J* = 5.1 Hz, H-1α), 0.102 and 0.046 (3H each, each s, 2 × MeSi); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.5 (C_5), 135.9 ($C_{2'}$), 116.3 ($C_{3'}$), 109.2 ($C_{1''}$), 86.0 (C_6), 73.0 (C_4), 71.8 ($C_{1'}$), 58.4 (C_{9a}), 54.6 (C_{1b}), 46.4 (C_{7a}), 41.3 (C_{3a}), 38.2 (C_3), 35.7 (C_8), 35.1 (C_{7b}), 29.5 (C_7), 29.2 (C_9), 29.0 (C_1), 25.8 (Me_3CSi), 22.4 (C_2), 22.2 (C_{1a}), 17.9 (Me_3CSi), 15.5 (Me-C_{1a}), 13.3 (Me-C_{3a}), 12.4 (Me-C_{7b}), −3.0 and −3.8 (2 × MeSi); MS (EI) *m*/*z* 460 (M^+, 14), 445 (4), 442 (4), 419 (6), 403 (23), 385 (6), 253 (6), 211 (87), 73 (100); HRMS *m*/*z* calcd for $C_{28}H_{48}O_3Si$ 460.3373, found 460.3373.

3β-((*tert*-Butyldimethylsilyl)oxy)-3α,18-cyclo-isospongia-13(15)-en-12α-ol (23). A solution of 1,4-benzoquinone (4 mg, 0.038 mmol) in CH_2Cl_2 (1 mL) was added over 30 min via a syringe pump to a stirred solution of Grubbs second-generation catalyst [(1,3-dimesityl-2-imidazolylidene)(PCy_3) Cl_2Ru=CHPh] (19.4 mg, 0.022 mmol) and diene **22** (71 mg, 0.154 mmol) in refluxing CH_2Cl_2 (8 mL). The reaction was refluxed for an additional 20 min period,

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cooled, concentrated under vacuum to 25% of its original volume, charged onto a silica gel chromatography column, and eluted with 97:3 $CHCl_3$–EtOAc to yield dihydrofuran **23** (60 mg, 90%) as a solid. Although pure by ^1H NMR analysis, the compound obtained in this way was slightly colored, presumably due to the presence of trace amounts of the Grubbs catalyst. This compound was used in the next step without further purification. An analytical sample was obtained by crystallization from hexanes–Et_2O: mp 184–185 °C (from hexanes–Et_2O); $[\alpha]^{20}_D$ +61 (*c* 0.46, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3396s, 1644 m, 830s, 758s; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.66 (1H, d, *J* = 1.8 Hz, H-15), 4.67 (1H, br s, H-12), 4.65 (1H, ddd, *J* = 11.4, 3.9, 1.2 Hz, H-16β), 4.57 (1H, ddd, *J* = 11.4, 6.0, 1.5 Hz, H-16α), 4.43 (1H, m, H-14), 2.09 (1H, ddd, *J* = 13.8, 6.3, 1.5 Hz, H-2α), 1.97–1.84 (2H, m, H-2β, H-7β), 1.79–1.67 (3H, m, H-1β, H-6α, H-11α), 1.56–1.38 (2H, m, H-6β, H-11β), 1.22 (1H, dd, *J* = 12.9, 1.8 Hz, H-9), 1.19 (1H, ddd, H-7α), 1.034 (3H, s, Me-C_4), 0.89 (1H, dd, *J* = 12.9, 3.3 Hz, H-5), 0.855 (9H, s, Me_3CSi), 0.813 (3H, s, Me-C_{10}), 0.802 (3H, s, Me-C_8), 0.65 (1H, ddd, *J* = 12.9, 12.9, 6.3 Hz, H-1α), 0.51 (1H, dd, *J* = 5.1, 0.9 Hz, H-18β), 0.25 (1H, d, *J* = 5.1 Hz, H-18α), 0.105 and 0.047 (3H each, each s, 2 × MeSi); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.3 (C_{13}), 120.5 (C_{15}), 93.5 (C_{14}), 75.9 (C_{16}), 65.4 (C_{12}), 58.4 (C_3), 54.5 (C_5), 44.1 (C_9), 41.6 (C_8), 38.9 (C_7), 35.8 (C_1), 35.0 (C_{10}), 29.3 (C_{11}), 29.3 (C_2), 28.9 (C_{18}), 25.8 (Me_3CSi), 22.2 (C_4), 22.0 (C_6), 17.9 (Me_3CSi), 15.5 (Me-C_4), 12.6* (Me-C_{10}), 12.5* (Me-C_8), −3.0 and −3.8 (2 × MeSi); MS (EI) *m*/*z* 432 (M^+, 12), 417 (4), 414 (28), 399 (15), 375 (12), 357 (35), 282 (12), 211 (66), 73 (100); HRMS *m*/*z* calcd for $C_{26}H_{44}O_3Si$ 432.3060, found 432.3068.

3β-((*tert*-Butyldimethylsilyl)oxy)-3α,18-cycloisospongia-13,15-dien-12α-ol (24). A solution of dihydrofuran **23** (112 mg, 0.258 mmol) and DDQ (39.4 mg, 0.335 mmol) in dry benzene (10 mL) was stirred at rt for 36 h under N_2. The reaction mixture was quenched with 5% $NaHCO_3$ solution, poured into water, and extracted with EtOAc. Workup and chromatography of the residue left after evaporation of the solvent on silica gel (8:2 hexanes–EtOAc) gave furan **24** (89 mg, 87% based on the starting material consumed) as an oil: $[\alpha]^{24}_D$ −14 (*c* 0.28, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 3328w, 1618w, 1257s, 831s; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20 (1H, d, *J* = 1.9 Hz, H-16), 6.30 (1H, d, *J* = 1.9 Hz, H-15), 4.70 (1H, br s, H-12), 2.20 (1H, ddd, *J* = 12.9, 3.1, 3.1 Hz, H-7β), 2.13 (1H, ddd, *J* = 13.9, 6.6, 1.6 Hz, H-2α), 1.98 (1H, m, H-2β), 1.90–1.60 (5H, m, 2 × H-11, 2 × H-6, H-1β), 1.44 (1H, dd, *J* = 12.5, 1.9 Hz, H-9α), 1.43 (1H, ddd, *J* = 12.9, 12.9, 3.5 Hz, H-7α), 1.173 (3H, s, Me-C_8), 1.065 (3H, s, Me-C_4), 0.91 (1H, dd, H-5α), 0.887 (3H, s, Me-C_{10}), 0.867 (9H, s, Me_3CSi), 0.64 (1H, ddd, *J* = 13.0, 12.9, 6.6 Hz, H-1α), 0.53 (1H, dd, *J* = 5.2, 1.0 Hz, H-18β), 0.25 (1H, d, *J* = 5.2 Hz, H-18α), 0.120 and 0.055 (3H each, each s, 2 × MeSi); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.0 (C_{14}), 140.8 (C_{16}), 116.3 (C_{13}), 109.1 (C_{15}), 63.1 (C_{12}), 58.3 (C_3), 54.7 (C_5), 47.3 (C_9), 36.5 (C_8), 35.9 (C_1), 35.5 (C_7), 34.9 (C_{10}), 29.2 (C_{18}), 29.1 (C_2), 28.9 (C_{11}), 25.8 (Me_3CSi), 22.2 (C_4), 22.0 (C_6), 20.7 (Me-C_8), 17.9 (Me_3CSi), 15.4 (Me-C_4), 12.2 (Me-C_{10}), −3.0 and −3.8 (2 × MeSi); MS (EI) *m*/*z* 430 (M^+, 17), 415 (7), 412 (8), 397 (24), 373 (38), 355 (9), 281 (14), 265 (11), 211 (100); HRMS *m*/*z* calcd for $C_{26}H_{42}O_3Si$ 430.2903, found 430.2900.

Further elution using the same eluent afforded the unreacted starting material **23** (10.5 mg, 9%).

3β-((*tert*-Butyldimethylsilyl)oxy)-3α,18-cycloisospongia-13,15-dien-12-one (25). NMO (48 mg, 0.408 mmol), 5 Å molecular sieves (114 mg), and TPAP (5 mg, 0.014 mmol) were added to a solution of furan alcohol **24** (100 mg, 0.232 mmol) in anhydrous CH_2Cl_2 (3.6 mL) at 0 °C under N_2. The reaction was stirred at rt until complete by TLC (approximately 25 min). The reaction mixture was directly transferred to the top of a silica gel chromatographic column, which was eluted with 9:1 hexanes–EtOAc to yield keto furan **25** (86 mg, 86%) as a white solid: mp 137–140 °C (from hexanes); $[\alpha]^{24}_D$ −86 (*c* 0.42, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 1667s, 1585w, 1432 m, 1246 m, 1000 m, 831 m, 771 m; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25 (1H, d, *J* = 2.0 Hz, H-16), 6.59 (1H, d, *J* = 2.0 Hz, H-15), 2.54 (1H, dd, *J* = 17.4, 3.5 Hz, H-11α), 2.44 (1H, dd, *J* = 17.4 13.0, Hz, H-11β), 2.29 (1H, ddd, *J* = 13.1, 3.2, 3.2, Hz, H-7β), 2.14 (1H, ddd, *J* = 14.1, 6.6, 1.6 Hz, H-2α), 1.96 (1H, dddd, *J* = 14.1, 12.7, 7.3, 1.2 Hz, H-2β), 1.87 (1H, dddd, *J* = 14.0, 3.7, 3.2, 3.3 Hz, H-6α), 1.72 (1H, m, H-6β), 1.72 (1H, m, H-1β), 1.69 (1H, dd, *J* = 13.0, 3.5 Hz, H-9), 1.55 (1H, ddd, *J* = 13.1, 13.1, 3.7 Hz, H-7α), 1.325 (3H, s, Me-C_8), 1.075 (3H, s, Me-C_4), 0.949 (3H, s, Me-C_{10}), 0.91 (1H, dd, *J* = 12.9, 3.7 Hz, H-5) 0.866 (9H, s, Me_3CSi), 0.61 (1H, ddd, *J* = 13.1, 13.1, 6.6 Hz, H-1α), 0.55 (1H, dd, *J* = 5.3, 1.2 Hz, H-18β), 0.25 (1H, d, *J* = 5.3 Hz, H-18α), 0.120 and 0.053 (3H each, each s, 2 × MeSi); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.8 (C_{12}), 175.9 (C_{14}), 142.2 (C_{16}), 118.4 (C_{13}), 106.3 (C_{15}), 58.0 (C_3), 54.3 (C_5), 52.6 (C_9), 37.00 (C_8), 35.8 (C_{11}), 35.5 (C_1), 35.4 (C_{10}), 34.6 (C_7), 29.1 (C_{18}), 28.9 (C_2), 25.8 (Me_3CSi), 22.0 (C_4), 21.7 (C_6), 20.2 (Me-C_8), 17.9 (Me_3CSi), 15.3 (Me-C_4), 12.0 (Me-C_{10}), −3.0 and −3.8 (2 × MeSi); MS (EI) *m*/*z* 428 (M^+, 19), 413 (11), 372 (30), 371 (100), 235 (10), 211 (63); HRMS *m*/*z* calcd for $C_{26}H_{40}O_3Si$ 428.2747, found 428.2753.

Isospongia-13,15-diene-3,12-dione (26). A solution of *tert*-butyldimethylsilyl ether **25** (60 mg, 0.14 mmol) in anhydrous MeCN (5 mL) was cooled to 0 °C and treated with 10 drops of 70% w/w HF in pyridine before being stirred at rt under N_2 for 24 h. The reaction mixture was quenched by the slow addition of a saturated Na_2CO_3 solution and then poured into a 5% $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with a saturated $CuSO_4$ solution and brine before drying. Chromatography (9:1 CHCl–EtOAc) of the residue remaining after solvent evaporation afforded the corresponding cyclopropanol (40 mg) as an amorphous white solid: ^1H NMR (C_6D_6, 300 MHz) δ 6.75 (1H, d), 6.22 (1H, d), 2.42 (1H, dd), 2.17 (1H, dd), 2.05 (1H, ddd), 1.95 (1H, ddd), 1.64 (1H, m), 1.47 (1H, dddd), 1.32 (1H, m), 1.23 (1H, dd), 1.22 (2H, m), 1.073 (3H, s), 0.931 (3H, s), 0.575 (3H, s), 0.51 (1H), 0.46 (1H, dd), 0.12 (1H, ddd), 0.086 (1H, d).

Both the product obtained above and NaOH (10.2 mg, 0.255 mmol) were dissolved under N_2 in a 4:1 mixture of dioxane–water (5 mL) previously degasified in an ultrasonic bath under a N_2 flow. The reaction mixture was heated to 90 °C for 6 h, cooled to 0 °C, acidified by the addition of 0.1 M hydrochloric acid, and extracted with EtOAc. The organic phase was washed with both a 5% $NaHCO_3$ solution and brine, dried and evaporated to afford a solid residue that was purified by column chromatography on silica gel (95:5 $CHCl_3$–EtOAc) to afford the 3-oxomarginatone (**26**, 40 mg, 91%): mp 167–169 °C (from hexanes–Et_2O); $[\alpha]^{20}_D$ −9 (*c* 0.65, $CHCl_3$), IR ν_{max}/cm^{-1} (KBr) 3109w, 1711s, 1661s, 1459 m, 1268 m, 1142 m, 771w; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.28 (1H, d, *J* = 2.0 Hz, H-16), 6.60 (1H, d, *J* = 2.0 Hz, H-15), 2.63–2.52 (3H, m, H-2α, 2 × H-11), 2.47 (1H, ddd, *J* = 15.9, 7.7, 4.24 Hz, H-2β), 2.35 (1H, br ddd, *J* = 5.6 3.3, 3.3, Hz, H-7β), 1.99–1.89 (2H, m, H-1β, H-9), 1.79–1.59 (3H, m, 2 × H-6, H-7α), 1.57–1.44 (2H, H-1β, H-5), 1.330 (3H, s, Me-C_8), 1.115 (3H, s, Meα-C_4), 1.090 (6H, s, Meβ-C_4 and Me-C_{10}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 216.4 (C_3), 194.1 (C_{12}), 175.1 (C_{14}), 142.5 (C_{16}), 118.4 (C_{13}), 106.3 (C_{15}), 55.1 (C_9), 54.7 (C_5), 47.3 (C_4), 38.3 (C_1), 37.2 (C_8), 36.6 (C_{10}), 35.6 (C_{11}), 34.7 (C_7), 33.6 (C_2), 26.5 (Meα-C_4), 20.9 (Meβ-C_4), 19.9 (Me-C_8), 18.9 (C_6), 15.7 (Me-C_{10}); MS (EI) *m*/*z* 314 (M^+, 43), 299 (16), 272 (15), 189 (21), 178 (57), 161 (100), 147 (39), 135 (45); HRMS *m*/*z* calcd for $C_{20}H_{26}O_3$ 314.1882, found 314.1880.

Isospongia-13,15-diene-3β,12β-diol (27). $CeCl_3 \cdot 7H_2O$ (68.4 mg, 0.182 mmol) was added to a solution of dienone **26** (38 mg, 0.122 mmol) in MeOH (2.4 mL). The mixture was stirred at rt until the cerium salt had completely dissolved. After addition of CH_2Cl_2 (1.2 mL), the mixture was cooled to −65 °C, and $NaBH_4$ was slowly added in small portions while the reaction was montiored by TLC (7:3 hexanes–EtOAc). Upon completion of the reduction (ca. 30 min), the reaction was quenched with acetone (0.4 mL), stirred for a few minutes, diluted with water, and extracted with EtOAc. The combined organic phases were washed with brine and dried. The solvent was removed and the residue was purified by column chromatography (7:3 hexanes–EtOAc) to afford isospongiadiol **27** (36.5 mg, 96%) as a white solid: mp 203–206 °C (from EtOAc); $[\alpha]^{25}_D$ −22 (*c* 0.45, $CHCl_3$), IR ν_{max}/cm^{-1} (KBr) 3399s, 1448w, 1388w, 1142w, 1039s, 899w 711w; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.21 (1H, d, *J* = 1.9 Hz, H-16), 6.34 (1H, d, *J* = 1.9 Hz, H-15), 4.64 (1H, dd, *J* = 9.4, 6.5 Hz, H-12), 3.20 (1H, dd, *J* = 11.1, 5.2 Hz, H-3), 2.28–2.12 (2H, m, H-7β,

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H-11α), 1.79 (1H, ddd, *J* = 12.8, 3.6, 3.6 Hz, H-1β), 1.76−1.35 (6H, m, 2 × H-2, 2 × H-6, H-7α, H-11β), 1.28 (1H, m, H-9), 1.247 (3H, s, Me-C_8), 1.03 (1H, dd, *J* = 12.6, 4.7 Hz, H-1α), 0.977 (3H, s, Meα-C_4), 0.924 (3H, s, Meβ-C_4), 0.85 (1H, dd, *J* = 11.6, 2.5 Hz, H-5), 0.804 (3H, s, Me-C_{10}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.6 (C_{14}), 141.1 (C_{16}), 118.0 (C_{13}), 108.1 (C_{15}), 78.7 (C_3), 67.2 (C_{12}), 55.5 (C_9), 55.1 (C_5), 38.9 (C_4), 38.1 (C_1), 36.8 (C_7), 36.8 (C_{10}), 36.7 (C_8), 30.2 (C_{11}), 27.9 (Meα-C_4), 27.1 (C_2), 22.3 (Me-C_8), 17.9 (C_6), 16.5 (Meβ-C_4), 15.1 (Me-C_{10}); MS (EI) *m*/*z* 318 (M^+, 15), 303 (18), 300 (13), 267 (18), 171 (23), 145 (29), 133 (42), 131 (100); HRMS *m*/*z* calcd for $C_{20}H_{30}O_3$ 318.2195, found 318.2203.

3β-Hydroxyisospongia-13,15-dien-12-one (28). A solution of diol **27** (36 mg, 0.112 mmol) in $CHCl_3$ (6 mL) was treated with active manganese dioxide (5 μm, activated 85%, 240 mg, 2.8 mmol) and stirred for 3 days at rt. The reaction mixture was diluted with EtOAc (6 mL) and centrifuged. The supernatant was decanted and the precipitate was washed/centrifuged with EtOAc. Evaporation of the solvent afforded a solid residue that was purified by column chromatography (9:1 $CHCl_3$−EtOAc) to yield 3β-hydroxymarginatone **28** (30.5 mg, 94% based on the starting material consumed) as a white solid: mp 163−164 °C (from hexanes−Et_2O); $[\alpha]^{26}_D$ −65 (*c* 0.40, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3439 m, 1671s, 1586w, 1440 m, 1133 m, 1052 m, 754 m; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (1H, d, *J* = 2.0 Hz, H-16), 6.58 (1H, d, *J* = 2.0 Hz, H-15), 3.21 (1H, dd, *J* = 11.4, 4.7 Hz, H-3), 2.51 (1H, dd, *J* = 17.2, 3.8 Hz, H-11α), 2.49 (1H, dd, *J* = 17.2, 16.5 Hz, H-11β), 2.30 (1H, ddd, *J* = 20.7, 13.0, 3.2 Hz, H-7β), 1.86 (1H, dd, *J* = 16.5, 3.8, Hz, H-9), 1.77 (1H, ddd, *J* = 11.9, 5.7, 2.2 Hz, H-6α), 1.74−1.53 (5H, m, H-1β, 2 × H-2, H-6β, H-7α,), 1.284 (3H, s, Me-C_8), 1.06 (1H, dd, *J* = 13.0, 4.4 Hz, H-1α), 1.002 (3H, s, Meα-C_4), 0.984 (3H, s, Meβ-C_4), 0.91 (1H, dd, *J* = 2.4, 11.5 Hz, H-5), 0.823 (3H, s, Me-C_{10}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.7 (C_{12}), 175.7 (C_{14}), 142.3 (C_{16}), 118.2 (C_{13}), 106.2 (C_{15}), 78.4 (C_3), 55.8 (C_9), 55.3 (C_5), 38.9 (C_4), 37.7 (C_1), 37.2 (C_8), 37.0 (C_{10}), 35.5 (C_7), 35.3 (C_{11}), 27.9 (Meα-C_4), 26.9 (C_2), 20.4 (Me-C_8), 17.7 (C_6), 16.1 (Meβ-C_4), 15.2 (Me-C_{10}); MS (EI) *m*/*z* 316 (M^+, 100), 301 (9), 298 (9), 283 (36), 274 (20), 187 (21), 178 (89), 161 (76), 147 (52); HRMS *m*/*z* calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2035.

Further elution with the same eluent afforded the unreacted starting diol (4 mg, 11%).

Isospongia-13,15-dien-12-one (Marginatone, 5). Pentafluorophenyl chlorothionoformate (20 μL, 0.12 mmol) was added to a solution of alcohol **28** (18 mg, 0.06 mmol) and DMAP (21.9 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (405 μL) at 0 °C under N_2. The mixture was stirred for 6 h at rt and then diluted with EtOAc. The mixture was transferred to a separatory funnel, washed with water and brine, dried, and concentrated. The obtained residue was purified by column chromatography (10:0 → 9:1 hexanes−EtOAc) to yield the pentafluorophenyl thionocarbonate intermediate (28.5 mg): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (1H, d, *J* = 2.0 Hz, H-16), 6.60 (1H, d, *J* = 2.0 Hz, H-15), 4.93 (1H, dd, *J* = 11.6, 4.7 Hz, H-3), 2.53 (1H, br s, H-11α), 2.50 (1H, d, *J* = 2.0, 16.5 Hz, H-11β), 1.310 (3H, s, Me-C_8), 1.065 (3H, s, Meα-C_4), 1.018 (3H, s, Meβ-C_4), 1.008 (3H, s, Me-C_{10}).

A solution of this compound and AIBN (2.5 mg) in anhydrous benzene (5 mL) was rigorously degassed using the freeze−thaw cycle, treated with Bu_3SnH (48 μL, 0.12 mmol), and refluxed for 6 h. The reaction mixture was cooled to rt, poured into a 5% $NaHCO_3$ solution, and extracted with EtOAc. The combined organic layers were washed three times with a 1 M aqueous solution of KF followed by water and brine before drying. Chromatography of the residue (9:1 hexanes−EtOAc) afforded (−)-marginatone (**5**, 13.5 mg, 79%) as a white solid: mp 174−175 °C (from hexanes) [lit.[20] mp 167−168 °C]; $[\alpha]^{25}_D$ −22 (*c* 0.45, $CHCl_3$) [lit.[20] −26 (*c* 0.36, $CHCl_3$), lit.[11] −16 (*c* 0.4, $CHCl_3$)]; IR ν_{max}/cm^{-1} (KBr) 1671s, 1268w, 1132 m, 1050w, 771w, 722w; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (1H, d, *J* = 2.0 Hz, H-16), 6.59 (1H, d, *J* = 2.0 Hz, H-15), 2.55 (1H, dd, *J* = 17.2, 3.7 Hz, H-11α), 2.46 (1H, dd, *J* = 17.2, 12.9 Hz, H-11β), 2.28 (1H, ddd, *J* = 12.2, 2.6, 2.6 Hz, H-7β), 1.90 (1H, dd, *J* = 12.9, 3.7 Hz, H-9), 1.75 (1H, m, H-2), 1.70−1.52 (4H, m, H-1β, H′-2, H-6 and H-7α), 1.48 (1H, ddd, *J* = 10.1, 6.9, 3.1 Hz, H′-6), 1.40 (1H, m, H-3β), 1.289 (3H, s, Me-C_8), 1.15 (1H, ddd, *J* = 13.5, 13.3, 4.0 Hz, H-3α), 0.982 (3H, s, Me-C_{10}), 0.94 (1H, m, H-5), 0.882 (4H, s overlapped with m, Meα-C_4 and H-1α), 0.856 (3H, s, Meβ-C_4); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.3 (C_{12}), 176.1 (C_{14}), 142.3 (C_{16}), 118.2 (C_{13}), 106.2 (C_{15}), 56.5 (C_5), 56.0 (C_9), 41.8 (C_3), 39.3 (C_1), 37.4 (C_8), 37.3 (C_{10}), 35.5 (C_7), 35.3 (C_{11}), 33.2 (C_4), 21.3 (Meα-C_4), 20.5 (Me-C_8), 18.2* (C_2), 17.9* (C_6), 16.0 (Meβ-C_4), 13.6 (Me-C_{10}); MS (EI) *m*/*z* 300 (M^+, 100), 285 (42), 258 (32), 242 (18), 203 (14), 189 (13), 176 (14), 161 (81); HRMS *m*/*z* calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2080.

(1*S*,3*R*,4*S*,6*S*)-4-(3-Chloroprop-1-en-2-yl)-3-(3,3-diethoxypropyl)-1,3-dimethyl-7-oxabicyclo[4.1.0]heptan-2-one (29). A solution of $CeCl_3 \cdot 7H_2O$ (3.666 g, 9.84 mmol, 1.5 equiv) in water (34 mL) was added to a well-stirred solution of **14** (2.025 g, 6.52 mmol) in CH_2Cl_2 (34 mL) at 0 °C. The resulting emulsion was treated dropwise with an aqueous solution of NaOCl (8% available chlorine, 10.5 mL, 4 equiv), and the mixture was vigorously stirred at 0 °C until TLC analysis (8:2 hexanes−EtOAc) indicated the conversion was nearly complete (ca. 1 h). A saturated $Na_2S_2O_3$ solution was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried. Evaporation of the solvent followed by chromatographic purification (9:1 hexanes−EtOAc) afforded chloride **29** (2.027 g, 90%) as a colorless oil: $[\alpha]^{21}_D$ −32 (*c* 1.8, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 1705s, 1443 m, 1372 m, 1121s, 1061s; ^{1}H NMR (C_6D_6, 300 MHz) δ 5.13 (1H, br s, H-1″), 4.66 (1H br s, H′-1″), 4.31 (1H, dd, *J* = 6.0, 4.0 Hz, H-3′), 4.05 (1H, dd, *J* = 12.3, 1.1 Hz, H-3″), 3.81 (1H, dd, *J* = 12.3, 0.6 Hz, H′-3″), 3.47 and 3.26 (2H each, each m, 2 × MeCH_2O), 3.19 (1H, dd, *J* = 12.2, 4.4 Hz, H-4), 2.75 (1H, d, *J* = 1.9 Hz, H-6), 2.04 (1H, ddd, *J* = 12.8, 12.8, 4.8 Hz, H-1′), 1.91−1.77 (2H, m, H-2′, H-5), 1.70 (1H, dddd, *J* = 12.5, 12.5, 4.3, 4.3 Hz, H′-2′), 1.54 (1H, ddd, *J* = 15.0, 12.0, 1.0 Hz, H′-5), 1.39 (1H, dd, *J* = 12.6, 3.6 Hz, H′-1′), 1.299 (3H, s, Me-C_1), 1.055 (6H, t, *J* = 7.0 Hz, 2 × *Me*CH_2O), 0.727 (3H, s, Me-C_3); ^{13}C NMR (C_6D_6, 75 MHz) δ 208.8 (C_2), 145.1 ($C_{2''}$), 118.5 ($C_{1''}$), 103.1 ($C_{3'}$), 62.2 (Me*CH*$_2$O), 60.6 (Me*CH*$_2$O), 60.1 (C_6), 58.1 (C_1), 49.9 ($C_{3''}$), 49.3 (C_3), 34.9 (C_4), 31.9 ($C_{1'}$), 29.0 ($C_{2'}$), 27.4 (C_5), 21.1 (Me-C_3), 16.4 (Me-C_1), 15.6 and 15.4 (2 × *Me*CH_2O); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{29}NaO_4Cl$ $[M + Na]^+$ 367.1652, found 367.1656.

2-((1*S*,3*R*,4*R*,6*S*)-4-(3,3-Diethoxypropyl)-4,6-dimethyl-5-oxo-7-oxabicyclo[4.1.0]heptan-3-yl)acrylaldehyde (30).). A solution of chloride **29** (467 mg, 1.36 mmol), LiI (353 mg, 2.63 mmol), and NEMO (2.12 mL of a 25% (m/v) solution in DMF, 4.04 mmol) in dry DMF (6 mL) was heated to 55 °C for 30 h. The reaction mixture was cooled to rt, diluted with water, and extracted with EtOAc. The organic extracts were successively washed with both 10% Na_2SO_3 and 1.5% LiCl solutions as well as brine, dried, and concentrated to dryness. Column chromatography of the residue (8:2 → 7:3 hexanes−EtOAc) gave, in order of elution, unreacted **29** (93 mg, 20%), formate **30b** (28 mg, 7% based on recovered starting material), and aldehyde **30** (261 mg, 74% based on recovered starting material).

Data for aldehyde **30**: oil; $[\alpha]^{28}_D$ −48 (*c* 0.375, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 1738 m, 1694s, 1132 m, 1061 m; ^{1}H NMR (C_6D_6, 300 MHz) δ 9.07 (1H, s, H-1), 5.54 (1H, s, H-3), 5.32 (1H, s, H′-3), 4.49 (1H, dd, *J* = 5.5, 5.5 Hz, H-3″), 3.65 (1H, dd, *J* = 12.1, 4.3 Hz, H-3′), 3.57 and 3.39 (2H each, each m, 2 × MeCH_2O), 2.74 (1H, d, *J* = 2.2 Hz, H-1′), 2.16 (1H, m, H-1″), 2.01 (1H, ddd, *J* = 12.5, 13.2, 3.9 Hz, H-2″), 1.81−1.61 (2H, m, H′-1″, H-2′), 1.52 (1H, ddd, *J* = 14.6, 3.9, 3.5 Hz, H′-2′), 1.24 (1H, dd, *J* = 13.2, 12.5, 3.9 Hz, H′-2″), 1.312 (3H, s, Me-$C_{6'}$), 1.116 (6H, t *J* = 7.0 Hz, 2x*Me*CH_2O), 0.721 (3H, s, Me-$C_{4'}$); ^{13}C NMR (C_6D_6, 75 MHz) δ 208.9 ($C_{5'}$), 193.3 (C_1), 149.5 (C_2), 137.2 (C_3), 103.2 ($C_{3''}$), 61,2 (Me*CH*$_2$O), 60.3, ($C_{1'}$), 60.1 (Me*CH*$_2$O), 58.7 ($C_{6'}$), 49.1 ($C_{4'}$), 32.7 ($C_{2''}$), 31.9 ($C_{3'}$), 28.7 ($C_{1''}$), 25.9 ($C_{2'}$), 21.4 (Me-$C_{4'}$), 16.4 (Me-$C_{6'}$), 15.6 (2x*Me*CH_2O); MS (EI) *m*/*z* 295 (M^+-CHO, 1), 279 (M^+-EtO, 1), 233 (2), 205 (1), 187 (3), 149 (2), 129 (2), 103 (100); HRMS *m*/*z* calcd for $C_{16}H_{23}O_4$ $[M - EtO]^+$ 279.1591, found 279.1592.

Further elution with 7:3 hexanes−EtOAc afforded alcohol **30a** (32 mg, 9% based on recovered starting material) as an oil.

Methyl 2-((1*S*,3*S*,4*R*,6*S*)-4-(3,3-Diethoxypropyl)-4,6-dimethyl-5-oxo-7-oxabicyclo[4.1.0]heptan-3-yl)acrylate (32). A solution of $NaClO_2$ (1.334 g, 11.7 mmol) and $NaH_2PO_4 \cdot H_2O$ (1.113 g,

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10.2 mmol) in water (7.5 mL) and 2-methyl-2-butene (1.6 mL 15.3 mmol) were consecutively added to a solution of aldehyde **30** (1.654 mg, 5.1 mmol) in *t*-BuOH (18 mL) cooled to 0 °C. The reaction flask was tightly closed, and the mixture was stirred for 3 h before pouring into a saturated NH_4Cl solution, extracting with EtOAc and working up as usual to afford acid **31** (1.66 g) as a semisolid. This compound was esterified by treating with freshly distilled diazomethane at 0 °C to yield methyl ester **32** (1.71 g, 95%) after concentrating to dryness under vacuum as a sufficiently pure oil to use in the next step without further purification: $[\alpha]^{20}_D$ −50 (*c* 1.35, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 1722s, 1694s, 1618w, 1252s, 1142s, 1061s, ^1H NMR(C_6D_6, 300 MHz) δ 6.14 (1H, d, *J* = 0.8 Hz, H-3), 5.05 (1H, sa, H′-3), 4.44 (1H, dd, *J* = 5.4, 5.4 Hz, H-3″), 3.81 (1H, dd, *J* = 9.6, 6.9 Hz, H-3′), 3.54 and 3.35 (2H each, each m 2 × MeCH_2O), 3.394 (3H, s, MeO), 2.75 (1H, dd, *J* = 2.0, 1.0 Hz, H-1′), 2.15 (1H, dddd, *J* = 12.6, 12.6, 5.6, 3.9 Hz, H-2″), 2.05 (1H, ddd, *J* = 12.6, 12.6, 3.1 Hz, H-1″), 1.80−1.65 (3H, m, H′-2″, 2 × H-2′), 1.41 (1H, ddd, *J* = 12.6, 12.6, 3.1 Hz, H′-1″), 1.311 (3H, s, Me-$C_{6'}$), 1.089 and 1.078 (3H each, each t, *J* = 7.1 Hz, 2x*Me*CH_2O), 0.783 (3H, s, Me-$C_{4'}$); ^{13}C NMR (C_6D_6, 75 MHz) δ 209.0 ($C_{5'}$), 168.0 (C_1), 141.0 (C_2), 126.9 (C_3), 103.3 ($C_{3''}$), 61.2 (MeCH_2O), 60.3 ($C_{1'}$), 60.0 (MeCH_2O), 58.6 ($C_{6'}$), 51.74 (MeO), 49.5 ($C_{4'}$), 34.4 ($C_{3'}$), 33.0 ($C_{2''}$), 28.8 ($C_{1''}$), 26.7 ($C_{2'}$), 20.9 (Me-$C_{4'}$), 16.4 (Me-$C_{6'}$), 15.6 and 15.5 (2x*Me*CH_2O); MS (EI) *m*/*z* 309 (M^+-EtO, 10), 263 (1), 231 (1), 203 (2), 175 (1), 163 (1), 147 (2), 103 (100); HRMS *m*/*z* calcd for $C_{17}H_{25}O_5$ $[M - EtO]^+$ 309.1697, found 309.1704.

Methyl 2-((1*S*,3*S*,4*R*,6*S*)-4,6-Dimethyl-5-oxo-4-(3-oxopropyl)-7-oxabicyclo[4.1.0]heptan-3-yl)acrylate (33). Aldehyde **33** was prepared from ketal **32** (1.77 g, 4.99 mmol) as described above for **15** using PPTS (1.26 g, 5.00 mmol) in 4% aqueous acetone (78 mL). The crude material was purified by column chromatography (6:4 hexanes−EtOAc) to yield the desired product (1.27 g, 91%) as a colorless oil: $[\alpha]^{21}_D$ −85 (*c* 0.75, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 1716s, 1694s, 1618w, 1257 m, 1153 m, 1082w, 995w; ^1H NMR (C_6D_6, 300 MHz) δ 9.29 (1H, br s, H-3″), 6.10 (1H, d, *J* = 0.6 Hz, H-3), 4.96 (1H, br s, H′-3), 3.68 (1H, dd, *J* = 11.9, 4.9 Hz, H-3′), 3.30 (3H, s, MeO), 2.71 (1H, dd, *J* = 2.9, 1.0 Hz, H-1′), 2.58 (1H, dddd, *J* = 18.0, 11.0, 2.9, 1.0 Hz, H-2″), 2.13 (1H, dddd, *J* = 18.0, 10.9, 5.3, 0.8 Hz, H′-2″), 2.00 (1H, ddd, *J* = 14.4, 11.3, 5.3 Hz, H-1″), 1.61 (1H, ddd, *J* = 15.2, 5.0, 3.3 Hz, H-2′), 1.53 (1H, ddd, *J* = 15.2, 11.9, 1.2 Hz, H′-2′), 1.43 (1H, ddd, *J* = 14.6, 11.1, 3.6 Hz, H′-1″), 1.306 (3H, s, Me-$C_{6'}$), 0.602 (3H, s, Me-$C_{4'}$); ^{13}C NMR (C_6D_6, 75 MHz) δ 208.1 ($C_{5'}$), 200.1 ($C_{3''}$), 167.7 (C_1), 140.2 (C_2), 126.7 (C_3), 60.0 ($C_{1'}$), 58.1 ($C_{6'}$), 51.9 (MeO), 48.7 ($C_{4'}$), 39.6 ($C_{2''}$), 32.8 ($C_{3'}$), 28.8 ($C_{1''}$), 26.3 ($C_{2'}$), 20.2 (Me-$C_{4'}$), 16.3 (Me-$C_{6'}$); MS (EI) *m*/*z* 280 (M^+, 0.3), 233 (2), 187 (4), 149 (2), 123 (3), 103 (100); HRMS *m*/*z* calcd for $C_{15}H_{20}O_5$ 280.1311, found 280.1306.

Methyl 2-((1*S*,3*S*,4*R*,6*S*)-4,6-Dimethyl-4-((*E*)-4-methyl-5-oxohex-3-en-1-yl)-5-oxo-7-oxabicyclo[4.1.0]heptan-3-yl)acrylate (34). A solution of aldehyde **33** (290 mg, 1.0 mmol) and 3-(triphenylphosphoranylidene)butan-2-one (450 mg, 1.4 mmol) en CH_2Cl_2 (10 mL) was stirred at 28 °C under N_2 for 36 h, after which the reaction mixture was concentrated to half its original volume by rotary evaporation and transferred to the head of a silica gel column. Elution with 8:2 hexanes−EtOAc afforded the methyl ketone **34** (327 mg, 94%) as an oil: $[\alpha]^{21}_D$ −23 (*c* 1.5, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 1716s, 1694s, 1667s, 1629w, 1263 m, 1148s; ^1H NMR (C_6D_6, 300 MHz) δ 6.24 (1H, ddq, *J* = 7.3, 7.3, 1.2 Hz, H-3″), 6.12 (1H, d, *J* = 0.5 Hz, H-3), 5.03 (1H, br s, H′-3), 3.82 (1H, dd, *J* = 11.5, 5.2 Hz, H-3′), 3.281 (3H, s, MeO), 2.76 (1H, dd, *J* = 2.8, 1.2 Hz, H-1′), 2.55 (1H, m, H-2″), 2.09 (1H, m, H′-2″), 1.962 (3H, s, Me-$C_{5''}$), 1.884 (3H, br d, *J* = 1.2 Hz, Me-$C_{4''}$), 1.86 (1H, ddd, *J* = 13.6, 11.7, 4.9 Hz, H-1″), 1.77−1.57 (2H, m, 2 × H-2′), 1.329 (3H, s, Me-$C_{6'}$), 1.16 (1H, ddd, *J* = 13.6, 11.6, 4.8 Hz, H′-1″), 0.729 (3H, s, Me-$C_{4'}$); ^{13}C NMR (C_6D_6, 75 MHz) δ 208.8 ($C_{5'}$), 198.0 ($C_{5''}$), 167.9 (C_1), 142.1 ($C_{3''}$), 140.7 (C_2), 138.1 ($C_{4''}$), 127.1 (C_3), 60.2 ($C_{1'}$), 58.6 ($C_{6'}$), 51.8 (MeO), 49.6 ($C_{4'}$), 36.6 ($C_{1''}$), 33.8 ($C_{3'}$), 26.7 ($C_{2'}$), 25.1 (Me-$C_{5''}$), 24.6 ($C_{2''}$), 20.9 (Me-$C_{4'}$), 16.4 (Me-$C_{6'}$), 11.3 (Me-$C_{4''}$); MS (EI) *m*/*z* 334 (M^+, 2), 319 (2), 303 (2), 277 (10), 224 (91), 206 (36), 192 (39), 174 (30), 147 (47), 139 (28), 111 (100); HRMS *m*/*z* calcd for $C_{19}H_{26}O_5$ 334.1780, found 334.1793.

Methyl 2-((1*S*,3*S*,4*R*,6*S*)-4-((*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-methylhexa-3,5-dien-1-yl)-4,6-dimethyl-5-oxo-7-oxabicyclo[4.1.0]heptan-3-yl)acrylate (35). Compound **34** (259 mg, 0.78 mmol) was reacted according to the procedure described above for **17** using CH_2Cl_2 (8.6 mL), Et_3N (248 μL, 1.76 mmol) and TBDMOTf (231 μL, 1.01 mmol). Purification of the crude product by column chromatography (9:1 hexanes−Et_2O with 0.2% of Et_3N) yielded dienol silyl ether **35** (339 mg, 97%) as a colorless oil: $[\alpha]^{21}_D$ −7° (*c* 0.55, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 1727s, 1700s, 1596w, 1263 m, 1148 m, 1011 m, 837s; ^1H NMR (C_6D_6, 300 MHz) δ 6.24 (1H, ddd, *J* = 7.6, 7.6, 0.8 Hz, H-3″), 6.12 and 5.03 (1H each, each br s, 2 × H-3), 4.46 and 4.34 (1H each, each s, 2 × H-6″), 3.87 (1H, dd, *J* = 10.9, 5.7 Hz, H-3′), 3.376 (3H, s, MeO), 2.76 (1H, dd, *J* = 2.6, 1.4 Hz, H-1′), 2.59 and 2.21 (1H each, each m, 2 × H-2″), 1.98 (1H, ddd, *J* = 13.6, 13.4, 4.8 Hz, H-1″), 1.807 (3H, d, *J* = 0.5 Hz, Me-$C_{4''}$), 1.79−1.67 (2H, m, 2 × H-2′), 1.33 (1H, m, H′-1″), 1.329 (3H, s, Me-$C_{6'}$), 1.007 (9H, s, Me_3CSi), 0.740 (3H, s, Me-$C_{4'}$), 0.159 (6H, s, 2 × MeSi); ^{13}C NMR (C_6D_6, 75 MHz) δ 208.8 ($C_{5'}$), 167.9 (COOMe) 158.1 ($C_{5''}$), 141.0 (C_2), 131.8 ($C_{4''}$), 128.5 ($C_{3''}$), 126.8 (C_3) 91.2 ($C_{6''}$), 60.3 ($C_{1'}$), 58.7 ($C_{6'}$), 51.7 (COO*Me*), 49.8 ($C_{4'}$), 37.9 ($C_{1''}$), 34.2 ($C_{3'}$), 26.7 ($C_{2'}$), 26.1 (*Me*$_3$CSi), 23.9 ($C_{2''}$), 20.9 (Me-$C_{4'}$), 18.5 (Me_3CSi), 16.4 (Me-$C_{6'}$), 13.4 (Me-$C_{4''}$), −4.5 (2 × MeSi); MS (EI) *m*/*z* 448 (M^+,14), 433 (3), 417 (3), 225 (100), 223 (10), 197 (13), 168 (30); HRMS *m*/*z* calcd for $C_{25}H_{40}O_5Si$ 448.2645, found 448.2651.

(4a*S*,6a*R*,7a*S*,8a*S*,9a*S*,9b*R*)-Methyl 3-((*tert*-Butyldimethylsilyl)oxy)-4,6a,7a-trimethyl-7-oxo-1,2,4a,5,6,6a,7,7a,8a,9,9a,9b-dodecahydrophenanthro[2,3-*b*]-oxirene-9b-carboxylate (36). Heating a solution of **35** (490 mg, 1.09 mmol) in toluene (14.4 mL) to 140 °C for 4 days as described above for **18** followed by chromatographic purification (8:2 hexanes−EtOAc) afforded a white solid (481 mg, 98%) that was shown by ^1H NMR to be an 83:17 mixture of Diels−Alder adducts **36** and **37**. Crystallization of this mixture from hexanes yielded two essentially pure crops of the single diastereomeric adduct **36** (288 mg, 60%): mp 153−154 °C (from hexanes); $[\alpha]^{20}_D$ −36 (*c* 0.225 $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 1732s, 1700s, 1678 m, 1219 m, 1192s, 1159s, 837s; ^1H RNMR (C_6D_6, 300 MHz) δ 3.243 (3H, s, MeO), 2.89 (1H, br d, *J* = 2.0 Hz, H-8a), 2.29 (1H, ddd, *J* = 13.5, 2.0, 2.0 Hz, H-9), 2.25−2.15 (2H, m, H-1, H-6), 2.10 (1H, ddd, *J* = 13.0, 13.0, 3.5 Hz, H-5), 1.97 (2H, m, 2 × H-2), 1.91 (1H, *J* = 13.5, 13.0, 1,0 Hz, H′-9), 1.84 (1H, dd, *J* = 13.0, 1.5 Hz, H-9a), 1.71 (1H, br dd, *J* = 13.0, 1.3 Hz, H-4a), 1.647 (3H, dd, *J* = 3.2, 1.5 Hz, Me-C_4), 1.59 (1H, m, H′-5), 1.434 (1H, dd, *J* = 13.6, 4.5 Hz, H′-6), 1.360 (3H, s, Me-C_{7a}), 0.998 (9H, s, Me_3-C-Si), 0.94 (1H, ddd, *J* = 11.7, 11.7, 6.9 Hz, H′-1), 0.727 (3H, s, Me-C_{6a}), 0.105 and 0.083 (3H each, each s, 2 × Me-Si); ^{13}C NMR (C_6D_6, 75 MHz) δ 207.4 (C_7), 175.0 (COO), 141.1 (C_3), 114.3 (C_4), 59.6 (C_{8a}), 56.4 (C_{7a}), 50.8 (MeO), 48.0 (C_{9b}), 46.5 (C_{4a}), 46.0 (C_{6a}), 40.9 (C_{9a}), 34.1 (C_6), 33.9 (C_1), 28.5 (C_2), 26.1 (*Me*$_3$-C-Si), 22.6 (C_9), 21.5 (C_5), 18.4 (Me_3-C-Si), 16.8 (Me-C_{7a}), 16.2 (Me-C_{6a}), 12.8 (Me-C_4), −3.5 and −4.0 (2 × Me-Si); MS (EI) *m*/*z* 448 (M^+, 100), 433 (18), 391 (24), 211 (11), 171 (11), 159 (8), 141 (16); HRMS *m*/*z* calcd for $C_{25}H_{40}O_5Si$ 448.2645, found 448.2646.

Analytically pure **37** was obtained by preparative reversed-phase HPLC of a small amount of the residue obtained from the crystallized mother liquor, which was an approximately 1:1 mixture of both adducts. HPLC separation was performed on a semipreparative C18 prepacked Spherisorb ODS2 (250 × 10 mm, 5 μm) column (Teknokroma) using a 65:15 CH_3CN−water mixture (by volume) as eluent and a flow rate of 1.5 mL/min. Retention times were 16.7 min for **36** and 18.8 min for **37**.

Adduct **37** was obtained as a white solid: mp 123−125 °C (by slow evaporation of a hexane solution); $[\alpha]^{20}_D$ −40 (*c* 0.25 $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 1727s, 1705s, 1645 m, 1175s, 1104s; ^1H NMR (C_6D_6, 400 MHz) δ 3.274 (3H, s, MeO), 2.97 (1H, br s, H-4a), 2.87 (1H, d, *J* = 2.5 Hz, H-8a), 2.51 (1H, dd, *J* = 13.3, 3.3 Hz, H-9a), 2.37 (1H, br dd, *J* = 14.7, 13.3 Hz, H-9), 2.16−1.82 (5H, m, H-1, H-2, H-5, H-6, H-9), 1.71 (1H, ddd, *J* = 15.0, 7.0, 3.5 Hz, H′-1), 1.562 (3H, d, *J* = 1.2 Hz, Me-C_4), 1.51 (1H, ddd, *J* = 12.6, 12.6, 6.3 Hz, H′-6), 1.43 (1H, ddd, *J* = 14.2, 14.2, 3.5 Hz, H′-5), 1.316 (3H, s, Me-C_{7a}), 0.99

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(1H, m, H′-2), 0.987 (9H, s, Me_3-C-Si), 0.823 (3H, s, Me-C_{6a}), 0.173 and 0.107 (3H each, each s, 2 × Me-Si); ^{13}C NMR (C_6D_6, 100 MHz) δ 208.1 (C_7), 177.3 (COO), 143.7 (C_3), 112.0 (C_4), 59.7 (C_{8a}), 56.8 (C_{7a}), 51.2 (MeO), 46.2 (C_{9b}), 45. Nine (C_{6a}), 40.8 (C_{4a}), 31.2 (C_6), 30.4 (C_{9a}), 29.5 (C_5), 27.0 (C_2), 26.1 (Me_3-C-Si), 23.0 (C_9), 21.0 (C_1), 18.3 (Me_3-*C*-Si), 17.0 (Me-C_{6a}), 16.8 (Me-C_{7a}), 13.5 (Me-C_4), −3.5 and −4.1 (2 × Me-Si); HRMS *m*/*z* calcd for $C_{25}H_{41}O_5Si$ [M + H]$^+$ 449.2723, found 449.2717.

(1a*S*,1b*S*,3a*R*,4a*S*,5a*S*,6a*S*,6b*R*,8a*R*)-Methyl 8a-((*tert*-Butyldimethylsilyl)oxy)-1a,3a,4a-trimethyl-4-oxotetradecahydro-1*H*-cyclopropa[7,8]phenanthro[2,3-*b*]oxirene-6b-carboxylate (38). Compound **36** (261 mg, 0.58 mmol) was treated as described above for **19** by stirring with CH_2I_2 (377 μL, 4.71 mmol), diethylzinc in hexane (1 M, 4.71 mL, 4.71 mmol), and toluene (15 mL) at 0 °C for 4 h. Workup and chromatography (9:1 hexanes−EtOAc) afforded cyclopropane **38** (258 mg, 96%) as a solid: mp 150−151 °C (from hexanes); $[\alpha]^{20}_D$ −68 (*c* 0.8, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 1722s, 1700s, 1252 m, 1192 m, 826s; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.689 (3H, s, MeO), 3.39 (1H, d, *J* = 1.9 Hz, H-5a), 2.50 (1H, ddd, *J* = 15.8, 3.3, 3.3 Hz, H-6α), 2.31 (1H, ddd, *J* = 15.6, 12.8, 1.0 Hz, H-6β), 2.20−1.90 (4H, m, H-2β, H-3, H-7, H-8α), 1.84 (1H, dddd, *J* = 10.4, 6.8, 3.7, 1.3 Hz, H-2α), 1.70 (1H, dd, *J* = 12.6, 3.9 Hz, H-6a), 1.61 (1H, dddd, *J* = 14.0, 14.0, 5.8, 1.2 Hz, H-8β), 1.382 (3H, s, Me-C_{4a}), 1.29 (1H, dd, *J* = 14.3, 4.3 Hz, H′-3), 1.129 (3H, s, Me-C_{1a}), 1.043 (1H, dd, *J* = 12.9, 3.8 Hz, H-1b), 0.828 (9H, s, Me_3CSi), 0.814 (3H, s, Me-C_{3a}), 0.73 (1H, dd, *J* = 13.8, 5.0 Hz, H′-7), 0.54 (1H, dd, *J* = 5.4, 1.2 Hz, H-1β), 0.24 (1H, d, *J* = 5.4 Hz, H-1α), 0.060 and 0.011 (3H each, each s, 2 × MeSi); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.3 (C_4), 175.6 (COOMe), 60.0 (C_{5a}), 59.2 (C_{8a}), 56.4 (C_{4a}), 52.6 (C_{1b}), 51.0 (COO*Me*), 46. 9* (C_{6b}), 45.7* (C_{3a}), 41.0 (C_{6a}), 33.9 (C_3), 33.5 (C_7), 29.7 (C_8), 29.4 (C_1), 25.7 (*Me*$_3$CSi), 23.4 (C_{1a}), 22.4 (C_2), 21.8 (C_6), 17.9 (Me_3*C*Si), 16.5 (Me-C_{3a}), 16.4 (Me-C_{4a}), 15.4 (Me-C_{1a}), −3.8 and −3.3 (2 × MeSi); MS (EI) *m*/*z* 462 (M$^+$, 27), 447 (10), 433 (10), 405 (48), 211 (96), 185 (7), 73 (100); HRMS *m*/*z* calcd for $C_{26}H_{42}O_5Si$ 462.2802, found 462.2812.

(1a*S*,1b*S*,3a*R*,4*S*,4a*R*,5a*S*,6a*S*,6b*S*,8a*R*)-Methyl 8a-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-1a,3a,4a-trimethyltetradecahydro-1*H*-cyclopropa[7,8]phenanthro[2,3-*b*]oxirene-6b-carboxylate (39). Compound **39** was prepared from **38** (145 mg, 0.33 mmol) as described above for **20** using $CeCl_3$·$7H_2O$ (123 mg, 0.33 mmol), $NaBH_4$ (23 mg, 0.58 mmol), MeOH (9.3 mL), and CH_2Cl_2 (4.7 mL). Chromatographic purification (8:2 → 7:3 hexanes−EtOAc) yielded epoxy alcohol **39** (141 mg, 97%) as a white solid: mp 181−184 °C (from benzene−hexanes); $[\alpha]^{20}_D$ +2 (*c* 0.85, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3453 m, 1738s, 1257 m, 1208 m, 1121 m, 1050 m, 842s; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.688 (3H, s, MeO), 3.25 (1H, d, *J* = 5.7 Hz, H-4), 3.11 (1H, br s, H-5a), 2.30−1.93 (6H, m, H-7, H-3, H-8, 2 × H-6, H-2), 1.75 (1H, ddd, *J* = 15.8, 7.8, 4.9 Hz, H′-2), 1.65 (1H, dddd, *J* = 14.0, 14.0, 6.4, 1.2 Hz, H′-8), 1.311 (3H, s, Me-C_{4a}), 1.13−0.93 (3H, m, H′-3, H-6a, H-1b), 1.117 (3H, s, Me-C_{1a}), 0.826 (9H, s, Me_3CSi), 0.716 (1H, dd, *J* = 13.3, 5.1 Hz, H′-7), 0.661 (3H, s, Me-C_{3a}), 0.54 (1H, dd, *J* = 5.2, 1.2 Hz, H-1β), 0.24 (1H d, *J* = 5.2 Hz, H-1α), 0.058 and 0.007 (3H each, each s, 2 × MeSi); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.5 (COOMe), 80.6 (C_4), 61.1 (C_{5a}), 59.3* (C_{8a}), 59.0* (C_{4a}), 53.0 (C_{1b}), 50.9 (COO*Me*), 47.1 (C_{6b}), 43.6 (C_{6a}), 39.1 (C_3), 36.9 (C_{3a}), 33.6 (C_7), 29.8 (C_8), 29.6 (C_1), 25.7 (*Me*$_3$CSi), 23.6 (C_{1a}), 22.7 (C_2), 22.6 (C_6), 19.6 (Me-C_{4a}), 17.9 (Me_3*C*Si), 15.5 (Me-C_{1a}), 11.1 (Me-C_{3a}), −3.2 and −3.7 (2 × MeSi); MS (EI) *m*/*z* 464 (M$^+$, 63), 450 (17), 449 (16), 446 (6), 435 (33), 407 (89) 389 (14), 255 (13), 211 (100); HRMS *m*/*z* calcd for $C_{26}H_{44}O_5Si$ 464.2958, found 464.2954.

(1a*S*,1b*S*,3a*R*,4*S*,4a*S*,5a*S*,6a*S*,6b*S*,8a*R*)-Methyl 4-(Allyloxy)-8a-((*tert*-butyldimethylsilyl)oxy)-1a,3a,4a-trimethyltetradecahydro-1*H*-cyclopropa[7,8]phenanthro[2,3-*b*]oxirene-6b-carboxylate (40). A solution of epoxy alcohol **39** (127 mg, 0.27 mmol) and allyl iodide (74 μL, 0.81 mmol) in dry DMF (4 mL) was added dropwise to a stirred suspension of NaH (27 mg of 60% dispersion in oil, 0.68 mmol, prewashed with pentane) at 0 °C. After being stirred at this temperature for 12 h, the mixture was quenched with a saturated NH_4Cl solution and diluted with water. Extracting with EtOAc, washing the extracts with a 1.5% LiCl solution and brine, drying, and evaporating the solvent afforded a residue that was chromatographed (9:1 → 8:2 hexanes−EtOAc) to yield the allyl ether **40** (130 mg, 94%) as a white solid: mp 116−117 °C (from hexanes); $[\alpha]^{20}_D$ −6 (*c* 1.8, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 1716s, 1252 m, 1203s, 1170 m, 1082s, 1055s, 831s; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.91 (1H, dddd, *J* = 16.7, 10.7, 5.5, 5.5 Hz, H-2′), 5.27 (1H, ddd, *J* = 16.7, 3.2, 1.5 Hz, H-3′), 5.15 (1H, br dd, *J* = 10.4, 1.4 Hz, H′-3′), 4.22 (1H, dddd, *J* = 12.5, 5.2, 1.2, 1.2 Hz, H-1′), 3.98 (1H, dddd, *J* = 12.5, 5.7, 1.2, 1.2 Hz, H′-1′), 3.673 (3H, s, MeO), 3.07 (1H, br s, H-5a), 2.82 (1H, s, H-4), 2.23−1.93 (6H, m, 2 × H-6, H-2, H-8, H-7, H-3), 1.75−1.53 (2H, m, H′-2, H′-8), 1.300 (3H, s, Me-C_{4a}), 1.109 (3H, s, Me-C_{1a}), 1.10−0.93 (3H, m, H-1b, H-3, H-6a), 0.821 (9H, s, Me_3-C-Si), 0.70 (1H, m, H′-7), 0.658 (3H, s, Me-C_{3a}), 0.52 (1H, dd, *J* = 5.2, 1.0 Hz, H-1β), 0.22 (1H, d, *J* = 5.2 Hz, H-1α), 0.053 and 0.003 (3H each, each s, 2 × Me-Si); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.4 (COOMe), 134.6 ($C_{2'}$), 116.6 ($C_{3'}$), 88.5 (C_4), 74.7 ($C_{1'}$), 61.2 (C_{5a}), 59.4* (C_{4a}), 59.3* (C_{8a}), 53.0 (C_{1b}), 50.8 (COO*Me*), 47.1 (C_{6b}), 44.2 (C_{6a}), 38.9 (C_3), 37.5 (C_{3a}), 33.6 (C_7), 29.8 (C_8), 29.5 (C_1), 25.7 (*Me*$_3$CSi), 23.6 (C_{1a}), 22.6 (C_2), 22.5 (C_6), 19.8 (Me-C_{4a}), 17.8 (Me_3CSi), 15.5 (Me-C_{1a}), 11.7 (Me-C_{3a}), −3.6 and −3.8 (2 × MeSi); MS EI) *m*/*z* 504 (M$^+$, 8), 475 (8), 447 (21), 317 (12), 211 (52), 172 (21), 141 (9), 116 (100); HRMS *m*/*z* calcd for $C_{29}H_{48}O_5Si$ 504.3271, found 504.3255.

(1a*S*,1b*S*,3a*R*,4*S*,6*S*,7a*S*,7b*S*,9a*R*)-Methyl 4-(Allyloxy)-9a-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-1a,3a-dimethyl-5-methylenetetradecahydro-1*H*-cyclopropa[*a*]phenanthrene-7b-carboxylate (41). BuLi (1.54 M in hexanes, 0.886 mL, 1.36 mmol) was added dropwise to a solution of 2,2,6,6-tetramethylpiperidine (238 μL, 1.42 mmol) in anhydrous toluene (1.6 mL) at 0 °C. After 10 min, the reaction mixture was treated with a 1 M solution of Et_2AlCl in hexane (1.32 mL, 1.32 mmol) and stirred for an additional 30 min at the same temperature. A solution of epoxide **40** (176 mg, 0.34 mmol) in toluene (8.8 mL) was added dropwise and the mixture stirred at 0 °C for 40 min. The reaction mixture was treated with 5% $NaHCO_3$ solution, poured into a 10% aqueous solution of sodium citrate, and extracted with Et_2O. The usual workup and subsequent silica gel chromatography (9:1 → 8:2 hexanes−EtOAc) produced allylic alcohol **41** (167 mg, 95%) as an amorphous solid: $[\alpha]^{20}_D$ −12 (*c* 0.65, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3431 m, 1727s, 1257 m, 1203 m, 1142 m, 1082 m, 837s; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.90 (1H, dddd, *J* = 17.2, 10.7, 5.5, 5.5 Hz, H-2′), 5.26 (1H, ddd, *J* = 17.2, 1.6, 1.4 Hz, H-3′), 5.14 (1H, dd, *J* = 10.4, 1.4 Hz, H′-3′), 4.95 (2H, m, 2 × H-1″), 4.48 (1H, dd, *J* = 2.7, 2.7 Hz, H-4), 4.07 (1H, dddd, *J* = 12.5, 5.3, 1.2, 1.2 Hz, H-1′), 3.87 (1H, dddd, *J* = 12.8, 5.8, 1.2, 1.2 Hz, H′-1′), 3.67 (1H, br s, H-6), 3.653 (3H, s, MeO), 2.2−2.0 (5H, m, H-3, H-8, H-7, H-9, H-2), 1.9−1.7 (2H, m, H′-7, H′-2), 1.65 (1H, dd, *J* = 13.1, 2.8 Hz, H-7a), 1.59 (1H, m, H′-9), 1.2−1.1 (2H, m, H-1b, H′-3), 1.156 (3H, s, Me-C_{1a}), 0.837 (9H, s, Me_3CSi), 0.75 (1H, m, H′-8), 0.575 (3H, s, Me-C_{3a}), 0.53 (1H, dd, *J* = 5.2, 0.8 Hz, H-1β), 0.25 (1H, d, *J* = 5.2 Hz, H-1α), 0.066 and 0.023 (3H each, each s, 2 × MeSi); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.5 (COOMe), 146.8 (C_5), 135.2 ($C_{2'}$), 116.4 ($C_{3'}$), 108.8 ($C_{1''}$), 85.0 (C_6), 72.8 (C_4), 71.8 ($C_{1'}$), 59.4 (C_{9a}), 53.3 (C_{1b}), 50.7 (COO*Me*), 47.0 (C_{7a}), 46.4 (C_{7b}), 41.5 (C_{3a}) 38.5 (C_3), 33.6 (C_8), 30.7 (C_7), 29.8 (C_9), 29.4 (C_1), 25.7 (*Me*$_3$CSi), 23.6 (C_{1a}), 23.1 (C_2), 17.8 (Me_3CSi), 15.5 (Me-C_{1a}), 10.7 (Me-C_{3a}), −3.2 and −3.8 (2 × MeSi); MS (EI) *m*/*z* 504 (M$^+$, 4), 486 (7), 447 (5), 429 (15), 237 (18), 211 (35), 187 (8), 173 (7), 155 (12), 73 (100); HRMS *m*/*z* calcd for $C_{29}H_{48}O_5Si$ 504.3271, found 504.3282.

Methyl 3β-((*tert*-Butyldimethylsilyl)oxy)-12α-hydroxy-3α,18-cycloisospongia-13(15)-en-20-oate (42). A solution of 1,4-benzoquinone (8 mg, 0.074 mmol), [(1,3-dimesityl-2-imidazolylidene)(PCy_3)Cl_2Ru=CHPh] (40 mg, 0.0046 mmol), and diene **41** (160 mg, 0.32 mmol) in dry CH_2Cl_2 (20 mL) was refluxed for 1 h. Evaporation of the solvent under vacuum followed by chromatography (9:1 → 7:3 $CHCl_3$−EtOAc) afforded the dihydrofuran **42** (132 mg, 88%). Although obtained as a slightly colored solid, the product was pure according to ^{1}H NMR analysis. A colorless sample could be obtained by crystallization from hexanes−Et_2O: mp 178−180 °C; $[\alpha]^{25}_D$ +20 (*c* 0.8, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3431s, 1716s, 1634w, 1208s, 1061s, 1039s, 837s; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.64 (1H, br d, *J* = 1.6 Hz, H-15), 4.68 (1H, br d, H-12), 4.64

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(1H, ddd, J = 12.5, 3.5, 1.2 Hz, H-16β), 4.54 (1H, ddd, J = 12.5, 6.1, 1.2 Hz, H-16α), 4.47 (1H, ddd, J = 5.8, 3.4, 2.0 Hz, H-14), 3.657 (3H, s, MeO), 2.20−2.00 (2H, m, H-6, H-11), 2.18 (1H, ddd, J = 7.3, 5.8, 2.0 Hz, H-1), 1.95 (1H, ddd, J = 13.0, 3.3, 2.9 Hz, H-7), 1.90−1.70 (2H, m, H′-6, H′-11), 1.65−1.50 (2H, m, H-2, H-9), 1.30−1.20 (2H, m, H′-2, H′-7), 1.16 (1H, dd, J = 12.0, 3.4 Hz, H-5), 1.142 (3H, s, Me-C_4), 0.828 (9H, s, Me_3CSi), 0.76 (1H, m, H′-1), 0.583 (3H, s, Me-C_8), 0.53 (1H, dd, J = 5.2, 1.0 Hz, H-18β), 0.26 (1H, d, J = 5.2 Hz, H-18α), 0.058 and 0.013 (3H each, each s, 2 × MeSi); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.5 (COOMe), 139.8 (C_{13}), 119.9 (C_{15}), 92.8 (C_{14}), 76.0 (C_{16}), 65.2 (C_{12}), 59.4 (C_3), 53.2 (C_5), 50.8 (COO*Me*), 47.0 (C_{10}), 44.3 (C_9), 41.8 (C_8), 39.4 (C_7), 33.9 (C_1), 30.5 (C_{11}), 29.9 (C_2), 29.4 (C_{18}), 25.7 (*Me*$_3$CSi), 23.6 (C_4), 22.8 (C_6), 17.9 (Me_3CSi), 15.6 (Me-C_4), 10.3 (Me-C_8), −3.2 and −3.7 (2 × MeSi); MS (EI) m/z 476 (M^+, 1), 458 (6), 419 (3), 401 (15), 267 (22), 211 (67), 192 (17), 73 (100); HRMS m/z calcd for $C_{27}H_{44}O_5Si$ 476.2958, found 476.2944.

Methyl 3β-((*tert*-Butyldimethylsilyl)oxy)-12α-hydroxy-3α,18-cycloisospongia-13,15-dien-20-oate (43). Dihydrofuran **42** (93 mg, 0.21 mmol) was oxidized with DDQ (58 mg, 0.0.50 mmol) in benzene (7.5 mL) as described for the preparation of **24**. Column chromatography (8:2 hexanes−EtOAc) of the crude product obtained afforded unreacted dihydrofuran **42** (7.5 mg, 8%) followed by the furan **43** (79.5 mg, 93% based on recovered starting material) as a colorless oil: $[\alpha]^{24}_D$ −87 (c 0.25, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 3431 m, 1722s, 1623w, 1252 m, 1213s, 1044 m, 842s; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (1H, d, J = 1.9 Hz, H-16), 6.30 (1H, d, J = 1.9 Hz, H-15), 4.72 (1H, dd, J = 3.7, 1.7 Hz, H-12), 3.680 (3H, s, MeO), 2.30−2.10 (5H, m, H-1, H-2, H-6, H-7, H-11), 2.10−1.80 (2H, m, H′-6, H′-11), 1.76 (1H, dd, J = 12.6, 1.3 Hz, H-9), 1.62 (1H, m, H′-2), 1.43 (1H, ddd, J = 13.2, 13.1, 4.2 Hz, H′-7), 1.19 (1H, m, H-5), 1.195 (3H, s, Me-C_4), 0.958 (3H, s, Me-C_8), 0.85 (1H, m, H′-1), 0.845 (9H, s, Me_3CSi), 0.55 (1H, dd, J = 5.3, 1.0 Hz, H-18β), 0.27 (1H, d, J = 5.3 Hz, H-18α), 0.077 and 0.029 (3H each, each s, 2 × MeSi); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.5 (COOMe), 160.9 (C_{14}), 141.2 (C_{16}), 116.5 (C_{13}), 109.1 (C_{15}), 62.8 (C_{12}), 59.5 (C_3), 53.6 (C_5), 50.9 (COO*Me*), 46.8 (C_9), 46.6 (C_{10}), 36.6 (C_8), 36.0 (C_7), 33.6 (C_1), 30.3 (C_{11}), 29.7 (C_2), 29.5 (C_{18}), 25.7 (*Me*$_3$CSi), 23.5 (C_4), 22.8 (C_6), 17.9 (Me-C_8), 17.9 (Me_3CSi), 15.4 (Me-C_4), −3.2 and −3.7 (2 × MeSi); HRMS (ESI) m/z calcd for $C_{27}H_{42}NaO_5Si$ [M + Na]$^+$ 497.2699, found 497.2705.

Methyl 3β-((*tert*-Butyldimethylsilyl)oxy)-12-oxo-3α,18-cycloisospongia-13,15-dien-20-oate (44). Alcohol **43** (86 mg, 0.18 mmol) was oxidized in anhydrous CH_2Cl_2 (4 mL) using NMO (42 mg, 0.36 mmol), TPAP (3.8 mg, 0.01 mmol), and 5 Å molecular sieves (86 mg) as described for **26** to yield ketone **44** (82.5 mg, 96%) as a white solid: mp 121−123 °C (from hexanes); $[\alpha]^{25}_D$ −76 (c 1.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 1727s, 1683s, 1246 m, 1213 m, 1142 m, 837s,; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (1H, d, J = 2.0 Hz, H-16), 6.59 (1H, d, J = 2.0 Hz, H-15), 3.713 (3H, s, MeO), 2.92 (1H, dd, J = 17.6, 13.0 Hz, H-11β), 2.81 (1H, dd, J = 17.6, 3.8 Hz, H-11α), 2.40−2.10 (4H, m, H-1, H-2, H-6, H-7), 1.95 (1H, m, H′-6), 1.93 (1H, dd, J = 13.0, 3.8 Hz, H-9), 1.56 (1H, m, H′-7), 1.199 (3H, s, Me-C_4), 1.16 (1H, m, H-5), 1.124 (3H, s, Me-C_8), 0.844 (9H, s, Me_3CSi), 0.80 (1H, m, H′-1), 0.57 (1H, dd, J = 5.4, 1.1 Hz, H-18β), 0.27 (1H, d, J = 5.4 Hz, H-18α), 0.076 and 0.027 (3H each, each s, 2 × MeSi); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.4 (C_{12}), 174.8* (COOMe), 174.4* (C_{14}), 142.6 (C_{16}), 118.6 (C_{13}), 106.2 (C_{15}), 59.2 (C_3), 53.3 (C_5), 51.4 (COO*Me*), 51.2 (C_9), 46.8 (C_{10}), 37.1 (C_{11}), 36.9 (C_8), 35.1 (C_7), 33.1 (C_1), 29.5 (C_2), 29.4 (C_{18}), 25.7 (*Me*$_3$CSi), 23.3 (C_4), 22.4 (C_6), 17.9 (Me_3CSi), 17.5 (Me-C_8), 15.4 (Me-C_4), −3.2 and −3.7 (2 × MeSi); HRMS (ESI) m/z calcd for $C_{27}H_{40}NaO_5Si$ [M + Na]$^+$ 495.2543, found 495.2543.

Methyl 3,12-Dioxoisospongia-13,15-dien-20-oate (45). A solution of *tert*-butyldimethylsily ether **44** (80 mg, 0.169 mmol) in anhydrous MeCN (2 mL) was cooled to 0 °C and treated with 10 drops of a 70% aqueous solution of H_2SiF_6. The mixture was stirred at 4 °C for 18 h, quenched by the addition of a saturated $NaHCO_3$ solution, and worked up using EtOAc as the extractant. Chromatographic purification (6:4 hexanes−EtOAc) yielded the intermediate cyclopropanol (59 mg) as a white solid: mp 171−173 °C (from hexanes−Et_2O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (1H, d), 6.60 (1H, d), 3.720 (3H, s), 2.88 (1H, dd), 2.79 (1H, dd), 2.40−2.25 (2H, m), 2.25−2.15 (2H, m), 2.00−1.90 (2H, m), 1.60−1.50 (2H, m), 1.312 (3H, s), 1.21 (1H, dd), 1.128 (3H, s), 0.88 (1H), 0.65 (1H, dd), 0.33 (1H, d)].

The cyclopropanol obtained above (59 mg, 0.164 mmol) and NaOH (13.1 mg, 0.33 mmol) were dissolved in a 4:1 mixture of dioxane−water (6 mL), previously degasified by passage of a N_2 stream and sonication. The mixture was heated at 90 °C for 6 h, then cooled to 0 °C, acidified with 0.1 M hydrochloric acid, and extracted with EtOAc. The extracts were washed with 5% $NaHCO_3$ solution and brine and dried. Column chromatography (8:2 hexanes−EtOAc) of the residue left after evaporation of the solvent afforded the diketone **45** (57.9 mg, 96%) as a white solid: mp 140−141 °C (from hexane−Et_2O); $[\alpha]^{27}_D$ −125 (c 0.8, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 1705s, 1672s, 1459 m, 1268 m, 1164 m, 1137s,; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (1H, d, J = 2.0 Hz, H-16), 6.61 (1H, d, J = 2.0 Hz, H-15), 3.724 (3H, s, MeO), 2.89−2.71 (2H, m, part AB of ABX system, 2 × H-11), 2.65 (1H, ddd, J = 13.1, 5.9, 2.9 Hz, H-1), 2.50−2.25 (4H, m, 2 × H-2, H-6, H-7), 2.16 (1H, dd, part X of ABX system, J = 11.4, 5.4 Hz, H-9), 1.80−1.60 (2H, m, H′-6, H′-7), 1.59 (1H, dd, J = 9.7, 2.4 Hz, H-5), 1.50 (1H, ddd, J = 13.1, 13.1, 5.5 Hz, H′-1), 1.199 (3H, s, Me-C_8), 1.182 (3H, s, Meβ-C_4), 1.159 (3H, s, Meα-C_4); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.9 (C_3), 193.5 (C_{12}), 174.4* (COOMe), 174.1* (C_{14}), 142.8 (C_{16}), 118.6 (C_{13}), 106.2 (C_{15}), 56.1 (C_5), 53.2 (C_9), 51.6 (COO*Me*), 48.0$^{\#}$ (C_{10}), 47.9$^{\#}$ (C_4), 37.3 (C_{11}), 37.2 (C_8), 35.3 (C_7), 35.0 (C_2), 34.8 (C_1), 27.5 (Meα-C_4), 22.1 (C_6), 19.6 (Meβ-C_4), 17.6 (Me-C_8); MS (EI) m/z 358 (M^+, 100), 326 (15), 299 (16), 289 (32), 276 (41), 248 (26), 229 (16) 204 (20), 176 (25), 161 (67), 148 (90); HRMS m/z calcd for $C_{21}H_{26}O_5$ 358.1780, found 358.1797.

Isospongia-13,15-dien-20-oic Acid (Marginatafuran, 3). A solution of diketone **45** (30 mg, 0.084 mmol) and hydrazine hydrate (0.4 mL) in diethylene glycol (2.6 mL) was heated to 120 °C for 1.5 h under N_2 The temperature was raised to 170 °C to remove any excess hydrazine, KOH (106 mg, 1.9 mmol) was added, and the reaction mixture was further heated to 185 °C for 8 h before being cooled to rt, poured into 1 M hydrochloric acid, and extracted with CH_2Cl_2. The extracts were washed with a 5% $NaHCO_3$ solution and brine before drying. Evaporating the solvent and purifying the residue by column chromatography (7:3 hexanes−EtOAc) yielded marginatafuran **3** (16 mg, 61%) as a white solid: mp 202−205 °C (from hexanes; crystals begin to change appearance at 180 °C) (lit.[7] mp 208 °C); $[\alpha]^{22}_D$ −91 (c 0.37, $CHCl_3$) (lit.[7] $[\alpha]_D$ −102); IR ν_{max}/cm^{-1} (KBr) 3437s, 1700s, 1454 m, 1388w, 1268w, 1230 m, 1181w, 1142w, 1039w, 940w; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.58 (1H, br s, COOH), 7.17 (1H, d, J = 1.8 Hz, H-16), 6.09 (1H, d, J = 1.8 Hz, H-15), 2.62 (1H, br d, J = 12.8 Hz, H-1), 2.47 (1H, dd, J = 15.0, 5.0 Hz, H-11), 2.35−2.20 (3H, m, H-6, H-7, H′-11), 2.14 (1H, dd, J = 12.5, 5.5 Hz, H-12), 1.75−1.35 (7H, 2 × H-2, H-3, H′-6, H′-7, H-9, H′-12), 1.19 (1H, ddd, J = 14.0, 13.7, 3.6 Hz, H′-3), 1.129 (3H, s, Me-C_8), 1.11 (1H, dd, J = 12.5, 2.5 Hz, H-5), 1.00 (1H, ddd, J = 12.8, 3.2, 3.2 Hz, H′-1), 0.927 (3H, s, Meα-C_4), 0.918 (3H, s, Meβ-C_4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.4 (COOH), 159.3 (C_{14}), 140.3 (C_{16}), 113.6 (C_{13}), 109.9 (C_{15}), 56.8 (C_5), 56.0 (C_9), 48.3 (C_{10}), 42.4 (C_3), 38.7 (C_1), 37.2 (C_7), 37.1 (C_8), 33.8 (C_4), 33.7 (Meα-C_4), 23.0 (C_{11}), 22.7 (Meβ-C_4), 20.4 (C_{12}), 20.2 (C_2), 19.7 (Me-C_8), 18.8 (C_6); MS (EI) m/z 316 (M^+, 46), 301 (100), 299 (1), 270 (10), 256 (67), 199 (2), 147 (4), 109 (9); HRMS m/z calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2025.

Methyl 3β,12β-Dihydroxyisospongia-13,15-dien-20-oate (46). $CeCl_3{\cdot}7H_2O$ (104 mg, 0.28 mmol) was added to a solution of diketone **45** (50 mg, 0.14 mmol) in MeOH (2.8 mL), which was stirred at rt until a homogeneous solution formed. CH_2Cl_2 (2.8 mL) was then added, and the reaction was cooled to −78° followed by the addition of $NaBH_4$ (23 mg, 0.58 mmol) in small portions over a 50 min period. After completion of the reduction reaction was confirmed by TLC (5:5 hexanes−EtOAc), the excess $NaBH_4$ was quenched by the addition of acetone (1 mL) and the reaction mixture diluted with a 10% aqueous solution of sodium citrate. The usual workup using EtOAc as the extractant yielded a solid residue, which was purified by chromatography (6:4 hexanes−EtOAc) to yield diol **46** (47.9 mg,

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95%) as a white solid: mp 155−158 °C ($CDCl_3$); $[\alpha]^{25}_D$ −73 (*c* 0.24, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3420s, 1738 m, 1711 m, 1175 m, 1137 m, 1033s; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.21 (1H, d, *J* = 1.9 Hz, H-16), 6.34 (1H, d, *J* = 1.9 Hz, H-15), 4.61 (1H, m, H-12), 3.64 (3H, s, MeO), 3.22 (1H, dd, *J* = 11.6, 4.1 Hz, H-3), 2.61 (1H, ddd, *J* = 13.0, 3.3, 3.3 Hz, H-1), 2.49 (1H, br dd, *J* = 11.2, 6.4, H-11), 2.34 (1H, dddd, *J* = 16.0, 16.0, 13.3, 3.0 Hz, H-6), 2.27 (1H, ddd, *J* = 13.3, 3.0, 3.0 Hz, H-7), 1.78−1.65 (2H, m, H-2, H′-6), 1.55−1.35 (3H, m, H′-7, H-9, H′-11), 1.32 (1H, br dd, *J* = 13.8, 3.0 Hz, H′-2), 1.14−0.98 (2H, m, H′-1, H-5), 1.093 (3H, s, Me-C_8), 1.033 (3H, s, Meα-C_4), 0.843 (3H, s, Meβ-C_4); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.8 (COOMe), 160.0 (C_{14}), 141.3 (C_{16}), 118.1 (C_{13}), 108.0 (C_{15}), 78.7 (C_3), 66.8 (C_{12}), 55.7 (C_5), 53.8 (C_9), 51.0 (COO*Me*), 47.7 (C_{10}), 39.4 (C_4), 36.9 (C_7), 36.6 (C_8), 36.2 (C_1), 31.7 (C_{11}), 28.5 (C_2), 28.4 (Meα-C_4), 19.4 (Me-C_8), 18.4 (C_6), 16.0 (Meβ-C_4); MS (EI) *m*/*z* 362 (M^+, 6), 344 (24), 311 (11), 251 (100), 215 (12), 197 (11); HRMS *m*/*z* calcd for $C_{21}H_{30}O_5$ 362.2093, found 362.2096.

Methyl 3β-Hydroxy-12-oxo-isospongia-13,15-dien-20-oate (47). Oxidation of diol **46** (44 mg, 0.122 mmol) with activated MnO_2 (352 mg, 4.2 mmol) in $CHCl_3$ (8 mL), as described for the oxidation of **27**, yielded the hydroxy ketone **47** (42 mg, 97%) as a white solid after chromatography with 8:2 $CHCl_3$−EtOAc: mp 164−167 °C (from hexanes−Et_2O); $[\alpha]^{28}_D$ −69 (*c* 0.7, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3344 m, 1732s, 1678s, 1585w; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26 (1H, d, *J* = 2.0 Hz, H-16), 6.58 (1H, d, *J* = 2.0 Hz, H-15), 3.674 (3H, s, MeO), 3.23 (1H, ddd, *J* = 11.5, 6.5, 4.7 Hz, H-3), 2.78 (1H, dd, *J* = 17.5, 3.2 Hz, H-11α), 2.60−2.38 (2H, m, H-1, H-6), 2.55 (1H, dd, *J* = 17.5, 13.5 Hz, H-11β), 2.38 (1H, ddd, *J* = 13.5, 3.2, 3.2 Hz, H-7), 2.06 (1H, dd, *J* = 13.5, 3.2, Hz, H-9), 1.85−1.55 (3H, m, H-2, H′-6, H′-7), 1.33 (1H, m, H′-2), 1.20−1.00 (2H, m, H′-1, H-5), 1.165 (3H, s, Me-C_8), 1.057 (3H, s, Meα-C_4), 0.831 (3H, s, Meβ-C_4); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.9 (C_{12}), 175.3* (COOMe), 174.3* (C_{14}), 142.5 (C_{16}), 118.4 (C_{13}), 106.2 (C_{15}), 78.4 (C_3), 55.4 (C_5), 53.9 (C_9), 51.2 (COO*Me*), 47.8 (C_{10}), 39.5 (C_4), 37.2 (C_8), 37.0 (C_{11}), 35.8 (C_1), 35.5 (C_7), 28.5 (C_2), 28.2 (Meα-C_4), 18.2 (C_6), 17.7 (Me-C_8), 16.0 (Meβ-C_4); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{28}NaO_5$ $[M + Na]^+$ 383.1834, found 383.1847.

Methyl 12-Oxoisospongia-13,15-dien-20-oate (48). Reaction of alcohol **47** (33 mg, 0.091 mmol) with pentafluorophenyl chlorothioformate (30 μL, 0.18 mmol) and DMAP (33 mg, 0.27 mmol) in CH_2Cl_2 (1.8 mL), as described for **28**, gave the corresponding thionocarbonate derivative (51.7 mg) after chromatographic purification (9:1 CH_2Cl_2−EtOAc): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (1H, d), 6.60 (1H, d), 4.93 (1H, dd), 2.79 (1H, dd), 2.68 (1H, ddd), 2.57 (1H, dd), 2.42 (1H, ddd), 2.11 (1H, dd), 1.84 (1H, ddd), 1.190 (3H, s), 1.072 (3H, s), 1.002 (3H, s). Following the same procedure described for the deoxygenation of **28**, this compound was treated with AIBN (4 mg) and Bu_3SnH (53 μL, 0.195 mmol) in toluene (2.5 mL) to yield keto ester **48** (28.5 mg, 90%) as a white solid after chromatography with 9:1 CH_2Cl_2-EtOAc: mp 131−133 °C (from hexanes); $[\alpha]^{26}_D$ −105 (*c* 0.4, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 1732s, 1678s, 1514 m, 1454 m, 1437 m, 1137s, 1044 m; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26 (1H, d, *J* = 2.0 Hz, H-16), 6.59 (1H, d, *J* = 2.0 Hz, H-15), 3.665 (3H, s, MeO), 2.81 (1H, dd, *J* = 17.6, 3.2 Hz, H-11α), 2.58 (1H, dd, *J* = 17.6, 13.5 Hz, H-11β), 2.53 (1H, m, H-1), 2.50−2.30 (2H, m, H-6, H-7), 2.11 (1H, dd, *J* = 13.5, 3.2 Hz, H-9), 1.78 (1H, m, H′-6), 1.64 (1H, m, H′-7), 1.53 (1H, m, H-2), 1.44 (1H, m, H-3), 1.35−1.20 (2H, m, H′-2, H′-3), 1.20−1.11 (1H, m, H-5), 1.161 (3H, s, Me-C_8), 1.05−0.90 (1H, m, H′-1), 0.943 (3H, s, Meα-C_4), 0.881 (3H, s, Meβ-C_4); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.6 (C_{12}), 175.7* (COOMe), 174.9* (C_{14}), 142.5 (C_{16}), 118.3 (C_{13}), 106.2 (C_{15}), 56.5 (C_5), 54.1 (C_9), 51.0 (COO*Me*), 48.3 (C_{10}), 42.2 (C_3), 38.2 (C_1), 37.4 (C_8), 37.0 (C_{11}), 35.6 (C_7), 33.8 (C_4), 33.5 (Meα-C_4), 22.5 (Meβ-C_4), 20.0 (C_2), 18.5 (C_6), 17.6 (Me-C_8); HRMS (ESI) calcd for $C_{21}H_{29}O_4$ $[M + H]^+$ 345.2066, found 345.2066.

12β-Hydroxyisospongia-13,15-dien-20-oic Acid (49). $LiAlH_4$·2THF (1 M in toluene, 140 μL, 0.14 mmol) was added to a solution of **48** (12 mg, 0.034 mmol) in diglyme (4 mL) at −78 °C under N_2. This mixture was allowed to warm slowly to rt before being heated to 120 °C for 5 h. After this time, the reaction mixture was cooled to −20 °C, carefully treated with acetone (0.2 mL), poured into a 5% hydrochloric acid solution containing 10% (w/v) sodium citrate, and extracted with EtOAc. The combined organic layers were washed with 5% $NaHCO_3$ and brine, dried, and concentrated to dryness. Purification of the residue after solvent evaporation (7:3 hexanes−EtOAc) yielded hydroxy acid **49** (8 mg, 69%) as a solid: mp 134−135 °C (from hexanes−Et_2O); $[\alpha]^{22}_D$ −40 (*c* 0.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3426s, 1710s, 1705s, 1656 m, 1612 m, 1142 m, 1039 m; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.21 (1H, d, *J* = 1.9 Hz, H-16), 6.35 (1H, d, *J* = 1.9 Hz, H-15), 4.63 (1H, ddd, J = 9.1, 6.2, 1.2 Hz, H-12), 2.61 (1H, m, H-1), 2.54 (1H, dd, *J* = 11.6, 6.5 Hz, H-11), 2.36−2.18 (2H, m, H-6, H-7), 1.70 (1H, m, H′-6), 1.65−1.50 (3H, m, H-2, H-9, H′-11), 1.50−1.37 (3H, m, H′-2, H-3, H′-7), 1.181 (3H, s, Me-C_8), 1.18 (1H, m, H′-3), 1.08 (1H, dd, *J* = 12.6, 2.8 Hz, H-5), 1.00 (1H, ddd, *J* = 12.9, 12.9, 3.4 Hz, H′-1), 0.924 (3H, s, Meα-C_4), 0.918 (3H, s, Meβ-C_4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.4 (COOH), 160.2 (C_{14}), 141.2 (C_{16}), 118.1 (C_{13}), 108.1 (C_{15}), 66.9 (C_{12}), 56.7 (C_5), 53.8 (C_9), 47.9 (C_{10}), 42.3 (C_3), 38.6 (C_1), 37.1 (C_8), 37.0 (C_7), 33.8 (C_4), 33.7 (Meα-C_4), 31.8 (C_{11}), 22.7 (C_2), 20.1 (Meβ-C_4), 19.5 (Me-C_8), 18.7 (C_6); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{27}O_4$ $[M - H]^+$ 331.1909, found 331.1913.

Isospongia-13,15-diene-12β,20-diol (50) and Isospongia-13,15-dien-20-ol (51). A solution of $LiAlH_4$·2THF (1 M in toluene, 0.6 mL, 0.60 mmol) was added dropwise to a solution of keto ester **48** (18 mg, 0.051 mmol) and 6,7-dihydrobenzofuran-4(5*H*)-one (18 μL, 0.15 mmol) in toluene (8 mL) at −78 °C under N_2. After being stirred for 10 min at the same temperature, the mixture was allowed to warm to rt before refluxing for 8 h. The workup described for the transformation of **48** into **49** was followed by chromatographic purification (8:2 → 6:4 hexanes−EtOAc) to afford spongiadiol **50** (15 mg, 90%) as a white solid: mp 153−154 °C (from hexanes−Et_2O); $[\alpha]^{19}_D$ −30 (*c* 0.13, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3382s, 1650w, 1137 m, 1055s, 1028s, 984 m; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.22 (1H, d, *J* = 1.9 Hz, H-16), 6.35 (1H, d, *J* = 1.9 Hz, H-15), 4.48 (1H, dd, *J* = 9.8, 6.1 Hz, H-12), 4.07 (1H, d, *J* = 11.8 Hz, C*H*HOH), 3.98 (1H, dd, *J* = 11.8, 1.7 Hz, CH*H*′OH), 2.43 (1H, dd, *J* = 12.9, 6.0 Hz, H-11), 2.29−2.21 (2H, m, H-1, H-7), 1.76 (1H, ddd, *J* = 12.7, 12.7, 9.8 Hz, H′-11), 1.70−1.44 (5H, m, 2 × H-2, 2 × H-6, H′-7), 1.42 (1H, m, H-3), 1.419 (3H, s, Me-C_8), 1.38 (1H, d, *J* = 12.7 Hz, H-9), 1.17 (1H, ddd, J = 13.6, 13.6, 4.4 Hz, H′-3), 1.03 (1H, dd, *J* = 11.8, 2.5 Hz, H-5), 0.864 (3H, s, Meα-C_4), 0.793 (1H, dddd, *J* = 13.1, 13.1, 4.2, 1.7 Hz, H′-1), 0.778 (3H, s, Meβ-C_4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.6 (C_{14}), 141.0 (C_{16}), 118.4 (C_{13}), 108.1 (C_{15}), 67.9 (C_{12}), 62.9 (CH_2OH), 57.3 (C_5), 55.2 (C_9), 42.3 (C_{10}), 41.8 (C_3), 37.5 (C_7), 37.0 (C_8), 34.5 (C_1), 33.74 (C_4), 33.72 (Meα-C_4), 33.1 (C_{11}), 21.7 (Meβ-C_4), 21.3 (Me-C_8), 18.4* (C_2), 18.0* (C_6); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{29}O_2$ $[M - OH]^+$ 301.2162, found 301.2168.

Small, variable amounts of a secondary, less polar compound also formed in the reduction of keto ester **48** with $LiAH_4$·2THF in toluene when the above reaction was carried out in the absence of dihydrobenzofuranone. This compound, obtained as an amorphous solid, was identified as isospongiadienol **51**: $[\alpha]^{20}_D$ −20 (*c* 0.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3437s, 1700w, 1148 m, 1033 m; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.19 (1H, d, *J* = 1.8 Hz, H-16), 6.10 (1H, d, *J* = 1.8 Hz, H-15), 4.07 (1H, d, *J* = 11.8 Hz, C*H*HOH), 4.00 (1H, dd, *J* = 11.8, 1.5 Hz, CH*H*′OH), 2.42 (1H, ddd, *J* = 15.7, 5.4, 1.4 Hz, H-11), 2.37−2.11 (3H, m, H-1, H-7, H′-11), 2.07 (1H, br dd, *J* = 13.4, 5.6 Hz, H-12), 1.78 (1H, ddd, *J* = 13.4, 5.5, 1.2 Hz, H′-12), 1.74−1.39 (7H, m, 2 × H-2, H-3, 2 × H-6, H′-7, H-9), 1.375 (3H, s, Me-C_8), 1.18 (1H, ddd, *J* = 13.6, 13.2, 4.0 Hz, H′-3), 1.06 (1H, dd, *J* = 12.0, 2.8 Hz, H-5), 0.872 (3H, s, Meα-C_4), 0.83 (1H, m, H′-1), 0.794 (3H, s, Meβ-C_4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.6 (C_{14}), 140.1 (C_{16}), 113.8 (C_{13}), 110.0 (C_{15}), 63.2 (CH_2OH), 57.5 (C_9), 57.4 (C_5), 42.7 (C_{10}), 41.9 (C_3), 37.7 (C_7), 37.0 (C_8), 34.5 (C_1), 33.9 (C_4), 33.1 (Meα-C_4), 24.2 (C_{11}), 22.2 (C_{12}), 21.7 (Meβ-C_4), 21.6 (Me-C_8), 18.5 (C_2), 18.1 (C_6); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{31}O_2$ $[M + H]^+$ 303.2324, found 303.2325.

20-Hydroxyisospongia-13,15-dien-12-one (52). The selective oxidation of diol **50** (12 mg, 0.0378 mmol) with activated MnO_2 (192 mg, 1.87 mmol) in $CHCl_3$ (4.5 mL) using the same procedure as

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described for **27**, afforded 20-hydroxymarginatone **52** (11.3 mg, 94%) as a white solid after chromatographic purification (8:2 $CHCl_3$−EtOAc): mp 176−177 °C (from hexanes−Et_2O); $[\alpha]^{23}_D$ −17 (*c* 0.12, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3426s, 1661s, 1563w, 1366 m, 1050 m, 1028 m; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26 (1H, d, *J* = 2.0 Hz, H-16), 6.59 (1H, d, *J* = 2.0 Hz, H-15), 4.14 (1H, d, *J* = 11.2 Hz, C*H*HOH), 4.03 (1H, dd, *J* = 11.4, 2.0 Hz, CH*H*′OH), 3.11 (1H, dd, *J* = 17.6, 13.7 Hz, Hβ-11), 2.72 (1H, dd, *J* = 17.6, 2.7 Hz, Hα-11), 2.35 (1H, br dd, *J* = 10.0, 2.9 Hz, H-7), 2.20 (1H, br dd, *J* = 13.1, 0.8 Hz, H-1), 1.94 (1H, dd, *J* = 13.7, 2.2 Hz, H-9), 1.76−1.51 (5H, m, 2 × H-2, 2 × H-6, H′-7), 1.45 (1H, m, H-3), 1.468 (3H, s, Me-C_8), 1.18 (1H, ddd, *J* = 13.5, 13.5, 4.4 Hz, H′-3), 1.08 (1H, dd, *J* = 12.0, 2.1 Hz, H-5), 0.887 (3H, s, Meα-C_4), 0.85 (1H, ddd, *J* = 13.1, 4.0, 1.4 Hz, H′-1), 0.797 (3H, s, Meβ-C_4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.9 (C_{12}), 175.9 (C_{14}), 142.1 (C_{16}), 118.2 (C_{13}), 106.1 (C_{15}), 62.7 (CH_2OH), 56.9 (C_5), 56.0 (C_9), 42.2 (C_{10}), 41.6 (C_3), 38.7 (C_{11}), 37.5 (C_8), 36.2 (C_7), 34.1 (C_1), 33.8 (Meα-C_4), 33.1 (C_4), 21.7 (Meβ-C_4), 19.5 (Me-C_8), 18.3 (C_2), 17.8 (C_6); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{29}O_3$ $[M + H]^+$ 317.2117, found 317.2117.

12-Oxoisospongia-13,15-dien-20-yl Acetate (20-Acetoxymarginatone, 6). Et_3N (112 μL, 1.08 mmol), Ac_2O (108 μL, 1.04 mmol) and a small crystal of DMAP were added to a solution of hydroxy ketone **52** (8 mg, 0.025 mmol) in anhydrous CH_2Cl_2 (2 mL). The mixture was stirred at rt for 1 h before diluting with water and extracting with EtOAc. The organic extracts were washed successively with 5% hydrochloric acid, 5% $NaHCO_3$ and brine. Evaporation of the dried solution produced a residue, which was purified by chromatography (9:1 hexanes−EtOAc) to yield 20-acetoxymarginatone **6** (8 mg, 88%) as a white solid: mp 60−64 °C (from cold hexanes) (lit.[9] clear colorless oil); $[\alpha]^{20}_D$ −30 (*c* 0.07, $CHCl_3$) ($[\alpha]_D$ has been not reported for this compound in the literature); IR ν_{max}/cm^{-1} (KBr) 1732s, 1683s, 1558 m, 1386w, 1235w, 1050w, 1030w; ^1H NMR (C_6D_6, 400 MHz) δ 6.79 (1H, d, *J* = 2.0 Hz, H-16), 6.66 (1H, d, *J* = 2.0 Hz, H-15), 4.66 (1H, br d, *J* = 12.3 Hz, C*H*HO), 4.03 (1H, dd, *J* = 12.3, 1.2 Hz, CH*H*′O), 2.82−2.72 (2H, m, 2 × H-11), 2.07 (1H, m, H-7), 1.77 (1H, br dd, *J* = 13.1, 1.5 Hz, H-1), 1.532 (3H, s, MeCOO), 1.51 (1H, m, H-9), 1.38−1.18 (6H, m, 2 × H-2, H-3, 2 × H-6, H′-7), 1.090 (3H, s, Me-C_8), 0.92 (1H, ddd, *J* = 13.8, 13.2, 4.5 Hz, H′-3), 0.688 (3H, s, Meα-C_4), 0.655 (3H, s, Meβ-C_4), 0.57 (1H, dd, *J* = 12.5, 1.9 Hz, H-5), 0.36 (1H, dddd, *J* = 13.6, 13.6, 4.0, 2.1 Hz, H′-1); ^{13}C NMR (C_6D_6, 100 MHz) δ 193.4 (C_{12}), 174.7 (C_{14}), 170.0 (MeCOO), 142.3 (C_{16}), 119.1 (C_{13}), 106.8 (C_{15}), 64.2 (CH_2O), 56.4 (C_5), 55.2 (C_9), 41.5 (C_3), 40.6 (C_{10}), 38.5 (C_{11}), 37.5 (C_8), 36.1 (C_7), 34.2 (C_1), 33.6 (Meα-C_4), 32.9 (C_4), 21.6 (Meβ-C_4), 20.3 (*Me*COO), 19.3 (Me-C_8), 18.3 (C_2), 17.9 (C_6); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{31}O_4$ $[M + H]^+$ 359.2222, found 359.2228.

Physical and Spectroscopic Data for Diels−alder Adducts 36a and 37a. See ref 46 and Scheme SI-2, Supporting Information.

Data for Diels−Alder adduct 36a [(4a*S*,6a*R*,7a*S*,8a-*S*,9a*R*,9b*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4,6a,7a-trimethyl-7-oxo-1,2,4a,5,6,6a,7,7a,8a,9,9a,9b-dodecahydrophenanthro-[2,3-*b*]oxirene-9b-carbaldehyde]: white solid; mp 156−158 °C (from hexanes); $[\alpha]^{22}_D$ −73 (*c* 0.55, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2891s, 2852s, 1705s, 1661 m, 1197s, 842s; ^1H NMR (C_6D_6, 300 MHz) δ 9.65 (1H, s, CHO), 2.77 (1H, d, *J* = 1.8 Hz, H-8a), 2.23−2.14 (2H, m, H-1, H-9), 2.02 (1H, ddd, *J* = 13.5, 3.0, 3.0 Hz, H-6), 1.97−1.78 (2H, m, H_2-2), 1.71−1.60 (2H, m, H-4a, H-9a), 1.582 (3H, dd, *J* = 3.3, 2.1 Hz, Me-C4), 1.53 (1H, ddd *J* = 13.0, 6.8, 3.4 Hz, H-5), 1.35 (1H, ddd, *J* = 13.5, 13.5, 3.0 Hz, H′-6 overlapped with Me-C7a), 1.293 (3H, s, Me-C7a), 1.23 (1H, m, H′-5 overlapped with Me-C7a), 0.959 (9H, s, Me_3C−Si), 0.69 (1H, m, H′-1), 0.487 (3H, s, Me-C6a), 0.041 and 0.035 (3H each, each s, 2 × MeSi); ^{13}C NMR (C_6D_6, 75 MHz) δ 206.8 (C7), 204.1 (CHO), 145.2 (C3), 113.9 (C4), 59.1 (C8a), 56.2 (C7a), 50.5 (C9b), 45.6 (C6a), 44.1 (C4a), 41.4 (C9a), 32.9 (C6), 30.7 (C1), 27.7 (C2), 26.0 (*Me*$_3$CSi), 21.6 (C9), 20.4 (C5), 19.0 (Me-C6a), 18.4 (Me_3*C*Si), 16.6 (Me-C7a), 12.7 (Me-C4), −3.5 and −3.9 (2 × MeSi); MS (EI) *m*/*z* 418 (M^+, 2), 361 (6), 333 (3), 315 (2), 305 (7), 213 (11), 173 (2), 73 (100); HRMS *m*/*z* calcd for $C_{24}H_{38}O_4Si$ 418.2539, found 418.2537.

Data for Diels−Alder adduct 37a [4a*R*,6a*R*,7a*S*,8a*S*,9a*R*,9b*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4,6a,7a-trimethyl-7-oxo-1,2,4a,5,6,6a,7,7a,8a,9,9a,9b-dodecahydrophenanthro[2,3-*b*]-oxirene-9b-carbaldehyde]: white solid; mp 134−136 °C (from hexanes); $[\alpha]^{22}_D$ −46 (*c* 0.65, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2710s, 1711 m, 1672 m, 1175s, 842s; ^1H NMR (C_6D_6, 300 MHz) δ 9.42 (1H, s, CHO), 2.76 (1H, br d, *J* = 1.0 Hz, H-8a), 2.49 (1H, s, H-4a), 2.26 (1H, dd, *J* = 13.0, 4.2 Hz, H-9a), 1.92 (1H, dd, *J* = 15.0, 1.3 Hz, H-5), 1.87 (1H, ddd, *J* = 13.0, 4.2, 1.3 Hz, H-9), 1.84−1.72 (3H, m, H-2, H-6, H′-9), 1.60 (1H, m, H-1), 1.509 (3H, s, Me-C4), 1.50−1.29 (3H, H′-1, H′-5, H′-6), 1.268 (3H, s, Me-C7a), 0.96 (1H, m, H′-2 overlapped with Me_3CSi signal), 0.959 (9H, s, Me_3CSi), 0.659 (3H, s, Me-C6a), 0.106 and 0.053 (3H each, each s, 2 × MeSi); ^{13}C NMR (C_6D_6, 75 MHz) δ 206.9 (C7), 204.8 (CHO), 144.0 (C3), 111.4 (C4), 58.9 (C8a), 56.5 (C7a), 48.8 (C9b), 45.4 (C6a), 38.7 (C4a), 30.0 (C9a), 28.3 (C6), 26.7 (C5), 26.5 (C2), 26.0 (Me_3CSi), 20.9 (C9), 20.4 (C1), 18.3 (Me_3CSi), 17.6 (Me-C6a), 16.7 (Me-C7a), 13.2 (Me-C4), −3.6 and −4.0 (2 × MeSi); MS (EI) *m*/*z* 418 (M + , 6), 390 (3), 387 (2), 372 (6), 361 (3), 333 (2), 316 (3), 275 (3), 235 (5), 73 (100); HRMS *m*/*z* calcd for $C_{24}H_{38}O_4Si$ 418.2539, found 418.2529.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Schemes SI-1 and SI-2, which were cited in refs 42 and 46, respectively, general experimental details, and copies of the ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: antonio.abad@uv.es.

Notes

The authors declare no competing financial interest.

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(31) The use of first-generation Grubbs' catalyst [$(PCy_3)_2Cl_2Ru$=CHPh] resulted in a slower reaction, leading to a low yield of the RCM product and the formation of significant amounts, up to 60%, of side products, mainly the cross-metathesis dimer of **22** (R-OCH_2CH=$CHCH_2O$-R, mixture of *E*/*Z* isomers).
(32) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160−17161.
(33) A similar result was obtained with the Hoveyda−Grubbs first-generation catalyst [$(Ph_3P)Cl_2Ru$=$CH(C_6H_4(o\text{-}OCHMe_2)$].
(34) Alternatively, the dihydrofuran D ring could also be transformed, after protection of the hydroxyl group as TBDMS ether, into a furan-2-one ring [as it is, for example, in polyrhaphin D (**4**)] by allylic oxidation with CrO_3/3,5-dimethylpyrazol.
(35) Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Meseguer, B.; Zaragozá, R. J. *J. Org. Chem.* **1998**, *63*, 5100−5106.
(36) The rigorous exclusion of oxygen was essential, since in its presence the cyclopropanol [**25**: R^1 = H; R^2 = O] easily experiences cleavage of the bicyclo[4.1.0]heptanol moiety to give a 3-hydroperoxycycloheptanone moiety. This transformation seems to imply a free-radical mechanism which involves ring opening of a cyclopropoxy radical to a β-keto radical. For related ring opening of other bicyclic fused cyclopropanols, see: (a) Gibson, D. H.; DePuy, C. H. *Tetrahedron Lett.* **1969**, 2203−2206. (b) Morisson, V.; Barnier, J. P.; Blanco, L. *Tetrahedron Lett.* **1999**, 4045−4046.
(37) (a) Javier Moreno-Dorado, F.; Guerra, F. M.; Manzano, F. L.; Aladro, F. J.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron Lett.* **2003**, *44*, 6691−6693. (b) Pisoni, D. S.; Gamba, D.; Fonseca, C. V.; da Costa, J. S.; Petzhold, C. L.; de Oliveira, E. R.; Ceschi, M. A. *J. Braz. Chem. Soc.* **2006**, *17*, 321−327.
(38) In some experiments, a variable percentage of the corresponding aldehyde was formed, probably due to inefficient stirring of the heterogeneous reaction mixture. In these cases, the diethyl ketal protective group was completely restored by treatment of the crude reaction mixture with triethyl ortoformate and catalytic PTSA in EtOH at rt prior to the chromatographic purification.
(39) Prepared from 4-ethylmorpholine according to: Craig, J. C.; Purushothaman, K. K. *J. Org. Chem.* **1970**, *35*, 1721−1722.
(40) Suzuki, S.; Onishi, T.; Fujita, Y.; Misawa, H.; Otera, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3287−3288.
(41) Tidwell, T. T. *Org. React.* **1990**, *39*, 297−572.
(42) Probably, the formation of the formate derivative occurs via nucleophilic substitution on the *N*-ethylmorpholinium intermediate (**i**) by DMF (see Scheme SI-1 in the Supporting Information), followed by hydrolysis of the resulting imidate salt (**ii**) during the aqueous workup.
(43) Shevchuk, M. I.; Volynskaya, E. M.; Dombrovskii, A. V. *Zh. Obshch. Khim.* **1970**, *40*, 48−57.
(44) The use of the Horner−Wadsworth−Emmons reaction led, in this case, to a lower yield of the α,β-unsaturated ketone **34**.
(45) The ^1H NMR spectrum of the crude reaction mixture also showed the presence of traces of the other two possible diastereomeric IMDA adducts.
(46) In parallel to the preparation of the dienol silyl ether **35**, we also carried out the preparation of the analogous system with an aldehyde function instead of the methyl ester group (see Scheme SI-2 in the Supporting Information, compound **35a**). It was prepared from unsaturated aldehyde **30** following a sequence of transformations identical to that used for the preparation of **35** from **32**. The IMDA reaction of this compound takes place at lower temperatures and shorter reaction times than that of **35** (115 °C, 64 h) to give a 66:34 mixture of chromatographically separable (9:1 hexanes−EtOAc) *trans-anti-trans*- and *cis-anti-trans*-adducts, **36a** and **37a**, respectively, in a 90% combined yield.
(47) For example, this bis-carbonyl reduction of **45** could be accomplished in a nonoptimized 50% overall yield through the three-step procedure involving transformation of both carbonyl groups to the corresponding bis-pentafluorophenylthiocarbonate derivative and subsequent treatment with Bu_3SnH.
(48) Hydrolysis of a hindered methyl ester group under similar deduction conditions has been observed previously; see, for example: Seebacher, W.; Hüfner, A.; Haslinger, E.; Weis., R. *Monatsh. Chem.* **1998**, *129*, 697−703.
(49) The reduction of the C−O bond adjacent to the furan ring was somewhat unexpected. We have found in the literature very few reports of a related process under similar reaction conditions; it has been proposed to occur through a single electron-transfer process; see: Ashby, E. C.; Goel, A. B. *Tetrahedron Lett.* **1981**, *22*, 1879−1880.

(50) The fact that **51** was not always formed, at least in detectable amounts, in all the runs, leads us to speculate on the possibility that its formation might be related with the occasional presence of varying amounts of tin derivatives contaminating **48**, due to the difficulty to completely eliminate them after the reduction reaction of the thionocarbonate derivative of **47** with Bu_3SnH.

(51) The alterations in the electron transfer chain are associated with multiple neurodegenerative diseases including Parkinson's and Huntingon's diseases; see: Sas, K.; Robotka, H.; Toldi, J.; Vécsei, L. *J. Neurol. Sci.* **2007**, *257*, 221−239. In addition, the inhibition of the integrated NADH oxidase enzymatic activity is frequently related to antitumor and pesticidal agents, see: (a) Degli Esposti, M. *Biochem. Biophys. Acta* **1998**, *1364*, 222−235. (b) Isman, M. B. *Annu. Rev. Entomol.* **2006**, *51*, 45−66.

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