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Biomimetic Synthesis of the Apoptosis-Inducing Thiazinoquinone Thiaplidiaquinone A

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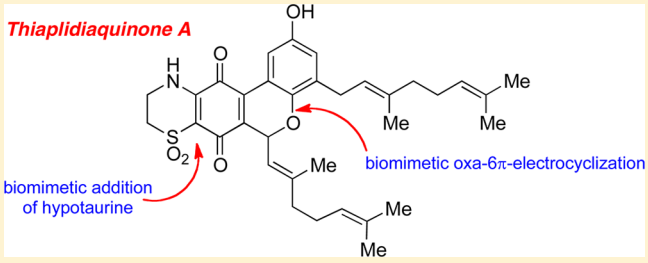
Supporting Information

ABSTRACT: A concise total synthesis of the apoptosis-inducing, marine metabolite thiaplidiaquinone A is described. The key ring forming steps are both based on biosynthetic considerations and involve the construction of the central benzo[*c*]chromene quinone unit by an extremely facile oxa-6π-electrocyclic ring closure reaction of an *ortho*-quinone intermediate, derived by tautomerization of a bis-benzoquinone, readily accessed from two simple phenolic precursors. This is followed by the installation of the 1,4-thiazine-dioxide ring by reaction of the benzo[*c*]chromene quinone with hypotaurine.



INTRODUCTION

Biomimetic synthesis, or synthesis inspired by biosynthetic consideration, is a powerful tool in organic chemistry and has been applied in numerous routes to complex natural products.[1,2] Within this rapidly expanding arena, pericyclic reactions (cycloadditions, electrocyclizations and sigmatropic rearrangements), long regarded as one of the cornerstones of synthesis, are playing an increasingly important role.[3−5] One subset of such processes, oxa-6π electrocyclizations, are of particular interest since they usually have low activation barriers, are often reversible, and are quite common in the biosynthesis of oxygen heterocycles such as chromenes from phenolic precursors.[4] We now report the use of such a process in a total synthesis of the apoptosis-inducing marine metabolite thiaplidiaquinone A **1**, a structurally unique benzo[*c*]chromene quinone. The key ring forming steps are both based on biosynthetic considerations, and involve the construction of the central chromene unit by an extremely facile oxa-6π-electrocyclic ring closure reaction that occurs under neutral conditions at room temperature, followed by installation of the 1,4-thiazine-dioxide ring by reaction with hypotaurine.

Chromene (2*H*-benzopyran) natural products are widely distributed[6] and are often isoprene derived, arising by an oxa-6π electrocyclic process on an *ortho*-quinone methide intermediate (Scheme 1A).[7] In nature, dehydrogenase enzymes appear to catalyze such processes as in the case of the biosynthesis of cannabichromenic acid (CBCA) from the corresponding *ortho*-geranyl phenol (CBGA) in *Cannabis sativa* (Scheme 1B).[8] The reversibility of oxa-6π electrocyclizations has been invoked to explain the observation that some chromenes such as smenochromene A are isolated as a racemate or undergo facile racemization via an electrocyclic ring-opening-electrocyclization sequence (Scheme 1C).[9,10]

An alternative entry into *ortho*-quinone methide intermediates that can undergo oxa-6π electrocyclization is by tautomerization of *ortho*-prenylated quinones.[11−13] Important contributions in this field include Trauner's syntheses of other naturally occurring chromenes such as microphyllaquinone[12] and exiguamine A,[14] two compounds belonging to a rare but biologically interesting subclass of naturally occurring chromenes, the benzo[*c*]chromene-7,10-diones (Figure 1). In addition to the cytotoxic microphyllaquinone and the potent inhibitor of indoleamine-2,3-dioxygenase exiguamine A, this class also includes tecomaquinone I isolated from teak[15,16] and the antimalarial scabellone B.[17] We now report the details of the first synthesis of a structurally unique member of this family of natural products, the 1,4-thiazine dioxide-containing, thiaplidiaquinone A **1**.

RESULTS AND DISCUSSION

Quinones are ubiquitous in nature occurring as secondary metabolites in many organisms,[18] as pollutants, for example, in automobile exhaust or cigarette smoke, or as molecules that are essential to life, being inextricably linked with oxidative processes in cells. Thus ubiquinones (coenzymes Q) are present in virtually all aerobic organisms from bacteria to higher plants and animals, and play a major role in electron transport in the respiratory chain. The closely related plastoquinones occur in the chloroplast of green plants and are essential for photosynthesis. As part of our ongoing studies on the synthesis of naturally occurring quinones,[19−22] we became interested in the highly unusual thiazine-containing quinones,[23] the thiaplidiaquinones, reported in 2005 by Fattorusso and co-workers.[24] Thiaplidiaquinones A and B were isolated from the

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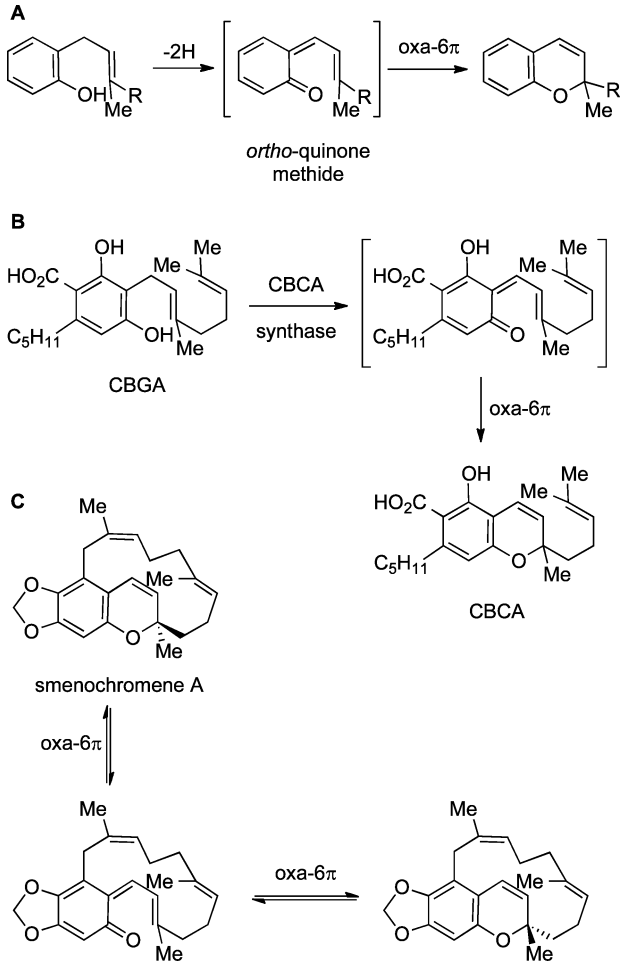
Scheme 1. Oxa-6π Electrocyclization Reactions in Biosynthesis[a]



[a](A) General scheme for cyclization of *ortho*-prenylated phenols via oxa-6π electrocyclization of an *ortho*-quinone methide intermediate; (B) biosynthesis of cannabichromenic acid (CBCA) from cannabigerolic acid (CBGA); (C) possible route for racemization of smenochrome A.

Mediterranean ascidian *Aplidium conicum*, collected off the coast of Sardinia. The compounds were isolated as racemates and their "unprecedented tetracyclic structures" were assigned by extensive NMR spectroscopic studies. Structurally the thiaplidiaquinones are related to other prenylated thiazinoquinones isolated from the same organism, namely the conicaquinones,[25] and the aplidinones (Figure 2).[26] Other marine natural products that contain the same 1,4-thiazine-1,1-dioxide-quinone chromophore[23] are adociaquinone A,[27] and ascidiathiazone A (Figure 2).[28] The thiaplidiaquinones are interesting from the biological perspective, inducing apoptosis, and hence cell death, in cancer cell lines by a mechanism that involves the production of intracellular reactive oxygen species.

Our plan for the synthesis of thiaplidiaquinone A was based on biosynthetic considerations, and involved a biomimetic late stage construction of the 1,4-thiazine-1,1-dioxide ring by addition of hypotaurine to the tricyclic pyranoquinone **3**, despite the fact that such an addition might be fraught with issues of regioselectivity (see below). The key pyranoquinone **3** would arise by the pivotal biomimetic oxa-6π electrocyclic ring closure of *ortho*-quinone methide intermediate **4**, obtained by

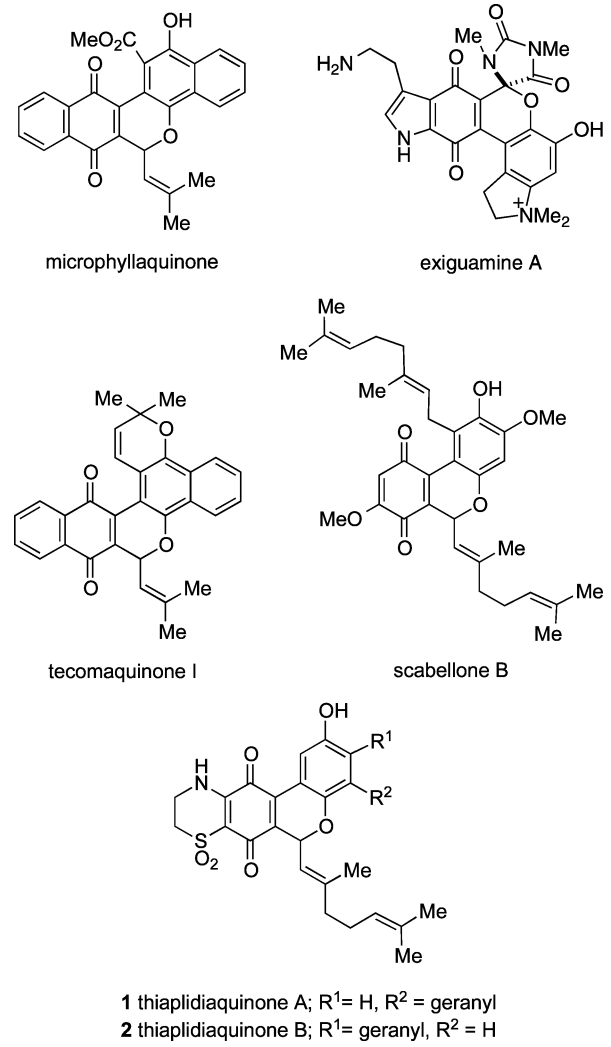


Figure 1. Benzo[*c*]chromene-7,10-dione natural products.

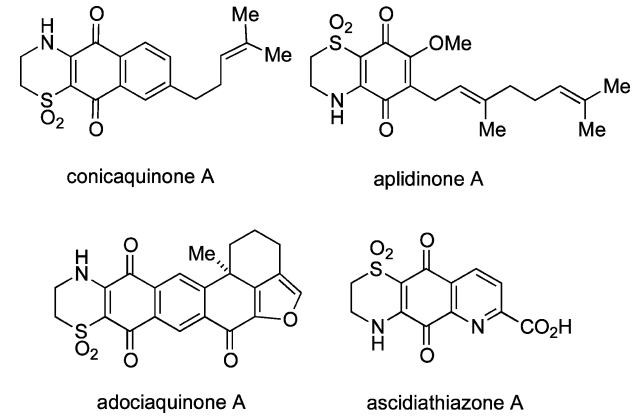


Figure 2. Marine natural products containing the 1,4-thiazine-1,1-dioxide-quinone moiety.

tautomerization of bis-benzoquinone **5** (Scheme 2). The fact that there would be no stereocontrol in such an oxa-6π electrocyclization is inconsequential since the natural product is racemic. Indeed one might speculate that the reason it is racemic is the facile reversibility of such oxa-6π electrocyclizations (cf. Scheme 1C). The required bis-benzoquinone **5** should be readily accessible by union of the hydroquinone

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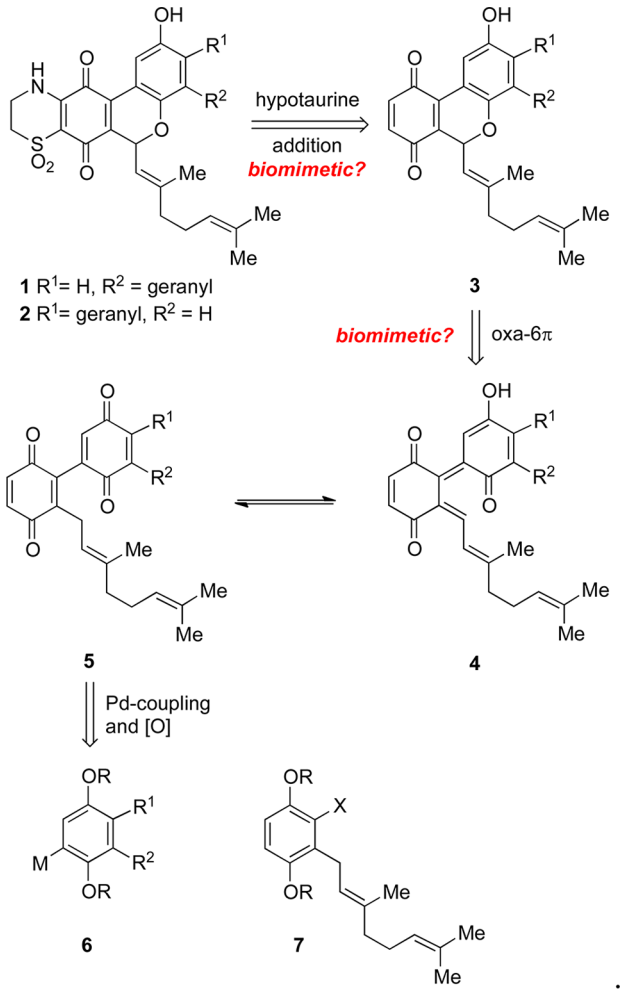
Scheme 2. Retrosynthesis of the Thiaplidiaquinones

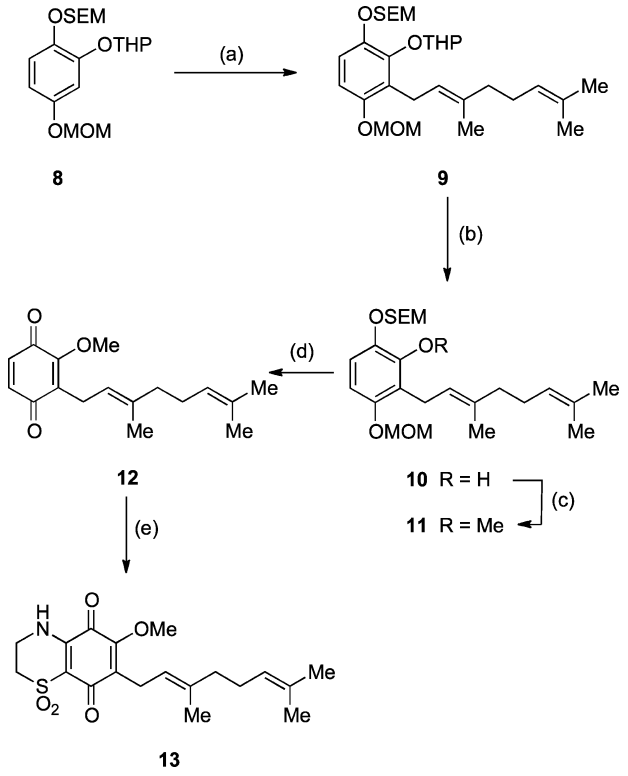


derivatives **6** [M = SnR_3 or $B(OR)_2$] and **7** (X = halide or OTf) under palladium catalysis followed by oxidation.

Hypotaurine occurs widely in nature and is an intermediate in the biosynthesis of taurine from cysteine. The co-occurrence in the same organism of metabolites such as adociaquinone A (Figure 2) with xestoquinone, the corresponding compound lacking the thiazinedioxide ring, strongly suggests that the two compounds are biosynthetically related by the addition of hypotaurine.[27,29] Indeed, such steps have been investigated in the laboratory. Thus, for example, addition of hypotaurine to the naturally occurring unsymmetrical naphthoquinone xestoquinone gives both regioisomers of the adduct, adociaquinones A and B, with a selectivity of 2−3:1,[27,29] while addition of hypotaurine to 2-methoxycarbonylquinoline-5,8-quinone was more selective, giving a 10:1 ratio of dioxothiazine adducts, with the desired precursor to ascidiathiazone A predominating.[28]

Notwithstanding the varying outcomes with respect to the addition to unsymmetrical quinones, one of the key steps in our approach to thiaplidiaquinone A remained the biomimetic addition of hypotaurine to benzoquinone **3** (Scheme 2). However, given the uncertainty of the outcome of this key step, we undertook a brief model study on a simpler geranyl substituted benzoquinone **12**, that contained both a geranyl side chain and an electron donating methoxy group on the quinone nucleus. Our route to benzoquinone **12** started with the triply protected 1,2,4-trihydroxybenzene **8**, chosen so that the three phenolic groups could be manipulated separately if necessary. This was readily prepared from 2,5-dihydroxybenzaldehyde by sequential protection of the two phenolic OH groups followed by Dakin oxidation and protection of the new OH group.[30] The geranyl substituent could then be installed by lithiation of protected 1,2,4-trihydroxybenzene **8** with *n*-butyllithium, followed by alkylation with geranyl bromide. This approach provided the desired geranylated compound **9** in good yield. Deprotection of the THP protecting group and methylation under standard conditions furnished diprotected methoxybenzene **11** in near quantitative yield for the two steps (Scheme 3). Deprotection of the two ether protecting groups

Scheme 3. Synthesis of Iso-Aplidinone A 13[a]



[a]Reagents and conditions: (a) (i) *n*-butyllithium, THF, 0 °C, 45 min, (ii) geranyl bromide, 0 °C to rt, 16 h, 69%; (b) HCl(aq), EtOH, rt, 30 min, 97%; (c) (i) NaH, DMF, 0 °C, 30 min, (ii) MeI, 0 °C to rt, 3.5 h, 95%; (d) CSA, MeOH, 16.5 h, then salcomine, O_2, MeCN, 50 min, 95% (2 steps); (e) hypotaurine, MeCN−EtOH, salcomine, rt (32%).

was efficiently achieved with camphorsulfonic acid in methanol to provide the hydroquinone, which without isolation was subsequently oxidized to quinone **12** using a catalytic amount of salcomine under an atmosphere of oxygen (Scheme 3). Quinone **12** was isolated as a bright yellow oil, with data identical to those previously published.[31] Addition of hypotaurine to 2-methoxy-3-geranyl-1,4-benzoquinone **12** carried out in the presence of salcomine to aid the reoxidation step, gave a single benzothiazine quinone in modest yield. The structure of the product was assigned as thiazino quinone **13**, a compound we term iso-aplidinone A since it is the regioisomer of the natural product aplidinone A,[26] on the basis of NMR spectroscopy (see Supporting Information). In particular, a multiple bond HMBC experiment with a large number of scans enabled correlations to be seen from the thiazine NH to carbons in the benzoquinone structure, confirming that the NH

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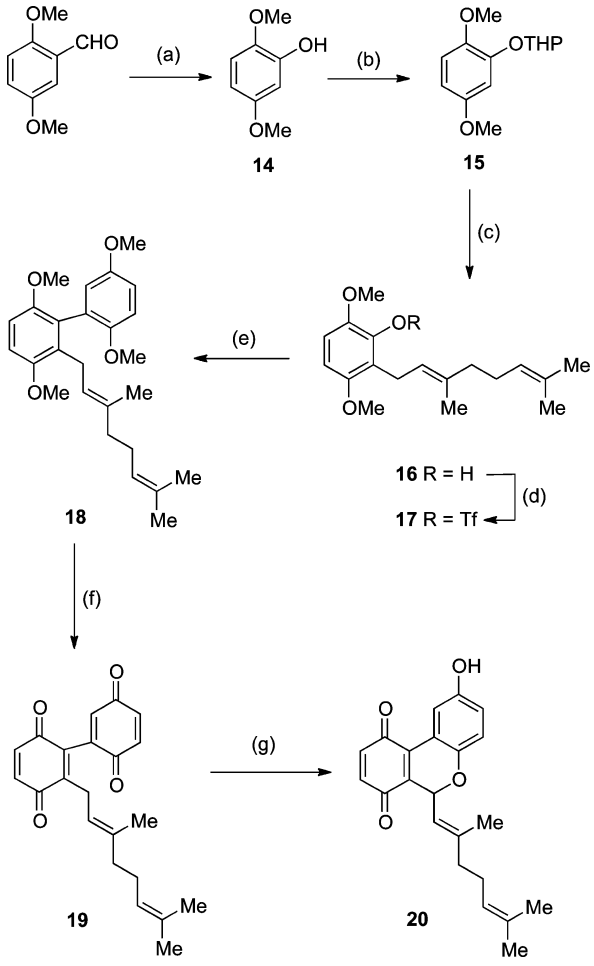
is attached to the opposite quinone carbonyl compared to the geranyl and sulfone methylene hydrogens. Hence in this model system the addition of hypotaurine appears to be regioselective, boding well for the crucial addition to the "real" quinone **3**.

We next decided to employ a model system in order to study the best conditions for the crucial 6π-electrocyclization, synthesizing a simpler biaryl compound **18** containing only one geranyl chain. This compound could be readily obtained through a Suzuki–Miyaura reaction between the commercially available 2,5-dimethoxybenzeneboronic acid and aryl triflate **17** (Scheme 4). Synthesis of triflate **17** began with the Dakin

Scheme 4. Synthesis of Model Benzo[*c*]chromene-7,10-dione 20[a]



[a]Reagents and conditions: (a) (i) *m*-CPBA, CH_2Cl_2, rt, 18 h, (ii) 2 M aq NaOH, MeOH, 3 h, 79%; (b) tetrahydro-2*H*-pyran-2-ol, ADDP, TBP, THF, rt, 18 h, 99%; (c) (i) *n*-BuLi, THF, rt, 30 min, (ii) geranyl bromide, rt, 18 h, 57%; (d) Tf_2O, CH_2Cl_2, −78 °C, 30 min, 81%; (e) 2,5-dimethoxybenzeneboronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, DMF–H_2O, MW (300 W), 140 °C, 10 min, 80%; (f) AgO, 6 M HNO_3, dioxane, rt, 30 min; (g) Et_3N, CH_2Cl_2, rt, 1 h, 73% (over 2 steps).

oxidation of commercially available 2,5-dimethoxybenzaldehyde in 79% yield,[32] followed by protection of the phenol **14** under Mitsunobu conditions, affording **15** in 99% yield. Directed lithiation of **15** by treatment with *n*-BuLi at −78 °C followed by addition of geranyl bromide gave compound **16** in 57% yield, deprotection of the THP-ether also occurring during this reaction or its workup. The subsequent reaction of **16** with triflic anhydride produced the desired aryl triflate **17** in 81% yield. Suzuki coupling between triflate **17** and the boronic acid using tetrakis(triphenylphosphine)palladium(0), cesium carbonate in a mixture of dimethylformamide–water under microwave irradiation gave biaryl compound **18** in 80% yield. Oxidation of **18** with silver(II) oxide in the presence of nitric acid[33] afforded the bis-*p*-benzoquinone **19**, a convenient starting material for 6π-electrocyclization. Treatment of the bis-*p*-benzoquinone **19** with triethylamine in dichloromethane at room temperature for 1 h initiated tautomerization to the *ortho*-quinone methide and 6π-electrocyclization to give the desired benzo[*c*]chromene-7,10-dione **20** in 73% yield (Scheme 4).

The tandem tautomerization–electrocyclization of bis-benzoquinone **19** is extremely facile and was also observed without the addition of the base, simply upon allowing the quinone to stir in solution in dichloromethane at room temperature, although the reaction proceeded very slowly (7 days) and with low yield (15%). Nevertheless the ease with which the reaction proceeded was encouraging for the projected synthesis of the thiaplidiaquinones. As an aside, we also investigated the direct functionalization of benzo[*c*]-chromene-7,10-dione **20** by regioselective introduction of a geranyl side chain *ortho* to the phenol with a view to the synthesis of thiaplidiaquinone B. A range of conditions was used, including the use of geranyl bromide in the presence of bases such as sodium hydride,[34] potassium carbonate,[35] or potassium hydroxide,[36] or geraniol in the presence of boron trifluoride-diethyl etherate,[37] Amberlyst-15,[38] or scandium(III) triflate,[39] but unfortunately all without success.

Hence in order to obtain the two natural compounds, it was necessary to introduce the second geranyl chain before cyclization, as part of the boronic acid partner used in the Suzuki coupling, requiring the synthesis of boronic esters **24** and **30**. The synthesis of boronate **24** started with protection of the known dibromide **21**[40] as its MOM-ether **22** in 73% yield. *ortho*-Lithiation of **22** with *n*-butyllithium at −78 °C was followed by addition of copper(I) bromide dimethylsulfide complex and geranyl bromide to give compound **23** in modest yield. The boronate moiety was installed via lithium–halogen exchange of the remaining bromine and reaction with *iso*-propoxypinacol boronate to provide the desired boronic ester **24**, which was used in the next step without purification (Scheme 5). With the two functionalized coupling partners, aryl triflate **17** and boronic ester **24**, we could access the oxa-6π cyclization precursor for thiaplidiaquinone A. The Suzuki reaction, using the same conditions described earlier, gave biaryl compound **25** in 41% yield. The subsequent deprotection of the MOM group with camphorsulfonic acid in methanol in 86% yield was followed by oxidation to afford bis-*p*-quinone **27**, the precursor for 6π-electrocyclization. However, treatment of **27** with triethylamine or other bases such as pyridine, or DBU, or with Lewis acid (boron trifluoride-diethyl etherate) in dichloromethane at room temperature, or at −50 °C, did not result in the desired cascade reactions to give benzo[*c*]-chromene-7,10-dione **28**, but only degradation of the starting material. However, on the basis of our observations with the model system, we speculated that the desired cyclization was probably quite facile, and indeed it occurred spontaneously simply by stirring quinone **27** in solution in dichloromethane at room temperature for 24 h in an open flask, affording the desired benzo[*c*]chromene-7,10-dione **28** in 52% yield (Scheme 5).

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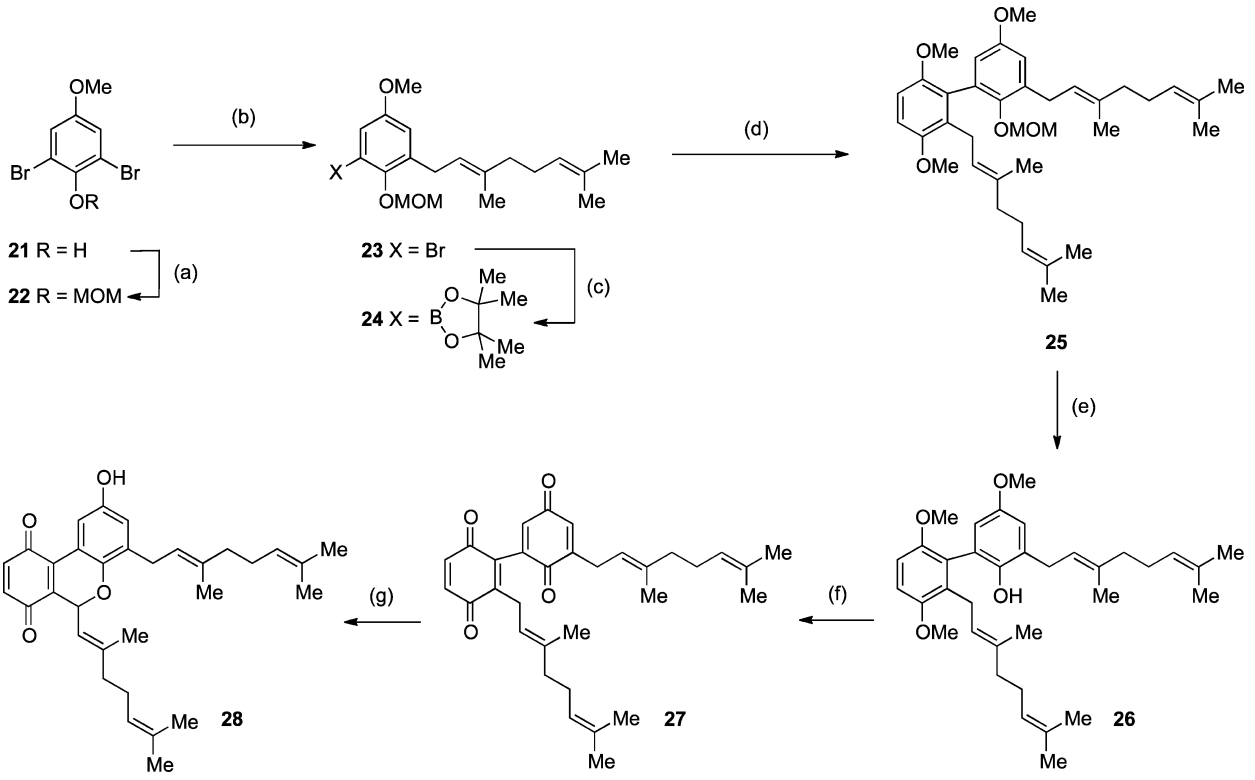
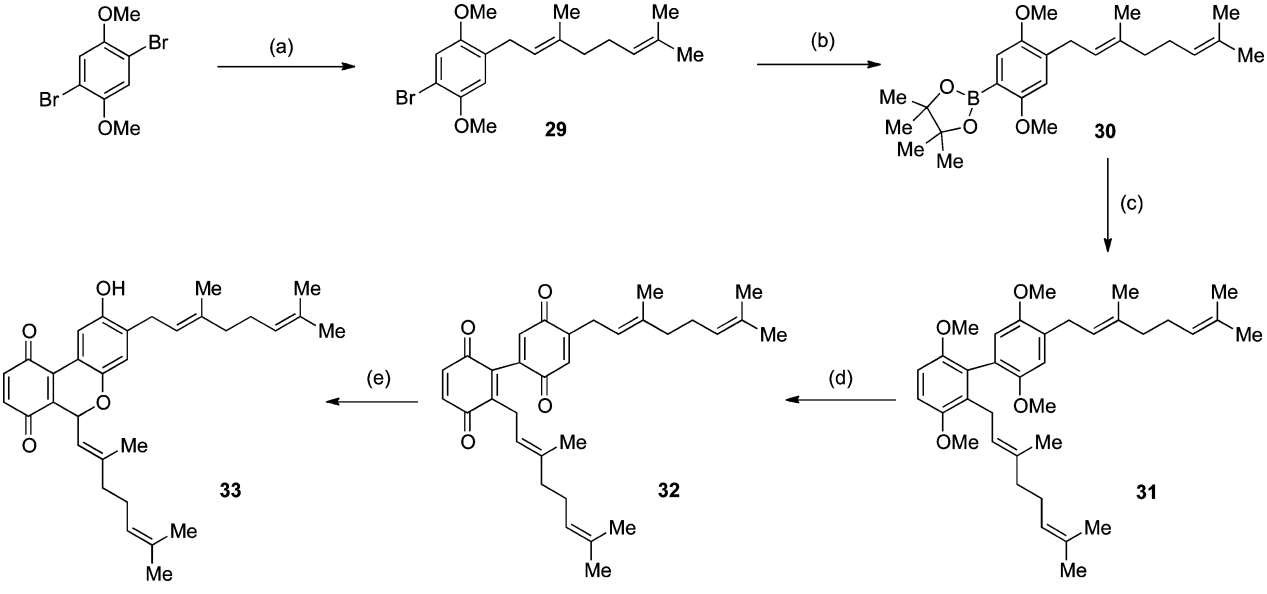
Scheme 5. Synthesis of Benzo[c]chromene-7,10-dione Precursor 28 to Thiaplidiaquinone A[a]



[a]Reagents and conditions: (a) MOMCl, DBU, acetone, 30 min, 73%; (b) (i) *n*-BuLi, THF, −78 °C, 1 h, (ii) CuBr·SMe_2, −78 °C, 1 h, (iii) geranyl bromide, −78 °C to rt, 18 h, 54%; (c) (i) *n*-BuLi, THF, −78 °C, 30 min, (ii) 2-isopropoxy-4,4,5,5-tetramethyl-1,2,3-dioxaborolane, −78 °C, 30 min; (d) aryl triflate **17**, $Pd(PPh_3)_4$, Cs_2CO_3, DMF−H_2O, MW (300 W, 140 °C, 10 min), 41% (over 2 steps); (e) CSA, MeOH, rt, 18 h, 86%; (f) AgO, 6 M HNO_3, dioxane, rt, 30 min; (g) CH_2Cl_2, rt, 24 h, 52%.

Scheme 6. Synthesis of Benzo[c]chromene-7,10-dione Precursor 33 to Thiaplidiaquinone B[a]



[a]Reagent and conditions: (a) *n*-BuLi, THF, CuBr·SMe_2, geranyl bromide, −78 to 0 °C, 2 h, 60%; (b) (i) *n*-BuLi, THF, −78 °C, 30 min, (ii) 2-isopropoxy-4,4,5,5-tetramethyl-1,2,3-dioxaborolane, −78 °C, 30 min; (c) aryl triflate **17**, $Pd(PPh_3)_4$, Cs_2CO_3, DMF−H_2O, MW (300W), 140 °C, 10 min, 43% (over 2 steps); (d) AgO, 6 M HNO_3, dioxane, rt, 30 min; (e) CH_2Cl_2, rt, 15 h, 52%.

The synthesis of the precursor to thiaplidiaquinone B was carried out in a similar manner (Scheme 6). The preparation of the boronic ester **30** followed the same method, using commercially available 1,4-dibromo-2,5-dimethoxybenzene as a convenient starting material, with monolithium−halogen exchange to install the geranyl substituent and the ensuing introduction of the boronate by a second lithium−halogen exchange. Using the boronic ester **30** and the same aryl triflate

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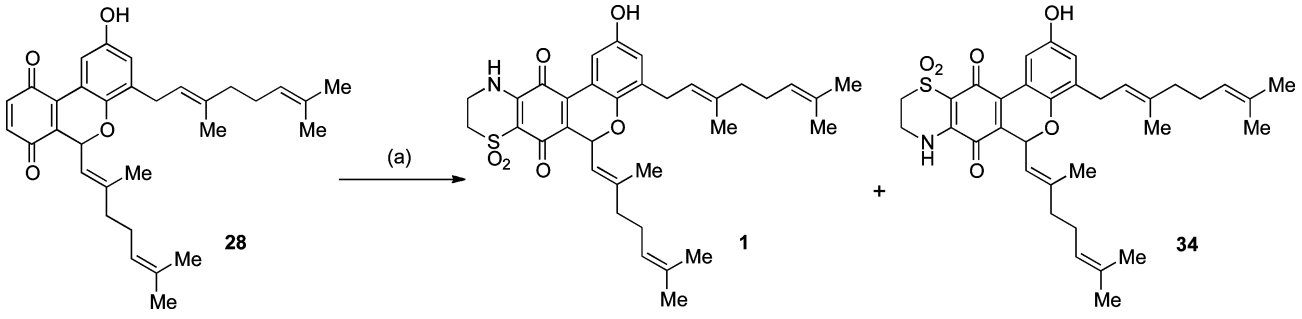
Scheme 7. Synthesis of Thiaplidiaquinone A 1[a]



[a]Reagents and conditions: (a) hypotaurine, salcomine, MeCN−EtOH, rt, 41 h, mixture 40% (14% for **1** and 26% for **34**).

17 we readily synthesized the oxa-6π cyclization precursor for thiaplidiaquinone B. The same Suzuki conditions gave biaryl compound **31** in 43% yield, and subsequent oxidation afforded bis-*p*-quinone **32**. In this case the desired tautomerization-oxa-6π-electrocyclization sequence was even more facile, and occurred spontaneously by leaving quinone **32** stirring in solution with dichloromethane at room temperature for 15 h in an open flask, affording **33** in 52% yield (Scheme 6).

With the two benzo[c]chromene-7,10-diones **28** and **33** in hand, we were ready for the second biomimetic step, the addition of hypotaurine. While, inexplicably, quinone **33** failed to react with hypotaurine under a range of conditions, the addition of hypotaurine to quinone **28** in the presence of a catalytic amount of salcomine in acetonitrile−ethanol at room temperature for 41 h proceeded smoothly, albeit in modest yield to give thiaplidiaquinone A **1** and its regioisomer **34** in a combined yield of 40% yield, thereby achieving the first synthesis of the natural product (Scheme 7).

The formation of both regioisomers in the final addition, while disappointing given the success of model studies (Scheme 3), was not entirely surprising given the reported fickle nature of such reactions.[27,29] The regioisomers **1** and **34** were readily separated by chromatography, and their structures were confirmed by NMR studies. While their ^{1}H NMR spectra were very similar to each other, significant differences were observed in the chemical shift values shown in their ^{13}C NMR spectra. The ^{13}C NMR spectrum of **1** was very similar to that reported in literature for the natural product,[24] while the ^{13}C spectrum of **34** showed very significant differences. Further confirmation came from distinctive long-range couplings that were observed in the HMBC spectrum of **1** between the NH proton at δ 9.11 and the carbonyl resonance at δ 179.0 (C-12), and between the proton at δ 5.95 (at C-6) and the other carbonyl resonance at δ 174.8 (C-7) (see Supporting Information), confirming the structure of this regioisomer as that of the natural product thiaplidiaquinone A.

CONCLUSIONS

In conclusion, a concise total synthesis of the apoptosis-inducing marine metabolite thiaplidiaquinone A has been described. The key ring forming steps are both based on biosynthetic considerations and involve the construction of the central benzo[*c*]chromene quinone unit by an extremely facile oxa-6π-electrocyclic ring closure reaction that occurs under neutral conditions at room temperature, followed by installation of the 1,4-thiazine-dioxide ring by reaction with hypotaurine.

EXPERIMENTAL SECTION

For general experimental details, see the Supporting Information.

1-(2-Trimethylsilylethoxy)methoxy)-2-((tetrahydro-2*H*-pyran-2-yl)oxy)-3-geranyl-4-(methoxymethoxy)benzene 9. To a stirred solution of 1-(2-trimethylsilylethoxy)methoxy)-2-((tetrahydro-2*H*-pyran-2-yl)oxy)-4-(methoxymethoxy)benzene **8**[30] (1.0 g, 2.6 mmol) in anhydrous THF (9 mL) under argon at 0 °C was added *n*-butyllithium (1.6 M; 1.8 mL, 2.9 mmol) dropwise, and the reaction mixture was stirred at this temperature for 45 min. Geranyl bromide (0.54 mL, 2.7 mmol) was added dropwise, and the reaction mixture was stirred at rt for 16 h, diluted with water (120 mL) and extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), concentrated under reduced pressure, and the residue was subjected to flash chromatography using ether and light petroleum (1:9) to yield the title compound as a colorless oil (0.93 g, 69%); (Found: C, 66.8; H, 9.3. $C_{29}H_{48}O_6Si$ requires C, 66.9; H, 9.3%); (Found: M + Na$^+$, 543.3112. $C_{29}H_{48}O_6Si$ + Na$^+$ requires 543.3112); δ_H (400 MHz; $CDCl_3$) 6.93 (1H, d, *J* 9.0), 6.77 (1H, d, *J* 9.0), 5.29−5.23 (2H, m), 5.16 (2H, s), 5.12 (2H, s), 5.12−5.05 (1H, m), 4.14−4.07 (1H, m), 3.83−3.72 (2H, m), 3.58−3.40 (3H, m), 3.47 (3H, s), 2.09−2.02 (2H, m), 2.00−1.88 (5H, m), 1.78 (3H, s), 1.66 (3H, s), 1.64−1.59 (3H, m), 1.58 (3H, s), 1.01−0.95 (2H, m), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 150.8 (C), 146.1 (C), 145.2 (C), 134.5 (C), 131.2 (C), 126.1 (C), 124.4 (CH), 123.1 (CH), 114.6 (CH), 109.7 (CH), 101.7 (CH), 94.9 (CH_2), 94.3 (CH_2), 66.1 (CH_2), 63.5 (CH_2), 55.8 (Me), 39.7 (CH_2), 30.8 (CH_2), 26.7 (CH_2), 25.6 (Me), 25.3 (CH_2), 23.8 (CH_2), 19.7 (CH_2), 18.0 (CH_2), 17.6 (Me), 16.2 (Me), −1.4 (Me); *m*/*z* (ESI) 543 ([M + Na]$^+$, 100%), 538 ([M + Na]$^+$, 9), 227 (10).

3-(Methoxymethoxy)-2-geranyl-6-((2-trimethylsilylethoxy)-methoxy)phenol 10. To a stirred solution of 1-(2-trimethylsilylethoxy)methoxy)-2-((tetrahydro-2*H*-pyran-2-yl)oxy)-3-geranyl-4-(methoxymethoxy)benzene **9** (86 mg, 0.17 mmol) in ethanol (2.0 mL) at room temperature under argon was added hydrochloric acid (1.0 M; 0.33 mL), and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution (30 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), concentrated under reduced pressure, and the residue was subjected to flash chromatography using ether and light petroleum (1:9) to yield the title compound as a colorless oil (70 mg, 97%); (Found: C, 65.8; H, 9.2. $C_{24}H_{40}O_5Si$ requires C, 66.0; H, 9.2%); (Found: M + Na$^+$, 459.2529. $C_{24}H_{40}O_5Si$ + Na$^+$ requires 459.2537); ν_{max} ($CHCl_3$)/cm^{-1} 3541; δ_H (400 MHz; $CDCl_3$) 6.88 (1H, d, *J* 8.9), 6.54 (1H, d, *J* 8.9), 6.21 (1H, s), 5.27 (1H, m), 5.17 (2H, s), 5.14 (2H, s), 5.11−5.05 (1H, m), 3.82−3.76 (2H, m), 3.48 (3H, s), 3.41 (2H, d, *J* 7.0), 2.10−2.03 (2H, m), 2.00−1.95 (2H, m), 1.80 (3H, d, *J* 0.7), 1.66 (3H, d, *J* 0.9), 1.58 (3H, s), 1.03−0.97 (2H, m), 0.03 (9H, s); δ_C (100 MHz; $CDCl_3$) 151.1 (C), 145.4 (C), 140.2 (C), 135.1 (C), 131.2 (C), 124.4 (CH), 122.3 (CH), 118.3 (C), 113.7 (CH), 105.4 (CH), 95.5 (CH_2), 94.9 (CH_2), 66.8 (CH_2), 55.9 (Me), 39.8 (CH_2), 26.7 (CH_2), 25.7 (Me), 22.9 (CH_2), 18.1 (CH_2), 17.6

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(Me), 16.1 (Me), −1.4 (Me); *m*/*z* (ESI) 459 ([M + Na]$^+$, 100%), 454 ([M + NH$_4$]$^+$, 6), 261 (11), 217 (11).

1-(2-Trimethylsilylethoxy)methoxy)-2-methoxy-3-geranyl-4-(methoxymethoxy)benzene 11. To a stirred solution of 3-(methoxymethoxy)-2-geranyl-6-((2-trimethylsilylethoxy)methoxy)-phenol **10** (50 mg, 0.11 mmol) in DMF (1.1 mL) at room temperature under argon was added sodium hydride (60% dispersion in mineral oils; 5 mg, 0.13 mmol), and the reaction mixture was stirred for 30 min. Iodomethane (8 μL, 0.13 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for a further 3.5 h. The reaction mixture was diluted with saturated ammonium chloride solution (30 mL) and extracted with ether (3 × 15 mL). The combined organic extracts were washed with water (2 × 20 mL), brine (30 mL), dried (MgSO$_4$), concentrated under reduced pressure, and the residue was subjected to flash chromatography using ethyl acetate and light petroleum (0:1 to 3:97) to yield the title compound as a colorless oil (49 mg, 95%); (Found: C, 67.0; H, 9.5. $C_{25}H_{42}O_5Si$ requires C, 66.6; H, 9.4%); (Found: M + Na$^+$, 473.2697. $C_{25}H_{42}O_5Si$ + Na$^+$ requires 473.2694); δ_H (400 MHz; $CDCl_3$) 6.95 (1H, d, *J* 9.0), 6.77 (1H, d, *J* 9.0), 5.23−5.18 (1H, m), 5.20 (2H, s), 5.13 (2H, s), 5.10−5.04 (1H, m), 3.82 (3H, s), 3.82−3.77 (2H, m), 3.48 (3H, s), 3.40 (2H, d, *J* 7.0), 2.10−2.01 (2H, m), 2.00−1.94 (2H, m), 1.79 (3H, s), 1.65 (3H, s), 1.58 (3H, s), 1.02−0.95 (2H, m), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 150.6 (C), 148.8 (C), 145.6 (C), 134.7 (C), 131.3 (C), 125.9 (C), 124.4 (CH), 123.0 (CH), 114.7 (CH), 109.8 (CH), 95.0 (CH_2), 94.2 (CH_2), 66.1 (CH_2), 60.8 (Me), 55.9 (Me), 39.8 (CH_2), 26.7 (CH_2), 25.6 (Me), 23.3 (CH_2), 18.1 (CH_2), 17.6 (Me), 16.1 (Me), −1.4 (Me); *m*/*z* (ESI) 473 ([M + Na]$^+$, 100%), 431 (10), 413 (10), 363 (11), 301 (9), 289 (6), 227 (14).

2-Methoxy-3-geranyl-1,4-benzoquinone 12. To a stirred solution of 1-(2-trimethylsilylethoxy)methoxy)-2-methoxy-3-geranyl-4-(methoxymethoxy)benzene **11** (52 mg, 0.12 mmol) in methanol (1.2 mL) at room temperature was added (±)-camphorsulfonic acid (56 mg, 0.24 mmol), and the reaction mixture was stirred for 16.5 h. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution (50 mL) and concentrated under reduced pressure. The aqueous was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts were washed with brine (40 mL), dried (MgSO$_4$), concentrated under reduced pressure, and the residue was dissolved in acetonitrile (6 mL). To a stirred solution of the crude reaction mixture under air was added salcomine (8 mg, 0.023 mmol), and air was bubbled through the solution. The reaction mixture was stirred for 50 min under air and concentrated under reduced pressure. The residue was diluted with water (50 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO$_4$), concentrated under reduced pressure, and the residue was subjected to flash chromatography using ether and light petroleum (1:9) to yield the title compound as a yellow oil (30 mg, 95%); (Found: M + Na$^+$, 297.1462. $C_{17}H_{22}O_3$ + Na$^+$ requires 297.1461); λ_{max} (MeOH)/nm 291 (log ε 3.39); ν_{max} ($CHCl_3$)/cm^{-1} 1670, 1650, 1593; δ_H (400 MHz; $CDCl_3$) 6.68 (1H, d, *J* 10.0), 6.60 (1H, d, *J* 10.0), 5.09−5.02 (2H, m), 4.02 (3H, s), 3.16 (2H, d, *J* 7.3), 2.09−2.02 (2H, m), 2.00−1.94 (2H, m), 1.74 (3H, d, *J* 0.4), 1.66 (3H, d, *J* 0.9), 1.58 (3H, s); δ_C (100 MHz; $CDCl_3$) 187.9 (C), 183.8 (C), 155.3 (C), 137.3 (C), 136.4 (CH), 134.6 (CH), 132.2 (C), 131.4 (C), 124.1 (CH), 119.7 (CH), 60.9 (Me), 39.7 (CH_2), 26.5 (CH_2), 25.7 (Me), 22.3 (CH_2), 17.7 (Me), 16.1 (Me); *m*/*z* (ESI) 297 ([M + Na]$^+$, 100%), 275 ([M + H]$^+$, 7). ^{1}H NMR consistent with the literature.[31]

Iso-aplidinone A 13. To a stirred solution of methoxy-3-geranyl-1,4-benzoquinone **12** (50 mg, 0.18 mmol) in acetonitrile/ethanol (1.8 mL; 1:1) was added a solution of hypotaurine (20 mg, 0.18 mmol) in water (0.6 mL) and salcomine (6 mg, 0.02 mmol), and the reaction mixture was stirred at room temperature for 43 h. The reaction mixture was diluted with water (20 mL) and extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried (MgSO$_4$), concentrated under reduced pressure, and the residue was subjected to preparatory thin-layer chromatography using ethyl acetate and light petroleum (1:1) to yield the title compound as a deep red/orange crystalline solid (22 mg, 32%); mp 86−89 °C; (Found: M + Na$^+$, 402.1353. $C_{19}H_{25}NO_5S$ + Na$^+$ requires 402.1346); λ_{max} (MeOH)/nm 266 (log ε 3.30), 328 (3.61); ν_{max} ($CHCl_3$)/cm^{-1} 3374, 1678, 1627, 1595; δ_H (400 MHz; $CDCl_3$) 6.69 (1H, br. s), 5.09−5.02 (2H, m), 4.07 (2H, td, *J* 6.0, 3.5), 3.91 (3H, s), 3.30 (2H, t, *J* 6.0), 3.22 (2H, d, *J* 7.3), 2.09−2.00 (2H, m), 1.99−1.92 (2H, m), 1.73 (3H, s), 1.66 (3H, s), 1.59 (3H, s); δ_C (100 MHz; $CDCl_3$) 178.2 (C), 176.8 (C), 152.9 (C), 143.0 (C), 138.0 (C), 137.2 (C), 131.5 (C), 124.1 (CH), 119.0 (CH), 110.0 (C), 60.8 (Me), 48.9 (CH_2), 39.9 (CH_2), 39.7 (CH_2), 26.6 (CH_2), 25.7 (Me), 22.9 (CH_2), 17.7 (Me), 16.2 (Me); *m*/*z* (ESI) 402 ([M + Na]$^+$, 100%), 249 (6), 173 (6).

2,5-Dimethoxyphenol 14. To a solution of 2,5-dimethoxybenzaldehyde (2.0 g, 12.0 mmol) in dichloromethane (80 mL) was added at 0 °C in small portions *m*-chloroperbenzoic acid (3.5 g, 20.3 mmol), and the reaction mixture was stirred at room temperature for 18 h. The organic solution was extracted with aqueous saturated sodium hydrogen carbonate solution (3 × 40 mL) and then with aqueous saturated sodium thiosulfate solution (3 × 40 mL). The dichloromethane layer was dried (MgSO$_4$), filtered and concentrated in vacuo to give a dark yellow oil that was dissolved in methanol (30 mL) and stirred with acqueous sodium hydroxide solution (2 M; 12.0 mL, 24 mmol) for 3 h. Then, the reaction mixture was acidified with hydrochloric acid (6 M) and extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, dried (MgSO$_4$), filtered and concentrated under reduced pressure. Column chromatography of the residue eluting with dichloromethane and light petroleum (6:4) gave the title compound as an oil (1.46 g, 79%); (lit.,[32] colorless oil); (Found: M + Na$^+$, 177.0517. $C_8H_{10}O_3$ + Na$^+$ requires 177.0522); ν_{max} ($CHCl_3$)/cm^{-1} 3539; δ_H (400 MHz; $CDCl_3$) 6.80 (1H, d, *J* 8.9), 6.62 (1H, d, *J* 3.0), 6.42 (1H, dd, *J* 8.9, 3.0), 5.97 (1H, s), 3.84 (3H, s), 3.78 (3H, s); δ_C (100 MHz; $CDCl_3$) 154.6 (C), 146.5 (C), 141.1 (C), 111.7 (CH), 104.3 (CH), 101.9 (CH), 56.6 (Me), 55.6 (Me); *m*/*z* (ESI) 177 (M + Na$^+$, 100%).

2-(2,5-Dimethoxyphenoxy)tetrahydro-2*H*-pyran 15. To a stirred solution of 2,5-dimethoxyphenol **14** (0.32 g, 2.08 mmol) and tetrahydro-2*H*-pyran-2-ol (0.32 g, 3.10 mmol) in anhydrous tetrahydrofuran (20 mL) under an argon atmosphere at 0 °C was added 1,1′-(azodicarbonyl)dipiperidine (1.0 g, 4.14 mmol) and tri-*n*-butylphosphine (1.0 mL, 4.14 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred for 18 h. After, the mixture was diluted with ether (30 mL), filtered, and the filtrate was concentrated under reduced pressure. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:9) gave the title compound as an oil (0.49 g, 99%); (lit.,[32] colorless oil); (Found: M + Na$^+$, 261.1096. $C_{13}H_{18}O_4$ + Na$^+$ requires 261.1097); ν_{max} ($CHCl_3$)/cm^{-1} 1610, 1595; δ_H (400 MHz; $CDCl_3$) 6.84 (1H, d, *J* 8.8), 6.81 (1H, d, *J* 2.9), 6.51 (1H, dd, *J* 8.8, 2.9), 5.41 (1H, t, *J* 3.2), 4.04−3.98 (1H, m), 3.83 (3H, s), 3.77 (3H, s), 3.65−3.60 (1H, m), 2.11−1.86 (3H, m), 1.72−1.61 (3H, m); δ_C (100 MHz; $CDCl_3$) 154.3 (C), 147.3 (C), 144.6 (C), 113.7 (CH), 105.8 (CH), 105.5 (CH), 97.6 (CH), 62.2 (CH_2), 57.1 (Me), 55.7 (Me), 30.4 (CH_2), 25.2 (CH_2), 18.9 (CH_2); *m*/*z* (ESI) 261 (M + Na$^+$, 100%).

2-Geranyl-3,6-dimethoxyphenol 16. A solution of *n*-butyllithium in hexane (2.5 M; 1.0 mL, 2.52 mmol) was added dropwise at 0 °C to a solution of 2-(2,5-dimethoxyphenoxy)tetrahydro-2*H*-pyran **15** (0.30 g, 1.26 mmol) in dry tetrahydrofuran (10 mL) under an argon atmosphere. The reaction mixture was stirred at room temperature for 30 min, and then geranyl bromide (0.30 mL, 1.50 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 18 h, quenched with a saturated aqueous ammonium chloride solution (10 mL), extracted with ethyl acetate (3 × 10 mL), dried (MgSO$_4$), filtered and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane and light petroleum (3:7) gave the title compound as a colorless oil (0.21 g, 57%); (Found: M + Na$^+$, 313.1781. $C_{18}H_{26}O_3$ + Na$^+$ requires 313.1780); ν_{max} ($CHCl_3$)/cm^{-1} 3539; δ_H (400 MHz; $CDCl_3$) 6.68 (1H, d, *J* 8.8), 6.37 (1H, d, *J* 8.8), 5.75 (1H, s), 5.27−5.30 (1H, m), 5.12−5.09 (1H, m), 3.87 (3H, s), 3.80 (3H, s), 3.42 (2H, d, *J* 7.1), 2.12−1.98 (4H, m), 1.82 (3H, s), 1.68 (3H, s), 1.61 (3H, s); δ_C (100 MHz; $CDCl_3$) 152.6 (C), 144.3 (C), 141.2 (C), 135.2 (C), 131.2 (C), 124.5 (CH), 122.3 (CH), 177.0 (C), 107.8 (CH), 101.1 (CH), 56.4

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(Me), 56.0 (Me), 39.8 (CH_2), 26.8 (CH_2), 25.7 (Me), 22.5 (CH_2), 17.7 (Me), 16.1 (Me); *m/z* (ESI) 313 (M + Na^+, 100%).

2-Geranyl-3,6-dimethoxyphenyl trifluoromethanesulfonate 17. To a stirred solution of 2-geranyl-3,6-dimethoxyphenol **16** (0.41 g, 1.41 mmol) in dry dichloromethane (7 mL) at −78 °C under an argon atmosphere was added triethylamine (0.40 mL, 2.79 mmol) and trifluoromethanesulfonic anhydride (0.33 mL, 1.97 mmol) dropwise, and the reaction mixture was stirred at −78 °C for 30 min. The reaction mixture was diluted with saturated ammonium chloride solution (10 mL), extracted with ethyl acetate (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane and light petroleum (4:6) gave the title compound as a colorless oil (0.48 g, 81%); (Found: M + Na^+, 445.1274. $C_{19}H_{25}F_3O_5S$ + Na^+ requires 445.1267); δ_H (400 MHz; $CDCl_3$) 6.84 (1H, d, *J* 9.0), 6.81 (1H, d, *J* 9.0), 5.16−5.13 (1H, m), 5.05−5.10 (1H, m), 3.86 (3H, s), 3.83 (3H, s), 3.45 (2H, d, *J* 6.9), 2.10−1.97 (4H, m), 1.76 (3H, s), 1.67 (3H, s), 1.59 (3H, s); δ_C (100 MHz; $CDCl_3$) 152.0 (C), 145.3 (C), 137.8 (C), 136.4 (C), 131.3 (C), 125.5 (C), 124.2 (CH), 120.6 (CH), 118.7 (q, *J* 320, CF_3), 110.0 (CH), 109.9 (CH), 56.3 (Me), 56.2 (Me), 39.7 (CH_2), 26.6 (CH_2), 25.6 (Me), 23.6 (CH_2), 17.6 (Me), 16.1 (Me); *m/z* (ESI) 445 (M + Na^+, 100%).

2-Geranyl-3,6,2′,5′-tetramethoxybiphenyl 18. To a degassed solution of 2-geranyl-3,6-dimethoxyphenyl trifluoromethanesulfonate **17** (10 mg, 0.024 mmol) and 2,5-dimethoxybenzeneboronic acid (5.46 mg, 0.03 mmol) in a sealed tube in dimethylformamide and water (0.15 mL, 9:1) was added tetrakis(triphenylphosphine)palladium(0) (5.55 mg, 20 mol %). The mixture was thoroughly degassed with argon under sonication, and cesium carbonate (25.4 mg, 0.072 mmol) was added. The sealed tube was subject to microwave irradiation (300 W) at 140 °C for 10 min. After cooling, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:9) gave the title compound as a colorless oil (7.9 mg, 80%); (Found: M + Na^+, 433.2352. $C_{26}H_{34}O_4$ + Na^+ requires 433.2349); δ_H (400 MHz; DMSO-*d*) 6.95−6.88 (3H, m), 6.84 (1H, d, *J* 8.9), 6.71 (1H, d, *J* 2.9), 5.08−5.11 (2H, m) 3.87 (3H, s), 3.79 (3H, s), 3.72 (3H, s), 3.71 (3H, s), 3.25 (1H, dd, *J* 14.2, 6.1), 3.09 (1H, dd, *J* 14.2, 6.1), 2.06−1.89 (4H, m), 1.70 (3H, s), 1.62 (3H, s), 1.37 (3H, s); δ_C (100 MHz; DMSO-*d*) 153.3 (C), 152.0 (C), 151.6 (C), 151.5 (C), 134.1 (C), 131.1 (C), 130.6 (C), 128.8 (C), 127.3 (C), 124.6 (CH), 122.8 (CH), 117.3 (CH), 113.3 (CH), 112.1 (CH), 110.1 (CH), 109.1 (CH), 56.5 (Me), 56.3 (Me), 56.0 (Me), 55.6 (Me), 39.9 (CH_2), 26.8 (2 × CH_2), 25.7 (Me), 17.7 (Me), 15.7 (Me); *m/z* (ESI) 433 (M + Na^+, 100%).

6-(2,6-Dimethylhepta-1,5-dienyl)-2-hydroxy-6*H*-benzo[*c*]-chromene-7,10-dione 20. (a) Nitric acid (6 M; 0.08 mL) was added at room temperature to a mixture of 2-geranyl-3,6,2′,5′-tetramethoxybiphenyl **18** (32.8 mg, 0.08 mmol), silver(II) oxide (79 mg, 0.64 mmol) and 1,4-dioxane (2 mL), and the mixture was stirred for 30 min. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was quickly purified by chromatography using ethyl acetate and light petroleum (1:9) as an eluent to give 3-geranyl-2,2′-bis-*p*-benzoquinone **19** immediately used for the next step. This compound could not be characterized because it readily cyclizes to 6-(2,6-dimethylhepta-1,5-dienyl)-2-hydroxy-6*H*-benzo[*c*]chromene-7,10-dione **20**, simply on standing in solution.

(b) To a solution of 3-geranyl-2,2′-bis-*p*-benzoquinone **19** (30 mg, 0.086 mmol) in dichloromethane (4.6 mL) at 0 °C was added triethylamine (0.06 mL, 0.43 mmol), and the mixture was stirred at room temperature for 1 h. The resulting dark red mixture was concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:9) gave the title compound as a purple oil (22.0 mg, 73%); (Found: M + Na^+, 373.1406. $C_{22}H_{22}O_4$ + Na^+ requires 373.1410); ν_{max} ($CHCl_3$)/cm^{-1} 1641, 1600; δ_H (400 MHz; DMSO-*d*) 9.26 (1H, s), 7.68 (1 H, s), 6.88−6.75 (4H, m), 5.90−5.87 (1H, m), 5.28 (1H, d, *J* 9.3), 4.88−4.85 (1H, m), 1.97−1.93 (4H, m), 1.86 (3H, s), 1.53 (3H s), 1.45 (3H, s); δ_C (100 MHz; DMSO-*d*) 187.0 (C), 185.3 (C), 152.2 (C), 147.4 (C), 143.2 (C), 137.9 (CH), 135.9 (CH), 134.5 (C), 131.4 (C), 130.2 (C), 123.9 (CH), 119.9 (CH), 118.9 (CH), 118.4 (CH), 118.0 (C), 115.1 (CH), 67.0 (CH), 39.3 (CH_2), 25.9 (CH_2), 25.8 (Me), 17.9 (Me), 17.3 (Me); *m/z* (ESI) 373 (M + Na^+, 100%).

2,6-Dibromo-4-methoxyphenol 21. To a stirred solution of 4-methoxyphenol (1.21 g, 9.75 mmol) in a mixture of dichloromethane (97.5 mL) and methanol (39.0 mL) at room temperature was added benzyltrimethylammonium tribromide (7.60 g, 19.5 mmol). The reaction mixture was stirred for 18 h and then concentrated in vacuo. Column chromatography of the residue eluting with dichloromethane and light petroleum (3:7) gave the title compound as a colorless solid: (2.2 g, 80%); mp 90−91 °C (lit.,[40] mp 89−90 °C); ν_{max} ($CHCl_3$)/cm^{-1} 3698; δ_H (400 MHz; $CDCl_3$) 7.05 (2H, s), 5.50 (1H, s), 3.77 (3H, s); δ_C (100 MHz; $CDCl_3$) 153.7 (C), 143.8 (C), 117.8 (CH), 109.7 (C), 56.1 (Me).

1,3-Dibromo-5-methoxy-2-(methoxymethoxy)benzene 22. To a stirred solution of 2,6-dibromo-4-methoxyphenol **21** (0.20 g, 0.71 mmol) and chloromethyl ether (0.53 mL, 7.0 mmol) in dry acetone (3 mL) was added a solution of 1,8-diazabicyclo[5.4.0]-undecen-7-ene (0.5 mL, 3.56 mmol) dropwise during 30 min. After the addition, the reaction mixture was acidified with 2 M hydrochloric acid and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Column chromatography of the residue eluting with dichloromethane and light petroleum (3:7) gave the title compound as an oil: (0.17 g, 73%); (Found: M + Na^+, 346.8877. $C_9H_{10}{}^{79}Br_2O_3$ + Na^+ requires 346.8889); δ_H (400 MHz; $CDCl_3$) 7.10 (2H, s), 5.12 (2H, s), 3.79 (3H, s), 3.74 (3H, s); δ_C (100 MHz; δ) 156.6 (C), 145.2 (C), 118.4 (C), 118.3 (CH), 99.6 (CH_2), 58.5 (Me), 56.0 (Me). *m/z* (ESI) 346 (M + Na^+, 51.2%), 348 (M + Na^+, 100%), 350 (M + Na^+, 48.7%),

1-Bromo-3-geranyl-5-methoxy-2-(methoxymethoxy)-benzene 23. To a stirred solution of 1,3-dibromo-5-methoxy-2-(methoxymethoxy)benzene **22** (0.25 g, 0.77 mmol) in dry tetrahydrofuran (10 mL) at −78 °C under an argon atmosphere was added dropwise a solution of *n*-butyllithium in hexane (2.7 M; 0.30 mL, 0.81 mmol), and the reaction was stirred at −78 °C for 1 h, then copper(I) bromide dimethylsulfide complex (0.17 g, 0.83 mmol) was added. After stirring at −78 °C for 1 h, geranyl bromide (0.16 mL, 1.10 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was diluted with saturated ammonium chloride solution (10 mL), extracted with ethyl acetate (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography of the residue eluting with dichloromethane and light petroleum (4:6) gave the title compound as a colorless oil (0.16 g, 54%); (Found: M + Na^+, 405.1035. $C_{19}H_{27}{}^{79}BrO_3$ + Na^+ requires 405.1036); δ_H (400 MHz; $CDCl_3$) 6.96 (1H, d, *J* 3.0), 6.71 (1H, d, *J* 3.0), 5.33−5.29 (1H, m), 5.05−5.05 (2H, s), 5.14−5.10 (1H, m), 3.77 (3H, s), 3.67 (3H, s), 3.46 (2H, d, *J* 7.1), 2.17−2.07 (4H, m), 1.72 (3H, s), 1.71 (3H, s), 1.63 (3H, s); δ_C (100 MHz; $CDCl_3$) 156.4 (C), 146.4 (C), 137.8 (C), 137.3 (C), 131.6 (C), 124.1 (CH), 121.8 (CH), 117.4 (C), 115.4 (CH), 115.1 (CH), 99.9 (CH_2), 57.8 (Me), 55.6 (Me), 39.7 (CH_2), 29.0 (CH_2), 26.6 (CH_2), 25.7 (Me), 17.7 (Me), 16.2 (Me); *m/z* (ESI) 405 (M + Na^+, 100%), 407 (M + Na^+, 97.5%).

2′,3-Digeranyl-5,3′,6′-trimethoxy-2-(methoxymethoxy)-biphenyl 25. (a) To a stirred solution of 1-bromo-3-geranyl-5-methoxy-2-(methoxymethoxy)benzene **23** (11.5 mg, 0.03 mmol) in anhydrous tetrahydrofuran (4 mL) under an argon atmosphere at −78 °C was added *n*-butyllithium (1.6 M; 0.02 mL, 0.033 mmol) dropwise, and the reaction mixture was stirred at this temperature for 30 min. 2-Isopropoxy-4,4,5,5-tetramethyl-1,2,3-dioxaborolane (6.73 μL, 0.033 mmol) was added dropwise, and the reaction mixture was stirred for 30 min at −78 °C. The mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude 2-[3-geranyl-5-methoxy-2-(methoxymethoxy)phenyl]-4,4,5,5-

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tetramethyl-[1,3,2]dioxaborolane **24** was used in the next step without purification.

(b) To a degassed solution of 2-geranyl-3,6-dimethoxyphenyl trifluoromethanesulfonate **17** (10 mg, 0.024 mmol) and the crude 2-[3-geranyl-5-methoxy-2-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane **24** (0.03 mmol) in a sealed tube in dimethylformamide and water (0.15 mL, 9:1) was added tetrakis-(triphenylphosphine)palladium(0) (5.55 mg, 20 mol %). The mixture was thoroughly degassed with argon under sonication, and cesium carbonate (25.4 mg, 0.072 mmol) was added. The sealed tube was subject to microwave irradiation (300 W) at 140 °C for 10 min. After cooling, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:9) gave the title compound as a colorless oil (5.7 mg, 41%); (Found: M + Na^+, 599.3706. $C_{37}H_{52}O_5$ + Na^+ requires 599.3707); δ_H (400 MHz; $CDCl_3$) 6.87 (1 H, d, *J* 8.9), 6.79 (1H, d, *J* 8.9), 6.77 (1H, d, *J* 3.2), 6.51 (1H, d, *J* 3.2), 5.38−5.42 (1H, m), 5.18−5.06 (3H, m), 4.64 (1H, d, *J* 5.2), 4.53 (1H, d, *J* 5.2), 3.85 (3H, s), 3.75 (3H, s), 3.72 (3H, s), 3.42−3.54 (2H, m), 3.38 (1H, dd, *J* 14.2, 6.1), 3.12 (3H, s), 2.99 (1H, dd, *J* 14.2, 6.1), 2.19−2.39 (8H, m), 1.75 (3H, s), 1.72 (3H, s), 1.67 (3H, s), 1.65 (3H, s), 1.59 (3H s), 1.33 (3H, s); δ_C (100 MHz; $CDCl_3$) 155.4 (C), 152.0 (C), 151.5 (C), 146.6 (C), 136.5 (C), 136.0 (C), 134.3 (C), 131.5 (C), 131.4 (C), 131.1 (C), 131.0 (C), 129.2 (C), 124.6 (CH), 124.3 (CH), 122.7 (CH), 122.6 (CH), 114.8 (CH), 114.1 (CH), 110.3 (CH), 108.6 (CH), 98.8 (CH_2), 56.6 (Me), 56.2 (Me), 56.1 (Me), 55.3 (Me), 39.9 (CH_2), 39.8 (CH_2), 28.6 (CH_2), 27.0 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 25.7 (Me), 25.6 (Me), 17.7 (Me), 17.6 (Me), 16.2 (Me), 15.7 (Me); *m*/*z* (ESI) 599 (M + Na^+, 100%).

2′,3-Digeranyl-5,3′,6′-trimethoxy-biphenyl-2-ol 26. To a stirred solution of 2′,3-digeranyl-5,3′,6′-trimethoxy-2-(methoxymethoxy)biphenyl **25** (60 mg, 0.10 mmol) in methanol (1 mL), at room temperature was added camphorsulforic acid (35 mg, 0.15 mmol), and the reaction mixture was stirred at room temperature for 18 h. Then, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the title compound as a colorless oil (46 mg, 86%); (Found: M + Na^+, 555.3458. $C_{35}H_{48}O_4$ + Na^+ requires 555.3445); ν_{max} ($CHCl_3$)/cm^{-1} 3550; δ_H (400 MHz; $CDCl_3$) 6.93 (1 H, d, *J* 8.9), 6.85 (1H, d, *J* 8.9), 6.76 (1H, d, *J* 3.1), 6.51 (1H, d, *J* 3.1), 5.40−5.44 (1H, m), 5.18−5.05 (3H, m), 4.56 (1H, s), 3.87 (3H, s), 3.75 (3H, s), 3.72 (3H, s), 3.43−3.40 (2H, m), 3.25 (1H, dd, *J* 14.0, 7.0), 3.11 (1H, dd, *J* 14.0, 7.0), 2.19−1.88 (8H, m), 1.75 (3H, s), 1.72 (3H, s), 1.68 (3H, s), 1.64 (3H, s), 1.60 (3H s), 1.34 (3H, s); δ_C (100 MHz; $CDCl_3$) 152.9 (C), 152.5 (C), 151.5 (C), 145.3 (C), 136.7 (C), 135.0 (C), 131.9 (C), 131.5 (C), 131.2 (C), 129.0 (C), 126.4 (C), 124.5 (CH), 124.3 (CH), 123.8 (C), 122.3 (CH), 122.1 (CH), 115.2 (CH), 112.9 (CH), 111.0 (CH), 109.2 (CH), 56.4 (Me), 56.1 (Me), 55.5 (Me), 39.8 (2 × CH_2), 28.7 (CH_2), 26.8 (CH_2), 26.7 (2 × CH_2), 25.7 (Me), 25.6 (Me), 17.7 (Me), 17.6 (Me), 16.2 (Me), 15.7 (Me); *m*/*z* (ESI) 555 (M + Na^+, 100%).

4-Geranyl-6-(2,6-dimethylhepta-1,5-dienyl)-2-hydroxy-6*H*-benzo[*c*]chromene-7,10-dione 28. (a) Nitric acid (6 M; 0.08 mL) was added at room temperature to a mixture of 2′,3-digeranyl-5,3′,6′-trimethoxy-biphenyl-2-ol **26** (40 mg, 0.08 mmol), silver(II) oxide (79 mg, 0.64 mmol) and 1,4 dioxane (2 mL), and the mixture was stirred for 30 min. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was quickly purified by chromatography using ethyl acetate and light petroleum (1:9) as an eluent to give 3,6′-digeranyl-2,2′-*p*-benzoquinone **27** (ca. 40 mg), immediately used for the next step. This compound could not be characterized because it readily cyclizes to 4-geranyl-6-(2,6-dimethylhepta-1,5-dienyl)-2-hydroxy-6*H*-benzo[*c*]-chromene-7,10-dione **28**, simply on standing in solution.

(b) A solution of 3,6′-gigeranyl-2,2′-*p*-benzoquinone **27** (10 mg, 0.021 mmol, one-quarter of the material from the previous step) in dichloromethane (2 mL) was stirred at room temperature for 24 h. The resulting dark brown mixture was concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:9) gave the title compound as a dark brown oil (5.3 mg, 52%); (Found: M + Na^+, 509.2665. $C_{32}H_{38}O_4$ + Na^+ requires 509.2662); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3603, 3048, 1653, 1602; δ_H (500 MHz; DMSO-*d*) 9.16 (1H, s), 7.49 (1 H, d, *J* 2.7), 6.88 (2H, s), 6.65 (1H, d, *J* 2.7), 5.91 (1H, d, *J* 9.3), 5.26 (1H, d, *J* 9.3), 5.18 (1H, t, *J* 7.2), 5.07−5.04 (1H, m), 4.92−4.86 (1H, m), 3.20−3.09 (2H, m), 2.05−1.92 (8H, m), 1.88 (3H, s), 1.64 (3H, s), 1.62 (3H, s), 1.55 (3H, s), 1.53 (3H s), 1.45 (3H, s); δ_C (125 MHz; DMSO-*d*) 187.1 (C), 185.4 (C), 151.7 (C), 145.2 (C), 143.5 (C), 137.9 (CH), 135.8 (CH), 134.6 (C), 131.4 (C), 131.3 (C), 131.2 (C), 130.6 (C), 124.5 (CH), 123.8 (CH), 122.4 (CH), 120.1 (CH), 119.3 (CH), 117.9 (C), 112.8 (CH), 66.8 (CH), 79.7 (C), 39.7 (CH_2), 39.3 (CH_2), 28.3 (CH_2), 26.6 (CH_2), 26.0 (CH_2), 25.9 (Me), 25.8 (Me), 18.0 (Me), 17.9 (Me), 17.3 (Me), 16.3 (Me); *m*/*z* (ESI) 509 (M + Na^+, 100%).

1-Bromo-4-geranyl-2,5-dimethoxybenzene 29. To a stirred solution of 1,4-dibromo-2,5-dimethoxybenzene (0.30 g, 1.0 mmol) in dry tetrahydrofuran (13 mL) at −78 °C under an argon atmosphere was added dropwise a solution of *n*-butyllithium in hexane (1.6 M; 0.63 mL, 1.0 mmol), copper(I) bromide dimethylsulfide complex (0.21 g, 1.0 mmol) and a solution of geranyl bromide (0.10 mL, 0.50 mmol) in tetrahydrofuran (2 mL). The reaction mixture was stirred at −78 °C for 1 h, and then the mixure was gradually warmed to 0 °C and stirred at this temperature for 1 h. The reaction mixture was diluted with saturated ammonium chloride solution (10 mL), extracted with ethyl acetate (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography of the residue eluting with dichloromethane and light petroleum (2:8) gave the title compound as a colorless oil (0.22 g, 60%); (lit.,[41] oil) (Found: M + Na^+, 375.0927. $C_{18}H_{25}{}^{79}BrO_2$ + Na^+ requires 375.0930); δ_H (400 MHz; $CDCl_3$) 7.04 (1H, s), 6.78 (1H, s), 5.33−5.29 (1H, m), 5.12−5.16 (1H, m), 3.86 (3H, s), 3.81 (3H, s), 3.31 (2H, d, *J* 7.1), 2.16−2.07 (4H, m), 1.73 (3H, s), 1.70 (3H, s), 1.63 (3H, s); δ_C (100 MHz; $CDCl_3$) 151.8 (C), 150.0 (C), 137.0 (C), 131.5 (C), 130.5 (C), 124.2 (CH), 121.7 (CH), 108.3 (C), 115.7 (CH), 114.0 (CH), 57.0 (Me), 56.2 (Me), 39.8 (CH_2), 28.2 (CH_2), 26.8 (CH_2), 25.7 (Me), 17.7 (Me), 16.1 (Me); *m*/*z* (ESI) 375 (M + Na^+, 100%), 377 (M + Na^+, 99%).

2,4′-Digeranyl-3,6-2′,5′-tetramethoxybiphenyl 31. (a) To a stirred solution of 1-bromo-4-geranyl-2,5-dimethoxybenzene **29** (10.6 mg, 0.03 mmol) in anhydrous tetrahydrofuran (4 mL) under an argon atmosphere at −78 °C was added *n*-butyllithium (1.6 M; 0.02 mL, 0.033 mmol) dropwise, and the reaction mixture was stirred for 30 min. 2-Isopropoxy-4,4,5,5-tetramethyl-1,2,3-dioxaborolane (6.73 μL, 0.033 mmol) was added dropwise, and the reaction mixture was stirred for 30 min at −78 °C. The mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude 2-(4-geranyl-2,5-dimethoxyphenyl)-4,4,5,5-tetramethyl[1,3,2]-dioxaborolane **30** was used in the next step without purification.

(b) To a degassed solution of 2-geranyl-3,6-dimethoxyphenyl trifluoromethanesulfonate **17** (10 mg, 0.024 mmol) and the crude 2-(4-geranyl-2,5-dimethoxyphenyl)-4,4,5,5-tetramethyl[1,3,2]-dioxaborolane **30** (0.03 mmol) in a sealed tube in dimethylformamide and water (0.15 mL, 9:1) was added tetrakis(triphenylphosphine)-palladium(0) (5.55 mg, 20 mol %). The mixture was thoroughly degassed with argon under sonication and cesium carbonate (25.4 mg, 0.072 mmol) was added. The sealed tube was subject to microwave irradiation (300 W) at 140 °C for 10 min. After cooling, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:9) gave the title compound as a colorless oil (5.6 mg, 43%); (Found: M + Na^+, 569.3600. $C_{36}H_{50}O_4$ + Na^+ requires 569.3601); δ_H

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(400 MHz; $CDCl_3$) 6.89 (1 H, d, *J* 8.9), 6.85−6.83 (2H, m), 6.62 (1H, s), 5.44−5.40 (1H, m), 5.21−5.08 (3H, m), 3.87 (3H, s), 3.77 (3H, s), 3.72 (3H, s), 3.71 (3H, s), 3.48−3.35 (2H, m), 3.25 (1H, dd, *J* 14.0, 6.0), 3.06 (1H, dd, *J* 14.0, 6.0), 2.22−1.89 (8H, m), 1.79 (3H, s), 1.73 (3H, s), 1.70 (3H, s), 1.67 (3H, s), 1.61 (3H s), 1.35 (3H, s); δ_C (100 MHz; $CDCl_3$) 152.0 (C), 151.7 (C), 151.1 (C), 151.0 (C), 136.2 (C), 134.0 (C), 131.4 (C), 131.1 (C), 130.8 (C), 129.7 (C), 129.1 (C), 124.6 (CH), 124.4 (CH), 124.3 (C), 123.0 (CH), 122.6 (CH), 114.2 (CH), 113.3 (CH), 110.0 (CH), 109.6 (CH), 56.5 (Me), 56.4 (Me), 56.0 (Me), 55.9 (Me), 39.9 (CH_2), 39.8 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 25.8 (Me), 25.7 (Me), 17.7 (Me), 17.6 (Me), 16.2 (Me), 15.7 (Me); *m*/*z* (ESI) 569 (M + Na^+, 100%).

3-Geranyl-6-(2,6-dimethylhepta-1,5-dienyl)-2-hydroxy-6*H*-benzo[*c*]chromene-7,10-dione 33. (a) Nitric acid (6 M; 0.08 mL) was added at room temperature to a mixture of 2,4′-digeranyl-3,6-2′,5′-tetramethoxybiphenyl **31** (44 mg, 0.08 mmol), silver(II) oxide (79 mg, 0.64 mmol) and 1,4-dioxane (2 mL), and the mixture was stirred for 30 min. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The obtained residue was quickly purified by chromatography using ethyl acetate and light petroleum (1:9) as an eluent to give 3,5′-digeranyl-2,2′-bis-*p*-benzoquinone **32**, immediately used for the next step. This compound could not be characterized because it readily cyclizes to 3-geranyl-6-(2,6-dimethylhepta-1,5-dienyl)-2-hydroxy-6*H*-benzo[*c*]chromene-7,10-dione **33**, simply on standing in solution.

(b) A solution of 3,5′-digeranyl-2,2′-bis-*p*-benzoquinone **32** (10 mg, 0.021 mmol, from the above crude material) in dichloromethane (2 mL) was stirred at room temperature for 15 h. The resulting dark brown mixture was concentrated in vacuo. Column chromatography of the residue eluting with ethyl acetate and light petroleum (1:9) gave the title compound as a dark brown oil (5.3 mg, 52%); (Found: M + Na^+, 509.2665. $C_{32}H_{38}O_4$ + Na^+ requires 509.2662); λ_{max} (MeOH)/nm 269 (log ε 3.4), 315 (3.67), 403 (3.29); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3602, 1650, 1600; δ_H (500 MHz; DMSO-*d*) 9.31 (1H, s), 7.72 (1 H, s), 6.86 (2H, s), 6.59 (1H, s), 5.85 (1H, d, *J* 9.5), 5.32−5.24 (2H, m), 5.09−5.07 (1H, m), 5.04−4.86 (1H, m), 3.21 (2H, d, *J* 7.2), 2.09−1.90 (8H, m), 1.84 (3H, s), 1.64 (3H, s), 1.63 (3H, s), 1.55 (3H, s), 1.52 (3H s), 1.45 (3H, s); δ_C (125 MHz; DMSO-*d*) 187.3 (C), 185.3 (C), 150.1 (C), 147.7 (C), 142.9 (C), 137.7 (CH), 136.5 (C), 135.9 (CH), 133.6 (C), 133.2 (C), 131.4 (C), 131.3 (C), 130.2 (C), 124.5 (CH), 123.9 (CH), 121.8 (CH), 119.2 (CH), 117.8 (CH), 115.4 (CH), 114.2 (C), 67.0 (CH), 39.7 (CH_2), 39.3 (CH_2), 28.4 (CH_2), 26.5 (CH_2), 25.9 (CH_2), 25.9 (Me), 25.8 (Me), 18.0 (Me), 17.9 (Me), 17.2 (Me), 16.3 (Me); *m*/*z* (ESI) 509 (M + Na^+, 100%).

Thiaplidiaquinone A 1. To a stirred solution of 4-geranyl-6-(2,6-dimethyl-hepta-1,5-dienyl)-2-hydroxy-6*H*-benzo[*c*]chromene-7,10-dione **28** (10 mg, 0.0205 mmol) in acetonitrile/ethanol (0.40 mL, 1:1) was added a solution of hypotaurine (2.9 mg, 0.0266 mmol) in water (0.1 mL) and salcomine (0.9 mg, 0.0028 mmol), and the reaction mixture was stirred at room temperature for 41 h, diluted with water (3 mL), extracted with ethyl acetate (3 × 5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography of the residue eluting with ethyl acetate and light petroleum (30:20 to 45:5) gave (i) the regioisomer **34** as a black oil (3.2 mg, 26%) and (ii) thiaplidiaquinone A **1** as a red oil (1.7 mg, 14%).

Regioisomer ***34***. (Found: M + Na^+, 614.2552. $C_{34}H_{41}N_1O_6S_1$ + Na^+ requires 614.2547); ν_{max} ($CHCl_3$)/cm^{-1} 3668, 1627; δ_H (500 MHz; DMSO-*d*) 9.19 (1H, s), 9.07 (1H, br s), 7.58 (1H, d, *J* 3.0), 6.68 (1H, d, *J* 3.0), 5.92 (1H, d, *J* 9.3), 5.26 (1H, d, *J* 9.3), 5.18 (1H, t, *J* 7.1), 5.06 (1H, t, *J* 6.8), 4.89 (1H, t, *J* 7.1), 3.85−3.75 (2H, m), 3.20−3.09 (2H, m), 2.04−1.90 (10H, m), 1.88 (3H, s), 1.64 (3H, s), 1.63 (3H, s), 1.55 (3H, s), 1.46 (3H, s); δ_C (125 MHz; DMSO-*d*) 178.0 (C), 176.8 (C), 151.8 (C), 146.3 (C), 145.3 (C), 143.5 (C), 135.9 (C), 132.7 (C), 132.2 (C), 131.4 (C), 131.3 (C), 127.9 (C), 124.4 (CH), 123.9 (CH), 122.3 (CH), 121.0 (CH), 119.0 (CH), 118.3 (C), 113.8 (CH), 111.0 (C), 66.9 (CH), 48.7 (CH_2), 39.9, (CH_2) 39.7 (CH_2), 39.3 (CH_2), 28.3 (CH_2), 26.6 (CH_2), 26.1 (CH_2), 26.0 (Me), 25.8 (Me), 18.0 (Me), 17.9 (Me), 17.3 (Me), 16.3 (Me); *m*/*z* (ESI) 614 (M + Na^+, 100%).

Thiapliaquinone A ***1***. (Found: M + Na^+, 614.2571. $C_{34}H_{41}N_1O_6S_1$ + Na^+ requires 614.2547); ν_{max} ($CHCl_3$)/cm^{-1} 3668, 1628; δ_H (500 MHz; DMSO-*d*) 9.15 (1H, s), 9.11 (1H, br s), 7.44 (1H, d, *J* 3.0), 6.62 (1H, d, *J* 3.0), 5.95 (1H, d, *J* 9.3), 5.23 (1H, d, *J* 9.3), 5.18 (1H, t, *J* 6.9), 5.04−5.07 (1H, m), 4.92−4.90 (1H, m), 3.83−3.85 (2H, m), 3.20−3.08 (2H, m), 2.04−1.92 (8H, m), 1.88 (3H, s), 1.64 (3H, s), 1.63 (3H, s), 1.55 (6H, s), 1.46 (3H, s); δ_C (125 MHz; DMSO-*d*) 179.0 (C), 174.8 (C), 151.5 (C), 146.5 (C), 144.3 (C), 143.8 (C), 137.7 (C), 135.8 (C), 131.5 (C), 131.3 (C), 131.1 (C), 128.9 (C), 124.5 (CH), 123.9 (CH), 122.4 (CH), 119.4 (CH), 118.9 (CH), 117.8 (C), 112.2 (CH), 108.7 (C), 67.0 (CH), 48.5 (CH_2), 39.8 (2 × CH_2), 39.4 (CH_2), 28.3 (CH_2), 26.6 (CH_2), 26.1 (CH_2), 26.0 (Me), 25.8 (Me), 18.0 (Me), 17.9 (Me), 17.3 (Me), 16.3 (Me); *m*/*z* (ESI) 614 (M + Na^+, 100%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental details and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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