JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

Access to 12-Membered Cyclic *ortho,meta*-Diarylheptanoids: Total Synthesis of Actinidione via Isomyricanone

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Cite This: *J. Org. Chem.* 2021, 86, 3033−3040 Read Online

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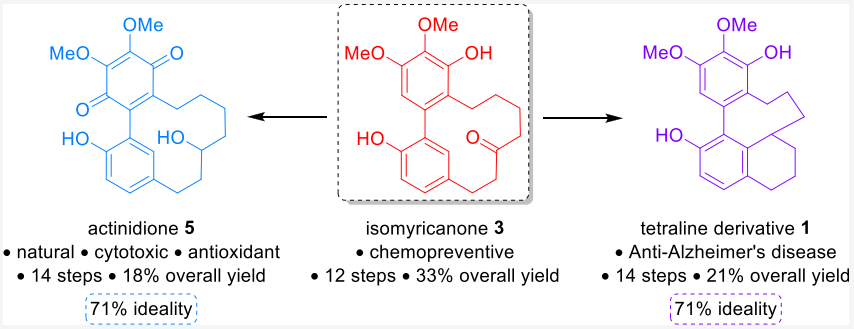


ABSTRACT: We describe herein the first access to 12-membered cyclic[7,0]*ortho,meta*-diarylheptanoids. The key features of the synthesis include both a Suzuki−Miyaura coupling and a ring closing metathesis. Actinidione, a promising natural product, along with a bioactive tetracyclic derivative were obtained in 14 steps for the first time from cheap commercially available substrates with an overall yield of 18−21%. Our modus operandi complies with the principles of the synthesis ideality by using notably strategic reactions.

Since the discovery of curcumin in 1815 by Vogel and Pelletier,[1] diarylheptanoids have been thoroughly investigated due to their unique architectural features as well as their broad range of biological activities.[2] Indeed, many approaches have been explored for the synthesis of the appealing family of cyclic 13-membered *meta,meta*-bridged biphenyls.[3] However, to the best of our knowledge, no route scouting has been described to prepare 12-membered *ortho,meta*-bridged biphenyls.

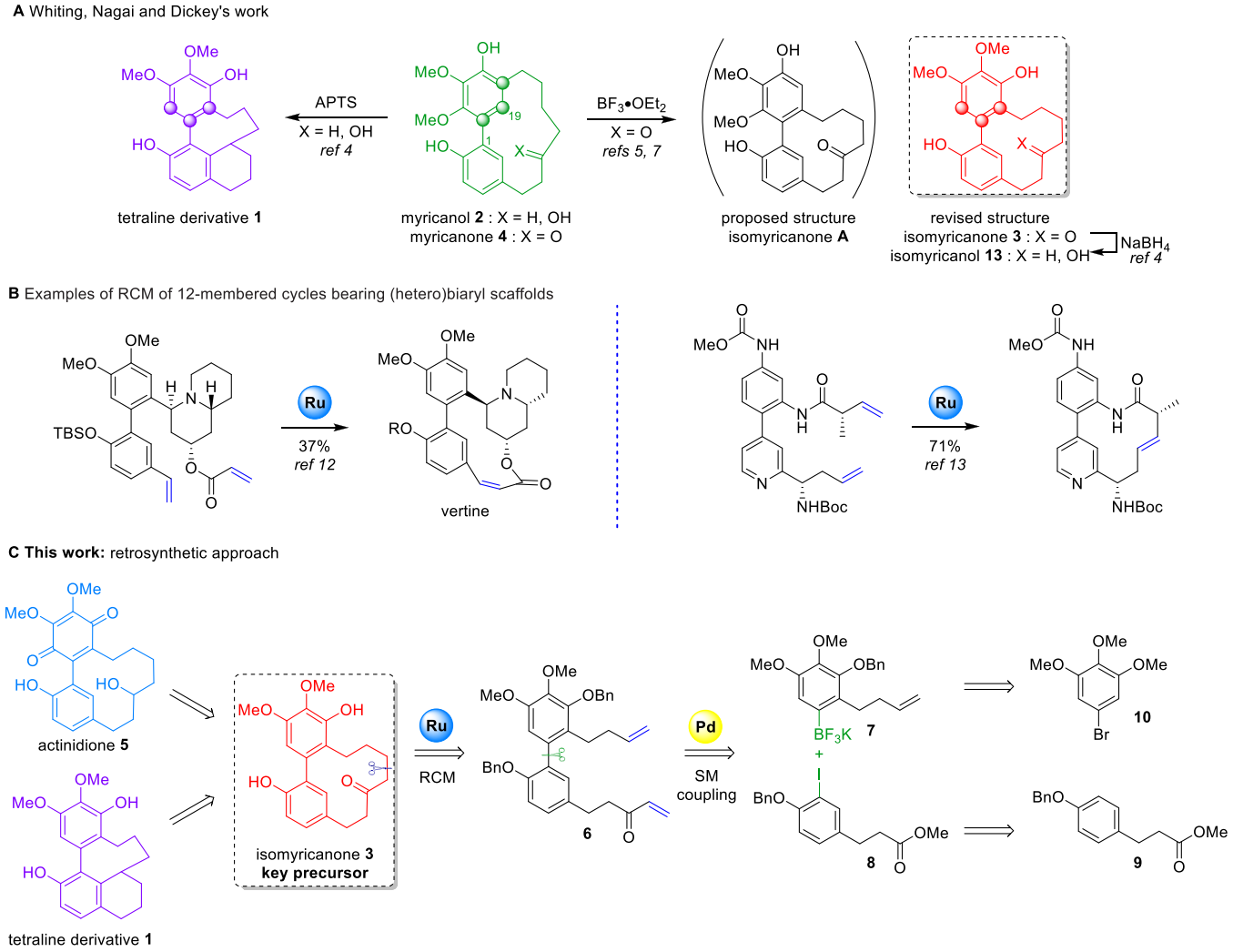
The tetracyclic diarylheptanoid **1** represents an interesting compound of this family. A structure−activity relationship study revealed that **1**, synthesized by Dickey et al. and resulting from an acid-catalyzed cyclodehydration of myricanol **2** (Scheme 1A), exhibits a robust protein tau reduction activity, hence an anti-Alzheimer's disease effect, on a par with (−)-a*S*,11*R*-myricanol (EC_{50} = 35 μM).[4] This rearranged molecule is unexpected due to its isomyricanone-type biaryl axis but also by the presence of the tetralin moiety. The two enantiomers have been studied separately and have commensurate activity.

Additionally, isomyricanone **3** was the first 12-membered [7,0]*ortho,meta*-cyclophane, prepared by Whiting et al. by isomerization of natural myricanone **4** with boron trifluoride etherate.[5] **3** unveils a potent inhibitory activity (IC_{50} = 350 mol ratio/TPA) against the Epstein−Barr virus early antigens, which induces lymphomas and carcinomas.[6] Initially, only a migration of the alkyl chain on the aromatic cycle from *meta* to *ortho* position to release the ring strain was inferred (Scheme 1A, structure **A**). Nonetheless, Nagai et al. reported in 1991 the revision of the structure based on further NMR studies (see Supporting Information for the proposed mechanism).[7]

Furthermore, actinidione **5** was isolated in 2006 by Zhang et al. from leaves and twigs of *Actinidiaceae*, endemic to China (Scheme 1C).[8] These species are employed as traditional medicine for hernia, hepatitis, hematemesis, and rheumatic diseases.[9] As far as we are aware, it is the first natural cyclic diarylheptanoid bearing both a [7,0]*ortho,meta*-cyclophane scaffold and a 1,4-benzoquinone. Its cytotoxicity has been shown to be promising against human breast cancer (Bre-04, GI_{50} = 26.67 μM), lung cancer (Lu-06, GI_{50} = 31.82 μM), and neuroma (Neu-04, GI_{50} = 15.02 μM) cell lines. This compound was then isolated from the bark of *Myrica nana*, *Myrica Rubra*, and *Myrica adenophora*.[10] As might be expected from the 1,4-benzoquinone motif, actinidione demonstrates a strong antioxidant activity (IC_{50} = 7.93 μM) against superoxide dismutase as well.[10b]

Received: October 20, 2020
Published: January 21, 2021

Scheme 1. Previous Work in the Literature and Our Retrosynthetic Approach



This paper details a versatile access to a large range of *ortho*,*meta*-bridged diarylheptanoids via a key intermediate, isomyricanone **3**, and exemplifies the preparation of **1** and **5**. This total synthesis was performed keeping in mind the outlines of the ideality to prepare a natural product.[11] The latter has been numerically expressed by Baran et al.[11a] and graphically crafted by Christmann et al.[11d] Hence, we envisaged a new retrosynthetic approach of **3** involving two evident disconnections and therefore two key reactions: a Suzuki−Miyaura coupling (SM coupling) along with a ring closing metathesis (RCM) between a type I and type II olefin for the macrocyclization step (Scheme 1C). Indeed, in the literature, only two examples for the formation of 12-membered macrocycles featuring a (hetero)biaryl scaffold have been described. The first one was illustrated by Kündig et al., who synthesized vertine, an alkaloid commonly known as cryogenine, by means of a RCM.[12] Macrocyclization was enabled by the Hoveyda-Grubbs second-generation catalyst on the preconformationally prone to cyclize seco-precursor, which allowed to isolate vertine in 37% yield (Scheme 1B). In the second instance, Bristol-Myers Squibb has described the synthesis of a 12-membered macrocyclic compound containing a heterocycle via RCM using Grubbs second-generation catalyst in 71% yield (Scheme 1B).[13] It is important to highlight that no cyclic diarylheptanoid has ever been prepared by RCM.

Our synthesis of isomyricanone **3**, the key precursor, begins with the preparation of the first coupling partner **7**, as depicted in Scheme 2. Thereupon, cheap 3,4,5-trimethoxybromobenzene **10** undergoes a Rieche formylation. Subsequently, successive $AlCl_3$-promoted regioselective demethylation in *ortho* position of the aldehyde,[14] addition of the allyl Grignard reagent to build the alkyl chain, and reduction of the resulting carbinol by triethylsilane were performed to afford **11** smoothly. Since a lithium−bromine exchange followed by insertion of a boron-containing electrophile ($B(OMe)_3$ or $B(OiPr)_3$) did not allow us to afford the required boronic acid as pure product, we ended up using a one-pot procedure to isolate trifluoroborate salt **7** on exposure to potassium hydrogen bifluoride, in 81% yield.

Concurrently, the second building block **8** was quantitatively obtained in one step through iodination of the commercially available **9** with I_2 and silver sulfate. Notwithstanding, during scale up, we observed predominantly the formation of a byproduct resulting from the rearrangement of the benzylic ether into the *ortho*-benzyl alkylated phenol.[15] In the aftermath of this displacement, we eventually had to tweak the conditions by using NIS in acidic medium, which afforded **8** in quantitative yield, regardless of the scale.

https://dx.doi.org/10.1021/acs.joc.0c02489
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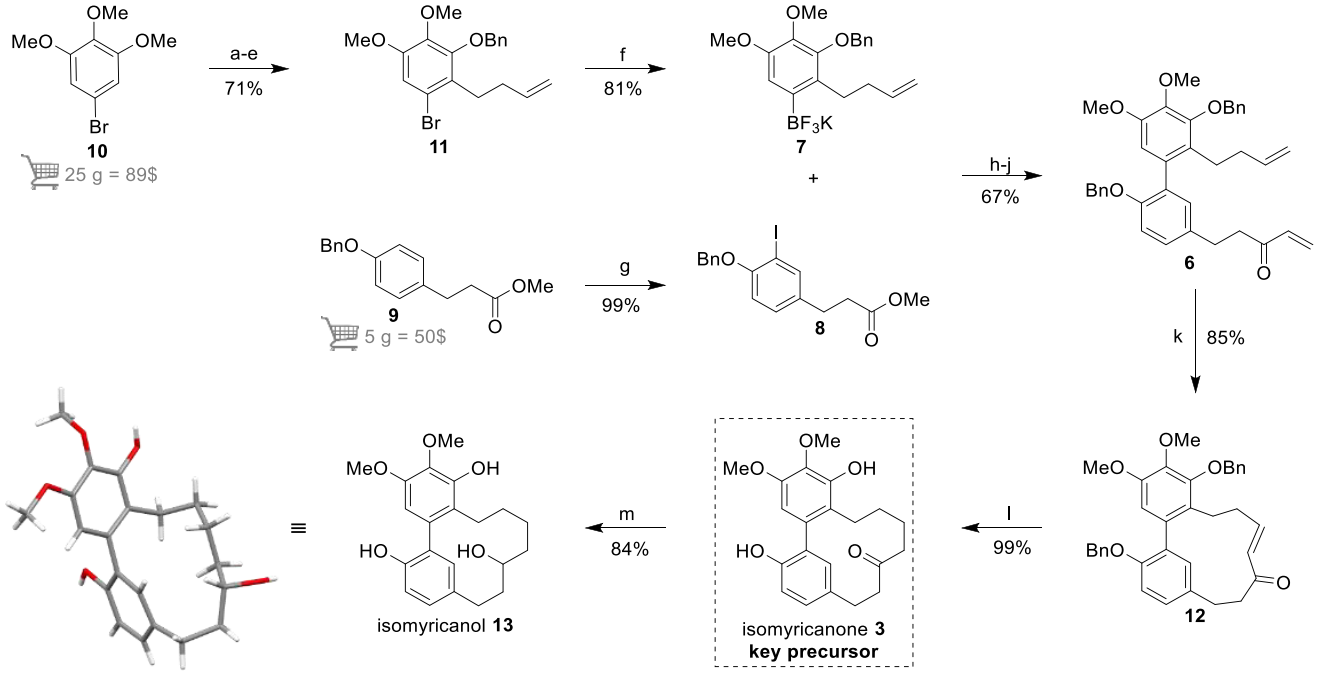
Scheme 2. Synthesis of Isomyricanone 3 and Isomyricanol 13[a] with Its Molecular Structure Showing 50% Ellipsoids



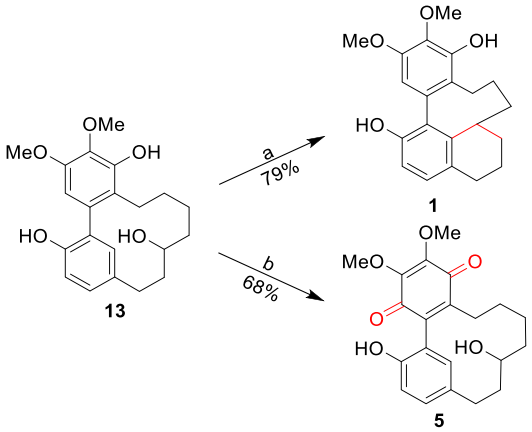
[a]Procedures: (a) Dichloromethyl methyl ether, $TiCl_4$, CH_2Cl_2, 0 °C to r.t.; (b) $AlCl_3$, CH_2Cl_2, 15 °C; (c) allylmagnesium bromide, THF, 0 °C; (d) Et_3SiH, TFAA, CH_2Cl_2, 0 °C then TBAF, THF; (e) BnBr, NaH, NaI, DMF, 0 °C; (f) *t*-BuLi, THF, −78 °C then *i*-PrOBpin, −78 to 40 °C then KHF_2, H_2O, MeOH, r.t.; (g) NIS, TFA, MeCN, r.t.; (h) $Pd(PPh_3)_4$, K_2CO_3, dioxane/H_2O (8/2), 100 °C; (i) CH_3NHOCH_3·HCl, $AlMe_3$, PhMe, 0 °C to r.t.; (j) vinylmagnesium bromide, THF, 0 °C; (k) Grubbs II, CH_2Cl_2, 40 °C; (l) H_2(55 psi), Pd/C, AcOEt, r.t.; (m) $NaBH_4$, MeOH, r.t.

With both coupling partners **7** and **8** in hand, obtained without column chromatography on multigram scale, the SM coupling proceeded in 35% yield in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in water. We observed the formation of the corresponding carboxylic acid due to in situ saponification. To overcome this problem, we tuned the solvent ratio to dioxane/H_2O (8/2) in order to get the coupled product in 67% yield.[16] Adding a ligand such as Xphos or SPhos led to the isomerization of the terminal olefin.[17] The preparation of the Weinreb amide at 0 °C ensued, pending treatment with vinyl Grignard to give rise to the terminal α,β-unsaturated ketone **6**, the seco-precursor of the RCM. RCM of **6** was performed using Grubbs second-generation catalyst at reflux in DCM in high-dilution conditions. Pleasingly, the conversion of starting material was complete and only one addition of catalyst was required to reach expected macrocyclized synthon **12** in 85% yield. This implies that the ring strain is fully released in an *ortho,meta*-diarylheptanoid compared to a *meta,meta*-diarylheptanoid.[18] Subsequently, an hydrogenation was achieved in order to saturate the heptylene chain and to deprotect the benzyl groups, giving prominence to pressure to ensure reproducibility. Finally, isomyricanone **3**, the 12-membered key intermediate was furnished in 12 steps with an overall yield of 33%.

At this stage, we envisaged the postderivation of **3** to access other derivatives of interest. The first one to be supplied was isomyricanol **13**, obtained as a pair of enantiomers, by reduction of **3** using sodium borohydride.[10] The latter was recrystallized out of a mixture of ethyl acetate and chloroform at room temperature to afford a single crystal, giving rise to an X-ray structure.

Stemming from **13**, challenging tetracyclic diarylheptanoid **1** was obtained by acid-dehydration on the heptylene chain followed by electrophilic aromatic substitution as a pair of enantiomers (presumably a*R*,*R* and a*S*,*S*)[4] in 79% yield after purification via semipreparative HPLC (Scheme 3).

Scheme 3. Synthesis of 1 and 5 from 13



[a]Procedures: (a) PTSA, $PhCH_3$, 90 °C; (b) salcomin, O_2, DMF, r.t.

The last envisaged postderivation delivered the natural bioactive actinidione **5**. Indeed, this *ortho,meta*-diarylheptanoid was obtained by a regioselective phenol oxidation of **13** in a satisfying yield of 68%, by engaging salcomin under oxygen atmosphere in DMF (Scheme 3).[19] To the best of our knowledge, no precedent synthesis was described in the literature. By using Frémy's catalyst,[20] we observed several

https://dx.doi.org/10.1021/acs.joc.0c02489
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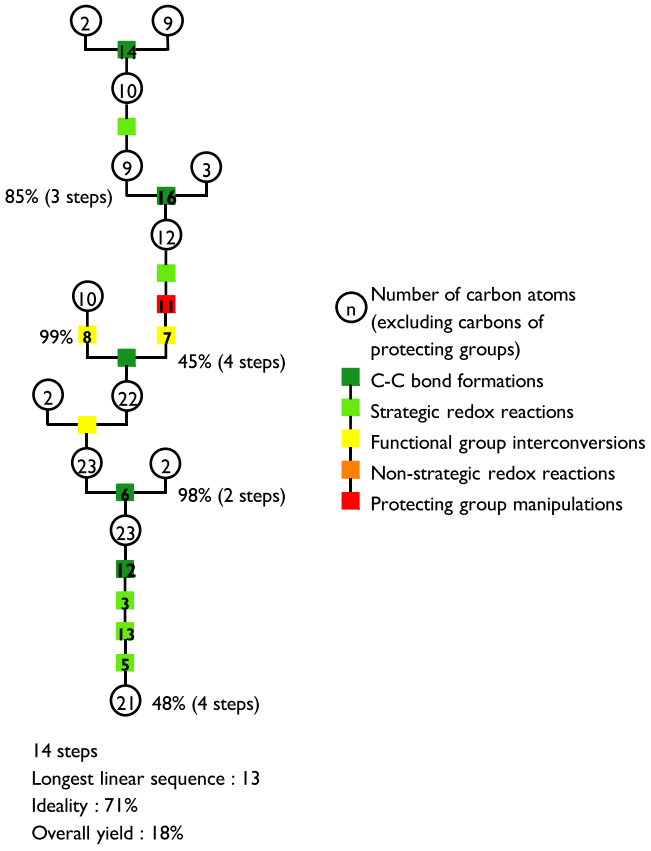
products including one stemming from a dehydrogenation followed by an *ipso*-hydroxylation in *ortho* of the phenol on the southern aromatic ring.

In the attempt to optimize our synthesis of **3**, we tackled the step-economy by avoiding protecting groups at most, in order to attain a sufficient ideality, still having in mind the complexity of our targeted molecule. Our tactic focused likewise on optimizing each step to get a high overall yield, even on scalability. Furthermore, we set out to develop a modular approach to gain access to diverse *ortho*,*meta*-diarylheptanoids through a common intermediate, **3**. To that extent, we decided to follow the model of Christmann et al., who recently promoted a color-coded flowchart to apprehend the ideality of a synthesis (Scheme 4).[11d] Concerning our synthesis of **5**, out

Scheme 4. Flowchart Representation of the Synthesis of 5



of 14 steps and an overall yield of 18%, it is unequivocal that most of the steps are green, to wit strategic. We exclusively account for three functional group interconversions (iodination, boronation, Weinreb amide preparation) and one required benzyl-protecting step. Accordingly, we have a high degree of ideality of 71%, which is calculated by the strategic steps out of the total number of steps.[11a]

In conclusion, we undertook a novel, rapid, efficient, and modular approach to the appealing family of 12-membered *ortho*,*meta*-diarylheptanoids via two key metal-mediated reactions (RCM and SM coupling). Attempts to prepare cyclic diarylheptanoids by RCM beforehand had failed.[21] It is worth noting that the key precursor **3** was obtained in 12 steps in 33% overall yield, and late-stage diversification thereof gives access to promising compounds **1**, **5**, and **13**. As an outcome, we have reached a high degree of ideality combined with a decent overall yield of 18% for the first synthesis of natural actinidione **5**.

EXPERIMENTAL SECTION

General Information. All reactions were conducted under argon atmosphere unless otherwise noted and THF was distilled by standard technique prior to use. Commercially available reagents were used without additional purification, unless otherwise stated. **9** was bought from Fluorochem and **10** from TCI Chemicals. Hydrogenation reactions were performed using a QianCapQ-Tube-Purging-12-SS system pressure reactor. NMR analyses were recorded in $CDCl_3$ or CD_3CN. ^1H and proton-decoupled ^{13}C NMR spectra were either recorded on Bruker AV 400 or Bruker AV 500. Chemical shifts are reported in parts per million (ppm) and are referenced to the residual solvent resonance as the internal standard ($CDCl_3$: δ [^1H] = 7.267 and accordingly δ [^{13}C] = 77.16 ppm). Coupling constants (J) are given in Hz. IR spectra were recorded on PerkinElmer Spectrum UATR two equipped with a diamond detector and an ATR unit. HRMS (Q-TOF) analysis were performed by the analytical facility at the University of Strasbourg. Crystal X-ray diffraction analyses were carried out by the Radiocrystallography Service of the University of Strasbourg by using a Bruker PHOTON III pixel detector diffractometer equipped with two microsources IμS Mo and IμS Diamond Cu. Chiral HPLC measurements were performed on a Shimadzu system with a quaternary low-pressure LC-20AD pump, an automatic SIL-20A HT injector, a CTO-10 AS oven and a SPD-M20 A diode array detector (DAD). The injection volume was 1 μL, the temperature of the oven set to 25 °C and the concentration of the sample 1 g/L. Semipreparative HPLC was performed with a Varian Prostar 210PDA apparatus equipped with a semipreparative Daicel column (Chiralpak IA 20 mm × 250 mm, 5 μm) at 215 nm.

Preparation of 3-(Benzyloxy)-1-bromo-2-(but-3-en-1-yl)-4,5-dimethoxybenzene (11) Starting from (10). *6-Bromo-2,3,4-trimethoxybenzaldehyde (**14**).* A magnetically stirred solution of dichloromethyl methyl ether (2.05 equiv, 15 mL, 165.75 mmol) and $TiCl_4$ (2.25 equiv, 20 mL, 182.4 mmol) in CH_2Cl_2 (300 mL) was treated with a solution of commercially available **10** (1 equiv, 20 g, 80.94 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 °C. The red mixture was stirred at room temperature for 5 h. HCl (10%, 40 mL) was added at 0 °C, the stirring was continued for 15 min. The organic layer was then separated, and the aqueous phase extracted with CH_2Cl_2 (3× 200 mL). The combined extracts were washed with a saturated solution of $NaHCO_3$(50 mL), brine, dried over $MgSO_4$, filtered off and concentrated under reduced pressure to afford **14** as a yellow solid. (22 g, 80.13 mmol, 99% yield) without further purification. Analytical data are consistent with those reported in the literature.[22]

*6-Bromo-2-hydroxy-3,4-dimethoxybenzaldehyde (**15**).* To a solution of **14** (1 equiv, 10 g, 36.35 mmol) in dry CH_2Cl_2 (300 mL) was added $AlCl_3$ (1 equiv, 4.85 g, 36.35 mmol) portionwise at 0 °C under inert atmosphere. After 1 h, another equivalent of $AlCl_3$ was added. The mixture was stirred for another 3 h below 15 °C. The flask was dived in an ice bath at 0 °C. The reaction mixture was then poured carefully into a mixture of ice and HCl (10%) over a few minutes, also dived in an ice bath. The mixture was stirred for 1 h. Aqueous phase was extracted with CH_2Cl_2 (3× 200 mL). The combined organic layer were washed successively with a saturated solution of $NaHCO_3$ (100 mL), brine, dried over anhydrous Na_2SO_4, filtered off through a pad of silica gel and concentrated under reduced pressure to afford **15** as a yellow oil (8.26 g, 31.62 mmol, 87% yield) without further purification. Analytical data are consistent with those reported in the literature.[23]

*3-Bromo-2-(1-hydroxybut-3-en-1-yl)-5,6-dimethoxyphenol (**16**).* Allylmagnesium bromide (2.09 equiv, 1 M in Et_2O, 72 mL, 72 mmol) was added dropwise over 5 min to a stirred solution of **15** (1 equiv, 9 g, 34.47 mmol) in THF (170 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched at 0 °C by addition of a saturated solution of NH_4Cl (150 mL). The aqueous phase was extracted with EtOAc (3× 200 mL). The combined organic

https://dx.doi.org/10.1021/acs.joc.0c02489
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layers were washed with brine (50 mL), dried over Na_2SO_4, filtered off and evaporated under reduced pressure. Crude was filtered through a pad of silica/Celite/activated charcoal to afford **16** as a yellow oil (10.44 g, 34.45 mmol, 99% yield) without further purification; R_f 0.41 (SiO_2, ^{C}Hex/EtOAc 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 6.58 (s, 1H), 5.88 (ddt, J = 17.2, 10.2, 7.1 Hz, 1H), 5.19−5.06 (m, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 2.62−2.50 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.3, 149.9, 136.0, 134.3, 120.3, 118.3, 115.8, 108.0, 74.7, 60.9, 56.1, 40.7; IR (cm^{-1}) ν 3389, 3078, 2935, 2841, 1603, 1571, 1493, 1444, 1417, 1301, 1244, 1123, 1045, 919, 811; HRMS (ESI+) m/z [M + Na]$^+$ calcd for $C_{12}H_{15}{}^{79}BrO_4Na$325.0046, found 325.0068.

3-Bromo-2-(but-3-en-1-yl)-5,6-dimethoxyphenol (17). Under inert atmosphere, **16** (1 equiv, 5.3 g, 17.52 mmol) was dissolved in CH_2Cl_2 (85 mL) and the mixture was cooled to 0 °C. Triethylsilane (1.13 equiv, 3.2 mL, 19.81 mmol) and trifluoroacetic anhydride (1.31 equiv, 3.2 mL, 23.0 mmol) were added. The reaction was stirred for 1.5 h at 0 °C. The reaction mixture was quenched with H_2O (10 mL) at 0 °C and the aqueous phase was extracted with CH_2Cl_2 (3× 100 mL). The combined organic layers were dried over Na_2SO_4, filtered off and evaporated under reduced pressure. The residue was dissolved in THF (105 mL) and TBAF (1.02 equiv, 1 M in THF, 18 mL, 18 mmol) was added. The mixture was stirred for 30 min at room temperature. HCl (10%, 50 mL) was added at 0 °C. Et_2O was added and the organic phase was washed with HCl (3× 80 mL). Organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered off and the solvent was concentrated under reduced pressure to afford **17** as a yellow oil (4.63 g, 16.12 mmol, 92% yield) without any further purification. R_f 0.36 (SiO_2, ^{C}Hex/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69 (s, 1H), 5.97−5.84 (m, 2H), 5.11−4.91 (m, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 2.88−2.77 (m, 2H), 2.32−2.27 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 150.6, 148.0, 138.4, 134.7, 121.2, 118.8, 114.7, 108.0, 61.1, 56.1, 33.0, 29.3. IR (cm^{-1}) ν 3495, 3071, 2998, 2935, 2853, 1639, 1576, 1607, 1493, 1454, 1421, 1315, 1237, 1197, 1123, 1043, 911, 797. HRMS (ESI−) m/z [M − H]$^+$ calcd for $C_{12}H_{14}{}^{79}BrO_3$285.0132, found 285.0130.

3-(Benzyloxy)-1-bromo-2-(but-3-en-1-yl)-4,5-dimethoxybenzene (11). To a solution of **17** (1 equiv, 4.25 g, 14.8 mmol) in DMF (60 mL) was added NaH (1.2 equiv, 710 mg, 17.82 mmol) at 0 °C. After 10 min of stirring, benzyl bromide (1.01 equiv, 1.77 mL, 14.8 mmol) and NaI (9 mol %, 200 mg, 1.32 mmol) were added. The reaction mixture was stirred at room temperature for 1.5 h. A saturated solution of NH_4Cl (25 mL) was added slowly to quench the reaction at 0 °C. The aqueous phase was extracted with Et_2O (3× 100 mL). Combined organic layers were washed with cold water (3× 250 mL), dried over Na_2SO_4, filtered off and concentrated under reduced pressure. Crude was purified by flash chromatography on silica gel (gradient was performed from 100/0, v/v cyclohexane/ethyl acetate to 8/2, v/v) to afford **11** (5.02 g, 13.32 mmol, 90% yield) as a yellow oil. R_f 0.56 (SiO_2, ^{C}Hex/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.44 (m, 2H), 7.43−7.32 (m, 3H), 6.90 (s, 1H), 5.87 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.07 (s, 2H), 5.05−4.93 (m, 2H), 3.86 (s, 6H), 2.82−2.73 (m, 2H), 2.28−2.19 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.2, 151.5, 142.1, 138.3, 137.7, 128.6, 128.4, 128.1, 128.1, 118.3, 114.8, 112.1, 75.5, 61.0, 56.3, 33.7, 29.9; IR (cm^{-1}) ν 3065, 3031, 2964, 2934, 2841, 1639, 1589, 1481, 1444, 1429, 1412, 1367, 1284, 1231, 1212, 1120, 1091, 1045, 996, 909, 795, 734, 696; HRMS (ESI+) m/z [M + K]$^+$ calcd for $C_{19}H_{21}{}^{79}BrO_3K$ 415.0306, found 415.0305.

Potassium (3-(benzyloxy)-2-(but-3-en-1-yl)-4,5-dimethoxyphenyl)trifluoroborate (7). To a solution of **11** (1 equiv, 4.42 g, 11.72 mmol) in THF (200 mL) was added *t*-BuLi (2.02 equiv, 1.7 M in pentane, 13.7 mL, 23.37 mmol) dropwise at −78 °C under argon. It was stirred for 30 min at −78 °C. Then, distilled 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5 equiv, 0.25 mL, 1.23 mmol) was added quickly at −78 °C. Dry ice bath was removed, and the reaction medium was stirred at room temperature for 4 h. Solvent was evaporated under reduced pressure. The residue was taken up in CH_3OH (120 mL) and a sonicated aqueous solution of potassium hydrogen fluoride (5.57 equiv, 5 g KHF_2, 4.5 M in H_2O, 14.5 mL H_2O, 65.25 mmol) was added at room temperature. The reaction was stirred for 1.5 h minutes at room temperature. $PhCH_3$ (3× 50 mL) was added, and the mixture was concentrated under reduced pressure to eliminate water and to afford a yellowish solid. Acetone was added and the mixture was filtered off to eliminate inorganic salts. The filtrate was evaporated to afford a yellowish solid. Hexane (3× 20 mL) was then added and supernatant was removed. White powder was washed thrice with Et_2O to afford **7** as a white solid (3.84 g, 9.49 mmol, 81% yield) without any further purification. ^{1}H NMR (500 MHz, CD_3CN) δ 7.52 (d, J = 6.9 Hz, 2H), 7.43−7.30 (m, 3H), 6.95 (s, 1H), 5.91 (ddt, J = 16.9, 10.2, 6.5 Hz, 1H), 4.98 (s, 2H), 4.98−4.93 (m, 1H, 20), 4.88 (ddt, J = 10.2, 2.4, 1.3 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.81−2.76 (m, 2H), 2.26−2.19 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, CD_3CN) δ 151.2, 151.0, 141.4, 139.9, 132.0, 129.3, 128.7, 128.5, 113.7, 112.8, 75.4, 60.9, 56.3, 36.8, 29.4; ^{11}B NMR (160 MHz, CD_3CN) δ 3.31; ^{19}F NMR (470 MHz, CD_3CN) δ −138.35; IR (cm^{-1}) ν 3622, 3564, 3034, 3001, 2967, 2938, 2878, 2838, 1648, 1413, 1372, 1318, 1121, 1069, 980, 920, 859, 796, 752, 697; HRMS (ESI−) m/z [M − K]$^+$ calcd for $C_{19}H_{21}BF_3O_3$365.1545, found 365.1530.

Methyl 3-(4-(benzyloxy)-3-iodophenyl)propanoate (8). To a solution of **9** (1 equiv, 10 g, 36.99 mmol) in CH_3CN (150 mL) and TFA (0.3 equiv, 0.82 mL, 11.10 mmol) was added NIS (1.5 equiv, 12.5 g, 55.56 mmol) at 0 °C. The mixture was stirred at room temperature for 5 h. EtOAc (300 mL) was added and the organic phase was washed with a saturated aqueous solution of $Na_2S_2O_3$ (70 mL) then NaOH (6 N, 200 mL), dried over Na_2SO_4, filtered off and concentrated under reduced pressure to afford **8** as a yellow oil (14.7 g, 36.97 mmol, 99% yield) without any further purification. R_f 0.33 (SiO_2, ^{C}Hex/EtOAc 9:1). The analytical data are consistent with those reported in the literature.[3b]

Preparation of 5-(3′,6-Bis(benzyloxy)-2′-(but-3-en-1-yl)-4′,5′-dimethoxy-[1,1′-biphenyl]-3-yl)pent-1-en-3-one (6) Starting from (7) and (8). *Methyl 3-(3′,6-bis(benzyloxy)-2′-(but-3-en-1-yl)-4′,5′-dimethoxy-[1,1′-biphenyl]-3-yl)propanoate (18).* To a round-bottomed flask was added **7** (1.5 equiv, 1.91 g, 4.71 mmol) and **8** (1 equiv, 1.27 g, 3.21 mmol). Then, H_2O (10 mL) and dioxane (40 mL) were added, followed by tetrakis-(triphenylphosphine)palladium(0) (11 mol %, 414 mg, 0.358 mmol) and dry K_2CO_3 (5 equiv, 2.22 g, 16.06 mmol). The reaction mixture was stirred at 100 °C using an aluminum heating block for 16 h. Once the reaction mixture was back at room temperature, H_2O (30 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3× 100 mL). The combined organic layers were dried over Na_2SO_4, filtered off and evaporated under reduced pressure. Crude was purified by flash chromatography on silica gel (gradient was performed from 100/0, v/v cyclohexane/ethyl acetate to 8/2, v/v) to afford **18** (1.2 g, 2.15 mmol, 67% yield) as a colorless oil. R_f 0.23 (SiO_2, ^{C}Hex/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.45 (m, 2H), 7.41−7.27 (m, 3H), 7.27−7.17 (m, 5H), 7.12 (dd, J = 8.4, 2.4 Hz, 1H), 7.03 (d, J = 2.3 Hz, 1H, 16), 6.92 (d, J = 8.4 Hz, 1H), 6.55 (s, 1H, 3), 5.59 (ddt, J = 17.0, 10.4, 6.7 Hz, 1H), 5.09 (AB, J = 10.8 Hz, $\Delta\nu_{AB}$ = 36.5 Hz, 2H), 5.00 (s, 2H), 4.79−4.71 (m, 2H), 3.94 (s, 3H), 3.82 (s, 3H), 3.66 (s, 3H), 2.92 (t, J = 7.8, 7.8 Hz, 2H), 2.69−2.56 (m, 3H), 2.43−2.30 (m, 1H), 2.16−1.91 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.4, 154.2, 151.0, 150.9, 141.6, 138.9, 138.2, 137.5, 134.1, 132.8, 131.4, 131.2, 128.5, 128.4, 128.3, 128.0, 127.8, 127.6, 127.3, 126.6, 114.1, 113.2, 109.9, 75.2, 70.3, 61.0, 56.0, 51.7, 36.0, 34.7, 30.2, 27.6; IR (cm^{-1}) ν 3065, 3031, 2929, 2856, 1737, 1636, 1599, 1487, 1453, 1414, 1341, 1251, 1126, 1045, 1024, 736, 697; HRMS (ESI+) m/z [M + Na]$^+$ calcd for $C_{36}H_{38}O_6Na$ 589.2561, found 589.2533.

3-(3′,6-Bis(benzyloxy)-2′-(but-3-en-1-yl)-4′,5′-dimethoxy-[1,1′-biphenyl]-3-yl)-N-methoxy-N-methylpropanamide (19). To a slurry mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (5 equiv, 1.04 g, 10.66 mmol) in dry $PhCH_3$ (6 mL) was added dropwise trimethylaluminum (5 equiv, 2 M in $PhCH_3$, 5.3 mL, 10.6 mmol) over 10 min at 0 °C under argon atmosphere (vigorous bubbling was observed). Then, the solution was allowed to warm to room temperature for 1 h. The mixture was recooled at 0 °C and a

https://dx.doi.org/10.1021/acs.joc.0c02489
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sonicated solution of **18** (1 equiv, 1.2 g, 2.12 mmol) in $PhCH_3$ (6 mL) was added. The yellow mixture was vigorously stirred at room temperature for 4 h. The reaction was hydrolyzed slowly at 0 °C with HCl (10%, 20 mL, vigorous bubbling was observed). An aqueous saturated solution of Rochelle's salt (potassium sodium tartrate, 30 mL) was added and it was stirred for 10 min. The aqueous layer was extracted with EtOAc (3× 150 mL). The combined organic layers were washed with an aqueous saturated solution of $NaHCO_3$ (100 mL), dried over Na_2SO_4, filtered off and evaporated under reduced pressure to afford **19** (1.25 g, 2.10 mmol, 99%) without any further purification as a colorless oil. R_f 0.22 (SiO_2, ^{C}Hex/EtOAc 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.46 (m, 2H), 7.43−7.29 (m, 3H), 7.29−7.19 (m, 5H), 7.17 (dd, J = 8.3, 2.4 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.57 (s, 1H), 5.61 (ddt, J = 17.0, 10.4, 6.7 Hz, 1H), 5.10 (AB, J = 12.0 Hz, $\Delta\nu_{AB}$ = 46.0 Hz, 2H), 5.00 (s, 2H), 4.83−4.65 (m, 2H), 3.94 (s, 3H), 3.83 (s, 3H), 3.61 (s, 2H), 3.18 (s, 3H), 2.97−2.91 (m, 2H), 2.77−2.71 (m, 2H), 2.66−2.57 (m, 1H), 2.44−2.33 (m, 1H), 2.20−1.96 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.8, 154.1, 151.0, 150.9, 141.6, 139.0, 138.2, 137.5, 134.2, 133.6, 131.3, 131.3, 128.5, 128.4, 128.0, 127.8, 127.6, 127.3, 126.7, 114.0, 113.2, 109.9, 75.2, 70.3, 61.3, 61.0, 56.0, 34.7, 34.0, 32.3, 29.9, 27.6; IR (cm^{-1}) ν 3065, 3028, 2933, 2853, 1664, 1596, 1571, 1487, 1453, 1414, 1374, 1341, 1251, 1125, 1024, 908, 736, 697; HRMS (ESI+) m/z [M + H]$^+$ calcd for $C_{37}H_{42}NO_6$ 596.3007, found 596.2994.

*5-(3′,6-Bis(benzyloxy)-2′-(but-3-en-1-yl)-4′,5′-dimethoxy-[1,1′-biphenyl]-3-yl)pent-1-en-3-one (**6**).* To a sonicated solution of **19** (1 equiv, 1.45 g, 2.10 mmol) in dry THF (6 mL) was added vinylmagnesium bromide (2.4 equiv, 1 M in THF, 6 mL, 5.0 mmol) at 0 °C. The yellow mixture was then stirred at 0 °C for 1 h. The reaction mixture was quickly quenched at 0 °C with HCl (10%, 40 mL). The aqueous phase was extracted with EtOAc (3× 150 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered off and concentrated under reduced pressure to afford **6** (1.37 g, 2.10 mmol, 99%) without any further purification as an orange oil. R_f 0.21 (SiO_2, ^{C}Hex/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.47 (m, 2H), 7.40−7.29 (m, 3H), 7.28−7.17 (m, 5H), 7.13 (dd, J = 8.4, 2.4 Hz, 1H), 7.03 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.56 (s, 1H), 6.35 (X(AMX), J = 17.7, 10.5 Hz, 1H), 6.02 (AM(AMX), J = 17.7, 10.5, 0.9 Hz, $\Delta\nu_{AM}$ = 156.5 Hz, 2H), 5.60 (ddt, J = 17.0, 10.4, 6.7 Hz, 1H), 5.14 (AB, J = 10.7 Hz, $\Delta\nu_{AB}$ = 36.3 Hz, 1H), 5.00 (s, 2H), 4.79−4.72 (m, 2H), 3.94 (s, 3H), 3.82 (s, 3H), 2.95−2.87 (m, 4H), 2.66−2.56 (m, 1H), 2.43−2.32 (m, 1H), 2.19−1.94 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 199.9, 154.2, 151.1, 150.9, 141.6, 139.0, 138.2, 137.5, 136.6, 134.1, 133.3, 131.4, 131.3, 128.5, 128.4, 128.3, 128.0, 127.9, 127.6, 127.3, 126.7, 114.0, 113.2, 109.9, 75.2, 70.3, 61.0, 56.1, 41.5, 34.7, 29.1, 27.6. IR (cm^{-1}) ν 3062, 3034, 2930, 2859, 1702, 1679, 1638, 1596, 1571, 1486, 1453, 1412, 1372, 1340, 1284, 1250, 1123, 1044, 1022, 908, 842, 811, 735, 696; HRMS (ESI+) m/z [M + H]$^+$ calcd for $C_{37}H_{39}O_5$ 563.2792, found 563.2804.

*(E)-13,26-Bis(benzyloxy)-14,15-dimethoxy-1(1,2),2(1,3)-dibenzenacyclononaphan-6-en-5-one (**12**).* A solution of **6** (1 equiv, 97 mg, 0.170 mmol) in CH_2Cl_2 (165 mL) was degassed for 30 min under a flow of argon. The reaction mixture was heated at reflux by using a glycerol bath. Then, Grubbs-II catalyst (20 mol %, 30 mg, 0.035 mmol) was added in one portion. The reaction mixture was stirred at reflux for 16 h. The reaction mixture was filtered through a pad of both activated charcoal and silica gel and solvent was evaporated under reduced pressure to **12** (78 mg, 0.15 mmol, 85%) without any further purification as a colorless oil. R_f 0.21 (SiO_2, ^{C}Hex/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.36 (m, 2H), 7.32−7.21 (m, 3H), 7.21−7.09 (m, 5H), 6.95 (dd, J = 8.2, 2.3 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.65 (d, J = 2.3 Hz, 1H), 6.53 (s, 1H), 5.83 (dt, J = 15.8, 7.8 Hz, 1H), 5.56 (d, J = 16.0 Hz, 1H), 5.07 (AB, J = 11.3 Hz, $\Delta\nu_{AB}$ = 63.9 Hz, 2H), 4.93 (AB, J = 12.2 Hz, $\Delta\nu_{AB}$ = 16.5 Hz, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 2.95−2.83 (m, 2H), 2.83−2.72 (m, 1H), 2.69−2.58 (m, 1H), 2.51−2.41 (m, 1H), 2.29−2.08 (m, 2H), 1.88−1.76 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 203.8, 154.3, 151.8, 151.2, 151.1, 141.4, 138.1, 137.4, 135.7, 134.9, 133.9, 131.9, 130.3, 128.6, 128.5, 128.4, 127.9, 127.9, 127.7, 126.7, 125.7, 112.8, 107.9, 75.1, 70.5, 61.0, 56.0, 40.8, 33.8, 33.5, 27.6; IR (cm^{-1}) ν 3031, 2924, 2854, 1685, 1654, 1596, 1486, 1415, 1374, 1344, 1249, 1126, 1104, 1023, 736, 697; HRMS (ESI+) m/z [M + K]$^+$ calcd for $C_{35}H_{34}O_5K$ 573.2038, found: 573.2048.

*1,2-Dihydroxy-14,15-dimethoxy-1(1,2),2(1,3)-dibenzenacyclononaphan-5-one (Isomyricanone, **3**).* To a solution of **12** (1 equiv, 50 mg, 0.094 mmol) in EtOAc (1 mL) was added palladium on activated charcoal (1 equiv, 10 mg, 0.103 mmol) and stirred for 16 h under a H_2 atmosphere (55 psi). The reaction mixture was filtered through a pad of Celite and solvent was evaporated under reduced pressure to afford isomyricanone **3** (33 mg, 0.093 mmol, 99% yield) without any further purification as a colorless oil. R_f 0.15 (SiO_2, ^{C}Hex/EtOAc 7:3); Analytical data are consistent with those reported in the literature.[4]

*1,1-Dimethoxy-1(1,2),2(1,3)-dibenzenacyclononaphane-1,2,5-triol, (Isomyricanol, **13**).* To a solution of isomyricanone **3** (1 equiv, 200 mg, 0.56 mmol) in CH_3OH (7 mL) was added sodium borohydride (6 equiv, 126 mg, 3.34 mmol) at 0 °C under inert atmosphere and was stirred for 1 h at room temperature. H_2O (5 mL) and EtOAc (25 mL) were added. The aqueous phase was extracted with EtOAc (3× 30 mL). Combined organic layers were dried over Na_2SO_4, filtered off and concentrated under reduced pressure to afford isomyricanol **13** (168 mg, 0.47 mmol, 84%) without any further purification as a white solid. Analytical data are consistent with those reported in the literature.[4] This compound is present as a 50:50 ratio of two enantiomers and chiral HPLC are available in the SI.

*1^6,7-Dihydroxy-2^4,2^5-dimethoxy-1(1,3)-benzena-2(1,2)-cyclohexanacyclononaphane-2^1,2^4-diene-2^3,2^6-dione (Actinidione, **5**).*[8] Isomyricanol **13** (1 equiv, 50 mg, 0.14 mmol) and salcomine (0.4 equiv, 18 mg, 0.054 mmol) were charged and DMF (2.5 mL) was added. Oxygen gas was continuously bubbled through the stirring mixture for 5 h. Afterward, an additional 18 mg of catalyst was added. The reaction was complete after 16 h under oxygen atmosphere. EtOAc (30 mL) was added. The organic phase was washed with cold H_2O (5× 10 mL), dried over anhydrous $MgSO_4$, filtered off and concentrated under reduced pressure to afford actinidione **5** (35 mg, 0.093 mmol, 68%) without any further purification as an orange oil. R_f 0.40 (SiO_2, ^{C}Hex/EtOAc 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (dd, J = 8.2, 2.2 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.81 (d, J = 2.2 Hz, 1H), 5.36 (s, 1H), 4.06 (s, 3H), 4.02 (s, 3H), 3.73 (t, J = 9.3, 9.3 Hz, 1H), 2.83 (dt, J = 13.8, 4.2, 4.2 Hz, 1H), 2.67 (td, J = 12.9, 12.3, 3.7 Hz, 1H), 2.41 (ddd, J = 12.1, 10.4, 7.6 Hz, 1H), 1.96 (dt, J = 13.7, 4.3, 4.3 Hz, 1H), 1.93−1.84 (m, 0H), 1.73−1.55 (m, 1H), 1.25−1.12 (m, 1H), 1.06−0.96 (m, 1H), 0.79 (t, J = 14.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 184.3, 184.2, 151.0, 146.6, 145.0, 144.5, 141.1, 133.7, 131.2, 130.6, 120.8, 117.6, 72.2, 61.4, 61.3, 39.9, 34.8, 33.7, 26.9, 26.4, 24.2; IR (cm^{-1}) ν 3391, 3013, 2925, 2854, 1651, 1613, 1599, 1507, 1454, 1287, 1202, 1144, 1130, 1070, 1016, 822, 758; HRMS (ESI+) m/z [M + Na]$^+$ calcd for $C_{21}H_{24}O_6Na$ 395.1465, found 395.1450.

(*S*)-8,9-Dimethoxy-2,3,3a,4,5,6-hexahydro-1*H*-benzo[4,5]-cycloocta[1,2,3-de]naphthalene-7,11-diol (1). To a solution of isomyricanol **13** (1 equiv, 50 mg, 0.139 mmol) in $PhCH_3$ (10 mL) was added *para*-toluenesulfonic acid (3.3 equiv, 79 mg, 0.459 mmol). The solution was heated at 90 °C with an aluminum heating block for 5 h under air atmosphere. After cooling, Et_2O (15 mL) was added. The organic phase was washed with a saturated solution of $NaHCO_3$(5 mL), dried over $MgSO_4$, filtered off and evaporated under reduced pressure. Crude was purified by semipreparative HPLC to afford **1** (37.4 mg, 0.110 mmol) as a pair of enantiomers. R_f 0.69 (SiO_2, ^{C}Hex/EtOAc 6:4). Analytical data are consistent with those reported in the literature.[4] This compound is present as a 50:50 ratio of two enantiomers and chiral HPLC are available in the SI.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02489.

https://dx.doi.org/10.1021/acs.joc.0c02489
J. Org. Chem. 2021, 86, 3033−3040

Proposed mechanism, detailed synthetic schemes, ^{1}H, $^{13}C\{^{1}H\}$, ^{19}F and ^{11}B NMR spectra of all compounds and X-ray molecular structure for compound **13** (PDF)

Accession Codes

CCDC 2012419 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We would like to thank Matthieu Chessé for the purification of tetracyclic **1** via semipreparative HPLC and the French government for Paul Massé's Ph.D. fellowship.

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https://dx.doi.org/10.1021/acs.joc.0c02489
J. Org. Chem. 2021, 86, 3033−3040