JOC The Journal of Organic Chemistry

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Synthesis of Coprinol and Several Alcyopterosin Sesquiterpenes by Regioselective [2 + 2 + 2] Alkyne Cyclotrimerization

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Cite This: J. Org. Chem. 2022, 87, 14909−14914 Read Online

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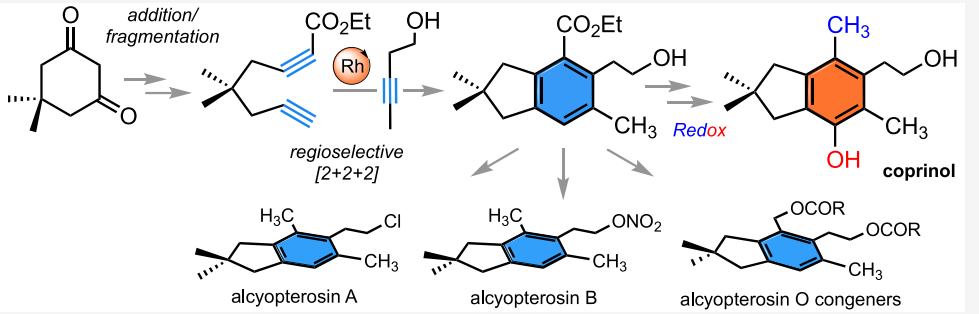


ABSTRACT: Alkyne [2 + 2 + 2] cyclotrimerization is a strategically attractive but tactically challenging approach to the synthesis of highly substituted benzene rings. Here, a bimolecular regioselective cyclotrimerization is applied to the total synthesis of the natural product coprinol and several related alcyopterosins from the illudalane family of sesquiterpenes. The synthesis of coprinol from dimedone was completed in six steps and a 57% overall yield. Alternative functional group manipulations lead to alcyopterosins A, B, and O and two additional congeners, all within six steps.

Natural products that incorporate highly substituted benzene rings pose considerable and persistent challenges in organic synthesis. Substituted benzene rings are most commonly prepared by the serial substitution of pre-existing benzene rings; the limitations of this stepwise approach are compounded with each substitution. Consequently, highly substituted benzene rings are underrepresented in medicinal chemistry.[1] Convergent benzannulation reactions are fundamentally more attractive for the synthesis of highly substituted benzene rings, but they often require target-specific innovations to establish the appropriate regiocontrol and yield.

We have been investigating the synthesis of illudalane sesquiterpenes[2] in conjunction with a fragmentation methodology to make high-value alkyne building blocks.[3] The illudalanes provide an array of biological activities along with the synthetic challenge of their highly substituted benzene rings. Interest in illudalane sesquiterpenes has surged in recent years, with >17 syntheses reported since 2016,[4] including 6 syntheses from our lab.[2] Our general approach involves the ring-opening fragmentation of dimedone (**1**) to generate neopentylene-tethered (NPT) 1,6-enynes[3b] or 1,6-diynes,[2e,5] followed by various benzannulation processes to deliver the target structures. Here we focus on coprinol (**8**, Figure 1), an illudalane sesquiterpene from the edible mushroom *Coprinopsis cinerea*[6a] (formerly known as *Coprinus cinereus*[6b]). A 10-step synthesis of coprinol by the serial substitution of 2,4-dimethylphenol (a trisubstituted benzene) was reported in 2016[4a] (*vide infra*). We apply a bimolecular, regioselective [2 + 2 + 2] alkyne cyclotrimerization to the six-step synthesis of coprinol from dimedone in addition to a similar approach to the synthesis of several alcyopterosins.

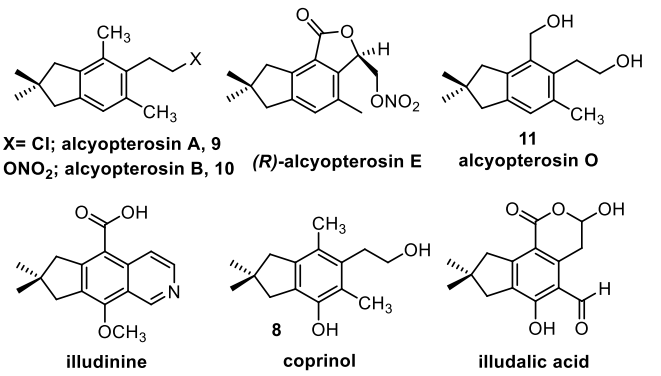


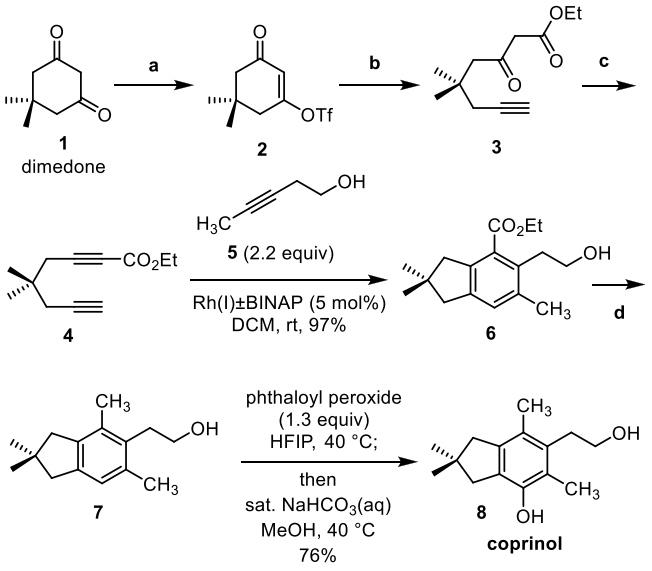
Figure 1. Representative illudalane sesquiterpenes.

We completed the synthesis of coprinol from dimedone (**1**) by way of ethyl 5,5-dimethylocta-2,7-diynoate (**4**), incorporat-

Received: July 21, 2022
Published: October 10, 2022

https://doi.org/10.1021/acs.joc.2c01741
J. Org. Chem. 2022, 87, 14909−14914

Scheme 1. Synthesis of Coprinol from Dimedone[a]



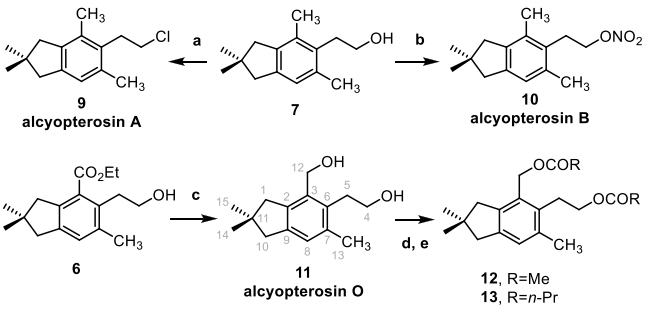
[a]See the Experimental Section for details. Reaction conditions are as follows: (a) Tf_2O and pyridine, 99%; (b) LDA/EtOAc then LDA, 89%; (c) Tf_2O and LiOH, then TBAF, 94%; (d) $LiAlH_4$ at 180 °C, 96%.

ing the recent synthesis of diyne **4** from our lab[5] (Scheme 1). The condensation of dimedone with trifluoromethanesulfonic anhydride (Tf_2O) provides vinylogous acyl triflate (VAT) **2**. The Claisen-type tandem addition/fragmentation of VAT **2** with ethyl acetate provides alkyne-tethered β-keto ester **3**, which can then be dehydrated with Tf_2O and base to provide NPT 1,6-diyne monoester **4** in an 82% yield over three steps from dimedone.

The rhodium-catalyzed cyclotrimerization of **4** with 3-pentynol (**5**) using modified Tanaka conditions[7] gave pentasubstituted benzene **6** as a single regioisomer in a 97% yield. The $Rh(cod)_2BF_4$ precatalyst was hydrogenated in the presence of (±)-BINAP to reduce the cyclooctadiene ligand and generate a more active cationic Rh(I) catalyst represented as either $Rh(BINAP)BF_4$ or, more precisely in a non-coordinating solvent, the dimeric arene-bridged species $[Rh(BINAP)]_2(BF_4)_2$.[8] Diyne **4** was then added slowly (over ca. 60 min) to a solution of alkyne **5** and $Rh(BINAP)BF_4$ in dichloromethane at room temperature with stirring, and the mixture was stirred for an additional 30 min to generate **6**. Slow addition prevents the homocoupling of **4**.

Redox adjustments are required to access coprinol and various alcyopterosins from pentasubstituted benzene **6**. The reduction of **6** with lithium aluminum hydride ($LiAlH_4$) under standard conditions provided alcyopterosin O (**11**, Scheme 2, below), which we previously made using a similar five-step route.[2e] At higher temperatures, $LiAlH_4$ reduces the ester to a methyl group through benzylic deoxygenation (Scheme 1), leaving the homobenzylic alcohol intact and providing illudalane **7** in a 96% yield (77% from dimedone over five steps). Pentasubstituted arene **7** was first made from 4-bromo-*m*-xylene in seven steps by serial substitution (9% overall yield)[9] and was recently made by a six-step synthesis featuring the regioselective cycloaddition of a fused bicyclic thiophene *S*,*S*-dioxide (18% overall yield).[4i] Finally, Siegel oxidation[10] of **7** using phthaloyl peroxide introduces the phenol substituent and completes the synthesis of coprinol (six steps, 57% overall from dimedone). The last two steps—reduction and oxidation—can be reversed, in which case the oxidation (of benzoate **6**) is less efficient but the ensuing reductive deoxygenation to coprinol proceeds smoothly in refluxing THF. Overall, the process as reported above (reduction first, cf. Scheme 1) provides the best overall yield of coprinol.

Scheme 2. Synthesis of Alcyopterosins A, B, and O and Derivatives[a]



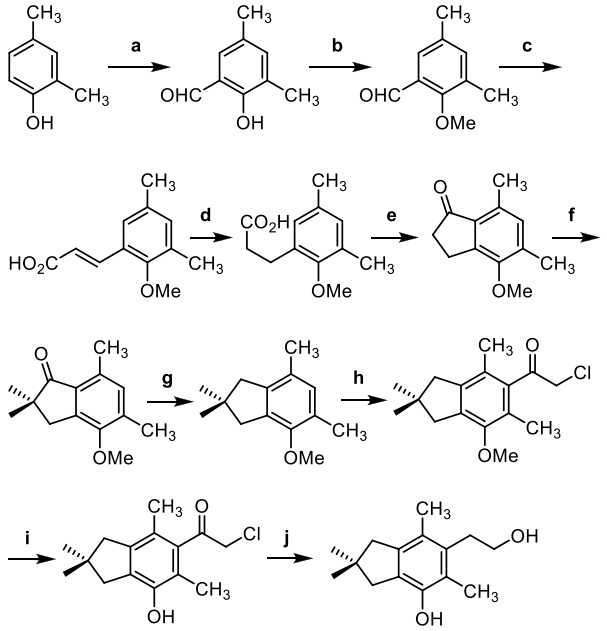
[a]Reaction conditions are as follows: (a) $SOCl_2$ and pyridine, quantitative; (b) PPh_3, NBS, and $AgNO_3$, 87%; (c) $LiAlH_4$ at rt, 92%; (d) Ac_2O, Et_3N, and 4-DMAP, 86%; (e) $(n\text{-}PrCO)_2O$, pyridine, and 4-DMAP, 88%

As noted above, this route can be diverted to several alcyopterosin natural products in addition to alcyopterosin O (Scheme 2). Chloridation or nitration of alcohol 7 provides alcyopterosin A (**9**) or B (**10**), respectively. This six-step route to alcyopterosins A and B is more efficient in terms of the overall yield and step count than the previous syntheses by us[2a] and others.[11] The acylation of alcyopterosin O with acetic or butyric anhydride yields two additional natural products, namely, 4,12-bis(acetyl)alcyopterosin O (**12**) and 4,12-bis-(butyryl)alcyopterosin O (**13**), from the Antarctic soft coral *Alcyonium grandis*.[12]

The previous 10-step synthesis of coprinol by serial aromatic substitution (Scheme 3) mirrors earlier approaches to illudalane sesquiterpenes, most notably those of illudalic acid[13] and alcyopterosin A[9] for medicinal chemistry applications. The fused neopentylene ring is crafted by first

https://doi.org/10.1021/acs.joc.2c01741
J. Org. Chem. 2022, 87, 14909−14914

Scheme 3. Previous Synthesis of Coprinol from 2,4-Dimethylphenol[a]



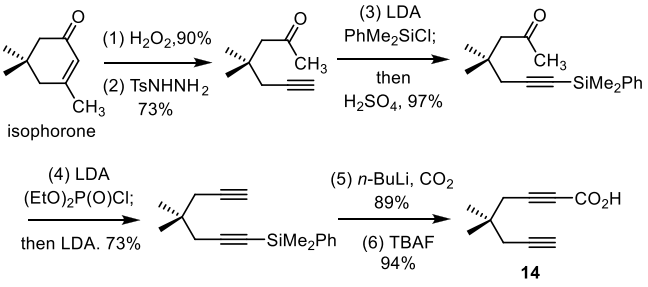
[a]Reaction conditions are as follows: (a) $(CHO)_n$, Et_3N, and $MgCl_2$, 90%; (b) CH_3I and K_2CO_3, 98%; (c) $CH_2(COOH)_2$ and piperidine, 98%; (d) Ni–Al alloy and $NaOH_{(aq)}$, 95%; (e) polyphosphoric acid, 88%; (f) NaH and CH_3I, 83%; (g) Zn amalgam and HCl, 90%; (h) $ClCOCH_2Cl$ and $AlCl_3$, 97%; (i) BBr_3, 90%; (j) $NaBH_4$, 77%.

annealing a fused cyclopentanone onto a pre-existing benzene core over several steps, followed by double methylation and the reduction of the ketone. One final aromatic substitution, namely, Friedel–Crafts acylation, and functional group manipulations provided coprinol.

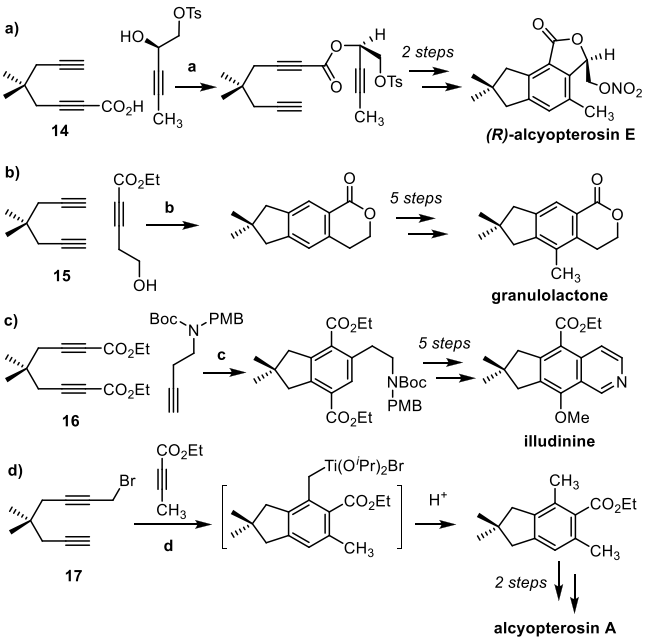
Previous syntheses of illudalanes featuring [2 + 2 + 2] alkyne cyclotrimerization highlight the regioselectivity challenges of this approach and thus the significance of the regioselective bimolecular cyclotrimerization featured herein. Witulski prepared alcyopterosin E[14] by fully intramolecular cyclotrimerization, which is cited as the most common means of controlling [2 + 2 + 2] alkyne cyclotrimerizations.[15] Zhang and co-workers attempted a bimolecular [2 + 2 + 2] alkyne cyclotrimerization of a nonsymmetrical diyne substrate en route to granulolactone, but after observing poor regioselectivity they resorted to using the symmetrical diyne **15**.[16] Deiters likewise employed a symmetrical diyne in cyclotrimerization to synthesize illudinine.[17] In each of these cases, regiocontrol was later achieved using aromatic substitution chemistry. The first synthesis of alcyopterosin A featured the bimolecular and regioselective, but not metal-catalyzed, [2 + 2 + 2] alkyne cyclotrimerization;[18] a stoichiometric low-valent titanium(II) reagent and a sacrificial bromine substituent were leveraged for regiocontrol in the cyclotrimerization.

The synthesis of NPT 1,6-diyne monoester **4** in three steps from dimedone is a recent ancillary innovation that enables more efficient syntheses of coprinol and other illudalanes. Analogous NPT diynes have been prepared from isophorone (Scheme 4) following a comprehensive study by Fleming.[19] For example, NPT 1,6-diyne monoacid **14** (which is also now available in three steps from dimedone[2e,5]) was previously prepared in six steps from isophorone and applied to the synthesis of alcyopterosin E (cf. Scheme 5a). Likewise, NPT

Scheme 4. Fleming Synthesis of NPT 1,6-Diyne Monoacid 14



Scheme 5. Previous Syntheses of Illudalanes Featuring 2-Component [2 + 2+2] Cyclotrimerization[a]



[a](a) Alcyopterosin E, (b) granulolactone, (c) illudinine, and (d) alcyopterosin A. Reaction conditions are as follows: (a) DCC and 4-DMAP, 70%; (b) $Rh(PPh_3)_3Cl$ and EtOH, then NaH, 60%; (c) $Ni(CO)_2(PPh_3)_3$, 84%; and (d) $Ti(O^iPr)_4$ and ^{i}PrMgCl, 73%.

diynes **15**–**17** (cf. Scheme 5b–d, respectively) were previously prepared from isophorone using this approach but are now more readily available from dimedone.[5] The new approach to NPT 1,6-diynes from dimedone formally shortens these prior syntheses and can streamline future synthetic approaches to the illudalane sesquiterpenes.

In summary, regioselective [2 + 2 + 2] alkyne cyclotrimerization and improved access to NPT 1,6-diynes enable the concise syntheses of coprinol and several alcyopterosins from dimedone. The penta- and hexasubstituted benzene cores of the illudalane sesquiterpenes present significant challenges for chemical synthesis, and the convergent benzannulation approach exemplified herein creates solutions that are strategically and tactically attractive for future efforts in synthetic and medicinal chemistry.

EXPERIMENTAL SECTION

General Information. The following general experimental methods apply to all procedures reported herein unless otherwise stated. All reactions were conducted in oven-dried glassware under an

https://doi.org/10.1021/acs.joc.2c01741
J. Org. Chem. 2022, 87, 14909–14914

atmosphere of nitrogen using anhydrous solvents. Dimedone (**1**), 3-pentynol (**5**), and all other chemicals were purchased from commercial sources and used as received. Syringes were used in all protocols that required the transfer of a liquid reactant of solvent unless otherwise stated. Tetrahydrofuran (THF) and dichloromethane (DCM) were dried under a column of molecular sieves in an argon atmosphere. A Schleck line was used in all reactions to purge reaction vessels and provide an inert nitrogen atmosphere. Column chromatography was performed using a Biotage Isolera One automated flash column system. Yields are reported as isolated yields of compounds considered to be ≥95% pure by ^{1}H NMR following flash chromatography. All new compounds were characterized using a JEOL 400 spectrometer to conduct ^{1}H and ^{13}C NMR spectroscopy in $CDCl_3$ (≥99.8 atom % D, contains 0.03% (v/v) TMS) purchased from Cambridge Isotope Laboratories. Chemical shifts (δ) are reported in units (ppm) referenced to 0.0 ppm TMS in the ^{1}H spectrum and 77.0 ppm $CDCl_3$ in the ^{13}C spectrum. Coupling constants (J) are reported in hertz (Hz). Mass spectrometry was performed on a Thermo Scientific Q Exactive Plus Hybrid Quadrupole-Orbitrap spectrometer, and spectra were recorded using electrospray ionization (ESI). Compounds **2**−**4** were prepared by our previously published methods.[2e,5]

2-(4-Carboethoxy-2,2,6-trimethylindan-5-yl)ethan-1-ol (6). To a 100 mL round-bottom flask were added a stir bar, (±)-BINAP (125 mg, 0.2 mmol, 5 mol %), and $[Rh(cod)_2]BF_4$ (81.2 mg, 0.2 mmol, 5 mol %). A rubber septum was attached, and the flask was evacuated and slowly backfilled with nitrogen before DCM (40 mL, 10 mL/mmol of diyne) was added. The nitrogen line was removed, and a hydrogen-filled balloon was inserted into the flask through the rubber septum. Another needle was inserted through the rubber septum, and the flask was purged with hydrogen for 5 min, at which point the needle was removed. The homogeneous orange solution was stirred at room temperature under the atmosphere of hydrogen gas for 1 h, at which point the active $Rh(BINAP)BF_4$ catalyst was assumed to have formed. The resulting mixture was concentrated by rotary evaporation, evacuated, and backfilled with nitrogen. To the mixture were then added DCM (10 mL, 0.4 M) and 3-pentynol (740 mg, 8.8 mmol, 2.2 equiv) separately. Immediately afterward, to the mixture was slowly added a solution of diyne monoester **4** (769 mg, 4.0 mmol, 1.0 equiv) in 20 mL of DCM over 1 h at room temperature using a syringe pump. The resulting solution was stirred for an additional 30 min, concentrated by rotary evaporation, and purified by column chromatography on silica gel (5−40% EtOAc/hexanes) to give **6** (1.08 g, 97% yield) as a thick colorless oil, R_f = 0.36 (40% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 4.38 (q, J = 7.2 Hz, 2H), 3.83 (dt, J = 6.6, 5.0 Hz, 2H), 2.97 (t, J = 6.6 Hz, 2H), 2.84 (t, J = 5.0 Hz, 1H), 2.76 (s, 2H), 2.67 (s, 2H), 2.32 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H), 1.13 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.4, 142.4, 135.4, 130.3, 129.3, 62.2, 61.2, 47.7, 47.3, 39.8, 33.4, 28.8, 19.9, 14.3 ppm. HRMS (ESI) $[M + H]^+$ calculated for $C_{17}H_{25}O_3^-$: 277.1798. Found: 277.1798. Structural assignments were made with additional information from NOESY experiments (see the SI for more details).

2-(2,2,4,6-Tetramethylindan-5-yl)ethan-1-ol (7). Two hot silicone oil baths were first prepared, one at 70 °C and the other one at 180 °C. A 15 mL pressure tube equipped with a stir bar was sealed using a septum. The tube was repeatedly evacuated and backfilled with nitrogen (three times), then to the tube were added **6** (304 mg, 1.10 mmol, 1.0 equiv) and THF (1.1 mL, 1 M). The tube was inserted into an ice bath and stirred for 10 min. To the tube was slowly added a solution of $LiAlH_4$ (11 mL, 1 M in THF, 11.0 mmol, 10 equiv) over 10 min using a syringe pump. The tube was then inserted into the 70 °C oil bath, and a needle was inserted through the rubber septum to allow for the evaporation of THF while the tube was purged with an increased flow of nitrogen. After ca. 15 min, when the volume decreased to about 4 mL, the needle was removed, and the tube was sealed using a seal-plug and O-ring and inserted into the 180 °C bath. The reaction mixture was stirred at 180 °C for 5 h, at which point it turned into a gray suspension. The flask was then placed in an ice bath, and the suspension was diluted using 10 mL of diethyl ether. The excess LiAlH4 was quenched by the sequential slow addition of 0.42 mL of H_2O, 0.42 mL of 15% NaOH(aq), and 1.3 mL of water. The ice bath was then removed, and the mixture was stirred at room temperature for 15 min. To the mixture was then added $MgSO_4$. The resulting mixture was then filtered and concentrated by rotary evaporation to provide a crude white solid, which was purified by column chromatography on silica gel (3−40% EtOAc/hexanes) to give **7** (231 mg, 96% yield) as a white solid, R_f = 0.46 (40% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (s, 1H), 3.74 (t, J = 7.5 Hz, 2H), 2.95 (t, J = 7.5 Hz, 2H), 2.69 (s, 2H), 2.65 (s, 2H), 2.32 (s, 3H), 2.21 (s, 3H), 1.42 (br s, 1H), 1.14 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.2, 140.7, 134.8, 132.9, 131.8, 124.2, 62.0, 47.9, 47.2, 39.2, 32.8, 29.3, 20.4, 16.1 ppm. HRMS (ESI) $[M + Na]^+$ calculated for $C_{15}H_{22}ONa^+$: 241.1563. Found: 241.1562.

2-(4-Hydroxy-2,2,5,7-tetramethylindan-6-yl)ethan-1-ol (Coprinol, 8). A 20 mL reaction vial equipped with a stir bar and a Teflon septum was charged with alcohol **7** (129 mg, 0.589 mmol, 1.0 equiv) and 5.9 mL hexafluoroisopropanol (0.1 M) under a nitrogen atmosphere. To the mixture was added phthaloyl peroxide (126 mg, 0.766 mmol, 1.3 equiv) was in small portions. The vial was inserted into a 40 °C oil bath, and the mixture was stirred for 24 h. The vial was then removed from the oil bath, and the solvent was removed in vacuo by rotary evaporation. MeOH (5.4 mL) and saturated sodium bicarbonate (0.56 mL) were added separately, and the mixture was heated again at 40 °C under a nitrogen atmosphere for 6 h. The oil bath was removed, and the reaction was diluted with 7 mL of pH 7 phosphate buffer. The solution was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under rotary evaporation. The crude brown oil was purified by column chromatography on silica gel (3−40% EtOAc/hexanes) to give **8** (105 mg, 76% yield) as an orange solid, R_f = 0.23 (40% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39 (s, 1H), 3.73 (t, J = 7.6 Hz, 2H), 2.96 (t, J = 7.6 Hz, 2H), 2.69 (s, 2H), 2.64 (s, 2H), 2.23 (s, 3H), 2.15 (s, 3H), 1.18 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.3, 141.5, 133.8, 125.7, 124.9, 120.5, 62.1, 47.6, 43.9, 39.5, 33.0, 29.5, 15.9, 11.8 ppm. HRMS (ESI) $[M - H]^-$ calculated for $C_{15}H_{21}O_2^-$: 233.1547. Found: 233.1537.

2-(4-Hydroxymethyl-2,2,6-trimethylindan-5-yl)ethan-1-ol (Alcyopterosin O, 11). To an ice-cooled THF (13 mL, 0.2 M) solution of **6** (750 mg, 2.71 mmol, 1.0 equiv) in a 50 mL round-bottom flask was added dropwise a solution of $LiAlH_4$ (14 mL, 1 M in THF, 10 equiv). The suspension was allowed to warm to room temp and stirred overnight. The reaction mixture was then cooled in an ice bath, and the reaction was quenched by the sequential slow addition of 0.51 mL of H_2O, 0.51 mL of 15% NaOH (aq), and 1.5 mL of water. The ice bath was then removed, and the mixture was stirred at room temperature for 15 min. To the mixture was then added $MgSO_4$. The resulting mixture was then filtered and concentrated by rotary evaporation to provide a crude colorless oil, which was purified by column chromatography on silica gel (5−40% EtOAc/hexanes) to give **11** (544 mg, 92% yield) as a thick colorless oil that froze into an off-white solid upon standing in the refrigerator, R_f = 0.17 (40% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (s, 1H), 4.57 (s, 2H), 3.80 (t, J = 5.8 Hz, 2H), 2.97 (t, J = 5.8 Hz, 2H), 2.79 (s, 2H), 2.69 (s, 2H), 2.28 (s, 3H), 1.14 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.9, 141.2, 135.6, 134.8, 133.7, 126.9, 61.3, 59.6, 47.8, 46.4, 39.5, 31.5, 29.1, 20.2 ppm. HRMS (ESI) $[M - H]^-$ calculated for $C_{15}H_{21}O_2^-$: 233.1547. Found: 233.1548.

4,12-Bis(acetyl)alcyopterosin O (12). Alcyopterosin O (140 mg, 0.597 mmol, 1.0 equiv) and DCM (3.0 mL, 0.2 M) were added to an 8 mL reaction vial under a nitrogen atmosphere. To the mixture was added Ac_2O (0.17 mL, 1.79 mmol, 3.0 equiv) dropwise before the flask was immersed in an ice bath for 10 min. To the mixture were added Et_3N (0.25 mL, 1.79 mmol, 3.0 equiv) dropwise and DMAP (7.4 mg, 10 mol %) was added in one-portion. After 10 min, the ice bath was removed and the reaction mixture was allowed to stir at room temp for 1 h, at which point sat. $NaHCO_3$ (15 mL) was added to the mixture and the aqueous layer was repeatedly extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed

https://doi.org/10.1021/acs.joc.2c01741
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with brine, dried over MgSO4, and concentrated by rotary evaporation. The white solid residue was purified by column chromatography on silica gel (1−10% EtOAc/hexanes) to give **12** (164 mg, 86% yield) as a white solid, R_f = 0.36 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H), 5.15 (s, 2H), 4.15 (t, J = 8.0 Hz, 2H), 3.03 (t, J = 8.0 Hz, 2H), 2.74 (s, 2H), 2.70 (s, 2H), 2.35 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.14 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.05, 170.98, 142.44, 142.42, 135.5, 132.7, 130.2, 127.7, 63.8, 62.1, 47.6, 46.4, 39.7, 29.0, 28.6, 21.04, 21.02, 20.0 ppm. HRMS (ESI) [M + Na]$^+$ calculated for $C_{19}H_{26}O_4Na^+$: 341.1723. Found: 341.1714.

4,12-Bis(butyryl)alcyopterosin O (13). Alcyopterosin O (140 mg, 0.597 mmol, 1.0 equiv) and DCM (3.0 mL, 0.2 M) were added to an 8 mL reaction vial under a nitrogen atmosphere. To the reaction mixture were added butyric anhydride (0.30 mL, 1.79 mmol, 3.0 equiv) and pyridine (0.15 mL, 1.79 mmol, 3.0 equiv) dropwise and DMAP (7.4 mg, 10 mol %) in one portion. After 10 min, the reaction mixture was warmed in an oil bath at 45 °C and stirred for 6 h. The oil bath was removed, the reaction was quenched with sat. $NaHCO_3$ (15 mL), and the aqueous layer was repeatedly extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with 1 M HCl and then brine, dried over MgSO4, and concentrated by rotary evaporation. The crude colorless oil was purified by column chromatography on silica gel (1−10% EtOAc/hexanes) to give **13** (197 mg, 88% yield) as a colorless oil, R_f = 0.51 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (s, 1H), 5.15 (s, 2H), 4.15 (t, J = 7.9 Hz, 2H), 3.03 (t, J = 7.9 Hz, 2H), 2.74 (s, 2H), 2.69 (s, 2H), 2.36 (s, 3H), 2.294 (t, J = 7.5 Hz, 2H), 2.289 (t, J = 7.5 Hz, 2H), 1.652 (sextet, J = 7.4, 2H), 1.647 (sextet, J = 7.4, 2H), 1.14 (s, 6H), 0.94 (t, J = 7.4 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.7, 173.6, 142.39, 142.36, 135.5, 132.8, 130.4, 127.6, 63.7, 61.9, 47.6, 46.4, 39.7, 36.17, 36.16, 29.0, 28.6, 20.0, 18.5, 18.4, 13.7 ppm. HRMS (ESI) [M + Na]$^+$ calculated for $C_{23}H_{34}O_4Na^+$: 397.2349. Found: 397.2336.

1-Chloro-2-(2,2,4,6-tetramethylindan-5-yl)ethane (Alcyopterosin A, 9). To a 5 mL pear-shaped flask equipped with a triangular stir bar were added alcohol 7 (65.0 mg, 0.298 mmol, 1.0 equiv) and pyridine (0.12 mL, 1.49 mmol, 5.0 equiv). The flask was capped with a rubber septum before DCM (1.9 mL, 0.16 M) was added under a positive nitrogen flow. The flask was then cooled in an ice bath, and the reaction mixture stirred for 10 min before a solution of thionyl chloride (0.11 mL, 1.49 mmol, 5.0 equiv) in 1 mL of DCM was added dropwise over a period of 20 min using syringe pump. The ice bath was removed, and the mixture was stirred at room temp for 2 h, then heated at a gentle reflux (45 °C) for 8 h. The reaction mixture was diluted with DCM (3 mL) and cooled in an ice bath before it was poured into cold DI water (10 mL). The DCM layer was separated, and the aqueous layer was repeatedly extracted with DCM (3 × 10 mL). The combined DCM layers were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The colorless crude oil was judged to be >95% pure by ^{1}H NMR, yielding 71 mg **9** (quantitative), R_f = 0.67 (20% EtOAc/hexanes). The product froze into a white solid upon standing in the refrigerator. Characterization data match those reported previously by us and others.[2a,9,18] ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (s, 1H), 3.52 (t, J = 8.3 Hz, 2H), 3.11 (t, J = 8.3 Hz, 2H), 2.68 (s, 2H), 2.64 (s, 2H), 2.31 (s, 3H), 2.20 (s, 3H), 1.14 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.8, 140.8, 134.6, 132.6, 131.9, 124.3, 47.9, 47.1, 42.5, 39.3, 33.5, 29.3, 20.2, 15.9 ppm.

2-(2,2,4,6-Tetramethylindan-5-yl)-1-nitroxyethane (Alcyopterosin B, 10). By analogy to a literature procedure,[20] alcohol 7 (75.0 mg, 0.344 mmol, 1.0 equiv) and triphenylphosphine (100 mg, 0.378 mmol, 1.1 equiv) were dissolved in a mixture of acetonitrile (0.38 mL, 0.9 M) and DCM (0.15 mL, 2.27 M) in a 8 mL reaction vial for about 10 min under a nitrogen atmosphere. The reaction mixture was then cooled to about −40 °C in a dry ice/acetone bath and *N*-bromosuccinimide (68.0 mg, 0.378 mmol, 1.1 equiv) was added in one portion. The cooling bath was removed, and *N*-bromosuccinimide was slowly dissolved in the solution. After 10 min, to the reaction mixture was added silver nitrate (88.4 mg, 0.515 mmol, 1.5 equiv) in one portion. The reaction mixture was then allowed to stir at room temp for 40 h. The suspension was diluted with DCM (5 mL) and filtered through a pad of Celite, then concentrated by rotary evaporation. The crude colorless oil was purified by column chromatography on silica gel (1−5% EtOAc/hexanes) to give **10** (78.8 mg, 87% yield) as a colorless oil that froze into a white solid upon standing in the refrigerator, R_f = 0.68 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 1H), 4.48 (t, J = 8.2 Hz, 2H), 3.07 (t, J = 8.2 Hz, 2H), 2.70 (s, 2H), 2.66 (s, 2H), 2.32 (s, 3H), 2.22 (s, 3H), 1.15 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 142.1, 141.0, 134.8, 132.9, 129.3, 124.5, 71.5, 47.9, 47.1, 39.3, 29.3, 27.1, 20.2, 16.0 ppm. HRMS (ESI) [M + Na]$^+$ calculated for $C_{15}H_{21}NO_3Na^+$: 286.1414. Found: 286.1412.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01741.

^{1}H NMR and ^{13}C NMR spectra for compounds **2**−**13** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by grants from the National Science Foundation (CHE-1834949 and CHE-2154773), with additional support from West Virginia University and the Eberly Family Foundation.

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https://doi.org/10.1021/acs.joc.2c01741
J. Org. Chem. 2022, 87, 14909−14914