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Total Synthesis of Clerobungin A via a Cascade Cyclization Reaction

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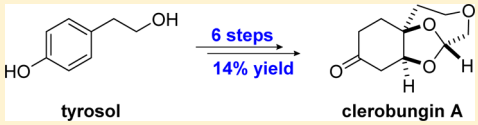
Supporting Information

ABSTRACT: The first total synthesis of the novel cyclohexylethanoid natural product clerobungin A has been achieved in six steps and 14% overall yield starting from commercially available tyrosol. Key steps in this sequence include a bioinspired oxidative dearomatization of a phenol and a hemiacetalization/oxa-Michael cascade to form the tricyclic ring system. Resolution of a late-stage intermediate via chiral HPLC allowed for the measurement of the chiroptical properties of both enantiomers of clerobungin A, supporting the scalemic nature of the natural product.



Flowering plants of the genus *Clerodendrum* have been used in traditional Indian and Chinese folk medicine to treat a wide range of ailments, including hypertension and rheumatism.[1−6] In 2014, Xue and Zhang reported the isolation of the novel cyclohexylethanoid clerobungin A (**1**), which was obtained from the aerial parts of the shrub *Clerodendrum bungei* (Figure 1).[7] Perhaps the most unusual structural feature

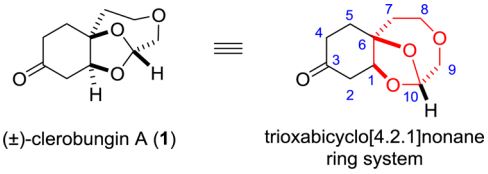


Figure 1. Structure of clerobungin A (**1**).

of **1** is the rigid trioxabicyclo[4.2.1] ring system, which is unique among natural products. Additionally, the authors report that **1** was isolated as a scalemic (i.e., chiral, nonracemic) mixture of enantiomers in a 55:45 ratio, as determined by HPLC using a chiral stationary phase.

Although the vast majority of chiral natural products are isolated as single enantiomers, the formation of enantiomeric and/or diastereomeric mixtures is especially common in plants that produce cyclohexylethanoids (Figure 2).[8] The biosynthetic precursor for this class of natural products is believed to be salidroside (**2**), which is the glucoside of tyrosol.[9] Inoue has demonstrated that oxidation of compound **2** with salidroside monooxygenase (a cytochrome P450 enzyme) forms cornoside (**3**),[10] a benzoquinol-containing natural product that is widely distributed among plant species.[11,12] Interestingly, the oxidative dearomatization of **2** (and its derivatives) has also been achieved in the laboratory, using either singlet oxygen[13,14] or thallium(III) perchlorate.[15]

The related natural products dihydrocornoside (**4**) and *syn*-diol **5** could presumably arise from biological semireduction or hydration of **3**, respectively. It is interesting to note that the aglycons of **4** and **5** were found to be racemic, and these compounds could serve as precursors to cleroindicins C and D (**6** and **7**) via intramolecular conjugate addition.[8] By a similar

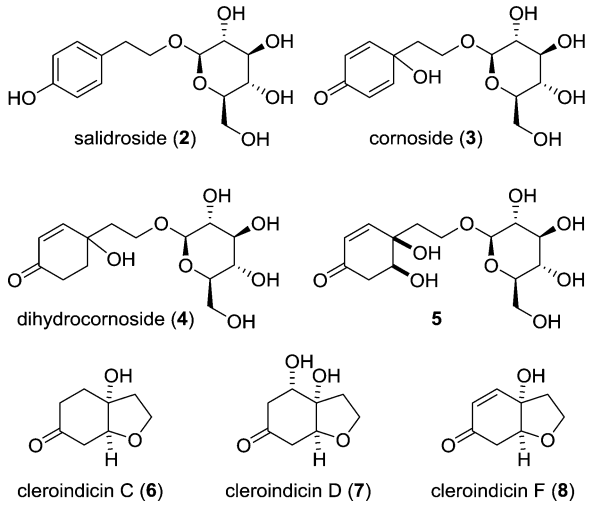


Figure 2. Representative cyclohexylethanoid natural products.

mechanism, the aglycon of **3** is known to spontaneously cyclize to form cleroindicin F (**8**),[13] which was coisolated with **1** in the extracts of *C. bungei*.[7] In 2009, Pettus clarified several discrepancies in the reported optical rotations and absolute configurations of the cleroindicins through enantioselective chemical synthesis.[16] In particular, this work confirmed the scalemic nature of the cleroindicins, and this result could have important implications for the biosynthesis of other members of the cyclohexylethanoid class of natural products, including **1**.

Clerobungin A differs from other cyclohexylethanoids in that it contains an additional two-carbon fragment formally derived from 2-hydroxyacetaldehyde (comprising C-9 and C-10). Although similar trioxabicyclo[4.2.1] ring systems have been prepared by intramolecular etherification[17] or gold-catalyzed cycloketalization of an alkyne,[18−20] we envisioned that this tricycle might be formed through the biomimetic cascade reaction sequence depicted in Scheme 1.

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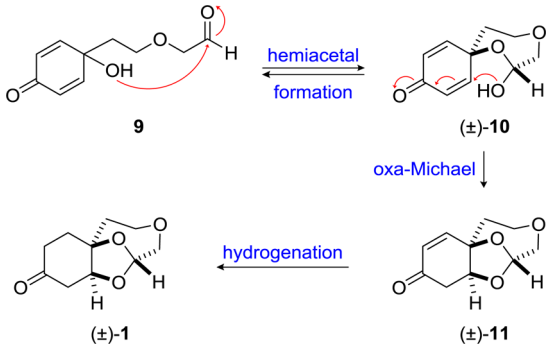
Scheme 1. A Cyclization Cascade To Form the Trioxabicyclo[4.2.1] Ring System of 1



The key intermediate for this cascade is benzoquinol **9**, which could be formed via oxidative dearomatization of a phenol. Under the reaction conditions, hydroxyaldehyde **9** could exist in equilibrium with cyclic hemiacetal **10**, forming a seven-membered ring and the first stereogenic center. A subsequent intramolecular oxa-Michael addition of the hydroxyl group to one of the prochiral faces of the dienone would give (±)-**11**, establishing the two remaining stereocenters and completing the trioxabicyclo[4.2.1] framework. In a final step, hydrogenation of **11** would directly form (±)-**1**.

It is important to note that hemiacetal formation in compound **9** should be reversible, and we would expect only a very small concentration of the cyclic tautomer **10** to exist at equilibrium.[21] However, we hoped to take advantage of the thermodynamically favorable oxa-Michael reaction to provide an overall driving force for the formation of tricycle **11**.[22] Notably, this proposed cascade would rapidly generate molecular complexity, forming two rings and three stereocenters in a single step.

Our synthesis started with known alcohol **12** (Scheme 2), which can be prepared in a single step from commercially available tyrosol.[23] Etherification of **12** with bromoacetaldehyde diethyl acetal under standard Williamson conditions furnished ether **13** in 61% yield (82% based on recovered **12**), which already contains all of the carbon atoms present in the natural product. Subsequent hydrogenolysis of the benzyl ether proceeded in quantitative yield to give free phenol **14**.

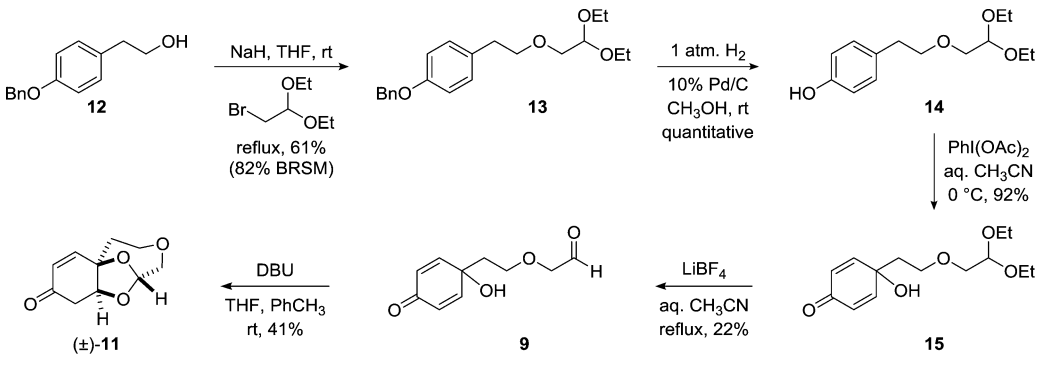
At this stage, we pursued several different strategies to prepare aldehyde **9**, which would serve as the substrate for our proposed cyclization cascade. In general, we found that yields were highest when oxidative dearomatization preceded acetal hydrolysis. Thus, treatment of phenol **14** with (diacetoxyiodo)-benzene in aqueous acetonitrile afforded benzoquinol **15** in 92% yield.[24]

By far, the most challenging aspects of our synthesis were chemoselectively hydrolyzing diethyl acetal **15** and dealing with the rather unstable aldehyde **9**. Indeed, complex mixtures of products were obtained when **15** was treated directly with aqueous Brønsted acids such as HCl or *p*-TsOH. However, we found that heating **15** with 1 equiv of lithium tetrafluoroborate[25] in aqueous acetonitrile resulted in essentially quantitative conversion to the desired aldehyde **9**, as determined by TLC. Unfortunately, serious complications arose when we tried to isolate compound **9** from the crude reaction mixture. For example, **9** is highly water-soluble, and it was difficult to extract this compound into organic solvents. We also found that significant amounts of insoluble polymeric material were formed when solutions of **9** were concentrated, further reducing the isolated yield to 22% after purification by column chromatography. Interestingly, only the aldehyde tautomer could be detected upon NMR analysis of **9** in $CDCl_3$ solution; none of the cyclic seven-membered hemiacetal **10** was observed.

Despite this low-yielding step, the brevity of the overall synthetic sequence and the high yields in the previous steps allowed us to prepare sufficient amounts of **9** to investigate the key cyclization cascade. After screening several different reagents, we were pleased to observe that treating aldehyde **9** with 30 mol % of the amidine base DBU effected the desired cyclization to form tricyclic enone (±)-**11** as a single diastereomer in 41% yield. As before, some polymeric material was formed in this reaction due to decomposition of the aldehyde, undoubtedly contributing to the moderate yield. Nevertheless, this transformation succeeded in forming the characteristic trioxabicyclo[4.2.1] ring system, provided that **9** was subjected to the reaction conditions immediately after purification.

In an effort to improve the overall yield of this cascade cyclization sequence, we sought to modify the route so that the problematic aldehyde intermediate **9** would not have to be isolated (Scheme 3). Although the deprotection of acetal **15** with $LiBF_4$ was quantitative by TLC, we never observed formation of tricyclic enone **11**, even after prolonged periods of reflux. Therefore, we attempted to induce cyclization by adding acids or bases *in situ* after acetal deprotection was complete. After extensive experimentation, we found that simply adding 20 mol % of *p*-TsOH to the refluxing solution of crude **9** promoted the desired cyclization cascade, giving tricyclic enone **11** in an improved 31% yield over the two steps.

Scheme 2. Synthesis of Tricycle 11



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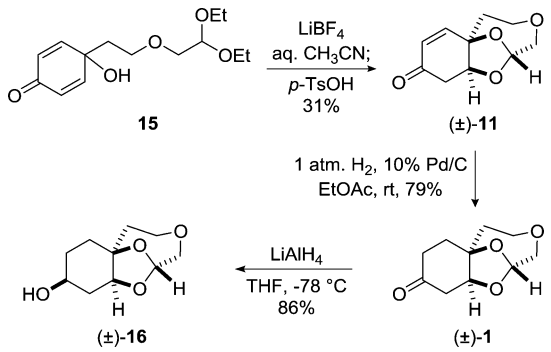
Scheme 3. An Improved One-Pot Two-Step Synthesis of (±)-11 and Its Conversion to (±)-1



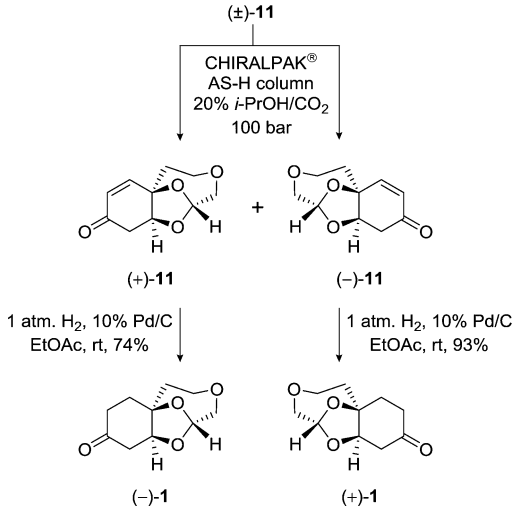
It is somewhat surprising that directly heating an aqueous solution of **15** in acetonitrile with the same amount of *p*-TsOH results in extensive decomposition, with less than 5% formation of enone **11**, as estimated by crude ^{1}H NMR. Although it is possible that the formation of **11** under aqueous acidic conditions proceeds via the same mechanism outlined in Scheme 1, we cannot rule out the possibility of acid-catalyzed enone hydration followed by intramolecular acetal formation. Regardless, we found that this one-pot two-step reaction sequence was highly reproducible whereas the two-step acetal hydrolysis/DBU-mediated cyclization sequence was far less reliable. With tricycle **11** in hand, all that remained to complete the synthesis was hydrogenation of the alkene using palladium on carbon as a catalyst, which afforded racemic clerobungin A (**1**) in 79% yield. The ^{1}H and ^{13}C NMR spectra for this synthetic material were identical to those reported by Xue and Zhang for the natural product (see the Supporting Information for a full spectral comparison).

At this stage, we pursued several strategies to resolve the enantiomers of (±)-**1** in order to verify the chiroptical properties reported for the scalemic natural product. Initially, we attempted to prepare diastereomeric derivatives of clerobungin A that could be separated using conventional column chromatography. For example, Fessner and Prinzbach pioneered the use of (2*R*,3*R*)-2,3-butanediol as a chiral derivatizing agent for the resolution of ketones.[26] Unfortunately, all attempts to prepare diastereomeric ketals from (±)-**1** using enantiopure vicinal diols were low-yielding and accompanied by significant decomposition of the starting material.

Pursuing alternative methods for resolution, we found that (±)-**1** could be reduced diastereoselectively using lithium aluminum hydride to form alcohol (±)-**16** in 86% yield (Scheme 3). The equatorial orientation of the hydroxyl group was determined by analyzing coupling constants for the corresponding methine signal at 3.16 ppm (dddd, J = 10.2 Hz, 10.2 Hz, 4.4 Hz, 4.4 Hz) and is consistent with the preference for axial delivery of hydride in similar conformationally biased cyclohexanones.[27] Although we were able to convert (±)-**16** to a mixture of diastereomeric carbamates using either (*R*) or (*S*) α-methylbenzyl isocyanate, these isomers proved to be inseparable by chromatography. Similarly, carbodiimide-mediated esterification of (±)-**16** with (1*S*)-(+)-ketopinic acid gave an inseparable mixture of diastereomers, as did esterification under Mitsunobu conditions to give the corresponding axial isomers.[28] In all cases, it seems that the newly introduced stereocenters were too remote from the tricycle to induce a substantial difference in polarity for the diastereomeric products.

Given these unsuccessful attempts to resolve (±)-**1** through chemical derivatization, we investigated separation of the enantiomers via preparative HPLC using a chiral stationary phase. Although we could not identify a suitable method for the direct resolution of (±)-**1**, we were able to resolve racemic enone **11** through supercritical fluid chromatography (20% isopropanol/CO_2) using a preparative CHIRALPAK AS-H column. This method provided enantiomerically pure samples of (+)-**11** and (−)-**11** that were subsequently hydrogenated to afford both enantiomers of clerobungin A (Scheme 4).

Scheme 4. Resolution of (±)-11 via Chiral HPLC and Synthesis of Both Enantiomers of Clerobungin A



Xue and Zhang report that scalemic clerobungin A had an observed optical rotation of +36.2° and that this corresponded to a 55:45 mixture of (+)-**1** and (−)-**1**, as determined by chiral HPLC. Our synthetic samples of (+)-**1** and (−)-**1** had specific rotations of +181.5° and −181.3°, respectively. Using these experimentally determined values, the observed optical rotation of the scalemic natural product would correspond to a 60:40 mixture of enantiomers, which is in good agreement with the reported data.

The circular dichroism spectra for both enantiomers of synthetic clerobungin A were also recorded, as shown in Figure 3. We were pleased to observe that the CD spectrum of (+)-**1** matched the one reported by Xue and Zhang for scalemic clerobungin A, exhibiting a positive Cotton effect at λ_{max} = 294

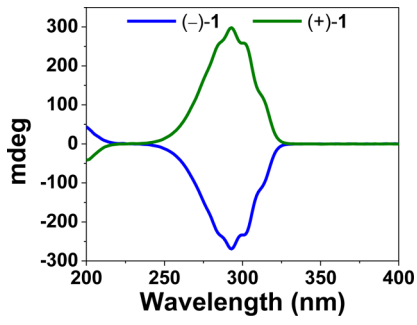


Figure 3. Circular dichroism spectra of (+)-**1** and (−)-**1** (3 mM in CH_3CN).

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nm. Moreover, the experimental CD spectra for both enantiomers were in good agreement with those calculated using time-dependent density functional theory, which established the absolute configuration of the major enantiomer (+)-**1**.[7]

In conclusion, we have achieved the first total synthesis of the novel cyclohexylethanoid natural product clerobungin A in six linear steps and 14% overall yield starting from commercially available tyrosol. The key steps in this sequence include a bioinspired oxidative dearomatization and a cyclization cascade to form the complex tricyclic ring system. The route described herein allows for the preparation of significant amounts of this scarce natural product along with several unnatural analogues (**11** and **16**). Finally, resolution of enone (±)-**11** via chiral preparative HPLC allowed us to examine the chiroptical properties of both enantiomers of synthetic clerobungin A. In particular, our data support the conclusion of Xue and Zhang that clerobungin A was isolated from the natural source as a scalemic mixture.

EXPERIMENTAL SECTION

General Protocols. All reactions were carried out in flame-dried glassware (unless water was present in the reaction mixture) with magnetic stirring under a positive pressure of argon. ACS reagent grade acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc), hexanes, methanol (CH_3OH), tetrahydrofuran (THF), and toluene ($PhCH_3$) were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using glass plates precoated with a 0.25 mm layer of silica gel containing a fluorescent indicator. TLC plates were visualized by exposure to ultraviolet light and subsequently stained with acidic ethanolic *p*-anisaldehyde solution followed by heating on a laboratory hot plate. Silica gel for flash column chromatography had a 60 Å pore size and 40−63 μm particle size and was 230−400 mesh.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were collected at 400 MHz and are calibrated to the residual monoprotio solvent peak ($CHCl_3$: 7.26 ppm; C_6D_6: 7.16 ppm). Coupling constants were extracted assuming first-order coupling. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were collected at 100 MHz and calibrated to the deuterated solvent peak ($CDCl_3$: 77.1 ppm; C_6D_6: 128.1 ppm). Infrared (IR) spectra for both solids and oils were recorded using an ATR accessory. High resolution mass spectral (HRMS) data were obtained using an electrospray ionization LC/MS equipped with a time-of-flight mass analyzer.

1-(Benzyloxy)-4-(2-(2,2-diethoxyethoxy)ethyl)benzene (13). A solution of benzyl-protected phenol **12** (5.82 g, 25.5 mmol, 1.00 equiv) in 125 mL of THF was cooled to 0 °C in an ice bath, and solid sodium hydride (60% dispersion in mineral oil, 3.06 g, 76.5 mmol, 3.00 equiv) was added portionwise over the course of 10 min. After hydrogen gas evolution had ceased, the reaction mixture was allowed to warm slowly to room temperature, and neat bromoacetaldehyde diethyl acetal (15.3 mL, 102 mmol, 4.00 equiv) was added dropwise over 5 min. The flask was then equipped with a condenser, and the reaction mixture was heated to reflux for 16 h, at which point TLC (3:1 hexanes/EtOAc, UV/anisaldehyde) showed a mixture of unreacted **12** (R_f = 0.13) and the desired ether **13** (R_f = 0.45). After cooling to room temperature, the reaction was quenched by the careful, dropwise addition of saturated aqueous NH_4Cl solution. The reaction mixture was diluted with water and EtOAc, and the layers were separated. The aqueous phase was extracted with two additional portions of EtOAc before the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give an oily solid that was taken up in 25 mL of petroleum ether, filtered, and washed with an additional 10 mL of petroleum ether to give 1.50 g of recovered **12** as a white solid. The filtrate was concentrated under reduced pressure to give an orange oil that was purified by column chromatography (9:1 hexanes/EtOAc → 3:1) to give ether **13** as a colorless oil (5.322 g, 61%, 82% based on recovered starting material).

IR (neat) ν 2974, 2867, 1611, 1510, 1454, 1379, 1238, 1176, 1111, 1060, 1024, 923, 821, 733, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.31 (5H, m), 7.16 (2H, d, J = 8.4 Hz), 6.92 (2H, d, J = 8.4 Hz), 5.05 (2H, s), 4.64 (1H, m), 3.75−3.66 (4H, m), 3.61−3.51 (4H, m), 2.86 (2H, t, J = 7.2 Hz), 1.24 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 137.2, 131.2, 129.9 (2C), 128.6, 127.9, 127.5, 114.7 (2C), 101.1, 72.8, 71.6, 70.0, 62.3, 35.4, 15.4; HRMS (ESI+) calcd for $C_{21}H_{28}NaO_4$ ([M + Na]$^+$): 367.1885, found 367.1882.

4-(2-(2,2-Diethoxyethoxy)ethyl)phenol (14). To a solution of ether **13** (4.30 g, 12.5 mmol, 1.00 equiv) in 200 mL of CH_3OH was cautiously added 10% palladium on carbon (664 mg, 0.62 mmol, 0.05 equiv) under an atmosphere of argon. The flask was then evacuated and put under an atmosphere of hydrogen gas using a balloon, and the reaction mixture was stirred vigorously at room temperature for 1.5 h. After this time, TLC (3:1 hexanes/EtOAc, UV/anisaldehyde) showed complete consumption of **13** (R_f = 0.45) and clean formation of **14** (R_f = 0.27). The reaction mixture was filtered through a pad of Celite, which was washed with an additional 100 mL of EtOAc. The filtrate was evaporated under reduced pressure to give phenol **14** as a colorless oil that was used without further purification (3.17 g, quantitative).

IR (neat) ν 3360, 2975, 2870, 1614, 1595, 1515, 1443, 1374, 1264, 1224, 1172, 1104, 1052, 828 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (2H, d, J = 8.5 Hz), 6.74 (2H, d, J = 8.5 Hz), 5.39 (1H, br s), 4.63 (1H, t, J = 5.3 Hz), 3.73−3.64 (4H, m), 3.60−3.53 (2H, m), 3.51 (2H, d, J = 5.3 Hz), 2.81 (2H, t, J = 7.2 Hz), 1.21 (6H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 130.2 (2C), 129.9, 115.3 (2C), 101.0, 72.9, 71.3, 62.5, 35.2, 15.3; HRMS (ESI+) calcd for $C_{14}H_{22}NaO_4$ ([M + Na]$^+$): 277.1416, found 277.1410.

4-(2-(2,2-Diethoxyethoxy)ethyl)-4-hydroxycyclohexa-2,5-dien-1-one (15). A solution of phenol **14** (1.50 g, 5.90 mmol, 1.00 equiv) in 45 mL of CH_3CN and 15 mL of water was cooled to 0 °C in an ice bath, and solid (diacetoxyiodo)benzene (2.09 g, 6.49 mmol, 1.10 equiv) was added in a single portion. The initially colorless reaction mixture immediately turned yellow and gradually darkened to orange/brown. After 10 min at 0 °C, TLC (1:1 hexanes/EtOAc, UV/anisaldehyde) showed complete consumption of **14** (R_f = 0.60) and formation of **15** (R_f = 0.20). The reaction was quenched with 20 mL of saturated aqueous $Na_2S_2O_3$ solution followed by 20 mL of saturated aqueous $NaHCO_3$ solution. The resulting mixture was further diluted with saturated aqueous NaCl solution and EtOAc, and the layers were separated. The aqueous phase was extracted with two additional portions of EtOAc before the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (2:1 hexanes/EtOAc → 1:1 → 1:2) to give dienone **15** as a pale yellow oil (1.47 g, 92%).

IR (neat) ν 3407, 2976, 2876, 1667, 1625, 1396, 1269, 1171, 1107, 1054, 1021, 955, 928, 860, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (2H, d, J = 10.2 Hz), 6.12 (2H, d, J = 10.2 Hz), 4.61 (1H, t, J = 5.2 Hz), 4.02 (1H, br s), 3.76 (2H, m), 3.73−3.66 (2H, m), 3.59−3.51 (2H, m), 3.49 (2H, d, J = 5.2 Hz), 1.97 (2H, t, J = 5.8 Hz), 1.21 (6H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.6, 151.2 (2C), 127.4 (2C), 100.7, 71.5, 69.2, 68.3, 62.7, 39.5, 15.4; HRMS (ESI+) calcd for $C_{14}H_{22}NaO_5$ ([M + Na]$^+$): 293.1365, found 293.1358.

2-(2-(1-Hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethoxy)-acetaldehyde (9). To a solution of dienone **15** (1.37 g, 5.08 mmol, 1.00 equiv) in 45 mL of CH_3CN and 15 mL of water was added solid lithium tetrafluoroborate (477 mg, 5.08 mmol, 1.00 equiv). The flask was then equipped with a condenser, and the reaction mixture was heated to reflux for 5 h, at which point TLC (1:3 hexanes/EtOAc, UV/anisaldehyde) showed complete consumption of **15** (R_f = 0.41) and clean formation of aldehyde **9** (R_f = 0.11). After cooling to room temperature, the reaction mixture was diluted with EtOAc, and 15 mL of saturated aqueous NaCl solution were added. The layers were separated, and the aqueous phase was extracted with 6 × 25 mL portions of EtOAc, at which point TLC of the last organic extract showed that no additional product had been extracted. The combined

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organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give 950 mg of crude organic residue. This material (which contained a significant amount of an insoluble polymeric substance) was purified by column chromatography (1:1 hexanes/EtOAc → 1:2 → 100% EtOAc, loaded in CH_2Cl_2) to give aldehyde **9** as a yellow oil (222 mg, 22%). Due to the instability of this compound, it was immediately taken on to the subsequent cyclization step.

IR (neat) ν 3403, 2924, 1732, 1668, 1625, 1396, 1271, 1122, 862 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.70 (1H, s), 7.01 (2H, d, J = 10.2 Hz), 6.18 (2H, d, J = 10.2 Hz), 4.18 (2H, s), 3.76 (2H, t, J = 5.8 Hz), 2.07 (2H, t, J = 5.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 185.5, 151.0 (2C), 127.7 (2C), 76.5, 69.0, 68.1, 39.7; HRMS (ESI+) calcd for $C_{10}H_{12}NaO_4$ ($[M + Na]^+$): 219.0633, found 219.0623.

(±)-Tricyclic Enone 11. *Procedure A: DBU-Mediated Cyclization.* To a solution of purified aldehyde **9** (222 mg, 1.13 mmol, 1.00 equiv) in 10 mL of THF and 10 mL of $PhCH_3$ was added neat DBU (50 μL, 0.33 mmol, 0.30 equiv). The reaction mixture immediately darkened to orange/brown and was left to stir at room temperature for 16 h. After this time, TLC (1:3 hexanes/EtOAc, UV/anisaldehyde) showed complete consumption of aldehyde **9** (R_f = 0.11) and formation of enone **11** (R_f = 0.49). The reaction was quenched with 10 mL of 1 M aqueous HCl solution and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with one additional portion of EtOAc before the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a brown residue (containing some insoluble polymeric material) that was purified by column chromatography (1:1 hexanes/EtOAc → 1:2 → 1:3, loaded in CH_2Cl_2) to give tricyclic enone **11** as a colorless oil (91 mg, 41%).

Procedure B: One-Pot Acetal Hydrolysis/Cyclization with p-TsOH. To a solution of dienone **15** (1.06 g, 3.70 mmol, 1.00 equiv) in 35 mL of CH_3CN and 7 mL of water was added solid lithium tetrafluoroborate (347 mg, 3.70 mmol, 1.00 equiv). The flask was then equipped with a condenser, and the reaction mixture was heated to reflux for 4 h, at which point TLC (1:3 hexanes/EtOAc, UV/anisaldehyde) showed complete consumption of **15** (R_f = 0.41) and clean formation of aldehyde **9** (R_f = 0.11). Solid p-TsOH·H_2O (150 mg, 0.79 mmol, 0.21 equiv) was then added, and the reaction was refluxed for an additional 4 h, at which point TLC (1:3 hexanes/EtOAc, UV/anisaldehyde) showed complete consumption of aldehyde **9** (R_f = 0.11) and formation of enone **11** (R_f = 0.49). The reaction was quenched with 15 mL of saturated aqueous $NaHCO_3$ solution and diluted with water and EtOAc. The layers were separated, and the aqueous phase was extracted with two additional portions of EtOAc before the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (1:1 hexanes/EtOAc → 1:2 → 1:3, loaded in CH_2Cl_2) to give tricyclic enone **11** as a colorless oil (223 mg, 31% over two steps).

IR (neat) ν 2944, 1679, 1389, 1350, 1247, 1217, 1155, 1069, 1045, 894, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (1H, d, J = 10.2 Hz), 6.10 (1H, d, J = 10.2 Hz), 5.60 (1H, d, J = 1.6 Hz), 4.63 (1H, dd, J = 8.1 Hz, 6.8 Hz), 4.03 (1H, ddd, J = 12.6 Hz, 6.7 Hz, 4.0 Hz), 3.87 (1H, ddd, J = 12.6 Hz, 7.2 Hz, 4.3 Hz), 3.79 (1H, d, J = 12.8 Hz), 3.65 (1H, ddd, J = 12.8 Hz, 1.8 Hz, 0.8 Hz), 2.79 (1H, dd, J = 15.9 Hz, 6.7 Hz), 2.65 (1H, ddd, J = 15.9 Hz, 8.2 Hz, 0.8 Hz), 2.13 (1H, ddd, J = 14.4 Hz, 7.2 Hz, 4.3 Hz), 1.99 (1H, ddd, J = 14.4 Hz, 7.2 Hz, 4.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 145.3, 130.4, 105.2, 78.1, 77.3, 73.8, 66.6, 42.1, 41.8; HRMS (ESI+) calcd for $C_{10}H_{12}NaO_4$ ($[M + Na]^+$): 219.0633, found 219.0630; UV (hexanes) λ_{max}, nm: 210, 283, 339 (sh).

(±)-Clerobungin A (1). To a solution of tricyclic enone **11** (223 mg, 1.14 mmol, 1.00 equiv) in 20 mL of EtOAc was cautiously added 10% palladium on carbon (60 mg, 0.06 mmol, 0.05 equiv) under an atmosphere of argon. The flask was then evacuated and put under an atmosphere of hydrogen gas using a balloon, and the reaction mixture was stirred vigorously at room temperature for 30 min. After this time, TLC (1:1 hexanes/EtOAc, UV/anisaldehyde) showed complete consumption of **11** (R_f = 0.29) and clean formation of **1** (R_f = 0.21). The reaction mixture was filtered through a pad of Celite, which was washed with an additional 50 mL of EtOAc. The filtrate was evaporated under reduced pressure to give the crude product, which was purified by column chromatography (2:1 hexanes/EtOAc → 1:1) to give (±)-clerobungin A (**1**) as a white solid (177 mg, 79%).

Mp 95−97 °C; IR (solid ATR) ν 2939, 1715, 1449, 1403, 1337, 1247, 1180, 1155, 1057, 1030, 1011, 967, 879, 860, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.32 (1H, s), 4.77 (1H, dd, J = 4.1 Hz, 2.4 Hz), 4.12 (1H, ddd, J = 12.1 Hz, 6.4 Hz, 0.7 Hz), 3.88 (1H, d, J = 12.8 Hz), 3.76 (1H, ddd, J = 11.9 Hz, 11.9 Hz, 4.9 Hz), 3.46 (1H, dd, J = 12.8 Hz, 0.6 Hz), 2.66 (1H, dd, J = 16.4 Hz, 2.3 Hz), 2.54 (1H, ddd, J = 18.9 Hz, 13.4 Hz, 5.0 Hz), 2.47 (1H, dd, J = 16.4 Hz, 4.3 Hz), 2.27 (1H, ddd, J = 18.9 Hz, 4.2 Hz, 2.2 Hz), 2.19 (1H, ddd, J = 11.5 Hz, 7.0 Hz, 3.8 Hz), 2.12 (1H, ddd, J = 14.7 Hz, 5.0 Hz, 2.4 Hz), 1.99−1.91 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.6, 103.1, 81.2, 79.7, 76.7, 69.1, 42.8, 41.4, 33.9, 31.4; HRMS (ESI+) calcd for $C_{10}H_{14}NaO_4$ ($[M + Na]^+$): 221.0790, found 221.0786; UV (1.5 mM in CH_3CN) λ_{max}, nm: 193, 264.

(±)-Tricyclic Alcohol 16. To a flame-dried 100 mL flask under argon equipped with a magnetic stirring bar was added a solution of (±)-clerobungin A (100 mg, 0.50 mmol, 1.00 equiv) in 10 mL of anhydrous THF. This solution was cooled to −78 °C in a dry ice/acetone bath, and a 3.5 M solution of $LiAlH_4$ in toluene (144 μL, 0.50 mmol, 1.00 equiv) was added dropwise. After 30 min at −78 °C, TLC (1:3 hexanes/EtOAc, anisaldehyde) showed complete consumption of the starting material (R_f = 0.34) and clean formation of the product (R_f = 0.14). The excess $LiAlH_4$ was quenched by the addition of 500 μL of EtOAc, and the reaction mixture was diluted with saturated aqueous sodium potassium tartrate solution and water. After stirring vigorously at room temperature for 20 min, the layers were separated, and the aqueous phase was extracted with two additional portions of EtOAc before the combined organic phases were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (1:3 hexanes/EtOAc → 100% EtOAc) to give alcohol (±)-**16** as a colorless oil (87 mg, 86%).

IR (neat) ν 3394, 2939, 1160, 1061, 1015, 892, 855, 779 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 5.15 (1H, d, J = 1.9 Hz), 3.79 (1H, ddd, J = 12.2 Hz, 8.4 Hz, 3.0 Hz), 3.63 (1H, dd, J = 9.1 Hz, 6.4 Hz), 3.62−3.56 (1H, m), 3.59 (1H, d, J = 12.4 Hz), 3.45 (1H, dd, J = 12.5 Hz, 1.9 Hz), 3.16 (1H, dddd, J = 10.2 Hz, 10.2 Hz, 4.4 Hz, 4.4 Hz), 1.90 (1H, dddd, J = 12.6 Hz, 4.1 Hz, 4.1 Hz,1.9 Hz), 1.84 (1H, ddd, J = 15.0 Hz, 3.4 Hz, 3.4 Hz), 1.63−1.42 (5H, m), 1.20 (1H, ddd, J = 14.5 Hz, 6.2 Hz, 3.0 Hz), 0.96 (1H, ddd, J = 14.5 Hz, 13.3 Hz, 4.8 Hz); ^{13}C NMR (100 MHz, C_6D_6): δ 102.9, 79.4, 78.5, 72.5, 66.9, 66.0, 43.6, 38.2, 31.4, 30.4; HRMS (ESI+) calcd for $C_{10}H_{16}NaO_4$ ($[M + Na]^+$): 223.0946, found 223.0941.

Resolution of Enone 11. A sample of enone (±)-**11** (87 mg) was dissolved in 17.4 mL of 1:1 EtOH/CH_2Cl_2. This solution was then injected onto a preparative CHIRALPAK AS-H column (1 mL injections, 2 × 25 cm, 20% i-PrOH/CO_2, 100 bar, flow rate = 70 mL/min, detector set at 220 nm, run time = 6 min). The first peak [corresponding to (+)-**11**] eluted at 1.70 min, and the second peak [corresponding to (−)-**11**] eluted at 1.92 min. These samples were concentrated to give 24 mg of (+)-**11** and 23 mg of (−)-**11** (54% recovery). (+)-**11**: $[\alpha]^{20}_D$ +30.4°(c 0.25, CH_2Cl_2); (−)-**11**: $[\alpha]^{20}_D$ −31.0° (c 0.20, CH_2Cl_2).

(+)-Clerobungin A. To a solution of tricyclic enone (−)-**11** (16 mg, 82 μmol, 1.00 equiv) in 5 mL of EtOAc was cautiously added 10% palladium on carbon (5 mg, 4.7 μmol, 0.06 equiv) under an atmosphere of argon. The flask was then evacuated and put under an atmosphere of hydrogen gas using a balloon, and the reaction mixture was stirred vigorously at room temperature for 30 min. After this time, TLC (1:1 hexanes/EtOAc, UV/anisaldehyde) showed complete consumption of (−)-**11** (R_f = 0.29) and clean formation of (+)-**1** (R_f = 0.21). The reaction mixture was filtered through a pad of Celite, which was washed with an additional 25 mL of EtOAc. The filtrate was evaporated under reduced pressure to give the crude product, which was purified by column chromatography (2:1 hexanes/

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EtOAc → 1:1) to give (+)-clerobungin A (**1**) as a white solid (15 mg, 93%). $[\alpha]^{20}_{D}$ +181.5° (*c* 1.75, $CHCl_3$).

(−)-Clerobungin A. To a solution of tricyclic enone (+)-**11** (20 mg, 102 μmol, 1.00 equiv) in 5 mL of EtOAc was cautiously added 10% palladium on carbon (5 mg, 4.7 μmol, 0.05 equiv) under an atmosphere of argon. The flask was then evacuated and put under an atmosphere of hydrogen gas using a balloon, and the reaction mixture was stirred vigorously at room temperature for 30 min. After this time, TLC (1:1 hexanes/EtOAc, UV/anisaldehyde) showed complete consumption of (+)-**11** (R_f = 0.29) and clean formation of (−)-**1** (R_f = 0.21). The reaction mixture was filtered through a pad of Celite, which was washed with an additional 25 mL of EtOAc. The filtrate was evaporated under reduced pressure to give the crude product, which was purified by column chromatography (2:1 hexanes/EtOAc → 1:1) to give (−)-clerobungin A (**1**) as a white solid (15 mg, 74%). $[\alpha]^{20}_{D}$ −181.3° (*c* 1.83, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02261.

^{1}H and ^{13}C NMR spectra for all new compounds, selected 2D-NMR spectra, full spectral assignments for (±)-**11**, (±)-**1**, and (±)-**16**, and a spectral comparison between natural and synthetic **1**; HPLC chromatograms for the preparative resolution of enone (±)-**11**, along with the UV−visible spectrum and circular dichroism spectra of (±)-**1** and (−)-**1** (PDF)

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Notes

The authors declare no competing financial interest.

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