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Total Synthesis of the Labdane Diterpenes Galanal A and B from Geraniol

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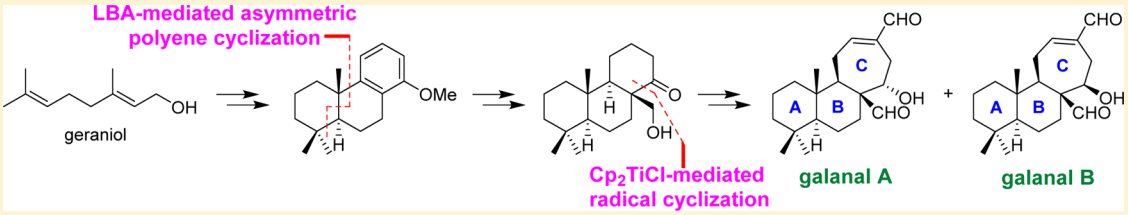
Supporting Information

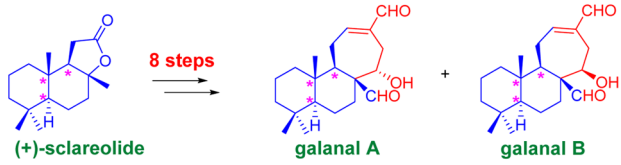


ABSTRACT: The first total synthesis of galanal A and B has been achieved from naturally occurring geraniol. Key steps in this synthesis are the use of a Lewis acid assisted chiral Brønsted acid (chiral LBA) mediated cationic polyene cyclization and a titanocene-mediated radical cyclization for the asymmetric assembly of the "AB" ring and the construction of the all-carbon quaternary center at the junction of the "BC" ring, respectively.

INTRODUCTION

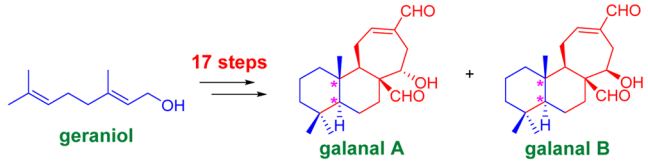
In recent decades, an increasing number of natural plant products with unique and remarkable biological activities have been discovered.[1] One class of these products is labdane-type diterpenes and their derivatives, which exhibit important pharmaceutical activities and serve as useful materials for chemical transformations.[2] In 1986, the tricyclic labdane-type diterpenes galanal A and B were first isolated from Zingiberaceae seeds (*Alpinia galanga*), and their structures were subsequently established by Morita et al.[3] In 2003, these dietary ginger constituents were also isolated from myoga (*Zingiber mioga Roscoe*) by Miyoshi et al., who determined that these compounds were novel anticancer agents by revealing that they induce apoptosis in p53-mutated Jurkat cells.[4] In 2004, Abe et al. reported that galanal A and B from myoga exhibited antimicrobial activities against Gram-positive bacteria and yeasts.[5] In 2014, Yamamoto et al. demonstrated that galanal A was an effective IDO1 inhibitor that inhibits the expression of IDO1 mRNA induced by the IFN-γ-dependent pathway.[6] Although studies have proven that galanals are important natural products, little research has addressed the synthesis of these products. Recently, our research group reported the first semisynthesis of galanal A and galanal B from sesquiterpene (+)-sclareolide.[7] Here, as part of our ongoing interest in the synthesis of labdane-type diterpenes with biological and pharmaceutical activities, we disclose the first total synthesis of galanal A and B from monoterpene geraniol. Different from our previous work using a chiral natural product as the starting material, all of the stereogenic centers in this work are introduced asymmetrically through a biomimetic synthetic strategy.

Previous work: The first semi-synthesis of galanal A and B from (+)–sclareolide



* Stereogenic centers derived from chiral pool

This work: The first total synthesis of galanal A and B from geraniol



* Asymmetric introduction of stereogenic centers through Yamamoto's methodology

RESULTS AND DISCUSSION

Biomimetic Synthetic Strategy. It has been established that diterpene cyclase is responsible for the cyclization of (*E*,*E*,*E*)-geranylgeranyl diphosphate; the resulting labdadienyl diphosphate is then elaborated into the large superfamily of

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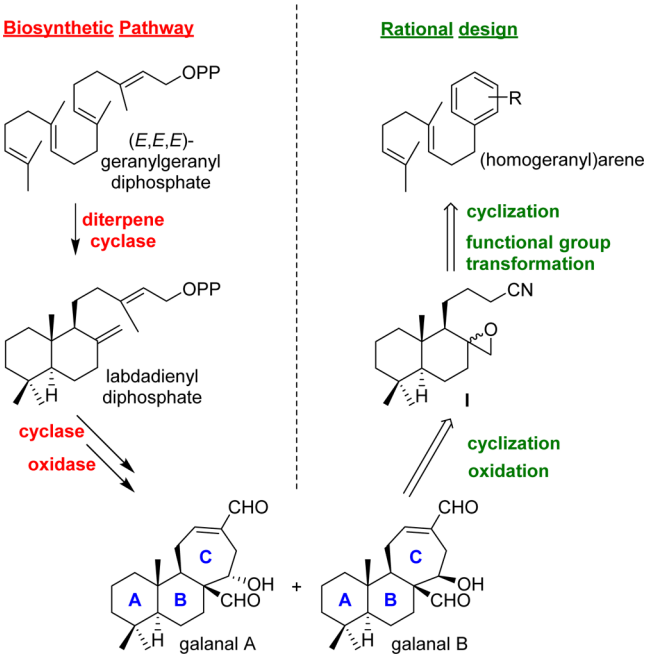
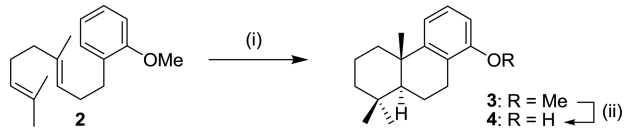
labdane-type diterpenoids.[8] Accordingly, we speculated that galanal A and B are downstream products of labdadienyl diphosphate in their natural biosynthetic pathway (Scheme 1, left column). This hypothesis led us to utilize a biomimetic synthetic strategy, as presented in the right column of Scheme 1. Ring C of galanals could be constructed at a late stage of the synthesis using a titanocene-mediated cyclization followed by functionalizations. The formation of the A and B rings could be accomplished biomimetically via a polycyclic cascade reaction.

Scheme 1. Hypothetical Biosynthetic Pathway and Rational Design



Cationic Polycyclization of Diene 2. On the basis of the strategy mentioned above, 2-(homogeranyl)anisole **2** was synthesized from geraniol via geraniol phosphate **1** using a modified procedure (Scheme 2).[9] The diene substrate **2** was then subjected to several cationic polycyclization conditions followed by methyl ether cleavage to afford phenol **4**, as indicated in Table 1. Polycyclic cyclization occurred rapidly when diene **2** was treated with an excess amount of chlorosulfonic acid at −78 °C.[10] After ether cleavage of the resulting product with BBr_3 in dichloromethane at 0 °C, **4** was isolated in 58% yield in two steps (entry 1). The yield was further improved to 76% when diene **2** was placed under a Ru (III)-catalyzed intramolecular electrophilic hydroarylation condition (entry 2).[11] Interestingly, we found that BBr_3 could initiate both polyene cyclization and demethylation in a one-pot manner, with a moderate yield of **4** (61%, entry 3). With a lower amount of BBr_3, both **3** and **4** were isolated from the reaction, which implies a faster polycyclization process than the demethylation one in this conversion.

Table 1. Cationic Polycyclization of Diene 2



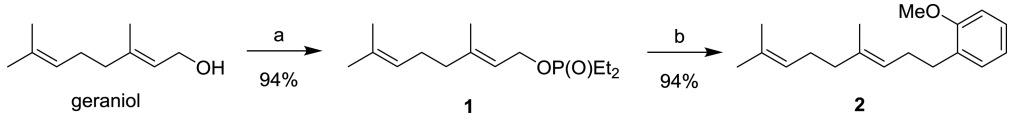
entry	conditions	yield for **4**[a] (%)
1	(i) 5.0 equiv of $ClSO_3H$, $EtNO_2$, −78 °C, 30 min	58
	(ii) 1.2 equiv of BBr_3, CH_2Cl_2, 0 °C, 2 h	
2	(i) 1 mol % of $RuCl_3{\cdot}xH_2O$, 2 mol % of AgOTf, $(CH_2)_2Cl_2$, 60 °C, 4 h	76
	(ii) 1.2 equiv of BBr_3, CH_2Cl_2, 0 °C, 2 h	
3	2.4 equiv of BBr_3, CH_2Cl_2, 0 °C, 4 h	61

[a]Isolated yield.

Enantioselective Cationic Polycyclization of Diene 2. After completion of the racemic polycyclization of diene **2**, an attempt at asymmetric polycyclization of **2** was then made based on Yamamoto's report of Lewis acid assisted chiral Brønsted acid (chiral LBA).[12] As summarized in Table 2, reaction of **2** with a mixture of $SnCl_4$ and BINOL (**L1**) in toluene gave a mixture of desired product (+)-**3** (33% ee) and the monocyclized products **3a** and **3b** in 50% yield (entry 1). The use of 3,3′-dichloro-BINOL (**L2**) as the chiral Brønsted acid improved the ee of (+)-**3** to 44% (entry 2). When the monobenzylether derivative of BINOL (**L3**) was used, the ee of (+)-**3** increased to 60% with 91% yield of the mixing products (entry 3), which were further treated with $SnCl_4$ and CF_3COOH in $EtNO_2$ at −78 °C to afford the fully cyclized product (+)-**3** in 86% total yield with 57% ee (Scheme 3). A similar ee was observed when the chiral Brønsted acid was changed to **L4** (entry 5). Unfortunately, when the 3 and 3′ positions of BINOL were equipped with a bulkier phenyl or triphenyl silyl group (**L5**−**L6**), the reactivity was much diminished (entry 7−10). The phenylalkynyl group at the ortho position (**L7**) gave ee similar to that of entry 1 (entry 11). Besides Yamamoto's protocol, Corey's method using $SbCl_5$ to promote Brønsted acid **L2** was also tested in the screening, but only racemic **3** was obtained in 50% yield (entry 12).[13]

After ether cleavage of compound **3** with BBr_3, the resulting phenol **4** was treated with Raney nickel under a high-pressure H_2 atmosphere to provide a mixture of hydrogenation products **5** and **6**[14] in a 1:5 ratio and 79% yield (Scheme 4). Following sequential pyridinium chlorochromate (PCC) oxidation and Baeyer−Villiger rearrangement, the mixture was transformed into lactone **8** in 75% yield (in two steps) and then converted to hydroxyl carboxamide **9** via Nelson's method[15] in 90% yield. After reviewing the literature, we found that Swern oxidation can be applied to substrate **9** for the dehydration of carboxamide in combination with the oxidation of the

Scheme 2. Synthesis of Diene 2[a]



[a]Reagents and conditions: (a) $(C_2H_5O)_2POCl$, py., $(C_2H_5)_2O$, −15 °C to rt, 3 h; (b) 1-(bromomethyl)-2-methoxybenzene, Mg, THF, −40 °C to rt, 12 h.

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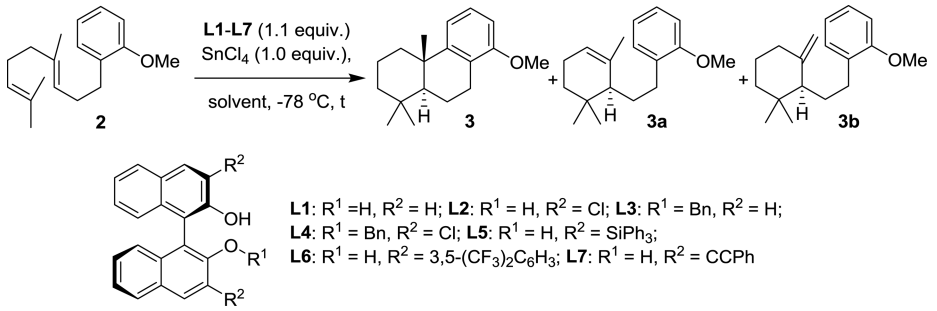
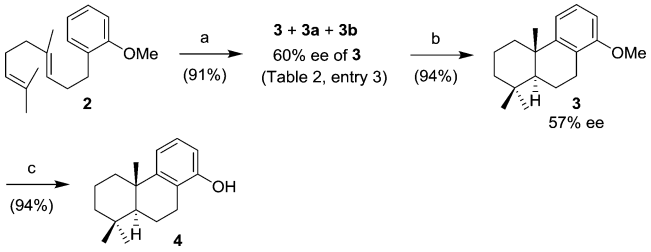
Table 2. Enantioselective Polycyclization with BINOL-Related Ligand Screening



entry	ligand	solvent	time (h)	yield (%) [ratio of **3**, **3a**, and **3b**][a]	ee of **3**[b]
1	L1	toluene	24	50 [1.0:1.4:1.9]	33
2	L2	toluene	24	88 [7.0:10.0:5.0]	44
3	L3	toluene	24	91 [1.0:3.8:5.0]	60
4	L3	CH_2Cl_2	24	86 [4.0:3.0:1.0]	47
5	L4	toluene	24	86 [3.0:10.0:5.0]	60
6	L4	CH_2Cl_2	24	83 [6.0:1.0:0]	38
7	L5	toluene	24	no reaction	
8	L5	CH_2Cl_2	96	22 [1.0:0: 0]	2
9	L6	toluene	24	no reaction	
10	L6	CH_2Cl_2	48	20 [1.0:0: 0]	1
11	L7	toluene	24	77 [1.0:1.4:1.0]	32
12[c]	L2	CH_2Cl_2	14	50 [1.0:0: 0]	1

[a]The ratio was determined by ^{1}H NMR. [b]ee of cyclized product **3** was determined by HPLC analysis with a Chiralcel OD-H column. [c]$SbCl_5$ was used instead of $SnCl_4$ according to Corey's method.

Scheme 3. Enantioselective Synthesis of (+)-3[a]

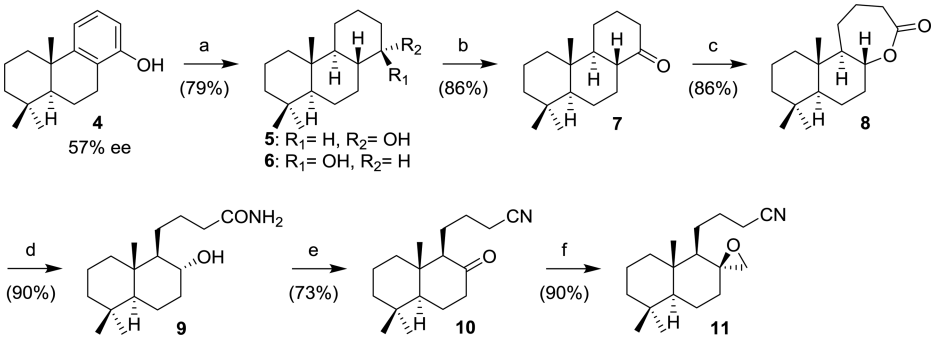


[a]Reagents and conditions: (a) $SnCl_4$, **L3**, toluene, −78 °C, 24 h; (b) $SnCl_4$, CF_3COOH, $EtNO_2$, −78 °C, 4 h; (c) BBr_3, CH_2Cl_2, 0 °C, 2 h.

secondary alcohol.[16] Thus, **9** was subjected to Swern oxidation, and the reaction proceeded smoothly to afford ketone nitrile **10** in 73% yield. The transformation of **10** via the Corey–Chaykovsky reaction stereoselectively afforded epoxynitrile **11**, which is a suitable precursor for the construction of the all-carbon quaternary center at the ring junction of the B and C rings.[17]

Construction of the All-Carbon Quaternary Center at the "BC" Ring Junction. In 1988, Nugent and RajanBabu introduced a Ti (III)-mediated radical cyclization of epoxyolefins that was subsequently used by Fernández-Mateos et al. to generate bicyclic *β*-hydroxycycloalkanones from epoxynitriles.[18] With epoxynitrile **11** in hand, we could proceed to the key titanocene-mediated intramolecular radical cyclization step. To our delight, upon treating epoxynitrile **11** with Ti(III) species generated in situ from Cp_2TiCl_2 and Zn in THF at room temperature, the homolytic regioselective cleavage of the oxirane ring and the following equatorial-oriented 6-*exo*-*dig* radical cyclization through intermediate **II** proceeded smoothly. Following an acidic workup, *β*-hydroxycycloalkanone **12** was isolated in 80% yield with the desired stereochemistry. The

Scheme 4. Synthesis of Epoxynitrile 11[a]



[a]Reagents and conditions: (a) Raney Ni, H_2 (550 psi), EtOH, 180 °C, 2 d; (b) PCC, DCM, rt, 5 h; (c) *m*-CPBA, $NaHCO_3$, rt, overnight; (d) Me_2AlNH_2, Cl_2CHCH_2Cl, 80 °C, 1 h; (e) $(COCl)_2$, DMSO, Et_3N, −78 °C to rt, overnight; (f) NaH, $(CH_3)_3SI$, DMSO/THF, rt, 3 h.

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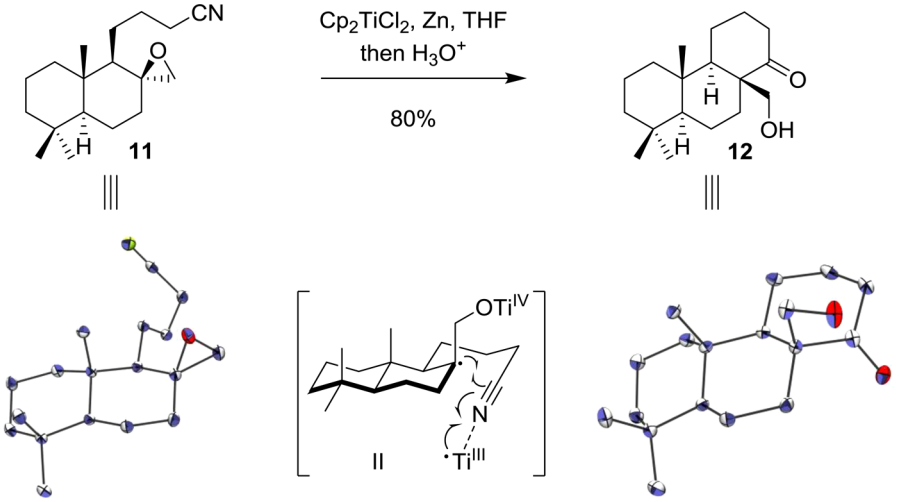
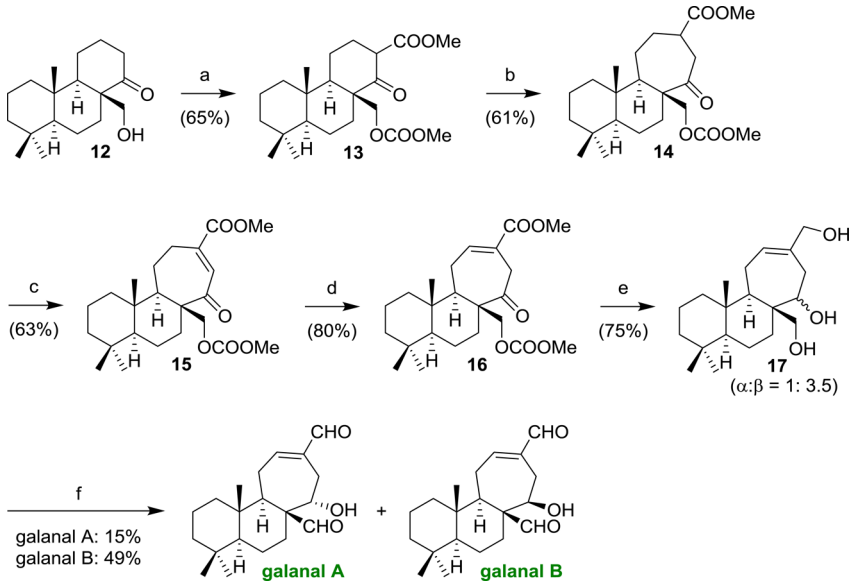
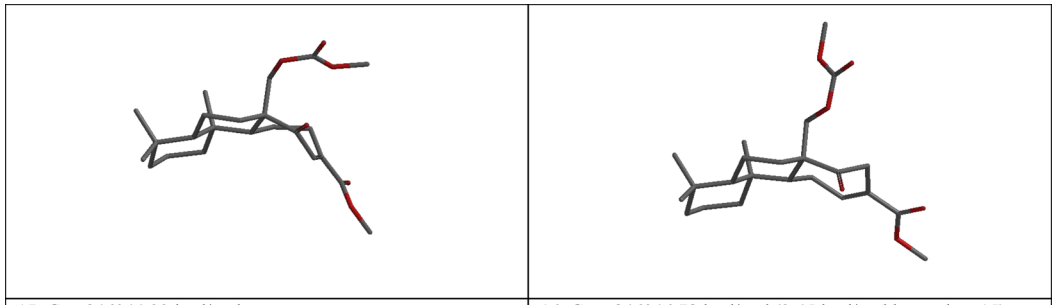
Scheme 5. Ti(III)-Mediated Radical Cyclization and X-ray Crystallographic Analysis of 11 and 12 (Hydrogen Atoms Omitted for Clarity)



Scheme 6. Total Synthesis of Galanal A and B[a]



[a]Reagents and conditions: (a) LiHMDS, NCCOOMe, THF, −78 °C to rt, overnight; (b) Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, rt, 14 h; (c) LiHMDS, PhSeCl, THF, −78 °C, 3 h; then $H_2O_{2(aq)}$, py, rt, 2h; (d) DBU, C_6H_6, reflux, 3 h; (e) DIBAL, CH_2Cl_2, −78 °C to rt, 12 h; (f) TEMPO, TBACl, NCS, $CH_2Cl_2/NaHCO_{3(aq)}/K_2CO_{3(aq)}$, rt, 12 h.



15, G =-846044.33 kcal/mol	**16**, G = -846046.78 kcal/mol (2.45 kcal/mol lower than 15)

Figure 1. Calculated structures of **15** and **16** (hydrogen atoms omitted for clarity).

structural connectivities of **11** and **12**, which are depicted in Scheme 5, were confirmed by X-ray crystallographic analysis.

Completion of the Syntheses of Galanal A and B. Following this stage, the remaining steps to complete the total

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synthesis were ring expansion and the functionalization of the C ring. First, **12** was treated with 4 equiv of LiHMDS and 6 equiv of methyl cyanoformate to introduce the methyl formate to the carbon α to the carbonyl group and to the primary alcohol to provide protection from interference with the following transformations.[19] The C ring of β-keto ester **13** was then expanded to a seven-membered ring via a Simmons–Smith cyclopropanation/ring-opening reaction cascade (Scheme 6).[20] 6,6,7-Tricyclic γ-ketoester **14** was subjected to a sequence of selenization, oxidation, and elimination to generate the double bond in **15**. This double bond was isomerized by DBU in refluxing benzene to afford the more thermodynamically stable isomer **16**.[21] Density functional theory (DFT) calculations at the RB3LYP/6-31G(d) level revealed that the Gibbs free energy of **16** is 2.45 kcal/mol lower than that of **15** (Figure 1). The double-conjugation system in ring C of **15** is countervailed by the ring strain, and the twisted ring conformation is converted to the chairlike conformation of **16** after double-bond migration to release this ring strain. The further reduction of **16** with DIBAL yielded diols **17*α*** and **17*β*** in a 1:3.5 ratio. Finally, the two primary alcohols of **17*α*** and **17*β*** were selectively oxidized using a mixture of TEMPO and NCS[22] to generate galanal A ($[\alpha]^{25}_{D}$ = −34.6 (*c* 0.8, $CHCl_3$), 53% ee, lit.[7] $[\alpha]^{25}_{D}$ = −65.3 (*c* 0.83, $CHCl_3$)) and galanal B ($[\alpha]^{25}_{D}$= −39.1 (*c* 1.0, $CHCl_3$), 55% ee, lit.[7] $[\alpha]^{25}_{D}$= −71.4 (*c* 0.97, $CHCl_3$)[7]) in the same ratio.

CONCLUSIONS

In summary, we completed the first total synthesis of galanal A and B in 17 steps. This synthesis features the use of a cationic polycyclization to assemble the "AB" ring and a Ti(III)-mediated radical cyclization to construct the all-carbon quaternary center at the "BC" ring junction as the key steps. We expect this new synthetic route to greatly facilitate bioactivity and SAR studies of galanal A and B and thereby contribute to pharmaceutical development related to these labdane-type diterpenes in the future.

EXPERIMENTAL SECTION

General Methods. All reactions using air-/moisture-sensitive reagents were performed in a flame-dried apparatus under an atmosphere of dry nitrogen, and standard syringe–septa techniques were followed. Solvents were freshly dried and purified by conventional methods prior to use. The progress of all of the reactions was monitored by TLC using TLC glass plates precoated with silica gel. ^{1}H and ^{13}C NMR spectra were recorded with 400, 500, or N600 MHz spectrometers, and chemical shifts were measured in δ (ppm) with residual solvent peaks as internal standards ($CDCl_3$, δ 7.26 ppm in ^{1}H NMR, δ 77.0 ppm in ^{13}C NMR; CD_3OD, δ 3.31 ppm in ^{1}H NMR, δ 49.0 ppm in ^{13}C NMR). Coupling constants (*J*) are reported in hertz, and the splitting abbreviations used were as follows: s, singlet; d, doublet; t, triplet; m, multiplet. HR MALDI (LR MALDI)-mass spectra were conducted on a proteomics analyzer equipped with an Nd/YAG laser (335 nm) operating at a repetition rate of 200 Hz. HR FAB (LR FAB) and HR EI (LR EI)-mass spectra were recorded on a double-focusing mass spectrometer with a resolution of 8000(3000) (5% valley definition). HR (LR) ESI (electrospray)-mass spectra were recorded using dual-ionization source options.

*(E)-3,7-Dimethylocta-2,6-dienyl Diethyl Phosphate (**1**).*[9,23] To a solution of geraniol (8.8 g, 57 mmol) and pyridine (13.8 mL, 171 mmol) in ether (30 mL) at −15 °C was added diethyl chlorophosphate (14.8 g, 85.5 mmol) dropwise. The reaction mixture was allowed to warm slowly to rt over the course of 3 h. Upon completion, the reaction was treated with 1 N HCl (150 mL) and extracted with EA (3 × 100 mL). The combined organic layers were then washed with satd $NaHCO_3$ (2 × 60 mL) and brine (60 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient from 1:9 → 2:3 EtOAc/hexanes) to give **1** (15.6 g, 94%) as a colorless oil. Data for **1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39–5.35 (m, 1H), 5.07–5.03 (m, 1H), 4.54 (t, *J* = 7.6 Hz, 2H), 4.11–4.03 (m, 4H), 2.07–2.00 (m, 4H), 1.68 (s, 3H), 1.65 (s, 3H), 1.57 (s, 3H), 1.33–1.28 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 131.8, 123.6, 118.9 (d, *J* = 6.3 Hz), 64.0 (d, *J* = 5.3 Hz), 63.5 (d, *J* = 5.5 Hz), 39.4, 26.2, 25.6, 17.6, 16.4, 16.0 (d, *J* = 6.5 Hz).

1-(Bromomethyl)-2-methoxybenzene. A stirred solution of 2-methylanisole (6 g, 49.7 mmol) and NBS (8.8 g, 49.7 mmol) in benzene (125 mL, 0.4 M) was refluxed for 4 h with irradiation by a 250 W IR lamp and a 250 W white light lamp at a close distance. After being cooled to rt, the reaction crude was diluted with hexanes, filtered through a pad of Celite, and concentrated in vacuo. To the crude was again added hexane follwed by filtering through a pad of Celite. The filtrate was concentrated, and the resulting 1-(bromomethyl)-2-methoxybenzene (10 g, 49.7 mmol) was used directly for the next step.

*(E)-1-(4,8-Dimethylnona-3,7-dienyl)-2-methoxybenzene (**2**).*[9] A solution of 1-(bromomethyl)-2-methoxybenzene (10.0 g, 49.7 mmol) in THF (100 mL) was added dropwise to Mg turnings (2.4 g, 98.7 mmol, flame-dried) under N_2 at 0 °C. After 1 h of stirring at 0 °C, the resultant magnesium bromide was cooled to −40 °C and added quickly via cannula to a solution of **1** (7.2 g, 25.0 mmol) in THF (25 mL) at −40 °C. The resulting reaction mixture was then allowed to warm slowly to room temperature over the course of 4 h and then was stirred at room temperature for another 8 h. The reaction contents were quenched with satd NH_4Cl (100 mL) and extracted with EtOAc/hexanes (1:2, 3 × 150 mL). The combined organic layers were washed with satd $NaHCO_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was coated on silica gel and purified by flash column chromatography (gradient from 0:1 → 2:98 EtOAc/hexanes) to give **2** (6 g, 94%) as a colorless oil. Data for **2**: IR (film) 2924, 2852, 1739, 1707, 1461, 1365, 1277, 1199, 1174 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.14 (m, 2H), 6.92–6.85 (m, 2H), 5.25 (t, *J* = 7.2 Hz, 1H), 5.14 (t, *J* = 7.2 Hz, 1H), 3.85 (s, 3H), 2.67 (t, *J* = 7.8 Hz, 2H), 2.30 (dd, *J* = 15.4 Hz, *J* = 7.4 Hz, 2H), 2.13–2.06 (m, 2H), 2.03–1.99 (m, 2H), 1.72 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 135.4, 131.2, 130.8, 129.9, 126.9, 124.5, 124.1, 120.3, 110.2, 55.2, 39.7, 30.5, 28.2, 26.8, 25.7, 17.7, 15.9; HRMS (APCI) calcd for $C_{18}H_{27}O$ $[M + H]^+$ 259.2062, found 259.2057.

*(±)-(4aS)-8-Methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (**3**).*[24] (Table 1, entry 1) To a solution of $ClSO_3H$ (3.9 mL, 58.05 mmol) in $EtNO_2$ (80 mL) was added **2** (3.0 g, 11.61 mmol) in $EtNO_2$ (40 mL) by low-temperature dropping funnel at −78 °C dropwise, and stirring was continued for 30 min. The reaction was quenched by satd $NaHCO_{3(aq)}$ (120 mL) and allowed to warm to room temperature gradually. The phases were separated, and the aqueous layer was extracted with ether (3 × 100 mL). The organic extracts were combined, washed with satd $NaHCO_{3(aq)}$ (300 mL) and brine (300 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient from 1:49 → 1:24 EtOAc/hexanes) to afford **3** (1.86 g, 62%) as a white solid. Data for **3**: mp 113–115 °C; IR (film) 3000, 2926, 2867, 2831, 1577, 1455, 1434, 1369, 1254, 1067, 1059, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 3.82 (s, 3H), 2.90 (dd, *J* = 18.0 Hz, *J* = 6.4 Hz, 1H), 2.66–2.56 (m. 1H), 2.33–2.26 (m, 1H), 1.98–1.90 (m, 1H), 1.83–1.57 (m, 3H), 1.53–1.45 (m, 1H), 1.40 (td, *J* = 13.0 Hz, *J* = 3.8 Hz, 1H), 1.33 (dd, *J* = 12.6 Hz, *J* = 2.1 Hz, 1H), 1.28–1.17 (m, 1H), 1.21 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 151.6, 126.0, 124.3, 116.6, 106.3, 55.2, 49.9, 41.6, 39.0, 37.8, 33.4, 33.3, 24.7, 24.5, 21.6, 19.3, 18.4; HRMS (EI) calcd for $C_{18}H_{26}O$ $[M]^+$ 258.1984, found 258.1983.

*(±)-(4bS)-4b,8,8-Trimethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthren-1-ol (**4**).* (Table 1, entry 1) To a solution of **3** (3.0 g, 11.46 mmol) in CH_2Cl_2 (28 mL) was added BBr_3 (1.3 mL, 13.75 mmol) dropwise at 0 °C, and stirring was continued for 2 h. The reaction was

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quenched by H_2O (30 mL) and allowed to warm to room temperature gradually. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, washed with satd $NaHCO_{3(aq)}$ (60 mL) and brine (60 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:19) to afford **4** (2.6 g, 94%) as a white solid. Data for **4**: mp 144−146 °C; IR (film) 3417, 2923, 1633, 1576, 1461, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (t, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.60 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H), 4.70 (s, 1H), 2.85 (dd, J = 17.0 Hz, J = 6.6 Hz, 1H), 2.67−2.58 (m, 1H), 2.32−2.24 (m, 1H), 2.22−1.93 (m, 1H), 1.82−1.57 (m, 3H), 1.53−1.45 (m, 1H), 1.44−1.30 (m, 1H), 1.28−1.17 (m, 1H), 1.20 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 152.1, 126.3, 121.6, 116.8, 111.4, 49.7, 41.6, 38.9, 37.8, 33.4, 33.3, 24.8, 24.0, 21.6, 19.3, 18.3; HRMS (EI) calcd for $C_{17}H_{24}O$ $[M]^+$ 244.1827, found 244.1820. (Table 1, entry 2) A mixture of $RuCl_3{\cdot}xH_2O$ (2.1 mg, 0.01 mmol) and AgOTf (5.1 mg, 0.02 mmol) in $ClCH_2CH_2Cl$ (2 mL) was stirred vigorously for 1 h. Then the cyclization precursor **2** (258 mg, 1.0 mmol) in $ClCH_2CH_2Cl$ (3 mL) was added at room temperature. The resulting solution was heated to 60 °C and stirred for 3 h. TLC analysis indicated that the reaction was completed, and the crude was filtered through a short pad of silica gel with the aid of CH_2Cl_2. The filtrate was concentrated in vacuo and under high vacuum for 20 min. The resulting residue was dissolved in CH_2Cl_2 (2.5 mL) and was added BBr_3 (115 μL, 1.2 mmol) dropwise at 0 °C. Stirring was continued for 2 h, and the reaction was quenched by H_2O (2.5 mL) and allowed to warm to room temperature gradually. The phases were separated, and the aqueous layer was extracted with DCM (3 × 5 mL). The organic extracts were combined, washed with satd $NaHCO_{3(aq)}$ (5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:19) and then recrystallized from hexanes/CH_2Cl_2 (1:1) to afford **4** as a white solid (185 mg, 76%). (Table 1, entry 3) To a solution of **2** (400 mg, 1.55 mmol) in CH_2Cl_2 (15.5 mL) was added BBr_3 (0.36 mL, 3.72 mmol) dropwise at −15 °C, and stirring was continued for 1 h. The reaction was warmed to 0 °C and stirred for another 4 h. The reaction was quenched by H_2O (15 mL), and then satd $NaHCO_{3(aq)}$ (15 mL) was added. The reaction was allowed to warm to room temperature gradually. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:19) to afford **4** (61%) as a white solid.

General Procedure for the Enantioselective Cyclization of 3 in Table 2. To a solution of (*R*)-binaphthalene ligand (0.21 mmol) in toluene (2.1 mL) was added a 1.0 M solution of $SnCl_4$ in heptane (0.19 mL, 0.19 mmol) at room temperature, and the solution was stirred for 5 min. After the solution of complex prepared in situ as above was cooled to −78 °C and stirred for another 30 min, 2-(homogeranyl)anisole **2** (50 mg, 0.19 mmol) in toluene (0.38 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 24 h, quenched with saturated $NaHCO_{3(aq)}$, and extracted with ether (3 × 8 mL). The combined organic phases were washed with brine (8 mL), dried over Na_2SO_4, and concentrated. The residue was coated on silica gel and purified by flash column chromatography (3:97 CH_2Cl_2/hexanes) to give a mixture of **3**, **3a**, and **3b**. The mixture of **3**, **3a**, and **3b** was used for the subsequent cyclization without further separation.

Diastereoselective Cyclization of 3, 3a, and 3b (Scheme 3). To a solution of trifluoroacetic acid (0.13 mL, 1.7 mmol) in $EtNO_2$ (1.7 mL) at −78 °C was added a 1.0 M solution of $SnCl_4$ in heptane (0.34 mL, 0.34 mmol), and the solution was stirred for 20 min. The mixture of **3**, **3a**, and **3b** (45.5 mg, 0.17 mmol, from Table 2, entry 3) in $EtNO_2$ (1.7 mL) was then added dropwise. The reaction mixture was stirred at −78 °C for 4 h, quenched with saturated $NaHCO_{3(aq)}$ (10 mL), and extracted with ether (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was coated on silica gel and purified by flash column chromatography (3:97 CH_2Cl_2/hexanes) to give (+)-**3** (42.8 mg, 94%). Enantioselectivity was determined by HPLC analysis (Daicel OD-H column, 0.3 mL/min, hexane/*i*-PrOH 99.7/0.3, 220 nm); t_R = 15.5 min ((−)-enantiomer) and 16.7 min ((+)-enantiomer). $[\alpha]^{30}_D$ = 29.5 (c 1.0, $CHCl_3$) for 57% ee.

(4bS)-4b,8,8-Trimethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthren-1-ol (4). Demethylation of (+)-**3** afforded (+)-**4** in 94% yield (the same procedure as the second step in Table 1, entry 1). $[\alpha]^{30}_D$ = 30.0 (c 1.0, $CHCl_3$).

(1S,4aS,4bR,10aS)-4b,8,8-Trimethyltetradecahydrophenanthren-1-ol (5) and (1R,4aS,4bR,10aS)-4b,8,8-Trimethyltetradecahydrophenanthren-1-ol (6).[14] A suspension of **4** (2 g, 8.19 mmol) and Raney nickel (52% slurry in EtOH, 2.36g, 1.23 mmol) in EtOH (20.5 mL) was placed in a Teflon container. The reaction contents in the container were put into an autoclave and hydrogenated at 180 °C and 550 psi pressure of hydrogen. After 2 d, the reaction mixture was cooled to room temperature gradually. The catalyst was removed by filtration through Celite and washed repeatedly with ethanol. The solvent was removed in vacuo. The crude was dissolved in EtOAc (30 mL), washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient from 1:19 → 1:9 EtOAc/hexanes) to afford **5** (0.29 g, 14%) and **6** (1.33 g, 65%). Both **5** and **6** are white solids. Data for **5**: $[\alpha]^{31}_D$ = 4.5 (c 1.0, $CHCl_3$); mp 97−99 °C; IR (film) 3397, 2935, 2865, 1442, 1380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74−3.73 (m, 1H), 1.82−1.74 (m, 1H), 1.72−1.57 (m, 4H), 1.57−1.49 (m, 3H), 1.49−1.41 (m, 3H), 1.41−1.33 (m, 3H), 1.33−1.23 (m, 1H), 1.18−1.05 (m, 2H), 0.98−0.85 (m, 3H), 0.84 (s, 3H), 0.82 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.9, 54.8, 48.1, 42.1, 40.6, 39.2, 36.7, 33.6, 33.5, 33.2, 30.5, 24.7, 22.0, 21.4, 20.0, 18.9, 14.1; HRMS (EI) calcd for $C_{17}H_{30}O$ $[M]^+$ 250.2297, found 250.2298. Data for **6**: $[\alpha]^{31}_D$ = −22.4 (c 1.0, $CHCl_3$); mp 116−118 °C; IR (film) 3297, 2927, 2865, 1446, 1385, 1362, 1056, 1039, 1007, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.15−3.08 (m, 1H), 2.26−2.20 (m, 1H), 1.92−1.85 (m, 1H), 1.79−1.71 (m, 1H), 1.71−1.57 (m, 4H), 1.57−1.47 (m, 1H), 1.45−1.33 (m, 2H), 1.33−1.13 (m, 4H), 1.13−1.07 (m, 1H), 1.03−0.78 (m, 4H), 0.84 (s, 3H), 0.82 (s, 3H), 0.81 (s, 3H), 0.73 (td, J = 11.5 Hz, J = 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.8, 55.0, 53.8, 44.1, 42.1, 39.3, 36.7, 35.3, 33.6, 33.2, 30.9, 24.4, 24.0, 21.9, 21.1, 18.9, 14.2; HRMS (EI) calcd for $C_{17}H_{30}O$ $[M]^+$ 250.2297, found 250.2301.

(4aS,4bR,10aS)-4b,8,8-Trimethyldodecahydrophenanthren-1-(4bH)-one (7).[25] To a solution of **5** (0.29 g, 1.19 mmol) and **6** (1.33 g, 5.44 mmol) in CH_2Cl_2 (33 mL) was added PCC (2.86 g, 13.26 mmol) at room temperature, and stirring was continued for 5 h. Dry ether (165 mL) was added and the mixture stirred for another 30 min. The supernatant solution was decanted from the black gum. The insoluble residue was washed thoroughly with dry ether whereupon it became a black granular solid. The combined organic solvents were passed through a short pad of Celite, and the solvent was removed in vacuo. The resulting brown oil was dissolved in dry ether (100 mL), and the above procedure was followed once again. The crude was directly coated on silica gel and purified by flash column chromatography (gradient from 1:49 → 1:19 EtOAc/hexanes) to afford **7** (1.38 g, 86%) as a white solid. Data for **7**: $[\alpha]^{31}_D$ = −11.9 (c 1.0, $CHCl_3$); mp 69−71 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.37−2.30 (m, 1H), 2.28−2.17 (m, 2H), 2.11−2.02 (m, 1H), 2.00−1.92 (m, 1H), 1.89−1.81 (m, 1H), 1.77−1.61 (m, 2H), 1.61−1.50 (m, 2H), 1.50−1.29 (m, 4H), 1.28−1.09 (m, 3H), 0.97−0.86 (m, 1H), 0.93 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H), 0.82−0.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.4, 57.0, 54.3, 49.4, 41.8, 41.6, 39.2, 37.3, 33.3, 33.0, 26.2, 26.1, 24.1, 21.7, 20.4, 18.8, 13.7.

(5aS,11aS,11bR)-8,8,11a-Trimethyldodecahydronaphtho[2,1-b]-oxepin-4(5aH)-one (8). To a suspension of **7** (638 mg, 2.41 mmol) and $NaHCO_3$ (810 mg, 9.64 mmol) in CH_2Cl_2 (24 mL) at room temperature was added *m*-CPBA (70−75% balance 3-chlorobenzoic acid and water, 1.2 g, 4.82 mmol), and stirring was continued overnight. The reaction was quenched by 1 M $Na_2SO_{3(aq)}$ (24 mL) and stirred for another 30 min. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine (30 mL), dried over

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Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (1:9 EtOAc/hexanes) to afford **8** (625 mg, 86%). Data for **8**: $[\alpha]^{30}_D$ = 34.7 (*c* 1.0, $CHCl_3$); mp 100−102 °C; IR (film): 2945, 2865, 1731, 1448, 1388, 1335, 1274, 1211, 1183, 1124, 1013 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.34−4.28 (m, 1H), 2.65−2.58 (m, 1H), 2.54−2.46 (m, 1H), 2.23−2.16 (m, 1H), 2.03−1.95 (m, 1H), 1.94−1.86 (m, 1H), 1.79−1.73 (m, 1H), 1.70−1.63 (m, 1H), 1.63−1.52 (m, 2H), 1.52−1.34 (m, 4H), 1.34−1.24 (m, 2H), 1.13 (td, *J* = 13.0 Hz, *J* = 4.0 Hz, 1H), 0.98−0.89 (m, 2H), 0.88 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 80.0, 53.7, 53.7, 41.4, 39.6, 38.6, 34.9, 33.9, 33.7, 33.1, 28.0, 22.1, 22.1, 20.4, 18.5, 15.2; HRMS (EI) calcd for $C_{17}H_{28}O_2$ $[M]^+$ 264.2089, found 264.2083.

*4-((1R,2R,8aS)-2-Hydroxy-5,5,8a-trimethyldecahydronaphthalen-1-yl)butanemide (**9**).* To dry 1,1,2-trichloroethane (5.7 mL) in a double-necked round-bottom flask, fitted with a reflux condenser topped with a rubber serum cap and connected to an oil tube, was bubbled anhydrous NH_3 at 0 °C for 25 min. After this time, $AlMe_3$ (2.0 M in toluene, 1.4 mL, 2.84 mmol) was added. The mixture was then heated to 80 °C and stirred at 80 °C for 1 h to bubble off excess NH_3. Then lactone **8** (300 mg, 1.14 mmol) in dry 1,1,2-trichloroethane (5.7 mL) was added and the mixture stirred at 80 °C for another 1 h. The mixture was cooled to 0 °C, 1 N HCl (20 mL) was added, and the mixture stirred for 30 min. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, washed with brine (60 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was coated on silica gel and purified by flash column chromatography (EtOAc/hexanes, 1:4 → CH_2Cl_2/MeOH, 9:1) to give **9** (286 mg, 90%) as a white solid. Data for **9**: $[\alpha]^{29}_D$ = −2.5 (*c* 1.0, MeOH); mp 154−156 °C; IR (film) 3445, 3415, 3330, 3179, 2935, 2915, 2863, 2848, 1680, 1657, 1619, 1441, 1411, 1384, 1363, 1303, 1097, 1032, 966, 880, 694, 592, 558 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (s, 1H), 5.63 (s, 1H), 3.52−3.46 (m, 1H), 2.35−2.28 (m, 1H), 2.23−2.16 (m, 1H), 2.06−2.03 (m, 2H), 1.86−1.75 (m, 1H), 1.75−1.69 (m, 1H), 1.69−1.62 (m, 1H), 1.62−1.57 (m, 1H), 1.57−1.52 (m, 1H), 1.52−1.37 (m, 3H), 1.37−1.31 (m, 1H), 1.31−1.20 (m, 3H), 1.13 (td, *J* = 14.0 Hz, *J* = 4.0 Hz, 1H), 0.91−0.86 (m, 2H), 0.86 (s, 3H), 0.78 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 73.3, 58.3, 54.7, 42.0, 38.7, 38.6, 36.6, 35.6, 33.4, 33.2, 27.3, 27.0, 21.7, 20.8, 18.4, 14.4; HRMS (ESI) calcd for $C_{17}H_{31}NO_2Na$ $[M + Na]^+$ 304.2252, found 304.2245.

*4-((1R,8aS)-5,5,8a-Trimethyl-2-oxodecahydronaphthalen-1-yl)-butanenitrile (**10**).* A solution of dimethyl sulfoxide (0.92 mL, 12.90 mmol) in CH_2Cl_2 (2.8 mL) was added to a stirred solution of oxalyl chloride (0.55 mL, 6.45 mmol) in CH_2Cl_2 (2.9 mL) at −78 °C. After 15 min, a solution of **9** (605 mg, 2.15 mmol) was added to the reaction mixture. Stirring was continued for 20 min at −78 °C, and then Et_3N was added. After 30 min at −78 °C, the reaction mixture was warmed to room temperature, and the reaction was quenched with satd $NH_4Cl_{(aq)}$ (20 mL) and CH_2Cl_2 (20 mL). The phases were separated, and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient from 1:19 → 1:4 EtOAc/hexanes) to give **10** (410 mg, 73%) as yellow oil. Data for **10**: $[\alpha]^{29}_D$ = −26.8 (*c* 1.0, $CHCl_3$); IR (film) 2947, 2868, 2845, 2245, 1709, 1460, 1429, 1389, 1365, 1185, 1122, 1105, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.45−2.39 (m, 1H), 2.39−2.23 (m, 3H), 2.09−2.01 (m, 2H), 1.82−1.67 (m, 3H), 1.67−1.61 (m, 1H), 1.61−1.48 (m, 3H), 1.48−1.33 (m, 3H), 1.28−1.12 (m, 2H), 0.96 (s, 3H), 0.84 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 119.7, 63.6, 54.2, 42.7, 42.4, 41.8, 39.3, 33.7, 33.5, 25.0, 23.9, 21.6, 21.2, 18.9, 17.4, 14.6; HRMS (EI) calcd for $C_{17}H_{27}NO$ $[M]^+$ 261.2093, found: 261.2093.

*4-((1R,2S,8aS)-5,5,8a-Trimethyloctahydro-1H-spiro[naphthalene-2,2′-oxirane]1-yl)butanenitrile (**11**).* NaH (60%, 140 mg, 3.48 mmol) was dissolved in DMSO (3.5 mL) and heated for 20 min to 75 °C (until the formation of hydrogen ended). After the mixture was cooled to room temperature, THF (1.75 mL) was added, and the mixture was cooled to 0 °C. To this solution was added $(CH_3)_3SI$ (738 mg, 3.61 mmol). After 5 min, **10** (183 mg, 0.70 mmol) in THF (1.75 mL) was added, and the reaction was allowed to warm to room temperature gradually. After 3 h, the reaction was quenched by satd $NaHCO_{3(aq)}$ (5 mL) and H_2O (5 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient from 1:9 → 1:4 EtOAc/hexanes) to give **11** (173 mg, 90%) as a white solid. Data for **11**: $[\alpha]^{30}_D$= 28.7 (*c* 1.0, $CHCl_3$); mp 100−102 °C; IR (film) 2930, 2859, 2843, 2245, 1470, 1457, 1443, 1433, 1386, 1366, 1205, 972, 939 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.48 (d, *J* = 4.0 Hz, 1H), 2.33 (d, *J* = 4.0 Hz, 1H), 2.31−2.22 (m, 2H), 1.88 (td, *J* = 13.5 Hz, *J* = 5.5 Hz, 1H), 1.78 (d, *J* = 12.5 Hz, 1H), 1.70−1.48 (m, 6H), 1.48−1.38 (m, 2H), 1.38−1.31 (m, 1H), 1.31−1.21 (m, 2H), 1.16 (td, *J* = 13.5 Hz, *J* = 4.0 Hz, 1H), 0.98 (dd, *J* = 12.0 Hz, *J* = 2.5 Hz, 1H), 0.95−0.90 (m, 1H), 0.89 (s, 3H), 0.87 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.5, 57.0, 55.1, 52.1, 48.7, 42.0, 39.8, 38.8, 35.8, 33.4, 27.3, 21.6, 20.7, 20.0, 18.4, 17.2, 14.3, 14.3; HRMS (EI) calcd for $C_{18}H_{29}NO$ $[M]^+$ 275.2249, found 275.2246.

*(4aR,4bS,10aR)-10a-(Hydroxymethyl)-4b,8,8-trimethyldodecahydrophenanthren-1(4bH)-one (**12**).* A mixture of Cp_2TiCl_2 (667 mg, 2.68 mmol) and Zn powders (526 mg, 8.05 mmol) in strictly deoxygenated THF (12 mL) was stirred at room temperature until the red solution turned green (around 20 min). Then **11** (335 mg, 1.22 mmol) in strictly deoxygenated THF (12 mL) was added to the mixture. After 3 h, the reaction was quenched by satd $NaH_2PO_{4(aq)}$ (24 mL), and zinc powder and titanocene reagent were removed by filtration through Celite. The phases were separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with satd $NaHCO_{3(aq)}$ (40 mL) and brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient from 1:19 → 1:4 EtOAc/hexanes) to give **12** (270 mg, 80%) as a white solid. Data for **12**: $[\alpha]^{27}_D$ = 20.0 (*c* 1.0, $CHCl_3$); mp 165−167 °C; IR (film) 3448, 2938, 2865, 2837, 1701, 1458, 1440, 1385, 1363, 1121, 1103, 1039, 1016, 969 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.11 (d, *J* = 11.0 Hz, 1H), 3.94 (d, *J* = 11.0 Hz, 1H), 2.62 (td, *J* = 13.8 Hz, *J* = 6.5 Hz, 1H), 2.31−2.24 (m, 1H), 2.16−2.07 (m, 1H), 1.94−1.87 (m, 1H), 1.77−1.47 (m, 9H), 1.45−1.22 (m, 3H), 1.17 (dd, *J* = 12.0 Hz, *J* = 3.5 Hz, 1H), 1.11 (td, *J* = 13.5 Hz, *J* = 4.0 Hz, 1H), 0.85 (s, 3H), 0.82 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 62.5, 59.0, 56.0, 41.8, 39.7, 39.0, 38.4, 33.3, 33.2, 29.1, 26.7, 21.4, 19.7, 18.7, 17.8, 17.8, 16.4; HRMS (EI) calcd for $C_{18}H_{30}O_2$ $[M]^+$ 278.2246, found 278.2251.

*(4aR,4bS,10aR)-Methyl 10a-((Methoxycarbonyloxy)methyl)-4b,8,8-trimethyl-1-oxotetradecahydrophenanthrene-2-carboxylate (**13**).* To a solution of **12** (144 mg, 0.52 mmol) in THF (10.4 mL) was added LiHMDS (0.5 M in THF, 4.1 mL, 2.07 mmol) at −78 °C. The mixture was allowed to warm slowly to −20 °C over the course of 2 h and then cooled to −78 °C. NCCOOMe (0.25 mL, 3.11 mmol) and TMEDA (0.42 mL, 3.11 mmol) were added dropwise to the reaction mixture, which was allowed to slowly warm to room temperature over the course of 4 h and then stirred at room temperature for another 8 h. The reaction contents were quenched with 1 N $HCl_{(aq)}$ (10 mL) under an ice bath and allowed to gradually warm to rt. The reaction crude was extracted with ether (3 × 10 mL). The organic extracts were combined, washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was coated on silica gel and purified by flash column chromatography (gradient from 1:19 → 1:4 EtOAc/hexanes) to give **13** (133 mg, 65%) as a white foam. Data for **13**: $[\alpha]^{31}_D$ = −5.5 (*c* 1.0, $CHCl_3$); IR (film) 2951, 2870, 2843, 1748, 1716, 1651, 1613, 1441, 1367, 1316, 1262, 956 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$; keto and enol tautomers, ca. 2:1) δ 12.32 (s, 0.3H, enol), 4.56 (d, *J* = 8.8 Hz, 0.7H, keto), 4.52 (d, *J* = 8.8 Hz, 0.7H, keto), 4.45 (d, *J* = 8.8 Hz, 0.3H, enol), 4.39 (d, *J* = 8.8 Hz, 0.3H, enol), 3.72 (s, 2H, keto), 3.71 (s, 1H, enol), 3.70 (s, 1H, enol), 3.69 (s, 2H, keto), 3.64−3.59 (m, 0.7H), 2.42−2.07 (m, 2H, keto/enol), 1.96−1.77 (m, 3H, keto/enol), 1.77−1.48 (m, 5H, keto/enol), 1.45−1.19 (m, 5H, keto/enol), 1.15−1.04 (m, 1H, keto/enol), 0.87 (s, 1H, enol), 0.85 (s, 2H, keto), 0.82 (s, 3H, keto/enol), 0.78 (s, 3H, keto/enol); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 175.1, 173.4, 170.5, 155.6, 97.0, 70.2, 67.1, 59.1, 56.3, 55.7, 54.9, 54.6, 54.1, 53.5, 51.9, 51.3, 42.9, 41.8, 41.5,

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39.4, 38.3, 37.3, 33.1, 33.1, 32.1, 29.2, 22.8, 21.3, 21.1, 18.7, 18.5, 18.4; HRMS (ESI) calcd for $C_{22}H_{34}O_6Na$ $[M + Na]^+$ 417.2253, found 417.2258.

*(6aR,11aR,11bS)-Methyl 6a-((Methoxycarbonyloxy)methyl)-4,4,11b-trimethyl-7-oxotetradecahydro-1H-cyclohepta[a]-naphthalene-9-carboxylate (**14**).* To a solution of **13** (23 mg, 0.058 mmol) in $ClCH_2CH_2Cl$ (0.6 mL) was added Et_2Zn (1.0 M in hexane, 93 μL, 0.093 mmol) at 0 °C. After 10 min, CH_2I_2 (8 μL, 0.093 mmol) was added, and the mixture was stirred at 0 °C for 2 h. Then the reaction mixture was allowed to warm to room temperature and stirred for another 14 h. The reaction contents were quenched with satd $NH_4Cl_{(aq)}$ (2 mL) at 0 °C and allowed to warm to room temperature. The phases were separated, and the aqueous layer was extracted with ether (3 × 2 mL). The organic extracts were combined, washed with satd $NaHCO_{3(aq)}$ (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient from 0:1 → 1:1 EtOAc/DCM) to afford **14** (16 mg, 61%) as a colorless liquid. Data for **14**: $[\alpha]^{31}_D$ = 9.1 (*c* 1.0, $CHCl_3$); IR (film) 2951, 2868, 2843, 1750, 1704, 1441, 1389, 1367, 1264, 1201, 1175, 1158, 1116, 961, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.72 (d, *J* = 11.2 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 2.99 (dd, *J* = 11.6 Hz, *J* = 6.8 Hz, 1H), 2.87−2.73 (m, 2H), 2.14−2.04 (m, 1H), 1.84−1.72 (m, 3H), 1.72−1.61 (m, 5H), 1.61−1.57 (m, 1H), 1.52−1.42 (m, 1H), 1.42−1.28 (m, 2H), 1.28−1.21 (m, 1H), 1.15 (td, *J* = 13.4 Hz, *J* = 4.0 Hz, 1H), 0.94−0.89 (m, 1H), 0.87 (s, 3H), 0.87 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 175.5, 155.6, 68.5, 56.4, 56.2, 54.8, 54.6, 52.1, 41.7, 39.6, 38.7, 38.5, 38.5, 33.4, 33.2, 31.5, 29.4, 21.4, 21.3, 18.6, 18.1, 16.0; HRMS (MALDI) calcd for $C_{23}H_{36}O_6Na$ $[M + Na]^+$ 431.2410, found 431.2422.

*(6aR,11aR,11bS)-Methyl 6a-((Methoxycarbonyloxy)methyl)-4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,10,11,11a,11b-dodecahydro-1H-cyclohepta[a]naphthalene-9-carboxylate (**15**).* To a solution of **14** (8.0 mg, 0.020 mmol) in THF (0.2 mL) was added LiHMDS (0.5 M in THF, 59 μL, 0.029 mmol) at −78 °C. The mixture was allowed to warm slowly to −20 °C over the course of 2 h and then cooled to −78 °C. A solution of PhSeCl (5.6 mg, 0.029 mmol) in THF (0.05 mL) was added at −78 °C. After 3 h, the reaction was quenched by satd $NaHCO_{3(aq)}$ (2 mL), and the aqueous layer was extracted with ether (3 × 2 mL). The organic extracts were combined, washed with brine (6 mL), dried over Na_2SO_4, and concentrated in vacuo. To a solution of the residue mentioned above in THF (0.4 mL) were added $H_2O_{2(aq)}$ (4 μL, 0.050 mmol) and pyridine (4 μL, 0.050 mmol) at room temperature. After 2 h, the reaction was quenched by satd $NaHCO_{3(aq)}$ (2 mL), and the aqueous layer was extracted with ether (3 × 2 mL). The organic extracts were combined, washed with brine (6 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient from 1:49 → 1:9 EtOAc/hexanes) to give **15** (5.0 mg, 63%) as a colorless oil. Data for **15**: $[\alpha]^{26}_D$ = −30.5 (*c* 1.0, $CHCl_3$); IR (film) 2952, 2865, 2845, 1752, 1721, 1693, 1440, 1389, 1363, 1264, 1210, 1134, 965, 948 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 2.0 Hz, 1H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.59 (d, *J* = 11.0 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 2.88−2.79 (m, 1H), 2.32−2.21 (m, 1H), 1.96−1.85 (m, 1H), 1.85−1.77 (m, 2H), 1.72−1.65 (m, 1H), 1.65−1.42 (m, 4H), 1.42−1.23 (m, 3H), 1.14 (td, *J* = 13.4 Hz, *J* = 4.0 Hz, 1H), 0.97−0.87 (m, 2H), 0.92 (s, 3H), 0.86 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 167.5, 155.5, 138.1, 137.0, 69.0, 56.2, 55.5, 54.9, 54.9, 52.5, 41.7, 39.3, 38.9, 33.4, 33.2, 32.4, 29.5, 21.8, 21.4, 18.5, 18.2, 16.2; HRMS (ESI) calcd for $C_{23}H_{34}O_6Na$ $[M + Na]^+$ 429.2253, found 429.2254.

*(6aR,11aR)-Methyl 6a-((Methoxycarbonyloxy)methyl)-4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1H-cyclohepta[a]naphthalene-9-carboxylate (**16**).* A solution of **15** (25 mg, 0.062 mmol) and DBU (19 μL, 0.124 mmol) in benzene (1.24 mL) was refluxed for 3 h. The reaction was cooled down to room temperature and then quenched by satd $NH_4Cl_{(aq)}$ (2 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with satd $NaHCO_{3(aq)}$ (5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (gradient from 1:49 → 1:9 EtOAc:hexanes) to give **16** (20 mg, 80%) as colorless oil. Data for **16**: $[\alpha]^{26}_D$= −0.7 (*c* 1.0, $CHCl_3$); IR (film) 2950, 2868, 2843, 1751, 1711, 1645, 1440, 1388, 1367, 1260, 1116, 1069, 963, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13−7.09 (m, 1H), 4.75 (d, *J* = 11.2 Hz, 1H), 4.63 (d, *J* = 11.2 Hz, 1H), 3.81 (dd, *J* = 13.8 Hz, *J* = 2.2 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.58 (d, *J* = 14.0 Hz, 1H), 2.78−2.66 (m, 1H), 2.60−2.50 (m, 1H), 2.08−2.01 (m, 1H), 1.86−1.78 (m, 1H), 1.73−1.54 (m, 3H), 1.54−1.44 (m, 1H), 1.44−1.23 (m, 3H), 1.16 (td, *J* = 13.4 Hz, *J* = 4.0 Hz, 1H), 0.95 (s, 3H), 0.94−0.88 (m, 2H), 0.87 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 167.0, 155.4, 144.0, 124.4, 69.3, 56.3, 55.8, 54.8, 52.2, 52.1, 41.6, 39.8, 38.3, 37.5, 33.7, 33.4, 33.1, 26.6, 21.3, 18.5, 18.5, 15.6; HRMS (EI) calcd for $C_{23}H_{34}O_6Na$ $[M + Na]^+$ 429.2253, found: 429.2260.

*((6aR,7S,11bS)-7-hydroxy-4,4,11b-trimethyl-2,3,4,4a,5,6,6a,-7,8,11,11a,11b-dodecahydro-1H-cyclohepta[a]naphthalene-6a,9-diyl)dimethanol (**17α**) and ((6aR,7R,11bS)-7-Hydroxy-4,4,11b-trimethyl-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1H-cyclohepta[a]naphthalene-6a,9-diyl)dimethanol (**17β**).* To a solution of **16** (20 mg, 0.05 mmol) in DCM (0.5 mL) at −78 °C was added DIBAL solution (1.0 M in toluene, 0.41 mL, 0.50 mmol), and the reaction was allowed to warm to room temperature gradually. After 12 h, the reaction was quenched by 1 N $HCl_{(aq)}$ (2 mL) and stirred for 1 h at room temperature. The phases were separated, and the aqueous layer was extracted with DCM (3 × 2 mL). The organic extracts were combined, washed with brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (gradient from 1:1 → 1:0 EtOAc/hexanes) to afford **17α** and **17β** (12 mg, 75%, 1:3.5 ratio) as white solids.

Galanal A and B. A solution of **17α** and **17β** (12.0 mg, 0.037 mmol), TEMPO (1.2 mg, 0.0074 mmol), and TBACl (2.1 mg, 0.0074 mmol) in CH_2Cl_2 (0.37 mL) and an aqueous solution of $NaHCO_3$ (0.5 M, 0.19 mL) and K_2CO_3 (0.05 M, 0.19 mL) were vigorously stirred at room temperature. NCS (20 mg, 0.148 mmol) was then added. Stirring was maintained and the reaction monitored by TLC. After 12 h, the reaction was quenched with satd NH_4Cl (2 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The CH_2Cl_2 extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was coated on silica gel and purified by flash column chromatography (gradient from 1:19 → 1:4 EtOAc/hexanes) to give galanal A (1.8 mg, 15%) and galanal B (5.9 mg, 49%). Both glanal A and B are white solids. Data for galanal A: $[\alpha]^{25}_D$= −34.6 (*c* 0.8, $CHCl_3$); mp 167−169 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 9.39 (s, 1H), 6.88 (d, *J* = 7.3 Hz, 1H), 4.06 (d, *J* = 8.1 Hz, 1H), 2.85−2.74 (m, 1H), 2.73−2.59 (m, 2H), 2.49 (dd, *J* = 18.6 Hz, *J* = 8.4 Hz, 1H), 2.30−2.26 (m, 1H), 2.05 (s, 1H), 1.83−1.75 (m, 2H), 1.63−1.59 (m, 1H), 1.61 (d, *J* = 10.4 Hz, 1H), 1.46−1.36 (m, 4H), 1.16 (td *J* = 13.4 Hz, *J* = 4.0 Hz, 1H), 0.95−0.90 (m, 1H), 0.89 (s, 3H), 0.84−0.81 (m, 1H), 0.80 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 193.2, 155.9, 142.2, 71.2, 55.7, 55.5, 53.5, 41.6, 38.6, 38.4, 33.4, 33.2, 28.4, 27.6, 23.5, 21.2, 18.6, 18.4, 16.5; HRMS (ESI) calcd for $C_{20}H_{30}O_3Na$ $[M + Na]^+$ 341.2093, found 341.2097. Data for galanal B: $[\alpha]^{25}_D$= −39.1 (*c* 1.0, $CHCl_3$); mp 142−144 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 9.41 (s, 1H), 7.04 (dd, *J* = 8.7 Hz, *J* = 4.0 Hz, 1H), 3.55 (d, *J* = 8.0 Hz, 1H), 3.16−3.08 (m, 1H), 2.92 (dd, *J* = 16.3 Hz, *J* = 9.0 Hz, 1H), 2.68 (d, *J* = 16.3 Hz, 1H), 2.61−2.52 (m, 2H), 1.87 (d, *J* = 12.6 Hz, 1H), 1.80−1.70 (m, 1H), 1.70−1.62 (m, 1H), 1.60−1.44 (m, 2H), 1.47 (d, *J* = 10.2 Hz, 1H), 1.43−1.36 (m, 1H), 1.36−1.27 (m, 1H), 1.20−1.08 (m, 2H), 0.90 (dd, *J* = 13.2 Hz, *J* = 4.0 Hz, 1H), 0.86 (s, 3H), 0.83 (d, *J* = 2.2 Hz, 1H), 0.78 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 193.3, 157.5, 140.8, 78.7, 55.6, 55.5, 55.4, 41.7, 38.9, 38.9, 34.5, 33.4, 33.3, 28.7, 24.1, 21.3, 19.0, 18.6, 15.9; HRMS (ESI) calcd for $C_{20}H_{30}O_3Na$ $[M + Na]^+$ 341.2093, found 341.2087. The NMR spectral data of galanal A and B were in accord with literature values.[7]

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■ ASSOCIATED CONTENT

Supporting Information

Calculated structure coordinates for **15** and **16**, X-ray crystallographic data for **11** and **12**, copies of ^{1}H and ^{13}C NMR spectra, and HPLC data for **3**. This material is available free of charge on the ACS Publications Web site. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02766.

Calculated structure coordinates for **15** and **16**, X-ray crystallographic data for **11** and **12**, copies of ^{1}H and ^{13}C NMR spectra, and HPLC data for **3** (PDF)

X-ray data for compound **11** (CIF)

X-ray data for compound **12** (CIF)

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Notes

The authors declare no competing financial interest.

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