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Synthesis of (±)-*epi*-Stegobinone Utilizing Silacyclopropanes as Synthetic Intermediates

Stacie A. Calad, Jelena Ćiraković, and K. A. Woerpel*

Department of Chemistry, University of California, Irvine, California 92697-2025

kwoerpel@uci.edu

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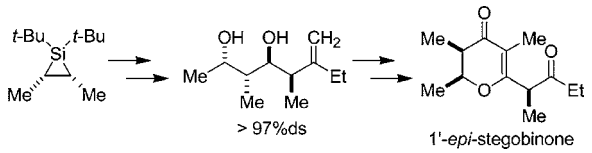


The synthesis of (±)-1′-*epi*-stegobinone has been accomplished in ten steps and 17% overall yield from a recently reported silacyclopropane-derived diol. All stereocenters of the final product were established relative to the stereochemistry of the initial silacyclopropane. This synthesis represents the first time silacyclopropane reactivity has been employed in a target-directed synthesis.

Stegobinone (**1**) is the female-produced sex pheromone of the drugstore beetle, *Stegobium paniceum*,[1,2] and the furniture beetle, *Anobium punctatum*.[3] Both species are economically important pests due to the damage they can cause to stored grain and wood products. The chemical structure of stegobinone[2] includes a dihydropyranone ring, a structural motif that is common to other polypropionate natural products.[4−6] The natural isomer, (2*S*,3*R*,1′*R*)-stegobinone (**1**),[7] readily isomerizes to *epi*-stegobinone (**2**), which is repellent to the male species instead of an attractant (Figure 1).[8,9] Due to its unique structure, several

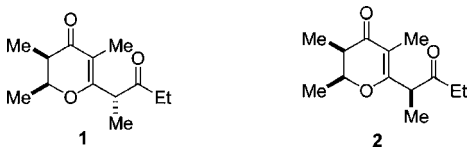
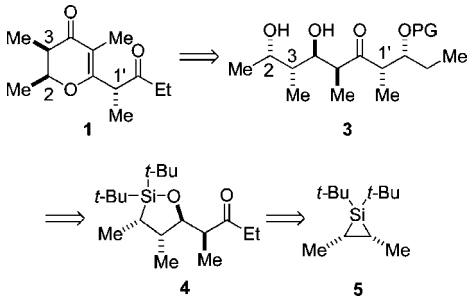


FIGURE 1. (2*S*,3*R*,1′*R*)-Stegobinone (**1**) and (2*S*,3*R*,1′*S*)-stegobinone (**2**).

approaches toward the synthesis of stegobinone have been undertaken.[10−15]

In this paper, we describe an approach to stegobinone utilizing silacyclopropanes as synthetic intermediates. The synthetic plan, which represents the first demonstration of silacyclopropanes as intermediates in target-directed synthesis, derives all the stereocenters in the final molecule from the stereochemistry of the starting silacyclopropane (Scheme 1). Disconnection of the

SCHEME 1. Retrosynthetic Analysis



dihydropyranone ring of **1** by an acid-promoted cyclization provides polypropionate fragment **3**. The desired stereochemistry at the 1′-position could be established by an *anti*,*syn*-selective aldol reaction of ethyl ketone **4** with propionaldehyde. We envisioned the 1,3-diol array of **3** arising through carbon−silicon bond oxidation of oxasilacyclopentane **4**, which could be derived from the silacyclopropane of *cis*-butene.

We recently reported the diastereoselective synthesis of ethyl ketone **4**, containing four contiguous stereocenters, in five steps from *cis*-butene (Scheme 2).[16] Silver-catalyzed silylene transfer from silacyclopropane **6** provided stereospecific formation of silacyclopropane **5**. Treatment of the in situ formed *cis*-dimethylsilacyclopropane **5** with *N*-methyl-*N*-benzylformamide and a catalytic amount of copper iodide resulted in an *N*,*O*-acetal, which was hydrolyzed and acetylated to provide oxasilacyclopentane **7** in 74% yield over four steps. Nucleophilic substitution with silyl enol ether **8**[17] produced ketone **4** in 95% yield and high diastereoselectivity.[18] The observed stereochemistry can be explained by approach of the silyl enol ether through an antiperiplanar transition state.[19,20]

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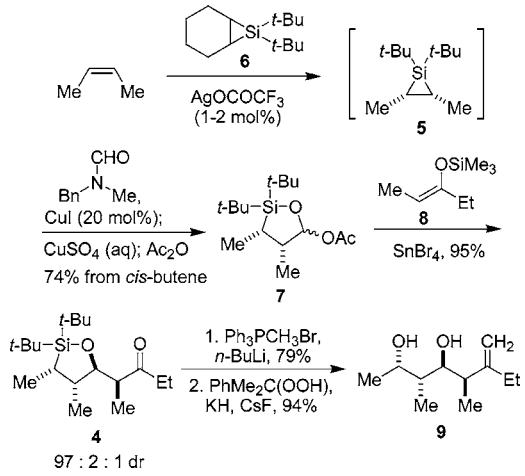
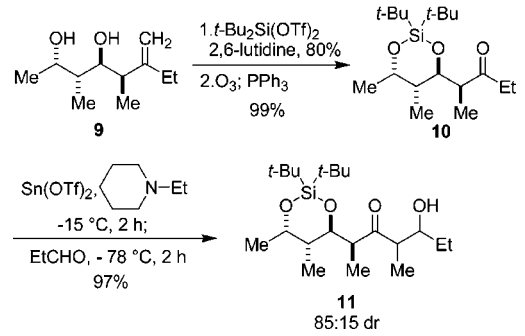
SCHEME 2. Synthesis of Diol 9



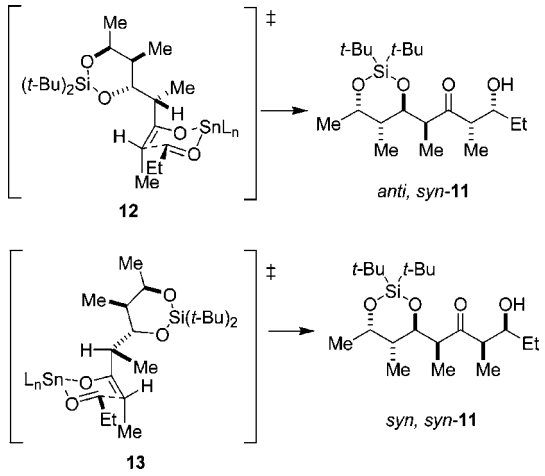
SCHEME 3. Synthesis of Aldol Adduct



The polypropionate functionality of the molecule was further revealed through oxidation of the hindered carbon−silicon bond, as was previously reported.[16] Due to the strongly basic conditions necessary for the oxidation, a protecting group for the enolizable ketone moiety of **4** was required. Masking the ketone as an alkene proved to be the best strategy (Scheme 2). The subsequent carbon−silicon bond oxidation[21] was achieved in 94% yield at ambient temperature using the conditions optimized in our laboratory.[22−24]

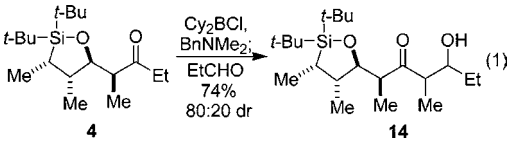
Installation of the remaining polypropionate unit of the carbon skeleton was accomplished by an aldol reaction. To prevent chelation of the diol oxygens in the aldol reaction,[25−27] the sterically hindered di-*tert*-butylsilyl protecting group was employed (Scheme 3).[28,29] Subsequent ozonolysis of the double bond afforded aldol precursor **10**. Aldol reactions of β-silyloxy lithium enolates have been reported to provide products containing the desired *anti*,*syn*-stereochemistry.[30] The lithium enolate

SCHEME 4. Analysis of Aldol Reaction



of ketone **10**, however, gave aldol product **11** as a 68:32 mixture of diastereomers. Other metal enolates were screened, and the reaction of $Sn(OTf)_2$ provided the highest yields and selectivities (Scheme 3).[31] The major isomer obtained from the tin aldol reaction was the same major diastereomer obtained from the lithium aldol reaction. Based on literature precedent,[30,31] we surmised that the aldol reaction had occurred through transition state **12** to provide *anti*,*syn*-**11**, and not through transition state **13**, which would provide the *syn*,*syn*-isomer (Scheme 4).[32] Attempts to crystallize **11** or its derivatives were unsuccessful, so its stereochemistry proof was left to be determined later in the synthesis.

An alternative sequence involving the aldol reaction between ketone **4** and propionaldehyde prior to carbon−silicon bond oxidation was unsuccessful. The (*E*)-boron enolate was employed to obtain the *anti*,*anti*-aldol product,[33] but only an 80:20 mixture of diastereomers was obtained (eq 1). In addition, attempts to protect the ketone moiety prior to the strongly basic carbon−silicon bond oxidation resulted in mixtures of elimination and retro-aldol products. Therefore, the original order of events (Schemes 2 and 3), involving oxidation followed by the aldol reaction, was employed.



The core structure of stegobinone was synthesized in five steps from aldol adduct **11** (Scheme 5). Protection of alcohol **11** as its acetate followed by deprotection of the diol with HF-pyridine[29] occurred cleanly. Selective monoprotection of the less sterically hindered hydroxyl group provided alcohol **15**.[34,35]

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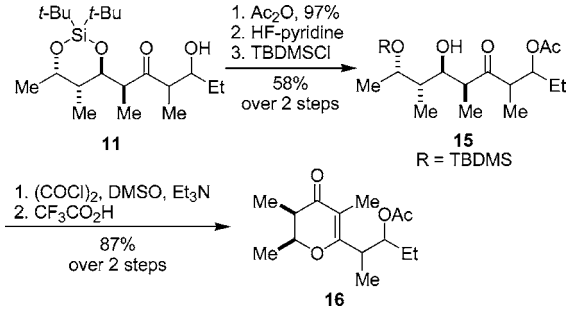
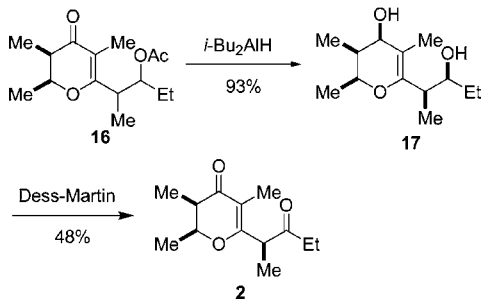
SCHEME 5. Synthesis of Dihydropyranone 16



SCHEME 6. Completion of 1′-*epi*-Stegobinone



Swern oxidation of alcohol **15** followed by treatment with trifluoroacetic acid afforded dihydropyranone **16** in 87% yield over two steps.[12,13]

The stereochemistry established in the aldol reaction was eventually determined, and the synthesis of 1′-*epi*-stegobinone was accomplished. Reduction of acetate **16** afforded crystalline diol **17**, which was analyzed by X-ray crystallography (Scheme 6). Unfortunately, the crystal structure of **17** showed that the key aldol reaction had established *syn*,*syn*-stereochemistry instead of the desired *anti*,*syn* relationship in aldol product **11**. These results suggest that the aldol reaction proceeded through transition structure **13**, in which the large di-*tert*-butylsilyl protected diol is positioned away from the forming bond and the methyl group is oriented away from the metal center (Scheme 4).[32] Attempts to establish a different stereochemical outcome in the aldol reaction were unsuccessful.[36,37] Synthesis of the 1′-epimer of stegobinone was completed by oxidation of **17** under previously optimized conditions.[15]

This work represents the first target-directed synthesis employing silacyclopropanes as synthetic intermediates and demonstrates their potential as polypropionate synthons. Diol **9**, containing four contiguous stereocenters, was prepared in six steps from the *cis*-butene-derived silacyclopropane and in greater than 97:3 diastereoselectivity. All stereocenters of the final product were established relative to the initial silacyclopropane stereochemistry. Using this methodology, the synthesis of (±)-1′-*epi*-stegobinone was accomplished in 17 steps and in 8.8% overall yield.

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(36) When diol **9** was protected as the benzyl ether, a boron-mediated aldol reaction provided a 66:34 ratio of diastereomers.

(37) When diol **9** was protected as an acetonide, a boron-mediated aldol reaction provided a 68:32 ratio of diastereomers. Titanium and tin enolates provided no reaction.

Experimental Section[38,39]

β-Hydroxyketone 11. To a suspension of tin(II) triflate[40] (2.97 g, 7.13 mmol) in CH_2Cl_2 (30.0 mL) was added 1-ethylpiperidine (1.22 mL, 8.84 mmol), and the yellow suspension was cooled to −15 °C. Ketone **29** (1.17 g, 3.56 mmol) was added dropwise as a solution in CH_2Cl_2 (7.0 mL and 2 × 2.0 mL rinses). The resulting mixture was allowed to stir at −15 °C for 4 h. The reaction mixture was then cooled to −78 °C, and freshly distilled propionaldehyde (0.970 mL, 14.3 mmol) was added by syringe. The mixture was allowed to stir at −78 °C for 4 h. The reagents were then diluted with 1 M aqueous $NaHSO_4$ solution (15.0 mL). The biphasic mixture was allowed to reach room temperature, and the layers were separated. The organic phase was washed with saturated aqueous sodium potassium tartrate (15.0 mL) and brine (15.0 mL), filtered through a cotton plug, and concentrated in vacuo. Purification by flash chromatography (10:0.3 to 10:0.5 pentane/EtOAc) afforded β-hydroxyketone **11** as a 85:15 mixture of diastereomers (1.34 g, 97%): IR (thin film) 3495, 2970, 2936, 1699, 1474, 1139 cm^{-1}; HRMS (electrospray) *m*/*z* calcd for $C_{21}H_{42}O_4SiNa$ $(M + Na)^+$ 409.2750, found 409.2766. Anal. Calcd for $C_{21}H_{42}O_4Si$: C, 65.23; H, 10.95. Found: C, 65.12; H, 11.03. Major diastereomer: ^1H NMR (500 MHz, $CDCl_3$) δ 4.46 (dd, J = 9.9, 2.4, 1H), 4.26−4.21 (m, 1H), 3.85 (m, 1H), 2.95 (dq, J = 2.1, 7.3, 1H), 2.67 (dq, J = 2.5, 6.8, 1H), 2.67−2.20 (m, 1H), 1.62−1.53 (m, 1H), 1.39−1.30 (m, 1H), 1.27 (d, J = 6.6, 3H), 1.13 (d, J = 6.8, 3H), 1.12 (d, J = 7.3, 3H), 1.00 (s, 9H), 0.95 (s, 9H and m, 3H), 0.76 (d, J = 7.0, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 218.2, 72.84, 72.79, 72.1, 48.1, 45.1, 38.4, 27.4, 27.2, 26.8, 21.2, 20.6, 17.9, 13.6, 10.5, 9.8, 7.4.

β-Hydroxyketone 14. To a cooled (0 °C) solution of chlorocyclohexylborane (0.14 mL, 0.64 mmol) in diethyl ether (0.40 mL) was added benzyldimethylamine (0.097 mL, 0.64 mmol), followed by the addition of ketone **4** (0.101 g, 0.32 mmol) in diethyl ether (0.2 mL). After being stirred for 2 h, the reaction mixture was cooled to −78 °C, and freshly distilled propionaldehyde was added (0.046 mL, 0.64 mmol). After being stirred for 6 h at −78 °C, the reaction mixture was poured into pH 7 phosphate buffer (5 mL) and diluted with 5 mL of diethyl ether. The aqueous layer was extracted with 3 × 5 mL of diethyl ether, and the combined organic extracts were concentrated in vacuo. The residue was dissolved in 3 mL of methanol and cooled to 0 °C. Phosphate buffer (0.72 mL, pH 7) and hydrogen peroxide (2.0 mL of 30% solution in water) were then added. The ice bath was removed, and the mixture was stirred for 12 h. The reaction mixture was then diluted with 10 mL of water and extracted with 3 × 15 mL of CH_2Cl_2. The combined organic layers were washed with 10 mL of 5% aqueous $NaHCO_3$ and 10 mL of brine, filtered through a cotton plug, and concentrated in vacuo to give **14** as an 80:20 mixture of diastereomers. Purification by flash chromatography (10:0.5 hexanes/EtOAc) afforded the product as a single diastereomer (0.880 g, 74%): ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (dd, J = 10.5, 2.5, 1H), 3.61 (m, 1H), 3.06 (quintet, J = 7.0, 1H), 2.77 (d, J = 6.4, 1H), 2.05 (m, 1H), 1.57 (m, 1H), 1.40 (m, 2H), 1.12 (m, 10H), 1.06 (s, 9H), 1.00 (s, 9H), 0.96 (t, J = 7.4, 3H), 0.91 (d, J = 7.0, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 218.5, 80.9, 76.1, 50.5, 47.0, 38.3, 29.6, 28.4, 28.0, 21.9, 20.5, 19.3, 14.8, 12.3, 10.8, 9.6, 7.9; IR (neat) 3441, 2967, 1708, 1469, 1387, 1365 cm^{-1}; HRMS (CI/isobutene) *m*/*z* calcd for $C_{21}H_{43}O_3Si$ $(M + H)^+$ 371.2981, found 371.2984. Anal. Calcd for $C_{21}H_{42}O_3Si$: C, 68.05; H, 11.42. Found: C, 68.04; H, 11.52.

Alcohol 15. To a solution of β-hydroxyketone **11** (0.397 g, 1.03 mmol) in CH_2Cl_2 (5.58 mL) were added Et_3N (3.11 mL, 22.3 mmol)

(38) For a description of the general experimental methods, see the Supporting Information.

(39) Although compounds **4**, **5**, **7**, and **9** have been prepared previously (ref 16), their synthesis has been optimized. The improved procedures are provided in the Supporting Information.

(40) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757−6761.

and acetic anhydride (1.05 mL, 11.1 mmol), followed by 4-(*N*,*N*-dimethyamino)pyridine (0.068 g, 0.56 mmol). After 14 h, the solution was concentrated in vacuo. Purification by column chromatography (hexanes to 95:5 hexanes/EtOAc) afforded an acetate as a clear oil (0.418 g, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (td, J = 5.3, 8.3, 1H), 4.41 (dd, J = 2.3, 10.0, 1H), 4.23 (quintet, J = 6.6, 1H), 3.11 (dq, J = 5.7, 7.0, 1H), 2.55 (dq, J = 2.3, 7.0, 1H), 2.21 (m, 1H), 2.05 (s, 3H), 1.57 (m, 2H), 1.25 (d, J = 6.6, 3H), 1.24 (d, J = 7.0, 3H), 1.08 (d, J = 7.0, 3H), 1.00 (s, 9H), 0.96 (s, 9H), 0.88 (t, J = 7.4, 3H), 0.72 (d, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.9, 170.7, 75.0, 73.3, 72.9, 48.7, 45.7, 38.4, 27.5, 27.2, 25.8, 21.3, 21.0, 20.7, 17.8, 13.5, 12.0, 10.2, 8.2; IR (thin film) 2970, 1742, 1237, 1139, 1002, 824 cm^{-1}; HRMS (electrospray) *m*/*z* calcd for $C_{23}H_{44}O_5SiNa$ $(M + Na)^+$ 451.2856, found 451.2854. Anal. Calcd for $C_{23}H_{44}O_5Si$: C, 64.44; H, 10.35. Found: C, 64.28; H, 10.35.

To a solution of the acetate (0.643 g, 1.50 mmol) in THF (5.00 mL) was added pyridine (2.70 mL) followed by HF−pyridine (0.250 mL). After 6 h, the solution was diluted with CH_2Cl_2 (45 mL) and poured into 50 mL of saturated aqueous $CuSO_4$. The layers were separated, and the organic layer was washed with saturated aqueous $CuSO_4$ (2 × 50 mL), washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), filtered through a cotton plug, and concentrated in vacuo to afford an oil. The resulting oil was dissolved in CH_2Cl_2 (7.00 mL), and to this solution were added Et_3N (0.314 mL), *tert*-butyldimethylsilyl chloride (0.271 g, 1.80 mmol, in 0.50 mL of CH_2Cl_2), and 4-(*N*,*N*-dimethyamino)pyridine (0.077 g, 0.63 mmol). After being stirred for 20 h, the solution was diluted with CH_2Cl_2 (45 mL) and washed with H_2O (50 mL), saturated aqueous NH_4Cl (50 mL), and brine (50 mL). The resulting organic layer was filtered through a cotton plug and concentrated in vacuo to afford an oil. Column chromatography (95:5 hexanes/EtOAc) afforded the product as a colorless oil (0.350 g, 58%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 (ddd, J = 4.1, 6.1, 9.3, 1H), 4.21 (dq, J = 2.1, 6.4, 1H), 3.96 (td, J = 1.6, 9.8, 1H), 3.80 (d, J = 1.6, 1H), 3.04 (quintet, J = 6.7, 1H), 2.73 (dq, J = 1.8, 5.2, 1H), 2.05 (s, 3H), 1.58 (m, 3H), 1.15 (d, J = 6.4, 3H), 1.08 (d, J = 7.1, 6H), 0.88 (m, 12H), 0.77 (d, J = 7.0, 3H), 0.06 (d, J = 5.0, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.1, 170.6, 75.6, 71.4, 69.5, 47.2, 47.1, 41.1, 25.8, 25.1, 20.9, 19.7, 18.0, 12.6, 10.8, 8.1, −4.4, −5.1; IR (thin film) 2972, 1743, 1237, 960, 837 cm^{-1}; HRMS (electrospray) *m*/*z* calcd for $C_{21}H_{42}O_5SiNa$ $(M + Na)^+$ 425.2699, found 425.2705. Anal. Calcd for $C_{21}H_{42}O_5Si$: C, 62.64; H, 10.51. Found: C, 62.70; H, 10.57.

Dihydropyranone 16.[12,13] To a cooled (−60 °C) solution of oxalyl chloride (0.132 mL, 1.53 mmol) in CH_2Cl_2 (2.00 mL) was added DMSO (0.135 mL, 1.92 mmol) dropwise, followed by alcohol **15** (0.309 g, 0.767 mmol) in CH_2Cl_2 (1.00 mL). Triethylamine (0.535 mL) was added to the solution after 25 min. Over the next 2.5 h, the solution was allowed to warm to 0 °C and was then diluted with water (15 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10.0 mL). The combined organic layers were washed with 5% HCl (10.0 mL), 5% Na_2CO_3 (10.0 mL), and brine (10.0 mL), filtered through a cotton plug, and concentrated in vacuo. The resulting oil was dissolved in CH_2Cl_2 (13.4 mL) and trifluoroacetic acid (4.50 mL). After 3 h, the solution was diluted with water (20.0 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15.0 mL). The combined organic layers were washed with 15.0 mL each of saturated aqueous $NaHCO_3$ and brine, filtered through a cotton plug, and concentrated in vacuo. Column chromatography (95:5 to 90:10 hexanes/EtOAc) afforded the product as a pale yellow oil (0.178 g, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (dt, J = 3.4, 8.3, 1H), 4.40 (dq, J = 3.4, 6.6, 1H), 2.96 (qd, J = 6.9, 8.6, 1H), 2.31 (dq, J = 3.4, 7.3, 1H), 2.09 (s, 3H), 1.74 (s, 3H), 1.67 (dq, J = 3.3, 7.5, 1H), 1.50 (qd, J = 7.2, 8.5, 1H), 1.28 (d, J = 6.6, 3H), 1.11 (d, J = 6.8, 3H), 1.04 (d, J = 7.3, 3H), 0.87 (t, J = 7.4, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 171.7, 170.7, 108.6, 76.7, 76.1, 43.7, 39.3, 25.4, 20.9, 16.1, 14.2, 9.4, 9.2, 9.1; IR (thin film) 2975, 1735, 1664, 1605, 1227 cm^{-1}; HRMS (electrospray) *m*/*z* calcd for $C_{15}H_{25}O_4$ $(M + H)^+$ 269.1753, found 269.1747. Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.11; H, 9.21.

Diol 17. To a cooled (−78 °C) solution of dihydropyran **16** (0.082 g) in toluene (1.0 mL) was added *i*-Bu_2AlH (0.61 mL, 1.5 M solution in toluene). The solution was allowed to warm to room temperature over 2 h, and additional *i*-Bu_2AlH (0.30 mL) was added after 6 h. After 30 min, EtOAc (0.10 mL) was added to the solution, followed by saturated, aqueous sodium potassium tartrate (5.0 mL). This mixture was stirred for 2 h, then poured into 15 mL of H_2O and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with 15 mL of brine, filtered through a cotton plug, and concentrated in vacuo. The resulting solid was recrystallized from MeOH and CH_2Cl_2 to afford the product as white crystals (0.065 g, 93%): mp 146−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (t, J = 6.6, 1H), 4.02 (dq, J = 2.4, 6.6, 1H), 3.64 (br s, 1H), 2.60 (d, J = 2.3, 1H), 2.55 (dq, J = 4.0, 7.1, 1H), 1.99 (doublet of quintets, J = 2.3, 6.8, 1H), 1.66 (s, 3H), 1.47 (m, 2H), 1.32 (d, J = 7.3, 1H), 1.24 (d, J = 6.6, 3H), 1.04 (d, J = 7.0, 3H), 0.95 (t, J = 7.4, 3H), 0.94 (d, J = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 102.7, 75.6, 73.6, 70.0, 37.9, 36.9, 27.5, 17.0, 13.0, 11.2, 10.5, 6.7; IR (thin film) 3583, 3442, 2968, 2360, 997 cm^{-1}; HRMS (ES) *m*/*z* calcd for $C_{13}H_{24}O_3Na$ $(M + Na)^+$ 251.1623, found 251.1621.

(±)-1′-*epi*-Stegobinone (2).[15] A buffered stock solution of Dess−Martin periodinane was prepared by dissolving the periodinane (0.170 g) in 6.5 mL of CH_2Cl_2 and 0.190 mL of pyridine. To a solution of diol **17** (0.0095 g, 0.042 mmol) in CH_2Cl_2 (0.7 mL) was added 6.0 mL of the buffered solution of Dess−Martin periodinane (0.36 mmol). After 2 h, starting material still remained, so solid periodinane (0.105 g) was added. After 2 h, the solution was diluted with Et_2O (5 mL) and $NaHCO_3$/$NaHSO_4$ (5 mL, saturated aqueous, 1:1). The organic layer was separated and washed with 5 mL each of saturated aqueous $NaHCO_3$ and brine, dried ($NaSO_4$), filtered, and concentrated in vacuo. Flash chromatography (100:0 to 80:20 pentane: Et_2O) afforded the product as a solid (0.0046 g, 48%): mp 46−48 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (dq, J = 3.5, 6.6, 1H), 3.65 (q, J = 7.0, 1H), 2.52 (qd, J = 7.3, 17.5, 1H), 2.43 (m, 1H), 2.36 (dq, J = 3.4, 7.3, 1H), 1.80 (s, 3H), 1.29 (d, J = 6.5, 3H), 1.28 (d, J = 7.0, 3H), 1.07 (t, J = 7.3, 3H), 1.05 (d, J = 7.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 197.2, 169.0, 109.5, 77.5, 49.4, 43.8, 33.9, 15.9, 12.7, 9.40, 9.38, 7.9. These data match those of the known compound.[9b]

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Supporting Information Available: Experimental procedures; spectroscopic, analytical, and X-ray data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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