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Total Synthesis of (+)-Iresin

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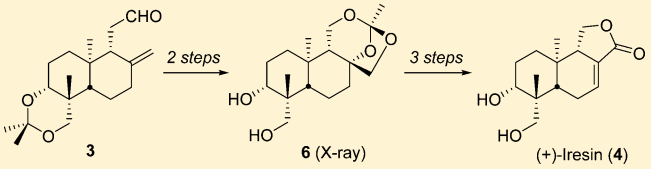
Supporting Information

ABSTRACT: The first asymmetric total synthesis of (+)-iresin (**4**), an historically important *ent*-Drimane sesquiterpene lactone, was realized from aldehyde **3** via cyclic orthoester **6** in 5 steps. Notable transformations in this synthesis include a tandem trifluoroperacetic acid (TFPAA)-mediated Baeyer–Villiger oxidation–olefin epoxidation–epoxy ester cyclization, regioselective Burgess dehydration, and regioselective Fétizon oxidative lactonization.



Drimane (known also as *Iresane*) sesquiterpenoids constitute a group of widely occurring terpene natural products possessing a characteristic *bicyclofarnesol* skeleton (Figure 1).[1] Thus, the Drimane was once regarded as the missing biogenetic link between the lower and higher terpenoids.[2] Oxygenated Drimane sesquiterpenoids exhibit a wide range of significant biological activities,[1,3] such as antifeedant, insecticidal, and cytotoxic, and have stimulated a great deal of attention on synthetic development.[4] (+)-Iresin (**4**), a unique *ent*-Drimane sesquiterpene lactone, was first isolated by Djerassi and co-workers[5] in 1954 from the Mexican herb plant *Iresine celosioides* (known as "herb of the mayas") and characterized[6] in 1958 by extensive chemical and spectroscopic methods and X-ray crystallographic study as the tricyclic dihydroxy lactone **4**. Full NMR spectroscopic assignments of **4** appeared in 2005.[7] The sole documented classical synthetic study on **4** by Pelletier and Prabhakar[8] in 1968 led to the total synthesis of isoiresin in a racemic form.

In a previous publication of this serial study,[9] we have reported the total synthesis of (−)-andrographolide (**1**) from a homoiodo allylsilane epoxide **2** by a conformationally directed biomimetic cationic cyclization to form aldehyde **3** as a pivotal intermediate (Figure 1). We describe in this Note the first asymmetric total synthesis of (+)-iresin (**4**) from the same intermediate **3**. The conversion of aldehyde **3** to lactone **4** requires the elaboration of an unsaturated γ-lactone function, which would be achieved via oxidative cleavage of the formyl carbon and regioselective olefin formation and subsequent lactonization.

The synthetic route to **4** commenced with aldehyde **3** and is outlined in Schemes 1 and 2. To facilitate the Baeyer–Villiger oxidation,[10] **3** was converted to the corresponding methyl ketone derivative **5** via a standard methylation–oxidation procedure. After screening of peroxy acids, freshly prepared trifluoroperacetic acid (TFPAA, ca. 0.2 M) was found to be the optimal oxidant in the presence of excess Na_2HPO_4 in CH_2Cl_2 at 0 °C. Keto olefin **5** was thus transformed to the cyclic orthoester **6**[11] as the major product (53%), along with the corresponding hydrolytic product monoacetates **7a** and **7b** (17%).[11a,e] The stereostructure of **6** was confirmed by a single-crystal X-ray diffraction analysis.[12] It is worthwhile to note that not only the Baeyer–Villiger oxygenation of the keto function occurred smoothly but also the olefin epoxidation and subsequent epoxide-opening–cyclization took place, leading to the cyclic orthoester **6**. The acetonide function of **5** was also unexpectedly cleaved under these reaction conditions. The unusual one-pot formation of cyclic orthoester **6** could be understood via the intramolecular rearrangement of an epoxy ester intermediate **5a**, as depicted in Scheme 1, based on serial mechanistic studies by Giner et al.[11c−e] Acidic hydrolysis of orthoester **6** afforded a product mixture of monoacetates **7a** and **7b**,[11a,e] which was subjected to acetylation to give the tetrakis-acetate **8** in 68% yield from **6** (Scheme 2). Standard dehydration of **8** employing various dehydrating agents (i.e., MsCl, $SOCl_2$, or $POCl_3$) in the presence of pyridine or Et_3N led to, after deacetylation, regioisomer **10** predominatedly (2.6–4.1:1) in good yield. In contrast, with Burgess reagent (3 equiv),[13] dehydration of **8** in warm benzene (50 °C) gave, after deacetylation, the desired regioisomer **9** as the major product (4.8:1) in 70% overall yield.[14]

With **9** and **10** in hand, we selected the Fétizon reagent[15] for the final oxidative lactonization (Scheme 2). To our delight, oxidation of **9** with freshly prepared Fétizon reagent in refluxing benzene produced the desired target lactone (+)-iresin (**4**) chemoselectively in 78% yield, along with aldehyde **11** in 14% yield. Reduction of **11** with $NaBH_4$ at 0 °C in methanol gave (+)-iresin (**4**) in 86% yield. Synthetic **4** exhibits identical spectroscopic data with those of reported (+)-iresin.[5,6] Further structural confirmation of synthetic **4** was provided by the X-ray crystallographic analysis of the bis-*para*-bromobenzoate derivative **14**.[6e,16] Interestingly, oxidation of **10** with excess Fétizon reagent in refluxing benzene furnished lactone aldehyde **12** chemoselectively in 91% yield, which was reduced with

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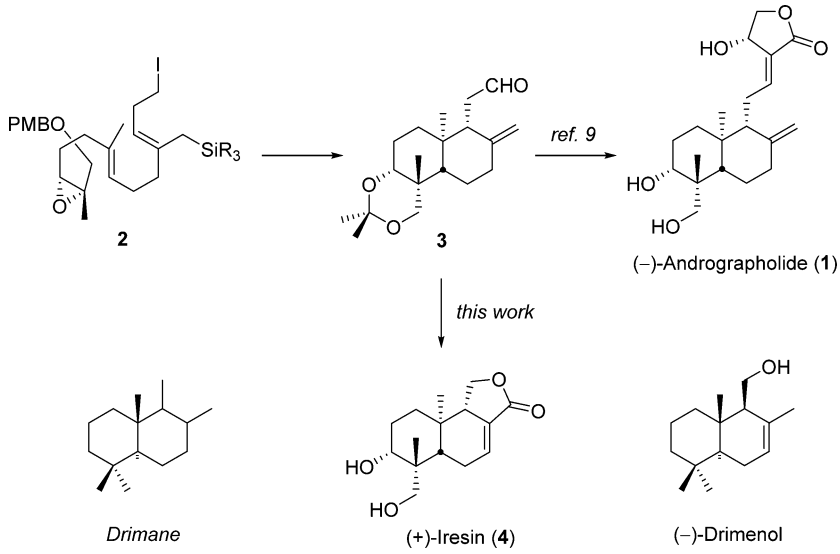
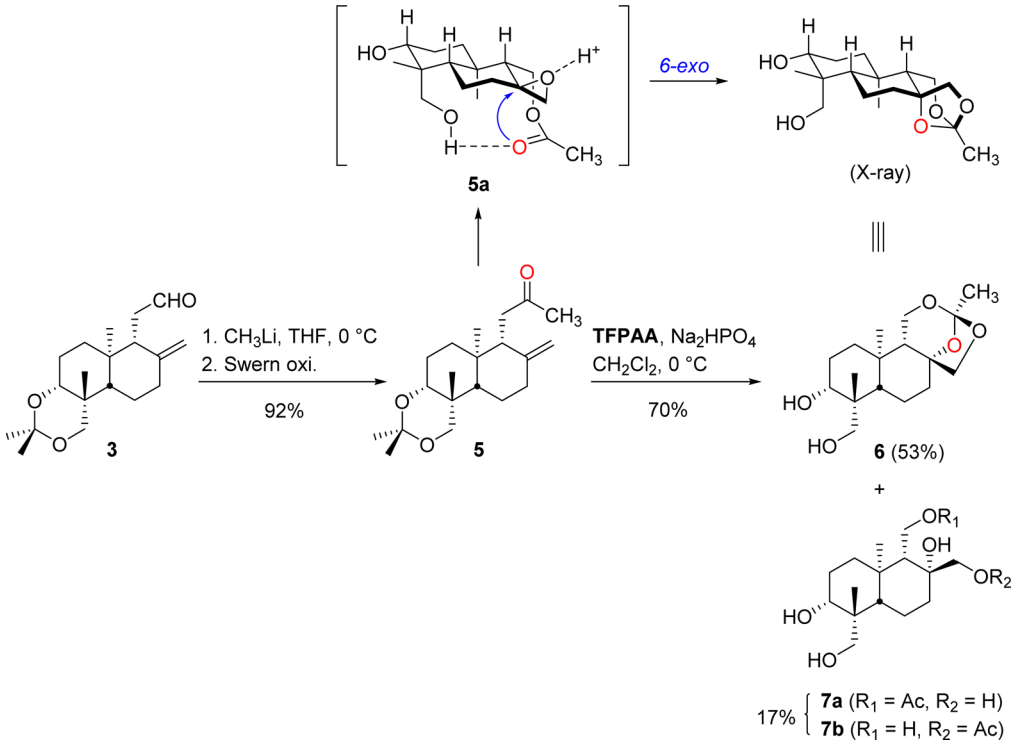


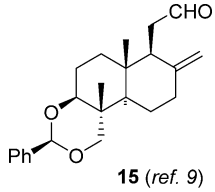
Figure 1. Structure of (+)-iresin and previous total synthesis of (−)-andrographolide (**1**) from homoiodo allylsilane epoxide **2** via aldehyde intermediate **3**.

Scheme 1. Synthesis of Orthoester 6 from Aldehyde 3



$NaBH_4$ at 0 °C to give lactone **13** in 92% yield. The structure of synthetic **13**, known as isoiresin,[8,17] was further confirmed by a single-crystal X-ray crystallographic analysis.[18]

In summary, the first asymmetric total syntheses of (+)-iresin (**4**) and (−)-isoiresin (**13**) were achieved from readily accessible aldehyde **3** in 5 and 6 steps, respectively. Notable transformations include the peroxidation of keto olefin **5** with TFPAA, leading to cyclic orthoester **6** via a tandem Baeyer−Villiger oxidation−olefin epoxidation−epoxy ester cyclization, regioselective dehydration of **8** with Burgess reagent, as well as the regioselective Fétizon oxidative γ-lactonization of **9** and **10**. The biomimetic synthetic approach[19] demonstrated here for the *ent*-Drimanes would be equally effective for other Drimane sesquiterpenoids, i.e., starting from synthetically readily accessible pseudo-antipodal intermediate **15**.[9]



EXPERIMENTAL SECTION

General. For product purification by flash column chromatography, silica gel (200−300 mesh) and petroleum ether (bp. 60−90 °C) were

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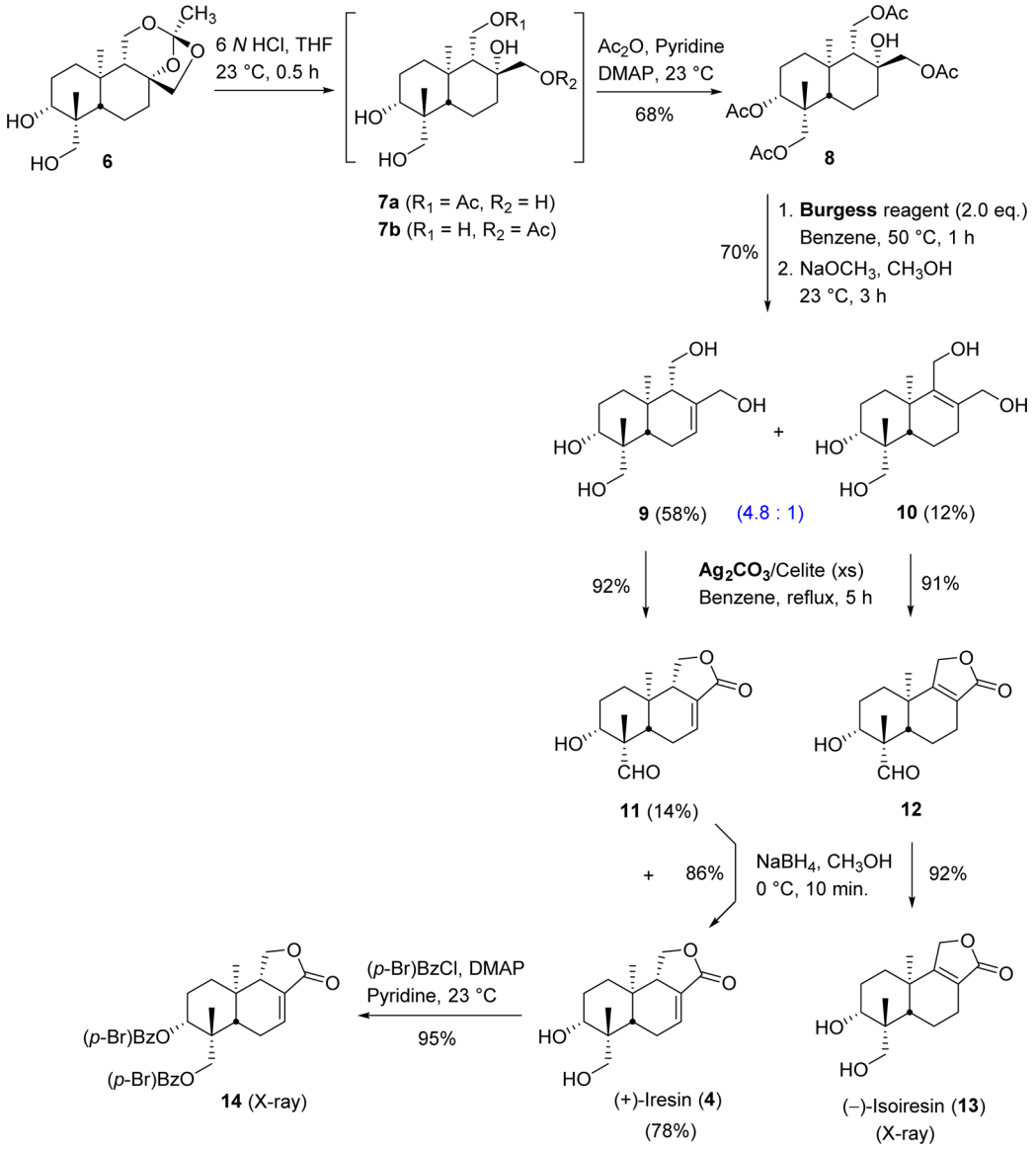
Scheme 2. Total Syntheses of (+)-Iresin (4) and (−)-Isoiresin (13)



used unless otherwise noted. All solvents were purified and dried by standard techniques, and distilled prior to use. Other commercially available reagents were used as received without further purification unless otherwise indicated. All organic extracts were dried over anhydrous sodium sulfate or magnesium sulfate. All moisture-sensitive reactions were carried out under an atmosphere of nitrogen in glassware that had been flame-dried under vacuum. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer with TMS as an internal reference and $CDCl_3$ as solvent, unless otherwise indicated. IR spectra were recorded on an FT-IR spectrometer as liquid film or KBr pellet. HRMS were acquired on an FT-ICR spectrometer. Melting points were measured on a hot stage and were uncorrected.

1-((4a*R*,6a*S*,7*R*,10a*S*,10b*R*)-3,3,6a,10b-Tetramethyl-8-methylenedecahydro-1*H*-naphtho[2,1-*d*][1,3]dioxin-7-yl)-propan-2-one (5). To a stirred solution of aldedyde (1.20 g, 3.92 mmol) in dry Et_2O (20 mL) was added 2.5 mL of CH_3Li (1.6 M in diethyl ether, 4.0 mmol) dropwise at 0 °C under N_2. After being stirred for 10 min, the reaction mixture was quenched with water (2.0 mL). The ethereal layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was used in the next step without further purification. DMSO (610 mg, 7.81 mmol) in CH_2Cl_2 (4.0 mL) was added dropwise to a solution of oxalic dichloride (0.33 mL, 3.87 mmol) in CH_2Cl_2 (4.0 mL) at −78 °C under N_2. After stirring for 15 min, the solution of crude alcohol in CH_2Cl_2 (6.0 mL) was added via syringe, and the reaction was stirred an additional 1 h at −78 °C. Et_3N (2.2 mL, 15.7 mmol) was added, and the reaction was stirred for 10 min at −78 °C. The bath was removed, and the resulting mixture was stirred for 20 min at room temperature. The mixture was partitioned between H_2O (15 mL) and CH_2Cl_2 (30 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (petroleum ether/EtOAc = 8:1) to give compound **5** (1.15 g, 92% from **3**) as a colorless oil: R_f = 0.51 (petroleum ether/EtOAc = 8:1); $[\alpha]_D^{20}$ +20 (*c* 1.0, $CHCl_3$); IR (film): ν_{max} 3078, 2936, 2891, 1717, 1644, 1374, 1227, 1095, 885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (s, 1H), 4.37 (s, 1H), 3.97 (d, J = 11.6 Hz, 1H), 3.50 (dd, J = 8.4, 4.0 Hz, 1H), 3.18 (d, J = 11.6 Hz, 1H), 2.68 (dd, J = 17.2, 10.4 Hz, 1H), 2.45−2.38 (m, 3H), 2.17 (s, 3H), 2.08 (td, J = 12.0, 4.8 Hz, 1H), 2.02−1.96 (m, 1H), 1.81−1.71 (m, 2H), 1.58 (ddd, J = 23.6, 7.6, 5.6 Hz, 1H), 1.41 (s, 3H), 1.37 (s, 3H), 1.35−1.26 (m, 3H), 1.21 (s, 3H), 0.91 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.3, 148.3, 107.2, 99.0, 76.4, 63.9, 52.0, 51.1, 40.1, 37.8, 37.7, 37.3, 34.4, 30.1, 27.2, 26.1, 25.3, 25.0, 23.0, 16.5 ppm; HRMS (ESI): calcd for $C_{20}H_{33}O_3$ $[M + H]^+$ 321.2424; found 321.2428.

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(3*S*,5a*R*,7a*S*,8*R*,9*R*,11a*R*,11b*R*)-8-(Hydroxymethyl)-3,8,11a-trimethyldecahydro-1*H*-3,5a-epoxynaphtho[1,2-*e*][1,3]-dioxepin-9-ol (6). To a stirred solution of 50% aq H_2O_2 (112 mg, 1.65 mmol) in CH_2Cl_2 (8.0 mL) was added TFAA (0.28 mL, 1.99 mmol) at 0 °C. After being stirred for 25 min, powdered Na_2HPO_4 (1.13 g, 7.96 mmol) was added to the mixture; then the solution of **5** (106 mg, 0.33 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise over 5 min. After stirring for 25 min at 0 °C, the reaction mixture was quenched with 5 mL of saturated aqueous $Na_2S_2O_3$. The resulting mixture was extracted with ethyl acetate (3 × 30 mL), and the combined organic extracts were washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography eluting with 1:2 petroleum ether/EtOAc to give **6** as white solids (55 mg, 53%) and the mixture of monoacetate products (**7a** and **7b**, 19 mg, 17%). Compound **6**: R_f = 0.39 (petroleum ether/EtOAc = 1:2); mp 118−121 °C; $[\alpha]_D^{20}$ +6 (*c* 1, $CHCl_3$); IR (KBr): ν_{max} 3365, 2938, 2886, 1463, 1402, 1301, 1134, 863 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.26 (d, *J* = 11.2 Hz, 1H), 4.03 (dd, *J* = 12.4, 5.6 Hz, 1H), 3.87 (d, *J* = 7.2 Hz, 1H), 3.82 (d, *J* = 12.4 Hz, 1H), 3.43−3.35 (m, 3H), 2.82 (d, *J* = 7.6 Hz, 1H), 2.73 (s, 1H), 1.92−1.84 (m, 3H), 1.78−1.67 (m, 2H), 1.62 (dd, *J* = 12.8, 3.2 Hz, 1H), 1.58−1.49 (m, 1H), 1.55 (s, 3H), 1.26 (s, 3H), 1.14 (s, 3H), 0.94−0.89 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.7, 80.3, 79.8, 74.8, 63.9, 58.7, 53.7, 50.2, 42.4, 37.4, 36.9, 33.6, 27.2, 22.7, 22.3, 18.5, 16.7 ppm; HRMS (ESI): calcd for $C_{17}H_{28}O_5$ $[M + H]^+$ 313.2010; found 313.2003. X-ray crystallographic data of **6**: $C_{17}H_{28}O_5$, triclinic, space group: *P*1, *a* = 6.108 (2) Å, *b* = 7.159 (3) Å, *c* = 20.206 (7) Å, α = 97.983(18)°, β = 91.80 (2)°, γ = 111.632(18)°, *Z* = 1, d_{calcd} = 1.281 g/cm^3, $R_1(I > 2\sigma(I))$ = 0.0451, wR_2 = 0.1065. Compound **7a**: ^1H NMR (400 MHz, CD_3OD): δ 4.15 (d, *J* = 11.2 Hz, 1H), 4.06 (d, *J* = 11.2 Hz, 1H), 3.95 (d, *J* = 10.8 Hz, 1H), 3.91 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.76 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.40−3.34 (m, 2H), 2.05 (s, 3H, $\underline{CH_3}CO$), 1.95 (d, *J* = 12.8 Hz, 1H), 1.85−1.70 (m, 3H), 1.65−1.63 (m, 2H), 1.54−1.49 (m, 1H), 1.21 (s, 3H), 1.45−1.37 (m, 2H), 1.06 (s, 3H), 0.97 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 173.0, 81.2, 74.6, 71.8, 65.2, 59.5, 56.5, 56.4, 43.8, 39.0, 38.7, 38.3, 28.4, 23.6, 21.0, 19.0, 17.8 ppm. Compound **7b**: ^1H NMR (400 MHz, CD_3OD): δ 4.25−4.24 (m, 2H), 4.14 (d, *J* = 11.2 Hz, 1H), 3.43 (d, *J* = 10.8 Hz, 1H), 3.40−3.34 (m, 2H), 3.20 (d, *J* = 10.8 Hz, 1H), 2.01 (s, 3H, $\underline{CH_3}CO$), 1.89 (dt, *J* = 13.2, 3.2 Hz, 1H), 1.82−1.79 (m, 1H), 1.73−1.63 (m, 6H), 1.40 (t, *J* = 3.6 Hz, 1H), 1.22 (s, 4H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 173.1, 81.1, 74.7, 69.8, 65.2, 63.0, 56.5, 53.6, 43.8, 39.0, 38.6, 38.1, 28.3, 23.5, 21.3, 19.0, 17.4 ppm.

((1*R*,2*R*,4a*S*,5*R*,6*R*,8a*R*)-6-Acetoxy-2-hydroxy-5,8a-dimethyldecahydronaphthalene-1,2,5-triyl)tris(methylene) Triacetate (8). To a stirred solution of **6** (260 mg, 0.83 mmol) in THF (4.0 mL) was added 6 N aq HCl (2.0 mL). After 30 min, the reaction mixture was diluted with water (5.0 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo to give a solid mixture of monoacetate products **7a** and **7b**. To a solution of products **7a** and **7b** in pyridine (2.0 mL) were added Ac_2O (0.50 mL, 5.3 mmol) and DMAP (9 mg, 0.074 mmol). After stirring overnight at room temperature, the reaction mixture was extracted with ethyl acetate, then washed with saturated $NaHCO_3$ solution, water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (petroleum ether/EtOAc = 3:1) to give compound **8** (257 mg, 68% from **6**, 80% from mixture of **7a** and **7b**) as a colorless oil. Compound **8**: R_f = 0.50 (petroleum ether/EtOAc = 1:1); $[\alpha]_D^{20}$ −27 (*c* 1.0, $CHCl_3$); IR (film): ν_{max} 3498, 2949, 1738, 1441, 1372, 1246, 1037, 985 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.59 (dd, *J* = 9.6, 7.2 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.28 (d, *J* = 4.0 Hz, 2H), 4.17 (d, *J* = 12.0 Hz, 1H), 3.98 (d, *J* = 11.2 Hz, 1H), 3.95 (d, *J* = 11.6 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.97 (d, *J* = 13.2 Hz, 1H), 1.85−1.80 (m, 2H), 1.76−1.69 (m, 4H), 1.49−1.41(m, 1H), 1.34−1.25 (m, 2H), 1.07 (d, *J* = 12.0 Hz, 1H), 1.04 (s, 3H), 1.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 170.9, 170.6, 170.5, 79.7, 72.6, 70.9, 65.0, 61.3, 55.1, 53.3, 41.1, 37.6, 37.5, 23.3, 22.7, 21.2, 21.1, 20.9, 18.1, 16.2 ppm; HRMS (ESI): calcd for $C_{23}H_{40}NO_9$ $[M + NH_4]^+$ 474.2698; found 474.2704.

((1*S*,4a*S*,5*R*,6*R*,8a*R*)-6-Hydroxy-5,8a-dimethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2,5-triyl)-trimethanol (9) and ((4a*S*,5*R*,6*R*,8a*R*)-6-Hydroxy-5,8a-dimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2,5-triyl)-trimethanol (10). Compound **8** (250 mg, 0.55 mmol) in 2 mL of benzene was added dropwise to a solution of Burgess reagent (390 mg, 1.64 mmol; Burgess reagent was prepared according to the literature methods[13d]) in 3 mL of benzene at 50 °C under N_2. After being stirred for 1 h at 50 °C, the reaction mixture was diluted with water (5.0 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo to give a liquid residue. The residue was dissolved in dry CH_3OH (5.0 mL), and $NaOCH_3$ (148 mg, 2.74 mmol) was added. The reaction mixture was stirred for 3 h, then filtered through a pad of Celite, eluting with $CHCl_3/CH_3OH$ (10:1). The resulting filtrate was concentrated under reduced pressure and purified by flash silica gel column chromatography $CHCl_3/CH_3OH$ (25:1) to give 86 mg (58%) of **9** as white solids and 18 mg (12%) of **10** as white amorphous solids. Compound **9**: R_f = 0.46 ($CHCl_3$/CH_3OH = 10:1); mp 160−162 °C; $[\alpha]_D^{20}$ −3 (*c* 1.0, CH_3OH); IR (KBr): ν_{max} 3327, 2930, 2858, 1707, 1448, 1363, 1024, 994 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 5.77 (t, *J* = 2.4 Hz, 1H), 4.23 (d, *J* = 12.8 Hz, 1H), 4.19 (d, *J* = 11.2 Hz, 1H), 3.95 (d, *J* = 12.8 Hz, 1H), 3.83 (dd, *J* = 11.2, 2.4 Hz, 1H), 3.62 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.48 (d, *J* = 11.2 Hz, 1H), 3.39 (dd, *J* = 11.2, 4.4 Hz, 1H), 2.19−2.05 (m, 3H), 1.96 (t, *J* = 14.8 Hz, 1H), 1.82−1.74 (m, 2H), 1.38−1.29 (m, 2H), 1.20 (s, 3H), 0.79 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 138.7, 126.3, 81.4, 66.8, 65.0, 61.3, 55.9, 51.7, 43.1, 38.8, 36.5, 28.8, 24.4, 23.3, 16.1 ppm; HRMS (ESI): calcd for $C_{15}H_{26}O_4Na$ $[M + Na]^+$ 293.1723; found 293.1727. Compound **10**: R_f = 0.55 ($CHCl_3/CH_3OH$ = 10:1); $[\alpha]_D^{20}$ −81 (*c* 1.2, CH_3OH); IR (film): ν_{max} 3340, 2937, 2858, 1700, 1448, 1359, 1017 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 4.20 (d, *J* = 12.0 Hz, 2.0H), 4.13 (d, *J* = 11.2 Hz, 1H), 4.02 (d, *J* = 11.6 Hz, 1H), 3.94 (d, *J* = 12.4 Hz, 1H), 3.41 (d, *J* = 11.2 Hz, 1H), 3.36 (dd, *J* = 10.8, 5.6 Hz, 1H), 2.35 (dd, *J* = 18.0, 5.6 Hz, 1H), 2.12 (ddd, *J* = 18.4, 11.6, 7.2 Hz, 1H), 1.95−1.77 (m, 4H), 1.51−1.42 (m, 2H), 1.22 (s, 3H), 1.23−1.21 (m, 1H), 1.00 (s, 3 H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 144.3, 136.8, 81.1, 65.2, 63.2, 57.6, 52.9, 43.7, 39.0, 35.5, 31.2, 28.9, 23.4, 21.6, 20.1 ppm; HRMS (ESI): calcd for $C_{15}H_{30}NO_4$ $[M + NH_4]^+$ 288.2169; found 288.2173.

Synthesis of (+)-Iresin (4). A mixture of **9** (57 mg, 0.21 mmol) and silver carbonate−Celite (0.57 g/mmol, 600 mg, 1.05 mmol; Fétizon reagent was prepared according to the literature methods[15d]) in 3 mL of benzene was heated to refluxed for 5 h, cooled, and filtered through a pad of Celite (ethyl acetate). The solvent was removed in vacuo, and the residue was then purified by silica gel column chromatography (petroleum ether/EtOAc = 1:1) to give (+)-iresin **1** (44 mg, 78%) as colorless crystals and aldehyde **11** (8 mg, 14%) as a white solid. $NaBH_4$ (2 mg, 0.052 mmol) at 0 °C was added to a solution of aldehyde in CH_3OH (1 mL). After stirring for 10 min at 0 °C, the reaction mixture was diluted with water (3.0 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with 1 N aq HCl, water, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (petroleum ether/EtOAc = 1:1) to give iresin (7 mg, 86% from **11**) as white solids. Iresin (**4**): R_f = 0.47 (AcOEt); mp 139−142 °C, (Lit.[5] mp 140−142 °C); $[\alpha]_D^{20}$ +20 (*c* 1.0, $CHCl_3$), (Lit.[5] $[\alpha]_D^{28}$ +21); IR (film): ν_{max} 3383, 2931, 2870, 1755, 1687, 1423, 1221, 1028, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.86 (ddd, *J* = 3.6, 3.6, 3.6 Hz, 1H), 4.40 (dd, *J* = 9.2, 9.2 Hz, 1H), 4.26 (d, *J* = 10.4 Hz, 1H), 4.02 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.54−3.49 (m, 2H), 3.12 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.00 (d, *J* = 4.4 Hz, 1H), 2.83−2.77 (m, 1H), 2.51(dddd, *J* = 20.0, 4.8, 4.0, 4.0 Hz, 1H), 2.18−2.10 (m, 1H), 1. 89−1.79 (m, 2H), 1.68 (ddd, *J* = 13.6, 3.6, 3.6 Hz, 1H), 1.50 (dd, *J* = 12.0, 5.2 Hz, 1H), 1.35 (ddd, *J* = 13.6, 13.6, 4.0 Hz, 1H), 1.28 (s, 3H), 0.77 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 135.8, 127.0, 80.4, 67.2, 63.3, 50.6, 50.0, 42.1, 37.1, 33.7, 27.3, 24.6, 22.1, 14.3 ppm; HRMS (ESI): calcd for $C_{15}H_{23}O_4$ [M

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+ H]$^+$ 267.1591; found 267.1585. Aldehyde **11**: R_f = 0.64 (AcOEt); mp 145−147 °C; $[\alpha]_D^{20}$ +35 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (d, *J* = 1.2 Hz, 1H), 6.86 (d, *J* = 3.2 Hz, 1H), 4.44 (dd, *J* = 8.8, 8.8 Hz, 1H), 4.03 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.37 (br d, *J* = 7.6 Hz, 1H), 2.85−2.80 (m, 2H), 2.67 (dddd, *J* = 20.4, 5.2, 4.0, 4.0 Hz, 1H), 2.49−2.45 (m, 1H), 1.97−1.94 (m, 2H), 1.75 (ddd, *J* = 13.6, 4.4, 4.4 Hz, 1H), 1.66 (dd, *J* = 11.6, 6.0 Hz, 1H), 1.42−1.35 (m, 1H), 1.34 (s, 3H), 0.74 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 169.5, 134.6, 127.1, 76.9, 67.2, 51.9, 50.6, 49.4, 37.3, 34.2, 27.7, 24.5, 19.6, 13.6 ppm.

Synthesis of (−)-Isoiresin (13). Lactonization of **10** to aldehyde **12** (91% yield) was carried out by a procedure analogous to that of **9**. Compound **12**: white solids; R_f = 0.57 (AcOEt); mp 151−154 °C; $[\alpha]_D^{20}$ −67 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (d, *J* = 2.4 Hz, 1H), 4.77−4.65 (m, 2H), 3.29 (br s, 1H), 3.16 (d, *J* = 10.0 Hz, 1H), 2.52−2.47 (m, 1H), 2.29−2.15 (m, 2H), 2.07−1.95 (m, 2H), 1.86−1.80 (m, 1H), 1.76 (ddd, *J* = 13.2, 3.6, 3.6 Hz, 1H), 1.55 (dd, *J* = 12.8, 4.4 Hz, 1H),1.47 (d, *J* = 12.0 Hz, 1H), 1.37 (s, 3H), 1.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9, 173.7, 167.9, 124.1, 77.0, 68.3, 52.5, 51.5, 36.4, 34.0, 27.8, 21.5, 20.1, 19.2, 18.2 ppm.

Reduction of aldehyde **12** to isoiresin (**13**) (92% yield) was carried out by a procedure analogous to that of aldehyde **11**. Isoiresin (**13**): colorless crystals; R_f = 0.46 (AcOEt); mp 217−220 °C; $[\alpha]_D^{20}$ −62 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 3303, 2924, 2853, 1736, 1670, 1643, 1430, 1384, 1196, 1011, 989 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.76−4.62 (m, 2H), 4.23 (dd, *J* = 11.2, 2.0 Hz, 1H), 3.54−3.49 (m, 1H), 3.41 (t, *J* = 9.6 Hz, 1H), 2.72 (dd, *J* = 8.8, 2.4 Hz, 1H), 2.61 (d, *J* = 4.0 Hz, 1H), 2.43 (dt, *J* = 18.0, 2.8 Hz, 1H), 2.17−2.10 (m, 1H), 2.03−1.86 (m, 3H), 1.73 (ddd, *J* = 12.8, 3.2, 3.2 Hz, 1H), 1.53−1.45 (m, 2H), 1.31 (s, 3H), 1.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 169.2, 123.8, 80.1, 68.1, 63.8, 51.0, 42.9, 36.0, 33.8, 27.5, 22.6, 21.7, 21.5, 18.1 ppm; HRMS (ESI): calcd for $C_{15}H_{23}O_4$ [M + H]$^+$ 267.1591; found 267.1586. X-ray crystallographic data of **13**: $C_{15}H_{22}O_4$, orthorhombic, space group: $C222_1$, *a* = 6.580 (6) Å, *b* = 12.892 (15) Å, *c* = 32.76 (3) Å, *Z* = 8, d_{calcd} = 1.359 g/cm^3, $R_1(I > 2\sigma(I))$ = 0.0357, wR_2 = 0.0836.

Preparation of Bis(4-Br)benzoate Derivative 14 of (+)-Iresin (4). To a stirred solution of (+)-iresin (**4**) (43 mg, 0.16 mmol) in dry pyridine (2 mL) were added *p*-bromobenzoyl chloride (177 mg, 0.81 mmol) and DMAP (2 mg, 0.016 mmol) at room temperature. When the consumption of iresin was complete (monitored by TLC), the reaction mixture was extracted with ethyl acetate, then washed with saturated $NaHCO_3$ solution, water, and brine, dried over Na_2SO_4, and concentrated to give a light yellow solid residue, which, after purification by flash column chromatography on silica gel (benzene/EtOAc = 30:1), afforded **14** (97 mg, 95%) as colorless crystals. R_f = 0.30 (petroleum ether/EtOAc = 1:2); mp 208−211 °C, (Lit.[6e] mp 211.5−212 °C); $[\alpha]_D^{20}$ −50 (*c* 1.6, $CHCl_3$); IR (KBr): ν_{max} 3014, 2890, 1760, 1741, 1689, 1590, 1480, 1291, 1012, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81−7.78 (m, 4H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 3.2 Hz, 1H), 4.96 (dd, *J* = 9.6, 6.4 Hz, 1H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.45 (dd, *J* = 9.2, 9.2 Hz, 1H), 4.08 (dd, *J* = 9.2, 9.2 Hz, 1H), 2.92−2.87 (m, 1H), 2.63 (dd, *J* = 20.0, 4.4 Hz, 1H), 2.53−2.45 (m, 1H), 1.96−1.91 (m, 2H), 1.81−1.75 (m, 2H), 1.60−1.52 (m, 1H), 1.23 (s, 3H), 0.92 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 165.8, 165.3, 135.1, 131.9, 131.6, 131.1, 130.9, 128.8, 128.7, 128.4, 128.3, 127.0, 80.2, 66.9, 64.1, 50.3, 50.2, 41.7, 36.9, 33.9, 25.1, 23.7, 22.1, 13.8 ppm; HRMS (ESI): calcd for $C_{29}H_{29}Br_2O_6$ [M + H]$^+$ 633.0305; found 633.0309. X-ray crystallographic data of **16**:[6e] $C_{29}H_{28}Br_2O_6$, monoclinic, space group: $P2_1$, *a* = 6.2860 (12) Å, *b* = 7.3672 (15) Å, *c* = 28.272 (6) Å, β = 92.047 (13)°, *Z* = 2, d_{calcd} = 1.605 g/cm^3, $R_1(I > 2\sigma(I))$ = 0.0530, wR_2 = 0.1339.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds **4**−**6**, **7a**, **7b**, **8**−**14**, X-ray crystallographic data for compounds **6**, **13**, **14**, and CIF files for compounds **6**, **13**, **14**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00365.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

In memory of Carl Djerassi.

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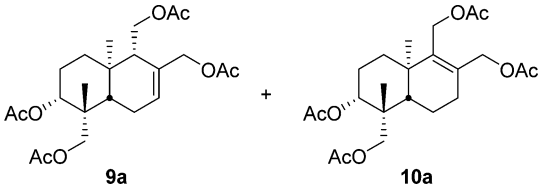

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(19) For earlier biomimetic approaches to the *bicyclofarnesol* skeleton, see: (a) van Tamelen, E. E.; Hessler, E. J. *J. Chem. Soc., Chem. Commun.* **1966**, 411−413. (b) van Tamelen, E. E.; Coates, R. M. *J. Chem. Soc., Chem. Commun.* **1966**, 413−415.

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