

Total Synthesis of (–)-Isopisiferin: Confirmation of Absolute Configuration

Ning-Wei Jan,^[a] Hsing-Jang Liu,^{*[a]} Min-Tsang Hsieh,^[b] and Kak-Shan Shia^{*[b]}**Keywords:** Natural products / Enantioselectivity / Terpenoids / Lithium / Configuration determination

Starting from 4,4-dimethyl-2-cyclohexenone, an enantioselective synthesis of (–)-isopisiferin has been accomplished in 15 steps with an overall yield of 11.4%. This work not only provides synthetic evidence for confirming the absolute con-

figuration of natural isopisiferin itself, but also serves as an additional correlation origin to which many related icetexane-type diterpenes, particular for the pisiferin family, can be referred.

Introduction

(–)-Isopisiferin (**1**) and its congeners pisiferin (**2**), pisiferanol (**3**), and 1 β -hydroxyisopisiferin (**4**), systematically named as 9(10 $\rightarrow$ 20)*abeo*-abietane-type diterpenoids with an icetexane skeleton consisting of a 6-7-6 tricyclic framework (Figure 1), were isolated from the seeds of *Chamaecyparis pisifera* (Cupressaceae).^[1–4] The structure and absolute configuration of **2** were determined by chemical correlation with barbatusol (**5**), isolated from *Coleus barbatus* (Labiatae) and structurally proposed on the basis of natural carnosol of known configuration,^[5] and thereof its double-bond isomer **1** was unambiguously assigned.^[1] To date, only three total syntheses of isopisiferin, in racemic form, have

been reported.^[6–8] Herein, we wish to present the first enantioselective synthesis of natural **1** in a simple and convergent route.

Results and Discussion

Key intermediate (–)-aldehyde **6**, readily prepared through a five-step synthetic sequence starting from 4,4-dimethylcyclohexenone (**I**) and successfully applied to the total synthesis of (+)-ricciocarpin A (Scheme 1),^[9a] was employed as the enantioenriched source for this asymmetric approach. The key operation to synthesize optically pure aldehyde **6** was based on asymmetric reduction of iodo enone **II** according to the procedure developed by Knochel et al.^[9b] to give the corresponding iodo alcohol **III** in high optical purity (98% *ee*), which was determined by HPLC [(Chiralcel OD, *n*-hexane/*i*PrOH = 96:4, flow rate = 0.3 mL/min): *t*_R = 18.90 (minor), 22.56 min (major)].^[9a] The analysis was further calibrated with racemic alcohol **III** produced by treating **II** with NaBH₄ in the presence of CeCl₃·7H₂O. Subsequent transformation of **III** by Claisen rearrangement afforded ester **IV**, the optical purity of which was again

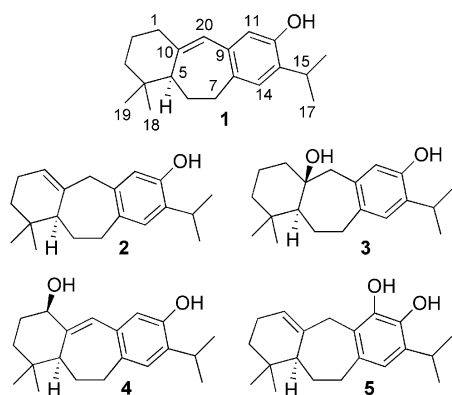
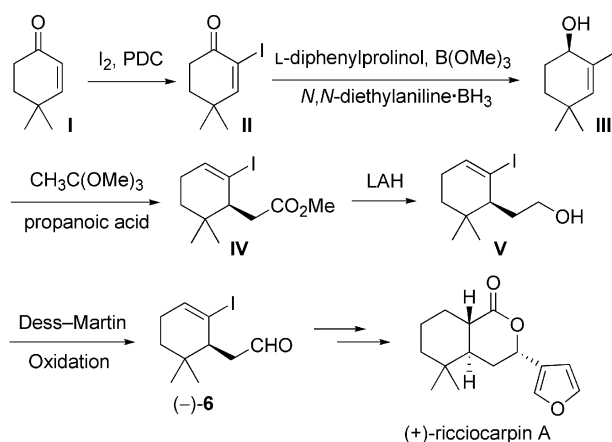


Figure 1. Pisiferin family, a class of icetexane-type diterpenoids characterized by a 6-7-6 tricyclic framework.



Scheme 1. Total synthesis of (+)-ricciocarpin A.

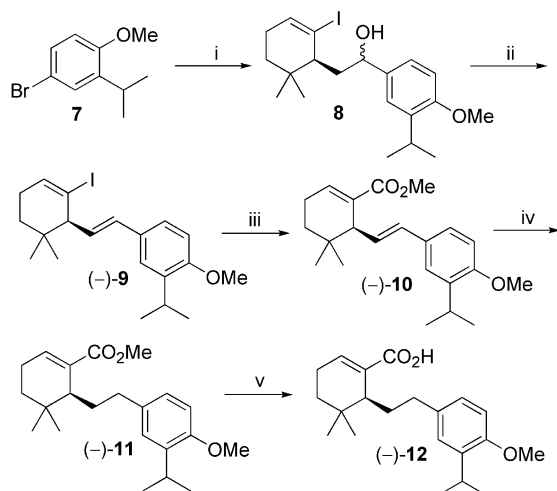
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identified as 98% *ee* by HPLC [(Chiralcel OD, *n*-hexane/*i*PrOH = 98:2, flow rate = 0.3 mL/min): t_R = 13.59 (major), 16.42 min (minor)], suggesting that a 3,3-sigmatropic rearrangement occurred in a suprafacial manner without incurring any racemization.^[9a] Ester **IV** was then subjected to reduction with lithium aluminum hydride (LAH) followed by Dess–Martin periodinane oxidation to provide aldehyde **6** in 60% over five steps. Accordingly, (–)-aldehyde **6** thus generated was assumed to possess 98% *ee* and was extended to the total synthesis of isopisiferin (**1**) as delineated in the following.

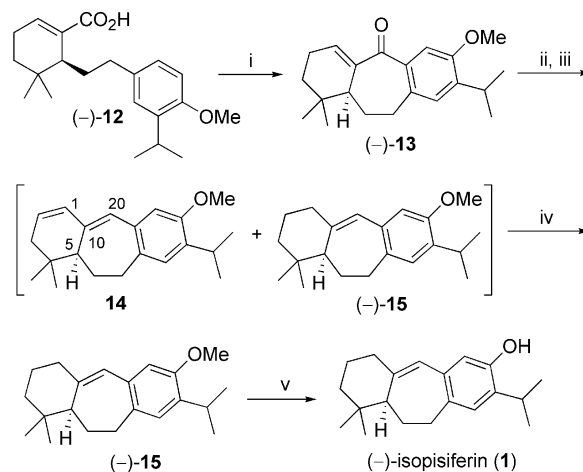
As illustrated in Scheme 2, our synthetic strategy began with addition of aldehyde (–)-**6** to the aryllithium reagent, prepared in situ from aryl bromide **7** and *n*BuLi by lithium–halogen exchange to afford alcohol **8** as a pair of diastereomers (1:2.2, 82% yield), which upon dehydration with *p*-TsOH in refluxing benzene gave rise to conjugated (–)-**9** in 91% yield. Compound (–)-**9** thus obtained was treated with *n*BuLi under lithium–halogen exchange to provide the corresponding vinyl lithium, which was trapped with methyl chloroformate to give ester (–)-**10** in 90% yield. The installation of the ester functionality causes a distinct difference in the electron density between the two olefinic bonds in (–)-**10**. Thus, subsequent hydrogenation (H_2 , Pd/C, MeOH/EtOAc = 1:9) occurred exclusively at the electron-rich *exo* double bond to furnish (–)-**11** in 97% yield, which in turn was subjected to basic hydrolysis to afford the corresponding carboxylic acid (–)-**12** in virtually quantitative yield.



Scheme 2. Reagents and conditions: (i) *n*BuLi, THF, –78 °C, 1 h, then (–)-**6**, –78 °C to room temp., 4 h, 82%; (ii) *p*-TsOH, PhH, reflux, 1 h, 91%; (iii) *n*BuLi, ClCO₂Me, Et₂O, –78 °C to room temp., 6 h, 90%; (iv) H_2 , Pd/C, EtOAc, MeOH, room temp., 30 min, 97%; (v) KOH, MeOH, H₂O, reflux, 6 h, 97%.

With (–)-**12** in hand (Scheme 3), and following the strategy of Ghatak,^[6] the central seven-membered ring was constructed in a straightforward manner by intramolecular Friedel–Crafts acylation^[10] to afford tricyclic ketone (–)-**13** in 52% yield.^[11] For further chemical transformations, the keto carbonyl of (–)-**13** was first reduced with NaBH₄/CeCl₃·7H₂O, known as Luche's conditions^[12] by which 1,2-addition was highly anticipated to take place, leading to the

desired allylic alcohol. Unfortunately, the resulting crude product, upon chromatographic purification, decomposed rapidly into a complex mixture, presumably due to the labile hydroxy group thus formed, possessing both allylic and benzylic characteristics. However, this problem was finally circumvented by the use of a two-step synthetic sequence. Instead of Luche's conditions, the keto carbonyl was simply reduced under treatment with an excess amount of NaBH₄, and the crude product, without purification, was mesylated immediately in the presence of NEt₃. As a result, an inseparable mixture of **14** and (–)-**15** in a 4:1 ratio, as determined by ¹H NMR spectroscopy, was obtained. Mechanistically, the former product might result from 1,4-elimination of the allylic mesylate, and the latter from 1,2-elimination of the benzylic mesylate, presumably derived from the corresponding benzylic alcohol through a double-reduction process with NaBH₄ (1,4-conjugate addition followed by 1,2-addition).



Scheme 3. Reagents and conditions: (i) TFAA, TFA, CH₂Cl₂, room temp., 6 h, 52%; (ii) NaBH₄, MeOH, room temp., 30 min; (iii) Et₃N, MsCl, CH₂Cl₂, 4 h; (iv) H_2 (1 atm), Pd/C EtOAc, room temp., 2 h, 79% over three steps; (v) NaH, EtSH, DMF, reflux, 16 h, 62%.

Because intermediate (–)-**15** is a highly potential precursor to reach the final target, tremendous efforts toward selective reduction on the $\Delta^{1(2)}$ over $\Delta^{10(20)}$ in compound **14** were then made. After extensive investigation in which reaction parameters, including catalysts, solvents, reaction temperatures, pressure, and time, were systematically varied, it was found that a mixture of (–)-**15** and **14** could undergo hydrogenation selectively under very mild conditions [4×10^{-3} M, H_2 (1 atm), Pd/C, EtOAc, 2 h, room temp.] to afford single enantiomer (–)-**15** without contamination with any over-reduced products in 79% yield over three steps from (–)-**13**.^[13] Finally, upon deprotection with EtSNa,^[14] as employed in the previous two arts,^[6,7] (–)-**15** was smoothly converted into target (–)-(**1**) in 62% yield. The spectroscopic data (¹H NMR, IR, and HRMS)^[15] and specific rotation of the synthetic molecule [$[\alpha]_D^{25} = -191.8$ ($c = 3.45$, CHCl₃)] were found to be in good agreement with those reported for natural product **1** [$[\alpha]_D^{25} = -193.1$ ($c = 2.56$, CHCl₃)].^[1]

Thus, the first asymmetric synthesis of (–)-isopisiferin was accomplished on the basis of a novel approach starting from 4,4-dimethyl-2-cyclohexenone in 15 steps with an overall yield of 11.4%. More encouragingly, the gram-scale production of optically pure aldehyde **6** was fulfilled through the aforementioned five-step sequence, which is expected to make up the foundation of synthesizing other naturally occurring icetexanes in optically active form. Currently, synthetic efforts devoted to many structurally related natural products^[3] (e.g., pisiferin^[16]) are under active investigation in our laboratories.

Conclusions

In conclusion, the successful synthesis of natural **1** appears significant in that not only does it provide synthetic evidence for confirming the absolute configuration of isopisiferin itself but also serves to provide an additional correlation origin to which many related icetexane-type diterpenes, particular for the pisiferin family, can be referred.

Experimental Section

General Information: All reactions were performed under an argon or nitrogen atmosphere unless otherwise stated. All solvents were dried prior to use and reagents were employed as received. Analytical thin-layer chromatography was performed on SiO₂ 60 F-254 plates, and flash column chromatography was carried out using SiO₂ 60 (particle size 0.040–0.055 mm, 230–400 mesh), both of which are available from Merck. Visualization was performed under UV irradiation at 254 nm followed by staining with vanillin (60 g of vanillin in 1 L of 95% ethanol containing 10 mL of conc. H₂SO₄) and charring by heat gun. Fourier-transform infrared spectra were recorded with a Bomem MB-100FT instrument. ¹H and ¹³C NMR spectra were recorded with a Bruker AVX-500, Bruker AVX-400, or Bruker AMX-400 instrument. [D]Chloroform was used as the solvent and TMS (δ = 0.00 ppm) was used as an internal standard. Chemical shifts are reported as δ values in ppm as referenced to TMS. Multiplicities are recorded as s (singlet), d (doublet), t (triplet), quint. (quintet), sept. (septet), dd (doublet of doublets), dt (doublet of triplets), br. (broad), m (multiplet). HRMS were taken with an A.E.I. model MS-50 spectrometer and spectroscopic data were recorded as m/z values.

2-[(1S)-2-Iodo-6,6-dimethylcyclohex-2-en-1-yl]-1-[4-methoxy-3-(propan-2-yl)phenyl]ethanol (8**):** To a solution of compound **7** (1.45 g, 6.33 mmol) in THF (10 mL) was added *n*BuLi (2.5 M in hexane, 2.6 mL, 6.50 mmol) dropwise at –78 °C. The resulting mixture was stirred at the same temperature for 1 h, and then compound **6** (1.47 g, 5.27 mmol) in anhydrous THF (10 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h and allowed to stir at room temperature for 4 h. Saturated aqueous NH₄Cl (10 mL) was added to quench the reaction. The aqueous layer was separated and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried with MgSO₄, filtered, and concentrated to give the crude product, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:19) to afford compound **8** as a pair of diastereomers (1:2.2) as a colorless oil (1.85 g, 82% yield). IR (CH₂Cl₂): $\tilde{\nu}$ = 3431, 2958, 2834, 1608, 1498, 1463 cm^{–1}. ¹H NMR (400 MHz, CDCl₃, 25 °C, major diastereomer): δ = 7.27–7.15 (m,

2 H, ArH), 6.80 (d, J = 8.3 Hz, 1 H, ArH), 6.25 (t, J = 3.8 Hz, 1 H, C=CH), 4.79 (quint., J = 4.3 Hz, 1 H, CHOH), 3.81 (s, 3 H, ArOCH₃), 3.30 (sept., J = 6.9 Hz, 1 H, CHMe₂), 2.31 (m, 1 H), 2.12–1.96 (m, 3 H), 1.93–1.81 (m, 3 H), 1.53–1.41 (m, 1 H), 1.20 [dd, J = 6.9, 1.1 Hz, 6 H, CH(CH₃)₂], 0.95 (s, 3 H, CH₃), 0.92 (s, 3 H, CH₃) ppm. ¹³C NMR (400 MHz, CDCl₃, 25 °C, minor diastereomer): δ = 6.81 (d, J = 8.3 Hz, 1 H, ArH), 6.29 (t, J = 3.8 Hz, 1 H, C=CH), 5.04 (br. t, J = 6.8 Hz, 1 H, CHOH), 2.20 (t, J = 5.1 Hz, 1 H), 1.71 (dt, J = 14.5, 5.6 Hz, 1 H), 1.21 [d, J = 6.9 Hz, 6 H, CH(CH₃)₂], 1.02 (s, 3 H, CH₃), 0.98 (s, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃, 25 °C, major diastereomer): δ = 156.3 (C_{arom.}), 137.1 (C_{arom.}), 136.8 (C_{arom.}), 136.2 (CH), 124.0 (CH), 123.8 (CH), 110.2 (CH_{arom.}), 105.8 (C, C=Cl), 74.0 (CH, COH), 55.5 (OCH₃), 52.8 (C=ClCH), 42.1 (CH₂), 35.3 (CMe₂), 29.7 (CH₂), 27.6 (CH₃), 27.19 (CH), 27.1 (CH₂), 26.7 (CH₃), 22.6 (2 CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃, 25 °C, minor diastereomer): δ = 137.0 (C_{arom.}), 136.7 (CH), 136.5 (C_{arom.}), 124.3 (CH), 124.1 (CH), 110.1 (CH_{arom.}), 103.7 (C=Cl), 73.4 (COH), 52.2 (C=ClCH), 35.3 (CMe₂), 30.4 (CH₂), 27.2 (CH₂), 27.0 [CH-(CH₃)₂], 26.9 [CH(CH₃)₂], 22.7 (2 CH₃) ppm. HRMS (EI): calcd. for C₂₀H₂₉IO₂ 428.1212; found 428.1219.

4-{(E)-2-[(1S)-2-Iodo-6,6-dimethylcyclohex-2-en-1-yl]ethenyl}-1-methoxy-2-(propan-2-yl)benzene (9**):** A two-necked, round-bottomed flask equipped with a Dean–Stark apparatus was charged with compound **8** (1.68 g, 3.32 mmol), *p*-TsOH (0.49 g, 2.84 mmol), and benzene (30 mL). The resulting mixture was stirred and heated to reflux for 1 h with azeotropic removal of water and then cooled to room temperature. The reaction residue was diluted with EtOAc (30 mL) and water (10 mL), and then neutralized with saturated aqueous NaHCO₃ (10 mL). The aqueous layer was separated and extracted with EtOAc (2 × 25 mL). The combined organic layer was washed with brine, dried with MgSO₄, filtered, and concentrated to give the crude product, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:99) to afford compound (–)-**9** (1.47 g, 91%) as a colorless oil. [α]_D²⁰ = –61.0 (c = 5.55, CHCl₃). IR (CH₂Cl₂): $\tilde{\nu}$ = 2959, 2869, 1628, 1604, 1494, 1463 cm^{–1}. ¹H NMR (500 MHz, CDCl₃, 25 °C): δ = 7.22–7.20 (m, 2 H, ArH), 6.79 (d, J = 8.6 Hz, 1 H, ArH), 6.43 (t, J = 3.7 Hz, 1 H, C=CH), 6.35 (d, J = 15.6 Hz, 1 H, CH=CHAr), 5.83 (dd, J = 15.6, 9.3 Hz, 1 H, CH=CHAr), 3.81 (s, 3 H, ArOCH₃), 3.29 (sept., J = 6.9 Hz, 1 H, CHMe₂), 2.77 (d, J = 9.3 Hz, 1 H, CHCH=CH), 2.16–2.13 (m, 2 H), 1.68–1.54 (m, 1 H), 1.33 (dt, J = 13.3, 5.1 Hz, 1 H), 1.22 [d, J = 6.9 Hz, 6 H, CH(CH₃)₂], 1.04 (s, 3 H, CH₃), 0.90 (s, 3 H, CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃, 25 °C): δ = 156.2 (C_{arom.}), 136.8 (CH), 136.6 (C_{arom.}), 133.0 (CH), 129.7 (C_{arom.}), 126.7 (CH), 124.3 (CH), 124.1 (CH), 110.3 (CH), 102.8 (C=Cl), 61.0 (CH), 55.3 (ArOCH₃), 35.2 (CMe₂), 30.7 (CH₂), 27.4 [CH(CH₃)₂], 27.2 [CH(CH₃)₂], 27.0 (CH₂), 26.7 (CH), 22.5 (2 CH₃) ppm. HRMS (EI): calcd. for C₂₀H₂₇IO 410.1107; found 410.1102.

Methyl (6S)-6-{(E)-2-[4-Methoxy-3-(propan-2-yl)phenyl]ethenyl}-5,5-dimethylcyclohex-1-ene-1-carboxylate (10**):** To a solution of compound (–)-**9** (1.00 g, 2.45 mmol) in anhydrous Et₂O (10 mL) was added *n*BuLi (2.5 M in hexane, 2.1 mL, 5.25 mmol) dropwise at –78 °C. The resulting mixture was stirred at the same temperature for 40 min, and then methyl chloroformate (1.16 g, 12.27 mmol) was added in one portion. The reaction mixture was warmed to room temperature and continued stirring for another 6 h. Saturated aqueous NaHCO₃ (10 mL) was added to quench the reaction. The aqueous layer was separated and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried with MgSO₄, filtered and concentrated to give the crude residue, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:49) to afford compound (–)-**10** (754 mg,

90% yield) as a colorless oil. $[\alpha]_D^{25} = -255.3$ ($c = 2.85$, CHCl_3). IR (CH_2Cl_2): $\tilde{\nu} = 2958, 2869, 1715, 1644, 1495, 1463 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 7.20\text{--}7.14$ (m, 2 H, ArH), 7.04 (t, $J = 3.7$ Hz, 1 H, ArH), 6.77 (d, $J = 8.4$ Hz, 1 H, $\text{CH}=\text{CCO}_2\text{Me}$), 6.30 (d, $J = 15.8$ Hz, 1 H, $\text{CH}=\text{CHAr}$), 5.96 (dd, $J = 15.8, 8.4$ Hz, 1 H, $\text{CH}=\text{CHAr}$), 3.80 (s, 3 H, ArOCH_3), 3.70 (s, 3 H, CO_2Me), 3.29 (sept., $J = 6.9$ Hz, 1 H, CHMe_2), 3.05 (d, $J = 8.4$ Hz, 1 H, $\text{CHCH}=\text{CH}$), 2.34–2.15 (m, 2 H), 1.63–1.52 (m, 1 H), 1.28–1.23 (m, 1 H), 1.22 [d, $J = 6.9$ Hz, 6 H, $\text{CH}(\text{CH}_3)_2$], 0.98 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, CDCl_3 , 25 °C): $\delta = 167.6$ (CO_2Me), 156.1 ($\text{C}_{\text{arom.}}$), 138.5 (CH), 136.8 (C), 131.8 (C), 131.2 (CH), 130.1 (C), 127.7 (CH), 124.2 (CH), 124.1 (CH), 110.3 (CH), 55.4 (OCH_3), 51.4 (CO_2CH_3), 47.5 (CH), 32.4 (CMe_2), 29.6 (CH_2), 28.6 [$\text{CH}(\text{CH}_3)_2$], 26.7 (CH), 26.1 [$\text{CH}(\text{CH}_3)_2$], 23.8 (CH_2), 22.5 (2 CH_3) ppm. HRMS (EI): calcd. for $\text{C}_{22}\text{H}_{30}\text{O}_3$ 342.2195; found 342.2211.

Methyl (6S)-6-{2-[4-Methoxy-3-(propan-2-yl)phenyl]ethyl}-5,5-dimethylcyclohex-1-ene-1-carboxylate (11): To a stirred solution of compound (–)-**10** (201 mg, 0.59 mmol) in EtOAc (9 mL) and MeOH (1 mL) was added Pd/C (104 mg, 10 wt.-%) in one portion. The resulting mixture was hydrogenated under an atmosphere of H_2 (1 atm) at room temperature. After the reaction was complete (ca. 30 min), the mixture was filtered through Celite and concentrated to give the crude product, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:9) to afford compound (–)-**11** (196 mg, 97% yield) as a colorless oil. $[\alpha]_D^{25} = -97.3$ ($c = 0.60$, CHCl_3). IR (CH_2Cl_2): $\tilde{\nu} = 2955, 2869, 1714, 1644, 1608, 1498, 1463 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 6.96$ (d, $J = 2.2$ Hz, 1 H, ArH), 6.93 (dd, $J = 8.2, 2.2$ Hz, 1 H, ArH), 6.89 (t, $J = 3.7$ Hz, 1 H, $\text{CH}=\text{CCO}_2\text{Me}$), 6.73 (d, $J = 8.2$ Hz, 1 H, ArH), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.26 (sept., $J = 6.9$ Hz, 1 H, CHMe_2), 2.59–2.46 (m, 2 H, CH_2Ar), 2.33 (t, $J = 5.9$ Hz, 1 H), 2.29–2.13 (m, 2 H), 1.81–1.72 (m, 1 H), 1.59–1.51 (m, 1 H), 1.46–1.36 (m, 1 H), 1.18 [dd, $J = 6.9, 0.9$ Hz, 6 H, $\text{CH}(\text{CH}_3)_2$], 1.01 (s, 3 H, CH_3), 0.85 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, CDCl_3 , 25 °C): $\delta = 168.7$ (CO_2Me), 154.8 ($\text{C}_{\text{arom.}}$), 137.7 (CH), 136.6 (C), 135.0 (C), 134.6 (C), 126.0 (CH), 125.8 (CH), 110.2 (CH), 55.3 (ArOCH_3), 51.4 (CO_2CH_3), 43.3 (CH), 35.9 (CH_2), 34.9 (CH_2), 32.1 (CMe_2), 29.5 (CH_2), 28.2 [$\text{CH}(\text{CH}_3)_2$], 26.7 [$\text{CH}(\text{CH}_3)_2$], 26.7 (CH), 23.7 (CH_2), 22.6 (2 CH_3) ppm. HRMS (FAB): calcd. for $\text{C}_{22}\text{H}_{32}\text{O}_3$ 344.2351; found 344.2357.

(6S)-6-{2-[4-Methoxy-3-(propan-2-yl)phenyl]ethyl}-5,5-dimethylcyclohex-1-ene-1-carboxylic Acid (12): To a solution of compound (–)-**11** (193 mg, 0.56 mmol) in methanol (5 mL) was added KOH solution [1.0 M in MeOH/ H_2O (1:1), 5 mL] at room temperature. The resulting mixture was kept stirring under reflux for 6 h. After cooling to room temperature, the solution was adjusted to pH 1 with 1 N HCl. The aqueous layer was separated and extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine, dried with MgSO_4 , filtered, and concentrated to give the crude residue, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:3) to afford (–)-**12** (180 mg, 97% yield) as a colorless oil. $[\alpha]_D^{25} = -73.2$ ($c = 2.67$, CHCl_3). IR (CH_2Cl_2): $\tilde{\nu} = 3372, 1681, 1638, 1498, 1463 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 7.09$ (t, $J = 3.7$ Hz, 1 H, $\text{CH}=\text{CCO}_2\text{H}$), 6.99 (d, $J = 2.2$ Hz, 1 H, ArH), 6.94 (dd, $J = 8.3, 2.2$ Hz, 1 H, ArH), 6.73 (d, $J = 8.3$ Hz, 1 H, ArH), 3.78 (s, 3 H, ArOMe), 3.26 (sept., $J = 6.9$ Hz, 1 H, CHMe_2), 2.70–2.53 (m, 2 H, CH_2Ar), 2.34 (t, $J = 5.8$ Hz, 1 H), 2.32–2.15 (m, 2 H), 1.84–1.74 (m, 1 H), 1.62–1.54 (m, 1 H), 1.51–1.40 (m, 1 H), 1.25–1.21 (m, 1 H), 1.19 [dd, $J = 6.9, 1.3$ Hz, 6 H, $\text{CH}(\text{CH}_3)_2$], 1.03 (s, 3 H, CH_3), 0.87 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, CDCl_3 , 25 °C): $\delta = 173.8$ (CO_2H), 154.8 ($\text{C}_{\text{arom.}}$), 140.7 (CH), 136.7 (C), 135.1 (C),

134.1 (C), 126.1 (CH), 125.9 (CH), 110.3 (CH), 55.4 (OCH_3), 43.0 (CH), 36.0 (CH_2), 35.0 (CH_2), 32.2 (CMe_2), 29.5 (CH_2), 28.3 [$\text{CH}(\text{CH}_3)_2$], 26.8 (CH), 26.7 [$\text{CH}(\text{CH}_3)_2$], 24.0 (CH_2), 22.7 (CH_3), 22.6 (CH_3) ppm. HRMS (EI): calcd. for $\text{C}_{21}\text{H}_{30}\text{O}_3$ 330.2195; found 330.2191.

(11aS)-7-Methoxy-1,1-dimethyl-8-(propan-2-yl)-1,2,3,10,11,11a-hexahydro-5H-dibenzo[a,d][7]annulen-5-one (13): To a solution of compound (–)-**12** (101 mg, 0.31 mmol) in CH_2Cl_2 (8 mL) was added trifluoroacetic anhydride (TFAA, 1 mL) and trifluoroacetic acid (TFA, 0.5 mL) sequentially at 0 °C. The resulting mixture was allowed to stir at room temperature for 6 h, and then H_2O (10 mL) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with brine, dried with MgSO_4 , filtered, and concentrated to give the crude residue, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:49) to afford compound (–)-**13** (50 mg, 52% yield) as a colorless oil. Upon further elution with EtOAc/*n*-hexane (1:3), starting material (–)-**12** (16 mg) was recovered intact. $[\alpha]_D^{25} = -138.8$ ($c = 1.12$, CHCl_3). IR (CH_2Cl_2): $\tilde{\nu} = 2959, 2867, 1666, 1602, 1566, 1496, 1463 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 7.17$ (s, 1 H, ArH), 7.09 (t, $J = 3.7$ Hz, 1 H, $\text{CH}=\text{CCO}$), 6.94 (s, 1 H, ArH), 3.84 (s, 3 H, ArOCH_3), 3.30 (sept., $J = 6.9$ Hz, 1 H, CHMe_2), 2.81–2.72 (m, 1 H, CH_2Ar), 2.70–2.61 (m, 1 H, CH_2Ar), 2.40–2.18 (m, 2 H, $\text{CH}_2\text{CH}=\text{C}$), 1.91–1.82 (m, 2 H), 1.63–1.52 (m, 2 H), 1.22 [d, $J = 6.9$ Hz, 3 H, $\text{CH}(\text{CH}_3)_2$], 1.18 [d, $J = 6.9$ Hz, 3 H, $\text{CH}(\text{CH}_3)_2$], 0.88 (s, 3 H, CH_3), 0.79 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, CDCl_3 , 25 °C): $\delta = 196.6$ ($\text{C}=\text{O}$), 155.7 ($\text{C}_{\text{arom.}}$), 141.6 (C), 139.8 (C), 137.3 (CH), 136.0 (C), 132.9 (C), 126.6 (CH), 110.3 (CH), 55.5 (ArOCH_3), 42.1 (CH), 31.7 (CMe_2), 30.8 (CH_2), 30.6 (CH_2), 29.3 (CH_2), 27.7 [$\text{CH}(\text{CH}_3)_2$], 26.9 (CH), 26.4 [$\text{CH}(\text{CH}_3)_2$], 24.0 (CH_2), 22.7 (CH_3), 22.3 (CH_3) ppm. HRMS (EI): calcd. for $\text{C}_{21}\text{H}_{28}\text{O}_2$ 312.2089; found 312.2079.

(11aS)-7-Methoxy-1,1-dimethyl-8-(propan-2-yl)-2,10,11,11a-tetrahydro-1H-dibenzo[a,d][7]annulene (14) and (11aS)-7-Methoxy-1,1-dimethyl-8-(propan-2-yl)-2,3,4,10,11,11a-hexahydro-1H-dibenzo[a,d][7]annulene (15): To a solution of compound (–)-**13** (22 mg, 0.07 mmol) in MeOH (2 mL) was added NaBH_4 (13 mg, 0.35 mmol) at 0 °C. The resulting mixture was allowed to stir at room temperature for 30 min, and then H_2O (2 mL) was added. The aqueous layer was separated and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine, dried with MgSO_4 , filtered, and concentrated to give the crude residue, which was dried under vacuum and employed in the next reaction without further purification. To a solution of the above crude product in CH_2Cl_2 (3 mL) was added Et_3N (29 mg, 0.28 mmol) and MsCl (16 mg, 0.14 mmol) sequentially at 0 °C. The resulting mixture was allowed to stir at room temperature for 4 h, and then H_2O (4 mL) was added. The aqueous layer was separated and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine, dried with MgSO_4 , filtered, and concentrated to give the crude residue, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:19) to afford an inseparable mixture of compounds **14** and (–)-**15** (19 mg) in a 4:1 ratio as determined by ^1H NMR spectroscopy. To a solution of the above mixture in EtOAc (15 mL, 4×10^{-3} M) was added Pd/C (8 mg, 10 wt.-%) in one portion. The resulting mixture was hydrogenated under an atmosphere of H_2 (1 atm) at room temperature. After the reaction was complete (ca. 2 h), the reaction solution was filtered through Celite, and the filtrate was concentrated to give the crude product, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:19) to afford compound (–)-**15** (16.5 mg, 79% yield over three steps) as a colorless oil. $[\alpha]_D^{25} = -201.4$ ($c = 1.17$,

CHCl₃), IR (CH₂Cl₂): $\tilde{\nu}$ = 2931, 2866, 1609, 1570, 1502, 1463 cm^{–1}. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 6.82 (s, 1 H, ArH), 6.60 (s, 1 H, ArH), 6.30 (s, 1 H, C=CHAr), 3.79 (s, 3 H, ArOCH₃), 3.23 (sept., J = 6.9 Hz, 1 H, CHMe₂), 2.70–2.52 (m, 2 H, CH₂Ar), 2.41–2.35 (m, 1 H), 2.31–2.12 (m, 3 H), 1.63–1.46 (m, 3 H), 1.42–1.36 (m, 2 H), 1.19 [d, J = 6.9 Hz, 3 H, CH(CH₃)₂], 1.16 [d, J = 6.9 Hz, 3 H, CH(CH₃)₂], 0.97 (s, 3 H, CH₃), 0.70 (s, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 154.7 (C_{arom.}), 144.7 (C), 134.8 (C), 134.4 (C), 134.2 (C), 125.6 (CH), 125.3 (CH), 112.4 (CH), 55.5 (ArOCH₃), 54.9 (CH), 42.3 (CH₂), 41.1 (CH₂), 36.6 (C), 33.0 (CH₂), 30.4 (CH₃), 30.2 (CH₂), 26.4 (CH), 24.4 (CH₂), 22.9 (CH₃), 22.7 (CH₃), 20.4 (CH₃) ppm. HRMS (FAB): calcd. for C₂₁H₃₀O 298.2297; found 298.2297.

(–)-Isopisiferin (1): To a solution of NaH (60% in mineral oil, 17 mg, 0.43 mmol) in DMF (2 mL) was added EtSH (26 mg, 0.43 mmol) dropwise at 0 °C. The resulting mixture was stirred at the same temperature for 1 h, and then compound (–)-15 (13 mg, 0.43 mmol) in DMF (3 mL) was added dropwise. The reaction mixture was allowed to stir at reflux for 16 h and after cooling, H₂O (3 mL) was added at 0 °C. The aqueous layer was separated and extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with brine, dried with MgSO₄, filtered, and concentrated to give the crude residue, which was purified by flash chromatography on silica gel (EtOAc/*n*-hexane, 1:9) to afford (–)-isopisiferin (**1**; 7.7 mg, 62% yield) as an amorphous product, which was recrystallized (CH₂Cl₂/*n*-hexane) to give fine crystals. M.p. 86.0–87.5 °C. [α]_D²⁵ = –191.8 (c = 3.45, CHCl₃). IR (CH₂Cl₂): $\tilde{\nu}$ = 3403, 2926, 2866, 1613, 1510, 1162 cm^{–1}. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 6.79 (s, 1 H, 14-H), 6.49 (s, 1 H, 17-H), 6.21 (s, 1 H, 20-H), 3.11 (sept., J = 6.9 Hz, 1 H, 15-H), 2.70 (dd, J = 14.1, 8.0 Hz, 1 H, 7-H), 2.56 (dd, J = 14.1, 10.3 Hz, 1 H), 2.37–2.32 (m, 1 H), 2.28–2.08 (m, 3 H), 1.69–1.45 (m, 3 H), 1.39–1.34 (m, 2 H), 1.23 [d, J = 6.9 Hz, 3 H, CH(CH₃)₂], 1.20 [d, J = 6.9 Hz, 3 H, CH(CH₃)₂], 0.96 (s, 3 H, CH₃), 0.68 (s, 3 H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 150.4 (C_{arom.}), 145.1 (C), 135.3 (C), 134.8 (C), 131.5 (C), 125.7 (CH), 124.6 (CH), 116.8 (CH), 54.9 (CH), 42.3 (CH₂), 41.1 (CH₂), 36.6 (C), 33.0 (CH₂), 30.3 (CH₃), 30.2 (CH₂), 26.8 (CH), 24.3 (CH₂), 22.7 (CH₃), 22.6 (CH₃), 20.4 (CH₃) ppm. HRMS (FAB): calcd. for C₂₀H₂₈O 284.2140; found 284.2134.

Natural (–)-Isopisiferin:^[1] M.p. 87–90 °C (colorless prisms). [α]_D²⁵ = –193.1 (c = 2.56, CHCl₃). IR (CH₂Cl₂): $\tilde{\nu}$ = 3350, 1610, 1500, 1160 cm^{–1}. ¹H NMR (100 MHz, CDCl₃): δ = 6.77 (s, 1 H, 14-H), 6.43 (s, 1 H, 11-H), 6.17 (br. s, 1 H, 20-H), 3.13 (sept., J = 7.0 Hz, 1 H, 15-H), 2.62 (m, 2 H, 7-H), 2.20 (m, 2 H, 1-H), 1.23 [d, J = 7.0 Hz, 3 H, CH(CH₃)₂], 1.20 [d, J = 7.0 Hz, 3 H, CH(CH₃)₂], 0.93 (s, 3 H, CH₃), 0.68 (s, 3 H, CH₃) ppm. No ¹³C NMR spectroscopic data were reported.

Synthetic (±)-Isopisiferin:^[6] M.p. 116.0–118.0 °C. IR (CH₂Cl₂): $\tilde{\nu}$ = 3520, 1640, 1610 cm^{–1}. ¹H NMR (100 MHz, CDCl₃): δ = 6.82 (s, 1 H, 14-H), 6.51 (s, 1 H, 11-H), 6.22 (br. s, 1 H, 20-H), 3.16 (m, 1 H, 15-H), 2.72–2.56 (m, 4 H), 2.40–2.14 (m, 4 H), 1.70–1.34 (m, 4 H), 1.25 [d, J = 7.0 Hz, 3 H, CH(CH₃)₂], 1.22 [d, J = 7.0 Hz, 3 H, CH(CH₃)₂], 0.93 (s, 3 H, CH₃), 0.70 (s, 3 H, CH₃) ppm. No ¹³C NMR spectroscopic data were reported.

Synthetic (±)-Isopisiferin:^[7] IR (CH₂Cl₂): $\tilde{\nu}$ = 3350, 1600 cm^{–1}. ¹H NMR (100 MHz, CDCl₃): δ = 6.80 (s, 1 H, 14-H), 6.49 (s, 1 H, 11-

H), 6.22 (br. s, 1 H, 20-H), 4.51 (br. s, 1 H, OH), 3.13 (m, 1 H, 15-H), 1.70–1.34 (m, 4 H), 1.24 [d, J = 6.8 Hz, 3 H, CH(CH₃)₂], 1.22 [d, J = 6.8 Hz, 3 H, CH(CH₃)₂], 0.98 (s, 3 H, CH₃), 0.70 (s, 3 H, CH₃) ppm. HRMS: calcd. for C₂₀H₂₈O 284.2140; found 284.2136. No ¹³C NMR spectroscopic data and m.p. were reported.

Supporting Information (see footnote on the first page of this article): ¹H and ¹³C NMR spectra for compounds **8**, (–)-**9**, (–)-**10**, (–)-**11**, (–)-**12**, (–)-**13**, (–)-**15**, and synthetic (–)-isopisiferin (**1**).

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