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Revised Structure, Total Synthesis, and Absolute Configuration of Kopeolin and Kopeolone

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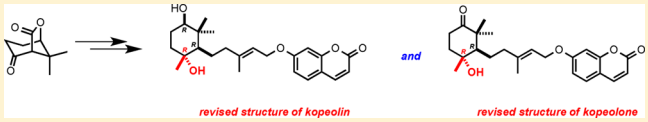
Supporting Information

ABSTRACT: An enantioselective total synthesis of two sesquiterpenoids, kopeolin and kopeolone, has been achieved. Using the diastereoselective addition of an organocerate as a key step, we controlled the absolute stereochemistry of a crucial stereocenter present in these natural products. This approach allowed us to confirm a structural revision that we previously proposed (*Chem.—Eur. J.* **2013**, *19*, 10632−10642) and to fully characterize these natural products while elucidating their absolute stereochemistry.



In 1973, the isolation of the sesquiterpenoid coumarins[1] kopeolin and kopeolone from the roots of *Ferula kopetdaghensis* was reported. In 1982, structures **1** and **2** (Figure 1) were proposed for these natural products on the basis of a comparison with the ^{1}H NMR spectrum of the known compound farnesiferol C (**3**), which was obtained after dehydration of kopeolin with H_2SO_4.[2] Recently, kopeolin showed strong inhibition of the proliferation of cultured human cells.[3] In the course of our work directed toward the enantioselective synthesis of sesquiterpene natural products,[4] we recently developed a synthetic pathway to prepare these proposed structures **1** and **2**.[5] However, the synthetic materials **1** and **2** did not match the reported data for natural kopeolin and kopeolone, strongly suggesting a structural misassignment during the isolation of the natural products.

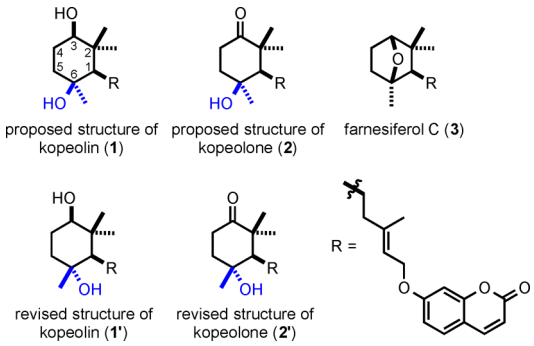


Figure 1. Proposed structures **1** for kopeolin and **2** for kopeolone, the structure of farnesiferol C (**3**), and the revised structures **1′** for kopeolin and **2′** for kopeolone as determined in this work.

We supposed that the misassignment occurred at the stereocenter at C-6 bearing the tertiary alcohol present in kopeolin and kopeolone.[5] Consequently, this stereocenter in the proposed structures **1** and **2** should be reversed to its C-6 epimer, as depicted in the revised structures **1′** and **2′** (Figure 1). Therefore, we focused our attention on proposing a new synthetic strategy to synthesize **1′** and **2′** with full control of all stereocenters. We planned to use an enantiopure building block, (1*R*,5*R*)-8,8-dimethyl-2,7-dioxo-6-oxabicyclo[3.2.1]-octane (**4**), for the introduction of the stereocenter at C-6, as this key intermediate already contains two of the required stereocenters present in the natural products. Moreover, the bicyclo[3.2.1]octane skeleton of **4** presents a unique and rigid conformation and could undergo a diastereoselective reaction affording the formation of the required stereocenter of the target compounds. DFT calculations supported this assumption (see Figure 2 and the Supporting Information). Thus, the approach of the reagent to the bicyclic system would be realized from the less-hindered *endo* face because of the presence of the methyl substituent in the axial position on the *exo* face. Moreover, possible Lewis acid/base interactions between the organometallic reagent and a lone pair of the oxygen atom of the lactone would also favor the approach on the *endo* face.

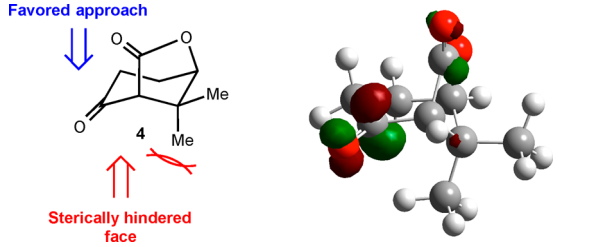


Figure 2. Optimized conformation of ketone **4** [calculated using the B3LYP/6-311G++(d,p) method] showing the accessibility of the red lobe for the diastereoselective alkylation by $MeCeCl_2$.

We previously reported a practical synthetic pathway for synthesizing the required enantiopure building block **4** (nine steps and 39% overall yield from commercially available 3-methylanisole) or its enantiomer using a chemoenzymatic process.[6] Thus, starting from **4**, addition of methylcerium

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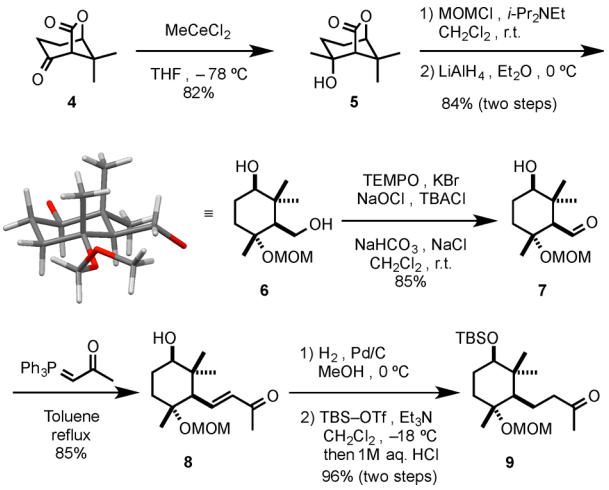
dichloride in THF proceeded with complete stereoselectivity, affording alcohol **5** in 82% yield (Scheme 1).[7] Protection of the

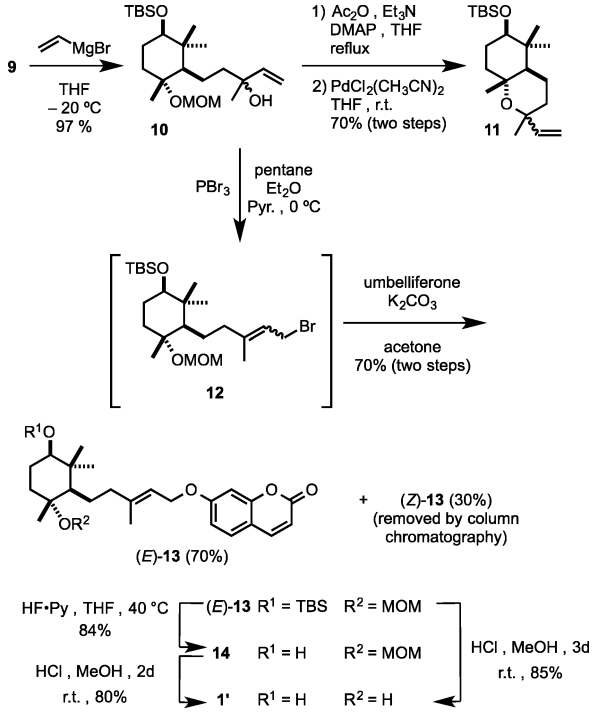
Scheme 1. Synthesis of Ketone 9



alcohol with chloromethyl methyl ether (MOMCl) in the presence of Hünig's base[8] followed by reduction of the lactone with $LiAlH_4$ afforded crystalline diol **6** in 84% yield over the two steps. The structure of **6**, and therefore the one of **5**, was secured by X-ray crystallography.[9] Selective oxidation of the primary hydroxyl function of **6** via the biphasic Anelli–Montanari protocol using TEMPO/NaOCl as the oxidizing agent gave exclusively the hydroxy aldehyde **7** in 85% yield.[10] To elaborate the coumarin side chain, the Horner–Wadsworth–Emmons (HWE) reaction was selected because it can prevent epimerization as a result of its mild conditions.[5,11] However, the reaction of **7** with diethyl 2-oxopropylphosphonate and $Ba(OH)_2$ failed whether the OH group was protected as a TBS ether or not, and the unreacted starting material was recovered. As a consequence, we turned our attention toward more reactive conditions. Aldehyde **7** was then subjected to a Wittig reaction with 1-(triphenylphosphoranylidene)-2-propanone in refluxing toluene, which furnished α,β-unsaturated ketone **8** in 85% yield as a single *E* isomer[12] without any detectable amount of the epimerized compound. Reduction of the double bond of **8** with H_2 in the presence of Pd/C in MeOH followed by protection of the alcohol with TBSOTf in the presence of triethylamine in CH_2Cl_2 afforded the corresponding TBS ether **9** in 96% yield over the two steps. During the TBS-protection step, concomitant formation of the silyl enol ether of the ketone was also observed, and this was hydrolyzed upon acidic aqueous workup, providing exclusively compound **9**.

With **9** in hand, we planned to use the same methodology employed for the synthesis of the structures **1** and **2** proposed for the natural products, which is a Pd-catalyzed rearrangement of a tertiary allylic acetate to elaborate the side chain of **1′** and **2′** with high *E* stereoselectivity.[13] Thus, subsequent treatment of **9** with vinylmagnesium bromide afforded tertiary allylic alcohol **10** in 97% yield (Scheme 2). Treatment of **10** with acetic anhydride/triethylamine in the presence of *N*,*N*-dimethylaminopyridine (DMAP) in THF yielded the corresponding tertiary allylic acetate. Unfortunately, treatment of the tertiary allylic acetate with dichlorobis(acetonitrile)palladium did not give the desired rearranged primary acetate but instead led exclusively to the cyclic tetrahydropyran derivative **11** in

Scheme 2. Synthesis of the Revised Kopeolin Structure 1′



70% yield over the two steps as a 3:1 diastereomeric mixture. The formation of the undesired product **11** could be explained by intramolecular nucleophilic attack of the MOM group to the π-allylpalladium intermediate, forming a stable six-membered ring.

To circumvent this issue, reaction of the diastereomeric mixture of tertiary allylic alcohol **10** with PBr_3 in the presence of pyridine in a mixture of Et_2O/pentane resulted in the formation of the unstable rearranged bromide **12**, which was immediately treated with umbelliferone and K_2CO_3 in acetone (Scheme 2).[14] Thus, the coupling reaction provided the two coumarin derivatives (*E*)-**13** and (*Z*)-**13** in a 70:30 ratio in favor of (*E*)-**13**. Fortunately, (*E*)-**13** and (*Z*)-**13** differ significantly in polarity and therefore proved to be chromatographically separable at this stage. A careful silica gel column chromatography separation performed using a gradient of petroleum ether/ethyl acetate gave a 21% yield of (*Z*)-**13** (first eluted) and 49% yield of (*E*)-**13** (second eluted) over two steps. The double-bond stereochemistries of (*E*)-**13** and (*Z*)-**13** were assigned using 2D NOESY experiments (see the Supporting Information). To complete the synthesis of kopeolin, desilylation of (*E*)-**13** was accomplished with HF·pyridine complex[15] in THF, affording **14** in 84% yield. Deprotection of the MOM group[16] was then achieved by treatment of **14** with a methanolic HCl solution, affording **1′** as a solid in 80% yield. To optimize the synthesis, simultaneous removal of the two protecting groups of (*E*)-**13** was also accomplished by methanolic HCl treatment with an extended reaction time, affording **1′** in 85% yield.

The spectral data (IR, ^1H and ^{13}C NMR, HRMS) of synthetic **1′** matched the data reported for natural kopeolin[1,3] (see the NMR spectra of natural kopeolin provided by Prof. Ryu and the comparison of the NMR data of natural kopeolin and **1′** in Table 1 in the Supporting Information), and the specific rotation was the same in sign and comparable in magnitude {**1′**: $[\alpha]_D^{25}$ −12 (*c* 1.0, EtOH); lit. $[\alpha]_D^{25}$ −16 (*c* 1.0,

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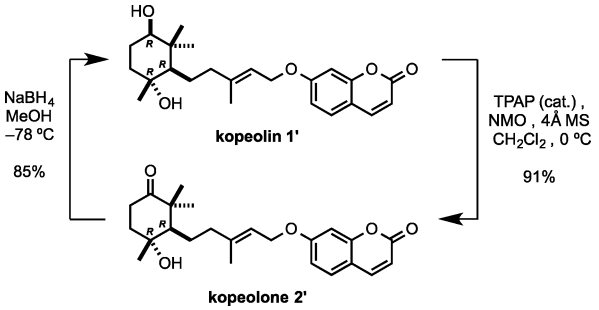
EtOH)}, confirming the synthesis of the natural enantiomer. The high optical purity of **1′** was confirmed using chiral HPLC by comparison with a racemic sample (see the Supporting Information).[17] Therefore, the absolute configuration of natural kopeolin was determined to be (1*R*,3*R*,6*R*) as depicted for **1′** in Scheme 3 and Figure 1.

Scheme 3. Synthesis of the Revised Kopeolone Structure 2′



With **1′** in hand, our attention was then focused on the synthesis of **2′**. To this end, we oxidized the secondary alcohol of **1′** with TPAP/NMO[18] in CH_2Cl_2, which afforded **2′** in 91% yield (Scheme 3). Reduction of **2′** with $NaBH_4$ using the same conditions described in the literature[2] afforded exclusively and cleanly kopeolin **1′** in 85% yield. The ^{1}H NMR spectrum of **2′** was identical to the one reported for natural kopeolone (see the comparison of the NMR data of natural kopeolone and **2′** in Table 2 in the Supporting Information).[2] The high optical purity of **2′** was also confirmed using chiral HPLC by comparison with a racemic sample (see the Supporting Information). However, the magnitude and the sign of the specific rotation of synthetic **2′** {$[\alpha]_D^{25}$ −7 (*c* 1.0, EtOH)} disagreed with that reported for natural kopeolone {lit. $[\alpha]_D^{18}$ +70 (*c* 1.0, EtOH)}. Nevertheless, as the natural products **1′** and **2′** are isolated from the same species,[1] they are undoubtedly related and share common biosynthetic pathways. Consequently, the absolute configuration of natural kopeolone is most likely to be (1*R*,6*R*) as depicted for **2′** in Scheme 3 and Figure 1.

In conclusion, we have accomplished the first total synthesis of natural kopeolin **1′** and kopeolone **2′** from an enantiopure keto lactone obtained by an enantioconvergent biocatalyzed reaction. The key step of this strategy is the diastereoselective addition of an organocerate while controlling the stereochemistry of the reassigned stereocenter present in the natural products. The achievements of this work are the confirmation of the revised structures, the full characterization of these natural products, and the elucidation of the absolute stereochemistry of all chiral centers present in the natural products.

EXPERIMENTAL SECTION

General Experimental Methods. All air- and/or water-sensitive reactions were carried out under an argon atmosphere with dry, freshly distilled solvents using standard syringe-cannula/septa techniques. All of the corresponding glassware was oven-dried (80 °C) and/or carefully dried in line with a flameless heat gun. All of the solvents were distilled under an argon atmosphere as follows: THF from a blue solution of sodium/benzophenone ketyl radical prior to use; CH_2Cl_2 from CaH_2; and Et_2O from $LiAlH_4$. Routine monitoring of reactions was performed using silica gel 60 F_{254} aluminum-supported TLC plates; spots were visualized using UV light and ethanolic acidic *p*-anisaldehyde solution or ethanolic phosphomolybdic solution, followed by heating. Purifications by means of column chromatography were performed with silica gel 60 (230−400 mesh) and gradients of Et_2O/petroleum ether or CH_2Cl_2/MeOH as eluents, unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or MeOH-d_4 solutions on a 300 or 400 MHz spectrometer. Chemical shifts (δ) in parts per million are reported using residual nondeuterated solvents as internal references to calibrate the spectra ($CHCl_3$ 7.26 ppm, MeOH 3.31 ppm for ^{1}H NMR; $CDCl_3$ 77.16 ppm, MeOH-d_4 49.00 ppm for ^{13}C NMR). Multiplicities are indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). Optical rotations were measured on a standard polarimeter. Melting points are uncorrected. Infrared spectra were obtained from films or KBr pellets using a standard IR spectrophotometer. High-resolution mass spectrometry (HRMS) was performed using a high-resolution mass spectrometer equipped with pneumatically assisted atmospheric pressure ionization. Samples were ionized by positive-mode electrospray under the following conditions: electrospray voltage (ISV), 2800 V; orifice voltage (OR), 20 V; nebulizing gas flow (nitrogen), 800 L/h. The mass spectra were obtained using a time-of-flight analyzer (TOF). The measurements were realized in triplicate with double internal standardization. Each sample was dissolved in CH_2Cl_2 (450 μL) and then diluted (dilution factor $1/10^3$) in a methanolic solution of ammonium acetate (3 mM). The sample solution was infused into the ionization source at a flow rate of 10 μL/min. Enantiomeric excesses (ee) were determined by chiral HPLC (Chiralpak IA, hexane/ethanol (6/4), 1 mL/min) by comparison with a racemic sample.

(1*R*,2*R*,5*R*)-2-Hydroxy-2,8,8-trimethyl-6-oxabicyclo[3.2.1]-octan-7-one (5). Finely crushed cerium(III) chloride heptahydrate (8.64 g, 23.2 mmol, 3.0 equiv) was placed in a 500 mL three-neck flask containing a stirring bar and evacuated (ca. 0.1 Torr). The apparatus was heated at 80 °C for 4 h, and then the temperature was increased slowly to 140 °C and maintained for 5 h. The white solid was cooled to rt, and the apparatus was blanketed with argon. THF (26 mL) was added, and the mixture was stirred for 12 h. A 1.5 M solution of methyllithium in Et_2O (15.5 mL, 23.2 mmol, 3.0 equiv) was added dropwise at −78 °C to the resulting mixture. After 1 h at −78 °C, a solution of **4** (1.30 g, 7.71 mmol) in THF (10 mL) was added dropwise, and the reaction mixture was allowed to warm to rt. After 12 h, the reaction mixture was diluted with ether, poured into an aqueous solution of NH_4Cl, and extracted with ether. The organic extracts were combined, washed with brine, dried, filtered, and concentrated. Purification by column chromatography afforded **5** (1.17 g, 82% yield) as white crystals. Mp = 94−95 °C; $[\alpha]_D^{25}$ = −29.0 (*c* 1.0, $CHCl_3$); IR (KBr) ν = 3397, 1763, 1148, 1054 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.31 (br d, *J* = 4.8 Hz, 1H), 2.15 (br s, 1H), 2.06 (dddd, *J* = 14.5, 11.6, 7.4, 0.6 Hz, 1H), 1.91−1.84 (m, 2H), 1.75−1.71 (m, 2H), 1.39 (s, 2 × 3H), 1.13 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 178.0 (C), 85.7 (CH), 70.6 (C), 59.7 (CH), 42.4 (C), 32.1 (CH_2), 30.8 (CH_3), 28.1 (CH_3), 22.3 (CH_2), 21.7 (CH_3) ppm; HRMS (ESI) calcd for $C_{10}H_{16}O_3Na^+$ $[M + Na]^+$ 207.0992, found 207.0992.

(1*R*,2*R*,5*R*)-2-(Methoxymethoxy)-2,8,8-trimethyl-6-oxabicyclo[3.2.1]octan-7-one (5′). To a stirred solution of **5** (1.40 g, 7.6 mmol) in CH_2Cl_2 (30 mL) were added diisopropylethylamine (15.9 mL, 91.2 mmol, 12.0 equiv) and chloromethyl methyl ether (4.1 mL, 53.2 mmol, 7.0 equiv) at 0 °C. After 48 h at rt, the reaction mixture was diluted with CH_2Cl_2, and the organic layer was washed with water. The aqueous washes were back-extracted, and the combined organic layers were successively washed with 1 M HCl, a saturated solution of $NaHCO_3$, and brine. The organic layer was dried, filtered, and concentrated to afford, after purification by column chromatography, **5′** (1.58 g, 91% yield) as a solid. Mp = 77 °C; $[\alpha]_D^{25}$ = +14.2 (*c* 1.0, $CHCl_3$); IR (KBr) ν = 1766, 1153, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.75 and 4.58 (AB, *J* = 7.2 Hz, 2H), 4.29 (br d, *J* = 4.5 Hz, 1H), 3.37 (s, 3H), 2.31 (br s, 1H), 2.08−1.83 (m, 3H), 1.63−1.55 (m, 1H), 1.37 (s, 3H), 1.33 (s, 3H), 1.11 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.5 (C), 91.1 (CH_2), 85.4 (CH), 75.4 (C), 57.7 (CH), 55.7 (CH_3), 42.2 (C), 30.3 (CH_2), 28.2 (CH_3), 25.5 (CH_3), 22.4 (CH_2), 21.4 (CH_3) ppm; HRMS (ESI) calcd for $C_{12}H_{24}NO_4^+$ $[M + NH_4]^+$ 246.1700, found 246.1698.

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(1*R*,3*S*,4*R*)-3-(Hydroxymethyl)-4-(methoxymethoxy)-2,2,4-trimethylcyclohexanol (6). A solution of **5′** (1.20 g, 5.3 mmol) in ether (30 mL) was slowly added at 0 °C to a stirred slurry of $LiAlH_4$ (503 mg, 13.3 mmol, 2.5 equiv) in ether (10 mL). The reaction mixture was allowed to warm to rt. After 3 h, Celite (10 g) and $Na_2SO_4{\cdot}10H_2O$ (10 g) were added, and the solution was stirred for a further 1 h. The mixture was filtered through a pad of $MgSO_4$ and concentrated. Column chromatography of the residue afforded **6** (1.12 g, 92% yield) as white crystals. Mp = 86 °C; $[\alpha]_D^{25}$ = −8.4 (*c* 1.0, $CHCl_3$); IR (KBr) ν = 3391, 1141, 1069 cm^{-1}; ^1H NMR (300 MHz, MeOH-d_4) δ = 4.71 and 4.67 (AB, *J* = 7.3 Hz, 2H), 3.82 and 3.66 (br ABX, *J* = 11.6, 3.8 Hz, 2H), 3.31 (s, 3H), 3.28 (partially overlapped br t, *J* = 8.6 Hz, 1H), 1.88−1.65 (m, 2H), 1.65−1.58 (m, 1H), 1.53−1.44 (m, 2H), 1.26 (s, 3H), 1.14 (s, 3H), 0.88 (br s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 335 K) δ = 89.3 (CH_2), 78.1 (CH), 74.8 (C), 58.6 (CH_2), 54.3 (CH_3), 53.9 (CH), 38.3 (CH_3), 34.3 (C), 28.9 (CH_3), 27.2 (CH_2), 21.3 (CH_2), 18.3 (br, CH_3) ppm; HRMS (ESI) calcd for $C_{12}H_{24}O_4Na^+$ $[M + Na]^+$ 255.1567, found 255.1566.

(1*R*,3*R*,6*R*)-3-Hydroxy-6-(methoxymethoxy)-2,2,6-trimethylcyclohexanecarbaldehyde (7). To a stirred solution of **6** (200 mg, 0.86 mmol) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (15 mg, 0.06 mmol) in CH_2Cl_2 (10 mL) was added a saturated aqueous solution of sodium bicarbonate (2 mL) containing potassium bromide (15 mg, 0.13 mmol) and tetrabutylammonium chloride (15 mg, 0.05 mmol). To this cooled (0 °C) and well-stirred mixture was added dropwise 2 mL of a solution containing household sodium hypochlorite (2.8 mL, 4.47 mmol) in a mixture of saturated sodium bicarbonate solution (5 mL) and brine (11 mL). This solution (1 mL) was added every hour until the starting material was totally consumed, as monitored by TLC. The aqueous phase was extracted with CH_2Cl_2, and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography afforded **7** (168 mg, 85% yield) as an oil. $[\alpha]_D^{25}$ = −43.0 (*c* 1.0, $CHCl_3$); IR (neat) ν = 3384, 2829, 1713, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.84 (d, *J* = 4.8 Hz, 1H), 4.76 and 4.64 (AB, *J* = 7.3 Hz, 2H), 3.55−3.46 (m, 1H), 3.35 (s, 3H), 2.34 (br d, *J* = 4.8 Hz, 1H), 2.11−2.03 (m, 1H), 1.92−1.84 (m, 2H), 1.77−1.70 (m, 1H), 1.66−1.59 (m, 1H), 1.30 (s, 3H), 1.16 (s, 3H), 0.99 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 205.3 (CH), 90.1 (CH_2), 75.9 (C), 74.6 (CH), 65.4 (CH), 55.5 (CH_3), 38.4 (C), 31.7 (br, CH_2), 28.6 (CH_3), 26.5 (CH_2), 24.3 (br, CH_3), 22.4 (br, CH_3) ppm; HRMS (ESI) calcd for $C_{12}H_{22}O_4Na^+$ $[M + Na]^+$ 253.1410, found 253.1410.

(*E*)-4-((1*R*,3*R*,6*R*)-3-Hydroxy-6-(methoxymethoxy)-2,2,6-trimethylcyclohexyl)but-3-en-2-one (8). To a stirred solution of **7** (450 mg, 1.95 mmol) in toluene (30 mL) under an argon atmosphere was added 1-(triphenylphosphoranylidene)propan-2-one (1.24 g, 3.90 mmol, 2.0 equiv). After 48 h at 130 °C, the solution was cooled to rt, and toluene was removed in vacuo. Purification by column chromatography gave **8** (448 mg, 85% yield) as a clear yellow oil. $[\alpha]_D^{25}$ = −16.0 (*c* 1.0, $CHCl_3$); IR (neat) ν = 3448, 2942, 1670, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.89 (dd, *J* = 15.7, 10.8 Hz, 1H), 6.07 (d, *J* = 15.7 Hz, 1H), 4.67 and 4.64 (AB, *J* = 7.4 Hz, 2H), 3.48−3.40 (m, 1H), 3.30 (s, 3H), 2.27 (s, 3H), 2.16 (br d, *J* = 10.8 Hz, 1H), 1.94−1.87 (m, 2H), 1.72−1.54 (partially overlapped m, 2H), 1.49 (br d, *J* = 4.5 Hz, 1H), 1.26 (s, 3H), 1.02 (s, 3H), 0.92 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.0 (C), 147.1 (br, CH), 134.7 (CH), 90.4 (CH_2), 78.0 (C), 76.6 (CH), 58.3 (CH), 55.5 (CH_3), 39.2 (C), 34.5 (br, CH_2), 29.3 (CH_3), 27.7 (CH_2), 27.4 (CH_3), 23.0 (br, CH_3), 19.8 (br, CH_3) ppm; HRMS (ESI) calcd for $C_{15}H_{26}O_4Na^+$ $[M + Na]^+$ 293.1723, found 293.1723.

4-((1*R*,3*R*,6*R*)-3-Hydroxy-6-(methoxymethoxy)-2,2,6-trimethylcyclohexyl)butan-2-one (8′). To a stirred solution of **8** (700 mg, 2.59 mmol) in methanol (40 mL) was added a catalytic amount of 10% palladium on activated charcoal. The mixture was stirred under a hydrogen atmosphere for 3 h, and then the reaction mixture was filtered and concentrated. Purification of the residue by column chromatography gave **8′** (691 mg, 98% yield) as a colorless oil. $[\alpha]_D^{25}$ = −7.5 (*c* 1.0, $CHCl_3$); IR (neat) ν = 3450, 2938, 1672, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.66 (s, 2H), 3.32 (s, 3H), 3.35−3.28 (partially overlapped m, 1H), 2.71 (ddd, *J* = 16.7, 10.5, 5.5 Hz, 1H), 2.51 (ddd, *J* = 16.7, 10.4, 5.5 Hz, 1H), 2.12 (s, 3H), 1.91 (dt, *J* = 12.8, 3.3 Hz, 1H), 1.80−1.38 (m, 6H), 1.28−1.23 (m, 1H), 1.22 (s, 3H), 1.03 (s, 3H), 0.82 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 209.7 (C), 90.0 (CH_2), 79.6 (C), 78.0 (CH), 55.2 (CH), 53.7 (CH_3), 46.5 (CH_2), 40.4 (C), 36.9 (CH_2), 29.9 (CH_3), 28.4 (CH_2), 28.3 (CH_3), 20.2 (CH_2), 19.4 (CH_3), 15.1 (CH_3) ppm; HRMS (ESI) calcd for $C_{15}H_{28}O_4Na^+$ $[M + Na]^+$ 295.1880, found 295.1880.

4-((1*R*,3*R*,6*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-6-(methoxymethoxy)-2,2,6-trimethylcyclohexyl)butan-2-one (9). To a stirred solution of **8′** (560 mg, 2.06 mmol) in CH_2Cl_2 (35 mL) at −20 °C was added triethylamine (720 μL, 6.18 mmol, 3.0 equiv) followed by TBSOTf (710 μL, 3.09 mmol, 1.5 equiv). The mixture was stirred at rt for 3 h and then diluted with CH_2Cl_2 (60 mL) and stirred with a 1 M solution of HCl (40 mL) for 1 h. After extraction with CH_2Cl_2, the organic layer was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by column chromatography gave **9** (779 mg, 98% yield) as a clear oil. $[\alpha]_D^{25}$ = −12.6 (*c* 1.0, $CHCl_3$); IR (neat) ν = 2951, 2855, 1716, 1093, 1033, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.66 (s, 2H), 3.32 (s, 3H), 3.25 (dd, *J* = 10.7, 4.1 Hz, 1H), 2.69 (ddd, *J* = 16.5, 10.6, 5.8 Hz, 1H), 2.50 (ddd, *J* = 16.5, 10.3, 5.5 Hz, 1H), 2.12 (s, 3H), 1.87−1.82 (m, 1H), 1.77−1.41 (m, 5H), 1.25−1.21 (partially overlapped m, 1H), 1.22 (s, 3H), 0.94 (s, 3H), 0.88 (s, 9H), 0.78 (s, 3H), 0.03 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 209.6 (C), 90.0 (CH_2), 79.7 (C), 78.6 (CH), 55.1 (CH), 53.6 (CH_3), 46.6 (CH_2), 41.0 (C), 36.8 (br, CH_2), 29.9 (CH_3), 28.8 (CH_2), 28.7 (CH_3), 25.9 (3 × CH_3), 20.4 (CH_2), 19.6 (CH_3), 18.1 (C), 15.5 (CH_3), −3.8 (CH_3), −4.9 (CH_3) ppm; HRMS (ESI) calcd for $C_{21}H_{46}NO_4Si^+$ $[M + NH_4]^+$ 404.3191, found 404.3191.

5-((1*R*,3*R*,6*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-6-(methoxymethoxy)-2,2,6-trimethylcyclohexyl)-3-methylpent-1-en-3-ol (10). To a stirred solution of **9** (500 mg, 1.29 mmol) in THF (30 mL) at −20 °C under an argon atmosphere was added dropwise vinylmagnesium bromide (1 M in THF, 2.33 mL, 2.33 mmol, 1.8 equiv). The mixture was stirred at −20 °C for 15 min and then allowed to warm to 0 °C, and the resulting solution was quenched with aqueous saturated NH_4Cl solution. After warming to rt, the reaction mixture was extracted with Et_2O, and the organic layer was dried and concentrated to give crude allylic alcohols. Purification by column chromatography gave an inseparable 60:40 mixture of diastereoisomers **10** (520 mg, 97% yield) as a colorless oil. IR (neat) ν = 3448, 2953, 2844, 1091, 1034, 834, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.95−5.83 (m, 1H, m + M), 5.25−5.19 (m, 1H, m + M), 3.07−5.01 (m, 1H, m + M), 4.74−4.67 (m, 2H, m + M), 3.36 (s, 3H, M), 3.35 (s, 3H, m), 3.29−3.24 (m, 1H, m + M), 3.21 (br s, 1H, M), 2.36 (br s, 1H, m), 1.90−1.82 (m, 1H, m + M), 1.75−1.31 (m, 8H, m + M), 1.27 (s, 3H, m), 1.24 (s, 3H, M), 1.21 (s, 3H, m), 1.19 (s, 3H, M), 0.94 (br s, 3H, m + M), 0.88 (s, 9H, m + M), 0.78 (s, 3H, m), 0.77 (s, 3H, M), 0.03 (s, 6H, m + M) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.8 (CH, m), 145.7 (CH, M), 111.9 (CH_2, M), 111.4 (CH_2, m), 90.1 (CH_2, m + M), 80.7 (C, M), 80.3 (C, m), 78.7 (CH, m), 78.6 (CH, M), 74.3 (C, M), 73.6 (C, m), 55.5 (CH, M), 55.4 (CH, m), 55.2 (CH_3, M), 54.2 (CH_3, m), 44.7 (CH_2, m), 44.2 (CH_2, M), 41.5 (C, M), 41.4 (C, m), 36.9 (CH_2, M), 36.8 (CH_2, m), 28.9 (CH_2, m + M), 28.8 (CH_3, m + M), 27.6 (CH_3, m + M), 26.0 (3 × CH_3, M + m), 20.4 (CH_2, m), 20.0 (CH_2, M), 19.7 (CH_3, m), 19.3 (CH_3, M), 18.2 (C, m + M), 15.7 (br, CH_3, m + M), −3.8 (2 × CH_3, m), −4.8 (2 × CH_3, M) ppm; HRMS (ESI) calcd for $C_{23}H_{46}O_4SiNa^+$ $[M + Na]^+$ 437.3058, found 437.3058.

***tert*-Butyldimethyl(((4a*R*,6*R*,8a*R*)-2,5,5,8a-tetramethyl-2-vinyloctahydro-2*H*-chromen-6-yl)oxy)silane (11).** To a solution of allylic alcohols **10** (215 mg, 0.52 mmol) in THF (15 mL) were added Et_3N (850 μL, 7.78 mmol, 15.0 equiv), DMAP (13 mg, 0.10 mmol, 0.2 equiv), Ac_2O (740 μL, 7.8 mmol, 15.0 equiv), and the mixture was heated under reflux for 3 days. After being cooled to rt, the reaction mixture was diluted with Et_2O and washed with aqueous $NaHCO_3$ and brine. The organic layer was dried and concentrated to give the crude allylic acetate as a colorless oil that was used in the next step without further purification. A solution of allylic acetate in THF (20 mL) at rt under an argon atmosphere was treated with a catalytic amount of

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dichlorobis(acetonitrile)palladium(II). After being stirred for 12 h at rt, the reaction mixture was filtered through a short pad of silica gel and washed with Et_2O. Concentration and purification by flash chromatography gave an inseparable 75:25 mixture of diastereoisomers **11** (128 mg, 70% yield from **10**) as a colorless oil. IR (neat) ν = 3015, 2923, 1646, 1252, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 6.00 (dd, J = 18.0, 11.4 Hz, 1H, m), 5.87 (dd, J = 17.4, 10.7 Hz, 1H, M), 5.14 (br d, J = 17.4 Hz, 1H, M), 4.96 (partially overlapped br d, J = 18.0 Hz, 1H, m), 4.92 (partially overlapped br d, J = 10.7 Hz, 1H, M and J = 11.4 Hz, 1H, m), 3.30−3.24 (m, 1H, m + M), 2.27−1.41 (m, 9H, m + M), 1.29 (partially overlapped s, 3H, M), 1.27 (partially overlapped s, 3H, M), 1.22 (s, 3H, m), 1.13 (s, 3H, m), 0.91 (partially overlapped s, 3H, m), 0.88 (partially overlapped s, 12H M + 9H m), 0.72 (s, 3H, M), 0.66 (s, 3H, m), 0.04 (s, 6H, m + M) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.0 (CH, M), 147.7 (CH, m), 110.5 (CH_2, M), 109.8 (CH_2, m), 79.1 (CH, m + M), 75.6 (C, m), 74.6 (C, M), 73.6 (C, m), 73.5 (C, M), 52.9 (CH, m), 50.1 (CH, M), 40.1 (CH_2, M), 39.9 (CH_2, m), 39.3 (C, M), 39.1 (C, m), 35.7 (CH_2, M), 35.0 (CH_2, m), 32.8 (CH_3, m), 29.4 (CH_2, m), 29.3 (CH_2, M), 28.7 (CH_3, M), 28.2 (CH_3, m), 27.8 (CH_3, M), 26.0 (3 × CH_3, m + M), 24.5 (CH_3, M), 22.9 (CH_3, m), 18.2 (C, m + M), 17.1 (CH_2, m), 16.4 (CH_2, M), 15.6 (CH_3, m), 15.2 (CH_3, M), −3.7 (CH_3, m + M), −4.8 (CH_3, m + M) ppm; HRMS (ESI) calcd for $C_{21}H_{41}O_2Si^+$ $[M + H]^+$ 353.2870, found 353.2877.

(*E*)- and (*Z*)-7-((5-((1*R*,3*R*,6*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-6-(methoxymethoxy)-2,2,6-trimethylcyclohexyl)-3-methylpent-2-en-1-yl)oxy)-2*H*-chromen-2-one [(*E*)- and (*Z*)-13]. The tertiary allylic alcohol **10** (500 mg, 1.21 mmol) was dissolved in 30 mL of a mixture of pentane, diethyl ether, and pyridine (65:43:1). The resulting solution was cooled to 0 °C and treated with a freshly prepared 2.7 M solution of phosphorus tribromide (715 μL, 1.93 mmol, 1.5 equiv) in Et_2O (2 mL). The reaction mixture was stirred at 0 °C for 30 min and then diluted with Et_2O and washed with 1 M HCl, aqueous $NaHCO_3$, and brine. The organic layer was dried and concentrated to give the crude bromide as a yellow oil that was immediately dissolved in acetone (10 mL) to prevent degradation. This solution was added to an ice-cold mixture of 7-hydroxycoumarin (293 mg, 1.81 mmol, 1.4 equiv) and K_2CO_3 (820 mg, 5.93 mmol, 4.6 equiv) in acetone (20 mL). The mixture was stirred at rt for 24 h, and then the residue was concentrated, diluted with AcOEt, and washed with water. The organic layer was dried and concentrated. Purification by flash chromatography gave pure compound (*E*)-**13** (330 mg, 49%) as a solid and (*Z*)-**13** (142 mg, 21%) as a colorless oil. Data for (*E*)-**13**: mp = 109−110 °C, $[\alpha]_D^{25}$ = −14.8 (c 1.0, $CHCl_3$); IR (KBr) ν = 3051, 2858, 1738, 1612, 1093, 1031, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.63 (d, J = 9.5 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 6.85 (dd, J = 8.5, 2.5 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.24 (d, J = 9.5 Hz, 1H), 5.47 (br t, J = 6.5 Hz, 1H), 4.72 and 4.64 (AB, J = 7.5 Hz, 2H), 4.58 (br d, J = 6.5 Hz, 2H), 3.33 (s, 3H), 3.28−3.24 (dd, J = 10.8, 4.0 Hz, 1H), 2.30−2.21 (m, 1H), 2.13−2.04 (m, 1H), 1.84−1.81 (m, 1H), 1.77 (br s, 3H), 1.63−1.40 (m, 5H), 1.27−1.20 (partially overlapped m, 1H), 1.21 (s, 3H), 0.95 (s, 3H), 0.88 (s, 9H), 0.78 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.3 (C), 161.3 (C), 156.0 (C), 143.7 (C), 143.5 (CH), 128.8 (CH), 118.0 (CH), 113.3 (CH), 113.0 (CH), 112.5 (C), 101.7 (CH), 90.0 (CH_2), 79.6 (C), 78.7 (CH), 65.7 (CH_2), 55.1 (CH), 53.9 (CH_3), 42.7 (CH_2), 41.1 (C), 36.6 (br, CH_2), 28.9 (CH_2), 28.9 (CH_3), 26.0 (3 × CH_3), 24.9 (CH_2), 19.9 (CH_3), 18.1 (C), 17.0 (CH_3), 15.4 (br, CH_3), −3.8 (CH_3), −4.8 (CH_3) ppm; HRMS (ESI) calcd for $C_{32}H_{54}NO_6Si^+$ $[M + NH_4]^+$ 576.3715, found 576.3716. Data for (*Z*)-**13**: $[\alpha]_D^{25}$ = −15.3 (c 1.0, $CHCl_3$); IR (neat) ν = 3050, 2857, 1735, 1610, 1090, 1030, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.63 (d, J = 9.5 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 6.84 (dd, J = 8.5, 2.5 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.24 (d, J = 9.5 Hz, 1H), 5.45 (br t, J = 7.0 Hz, 1H), 4.65 (s, 2H), 4.59 (br d, J = 7.0 Hz, 2H), 3.30 (s, 3H), 3.25 (dd, J = 10.8, 4.3 Hz, 1H), 2.39−2.32 (m, 1H), 2.14−2.04 (m, 1H), 1.85−1.81 (partially overlapped m, 1H), 1.83 (br s, 3H), 1.62−1.36 (m, 5H), 1.27−1.20 (partially overlapped m, 1H), 1.20 (s, 3H), 0.95 (s, 3H), 0.87 (s, 9H), 0.77 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.2 (C), 161.2 (C), 155.9 (C), 144.4 (C), 143.5 (CH), 128.7 (CH), 118.5 (CH), 113.2 (CH), 112.9 (CH), 112.4 (C), 101.5 (CH), 90.0 (CH_2), 79.6 (C), 78.6 (CH), 65.3 (CH_2), 55.0 (CH), 54.3 (CH_3), 40.9 (C), 36.6 (br, CH_2), 35.7 (CH_2), 28.8 (CH_2), 28.7 (CH_3), 25.9 (3 × CH_3), 25.4 (CH_2), 23.7 (CH_3), 19.7 (CH_3), 18.1 (C), 15.8 (br, CH_3), −3.9 (CH_3), −4.9 (CH_3) ppm; HRMS (ESI) calcd for $C_{32}H_{54}NO_6Si^+$ $[M + NH_4]^+$ 576.3715, found 576.3715.

7-(((*E*)-5-((1*R*,3*R*,6*R*)-3-Hydroxy-6-(methoxymethoxy)-2,2,6-trimethylcyclohexyl)-3-methylpent-2-en-1-yl)oxy)-2*H*-chromen-2-one (14). In a Teflon round-bottom flask, HF·pyridine complex (70 wt % HF, 440 μL, 24.16 mmol, 50.0 equiv) was carefully added to an ice-cold solution of silyl ether (*E*)-**13** (270 mg, 0.48 mmol) in THF (15 mL) under an argon atmosphere, and the mixture was heated at 40 °C for 24 h. Then the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether, and the combined organic layers were washed with saturated aqueous $NaHCO_3$, water, and brine, dried over $MgSO_4$, and concentrated. After purification by column chromatography, alcohol **14** (180 mg, 84% yield) was obtained as a foam. $[\alpha]_D^{25}$ = +1.0 (c 1.0, $CHCl_3$); IR (KBr) ν = 3444, 2932, 1735, 1712, 1609, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.63 (d, J = 9.5 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 6.84 (dd, J = 8.5, 2.5 Hz, 1H), 6.83 (d, J = 2.5 Hz, 1H), 6.25 (d, J = 9.5 Hz, 1H), 5.47 (br t, J = 6.5 Hz, 1H), 4.72 and 4.66 (AB, J = 7.3 Hz, 2H), 4.59 (br d, J = 6.5 Hz, 2H), 3.33 (s, 3H), 3.32 (partially overlapped dd, J = 10.0, 4.3 Hz, 1H), 2.34−2.26 (m, 1H), 2.13−2.06 (m, 1H), 1.89 (dt, J = 12.6, 3.3 Hz, 1H), 1.78−1.71 (partially overlapped m, 1H), 1.78 (br s, 3H), 1.68−1.35 (m, 5H), 1.27 (t, J = 4.5 Hz, 1H), 1.22 (s, 3H), 1.04 (s, 3H), 0.82 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.1 (C), 161.3 (C), 155.8 (C), 143.5 (CH), 143.3 (C), 128.7 (CH), 118.0 (CH), 113.2 (CH), 112.8 (CH), 112.4 (C), 101.5 (CH), 89.8 (CH_2), 79.4 (C), 77.9 (CH), 65.5 (CH_2), 55.0 (CH), 53.8 (CH_3), 42.5 (CH_2), 40.3 (C), 36.7 (CH_2), 28.3 (CH_2), 28.3 (CH_3), 24.6 (CH_2), 19.6 (CH_3), 16.8 (CH_3), 15.3 (CH_3) ppm; HRMS (ESI) calcd for $C_{26}H_{36}O_6Na^+$ $[M + Na]^+$ 467.2404, found 467.2404.

Kopeolin (1′). *Method A*: To an ice-cold solution of **14** (108 mg, 0.24 mmol) in methanol (10 mL) was added 10 drops of a methanolic solution of hydrochloric acid [10 drops of conc. HCl (35 wt % in H_2O) in 5 mL of methanol]. After 48 h of stirring at rt, the reaction mixture was cooled, neutralized with Amberlyst IRA-67, filtered, and concentrated. Purification of the residue by column chromatography gave **1′** (78 mg, 80% yield) as a white solid. *Method B*: Starting from (*E*)-**13** (146 mg, 0.26 mmol), **1′** was prepared according to method A with a reaction time of 72 h and was obtained as a white solid (89 mg, 85% yield). *Method C*: To a stirred solution of **2′** (30 mg, 0.07 mmol) in MeOH (10 mL) at −78 °C under an argon atmosphere was added $NaBH_4$ (9.0 mg, 0.24 mmol, 3.0 equiv). The reaction mixture was stirred for 30 min and then poured into a saturated aqueous NH_4Cl solution. The aqueous layer was extracted with AcOEt, and the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. After purification by column chromatography, pure alcohol **1′** (23 mg, 85%) was obtained as a white solid. Mp = 120 °C; $[\alpha]_D^{25}$ = −12.0 (c 1.0, EtOH); IR (KBr) ν = 3440, 2934, 1730, 1708, 1613, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, J = 9.5 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 6.85 (dd, J = 8.5, 2.5 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.24 (d, J = 9.5 Hz, 1H), 5.50 (br t, J = 6.3 Hz, 1H), 4.59 (d, J = 6.3 Hz, 2H), 3.31 (dd, J = 11.0, 4.0 Hz, 1H), 2.29−2.12 (m, 2H), 1.78 (br s, 3H), 1.78−1.72 (partially overlapped m, 1H), 1.67−1.40 (m, 4H), 1.25−1.17 (partially overlapped m, 1H), 1.17 (s, 3H), 1.13 (t, J = 4.3 Hz, 1H), 1.03 (s, 3H), 0.80 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.0 (C), 161.3 (C), 155.8 (C), 143.5 (CH), 143.4 (C), 128.7 (CH), 118.3 (CH), 113.2 (CH), 112.8 (CH), 112.4 (C), 101.5 (CH), 78.0 (CH), 73.4 (C), 65.4 (CH_2), 55.2 (CH), 42.4 (CH_2), 40.9 (CH_2), 40.3 (C), 28.9 (CH_2), 28.0 (CH_3), 23.9 (CH_2), 23.0 (CH_3), 16.8 (CH_3), 14.8 (CH_3) ppm; HRMS (ESI) calcd for $C_{24}H_{33}O_5^+$ $[M + H]^+$ 401.2323, found 401.2319.

Kopeolone (2′). A catalytic amount of tetrapropylammonium perruthenate was added to an ice-cold solution of **1′** (24 mg, 0.060 mmol), *N*-methylmorpholine *N*-oxide (28 mg, 0.24 mmol, 4.0 equiv),

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and powdered 4 Å molecular sieves in CH_2Cl_2 (5 mL) under an argon atmosphere. After 40 min of stirring at 0 °C, the reaction mixture was filtered through a short pad of Celite, and the filtrate was poured into an aqueous Na_2SO_3 solution. The aqueous layer was extracted with CH_2Cl_2, and then the organic layers were combined, washed with water and brine, and dried with $MgSO_4$. Concentration in vacuo and purification of the residue by silica gel column chromatography afforded **2′** (22 mg, 91% yield) as white solid. Mp = 116 °C; $[\alpha]_D^{25}$ = −7.0 (*c* 1.0, EtOH); IR (KBr) ν = 3445, 2928, 1735, 1712, 1610, 1134 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 9.5 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 6.77 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 6.18 (d, *J* = 9.5 Hz, 1H), 5.42 (br t, *J* = 6.5 Hz, 1H), 4.52 (d, *J* = 6.5 Hz, 2H), 2.45−2.41 (m, 2H), 2.21 (ddd, *J* = 14.0, 10.0, 6.0 Hz, 1H), 2.10 (ddd, *J* = 14.0, 10.0, 5.3 Hz, 1H), 1.94 (dt, *J* = 13.5, 5.8 Hz, 1H), 1.74 (partially overlapped ddd, *J* = 13.5, 8.8, 6.8 Hz, 1H), 1.71 (br s, 3H), 1.67−1.56 (m, 1H), 1.53 (dd, *J* = 5.0, 4.3 Hz, 1H), 1.48−1.36 (m, 1H), 1.32 (s, 3H), 1.10 (s, 3H), 0.99 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 215.2 (C), 162.2 (C), 161.4 (C), 156.0 (C), 143.6 (CH), 142.9 (C), 128.9 (CH), 119.0 (CH), 113.3 (CH), 113.2 (CH), 112.7 (C), 101.7 (CH), 73.0 (C), 65.5 (CH_2), 55.8 (CH), 48.4 (C), 41.4 (CH_2), 40.1 (CH_2), 35.4 (CH_2), 26.3 (CH_3), 25.2 (CH_2), 24.5 (CH_3), 21.9 (CH_3), 17.0 (CH_3) ppm; HRMS (ESI) calcd for $C_{24}H_{31}O_5^+$ $[M + H]^+$ 399.2166, found 399.2166.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of compounds **5**, **5′**, **6**, **7**, **8**, **8′**, **9**, **10**, **11**, (*E*)-**13**, (*Z*)-**13**, **14**, **1′**, **2′**, and natural kopeolin; 2D NOESY spectra of (*E*)- and (*Z*)-**13**; comparison tables; ORTEP view and X-ray data (CIF) for **6**; and calculation details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kamilov, K. M.; Nikonov, G. K. *Khim. Prir. Soedin.* **1973**, *9*, 308−313.

(2) Nabiev, A. A.; Khasanov, T. K.; Malikov, V. M. *Khim. Prir. Soedin.* **1982**, *17*, 48−51.

(3) Personnal communication from Prof. Shi Yong Ryu.

(4) (a) Monti, H.; Audran, G. *Mini-Rev. Org. Chem.* **2005**, *2*, 265−281. (b) Uttaro, J.-P.; Audran, G.; Monti, H. *J. Org. Chem.* **2005**, *70*, 3484−3489. (c) Palombo, E.; Audran, G.; Monti, H. *Synlett* **2005**, 2104−2106. (d) Palombo, E.; Audran, G.; Monti, H. *Tetrahedron* **2005**, *61*, 9545−9549. (e) Brémond, P.; Audran, G.; Juspin, T.; Monti, H. *Eur. J. Org. Chem.* **2007**, 2802−2807. (f) Brémond, P.; Audran, G.; Monti, H. *J. Org. Chem.* **2008**, *73*, 6033−6036.

(5) Miquet, S.; Vanthuyne, N.; Brémond, P.; Audran, G. *Chem.—Eur. J.* **2013**, *19*, 10632−10642.

(6) (a) Galano, J.-M.; Audran, G.; Monti, H. *Tetrahedron* **2000**, *56*, 7477−7481. (b) Palombo, E.; Audran, G.; Monti, H. *Synlett* **2006**, 403−406.

(7) Reviews: (a) Imamoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. *1*, pp 231−250. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68. (c) Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, U.K., 1995; Vol. *2*, pp 1031−1034.

(8) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275−1276.

(9) Details of the X-ray structure can be obtained from the Cambridge Crystallographic Data Centre as entry CCDC 271219.

(10) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562. (b) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970−2972.

(11) (a) Alvarez-Ibarra, C.; Arias, S.; Fernández, M. J.; Serrano, D.; Sinisterra, J. V. *J. Chem. Soc., Perkin Trans. 2* **1989**, 503−508. (b) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774−776. (c) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745−4749. Review: (d) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

(12) (a) Harris, T. M.; Harris, C. M. *Org. React.* **1969**, *17*, 155−212. (b) Baoyu, M.; Maleczka, R. E., Jr. *Org. Lett.* **2001**, *3*, 1491−1494. (c) Oritani, T.; Yamashita, K. *Agric. Biol. Chem.* **1987**, *51*, 1271−1275.

(13) Reviews: (a) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205−247. (b) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579−587. (c) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, U.K., 1999; pp 399−404.

(14) Demnitz, F. W. J.; Philippini, C.; Raphael, R. A. *J. Org. Chem.* **1995**, *60*, 5114−5120.

(15) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011−4013.

(16) Auerbach, J.; Weinreb, S. M. *J. Chem. Soc., Chem. Commun.* **1974**, 298−299.

(17) Racemic samples of **1′** and **2′** were prepared from racemic **4** using the synthetic pathway described in this article.

(18) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625−1627. (b) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13−19.