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Enantioselective Syntheses of the Proposed Structures of Kopeolin and Kopeolone

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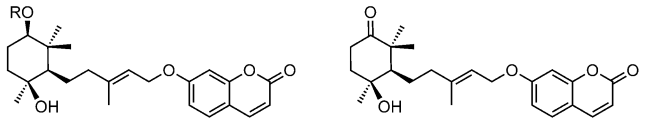
Abstract: The first total syntheses of the proposed structures of kopeolin (**1**) and kopeolone (**3**) have been achieved from a common enantiopure chiral building block obtained by a chemoenzymatic enantioconvergent methodology. The syntheses feature two key steps: a one-pot reduction/diastereoselective protonation followed by a highly diastereoselective addition of an organocerate. The synthetic structures were fully characterized and all stereocenters were confirmed. The results show that the two previously reported structures were not assigned correctly, and suggest an initial structural misassignment during the isolation of the natural products. Thus, two revised structures, **1′** for kopeolin and **3′** for kopeolone, are proposed.

Keywords: enantioselectivity · natural products · structure elucidation · terpenoids · total synthesis

Introduction

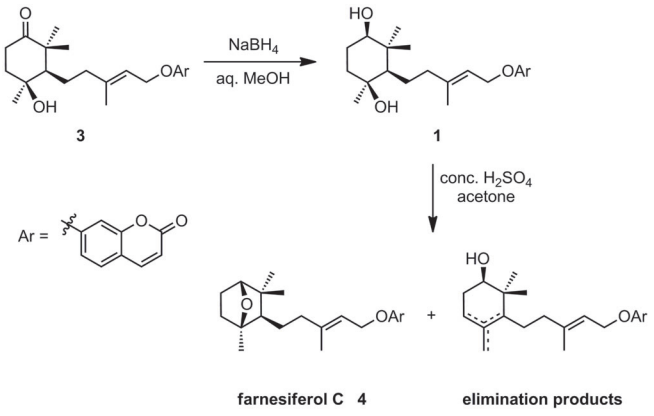
Monocyclic terpenoids are not very common metabolites in nature and their biosynthetic processes are usually based on polycyclization. However, during the last few years, identification of several natural oxygenated monocyclic sesquiterpenes suggests that they may be more prevalent within the plant kingdom than previously assumed.[1] In 1973, the isolation from roots of *Ferula kopetdaghensis* of the sesquiterpenoid coumarins kopeolin (**1**) and kopeoside (**2**), which are ethers of umbelliferone, were reported (Figure 1).[2]

Kopeolin (**1**) presents a six-membered ring carrying a *gem*-dimethyl group, secondary and tertiary alcohol functions, and a sidechain extended by a 7-hydroxycoumarin moiety (umbelliferone). Kopeolin (**1**) has three stereocenters and an *E*-double bond, and is the aglycon part of kopeoside (**2**), the glycone part being the β-D-glucopyranose. Their structures were established on the basis of their spectroscopic properties (IR, MS, ^{1}H NMR spectroscopic data), however, at that time, the stereostructures of **1** and **2** could not be established with certainty. In 1982, kopeolone (**3**),[3] another terpenoid coumarin, was also isolated from the same species (Figure 1). The structure of kopeolone (**3**) is similar to that of kopeolin (**1**) except that the secondary alcohol is oxidized to the ketone. The stereostructures of these natural compounds were proposed based on chemical transformations; indeed, $NaBH_4$-mediated reduction of kopeolone (**3**) into kopeolin (**1**) followed by H_2SO_4 catalyzed dehydration provided known farnesiferol C (**4**) as well as three elimination products (Scheme 1). As reported, discussions on the stereostructure of kopeolin (**1**) and kopeolone (**3**) were only based on comparison of their ^{1}H NMR spectra (90 MHz).[3]



kopeolin **1** (R = H) **kopeolone** **3**
kopeoside **2** (R = β–D–glucopyranose)

Figure 1. Structure of kopeolin (**1**), kopeoside (**2**), and kopeolone (**3**).



Scheme 1. Chemical transformations conducted to elucidate the stereostructures of **1** and **3**.

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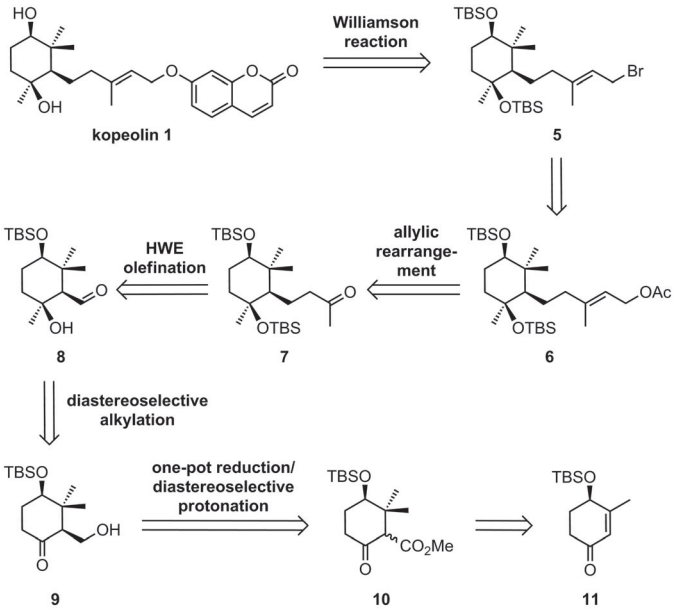
In 1991, kopeolin (**1**) was also isolated from the ethanol extract of the resin of *Ferula gummosa*, which is widespread in India.[4] Incidentally, the gum resin obtained by incision from the stem is used as a traditional medicine in India.[5] Kopeolin (**1**) was also isolated from *Ferula assafoetida* and its antiproliferative properties were studied, showing strong inhibition of the proliferation of cultured human cells.[6] To date, no synthesis of kopeolin (**1**) or kopeolone (**3**) has been described. Starting from an enantiopure building block for the introduction and determination of the absolute stereochemistry, we report herein the first enantioselective synthesis of kopeolin (**1**) and kopeolone (**3**) to fully characterize these natural compounds and to determine the absolute stereochemistry of all the chiral centers.

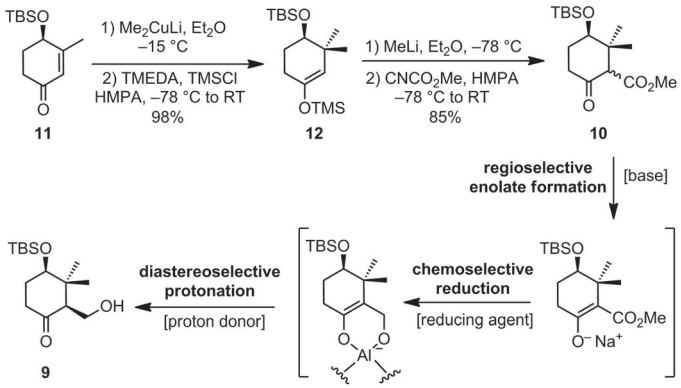
Results and Discussion

Our retrosynthetic analysis of kopeolin (**1**) is outlined in Scheme 2. Initial disconnection reduced kopeolin (**1**) to intermediate **5** and to the commercially available umbelliferone. The strategy then indicated that the sidechain of **5** could be prepared by its chemical transformation from acetate **6**, which could, in turn, arise by allylic rearrangement of an intermediate stemming from ketone **7**. The latter would be prepared by Horner–Wadworth–Emmons (HWE) olefination from aldehyde **8**. The critical point of the synthesis involved the installation of the required stereogenic centers of the alcohols. The stereocontrol of the tertiary alcohol would be realized by diastereoselective addition of an organometallic to β-ketoalcohol **9**, which would be prepared by diastereoselective protonation of a chiral enolate generated from β-ketoester **10**. Finally, β-ketoester **10** could be obtained from enone **11**, as starting material, by the 1,4-addition of dimethyl cuprate, followed by quenching with methyl cyanoformate. We have already reported the synthesis of both enantiomers of the required enone **11** with good yields and excellent enantiomeric excesses through a chemoenzymatic enantioconvergent methodology,[7] and demonstrated the usefulness of these building blocks in the synthesis of natural products.[8]



Scheme 2. Retrosynthetic analysis of kopeolin (**1**).

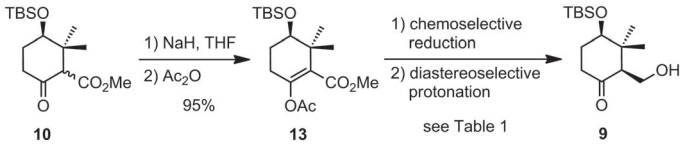
As shown in Scheme 3, enone **11** was converted into enol ether **12** in 98% yield by the 1,4-addition of lithium dimethyl cuprate in diethyl ether followed by quenching of the intermediate enolate with chlorotrimethylsilane (TMSCl) in the presence of hexamethylphosphoramide (HMPA) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). The enolate regenerated in situ from **12** by addition of methyllithium was then quenched with methylcyanoformate (Mander's reagent) in a mixture of THF and HMPA in 85% yield. Next, the transformation used to obtain β-ketoalcohol **9** from β-ketoester **10** involved a one-pot, three-step sequence: 1) regioselective formation of an enolate 2) chemoselective reduction of the ester function, and 3) stereoselective C-protonation of an ambident enolate. Chemoreduction using alane (AlH_3) as the reducing agent of the ester group of a β-ketoester into an enolate salt of β-ketoalcohol has already been reported.[9] Moreover, diastereoselective protonation of chiral enolates with proton donors has been reviewed.[10] Thus, attempts to realize this one-pot, three-step sequence were made using NaH as the base and AlH_3 as the reductant with a range of proton donors (*tert*-BuOH, MeOH, NH_4Cl, HCl, ethyl salicylate). The best result was obtained by using MeOH, giving pure β-ketoalcohol **9**, albeit in only 28% yield accompanied by a complex mixture of byproducts.



Scheme 3. Preparation of β-ketoalcohol **9**.

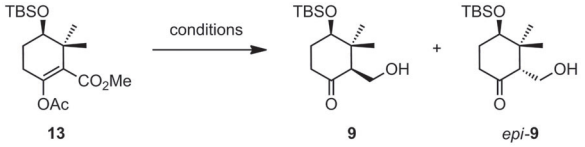
Because the results were not satisfactory due to the instability of β-ketoalcohol **9** in this complex reaction mixture containing many salts, we slightly changed the strategy to realize the diastereoselective protonation from enol acetate **13** (Scheme 4).

Thus, treatment with acetic anhydride of the sodium enolate generated from β-ketoester **10** by NaH in THF occurred



Scheme 4. Preparation of β-ketoalcohol **9**.

Table 1. One-pot reduction/diastereoselective protonation to prepare β-ketoalcohol **9**.



Entry	Reductant	Proton donor	Yield of **9** [%][a]	Yield of *epi*-**9** [%][a]
1[b]	AlH_3	MeOH/Rochelle salt	55	12
2[c]	AlH_3	*tert*-BuOH/Rochelle salt	35	16
3[c]	DIBAL-H	MeOH/Rochelle salt	20	12
4[c]	LAH	MeOH/Rochelle salt	40	15

[a] Isolated yield after column chromatography. [b] These conditions afford cleanly β-ketoalcohol **9** and *epi*-**9**. [c] Elimination product was also isolated.

exclusively by O-acetylation to give enol acetate **13** in excellent yield. The next reaction involved reduction of **13** and the reduced intermediate should be diastereoselectively protonated in situ. As shown in Table 1, three different reductants were tested (AlH_3, diisobutylaluminum hydride (DIBAL-H), lithium aluminum hydride (LAH)) with different proton donors. The best result was observed when the reaction was performed in THF at −80 °C with AlH_3 as the reductant, MeOH as the proton donor, and by quenching of the reaction mixture with an aqueous solution of Rochelle salt. Under these conditions, the reaction cleanly provided the corresponding β-ketoalcohol **9** and *epi*-**9** in 55 and 12% yield, respectively, after separation by silica gel column chromatography.

The observed stereoselectivity was explained by calculation at the B3LYP/6-311G++(d,p) level of the optimized conformation of the intermediate enolate (Figure 2). The low-energy twist conformation of the enolate, which minimizes the steric interactions of the methyl groups and the TBS ether in the pseudoequatorial position, presented a less-hindered lower face, the upper face being more crowded due to the pseudoaxial position of the β-methyl group. The axial approach of the proton donor to the α-face was thus clearly favored and led to β-ketoalcohol **9**.

Having obtained β-ketoalcohol **9**, methylcerium dichloride ($MeCeCl_2$)[11] was selected as a suitable alkylating reagent, which, due to its low basicity, should prevent epimerization or elimination of the sensitive hydroxymethyl moiety. Thus, $MeCeCl_2$ reacted with **9** to afford diol **14** as a single diastereomer in 76% yield (Scheme 5).

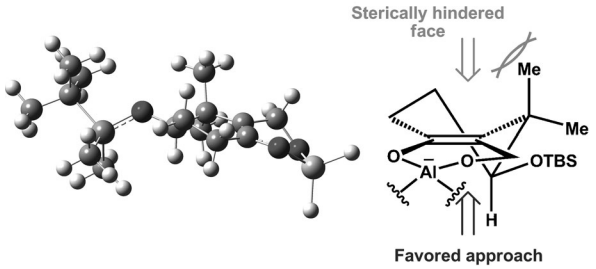


Figure 2. Optimized conformation of the intermediate enolate for diastereoselective protonation, calculated using the B3LYP/6-311G++(d,p) method.

To establish the stereochemistry of the newly generated stereocenters, the TBS protecting group of diol **14** was removed with tetrabutylammonium fluoride (TBAF) in THF to give the crystalline triol **15** in 82% yield. The structure of **15**, and therefore that of **14**, was confirmed by X-ray crystallography.[12]

The diastereoselectivity was explained by calculation at the B3LYP/6-311G++(d,p) level of the preferred chair conformation of the β-ketoalcohol **9** (Figure 3). This conformation is stabilized by a hydrogen bond between the ketone and the hydrogen of the primary alcohol function, thus forming a tethering six-membered ring. As a consequence,

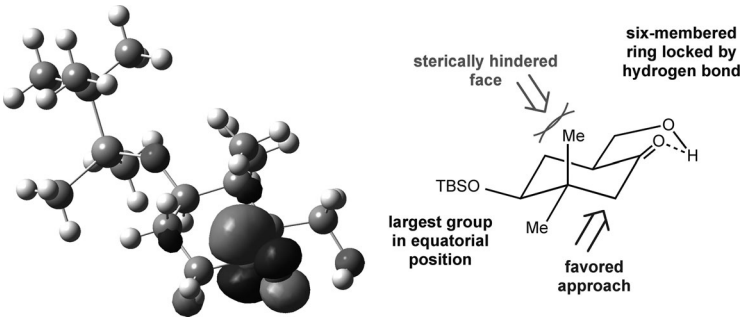
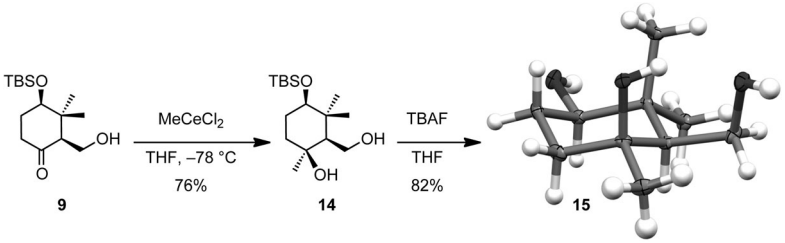


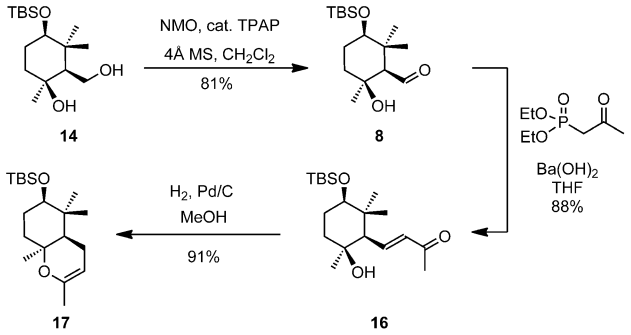
Figure 3. Optimized conformation [B3LYP/6-311G++(d,p)] of ketone **9** and the corresponding LUMO orbital showing the accessibility of the lobe for the diastereoselective alkylation by $MeCeCl_2$.



Scheme 5. Formation of triol **15**.

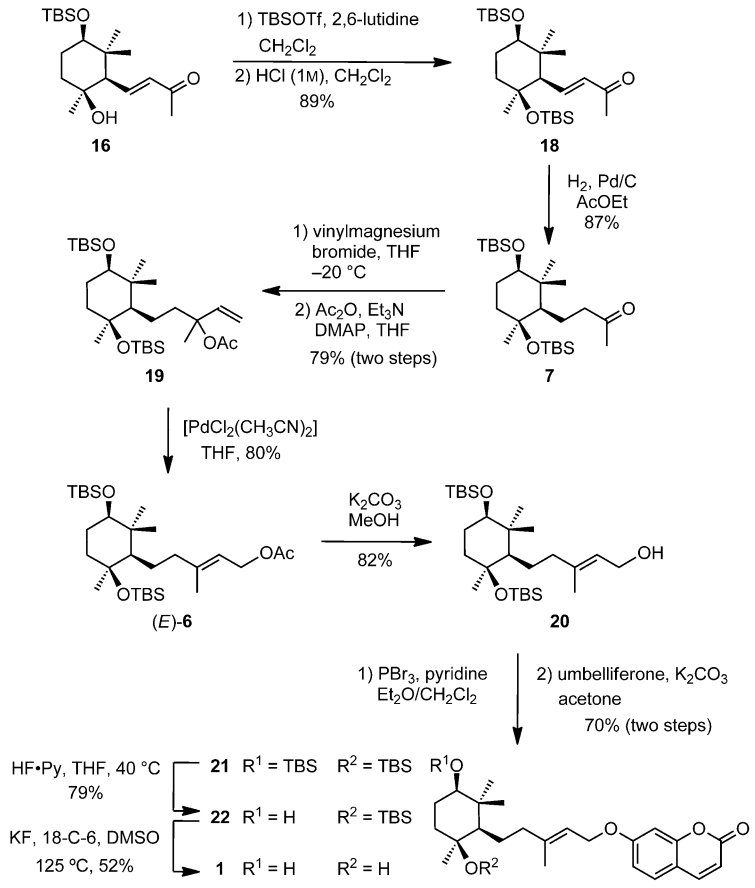
the approach of the organocerate occurred at the less-hindered lower face of **9** in respect of the Bürgi–Dunitz angle, nicely illustrated by the lower lobe of the lowest unoccupied molecular orbital (LUMO), the upper lobe of the LUMO being inaccessible due to the proximity of the β-methyl group. Consequently, this led to the formation of the tertiary alcohol function *cis* to the CH_2OH and TBS ether groups.

With the stereostructure of diol **14** confirmed, the synthesis of kopeolin (**1**) was continued by elaboration of the coumarin sidechain. Careful oxidation of diol **14** with a catalytic amount of tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) as the co-oxidant in dichloromethane provided aldehyde **8** in 81% yield (Scheme 6).[13] The Horner–Wadsworth–Emmons (HWE) reaction is an efficient methodology for coupling of β-ketophosphonate, and numerous modifications have been reported.[14] Among them, the $Ba(OH)_2$ promoted HWE reaction is a mild method for use with epimerizable aldehydes.[14c] Thus, application of these conditions to aldehyde **8** in wet THF afforded enone **16** in 88% yield as a single *E* isomer. At this stage, hydrogenation of the double bond of enone **16** by a standard method (H_2, Pd/C, MeOH) did not give the desired reduced compound but instead gave dihydropyrane **17** as a unique product in 91% yield. The formation of the undesired product **17** could be explained by reduction of the double bond, followed by the hemiketalization of the ketone by the tertiary alcohol and finally β-elimination.



Scheme 6. Preparation of enone **16** and undesired dihydropyrane **17**.

To circumvent this problem, the tertiary alcohol was protected as the TBS ether, that is, with the same protecting group already used for the secondary alcohol, to allow simultaneous deprotection of both TBS ethers at the final stage of the synthesis. Treatment of the hindered tertiary alcohol **16** with TBS-OTf in the presence of 2,6-lutidine in CH_2Cl_2 afforded the corresponding TBS ether with concomitant formation of the silyl enol ether of the ketone, which was hydrolyzed upon acidic aqueous workup providing compound **18** in 89% yield (Scheme 7). Hydrogenation of **18** in ethyl acetate with H_2 in the presence of Pd/C occurred smoothly to give ketone **7** in 87% yield. To obtain the sidechain of kopeolin (**1**) with high *E* stereoselectivity starting from ketone **7**, we selected a rearrangement of a tertiary allylic acetate in the presence of a palladium catalyst.[15] Thus, subsequent exposure of **7** to vinylmagnesium bromide followed by treatment with acetic anhydride/triethylamine in the presence of *N*,*N*-dimethylaminopyridine (DMAP) yielded the tertiary allylic acetates **19** (79%) as a 60:40 diastereomeric mixture. To install the umbelliferone to the side chain of **19** in one step, a palladium-catalyzed cross-coupling reaction with allylic acetates **19** and the sodium or potassium salt of umbelliferone was first investigated. However, no reaction was observed despite the screening of several different conditions ($[Pd(PPh_3)_4]$, K_2CO_3 or NaH, umbelliferone) and the unreacted starting



Scheme 7. Completion of the synthesis of kopeolin (**1**).

material was recovered. As a consequence, the umbelliferone was added using a linear methodology. Treatment of tertiary allylic acetates **19** with dichlorobis(acetonitrile)palladium afforded a 87:13 mixture of (*E*/*Z*)-**6** (analyzed by ^{1}H NMR spectroscopy) in 93% yield.

Separation of the geometric isomers on silica gel column afforded pure acetate (*E*)-**6** in 80% yield. Treatment of (*E*)-**6** with excess K_2CO_3 in methanol at room temperature cleaved the acetate group and cleanly provided alcohol **20** as the precursor to the natural product in 82% yield. Reaction of alcohol **20** with PBr_3 afforded the corresponding allylic bromide,[16] which was directly used in the next step without any further purification due to its instability. Thus, coupling of the potassium salt of umbelliferone and the crude allylic bromide in acetone yielded coumarin derivative **21** in 70% yield over two steps. To complete the synthesis of kopeolin (**1**), we needed to simultaneously remove both TBS protecting groups. The use of several fluorine sources (TBAF, aq. HF or H_2SiF_6) to deprotect **21** proved to be unworkable, leading only to a complex mixture of products composed of starting material, monodeprotected product, and the desired kopeolin (**1**) in very poor yield along with extensive decomposition. To solve this problem, the deprotections were carried out in two separate steps. First, of the different attempts used to remove the secondary TBS ether by using standard methods,[17] only the action of HF·pyridine complex[18] in THF at 40 °C cleanly afforded the monodeprotected derivative **22** in 79% yield. To remove the last TBS ether group of **22**, the same methods described before were used, but again without any success. Fortunately, after extensive screening of several deprotection conditions, desilylation was accomplished with KF in the presence of [18]crown-6 in DMSO at 125 °C.[19] Under these conditions, **1** was obtained, after purification on silica gel column, as a foam in 52% yield together with 45% yield of recovered **22**. Attempts to reach full conversion led only to decomposition of the reaction mixture.

The high optical purity of **1** was confirmed by chiral HPLC analysis by comparison with a racemic sample (Figure 4). ^{1}H and ^{13}C NMR data for **1** were fully ascribed by COSY and HMQC experiments, and the relative configuration of the three stereocenters in **1** was assigned on the basis of ^{1}H NMR NOESY experiments; NOE effects between H_{ax}–C_3 and H_{ax}–C_1, and between H_{ax}–C_1 and Me_{eq}–C_6 established the *cis* spatial orientation of these protons and the methyl group (Figure 4). Moreover, strong NOE effects between the two protons of H–C_8 and H–C_{10}, and between Me–C_9 and the two protons of H–C_{11}, established the *E* double-bond configuration.

Kopeolin was also extracted recently from *Ferula assafoetida* by Ryu[6] and the spectroscopic data were in agreement with the NMR data previously reported in the literature[2] (see ^{1}H and ^{13}C NMR data of natural kopeolin provided by Ryu in the Supporting Information). Surprisingly, we observed that the ^{1}H and ^{13}C NMR data of our synthetic compound were not consistent with the reported data of natural

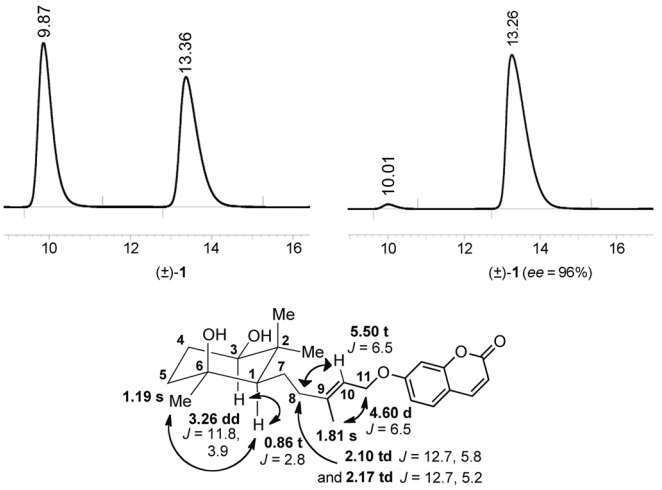
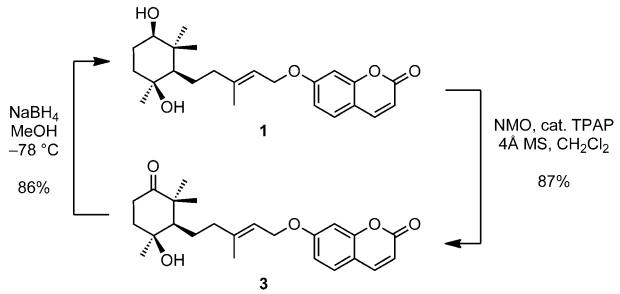


Figure 4. HPLC chromatogram of (±)-**1** and (+)-**1** and selected NOESY correlations of **1**.

kopeolin reported by Kamilov and Nikonov[2] or by Ryu.[6] Indeed, the chemical shifts of the axial methyl of the *gem*-dimethyl group, Me_{ax}–C_2 (reported: $\delta_H = 0.80$ ppm; synthetic: $\delta_H = 0.95$ ppm) as well as the chemical shift of H_{ax}–C_1 (reported: $\delta_H = 1.19$–1.11 ppm; synthetic: $\delta_H = 0.86$ ppm) differed significantly. Moreover, several carbon chemical shifts were also quite different (see the Supporting Information). In addition, the magnitude and the sign of the specific rotation of our synthetic **1** ($[\alpha]_D^{25} = +7$ (*c* 1.0, EtOH)) were not consistent with the reported data ($[\alpha]_D^{25} = -16$ (*c* 1.0, EtOH)), and synthetic **1** was obtained as a foam and not as a solid.[2] Thus, the differences in the spectral data and the physical properties between **1** and natural kopeolin strongly suggested a structural misassignment during the isolation of kopeolin.

To investigate this possible misassignment in the structure of natural kopeolin, we decided to examine the possibility of a misattribution of the configuration of the secondary alcohol. To this end, we oxidized the secondary alcohol with TPAP/NMO, which gave the proposed structure of kopeolone **3** in 87% yield (Scheme 8). Moreover, reduction of **3** with $NaBH_4$ afforded exclusively and cleanly **1**, once again as a foam, with 86% yield.



Scheme 8. Synthesis of kopeolone (**3**).

The structure of **3** was assigned on the basis of ^{1}H, ^{13}C, COSY, HMQC and NOESY NMR analyses. The chemical shifts and the large coupling constant of two signals resonating as a triplet of doublets at $\delta_H = 3.07$ ($J = 14.2$, 5.8 Hz) and 1.82 ppm ($J = 14.2$, 4.3 Hz) allowed us to identify anticoplanar orientation protons, H_{ax}–C_4 and H_{ax}–C_5, respectively. Thus, NOE effects between H_{ax}–C_4 and Me_{ax}–C_2 established the *cis* spatial orientation of this proton and the methyl group. In addition, strong NOE effects between H_{ax}–C_5, Me_{eq}–C_6, H_{ax}–C_1, and Me_{eq}–C_2 established the *cis* orientation of these protons and this methyl group. The high optical purity of **3** was also confirmed by chiral HPLC by comparison with a racemic sample (Figure 5).

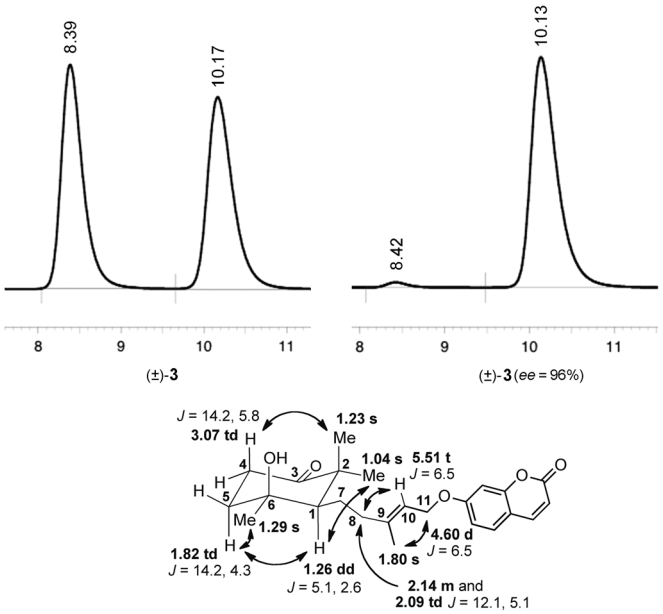
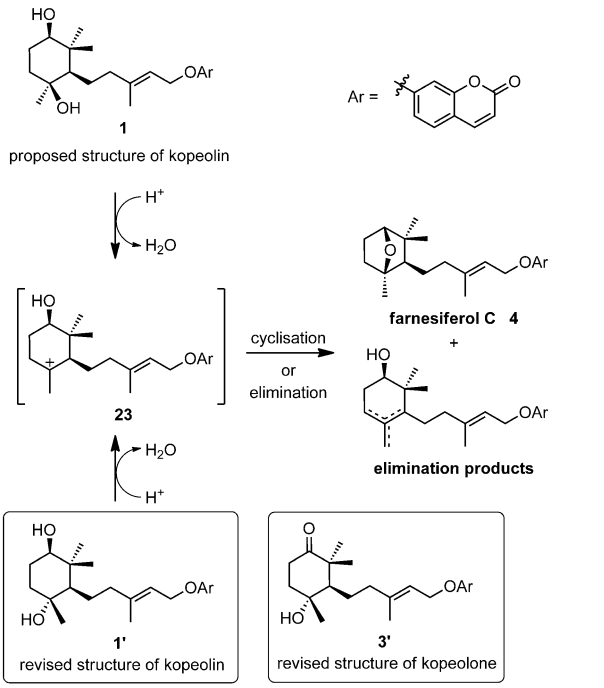


Figure 5. HPLC chromatogram of (±)-**3** and (+)-**3** and selected NOESY correlations of **3**.

Unfortunately, the spectral data of synthetic **3** were also not consistent with the data reported for natural kopeolone, confirming a structural misassignment of both kopeolin and kopeolone. The chemical shifts in the ^{1}H NMR spectrum of the axial methyl of the *gem*-dimethyl group (reported: $\delta_H = 1.12$ ppm; synthetic: $\delta_H = 1.23$ ppm) were also not in agreement. Because no ^{13}C NMR data were reported in the literature for kopeolone, we could not make any comparison. However, the melting point of our synthetic **3** (m.p. 105–106 °C) was also not in agreement with that reported in the literature (m.p. 125–126 °C), nor was the magnitude of the specific rotation (synthetic **3**: $[\alpha]_D^{25} = +32$ (c 1.0 in EtOH); lit.: $[\alpha]_D^{25} = +70$ (c 1.0, EtOH)[3]).

Previously, the determination of the stereostructure of the isolated natural compounds, kopeolin and kopeolone, was based on the dehydration of kopeolin with sulfuric acid into known farnesiferol C (**4**) together with elimination products (Scheme 9).[3] With this in mind, two of the three stereocenters of kopeolin, C-1 and C-3, could undoubtedly be assigned, but the tertiary alcohol stereocenter C-6 remained unknown. Our hypothesis is that, taking into account the quite harsh conditions of the cyclization (conc. H_2SO_4 in acetone at reflux), the intramolecular ether formation of farnesiferol C (**4**) follows an S_N1 pathway with the intermediate formation of carbocation **23**. The latter can either react with the secondary alcohol to give farnesiferol C (**4**), or can eliminate one of the three types of β-neighboring protons to give the elimination products. Carbocation **23** can indeed be obtained by loss of the tertiary hydroxyl group from the proposed structure of kopeolin (**1**) after protonation, but it can also be obtained from the diastereomer carrying the opposite configuration of the tertiary alcohol. Thus, based on these observations and according to our results, we postulate that the configuration of the tertiary alcohol of the proposed structure of kopeolin (**1**) and kopeolone (**3**) was missassigned and should be reassigned the opposite configuration. As a consequence, the only remaining possible structures for kopeolin and kopeolone that could explain these chemical transformations are compounds **1′** and **3′** depicted in Scheme 9. To confirm the revised structures of kopeolin **1′** and kopeolone **3′**, we plan to synthesize these molecules using a new strategy that will permit the correct configuration of the tertiary alcohol at C-6 to be obtained.



Scheme 9. Revised structures for kopeolin and kopeolone.

Conclusion

The total syntheses of the proposed structures of kopeolin (**1**) and kopeolone (**3**) have been completed in 17 and 18 steps, respectively. The synthetic materials **1** and **3** do not correspond to the reported structure of natural kopeolin

and kopeolone, strongly suggesting a structural misassignment during the isolation of the natural products. Based on our current synthesis and the previously reported data, we propose the structural revision of kopeolin to compound **1′** and kopeolone to compound **3′**. Their total syntheses are now under investigation and will be reported in due course.

Experimental section

General: All air- and/or water-sensitive reactions were carried out under an argon atmosphere with anhydrous, freshly distilled solvents using standard syringe/cannula/septa techniques. All corresponding glassware were oven-dried (80 °C) and/or carefully dried in-line with a flameless heat gun. All solvents were distilled under an argon atmosphere: THF from a blue solution of sodium-benzophenone ketyl radical prior to use; CH_2Cl_2 from CaH_2; Et_2O from $LiAlH_4$. Routine monitoring of reactions was performed using Merck Silica gel 60 F_{254}, aluminum-supported TLC plates; spots were visualized using UV light and ethanolic acidic *para*-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 (PE) or CH_2Cl_2/MeOH as eluent, unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD or C_6D_6 solutions with Bruker Avance DPX-300 or Bruker AM-400 spectrometers. Chemical shifts (δ) in ppm are reported using residual non-deuterated solvents as internal reference. Optical rotations were measured with a PerkinElmer 241 polarimeter. Melting points are uncorrected. Infrared spectra were obtained as films or KBr pellets with a Bruker Vertex 70 spectrophotometer. High-resolution mass spectra (HRMS) were performed with a SYNAPT G2 HDMS (Waters) mass spectrometer equipped with a pneumatically assisted atmospheric pressure ionization. The sample was ionized in positive mode electrospray under the following conditions: electrospray voltage (ISV): 2800 V; orifice voltage (OR): 20 V; nebulizing gas flow (nitrogen): 800 L h^{-1}. The mass spectrum was obtained with a time of flight analyzer (TOF). The measurements were realized in triplicate, with double internal standardization. The sample was dissolved in CH_2Cl_2 (450 μL) then diluted (dilution factor 1/10^3) in a methanolic solution of ammonium acetate (3 mM). The sample solution was infused in the ionization source at a 10 μL min^{-1} flow rate. Enantiomeric excesses (*ee*) were determined by chiral HPLC by comparison with a racemic sample: Chiralpak IA, hexane/ethanol (6:4), 1 mL min^{-1}.

(*R*)-4-(*tert*-Butyldimethylsilanyloxy)-3,3-dimethyl-1-trimethylsilanyloxycyclohexene (12): MeLi (1.6 M in Et_2O, 39.0 mL, 62.4 mmol, 3.0 equiv) was added dropwise to a stirred suspension of copper(I) iodide (5.95 g, 31.2 mmol, 1.5 equiv) in Et_2O (75 mL) at −15 °C, under an argon atmosphere. The mixture was stirred for 1 h at −15 °C and a solution of **11** (5.00 g, 20.8 mmol, 96 % *ee*) in Et_2O (15 mL) was added dropwise. The reaction mixture was stirred for a further 1 h at −15 °C, HMPA (7.50 mL, 43.2 mmol, 2.1 equiv) was added dropwise under vigorous stirring, the mixture was slowly cooled to −78 °C, then TMEDA (5.30 mL, 35.4 mmol, 1.7 equiv) and TMSCl (3.10 mL, 31.2 mmol, 1.5 equiv) were added dropwise. The temperature of the solution was allowed to rise to RT, then the solution was poured into an aqueous ammonium hydroxide solution (300 mL) and extracted with a Et_2O/pentane (1:1) mixture. The organic layers were combined, washed with brine, dried, and evaporated to furnish **12** (6.70 g, 98 % yield) as a yellow oil. This compound was used in the next step without further purification. ^1H NMR (300 MHz, C_6D_6): δ = 4.73 (br s, 1H), 3.50 (dd, J = 9.7, 3.4 Hz, 1H), 2.13 (br t, J = 7.2 Hz, 2H), 1.82–1.58 (m, 2H), 1.11 (s, 3H), 1.05 (s, 3H), 0.99 (s, 9H), 0.20 (s, 9H), 0.05 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ = 148.9 (C), 114.4 (CH), 76.1 (CH), 37.4 (C), 30.0 (CH_3), 29.2 (CH_2), 28.6 (CH_2), 26.5 (3×CH_3), 24.8 (CH_3), 18.7 (C), 0.75 (3×CH_3), −3.7 (CH_3), −4.5 ppm (CH_3); IR (neat): $\tilde{\nu}$ = 3020, 1660, 1255, 834 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{37}O_2Si_2^+$: 329.2332 $[M+H]^+$; found: 329.2333.

(*R*)-3-(*tert*-Butyldimethylsilanyloxy)-2,2-dimethyl-6-oxocyclohexane carboxylic acid methyl ester (10): MeLi (1.6 M in Et_2O, 10.50 mL, 16.8 mmol, 1.1 equiv) was added to a stirred solution of **12** (5.00 g, 15.2 mmol) in Et_2O (40 mL) at −78 °C. The reaction mixture was stirred for a further 2 h at −78 °C, HMPA (3.95 mL, 22.8 mmol, 1.5 equiv) was added dropwise under vigorous stirring, then methyl cyanoformate (1.80 mL, 22.8 mmol, 1.5 equiv) was added. The temperature of the solution was allowed to rise to RT, then the solution was poured into water and extracted with Et_2O. The organic layers were combined, washed with brine, and dried with $MgSO_4$. Concentration and purification by flash chromatography gave **10** as a mixture of diastereoisomers (4.06 g, 85 % yield; *trans*/*cis*, 4:1) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 1H; M), 3.72 (s, 3H; M), 3.70 (s, 3H; m), 3.64 (t, J = 6.3 Hz, 1H; M), 3.43–3.38 (m, 1H; m), 3.18 (s, 1H; m), 2.70–2.55 (m, 1H; M+m), 2.40–2.30 (m, 1H; M+m), 2.16–2.02 (m, 1H; M+m), 1.93–1.81 (m, 1H; M+m), 1.11 (s, 3H; m), 1.08 (s, 3H; M), 1.04 (s, 3H; M), 1.01 (s, 3H; m), 0.94 (s, 9H; M), 0.90 (s, 9H; m), 0.11 (s, 6H; M), 0.06 ppm (s, 6H; m); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.3 (C, M), 205.2 (C, m), 169.3 (C, M), 168.5 (C, m), 75.4 (CH, m), 74.6 (CH, M), 64.5 (CH, m), 61.9 (CH, M), 51.6 (CH_3, m), 51.5 (CH_3, M), 43.6 (C, M), 43.0 (C, m), 37.7 (CH_2, m), 35.7 (CH_2, M), 30.0 (CH_2, m), 29.3 (CH_2, M), 26.5 (CH_3, m), 25.8 (3×CH_3, M), 25.7 (3×CH_3, m), 24.7 (CH_3, M), 22.6 (2×CH_3, M+m), 18.0 (C, M), 17.6 (C, m), −4.2 (CH_3, m), −4.3 (CH_3, m), −4.5 (CH_3, M), −4.9 ppm (CH_3, M); IR (neat): $\tilde{\nu}$ = 1766, 1722, 1262, 1130, 1086, 834 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{31}O_4Si^+$: 315.1992 $[M+H]^+$; found: 315.1994.

(*R*)-2-Acetoxy-5-(*tert*-butyldimethylsilanyloxy)-6,6-dimethylcyclohex-1-ene carboxylic acid methyl ester (13): Sodium hydride (2.31 g, 57.3 mmol, 3.0 equiv, 60 % dispersion in mineral oil) was added to an ice-cold stirred solution of β-ketoester **10** (6.01 g, 19.1 mmol) in THF (300 mL), under argon. The mixture was stirred at RT for 40 min and then acetic anhydride (4.50 mL, 47.7 mmol, 2.5 equiv) was added dropwise. After stirring for 18 h at RT, the mixture was poured into aqueous saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O, then the organic layers were combined, washed with H_2O, brine, and dried with $MgSO_4$. Concentration in vacuo and purification by column chromatography gave compound **13** (6.47 g, 95 % yield) as a yellow oil. $[\alpha]_D^{25} = -2.2$ (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 3H), 3.58 (br t, J = 6.3 Hz, 1H), 2.45–2.25 (m, 2H), 2.09 (s, 3H), 1.85–1.78 (m, 2H), 1.16 (s, 3H), 1.12 (s, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3 (C), 167.1 (C), 148.2 (C), 126.6 (C), 74.4 (CH), 51.3 (CH_3), 38.7 (C), 26.3 (CH_2), 25.8 (CH_3), 25.7 (3×CH_3), 25.3 (CH_2), 21.9 (CH_3), 20.6 (CH_3), 18.0 (C), −4.3 (CH_3), −5.0 ppm (CH_3); IR (neat): $\tilde{\nu}$ = 3024, 1768, 1613, 1125, 1083 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{33}O_5Si^+$: 357.2091 $[M+H]^+$; found: 357.2091.

(2*S*,4*R*)-4-(*tert*-Butyldimethylsilanyloxy)-2-hydroxymethyl-3,3-dimethylcyclohexanone (9) and *epi*-(2*R*,4*R*)-9: Freshly prepared AlH_3 (0.5 M in THF, 35.00 mL, 16.8 mmol, 6.0 equiv) was slowly added dropwise, under an argon atmosphere, to a stirred solution of enol acetate **13** (1.00 g, 2.8 mmol) in THF (50 mL) at −78 °C. The mixture was stirred for 3 h and temperature was allowed to slowly rise to −20 °C. The reaction was then quenched by the addition of MeOH (5 mL) and poured into an ice-cold mixture of H_2O/Et_2O (1:1, 1 L) containing Rochelle salt (100 g). The mixture was stirred for 3 h and the temperature was allowed to rise to RT. The aqueous layer was extracted with Et_2O, then the organic layers were combined, washed with H_2O, brine, and dried with $MgSO_4$. Concentration in vacuo and purification by column chromatography gave pure compound **9** (441 mg, 55 % yield) and *epi*-**9** (96 mg, 12 % yield) as colorless oils.

Compound 9: $[\alpha]_D^{25} = -20.6$ (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.01 (ddd, J = 11.7, 8.3, 3.8 Hz, 1H), 3.73 (dd, J = 9.8, 4.3 Hz, 1H), 3.66 (ddd, J = 11.7, 10.0, 3.3 Hz, 1H), 2.72 (dd, J = 10.0, 3.8 Hz, 1H), 2.50–2.32 (m, 3H), 2.06–1.99 (m, 1H), 1.89–1.79 (m, 1H), 1.06 (s, 3H), 0.92 (s, 9H), 0.81 (s, 3H), 0.12 (s, 3H), 0.11 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.4 (C), 75.6 (CH), 60.3 (CH), 59.0 (CH_2), 42.2 (C), 38.6 (CH_2), 30.3 (CH_2), 26.3 (CH_3), 25.8 (3×CH_3), 18.0 (C), 16.9 (CH_3), −4.2 (CH_3), −4.9 ppm (CH_3); IR (neat): $\tilde{\nu}$ = 3582, 1710, 1235, 1041 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{31}O_3Si^+$: 287.2037 $[M+H]^+$; found: 287.2037.

Compound *epi*-9: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.93$ (dd, $J=11.4$, 9.1 Hz, 1H), 3.59 (dd, $J=11.4$, 3.0 Hz, 1H), 3.44 (br s, 1H), 2.89 (dd, $J=$ 9.1, 3.0 Hz, 1H), 2.68 (dt, $J=13.6$, 7.1 Hz, 1H), 2.20–1.82 (m, 2H), 1.66–1.54 (m, 2H), 1.05 (s, 3H), 0.91 (s, 9H), 0.75 (s, 3H), 0.08 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=15.8$ (C), 75.9 (CH), 58.7 (CH), 55.8 (CH_2), 43.4 (C), 36.4 (CH_2), 29.7 (CH_2), 26.0 ($3\times CH_3$), 25.7 (CH_3), 22.7 (CH_3), 18.2 (C), −4.3 (CH_3), −4.8 ppm (CH_3); IR (neat): $\tilde{\nu}=3585$, 1708, 1237, 1035 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{31}O_3Si^+$: 287.2037 $[M+H]^+$; found: 287.2038.

(1*S*,2*S*,4*R*)-4-(*tert*-Butyldimethylsilanyloxy)-2-hydroxymethyl-1,3,3-trimethylcyclohexanol (14): Finely crushed cerium(III) chloride heptahydrate (10.15 g, 27.3 mmol, 6.0 equiv) was placed in a three-necked flask containing a stirring bar and evacuated (ca. 0.1 Torr). The apparatus was heated at 80 °C for 4 h, then the temperature was increased slowly to 140 °C and maintained for 5 h. The white solid was cooled to RT, the apparatus was blanketed with argon, THF (25 mL) was added, and the mixture was stirred for 12 h at RT. Methyllithium (1.6 M in Et_2O, 17.1 mL, 27.3 mmol, 6.0 equiv) was added dropwise at −78 °C to the resulting mixture. After 1 h at −78 °C, a solution of **9** (1.30 g, 4.6 mmol) in THF (10 mL) was added dropwise and the reaction mixture was allowed to rise to RT. After 18 h, the reaction mixture was diluted with Et_2O, poured in aqueous saturated NH_4Cl and extracted with Et_2O. The organic layers were combined, washed with H_2O, brine, and dried with $MgSO_4$. Concentration in vacuo and purification by column chromatography gave compound **14** (1.06 g, 76% yield) as a white powder. M.p. 103–104 °C; $[\alpha]_D^{25}=-9.0$ (*c* 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=4.16$–4.10 (m, 2H), 3.24 (dd, $J=11.2$, 3.9 Hz, 1H), 2.26 (br s, 2H), 1.99–1.81 (m, 1H), 1.70–1.62 (m, 1H), 1.55–1.41 (m, 2H), 1.35 (s, 3H), 1.15 (s, 3H), 1.01 (s, 3H), 1.01–0.96 (m, 1H; partially overlapped), 0.91 (s, 9H), 0.07 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=78.5$ (CH), 73.2 (C), 60.8 (CH_2), 52.6 (CH), 39.9 (C), 39.0 (CH_2), 30.5 (CH_3), 28.1 (CH_3), 27.2 (CH_2), 25.9 ($3\times CH_3$), 18.1 (C), 17.2 (CH_3), −3.9 (CH_3), −4.9 ppm (CH_3); IR (KBr): $\tilde{\nu}=3381$, 2921, 1227, 1036 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{35}O_3Si^+$: 303.2350 $[M+H]^+$; found: 303.2349.

(1*S*,2*S*,4*R*)-2-Hydroxymethyl-1,3,3-trimethylcyclohexane-1,4-diol (15): TBAF (1.0 M in THF, 0.58 mL, 0.58 mmol, 2.0 equiv) was added dropwise to an ice-cold solution of silyl ether **14** (88 mg, 0.29 mmol) in THF (5 mL), under argon. After stirring for 12 h at RT, the mixture was poured into water (5 mL), the aqueous layer was extracted with EtOAc, then the organic layers were combined, washed with water, brine, and dried with $MgSO_4$. Concentration in vacuo, purification by column chromatography, and recrystallization (Et_2O/hexane) afforded triol **15** (45 mg, 82% yield) as white crystals. M.p. 149–150 °C; ^{1}H NMR (300 MHz, CD_3OD): $\delta=3.94$ (br t, $J=3.5$ Hz, 2H), 3.15 (dd, $J=11.9$, 3.9 Hz, 1H), 1.93–1.79 (m, 1H), 1.65–1.58 (m, 1H), 1.52–1.43 (m, 2H), 1.25 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.98 ppm (t, $J=3.5$ Hz, 1H; partially overlapped); ^{13}C NMR (75 MHz, CD_3OD): $\delta=79.0$ (CH), 73.6 (C), 60.5 (CH_2), 55.0 (CH), 40.4 (C), 40.0 (CH_2), 30.7 (CH_3), 27.9 (CH_3), 27.7 (CH_2), 16.3 ppm (CH_3). IR (KBr): $\tilde{\nu}=3374$, 2925, 1505, 1224, 1019 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{21}O_3^+$: 189.1481 $[M+H]^+$; found: 189.1480.

(1*R*,3*R*,6*S*)-3-(*tert*-Butyldimethylsilanyloxy)-6-hydroxy-2,2,6-trimethylcyclohexane carbaldehyde (8): A catalytic amount of tetrapropylammonium perruthenate was added to a stirred solution of **14** (2.00 g, 6.6 mmol), *N*-methylmorpholine *N*-oxide (3.01 g, 26.4 mmol, 4.0 equiv) and powdered 4 Å molecular sieves in CH_2Cl_2 (150 mL) at RT under an argon atmosphere. After 45 min stirring at RT, the reaction mixture was filtered through a short pad of Celite, and the filtrate was poured into aqueous Na_2SO_3 solution. The aqueous layer was extracted with CH_2Cl_2, then the organic layers were combined, washed with H_2O, brine, and dried with $MgSO_4$. Concentration in vacuo and purification of the residue by silica gel column chromatography and recrystallization (Et_2O/hexane) afforded aldehyde **8** (1.61 g, 81% yield) as a white solid. M.p. 50–51 °C; $[\alpha]_D^{25}=+55.7$ (*c* 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=10.04$ (d, $J=$ 2.8 Hz, 1H), 3.31 (dd, $J=11.2$, 3.8 Hz, 1H), 2.81 (br s, 1H), 2.15 (d, $J=$ 2.8 Hz, 1H), 1.98–1.80 (m, 1H), 1.70 (dt, $J=14.1$, 3.8 Hz, 1H), 1.55–1.30 (m, 2H), 1.19 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=207.9$ (CH), 78.8 (CH), 70.7 (C), 64.4 (CH), 39.6 (C), 38.1 (CH_2), 30.6 (CH_3), 27.7 (CH_3), 27.0 (CH_2), 25.8 ($3\times CH_3$), 18.1 (C), 16.6 (CH_3), −4.0 (CH_3), −5.0 ppm (CH_3); IR (KBr): $\tilde{\nu}=3370$, 2731, 1716, 1014 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{33}O_3Si^+$: 301.2194 $[M+H]^+$; found: 301.2194.

4-[(1*R*,3*R*,6*S*)-3-(*tert*-Butyldimethylsilanyloxy)-6-hydroxy-2,2,6-trimethylcyclohexyl]-but-3-en-2-one (16): A mixture of diethyl 2-oxopropylphosphonate (3.80 mL, 20.0 mmol, 4.0 equiv) and $Ba(OH)_2{\cdot}8H_2O$ (2.50 g, 8.0 mmol, 1.6 equiv, heated at 140 °C for 2 h under a flux of argon before use) in THF (60 mL) was stirred at RT for 45 min under an argon atmosphere. A solution of **8** (1.50 g, 5.0 mmol) in wet THF (40 mL, 40:1 THF/H_2O) was added at this temperature. After stirring for 18 h at RT, the reaction mixture was diluted with Et_2O, washed with aqueous $NaHCO_3$, and brine. The organic extract was dried with $MgSO_4$, concentration in vacuo, purified by flash chromatography and recrystallized (Et_2O/hexane) to give **16** (1.50 g, 88%) as a white solid. M.p. 91–92 °C; $[\alpha]_D^{25}=+1.5$ (*c* 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=6.97$ (dd, $J=16.2$, 10.4 Hz, 1H), 6.03 (d, $J=16.2$ Hz, 1H), 3.27 (dd, $J=11.3$, 3.8 Hz, 1H), 2.32 (s, 3H), 1.95–1.70 (m, 2H), 1.73 (d, $J=10.4$ Hz, 1H), 1.60–1.45 (m, 2H), 1.35 (br s, 1H), 1.07 (s, 3H), 1.02 (s, 3H), 0.90 (s, 9H), 0.83 (s, 3H), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=198.7$ (C), 146.5 (CH), 135.0 (CH), 78.2 (CH), 71.1 (C), 58.1 (CH), 39.6 (C), 39.0 (CH_2), 31.2 (CH_3), 28.4 (CH_3), 27.0 (CH_2), 26.6 (CH_3), 25.8 ($3\times CH_3$), 18.0 (C), 15.6 (CH_3), −4.0 (CH_3), −5.0 ppm (CH_3); IR (KBr): $\tilde{\nu}=3352$, 3016, 1689, 1652, 1035 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{37}O_3Si^+$: 341.2507 $[M+H]^+$; found: 341.2506.

(4a*R*,6*R*,8a*S*)-*tert*-Butyldimethyl-(2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromen-6-yloxy)-silane (17): A catalytic amount of 10% palladium on activated charcoal was added to a stirred solution of **16** (26 mg, 0.08 mmol) in MeOH (5 mL). The mixture was stirred under a hydrogen atmosphere for 12 h, then the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography gave **17** (23 mg, 91% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=4.40$ (br d, $J=5.1$ Hz, 1H), 3.24 (dd, $J=11.3$, 3.5 Hz, 1H), 2.23–2.13 (m, 1H), 2.01–1.93 (m, 1H), 1.91–1.77 (m, 2H), 1.65 (br s, 3H), 1.52–1.37 (m, 2H), 1.14 (t, $J=4.1$ Hz, 1H; partially overlapped), 1.14 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.80 (s, 3H), 0.04 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 148.8 (C), 94.9 (CH), 79.2 (CH), 74.1 (C), 43.9 (CH), 40.1 (C), 37.6 (CH_2), 28.1 (CH_3), 27.1 (CH_2), 26.4 (CH_3), 26.1 ($3\times CH_3$), 20.6 (CH_3), 19.9 (CH_2), 18.3 (C), 14.4 (CH_3), −3.7 (CH_3), −4.7 ppm (CH_3); IR (neat): $\tilde{\nu}=3019$, 2925, 1246, 1019 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{37}O_2Si^+$: 325.2563 $[M+H]^+$; found: 325.2565.

4-[(1*S*,3*R*,6*S*)-3,6-Bis-(*tert*-butyldimethylsilanyloxy)-2,2,6-trimethylcyclohexyl]-but-3-en-2-one (18): 2,6-Lutidine (5.10 mL, 44.1 mmol, 10.0 equiv) followed by TBSOTf (5.10 mL, 22.0 mmol, 5.0 equiv) were added to a stirred solution of **16** (1.50 g, 4.4 mmol) in CH_2Cl_2 (60 mL) at −20 °C. The mixture was stirred at RT for 18 h, then diluted with CH_2Cl_2 (60 mL) and stirred with 1 M HCl (60 mL) for 1 h. After extraction with CH_2Cl_2, the organic layer was washed with water, brine, dried with $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by column chromatography and recrystallization (Et_2O/hexane) gave **18** (1.78 g, 89% yield) as a white solid. M.p. 88–89 °C; $[\alpha]_D^{25}=+21.7$ (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.00$ (dd, $J=16.5$, 10.3 Hz, 1H), 5.97 (d, $J=16.5$ Hz, 1H), 3.24 (dd, $J=11.3$, 3.8 Hz, 1H), 2.30 (s, 3H), 1.95–1.75 (m, 2H), 1.64 (d, $J=10.3$ Hz, 1H), 1.50–1.35 (m, 2H), 1.10 (s, 3H), 1.01 (s, 3H), 0.94 (s, 9H), 0.90 (s, 9H), 0.80 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=198.7$ (C), 147.9 (CH), 134.8 (CH), 78.5 (CH), 74.3 (C), 60.2 (CH), 39.5 (C), 39.0 (CH_2), 31.0 (CH_3), 28.2 (CH_3), 27.2 (CH_2), 26.0 (CH_3), 26.0 ($3\times CH_3$), 25.9 ($3\times CH_3$), 18.4 (C), 18.1 (C), 15.6 (CH_3), −1.7 (CH_3), −2.1 (CH_3), −3.9 (CH_3), −4.9 ppm (CH_3); IR (KBr): $\tilde{\nu}=3027$, 1676, 1637, 1250, 853 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{25}H_{50}O_3Si_2Na^+$: 477.3191 $[M+Na]^+$; found: 477.3191.

4-[(1*R*,3*R*,6*S*)-3,6-Bis-(*tert*-butyldimethylsilanyloxy)-2,2,6-trimethylcyclohexyl]-butan-2-one (7): A catalytic amount of 10% palladium on activated charcoal was added to a stirred solution of **18** (1.50 g, 3.3 mmol) in ethyl acetate (70 mL). The mixture was stirred under a hydrogen atmosphere for 3 h, then the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by

column chromatography gave **7** (1.32 g, 87%) as a colorless oil. $[\alpha]_D^{25} = -4.5$ (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.18$ (dd, $J = 11.5$, 3.8 Hz, 1H), 2.55–2.35 (m, 2H), 2.15 (s, 3H), 1.90–1.55 (m, 4H), 1.45–1.35 (m, 2H), 1.18 (s, 3H), 0.91 (s, 3H), 0.90 (s, 18H), 0.86 (s, 3H), 0.70 (dd, $J = 4.3$, 3.0 Hz, 1H), 0.11 (s, 6H), 0.04 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 208.9$ (C), 79.1 (CH), 75.6 (C), 55.2 (CH), 47.5 (CH_2), 40.8 (C), 39.0 (CH_2), 30.5 (CH_3), 29.6 (CH_3), 27.6 (CH_3), 27.3 (CH_2), 26.0 ($3\times CH_3$), 25.9 ($3\times CH_3$), 20.2 (CH_2), 18.5 (C), 18.1 (C), 15.2 (CH_3), −1.7 (CH_3), −2.0 (CH_3), −3.9 (CH_3), −4.9 (CH_3); IR (neat): $\tilde{\nu} = 2920$, 1789, 1243, 1029 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{25}H_{52}O_3Si_2Na^+$: 479.3347 $[M+Na]^+$; found: 479.3348.

Acetic acid 1-{2-[(1*R*,3*R*,6*S*)-3,6-bis-(*tert*-butyldimethylsilanyloxy)-2,2,6-trimethyl-cyclohexyl]-ethyl}-1-methylallyl ester (19): Vinylmagnesium bromide (1 M in THF, 3.90 mL, 3.9 mmol, 1.8 equiv) was added dropwise to a stirred solution of **7** (1.00 g, 2.2 mmol) in THF (50 mL) at −20 °C under an argon atmosphere. The mixture was stirred at −20 °C for 15 min, allowed to warm to 0 °C and the reaction was quenched by addition of 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 as a colorless oil, which was used for the next step without further purification. The solution of allylic alcohols in THF (50 mL) was treated with Et_3N (4.60 mL, 32.8 mmol, 15.0 equiv), DMAP (53 mg, 0.4 mmol, 0.2 equiv), and Ac_2O (3.10 mL, 32.8 mmol, 15.0 equiv), and heated to reflux for 2 days. After cooling to RT, the reaction mixture was diluted with Et_2O, washed with aqueous $NaHCO_3$, and brine, and dried. Concentration and purification by flash chromatography gave an inseparable 60:40 mixture of diastereoisomers **19** (916 mg, 79% yield from 7) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.02$–5.94 (m, 1H; m+M), 5.19–5.11 (m, 2H; m+M), 3.17 (m, 1H; m+M), 2.02 (s, 3H; m+M), 1.90–1.60 (m, 4H; m+M), 1.56 (s, 3H; m), 1.55 (s, 3H; M), 1.45–1.25 (m, 4H; m+M), 1.16 (s, 3H; m+M), 0.90 (s, 9H; m+M), 0.89 (s, 9H; m+M), 0.88 (s, 3H; m+M), 0.84 (s, 3H; m+M), 0.64 (dd, $J = 6.7$, 2.9 Hz, 1H; m+M), 0.10 (s, 6H; m+M), 0.04 (s, 3H; m+M), 0.03 ppm (s, 3H; m+M); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.9$ (C, m+M), 142.1 (CH, m), 141.9 (CH, M), 113.1 (CH_2, M), 113.0 (CH_2, m), 83.3 (C, M), 83.2 (C, m), 79.2 (CH, m+M), 75.8 (C, m+M), 55.4 (CH, m+M), 43.5 (CH_2, M), 43.3 (CH_2, m), 41.0 (C, m+M), 39.1 (CH_2, m+M), 30.4 (CH_3, m+M), 27.5 (CH_3, m+M), 27.4 (CH_2, m+M), 26.0 ($3\times CH_3$, M+m), 25.9 ($3\times CH_3$, M+m), 23.6 (CH_3, m+M), 22.2 (CH_3, m+M), 19.7 (CH_2, m+M), 18.5 (C, m+M), 18.1 (C, m+M), 15.3 (CH_3, m+M), −1.7 (CH_3, m+M), −2.0 (CH_3, m+M), −3.9 (CH_3, m+M), −4.9 ppm (CH_3, m+M); IR (neat): $\tilde{\nu} = 3037$, 1771, 1652, 1250, 1023 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{29}H_{62}NO_4Si_2^+$: 544.4212 $[M+NH_4]^+$; found: 544.4212.

(*E*)- and (*Z*)-Acetic acid 5-[(1*R*,3*R*,6*S*)-3,6-bis-(*tert*-butyldimethylsilanyloxy)-2,2,6-trimethylcyclohexyl]-3-methylpent-2-enyl ester (*E*)-6 and (*Z*)-6: A catalytic amount of dichlorobis(acetonitrile)palladium(II) was added to a stirred solution of **19** (900 mg, 1.71 mmol) in THF (50 mL) at RT under an argon atmosphere. After stirring for 5 h at RT, the solution mixture was filtered through a short pad of silica gel, washed with Et_2O, and concentrated to give a yellow oil, which was purified by flash chromatography to give pure *E*-diastereoisomer (*E*)-**6** (720 mg, 80% yield) and pure Z-diastereoisomer (*Z*)-**6** (107 mg, 12% yield) as a colorless oil.

Compound (*E*)-6: $[\alpha]_D^{25} = +2.3$ (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.35$ (brt, $J = 7.0$ Hz, 1H), 4.60 (d, $J = 7.0$ Hz, 2H), 3.18 (dd, $J = 11.5$, 3.5 Hz, 1H), 2.12–1.98 (m, 2H; partially overlapped), 2.07 (s, 3H), 1.84–1.63 (m, 3H; partially overlapped), 1.74 (brs, 3H), 1.44–1.34 (m, 3H), 1.18 (s, 3H), 0.90 (s, 9H), 0.89 (s, 12H), 0.86 (s, 3H), 0.69 (dd, $J = 3.9$, 2.9 Hz, 1H), 0.10 (s, 6H), 0.04 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.1$ (C), 143.1 (C), 118.0 (CH), 79.3 (CH), 75.8 (C), 61.4 (CH_2), 55.3 (CH), 43.3 (CH_2), 40.8 (C), 39.1 (CH_2), 30.5 (CH_3), 27.6 (CH_3), 27.4 (CH_2), 26.0 ($3\times CH_3$), 25.9 ($3\times CH_3$), 24.6 (CH_2), 21.0 (CH_3), 18.5 (C), 18.1 (C), 16.5 (CH_3), 15.3 (CH_3), −1.7 (CH_3), −2.0 (CH_3), −3.9 (CH_3), −4.9 ppm (CH_3). IR (neat): $\tilde{\nu} = 3051$, 1764, 1646, 1243, 1020 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{29}H_{58}O_4Si_2Na^+$: 549.3766 $[M+Na]^+$; found: 549.3766.

Compound (*Z*)-6: $[\alpha]_D^{25} = -4.8$ (*c* 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.34$ (brt, $J = 7.1$ Hz, 1H), 4.56 (brd, $J = 7.4$ Hz, 2H), 3.18 (dd, $J = 11.4$, 3.6 Hz, 1H), 2.14–1.98 (m, 2H; partially overlapped), 2.00 (s, 3H), 1.80 (brs, 3H), 1.77–1.58 (m, 3H), 1.42–1.26 (m, 3H), 1.21 (s, 3H), 0.89 (s, 12H), 0.88 (s, 12H), 0.70 (brt, $J = 3.2$ Hz, 1H), 0.10 (s, 6H), 0.04 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.2$ (C), 144.0 (C), 118.6 (CH), 79.4 (CH), 75.8 (C), 61.2 (CH_2), 56.0 (CH), 40.9 (C), 39.2 (CH_2), 36.1 (CH_2), 30.6 (CH_3), 27.7 (CH_3), 27.6 (CH_2), 26.2 ($3\times CH_3$), 26.1 ($3\times CH_3$), 25.2 (CH_2), 23.8 (CH_3), 21.2 (CH_3), 18.7 (C), 18.3 (C), 15.4 (CH_3), −1.5 (CH_3), −1.9 (CH_3), −3.7 (CH_3), −4.7 ppm (CH_3); IR (neat): $\tilde{\nu} = 3077$, 1766, 1641, 1246, 1028 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{29}H_{58}O_4Si_2Na^+$: 549.3766 $[M+Na]^+$; found: 549.3766.

5-[(1*R*,3*R*,6*S*)-3,6-Bis-(*tert*-butyldimethylsilanyloxy)-2,2,6-trimethylcyclohexyl]-3-methylpent-2-en-1-ol (20): A solution of (*E*)-**6** (700 mg, 1.33 mmol) in MeOH (50 mL) at 0 °C was treated with K_2CO_3 (367 mg, 2.66 mmol, 2.0 equiv) and stirred for 2 h. The mixture was concentrated, diluted with Et_2O, filtered, and concentrated in vacuo. Purification by flash chromatography and recrystallization (Et_2O/hexane) gave **20** (529 mg, 82% yield) as a white solid. M.p. 56–57 °C; $[\alpha]_D^{25} = +1.4$ (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.43$ (brt, $J = 6.6$ Hz, 1H), 4.17 (t, $J = 6.6$ Hz, 2H), 3.19 (dd, $J = 11.3$, 3.5 Hz, 1H), 2.10–1.97 (m, 2H), 1.84–1.63 (m, 3H; partially overlapped), 1.71 (brs, 3H), 1.44–1.34 (m, 3H), 1.19 (s, 3H), 0.90 (s, 9H), 0.89 (s, 12H), 0.86 (s, 3H), 0.70 (brt, $J = 3.5$ Hz, 1H), 0.10 (s, 6H), 0.04 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 140.6$ (C), 123.0 (CH), 79.3 (CH), 75.8 (C), 59.4 (CH_2), 55.3 (CH), 43.4 (CH_2), 40.8 (C), 39.1 (CH_2), 30.4 (CH_3), 27.6 (CH_3), 27.4 (CH_2), 26.0 ($3\times CH_3$), 25.9 ($3\times CH_3$), 24.7 (CH_2), 18.5 (C), 18.1 (C), 16.3 (CH_3), 15.3 (CH_3), −1.6 (CH_3), −2.0 (CH_3), −3.9 (CH_3), −4.9 ppm (CH_3); IR (KBr): $\tilde{\nu} = 3521$, 3077, 1646, 1250, 1016 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{27}H_{56}O_3Si_2Na^+$: 507.3660 $[M+Na]^+$; found: 507.3661.

7-{5-[(1*R*,3*R*,6*S*)-3,6-Bis-(*tert*-butyldimethylsilanyloxy)-2,2,6-trimethylcyclohexyl]-3-methyl-pent-2-enyloxy}-chromen-2-one (21): Phosphorous tribromide (49 μL, 0.52 mmol, 0.50 equiv) and pyridine (33 μL, 0.41 mmol, 0.4 equiv) in CH_2Cl_2 (1 mL) were added to an ice-cold solution of **20** (500 mg, 1.03 mmol) in Et_2O (13 mL). The reaction was stirred for 1 h at this temperature, then the mixture was diluted with Et_2O, and washed with aqueous $NaHCO_3$. The organic layer was dried and concentrated to give the crude bromide as a yellow oil, which was directly used for the next step without further purification. The above bromide was diluted in acetone (4 mL) and added to an ice-cold mixture of 7-hydroxycoumarin (234 mg, 1.44 mmol, 1.4 equiv) and K_2CO_3 (656 mg, 4.74 mmol, 4.6 equiv) in acetone (8 mL). The reaction was stirred for 48 h at RT, then the mixture was concentrated, diluted with EtOAc, and washed with H_2O. The organic layer was dried and concentrated. Purification by flash chromatography gave **21** (453 mg, 70% yield from **20**) as a yellowish oil. $[\alpha]_D^{25} = +3.7$ (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.64$ (d, $J = 9.5$ Hz, 1H), 7.37 (d, $J = 8.5$ Hz, 1H), 6.88–6.84 (m, 2H), 6.26 (d, $J = 9.5$ Hz, 1H), 5.48 (brt, $J = 6.3$ Hz, 1H), 4.62 (d, $J = 6.3$ Hz, 2H), 3.19 (dd, $J = 11.6$, 3.5 Hz, 1H), 2.17–2.01 (m, 2H), 1.80 (brs, 3H),1.79–1.62 (m, 3H), 1.45–1.34 (m, 3H), 1.19 (s, 3H), 0.90 (s, 9H), 0.89 (s, 3H), 0.88 (s, 9H), 0.87 (s, 3H), 0.71 (brt, $J = 3.5$ Hz, 1H), 0.10 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.1$ (C), 161.2 (C), 155.9 (C), 143.4 (CH), 143.2 (C), 128.6 (CH), 118.1 (CH), 113.2 (CH), 112.9 (CH), 112.4 (C), 101.6 (CH), 79.2 (CH), 75.7 (C), 65.5 (CH_2), 55.3 (CH), 43.3 (CH_2), 40.8 (C), 39.1 (CH_2), 30.5 (CH_3), 27.6 (CH_3), 27.4 (CH_2), 26.0 ($3\times CH_3$), 25.9 ($3\times CH_3$), 24.6 (CH_2), 18.5 (C), 18.1 (C), 16.8 (CH_3), 15.3 (CH_3), −1.7 (CH_3), −2.0 (CH_3), −3.9 (CH_3), −4.9 ppm (CH_3); IR (neat): $\tilde{\nu} = 3070$, 1754, 1621, 1132 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{36}H_{64}NO_5Si_2^+$: 646.4318 $[M+NH_4]^+$; found: 646.4315.

7-{5-[(1*R*,3*R*,6*S*)-6-(*tert*-Butyldimethylsilanyloxy)-3-hydroxy-2,2,6-trimethylcyclohexyl]-3-methyl-pent-2-enyloxy}-chromen-2-one (22): In a Teflon round-bottomed flask, HF·pyridine complex (70 wt.% HF, 0.20 mL, 7.95 mmol, 50.0 equiv) was carefully added to an ice-cold solution of silyl ether **21** (100 mg, 0.16 mmol) in THF (4 mL) under an argon atmosphere and the mixture was heated at 40 °C for 24 h. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution, then the aqueous layer was extracted with Et_2O, and the combined organic layers were washed with saturated aqueous $NaHCO_3$, water, brine, dried over

$MgSO_4$, and concentrated. After purification by column chromatography, alcohol **22** (65 mg, 79% yield) was obtained as a yellowish foam. $[\alpha]_D^{25} = +8.1$ (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.64$ (d, $J = 9.4$ Hz, 1H), 7.37 (d, $J = 8.4$ Hz, 1H), 6.86 (dd, $J = 8.4$, 2.4 Hz, 1H), 6.84 (d, $J = 2.4$ Hz, 1H), 6.25 (d, $J = 9.4$ Hz, 1H), 5.48 (brt, $J = 6.3$ Hz, 1H), 4.62 (d, $J = 6.3$ Hz, 2H), 3.23 (dd, $J = 11.4$, 3.9 Hz, 1H), 2.18–2.04 (m, 2H), 1.80 (brs, 3H), 1.79–1.62 (m, 3H), 1.60–1.34 (m, 3H), 1.20 (s, 3H), 0.96 (s, 3H), 0.92 (s, 3H), 0.87 (s, 9H), 0.74 (dd, $J = 4.3$, 2.5 Hz, 1H), 0.10 (s, 3H), 0.09 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.1$ (C), 161.3 (C), 155.9 (C), 143.4 (CH), 143.0 (C), 128.7 (CH), 118.2 (CH), 113.2 (CH), 112.9 (CH), 112.4 (C), 101.6 (CH), 78.7 (CH), 75.8 (C), 65.4 (CH_2), 55.1 (CH), 43.2 (CH_2), 40.2 (C), 39.1 (CH_2), 30.3 (CH_3), 27.0 (CH_2), 26.9 (CH_3), 26.0 ($3\times CH_3$), 24.5 (CH_2), 18.5 (C), 16.8 (CH_3), 15.0 (CH_3), −1.7 (CH_3), −2.0 ppm (CH_3); IR (KBr): $\tilde{\nu} = 3464$, 3035, 1729, 1624, 1137, 890 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{30}H_{46}O_5SiNa^+$: 537.3007 $[M+Na]^+$; found: 537.3007.

7-{5-[(1*R*,3*R*,6*S*)-3,6-Dihydroxy-2,2,6-trimethylcyclohexyl]-3-methylpent-2-enyloxy}-chromen-2-one (1) by deprotection of 22: In a Teflon round-bottomed flask, KF (9 mg, 0.16 mmol, 4.0 equiv) and 18-crown-6 (42 mg, 0.16 mmol, 4.0 equiv) were carefully added to a stirred solution of silyl ether **22** (20 mg, 0.039 mmol, 1 equiv) in anhydrous DMSO (10 mL) under an argon atmosphere, and the mixture was heated at 125 °C for 3 days. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution, then the aqueous layer was extracted with EtOAc, and the combined organic layers were washed with saturated aqueous $NaHCO_3$, water, brine, dried over $MgSO_4$, and concentrated. After purification by column chromatography, **1** (8.1 mg, 52% yield) was obtained as a yellowish foam. $[\alpha]_D^{25} = +7$ (*c* 1.0 in EtOH); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.64$ (d, $J = 9.4$ Hz, 1H; H-C_{16}), 7.36 (d, $J = 8.5$ Hz, 1H; H-C_{14}), 6.86 (dd, $J = 8.5$, 2.3 Hz, 1H; H-C_{13}), 6.84 (d, $J = 2.3$ Hz, 1H; H-C_{20}), 6.25 (d, $J = 9.4$ Hz, 1H; H-C_{17}), 5.50 (brt, $J = 6.5$ Hz, 1H; H-C_{10}), 4.60 (d, $J = 6.5$ Hz, 2H; H-C_{11}), 3.26 (dd, $J = 11.8$, 3.9 Hz, 1H; H-C_3), 2.17 (td, $J = 12.7$, 5.2 Hz, 1H; H-C_8), 2.10 (td, $J = 12.7$, 5.8 Hz, 1H; H-C_8), 1.81 (brs, 3H; CH_3-C_9), 1.81 (qd, $J = 11.8$, 3.9 Hz, 1H; partially overlapped, H_{ax}-C_4), 1.69 (dt, $J = 13.9$, 3.9 Hz, 1H; H_{eq}-C_5), 1.62 (m, 2H; H-C_7 and H_{eq}-C_4), 1.53 (td, $J = 13.9$, 3.9 Hz, 1H; H_{ax}-C_5), 1.51–1.44 (m, 1H; H-C_7), 1.19 (s, 3H; CH_3-C_6), 1.01 (s, 3H; CH_{3eq}-C_2), 0.95 (s, 3H; CH_{3ax}-C_2), 0.86 ppm (brt, $J = 2.8$ Hz, 1H; H-C_1); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 162.3 (C-12), 161.4 (C-18), 156.0 (C-19), 143.6 (CH-16), 142.7 (C-9), 128.9 (CH-14), 118.6 (CH-10), 113.4 (CH-13), 113.2 (CH-17), 112.6 (C-15), 101.7 (CH-20), 78.6 (CH-3), 72.6 (C-6), 65.6 (CH_2-11), 53.2 (CH-1), 43.3 (CH_2-8), 40.5 (C-2), 39.2 (CH_2-5), 30.7 (CH_3-C-6), 27.1 (CH_{3eq}-C-2), 27.0 (CH_2-4), 24.2 (CH_2-7) 17.1 (CH_3-C-9), 14.8 ppm (CH_{3ax}-C-2); IR (neat): $\tilde{\nu} = 3461$, 2923, 1718, 1628, 1141, 892 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{33}O_5^+$: 401.2323 $[M+H]^+$; found: 401.2319.

Synthesis of 1 by reduction of ketone 3: $NaBH_4$ (5.6 mg, 0.15 mmol, 3 equiv) was added to a stirred solution of ketone **3** (20 mg, 0.050 mmol) in MeOH (10 mL) at −78 °C under an argon atmosphere. The reaction mixture was stirred for an additional 30 min before being concentrated under reduced pressure to provide a residue that was partitioned between water and Et_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. After purification by column chromatography, pure alcohol **1** (17.2 mg, 86%) was obtained as a yellowish foam. Physical data were identical to those described above.

7-{5-[(1*R*,6*S*)-6-Hydroxy-2,2,6-trimethyl-3-oxocyclohexyl]-3-methylpent-2-enyloxy}-chromen-2-one (3): A catalytic amount of tetrapropylammonium perruthenate was added to an ice-cold solution of **1** (30 mg, 0.07 mmol), *N*-methylmorpholine *N*-oxide (33 mg, 0.28 mmol, 4.0 equiv), and powdered 4 Å molecular sieves in CH_2Cl_2 (5 mL) under an argon atmosphere. After 40 min stirring at 0 °C, the reaction mixture was filtered through a short pad of Celite, and the filtrate was poured into aqueous Na_2SO_3 solution. The aqueous layer was extracted with CH_2Cl_2, 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 and recrystallization (Et_2O/hexane) afforded kopeolone **3** (26 mg, 87% yield) as white crystals. M.p. 105–106 °C; $[\alpha]_D^{25} = +32.0$ (*c* 0.8 in EtOH); ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.64 (d, $J = 9.3$ Hz, 1H; H-C_{16}), 7.37 (d, $J = 8.5$ Hz, 1H; H-C_{14}), 6.85 (dd, $J = 8.5$, 2.2 Hz, 1H; H-C_{13}), 6.82 (d, $J = 2.2$ Hz, 1H; H-C_{20}), 6.25 (d, $J = 9.3$ Hz, 1H; H-C_{17}), 5.51 (brt, $J = 6.5$, 1H; H-C_{10}), 4.60 (d, $J = 6.5$ Hz, 2H; H-C_{11}), 3.07 (td, $J = 14.2$, 5.8 Hz, 1H; H_{ax}-C_4), 2.19–2.14 (m, 2H; H_{eq}-C_4 and H-C_8), 2.09 (td, $J = 12.1$, 5.1 Hz, 1H; H-C_8), 1.97 (ddd, $J = 14.2$, 5.8, 2.8 Hz, 1H; H_{eq}-C_5), 1.82 (td, $J = 14.2$, 4.3 Hz, 1H; H_{ax}-C_5, partially overlapped), 1.80 (brs, 3H, CH_3-C_9), 1.75 (ddt, $J = 14.6$, 11.5, 5.1 Hz, 1H; H-C_7), 1.54 (dddd, $J = 14.6$, 12.1, 5.6, 2.6 Hz, 1H; H-C_7), 1.29 (s, 3H; CH_3-C_6), 1.26 (dd, $J = 5.1$, 2.6 Hz, 1H; H-C_1), 1.23 (s, 3H; CH_{3ax}-C_2), 1.04 ppm (s, 3H; CH_{3eq}-C_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 215.$ 9 (C-3), 162.1 (C-12), 161.2 (C-18), 155.9 (C-19), 143.4 (CH-16), 142.6 (C-9), 128.7 (CH-14), 118.8 (CH-10), 113.2 (CH-13), 113.0 (CH-17), 112.5 (C-15), 101.6 (CH-20), 72.2 (C-6), 65.4 (CH_2-11), 54.3 (CH-1), 49.0 (C-2), 42.5 (CH_2-8), 40.5 (CH_2-5), 34.0 (CH_2-4), 30.1 (CH_3-C-6), 24.3 (CH_2-7), 23.6 (CH_{3eq}-C-2), 22.0 (CH_{3ax}-C-2), 16.9 ppm (CH_3-C-9); IR (KBr): $\tilde{\nu} = 3475$, 2910, 1730, 1705, 1603, 1128, 890 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{31}O_5^+$: 399.2166 $[M+H]^+$; found: 399.2166.

Calculations: All calculations were performed with the Gaussian 09, revision C01, suites of program.[20] Structures of the compounds were calculated at the B3LYP[21] level using the 6-311G++(d,p) basis set.

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