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Biomimetic Transformation of *p*-Menthene Glucosides into *p*-Cymenes and Carvotanacetone

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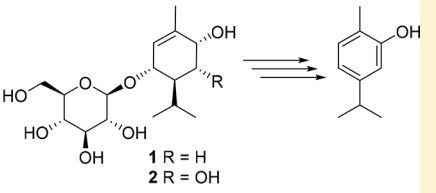
Supporting Information

ABSTRACT: A biomimetic transformation of *p*-menthene glucosides into aromatic monoterpenoids that alluded to mechanisms for essential oil metabolism, which lines up with the precepts of molecular economy, is described. Acid treatment of (−)-(3*S*,4*S*,6*R*)-3,6-dihydroxy-1-menthene 3-*O*-*β*-D-glucopyranoside (**1**) and (−)-(3*S*,4*R*,5*R*,6*S*)-3,5,6-trihydroxy-1-menthene 3-*O*-*β*-D-glucopyranoside (**2**), from *Ageratina glabrata*, yielded *p*-cymene (**7**) and carvacrol (**9**). The stable oxidized intermediates (+)-(3*S*,4*S*,6*R*)-3,6-dihydroxy-1-menthene (**3**), (+)-(1*S*,4*S*,6*R*)-1,6-dihydroxy-2-menthene (**4**), (+)-(1*R*,4*S*,6*R*)-1,6-dihydroxy-2-menthene (**5**), (+)-(4*S*,6*R*)-yabunikkeol (**6**), (+)-(4*S*)-carvotanacetone (**8**), (+)-(1*S*,4*S*,5*R*,6*R*)-1,5,6-trihydroxy-2-menthene (**15**), (+)-(1*R*,4*S*,5*R*,6*R*)-1,5,6-trihydroxy-2-menthene (**16**), and the new (+)-(4*S*,5*R*,6*S*)-1(7),2-menthadiene (**17**) permitted establishment of the reaction mechanisms. The reactivity of the hydroxy groups of **4** and **5**, as well as those of **15** and **16**, was compared by acetylation reactions and supported by DFT calculations, revealing diminished reactivity in **4** and **15** due to the *cis* configuration of their hydroxy groups at C-1 and C-6. In addition, *p*-cymene (**7**) was detected as one of the major constituents of the essential oil of *A. glabrata*, which matches well with the biomimetic study.

Ageratina glabrata



The biosynthetic pathway of *p*-menthenes assumes the isomerization of geranyl diphosphate to neryl diphosphate, followed by cyclization through an allylic cation−diphosphate ion-pair to afford an *α*-terpinyl cation, which is an intermediate in the formation of several mono- and bicyclic monoterpenes.[1] Oxidation, isomerization, transposition, and other reactions lead to an extensive variety of monoterpenes, of which many are found in essential oils. The biosynthetic pathway of aromatic monoterpenes is closely related to *γ*-terpinene,[2] limonene, menthene, and carvone through dehydrogenation reactions,[3] while the storage of volatile compounds in plants proceeds through nonvolatile glycosides, which after enzymatic glycolysis liberate the volatile aglycone and the sugar residue.[4−7] Nonetheless, due to the molecular economy observed in cell metabolic processes, we can visualize the relationship between the storage of volatile compounds and the presence of a few strategic precursors capable of providing essential oil constituents. Therefore, the understanding of anabolic and catabolic mechanisms, related to volatile compounds, becomes relevant to the biosynthetic pathways of these metabolites for subsequent chemical, biological, biotechnological, and industrial applications.[8]

Previously we described the absolute configuration determination of (−)-(3*S*,4*S*,6*R*)-3,6-dihydroxy-1-menthene 3-*O*-*β*-D-glucopyranoside (**1**) and (−)-(3*S*,4*R*,5*R*,6*S*)-3,5,6-trihydroxy-1-menthene 3-*O*-*β*-D-glucopyranoside (**2**), from *Ageratina glabrata*, and their derivatives (+)-(3*S*,4*S*,6*R*)-3,6-dihydroxy-1-menthene (**3**), (+)-(1*S*,4*S*,6*R*)-1,6-dihydroxy-2-menthene (**4**), (+)-(1*R*,4*S*,6*R*)-1,6-dihydroxy-2-menthene (**5**), (+)-(1*S*,4*S*,5*R*,6*R*)-1,5,6-trihydroxy-2-menthene (**15**), and (+)-(1*R*,4*S*,5*R*,6*R*)-1,5,6-trihydroxy-2-menthene (**16**), obtained by acid hydrolysis.[9]

In this paper the biomimetic transformations of **1** and **2** into aromatic monoterpene derivatives and other essential oil constituents, by dehydration and oxidation processes, are described. Dihydroxy-*p*-menthene derivatives **3**−**5**, (+)-(4*S*,6*R*)-yabunikkeol (**6**), 1,5,6-triols **15** and **16**, and the new (+)-(4*S*,5*R*,6*S*)-1(7),2-menthadiene (**17**), as reaction intermediates in the formation of *p*-cymene (**7**) and carvacrol

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(**9**), were suggested. (+)-(4*S*)-Carvotanacetone (**8**) was also observed as a dehydration product of **4** and **5**, while oxidation with iodine suggested that *p*-cymene (**7**) and carvacrol (**9**) could arise from a common precursor, **4**. The reactivity of the tertiary hydroxy group of **4**, **5**, **15**, and **16** was studied through the preparation of their respective acetyl derivatives **10**−**13** and **18**−**21**, determining that the *trans*-1,6-diol disposition found in **5** and **16** was more reactive than the *cis* arrangement found in **4** and **15** and that the steric effects of the isopropyl group are insignificant, while fewer hydroxy group intramolecular interactions favor reactivity. All compounds were characterized by physical and spectroscopic data, while GC-MS analysis of the essential oil of the aerial parts from *A. glabrata* revealed *p*-cymene (**7**) as a main constituent,[10] supporting the herein proposed chemical pathways.

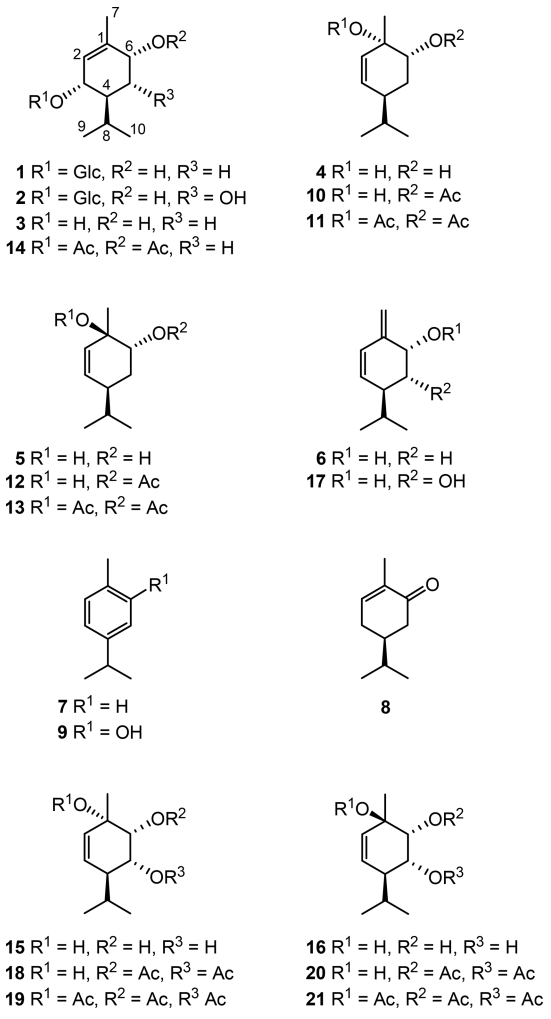

Figure 1. Formulas of *p*-Menthenes **1**−**21**.

RESULTS AND DISCUSSION

Menthene glucosides **1** and **2** were individually hydrolyzed using diluted HCl to generate hydroxy-*p*-menthenes **3**−**5** from **1**, and **15** and **16** from **2**.[9] Considering **4**, **5**, **15**, and **16** arise from H_2O trapping an allylic carbocation, induced by elimination at C-3 in **2** or **3**, these molecules were considered as possible essential oil constituent intermediates. Such an idea is in accord with several investigations where glycosides function as a storage mechanism for volatile compounds.[4−7] Carbocation formation was induced by acid hydrolysis in a polar protic medium. Dehydration of *p*-menthene **4** and/or **5** using 10% HCl yielded a mixture of (+)-yabunikkeol (**6**), *p*-cymene (**7**), and (+)-(4*S*)-carvotanacetone (**8**) in a 1:4:10 ratio, establishing **8** as the most favored isomer. Furthermore, acid hydrolysis of **6**, under the same reaction conditions used for **4** or **5**, afforded *p*-cymene (**7**), suggesting that **6** is a subsequent intermediate in the aromatization process from glucoside **1** to **7**. Thus, (Scheme 1), acid hydrolysis of **1** provides *p*-menthene **3**[9] as the first intermediate, followed by protonation of the C-3 hydroxy group and subsequent dehydration to give allylic carbocation **I**, which is quenched by addition of water at C-1, yielding **4** and **5** as the next diol intermediates. Based on steric considerations a less probable route for generating **4** and **5** would involve an allylic alcohol exchange via hydroxylation at C-1 of **3**. Activation of **4** or **5** via protonation at the tertiary hydroxy group favors dehydration at C-1 by proton loss from CH_3-7 to give **6**. Finally, loss of the C-5 protonated hydroxy group from **6** to give **II** (path a) and subsequent deprotonation at C-5 provides triene **III**, whose acid-catalyzed rearrangement leads to *p*-cymene (**7**). The aromatization could occur by a concerted mechanism or via a carbocation pathway as depicted in Scheme 1.

For the generation of (+)-(4*S*)-carvotanacetone (**8**) from **1**, the aforementioned steps leading to the formation of **4** or **5** could afford the allylic carbocation **IV**, directly or through **6** followed by protonation of the $\Delta^{1(7)}$ double bond (path b). A subsequent 1,3-hydride shift from C-5 to C-3 would give **V**, which would be susceptible to a 1,2-hydride shift from C-6 to C-5 in concert with deprotonation of the 6-hydroxy group to afford ketone **8**. The above route is supported by density functional theory (DFT) calculations at the B3LYP/6-31G(d) level of theory of the reaction intermediates **IV** and **V**, as in several mechanistic proposals for terpene syntheses, including those for *p*-menthene derivatives.[11−14] In the present case 98.6% of the population of **IV** showed an H-3−C-3−C-5−H-5 relative orientation of −75.5 ± 4.7° and a C-3−C-5 distance of 2.47 ± 0.008 Å to favor the 1,3-hydride shift. The measured parameters for **V** (P = 97.7%) revealed a H-5−C-5−C-6−H-6 dihedral angle (θ = −71.5 ± 3.9°) and a C-5−C-6 bond distance (d = 1.47 Å) to permit the 1,2-hydride shift.

(+)-Yabunikkeol (**6**) was described as an oxidation derivative of (−)-α-phellandrene,[15] although the (4*R*,6*S*) absolute configuration was wrongly assigned, while *p*-cymene (**7**) and (+)-(4*S*)-carvotanacetone (**8**) are widely reported as essential oil components. In addition, **7** has been considered a good-quality essential oil ingredient in *Origanum* species[16] or a low-quality ingredient in lemon essential oil.[17]

Since allylic alcohol intermediates **4**−**6** lead to aromatic **7**, iodine was considered as the aromatization reagent.[18,19] Thus, *p*-menthenediol **4** was refluxed in the presence of iodine for 3 h to yield **8** and **9** (1:2), while aromatization for 5 h only provided carvacrol (**9**). Therefore, **8** is an intermediate in the aromatization process as suggested in Scheme 1, where the coordination of iodine to the tertiary hydroxy group of **4**, as depicted in **IX**, facilitates dehydration and formation of **6**, whose protonation at C-7 by HI favors allylic carbocation **IV**. Subsequent 1,3-hydride shifts to **V** and 1,2-hydride shifts afforded **8**. Formation of the iodoiranium intermediate **VI** is followed by rupture of the C-2−I bond to allow formation of the Δ^2 double bond in intermediate **VII**. Deiodination affords carbocation **VIII**, which on deprotonation at C-4 and spontaneous tautomerization would generate **9**. Thus,

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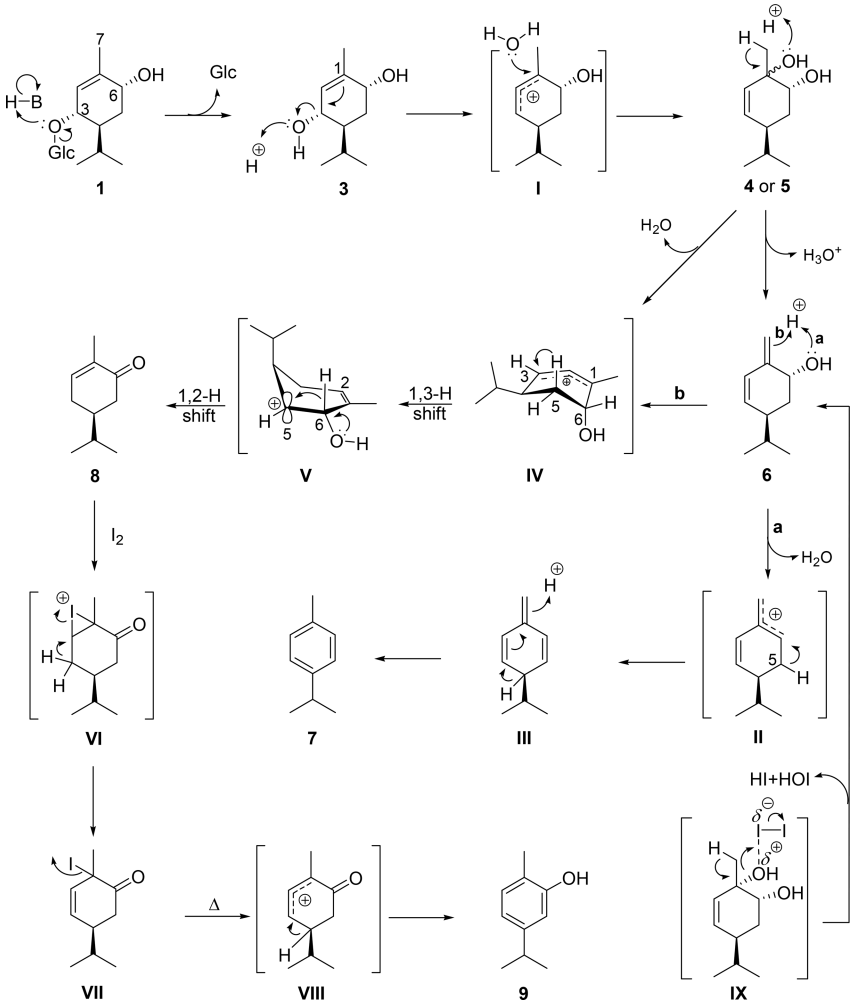
Scheme 1. Putative Mechanism for the Aromatization of *p*-Menthenes 4 and 5



iodoiranium-assisted aromatization intermediates become plausible since acid conditions deactivate the carbonyl moiety in **8**, via keto−enol tautomerism, which at the end may contribute to the aromatization process, but avoiding dehydration by acid catalysis as in the formation of *p*-cymene (**7**). Consequently, (+)-(4*S*)-carvotanacetone (**8**) can be considered as a common constituent in essential oils related to the aromatic monoterpene biosynthesis. This mechanistic proposal is based on those described for terpene aromatization using iodine as a mild reagent.[18,19]

Although **4** and **5** provided the same aromatization products, their reactivity was assessed by acetylation of the C-1 hydroxy group, since reactivity variations in the crude reaction outcomes were observed by ^{1}H NMR. A 25:1 mixture of **10** and **11** was obtained from **4**, while **5** yielded the *p*-menthene mixture of **12** and **13** in a 10:1 ratio. Thus, the 1-hydroxy group in **5** is a more favorable nucleophile than that at **4**, perhaps due to a reduced hydroxy group interaction due to their *trans* disposition. These results also discard possible steric effects exerted by the isopropyl group, as revealed by **5**. In support of conformational preferences of **4** and **5**, calculations were done with the Monte Carlo protocol using a molecular model force field (MMFF). All conformer energies were optimized at the DFT B3LYP/6-31G(d) level of theory, a methodology successfully employed for the conformational analysis of aliphatic[9] and aromatic *p*-menthene derivatives,[20] thus providing 29 conformers for **4** and 43 conformers for **5** in 10 kcal/mol energy gaps. Measurements of the O-1−H-1···O-6, O-6−H-6···O-1, and O-1···O-6 bond lengths and angles (Table S1, Supporting Information) suggested that 99.9% of the conformational population of **4** favor weak hydrogen-bonding interactions, while in **5** only 50% of the conformational population favor probable hydrogen-bonding interactions.[21,22] In turn, acetylation of **3** gave the expected diacetate **14**.

Once the behavior of *p*-menthenediols **4** and **5** was studied under acid- and iodine-catalyzed reaction conditions, glucoside **2** was evaluated under the same conditions. Acid hydrolysis of **2** yielded the triol epimers **15** and **16**,[9] which were individually dissolved in tetrahydrofuran (THF) and treated with 10% HCl. In either case two compounds were obtained and separated by column chromatography, affording carvacrol (**9**) and a sample of amorphous material, whose ^{1}H NMR data suggested the Δ^2 endocyclic double bond conjugated with an exocyclic $\Delta^{1(7)}$ olefinic bond, whose signals were observed in the δ 6.18−5.12 range. In addition, two hydrogen signals geminal to hydroxy groups resonated at δ 4.33 (H-6) and 3.75 (H-5). The ^{13}C NMR spectrum showed the expected 10 signals for a *p*-menthene skeleton, including four signals assigned to the conjugated diene moiety in the δ 143.5−115.2 range and two signals at δ 71.6 and 71.4 attributed to C-6 and C-5, respectively. The HRESIMS data confirmed the $C_{10}H_{16}O_2$

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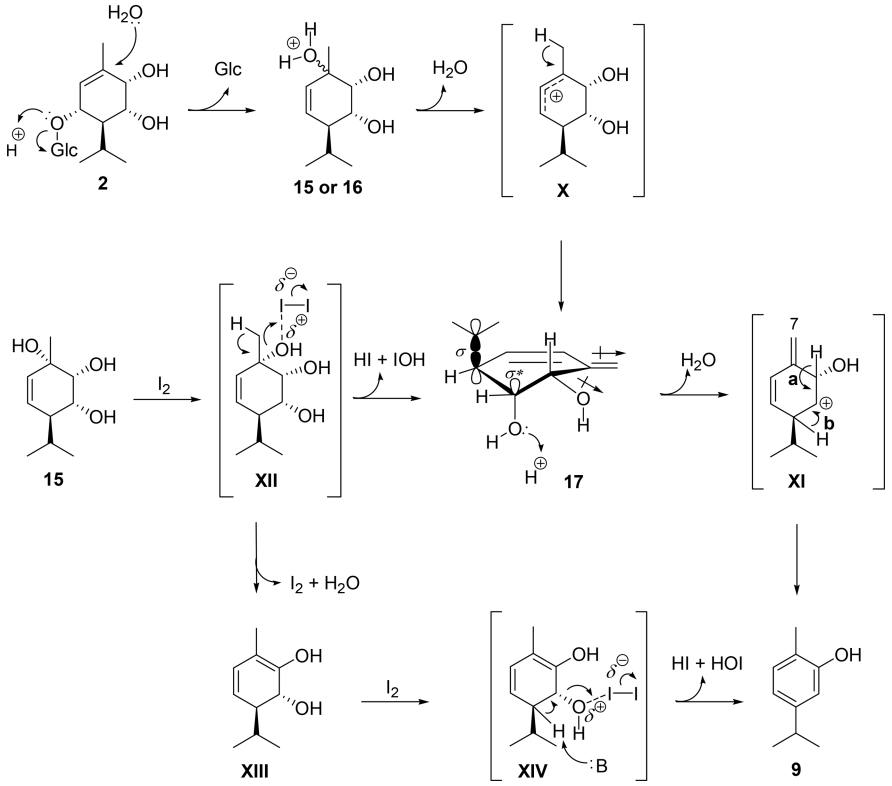
Scheme 2. Putative Mechanism for the Aromatization of *p*-Menthenes 15 and 16



composition showing the $[M + NH_4]^+$ molecular ion at m/z 186.1497 (calcd as $C_{10}H_{16}O_2 + NH_4^+$, 186.1494), while the specific rotation was dextrorotatory. These data suggested the identity of the compound as the new *p*-menthene derivative (+)-(4*S*,5*R*,6*S*)-5,6-dihydroxy-1(7),2-menthadiene (**17**). Unequivocal structure assignment of **17** was supported by HETCOR, COSY, NOESY, and HMBC spectra. Treatment of **17** with 10% HCl for 24 h yielded carvacrol (**9**).

Based on the overall chemical transformations, an aromatization reaction mechanism of **2**, through **15**−**17** to carvacrol (**9**), including stable reaction intermediates, is suggested in Scheme 2, which involves protonation of the allylic tertiary hydroxy group of **15** and/or **16** followed by dehydration. The allylic carbocation intermediate **X** is stabilized through deprotonation at C-7, yielding **17**. This stable diol has the potential to also undergo a dehydration at C-5 affording conjugated diene carbocation **XI**, which can be deprotonated at C-6 as shown in **XI** (shift a), followed by protonation at C-7 and concomitant deprotonation at C-4 to generate carvacrol (**9**). The other alternative, shown in **XI** (shift b), involves deprotonation at C-4, providing a conjugated triene, which aromatizes to **9**. The possibility to obtain thymol as the final aromatic compound, via dehydration at C-6, was unsuccessfully searched.

To explain the regiospecific dehydration in **17**, conformational population calculations were done by the Monte Carlo protocol using MMFF. All conformer energies were optimized at the DFT B3LYP/6-31G(d) level of theory as described above. This procedure provided 22 conformers in a 10 kcal/mol range, of which 74% of the conformer population revealed the C-5 hydroxy group and the isopropyl group in a *pseudo-trans* diaxial arrangement with a dihedral angle of 152 ± 7.4°, favoring $\sigma-\sigma^*$ conformational interactions, as depicted in Scheme 2, increasing the reactivity of the 5-hydroxy group and directing regiospecificity toward formation of **9**. In addition, the polar reaction medium stabilizes the equatorial 6-hydroxy group via a dipole−dipole interaction with the exocyclic double bond.[23] Coupling constant analysis was not used for the conformational analysis since H-5 and H-6 resonated as undefined broad signals.

A reactivity comparison of the hydroxy groups at C-1 in **15** and **16** was done as for **4** and **5**. Acetylation of **15** gave a 10:1 mixture of **18** and **19**. From the acetylation of **16** the formation of compounds **20** and **21** was expected. However, the ^{1}H NMR spectrum revealed the presence of **20**, a complex mixture of acetylated compounds of undefined identity, and traces of **21**, readily recognized by its typical H-2 signal at δ 6.13 (Figure S54, Supporting Information). It thus seems that **20** suffers degradation via reaction of the hydroxy group at C-1 since hydrogen atoms geminal to the C-5 and C-6 acetoxy groups at δ 5.72−4.76 and acetoxy signals at δ 2.23−2.00 were observed. This evidences a higher reactivity of the hydroxy group at C-1 in **16** than in **15**, which is similar to the case of **5**. As done for **4** and **5**, DFT calculations for **15** and **16** were performed, affording 37 conformers for **15** and 48 conformers for **16** in 10 kcal/mol gaps. These calculations revealed intramolecular hydrogen bonding interactions in 99.7% of the conformational population of **15**, of which essentially all involve the oxygen atom at C-1. In turn, only 24% of the conformational population of **16** shows this type of interaction, thus inhibiting the tertiary hydroxy group from interacting, and consequently the nucleophilicity of the hydroxy group at C-1 in **16** is higher than in **15**. Modification of reaction conditions for the acetylation permitted the preparation of **20** and **21** (see Experimental Section).

The iodine aromatization reaction of **15** gave carvacrol (**9**) as the regiospecific aromatization product. This reaction is similar to the acid-catalyzed aromatization of **15**, despite the

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fact that thymol and/or carvacrol (**9**) formation might be possible. Thus, a plausible reaction mechanism (Scheme 2) for the transformation of **15** involves the charged iodine-bonded adduct at the tertiary hydroxy group in **XII** followed by dehydration, yielding the $\Delta^{1(6)}$ double bond in **XIII**. Since keto−enol tautomerism of this intermediate is expected, deactivation of the hydroxy group at C-6 leads to dehydration at C-5 to yield **9**, via adduct **XIV**. Alternatively, dehydration of the hydroxy group at C-1, via iodine charged complex **XII**, to form **17** followed by dehydration of the hydroxy group at C-5, via **XI** (shift a or b), favors aromatization to **9**. In the latter alternative, regiospecificity could be induced by conformational effects, as well as dipole−dipole interactions in the considered intermediate **17**, since the polarity of the reaction medium increases due to H_2O and HI formation during the reaction process.

Interestingly, NMR and GC-MS essential oil analysis of the leaves revealed the presence of *p*-cymene (**7**) as a main constituent in the mixture, thus supporting the present biomimetic study. On the above basis it seems that several biochemical processes may be related to laboratory studies, under the principle that chemistry rules are applied in any reaction system, but probably stereospecificity and reaction rates are the most important differences between enzymatic and chemical systems. In addition, biomimetic studies provide chemical pathways applied to two targets: the synthesis of organic molecules of interest[24−26] and understanding the observed biosynthetic pathways of natural products in living systems.[27] Moreover, glucosides **1** and **2** may favor the formation of aromatic *p*-menthene derivatives **7** and **9** through catabolic processes, which could be related to several anabolic pathways providing multifunctionalized thymol derivatives, similar to those reported from *Ageratina glabrata*.[20,28,29] Other relevant conclusions are the observation of precise chemical routes for molecular transformations and the observation of chemical economy during these processes.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points (uncorrected) were determined on a Fisher−Johns apparatus. Optical rotations were recorded in $CHCl_3$ solutions at room temperature on a PerkinElmer 341 polarimeter. 1D and 2D NMR spectra were measured at 300 or 400 MHz for ^{1}H and at 75.4 or 100 MHz for ^{13}C on Varian Mercury 300 or 400 spectrometers from $CDCl_3$ solutions using tetramethylsilane as the internal reference. Chemical shift values are reported in parts per million, and coupling constants (*J*) are in Hz. HRMS data were acquired on a Waters Synapt G2 spectrometer at the Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO, USA. Silica gel 230−400 mesh (Merck) was used for column chromatography.

Compounds. Menthene derivatives **1**−**5**, **15**, and **16** were obtained as described.[9] A combination of vibrational circular dichroism, single-crystal X-ray diffraction, and chemical correlations allowed securing[9] their absolute configuration (AC). Since all other chiral molecules of the present study were also chemically correlated with the above molecules, their AC is also fully substantiated. In turn, monoterpenes **7**−**9** are known molecules.[30−33] In cases when more than one acetyl group was present, the signal distinction followed from gHSQC and gHMBC NMR measurements.

Dehydration and Aromatization Reactions. Solutions of **4** or **5** (100 mg each) in THF (1 mL) were treated with aqueous 10% HCl (5 mL) and stirred at room temperature for 5 h. Each reaction mixture was washed with a saturated $NaHCO_3$ solution, poured over ice−H_2O, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. Each residue was column chromatographed on silica gel using hexanes−CH_2Cl_2 mixtures as eluent. Fractions 4−7 (hexanes−CH_2Cl_2, 4:1) afforded **8** (24 mg, 30%), fractions 8−12 (hexanes−CH_2Cl_2, 1:1) yielded **6** (11 mg, 12%), and fractions 15−17 (hexanes−CH_2Cl_2, 3:7) gave **7** (52 mg, 58%). Similarly, a solution of **15** and **16** (70 mg) was treated as above. Column chromatography of the residue afforded **9** (19 mg, 34%) in fractions 8−11 (hexanes−CH_2Cl_2, 3:2) and **17** (42 mg, 66%) in fractions 15−19 (CH_2Cl_2−MeOH, 49:1). Acid treatment of **6** (20 mg), as above, yielded **7** (11 mg, 63%) in fractions 3−5 (hexanes−CH_2Cl_2, 4:1), while **17** (40 mg) for 5 h afforded **9** (28 mg, 80%) in fractions 5−7 (hexanes−CH_2Cl_2, 3:2).

Samples of **4** or **15** (40 mg each) were dissolved in toluene (10 mL), and iodine (40 mg) was added. Each reaction mixture was stirred under reflux for 5 h. Each residue was washed with a saturated $Na_2S_2O_3$ solution, $NaHCO_3$, and NaCl, poured over ice−H_2O, extracted with hexanes, dried over anhydrous Na_2SO_4, filtered, and evaporated to yield 28 mg (80%) of **9** from **4** and 30 mg (94%) from **15**. Similarly, a solution of **4** (30 mg) in toluene (10 mL) was treated with iodine (30 mg) for 3 h. The residue was column chromatographed on silica gel using hexanes−CH_2Cl_2. Fractions 3−5 (hexanes−CH_2Cl_2, 3:2) afforded **9** (17 mg, 64%), and fractions 5−7 (hexanes−CH_2Cl_2, 3:7) gave **8** (7 mg, 26%).

Acetylation Reactions. Solutions of **3** (40 mg), **4**, **5**, **15**, or **16** (30 mg each) were dissolved in pyridine (1 mL), and Ac_2O (1 mL) was added. Each reaction mixture was stirred at room temperature for 24 h, or 3 h for **3**, poured over ice−H_2O, and extracted with EtOAc. Each organic layer was washed with aqueous 10% HCl, H_2O, aqueous $NaHCO_3$, and H_2O, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue from the reaction of **3** was extracted to yield **14** (38 mg, 85%). Column chromatography of the reaction of **4** afforded **10** (18 mg, 48%) and **11** (11 mg, 25%), while that of **5** yielded **12** (26 mg, 70%) and **13** (3 mg, 7%). Chromatography of the residue from **15** afforded **18** (25 mg, 57%) and **19** (3 mg, 6%), while that from **16** yielded **20** (20 mg, 46%) and **21** (8 mg, 16%).

Reactivity Assay of 4, 5, 15, and 16. The studies were done by acetylation using the above reaction conditions for 12 h, and the crude reaction mixtures were analyzed by ^{1}H NMR spectroscopy.

*(+)-(4S,6R)-Yabunikkeol (**6**):* colorless oil; $[\alpha]_{589}$ +5, $[\alpha]_{578}$ +5, $[\alpha]_{546}$ +5, $[\alpha]_{436}$ +13, $[\alpha]_{365}$ +23 (*c* 0.1, $CHCl_3$); lit.[30] $[\alpha]_{589}$ +5.0 (*c* 0.8, $CHCl_3$); lit.[15] $[\alpha]_{589}$ +4.2 (*c* 3.1, $CHCl_3$); IR ($CHCl_3$) ν_{max} cm^{-1} 3411, 2957, 2925, 1675, 1464, 1038, 892; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.14 (1H, dd, *J* = 10.1, 2.6 Hz, H-3), 5.83 (1H, dd, *J* = 10.1, 1.0 Hz, H-2), 5.06 (1H, br s, H-7), 4.96 (1H, br s, H-7′), 4.42 (1H, m, H-6), 2.34 (1H, m, H-4), 1.91 (1H, m, H-5), 1.72 (1H, septd, *J* = 6.8, 1.1 Hz, H-8), 1.55 (1H, m, H-5′), 0.93 (6H, d, *J* = 6.8 Hz, CH_3-9 and CH_3-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.3 (C, C-1), 134.0 (CH, C-2), 126.6 (CH, C-3), 112.9 (CH_2, C-7), 69.4 (CH, C-6), 37.2 (CH, C-4), 32.5 (CH_2, C-5), 31.5 (CH, C-8), 19.6 (CH_3, C-9), 19.60 (CH_3, C-10); IR and ^{1}H and ^{13}C NMR data in agreement with published values.[15,34,35]

*(+)-(1S,4S,6R)-6-Acetoxy-1-hydroxy-2-menthene (**10**):* colorless oil; $[\alpha]_{589}$ +9, $[\alpha]_{578}$ +9, $[\alpha]_{546}$ +12, $[\alpha]_{436}$ +28, $[\alpha]_{365}$ +64 (*c* 2.7, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3582, 2959, 2870, 1727, 1464, 1375 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (1H, ddd, *J* = 10.4, 2.8, 1.2 Hz, H-3), 5.59 (1H, ddd, *J* = 10.4, 2.4, 1.2 Hz, H-2), 4.94 (1H, ddd, *J* = 6.4, 2.4, 1.2 Hz, H-6), 2.10 (3H, s, Ac), 2.10 (1H, m, H-4), 2.02 (1H, tdd, *J* = 13.0, 6.0, 1.2 Hz, H-5), 1.64 (1H, m, H-8), 1.58 (1H, ddd, *J* = 13.0, 8.8, 2.4 Hz, H-5′), 1.29 (3H, s, CH_3-7), 0.89 (3H, d, *J* = 7.0 Hz, CH_3-9), 0.88 (3H, d, *J* = 7.0 Hz, CH_3-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C, Ac), 131.9 (CH, C-2), 131.2 (CH, C-3), 75.8 (CH, C-6), 69.0 (C, C-1), 38.1 (CH, C-4), 31.4 (CH, C-8), 26.9 (CH_2, C-5), 21.3 (CH_3, Ac) 27.0 (CH_3, C-7), 19.5 (CH_3, C-9), 19.4 (CH_3, C-10); HRESIMS *m*/*z* 235.1312 $[M + Na]^+$ (calcd for $C_{12}H_{20}O_3 + Na^+$, 235.1308).

*(+)-(1S,4S,6R)-1,6-Diacetoxy-2-menthene (**11**):* colorless oil; $[\alpha]_{589}$ +65, $[\alpha]_{578}$ +68, $[\alpha]_{546}$ +78, $[\alpha]_{436}$ +144, $[\alpha]_{365}$ +253 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2058, 1728, 1370 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (1H, ddd, *J* = 10.0, 2.4, 0.7 Hz, H-2), 5.73 (1H, dd, *J* = 10.0, 2.8 Hz, H-3), 5.23 (1H, dd, *J* = 8.0, 2.8 Hz, H-6), 2.16 (1H, m, H-4), 2.10 (3H, s, Ac), 2.03 (1H, m, H-5), 2.01 (3H, s, Ac),

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1.71 (1H, m, H-8), 1.65 (3H, s, CH_3-7), 1.64 (1H, m, H-5′), 1.57 (3H, s, H-7), 0.92 (6H, d, J = 7.0 Hz, CH_3-9, CH_3-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C, Ac), 170.1 (C, Ac), 132.5 (CH, C-3), 128.8 (CH, C-2), 78.3 (C, C-1), 73.4 (CH, C-6), 38.8 (CH, C-4), 31.7 (CH, C-8), 25.9 (CH_2, C-5), 23.3 (CH_3, C-7), 22.1 (CH_3, Ac), 21.2 (CH_3, Ac), 19.7 (CH_3, C-9), 19.5 (CH_3, C-10); HRESIMS m/z 277.1414 $[M]^+$ (calcd for $C_{14}H_{22}O_4$, 277.1410).

*(+)-(1R,4S,6R)-6-Acetoxy-1-hydroxy-2-menthene (**12**):* colorless oil; $[\alpha]_{589}$ +1, $[\alpha]_{578}$ +1, $[\alpha]_{546}$ +2, $[\alpha]_{436}$ +7, $[\alpha]_{365}$ +22 (c 0.8, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3592, 2956, 1722, 1374, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (1H, dd, J = 10.2, 2.7 Hz, H-3), 5.61 (1H, ddd, J = 10.2, 2.3, 1.0 Hz, H-2), 4.97 (1H, dd, J = 6.0, 3.8 Hz, H-6), 2.08 (3H, s, Ac), 2.06 (1H, m, H-4), 1.81 (1H, m, H-8), 1.79 (1H, m, H-5), 1.68 (1H, m, H-5′), 1.27 (3H, s, CH_3-7), 0.91 (3H, d, J = 6.8 Hz, CH_3-10), 0.92 (3H, d, J = 6.8 Hz, CH_3-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (C, Ac), 132.4 (CH, C-2), 131.6 (CH, C-3), 75.6 (CH, C-6), 69.3 (C, C-1), 38.4 (CH, C-4), 31.6 (CH, C-8), 26.4 (CH_2, C-5), 24.3 (CH_3, C-7), 21.3 (CH_3, Ac), 19.8 (CH_3, C-9), 19.7 (CH_3, C-10); HRESIMS m/z 235.1310 $[M]^+$ (calcd for $C_{12}H_{20}O_3$, 235.1308).

*(−)-(1R,4S,6R)-1,6-Diacetoxy-2-menthene (**13**):* colorless oil; $[\alpha]_{589}$ −77, $[\alpha]_{578}$ −80, $[\alpha]_{546}$ −92, $[\alpha]_{436}$ −164, $[\alpha]_{365}$ −275 (c 1.8, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1731, 1370, 1248, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (1H, ddd, J = 10.3, 2.8, 1.0 Hz, H-2), 5.80 (1H, ddd, J = 10.3, 2.8, 0.6 Hz, H-3), 5.21 (1H, ddd, J = 4.6, 3.1, 1.0 Hz, H-6), 2.08 (1H, m, H-4), 2.07 (3H, s, Ac), 1.95 (3H, s, Ac), 1.83 (1H, m, H-5), 1.80 (1H, m, H-5′), 1.71 (1H, septd, J = 6.8, 1.3 Hz, H-8), 1.49 (3H, s, CH_3-7), 0.90 (3H, d, J = 6.8 Hz, CH_3-9), 0.89 (3H, d, J = 6.8 Hz, CH_3-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C, Ac), 169.6 (C, Ac), 133.6 (CH, C-3), 128.4 (CH, C-2), 77.9 (C, C-1), 72.5 (CH, C-6), 37.7 (CH, C-4), 31.3 (CH, C-8), 25.5 (CH_2, C-5), 22.1 (CH_3, Ac), 21.2 (CH_3, Ac), 21.1 (CH_3, C-7), 19.5 (CH_3, C-9), 19.2 (CH_3, C-10); HRESIMS m/z 277.1418 $[M + Na]^+$ (calcd for $C_{14}H_{22}O_4 + Na^+$, 277.1410).

*(−)-(3S,4S,6R)-3,6-Diacetoxy-1-menthene (**14**):* colorless oil; $[\alpha]_{589}$ −85, $[\alpha]_{578}$ −88, $[\alpha]_{546}$ −99, $[\alpha]_{436}$ −160, $[\alpha]_{365}$ −234 (c 2.6, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1721, 1466, 1371, 1022 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (1H, dd, J = 2.3, 1.5 Hz, H-2), 5.22 (1H, m, H-3), 5.20 (1H, m, H-6), 2.08 (3H, s, Ac), 2.07 (3H, s, Ac), 1.83 (1H, m, H-5), 1.78 (1H, m, H-8), 1.77 (1H, m, H-4), 1.71 (3H, br t, J = 1.4, CH_3-7), 1.58 (1H, m, H-5′), 0.92 (3H, d, J = 6.7, CH_3-9), 0.83 (3H, d, J = 6.7, CH_3-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (C, Ac), 170.6 (C, Ac), 135.3 (C, C-1), 127.4 (CH, C-2), 71.0 (CH, C-3), 69.2 (CH, C-6), 39.4 (CH, C-4), 26.9 (CH_2, C-5), 26.4 (CH, C-8), 21.1 (CH_3, Ac), 21.0 (CH_3, Ac), 20.3 (CH_3, C-9), 19.9 (CH_3, C-7), 17.2 (CH_3, C-10); HRESIMS m/z 277.1408 $[M + Na]^+$ (calcd for $C_{14}H_{22}O_4 + Na^+$, 277.1410).

*(+)-(4S,5R,6S)-5,6-Dihydroxy-1(7),2-menthadiene (**17**):* white solid; mp 86−88 °C ($CHCl_3$); $[\alpha]_{589}$ +113, $[\alpha]_{578}$ +118, $[\alpha]_{546}$ +135, $[\alpha]_{436}$ +235, $[\alpha]_{365}$ +377 (c 1.1, $CHCl_3$); IR ν_{max} 3556, 2958, 1389 1056 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (1H, dd, J = 10.0, 2.1 Hz, H-2), 5.70 (1H, dd, J = 10.0, 2.6 Hz, H-3), 5.26 (1H, br s, H-7), 5.12 (1H, br s, H-7′), 4.33 (1H, br s, H-6), 3.75 (1H, br s, H-5), 2.25 (1H, m, H-4), 1.96 (1H, septd, J = 6.8, 1.7 Hz, H-8), 1.05 (3H, d, J = 6.8 Hz, CH_3-9), 0.89 (3H, d, J = 6.8 Hz, CH_3-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5 (C, C-1), 129.0 (CH, C-3), 127.3 (CH, C-2), 115.2 (CH_2, C-7), 71.8 (CH, C-6), 71.4 (CH, C-5), 46.8 (CH, C-4), 28.3 (CH, C-8), 21.1 (CH_3, C-9), 18.5 (CH_3, C-10); HRESIMS m/z 186.1497 $[M + NH_4]^+$ (calcd for $C_{10}H_{16}O_2 + NH_4^+$, 186.1489).

*(+)-(1S,4S,5R,6R)-5,6-Diacetoxy-1-hydroxy-2-menthene (**18**):* white solid; mp 78−80 °C; $[\alpha]_{589}$ +113, $[\alpha]_{578}$ +118, $[\alpha]_{546}$ +134, $[\alpha]_{436}$ +234, $[\alpha]_{365}$ +379 (c 0.1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3584, 2963, 2875, 1743, 1371 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (1H, ddd, J = 10.4, 2.3, 1.1 Hz, H-2), 5.59 (1H, dd, J = 10.4, 2.5 Hz, H-3), 5.20 (1H, dd, J = 2.2, 1.1 Hz, H-6), 5.11 (1H, dd, J = 8.3, 2.2 Hz, H-5), 2.38 (1H, ddt, J = 8.4, 3.6, 2.5 Hz, H-4), 2.15 (3H, s, Ac), 2.05 (3H, s, Ac), 1.80 (1H, septd, J = 6.8, 3.6 Hz, H-8), 1.38 (3H, d, J = 1.0 Hz CH_3-7), 1.02 (3H, d, J = 6.8 Hz, CH_3-10), 0.83 (3H, d, J = 6.8 Hz, CH_3-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C, Ac), 170.5 (C, Ac) 132.9 (CH, C-2), 126.1 (CH, C-3), 74.8 (CH, C-6), 70.7 (CH, C-5), 70.2 (C, C-1), 43.0 (CH, C-4), 27.5 (CH, C-8), 26.8 (CH_3, C-7), 21.1 (CH_3, Ac), 21.1 (CH_3, Ac), 20.5 (CH_3, C-10), 17.8 (CH_3, C-9); HRESIMS m/z 293.1365 $[M]^+$ (calcd for $C_{14}H_{22}O_5$, 293.1359).

*(+)-(1S,4S,5R,6R)-1,5,6-Triacetoxy-2-menthene (**19**):* colorless oil; $[\alpha]_{589}$ +96, $[\alpha]_{578}$ +103, $[\alpha]_{546}$ +116, $[\alpha]_{436}$ +204, $[\alpha]_{365}$ +333 (c 0.8, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2954, 1731, 1369, 1053 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (1H, ddd, J = 10.4, 2.5, 1.6 Hz, H-2), 5.70 (1H, t, J = 2.0 Hz, H-6), 5.66 (1H, dd, J = 10.4, 2.2 Hz, H-3), 5.08 (1H, dd, J = 9.6, 2.0 Hz, H-5), 2.50 (1H, dq, J = 9.6, 2.9 Hz, H-4), 2.12 (3H, s, Ac), 2.05 (3H, s, Ac), 1.99 (3H, s, Ac), 1.84 (1H, septd, J = 6.8, 2.9 Hz, H-8), 1.71 (3H, s, CH_3-7), 1.02 (3H, d, J = 6.8 Hz, CH_3-10), 0.81 (3H, d, J = 6.8 Hz, CH_3-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (C, Ac), 170.1 (C, Ac), 169.6 (C, Ac), 129.2 (CH, C-2), 126.9 (CH, C-3), 79.8 (C, C-1), 72.7 (CH, C-6), 69.4 (CH, C-5), 42.0 (CH, C-4), 26.7 (CH, C-8), 24.7 (CH_3, C-7), 22.0 (CH_3, Ac), 20.9 (CH_3, Ac), 20.9 (CH_3, Ac), 20.3 (CH_3, C-10), 19.3 (CH_3, C-9); HRESIMS m/z 335.1473 $[M + Na]^+$ (calcd for $C_{16}H_{24}O_6 + Na^+$, 335.1465).

*(+)-(1R,4S,5R,6R)-5,6-Diacetoxy-1-hydroxy-2-menthene (**20**):* colorless oil; $[\alpha]_{589}$ +47, $[\alpha]_{578}$ +49, $[\alpha]_{546}$ +56, $[\alpha]_{436}$ +97 (c 1.2, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3594, 2964, 2875, 1734, 1600, 1370 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (1H, dd, J = 10.3, 2.2 Hz, H-3), 5.63 (1H, ddd, J = 10.3, 2.2, 1.3 Hz, H-2), 5.29 (1H, dd, J = 9.0, 2.5 Hz, H-5), 5.21 (1H, dd, J = 2.5, 1.3 Hz, H-6), 2.36 (1H, m, H-4), 2.09 (3H, s, Ac), 2.02 (3H, s, Ac), 1.84 (1H, septd, J = 7.0, 3.6 Hz, H-8), 1.27 (3H, s, CH_3-7), 1.02 (3H, d, J = 7.0 Hz, CH_3-10), 0.82 (3H, d, J = 7.0 Hz, CH_3-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (C, Ac), 170.6 (C, Ac) 131.2 (CH, C-2), 128.7 (CH, C-3), 74.7 (CH, C-6), 70.4 (C, C-1), 69.5 (CH, C-5), 42.2 (CH, C-4), 27.0 (CH, C-8), 25.1 (CH_3, C-7), 21.0 (CH_3, Ac), 21.0 (CH_3, Ac), 20.4 (CH_3, C-10), 17.5 (CH_3, C-9); HRESIMS m/z 293.1358 $[M]^+$ (calcd for $C_{14}H_{22}O_5$, 293.1359).

*(−)-(1R,4S,5R,6R)-1,5,6-Triacetoxy-2-menthene (**21**):* colorless oil; $[\alpha]_{589}$ −35, $[\alpha]_{578}$ −36, $[\alpha]_{546}$ −43, $[\alpha]_{436}$ −80, $[\alpha]_{365}$ −145 (c 0.6, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2959, 1735, 1463, 1369, 1052 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (1H, ddd, J = 10.3, 2.4, 1.2 Hz, H-2), 5.75 (1H, dd, J = 10.3, 2.7 Hz, H-3), 5.39 (1H, dd, J = 2.6, 1.2 Hz, H-6), 5.30 (1H, dd, J = 9.0, 2.6 Hz, H-5), 2.35 (1H, ddd, J = 9.0, 3.0, 2.7 Hz, H-4), 2.10 (3H, s, Ac), 2.03 (3H, s, Ac), 2.00 (3H, s, Ac), 1.85 (1H, septd, J = 7.0, 3.0 Hz, H-8), 1.51 (3H, s, CH_3-7), 1.01 (3H, d, J = 7.0 Hz, CH_3-10), 0.80 (3H, d, J = 7.0 Hz, CH_3-9); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.5 (C, Ac), 170.3 (C, Ac), 169.5 (C, Ac), 130.1 (CH, C-3), 128.6 (CH, C-2), 79.1 (C, C-1), 72.2 (CH, C-6), 68.9 (CH, C-5), 42.2 (CH, C-4), 27.1 (CH, C-8), 22.0 (CH_3, Ac), 21.0 (CH_3, Ac), 20.9 (2CH_3, Ac and C-7), 20.8 (CH_3, C-10), 20.3 (CH_3, C-9); HRESIMS m/z 335.1479 $[M + Na]^+$ (calcd for $C_{16}H_{24}O_6 + Na^+$, 335.1465).

Conformational Calculations. Monte Carlo search protocols using the Merck molecular force field (MMFF94) followed by single-point energy calculations using DFT at the B3LYP/6-31G(d) level of theory, both implemented in the Spartan'04 software, were carried out. The MMFF step provided 29, 43, 37, 48, 22, six, and six conformers for **4**, **5**, **15**, **16**, **17**, **IV**, and **V**, respectively, in energy gaps of 10 kcal/mol, while after single-point calculations these conformers appeared in 8.79, 5.51, 8.53, 7.61, 5.68, 3.90, and 5.10 kcal/mol energy gaps, respectively. Bond distances and dihedral angles of each conformer were extracted using the Spartan'04 software. Averaged and standard errors of these data were estimated using the Microsoft Excel program. Calculations were performed using a laptop computer operating at 2.20 GHz with 8 Gb RAM.

■ ASSOCIATED CONTENT

Supporting Information

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Copies of 1D and 2D NMR spectra of **1**−**21**; minimum energy conformers, bond lengths, and angles of **4**, **5**, **15**, **16**, **17**, **IV**, and **V** (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

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