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Mechanistic Studies on the Autoxidation of α-Guaiene: Structural Diversity of the Sesquiterpenoid Downstream Products

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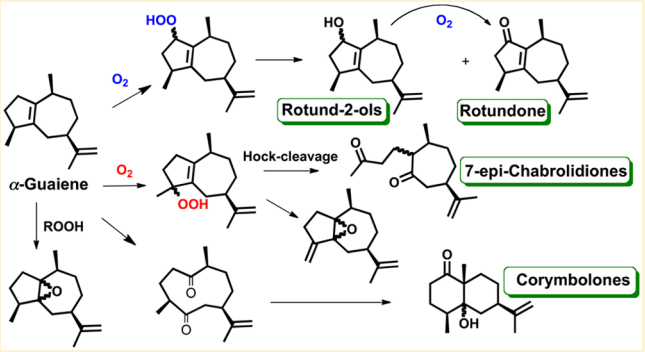
Supporting Information

ABSTRACT: Two unstable hydroperoxides, **6b** and **10a**, and 13 downstream sesquiterpenoids have been isolated from the autoxidation mixture of the bicyclic sesquiterpene α-guaiene (**1**) on cellulose filter paper. One of the significant natural products isolated was rotundone (**2**), which is the only known impact odorant displaying a peppery aroma. Other products included corymbolone (**4a**) and its C-6 epimer **4b**, the (2*R*)- and (2*S*)-rotundols (**7a**/**b**), and several hitherto unknown epimers of natural chabrolidione A, namely, 7-epi-chabrolidione A (**3a**) and 1,7-epi-chabrolidione A (**3b**). Two 4-hydroxyrotundones (**8a**/**b**) and a range of epoxides (**9a**/**b** and **5a**/**b**) were also formed in significant amounts after autoxidation. Their structures were elucidated on the basis of spectroscopic data and X-ray crystallography, and a number of them were confirmed through total synthesis. The mechanisms of formation of the majority of the products may be accounted for by initial formation of the 2- and 4-hydroperoxyguaienes (**6a**/**b** and **10a**/**b**) followed by various fragmentation or degradation pathways. Given that α-guaiene (**1**) is well known to exist in the essential oils of numerous plants, coupled with the fact that aerial oxidation to form this myriad of downstream oxidation products occurs readily at ambient temperature, suggests that many of them have been overlooked during previous isolation studies from natural sources.



The vast structural diversity of sesquiterpenoids and their accompanying intriguing biological properties have driven longstanding research interests in understanding their biosynthesis. Sesquiterpenoids are known to be derived from the achiral precursor farnesyl pyrophosphate (FPP) biosynthesized via the mevalonate pathway in plastids.[1,2] The enzymatically generated intermediate carbocations of FPP can subsequently cyclize and rearrange in a number of ways to furnish a myriad of structurally diverse sesquiterpenoids, which often display highly complex stereochemical arrays.[3] The position of the carbocation formation on FPP is governed by the conformation and geometric constraints of the various substrates and the active sites of the natural cellular cyclase enzymes.[4] Furthermore, the way the carbocations cyclize via their various transition states to often yield their thermodynamically favored products has been studied in great detail theoretically through the use of quantum chemical calculations.[5−12] These calculations have also permitted the prediction of the formation of downstream products based on the transition states of the intermediate carbocations,[13] and the findings have been supported from studies on the acid-catalyzed cyclization of sesquiterpene precursors.[14−16]

While these cationic intermediate-based cyclizations and rearrangements have been well studied and provide a comprehensive understanding of the diverse scaffolds of sesquiterpene formation, free radical-associated reactions including autoxidation should also be able to modify sesquiterpenes at various stages throughout their formation. Such processes would boost the natural diversity of these compounds. A growing body of work has demonstrated the potential of harnessing free radical approaches for the synthesis of terpenes and also provide further insight into their biosynthesis.[17] However, in comparison to the understanding of the biogenesis of sesquiterpene hydrocarbons, knowledge of postcyclization chemical transformations of sesquiterpenoids is far from complete. One possible free radical associated mechanism exploited by Nature in the biosynthesis of postcyclization sesquiterpeniods is oxidative transformations catalyzed by oxidases, such as cytochrome P450 monooxygenases,[18] the mechanisms of which resemble those of free radical autoxidation. Indeed, a recent study has demonstrated

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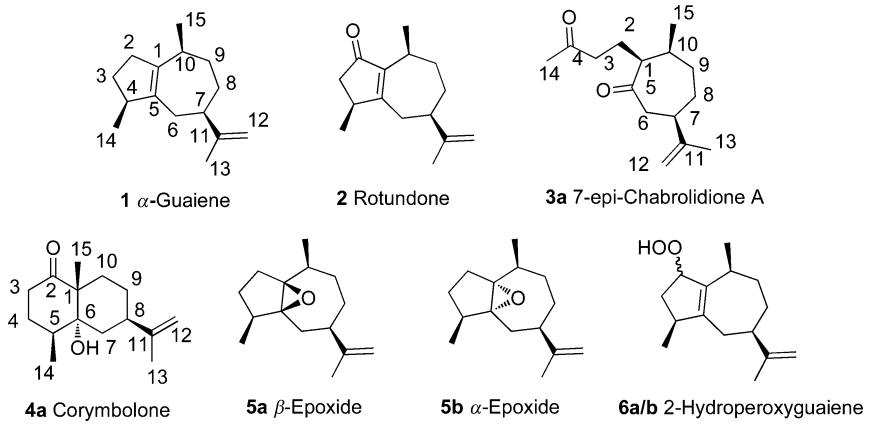

Figure 1. α-Guaiene (**1**) and several major autoxidation products (**2**−**5a**/**b**) of **1** previously identified.

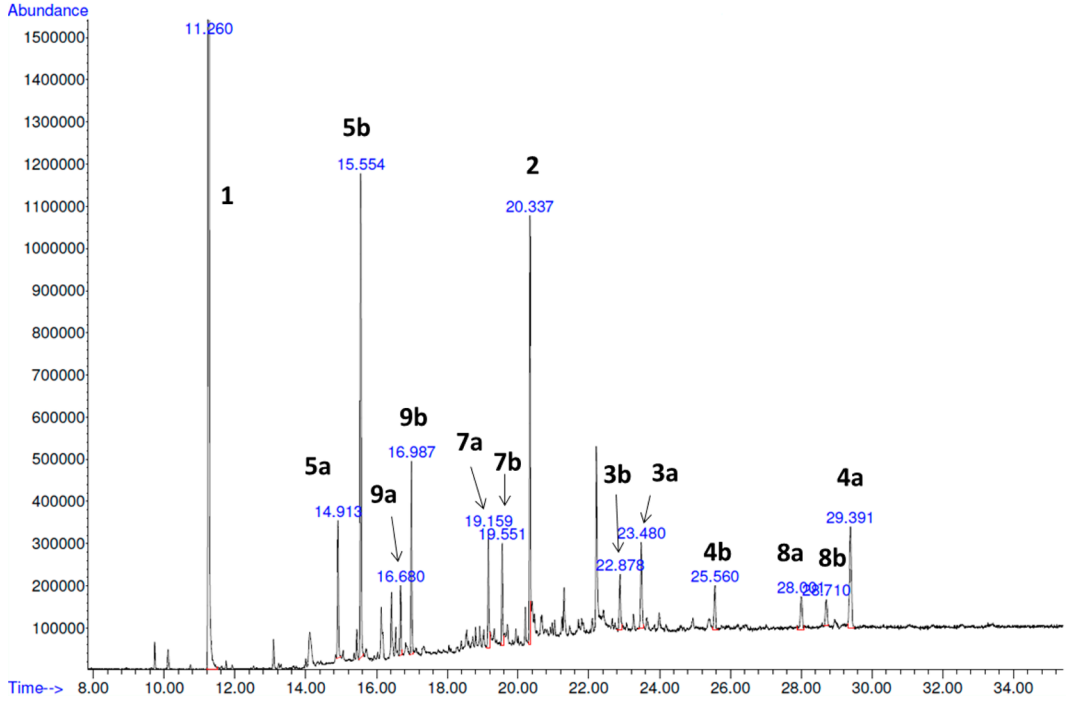

Figure 2. GC chromatogram of the aerial oxidation of α-guaiene (**1**, neat, coated on filter paper) at 50 °C after 15 h.

that oxidases are able to modify sesquiterpene substrates and produce miscellaneous oxygenated sesquiterpenoids.[19]

We have recently reported that the sesquiterpene α-guaiene (**1**), which is known to exist in the essential oils of numerous plants, undergoes aerial oxidation to form a host of downstream oxidation products.[20,21] One of the major oxygenated products formed was identified as the natural product (−)-rotundone (**2**), which is the only known impact odorant displaying a peppery aroma and which has recently been identified in some wine varieties and in a large range of common herbs and spices (Figure 1).[22] Although the concentration of **2** found in products of natural origin is known to be small (from ng/L amounts in red wines up to 2 mg/kg in peppercorns), the odor detection threshold (ODT) of rotundone (8 ng/L in water, 16 ng/L in red wine) is among the lowest of any known natural product.[22] Thus, a trace of rotundone imparts strong pepper notes to foods and beverages.

This discovery serves as an excellent example and highlights that the postoxidation of natural sesquiterpenes, even to a small extent, will lead to downstream oxygenated sesquiterpene products which (a) may have been or are being formed in Nature and thus can be considered as natural products and (b) may display yet to be discovered important aroma or biochemical properties. Four other major products formed during the natural autoxidation of **1** were identified as 7-epi-chabrolidione A (**3a**), corymbolone (**4a**), and the epoxides **5a**/**b**, with the latter three derivatives being previously identified natural products, Figure 1.[20,21] Moreover, we hypothesized that the key initiation step in the formation of these downstream oxidation products was the initial formation of the secondary radical at C-2 of **1** followed by formation of the hydroperoxides **6a**/**b** and subsequent decomposition/fragmentation. The formation of such sesquiterpene hydroperoxides in Nature is not unusual, with a number previously being isolated from natural sources including *Magnolia grandiflora*, *Pogostemone cablin*, and *Aster spathulifolius*.[23−25] Intrigued by the fact that the GC chromatogram of the autoxidation mixture of **1** indicated the presence of a large number of additional oxidation

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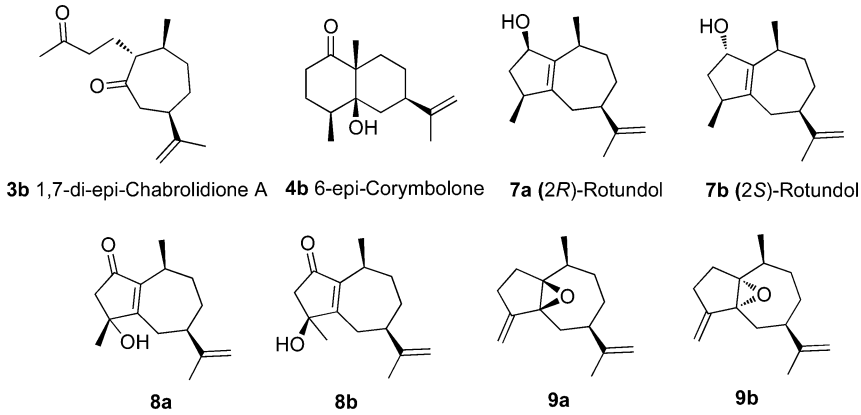

Figure 3. Additional downstream oxygenated sesquiterpenoids isolated from the autoxidation of α-guaiene (**1**).

products, many of which were potentially known natural products, coupled with the fact the hydroperoxides **6** were yet to be identified and characterized as the key intermediates, we have now explored the product mixture in great detail and report our findings herein along with mechanistic rationales for product formation.

RESULTS AND DISCUSSION

Autoxidation of α-Guaiene (1). The autoxidation of **1** had previously been carried out by bubbling O_2 through a solution containing **1** at ambient temperature, and it was found that the complete consumption of **1** was rather slow and took several weeks.[20] However, when the same autoxidation was conducted on cellulose filter paper, a noticeable acceleration was seen, particularly if the temperature was raised to 50 °C. Consequently filter paper was once again exploited as the supporting medium to perform a large-scale autoxidation of **1** in air at 50 °C for 20 h, after which time the substrate-coated filter paper was extracted (Soxhlet) with CH_2Cl_2 under a N_2 atmosphere. Analysis by GC-MS (after 15 h) once again revealed the formation of rotundone (**2**), 7-epi-chabrolidione A (**3a**), corymbolone (**4a**), and the epoxides **5a**/**b** along with numerous yet to be identified oxidation products (Figure 2). These latter products were also observed previously during GC analysis of the autoxidation of **1** in solution after an extended period of time.[23] The crude extract of the products was first purified by silica column chromatography (SCC, pretreated with 5% Et_3N/hexanes due to the acid sensitivity of a number of the products) to obtain seven fractions, which were further separated by repeated chromatography including SCC, multilayer coil counter-current chromatography (MLCCC), and preparative TLC. A total of five oxygenated sesquiterpenes previously described (**2**, **3a**, **4a**, and **5a**/**b**) and eight new analogues (**3b**, **4b**, **7a**/**b**, **8a**/**b**, and **9a**/**b**) were successfully isolated from the reaction mixture (Figures 1 and 3, respectively). The fact that the majority of the major compounds seen within the GC chromatogram (Figure 2) can be attributed to the isolated compounds themselves indicates that these are true products of the autoxidation process and are not simply artifacts of decomposition of more reactive intermediates in the GC injector block (*vide infra*).

Diketone **3a** was previously isolated as one of the major products resulting from the autoxidation of **1** in solution (CH_2Cl_2) and again found here to form during oxidation on filter paper.[20] Related epimer **3b** was also found as an autoxidation product in these studies; however, it was difficult to obtain in a pure state for characterization. Consequently, **3b** was confirmed unequivocally to be an authentic autoxidation product via total synthesis (*vide infra*). The ^{13}C NMR spectrum of β-ketol **4b** displayed 15 carbon signals including one carbonyl (δ_C 212.7), two olefinic (δ_C 149.8 and 111.1), and one oxygenated carbon (δ_C 79.0). The ^1H NMR spectrum showed two vinyl protons, two methyl singlets, and one methyl doublet. Both the ^1H and ^{13}C NMR spectra of **4b** closely resembled those of corymbolone (**4a**), indicating that **4b** was highly likely to be an isomer of **4a**. Analysis of the 2D NMR spectra confirmed that **4b** shared a carbon skeleton with **4a** except for the configuration of the bridged carbon C-6. On the basis of the known stereochemistry of **1** and the possible mechanism of oxidative cleavage of the bridged double bond to form a diketone, which then cyclizes to form **4b**, C-5 and C-8 of **4b** should remain intact during its formation and thus maintain the same *R* configurations. Moreover, key ROESY correlations between both H_3-14 and H_3-15 and the hydroxyl proton of **4b** were observed, suggesting the hydroxy moiety at C-6 and Me-15 should both adopt the same β-orientation as Me-14. Therefore, the structure of **4b** was assigned as 6-epi-corymbolone (**4b**) as depicted in Figure 3. (2*R*)-Rotundol (**7a**) and (2*S*)-rotundol (**7b**) are aroma compounds with peppery and woody notes and have been recently synthesized by reduction of rotundone **2** and identified as components from the laccase-catalyzed oxidation products of essential oils containing **1**.[26] Consequently their identification was confirmed by direct comparison of experimental and reported spectroscopic data.[26]

The two hitherto unknown β-ketols **8a** and **8b** displayed similar ^1H and ^{13}C NMR spectra that closely resembled those of rotundone (**2**) except for the presence of one additional oxygenated carbon and the replacement of one methyl doublet by a methyl singlet at approximately δ_H 1.00, suggesting that they could be isomeric hydroxy derivatives of **2**. Analysis of their 2D NMR spectra (COSY, HSQC, and HMBC) confirmed the presence of an additional epimeric hydroxy moiety at C-4 of rotundone. The configurations of C-4 of **8a** and **8b** were determined by analysis of their ROESY spectra. A key ROESY correlation between H_3-14 and H-10 for **8b** indicated that Me-14 is α-oriented. No such correlation between H_3-14 and H-10 was observed for **8a**. Therefore, the C-4 configurations of **8a** and **8b** were established as *R* and *S*, respectively. Finally, the two new epoxides **9a** and **9b** displayed highly similar ^{13}C and ^1H NMR spectra. Both of them displayed a pair of ^{13}C signals between δ_C 70−80 and 60−70 and two other pairs at ca. δ_C 150

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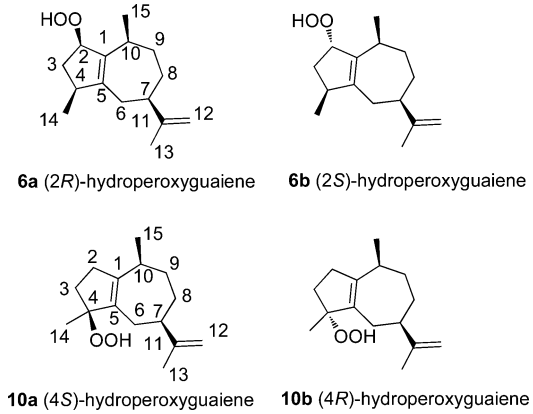
and 110, suggesting the presence of two C−O bonds along with the presence of two C═C bonds for each analogue. Their ^{1}H NMR spectra indicated the presence of two methyl groupings, one as a deshielded singlet around δ_H 1.6 and one more shielded doublet near δ_H 1.0. Two additional deshielded vinyl proton signals at around δ_H 5.0 for each isomer also indicated the presence of two ═CH_2 groupings for each isomer. HMBC spectra of both analogues showed correlations from the vinylic H-14 to quaternary carbon C-4 and the oxygenated C-5 and from the shielded Me-15 to the other oxygenated tertiary carbon C-1, supporting the presence of an epoxy ring at the bridged carbons. On the basis of further analysis of their 2D NMR spectra, the structures of **9a** and **9b** were elucidated as shown in Figure 3. The orientations of the epoxy moiety in these two sesquiterpenoids were not resolved due to the lack of any NOE associations. However, as noted in our previous study showing that the β-epoxides of guaiene and guaiol displayed shorter GC retention times than their α-isomers and the fact that **9a** displayed a shorter retention time than **9b**, the epoxy moiety of **9a** was tentatively characterized as being β-oriented and that of **9b** α-oriented.[27]

Identification of the C-2 and C-4 Hydroperoxides as Intermediates during the Autoxidation of α-Guaiene (1). The diverse structures of the oxygenated sesquiterpenoids formed during the autoxidation of **1** as described above display one or more of three types of oxygen moieties, namely, carbonyl, hydroxy, and epoxy moieties, the majority of which could be foreseen as being generated by the decomposition/consumption of the C-2 or C-4 hydroperoxides (**6a**/**b** and **10a**/**b**) of α-guaiene (**1**) (Figure 4). Taking into account the



6a (2*R*)-hydroperoxyguaiene **6b** (2*S*)-hydroperoxyguaiene

10a (4*S*)-hydroperoxyguaiene **10b** (4*R*)-hydroperoxyguaiene

Figure 4. C-2 and C-4 hydroperoxides of α-guaiene (**1**).

likelihood of decomposition of any unstable hydroperoxy intermediates on silica-based chromatography during purification, we performed another large-scale isolation of the autoxidation products of **1** employing MLCCC, which is a neutral method of isolation, as it does not require a solid support phase, in order to search for the presence of the C-2 and C-4 guaiene hydroperoxides. The solvent system MeCN/*t*-BuOMe/*n*-hexane (10:1:10, descending mode) was found to be effective for separation. Two pure hydroperoxides, **6b** and **10a**, substrates **2**, **4a**, and **7a**/**b**, and the acid-sensitive guaiene-bridged monoepoxides **5a** and **5b** were successfully isolated along with several inseparable mixtures of hydroperoxides containing **6a** and **10b**. The pair of epoxides **5a** and **5b** accounted for 2% and 9% of the products by GC and were identical to authentic standards.[20]

HRMS analysis of **6b** and **10a** showed $[M + H]^+$ m/z values of 237.1840 and 237.1837, respectively, indicative of a common molecular formula, $C_{15}H_{24}O_2$ (calcd for $C_{15}H_{25}O_2$ 237.1855). Both hydroperoxides **6b** and **10a** displayed characteristic −OO*H* moieties, as indicated by their ^{1}H signals at δ_H 7.00 and 6.71 and ^{13}C signals at δ_C 92.6 and 97.6 in the ^{1}H and ^{13}C NMR spectra, respectively. Compound **6b** differed from **10a** in having an extra signal of an allylic proton on the carbon bearing the −OOH at δ_H 4.96 and a more shielded methyl doublet at δ_H 0.84 as opposed to the methyl singlet of **10a** appearing at δ_H 1.21 in the ^{1}H NMR spectra. The connectivity of all carbons and full assignment of ^{1}H and ^{13}C signals were established on the basis of 2D NMR analysis including COSY, HSQC, and HMBC correlations. The C-2 configuration of **6b** was determined as *S* with the −OOH α-oriented based on the analysis of the ROESY spectrum, which showed correlations between H-2 and H_3-15, H-2, and H-3b, and H-3b and H_3-14 (Supporting Information). Moreover, reduction of **6b** with $LiAlH_4$ afforded (2*S*)-rotundol (**7b**), confirming the stereochemical assignments made for **6b**. The ROESY spectrum of **10a** showed interactions between H_3-15 and H-9b, H-9a and H-6b, and H-6a and H_3-14, indicative of opposite orientations of Me-14 and Me-15. Since the orientation of Me-15 would remain β from the starting material **1**, Me-14 of **10a** was therefore assigned as α-oriented. Furthermore, the observation that **10a**, with a β-oriented hydroperoxy moiety, decomposed upon GC-MS analysis to afford significant amounts of the β-epoxide **9a** with a retention time at 16.86 min without the formation of **9b** was consistent with the aforementioned tentative assignment of β-epoxy **9a** and supported the previous stereochemical assignments of **9a**/**b**.

The two hydroperoxides **6b** and **10a** decomposed readily upon GC-MS analysis (Figure 5A and B) but were relatively stable in the pure state, with only slow decomposition seen by TLC analysis. Decomposition of 2-hydroperoxyguaiene (**6b**) during GC analysis afforded rotundone (**2**) and the (2*S*)-rotundol (**7b**) as the major products, while decomposition of 4-hydroperoxyguaiene (**10a**) under the same conditions afforded the diketone chabrolidiones A **3a**/**b** and the monoepoxide **9a** as significant products. It is clear that the secondary hydroperoxide **6b** prefers to undergo the common decomposition routes to afford an alcohol and/or ketone, while the tertiary hydroperoxide **10a** prefers fragmentation or elimination pathways, as discussed in greater detail in the mechanistic section below.

Apart from the pure isolated hydroperoxides **6b** and **10a**, we also obtained three fractions of hydroperoxide mixtures (MF2, -4, and -5) that were inseparable due to their extremely similar polarities. Among the three mixtures, the (2*R*)-hydroperoxide **6a** and the (4*S*)-hydroperoxide **10b** could be tentatively identified as two major components in fractions MF2 and MF4, respectively. Reduction of MF2 with $LiAlH_4$ furnished (2*R*)-rotundol (**7a**) as a major product, whereas GC-MS analysis of MF4 gave the α-bridged monoepoxide **9b** as the main product with a small proportion of β-bridged epoxide **9a**. MF5 contained mainly peroxides that were relatively nonpolar and displayed one spot on TLC (Et_2O/*n*-hexane, 20%) with an R_f of 0.93 and one major peak (ca. 80%) at t_R = 22.02 min upon GC-MS analysis. However, ^{1}H and ^{13}C NMR spectra of this fraction indicated it to be a complex mixture of peroxide isomers displaying typical double-bond and hydroperoxy moieties. The identities of these peroxide species were not established.

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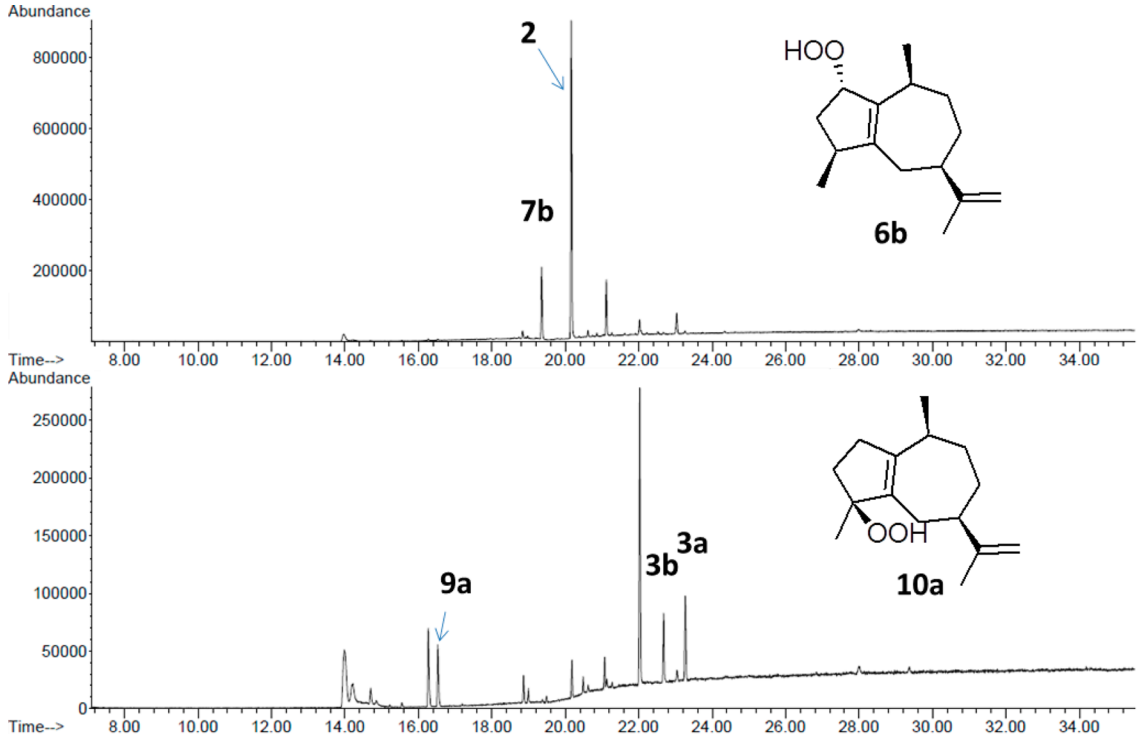

Figure 5. (A) GC chromatogram of hydroperoxide **6b**; (B) GC chromatogram of hydroperoxide **10a**.

Overoxidation of Rotundone (2) and the Rotundols (7a/b). In our previous preliminary study on the autoxidation of α-guaiene (**1**) and the formation of rotundone (**2**) we noted that overoxidation of **2** may be occurring during prolonged periods of autoxidation.[20] Furthermore, the formation of β-ketols **8a** and **8b** in the current autoxidation studies also suggests that the initially formed oxidation product **2** could be undergoing further oxidation via the formation and decomposition of the 4-hydroperoxyrotundone. With a view to identifying any additional secondary oxidation products of **2** and the rotundols **7a/b** such as the epoxides **11a/b**, **12a/b**, and **13a/b**, we carried out the formal syntheses of these compounds as depicted in Scheme 1.

Epoxidation of **2** with excess *m*-CPBA in CH_2Cl_2 yielded only the terminal epoxide epimers **11a** and **11b** in average yields without the formation of bridged epoxides **13a/b**. Attempts to synthesize **13a/b** by epoxidation of the electron-poor bridged enone C═C bond of **2** with other epoxidizing reagents (e.g., DMDO, H_2O_2, or TBHP with bases) gave predominantly terminal epoxides in low yields. In order to prepare **13a/b**, we therefore resorted to utilizing the hydroxyl directing effect of the hydroxy moiety within the rotundols **7a/b** to realize the epoxidation of the centrally bridged double bond. Both **7a/b** were prepared in one pot via the reduction of rotundone (**2**), with the structure of **7a** confirmed by X-ray analysis (Supporting Information). Epoxidation of **7a** and **7b** employing stoichiometric *m*-CPBA in CH_2Cl_2 permitted installation of the bridged epoxy moiety in both a regio- and stereoselective manner, yielding β-epoxy-(2*R*)-rotundol (**12a**) and α-epoxy-(2*S*)-rotundol (**12b**) in 76% and 95% yields, respectively. Further oxidation of **12a/b** with pyridinium chlorochromate (PCC) in CH_2Cl_2 furnished the bridged β-epoxyrotundone (**13a**) and α-epoxyrotundone (**13b**) in excellent yields of 91% and 94%, respectively. The stereochemistries of the bridged and terminal epoxides within these substrates were established by X-ray diffraction analyses of (11*R*)-epoxyrotundone (**11a**) and α-1,5-epoxyrotundone (**13b**) (Supporting Information). Finally, attempts to synthesize **8a** via simple allylic oxidation with SeO_2 and *tert*-butylhydroperoxide (TBHP) gave terminal aldehyde **14** as the dominant product in 54% yield.

Scrutiny of the GC-MS chromatograms of the crude autoxidation products by comparing the retention times and MS of these synthetic standards failed to identify the epoxides **11a/b** and **13a/b** as autoxidation products of α-guaiene (**1**), possibly due to low levels of formation of these compounds after a relatively short period (20 h) of oxidation. However, since pure rotundone (**2**) was readily available, we left neat **2** under a pure O_2 atmosphere at ambient temperature and monitored its autoxidation by GC-MS over a 46-day period, after which time only 26% of **2** had been consumed. At this time point, the major products of autoxidation were the β-ketols **8a/b** (10%) along with the terminal epoxides **11a/b** (8%) and minor amounts of the bridged epoxides **13a/b** (0.4%). Formation of **8a/b** and **11a/b** was observed to be much faster than the formation of **13a/b**. After one year, approximately 75% of **2** was consumed in the neat state with many other unidentified highly oxidized products observed by GC-MS, as indicated by their longer retention times and increased molecular weights. The autoxidation of rotundols **7a** and **7b** was also monitored; both readily afforded **2** as the dominant product at varying reaction rates. For example, oxidation of neat **7a** under a pure O_2 atmosphere at room temperature was complete within 72 h and afforded **2** (32%), **8a** (6%), and **8b** (8%) as the major products. Oxidation of **7b** was much slower and took up to 17 days to initiate; however it was completed quickly within 2 days after initiation had commenced. This demonstrates the dynamics of these autoxidation reactions.

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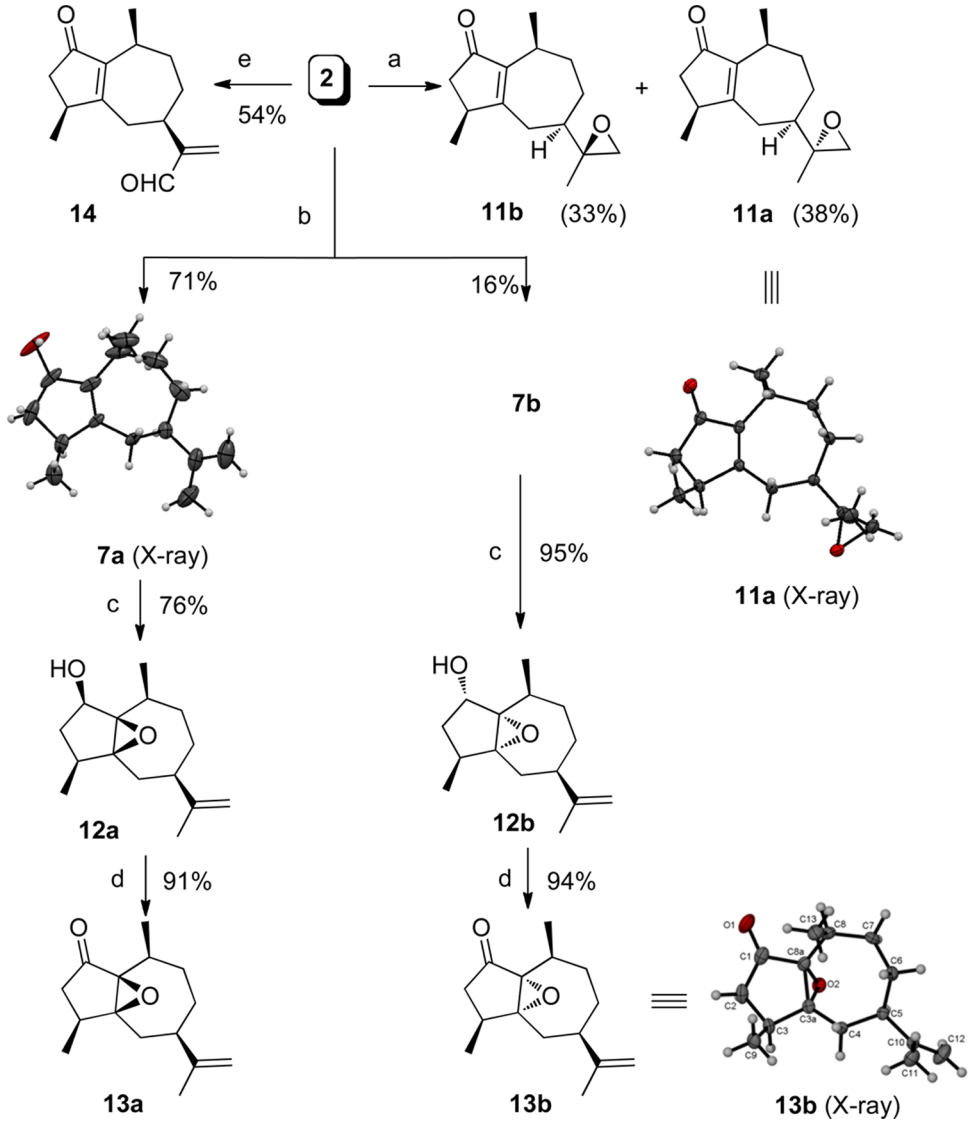
Scheme 1. Synthesis of Epoxides 11a/b, 12a/b, and 13a/b and Aldehyde 14



Synthesis of 7-epi-Chabrolidione A (3a), 1,7-Di-epi-chabrolidione A (3b), and Ketoaldehyde (3c) as Potential Hock Cleavage Products. The formation of the chabrolidiones **3a**/**b** appeared to result from the oxidative cleavage of the five-membered ring of α-guaiene (**1**), and they feature the presence of two carbonyl moieties. The formation of dicarbonyls from allylic hydroperoxides has long been known to proceed via the acid-catalyzed Hock cleavage mechanism.[28] Given that the presence of the hydroperoxides **6a**/**b** and **10a**/**b** had been established as autoxidation products, coupled with the fact that thermal decomposition of pure **10a** during GC-MS analysis afforded **3a**/**b**, we suspected that exposure to trace amounts of acid during workup or during the autoxidation reactions themselves was inducing Hock cleavage of the C-4 guianene hydroperoxides of guaiene **10a**/**b** and resulting in the formation of the epimers of chabrolidione A **3a**/**b** as depicted in Scheme 2. Furthermore, Hock cleavage of the C-2 guianene hydroperoxides of **6a**/**b** has a similar propensity to form the downstream ketoaldehydes **3c**/**d** under acid conditions, although the latter derivatives were not isolated from the original autoxidation mixture (Scheme 2).

In order to establish whether the ketoaldehydes **3c**/**d** were present as products of autoxidation of **1** and to further confirm the structures of diketones **3a**/**b**, we carried out short syntheses of three of these four compounds (**3a**–**c**). The key protocol involved the oxidative cleavage of various olefins with ozone (Scheme 3). The appropriate precursors **15**, **19**, and **21** were prepared from α-guaiene (**1**) and guaiol (**15**) by ring-opening of their bridged epoxides followed by selective dehydration as described recently.[27] Ozonolysis of benzylate **16** gave the diketone **17** in 54% yield, which upon hydrogenolysis furnished the diketoalcohol **18** quantitatively. Dehydration of **18** with $SOCl_2$ in benzene afforded the 7-epi-chabrolidione A (**3a**) in 51% yield. The ^1H and ^{13}C NMR spectra of synthetic **3a** were identical to reported data.[20] Attempted epimerization of **3a** into **3b** under either basic or acidic conditions [e.g., Na_2CO_3/MeOH, NaOH/EtOH, or Amberlite resin (H^+)] failed, presumably due to competing facile aldol condensation reactions. Alternatively, and with synthetic (1*R*)-4-isoguaiol (**19**) in hand,[27] **3b** was readily prepared via ozonolysis of **19** followed by dehydration utilizing $SOCl_2$ in benzene in 42% yield over two steps (Scheme 3). The identity of **3b** as one of the Hock cleavage products of tertiary hydroperoxide **10a** or

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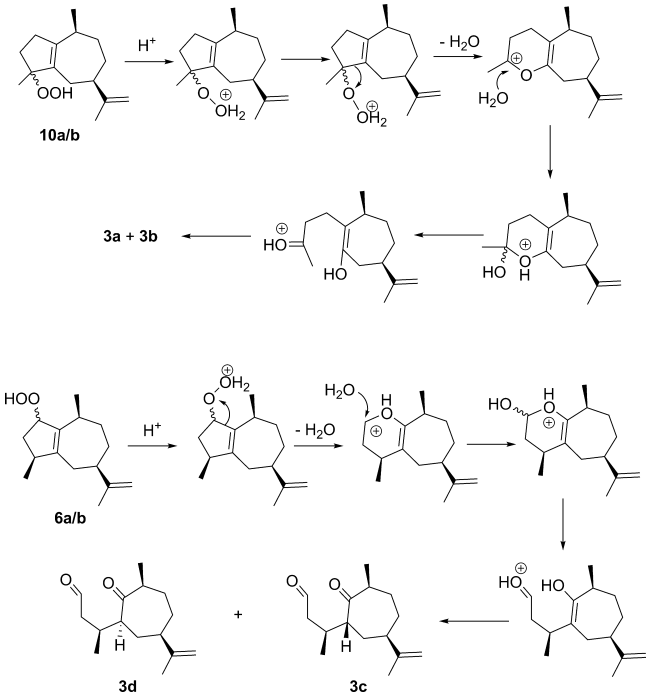
Scheme 2. Formation of 3a/b and 3c/d by Hock Cleavage of 10a/b and 6a/b, Respectively



10b was established by co-injection of pure synthetic derivatives with the autoxidation crude products and by comparison of their retention time and MS data by GC-MS analysis utilizing several different columns.

Since the presence of **3a** and **3b** as potential Hock cleavage products of **10a** and **10b** was now confirmed, we shifted our focus to the synthesis of **3c**. Synthesis of **3c** using ozonolysis would require the installation of a C-1−C-2 double bond via dehydration of C-1 alcohol **21**.[27] However, the additional terminal double bond would require protection prior to ozonolysis. Consequently the terminal double bond was converted into epoxide **22**, the C-1 alcohol dehydrated, and epoxide **23** ring-opened with AlH_3 to afford **24** in 41% yield over three steps (Scheme 3). The stereochemistry of guaia-1(2)-en-11-ol (**24**) was confirmed by X-ray crystallography (Supporting Information). Ozonolysis of **24** proceeded smoothly to yield the ketohydroxyaldehyde (**25**) in 58% yield. The terminal hydroxyl group was eliminated with $SOCl_2$ in toluene to form a mixture of the diketo-alkenes **3c** and **26** in a ratio of 1:1 in 94% yield. Purification of this mixture by SCC resulted in significant mass loss due to tight separation and acid-induced decomposition. Repeated separation of the reaction products employing MLCCC (MeCN/*t*-BuOMe/PE, 10:1:10, descending mode) afforded **3c** in pure form. The configuration at C-5 of **3c** was established as *R* on the basis of ROESY correlations displayed between H-5 and H_3-13, H_3-14, and H_3-15 and the confirmed stereochemistry of its precursor (**24**). The identity of **26** was tentatively elucidated as shown based on EIMS showing *m*/*z* 236 as the $[M]^+$ peak and the ^1H NMR spectrum showing the presence of an additional methyl singlet at δ_H 1.45 and the absence of two terminal olefinic proton signals at δ_H 4.76 and 4.67 as compared to that of **3c**. Examination by GC-MS of the retention time, MS of **3c**, and the GC chromatograms after injection of a mixture of **6a/b** and also with the crude autoxidation reaction products of **1** employing several different GC columns precluded the presence of **3c** as a product of the autoxidation of **1**.

Mechanistic Rationale of the Autoxidation of α-Guaiene (1). The autoxidation of α-guaiene (**1**) resembles that of lipids whose mechanisms have recently been reviewed.[29] On the basis of the autoxidation products isolated and identified, several mechanistic pathways may be proposed for the formation of the autoxidation products reported herein and are outlined in Scheme 4.

The autoxidation may begin with H atom abstraction by oxygen of an allylic hydrogen from four potential sites within the bicyclic [5,7]-fused structure of α-guaiene (**1**). There was no clear evidence for the formation of oxidized products resulting from allylic hydrogen abstraction within the seven-membered ring; however the isolation of the C-2 and C-4 hydroperoxides **6a/b** and **10a/b** clearly suggests that abstraction is preferred from within the smaller five-membered ring of **1** as observed previously.[30,31] Once formed, the secondary hydroperoxides **6a/b** may decompose via O−O bond cleavage to furnish alcohols and ketones as major products as typically expected.[28,29] Consequently, (2*R*)-hydroperoxyguaiene (**6a**) would afford (2*R*)-rotundol (**7a**), and (2*S*)-hydroperoxyguaiene (**6b**) would lead to the formation of (2*S*)-rotundol (**7b**). Both epimeric C-2 hydroperoxides **6a/b** would also lead to the formation of rotundone (**2**). In addition, once the rotundols **7a/b** are formed, they may themselves undergo further oxidation to form **2**, as was confirmed herein through overoxidation studies on pure samples of the rotundols **7a/b**. Moreover, the formation of the observed 4-hydroxyrotundones **8a/b** presumably results from the overoxidation of **2** itself. Indeed, we found that allowing pure **2** to oxidize under an oxygen atmosphere led to the formation of **8a/b** and presumably occurred via the requisite 4-hydroperoxy intermediates.

Unlike the secondary 2-hydroperoxides **6a/b**, the tertiary C-4 hydroperoxides **10a/b** lack an allylic hydrogen on the carbon bearing the OOH moiety and consequently decompose in a different fashion (Scheme 4). The preferential decomposition route for **10a/b** appears to be via the known Hock cleavage pathway, as outlined above, and would be catalyzed by trace amounts of acid, resulting in the formation of **3a/b**. Direct thermal decomposition of **10a** during GC analysis also afforded **3a/b**, suggesting that a thermally induced fragmentation pathway may also be operating in the background. The formation of **9a/b** is also quite intriguing and requires both an epoxidation and elimination step. Given that **10a** thermally decomposed during GC analysis to also afford a significant amount of **9a**, it appears that the 4-hydroperoxides **10a/b** either are the direct precursors to epoxides **9a/b** or at least suggest that activation of the C-4 position as a hydroperoxide can lead to a pathway of elimination upon decomposition and the installation of the requisite double bond within **9a/b**. Presumably, the formation of the bridged epoxide moiety within these derivatives is simply a result of the fact that one or more of the hydroperoxides being formed *in situ* is acting as a peroxidizing agent and provides for the formation of the epoxides in a similar fashion as has been seen for the epoxidization of α-guaiene (**1**) itself with various peracids.[27] Furthermore, the observed monoepoxides **5a/b** presumably are being formed in a similar fashion and once formed may also be able to undergo additional oxidation at C-4 followed by elimination to provide for an alternative route to **9a/b**.

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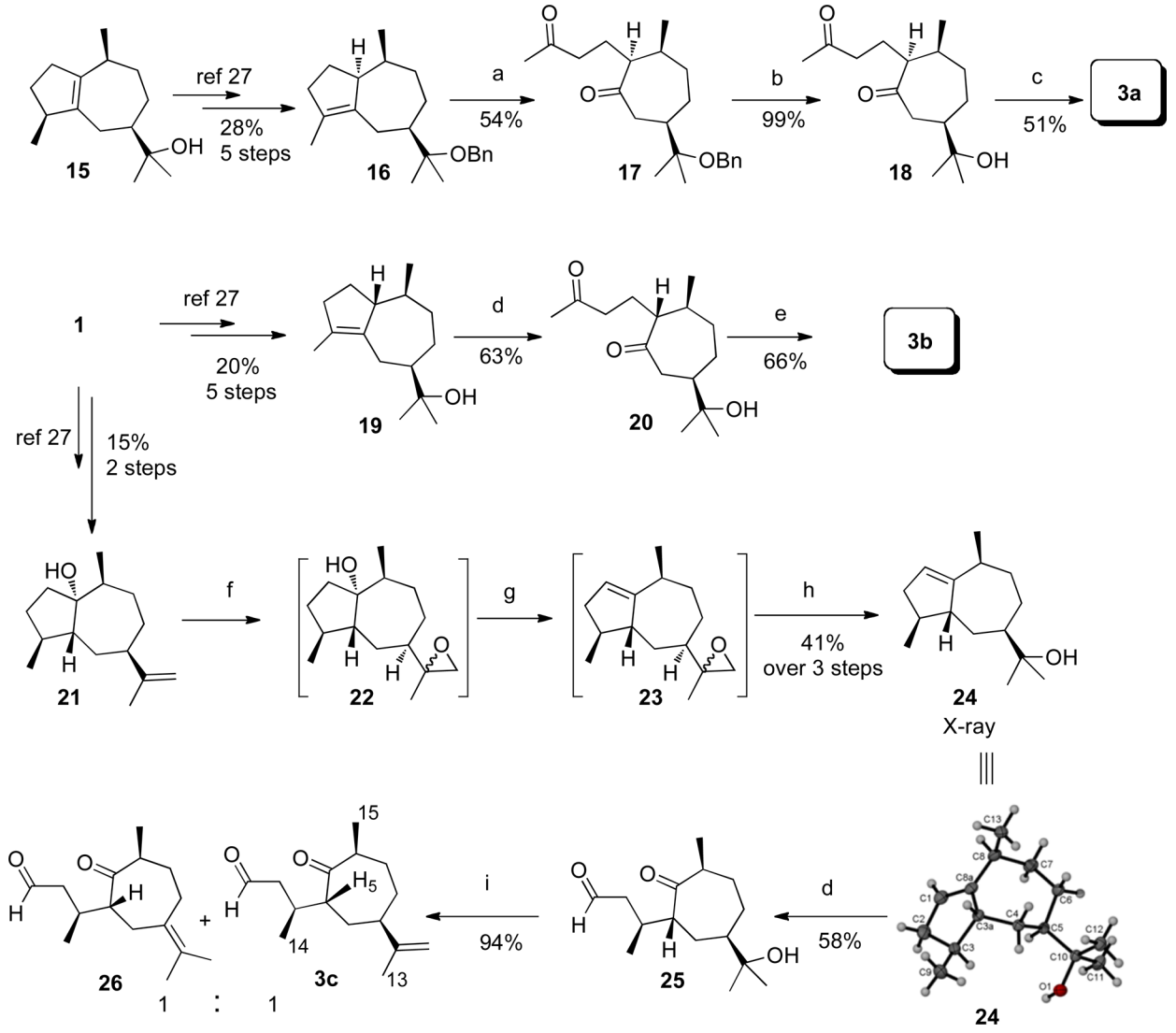
Scheme 3. Synthesis of 7-epi-Chabridione A (3a), 1,7-Di-epi-chabridione A (3b), and Ketoaldehyde 3c



Finally, the formation of corymbolone (**4a**) and its C-6 epimer **4b** required the oxidative cleavage of the central C═C bond of α-guaiene **1**. While the oxidizing species that performs this cleavage is currently unknown, it is highly likely that this oxidative process proceeds via the 1,2-dioxetane of **1** and results in the formation of the cyclic diketone, which simply undergoes an aldol-type cyclization to form the observed corymbolones **4a**/**b**. Indeed such aldol-type cyclizations have been reported previously for these systems.[28]

Autoxidation has been an important topic in lipid and steroid chemistry due to the wide exposure of lipids to molecular oxygen in Nature.[29] However, its role in terpene chemistry has not been extensively explored. We have demonstrated herein a case study of the autoxidation of α-guaiene (**1**), showing that this could lead to the generation of a range of oxygenated sesquiterpenoids. Two unstable hydroperoxides, **6b** and **10a**, and 13 downstream sesquiterpenoids have been isolated from the autoxidation mixture of the bicyclic sesquiterpene α-guaiene (**1**) on cellulose filter paper. One of the natural products isolated of significance was rotundone (**2**), which is the only known impact odorant displaying a peppery aroma. Other products included corymbolone (**4a**) and its C-6 epimer **4b**, the (2*R*)- and (2*S*)-rotundols (**7a**/**b**), and several hitherto unknown epimers of natural chabrolidione A, namely, 7-epi-chabrolidione A (**3a**) and 1,7-di-epi-chabrolidione A (**3b**). Two 4-hydroxyrotundones (**8a**/**b**) and a range of epoxides (**9a**/**b** and **5a**/**b**) were also formed in significant amounts during autoxidation. The mechanisms of formation of the majority of the products may be accounted for by initial formation of the C-2- and C-4 hydroperoxyguaienes (**6a**/**b** and **10a**/**b**) followed by various fragmentation or degradation pathways. Given that α-guaiene (**1**) is well known to exist in the essential oils of numerous plants, coupled with the fact that aerial oxidation to form this myriad of downstream oxidation products occurs readily at ambient temperature, suggests that many of them have been overlooked during previous isolation studies from natural sources.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points are uncorrected and were obtained on a Buchi B-540 melting point apparatus. All reagents were purchased from commercial sources and used directly unless otherwise stated. Solvents for synthesis were purified according to known procedures where necessary.[32] Solvents for general chromatography were AR grade, and those used for GC-MS and HRMS analysis were HPLC grade. All reactions were

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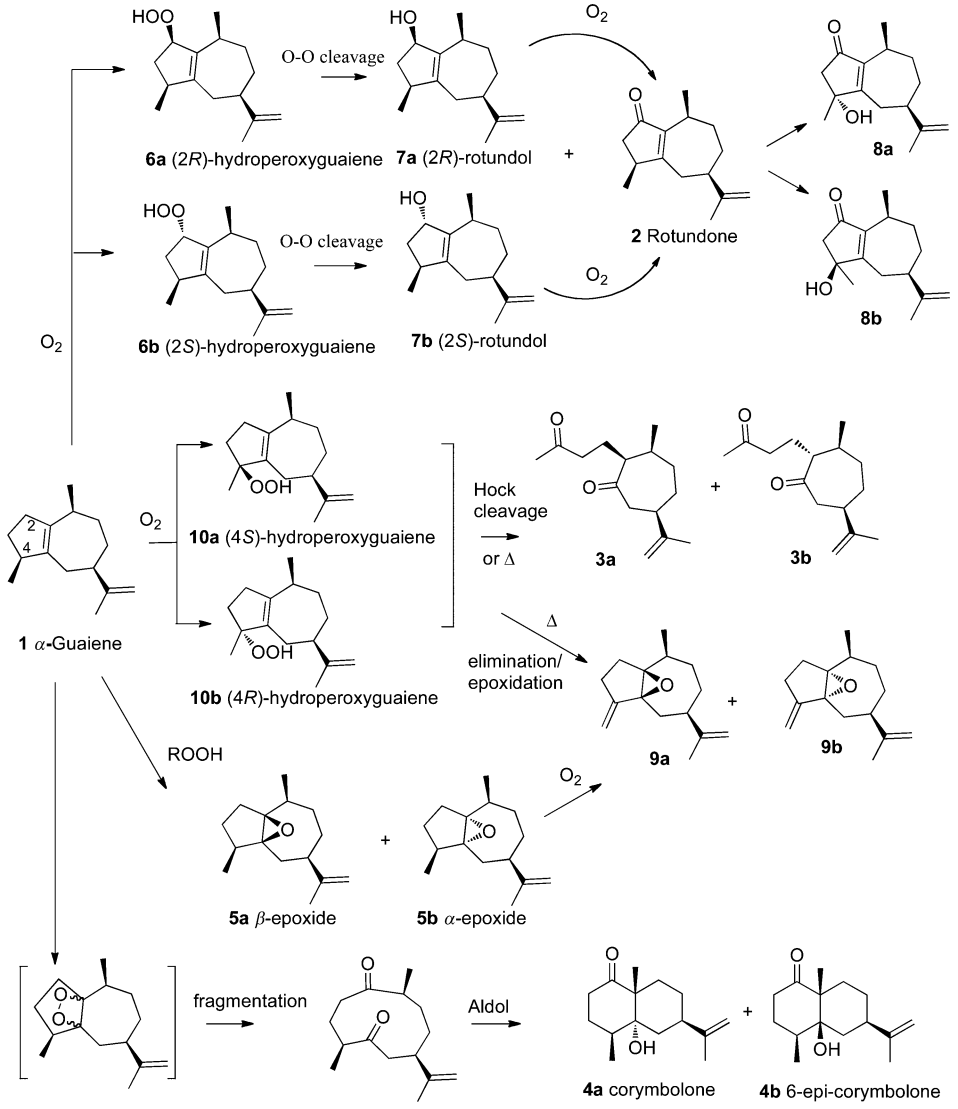
Scheme 4. Mechanistic Rationale of the Autoxidation of α-Guaiene (1)



conducted under a N_2 atmosphere except for ozonolysis. Silica column chromatography was performed using either LC60A 40−63 μm silica (Grace Davison) or silica gel 60 (0.015−0.040 mm) from Merck. TLC and preparative TLC were conducted with TLC silica gel 60 F_{254} plates (Merck KGaA) using standard vanillin stain for visualization. Silver nitrate impregnated silica (SNIS) was prepared according to the literature.[33] GC-MS/FID analysis was performed on a 6890 GC coupled with a 5973N MSD or a 7890A GC-FID (Agilent Technologies). VF-Wax (60 m × 0.25 mm, i.d. × 0.25 μm film thickness), DB-5 (60 m × 0.32 mm, i.d. × 0.25 μm film thickness), and HP-5 (30 m × 0.32 mm, i.d. × 0.25 μm film thickness) capillary columns (Agilent Technologies) were used for GC-MS/FID analyses in this study. HRMS (ESI-TOF) analysis was performed on a Triple TOF 5600 mass spectrometer from AB Sciex Instruments. MLCCC separation was carried out on an MK5 LabPrep 1000 machine (AECS QuikPrep) coupled with two LC1110 HPLC pumps (GBC) and a FRAC-100 fraction collector (Phamacia Fine Chemicals). NMR data were recorded on Varian-Inova 500/600 MHz spectrometers. All compounds for NMR analysis were dissolved in either $CDCl_3$ or benzene-d_6. All ^1H and ^{13}C NMR spectra were calibrated with residual deuterated solvent signals set at 7.26 and 77.0 ppm for $CDCl_3$ and 7.16 and 128.06 ppm for benzene-d_6, respectively. COSY, ROESY, HSQC, and HMBC were common 2D NMR techniques used for full assignment of ^1H and ^{13}C NMR signals.

Isolation of Autoxidation Products by SCC. α-Guaiene (**1**, 2 g, 9.8 mmol) was loaded onto a single sheet of filter paper (Whatman grade 1, 180 mm diameter) that was prerolled and placed into a 10 mL test tube. The test tube was initially filled with CH_2Cl_2, and the solvent evaporated under a N_2 stream to enable an even coating of **1** onto the filter paper. The test tube was placed in an oven (50 °C) for ca. 20 h, and the autoxidation monitored by TLC and GC-MS regularly. The reaction products were extracted with CH_2Cl_2 using continuous Soxhlet extraction under N_2 for 12 h. The extract was concentrated *in vacuo*, and the residue loaded onto base-treated silica (pretreated with 5% Et_3N). Gradient elution with Et_2O/*n*-hexane (2:98, 5:95, 6:94, 8:92, 12:88, 15:85, 16:84, 17:83, 19:81, 20:80, 23:77, 26:74, and 50:50) gave mixtures of compounds in different fractions, which were combined accordingly (based on TLC and GC-MS) to give seven main fractions: F1 (from 2:98 to 6:94), F2 (from 8:92 to 12:88), F3 (from 15:85 to 17:83), F4 (from 19:81 to 20:80), F5 (from 20:80 to 23:77), F6 (from 23:77 to 26:74), F7 (50:50). F1, containing mainly compounds of retention times 16.86 and 17.06 min, was subjected to repeated silica chromatography (15−40 μm, Et_2O/*n*-hexane, 0.5:99.5) to furnish pure **9a** (2 mg, t_R = 16.86 min) as a colorless liquid and **9b** (2.5 mg, t_R = 17.07 min) as a colorless oil. F2 contained ca. 10% **4b** (t_R = 25.6 min) based on the GC chromatogram and several other known compounds including rotundone (**2**) and the epimeric rotundols (**7a** and **7b**). This mixture was subjected to MLCCC utilizing the solvent system MeCN/*t*-BuOMe/*n*-hexane (10:1:10, ascending mode) to

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afford **4b** of ca. 60% purity, pure **2** (108 mg) as a pale yellow oil, **7a** (13 mg) as white crystals, and **7b** (5 mg) as a colorless liquid. **4b** of 60% purity was further purified by SCC (15−40 μm, Et_2O/*n*-hexane, 8:92) to give pure **4b** (5 mg) as a colorless liquid. F3, containing diketone **3a** as the relatively more abundant compound in the mixture, was purified by repeated SCC (15−40 μm, Et_2O/*n*-hexane, 15:85) to afford **3a** (2 mg) as a colorless oil. F4 contained a complex mixture of minor products, and so no separation was attempted. F5, containing mainly corymbolone (**4a**), was recrystallized from Et_2O/*n*-hexane (8:92) to give pure **4a** (52 mg) as colorless crystals. F6, containing **8a** and **8b**, was purified by repeated SCC (Et_2O/*n*-hexane, 25:75) to give a relatively pure mixture of the keto alcohols **8a** and **8b**, which were further purified by repeated preparative TLC (MeOH/EtOAc/*n*-hexane, 4:20:76) to furnish pure **8a** (5.3 mg) and **8b** (4.1 mg) as colorless liquids. F7 simply contained small amounts of column residues.

Isolation of Autoxidation Products Using MLCCC. α-Guaiene (**1**, 1.0 g, 5 mmol) was coated onto a single sheet of filter paper in a test tube according to the procedure described above. The α-guaiene-coated filter paper was kept in a 50 °C oven for 16 h. The oxidation products were extracted by Soxhlet extraction from refluxing CH_2Cl_2 under N_2 for 12 h. The extracts were concentrated *in vacuo*, and the residue was separated by MLCCC (MeCN/*t*-BuOMe/*n*-hexane, 10:1:10, descending mode) to give five main fractions of hydroperoxides (MF1−MF5), monoepoxides **5a** (3 mg) and **5b** (11 mg), unreacted **1** (280 mg), and several of the previously isolated compounds **2**, **4a**, **7a**, and **7b**. MF1 (80 mg) and MF3 (86 mg) contained mainly hydroperoxides **6b** and **10a**, respectively. MF2 (93 mg) contained mixtures of hydroperoxides **6b**, **10a**, and **10b**, judging from the presence of their corresponding decomposition products **7b**, **9a**, and **9b** in the GC chromatogram. MF4 (220 mg) contained mixtures of hydroperoxides including **6a**, **10a**, and **10b**, with **6a** being the main product identified by the formation of **7a** as one main product after the reduction of the mixture with $LiAlH_4$. MF5 (39 mg) showed one main spot upon TLC analysis and one main peak upon GC-MS analysis. All fractions (MF1−MF5) were further purified by MLCCC separately using the same solvent system. Pure hydroperoxide **6b** (45 mg) and **10a** (50 mg) were obtained as colorless oils from MF1 and MF3, respectively. Repeated separation of MF2, MF4, and MF5 with MLCCC failed to furnish pure compounds. MF2 and MF4 gave mixtures of hydroperoxides in different ratios. Purified MF5 (17 mg) appeared to be pure, as it displayed only one single spot on TLC (*n*-hexane) and one major peak accounting for 83% in GC-MS analysis. However, ^1H and ^{13}C NMR analysis indicated the purified fraction MF5 was a mixture of peroxides that were not able to be characterized herein due to the large extent of overlapping signals in the NMR spectra.

(4*S*,4a*R*,6*R*,8a*R*)-4a-Hydroxy-4,8a-dimethyl-6-(prop-1-en-2-yl)octahydronaphthalen-1(2*H*)-one (corymbolone) (4a): EIMS *m*/*z* (rel intensity) 236 (10), 218 (18), 203 (33), 194 (9), 175 (28), 161 (16), 147 (13), 135 (43), 124 (38), 109 (100), 93 (48), 69 (59), 55 (52). All physical and chemical properties were identical to those previously reported.[21]

(4*S*,4a*S*,6*R*,8a*R*)-4a-Hydroxy-4,8a-dimethyl-6-(prop-1-en-2-yl)octahydronaphthalen-1(2*H*)-one-methane (4b): ^1H NMR (benzene-d_6, 600 MHz) δ 4.88 (1H, s, H-12a), 4.66 (1H, s, H-12b), 2.57 (1H, d, *J* = 1.8 Hz, -O*H*), 2.37 (1H, ddd, *J* = 15.0, 13.2, 7.8 Hz, H-3a), 2.32 (1H, ddd, *J* = 15.0, 14.4, 4.2 Hz, H-10a), 2.25 (1H, ddd, *J* = 15.0, 6.0, 1.8 Hz, H-3b), 1.98 (1H, qd, *J* = 13.2, 6.0 Hz, H-4a), 1.89 (1H, br t, *J* = 6.6 Hz, H-8), 1.81 (2H, m, H-7a, H-9a), 1.60 (1H, qdd, *J* = 6.6, 4.8, 1.8 Hz, H-5), 1.58 (3H, s, H-13), 1.52 (1H, ddd, *J* = 15.0, 4.5, 3.0, H-10b), 1.42 (1H, dddd, *J* = 15.0, 14.4, 6.6, 4.5 Hz, H-9b), 1.33 (1H, dddd, *J* = 13.2, 7.8, 4.8, 1.8 Hz, H-4b), 1.15 (1H, dd, *J* = 14.4, 6.6 Hz, H-7b), 0.87 (3H, s, H-15), 0.86 (3H, d, *J* = 6.6 Hz, H-14); ^{13}C NMR (benzene-d_6, 150 MHz) δ 212.7 (C-2), 149.8 (C-11), 111.1 (C-12), 79.0 (C-6), 52.1 (C-1), 37.2 (C-8), 36.5 (C-3), 34.0 (C-5), 30.7 (C-7), 29.4 (C-4), 24.9 (C-10), 22.8 (C-13), 22.1 (C-9), 20.8 (C-15), 14.6 (C-14); EI-MS *m*/*z* (rel intensity) 236 (25), 218 (10), 203 (28), 185 (5), 175 (38), 161 (28), 147 (16), 137 (85), 109 (100), 93 (66), 69 (77), 55 (78); HRMS (ESI-TOF) *m*/*z* 237.1827 $[M + H]^+$ (calcd for $C_{15}H_{25}O_2$ 237.1855).

(1*R*,3*S*,5*R*,8*S*)-3,8-Dimethyl-5-(prop-1-en-2-yl)-1,2,3,4,5,6,7,8-octahydroazulen-1-ol (7a) and (1*S*,3*S*,5*R*,8*S*)-3,8-Dimethyl-5-(prop-1-en-2-yl)-1,2,3,4,5,6,7,8-octahydroazulen-1-ol (7b). To a solution of rotundone (**2**, 114.2 mg, 0.5 mmol) in MeOH (10 mL) was added $CeCl_3{\cdot}7H_2O$ (200.1 mg, 0.537 mmol). The resulting mixture was stirred under N_2 for 0.5 h and cooled to −78 °C, followed by the addition of $NaBH_4$ (19.9 mg, 0.53 mmol) in one portion. After 2 min, the reaction was quenched with saturated NH_4Cl solution (10 mL), and the reaction temperature allowed to rise to ambient temperature. The reaction mixture was extracted with ether (3 × 25 mL), and the combined ether layers were further washed with brine (20 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*, and the residue separated by SCC (15−40 μm, Et_2O/hexanes, 6:94) to recover rotundone (**2**, 25.0 mg, 21%), **7a** (63.8 mg, 71% based on 21% recovery) as colorless crystals, and **7b** (14.8 mg, 16% based on 21% recovery) as a colorless oil. Spectroscopic data of **7a** and **7b** were in agreement with those reported previously.[26] **7a:** mp 78−80 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 4.62 (1H, br s, H-12a), 4.57 (1H, br s, H-12b), 4.47 (1H, dq, *J* = 1.8, 1.2 Hz, H-2), 2.48 (1H, qdd, *J* = 7.2, 4.2, 3.6 Hz, H-10), 2.46 (2H, m, H-3a, H-4), 2.30 (1H, dd, *J* = 15.0, 12.6 Hz, H-6a), 2.02 (1H, dd, *J* = 15.0, 2.4 Hz, H-6b), 1.90 (1H, ddd, *J* = 12.6, 10.8, 2.4 Hz, H-7), 1.85 (1H, dddd, *J* = 12.0, 11.4, 10.8, 1.5 Hz, H-8a), 1.66 (3H, br s, H-13), 1.65 (1H, m, H-8b), 1.61 (1H, m, H-9a), 1.58 (1H, dddd, *J* = 14.4, 11.4, 3.6, 2.1 Hz, H-9b), 1.18 (1H, m, H-3b), 1.17 (3H, d, *J* = 7.2 Hz, H-15), 1.04 (3H, d, *J* = 7.0 Hz, H-14); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 152.2 (C-11), 143.9 (C-5), 143.6 (C-1), 108.14 (C-12), 81.4 (C-2), 46.4 (C-7), 42.6 (C-4), 41.9 (C-3), 33.7 (C-9), 3.6 (C-6), 31.6 (C-10), 31.1 (C-8), 21.1 (C-13), 20.4 (C-15), 19.2 (C-14); EIMS *m*/*z* (rel intensity) 220 ($[M]^+$, 20), 205 (10), 187 (16), 176 (12), 163 (100), 145 (30), 138 (22), 119 (61), 107 (40), 95 (49), 79 (30), 67 (28), 55 (33). **7b:** ^1H NMR (benzene-d_6, 600 MHz) δ 4.80 (1H, s, H-12a), 4.74 (1H, s, H-12b), 4.57 (1H, dd, *J* = 7.2, 4.2 Hz, H-2), 2.65 (1H, m, H-10), 2.52 (1H, m, H-4), 2.20−2.13 (2H, m, H-6a, and H-7), 2.01 (1H, d, *J* = 13.8 Hz, H-6b), 1.80 (1H, ddd, *J* = 13.8, 8.1, 4.2 Hz, H-3a), 1.74−1.71 (2H, m, H-8a, H-8b), 1.69 (1H, m, H-9a), 1.65 (3H, s, H-13), 1.65 (1H, ddd, *J* = 13.8, 7.2, 3.6 Hz, H-3b), 1.62- 1.57 (1H, m, H-9b), 1.01 (3H, d, *J* = 7.2 Hz, H-15), 0.84 (3H, d, *J* = 7.2 Hz, H-14); ^{13}C NMR (benzene-d_6, 150 MHz) δ 152.2 (C-11), 144.5 (C-5), 143.3 (C-1), 109.1 (C-12), 79.0 (C-2), 47.3 (C-7), 43.7 (C-4), 43.1 (C-3), 34.8 (C-9), 34.4 (C-6), 31.8 (C-8), 30.9 (C-10), 20.8 (C-13), 20.7 (C-14), 18.4 (C-15); EIMS *m*/*z* (rel intensity) 220 ($[M]^+$, 20), 205 (10), 187 (10), 177 (14), 163 (100), 145 (24), 137 (19), 119 (41), 105 (29), 95 (33), 79 (21), 67 (19), 55 (23).

(3*R*,5*R*,8*S*)-3-Hydroxy-3,8-dimethyl-5-(prop-1-en-2-yl)-3,4,5,6,7,8-hexahydroazulen-1(2*H*)-one (8a): ^1H NMR (benzene-d_6, 600 MHz) δ 4.73 (1H, dq, *J* = 1.8, 0.9 Hz, H-12a), 4.70 (1H, dq, *J* = 1.8, 1.5 Hz, H-12b), 3.22 (1H, qdd, *J* = 7.2, 4.2, 3.6 Hz, H-10), 2.45 (1H, dt, *J* = 15.6, 2.4 Hz, H-6a), 2.31 (1H, d, *J* = 18.0 Hz, H-3a), 2.28 (1H, dd, *J* = 15.6, 12.0 Hz, H-6b), 2.23 (1H, d, *J* = 18.0 Hz, H-3b), 1.77 (1H, tt, *J* = 12.0, 2.4 Hz, H-7), 1.70 (1H, dddd, *J* = 14.4, 12.0, 12.0, 2.4 Hz, H-8a), 1.63−1.58 (1H, m, H-8b), 1.58 (3H, s, H-13), 1.54 (1H, dddd, *J* = 14.4, 6.0, 4.2, 2.4 Hz, H-9a), 1.34 (1H, dddd, *J* = 14.4, 12.0, 3.6, 2.4 Hz, H-9b), 1.01 (3H, d, *J* = 7.2 Hz, H-15), 0.99 (3H, s, H-14); ^{13}C NMR (benzene-d_6, 150 MHz) δ 202.3 (C-2), 172.2 (C-5), 150.9 (C-11), 145.6 (C-1), 109.3 (C-12), 75.7 (C-4), 51.2 (C-3), 46.8 (C-7), 32.7 (C-9), 32.4 (C-6), 31.1 (C-8), 26.9 (C-10), 26.2 (C-14), 20.3 (C-13), 17.0 (C-15); EIMS *m*/*z* (rel intensity) 234 (4), 216 (78), 201 (20), 188 (22), 173 (32), 159 (43), 145 (34), 132 (52), 119 (33), 111 (57), 95 (100), 91 (72), 67 (41); HRMS (ESI-TOF) *m*/*z* 235.1684 $[M + H]^+$ (calcd for $C_{15}H_{23}O_2$, 235.1698).

(3*S*,5*R*,8*S*)-3-Hydroxy-3,8-dimethyl-5-(prop-1-en-2-yl)-3,4,5,6,7,8-hexahydroazulen-1(2*H*)-one (8b): ^1H NMR (benzene-d_6, 600 MHz) δ 4.76 (1H, dq, *J* = 1.8, 0.9 Hz, H-12a), 4.74 (1H, dq, *J* = 1.8, 1.5 Hz, H-12b), 3.24 (1H, qdd, *J* = 7.2, 4.2, 3.6 Hz, H-10), 2.56 (1H, d, *J* = 15.6 Hz, H-6a), 2.27, 2.22 (2H, ABq, *J* = 18.0 Hz, H-3a and H-3b), 2.11 (1H, dd, *J* = 15.6, 12.0 Hz, H-6b), 1.89 (1H, m, H-7), 1.67−1.63 (2H, m, H-8a and H-8b), 1.62 (3H, s, H-13), 1.58−1.52

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(1H, m, H-9a), 1.41 (1H, dt, J = 14.4, 3.6 Hz, H-9b), 0.96 (3H, d, J = 7.2 Hz, H-15), 0.93 (3H, s, H-14); ^{13}C NMR (benzene-d_6, 150 MHz) δ 202.7 (C-2), 171.9 (C-5), 151.1 (C-11), 145.6 (C-1), 109.3 (C-12), 75.7 (C-4), 51.0 (C-3), 46.8 (C-7), 32.7 (C-9), 32.1 (C-6), 31.0 (C-8), 27.1 (C-10), 26.1 (C-14), 20.5 (C-13), 17.3 (C-15); EIMS m/z (rel intensity) 234 (57), 219 (62), 201 (25), 191 (27), 176 (71), 59 (54), 148 (54), 133 (65), 119 (51), 111 (97), 10 (70), 91 (100), 79 (72); HRMS (ESI-TOF) m/z 235.1683 $[M + H]^+$ (calcd for $C_{15}H_{23}O_2$, 235.1698).

(3a*S*,4*S*,7*R*,8a*S*)-4-Methyl-1-methylidene-7-(prop-1-en-2-yl)-hexahydro-1*H*,4*H*-3a,8a-epoxyazulene (9a): ^{1}H NMR (benzene-d_6, 600 MHz) δ 5.09 (1H, dd, J = 2.7, 1.2 Hz, H-14a), 4.99 (1H, dd, J = 2.7, 1.2 Hz, H-14b), 4.74 (1H, dq, J = 2.4, 0.9 Hz, H-12a), 4.69 (1H, dq, J = 1.5, 1.2 Hz, H-12b), 2.34 (1H, d, J = 14.4 Hz, H-6a), 2.27 (1H, dddt, J = 15.0, 9.6, 9.0, 2.7 Hz, H-3a), 2.12 (1H, m, H-7), 1.97 (1H, ddt, J = 15.0, 9.0, 1.2 Hz, H-3b), 1.89 (1H, dqd, J = 9.0, 7.2, 2.4 Hz, H-10), 1.85 (1H, d, J = 14.4 Hz, H-6b), 1.83 (1H, dd, J = 13.2, 9.0 Hz, H-2a), 1.61−1.56 (1H, m, H-9a), 1.57 (3H, s, H-13), 1.52−1.48 (2H, m, H-8a and H-8b), 1.35 (1H, ddd, J = 13.2, 9.6, 9.0 Hz, H-2b), 1.22 (1H, dtd, J = 15.0, 4.8, 2.4 Hz, H-9b), 1.05 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 151.8 (C-4), 150.4 (C-11), 109.1 (C-12), 108.4 (C-14), 74.6 (C-1), 69.1 (C-5), 44.0 (C-7), 34.8 (C-10), 31.6 (C-8), 30.4 (C-2), 30.0 (C-6), 29.3 (C-9), 28.2 (C-3), 20.1 (C-13), 17.5 (C-15); EIMS m/z (rel intensity) 220 (1), 205 (13), 187 (29), 177 (18), 162 (22), 147 (33), 135 (11), 123 (46), 107 (100), 95 (58), 81 (70), 67 (51), 55 (47); HRMS (ESI-TOF) m/z 219.1732 $[M + H]^+$ (calcd for $C_{15}H_{23}O_1$, 219.1749).

3a*R*,4*S*,7*R*,8a*R*)-4-Methyl-1-methylidene-7-(prop-1-en-2-yl)-hexahydro-1*H*,4*H*-3a,8a-epoxyazulene (9b): ^{1}H NMR (benzene-d_6, 600 MHz) δ 4.99 (1H, dd, J = 2.7, 1.2 Hz, H-14a), 4.94 (1H, dd, J = 2.7, 1.2 Hz, H-14b), 4.76 (1H, dq, J = 1.8, 0.9 Hz, H-12a), 4.72 (1H, dq, J = 1.8, 1.5 Hz, H-12b), 2.51 (1H, br d, J = 14.4 Hz, H-6a), 2.46 (1H, tt, J = 11.4, 2.0 Hz, H-7), 2.36 (1H, dtt, J = 15.0, 9.0, 2.7 Hz, H-3a), 2.22 (1H, qd, J = 7.2, 6.0 Hz, H-10), 1.99 (1H, ddt, J = 15.0, 9.0, 1.2 Hz, H-3b), 1.96 (1H, m, H-9a), 1.82 (1H, dd, J = 14.4, 11.4 Hz, H-6b), 1.68 (1H, dt, J = 13.2, 9.0 Hz, H-2a), 1.61 (3H, s, H-13), 1.59 (1H, dd, J = 13.2, 9.0 Hz, H-2b), 1.50 (1H, m, H-8a), 1.32 (1H, dddd, J = 13.8, 6.0, 4.2, 2.0 Hz, H-9b), 1.28 (1H, ddd, J = 14.4, 11.4, 2.0 Hz, H-8b), 0.84 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 153.7 (C-4), 151.5 (C-11), 109.1 (C-12), 108.0 (C-14), 76.4 (C-1), 67.8 (C-5), 43.7 (C-7), 33.6 (C-10), 31.6 (C-6), 31.2 (C-9), 29.8 (C-8), 29.4 (C-2), 28.1 (C-3), 20.9 (C-13), 16.0 (C-15); EIMS m/z (rel intensity) 218 (18), 203 (24), 189 (9), 175 (48), 161 (35), 147 (35), 133 (100), 119 (46), 107 (43), 95 (39), 81 (34), 67 (41), 55 (38); HRMS (ESI-TOF) m/z 219.1732 $[M + H]^+$ (calcd for $C_{15}H_{23}O_1$, 219.1749).

Epoxides 5a/b. Spectroscopic data were identical to those reported by us recently.[20]

(1*S*,3*S*,5*R*,8*S*)-3,8-Dimethyl-5-(prop-1-en-2-yl)-1,2,3,4,5,6,7,8-octahydroazulen-1-yl hydroperoxide (6b): ^{1}H NMR (benzene-d_6, 600 MHz) δ 7.00 (1H, d, J = 1.8 Hz, −OO*H*), 4.95 (1H, ddd, J = 7.2, 2.4, 1.8 Hz, H-2), 4.75 (1H, dq, J = 2.4, 1.2 Hz, H-12a), 4.72 (1H, dq, J = 1.8, 1.5 Hz, H-12b), 2.70−2.64 (2H, m, H-4 and H-10), 2.32 (1H, ddd, J = 13.8, 7.8, 2.4 Hz, H-3a), 2.18 (1H, tq, J = 12.0, 1.8 Hz, H-7), 2.15 (1H, dd, J = 12.0, 3.6 Hz, H-6a), 2.04 (1H, d, J = 12.0 Hz, H-6b), 1.75−1.60 (4H, m, H-8a, H-8b, H-9a and H-9b), 1.62 (3H, s, H-13), 1.45 (1H, ddd, J = 13.8, 7.2, 5.4 Hz, H-3b), 1.02 (3H, d, J = 6.6 Hz, H-15), 0.84 (3H, d, J = 7.2 Hz, H-14); ^{13}C NMR (benzene-d_6, 150 MHz) δ 151.6 (C-11), 148.1 (C-5), 139.3 (C-1), 108.9 (C-12), 92.6 (C-2), 46.5 (C-7), 43.7 (C-4), 37.6 (C-3), 34.0 (C-9), 33.8 (C-6), 31.5 (C-8), 31.2 (C-10), 20.4 (C-13), 20.2 (C-15), 18.4 (C-14); HRMS (ESI-TOF) m/z 237.1840 $[M + H]^+$ (calcd for $C_{15}H_{25}O_2$, 237.1855), decomposed upon heating.

Reduction of (2*R*)-Hydroperoxyguaiene 6b with $LiAlH_4$. $LiAlH_4$ (6 mg, 158 μmol) was suspended in dry THF (0.8 mL) at room temperature under N_2. To the stirred suspension was added slowly a solution of **6b** (2 mg, 8 μmol) in THF (0.5 mL) followed by quenching of the reaction with H_2O after a further 10 min. The resulting aqueous mixture was extracted with Et_2O (3 × 5 mL), and the combined ether layers were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*, redissolved in CH_2Cl_2, and analyzed by TLC and GC-MS. TLC analysis showed the full consumption of **6b**, whereas GC-MS analysis showed the formation of (2*S*)-rotundol (**7b**) as the major product, accounting for ca. 40% along with two other unidentified products.

(1*S*,4*S*,7*R*)-1,4-Dimethyl-7-(prop-1-en-2-yl)-1,2,3,4,5,6,7,8-octahydroazulen-1-yl hydroperoxide (10a): ^{1}H NMR (benzene-d_6, 600 MHz) δ 6.71 (1H, s, −OO*H*), 4.83 (1H, s, H-12a), 4.75 (1H, dq, J = 1.8, 1.5 Hz, H-12b), 2.38 (1H, ddt, J = 16.2, 9.0, 4.2 Hz, H-2a), 2.31 (1H, ddd, J = 13.2, 9.0, 4.2 Hz, H-3a), 2.27 (1H, d, J = 15.6, 1.8 Hz, H-6a), 2.23−2.15 (2H, m, H-6b and H-10), 2.04−1.95 (2H, m, H-2b and H-7), 1.81−1.69 (2H, m, H-8a and H-8b), 1.69 (3H, s, H-13), 1.65 (1H, ddd, J = 13.2, 9.0, 4.2 Hz, H-3b), 1.59 (1H, ddd, J = 13.8, 7.2, 3.0 Hz, H-9a), 1.51 (1H, dddd, J = 13.8, 10.2, 7.2, 3.0 Hz, H-9b), 1.22 (3H, s, H-14), 1.00 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 151.7 (C-11), 147.7 (C-1), 135.8 (C-5), 108.8 (C-12), 97.6 (C-4), 47.1 (C-7), 34.9 (C-10), 34.3 (C-2), 33.6 (C-3), 33.2 (C-9), 31.5 (C-8), 30.5 (C-6), 22.1 (C-14), 20.7 (C-13), 17.6 (C-15); HRMS (ESI-TOF) m/z 237.1837 $[M + H]^+$ (calcd for $C_{15}H_{25}O_2$, 237.1855), decomposed upon heating.

(3*S*,5*R*,8*S*)-3,8-Dimethyl-5-[(2*R*)-2-methyloxiran-2-yl]-3,4,5,6,7,8-hexahydroazulen-1(2*H*)-one (11a) and (3*S*,5*R*,8*S*)-3,8-Dimethyl-5-[(2*S*)-2-methyloxiran-2-yl]-3,4,5,6,7,8-hexahydroazulen-1(2*H*)-one (11b). To a solution of rotundone (**2**, 11 mg, 50 μmol) in CH_2Cl_2 (2 mL) was added *m*-CPBA (46 mg, 210 μmol). After stirring for 1 h, the reaction was quenched with solid KI (10 mg), aqueous $Na_2S_2O_3$ (2 mL), and saturated aqueous $NaHCO_3$ (5 mL). The products were extracted with Et_2O (3 × 5 mL), and the combined ether extracts washed with brine (5 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*, and the residue purified by SCC (15−40 μm, Et_2O/petroleum ether, 8:92) to give pure **11a** (4.5 mg, 38%) as a colorless solid and **11b** (3.5 mg, 33%) as an oil. **11a:** mp 94.5−95.0 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.00 (1H, qt, J = 7.2, 3.6 Hz, H-10), 2.75 (1H, quint, J = 6.6 Hz, H-4), 2.65 (1H, d, J = 6.6 Hz, H-12a), 2.62 (1H, d, J = 6.6 Hz, H-12b), 2.58 (1H, dd, J = 18.6, 6.6 Hz, H-3a), 2.58 (1H, dd, J = 15.6, 3.6 Hz, H-6a), 2.53 (1H, dd, J = 15.6, 12.0 Hz, H-6b), 1.97 (1H, d, J = 18.6 Hz, H-3b), 1.83−1.76 (3H, m, H-8a, H-8b, and H-9a), 1.49−1.45 (1H, m, H-9b), 1.30 (3H, s, H-13), 1.50 (3H, d, J = 6.6 Hz, H-14), 1.08 (1H, tt, J = 12.0, 3.0 Hz, H-7), 1.01 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 207.9 (C-2), 176.4 (C-5), 145.4 (C-1), 60.6 (C-11), 55.4 (C-12), 45.9 (C-7), 42.9 (C-3), 37.7 (C-4), 33.0 (C-6), 32.3 (C-9), 28.3 (C-8), 26.8 (C-10), 19.1 (C-14), 17.5 (C-15), 16.5 (C-13); EI-MS m/z (rel intensity) 234 (1), 219 (3), 205 (24), 187 (23), 177 (100), 161 (47), 147 (70), 133 (37), 119 (41), 105 (52), 91 (44), 77 (25), 55 (20); HRMS (ESI-TOF) m/z 235.1672 $[M + H]^+$ (calcd for $C_{15}H_{23}O_2$, 235.1698).

11b: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.99 (1H, qt, J = 7.2, 3.6 Hz, H-10), 2.70 (1H, qd, J = 7.2, 6.6 Hz, H-4), 2.64 (1H, d, J = 4.8 Hz, H-12a), 2.63 (1H, d, J = 4.8 Hz, H-12b), 2.58 (1H, dd, J = 18.6, 6.6 Hz, H-3a), 2.44−2.37 (2H, m, H-6a and H-6b), 2.02 (1H, dddd, J = 13.8, 6.0, 2.4, 1.8 Hz, H-8a), 1.97 (1H, d, J = 18.6 Hz, H-3b), 1.84−1.79 (2H, m, H-9a and H-8b), 1.48 (1H, dddd, J = 15.6, 13.8, 3.6, 1.8 Hz, H-9b), 1.31 (3H, s, H-13), 1.18 (1H, dddd, J = 12.6, 11.4, 4.2, 2.4 Hz, H-7), 1.14 (3H, d, J = 7.2 Hz, H-14), 1.00 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 207.2 (C-2), 175.5 (C-5), 145.6 (C-1), 60.5 (C-11), 54.4 (C-12), 45.2 (C-7), 42.9 (C-3), 37.8 (C-4), 34.0 (C-6), 32.2 (C-9), 27.2 (C-8), 26.9 (C-10), 19.2 (C-14), 17.6 (C-15), 17.4 (C-13); EIMS m/z (rel intensity) 234 (9), 219 (6), 205 (35), 187 (42), 177 (100), 161 (58), 147 (94), 133 (29), 119 (54), 105 (67), 91 (73), 77 (35), 55 (25); HRMS (ESI-TOF) m/z 235.1670 $[M + H]^+$ (calcd for $C_{15}H_{23}O_2$, 235.1698).

(1*R*,3*S*,3a*S*,5*R*,8*S*,8a*R*)-3,8-Dimethyl-5-(prop-1-en-2-yl)-hexahydro-1*H*,4*H*-3a,8a-epoxyazulen-1-ol (12a). To a solution of *m*-CPBA (77%, 16 mg, 72 μmol) in CH_2Cl_2 (1 mL) at 0 °C was added a solution of **7a** (10 mg, 45 μmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at 0 °C until TLC showed the complete consumption of the starting alcohol (1 h). The reaction was quenched with solid KI (5 mg), saturated aqueous $Na_2S_2O_3$ (2 mL), and saturated aqueous $NaHCO_3$ (5 mL), and the mixture was stirred for 1

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h. The mixture was extracted with Et_2O (3 × 10 mL), and the combined ether layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* and purified by SCC (Et_2O/hexanes, 18:82) to yield **12a** (8.1 mg, 76%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.66 (1H, dq, J = 1.2, 0.9 Hz, H-12a), 4.64 (1H, dq, J = 1.8, 1.5 Hz, H-12b), 4.07 (1H, dd, J = 8.0, 7.8 Hz, H-2), 2.53 (1H, qdd, J = 7.2, 6.6, 3.0 Hz, H-10), 2.09 (1H, ddd, J = 12.6, 7.8, 7.8 Hz, H-3a), 2.04 (1H, m, H-7), 2.04 (1H, d, J = 14.4 Hz, H-6a), 1.97 (1H, ddq, J = 9.6, 7.8, 6.6 Hz, H-4), 1.69 (3H, s, H-13), 1.68−1.56 (5H, m, H-6b, H-8a, H-8b, H-9a and H-9b), 1.05 (3H, d, J = 7.2 Hz, H-15), 1.01 (3H, d, J = 6.6 Hz, H-14), 0.88 (1H, ddd, J = 12.6, 9.6, 7.8 Hz, H-3b); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 150.6 (C-11), 108.7 (C-12), 75.4 (C-2), 73.4 (C-1), 71.4 (C-5), 44.6 (C-7), 37.7 (C-3), 33.6 (C-6), 33.4 (C-4), 30.77 (C-9), 30.73 (C-8), 30.2 (C-10), 20.2 (C-13), 15.9 (C-15), 13.3 (C-14); EIMS m/z (rel intensity) 221 (13), 203 (9), 193 (23), 175 (23), 165 (57), 152 (75), 135 (57), 123 (70), 107 (78), 97 (100), 81 (67), 69 (98); HRMS (ESI-TOF) m/z 237.1829 $[M + H]^+$ (calcd for $C_{15}H_{25}O_2$, 237.1855).

(1*S*,3*S*,3a*R*,5*R*,8*S*,8a*S*)-3,8-Dimethyl-5-(prop-1-en-2-yl)-hexahydro-1*H*,4*H*-3a,8a-epoxyazulen-1-ol (12b). To a solution of *m*-CPBA (77%, 17 mg, 78 μmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added dropwise a solution of **7b** (13 mg, 59 μmol) in CH_2Cl_2 (0.5 mL). The resulting mixture was stirred under N_2 for 1 h and quenched with solid KI (5 mg), saturated aqueous $Na_2S_2O_3$ (2 mL), and saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with Et_2O (3 × 10 mL), and the combined ether layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* and purified by SCC (Et_2O/hexanes, 24:76) to yield **12b** (13.3 mg, 95%) as a colorless liquid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.69 (1H, br s, H-12a), 4.65 (1H, dq, J = 1.5, 1.2 Hz, H-12b), 4.31 (1H, t, J = 7.8 Hz, H-2), 2.67 (1H, qt, J = 7.2, 3.6 Hz, H-10), 2.18 (1H, tdd, J = 11.4, 3.6, 1.8 Hz, H-7), 2.15 (1H, dq, J = 7.8, 7.2 Hz, H-4), 1.98−1.91 (2H, m, H-9a and H-9b), 1.76−1.71 (1H, m, H-6a), 1.72 (3H, s, H-13), 1.65 (1H, dd, J = 13.2, 7.8 Hz, H-3a), 1.57−1.43 (3H, m, H-3b, H-6b and H-8a), 1.33 (1H, dd, J = 13.2, 11.4 Hz, H-8b), 1.11 (3H, d, J = 7.2 Hz, H-15), 0.91 (3H, d, J = 7.2 Hz, H-14); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 151.4 (C-11), 108.6 (C-12), 74.8 (C-1), 72.9 (C-5), 72.4 (C-2), 43.3 (C-7), 37.48 (C-4), 37.42 (C-3), 34.1 (C-9), 30.8 (C-6), 29.4 (C-8), 27.7 (C-10), 20.8 (C-13), 17.8 (C-14), 15.2 (C-15); EIMS m/z (rel intensity) 236 (3), 218 (53), 203 (34), 189 (8), 175 (47), 161 (37), 147 (49), 134 (94), 107 (100), 95 (91), 69 (90); HRMS (ESI-TOF) m/z 237.1828 $[M + H]^+$ (calcd for $C_{15}H_{25}O_2$, 237.1855).

(3*S*,3a*S*,5*R*,8*S*,8a*S*)-3,8-Dimethyl-5-(prop-1-en-2-yl)-hexahydro-1*H*,4*H*-3a,8a-epoxyazulen-1-one (13a). To a stirred suspension of PCC (26 mg, 121 μmol) in CH_2Cl_2 (0.8 mL) at 0 °C was added a solution of **13a** (8.0 mg, 34 μmol) in CH_2Cl_2 (0.4 mL) in one portion. The resulting suspension was stirred under N_2, and the temperature allowed to rise to ambient temperature overnight. The reaction mixture was loaded on a silica pipet and purified by SCC (CH_2Cl_2) to afford pure **13a** (7.0 mg, 91%) as a colorless glass: ^{1}H NMR (benzene-d_6, 600 MHz) δ 4.65 (2H, s, H-12a and H-12b), 2.72 (1H, qdd, J = 7.2, 7.2, 4.2 Hz, H-4), 1.94−1.90 (2H, m, H-6a and H-7), 1.88 (1H, dd, J = 17.4, 8.4 Hz, H-9a), 1.76 (1H, dd, J = 17.4, 8.4 Hz, H-9b), 1.70 (1H, dd, J = 14.4, 12.0 Hz, H-6b), 1.66 (1H, q, J = 7.2 Hz, H-10), 1.49 (3H, s, H-13), 1.44−1.38 (2H, m, H-3a and H-8a), 1.38−1.31 (1H, m, H-8b), 1.16 (1H, dd, J = 13.2, 4.2 Hz, H-3b), 1.12 (3H, d, J = 7.2 Hz, H-14), 0.83 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 210.3 (C-2), 150.1 (C-11), 109.3 (C-12), 74.6 (C-1), 70.4 (C-5), 43.9 (C-7), 40.2 (C-9), 32.6 (C-6), 31.9 (C-8), 31.3 (C-10), 29.5 (C-3), 26.7 (C-4), 20.0 (C-13), 16.4 (C-14), 13.5 (C-15); EIMS m/z (rel intensity) 234 (1), 219 (6), 191 (11), 177 (100), 163 (100), 149 (30), 135 (44), 121 (41), 109 (63), 69 (75); HRMS (ESI-TOF) m/z 235.1669 $[M + H]^+$ (calcd for $C_{15}H_{23}O_2$, 235.1698).

(3*S*,3a*R*,5*R*,8*S*,8a*R*)-3,8-Dimethyl-5-(prop-1-en-2-yl)-hexahydro-1*H*,4*H*-3a,8a-epoxyazulen-1-one (13b). To a stirred suspension of PCC (12 mg, 55 μmol) in CH_2Cl_2 (0.8 mL) at 0 °C was added a solution of **13b** (4.4 mg, 19 μmol) in CH_2Cl_2 (0.5 mL). The resulting mixture was stirred for 2 h under N_2, and the reaction mixture was loaded on a silica pipet and purified by SCC (CH_2Cl_2) to afford pure **13b** (4.1 mg, 94%) as a white solid: mp 90.9−91.3 °C; ^{1}H NMR (benzene-d_6, 600 MHz) δ 4.70 (2H, s, H-12a, H-12b), 2.84 (1H, qt, J = 7.2, 3.6 Hz, H-10), 2.47 (1H, dd, J = 11.4, 8.4 Hz, H-3a), 2.31 (1H, tt, J = 11.4, 1.8 Hz, H-7), 1.95−1.91 (2H, m, H-4 and H-6a), 1.86 (1H, dd, J = 15.0, 11.4 Hz, H-6b), 1.69 (1H, dddd, J = 14.4, 13.8, 3.6, 1.8 Hz, H-9a), 1.57 (3H, s, H-13), 1.42−1.36 (2H, m, H-3b and H-8a), 1.30 (1H, dddd, J = 14.4, 6.0, 3.6, 1.8 Hz, H-9b), 1.15 (1H, dddd, J = 14.4, 13.8, 11.4, 1.8 Hz, H-8b), 0.91 (3H, d, J = 7.2 Hz, H-15), 0.50 (3H, d, J = 7.2 Hz, H-14); ^{13}C NMR (benzene-d_6, 150 MHz) δ 210.8 (C-2), 151.6 (C-11), 109.9 (C-12), 74.7 (C-5), 70.6 (C-1), 44.0 (C-7), 42.0 (C-3), 35.0 (C-6), 34.6 (C-4), 30.7 (C-9), 30.5 (C-8), 26.5 (C-10), 21.4 (C-13), 18.7 (C-14), 15.9 (C-15); EIMS m/z (rel intensity) 218 (9), 203 (8), 191 (9), 177 (25), 163 (100), 149 (28), 135 (28), 121 (40), 109 (70), 69 (81); HRMS (ESI-TOF) m/z 235.1672 $[M + H]^+$ (calcd for $C_{15}H_{23}O_2$, 235.1698).

2-[(3*S*,5*R*,8*S*)-3,8-Dimethyl-1-oxo-1,2,3,4,5,6,7,8-octahydroazulen-5-yl]prop-2-enal (14). To a stirred suspension of SeO_2 (4.6 mg, 41 μmol) in CH_2Cl_2 (1 mL) at 0 °C was added slowly a solution of TBHP (5−6 M in decane, 20 μL) in CH_2Cl_2 (1 mL) and a solution of **2** (9 mg) in CH_2Cl_2 after 2 min. The reaction was allowed to warm to RT over 1 h and stirred at RT for 30 h. The reaction mixture was filtered through a pad of silica and eluted with CH_2Cl_2 (2 × 6 mL). The filtrate was concentrated *in vacuo*, and the residue purified by SCC (Et_2O/*n*-hexane, 15:85) to give **14** (5.4 mg, 54%) as a colorless liquid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.53 (1H, s, −C*H*O), 6.35 (1H, s, H-12a), 6.04 (1H, s, H-12b), 3.05−3.00 (1H, m, H-10), 2.75 (1H, dq, J = 7.2, 7.2 Hz, H-4), 2.62 (1H, m, H-7), 2.61 (1H, dd, J = 18.6, 6.6 Hz, H-3a), 2.56 (1H, dd, J = 15.6, 12.0 Hz, H-8a), 2.34 (1H, br d, J = 15.6 Hz, H-8b), 1.97 (1H, d, J = 18.6 Hz, H-3b), 1.95 (1H, ddd, J = 14.4, 10.8, 1.8 Hz, H-6a), 1.81−1.75 (2H, m, H-6b and H-9a), 1.59 (1H, dddd, J = 15.0, 12.0, 3.6, 1.8 Hz, H-9b), 1.09 (3H, d, J = 7.2 Hz, H-14), 1.03 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 208.0 (C-2), 194.0 (C-13), 175.7 (C-5), 155.4 (C-11), 145.8 (C-1), 133.2 (C-12), 43.0 (C-3), 37.8 (C-4), 36.4 (C-8), 36.2 (C-7), 32.5 (C-9), 30.4 (C-6), 26.7 (C-10), 19.1 (C-14), 17.5 (C-15); EIMS m/z (rel intensity) 232 (81), 217 (25), 203 (52), 189 (63), 175 (62), 161 (63), 147 (73), 133 (38), 119 (48), 105 (65), 91 (100), 77 (66); HRMS (ESI-TOF) m/z 233.1528 $[M + H]^+$ (calcd for $C_{15}H_{21}O_2$, 233.1542).

Autoxidation of Rotundone (2). Neat rotundone (**2**, 112 mg, 0.5 mmol) was allowed to oxidize under a pure O_2 atmosphere with stirring. A small portion of the crude reaction mixture was dissolved in CH_2Cl_2 and analyzed by GC-MS at different time points. After 6 months, the pure O_2 atmosphere was removed, and the crude mixture was left in the open air for the remaining time of the oxidation and monitored by GC-MS.

Autoxidation of Rotundols 7a/b. (2*R*)-Rotundol (**7a**, 2 mg, 9 μmol) and (2*S*)-rotundol (**7b**, 2 mg, 9 μmol) were dissolved with CH_2Cl_2 (1 mL), respectively. The solvent was allowed to evaporate under an O_2 atmosphere, and the neat compounds allowed to oxidize under pure O_2 and monitored periodically by GC-MS. A small volume of CH_2Cl_2 (ca. 100 μL) was added to the reaction mixture, and a small aliquot (ca. 1 μL) was further diluted with CH_2Cl_2 (ca. 200 μL) for GC-MS analysis. The solvent in the reaction mixture was again removed under the O_2 stream at each analysis time point.

(2*S*,3*S*,6*R*)-6-[2-(Benzyloxy)propan-2-yl]-3-methyl-2-(3-oxobutyl)cycloheptanone (17). Ozone was bubbled through a solution of benzyl 4,5-ene-guaiol (**16**, 31.5 mg, 101 μmol), CH_2Cl_2 (2.5 mL), and dry pyridine (10 μL, 124 μmol) at −78 °C via a pipet until the solution turned blue. After 3 min, O_3 purging was ceased and the solution was sparged with N_2 until the blue color of the solution disappeared. Zn powder (87 mg, 1.3 mmol) and HOAc (100 μL, 1.8 mmol) were added, and the resulting mixture was stirred until TLC indicated the consumption of ozonide. Saturated aqueous $NaHCO_3$ solution (5 mL) was added, the mixture was extracted with Et_2O (3 × 15 mL), and the combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*, and the residue purified by SCC (Et_2O/petroleum ether, 8:92) to yield **17** (18.7 mg, 54%) as a pale yellow

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liquid: ^{1}H NMR (benzene-d_6, 600 MHz) δ 7.32 (2H, d, J = 7.2 Hz, ArH), 7.20 (2H, dd, J = 7.2, 6.6 Hz, ArH), 7.11 (1H, d, J = 6.6 Hz, ArH), 4.22 (2H, s, PhCH_2), 2.73 (1H, ddd, J = 9.6, 4.2, 2.4 Hz, H-1), 2.58 (1H, ddd, J = 17.4, 4.8, 2.4 Hz, H-6a), 2.29 (1H, dd, J = 17.4, 12.0 Hz, H-6b), 2.25 (1H, dddd, J = 13.8, 9.6, 8.4, 6.0 Hz, H-2a), 2.09 (1H, ddd, J = 16.8, 8.4, 6.0 Hz, H-3a), 1.97 (1H, dddd, J = 12.0, 10.2, 4.8, 1.2 Hz, H-7), 1.87 (1H, ddd, J = 16.8, 8.4, 6.6 Hz, H-3b), 1.72−1.66 (1H, m, H-10), 1.63 (3H, s, H-14), 1.51 (2H, m, H-9a and H-9b), 1.43 (1H, dddd, J = 13.8, 8.4, 6.6, 4.2 Hz, H-2b), 0.98−1.03 (1H, m, H-8b), 0.96 (3H, s, H-12), 0.90 (3H, s, H-13), 0.73 (3H, d, J = 6.6 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 211.4 (C-5), 206.6 (C-4), 140.3 (Ar C), 128.6 (Ar C), 127.5 (Ar C),127.4 (Ar C), 77.4 (C-11), 63.6 (PhCH$_2$), 53.8 (C-1), 47.2 (C-6), 44.5 (C-7), 41.6 (C-3), 37.3 (C-9), 35.3 (C-10), 29.3 (C-14), 25.2 (C-8), 24.9 (C-2), 22.3 (C-12), 21.9 (C-13), 14.3 (C-15); EIMS m/z (rel intensity) 236 (0.6), 195 (8), 180 (4), 149 (18), 124 (4), 109 (11), 91 (100), 79 (5), 67 (6); HRMS (ESI-TOF) m/z 345.2434 [M + H]$^+$ (calcd for $C_{22}H_{33}O_3$, 345.2429).

(2*S*,3*S*,6*R*)-6-(2-Hydroxypropan-2-yl)-3-methyl-2-(3-oxobutyl)cycloheptanone (18). To a solution of **17** (76.7 mg, 223 μmol) in MeOH (3 mL) was added 5% Pd/C (73.3 mg, 34 μmol). The resulting mixture was evacuated under vacuum, refilled with H_2 three times, and stirred under a H_2 atmosphere (in a balloon) for 16 h. The reaction mixture was quenched by filtration through a pad of silica and eluted with CH_2Cl_2 (10 mL). The filtrate was concentrated *in vacuo*, and the residue purified by SCC (Et_2O/petroleum ether, gradient elution from 20:80 to 50:50) to give **18** (56 mg, 99%) as a colorless oil: ^{1}H NMR (benzene-d_6, 600 MHz) δ 2.71 (1H, ddd, J = 9.6, 4.2, 2.4 Hz, H-1), 2.54 (1H, ddd, J = 17.4, 4.2, 2.4 Hz, H-6a), 2.24 (1H, dddd, J = 18.0, 9.6, 7.8, 6.0 Hz, H-2a), 2.18 (1H, dd, J = 17.4, 12.0 Hz, H-6b), 2.11 (1H, ddd, J = 16.8, 7.8, 6.0 Hz, H-3a), 1.88 (1H, ddd, J = 16.8, 7.8, 6.6 Hz, H-3b), 1.69 (1H, m, H-10), 1.66 (3H, s, H-14), 1.66−1.65 (1H, m, H-7), 1.61−1.59 (1H, m, H-8a), 1.51 (2H, m, H-9a and H-9b), 1.43 (1H, dddd, J = 18.0, 7.8, 6.6, 4.2 Hz, H-2b), 0.98−0.92 (1H, m, H-8b), 0.90 (3H, s, H-12), 0.85 (3H, s, H-13), 0.72 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 211.6 (C-5), 206.7 (C-4), 72.2 (C-11), 53.8 (C-1), 47.3 (C-6), 46.8 (C-7), 41.6 (C-3), 37.3 (C-9), 35.2 (C-10), 29.3 (C-14), 26.6 (C-12), 26.5 (C-13), 25.4 (C-8), 24.8 (C-2), 14.3 (C-15); EIMS m/z (rel intensity) 236 (22), 221 (14), 196 (5), 177 (54), 163 (10), 150 (18), 138 (100), 123 (37), 109 (37), 95 (38), 59 (73); HRMS (ESI-TOF) m/z 255.1949 [M + H]$^+$ (calcd for $C_{15}H_{27}O_3$, 255.1960).

(2*S*,3*S*,6*R*)-3-Methyl-2-(3-oxobutyl)-6-(prop-1-en-2-yl)-cycloheptanone (3a). To a solution of **18** (19 mg, 75 μmol) in benzene (1 mL) was added pyridine (25 μL, 0.3 mmol). The resulting mixture was cooled to 0 °C with stirring followed by the slow addition of $SOCl_2$ (20 μL, 282 μmol). After stirring for 5 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with Et_2O (3 × 10 mL), and the combined ether layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*, and the residue purified by SNIS column chromatography (Et_2O/petroleum ether, 12:88) to give **3a** (9 mg, 51%) as a pale yellow oil. Spectroscopic data were identical to those reported by us recently.[20]

(2*R*,3*S*,6*R*)-6-(2-Hydroxypropan-2-yl)-3-methyl-2-(3-oxobutyl)cycloheptanone (20). 1-*epi*-4,5-Ene-guaiol (**19**, 29 mg, 131 μmol) was dissolved in CH_2Cl_2 (8 mL), and the resulting solution cooled to −78 °C under N_2. Through this stirred solution was bubbled a stream of O_3 via a pipet (N_2 atmosphere was removed) until the blue color of the solution persisted. The introduction of O_3 was ceased, and the reaction allowed to warm to room temperature (RT) while the solution was sparged with N_2 until the blue color disappeared. Zn powder (89 mg, 1.4 mmol) and HOAc (30 μL, 0.5 mmol) were added, and the mixture was stirred at RT until TLC showed the full consumption of ozonide. Saturated aqueous $NaHCO_3$ solution (5 mL) was added, the mixture was extracted with Et_2O (3 × 15 mL), and the combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*, and the residue purified by SCC (EtOAc/petroleum ether, 24:76) to yield **20** (20.8 mg, 63%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.62 (1H, ddd, J = 12.0, 5.4, 1.5 Hz, H-6a), 2.45 (1H, ddd, J = 17.4, 8.4, 6.0 Hz, H-3a), 2.37 (1H, dd, J = 12.0, 11.4 Hz, H-6b), 2.32 (1H, ddd, J = 17.4, 8.4, 6.6 Hz, H-3b), 2.29 (1H, ddd, J = 10.2, 7.8, 3.6 Hz, H-1), 2.12 (3H, s, H-14), 1.94 (1H, dddd, J = 13.2, 10.2, 8.4, 6.0 Hz, H-2a), 1.78 (1H, dddd, J = 13.2, 8.4, 6.6, 3.6 Hz, H-2b) 1.76−1.57 (4H, m, H-7, H-8a, H-9a and H-10), 1.53 (1H, m, H-8b), 1.21 (3H, s, H-12), 1.20 (3H, s, H-13), 1.08 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 214.9 (C-5), 208.6 (C-4), 72.9 (C-11), 58.1 (C-1), 47.1 (C-7), 45.3 (C-6), 42.2 (C-3), 37.3 (C-10), 32.6 (C-8), 30.0 (C-14), 27.2 (C-12, C-13), 24.3 (C-2), 23.8 (C-9), 21.1 (C-15); EI-MS m/z (rel intensity): 236 (54), 221 (76), 203 (13), 178 (43), 161 (16), 138 (100), 123 (58), 109 (59), 95 (70), 69 (49); HRMS (ESI-TOF) m/z 255.1947 [M + H]$^+$ (calcd for $C_{15}H_{27}O_3$, 255.1960).

(2*R*,3*S*,6*R*)-3-Methyl-2-(3-oxobutyl)-6-(prop-1-en-2-yl)-cycloheptanone (3b). To a stirred solution of **20** (9.0 mg, 35 μmol) in CH_2Cl_2 (1.0 mL) was added Et_3N (20 μL, 144 μmol). The mixture was cooled to −78 °C, and $SOCl_2$ (20 μL, 282 μmol) introduced slowly. After 0.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL) and extracted with Et_2O (3 × 10 mL), and the combined ether layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*, and the residue purified by SNIS column chromatography (Et_2O/petroleum ether, 12:88) to give **3b** (5.8 mg, 66%) as a pale yellow liquid: ^{1}H NMR (benzene-d_6, 600 MHz) δ 4.71 (1H, dq, J = 1.8, 1.5 Hz, H-12a), 4.69 (1H, dq, J = 1.8, 0.9 Hz, H-12b) 2.49 (1H, ddd, J = 11.4, 5.1, 1.2 Hz, H-6a), 2.31 (1H, t, J = 11.4 Hz, H-6b), 2.21 (1H, m, H-7), 2.14−2.08 (2H, m, H-1 and H-3a), 2.01−1.93 (2H, m, H-2a and H-3b), 1.73 (1H, ddd, J = 13.8, 6.6, 3.6 Hz, H-2b), 1.64 (3H, s, H-14), 1.56 (3H, s, H-13), 1.56−1.50 (1H, m, H-8a), 1.42−1.29 (4H, m, H-8b, H-9a, H-9b, and H-10), 0.86 (3H, d, J = 6.6 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 211.8 (C-5), 206.3 (C-4), 148.9 (C-11), 109.9 (C-12), 58.2 (C-1), 48.7 (C-6), 44.0 (C-7), 41.5 (C-3), 35.2 (C-10), 32.9 (C-9), 29.4 (C-14), 28.6 (C-8), 25.0 (C-2), 21.2 (C-15), 20.8 (C-13); EIMS m/z (rel intensity) 236 (24), 221 (16), 203 (9), 179 (27), 161 (23), 150 (16), 135 (20), 123 (62), 109 (75), 95 (100), 67 (81); HRMS (ESI-TOF) m/z 237.1845 [M + H]$^+$ (calcd for $C_{15}H_{25}O_2$, 237.1855).

2-[(3*S*,3a*R*,5*R*,8*S*)-3,8-Dimethyl-2,3,3a,4,5,6,7,8-octahydroazulen-5-yl]propan-2-ol (24). To a stirred solution of 1-α-hydroxyguaiene **21** (180 mg, 0.81 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (77%, 330 mg, 1.5 mmol) in one portion. The resulting mixture was stirred under N_2 for 30 min and quenched with solid KI, aqueous $Na_2S_2O_3$, and aqueous $NaHCO_3$. The products were extracted with Et_2O (4 × 20 mL), and the combined ether layers washed with brine (20 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* to give the crude epoxide mixture **22** (192 mg), which was used directly for the next step without purification. To a stirred solution of **22** (192 mg) in Et_2O (20 mL) was added Et_3N (0.5 mL). The resulting mixture was cooled to 0 °C, and $SOCl_2$ (100 μL, 1.4 mmol) introduced slowly. After 15 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (4 × 20 mL), and the combined ether layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* to give the crude epoxy olefinic mixture **23** (160 mg), which was used for the next step without purification. To a stirred solution of $LiAlH_4$ (190 mg, 5 mmol) in dry THF (3 mL) was added dropwise a solution of anhydrous $AlCl_3$ (115 mg, 0.86 mmol) in dry THF (2 mL). To the resulting mixture was added dropwise a solution of **23** (160 mg) in THF (3 mL). After stirring for 2 h, the reaction was cooled to 0 °C and quenched with H_2O (5 mL). The products were extracted with Et_2O (3 × 20 mL), and the combined ether layers washed with brine (20 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*, and the residue purified by repeated SNIS column chromatography (Et_2O/PE, 8:92) to give pure **24** (5.4 mg) and a mixture of **24** and an uncharacterized isomer (142 mg, with a ratio of 48:52, 41%). Considering the difficulty in separating these two isomers and the fact that ozonolysis in the next step would generate more polar compounds that would be easier to separate, the mixture was used in the next step directly without further purification. ^{1}H NMR (benzene-d_6, 600 MHz) δ 5.38 (1H, s, H-2), 2.77−2.72 (1H, m, H-10), 2.39−2.34 (2H, m, H-

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3a and H-4), 1.94−1.89 (2H, m, H-3b and H-5), 1.84 (1H, dt, J = 12.0, 4.8 Hz, H-7), 1.71 (1H, d, J = 13.8 Hz, H-9a), 1.66 (1H, m, H-6a), 1.49−1.42 (2H, m, H-6b and H-9b), 1.27−1.21 (2H, m, H-8a and H-8b), 1.09 (3H, d, J = 6.0 Hz, H-14), 1.03 (3H, d, J = 7.2 Hz, H-15), 1.01 (6H, s, H-12 and H-13); ^{13}C NMR (benzene-d_6, 150 MHz) δ 152.6 (C-1), 123.8 (C-2), 72.7 (C-11), 50.3 (C-4), 46.9 (C-8), 41.3 (C-5), 39.3 (C-3), 37.0 (C-6), 36.0 (C-10), 32.7 (C-9), 28.1 (C-7), 27.0 (C-12), 26.6 (C-13), 18.8 (C-14), 17.9 (C-15); EIMS m/z (rel intensity) 207 (1), 204 (27), 189 (13), 175 (1), 161 (100), 147 (30), 133 (11), 122 (44), 107 (54), 93 (33), 81 (24), 59 (42); HRMS (ESI-TOF) m/z 223.2041 $[M + H]^+$ (calcd for $C_{15}H_{27}O_1$, 223.2062).

(3*S*)-3-[(1*R*,3*S*,6*R*)-6-(2-Hydroxypropan-2-yl)-3-methyl-2-oxocycloheptyl]butanal (25). A mixture containing 48% **24** (110 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (6 mL), and the resulting mixture cooled to −78 °C under N_2. To the stirred solution was introduced a stream of O_3 via a pipet until the blue color persisted. Bubbling of O_3 was ceased, the reaction mixture was sparged with N_2, and the reaction temperature allowed to warm to RT. Zn powder (240 mg, 3.7 mmol) and HOAc (100 μL, 1.7 mmol) were added, and the resulting mixture was stirred at RT until TLC indicated the complete consumption of ozonides. Saturated aqueous $NaHCO_3$ solution (10 mL) was added, the resulting mixture was extracted with Et_2O (3 × 20 mL), and the combined ether layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* and purified by SCC (Et_2O/petroleum ether, 50:50) to give **25** (34.8 mg, 58%): ^{1}H NMR (benzene-d_6, 600 MHz) δ 9.38 (1H, dd, J = 2.4, 1.2 Hz, C*H*O), 2.44 (1H, q, J = 7.8 Hz, H-5), 2.42−2.35 (1H, m, H-4), 2.31 (1H, appr sext, J = 7.2 Hz, H-10), 2.12 (1H, ddd, J = 16.8, 4.2, 1.2 Hz, H-3a), 1.91 (1H, ddd, J = 16.8, 7.8, 2.4 Hz, H-3b), 1.54 (1H, ddd, J = 13.8, 7.8, 4.2 Hz, H-6a), 1.48 (1H, m, H-9a), 1.35−1.24 (3H, m, H-6b and H-8a and H-8b), 1.27 (1H, tt, J = 11.4, 4.2 Hz, H-7), 1.07−1.00 (1H, m, H-9b), 0.90 (3H, d, J = 7.2 Hz, H-15), 0.88 (3H, s, H-12), 0.86 (3H, s, H-13), 0.80 (3H, d, J = 6.6 Hz, H-14); ^{13}C NMR (benzene-d_6, 150 MHz) δ 215.8 (C-1), 200.7 (C-2), 72.6 (C-11), 50.5 (C-5), 49.5 (C-3), 46.2 (C-7), 45.5 (C-10), 30.7 (C-8), 29.9 (C-4), 27.83 (C-12), 27.82 (C-6), 26.3 (C-13), 25.9 (C-9), 17.7 (C-15), 17.3 (C-14). EI-MS m/z (rel. intensity): 254 (1), 236 (6), 221 (11), 203 (6), 193 (11), 166 (20), 138 (12), 123 (33), 109 (39), 83 (70), 59 (100); HRMS (ESI-TOF) m/z 255.1946 $[M + H]^+$ (calcd for $C_{15}H_{27}O_3$, 255.1960).

(3*S*)-3-[(1*R*,3*S*,6*R*)-3-Methyl-2-oxo-6-(prop-1-en-2-yl)-cycloheptyl]butanal (3c). To a stirred solution of alcohol **24** (25 mg, 10 μmol) in dry toluene (1.5 mL) was added pyridine (100 μL) and $SOCl_2$ (20 μL) successively under N_2. After stirring for 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL), the products were extracted with Et_2O (3 × 10 mL), and the combined ether layers were further washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*, and the residue filtered through Celite to give a mixture of two closely related isomers, **3c** and **26**, in a ratio of 1:1 (22 mg, colorless oil, 94% overall and 47% calculated for **3c**) based on GC-MS analysis. Owing to the decomposition of **3c** when using SCC for purification in previous experiments, the mixture was further purified by MLCCC (MeCN/*t*-BuOMe/PE, 10:1:10, descending mode) to furnish pure **3c** (2 mg) as a colorless oil: ^{1}H NMR (benzene-d_6, 600 MHz) δ 9.33 (1H, dd, J = 2.4, 1.2 Hz, C*H*O), 4.76 (1H, s, H-12a), 4.67 (1H, s, H-12b), 2.42 (1H, ddd, J = 9.9, 7.8, 5.4 Hz, H-5), 2.34 (1H, m, H-4), 2.29 (1H, sext, J = 7.2 Hz, H-10), 2.07 (1H, m, H-7), 2.06 (1H, ddd, J = 16.8, 6.0, 1.2 Hz, H-3a), 1.88 (1H, ddd, J = 16.8, 8.4, 2.4 Hz, H-3b), 1.56 (1H, ddd, J = 13.8, 7.8, 5.4 Hz, H-6a), 1.50 (3H, s, H-13), 1.49 (1H, m, H-8a), 1.30 (1H, ddd, J = 13.8, 9.9, 4.5 Hz, H-6b), 1.30−1.26 (3H, m, H-8b, H-9a, and H-9b), 0.88 (3H, d, J = 7.2 Hz, H-15), 0.73 (3H, d, J = 6.6 Hz, H-14); ^{13}C NMR (benzene-d_6, 150 MHz) δ 215.6 (C-1), 200.4 (C-2), 148.3 (C-11), 110.5 (C-12), 50.3 (C-5), 49.3 (C-3), 46.1 (C-10), 42.3 (C-7), 31.6 (C-6), 29.9 (C-4), 29.8 (C-8), 29.3 (C-9), 21.4 (C-13), 17.7 (C-15), 17.3 (C-14); EI-MS m/z (rel intensity) 236 (2), 218 (6), 203 (9), 193 (23), 176 (12), 165 (40), 151 (21), 135 (22), 123 (54), 110 (91), 95 (100), 81 (63), 67 (81), 55 (83); HRMS (ESI-TOF) m/z 237.1843 $[M + H]^+$ (calcd for $C_{15}H_{25}O_2$, 237.1855). **26:** ^{1}H NMR (C_6D_6, 500 MHz) δ 9.27 (1H, s), 2.52−2.45 (3H, m), 2.18−2.08 (3H, m), 1.78 (1H, ddd, J = 18.0, 9.0, 1.8 Hz), 1.60−1.50 (3H, m), 1.46 (3H, s), 1.44 (3H, s), 1.17 (1H, dd, J = 12.0, 4.5 Hz), 1.02 (3H, d, J = 6.5 Hz), 0.71 (3H, d, J = 6.5 Hz); EI-MS m/z (rel intensity) 236 (12), 218 (13), 207 (25), 193 (14), 165 (65), 138 (50), 123 (100), 109 (39), 95 (48), 67 (50).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds; ROESY NMR spectra of **8a**, **8b**, **6b**, **10a**, **4b**, **3a**, and **3c**; X-ray crystallographic data for **7a**, **11a**, **13b**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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