JOURNAL OF NATURAL PRODUCTS

Article

pubs.acs.org/jnp

Synthesis of Guaia-4(5)-en-11-ol, Guaia-5(6)-en-11-ol, Aciphyllene, 1-*epi*-Melicodenones C and E, and Other Guaiane-Type Sesquiterpenoids via the Diastereoselective Epoxidation of Guaiol

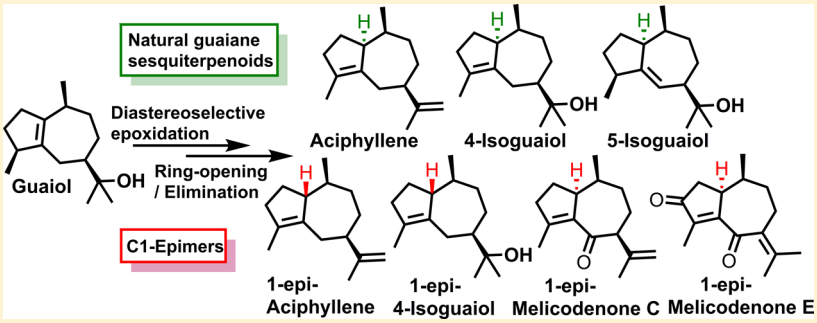
An-Cheng Huang,[†] Christopher J. Sumby,[§] Edward R. T. Tiekink,[‡] and Dennis K. Taylor*[,†]

[†]School of Agriculture, Food and Wine, The University of Adelaide, Waite Campus, Glen Osmond 5064, Adelaide, South Australia, Australia

[§]School of Chemistry and Physics, The University of Adelaide, North Terrace 5000, Adelaide, South Australia, Australia

[‡]Department of Chemistry, University of Malaya, Kuala Lumpur 50603, Malaysia

Supporting Information



ABSTRACT: The diastereomeric ratio of epoxidation of the internally bridged carbon−carbon double bond of guaiol (**1a**) is strongly influenced by the combined effects of the types of remote protecting groups on the hydroxyisopropyl side chain, choice of solvent, and epoxidizing reagent. This observation has allowed us to devise concise stereoselective syntheses of a range of guaiane-type sesquiterpenoids via an epoxidation, ring-opening/elimination, and functionality manipulation sequence. Natural products guaia-4(5)-en-11-ol (**2a**), guaia-5(6)-en-11-ol (**3**), and aciphyllene (**4a**) and epimers of the recently isolated natural products, 1-*epi*-guaia-4(5)-en-11-ol (**2b**), 1-*epi*-aciphyllene (**4b**), and 1-*epi*-melicodenones C (**5a**) and E (**6a**), were synthesized in good yields in relatively few steps.

Guaiane-type sesquiterpenoids occur widely in nature and have been isolated and identified in many different hosts including plants, fungi, and marine life with dozens reported on an annual basis.[1,2] The continual discovery of these structurally intriguing organics and their well-documented important bioactivities coupled with their often low natural abundance in nature have rendered them exciting targets for numerous organic synthesis groups.[2,3] Key synthesis strategies to construct the guaiane skeleton are annulation, ring-expansion/contraction, or direct cyclization through acid/base-mediated and free radical routes.[3−8] Total syntheses of guaiane-type sesquiterpenoids including guaiol (**1a**),[9,10] aciphyllene (**4a**),[11] indicanone,[12] pesudolaric acid A,[13] and englerin A and its analogues[7,14−20] have been accomplished. However, the overall yields are often low, and challenges have been experienced in installing the proper stereochemistry and functionalities when constructing the fused [5.3.0]-bicyclic ring cores. Alternative approaches to enable rapid access to different guaiene sesquiterpenoids are thus warranted. A plausible solution noted by us hinged on developing synthesis routes starting with cheap guaiane natural products such as guaiol (**1a**), which can be easily isolated in large quantities from guaiac wood essential oil[21] and which already has the bicyclic [5.3.0]-core installed with three defined stereogenic centers near the bridged C═C bond.

Indeed others have utilized guaiol (**1a**) to prepare several sesquiterpenes including (+)-hedycaryol and (+)-γ-eudesmol[21] and cadalane,[22] by either beginning with the oxidative cleavage of the bridged C═C bond or direct acid-catalyzed dehydration of the hydroxyisopropyl side-chain. We speculated that epoxidation of **1a** would allow for diastereoselective installation of a centrally positioned epoxy moiety, based on its sterically biased structure and choice of epoxidizing agent, which should be able to be further fine-tuned based on the influence of varying steric effects imposed by protecting groups on the remote hydroxyisopropyl moiety of guaiol (**1a**). Ring-opening reactions of the resultant epoxide(s) would then allow for the regio- and stereoselective installation of hydroxy moieties, which upon dehydration should realize the migration of the bridged double bond and allow for rapid access to a range of recently isolated sesquiterpenes. The epoxidation of **1a** has

Received: August 1, 2014
Published: October 20, 2014

dx.doi.org/10.1021/np500611z | *J. Nat. Prod.* 2014, 77, 2522−2536

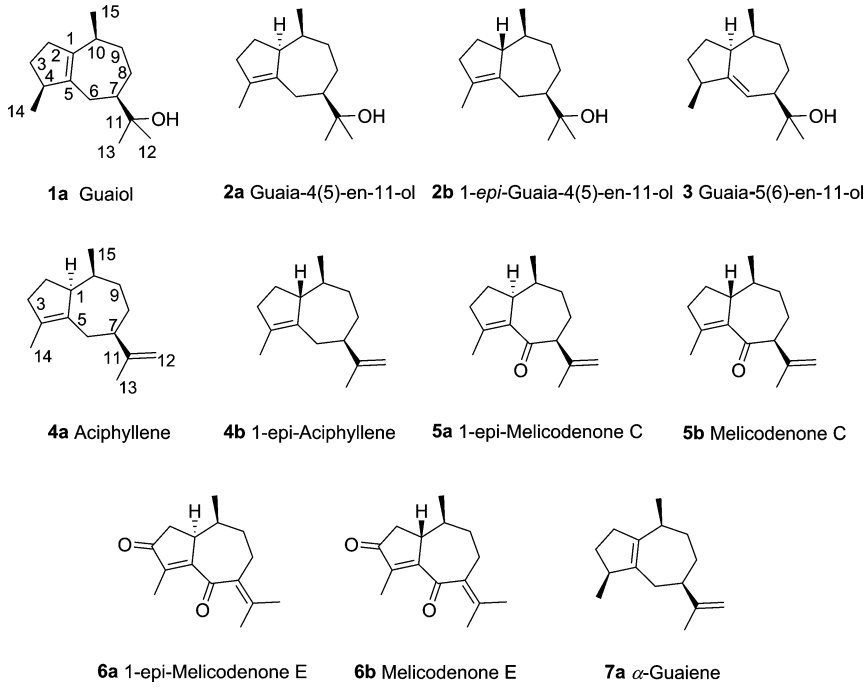


Figure 1. Aciphyllene, melicodenones (C and E), and their C-1 epimers along with several isomeric guaiols.

been visited previously with the focus placed mainly on the characterization of the epoxidation products.[23]

To evaluate the feasibility of this strategy, a range of natural sesquiterepenes with structures related to guaiol (**1a**) including guaia-4(5)-en-11-ol (**2a**), guaia-5(6)-en-11-ol (**3**), aciphyllene (**4a**), and melicodenones C (**5b**) and E (**6b**) were chosen as targets. Guaia-4(5)-en-11-ol (**2a**) and guaia-5(6)-en-11-ol (**3**) are natural sesquiterpenes with anti-inflammatory activity and were recently isolated from the methanol extracts of the fruit of the highly invasive weed *Pittosporum undulatum*.[24] Aciphyllene (**4a**) was first isolated from the essential oils of *Lindera glauca* in 1983[25] and later isolated and identified from *Dumotiera hirsuta*[26] and numerous other natural sources.[27−30] Melicodenones C and E (**5b** and **6b**) are novel guaiane-type sesquiterpenoids isolated from the roots of *Melicope denhamii*, one of ca. 230 species of *Melicope* (Rutaceae) distributed from Madagascar east to the Hawaiian Islands and south to New Zealand.[31] We report herein that by controlling the initial diastereoselective epoxidation of guaiol (**1a**), subsequent ring-opening and elimination allow for the ready migration and installation of the requisite C═C bonds at the cores of these structures along with tight control of the C-1 stereochemistry and consequently, with further simple functional group manipulation, allow for rapid access to the natural products (**2a**, **3**, and **4a**) and the ready synthesis of the C-1 epimers of targeted natural products (**2b**, **4b**, **5a**, and **6a**) and their derivatives in moderate to good yields.

RESULTS AND DISCUSSION

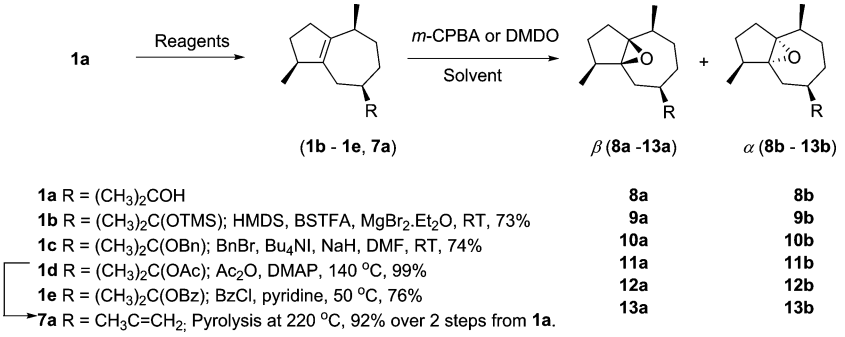
Diastereoselective Epoxidation of Guaiol (1a). The first step in the synthesis of the guaiane-type natural products depicted above was to efficiently control the π facial selectivity of the epoxidation of the centrally bridged double bond of guaiol (**1a**) or its hydroxy-protected derivatives, namely, the trimethylsilyl ether (**1b**), benzyl ether (**1c**), acetate (**1d**), and benzoate (**1e**). These latter derivatives were prepared in good to excellent yields as depicted in Table 1. Both *m*-chloroperbenzoic acid (*m*-CPBA) and dimethyl dioxirane (DMDO) were utilized as potential epoxidizing agents, while other common epoxidizing reagents such as peracetic acid in acetic acid were not pursued due to the sensitivity of most epoxides of guaiol (**1a**) and its derivatives to acid-induced fragmentation.[32]

Epoxidation of guaiol (**1a**) with *m*-CPBA in CH_2Cl_2 revealed little π facial selectivity with a preference for formation of the β-epoxide (**8a**) of 1.3:1 (entry 1). In contrast, epoxidation with DMDO afforded the α-epoxide (**8b**) as the major stereoisomer (19:1) in 65% yield (entry 7). Changing the solvent system (entries 13−22) had only a minor beneficial effect on the observed π facial selectivity of epoxidation of **1a** when employing *m*-CPBA, with DMF returning the best π facial selectivity in favor of β-epoxide (**8a**) of 2.1:1. In order to improve the preference for β π facial selectivity, we next explored the effects that the remote hydroxy protecting groups would have on epoxidation, entries 1−12. The benzoate (**1e**) yielded the highest π facial selectivity with 80% β-orientation (**12a**) followed by acetate (**11a**, 75%), TMS ether (**9a**, 71%), and benzyl (**10a**, 59%) when *m*-CPBA was employed as oxidant in CH_2Cl_2 at RT. When using DMDO as oxidant, the α-epoxide (**8b**−**12b**) was the dominant stereoisomer in all cases, although minor differences were observed due to the nature of the protecting group, Table 1.

In sharp contrast to the observed preference for β facial epoxidation of **1a**−**1e**, regioselective epoxidation of guaiene (**7a**) with *m*-CPBA in CH_2Cl_2 at −78 °C yielded the α-mono-epoxide (**13b**) as the major epoxide (65%, entry 6) similar to the predominant α-epoxy orientation observed in the regioselective epoxidation of β-himachalene.[33] Performing the epoxidation of **7a** but with 1 equiv of *m*-CPBA at ambient temperature yielded the same mixture of mono-epoxides (**13a** and **13b**) in a 35:65 ratio, along with the bis-epoxides (**14a**−**14d**) (Scheme 1). Addition of excess oxidant furnished the two pairs of bis-epoxides (**14a**/**14b** and **14c**/**14d**) in a ratio of 36:64, consistent with that found for mono-epoxide formation

dx.doi.org/10.1021/np500611z | J. Nat. Prod. 2014, 77, 2522−2536

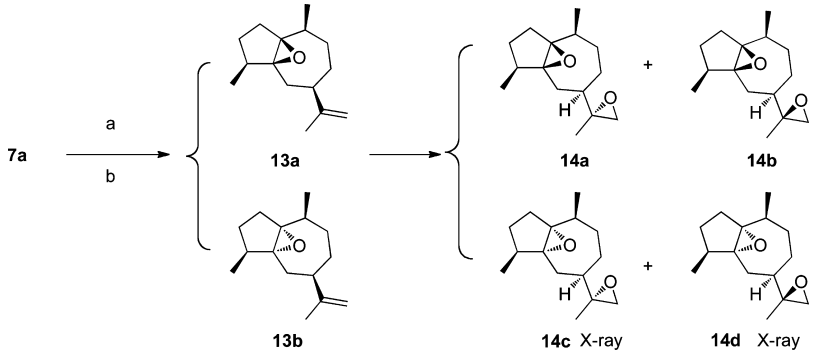
Table 1. Effects of Remote Substituents, Reagents, and Choice of Solvent on Diastereoselective Epoxidation of Guaiol Derivatives 1a−1e and α-Guaiene 7a



entry	solvent	substrate	reagent	β:α[f]	yield (%)
1	CH_2Cl_2	**1a**	*m*-CPBA[a]	56:44	97
2	CH_2Cl_2	**1b**	*m*-CPBA[a]	71:29	96
3	CH_2Cl_2	**1c**	*m*-CPBA[a]	59:41	95
4	CH_2Cl_2	**1d**	*m*-CPBA[a]	75:25	94
5	CH_2Cl_2	**1e**	*m*-CPBA[a]	80:20	95
6	CH_2Cl_2	**7a**	*m*-CPBA[b]	35:65	93
7	acetone	**1a**	DMDO[c]	5:95	65
8	acetone	**1b**	DMDO[c]	11:89	64[f]
9	acetone	**1c**	DMDO[c]	6:94	45
10	acetone	**1d**	DMDO[c]	30:70	60[f]
11	acetone	**1e**	DMDO[c]	13:87	52[f]
12	acetone	**7a**	DMDO[d]	2:98	14[f]
13	toluene	**1a**	*m*-CPBA[e]	60:40	89
14	1,4-dioxane	**1a**	*m*-CPBA[e]	60:40	89
15	Et_2O	**1a**	*m*-CPBA[e]	65:35	97
16	$CHCl_3$	**1a**	*m*-CPBA[e]	57:43	99
17	$(CH_2Cl)_2$	**1a**	*m*-CPBA[e]	57:43	99
18	acetone	**1a**	*m*-CPBA[e]	62:38	91
19	EtOAc	**1a**	*m*-CPBA[e]	67:33	100
20	MeCN	**1a**	*m*-CPBA[e]	61:39	100
21	DMF	**1a**	*m*-CPBA[e]	71:29	84[g]
22	MeOH	**1a**	*m*-CPBA[e]	68:32	90
23	Et_2O	**1d**	*m*-CPBA[e]	84:16	100
24	EtOAc	**1d**	*m*-CPBA[e]	83:17	96
25	DMF	**1d**	*m*-CPBA[e]	78:22	80[g]
26	MeOH	**1d**	*m*-CPBA[e]	78:22	99

[a]Substrate (0.1 mmol) and *m*-CPBA (0.2 mmol) in CH_2Cl_2 (1 mL) at RT for 10 min. [b]Substrate (0.50 mmol) and *m*-CPBA (0.57 mmol) in CH_2Cl_2 (6 mL) at −78 °C for 30 min. [c]Substrate (20 μmol) and DMDO (30 μmol) in acetone (1 mL) at RT for 1 h. [d]**7a** (50 μmol) and DMDO (50 μmol) in acetone (1 mL) at −78 °C. Epoxy orientation confirmed by X-ray crystallographic analysis of the two bis-epoxides (**14c** and **14d**, *vide infra*). [e]**1a** or **1d** (20 μmol) and *m*-CPBA (40 μmol) in above solvents (1 mL) at RT for 30 min. [f]Determined by GC-MS/FID. [g]Based on 75% conversion.

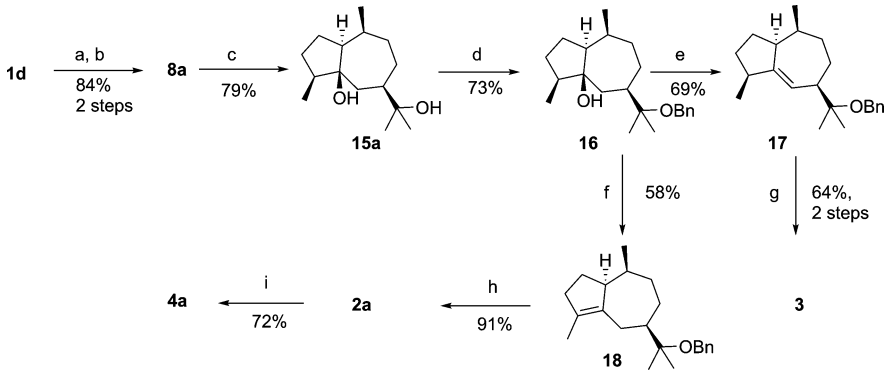
Scheme 1. Synthesis of Epoxides (13a,b) and Bis-epoxides (14a−14d) Derived from Guaiene 7a[a]



[a]Conditions: (a) *m*-CPBA (1 equiv), CH_2Cl_2, −78 °C, **13a**:**13b** = 35:65; (b) *m*-CPBA (6 equiv), CH_2Cl_2, RT, (**14a** + **14b**):(**14c** + **14d**) = **36**:**64**.

dx.doi.org/10.1021/np500611z | J. Nat. Prod. 2014, 77, 2522−2536

Scheme 2. Synthesis of Guaia-4(5)-en-11-ol (2a), Guaia-5(6)-en-11-ol (3), and Aciphyllene (4a)[a]



[a]Reagents and conditions: (a) *m*-CPBA, Et_2O, −78 °C to RT, 80 min; (b) Na, MeOH, RT, 12 h; (c) $LiAlH_4$, $AlCl_3$ anhydrous, THF, 4 h: (d) BnBr, Bu_4NI, NaH, DMF, RT, 12 h: (e) $SOCl_2$, Et_3N, benzene, RT, 20 min: (f)$TsOH{\cdot}H_2O$, CH_3CN, RT, 6 h; (g) Li wire, naphthalene, THF, −78 °C to RT, 18 h; (h) $LiAlH_4$, THF, RT, 12 h; (i) $SOCl_2$, benzene, pyridine, RT, 10 min.

and merely reflects that the more electron-rich bridged C═C is epoxidized at a much faster rate than the external isopropylene unit (Scheme 1). The facial selectivity of epoxidation of **7a** was lifted to 98% α-orientation (**14b**) when employing DMDO as oxidant at −78 °C; however, isolatable yields were diminished by the formation of several other uncharacterized products. The orientations of the α- and β-epoxides derived from substrates **1a**−**1e** and **7a** were confirmed by comparison with the known epoxides **8a** and **8b**,[23] the observed trend that the β-oriented epoxides of guaiol derivatives (**1a**−**1e**) all displayed shorter GC rention times than their α-oriented counterparts, and also via X-ray crystallographic analysis of the bis-epoxides (**14c** and **14d**; see Supporting Information) derived from the α-oriented bridged mono-epoxide (**13b**) as depicted in Scheme 1.

The differences in whether α or β π facial selectivity is preferred in the epoxidation reactions of these guaiene substrates can be attributed to a number of factors based on the combined effects of the types of remote protecting groups on the hydroxyisopropyl side chain, choice of solvent, and epoxidizing reagent, with the latter influencing the stereochemical outcome to the greatest extent. Theoretical calculations to determine the equilibrium conformation of guaiol (**1a**) reveal that the β-face of the central bridged double bond is sterically encumbered by the C-4 and C-10 methyl substituents (Supporting Information). Similar calculations of the α- and β-epoxides of **1a**, namely, **8a** and **8b**, reveal that the α-epoxide **8b** is the thermodynamic product by some 1.06 kcal/mol (Supporting Information). Thus, given that DMDO has a spiro geometrical relationship between its *gem*-dimethyl groups and the dioxirane ring, its approach to the β-face of the central double bond of guaiol (**1a**) is sterically disfavored by the C-4 and C-10 methyl substituents, resulting in approach to the sterically less hindered α-face and formation of the thermodynamically more stable α-epoxides. However, α or β π facial selectivity when employing *m*-CPBA as the epoxidizing agent is clearly influenced by the sterics of the protecting group on the remote hydroxyisopropyl side chain as we first thought. It appears that the sterics of the remote protecting groups aid in blocking the approach of *m*-CPBA to the α-face; thus the more "cylindrically planar" peracid moiety is forced to approach between the C-4 and C-10 methyl groups, resulting in the formation of the β-epoxides as the major products. The most dramatic demonstration of this effect is seen when the protected hydroxyisopropyl moiety is replaced with an isopropylene unit as in **7a** (entry 6), which results in a complete reversal of the β-facial selectivity seen for substrates **1a**−**1e** to once again favor approach from the less hindered α-face and formation of the thermodynamic epoxide **13b**. The fact that guaiol (**1a**), with an unprotected hydroxy group, displays the poorest β vs α facial selectivity when compared to the protected derivatives also supports this argument. Solvent choice was also found to have a small but still significant influence for these stereoselective epoxidations.

With a preference for α- or β-epoxide stereoselectivity now achievable based on choice of protecting group, we decided to further refine the potential for β-stereoselectivity based on solvent choice. Even though **1e** gave the highest β-orientation for epoxidation with *m*-CPBA, the acetate **1d** was chosen as the optimal protecting group owing to the higher yield (99%) for the synthesis of **1d** from guaiol (**1a**). Solvent screening (entries 13−22, Table 1) using **1a** as substrate across a wide spectrum of general solvents suggested DMF, MeOH, EtOAc, and Et_2O may be optimal solvents with β-stereoselectivities of >65%. Further trials using **1d** as substrate with a range of solvents (entries 23−26, Table 1) distinguished Et_2O as the optimal solvent, furnishing a π facial selectivity of 84% for the β-orientation. Attempts to improve this selectivity by lowering the reaction temperature to −78 °C gave a slight enhancement of 2% to 86% β-orientation.

Synthesis of Guaia-4(5)-en-11-ol (2a), Guaia-5(6)-en-11-ol (3), and Aciphyllene (4a) from β-Epoxyguaiol (8a), and 1-*epi*-Guaia-4(5)-en-11-ol (2b) and 1-*epi*-Aciphyllene (4b) from Bridged α-Epoxyguaiol (8b). With the β-epoxide of acetate **1d** identified as an optimal precursor to various naturally occurring bridged sesquiterpenes, we next focused on the synthesis of the natural sesquiterpenes guaia-4(5)-en-11-ol (**2a**), guaia-5(6)-en-11-ol (**3**), and aciphyllene (**4a**) employing an epoxidation, ring-opening, and elimination sequence (Scheme 2). Epoxidation of **1d** followed by basic hydrolysis of the acetate moiety of **11a** afforded β-epoxyguaiol (**8a**) in 84% yield over two steps. Reductive ring-opening of **8a** furnished diol **15a** as the predominant product in 79% yield and whose hydroxy moiety was introduced at C-5 with β-orientation. Regioselective hydride delivery to the α-face of epoxide **8a** at C-1 as opposed to delivery at C-5 is presumably a reflection of steric crowding around C-5. The C-5 tertiary hydroxy group is more sterically hindered than the terminal hydroxyisopropyl group, allowing for selective benzylation via

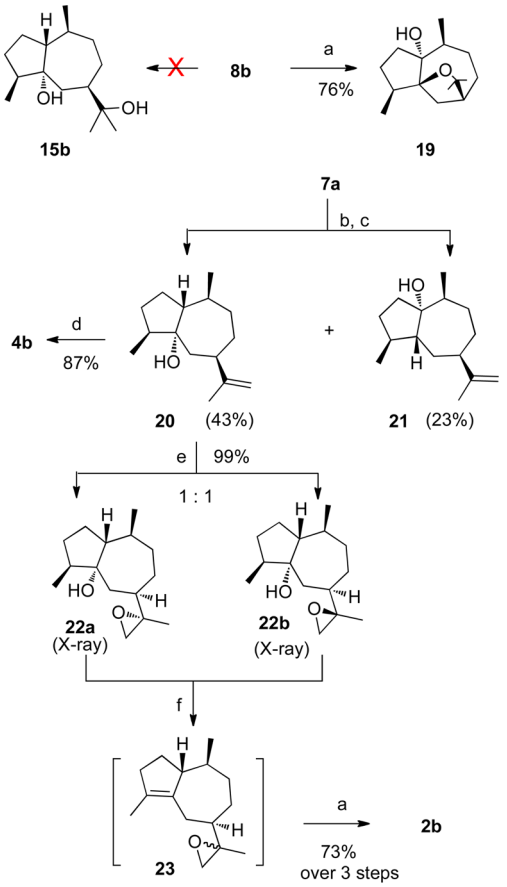
dx.doi.org/10.1021/np500611z | *J. Nat. Prod.* 2014, 77, 2522−2536

in situ generation of benzyl iodide using Ogawa's method[34] in 73% yield and high regioselectivity. Dehydration of **16** with $SOCl_2$ in benzene gave predominantly the 5,6-ene (**17**) in 69% yield, whereas treatment of **16** with a trace of $TsOH{\cdot}H_2O$ in MeCN afforded a mixture of **1a**, 4,5-ene **18**, and α-bulnesol[35] as the major products in a ratio of 22%, 66%, and 7%, respectively, by GC analysis. Fractionation of this alkenic mixture with $AgNO_3$-impregnated silica (SNIS) column chromatography furnished pure **18** in a good yield of 58%. At this stage we thus had control of installing the double bond as either a 4,5- or a 5,6-ene unit within these bicyclic sesquiterpenes. Cleavage of the benzyl ether function of **17** with Li and naphthalene furnished guaia-5(6)-en-11-ol (**3**) in 64% yield over two steps, while treatment of isomeric **18** with excess $LiAlH_4$ in THF furnished guaia-4(5)-en-11-ol (**2a**) in 91% yield.[36] This represents the first synthesis of the naturally occurring sesquiterpene guaia-5(6)-en-11-ol (**3**) and also offers access to natural guaia-4(5)-en-11-ol (**2a**) in one sequence in 31% and 26% overall yields, respectively. Dehydration of alcohol **2a** followed by purification on SNIS chromatography also afforded the natural product aciphyllene (**4a**) in 72% yield. Overall, our synthetic approach offers a more rapid route to aciphyllene (**4a**) in 18% overall yield over seven steps from guaiol (**1a**) when compared with the 2% overall yield over 15 steps reported when starting with (*R*)-limonene.[11,37]

In order to further explore the feasibility for rapid access to additional guaiol analogues, we repeated the sequence beginning with the α-epoxides of various guaiol derivatives (**8b**–**13b**), which upon ring-opening should afford the β-oriented C-1 epimeric counterparts of the natural sesquiterpenes synthesized above (Scheme 3). As highlighted in Table 1, α-epoxyguaiol (**8b**) may be prepared with a π facial selectivity of 95% α-orientation in 65% overall yield when using DMDO as oxidant. Ring-opening of **8b** with AlH_3 in THF simply led to the formation of tricyclic guaioxide (**19**) via nucleophilic attack of the terminal hydroxy moiety on the bridged epoxy moiety without the formation of the expected diol (**15b**) (Scheme 3). Employing the α-epoxybenzyl ether (**10b**) under the same conditions (AlH_3 in THF) resulted in no reaction at RT, while employing elevated temperatures simply resulted in dehydration to regenerate the bridged olefin (**1c**). Employing α-guaiene (**7a**), which does not have the exocyclic tertiary alcohol moiety, furnished alcohol **20** in 43% yield with a 5-OH moiety and the appropriate H-1β orientation, along with isomeric **21** in 23% yield when employing regioselective epoxidation of **7a** with *m*-CPBA at −78 °C followed by ring-opening with AlH_3 in THF under reflux.[38] Dehydration of **20** with $SOCl_2$ in Et_2O followed by SNIS chromatography furnished the yet to be naturally identified 1-*epi*-aciphyllene (**4b**) in 87% yield, whereas guaia-11-en-1-ol (**21**) gave an inseparable mixture of various dienes regardless of the types of solvent and reagents (e.g., $SOCl_2$, $POCl_3$, $MeSO_2Cl$) employed. Epoxidation of **20** afforded a mixture of epoxide epimers (**22a**,**b**) in near-quantitative yield with the C-1 configurations confirmed by X-ray diffraction analysis of the individual epoxy alcohols (**22a** and **22b**; see Supporting Information). Dehydration of a mixture of **22a**,**b** with $SOCl_2/Et_3N$ in CH_2Cl_2 installed the C4−C5 double bond regioselectively, furnishing epoxide epimers **23**, which upon reduction of the epoxide moiety with AlH_3 followed by SNIS chromatography afforded 1-*epi*-guaia-4(5)-en-11-ol (**2b**) in a 73% yield over three steps.

At this stage, we have obtained rapid access to two epimeric analogues of the natural sesquiterpenes aciphyllene (**4b**, 22%, over five steps) and guaia-4(5)-en-11-ol (**2b**, 19%, over seven steps) from guaiol (**1a**). Overall, these short syntheses utilizing bridged sesquiterpene epoxides demonstrate the ease with which the C-1 stereochemistry along with instillation of the appropriate double bonds at either the 4,5- or 5,6-positions of these sesquiterpenes may be controlled.

Scheme 3. Synthesis of 1-*epi*-Guaia-4(5)-en-11-ol (2b) and 1-*epi*-Aciphyllene (4b)[a]

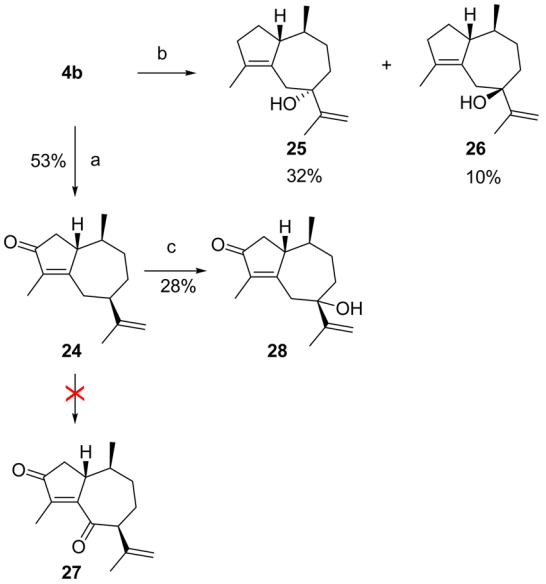


[a](a) $LiAlH_4$, $AlCl_3$, THF, RT, 4 h; (b) *m*-CPBA, CH_2Cl_2, −78 °C, 2 h; (c) $LiAlH_4$, $AlCl_3$, THF, 90 °C, 22 h; (d) $SOCl_2$, Et_2O, Et_3N, 0 °C, 30 min; (e) *m*-CPBA, CH_2Cl_2, RT, 1 h; (f) $SOCl_2$, Et_3N, CH_2Cl_2, RT, 10 min.

Potential of 1-*epi*-Aciphyllene (4b) and Aciphyllene (4a) as Precursors for the Synthesis of Melicodenones C (5b) and E (6b) and 1-*epi*-Melicodenones C (5a) and E (6a) and Related Derivatives, Respectively. With aciphyllene (**4a**) and 1-*epi*-aciphyllene (**4b**) in hand, we next explored a possible concise synthesis of the recently isolated natural sesquiterpenoids melicodenones C and E via functional group manipulation. Owing to the fact that 1-*epi*-aciphyllene (**4b**) shares the same β-orientation of H-1 as that of the natural melicodenones, we expected that allylic oxidation of 1-*epi*-aciphyllene would furnish natural melicodenone C (**5b**) in two steps. However, allylic oxidation of **4b** with PDC and TBHP afforded enone **24** with the carbonyl moiety selectively installed at C-3 (53% yield) rather than C-6 (Scheme 4). Alternatively, treatment of **4b** with SeO_2 and TBHP[39] afforded the two epimeric allylic alcohols **25** and **26** in a ratio of 3:1. Attempts to access isomeric derivative **27** of melicodenone E (**6b**) via further oxidation of **24** with CrO_3 and DMP did not generate the target enedione with almost full recovery of the starting

dx.doi.org/10.1021/np500611z | *J. Nat. Prod.* 2014, 77, 2522−2536

Scheme 4. Attempted Synthesis of Melicodenone C (5b) via Allylic Oxidation of 1-*epi*-Aciphyllene (4b)[a]



[a]Reagents and conditions: (a) PDC, TBHP, 3 Å molecular sieves, CH_2Cl_2, 0 °C, 5 h; (b) SeO_2, TBHP, CH_2Cl_2, 0 °C, 4 h; (c) SeO_2, TBHP, CH_2Cl_2, 0 °C, 8 h.

material. Allylic oxidation of **24** with SeO_2 and TBHP simply furnished allylic alcohol **28**, with a 7-OH moiety, as observed previously.[40] Installation of the hydroxy moiety on the α-face was confirmed from the ROESY correlations between O*H* and H-6b, H-6a, and H-13 as well as H-6a and H-15 (Figure 2). Further attempts at oxidation including $Pd(OH)_2/C$ with TBHP,[41] PDC in DMF,[42] and CrO_3 in HOAc[43] all failed to generate the target enedione (**27**).

In stark contrast to the attempted allylic oxidation at C-6 described for 1-*epi*-aciphyllene (**4b**), allylic oxidation of aciphyllene (**4a**) employing stoichiometric SeO_2 and TBHP as oxidants[39] afforded allylic alcohol **29** in 33% yield (Scheme 5). The α-orientation of the C-6 hydroxy moiety was established via ROESY, which showed interactions between H-6 and the β-oriented H-15. The dramatic differences of potential allylic oxidation sites between aciphyllene (**4a**) and 1-*epi*-aciphyllene (**4b**) may be a combined result of steric effects and subtle changes in bond strengths of the allylic C−H bonds at C-6 vs C-7 caused by varying through-bond hyperconjugative effects after conformational adjustment of the [5.3.0] bicyclic core depending on whether H-1 is α- or β-oriented. Indeed, the calculated equilibrium comformers of aciphyllene (**4a**) and 1-*epi*-aciphyllene (**4b**) at the semiempirical AM1 level of theory clearly show pronounced differences in the sterics surrounding C-6 and C-7 along with significant changes in the associated C−H bond lengths (see Supporting Information). Attempts to improve the yield of the allylic oxidation[44] of **4a** employing TBHP coupled with various metal-based oxidants including PDC, CrO_3, $Mn(OAc)_3$, $Co(OAc)_2$, $Pd(OAc)_2$, or the metal-free co-oxidant diacetoxyiodobenzene (DIB)[45] proved to be unsatisfactory and either afforded complex mixtures of oxidation products or suffered from low conversion or recovery. Nonetheless, access to 1-*epi*-melicodenone C (**5a**) was readily achieved via oxidation of **29** employing Dess−Martin periodinane in 72% yield. The α-oriented H-1 of **5a** was substantially deshielded and displayed a ^{1}H NMR chemical shift at 3.29 ppm, which differed significantly from the shielded 2.60−2.80 ppm multiplet displayed for the more shielded β-oriented H-1 of natural melicodenone C (**5b**).[31] The C-1 configuration also affected the chemical environments of nearby C-10 and C-15 such that 0.52 and 0.17 ppm differences in the ^{1}H NMR chemical shifts for H-10 and H-15 between the two C-1 epimers were observed, respectively (see Supporting Information for table of ^{1}H and ^{13}C NMR data for **5a** and **5b**). Treatment of **5a** with NaOMe (1 M in EtOH) resulted in the migration of the terminal double bond to afford the related dienone **30** in near-quantitative yield. No epimerization to **5b** was observed in this reaction.

With the related dienone **30** as precursor to the melicodenone series of derivatives in hand we now had the opportunity to carry out oxidation at C-3 to accomplish the first synthesis of 1-*epi*-melicodenone E (**6a**) (Scheme 5). Thus, dienone **30** was subjected to exhaustive oxidation with CrO_3 (8 equiv) and 3,5-dimethylpyrazole (DMP) (9 equiv) in CH_2Cl_2,[46,47] which furnished a mixture of 1-*epi*-melicodenone E (**6a**), epoxyenone **31**, and epoxyenedione **32** in 13%, 24%, and 15% yields, respectively. Altering the stoichiometry of the oxidation reagents led to a significantly different product distribution as depicted in Scheme 5. 1-*epi*-Melicodenone E (**6a**) was generated as the main isolable product in 32% yield (based on 16% recovery of **30**) when 13 equiv of CrO_3 and 28 equiv of DMP were employed. Furthermore, oxidation of **30** with excess CrO_3 (19 equiv) and DMP (19 equiv) resulted in the further oxidation of any **31** and **6a** formed and afforded highly oxidized **32** as the dominant product in 40% isolated yield. While epoxidations have been observed when employing CrO_3 previously,[48] given the complex nature of the species involved in these oxidative processes,[46] it is difficult to clearly rationalize why the product outcomes are so affected by the stoichiometry of the reagents employed here. However, it may simply be a case that lower levels of DMP result in less ligation with the CrO_3, thus allowing epoxidation to compete with allylic oxidation. Comparison of the ^{1}H NMR chemical shifts of *epi*-**6a** to those of the natural product **6b**[31] again displayed the same pattern of chemical shift differences for H-1, H-10, and H-15 as those highlighted above for **5a** and **5b** (Supporting Information). X-ray analysis of **32** confirmed its full structural assignment (Supporting Information).

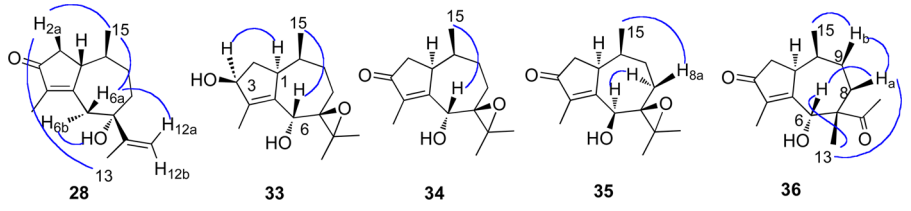
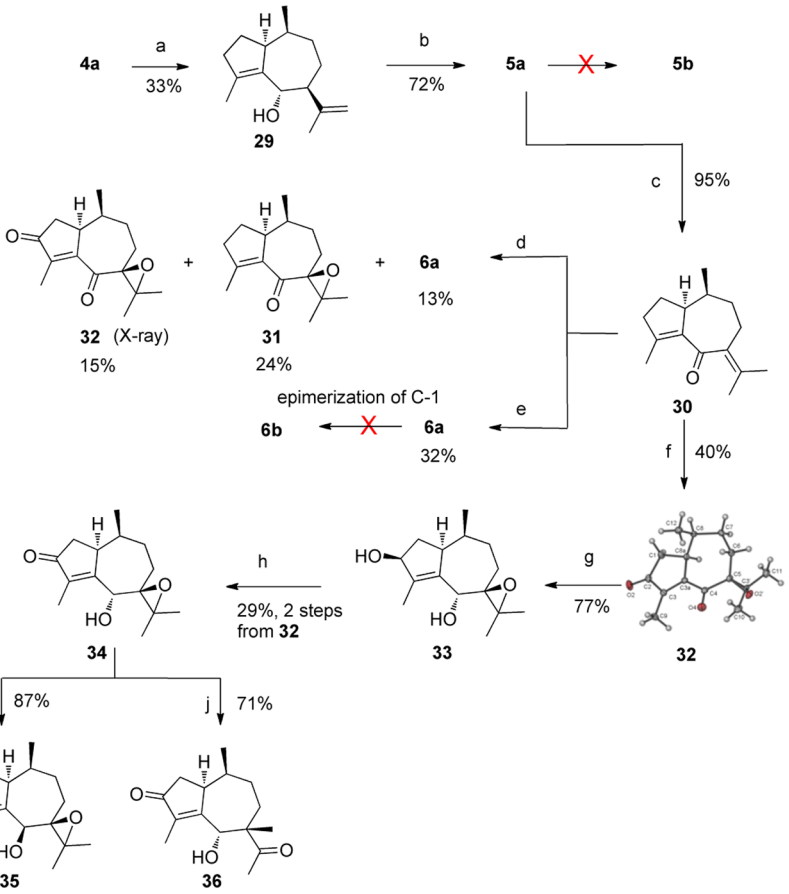


Figure 2. Key ROESY correlations for compounds **28** and **33**−**36**.

dx.doi.org/10.1021/np500611z | J. Nat. Prod. 2014, 77, 2522−2536

Scheme 5. Synthesis of 1-*epi*-Melicodenones C (5a) and E (6a)[a]



[a]Reagents and conditions: (a) SeO_2, TBHP, CH_2Cl_2, 0 °C, 4 h; (b) Dess−Martin periodinane, CH_2Cl_2, RT, 4 h; (c) NaOMe, EtOH, RT, 14 h; (d) CrO_3 (8 equiv), 3,5-dimethylpyrazole (DMP, 9 equiv), CH_2Cl_2, reflux, 24 h; (e) CrO_3 (13 equiv), DMP (28 equiv), CH_2Cl_2, relux, 24 h; (f) CrO_3 (19 equiv), DMP (19 equiv), CH_2Cl_2, reflux, 24 h; (g) $CeCl_3{\cdot}H_2O$, MeOH, 0 °C, 30 min, then $NaBH_4$, 10 min; (h) IBX, DMSO, RT, 3 h; (i) 3% KOH (in MeOH), 40 °C, 1 h; (j) $TsOH{\cdot}H_2O$ (cat.), CH_2Cl_2, RT, 1 h.

Given that the conjugated enone moiety has now been installed for **6a**, epimerization at H-1 was expected to have readily taken place under basic conditions given literature precedents;[49−52] however, extensive trials with bases from mild $NaHCO_3$ to stronger NaOMe and acids including $TsOH{\cdot}H_2O$ under various conditions failed to affect epimerization at C-1. It was found that enediones **6a** and **32** decomposed considerably over time under various basic conditions possibly due to intra- or intermolecular Aldol-type condensations. However, compound **6a** remained intact under acidic conditions. As an alternative we considered that removal of the fully conjugated enedione systems from these derivatives while still maintaining the en-3-one conjugated system would hinder decomposition and in turn allow C-1 epimerization. Concealing the C-6 carbonyl moiety as a ketal proved infeasible, as experimental trials showed that the C-6 carbonyl moiety of **6a** was much harder to ketalize than the C-3 enone using various alcohols and diols under acidic conditions.

Alternatively, reducing the two carbonyl moieties to form a diol followed by selective oxidation of the less hindered alcohol appeared attractive. Interestingly, Luche reduction of **6a** with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ saw the full recovery of **6a**; however, reduction of epoxyenedione **32** was effective in furnishing epoxydiol **33** in 77% yield. Oxidation of **33** with IBX in DMSO yielded epoxyenone **34** in 29% yield accompanied by regeneration of **32** in 36% yield. Epimerization of C-1 of enone alcohol **34** under basic and acidic conditions, however, again failed to afford the targeted C-1 epimer. Treatment of allylic alcohol **34** with 3% methanolic KOH[49,51] simply furnished **35**, in which the allylic C-6 secondary alcohol moiety underwent preferential epimerization. Attempts to epimerize C-1 of **34** under acid-catalyzed conditions[52] with $TsOH{\cdot}H_2O$ in CH_2Cl_2 afforded the rearranged product **36** in 71% yield without epimerization at C-1. The stereochemistries of **33**−**36** were established on the basis of ROESY analyses as outlined in Figure 2. ROESY correlation from H-6 to H-15 was observed for both **33** and **34**, indicative of the α-orientation of the 3-hydroxy moiety for both **33** and **34**. The ROESY spectrum of **33** also displayed correlations from H-3 to H-1, suggesting the 3-OH moiety is β-oriented. The β-orientation of H-13 of **36** was deduced from the ROESY correlations observed between H-13 and H-8a, H-13 and H-6, H-8a and H-9b, and H-9b and H-15, whereas that of the 6-OH moiety of **35** was established based on the ROESY correlations seen between H-8a and H-15, and H-6 and H-8b. Together with the fact that **34** is the precursor of **35** and **36** and the similar ^1H and ^{13}C NMR spectra of **35** and **34**, the stereochemistry of **35** and **36** were thus elucidated as shown in Figure 2.

Herein we have demonstrated that a simple epoxidation, ring-opening/elimination sequence on naturally occurring guaiol (**1a**) allows for the efficient synthesis of a range of bridged sesquiterpenes in a facile manner. Key features include

dx.doi.org/10.1021/np500611z | J. Nat. Prod. 2014, 77, 2522−2536

that the epoxidation of the centrally bridged double bond of guaiol (**1a**) may be diastereoselectively controlled by manipulating the epoxidizing reagent, solvent choice, and the steric effects of the remote protecting groups on the hydroxyisopropyl moiety. Notably, the geometries of *m*-CPBA and DMDO play an important role in the facial selectivity of epoxidation of sterically biased bicyclic ring systems such as guaiol (**1a**). The ring-opening of the central epoxide and subsequent dehydration may be highly controlled, allowing for the rapid synthesis of guaia-4(5)-en-11-ol (**2a**), guaia-5(6)-en-11-ol (**3**), aciphyllene (**4a**), and their epimers (**2b** and **4b**). The potential of 1-*epi*-aciphyllene (**4b**) and aciphyllene (**4a**) as precursors for the synthesis of melicodenones C (**5b**) and E (**6b**) and 1-*epi*-melicodenones C (**5a**) and E (**6a**) and related derivatives was also explored, with aciphyllene (**4a**) being an excellent precursor for the first synthesis of **5a** and **6a**. Interestingly, the conformationl differences between **4a** and **4b** caused by the C-1 configuration dramatically manifest themselves in potential allylic oxidation sites when employing SeO_2 and TBHP as oxidants.

EXPERIMENTAL SECTION

General Experimental Procedures. All reagents were purchased from commercial sources and were used directly unless otherwise stated. Solvents for synthesis were dried according to known procedures where necessary.[53] Solvents for general chromatography were AR grade except that those used for GC-MS and HRMS analysis were HPLC grade. All reactions were conducted under a N_2 atmosphere. SNIS and DMDO (50 μM in acetone) were prepared according to the literature.[54,55] Guaiol (**1a**) was obtained by repeated recrystallization of commercial guaiac wood essential oil from MeCN.[21] Melting points are uncorrected and were obtained on a Buchi B-540 melting point apparatus. Silica column chromatography (SCC) was performed using either LC60A 40−63 μm silica (Grace Davison) or silica gel 60 (0.015−0.040 mm) from Merck. TLC was conducted with TLC silica gel 60 F_{254} plates (Merck KGaA) using standard vanillin stain for visualization. GC-MS/FID analysis was performed with a 6890 GC coupled with a 5973N MSD or a 7890A GC-FID (Agilent Technologies). DB-5 or HP-5 capillary columns were used for GC-MS/FID analysis throughout this study. HRMS (ESI-TOF) analysis was performed with a Triple TOF 5600 mass spectrometer from AB Sciex Instruments. Density functional theory (DFT) calculations of guaiol (**1a**) and **8a**,**b** were carried out at the B3LYP/6-31G(d) level. Geometry optimization of **4a**,**b** was carried out at the semiempirical AM1 level. All calculations were performed using the Spartan 08 package of programs. NMR spectra were recorded with a Varian-Inova 500/600 MHz spectrometer. All compounds for NMR analysis were dissolved in either $CDCl_3$ or benzene-d_6. All ^{1}H 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 wherever full assignment of ^{1}H and ^{13}C NMR signals were made.

*{2-[(3S,5R,8S)-3,8-Dimethyl-1,2,3,4,5,6,7,8-octahydroazulen-5-yl]-propan-2-yl-oxy}(trimethyl)silane (**1b**).* A mixture of **1a** (21.5 mg, 0.1 mmol), hexamethyldisilane (HMDS, 55 μL, 269 μmol), $MgBr_2.Et_2O$ (21 mg, 81 μmol), and *N*,*O*-bistrimethylsilyl trifluoroacetamide (BSTFA, 25 μL, 94 μmol) was stirred at RT until TLC showed complete consumption of **1a**. The reaction was quenched with brine (10 mL) and extracted with petroleum ether (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and filtered through a short silica plug, and the volatiles were removed *in vacuo* to afford **1b** (20.8 mg, 73%) as a colorless liquid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.53 (1H, appr sext, J = 6.6 Hz), 2.41 (1H, m), 2.28 (1H, appr quint, J = 7.8 Hz), 2.15 (1H, d, J = 9.0 Hz), 2.11 (1H, m), 1.97 (1H, dddd, J = 12.6, 9.6, 8.4, 5.4 Hz), 1.86 (1H, t, J = 13.5 Hz), 1.79−1.72 (1H, m), 1.69 (1H, dddd, J = 13.5, 9.6, 7.8, 3.0 Hz), 1.56−1.51 (2H, m), 1.39 (1H, m), 1.28 (1H, ddt, J = 12.6, 9.0, 5.4 Hz), 1.17 (3H, s), 1.16 (3H, s), 0.99 (3H, d, J = 7.2 Hz), 0.96 (3H, d, J = 7.2 Hz), 0.01 (9H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 139.8, 139.3, 76.7, 50.1, 46.3, 35.4, 33.85, 33.77, 31.1, 27.76, 27.67, 27.3, 26.3, 19.9, 19.7, 2.6; EIMS m/z (rel intensity) 204 (20), 189 (6), 161 (35), 147 (5), 131 (100), 117 (6), 105 (13), 91 (8), 79 (5), 73 (38); HRMS (ESI-TOF) m/z [M − OTMS]$^+$ 205.1938 (calcd for $C_{15}H_{25}$ 205.1956).

*(1S,4S,7R)-7-[2-(Benzyloxy)propan-2-yl]-1,4-dimethyl-1,2,3,4,5,6,7,8-octahydroazulene (**1c**).* NaH (60% dispersion in mineral oil, 2.2 g, 55 mmol) and **1a** (1.15 g, 5.2 mmol) were dissolved in dry DMF (25 mL). To the resulting solution were added BnBr (3 mL, 25 mmol) and Bu_4NI (85 mg, 0.23 mmol) sequentially. The resulting mixture was stirred at RT until TLC indicated no starting material remained. The reaction was quenched by the slow addition of brine (40 mL), and the products were extracted with Et_2O/petroleum ether (20:80, 3 × 100 mL). The combined organic layers were washed with brine (80 mL), dried over $MgSO_4$ anhydrous, and filtered. The volatiles were removed *in vacuo* followed by short-path distillation (190 °C, 0.7 Torr, Kugelroh), giving a distillate containing **1a**, which was further purified by SCC to recover **1a** (401 mg, 35%). The higher boiling nondistilled fraction of the benzyl guaiol (**1c**) was purified by SCC (petroleum ether) to furnish **1c** (736 mg, 74%) as a colorless liquid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.24 (5ArH), 4.39 (2H, s), 2.54 (1H, appr sext, J = 7.8 Hz), 2.44 (1H, m), 2.32 (1H, appr quint, J = 9.0 Hz), 2.20 (1H, d, J = 18.0 Hz), 2.13 (1H, m), 2.01−1.92 (2H, m), 1.90−1.79 (2H, m), 1.74 (1H, m), 1.62−1.50 (2H, m), 1.30 (1H, m), 1.23 (3H, s), 1.20 (3H, s), 1.01 (3H, d, J = 8.4 Hz), 0.96 (3H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.0, 139.9, 139.3, 128.2, 127.3, 127.0, 78.0, 63.0, 46.5, 46.6, 35.5, 33.81, 33.79, 31.0, 27.6, 27.1, 23.2, 22.7, 19.9, 19.6; EIMS m/z (rel intensity) 204 (29), 189 (8), 161 (41), 149 (11), 119 (9), 107 (18), 91 (100), 79 (15), 67 (5); HRMS (ESI-TOF) m/z [M − OBn]$^+$ 205.1973 (calcd for $C_{15}H_{25}$ 205.1956).

*Guaiyl Acetate (**1d**) and α-Guaiene (**7a**).* Both **1d** and **7a** were prepared according to a literature procedure.[56] Guaiol (**1a**, 10.2 g, 50 mmol) was added to a mixture of Ac_2O (100 mL, 847 mmol) and DMAP (245 mg, 1.7 mmol) under N_2 and heated under reflux at 150 °C for 6 h until TLC analysis showed the reaction to be complete. The reaction mixture was allowed to cool to RT and extracted with *n*-hexane (4 × 100 mL). The organic extracts were combined, and silica (ca. 50 g) added. The resulting suspension was well mixed before being filtered through a pad of silica (ca. 50 g). The silica sorbent was further rinsed with *n*-hexane (3 × 200 mL) and filtered through the same pad of silica. The combined filtrate was concentrated *in vacuo* to furnish acetate **1d** (13.1 g, 99%) as a yellowish oil. Crude **1d** (ca. 30 g) prepared as described above using **1** (21.0 g, 95 mmol), Ac_2O (80 mL, 847 mmol), and DMAP (210 mg, 1.7 mmol) was subjected to pyrolysis without purification. The crude **1d** was heated to 220 °C under N_2 for 6 h, while the acetic acid liberated was collected by distillation into a receiving flask. The resulting mixture was cooled to ambient temperature, and *n*-hexane (100 mL) and silica (50 g) were added. The suspension was well mixed before being filtered through a plug of silica (ca. 70 g) under reduced pressure and further rinsed with *n*-hexane (4 × 150 mL). The *n*-hexane fractions were combined, and the volatiles removed *in vacuo* to furnish **7a** as a colorless oil (17.8 g, 92%, 2 steps): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.68 (1H, dq, J = 1.2, 0.9 Hz, H-12α), 4.62 (1H, dq, J = 2.1, 1.5 Hz, H-12β), 2.56 (1H, m, H-4), 2.44 (1H, dtd, J = 14.4, 6.0, 2.4 Hz, H-2α), 2.35 (1H, qd, J = 7.2, 6.0 Hz, H-10), 2.19−2.14 (2H, m, H-6α and H-2β), 2.13 (1H, m, H-7), 1.99−1.96 (2H, m, H-3α and H-6β), 1.73 (3H, dd, J = 1.5, 0.9 Hz, H-13), 1.71 (2H, m, H-8α and H-8β), 1.68 (1H, m, H-9α), 1.61 (1H, m, H-9β), 1.29 (1H, m, H-3β), 1.01 (3H, d, J = 7.2 Hz, H-15), 0.94 (3H, d, J = 7.2 Hz, H-14); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 152.4 (C-11), 140.5 (C-1), 138.5 (C-5), 107.9 (C-12), 46.5 (C-7), 46.1 (C-4), 36.2 (C-2), 33.8 (C-9), 33.7 (C-10), 33.3 (C-6), 31.1 (C-8), 31.0 (C-3), 20.4 (C-13), 19.8 (C-14), 18.5 (C-15); EIMS m/z (rel intensity) 204 (57), 189 (51), 175 (8), 161 (28), 147 (89), 133 (58), 119 (36), 105 (100), 93 (64), 79 (47), 67 (23), 55 (23).

dx.doi.org/10.1021/np500611z | J. Nat. Prod. 2014, 77, 2522−2536

*2-[(3S,5R,8S)-3,8-Dimethyl-1,2,3,4,5,6,7,8-octahydroazulen-5-yl]-propan-2-yl Benzoate (**1e**).* The synthesis was conducted according to that in the literature.[57] To a stirred solution of **1a** (53 mg, 239 μmol) in pyridine (1 mL, 13 mmol) was added BzCl (150 μL, 1.3 mmol). The resulting mixture was heated to 50 °C until TLC indicated the consumption of **1a**. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). Standard workup and purification yielded **1e** (58.8 mg, 76%) as a colorless oil. Spectroscopic data were in agreement with those reported.[57]

*2-[(3S,3aS,5R,8S,8aS)-3,8-Dimethylhexahydro-1H,4H-3a,8a-epoxyazulen-5-yl]propan-2-ol (**8a**).* To a stirred solution of **1d** (4.0 g, 15.2 mmol) in Et_2O (40 mL) at −78 °C was added dropwise a solution of *m*-CPBA (77%, 3.56 g, 15.9 mmol) in Et_2O (50 mL). The solution was allowed to warm to RT over 80 min. After cessation of the reaction (TLC), the reaction was quenched with solid KI (500 mg) and washed with saturated $Na_2S_2O_3$ solution (100 mL) followed by saturated $NaHCO_3$ solution (100 mL). Standard workup afforded the crude epoxy-guaiyl acetate diastereomeric mixture (*β*:*α*, 84:16, based on GC-MS), which was used directly without further purification due to its sensitivity on silica. To a stirred solution of the crude mixture of epoxy-guaiyl acetates (4.3 g) in MeOH (50 mL) under N_2 was added Na metal (1.8 g, 78 mmol) in portions. The resulting mixture was stirred at RT until TLC indicated the consumption of the starting materials (ca. 12 h). The reaction mixture was then concentrated *in vacuo* to ca. 10 mL. Brine (80 mL) was added, and the mixture extracted with Et_2O (3 × 50 mL). The combined ether extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to yield 3.6 g of crude products. Purification by SCC (Et_2O/petroleum ether, 15:85) furnished pure **8a** (3.03 g, 84%) as a pale yellow oil: EIMS *m*/*z* (rel intensity) 220 (14), 202 (6), 187 (12), 159 (16), 138 (35), 123 (62), 105 (28), 95 (48), 59 (100). ^1H and ^{13}C NMR spectroscopic data were in accord with those reported previously.[58]

*2-[(3S,3aR,5R,8S,8aR)-3,8-Dimethylhexahydro-1H,4H-3a,8a-epoxyazulen-5-yl]propan-2-ol (**8b**).* **1a** (228 mg, 1.0 mmol) and DMDO (0.05 M in acetone, 25 mL, 1.3 mmol) were mixed at 0 °C under N_2. The mixture was allowed to warm to RT over 3 h and then concentrated *in vacuo*, and the residue purified by SCC (Et_2O/petroleum ether, 20:80) to afford **8b** (158.8 mg, 65%) as a white solid. **8b**: mp 83.1−85.5 °C; ^1H NMR (benzene-d_6, 600 MHz) *δ* 2.39 (1H, br d, *J* = 14.4 Hz), 2.27 (1H, m), 2.10 (1H, quint, *J* = 7.2 Hz), 1.92 (1H, tdd, *J* = 13.2, 3.6, 2.4 Hz), 1.86−1.78 (2H, m), 1.69−1.60 (3H, m), 1.57 (1H, dd, *J* = 14.4, 12.0 Hz), 1.43−1.38 (1H, m), 0.99 (3H, s), 0.98 (3H, s), 0.96 (1H, m), 0.90 (3H, d, *J* = 7.2 Hz), 0.89−0.84 (1H, m), 0.74 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (benzene-d_6, 150 MHz) *δ* 72.8, 72.4, 72.0, 47.4, 40.8, 32.8, 31.7, 29.74, 29.67, 27.8, 27.7, 26.5, 25.3, 17.0, 16.2; EIMS *m*/*z* (rel intensity) 220 (27), 202 (15), 187 (28), 159 (58), 138 (32), 123 (57), 105 (46), 95 (47), 59 (100).

General Procedure for 9a−12b. To a stirred solution of substrate (0.1 mmol) in CH_2Cl_2 (1 mL) was added *m*-CPBA (77%, 40 mg, 0.18 mmol) at RT. After 10 min, the reaction was quenched with solid KI (5 mg) and washed with saturated $Na_2S_2O_3$ solution (1 mL) followed by saturated $NaHCO_3$ solution (2 mL). The resulting mixture was extracted with Et_2O (3 × 5 mL). The combined ether layers were further washed with brine (5 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* and purified on neutral alumina to furnish the epoxides of guaiol derivatives **9a** and **9b** (29.3 mg, 96%), **10a** and **10b** (30 mg, 95%), **11a** (20 mg, 75%) and **11b** (5 mg, 19%), and **12a** and **12b** (9 mg, 95%) as colorless oils. **9a**: ^1H NMR (benzene-d_6, 500 MHz) *δ* 2.23 (1H, d, *J* = 13.0 Hz), 2.00−1.4 (11H, m), 1.22 (1H, ddd, *J* = 13.5, 10.5, 8.0 Hz), 1.17 (3H, d, *J* = 6.5 Hz), 1.10 (3H, d, *J* = 6.5 Hz), 1.09 (3H, s), 0.92 (3H, s), 0.17 (9H, s); ^{13}C NMR (benzene-d_6, 125 MHz) *δ* 76.5, 72.7, 72.1, 47.83, 37.8, 34.9, 31.2, 28.7, 28.3, 28.2, 28.1, 26.5, 25.1, 19.1, 13.9, 2.7.

9b: ^1H NMR (benzene-d_6, 500 MHz) *δ* 2.41 (1H, br d, *J* = 13.0 Hz), 2.27 (1H, m), 2.14 (1H, quint, *J* = 7.0 Hz), 2.00−1.4 (9H, m), 1.14 (1H, m) 1.16 (3H, s), 1.13 (3H, s), 0.92 (3H, d, *J* = 7.0 Hz), 0.79 (3H, d, *J* = 7.0 Hz), 0.20 (9H, s); ^{13}C NMR (benzene-d_6, 125 MHz) *δ* 76.7, 73.8, 71.8, 47.8, 40.9, 32.8, 31.7, 29.9, 29.7, 28.0, 27.7, 27.4, 25.2, 17.1, 16.2, 2.9.

10a: ^1H NMR (benzene-d_6, 500 MHz) *δ* 7.38 (2H, br d, *J* = 8.0 Hz), 7.23 (2H, t, *J* = 7.5 Hz), 7.12 (1H, tt, *J* = 7.7, 3.5 Hz), 4.29 (2H, d, *J* = 4.5 Hz), 2.30 (1H, d, *J* = 14.0 Hz), 1.93 (1H, dd, *J* = 13.0, 8.2 Hz), 1.90−1.65 (4H, m), 1.64 (1H, dd, *J* = 14.5, 11.8 Hz), 1.53 (1H, dd, *J* = 14.2, 11.0 Hz), 1.45 (1H, m), 1.28−1.21 (2H, m), 1.13 (2H, m), 1.11 (3H, d, *J* = 6.8 Hz), 1.10 (3H, d, *J* = 6.8 Hz), 1.01 (3H, s), 0.96 (3H, s); ^{13}C NMR (benzene-d_6, 125 MHz) *δ* 140.63, 128.6, 128.5, 127.3, 127.2, 77.5, 73.7, 72.2, 63.3, 44.3, 38.1, 35.0, 31.3, 28.5, 28.3, 28.1, 26.4, 22.9, 21.0, 19.0, 13.9.

10b: To a stirred solution of **1c** (51 mg, 0.16 mmol) in acetone (1 mL) at 0 °C was added DMDO (50 μmol, 6 mL, 0.3 mmol). The reaction mixture was stirred for 2 h and allowed to warm to RT. After 2 h, the reaction crude mixture was concentrated *in vacuo* and purified on neutral alumina (Et_2O/petroleum ether, 5−8%) to give **10b** (24 mg, 45%) as a colorless oil: ^1H NMR (benzene-d_6, 500 MHz) *δ* 7.38 (2H, d, *J* = 8.0 Hz), 7.20 (2H, t, *J* = 7.5 Hz), 7.10 (1H, t, *J* = 7.5 Hz), 4.34, 4.29 (2H, ABq, *J* = 11.5 Hz), 2.37 (1H, br d, *J* = 15.0 Hz), 2.29 (1H, m), 2.12 (1H, tt, *J* = 11.5, 1.5 Hz), 2.08 (1H, quint, *J* = 7.0 Hz), 1.96 (1H, tt, *J* = 13.5, 2.8 Hz), 1.87−1.77 (2H, m), 1.71−1.58 (3H, m), 1.42 (1H, m), 1.11 (3H, s), 1.10 (3H, s), 0.99−0.94 (2H, m), 0.92 (3H, d, *J* = 7.0 Hz), 0.73 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (benzene-d_6, 125 MHz) *δ* 140.6, 128.5, 127.6, 127.2, 77.5, 73.0, 72.0, 63.3, 43.1, 40.8, 32.9, 31.8, 29.7, 29.6, 27.7, 25.1, 23.7, 23.5, 17.0, 16.2.

Following the above procedure with **1c** (68 mg, 0.22 mmol), acetone (2 mL), and DMDO (0.05 M, 6 mL) gave crude **10b** (66 mg), which was directly used for reduction with AlH_3. To a stirred solution of $LiAlH_4$ (95 mg, 2.5 mmol) in dry THF (1 mL) was added dropwise a solution of anhydrous $AlCl_3$ (25 mg, 0.19 mmol) in dry THF (1 mL) at RT. The resulting mixture was stirred for 5 min before the further dropwise addition of a solution of crude **10b** (66 mg) in dry THF (2 mL). The reaction was stirred at RT for 6 h and then heated under reflux at 70 °C for an additional 7 h. The reaction was quenched with H_2O (5 mL), and resulting solution was extracted with Et_2O (3 × 10 mL). 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 SCC (petroleum ether) to recover **1c** (23 mg, 34% over 2 steps).

11a: ^1H NMR (benzene-d_6, 500 MHz) *δ* 2.30 (1H, m), 1.98 (1H, d, *J* = 14.0 Hz), 1.91−1.84 (2H, m), 1.74 (1H, ddd, *J* = 10.5, 7.0, 1.8 Hz), 1.70 (3H, s), 1.60 (1H, m), 1.48 (1H, dd, *J* = 14.5, 11.2 Hz), 1.47−1.39 (2H, m), 1.36 (3H, s), 1.24 (3H, s), 1.22 (1H, ddd, *J* = 13.5, 10.5, 8.0 Hz), 1.17−1.08 (3H, m), 1.08 (3H, d, *J* = 7.0 Hz), 1.06 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (benzene-d_6, 125 MHz) *δ* 169.6, 84.8, 72.3, 72.1, 43.1, 37.9, 34.7, 31.1, 28.3, 28.0, 27.9, 26.7, 23.6, 22.4, 22.1, 18.9, 13.8.

11b: ^1H NMR (benzene-d_6, 500 MHz) *δ* 2.36 (1H, tt, *J* = 11.5, 1.8 Hz), 2.24 (1H, m), 2.21 (1H, dtd, *J* = 14.5, 2.4, 1.0 Hz), 2.10 (1H, quint, *J* = 6.7 Hz), 1.92 (1H, tdd, *J* = 12.6, 3.3, 2.0 Hz), 1.85−1.75 (2H, m), 1.68 (3H, s), 1.64−1.53 (3H, m), 1.42 (3H, s), 1.41 (3H, s), 1.41−1.35 (2H, m), 0.95 (1H, m), 0.89 (3H, d, *J* = 7.0 Hz), 0.75 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (benzene-d_6, 125 MHz) *δ* 169.5, 84.7, 72.8, 71.6, 45.0, 40.8, 32.7, 31.4, 29.6, 29.5, 27.6, 24.6, 23.6, 23.4, 22.2, 17.0, 16.2.

12a: ^1H NMR (benzene-d_6, 500 MHz) *δ* 8.16 (1H, t, *J* = 1.5 Hz), 8.15 (1H, t, *J* = 1.5 Hz), 7.14−7.06 (3H, m), 2.38 (1H, td, *J* = 11.5, 6.5 Hz), 2.11 (1H, d, *J* = 14.5 Hz), 1.93−1.87 (2H, m), 1.83−1.55 (4H, m), 1.48 (3H, s), 1.42 (1H, m), 1.37 (3H, s), 1.26−1.17 (2H, m), 1.10 (2H, m), 1.07 (3H, d, *J* = 7.0 Hz), 1.02 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (benzene-d_6, 125 MHz) *δ* 165.5, 132.6, 129.7, 128.5, 85.8, 73.3, 72.1, 43.6, 37.9, 34.7, 31.1, 28.3, 28.1, 27.9, 26.7, 23.8, 22.2, 18.9, 13.7.

12b: ^1H NMR (benzene-d_6, 500 MHz) *δ* 8.18 (1H, t, *J* = 1.5 Hz), 8.17 (1H, t, *J* = 1.5 Hz), 7.15−7.03 (3H, m), 2.54 (1H, tt, *J* = 11.5, 1.8 Hz), 2.38 (1H, td, *J* = 11.5, 6.5 Hz), 2.30 (1H, dt, *J* = 14.5, 3.0 Hz), 2.25 (1H, m), 2.06 (1H, t, *J* = 7.0 Hz), 1.95 (1H, m), 1.88 (1H, m), 1.80 (1H, m), 1.80−1.50 (3H, m), 1.54 (3H, s), 1.52 (3H, s), 1.48 (1H, m), 1.18 (1H, m), 0.94 (1H, m), 0.89 (3H, d, *J* = 7.0 Hz), 0.72 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (benzene-d_6, 125 MHz) *δ* 165.3, 132.8, 132.7, 132.5, 129.8, 85.8, 72.8, 71.6, 45.3, 40.8, 32.7, 31.4, 29.7, 29.6, 27.6, 24.8, 23.6, 23.5, 17.0, 16.2.

13a,b: Prepared as described by us previously.[59]

*(1S,3aR,4S,7R,8aR)-1,4-Dimethyl-7-[(2R)-2-methyloxiran-2-yl]-hexahydro-1H,4H-3a,8a-epoxyazulene (**14c**) and (1S,3aR,4S,7-R,8aR)-1,4-Dimethyl-7-[(2S)-2-methyloxiran-2-yl]hexahydro-1H,4H-3a,8a-epoxyazulene (**14d**).* To a stirred solution of α-guaiene (**7a**, 51.8 mg, 250 μmol) in CH_2Cl_2 (3 mL) was added *m*-CPBA (320 mg, 1.4 mmol). The mixture was stirred at ambient temperature for 30 min and quenched with KI (30 mg), saturated $Na_2S_2O_3$, and $NaHCO_3$ solution. The resulting mixture was extracted with Et_2O (3 × 50 mL), and the combined ether layers were further washed with brine (100 mL) and dried over anhydrous $MgSO_4$. The volatiles were removed *in vacuo* with the residue purified by silica column chromatography (silica pretreated with 5% Et_3N/hexanes, eluted with 8% Et_2O/hexanes) to yield **14c** (14 mg, 24%) as a colorless liquid and **14d** (12 mg, 20%) as a colorless liquid along with a mixture of bis-epoxides (**14a,b**, 12 mg, 20%) as a colorless oil. Crystals of **14c** and **14d** were obtained by slow evaporation from an *n*-hexane solution. **14a** (or **14b**): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.59, 2.57 (2H, ABq, *J* = 4.8 Hz), 2.13 (1H, d, *J* = 8.4 Hz), 2.05−1.91 (3H, m), 1.88 (1H, m), 1.77 (1H, m), 1.64−1.54 (1H, m), 1.54−1.43 (3H, m), 1.36−1.24 (2H, m), 1.21 (3H, s), 1.03 (6H, d, *J* = 7.2 Hz), 0.94 (1H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 73.2, 73.1, 59.8, 54.5, 43.0, 37.8, 34.0, 31.1, 28.7, 28.5, 27.7, 27.8, 18.0, 16.6, 13.5; EIMS *m/z* (rel intensity) 236 (6), 207 (19), 179 (34), 163 (44), 137 (50), 107 (80), 81 (83), 67 (83), 55 (100). **14b** (or **14a**): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.55 (2H, s), 2.05−1.91 (3H, m), 1.64−1.54 (4H, m), 1.54−1.43 (3H, m), 1.36−1.24 (2H, m), 1.24 (3H, s), 1.03 (3H, d, *J* = 6.6 Hz), 1.01 (3H, d, *J* = 6.6 Hz), 0.94 (1H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 73.1, 73.0, 59.8, 53.2, 41.6, 37.8, 34.0, 31.1, 28.4, 28.0, 27.9, 27.8, 18.0, 17.9(5), 13.5; EIMS *m/z* (rel intensity) 236 (15), 207 (35), 179 (37), 163 (71), 135 (49), 107 (89), 81 (86), 67 (78), 55 (100). **14c**: R_f 0.57 (30% Et_2O/hexanes); mp 61.3−61.5 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.61, 2.58 (2H, ABq, *J* = 4.8 Hz), 2.38 (1H, qt, *J* = 7.2, 3.6 Hz), 2.23 (1H, d, *J* = 14.4 Hz), 2.15 (1H, quint, *J* = 7.2 Hz), 1.99 (1H, dd, *J* = 8.4, 3.6 Hz), 1.87 (1H, dd, *J* = 14.4, 12.0 Hz), 1.73 (1H, ddd, *J* = 13.2, 12.0, 3.0 Hz), 1.67−1.60 (2H, m), 1.51−1.42 (2H, m), 1.32 (1H, t, *J* = 12.0 Hz), 1.22 (3H, s), 1.17 (1H, q, *J* = 12.6 Hz), 1.10 (1H, m), 1.08 (3H, d, *J* = 7.2 Hz), 0.93 (3H, d, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 73.4, 72.3, 60.3, 55.3, 42.8, 39.9, 32.1, 30.5, 29.9, 29.3, 27.2, 26.6, 17.2, 16.8, 15.7; EIMS *m/z* (rel intensity) 236 (3), 207 (15), 179 (43), 161 (46), 145 (58), 137 (48), 123 (100), 93 (94), 79 (73), 67 (73), 55 (96). **14d**: R_f 0.49 (30% Et_2O/hexanes); mp 61.1−61.3 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.62, 2.58 (2H, ABq, *J* = 4.8 Hz), 2.39 (1H, qt, *J* = 7.2, 3.6 Hz), 2.13 (1H, quint, *J* = 7.2 Hz), 2.04 (1H, br d, *J* = 14.4 Hz), 1.99 (1H, dd, *J* = 8.4, 3.6 Hz), 1.81 (1H, dd, *J* = 14.4, 12.0 Hz), 1.73 (1H, tt, *J* = 13.2, 3.0 Hz), 1.70−1.60 (3H, m), 1.50 (1H, m), 1.32 (1H, tt, *J* = 12.0, 1.8 Hz), 1.25 (1H, m), 1.22 (3H, s), 1.11 (1H, m), 1.08 (3H, d, *J* = 7.2 Hz), 0.92 (3H, d, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 73.8, 72.1, 60.6, 55.1, 42.9, 40.0, 32.1, 31.3, 30.5, 29.4, 27.2, 25.5, 17.3, 16.8, 15.9; EIMS *m/z* (rel intensity) 236 (2), 203 (18), 179 (35), 161 (46), 145 (48), 137 (45), 123 (80), 109 (80), 93 (87), 79 (76), 67 (75), 55 (100).

*(3S,3aS,5R,8S,8aS)-5-(2-Hydroxypropan-2-yl)-3,8-dimethyl-octahydroazulen-3a(1H)-ol (**15a**).* To a stirred solution of $LiAlH_4$ (165 mg, 4.1 mmol) in dry THF (3 mL) was added dropwise a solution of anhydrous $AlCl_3$ (197 mg, 1.5 mmol) in dry THF (3 mL) at RT. The resulting mixture was stirred for 5 min before the further dropwise addition of a solution of **8a** (476 mg, 2.0 mmol) in dry THF (2 mL). After stirring at RT for 4 h, the reaction was quenched by slowly adding a H_2SO_4 solution (6 N, 0.5 mL) and H_2O (5 mL) sequentially at 0 °C. The crude mixture was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, and filtered. The volatiles were removed *in vacuo*, and the residue was purified by SCC (Et_2O/petroleum ether, 17:83) to yield **15a** (377 mg, 79%) as a yellow oil: ^{1}H NMR (benzene-d_6, 600 MHz) δ 2.05 (1H, br s, O*H*), 1.95−1.89 (1H, m, H-10), 1.88−1.81 (2H, m, H-2a and H-6a), 1.81−1.72 (3H, m, H-3a, H-8a and H-9a), 1.63−1.55 (3H, m, H-1, H-6b and H-8b), 1.54−1.50 (2H, m, H-4 and H-9b), 1.46 (1H, ddd, *J* = 13.2, 8.4, 4.9 Hz, H-2b), 1.41−1.36 (1H, m, H-7), 1.36−1.32 (1H, m, H-3b), 1.25 (3H, d, *J* = 7.2 Hz, H-15), 1.03 (3H, s, H-12), 0.99 (3H, s, H-13), 0.93 (3H, d, *J* = 6.6 Hz, H-14); ^{13}C NMR (benzene-d_6, 150 MHz) δ 82.8 (C-5), 72.9 (C-11), 52.5 (C-1), 46.8 (C-7), 44.9 (C-4), 36.0 (C-8), 34.4 (C-9), 33.5 (C-10), 29.9 (C-3), 29.1 (C-12), 27.8 (C-13), 25.9 (C-2), 23.6 (C-6), 16.2 (C-15), 13.0 (C-14); EIMS *m/z* (rel intensity) 222 (10), 207 (51), 189 (41), 151 (59), 125 (91), 109 (82), 95 (77), 81 (96), 55 (100). Other physical data were in accord with those reported previously.[23]

*(3S,3aS,5R,8S,8aS)-5-[2-(Benzyloxy)propan-2-yl]-3,8-dimethyl-octahydroazulen-3a(1H)-ol (**16**).* This synthesis followed the same procedure as for **1c** except that NaH (163 mg, 4.1 mmol), **15a** (106 mg, 442 μmol), dry DMF (2 mL), BnBr (250 μL, 2.1 mmol), and Bu_4NI (6 mg, 16 μmol) were utilized. The reaction was quenched by the slow addition of brine (10 mL), after which the products were extracted with Et_2O/petroleum ether (20:80, 3 × 25 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and filtered. The volatiles were removed *in vacuo*, and the residue was purified by SCC (petroleum ether/Et_2O, gradient elution from 100:0 to 92:8), affording **16** (107 mg, 73%) as a colorless oil: ^{1}H NMR (benzene-d_6, 600 MHz) δ 7.33−7.09 (5ArH), 4.23 (2H, s), 1.93−1.84 (3H, m), 1.83−1.78 (2H, m), 1.77−1.73 (1H, m), 1.70 (1H, dd, *J* = 15.0, 7.8 Hz), 1.66−1.61 (2H, m), 1.61−1.58 (1H, m), 1.57−1.50 (2H, m), 1.45 (1H, dtd, *J* = 12.6, 9.0, 4.2 Hz), 1.37 (1H, dddd, *J* = 12.6, 11.4, 9.6, 4.2 Hz), 1.24 (3H, d, *J* = 7.2 Hz), 1.08 (3H, s), 1.05 (3H, s), 0.87 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (benzene-d_6, 150 MHz) δ 140.0, 128.6, 128.3, 127.5, 82.6, 78.2, 63.9, 51.7, 45.5, 44.8, 36.2, 34.8, 33.6, 29.9, 25.9, 24.4, 23.9, 23.0, 16.5, 12.9; EIMS *m/z* (rel intensity) 222 (1), 207 (6), 189 (4), 161 (6), 149 (25), 125 (6), 107 (15), 91 (100), 79 (18), 55 (15); HRMS (ESI-TOF) *m/z* $[M + H]^+$ 331.2653 (calcd for $C_{22}H_{35}O_2$, 331.2637).

*(1S,3aS,4S,7R)-7-[2-(Benzyloxy)propan-2-yl]-1,4-dimethyl-1,2,3,3a,4,5,6,7-octahydroazulene (**17**).* To a stirred solution of **16** (12.5 mg, 38 μmol) in benzene (1 mL) were added Et_3N (20 μL, 0.21 mmol) and $SOCl_2$ (20 μL, 0.28 mmol). The resulting mixture was stirred at RT for 20 min, and then the reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with Et_2O (3 × 30 mL). The combined ether layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and filtered. Removal of the volatiles *in vacuo* followed by purification by SCC (*n*-hexane) afforded **17** (8.1 mg, 69%) as a colorless oil: ^{1}H NMR (benzene-d_6, 600 MHz) δ 7.40−7.10 (5ArH), 5.77 (1H, d, *J* = 1.8 Hz, H-6), 4.35 (2H, s, PhCH_2), 2.84 (1H, m, H-7), 2.51−2.45 (2H, m, H-1 and H-10), 1.87−1.84 (1H, m, H-8a), 1.78−1.70 (3H, m, H-4, H-8b and H-2a), 1.68−1.62 (2H, m, H-3a and H-9a), 1.51−1.47 (1H, m, H-2b), 1.37 (1H, td, *J* = 6.6, 2.4 Hz, H-9b), 1.29 (1H, dq, *J* = 12.0, 7.8 Hz, H-3b), 1.21 (3H, s, H-12), 1.19 (3H, s, H-13), 1.06 (3H, d, *J* = 6.6 Hz, H-15), 0.86 (3H, *J* = 6.6 Hz, H-14); ^{13}C NMR (benzene-d_6, 150 MHz) δ 151.1 (C-5), 140.7 (ArC), 128.6 (ArC), 128.5 (ArC), 128.3 (ArC), 127.7 (ArC), 127.2 (ArC), 123.3 (C-6), 77.5 (C-11), 63.5 (phCH_2), 49.3(C-10), 48.4 (C-7), 41.0 (C-1), 39.6 (C-8), 34.6 (C-3), 33.8 (C-4), 31.3(C-2), 23.6 (C-12), 22.8 (C-13), 22.1(C-19), 19.5 (C-15), 14.6 (C-14); EIMS *m/z* (rel intensity) 204 (3), 189 (2), 163 (9), 149 (16), 119 (4), 107 (14), 91 (100), 79 (9), 67 (4); HRMS (ESI-TOF) *m/z* $[M - OBn]^+$ 205.1918 (calcd for $C_{15}H_{25}$, 205.1956).

*2-[(3S,5R,8S,8aS)-3,8-Dimethyl-1,2,3,5,6,7,8,8a-octahydroazulen-5-yl]propan-2-ol; Guaia-5(6)-en-11-ol (**3**).* This synthesis followed the procedure of **17** except that **16** (41 mg, 0.13 mmol), benzene (2 mL), Et_3N (50 μL, 0.53 mmol), and $SOCl_2$ (40 μL, 0.56 mmol) were used to yield crude **17** (40 mg), which was used in the next step without further purification. Crude **17** (40 mg) was dissolved in dry THF (3 mL), and naphthalene (23 mg, 0.18 mmol) and Li wire (30 mg, 4.3 mmol) were added at −78 °C, after which time the mixture was allowed to attain room temperature. After stirring for a total of 18 h, the reaction was quenched with H_2O (3 mL) and extracted with Et_2O (3 × 10 mL). The combined ether layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and filtered. The volatiles were removed *in vacuo*, and the residue was purified by SNIS to furnish **3** (17 mg, 64% over 2 steps) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.51 (1H, br s), 2.86 (1H, m), 2.45 (1H, appr sext, *J* = 7.2 Hz), 2.15 (1H, br d, *J* = 11.0 Hz), 1.87 (1H, m), 1.85−

dx.doi.org/10.1021/np500611z | J. Nat. Prod. 2014, 77, 2522−2536

1.76 (3H, m), 1.74 (1H, m), 1.69 (1H, m), 1.53 (1H, ddd, J = 12.5, 5.0, 2.3 Hz), 1.31−1.25 (2H, m), 1.22 (3H, s), 1.21 (3H, s), 1.02 (3H, d, J = 7.0 Hz), 0.82 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.7, 122.2, 73.3, 52.5, 48.0, 40.5, 39.3, 34.3, 33.4, 30.9, 27.0, 26.7, 22.1, 19.0, 14.4; EIMS m/z (rel intensity) 204 (11), 189 (6), 175 (1), 164 (30), 149 (55), 135 (26), 121 (21), 107 (38), 93 (26), 81 (29), 67 (16), 59 (100).

*(5R,8S,8aS)-5-[2-(Benzyloxy)propan-2-yl]-3,8-dimethyl-1,2,4,5,6,7,8,8a-octahydroazulene (**18**).* To a stirred solution of **16** (1.12 g, 3.4 mmol) in MeCN (10 mL) was added TsOH·H_2O (39 mg, 0.21 mmol). The resulting mixture was stirred under N_2 at RT until TLC indicated the consumption of the starting material (6 h). The reaction was quenched with saturated $NaHCO_3$ solution (20 mL) and extracted with Et_2O (3 × 30 mL). The combined ether layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and filtered. The volatiles were removed *in vacuo*, and the concentrate was purified by SNIS (*n*-hexane) to give **18** (611 mg, 58%) as a pale yellow oil: ^{1}H NMR (benzene-d_6, 600 MHz) δ 7.38−7.10 (5ArH), 4.31 (2H, s, PhCH_2), 2.96 (1H, br s, H-1), 2.75 (1H, d, J = 16.8 Hz, H-2a), 2.34−2.18 (2H, m, H-9a and H-9b), 2.00−1.84 (4H, m, H-2b, H-6a, H-8a and H-10), 1.78 (1H, td, J = 10.8, 2.4 Hz, H-7), 1.71 (1H, dddd, J = 13.8, 4.8, 4.2, 3.0 Hz, H-3a), 1.60 (3H, s, H-14), 1.55−1.47 (2H, m, H-3b and H-8b), 1.23 (1H, m, J = H-6b), 1.13 (3H, s, H-12), 1.12 (3H, s, H-13), 0.84 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 140.6 (ArC), 135.6 (C-4), 132.6(C-5), 128.5(ArC), 127.6(ArC), 127.2(ArC), 77.9 (C-11), 63.4 (PhCH_2), 53.4 (C-1), 45.9 (C-7), 37.8 (C-9), 37.4 (C-3), 37.3 (C-10), 30.7 (C-2), 28.9 (C-8), 27.4 (C-6), 22.9 (C-12), 22.8 (C-13), 14.3 (C-14), 13.6 (C-5); EIMS m/z (rel intensity) 204 (66), 189 (26), 175 (3), 161 (24), 149 (11), 133 (8), 119 (8), 105 (18), 91 (100), 79 (18), 65 (8), 55 (9); HRMS (ESI-TOF) m/z $[M - OBn]^+$ 205.1970 (calcd for $C_{15}H_{25}$, 205.1956).

*2-[(5R,8S,8aS)-3,8-Dimethyl-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl]propan-2-ol; Guaia-4(5)-en-11-ol (**2a**).* To a stirred solution of $LiAlH_4$ (47.2 mg, 1.2 mmol) in dry THF (1.5 mL) was added dropwise a solution of **18** (21.7 mg, 70 μmol) in dry THF (1.5 mL). The resulting solution was stirred at RT for 12 h before being quenched with 6 N aqueous H_2SO_4 (ca. 300 μL) and H_2O (5 mL) sequentially at 0 °C. The resulting mixture was extracted with Et_2O (3 × 15 mL), and the combined ether layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and filtered. The organics were concentrated *in vacuo*, and the residue was purified by fractional distillation (to remove benzyl alcohol) under high vacuum to yield **2a** (14 mg, 91%) as a white solid. **2a**: mp 73.1−74.5 °C; ^{1}H NMR (benzene-d_6, 600 MHz) δ 2.92 (1H, br s, H-7), 2.69 (1H, br d, J = 16.2 Hz, H-6a), 2.36−2.29 (1H, m, H-3a), 2.25−2.18 (1H, m, H-3b), 1.97 (1H, dddd, J = 12.6, 9.6, 8.4, 5.4 Hz, H-2a), 1.90−1.78 (3H, m, H-6a, H-8a and H-10), 1.69 (1H, dtd, J = 13.2, 4.5, 3.0 Hz, H-9a), 1.60 (3H, s, H-14), 1.53−1.46 (2H, m, H-2b and H-9b), 1.39 (1H, ddd, J = 10.8, 9.6, 3.0 Hz, H-1), 1.14 (1H, tdd, J = 13.2, 10.2, 3.0 Hz, H-8b), 1.03 (3H, s, H-12), 1.02 (3H, s, H-13), 0.83 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 135.5 (C-5), 132.5 (C-4), 72.9 (C-11), 53.3 (C-7), 49.7 (C-1), 37.9 (C-3), 37.4(9) (C-9), 37.4(8) (C-10), 30.9 (C-6), 28.9 (C-2), 27.5 (C-8), 26.9 (C-12), 26.7 (C-13), 14.3 (C-14), 13.6 (C-15); EIMS m/z (rel intensity) 222 (3), 204 (100), 189 (84), 175 (13), 161 (84), 147 (32), 133 (29), 119 (34), 105 (49), 91 (49), 79 (46), 59 (57). Other physical and spectroscopic data were in accord with those reported previously.[60]

*(5R,8S,8aS)-3,8-Dimethyl-5-(prop-1-en-2-yl)-1,2,4,5,6,7,8,8a-octahydroazulene; Aciphyllene (**4a**).* To a stirred solution of **2a** (130 mg, 586 μmol) in benzene (3 mL) under N_2 were added pyridine (50 μL, 620 μmol) and $SOCl_2$ (120 μL, 1.7 mmol) sequentially. After 10 min the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with Et_2O (3 × 30 mL). The combined ether layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and filtered. Solvent removal under reduced pressure followed by purification by SNIS chromatography (*n*-hexane) yielded **4a** (86.3 mg, 72%) as a colorless oil. Spectroscopic data were in agreement with those reported previously.[11]

*(1S,3aS,4S,7R,8aR)-1,4,9,9-Tetramethylhexahydro-1H-3a,7-(epoxymethano)azulen-8a(4H)-ol (**19**).* This synthesis followed the same procedure as for diol **15a** except that $LiAlH_4$ (41 mg, 1.1 mmol), anhydrous $AlCl_3$ (22 mg, 166 μmol), and **8b** (29 mg, 122 μmol) were used. Purification by SCC (petroleum ether) yielded **19** (22.1 mg, 76%) as a colorless oil: ^{1}H NMR (benzene-d_6, 600 MHz) δ 2.45 (1H, tq, J = 9.0, 7.2 Hz), 2.05 (1H, ddd, J = 13.2, 11.4, 7.2 Hz), 1.98 (1H, dd, J = 13.2, 6.0 Hz), 1.90 (1H, d, J = 13.2 Hz), 1.86 (1H, dtd, J = 12.6, 9.0, 7.2 Hz), 1.82−1.73 (2H, m), 1.65 (1H, td, J = 6.0, 3.0 Hz), 1.62−1.52 (2H, m), 1.42 (1H, dddd, J = 12.6, 11.4, 9.0, 3.0 Hz), 1.31−1.25 (1H, m), 1.26 (3H, s), 1.15 (1H, ddd, J = 13.2, 9.0, 3.0 Hz), 1.07 (3H, s), 1.04 (3H, d, J = 7.2 Hz), 1.03 (3H, d, J = 7.2 Hz), 0.69 (1H, s); ^{13}C NMR (benzene-d_6, 150 MHz) δ 94.9, 85.9, 82.5, 44.3, 42.6, 37.9, 31.5, 31.18, 31.14, 29.48, 29.43, 28.8, 23.4, 18.3, 15.0; EIMS m/z (rel intensity) 238 (M^+, 15%), 220 (57), 205 (100), 187 (35), 159 (75), 139 (61), 125 (35), 109 (68), 85 (53); other physical and spectroscopic data were in agreement with reported data.[61]

*(3S,3aR,5R,8S,8aR)-3,8-Dimethyl-5-(prop-1-en-2-yl)octahydroazulen-3a(1H)-ol (**20**) and (1S,3aR,4S,7R,8aR)-1,4-Dimethyl-7-(prop-1-en-2-yl)octahydroazulen-3a(1H)-ol (**21**).* To a stirred solution of α-guaiene (**7a**, 618 mg, 3.0 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added dropwise a solution of *m*-CPBA (690 mg, 3.1 mmol) in CH_2Cl_2 (20 mL). The cooling bath was removed upon the completion of addition, and the resulting mixture stirred for 2 h and allowed to attain RT. Solid KI (ca. 50 mg), saturated aqueous $Na_2S_2O_3$ solution (20 mL), and saturated aqueous $NaHCO_3$ solution (40 mL) were then added, and the resulting mixture was stirred for 1 h before being extracted with Et_2O (3 × 25 mL). The combined ether layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and filtered. The volatiles were removed *in vacuo*, and the crude epoxide mixture (**13a**,**b**, ca. 650 mg, ratio 35:65) was used directly for the next step without purification due to their vulnerability to silica gel. Following the same procedure as for the ring-opening of **15a** except that $LiAlH_4$ (868 mg, 22.8 mmol), anhydrous $AlCl_3$ (300 mg, 1.6 mmol), and the above crude epoxidation products were used, the reaction was heated under reflux at 90 °C for 22 h after the complete addition of all reagents. Purification by SCC (20−40 μm, petroleum ether/Et_2O, gradient elution from 100:0 to 85:15) yielded **20** (191.3 mg, 43% over 2 steps) as a colorless oil and **21** (98.8 mg, 23% over 2 steps) as a colorless oil. Note that the yields here have been corrected for the fact that **13b** was formed as only 65% of the combined mixture of epoxides **13a** and **13b**. Isomeric alcohols resulting from reductive ring-opening of **13a** were also present but not characterized.

20: ^{1}H NMR (benzene-d_6, 600 MHz) δ 4.85 (1H, br s, H-12a), 4.77 (1H, br s, H-12b), 2.47 (1H, m, H-7), 2.02 (1H, dddd, J = 15.6, 9.6, 7.8, 5.4 Hz, H-3a), 1.89 (1H, dddd, J = 14.4, 10.2, 6.0, 2.6 Hz, H-9a), 1.86−1.80 (1H, m, H-6a), 1.75−1.69 (3H, m, H-2a, H-6b/8a and H-10), 1.70 (3H, s, H-13), 1.60 (1H, dqd, J = 7.8, 7.2, 3.0 Hz, H-4), 1.49 (1H, dddd, J = 13.2, 10.2, 9.0, 2.4 Hz, H-8a/6b), 1.44−1.33 (4H, m, H-1, H-2b, H-8b and H-9b), 1.06 (1H, dddd, J = 15.6, 8.4, 5.4, 3.0 Hz, H-3b), 0.90 (3H, d, J = 6.6 Hz, H-15), 0.74 (3H, d, J = 7.2 Hz, H-14); ^{13}C NMR (benzene-d_6, 150 MHz) δ 152.2 (C-11), 108.7 (C-12), 82.8 (C-5), 51.7 (C-1), 49.8 (C-4), 43.4 (C-7), 42.7 (C-2), 34.9 (C-9), 34.2 (C-10), 31.1 (C-3), 30.34 (C-6) 30.31 (C-8), 22.9 (C-15), 20.9 (C-13), 18.2 (C-14); EIMS m/z (rel intensity) 207 (2), 204 (85), 189 (100), 175 (18), 161 (70), 147 (46), 133 (30), 121 (48), 107 (58), 95 (75), 81 (59), 55 (65); HRMS (ESI-TOF) m/z $[M + H]^+$ 223.2057 (calcd for $C_{15}H_{27}O$, 223.2062).

21: ^{1}H NMR (benzene-d_6, 600 MHz) δ 4.85 (1H, s, H-12a), 4.83 (1H, s, H-12b), 2.62 (1H, dddd, J = 10.8, 8.4, 7.2, 2.4 Hz, H-7), 1.92 (1H, dddd, J = 13.8, 12.0, 4.8, 1.8 Hz, H-9a), 1.86 (1H, ddd, J = 13.8, 9.6, 4.2 Hz, H-2a), 1.79−1.74 (3H, m, H-3a, H-6a and H-10), 1.70 (3H, s, H-13), 1.70−1.64 (1H, m, H-4), 1.58−1.52 (2H, m, H-6b and H-8a), 1.43 (1H, dddd, J = 14.4, 7.2, 2.4, 1.8 Hz, H-8b), 1.37 (1H, ddd, J = 13.8, 7.2, 1.2 Hz, H-9b), 1.31 (1H, dt, J = 13.8, 8.4 Hz, H-2b), 1.27 (1H, td, J = 10.8, 5.4 Hz, H-5), 0.96−0.89 (1H, m, H-3b), 0.91 (3H, d, J = 6.6 Hz, H-14), 0.79 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 152.5 (C-11), 108.3 (C-12), 85.6 (C-1), 47.5 (C-5), 45.7 (C-7), 40.73 (C-4), 40.5(C-2 and C-10), 33.2 (C-3), 32.2 (C-9), 31.2 (C-6), 26.6 (C-8), 20.0 (C-13), 19.0 (C-14), 15.9 (C-15); EIMS m/z (rel intensity) 204 (35), 189 (61), 175 (9), 161 (82), 147 (44), 133 (28), 122 (53), 107 (100), 93 (57), 81 (49), 55 (44);

dx.doi.org/10.1021/np500611z | J. Nat. Prod. 2014, 77, 2522−2536

HRMS (ESI-TOF) m/z $[M + H]^+$ 223.2048 (calcd for $C_{15}H_{27}O$, 223.2062).

*(5R,8S,8aR)-3,8-Dimethyl-5-(prop-1-en-2-yl)-1,2,4,5,6,7,8,8a-octahydroazulene; 1-epi-Aciphyllene (**4b**).* To a stirred solution of **20** (315 mg, 1.4 mmol) in Et_2O (10 mL) at 0 °C under N_2 were added Et_3N (600 μL, 4.34 mmol) and $SOCl_2$ (250 μL, 3.5 mmol) sequentially. After stirring at 0 °C for 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) solution, and the resulting mixture extracted with petroleum ether (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and filtered. Removal of the volatiles *in vacuo* and purification of the residue by SNIS chromatography (petroleum ether) yielded **4b** (251 mg, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.69 (1H, dq, J = 1.8, 0.9 Hz, H-12a), 4.66 (1H, quint, J = 1.8 Hz, H-12b), 2.42 (1H, dd, J = 12.6, 3.6 Hz, H-6a), 2.24 (m, 1H, H-3a), 2.16 (1H, m, H-1), 2.16−2.10 (2H, m, H-3b and H-7), 2.00 (1H, ddd, J = 12.6, 8.4, 4.2 Hz, H-2a), 1.97 (1H, t, J = 12.6 Hz, H-6b), 1.74 (3H, s, H-13), 1.66 (1H, dddd, J = 15.6, 7.8, 6.0, 4.2 Hz, H-8a), 1.61 (3H, s, H-14), 1.58 (1H, ddd, J = 15.6, 6.0, 4.2 Hz, H-8b), 1.50 (2H, m, H-9a and H-9b), 1.39 (1H, ddd, J = 12.6, 9.0, 6.6 Hz, H-2b), 1.38 (1H, m, H-10), 0.95 (3H, d, J = 6.6 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 151.3 (C-11), 138.3 (C-5), 131.9 (C-4), 108.2 (C-12), 57.2 (C-1), 45.1 (C-7), 39.2 (C-10), 36.5 (C-3), 32.1 (C-9), 31.1 (C-6), 30.6 (C-8), 30.2 (C-2), 22.2 (C-15), 20.6 (C-13), 13.9 (C-14); EIMS m/z (rel intensity) 204 (100), 189 (92), 175 (16), 161 (46), 147 (38), 133 (35), 119 (39), 105 (59), 95 (66), 79 (65), 55 (28); HRMS (ESI-TOF) m/z $[M + H]^+$ 205.1935 (calcd for $C_{15}H_{25}$, 205.1956).

*(3S,3aR,5R,8S,8aR)-3,8-Dimethyl-5-[(2R)-2-methyloxiran-2-yl]-octahydroazulen-3a(1H)-ol (**22a**) and (3S,3aR,5R,8S,8aR)-3,8-Dimethyl-5-[(2S)-2-methyloxiran-2-yl]octahydroazulen-3a(1H)-ol (**22b**).* Alcohol **20** (225 mg, 1 mmol) was dissolved in CH_2Cl_2 (5 mL) followed by the addition of *m*-CPBA (77%, 335 mg, 1.5 mmol) in one portion. After 1 h of stirring, the reaction was quenched with KI solid, saturated aqueous $Na_2S_2O_3$ solution, and saturated aqueous $NaHCO_3$ solution and left stirring for an additional 1 h. The resulting mixture was extracted with Et_2O (3 × 50 mL), and the combined ether layers were further washed with saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, and filtered. The organics were concentrated under reduced pressure to give **22a,b** (241 mg, 99%) as a diastereomeric mixture in a ratio of 1:1.

22a: mp 72.1−72.5 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.63, 2.58 (2H, ABq, J = 5.1 Hz), 2.07 (1H, dddd, J = 15.6, 10.2, 7.8, 5.4 Hz), 1.94 (1H, dd, J = 13.8, 3.0 Hz), 1.91 (1H, m), 1.84 (1H, dqd, J = 7.8, 7.2, 3.0 Hz), 1.79−1.75 (1H, m), 1.70−1.64 (2H, m), 1.57−1.52 (1H, m), 1.49 (1H, dd, J = 18.0, 9.6 Hz), 1.45−1.38 (4H, m), 1.24 (3H, s), 1.19 (1H, dddd, J = 15.6, 9.0, 6.0, 3.0 Hz), 0.92 (6H, d, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 82.9, 60.6, 54.9, 51.6, 49.1, 41.6, 38.4, 34.3, 35.6, 30.5, 29.7, 27.4, 22.6, 18.3, 17.5; EIMS m/z (rel intensity) 220 (30), 202 (15), 189 (27), 175 (8), 162 (100), 147 (61), 133 (38), 119 (51), 105 (71), 91 (89), 79 (71), 55 (68); HRMS (ESI-TOF) m/z $[M + H]^+$ 239.1996 (calcd for $C_{15}H_{27}O_2$, 239.2011).

22b: mp 113.5−113.9 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.61, 2.59 (2H, ABq, J = 5.1 Hz), 2.06 (1H, dddd, J = 15.6, 10.2, 7.8, 5.4 Hz), 1.95 (1H, dtd, J = 13.2, 8.4, 5.4 Hz), 1.85 (1H, dqd, J = 7.8, 7.2, 4.2 Hz), 1.84−1.75 (3H, m), 1.64 (1H, m), 1.56−1.48 (2H, m), 1.48−1.39 (3H, m), 1.34 (1H, t, J = 12.9 Hz), 1.24 (3H, s), 1.19 (1H, dddd, J = 15.6, 9.0, 6.0, 3.0 Hz), 0.94 (3H, d, J = 6.6 Hz), 0.91 (3H, d, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 83.0, 61.0, 54.9, 51.5, 48.7, 42.3, 39.6, 34.3, 33.6, 30.6, 29.8, 26.7, 22.7, 18.1, 17.4; EIMS m/z (rel intensity) 220 (6), 204 (24), 189 (33), 175 (11), 161 (44), 147 (46), 133 (38), 119 (48), 105 (80), 91 (100), 79 (70), 55 (80); HRMS (ESI-TOF) m/z $[M + H]^+$ 239.1998 (calcd for $C_{15}H_{27}O_2$, 239.2011).

*Epoxides **23**.* To a mixture of **22a** and **22b** (1:1, 204 mg, 857 μmol) in CH_2Cl_2 (12 mL) was added Et_3N (2 mL, 14.3 mmol) followed by the dropwise addition of $SOCl_2$ (ca. 80 μL, 1.1 mmol) under N_2. The resulting mixture was stirred under N_2 at RT and monitored with TLC, which showed the full consumption of the starting materials in 10 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with Et_2O (3 × 50 mL). The combined ether layers were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The volatiles were removed under reduced pressure, and the crude product **23** was used for the next step without further purification.

*2-[(5R,8S,8aR)-3,8-Dimethyl-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl]propan-2-ol; 1-epi-Guaia-4(5)-en-11-ol (**2b**).* To a stirred solution of $LiAlH_4$ (147 mg, 3.9 mmol) in THF (2 mL) was added a solution of $AlCl_3$ (80 mg, 0.6 mmol) in THF (1 mL) dropwise. The resulting mixture was stirred for 5 min before the dropwise addition of crude **23** in THF (1 mL, rinsed with 3 × 1 mL). The resulting mixture was stirred for 1 h followed by quenching with distilled H_2O. The quenched mixture was extracted with Et_2O (3 × 25 mL), and the combined ether layers were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The volatiles were removed under reduced pressure followed by purification of the residue on silver nitrate-impregnated silica column chromatography (petroleum ether/Et_2O, gradient elution from 94:6 to 87:13) to afford pure **2b** (133 mg, 73% over 2 steps) as a colorless oil: ^{1}H NMR (benzene-d_6, 600 MHz) δ 2.68 (1H, dd, J = 13.2, 1.7 Hz, H-3a), 2.26−2.15 (3H, m, H-1 and H-6a, H-6b), 2.04 (1H, dtd, J = 12.0, 7.8, 4.0 Hz, H-8a), 1.65 (3H, s, H-14), 1.62 (1H, br t, J = 13.2 Hz, H-3b), 1.55 (1H, m, H-9a), 1.51−1.38 (4H, m, H-2a H-2b, H-7, H-9b), 1.36 (1H, ddt, J = 12.0, 9.0, 7.8 Hz, H-8b), 1.25 (1H, m, H-10), 1.03 (3H, s, H-12), 1.02 (3H, s, H-13), 0.94 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 139.5 (C-5), 130.9 (C-4), 73.0 (C-11), 58.2 (C-1), 48.9 (C-7), 39.6 (C-10), 37.0 (C-6), 33.1 (C-2), 30.4 (C-8), 27.8 (C-3), 27.7 (C-12), 26.7 (C-9), 26.1 (C-13), 22.7 (C-15), 14.1 (C-14); EI-MS m/z (rel intensity) 222 (3), 204 (100), 189 (91), 175 (14), 161 (76), 147 (30), 133 (30), 119 (43), 105 (57), 91 (57), 79 (52), 55 (27); HRMS (ESI-TOF) m/z $[M + H]^+$ 223.2030 (calcd for $C_{15}H_{27}O_1$, 223.2062).

*(5R,8S,8aR)-3,8-Dimethyl-5-(prop-1-en-2-yl)-4,5,6,7,8,8a-hexahydroazulen-2(1H)-one (**24**).* Pyridinium dichromate (104 mg, 0.3 μmol) and CH_2Cl_2 (3 mL) were combined under N_2, and the resulting mixture was chilled in an ice-bath. To this stirred suspension was added slowly a solution of TBHP (5−6 M in decane, 60 μL) in CH_2Cl_2 (1 mL) and a solution of **4b** (64 mg, 0.3 μmol) in CH_2Cl_2 (3 mL) after stirring for 20 min. The resulting mixture was stirred at 0 °C under N_2 for 4 h before adding a solution of TBHP (5−6 M in decane, 50 μL) in CH_2Cl_2 (1 mL). After stirring for an additional 4 h at 0 °C, petroleum ether (10 mL) was added, and the mixture filtered through a pad of Celite and further eluted with petroleum ether (3 × 10 mL). Removal of the volatiles *in vacuo* followed by SCC (Et_2O/petroleum ether, gradient elution from 0:100 to 12:88) recovered **4b** (34 mg, 53%) and yielded the enone (**24**, 17 mg, 53% based on 47% conversion) as a pale yellow oil. ^{1}H and ^{13}C NMR and mass spectral data were identical to reported data.[51]

*(5S,8S,8aR)-3,8-Dimethyl-5-(prop-1-en-2-yl)-1,2,4,5,6,7,8,8a-octahydroazulen-5-ol (**25**) and (5R,8S,8aR)-3,8-Dimethyl-5-(prop-1-en-2-yl)-1,2,4,5,6,7,8,8a-octahydroazulen-5-ol (**26**).* SeO_2 (2.3 mg, 21 μmol) was added to CH_2Cl_2 (1 mL) under N_2 at 0 °C. To the stirred suspension was added dropwise a solution of TBHP (5−6 M in decane, 40 μL, 200−240 μmol) in CH_2Cl_2 (1 mL). After stirring for 10 min, a solution of **4b** (8.5 mg, 44 μmol) in CH_2Cl_2 (1 mL) was added dropwise, and the resulting mixture was further stirred at 0 °C for 4 h and then quenched by filtering the mixture through a silica plug. The filtrate was concentrated *in vacuo*, and the residue purified by SCC (20−40 μm, EtOAc/*n*-hexane, 5:95) to give **25** (3 mg, 32%) and **26** (1 mg, 10%) as colorless oils. **25**: ^{1}H NMR (benzene-d_6, 600 MHz) δ 5.22 (1H, br s, H-12a), 4.86 (1H, br s, H-12b), 2.54 (1H, d, J = 14.4 Hz, H-6a), 2.30 (1H, d, J = 14.4 Hz, H-6b), 2.18−2.13 (2H, m, H-1 and H-3a), 2.07 (1H, m, H-3b), 2.03 (1H, ddd, J = 14.4, 9.6, 1.8 Hz, H-8a), 1.93 (1H, dddd, J = 12.6, 9.0, 7.8, 3.6 Hz, H-2a), 1.85 (3H, s, H-13), 1.58 (3H, s, H-14), 1.56−1.48 (2H, m, H-8b and H-9a), 1.38 (1H, m, H-10), 1.30 (1H, ddt, J = 12.6, 9.0, 7.8 Hz, H-2b), 1.23 (1H, dtd, J = 15.0, 9.6, 1.8 Hz, H-9b), 0.90 (3H, d, J = 6.6 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 152.0 (C-11), 137.2 (C-5), 134.7 (C-4), 109.1 (C-12), 76.0 (C-7), 56.9 (C-1), 39.9 (C-10), 38.7 (C-8), 38.4 (C-6), 37.0 (C-3), 30.6 (C-2), 29.9 (C-9), 21.9 (C-15), 19.3 (C-13), 14.6 (C-14); EIMS m/z (rel intensity) 220 (5), 202 (38), 187 (16), 173 (5), 159 (20), 146 (23), 135 (35), 105 (24), 95 (100), 79

dx.doi.org/10.1021/np500611z | J. Nat. Prod. 2014, 77, 2522−2536

(20), 55 (13); HRMS (ESI-TOF) m/z $[M + H]^+$ 221.1871 (calcd for $C_{15}H_{25}O$, 221.1905).

26: ^1H NMR (benzene-d_6, 600 MHz) δ 5.04 (1H, s, H-12a), 4.75 (1H, s, H-12b), 2.63, 2.40 (2H, ABq, J = 12.3 Hz, H-6a and H-6b), 2.35−2.28 (1H, m, H-1), 2.18 (1H, m, H-3a), 2.09 (1H, ddd, J = 14.4, 8.4, 7.2 Hz, H-3b), 1.96 (1H, dddd, J = 12.0, 8.4, 7.8, 4.2 Hz, H-2a), 1.78 (3H, s, H-13), 1.71 (3H, dddd, J = 13.2, 11.4,11.4, 1.8 Hz, H-8a), 1.64 (1H, ddd, J = 13.2, 11.4, 2.4 Hz, H-9a), 1.58 (1H, dd, J = 13.2, 7.2 Hz, H-8b), 1.50 (3H, s, H-14), 1.48−1.35 (2H, m, H-2b and H-9b), 1.24−1.17 (1H, m, H-10), 0.92 (3H, d, J = 6.6 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 153.8 (C-11), 135.7 (C-5), 134.4 (C-4), 108.5 (C-12), 76.1 (C-7), 57.7 (C-1), 41.3 (C-10), 39.9 (C-8), 49.6 (C-6), 37.0 (C-3), 32.7 (C-9), 30.2 (C-2), 22.2 (C-15), 19.6 (C-13), 14.8 (C-14); EIMS m/z (rel intensity) 220 (5), 202 (43), 187 (32), 173 (10), 159 (45), 146 (74), 135 (30), 105 (43), 95 (100), 79 (31), 55 (18); HRMS (ESI-TOF) m/z $[M + H]^+$ 221.1877 (calcd for $C_{15}H_{25}O$, 221.1905).

*(5S,8S,8aR)-5-Hydroxy-3,8-dimethyl-5-(prop-1-en-2-yl)-4,5,6,7,8,8a-hexahydroazulen-2(1H)-one (**28**).* SeO_2 (10 mg, 91 μmol) was added to CH_2Cl_2 (2 mL) under N_2 at 0 °C. To the resulting suspension was added dropwise a solution of TBHP (5−6 M in decane, 50 μL, 250−300 μmol) in CH_2Cl_2 (1.5 mL). After stirring for 10 min, a solution of **25** (29 mg, 133 μmol) in CH_2Cl_2 (2 mL) was added dropwise, and the resulting mixture further stirred at 0 °C for 8 h and then quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the organic layers were combined, further washed with brine (10 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*, and the residue purified on alumina (EtOAc/petroleum ether, gradient elution from 5:95 to 25:75) to recover **25** (6 mg, 21%) and furnish **28** (7 mg, 28%) as a pale yellow oil: ^1H NMR (benzene-d_6, 500 MHz) δ 4.86 (1H, dq, J = 1.3, 1.3 Hz), 4.73 (1H, quint, J = 1.4 Hz), 2.58 (1H, d, J = 13.5 Hz), 2.34 (1H, dd, J = 18.2, 6.5 Hz), 2.19 (1H, d, J = 13.5 Hz), 1.89 (1H, dd, J = 14.5, 8.5 Hz), 1.82 (3H, d, J = 1.8 Hz), 1.75 (1H, br t, J = 8.0 Hz), 1.70 (3H, dd, J = 1.5, 0.2 Hz), 1.18 (1H, dddd, J = 14.5, 8.5, 2.5, 1.5 Hz), 1.11 (1H, ddd, J = 14.5, 12.0, 1.5 Hz), 0.97 (1H, dddd, J = 14.5, 12.0, 10.5, 1.5 Hz), 0.85 (1H, br s), 0.83−0.76 (1H, m), 0.66 (3H, d, J = 6.5 Hz); ^{13}C NMR (benzene-d_6, 125 MHz) δ 206.3, 169.5, 151.0, 139.4, 109.8, 76.9, 50.2, 43.3, 42.6, 40.8, 39.9, 31.7, 22.6, 18.8, 8.8; EIMS m/z (rel intensity) 234 (2), 216 (5), 178 (3), 150 (18), 137 (33), 110 (100), 95 (11), 69 (14); HRMS (ESI-TOF) m/z $[M + H]^+$ 235.1695 (calcd for $C_{15}H_{23}O_2$, 235.1698).

*(4S,5S,8S,8aS)-3,8-Dimethyl-5-(prop-1-en-2-yl)-1,2,4,5,6,7,8,8a-octahydroazulen-4-ol (**29**).* This synthesis followed the same procedure for **25** except that SeO_2 (6 mg, 59 μmol), TBHP (5−6 M in decane, 40 μL), and **4a** (22 mg, 108 μmol) were used. Purification by SCC (EtOAc/*n*-hexane, 5:95) gave **29** (7.8 mg, 33%) as a pale yellow oil: ^1H NMR (benzene-d_6, 600 MHz) δ 4.82 (1H, s, H-12a), 4.75 (1H, s, H-12b), 4.28 (1H, d, J = 9.6 Hz, H-6), 3.01 (1H, d, J = 9.6 Hz, H-1), 2.34−2.27 (2H, m, H-7 and H-3a), 2.11 (1H, dd, J = 16.2, 9.6 Hz, H-3b), 2.02 (1H, ddd, J = 12.6, 9.6, 8.4 Hz, H-2a), 1.80 (1H, qd, J = 7.2, 3.6 Hz, H-10), 1.78 (3H, s, H-14), 1.61 (3H, s, H-13), 1.54−1.41 (3H, m, H-9a, H-9b and H-2b), 1.33−1.28 (2H, m, H-8a and H-8b), 0.73 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR (benzene-d_6, 150 MHz) δ 149.3 (C-11), 140.7 (C-4), 137.5 (C-5), 111.9 (C-12), 69.0 (C-6), 55.5 (C-7), 49.9 (C-1), 38.4 (C-10), 38.3 (C-3), 37.2 (C-9), 30.0 (C-2), 26.1 (C-8), 18.8 (C-13), 14.5 (C-14), 13.5 (C-15); EIMS m/z (rel intensity) 220 (3), 202 (89), 187 (44), 159 (51), 145 (100), 131 (82), 105 (90), 91 (89), 77 (54); HRMS (ESI-TOF) m/z $[M + H]^+$ 221.1865 (calcd for $C_{15}H_{25}O$, 221.1905).

*(5S,8S,8aS)-3,8-Dimethyl-5-(prop-1-en-2-yl)-2,5,6,7,8,8a-hexahydroazulen-4(1H)-one; 1-epi-Melicodenone C (**5a**).* To a stirred solution of Dess−Martin periodinane (48 mg, 113 μmol) in CH_2Cl_2 (1 mL) at RT was added a solution of 6-hydroxyaciphyllene **29** (5.2 mg, 24 μmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at RT until TLC showed no starting material remained (4 h). The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, and filtered. The volatiles were removed *in vacuo*, and the product was purified by SCC (Et_2O/*n*-hexane, 8:92) to yield **5a** (3.7 mg, 72%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 4.90 (1H, br s, H-12a), 4.71(1H, br s, H-12b), 3.29 (1H, m, H-1), 3.16 (1H, dd, J = 10.5, 2.1 Hz, H-7), 2.45, 2.38 (2H, ABqdd, J = 17.4, 9.6, 7.2 Hz, H-3a, H-3b), 2.10−1.97 (1H, m, H-2a), 2.08 (3H, s, H-14), 1.97 (1H, qt, J = 7.2, 3.6 Hz, H-10), 1.86−1.83 (3H, m, H-8a, H-9a and H-9b), 1.78 (3H, s, H-13), 1.75−1.69 (1H, m, H-8b), 1.51 (1H, dddd, J = 12.6, 9.6, 7.2, 6.0 Hz, H-2b), 0.75 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.9 (C-6), 156.6 (C-5), 146.0 (C-11), 136.2 (C-4), 111.7 (C-12), 59.9 (C-7), 50.6 (C-1), 39.6 (C-3), 37.2 (C-9), 36.2 (C-10), 27.7 (C-2), 25.2 (C-8), 21.7 (C-13), 16.8 (C-14), 12.1 (C-15); EIMS m/z (rel intensity) 218 (97), 203 (38), 189 (8), 175 (28), 161 (100), 147 (61), 133 (29), 121 (22), 109 (68), 79 (97); HRMS (ESI-TOF) m/z $[M + H]^+$ 219.1758 (calcd for $C_{15}H_{23}O$, 219.1749).

*(8S,8aS)-3,8-Dimethyl-5-(propan-2-ylidene)-2,5,6,7,8,8a-hexahydroazulen-4(1H)-one (**30**).* Both **5a** (5.5 mg, 25 μmol) and NaOMe (27 mg, 0.5 mmol) were dissolved in EtOH (0.5 mL) under N_2, and the resulting mixture was left standing at RT for 14 h. Brine (2 mL) was then added, and the aqueous solution extracted with Et_2O (3 × 5 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and filtered. The volatiles were removed *in vacuo*, and the residue was purified by SCC (Et_2O/*n*-hexane, 8:92) to yield **30** (5.2 mg, 95%) as a yellowish oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 3.08 (1H, d, J = 9.3 Hz, H-1), 2.52 (1H, br dt, J = 18.6, 9.6 Hz, H-3a), 2.40 (1H, ddd, J = 15.0, 6.0, 3.0 Hz, H-8a), 2.42−2.32(1H, dddt, J = 18.6, 10.2, 3.6, 0.9 Hz, H-3b), 2.17, (3H, s, H-14), 2.08−1.95 (3H, m, H-2a, H-8b and H-10), 1.73 (6H, s, H-12 and H-13), 1.76−1.68 (1H, m, H-9a), 1.67−1.63 (1H, m, H-9b), 1.60−1.52 (1H, m, H-2b), 0.85 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 199.4 (C-6), 157.5(C-5), 139.0 (C-7), 135.3 (C-4), 132.7 (C-11), 50.6 (C-1), 40.1 (C-3), 37.2 (C-10), 36.0 (C-9), 28.4 (C-2), 23.7 (C-8), 21.6 (C-12), 19.8 (C-13), 16.8 (C-14), 12.7 (C-15); EIMS m/z (rel intensity) 218 (100), 203 (23), 189 (5), 175 (48), 161 (31), 147 (33), 133 (23), 121 (29), 109 (36), 79 (38); HRMS (ESI-TOF) m/z $[M + H]^+$ 219.1738 (calcd for $C_{15}H_{23}O$, 219.1749).

*(8S,8aS)-3,8-Dimethyl-5-(propan-2-ylidene)-1,5,6,7,8,8a-hexahydroazulene-2,4-dione; 1-epi-Melicodenone E (**6a**), (5S,8S,8aS)-3,3′,3′,8-Tetramethyl-1,2,6,7,8,8a-hexahydro-4H-spiro[azulene-5,2′-oxiran]-4-one (**31**), and (5S,8S,8aS)-3,3′,3′,8-Tetramethyl-6,7,8,8a-tetrahydro-1H-spiro[azulene-5,2′-oxirane]-2,4-dione (**32**).* To a stirred solution of **30** (44 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) were added CrO_3 (146 mg, 1.5 mmol) and 3,5-dimethylpyrazole (165 mg, 1.7 mmol). The resulting mixture was heated under reflux for 24 h. The reaction mixture was cooled to room temperature, diluted with Et_2O (10 mL), percolated through a pad of silica, and further eluted with Et_2O (3 × 20 mL). The volatiles were removed *in vacuo*, and the residue was purified by SCC to recover **30** (5.9 mg, 13%) and afford **6a** (5.2 mg, 13%) and **31** (10 mg, 24%) as colorless crystals and **32** (6.7 mg, 15%) as yellowish crystals. **6a**: ^1H NMR ($CDCl_3$, 600 MHz) δ 3.19 (1H, ddq, J = 7.2, 1.8, 1.8 Hz, H-1), 2.59 (1H, dd, J = 19.2, 7.2 Hz, H-2a), 2.54 (1H, ddd, J = 15.0, 6.0, 3.0 Hz, H-8a), 2.28−2.24 (1H, m, H-10), 2.21 (1H, dd, J = 19.2, 1.8 Hz, H-2b), 2.10 (3H, d, J = 1.8 Hz, H-14), 2.06 (1H, d, J = 15.0 Hz, H-8b), 1.87−1.81 (1H, m, H-9a), 1.82 (3H, s, H-12), 1.81 (3H, s, H-13), 1.78−1.73 (1H, m, H-9b), 0.72 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 209.1 (C-3), 198.8 (C-6), 160.8 (C-4), 147.7 (C-5), 137.7 (C-7), 136.9 (C-11), 43.1 (C-1), 41.5 (C-2), 35.8 (C-10), 35.2 (C-9), 23.5 (C-8), 21.9 (C-12), 20.3 (C-13), 12.3 (C-15), 9.9 (C-14); EIMS m/z (rel intensity) 232 (79), 217 (18), 189 (35), 175 (18), 161 (30), 147 (28), 133 (16), 119 (20), 109 (15), 91 (24); HRMS (ESI-TOF) m/z $[M + H]^+$ 233.1536 (calcd for $C_{15}H_{21}O_2$, 233.1542).

31: mp 100.8−101.0 °C (MeCN); ^1H NMR ($CDCl_3$, 600 MHz) δ 3.13−3.07 (1H, m, H-1), 2.57−2.51 (1H, m, H-3a), 2.40 (1H, dddt, J = 18.6, 10.2, 5.4, 1.2 Hz, H-3b), 2.20−2.16 (1H, m, H-10), 2.17 (3H, s, H-14), 2.16−2.10 (1H, m, H-8a), 2.02 (1H, qt, J = 7.2, 3.6 Hz, H-10), 1.89 (1H, tt, J = 13.8, 3.6 Hz, H-9a), 1.77 (1H, dq, J = 13.8, 3.6 Hz, H-9b), 1.65−1.59 (1H, m, H-2b), 1.53 (1H, dt, J = 15.0, 3.6 Hz, H-8b), 1.52 (3H, s, H-12), 1.13 (3H, s, H-13), 0.82 (3H, d, J = 7.2 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 196.8 (C-6), 160.3 (C-5),

132.6 (C-4), 72.3 (C-7), 61.9 (C-11), 50.5 (C-1), 39.8 (C-3), 36.2 (C-10), 33.1 (C-9), 28.3 (C-2), 25.3 (C-8), 20.7 (C-12), 20.2 (C-13), 17.1 (C-15), 12.1 (C-14); EIMS *m/z* (rel intensity) 234 (64), 219 (59), 203 (5), 175 (14), 161 (20), 147 (25), 133 (26), 121 (100), 107 (52), 79 (87); HRMS (ESI-TOF) *m/z* $[M + H]^+$ 235.1689 (calcd for $C_{15}H_{23}O_2$, 235.1698).

32: mp 158.8−159.0 °C (MeCN); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.17 (1H, ddq, *J* = 7.2, 2.1 Hz, H-1), 2.75 (1H, dd, *J* = 19.2, 7.2 Hz, H-2a), 2.32−2.27 (1H, m, H-10), 2.26 (1H, dd, *J* = 19.2, 2.1 Hz, H-2b), 2.23 (1H, dd, *J* = 13.8, 3.6 Hz, H-8a), 2.13 (3H, d, *J* = 2.1 Hz, H-14), 2.00 (1H, tt, *J* = 13.8, 3.6 Hz, H-9a), 1.87 (1H, dq, *J* = 13.8, 3.6 Hz, H-9b), 1.69 (1H, dt, *J* = 13.8, 3.6 Hz, H-8b), 1.51 (3H, s, H-12), 1.16 (3H, s, H-13), 0.73 (3H, d, *J* = 7.2 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 208.2 (C-3), 197.9 (C-6), 156.1 (C-4), 149.9 (C-5), 72.4 (C-7), 62.4 (C-11), 43.0 (C-1), 41.3 (C-2), 35.0 (C-10), 32.2 (C-9), 25.1 (C-8), 20.8 (C-12), 20.0 (C-13), 11.6 (C-15), 10.3 (C-14); EIMS *m/z* (rel intensity) 248 (69), 233 (100), 207 (15), 179 (26), 161 (14), 149 (24), 135 (21), 121 (15), 105 (15), 91 (33); HRMS (ESI-TOF) *m/z* $[M + H]^+$ 249.1483 (calcd for $C_{15}H_{21}O_3$, 249.1491).

*(8S,8aS)-3,8-Dimethyl-5-(propan-2-ylidene)-1,5,6,7,8,8a-hexahydroazulene-2,4-dione (**6a**).* This synthesis followed the same procedure as for the synthesis of **31** except that **30** (8.3 mg, 38 μmol), CH_2Cl_2 (2 mL), CrO_3 (48 mg, 480 μmol), and 3,5-dimethylpyrazole (105 mg, 1.05 mmol) were used. Purification by SCC (Et_2O/petroleum ether, 12:88) recovered **30** (1.3 mg, 16%) and furnished **6a** (2.4 mg, 32%).

*(8S,8aS)-3,3′,3′,8-Tetramethyl-6,7,8,8a-tetrahydro-1H-spiro-[azulene-5,2′-oxirane]-2,4-dione (**32**).* This synthesis followed the same procedure as for the synthesis of **31** except that **30** (13.5 mg, 62 μmol), CH_2Cl_2 (2 mL), 4 Å molecular sieves (104 mg), CrO_3 (115 mg, 1.15 mmol), and 3,5-dimethylpyrazole (110 mg, 1.15 mmol) were used and a second portion of CrO_3 (82 mg, 0.8 mmol) was added after 12 h. The mixture was heated under reflux for an additional 12 h. Purification by SCC (Et_2O/petroleum ether, gradient elution from 20:80 to 50:50) furnished **32** (6.2 mg, 40%).

*(2S,4R,5R,8S,8aS)-3,3′,3′,8-Tetramethyl-2,4,6,7,8,8a-hexahydro-1H-spiro[azulene-5,2′-oxirane]-2,4-diol (**33**).* To a stirred solution of epoxyenedione (**32**) (38.3 mg, 154 μmol) in MeOH (10 mL) was added $CeCl_3 \cdot 7H_2O$ (75 mg, 0.2 mmol). The resulting mixture was cooled to 0 °C and stirred for 30 min. To this mixture was added $NaBH_4$ (28 mg, 737 μmol) in one portion. After 10 min the reaction was quenched with saturated NH_4Cl solution (15 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered, the volatiles were removed *in vacuo*, and the residue was purified by SCC (EtOAc/petroleum ether, gradient elution from 40:60 to 50:50) to yield **33** (30 mg, 77%) as a colorless gum: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.62 (1H, s, H-6), 4.49 (1H, t, *J* = 7.2 Hz, H-3), 2.82−2.76 (1H, m, H-1), 2.41 (1H, dt, *J* = 12.9, 7.2 Hz, H-2a), 2.20−2.12 (1H, m, H-10), 2.01 (1H, ddd, *J* = 15.0, 9.6, 3.0 Hz, H-8a), 1.77 (3H, d, *J* = 1.2 Hz, H-14), 1.68 (1H, ddd, *J* = 15.0, 8.4, 2.4 Hz, H-8b), 1.62−1.54 (1H, m, H-9a), 1.47 (3H, s, H-12), 1.41−1.37 (1H, m, H-9b), 1.37 (3H, s, H-13), 1.25 (1H, m, H-2b), 0.89 (3H, d, *J* = 7.2 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 139.8 (C-4), 137.5 (C-5), 78.9 (C-3), 70.8 (C-6), 68.0 (C-7), 63.5 (C-11), 47.3 (C-1), 37.2 (C-2), 35.7 (C-10), 30.1 (C-8), 28.8 (C-9), 21.9 (C-12), 20.5 (C-13), 17.4 (C-15), 11.8 (C-14); EIMS *m/z* (rel intensity) 252 (9), 234 (19), 216 (44), 193 (30), 173 (58), 147 (58), 135 (100), 121 (87), 105 (86), 91 (89); HRMS (ESI-TOF) *m/z* $[M + H]^+$ 253.1789 (calcd for $C_{15}H_{25}O_3$, 253.1804).

*(4R,5R,8S,8aS)-4-Hydroxy-3,3′,3′,8-tetramethyl-6,7,8,8a-tetrahydro-1H-spiro[azulene-5,2′-oxiran]-2(4H)-one (**34**).* To a stirred solution of **33** (14.8 mg, 59 μmol) in DMSO (2 mL) was added IBX (140 mg, 500 μmol) in one portion, and the resulting mixture stirred under N_2 at RT for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were further washed with brine (10 mL), dried over anhydrous $MgSO_4$, and filtered. The volatiles were removed *in vacuo*, and the residue was purified by SCC (Et_2O/petroleum ether, gradient elution from 32:68 to 50:50) to give **34** (4.2 mg, 29%) as a colorless liquid and **32** (5.2 mg, 36%). **34**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.90 (1H, s, H-6), 3.04−2.98 (1H, m, H-1), 2.59 (1H, dd, *J* = 18.6, 6.6 Hz, H-2a), 2.28 (1H, m, H-10), 2.11 (1H, dd, *J* = 18.6, 2.4 Hz, H-2b), 1.99 (1H, ddd, *J* = 15.0, 6.6, 3.6 Hz, H-8a), 1.85 (3H, t, *J* = 1.2 Hz, H-14), 1.82 (1H, ddd, *J* = 15.0, 10.8, 6.6 Hz, H-8b), 1.69−1.59 (2H, m, H-9a and H-9b), 1.45 (3H, s, H-12), 1.41 (3H, s, H-13), 0.80 (3H, d, *J* = 7.2 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 208.6 (C-3), 168.6 (C-4), 140.3 (C-5), 72.5 (C-6), 67.5 (C-7), 63.1 (C-11), 44.3 (C-1), 40.0 (C-2), 34.2 (C-10), 30.3 (C-9), 29.9 (C-8), 22.1 (C-12), 20.4 (C-13), 14.5 (C-15), 9.1 (C-14); EIMS *m/z* (rel intensity) 250 (3), 232 (5), 204 (14), 192 (44), 163 (95), 136 (75), 123 (53), 91 (32), 59 (100); HRMS (ESI-TOF) *m/z* $[M + H]^+$ 251.1637 (calcd for $C_{15}H_{23}O_3$, 251.1647).

*(4S,5R,8S,8aS)-4-Hydroxy-3,3′,3′,8-tetramethyl-6,7,8,8a-tetrahydro-1H-spiro[azulene-5,2′-oxiran]-2(4H)-one (**35**).* Epoxyenone **34** (3 mg, 12 μmol) was dissolved in 3% methanolic KOH (0.2 mL) under N_2 and heated to 40 °C in a sealed tube. After 1 h, brine (2 mL) was added, and the resulting mixture extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. Removal of the volatiles *in vacuo* followed by purification by SCC (EtOAc/petroleum ether, 25:75) furnished **35** (2.6 mg, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.23 (1H, s, H-6), 3.14−3.09 (1H, m, H-1), 2.50 (1H, dd, *J* = 18.6, 6.6 Hz, H-2a), 2.14 (1H, dd, *J* = 18.6, 1.2 Hz, H-2b), 2.08−2.04 (2H, m, H-8a and H-10), 1.99 (1H, dd, *J* = 13.2, 2.4 Hz, H-8b), 1.87 (1H, ddt, *J* = 13.8, 12.6, 2.4 Hz, H-9a), 1.83 (3H, d, *J* = 1.2 Hz, H-14), 1.60 (1H, dtd, *J* = 13.8, 5.4, 2.4 Hz, H-9b), 1.37 (3H, s, H-12), 1.33 (3H, s, H-13), 0.56 (3H, d, *J* = 7.2 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 208.3 (C-3), 166.8 (C-4), 141.6 (C-5), 71.3 (C-7), 71.2 (C-11), 56.4 (C-6), 43.2 (C-1), 40.5 (C-2), 32.7 (C-10), 29.3 (C-9), 26.2 (C-12), 25.3 (C-13), 22.7 (C-8), 10.3 (C-15), 8.0 (C-14); EIMS *m/z* (rel intensity) 250 (13), 232 (8), 204 (6), 192 (18), 163 (60), 151 (100), 136 (40), 123 (73), 91 (45), 59 (89); HRMS (ESI-TOF) *m/z* $[M + H]^+$ 251.1638 (calcd for $C_{15}H_{23}O_3$, 251.1647).

*(4R,5S,8S,8aS)-5-Acetyl-4-hydroxy-3,5,8-trimethyl-4,5,6,7,8,8a-hexahydroazulen-2(1H)-one (**36**).* To a stirred solution of **34** (3.9 mg, 16 μmol) in CH_2Cl_2 (1 mL) was added several crystals of TsOH·H_2O. The reaction was stirred under N_2 at RT for 1 h. Saturated aqueous $NaHCO_3$ (2 mL) was then added, and the resulting mixture extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (3 mL), dried over anhydrous $MgSO_4$, and filtered. The volatiles were removed *in vacuo*, and the residue was purified by SCC (EtOAc/petroleum ether, gradient elution from 20:80 to 25:75) to afford **36** (2.7 mg, 71%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.77 (1H, d, *J* = 3.6 Hz, H-6), 3.18−3.12 (1H, m, H-1), 2.77 (1H, ddd, *J* = 13.2, 12.6, 6.6 Hz, H-8a), 2.47−2.43 (1H, m, H-10), 2.44 (1H, dd, *J* = 18.6, 6.6 Hz, H-2a), 2.28 (1H, dd, *J* = 18.6, 4.2 Hz, H-2b), 2.10 (1H, d, *J* = 3.6 Hz, O*H*), 1.93 (1H, td, *J* = 12.6, 6.6, 2.4 Hz, H-8b), 1.91−1.86 (1H, m, H-9a), 1.82 (3H, d, *J* = 2.4 Hz, H-13), 1.45−1.40 (1H, m, H-9b), 1.32 (3H, s, H-12), 1.21 (3H, s, H-14), 0.92 (3H, d, *J* = 6.6 Hz, H-15); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 214.3 (C-11), 207.9 (C-3), 173.4 (C-5), 137.3 (C-4), 77.5 (C-6), 56.6 (C-7), 45.4 (C-1), 34.9 (C-8), 34.3 (C-2), 29.8 (C-10), 29.4 (C-9), 23.1 (C-14), 21.5 (C-15), 21.0 (C-12), 10.4 (C-13); EIMS *m/z* (rel intensity) 250 (16), 232 (11), 207 (13), 189 (38), 161 (100), 136 (35), 123 (46), 91 (30), 55 (47); HRMS (ESI-TOF) *m/z* $[M + H]^+$ 251.1639 (calcd for $C_{15}H_{23}O_3$, 251.1647)

■ ASSOCIATED CONTENT

Supporting Information

DFT/B3LYP-6-31G* calculation details for **1a**, **8a**, and **8b**; semiempirical/AM1 calculations for **4a** and **4b**; ^{1}H and ^{13}C NMR spectra for compounds **1b**, **1c**, **9** (**a** and **b**), **10** (**a** and **b**), **10b**, **11a**, **11b**, **12** (**a** and **b**), **13a**, **13b**, **14** (**a** and **b**), **14c**, **14d**, **15**−**21**, **3**, **2a**, **4b**, **22a**, **22b**, **2b**, **25**, **26**, **5a**, **6a**, and **28**−**36**; ROESY NMR spectra for **25**, **28**, **29**, **33**, and **36**; X-ray data of **14c**, **14d**, **22a**, **22b**, and **32**; tabulated ^{1}H and ^{13}C NMR data of **5a**, **5b**, **6a**, and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/np500611z | *J. Nat. Prod.* 2014, 77, 2522−2536

AUTHOR INFORMATION

Corresponding Author

*E-mail: dennis.taylor@adelaide.edu.au. Tel: (+61) 08 83137239. Fax: (+61) 08 83137116.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the School of Agriculture, Food and Wine, The University of Adelaide. A.C.H. is indebted to the University of Adelaide and the China Scholarship Council for a joint Ph.D. scholarship. C.J.S. acknowledges the ARC for funding the Bragg Crystallography Facility (LE0989336 and LE120100012). This research was also supported by High Impact Research MoE Grant UM.C/625/1/HIR/MoE/SC/03 from the Ministry of Higher Education Malaysia and the University of Malaya.

REFERENCES

(1) Fraga, B. M. *Nat. Prod. Rep.* **2012**, *29*, 1334−1366.
(2) Fraga, B. M. *Nat. Prod. Rep.* **2013**, *30*, 1226−1264.
(3) Foley, D. A.; Maguire, A. R. *Tetrahedron* **2010**, *66*, 1131−1175.
(4) Hudlicky, T.; Govindan, S. V.; Frazier, J. O. *J. Org. Chem.* **1985**, *50*, 4166−4171.
(5) Saha, M.; Muchmore, S.; Van der Helm, D.; Nicholas, K. M. *J. Org. Chem.* **1986**, *51*, 1960−1966.
(6) Foehlisch, B.; Flogaus, R.; Henle, G. H.; Sendelbach, S.; Henkel, S. *Eur. J. Org. Chem.* **2006**, 2160−2173.
(7) Willot, M.; Radtke, L.; Koenning, D.; Froehlich, R.; Gessner, V. H.; Strohmann, C.; Christmann, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9105−9108.
(8) Coquerel, Y.; Greene, A. E.; Depres, J.-P. *Org. Lett.* **2003**, *5*, 4453−4455.
(9) Marshall, J. A.; Greene, A. E. *J. Org. Chem.* **1972**, *37*, 982−985.
(10) Buchanan, G. L.; Young, G. A. R. *J. Chem. Soc. D* **1971**, 643.
(11) Srikrishna, A.; Pardeshi, V. H. *Tetrahedron* **2010**, *66*, 8160−8168.
(12) Hayashi, Y.; Ogawa, K.; Inagaki, F.; Mukai, C. *Org. Biomol. Chem.* **2012**, *10*, 4747−4751.
(13) Geng, Z.; Chen, B.; Chiu, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6197−6201.
(14) Zahel, M.; Kessberg, A.; Metz, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 5390−5392.
(15) Li, Z.; Nakashige, M.; Chain, W. J. *J. Am. Chem. Soc.* **2011**, *133*, 6553−6556.
(16) Akee, R. K.; Ransom, T.; Ratnayake, R.; McMahon, J. B.; Beutler, J. A. *J. Nat. Prod.* **2012**, *75*, 459−463.
(17) Nicolaou, K. C.; Kang, Q.; Ng, S. Y.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2010**, *132*, 8219−8222.
(18) Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 3513−3516.
(19) Ushakov, D. B.; Navickas, V.; Strobele, M.; Maichle-Mossmer, C.; Sasse, F.; Maier, M. E. *Org. Lett.* **2011**, *13*, 2090−2093.
(20) Zhang, J.; Zheng, S.; Peng, W.; Shen, Z. *Tetrahedron Lett.* **2014**, *55*, 1339−1341.
(21) Minnaard, A. J.; Wijnberg, J. B. P. A.; De Groot, A. *Tetrahedron* **1994**, *50*, 4755−4764.
(22) Mehta, G.; Singh, B. P. *Tetrahedron Lett.* **1975**, 1585−1586.
(23) Pesnelle, P. *Recherches (Paris)* **1966**, *15*, 33−40.
(24) Mendes, S. A. C.; Mansoor, T. A.; Rodrigues, A.; Armas, J. B.; Ferreira, M.-J. U. *Phytochemistry* **2013**, *95*, 308−314.
(25) Nii, H.; Furukawa, K.; Iwakiri, M.; Kubota, T. *Nippon Nogei Kagaku Kaishi* **1983**, *57*, 733−741.
(26) Saritas, Y.; Bulow, N.; Fricke, C.; Konig, W. A.; Muhle, H. *Phytochemistry* **1998**, *48*, 1019−1023.
(27) Kaur, S.; Dayal, R.; Varshney, V. K.; Bartley, J. P. *Planta Med.* **2001**, *67*, 883−886.
(28) Bure, C. M.; Sellier, N. M. *J. Essent. Oil Res.* **2004**, *16*, 17−19.
(29) Cardeal, Z. L.; Gomes da Silva, M. D. R.; Marriott, P. J. *Rapid Commun. Mass Spectrom.* **2006**, *20*, 2823−2836.
(30) Grison-Pige, L.; Hossaert-McKey, M.; Greeff, J. M.; Bessiere, J.-M. *Phytochemistry* **2002**, *61*, 61−71.
(31) Nakashima, K.-i.; Oyama, M.; Ito, T.; Witono, J. R.; Darnaedi, D.; Tanaka, T.; Murata, J.; Iinuma, M. *Chem. Biodiversity* **2012**, *9*, 2195−2202.
(32) We have observed the sensitivity of epoxyguaiene (**13a**,**b**) and epoxyguaiyl acetate (**11a**,**b**) to ring-opening when peracetic acid in acetic acid is employed.
(33) Chekroun, A.; Jarid, A.; Benharref, A.; Boutalib, A. *J. Org. Chem.* **2000**, *65*, 4431−4434.
(34) Kanai, K.; Sakamoto, I.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1529−31.
(35) α-Bulnesol was identified by comparing its retention time and MS to a sample of the authentic compound.
(36) $LiAlH_4$ may also be utilized for the cleavage of the benzyl ether to afford guaia-5(6)-en-ol (**3**) in comparable yield; however, workup when using Li and naphthalene was found to be simpler.
(37) Srikrishna, A.; Babu, N. C. *Tetrahedron Lett.* **2001**, *42*, 4913−4914.
(38) Employing DMDO as oxidant gave a better dr of the bridged α-guaiene epoxides; however, the low yields and poor regioselectivity precluded us from using it as oxidant to access the bridged α-epoxyguaienes.
(39) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526−5528.
(40) Blay, G.; Garcia, B.; Molina, E.; Pedro, J. R. *Tetrahedron* **2007**, *63*, 9621−9626.
(41) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232−3233.
(42) D'Auria, M.; De Mico, A.; D'Onofrio, F.; Scettri, A. *Synthesis* **1985**, 988−990.
(43) Rosenthal, D.; Grabowich, P.; Sabo, E. F.; Fried, J. *J. Am. Chem. Soc.* **1963**, *85*, 3971−3979.
(44) Nakamura, A.; Nakada, M. *Synthesis* **2013**, *45*, 1421−1451.
(45) Zhao, Y.; Yeung, Y.-Y. *Org. Lett.* **2010**, *12*, 2128−2131.
(46) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057−2059.
(47) Shing, T. K. M.; Yeung, Y. Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 7981−7984.
(48) Muzart, J. *Tetrahedron Lett.* **1987**, *28*, 4665−4668.
(49) Ishii, H.; Tozyo, T.; Nakamura, M.; Minato, H. *Tetrahedron* **1970**, *26*, 2751−2757.
(50) Zdero, C.; Bohlmann, F.; Niemeyer, H. M. *J. Nat. Prod.* **1988**, *51*, 509−512.
(51) Blay, G.; Garcia, B.; Molina, E.; Pedro, J. R. *Tetrahedron* **2005**, *61*, 11156−11162.
(52) Silva, M.; Wiesenfeld, A.; Sammes, P. G.; Tyler, T. W. *Phytochemistry* **1977**, *16*, 379−385.
(53) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals (Fifth ed.)*; Elsevier Inc., 2003.
(54) Gupta, A. S.; Dev, S. *J. Chromatogr.* **1963**, *12*, 189−195.
(55) Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91−100.
(56) Marshall, J. A.; Ruden, R. A. *J. Org. Chem.* **1971**, *36*, 2569−2571.
(57) Kadival, M. V.; Nair, M. S. R.; Bhattacharyya, S. C. *Tetrahedron* **1967**, *23*, 1241−1249.
(58) Burrett, S.; Taylor, D. K.; Tiekink, E. R. T. *Acta Crystallogr.* **2014**, *E70*, o67−o777.
(59) Huang, A.-C.; Burrett, S.; Sefton, M.; Taylor, D. K. *J. Agric. Food Chem.* **2014**, accepted.
(60) Van der Gen, A.; Van der Linde, L. M.; Witteveen, J. G. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 1433−1440.
(61) Tori, M.; Sono, M.; Asakawa, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1770−1775.