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Substituent effects in the transannular cyclizations of germacranes. Synthesis of 6-*epi*-costunolide and five natural steiractinolides

Redouan Azarken, Francisco M. Guerra, F. Javier Moreno-Dorado, Zacarías D. Jorge, Guillermo M. Massanet *

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, Polígono Río San Pedro s/n, 11510 Puerto Real, Cádiz, Spain

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ABSTRACT

The occurrence and orientation of substituents in the 10-membered ring characteristic of germacranes is determinant in the stereochemical outcome of the acid-promoted transannular cyclization of these metabolites. An explanation of the synthesis of eudesmanolides and guaianolides produced by the Umbelliferae family of plants is advanced. The syntheses of the natural products 6-*epi*-costunolide and five steiractinolides are reported.

1. Introduction

Sesquiterpenolides are metabolites produced mainly by the Compositae (Asteraceae) family of plants although some of them originate in other Angiosperm families as Umbelliferae (Apiaceae), Magnoliaceae, and even in fungi.[1]

A great majority of sesquiterpenolides can be classified into four major groups according to their carbocyclic skeleton: germacranolides (10-membered ring), eudesmanolides (6,6-bicyclic compounds), guaianolides (5,7-bicyclic compounds), and elemanolides (six-membered ring).[2]

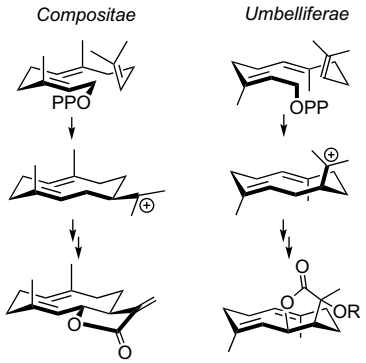
Some sesquiterpenolides display interesting biological properties. For instance, thapsigargin is a guaianolide, which has become an important tool in the study of the mechanism of intracellular calcium signaling.[3] It presents a remarkable selectivity for the SERCA pumps involved in the active transport of calcium ions to the intracellular stores that has made of it a widely used SERCA inhibitor. In addition, thapsigargin has been appointed as a possible therapeutic agent against prostate cancer, given its ability to induce apoptosis in prostate cancer cells.[4] This molecule has been targeted by the Ley group, which recently published its first and only total synthesis.[5] We have also reported a synthetic approach to 11,13-dihydroxyguaianolides closely related to thapsigargin.[6]

This interesting metabolite is produced by plants of the genus *Thapsia*,[7] which belongs to the Umbelliferae family of plants. This botanic family encompasses about 3000 species of plants distributed along 300 genera.[8]

Sesquiterpenolides produced by Umbelliferae plants present a stereochemical pattern different to that found in Compositae plants. This particularity was reported by Holub and Budesinsky, who corrected the structures of more than 90 sesquiterpenolides produced by umbelliferous plants based on their spectroscopic data.[9]

Three main features are displayed by the majority of these compounds: (i) a hydroxyl or acyloxy group α to the carbonyl of the lactone instead of the typical *exo*-methylene system, (ii) a *cis*-β,β lactone fusion, epimer at C-6 to most natural sesquiterpenolides, and (iii) an A/B ring junction different to that found in sesquiterpenes from Compositae plants.

Holub and Budesinsky proposed that these features can be explained by admitting that the enzymatic pool of the Umbelliferae and Compositae plants cyclize the *trans*,*trans*-farnesyl diphosphate in different conformations (Scheme 1).[10]



Scheme 1. Holub's proposed conformation of *trans*,*trans*-farnesyl diphosphate in Compositae and Umbelliferae plants.

* Corresponding author. Tel.: +34 956 016366; fax: +34 956 016393.
E-mail address: g.martinez@uca.es (G.M. Massanet).

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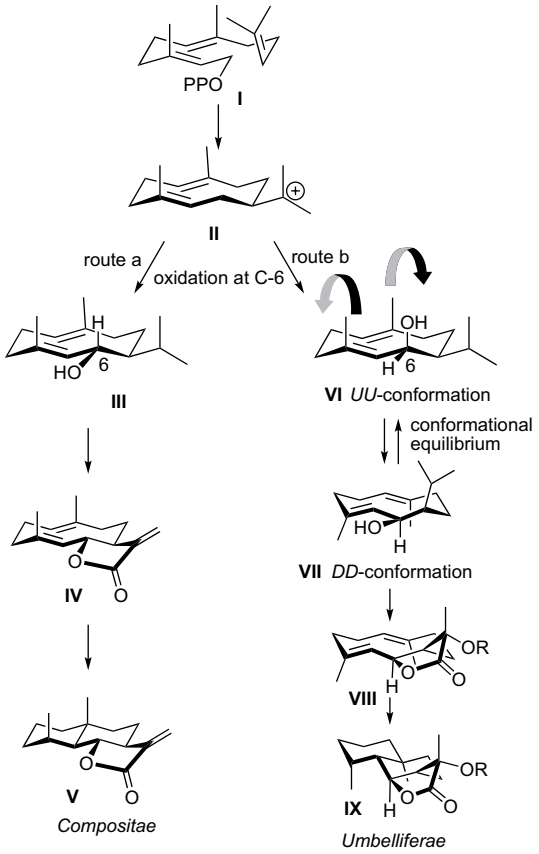
Nevertheless, since several Umbelliferae-type sesquiterpenes have also been isolated from some Compositae plants, an alternative hypothesis can be advanced to explain the differences in the stereochemistry (Fig. 1). Starting from the accepted conformation of the *trans*,*trans*-farnesyl diphosphate (structure I, Scheme 2), sesquiterpenolides from Umbelliferae can be formed through a different sequence of events following the formation of the germacrane intermediate (structure II, Scheme 2). A different orientation of the oxidation step, in which a β-oriented hydroxyl group is set (structure VI, Scheme 2), would lead to a conformational equilibrium, the conformation with both methyl groups down prevailing (structure VII, Scheme 2). Further cyclization of the cyclodecadiene ring would lead to generic structure IX (Scheme 2) typical of umbelliferous plants.

In this paper, we will demonstrate that the obscure role of the enzymes that catalyze the biogenesis of sesquiterpenolides in Umbelliferae plants can be explained in terms of stability of the different conformers of the germacradiene precursor. The main idea is that it is possible to transform a germacrane in a dominant UU-conformation[11] (a germacrane from Compositae) into a DD-conformation germacrane (a germacrane from Umbelliferae) just by installing a β-oriented hydroxyl group at carbon C-6 (Scheme 2, route b). This would cause such a steric hindrance in the UU-conformation so as to induce the flipping to a DD-conformation.

The cyclization of this DD-conformer would lead to eudesmanolides or guaianolides with the stereochemistry typical of Umbelliferae. The basis of our expectations regarding this conformational equilibrium is depicted in Scheme 3.

The confirmation of this hypothesis would not only explain the biogenetic origin of these metabolites but more importantly, would open up a synthetic route to compounds such as thapsigargin.



Scheme 2. Alternative explanation to the biosynthesis of sesquiterpenolides from Compositae and Umbelliferae plants.

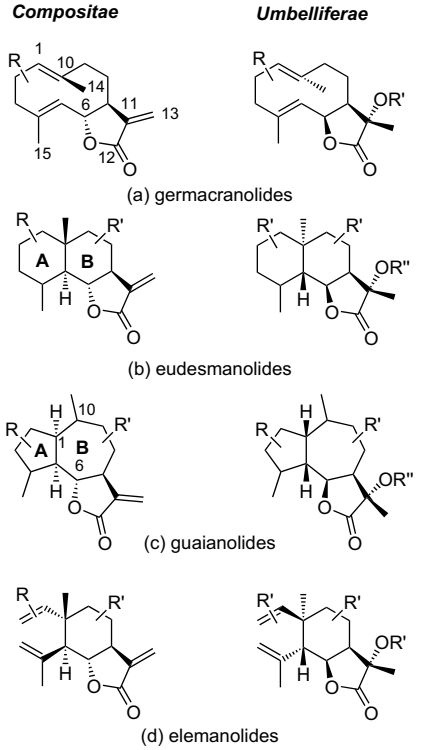


Figure 1. Main differences between sesquiterpenolides from Compositae and Umbelliferae plants.

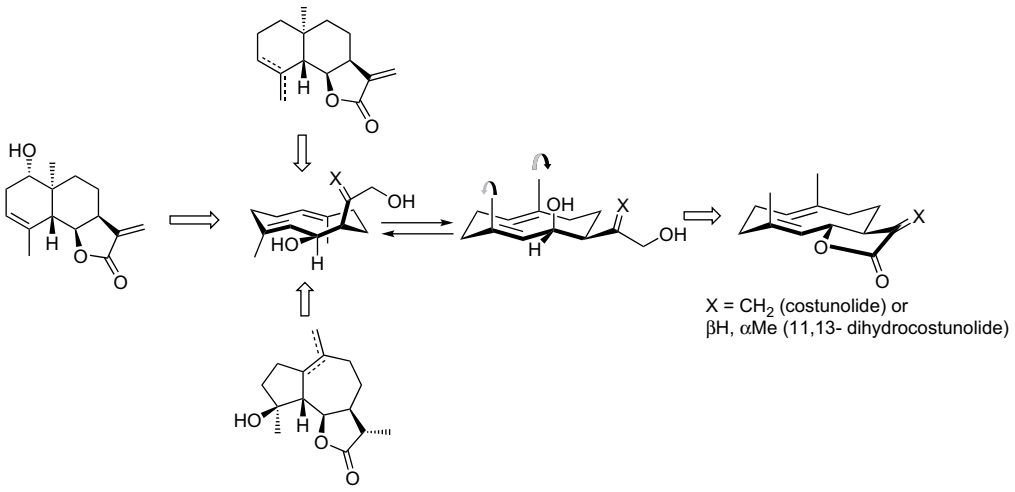
2. Results and discussion

Commercial germacranolides are scarce but fortunately, costunolide **1**, a germacranolide available from the roots of *Saussurea lappa*, seemed a suitable substrate to be transformed into a 6β-hydroxygermacrane (Scheme 4). When it comes to germacranes, two important problems must be addressed. First, these metabolites are very prone to cyclize under acidic conditions, so acid medium should carefully be avoided. Second, the flexibility of the 10-membered ring is very often manifested as broad signals in the ^{1}H NMR spectrum and duplicated signals in the ^{13}C NMR, complicating the interpretation of the data.

The synthetic sequence commenced with the reduction of the lactone ring present in costunolide **1** (Scheme 4). Direct reduction with lithium aluminum hydride led to a complex mixture.

This transformation had to be carried out in two steps. A first reduction with DIBAL produced a mixture of lactols **2** in 76% yield, which displayed a complex ^{1}H NMR spectrum, and that was submitted directly to a subsequent reduction with sodium borohydride, affording diol **3** in 82% yield.[12] The next step consisted in the selective protection of the primary alcohol as a *tert*-butyldimethylsilyl ether by treatment of **3** with TBDMSCl and triethylamine, yielding **4** in 83% yield.

Inversion of the configuration of carbon C-6 proved to be very troublesome. Some Mitsunobu procedures were assayed, with negative results. We opted then for an oxidation–reduction sequence. Nevertheless, the oxidation of alcohol **4** to germacranone **5** also resulted to be very difficult as the treatment under most common oxidative conditions only led to complex mixtures. After exhaustive experimentation, finally Dess–Martin periodinane afforded germacranone **5** in good yield (80%).[13] The acetic acid



Scheme 3. Retrosynthetic analysis of Umbelliferae-type eudesmanolides and guaianolides.

produced in this oxidation had to be carefully neutralized with pyridine to avoid the cyclization to the corresponding eudesmane.[14]

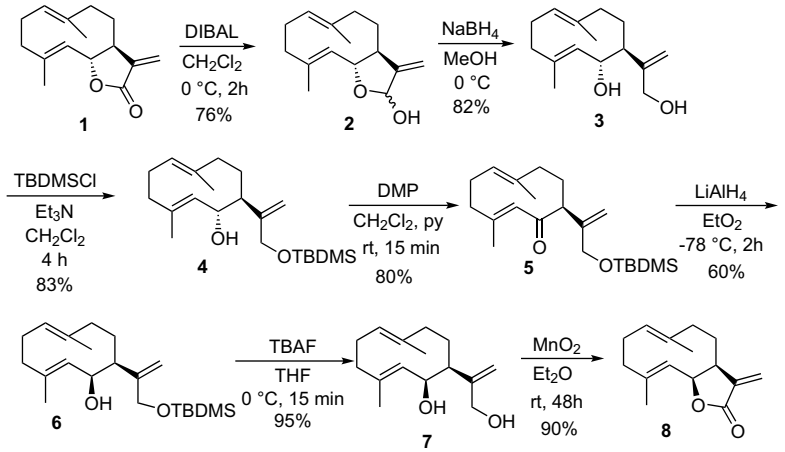
The carbonyl group in germacranone **5** could not be reduced with sodium borohydride, the starting material being recovered unreacted. The reduction was then carried out with lithium aluminum hydride affording the desired β-hydroxygermacrane **6** in 60% yield.

At this stage, germacrane **6** already bears the appropriate 6-β-hydroxyl group needed for the conformational change to occur. To confirm this fact, alcohol **6** was treated with *p*-toluenesulfonic acid, giving rise to a complex mixture that displayed in the ^{1}H NMR spectrum a series of overlapped signals corresponding to a mixture of furan rings, from which little information could be obtained.

We decided then to continue the sequence in order to transform **6** into 6-*epi*-costunolide **8**, where the cyclization outcome could be tested again. To this end, alcohol **6** was deprotected with TBAF in THF at 0 °C, affording diol **7** in nearly quantitative yield. The allylic hydroxyl group was then oxidized to the corresponding lactone, by employing MnO_2/C, giving rise to 6-*epi*-costunolide **8** in 90% yield. Extensive NOE studies of **8** showed that methyls at C-4 and C-10 were below the plane of the molecule (Fig. 2a). This finding is in accordance with Bohlmann and Zdero earlier observations. These two authors reported the isolation of 6-*epi*-costunolide **8** from *Geigeria rigida*.[15] The occurrence of this germacranolide in a DD-conformation suggests that its cyclization should lead to a 10αMe,5βH-eudesmane.

Effectively, when **8** was submitted to treatment with *p*-toluenesulfonic acid in dichloromethane, natural steiractinolide[16] **9** was isolated in 70% yield together with a minor amount of steiractinolide **10**[17] that could be identified by comparing its ^{1}H and ^{13}C NMR data with those reported in the literature (Scheme 5).[17] Compound **9** displayed NOEs showed in Figure 2b, confirming its structure as 5βH,6αH,7αH,10αMe-eudesman-4,15-en-6,7-olide. Thus, we have proven that the stereochemical course of the hydroxylation at C-6, or more appropriately, the conformational lock produced by the fashioning of a γ-lactone ring determines the conformation of the germacrane and the resultant stereochemistry of the eudesmane after the cyclization.

Many eudesmanolides from Umbelliferae plants bear a hydroxyl group at C-1.[2] This hydroxyl group can be prepared by incorporating an epoxide ring in carbons C-1 and C-10 of the germacradiene precursor. To this end, 6-*epi*-costunolide **8** was treated with *m*-CPBA, giving rise to epoxide **11** that spontaneously opened when it was submitted to purification by chromatography on silica gel affording alcohol **12** (64% yield) and minor amounts of the isomeric alkenes **13** and **14** (Scheme 5). Lactones **12**–**14** displayed an α-oriented angular methyl, and definitively all the stereochemical features found in eudesmanolides from Umbelliferae plants. Lactones **12**–**14** have also been isolated from *G. rigida*.[15]



Scheme 4. Synthetic approach to 6-*epi*-costunolide **8**.

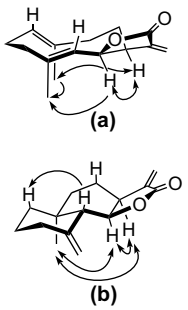
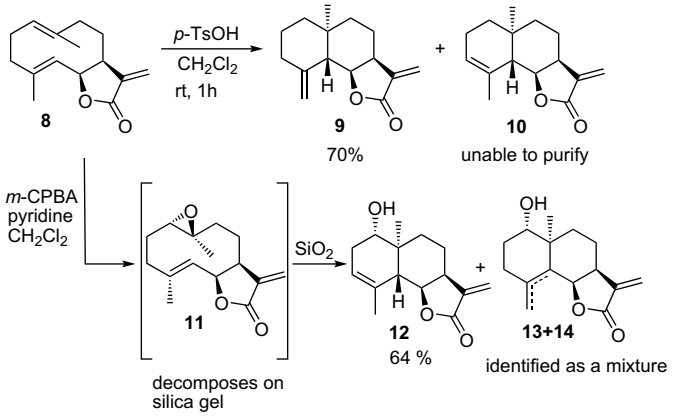


Figure 2. Observed NOEs in 6-*epi*-costunolide **8** (a) and eudesmanolide **9** (b).

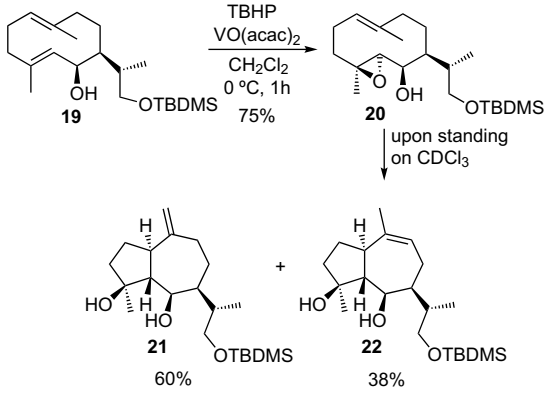


Scheme 5. Synthesis of steiractinolides **9** and **10** and **12**–**14** from 6-*epi*-costunolide.

We wondered next whether it was possible to access to Umbelliferae-type guaianolides through this method as they share with eudesmanolides a common biogenetic pathway. The preparation of guaianolides from 4,5-epoxygermacranes is well documented.[18] The most direct way consists in the epoxidation of the C-4–C-5 double bond of a germacrane, and further treatment with acid to promote the cyclization to the guaiane framework.

As suspected, epoxidation of **6** with *m*-CPBA was far to be regioselective and a mixture of epoxides **15** (5%), **16** (34%), and **17** (9%) was formed (Scheme 6). The allylic epoxidation with *tert*-butyl hydroperoxide and $VO(acac)_2$ did not show regioselection either and both C-4–C-5 and C-11–C-13 double bonds were simultaneously epoxidated, affording **15** and **18** in 9% and 88% yields, respectively.[19]

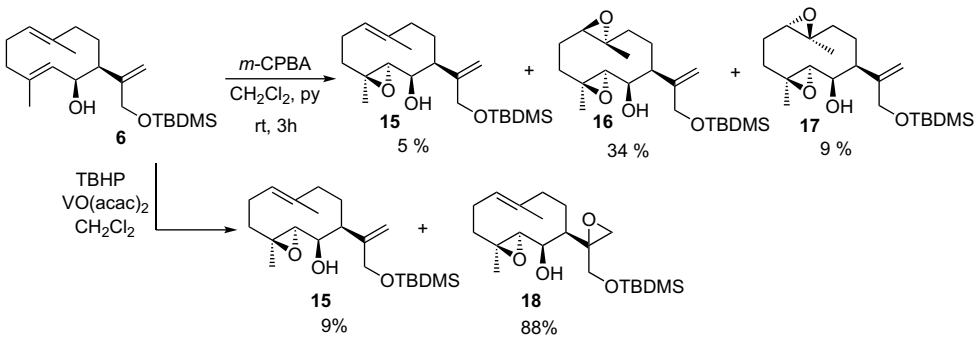
We realize that the selective epoxidation of the C-4–C-5 double bond in the presence of an additional C-11–C-13 double bond would be very difficult in compound **6**, so we decided as an alternative to employ its congener **19** where the *exo*-methylene group was reduced to a methyl group. This compound was prepared starting from 11,13-dihydrocostunolide by a similar sequence to that described for **10**. When compound **19** was submitted to Sharpless allylic epoxidation, the epoxyalcohol **20** was formed in 75% yield. Finally, it was observed that **20**, upon standing in $CDCl_3$, smoothly transformed into a mixture of guaianes **21** and **22** in 60% and 38% yields, respectively (Scheme 7). Nevertheless, the stereochemistry of the ring fusion in both guaianes was not that found in Umbelliferae guaianes (see Fig. 1), suggesting a UD-conformation for the parent epoxyalcohol **20**. Mono- and bidimensional low temperature ^1H NMR experiments and NOE study of **20** confirmed effectively the occurrence of two conformers at room temperature: UD (78% population) and DD (22% population).



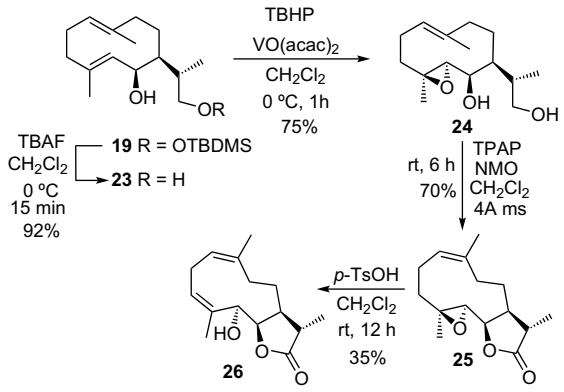
Scheme 7. Sharpless epoxidation of alcohol **19**.

In view that the presence of a β-oriented hydroxyl group at C-6 did not exert enough influence as to induce the DD-conformer to be predominant, we rationalize that the presence of a lactone ring attached to the cyclodecadiene ring could effectively induce the change in the conformation. Compound **19** was then deprotected with TBAF in dichloromethane, affording diol **23** in 92% yield (Scheme 8).

Epoxidation of **23** with *tert*-butyl hydroperoxide and $VO(acac)_2$ afforded the epoxydiol **24** (75% yield). The oxidation of the primary hydroxyl group resulted to be troublesome, leading to a complex mixture under several conditions. Surprisingly, it was discovered, that the use of TPAP[20] and NMO for 6 h led to melampolide **25** in which the isomerization of the C-1–C-10 double bond had taken place. We have found precedents in which Ru(III), produced in the TPAP catalytic cycle, is able to promote double bonds isomerizations but not a change in their configuration.[21] Treatment of **25** with *p*-TsOH did not lead to a cyclization product but to the formation of the allylic alcohol **26**. A careful optimization of the TPAP oxidation conditions of **24**, allowed us to prepare epoxylactone **27** only after 2 h of reaction in 76% yield. When **27** was

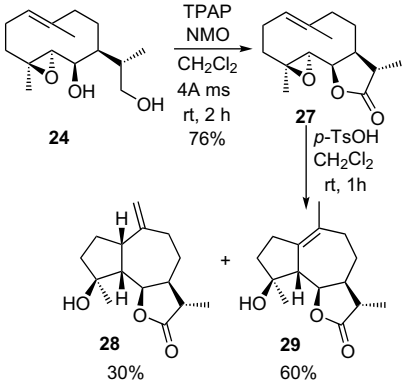


Scheme 6. Epoxidation of alcohol **6**.



Scheme 8. Synthesis of melampolide **26**.

treated with *p*-TsOH in dichloromethane, guaianolides **28** and **29** were formed in 30% and 60% yields, respectively (Scheme 9). The Umbelliferae stereochemistry of **28** and **29** was confirmed by NOE studies. Closely related guaianolides have been isolated from *Ferula oopoda*[22] and *Ferula koso-poljanskyi*[23] (Umbelliferae).



Scheme 9. Synthesis of guaianolides **28** and **29**.

The syntheses of **9**, **10**, **12**–**14**, **28**, and **29** demonstrate that conformational changes in the structure of germacranolides can be induced by setting an oxygenated functionality at carbon C-6 with the appropriate orientation. In some cases, the presence of a hydroxyl group is not enough to lock the cyclodecadiene ring in the DD-conformation and it is necessary to set a γ-lactone ring, which provides more important steric constraints, obliging the conformational flipping to occur. Finally, the methodology described herein seems suitable for the preparation of eudesmanolides and guaianolides from umbelliferous plants. Promising results have been obtained by using cnicin, an easily available 8-acyloxygermacranolide, as starting material en route to thapsigargin. Results of these efforts will be reported in due course.

3. Experimental part

3.1. Reduction of costunolide 1 with DIBAL

Costunolide **1** (500 mg, 2.16 mmol) was dissolved in dry dichloromethane (25 mL) under argon atmosphere and a 1.5 M solution of DIBAL (1.6 mL, 2.4 mmol) was added at 0 °C. The reaction mixture was stirred for 2 h, after which time aqueous saturated NH_4Cl (25 mL) was added. The crude mixture was filtered off through a Celite path and then extracted with dichloromethane (3×25 mL). The organic layers were washed with brine (25 mL) and dried over sodium sulfate. After removal of the solvent and purification by flash chromatography (1:4 EtOAc/hexanes) the inseparable mixture of anomeric lactols **2** (386 mg, 76%) was obtained.

3.2. Lactols 2 (as a mixture of anomers)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (1H, s, H-12, major isom.), 5.52 (1H, s, H-12, minor isom.), 5.32 (1H, dd, *J*=3.1, 1.2 Hz, H-13, major isom.), 5.25 (1H, dd, *J*=3.2, 1.2 Hz, H-13, minor isom.), 5.11 (1H, br s, H-13′, major isom.), 5.04 (1H, br s, H-13′, minor isom.), 4.78 (1H, m, H-1), 4.66 (1H, d, *J*=10.4 Hz, H-5), 4.36 (1H, dd, *J*=9.2 Hz, H-6, major isom.), 4.09 (1H, dd, *J*=7.1 Hz, H-6, minor isom.), 1.66 (3H, s, 3H-15), 1.36 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$, 100 MHz): 155.2, 136.7, 131.4, 130.6, 126.9, 126.7, 108.1, 106.9, 98.8, 97.8, 81.1, 79.7, 53.2, 50.6, 41.6, 41.5, 39.7, 39.6, 27.5, 26.7, 26.6, 17.1, 17.0, 16.1; IR ν_{max} (cm^{-1}): 3403, 2927, 1763, 1642, 1219, 1011, 898, 754; EM *m*/*z* (rel int.): 234 (8), 217 (12), 213 (26), 207 (28), 185 (30), 175 (31), 161 (62), 159 (78), 83 (100).

3.3. Reduction of lactol 2 with sodium borohydride

A solution of the mixture of lactols **2** (158 mg, 0.68 mmol) in methanol (5 mL) was cooled to 0 °C and treated with $NaBH_4$ (25.5 mg, 0.68 mmol). The mixture was stirred for 3 h, after which time brine (10 mL) was added. Methanol was reduced to a half of the volume under vacuum. The remaining aqueous solution was extracted with EtOAc (3×25 mL) and the organic layer was dried over anhydrous sodium sulfate. Removal of the solvent and purification by column chromatography (3:7 EtOAc/hexanes) led to diol **3** (131 mg, 82%) as a colorless oil.

3.4. Diol 3

Colorless oil; $[\alpha]_D^{20}$ +109.4 (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 5.19 (1H, s, H-13), 4.95 (1H, s, H-13′), 4.68 (1H, br d, *J*=10.4 Hz, H-1), 4.61 (1H, br d, 10.0 Hz, H-5), 4.13 (3H, m, H-6, 2H-12), 2.17 (1H, m, H-7), 2.10–1.77 (7H, m, 2H-3, 2H-2, 2H-9, H-8α), 1.55 (1H, m, H-8β), 1.48 (3H, s, 3H-15), 1.24 (3H, s, 3H-14); ^{13}C NMR (C_6D_6, 100 MHz): 153.8, 137.7, 134.0, 133.4, 126.9, 111.8, 71.5, 65.1, 55.6, 41.8, 39.7, 32.5, 26.1, 16.8, 16.3; IR ν_{max} (cm^{-1}): 3370, 2929, 2858, 1646, 1439, 1383, 1014, 899; EM *m*/*z* (rel int.): 236 (1), 218 (9), 203 (10), 185 (11), 149 (29), 121 (47), 107 (78), 93 (82), 84 (98), 81 (100).

3.5. Protection of diol 3 with *tert*-butyldimethylsilyl chloride

A solution of compound **3** (972 mg, 4.12 mmol), catalytic DMAP (50 mg, 041 mmol), and Et_3N (1 mL) in dry dichloromethane (20 mL) was cooled to 0 °C and TBDMSCl (1 M in dichloromethane, 4.6 mL, 4.6 mmol). The mixture was stirred for 4 h, after which time brine (20 mL) was added. The aqueous layer was extracted with dichloromethane (3×25 mL) and the resulting organic layer was dried over anhydrous sodium sulfate. After removal of solvent, the resulting crude mixture was purified by column chromatography (1:9 EtOAc/hexanes), affording pure **4** (1196 mg, 83%).

3.6. Alcohol 4

Colorless oil; $[\alpha]_D^{20}$ +43.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (1H, s, H-13), 4.99 (1H, s, H-13′), 4.79 (1H, br d, *J*=10.0 Hz, H-1), 4.63 (1H, br d, *J*=9.2 Hz, H-5), 4.12 (3H, m, H-6, 2H-12), 2.33 (1H, m, H-7), 2.28–1.83 (7H, m, 2H-3, 2H-2, 2H-9, H-8α), 1.67 (1H, m, H-8β), 1.64 (3H, s, 3H-15), 1.40 (3H, s, 3H-14), 0.92 (9H, s, –OSi^t*Bu*Me$_2$), 0.10 (6H, s, –OSi^{t}Bu*Me*$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): 152.0, 137.6, 134.2, 132.9, 126.9, 112.3, 70.6, 65.3, 55.8, 41.7, 39.5, 32.0, 25.9, 25.8, 18.3, 16.9, 16.3, −5.5; IR ν_{max} (cm^{-1}):

3461, 2927, 1458, 1253, 1105, 1005, 835, 776; MS (CI) *m*/*z* (rel int.): 350 (13), 293 (4), 275 (5), 218 (12), 201 (32), 159 (46), 145 (83), 119 (55), 105 (82), 81 (78), 75 (100); HRMS (CI) calcd for $C_{21}H_{39}O_2Si$ 351.2719, found 351.2722.

3.7. Oxidation of 4 with Dess–Martin periodinane

A solution of alcohol **4** (100 mg, 0.29 mmol) and pyridine (10 μL) in dichloromethane (5 mL) was treated at room temperature with DMP (243 mg, 0.572 mmol). After stirring for 15 min, aqueous saturated $NaHCO_3$ (5 mL) was added and the resulting aqueous layer was extracted with dichloromethane (3×25 mL). Drying over sodium sulfate and removal of the solvent under vacuum, afforded pure germacranone **5** (80 mg, 0.23 mmol, 80%).

3.8. Germacranone 5

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (1H, s, H-5), 5.34 (1H, dd, *J*=1.4 Hz, H-13), 5.18 (1H, s, H-13′), 4.64 (1H, dd, *J*=10.1, 4.7 Hz, H-1), 4.43 (1H, d, *J*=13.6 Hz, H-12), 4.20 (1H, d, *J*=13.6 Hz, H-12′), 1.4 (3H, s, 3H-15), 1.08 (3H, s, 3H-14), 0.99 (9H, s, –OSi^t*Bu*Me$_2$), 0.28 (6H, s, –OSi^{t}Bu*Me*$_2$), 0.10 (s, 3H, –OSi^{t}Bu*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 150.0, 149.6, 140.3, 133.5, 125.9, 110.3, 66.1, 57.7, 42.0, 41.1, 32.4, 30.0, 25.9, 19.1, 14.8, 1.8, −5.4; IR ν_{max} (cm^{-1}): 2954, 2928, 2856, 1677, 1604, 1461, 1256, 1096, 835, 800; MS (CI) *m*/*z* (rel int.): 349 $[M+1]^+$ (31), 331 (22), 217 (42), 211 (12), 199 (100), 143 (18.2), 80 (28.0); HRMS (CI) calcd for $C_{21}H_{37}O_2Si$ $[M+1]^+$ 349.2562, found 349.2557.

3.9. Reduction of germacranone 5 with $LiAlH_4$

A suspension of $LiAlH_4$ (4.6 mg, 12 mmol) in diethyl ether (5 mL) was cooled to −78 °C and a solution of germacranone **5** (35 mg, 0.10 mmol) in diethyl ether (5 mL) was added. The mixture was stirred at −78 °C for 2 h, after which time aqueous saturated ammonium chloride (5 mL) was added. The aqueous layer was extracted with diethyl ether (3×25 mL) and the organic layer was washed with brine (25 mL). Drying with anhydrous sodium sulfate and removal of the solvent afforded a crude mixture, which was purified by column chromatography (1:9 EtOAc/hexanes), affording pure **6** (21 mg, 0.060 mmol, 60%).

3.10. Alcohol 6

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (1H, br s, H-5), 5.11 (1H, br s, H-13), 5.05 (1H, br s, 1H, H-13), 4.97 (3H, m, H-1, H-5, H-13), 4.36 (1H, br s, H-6), 4.24 (1H, br d, *J*=12.4 Hz, H-12), 4.07 (1H, d, *J*=12.4 Hz, H-12′), 2.35 (1H, m, H-2α), 2.30 (1H, m, H-3α), 2.17 (1H, m, H-3β), 1.96–2.14 (3H, m, H-7, H-9β, H-2α), 1.90 (1H, dd, *J*=12.7 Hz, H-8α), 1.78 (1H, dd, *J*=12.6 Hz, H-9α), 1.56 (3H, s, 3H-15), 1.50 (3H, s, 3H-14), 1.41 (1H, m, H-8β), 0.91 (9H, s, –OSi^t*Bu*Me$_2$), 0.11 (3H, s, –OSi^{t}Bu*Me*$_2$), 0.10 (3H, s, –OSi^{t}Bu*Me*$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz, conformers mixture): 132.3, 130.1, 129.1, 121.6, 114.4, 113.3, 72.4, 70.6, 66.9, 65.6, 51.4, 49.3, 40.7, 39.0, 37.0, 33.6, 29.7, 28.3, 25.9, 24.4, 24.1, 16.8, 16.6, −5.3, −5.4; IR ν_{max} (cm^{-1}): 3472, 2923, 2852, 1463, 1260, 1091, 801; MS (CI) *m*/*z* (rel int.): 350 (0.1), 293 (3), 267 (4), 237 (5), 219 (4), 221 (12), 159 (22), 145 (46), 119 (32), 105 (46), 93 (54), 75 (100); HRMS (CI) calcd for $C_{21}H_{39}O_2Si$ $[M+1]^+$ 351.2719, found 351.2711.

3.11. Deprotection of 6 with TBAF

A solution of alcohol **6** (95 mg, 0.27 mmol) in THF (15 mL) was treated with TBAF (1 M in THF, 0.5 mL) at 0 °C. After stirring for 15 min, aqueous saturated ammonium chloride (20 mL) was added. The aqueous layer was extracted with EtOAc (3×10 mL). The organic layers were combined and dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Purification by column chromatography (3:7 EtOAc/hexanes) afforded diol **7** (60 mg, 0.25 mmol, 95%).

3.12. Diol 7

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (1H, br s, H-5), 5.06 (1H, br s, H-13), 4.97 (3H, m, H-1, H-5, H-13), 4.41 (1H, d, *J*=7.3 Hz, 1H, H-6), 4.20 (1H, br d, *J*=12.9 Hz, H-12), 4.08 (1H, d, *J*=12.8 Hz, H-12′), 2.68 (1H, m, H-2α), 2.36 (1H, m, H-3α), 2.12–1.82 (4H, m, H-3′,H-9, H-9′, H-2′), 1.64 (1H, m, H-7), 1.56 (3H, s, 3H-15), 1.49 (3H, s, 3H-14), 1.30 (1H, m, H-8β), 0.90 (1H, ddd, *J*=14.8, 7.4, 7.3 Hz, H-8α); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 121.6, 114.7, 113.8, 71.3, 71.1, 64.9, 52.3, 51.6, 49.4, 44.3, 40.6, 38.9, 36.9, 33.4, 29.7, 28.3, 26.7, 24.1, 20.5, 19.9, 16.6; IR ν_{max} (cm^{-1}): 3305, 2924, 2853, 1449, 1383, 1087, 1030, 908, 848; MS (CI) *m*/*z* (rel int.) 237 $[M+1]^+$ (14.6), 219 (100), 189 (22), 175 (20), 163 (39), 121 (60), 95 (47), 80 (37); HRMS (CI): calcd for $C_{15}H_{25}O_2[M+1]^+$ 237.1854, found 237.1852.

3.13. Oxidation of diol 7 with manganese dioxide

Diol **7** (40 mg, 0.17 mmol) was dissolved in diethyl ether (10 mL) and MnO_2/C[24] (148 mg, 1.71 mmol) was added. The mixture was stirred for 48 h, after which time it was filtered off through a Celite path, giving a crude mixture. Purification by HPLC (1:9, EtOAc/hexanes) afforded 6-*epi*-costunolide **8** (35.5 mg, 0.153 mmol, 90%).

3.14. 6-*epi*-Costunolide 8

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (1H, d, *J*=2.8 Hz, H-13a), 5.61 (1H, d, *J*=2.8 Hz, H-13b), 5.20 (1H, dd, *J*=10.4, 6.8 Hz, H-6), 4.96 (1H, dd, *J*=8.8 Hz, H-1), 4.87 (1H, d, *J*=10.4 Hz, H-5), 3.08 (1H, dd, *J*=8.4 Hz, H-7), 2.54 (1H, dt, *J*=13.6 Hz, H-9), 2.28 (1H, dt, *J*=14.8, 3.6 Hz, H-3α), 2.21–2.18 (4H, m, H-9, H-3β, 2H-2), 2.16 (1H, ddd, *J*=13.2, 8.8, 3.2 Hz, H-8β), 1.90 (1H, ddd, *J*=13.2, 8.8, 4.4 Hz, H-8α), 1.70 (3H, s, H-15), 1.45 (3H, s, 3H, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 141.6, 138.6, 137.3, 126.7, 124.4, 122.9, 77.2, 44.3, 40.1, 37.5, 34.7, 25.5, 21.0, 17.9; IR ν_{max} (cm^{-1}): 2920, 2850, 1764, 1450, 1409, 1260, 1060, 800; MS (CI) *m*/*z* (rel int.): 233 $[M+1]^+$ (79), 213 (15), 189 (17), 187 (100), 121 (36), 109 (37), 95 (59), 80(80); HRMS (CI): calcd for $C_{15}H_{21}O_2$ $[M+1]^+$ 233.1541, found 233.1537.

3.15. Cyclization of 6-*epi*-costunolide 8 with *p*-TsOH

6-*epi*-Costunolide **8** (20 mg, 0.086 mmol) was dissolved in dichloromethane (2 mL) and *p*-TsOH (1 mg) was added. The reaction mixture was stirred for 1 h. Aqueous saturated sodium bicarbonate (5 mL) was added and the aqueous layer was extracted with brine (3×5 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Purification by column chromatography (1:19 EtOAc/hexanes) afforded eudesmanolide **9** (14 mg, 0.06 mmol, 70%) and a minor amount of impure eudesmanolide **10** that was identified by comparison of the ^{1}H NMR spectrum with reported data.

3.16. Eudesmanolide 9

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (1H, d, *J*=3.6 Hz, H-13a), 5.51 (1H, d, *J*=3.3 Hz, H-13b), 4.4 (1H, d, *J*=1.28 Hz, H-15a), 4.80 (1H, dd, *J*=7.8, 10.5 Hz, H-6), 4.78 (1H, d, *J*=1.28 Hz, H-15b), 3.28 (1H, m, H-7), 2.33 (1H, dddd, *J*=13.2, 5.7, 3.9, 1.8 Hz, H-3β), 2.84–1.97 (2H, m, 2H-8), 1.87 (1H, m, H-3α), 1.65 (1H, d, *J*=10.7 Hz, H-5), 1.61–1.55 (2H, m, 2H-2), 1.40 (1H, dddd, *J*=13.3, 6.5, 3.2, 1.7 Hz, H-1α), 1.32–1.27 (2H, m, 2H-9), 1.24 (1H, m, H-1β), 0.77 (3H, s, Me-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C-12), 144.3 (C-4),

137.5 (C-11), 119.3 (C-13), 108.4 (C-15), 76.3 (C-6), 52.8 (C-5), 41.3 (C-1), 39.4 (C-7), 36.2 (C-10),35.9 (C-3), 34.7 (C-9), 23.1 (C-2), 19.8 (C-8), 16.3 (C-14); IR ν_{max} (cm^{-1}): 2930, 2853, 1773, 1458, 1256, 1126, 1005, 965, 892; MS (CI) *m*/*z* (rel int.) 233 $[M+1]^+$ (100), 213 (6.5), 189 (16.0), 187 (75.2), 121 (11.6), 109 (13.8), 95 (31.8), 80 (38.9); HRMS (CI): calcd for $C_{15}H_{21}O_2$ $[M+1]^+$ 233.1541, found 233.1537.

3.17. Epoxidation of 6-*epi*-costunolide 8 with *m*-CPBA

A solution of 6-*epi*-costunolide **8** (30 mg, 0.12 mmol) and pyridine (0.5 mL) in dichloromethane (5 mL) was treated with *m*-CPBA at room temperature. The reaction mixture was stirred for 3 h, after which time it was diluted with dichloromethane (25 mL). The organic layer was washed with aqueous saturated sodium sulfite and then with brine. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under vacuum, giving rise to impure epoxide **11** (as shown by the ^1H NMR analysis of the crude mixture). Flash chromatography of the crude mixture gave rise to a mixture of steiractinolides **12**–**14** that was submitted to HPLC chromatography affording **12** (19 mg, 0.076 mmol, 64%). Steiractinolides **13** and **14** could not be purified and they have been identified in the mixtures by comparison with the spectroscopic reported data.

3.18. Steiractinolide 12

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (1H, dd, *J*=3.4, 0.5 Hz, H-13a), 5.54 (1H, d, *J*=3.1 Hz, H-13b), 5.35 (1H, m, H-3), 4.65 (1H, dd, *J*=10.3, 7.5 Hz, H-6), 3.50 (1H, dd, *J*=9.6, 6.5 Hz, H-1), 3.27 (1H, m, H-7), 2.30 (1H, m, H-2), 2.02 (3H, m, H-2́, 2H-8), 1.86–1.83 (4H, m, H-5, 3H-15), 1.76 (1H, dt, *J*=13.1, 4.6 Hz, H-9α), 1.26 (1H, m, H-9β), 0.82 (3H, s, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 (C-12), 135.4 (C-11), 125.0 (C-4), 121.2 (C-3), 119.3 (C-13), 78.8 (C-6), 76.6 (C-1), 49.1 (C-7), 39.5 (C-5), 32.5 (C-10), 29.8 (C-9), 26.7 (C-2), 23.6 (C-8), 20.9 (C-15), 10.3 (C-14); IR ν_{max} (cm^{-1}): 3443, 2923, 2852, 1747, 1454, 1260, 1106, 965, 817; MS (CI) *m*/*z* (rel int.) 249 $[M+1]^+$ (26), 231 (77), 213 (100), 185 (70), 157 (29), 119 (10), 95 (16), 80 (16); HRMS (CI): calcd for $C_{15}H_{21}O_3$ [M+1] 249.1490, found 249.1483.

3.19. Epoxidation of alcohol 6 with *m*-CPBA

A solution of alcohol **6** (30 mg, 0.086 mmol) and pyridine (0.5 mL) in dichloromethane (5 mL) was treated with *m*-CPBA (30 mg, 0.12 mmol) at room temperature. After 3 h, the reaction mixture was diluted with dichloromethane (20 mL) and the organic layer was washed with aqueous saturated sodium sulfite, and then washed with brine. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Consecutive purification by column chromatography (2:3 EtOAc/hexanes) and HPLC (1:1 EtOAc/hexanes) led to compounds **15** (1.5 mg, 0.004 mmol, 5%), **16** (11 mg, 0.028 mmol, 34%), and **17** (3.0 mg, 0.008 mmol, 9%).

3.20. Epoxide 15

Yellow oil; ^1H NMR (400 MHz, $CDCl_3$, mixture of conformers) δ 5.30 (m, 1H, H-1), 5.05 (d, *J*=0.9 Hz, 1H, H-13a), 4.96 (s,1H, H-13b), 4.23 (dd, *J*=1, 12.6 Hz, 1H, H-12a), 4.06 (dd, *J*=1, 12.6 Hz, 1H, H-12b), 3.42 (d, *J*=8 Hz, 1H, H-6), 2.60 (m, 1H, H-5), 2.31–2.35 (m, 1H, H-2α), 2.28 (br s, 1H, H-7), 2.22–2.11 (m, 1H, H-9β), 2.08–2.01 (m,1H, H-2β), 1.96 (dt, *J*=2.9, 13.5 Hz, H-8α), 1.78 (m, 1H, H-9α), 1.66 (s, 3H, H-14), 1.50–1.58 (m,1H, H-8β), 1.27–1.32 (m, 2H, 2H-3), 1.23 (s, 3H, H-15), 0.90 (s, 9H, –OSi^t*Bu*Me$_2$), 0.09 (3H, s, –OSi^{t}BuMe$_2$), 0.08 (3H, s, –OSi^{t}BuMe$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of conformers) δ 151.2, 123.5, 113.9, 73.7, 67.7, 65.4, 59.6, 46.2, 37.2, 36.6, 31.8, 31.7, 29.6, 25.8, 18.3, 16.5, −5.3; IR ν_{max} (cm^{-1}): 3440, 2953, 2928, 2856, 1463, 1387, 1253, 1098, 837, 779; MS (CI) *m*/*z* (rel int.) 367 $[M+1]^+$ (11), 349 (43), 331 (18), 309 (8), 291 (14), 275 (7), 251 (9), 235 (34), 217 (100), 199 (74), 189 (30), 175 (26), 159 (66), 145 (26), 133 (43), 121 (27), 109 (38), 95 (50); HRMS (CI): calcd for $C_{15}H_{39}O_3Si$ $[M+1]^+$ 367.2668, found 367.2657.

3.21. Diepoxide 16

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.03 (1H, d, *J*=1.1 Hz, H-13a), 4.94 (1H, br s, H-13b), 4.22 (1H, dd, *J*=12.5, 1.0 Hz, H-12a), 4.02 (1H, dd, *J*=12.5, 1.0 Hz, H-12b), 3.47 (1H, d, *J*=8.1 Hz, H-6), 3.05 (1H, dd, *J*=9.0, 5.7 Hz, H-1), 2.85 (1H, d, *J*=8.4 Hz, H-5), 2.28 (1H, m, H-2α), 2.27 (1H, br s, H-7), 2.19 (1H, dd, *J*=13.4, 7.0 Hz, H-9α), 2.14 (1H, m, H-3), 2.07 (1H, m, H-8β), 1.60 (1H, m, H-8α), 1.52 (1H, m, H-2β), 1.40 (3H, s, H-15), 1.33 (3H, s, H-14), 1.23 (1H, m, H-3′), 1.03 (1H, dd, *J*=13.0 Hz, H-9β), 0.89 (9H, s, –OSi^t*Bu*Me$_2$), 0.08 (3H, s, –OSi^t-BuMe$_2$), 0.09 (3H, s, –OSi^{t}BuMe$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 114.5, 72.4, 67.2, 65.0, 60.3, 59.9, 58.9, 48.6, 39.7, 34.3, 25.8, 24.6, 21.8, 18.3, 16.9, 16.6, −5.2; IR ν_{max} (cm^{-1}): 3437, 2955, 2928, 2856, 1462, 1389, 1253, 1068, 836, 777; MS (CI) *m*/*z* (rel int.) 383 $[M+1]^+$ (4), 365 (21), 349 (10), 307 (6), 251 (30), 233 (100), 215 (68), 205 (74), 187 (28), 175 (46), 161 (32), 145 (35), 133 (66), 115 (73), 109 (70), 95 (62); HRMS (CI): calcd for $C_{15}H_{39}O_4Si$ $[M+1]^+$ 383.2676, found 383.2613.

3.22. Diepoxide 17

^1H NMR (400 MHz, $CDCl_3$) δ 5.13 (1H, s, H-13a), 5.00 (1H, s, H-13b), 4.25 (1H, d, *J*=12.2 Hz, H-12a), 4.05 (1H, d, *J*=12.2 Hz, H-12b), 3.52 (1 Hz, dd, *J*=7.0, 1.2 Hz, H-6), 3.03 (1H, d, *J*=7.1 Hz, H-5), 3.00 (1H, br d, *J*=10.7 Hz, H-1), 2.49 (1H, d, *J*=8.3 Hz, H-7), 2.20 (1H, ddd, *J*=13.3, 9.5, 3.1 Hz, H-2α), 2.07 (1H, ddd, *J*=14.3, 10.4, 3.5 Hz, H-9α), 2.03 (1H, m, H-3β), 1.91 (1H, ddd, *J*=14.1, 10.1, 3.2 Hz, H-8β), 1.66–1.50 (2H, m, H-2β, H-8α), 1.45 (3H, s, H-15), 1.33 (1H, m, H-3α), 1.31 (3H, s, H-14), 1.24 (1H, m, H-9β), 0.90 (9H, s, –OSi^t*Bu*Me$_2$), 0.10 (3H, s, –OSi^{t}BuMe$_2$), 0.09 (3H, s, –OSi^{t}BuMe$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 115.9, 72.6, 67.9, 65.2, 61.5, 60.9, 57.6, 45.8, 40.2, 36.6, 25.8, 23.9, 23.6, 23.2, 18.3, 16.7, −5.3; IR ν_{max} (cm^{-1}): 3437, 2955, 2928, 2856, 1463, 1388, 1253, 1070, 836, 778; MS (CI) *m*/*z* (rel int.) 383 $[M+1]^+$ (5), 365 (20), 349 (6), 307 (6), 251 (27), 233 (100), 215 (67), 205 (27), 187 (41), 175 (50), 161 (25), 145 (30), 133 (45), 115 (39), 109 (76), 95 (56); HRMS (CI): calcd for $C_{15}H_{39}O_4Si$ $[M+1]^+$ 383.2617, found 383.2618.

3.23. Epoxidation of alcohol 6 with TBHP and VO(acac)$_2$

A solution of alcohol **6** (62 mg, 0.17 mmol) and VO(acac)$_2$ (12 mg, 0.034 mmol) in dichloromethane (4 mL) was cooled to 0 °C and TBHP (0.55 M in nonane, 0.68 mL, 0.37 mmol) was added. After stirring for 1 h, aqueous saturated sodium sulfite (5 mL) was added and the aqueous layer was extracted with dichloromethane (3×5 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent and purification by column chromatography (3:7 EtOAc/hexanes) afforded **15** (6 mg, 0.016 mmol, 9%) and **18** (57 mg, 0.15 mmol, 88%).

3.24. Diepoxide 18

Colorless oil; ^1H NMR (300 MHz, $CDCl_3$, mixture of conformers) δ 5.27 (1H, m, H-1), 3.98 (1H, d, *J*=11.4 Hz, H-12a), 3.65 (1H, d, *J*=8.0 Hz, H-6), 3.40 (1H, d, *J*=11.2 Hz, H-12b), 2.73 (1H, d, *J*=4.2 Hz, H-13), 2.64 (1H, d, *J*=4.2 Hz, H-13′), 2.55 (1H, m, H-5), 2.34 (1H, m, H-2α), 2.22 (1H, m, H-9α), 2.05 (1H, m, H-7), 1.96 (1H, dd, *J*=8.7 Hz, H-2β), 1.90 (1H, ddd, *J*=10.9, 2.7 Hz, H-8α), 1.66 (1H, m, H-9β), 1.63 (3H, s, H-14), 1.57 (3H, s, H-14′), 1.55 (1H, m, H-8α), 1.24 (2H, m, 2H-3),

1.19 (3H, s, H-15), 0.90 (9H, s, –OSi^t*Bu*Me$_2$), 0.08 (3H, s, –OSi^{t}Bu*Me*$_2$), 0.06 (3H, s, –OSi^{t}Bu*Me*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 77.2, 71.7, 67.5, 65.8, 59.6, 51.5, 44.1, 37.0, 29.7, 25.8, 22.5, 18.2, 16.5, −5.4; IR ν_{max} (cm^{-1}): 3439, 2953, 2928, 2856, 1463, 1387, 1253, 1098, 837, 779; MS (CI) *m*/*z* (rel int.) 383 [M+1]$^+$ (3), 365 (16), 347 (18), 307 (7), 267 (5), 251 (16), 233 (95), 215 (100), 187 (64), 159 (85), 133 (74), 115 (66), 95 (62); HRMS (CI): calcd for $C_{21}H_{39}O_4Si$ [M+1]$^+$ 383.2617, found 383.2615.

3.25. Epoxidation of alcohol 19 with TBHP and VO(acac)$_2$

A solution of alcohol **19** (78 mg, 0.22 mmol) and VO(acac)$_2$ (16 mg, 0.036 mmol) in dichloromethane (5 mL) was cooled to 0 °C and TBHP (0.55 M in nonane, 2.6 mL, 0.01 mmol) was added. The reaction was worked up as in the formation of diepoxide **18**, affording epoxide **20** (61 mg, 0.16 mmol, 75%). Compound **20** was allowed to stand on deuterochloroform for 2 days, affording a mixture of compounds, which was purified by column chromatography (2:3 EtOAc/hexanes) giving rise to pure **21** (36 mg, 0.09 mmol 60%) and **22** (23 mg, 0.06, 38%).

3.26. Epoxide 20

Colorless oil; $[\alpha]_D^{20}$ +27.7 (*c* 0.007, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of conformers) δ 5.25 (1H, m, H-1), 3.77 (1H, dd, *J*=10.6, 2.5 Hz, H-12β), 3.59 (1H, d, *J*=8.0 Hz, H-6), 3.50 (1H, dd, *J*=10.5, 5.0 Hz, H-12α), 2.60 (1H, m, H-5), 2.33 (1H, m, H-3α), 1.69 (1H, ddd, *J*=12.2, 9.9, 7.1, 2.5 Hz, H-11), 1.64 (3H, s, H-14), 1.34 (1H, br d, *J*=6.7 Hz, H-7), 1.25 (1H, m, H-3β), 1.24 (3H, s, H-15), 1.20 (3H, s, H-15′), 0.98 (1H, d, *J*=7 Hz, H-13), 0.88 (9H, s, –OSi^t*Bu*Me$_2$), 0.86 (1H, m, H-8α), 0.08 (3H, s, –OSi^{t}Bu*Me*$_2$), 0.07 (3H, s, –OSi^{t}Bu*Me*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 137.2, 125.3, 125.0, 108.3, 70.2, 68.1, 65.2, 59.7, 44.5, 44.4, 44.1, 42.5, 39.4, 37.2, 31.9, 31.6, 29.6, 25.8, 22.8, 18.3, 16.5, 16.1, −5.5; IR ν_{max} (cm^{-1}): 3440, 2953, 2928, 2856, 1463, 1388, 1253, 1098, 838, 779; MS (CI) *m*/*z* (rel int.) 369 [M+1]$^+$ (35), 351 (94), 333 (64), 311 (24), 293 (41), 237 (65), 219 (100), 201 (99), 161 (90), 145 (42), 121 (39), 95 (41); HRMS (CI): calcd for $C_{21}H_{41}O_3Si$ [M+1]$^+$ 369.2824, found 369.2828.

3.27. Guaiane 21

Colorless oil; $[\alpha]_D^{20}$ −78.0 (*c* 0.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (1H, s, H-14a), 4.71 (1H, s, H-14b), 3.98 (1H, dd, *J*=10.2, 6.9 Hz, H-6), 3.72 (1H, dd, *J*=10.4, 2.4 Hz, H-12a), 3.52 (1H, dd, *J*=10.4, 6.6 Hz, H-12b), 2.52 (1H, m, H-9α), 2.28 (1H, m, H-1), 2.18 (1H, m, H-9β), 1.90 (1H, dd, *J*=11.7, 10.1 Hz, H-5), 1.82–1.86 (1H, m, H-2α), 1.71–1.80 (2H, m, H-11, H-8α), 1.65 (1H, m, H-2β), 1.45–1.53 (2H, m, H-7, H-8β), 1.27 (3H, s, H-15), 0.93 (3H, d, *J*=6.8 Hz, H-13), 0.90 (2H, m, 2H-3), 0.89 (9H, s, –OSi^t*Bu*Me$_2$), 0.08 (3H, s, –OSi^{t}Bu*Me*$_2$), 0.06 (3H, s, –OSi^{t}Bu*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 108.3, 76.5, 72.5, 67.6, 58.4, 47.0, 42.9, 39.6, 36.4, 34.5, 27.4, 25.8, 24.5, 24.3, 18.2, 17.2, −5.6; IR ν_{max} (cm^{-1}): 3422, 2955, 2928, 2856, 1464, 1387, 1254, 1077, 837, 776; MS (CI) *m*/*z* (rel int.) 369 [M+1]$^+$ (5), 333 (11), 293 (14), 235 (8), 219 (100), 201 (99.9), 161 (21), 145.1 (15), 115 (12), 95 (9); HRMS (CI): calcd for $C_{21}H_{41}O_3Si$ [M+1]$^+$ 369.2825, found 369.2822.

3.28. Guaiane 22

Colorless oil; $[\alpha]_D^{20}$ −62.2 (*c* 0.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (1H, m, H-9), 4.08 (1H, dd, *J*=10.1, 6.9 Hz, H-6), 3.67 (1H, dd, *J*=10.4, 2.5 Hz, H-12a), 3.52 (1H, dd, *J*=10.3, 7.4 Hz, H-12b), 2.25–2.44 (2H, m, H-1, H-8α), 2.10 (1H, dd, *J*=11.9, 10.1 Hz, H-5), 2.01 (1H, m, H-8β), 1.67–1.81 (2H, m, 2H-2), 1.65 (1H, m, H-11), 1.54 (3H, s, H-14), 1.52 (1H, m, H-7), 1.42 (1H, m, H-3α), 1.27 (3H, s, H-15), 0.98 (3H, d, *J*=7 Hz, H-13), 0.90 (1H, m, H-3β), 0.89 (9H, s, –OSi^t*Bu*Me$_2$), 0.09 (3H, s, –OSi^{t}Bu*Me*$_2$), 0.07 (3H, s, –OSi^{t}Bu*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.4, 117.5, 77.4, 68.0, 65.3, 57.4, 56.0, 42.5, 39.1, 36.5, 29.7, 26.1, 25.8, 24.5, 23.1, 18.2, 17.0, −5.5; IR ν_{max} (cm^{-1}): 3420, 2955, 2928, 2856, 1464, 1387, 1255, 1077, 837, 777; MS (CI) *m*/*z* (rel int.) 369 [M+1]$^+$ 369 [M+1]$^+$ (8), 333 (13), 293 (13), 235 (14), 219 (92), 201 (100), 161 (32), 145.1 (18), 119 (10), 95 (14); HRMS (CI): calcd for $C_{21}H_{41}O_3Si$ [M+1]$^+$ 369.2825, found 369.2824.

3.29. Deprotection of alcohol 19 with TBAF

A solution of alcohol **19** (100 mg, 0.28 mmol) in THF (15 mL) was treated with TBAF (1 M in THF, 0.5 mL) at 0 °C. The reaction mixture was stirred for 15 min, after which time aqueous saturated ammonium chloride (20 mL) was added. The aqueous layer was extracted with EtOAc (3×10 mL) and the organic layers were combined, dried over sodium sulfate, and the solvent was removed under vacuum. The resulting residue was purified by column chromatography (3:7 EtOAc/hexanes) giving rise to diol **23** (61 mg, 0.26 mmol, 92%).

3.30. Diol 23

Colorless oil; $[\alpha]_D^{20}$ −35.7 (*c* 0.002, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of conformers) δ 5.09 (1H, m, H-5), 4.98 (1H, d, *J*=7.8 Hz, H-5′), 4.96 (1H, m, H-1), 4.65 (1H, d, *J*=7.8 Hz, H-6), 3.75 (1H, dd, *J*=11.8, 2.6 Hz, H-12a), 3.57 (1H, m, H-12b), 2.34 (1H, m, H-2α), 2.20–2.00 (2H, m, H-2β, H-9α), 1.99–1.52 (4H, m, H-11, 2H-3, H-9β), 1.60 (3H, s, H-14), 1.55 (3H, s, H-14′), 1.46 (3H, br s, H-15), 1.31 (1H, m, H-8α), 1.24 (1H, m, H-7), 1.05 (1H, d, *J*=7.1 Hz, H-13), 0.90 (1H, ddd, *J*=2.6, 9 Hz, H-8β), 0.87 (1H, m, H-11); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of conformers) δ 138.7, 133.5, 132.8, 130.83, 128.7, 121.5, 110.4, 106.37, 77.2, 69.9, 67.7, 67.0, 65.5, 64.9, 60.8, 60.3, 58.2, 49.9, 47.3, 45.3, 41.7, 40.9, 40.3, 39.0, 36.9, 34.8, 30.1, 29.6, 25.9, 24.5, 21.5, 21.0, 16.4, 16.1; IR ν_{max} (cm^{-1}): 3314, 2927, 1455, 1255, 1019, 835, 774; MS (CI) *m*/*z* (rel int.) 239 [M+1]$^+$ (22), 221 (98), 203 (94), 189 (26), 163 (100), 147 (53), 137 (43), 121 (77), 109 (71), 95 (67); HRMS (CI): calcd for $C_{15}H_{27}O_2$ [M+1]$^+$ 239.2011, found 239.2011.

3.31. Epoxidation of diol 23 with TBHP and VO(acac)$_2$

Compound **16** was treated with TBHP and VO(acac)$_2$ following the same experimental procedure followed in the synthesis of **20** with the following amounts: alcohol **23** (100 mg, 0.42 mmol), VO(acac)$_2$ (20 mg, 0.04 mmol), dichloromethane (5 mL), and TBHP (0.03 mL). Compound **24** (81 mg, 0.31 mmol) was thus obtained in 75% yield.

3.32. Epoxide 24

Colorless oil; $[\alpha]_D^{20}$ +21.2 (*c* 0.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of conformers) δ 5.27 (1H, m, H-1), 3.76 (1H, dd, *J*=11.2, 3.0 Hz, H-12β), 3.66 (1H, d, *J*=8.1 Hz, H-6), 3.54 (1H, dd, *J*=11.1, 5.6 Hz, H-12α), 2.63 (1H, m, H-5), 2.36 (1H, m, H-2β), 2.16 (1H, m, H-9β), 2.06 (1H, m, H-9α), 2.00–1.70 (3H, m, H-8β, H-3α, H-11), 1.64 (3H, s, 3H-14), 1.39 (1H, m, H-7), 1.25 (1H, m, H-3β), 1.21 (3H, s, H-15), 1.02 (1H, d, *J*=7.0 Hz, H-13), 0.89 (1H, m, H-8α). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of conformers) δ 137.7, 122.9, 77.2, 70.0, 69.1, 68.4, 64.4, 60.7, 60.1, 46.8, 44.5, 37.1, 26.5, 24.6, 16.6, 16.4, 16.3, 16.0, 15.9; IR ν_{max} (cm^{-1}): 3439, 2953, 2928, 2856, 1463, 1386, 1252, 1098, 838, 778; MS (CI) *m*/*z* (rel int.) 255 [M+1]$^+$ (4), 237 (55), 219 (100), 189 (26), 201 (45), 191 (16), 161 (62), 149 (30), 135 (32), 123 (24), 109 (37), 95 (45); HRMS (CI): calcd for $C_{15}H_{27}O_2$ [M+1]$^+$ 255.1960, found 255.1955.

3.33. Oxidation of diol 24 with TPAP and NMO

A solution of diol **24** (34 mg, 0.12 mmol), NMO (30 mg, 0.26 mmol), and 4 Å molecular sieves (30 mg) were treated with TPAP (7 mg, 0.02 mmol). After stirring for 6 h, the reaction mixture was filtered with EtOAc through a silica pad. After removal of the solvent, the crude mixture was purified by column chromatography (2:3 EtOAc/hexanes), affording melampolide **25** (21 mg, 0.084 mmol, 70%).

3.34. Melampolide 25

Amorphous solid; $[\alpha]_D^{20}$ +12.4 (*c* 0.008, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.25 (1H, t, *J*=7.1 Hz, H-1), 4.25 (1H, dd, *J*=8.2, 6.3 Hz, H-6), 3.08 (1H, d, *J*=8.3 Hz, H-5), 2.42 (1H, m, H-9β), 2.30 (1H, m, H-11), 2.21 (1H, m, H-9α), 2.14–1.99 (5H, m, 2H-2, H-3β, H-8α, H-7), 1.65 (3H, br s, H-14), 1.60 (1H, m, H-8β), 1.41 (3H, s, H-15), 1.29 (3H, dd, *J*=7.4, 2.0 Hz, H-13), 1.22 (1H, m, H-3α); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 136.8, 121.8, 81.8, 62.2, 53.4, 46.1, 42.3, 38.6, 29.6, 28.5, 26.6, 23.1, 22.1, 15.2; IR ν_{max} (cm^{-1}): 2930, 2873, 1771, 1458, 1380, 1186, 1072, 962, 811; MS (CI) *m*/*z* (rel int.) 251 $[M+1]^+$ (14), 233 (100), 215 (9), 205 (64), 177 (53), 159 (73), 147 (26), 135 (32), 133 (14), 119 (23),107 (14), 81 (7); HRMS (CI): calcd for $C_{15}H_{23}O_3$ $[M+1]^+$ 251.1647, found 251.1650.

3.35. Treatment of lactone 25 with *p*-TsOH

A solution of alcohol **25** (20 mg, 0.08 mmol) in dichloromethane (5 mL) was treated with *p*-TsOH (1 mg) at room temperature. After stirring for 12 h, aqueous saturated $NaHCO_3$ (5 mL) was added and the resulting mixture was extracted with dichloromethane (3×10 mL). The organic layer was dried over sodium sulfate and the solvent was removed under vacuum. Purification of the crude mixture by HPLC (2:3 EtOAc/hexanes) afforded melampolide **26** (7 mg, 0.028 mmol, 35%).

3.36. Melampolide 26

Colorless oil; $[\alpha]_D^{20}$ +51.0 (*c* 0.02, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 5.61 (1H, dd, *J*=11.7, 1.8 Hz, H-3), 5.29 (1H, d, *J*=8.8 Hz, H-1), 4.48 (1H, dd, *J*=10.4, 7.9 Hz, H-6), 4.27 (1H, d, *J*=10.4 Hz, H-5), 3.02 (1H, br t, *J*=13.6 Hz, H-2α), 2.53 (1H, m, H-2β), 2.28 (1H, dt, *J*=13.0, 6.9 Hz, H-11), 2.19 (1H, ddd, *J*=13.0, 7.8, 4.1 Hz, H-7), 2.18–2.13 (2H, m, 2H-9), 1.93 (1H, m, H-8α), 1.80 (3H, s, 3H, H-15), 1.68 (3H, s, H-14), 1.47 (1H, m, H-8β), 1.23 (3H, d, *J*=7.0 Hz, 3H-13); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 140.7, 130.1, 120.0, 94.7, 79.8, 75.6, 45.6, 39.3, 30.8, 29.9, 29.6, 25.2, 13.7, 11.3; IR ν_{max} (cm^{-1}): 3610, 2930, 2873, 1770, 1458, 1189, 1070, 964, 809; MS (CI) *m*/*z* (rel int.) 251 $[M+1]^+$ (18), 233 (95), 219 (47), 203 (51), 175 (54), 159 (100), 147 (39), 135 (25), 133 (31), 119 (34), 107 (35), 81 (38); HRMS (CI): calcd for $C_{15}H_{23}O_3$ $[M+1]^+$ 251.1647, found 251.1648.

3.37. Oxidation of diol 24 with TPAP and NMO

A solution of diol **24** (34 mg, 0.12 mmol), NMO (30 mg, 0.26 mmol), and 4 Å molecular sieves (30 mg) were treated with TPAP (7 mg, 0.02 mmol). After stirring for 2 h, the reaction mixture was filtered with EtOAc through a silica pad. After removal of the solvent, the crude mixture was purified by column chromatography (3:7 EtOAc/hexanes), affording lactone **27** (24 mg, 0.096 mmol, 76%).

3.38. Lactone 27

Amorphous solid; $[\alpha]_D^{20}$ +16.0 (*c* 0.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, mixture of conformers) δ 5.26 (1H, m, H-1), 4.18 (1H, dd, *J*=9.1, 5.1 Hz, H-6), 2.78 (1H, m, H-5), 2.43 (1H, dddd, *J*=7.5, 7.4, 7.4, 2.7 Hz, H-11), 2.33 (1H, m, H-2β), 2.08 (1H, m, H-2α, H-9β), 2.03 (2H, m, H-7, H-3β), 2.00 (2H, m, H-8β, H-9α), 1.68 (3H, br s, 3H-14), 1.52 (1H, m, H-8α), 1.30 (1H, d, *J*=7.4 Hz, H-13), 1.28 (3H, br s, 3H-15), 1.25 (1H, m, H-3α); ^{13}C NMR (150 MHz, $CDCl_3$, mixture of conformers) δ 178.8, 130.8, 125.1, 80.1, 79.1, 62.1, 61.2, 60.5, 60.3, 48.4, 47.2, 47.1, 46.1, 41.0, 38.6, 36.7, 35.7, 33.9, 32.2, 31.7, 29.6, 26.5, 24.4, 23.1, 16.7, 15.2; IR ν_{max} (cm^{-1}): 2930, 2873, 1771, 1458, 1380, 1186, 1072, 965, 807; MS (CI) *m*/*z* (rel int.) 251 $[M+1]^+$ (10), 233 (100), 215 (10), 205 (37), 187 (28), 159 (49), 147 (22), 133 (13), 119 (18), 107 (11), 81 (11); HRMS (CI): calcd for $C_{15}H_{23}O_3$ $[M+1]^+$ 251.1647, found 251.1644.

3.39. Treatment of lactone 27 with *p*-TsOH

A solution of lactone **27** (10 mg, 0.04 mmol) and *p*-TsOH (1 mg) in dichloromethane (5 mL) was stirred at room temperature for 12 h. Aqueous saturated $NaHCO_3$ (5 mL) was added and the mixture was extracted with dichloromethane (3×10 mL). The organic layer was dried over sodium sulfate and the solvent was removed under vacuum. Purification of the crude mixture by HPLC (2:3 EtOAc/hexanes) afforded guaianolide **28** (3 mg, 0.012 mmol, 30%) and **29** (6 mg, 0.024 mmol, 60%).

3.40. Guaianolide 28

Amorphous solid. $[\alpha]_D^{20}$ +8.1 (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (1H, br s, H-14a), 4.77 (1H, d, *J*=1.8 Hz, H-14b), 4.66 (1H, dd, *J*=11.4, 7.6 Hz, H-6), 2.51 (1H, dd, *J*=13.8, 7.6 Hz, H-1), 2.42–2.21 (3H, m, H-7, H-11, H-9α), 2.14 (1H, m, H-8β), 2.02 (1H, t, *J*=11.1 Hz, H-5), 1.98–1.65 (5H, m, 2H-2, 2H-3, H-9β), 1.51 (1H, m, H-8α), 1.38 (3H, s, 3H-15), 1.27 (3H, d, *J*=7.0 Hz, 3H-13); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.6, 150.9, 108.8, 82.7, 80.1, 54.7, 46.1, 44.6, 40.5, 35.3, 32.2, 28.8, 26.4, 23.4, 14.6; IR ν_{max} (cm^{-1}): 3340, 2930, 2873, 1770, 1170, 892, 807; MS (CI) *m*/*z* (rel int.) 251 $[M+1]^+$ (6), 233 (100), 215 (11), 205 (35), 187 (30), 159 (68), 119 (12), 107 (6), 81 (11); HRMS (CI): calcd for $C_{15}H_{23}O_3$ $[M+1]^+$ 251.1647, found 251.1643.

3.41. Guaianolide 29

Amorphous solid. $[\alpha]_D^{20}$ +11.3 (*c* 0.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 (1H, dd, *J*=11.6, 8.4 Hz, H-6), 2.82 (1H, d, *J*=11.6 Hz, H-5), 2.33 (3H, m, H-7, H-11, H-2α), 2.25 (1H, m, H-9α), 2.13 (2H, m, H-2β, H-9β), 1.95 (2H, m, 2H-8), 1.78 (1H, m, H-3α), 1.69 (1H, ddd, *J*=12.0, 7.6, 1.5 Hz, H-3β), 1.56 (3H, s, 3H-14), 1.29 (3H, s, 3H-15), 1.24 (1H, d, *J*=6.7 Hz, 3H-13); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 130.9, 130.7, 82.2, 80.3, 51.6, 46.1, 39.7, 38.1, 33.5, 29.0, 26.6, 22.3, 21.4, 13.7; IR ν_{max} (cm^{-1}): 3344, 2930, 2873, 1175, 1182, 987, 811; MS (CI) *m*/*z* (rel int.) 251 $[M+1]^+$ (34), 233 (100), 215 (10), 205 (43), 187 (53), 159 (80), 119 (27),107 (10), 81 (9); HRMS (CI): calcd for $C_{15}H_{23}O_3$ $[M+1]^+$ 251.1647, found 251.1649.

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