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The Reaction of 6,8-Disubstituted *E,E*-Germacra-1(10),4-diene 4-Epoxides with Oxyphilic Reagents

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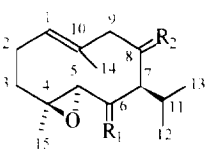
Abstract: Treatment of a group of closely related 1,4-germacradiene-4-epoxides with various oxyphilic reagents gave a remarkable array of sesquiterpenoid structures, effectively "amplifying" the skeletal diversity of the starting library. © 1997 Elsevier Science Ltd.

The cyclisation of 1,5-(poly)ene epoxides has attracted considerable attention, being featured, in a cascade version, in the biosynthesis of steroids and, in a transannular fashion, in the cyclisation of germacranes to guaianes and eudesmanes (or higher prenylogues of germacranes to their corresponding bicyclic systems).[1,2] Polar substituents play a pivotal role in these reactions, steering the propagation and termination steps. Thus, the cyclisation of oxidosqualenoids failed to give tetracyclic steroids under non-enzymatic conditions,[3] but could be re-routed using carbocation-stabilizing auxiliaries, like an isobutenyl group[4] or a fluorine atom.[5] The effect of substituents on the transannular version of the reaction has instead received little attention.[6] This is somewhat surprising, since the cyclisation of germacranes has great relevance in the biogenesis of sequiterpenoids,[7] and its central role was already postulated at a time when no ten-membered ring terpenoid had been recognised as such.[8]

We have now studied the transannular cyclisation of a series of closely related *E,E*-germacra-1(10),4-diene-4-epoxides bearing oxygen substituents at C-6 and C-8, the carbons adjacent to the isopropyl group. Oxygenation at these positions is very common in natural germacranes, and compounds of this type are available from commercial plant sources.[9] Transannular cyclisations initiated by ionisation of the oxygen functions at C-6 and C-8 are prevented by the *trans*-stereochemistry of the epoxide ring, which would raise considerably the energy of the resulting bicyclic products.[10] Furthermore, the rear face of the epoxide is shielded by the endocyclic double bond, and its opening through a concerted Sn2-type reaction is only possible in a transannular way. Though the initiation step is well defined (attack of the endocyclic double bond on the epoxide), the transannular cyclisation of epoxygermacrenes can afford different types of products, since the compact shape of the ten-membered ring makes the involvement of polar substituents a likely event in the propagation and termination steps. Furthermore, germacra1,4-dienes and their monoepoxides are flexible from a conformational point of view, and, depending on the substitution pattern, can exist in solution in a crossed (C-4 and C-10 methyls *syn*) or a parallel (C-4 and C-10 methyls *anti*) conformation (Scheme 1, A and B, respectively), or as a mixture of both.[11]

Scheme 1. Conformational equilibration of *E,E*-1(10),4-germacradiene-4-epoxides (A= crossed conformation, B= parallel conformation)

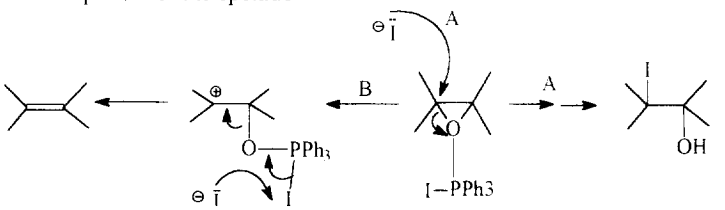
The choice of the catalyst can have great effect on the course of the cyclisation, steering the propagation and termination steps and discriminating the reacting conformation. Oxyphilic species like phosphorous reagents and certain ions (Mg^{2+}, Tl^{3+}) should favour the involvement of polar oxygen substituents in the reaction, via co-ordination and/or bridging effects. Corollary expectations were that the use of mild reaction conditions should avoid the formation of complex mixtures, while differences in the oxygenation pattern (carbonyl *vs* hydroxyl and α-*vs* β- orientation of the hydroxyls) should lead to different reaction pathways, an effect ultimately translating into an amplification of skeletal diversity. To test this concept, we investigated the reaction of the germacrene epoxide shiromodiol (**1**)[12] and three closely related derivatives, the C-8 epimer (echinadiol, **2a**),[13] the 8-dehydroderivative (**3**), and the 6,8-bisdehydroderivative (**4**).[14] Compounds **2a-4** can easily be prepared from **1**.[14,15] obtained in about 5% yield from the commercial gum-resin Asafoetida (see experimental). Shiromodiol derivatives show anti-feedant activity,[12] and certain echinadiol esters have immunostimulating activity,[13] making the library of biological relevance. Furthermore, the *E,E*-germacra-1(10),4-diene-4-epoxide system also occur in parthenolide, the alleged antimigraine principle of feverfew (*Tanacetum parthenium* (L.) Schulz Bip.),[16] pointing to other appealing extensions of this approach



	R_1	R_2
1	α-H, β-OH	β-H, α-OH
2a	α-H, β-OH	α-H, β-OH
3	α-H, β-OH	=O
4	=O	=O

Reactions with the triphenylphosphine-iodine complex

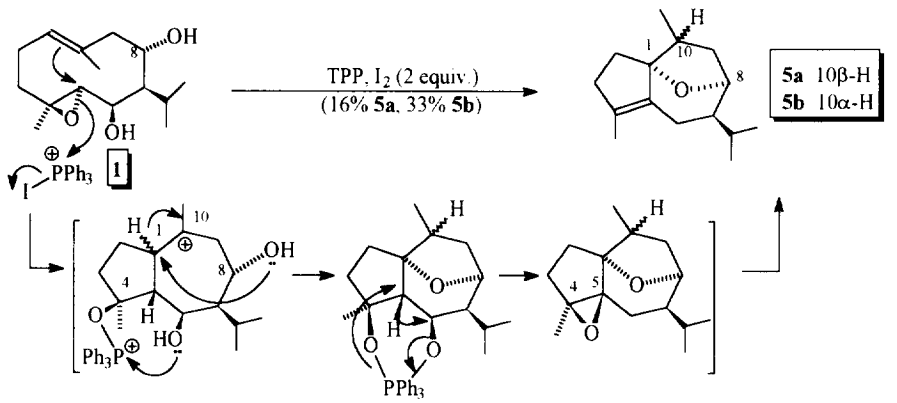
The triphenylphospine-iodine complex (TPP-I_2) is one of the mildest reagents to turn epoxides into iodohydrines[17] or olefins.[18] The outcome of the reaction depends on the regiochemistry of iodide attack on the initial phosphorylated adduct (carbon *vs* iodine attack, Scheme 2, A and B respectively), and seems mainly dictated by the substitution pattern of the epoxide



Scheme 2. Reaction of epoxides with the triphenylphosphine-iodine complex

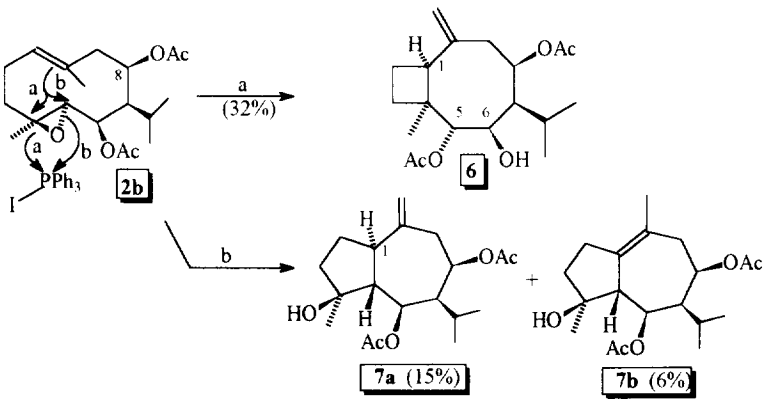
When treated with one equivalent of the TPP-I_2 complex, shiromodiol (**1**) gave in low yield (15%) a 1:2 mixture of the ethers **5a,b**, the result of a complex reaction triggered by the anti-Markovnikov transannular cyclisation of the epoxygermacrene system to a guaiane derivative (Scheme 3). Quenching of the C-10 cation by hydride shift from C-1, and formation of a 8,1 oxygen bridge brings the oxygens at C-4 and C-6 close enough to allow formation of a six-membered phosphadioxane. The latter then loses triphenylphosphine oxide and

undergoes rearrangement to a 4,5-epoxide, whose deoxygenation by unreacted I_2-TPP complex eventually gives the guaiane ethers **5a,b**. The requirement of two equivalents of the I_2-TPP adduct was evident from the increased yield (49% *vs* 15%) when two equivalents of the complex were employed. The formation of a mixture of C-10 epimers shows that both conformations of **1** can take part in the reaction. Formation of **5a** from the crossed conformation of **1** takes place via an anti-parallel propagation sequence,[19] whereas in the sequence leading to **5b**, C-10 hydride migration and closure of the oxygen bridge must take place with a non-concerted mechanism.[19] Though not natural products, **5a** and **5b** are closely related to one of the two incorrect structures assigned to germacrone before its cyclodecadiene structure was recognised.[9a] Guaianolides with a 1,8-oxygen bridge are also known.[20]



Scheme 3. Reaction of **1** with the TPP-I_2 complex.

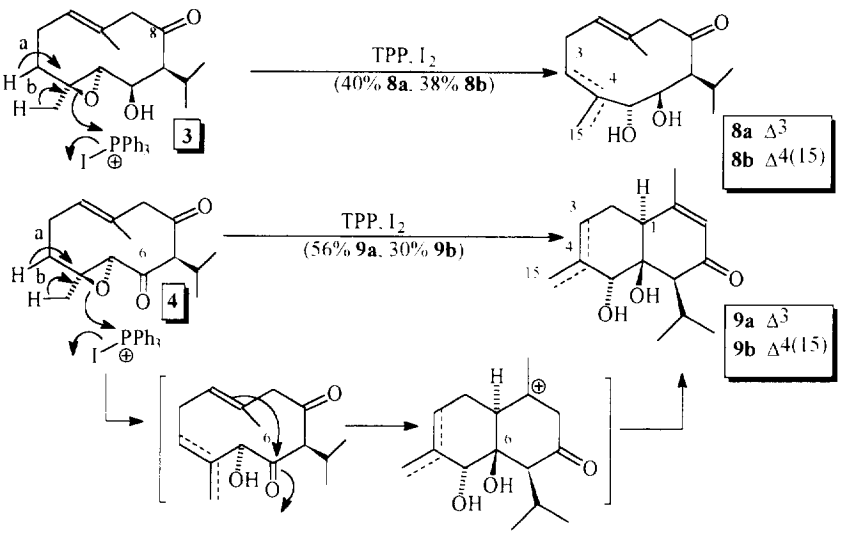
When echinadiol (**2a**) was treated with TPP-I_2, a complex reaction mixture was obtained, but its acetate (**2b**) gave a clean reaction. The major reaction product was the cyclobutane **6**, the result of a transannular Markovnikov-type opening of the epoxide, followed by acetyl migration from O(6) to O(5) (Scheme 4, a). Minor amounts of the cycloechinadiol acetates **7a,b** were also obtained through an anti-Markovnikov cyclisation (Scheme 4, b). In **6** and **7a**, H-1 is α-oriented, showing that these compounds derive from a parallel conformation of **2b**.



Scheme 4. Reaction of **2b** with the TPP-I_2 complex

Surprisingly, the epoxide ring of **3** was not opened in a transannular fashion by the I_2/TPP complex. An epoxide-allyl alcohol isomerisation took place instead, and the germacradienes **8a,b** were obtained (Scheme 5).

The same reaction occurred with the 6,8-bisdehydroderivative **4**, but the opening of the epoxide was followed by the transannular attack of the endocyclic double bond on the 6-carbonyl, leading to the cadinanes **9a,b**. The 1α-H stereochemistry of **9a,b** shows that these compounds derive from the parallel conformation of the cyclodecene system. Only few examples of germacrane to cadinane cyclisation are known,[21] and the driving force for the formation of **9a,b** from **4** is presumably the formation of a conjugated enone system.



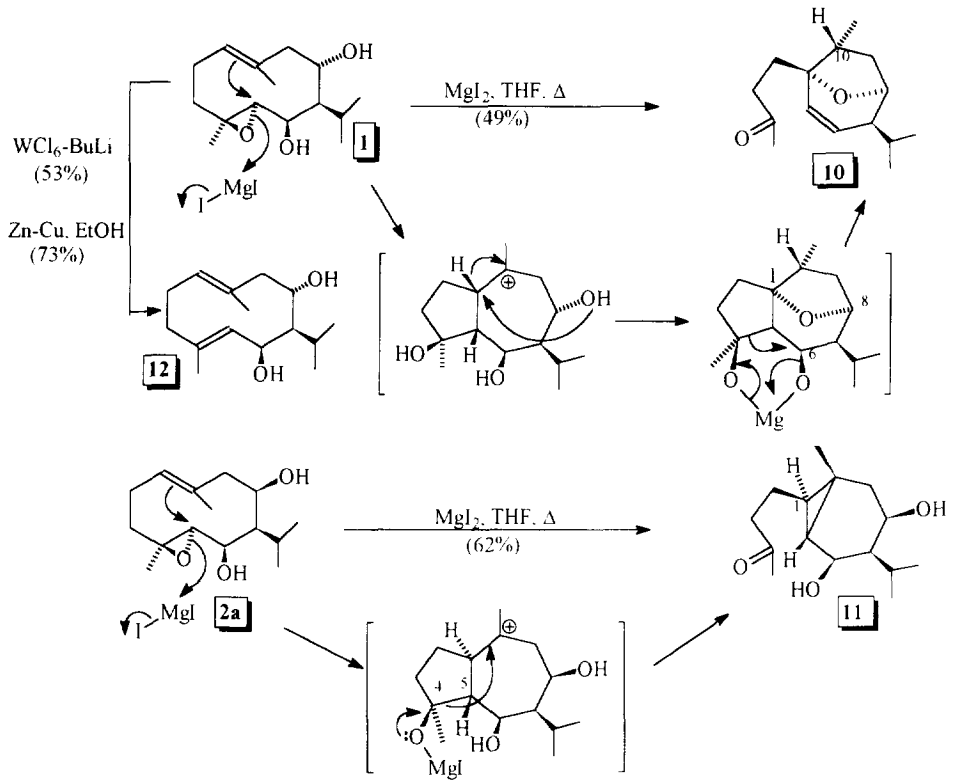
Scheme 5. Reaction of **3** and **4** with the TPP-I_2 complex

The results obtained with **1**, **2a**, **3** and **4** show that modifications at the carbons α-(C-6) and γ-(C-8) to the epoxide have a dramatic effect on the regiochemistry of epoxide opening (Markovnikov / anti-Markovnikov), on its mode of opening (transannular / non-transannular), and on the conformation of the cyclodecene ring involved in the reaction (crossed / parallel).

Reactions with MgI_2

Treatment of **1** with MgI_2 gave the xanthane derivative **10**, whereas **2a** gave the cyclopropane **11**. The stereochemistry at C-10 of **10** (β-hydrogen) and that at C-1 of **11** (α-hydrogen) shows that these compounds derive from different conformations of the starting cyclodecene epoxides (crossed and parallel, respectively). The resulting guaiane cations then undergo cleavage of the C-4/C-5 bond. In the cation derived from **1**, cleavage is triggered by the formation of a 8,1-ether and might occurs through a chelate magnesium complex, eventually affording the xanthane **10**. Alternatively, the C-10 cation is quenched by the cleavage of the C-4/C-5 bond, resulting in the formation of the bicyclo[4.1.0]heptane **11**, having the skeleton of carabrone.[22] The formation of cyclopropane derivatives in cationic reactions is very rare,[23] but a similar homofragmentation reaction was observed when germacrone 4-epoxide was kept in a buffered (pH=7) aqueous medium.[5] Compound **3** gave an equimolecular mixture of the same allylic alcohols obtained from the reaction with the TPP-I_2 complex (**8a,b**), whereas **4** gave a complex mixture, mainly consisting of the starting material. These observations confirmed that a carbonyl at C-8 makes the epoxide refractory toward transannular cyclisations.

MgI_2 and the TPP-I_2 complex have been used to deoxygenate epoxides.[18,24] The different reaction course with the germacrane epoxides **1-4** is presumably due to presence of the endocyclic double bond, which shields the rear face of the epoxide and is suitably located to attack it. Interestingly, when **1** was treated with WCl_6-BuLi[25] or the Zn-Cu couple,[26] clean deoxygenation to the germacradiene **12**[27] was observed, without any transannular cyclisation (Scheme 6).



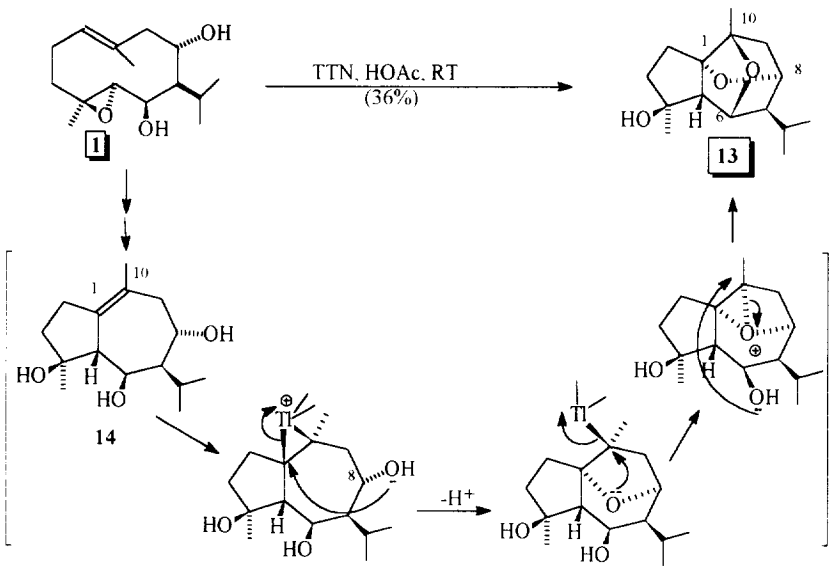
Scheme 6 Reaction of **1** and **2a** with MgI_2 and of **1** with WCl_6-BuLi or the Cu-Zn couple

Reactions with thallium trinitrate (TTN)

Tl (III) salts have been used as soft acids[28] to trigger rearrangement reactions of terpenoids.[29] When **1** was treated with TTN (thallium trinitrate) in acetic acid, a remarkable reaction occurred, with formation of the bis-ether **13** (Scheme 7). The dioxatricyclononane moiety of **12** is rather unusual from a chemical point of view, and till recently was totally unprecedented within natural and synthetic products.[30] However, the discovery of a related system in the algal diterpenoid dictyoxetane has spurred synthetic activity aimed at the synthesis of cycloheptane-bis-ethers, and a multi-step synthesis of the dioxatricyclo [4.2.1.$0^{3,8}$]nonane system of the natural product was reported.[30] Though thallium (III) salts have been used for cyclic ether formation,[31] the obtaining of the bis-ether **13** points to a potential use of Tl(III) reagents for the synthesis of more complex systems as well.

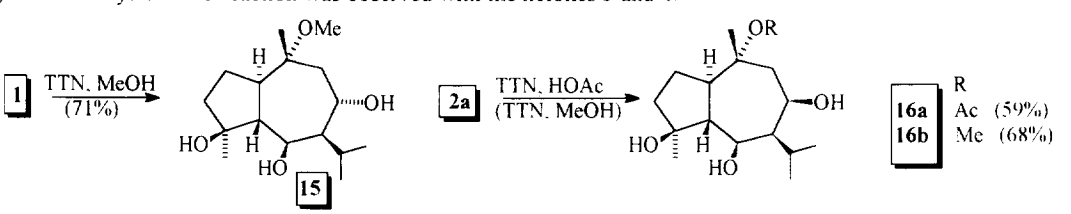
The formation of **13** (Scheme 7) presumably involves the transannular cyclization of **1** to the olefin **14**, which then undergoes intramolecular oxythallation, followed by oxygen-assisted dethallation. It is worth noting that thallium plays a different role in the reaction course, acting as a Lewis acid in the initiation step (activation of the epoxide toward transannular attack), as an electrophile in the propagation step (oxythallation of the olefinic bond), and finally as a leaving group in the termination step. The formation of the 1,8-ethers **5a,b** and **10** when **1** was treated with TPP-I_2 and MgI_2, respectively, suggests that the initial oxythallation involves the reaction of the 8-hydroxyl. Formation of a 8,1-α-ether makes it possible the intramolecular dethallation, bringing the 6β-hydroxyl and C-10 spatially close. Retention of configuration at C-10 implies anchimeric assistance by the 8,1-ether oxygen, with formation of a oxabutonium ion. Intermediates of this type have been postulated to explain the stereochemical course of cyclic ether formation in other oxythallated adducts.[31] Support for this mechanism came from the obtaining of the bis-ether **13** from the thallation of the guaiane olefin **14** (29% yield).

When the reaction was carried out in methanol, the methyl ether **15** was obtained instead, showing that the formation of the guaiane olefin **14** is precluded by the presence of an efficient cation quencher in the reaction mixture.



Scheme 7. Formation of the bis-ether **13** from the reaction of **1** with TTN in acetic acid

The reaction of **2** with TTN gave the guaiane acetate **16a** in acetic acid, and the methyl ether **16b** in methanol, highlighting the relevance of the stereochemistry at C-6 for the intramolecular oxythallation step. The *trans*-stereochemistry of the guaianes **15-16a,b** implies reaction from the parallel conformation of the germacrane system. No reaction was observed with the ketones **3** and **4**.



Structure elucidation

Structures were formulated according to spectroscopic data which included, for each compound, 1D- and 2D (COSY, ^{1}J ^{1}H-^{13}C correlation spectra) NMR results, as well as NOE studies (NOE-difference spectra). For some compounds, HMBC spectra were also run to confirm the proposed structure or to assign the quaternary carbons in the ^{13}C NMR spectrum. At 400 MHz, most proton signals were clearly resolved into first-order or pseudo first-order spin patterns, and could be completely analysed. The fully assigned ^{1}H-and ^{13}C NMR spectra of all reaction products are presented in the experimental part, along with diagnostical NOE-effects and/or HMBC correlations. Only the structure elucidation of **13** is detailed here.

Compared to **1**, the molecular formula of **13** ($C_{15}H_{24}O_3$, MS) showing the presence of a further unsaturation degree. The NMR spectra showed an extensive reorganisation of the carbon-carbon and carbon-oxygen connectivities. Thus, no olefinic carbons were present, and there were five signals in the region of oxygenated sp^3-carbons. Among the remaining signals, the presence of an additional aliphatic methine (C-5)

besides those of C-7 and C-11 suggested a bicyclic guaiane system. The ^{1}H NMR spectrum revealed the presence of two oxymethine protons, identified as H-6 and H-8 on the basis of their coupling with H-7. The IR spectrum disclosed the presence of a band at 3300 cm^{-1}, but **13** was not affected by treatment with Ac_2O-pyridine, suggesting the presence of a tertiary hydroxy group. Since only one hydroxyl was present (TAI experiments)[32], the four remaining oxygenated carbons were part of a bis-ether moiety. The combination of these structural data to meet the requirements of the degree of unsaturation, led to a guaiane structure with a hydroxyl at C-4 and two ether bridges between C-6, C-8, C-9 and C-10. The downfield chemical shift of the oxygenated carbons (> 70 ppm) ruled out the presence of a epoxide moiety, leaving only two possibilities, the one depicted in **13**, and an alternative bis-oxetane structure, with C-6/C-10, and C-8/C-1 oxygen bridges, a situation too strained to be accommodated in a cycloheptane ring. The location of the ether bridges was confirmed by the HMBC spectrum, which showed diagnostical correlations between H-6 and C-10, and between H-8 and C-1.

Conclusions

Oxygen-substituted germacrane epoxides have the potential to generate remarkable chemical diversity upon treatment with oxyphilic reagents. Changes in the functionalisation of the starting compounds led to dramatic differences in the skeletal type of the final products, and the reaction course could be steered in a highly specific way using different reagents and reaction conditions. Though the mechanistic rationalisation of the results is unclear, a bewildering skeletal diversity could be generated, making this approach appealing for drug- and flavour research.

EXPERIMENTAL

General Experimental Procedures - Anhydrous conditions were achieved (when indicated) by flame-drying flasks and equipments. THF was dried by distillation from Na-benzophenone, and benzene by distillation from CaH_2. Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates, which were visualised with 5% H_2SO_4 and heating on a hot plate in the hood. Merck silica gel (70-230 mesh) was used for open-column chromatography (CC). A Waters Microporasil column (0.8 x 30 cm) was used for HPLC, with detection by a Waters differential refractometer 340. Melting points were obtained on a Buchi SMP-20 apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker AM400 apparatus. ^{1}H- and ^{13}C chemical shifts refer to $C\underline{H}Cl_3$ at 7.26 ppm, and $\underline{C}DCl_3$ at 77.0 ppm, respectively. Biogenetic numbering was used for all assignments, and, whenever possible, named based on skeletal types or known natural products were employed for sake of consistency. All compounds obtained in yields lower than 5% were not further investigated.

Obtaining of the Starting Library - To a suspension of Asafoetida[33] (200 g, coarsely crushed) in MeOH (technical, 1 L), NaOH (50 g) was added, and the suspension was stirred mechanically for 24 h. The reaction was then filtered on a celite bed and the foul smelling reddish filtrate was concentrate at reduced temperature to remove most of the solvent. The resulting paste was taken up in water (1 L) and extracted with EtOAc (4 x 200 mL). The pooled organic phases were evaporated, and the residue was purified by CC (200 g silica gel, hexane-EtOAc 1:1 as eluant) to give 20.2 g of crude shiromodiol (**1**) as a yellowish oil, which slowly crystallised to give a white powder (12.8 g, 6.4%). Alternatively, the residue of the EtOAc extraction was directly dissolved in toluene (800 mL) and treated with activated MnO_2 (Merck, 400 g). After stirring overnight, the mixture was filtered on celite, and the filtrate was evaporated. The residue was taken up in hexane-ether (1:1, 350 mL) and cooled (-5°C). Crystals of 8-dehydroshiromodiol (**3**) were obtained (12.5 g, 6.3% on the crude gum resin). Reduction of **3** with $NaBH_4$ gave **1** and **2a**,[15] and oxidation with PCC afforded **4**.[14]

Reactions with the Triphenylphosphine-Iodine Complex (TPP-I_2) Reaction with **2b** as representative. Triphenylphosphine (280 mg, 1.07 mmol, 1.2 mol. equiv.) was added to a stirred solution of iodine (271 mg, 1.07 mmol, 1.2 mol. equiv.) in CH_2Cl_2 (15 mL). To this colourless solution, **2b** (300 mg, 0.89 mmol) was added,

resulting in the development of a brown colour. After stirring 30 min. at room temperature, the reaction mixture was diluted with CH_2Cl_2 (*ca* 10 mL), washed with sat. $Na_2S_2O_3$ and brine. After drying ($MgSO_4$) and removal of the solvent, the residue was purified by CC (20 g silica gel, hexane-EtOAc 8:2 as eluant) to give 96 mg **6** (32%), 45 mg **7a** (15%) and 18 mg **7b** (6%). The compounds obtained from the reaction of **1**, **3** and **4** were separated by CC using mixtures of hexane-EtOAc as eluant. The separation of **5a** and **5b** required HPLC (hexane-EtOAc 4:1 as eluant).

7αH, 10βH-Guaia-4-en-8α,1α-epoxide (**5a**). Colourless oil. IR vmax (liquid film): 1460, 1369, 1269, 1076, 1030 cm^{-1}; CIMS (i-butane): 221 ($C_{15}H_{24}O$ + H)$^+$ (M+H)$^+$(100). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84 (ddd, J=15.0, 10.0, 5.5 Hz, H-2α), 2.07 (ddd, J=15.0, 9.0, 4.0 Hz, H-2β), 2.31 (m, H-3α), 2.21 (m, H-3β), 2.50 (m, H-6α), 1.59 (m, H-6β), 1.31 (m, H-7), 4.32 (br d, J=8.0 Hz, H-8), 1.45 (ddd, J= 14.0, 8.0, 4.0 Hz, H-9α), 2.13 (ddd, J=14.0, 9.2, 1.0 Hz, H-9β), 1.92 (m, H-10), 1.31 (m, H-11), 0.91 (d, J=6.5 Hz, H-12), 0.89 (d, J=6.5 Hz, H-13), 0.99 (d, J=7.0 Hz, H-14), 1.59 (br s, H-15). ^{13}C NMR (100 MHz, $CDCl_3$): δ 95.5 (s, C-1), 27.5 (t, C-2), 35.1 (t, C-3), 129.3 (s, C-4), 136.1 (s, C-5), 24.2 (t, C-6), 47.8 (d, C-7), 75.6 (d, C-8), 34.2 (t, C-9), 37.8 (d, C-10), 29.9 (d, C-11), 20.5 (q, C-12), 20.9 (q, C-13), 19.9 (q, C-14), 13.4 (q, C-15). Diagnostical NOE-effects: H-10/H-9β; H-14/H-9α, H-15/H-6α. Diagnostical HMBC correlations: H-8/C-1, H-10/C-5.

7αH, 10αH-Guaia-4-en-8α,1α-epoxide (**5b**). Colourless oil. IR vmax (liquid film): 1462, 1109, 1059, 1028, 947 cm^{-1}; CIMS (i-butane): 221 ($C_{15}H_{24}O$ + H)$^+$ (M+H)$^+$(100). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (ddd, J=14.0, 9.0, 6.5 Hz, H-2α), 1.90 (ddd, J=14.0, 8.0, 4.5 Hz, H-2β), 2.25 (m, H-3α + H-3β), 2.59 (br dd, J= 14.0, 5.3 Hz, H-6α), 1.59 (br dd, J=14.0, 5.3 Hz, H-6β), 1.41 (dddd, J=11.0, 10.0, 5.5, 3.0 Hz, H-7), 4.36 (br d, J=8.0 Hz, H-8), 2.19 (ddd, J= 12.0, 11.0, 8.4 Hz, H-9α), 1.29 (m, H-9β), 2.09 (ddq, J= 11.0, 7.0, 7.0 Hz, H-10), 1.29 (m, H-11), 0.91 (d, J=6.5 Hz, H-12), 0.90 (d, J=6.5 Hz, H-13), 0.83 (d, J=6.5 Hz, H-14), 1.63 (br s, H-15). ^{13}C NMR (100 MHz, $CDCl_3$): δ 95.6 (s, C-1), 30.5 (t, C-2), 35.5 (t, C-3), 132.6 (s, C-4), 132.6 (s, C-5), 25.1 (t, C-6), 47.4 (d, C-7), 76.3 (d, C-8), 32.3 (t, C-9), 41.0 (d, C-10), 29.9 (d, C-11), 20.5 (q, C-12), 21.0 (q, C-13), 12.8 (q, C-14), 13.5 (q, C-15). Diagnostical NOE-effects: H-14/H-9β, H-15/H-6α, H-10/H-9α.

1αH,7αH-5α,8β-Diacetoxy-cis-michamp-10(14)-en-6β-ol (**6**). Colourless oil, IR vmax (liquid film): 3602, 1743, 1636, 1372, 1248, 1049, 1026, 947 cm^{-1}, CIMS (i-butane): 339 ($C_{19}H_{30}O_5$ + H)$^+$ (M+H)$^+$(25), ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (m, H-1), 2.07 (m, H-2α), 1.90 (m, H-2β), 1.90 (m, H-3α), 1.85 (m, H-3β), 5.60 (d, J=10.0 Hz, H-5), 3.76 (br t, J=10.0, H-6), 1.25 (m, H-7), 5.21 (dd, J=6.5, 5.0 Hz, H-8), 2.18 (dd, J= 14.0, 5.5 Hz, H-9α), 2.83 (dd, J=14.0, 6.5 Hz, H-9β), 1.51 (m, H-11), 1.01 (d, J=6.8 Hz, H-12), 0.99 (d, J=6.0 Hz, H-13), 5.18 (br s, H-14a), 4.91 (br s, H-14b), 1.26 (s, H-15), 2.14, 2.09 (s, OAc). ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.1 (d, C-1), 20.2 (t, C-2), 29.9 (t, C-3), 42.7 (s, C-4), 78.6 (d, C-5), 72.5 (d, C-6), 46.2 (d, C-7), 75.1 (d, C-8), 42.9 (t, C-9), 143.4 (s, C-10), 30.5 (d, C-11), 21.1 (q, C-12), 21.2 (q, C-13), 115.5 (t, C-14), 21.2 (q, C-15), 172.1, 169.6 (s, OAc), 21.2, 21.0 (q, OAc). Diagnostical NOE-effects: H-1/H-15; H-6/H-15. Diagnostical HMBC correlations: H-1/C-5.

β-Cycloechinadiol diacetate (**7a**). White powder, m.p. 78°C; IR vmax (KBr disc): 3415, 3078, 1743, 1722, 1641, 1464, 1375, 1244, 1197, 1028 cm^{-1}, CIMS (i-butane): 339 ($C_{19}H_{35}O_5$ + H)$^+$ (M+H)$^+$(100). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (m H-1), 1.90 -1.70 (overlapped m, H-2α + H-2β + H-3α+ H-3β), 2.16 (dd, J= 13.0, 7.0 Hz, H-5), 5.42 (dd, J=7.0, 3.0 Hz, H-6), 1.50 (dt, J=8.0, 3.0, 3.0 Hz, H-7), 5.17 (td, J=7.0, 7.0, 3.0 Hz, H-8), 2.61 (d, J=7.0 Hz, H-9α + H-9β), 1.83 (m, H-11), 0.96 (d, J=6.8 Hz, H-12), 0.92 (d, J=6.8 Hz, H-13), 4.90 (br s, H-14), 4.87 (br s, H-14b), 1.30 (s, H-15), 2.04, 2.02 (s, OAc). ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.4 (d, C-1), 27.4 (t, C-2), 39.3 (t, C-3), 79.3 (s, C-4), 58.6 (d, C-5), 72.7 (d, C-6), 49.6 (d, C-7), 71.8 (d, C-8), 40.1 (t, C-9), 147.0 (s, C-10), 26.8 (d, C-11), 21.8 (q, C-12), 21.2 (q, C-13), 112.2 (t, C-14), 24.1 (q, C-15), 172.1, 170.5 (s, OAc), 21.4, 21.2 (q, OAc). Diagnostical NOE-effects:H-6/H-15, H-1/H-6.

α-Cycloechinadiol diacetate (**7b**). White powder, m.p. 134°C; IR vmax (KBr disc): 3491, 3078, 1724, 1707, 1375, 1267, 1246, 1146, 1024 cm^{-1}; CIMS (i-butane): 339 ($C_{19}H_{35}O_5$ + H)$^+$ (M+H)$^+$(100). ^{1}H NMR (400 MHz, $CDCl_3$, 57 °C): δ 2.33 (overlapped m, H-2α + H-2β), 1.78 (overlapped m, H-3α+ H-3β), 2.64 (br s H-5), 5.29 (br s, H-6), 1.51 (dd, J=9.2, 5.8 Hz, H-7), 5.15 (ddd, J=12.0, 6.0, 5.8 Hz, H-8), 2.31 (dd, J=12.0, 6.0 Hz, H-9α), 2.49 (t, J=12.0 Hz, H-9β) 1.82 (m, H-11), 0.99 (d, J=6.8 Hz, H-12), 0.86 (d, J=6.8 Hz, H-13), 1.71 (br s, H-14), 1.20 (s, H-15), 2.12, 2.05 (s, OAc). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0 (s, C-1), 28.0 (t, C-2), 39.1

(t, C-3), 79.8 (s, C-4), 60.5 (d, C-5), 69.8 (d, C-6), 47.7 (d, C-7), 69.9 (d, C-8), 36.9 (t, C-9), 124.9 (s, C-10), 27.1 (d, C-11), 21.3 (q, C-12), 21.4 (q, C-13), 20.8 (q, C-14), 23.4 (q, C-15), 172.5, 170.7 (s, OAc), 21.5, 21.2 (q, OAc). Diagnostical NOE-effects: H-6/H-15.

1(10)E,3Z-7αH-5α,6β-Dihydroxygermacra-1(10)-3-dien-8-one (**8a**). White powder, m.p. 86°C; IR νmax (KBr disc): 3528, 3387, 1674, 1657, 1461, 1242, 1171, 1171, 1042 cm^{-1}; CIMS (i-butane): 253 ($C_{15}H_{24}O_3$ + H)$^+$ (M+H)$^+$ (100), ^{1}H NMR (400 MHz, $CDCl_3$, 57 °C): δ 5.78 (br s, H-1), 2.61 (overlapped m, H-2α + H-2β), 5.44 (br d, J=9.5 Hz, H-3), 4.67 (br d, J=7.6 Hz, H-5), 3.74 (br s, H-6), 2.95 (m, H-7), 3.06 (m, H-9α + H-9β) 2.19 (m, H-11), 1.01 (d, J=6.9 Hz, H-12), 1.06 (d, J=6.9 Hz, H-13), 1.69 (br s, H-14), 1.65 (br s, H-15). ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.3 (d, C-1), 26.5 (t, C-2), 134.0 (d, C-3), 138.8 (s, C-4), 69.8 (d, C-5), 70.8 (d, C-6), 52.4 (d, C-7), 213.1 (s, C-8), 59.0 (t, C-9), 120.3 (s, C-10), 30.6 (d, C-11), 21.2 (q, C-12), 21.4 (q, C-13), 15.5 (q, C-14), 17.7 (q, C-15). Diagnostical HMBC correlations: H-6/C-4.

1(10)E-7αH-5α,6β-Dihydroxygermacra-1(10)-4(15)-dien-8-one (**8b**). White powder, m.p. 70°C; IR νmax (KBr disc): 3500, 1682, 1645, 1080, 1065, 1050, 1020, 908 cm^{-1}; CIMS (i-butane): 253 ($C_{15}H_{24}O_3$ + H)$^+$ (M+H)$^+$ (100), ^{1}H NMR (400 MHz, $CDCl_3$, TMS as reference, 57 °C): δ 5.42 (br s, H-1), 2.45 (m, H-2a), 2.38 (m, H-2b), 2.56 (m, H-3a), 2.42 (m, H-3b), 4.01 (d, J=9.0 Hz, H-5), 3.88 (td, J=9.0, 9.0, 2.0 Hz, H-6), 2.65 (d, J=9.0 Hz, H-7), 2.98 (d, J=13.0 Hz, H-9a), 2.84 (d, J=13.0 Hz, H-9b), 2.25 (m, H-11), 1.08 (d, J=6.6 Hz, H-12), 0.97 (d, J=6.6 Hz, H-13), 1.75 (br s, H-14), 5.11 (br s, H-15a), 4.91 (br s, H-15b). ^{13}C NMR (100 MHz, $CDCl_3$, TMS as reference): δ 131.9 (d, C-1), 27.7 (t, C-2), 34.6 (t, C-3), 148.6 (s, C-4), 73.4 (d, C-5), 76.7 (d, C-6), 53.6 (d, C-7), 215.0 (s, C-8), 56.2 (t, C-9), 126.4 (s, C-10), 29.8 (d, C-11), 21.2 (q, C-12), 21.6 (q, C-13), 18.6 (q, C-14), 113.6 (t, C-15). Diagnostical HMBC correlations: H-6/C-4.

5α,6β-Dihydroxy-1αH-7αH-cadina-3,9-dien-8-one (**9a**). White powder, m.p. 150-1°C, IR νmax (KBr disc): 3460, 1650, 1390, 1230, 1210, 1030, 1020 cm^{-1}; CIMS (i-butane): 251 ($C_{15}H_{22}O_3$ + H)$^+$ (M+H)$^+$ (100). ^{1}H NMR (400 MHz, $CDCl_3$, 57 °C): δ 2.80 (br d, J=6.0 Hz, H-1), 2.43 (m, H-2α), 2.08 (m, H-2β), 5.70 (br s, H-3), 3.87 (br s, H-5), 2.82 (d, J=2.0 Hz, H-7), 5.90 (s, H-9), 2.29 (m, H-11), 1.27 (d, J=6.8 Hz, H-12), 1.24 (d, J=6.8 Hz, H-13), 1.89 (br s, H-14), 1.88 (br s, H-15), 1.90 (br s, 5-OH), 1.53 (br s, 6-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.2 (d, C-1), 25.5 (t, C-2), 124.2 (d, C-3), 132.9 (s, C-4), 71.6 (d, C-5), 78.8 (s, C-6), 55.9 (d, C-7), 198.8 (s, C-8), 127.9 (d, C-9), 155.2 (s, C-10), 25.3 (d, C-11), 21.5 (q, C-12), 18.4 (q, C-13), 23.6 (q, C-14), 21.0 (q, C-15). Dignostical NOE-effects: H-15/H-5, no NOE H-1/H-5.

5α,6β-Dihydroxy-1αH-cadina-4(15), 9-dien-8-one (**9b**). White powder, m.p. 193-4°C; IR νmax (KBr disc): 3450, 3075, 1700, 1390, 1220, 1035, 990, 910 cm^{-1}; CIMS (i-butane): 251 ($C_{15}H_{22}O_3$ + H)$^+$ (M+H)$^+$ (100); ^{1}H NMR (400 MHz, $CDCl_3$, 57 °C): δ 2.99 (br d, J=13.0 Hz, H-1), 2.05 (m, H-2α), 1.47 (m, H-2β), 2.55 (m, H-3α), 2.28 (m, H-3β), 4.20 (br d, J=2.5 Hz, H-5), 2.79 (d, J=2.0 Hz, H-7), 5.89 (br s, H-9), 2.31 (m, H-11), 1.26 (d, J=6.8 Hz, H-12), 1.20 (d, J=6.8 Hz, H-13), 1.87 (br s, H-14), 5.07 (br s, H-15a), 5.05 (H-15b), 1.74 (br d, J=2.5 Hz, 5-OH), 1.39 (br s, 6-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.8 (d, C-1), 24.7 (t, C-2), 28.8 (t, C-3), 146.2 (s, C-4), 75.3 (d, C-5), 79.7 (s, C-6), 56.7 (d, C-7), 198.8 (s, C-8), 127.9 (d, C-9), 156.8 (s, C-10), 24.7 (d, C-11), 21.8 (q, C-12), 18.3 (q, C-13), 23.4 (q, C-14), 115.0 (t, C-15). Dignostical NOE-effects: H-15/H-5; H-1/H-7, no NOE H-1/H-5.

Reactions with MgI_2. Reaction with **2a** as representative. To a solution of **2a** (400 mg, 1.57 mmol) in dry benzene (25 mL), a freshly prepared[23] ether solution of MgI_2 (0.4 M, 8 mL, 3.2 mmol, 2 mol. equiv.) was added, and the solution was refluxed under a nitrogen atmosphere for 5 min. The cooled reaction was then worked up by dilution with CH_2Cl_2 and washing with brine. After drying ($MgSO_4$), the residue was purified by CC (20 mL silica gel, hexane-EtOAc 8:2 as eluant) to give 248 mg **11** (62%).

1α,8α-Epoxy-10βH-xantha-5-en-4-one (**10**). Colourless oil; IR νmax (liquid film): 1717, 1669, 1588, 1356, 1263, 1155, 993 cm^{-1}; CIMS (i-butane): 237 ($C_{15}H_{24}O_2$ + H)$^+$ (M+H)$^+$ (100), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 (ddd, J=16.0, 10.0, 6.0 Hz, H-2a), 1.67 (ddd, J=16.0, 10.0, 6.0 Hz, H-2b), 2.64 (ddd, J=18.0, 10.0, 5.5 Hz, H-3a), 2.50 (ddd, J=18.0, 10.0, 5.5 Hz, H-3b), 5.60 (dd, J=10.0, 2.0 Hz, H-5), 5.65 (br d, J=10.0 Hz, H-6), 2.16 (m, H-7), 4.47 (m, H-8), 2.20 (ddd, J=13.0, 8.0, 2.0 Hz, H-9α), 1.45 (ddd, J=13.0, 8.0, 1.5 Hz, H-9β), 2.11 (m, H-11), 0.90 (d, J=6.6 Hz, H-12), 0.87 (d, J=6.6 Hz, H-13), 0.97 (d, J=6.8 Hz, H-14), 2.14 (s, H-15). ^{13}C NMR

(100 MHz, $CDCl_3$): δ 81.9 (s, C-1), 26.7 (t, C-2), 39.1 (t, C-3), 209.2 (s, C-4), 133.9 (d, C-5), 127.4 (d, C-6), 47.6 (d, C-7), 76.2 (d, C-8), 34.2 (t, C-9), 43.0 (d, C-10), 28.2 (d, C-11), 20.9 (q, C-12), 20.5 (q, C-13), 18.0 (q, C-14), 30.1 (q, C-15). Diagnostical NOE-effects: H-14/H-9α, H-10/H-2a,b. Diagnostical HMBC correlations: H-10/C-5; H-7/C-5.

1'R,2'S,3'S,4'R,6'S,7'R-4-[2,4-dihydroxy-3-(1-methylethyl)-6-methyl-bicyclo[4.1.0]hept-7-yl]-2-butanone (**11**). Colourless oil; IR νmax (liquid film): 3370, 1714, 1431, 1367, 1047, 1022, 961 cm^{-1}; CIMS (i-butane): 255 ($C_{15}H_{26}O_3$ + H)$^+$ (M+H)$^+$(100); ^{1}H NMR (400 MHz, $CDCl_3$, 57 °C): δ 0.21 (q, J=5.5 Hz, H-1), 1.62 (ddd, J=14.5, 11.0, 5.6 Hz, H-2a), 1.56 (ddd, J=14.5, 10.0, 5.0 Hz, H-2b), 2.49 (d, J=7.0 Hz, H-3a + H-3b), 0.82 (br d, J=5.5 Hz, H-5), 4.24 (br s, H-6), 0.45 (brd, J=10.0 Hz, H-7), 3.99 (br s, H-8), 1.67 (dd, J=15.0, 4.0 Hz, H-9α), 2.00 (dd, J=15.0, 2.2 Hz, H-9β), 2.08 (m, H-11), 0.98 (d, J=6.8 Hz, H-12), 0.94 (d, J=6.8 Hz, H-13), 1.15 (s, H-14), 2.14 (s, H-15). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.5 (d, C-1), 23.7 (t, C-2), 43.0 (t, C-3), 209.1 (s, C-4), 34.8 (d, C-5), 66.8 (d, C-6), 45.0 (d, C-7), 66.8 (d, C-8), 43.8 (t, C-9), 15.5 (s, C-10), 24.5 (d, C-11), 20.5 (q, C-12), 21.1 (q, C-13), 22.6 (q, C-14), 30.0 (q, C-15). Diagnostical NOE-effects: H-5/H-14; H-1/H-6; H-1/H-7.

Deoxygenation of shiromodiol (**1**) A) With WCl_6- BuLi. To a cooled (-70°C) suspension of WCl_6 (624 mg, 1.57 mmol, 2 mol. equiv.) in dry THF (15 ml), BuLi (1.6 M, 3.94 ml, 6.30 mmol, 8 mol. equiv.) was added. After stirring 10 min. at -70° C, the suspension was brought to room temp. and stirred 1 h. After recooling to -70° C, a solution of **1** (200 mg, 0.79 mmol) in dry THF (3 ml) was added, and the mixture was stirred 10 min. at -70° and then 1 h at room temp. The reaction was worked up by the addition of 1.5 M NaOH-sodium tartrate (8 mL). After separation of the phases, the water phase was reextracted with CH_2Cl_2 and the pooled organic phases were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by CC (8 ml silica gel, hexane-EtOAc 1:1 as eluant) to give 112 mg **12** (53%)[26] and 62 mg unreacted starting material. B) With the Zn-Cu couple. To a solution of shiromodiol (100 mg, 0.39 mmol) in EtOH (20 mL), Zn-Cu couple (6 g, freshly prepared)[34] was added, and the reaction was refluxed for 4h. After coling, the reaction mixture was filtered on celite and evaporated. The residue was purified by CC(10 g silica gel, hexane-EtOAc 1:1) to give 72 mg **12** [26]

Reactions with TTN. Reaction with **1** in AcOH as representative. To a solution of **1** (500 mg, 1.97 mmol) in glacial acetic acid (20 ml), $Tl(NO_3)_3.3H_2O$ (TTN, 875 mg, 1.97 mmol, 1 mol. equiv.) was added, and the reaction was stirred for 30 min. at room temp. The mixture was filtered through celite, and the filtrate was diluted with water (60 ml) and extracted with hexane-EtOAc 1:1. The organic phase was washed with $NaHCO_3$ and brine. After removal of the solvent, the residue was purified by CC (30 g silica gel, hexane-EtOAc 7:3 as eluant) to give 220 mg **13** (44%).

(1α,8α), (6β,10β) Diepoxy-5βH,7αH-guaian-4β-ol (**13**). Colourless oil; IR νmax (liquid film): 3432, 1450, 1246, 1044, 941, 891 cm^{-1}; CIMS (i-butane): 253 ($C_{15}H_{24}O_3$ + H)$^+$ (M+H)$^+$(100); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 (m, H-2α), 1.58 (m, H-2β), 2.31 (ddd, J=18.5, 10.0, 1.5 Hz, H-3α), 2.49 (ddd, J=18.5, 10.0, 9.0 Hz, H-3β), 2.57 (d, J=4.5 Hz, H-5), 4.29 (d, J=4.5 Hz, H-6), 1.37 (dd, J=10.0, 4.0 Hz, H-7), 4.36 (dd, J=5.2, 4.0 Hz, H-8), 2.18 (d, J=10.9 Hz, H-9α), 1.61 (dd, J=10.9, 5.2 Hz, H-9β), 1.87 (m, H-11), 0.94 (d, J=6.8 Hz, H-12), 0.90 (d, J=6.8 Hz, H-13), 1.30 (s, H-14), 1.58 (s, H-15); ΔTAI (ppm): H-15 (+0.21), H-5 (+0.19), H-6 (+0.09). ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.0 (s, C-1), 27.4 (t, C-2), 47.9 (t, C-3), 75.9 (s, C-4), 65.9 (d, C-5), 74.7 (d, C-6), 43.6 (d, C-7), 75.3 (d, C-8), 42.0 (t, C-9), 82.7 (s, C-10), 26.3 (d, C-11), 21.3 (q, C-12), 20.0 (q, C-13), 19.2 (q, C-14), 29.9 (q, C-15). Diagnostical HMBC correlations: H-6/C-10; H-8/C-1.

10α-Methoxy-1αH,5βH,7αH-guaian-4β,6β,8α-triol (**15**). Colourless powder; IR νmax (KBr): 3407, 1470, 1379, 1236, 1171, 1086, 961 cm^{-1}; CIMS (i-butane): 287 ($C_{16}H_{30}O_4$ + H)$^+$ (M+H)$^+$(5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (m, H-1), 1.70 (m, H-2α + H-2β +H-3α+H-3β), 1.72 (dd, J=11.0, 3.0 Hz, H-5), 4.27 (br s, H-6), 1.37 (td, J=7.0, 7.0, 2.5 Hz, H-7), 3.85 (br m, H-8), 2.14 (m, H-9α+ H-9β), 1.95 (m, H-11), 1.11 (d, J=6.8 Hz, H-12), 1.06 (d, J=6.8 Hz, H-13), 1.18 (s, H-14), 1.18 (s, H-15), 3.22 (s, OMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.2 (d, C-1), 21.9 (t, C-2), 40.6 (t, C-3), 79.9 (s, C-4), 58.5 (d, C-5), 68.7 (d, C-6), 55.4 (d, C-7),

71.7 (d, C-8), 40.7 (t, C-9), 81.4 (s, C-10), 30.0 (d, C-11), 22.0 (q, C-12), 21.1 (q, C-13), 19.2 (q, C-14), 22.2 (q, C-15), 49.4 (q, OMe). Diagnostical NOE-effects: H-15/H-6; H-1/OMe, no NOE H-5/H-7.

10α-Acetoxy-1αH,5βH,7αH-guaian-4β,6β,8β-triol (**16a**). Colourless oil; IR νmax (liquid film): 3403, 1726, 1370, 1254, 1090, 1018, 1086, 736 cm^{-1}; CIMS (i-butane): 297 $(C_{17}H_{30}O_5 - H_2O + H)^+$ (M- 18 +H)$^+$(100); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.77 (td, J=11.0, 11.0, 3.5 Hz, H-1), 1.70 (m, H-2α), 1.52 (m, H-2β), 1.70 (m, H-3α+H-3β), 2.30 (dd, J=11.5, 6.5 Hz, H-5), 4.13 (br s, H-6), 1.34 (m, H-7), 4.33 (br s, H-8), 2.47 (dd, J=14.0, 5.2 Hz, H-9α), 2.11 (br d, J=14.0 Hz, H-9β), 1.99 (m, H-11), 1.07 (d, J=6.8 Hz, H-12), 0.99 (d, J=6.8 Hz, H-13), 1.60 (s, H-14), 1.25 (s, H-15), 1.92 (s, OAc). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.7 (d, C-1), 22.8 (t, C-2), 40.5 (t, C-3), 80.8 (s, C-4), 54.8 (d, C-5), 71.2 (d, C-6), 51.1 (d, C-7), 70.7 (d, C-8), 46.1 (t, C-9), 88.5 (s, C-10), 28.0 (d, C-11), 21.3 (q, C-12), 21.3 (q, C-13), 22.3 (q, C-14), 22.8 (q, C-15), 170.4 (s, OAc), 22.5 (q, OAc). Diagnostical NOE-effects: H-15/H-6, H-1/OAc, no NOE H-5/H-7.

10α-Methoxy-1αH,5βH,7αH-guaian-4β,6β,8β-triol (**16b**). Colourless powder; m.p. 168 °C; IR νmax (KBr): 3507, 3385, 3328, 1469, 1375, 1074, 1011, 667 cm^{-1}; CIMS (i-butane): 287 $(C_{16}H_{30}O_4 + H)^+$ (M+H)$^+$(80); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (overlapped m, H-1 + H-2α + H-2β + H3α+H-3β), 1.72 (dd, J=11.0, 3.0 Hz, H-5), 4.38 (br s, H-6), 1.21 (m, H-7), 4.16 (br m, H-8), 2.36 (dd, J=11.0, 8.5 Hz, H-9α), 1.99 (dd, J=11.0, 3.5 Hz, H-9β), 2.04 (m, H-11), 1.09 (d, J=6.8 Hz, H-12), 1.02 (d, J=6.8 Hz, H-13), 1.38 (s, H-14), 1.26 (s, H-15), 3.13 (s, OMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.0 (d, C-1), 22.8 (t, C-2), 40.9 (t, C-3), 80.1 (s, C-4), 55.1 (d, C-5), 71.5 (d, C-6), 51.8 (d, C-7), 71.0 (d, C-8), 45.9 (t, C-9), 81.1 (s, C-10), 28.2 (d, C-11), 21.7 (q, C-12), 21.8 (q, C-13), 21.7 (q, C-14), 23.0 (q, C-15), 48.5 (q, OMe). Diagnostical NOE-effects: H-15/H-6, H-1/OMe, no NOE H-5/H-7.

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