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An easy access to bioactive 13-hydroxylated and 11,13-dihydroxylated sesquiterpene lactones (SLs) through Michael addition of a nucleophilic hydroxyl group

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ABSTRACT

The addition of a hydroxyl group to α,β-unsaturated carbonyl systems provides a new and easy access to bioactive difunctionalized sesquiterpene lactones (SLs) through a Michael addition to the α-methylene-γ-lactone system. The use of HMPA to enhance the nucleophilic properties of the hydroxyl groups and to stabilize the enolate is discussed. Also, we present a proposal for the mechanism based on the experimental data obtained. The scope and usefulness of the reaction are explored with other substrates and is limited by the need for a certain level of steric hindrance to avoid chain polycondensations. Nevertheless, the reaction works with esters, ketones and aldehydes. The absolute stereochemistry of some products has been elucidated by X-ray diffraction analysis. The synthesis of a natural SL using this methodology and the correction of the structure of another illustrate the usefulness of this reaction.

1. Introduction

Sesquiterpene lactones (SLs) constitute a large group of natural products[1] with a wide range of biological activities.[2] Though the number of different skeletons is not particularly high, SLs contain a wide variety of functional groups. Nevertheless, the biological activity profiles have usually been related with the presence of an α-methylene-γ-lactone group,[3] which is very common in these compounds. However, the number of known bioactive SLs without such a feature is increasing.[4] Among them, we have focused our attention on those examples in which the lactone ring has different degrees of oxidation, carrying either one or two hydroxyl groups at positions C-11 and C-13. Other minor modifications include the presence of epoxide or oxetane rings. Most of the 13-hydroxyl or 11,13-dihydroxyl-SLs reported to date are guaianolides (compounds **1**–**26**) or pseudoguaianolides (**27**–**33**). In addition, hydroxymethylene groups attached to a lactone ring are present in the monoterpene lactones the iridoids (**34**–**36**) (Fig. 1, Table 1). In many cases these compounds have proven to be bioactive in a wide array of situations.

Hence, it is of interest to look for synthetic routes to access the lactone ring and the nearby positions. However, the total synthesis of SLs is expensive and time consuming and hemisynthesis using naturally abundant SLs with an exocyclic double bond at the lactone ring (e.g., dehydrocostuslactone or cynaropicrin) can be envisaged as a feasible alternative. Notwithstanding, the $\Delta^{11,13}$ double bond present in most guaianolides and pseudoguaianolides is electron-deficient, making reactions such as epoxidations or allylic oxidations in the lactone ring difficult or impossible. Other potential methods to introduce an oxygen atom in the lactone ring could exploit the α,β-unsaturated carbonyl system through Michael addition reactions. This approach is challenged by the fact that nucleophilic oxygen species that can be smoothly converted into free hydroxyl groups are not easy to obtain. Our previous results[30] show that magnesium methoxide [$(MeO)_2Mg$] can act as a good nucleophile and undergoes Michael addition to the exocyclic double bond of the lactone. Unfortunately, demethylation needs to be carried out under strongly acidic conditions with Lewis acids such as BBr_3.[31] All attempts to demethylate the hydroxyl group in the adduct of dehydrocostuslactone and magnesium methoxide resulted in isomerization of the exocyclic double bonds to give unstable azulene-like compounds (unpublished results).

The most direct access to 13-hydroxylated SLs should be the synthetic equivalent of a Michael addition where a hydroxyl group

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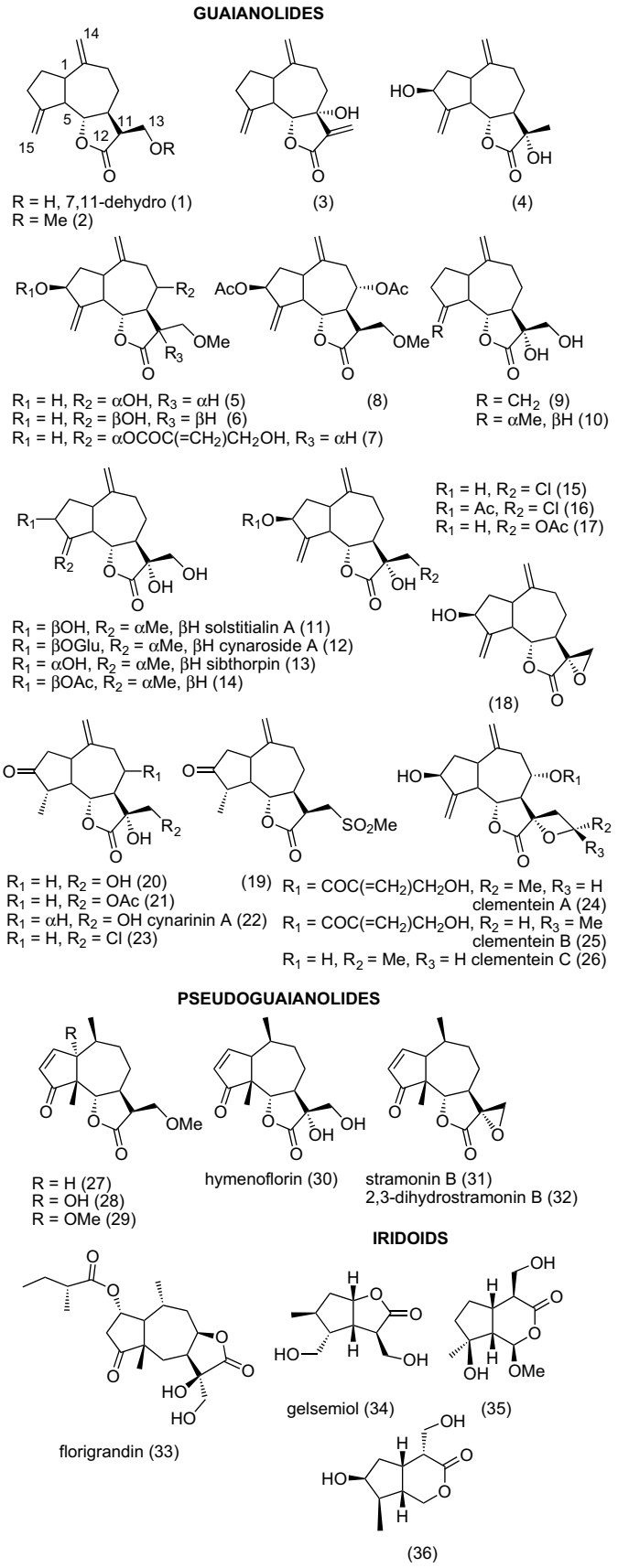


Figure 1. Natural SLs and iridoids with a hydroxymethylene group.

Table 1
Sources of compounds named in Figure 1

Source	Compound	Refs.
Ambrosia maritime	32	5
Centaurea clementei	24, 25, 26	6
Centaurea imperialis	11, 16, 17	7,8
Centaurea behen	20, 21	9,10
Centaurea musimomum	20, 21	11
Centaurea solstitialis	11, 14, 17	12,13
Cymbaria mongolica	35	14
Cynara cardunculus	11, 12	15,16
Cynara humilis	15, 16, 18	17
Cynara scolymus	11, 19, 20, 22, 23	18,19
Cynara sibthorpiana	11, 13	7
Helianthus petiolaris	9: corrected as 11(*S*)	20
Hemisteptia lyrata	5, 7	21
Hymenoxis grandiflora	33	22
Parthenium hysterophorus	27, 28, 29	23
Parthenium tomentosum	31	24
Podachaenium eminens	1, 3	25
Saussurea lappa	2	26
Saussurea amara	6	27
Scorzonera austriaca	4	28
Verbena littoralis	34	29

attacks the α,β-unsaturated carbonyl system. However, the hydroxyl group usually acts as a base and not as a nucleophile. Consequently, methods to increase the nucleophilicity of the hydroxyl group should be used to achieve this aim. Indeed, there is only one previous report that describes nucleophilic additions of hydroxyl groups to unsaturated carbonyl systems.[32] Herein, a Michael addition reaction between a hydroxyl group and the α-methylene group of a SL is presented. In this reaction the generation of the corresponding stabilized enolate at high temperature leads to the corresponding 13-hydroxyl-derivatives and an unexpected 11,13-dihydroxylated compound. The use of the aprotic solvent HMPA is crucial to enhance the nucleophilic properties of the hydroxyl group and to stabilize the enolate at high temperature. There are no previous reports of the use of HMPA as a solvent to allow the 1,4-nucleophilic addition of hydroxyl groups to α,β-unsaturated carbonyl systems at such temperatures. In SLs the reaction proceeds with high regioselectivity. However, the scope of the reaction in other systems is challenged by the possibility of chain reactions, which can be avoided only with high levels of steric hindrance.

2. Results and discussion

Treatment of a solution of dehydrocostuslactone (DHC, **37**) in HMPA with an aqueous solution of Na_2CO_3 at 90–95 °C (7 days) yielded the hydroxylated compounds **38**, **39** and **40** (Fig. 2), with some starting material remaining (30%).

Compounds **38** and **39** correspond to the Michael addition of the hydroxyl group to the unsaturated carbonyl system of the lactone ring. The relative stereochemistry of compound **39** at C-11 was initially assigned through NOESY experiments and was unequivocally established by X-ray diffraction as 11(*R*) (Fig. 3). Moreover, the allylic oxidation of **39** using SeO_2/TBTHP yielded, in addition to the 3α-hydroxyl derivative **41**, the crystalline 1α,3α-trihydroxylderivative **42**, which again confirmed the proposed absolute stereochemistry as 11(*R*). The absolute stereochemistry of **38** was established as 11(*S*) by comparison of the respective ^{1}H NMR and EIMS data of **38** and **39**.

The absolute stereochemistry at C-11 of compound **40** was initially established as 11(*R*) through NOE experiments (Fig. 4) and was further confirmed by derivatization with tosyl chloride.

The reaction of **40** with tosyl chloride in pyridine afforded the expected 13β-tosyl derivative **43** and the 11β-chloro-13-tosyl derivative **44**, obtained by the nucleophilic substitution of the

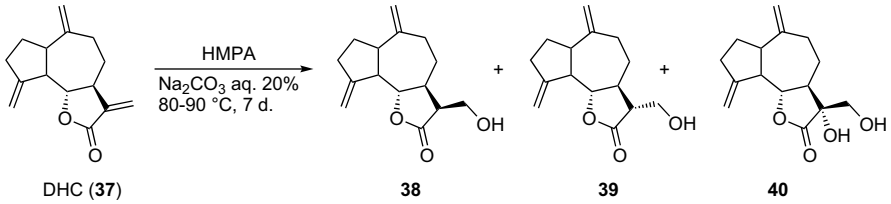


Figure 2. Michael addition of a nucleophilic hydroxyl group to the lactone **37**.

11,13-ditosyl intermediate (Fig. 5). X-ray diffraction of **44** showed the stereochemistry at C-11 to be 11(*S*), thus confirming the initial assignment for **40**. The chloride derivative **44** can be obtained either through an SN_1 or an SN_2 mechanism, with the SN_1 option being more likely when good tertiary leaving groups are involved, particularly in polar aprotic solvents such as pyridine. In this case, molecular calculations of the $\Delta H^{\#}$ and the ΔH_f^o values for both possibilities (11α- and 11β-chloro) show the difference to be too small (ca. −2.7 kcal/mol, Fig. 5) to explain the enantioselectivity obtained for **44**. Consequently, if a racemic mixture is not obtained, the reaction must proceed mainly through an SN_2 pathway, thus supporting the stereochemistry of the diol **40**.

The characterization of compound **9** from *Helianthus petiolaris*[20] has previously been reported and this has the same structure as compound **40**. However, the spectroscopic data supporting the structure are not fully consistent with those presented here. The main differences concern the chemical shift of H-6: δ 4.31 (t, J=9.4 Hz) for the natural product **9** and δ 4.06 (dd, J=8.9, 9.9 Hz) for the synthetic compound **40**. Since the relative stereochemistry at C-11 is unequivocally assigned in the synthetic compound, the stereochemistry at this centre must be corrected in the natural product **9** as 11(*S*). This is in good agreement with the deshielding effect observed in the signal corresponding to H-6 in the natural product due to the effect of the β-oriented hydroxyl group (Fig. 6).

2.1. Mechanism and scope of the reaction

The mechanism proposed for this reaction is depicted in Figure 7. The initial Michael addition of the hydroxyl group to the α-methylene-γ-lactone group yields compounds **38** and **39**. Furthermore, trapping of molecular oxygen leads to a peroxyadduct that, after dismutation with the enolate intermediate, gives the deprotonated alkoxide that finally renders compound **40**. This reaction has some novel aspects that require further discussion.

There is only one previous report of a hydroxyl group acting as a nucleophile and not as a base: treatment of DHC (**37**) with an aqueous solution of K_2CO_3 at 50 °C over 5 days yielded **38** as the only product,[32] and this is a unique example of an enantioselective Michael addition. The use of HMPA changes the situation drastically. It has been reported that polar aprotic solvents with low levels of proton exchange by hydrogen bonds (e.g., HMPA, DMSO) allow a better equilibrium between an enolate and its corresponding ketone, thus prolonging the life of these very reactive species. The chelating effect of HMPA on metallic cations has also been reported to enhance the nucleophilic properties of the counter ion.[33] This is the reason why HMPA is so valuable for SN_2 displacement reactions with anionic nucleophiles.[34] Moreover, there is an enhanced regioselectivity in the addition of organolithium reagents to enones in the presence of HMPA,[33c] with 1,4-additions favoured in comparison to 1,2-additions. In this particular case, we tried to obtain the same results with other aprotic polar solvents like DMSO or DMF, but in these cases reaction products were not formed. DMSO is not able to chelate metallic cations or to enhance the nucleophilic properties of the hydroxyl group. In the case of DMF, its chelating properties are probably not strong enough. Our previous results[32] show that the use of an aqueous solution of K_2CO_3 only leads to the 11(*S*) enantiomer **38**. Curiously, traces of the 11(*R*) epimer were not obtained. When the reaction is carried out in an HMPA/water mixture, the protonation of the enolate leads to a mixture of α and β enantiomers.

Regarding the dihydroxyl-derivative **40**, there are some previous reports concerning effective auto-oxidation of a large number of compounds including ketones[35] and the possibility of peroxy-radical formation in HMPA. It is also important to note that HMPA does not undergo auto-oxidation as DMSO does.[36] The high stereoselectivity obtained in this reaction, where only the 11α-hydroxy-11β-hydroxymethylene enantiomer is obtained, comes from the necessary face-to-back approach (Fig. 7) to give attack of the enolate to the peroxyadduct. The formation of the 11α-peroxy-derivative **43** as the sole product is crucial to explain the stereochemical path of the reaction. In this case, MOPAC molecular modelling using the PM3 algorithm showed the 11α-peroxyl enantiomer to be more stable (ca. −5 kcal/mol) than the 11β-peroxy adduct (ΔH_f^o = −241.64 kcal/mol and

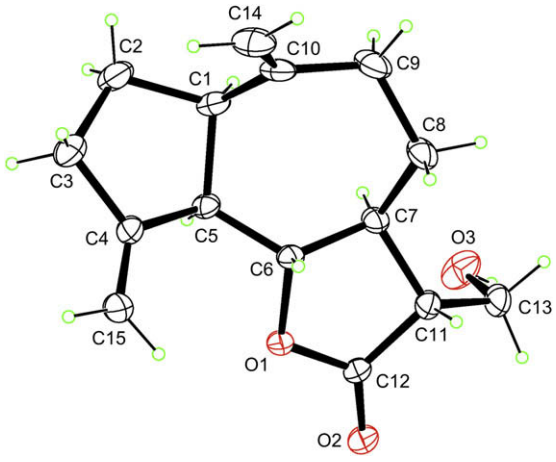


Figure 3. X-ray structure of compound **39** showing the absolute stereochemistry at C-11 to be 11(*R*).

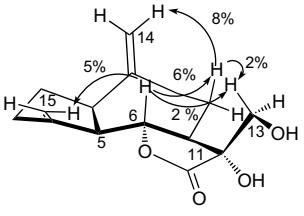


Figure 4. NOE effects observed for compound **40**.

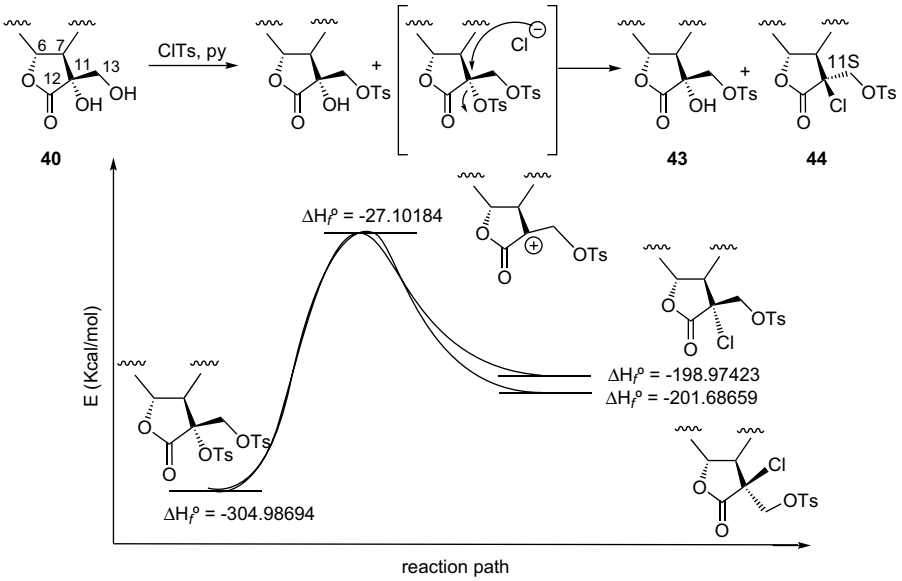


Figure 5. PM3 calculations supporting the stereochemistry assigned for **40**.

$\Delta H_f^o = -236.85$ kcal/mol, respectively), thus supporting the mechanism proposed.[37]

An increase in the reaction yield and the speed of the reaction is observed if vigorous stirring is used or if oxygen is bubbled through. In both cases a larger amount of oxygen in solution is available, thus substantiating the mechanism proposed. We also need to highlight the fact that the reaction reaches equilibrium at a point where the starting material **37** and the three end-products (**38**–**40**) co-exist and no further evolution can be observed. Moreover, similar proportions of compounds **38**–**39** are obtained if any of them are used as starting materials under the same conditions as for compound **37**.

In order to explore the scope of this reaction we tested several Michael acceptors, including different types of SL backbones. The results obtained show that this reaction is general to any type of unsaturated carbonyl system, but a certain degree of steric hindrance is needed to avoid multiple Michael additions of the enolate to the remaining starting material, as can be observed in Table 2.

These results show that the hydroxyl group effectively acts as a nucleophile under aqueous HMPA basic conditions with a variety of unsaturated carbonyl systems (ketones, aldehydes and lactones), but the evolution of the reaction—and thus its usefulness—is limited by the need to avoid chain reactions. If such a condition fails, autocondensation of the enolate intermediate leads to high molecular weight adducts, which is the case for mesityl oxide (**49**) and cinnamaldehyde (**50**) (Table 2). Attempts to perform the reaction at room temperature or lower with **49** and **50** resulted in no reaction, even after several days.

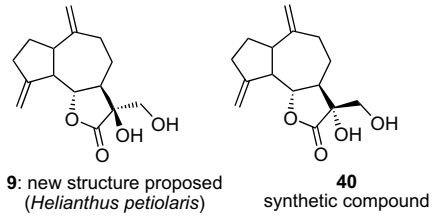


Figure 6. Corrected structure for the 11,13-dihydroxylactone isolated from *Helianthus petiolaris*, compound **9**.

In the case of the 4-methoxychalcone (**51**) the steric hindrance becomes sufficient to allow the isolation of the dihydroxyl-derivative. However, the high acidity of Hα in the Michael monohydroxylated adduct, caused by the conjugation of the aromatic ring, makes it a very reactive species that easily undergoes oxidation to yield the dihydroxylated compound **54** and the mixture of diastereomeric epoxides **55a** and **55b**. This is not unexpected, since the peroxide intermediate proposed in the general mechanism (Fig. 7) may undergo intramolecular nucleophilic substitution by the hydroxyl group to yield the epoxide with a superoxide anion as a leaving group. Such epoxides could not be detected with sesquiterpene lactones. In any case, the major products are still those resulting from polycondensation of the enol intermediate with

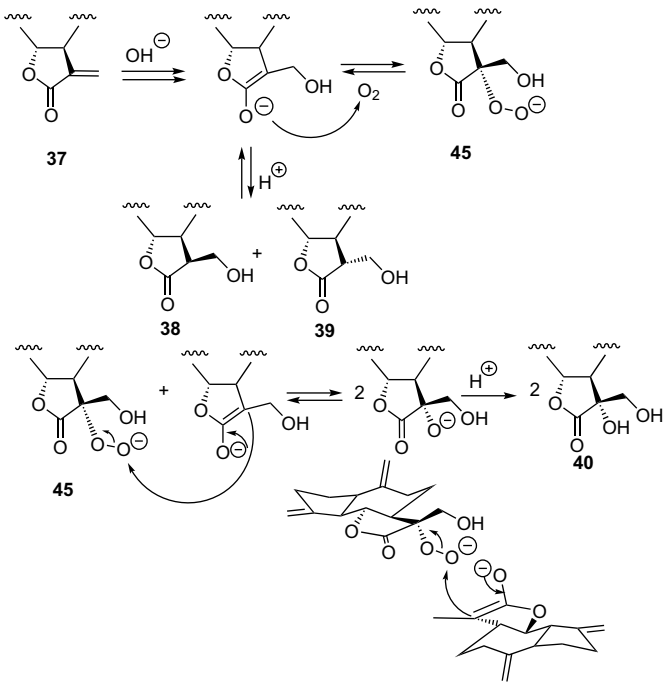
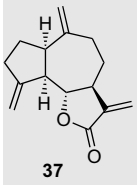
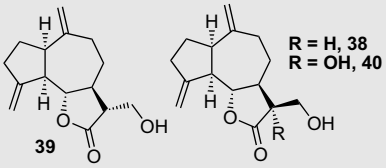
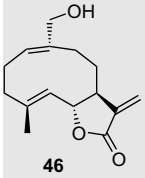
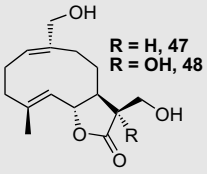
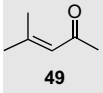
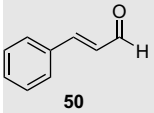
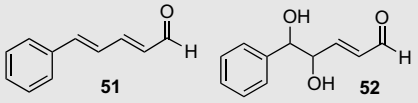
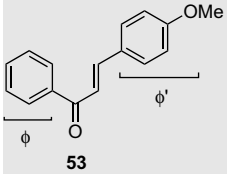
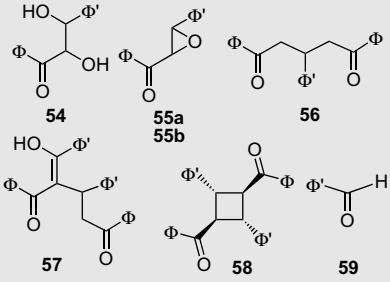


Figure 7. Proposed mechanism for the generation of the dihydroxyl-derivative.

Table 2
Scope of the reaction: entries 1 and 2, SLs; entries 3 and 5, unsaturated ketones; entry 4, unsaturated aldehyde

Starting material	Final products	Conditions	Yield (%)
 **37**	 **39** R = H, **38** R = OH, **40**	20% aq $CaCO_3$, HMPA, 90 °C, 5 days	**38**: 21% **39**: 30% **40**: 6%
 **46**	 R = H, **47** R = OH, **48**	20% aq $CaCO_3$, HMPA, 90 °C, 5 days	**47**: 22% **48**: 5%
 **49**	Complex mixture of polymers	(a) 100 mmol, 5 mL HMPA, 20% aq $CaCO_3$, 110 °C, 2 days (b) 4 mmol, 3 mL HMPA, 20% aq $CaCO_3$, 80 °C, 1 day	—
 **50**	 **51** **52** + benzaldehyde (**53**) + high molecular weight adducts	(a) 80 mmol, 4 mL HMPA, 20% aq Na_2CO_3, 80 °C, 1 day (b) 4 mmol, 3 mL HMPA, 20% aq Na_2CO_3, 80 °C, 90 min	Traces of the low mol. wt. compounds **51** and **52**
 **53**	 **54** **55a** **55b** **56** **57** **58** **59**	400 mmol, 2 mL HMPA, $CaCO_3$, 100 °C, 20 h	Traces of **54**, **55a** and **55b** **53**: 28% **56**: 20% **57**: 14% **58**: 10% **59**: 21%

another molecule of starting material through successive Michael additions, as occurred with cinnamaldehyde. Compounds **57**, **58** and **59** could be isolated and identified as the major compounds from the reaction mixture. Benzaldehyde (**53**) and *p*-methoxybenzaldehyde (**59**) are the result of a McLafferty rearrangement (Fig. 8), which takes place under high temperature conditions. Finally, compound **58**, obtained through a [2+2] cycloaddition, was an unexpected final product that was not detected in the other reactions (Table 2).

2.2. Synthesis of natural SLs

In order to illustrate the utility of this new route to access functionalized lactone rings in SLs, we achieved the synthesis of the SLs **63** and **65** (Fig. 9). On using compound **40** as the starting material, treatment with thionyl chloride in dry pyridine led to a mixture of compounds **60**–**62**, which have a similar polarity to **40**. The presence of the chlorine atom was confirmed by the EIMS spectra. The absolute stereochemistry was unequivocally established by the deshielding effect observed in the ^{1}H NMR signal corresponding to H-6 in compounds **60** and **62** (δ 4.15 ppm), in comparison with that of **61** (δ 4.07 ppm). Further treatment of **60** and **62** with lithium carbonate led to the dehydrohalogenated compounds **63** and **64**, respectively. Finally, reduction of **64** with TBTH/AIBN led to the natural guaianolide **65**. The spectroscopic data for the synthetic compound **65** are in full agreement with those previously reported for the natural product.[25a,38]

Some carbon and proton values reported in the literature for compound **65** must be corrected since their assignment has been unequivocally made here by high resolution ^{1}H and ^{13}C NMR correlation techniques (COSY and HSQC) (see Section 4 and Table 3). In the case of compound **63**, only the ^{1}H NMR spectroscopic data of the acetylated derivative have been published (Table 3). The synthesis of these bioactive natural products illustrates the usefulness of this method.

3. Conclusions

We report the effective Michael addition of a hydroxyl group to α,β-unsaturated carbonyl systems in a biphasic solvent system (HMPA/water). The mechanism proceeds through a 1,4-Michael addition of the hydroxyl group to yield the corresponding monohydroxylated derivatives. The formation of the dihydroxylated adduct is explained through the generation of a hydroperoxide

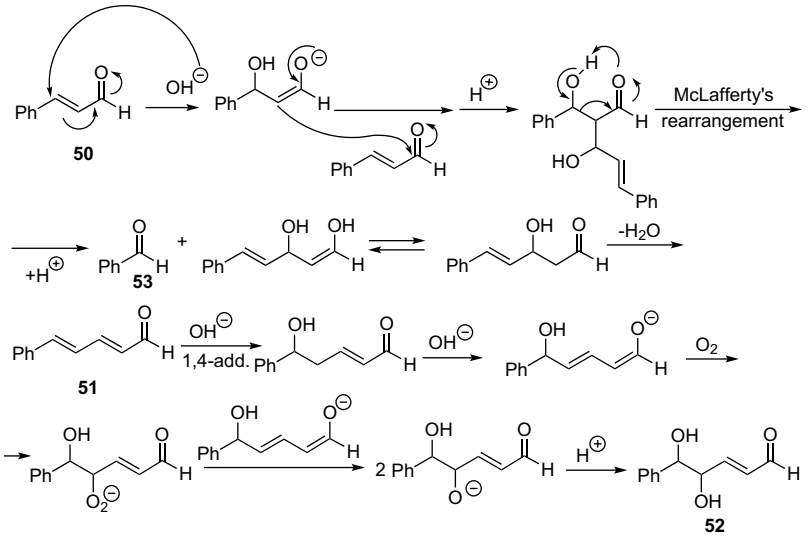


Figure 8.

intermediate obtained by trapping of molecular oxygen by the enol intermediate and dismutation. The role of HMPA as an effective chelator of the cationic counter ion is crucial to enhance the nucleophilicity of the hydroxyl group. The addition proceeds with all types of unsaturated carbonyl systems (lactones, ketones and aldehydes) but the scope of the reaction is challenged by the possibility of side polycondensations. Thus, its applicability is limited to substrates where the hydroxyl intermediates have the necessary level of steric hindrance to avoid the nucleophilic addition of the enolate with the remaining starting material or with other carbonyl intermediates.

4. Experimental

4.1. General

All reagents and solvents were used as obtained from commercial suppliers, apart from compound **37**. Dehydrocostuslactone (**37**) was isolated by column chromatography from Costus Resin Oil (Pierre Chauvet, S.A.) and purified by recrystallization from hexane/ethyl acetate mixtures. Solvents were distilled from glass prior to use. Column chromatography was performed on silica gel (35–75 mesh) and TLC analysis was carried out using aluminium-packed precoated silica gel plates. For HPLC, LiChrosorb silica 60 was used in the normal-phase mode with a differential refractometer (RI) in a Hitachi L-6020 HPLC instrument. ^{1}H and ^{13}C NMR spectra were recorded using a Varian UNITY-400 spectrometer (at 400 MHz and 100 MHz, respectively) and a Varian INOVA-200 spectrometer (at 200 MHz and 50 MHz, respectively) using $CDCl_3$ as solvent. The resonance of residual chloroform at δ_H 7.25 ppm in the ^{1}H and δ_C 77.00 ppm for $CDCl_3$ in the ^{13}C spectra was used as internal references. Mass spectra were obtained using a VG 1250 or a VG AUTOSPEC instruments at 70 eV. IR spectra were recorded on a Mattson 5020 spectrophotometer.

4.2. Hydroxylation of 37 with HMPA/Na_2CO_3 aq: general procedure

An aqueous solution of Na_2CO_3 (20%) was added dropwise to a solution of **37** (150 mg, 0.619 mmol) in HMPA (15 mL) until it remained turbid (15 mL). The reaction mixture was vigorously stirred and heated at 90–95 °C for 7 days, after which the equilibrium was established (as shown by TLC). Work up: the reaction mixture was extracted with AcOEt (5×) and the combined organic phases washed successively with 1 N aq HCl (3×), Na_2CO_3 (w/v, 3×) and brine (3×). The organic phase was dried over anhydrous Na_2SO_4, concentrated under vacuum and purified by column chromatography (CC, hexane/EtOAc 3:2), yielding **37** (30%), **38** (21%), **39** (30%) and **40** (6%).

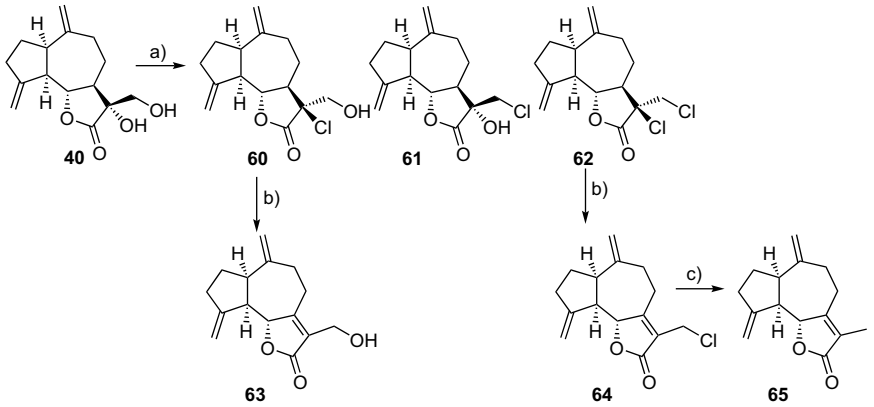


Figure 9. Key: (a) SO_2Cl, dry py, 70 °C, 24 h; (b) Li_2CO_3/LiCl, DMF, reflux; (c) TBTH, AIBN, toluene.

Table 3
^{13}C NMR chemical shifts of compounds **38–40**, **43** and **71–73**. (50.3 MHz, $CDCl_3$, signal of residual $CHCl_3$ centred at δ 77.0 ppm)[a]

C	38	39	40	43	71	72	73
1	51.8 d	52.1	52.5	47.1[b]	49.0	48.7	48.9
2	32.7 t	23.1	32.4	32.4	30.0	28.8	28.9
3	30.2 t	30.6	26.7	29.9	30.6	29.9	30.4
4	152.0 s	152.0	152.0	150.8	148.0	148.7[b]	149.3
5	47.0 d	14.3	48.1	51.0	51.2	51.0	51.6
6	85.6 d	85.6	83.9	83.4	81.1	80.8	80.6
7	49.6 d	48.0	50.8	47.3[b]			162.8
8	32.6 t	23.0	29.9	27.9	30.0	29.7	29.7
9	37.7 t	38.0	37.5	35.9	31.0	30.3	30.7
10	149.5 s	150.1	146.5	149	148.0	148.5[b]	149.3
11	43.1 d	43.7	77.0 s	66.3	124.6	123.0	123.0
12	177.5 s	176.5	177.5	183.3	164.8	168.8	174.1
13	59.2 t	67.8	63.2	67.4	55.0	33.1	8.6
14	109.1 t	109.2	109.8	110.2	112.9	113.7	113.1
15	112.0 t	112.2	112.0	112.7	112.0	112.7	112.2

Compound **41**: δ 128.1 (C-2′, C-6′); δ 130.1 (C-3′, C-5′); δ 145.9 (C-4′); δ 21.7 (Me–Ar).
[a] Degree of protonation and assignments were established by APT, HETCOR and HMQC experiments; multiplicities are not repeated if identical with those in the preceding column.
[b] May be interchanged within the same column.

*4.2.1. (11S)-13-Hydroxy-guaian-4(15),10(14)-diene-6,12-olide (**38**)*

$C_{15}O_3H_{20}$; amorphous white solid; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3425 (OH, st), 2929 (C–H), 1766 (γ-lactone), 1640 (C=C). HRMS calcd for $C_{15}O_3H_{20}$ 248.1412, found 248.1399; EIMS (70 eV) *m/z* (rel int.): 248 $[M]^+$ (2), 230 $[M-H_2O]^+$ (3), 218 $[M-CH_2O]^+$ (17). ^1H NMR (200 MHz): δ 5.19 (1H, br d, *J*=1.9 Hz, H-15), 5.04 (1H, dd, *J*=2.1, 0.8 Hz, H-15′), 4.87 (1H, s, H-14), 4.76 (1H, s, H-14′), 3.95 (1H, dd, *J*=9.3 Hz, H-6), 3.86 (1H, dd, *J*=3.3, 9.7 Hz, H-13), 3.69 (1H, dd, *J*=9.7, 2.8 Hz, H-13′), 2.90 (1H, ddd, *J*=4.8, 7.1, 11.6 Hz, H-1), 2.76 (1H, br dd, *J*=8.9 Hz, H-5), 2.16 (1H, m, H-8α), 1.88 (1H, m, H-2β), 1.33 (1H, ddd, *J*=2.9, 11.7 Hz, H-8β). ^{13}C NMR: see Table 3.

*4.2.2. (11R)-13-Hydroxy-guaian-4(15),10(14)-diene-6,12-olide (**39**)*

$C_{15}O_3H_{20}$; white crystals; mp ($CHCl_3$, uncorrected) 148–150 °C; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3390 (OH, st), 2931 (C–H), 1769 (γ-lactone), 1642 (C=C). HRMS calcd for $C_{15}O_3H_{20}$ 248.1412, found 248.1423; EIMS (70 eV) *m/z* (rel int.): 248 $[M]^+$ (3), 230 $[M-H_2O]^+$ (6), 218 $[M-CH_2O]^+$ (22). ^1H NMR (200 MHz): δ 5.16 (1H, br dd, *J*=1.9, 4.1 Hz, H-15), 5.03 (1H, br dd, *J*=2.1, 3.6 Hz, H-15′), 4.88 (1H, s, H-14), 4.78 (1H, s, H-14′), 4.00 (1H, dd, *J*=9 Hz, H-6), 4.00 (1H, br d, *J*=11.5 Hz, H-13), 3.73 (1H, dd, *J*=11.5, 4.5 Hz, H-13′), 2.88 (1H, ddd, *J*=8.0, 4.4 Hz, H-1), 2.82 (1H, dd, *J*=9.0 Hz, H-5), 2.51 (1H, m, H-3), 2.48 (1H, m, H-3), 2.44 (1H, br dd, *J*=4.2, 12.3 Hz, H-9β), 2.38 (1H, m, H-11), 2.33 (1H, dddd, *J*=4.9, 9.0, 12.1 Hz, H-7), 2.10 (1H, m, H-8α), 2.01 (1H, m, H-9α), 1.34 (1H, dddd, *J*=12.1, 10.9, 4.2 Hz, H-8β). ^{13}C NMR: see Table 3. X-ray analysis: complete tables of distances, angles, torsion angles, least-square planes, anisotropic thermal parameters and structure factors have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 667537). Copies may be obtained through the Executive Secretary. Bond lengths (Å) with e.s.d. values in parenthesis: O_1–C_6: 1.473(1); C_1–C_2: 1.541(3); C_3–C_4: 1.499(2); C_6–C_7: 1.522(2); C_9–C_{10}: 1.505(3); O_1–C_{12}: 1.334(2); C_1–C_5: 1.556(2); C_4–C_5: 1.520(2); C_7–C_8: 1.529(2); C_{10}–C_{15}: 1.332(3); O_2–C_{12}: 1.217(2); C_1–C_{10}: 1.521(3); C_4–C_{14}: 1.317(3); C_7–C_{11}: 1.534(2); C_{11}–C_{12}: 1.508(2); O_3–C_{13}: 1.411(4); C_2–C_3: 1.533(4); C_5–C_6: 1.514(2); C_8–C_9: 1.541(3); C_{11}–C_{13}: 1.511(3).

Bond angles (°) with e.s.d. values in parenthesis: C_6–O_1–C_{12}: 109.9(1); C_3–C_4–C_5: 109.0(2); O_1–C_6–C_5: 107.1(1); C_8–O_7–C_{11}: 113.5(2); C_7–C_{11}–C_{12}: 102.2(1); C_2–C_1–C_5: 102.3(1); C_3–C_4–C_{14}: 125.0(2); O_1–C_6–C_7: 104.3(1); C_7–C_8–C_9: 114.1(2); C_7–C_{11}–C_{13}: 116.9(2); C_2–C_1–C_{10}: 115.6(2); C_5–C_4–C_{15}: 126.0(1); O_2–C_{12}–C_{11}: 128.5(1); C_8–C_9–C_{10}: 115.1(2); C_{11}–C_{12}–C_{13}: 114.1(2); C_5–C_1–C_{10}: 114.5(1); C_1–C_5–C_4: 104.0(1); C_5–C_6–C_7: 108.5(1); C_1–C_{10}–C_9: 115.3(2); O_1–C_{12}–O_2: 121.0(1); C_1–C_2–C_3: 106.5(2); C_1–C_5–C_6: 158.8(1); C_6–C_7–C_8: 112.9(1); C_1–C_{10}–C_{15}: 123.4(2); O_1–C_{12}–C_{11}: 110.6(1); C_2–C_3–C_4: 105.7(2); C_4–C_5–C_6: 114.4(1); C_6–C_7–C_{11}: 101.4(1); C_9–C_{10}–C_{15}: 121.2(2); O_3–C_{13}–C_{11}: 109.2(2).

*4.2.3. (11R)-11,13-Dihydroxy-guaian-4(15),10(14)-diene-6,12-olide (**40**)*

$C_{15}O_4H_{20}$; amorphous white solid; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3382 (OH, st), 3085 (C–H, st), 2932 (C–H), 1748 (γ-lactone), 1642 (C=C). HRMS calcd for $C_{15}O_4H_{20}$ 264.1362, found 264.1364; EIMS (70 eV) *m/z* (rel int.): 264 $[M]^+$ (3), 246 $[M-H_2O]^+$ (1), 233 $[M-CH_3O]^+$ (18). ^1H NMR (200 MHz): δ 5.18 (1H, br d, *J*=1.8 Hz, H-15), 5.07 (1H, br d, *J*=2.1 Hz, H-15′), 4.89 (1H, br s, H-14), 4.79 (1H, br s, H-14′), 4.06 (1H, dd, *J*=8.9, 9.9 Hz, H-6), 3.80 (1H, d, *J*=11.4 Hz, H-13), 3.72 (1H, d, *J*=11.4 Hz, H-13′), 3.35 (1H, s, –O*H*), 2.88 (1H, ddd, *J*=8.9, 4.8 Hz, H-1), 2.83 (1H, dd, *J*=8.9 Hz, H-5), 2.51 (4H, m, H-3α, H-3β, H-7, H-9β), 2.10 (1H, ddd, *J*=4.4, 7.5, 11.9 Hz, H-8α), 1.84 (1H, m, H-2β), 1.41 (1H, ddd, *J*=4.6, 12.6 Hz, H-8β). ^{13}C NMR: see Table 3.

4.3. Hydroxylation of 39 with SeO_2/TBTPH

Treatment of **39** with SeO_2 (0.5 equiv) and *tert*-butylhydroperoxide (TBTPH) (2 equiv) in DCM (0.01 M) according to the previously reported conditions[4c] yielded after 1 h compounds **41** (63%) and **42** (12%).

*4.3.1. (3R,11R)-3,13-Dihydroxy-guaian-4(15),10(14)-diene-6,12-olide (**41**)*

$C_{15}O_4H_{20}$; amorphous white solid; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3450 (OH, st), 2930 (C–H), 1746 (γ-lactone), 1651 (C=C). HRMS calcd for $C_{15}O_4H_{20}$ 248.1412, found 248.1895; EIMS (70 eV) *m/z* (rel int.): 264 $[M]^+$ (2), 246 $[M-H_2O]^+$ (5), 228 $[M-2H_2O]^+$ (4). ^1H NMR (400 MHz): δ 5.35 (1H, dd, *J*=1.9 Hz, H-15), 5.29 (1H, dd, *J*=1.9 Hz, H-15′), 4.86 (1H, s, H-14), 4.68 (1H, s, H-14′), 4.63 (1H, dd, *J*=6.9 Hz, H-3), 3.96 (1H, dd, *J*=11.8, 3.3 Hz, H-13), 3.88 (1H, dd, *J*=9.3 Hz, H-6), 3.68 (1H, dd, *J*=11.8, 4.4 Hz, H-13), 3.06 (1H, m, H-5), 3.01 (1H, m, H-1), 2.45 (1H, ddd, *J*=12.9, 11.8, 4.1 Hz, H-9α), 2.37 (1H, m, H-7), 2.33 (1H, m, H-11), 2.15 (1H, m, H-2α), 2.10 (1H, m, H-8α), 1.99 (1H, ddd, *J*=12.9, 4.6, 4.1 Hz, H-9β), 1.83 (1H, ddd, *J*=13.2, 7.3, 6.9 Hz, H-2β), 1.27 (1H, dddd, *J*=12.6, 11.8, 4.6, 4.1 Hz, H-8β). ^{13}C NMR (100 MHz): δ 177.4 (C-12), 154.4 (C-4), 149.1 (C-10), 112.4 (C-14, C-15 overlapped), 85.9 (C-6), 7.4 (C-3), 58.6 (C-13), 49.6 (C-1), 49.3 (C-5), 43.6 (C-7)*, 43.1 (C-11)*, 39.7 (C-9), 38.0 (C-2), 32.4 (C-8). *: these values may be interchanged.

*4.3.2. (3R,11R)-1,3,13-Trihydroxy-guaian-4(15),10(14)-diene-6,12-olide (**42**)*

$C_{15}O_4H_{20}$; white crystals; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3280 (OH, st), 2932 (C–H), 1754 (γ-lactone), 1650 (C=C). HRMS calcd for $C_{15}O_5H_{20}$ 280.1311, found 280.1401; EIMS (70 eV) *m/z* (rel int.): 280 $[M]^+$ (1), 262 $[M-H_2O]^+$ (7), 244 $[M-2H_2O]^+$ (4). ^1H NMR (200 MHz): δ 5.53 (1H, dd, *J*=2.1, 1.2 Hz, H-15), 5.50 (1H, dd, *J*=2.1, 1.2 Hz, H-15′), 5.12 (1H, br s, H-14), 5.07 (1H, br s, H-14′), 4.60 (1H, br s, H-3β), 3.98 (1H, br d, *J*=11.3 Hz, H-13), 3.79 (1H, dd, *J*=10.0 Hz, H-6), 3.74 (1H, br dd, *J*=11.3, 4.5 Hz, H-13′), 3.02 (1H, d, *J*=10.0 Hz, H-5), 2.54 (1H, m, H-9α), 2.48 (1H, m, H-7), 2.40 (1H, m, H-2α), 2.38 (1H, m, H-9β), 2.15 (1H, dddd, *J*=13.3, 4.6 Hz, H-8α), 2.04 (1H, ddd, *J*=14.3, 6.3, 1.2 Hz, H-2β), 1.32 (1H, dddd, *J*=13.3, 11.4, 4.6 Hz, H-8β). X-ray analysis: complete tables of distances, angles, torsion angles, least-square planes, anisotropic thermal parameters and structure factors have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 697081). Copies may be obtained through the Executive Secretary.

4.4. Hydroxylation of 46

Compound **46** was obtained from costunolide as previously described.[39] Then, **46** was treated as **37**, yielding **47** (22%) and **48** (5%).

*4.4.1. (11R)-(1E,4E)-13,14-Dihydroxy-germacrane-1(10),4(5)-diene-6,12-olide (**47**)*

$C_{15}O_4H_{22}$; colourless oil; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3518 (OH, st), 2927 (C–H, st), 2851 (C–H), 1754 (γ-lactone). HRMS calcd for $C_{15}O_4H_{22}$ 248.1412, found 248.1895; EIMS (70 eV) *m*/*z* (rel int.): 266 $[M]^+$ (1), 248 $[M-H_2O]^+$ (4), 230 $[M-2H_2O]^+$ (4). ^1H NMR (400 MHz): δ 5.47 (1H, dd, *J*=7.8 Hz, H-1), 5.00 (1H, br d, *J*=9.9 Hz, H-5), 4.68 (1H, dd, *J*=9.9 Hz, H-6), 4.13 (1H, d, *J*=12.5 Hz, H-14), 4.03 (1H, d, *J*=12.5 Hz, H-14′), 3.98 (1H, dd, *J*=3.7, 11.6 Hz, H-13), 3.74 (1H, dd, *J*=5.2, 11.6 Hz, H-13′), 2.38 (1H, ddd, *J*=12.5, 5.2, 3.7 Hz, H-11), 1.85 (1H, d, *J*=1.1 Hz, H-15), 1.51 (1H, m, H-8β). ^{13}C NMR (100 MHz): δ 177.7 (C-12), 140.9 (C-4), 137.4 (C-10), 126.5 (C-1), 125.4 (C-5), 81.1 (C-6), 66.6 (C-14), 59.1 (C-13), 49.0 (C-11), 42.8 (C-7), 38.4 (C-9), 26.3 (C-8), 24.7 (C-3), 21.1 (C-2), 17.1 (C-15).

*4.4.2. (11R)-(1E,4E)-11,13,14-Trihydroxy-germacrane-1(10),4(5)-diene-6,12-olide (**48**)*

$C_{15}O_5H_{22}$; colourless oil; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3468 (OH, st), 2931 (C–H, st), 2864 (C–H), 1755 (γ-lactone). HRMS calcd for $C_{15}O_4H_{22}$ 248.1412, found 248.1895; EIMS (70 eV) *m*/*z* (rel int.): 282 $[M]^+$ (1), 264 $[M-H_2O]^+$ (1), 250 $[M-CH_3OH]^+$ (3). ^1H NMR (400 MHz): δ 5.47 (1H, dd, *J*=4.2 Hz, H-1), 4.95 (1H, br d, *J*=10.0 Hz, H-5), 4.83 (1H, dd, *J*=10.0 Hz, H-6), 4.14 (1H, d, *J*=12.8 Hz, H-13), 4.03 (1H, d, *J*=12.8 Hz, H-13′), 3.81 (1H, d, *J*=11.5 Hz, H-14), 3.77 (1H, d, *J*=11.5 Hz, H-13′), 1.92 (3H, s, H-15).

4.5. Hydroxylation of cinnamaldehyde (50)

The reaction was carried out as described above for the other SLs under various conditions (see Table 2), yielding in all cases a complex mixture of high molecular weight products. The major compound isolated was benzaldehyde **53**. Compounds **51** and **52** could be isolated as minor compounds after several tedious purifications by HPLC.

*4.5.1. (2E,4E)-5-Phenyl-penta-2,4-diene-1-al (**51**)*

$C_{11}OH_{10}$; colourless oil; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 2864 (C–H), 1680 (C=O). HRMS calcd for $C_{11}OH_{10}$ 158.3702, found 158.3895; EIMS (70 eV) *m*/*z* (rel int.): 158 $[M]^+$ (88), 129 $[M-:COH]^+$ (100), 128 $[M-:CHOH]^+$ (94). ^1H NMR (400 MHz): δ 9.61 (1H, d, *J*=7.9 Hz, H-1), 7.51 (2H, dd, *J*=7.9, 1.7 Hz, H-2′, H-6′), 7.37 (3H, H-3′, H-4′, H-5′), 7.26 (1H, ddd, *J*=15.1, 7.9, 3.0 Hz, H-3), 7.00 (1H, dd, *J*=15.1 Hz, H-4), 7.00 (1H, d, *J*=7.3 Hz, H-5), 6.26 (1H, dd, *J*=15.1, 7.9 Hz, H-2). ^{13}C NMR (100 MHz): δ 193.4 (C-1), 151.9 (C-3), 142.3 (C-5), 135.5 (C-1′), 132.6 (C-2), 129.7 (C-4), 128.9 (C-3′, C-5′), 127.5 (C-2′, C-6′), 126.1 (C-4′).

*4.5.2. (2E)-2,4-Dihydroxy-5-phenyl-hepta-2-ene-1-al (**52**)*

$C_{11}O_3H_{12}$; colourless oil; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 2931 (C–H, st), 2864 (C–H), 1685 (C=O). HRMS calcd for $C_{11}O_3H_{12}$ 192.0786, found 192.0618; EIMS (70 eV) *m*/*z* (rel int.): 174 $[M-H_2O]^+$ (15), 158 $[M-2H_2O]^+$ (22), 129 (100), 128 (81). ^1H NMR (400 MHz): δ 9.61 (1H, d, *J*=7.6 Hz, H-1), 7.37 (3H, m, H-3′, H-4′, H-5′), 7.30 (2H, dd, *J*=7, 1.5 Hz, H-2′, H-6′), 6.67 (1H, dd, *J*=15.9, 6.7 Hz, H-3), 6.44 (1H, dd, *J*=15.8, 7.7 Hz, H-2), 3.89 (1H, s, *J*=1.4 Hz, H-5), 3.58 (1H, dd, *J*=6.8, 1.8 Hz, H-2).

4.6. Hydroxylation of 53

4-Methoxychalcone **53** was purchased from Lancaster and treated according to the general methodology under conditions described in Table 3. Compounds **54**, **55a** and **55b** were obtained only in traces. Benzaldehyde **53** (28%) and *p*-methoxybenzaldehyde **59** (31%) were the major compounds, followed by **56** (20%), **57** (14%) and **58** (10%).

*4.6.1. 2,3-Dihydroxy-3-(4-methoxy-phenyl)-1-phenyl-1-oxa-propane (**54**)*

$C_{16}O_4H_{16}$; white powder; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3480 (O–H, st), 2918 (C–H), 1700 (C=O). HRMS calcd for $C_{11}O_3H_{12}$ 272.1049, found 272.1495; EIMS (70 eV) *m*/*z* (rel int.): 254 $[M-H_2O]^+$ (4), 238 $[M-H_2O-O^{\bullet}]^+$ (6), 149 $[p\text{-MeO–Ph–CO–CH}_2]^+$ (25), 135 $[p\text{-MeO–Ph–CO}]^+$ (51), 105 $[Ph–CO]^+$ (100), 77 $[Ph]^+$ (84). ^1H NMR (400 MHz): δ 7.91 (2H, dd, *J*=8.5, 1.5 Hz, H-2′, H-6′), 7.66 (1H, tt, *J*=7.6, 2.2 Hz, H-4′), 7.52 (2H, t, *J*=7.6 Hz, H-3′, H-5′), 7.47 (2H, d, *J*=8.8 Hz, H-2″, H-6″), 6.88 (2H, d, *J*=8.8 Hz, H-3″, H-5″), 5.37 (1H, dd, *J*=7.1, 2.2 Hz, H-3), 5.21 (1H, d, *J*=2.2 Hz, C_3–O*H*), 4.08 (1H, d, *J*=7.3 Hz, H-2), 3.80 (3H, s, –O*Me*). ^{13}C NMR (100 MHz): δ 198.0 (C-1), 134.2 (C-4′), 133.8 (C-1″), 130.4 (C-1′), 129.3 (C-2″, C-6″), 129.1 (C-3′, C-5′), 128.6 (C-2′, C-6′), 113.9 (C-3″, C-5″), 76.3 (C-3), 63.7 (C-2), 55.3 (–O*Me*).

*4.6.2. [3-(4-Methoxy-phenyl)-oxiranyl]-phenyl-methanone (**55a**)*

$C_{16}O_3H_{14}$; white powder; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 2931 (C–H, st), 2864 (C–H), 1700 (C=O), 1275 (epox., C–O–C). HRMS calcd for $C_{11}O_3H_{12}$ 254.0943, found 254.1112; EIMS (70 eV) *m*/*z* (rel int.): 254 $[M]^+$ (4), 238 $[M-O^{\bullet}]^+$ (6), 149 $[p\text{-MeO–Ph–CO–CH}_2]^+$ (25), 135 $[p\text{-MeO–Ph–CO}]^+$ (51), 105 $[Ph–CO]^+$ (100), 77 $[Ph]^+$ (84). ^1H NMR (400 MHz): δ 7.80 (2H, d, *J*=8.2, 1.3 Hz, H-2′, H-6′), 7.46 (1H, br t, *J*=8.2 Hz, H-4′), 7.35 (2H, t, *J*=8.2 Hz, H-3′, H-5′), 6.94 (2H, d, *J*=8.7 Hz, H-2″, H-6″), 6.72 (2H, d, *J*=8.7 Hz, H-3″, H-5″), 4.68 (1H, br d, *J*=6.1 Hz, H-2), 4.34 (1H, br d, *J*=6.1 Hz, H-3), 3.74 (3H, s, –O*Me*). ^{13}C NMR (100 MHz): δ 198.0 (C-1), 158.1 (C-4″), 136.0 (C-1″), 132.8 (C-4′), 131.3 (C-1′), 129.1 (C-2″, C-6″), 128.6 (C-3′, C-5′), 128.0 (C-2′, C-6′), 113.7 (C-3″, C-5″), 55.2 (–O*Me*), 49.5 (C-2), 44.2 (C-3).

*4.6.3. [3-(4-Methoxy-phenyl)-oxiranyl]-phenyl-methanone (**55b**)*

$C_{16}O_3H_{14}$; white powder; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 2931 (C–H, st), 2864 (C–H), 1700 (C=O), 1275 (epox., C–O–C). HRMS calcd for $C_{11}O_3H_{12}$ 254.0943, found 254.1024; EIMS (70 eV) *m*/*z* (rel int.): 254 $[M]^+$ (6), 238 $[M-O^{\bullet}]^+$ (19), 149 $[p\text{-MeO–Ph–CO–CH}_2]^+$ (23), 135 $[p\text{-MeO–Ph–CO}]^+$ (87), 105 $[Ph–CO]^+$ (93), 77 $[Ph]^+$ (100). ^1H NMR (400 MHz): δ 7.77 (2H, d, *J*=7.1, 1.5 Hz, H-2′, H-6′), 7.46 (1H, br t, *J*=7.3 Hz, H-4′), 7.30 (2H, t, *J*=7.7 Hz, H-3′, H-5′), 7.21 (2H, d, *J*=8.8 Hz, H-2″, H-6″), 6.82 (2H, d, *J*=8.8 Hz, H-3″, H-5″), 4.53 (1H, dd, *J*=5.6 Hz, $J_{2,OH}$=3.4 Hz, H-2), 3.82 (1H, br d, *J*=5.7 Hz, H-3), 3.74 (3H, s, –O*Me*). ^{13}C NMR (100 MHz): δ 135.7 (C-1″)*, 133.6 (C-1′)*, 133.3 (C-4′), 128.8 (C-2″, C-6″)†, 128.5 (C-3′, C-5′), 128.5 (C-2′, C-6′)†, 114.1 (C-3″, C-5″), 55.3 (–O*Me*), 48.0 (C-2), 48.8 (C-3). *,†: these values may be interchanged.

*4.6.4. 3-(4-Methoxy-phenyl)-1,5-diphenyl-pentane-1,5-dione (**56**)*

$C_{24}O_3H_{22}$; colourless oil; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 2931 (C–H, st), 1700 (C=O). HRMS calcd for $C_{24}O_3H_{22}$ 358.1569, found 358.1589; EIMS (70 eV) *m*/*z* (rel int.): 358 $[M]^+$ (2), 239 $[M-Ph–CO–CH_2^{\bullet}]^+$ (96), 105 $[Ph–CO]^+$ (100), 77 $[Ph]^+$ (70). ^1H NMR (400 MHz): δ 7.93 (4H, dd, *J*=8.6, 1.2 Hz, H-2′, H-2″, H-6′, H-6″), 7.53 (2H, tt, *J*=8.6, 1.2 Hz, H-4′, H-4″), 7.43 (4H, dd, *J*=8.6 Hz, H-3′, H-3″, H-5′, H-5″), 7.18 (2H, d, *J*=8.8 Hz, H-2′, H-6′), 6.80 (2H, d, *J*=8.8 Hz, H-3′, H-5′), 4.01 (1H, tt, *J*=7.0 Hz, H-3), 3.75 (3H, s, –O*Me*), 3.45 (2H, ddd, *J*=16.6, 6.8 Hz, H-2a, H-4a), 3.31 (2H, ddd, *J*=16.6, 7.2 Hz, H-2b, H-4b). ^{13}C NMR (100 MHz): δ 198.7 (C-1, C-5), 158.3 (C-4′), 137.1 (C-1′)*, 135.8 (C-1″)*, 133.0 (C-4′, C.4″), 128.6 (C-2′, C-2″, C-6′, C-6″), 128.4 (C-2′, C-6′), 128.1 (C-3′, C-3″, C-5′, C-5″), 127.6 (C-1′), 114.0 (C-3″, C-5″), 55.2 (–O*Me*), 45.2 (C-2, C-4), 36.6 (C-3). *: these values may be interchanged.

*4.6.5. 2-[Hydroxy-(4-methoxy-phenyl)-methylene]-3-(4-methoxy-phenyl)-1,5-diphenyl-pentane-1,5-dione (**57**)*

$C_{32}O_5H_{28}$; colourless oil; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3180 (*HO*–C=C, st), 2980 (C–H, st), 2892 (C–H), 1700 (C=O), 1612 (Ph–C=O–*C*=*C*–OH). HRMS calcd for $C_{32}O_5H_{28}$ 492.1937, found 374.1843$C_{24}O_4H_{21}^+$

[M−Ph–CO–CH_2]; EIMS (70 eV) *m*/*z* (rel int.): 374 [M−Ph–CO–CH_2]$^+$ (7), 239 [M−Ph–CO–CH_2–*p*-MeO–Ph–CO]$^+$ (96), 135 [*p*-MeO–Ph–CO]$^+$ (100), 105 [Ph–CO]$^+$ (37), 77 [Ph]$^+$ (36). ^{1}H NMR (400 MHz): δ 8.0 (2H, d, *J*=9.0 Hz, H-2^{IV}, H-6^{IV}), 8.0 (2H, d, *J*=9.0 Hz, H-2^{IV}, H-6^{IV}), 7.96 (4H, d, *J*=7.8 Hz, H-2′, H-2″, H-6′, H-6″), 7.53 (2H, tt, *J*=7.2, 1.2 Hz, H-4′, H-4″), 7.42 (4H, br t, *J*=7.3 Hz, H-3′, H-3″, H-5′, H-5″), 6.86 (2H, d, *J*=8.8 Hz, H-3′, H-5′), 6.82 (2H, d, *J*=8.6 Hz, H-3^{IV}, H-5^{IV}), 5.23 (1H, dd, *J*=9.8, 3.9 Hz, H-3), 4.13 (1H, dd, *J*=18.1, 9.4 Hz, H-4a), 3.81 (3H, s, –O*Me*), 3.74 (3H, s, –O*Me*), 3.24 (1H, dd, *J*=17.9, 3.9 Hz, H-3b).

4.6.6. 2,4-Bis-(4-methoxy-phenyl)-1,3-bis-benzoyl-cyclobutane (**66**)

$C_{32}O_4H_{28}$; colourless oil; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 2995 (C–H, st), 1700 (C=O). HRMS calcd for $C_{32}O_4H_{28}$ 476.1988, found 476.21805; EIMS (70 eV) *m*/*z* (rel int.): 476 [M]$^+$ (1), 370 [M−Ph–CO]$^+$ (3), 265 [M−2Ph–CO]$^+$ (3), 238 [*p*-MeO–Ph–C=C–CO–Ph]$^+$ (100), 108 [*p*-MeO–Ph]$^+$ (23), 105 [Ph–CO]$^+$ (48), 77 [Ph]$^+$ (40). ^{1}H NMR (400 MHz): δ 8.30 (2H, d, *J*=7.0 Hz, H-2″, H-6″), 7.68 (2H, d, *J*=7.1 Hz, H-2′, H-6′), 7.58 (2H, tt, *J*=7.5, 1.8 Hz, H-4″), 7.48 (4H, br t, *J*=7.1 Hz, H-3″, H-5″), 7.41 (1H, br t, *J*=7.3 Hz, H-4′), 7.29 (2H, t, *J*=6.1 Hz, H-3′, H-5′), 6.78 (2H, d, *J*=7.7 Hz, H-2^{IV}, H-6^{IV}), 6.76 (2H, d, *J*=8.5 Hz, H-2′, H-6′), 6.62 (2H, d, *J*=8.6 Hz, H-3^{IV}, H-5^{IV}), 6.44 (2H, d, *J*=8.8 Hz, H-3″, H-5″), 5.43 (1H, dd, *J*=9.6 Hz, H-1), 4.71 (1H, dd, *J*=9.5 Hz, H-2), 4.68 (1H, dd, *J*=9.8 Hz, H-4), 4.49 (1H, dd, *J*=10.0 Hz, H-3), 3.68 (3H, s, –O*Me*), 3.60 (3H, s, –O*Me*). ^{13}C NMR (100 MHz): δ 200.8 (2C=O), 157.9 (C-4^{IV})^a, 157.8 (C-4′)^a, 136.5 (C-1′)^b, 136.1 (C-1″)^b, 133.4 (C-4′)^c, 132.9 (C.4″)^c, 130.9 (C-1′)^d, 128.7 (C-3″, C-5″)^e, 128.6 (C-1^{IV})^d, 128.4 (C-2″, C-6″)^e, 128.3 (C-2′, C-6′)^e, 128.1 (C-2^{IV}, C-6^{IV})^e, 113.4 (C-3^{IV}, C-5^{IV})^f, 113.0 (C-3′, C-5′)^f, 55.1 (–O*Me*), 54.9 (–O*Me*), 47.9 (C-3)^g, 47.9 (C-1)^g, 44.2 (C-4)^h, 42.7 (C-2)^h. a, b, c, d, e, f, g, h: values with the same superscript may be interchanged.

4.7. Tosylation of 40

p-Toluensulfonyl chloride (500 mg, 2.623 mmol) was added to a solution of **40** (200 mg, 0.758 mmol) in dry pyridine. The reaction mixture was stirred at room temperature over 3 days. Work-up was as follows: the crude mixture was dissolved in ethyl acetate and washed with aqueous solutions of 1 N hydrochloric acid (3×), sodium hydrogen carbonate (10% w/v, 3×) and brine (3×). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude mixture chromatographed by CC yielding 180 mg of **41** (57%) and a 20 mg of **43** (6%). Compound **44** was recrystallized from hexane/AcOEt.

4.7.1. (11R)-11-Hydroxy-13-(p-toluensulfonate)-guaian-4(15),10(14)-diene-6,12-olide (**43**)

$C_{22}O_6SH_{26}$; white crystals; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3453 (OH), 2928 (C–H, st), 1761 (γ-lactone), 1344, 1170 (–SO_2 st. as., st. s.), 749 (C–C ar). HRMS calcd for $C_{22}O_6SH_{26}$ 418.1450, found 246.1518$C_{15}O_3H_{18}$ according to [M−$C_7O_3SH_8$]$^+$; EIMS (70 eV) *m*/*z* (rel int.): 246 [M−$C_7O_3SH_8$]$^+$ (10), 228 [M−$C_7O_3SH_8$−H_2O]$^+$ (2). ^{1}H NMR (200 MHz): δ 7.75 (2H, d, *J*=8.5 Hz, H-3′, H-5′), 7.35 (2H, d, *J*=8.1 Hz, H-2′, H-6′), 5.09 (1H, br d, *J*=1.8 Hz, H-15), 5.04 (1H, br d, *J*=1.8 Hz, H-15′), 4.88 (1H, br s, H-14), 4.79 (1H, br s, H-14′), 4.14 (1H, d, *J*=10.1 Hz, H-13), 4.00 (1H, d, *J*=10.0 Hz, H-13′), 4.00 (1H, dd, *J*=8.8, 9.7 Hz, H-6), 2.87 (1H, br dd, *J*=6.4 Hz, H-1), 2.76 (1H, dd, *J*=8.9 Hz, H-5), 1.44 (1H, dddd, *J*=3.3, 11.4 Hz, H-8β).

4.7.2. (11S)-11-Chloro-13-(p-toluensulphonate)-guaian-4(15),10(14)-diene-6,12-olide (**44**)

$C_{22}ClO_5SH_{25}$; white crystals; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 2932 (C–H, st), 1773 (γ-lactone), 1358, 1172 (–SO_2 st. as., st. s.), 805 (C–Cl), 742 (C–C ar). HRMS calcd for $C_{22}ClO_5SH_{25}$ 436.1111, found 436.1495; EIMS (70 eV) *m*/*z* (rel int.): 438 [M+2]$^+$ (2), 437 [M+1]$^+$ (7), 436 [M]$^+$ (18), 401 [M−Cl]$^+$ (2), 281 [M−$C_7O_2SH_7$]$^+$ (2), 264 [M−$C_7O_3SH_8$]$^+$ (3), 229 [M−$C_7O_3SH_8$−Cl]$^+$ (55). ^{1}H NMR (200 MHz): δ 7.78 (2H, d, *J*=8.3 Hz, H-3′, H-5′), 7.37 (2H, d, *J*=8.2 Hz, H-2′, H-6′), 5.15 (1H, br d, *J*=1.8 Hz, H-15), 5.06 (1H, br d, *J*=1.8 Hz, H-15′), 4.91 (1H, br s, H-14), 4.81 (1H, br s, H-14′), 4.25 (1H, d, *J*=10.6 Hz, H-13), 4.22 (1H, d, *J*=10.6 Hz, H-13′), 4.13 (1H, dd, *J*=9.3 Hz, H-6), 2.89 (1H, br dd, *J*=7.24 Hz, H-1), 2.83 (1H, dd, *J*=8.9 Hz, H-5), 2.62 (1H, ddd, *J*=3.6, 9.5, 11.2 Hz, H-7), 2.45 (3H, s, *Me*–Ar), 2.04 (1H, ddd, *J*=4.3, 12.3 Hz, H-9), 1.97 (2H, m, H-2β*, H-8α), 1.82 (1H, ddd, *J*=6.4, 8.7, 13.0 Hz, H-2α*), 1.61 (1H, ddd, *J*=4.4, 11.6 Hz, H-8β). ^{13}C NMR: see Table 3. Complete tables of distances, angles, torsion angles, least-square planes, anisotropic thermal parameters and structure factors have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 667538). Copies may be obtained through the Executive Secretary. Bond lengths (Å) with e.s.d. values in parenthesis: Cl–C_{11}: 1.802(1); O_2–C_{12}: 1.192(2); C_4–C_5: 1.516(2); C_9–C_{10}: 1.506(3); C_{16}–C_{21}: 1.379(3); S–O_3: 1.588(1); O_3–C_{13}: 1.444(4); C_4–C_{14}: 1.308(3); C_{10}–C_{15}: 1.327(3); C_{17}–C_{18}: 1.380(3); S–O_4: 1.420(2); C_1–C_2: 1.543(3); C_5–C_6: 1.513(2); C_{11}–C_{12}: 1.528(2); C_{19}–C_{22}: 1.501(3); S–O_5: 1.413(2); C_1–C_5: 1.554(2); C_6–C_7: 1.523(2); C_{11}–C_{13}: 1.508(2); C_{20}–C_{21}: 1.371(3); S–C_{16}: 1.753(2); C_1–C_{10}: 1.512(2); C_7–C_8: 1.524(2); C_{18}–C_{19}: 1.370(3); O_1–C_6: 1.473(2); C_2–C_3: 1.509(3); C_7–C_{11}: 1.530(2); C_{19}–C_{20}: 1.384(3); O_1–C_{12}: 1.340(2); C_3–C_4: 1.505(2); C_8–C_9: 1.528(3); C_{16}–C_{17}: 1.373(3).

Bond angles (°) with e.s.d. values in parenthesis: C_6–O_1–C_{12}: 111.3(1); C_1–C_5–C_6: 115.7(1); C_1–C_{10}–C_9: 115.3(2); O_3–S–O_4: 103.8(2); Cl–C_{11}–C_{12}: 104.3(1); C_2–C_1–C_5: 101.9(2); C_4–C_5–C_6: 114.8(1); C_1–C_{10}–C_{15}: 123.1(2); O_3–S–O_5: 108.63(9); Cl–C_{11}–C_{13}: 106.5(1); C_2–C_1–C_{10}: 116.6(2); O_1–C_6–C_5: 107.2(1); C_9–C_{10}–C_{15}: 121.6(2); O_3–S–C_{16}: 102.65(7); C_{17}–C_{16}–C_{21}: 120.0(2); C_5–C_1–C_{10}: 112.1(1); O_1–C_6–C_7: 104.9(1); C_7–C_{11}–C_{12}: 103.7(1); O_4–S–O_5: 121.0(1); C_{16}–C_{17}–C_{18}: 119.1(1); C_1–C_2–C_3: 107.7(2); C_5–C_6–C_7: 116.8(1); C_7–C_{11}–C_{13}: 116.8(1); O_4–S–C_{16}: 109.8(1); C_{17}–C_{18}–C_{19}: 121.8(2); C_2–C_3–C_4: 105.9(2); C_6–C_7–C_8: 114.2(1); C_{11}–C_{12}–C_{13}: 112.5(1); O_5–S–C_{16}: 109.3(1); C_{18}–C_{19}–C_{20}: 118.2(2); C_3–C_4–C_5: 108.4(2); C_6–C_7–C_{11}: 102.7(1); O_1–C_{12}–O_2: 122.8(1); S–O_3–C_{13}: 120.2(1); C_{18}–C_{19}–C_{22}: 121.1(2); C_3–C_4–C_{14}: 125.6(2); C_8–C_7–C_{11}: 116.0(1); O_1–C_{12}–C_{11}: 109.4(1); S–C_{16}–C_{17}: 121.2(1); C_{19}–C_{20}–C_{21}: 120.9(2); C_5–C_4–C_{14}: 125.9(1); C_7–C_8–C_9: 115.3(2); O_2–C_{12}–C_{11}: 127.8(1); S–C_{16}–C_{21}: 118.8(2); C_{20}–C_{19}–C_{22}: 120.8(2); C_1–C_5–C_4: 104.0(1); C_8–C_9–C_{10}: 115.2(2); O_3–C_{13}–C_{11}: 106.7(1); Cl–C_{11}–C_7: 112.5(1); C_{16}–C_{17}–C_{18}: 120.0(2).

4.8. Chlorination of 40

Compound **40** (150 mg, 0.568 mmol) was dissolved in dry pyridine (25 mL) and the mixture was vigorously stirred. A solution of $SOCl_2$ in dry pyridine (10% v/v) (1 mL) was added dropwise during 1 h. The reaction mixture was heated at 70 °C for 24 h. The work up was carried out as for the tosylation of **36**. Purification of the crude mixture by CC yielded **68** (8%), **69** (12%) and **70** (3%).

4.8.1. (11S)-11-Chloro-13-hydroxy-guian-4(15),10(14)-diene-6,12-olide (**68**)

$C_{15}ClO_3H_{19}$; amorphous solid; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3450 (OH, st), 2945 (C–H, st), 1765 (γ-lactone), 1636 (C=C), 775 (C–Cl). HRMS calcd for $C_{15}ClO_3H_{19}$ 282.1023, found 282.0995; EIMS (70 eV) *m*/*z* (rel int.): 282 [M]$^+$ (1), 264 [M−H_2O]$^+$ (5), 229 [M−H_2O−Cl]$^+$ (92). ^{1}H NMR (200 MHz): δ 5.13 (1H, br s, H-15), 5.02 (1H, br s, H-15′), 4.83 (1H, br s, H-14), 4.75 (1H, br s, H-14′), 4.15 (1H, dd, *J*=9.4 Hz, H-6), 3.68 (1H, d, *J*=11.2 Hz, H-13), 3.56 (1H, d, *J*=11.2 Hz, H-13′), 2.85 (1H, dd, *J*=9.4, 14.7 Hz, H-5), 2.71 (1H, dd, *J*=14.7 Hz, H-1).

*4.8.2. (11R)-11-Hydroxy-13-chloro-guian-4(15),10(14)-diene-6,12-olide (**69**)*

$C_{15}ClO_3H_{19}$; amorphous solid; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3429 (OH, st), 2939 (C–H, st), 1756 (γ-lactone), 1635 (C=C), 782 (C–Cl). HRMS calcd for $C_{15}ClO_3H_{19}$ 282.1023, found 282.1395; EIMS (70 eV) *m*/*z* (rel int.): 284 $[M+2]^+$ (3), 282 $[M]^+$ (9), 254 $[M-CO]^+$ (23), 246 $[M-HCl]^+$ (4), 233 $[M-CH_2Cl]^+$ (10). ^1H NMR (200 MHz): δ 5.12 (1H, br s, H-15), 5.00 (1H, br s, H-15′), 4.83 (1H, br s, H-14), 4.74 (1H, br s, H-14′), 4.07 (1H, dd, *J*=9.9 Hz, H-6), 3.56 (2H, s, H-13, H-13′), 2.80 (2H, m, H-1, H-5), 2.56 (3H, m, H-2α, H-7, H-9α), 2.52 (1H, m, H-3α), 1.67 (1H, dddd, *J*=4.6, 12.6 Hz, H-8β).

*4.8.3. (11R)-11,13-Dichloro-guian-4(15),10(14)-diene-6,12-olide (**70**)*

$C_{15}Cl_2O_2H_{18}$; amorphous solid; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 2949 (C–H, st), 1779 (γ-lactone), 1637 (C=C), 731 (C–Cl). HRMS calcd for $C_{15}Cl_2O_2H_{18}$ 300.0684, found 300.0817; EIMS (70 eV) *m*/*z* (rel int.): 302 $[M+2]^+$ (28), 300 $[M]^+$ (38), 264 $[M-Cl]^+$ (30), 229 $[M-Cl-HCl]^+$ (16). ^1H NMR (200 MHz): δ 5.19 (1H, br s, H-15), 5.07 (1H, br s, H-15′), 4.90 (1H, br s, H-14), 4.81 (1H, br s, H-14′), 4.15 (1H, dd, *J*=8.9, 10.0 Hz, H-6), 3.64 (2H, s, H-13, H-13′), 2.86 (2H, m, H-1, H-5), 2.60 (1H, m, H-3α), 2.50 (3H, m, H-2α, H-7, H-9α), 1.60 (1H, m, H-8β).

4.9. Dehydrohalogenation of 68 and 70

Each compound (50 mmol) was dissolved in dry DMF (5 mL) and the solution was vigorously stirred. The Li_2CO_3/LiCl (100 mg) was added and the mixture was heated at 120 °C for 1 h. Purification of the crude product yielded **71** (84%) and **72** (96%), respectively.

*4.9.1. 13-Hydroxy-guaian-4(15),7(11),10(14)-triene-6,12-olide (**71**)*

$C_{15}O_3H_{18}$; amorphous solid; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 3196 (OH, st), 2926 (C–H, st), 1725 (γ-lactone), 1650 (C=C). HRMS calcd for $C_{15}O_3H_{18}$ 246.1256, found 246.1149; EIMS (70 eV) *m*/*z* (rel int.): 247 $[M+1]^+$ (32), 246 $[M]^+$ (10), 228 $[M-H_2O]^+$ (100). ^1H NMR (200 MHz): δ 5.19 (1H, br s, H-15), 5.13 (1H, br s, H-15′), 4.98 (1H, br s, H-14), 4.94 (1H, br s, H-14′), 4.69 (1H, dd, *J*=11.2 Hz, H-6), 4.52 (1H, d, *J*=16.1 Hz, H-13), 4.37 (1H, d, *J*=16.1 Hz, H-13′), 3.01 (1H, ddd, *J*=3.7, 7.2, 17.1 Hz, H-8β), 2.91 (1H, ddd, *J*=7.4, 12.0 Hz, H-1), 2.43 (1H, dddd, *J*=2.4, 8.3, 10.5 Hz, H-3α), 2.23 (1H, ddd, *J*=8.2, 10.2, 14.0 Hz, H-9α), 2.03 (1H, dddd, *J*=2.6, 9.0, 12.0 Hz, H-2α), 1.85 (1H, dddd, *J*=9.7, 10.9, 12.6 Hz, H-2β). ^{13}C NMR: see Table 3.

*4.9.2. 13-Chloro-guaian-4(15),7(11),10(14)-triene-6,12-olide (**72**)*

$C_{15}ClO_2H_{17}$; amorphous solid; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 2947 (C–H, st), 1737 (γ-lactone), 1645 (C=C), 778 (C–Cl). HRMS calcd for $C_{15}ClO_2H_{17}$ 264.0917, found 264.1122; EIMS (70 eV) *m*/*z* (rel int.): 266 $[M+2]^+$ (32), 264 $[M]^+$ (4), 229 $[M-Cl]^+$ (15), 236 $[M-CO]^+$ (13). ^1H NMR (200 MHz): δ 5.18 (1H, br s, H-15), 5.12 (1H, br s, H-15′), 4.98 (1H, br s, H-14), 4.95 (1H, br s, H-14′), 4.71 (1H, d, *J*=10.2 Hz, H-6), 4.24 (1H, d, *J*=11.8 Hz, H-13), 4.20 (1H, d, *J*=12.0 Hz, H-13′), 3.03 (1H, ddd, *J*=3.6, 7.6, 17.5 Hz, H-8β), 2.91 (1H, ddd, *J*=7.1, 12.8 Hz, H-1), 2.64 (1H, ddd, *J*=4.5, 9.7, 17.5 Hz, H-8α), 2.59 (1H, m, H-3β), 2.56 (1H, m, H-5), 2.52 (1H, m, H-9β), 2.44 (1H, ddddd, *J*=2.4, 8.2, 10.6 Hz, H-3α), 2.26 (1H, ddd, *J*=3.6, 9.4, 13.2 Hz, H-9α), 2.02 (1H, dddd, *J*=2.7, 6.3, 8.9, 12.5 Hz, H-2α), 1.84 (1H, dddd, *J*=9.9, 11.5, 12.9 Hz, H-2β). ^{13}C NMR: see Table 3.

4.10. Reduction of 72 with TBTH

A 1 M solution of tributyltin hydride (TBTH, 0.4 mmol) (400 μL) in toluene and a catalytic amount of azaisobutyronitrile (AIBN) were added to a solution of **72** (100 mg, 0.379 mmol) in dry toluene (15 mL). The reaction mixture was heated under reflux for 2 h. Work up was as follows: the solvent was evaporated under vacuum and the residue was diluted with acetonitrile; the solution was washed twice with light petroleum and the final acetonitrile phase was evaporated under reduced pressure. The crude product was chromatographed by CC (hexane/AcOEt) yielding 85% of **73**.

*4.10.1. Guaian-4(15),7(11),10(14)-triene-6,12-olide (**73**)*

$C_{15}O_2H_{18}$; amorphous solid; IR $\nu_{max}^{neat,\ KBr}$ cm^{-1}: 2948 (C–H, st), 1727 (γ-lactone), 1644 (C=C). HRMS calcd for $C_{15}O_2H_{18}$ 230.1307, found 230.1518; EIMS (70 eV) *m*/*z* (rel int.): 230 $[M]^+$ (4). ^1H NMR (200 MHz): δ 5.17 (1H, ddd, *J*=1.2, 2.3, 3.5 Hz, H-15), 5.10 (1H, br s, *J*=1.1, 2.1, 3.2 Hz, H-15′), 4.94 (1H, br s, H-14), 4.91 (1H, dd, *J*=1.4 Hz, H-14′), 4.62 (1H, br d, *J*=11.1 Hz, H-6), 2.89 (1H, m, H-1), 2.84 (1H, m, H-8β), 2.60 (1H, ddddd, *J*=1.2, 2.5, 4.9, 9.6, 17.1 Hz, H-3β), 2.50 (3H, m, H-5, H-8α, H-9β), 2.43 (1H, ddddd, *J*=2.5, 8.6, 10.0 Hz, H-3α), 2.21 (1H, dddd, *J*=3.7, 11.9 Hz, H-9α), 1.99 (1H, dddd, *J*=2.7, 6.6, 9.4, 12.9 Hz, H-2α), 1.84 (1H, dddd, *J*=9.9, 11.4, 12.8 Hz, H-2β), 1.78 (3H, br s, H-13). ^{13}C NMR: see Table 3.

4.11. Molecular modelling

Minimum energy conformations and molecular properties were obtained using MM2 and MOPAC calculations (Chem3D ULTRA ver. 7.0©, 2001 Cambridge Soft, Cambridge, MA, USA; MOPAC, ver. 6.00). Spatial geometry was optimized using MM2 calculations. Heats of formation were obtained by semiempiric minimization with MOPAC using the PM3 method. For semiempiric calculations the parameters PRECISE, GEO-OK, and *T*=86,400 were used.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.024.

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