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Synthesis and Antitumor Activity of Puupehedione and Related Compounds#

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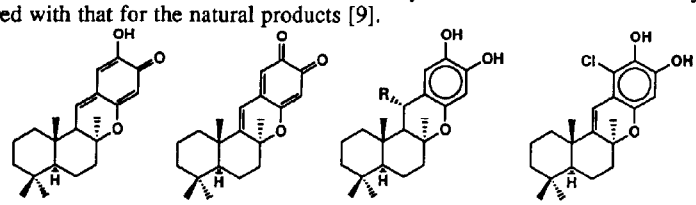
Abstract:

The first enantiospecific synthesis of bioactive marine puupehedione (**2**) and related compounds from (-)-sclareol (**11**) is reported. The antitumor activity of these compounds was assayed and compared with that of the natural products.

Keywords: Terpenes; antitumour compounds; marine metabolites.

Introduction

Over the last few years marine flora and fauna have proven to be an unexploited source of compounds showing a great variety of chemical structures and a wide range of biological activities [1]. Among these, those substances which consist of drimane and polyphenolic moieties have attracted our attention because, despite their apparent structural simplicity, they are among the most active marine metabolites showing a wide range of potent biological activities, including cytotoxic, antifungal, inmunomodulatory or cholesteryl ester transfer protein (CETP) inhibitory properties. Some representative examples of this type of substances are (+)-puupehenone (**1**) and related compounds such as puupehedione (**2**), puupehediol (**3**), cyanopuupehenol (**4**), 15-oxo-puupehenol (**5**) or 21-chloropuupehediol (**6**) [2,3]; wiedendiol A (**7**) and wiedendiol B (**8**) are also related metabolites [4,5]. Over the last few years our group has developed enantiospecific syntheses for compounds **1**, **7**, and **8** from labdane diterpenes [6-8]. Moreover, the present authors have prepared monoterpenic analogues of **1** and **2**, such as **9** and **10** and assayed their antitumoral activity which was compared with that for the natural products [9].



1 **2** **3** R: H; **4** R: CN; **5** R: =O **6**

In memoriam of Professor Joaquin de Pascual Teresa (University of Salamanca, Spain)

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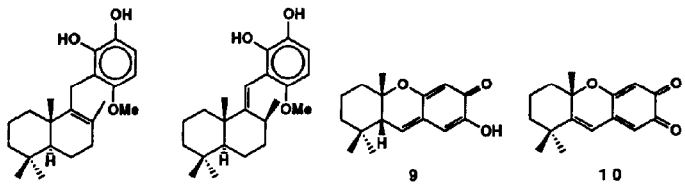
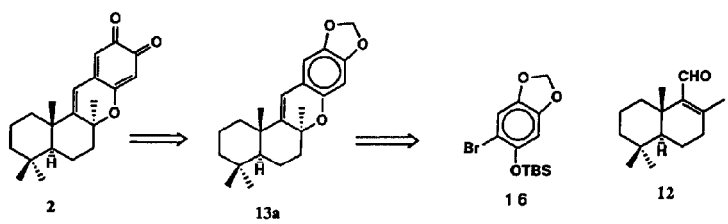


In this paper the first enantiospecific synthesis of the Verongid sponge metabolite puupehedione (**2**) from (-)-sclareol (**11**), and using different strategies, is described. A number of related compounds are also prepared and their antitumor activities assayed and compared with those reported for related natural products.

Results and Discussion

A first route to **2** was planned on the basis of the previous results from the present authors and from studies described in the literature. The efficient synthesis of **10** from β-cyclocitral and the aryllithium derived from **16** [9], besides the research published by Trammel concerning the synthesis of puupehenone (**1**) by acid-mediated cyclization of sesamol derivatives [10] prompted us to design the retrosynthesis shown in Scheme 1. The merosesquiterpene skeleton is generated by condensation of the drimanic aldehyde **12** [7,8] with the aryllithium derived from **16**. **13a** will be converted into puupehedione (**2**), following the same methodology described for **10** [9].

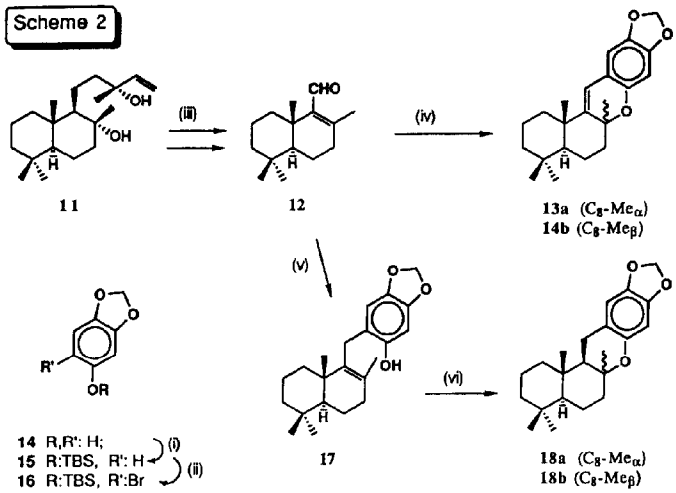
Scheme1



The aromatic synthon **16** was prepared in high yield from sesamol (**14**) by bromination of the intermediate *t*-buthyldimethylsilylether **15** with *N*-bromosuccinimide. Condensation of aryllithium derived from **16** with the aldehyde **12** gave a crude which after treating with p-toluenesulphonic acid afforded the mixture of epimers **13a** and **13b**. The configuration at C-8 of **13b** was established by mono and bidimensional nOe experiments. The relative proportion of these isomers depends upon the reaction temperature, but the puupehedione precursor **13a** was always the minor component (Scheme 2).

In view of the low proportion of **13a** obtained following the above sequence, a different synthetic strategy based on Trammel's methodology [10], which uses **17** as an intermediate, was planned. This author described that β-naphthalenesulphonic acid-mediated

Scheme 2



(i) TBSCl, imidazole, DMF, rt, 14 h (92 %). (ii) NBS, silica gel, CCl_4, rt, 10 min (96 %).(iii) Ref. [8]. (iv) t-BuLi, **16**, Et_2O, -78°C, 45 min, Ar; **12**, -78°C, 1 h: TsOH, benzene, rt, 16 h (92 %). (v) t-BuLi, **16**, Et_2O, -78°C, 45 min, Ar; **12**, -78°C, 1 h; Et_3SiH, TFA, CH_2Cl_2, -78°C, 45 min; TBAF, THF, rt, 10 min (86 %). (vi) Acid (76-93 %).

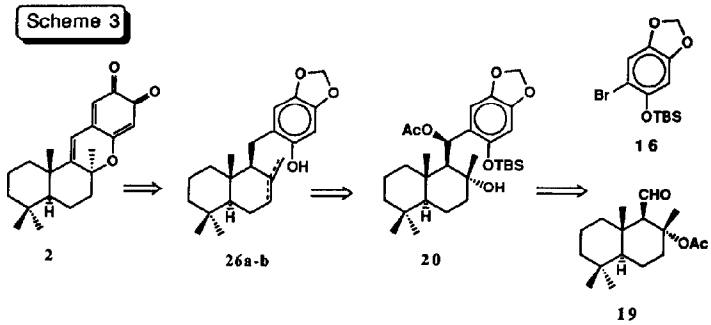
cyclization of **17** lead to a 2.4:1 mixture of epimers Meα-C8 and Meβ-C8. The phenol **17** was prepared by condensation of aryllithium derived from **16** with the aldehyde **12**, reduction of the resulting hydroxyl group and deprotection of the *tert*-butyldimethylsilyl group. The acid mediated cyclization of **17** under different conditions was studied (Scheme 2) and the most significant results are set out in Table 1. As may be seen, the natural product precursor **18a** was the minor component of crude reaction in all cases. The β disposition of methyl on C-8 was established by NOESY experiments. **18b** was the only product when etherate-boron trifluoride was used as a cyclizing agent. These results suggest that under kinetic and thermodynamic conditions the main product arises from the hydroxyl attack on the less hindered α side.

Table 1. Acid mediated cyclization of **17**

Acid	Solvent	Temperature	Time	Compound (%)
$BF_3.Et_2O$	CH_2Cl_2	0°C	15 min	**18b** (85)
2-Naphthalenesulph	CH_2Cl_2	Reflux	2 h	**18a-b** (1:2.4) (76)
TsOH	Benzene	Reflux	50 h	**18a-b** (1:4) (90)
Conc. SO_4H_2	Nitropropane	0-10°C	30 min	**18a-b** (1:9) (93)

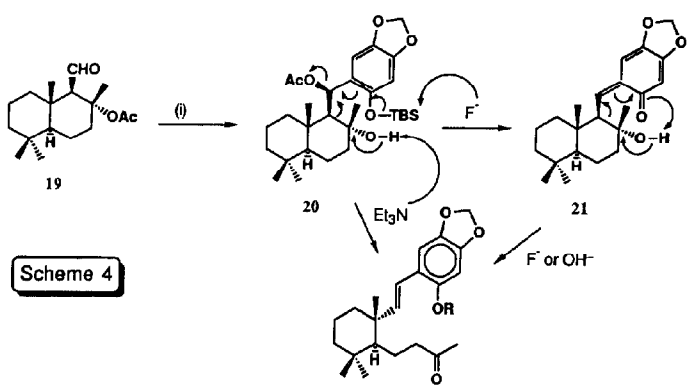
The unfavourable stereoselectivity observed during the cyclization of tetrasubstituted derivative **17**, inclined us to try the cyclization of the related di- and trisubstituted **26a-b**, generated by elimination of an oxygenated function on C-8. The new retrosynthetic sequence is depicted in Scheme 3. The puupehedione skeleton is now prepared by condensation of acetoxyaldehyde **19** with the aryllithium derived from **16**, which will provide the acetoxyalcohol **20**, which could be easily converted into **26a-b** [11,12].

Scheme 3



Condensation of aryllithium derived from **16** with the acetoxyaldehyde **19**, the efficient preparation of which from (-)-sclareol (**11**) has already been described [12], afforded the acetoxyalcohol **20** in a high yield, which demonstrated considerable instability. Thus, compounds **21** and **22** were eluted when **20** was chromatographed on silicagel (Scheme 4). In view of this result, the chemical behaviour of **20** under different basic and acid conditions was studied before achieving its dehydration to the di- and trisubstituted substrates **26a-b** of cyclization. The most relevants results are shown in Table 2.

Scheme 4



(i) t-BuLi, **16**, Et_2O, -78°C, 45 min, Ar; **19**, Et_2O, -78°C, 45 min.

Table 2. Treatment of **20** with acids and bases

Reagent	Solvent	Temperature	Time	Product (%)
Resine (H^+)	THF	Reflux	45 min	**22** (95)
KOH	MeOH	r.t.	30 min	**22** (86)
Et_3N	DME	Reflux	2 h	**23** (92)
Pyridine	Pyridine	r.t.	10 h	No Reaction
TBAF	THF	r.t.	1 h	**22** (87)

As may be seen, **20** underwent Grob scission [13] to give the methylketone **23**, when it was treated with triethylamine. Simultaneous deprotection of silylether took place when stronger bases or acids were used, resulting in **22**. The possible mechanism for these transformations is shown in Scheme 4. **21** is postulated as an intermediate, even though its presence was not detected. The formation of **22** from **21**, being prepared by treating **20** with silicagel, when it was treated with base was in agreement with this suposition.

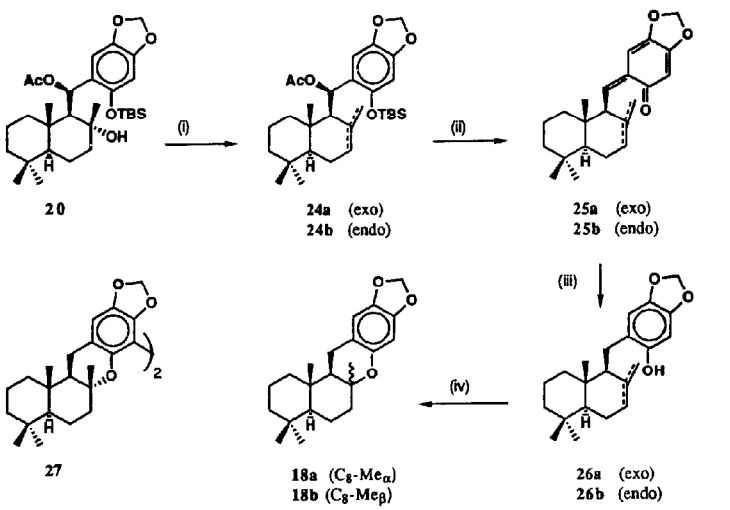
Next dehydration of acetoxyalcohol **20** under different conditions was studied (Table 3). These reactions were carried out in pyridine taking into account the unreactivity of this base against **20**. In all cases a regioisomer mixture (**24a-b**) was obtained, with the endocyclic alkene being in a minority.

Table 3. Dehydration of **20**

Reagent	Solvent	Time	**24a-b** (%)
$POCl_3$	Pyridine	2 h	(3:2) (70)
MsCl	Pyridine	12 h	(3:1) (55)
$SOCl_2$	Pyridine	1 h	(2:1) (92)

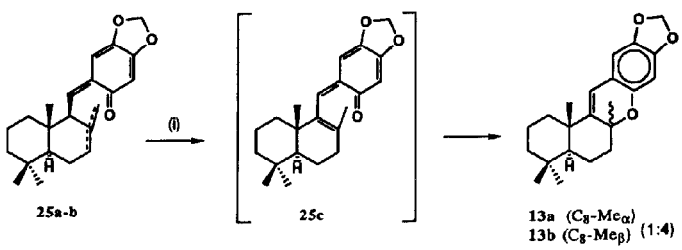
Deprotection of phenolic hydroxyl of **24a-b** with tetrabutylammonium fluoride afforded the regioisomer alkylidencyclohexadienones **25a-b** in a high yield (Scheme 5). This result is in agreement with the behaviour of **20** when it is chromatographed on silicagel and supports the proposed mechanism in Scheme 4. Reduction of **25a-b** with sodium borohydride gave phenols **26a-b**, which were cyclized under acid conditions. The dependence of the cyclization process on the acid nature is observed again. **18b**, along with small quantities of the dimer **27**, was obtained when etherate-boron trifluoride was used. A 1:4 mixture of **18a-b** was obtained when p-toluenesulphonic acid in refluxing benzene was used as the cyclizing acid; it should be pointed out that the relative proportion of C-8 epimers was independent from the exo/endo ratio of alkenes under cyclization. Variable quantities of tetrasubstituted phenol **17** were also obtained during the reaction, which suggests that the cyclization of di- and tetrasubstituted alkenes **26a** and **26b** is slow, being partially isomerized to the tetrasusbtituted compound **17**, which then underwent fast cyclization. On the basis of this isomerization, **25a-b** was converted into a 1:4 mixture of regioisomers **13a-b**, *via* an electrocyclic proccess (Scheme 6) [9].

Scheme 5



(i) $SOCl_2$, Py, rt, 1 h (92 %). (ii) TBAF, THF, rt, 15 min (94 %). (iii) $NaBH_4$, EtOH, rt, 30 min (89 %). (iv) Acid (86-90 %).

Scheme 6

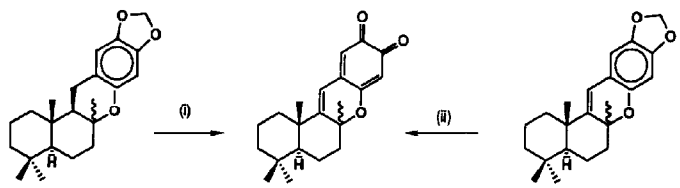


(i) TsOH, benzene, reflux, 15 min (93 %).

Finally, the transformation of cyclic compounds **13a-b** and **18a-b** into puupehedione (**2**) and 8-epipuupehedione (**28**) was undertaken. The oxidative rupture of the methylenedioxy group to the o-quinone system was achieved following a methodology developed by the present authors [9]. Unfortunately, again the major compound is the C8-Meβ epimer. A 1:4 mixture of epimers **2** and **28** was obtained when **13a-b** or **18a-b** were treated with DDQ

and p-toluenesulphonic acid in refluxing dioxane (Scheme 7); the stereochemistry was established by comparison of the NMR data with those reported in the literature [2]. It should be pointed out that the relative proportion of **2** and **28** was not dependent on the C-8 epimeric ratio for the starting compounds. Thus, when **18b** was reacted under these conditions gave **2** and its 8-epimer **28** in the same 1:4 relative proportion. It proves that this process involves ring opening and subsequent cyclization.

Scheme 7



18a (C_8-Me_α) **18b** (C_8-Me_β) (1:3)

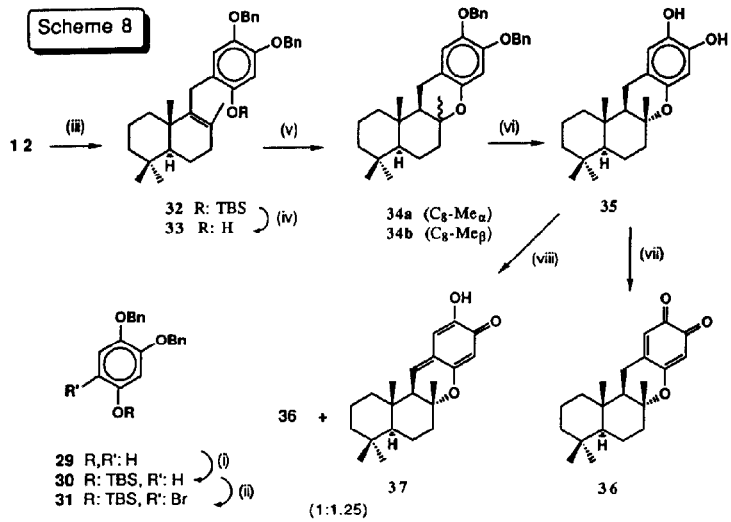
28 (C_8-Me_α) **2** (C_8-Me_β) (1:4)

13a (C_8-Me_α) **13b** (C_8-Me_β) (1:1)

(i) DDQ, TsOH, dioxane, reflux, 1 h 40 min (85 %). (ii) DDQ, TsOH, dioxane, reflux, 1 h (74 %).

It may be summarized that acid-mediated cyclizations of phenolic alkenes **17** and **26a-b** have not the suitable stereoselectivity to achieve the natural epimer, which was obtained as a 20% of the epimer mixture. This result induced us to investigate alternative routes to reach a more favourable stereoselectivity, including the use of a protective group for diphenol, the removal of which takes place under less strong conditions than those required by the previously used methylenedioxy group.

The bromoderivative **31** was prepared as an alternative aromatic synthon to **16**. It was easily prepared from phenol **29** [8] by silylation and further treatment with *N*-bromosuccinimide. The synthesis of the puupehedione precursor **33** was planned following a procedure similar to that previously used for the sesamol derivative. Condensation of aldehyde **12** with the aryllithium derived from **31** and subsequent cationic reduction of the resulting allylic alcohol afforded **32**, which after treating with tetrabutylammonium fluoride gave **33** (Scheme 8). Prior to the research into the electrophilic cyclization of **33** induced by reagents other than acids, the behaviour of this tetrasubstituted alkene against acidic reagents was revised (Table 4). As may be seen the process is highly stereoselective, affording the 8-epiderivative **34b** as the only product in most cases. The configuration at C-8 was established through nOe experiments again. It should be pointed out that the stereochemistry at this carbon may be easily established by analyzing the ^1H NMR spectrum, which show for each stereoisomer a different pattern for the signals of benzyl methylene: these protons appear as a doublet and a double doublet for the C_8-Me_α derivative, whereas they cause only a doublet in the spectrum of the C_8-Me_β derivative. Moreover, cyclization was faster than that for the methylenedioxyderivatives, such as **17**, which reflects the lower acidity of the *O*-benzylderivatives.



(i) Imidazole, anh. DMF, rt, 20 min; TBSCl, rt, 15 h (92 %). (ii) NBS, silica gel, anh. CCl_4, rt, 15 min (97 %). (iii) t-BuLi, **31**, Et_2O, -78°C, 50 min, Ar; **12** Et_2O, -78°C, 40 min; Et_3SiH, TFA, CH_2Cl_2, -78°C, 45 min (79 %). (iv) TBAF, THF, rt, 15 min (95 %). (v) Acid (87-92 %). (vi) BF_3-Et_2O, EtSH, rt, 2.5 h (91 %). (vii) Jones, acetone, 0°C, 30 min (87 %). (viii) DDQ, dioxane, rt, 25 min.

Table 4. Acid-mediated cyclization of **33**

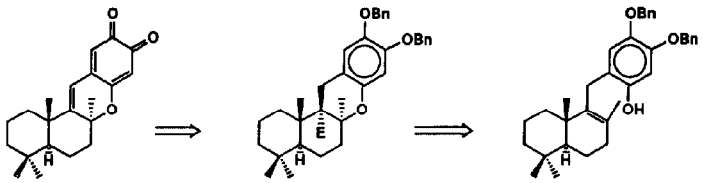
Reagent	Solvent	Temperature	Time	Product (%)
β-Naphthalenesulph	CH_2Cl_2	Reflux	30 min	**34a-b** (1:9) (92)
Conc. SO_4H_2	Nitropropane	0-10 °C	25 min	**34b** (93)
TsOH	Benzene	Reflux	50 h	**34b** (90)

The treatment of β-epimer **34b** with ethanethiol and etherate-boron trifluoride yielded 8-epipuupehenol (**35**). In order to establish the viability of achieving the oxidation level of puupehedione (**2**), **35** was subjected to different oxidation reactions. The treatment of **35** with Jones reagent gave 8-epi-9-dihydropuupehedione (**36**) in a high yield. The same result was obtained when cerium ammonium nitrate (CAN) was used as the oxydizing agent. A 1:1.25 mixture of the oxidation products **36** and 8-epipuupehenone (**37**) was obtained when **35** was reacted with DDQ in dioxane at room temperature (Scheme 8). These results demonstrate the difficulty of preparing puupehedione (**2**) by oxidation of the inmediate precursors and forced us to try the cyclization induced by alternatives electrophiles.

The new retrosynthetic strategy towards puupehedione (**2**) is shown in Scheme 9. The C_9-C_{11} double bond of **2** will be formed by the elimination of the eletrophile E, introduced

to achieve the regio and stereospecific cyclization in **33**. A suitable electrophile may attack on the less hindered α side of tetrasubstituted double bond of **33**, thus favoring the phenolic oxygen attack on C-8 by the β side.

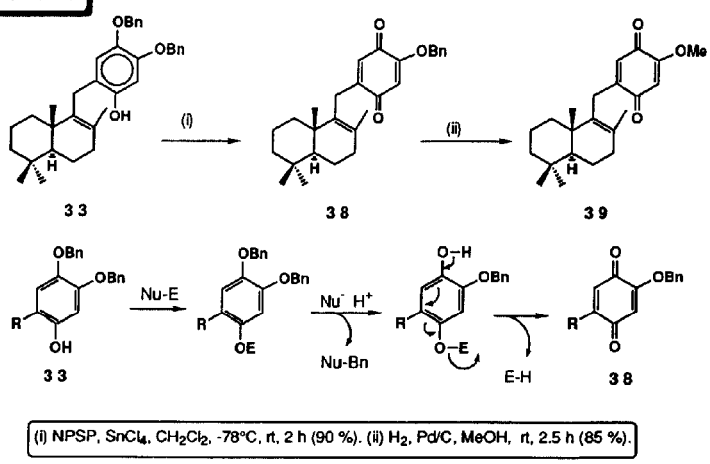
Scheme 9



2 **33**

Selenium-induced cyclization was first attempted. The treatment of **33** with *N*-phenylselenophthalimide (NPSP) or phenylselenyl chloride at -30°C or higher temperatures afforded the quinone **38** as the only product; no reaction took place at lower temperature. The ^{1}H NMR spectrum of **38** showed a singlet at δ 1.45, due to the methyl on the carbon-carbon double bond, and two singlets at 6.0 and 6.4 ppm, corresponding to the quinone protons; the ^{13}C NMR spectrum confirmed the presence of the quinone ring, showing olefinic methynes at δ 109.1 and 131.0, quaternary carbons at 149.6 and 157.6 ppm, and the carbonyl groups at 182.8 and 187.9 ppm. The methoxyderivative **39** was formed when deprotection of benzyl ether was tried by catalytic hydrogenation. **38** was also obtained when iodine was used to induce the cyclization (Scheme 10). A possible mechanism for this transformation is depicted in Scheme 10.

Scheme 10



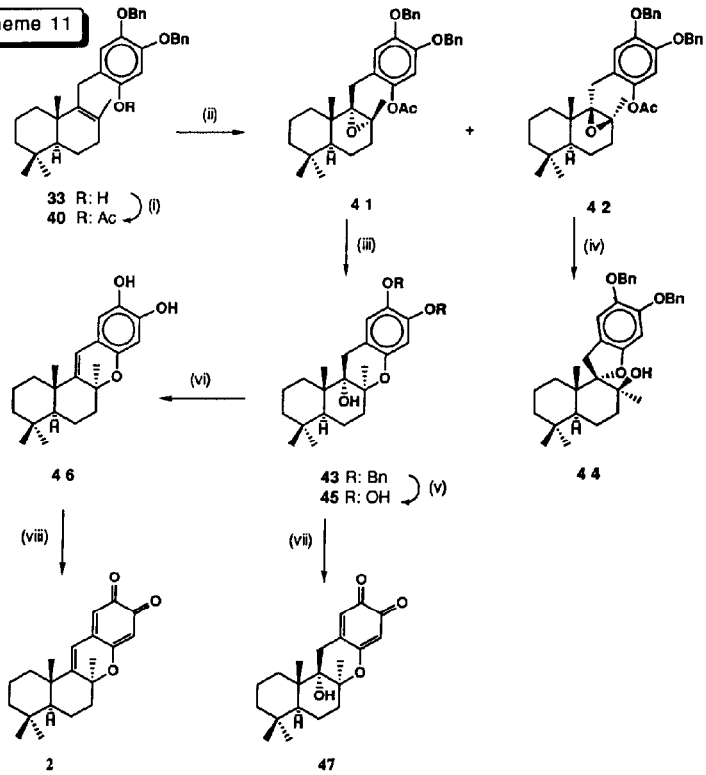
33 **38** **39**

33 **38**

(i) NPSP, $SnCl_4$, CH_2Cl_2, -78°C, rt, 2 h (90 %). (ii) H_2, Pd/C, MeOH, rt, 2.5 h (85 %).

A further alternative route toward puupehedione (**2**), which involves a base-mediated cyclization *via* the 8,9-epoxyderivative, was studied. The treatment of phenol **33** with m-chloroperbenzoic acid in the presence of sodium bicarbonate gave a complex mixture of compounds. Epoxidation of the acetyl derivative **40** under different conditions was not stereoselective; in all cases a 1:1 mixture of diastereomers epoxydes was obtained. Thus, the treatment of **40** with m-chloroperbenzoic acid afforded a 1:1 mixture of epoxydes **41** and **42**, which was separed by column chromatography. The alcohol **43** was obtained in high yield when the 8α,9α-epoxyde **41** was treated with KOH in methanol. Under similar conditions **42** was converted into the spirane **44**. All attempts at dehydrating the alcohol **43**

Scheme 11



(i) Ac_2O, NaAcO, reflux, 2 h (98 %). (ii) MCPBA, $NaHCO_3$, CH_2Cl_2, -20°C, 2 h (98 %). (iii) 2N KOH-MeOH, rt, 48 h (95 %). (iv) 2N KOH-MeOH, rt, 48 h (89 %). (v) H_2, 10 % Pd/C, MeOH, rt, 1 h (91 %). (vi) Silica gel (45 %). (vii) $NaIO_4$, EtOH-H_2O, rt, 30 min (95 %).(viii) $NaIO_4$, EtOH-H_2O, rt, 15 min (80 %).

were unsuccessful; the treatment of **43** with a variety of reagents, such as thionyl chloride, mesyl chloride, p-toluenesulphonic acid, phosphorus oxychloride or etherate-boron trifluoride, lead to a complex mixture of compounds, which probably resulted from rearrangement proccesses. Deprotection of benzylether groups with palladium on carbon gave **45**, which underwent dehydration when it was chromatographed on silica gel, affording the diphenol **46** in 45% yield. The oxidation of **46** with sodium metaperiodate gave puupehedione (**2**) in high yield, whose spectroscopic properties were identical to those of the natural compound [2] (Scheme 11).

An alternative route to puupehedione (**2**) from **45**, which involves oxidation and further dehydration, was assayed. Treatment of **45** with sodium metaperiodate in aqueous ethanol gave the o-quinone **47**. Unfortunately, all attempts at dehydrating **47** were unsuccessful. A complex mixture of compounds, in which small quantities of **2** were detected, was obtained when **47** was treated with the same reagents used for **45**.

In summary, the synthesis of puupehedione (**2**) presents some difficulties, which could be attributed to the molecular strain caused by the C_9-C_{15} double bond. The formation of this double bond, *via* dehydration of 9-hydroxyderivatives or by oxidation proccesses, turned out to be highly unfavourable. However, it seems that the strain is slower when the configuration at C-8 is changed. This could explain the relatively easy formation of 8-epipuupehedione (**28**) in high yield during the above described reactions [7,8].

Antitumor activity of puupehedione (**2**) and related compounds, such as **3**, **13b**, **18b**, **21**, **22**, **25a-b**, **28**, **35** and **36** were assayed againts the cell lines P-388, A-549, HT-29 and MEL-28, following the method reported by Bergeron et al [14]. The results obtained and those reported for some natural products are shown in Table 5.

Table 5. Antitumor activity of puupehedione (**2**) and related compounds

Compound	P-388	A-549	HT-29	MEL-28
2	1	1-2	1-2	----
3	1	2.5	2.5	2.5
4	2	2	2	----
13b	5	5	5	5
18b	5	5	5	5
28	0.25	0.25	0.25	0.25
21	2.5	2.5	2.5	2.5
36	5	5	5	5
25a-b	2.5	2.5	2.5	2.5
35	1.2	1.2	1.2	1.2
22	5	5	5	5

Some conclusions may be obtained from Table 5. The β disposition of methyl on C-8 which characterized the 8-epiderivatives increases the antitumor activity in some cases (**28** compared with **2**, and **35** compared with **3**). In fact, 8-epipuupehedione (**28**) was the most

active compound of all those tested, even when it was compared with natural products, such as puupehedione (**2**) and 15-cianopuupehenol (**4**). It may be also noted that quinones are more active than phenols and in turn these are more active than ethers, which was also observed for the monoterpenic analogues [9].

Experimental

IR spectra were obtained on Perkin-Elmer Models 782 and 983G spectrometers with samples between sodium chloride plates or as potassium bromide pellets. Proton nuclear magnetic resonance spectra were taken on a Bruker AM 300 (300 MHz), Bruker ARX 400 (400 MHz) and Bruker AMX 500 (500 Mhz) spectrometers using $CDCl_3$, and CD_3COCD_3 as solvent and TMS or residual protic solvent $CHCl_3$ (δ_H= 7.25 ppm) as internal reference, and the multiplicity of a signal is a singlet unless otherwise stated, when the following abbreviations are used: s, singlet; bs, broad singlet; d, doublet; bd, broad doublet; dd, double doublet; t, triplet; m, multiplet. ^{13}C NMR spectra were run at 75 MHz on Bruker AM 300, ARX 400 and AMX 500 instruments. Chemical shifts are in ppm (δ scale) and the coupling constants are in Hertz. Carbon substitution degrees were established by DEPT pulse sequence. MS were recorded on a Hewlett-Packard 5988A spectrometer using an ionizing voltage of 70 eV. HRMS were obtained on a trisector WG AutoSpecQ spectrometer. For analytical TLC Merck silica gel 60G in 0.25 mm thick layers was used. Chromatographic separations were carried out by conventional column on Merck silica gel 60 (70-230 mesh) and by flash column on Merck silica gel 60 (230-400 mesh) using hexane-MeO^{t}Bu (H-E) mixtures of increasing polarity. Routinely, dry organic solvents were stored under argon, over freshly activated molecular sieves. Ether, benzene, and THF, were dried over sodium-benzophenone ketyl, dichloromethane over calcium hydride, and methanol from magnesium methoxide. Where necessary reactions were carried out under a nitrogen or argon atmosphere.

Synthesis of 1,2-methylenedioxy-4-*tert*-butyldimethylsiyloxybenzene (**15**)

tert-Butyldimethylsilyl chloride (2.6 g, 17.38 mmol) and imidazole (1 g, 14.6 mmol) were added to solution of sesamol (**14**) (2 g, 14.49 mmol) in anhydrous dimethylformamide and the mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with Et_2O (120 ml), and washed with 2N HCl (3 x 30 ml) and brine. The organic phase was dried over anh. Na_2SO_4 and evaporated to give a crude, which after chromatography on silica gel (H-E 95:5) afforded 3.4 g of **15** (92%) as a colourless oil. IR (film): 2925, 1605, 1503, 1445, 1260, 1060, 945, 693 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 6.64 (1H, d, J=8.4 Hz, H-6), 6.38 (1H, d, J=3.8 Hz, H-3), 6.26 (1H, dd, J=8.4, 3.8 Hz, H-5), 5.91 (2H, s, OCH_2O), 0.95 (9H, s, *t*-butylSi), 0.17 (6H, s, Me_2-Si). HREIMS *m/z* calcd for $C_{13}H_{20}O_3Si$ M^+ 252.1182, found 252.1177.

Synthesis of 2-bromo-1-*tert*-butyldimethylsilyloxy-4,5-methylenedioxybenzene (**16**)

N-Bromosuccinimide (1.2 g, 6.74 mmol) and silica gel (1.0 g) were added to a solution of **15** (1.65 g, 6.54 mmol) in CCl_4 and the mixture was stirred at room temperature for 10 min. After filtration of precipitate, washing with small portions of CCl_4, the solvent was evaporated, yielding a crude which was filtered through silica gel, to give 2.09 g of **16**

(96%) as a colourless oil. IR (film): 2956, 2931, 1624, 1500, 1473, 1253, 1187, 1120, 1039, 994, 939, 873 cm^{-1}. EIMS *m/z* (rel.int.): 332 [M^+] (19), 330 (20), 275 (100), 273 (100), 245 (34), 243 (34), 217 (12), 214 (12), 194 (23), 163 (84), 137 (28).^1H NMR ($CDCl_3$, 300 MHz): 6.94 (1H, s, H-6), 6.44 (1H, s, H-3), 5.91 (2H, s, OCH_2O), 1.02 (9H, s, *t*-butylSi), 0.22 (6H, s, Me_2-Si).^{13}C NMR ($CDCl_3$, 75 MHz): -4.2(C-Si(CH_3)2), 18.4 (C-*t*-butylSi), 25.8 ($3CH_3$-*t*-butyl), 101.7 (OCH_2O), 102.3 (C-3), 104.9 (C-1), 112.2 (C-6), 142.4 (C-5), 147.2 (C-4), 147.5 (C-2). HREIMS *m/z* calcd for $C_{13}H_{19}O_3SiBr$ M^+ 330.0287, found 330.0291.

Synthesis of 9-dehydro-19,20-di-O-methylenepuupehenol (**13a**) and 9-dehydro-8-epi-19,20-di-O-methylenepuupehenol (**13b**)

A 1.7 M solution of *tert*-butyllithium in pentane (3,1 ml) was added at -78°C to a solution of **16** (1.5 g, 5 mmol) in Et_2O (40 ml), under argon atmosphere. After stirring for 45 min, **12** (0.45 g, 2.04 mmol) was added and the mixture was further stirred for 1 h at -78°C. H_2O (10 ml) was added and the mixture was extracted with Et_2O (2 x 50 ml). The combined organic phases were dried and concentrated to give a crude. A solution of this residue (0.8 g) in benzene (25 ml) and p-toluenesulphonic acid (0.1g, 0.636mmol) were stirred at room temperature for 16h. Then the solvent was evaporated and the crude chromatographed on silicagel column (H-E 9:1) to give 320 mg of **13a-b** (ratio 2:5) (92 %) as a colourless oil. IR (film): 2928, 1625, 1450, 1240, 1123, 1078, 935, 764, 700 cm^{-1}. ^1H RMN ($CDCl_3$, 400 MHz) Signals asignables to **13b**: 6.50 (1H, s), 6.40 (1H, s), 6.02 (1H, s), 5.87 (2H, s, OCH_2O), 1.37 (3H, s, Me-13), 1.13 (3H, s, Me-12), 0.91 (3H, s, Me-11), 0.86 (3H, s, Me-14). Signals asignables to **13a**: 6.46 (1H, s), 6.38 (1H, s), 6.04 (1H, s), 5.87 (2H, s, OCH_2O), 1.34 (3H, s, Me-13), 1.20 (3H, s, Me-12), 0.94 (3H, s, Me-11), 0.86 (3H, s, Me-14). ^{13}C RMN ($CDCl_3$, 100 MHz): Signals asignables to **13b**: 38.1 (C-1), 18.9 (C-2), 41.6 (C-3), 33.7 (C-4), 52.2 (C-5), 19.4 (C-6), 41.6 (C-7), 78.1 (C-8), 114.3 (C-9), 39.2 (C-10), 33.4 (C-11), 23.5 (C-12), 25.9 (C-13), 21.7 (C-14), 114.4 (C-15), 116.3 (C-16), 141.6 (C-17), 98.7 (C-18), 146.8* (C-19), 149.6* (C-20), 105.5 (C-21), 100.8 (OCH_2O) (* interchangeable signals). HREIMS *m/z* calcd for $C_{22}H_{28}O_3$ M^+ 340.2038, found 340.2045.

Synthesis of 2-(8-drimen-11-yl)-4,5-methylenedioxyphenol (**17**)

To a solution of the crude (0.8g) resulting of the condensation of **12** with the aryllithium derived from **16** in CH_2Cl_2 (20 ml) were successively added a solution of Et_3SiH (0.6 ml) in CH_2Cl_2 (5 ml) and trifluoroacetic acid (0.4ml) in CH_2Cl_2 (5 ml) at -78°C. After stirring for 45 min at -78°C, sat. $NaHCO_3$ (3 ml) was added, and the cooling bath removed to allow the solution to warm to room temperature with vigorous stirring. Then the mixture was extracted with CH_2Cl_2 (2 x 50 ml). and the combined organic phases were washed with sat. $NaHCO_3$ (2 x 20 ml) and brine. After drying, the solvent was evaporated to afford a crude. This was solved in THF (20 ml) and tetrabutylammonium fluoride (350 mg, 1.11 mmol) was added. After stirring for 10 min at room temperature, H_2O (10 ml) was added and the mixture was extracted with Et_2O (3 x 30 ml). The organic layer was dried and the solvent was evaporated to afford a crude, which was chromatographed on silicagel (H-E 8:2)

to give 0.3 g of **17** (86%) as a colourless oil. IR (film): 3365, 2925, 1607, 1499, 1480, 1445, 1170, 1051, 975, 939, 760 cm^{-1}. CIMS *m/z* (rel. int.): 341 $[M-1]^+$ (24), 312 (17), 303 (15), 166 (63), 155 (62), 150 (100). ^1H NMR ($CDCl_3$, 300 MHz): 6.53 (1H, s, H-3), 6.36 (1H, s, H-6), 5.87 (2H, s, OCH_2O), 5.38 (1H, s, OH), 3.27 (1H, d, J=16.7 Hz, H_A-11'), 3.22 (1H, d, J=16.7 Hz, H_B-11'), 2.13 (2H, m, H-7'), 1.55 (3H, s, Me-12'), 0.98 (3H, s, Me-15'), 0.90 (3H, s, Me-14'), 0.83 (3H, s, Me-13'). ^{13}C NMR ($CDCl_3$, 75 MHz): 121.8 (C-1), 141.5 (C-2), 98.2 (C-3), 147.2* (C-4), 145.8* (C-5), 109.1 (C-6), 36.4 (C-1'), 18.9 (C-2'), 41.6 (C-3'), 33.2 (C-4'), 49.5 (C-5'), 19.1 (C-6'), 36.2 (C-7'), 134.7# (C-8'), 136.6# (C-9'), 39.2 (C-10'), 29.7 (C-11'), 20.8 (C-12'), 33.2 (C-13'), 21.8 (C-14'), 19.5 (C-15') (*, #: interchangeable signals). HREIMS *m/z* calcd for $C_{22}H_{30}O_3$ M^+ 342.2195, found 342.2192.

Treatment of **17** with $BF_3.Et_2O$

$BF_3.Et_2O$ (0.1 g, 0.7 mmol) was added to a solution of **17** (0.2 g, 0.58 mmol) in CH_2Cl_2 (8 ml) at 0°C. After stirring for 1 h at 0°C, the mixture was poured into ice and extracted with Et_2O (2 x 50 ml). The organic phase was washed with sat. $NaHCO_3$ (2 x 50 ml) and brine, dried and the solvent was evaporated to afford a crude, which after being chromatographed on silica gel (H-E 95:5) gave 0.17 g of *8-epi-19,20-di-O-methylenepuupehenol* (**18b**) (85 %) as a colourless oil. IR (film): 2925, 1628, 1478, 1240, 1128, 1081, 938, 768, 699 cm^{-1}. CIMS *m/z* (rel. int.): 342 $[M+1]^+$ (38), 237 (6), 205 (16), 191 (27), 151 (100). ^1H NMR ($CDCl_3$, 300 MHz): 6.50 (1H, s, H-21), 6.32 (1H, s, H-18), 5.85 (1H, d, J=1.3 Hz, OCH_2O), 5.48 (1H, d, J=1.3 Hz, OCH_2O), 2.50 (2H, d, J=9.1, H-15), 2.02 (dt, J=12.2, 3.0 Hz, H-7), 1.17 (3H, s, Me-13), 1.01 (1H, dd, J=12.2, 2.2 Hz, H-5), 0.90 (3H, s, Me-11), 0.87 (3H, s, Me-12), 0.84 (3H, s, Me-14). ^{13}C NMR ($CDCl_3$, 75 MHz): 39.3 (C-1), 18.6 (C-2), 41.) (C-3), 33.3 (C-4), 52.1 (C-5), 19.8 (C-6), 41.9 (C-7), 77.2 (C-8), 56.2 (C-9), 36.8 (C-10), 33.5 (C-11), 20.6 (C-12), 21.7 (C-13), 14.9 (C-14), 22.5 (C-15), 113.7 (C-16), 140.9 (C-17), 98.8 (C-18), 146.3* (C-19), 147.6* (C-20), 108.4 (C-21), 100.7 (OCH_2O) (*: interchangeable signals). HREIMS *m/z* calcd for $C_{22}H_{30}O_3$ M^+ 342.2195, found 342.2186.

Treatment of **17** with β–naphthalenesulphonic acid

β-Naphthalenesulphonic acid (0.51 g, 0.3 mmol) was added to a solution of **17** (0.1 g, 0.29 mmol) in CH_2Cl_2 (10 ml) and the mixture was refluxed for 2 h. Then it was diluted with Et_2O (40 ml) and washed with sat. $NaHCO_3$ (2 x 50 ml) and brine. The organic phase was dried and the solvent evaporated to yield 91 mg of **18a-b** (ratio 1:2.4) (76 %) as a colourless oil. ^1H NMR ($CDCl_3$, 300 MHz): Signals asignables to *19,20-di-O-methylenepuupehenol* (**18a**): 6.48 (1H, s, H-21), 6.30 (1H, s, H-18), 5.84 (1H, d, J=1.3 Hz, OCH_2O), 5.83 (1H, d, J=1.3 Hz, OCH_2O), 2.82 (1H, dd, J=17.3, 8.0 Hz, H_A-15), 2.62 (1H, d, J=17.3 Hz, H_B-15), 1.15 (3H, s, Me-13), 0.89 (3H, s, Me-11), 0.82 (3H, s, Me-12), 0.72 (3H, s, Me-14).

Treatment of **17** with p-toluenesulphonic acid

p-Toluenesulphonic acid (44 mg, 0.252 mmol) was added to a solution of **17** (0.1 g, 0.25 mmol) in benzene (5 ml) and the mixture was stirred at 85°C for 50 h. The solvent was evaporated and the crude chromatographed on silica gel (H-E, 9:1) to afford 90 mg of **18a-b** (ratio 1:4) (90%).

Treatment of **17** with conc. sulphuric acid

Conc. sulphuric acid (15 mg) was added dropwise to a stirred solution of **17** (0.15 g, 0.4 mmol) in nitropropane (25 ml) at -78°C, and the mixture was further stirred at 0-10°C for 1 h 30 min. Then it was diluted with Et_2O (150 ml) and washed with sat. $NaHCO_3$ (2 x 50 ml) and brine (2 x 50 ml). The organic phase was dried and the solvent evaporated to give 0.14 g of **18a-b** (ratio 1:9) (93%).

Condensation of 8α-acetoxydriman-11-al (**19**) with the aryllithium derived from **16**: Obtention of **20**, **21** and **22**

A 1.7 M solution of tert-butyllithium in pentane (3 ml) was added slowly to a stirred solution of **16** (1.5 g, 4.8 mmol) in Et_2O at -78°C, under argon atmosphere. After stirring for 45 min, a solution of **19** (0.8 g, 2.8 mmol) in Et_2O (25 ml) was added and the mixture was further stirred at -78°C for 45 min. Then H_2O (20 ml) was added and the mixture was extracted with Et_2O (3 x 50 ml). The organic layer was washed with brine, dried and the solvent evaporated to afford a crude which was chromatographed on silica gel (H-E, 7:3) to give 1.16 g of *11-acetoxy-11-(2-tert-butyldimethylsilyloxy-4,5-methylenedioxy)phenyl-driman-8α-ol* (**20**) (78%) (colourless oil), 50 mg of *6-(8α-hydroxydriman-11-yliden)-3,4-methylenedioxy-2,4-cyclohexadienone* (**21**) (5%) (colourless oil), and 0.1 g of *(1'S, 6'S)-4-[2', 2', 6'-trimethyl-6'-(2"-hydroxy-4", 5"-methylenedioxyphenylvinyl)cyclohexyl]-2-butanone* (**22**) (10%) (colourless oil). **20** IR (film): 3583, 2931, 1736, 1625, 1499, 1482, 1426, 1388, 1365, 1236, 1177, 1119, 1084, 1040, 971, 940, 897, 844, 785, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 6.82 (1H, s, H-6), 6.27 (1H, s, H-3), 6.23 (1H, d, J=5.5 Hz, H-11'), 5.82 (1H, d, J=1.4 Hz, OCH_2O), 5.80 (1H, d, J=1.4 Hz, OCH_2O), 2.46 (1H, s, OH), 1.93 (3H, s, OAc-12'), 1.89 (2H, m, H-7'), 1.66 (1H, da, J=12.4 Hz), 1.56 (2H, m), 1.33 (4H, m), 1.18 (3H, s, Me-12'), 0.98 (3H, s, Me-15'), 0.97 (9H, s, *t*-butylSi), 0.89 (1H, bd, J=11.9 Hz, H-5'), 0.80 (3H, s, Me-14'), 0.75 (3H, s, Me-13'), 0.31 (3H, s, Me-Si), 0.19 (3H, s, Me-Si). ^{13}C NMR ($CDCl_3$, 100 MHz): 40.2 (C-1), 18.8 (C-2), 41.7 (C-3), 33.6 (C-4), 56.2 (C-5), 20.1 (C-6), 44.0 (C-7), 73.3 (C-8), 65.3 (C-9), 40.4 (C-10), 70.7 (C-11), 25.4 (C-12), 33.7 (C-13), 21.6* (C-14), 17.1 (C-15), 141.9 (C-1'), 125.1 (C-2'), 108.1 (C-3'), 146.7 (C-4'), 147.1 (C-5'), 100.8 (C-6'), 101.2 (OCH_2O), 21.7* ($OCO\underline{C}H_3$), 169.4 ($O\underline{C}OCH_3$), -3.6 ($SiCH_3$), -4.4 ($SiCH_3$), 18.6 ($Si\underline{C}(CH_3)_3$), 26.1 ($SiC(\underline{C}H_3)_3$). HREIMS *m/z* calcd for $C_{30}H_{48}O_6Si$ M^+ 532.3220, found 532.3216. **21** IR (film): 3402, 2925, 1625, 1549, 1419, 1222, 1033, 975, 863, 836, 757 cm^{-1}. EIMS *m/z*: 358

$[M]^+$ (83), 343 (10), 325 (8), 217 (55), 189, (95),151 (100).^{1}H NMR ($CDCl_3$, 400 MHz): 7.24 (1H, d, J=11.9, H-11'), 6.44 (1H, s, H-3), 5.82 (1H, s, H-6), 5.80 (1H, s, OCH_2O), 5.79 (1H, s, OCH_2O), 2.36 (1H, d, J=11.9, H-9'), 2.12 (1H, s, OH), 1.90 (1H, dt, J=12.5, 3.5 Hz, H-7), 1.29 (3H, s, Me-12'), 0.96 (dd, J=12.1, 2.1 Hz, H-5'), 0.89 (3H, s, Me-15'), 0.83 (3H, s, Me-13'), 0.72 (3H, s, Me-14'). ^{13}C NMR ($CDCl_3$, 100 MHz): 135.3 (C-1), 184.3 (C-2), 99.0 (C-3), 162.2* (C-4), 145.6* (C-5), 101.5 (C-6), 41.1 (C-1'), 18.4 (C-2'), 41.9 (C-3'), 33.5 (C-4'), 55.9 (C-5'), 20.2 (C-6'), 42.9 (C-7'), 73.8 (C-8'), 61.0 (C-9'), 39.1 (C-10'), 145.6 (C-11'), 25.4 (C-12'), 33.4 (C-13'), 21.7 (C-14'), 15.8 (C-15'), 101.8 (OCH_2O). HREIMS *m/z* calcd for $C_{22}H_{30}O_4$ M^+ 358.2144, found 358.2140. **22** IR (film): 3362, 2925, 1699, 1625, 1480, 1442, 1173, 1040, 977, 938, 761 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) : 6.77 (1H, s, H-8"), 6.43 (1H, d, J=16.2 Hz, H-1"), 6.41 (1H, s, H-5"), 5.85 (2H, s, OCH_2O), 5.76 (1H, d, J=16.2 Hz, H-2"), 2.40 (1H, d, J=7.1 Hz, H-3), 2.38 (1H, J=7.1 Hz, H-3), 1.99 (3H, s, Me-1), 1.12 (3H, s, Me-6'), 0.90 (3H, s, Me-2'), 0.88 (3H, s, Me-2'). ^{13}C NMR ($CDCl_3$, 100 MHz): 29.9 (C-1), 210.9 (C-2), 46.9 (46.9), 21.3 (C-4), 53.3 (C-1'), 34.6 (C-2'), 42.1 (C-3'), 18.7 (C-4'), 40.7 (C-5'), 41.4 (C-6'), 120.3 (C-7'), 143.3 (C-8') 33.7 (C-9'), 21.9 (C-10'), 18.1 (C-11'), 117.9 (C-1"), 141.8 (C-2"), 98.8 (C-3"), 147.0* (C-4"), 148.0* (C-5"), 105.3 (C-6"). HREIMS *m/z* calcd for $C_{22}H_{30}O_4$ M^+ 358.2144, found 358.2140.

Treatment of **20** with tetrabutylammonium fluoride

Tetrabutylammonium fluoride (60 mg, 0.19 mmol) was added to a solution of **20** (100 mg, 0.19 mmol) in THF (7 ml) and the mixture was stirred at room temperature for 1 h. H_2O (1 ml) was added and the mixture was extracted with Et_2O. The organic phase was washed with brine (2 x 10 ml), dried and the solvent evaporated, affording 0.58 g of **22** (87%).

Treatment of **20** with Amberlyst A-15

Amberlyst A-15 (0.2 g) was added to a solution of **20** (0.1 g, 0.19 mmol) in THF (20 ml) and the mixture was refluxed for 45 min. After filtering and evaporating the solvent 64 mg of **22** (95%) were obtained.

Treatment of **20** with 2N KOH-MeOH

To a solution of **20** (0.1 g, 0.19 mmol) in MeOH (10 ml) 1 ml of 2N KOH in MeOH was added and the mixture was stirred at room temperature for 30 min. The mixture was acidified with 2N HCl (10 ml) and extracted with Et_2O (2 x 50 ml). The organic layer was washed with brine (3 x 50 ml), dried over anh. Na_2SO_4 and the solvent evaporated, affording 58 mg of **22** (86%).

Treatment of **20** with triethylamine

Et_3N (2 ml) was added to a solution of **20** (0.1 g, 0.19 mmol) in DMF (16 ml) and the mixture was heated at 60°C for 2 h. Then it was diluted with ether (60 ml), washed with 2N

HCl (3 x 20 ml) and sat. aqueous NaCl (3 x 20 ml). The organic phase was dried and the solvent was evaporated to give 82 mg of **23** (92%) as a colourless oil. IR (film): 2926, 1698, 1626, 1480, 1450, 1165, 1045, 970, 940, 763 cm^{-1}. CIMS *m/z*: (rel. int.): 473 $[M+1]^+$ (25), 356 (5), 281 (70), 223 (100). ^1H NMR ($CDCl_3$, 500 MHz): 6.91 (1H, s), 6.53 (1H, d, J=16.4 Hz), 6.34 (1H, s), 5.90 (1H, d, J=1.3 Hz, OCH_2O), 5.89 (1H, d, J=1.3 Hz, OCH_2O), 5.75 (1H, d, J=16.4 Hz), 2.40 (1H, d, J=7.1 Hz), 2.38 (1H, d, J=7.1 Hz), 1.97 (3H, s, $COCH_3$), 1.19 (3H, s), 1.01 (9H, s, *t*-butylSi), 0.93 (3H, s), 0.90 (3H, s), 0.17 (6H, s, Me-Si). HRFABMS *m/z* calcd for $C_{28}H_{44}O_4Si$ $(M+Na)^+$ 495.2906, found 495.2915.

Treatment of **20** with pyridine

A solution of **20** (50 mg, 0.09 mmol) in pyridine (2.5 ml) was kept at room temperature for 10 h. Then it was diluted with ether (30 ml) and washed with 2N HCl (3 x 10 ml) and sat. aqueous NaCl (3 x 10 ml). After drying, the solvent was evaporated to give 40 mg of the starting material.

Treatment of **20** with $POCl_3$ in pyridine

Phosphorous oxychloride (1 ml) was added to a solution of **20** (0.2 g, 0.36 mmol) in dry pyridine (6 ml) and the mixture was stirred at room temperature under argon atmosphere for 2 h. Then it was poured into ice and extracted with Et_2O (3 x 50 ml). The organic phase was washed with 2N HCl (3 x 50 ml) and brine (3 x 100 ml). After drying and evaporating the solvent, the crude was chromatographed on silica gel (H-E 8:2) affording 134 mg of a mixture of regioisomers *11-(2-tert-butyldimethylsilyl-4,5-methylenedioxyphenyl)-11-acetoxy-drim-8(12)-ene* (**24a**) and *11-(2-tert-butyldimethylsilyl-4,5-methylenedioxyphenyl)-11-acetoxy-drim-7-ene* (**24b**) (ratio 3:2) (70%) were obtained as a colourless oil. IR (film): 3060, 3030, 1734, 1611, 1510, 1450, 1185, 1110, 913, 731 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): Signals asignables to **24a** : 6.65 (1H, s), 6.29 (1H, s), 5.84 (2H, m), 4.64 (1H, s), 4.35 (1H, bs), 2.52 (1H, m), 2.22 (1H, m), 1.95 (3H, s, $COCH_3$), 1.01 (9H, s, *t*-butil-Si), 0.96 (3H, s, Me-14), 0.85 (3H, s, Me-13), 0.81 (3H, s, Me-C15), 0.27 (3H, s, Me-Si), 0.25 (3H, s, Me-Si). Signals asignables to **24b**: 6.77 (1H, s), 6.34 (1H, s), 6.30 (1H, d, J=3.8), 5.76 (2H, m), 5.58 (1H, m), 2.73 (1H, sa), 1.95 (3H, s, $COCH_3$), 1.73 (3H, s, Me-12'), 0.99 (9H, s, *t*-butylSi), 0.93 (3H, s, Me-14'), 0.83 (3H, s, Me-13'), 0.82 (3H, s, Me-15'), 0.28 (3H, s, MeSi), 0.26 (3H, s, MeSi). HREIMS *m/z* calcd for $C_{30}H_{46}O_5Si$ M^+ 514.3114, found 514.3121.

Treatment of **20** with MsCl in pyridine

Mesyl chloride (0.5 ml) was added to a solution of **20** (0.1 g, 0.19 mmol) in pyridine (3 ml) and the mixture was stirred at room temperature for 12 h. H_2O (5 ml) was added and the mixture was extracted with Et_2O (3 x 20 ml). The organic phase was washed with 2N HCl (3 x 20 ml) and brine (3 x 50 ml), dried and the solvent evaporated to give a crude

which after chromatography on silica gel (H-E 8:2) afforded 53 mg of **24a-b** (ratio 2:1) (55%) as a colourless oil.

Treatment of **20** with $SOCl_2$ in pyridine

Thionyl chloride (0.5 ml) was added to a stirred solution of **20** (0.1 g, 0.19 mmol) in pyridine (3 ml) and the mixture was further stirred for 1 h. Following the same work-up described for the treatment with $POCl_3$ 89 mg of **24a-b** (ratio 5:2) (92%) were obtained.

Treatment of **24a-b** with tetrabutylammonium fluoride: Synthesis of **25a-b**

Tetrabutylammonium fluoride (0.26 g, 0.85 mmol) was added to a solution of **24a-b** (0.4 g, 0.75 mmol) in THF (25 ml) and the mixture was stirred at room temperature for 15 min. After evaporating the solvent, the crude was chromatographed on silica gel (H-E 7:3) to afford 0.25 g (94%) of *6-(8(12)-drimen-11-yliden)-3,4-methylenedioxy-2,4-cyclohexadienone (25a) and 6-(7-drimen-11-yliden)-3,4-methylenedioxy-2,4-cyclohexadienone (25b)* as a colourless oil. IR: 2928, 1648, 1612, 1430, 1358, 890 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): Signals asignables to **25a**: 7.28 (1H, d, J=10.8 Hz, H-11'), 6.23 (1H, s, H-3), 5.89 (1H, s, H-6), 5.85 (1H, s, OCH_2O), 5.84 (1H, s, OCH2O), 4.77 (1H, sa, H-12'), 4.38 (1H, s, H-12'), 2.80 (1H, d, J=10.8 Hz, H-9'), 2.47 (1H, m, H-7'), 0.98 (3H, s, Me-14'), 0.89 (3H, s, Me-13'), 0.85 (3H, s, Me-15'). Signals asignables to **25b**: 7.10 (1H, d, J=12.7 Hz, H-11'), 6.39 (1H, s, H-3), 5.89 (1H, s, H-6), 5.86 (2H, s, OCH_2O), 5.57 (1H, bs, H-7'), 2.95 (1H, d, J=12.7 Hz, H-9'), 1.57 (3H, s, Me-12'), 0.97 (3H, s, Me-14'), 0.91 (3H, s, Me-13'), 0.88 (3H, s, Me-15'). ^{13}C NMR ($CDCl_3$, 75 MHz) (**25b**): 131.8 (C-1), 184.3 (C-2), 98.2 (C-3), 162.1 (C-4), 145.3 (C-5), 101.9 (C-6), 38.5 (C-1'), 18.7 (C-2'), 42.4 (C-3'), 33.5 (C-4'), 49.9 (C-5'), 23.8 (C-6'), 123.2 (C-7'), 133.6 (C-8'), 54.6 (C-9'), 41.0 (C-10'), 149.8 (C-11'), 22.2 (C-12'), 33.5 (C-13'), 22.5 (C-14'), 15.1 (C-15'), 101.8 (OCH_2O). HREIMS *m/z* calcd for $C_{22}H_{28}O_3$ M^+ 340.2038, found 340.2037.

Synthesis of 2-(8(12)-drimen-11-yl)-4,5-methylenedioxyphenol (**26a**) and 2-(7-drimen-11-yl)-4,5-methylenedioxyphenol (**26b**)

Sodium borohydride (60 mg, 1.6 mmol) was added to solution of **25a-b** (0.28 g, 0.82 mmol) in EtOH (16 ml) and the mixture was stirred at room temperature for 30 min. Then 2N HCl (10 ml) was added to the mixture cooled at -10°C and it was extracted with Et_2O (3 x 50 ml). The organic phase was washed with brine (3 x 50 ml), dried and the solvent evaporated to give a crude which after chromatography on silica gel (H-E 7:3) afforded 0.25 g of **26a-b** (89%) as a colourless oil. IR: 3390, 2925, 1611, 1502, 1448, 1179, 1110, 1075, 910, 730 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): Signals asignables to **26a**: 6.57 (1H, s, H-3), 6.34 (1H, s, H-6), 5.84 (2H, s, OCH_2O), 4.82 (1H, s, H-12'), 4.69 (1H, s, H-12'), 2.63 (2H, d, J=6.1Hz, H-11'), 2.37 (1H, m, H-11'), 0.88 (3H, s, Me-13'), 0.83 (3H, s, Me-14'), 0.80 (3H, s, Me-15').Signals asignables to **26b**: 6.68.(1H, s, H-3), 6.32 (1H, s, H-6), 5.85.(2H, s, OCH_2O), 5.38 (1H, sa, H-7'), 2.50 (2H, d, J=6.1Hz, H-11'), 2.25 (1H, sa), 1.45 (3H, sa, Me-

12'), 0.82 (3H, s, Me-15'), 0.85 (6H, s, Me-13', Me-14'). ^{13}C NMR ($CDCl_3$, 75 MHz): Signals asignables to **26b**: 121.8 (C-1), 141.5 (C-2), 98.1 (C-3), 147.4* (C-4), 145.9* (C-5), 109.1 (C-6), 39.7 (C-1'), 19.0 (C-2'), 42.3 (C-3'), 33.2 (C-4'), 50.4 (C-5'), 23.8 (C-6'), 122.4 (C-7'), 135.5 (C-8'), 54.6 (C-9'), 37.0 (C-10'), 26.2 (C-11'), 22.3 (C-12'), 33.4 (C-13'), 22.0 (C-14'), 14.0 (C-15'), 100.9 (OCH_2O). HREIMS *m/z* calcd for $C_{22}H_{30}O_3$ M^+ 342.2195, found 342.2186.

Treatment of **26a-b** with $BF_3.Et_2O$

Etherate-boron trifluoride (80 mg, 0.56 mmol) was added to a solution of **26a-b** (0.1 g, 0.29 mmol) in CH_2Cl_2 (3 ml) and the mixture was stirred at room temperature for 20 min. Then it was poured into ice-H_2O and was extracted with Et_2O (2 x 50 ml). The organic phase was washed with sat. $NaHCO_3$ (2 x 50 ml) and brine (3 x 50 ml). After drying and evaporating the solvent a crude was obtained, which after being chromatographed on silicagel (H-E 95:5) gave 12 mg of *18-bis(8-epi-19,20-di-O-methylenepuupehenol)* (**27**) (6%) (colourless oil) and 86 mg of *8-epi-19,20-di-O-methylenepuupehenol* (**18b**) (86%) (colourless oil). **27** IR (film): 2925, 1450, 1407, 1261, 1128, 1080, 972, 947, 839, 802 cm^{-1}. CIMS *m/z* (rel. int.): 682 $[M-1]^+$ (2), 517 (3), 397 (35), 370 (30), 248 (53). ^1H NMR ($CDCl_3$, 300 MHz): 6.39 (1H, s, H-6), 5.74 (1H, d, J=1.3, OCH_2O), 5.48 (1H, d, J=1.3 Hz, OCH_2O), 2.50 (2H, d, J=9.1 Hz, H-15), 2.02 (1H, dt, J=12.2, 3.0 Hz, H-7), 1.17 (3H, s, Me-13), 1.01 (1H, dd, J=12.2, 2.2 Hz), 0.90 (3H, s, Me-12), 0.87 (3H, s, Me-11), 0.84 (3H, s, Me-14). ^{13}C NMR ($CDCl_3$, 75 MHz): 39.1 (C-1), 18.2 (C-2), 41.2 (C-3), 33.2 (C-4), 51.9 (C-5), 19.8 (C-6), 42.0 (C-7), 76.5 (C-8), 56.2 (C-9), 35.7 (C-10), 33.5 (C-11), 20.3 (C-12), 21.6 (C-13), 14.8 (C-14), 23.2 (C-15), 114.2 (C-16), 140.6 (C-17), 121.0 C-18), 143.6* (C-19), 146.6* (C-20), 106.4 (C-21), 99.2 (OCH_2). HRFABMS *m/z* calcd for $C_{44}H_{58}O_6$ $(M+Na)^+$ 705.4131, found 705.4125.

Treatment of **26a-b** with p-toluenesulphonic acid

26a-b (0.1 g, 0.29 mmol) and p-toluenesulphonic acid (44 mg, 0.29 mmol) in benzene (10 ml) were heated at 85°C for 45 h. After evaporating the solvent a crude was obtained, which was chromatographed on silica gel (H-E 9:1) to afford 90 mg of **18a-b** (ratio 1:4) (90%) and 10 mg of **17** (10%).

Treatment of **25a-b** with p-toluenesulphonic acid: Synthesis of **13a-b**

25a-b (0.1 g, 0.29 mmol) and p-toluenesulphonic acid (30 mg, 0.19 mmol) in benzene were refluxed for 15 min. Following the same work-up used for **17**, 74 mg of **13a-b** (ratio 1:4) (93%) was obtained.

Oxidative rupture of the methylenedioxy group: Synthesis of puupehedione (2) and 8-epi-puupehedione (28)

Treatment of **18a-b** with DDQ-APTS

2,3-dichloro-5,6-dicyano-1.4-benzoquinone (DDQ) (0.33 g, 1.46 mmol) and p-toluenesulphonic acid (115 mg, 0.73 mmol) were added to a solution of **18a-b** (ratio 1:3) (0.25 g, 0.73 mmol) in dioxane (25 ml) and the mixture was refluxed for 1 h 40 min. It was filtered and the solvent was evaporated to give a crude which after chromatography on silica gel (H-E 1:1) afforded 203 mg of *8-epipuupehedione* (**28**) and *puupehedione* (**2**) (ratio 4:1) (85%) as a colourless oil. IR (film): 2938, 1737, 1675, 1650, 1641, 1602, 1559, 1460, 1400, 1239, 1159, 1114, 1059, 920, 838, 755 cm^{-1}. HREIMS *m/z* calcd for $C_{21}H_{26}O_3$ M^+ 326.1882, found 326, 1876. A further carefull chromatographic separation allowed to obtain fractions enriched in each epimer. **28** ^1H NMR ($CDCl_3$, 300 MHz): 6.26 (1H, s, H-15), 6.12 (1H, s, H-21), 5.92 (1H, s, H-18), 2.23 (1H, m, H-1), 2.07 (2H, m, H-7), 1.60 (3H, s, Me-13), 1.17 (3H, s, Me-12), 1.09 (1H, dd, J=12.1, 2.0 Hz), 0.92 (3H, s, Me-11), 0.88 (3H, s, Me-14). ^{13}C NMR ($CDCl_3$, 75 MHz) 40.4 (C-1), 18.6 (C-2), 41.5 (C-3), 33.8 (C-4), 43.2 (C-5), 16.6 (C-6), 29.4 (C-7), 83.1 (C-8), 166.3 (C-9), 41.1 (C-10), 33.2 (C-11), 21.7 (C-12), 30.7 (C-13), 22.0 (C-14), 115.3 (C-15), 137.8 (C-16), 164.2 (C-17), 108.1 C-18), 179.6* (C-19), 181.1* (C-20), 122.2 (C-21). **2** ^1H NMR ($CDCl_3$, 300 MHz): 6.32 (1H, s, H-15), 6.13 (1H, s, H-21), 5.97 (1H, s, H-18), 2.07 (1H, m, H-1), 2.04 (2H, m, H-7), 1.54 (3H, s, Me-12), 1.25 (3H, s, Me-12), 0.96 (3H, s, Me-11), 0.88 (3H, s, Me-14). ^{13}C NMR ($CDCl_3$, 75 MHz): 38.3 (C-1), 18.6 (C-2), 41.5 (C-3), 33.9 (C-4), 43.2 (C-5), 16.6 (C-6), 29.4 (C-7), 81.8 (C-8), 169.5 (C-9), 40.7 (C-10), 32.6 (C-11), 21.0 (C-12), 30.8 (C-13), 25.0 (C-14), 115.2 (C-15), 138.3 (C-16), 164.6 (C-17), 109.0 C-18), 179.4* (C-19), 181.0* (C-20), 121.9 (C-21).

Treatment of **13a-b** with DDQ-APTS

2,3-dichloro-5,6-dicyano-1.4-benzoquinone (DDQ) (70 mg, 0.31 mmol) and p-toluenesulphonic acid (46 mg, 0.29 mmol) were added to a solution of **13a-b** (ratio 1:3) (100 mg, 0.29 mmol) in dioxane (10 ml) and the mixture was refluxed for 1 h. Following the same procedure described for **18a-b** 70 mg of *8-epipuupehedione* (**28**) and *puupehedione* (**2**) (ratio 4:1) (74 %) was obtained.

Synthesis of 1,2-di-*O*-benzyl-4-*O*-*tert*-butyldimethylsilylbenzenetriol (**30**).

Imidazole (0.37 g, 5.5 mmol) was added to a solution of **29** (1.5 g, 4.9 mmol) in anhydrous DMF (50 ml) and the mixture was stirred at room temperature for 20 min. Then *tert*-butyldimethylsilyl chloride (0.75 g, 5 mmol) was added and the mixture was further stirred for 15 h. Then it was fractionated in Et_2O (150 ml) - H_2O (20 ml) and the organic phase was washed with 2N HCl (3 x 40 ml) and brine (3 x 50 ml). After drying, the solvent was evaporated to afford 1.9 g of **30** (92%) as a colourless oil. IR (film): 3033, 2954, 2930, 2857, 1591, 1500, 1455, 1378, 1283, 986 cm^{-1}. CIMS *m/z* (rel. int.): 421 $[M+1]^+$ (88), 405

(12), 387 (2), 343 (8), 329 (32), 301 (12), 181 (9).^{1}H NMR ($CDCl_3$, 300 MHz): 7.40-7.24 (m, 10H), 6.76 (d, J=8.6 Hz, 1H), 6.42 (d, J=2.7 Hz, 1H), 6.30 (dd, J=8.6, 2.6 Hz, 1H), 5.04 (s, 2H), 5.02 (s, 2H), 0.91 (s, 9H), 0.06 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): 143.6 (C-1), 149.7 (C-2), 108.1 (C-3), 150.5 (C-4), 111.9 (C-5), 116.9 (C-6), -4.5 (CH_3, -Si(CH_3)2), 18.2 (C, *t*-butylSi), 25.7 (CH_3, *t*-butylSi), 71.2 (CH_2, Bn), 72.5 (CH_2, Bn), 137.2 (C, Bn), 137.7 (C, Bn), 150.5 (C-4), 127.2-128.5 (10 C, 2 Bn). HREIMS *m/z* calcd for $C_{26}H_{32}O_3Si$ M^+ 420.2121, found 420.2115.

Synthesis of 3,4-di-*O*-benzyl-2-bromo-1-*O*-*tert*-butyldimethylsilylbenzenetriol (**31**)

N-bromosuccinimide (0.89 g, 5.0 mmol) and silica gel (1.0 g) were added to a solution of **30** (2.0 g, 4.76 mmol) in anhydrous CCl_4 (45 ml) and the mixture was stirred for 15 min at room temperature. Then it was filtered and the solvent was evaporated, affording 2.3 g of **31** (97%) as a colourless oil. IR (film): 3031, 1495, 1460, 1384, 1254, 1204, 993 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.35 (m, 10H), 7.08 (s, 1H), 6.44 (s, 2H), 5.09 (s, 2H), 5.03 (s, 2H), 0.99 (s, 9H), 0.09 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): 105.2 (C-1), 148.7 (C-2), 108.5 (C-3), 147.1 (C-4), 144.0 (C-5), 120.1 (C-6), -4.6 (CH_3, -Si(CH_3)2), 18.3 (C, *t*-butylSi), 26.0 (CH_3, *t*-butylSi), 71.5 (CH_2, Bn), 72.4 (CH_2, Bn), 136.9 (C, Bn), 137.0 (C, Bn), 127.2 - 128.5 (10 C, 2 Bn). HREIMS *m/z* calcd for $C_{26}H_{32}O_3SiBr$ M^+ 498.1226, found 498.1234.

Synthesis of 11-(2-*tert*-butyldimethylsilyloxy-4,5-di-benzyloxyphenyl)-8-drimene (**32**)

A 1.7M solution of *tert*-butyllithium in pentane (1.6 ml) was added to a solution of **31** (1.3 g, 2.6 mmol) in Et_2O (30 ml) at -78°C, under argon atmosphere, and the mixture was stirred at this temperature for 50 min. Then a solution of **12** (0.4 g, 1.81 mmol) in Et_2O (15 ml) was added at -78 °C and the mixture was further stirred for 40 min. The mixture was warmed to room temperature and H_2O (15 ml) was added, and then was extracted with Et_2O (2 x 50 ml). The organic phase was dried and the solvent evaporated to afford a crude, a solution of which in CH_2Cl_2 (25 ml) was cooled at -78°C and then a solution of Et_3SiH (6.29 mg, 5.43 mmol) and trifluoroacetic acid (0.51 g, 4.5 mmol) in CH_2Cl_2 (10 ml) was added, and the mixture was stirred at -78°C for 45 min. Sat. $NaHCO_3$ (15 ml) was added and the mixture was extracted with CH_2Cl_2 (2 x 30 ml). The organic phase was washed with sat. $NaHCO_3$ (2 x 50 ml) and brine (3 x 50 ml). After drying, the solvent was evaporated affording 1.5 g of a crude which after chromatography on silica gel (hexane) afforded 0.89g (79%) of **32** as a colourless oil. IR (film): 3061, 2925, 2869, 1602, 1495, 1450, 1370, 1290, 1085, 907 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.40-7.24 (m, 10H), 6.55 (s, 1H, H-6'), 6.34 (s, 1H, H-3'), 5.10 (s, 2H), 5.05 (s, 2H), 3.16 (d, J=16.8 Hz), 3.01 (d, J=16.8 Hz), 2.04 (m, 2H), 1.30 (s, 3H), 0.95 (s, 9H), 0.88 (s, 3H), 0.87 (s, 3H), 0.80 (s, 3H), 0.09 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): 36.1 (C-1'), 18.9 (C-2'), 41.7 (C-3'), 33.9 (C-4'), 51.9 (C-5'), 18.9 (C-6'), 33.4 (C-7'), 137.7 (C-8'), 138.3 (C-9'), 38.9 (C-10'), 27.0 (C-11'), 20.1 (C-12'), 33.3 (C-13'), 21.8 (C-14'), 20.2 (C-15'), 124.3 (C-1), 142.8 (C-2), 107.2 (C-3), 147.0 (C-4)*,

146.6 (C-5)*, 117.0 (C-6).-4.2 (C-$SiCH_3$), 18.3 (C-$\underline{C}(CH_3)_3$), 25.8 (C-C($\underline{C}H_3$)$_3$). HREIMS *m/z* calcd for $C_{41}H_{56}O_3Si$ M^+ 624.3999, found 624.4008.

Synthesis of 2-(8-drimen-11-yl)-4,5-dibenzyloxyphenol (**33**)

Tetrabutylammonium fluoride (0.81 g) was added to a solution of **32** (500 mg, 0.8 mmol) in THF (20 ml) and the mixture was stirred at room temperature for 15 min. Following the same work-up used to prepare **17** a crude was obtained which by silicagel chromatography (H-E 8:2) gave 390 mg of **33** (95%) as a colourless oil. IR (film): 3411, 3064, 2866, 1871, 1605, 1452, 1374, 1289, 1091. 911 cm^{-1}. CIMS *m/z* (rel. int.): 510 $[M+1]^+$ (10), 420 (5), 319 (8), 229 (14), 205 (43), 107 (50), 91 (100). ^1H NMR ($CDCl_3$, 300 MHz): 7.26-7.44 (m, 10H), 6.56 (1H, s, H-2), 6.44 (1H, s, H-5), 5.11 (2H, s, CH_2-Bn), 5.08 (2H, s, CH_2-Bn), 3.26 (1H, d, J=16.6 Hz, H-11'), 3.20 (1H, d, J=16.6 Hz, H-11'), 1.42 (3H, s, Me-12'), 0.93 (3H, s, Me-15'). ^{13}C NMR ($CDCl_3$, 75 MHz): 130.0 (C-1), 142.3 (C-2), 103.5 (C-3), 147.9* (C-4), 148.4* (C-5), 118.2 (C-6), 36.3 (C-1'), 18.9 (C-2'), 41.7 (C-3'), 33.4 (C-4'), 51.8 (C-5'), 19.0 (C-6'), 33.5 (C-7'), 137.4# (C-8'), 138.1# (C-9'), 39.1 (C-10'), 27.4 (C-11'), 20.3 (C-12'), 33.3 (C-13'), 21.8 (C-14'), 20.2 (C-15') (*, #: interchangeable signals). HRFABMS *m/z* calcd for $C_{35}H_{42}O_3$ $(M+Na)^+$ 533.3032, found 533.3041.

Treatment of **33** with β-naphthalenesulphonic acid

β–Naphthalenesulphonic acid (34 mg, 0.2 mmol) was added to a solution of **33** (0.1 g, 0.19 mmol) in CH_2Cl_2 and the mixture was stirred for 30 min. Following the same work-up used for **17**, 92 mg of *19,20-di-O-benzylpuupehenol* (**34a**) and its 8-epimer **34b** (ratio 1:9) (92%) was obtained as a colourless oil. **34b**. IR (film): 3030, 1600, 1495, 1448, 1372, 1285, 1087, 905 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 7.50-7.30 (m, 10H, 2 Bn), 6.68 (s, 1H), 6.45 (s, 1H), 5.07 (m, 4H), 2.52 (d, J=8.2 Hz, 2H), 2.05 (dt, J=12.1 and 3.3 Hz, 1H), 1.19 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 39.6 (C-1), 18.6 (C-2), 41.9 (C-3), 33.8 (C-4), 52.3 (C-5), 19.8 (C-6), 41.2 (C-7), 76.9 (C-8), 56.2 (C-9), 36.9 (C-10), 33.5 (C-11), 20.8 (C-12), 21.7 (C-13), 14.9 (C-14), 21.9 (C-15), 113.9 (C-16), 148.9* (C-17), 103.8 (C-18), 148.0* (C-19), 142.4 (C-20), 117.8 (C-21). HREIMS *m/z* calcd for $C_{35}H_{42}O_3$ M^+ 510.3134, found 510.3127.

Treatment of **33** with p-toluenesulphonic acid

p-Toluenesulphonic acid (56 mg, 0.36 mmol) was added to a solution of **33** (0.12 g, 0.23 mmol) in benzene (20 ml) and the mixture was refluxed for 70 min. Following the same work-up described for **17** 104 mg of **34b** (88%) was obtained.

Treatment of **33** with conc. sulphuric acid

Conc. sulphuric acid (10 mg) was added to a stirred solution of **33** (0.1 g, 0.19 mmol) in nitropropane (12 ml) at -78°C and the mixture was further stirred at 0°C for 1 h. After following the same work-up used for **17**, 86 mg of **34b** (87%) was obtained.

Synthesis of 8-epipuupehenol (35)

$BF_3.Et_2O$ (1 ml) was added to a solution of **34b** (0.3 g, 0.58 mmol) in EtSH (10 ml) and the mixture was stirred at room temperature for 2.5 h. Sat. $NaHCO_3$ was added and the mixture was extracted with Et_2O (3 x 30 ml). The organic phase was washed with brine (3 x 50 ml), dried and the solvent evaporated to afford a crude wich after being passed through a silicagel bed yielded 177 mg of **35** (91%) as a colourless oil. IR (film): 3405, 3070, 2862, 1598, 1453, 1376, 1284, 1090, 902 cm^{-1}. ^1H NMR (CD_3COCD_3, 300 MHz): 7.60 (bs, 1H), 7.20 (bs, 1H), 6.49 (s, 1H), 6.18 (s, 1H), 2.47 (d, J=2.0 Hz, 1H), 2.44 (s, 1H), 1.95 (dt, J=12.2, 2.9 Hz, 1H), 1.25 (s, 3H), 0.89 (s, 3H), 0.89 (s, 6H). ^{13}C NMR (CD_3COCD_3, 75 MHz): 39.8 (C-1), 19.2 (C-2), 41.9 (C-3), 34.0 (C-4), 53.4 (C-5), 21.0 (C-6), 42.5 (C-7), 76.5 (C-8), 56.8 (C-9), 37.4 (C-10), 33.7 (C-11), 21.9 (C-12), 21.3 (C-13), 15.2 (C-14), 22.3 (C-15), 115.2 (C-16), 139.2 (C-17), 104.5 (C-18), 144.8* (C-19), 147.0* (C-20), 116.2 (C-21). HREIMS *m/z* calcd for $C_{21}H_{30}O_3$ M^+ 330.2195, found 330.2188.

Treatment of **35** with Jones reagent: Synthesis of 9,15-dihydro-8-epipuupehedione (**36**)

A solution (0.05 ml) of Jones reagent was added to a solution of **35** (0.14 g, 0.42 mmol) in acetone (10 ml) at 0°C and the mixture was stirred at this temperature for 30 min. H_2O (5 ml) was added and the mixture was extracted with Et_2O (3 x 50 ml). The organic phase was washed with brine (3 x 50 ml), dried and the solvent evaporated to give 0.12 g of **36** (87%) as a colourless oil. IR (film): 2925, 1725, 1602, 1460, 1234, 1145, 1113, 1052, 918, 830, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 6.20 (s, 1H), 5.78 (s, 1H), 2.64 (d, J=8.4 Hz, 2H-15), 2.10 (d, J=12.5 Hz, 1H), 1.35 (s, 3H), 0.92 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 38.6 (C-1), 18.3 (C-2), 41.6 (C-3), 33.4 (C-4), 51.6 (C-5), 19.7 (C-6), 40.7 (C-7), 82.1 (C-8), 55.8 (C-9), 37.2 (C-10), 33.2 (C-11), 21.5 (C-12), 22.1 (C-13), 14.8 (C-14), 23.7 (C-15), 145.4 (C-16), 165.4 (C-17), 108.0 (C-18), 178.9 (C-19), 180.5 (C-20), 128.4 (C-21). HREIMS *m/z* calcd for $C_{21}H_{28}O_3$ M^+ 328.2038, found 328.2046.

Treatment of **35** with DDQ

DDQ (92 mg, 0.4 mmol) was added to a solution of **35** (0.12 g, 0.36 mmol) in dioxane (12 ml) and the mixture was stirred at room temperature for 25 min. The solvent was evaporated and the crude was chromatographed on silica gel (H-E 4:6) affording 70 mg of a unresolvable mixture of compounds **36** and *8-epipuupehenone* (**37**) (ratio 1:1.25) as a colourless oil. ^1H NMR ($CDCl_3$, 300 MHz): Signals asignables to **37**: ^1H RMN ($CDCl_3$, 300 MHz): 6.82 (d, J=6.8 Hz, 1H), 6.23 (s, 1H), 5.63 (s, 1H), 2.20 (d, J=6.8 Hz, 1H), 1.06 (s, 3H), 0.87 (s, 3H), 0.81 (s, 3H), 0.79 (s, 3H).

Treatment of **33** with NPSP: Synthesis of **38**

N-phenylselenophtalimide (NPSP) (70 mg, 0.25 mmol) and $SnCl_4$ (0.03 ml) was added to a stirred solution of **33** (0.1 mg, 0.196 mmol) in CH_2Cl_2 (10 ml) at -78°C. The resulting yellow solution was slowly warmed to room temperature, stirred for 2 h, and then quenched with sat. $NaHCO_3$ (1 ml), and the mixture was extracted with ether (3 x 20 ml). The combined extracts were washed with sat. NaCl, dried and then concentrated to afford after chromatography of the crude on silica gel (H-E 1:1) 74 mg of **38** (90%) as a colourless oil. IR (film): 2928, 1673, 1648, 1602, 1183, 756 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 7.39 (m, 5H), 6.4 (s, 1H), 6.0 (s, 1H), 5.0 (s, 2H), 3.20 (d, J= 20 Hz, 1H), 3.05 (d, J= 20 Hz, 1H), 1.40 (s, 3H), 0.96 (s, 3H), 0.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 182.8 (C-1), 149.6 (C-2), 131.0 (C-3), 187.9 (C-4), 157.6 (C-5), 109.1 (C-6), 36..2 (C-1'), 18.9* (C-2'), 41.6 (C-3'), 33.4 (C-4'), 51.9 (C-5'), 18.9* (C-6'), 33.4 (C-7'), 134.1# (C-8'), 134.7# (C-9'), 39.9 (C-10'), 27.0 (C-11'), 20.1& (C-12'), 33.3 (C-13'), 21.7(C-14'), 20.0& (C-15'), 71.2 (CH_2-Bn) (*, #, &: interchangeable signals). HRFABMS *m/z* calcd for $C_{28}H_{34}O_3$ $(M+Na)^+$ 441.2405, found 441.2409.

Treatment of **33** with phenylselenyl chloride

To a solution of **33** (100 mg, 0.196 mmol) in CH_2Cl_2 (10 ml) was added phenylselenyl chloride (41 mg, 0.22 mmol) and the mixture was stirred at room temperature for 45 min and then concentrated to afford a crude which was chromatographed on silica gel (H-E 1:1) to give 65 mg of **38** (79%).

Treatment of **33** with iodine

Resublimed iodine (47mg, 0.182 mmol) was added to a stirred solution of **33** (62 mg, 0.122 mmol) in dry acetonitrile (5 ml) at -60°C under argon atmosphere and the mixture was further stirred for 1h 45 min below -5°C. Then aqueous sodium thiosulphate (3 ml) was added and the mixture was stirred for 5 min. Et_2O (50 ml) was added and the organic phase was washed with brine (3 x 10 ml), dried and the solvent evaporated to afford 43 mg of **38** (84%).

Treatment of **38** with Pd-C

A solution of **38** (50 mg, 0.119 mmol) in dry MeOH (5 ml), was stirred with 10% Pd-C (10 mg) at room temperature for 2.5 h under hydrogen atmosphere. Filtration and concentration gave *2-(8-drimen-11-yl)-5-methoxy-p-benzoquinone* (**39**) (35 mg, 85%) as a colourless oil. IR (film): 2925, 1670, 1645, 1598, 1175, 842, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 6.35 (s, 1H), 5.95 (s, 1H), 3.6 (s, 3H), 3.20 (d, J= 20 Hz, 1H), 3.05 (d, J= 20 Hz, 1H), 1.42 (s, 3H), 0.95 (s, 3H), 0.89 (s, 3H), 0.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 182.8 (C-1), 149.9 (C-2), 130.9 (C-3), 187.8 (C-4), 157.8 (C-5), 107.8 (C-6), 36..2 (C-1'), 18.9* (C-2'), 41.6 (C-3'), 33.3 (C-4'), 51.9 (C-5'), 19.0* (C-6'), 33.4 (C-7'), 134.3# (C-8'), 134.9# (C-9'), 39.6 (C-10'), 27.0 (C-11'), 20.0& (C-12'), 33.2 (C-13'), 21.7(C-14'), 20.1& (C-15'),

56.3 (CH_3-O) (*, #, &: interchangeable signals). HRFABMS *m/z* calcd for $C_{22}H_{30}O_3$ $(M+Na)^+$ 365.2092, found 365.2088.

Acetylation of **33**

Sodium acetate (0.88 g, 10.7 mmol) was added to a stirred solution of **33** (0.36 g, 0.70 mmol) in acetic anhydride (3 ml) and the mixture was refluxed for 2 h. The mixture was cooled at room temperature and then poured into ice. It was extracted with Et_2O (2 x 50 ml). and the organic phase was washed with sat K_2CO_3 until neutralization and with brine (3 x 50 ml). After drying and evaporating the solvent 0.38 g of *acetate of 2-(8-drimen-11-yl)-4,5-dibenzyloxyphenyl* (**40**) (98%) was obtained as a colourless oil. IR (film): 3070, 2928, 1732, 1635, 1602, 1495, 1448, 1175, 1115, 1080, 1038, 842, 782, 754 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.40-7.25 (m, 10H), 6.65 (s, 1H), 6.59 (s, 1H), 5.15 (s, 2H), 5.12 (s, 2H), 3.05 (s, 2H), 2.29 (s, 3H), 1.29 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 142.1 (C-1), 129.6 (C-2), 115.8 (C-3), 147.0* (C-4), 146.4* (C-5), 108.9 (C-6), 36.1 (C-1'), 18.9 (C-2'), 41.7 (C-3'), 33.4 (C-4'), 51.9 (C-5'), 19.0 (C-6'), 33.3 (C-7'), 137.1# (C-8'), 137.8# (C-9'), 38.8 (C-10'), 26.3 (C-11'), 20.0& (C-12'), 33.3 (C-13'), 21.7 (C-14'), 20.3& (C-15'), 71,6 (CH_2, Bn), 71,5 (CH_2, Bn), 136.5 (C, Bn), 128.6-126.6 (CH, Bn), 169.5 ($O\underline{C}OCH_3$), 20.8 ($OCO\underline{C}H_3$) (*, #, &: interchangeable signals). HRFABMS *m/z* calcd for $C_{37}H_{44}O_4$ $(M+Na)^+$ 575.3137, found 575.3141.

Epoxidation of **40**: Synthesis of **41** and **42**

m-Chloroperbenzoic acid (80 mg, 0.46 mmol) and sodium bicarbonate (0.24 g) were added to a stirred solution of **40** (0.16 g, 0.29 mmol) in methylene chloride (4 ml) at -20°C and the mixture was further stirred at this temperature for 2 h. Then a solution of sodium sulphite (0.5 g) in H_2O (5 ml) was added and the mixture was vigorously stirred for 2 h. It was extracted with Et_2O and the organic phase was washed with sat. K_2CO_3 until nautralization and with brine (3 x 20 ml). The organic layer was dried and the solvent evaporated to give 0.15 g of a 1:1 mixture of *acetate of 2-(8α, 9α-epoxy-driman-11-yl)-4, 5-dibenzyloxyphenyl* (**41**) and *acetate of 2-(8β, 9β-epoxy-driman-11-yl)-4, 5-dibenzyloxyphenyl* (**42**) (98%), wich was separated after being chromatographed on silica gel (Benzene-Ether 7:3). **41** (colourless oil) IR (film): 3050, 2925, 1735, 1598, 1500, 1452, 1376, 1169, 1110, 1060, 1025, 785, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.42-7.28 (m, 10H), 6.96 (s, 1H), 6.60 (s, 1H), 5.17 (s, 2H), 5.09 (s, 2H), 2.86 (d, J=16.6 Hz, 1H), 2.65 (d, J=16.6 Hz, 1H), 2.28 (s, 3H), 1.10 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H), 0.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 141.9 (C-1), 123.9 (C-2), 117.2 (C-3), 147.5* (C-4), 146.4* (C-5), 108.9 (C-6), 35.1 (C-1'), 17.4 (C-2'), 41.3 (C-3'), 33.0 (C-4'), 42.9 (C-5'), 18.6 (C-6'), 29.7 (C-7'), 62.9(C-8'), 72.9 (C-9'), 39.1 (C-10'), 26.4 (C-11'), 21.5 (C-12'), 33.7 (C-13'), 22.6 (C-14'), 17.9 (C-15'), 71,5 (CH_2, Bn), 136.5 (C, Bn), 128.6-126.6 (CH, Bn), 169.5 ($O\underline{C}OCH_3$), 20.9 ($OCO\underline{C}H_3$). HRFABMS *m/z* calcd for $C_{37}H_{44}O_5$ $(M+Na)^+$ 591.3086, found 591.3082. **42** (colourless oil) IR (film): 3051, 2925, 1735, 1600, 1498, 1452, 1169, 1108, 1055, 1025,

786, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.50-7.30 (m, 10H), 6.80 (s, 1H), 6.68 (s, 1H), 5.18 (s, 2H), 5.12 (s, 2H), 3.2 (d, J= 17.6 Hz, 1H), 2.28 (s, 3H), 2.25 (d, J= 17.6 Hz, 1H), 1.03 (s, 3H), 1.00 (s, 3H), 0.87 (s, 3H), 0.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 141.9 (C-1), 123.6 (C-2), 115.9 (C-3), 147.5* (C-4), 146.3* (C-5), 109.1 (C-6), 35.8# (C-1'), 16.9 (C-2'), 41.5 (C-3'), 33.9 (C-4'), 53.6 (C-5'), 19.6 (C-6'), 35.1# (C-7'), 64.6(C-8'), 71.4 (C-9'), 38.9 (C-10'), 29.6 (C-11'), 20.8 (C-12'), 33.3 (C-13'), 21.8 (C-14'), 16.4 (C-15'), 71,7 (CH_2, Bn), 71,4 (CH_2, Bn), 136.5 (C, Bn), 128.6-126.6 (CH, Bn), 169.3 ($O\underline{C}OCH_3$), 20.8 ($OCO\underline{C}H_3$)(*, #: interchangeable signals). HRFABMS *m/z* calcd for $C_{37}H_{44}O_5$ $(M+Na)^+$ 591.3086, found 591.3092.

Treatment of **41** with KOH-MeOH: Synthesis of **43**

2N KOH-MeOH (2 ml) was added to a solution of **41** (0.2 g, 0.352 mmol) in MeOH (3 ml) and the mixture was stirred at room temperature for 48 h. Then 2N HCl was added till neutralization and the mixture was extracted with Et_2O (2 x 50 ml). Combined organic phases were washed with brine (3 x 30 ml), dried and the solvent evaporated to afford 0.18 g of *9α-hydroxy-di-O-benzylpuupehenol (43)* (95%) as a colourless oil. IR (film): 3580, 2925, 1605, 1580, 1510, 1455, 1157, 1082 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.50-7.30 (m, 10H), 6.64 (s, 1H), 6.50 (s, 1H), 5.11 (s, 2H), 5.08 (s, 2H), 2.90 (d, J= 17.0 Hz, 1H), 2.50 (d, J= 17.0 Hz, 1H), 1.20 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (CD_3COCD_3, 75 MHz): 36.1 (C-1), 18.1 (C-2), 41.6 (C-3), 33.4 (C-4), 47.5 (C-5), 18.3 (C-6), 32.6 (C-7), 73.6 (C-8), 78.8 (C-9), 33.6 (C-10), 33.9 (C-11), 22.1 (C-12), 23.2 (C-13), 14.2 (C-14), 29.7 (C-15), 115.7 (C-16), 142.7 (C-17), 103.8 (C-18), 148.4* (C-19), 148.8* (C-20), 116.0 (C-21), 72.9 (CH_2, Bn), 71.0 (CH_2, Bn), 137.8 (C, Bn), 137.2 (C, Bn), 128.4-127.4 (CH, Bn). HRFABMS *m/z* calcd for $C_{35}H_{42}O_4$ $(M+Na)^+$ 549.2981, found 549.2986.

Treatment of **42** with KOH-MeOH: Synthesis of **44**

A solution of **42** (0.15 g, 0.26 mmol) in MeOH (2.5 ml) was stirred at room temperature with 2N KOH-MeOH (1.5 ml) for 48 h. Following the same work-up used for **41**, 0.12 g of **44** (89 %) were obtained as a colourless oil. IR (film): 3572, 2928, 1600, 1575, 1500, 1448, 1160, 1078, 1050 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 7.50-7.30 (m, 10H), 6.80 (s, 1H), 6.50 (s, 1H), 5.08 (s, 2H), 5.03 (s, 2H), 3.13 (d, J= 16.5 Hz, 1H), 3.00 (d, J= 16.5 Hz, 1H), 1.10 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H), 0.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 37.9 (C-1), 17.8* (C-2), 41.5 (C-3), 33.3 (C-4), 47.1 (C-5), 17.9* (C-6), 31.5 (C-7), 74.9 (C-8), 96.6 (C-9), 33.5 (C-10), 33.4 (C-11), 22.1 (C-12), 26.1 (C-13), 16.3 (C-14), 31.4 (C-15), 118.9 (C-16), 142.5 (C-17, 96.7 (C-18), 113.7 (C-21). HRFABMS *m/z* calcd for $C_{35}H_{42}O_4$ $(M+Na)^+$ 549.2981, found 549.2985.

Treatment of **43** with Pd-C: Synthesis of **45**

A solution of **43** (200 mg, 0.38 mmols) in dry MeOH (10 ml), was stirred with 10% Pd-C (50 mg) at room temperature for 1 h under hydrogen atmosphere. Filtration and

concentration yielded 120 mg of **45** (91%) as a colourless oil. IR (film): 3590, 2928, 1601, 1578, 1500, 1448, 1280, 1250, 1155, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.65 (s, 1H, OH), 7.19 (s, 1H, OH), 6.45 (s, 1H), 6.24 (s, 1H), 2.90 (d, J= 17.1 Hz, 1H), 2.54 (d, J= 17.1 Hz, 1H), 1.15(s, 3H), 0.88 (s, 3H), 0.85 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (CD_3COCD_3, 75 MHz): 36.6 (C-1), 18.7 (C-2), 42.4 (C-3), 34.1 (C-4), 46.9 (C-5), 18.9 (C-6), 32.8 (C-7), 73.5 (C-8), 79.2 (C-9), 43.4 (C-10), 33.6 (C-11), 22.3 (C-12), 23.5 (C-13), 16.0 (C-14), 32.5 (C-15), 115.7 (C-16), 139.2 (C-17), 104.6 (C-18), 147.5 (C-19), 156.9 (C-20), 114.4(C-21). The chromatography of **45** (50 mg) afforded 22 mg of **46** (45%) as a colurless oil. IR (film): 3574, 2925, 1620, 1598, 1495, 1450, 1278, 1148, 1082 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 6.26 (1H, s, H-15), 6.17 (1H, s, H-21), 5.89 (1H, s, H-18), 1.35 (3H, s, Me-13), 1.03 (3H, s, Me-12), 0.95 (3H, s, Me-11), 0.89 (3H, s, Me-14). ^{13}C NMR ($CDCl_3$, 75 MHz) 38.9 (C-1), 19.5 (C-2), 42.4* (C-3), 33.7 (C-4), 53.2 (C-5), 19.9 (C-6), 42.3* (C-7), 77.9 (C-8), 149.7 (C-9), 40.6 (C-10), 33.6 (C-11), 22.3 (C-12), 26.4 (C-13), 23.9 (C-14), 113.4 (C-15), 116.1 (C-16), 139.7 (C-17), 104.3 C-18), 145.8 (C-19)#, 146.2 (C-20)#, 115.2 (C-21)(*,#: interchangeable signals). HRFABMS *m/z* calcd for $C_{21}H_{28}O_3$ $(M+Na)^+$ 351.1936, found 351.1944.

Treatment of **45** with $NaIO_4$;Synthesis of **47**

$NaIO_4$ (150 mg, 0.7 mmol) was added to a solution of **45** (100 mg, 0.29 mmol) in ethanol-water 7:1 (8 ml) and the mixture was stirred at room temperature for 30 min. Then it was diluted with ether (50 ml) and washed with water (2 x 10 ml) and brine (2 x 10 ml). The organic phase was dried and concentrated to give 93 mg of **47** (95%) as a colourless oil. IR (film): 3585, 1640, 1602, 1478, 1395, 1217, 1155, 1067 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 6.11 (s, 1H, H-21), 5.87 (s, 1H, H-18), 3.02 (bd, J= 19.9 Hz, H-15), 2.73 (dd, J= 19.9, 2.6 Hz, H-15'), 1.35 (s, 3H, Me-13), 0.99 (s, 3H, Me-14), 0.91 (s, 3H, Me-11), 0.84 (s, 3H, Me-12). ^{13}C NMR (CD_3COCD_3, 75 MHz): 35.5 (C-1), 17.9 (C-2), 41.2 (C-3), 33.9 (C-4), 46.7 (C-5), 18.0 (C-6), 32.9 (C-7), 83.1* (C-8), 81.5* (C-9), 42.6 (C-10), 33.3 (C-11), 21.8(C-12), 24.8 (C-13), 17.1 (C-14), 29.7 (C-15), 146.2 (C-16), 165.3 (C-17), 109.1 (C-18), 178.9 (C-19), 180.5 (C-20), 125.9 (C-21). HRFABMS *m/z* calcd for $C_{21}H_{28}O_4$ $(M+Na)^+$ 367.1885, found 367.1888.

Treatment of **46** with $NaIO_4$;Synthesis of **2**.

$NaIO_4$ (60 mg, 0.93 mmol) was added at room temperature to a solution of **46** (60 mg, 0.18 mmol) in ethanol-water 7:1 (12 ml) and the mixture was stirred for 15 min. Then it was diluted with ether (50 ml) and washed with water (2 x 30 ml), brine (2 x 30 ml). After drying and evaporating the solvent 48 mg of **2** (80 %) were obtained as a colourless oil.

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