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Functionalisation of tetraalkylsilanes derived from C–H activation; towards annulations of diterpenoids

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Abstract

Vinyl trialkylsilanes are efficient substrates for use in the *ortho* alkylation of aromatic ketones catalysed by zerovalent ruthenium complexes, giving, e.g. (2-trimethylsilylethyl)acetophenones. Methods for the selective desilylation–functionalisation of such tetraalkylsilanes are investigated. Some diterpenoid tetraalkylsilanes derived from the ruthenium-catalysed insertion of vinyltrimethylsilane have been functionalised by benzylic bromination of an $ArCH_2CH_2SiMe_3$ fragment with $NaBrO_3$–$Na_2S_2O_5$ (optimally), leading to a 1,2-dibromoethyl derivative. Further transformations culminated in the overall conversion of $ArCH_2CH_2SiMe_3$ into $ArCOCH_3$. Attempted aldol coupling of the resulting 1,4-diketone provoked skeletal reorganisation. A tetraalkylsilane was converted into a silanol ($ArCH_2CH_2SiMe_2OH$) by the action of aluminium chloride and water, but further oxidation of this silanol to the primary alcohol ($ArCH_2CH_2OH$) was unsuccessful.

Keywords: Ruthenium catalysis; Aromatic ketones; Tetraalkylsilane; Bromination/desilylation; Oxidation

1. Introduction

We [1,2] and others [3] have reported previously on the ruthenium-catalysed coupling of an *ortho* C–H bond of an aromatic ketone with vinyltrimethylsilane, resulting in high yields of *ortho* alkylated (2-trimethylsilylethyl) products. This catalysed C–H activation process offers a straightforward entry into a range of *ortho*-substituted acetophenones (or analogues), useful as relays in the synthesis of metal-free polyfunctional organic molecules. Such applications, however, will usually require the substitution of a trialkylsilyl moiety in the newly introduced side chain by a typical organic functional group. In particular, the adducts arising from incorporation of vinyltrimethylsilane require modification by displacement of a trimethylsilyl group, in order to yield compounds suitable for construction of further rings, either carbocyclic or heterocyclic. While many methods are known for the functionalisation of a carbon–silicon bond when the silicon carries an electronegative substituent [4,5], the reactivity of tetraalkylsilanes, in which the silicon is generally regarded as 'unactivated', has received much less attention. We now disclose our efforts to extend the possibilities inherent in the ruthenium-catalysed *ortho* alkylation procedure, by exploring the chemistry of the silicon centre. Thus, adducts of ketones containing an $ArCH_2CH_2SiMe_3$ moiety are elaborated into precursors suitable for the potential construction of tetracyclic compounds derived from podocarpic acid.

2. Results and discussion

2.1. Brominative desilylation of 7-oxopodocarpanes

Since β-ketosilanes and related moieties are known [6,7] to be synthons for the formation of an enolate (or related) ion, initial studies on functionalisation of the (2-trimethylsilylethyl) substituent were directed towards oxidation of its benzylic methylene group. However, repeated attempts to convert the benzylic methylene at C(14) of the 7-oxo diterpenoid **1** into a ketone, using either CrO_3–HOAc or DDQ, were unproductive. This

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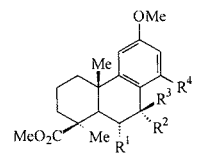
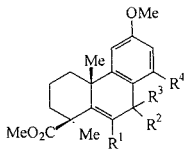
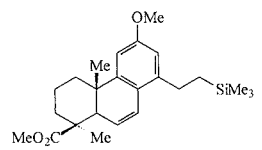
was presumed to reflect electron withdrawal by the carbonyl group already present in ring B. Moderating this effect by reduction ($NaBH_4$; 85%) of the 7-ketone, followed by attempted protection (Ac_2O–Py; or TBDMSCl, or TBDMSOTf) of the resulting alcohol(s) resulted only in elimination to give the Δ^6 alkene **2**.





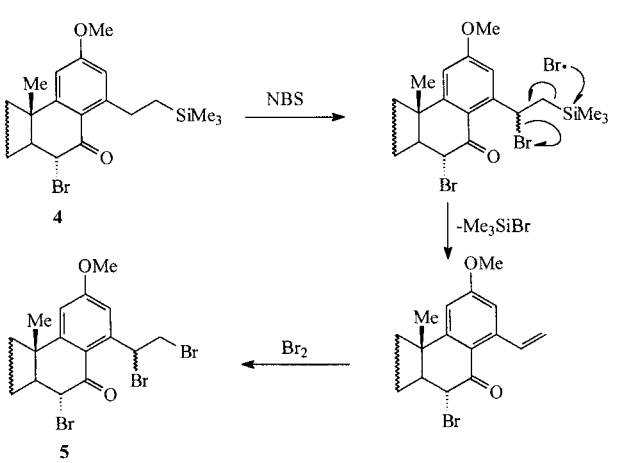
1: R^1 = H, R^2 = R^3 = O, R^4 = $CH_2CH_2SiMe_3$
4: R^1 = Br, R^2 = R^3 = O, R^4 = $CH_2CH_2SiMe_3$
5: R^1 = Br, R^2 = R^3 = O, R^4 = $CH(Br)CH_2Br$
6: R^1 = R^2 = H, R^3 = OH, R^4 = $CH_2CH_2SiMe_3$
7: R^1 = R^3 = H, R^2 = OH, R^4 = $CH_2CH_2SiMe_3$
8: R^1 = R^2 = R^3 = H, R^4 = $CH_2CH_2SiMe_3$
15: R^1 = H, R^2 = R^3 = O, R^4 = C(Br)=CH_2
17: R^1 = Br, R^2 = R^3 = O, R^4 = C(Br)=CH_2
18: R^1 = H, R^2 = R^3 = O, R^4 = $COCH_3$

3: R^1 = H, R^2 = R^3 = O, R^4 = $CH_2CH_2SiMe_3$
11: R^1 = Br, R^2 = R^3 = O, R^4 = $COCHBr_2$
12: R^1 = Br, R^2 = R^3 = O, R^4 = $COCH_3$
16: R^1 = H, R^2 = R^3 = O, R^4 = C(Br)=CH_2
42: R^1 = H, R^2 = R^3 = O, R^4 = $COCH_3$



2

However, as the styrene **2** is less electron poor than the 7-ketone **1**, oxidation of **2** could occur at the benzylic position of the side chain to yield the desired β-ketosilane. In the event, treatment of **2** with PCC (five molar equivalents) absorbed on Celite in refluxing benzene for 18 h resulted in oxidation in ring B, giving the Δ^5-en-7-one **3** (51%). The α,β-unsaturated ketone moiety in **3** was clearly evident in the ^{1}H- (H(6), 6.47 ppm) and ^{13}C-NMR spectra (CO, 185.8 ppm), and in the IR spectrum (1653 cm^{-1}). Conversion of **2** into **3** requires oxidation of an allylic C–H bond or an allylic alcohol, which are well-known processes [8,9]. Rearrangement is known to occur during oxidation of an allylic tertiary alcohol to an enone [10], and Nicolaou has reported that PCC in refluxing benzene can cleanly oxidise an allylic CH_2 to the α,β-unsaturated ketone [11]. Inclusion of NaOAc in the oxidising medium for **2** resulted in not only a slower reaction and a lower yield (28%) of



Scheme 1.

3, but also other products. Attempted modification of the 7-ketone in **1** as either a 1,3-dioxolane or as a dimethyl acetal using a variety of conditions was unsuccessful. Consequently, further investigations into benzylic oxidations as a route to the functionalisation of tetraalkylsilanes via derived β-ketosilanes were not undertaken.

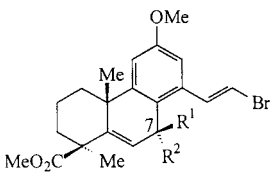
In another approach, it was expected that benzylic bromination of $ArCH_2CH_2SiMe_3$ would yield a β-bromosilane which would undergo rapid β-elimination of Me_3SiBr [12,13]. However, treatment of **1** with NBS (1.3 molar equivalents) in refluxing carbon tetrachloride for 16 h gave only the 6α-bromo-7-ketone **4**. The configuration at C(6) was assigned from the ^{1}H-NMR spectrum ($J_{H(5)–H(6)} = 6.6$ Hz) [14] and was supported by X-ray crystallographic analysis of the related compound **30** (see Section 2.7). It was apparent that more than one molar equivalent of NBS was required to ensure bromination of the C(14) side chain also. Indeed, addition of six equivalents of NBS portionwise (one equivalent at 2 h intervals) to a refluxing solution of **1** and then refluxing overnight resulted in total conversion of the starting material. The 6α-bromo-14-(1,2-dibromoethyl)-7-oxo diterpenoid (**5**, 27%) was isolated as an inseparable mixture (1:1.02), epimeric at the newly created stereocentre in the side chain. In the ^{1}H-NMR spectrum the signal due to the benzylic Br–C–*H* was a doublet of doublets ($J = 9.2$, 6.0 Hz) at 5.93 ppm in one stereoisomer, and a triplet ($J = 6.9$ Hz) at 5.99 ppm in its epimer. Separate chemical shifts were also observed for H(6eq), for H(11) and for H(13). Accurate measurement of the peak at highest m/z in the mass spectrum was consistent with the formula $C_{21}H_{25}O_4Br_2$, indicating that rapid loss of HBr occurred before the molecular ion could be detected. Microanalytical data was, however, in accord with formulation of the product as the tribromide. Compound **5** is proposed to form from **4** by initial radical bromination at the benzylic position followed by rapid elimination of Me_3SiBr to yield a styrene, which then undergoes electrophilic addition of bromine (Scheme 1).

Although functionalisation of the tetraalkylsilane had been achieved, this approach requires that the C(6) bromide would have to be removed eventually. Therefore the C(7) ketone was removed in order to avoid initial bromination at C(6) via the enol. The required C(7) methylene compound **8** was synthesised from the epimeric alcohols **6**/**7** by either ionic hydrogenation (CF_3COOH–Et_3SiH; 96%) or heterogeneous catalysed hydrogenation (H_2–Pd–C–HOAc; 75%). However, reaction of **8** with excess NBS under the conditions described above gave a complicated mixture (TLC, ^{1}H-NMR). In order to simplify this mixture it was refluxed with DBU to effect elimination.

Table 1
Brominations of **1** in the presence of $(PhCO)_2O$ and an added base

Run	NBS (equivalents)	Base (equivalents)	Solvent	Time (h)	Yields (%) **5**/**11**
1	4	K_2CO_3/4.5	C_6H_6	24	19/12 [a]
2	6	K_2CO_3/12	C_6H_6	24	23/15
3	12	K_2CO_3/12	C_6H_6	24	12/13
4 [b]	9	K_2CO_3/9	C_6H_6	21	18
5	6	K_2CO_3/9	CCl_4	8	23/33
6	6	$NaHCO_3$/6	CCl_4	23	28
7	6	KOH/6	CCl_4	12	No reaction
8	6	DBU/6.5	C_6H_6	5	Mixture

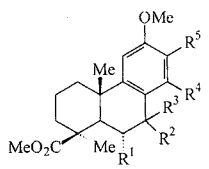
[a] C(6) monobromide **4** also isolated (28%).
[b] Reaction using C(6) monobromide **4**.



9: R^1 = N-succinimidoyl, R^2 = H
10: R^1 = H, R^2 = N-succinimidoyl

While bromination–elimination in the side chain had taken place as desired, leading to the vinyl bromides **9** and **10** (1:1), a Δ^5-7-*N*-succinimidoyl unit had also been incorporated. The changes in ring B occur presumably via radical bromination at C(7) followed by loss of HBr to give a C(6)–C(7) double bond. Addition of NBS (cf. [15]) to this double bond followed by elimination of HBr yields the Δ^5-7-*N*-succinimidoyl alkene. NBS is known to be able to introduce double bonds into a molecule via bromination–dehydrobromination. For example, Ogawa and co-workers [16] have reported that some dihydrobenzofuran derivatives can be transformed into benzofurans in a one-pot sequence using NBS in the presence of K_2CO_3, and dibenzoyl peroxide as initiator. Application of this procedure to 14-(2-trimethylsilylethyl)-7-oxo diterpenoid (**1**) would be expected to promote the elimination of two molecules of HBr from the intermediate tribromide **5**; the results from bromination of **1** with NBS in the presence of various bases are given in Table 1. Use of the Ogawa conditions (run 1) afforded **5** in only 19% yield, lower than that when base was absent. A more polar compound ($C_{21}H_{22}Br_3O_5$) was also isolated (12%), and was assigned as 6-bromo-14-(2,2-dibromoethan-1-oyl)-Δ^5-7-ketone (**11**). The structure of this α,α-dibromoketone was confirmed by reductive removal of the two bromine atoms in the side chain by treatment with Zn–HOAc, to give the acetophenone derivative **12** ($COCH_3$, δ_H 2.52 ppm). As an alternative to either benzoyl peroxide or AIBN, visible light can also promote the radical sequence resulting in benzylic bromination of alkylbenzenes. Pleasingly, treatment of **1** with NBS (six equivalents) in CCl_4 for 90 min under irradiation with a tungsten lamp gave the tribromide **5** in much improved yield (46%), and under milder conditions (room temperature, short time) relative to the reactions using NBS–$(PhCO)_2O$.

Two other methods for selective bromination/desilylation were also investigated. For simple benzene derivatives which contain electron-withdrawing substituents, bromination in an alkyl side chain can be accomplished readily using ceric ammonium nitrate (CAN)–KBr in HOAc at 80°C [17]. However, application of this method to the 7-oxo diterpenoid **1** resulted in dibromination only, at C(6) and C(13), to give **13**. Ishii and co-workers have recently reported [18] that either benzylic or ring bromination of alkylbenzenes can be achieved using $NaBrO_3$–$NaHSO_3$, in either a two-phase or a homogeneous solvent system.



13: R^1 = Br, R^2 = R^3 = O, R^4 = $CH_2CH_2SiMe_3$, R^5 = Br
14: R^1 = H, R^2 = R^3 = O, R^4 = $CH_2CH_2SiMe_3$, R^5 = Br
19: R^1 = R^5 = H, R^2 = R^3 = O, R^4 = CH_2CH_3
20: R^1 = R^5 = H, R^2 = R^3 = O, R^4 = $CH{=}CH_2$
21: R^1 = H, R^2 = R^3 = O, R^4 = CH_2CH_3, R^5 = HgBr

For the alkylbenzenes studied by these workers, the use of EtOAc as the organic solvent favoured bromination in the alkyl side chain. Therefore, **1** was treated with an excess of $NaBrO_3$–$Na_2S_2O_5$ in EtOAc–H_2O. Unexpectedly, however, the 6,13-dibromide **13** was the sole product isolated (66%). Presumably, preferential electrophilic arene bromination at C(13) inhibits bromination in the C(14) side chain. Changing the organic solvent to hexane yielded, on one occasion, the desired tribromide **5** in 66% yield after only 20 min, but unfortunately this outcome could not be reproduced. After much experimentation the conditions required to induce brominative desilylation of **1** to give tribromide **5** consistently were established to be: (i) 12 molar equivalents of sodium bromate; (ii) 12 molar equivalents of sodium metabisulfite (reputable source); (iii) 3:1 hexane–H_2O (v/v) as solvents; (iv) addition of the sodium metabisulfite as quickly as possible to the mixture of diterpenoid and sodium bromate. As reaction of **1** using the Ishii method was quite exothermic, in one variation $Na_2S_2O_5$ was added at 0°C and the mixture

was allowed to warm to room temperature; under these conditions, however, only arene bromination occurred to give the 13-bromo derivative **14** (78%).

2.2. Further transformations of the desilylated tribromide **5**

Since modification of the Ishii conditions had permitted efficient brominative desilylation of the 14-(2-trimethylsilylethyl) diterpenoid **1** to give the 14-(1,2-dibromoethyl) derivative **5**, routes for conversion of this intermediate into compound(s) suitable for construction of an additional ring were sought. The 1,4-diketone **18** was regarded as such a compound. Clearly, reactions of **5** would mainly involve familiar chemistry of the carbon–bromine bond, such as reduction, or elimination or substitution. In an exploratory experiment, treatment of a mixture (3:2) of 6α-bromo-14-(2-trimethylsilylethyl)-7-oxo-diterpenoid (**4**) and its 14-(1,2-dibromoethyl) congener **5** with DBU (five equivalents) in refluxing benzene for 22 h returned the debrominated ketone **1** (68%, based on **4**) [19,20] and its Δ^5 derivative **3** (18%). The corresponding vinyl bromides **15** (15%, based on **5**) and its Δ^5 derivative **16** (46%), which result from elimination of HBr from the side chain of **5**, were also formed. Interestingly, these 14(1-bromoethenyl) compounds **15** and **16** have formed by elimination in the opposite regiochemical sense to vinyl bromides **9** and **10**.

In contrast to the outcome under reflux, treatment of the 6α-bromo-14-(2-trimethylsilylethyl)-7-oxo diterpenoid **4** with either DBU or Et_3N at room temperature for two days did not result in either reductive debromination or elimination. It therefore appeared that selective elimination in the side chain of **5** could be achieved by controlling both the reaction temperature and time. Heating under reflux, and for a relatively short time, was essential. Thus, refluxing the tribromide **5** with DBU (three equivalents) in benzene for 1–2 h afforded the 6α-bromo-14(1-bromoethenyl) derivative **17** as the sole product, and in quantitative yield. Retention of the 6α-bromide was evident by a doublet ($J = 6.17$ Hz) at 5.69 ppm in the ^{1}H-NMR spectrum, while the terminal methylene group in **17** was characterised by doublets ($J = 1.8$ Hz) at 5.73 and 5.86 ppm. Stirring the crude α-bromo ketone **17** with Zn (two equivalents)–HOAc [21] at room temperature [22] for 2 h resulted in quantitative and selective reduction of the C(6) halogen to give the 14(1-bromoethenyl) derivative **15**. Although this vinyl bromide did not hydrolyse during exposure to either silica gel in THF–H_2O, or to HCl (50% aqueous), the 14-acetyl-7-oxo diterpenoid **18** was formed in good yield overall (59%, three steps from **1**) using $Hg(OCOCF_3)_2$–CF_3COOH–HCOOH.

In contrast, four products were obtained from reaction of the tribromide **5** with DBU (three equivalents) in benzene at room temperature for 2 h, followed by treatment of the crude mixture with Zn–HOAc and then with $Hg(OCOCF_3)_2$–CF_3COOH–HCOOH. The 14-ethyl-7-ketone **19** (11%) arises from the styrene **20** (8%). The carbonyl group at C(7) in **20** promotes conjugate attack of zinc at the terminal methylene group in **19** to yield a 14-(ethylzinc) species, which undergoes protonolysis to the alkane; similar reduction of a remote conjugated double bond has been reported recently [23]. In turn, **20** results from reductive debromination of some 6α-bromide remaining after reaction of **5** with DBU. Formation of the 13-mercurated compound **21** was unexpected since this had not occurred during previous Hg(II)-catalysed hydrolyses of the vinyl bromide, although mercuration is known to be facilitated by electron-donating groups on an aromatic ring [24].

Since terminal alkenes are excellent synthons for the preparation of methyl ketones [25], an alternative route for the synthesis of the 1,4-diketone **18** involves conversion of the tribromide **5** into the styrene **20**, and then a Wacker-type oxidation [26]. Thus, treatment of the 14-(2-trimethylsilylethyl)-7-ketone **1** with $NaBrO_3$–$Na_2S_2O_5$ (12 equivalents each) followed by reaction of the crude product with Zn–HOAc gave **20** (58%). The results from attempted conversion of this styrene into a methyl ketone are given in Table 2. The Wacker oxidation of alkenes to ketones is usually accomplished with a catalytic amount of palladium(II) and a re-oxidant such as copper(II) chloride. In the present case, however, even an excess of $PdCl_2$ (6.5 equivalents, run 1) in DMF–water gave only a trace of the methyl ketone (^{1}H-NMR), together with unidentified components. Mercury(II) acetate in combination with $PdCl_2$ is known to promote the efficient oxidation of a terminal alkene to a methyl ketone [27], but treatment of the styrene **20** with $Hg(OAc)_2$ (one equivalent) for 10 min followed by the addition of $PdCl_2$ (one equivalent) returned mostly starting material (run 2). An alternative procedure was to isolate the hydration product before addition of an oxidising agent (run 3). Thus, hydroxymercuration of the alkene followed by reductive demercuration with $NaBH_4$ gave a mixture of the 7β-14(1ξ-hydroxyethyl) epimeric diols, Jones' oxidation of which gave the 1,4-diketone **18** (26% from **20**).

Table 2
Oxidations of the alkene **20**

Run	Conditions	Result
1	$PdCl_2$–DMF–H_2O (4 h)	Ketone (trace)
2	$Hg(OAc)_2$–THF–H_2O (10 min); $PdCl_2$ (4 h)	Ketone (trace)
3	$Hg(OAc)_2$–THF–H_2O (30 min); $NaBH_4$–NaOH(aq.); Jones	Ketone (26%)

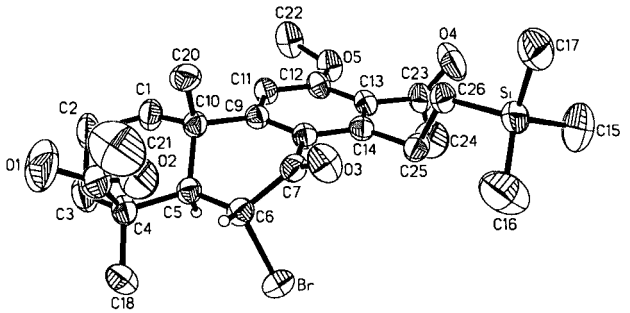
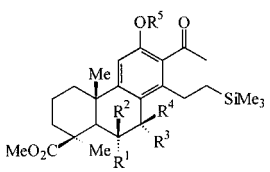


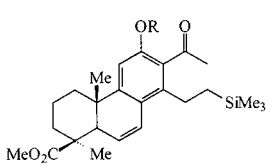
Fig. 1. The atomic arrangement in **30**.

2.3. Attempted brominative desilylation of 13-acetyl analogues

Since a sequence for the conversion of $ArCH_2CH_2SiMe_3$ into $ArCOCH_3$ in 14-(2-trimethylsilylethyl)-7-oxo diterpenoid (**1**) had been established, the route was attempted on related compounds containing a 13-acetyl group, the aim being to generate a 1,4-diketone which might allow cyclopentaannulation across C(13)/C(14), leading to steroidal analogues with an aromatic ring C. Thus, 13-acetyl-12-(((1,1-dimethylethyl)dimethylsilyl)-oxy)-14-(2-trimethylsilylethyl) diterpenoid (**22**) was treated with $NaBrO_3$–$Na_2S_2O_5$ (six equivalents each) in hexane–water for 30 min (optimum conditions for formation of **5** from **1**). Although three products were formed, none had undergone desilylation/bromination in the C(14) side chain. Instead, the Δ^6-alkene **23** (30%) and a mixture of the derived *cis* bromohydrins **24** and **25** were isolated. The regiochemistry of addition of HOBr to the alkene was determined by correlations in the 2D-NMR spectra, and the stereochemistry was deduced from relative *J* values. The *cis* stereochemistry was unexpected as *trans* bromohydrins are usually formed under these conditions [28]. Isolation of **24** and **25** suggests that the Δ^6 alkene **23** reacts with electrophilic bromine to yield a mixture of 6α-bromo and 6β-bromo open C(7) carbocations stabilised by the *p*-methoxyphenyl ring. Water then approaches from the same face (internal delivery?) as the bromine atom, leading to the stereoisomeric *cis* adducts.



22: $R^1 = R^2 = R^3 = R^4 = H$, R^5 = TBDMS
24: R^1 = Br, $R^2 = R^4 = H$, R^3 = OH, R^5 = TBDMS
25: $R^1 = R^3 = H$, R^2 = Br, R^4 = OH, R^5 = TBDMS
26: $R^1 = R^2 = R^3 = R^4 = H$, R^5 = COMe
28: $R^1 = R^2 = R^3 = R^4 = H$, R^5 = Me
29: $R^1 = R^2 = H$, $R^3 = R^4 = O$, R^5 = Me
30: R^1 = Br, $R^2 = H$, $R^3 = R^4 = O$, R^5 = Me



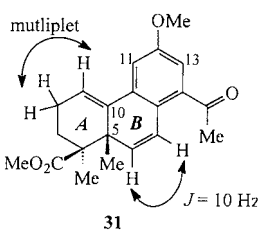
23: R = TBDMS
27: R = COMe

Clearly, the desired bromination/desilylation in the C(14) side chain of **22** had not occurred, and instead generation of a carbocation at C(7) was favoured. On the basis that carbocation formation might be disfavoured by moderating electron donation from the substituent *para* to C(7), the C(12)-acetate **26** was synthesised (96%) from the C(12)–TBDMS ether **22**. However, treatment of **26** with $NaBrO_3$–$Na_2S_2O_5$ (12 equivalents each) in 3:1 hexane–water for 30 min also resulted in reaction at C(7), to give a 7-bromo derivative which eliminated HBr during silica gel chromatography to afford the alkene **27** (68%). Extending the reaction time to 4 h resulted in bromination not only at C(7) but also of the C(13) acetyl group. That is, while an acetate at C(12) had prevented secondary formation of the 6,7-bromohydrins, initial bromination was still favoured at C(7) rather than in the 14(2-trimethylsilylethyl) side chain. The C(7) methylene group in **22** was therefore converted into the C(7) ketone. Since TBDMS derivatives are known to cleave under oxidising conditions (I_2–MeOH [29], CAN [30]) to give a phenol, which could lead to oxidation of the arene ring, the silyl ether at C(12) in **22** was first transformed into the methyl ether **28** using TBAF–MeI [31]. Treatment of **28** with CAN then gave the desired 13-acetyl-7-ketone **29** (45%). Based on our previous work it was expected that exposure of **29** to $NaBrO_3$–$Na_2S_2O_5$ would effect bromination initially at C(6), and then in the C(14) side chain. In the event, treatment of **29** for 1 h with $NaBrO_3$–$Na_2S_2O_5$ (12 equivalents each) in 7:2 hexane–water gave only monobromination, at C(6) (93%). The stereochemistry of monobromide **30** was confirmed as 6α by single-crystal X-ray diffraction analysis (Fig. 1). These studies established that in contrast to the 7-oxo analogue **1**, the 13-acetyl-14(2-trimethylsilylethyl) diterpenoid **22** was not a suitable substrate for brominative desilylation.

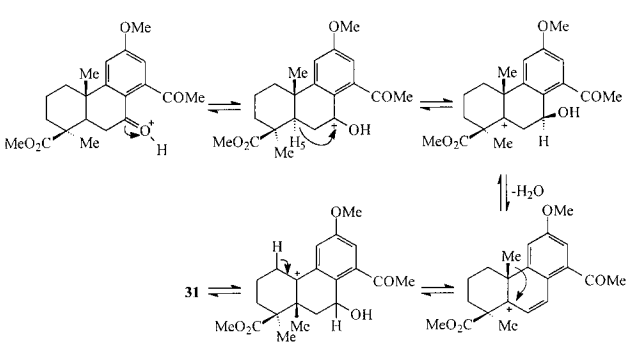
2.4. Attempted annulation of *18* by aldol coupling

In the expectation that a bulky base would favour deprotonation at the more accessible acetyl group, the 1,4-diketone **18** was refluxed in THF with potassium *t*-butoxide for 16 h, but no reaction occurred. Similarly, refluxing **18** with 10% KOH in methanol for 15 h returned only the starting diketone. The use of either LDA at -78°C or NaH in refluxing THF for 3 h also did not effect the aldol transformation. Since aldol reactions between two ketones are invariably easily reversible [32], the product of cyclopentaannulation may not be stable. Guthrie has reported [33] that self-condensation of acetophenone is endothermic (computed ΔG, $+22.5$ kJ mol^{-1}), indicating that the annulation required in the present work might be difficult. Should the aldol form, however, then loss of water to form the conjugated ketone should be rapid (exothermic, -13.3 kJ mol^{-1}).

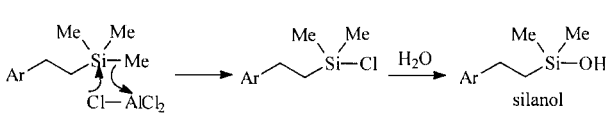
Since base did not promote aldol cyclisation in **18**, attention was turned to the use of an acidic catalyst. Refluxing the 1,4-diketone with $ZnCl_2$ (one equivalent) in either benzene or toluene for 24 h returned starting material, while *p*-TsOH/4 Å sieves in refluxing toluene for 5 h gave a product whose spectroscopic data were not consistent with an aldol. Prominent peaks at m/z 43 and (M-43) in the mass spectrum indicated that $COCH_3$ was still present, as did absorption at 1685 cm^{-1} in the IR spectrum (cf. enone, ν_{max} expected 1650 cm^{-1}). After extensive 2D-NMR analysis the structure was proposed to be **31**. The ^{1}H-NMR spectrum of **31** confirmed the presence of two quaternary methyl groups, and of COMe, 19-OMe and 12-OMe. The signals due to the protons of ring A were multiplets (1.86–1.73 and 2.30–2.36 ppm) that integrated for only four hydrogens, and there were five aromatic/vinyl protons evident. Two of these were clearly H(11) and H(13) (d, $J = 2.6$ Hz). Doublets at 6.86 and 6.48 ppm were mutually coupled ($J = 10.3$ Hz), indicating an isolated double bond. The remaining hydrogen bound to sp^2 carbon gave a multiplet at 6.05 ppm; the ^{1}H COSY spectrum showed coupling with the multiplet at 2.30–2.36 ppm, and therefore the latter hydrogens were allylic. Hence ring A contained a double bond. The ^{13}C-NMR spectrum revealed that there were only two CH_2 groups present, and that C(5) was quaternary. A methyl group was placed at C(5) because ^3J coupling from H(7) was detected, and also because of the significant upfield shift (19.9 ppm) of the signal due to C(18).



31



Scheme 2.



Scheme 3.

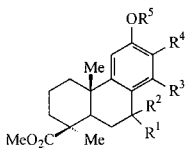
The skeletal reorganisation required to form **31** is proposed to occur via methyl migration in a stabilised allylic cation, itself formed by a 1,3-hydride shift [34–36] from H(5α) to C(7) followed by loss of water (Scheme 2).

*2.5. Lewis acid-promoted cleavage of the carbon–silicon bond in **1***

Reports of the functionalisation of a carbon–silicon bond when the silicon contains only alkyl groups and is therefore regarded as unactivated are limited to electrochemical or photochemical methods [5] and to the use of electrophilic species such as BCl_3, $GaCl_3$, $Tl(OCOCF_3)_3$, $HgCl_2$, $Hg(NO_3)_2$, $[(C_2H_4)PtCl_2]_2$, $H_2PtCl_6{\cdot}6H_2O$ [37] or [PhTl(crown ether)][Otf]$_2$ [38], each of which shows varying degrees of efficiency and selectivity. In the present work, oxidative cleavage of a silicon–methyl bond occurred during treatment of 12-methoxy-14-(2-trimethylsilylethyl)-7-ketone (**1**) with $AlCl_3$ (five equivalents) in refluxing CH_2Cl_2 [39]. The expected phenol **32**, which was isolated in only 4% yield, gave the correct accurate measurement for the molecular ion in the mass spectrum, and expulsion of $^{\bullet}SiMe_3$ occurred to yield a strong fragment ion at m/z 329. Accurate measurement of the molecular ion of the major product, the polar silanol **33** (89%), revealed that an extra oxygen atom was present, and the base peak in the spectrum (in contrast to that of **32**) was due to loss of water. The ^{1}H-NMR spectrum of **33** confirmed that one methyl group had been lost from silicon. This transformation represents important methodology for the functionalisation of tetraalkylsilanes, since the reaction is high yielding with minimum formation of by-products. Transfer of a methyl group from silicon to aluminium is proposed to be concomitant with transfer of a chlorine atom from the metal centre to the silicon [40]; the resulting trialkylchlorosilane reacts with water to yield the silanol (Scheme 3).

The ketone at C(7) is crucial to conversion of the tetraalkylsilane into the silanol by the Lewis acid. Thus, treatment of methyl 12-methoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**8**) with $AlCl_3$ (five equivalents) in refluxing CH_2Cl_2 for 24 h did not lead to any silanols or disiloxanes. Instead, loss of the 14-(2-trimethylsilylethyl) side chain occurred (13%), as did cleavage of the CH_2–$SiMe_3$ bond to give the 14-ethyl derivative (52%; GC–MS), disproportionation of which afforded the 14-methyl (14%) and 14-propyl (11%) congeners. The 13-acetyl-12-hydroxy-14-(2-trimethylsilylethyl)-7-ketone **38** (12%) was also isolated [ν_{max} 1726 (ester), 1704 and 1681 cm^{-1} (C=O ketone)]. This diketone probably arises from alkylation of a phenol at C(13) by either an ethyl or ethylsilyl group which oxidises to the acetyl group on exposure to air.

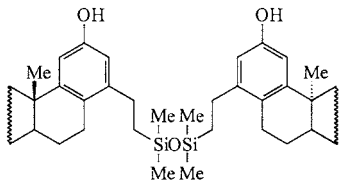
The fact that cleavage of $ArCH_2CH_2SiMe_3$ to $ArCH_2CH_2SiMe_2OH$ by $AlCl_3$ is promoted by the presence of the C(7) ketone in **1** reflects a combination of factors. The electron-withdrawing effect of the carbonyl group will inhibit dealkylation via carbocation intermediates (cf. **8**). Perhaps more significantly, coordination of aluminium chloride to the ketone oxygen may serve to deliver the chlorine atom to silicon.



32: $R^1 = R^2 = O$, $R^3 = CH_2CH_2SiMe_3$, $R^4 = R^5 = H$
33: $R^1 = R^2 = O$, $R^3 = CH_2CH_2SiMe_2OH$, $R^4 = R^5 = H$
34: $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = Me$
35: $R^1 = R^2 = R^4 = H$, $R^4 = R^5 = Me$
36: $R^1 = R^2 = R^4 = H$, $R^4 = Et$, $R^5 = Me$
37: $R^1 = R^2 = R^4 = H$, $R^4 = Pr$, $R^5 = Me$
38: $R^1 = R^2 = O$, $R^3 = CH_2CH_2SiMe_3$, $R^4 = COMe$, $R^5 = H$
39: $R^1 = R^2 = O$, $R^3 = CH_2CH_2SiMe_2OH$, $R^4 = H$, $R^5 = COMe$
41: $R^1 = R^2 = R^4 = H$, $R^3 = CH_2CH_2SiMe_2OH$, $R^5 = SiEt_3$

2.6. Investigation of carbon–silicon cleavage in silanol *33*

There have been few reports of cleavage of the carbon–silicon bond in silanols, although they are likely intermediates in the oxidation reaction [41]. In the current investigation, treatment of 12-hydroxy-14(2-hydroxydimethylsilylethyl) (**33**) with an excess of H_2O_2–KF–$NaHCO_3$ at either reflux or room temperature was unproductive. The first step during oxidation of a carbon–silicon bond under these conditions is usually coordination of fluoride to create a hypervalent silicon species. It appeared likely that trialkylsilanol **33**, which already has a hydroxy group on silicon, was too electron-rich for this nucleophilic step to occur. Since an acetate group on silicon would attenuate electron donation and might therefore allow such attack, the silanol **33** was stirred with an excess of Ac_2O in pyridine containing a catalytic amount of DMAP. However, only the phenol was esterified, giving the 12-acetate **39**. Acylation of a silanol is known to be difficult, even when an excess of acetic anhydride is used [42]. Acetyl chloride, which is more reactive than acetic anhydride, also gave **39** (63%). Treatment of the 12-acetoxy trialkylsilanol **39** with H_2O_2 (24 equivalents) and KF–$NaHCO_3$ in THF–MeOH at 60°C returned starting material after 18 h, while *m*-CPBA (three or 12 equivalents)–KF in DMF [42] at either room temperature or 90°C gave either no reaction or a complicated mixture (in which oxidation had not occurred). Since cyclic alkoxysilanes usually undergo oxidative cleavage more readily than straight chain analogues, an alternative strategy was proposed, involving reduction of a 7-ketone to an alcohol followed by intramolecular capture by the 14-ethylsilanol prior to exposure to H_2O_2. In the event, treatment of the 7-ketone **33** with $NaBH_4$ (six equivalents) in ethanol at either r.t. or reflux gave only starting material, while BH_3·DMS (four equivalents) resulted in both deoxygenation of the ketone and intermolecular reaction to give the disiloxane **40** (34%). Deoxygenation also occurred with CF_3COOH–Et_3SiH, concomitant with triethylsilylation at C(12) to give **41** (24%). Since we have shown in related work that oxidation of a silicon–carbon bond in the 14-(2-trimethylsilylethyl) side chain results also in Baeyer–Villiger oxidation of a C(7) ketone [43], these results are noteworthy as ketone deoxygenation provides a way of avoiding the undesired lactone formation. In the context of the present work, however, cleavage of a silicon–ethyl carbon bond in the diterpenoid silanol could not be induced.



40

2.7. X-ray crystal structure of *30*

Data were collected on a Siemens SMART area detector diffractometer using 0.3° frames and profile fitting. Lorentz, polarisation and absorption corrections [44] were applied and equivalent reflections averaged to give 6173 unique data. Unit cell parameters were obtained by a least-squares fit to all data with $I > 10\sigma(I)$. The structure was solved by direct methods [45] and refined by full-matrix least-squares on F^2 [46]. Hydrogen atoms were placed geometrically and refined with a riding model, including free rotation for methyl groups, with thermal parameter 20% (50% for methyl groups) greater than U_{iso} of the carrier atom. All non-hydrogen atoms were refined with anisotropic thermal parameters. Refinement converged to R_1 (observed data) 0.0476. Crystal data and refinement parameters are given in Table 3 and the structure is shown in Fig. 1, which shows the absolute configuration.

2.8. Summary

These investigations have shown that the tetraalkylsilanes readily available from the ruthenium-catalysed *ortho* alkylation of some diterpenoid ketones with vinyltrimethylsilane can undergo brominative desilylation. The resulting silicon-free compounds have been used to explore routes for annulation of ring C aromatic diterpenoids.

Table 3
Data collection and processing parameters for **30**

Formula	$C_{26}H_{37}BrO_5Si$
Molecular weight	537.56
Temperature (K)	203
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	8.3704(1)
b (Å)	14.3873(2)
c (Å)	22.6929(1)
V (Å^3)	2732.85(5)
Z	4
D_{calc} (g cm^{-3})	1.307
F(000)	1128
μ (mm^{-1})	1.580
Crystal size (mm)	$0.64 \times 0.35 \times 0.22$
2θ Range (°)	1.7–27.5
Index ranges	$-10 \le h \le 10$, $0 \le k \le 18$, $0 \le l \le 29$
Reflections collected	25 771
Independent reflections	6173 [$R_{int} = 0.0368$]
A (min/max)	0.431, 0.722
Function minimised	$\Sigma w(F_o^2 - F_c^2)^2$
Data/restraints/parameters	6173/0/306
Goodness of fit on F^2	1.026
Flack parameter	0.014(9)
R_1 (observed data)	0.0476
wR_2 (all data)	0.1402
Difference map (min/max) (e Å^{-3})	1.78 and −0.30
$R_1 = \Sigma\|\|F_o\| - \|F_c\|\|/\Sigma\|F_o\|$	$wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$

3. Experimental

For general experimental details see Ref. [2].

3.1. Methyl 12-methoxy-14-(2-trimethylsilylethyl)-podocarpa-6,8,11,13-tetraen-19-oate (2)

To a stirred solution of methyl 12-methoxy-14-(2-trimethylsilylethyl) - 7 - oxopodocarpa-8,11,13-trien-19-oate (**1**, 154 mg, 0.370 mmol) in ethanol (3 ml) was added $NaBH_4$ (41 mg, 1.11 mmol). After 11 h saturated aqueous ammonium chloride was added, and the product was extracted with dichloromethane. The combined extracts were dried and the solvent removed in vacuo to give a colourless oil (135 mg, 87%). This was dissolved in dichloromethane (2 ml), and acetic anhydride (0.121 ml, 1.29 mmol) and pyridine (0.103 ml, 1.29 mmol) were added. After stirring overnight the mixture was poured into ice and extracted with dichloromethane. Work-up gave methyl 12-methoxy-14-(2-trimethylsilylethyl)podocarpa-6,8,11,13-tetraen-19-oate (**2**, 106 mg, 81%) as a colourless oil. ν_{max} 1727 (C=O ester), 1600, 1464 (C=C), 1247, 861, 835 cm^{-1} (Si–C). δ_H 0.082, s, 9H, SiMe_3; 0.8–0.87, m, 2H, 14-$CH_2CH_2SiMe_3$; 0.87, s, 3H, H(20); 1.14, td, $J = 13.5$, 3.9 Hz, 1H, H(3ax); 1.34, s, 3H, H(18); 1.60, td, $J = 13.5$, 4.1 Hz, 1H, H(1ax); 1.73, dp, $J = 13.5$, 4.3, 1H, H(2eq); 1.95, qt, $J = 13.9$, 3.6 Hz, 1H, H(2ax); 2.21 bd, $J = 12.4$ Hz, 1H, H(1eq); 2.34, t, $J = 2.84$ Hz, 1H, H(5); 2.36, bd, 1H, H(3eq); 2.62–2.70, m, 2H, 14-$CH_2CH_2SiMe_3$; 3.71, s, 3H, 19-OMe; 3.82, s, 3H, 12-OMe; 6.44, dd, $J = 10.1$, 2.44 Hz, 1H, H(6); 6.58, d, $J = 2.52$ Hz, 1H, H(13); 6.63, dd, $J = 10.1$, 3.1 Hz, 1H, H(7); 6.68, d, $J = 2.52$ Hz, 1H, H(11). δ_C −1.89, SiMe_3; 18.8, 14-$CH_2CH_2SiMe_3$; 19.05, C(20); 19.7, C(2); 27.6, 14-$CH_2CH_2SiMe_3$; 27.7, C(18); 36.3, C(1); 37.2, C(3); 38.4, C(10); 43.4, C(4); 50.8, C(5); 51.4, 19-OMe; 55.0, 12-OMe; 106.9, C(11); 110.6, C(13); 121.2, C(6); 122.9, C(8); 127.3, C(7); 142.2, C(14); 148.7, C(9); 158.2, C(12); 177.5, C(19). m/z 400 (100, M^+), 73 (55, $SiMe_3$). Found: M^+, 400.2416. Calc. for $C_{24}H_{36}O_3Si$: M, 400.2434.

3.2. Methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-5,8,11,13-tetraen-19-oate (3)

To a solution of methyl 12-methoxy-14-(2-trimethylsilylethyl)podocarpa-6,8,11,13-tetraen-19-oate (**2**, 106 mg, 0.265 mmol) in benzene (15 ml) was added a homogenized mixture of PCC (0.284 g, 1.325 mmol) and Celite (1 g). The mixture was stirred and refluxed for 18 h and then ether was added. Filtration through a short pad of Celite–$MgSO_4$ followed by solvent removal and flash chromatography (silica gel, 3:1 hexanes–ether) gave methyl 12-methoxy-14-(2-trimethylsilylethyl) - 7 - oxopodocarpa - 5,8,11,13 - tetraen - 19-oate (**3**, 51%, 56 mg) as an orange oil. ν_{max} 1731 (C=O ester), 1653 (C=O enone), 1600 (C=C), 1290, 1246, 861, 835 cm^{-1} (Si–C). δ_H 0.1, s, 9H, SiMe_3; 0.78–0.85, m, 2H, 14-$CH_2CH_2SiMe_3$; 1.22, td, $J = 13.6$, 4.2 Hz, 1H, H(3ax); 1.29, s, 3H, H(20); 1.47, s, 3H, H(18); 1.52, td, $J = 13.5$, 4.1 Hz, 1H, H(1ax); 1.69–1.73, m, 1H, H(2eq); 2.11, qt, $J = 13.8$, 3.6 Hz, 1H, H(2ax); 2.32, bd, $J = 13.2$ Hz, 1H, H(1eq); 2.51, bd, $J = 13.3$, 1H, H(3eq); 3.0–3.23, m, 2H, 14-$CH_2CH_2SiMe_3$; 3.63, s, 3H, 19-OMe; 3.87, s, 3H, 12-OMe; 6.47, s, 1H, H(6); 6.72, d, $J = 2.48$ Hz, 1H, H(11); 6.84, d, $J = 2.48$ Hz, 1H, H(13). δ_C −1.76, SiMe_3; 18.9, 14-$CH_2CH_2SiMe_3$; 19.3, C(2); 27.0, C(20); 28.4, C(18); 30.7, 14-$CH_2CH_2SiMe_3$; 37.0, C(3); 40.4, C(1); 42.4, C(10); 47.3, C(4); 51.9, 19-OMe; 55.1, 12-OMe; 109.0, C(13); 114.4, C(11); 121.2, C(8); 128.2, C(6); 151.4, C(14); 156.8, C(9); 161.0, C(5); 161.9, C(12); 175.7, C(19); 185.8, C(7). m/z 414 (70, M^+), 399 (50, $M-15$), 341 (70, $M - SiMe_3$), 73 (100, $SiMe_3$). Found: M^+, 414.2210. Calc. for $C_{24}H_{34}O_4Si$: M, 414.2226.

3.3. Methyl 6α-bromo-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (4)

Methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**1**, 0.122 g, 0.293 mmol), *N*-bromosuccinimide (0.067 g, 0.380 mmol) and benzoyl peroxide (0.014 g, 0.058 mmol) were refluxed in CCl_4 (4 ml) for 16 h. The cooled mixture was filtered and the residue washed with CCl_4. Flash chromatography (silica gel, benzene) gave methyl 6α-bromo-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,-11,13-trien-19-oate (**4**, 59%, 86 mg) as a brown oil. ν_{max} 1727 (C=O ester), 1682 (C=O ketone), 1596 (C=C), 861, 835 cm^{-1} (Si–C). δ_H 0.04, s, 9H, Si*Me*$_3$; 0.88, s, 3H, H(20); 0.83–0.92, m, 2H, 14-$CH_2CH_2SiMe_3$; 1.19, td, $J = 13.4$, 3.7 Hz, 1H, H(3ax); 1.53, s, 3H, H(18); 1.70–1.78, m, 2H, H(2eq) and H(1ax); 1.93, qt, $J = 14.0$, 3.3 Hz, 1H, H(2ax); 2.12. bd, $J = 12.3$ Hz, 1H, H(1eq); 2.37, bd, $J = 13.6$ Hz, 1H, H(3eq); 2.43, dd, $J = 6.52$, 1H, H(5); 2.74, td, $J = 13.2$, 4.8 Hz, 1H, 14-$CHCH_2SiMe_3$; 2.96, td, $J = 13.4$, 4.4 Hz, 1H, 14-$CHCH_2SiMe_3$; 3.73, s, 3H, 19-OMe; 3.87, s, 3H, 12-OMe; 5.72, d, $J = 6.56$ Hz, H(6ax); 6.69, d, $J = 2.4$ Hz, 1H, H(11); 6.73, d, $J = 2.32$ Hz, 1H, H(13). δ_C −1.87, Si*Me*$_3$; 18.3, C(2); 19.4, 14-$CH_2CH_2SiMe_3$; 23.6, C(20); 27.5, 14-$CH_2CH_2SiMe_3$; 28.6, C(18); 37.3, C(1); 37.9, C(3); 39.0, C(10); 45.2, C(4); 51.0, C(6); 51.5, 19-OMe; 55.2, 12-OMe; 57.1, C(5); 106.6, C(11); 112.4, C(13); 123.4, C(8); 149.9, C(14); 153.7, C(9); 162.4, C(12); 176.2, C(19); 192.7, C(7). *m*/*z* 494/496 (5, M^+), 415 (100, M − Br), 73 (60, $SiMe_3$). Found: M^+, 494.1473. Calc. for $C_{24}H_{35}BrO_4Si$: M, 496.1468.

3.4. Methyl 6α-bromo-14-(1,2-dibromoethyl)-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (5)

To a suspension of methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**1**, 95 mg, 0.228 mmol) in hexane (4 ml) and sodium bromate (206 mg, 1.37 mmol) in water (1 ml) was added sodium metabisulfite (260 mg, 1.37 mmol) in water (1 ml) over 10 min. After 20 min ether was added and the yellow organic layer was separated, washed with saturated aqueous sodium thiosulfate solution (resulting in a colourless organic layer) and dried ($MgSO_4$). Flash chromatography (silica gel, 4:1 hexanes–ether) yielded methyl 6α-bromo-14-(1,2-dibromoethyl)-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**5**, 87 mg, 66%) as a colourless oil [mixture (1.02:1) of diastereoisomers]. ν_{max} 1727, 1716 (C=O ester), 1687, 1682 (C=O ketone), 1596, 1463 (C=C), 737 cm^{-1}. δ_H 0.89, s, 3H, H(20) major; 0.90, s, 3H, H(20) minor; 1.20, td, $J = 13.6$, 2.6 Hz, 1H, H(3ax) both isomers; 1.54, s, 3H, H(18) both isomers; 1.70–1.81, m, 2H, H(2eq), H(1ax) both isomers; 1.91, qd, $J = 13.5$, 2.9 Hz, 1H, H(2ax) both isomers; 2.13–2.16. m, 2H, H(1eq) both isomers; 2.38, bd, $J = 13.5$ Hz, 1H, H(3eq) both isomers; 2.46, t, $J = 6.2$ Hz, 1H, H(5) both isomers; 3.74, s, 3H, 19-OMe both isomers; 3.92, s, 3H, 12-OMe both isomers; 4.02–4.14, m, 2H, 14-$CH(Br)CH_2Br$ both isomers; 5.77, d, $J = 6.45$ Hz, H(6ax) major; 5.78, d, $J = 6.45$ Hz, H(6eq) minor; 5.93, dd, $J = 9.2$, 6.0 Hz, 1H, 14-C(Br)*H* major; 5.99, t, $J = 6.9$ Hz, 1H, 14-C(Br)*H* minor; 6.86, d, $J = 1.76$ Hz, 1H, H(11) major; 6.88;, d, $J = 1.76$ Hz, 1H, H(11) minor; 7.09, d, $J = 1.76$ Hz, 1H, H(13) major; 7.22, d, $J = 1.76$ Hz, 1H, H(13) minor. δ_C 19.2, C(2) both isomers; 23.6, C(20) minor; 23.6, C(20) major; 28.6, C(18) both isomers; 34.7, 14-$CH(Br)CH_2Br$ major; 36.8, 14-$CH(Br)CH_2Br$ minor; 37.24, C(1) minor; 37.28, C(1) major; 37.8, C(3) both isomers; 39.1, C(10) both isomers; 44.8, 14-Ph*C*(H)Br major; 45.2, C(4) both isomers; 46.7, 14-Ph*C*(H)Br minor; 50.0, C(6) minor; 50.15, C(6) major; 51.9, 19-OMe both isomers; 55.4, 12-OMe both isomers; 56.8, C(5) minor; 56.9, C(5) major; 109.7, C(11) both isomers; 110.9, C(13) major; 112.5, C(13) minor; 123.4, C(8) both isomers; 141.4, C(14) minor; 142.1, C(14) major; 153.5, C(9) minor; 153.7, C(9) major; 162.7, C(12) minor; 162.9, C(12) major; 176.5, C(19) both isomers; 192.4, C(7) major; 192.6, C(7) minor. *m*/*z* 499/501/503 (2, M^+). Found: M^+ 501.0084. Calc. for $C_{21}H_{25}^{79}Br^{81}BrO_4$: M, 501.0099. Found: C, 42.3; H, 4.2. Anal. Calc. for $C_{21}H_{26}O_4Br_3$: C, 43.3; H, 4.3%.

3.5. Reduction of methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (1)

Sodium borohydride (216 mg, 5.84 mmol) was added to a stirred solution of methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**1**, 0.81 mg, 1.94 mmol) in methanol (10 ml). After 12 h sodium borohydride (one equivalent) was added and the mixture was stirred for 3 h. Saturated aqueous ammonium chloride was added and the mixture was extracted with dichloromethane. Flash chromatography (silica gel, 3:1 hexanes–ether) gave the crude alcohols (0.688 g, 85%). A portion of the crude material was subjected to PLC (4:1 hexanes–ether) to give (i) methyl 7α-hydroxy-12-methoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**7**) as white flakes, m.p. 111–113°C. ν_{max} 3429 (OH), 1728 (C=O ester), 1600 (C=C), 1247, 861, 837 cm^{-1} (Si–C). δ_H 0.082, s, 9H, Si*Me*$_3$; 0.82–0.94, m, 2H, 14-$CH_2CH_2SiMe_3$; 0.98, s, 3H, H(20); 1.16, td, $J = 13.6$, 4.2 Hz, 1H, H(3ax); 1.30, s, 3H, H(18); 1.44, td, $J = 13.3$, 4.1 Hz, 1H, H(1ax); 1.64–1.69, m, 1H, H(2eq); 1.94–2.05, m, 2H, H(5), H(2ax); 2.16, td, $J = 11.4$, 3.4 Hz, 1H, H(6ax); 2.23, bd, $J = 12.8$ Hz, 1H, H(1eq); 2.31–2.34, m, 2H, H(3eq), H(6eq); 2.70, dddd, $J = 13.4$, 12.2, 5.9 Hz, 1H, 14-$CHCH_2SiMe_3$; 2.85, dddd, $J = 13.4$, 12.2, 5.9 Hz, 1H,

14-C*H*CH_2SiMe_3; 3.67, s, 3H, 19-OMe; 3.80, s, 3H, 12-OMe; 4.99, t, $J = 2.91$ Hz, 1H, H(7eq); 6.69, s, 2H, H(11), H(13). δ_C −1.91, Si*Me*$_3$; 19.3, 14-CH_2*C*H_2SiMe_3; 19.9, C(2); 21.9, C(20); 26.0, 14-*C*$H_2CH_2SiMe_3$; 28.2, C(18); 30.3, C(6); 37.3, C(3); 39.15, C(10); 39.24, C(1); 43.4, C(4); 45.2, C(5); 51.2, 19-OMe; 55.0, 12-OMe; 64.6, C(7); 108.4, C(11); 112.1, C(13); 125.7, C(8); 146.9, C(14); 150.3, C(9); 159.2, C(12); 177.9, C(19). *m*/*z* 418 (10, M^+), 400 (100, $M - H_2O$), 73 (65, $SiMe_3$). Found: M^+, 418.2519. Calc. for $C_{24}H_{38}O_4Si$: M, 418.2539; and (ii) methyl 7β-hydroxy-12-methoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,-13-trien-19-oate (**6**) as a colourless oil. ν_{max} 3510 (OH), 1725 (C=O ester), 1600 (C=C), 1246, 861, 836 cm^{-1} (Si–C). δ_H 0.073, s, 9H, Si*Me*$_3$; 0.80–0.97, m, 2H, 14-CH_2C*H*$_2SiMe_3$; 1.05, td, $J = 13.6$, 4.2 Hz, 1H, H(3ax); 1.17, s, 3H, H(20); 1.30, s, 3H, H(18), H(1ax) obscured; 1.46, dd, $J = 13.2$, 1.7 Hz, 1H, H(5); 1.59–1.64, m, 1H, H(2eq); 1.93–2.04, m, 2H, H(6ax), H(2ax); 2.19, bd, $J = 13.4$ Hz, 1H, H(3eq); 2.31–2.34, bd, $J =$ 13.4 Hz, 1H, H(1eq); 2.72, dddd, $J = 13.4$, 13.6, 7.6, 1.6 Hz, 1H, H(6eq); 2.76–2.90, m, 2H, 14-C*H*$_2CH_2SiMe_3$; 3.70, s, 3H, 19-OMe; 3.81, s, 3H, 12-OMe; 4.98, bs, 1H, H(7ax); 6.66, d, $J = 2.8$ Hz, 1H, H(11); 6.71, d, $J = 2.80$ Hz, 1H, H(13). δ_C −1.85, Si*Me*$_3$; 18.8, 14-CH_2*C*H_2SiMe_3; 19.9, C(2); 22.0, C(20); 27.4, 14-*C*$H_2CH_2SiMe_3$; 28.2, C(18); 32.4, C(6); 37.3, C(3); 39.2, C(10); 40.3, C(1); 43.6, C(4); 49.4, C(5); 51.3, 19-OMe; 55.0, 12-OMe; 68.7, C(7); 108.1, C(11); 112.5, C(13); 127.7, C(8); 147.5, C(14); 150.9, C(9); 158.7, C(12); 177.4, C(19). *m*/*z* 418 (5, M^+), 400 (100, $M - H_2O$), 73 (30, $SiMe_3$). Found: M^+, 418.2519. Calc. for $C_{24}H_{38}O_4Si$: M, 418.2539.

3.6. Methyl 12-methoxy-14-(2-trimethylsilylethyl)-podocarpa-8,11,13-trien-19-oate (8)

Trifluoroacetic acid (142 mg, 1.24 mmol) was added to a stirred solution of the alcohols (**6**/**7**, 104 mg, 0.248 mmol) and triethylsilane (434 mg, 3.73 mmol), in dichloromethane (3 ml). After 2 min solid sodium hydrogencarbonate was added and the product was extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and the solvent removed to give methyl 12-methoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**8**, 96 mg, 96%) as yellow chunks, m.p. 85–88°C. ν_{max} 1726 (C=O ester), 1603, 1466 (C=C), 1246 (Si–C), 1144, 860, 836 cm^{-1} (Si–C). δ_H 0.115, s, 9H, Si*Me*$_3$; 0.83–0.87, m, 2H, 14-CH_2C*H*$_2SiMe_3$; 1.10, s, 3H, H(18); 1.12, td, $J = 13.5$, 4.2 Hz, 1H, H(3ax); 1.32, s, 3H, H(20); 1.41, td, $J =$ 13.3, 4.0 Hz, 1H, H(1ax); 1.55, d, $J = 11.1$ Hz, 1H, H(5); 1.66, bdp, $J = 15.4$, 3.0 Hz, 1H, H(2eq); 1.92–2.10, m, 2H, H(6ax), H(2ax); 2.26–2.33, m, 3H, H(3eq), H(1eq), H(6eq); 2.53–2.58, m, 2H, 14-C*H*$_2CH_2SiMe_3$, H(7ax) obscured; 2.88, dd, $J = 16.5$, 4.2 Hz, 1H, H(7eq); 3.72, s, 3H, 19-OMe; 3.82, s, 3H, 12-OMe; 6.68, d, $J = 2.4$ Hz, 1H, H(13); 6.74, d, $J = 2.4$ Hz, 1H, H(11). δ_C −1.81, Si*Me*$_3$; 17.0, 14-CH_2*C*H_2SiMe_3; 20.0, C(2); 20.9, C(6); 22.8, C(20); 27.2, 14-*C*$H_2CH_2SiMe_3$; 28.0, C(7); 28.4, C(18); 37.5, C(3); 38.8, C(10); 39.8, C(1); 43.9, C(4); 51.1, 19-OMe; 52.4, C(5); 55.0, 12-OMe; 108.5, C(11); 111.0, C(13); 125.8, C(8); 144.3, C(14); 149.5, C(9); 157.5, C(12); 177.8, C(19). *m*/*z* 402 (100, M^+), 327 (25, $M - 75$), 73 (60, $SiMe_3$). Found: M^+, 402.2584. Calc. for $C_{24}H_{38}O_3Si$: M, 402.2590.

3.7. Bromination of methyl 12-methoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (8)

Methyl 12-methoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**8**, 222 mg, 0.55 mol), *N*-bromosuccinimide (589 mg, 3.31) and benzoyl peroxide (13 mg, 0.055 mmol) were refluxed in carbon tetrachloride (15 ml) for 3.5 h. The mixture was cooled to room temperature and the filtrate washed with carbon tetrachloride. The solvent was removed to afford an oil (448 mg), which was dissolved in benzene (10 ml). DBU (250 mg, 1.65 mmol) was added and the mixture refluxed for 12 h. Work-up and flash chromatography (silica gel, 4:1 benzene–ether) gave a mixture of compounds. PLC (1:1 benzene–ether) on 46 mg of this mixture gave (i) methyl 12-methoxy-14-(*Z*-2-bromoethenyl)-7α-succinimidoylpodocarpa-5,8,11,13-tetraen-19-oate (**10**, 8 mg) as golden rods, m.p. 155–156°C. ν_{max} 1722 (C=O ester), 1704 (C=O amide), 1595 (C=C), 1080 cm^{-1} (C–O). δ_H 1.18, td, $J = 13.2$, 4.1 Hz, 1H, H(3ax); 1.24, s, 3H, H(20); 1.34, s, 3H, H(18); 1.66–1.69, m, 1H, H(2eq); 1.92, td, $J = 12.2$, 5.6 Hz, 1H, H(1ax); 2.05–2.19, m, 2H, H(2ax), H(1eq); 2.40, bd, $J = 10.9$ Hz, 1H, H(3eq); 2.42–2.55, bs, 4H, C*H*$_2$C*H*$_2$; 3.63, s, 3H, 19-OMe; 3.82, s, 3H, 12-OMe; 5.53, d, $J = 3.64$ Hz, 1H, H(6); 5.97, d, $J = 3.60$ Hz, 1H, H(7eq); 6.45, d, $J = 13.6$, Hz, 1H, 14-C(H)=C(*H*)Br; 6.65, d, $J = 2.56$ Hz, 1H, H(13); 6.92, d, $J = 2.56$ Hz, 1H, H(11); 7.12, d, $J = 13.6$, Hz, 1H, 14-C(*H*)=C(H)Br. δ_C 19.5, C(2); 27.4, 27.7, C(18), C(20); 28.0, *C*H_2*C*H_2; 37.0, C(3); 39.4, C(1); 40.0, C(10); 46.1, C(7); 46.9, C(4); 51.7, 19-OMe; 55.0, 12-OMe; 106.7, 14-C(H)=*C*(H)Br; 110.7, C(13); 111.0, C(11); 117.2, C(6); 118.9, C(8); 134.9, C(14); 137.2, 14-*C*(H)=C(H)Br; 144.7, C(5); 148.5, C(9); 158.9, C(12); 175.0, *C*=O amide; 177.0, C(19). *m*/*z* 501/503 (58, M^+), 424/426 (100, $M - 77$). Found: M^+, 501.1151. Calc. for $C_{25}H_{28}^{79}BrNO_5$: M, 501.1149; and (ii) methyl 12-methoxy-14-(*Z*-2-bromoethenyl)-7β-succinimidoylpodocarpa-5,8,11,13-tetraen-19-oate (**9**, 8 mg) as a brown oil. ν_{max} 1722 (C=O ester), 1704 (C=O amide), 1595 (C=C), 1080 cm^{-1} (C–O). δ_H 1.15, td, $J = 13.6$, 4.2 Hz, 1H, H(3ax); 1.37, s, 3H, H(18); 1.42, s, 3H,

H(20); 1.49, td, $J = 13.0$, 4.2 Hz, 1H, H(1ax); 1.63–1.68, m, 1H, H(2eq); 2.08–2.22, m, 2H, H(2ax), H(1eq); 2.39, bd, $J = 13.0$ Hz, 1H, H(3eq); 2.50–2.80, bs, 4H, CH_2CH_2; 3.62, s, 3H, 19-OMe; 3.82, s, 3H, 12-OMe; 5.66, d, $J = 4.76$ Hz, 1H, H(6); 5.17, d, $J = 4.76$ Hz, 1H, H(7ax); 6.46, d, $J = 13.6$, Hz, 1H, 14-C(H)=C(*H*)Br; 6.66, d, $J = 2.56$ Hz, 1H, H(13); 6.91, d, $J = 2.56$ Hz, 1H, H(11); 7.12, d, $J = 13.6$, Hz, 1H, 14-C(*H*)=C(H)Br. δ_C 19.4, C(2); 25.4, C(20); 27.3, C(18); 27.9, CH_2CH_2; 36.8, C(3); 40.0, C(10); 41.2, C(1); 46.0, C(7); 46.7, C(4); 51.2, 19-OMe; 55.1, 12-OMe; 107.1, 14-C(H)=*C*(H)Br; 110.4, C(13); 111.9, C(11); 116.9, C(6); 118.6, C(8); 136.0, C(14); 136.7, 14-*C*(H)=C(H)Br; 146.0, C(5); 149.4, C(9); 158.9, C(12); 176.8, C(19); amide C=O not detected. m/z 501/503 (58, M^+), 424/426 (100, $M-77$). Found: M^+, 501.1151. Calc. for $C_{25}H_{28}^{79}BrNO_5$: M, 501.1149.

3.8. Bromination of methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (*1*) with NBS and K_2CO_3

Methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**1**, 0.184 g, 0.442 mmol), *N*-bromosuccinimide (0.272 g, 2.65 mmol), potassium carbonate (0.366 g, 2.65 mmol) and benzoyl peroxide (20 mg) were refluxed in carbon tetrachloride (8 ml) under a nitrogen atmosphere for 8 h. The reaction mixture was filtered and the filtrate washed with carbon tetrachloride. The solvent was removed from the filtrate and the residue flash chromatographed (silica gel, 4:1, 3:1 hexanes–ethyl acetate) to give (i) starting material (5 mg, 3%); (ii) methyl 6α-bromo-14-(1,2-dibromoethyl)-12-methoxy-7-oxopodocarpa-8,11,-13-trien-19-oate (**5**, 59 mg, 23%); and (iii) methyl 6-bromo-14-(2,2-dibromoethan-1-oyl)-12-methoxy-7-oxopodocarpa-5,8,11,13-tetraen-19-oate (**11**, 88 mg, 33%) as a brown oil. ν_{max} 1725, (C=O ester), 1714, (C=O ketone), 1643 (C=O enone), 1582 (C=C), 1309, 1254, 1123 cm^{-1}. δ_H 1.66, s, 3H, H(20); 1.69, s, 3H, H(18); 1.85–1.90, m, 2H, H(1), H(3); 2.06–2.16, m, 2H, H(2); 2.44–2.54, m, 2H, H(1), H(3); 3.74, s, 3H, 19-OMe; 3.93, s, 3H, 12-OMe; 6.28, s, 1H, 14-COC*H*Br_2; 7.02, d, $J = 2.32$ Hz, 1H, H(13); 7.12, d, $J = 2.30$ Hz, 1H, H(11). δ_C 14.2, C(2); 21.6, C(20); 28.6, C(3) or C(1); 30.3, C(3) or C(1); 31.3, H(18); 44.3, 14-CO*C*HBr_2; 45.0, C(10); 51.5, C(4); 52.8, 19-OMe; 55.9, 12-OMe; 112.5, C(11); 115.5, C(13); 119.8, C(8); 128.8, C(6); 139.4, C(14); 154.0, C(9); 163.1, C(12); 166.0, C(5); 177.0, C(19); 191.5, 14-*C*OCHBr_2; C(7) not detected. m/z 591/593/595/597 (7, $M^+ + H$), 189 (55), 94 (100), 43 (80, $COCH_3$). Found: ($M^+ + H$), 596.8957. Calc. for $C_{21}H_{22}^{81}Br_3O_5$: (M + H), 596.8956.

3.9. Reduction of methyl 6-bromo-14-(2,2-dibromoethan-1-oyl)-12-methoxy-7-oxopodocarpa-5,8,11,13-tetraen-19-oate (*11*) with Zn–acetic acid

Methyl 6-bromo-14-(2,2-dibromoethan-1-oyl)-12-methoxy-7-oxopodocarpa-5,8,11,13-tetraen-19-oate (**11**, 61 mg, 0.103 mmol) and zinc (0.026 g, 0.412 mmol) were stirred in acetic acid (3 ml) for 16 h. Dichloromethane was then added and mixture washed with brine, sodium hydrogencarbonate and dried. Work-up and PLC (2:1 hexanes–ethyl acetate) gave methyl 14-acetyl-6-bromo-12-methoxy-7-oxopodocarpa-5,8,11,13-tetraen-19-oate (**12**, 10 mg, 22%) as needles, m.p. 246–249°C. ν_{max} 1732, (C=O ester), 1701, (C=O ketone), 1651 (C=O enone), 1585 cm^{-1}. δ_H 1.65, s, 3H, H(20); 1.69, s, 3H, H(18); 1.80–1.89, m, 2H, H(1), H(3); 1.99–2.18, m, 2H, H(2); 2.44–2.50, m, 2H, H(1), H(3); 2.52, s, 3H, 14-CO*Me*; 3.74, s, 3H, 19-OMe; 3.91, s, 3H, 12-OMe; 6.69, d, $J = 2.3$ Hz, 1H, H(13); 7.02, d, $J = 2.30$ Hz, 1H, H(11). δ_C 14.3, C(2); 21.8, C(20); 28.8, C(3) or C(1); 30.4, C(3) or C(1); 30.7, 14-CO*Me*; 31.4 H(18); 44.8, C(10); 51.4, C(4); 52.8, 19-OMe; 55.6, 12-OMe; 109.9, C(13); 111.1, C(11); 118.8, C(8); 125.1, C(6); 147.3, C(14); 154.1, C(9); 163.2, C(12); 164.3, C(5); 175.6, C(19); 176.8, C(7); 204.5, 14-*C*OMe. m/z 434/436 (6, M^+), 341 (30, $M - CH_2Br$), 189 (100). Found: M^+, 436.0712. Calc. for $C_{21}H_{23}^{81}BrO_5$: M, 436.0708.

3.10. Methyl 6α,13-dibromo-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (*13*)

A solution of sodium metabisulfite (1.06 g, 5.6 mmol) in water (4 ml) was added to a stirred suspension of methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**1**, 0.296 g, 0.936 mmol) in ethyl acetate (3 ml) and sodium bromate (0.843 g, 5.6 mmol) in water (4 ml). A slight exotherm was observed and the mixture became orange. After 4 h ether was added and the organic layer was removed and dried ($MgSO_4$). Flash chromatography (silica gel, 2:1 hexanes–ether) gave methyl 6α,13-dibromo-12-methoxy-14-(2-(trimethylsilyl)ethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**13**, 272 mg, 66%) as colourless needles, m.p. 151–153°C. ν_{max} 1726 (C=O ester), 1688 (C=O ketone), 1575 (C=C), 1222, 8611, 835 cm^{-1} (Si–C). δ_H 0.085, s, 9H, Si*Me*$_3$; 0.86, s, 3H, H(20); 0.95, td, $J = 12.5$, 4.2, 1H, 14-$CH_2CH_2SiMe_3$; 1.0, td, $J = 13.7$, 4.4, 1H, 14-$CH_2CH_2SiMe_3$; 1.15, td, $J = 13.6$, 3.6 Hz, 1H, H(3ax); 1.49, s, 3H, H(18); 1.67–1.76, m, 2H, H(1ax), H(2eq); 1.83–1.92, m, 1H, H(2ax); 2.13, bd, $J = 12.2$ Hz, 1H, H(1eq); 2.34, bd, $J = 13.8$ Hz, 1H, H(3eq), 2.38, d, $J = 6.4$ Hz, 1H, H(5); 2.74, td, $J = 13.0$, 4.6, 1H, 14-$CH_2CH_2SiMe_3$; 3.12, td, $J = 13.0$, 4.0, 1H, 14-$CH_2CH_2SiMe_3$; 3.71, s, 3H, 19-OMe; 3.92, s, 3H,

12-OMe; 5.71, d, $J = 6.4$ Hz, 1H, H(6ax); 6.70, s, 1H, H(11). δ_C −1.92, Si*Me*$_3$; 12.4, 14-$CH_2CH_2SiMe_3$; 19.2, C(2); 23.3, C(20); 27.6, 14-$CH_2CH_2SiMe_3$; 28.5, C(18), 37.4, C(1); 37.8, C(3); 39.0, C(10); 45.4, C(4); 50.6, C(6); 51.9, 19-OMe; 56.1, 12-OMe; 57.1, C(5); 103.4, C(11); 113.7, C(13); 125.0, C(8); 147.7, C(14); 152.1, C(9); 176.1, C(19); 192.1, C(7). *m/z* 572/574/576 (5, M^+), 494/496 (80, M − Br), 73 (100, $SiMe_3$). Found: M^+, 572.0585. Calc. for $C_{24}H_{34}^{79}Br_2O_4Si$: M, 572.0593.

3.11. Methyl 13-bromo-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (14)

A solution of sodium metabisulfite (0.926 g, 4.88 mmol) in water (4 ml) was added over 15 min to a stirred suspension of methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**1**, 0.312 g, 0.75 mmol) in hexane (8 ml) and sodium bromate (0.0.731 g, 4.88 mmol) in water (3 ml) at 0°C. After 5 min the cooling bath was removed and the mixture was stirred for 3 h. Ether was added and the organic layer was removed, washed with a dilute solution of sodium thiosulfate and dried ($MgSO_4$). Flash chromatography (silica gel, 4:1, 2:1 hexanes–ether) gave methyl 13-bromo-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**14**, 292 mg, 78%) as a colourless oil. ν_{max} 1725 (C=O ester), 1672 (C=O ketone), 1572 (C=C), 1298, 1267, 862, 837 cm^{-1} (Si–C). δ_H 0.087, s, 9H, Si*Me*$_3$; 0.76–0.86, m, 2H, 14-$CH_2CH_2SiMe_3$; 1.06, s, 3H, H(20); 1.08, td, $J = 13.6$, 3.9 Hz, 1H, H(3ax); 1.21, s, 3H, H(18); 1.52, td, $J = 13.2$, 4.0 Hz, 1H, H(1ax); 1.69, dp, $J = 14.4$, 3.2 Hz, H(2eq); 1.96, dd, $J = 14.0$, 4.0, 1H, H(5), H(2ax) obscured; 2.24–2.30, m, 2H, H(1eq), H(3eq); 2.88, dd, $J = 17.8$, 4.1 Hz, 1H, H(6eq); 3.02–3.10, bs, 2H, 14-$CH_2CH_2SiMe_3$; 3.22, dd, $J = 17.8$, 14.1 Hz, 1H, H(6ax); 3.66, s, 3H, 19-OMe; 3.90, s, 3H, 12-OMe; 6.76, s, 1H, H(11). δ_C −1.87, Si*Me*$_3$; 16.3, 14-$CH_2CH_3SiMe_3$; 19.6, C(2); 21.3, C(20); 27.6, C(18), 28.8, 14-$CH_2CH_3SiMe_3$; 37.2, C(3); 38.9, C(6); 39.1, C(1); 39.4, C(10); 43.8, C(4); 49.0, C(5); 51.5, 19-OMe; 56.1, 12-OMe; 104.9, C(11); 114.5, C(13); 124.2, C(8); 149.2, C(14); 156.8, C(9); 158.5, C(12); 176.2, C(19); 198.2, C(7). *m/z* 494/496 (35, M^+), 479/481 (100, M − 15), 73 (75, $SiMe_3$). Found: M^+, 496.1468. Calc. for $C_{24}H_{35}^{81}BrO_4Si$: M, 496.1468.

3.12. Reaction of the monobromide 4 and tribromide 5 with DBU

A mixture of methyl 6α-bromo-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**4**, 0.256 mmol), methyl 6α-bromo-14-(1,2-dibromoethyl)-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**5**, 0.144 mmol) and DBU (160 mg, 1.04 mmol) was refluxed in benzene for 8 h. DBU (106 mg, 0.7 mmol) was added and refluxing continued for 14 h. Work-up and flash chromatography (silica gel, benzene, then 7:3 benzene–ether) yielded (i) methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**1**, 44 mg, 41%); (ii) a mixture (7:3, 48 mg) of methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**1**) and methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-5,8,11,13-tetraen-19-oate (**3**); and (iii) a mixture (1:2, 37 mg) of methyl 14-(1-bromoethenyl)-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**15**) and methyl 14-(1-bromoethenyl)-12-methoxy-7-oxopodocarpa-5,8,11,13-tetraen-19-oate (**16**). ν_{max} 1729 (C=O ester), 1658, 1661 (C=O ketone), 1589 cm^{-1} (C=C). δ_H 1.12, s, 3H, H(20) minor; 1.15, td, $J = 13.7$, 3.96 Hz, 1H, H(3ax) minor; 1.25, td, $J = 13.6$, 4.3 Hz, 1H, H(3ax) major; 1.28, s, 3H, H(18) minor; 1.32, s, 3H, H(20) major; 1.49, s, 3H, H(18) major; 1.55, td, $J = 13.5$, 4.1 Hz, 1H, H(1ax) both isomers; 1.71–1.78, m, 1H, H(2eq) both isomers; 1.98–2.20, m, 1H, H(2ax) both isomers; 2.32, dd, $J = 13.2$, 2.8, H(5) minor, H(1eq) or H(3eq) obscured (both isomers); 2.52, bd, $J = 13.6$ Hz, 1H, H(1eq) or H(3eq) both isomers; 2.95, dd, $J = 18.0$, 3.7 Hz, 1H, H(6eq) minor; 3.23, dd, $J = 18.0$, 14.3 Hz, 1H, H(6ax) minor; 3.65, s, 3H, 19-OMe minor; 3.71, s, 3H, 19-OMe major; 3.86, s, 3H, 12-OMe minor; 3.90, s, 3H, 12-OMe major; 5.06, d, $J = 1.80$ Hz, 1H, 14-C(Br)=CH_2 minor; 5.69, d, $J = 1.70$ Hz, 1H, 14-C(Br)=CH_2 major; 5.71, d, $J = 1.70$ Hz, 1H, 14-C(Br)=CH_2 minor; 5.77, d, $J = 1.70$ Hz, 1H, 14-C(Br)=CH_2 major; 6.52, s, 1H, H(6) major; 6.70, d, $J = 2.5$ Hz, 1H, H(11) or H(13) minor; 6.79, d, $J = 2.56$ Hz, 1H, H(11) or H(13) major; 6.93, d, $J = 2.56$ Hz, 1H, H(11) or H(13) minor; 7.01, d, $J = 2.56$ Hz, 1H, H(11) or H(13) major. δ_C 19.1, C(2) major; 19.6, C(2) minor; 21.3, C(20) minor; 27.0, C(18) major; 27.7, C(18) minor; 28.0, C(20) major; 36.9 major, 37.2 minor, 38.1 minor, 38.8 minor all CH_2; 39.2, C(10) minor; 40.2, C(1) major; 42.3, C(10) major; 43.8, C(4) minor; 47.5, C(4) major; 49.3, C(5) minor; 51.5, 19-OMe minor; 52.0, 19-OMe major; 55.4, 12-OMe both isomers; 111.1, 114.5, C(11), C(13) minor; 111.9, 115.2, C(11), C(13) major; 117.1, 14-C(Br)=CH_2 minor; 117.2, 14-C(Br)=CH_2 major; 120.7, 121.7, 127.4, 130.6, 130.7, 142.8, 143.7, 155.9, 157.9, Ar-*C*; 161.7, C(5) major; 162.1, C(12) major; 162.5, C(12) minor; 175.5, C(19) major; 176.9, C(19) minor; 183.2, C(7) major; 196.0, C(7) minor. These compounds hydrolysed readily on standing or during flash chromatography (silica gel, 3:1 hexanes–ethyl acetate) to give (i) methyl 14-acetyl-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**18**, 7 mg) as clear needles, m.p. 135–140°C. ν_{max} 1714 (C=O ester), 1696 (C=O ketone), 1672 (C=O ketone), 1158 (C=C), 1288 cm^{-1} (C–O). δ_H 1.12, s, 3H, H(20); 1.15, td, $J = 13.7$, 4.0 Hz, 1H, H(3ax); 1.28, s, 3H, H(18); 1.55, td, $J = 13.4$, 4.2 Hz, 1H, H(1ax); 1.73, dp, $J = 14.4$, 3.1 Hz, 1H, H(2eq); 2.05, qt, $J = 14.0$, 3.7

Hz, 1H, H(2ax); 2.09, dd, $J = 14.5$, 3.4 Hz, 1H, H(5); 2.34, dt, $J = 13.3$, 3.2 Hz, 2H, H(1eq), H(3eq); 2.47, s, 3H, 14-CO*Me*; 2.95, dd, $J = 18.2$, 3.4 Hz, H, H(6eq); 3.21, dd, $J = 18.2$, 14.4 Hz, 1H, H(6ax); 3.72, s, 3H, 19-OMe; 3.87, s, 3H, 12-OMe; 6.38, d, $J = 2.4$ Hz, 1H, H(13); 6.92, d, $J = 2.4$ Hz, 1H, H(11). δ_C 19.5, C(2); 21.3, C(20); 27.8, C(18); 30.6, 14-CO*Me*; 36.9, C(6); 37.3, C(3); 38.4, C(1); 38.9, C(10); 43.8, C(4); 49.7, C(5); 51.6, 19-OMe; 55.5, 12-OMe; 108.9, C(13); 110.8, C(11); 121.2, C(8); 147.2, C(14); 157.7, C(9); 163.8, C(12); 176.8, C(19); 196.8, C(7); 205.4, 14-*C*OMe. *m/z* 358 (20, M^+), 343 (65, $M-15$), 283 (60, $M-HCO_2Me$), 43 (48, COMe). Found: M^+, 358.1774. Calc. for $C_{21}H_{26}O_5$: M, 358.1780; and (ii) methyl 14-acetyl-12-methoxy-7-oxopodocarpa-5,8,11,13-tetraen-19-oate (**42**, 13 mg) as golden chunks, m.p. 198–200°C. ν_{max} 1723 (C=O ester), 1993 (C=O ketone), 1651 cm^{-1} (C=O ketone). δ_H 1.24, td, $J = 13.6$, 4.4 Hz, 1H, H(3ax); 1.33, s, 3H, H(20); 1.49, s, 3H, H(18); 1.54, td, $J = 13.5$, 4.1 Hz, 1H, H(1ax); 1.71–1.77, m, 1H, H(2eq); 2.16, qt, $J = 14.0$, 3.7 Hz, 1H, H(2ax); 2.34, bd, $J = 13.3$ Hz, 1H, H(1eq); 2.52, s, 3H, 14-CO*Me*; 2.54, m, 1H, H(3eq); 3.66, s, 3H, 19-OMe; 3.87, s, 3H, 12-OMe; 6.54, s, 1H, H(6); 6.69, d, $J = 2.4$ Hz, 1H, H(13); 7.0, d, $J = 2.4$ Hz, 1H, H(11). δ_C 19.0, C(2); 27.1, C(18); 27.7, C(20); 30.8, 14-CO*Me*; 37.0, C(3); 40.1, C(1); 42.4, C(10); 47.8, C(4); 52.1, 19-OMe; 55.4, 12-OMe; 109.7, C(13); 111.6, C(11); 120.5, C(8); 125.9, C(6); 146.0, C(14); 155.4, C(9); 162.9, C(12); 164.8, C(5); 175.2, C(19); 183.4, C(7); 205.4, 14-*C*OMe. *m/z* 356 (25, M^+), 341 (100, $M-15$), 281 (60, $M-HCO_2Me$), 43 (48, COMe). Found: M^+, 356.1615. Calc. for $C_{21}H_{24}O_5$: M, 356.1624.

3.13. Methyl 14-acetyl-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (*18*)

Methyl 6α-bromo-14-(1,2-dibromoethyl)-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**5**, 97 mg, 0.166 mmol) and DBU (76 mg, 0.5 mmol) were refluxed in benzene (4 ml) for 1 h. The mixture was cooled to r.t., poured into a separatory funnel, washed with brine and dried. Evaporation of the solvent yielded an oil (46 mg) which was dissolved in acetic acid (2 ml). Zinc dust (21 mg, 0.325 mmol) was added and the mixture stirred for 2 h. Work-up gave an oil (49 mg) which was dissolved in 1:1 trifluoroacetic acid–90% formic acid (4 ml, v/v). To the stirred solution was added mercury(II) bis(trifluoroacetate) (74 mg, 0.174 mmol) and the mixture stirred for 24 h. Work-up followed by flash chromatography (silica gel, 2:1 hexanes–ethyl acetate) yielded methyl 14-acetyl-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**18**, 34 mg, 59%, three steps).

3.14. Reaction of tribromide *5* with DBU at r.t.

Methyl 6α-bromo-14-(1,2-dibromoethyl)-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**5**, 0.155 g, 0.261 mmol) and DBU (0.119 g, 0.785 mmol) were stirred at r.t. in benzene (4 ml) for 2 h. Work-up gave a brown oil (0.142 g) which was dissolved in acetic acid (2 ml). An excess of zinc dust was added and the mixture stirred overnight. The zinc dust was removed by filtration and potassium carbonate was added to the filtrate. The organic layer was run off and the solvent removed to reveal a yellow oil (84 mg) which was dissolved in 3:3 trifluoroacetic acid–90% formic acid (6 ml, v/v) and mercury(II) bis(trifluoroacetate) (0.166 g, 0.39 mmol) was added and the reaction stirred overnight. Dichloromethane was then added and the organic layer removed. Work-up gave an oil (50 mg) which was purified by PLC (4:1 hexanes–ethyl acetate, four sweeps) to give (i) methyl 14-ethyl-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**19**, 10 mg, 11%) as a white smear. ν_{max} 1725 (C=O ester), 1668 (C=O ketone), 1595 (C=C), 1277 cm^{-1} (C–O). δ_H 1.11, s, 3H, H(20); 1.15, td, $J = 13.6$, 4.0 Hz, 1H, H(3ax); 1.24, t, $J = 7.4$ Hz, 3H, 14-CH_2CH_3; 1.27, s, 3H, H(18); 1.55, td, $J = 13.4$, 4.1 Hz, 1H, H(1ax); 1.71, dp, $J = 14.3$, 3.2 Hz, H(2eq); 1.98–2.10, m, 2H, H(2ax), H(5); 2.29–2.33, m, 2H, H(1eq), H(3eq); 2.89, dd, $J = 17.8$, 3.8 Hz, 1H, H(6eq); 3.01–3.16, m, 2H, 14-CH_2CH_3; 3.22, dd, $J = 17.8$, 14.3 Hz, 1H, H(6ax); 3.71, s, 3H, 19-OMe; 3.86, s, 3H, 12-OMe; 6.67, d, $J = 2.6$ Hz, 1H, H(13); 6.79, d, $J = 2.6$ Hz, 1H, H(11). δ_C 15.4, 14-CH_2CH_3; 19.7, C(2); 21.4, C(20); 27.8, C(18), 29.1, 14-CH_2CH_3; 37.3, C(3); 39.1, C(6), C(1); 39.3, C(10); 43.8, C(4); 49.3, C(5); 51.5, 19-OMe; 55.1, 12-OMe; 108.1, C(11); 113.7, C(13); 122.8, C(8); 150.4, C(14); 158.4, C(9); 162.4, C(12); 177.0, C(19); 198.8, C(7). *m/z* 344 (100, M^+), 327 (45, $M-17$). Found: M^+, 344.1988. Calc. for $C_{21}H_{28}O_4$: M, 344.1988; (ii) methyl 14-ethenyl-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**20**, 7 mg, 8%) as a colourless oil. ν_{max} 1724 (C=O ester), 1666 (C=O ketone), 1590 (C=C), 1281 cm^{-1} (C–O). δ_H 1.11, s, 3H, H(20); 1.13, td, $J = 13.6$, 4.0 Hz, 1H, H(3ax); 1.27, s, 3H, H(18); 1.54, td, $J = 13.4$, 4.1 Hz, 1H, H(1ax); 1.71, dp, $J = 14.3$, 3.2 Hz, H(2eq); 2.03, dd, $J = 13.8$, 2.9 Hz, 1H, H(5), H(2ax) obscured; 2.23, dd, $J = 12.6$, 3.3 Hz, 2H, H(1eq), H(3eq); 2.92, dd, $J = 18.0$, 3.8 Hz, 1H, H(6eq); 3.21, dd, $J = 18.0$, 14.3 Hz, 1H, H(6ax); 3.71, s, 3H, 19-OMe; 3.89, s, 3H, 12-OMe; 5.32, dd, $J = 10.8$, 1.5 Hz, 1H, 14-C(H)=CH_2(*cis*); 5.51, dd, $J = 17.3$, 1.5 Hz, 1H, 14-C(H)=CH_2(*trans*); 6.87, d, $J = 2.5$ Hz, 1H, H(13); 6.88, d, $J = 2.5$ Hz, 1H, H(11); 7.56, dd, $J = 17.3$, 10.8 Hz, 1H, 14-C(*H*)=CH_2. δ_C 19.7, C(2); 21.3, C(20); 27.8, C(18); 37.3, C(3); 38.6, C(6); 38.9, C(1); 39.1, C(10); 43.8, C(4); 49.3, C(5); 51.5, 19-OMe; 55.2, 12-OMe; 110.0, C(11); 111.5, C(13); 115.1, 14-C(H)=*C*H_2; 127.4, C(8); 139.1, 14-*C*(H)=CH_2;

143.6, C(14); 157.9, C(9); 162.6, C(12); 176.9, C(19); 198.8, C(7). m/z 342 (80, M^+), 341 (100, $M-H$). Found: M^+, 342.1833. Calc. for $C_{21}H_{26}O_4$: M, 342.1831; (iii) (methyl 14-ethyl-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate-C^{13})mercury(II) bromide (**21**, 7 mg, 4%) as brown crystals, m.p. 156–160°C. ν_{max} 1724 (C=O ester), 1667 (C=O ketone), 1564 (C=C), 1277 (C–O), 1277, 1261, 1232, 1097, 1053, 736 cm^{-1}. δ_H 1.13, s, 3H, H(20); 1.15, td, $J=13.6$, 3.9 Hz, 1H, H(3ax); 1.27–1.31, m, 7H, 14-CH_2CH_3, H(18); 1.58, td, $J=13.3$, 4.1 Hz, 1H, H(1ax); 1.71, dt, $J=14.2$, 3.2 Hz, H(2eq); 2.03, dd, $J=14.2$, 3.9, 1H, H(5); 2.06, qt, $J=13.9$, 3.5, 1H, H(2ax); 2.30–2.35, m, 2H, H(1eq), H(3eq); 2.91, dd, $J=17.9$, 4.0 Hz, 1H, H(6eq); 3.0–3.15, m, 2H, 14-CH_2CH_3; 3.24, dd, $J=17.8$, 14.2 Hz, 1H, H(6ax); 3.72, s, 3H, 19-OMe; 3.87, s, 3H, 12-OMe; 6.83, s, 1H, H(11). δ_C 17.0, 14-CH_2CH_3; 19.7, C(2); 21.4, C(20); 27.7, C(18); 34.1, 14-CH_2CH_3; 37.2, C(3); 39.1, C(6), C(1); 39.8, C(10); 43.8, C(4); 49.2, C(5); 51.5, 19-OMe; 55.3, 12-OMe; 104.4, C(11); 112.8, C(13); 124.5, C(8); 153.3, C(14); 160.4, C(9); 163.5, C(12); 176.9, C(19); 198.6, C(7). m/z 624 (15, M^+), 580 (60, $M-44$), 341 (100, $M-HgBr$). Found: M^+, 624.0791. Calc. for $C_{21}H_{27}^{79}Br^{202}HgO_4$: M, 624.0800; and (iv) methyl 14-acetyl-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**18**, 9 mg, 10%).

3.15. Methyl 14-ethenyl-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (20)

To a suspension of methyl 12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**1**, 126 mg, 0.302 mmol) in hexane (10 ml) and sodium bromate (548 mg, 3.63 mmol) in water (2 ml) was added sodium metabisulfite (690 mg, 3.63 mmol) in water (1 ml) over 1 min. After 40 min ether was added, and usual work-up yielded an oil (228 mg) which was dissolved in acetic acid (5 ml). Zinc dust (200 mg, 3.02 mmol) was added and the mixture was stirred at r.t. for 20 min. Flash chromatography (silica gel, 4:1 hexanes–ether) gave methyl 14-ethenyl-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**20**, 103 mg, 58%, two steps).

3.16. Attempted bromination of methyl 13-acetyl-12-(((1,1-dimethylethyl)dimethyl-silyl)oxy)14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (22)

To a stirred suspension of methyl 13-acetyl-14-(2-(trimethylsilyl)ethyl)-12-(((1,1-dimethylethyl)dimethylsilyl)oxy)podocarpa-8,11,13-trien-19-oate (**22**, 0.270 g, 0.496 mmol) and sodium bromate (0.168 mmol, 1.13 mmol) in 9:1 hexane–water (10 ml, v/v) was added a solution of sodium metabisulfite (0.123 g, 1.13 mmol) in water (1 ml) over 1 min. After 30 min ether was added and the organic layer was removed, washed with a dilute solution of sodium thiosulfate and dried. Removal of the solvent in vacuo afforded a yellow oil which was flash chromatographed (silica gel, 2:1 hexanes–ether) to give (i) methyl 13-acetyl-12-(((1,1-dimethylethyl)dimethylsilyl)oxy) - 14 - (2 - trimethylsilylethyl)-podocarpa-6,8,11,13-tetraen-19-oate (**23**, 32 mg, 31%) as an unstable colourless oil. ν_{max} 1728 (C=O ester), 1703 (C=O ketone), 1248, 861, 839 cm^{-1} (Si–C). δ_H 0.06, s, 9H, $SiMe_3$; 0.21, s. 3H, $SiMe$; 0.22, s. 3H, $SiMe$; 0.72–0.82, m, 2H, 14-$CH_2CH_2SiMe_3$; 0.84, s, 3H, H(20); 0.97, s, 9H, CMe_3; 1.12, td, $J=13.7$, 4.1 Hz, 1H, H(3ax); 1.33, s, 3H, H(18); 1.60, td, $J=12.9$, 3.9 Hz, 1H, H(1ax); 1.74, dp, $J=14.2$, 3.1 Hz, 1H, H(2eq); 1.95, qt, $J=13.8$, 3.4 Hz, 1H, H(2ax); 2.10, bd, $J=12.6$ Hz, 1H, H(1eq); 2.32, t, $J=2.60$ Hz, 1H, H(5), H(3eq) obscured; 2.40–2.54, m, 2H, 14-$CH_2CH_2SiMe_3$; 2.49, s, 3H, 13-COMe; 3.70, s, 3H, 19-OMe; 6.47, dd, $J=10.2$, 2.50 Hz, 1H, H(6); 6.55, dd, $J=10.2$, 3.0 Hz, 1H, H(7); 6.57, s, 1H, H(11). δ_C −4.35, $SiMe$; −4.22, $SiMe$; −2.10, $SiMe_3$; 18.0, CMe_3; 19.05, H(20); 19.5, 19.6, C(2), 14-$CH_2CH_3SiMe_3$; 23.9, 14-$CH_2CH_3SiMe_3$; 25.6, CMe_3; 27.6, C(18); 32.8, 13-COMe; 36.3, C(3); 37.1, C(1); 38.3, C(10); 43.4, C(4); 50.4, C(5); 51.5, 19-OMe; 111.2, C(11); 121.0, C(6); 123.6, C(8); 128.3, C(7); 131.4, C(13); 138.2, C(14); 148.8, C(9); 150.8, C(12); 177.4, C(19); 206.3, 13-COMe. m/z 542 (10, M^+), 485 (60, $M-{}^tBu$), 73 (100, $SiMe_3$). Found: M^+, 542.3228. Calc. for $C_{31}H_{50}O_4Si_2$: M, 542.3248; and (ii) a mixture (1:1) of methyl 13-acetyl-6α-bromo-7α-hydroxy-12-(((1,1-dimethylethyl)dimethylsilyl)oxy)-14-(2-trimethylsilylethyl)podo-carpa-8,11,13-trien-19-oate (**24**) and methyl 13-acetyl-6β-bromo-7β-hydroxy-12-(((1,1-dimethylethyl)dimethylsilyl)oxy)-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**25**, 35 mg, 30%) as an unstable yellow foam. ν_{max} 3484 (OH), 1728 (C=O ester), 1704 (C=O ketone), 1593, 1463 (C=C), 1249, 860, 840 cm^{-1} (Si–C). δ_H 0.06, 0.063, s, 9H, $SiMe_3$; 0.11, 0.13, s, 6H, $SiMe_2$; 0.83–0.89, 2H, 14-$CH_2CH_2SiMe_3$; 0.97, s, 9H, CMe_3; 1.15–1.19, m, 1H, H(3ax); 1.24, s, 3H, H(20); 1.37, s, 3H, H(18); 1.44, s, 3H, H(20); 1.55, s, 3H, H(18), H(1ax) obscured; 1.64–1.74, m, 1H, H(2eq); 1.95–2.04, m, 1H, H(2ax); 2.12, bd, $J=12.2$ Hz, 1H, H(1eq); 2.19–2.26, m, 1H, H(2ax); 2.32, d, $J=6.1$ Hz, 1H, H(5), H(3eq) obscured; 2.45–2.54, m, 5H, 13-COMe, 14-$CH_2CH_2SiMe_3$; 2.57, s, 1H, H(5); 2.66–2.72, m, 2H, 14-$CH_2CH_2SiMe_3$; 3.72, 3.73 s, 3H, 19-OMe; 4.85, d, $J=2.5$ Hz, 1H, H(6eq); 5.17, d, $J=2.8$ Hz, 1H, H(7ax); 5.54, s, 1H, H(7eq); 5.63, d, $J=6.1$ Hz, 1H, H(6ax); 6.62, 6.70, s, 1H, H(11). δ_C −4.3, −4.27, −4.21, −3.7, $SiMe_2$; −2.1, $SiMe_3$; 17.9, CMe_3; 19.5, 19.9, C(2); 20.1, 20.3, 14-$CH_2CH_2SiMe_3$; 23.3, 23.9, 14-$CH_2CH_2SiMe_3$; 24.3, C(20); 25.5, CMe_3; 28.0. 29.0, C(18); 32.62, 32.67, 13-COMe; 37.9, 38.3, C(3); 39.5, C(10); 39.9, C(1); 40.0, C(10); 43.2, C(4); 44.3, C(1); 45.0, C(4); 47.8,

C(5); 50.1, C(6); 51.3, 51.6, 19-OMe; 54.6, C(6); 59.4, C(5); 70.9, 71.9, C(7); 112.0, 114.3, C(11); 123.4, 124.6, C(8); 132.0, 132.6, C(13); 142.3, 143.1, C(14); 149.9, 150.9, C(9); 151.9, 152.0, C(12); 176.8, 177.6, C(19); 206.1, 13-*C*OMe. *m*/*z* 639/641 (5, $M^+ + H$), 621/623 (60, $[M + H] - H_2O$), 73 (100, $SiMe_3$). Found: ($M^+ +$ H), 641.2510. Calc. for $C_{31}H_{52}^{81}BrO_5Si_2$: (M + H), 641.2516.

3.17. Methyl 13-acetyl-12-acetoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**26**)

A solution of TBAF in THF (0.745 ml, 0.744 mmol) was added to a stirred solution of methyl 13-acetyl-12-(((1,1-dimethylethyl)dimethylsilyl)oxy)-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**22**, 0.270 g, 0.496 mmol) in THF (3 ml). After 1 h ethyl acetate and brine were added. Work-up yielded an oil (270 mg) which was dissolved in pyridine (4 ml). Acetic anhydride (0.101 g, 0.992 mmol) and DMAP (20 mg) were added and the mixture was stirred overnight. Brine was then added and the product extracted with ether. Work-up and flash chromatography (silica gel, 3:1 hexanes–ether) gave methyl 13-acetyl-12-acetoxy-14-(2-(trimethylsilyl)ethyl)podocarpa-8,11,13-trien-19-oate (**26**, 0.224 g, 96%) as white needles, m.p. 130–133°C. ν_{max} 1769 (C=O ester aromatic), 1725 (C=O ester aliphatic), 1703 (C=O ketone), 1248, 1267, 861, 836 cm^{-1} (Si–C). δ_H 0.036, s, 9H, Si*Me*$_3$; 0.64–0.81, m, 2H, 14-$CH_2CH_2SiMe_3$; 1.03, s, 3H, H(20); 1.06, td, $J = 13.5$, 4.1 Hz, 1H, H(3ax); 1.27, s, 3H, H(18); 1.37, td, $J =$ 13.5, 4.1 Hz, 1H, H(1ax); 1.49, d, $J = 12.0$ Hz, 1H, H(5); 1.60, bd, $J = 14.1$, 1H, H(2eq); 1.89–2.06, m, 2H, H(6ax), H(2ax); 2.14, bd, $J = 12.9$ Hz, 1H, H(1eq); 2.22–2.28, m, 5H, 12-OCO*Me*, H(3eq), H(6eq); 2.36–2.49, m, 2H, 14-$CH_2CH_2SiMe_3$; 2.42, s, 3H, 13-CO*Me*; 2.59, ddd, $J = 16.7$, 12.5, 6.3 Hz, 1H, H(7ax); 2.88, dd, $J = 16.8$, 4.5 Hz, 1H, H(7eq); 3.67, s, 3H, 19-OMe; 6.89, s, 1H, H(11). δ_C −2.10, Si*Me*$_3$; 17.9, 14-$CH_2CH_3SiMe_3$; 19.7, C(2); 20.7, C(6); 20.9, 12-OCO*Me*; 22.6, C(20); 23.9, 14-$CH_2CH_3SiMe_3$; 28.2, C(7); 28.3, C(18), 32.2, 13-CO*Me*; 37.2, C(3); 38.9, C(10); 39.4, C(1); 43.7, C(4); 51.2, 19-OMe; 51.7, C(5); 117.2, C(11); 131.2, C(8); 131.9, C(13); 140.4, C(14); 144.4, C(12); 150.9, C(9); 169.0, 12-O*C*OMe; 177.5, C(19); 203.9, 13-*C*OMe. *m*/*z* 472 (15, M^+), 457 (50, M − 15), 430 (100, M − O=C=CH_2), 415 (80, 430–15). Found: M^+, 472.2643. Calc. for $C_{27}H_{40}O_5Si$: M, 472.2645.

3.18. Methyl 13-acetyl-12-acetoxy-14-(2-trimethylsilylethyl)podocarpa-6,8,11,13-tetraen-19-oate (**27**)

A solution of sodium metabisulfite (0.275 g, 1.44 mmol) in water (1 ml) was added over 1 min to a stirred suspension of methyl 13-acetyl-12-acetoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**26**, 0.057 g, 0.120 mmol) and sodium bromate (0.217 mmol, 1.44 mmol) in 8:1 hexane–water (9 ml, v/v). After 30 min ether was added and the organic layer was removed. Work-up and flash chromatography (silica gel, 3:1 hexanes–ether) gave methyl 13-acetyl-12-acetoxy-14-(2-trimethylsilylethyl)podocarpa-6,8,11,13-tetraen-19-oate (**27**, 0.038 g, 68%) as brown needles, m.p. 112–115°C. ν_{max} 1770 (C=O ester aromatic), 1727 (C=O ester aliphatic), 1704 (C=O ketone), 1248 (Si–C), 1196 (C–O), 861, 837 cm^{-1} (Si–C). δ_H 0.07, s, 9H, Si*Me*$_3$; 0.71–0.82, m, 2H, 14-$CH_2CH_2SiMe_3$; 0.87, s, 3H, H(20); 1.13, td, $J = 13.4$, 3.8 Hz, 1H, H(3ax); 1.33, s, 3H, H(18); 1.58–1.75, m, 2H, H(1ax), H(2eq); 1.94, qt, $J = 13.8$, 3.4 Hz, 1H, H(2ax); 2.12, bd, $J = 12.4$ Hz, 1H, H(1eq); 2.26, s, 3H, 12-OCO*Me*; 2.33–2.35, m, 2H, H(3eq), H(5); 2.42–2.61, m, 2H, 14-$CH_2CH_2SiMe_3$; 2.45, s, 3H, 13-CO*Me*; 3.71, s, 3H, 19-OMe; 6.60, s, 2H, H(6), H(7); 6.84, s, 1H, H(11). δ_C −2.10, Si*Me*$_3$; 18.9, C(20); 19.4, 14-$CH_2CH_2SiMe_3$; 19.5, C(2); 20.9, 12-OCO*Me*; 24.0, 14-$CH_2CH_2SiMe_3$; 27.6, C(18); 32.2, 13-COCH_3; 36.1, C(1); 37.0, C(3); 38.4, C(10); 43.2, C(4); 50.2, C(5); 51.6, 19-OMe; 114.9, C(11); 120.7, C(6); 128.2, C(8); 130.8, C(7); 132.3, C(13); 137.9, C(14); 145.3, C(12); 148.9, C(9); 169.0, 12-O*C*OMe; 177.3, C(19); 203.9, 13-*C*OMe. *m*/*z* 470 (11, M^+), 428 (100, M − O=C=CH_2), 73 (45, $SiMe_3$). Found: M^+, 470.2486. Calc. for $C_{27}H_{38}O_5Si$: M, 472.2486.

3.19. Methyl 13-acetyl-12-methoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**28**)

A solution of TBAF (1.43 ml, 1.43 mmol) in THF (3 ml) that had been pre-dried over 3 Å molecular sieves was added to a stirred solution of methyl 13-acetyl-12-(((1,1-dimethylethyl)dimethylsilyl)oxy)-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**22**, 0.389 g, 0.715 mmol) and iodomethane (0.202 g, 1.43 mmol) in THF (5 ml) under nitrogen. After stirring overnight the reaction mixture was filtered, poured onto brine and extracted with ether. Work-up and flash chromatography (silica gel, 3:1 hexanes–ether) gave methyl 13-acetyl-12-methoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**28**, 0.284 g, 89%) as colourless needles, m.p. 115–118°C. ν_{max} 1726 (C=O ester), 1698 (C=O ketone), 1456, 1462 (C=C), 1247 (Si–C), 1146 (C–O), 861, 835 cm^{-1} (Si–C). δ_H 0.065, s, 9H, Si*Me*$_3$; 0.65–0.83, m, 2H, 14-$CH_2CH_2SiMe_3$; 1.07, s, 3H, H(20); 1.10, td, $J = 13.6$, 4.2 Hz, 2H, H(3ax); 1.30, s, 3H, H(18); 1.40, td, $J = 13.3$, 4.1 Hz, 1H, H(1ax); 1.52, dd, $J = 12.3$, 1.4 Hz, 1H, H(5); 1.63–1.68, m, 1H, H(2eq); 1.88–2.09, m, 2H, H(2ax), H(6ax); 2.22–2.32, m, 3H, H(1eq), H(3eq), H(6eq); 2.34–2.47, m, 2H, 14-$CH_2CH_2SiMe_3$; 2.48, s, 3H, 13-CO*Me*; 2.56, ddd, $J = 16.5$, 12.6, 6.2 Hz, 1H, H(7ax), 2.86, dd, $J = 16.5$, 3.9 Hz, 1H, H(7eq); 3.68, s, 3H, 19-OMe;

3.78, s, 3H, 12-OMe; 6.70, s, 1H, H(11). δ_C −2.1, Si*Me*$_3$; 18.1, 14-CH$_2$*C*H$_2$SiMe$_3$; 19.9, C(2); 20.9, C(6); 22.6, C(20); 23.8, 14-*C*H$_2$CH$_2$SiMe$_3$; 27.9, C(7); 28.3, C(18); 32.6, 13-CO*Me*; 37.3, C(3); 39.1, C(10); 39.7, C(1); 43.8, C(4); 51.1, 19-OMe; 52.2, C(5); 55.3, 12-OMe; 105.6, C(11); 125.6, C(8); 129.2, C(13); 140.2, C(14); 150.2, C(9); 153.8, C(12); 177.7, C(19); 206.3, 13-*C*OMe. *m*/*z* 444 (25, M$^+$), 429 (100, M − 15), 73 (28, SiMe$_3$). Found: M$^+$, 444.2694. Calc. for $C_{26}H_{40}O_4Si$: M, 444.2696.

3.20. Methyl 13-acetyl-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (29)

Ceric ammonium nitrate (0.302 g, 0.551 mmol) in water (1 ml) was added to a stirred solution of methyl 13-acetyl-12-methoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**28**, 49 mg, 0.11 mmol) in acetonitrile (4 ml). The mixture was stirred for 2 h and then extracted with ethyl acetate. PLC (3:1 hexanes–ether) gave methyl 13-acetyl-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**29**, 23 mg, 45%) as a colourless oil. ν_{max} 1725 (C=O ester), 1705 (C=O ketone), 1670 (C=O ketone), 1583 (C=C), 1267, 862, 835 cm^{-1} (Si–C). δ_H 0.066, s, 9H, Si*Me*$_3$; 0.72–0.87, m, 2H, 14-CH$_2$C*H*$_2$SiMe$_3$; 1.11, s, 3H, H(20); 1.14, td, J = 13.9, 4.1 Hz, 1H, H(3ax); 1.26, s, 3H, H(18); 1.55, td, J = 13.1, 3.9 Hz, 1H, H(1ax);.1.73, dp, J = 14.3, 3.1 Hz, 1H, H(2eq); 2.0, dd, J = 14.2, 4.0 Hz, 1H, H(5); 2.09, qt (partially obscured), J = 13.9, 3.5 Hz, 1H, H(2ax); 2.31, dt, J = 13.2, 2.9 Hz, 2H, H(1eq), H(3eq); 2.48, s, 3H, 13-CO*Me*; 2.78, td, J = 12.7, 4.5 Hz, 1H, 14-C*H*$_2$CH$_2$SiMe$_3$; 2.88–2.96, m, 2H, H(6eq), 14-C*H*$_2$CH$_2$SiMe$_3$; 3.22, dd, J = 17.7, 14.2 Hz, 1H, H(6ax); 3.68, s, 3H, 19-OMe; 3.86, s, 3H, 12-OMe; 6.79, s, 1H, H(11). δ_C −2.0, Si*Me*$_3$; 19.0, 14-CH$_2$*C*H$_2$SiMe$_3$; 19.6, C(2); 21.3, C(20); 26.0, 14-*C*H$_2$CH$_2$SiMe$_3$; 27.7, C(18); 32.5, 13-CO*Me*; 37.2, C(3); 39.1, C(1); 39.3, C(6); 39.7, C(10); 43.8, C(4); 49.2, C(5); 51.5, 19-OMe; 55.4, 12-OMe; 104.3, C(11); 122.6, C(8); 131.2, C(13); 146.2, C(14); 158.3, C(9); 158.9, C(12); 176.9, C(19); 198.5, C(7); 205.1, 13-*C*OMe. *m*/*z* 458 (40, M$^+$), 443 (100, M − 15), 73 (31, SiMe$_3$). Found: M$^+$, 458.2490. Calc. for $C_{26}H_{38}O_5Si$: M, 458.2490.

3.21. Methyl 13-acetyl-6α-bromo-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (30)

A solution of sodium metabisulfite (0.373 g, 1.96 mmol) in water (1 ml) was added over 1 min to a stirred suspension of methyl 13-acetyl-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**29**, 0.075 g, 0.103 mmol) and sodium bromate (0.294 mmol, 1.96 mmol) in 7:1 hexane–water (8 ml, v/v). After 1 h ether was added and the organic layer was removed. Work-up and flash chromatography (silica gel, 3:1 hexanes–ether) gave methyl 13-acetyl-6α-bromo-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**30**, 88 mg, 93%) which was recrystallised from CH_2Cl_2–hexanes as golden rods, m.p. 202–205°C. ν_{max} 1730 (C=O ester), 1704 (C=O ketone), 1681 (C=O ketone), 1584 (C=C), 1267, 1246, (Si–C), 1208, (C–O), 862, 835 cm^{-1} (Si–C). δ_H 0.04, s, 9H, Si*Me*$_3$; 0.87, td, J = 13.8, 3.8 Hz, 1H, 14-CH$_2$C*H*$_2$SiMe$_3$; 0.89, s, 3H, H(20); 1.03, td, J = 13.9, 4.2 Hz, 1H, 14-CH$_2$C*H*$_2$SiMe$_3$; 1.19, td, J = 13.5, 3.6 Hz, 1H, H(3ax); 1.52, s, 3H, H(18); 1.73–1.82, m, 2H, H(1ax), H(2eq); 1.97, qt, J = 14.2, 3.4 Hz, 1H, H(2ax); 2.14, bd, J = 14.0 Hz, 1H, H(1eq); 2.29–2.46, m, 3H, H(3eq), H(5), 14-C*H*$_2$CH$_2$SiMe$_3$; 2.50, s, 3H, 13-CO*Me*; 2.93, td, J = 13.4, 4.0, 1H, 14-C*H*$_2$CH$_2$SiMe$_3$; 3.73, s, 3H, 19-OMe; 3.87, s, 3H, 12-OMe; 5.70, d, J = 6.5 Hz, 1H, H(6ax); 6.72, s, 1H, H(11). δ_C −2.1, Si*Me*$_3$; 19.2, 14-CH$_2$*C*H$_2$SiMe$_3$; 20.0, C(2); 23.4, C(20); 24.1, 14-*C*H$_2$CH$_2$SiMe$_3$; 28.6, C(18); 32.4, 13-CO*Me*; 37.4, C(1); 37.9, C(3); 39.3, C(10); 45.2, C(4); 50.6, C(6); 51.9, 19-OMe; 55.4, 12-OMe; 56.9, C(5); 102.5, C(11); 124.2, C(8); 130.6, C(13); 144.8, C(14); 154.3, C(9); 158.5, C(12); 176.5, C(19); 192.4, C(7); 204.6, 13-*C*OMe. *m*/*z* 537/539 (40, M$^+$ + H), 457 (60, [M + H] − Br), 73 (100, SiMe$_3$). Found: (M$^+$ + H), 537.1672. Calc. for $C_{26}H_{38}BrO_5Si$: (M + H), 537.1672.

3.22. Methyl 14-acetyl-12-methoxy-5β-methyl-10-norpodocarpa-6,8,10,11,13-pentaen-19-oate (31)

Methyl 14-acetyl-12-methoxy-7-oxopodocarpa-8,11,-13-trien-19-oate (**18**, 24 mg, 0.067 mmol) and *p*-toluenesulfonic acid (two crystals) were refluxed in toluene (4 ml) with 4 Å molecular sieves for 3.5 h. More *p*-toluenesulfonic acid was added and refluxing continued for a further 3 h. Work-up followed by flash chromatography (silica gel, 3:1 hexanes–ethyl acetate) gave methyl 14-acetyl-12-methoxy-5β-methyl-10-norpodocarpa-6,8,10,11,13-pentaen-19-oate (**31**, 16 mg, 67%) as a colourless oil. ν_{max} 1723 (C=O ester), 1685 (C=O ketone), 1594, 1463 (C=C), 1203, cm^{-1} (C–O). δ_H 1.10, s, 3H, 5-Me; 1.32, s, 3H, H(18); 1.68–1.73, m, 2H, H(2); 2.30–2.36, m, 2H, H(3); 2.56, s, 3H, 14-CO*Me*; 3.75, s, 3H, 19-OMe; 3.86, s, 3H, 12-OMe; 6.05, m, 1H, H(1); 6.48, d, J = 10.3 Hz, 1H, H(6); 6.48, d, J = 10.3 Hz, 1H, H(7); 6.98, d, J = 2.6 Hz, 1H, H(13); 7.02, d, J = 2.6 Hz, 1H, H(11). δ_C 19.9, C(18); 22.9, C(2); 23.7, 5-Me; 26.9, C(3); 30.1, 14-CO*Me*; 41.8, C(5); 45.7, C(4); 51.6, 19-OMe; 55.4, 12-OMe; 112.8, C(13); 113.6, C(11); 121.3, C(7); 122.6, C(8); 125.3, C(1); 135.0, C(6); 136.6, 136.8, Ar-*C*(quaternary); 138.3, C(9); 158.0, C(12); 176.8, C(19); 202.3, 14-*C*OMe. *m*/*z* 340 (40, M$^+$), 240 (100, M − 100), 197 (890, 240 − COMe), 43

(80, COMe). Found: M^+, 340.1680. Calc. for $C_{21}H_{24}O_4$: M, 340.1675.

3.23. Reaction of methyl-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (1) with $AlCl_3$

Methyl-12-methoxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**1**, 0.320 g, 0.79 mmol) and aluminium chloride (0.5 g, 3.84 mmol) were refluxed in dry dichloromethane (10 ml) for 48 h. Methanol was added, the mixture poured onto brine and extracted with dichloromethane. The solvent was removed to yield an oil (316 mg) which was purified by flash chromatography (silica gel, 1:1 hexanes–ether) to give (i) methyl 12-hydroxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**32**, 13 mg, 4%) as a colourless oil. ν_{max} 3369 (OH), 1726 (C=O ester), 1644 (C=O ketone), 1599 (C=C), 1247, 861, 831 cm^{-1} (Si–C). δ_H 0.039, s, 9H, SiMe_3; 0.74–0.88, m, 2H, 14-$CH_2CH_2SiMe_3$; 1.07, s, 3H, H(20); 1.11, td, $J = 13.5$, 3.6 Hz, 1H, H(3ax); 1.23, s, 3H, H(18); 1.51, td, $J = 13.2$, 3.6 Hz, 1H, H(1ax); 1.61, bd, $J = 14.1$, 1H, H(2eq); 1.93–2.02, m, 2H, H(2ax), H(5); 2.21–2.30, m, 2H, H(3eq), H(1eq); 2.91, dd, $J = 17.9$, 3.44 Hz, 1H, H(6eq); 2.95–3.08, m, 2H, 14-$CH_2CH_2SiMe_3$; 3.22, dd, $J = 17.8$, 14.3 Hz, 1H, H(6ax); 3.68, s, 3H, 19-OMe; 6.67, s, 1H, H(13); 6.63, d, $J = 1.60$ Hz, 1H, H(11); 7.73, bs, 1H, 12-O*H*. δ_C −1.85, SiMe_3; 18.6, 14-$CH_2CH_2SiMe_3$; 19.7, C(2); 21.3, C(20); 27.7, C(18); 30.3, 14-$CH_2CH_2SiMe_3$; 37.2, C(3); 38.9, C(6), C(1); 39.2, C(10); 43.8, C(4); 49.3, C(5); 51.5, 19-OMe; 109.4, C(11); 116.0, C(13); 121.7, C(8); 152.4, C(14); 159.3, C(9); 160.4, C(12); 177.3, C(19); 199.9, C(7). m/z 402 (100, M^+), 387 (70, M − 15), 329 (85, M − $SiMe_3$). Found: M^+, 402.2216. Calc. for $C_{23}H_{34}O_4Si$: M, 402.2226; and (ii) methyl 12-hydroxy-14-(2-hydroxydimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**33**, 276 mg, 89%) as a white foam. ν_{max} 3328 (OH), 1725 (C=O ester), 1643 (C=O ketone), 1599 (C=C), 1252, 841 cm^{-1} (Si–C). δ_H 0.063, s, 6H, SiMe_2OH; 0.84–0.99, m, 2H, 14-$CH_2CH_2SiMe_2OH$; 1.07, s, 3H, H(20), H(3ax) obscured; 1.23, s, 3H, H(18); 1.51, bt, $J = 13.0$ Hz, 1H, H(1ax); 1.61, bd, 1H, H(2eq); 1.99, dd, $J = 13.9$, 3.5 Hz, 1H, H(5), H(2ax) obscured; 2.26, m, 2H, H(3eq), H(1eq); 2.91, dd, $J = 17.9$, 3.4 Hz, 1H, H(6eq); 3.02–3.17, m, 2H, 14-$CH_2CH_2SiMe_2OH$; 3.25, dd, $J = 17.9$, 14.3 Hz, 1H, H(6ax); 3.68, s, 3H, 19-OMe; 6.81, s, 1H, H(11); 6.85, s, 1H, H(13); 9.1, bs, 1H, 12-O*H*. δ_C 0.38, SiMe_2OH; 19.8, C(2), 14-$CH_2CH_2SiMe_2OH$; 21.3, C(20); 27.7, C(18); 29.7, 14-$CH_2CH_2SiMe_2OH$; 37.2, C(3); 38.9, C(6), C(1); 39.1, C(10); 43.7, C(4); 49.2, C(5); 51.6, 19-OMe; 109.7, C(11); 116.4, C(13); 121.4, C(8); 152.2 C(14); 159.6, C(9); 161.3, C(12); 177.2, C(19); 200.7, C(7). m/z 404 (10, M^+), 386 (100, M − 18). Found: M^+, 404.2045. Calc. for $C_{22}H_{32}O_5Si$: M, 404.2019.

3.24. Reaction of methyl 12-methoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (8) with $AlCl_3$

Methyl 12-methoxy-14-(2-trimethylsilylethyl)podocarpa-8,11,13-trien-19-oate (**8**, 142 mg, 0.35 mmol) and aluminium chloride (235 mg, 1.76 mmol) were refluxed in dichloromethane (6 ml) for 24 h. Saturated sodium hydrogencarbonate was added and the mixture extracted with dichloromethane, washed with brine and dried ($MgSO_4$). Flash chromatography (silica gel, 3:1, 1:1 hexanes–ether) gave (i) a mixture of 12-methoxypodocarpa-8,11,13-trien-19-oate (**34**, 13%) and methyl 14-alkylated [methyl (**35**, 14%), ethyl (**36**, 52%), propyl (**37**, 11%)]-12-methoxypodocarpa-8,11,13-trien-19-oate (GC–MS analysis, 114 mg) which was repurified by chromatography to give 48 mg of the above components; and (ii) methyl 13-acetyl-12-hydroxy-14-(2-trimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**38**) which was repurified by flash chromatography (1:1 hexanes–ether) to give (18 mg, 12%) of the pure compound. ν_{max} 1726 (C=O ester), 1704, (C=O ketone), 1681, (C=O ketone) 1583 (C=C) 1246, 862, 836, cm^{-1} (Si–C). δ_H 0.078, s, 9H, SiMe_3; 0.74, td, $J = 14.0$, 4.5 Hz, 1H, 14-$CH_2CH_2SiMe_3$; 0.84, td, $J = 13.0$, 4.3 Hz, 1H, 14-$CH_2CH_2SiMe_3$; 1.08, s, 3H, H(20); 1.12, td, $J = 13.4$, 4.1 Hz, 1H, H(3ax); 1.26, s, 3H, H(18); 1.51, td, $J = 13.4$, 4.4, 1H, H(1ax); 1.70, dp, $J = 14.3$, 3.1 Hz, 1H, H(2eq); 2.01, dd, $J = 14.0$, 4.4 Hz, 1H, H(5); 2.01, qt (partially obscured), $J = 14.0$, 3.5 Hz, 1H, H(2ax); 2.24, bd, $J = 12.8$ Hz, 1H, (1eq); 2.30, bd, $J = 13.8$ Hz, 1H, H(3eq); 2.62, s, 3H, 13-CO*Me*; 2.91, dd, $J = 18.0$, 4.3 Hz, 1H, H(6eq); 3.06, td, $J = 12.9$, 4.3 Hz, 1H, 14-$CH_2CH_2SiMe_3$; 3.28, dd, $J = 18.0$, 14.4 Hz, 1H, H(6ax), 14-$CH_2CH_2SiMe_3$ obscured; 3.70, s, 3H, 19-OMe; 6.83 s 1H, H(11); 9.42, bs, 1H, 12-O*H*. δ_C −1.98, SiMe_3; 19.6, 14-$CH_2CH_2SiMe_3$; 19.9, C(2); 21.2, C(20); 26.5, 14-$CH_2CH_2SiMe_3$; 27.7, C(18); 32.7, 13-CO*Me*; 37.3, C(3); 38.7, C(6); 39.3, C(1) and C(10); 43.8, C(4); 48.7, C(5); 51.5, 19-OMe; 110.9, C(11); 125.7, C(8); 150.2, C(14); 159.4, C(9); 160.9, C(12); 176.8, C(19); 199.1, C(7); 206.6, 13-*C*OMe. C(13) not detected. m/z 444 (90, M^+), 429 (85, M − 15), 73 (100, $SiMe_3$). Found: M^+, 444.2327. Calc. for $C_{25}H_{36}O_5Si$: M, 444.2332.

3.25. Methyl 12-acetoxy-14-(2-hydroxydimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (39)

Methyl 12-hydroxy-14-(2-hydroxydimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**33**, 40 mg, 0.099 mmol) was stirred with acetic anhydride (101 mg, 0.99 mmol) in pyridine (2 ml) for 2 days. The mixture was

poured onto brine and extracted with dichloromethane. The combined extracts were washed with 2 M HCl, dried ($MgSO_4$) and the solvent removed to reveal an oil (40 mg) which was purified by flash chromatography (silica gel, 6:1 hexanes–ethyl acetate) to give methyl 12-acetoxy-14-(2-hydroxydimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**39**, 24 mg, 53%) as a colourless oil. ν_{max} 3437 (OH), 1768 (C=O ester aromatic), 1726 (C=O ester aliphatic), 1679 (C=O ketone), 1593 (C=C), 1198 (C–O), 736 cm^{-1}. δ_H 0.18, s, 6H, Si*Me*$_2$OH; 0.81–0.95, m, 2H, 14-CH_2CH_2SiMe$_2$OH 1.04, s, 3H, H(20); 1.13, td, $J = 13.6$, 3.9 Hz, 1H, H(3ax); 1.26, s, 3H, H(18); 1.55, td, $J = 13.3$, 3.9 Hz, 1H, H(1ax); 1.67–1.72, m, 1H, H(2eq); 2.04, dd, $J =$ 14.2, 3.8, 1H, H(5), H(2ax) obscured; 2.24–2.31, m, 5H, 12-OCO*Me*, H(1eq), H(3eq); 2.92, dd, $J = 17.8$, 3.8 Hz, 1H, H(6eq); 2.98, m, 2H, 14-CH_2CH_2SiMe$_2$OH; 3.26, dd, $J = 17.8$, 14.2 Hz, H(6ax); 3.70, s, 3H, 19-OMe; 6.91, d, $J = 2.20$ Hz, 1H, H(13); 7.01, d, $J = 2.20$ Hz, 1H, H(11). δ_C 0.22, Si*Me*$_2$OH; 19.6, C(2); 21.1, 12-OCO*Me*; 20.1, 14-CH_2CH_2SiMe$_2$OH; 21.4, C(20); 27.7, C(18); 29.3, 14-CH_2CH_2SiMe$_2$OH; 37.2, C(1); 38.9, C(3); 39.15, C(6); 39.3, C(10); 43.8, C(4); 49.2, C(5); 51.5, 19-OMe; 115.5, C(11); 121.7, C(13); 126.7, C(8); 151.1, C(14); 153.5 C(12); 157.7, C(9); 168.8, 12-O*C*OMe; 176.9, C(19); 199.2 C(7). m/z 446 (< 1, M^+), 428 (100, $M - H_2O$), 43 (98, $COCH_3$). Found: M^+, 446.2118. Calc. for $C_{24}H_{34}O_6Si$: M, 466.2125.

*3.26. Reaction of methyl 12-hydroxy-14-(2-hydroxydimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**33**) with BH_3·DMS*

To a stirred solution of methyl 12-hydroxy-14-(2-hydroxydimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**33**, 0.040 g, 0.099 mmol) was added borane-dimethyl sulfide (0.030 g, 0.396 mmol) under an atmosphere of nitrogen, causing the evolution of hydrogen. The solution was stirred for 19 h, diluted carefully with methanol, then brine and the organic layer removed. The aqueous layer was extracted with dichloromethane and the combined layers washed with brine and dried. Removal of the solvent in vacuo afforded an oil (48 mg) which was purified by flash chromatography (silica gel, 1:1 hex-anes–ether) to give bis[2-(14-(methyl 12-hydroxypodocarpa-8,11,13-trien-19-oate)ethyl)dimethyl]-disiloxane (**40**, 26 mg, 34%) as white flakes, m.p. 160–170°C. ν_{max} 3319 (OH), 1726 (C=O ester), 1456 (C=C), 1252 (Si–C), 1059 (Si–O), 843 cm^{-1} (Si–C). δ_H 0.155, s, 6H, Si*Me*$_2$OR; 0.81–0.98, m, 4H, 14-CH_2CH_2SiMe$_2$OR; 1.04, s, 6H, H(20); 1.07, td, $J =$ 13.8, 3.8 Hz, 2H, H(3ax); 1.29, s, 6H, H(18); 1.36, td, $J = 13.3$, 4.0 Hz, 2H, H(1ax); 1.52, d, $J = 12.7$ Hz, 1H, H(5); 1.60–1.64, m, 2H, H(2eq); 1.89–2.04, m, 4H, H(2ax), H(6ax); 2.17–2.29, m, 6H, H(1eq), H(3eq), H(6eq); 2.49–2.58, m, 6H, H(7ax), 14-CH_2CH_2SiMe$_2$OR; 2.84, dd, $J = 16.4$, 4.3 Hz, 2H, H(7eq); 3.68, s, 3H, 19-OMe; 5.17, s, 2H, bs, 12-O*H*; 6.61, d, $J = 2.4$ Hz, 2H, H(13); 6.65, $J = 2.4$ Hz, 2H, H(11). δ_C 0.17, Si*Me*$_2$OR; 18.6, 14-CH_2CH_2SiMe$_2$OR; 20.0, C(2); 20.9, C(6); 22.7, C(20); 26.3, 14-CH_2CH_2SiMe$_2$OR; 28.0, C(7); 28.4, C(18); 37.3, C(3); 38.7, C(10); 39.7, C(1); 43.8, C(4); 51.3, 19-OMe; 52.3, C(5); 109.7, C(11); 112.6, C(13); 125.0, C(8); 144.3, C(14); 149.8, C(9); 153.5, C(12); 178.0, C(19). m/z 762 (16, M^+), 55 (100). Found: M^+, 762.4339. Calc. for $C_{44}H_{66}O_7Si_2$: M, 762.4347.

*3.27. Attempted ionic hydrogenation of methyl 12-triethylsilyloxy-14-(2-hydroxydimethylsilylethyl)-podocarpa-8,11,13-trien-19-oate (**33**)*

Methyl 12-hydroxy-14-(2-hydroxydimethylsilylethyl)-7-oxopodocarpa-8,11,13-trien-19-oate (**33**, 115 mg, 284 mmol), trifluoroacetic acid (0.325 g, 2.84 mmol) and triethylsilane (0.165 g, 1.54 mmol) were dissolved in dichloromethane (3 ml) and stirred at r.t. for 20 h. Solid sodium hydrogencarbonate and brine were added and the organic layer was removed. The aqueous layer was extracted with dichloromethane and the combined extracts were washed with saturated sodium hydrogencarbonate and dried ($MgSO_4$). Flash chromatography (silica gel, 3:1 hexanes–ether) gave methyl 12-triethylsilyloxy-14-(2-hydroxydimethylsilylethyl)podocarpa-8,-11,13-trien-19-oate (**41**, 35 mg, 24%) as a white foam. ν_{max} 3426 (OH), 1727 (C=O ester), 1610 (C=C), 1250, 740, 776 (Si–C), 1068 cm^{-1} (Si–O). δ_H 0.16, s, 6H, Si*Me*$_2$OH; 0.56, q, $J = 8.0$ Hz, 6H, SiCH_2CH_3; 0.81–0.85, m, 2H, 14-CH_2CH_2SiMe$_2$OH; 0.97, m, 6H, SiCH_2CH_3; 1.06, s, 3H, H(20); 1.10, td, $J = 13.5$, 4.1, 1H, H(3ax); 1.30, s, 3H, H(18); 1.38, td, $J = 13.4$, 4.0, 1H, H(1ax); 1.52, dd, $J = 12.3$, 1.2 Hz, 1H, H(5); 1.63, dp, $J = 14.2$, 2.9 Hz, 1H, H(2eq); 1.89–2.06, m, 2H, H(2ax), H(6ax); 2.18–2.30, m, 3H, (1eq), H(3eq), H(6eq); 2.49–2.58, m, 3H, H(7ax), 14-CH_2CH_2SiMe$_2$-OH; 2.83, dd, $J = 16.6$, 4.1 Hz, 1H, H(7eq); 3.69, s, 3H, 19-OMe; 6.58, d, $J = 2.52$ Hz, 1H, H(13); 6.65, d, $J = 2.52$ Hz, 1H, H(11). δ_C 0.18, Si*Me*$_2$OH; 2.3, SiCH_2CH_3; 6.7, SiCH_2CH_3; 18.4, 14-CH_2CH_2SiMe$_2$-OH; 19.9, C(2); 20.9, C(6); 22.7, C(20); 26.3, 14-CH_2CH_2SiMe$_2$OH; 28.0, C(7); 28.4, C(18); 37.4, C(3); 38.7, C(10); 39.7, C(1); 43.9, C(4); 51.2, 19-OMe; 52.3, C(5); 109.6, C(11); 112.4, C(13); 125.1, C(8); 144.4, C(14); 149.7, C(9); 153.5, C(12); 178.0, C(19). m/z 504 (90, M^+), 475 (100, $M - 29$). Found: M^+, 504.3114. Calc. for $C_{28}H_{48}O_4Si_2$: M, 504.3091.

4. Supplementary material

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge

Crystallographic Data Centre, CCDC no. 137248. Copies are available free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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