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Functionalisation of Alkylalkoxysilanes. Studies Towards Annulations of Diterpenoids

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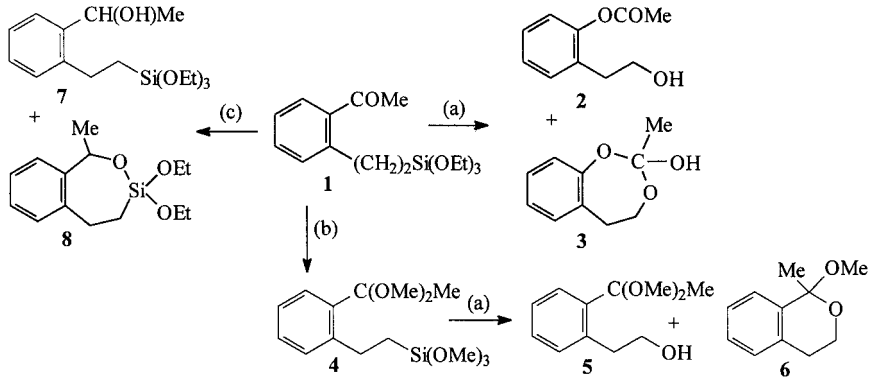
Abstract—*Ortho*-(2-triethoxysilylethyl) derivatives of aryl ketones undergo oxidative desilylation with H_2O_2. Tetralone derivatives have served as model substrates for 14-2-(triethoxysilylethyl)-7-oxopodocarpanes, which have been converted into 2-arylethanols in a four-step sequence (BH_3·BMS, H_2O_2, Et_3SiH/CF_3COOH, TBAF) without isolation of intermediate products (oxasilepin, diol, trifluoroacetate). Use of the 14-(2-diethoxysilylmethyl) analogue improved the overall yield significantly (75 versus 40%). Re-oxidation of ring B with CAN gave the Δ^5-7-oxo derivative, which was converted into an enone–aldehyde by treatment with Collins' reagent. The conjugated alkene was reduced stereoselectively with SmI_2, which, however, did not promote pinacol coupling of the resulting 1,5-keto aldehyde.

Introduction

We[1,2] and others[3–5] have reported the ruthenium-catalysed coupling of an *ortho* C–H bond of an aromatic ketone with alkoxyvinylsilanes, resulting in high yields of *ortho* alkylated products. These adducts, in which the side-chain is saturated and the silicon bears an electronegative substituent, are amenable to oxidative cleavage of a silicon–carbon bond.[6,7] Subsequent functional group manipulations should afford compounds that are synthetically useful. We now report on the functionalisation of compounds containing an $ArCH_2CH_2Si(OR)_xMe_{4-x}$ moiety, as part of an investigation directed towards either cyclopentaannulation or heteroannulation of arenes.

Results and Discussion

It was expected that the *ortho* 2-alkoxysilylethyl acetophenones could be converted into 1,5-dicarbonyl compounds via initial oxidation of the silicon–carbon bond. Treatment of 1-(2-(2-triethoxysilylethyl)phenyl)-ethanone (**1**) with H_2O_2(12 equiv.)/KHF_2/Ac_2O[8] (acidic conditions) gave the ring-chain tautomers **2** (mainly) and **3**, from oxidation of the $(EtO)_3Si$–C bond and Baeyer–Villiger rearrangement[9–11] of the acetophenone (Scheme 1). The use of either 6 equiv. each of H_2O_2 and Ac_2O, or of Tamao's basic conditions (H_2O_2/$NaHCO_3$/THF/MeOH),[8] gave complicated mixtures. Apparently, modification of the carbonyl group was required to avoid the Baeyer–Villiger



Scheme 1. (a) H_2O_2, KHF_2, Ac_2O; (b) $HC(OMe)_3$, *p*-TsOH; (c) Red-Al.

Keywords: aromatic ketones; alkoxysilanes; oxidation; annulation studies.

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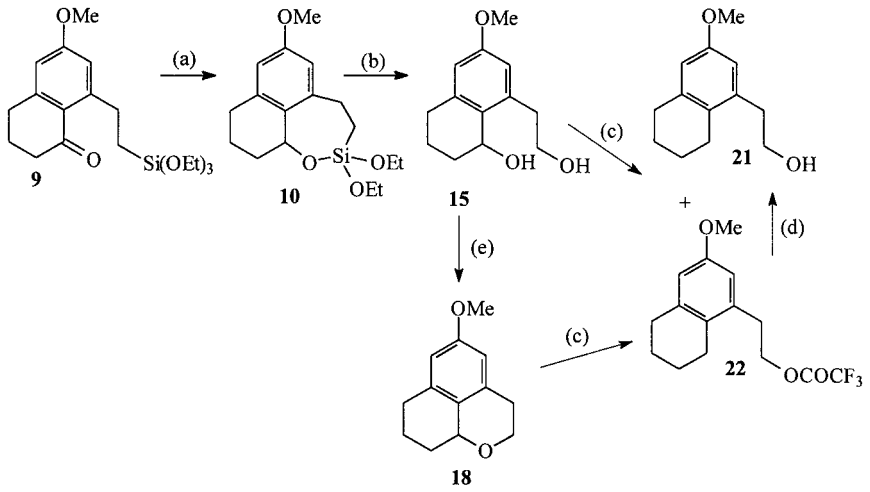


Scheme 2. (a) Red-Al; (b) H_2O_2, KF, $NaHCO_3$; (c) Et_3SiH, CF_3COOH; (d) TBAF; (e) PCC, NaOAc.

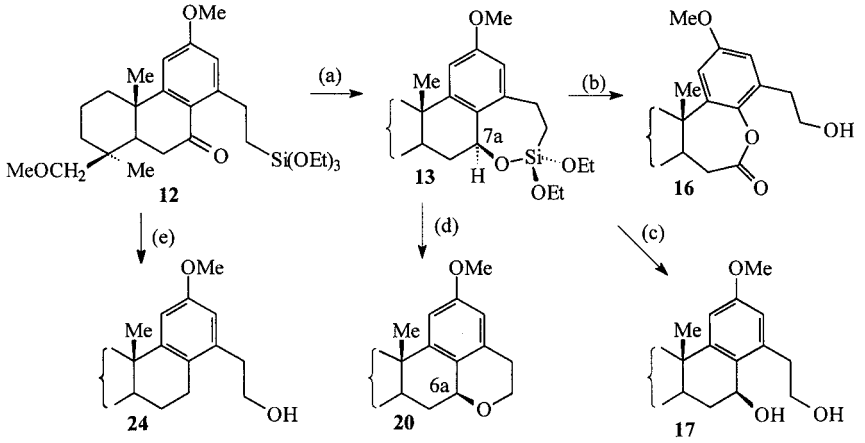
oxidation. The dimethyl acetal **4** prepared from **1** underwent oxidative desilylation (basic conditions) to give a mixture (1:1) of the primary alcohol **5** and the dihydropyran **6**. This route could not, however, be applied to 7-oxo derivatives of podocarpic acid, since their conversion into either a dimethyl acetal or a 1,3-dioxolane ($HOCH_2CH_2OH$/*p*-TsOH/heat) was not possible.

Reduction of the ketone

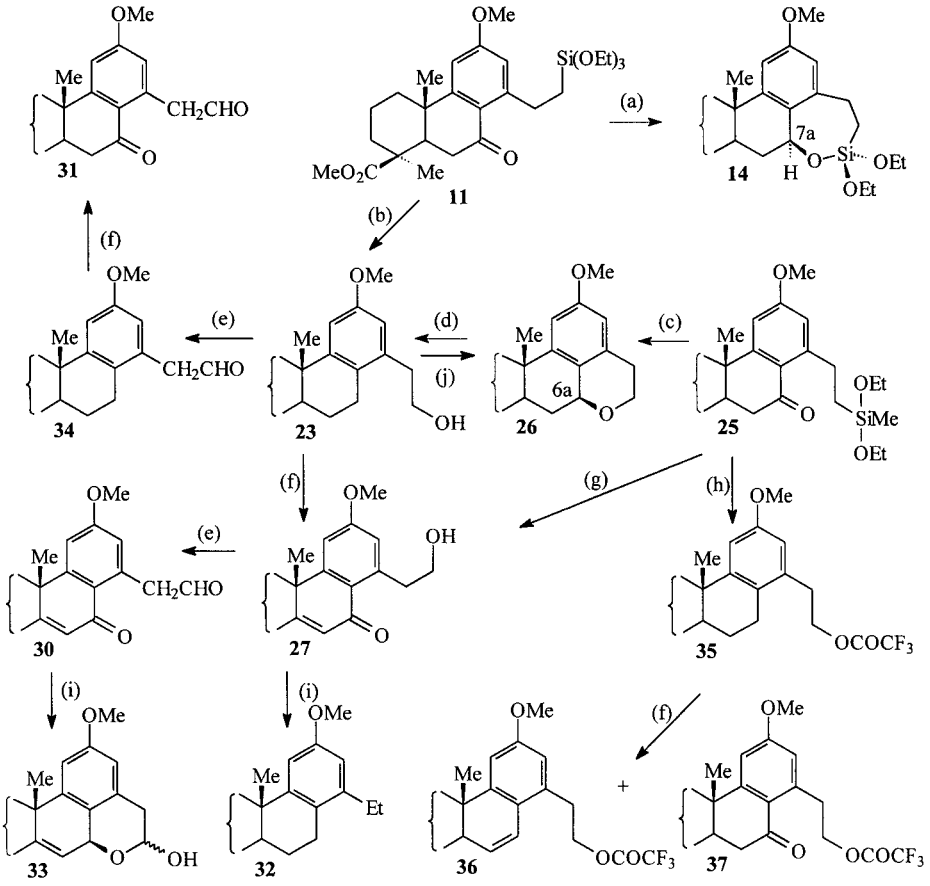
Reduction of the proximal ketone provides an alternative approach to avoid the Baeyer–Villiger reaction. Although reaction of the acetophenone **1** with sodium borohydride in ethanol or DMF led to polysiloxanes,[12] Red-Al (1 equiv., −18°C; then 2 equiv., 0°C) gave the alcohol **7** (73%) and the derived oxasilepin **8** (27%) (Scheme 1). Reduction (Red-Al, 2 equiv.) of 8-(2-triethoxysilylethyl)-6-methoxy-3,4-dihydro-1-2*H*-naphthalenone (**9**) gave the oxasilepin **10** quantitatively (Scheme 2). However, treatment of the 14-(2-triethoxysilylethyl)-7-oxo diterpenoid ester **11** with Red-Al gave a mixture from reduction of both the ketone and the ester, and from attack at silicon. To avoid interference by the C(19) ester, the methyl ether **12** was utilised; sequential additions of Red-Al (1 equiv., −25°C to rt; 1 equiv., 0°C to rt), gave the 7β-1,2-oxasilepin **13** (Scheme 3). However, reduction of the diterpenoids with Red-Al always gave polar polysiloxanes as well as the desired product, the experimental procedure was cumbersome, and losses occurred during chromatography. In contrast, treatment of the 14-(2-triethoxysilylethyl)-7-oxo methyl ester **11** with BH_3·DMS gave the 7β-1,2-oxasilepin **14** (37%) (Scheme 4), but some demethylation (of the aryl methoxy group, 20%) also occurred.

Oxidation of the oxasilepins to diols

The tetralone-derived oxasilepin **10** was oxidised using H_2O_2/KF/$NaHCO_3$ at rt to give the expected diol **15** quantitatively (Scheme 2). Although the diterpenoid 1,2-oxasilepin **13** did not react under these conditions, and heating to reflux overnight gave only the lactone **16**, use of 24 equiv. of H_2O_2 gave the 7β-hydroxy-14(2-arylethanol) **17** (Scheme 3). Attempts to purify diols **15** and **17** by chromatography on silica gel resulted not only in substantial losses of material but also in the formation of unidentified compounds. Reduction of the ketone and oxidation of silicon–carbon bond were therefore carried out without purification or isolation of the intermediates.



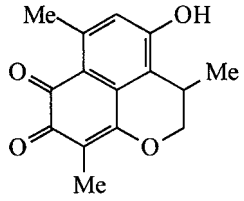
Scheme 3. (a) Red-Al; (b) H_2O_2(12 equiv.), KF, $NaHCO_3$; (c) H_2O_2(24 equiv.), KF, $NaHCO_3$ (d) PDC; (e) BH_3·Me_2S then H_2O_2 then CF_3COOH, Et_3SiH then TBAF.



Scheme 4. (a) $BH_3{\cdot}SMe_2$; (b) $BH_3{\cdot}SMe_2$ then H_2O_2, then CF_3COOH, Et_3SiH then TBAF; (c) $NaBH_4$ then H_2O_2, KF, $NaHCO_3$ then CF_3COOH; (d) Et_3SiH then TBAF; (e) $CrO_3{\cdot}Py_2$; (f) CAN; (g) $NaBH_4$ or $BH_3{\cdot}SMe_2$ then H_2O_2 then CAN; (h) $NaBH_4$ then H_2O_2 then CF_3COOH, Et_3SiH; (i) H_2, Pd–C.

Oxidation of the diols

For the present purpose, it was required to oxidise a secondary alcohol to a ketone and also a primary alcohol to an aldehyde, to yield a 1,5-dicarbonyl compound as a synthon for a pinacol transform. The crude bicyclic diol **15** was therefore treated with PCC[13] (2 equiv.), and with PCC/NaOAc; the only product isolated was the dihydropyran **18** (29%) (Scheme 2). This heterocycle has the ring structure characteristic of Mansonone H (**19**), isolated from a shrubby weed species that has yielded a number of antitumour compounds.[14]



19 Mansonone H

Formation of the heterocycle reflects the acidic nature of PCC,[15] since exposure of the diol to *p*-TsOH in benzene also gave the dihydropyran. Pyridinium dichromate (PDC),[16] a near-neutral reagent, also resulted in heterocyclisation to give the analogous diterpenoid dihydropyran **20** (35%, two steps from **13**) (Scheme 3), even in the presence of basic alumina. The decahydro-6-oxabenzo-[*de*]anthracene ring system embedded in the tetracycle **20** occurs in the cleistanthane family of diterpenes.[17] The above results suggest that Cr(VI) reagents can lead directly to the dihydropyran by intramolecular displacement of a chromate ester by the proximal secondary hydroxy group. It was therefore decided to remove the benzylic [C(7) diterpenoid] oxygen functionality to yield a methylene group, but to retain the 2-hydroxyethyl side chain for further functionalisation.

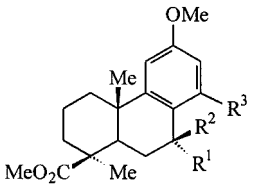
Attempts to remove the benzylic oxygen

Attempted hydrogenolysis (1 atm H_2, Pd/C) of the benzylic ether in the diterpenoid oxasilepin **13** was either unsuccessful (rt) or gave a mixture [reflux; or $Pd(OH)_2$] which included an alkene. However, treatment of the crude bicyclic diol **15** with Et_3SiH/CF_3COOH gave the desired 2-arylethanol **21** (43%) and its trifluoroacetate **22** (21%), which was also available from the dihydropyranyl ether **18** by treatment with Et_3SiH/CF_3COOH (Scheme 2). Exposure of **22** to TBAF resulted in quantitative deprotection to regenerate the primary alcohol **21**. This sequence, combined with prior reduction of the ketone and oxidation of the silicon–carbon bond, was applied to the diterpenoids **11** (Scheme 4) and **12** (Scheme 3) to give **23** and **24**, respectively.

While the overall yields (four steps) of the diterpenoid 14-(2-hydroxyethyl) products **23** (40%) and **24** (28%) were satisfactory, they were not sufficiently high for an initial sequence in multi-step organic syntheses. The first reduction step, in which silicon competes with carbonyl for hydride delivery from boron, offered potential interference. Decreasing the susceptibility of the silicon to hydride attack by modifying its electronic properties was therefore examined. Thus, the diethoxymethylsilyl analogue **25** was stirred with $NaBH_4$ in ethanol (Scheme 4). Remarkably, quantitative conversion into reduction products [C(7) alcohols and oxasilepin(s)] occurred, and polysiloxanes were absent. Treatment of the crude mixture with H_2O_2/KF/$NaHCO_3$ and then CF_3COOH gave the acid-sensitive dihydropyranyl ether **26** (28%). Clearly, the change in the substituents on silicon resulted in a significant effect on the efficiency of reduction of the ketone. These consequences were illustrated spectacularly by subjecting the diethoxymethylsilyl diterpenoid **25** to the identical sequence developed for the triethoxysilyl analogue, the 2-arylethanol **23** being isolated in an overall yield of 75%, and without purification of any intermediate compounds.

Since $NaBH_4$ efficiently reduced the ketone in **25**, there was no requirement to use BH_3·DMS [necessary for the congeners containing a $Si(OEt)_3$ group], and in fact its use resulted in a slight decrease in the yield of **23** (67%, four steps). However, reduction using BH_3·DMS required only one hour ($NaBH_4$, 8 h), and therefore the four-step sequence could be completed within one day. Since ethers undergo reductive cleavage with $NaBH_4$/CF_3COOH to yield the corresponding alcohol,[18] use of this combination instead of Et_3SiH/CF_3COOH would avoid the need for the TBAF step. In the event, $NaBH_4$/CF_3COOH gave the alcohol **23** in lower overall yield (57%, 3 steps) and required hydrolysis of the trifluoroacetate.

Because removal of oxygen-containing functionality at C(7) had been mandatory in the above sequence in order to permit clean oxidation of the silicon–carbon bond in the side chain, such functionality now had to be re-introduced in order to allow a 1,5-dicarbonyl compound to be obtained. The 2-arylethanol **23** was therefore stirred with CrO_3 in HOAc/H_2O, but no ketone formed despite the use of excess (2 equiv.) oxidant, and the dihydropyranyl ether **26** (60%) was formed instead (Scheme 4). The heterocycle apparently arises via oxidation of C(7) to a secondary alcohol, and then cyclisation of the diol as before. Thus a reagent was required that would oxidise the benzylic secondary alcohol sufficiently rapidly to avoid internal displacement by the primary alcohol. Moreover, oxidation of the primary alcohol must not occur preferentially. Treatment of **23** with CAN (5 or 2.2 equiv.) in CH_3CN/H_2O for 1 h gave only the Δ^5-7-ketone **27** (70 or 86%) (Scheme 4), while a reaction time of 5 min gave **27** (52%) together with dihydropyran **26** and starting material **23**. Apparently, the 7-ketone formed initially is converted rapidly into the α,β-unsaturated ketone **27**. Neither the 7-oxo diterpenoid **28** nor its 14-(2-trimethylsilylethyl) derivative **29** afforded the respective enones, even with excess CAN and prolonged reaction times.



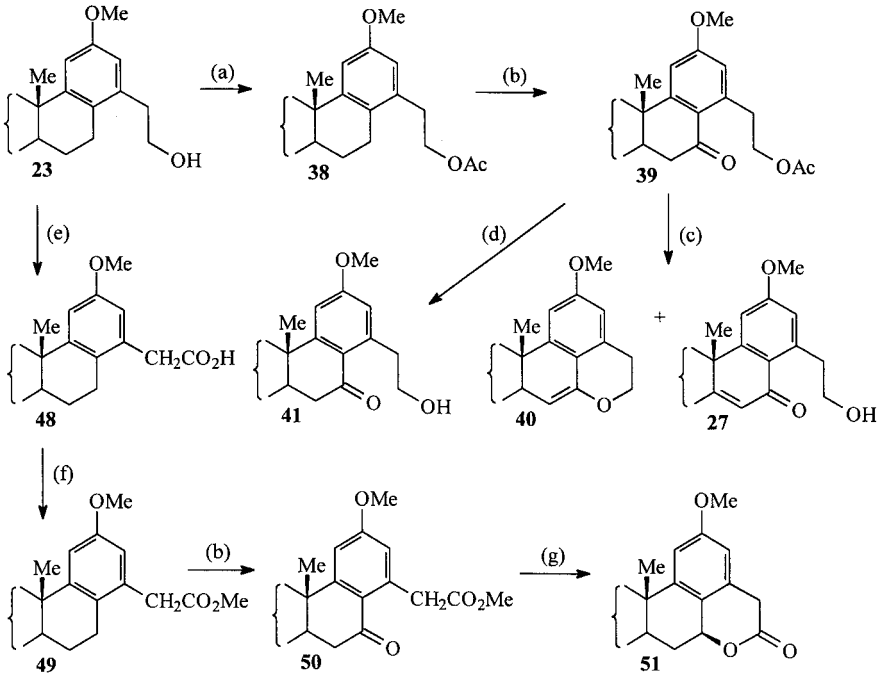
28: R^1, R^2 = O, R^3 = H
29: R^1, R^2 = O, R^3 = $CH_2CH_2SiMe_3$
47: R^1 = H, R^2 = OH, R^3 = CH_2CH_2OH

These results suggested that a 7β-hydroxy-2-arylethanol might also undergo reaction with CAN, and therefore yield the Δ^5-7-ketone in only three steps from the starting diterpenoid. Thus, the 14-(2-triethoxysilylethyl)-7-ketone **11** was reduced/cyclised to the oxasilepin, which was oxidised with H_2O_2 to the diol, treatment of which with CAN for 1 h gave the enone **27**. Since a triethoxysilyl moiety was present in the side chain of **11** the overall yield from this sequence was only moderate (26%, three steps). As expected, however, use of the diethoxymethylsilyl analogue **25** improved the yield from the reduction/initial oxidation steps, and increased the overall yield of the enone **27** significantly (70%, $NaBH_4$; 60%, BH_3·DMS) (Scheme 4).

The primary alcohol **27** was converted into the aldehyde **30** (87%) (Scheme 4) by treatment with CrO_3·$2C_5H_5N$[19] generated in situ.[20] However, the keto-aldehyde **31** rather than the enone–aldehyde **30** was preferred for annulation studies, as single electron reduction of **30** to generate a carbon radical at C(7) during the pinacol-type coupling would be difficult. A route for synthesis of **31** involves reduction of the Δ^5 double bond in **27**, followed by oxidation of the primary alcohol. However, exposure of **27** to H_2 (1 atm., 10% Pd–C) resulted in saturation and deoxygenation of the enone as well as hydrogenolysis of the homobenzylic primary alcohol, to give methyl 14-ethyl-12-methoxypodocarpa-8,11,13-trien-19-oate (**32**) (63%). Treatment of **27** with Et_3SiH/CF_3COOH[21] resulted in elimination of water to give a styrene, while no reaction occurred with Pd–C/$HCOONH_4$.[22] Stirring the enone–aldehyde **30** with Pd–C (20%w/w) under H_2 (1 atm.) for 3 h gave an unstable compound identified provisionally as the hemiacetal **33**.

Oxidation of C(7) methylene to C(7) ketone

Attempts to oxidise the 2-arylethanol **23** to the C(7) ketone using minimal oxidant had been unsuccessful, as discussed previously. These failures could reflect interaction involving the primary alcohol, and therefore its prior conversion into an aldehyde might prove beneficial. Therefore, **23** was converted into 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethanal (**34**) (75%) using Collins' reagent (Scheme 4). Attempted benzylic oxidation of the aldehyde **34** to the 7-keto derivative **31** with CAN (5 equiv.) at room temperature gave either (45 min) enone **27**, or (20 min) a mixture (1:1) of enone **27** and ketone **31** (5% isolated, 2



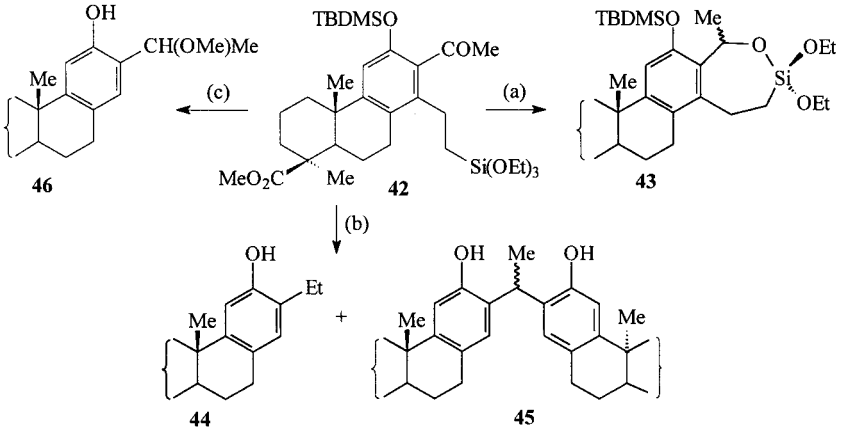
Scheme 5. (a) CH_3COCl, Et_3N; (b) CAN; (c) K_2CO_3, MeOH; (d) Mg, MeOH; (e) Jones' reagent; (f) Me_3SiCl, MeOH; (g) SmI_2.

steps). A superior strategy might be to mask the side-chain oxygen with a group that is unable to enolise and yet is more electron-withdrawing than a primary alcohol, such as a trifluoroacetate. 2-[14-(Methyl 12-methoxypodocarpa-8,11, 13-trien-19-oate)]ethyl trifluoroacetate (**35**) was therefore prepared from **25** in three steps ($NaBH_4$, H_2O_2, Et_3SiH/ CF_3COOH, 46% overall).

Treatment of the trifluoroacetate **35** with CAN (5 equiv.) gave the Δ^6- and 7-oxo-14(2-ethyl)diterpenoid trifluoroacetates **36** (17%) and **37** (13%). While the recovery of the ketone **37** was low, this result confirmed that over-oxidation to the enone could be retarded by an appropriate choice of the 2-oxaethyl substituent at C(14), and suggested that a more stable ester might give the C(7) ketone only. This expectation was realised: oxidation of the acetate **38** with CAN (15 equiv.) gave the 7-oxo derivative **39** (58%, 2 steps) (Scheme 5). Synthesis of the 1,5-dicarbonyl substrate required for investigation of pinacol coupling would be completed by deprotection to liberate the primary alcohol, followed by oxidation to the aldehyde. Treatment of the acetate **39** with K_2CO_3 in MeOH gave a mixture of the enone **27** and the cyclic enol ether **40** [$\delta_{H(6)}$ 5.51, J=2.5 Hz]. Milder conditions were therefore required (to prevent formation of the enol ether), as was an inert atmosphere (to avoid oxidation). Cleavage of the acetate **39** with Mg/MeOH[23] gave the required alcohol **41**. Disappointingly, however, reaction of this primary alcohol with Collins' reagent led to a mixture of aldehyde, enone (with/without oxidation of the side chain) and other products, while Swern conditions gave three products resulting from chlorination α to the ketone[24] and/or cyclisation.

Functionalisation of the 13-acetyl derivative

Application of the synthetic transformations discussed earlier to the 13-acetyl-14-(2-triethoxysilylethyl) diterpenoid **42** would give a 1,5-keto aldehyde, a potential



Scheme 6. (a) $BH_3{\cdot}SMe_2$; (b) $BH_3{\cdot}SMe_2$ then H_2O_2 then CF_3COOH, Et_3SiH then TBAF; (c) $BH_3{\cdot}SMe_2$ then H_2O_2 then *p*-TsOH.

precursor to a ring C aromatic steroidal analogue. The use of $BH_3{\cdot}SMe_2$ resulted in reduction of the 13-COMe group, leading to the stable oxasilepin epimers **43** (64% (Scheme 6)).

Oxidation (H_2O_2/KF/$NaHCO_3$) of the silicon–carbon bond in **43** gave the expected diol. However, treatment of the crude diol with CAN (5 equiv.) resulted in a complicated mixture; this oxidant has been reported to cleave TBDMS ethers,[25] perhaps allowing quinone formation and then further oxidation reactions.

The sequence that had been successful for the 7-oxo diterpenoid derivatives involved $BH_3{\cdot}SMe_2/H_2O_2$ and stirring the resulting crude diol with Et_3SiH/CF_3COOH, followed by hydrolysis with TBAF. However, application of these reactions to the 13-acetyl diterpenoid **42** gave the 14-ethyl diterpenoid **44** (30%) and the dimer **45** (22%) (Scheme 6), both of which have undergone dealkylation at C(14). Dealkylation of **42** at C(14) also occurred using $BH_3{\cdot}$DMS/H_2O_2 and then *p*-TsOH, giving the 12-hydroxy-13-(1-methoxyethyl) derivative **46** (20%, 1:1 mixture of epimers; the methyl ether arises from methanol which had been used as solvent during oxidation of the silicon–carbon bond).

Investigation of pinacol coupling

The formation of five- or six-membered rings by the intramolecular coupling of two carbonyl groups is well documented.[26] Although enone–aldehyde coupling is less well known, an example involving a benzylic ketone and a saturated aldehyde has been reported.[27] However, under either these conditions (Bu_3SnH/AIBN/heat), or Zn/Me_3SiCl/2,6-lutidine,[28] the enone–aldehyde **30** (Scheme 4) returned mainly starting material. Reaction of SmI_2[29–31] with the enone–aldehyde **30** in THF-HMPA[32–34] gave stereoselectively the 5α-7-oxo aldehyde **31** (93%). Further treatment of keto-aldehyde **31** with SmI_2/HMPA (followed by *p*-TsOH) did not result in pinacol coupling.[35,36]

Approaches to the quassinoid ring system

Some of the compounds available from the present work are related structurally to the quassinoid system. Quassinoids[37,38] are highly oxygenated and biologically active (but cytotoxic) triterpenes containing a tetracyclic skeleton which includes a lactone spanning C(7)–C(14) (diterpene numbering). It was envisaged that such a lactone could be formed by simple functional group manipulation of a suitable diterpenoid precursor. Attempts to effect this transformation by oxidation of the 7β-hydroxy-2-arylethanol **47** with various reagents (e.g. Jones' reagent, $NaBrO_3/Na_2S_2O_5$[39]) were unsuccessful, as were attempts to reduce the enone–aldehyde **30**. An alternative strategy, in which a carboxylic acid was prepared and converted into an ester prior to oxidation at C(7) was investigated. Transformation of the 2-arylethanol **23** into the δ-keto ester **50** was accomplished in three steps [Jones' oxidation to **48**, methylation with Me_3SiCl/MeOH to **49**, CAN oxidation at C(7) to **50**, 51% overall] (Scheme 5) without isolation of the intermediate products. This concludes a remarkable set of reactions involving oxidation of C(7) for these diterpenoids having various side chains at C(14). Thus, when the side chain was either CH_2CH_2OH or CH_2CHO, over-oxidation to the Δ^5-7-ketone was common using CAN. The presence of CH_2CH_2OAc gave the saturated C(7) ketone cleanly, but required an excess (usually 15 equiv.) of CAN. Apparently, CH_2CO_2Me on C(14) creates the correct electronic balance to ensure formation of the 7-oxo diterpenoid rapidly and without the need for excess oxidising agent. Treatment of the δ-keto ester **50** in THF/HMPA with SmI_2 (3 equiv.) gave the lactone **51** [27%, mixture of epimers at C(6a)]. The major compound was assigned as the β epimer on the basis of the chemical shift of C(6a) in the ^{13}C NMR spectrum (77.3 ppm, cf. **26**).

Summary

These studies have extended the potential applicability of the ruthenium-catalysed *ortho* (2-alkoxysilylethyl)ation reaction by demonstrating that 1,2-oxasilepins, and then diols and 2-arylethanols, are available in good yields, particularly from the 2-diethoxysilylethyl adducts. A variety of further oxidation products have been investigated with a view to achieving annulation of the diterpenoid derivatives via 1,5-dicarbonyl substrates.

Experimental

For general experimental details see Ref. 2.

1-(2-(2-Trimethoxysilylethyl)-1,1-dimethoxyphenyl)-ethane (4)

1-(2-(2-Triethoxysilylethyl)phenyl)ethanone (1) (287 mg, 0.912 mmol) and trimethyl orthoformate (0.199 mL, 1.82 mmol) in methanol (3 mL) containing a trace of *p*-toluenesulfonic acid were heated gently for 10 min, refluxed for 90 min, and more trimethyl orthoformate (0.199 mL, 1.82 mmol) was added. After 1 h K_2CO_3 and brine was added to the cooled mixture. Extraction with dichloromethane and workup gave 1-(2-(2-trimethoxysilylethyl)-1,1-dimethoxyphenyl)ethane (**4**) (259 mg, 90%) as a yellow oil; ν_{max} 1190 (C–O), 1086 (Si–O), 796 cm^{-1}; δ_H 0.96–1.05 (m, 2H, CH_2Si), 1.56 (s, 3H, Me), 2.91–3.0 (m, 2H, $PhCH_2$), 3.18 (s, 6H, $C(OMe)_2$), 3.60 (s, 9H, $Si(OMe)_3$), 7.13–7.24 (m, 3H, Ar-*H*), 7.56 (d, *J*=7.2 Hz, 1H, Ar-*H*); δ_C 12.3, CH_2Si, 25.0, Me, 25.3, CH_2Ph, 48.6, $Si(OMe)_3$, 50.5, $C(OMe)_2$, 102.3, $C(OMe)_2$, 125.4, 127.4, 127.8, 130.2, Ar-*C*H, 139.4, 142.7, Ar-*C*(quaternary); *m*/*z* 299 (1, M−Me), 282 (20, M−MeOH), 267 (38, 282-Me), 121 (100, $Si[OMe]_3$). Found: (M^+−15), 299.1332. $C_{14}H_{23}O_5Si$ calcd: (M−15), 299.1314. Chromatography (silica gel, hexanes/ether, 3:1) resulted in significant decomposition.

Oxidation of 1-(2-(2-triethoxysilylethyl)phenyl)-ethanone (1)

To a stirred suspension of 1-(2-(2-triethoxysilylethyl)-phenyl)ethanone (**1**) (314 mg, 1.01 mmol) and KHF_2 (157 mg, 2.02 mmol) in DMF (5 mL) was added acetic anhydride (1.14 mL, 12.1 mmol) and then H_2O_2 (1.21 mL, 12.1 mmol). After 17 h aqueous sodium thiosulfate was added and the product extracted with ether to yield an oil (**2** and **3**); ν_{max} 3371 (OH), 1731 (C=O ester), 1456 (C=C),

1266, 1245, 1112 (C–O), 757, 736 (C–H) cm^{-1}; δ_H 1.88 (s, 3H, Me), 2.05 (s, 3H, OCO*Me*), 2.96 (t, *J*=7.0 Hz, 2H, PhCH_2), 3.04 (t, *J*=6.0 Hz, 2H, PhCH_2), 4.29 (t, *J*=7.0 Hz, 2H, CH_2OH), 4.52 (t, *J*=7.0 Hz, 2H, CH_2OH), 6.82 (t, *J*=7.1 Hz, 2H, Ar-*H*), 7.08 (t, *J*=7.5 Hz, 2H, Ar-*H*); δ_C 20.9, OCO*Me*, 27.4, Ph*C*H_2, 29.8, Ph*C*H_2, 64.3, *C*H_2OH, 67.3, *C*H_2OH, 109.0, Ar-$C_{quaternary}$, 115.5, 120.1, 127.9, 130.7, Ar-*C*H, 154.6, Ar-$C_{quaternary}$, 171.6, O*C*OMe; *m/z* 180 (5, M^+), 120 (100, M−HOAc), 43 (55, COMe). Found: M^+, 180.0788. $C_{10}H_{12}O_3$ calcd: M, 180.0786.

Reduction of 1-(2-(2-triethoxysilylethyl)phenyl)-ethanone (1)

To a stirred solution of 1-(2-(2-triethoxysilylethyl)phenyl)-ethanone (**1**) (74 mg, 0.238 mmol) in toluene (1.5 mL) was added Red-Al (48 mg, 0.238 mmol) in toluene at −18°C. The solution was warmed to rt over 2.5 h, cooled to 0°C, and another equivalent of Red-Al was added. After 30 min another equivalent of Red-Al was added. After 30 min ethanol was added, and then dichloromethane and water. Workup and flash chromatography (silica gel, hexanes/ether, 3:1, then 1:1) gave (i) 7,7-diethoxy-5-methyl-5,7,8,9-tetrahydro-6-oxa-7-sila-benzocycloheptane (**8**) (4 mg, 6%) as a colourless oil; ν_{max} 1104, 1077 cm^{-1}; δ_H 0.83 (dddd, *J*=14.7, 12.40, 4.0 Hz, 1H, $H8_{ax}$), 1.17 (dddd, *J*=16.0, 7.40, 4.3 Hz, 1H, $H8_{eq}$), 1.21 (t, *J*=7.0 Hz, 3H, SiOCH_2CH_3), 1.24, (t, *J*=7.0 Hz, 3H, SiOCH_2CH_3), 1.68, d, *J*=6.5 Hz, 3H, 5−Me), 2.93 (dddd, *J*=13.4, 7.4, 4.1 Hz, 1H, $H9_{eq}$), 3.06 (td, *J*=13.3, 3.0 Hz, 1H, $H9_{ax}$), 3.79–3.89 (m, 4H, SiOCH_2CH_3), 5.33 (q, *J*=6.5 Hz, 1H, H5), 7.19–7.25 (m, 3H, Ar-*H*), 7.36–7.38 (m, 1H, Ar-*H*); δ_C 12.9 (C8), 18.0 (SiOCH_2*C*H_3), 18.2 (SiOCH_2*C*H_3), 21.6 (5−Me), 28.1 (C9), 58.2 (SiO*C*H_2CH_3), 58.3 (SiO*C*H_2CH_3), 67.8, (C5), 125.2, 126.3, 128.0 and 129.0 (Ar-*C*H), 140.7 and 143.0 (Ar-$C_{quaternary}$); *m/z* 266 (18, M^+), 251 (100, M−15). Found: M^+, 266.1336. $C_{14}H_{22}O_3Si$ calcd: M, 266.1338: and (ii) 1-(2-(2-triethoxysilylethyl)phenyl)ethan-1-ol (7) (15 mg, 20%) as a colourless oil; ν_{max} 3442 (OH), 1099, 1077 cm^{-1}; δ_H 0.96–1.02 (m, 2H, CH_2Si), 1.23 (t, *J*=7.0 Hz, 9H, SiOCH_2CH_3), 1.51 (d, *J*=6.40 Hz, 3H, Me), 2.73–2.88 (m, 2H, PhCH_2), 3.76–3.87 (m, 6H, SiOCH_2CH_3), 5.24 (q, *J*=6.40 Hz, 1H, O–C–*H*), 7.18–7.27 (m, 3H, Ar-*H*), 7.35–7.55 (m, 1H, Ar-*H*); δ_C 12.7 (*C*H_2Si), 18.1 (SiOCH_2*C*H_3), 24.3 (Me), 24.9 (*C*H_2Ph), 58.03 (SiO*C*H_2CH_3), 65.7 (O–C–*H*), 125.1, 126.3, 127.3 and 128.7 (Ar-*C*H), 140.7 and 143.0 (Ar-$C_{quaternary}$); *m/z* 294 (5, M−18), 266 (12, M−EtOH), 251 (35, 266−15), 163 (100, $Si(OEt)_3$). Found: (M^+−18), 294.1653. $C_{16}H_{26}O_3Si$ calcd: (M−18), 294.1651.

8,8-Diethoxy-2-methoxy-5,6,6a,8,9,10-hexahydro-4H-7-oxa-8-silacyclohepta[de]-naphthalene (10)

Red-Al (61 mg, 0.346 mmol) in toluene was added to 8-(2-triethoxysilylethyl)-6-methoxy-3,4-dihydro-1-2*H*-naphthalenone (**9**) (111 mg, 0.308 mmol) in toluene (5 mL) at −23°C. After 2 h the solution was warmed to rt, then cooled to 0°C and another equivalent of Red-Al added. After 2 h saturated aqueous potassium sodium tartrate was added and the product was extracted into ether. Workup gave 8,8-diethoxy-2-methoxy-5,6,6a,8,9,10-hexahydro-4*H*-7-oxa-8-silacyclohepta[*de*]naphthalene (**10**) (86 mg, 87%) as an oil, used without purification for the next step; ν_{max} 1604 (C=C), 1072, 1011 cm^{-1}; δ_H 0.75 (td, *J*=14.6, 3.9 Hz, 1H, $H9_{ax}$), 1.22 (dddd, *J*=15.0, 5.9, 2.4 Hz, 1H, $H9_{eq}$), 1.13 (t, *J*=7.1 Hz, 3H, SiOCH_2CH_3), 1.35 (t, *J*=7.1 Hz, 3H, SiOCH_2CH_3), 1.76–1.84 (m, 2H, H5, $H6_{ax}$), 2.02–2.14, (m, 1H, H5), 2.22 (bd, *J*=13.6 Hz, 1H, $H6_{eq}$), 2.69–2.85 (m, 3H, H4, $H10_{eq}$), 3.1(td, *J*=14.0, 2.2 Hz, 1H, $H10_{ax}$), 3.65 (q, *J*=7.0 Hz, 2H, SiOCH_2CH_3), 3.81 (s, 3H, 2−OMe), 3.96 (q, *J*=7.0 Hz, 2H, SiOCH_2CH_3), 5.19 (t, *J*= 2.8 Hz, 1H, $H6a_{eq}$), 6.55(d, *J*=2.32 Hz, 1H, H3), 6.65 (d, *J*=2.5 Hz, 1H, H1); δ_C 12.8 (C9), 17.2 (C5), 18.0 (SiOCH_2*C*H_3), 18.3 (SiOCH_2*C*H_3), 27.9 (C10), 30.6 (C4), 32.5 (C6), 55.0 (2−OMe), 57.9 (SiO*C*H_2CH_3), 58.2 (SiO*C*H_2CH_3), 64.1 (C6a), 111.4 (C3), 113.5 (C1), 128.9 (C10b), 139.0 (C3a), 145.0 (C10a), 158.6 (C2); *m/z* 322 (100, M^+). Found: M^+, 322.1571. $C_{17}H_{26}O_4Si$ calcd: M, 322.1600.

6,6-Diethoxy-2-methoxy-9-methoxymethyl-9,12a-dimethyl-5,6,7a,8,8a,9,10,11,12,12a-decahydro-4H-7-oxo-6-silacyclohepta[jk]phenanthrene (13)

A solution of 14-(2-triethoxysilylethyl)-12,19-dimethoxy-podocarpa-8,11,13-trien-7-one (**12**) (370 mg, 0.752 mmol) in toluene (5 mL) was cooled to −25°C. Red-Al (151 mg, 0.752 mmol) in toluene was added, the temperature warmed to 5°C over 2 h, and then more Red-Al (151 mg, 0.752 mmol) was added at 0°C. After 2 h saturated aqueous potassium sodium tartrate was added and the mixture was extracted with ether. Workup gave 6,6-diethoxy-2-methoxy-9-methoxymethyl-9,12a-dimethyl-4,5,7a,8,8a,9,10,11,12,12a-decahydro-4*H*-7-oxo-6-silacyclohepta[*jk*]phenanthrene (**13**) (322 mg) as an oil, used without purification for the next step; ν_{max} 1602, 1463 (C=C), 1106 (C–O), 1076 (Si–O) cm^{-1}; δ_H 0.82 (td, *J*=14.5, 4.1 Hz, 1H, $H5_{ax}$), 0.92 (td, *J*=13.5, 4.2 Hz, 1H, $H10_{ax}$), 1.03 (s, 3H, 9−Me), 1.03 (t, *J*=7.0 Hz, 3H, SiOCH_2CH_3), 1.19 (m, 1H, $H5_{eq}$), 1.30 (t, *J*=7.0 Hz, 3H, SiOCH_2CH_3), 1.31 (m, 4H, 12a−Me, H8a obscured), 1.35 (td, *J*=13.0, 3.6 Hz, 1H, $H12_{ax}$), 1.55–1.73 (m, 2H, $H11_{ax}$, $H11_{eq}$), 1.81–1.92 (m, 2H, $H8_{eq}$, $H10_{eq}$), 2.23 (bd, *J*=12.5 Hz, 1H, $H12_{eq}$), 2.52 (ddd, *J*=13.5, 9.1, 1.92 Hz, 1H, $H8_{ax}$), 2.78 (dt, *J*=13.6, 4.7 Hz, 1H, $H4_{eq}$), 2.90 (td, *J*=13.3, 2.4 Hz, 1H, $H4_{ax}$), 3.22 (d, *J*=9.0 Hz, 1H, 9−CH_2OMe), 3.34 (s, 3H, 9−CH$_2$O*Me*), 3.52 (q, *J*=7.0 Hz, 2H, SiOCH_2CH_3), 3.60 (d, *J*=9.0 Hz, 1H, 9−CH_2OMe), 3.77 (s, 3H, 2−OMe), 3.89 (q, *J*=7.0 Hz, 2H, SiOCH_2CH_3), 5.33 (t, *J*=8.4 Hz, 1H, $H7a_{ax}$), 6.59 (d, *J*=2.5 Hz, 1H, H3), 6.70 (d, *J*=2.5 Hz, 1H, H1); δ_C 12.8, (C5), 17.9 (SiOCH_2*C*H_3), 18.3 (SiOCH_2*C*H_3), 18.8 (C11), 24.9 (12a−Me), 27.1 (9−Me), 28.9 (C4), 30.4 (C8), 35.4 (C10), 37.6 (C9), 38.2 (C12a), 39.5 (C12), 49.2 (C8a), 54.9 (2−OMe), 57.9, 58.2 (SiO*C*H_2CH_3), 59.3 (9−CH$_2$O*Me*), 68.6 (C7a), 75.2 (9−*C*H$_2$OMe), 107.9 (C1), 112.8 (C3), 125.2 (C12c), 144.7 (C3a), 153.5 (C12b), 158.7 (C2); *m/z* 448 (90, M^+), 447 (35, M−H), 433 (30, M−15), 403 (40, M−EtOH), 336 (100). Found: M^+, 448.2634. $C_{25}H_{40}O_5Si$ calcd: M, 448.2645.

6,6-Diethoxy-2-methoxy-9,12a-dimethyl-5,6,7a,8,8a,9,10,11,12,12a-decahydro-4H-7-oxo-6-silacyclohepta[jk]-phenanthrene-9-carboxylic acid methyl ester (14)

$BH_3{\cdot}SMe_2$ (0.044 mL, 0.462 mmol) was added to methyl 14-(2-triethoxysilylethyl)-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**11**) (117 mg, 0.231 mmol) in dry

dichloromethane (4 mL) and the solution refluxed for 1.5 h. Saturated aqueous potassium sodium tartrate was added at 0°C. Workup and flash chromatography (silica gel, hexanes/ether, 1:1) gave 6,6-diethoxy-2-methoxy-9,12a-dimethyl-5,6,7a,8,8a,9,10,11,12,12a-decahydro-4*H*-7-oxo-6-silacyclohepta-[*jk*]phenanthrene-9-carboxylic acid methyl ester (**14**) (40 mg, 37%) as a yellow oil; ν_{max} 1725 (C=O ester), 1076 cm^{-1} (Si-O); δ_H 0.88 (td, *J*=14.2, 4.5 Hz, 1H, $H5_{ax}$), 1.01 (t, *J*=7.0 Hz, 3H, $SiOCH_2C\mathit{H}_3$), 1.17 (m, 4H, 12a−Me, $H10_{ax}$ obscured), 1.22–1.34 (m, 8H, $H12_{ax}$, $SiOCH_2C\mathit{H}_3$, 9−Me, $H5_{eq}$), 1.42 (d, *J*= 13.4 Hz, 1H, H8a), 1.61 (dp, *J*=14.0, 3.1, Hz, 1H, $H11_{eq}$), 1.99 (qt, *J*=13.8, 3.4 Hz, 1H, $H11_{ax}$), 2.11–2.27 (m, 3H, $H8_{ax}$, $H12_{eq}$, $H10_{eq}$), 2.70 (dd, *J*=13.7, 8.3, Hz, 1H, $H8_{eq}$), 2.75–2.92 (m, 2H, $H4_{ax}$, $H4_{eq}$), 3.52 (q, *J*=7.0 Hz, 2H, $SiOC\mathit{H}_2CH_3$), 3.70 (s, 3H, 9−$CO_2\mathit{Me}$), 3.78 (s, 3H, 2−OMe), 3.92 (q, *J*=7.0 Hz, 2H, $SiOC\mathit{H}_2CH_3$), 5.30 (t, *J*=8.3 Hz, 1H, $H7a_{ax}$), 6.60 (d, *J*=2.4 Hz, 1H, H3), 6.71 (d, *J*=2.4 Hz, 1H, H1); δ_C 12.9 (C5), 17.9 and 18.3 ($SiOCH_2\mathit{C}H_3$), 19.9 (C11), 21.8 (12a−Me), 28.2 (9−Me), 29.3 (C4), 31.8 (C8), 37.4 (C10), 39.0 (C12a), 40.4 (C12), 43.6 (C9), 49.2 (C8a), 51.3 (9−$CO_2\mathit{Me}$), 55.0 (2−OMe), 57.9 and 58.0 ($SiO\mathit{C}H_2CH_3$), 70.2 (C7a), 109.0 (C1), 113.4 (C3), 129.2 (C12c), 144.5 (C3a), 151.6 (C12b), 158.7 (C2), 177.4 (9−$\mathit{C}O_2$Me); *m/z* 462 (70, M^+), 45 (100, OCH_2CH_3). Found: M^+, 462.2428. $C_{25}H_{38}O_6Si$ calcd: M, 462.2437.

5-Methoxy-2,3,7,8,9,9a-hexahydrobenzo[de]chromene (18)

Aqueous H_2O_2 (31%, 0.197 mL, 1.98 mmol) was added to a stirred suspension of crude 8,8-diethoxy-2-methoxy-5,6,6a,8,9,10,-hexahydro-4*H*-7-oxa-8-silacyclohepta[*de*]-naphthalene (10) (53 mg), $NaHCO_3$ (27 mg, 0.329 mmol) in thf/MeOH (1:1, 2 mL). The mixture was stirred overnight, aqueous sodium thiosulfate was added to give a negative starch–iodine test, and the mixture was extracted with ether. Workup gave crude diol **15** (42 mg), which was dissolved in dichloromethane (3 mL) and added to PCC (83 mg, 0.390 mmol) in dichloromethane (2 mL) at rt After 5 h ether (10 mL) was added, and the solvents were decanted and passed through a pad of Florisil. Chromatography (silica gel, dichloromethane) gave 5-methoxy-2,3,7,8,9,9a-hexahydrobenzo[*de*]chromene (**18**) (16 mg, 29% from **9**) as a colourless oil; ν_{max} 1603, 1479 cm^{-1} (C=C); δ_H 1.55–1.65 (m, 2H, H9), 1.77–1.89 (m, 1H, H8), 1.95–2.03 (m, 1H, H8), 2.71 (dd, *J*=16.6, 4.2 Hz, 1H, $H3_{eq}$), 2.79 (dd, *J*=8.6, 4.7 Hz, 2H, H7), 3.06–3.15 (m, 1H, $H3_{ax}$), 3.78 (s, 3H, 5−OMe), 3.94 (td, *J*=11.3, 4.7 Hz, 1H, $H2_{ax}$), 4.22 (dddd, *J*=11.3, 7.04, 1.80 Hz, 1H, $H2_{eq}$), 4.47 (dd, *J*=11.2, 5.1 Hz, 1H, $H9_{ax}$), 6.51 (s, 2H, H4, H6); δ_C 20.6 (C8), 28.5 (C7), 28.7 (C3), 29.4 (C9), 55.0 (5−OMe), 65.4 (C2), 74.6 (C9a), 111.16 and 111.21 (C4 and C6), 127.8 (C9b), 136.5 (C6a), 133.8 (C3a), 158.2 (C5); *m/z* 204 (50, M^+), 203 (100, M−H), 176 (65, M−28). Found: M^+, 204.1132. $C_{13}H_{16}O_2$ calcd: M, 204.1150.

2-Methoxy-8-methoxymethyl-8,11a-dimethyl-4,5,6aξ,7,7a,8,9,10,11,11a-decahydro-6-oxabenzo[de]anthracene (20)

The crude diol (**17**) (168 mg) in dichloromethane (6 mL) was added to PDC (0.518 g, 1.38 mmol) and alumina (1.554 g) in dichloromethane (5 mL). After 2 h, ether was added and the mixture was filtered through Celite/$MgSO_4$, Vacuum chromatography (silica gel/K_2CO_3, hexanes/ethyl acetate, 4:1) gave an epimeric mixture (10:1) of 2-methoxy-8-methoxymethyl-8,11a-dimethyl-4,5,6aξ,7,7a,8,9,10,11,11a-decahydro-6-oxabenzo[*de*]anthracene (**20**) (53 mg, 35%, two steps from **13**) as a colourless oil; ν_{max} 1601 (C=C), 1106 cm^{-1} (C=O); δ_H 0.89 (td, *J*=13.5, 4.2 Hz, 1H, $H9_{ax}$), 0.98 (s, 3H, 8−Me), 1.12 (s, 3H, 11a−Me), 1.43 (dd, *J*=12.6, 7.6 Hz, 1H, H7a), 1.50–1.73 (m, 3H, $H10_{ax}$, $H10_{eq}$, $H11_{ax}$), 1.89–1.96 (m, 2H, $H7_{eq}$, $H9_{eq}$), 2.16, bd, *J*=14.0 Hz, 1H, (11_{eq}), 2.32–2.41 (m, 1H, $H7_{ax}$), 2.68 (bd, *J*=16.2 Hz, 1H, $H4_{eq}$), 3.07 (dq, *J*=16.2, 10.3, 6.7 Hz, 1H, $H4_{ax}$), 3.35 (s, 3H, 8−$CH_2O\mathit{Me}$), 3.38 (d, *J*=9.1 Hz, 1H, 8−$C\mathit{H}_2$OMe), 3.59 (d, *J*=9.1 Hz, 1H, 8−$C\mathit{H}_2$OMe), 3.77 (s, 3H, 2−OMe), 3.94 (td, *J*=10.7, 4.5 Hz, 1H, $H5_{ax}$), 4.08–4.13 (m, 1H, $H5_{eq}$), 4.37 (dd, *J*=11.0, 5.0 Hz, 1H, $H6a_{ax}$ minor), 4.70 (dd, *J*=9.3, 5.1 Hz, 1H, $H6a_{ax}$ major), 6.51 (s, 1H, H3), 6.65 (d, *J*=2.1 Hz, 1H, H1); δ_C 18.4 (C10), 21.6 (11a−Me), 26.5 (8−Me and C7), 28.7 (C4), 35.9 (C9), 37.5 (C8), 37.6 (C11a), 38.4 (C11), 47.4 (C7a), 54.8 (2−OMe), 59.1 (8−$CH_2O\mathit{Me}$), 64.6 (C5), 69.9 (C6a), 75.0 (8−$C\mathit{H}_2$OMe), 106.9 (C1), 109.7 (C3), 125.0 (C11c), 133.9 (C3a), 150.3 (C11b), 157.9 (C2); *m/z* 330 (50, M^+), 329 (100, M−H). Found: M^+, 330.2171. $C_{21}H_{30}O_3$ calcd: M, 330.2194.

Reduction of 2-[1-(3-methoxy-5,6,7,8-tetrahydronaphthalen-1-ol)]ethanol (15)

2-[1-(3-Methoxy-5,6,7,8-tetrahydronaphthalen-1-ol)]ethanol (**15**) (0.056 g, 0.252 mmol) and trifluoroacetic acid (0.03 g, 0.263 mmol) in dichloromethane (1.5 mL) were stirred for 2 h. Triethylsilane (0.440 g, 3.78 mmol) and trifluoroacetic acid (0.07 g, 0.614 mmol) were added. After 20 min aqueous sodium hydrogencarbonate was added. Workup and chromatography (silica gel, hexanes, ethyl acetate, 2:1, 1:1) gave (i) 2-[1-(3-methoxy-5,6,7,8-tetrahydronaphthalene)]ethyl trifluoroacetate (**22**) (16 mg, 21%) as an oil; δ_H 1.76 (m, 4H, H6, H7), 2.64, 2.75 (2t, J=6.1 Hz, H5, H8), 2.98 (t, *J*=7.4 Hz, 2H, 1−$C\mathit{H}_2$), 3.75 (s, 3H, 3−OMe), 4.48 (t, *J*=7.4 Hz, 2H, $C\mathit{H}_2OCOCF_3$), 6.55 (s, 2H, H2, H4); δ_C 22.8, 23.5, 25.6, 30.3 and 35.9 ($\mathit{C}H_2$), 55.1 (3−OMe), 62.4 ($\mathit{C}H_2OCOCF_3$), 112.0, 113.4 (C2, C4), 127.6, 132.0, 137.6, and 157.0 (Ar-*C*), $\mathit{C}OCF_3$ not detected: and (ii) 2-[1-(3-methoxy-5,6,7,8-tetrahydronaphthalene)]ethanol (**21**) (22 mg, 43%) as an oil; ν_{max} 3379 (OH), 1605 (C=C), 1143, 1051 cm^{-1}; δ_H 1.71 (m, 4H, H6, H7), 2.67 (t, *J*=5.9 Hz, 2H, H8), 2.75 (t, *J*=6.2 Hz, 2H, H5), 2.83 (t, *J*=6.8 Hz, 2H, 1−$C\mathit{H}_2$), 3.76 (s, 3H, 3-OMe), 3.82 (t, *J*=6.8 Hz, 2H, $C\mathit{H}_2$OH), 6.51 (d, *J*=2.2 Hz, 1H, H2), 6.60 (d, *J*=2.4 Hz, 1H, H4); δ_C 23.5, 24.2 (C6, C7), 26.3 (C8), 31.2 (C5), 36.6 (1−$C\mathit{H}_2$), 55.7 (3−OMe), 63.0 (1−$CH_2C\mathit{H}_2$OH), 112.7 (C2), 114.0 (C4), 128.3 (C8a), 138.3 (C1), 139.4 (C4a), 157.7 (C3); *m/z*206 (50, M^+), 161 (100, M−CH_2CH_2OH). Found: M^+, 206.1304. $C_{13}H_{18}O_2$ calcd: M, 206.1307.

2-[14-(12,19-Dimethoxypodocarpa-8,11,13-triene)]-ethanol (24)

$BH_3{\cdot}SMe_2$ (181 mg, 2.40 mL) was added to 14-(2-triethoxysilylethyl)-12,19-dimethoxypodocarpa-8,11,13-trien-7-one (**12**) (588 mg, 1.20 mmol) in dry dichloromethane (7 mL) and the mixture was refluxed for 2 h. Saturated aqueous

potassium sodium tartrate was added at 0°C. Workup gave a yellow oil (459 mg) which was dissolved in THF/MeOH (1:1,10 mL). KF (140 mg, 2.40 mmol), $NaHCO_3$ (204 mg, 2.40 mmol), and then aqueous H_2O_2 (31%, 2.4 mL, 24 mmol) were added. After 45 min a solution of sodium thiosulfate was added at 0 °C. After a negative starch–iodine test the mixture was extracted with ether to give an oil (294 mg) which was dissolved in dichloromethane (3 mL) and stirred with trifluoroacetic acid (0.65 mL, 8.5 mmol) for 30 min. Triethylsilane (0.420 mL, 2.5 mmol) was added. After 1 h $NaHCO_3$ was added, and the mixture was extracted with dichloromethane. Workup gave an oil (294 mg) contaminated (^{1}H NMR) with triethylsilane. The oil was dissolved in THF (3 mL), TBAF (1 mol L^{-1}, 0.7 mL) was added, and the mixture stirred for 2 h. Brine was added and the product was extracted with dichloromethane. Workup and flash chromatography (silica gel, hexanes/ethyl acetate, 2.5:1) gave 2-[14-(12,19-dimethoxypodocarpa-8,11,13-triene)]ethanol (**24**) (110 mg, 28%, four steps) as an oil; ν_{max} 3476 (OH), 1603, 1466 (C=C), 1108 cm^{-1} (C–O); δ_H 1.02 (td, J=12.9, 4.9 Hz, 1H, (3_{ax}), 1.06 (s, 3H, H18), 1.23 (s, 3H, H20), 1.42 (dd, J=12.8, 1.9 Hz, 2H, H5, $H1_{ax}$ obscured), 1.60–1.79 (m, 3H, $H2_{ax}$, H_{eq}, $H6_{ax}$), 1.89 (bd, J=13.6 Hz, 1H, $H3_{eq}$), 2.05 (bdd, J=13.3, 7.5 Hz, $H6_{eq}$), 2.30 (bd, J=12.4 Hz, 1H, $H1_{eq}$), 2.65 (dddd, J=16.9, 11.6, 7.5 Hz, 1H, $H7_{ax}$), 2.84 (t, J=6.9 Hz, 2H, 14−CH_2, $H7_{eq}$ obscured), 3.26 (d, J=9.1 Hz, 1H, 4−CH_2OMe), 3.35 (s, 3H, 4−CH_2O*Me*), 3.55 (d, J=9.1 Hz, 1H, 4−CH_2OMe), 3.80 (s, 3H, 12−OMe), 3.86 (t, J=6.9 Hz, 2H, CH_2OH), 6.61 (d, J=2.6 Hz, 1H, H13), 6.77 (d, J=2.6 Hz, 1H, H11); δ_C 19.2 (C2, C6), 25.6 (C20), 27.5 (C18), 27.6 (C7), 35.8 (C3), 36.2 (14−*C*H_2CH_2OH), 37.9 (C4), 38.2 (C10), 39.3 (C1), 50.7 (C5), 55.1 (12−OMe), 59.3 (4−CH_2O*Me*), 62.3 (14−CH_2*C*H_2OH), 75.8 (4−*C*H_2OMe), 108.7 (C11), 112.4 (C13), 125.7 (C8), 137.2 (C14), 151.9 (C9), 157.4 (C12); m/z 332 (100, M^+). Found: M^+, 332.236. $C_{21}H_{32}O_3$ calcd: M, 332.235.

A longer reaction time for the hydrogen peroxide step gave (silica gel, hexanes/ethyl acetate 2:1, 1:1) a small amount of the hydroxy lactone (**16**); ν_{max} 3448, (OH), 1747 (C=O ester), 1459 (C=C), 1200 (C–O), 736 cm^{-1}; δ_H 0.95 (s, 3H, H18), 0.98–1.04 (m, 1H, $H3_{ax}$), 1.47 (s, 3H, H20), 1.69–1.95 (m, 6H, $H1_{ax}$, $H2_{eq}$, H5, $H2_{ax}$, $H3_{eq}$, $H1_{eq}$), 2.57 (dd, J=13.7, 11.9 Hz, 1H, $H6_{ax}$), 2.68 (d, J=13.7, $H6_{eq}$), 2.83 (p, J=6.2 Hz, 1H, 14−CH_2), 3.01 (p, J=6.2 Hz, 1H, 14−CH_2), 3.39 (s, 3H, 4−CH_2OMe), 3.51 (d, J=9.1 Hz, 1H, 4−CH_2OMe), 3.60 (d, J=9.1 Hz, 1H, 4−CH_2OMe), 3.77–3.89 (m, 2H, 14−CH_2), 3.82 (s, 3H, 12−OMe), 6.71 (d, J=2.96 Hz, 1H, H13), 6.80 (d, J=2.96 Hz, 1H, H11); δ_C 18.5 (C2), 20.7 (C20), 27.4 (C18), 31.3 (C6), 34.4 (14−*C*H_2), 35.6 (C3), 38.8 (C1), 39.6 (C10), 40.6 (C4), 55.3 (C5), 55.4 (12−OMe), 59.2 (4−CH_2O*Me*), 62.7 (*C*H_2OH), 74.4 (4−*C*H_2OMe), 109.5 (C11), 112.9 (C13), 130.9 (C8), 142.9 (C9), 143.5 (C14), 156.5 (C12), 173.1 (C7); m/z 362 (100, M^+), 45 (70, CH_2CH_2OH). Found: M^+, 362.2098. $C_{21}H_{30}O_5$ calcd: M, 362.2093.

2-Methoxy-8,11a-dimethyl-4,5,6a,7,7a,8,9,10,11,11a-decahydro-6-oxabenzo[de]-anthracene-8-carboxylic acid methyl ester (26)

Sodium borohydride (11 mg, 0.289 mmol) was added to methyl 14-(2-diethoxymethylsilylethyl)-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**25**) (69 mg, 0.145 mmol) in EtOH (1 mL). After 12 h brine was added and the mixture was extracted with dichloromethane. Workup gave an oil (76 mg) which was dissolved in THF/MeOH (1:1, 1.5 mL). KF (16 mg, 0.190 mmol), $NaHCO_3$ (24 mg, 0.190 mmol) and then aqueous H_2O_2 (31%, 0.173 mL, 1.73 mmol) were added. After 3 h a solution of sodium thiosulfate was added at 0°C. After a negative starch–iodine test the product was extracted with ether. Workup gave an oil (59 mg) which was dissolved in dichloromethane (2 mL) and stirred with a catalytic amount of trifluoroacetic acid for 1 h. The mixture was poured into 10% aqueous K_2CO_3 and extracted with dichloromethane. Workup and flash chromatography (silica gel, hexanes/ethyl acetate, 3:1) gave 2-methoxy-8,11a-dimethyl-4,5,6a,7,7a,8,9,10,11,11a-decahydro-6-oxabenzo-[*de*]anthracene-8-carboxylic acid methyl ester (**26**) (14 mg, 28%, three steps) as a colourless oil; ν_{max} 1726 (C=O ester), 1260, 1027 cm^{-1}; δ_H 1.04 (s, 3H, 11a−Me), 1.12 (td, J=13.5, 4.3 Hz, 1H, $H9_{ax}$), 1.30 (s, 3H, 8−Me), 1.45 (td, J=13.4, 4.0 Hz, 1H, $H11_{ax}$), 1.68 (d, J=12.7 Hz, 2H, H7a, $H10_{eq}$ obscured), 1.94–2.05 (m, 2H, $H10_{ax}$, $H7_{ax}$), 2.21 (bd, J=13.0, 1H, $H11_{eq}$), 2.33 (bd, J=13.5, 1H, $H9_{eq}$), 2.47 (dd, J=12.6, 5.4 Hz, 1H, $H7_{eq}$), 2.79 (ddd, J=16.6, 5.6, 3.1 Hz, 1H, $H4_{eq}$), 3.10 (ddd, J=16.8, 9.6, 7.6 Hz, 1H, $H4_{ax}$), 3.65 (s, 3H, 8−CO_2*Me*), 3.78 (s, 3H, 2−OMe), 4.02 (ddd, J=10.9, 10.8, 5.6 Hz, 1H, $H5_{ax}$), 4.20 (ddd, J=11.0, 7.3, 3.0 Hz, 1H, $H5_{eq}$), 4.21 (dd, J=11.5, 5.5 Hz, 1H, $H6a_{ax}$), 6.53 (d, J=2.4 Hz, 1H, H3), 6.65 (d, J=2.4 Hz, 1H, H1); δ_C 19.6 (C10), 23.3 (11a−Me), 28.1 (C7), 28.3 (8−Me), 28.8 (C4), 37.4 (C9), 38.9 (C11), 39.9 (C11a), 43.6 (C8), 50.5 (C7a), 51.1 (8−CO_2*Me*), 55.1 (2−OMe), 65.2 (C5), 76.3 (C6a), 109.2 (C3), 110.8 (C1), 126.3 (C11c), 134.0 (C3a), 147.8 (C11b), 158.6 (C2), 177.6 (8−*C*O_2Me); m/z345 (90, M^++H), 343 (100, [M+H]−H), 176 (95). Found: (M^++H), 345.2055. $C_{21}H_{29}O_4$ calcd: (M+H), 345.2060.

2-[14-(Methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethanol (23)

Sodium borohydride (292 mg, 7.90 mmol) was added to methyl 14-(2-diethoxymethylsilylethyl)-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**25**) (752 mg, 1.57 mmol) in EtOH/THF (4:1, 5 mL). After 6 h brine was added and the mixture was extracted with dichloromethane. Workup gave an oil (730 mg) which was dissolved in THF/MeOH (1:1, 14 mL). KF (182 mg, 3.14 mmol), $NaHCO_3$ (263 mg, 3.14 mmol), and then aqueous H_2O_2 (31%, 3.1 mL, 34.1 mmol) were added. After 2 h aqueous sodium thiosulfate was added at 0°C. After a negative starch–iodine test the product was extracted with ether. Workup gave an oil (688 mg) which was dissolved in dichloromethane (4 mL) and stirred with trifluoroacetic acid (1.2 mL, 15.7 mmol) for 30 min, when triethylsilane (0.750 mL, 4.71 mmol) was added. After 4 h $NaHCO_3$ was added, followed by brine, and the mixture extracted with dichloromethane. Workup gave an oil (890 mg, contaminated with triethylsilane). The oil was dissolved in THF (5 mL), TBAF (2 mL, 1 mol L^{-1}) was added, and the mixture stirred for 3 h. Brine was added and the mixture was extracted with dichloromethane. Workup and chromatography (silica gel, hexanes/ethyl acetate, 2:1, 1:1) gave 2-[14-(methyl

12-methoxypodocarpa-8,11,13-trien-19-oate)]ethanol (**23**) (0.406 g 75%, four steps) as an oil; ν_{max} 3417 (OH), 1727 (C=O ester), 1604 (C=C) 1469, 1145, 1060 cm^{-1}; δ_H 1.04 (s, 3H, H20), 1.07 (td, *J*=13.6, 4.2 Hz, 1H, $H3_{ax}$), 1.27 (s, 3H, H18), 1.35 (td, *J*=13.3, 3.9, 1H, $H1_{ax}$), 1.50 (d, *J*=11.5 Hz, 1H, H5), 1.61 (dp, *J*=14.1, 2.9 Hz, 1H, $H2_{eq}$), 1.86-2.04 (m, 2H, $H2_{ax}$, $H6_{ax}$), 2.20–2.28 (m, 3H, 1_{eq}, $H3_{eq}$, $H6_{eq}$), 2.56 (ddd *J*=16.4, 12.6, 6.3 Hz, 1H, $H7_{ax}$), 2.83 (t, *J*=6.8 Hz, 2H, 14−CH_2), 2.85 (dd, *J*=16.6, 4.4 Hz, 1H, $H7_{eq}$), 3.66 (s, 3H, 19−OMe), 3.76 (s, 3H, 12−OMe), 3.83 (t, *J*=6.8 Hz, 2H, CH_2OH), 6.60 (d, *J*=2.52 Hz, 1H, H11), 6.74 (d, *J*=2.52 Hz, 1H, H13); δ_C 20.0 (C2), 20.9 (C6), 22.8 (C20), 28.4 (C18, C7), 36.3 (14−CH_2CH_2OH), 37.4 (C3), 38.9 (C10), 39.8 (C1), 43.9 (C4), 51.2 (19−OMe), 52.3 (C5), 55.1 (12−OMe), 62.3 (14−CH_2CH_2OH), 109.5 (C13), 112.7 (C11), 126.2 (C8), 137.3 (C14), 150.0 (C9), 157.4 (C12), 177.8 (C19); *m/z* 346 (100, M^+), 271 (50, M). Found: M^+, 346.2144. $C_{21}H_{30}O_4$ calcd: M, 346.2144.

2-[14-(Methyl 12-methoxy-7-oxopodocarpa-5,8,11,13-tetraen-19-oate)]ethanol (27)

Sodium borohydride (92 mg, 2.44 mmol) was added to methyl 14-(2-diethoxymethylsilylethyl)-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**25**) (233 mg, 0.489 mmol) in MeOH/THF (3:1, 4 mL). After 19 h brine was added and the mixture was extracted with dichloromethane. Workup gave an oil (252 mg) which was dissolved in THF/MeOH (1:1, 6 mL). KF (56 mg, 0.978 mmol), $NaHCO_3$ (82 mg, 0.978 mmol) and then H_2O_2 (31%, 1.17 mL, 11.7 mmol) were added. After 2 h aqueous sodium thiosulfate was added at 0°C. After a negative starch–iodine test the product was extracted with ether to give an oil (220 mg) which was dissolved in acetonitrile (10 mL). Ceric ammonium nitrate (1.34 g, 2.44 mmol) in water (2 mL) was then added in one portion. After 1 h brine was added and the product extracted with ethyl acetate. Workup and flash chromatography (silica gel, hexanes/ethyl acetate, 1:1) gave 2[14-(methyl 12-methoxy-7-oxopodocarpa-5,8,11,13-tetraen-19-oate)]ethanol (**27**) (123 mg, 70%, three steps) as an oil; ν_{max} 3425 (OH), 1729 (C=O ester), 1651, (C=O enone) 1594 cm^{-1} (C=C); δ_H 1.22 (td, *J*=13.6, 4.2 Hz, 1H, $H3_{ax}$), 1.30 (s, 3H, H20), 1.48 (s, 3H, H18), 1.52 (td, *J*=13.6, 4.2, 1H, $H1_{ax}$), 1.70 (bdp, *J*=14.3, 2.7 Hz, 1H, $H2_{eq}$), 2.12 (qt, *J*=13.9, 3.6 Hz, 1H, $H2_{ax}$), 2.32 (bd, *J*=13.1 Hz, 1H, $H1_{eq}$), 2.52 (bd, *J*=11.4 Hz, 1H, $H3_{eq}$), 3.28–3.33 (m, 1H, 14−CH_2), 3.53–3.57 (m, 1H, 14−CH_2), 3.64 (s, 3H, 19−OMe), 3.89 (s, 3H, 12−OMe), 3.91–3.95 (m, 1H, CH_2OH), 3.99–4.04 (m, 1H, 14−CH_2CH_2OH), 6.48 (s, 1H, H6), 6.77 (d, *J*=2.44, 1H, H13), 6.90 (d, *J*=2.44, 1H, H11); δ_C 19.2 (C2), 26.9 (C18), 28.4 (C20), 36.9 (C3), 38.6 (14−CH_2), 40.4 (C1), 42.6 (C10), 47.5 (C4), 51.5 (19−OMe), 55.3 (12−OMe), 65.1 (CH_2OH), 110.0 (C11), 116.3 (C13), 122.2 (C8), 127.6 (C6), 144.3 (C14), 156.9 (C9), 162.0 (C12), 162.6 (C5), 175.4 (C19), 186.8 (C7); *m/z* 358 (8, M^+), 340 (100, M−H_2O). Found: M^+, 358.1778. $C_{21}H_{26}O_5$ calcd: M, 358.1780.

2-[14-(Methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethyl trifluoroacetate (35)

Methyl 14-(2-diethoxymethylsilylethyl)-12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate (**25**) (325 mg, 0.682 mmol) was subjected to the $NaBH_4$ reduction/Si–C oxidation/CF_3COOH/$HSiEt_3$ sequence to give an oil (306 mg) which was chromatographed (silica gel, hexanes/ether, 3:1) to give 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethyl trifluoroacetate (**35**) (139 mg, 46%) as white microcrystals, mp 72–74°C; ν_{max} 1786 ($OCOCF_3$), 1722 (C=O ester), 1468, 1145 cm^{-1}; δ_H 1.04 (m, 4H, H20, $H3_{ax}$ obscured), 1.30 (s, 3H, H18), 1.38 (td, *J*=13.2, 3.8 Hz, 1H, $H1_{ax}$), 1.52 (d, *J*=11.3 Hz, 1H, H5), 1.64 (bd, *J*=14.0 Hz, 1H, $H2_{eq}$), 1.93–2.04 (m, 2H, $H2_{ax}$, $H6_{ax}$), 2.23–2.31 (m, 3H, 1_{eq}, $H3_{eq}$, $H6_{eq}$), 2.60 (ddd *J*=16.2, 12.6, 6.2 Hz, 1H, $H7_{ax}$), 2.89 (dd, *J*=16.4,. 4.2 Hz, 1H, $H7_{eq}$), 3.01 (t, *J*=7.4 Hz, 2H, 14−CH_2), 3.68 (s, 3H, 19−OMe), 3.77 (s, 3H, 12−OMe), 4.52 (t, *J*=7.4 Hz, 2H, CH_2OCOCF_3), 6.60 (d, *J*=2.52 Hz, 1H, H11), 6.80 (d, *J*=2.52 Hz, 1H, H13); δ_C 19.9 (C2), 20.8 (C6), 22.7 (C20), 28.2 (C18), 28.3 (C7), 31.6 (14−CH_2), 37.3 (C3), 38.9 (C10), 39.7 (C1), 43.8 (C4), 51.1 (19−OMe), 52.2 (C5), 54.9 (12−OMe), 67.3 (CH_2OCOCF_3), 110.4 (C13), 112.6 (C11), 125.9 (C8), 134.9 (C14), 150.3 (C9), 157.5 (C12), 177.7 (C19); *m/z* 442 (100, M^+), 367 (90, M−75).

Elution with dichloromethane then hexanes/ethyl acetate (1:1) gave the alcohol (**23**) (29 mg, 12%), and a mixture (35 mg) of the alcohol and a silicon-containing product

Oxidation of 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethyl trifluoroacetate (35)

Ceric ammonium nitrate (0.8 g, 1.46 mmol) in water (1 mL) was added to 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethyl trifluoroacetate (**35**) (0.135 g, 0.305 mmol) in acetonitrile (4 mL). After 10 min the solution was poured into brine and extracted with ether. Workup and flash chromatography (silica gel, hexanes/ether, 2:1, 3:1) gave (i) 2-[14-(methyl 12-methoxy-podocarpa-6,8,11,13-tetraen-19-oate)]ethyl trifluoroacetate (**36**) (23 mg, 17%) as an oil; ν_{max} 1785 ($OCOCF_3$), 1727 (C=O ester), 1602 (C=C) 1466, 1220, 1146 cm^{-1}; δ_H 0.86 (s, 3H, H20), 1.12 (td, *J*=13.5, 4.0 Hz, 1H, $H3_{ax}$), 1.32 (s, 3H, H18), 1.61–1.76 (m, 2H, $H1_{ax}$, $H2_{eq}$), 1.95 (qt, *J*=13.8, 3.6 Hz, 1H, $H2_{ax}$), 2.30 (bd, *J*=12.4 Hz, 1H, 1_{eq}), 2.31 (t, *J*=2.8 Hz, 1H, H5), 2.34 (bd, *J*=13.7 Hz, 1H, $H3_{eq}$), 3.02–3.22 (m, 2H, 14−CH_2CH_2OCOCF_3), 3.70 (s, 3H, 19−OMe), 3.79 (s, 3H, 12-OMe), 4.48–4.52 (m, 2H, 14−CH_2CH_2OCOCF_3), 6.50 (dd, *J*=10.1, 2.4 Hz, 1H, H6), 6.57 (d, *J*=2.5 Hz, 1H, H13), 6.63 (dd, *J*=10.1, 3.1 Hz, 1H, H7), 6.76 (d, *J*=2.52 Hz, 1H, H11); δ_C 19.1 (C20), 19.6 (C2), 27.6 (C18), 31.9 (14−CH_2), 36.3 (C3), 37.1 (C1), 38.4 (C10), 43.4 (C4), 50.5 (C5), 51.5 (19−OMe), 55.1 (12−OMe), 67.8 (CH_2OCOCF_3), 108.9 (C11), 111.9 (C13), 120.4 (C6), 124.0 (C8), 128.8 (C7), 132.3 (C14), 149.1 (C9), 158.8 (C12), 177.4 (C19), *COC*F_3 not detected; *m/z* 440 (100, M^+). Found: M^+, 440.1799. $C_{23}H_{27}F_3O_5$ calcd: M, 440.1810: and (ii) 2-[14-methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate)]ethyl trifluoroacetate (**37**) (18 mg, 13%) as an oil; ν_{max} 1784 ($OCOCF_3$), 1725 (C=O ester), 1667 (C=O ketone), 1597 (C=C), 1148 cm^{-1}; δ_H 1.12 (s, 3H, H20), 1.16 (td, *J*=13.6, 4.0 Hz, 1H, $H3_{ax}$), 1.28 (s, 3H, H18), 1.55 (td, *J*=13.2, 4.0 Hz, 1H, $H1_{ax}$), 1.58–1.68 (m, 1H, $H2_{eq}$), 1.98–2.10 (m, 2H, $H2_{ax}$, H5), 2.30–2.33 (m, 2H, $H1_{eq}$, $H3_{eq}$), 2.91 (dd, *J*=17.9, 3.6 Hz, 1H, $H6_{eq}$), 3.23

(dd, J=17.8, 14.4 Hz, 1H, $H6_{ax}$), 3.39–3.55 (m, 2H, 14−CH_2), 3.72 (s, 3H, 19−OMe), 3.85 (s, 3H, 12−OMe), 4.67 (t, J=6.2 Hz, 2H, CH_2OCOCF$_3$), 6.60 (d, J=2.5 Hz, 1H, H13), 6.76 (d, J=2.52 Hz, 1H, H11); δ_C 19.6 (C2), 21.4 (C20), 27.7 (C18), 35.1 (14-CH_2), 37.2 (C6), 38.9, 39.0, (C1, C3), 39.3 (C10), 43.8 (C4), 49.3 (C5), 51.5 (19−OMe), 55.1 (12−OMe), 68.4 (14−CH_2CH_2OCOCF$_3$), 110.0 (C11), 115.7 (C13), 122.9 (C8), 141.7 (C14), 158.8 (C9), 162.4 (C12), 176.9 (C19), 199.1 (C7), $COCF_3$ not detected; m/z 342 (95, M-OCOCF$_3$), 283 (50), 227 (60), 216 (100). Found: (M$^+$−OCOCF$_3$), 342.1824. $C_{21}H_{26}O_4$ calcd: (M−OCOCF$_3$), 342.1831.

2-[14-(Methyl 12-methoxy-7-oxopodocarpa-6,8,11,13-tetraen-19-oate)]ethanal (30)

Chromium trioxide (56 mg, 0.567 mmol) was added to pyridine (89 mg, 1.13 mmol) in dichloromethane (3 mL). After 15 min 2-[14-(methyl 12-methoxy-7-oxopodocarpa-6,8,11,13-tetraen-19-oate)]ethanol (**27**) (29 mg, 0.081 mmol) in dichloromethane (2 mL) was added. After 30 min the dichloromethane was decanted. Work up and chromatography (silica gel, hexanes/ethyl acetate, 1:1) gave 2-[14-(methyl 12-methoxy-7-oxopodocarpa-6,8,11,13-tetraen-19-oate)]ethanal (**30**) (25 mg, 87%) as an oil; ν_{max} 1728 (broad, C=O ester, C=O aldehyde), 1650 (C=O enone), 1596 cm^{-1} (C=C); δ_H 1.22 (td, J=13.6, 4.3 Hz, 1H, $H3_{ax}$), 1.31 (s, 3H, H20), 1.47 (s, 3H, H18), 1.53 (td, J=13.4, 4.0 Hz, 1H, $H1_{ax}$), 1.72 (bd, J=14.2 Hz, 1H, $H2_{eq}$), 2.12 (qt, J=14.0, 3.4 Hz, 1H, $H2_{ax}$), 2.33 (bd, J=12.4 Hz, 1H, $H1_{eq}$), 2.51 (bd, J=12.6 Hz, 1H, $H3_{eq}$), 3.64 (s, 3H, 19−OMe), 3.88 (s, 3H, 12−OMe), 4.10 (d, J=15.4 Hz, 1H, 14−CH_2CHO), 4.17 (d, J=15.4 Hz, 1H, 14−CH_2CHO), 6.45 (s, 1H, H6), 6.70 (d, J=2.0 Hz, 1H, H13), 6.98 (d, J=2.0 Hz, 1H, H11), 9.83 (s, 1H, 14−CH_2CHO); δ_C 18.7 (C2), 26.6 (C18), 27.8 (C20), 36.3 (C3), 39.9 (C1), 42.0 (C10), 47.0 (C4), 49.9 (1−CH_2CHO), 51.6 (19−OMe), 55.2 (12-OMe), 110.3 (C13), 117.0 (, C11), 120.9 (C8), 128.9 (C6), 136.8 (C14), 156.3 (C9), 161.7 (C12), 162.4 (C5), 174.9 (C19), 184.9 (C7), 198.3 (14−CH_2CHO); m/z 356 (20, M$^+$), 339 (30, M−OH), 328 (100, M−CO). Found: M$^+$, 356.1621. $C_{21}H_{24}O_5$ calcd: M, 356.1623.

Methyl 14-ethyl-12-methoxypodocarpa-8,11,13-trien-19-oate (32)

2-[14-(Methyl 12-methoxy-7-oxopodocarpa-6,8,11,13-tetraen-19-oate)]ethanol (**27**) (0.045 g, 0.125 mmol) and Pd/C were stirred overnight in ethanol (3 mL) under a hydrogen atmosphere. Filtration and p.l.c. (hexanes/ether, 3:1) gave methyl 14-ethyl-12-methoxypodocarpa-8,11,13-trien-19-oate (**32**) (0.026 g, 63%) as white crystals, mp 78–81°C; ν_{max} 1726 (C=O ester), 1604 (C=C), 1192, 1144 cm^{-1} (C–O); δ_H 1.08 (s, 3H, H20), 1.10 (td, J=13.5, 4.2 Hz, 1H, $H3_{ax}$), 1.24 (t, J=7.5 Hz, 3H, 14−CH_2CH_3), 1.30 (s, 3H, H18), 1.40 (td, J=13.3, 4.0 Hz, 1H, $H1_{ax}$), 1.52 (dd, J=12.4, 1.6 Hz, 1H, H5), 1.61–1.68 (m, 1H, $H2_{eq}$), 1.89–2.03 (m, 2H, $H2_{ax}$, $H6_{ax}$), 2.23–2.31 (m, 3H, $H1_{eq}$, $H3_{eq}$, $H6_{eq}$), 2.52–2.63 (m, 3H, $H7_{ax}$, 14−CH_2CH$_3$), 2.86 (dddd, J=16.6, 5.4, 1.5 Hz, 1H, $H7_{eq}$), 3.69 (s, 3H, 19−OMe), 3.80 (s, 3H, 12−OMe), 6.64 (d, J=2.6 Hz, 1H, H13), 6.73 (d, J=2.6 Hz, 1H, H11); δ_C 13.9 (14−CH_2CH_3), 20.0 (C2), 20.9 (C6), 22.8 (C20), 25.6 (14−CH_2CH$_3$), 28.1 (C7), 28.4 (C18), 37.3 (C3), 38.9 (C10), 39.7 (C1), 43.9 (C4), 51.2 (19-OMe), 52.3 (C5), 55.0 (12−OMe), 108.4 (C11), 111.0 (C13), 125.5 (C8), 143.0 (C14), 149.5 (C9), 157.5 (C12), 177.8 (C19); m/z330 (100, M$^+$), 255 (92, M−75). Found: M$^+$, 330.2195. $C_{21}H_{30}O_3$ calcd: M, 330.2195.

2-[14-(Methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethanal (34)

Chromium trioxide (152 mg, 1.52 mmol) was added to pyridine (241 mg, 3.05 mmol) in dichloromethane (4 mL). After 15 min 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethanol (**23**) (88 mg, 0.254 mmol) in dichloromethane (2 mL) was added. After 30 min the dichloromethane was decanted. Workup gave 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethanal (**34**) (66 mg, 75%) as an oil; ν_{max} 1722 (C=O ester, C=O aldehyde), 1605 (C=C) 1469, 1145, 736 cm^{-1}; δ_H 1.07 (s, 3H, H20), 1.08 (td, J=13.4, 4.3 Hz, 1H, $H3_{ax}$), 1.28 (s, 3H, H18), 1.40 (td, J=13.3, 4.1 Hz, 1H, $H1_{ax}$), 1.50 (dd, J=12.4, 1.4 Hz, 1H, H5), 1.74 (dt, J=14.2, 3.0 Hz, 1H, $H2_{eq}$), 1.95 (ddd, J=12.6, 5.5 Hz, 1H, $H6_{ax}$), 2.01 (qt, J=13.9, 3.6 Hz, 1H, $H2_{ax}$), 2.22–2.30 (m, 3H, $H1_{eq}$, $H3_{eq}$, $H6_{eq}$), 2.49 (ddd, J=16.4, 12.5, 6.4 Hz, 1H, $H7_{ax}$), 2.74 (ddd, J=16.5, 5.5, 1.4 Hz, 1H, $H7_{eq}$), 3.64 (d, J=2.4 Hz, 1H, 14−CH_2CHO), 3.66 (d, J=2.4 Hz, 1H, 14−CH_2CHO), 3.67 (s, 3H, 19−OMe), 3.80 (s, 3H, 12−OMe), 6.60 (d, J=2.6 Hz, 1H, H11), 6.84 (d, J=2.5 Hz, 1H, H13), 9.69 (t, J=2.4 Hz, 1H, 14−CH_2CHO); δ_C 19.9 (C2), 20.7 (C6), 22.7 (C20), 28.3 (C18), 28.8 (C7), 37.3 (C3), 38.8 (C10), 39.7 (C1), 43.8 (C4), 48.7 (14−CH_2CHO), 51.2 (19−OMe), 52.0 (C5), 55.1 (12−OMe), 110.8 (C13), 113.7 (C11), 126.7 (C8), 131.3 (C14), 150.5 (C9), 157.6 (C12), 177.7 (C19), 199.5 (14−CH_2CHO); m/z 344 (100, M$^+$), 269 (50). Found: M$^+$, 344.1988. $C_{21}H_{28}O_4$ calcd: M, 344.1988.

2-[14-(Methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethyl acetate (38)

Acetyl chloride (11.5 mg, 0.146 mmol) was added to 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]-ethanol (**23**) (25 mg, 0.073 mmol) and triethylamine (30 mg, 0.292 mmol) in dichloromethane (1 mL). After 20 min workup gave methyl 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethyl acetate (**38**) (19 mg, 67%) as an oil, used without purification; ν_{max} 1738, 1726 (C=O ester), 1605, 1468 (C=C), 1236, 1144 cm^{-1}; δ_H 1.07 (s, 3H, H20), 1.11 (td, J=13.6, 4.2 Hz, 1H, $H3_{ax}$), 1.29 (s, 3H, H18), 1.39 (td, J=13.2, 4.0 Hz, 1H, $H1_{ax}$), 1.52 (d, J=12.2 Hz, 1H, H5), 1.64 (bd, J=14.0, 1H, $H2_{eq}$), 1.89–2.03 (m, 2H, $H2_{ax}$, $H6_{ax}$), 2.08 (s, 3H, 14−CH_2CH_2O-COMe), 2.23–2.31 (m, 3H, $H1_{eq}$, $H3_{eq}$, $H6_{eq}$), 2.59 (ddd, J=16.4, 12.6, 6.2 Hz, 1H, $H7_{ax}$), 2.88–2.93 (m, 3H, $H7_{eq}$, 14−CH_2CH$_2$OAc), 3.68 (s, 3H, 19−OMe), 3.78 (s, 3H, 12−OMe), 4.22–4.32 (m, 2H, 14−CH_2CH_2OAc), 6.61 (d, J=2.4 Hz, 1H, H13), 6.77 (d, J=2.4 Hz, 1H, H11); δ_C 19.9 (C2), 20.8 (C6), 20.9 (OCOMe), 22.8 (C20), 28.3 (C7), 28.4 (C18), 32.3 (14−CH_2CH_2OAc), 37.4 (C3), 38.9 (C10), 39.8 (C1), 43.8 (C4), 51.1 (19−OMe), 52.5 (C5), 55.0 (12−OMe), 63.8 (14−CH_2CH_2OAc), 109.7 (C11), 112.5

(C13), 126.0 (C8), 136.5 (C14), 150.0 (C9), 157.4 (C12), 170.9 (O*C*OMe), 177.7 (C19); *m/z* 388 (50, M^+), 328 (100, M−HOAc), 253 (60). Found: M^+, 388.2247. $C_{23}H_{32}O_5$ calcd: M, 388.2250.

2-[14-(Methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate)]ethyl acetate (39)

Ceric ammonium nitrate (0.4 g, 0.73 mmol) in water (1 mL) was added to crude acetate (**38**) (19 mg) in acetonitrile (2 mL). After 3 h, extraction with ethyl acetate and flash chromatography (silica gel, hexanes/ethyl acetate, 2:1) gave 2-[14-(methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate)]ethyl acetate (**39**) (17 mg, 58%, 2 steps) as an oil; ν_{max} 1737, 1731 (C═O ester), 1667, (C═O ketone), 1595 (C═C), 1277, 1236, 1147 cm^{-1} (C-O); δ_H 1.11 (s, 3H, H20), 1.15 (td, *J*=13.6, 3.9 Hz, 1H, $H3_{ax}$), 1.27 (s, 3H, H18), 1.54 (td, *J*=13.4, 4.0 Hz, 1H, $H1_{ax}$), 1.71 (dp, *J*=14.4, 3.1 Hz, 1H, $H2_{eq}$), 1.99–2.09 (m, 5H, $H2_{ax}$, H5, OCO*Me*), 2.31 (bd, *J*=13.5 Hz, 2H, $H1_{eq}$, $H3_{eq}$), 2.89 (dd, *J*=17.8, 3.7 Hz, 1H, $H6_{eq}$), 3.20 (dd, *J*=17.8, 14.3, 1H, $H6_{ax}$), 3.29–3.35 (m, 1H, 14−C*H*$_2$CH$_2$OAc), 3.41–3.48 (m, 1H, 14−C*H*$_2$CH$_2$OAc), 3.71 (s, 3H, 19−OMe), 3.85 (s, 3H, 12−OMe), 4.32 (t, *J*=6.8 Hz, 3H, 14−CH$_2$C*H*$_2$OAc), 6.65 (d, *J*=2.5 Hz, 1H, H13), 6.84 (d, *J*=2.5 Hz, 1H, H11); δ_C 19.7 (C2), 20.9 (OCO*Me*), 21.4 (C20), 27.7 (C18), 35.2 (14−*C*H$_2$CH$_2$OAc), 37.2 (C3), 38.9 (C6), 39.0 (C1), 39.3 (C10), 43.8 (C4), 49.2 (C5), 51.5 (19−OMe), 55.2 (12−OMe), 64.8 (14−CH$_2$*C*H$_2$OAc), 109.2 (C11), 115.7 (C13), 123.0 (C8), 143.2 (C14), 158.6 (C9), 162.2 (C12), 171.0 (O*C*OMe), 176.9 (C19), 198.8 (C7); *m/z* 402 (<1, M^+), 342 (100, M−HOAc), 341 (85, 342−H). Found: (M^++H), 403.2129. $C_{23}H_{31}O_6$ calcd: (M+H), 403.2121.

2-[14-(Methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate)]ethanol (41)

Magnesium (1.44 mg, 0.059 mmol) was added to 2-[14-(methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate)]ethyl acetate (**39**) (20 mg, 0.049) in MeOH (2 mL) under a nitrogen atmosphere. After 2 and 4 h the same quantity of magnesium was added. After a further 2 h the methanol was removed and the residue triturated with ether to give 2-[14-(methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate)]ethanol (**41**); δ_H 1.08 (s, 3H, H20), $H3_{ax}$ obscured), 1.25 (s, 3H, H18), 1.50–1.74 (m, 2H, $H1_{ax}$, $H2_{eq}$), 1.95–2.05 (m, 2H, H5, $H2_{ax}$), 2.29 (bd, 2H, *J*=13.5 Hz, 2H, $H3_{eq}$, $H1_{eq}$), 2.96 (dd, *J*=17.9, 4.0 Hz, 1H, $H6_{eq}$), 3.05 (t, *J*=5.6 Hz, 2H, 14–C*H*$_2$CH$_2$OH), 3.20–3.30 (m, 1H, $H6_{ax}$), 3.70 (s, 3H, 19−OMe), 3.84 (s, 3H, 12−OMe), 3.94 (t, *J*=5.4 Hz, 2H, 14−CH$_2$C*H*$_2$OH), 6.68 (d, *J*=2.4 Hz, 1H, H13), 6.81 (d, *J*=2.4 Hz, 1H, H11).

9,9-Diethoxy-1,4a,7ξ-trimethyl-6-(((1,1-dimethylethyl)-dimethylsilyl)oxy)-1,2,3,4,4a,7,9,10,-11,12,13,13a-dodeca-8-oxa-9-silacyclohepta[a]phenanthrene-1-carboxylic methyl ester (43)

BH_3·SMe_2 (0.106 g, 1.4 mmol) was added to methyl 13-acetyl-14-(2-triethoxysilylethyl)-12-(((1,1-dimethylethyl)-dimethylsilyl)oxy)podocarpa-8,11,13-trien-19-oate (**42**) (0.445 g, 0.701 mmol) in dichloromethane (8 mL). The mixture was stirred for 30 min then refluxed for 1 h. BH_3·SMe_2 (0.106 g, 1.4 mmol) was added and the mixture was refluxed for 9 h, cooled to 0°C, and aqueous potassium sodium tartrate added. Extraction with dichloromethane and workup gave an oil which was chromatographed (silica gel, hexanes/ether, 2:1) to give a mixture of 9,9-diethoxy-1,4a,7ξ-trimethyl-6-(((1,1-dimethylethyl)-dimethylsilyl)-oxy)-1,2,3,4,4a,7,9,10,11,12,13,13a-dodeca-8-oxa-9-sila-cyclohepta[*a*]phenanthrene-1-carboxylic methyl ester epimers (**43**) (266 mg, 64%) as a colourless oil; ν_{max} 1718 (C═O ester), 1101, 1084 (Si–O), 853, 839 cm^{-1} (Si–C); δ_H 0.10, 0.21, 0.23, 0.23, (4s, 6H, Si*Me*$_2$), 0.83 (t, *J*=7.0 Hz, 3H, OCH$_2$C*H*$_3$), 0.91 (s, 3H, 4a−Me), 0.99 (s, 9H, C*Me*$_3$), 1.21–1.27 (m, 9H, OCH$_2$C*H*$_3$, 1−Me, H10, $H2_{ax}$), 1.33–1.48 (m, 2H, $H4_{ax}$, H13a), 1.51 (d, *J*=6.8 Hz, 3H, 7−Me), 1.55 (d, *J*=6.7 Hz, 3H, 7−Me), 1.59–1.63 (m, 1H, $H3_{eq}$), 1.85–2.0 (m, 2H, $H13_{ax}$, $H3_{ax}$), 2.07 (bd, *J*=12.8, 1H Hz, $H4_{eq}$), 2.20–2.27 (m, 2H, $H2_{eq}$, $H13_{eq}$), 2.47–2.63 (m, 2H, $H12_{ax}$, H11), 2.78–3.01 (m, 2H, $H12_{eq}$, H11), 3.33–3.48 (m, 4H, Si(OC*H*$_2$CH$_3$)$_2$), 3.65 (s, 3H, 1−CO$_2$*Me*), 3.72 (q, *J*=7.0 Hz, 2H, SiOC*H*$_2$CH$_3$), 3.72 (m, 2H, SiOC*H*$_2$CH$_3$), 5.60 (q, *J*=6.8 Hz, 1H, H7), 6.56 (s, 1H, H5); δ_C −4.15 (Si*Me*$_2$), 11.3, 11.4 (C10), 17.1, 17.8 (SiOCH$_2$*C*H$_3$), 18.2 (4a−Me), 20.1 (C2), 20.9, 21.2 (C13), 22.9 (4a−Me), 23.4 (7−Me), 25.7 (C*Me*$_3$), 27.5, 28.0 (C12, C11), 28.3 (1−Me), 37.4, 37.5 (C2), 38.5, 38.6 (C4a), 39.8, 40.1 (C4), 43.8 (C1), 51.1 (1−CO$_2$*Me*), 51.9, 52.0 (C13a), 57.7, 58.2 (SiO*C*H$_2$CH$_3$), 67.5 (C7), 113.1 (H5), 125.8, 126.1 (C11b), 129.6, 129.9 (C6a), 140.6, 141.0 (C11a), 148.0, 148.5 (C4b), 150.2(C6), 177.1 (1−*C*O$_2$Me); *m/z* 590 (75, M^+), 575 (100, M−Me), 73 (52, $SiMe_3$), 57 (42, ^{t}Bu). Found: M^+, 590.3541. $C_{32}H_{54}O_6Si_2$ calcd: M, 590.3460.

Reaction of 9,9-diethoxy-1,4a,7ξ-trimethyl-6-(((1,1-dimethylethyl)-dimethylsilyl)oxy)-1,2,3,4,4a,7,9,10,11,12,13,13a-dodeca-8-oxa-9-silacyclohepta[a]phenanthrene-1-carboxylic methyl ester (43)

BH_3·SMe_2 (61 mg, 0.8 mmol) was added to methyl 13-acetyl-14-(2-triethoxysilylethyl)-12-(((1,1-dimethylethyl)-dimethylsilyl)oxy)podocarpa-8,11,13-trien-19-oate (**42**) (0.170 g, 0.268 mmol) in dichloromethane (5 mL). After refluxing for 3 h the mixture was cooled to 0°C, aqueous potassium sodium tartrate was added, and the mixture was extracted with dichloromethane. Workup afforded crude **43** as an oil (152 mg) which was dissolved in THF/MeOH (1:1, 4 mL). KF (31 mg, 0.54 mmol), $NaHCO_3$ (45 mg, 0.54 mmol), and then aqueous H_2O_2 (31%, 0.650 mL, 6.4 mmol) were added. After 8 h aqueous sodium thiosulfate was added at 0°C. After a negative starch–iodine test the product was extracted with ether. Workup gave an oil (114 mg) which was dissolved in dichloromethane (2 mL) and stirred with trifluoroacetic acid (0.180 mL, 2.32 mmol) for 30 min. Triethylsilane (0.110 mL, 0.696 mmol) was then added. After 2.5 h K_2CO_3 was added, followed by brine, and the mixture was extracted with dichloromethane. Workup gave an oil (118 mg, contains some triethylsilane) which was dissolved in THF (3 mL). TBAF (0.373 mL, 1 mol L^{-1}) was added, the mixture was stirred overnight, and brine and then ether were added. Workup and chromatography (silica gel, hexanes/ethyl acetate, 4:1) gave (i) methyl 13-ethyl-12-hydroxypodocarpa-8,11,13-trien-19-

oate (**44**) (26 mg, 30%, three steps) as a white solid, mp 150–160°C; ν_{max} 3437 (OH), 1725 (C═O ester), 1417, 1249 cm^{-1} (C–O); δ_H 1.03 (s, 3H, H20), 1.10 (td, *J*=13.5, 4.2 Hz, 1H, $H3_{ax}$), 1.24 (t, *J*=7.5 Hz, 3H, 13−CH_2CH_3), 1.29 (s, 3H, H18), 1.40 (td, *J*=13.3, 4.2, 1H, $H1_{ax}$), 1.53 (dd, *J*=12.2, 1.4 Hz, 1H, H5), 1.64 (dp, *J*=14.3, 2.9 Hz, 1H, $H2_{eq}$), 1.90-2.06 (m, 2H, $H2_{ax}$, $H6_{ax}$), 2.18 (bd, *J*=13.4 Hz, 2H, $H3_{eq}$, $H6_{eq}$ obscured), 2.29 (bd, *J*=13.5 Hz, 1H, $H1_{eq}$), 2.58 (q, *J*=7.5 Hz, 1H, 14−CH_2CH_3), 2.71 (ddd, *J*=16.11, 12.6, 5.9 Hz, 1H, $H7_{ax}$), 2.84 (ddd, *J*=16.4, 5.4, 1.3 Hz, 1H, $H7_{eq}$), 3.68 (s, 3H, 19−OMe), 4.76 (bs, 1H, 12−O*H*), 6.68 (s, 1H, H11), 6.82 (s, 1H, H14); δ_C 13.8 (14−CH_2CH_3), 19.8 (C2), 21.0 (C6), 22.4 (14−CH_2CH_3), 22.7 (C20), 28.4 (C18), 31.0 (C7), 37.5 (C3), 38.0 (C10), 39.3 (C1), 43.8 (C4), 51.1 (19−OMe), 52.7 (C5), 111.7 (C11), 127.2 (C8, C13), 129.3 (C14), 146.6 (C9), 151.3 (C12), 177.9 (C19); *m/z* 316 (45, M^+), 241 (100, M−75). Found: M^+, 316.2040. $C_{20}H_{28}O_3$ calcd: M, 316.2038: and (ii) 1,1ξ-bis[13-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethane (**45**) (36 mg, 22%, three steps) as an oil; ν_{max} 3459 (OH), 1724 (C═O ester), 1495, 1469 (C═C), 1249, 1143 cm^{-1}; δ_H 0.96 (1.0, s, 6H, H20′, H20″), 1.03–1.13 (m, 3H, $H3_{ax}$′, $H3_{ax}$″, $H1_{ax}$″), 1.25, 1.27 (2s, 7H, H18′, H18″, $H1_{ax}$″ obscured), 1.20–1.41 (m, 1H, $H1_{ax}$′), 1.48–1.59 (m, 4H, H5′, H5″, $H2_{eq}$′, $H2_{eq}$″), 1.62 (d, *J*=7.0 Hz, 3H, H2), 1.82–2.03 (m, 5H, $H2_{ax}$′, $H2_{ax}$″, $H6_{ax}$′, $H6_{ax}$″, $H1_{ax}$″), 2.08–2.26 (m, 6H, $H6_{eq}$′, $H6_{eq}$″, $H1_{eq}$′, $H1_{eq}$″, $H3_{eq}$′, $H3_{eq}$″), 2.67–2.90 (m, 4H, $H7_{eq}$′, $H7_{eq}$″, $H7_{ax}$′, $H7_{ax}$″), 3.65 (s, 3H, 19′-OMe), 3.67(s, 3H, 19″−OMe), 4.50 (q, *J*=7.1 Hz, 1H, H1), 6.64 (m, 2H, H11′, H11″), 6.96 (m, 2H, H14′, H14″); δ_C 19.4 (C2), 19.7, 19.8 (C2′, C2″), 21.0 (C6′, C6″), 22.8 (C20′, C20″), 28.38, 28.45 (C18′, C18″), 28.9 (C1), 31.24, 31.29 (C7′, C7″), 37.5 (C3′, C3″), 37.97, 38.02 (C10′, C10″), 38.7, 39.3 (C1′, C1″), 43.8 (C4′, C4″), 51.2 (19′−OMe, 19″−OMe), 52.6 (C5′, C5″), 112.2, 112.3, (C11′, C11″), 127.0, 127.1 (C14′, C14″), 127.7, 127.8 (C8′, C8″), 128.9, 129.0 (C13′, C13″), 147.0 (C9′, C9″), 150.3 (C12′, C12″), 177.85, 177.96 (C19′, C19″); *m/z* 602 (5, M^+), 316 (50, M−316), 241 (100). Found: M^+, 602.3645. $C_{38}H_{50}O_6$ calcd: M, 602.3607.

Methyl 12-hydroxy-13-(1ξ-methoxyethyl)podocarpa-8,11,13-trien-19-oate (46)

BH_3·DMS (0.064 mL, 0.68 mmol) was added to methyl 13-acetyl-14-(2-triethoxysilylethyl)-12-(((1,1-dimethylethyl)-dimethylsilyl)oxy)podocarpa-8,11,13-trien-19-oate (**42**) (0.145 g, 0.225 mmol) in dichloromethane (5 mL). After refluxing the mixture for 4 h, aqueous potassium sodium tartrate was added at 0°C and the mixture was extracted with dichloromethane. Workup gave an oil (108 mg) which was dissolved in THF/MeOH (1:1, 6 mL). KF (26 mg, 0.45 mmol), $NaHCO_3$ (38 mg, 0.45 mmol), and then H_2O_2 (31%, 0.54 mL, 5.4 mmol) were added. After 1.5 h aqueous sodium thiosulfate was added at 0°C, to give a negative starch–iodine test. Extraction with ether and workup gave an oil (94 mg) which was dissolved in benzene (8 mL), and *p*-toluenesulfonic acid (10 mg) was added. After 4 h, workup and p.l.c. (hexanes/ether, 1.5:1) gave an epimeric mixture of methyl 12-hydroxy-13-(1ξ-methoxyethyl)podocarpa-8,11,13-trien-19-oate (**46**) (15 mg, 20%, three steps) as an oil; ν_{max} 3388 (OH), 1725 (C═O ester), 1140, 1081 cm^{-1}; δ_H 1.033, 1.038 (2s, 3H, H20), 1.05–1.13 (m, 1H, $H3_{ax}$), 1.28 (s, 3H, H18), 1.55 (btd, *J*=13.4, 2.9 Hz, 1H, $H1_{ax}$), 1.50–1.54 (m, 4H, H5, 13−C(OMe)*Me*), 1.58–1.65 (m, 1H, $H2_{eq}$), 1.99–2.01 (m, 2H, $H2_{ax}$, $H6_{ax}$), 2.15–2.33 (m, 3H, $H1_{eq}$, $H3_{eq}$, $H6_{eq}$), 2.65–2.83 (m, 2H, $H7_{ax}$, $H7_{eq}$), 3.38, 3.39 (2s, 3H, 13−C(O*Me*)Me), 3.67 (s, 3H, 19-OMe), 4.41 (q, *J*=6.6 Hz, 1H, 13−C(*H*)OMe), 6.6 (s, 1H, H14), 6.77 (s, 1H, H11), 7.59 (s, 1H, 12−OH); δ_C 19.9 (C2), 21.0 (C6), 21.8 (13−C(OMe)*Me*), 22.7, 22.74 (C20), 28.5 (C18), 31.0, 31.1 (C7), 37.5 (C3), 38.3 (C10), 39.2, 39.3 (C1), 43.9 (C4), 51.1 (19−OMe), 52.65, 52.69 (C5), 56.6 (13−C(O*Me*)Me), 81.0, 81.2 (13−*C*(OMe)H), 113.3, 113.5 (C11), 123.7 (C13), 126.4 (C8), 127.8 (C14), 148.8, 148.9 (C9), 152.9 (C12), 177.7 (C19); *m/z* 346 (20, M^+), 314 (100, M−MeOH), 239 (100). Found: M^+, 346.2137. $C_{21}H_{30}O_4$ calcd: M, 346.2144.

2-[14-(Methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate)]ethanal (31)

THF (4 mL) and HMPA (0.4 mL) were added to 2-[14-(methyl 12-methoxy-7-oxopodocarpa-6,8,11,13-tetraen-19-oate)]ethanal (**30**) (11 mg, 0.030 mmol) in a Schlenk tube and subjected to six freeze-pump-thaw cycles. SmI_2 (0.1 mol L^{-1}, 0.92 mL, 0.092 mmol,) was added under a fast flow of nitrogen. After 10 min aqueous K_2CO_3/potassium sodium tartrate (1:10) was added and the mixture was extracted with ethyl acetate. Workup and vacuum flash chromatography (silica gel, hexanes/ethyl acetate, 1:1) gave 2-[14(methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate)]ethanal (**31**) (10 mg, 93%) as a yellow oil; ν_{max} 1726 (C═O ester, C═O aldehyde), 1663 (C═O ketone), 1596 (C═C), 1278, 1144 cm^{-1} (C-O); δ_H 1.13 (s, 3H, H20), 1.16 (td, *J*=13.6, 3.9 Hz, 1H, $H3_{ax}$), 1.27 (s, 3H, H18), 1.54 (td, *J*=13.4, 3.6 Hz, 1H, $H1_{ax}$), 1.69–1.75 (m, 1H, $H2_{eq}$), 2.05 (dd, *J*=14.3, 3.6 Hz, 2H, H5, $H2_{ax}$ obscured), 2.23–2.31 (m, 2H, $H1_{eq}$, $H3_{eq}$), 2.90 (dd, *J*=17.9, 3.5 Hz, 1H, $H6_{eq}$), 3.21 (dd, *J*=17.9, 14.4 Hz, 1H, $H6_{ax}$), 3.71 (s, 3H, 19−OMe), 3.87 (s, 3H, 12−OMe), 3.98 (d, *J*=16.3 Hz, 1H, 14−CH_2CHO), 4.08 (d, *J*=16.3 Hz, 1H, 14−CH_2CHO), 6.61 (d, *J*=2.5 Hz, 1H, H13), 6.91 (d, *J*=2.5 Hz, 1H, H11), 9.80 (t, *J*=0.9 Hz, 1H, 14−CH_2C*H*O); δ_C 19.6 (C2), 21.4 (C20), 27.7 (C18), 37.2 (C3), 38.4 (C6), 38.9 (C1), 39.3 (C10), 43.8 (C4), 49.3 (C5), 50.5 (14−*C*H_2CHO), 51.5 (19−OMe), 55.2 (12−OMe), 109.9 (C13), 116.2 (C11), 122.4 (C8), 138.0 (C14), 158.7 (C9), 162.8 (C12), 176.9 (C19), 198.62 (14−CH_2*C*HO), 198.64 (C7); *m/z*358 (80, M^+), 330 (100, M−CO). Found: M^+, 358.178. $C_{21}H_{26}O_5$ calcd: M, 358.178.

2-[14-(Methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethanoic acid (48)

Jones' reagent (0.167 mmol CrO_3) was added to 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]-ethanol (**23**) (29 mg, 0.084 mmol) in acetone (3 mL) at 0°C. After 1 h, extraction with dichloromethane, workup and chromatography (silica gel, hexanes/ethyl acetate, 3:1, 1:1, 1:1.5) gave 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethanoic acid (**48**) (7.3 mg, 24%) as an oil; ν_{max} 3500–2500 (broad, OH), 1725 (C═O ester), 1704 (C═O acid), 1605, 1470 (C═C), 1195, 1145 cm^{-1} (C-O); δ_H 1.06 (s, 3H, H20), 1.10 (td, *J*=13.6, 4.2 Hz, 1H, $H3_{ax}$), 1.28 (s, 3H, H18), 1.40 (td, *J*=13.2, 4.2 Hz,

1H, $H1_{ax}$), 1.52 (d, J=14.0 Hz, 1H, H5), 1.64 (bd, J=14.2 Hz, 1H, $H2_{eq}$), 1.89–2.06 (m, 2H, $H2_{ax}$, $H6_{ax}$), 2.22–2.30 (m, 3H, $H1_{eq}$, $H3_{eq}$, $H6_{eq}$), 2.57 (ddd, J=16.4, 12.4, 6.3 Hz, 1H, $H7_{ax}$), 2.83 (dd, J=16.3, 4.8 Hz, 1H, $H7_{eq}$), 3.63 (d, J=15.6 Hz, 1H, 14−CH_{2a}CO$_2$H), 3.68 (s, 4H, 19−OMe, 14−CH_{2b}CO$_2$H), 3.78 (s, 3H, 12−OMe), 6.66 (d, J=2.3 Hz, 1H, H13), 6.82 (d, J=2.3 Hz, 1H, H11); δ_C 19.9 (C2), 20.7 (C6), 22.8 (C20), 28.3 (C18), 28.4 (C7), 37.3 (C3), 38.82 (C10), 38.9 (14−*C*H$_2$CO$_2$H), 39.6 (C1), 43.9 (C4), 51.1 (19−OMe), 52.0 (C5), 55.1 (12−OMe), 110.8 (C11), 113.3 (C13), 126.6 (C8), 132.8 (C14), 150.1 (C9), 157.4 (C12), 176.9 (14−CH$_2$*C*O$_2$H), 177.8 (C(19); *m/z* 360 (100, M$^+$), 285 (80). Found: M$^+$, 360.1934. $C_{21}H_{28}O_5$ calcd: M, 360.1937.

Methyl 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethanoate (49)

Jones' oxidation of 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethanol (**23**) (25 mg, 0.072 mmol) as above gave an oil (16 mg), which was dissolved in dry methanol (3 mL) and chlorotrimethylsilane (15.6 mg, 0.144 mmol) was added. After 22 h workup and flash chromatography (silica gel, hexanes/ether, 1:1) gave methyl 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]-ethanoate (**49**) (13 mg, 48%, 2 steps) as an oil; ν_{max} 1726 (broad, C=O ester), 1605, 1469 (C=C), 1145 cm^{-1}; δ_H 1.06 (s, 3H, H20), 1.10 (td, J=13.6, 4.3 Hz, 1H, $H3_{ax}$), 1.29 (s, 3H, H18), 1.41 (td, J=13.4, 4.0 Hz, 1H, $H1_{ax}$), 1.52 (dd, J=12.4, 1.3 Hz, 1H, H5), 1.59–1.66 (m, 1H, $H2_{eq}$), 1.89–2.07 (m, 2H, $H2_{ax}$, $H6_{ax}$), 2.22–2.33 (m, 3H, $H1_{eq}$, $H3_{eq}$, $H6_{eq}$), 2.55 (ddd, J=16.4, 12.7, 5.5 Hz, 1H, $H7_{ax}$), 2.82 (dd, J=16.4, 4.1 Hz, 1H, $H7_{eq}$), 3.57 (d, J=15.6 Hz, 1H, 14−CH_{2a}CO$_2$Me), 3.62 (d, J=15.6 Hz, 1H, 14−CH_{2b}CO$_2$Me), 3.68 (s, 3H, 19−OMe), 3.72 (s, 3H, 14−CH$_2$CO$_2$*Me*), 3.78 (s, 3H, 12−OMe), 6.64 (d, J=2.6 Hz, 1H, H13), 6.81 (d, J=2.6 Hz, 1H, H11); δ_C 19.9 (C2), 20.6 (C6), 22.7 (C20), 28.3 (C7), 28.4 (C18), 37.3 (C3), 38.8 (C10), 39.0 (14−*C*H$_2$CO$_2$Me), 39.7 (C1), 43.8 (C4), 51.1 (19−OMe), 51.9 (14−CH$_2$CO$_2$*Me*), 52.0 (C5), 55.1 (12−OMe), 110.5 (C11), 113.3 (C13), 126.4 (C8), 133.3 (C14), 150.9 (C9), 157.3 (C12), 171.9 (14−CH$_2$*C*O$_2$Me), 177.8 (C19); *m/z* 374 (100, M$^+$), 299 (50), 241 (60). Found: M$^+$, 374.2089. $C_{22}H_{30}O_5$ calcd: M, 374.2093.

Methyl 2-[14-(methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate)]ethanoate (50)

Ceric ammonium nitrate (73 mg, 0.133 mmol) in water (0.5 mL) was added to methyl 2-[14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate)]ethanoate (**49**) (10 mg, 0.026 mmol) in acetonitrile (2 mL). After 1 h the mixture was extracted with ether. Workup and flash chromatography (silica gel hexanes/ethyl acetate, 3:3) gave methyl 2-[14-(methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate)]ethanoate (**50**) (6 mg, 60%) as golden rods, mp 145–150°C; ν_{max} 1739 (C=O ester), 1723 (C=O ester), 1665 (C=O ketone), 1597 (C=C), 1284, 1149 cm^{-1}; δ_H 1.12 (s, 3H, H20), 1.14 (td, J=13.6, 4.0 Hz, 1H, $H3_{ax}$), 1.26 (s, 3H, H18), 1.55 (td, J=13.3, 4.0 Hz, 1H, $H1_{ax}$), 1.72 (dp, J=14.3, 3.2 Hz, 1H, $H2_{eq}$), 1.98–2.10 (m, 2H, $H2_{ax}$, H5), 2.30–2.34 (m, 2H, $H1_{eq}$, $H3_{eq}$), 2.88 (dd, J=17.8, 3.6 Hz, 1H, $H6_{eq}$), 3.19 (dd, J=17.8, 14.4 Hz, 1H, $H6_{ax}$), 3.70 (s, 3H, 19−OMe), 3.75 (s, 3H, 14−CH$_2$CO$_2$*Me*), 3.87 (s, 3H, 12−OMe), 3.91 (d, J=16.5 Hz, 1H, 14−CH_2CO$_2$Me), 4.04 (d, J=16.5 Hz, 1H, 14−CH_2CO$_2$Me), 6.62 (d, J=2.4 Hz, 1H, H13), 6.90 (d, J=2.4 Hz, 1H, H11); δ_C 19.6 (C2), 21.4 (C20), 27.7 (C18), 37.2 (C3), 38.4 (C6), 38.9 (C1), 39.3 (C10), 42.2 (14−*C*H$_2$CO$_2$Me), 43.8 (C4), 49.3 (C5), 51.4 (19−OMe), 51.6 (14−CH$_2$CO$_2$*Me*), 55.2 (12-OMe), 109.7 (C11), 116.5 (C13), 123.0 (C8), 138.8 (C14), 158.4 (C9), 162.5 (C12), 172.9 (14−CH$_2$*C*O$_2$Me), 177.0 (C19), 198.8 (C7); *m/z* 388 (30, M$^+$), 356 (60, M−MeOH), 328 (100, 356−CO). Found: M$^+$, 388.1886. $C_{22}H_{28}O_6$ calcd: M, 388.1886.

2-Methoxy-8,11a-dimethyl-5-oxo-4,5,6aξ,7,7a,8,9,10,11,11a-decahydro-6-oxabenzo-[de]anthracene-8-carboxylic acid methyl ester (51)

THF (3 mL) and HMPA (0.3 mL) were added to methyl 2-[14-(methyl 12-methoxy-7-oxopodocarpa-8,11,13-trien-19-oate)]ethanoate (**50**) (10 mg, 0.0257 mmol) in a Schlenk tube and subjected to six freeze–pump–thaw cycles. SmI_2 (0.1 mol L^{-1}, 0.77 mL, 0.077 mmol) was added while maintaining a fast flow of nitrogen. After 30 min, workup and p.l.c. (hexanes/ethyl acetate, 1:1) gave a mixture (1:2.3) of epimers of 2-methoxy-8,11a-dimethyl-5-oxo-4,5,6aξ, 7,7a,8,9,10,11,11a-decahydro-6-oxa-benzo[*de*]anthracene-8-carboxylic acid methyl ester (**51**) (2.5 mg, 27%) as an oil; ν_{max} 1731 (C=O ester, C=O lactone), 1609 (C=C), 1273, 1144 cm^{-1} (C–O); δ_H 1.06 (s, 3H, 11a−Me minor), 1.08 (s, 3H, 11a−Me major), 1.10–1.16 (m, 1H, $H9_{ax}$ both epimers), 1.31 (s, 3H, 8−Me minor), 1.32 (s, 3H, 8−Me major), 1.37–1.44 (m, 1H, $H11_{ax}$ both epimers), 1.59–1.69 (m, 2H, $H10_{eq}$, H7a both epimers), 2.02 (qt, J=13.8, 3.4 Hz, 1H, $H10_{ax}$ both epimers), 2.19–2.37 (m, 3H, $H7_{ax}$ major, $H11_{eq}$, $H9_{eq}$), 2.62 (dd, J=16.4, 3.1 Hz, 1H, $H7_{eq}$ minor), 2.73 (dd, J=12.3, 7.0 Hz, 1H, $H7_{eq}$ major), 2.76–2.82 (m, 1H, $H7_{ax}$ minor), 3.69 (s, 3H, 8−CO$_2$*Me* major), 3.72 (s, 3H, 8−CO$_2$*Me* minor), 3.64–3.75 (m, 2H, H4), 3.81 (s, 3H, 2−OMe major), 3.82 (s, 3H, 2−OMe minor), 5.26–5.32 (m, 1H, H6a both epimers), 6.61 (s, 1H, H3 major), 6.69 (s, 1H, H3 major), 6.74 (d, J=2.1 Hz, 1H, H1 major), 6.80 (d, J=2.0 Hz, 1H, H1 minor); δ_C 19.4 (C10 major), 19.6 (C10 minor), 21.2 (11a−Me minor), 22.4 (11a−Me major), 25.6 (C7 minor), 26.9 (C7 major), 28.2 (8−Me major), 28.3 (8−Me minor), 37.4, 37.45, 37.5, 38.1, 38.6, 38.8 (C11, C9, C4), 43.5 (C8 major), 43.9 (C8 minor), 46.6 (C7a minor), 49.3 (C7a major), 51.3 (8−CO$_2$*Me* major), 51.4 (8−CO$_2$*Me* minor), 55.2 (2−OMe major), 55.3 (2−OMe minor), 73.0 (C6a minor), 77.3 (C6a major), 108.9 (C1 minor), 109.8 (C3 minor), 109.83 (C3 major), 109.9 (C1 major), 121.6 (C11c minor), 122.2 (C11c major), 132.3 (C3a major), 133.8 (C3a minor), 149.0 (C11b major), 149.5 (C11b minor), 160.1 (C2 both epimers), 170.9 (C5 major), 172.0 (C5 minor), 177.1 (8−*C*O$_2$Me major), 177.5 (8−*C*O$_2$Me minor); *m/z* 358 (100, M$^+$), 343 (40, M−Me), 314 (40, M−CO$_2$), 283, (70, 314−OMe). Found: M$^+$, 358.1777. $C_{21}H_{26}O_5$ calcd: M, 358.1780.

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