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Chemistry of the podocarpaceae

LXXIII *. Reactions of a diterpenoid (η^6-arene)tricarbonylchromium(0) complex: functionalization of C(14)

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Abstract

The reactions of the (η^6-arene)tricarbonylchromium(0) complex of methyl 12-methoxypodocarpa-8,11,13-trien-19-oate with a variety of organolithium reagents have been investigated, with the aim of functionalizing C(14) and then synthesising ring-C aromatic steroidal derivatives.

Introduction

Recently we reported [1] the reactions of a pentacarbonylcarbene chromium(0) complex of the diterpenoid methyl 12-methoxypodocarpa-8,11,13,trien-19-oate (**1**) with some alkynes; the reaction with diphenylacetylene leading to steroidal derivatives. The preparation, structure and reactivity of the (η^6-arene)tricarbonylchromium(0) complexes (**5**) have also been studied, nucleophilic attack by a range of carbanions occurring with varying degrees of regioselection at C(13) [2]. We report here concurrent studies of the reactions of the 12-methoxy(η^6-arene)tricarbonylchromium(0) complexes (**6**) with some organolithium reagents, together with attempts to form cyclopentaannulated derivatives from the products. The preparation of the stereoisomers of **6** and determination of their crystal structures by X-ray diffraction have been described earlier [3].

* For part LXXII see Aust. J. Chem., in press.

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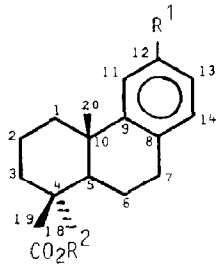
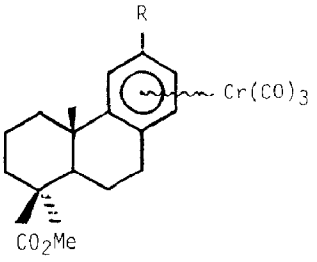


(1: R^1 = OMe, R^2 = Me
2: R^1 = OH, R^2 = H
3: R^1 = $OSi(Me)_2Bu^t$, R^2 = Me
4: R^1 = H, R^2 = Me)



(5: R = H
6: R = OMe
7: R = $OSi(Me)_2Bu^t$)

Results and discussion

In addition to preparation of the α- and β-forms of the complex **6**, attempts were made to form (η^6-arene)tricarbonylchromium(0) complexes of a derivative of podocarpic acid (**2**) which possessed a bulky group in the C(12) position. It was thought that steric crowding might not only hinder approach of an attacking nucleophile at the C(13) position but also force the $Cr(CO)_3$ moiety away from the C(9), C(12), C(14) *syn*-eclipsed conformation expected for the α-stereoisomer into a staggered or *anti*-eclipsed conformation that would enhance the regioselectivity of substitution at C(14) [cf. 4]. Thus, preparation of methyl 12-t-butyldimethylsiloxypodocarpa-8,11,13-trien-19-oate (**3**) [5] followed by reaction with hexacarbonylchromium [6] gave a mixture (ca. 2/1) of the α- and β-diastereomers of the complex **7**.

Apart from permitting rapid proof that complexation has occurred, the application of NMR spectroscopy provides valuable insights into the structures of these complexes. A characteristic feature of the ^{1}H NMR spectra of the (η^6-arene)tricarbonylchromium(0) complexes **6** and **7** is an upfield shift of ca. 2 ppm of the arene protons relative to those of the corresponding uncomplexed species. Also, the arrangement of spectral lines arising from the trisubstituted ring is markedly affected by the conformational preferences shown by the complex. A detailed analysis [2] of the aromatic proton chemical shifts of the complexes **5** showed that ^{1}H NMR spectroscopy was a useful probe of the conformational preference in solution. Provided that protons eclipsed by carbonyl groups are deshielded relative to staggered protons [7] and that substituent effects do not vary between the free ligand and its complex [8], the chemical shift difference ($\sigma\delta(H_x)$) of a proton (x) before and after complexation may be defined by relating observed chemical shifts to those of benzene and its tricarbonylchromium(0) complex (Table 1).

The downfield shifts exhibited by H(11) and H(13) relative to H(14) in the spectrum of the 12-methoxy complex **6** (β-isomer) indicate that the chromium–carbonyl bonds eclipse C(11) and C(13), a conformation the same as that determined for the solid state by X-ray diffraction [3]. In the case of the predominant α-diastereomer of **6**, the similarity of the three $\sigma\delta$ values indicates a slightly staggered conformation, similar to that revealed by an X-ray study [3], and leading to the expectation of preferential nucleophilic attack at C(14).

Table 1

^{1}H NMR analysis of aryl protons in the α- and β-isomers of **6**

Proton	Free ligand		**6** (β-isomer)			**6** (α-isomer)		
	δ	$\Delta\delta$ [a]	δ	$\Delta\delta$ [b]	$\sigma\delta$ [c]	δ	$\Delta\delta$	$\sigma\delta$
H(11)	6.80	−0.55	5.65	+0.32	+0.87	5.35	+0.02	+0.57
H(13)	6.65	−0.70	5.45	+0.12	+0.82	5.20	−0.13	+0.57
H(14)	7.00	−0.35	5.25	−0.08	+0.32	5.50	+0.17	+0.52

[a] $\Delta\delta = \delta(\text{arene}) - \delta(C_6H_6)$; $\delta(C_6H_6) = 7.35$. [b] $\Delta\delta = \delta(\text{complex}) - \delta((\eta^6\text{-}C_6H_6)Cr(CO)_3)$; $\delta((\eta^6\text{-}C_6H_6)Cr(CO)_3) = 5.33$. [c] $\sigma\delta(H_x) = \Delta\delta_x(\text{complex}) - \Delta\delta_x(\text{arene})$.

Table 2

^{1}H NMR analysis of aryl protons in the α-isomer of **7**

Proton	Free ligand		**7** (α-isomer)		
	δ	$\Delta\delta$	δ	$\Delta\delta$	$\sigma\delta$
H(11)	6.55	−0.80	5.18	−0.15	+0.65
H(13)	6.40	−0.95	5.12	−0.21	+0.74
H(14)	6.74	−0.61	5.33	0.00	+0.61

In the case of the 12-t-butyldimethylsiloxy derivative **7**, only the α-complex was obtained pure. The ^{1}H NMR data (Table 2) indicated that the preferred conformation of this diastereomer was similar to that of the α-isomer of **6**. However, attempts to form an addition-oxidation product from **7** with lithioacetonitrile, 2-lithio-t-butyl acetate, or 2-lithio-2-cyano-2-methylpropane were unsuccessful, only dimers, starting material, and the 12-hydroxy analogue being recovered in each case.

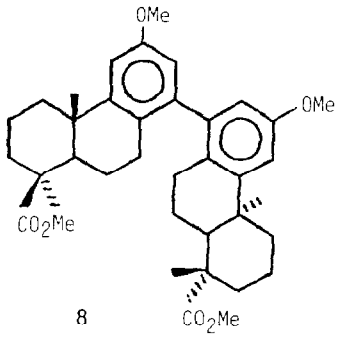
In contrast, reaction of the complexes **6** with a range of lithium salts of variously substituted stabilised carbanions was successful (Table 3). The reaction time, and temperature, the nature and molar quantities of reactants, and the order of their mixing all affected significantly the final yield of addition–oxidation products. In general the best yields were obtained when reactions were carried out for 30 minutes with equimolar mixtures of the organolithium compound and the substrate [cf. 6] in a mixture (4/1) of tetrahydrofuran and hexamethylphosphoric triamide (HMPT). When the HMPT was added to the reaction mixture after the chromium complex the yield of the required addition-oxidation product dropped to zero owing to competitive formation of a mixture of dimeric compounds (**8**, **9**), small amounts of

Table 3

Reaction of **6** with lithio anions

LiNu	*ortho*/*meta*	Yield (%)	Products
$LiCH_2CO_2Bu^+$	1/4	66	**10**, **18**
$LiCH_2CN$	1/3	86	**11**, **19**
2-Li-2-Me-1,3-dithianyl	–	6	**12**, **20**
$LiC(Me)_2CN$	1/2.6	68	**15**, **23**
$LiCH(CN)CH_2\overset{\frown O \frown}{CHOCH_2CH_2}$	a	54	**24**

[a] See Experimental.



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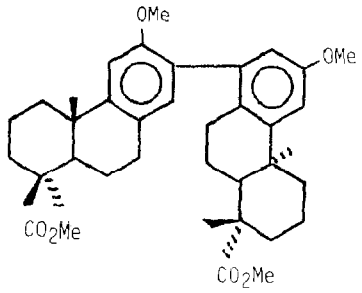

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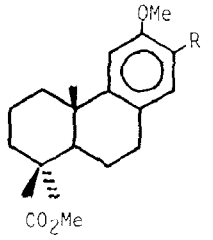
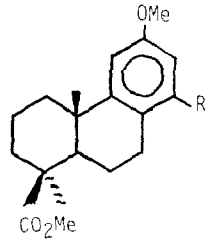
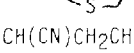
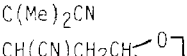
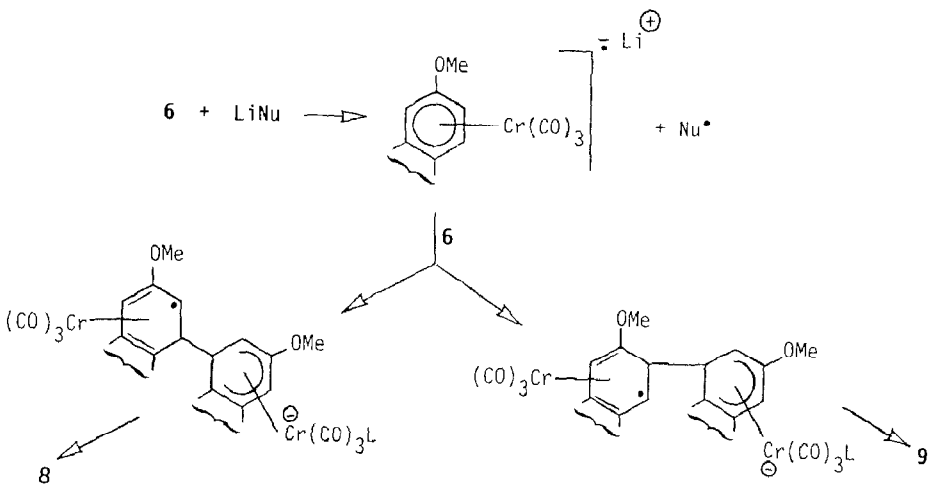




(10: R = $CH_2CO_2Bu^t$
11: R = CH_2CN
12: R = C(Me) 
13: R = $CH(CN)CH_2CH_2CN$
14: R = $CH(CN)CH_2CH(I)CN$
15: R = $C(Me)_2CN$
16: R = $CH(CN)CH_2CH$ 
17: R = I)

(18: $CH_2CO_2Bu^t$
19: CH_2CN
20: C(Me) 
21: $CH(CN)CH_2CH_2CN$
22: $CH(CN)CH_2CH(I)CN$
23: $C(Me)_2CN$
24: $CH(CN)CH_2CH$ 
25: $CH(CN)CH_2CHO$)



Scheme 1

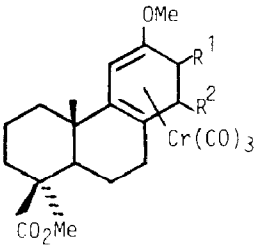
which were formed in all reactions involving organolithium reagents. Moreover, treatment of the complexes **6** with t-butyllithium followed by iodine gave only a mixture of dimeric products, in which the *ortho-meta* coupled isomer **9** predominated. A possible route to the dimers via a single-electron transfer process is shown in Scheme 1.

Also, it was found that for optimum recovery of an addition-oxidation product it was necessary to use an excess of iodine added at −78°C. Of the organolithium species investigated, those stabilized by strong electron-withdrawing groups were the most successful. Thus 2-lithio-t-butyl acetate and lithioacetonitrile gave a mixture of the regioisomeric products methyl 13-(2-t-butoxycarbonylmethyl)-12-methoxypodocarpa-8,11,13-trien-19-oate (**10**) and its C(14) isomer (**18**), and a mixture of methyl 13-cyanomethyl-12-methoxypodocarpa-8,11,13-trien-19-oate (**11**) and its C(14) isomer **19**, respectively. From both of these anions the C(14) (*meta*) substituted products were the predominant regioisomers, as expected [6]. Since lithioacetonitrile had given the highest yield of products (Table 3), a logical extension was to use an anion from 1,5-pentanedinitrile, since then a side-chain appropriate for the proposed cyclopentaannulation would be available. Since proton transfer processes could quench the η^5-anionic adduct if the monoanion of this symmetrical dinitrile was used, leading to a diene rather than an aromatic product, four molar equivalents of lithium diisopropylamide were used, to permit potential generation of a tetraanion (dianions of mononitriles are well documented). Addition of **6** followed by oxidation with iodine then afforded the monoarylated product methyl 13-(1,3-biscyano-1-propyl)-12-methoxypodocarpa-8,11,13-trien-19-oate (**13**) (30%) and its C(14) regioisomer **21** in a ratio of 1/3. Careful flash chromatography and examination by ^{1}H NMR spectroscopy indicated that the unstable [9] arylated α-iodonitriles **14** and **22** were present in the remaining oily product. Consequently, addition of trifluoroacetic acid to protonate anionic centres prior to the addition of iodine increased the yield of **13** and **21** to 64%.

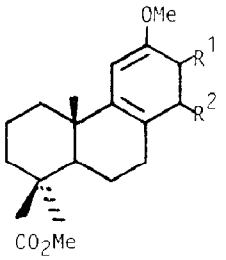
Addition of 2-lithio-2-methylpropanonitrile to the complexes **6** followed by quenching of the η^5-cyclohexadienyl anion with iodine gave a 68% yield of 1-(2-cyano-2-methylpropyl)-12-methoxypodocarpa-8,11,13-trien-19-oate (**15**) and (mainly) its C(14) regioisomer **23**. Use of an addition-protonation sequence [6] of 2-lithio-2-methylpropanonitrile with **6** was also investigated. Addition of an excess of trifluoroacetic acid instead of iodine to the mixture at −78°C produced a deep red colour [6] and then a dark green colour. Decomplexation of the putative η^4-cyclohexadiene adducts **26** and **27** with ammonium hydroxide gave an isomeric mixture (26%) of the dienes **28** and **29**, and **1** (ca. 1/1). A small amount of the demethoxylated product **4** [cf. 11,12] was also formed.

In order to produce a synthon which would give only C(14) substitution, attention was focussed on the addition to **6** of 2-(2′-cyanoethyl)-1,3-dioxolane, another compound in which a nitrile-stabilized anion could be generated at one end of the chain while a potentially electrophilic carbon was present at the other. The reagent was prepared from propenal by conversion into 2-(2′-iodoethyl)-1,3-dioxolane by the method described by Larsen and Klesse [13] and then replacement of the iodine atom with a cyanide group by treatment with potassium cyanide in a 6/1 mixture of 1,2-ethanediol and water.

In model experiments the (η^6-arene)tricarbonylchromium(0) complexes of benzenes and anisole were treated with 2-(2′-lithio-2′-cyanoethyl)-1,3-dioxolane. Thus,



(26: $R^1 = C(Me)_2CN$, $R^2 = H$
27: $R^1 = H$, $R^2 = C(Me)_2CN$)

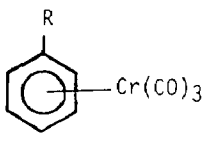


(28: $R^1 = C(Me)_2CN$, $R^2 = H$
29: $R^1 = H$, $R^2 = C(Me)_2CN$)

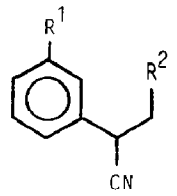
reaction of **30** for 5 h at −78 °C followed by 0.5 h at 0 °C and then quenching with iodine at −78 °C gave the addition-oxidation product **32** (30%), while reaction of **31** for 3 h at 0 °C with similar work-up gave only the regioisomer **33** (63%). Examination of the ^{13}C NMR spectrum of the latter compound confirmed the *meta* relationship of its substituents. Analysis of the multiplicities of the aromatic carbons in each of the three possible regioisomeric structures indicated that the compound isolated could produce the recorded spectrum only if it had one protonated carbon in the ring which did not bear a *meta* proton. In the *meta* regioisomer **33** C(5′) is the only ring carbon fulfilling this requirement, and it appeared in the SFORD spectrum as a clean doublet at δ130.1 ppm. The *ortho* regioisomer is ruled out because all of its protonated carbons have *meta*-related protons, and would therefore show more splitting than the simple doublet observed in the SFORD spectrum. The *para* regioisomer was excluded by symmetry considerations.

The *ortho-meta* coupled dimer **36** was also isolated from the reactions of **31** with the anion from 2-(2′-cyanoethyl)-1,3-dioxolane. The unsymmetrical nature of the product was shown by the ^1H NMR spectrum which exhibited two distinct methoxy peaks and by the ^{13}C NMR spectrum in which all of the ring carbons showed unique peaks. *Para*-substituted rings would create pairs of carbons with identical chemical shifts while symmetry would result in a similar decrease in the number of separate peaks in the spectra of *ortho–ortho* and *meta–meta* coupled rings. Examination of resonance contributors for a single electron transfer mechanism [6] show that only resonance form **37** gives a radical localised on the methoxy-substituted ring carbon. Delocalisation of the radical by the methoxy group would make an intermediate from *ortho* attack preferable to radicals formed from *meta* or *para* attack, thereby facilitating formation of the dimer **36** (cf. **9**).

Addition-oxidation reactions between 2′-lithio-2-(2′-cyanoethyl)-1,3-dioxolane and the diterpenoid complex **6** gave the desired C(14) substituted product **24** cleanly in a maximum yield of 54%, and under other conditions gave the C(13) isomer **16** or a mixture of these compounds. The position of the new ring substituent in **24** was established from the downfield shift (+4.9 ppm) of C(14) in the ^{13}C NMR spectrum together with an upfield shift of the two *ortho* carbon (C(13), −0.6 ppm; C(8), −2.8 ppm) signals. ^{13}C–^1H NMR correlation analysis enabled assignment of other signals. Other products isolated from some reactions were 2-(2′-cyano-2′-iodoethyl)-1,3-dioxolane (**38**), methyl 13-iodo-12-methoxypodocarpa-8,11,13-trien-



(30: R = H
31: R = OMe)

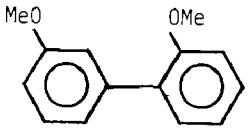


(32: R^1 = H, R^2 = CH(O)(O)]

33: R^1 = OMe, R^2 = CH(O)(O)]

34: R^1 = OMe, R^2 = CHO

35: R^1 = OMe, R^2 = $\overset{+}{C}$HOCH$_2$CH$_2$OH)



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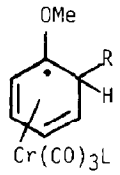
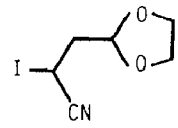


37



38

19-oate (**17**), and a dimer which appeared to differ from **8** or **9**, probably the C(13)–C(13) coupled isomer.

Attempts to cyclise the nitrile **33** by use of tin(IV) chloride [14], titanium(IV) chloride [15], trimethylsilyl trifluoromethanesulfonate [16], or trifluoromethanesulfonic acid [17] as catalysts were unsuccessful. However, the metal catalysts generated the aldehyde **34**, which indicated that the desired oxonium cation **35** had been formed but did not cyclise. Attempts to cyclise the compound **24** with all four catalysts were also unsuccessful, the only material obtained pure being the aldehyde **25** when titanium(IV) chloride was used.

Experimental

For general experimental details see [1,2]. In ref. 1 the ^{1}H NMR assignments given for H(18) and H(20) in the diterpenoids should be reversed.

Methyl t-butyldimethylsiloxypodocarpa-8,11,13-trien-19-oate (3)

t-Butylchlorodimethylsilane (0.64 g, 4.2 mmol) was added to a solution of methyl 12-hydroxypodocarpa-8,11,13-trien-19-oate [18] (0.60 g, 0.2 mmol) in dimethylformamide (20 ml) under argon and the mixture was stirred for 0.5 h. *N,N*-Diisopropylethylamine (0.85 g) was added from a syringe pump and the mixture was stirred for a further 0.5 h, treated with water (0.78 μl), and washed with saturated aqueous

sodium hydrogencarbonate. Removal of solvent in vacuo from the filtered mixture yielded an oil which, after flash chromatography (ethyl acetate/hexane, 1/99), gave methyl 12-t-butyldimethylsiloxypodocarpa-8,11,13-trien-19-oate (1.41 g, 86%) as a colourless oil, b.p. 161°C/0.2 mmHg (Found: C, 71.2; H, 9.5. $C_{24}H_{38}O_3Si$ calcd.: C, 71.6, H 9.5%). ν_{max} 1700(CO, methoxycarbonyl), 1055 cm^{-1} (SiO). δ(H) (ppm) 0.20, s, Me_2Si; 1.00, s, Bu^t; 1.05, s, 3H(20); 1.25, s, 3H(18); 3.65, s, 3H(OMe); 6.55, dxd, $J_{13,14}$ 7 Hz, $J_{11,13}$ 2 Hz, H(13); 6.73, d, $J_{11,13}$ 2 Hz, H(11); 6.9, d, $J_{13,14}$ 7 Hz, H(14). *m/z* 402 (*M*), 345, 387, 327.

Tricarbonyl[8,9,11,12,13,14-η)-methyl t-butyldimethylsiloxypodocarpa-8,11,13-trien-19-oate]chromium(0) (7)

Dibutyl ether (40 ml) and heptane (20 ml) were added to **3** (0.9 g, 0.22 mmol) and hexacarbonylchromium(0) (0.53 g, 0.24 mmol) in a flask equipped with a Strohmeier multiple condenser under the conditions reported [3] for the preparation of **6**. The mixture was heated under reflux for 50 h then filtered through Celite, and solvents were removed by distillation at 20°C/1 mmHg. Flash chromatography (ether/hexane, 1/9) gave an inseparable mixture (4/1) of the α- and β-stereoisomers of tricarbonyl[(8,9,11,12,13,14-η)-methyl 12-t-butyldimethylsiloxypodocarpa-8,11,13-trien-19-oate]chromium(0) (0.46 g, 42%). A sample of the pure α stereoisomer was obtained by isopiestic recrystallisation from ethyl acetate/hexane as orange-yellow needles, m.p. 135–137°C (Found: C, 60.2; H, 7.1. $C_{27}H_{38}CrO_6Si$ calcd.: C, 60.2; H 7.1%). ν_{max} 1883(CO), 1960(CO), 1700(CO, methoxycarbonyl), 1055 cm^{-1} (SiO). δ(H) (ppm) 0.20, s, 6H(Me_2Si); 0.92, s, 9H(Bu^t); 1.11, s, 3H(2O, α-isomer); 1.21, s, 6H(18,20, β-isomer); 1.28, s, 3H(18, α-isomer); 3.63, s, 3H(OMe, α-isomer); 3.68, s, 3H(OMe, β-isomer); 5.12, dxd, $J_{13,14}$ 6 Hz, H(13, α-isomer); 5.18, d, $J_{11,13}$ 2 Hz, H(11, α-isomer); 5.35, dxd, $J_{13,14}$ 6 Hz, H(14, α-isomer).

*Methyl 13- and 14-(2-t-butoxycarbonylmethyl)-12-methoxypodocarpa-8,11,13-trien-19-oate (**10, 18**)*

Lithio-t-butyl acetate, prepared in THF (4 ml) from a hexane solution of butyllithium (1.17 mol l^{-1}, 0.33 ml, 0.85 mmol), diisopropylamine (86 mg, 0.85 mmol) and t-butyl acetate (98 mg, 0.85 mmol), at −78°C under argon, was treated with a solution of the complexes **6** (0.19 g, 0.43 mmol) in THF (4 ml) followed by HMPT (2 ml). The mixture was stirred for 5 h at −78°C, iodine (0.98 g, 3.8 mmol) in THF (10 ml) was added rapidly and the stirring was continued for 8 h while the temperature was raised to 20°C. Work-up as before gave an oil which, after flash chromatography (ethyl acetate/hexane, 1/49) gave an inseparable mixture (1/4) of methyl 13-(2-t-butoxycarbonylmethyl)-12-methoxypodocarpa-8,11,13-trien-19-oate and its C(14) isomer (0.12 g, 66%) as a colourless oil, b.p. 159°C/0.2 mmHg (Found: C, 72.1; H, 9.0. $C_{25}H_{36}O_5$ calcd.: C, 72.1; H, 9.0%). ν_{max} 1710(CO, methoxycarbonyl), 1690(CO, t-butyl ester), 1140 cm^{-1} (CO_2-t-Bu). 14-isomer **18**: δ(H) (ppm) 1.01, s, 3H(18); 1.21, s, 3H(20); 1.47, s, 9H(Bu^t); 3.50, s, 2H(CH_2CO); 3.65, s, 3H(CO_2Me); 3.78, s, 3H(OMe); 6.60, d, $J_{13,14}$ 3.8 Hz, 2H(13, 14); 6.79, d, $J_{11,13}$ 3.8 Hz, H(11). δ(C) (ppm) 20.0, C(2); 20.8, C(6); 22.8, C(20); 28.0, CMe_3; 28.4, C(7, 18); 37.4, C(3); 38.8, C(10); 39.7, C(1); 40.4, CH_2CO; 43.9, C(4); 51.1, CO_2CH_3; 52.2, C(5); 55.0, OCH_3; 80.7, CMe_3; 110.4, C(11); 113.1, C(13); 126.4, C(8); 134.07, C(14); 149.8, C(9); 157.3, C(12); 170.8, (CO); 177.7, C(19). *m/z* 416 (*M*), 360, 315, 299, 285, 241, 227, 57, 41.

*Methyl 13- and 14-cyanomethyl-12-methoxypodocarpa-8,11,13-trien-19-oate (**11, 19**)*

Lithioacetonitrile, prepared in THF (10 ml) from butyllithium (1.9 ml, 2.28 mmol), diisopropylamine (0.32 ml, 2.28 mmol), and acetonitrile (119 μl, 2.28 mmol) was treated at −78°C under argon with HMPT (5.2 ml) and then a solution of the complexes **6** (0.50 g, 1.14 mmol) in THF (10 ml). After 6.5 h, iodine (2.55 g, 10.0 mmol) in THF (20 ml) was added at −78°C and the mixture was allowed to warm to room temperature during 10 h. Work-up as before gave an oil, flash chromatography (ether/hexane, 1/9, 7/3, and 100/0), of which gave (i) methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (39 mg, 11%), (ii) methyl 13-cyanomethyl-12-methoxypodocarpa-8,11,13-trien-19-oate (81 mg, 21%), b.p. (Kugelrohr) 140°C/0.05 mmHg (Found: $M^{+\cdot}$ 341.1999. $C_{21}H_{27}NO_3$ calcd.: M 341.1991). ν_{max} (neat) 2210(CN), 1720(ester CO), 1600 cm^{-1} (aryl C=C). δ(H) (ppm) 1.05, s, 3H(20); 1.30, s, 3H(18); 1.49–2.87, m, 11H(CH/CH_2); 3.62, m, 5H, CO_2Me, 2H(1′); 3.79, s, OMe; 6.80, s, H(11); 7.01, s, H(14). δ(C) (ppm) 18.2, C(2); 19.9, C(6); 20.9, C(1′); 22.8, C(20); 28.5, C(18); 31.1, C(7); 37.6, C(3); 38.7, C(10); 39.5, C(1); 43.9, C(4); 51.3, CO_2CH_3; 52.7, C(5); 55.4, OCH_3; 107.3, C(11); 116.1, C(13); 118.3, CN; 127.8, C(8); 129.6, C(14); 149.2, C(9); 154.8, C(12); 177.8, C(19). *m/z* 341 (*M*), 266, 226; (iii) methyl 14-cyanomethyl-12-methoxypodocarpa-8,11,13-trien-19-oate (0.25 g, 65%) as microcrystals, m.p. 122–124°C (Found: C, 73.8; H, 8.5; N, 4.0. $C_{21}H_{27}NO_3$ calcd.: C, 73.9; H, 8.0; N, 4.1%). ν_{max} 2250(CN), 1715(CO, methoxycarbonyl), 1160 cm^{-1} (ester CO). δ(H) (ppm) 1.05, s, 3H(20); 1.30, s, 3H(18); 1.41–2.82, m, 11H(CH/CH_2); 3.64, s, 2H(1′); 3.70, s, CO_2Me; 3.82, s, OMe; 6.70, d, $J_{11,13}$ 2.4 Hz, H(13); 6.89, d, $J_{11,13}$ 2.4 Hz, H(11); δ(C) (ppm) 19.9, C(2); 20.6, C(1′); 21.9, C(6); 22.8, C(20); 28.3, C(7); 28.4, C(18); 37.4, C(3); 38.8, C(10); 39.7, C(1); 43.0, C(4); 51.2, CO_2CH_3; 51.9, C(5); 55.0, OCH_3; 111.5, C(13); 111.8, C(11); 117.6, CN; 125.6 C(8); 129.0, C(14); 150.7, C(9); 157.8, C(12); 177.0, C(19). *m/z* 341 (*M*), 266, 226; (iv) an unidentified oil (38 mg), *m/z* 341.

*Methyl 13- and 14-(1,3-biscyano-1-propyl)-12-methoxypodocarpa-8,11,13-trien-19-oate (**13, 21**)*

Lithio-1,5-pentanedinitrile, prepared in THF 94 ml) from butyllithium (1.5 mol l^{-1}, 1.7 ml, 0.27 mmol), diisopropylamine (0.32 g, 0.27 mmol), and 1,5-pentanedinitrile [19] (70 mg, 0.07 mmol) was treated at −78°C under argon with HMPT (2 ml) and then a solution of the complexes **6** (0.30 g, 0.07 mmol) in THF (4 ml). After 0.5 h, trifluoroacetic acid (0.26 ml, 3.4 mmol) was added and the stirring was continued for 1.5 min whereupon iodine (1.52 g, 5.9 mmol) in THF (10 ml) was added to the mixture which was warmed to room temperature over 12 h. Work-up as before gave a solid, flash chromatography (ether/hexane, 3/17, 1/4, and 1/1) of which afforded a mixture (1/3, ^1H NMR) of methyl 13-(1,3-biscyano-1-propyl)-podocarpa-8,11,13-trien-19-oate and its 14-isomer. Further flash chromatography afforded fractions enriched in each isomer. 13-isomer **13**, b.p. (Kugelrohr) 120°C/0.5 mmHg (Found: $M^{+\cdot}$ 394.2258. $C_{24}H_{30}N_2O_3$ calcd.: *M* 394.2249). ν_{max} 2260(CN), 1720 cm^{-1} (CO, methoxycarbonyl). δ(H) (ppm) 1.01, s, 3H(20); 1.28, s, 3H(18); 3.65, s, CO_2Me; 3.80, s, ArOMe; 6.76, s, H911); 7.00, s, H(14). δ(C) (ppm); 19.8, C(2); 20.8, C(6); 22.6, CH_2; 22.8, C(20); 28.4, C(18); 29.2, C(7); 33.8, *C*HCN; 37.5, C(3); 38.7, C(10); 39.4, C(1); 43.9, C(4); 51.2, CO_2CH_3; 52.5, C(5); 55.4, OCH_3; 107.9, C(11); 118.2, C(14); 119.0, CN; 119.6, CN; 128.1, C(13); 128.8, C(8); 150.0, C(9); 164.0, C(12); C(12); 177.0, C(19). 14-isomer **21** Found: ($M^{+\cdot}$ 394.2253.

$C_{24}H_{30}N_2O_3$ calcd.: *M* 394.2249). δ(H) (ppm) 1.04, s, 3H(20); 1.28, s, 3H(18); 3.67, s, CO_2CH_3; 3.79, s, ArOMe; 6.84, br s, 2H(11, 13). δ(C) (ppm) 19.9, C(2); 20.7, C(6); 22.1, CH_2; 22.8, C(20); 28.4, C(18); 31.5, C(7); 32.4, *C*HCN; 37.5, C(3); 39.1, C(10); 39.8, C(1); 43.9, C(4); 51.3, CO_2CH_3; 51.8, C(5); 55.3, OCH_3; 107.9, C(13); 110.4, C(11); 132.9, C(14); 119.6, CN; 119.8, CN; 124.5, C(8); 151.3, C(9); 158.1, C(12); 177.6, C(19). *m/z* 394 (*M*), 319, 292, 266, 226.

*Methyl 13- and 14-(2-cyano-2-methylpropyl)-12-methoxypodocarpa-8,11,13-trien-19-oate (**15, 23**)*

2-Lithio-2-methylpropanonitrile, prepared in THF (2 ml) from butyllithium (1.6 mol l^{-1}, 0.21 ml, 0.34 mmol), diisopropylamine (0.04 ml, 0.34 mmol), and 2-methylpropanonitrile [20] (32 μl, 0.34 mmol), was treated at −78 °C with HMPT (1 ml) and a solution of the complexes **6** (0.15 g, 0.34 mmol) in THF (2 ml). After 0.5 h, iodine (0.76 g, 3 mmol) in THF (10 ml) was added and the mixture was warmed to 20 °C over 12 h. The usual work-up yielded an oil, flash chromatography (ethyl acetate/hexane, 1/9) of which gave methyl 14-(2-cyano-2-methylpropyl)-12-methoxypodocarpa-8,11,13-trien-19-oate (86 mg, 68%) as needles, m.p. 158–159 °C; and methyl 13-(2-cyano-2-methylpropyl)-12-methoxypodocarpa-8,11,13-trien-19-oate (32 mg, 26%) as a colourless oil, b.p. 140 °C/0.15 mmHg. 14-isomer **23** (Found: C, 74.6; H, 8.9; N, 3.8. $C_{23}H_{31}NO_3$ calcd.: C, 74.8; H, 8.4; N, 3.8%). ν_{max} 2240(CN), 1725 cm^{-1} (CO, methoxycarbonyl). λ_{max} 281 (ε 2761), 239 (ε 2389), 206 nm (ε 653). δ(H) (ppm) 1.06, s, 3H(20); 1.28, s, 3H(18); 1.75, s, CH_3; 1.83, s, CH_3; 3.62, s, CO_2CH_3; 3.70, s, 3H, ArOMe; 6.67, dxd, $J_{11,13}$ 2 Hz, H(11); 6.75, dxd, $J_{11,13}$, H(13). δ(C) (ppm) 20.0, C(2); 21.2, C(6); 23.3, C(20); 27.0, CH_3; 28.5, C(18); 28.6, CH_3; 34.8, *C*CN; 31.2, C(7); 37.5, C(3); 39.3, C(10); 39.9, C(1); 43.8, C(4); 51.1, CO_2CH_3; 52.4, C(5); 55.1, OCH_3; 109.8, C(11); 110.4, C(13); 124.9, CN; 127.0, C(8); 138.0, C(14); 151.0, C(9); 177.0, C(19). *m/z* 369 (*M*), 354, 294, 226. 13-isomer **15** (Found: C, 74.6; H, 8.6; N, 3.8. $C_{23}H_{31}NO_3$ calcd.: C, 74.8; H, 8.4; N, 3.8%). ν_{max} 2240 (CN), 1725 cm^{-1} (CO, methoxycarbonyl). δ(H) (ppm) 1.00, s, 3H(20); 1.25, s, 3H(18); 1.70, s, 6H(CMe_2); 3.62, s, CO_2CH_3; 3.86, s, ArOMe; 6.67, br s, H(11); 6.88, br s, H(14). δ(C) (ppm) 19.1, C(2); 21.0, C(6); 22.7, C(20); 28.3, C(18); 28.6, 2CH_3; 34.2, *C*Me; 37.3, C(3); 38.5, C(10); 39.8, C(1); 43.8, C(4); 51.2, CO_2CH_3; 52.4, C(5); 55.1, OCH_3; 109.0, C(11); 124.5, C(13); 124.9, CN; 126.2, C(8); 126.5, C(14); 148.0, C(9); 155.0, C(12); 177.0, C(19).

Dimer formation from complexes 5

t-Butyllithium (1.4 mol l^{-1}, 0.61 ml, 0.85 mmol) in THF (3 ml), was treated with HMPT (1 ml) and then added to the complexes **6** (0.19 g, 0.43 mmol) at −78 °C. The mixture was stirred for 6 h, iodine (0.98 g) in THF (10 ml) was added, and the mixture was warmed to room temperature over 12 h. The usual work-up left an oil, which after flash chromatography (ether/hexane, 1/4), gave the dimers bis-13- and 14-(methyl 12-methoxypodocarpa-8,11,13-trien-19-oate) (**8, 9**) as a white solid, b.p. (Kugelrohr) 200 °C/10^{-2} mmHg. δ(H) (ppm) 1.12, s, 6H(20); 1.28, br s, 6H(18); 3.6–3.8, 5S, 12H, OCH_3, CO_2CH_3; 6.55, d, *J* 3.8 Hz, ArH; 6.79, m, 3H, ArH.

*Methyl 13- and 14-(2-cyano-1-methylpropyl)-12-methoxypodocarpa-8,11-dien-19-oate (**28, 29**)*

2-Lithio-2-methylpropionitrile, prepared from butyllithium (1.8 mol l^{-1}, 0.9 mmol), diisopropylamine (0.11 g, 0.9 mmol), and 2-methylpropanonitrile (62 mg, 0.9

mmol), was treated with HMPT (1 ml) and then the complexes **6** (0.20 g, 0.45 mmol) in THF (2 ml). Trifluoroacetic acid (0.26 ml, 3.3 mmol) was added dropwise at −78 °C, and after 5 h at 25 °C the mixture was poured into cold concentrated aqueous ammonia (10 ml). Extraction with ether and flash chromatography (ether/hexane, 1/9) of the extract gave **1** and methyl 13- and 14-(2-cyano-1-methylpropyl)-12-methoxypodocarpa-8,11-dien-19-oate (50 mg) as a colourless oil. ν_{max} 2250 (CN), 1720 (CO, methoxycarbonyl), 1650 (vinylic CH), 1600 cm^{-1} (C=C–C=C). δ(H) (ppm) 0.88, s, 3H(20); 1.30, s, 3H(18); 1.20, s, 6H, CMe_2 of **28**; 1.33, s, 6H, CMe_2 of **29**; 3.55, s, OCH_3; 3.62, s, CO_2CH_3; 4.55, s, H(11) of **29**; 4.65, s, H(11) of **28**.

*Methyl 12-methoxy-13- and 14-[2-(2′-methyl-1′,3′-dithianyl)]podocarpa-8,11,13-trien-19-oate (**12, 20**)*

2-Lithio-2-methyl-1,3-dithiane, prepared in THF (3 ml) from butyllithium (0.62 ml, 0.9 mmol), and 2-methyl-1,3-dithiane [21] (95 μl, 0.9 mmol), was treated with HMPT (0.75 ml) and the complexes **6** (0.19 g, 0.43 mmol) at −78 °C. After 6 h the mixture was treated with iodine (0.98 g) in THF (10 ml) and warmed to room temperature over 12 h. Work-up as usual yielded an oil which on flash chromatography (ethyl acetate/hexane, 1/99 and 1/1) gave a mixture of methyl 12-methoxy-13- and 14-[2(2′-methyl-1′,3′-dithianyl)]podocarpa-8,11,13-trien-19-oate (11 mg, 6%). δ(H) (ppm) 1.05, s, 6H(20) of **12** and **20**; 1.28, s, 6H(18) of **12** and **20**; 1.55, s, 6H, CMe of **12** and **20**; 2.80, m, 8H, CH_2; 3.63, s, CO_2CH_3 of **12** and **20**; 3.75, s, ArOMe of **20**; 3.80, s, ArOMe of **12**; 6.80, s, H(11) of **12**; 6.83, $J_{11,13}$ 2 Hz, H(11) of **20**; 7.48, s, H(14) of **12**; 7.52, d, *J* 2 Hz, H(13) of **20**. *m/z* 434 (*M*), 359, 328, 302, 253, 285.

2-(2′-Iodoethyl)-1,3-dioxolane

Propenal (1.7 ml, 25 mmol) and chlorotrimethylsilane (3.8 ml, 30 mmol) were added to a mixture of dry sodium iodide (4.5 g, 30 mmol) and acetonitrile (75 ml) under argon and the mixture was stirred at room temperature for 0.5 h. 1,2-Ethanediol (1.7 ml, 30 mmol) was added and the mixture was stirred for a further 50 min, then poured into aqueous sodium hydrogencarbonate solution (25 ml) under pentane (75 ml). The organic phase was washed with 5% aqueous sodium thiosulphate solution (25 ml) and brine, and solvent was removed in vacuo from the dried solution to yield 2-(2′-iodoethyl)-1,3-dioxolane as an oil. The product was chromatographed on alumina and eluted with hexane to give the pure iodoacetal (3.7 g, 65%). δ(H) (ppm) [cf. 22] 2.16, st, $J_{1',2}$ 4 Hz, $J_{1',2'}$ 14 Hz, 2H(1′); 3.15, t, $J_{1',2'}$ 14 Hz, 2H(2′); 3.85, br s, 4H(4, 5); 4.81, t, $J_{1',2'}$ 4 Hz, H(2).

2-(2′-Cyanoethyl)-1,3-dioxolane

2-(2′-Iodoethyl)-1,3-dioxolane (17.0 g, 75 mmol) was treated with a solution of potassium cyanide (15.8 g, 89 mmol) in water (10 ml), followed by 1,2-ethanediol (60 ml). The stirred mixture was heated at 100 °C for 1.5 h, cooled, poured into water, and extracted with chloroform. Removal of solvent in vacuo from the dried solution gave 2-(2′-cyanoethyl)-1,3-dioxolane (9.3 g, 98%) as an oil, b.p. (Kugelrohr) 55 °C/0.2 mmHg (lit. [23] b.p. 82 °C/3 mmHg) (Found: $M^{+\cdot} - H^{\cdot}$ 126.0553. $C_6H_8NO_2$ calcd.: $M - H$ 126.0555). ν_{max} (neat) 2250(CN), 1135(1,3-dioxolane), 1040 cm^{-1} (1,3-dioxolane). δ(H) (ppm) 2.0, m, 2H(1′); 2.5, m, 2H(2′); 3.95, br s,

4H(4,5); 4.97; t, $J_{1',2'}$ 4 Hz, H(2). δ(C) (ppm) 11.2, C(1'); 29.3, C(2'); 65.2, C(4,5); 101.7, C(2); 119.5, CN. *m/z* 126 (*M* − H), 82. 73, 54, 45.

*2-(2'-Cyano-2'-phenylethyl)-1,3-dioxolane (**32**)*

2'-Lithio-2-(2'-cyanoethyl)-1,3-dioxolane, prepared in THF (4 ml) from butyllithium (2.0 mol l^{-1}, 0.70 ml, 1.40 mmol), diisopropylamine (196 μl, 1.40 mmol) and 2-(2'-cyanoethyl)-1,3-dioxolane (0.18 g, 1.40 mmol), was treated at −78 °C with HMPT (2.5 ml) and η^6-(benzene)tricarbonylchromium(0) (**30**) (0.30 g, 1.40 mmol) in THF (6 ml). The solution was stirred at −78 °C for 5 h and at 0 °C for 0.5 h and then treated at −78 °C with iodine (1.78 g, 7.00 mmol) in THF (15 ml), and warmed to room temperature overnight, The usual work-up gave an oil which on PLC (hexane/diethyl ether, 7/3) gave 2-(2'-cyano-2'-phenylethyl)-1,3-dioxolane (85 mg, 30%), b.p. (Kugelrohr) 65 °C/0.01 mmHg (Found: C, 70.2; H, 6.5; N, 6.5; $M^{+\cdot}$ 203.0949. $C_{12}H_{13}NO_2$ calcd.: C, 70.9; H, 6.5; N, 6.9; M 203.0947). ν_{max} (neat) 2250(CN), 1140(1,3-dioxolane), 1020 cm^{-1} (1,3-dioxolane). δ(H) (ppm) 2.25, m 2H(1'); 4.0, m, 5H(4,5,2'); 5.01, t, $J_{2,1'}$ 4 Hz, H(2); 7.3, m, 5H(aryl H). δ(C) (ppm) 32.4, C(2'); 39.5, C(1'); 65.1, 65.2, C(4,5); 101.3, C(2); 120.4, (CN); 127.3, C(2'',6''); 128.1, C(4''); 129.1, C(3'',5''); 135.4, C(1''). *m/z* 203 (*M*), 125, 73, 45.

*2-[2'-Cyano-2'-(3''-methoxybenzene)ethyl]-1,3-dioxolane (**33**)*

2'-Lithio-2-(2'-cyanoethyl)-1,3-dioxolane, prepared in THF (4 ml) from butyllithium (1.2 mol l^{-1}, 1.02 ml, 1.23 mmol), diisopropylamine (172 μl, 1.23 mmol) and 2-(2'-cyanoethyl)-1,3-dioxolane (0.16 g, 1.26 mmol) was treated with HMPT (2.5 ml) and tricarbonyl(η^6-methoxybenzene)chromium(0) (**31**) (0.30 g, 1.23 mmol) in THF (6 ml) at −78 °C. The mixture was stirred at −78 °C for 0.5 h and then at 0 °C for 3 h. Iodine (2.75 g, 10.8 mmol) in THF (10 ml) was added at −78 °C and the mixture warmed to room temperature over 8 h. Work-up as usual gave an oil, which on PLC (hexane/diethyl ether, 7/3) gave (i) 2-(2'-cyano-2'-(3''-methoxybenzene) ethyl)-1,3-dioxolane (0.18 g, 63%) as an oil, b.p. (Kugelrohr) 83 °C/0.04 mmHg (Found: C, 66.9; H, 6.7; N, 6.0. $C_{13}H_{15}NO_3$ calcd.: C, 66.9; H, 6.5; N, 6.0%). ν_{max} (neat) 1600(aryl C=C), 1135(1,3-dioxolane), 1030 cm^{-1} (1,3-dioxolane). δ(H) (ppm) 2.24, m, 2H(1'); 3.81, s, OCH_3; 4.0, m, 5H(4,5,2'); 5.02, t, $J_{2,1'}$ 5 Hz, H(2); 7.0, m, 4H(aryl H). δ(C) (ppm) 32.4, C(2'); 39.4, C(6''); 55.3, OCH_3; 65.1, 65.2, C(4,5); 101.3, C(2); 113.0, C(6''); 113.5, C(2''); 119.5, C(4''); 120.4, CN; 130.2, C(5''); 136.8, C(3''); 160.1, C(1''). *m/z* 233 (*M*), 160, 147, 87, 73, 45. (ii) 2,3'-dimethoxybiphenyl (25 mg, 19%), as an oil, b.p. (Kugelrohr) 68 °C/4.0 mmHg. (Found: $M^{+\cdot}$ 214.0988. $C_{14}H_{14}O_2$ calcd.: *M* 214.0994). ν_{max} (neat) 1600 cm^{-1} (aryl C=C). δ(H) (ppm) 3.84, s, OCH_3; 3.85, s, OCH_3; 7.1, m, 8H(aryl H). δ(C) (ppm) 52.2, 55.5, OCH_3; 111.2, C(4'); 112.4, C(2'); 115.3, C(3); 120.7, C(6'); 122.0, C(5); 128.6, C(4); 128.8, C(6); 130.5, C(1); 130.7, C(5'); 139.9, C(1'); 156.4, C(2); 159.1, C(3'). *m/z* [24] 214 (*M*), 199, 168, 139, 124, 109.

*2'-[2'-Cyano-2'-(14''-(methyl 12''-methoxypodocarpa-8'',11'',13''-trien-19''-oate)) ethyl]-1,3-dioxolane (**24**)*

2'-Lithio-2-(2'-cyanoethyl)-1,3-dioxolane, prepared in THF (5.2 ml) from butyllithium (1.2 mol l^{-1}, 0.95 ml, 1.14 mol) diisopropylamine (160 μl, 1.14 mmol), and 2-(2'-cyanoethyl)-1,3-dioxolane (0.15 g, 1.14 mmol) at −78 °C was treated with HMPT (2.6 ml) and the complexes **6** (0.25 g, 0.57 mmol) in THF (5.2 ml). After 6.5

h at −78 °C, quenching with iodine, work-up, and PLC (hexane/ether, 7/3 and 6/4) gave (i) 2-[2′-cyano-2′-(14″-(methyl 12″-methoxypodocarpa-8″,11″,13″-trien-19″-oate))ethyl]-1,3-dioxolane (80 mg, 33%) (Found: $M^{+\cdot}$ 427.2360. $C_{25}H_{33}NO_5$ calcd.: M 427.2359). ν_{max} 2250(CN), 1720(ester CO), 1600(aryl C=C), 1145(1,3-dioxolane), 1025 cm^{-1} (1,3-dioxolane). δ(H) (ppm) (60 MHz) 1.04, s, 3H(20″); 1.30, s, 3H(18″); 1.49–2.81, m, 13H, CH/CH_2; 3.68, s, CO_2CH_3; 3.81, s, $ArOCH_3$; 4.1, m, 5H(4,5,2′); 5.10, t, $J_{2,1'}$ 4 Hz, H(2); 6.84, br s, 2H(11″,13″). δ(H) (ppm) (400 MHz) 3.96, m, 2H(4 or 5); 4.08, m, 4H(4 or 5); 4.14, dxd, $J_{1'a,2'}$ 6.1 Hz, $J_{1'b,2'}$ 4.4 Hz, H(2′); 6.83, d, $J_{11'',13''}$ 2.6 Hz, H(13″); 6.86, d, $J_{11'',13''}$ 2.6 Hz, H(11″). δ(C) (ppm) 20.0, C(2″); 20.7, C(6″); 22.9, C(20″); 27.8, C(7″); 28.4, C(2′,18″); 37.3, C(3″); 38.5, C(10″); 39.0, C(1″); 39.8, C(1′); 43.8, C(4″); 51.2, CO_2CH_3; 51.9, C(5″); 55.2, OCH_3; 65.1, 65.2, C(4,5); 101.5, C(2); 110.4, C(13″); 111.6, C(11′); 120.9, CN; 124.6, C(8″); 134.5, C(14″); 150.8, C(9″); 158.0, C(12″); 177.5, C(19″). m/z 427 (M), 341, 73; (ii) 2-(2′-cyano-2′-iodoethyl)-1,3-dioxolane (**38**) (37 mg, 13%) as an oil, b.p. (Kugelrohr) 50 °C/0.05 mmHg (Found: C, 28.5; H, 3.5; N, 5.8. $C_6H_8HINO_2$ calcd.: C, 28.5; H, 3.2; N, 5.5%). ν_{max} 2250(CN), 1130(1,3-dioxolane), 1025 cm^{-1} (1,3-dioxolane). δ(H) (ppm) 2.5, m, 2H(1′); 4.08, s, 4H(4,5); 4.43, t, $J_{1',2'}$ 10 Hz, H(2′); 5.07, t, $J_{1',2}$ 5 Hz, H(2). δ(C) (ppm) −12.6, C(2′); 41.7, C(1′); 65.2, C(4,5); 102.9, C(2); 118.9, CN. m/z 252 (M − H), 227, 180, 125, 73, 45; (iii) a dimer (probably C(13)–C(13) coupled) of methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (25 mg, 15%) as an oil. δ(H) (ppm) 1.05, s, 6H(20); 1.28, s, 6H(18); 1.49–2.81, m, 26H, CH/CH_2; 3.68, m, 12H, OCH_3; 6.67, m, 4H, aryl H. m/z 602 (M); (iv) methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (31 mg, 18%) (correct ^{1}H NMR and TLC). When this reaction was scaled up ten times, the yield of **24** after flash chromatography was increased to 54% and the recovery of **1** was 26%.

Repetition of the reaction but with a 3/2 molar ratio of 2′-lithio-2-(2′-cyanoethyl)-1,3-dioxolane to the complexes **6** and separation by PLC (hexane/ether, 4/1) gave (i) 2-[2′-cyano-2′-(14″-(methyl 12″-methoxypodocarpa-8″,11″,13″-trien-19″-oate))ethyl]-1,3-dioxolane (**24**) (11%), (ii) methyl 13-iodo-12-methoxypodocarpa-8,11,13-trien-19-oate (**17**) (4%), m.p. 138–140 °C (Found: C, 53.1; H, 6.0. $C_{19}H_{25}IO_3$ calcd.: C, 53.3; H, 5.9%). ν_{max} (KBr) 1720(ester CO), 1600 cm^{-1} (aryl C=C). δ(H) (ppm) 1.06, s, 3H(20); 1.28, s, 3H(18); 1.49–2.81, m, 13H(CH/CH_2); 3.68, s, CO_2CH_3; 3.81, s, OCH_3; 6.76, s, H(11); 7.44, s, H(14). m/z 428 (M), 413, 353, 226.

Repetition of the reaction for 8.5 h at −78 °C, then at −20 °C for 0.5 h, then at 3 h at −78 °C and PLC (hexane/ether, 3/2) gave, in order of increasing R_f: (i) a mixture (30%, 1/2) of the regioisomers **16** and **24**, (ii) a dimer (70 mg, 17%), m/z 602 (M), (iii) methyl 12-methoxypodocarpa-8,11,13-trien-19-oate, (correct ^{1}H NMR and TLC.)

Repetition of the reaction with a 1/1 molar ratio 2′-lithio-2-(2′-cyanoethyl)-1,3-dioxolane to the complexes **6** at −78 °C for 0.5 h and then 0 °C for 3 h and PLC (hexane/ether, 7/3) gave 2-[2′-cyano-2′-(13″-(methyl 12″-methoxypodocarpa-8″,11″,13″-trien-19″-oate))ethyl]-1,3-dioxolane (**16**) (12%), b.p. (Kugelrohr) 120 °C/0.1 mmHg, m.p. 185–187 °C (Found: $M^{+\cdot}$ 427.2379. $C_{25}H_{33}NO_5$ calcd.: M 427.2359). ν_{max} 2325(CN), 1720(ester CO), 1600(aryl C=C), 1135(1,3-dioxolane), 1025 cm^{-1} (1,3-dioxolane). δ(H) (ppm) 1.04, s, 3H(20″); 1.30, s, 3H(18″); 1.49–2.81, m, 13H(CH/CH_2); 3.68, s, CO_2CH_3; 3.81, s, OCH_3; 4.1, m, 5H(4,5,2′); 5.08, t, $J_{1',2}$

4Hz, H(2); 6.74, s, H(11″); 7.01, s, H(14″). δ(C) (ppm) 19.2, C(2″); 20.9, C(6″); 22.8, C(20″); 26.8, C(2′); 28.4, C(18″); 31.1, C(7″); 37.1, C(1′); 37.5, C(3″); 38.6, C(10″); 39.4, C(1″); 43.9, C(4″); 51.1, CO_2CH_3; 52.6, C(5″); 55.4, OCH_3; 64.9, 65.1, C(4,5); 101.8, C(2); 107.8, C(11″); 121.1, CN; 125.4, C(13″); 127.8, C(8″); 128.8, C(14″); 149.2, C(9″); 154.3, C(12″); 177.6, C(19″). *m/z* 427 (*M*), 341, 125.

Attempts to cyclise 2-[2′-cyano-2′-(3″-methoxybenzene)ethyl]-1,3-dioxolane (33)

Using tin(IV) chloride. Tin(IV) chloride in dichloromethane (1.0 mol l^{-1}, 0.65 ml, 0.65 mmol) was added to a cooled (−78°C) and stirred solution of 2-[2′-cyano-2′-(3″-methoxybenzene)ethyl]-1,3-dioxolane (50 mg, 0.21 mmol) in dichloromethane (1 ml) under argon. The solution was left for 1 h, diluted with dichloromethane (3 ml) and treated at −78°C with 10% aqueous potassium fluoride solution (3 ml). The mixture was extracted with dichloromethane (10 ml) and the extract was washed with potassium fluoride solution (10 ml), water (10 ml), and brine (10 ml). Removal of solvent in vacuo from the dried solution and PLC (hexane/diethyl ether, 1/1) gave (i) starting material (34 mg, 68%), (ii) 3-cyano-3-(3′-methoxyphenyl)propanal (13 mg, 30%) (Found: $M^{+\cdot}$ 189.0791). $C_{11}H_{11}NO_2$ calcd.: *M* 189.0790). ν_{max} (neat) 2250(CN), 1720(CHO), 1600 cm^{-1} (aryl C=C). δ(H) (ppm) 3.10, q, $J_{1,2'}$ 8 Hz, $J_{2',3'}$ 3 Hz, 2H(2′); 3.83, s, OCH_3; 4.38, t, $J_{1',2'}$ 8 Hz, H(1′); 6.89, m, 4H, aryl H; 10.05, s, CHO. δ(C) (ppm) 30.2, C(3); 48.6, C(2); 55.3, $ArOCH_3$; 113.1, C(6′); 113.8, C(2′); 119.4, C(4′); 119.7, CN; 130.4, C(5′); 135.8, C(3′); 160.2, C(1′); 196.3, CO. *m/z* 189 (*M*), 160, 108.

Repetition of the above experiment using titanium(IV) tetrachloride (50 μl, 0.45 mmol) in place of tin(IV) chloride and PLC (hexane/ether, 2/3) gave: (i) starting material (9%); (ii) 3-cyano-3-(3′-methoxyphenyl)propanal (39%); and (iii) a mixture of at least three other components. Use of trimethylsilyl trifluoromethanesulfonate or trifluoromethanesulfonic acid gave no identified products.

*Attempted cyclisation of 2-[2′-cyano-2′-(14″-(methyl 12″-methoxypodocarpa-8″,11″,13″-trien-19-oate))ethyl]-1,3-dioxolane (**24**)*

Using titanium(IV) chloride. Titanium(IV) chloride in dichloromethane (0.23 ml, 1 mol l^{-1}, 0.23 mmol) was added to a cooled (−78°C) solution of the acetal **24** (98 mg, 0.23 mmol) in dichloromethane (1 ml) and the mixture was stirred at −78°C for 1 h, and then at 0°C for 1.3 h. Water (5 ml) was added, and the mixture extracted with dichloromethane (30 ml). The usual work-up of the extract and PLC (hexane/ether, 1/4) gave 3-cyano-3-[14′-(methyl 12′-methoxypodocarpa-8′,11′,13′-trien-19-oate)]propanal (**25**) (25 mg, 28%), as an oil (Found: $M^{+\cdot}$ 383.2083. $C_{23}H_{29}NO_4$ calcd.: *M* 383.2096). ν_{max} 2950(CH), 2250(CN), 1720(ester CO, CHO), 1600 cm^{-1} (aryl C=C). δ(H) (ppm) 1.07, s, 3H(20′); 1.33, s, 3H(18′); 1.50–3.28, m, 14H(CH/CH_2); 3.59, s, CO_2CH_3; 3.81, s, OCH_3; 3.86, s, H(3); 6.82, br s, 2H(11′,13′); 10.15, s, H(1). δ(C) (ppm) 19.98, C(2′); 20.65, C(6′); 22.85, C(20′); 37.33, C(3′); 38.82, C(10′); 39.19, C(1′); 43.91, C(4′); 47.39, C(2); 51.35, CO_2CH_3; 51.83, C(5′); 55.32, OCH_3; 110.70, C(13′); 111.88, C(11′); 120.17, CN; 124.74, C(14′); 151.29, C(9′); 158.10, C(12′); 177.67, CO; 196.70, CHO. *m/z* 383 (*M*), 356, 308.

Attempts to cyclise **24** with tin(IV) chloride, trimethylsilyl trifluoromethanesulfonate, and trifluoromethanesulfonic acid, were unsuccessful.

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