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Addition–protonation reactions of (η^6-arene)tricarbonylchromium(0) complexes of podocarpic acid derivatives: synthesis of steroidal alicyclic skeletons

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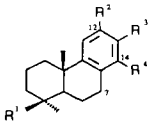
Abstract

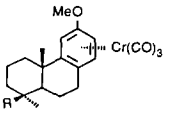
Functionalization of the (η^6-arene)tricarbonylchromium(0) complexes of some podocarpic acid (**1**) derivatives has been achieved through the addition–protonation route. The resulting dienol ethers underwent acid-promoted hydrolysis giving enones which were subsequently reduced to saturated ketones. Acid-promoted cyclopentaannulation of these ketones produced compounds with tetracyclic steroidal skeletons in good yield.

Keywords: Chromium; Carbonyl; Arene complexes; Addition-protonation; Podocarpic acid

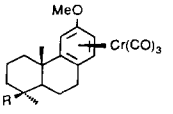


(**1**: $R^1 = CO_2H$, $R^2 = OH$, $R^3 = H$, $R^4 = H$
2: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = H$, $R^4 = H$
3: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = H$, $R^4 = H$
4: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = H$, $R^4 = H$
5: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = H$, $R^4 = CH(CN)CH_2\overline{CHO(CH_2)_2O}$
6: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = H$, $R^4 = CH(CN)CH_2\overline{CHO(CH_2)_2O}$
7: $R^1 = CH_2OMe$, $R^2 = H$, $R^3 = H$, $R^4 = CH(CN)CH_2\overline{CHO(CH_2)_2O}$
8: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = H$, $R^4 = \overline{CH(CN)CH_2CHO(CH_2)_2O}$
9: $R^1 = CO_2H$, $R^2 = H$, $R^3 = H$, $R^4 = (CH_2)_2\overline{CHO(CH_2)_2O}$
10: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = CH(CN)\overline{CH_2CHO(CH_2)_2O}$, $R^4 = H$
11: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = COCH_2\overline{CHO(CH_2)_2O}$, $R^4 = H$
12: $R^1 = CO_2H$, $R^2 = H$, $R^3 = (CH_2)_2\overline{CHO(CH_2)_2O}$, $R^4 = H$
13: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = H$, $R^4 = CH(CN)CH_2CHO$
14: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = CH(CN)CH_2CHO$, $R^4 = H$
15: $R^1 = CO_2H$, $R^2 = OMe$, $R^3 = H$, $R^4 = (CH_2)_2\overline{CHO(CH_2)_2O}$
16: $R^1 = CO_2H$, $R^2 = OH$, $R^3 = H$, $R^4 = (CH_2)_2\overline{CHO(CH_2)_2O}$)

(17:R=CO_2Me
18:R=CH_2OMe)



(19:R=CO_2Me
20:R=CH_2OMe)



(21:R=CO_2Me
22:R=CH_2OMe)

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1. Introduction

Recently we reported [1] the functionalization of the (η^6-arene)tricarbonylchromium(0) complexes of some podocarpic acid (**1**) derivatives through the addition–oxidation sequence. The resulting decomplexed products underwent Lewis acid-mediated cyclopentaannulation to give ring-C aromatic androstane analogues in high yield. Earlier we reported [2] the addition–protonation sequence of 2-lithio-2-methylpropanonitrile with complexes **17**. Decomplexation of the resulting η^4-cyclohexadienyl adducts gave an isomeric mixture (13%) of the dienol ethers **24** and **25**, together with a small amount of the demethoxylated product **2**. We report here studies of the addition–protonation sequences of the (η^6-arene)$Cr(CO)_3$ complexes **17** and **18** with a nitrile-stabilized lithio-anion to give dienol ethers, which undergo acid-promoted hydrolysis to give enones. 1,4-Reduction of the enones leads to saturated ketones, while acid-promoted cyclopentaannulation of these ketones produces compounds with tetracyclic steroidal skeletons in high yield.

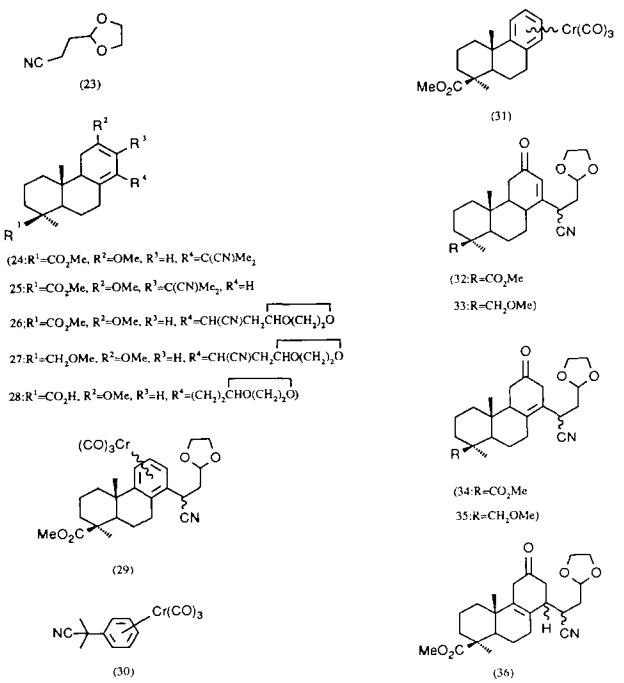
2. Results and discussion

The addition of a three-carbon moiety using 2-(2′-cyanoethyl)-1,2-dioxolane (**23**) [1,2] via an addition–oxidation sequence across C13/C14 of the (η^6-arene)$Cr(CO)_3$ complexes **19** and **20** [1,3] of the podocarpic acid derivatives **3** and **4** afforded ring-C aromatic steroidal analogues.

(η^6-Arene)$Cr(CO)_3$ complexes may also undergo nucleophilic addition–protonation. Semmelhack et al. [4] have used a nucleophilic addition–protonation sequence to produce, after hydrolysis, substituted 2-cyclohexenones from anisole derivatives. Thus, treatment of (η^6-methoxybenzene)$Cr(CO)_3$ with 2-lithio-2-methylpropanonitrile followed by the addition of trifluoroacetic acid yielded, after decomplexation with concentrated aqueous ammonia, a mixture of dienol ethers. The metal is bound more weakly to the η^4-diene than it was to the η^6-arene, and thus decomplexation is achieved easily with concentrated aqueous ammonia. Subsequent hydrolysis in aqueous acid gave substituted cyclohexenones, the product ratio being dependent on the reaction conditions. Application of the addition–protonation procedure to suitable tricarbonylchromium(0) complexes of podocarpic acid derivatives, followed by cyclization, could conceivably give non-aromatic ring-C androstane analogues.

The addition–protonation reaction between the lithio-anion derived from **23** and a mixture (4:1) of the complexes **19 / 21** produced a mixture of the 8″(14″),12″-dienol ethers **26** (55%) and one or more of its diene regioisomers, the 12″-desmethoxy arenes **5** (18%,diastereoisomeric ratio, 3:1), and the arenes **6** [1] (5%). Similarly, the reaction between the lithio-anion derived from **23** and a mixture (5:1) of complexes **20 / 22** produced a mixture of the 8″(14″),12″-dienol ethers **27** (60%) and one or more of its regioisomers, the 12″-desmethoxy arenes **7** (23%, diastereoisomeric ratio, 3:1), and the arenes **8** [1] (3%). C13″-Substituted regioisomers of some products were also formed. Dioxolanes **6** and **8** are assumed to arise from aromatization of the dienol ethers **26** and **27**.

Formation of the 12″-desmethoxy arenes **5** and **7** requires further comment. A mixture of the η^6-$Cr(CO)_3$ precursor complexes **29** of arenes **5** was also isolated; since they are more stable than the η^4-complexes, exposure to photolysis and oxygen was required to effect their complete decomplexation. The aromatic region in the ^{1}H NMR spectra of the 12″-desmethoxy dioxolanes **5** and **7** was not resolved sufficiently (diastereoisomers at C2′) to allow assignment of individual signals, and thus initially it was uncertain whether the newly introduced side-chain was at C12″, C13″, or C14″. Semmelhack et al. [4] and Boutonnet et al. [5,6] have obtained the desoxy aromatic product **30** from (η^6-methoxybenzene)$Cr(CO)_3$. Two mechanisms [5,6] were postulated in the monocyclic series, the first of which (S_NAr *tele*: the entering group takes up a position more than one atom away from the atom to which the leaving group was attached) when applied to the present results would lead to a C14″-substituted C12″-



desoxy diterpenoid product, whereas the second (S_NAr *ipso*) would give the C12″-substituted product.

In order to simplify the ^1H NMR spectrum the desmethoxy dioxolanes **5** were subjected to reductive decyanation under Birch reduction conditions [1] to remove the side-chain stereogenic centre and at the same time cleave the C19″ ester. The aromatic region of the spectrum of the 19″-carboxylic acid **9** showed two doublets (δ 6.98, 7.16, J 7.3 Hz) and one triplet (7.09, J 7.3 Hz), as expected for a C14″-substituted product. Furthermore, irradiation of the signal due to H7″β did not result in an nOe on the signals assigned to any of the aromatic protons, implying the probable absence of a proton at C14″, in both **5** and **7**. In contrast, an nOe of 5.0% was detected for H14″ when the signal due to H7″β in the C13″-substituted isomers **10** was irradiated. An authentic sample of the latter regioisomer was obtained (87%, diastereoisomeric ratio, 10:9) from the reaction between the lithio-anion derived from **23** and the 12-desmethoxy complexes **31** [7]. Three sets of doublets (δ 6.86, 6.88, J 1.9 Hz, H14″, diastereoisomers; 7.04, J 8.3 Hz, H11″) and two doublets of doublets (6.95, 6.97, J 8.3, 1.9 Hz, H12″, diastereoisomers) were observed in the aromatic region of the ^1H NMR spectrum of **10**, confirming the assignment of **5** (and **7**), and thus their formation via the S_NAr *tele* route.

One run of this latter experiment also gave the C2′-ketone **11**, the structure of which was indicated by the presence of a carbonyl absorption (1682 cm^{-1}) due to a conjugated ketone in the IR spectrum. A doublet (δ 7.35, J 8.4 Hz, H11″), a broadened singlet (7.65, H14″), and a doublet of doublets (7.70, J 8.4, 1.6 Hz, H12″) were observed in the aromatic region of the ^1H NMR spectrum, while the ^{13}C NMR spectrum showed a signal at δ 196.3 for the conjugated ketone carbon. An nOe of 2.3% was detected for the signal due to H14″ when the signal due to H7″β was irradiated. This benzylic ketone arises presumably via oxidative decyanation during workup.

When the dioxolanes **10** were subjected to reductive decyanation [1], the 19″-carboxylic acid **12** was obtained (**5** above). This structure was indicated by the presence of a broad hydroxy absorption (3500–2500 cm^{-1}) and by a carbonyl absorption (1694 cm^{-1}) due to a carboxylic acid in the IR spectrum. A singlet (δ 6.88, H14″), a broadened doublet (7.16, J 8.2 Hz, H12″), and a doublet (7.16, J 8.2 Hz, H11″) were observed in the aromatic region of the ^1H NMR spectrum, and the ^{13}C NMR spectrum showed a signal at δ 183.6 for the carboxylic acid carbon. An nOe of 5.4% was detected for the signal owing to H14″ when the signal owing to H7″β was irradiated.

Attempted titanium(IV) chloride-mediated cyclization [1] of either of the 12″-desmethoxy dioxolanes **5** or **11** was unsuccessful, giving only the corresponding aldehydes **13** (32%) and **14** (25%). The structures of compounds **13** and **14** were indicated by the signals due to aldehyde carbonyl carbons ((δ 196.8 and 196.6, respectively) in the ^{13}C NMR spectra. Attempted cyclization of the 14″-substituted dioxolanes **5** with Eaton's reagent (P_2O–$MeSO_3H$) gave a complicated mixture.

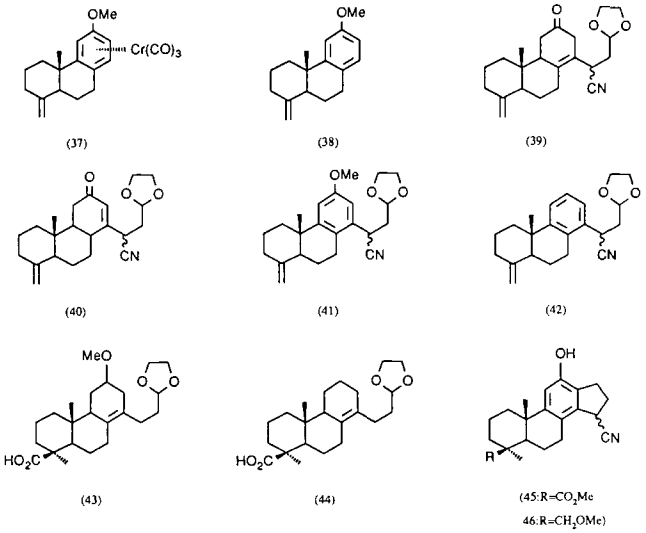
Hydrolysis of the mixture of dienol ethers **26** with aqueous HCl/THF gave the 13″-en-12″-ones **32** (97%) as a mixture of several diastereoisomers. The structure of **32** followed from the presence of an absorption (1676 cm^{-1}) owing to a conjugated enone in the IR spectrum, and to a ketone carbonyl signal (δ 199.1) in the ^{13}C NMR spectrum. Signals due to one olefinic proton (δ 6.33, H13″) and one olefinic carbon (127.2, C13″) were observed in the respective NMR spectra. The signal caused by the C20″ methyl protons was at relatively high field (δ 0.72) in the ^1H NMR spectrum [8], reflecting the loss of ring-C aromaticity.

From further runs of this hydrolysis reaction, both of the non-conjugated enones **34** and **36** were also isolated. These structures were indicated by the signals at δ 208.6 owing to the carbonyl of a non-conjugated ketone in the ^{13}C NMR spectra, and by the absence of absorption owing to protonated vinyl carbons. The signals owing to the C20″ protons [8] (δ 0.76 and 0.49 respectively) in the ^1H NMR spectra indicated the position of the double bond in both **34** and **36**.

Hydrolysis of the mixture of dienol ethers **27** gave a mixture (3:1) (79%) of the enones **33** and **35**, each as a mixture of several diastereoisomers.

The addition–protonation sequence between the α-$Cr(CO)_3$ complex **37** of the 4(18)-alkene **38** [3] and the lithio-anion derived from **23**, followed by aqueous HCl/THF-promoted hydrolysis, resulted in the formation of the 8″(14″)-en-12″-ones **39** (26%), the 13″-en-12″-ones **40** (36%), the arene dioxolanes **41** (4%), and the desmethoxy arene dioxolanes **42** (24%). The structure of the diastereoisomeric non-conjugated enones **39** was indicated by the carbonyl absorption (1721 cm^{-1}) in the IR spectrum and by the signal at δ 208.5 (C12″, major diastereoisomer) in the ^{13}C NMR spectrum. The signal (δ 0.61) due to $(H20'')_3$ [8] was again observed at unusually high field in the ^1H NMR spectrum. The structure of the diastereoisomeric conjugated enones **40** was suggested by the appearance of the carbonyl absorption at lower wavenumber (1676 cm^{-1}) in the IR spectrum, and by the signal at lower chemical shift (δ 198.93, C12″, major diastereoisomer) in the ^{13}C NMR spectrum. Again, the signal attributed to $(H20'')_3$ was at relatively high field (δ 0.74) in the ^1H NMR spectrum [8].

An alternative approach to a ring-C alicyclic steroidal analogue was to reduce the substituted (from addition–oxidation) aromatic ring by either the Birch [9–12] or Benkeser (alkali metals in low molecular



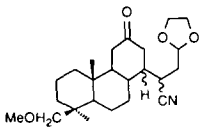
weight amines) [13–15] methods. In the event, Birch reduction of the 19″-carboxylic acid dioxolane **15** [1] gave three fractions: (i) an inseparable mixture of starting material and a mixture of dienol ethers **28**; (ii) an inseparable mixture of dienol ethers **28**, the 8″(14″)-enol ethers **43**, and the 8″(14″)-enes **44**; and (iii) the 8″(14″)-enes **44**. When 2-propanol instead of *t*-butyl alcohol was used as the proton source only starting material was recovered. In general the Benkeser reduction is more powerful but less selective than the Birch reduction. Although phenols are normally resistant to reduction (as a consequence of ionisation) phenol has been converted into cyclohexanone in 96% yield by lithium in methylamine or ethylamine, provided that hydrolysis of the reaction mixture is carried out rapidly with only a trace of excess lithium remaining [15]. However, when the 12″-methoxy-19″-carboxylic acid **15** was treated with lithium in ethylamine in the present work, only the 12″-hydroxy derivative **16** (69%) was produced. Moreover, when podocarpic acid (**1**) was used as a model for the 12″-hydroxy diterpenoid **16** to investigate whether such a phenol could be reduced with lithium/ethylamine, only starting material was recovered after prolonged reaction. It has been reported [16] that sodium in hexamethylphosphoric triamide (HMPA) containing *t*-butyl alcohol is capable of reducing the highly substituted arene hexamethylbenzene to the corresponding cyclohexane. However, after prolonged treatment with this medium, podocarpic acid was not reduced. Likewise, treatment of podocarpic acid with either lithium/1,2-diaminoethane/100°, or lithium/1,2-diaminoethane/ HMPA/100° gave only unchanged starting material.

Aqueous HCl-promoted intramolecular cyclizations of cyclic acetals to saturated centres adjacent to a ketone have been reported [17,18]. Prolonged treatment of either of the dioxolanes **34** or **36** with aqueous HCl/THF gave the 12-hydroxy-15-cyano ring-C aromatic androstane analogues **45** (diastereoisomeric ratio, 9:8) in 65% and 39% yield, respectively. The composition of the product mixture was apparent from the phenolic absorption (3412 cm^{-1}) in the IR spectrum, and the broad phenolic signal (δ 5.69) in the ^1H NMR spectrum. Similarly, the 19″-methoxy analogue **35** gave the aromatic androstane analogues **46** (diastereoisomeric ratio, 3:1) in 75% yield. It appears, therefore, that the olefinic bond of the diterpenoid enones (either conjugated or non-conjugated) must be reduced before acid-promoted cyclization to form a non-aromatic ring-C androstane analogue can be achieved.

Prolonged reduction (60 h) of the conjugated enones **33** in methanol with hydrogen over Pd/C under pressure (4 atm) gave the saturated ketones **47** (97%). The structure of the diastereoisomeric products was indicated by the carbonyl absorption (1712 cm^{-1}) in the IR spectrum and by the resonance (δ 209.8) in the ^{13}C NMR spectrum. Interestingly, when the 19″-methoxycarbonyl analogues **32** were subjected to these reduction conditions the dimethyl acetal **48** (96%) was produced as a single diastereoisomer. Presumably, acetalization is promoted by traces of HCl generated from $PdCl_2$ in the commercial reduction catalyst. The isolation of a single stereoisomer suggests that acetalization may precede (and control) double bond isomerization/reduction. Attempted 1,4-reduction of the α,β-unsaturated ketones **32** or **33** by other methods [19–23] was unsuccessful. Direct reduction of the nonconjugated enones **34**, **35**, or **36** could not be achieved. However, when a trace of sodium methoxide was added to the mixture prior to application of the above reduction conditions, the nonconjugated enones **35** were reduced (presumably via the conjugated enones **33**) to the saturated ketones **47** (95%).

The key step in synthesizing the tetracyclic steroidal skeleton was the cyclopentaannulation promoted by aqueous HCl/THF [17,18]. Thus the androstane analogues **49** (88%) were produced from the ketones **47**. The structure of the diastereoisomeric products was supported by the carbonyl absorption (1686 cm^{-1}) in the IR spectrum, and by the resonances due to an olefinic proton (δ 6.45) in the ^1H NMR spectrum and to a conjugated carbonyl carbon (198.0) in the ^{13}C NMR spectrum. Under similar conditions the dimethyl acetal **48** gave the tetracyclic enone **50** (85%) as a single diastereoisomer.

Thus, conversion of tricyclic ring-C aromatic substrates into alicyclic steroidal analogues has been demonstrated. The key element in the overall transformation is the highly regioselective nucleophilic addition–protonation reaction of the diterpenoid (η^6-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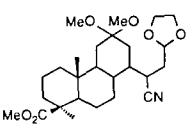
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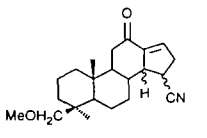
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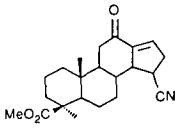
(50)

arene)$Cr(CO)_3$ complexes. This one-pot sequence not only effects loss of ring-C aromaticity (not possible via Birch methodology) but also a side-chain appropriate for subsequent closure to form ring D. The resulting tetracycles **49** and **50** are set up for further elaboration at C17 via conjugate addition.

3. Experimental

For general experimental details see Refs. [2] and [24]. High field ^1H and ^{13}C NMR spectra were determined in $CDCl_3$ (unless otherwise stated) on a Bruker AM400 or Bruker AC200 instrument. All air-sensitive reactions were carried out in a flame-dried nitrogen-flushed multi-necked flask under nitrogen. Air sensitive reagents were added by means of a syringe.

3.1. Reaction of tricarbonyl[{8,9,11,12,13,14-η}-methyl 12-methoxypodocarpa-8,11,13-trien-19-oate]chromium (0) (17) with 2-(2'-cyanoethyl)-1,3-dioxolane (23) followed by quenching with trifluoroacetic acid

Butyllithium (1.96 ml, 1.00 mol l^{-1} in hexanes, 1.96 mmol) was added dropwise to a cooled (−78°C) solution of tetrahydrofuran (THF) (10 ml) and diisopropylamine (0.23 ml, 1.96 mmol) and the mixture was stirred for 30 min. A solution of the dioxolane **23** (0.25 g, 1.96 mmol) in THF (1 ml) was added and the mixture was stirred for a further 30 min. HMPA (4 ml) was added, followed by a precooled (−78°C) solution of the complexes **17** (0.43 g, 0.98 mmol) in THF (10 ml). The mixture was stirred at −78°C for 2.5 h, and then cooled to −100°C. After 10 min a solution of trifluoroacetic acid (1.14 ml, 14.74 mmol) in THF (3 ml), precooled to −100°C was added, and the mixture became deep red. It was stirred at −100°C for 1 h, after which the cooling bath was removed. After 15 min at room temperature the mixture was cooled to 0° and poured into cold concentrated aqueous ammonia (40 ml). The mixture was diluted with ether and the organic layer washed with water then brine, and dried ($MgSO_4$). The organic extracts were then subjected to photolysis with a tungsten halogen lamp (800 W) and exposed to air for 1.5 h. PLC (hexanes/ether, 3:2, 5 sweeps) of the product gave (i) a mixture of 2-[2'ξ-cyano-2'-(14''-(methyl 12''-methoxypodocarpa-8'' (14''),12''-dien-19''-oate))ethyl]-1,3-dioxolane (**26**) and its diene regioisomer(s) (0.23 g, 55%) as a colourless oil (found: M^+, 429.2511. $C_{25}H_{35}NO_5$ calcd.: M, 429.2515). ν_{max} 2238 (CN), 1722 (C=0), 1608, 1467, 1229, 1143 cm^{-1}. δ_H 0.65, s, $(H20'')_3$; 1.24, s, $(H18'')_3$; 3.60, s, $ArOCH_3$; 3.92, m, $(H4)_2$, $(H5)_2$; 4.30, m, H2'; 4.90, m, H2; 4.98, m, H13''. *m/z* 429 (7,M^+), 341 (33, M−$H_2CCHOCH_2CH_2O$−H), 335 (12), 275 (14), 260 (15), 121 (68), 87 (39, *M*−diterpenoid−CHCN), 73 (100, M−diterpenoid−$CHCNCH_2$); (ii) 2-[2'ξ-cyano-2'-(14''-(methyl 12''-methoxypodocarpa-8'',11'',13''-trien-19''-oate))ethyl]-1,3-dioxolane [1] (**6**) (21 mg 5%); (iii) 2-[2'ξ-cyano-2'-(14''-(methyl podocarpa-8'',11'',13''-trien-19''-oate))ethyl]-1,3-dioxolane (**5**) (70 mg, 18%) as a colourless oil, b.p. 180°C/0.05 mm Hg (Kugelrohr) (Found: C, 72.3; H, 8.0; N, 3.7. $C_{24}H_{31}NO_4$ calcd.: C, 72.5; H, 7.9; N, 3.5%) (Found: M^+, 397.2261. $C_{24}H_{31}NO_4$ calcd.: M, 397.2253). ν_{max}) 2240 (CN), 1724 (C=O), 1436, 1145 cm^{-1}. δ_H 1.05, s, $(H20'')_3$; 1.08, td, *J* 13.7, 4.1 Hz, H3''ax; 1.28, s, $(H18'')_3$; 1.35, td, *J* 12.9, 4.3 Hz, H1''ax; 1.52, d, *J* 12.7 Hz, H5''; 1.64, bd, *J* 14.1 Hz, H2''eq; 1.99, m, H2''ax, H6''ax, $(H1')_1$; 2.27, m, H1''eq, H3''eq, H6''eq, $(H1')_1$; 2.51, ddd, *J* 16.5, 12.4, 6.2 Hz, H7''ax; 2.86, dd, 16.5, 4.4 Hz, H7''eq; 3.66, s, CO_2CH_3; 3.93, 4.02, m, $(H4)_2$, $(H5)_2$; 4.17, dd, *J* 10.5, 4.4 Hz, H2'; 5.07, dd, *J* 5.5, 3.3 Hz, H2; 7.21, d, *J* 7.6 Hz, H13''; 7.27, t, *J* 7.6 Hz, H12''; 7.28, d, *J* 7.6 Hz, H11''. δ_C 20.0, C2''; 20.6, C6''; 23.0, C20''; 28.2, C2'; 28.5, C18''; 31.8, C7''; 37.3, C3''; 38.4, C1'; 38.8, C10''; 39.7, C1''; 43.9, C4''; 51.3, CO_2CH_3; 51.8, C5''; 65.2, 65.3, C4, C5; 101.6, C2; 121.1, CN; 124.6, C13''; 126.0, C12''; 126.6, C11''; 132.5, C8''; 133.5, 14''; 149.4, C9''; 177.7, C=O. *m/z* 397 (3, M^+), 335 (54), 322 (31), 311 (10, M−$H_2CCHOCH_2CH_2O$ + H), 275 (42), 260 (50), 87 (100, M−diterpenoid−CHCN), 73 (72, M−diterpenoid−$CHCNCH_2$); and (iv) methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (**3**) (20 mg, 7%).

On one run of the above experiment tricarbonyl [(8'',9'',11'',12'',13'',14''-η)-2-(2'ξ-cyano-2'-(14''-(methyl podocarpa-8'',11'',13''-trien-19''-oate))ethyl)-1,3-dioxolane]chromium(0) (**29**) was also isolated as a yellow solid (found: M^+, 533.1499. $C_{27}H_{31}NO_7Cr$ calcd.: M, 533.1506). *m/z* 533 (10, M^+), 474 (3), 449 (100, M−3C=O), 405 (22), 361 (12), 73 (18, M−diterpenoid−$CHCNCH_2$), 52 (22). This compound was decomplexed by photolysis (as described above) to give the dioxolanes **5**.

C13''-Substituted regioisomers of the dioxolanes **26** and **6** were also formed (as was also the case when iodine was used as the decomplexing reagent [1]). How-

ever, spectral data for these regioisomers were not obtained.

3.2. Reaction of tricarbonyl [(8,9,11,12,13,14-η)-12,19-dimethoxypodocarpa-8,11,13-triene]chromium(0) (18) with 2-(2'-cyanoethyl)-1,3-dioxolane (23), followed by quenching with trifluoroacetic acid

Butyllithium (0.39 ml, 1.2 mol l^{-1} in hexanes, 0.47 mmol) was added to a cooled (−78°C) solution of THF (8 ml) and diisopropylamine (66 μl, 0.47 mmol) and the mixture was stirred for 30 min. A solution of the dioxolane **23** (54 mg, 0.47 mmol) in THF (0.5 ml) was added and the mixture was stirred for a further 30 min. HMPA (0.6 ml) was added, followed by a precooled (−78°C) solution of the complexes **18** (0.10 g, 0.24 mmol) in THF (1 ml). The solution was stirred at −78°C for 2.5 h, and then cooled to −100°C. After 10 min a solution of trifluoroacetic acid (0.29 ml, 3.5 mmol) in THF (1 ml), precooled to −100°C was added. After 1 h the deep red solution was allowed to warm to room temperature, then again cooled (0°) and poured into cold concentrated aqueous ammonia. Work-up followed by flash chromatography (hexanes/ether, 9:1, 4:1) gave (i) 12,19-dimethoxypodocarpa-8,11,13-triene (**4**) (7 mg, 10%); (ii) 2-[2'ξ-cyano-2'-(14''-(12'',19''-dimethoxypodocarpa-8''(14''),12''-diene))ethyl]-1,3-dioxolane (**27**) and diene regioisomer(s) (59 mg, 60%) (Found: M^+, 415.2711. $C_{25}H_{37}NO_4$ calcd.: M, 415.2725); (iii) 2-[2'ξ-cyano-2'-(14''-(12'',19''-dimethoxypodocarpa-8'',11'',13''-triene))ethyl]-1,3-dioxolane (**7**) (2 mg, 3%); and (iv) 2-[2'ξ-cyano-2'-(14''-(19''-methoxypodocarpa-8'',11'',13''-triene))ethyl]-1,3-dioxolane (**8**) (21 mg, 23%) (found: M^+, 383.2443. $C_{24}H_{33}NO_3$ calcd.: M, 383.2460). ν_{max} 2240 (CN), 1450 cm^{-1} (C=C). δ_H (major diastereoisomer) 1.02, td, *J* 13.3, 4.3 Hz, H3''ax; 1.05, s, $(H18'')_3$; 1.20, s, $(H20'')_3$; 1.38, m, H1''ax; 1.41, dd, *J* 13.0, 2.0 Hz, H5''; 1.66, m, H2''eq, H2''ax, H6''ax; 1.85, bd, *J* 12.5 Hz, H3''eq; 1.95-2.15, m, $(H1')_2$; 2.31, m, H6'', H1''eq; 2.75, ddd, *J* 16.4, 11.3, 7.1 Hz, H7''ax; 2.84, dd, *J* 16.4, 5.9 Hz, H7''eq; 3.29, 3.49, 2d, *J* 9.0 Hz, $(H19'')_2$; 3.33, s, CH_2OCH_3; 3.92, 4.04, 2m, $(H4)_2$, $(H5)_2$; 4.15, dd, *J* 13.5, 4.5 Hz, H2'; 5.06, dd, *J* 5.8, 3.3 Hz, H2; 7.21, d, *J* 7.7 Hz, H13''; 7.27, t, *J* 7.7 Hz, H12''; 7.27, d, *J* 7.7 Hz, H11''. δ_C (major diastereoisomer) 19.1, C2''; 19.2, C6''; 25.7, C20''; 27.6, C18''; 27.7, C7''; 28.1, C2'; 35.9, C3''; 37.9, C4''; 38.1, C10''; 38.4, C1'; 39.3, C1''; 50.4, C5''; 59.4, CH_2OCH_3; 65.1, 65.2, C4, C5; 76.0, C19''; 101.6, C2; 121.1, CN; 124.5, C13''; 125.0, C12''; 126.5, C11''; 132.0, C8''; 133.6, C14''; 151.2, C9''. *m/z* 383 (3, M^+), 368 (4, M−Me), 336 (14), 321 (69), 306 (9, 321-Me), 297 (5, M−$H_2CCHOCH_2CH_2O$ + H), 274 (30), 256 (50), 87 (100, M−diterpenoid-CHCN), 73 (58, M−diterpenoid−$CHCNCH_2$), 45 (62, $H_2C{=}OCH_3^+$).

3.3. Hydrolysis of 2-[2'ξ-cyano-2'-(14''-(methyl 12''-methoxypodocarpa-8''(14''),12''-dien-19''-oate))ethyl]-1,3-dioxolane (26) and diene regioisomer(s)

A solution of dienes **26** (0.27 g, 0.64 mmol) in THF (7 ml) was stirred for 1 h with aqueous HCl (5 drops, 2 mol l^{-1}). Saturated aqueous sodium hydrogencarbonate was added, and THF removed. PLC (hexanes/ether, 7:3) of the product gave 2-[2'ξ-cyano-2'-(14''-(methyl 12''-oxopodocarp-13''-en-19''-oate))ethyl]-1,3-dioxolane (**32**) (0.26 g, 97%) as a colourless oil, b.p. 190°/0.01 mm Hg (Kugelrohr) (Found: C, 69.1; H, 7.8; N, 3.3. $C_{24}H_{33}NO_5$ calcd.: C, 69.4; H, 8.0; N, 3.4%) (found: M^+, 415.2361. $C_{24}H_{33}NO_5$ calcd.: M, 415.2359). ν_{max} 2243 (CN), 1722 (C=O ester), 1676 (C=O ketone), 1448, 1233, 1144 cm^{-1}. δ_H (major diastereoisomer) 0.72, s, $(H20'')_3$; 1.02, td, *J* 13.5, 3.7 Hz, H3''ax; 1.04, td, *J* 12.9, 3.8 Hz, H1''ax; 1.16, dd, *J* 13.0, 2.3 Hz, H5''; 1.19, s, $(H18'')_3$; 1.45–2.60, m, H1''eq, H2''ax, H2''eq, H3''eq, H6''ax, H6''eq, H7''ax, H7''eq, $(H1')_2$; 3.67, s, $ArOCH_3$; 3.83, dd, *J* 10.1, 3.6 Hz, H2'; 3.93, 4.05, 2m, $(H4)_2$, $(H5)_2$; 5.09, dd, *J* 5.6, 3.0 Hz, H2; 6.33, d, *J* 1.4 Hz, H13''. δ_C (major diastereoisomer) 12.7, C20''; 19.1, C2''; 23.1, C6''; 28.4, C18''; 30.0, C7''; 30.3, C2'; 35.7, C11''; 37.1, C10''; 37.2, C8''; 37.4, C3''; 37.6, C1'; 38.2, C1''; 43.7, C4''; 51.3, $ArOCH_3$; 52.1, C5''; 54.8, C9''; 65.0, 65.3, C4, C5; 101.1, C2; 118.4, CN; 127.2, C13''; 158.8, C14''; 171.3, C=O ester, 199.1, C=O ketone. *m/z* 415 (2, M^+), 400 (2, M−Me), 356 (2), 294 (2), 229 (2), 86 (22, M−diterpenoid−CHCN−H), 73 (100, M−diterpenoid−$CHCNCH_2$).

From one run of the above hydrolysis 2-[2'ξ-cyano-2'-(14''-methyl 12''-oxopodocarp-8''(9'')-en-19''-oate))-ethyl]-1,3-dioxolane (**34**) was isolated as a colourless oil (found: M^+, 415.2356. $C_{24}H_{33}NO_5$ calcd.: M, 415.2359). ν_{max} 2239 (CN), 1721 (C=O ester and ketone), 1438, 1234, 1143 cm^{-1}. δ_H 0.76, s, $(H20'')_3$; 0.96, td, *J* 13.4 Hz, H1''ax; 1.05, td, *J* 13.5, 4.2 Hz, H3''ax; 1.13, s, $(H18'')_3$; 1.35, d, *J* 12.4 Hz, H5''; 1.48, bd, *J* 13.8 Hz, H2''eq; 1.62, m, $(H1')_1$, H3''eq; 1.78, m, H2''ax, H6''ax; 1.88–1.26, m, H7''ax, H7''eq, H1''eq, $(H1')_1$, H6''eq; 2.43, m, H14''; 2.48, m, H13''; 2.82, bs, H11''; 3.01, m, H2'; 3.54, 3.55, 2s, CO_2CH_3; 3.79, 3.89, 2m, $(H4)_2$, $(H5)_2$; 4.90, m, H2. δ_C 17.7, C20''; 19.2, C2''; 20.3, C6''; 28.0, C18''; 29.1, C2'; 30.4, C7''; 33.9, C1'; 36.3, C3''; 37.3, C1''; 38.0, C11''; 38.1, C10''; 39.8, C13''; 41.7, C14''; 43.5, C4''; 51.0, CO_2CH_3; 52.2, C5''; 64.8, 64.9, C4, C5; 101.3, C2; 119.5, CN; 127.2, C8''; 138.9, C9''; 177.3, C=O ester; 208.6, C=O ketone. *m/z* 415 (23, M^+), 400 (2, M−Me), 353 (12, M−$HOCH_2CH_2OH$), 343 (6), 327 (21, M−$H_2CCHOCH_2CH_2O$−H), 312 (4), 289 (36), 229 (100), 125 (56), 107 (59), 73 (76, M−diterpenoid−$CHCNCH_2$).

Another repetition of the above hydrolysis gave 2-[2'ξ-cyano-2'-(14''-(methyl 12''-oxopodocarp-8''(14'')-en-19''-oate))ethyl]-1,3-dioxolane (**36**) as a colourless oil

(Found: M^+, 415.2356. $C_{24}H_{33}NO_5$ calcd.: M, 415.2359). ν_{max} (KBr disc) 2240 (CN), 1720 (C=O ester), 1705 (C=O ketone), 1468, 1220, 1137 cm^{-1}. δ_H 0.49 s, $(H20'')_3$; 1.05, m, H1″ax, H3″ax; 1.20, s, $(H18'')_3$; 1.35, bd, *J* 12.5 Hz, H9″; 1.52, m, H2″eq; 1.70–1.93, m, $(H1')_1$, H2″ax, H3″eq, H6″ax, H7″ax; 2.02, d, *J* 12.9 Hz, H6″eq; 2.19, m, H1″eq; 2.31, bd, *J* 9.0 Hz, H5″; 2.39, 2.60, 2d, *J* 14.9 Hz, $(H11'')_2$; 2.81, 3.10, 2d, *J* 19.9 Hz, $(H13'')_2$; 3.61, s, CO_2CH_3. 3.90, 4.04, 2m, $(H4)_2$, $(H5)_2$; 4.08, dd, *J* 8.6, 7.0 Hz, H2′; 4.95, t, *J* 4.7 Hz, H2. δ_C 13.0, C20″; 19.6, C2″; 25.2, C6″; 28.7, C2′; 28.8, C18″; 31.5, C7″; 35.4, C1′; 37.9, C1″; 38.36, C11″; 38.41, C3″; 39.4, C13″; 41.7, C10″; 44.1, C4″; 51.4, CO_2CH_3; 54.2, C5″; 56.1, C9″; 65.1, 65.3, C4, C5; 101.4, C2; 119.7, C8″, CN; 137.0, C14″; 177.2, C=O ester, 208.6, C=O ketone. *m/z* 415 (19, M^+), 400 (2, M–Me), 368 (3), 353 (12, M–$HOCH_2CH_2OH$), 327 (14, M–$H_2CCHOCH_2$-CH_2O–H), 294 (13), 267 (17), 181 (45), 125 (52), 121 (100), 73 (84, M–diterpenoid–$CHCNCH_2$).

3.4. Hydrolysis of 2-[2′ξ-cyano-2′-(14″-(12″,19″-dimethoxypodocarpa-8″,11″,13″-diene))ethyl]-1,3-dioxolane (27) and diene regioisomer(s)

A solution of dienes **27** (59 mg, 0.14 mmol) in THF (5 ml) and aqueous HCl (5 drops, 2 mol l^{-1}) was heated under reflux for 10 min. Workup and PLC (hexanes/ether, 1:1) gave a mixture (3:1) (45 mg, 79%) of 2-[2′ξ-cyano-2′-(14″-(19″-methoxypodocarp-13″-en-12″one))ethyl]-1,3-dioxolane (**33**) and 2-[2′ξ-cyano-2′-(14″-(19″-methoxypodocarp-8″(14″)-en-12″-one))ethyl]-1,3-dioxolane (**35**) (found: M^+, 401.2556. $C_{24}H_{35}NO_4$ calcd.: M, 401.2566). ν_{max} 2243 (CN), 1729 (C=O), 1675 (C=O), 1615, 1449, 1141, 1109 cm^{-1}. δ_H 0.68, 0.91, 2s, $(H20'')_3$; 0.96, 0.98, 2s, $(H18'')_3$; 3.15, 3.42, 2d, *J* 9.1 Hz, $(H19'')_2$; 3.27, 3.30, 3.31, 3.32, 4s, CH_2OCH_3; 3.80, H2′; 3.91, 4.01, 2m, $(H4)_2$, $(H5)_2$; 4.90–5.12, m, H2; 6.30, bs, H13″.

3.5. Reaction of tricarbonyl [(8,9,11,12,13,14-η)-12-methoxy-19-norpodocarpa-4(18),8,11,-13-tetraene]chromium(0) (37) with 2-(2′-cyanoethyl)-1,3-dioxolane (23), followed by quenching with trifluoroacetic acid and aqueous acid-promoted hydrolysis

Butyllithium (0.88 ml, 1.2 mol l^{-1} in hexanes, 1.06 mmol) was added to a cooled (−78°C) solution of THF (6 ml) and diisopropylamine (0.15 ml, 1.06 mmol) and the mixture stirred for 30 min. A solution of the dioxolane **23** (0.13 g, 1.06 mmol) in THF (1 ml) was added and the mixture was stirred for a further 30 min. HMPA (2.5 ml) was added, followed by a precooled (−78°C) solution of the complex **37** (0.20 g, 0.53 mmol) in THF (3 ml). The mixture was stirred at −78°C for 2 h and then cooled to −100°C. After 10 min a solution of trifluoroacetic acid (0.61 ml, 7.94 mmol) in THF (2 ml) precooled to −100°C was added. The resulting red solution was stirred for 1 h and then allowed to warm to room temperature. The solution was again cooled (0°) and poured into cold concentrated aqueous ammonia. The mixture was diluted with ether and the organic layer was washed with water and brine, and dried ($MgSO_4$). A solution of the crude product in THF and aqueous HCl (2 mol l^{-1}) was heated under reflux for 10 min. Workup followed by PLC (hexanes/ether, 1:1, 3 sweeps) gave (i) 12-methoxy-19-norpodocarpa-4(18),8,11,13-tetraene (**38**) (5 mg, 4%); (ii) 2-[2′ξ-cyano-2′-(14″-(19″-norpodocarpa-4″(18″),8″(14″)-dien-12″-one))ethyl]-1,3-dioxolane (**39**) (49 mg, 26%) as a yellow oil (found: M^+, 355.2149. $C_{22}H_{29}NO_3$ calcd.: M, 355.2147). ν_{max} 2241 (CN), 1721 (C=O), 1441, 1269, 1143 cm^{-1}. δ_H (major diastereoisomer) 0.61, s, $(H20'')_3$; 3.91, 4.03, 2m, $(H4)_2$, $(H5)_2$; 4.00, m, H2′; 4.48, 4.80, 2bs, $(H18'')_2$; 4.98, t, *J* 4.2 Hz, H2. δ_C (50 MHz) (2 major diastereoisomers) 12.8, C20″; 23.14, 23.33, C2″; 25.6, C6″; 28.22, 28.52, C2′; 29.68, 29.99, C7″; 35.1, C3″; 36.14, 36.40, C1″; 38.0, C13″; 38.9, C11″; 40.2, C1′; 43.0, C10″; 50.18, 51.06, C5″; 52.9, C9″; 65.13, 65.20, C4, C5; 101.38, 101.57, C2; 107.05, 107.90, C18″; 119.8, C8″; 120.7, 122.1, CN; 136.9, C14″; 149.2, C4″; 208.5, C=O. *m/z* 355 (23, M^+), 340 (13, M–Me), 329 (4), 311 (5), 293 (20, M–$HOCH_2CH_2OH$), 267 (10, M–$H_2CCHOCH_2CH_2O$–H), 229 (23), 125 (60), 73 (100, M–diterpenoid–$CHCNCH_2$); (iii) 2-[2′ξ-cyano-2′-(14″-(19″-norpodocarpa-4″(18″),13″-dien-12″-one))ethyl]-1,3-dioxolane (**40**) (68 mg, 36%) as a yellow oil (found: M^+, 355.2147. $C_{22}H_{29}NO_3$ calcd.: M, 355.2147). ν_{max} 2242 (CN), 1676 (C=O), 1619, 1440, 1143, 1037 cm^{-1}. δ_H(3 major diastereoisomers) 0.74, 0.77, 2s, $(H20'')_3$; 3.83, dd, *J* 10.6, 3.9 Hz, H2′; 3.93, 4.04, 2m, $(H4)_2$, $(H5)_2$; 4.48, 4.79, 2d, *J* 1.4 Hz, $(H18'')_2$; 5.08, dd, *J* 5.6, 3.0 Hz, H2; 6.01, 6.05, 6.36, 3s, H13″. δ_C (2 major diastereoisomers) 12.8, C20″; 23.08, 23.17, C2″; 24.04, 24.13, C6″; 28.47, 28.55, C7″; 30.02, 30.37, C2′; 35.99, 36.17, C11″; 36.25, 36.34, C3″; 37.25, C8″; 37.93, 38.05, C1″; 38.13, 38.19, C1′; 38.89, 38.95, C10″; 50.03, 50.22, C5″; 50.86, 50.92, C9″; 65.14, 65.43, C4, C5; 101.21, 101.99, C2; 106.56, 107.75, C18″; 118.51, 121.4, CN; 127.62, 127.88, C18″; 148.98, 149.53, C4″; 158.71, 158.91, C14″; 198.93, C=O. *m/z* 355 (2, M^+), 340 (2, M–Me), 311 (2), 293 (2, M–$HOCH_2CH_2OH$), 278 (2), 224 (5), 86 (25, M–diterpenoid–CHCN), 73 (100, M–diterpenoid-$CHCNCH_2$); (iv) 2-[2′ξ-cyano-2′-(14″-(12″-methoxy-19″-norpodocarpa-4″(18″),8″,11″,13″-tetraene))ethyl]-1,3-dioxolane (**41**) (8 mg, 4%); and (v) 2-[2′ξ-cyano-2′-(14″-(19″-norpodocarpa-4″(18″),8″,11″,13″-tetraene))ethyl]-1,3-dioxolane (**42**) (43 mg, 24%) as a pale yellow oil (found: M^+, 337.2042. $C_{22}H_{27}NO_2$ calcd.: M, 337.2042). ν_{max} 2240 (CN), 1647, 1583, 1140, 1023 cm^{-1}. δ_H (2 diastereoisomers) 1.02, 1.03, 2s, $(H20'')_3$; 1.53, td, *J* 12.8, 4.8 Hz, H1″ax; 1.78, m, H2″ax, H2″eq, H6″ax; 2.01, m, $(H1')_1$, H3″ax, H6″eq; 2.19, bd,

J 13.1 Hz, H5″; 2.29, dd, *J* 12.8, 1.8 Hz, H1″eq; 2.39, m, H3″eq, $(H1')_1$; 2.78, ddd, *J* 17.1, 12.0, 7.4 Hz, H7″ax; 2.88, ddd, *J* 17.1, 6.6, 1.7 Hz, H7″eq; 3.93, 4.04, 2m, $(H4)_2$, $(H5)_2$; 4.20, 4.25, 2dd, *J* 10.5, 4.5 Hz, H2′; 4.60, 4.88, 2d, *J* 1.2 Hz, $(H18'')_2$; 5.05, 5.08, 2dd, *J* 5.8, 3.3 Hz, H2; 7.23, d, *J* 7.7 Hz, H13″; 7.33, t, *J* 7.7 Hz, H12″; 7.33, d, *J* 7.7 Hz, H11″. δ_C (2 diastereoisomers) 20.82, 20.91, C6″; 22.65, 22.78, C20″; 23.6, C2″; 26.30, 26.37, C7″; 28.2, C2′; 36.1, C3″; 38.20, 38.52, C1′; 38.64, 38.72, C1″; 39.7, C10″; 46.77, 46.86, C5″; 65.12, 65.28, C4, C5; 101.6, C2; 106.63, 106.72, C18″; 121.1, CN; 124.8, C13″; 125.8, C12″; 126.5, C11″; 132.1, C8″; 133.8, C14″; 148.5, C4″; 149.92, 150.04, C9″. *m/z* 337 (5, M^+), 322 (59, M–Me), 275 (84, M–$HOCH_2CH_2OH$), 260 (92, 275–Me), 249 (16, M–$H_2CCHOCH_2CH_2O$–H), 234 (32), 87 (100, M–diterpenoid–CHCN), 73 (82, M–diterpenoid–$CHCNCH_2$).

3.6. Cyclization of 2-[2′ξ-cyano-2′-(14″-(methyl 12″-oxopodocarp-8″(9″)-en-19″-oate))ethyl]-1,3-dioxolane (34)

A degassed solution of the enones **34** (0.10 g, 0.24 mmol) in THF (10 ml) and aqueous HCl (4 ml, 2 mol l^{-1}) was heated under reflux for 3 days. The cooled solution was diluted with ether. Workup and flash chromatography (hexanes/ether, 1:1) of the product gave methyl 15ξ-cyano-12-hydroxy-4α-methyl-18-nor-5α-androsta-8,11,13-triene-4β-carboxylate (**45**) (55 mg, 65%) as white crystals, m.p. 163–168°C (hexanes) (found: C, 74.6; H, 7.7; N, 3.9. $C_{22}H_{27}NO_3$ calcd.: C, 74.8; H, 7.7; N, 4.0%) (found: M^+, 353.1993. $C_{22}H_{27}NO_3$ calcd.: M, 353.1991). ν_{max} 3412 (OH), 2239 (CN), 1724 (C=O), 1604 (C=C), 1436 cm^{-1}. δ_H (major diastereoisomer) 1.02, s, 4α-Me; 1.05, td, *J* 13.6, 4.2 Hz, H3ax; 1.28, s, $(H19)_3$; 1.32, td, *J* 13.3, 3.9 Hz, H1ax; 1.48, dd, *J* 12.4, 1.3 Hz, H5; 1.59, dp, *J* 14.2, 3.0 Hz, H2eq; 1.95, qt, *J* 14.2, 3.8 Hz, H2ax; 1.98, qd, *J* 12.5, 5.6 Hz, H6ax; 2.12, bd, *J* 12.8 Hz, H1eq; 2.22, dd, *J* 12.5, 6.3 Hz, H6eq; 2.28, bd, *J* 13.6 Hz, H3eq; 2.41, dd, *J* 13.3, 9.1 Hz, $(H16)_1$; 2.51, m, $(H16)_1$, H7ax; 2.92, ddd, *J* 15.8, 8.8, 2.8 Hz, $(H17)_1$; 3.03, m, H7eq, $(H17)_1$; 3.68, s, CO_2CH_3; 3.93, dd, *J* 8.9, 2.5 Hz, H15; 5.69, bs, OH; 6.72, s, H11. δ_C (major diastereoisomer) 19.8, C2; 20.4, C6; 22.8, 4α-Me; 27.6, C7; 27.9, C16; 28.3, C19; 30.7, C17; 33.3, C15; 37.5, C3; 38.4, C10; 39.7, C1; 43.9, C4; 51.3, CO_2CH_3; 52.2, C5; 112.6, C11; 120.7, CN; 123.7, C8; 127.2, C13; 136.8, C14; 149.2, C12; 150.6, C9; 178.0, C=O. *m/z* 353 (43, M^+), 338 (14, M–Me), 278 (100,338-CH_3CO_2H), 251 (21, 278-HCN).

3.7. Cyclization of 2-[2′ξ-cyano-2′-(14″-(methyl 12″-oxopodocarp-8″(14″)-en-19″-oate))ethyl]-1,3-dioxolane (36)

A degassed solution of the enones **36** (30 mg, 0.07 mmol) in THF (8 ml) and aqueous HCl (0.5 ml, 2 mol l^{-1}) was heated under reflux for 5 h. Workup gave **45** (10 mg, 39%).

3.8. Cyclization of 2-[2′ξ-cyano-2′-(14″-(19″-methoxy-podocarp-8″(14″)-en-12″-one))ethyl]-1,3-dioxolane (35)

A degassed solution of the enones **35** (30 mg, 0.07 mmol) in THF (5 ml) and aqueous HCl (2 ml, 2 mol l^{-1}) was heated under reflux for 2 h. Workup and PLC (hexanes/ether, 1:1) gave 12-hydroxy-4β-methoxymethyl-4α-methyl-18-nor-5α-androsta-8,11,13-triene--15ξ-carbonitrile (**46**) (19 mg, 75%) (found: M^+, 339.2199. $C_{22}H_{29}NO_2$ calcd.: M, 339.2198). ν_{max} 3375 (OH), 2240 (CN), 1603, 1446, 1306, 1103 cm^{-1}. δ_H (major diastereoisomer) 1.02, td, *J* 13.4, 4.1 Hz, H3ax; 1.05, s, $(H19)_3$; 1.18, s, 4α-Me; 1.41, td, *J* 12.6, 3.5 Hz, H1ax; 1.45, dd, *J* 12.7, 1.6 Hz, H5; 1.70, m, H2ax, H2eq, H6ax; 1.87, bd, *J* 13.4 Hz, H3eq; 2.05, dd, *J* 13.3, 7.4 Hz, H6eq; 2.21, bd, *J* 12.5 Hz, H1eq; 2.50, m, $(H16)_2$, H7ax; 2.72–3.12, m, $(H17)_2$, H7eq; 3.25, 3.51, 2d, *J* 9.1 Hz, $(H19)_2$; 3.33, s, CH_2OCH_3; 4.01, dd, *J* 6.7, 6.4 Hz, H15; 4.71, bs, OH; 6.70, s, H11. δ_C (major diastereoisomer) 19.0, C2; 19.2, C6; 25.8, 4α-Me; 27.6, C7, C19; 28.1, C16; 30.5, C17; 33.5, C15; 39.9, C3; 38.0, C4; 39.3, C1; 39.4, C10; 50.9, C5; 59.4, CH_2OCH_3; 76.0, CH_2OCH_3; 111.9, C11; 120.4, CN; 124.3, C8; 126.5, C13; 137.0, C14; 150.1, C12; 151.3, C9. *m/z* 339 (63, M^+), 324 (5, M–Me), 292 (35, 324–MeOH), 224 (29), 212 (100), 198 (28).

3.9. 2-[2′ξ-Cyano-2′-(13″-(methyl podocarpa-8″,11″,13″-trien-19″-oate))ethyl]-1,3-dioxolane (31)

Butyllithium (0.49 ml, 1.00 mol l^{-1} in hexanes, 0.49 mmol) was added to a cooled (−78°C) solution of THF (2 ml) and diisopropylamine (69 μl, 0.49 mmol) and the mixture stirred for 30 min. A solution of the dioxolane **23** (62 mg, 0.49 mmol) in THF (0.2 ml) was added and the mixture was stirred for a further 30 min. HMPA (1 ml) was added, followed by a precooled (−78°C) solution of the complexes **31** [7] (0.10 g, 0.25 mmol) in THF (3 ml). The solution was stirred at −78°C for 3.5 h. A solution of iodine (0.3 g, 1.18 mmol) in THF (2.5 ml) precooled to −78°C was added dropwise, and the mixture was allowed to warm to room temperature overnight. Workup and PLC (hexanes/ether, 3:2, 3 sweeps) gave 2-[2′ξ-cyano-2′-(13″-(methyl podocarpa-8″,11″,13″-trien-19″-oate))ethyl]-1,3-dioxolane (**10**) (84 mg, 87%) as white crystals, m.p. 112–114°C (hexanes) (found: C, 72.2; H, 7.7; N, 3.6. $C_{24}H_{31}NO_4$ calcd.: C, 72.5; H, 7.9; N, 3.5%) (found: M^+, 397.2258. $C_{24}H_{31}NO_4$ calcd.: M, 397.2253). ν_{max} 2242 (CN), 1724 (C=O), 1141 cm^{-1}. δ_H (C_6D_6) 0.88, td, *J* 13.4, 4.1 Hz, H3″ax; 1.00, s, $(H20'')_3$; 1.10, s, $(H18'')_3$; 1.18, td, *J* 12.0, 3.7 Hz, H1″ax; 1.26, 1.27, 2dd, *J* 12.0, 2.0 Hz, H5″ (diastereoisomers); 1.50, dp, *J* 14.8, 3.1 Hz, H2″eq; 1.93, m, H6″ax, H2″ax; 2.02, m, $(H1')_2$, H3″eq; 2.20, dd,

J 13.7, 9.7 Hz, H6″eq; 2.32, bd, *J* 13.2 Hz, H1″eq; 2.51, ddd, *J* 17.2, 13.4, 6.9 Hz, H7″ax; 2.62, d, *J* 17.1 Hz, H7″eq; 3.31, s, CO_2CH_3; 3.46, 3.49, m, $(H4)_2$, $(H5)_2$; 3.83, dd, *J* 9.7, 5.0 Hz, H2′; 4.87, t, *J* 4.5 Hz, H2; 6.86, 6.88, 2d, *J* 1.9 Hz, H14″ (diastereoisomers); 6.95, 6.97, 2dd, *J* 8.3, 1.9 Hz, H12″ (diastereoisomers); 7.04, d, *J* 8.3 Hz, H11″. δ_C 20.3, C2″; 21.2, C6″; 23.1, C20″; 28.4, C18″; 32.0, C7″; 32.3, C2′; 37.8, C3″; 38.5, C10″; 39.4, C1″; 44.0, C4″; 50.8, CO_2CH_3; 52.6, C5″; 64.9, 65.1, C4, C5; 101.7, C2; 120.8, CN; 125.1, C14″; 126.7, C12″; 128.1, C11″; 133.2, C8″; 136.5, C13″; 148.2, C9″; 177.1, C=O. *m/z* 397 (4, M^+), 382 (3, M–Me), 335 (15, M–$HOCH_2CH_2OH$)), 322 (38), 320 (20, 335-Me), 311 (10, M–$H_2CCHOCH_2CH_2O$ + H), 87 (100, M–diterpenoid–CHCN), 73 (37, M–diterpenoid–CHCN-CH_2).

One run of the above experiment also gave 2-[2′-(13″-(methyl podocarpa-8″,11″,13″-trien-19″-oate)2′-0 × 8)ethyl]-1,3-dioxolane (**11**) (15%) (found: M^+, 386.2090. $C_{23}H_{30}O_5$ calcd.: M, 386.2093). ν_{max} 1725 (C=O ester), 1682 (C=O ketone), 1603, 1565 (C=C), 1138 cm^{-1}. δ_H 1.04, s, $(H20'')_3$; 1.09, td, *J* 13.6, 4.3 Hz, H3″ax; 1.29, s, $(H18'')_3$; 1.39, td, *J* 13.3, 4.1 Hz, H1″ax; 1.53, dd, *J* 12.3, 1.6 Hz, H5″; 1.64, dp, *J* 12.0, 2.9 Hz, H2″eq; 1.98, qd, *J* 13.8, 5.5 Hz, H6″ax; 2.01, qt, *J* 12.1, 4.0 Hz, H2″ax; 2.21, dd, *J* 13.9, 6.1 Hz, H6″eq; 2.24, m, H3″eq; 2.28, dd, *J* 13.2, 3.3 Hz, H1″eq; 2.82, ddd, *J* 16.9, 12.6, 6.2 Hz, H7″ax; 2.98, dd, *J* 16.9, 4.2 Hz, H7″eq; 3.29, d, *J* 5.0 Hz, $(H1')_2$; 3.67, s, CO_2CH_3; 3.90, 4.00, 2m, $(H4)_2$, $(H5)_2$; 5.43, t, *J* 5.0 Hz, H2; 7.35, d, *J* 8.4 Hz, H11″; 7.65, s, H14″; 7.70, dd, *J* 8.4, 1.6 Hz, H12″. δ_C 19.8, C2″; 20.8, C6″; 22.7, C20″; 28.5, C18″; 32.0, C7″; 37.5, C3″; 38.9, C10″; 39.1, C1″; 43.3, C1′; 44.0, C4″; 51.3, CO_2CH_3; 52.4, C5″; 65.0, C4, C5; 101.5, C2; 125.7, 126.0, C12″, C14″; 129.3, C11″; 134.2, C8″; 135.8, C13″; 153.9, C9″; 177.7, C=O ester; 196.3, C=O ketone. *m/z* 386 (18, M^+), 371 (4, M–Me), 343 (21), 311 (13, 371-CH_3CO_2H), 299 (40, M–$H_2CCHOCH_2CH_2O$), 283 (45, 311-CO), 73 (100, M–diterpenoid–$COCH_2$).

3.10. Attempted cyclization of 2-[2′ξ-cyano-2′-(14″-(methyl podocarpa-8″,11″,13″-trien-19″-oate))ethyl]-1,3-dioxolane (5)

Titanium(IV) chloride (17 μl, 0.15 mmol) in dichloromethane (0.1 ml) was added slowly to a cooled (−78°C) solution of the dioxolanes **5** (50 mg, 0.13 mmol) in dichloromethane (4 ml). After 5 min the cooling bath was removed and the mixture was stirred for 1 h before more titanium(IV) chloride (14 μl, 0.13 mmol) in dichloromethane (0.1 ml) was added. After 30 min the mixture was cooled to 0°C, and aqueous HCl (2 mol l^{-1}) was added. Workup and PLC (hexanes/ether, 3:7, 2 sweeps) gave 1-[3ξ-cyano-3-(14′-(methyl podocarpa-8′,11′,13′-trien-19′-oate))]propanal (13) (14 mg, 32%) (found: M^+, 353.2006. $C_{22}H_{27}NO_3$ calcd.: M, 353.1991). ν_{max} 2242 (CN), 1725 (C=O ester and aldehyde), 1451, 1149, 733 cm^{-1}. δ_H (200 MHz) 1.05, s, $(H20')_3$; 1.29, s, $(H18')_3$; 3.67, s, CO_2CH_3; 4.50, dd, *J* 9.1, 4.9 Hz, H3; 7.25, m, H11′, H12′, H13′; 9.12, s, H1. δ_C (50 MHz) 19.9, C2′; 20.5, C6′; 22.9, C20′; 26.2, C3; 28.4, C18′; 28.6, C7′; 37.3, C3′; 38.8, C10′; 39.7. C1′; 43.9, C4′; 47.3, C2; 51.3, CO_2CH_3; 51.7, C5′; 120.2 CN; 124.5, C13′; 126.5, C12′; 126.7, C11′; 132.1, C8′; 132.6, C14′; 149.8, C9′; 177.6, C=O ester, 196.8, C=O aldehyde. *m/z* 353 (6, M^+), 338 (21, M–Me), 321 (5), 293 (6), 278 (100, 321-$OCHCH_2$), 260 (40), 41 (42).

3.11. Attempted cyclization of 2-[2′ξ-cyano-2′-(13″-(methyl podocarpa-8″,11″,13″-trien-19″-oate))ethyl]-1,3-dioxolane (11)

Use of the above reaction conditions for the dioxolanes **11** gave 1-[3ξ-cyano-3-(13′-(methyl podocarpa-8′,11′,13′-trien-19′-oate))]propanal (**14**) (25%) (found: M^+, 353.1972. $C_{22}H_{27}NO_3$ calcd.: M, 353.1991). ν_{max} 2243 (CN), 1726 (C=O ester and aldehyde), 1435, 1238, 736 cm^{-1}. δ_H (200 MHz) 1.01, s, $(H20')_3$; 1.28, s, $(H18')_3$; 3.66, s, CO_2CH_3; 4.19, dd, *J* 7.4, 6.5 Hz, H3; 7.03, s, H14′; 7.09, bd, *J* 8.2 Hz, H12′; 7.28, d, *J* 8.2 Hz, H11′δ_C (50 MHz) 19.9, C2′; 20.7, C6′; 22.9, C20′; 28.5, C18′; 29.8, C3; 31.9, C7′; 37.5, C3′; 38.4, C10′; 39.3, C1′; 44.0, C4′; 48.5, C2; 51.3, CO_2CH_3; 52.6, C5′; 121.5, CN; 124.7, C14′; 126.8, C12′; 127.8, C11′; 131.2; C8′; 136.7, C13′; 148.6, C9′; 177.7, C=O ester; 196.6, C=O aldehyde. *m/z* 353 (12, M^+), 338 (21, M–Me), 321 (5), 294 (5), 278 (100, 321-$OCHCH_2$), 260 (7).

3.12. Reductive decyanation of 2-[2′ξ-cyano-2′-(14″-(methyl podocarpa-8″,11″,13″-trien-19″-oate))ethyl]-1,3-dioxolane (5)

A solution of the dioxolanes **5** (30 mg, 0.08 mmol) in THF (1 ml) and 2-propanol (1 drop) was added to cooled (−78°C) redistilled (from sodium) liquid ammonia (10 ml). Sodium was added in very small portions in order to just maintain the blue colour. After 20 min solid ammonium chloride was added, and liquid ammonia allowed to evaporate. Workup and PLC (hexanes/ether, 2:3) gave 2-[2′-(14″-(podocarpa-8″,11″,13″-trien-19″-oic acid))ethyl]-1,3-dioxolane (**9**) (24 mg, 89%) as white crystals, m.p. 106–109°C (hexanes) (found: C, 73.5; H, 8.2. $C_{22}H_{30}O_4$ calcd.: C, 73.7; H, 8.4%) (found: M^+, 358.2145. $C_{22}H_{30}O_4$ calcd.: M, 358.2144). ν_{max} 3500-2500 (OH), 1695 (C=O), 1582, 1469 cm^{-1} (C=C). δ_H 1.08, td, *J* 13.5, 4.1 Hz, H3″ax; 1.14, s, $(H20'')_3$; 1.34, s, $(H18'')_3$; 1.36, td, *J* 13.5, 4.0 Hz; 1.53, d, *J* 11.4 Hz, H5″; 1.61, bd, *J* 14.0 Hz, H2″eq; 1.99, m, $(H1')_2$, H6″ax, H2″ax; 2.24, m, H1″eq, H3″eq, H6″eq; 2.64, ddd, *J* 14.0, 10.5, 5.8 Hz, H7″ax; 2.68, dd, *J* 10.8, 8.2 Hz, H2′; 2.94, dd, *J* 14.0, 4.4 Hz, H7″eq; 3.89, 4.01, 2m,

$(H4)_2$, $(H5)_2$; 4.94, t, *J* 4.7 Hz, H2; 6.98, d, *J* 7.3 Hz, H13″; 7.09, *J* 7.3 Hz, H12″; 7.16, d, *J* 7.3 Hz, H11″. δ_C 20.0, C2″; 20.7, C6″; 23.1, C20″; 27.1, C7″; 28.6, C18″; 28.8, C2′; 35.3, C1′; 37.2, C3″; 38.9, C10″; 39.7, C1″; 43.8, C4″; 52.3, C5″; 64.9, C4, C5; 104.2, C2; 123.7, C13″; 125.69, C12″; 125.74, C11″; 133.4, C8″; 139.3, C14″; 148.4, C9″; 183.9, C=O. *m/z* 358 (2, M^+), 313 (2, $M-CO_2-H$), 296 (100, $M-HOCH_2CH_2OH$), 270 (8), 255(7), 235 (24), 73 (42, M–diterpenoid–C_2H_4).

3.13. Reductive decyanation of 2-[2′ξ-cyano-2′-(13″-(methyl podocarpa-8″,11″,13″-trien-19″-oate))ethyl]-1,3-dioxolane (10)

Use of the above reaction conditions for the dioxolanes **10**, but at −78°C for 1 h, gave 2-[2′-(13″-(podocarpa-8″,11″,13″-trien-19″-oic acid))ethyl]-1,3-dioxolane (**12**) (12 mg, 44%) (found: M^+, 358.2132. $C_{22}H_{30}O_4$ calcd.: M, 358.2144). ν_{max} 3500-2500 (OH), 1694 (C=O), 1138 cm^{-1}. δ_H 1.09, td, *J* 13.4, 3.9 Hz, H3″ax; 1.11, s, $(H20'')_3$; 1.33, s, $(H18'')_3$; 1.37, td, *J* 13.6, 4.2 Hz, H1″ax; 1.55, dd, *J* 12.1, 1.5 Hz, H5″; 1.61, bd, *J* 14.3 Hz, H2″eq; 1.65–2.20, m, OH, H6″ax, H2″ax, $(H1')_2$, H3″eq, H6″eq; 2.27, bd, *J* 12.6 Hz, H1″eq; 2.67, dd, *J* 8.1, 6.0 Hz, H2′; 2.77, ddd, *J* 16.9, 12.3, 6.1 Hz, H7″ax; 2.87, dd, *J* 16.9, 4.3 Hz, H7″eq; 3.87, 3.99, 2m, $(H4)_2$, $(H5)_2$; 4.90, t, *J* 4.7 Hz, H2; 6.88, s, H14″; 6.95, bd, *J* 8.2 Hz, H12″; 7.16, d, *J* 8.2 Hz, H11″. δ_C 19.9, C2″; 20.9, C6″; 23.1, C20″; 28.7, C18″; 29.5, C2′; 31.9, C7″; 35.4, C1′; 37.4, C3″; 38.3, C10″; 39.3, C1″; 43.9, C4″; 52.8, C5″; 64.9, C4, C5; 104.0, C2; 125.6, 125.9, C12″, C14″; 128.8, C11″; 135.3, C8″; 138.4, C13″; 145.6, C9″; 183.6, C=O. *m/z* 358 (14, M^+), 343 (5, M–Me), 296 (12), 281 (23, 296-Me), 272 (17, $M-H_2CCHOCH_2CH_2O+H$), 254 (21), 87 (44, M–diterpenoid–CH_2), 73 (100, M–diterpenoid–C_2H_4).

3.14. Reduction of 2-[2′ξ-cyano-2′-(14″-(19″-methoxypodocarp-13″-en-12″-one))ethyl]-1,3-dioxolane (33)

A solution of dioxolanes (**33**) (30 mg, 0.08 mmol) in methanol (5 ml) was treated with hydrogen over 10% Pd/C (5 mg) under pressure (4 atm) for 60 h. Filtration through Celite gave 2-[2′ξ-cyano-2′-(14″-(19″-methoxypodocarpan-12″-one))ethyl]-1,3-dioxolane (**47**) (29 mg, 97%) (found: M^+, 403.2721. $C_{24}H_{37}NO_4$ calcd.: M, 403.2723). ν_{max} 2238 (CN), 1712 (CO), 1449, 1144, 1010 cm^{-1}. δ_H (major diastereoisomer) 0.88, s, $(H18'')_3$; 0.96, s, $(H20'')_3$; 3.20, 3.39, 2d, *J* 9.1 Hz, $(H19'')_2$; 3.30, s, CH_2OCH_3; 3.32, m, H2′; 3.91, 4.02, 2m, $(H4)_2$, $(H5)_2$; 5.05, dd, *J* 6.2, 2.7 Hz, H2. δ_C (major diastereoisomer) 14.4, C20″; 18.4, C2″; 21.3, C6″; 23.1, C18″; 27.6, C2′; 30.3, 31.1, 36.2, 38.8, 41.0, 42.7, C7″, C3″, C1″, C1′, C11″, C13″; 36.6, C8″; 37.3, C4″; 37.5, C10″; 44.9, C14″; 54.5, C5″; 55.4, C9″; 59.4, CH_2OCH_3; 65.1, 65.3, C4, C5; 76.2, CH_2OCH_3; 101.7, C2; 120.7, CN; 209.8, C=O. *m/z* 403 (10, M^+), 388 (2, M–Me), 358 (100, $M-CO_2-H$), 340 (15), 296 (38), 73 (M–diterpenoid–$CH(CN)CH_2$), 45 (55, $CH_2{=}OCH_3^+$).

3.15. Reduction of 2-[2′ξ-cyano-2′-(14″-(methyl 12″-oxopodocarpa-13″-en-19″-oate))ethyl]-1,3-dioxolane (32)

A solution of dioxolanes **32** (16 mg, 0.04 mmol) in methanol (5 ml) was treated with hydrogen over 10% Pd/C (5 mg) under pressure (4 atm) for 60 h. Filtration through Celite gave 2-[2′ξ-cyano-2′-(14″-(methyl 12″-dimethoxypodocarp-19″-oate))ethyl]-1,3-dioxolane (**48**) (17 mg, 96%) (found: M^+, 463.2931. $C_{26}H_{41}NO_6$ calcd.: M, 463.2934). ν_{max} 2237 (CN), 1722 (CO), 1464, 1373, 1233, 1150, 1093 cm^{-1}. δ_H 0.87, s, $(H20'')_3$; 0.97, td, *J* 13.5, 3.9 Hz, H1″ax; 1.14, s, $(H18'')_3$; 2.65, m, H2′; 3.11, 3.23, 2s, 2OMe; 3.64, s, CO_2CH_3; 3.91, 4.03, m, H4, H5; 5.09, dd, *J* 6.5, 3.0 Hz, H2. δ_C 19.5, C2″; 19.7, C6″; 20.0, C20″; 23.3, C7″; 27.7, C11″; 28.6, C18″; 30.1, C2′; 31.7, C13″; 33.5, C8″; 34.1, C1′; 36.8, C3″; 37.2, C4″; 38.5, C1″; 39.5, C14″; 44.1, C10″; 46.2, C9″; 47.3, 47.6, 20Me; 48.3, C5″; 51.3, CO_2CH_3; 65.0, 65.2, C4, C5; 100.5, C12″; 102.0, C2; 121.3, CN; 177.8, C=O. *m/z* 463 (3, M^+), 448 (1, M–Me), 432 (18, M–OMe), 416 (2, 448-MeOH), 372 (10, 432-CH_3CO_2H), 343 (41, 372-CHO(CH_2)$_3$O), 337 (100, M–(NC)CHCH$_2$CHO(CH$_2$)$_2$O), 305 (40, 337-MeOH).

3.16. Cyclopentaannulation of 2-[2′ξ-cyano-2′-(14″-(19″-methoxypodocarpan-12″-one))ethyl]-1,3-dioxolane (47)

A solution of the dioxolanes **47** (27 mg, 0.07 mmol) in THF (3 ml) and aqueous HCl (1.5 ml, 2 mol l^{-1}) was heated under reflux for 4 h. Workup and PLC (hexanes/ether, 1 : 1) gave 4β-methoxymethyl-4α-methyl-18-nor-12-oxo-5α-androsta-13(17)-ene-15ξ-carbonitrile (**49**) (20 mg, 88%) (found: $M^{+\cdot}$, 341.2359. $C_{22}H_{31}NO_2$ calcd.: M, 341.2355). ν_{max} 2241 (CN), 1686 (CO enone), 1624 (C=C), 1446, 1252, 1109 cm^{-1}. δ_H (major diastereoisomer) 0.85, s, 4α-Me; 0.98, s, 10-Me; 3.17, 3.43, 2d, *J* 9.0 Hz, 4β-CH_2; 3.30, s, CH_2OCH_3; 6.45, q, *J* 2.2 Hz, H17. δ_C (major diastereoisomer) 14.5, 10-Me; 18.4, C2; 20.9, C6; 27.9, 4α-Me; 32.5, C7; 33.5, C15; 36.1, C11; 36.8, C8; 37.0, C4; 37.7, C10; 39.1, C11; 40.2, C1; 41.7, C3; 52.2, C14; 55.4, C5; 56.6, C9; 59.4, CH_2OCH_3; 76.0, CH_2OCH_3; 121.5, CN; 133.6, C17; 141.9, C13; 198.0, C=O. *m/z* 341 (2, M^+), 326 (2, M–Me), 309 (5, M–MeOH), 296 (100, $M-CO_2-H$), 278 (12), 214 (15).

3.17. Cyclopentaannulation of 2-[2′ξ-cyano-2′-(14″-(methyl 12″-dimethoxypodocarp-19″-oate))ethyl]-1,3-dioxolane (48)

A solution of the dioxolane **48** (17 mg, 0.04 mmol) in THF (5 ml) and aqueous HCl (1 ml, 2 mol l^{-1}) was

heated under reflux for 6 h. Workup and PLC (hexanes/ether, 3 : 7) gave methyl 15ξ-cyano-4α-methyl-18-nor-12-oxo-5α-androst-13(17)-en-4β-oate (**50**) (11 mg, 85%) (found: $M^{+\cdot}$, 355.2146. $C_{22}H_{29}NO_3$ calcd.: M, 355.2147). ν_{max} 2238 (CN), 1725 (CO ester), 1683 (CO enone), 1638 (C=C), 1444, 1228, 1158 cm^{-1}. δ_H 0.96, td, *J* 13.5, 4.1 Hz, H1ax; 0.97, s, $(H19)_3$; 1.11, m, H2eq, H3ax; 1.17, s, 4α-Me; 1.34, dd, *J* 12.4, 3.5 Hz, H5; 1.39, m, H3eq; 1.47, dp, *J* 14.0, 3.0 Hz, H6ax; 1.77, ddd, *J* 11.0, 6.5, 3.1 Hz, H9; 1.95, m, H2ax, H6eq, H7ax, H7eq; 2.19, ddd, *J* 13.4, 3.1, 1.6 Hz, H1eq; 2.37, dd, *J* 18.8, 11.9 Hz, H11ax; 2.51, m, H8; 2.56, dd, *J* 18.7, 6.7, Hz, H11eq; 2.74, ddt, *J* 18.5, 8.8, 2.6 Hz, H16eq; 3.29, m, H14; 3.42, q, *J* 9.2 Hz, H15; 3.67, s, CO_2CH_3; 6.27, q, *J* 2.2 Hz, H17. δ_C 19.3, C6; 20.2, 10-Me; 21.6, C2; 23.0, C7; 28.2, C15; 28.6, 4α-Me; 35.6, C8; 36.2, C3; 37.9, C16; 38.0, C4; 38.2, C11; 38.5, C1; 44.0, C10; 47.3, C5; 48.5, C9; 51.4, CO_2CH_3; 51.6, C14; 120.1, CN; 132.1, C17; 141.9, C13; 177.7, C=O ester; 199.5, C=O enone. *m/z* 355 (55, M^+), 340 (6, M–Me), 323 (19, M–MeOH), 305 (3, 323-H_2O), 296 (100, 340-CO_2), 281 (70, 296-Me).

3.18. Attempted reduction of 2-[2′-(14″-(12″-methoxypodocarpa-8″,11″,13″-trien-19″-oic acid))ethyl]-1,3-dioxolane (15)

(A) Lithium (5 mg, 0.71 mmol) was added to dry ethylamine (2 ml) and a solution of the dioxolane **15** (17 mg, 0.04 mmol) in THF (1 ml) was added, followed during 2h by further portions of lithium (50 mg, 7.1 mmol) to maintain the blue colour. *t*-Butyl alcohol and ammonium chloride were then added, and ethylamine was removed. Dilute aqueous acetic acid was added and the solution was extracted with dichloromethane. Workup and PLC (hexanes/ether, 3 : 7) gave 2-[2′-(14″-(12″-hydroxypodocarpa-8″,11″,13″-trien-19″-oic acid))-ethyl]-1,3-dioxolane (**16**) (11 mg, 69%) (found: $M^{+\cdot}$, 374.2093. $C_{22}H_{30}O_5$ calcd.: M, 374.2093). ν_{max} 3500-2500 (OH acid), 3350 (OH phenol), 1695 (C=O), 1609, 1456 (C=C), 1140 cm^{-1}. δ_H 1.05, td, *J* 13.6, 4.2 Hz, H3″ax; 1.10, s, $(H20'')_3$; 1.32, s, $(H18'')_3$; 1.37, td, *J* 13.5, 4.8 Hz, H1″ax; 1.49, d, *J* 11.9 Hz, H5″; 1.59, bd, *J* 13.5 Hz, H2″eq; 1.93, m, H6″ax, H2″ax, $(H1')_2$; 2.20, m, H3″eq, H6″eq; 2.23, bd, *J* 13.7 Hz, H1″eq; 2.51, ddd, *J* 16.5, 12.9, 6.3 Hz, H7″ax; 2.65, dd, *J* 10.8, 8.3 Hz, H2′; 2.84, dd, *J* 16.5, 4.5 Hz, H7″eq; 3.89, 4.02, 2m, $(H4)_2$, $(H5)_2$; 4.94, t, *J* 4.6 Hz, H2; 6.51, d, *J* 2.4 Hz, H11″; 6.62, d, *J* 2.4 Hz, H13″. δ_C 20.0, C2″; 20.8, C6″; 23.0, C20″; 27.1, C7″; 28.2, C2″; 28.6, C18″; 33.8, C1′; 37.2, C3″; 39.0, C1″; 39.7, C10″; 43.8, C4″; 52.3, C5″; 64.9, C4, C5; 104.1, C2; 110.1, C13″; 113.4, C11″; 125.6, C8″; 140.8, C14″; 150.0, C9″; 153.5, C12″; 183.3, C=O. *m/z* 374 (22, M^+), 312 (100, M–$HOCH_2CH_2OH$), 297 (8, 312-Me), 288 (58, M–$H_2CCHOCH_2CH_2O$ + H), 87 (95, M–diterpenoid–CH_2), 73 (43, M–diterpenoid–C_2H_4).

(B) A solution of the dioxolane (**15**) (45 mg, 0.12 mmol) and *t*-butyl alcohol (1.5 ml) in THF (1.5 ml) was added to liquid ammonia (3 ml). Lithium (33 mg, 4.64 mmol) was added in portions, and after 5.5 h solid ammonium chloride was added. Liquid ammonia was allowed to evaporate and the residue was acidified with acetic acid. The mixture was extracted with dichloromethane. PLC (hexanes/ether, 1 : 1, 4 sweeps) gave (i) a mixture of starting material and 2-[2′-(14″-(12″-methoxypodocarpa-8″(14″),12″-dien-19″-oic acid))ethyl]-1,3-dioxolane (**28**) and olefinic regioisomer(s) (26 mg) (found: $M^{+\cdot}$, 390.2394. $C_{23}H_{34}O_5$ calcd.: M, 390.2406); (ii) a mixture of 2-[2′-(14″-(12″-methoxypodocarpa-8″(14″),12″-dien-19″-oic acid))ethyl]-1,3-dioxolane (**28**) and olefinic regioisomer(s); 2-[2′-(14″-(12″-methoxypodocarp-8″(14″)-en-19″-oic acid))ethyl]-1,3-dioxolane (**43**) (found: $M^{+\cdot}$, 392.2534. $C_{23}H_{36}O_5$ calcd.: M, 392.2563); and 2-[2′-(14″-(podocarp-8″(14″)-en-19″-oic acid))ethyl]-1,3-dioxolane (**44**) (4 mg) (found: $M^{+\cdot}$, 362.2426. $C_{22}H_{34}O_4$ calcd.: M, 362.2457); and (iii) 2-[2′-(14″-(podocarp-8″(14″)-en-19″-oic acid))ethyl]-1,3-dioxolane (**44**) (7 mg) (found: $M^{+\cdot}$, 362.2462. $C_{22}H_{34}O_4$ calcd.: M, 362.2457). ν_{max} 3500–2300 (OH), 1694 (C=O), 1469, 1408, 1139 cm^{-1}. δ_H 0.87, s, $(H20'')_3$; 1.25, s, $(H18'')_3$; 3.85, 3.98, 2m, $(H4)_2$, $(H5)_2$; 4.83, t, *J* 4.6 Hz, H2. δ_C 16.9, C20″; 19.4, C2″; 20.6, C6″; 22.6, C13″; 24.4, C12″; 27.1, C11″; 28.5, C18″; 28.8, C7″; 30.1, C1′; 31.1, C2′; 36.8, C3″; 37.3, C1″; 38.9, C10″; 39.4, C9″; 43.6, C4″; 53.5, C5″; 64.81, 64.85, C4, C5; 105.1, C2; 128.9, C8″; 139.2, C14″; 184.1, C=O. *m/z* 362 (13, M^+), 300 (19, M–$HOCH_2CH_2OH$), 285 (11, 300-Me), 274 (100, M–$H_2CCHOCH_2CH_2O$–H), 259 (51, 274-Me), 99 (45), 73 (43, M–diterpenoid–C_2H_4).

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