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Cyclopentaannulation of podocarpic acid derivatives *via* (η^6-arene)tricarbonylchromium(0) complexes; ring D modification

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Abstract

Functionalization of the (η^6-arene)tricarbonylchromium(0) complexes of some podocarpic acid (**1**) derivatives has been achieved *via* addition-oxidation methodology. The resulting decomplexed products underwent Lewis acid-mediated cyclopentaannulation to give ring-C aromatic androstane analogues in high yield. The D rings of these steroidal analogues were modified by both oxidation and reduction sequences, becoming structurally similar to some of the C15- or C17-oxygenated naturally occurring steroids.

Key words: Chromium; Carbonyl; Diterpenoid; Steroid synthesis

1. Introduction

Earlier we reported [1] the reactions of a pentacarbonylcarbene chromium(0) complex of the diterpenoid methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (**2**) with some alkynes, the reaction with diphenylacetylene leading to ring-C aromatic androstane analogues in moderate yield. Formation of the tricarbonyl(η^4-diene)iron(0) complexes from the 1,4-dienes obtained by Birch reduction of the methyl ether **4** or the alcohol **5**, with the aim of functionalizing the derived η^5-dienyl complexes, was not useful synthetically [2]. The diastereoisomeric (η^6-arene)tricarbonylchromium(0) complexes of methyl podocarpa-8,11,13-trien-19-oate (**3**) were prepared and their nucleophilic addition-oxidation reactions with two 2-lithio-1,3-dithianes gave low yields of C13″-substituted products [3]. In contrast, the addition-oxidation reactions of the (η^6-arene)tricarbonylchromium(0) complexes **19** with some organolithium reagents gave mostly C14″-substituted products. Attempts to form cyclopentaannulated derivatives from some of these products were unsuccessful [4]. Recently, the syntheses of a number of ring-C aromatic androstane analogues from reaction of an alkene with an η^2-7-oxotetracarbonylmanganese(I) complex derived from podocarpic acid (**1**) derivatives, and from reaction of an alkene or alkyne with a diterpenoid η^2-13-acyltetracarbonylmanganese(I) complex, were achieved in high yield [5–7]. We report here studies of the reactions of the (η^6-arene)tricarbonylchromium(0) complexes **19** and **20** with nitrile-stabilized anions, together with the successful Lewis acid-mediated cyclopentaannulation of the products. The D rings of these ring-C aromatic androstane analogues were further modified.

2. Results and discussion

The addition of a three-carbon moiety across C13 and C14 of a podocarpic acid derivative (*e.g.* **2** or **4**) would afford a ring-C aromatic steroidal skeleton. Nitrile-stabilized anions have been shown [8] to be most successful in aromatic nucleophilic substitution reactions with (η^6-arene)tricarbonylchromium(0) complexes, and thus a three-carbon moiety was chosen so that such an anion could be generated at one end of the chain. The other terminal carbon was required to be potentially electrophilic in order subsequently to append to the nucleophilic aromatic ring. 2-(2′-Cyanoethyl)-1,3-dioxolane (**25**) [4,9] was selected because it has the required reactivity types at both termi-

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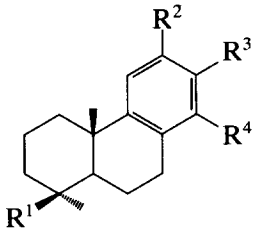
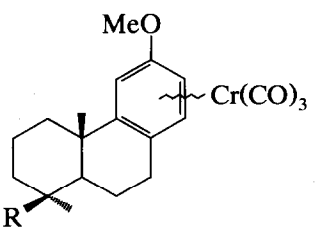
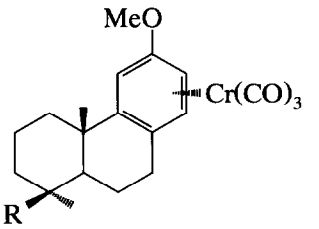
nal carbons 2 and 2'. The potentially electrophilic carbon, a protected aldehyde, would be tolerated by the metal-mediated addition-oxidation process. The dioxolane **25**, after attachment to the diterpenoid tricarbonylchromium(0) complex and then decomplexation, should cleave under acidic conditions to form an oxygen-stabilized carbocation, aromatic electrophilic substitution then giving the desired cyclopentaannulation.



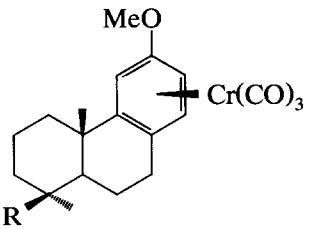
(**1**: $R^1 = CO_2H$, $R^2 = OH$, $R^3 = H$, $R^4 = H$
2: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = H$, $R^4 = H$
3: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = H$, $R^4 = H$
4: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = H$, $R^4 = H$
5: $R^1 = CH_2OH$, $R^2 = H$, $R^3 = H$, $R^4 = H$
6: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = H$, $R^4 = CH(CN)CH_2\overline{CHO(CH_2)O}$
7: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = CH(CN)CH_2\overline{CHO(CH_2)_2O}$, $R^4 = H$
8: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = H$, $R^4 = CH(CN)CH_2\overline{CHO(CH_2)_2O}$
9: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = CH(CN)CH_2\overline{CHO(CH_2)_2O}$, $R^4 = H$
10: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = H$, $R^4 = OH$
11: $R^1 = CH_2OMe$, $R^2 = OH$, $R^3 = I$, $R^4 = H$
12: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = H$, $R^4 = CH(CN)CH_2\overline{CHO(CH_2)_3O}$
13: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = CH(CN)CH_2\overline{CHO(CH_2)_3O}$, $R^4 = H$
14: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = H$, $R^4 = CH(CN)CH_2CHO$
15: $R^1 = CO_2H$, $R^2 = OMe$, $R^3 = H$, $R^4 = (CH_2)_2\overline{CHO(CH_2)_2O}$,
16: $R^1 = CO_2H$, $R^2 = OMe$, $R^3 = (CH_2)_2\overline{CHO(CH_2)_2O}$, $R^4 = H$
17: $R^1 = CH_2OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = (CH_2)_2\overline{CHO(CH_2)_2O}$
18: $R^1 = CH_2OH$, $R^2 = OMe$, $R^3 = (CH_2)_2\overline{CHO(CH_2)_2O}$, $R^3 = H$)



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

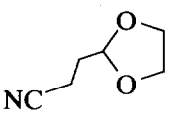


(**21**: R = CO_2Me
22: R = CH_2OMe)

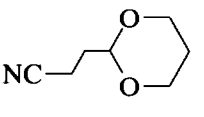


(**23**: R = CO_2Me
24: R = CH_2OMe)

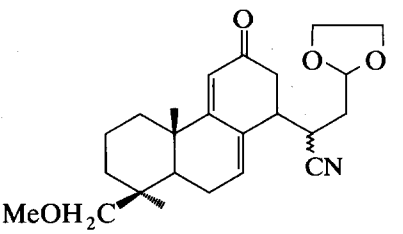
Tricarbonyl[(8,9,11,12,13,14-η)-methyl 12-methoxypodocarpa-8,11,13-trien-19-oate]chromium(0) (**19**) was prepared in refluxing (39 h) dibutyl ether/tetrahydrofuran (THF) (12:1) [10] as a mixture (4:1) (90%) of α (**21**) and β (**23**) diastereoisomers. Tricarbonyl[(8,9,11,12,13,14-η)-12,19-dimethoxypodocarpa-8,11,13-triene]-chromium(0) (**20**) was obtained as a mixture (5:1) (91%) of α(**22**) and β (**24**) diastereoisomers under similar conditions.



(**25**)



(**26**)



(**27**)

The addition-oxidation (iodine) reaction between the lithio anion derived from **25** and a mixture (4:1) of **21** and **23** produced an inseparable mixture (9:1) (93%) of **6** and its C13''-substituted regioisomer **7**. A similar reaction between the lithio anion of **25** and a mixture (5:1) of **22** and **24** produced a mixture (9:1) (79%) of the 19''-methoxymethyl analogues (of **6** and **7**) **8** and **9**. The results and reaction conditions are summarized in Table 1.

TABLE 1. Reaction of $Cr(CO)_3$ complexes with the anion of **25**[a-c]

Complexes	Yield (%)	C14″/C13″	C14″ diast.	C13″ diast.
21/23, 4:1	91	9:1	2:1	6:5
22/24, 5:1	76	9:1	2:1	6:5

[a] The solvent was THF/HMPA, 4:1; [b] The ratio of carbanion/complexes was 2:1; [c] −78°C.

From both sets of complexes the desired C14″-substituted regioisomer (kinetically favoured at −78°C/hexamethylphosphoric triamide (HMPA)) was the dominant product (^{1}H NMR spectra). The adducts contain a newly introduced stereocentre at C2′, and it is interesting to note that the diastereoisomeric ratios (2:1) for the C14″-substituted products **6** and **8** differ from those (6:5) for the C13″-substituted products **7** and **9**. Although it was previously reported [4] that 100% regioselectivity (C14″ substitution) was obtained in the reaction of the lithio anion derived from **25** with complexes **19**, detailed analysis of 400 MHz ^{1}H NMR spectra in the present work revealed that this was not correct; the actual C14″/C13″ ratios were 4.1:1.

While investigating the addition-oxidation reaction between lithioacetonitrile and complexes **19**, we reported [4] that adding HMPA to the reaction mixture after addition of **19** decreased the yield of the desired product to zero at the expense of the formation of dimer(s). This was not the case for reaction between the lithio anion derived from the cyano dioxolane **25** and complexes **19** in the present work, where similar yields of the desired products were obtained irrespective of whether HMPA was added to the mixture before or after the (η^6-arene)$Cr(CO)_3$ substrates.

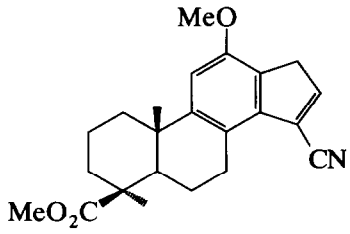
A few runs of the addition-oxidation reaction between the lithio anion derived from **25** and complexes **19** gave methyl 14-hydroxy-12-methoxypodocarpa-8,11,13-trien-19-oate (**10**) as the major product. Hydroxy substitution at C14 was verified by the presence of *meta* coupling (J 2.3 Hz) between H11 (δ 6.24) and H13 (δ 6.45) in the ^{1}H NMR spectrum. Formation of the 14-hydroxy compound **10** is not only highly desirable in the context of further modification of ring C, but is unprecedented, as a heteroatom nucleophile does not generally substitute directly for hydride in (η^6-arene)$Cr(CO)_3$ complexes. In the present case, the source of C14-oxygenation cannot be adventitious molecular oxygen, as this electrophile would attack the $Cr(CO)_3$ complexes at C13. Therefore, in an attempt to determine the source of the (apparent) nucleophilic substitution at C14, four experiments were performed: (i) treatment of complexes **20** in THF with HMPA (as potential oxidant); (ii) treatment of **20** in THF/HMPA (4:1) with lithium hydroxide (potentially present in commercial BuLi/hexanes); (iii) treatment of **20** in THF/HMPA (4:1) with butyllithium and butan-1-ol (lithium butoxide is potentially present in commercial BuLi/hexanes); and (iv) treatment of **20** in THF/HMPA (4:1) with butyllithium and ^{t}butyl hydroperoxide (as an analogue of lithium butyl hydroperoxide, potentially present in commercial BuLi/hexanes). All reactions were stirred at −78°C for 2.5 h, and then quenched with iodine; unfortunately, none of them gave the desired 14-hydroxy product **10**. Only 12,19-dimethoxypodocarpa-8,11,13-triene (**4**) was recovered from reactions (i), (ii), and (iii). Although diterpenoid **4** was also the major product in reaction (iv), a small amount of the 12-hydroxy-13-iodo derivative **11** was also present.

From one reaction of a mixture (5:1) of complexes **22/24** with the lithio anion derived from **25**, the 7,9-dienone **27** was recovered as a minor product (19%). The linear dienone system was indicated by the presence of two olefinic proton signals (H11″, δ 5.81; H7″, 6.30, dd, J 3.6, 3.3 Hz) in the ^{1}H NMR spectrum, and by the presence of signals due to two olefinic carbons (C11″, δ 118.4; C7″, 135.7) in the ^{13}C NMR spectrum. ^{1}H-^{13}C shift-correlated two-dimensional NMR spectroscopy was used to ascertain the position of the double bonds, and to fully assign the proton and carbon signals. The dienone **27** presumably arises *via* iodine-promoted ether cleavage of the 12-methoxy-7,9,12-triene generated by formal hydride loss from C7 (rather than from C14) during oxidative workup.

There is evidence that an increase in the bulk of a substituent on the aromatic ring of an (η^6-arene)$Cr(CO)_3$ complex causes a decrease in amount of nucleophilic attack *ortho* to that substituent [11]. It has also been demonstrated that increasing the steric bulk of the attacking nucleophile, particularly adjacent to or at the carbanion centre, plays a significant role in inhibiting *ortho* substitution. With the latter effect in mind, a mixture (4:1) of **21/23** was reacted with the lithio anion derived from the 1,3-dioxane **26** [12]. The standard conditions gave a mixture (9:1) (90%) of **12** and its C13″-substituted regioisomer **13**. Although the overall yield was high, the C14″/C13″ product ratio was identical with that obtained when the lithio anion derived from the 1,3-dioxolane **25** had been used. Since the methoxy substituent in complexes **19** and **20** is bent towards C13, it is possible that an even bulkier dioxolane or dioxane, or a larger alkoxy group at C12, may minimize attack at C13. However, an alternative source of the C13″-substituted products is a β $Cr(CO)_3$ stereoisomer, **23** or **24**, in which a carbonyl ligand almost eclipses C13 [13].

We previously reported [4] that attempts to cyclize a mixture (4.1:1) of dioxolanes **6/7** were unsuccessful. We now report that with very careful control of reaction conditions, cyclopentaannulation can be achieved with a number of Lewis acids. The results from reactions of **6** with a number of acids are presented in Table 2 (since no cyclization products resulted from the C13″ regioisomer **7**, it is not included in this table). Best results were obtained using titanium(IV) chloride. This involved the addition of $TiCl_4$ (1.2 molar equivalents in the first instance) dropwise (2 min) to a cooled (−78°C) solution of the 19″-methoxycarbonyl dioxolanes **6/7** in dichloromethane. After 1.5 h at room temperature, one more molar equivalent of $TiCl_4$ was added to the mixture at −78°C. Workup followed by chromatography gave the indenenitrile **28** (14%), and the cyanoindanols **30** (84%) as a mixture (10:9:4.2) of four diastereoisomers. The indanols **30** clearly form first, acid-catalysed dehydration then affording the minor product **28**. Since a 2-hydroxyethyl ether group arising from initial C–O cleavage of the acetal was not present in the products, it is apparent that the C17-oxygen bond was also cleaved in the acid medium, affording a stabilized benzylic cation. Aqueous workup re-oxygenates C17, giving a mixture of diastereoisomeric alcohols **30**, which to some extent undergo elimination/isomerization to produce the more highly conjugated Δ^{15} (*cf.* Δ^{16}) tetraene **28**.

An analogous reaction involving a mixture (9:1) of the 19″-methoxymethyl dioxolanes **8/9** was found to require only 1.2 molar equivalents of $TiCl_4$, and gave the cyanoindane **29** (7%) and the cyanoindanols **31** (78%) as a mixture (10:9:4) of three detectable (although a fourth cannot be discounted) diastereoisomers.



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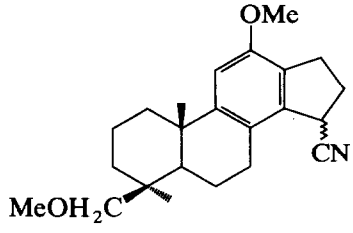

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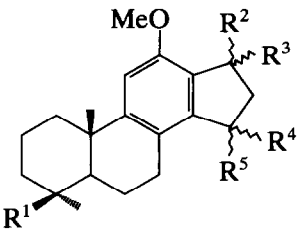
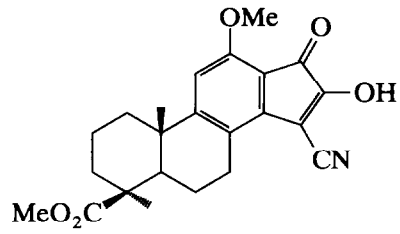


(**30**: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = OH$, $R^4 = CN$, $R^5 = H$
31: $R^1 = CH_2OMe$, $R^2 = H$, $R^3 = OH$, $R^4 = CN$, $R^5 = H$
32: $R^1 = CO_2Me$, $R^2/R^3 = O$, $R^4 = CN$, $R^5 = H$
33: $R^1 = CH_2OMe$, $R^2/R^3 = O$, $R^4 = CN$, $R^5 = H$
34: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = OH$, $R^4/R^5 = O$
35: $R^1 = CO_2H$, $R^2 = R^3 = R^4 = R^5 = H$
36: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = OH$, $R^4 = R^5 = H$
37: $R^1 = CH_2OMe$, $R^2 = H$, $R^3 = OH$, $R^4 = R^5 = H$
38: $R^1 = CH_2OMe$, $R^2 = R^3 = R^4 = R^5 = H$)



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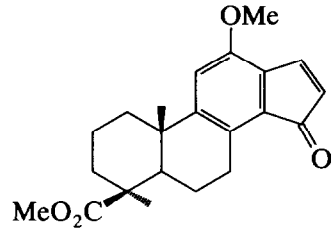


(40)

When $TiCl_4$ (2.2 molar equivalents) was added rapidly in one portion to a cooled (−78°C) solution of a mixture of dioxolanes **6/7** in dichloromethane and the mixture was warmed to room temperature, a highly fluorescent (TLC) compound was the major component. High resolution mass spectrometry (M^+, 730.3975) showed it to have the molecular formula $C_{46}H_{54}N_2O_6$, and accurate mass measurement of the relatively abundant ion of *m/z* 366.2057 ($M-C_{23}H_{26}NO_3$) indicated that the compound was a dimer **41** of an androstane analogue. An identical experiment involving the 1,3-dioxolanes **8/9** gave the analogous dimer **42** (M^+, 702.4402). ^1H-^1H COSY and ^1H-^{13}C shift-correlated two-dimensional NMR spectroscopy were used to determine the structure of the mixture of diastereoisomers **42**. The sets of signals at δ 4.09 and

TABLE 2. Reactions of dioxolane **6** with various acids

Acid	Solvent	Molar equiv.	Conditions	Products
$TiCl_4$	CH_2Cl_2	2.2 [a]	−78°C → r.t./2 h	**28/30**, 14/84%
$TiCl_4$	CH_2Cl_2	2.2 [b]	−78°C → r.t./2 h	**41**, > 50%
$TiCl_4$	CH_3CN	1.2	−23°C → r.t./14.5 h	**14**, 83%
$TiCl_3(O^iPr)$	CH_2Cl_2	3.2 [a]	−78°C → r.t./51 h	**28/30**, 32/50%
$TiCl_2(O^iPr)_2$	CH_2Cl_2	2.2 [a]	−78°C → r.t./24.5 h	**28/30**, 27/31%
$SnCl_4$	CH_3CN	1.2	−23°C → r.t./14.5 h	**14**, 23%
$BF_3.OEt_2$	CH_2Cl_2	3.2 [a]	−78°C → r.t./21 h	**28**, 15%
$AlCl_3$	CH_2Cl_2	3.2 [a]	−78°C → r.t./21 h	c.m.
Et_2AlCl	CH_2Cl_2	2.2	−78°C → r.t./24 h	s.m.
$MeSO_2OH$	-	Excess	0°C → r.t./1 h	c.m.
PPA	C_6H_6	Excess	r.t. → Δ/4 h	c.m.
Eaton's reagent	-	Excess	0°C → r.t./3 h	c.m.
Eaton's reagent	CH_2Cl_2	0.1	0°C → r.t./2 h	c.m.
Polyphosphate ester	$CHCl_3$	5	Δ/23 h	c.m.

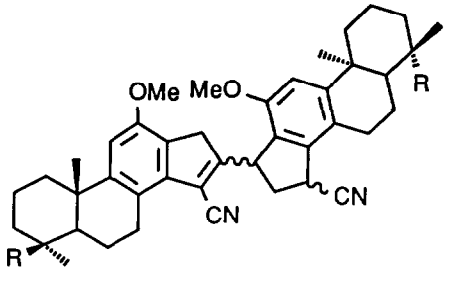
[a] Portionwise; [b] at once; c.m. complicated mixture; Δ reflux.

4.23 (H15′, diastereoisomers), and those at δ 4.88 and 5.00 (H17′, diastereoisomers) were not coupled to each other, but both sets were coupled to the signals at δ 2.30 and 3.10 ($(H16')_2$). Although both H15′ and H17′ were methine protons, neither was olefinic (C15′, δ 32.7; C17′, 42.8); $(H16')_2$ was part of a saturated methylene group (C16′, δ 36.5).

The relatively low-field ^1H NMR chemical shifts of H17′ (δ 4.90, 5.01 in dimer **41**, and 4.88, 5.00 in dimer **42**) were unexpected. However, computed models (ALCHEMY III, TRIPOS Associates) of both *cis* (H15′ *vs.* H17′) and *trans* stereoisomers of these dimers showed H17′ to lie in the deshielding zone of C16–C15–CN (*i.e.* to be almost coplanar with this α,β-unsaturated system (Fig. 1). The consequential magnetic anisotropy effect could thus explain the relatively high δ value observed for the signal due to H17′. The computed models for the diastereoisomers of dimer **42** showed the *trans* (H15′α, H17′β; H15′β, H17′α) stereoisomers to have a minimized energy of 72.7 and 72.3 kJ mol^{-1}, and the *cis* (H15′β, H17′β; H15′α, H17′α) stereoisomers to have a minimized energy of 74.6 and 73.4 kJ mol^{-1}. On this basis a *trans* relationship would be preferred for the major stereoisomer in both dimers **41** and **42**.

The experimental protocol developed previously for acid-induced cyclization (2.2 molar equivalents of $TiCl_4$, added porionwise) was also applied to a mixture of the dioxanes **12/13**, to give the steroidal analogues **28** (22%) and **30** (64%).

Since the androstane analogues **30** and **31** were each a mixture of diastereoisomers, it was decided to destroy one stereocentre by oxidizing the 17-hydroxy group to a ketone. Not only would this transformation simplify spectroscopic analysis, but also some important naturally occurring steroids are 17-ones. Treatment of the alcohols **30** with pyridinium chlorochromate (PCC)/powdered molecular sieves (3 Å)/anhydrous sodium acetate [14–17] gave the 17-oxo com-



(**41**:R=CO_2Me
42:R=CH_2OMe)

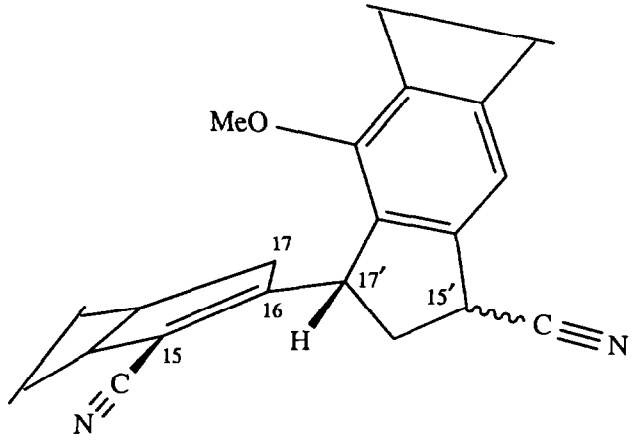
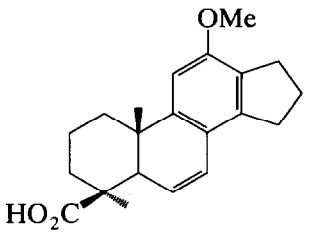


Fig. 1. The *cis* and *trans* stereoisomers of dimers **41** and **42**.

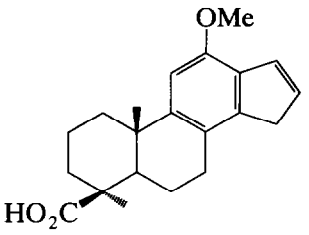
pounds **32** (79%); **33** (82%) was obtained similarly from alcohols **31**. An attempt to oxidize **30** with PCC alone gave **32** (59%), together with the enolic diketone **39** (27%). Treatment of **30** with PCC/powdered molecular sieves (3 Å)/anhydrous acetic acid [18] gave **32** in 67% yield.

In order to obtain an androstane analogue more closely related to naturally occurring steroids, the cyano group of compounds **30** and **31**, or of their precursors **6** and **8**, should be removed. Such oxidative or reductive decyanation would also remove one of the stereocentres, again simplifying the mixtures. Oxidative decyanation of nitriles **30** by reaction with molecular oxygen and base under phase-transfer catalysis [19] gave the 15-oxo-17-alcohols **34** (82%) as a mixture (5:4) of two epimers. Treatment of the alcohols **34** with a catalytic amount of *p*-TsOH in boiling benzene [20] gave the 16-en-15-one **40** (73%).

The reductive decyanation procedure used by Kametani *et al.* [21] was applied to a mixture (9:1) of cyano dioxolanes **6/7**, producing the 2'-descyano-19''-carboxylic acid **15** (80%), and its C13''-substituted regioisomer **16** (6%). The addition of sodium in very small portions was essential to give optimum yields of the acids **15** and **16** [22]. The addition of a large excess of sodium in one portion gave high yields of 19''-alcohols **17** and **18**. Although the starting cyano dioxolanes **6/7** were inseparable chromatographically, the reduced products **15** and **16** were easily separated by PLC.



(43)



(44)

Titanium(IV) chloride-mediated cyclization of the 14''-substituted 19''-carboxylic acid **15** resulted in a mixture (5:1, ^{1}H NMR spectrum) of the Δ^6 tetraene **43** (68%) and its dihydro analogue **35** (17%). The unexpected position of the double bond between C6–C7 in the styrene **43** was confirmed by ^{1}H-^{1}H COSY and ^{1}H-^{13}C shift-correlated two-dimensional NMR spectroscopy. Thus, the olefinic protons H6 (δ 6.39, dd, *J* 9.9, 2.4 Hz) and H7 (δ 6.49, dd, *J* 9.9, 3.0 Hz) were both correlated to H5 (δ 2.35), whose signal was downfield relative to its chemical shift in analogous compounds in which C6–C7 is saturated. The Δ^6-androstene analogue **43** is presumed to have arisen *via* cyclization followed by cleavage of the ether side-chain and proton loss from C16 to give the indene **44** [5]. Proton-catalyzed isomerization of the olefinic double bond then affords the more stable dihydronaphthalene **43**. Evidence for the intermediacy of the tetraene **44** comes from the fact that, in one run, a small amount (10%) of this indene was detected (^{1}H NMR spectrum) in the product mixture. Also unexpected was the degree of saturation in the triene **35**, as its formation requires the presence of a formal hydride donor. Although intermolecular hydride transfer, or disproportionation [23], is a possibility, a redox-counterpart for the triene **35** was not isolated. However, an unidentified compound ($M^{+\bullet}$, 396.2650, $C_{26}H_{36}O_3$) was observed (up to 20%) in the product mixture.

Reductive decyanation of the nitriles **30** with Na/liq. NH_3 gave a separable (PLC) mixture (1:1) of the alcohol epimers **36** (83%); the 4β-methoxymethyl congeners **31** gave a mixture (1:1) of the analogous epimers **37** (72%), together with the 17-desoxy product **38** (11%). It had been assumed that the 4β-methoxycarbonyl group of **30** would undergo concomitant reductive cleavage (*cf.* above). It was apparent, however, that the reductive decyanation occurred very rapidly at −78°C, while reductive ester cleavage was slower. It is likely that sodium reacts with the 17-hydroxy group in **30** and **31** to form the alkoxide salt, which may be insoluble. Although there is no obvious explanation for the selectivity observed, it is apparent that the presence of the 17-OH group in **30** results in rapid decyanation without concomitant ester cleavage.

We have shown that ring-C aromatic androstane analogues can be obtained readily from podocarpic acid derivatives. Highly regioselective attack of a carbanion on the derived $Cr(CO)_3$ complexes provides the cornerstone of the annulation strategy.

3. Experimental details

For general experimental details see refs. 1 and 3. High field ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ 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. 2-[2'ξ-Cyano-2'-(14''-(methyl 12''-methoxypodocarpa-8'',11'',13''-trien-19''-oate))ethyl]1,3-dioxolane (6)

Butyllithium (7.99 mL, 1.60 mol l^{-1} in hexanes, 12.8 mmol) was added dropwise to a cooled (−78°C) solution of THF (60 ml) and diisopropylamine (1.80 ml, 12.8 mmol) and stirring was continued for 30 min. **25** (1.63 g, 12.8 mmol) in THF (5 ml) was added and the mixture was stirred for a further 30 min. HMPA (28.7

ml) was added, followed by a solution of **19** (2.80 g, 6.4 mmol) in THF (10 ml) precooled to −78°C. The caramel-coloured mixture was then stirred at −78°C for 6.5 h. A solution of iodine (8.12 g, 32 mmol) in THF (60 ml) was precooled to −78°C and added dropwise, and the mixture was warmed to room temperature overnight. The mixture was then diluted with ether and the organic layer was washed with 5% aqueous sodium hydrogensulfite (×2), water, brine, and dried ($MgSO_4$), and filtered through alumina. Flash chromatography (hexanes/ether, 7:3, 3:2, 1:1; and benzene/ether, 40:1) gave (i) methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (**2**) (0.11 g, 6%), and (ii) an inseparable mixture (9:1) of the regioisomers 2-[2′ξ-cyano-2′-(14″-(methyl 12″-methoxypodocarpa-8″,11″,13″-trien-19″-oate))-ethyl]1,3-dioxolane (**6**) (diastereoisomeric ratio, 2:1) and 2-[2′ξ-cyano-2′-(13″-(methyl 12″-methoxypodocarpa-8″,11″,13″-trien-19″-oate))ethyl]1,3-dioxolane (**7**) (diastereoisomeric ratio, 6:5) (2.50 g, 91%); b.p. 180°C/0.05 mmHg (Kugelrohr) (Found: C, 70.4; H, 8.1; N, 3.3. $C_{25}H_{33}NO_5$ calcd.: C, 70.2; H, 7.8; N, 3.3%). ν_{max} 2240 (CN), 1725 (CO), 1607, 1469 (C=C), 1144 cm^{-1}. δ_H (major diastereoisomer of **6**): 1.04, s, $(H20'')_3$; 1.08, td, *J* 13.8, 4.2 Hz, H3″ax; 1.28, s, $(H18'')_3$; 1.38, td, *J* 13.5, 3.9 Hz, H1″ax; 1.50, bd, *J* 11.9 Hz, H5″; 1.63, bd, *J* 13.4 Hz, H2″eq; 1.93, m, H6″ax, H2″ax, $(H1')_1$; 2.27, m, H1″eq, H3″eq, H6″eq, $(H1')_1$; 2.62, ddd, *J* 16.3, 12.7, 6.2 Hz, H7″ax; 2.82, dd, *J* 16.3, 4.2 Hz, H7″eq; 3.66, s, CO_2CH_3; 3.79, s, $ArOCH_3$; 3.82, 4.04, 2m, $(H4)_2$, $(H5)_2$; 4.15, dd, *J* 10.5, 4.4 Hz, H2′; 5.04, dd, *J* 5.6, 3.3 Hz, H2; 6.82, d, *J* 2.3 Hz, H11″; 6.86, d, *J* 2.3 Hz, H13″; (major diastereoisomer of 7): 6.76, s, H11″; 7.02, s, H14″. δ_C (major diastereoisomer of **6**): 19.5, C2″; 20.3, C6″; 22.4, C20″; 27.3, C7″; 27.9, C18″; 28.0, C2′; 36.9, C3″; 38.0, C10″; 38.5, C1′; 39.3, C1″; 43.3, C4″; 50.7, CO_2CH_3; 51.4, C5″; 54.6, $ArOCH_3$; 64.7, 64.8, C4, C5; 101.0, C2; 110.1, C13″; 111.0, C11″; 120.5, CN; 124.1, C8″; 134.3, C14″; 150.4, C9″; 157.6, C12″; 176.9, CO; (major diastereoisomer of 7): 107.5, C11″; 127.3, C14″; 148.8, C9″; 153.9, C12″: *m/z* 427 (12, M^+), 397 (3), 365 (15), 341 (100, *M*–$H_2CHOCH_2CH_2O$ + H), 73 (32, *M*–diterpenoid–$CH(CN)CH_2$).

Repetition of the above reaction sometimes gave methyl 14-hydroxy-12-methoxy-podocarpa-8,11,13-trien-19-oate (**10**) as a major product (Found: $M^{+\bullet}$, 318.1825. $C_{19}H_{26}O_4$ calcd.: M, 318.1831). ν_{max} 3435 (OH), 1726 (CO), 1614, 1588, 1504 cm^{-1}. δ_H 1.04, s, $(H20)_3$; 1.06, td, *J* 13.4, 4.1 Hz, H3ax; 1.28, s, $(H18)_3$; 1.36, td, *J* 13.7, 3.7 Hz, H1ax; 1.51, d, *J* 12.1 Hz, H5; 1.61, bd, *J* 14.1 Hz, H2eq; 1.97, qd, *J* 12.6, 5.3 Hz, H6ax; 1.98, qt, *J* 13.8, 3.7 Hz, H2ax; 2.25, m, H1eq, H6eq, H3eq; 2.43, ddd, *J* 16.2, 9.8, 6.4 Hz, H7ax; 2.78, dd, *J* 16.3, 5.1 Hz, H7eq; 3.67, s, CO_2CH_3; 3.74, s, $ArOCH_3$; 5.02, bs, OH; 6.24, d, *J* 2.3 Hz, H11; 6.45, d, *J* 2.3 Hz, H13. δ_C 20.0, C2; 20.2, C6; 22.6, C20; 24.8, C7; 28.5, C18; 37.5, C3; 38.7, C10; 39.6, C1; 44.0, C4; 51.3, CO_2CH_3; 52.3, C5; 55.2, $ArOCH_3$; 98.4, C13; 103.5, C11; 114.2, C8; 150.7, C9; 153.9, C14; 158.3, C12; 177.9, CO. *m/z* 318 (100, M^+), 303 (8, *M*–Me), 271 (7), 243 (84, 303–CH_3CO_2H).

3.2. Attempts to determine the source of C-14 oxygenation

(i) A pre-cooled (−78°C) solution of **20** (50 mg, 0.12 mmol) in THF (1 ml) was added to a cooled (−78°C) mixture of THF (4 ml) and HMPA (1 ml). After 2.5 h a solution of iodine (0.15 g, 0.59 mmol) in THF (1 ml) precooled to −78°C was added, and the mixture was warmed to room temperature overnight. Workup gave 12,19-dimethoxypodocarpa-8,11,13-triene (**4**).

(ii) Repetition of (i) but with the addition of anhydrous lithium hydroxide (2 molar equivalents) gave **4**.

(iii) A cooled (−78°C) solution of butyllithium (2 molar equivalents) and butyl alcohol (2 molar equivalents) in THF was stirred for 30 min. HMPA was added, followed by a solution of **20** in THF precooled to −78°C. After 2.5 h, addition of iodine and workup as in (i) gave **4**.

(iv) Repetition of (iii) but with the addition of t-butyl hydroperoxide (2 molar equivalents) and without butyl alcohol gave mostly **4**, and a small amount of 12-hydroxy-13-iodo-19-methoxypodocarpa-8,11,13-triene (**11**) (Found: $M^{+\bullet}$, 400.0895. $C_{18}H_{25}O_2I$ calcd.: M, 400.0899). ν_{max} 3322 (OH), 1655, 1592, 1478, 1108, 1079 cm^{-1}. δ_H 1.00, td, *J* 13.9, 4.4 Hz, H3ax; 1.03, s, $(H18)_3$; 1.17, s, $(H20)_3$; 1.38, dd, *J* 12.7, 1.9 Hz, H5; 1.39, m, H1ax; 1.67, m, H2ax, H2eq, H6ax; 1.87, dd, *J* 13.6, 1.3 Hz, H3eq; 1.90, dd, *J* 13.5, 7.1 Hz, H6eq; 2.22, bd, *J* 12.9 Hz, H1eq; 2.71, ddd, *J* 16.8, 11.8, 7.4 Hz, H7ax; 2.82, dd, *J* 16.8, 5.8 Hz, H7eq; 3.24, 3.50, 2d, *J* 9.1 Hz, CH_2OCH_3; 3.22, s, CH_2OCH_3; 5.04, s, OH; 6.89, s, H11; 7.31, s, H14. δ_C 19.1, C2; 19.2, C6; 25.5, C20; 27.7, C18; 29.7, C7; 36.0, C3; 38.0, C4, C10; 38.8, C1; 51.0, C5; 59.4, CH_2OCH_3; 76.0, CH_2OCH_3; 111.1, C11; 117.6, C13; 132.5, C8; 138.0, C14; 144.0, C9; 152.7, C12. *m/z* 400 (100, M^+), 385 (10, *M*–Me), 353 (30, 385–MeOH), 285 (22), 273 (88, *M*–I), 258 (20), 226 (23).

3.3. 2-[2′ξ-Cyano-2′-(14″-(12″,19″-dimethoxypodocarpa-8″,11″,13″-triene))ethyl]-1,3-dioxolane (8)

A mixture of THF (6 ml) and diisopropylamine (0.13 ml, 0.94 mmol) was cooled to −78°C and butyllithium (0.79 ml, 1.2 mol l^{-1} in hexanes, 0.94 mmol) was added dropwise and the solution was stirred for 30 min. **25** (0.12 g, 0.94 mmol) in THF (1 ml) was added and the

mixture stirred for a further 30 min. HMPA (2.5 ml) was added, followed by a solution of **20** (0.20 g, 0.47 mmol) in THF (3 ml) precooled to −78°C. The solution was then stirred at −78°C for 2 h. A solution of iodine (0.6 g, 2.4 mmol) in THF (6 ml) precooled to −78°C was added dropwise and the mixture was warmed to room temperature overnight. Work-up as above followed by PLC (hexanes/ether, 1:1, 3 sweeps) of the crude product gave (i) an inseparable mixture (9:1) (0.15 g, 79%) of 2-[2′ξ-cyano-2′-(14″-(12″,19″-dimethoxypodocarpa-8″,11″,13″-triene))-ethyl]-1,3-dioxolane (**8**) (diastereoisomeric, ratio, 2:1) and 2-[2′ξ-cyano-2′-(13″-(12″,19″-dimethoxypodocarpa-8″,11″,13″-triene))-ethyl]-1,3-dioxolane (**9**) (diastereoisomeric ratio, 6:5) as a colourless oil (Found: $M^{+\bullet}$, 413.2554. $C_{25}H_{37}NO_4$ calcd.: M, 413.2566). ν_{max} 2241 (CN), 1607, 1468 (C=C), 1142, 1108 cm^{-1}. δ_H (major diastereoisomer of **8**): 1.10, td, *J* 13.4, 4.4 Hz, H3″ax; 1.04, s, $(H18'')_3$; 1.19, s, $(H20'')_3$; 1.39, dd, *J* 12.8, 1.8 Hz, H5″; 1.40, td, *J* 13.1, 4.1 Hz, H1″ax; 1.65, m, H2″eq, H2″ax, H6″ax; 1.85, bd, *J* 13.4 Hz, H3″eq; 1.99, ddd, *J* 14.1, 10.2, 5.7 Hz, $(H1')_1$; 2.07, dd, *J* 13.4, 7.1 Hz, H6″eq; 2.27, bd, *J* 13.0 Hz, H1″eq; 2.35, ddd, *J* 14.0, 10.6, 3.3 Hz, $(H1')_1$; 2.69, ddd, *J* 16.6, 11.4, 7.1 Hz, H7″ax; 2.78, dd, *J* 16.6, 6.7 Hz, H7″eq; 3.26, 3.49, 2d, *J* 9.1 Hz, $(H19'')_2$; 3.33, s, CH_2OCH_3; 3.80, s, $ArOCH_3$; 3.93, 4.05, 2m, $(H4)_2$, $(H5)_2$; 4.13, dd, *J* 10.6, 4.4 Hz, H2′; 5.06, dd, *J* 5.7, 3.3, H2; 6.83, d, *J* 2.4 Hz, H11″; 6.85, d, *J* 2.4 Hz, H13″; (major diastereoisomer of **9**): 6.77, s, H11″; 7.02, s, H14″. δ_C (major diastereoisomer of **8**): 19.2, C2″, C6″; 25.7, C20″; 27.1, C7″; 27.6, C18″; 28.4, C2′; 35.9, C3″; 38.0, C10″; 38.4, C4″; 38.5, C1′; 39.4, C1″; 50.5, C5″; 55.3, $ArOCH_3$; 59.4, CH_2OCH_3; 65.1, 65.3, C4, C5; 76.1, C19″; 101.6, C2; 110.1, C13″; 111.0, C11″; 121.0, CN; 124.3, C8″; 134.7, C14″; 152.8, C9″; 158.1, C12″; (major diastereoisomer of **9**): 106.9, C11″; 128.6, C14″. *m/z* 413 (14, M^+), 351 (18, *M*−$HOCH_2CH_2OH$), 327 (100, *M*−$H_2CCHOCH_2CH_2O$ + H), 87 (12, *M*−diterpenoid−CHCN), 73 (24, *M*−diterpenoid−$CHCNCH_2$), 45 (32, $H_2C{=}OCH_3^+$); and (ii) **4** (12 mg, 9%).

From one run of the above reaction 2-[2′ξ-cyano-2′-(14″-(19″-methoxypodocarpa-7″,9″(11″)-dien-12″-one))ethyl]-1,3-dioxolane (**27**) was also obtained (Found: $M^{+\bullet}$, 399.2403. $C_{24}H_{33}NO_4$ calcd.: M, 399.2410). ν_{max} 2240 (CN), 1666 (CO), 1643, 1579, 1465 (C=C), 1264, 1108 cm^{-1}. δ_H 0.97, td, *J* 13.6, 4.1 Hz, H3″ax; 0.98, s, $(H18'')_3$; 1.12, s, $(H20'')_3$; 1.42, td, *J* 12.4, 5.4 Hz, H1″ax; 1.58, m, H2″ax, H2″eq, H5″; 1.85, m, $(H1')_2$; 1.92, m, H1″eq, H3″eq; 2.60, dd, *J* $(H13'')_1$; 2.42, m, $(H6'')_2$; 2.70, dd, *J* 16.7, 5.5 Hz, $(H13'')_1$; 2.76, ddd, *J* 14.0, 9.2, 4.6 Hz, H2′; 2.88, ddd, *J* 10.1, 5.5, 1.9 Hz, H14″; 3.31, s, CH_2OCH_3; 3.32, 3.46, 2d, *J* 9.3 Hz, $(H19'')_2$; 3.84, 3.96, 2m, $(H4)_2$, $(H5)_2$; 5.06, dd, *J* 5.6, 3.8 Hz, H2; 5.81, s, H11″; 6.30, dd, *J* 3.6, 3.3 Hz, H7″. δ_C 18.4, C2″; 20.5, C20″; 24.5, C6″; 27.1, C18″; 30.3, C2′; 33.6, C1″; 36.3, C1′; 36.4, C3″; 37.7, C10″; 37.9, C4″; 39.6, C13″; 43.6, C14″; 48.0, C5″; 59.4, CH_2OCH_3; 64.9, 65.2, C4, C5; 76.1, C19″; 101.7, C2; 118.4, C11″; 120.2, CN; 130.1, C8″; 135.7, C7″; 165.6, C9″; 197.3, CO. *m/z* 399 (37, M^+), 384 (2, *M*−Me), 367 (2, *M*−MeOH), 354 (9), 241 (54), 171 (96), 125 (100), 73 (63, *M*−diterpenoid−$CHCNCH_2$).

3.4. 2-[2′ξ-Cyano-2′-(14″-(methyl 12″-methoxypodocarpa-8″,11″,13″-trien-19″-oate))ethyl]-1,3-dioxane (12)

A mixture of THF (5.2 ml) and diisopropylamine (0.14 ml, 0.97 mmol) was cooled to −78°C and butyllithium (0.88 ml, 1.10 mol l^{-1} in hexanes, 0.97 mmol) was added dropwise and the solution was stirred for 30 min. **26** (0.14 g, 0.97 mmol) was added and the mixture stirred for a further 30 min. HMPA (2.6 ml) was added, followed by a solution of **19** (0.21 g, 0.49 mmol) in THF (5.3 ml) precooled to −78°C. The mixture was then stirred at −78°C for 1 h. A solution of iodine (0.72 g, 2.9 mmol) in THF (6 ml) precooled to −78°C was added dropwise and the mixture then warmed to room temperature overnight. Workup as above followed by PLC (hexanes/ether, 1:1, 2 sweeps) of the crude product gave (i) an inseparable mixture (9:1) (0.19 g, 90%) of 2-[2′ξ-cyano-2′-(14″-(methyl 12″-methoxypodocarpa-8″,11″,13″-trien-19″-oate))ethyl]-1,3-dioxane (**12**) (diastereoisomeric ratio, 2:1) and 2-[2′ξ-cyano-2′-(13″-(methyl 12″-methoxypodocarpa-8″,11″,13″-trien-19″-oate))ethyl]-1,3-dioxane (**13**) (diastereoisomeric ratio, 1:1) as a colourless oil, b.p. 180°C/0.05 mmHg (Kugelrohr) (Found: C, 70.5; H, 8.0; N, 3.0. $C_{26}H_{35}NO_5$ calcd.: C, 70.7; H, 8.0; N, 3.2%) (Found: $M^{+\bullet}$, 441.2513. $C_{26}H_{35}NO_5$ calcd.: M, 441.2515). ν_{max} 2240 (CN), 1723 cm^{-1} (CO). δ_H (major diastereoisomer of **12**): 1.03, s, $(H20'')_3$; 1.09, td, *J* 13.5, 4.3 Hz, H3″ax; 1.27, s, $(H18'')_3$; 1.37, td, *J* 13.1, 3.8 Hz, H1″ax; 1.49, d, *J* 11.9 Hz, H5″; 1.63, bd, *J* 14.2 Hz, H2″eq; 1.83–2.33, m, $(H1')_2$, H2″ax, H6″ax, H3″eq, H1″eq, H6″eq; 2.46, t, *J* 7.4 Hz, H5; 2.59, ddd, *J* 16.4, 12.6, 6.3 Hz, H7″ax; 2.81, dd, *J* 16.3, 4.4 Hz, H7″eq; 3.66, s, CO_2CH_3; 3.78, s, $ArOCH_3$; 4.12, m, H2′, $(H4)_2$, $(H6)_2$; 4.74, dd, *J* 7.0, 3.6 Hz, H2; 6.82, d, *J* 2.3 Hz, H11″; 6.83, d, *J* 2.3 Hz, H13″; (major diastereoisomer of **13**): 6.75, s, H11″; 6.99, s, H14″. δ_C (major diastereoisomer of **12**): 20.0, C2″; 20.6, C6″; 23.0, C20″; 25.6, C5; 27.8, C7″; 28.4, C18″; 28.5, C2′; 37.3, C3″; 38.7, C10″; 39.2, C1′; 39.4, C1″; 43.9, C4″; 51.3, CO_2CH_3; 52.0, C5″; 55.2, $ArOCH_3$; 66.8, 66.9, C4, C6; 99.1, C2; 110.4, C13″; 111.7, C11″; 121.1, CN; 124.8, C8″; 134.6, C14″; 150.8, C9″; 158.0, C12″; 177.7, CO; (major diastereoisomer of **13**): 107.9, C11″; 127.8, C14″. *m/z* 441 (25, M^+), 365 (100, M−$HO(CH_2)_3OH$),

341 (65, $M-H_2CCHO(CH_2)_3O + H$), 305 (18), 279 (58), 87 (28, M–diterpenoid–$CH(CN)CH_2$); and (ii) **2** (4 mg, 3%).

3.5. Cyclization of 2-[2'ξ-cyano-2'-(14"-(methyl 12"-methoxypodocarpa-8",11",13"-trien-19"-oate))ethyl]-1,3-dioxolane (6)

(i) Titanium(IV) chloride (15 μl, 0.14 mmol) in dichloromethane (0.1 ml) was added slowly (during 2 min) to a cooled (−78°C) solution of **6** (50 mg, 0.12 mmol) in dichloromethane (5 ml). After 5 min the cooling bath was removed and the reddish mixture was stirred for 1.5 h before more titanium(IV) chloride (13 μl, 0.12 mmol) in dichloromethane (0.1 ml) was added slowly. After a further 30 min the system was cooled to 0°C and acidified with aqueous HCl (2 mol l^{-1}). The organic layer was washed with saturated aqueous sodium hydrogencarbonate, water, brine, and dried ($MgSO_4$). Flash chromatography (hexanes/ether, 7:3, 1:1) of the product gave (i) methyl 15-cyano-12-methoxy-4α-methyl-18-nor-5α-androsta-8,11,13,15-tetraene-4β-carboxylate (**28**) (6 mg, 14%) (Found: $M^{+\bullet}$, 365.1973. $C_{23}H_{27}NO_3$ calcd.: M, 365.1991). ν_{max} (KBr disc) 2224 (CN), 1724 (CO), 1597, 1560, 1467 (C=C), 1141 cm^{-1}. δ_H 1.09, td, J 13.8, 4.2 Hz, H3ax; 1.10, s, $(H19)_3$; 1.30, s, 4α-CH_3; 1.41, td, J 13.6, 4.2 Hz, H1ax; 1.55, dd, J 12.5, 1.4 Hz, H5; 1.64, dp, J 14.3, 2.9 Hz, H2eq; 1.99, qd, J 12.7, 5.5 Hz, H6ax; 2.01, qt, J 13.9, 3.7 Hz, H2ax; 2.28, m, H1eq, H3eq, H6eq; 3.02, ddd, J 16.9, 12.6, 6.4 Hz, H7ax; 3.48, dd, J 3.5, 1.8 Hz, $(H17)_2$; 3.51, ddd, J 16.9, 5.3, 1.3 Hz, H7eq; 3.68, s, CO_2CH_3; 3.86, s, $ArOCH_3$; 6.78, s, H11; 7.35, t, J 1.8 Hz, H16. δ_C 20.1, C2; 20.5, C6; 22.9, C19; 28.0, C7; 28.5, 4α-CH_3; 36.8, C17; 37.5, C3; 39.2, C10; 40.3, C1; 44.0, C4; 51.3, CO_2CH_3; 52.5, C5; 55.2, $ArOCH_3$; 102.9, C11; 116.3, CN; 117.0, C15; 122.5, C8; 127.6, C13; 138.7, C14; 149.6, C9; 149.8, C16; 153.4, C12; 177.8, CO. m/z 365 (87, M^+), 350 (8, M–Me), 305 (15, $M-CH_3CO_2H$), 290 (100, 305–Me), 234 (24), 210 (15), 183 (20, 210–HCN), 69 (76), 43 (78, CH_3CO^+); and (ii) methyl 15ξ-cyano-17ξ-hydroxy-12-methoxy-4α-methyl-18-nor-5α-androsta-8,11,13-triene-4β-carboxylate (**30**) (38 mg, 84%) (Found: M^+, 383.2098. $C_{23}H_{29}NO_4$ calcd.: M, 383.2097). ν_{max} 3435 (OH), 2238 (CN), 1723 (CO), 1608, 1464 cm^{-1}. δ_H 1.03, s, $(H19)_3$; 1.09, td, J 13.6, 4.2 Hz, H3ax; 1.29, s, 4α-CH_3; 1.39, td, J 13.5, 4.1 Hz, H1ax; 1.57, bd, J 12.5 Hz, H5; 1.66, m, H2eq; 1.98, m, H2ax, H6ax; 2.25, m, H1eq, H3eq, H6eq; 2.50, m, H7ax, OH; 2.78, m, H7eq, $(H16)_2$; 3.67, s, CO_2CH_3; 3.84, s, $ArOCH_3$; 3.88, 4.20, 2dd, J 9.0, 4.8 Hz, H15 diastereoisomers; 5.36, 5.58, 2dd, J 7.2, 4.5 Hz, H17 diastereoisomers; 6.77, 6.78, 6.82, 3s, H11 diastereoisomers. δ_C (major diastereoisomer) 19.9, C2; 20.3, C6; 22.9, C19; 28.4, 4α-CH_3; 28.5, C7; 31.1, C15; 37.4, C3; 37.5, C10; 39.2, C16; 39.9, C1; 44.0, C4; 51.3, CO_2CH_3; 52.3, C5; 55.2, $ArOCH_3$; 72.7, C17; 108.2, C11; 120.3, CN; 124.7, C8; 129.7, C13; 136.3, C14; 151.6, C9; 154.4, C12; 177.7, CO. m/z 383 (61, M^+), 365 (6, $M-H_2O$), 350 (13, 365–Me), 308 (100, M–Me–CH_3CO_2H), 281 (10, 308–HCN), 242 (15), 216 (8), 129 (15).

The C13" regioisomer **7** did not undergo cyclization here, or in any of the following reactions, and so is not included in the experimental details.

When two or more molar equivalents of titanium(IV) chloride were added at one time the only product recovered, whose formation could be observed by the appearance of a highly fluorescent spot on TLC, was methyl 16-[17'ξ-(methyl 15'ξ-cyano-12'-methoxy-4'β-methoxymethyl-4'α-methyl-18'-nor-5'α-androsta-8',11',13'-triene-4'β-carboxylate)]-15-cyano-12-methoxy-4β-methoxymethyl-4α-methyl-18-nor-5α-androsta-8,11,13,15-tetraene-4β-carboxylate (**41**) as a mixture of diastereoisomers (Found M^+, 730.3975. $C_{46}H_{54}N_2O_6$ calcd.: M, 730.3982). ν_{max} (KBr disc) 2224, 2220 (CN), 1727 (CO), 1598, 1487, 1464 (C=C), 1384, 1140 cm^{-1}. δ_H 1.05, 1.09, 2s, $(H19)_3$, $(H19')_3$; 1.30, 1.31, 2s, 4α-CH_3, 4'α-CH_3; 3.67, 3.68, 2s, CO_2CH_3, CO_2CH_3'; 3.77, 3.79, 2s, $ArOCH_3$, $ArOCH_3'$; 4.10, dd, J 9.9, 3.7 Hz, H15 (diastereoisomer); 4.28, dd, J 8.6, 5.8 Hz, H15 (diastereoisomer); 4.90, dd, J 9.6, 3.7 Hz, H17' (diastereoisomer); 5.01, dd, J 8.7, 5.6 Hz, H17' (diastereoisomer); 6.71, s, H11, H11'. δ_C (major diastereoisomer) 19.96, 20.04, C2, C2'; 20.5, C6, C6'; 22.86, 22.92, C19, C19'; 28.2, 28.8, C7, C7'; 28.5, 4α-CH_3, 4'α-CH_3; 32.8, C15'; 36.9, C16'; 37.5, C17; 39.1, 39.3, C10, C10'; 39.7, 39.8, C3, C3'; 40.3, C1, C1'; 42.9, H17'; 44.0, C4, C4'; 51.3, CO_2CH_3, CO_2CH_3'; 52.2, 52.5, C5, C5'; 55.1, 55.2, $ArOCH_3$, $ArOCH_3'$; 106.0, 108.4, C11, C11'; 111.3, C15; 116.7, CN; 120.3, CN'; 121.9, 124.5, C8, C8'; 126.2, 128.6, C13, C13'; 136.6, 139.1, C14, C14'; 149.5, 150.9, C9, C9'; 153.3, 154.5, C12, C12'; 168.3, C16; 177.8, CO, CO'. m/z 730 (2, M^+), 671 (1), 589 (1), 548 (1), 369 (12), 366 (49, $M-C_{23}H_{26}NO_3$), 84 (42), 44 (100).

(ii) A solution of titanium(IV) trichloroisopropoxide (24 mg, 0.11 mmol) (prepared from titanium(IV) chloride and titanium(IV) isopropoxide, 3:1) in dichloromethane (0.1 ml) was added slowly to a cooled (−78°C) solution of **6** (40 mg, 0.09 mmol) in dichloromethane (5 ml). After 1 h the golden-yellow solution was warmed to room temperature. After 14 h another aliquot of titanium(IV) trichloroisopropoxide (20 mg, 0.09 mmol) was added, and again after a further 12 h. After a further 24 h aqueous HCl (2 mol l^{-1}) was added and workup as above followed by flash chromatography (hexanes/ether, 7:3, 1:1) of the product gave (i) (**28**) (11 mg, 32%), and (ii) (**30**) (18 mg, 50%).

(iii) A solution of titanium(IV) dichlorodiisopropox-

ide (27 mg, 0.11 mmol) (prepared from titanium(IV) chloride and titanium(IV) isopropoxide, 1:1) in dichloromethane (0.1 ml) was added slowly to a cooled solution (−78°C) of **6** (40 mg, 0.09 mmol) in dichloromethane (2 ml). After 30 min the mixture was warmed to room temperature, and after a further 12 h another aliquot of titanium(IV) dichlorodiisopropoxide (22 mg, 0.09 mmol) was added. After a further 12 h workup as above and PLC (hexanes/ether, 3:2) gave (i) (**28**) (9 mg, 27%), and (ii) (**30**) (11 mg, 31%).

(iv) Tin(IV) chloride (16 μl, 0.14 mmol) was added to a cooled (−23°C) solution of **6** (48 mg, 0.11 mmol) in acetonitrile (5 ml). After 2.5 h the solution was warmed to room temperature. After a further 12 h the mixture was diluted with ether and worked up. Flash chromatography (hexanes/ether, 1:1) of the product gave (i) starting material (13 mg, 27%), and (ii) 1-[3ξ-cyano-3-(14'-(methyl 12'-methoxypodocarpa-8',11',13'-trien-19'-oate))]propanal (**14**) (10 mg, 23%) as a colourless oil, b.p. 140°C/0.04 mmHg (Kugelrohr) (Found: M^+, 383.2096. $C_{23}H_{29}NO_4$ calcd.: M, 383.2097). ν_{max} 2241 (CN), 1727 (CO ester, aldehyde), 1607, 1582, 1470 cm^{-1} (C=C). δ_H (major diastereoisomer) 1.04, s, $(H20')_3$; 1.08, td, *J* 13.6, 4.1 Hz, H3'ax; 1.28, s, $(H18')_3$; 1.37, td, *J* 13.2, 3.6 Hz, H1'ax; 1.50, dd, *J* 12.4, 1.3 Hz, H5'; 1.63, m, H2'eq; 1.97, m, H2'ax, H6'ax; 2.26, m, H1'eq, H3'eq, H6'eq; 2.70, m, H2; 2.96, dd, *J* 18.8, 4.8 Hz, H7'ax; 3.21, dd, *J* 18.8, 9.2 Hz, H7'eq; 3.66, s, CO_2CH_3; 3.79, s, $ArOCH_3$; 4.47, dd, *J* 9.3, 4.7 Hz, H3; 6.81, d, *J* 2.5 Hz, H11'; 6.84, d, *J* 2.5 Hz, H13'; 9.34, s, H1. δ_C 20.0, C2'; 20.6, C6'; 22.9, C20'; 26.5, C3; 28.0, C7'; 28.4, C18'; 37.3, C3'; 39.1, C10'; 39.8, C1'; 43.9, C4'; 47.4, C2; 51.3, CO_2CH_3; 51.6, C5'; 55.3, $ArOCH_3$; 110.7, C13'; 111.9, C11'; 120.1, CN; 124.7, C8'; 133.2, C14'; 151.3, C9'; 158.1, C12'; 177.6, CO ester; 196.7, CO aldehyde. *m/z* 383 (100, M^+), 365 (10, $M-H_2O$), 339 (10), 308 (56), 279 (40), 187 (30), 41 (29).

For other attempted cyclizations, see Table 2.

3.6. Cyclization of 2-[2'ξ-cyano-2'-(14''-(12'',19''-dimethoxypodocarpa-8'',11'',13''-triene))ethyl]-1,3-dioxolane (8)

Titanium(IV) chloride (63 μl, 0.58 mmol) in dichloromethane (0.1 ml) was added slowly to a cooled (−78°C) solution of **8** (0.20 g, 0.48 mmol) in dichloromethane (9 ml). After 30 min the cooling bath was removed and the mixture warmed to room temperature. Workup followed by flash chromatography (hexanes/ether, 9:1, 7:3) gave (i) 12-methoxy-4β-methoxymethyl-4α-methyl-18-nor-5α-androsta-8,11,13-triene-15ξ-carbonitrile (**29**) (12 mg, 7%) (Found: M^+, 353.2341. $C_{23}H_{31}NO_2$ calcd.: M, 353.2355). ν_{max} 2235 (CN), 1601, 1464 (C=C), 1297, 1109 cm^{-1}. δ_H 1.04, td, *J* 13.9, 4.8 Hz, H3ax; 1.05, s, 4α-CH_3; 1.21, s, $(H19)_3$; 1.42, m, H1ax; 1.47, dd, *J* 12.7, 1.6 Hz, H5; 1.67, m, H2ax, H2eq, H6ax; 1.87, bd, *J* 13.8 Hz, H3eq; 2.08, dd, *J* 13.4, 7.2 Hz, H6eq; 2.28, bd, *J* 13.5 Hz, H1eq; 2.47, m, $(H16)_2$; 2.69, dd, *J* 16.9, 5.2 Hz, H7ax; 2.87–3.15, m, H7eq, $(H17)_2$; 3.24, 3.51, 2d, *J* 9.1 Hz, CH_2OCH_3; 3.33, s, CH_2OCH_3; 3.80, s, $ArOCH_3$; 4.00, dd, *J* 6.9, 6.3 Hz, H15; 6.74, s, H11. δ_C 19.0, C2; 19.2, C6; 25.8, C19; 27.7, 4α-CH_3; 28.06, C7; 28.10, C16; 30.5, C17; 33.5, C15; 35.9, C3; 38.0, C4; 38.3, C10; 39.4, C1; 51.1, C5; 55.3, $ArOCH_3$; 59.4, CH_2OCH_3; 76.0, CH_2OCH_3; 107.1, C11; 120.6, CN; 123.9, C8; 128.8, C13; 136.7, C14; 150.9, C9; 154.3, C12. *m/z* 353 (100, M^+), 338 (5, *M*–Me), 326 (7, *M*–HCN), 306 (47, 338–MeOH), 292 (18), 279 (20), 226 (81); and (ii) 17ξ-hydroxy-12-methoxy-4β-methoxymethyl-4α-methyl-18-nor-5α-androsta-8,11,13-triene-15ξ-carbonitrile (**31**) (0.14 g, 78%) (Found: $M^{+\bullet}$, 369.2309. $C_{23}H_{31}NO_3$ calcd.: M, 369.2304). ν_{max} 3480 (OH), 2237 (CN), 1605, 1485, 1464 (C=C), 1108 cm^{-1}. δ_H 1.00, td, *J* 13.9, 4.8 Hz, H3ax; 1.04, 1.057, 1.062, 3s, 4α-CH_3; 1.20, 1.23, 1.24, 3s, $(H19)_3$; 1.39, td, *J* 12.8, 4.0 Hz, H1ax; 1.45, 1.48, 2dd, *J* 12.9, 1.6 Hz, H5; 1.64, m, H2eq, H6ax; 1.72, qt, *J* 13.7, 3.3 Hz, H2ax; 1.88, bd, *J* 12.7 Hz, H3eq; 2.09, dd, *J* 13.3, 7.4 Hz, H6eq; 2.28, bd, *J* 12.4 Hz, H1eq; 2.42, 2.69, 2m, $(H16)_2$; 2.78, ddd, *J* 17.3, 11.5, 7.3 Hz, H7ax; 2.95, 3.14, 2dd, *J* 17.3, 7.6 Hz, H7eq; 3.25, 3.49, 2d, *J* 9.1 Hz, CH_2OCH_3; 3.332, 3.333, 3.344, 3s, CH_2OCH_3; 3.85, s, $ArOCH_3$; 3.89, 4.18, 2dd, *J* 9.1, 4.3 Hz, H15; 5.39, 5.61, 2m, H17; 6.79, 6.80, 2s, H11. δ_C 18.6, 18.9, C2; 19.1, 19.2, C6; 25.5, 25.7, 26.7, C19; 27.6, 4α-CH_3; 26.7, 27.7, 27.8, C7; 31.1, 31.6, C15; 35.9, C3; 38.0, C4; 38.4, 38.5, 38.6, C10; 39.0, 39.2, 39.3, C16; 39.4, 39.5, C1; 50.84, 50.97, 51.04, C5; 55.21, 55.23, $ArOCH_3$; 59.4, CH_2OCH_3; 72.3, 72.5, 73.0, C17; 75.7, 76.01, 76.04, CH_2OCH_3; 107.3, 107.5, C11; 120.1, 120.3, 120.5, CN; 124.1, 124.3, C8; 128.3, 129.5, 129.6, C13; 135.9, 136.6, 136.9, C14; 153.2, 153.5, 153.7, C9; 154.4, 154.5, C12. *m/z* 369 (19, M^+), 351 (100, $M-H_2O$), 336 (5, 351–Me), 319 (5, 351–MeOH), 305, (37), 291 (14), 224 (76).

As expected the C13'' regioisomer **9** did not undergo cyclization.

When two or more molar equivalents of titanium(IV) chloride were added at one time (−78°C) the only product recovered, whose formation could be observed by the appearance of a highly fluorescent spot on TLC, was 16-[17'ξ-(12'-methoxy-4'β-methoxy-methyl-4'α-methyl-18'-nor-5'α-androsta-8',11',13'-triene-15'ξ-carbonitrile)]-12-methoxy-4β-methoxymethyl-4α-methyl-18-nor-5α-androsta-8,11,13,15-tetraene-15-carbonitrile (**42**) as a mixture of diastereoisomers (Found: $M^{+\bullet}$, 702.4402. $C_{46}H_{58}N_2O_4$ calcd.: M, 702.4397). ν_{max} 2224, 2221 (CN), 1600, 1482 (C=C), 1290, 1110 cm^{-1}. δ_H 1.00, m, H3ax, H3'ax; 1.06, 1.08, 2s, 4α-CH_3, 4'α-CH_3; 1.22, 1.25, 2s, $(H19)_3$, $(H19')_3$; 1.45, m, H5, H5',

H1ax, H1'ax; 1.70, m, H2ax, H2'ax, H2eq, H2'eq, H6ax, H6'ax; 1.89, m, H3eq, H3'eq; 2.11, m, H6eq, H6'eq; 2.30, m, H1eq, H1'eq, $(H16')_1$; 2.69, 3.10, 2m, H7eq, H7'eq; 2.92, 3.50, 2m, H7ax, H7'ax; 3.10, m, $(H16')_1$, $(H17)_1$; 3.20, 3.50, CH_2OCH_3, CH_2OCH_3'; 3.345, 3.348, 2s, CH_2OCH_3, CH_2OCH_3'; 3.50, m, $(H17)_1$; 3.66, 3.78, 2s, $ArOCH_3$, $ArOCH_3'$; 4.09, dd, *J* 10.0, 3.4 Hz, H15' (diastereoisomer); 4.23, m, H15' (diastereoisomer); 4.88, dd, *J* 9.7, 3.4 Hz, H17' (diastereoisomer); 5.00, m, H17' (diastereoisomer); 6.72, s, H11, H11'. δ_C (major diastereoisomer) 18.8, 18.9, C6, C6'; 19.1, 19.2, C2, C2'; 25.71, 25.73, C19, C19'; 27.3, 28.0, C7, C7'; 27.6, 4α-CH_3, 4'α-CH_3; 32.7, C15'; 35.5, 35.8, C3, C3'; 36.5, C16'; 36.9, C17; 38.0, C4, C4'; 38.37, 38.43, C10, C10'; 39.2, 39.7, C1, C1'; 42.8, C17'; 50.8, 51.0, C5, C5'; 55.1, 55.2, $ArOCH_3$, $ArOCH_3'$; 59.3, CH_2OCH_3, CH_2OCH_3'; 75.6, 75.9, CH_2OCH_3, CH_2OCH_3'; 105.0, 107.5, C11, C11'; 111.2, C15; 116.7, CN; 120.2, CN'; 121.3, 124.0, C8, C8'; 126.0, 128.4, C13, C13'; 136.5, 139.0, C14, C14'; 151.2, 152.5, C9, C9'; 153.2, 154.5, C12, C12'; 168.4, C16. *m/z* 702 (6, M^+), 413 (25), 366 (5), 352 (92, $M-C_{23}H_{28}NO_2$), 327 (15), 125 (100), 73 (57).

3.7. Cyclization of 2-[2'ξ-cyano-2'-(14"-(methyl 12"-methoxypodocarpa-8",11",13"-trien-19"-oate))ethyl]-1,3-dioxane (12)

A solution of titanium(IV) chloride (18 μl, 0.16 mmol) in dichloromethane (0.1 ml) was added slowly to a cooled (−78°C) solution of **12** (60 mg, 0.14 mmol) in dichloromethane (5 ml). After 10 min the cooling bath was removed and the mixture was stirred for 1 h at room temperature. The mixture was again cooled to −78°C and another aliquot of titanium(IV) chloride (15 μl, 0.14 mmol) in dichloromethane (0.1 ml) was added. The cooling bath was removed, and after 30 min the mixture was cooled to 0°C. Workup followed by flash chromatography (hexanes/ether, 7:3, 3:2) of the crude product gave (i) **28** (10 mg, 22%), and (ii) **30** (30 mg, 64%).

Again, regioisomer **13** did not undergo cyclization and so is not included in the experimental details.

3.8. Oxidation of methyl 15ξ-cyano-17ξ-hydroxy-12-methoxy-4α-methyl-18-nor-5α-androsta-8,11,13-triene-4β-carboxylate (30)

(i) Freshly prepared pyridinium chlorochromate (12 mg, 0.06 mmol) was added to a stirred solution of **30** (14 mg, 0.04 mmol), anhydrous sodium acetate (2 mg, 0.02 mmol) and flame-dried powdered molecular sieves (3 A, 80 mg) in dichloromethane (2 ml). After 1 h aqueous HCl (2 mol l^{-1}) and Celite were added and the mixture was stirred for 10 min. The mixture was then filtered and the organic layer washed with saturated aqueous sodium hydrogencarbonate, water, brine, and dried ($MgSO_4$). Flash chromatography (hexanes/ether, 1:9) of the crude product gave an epimeric mixture (3:1) of methyl 15ξ-cyano-12-methoxy-4α-methyl-17-oxo-18-nor-5α-androsta-8,11,13-triene-4β-carboxylate (**32**) (11 mg, 79%), as a colourless oil (Found: $M^{+\bullet}$, 381.1956. $C_{23}H_{27}NO_4$ calcd.: M, 381.1940). ν_{max} 2241 (CN), 1716 (CO ester and ketone), 1604, 1578, 1458 (C=C), 1244, 1042 cm^{-1}. δ_H (major epimer) 1.08, s, $(H19)_3$; 1.14, td, *J* 13.7, 4.2 Hz, H3ax; 1.32, s, 4α-CH_3; 1.46, td, *J* 13.6, 4.2 Hz, H1ax; 1.62, dd, *J* 12.3, 1.3 Hz, H5; 1.69, bd, *J* 13.9 Hz, H2eq; 1.99, qd, *J* 12.6, 5.1 Hz, H6ax; 2.03, qt, *J* 13.9, 3.2 Hz, H2ax; 2.37, m, H1eq, H3eq, H6eq; 2.79, ddd, *J* 16.8, 5.3, 1.5 Hz, H7eq; 2.98, m, H7ax; 2.99, dd, *J* 18.8, 3.8 Hz, $(H16)_1$; 3.10, dd, *J* 18.7, 8.7 Hz, $(H16)_1$; 3.11, dd, *J* 16.8, 8.7 Hz, H7ax; 3.69, s, CO_2CH_3; 3.93, s, $ArOCH_3$; 4.17, dd, *J* 8.6, 3.7 Hz, H15; 6.89, s, H11. δ_C (major epimer) 19.9, C2; 20.3, C6; 22.8, C19; 26.5, C15; 27.8, C7; 28.4, 4α-CH_3; 37.2, C3; 39.5, C1; 40.0, C10; 41.0, C16; 44.0, C4; 51.4, CO_2CH_3; 55.8, $ArOCH_3$; 109.4, C11; 118.6, C8; 122.1, CN; 125.8, C13; 147.8, C14; 156.3, C9; 159.1, C12; 177.6, CO ester; 198.5, CO ketone. *m/z* 381 (100, M^+), 366 (4, *M*–Me), 354 (12, *M*–HCN), 322 (8), 306 (88, 366–CH_3CO_2H), 279 (15), 240 (25), 45 (31).

(ii) Repetition of the above but with dry glacial acetic acid (1 drop) instead of sodium acetate, and stirring for 15 h, gave **32** (67%).

(iii) A solution of **30** (17 mg, 0.04 mmol) in dichloromethane (1 ml) was added to a stirred solution of pyridinium chlorochromate (14 mg, 0.07 mmol) in dichloromethane (4 ml). After 24 h, workup as above gave (i) **32** (10 mg, 59%), and (ii) methyl 15-cyano-16-hydroxy-12-methoxy-4α-methyl-17-oxo-18-nor-5α-androsta-8,11,13,15-tetraene-4β-carboxylate (**39**) (5 mg, 27%) (Found: $M^{+\bullet}$, 395.1711. $C_{23}H_{25}NO_5$ calcd.: M, 395.1733). ν_{max} 3390 (OH), 2347 (CN), 1715 (CO ester), 1680 (CO ketone), 1652, 1592 (C=C), 1133, 1084 cm^{-1}. δ_H 1.16, s, $(H19)_3$; 1.18, m, H3ax; 1.31, s, 4α-CH_3; 1.35, td, *J* 13.5, 4.3 Hz, H1ax; 1.70, m, H5, H2eq, OH; 1.95–2.45, m, H6ax, H2eq, H1eq, H3eq, H6eq; 3.05, ddd, *J* 17.5, 13.0, 6.3 Hz, H7ax; 3.29, ddd, *J* 17.5, 6.2, 2.3 Hz, H7eq; 3.73, s, CO_2CH_3; 4.04, s, $ArOCH_3$; 7.01, s, H11. *m/z* 395 (100, M^+), 335 (15, *M*–CH_3CO_2H), 320 (18, 335–Me), 293 (10, 320–HCN), 279 (21), 254 (18), 129 (8).

3.9. Oxidation of 17ξ-hydroxy-12-methoxy-4β-methoxymethyl-4α-methyl-18-nor-5α-androsta-8,11,13-triene-15ξ-carbonitrile (31)

Pyridinium chlorochromate (53 mg, 0.25 mmol) was added to a stirred solution of **31** (60 mg, 0.16 mmol), anhydrous sodium acetate (9 mg, 0.11 mmol), and flame-dried powdered molecular sieves (3 A, 0.15 g) in

dichloromethane (4 ml). After 3 h, aqueous HCl (2 mol l^{-1}) was added and the mixture was filtered through Celite. Workup followed by PLC (hexanes/ether, 3:7, 4 sweeps) gave a mixture (3:1) of epimers of 12-methoxy-4β-methoxymethyl-4α-methyl-18-nor-3-oxo-α-androsta-8,11,13-triene-15ξ-carbonitrile (**33**) (49 mg, 82%) (Found: $M^{+\bullet}$ 367.2143. $C_{23}H_{29}NO_3$ calcd.: M, 367.2147). ν_{max} 2240 (CN), 1713 (CO), 1604, 1579, 1481 (C=C), 1304, 1247, 1105 cm^{-1}. δ_H (major epimer) 1.03, td, *J* 13.7, 4.5 Hz, H3ax; 1.09, s, 4α-CH_3; 1.24, s, $(H19)_3$; 1.46, td, *J* 12.5, 4.0 Hz, H1ax; 1.51, dd, *J* 12.9, 1.6 Hz, H5; 1.71, m, H2ax, H2eq, H6ax; 1.88, bd, *J* 13.6 Hz, H3eq; 2.15, dd, *J* 13.5, 7.4 Hz, H6eq; 2.31, bd, *J* 12.4 Hz, H1eq; 2.77, dd, *J* 17.0, 5.0 Hz, H7eq; 2.80, ddd, *J* 18.7, 6.9 Hz, $(H16)_1$; 3.02, m, H7ax; 3.10, dd, *J* 18.8, 8.7 Hz, $(H16)_1$; 3.31, 3.49, 2d, *J* 9.1 Hz, CH_2OCH_3; 3.34, s, CH_2OCH_3; 3.93, s, $ArOCH_3$; 4.17, dd, *J* 8.7, 3.5 Hz, H15; 6.91, s, H11. δ_C (major epimer) 18.7, C2; 19.0, C6; 25.4, C19; 26.4, 4α-CH_3; 27.0, C7; 27.6, C15; 35.8, C3; 38.0, C4; 39.0, C1; 39.3, C10; 41.0, C16; 50.6, C5; 55.7, $ArOCH_3$; 59.3, CH_2OCH_3; 76.1, CH_2OCH_3; 108.5, C11; 118.5, C8; 121.7, CN; 125.3, C13; 147.6, C14; 156.2, C9; 160.8, C12; 198.6, CO. *m/z* 367 (46, M^+), 352 (2, *M*–Me), 320 (8), 300 (8), 252 (18), 240 (100).

3.10. Oxidative decyanation of methyl 15ξ-cyano-17ξ-hydroxy-12-methoxy-4α-methyl-18-nor-5α-androsta-8, 11,13-triene-4β-carboxylate (30)

A solution of **30** (40 mg, 0.10 mmol) in dimethyl sulfoxide (1 ml) was added to a stirred mixture of sodium hydroxide (5 mg, 0.13 mmol) and benzyltriethylammonium chloride (1 mg, 0.005 mmol) in dimethyl sulfoxide (2 ml)/water (2 drops). Oxygen was bubbled through the reddish-brown mixture for 40 min. Workup followed by PLC (hexanes/ether, 3:7) gave a mixture (5:4) of epimers of methyl 17ξ-hydroxy-12-methoxy-15-oxo-18-nor-5α-androsta-8,11,13-triene-4β-carboxylate (**34**) (32 mg, 83%) (Found: $M^{+\bullet}$, 372.1930. $C_{22}H_{28}O_5$ calcd.: M, 372.1937). ν_{max} 3486 (OH), 1709 (CO, ester, ketone), 1605, 1486, 1463 (C=C), 1287, 1159 cm^{-1}. δ_H 1.07, s, $(H19)_3$; 1.08, td, *J* 13.5, 4.0 Hz, H3ax; 1.280, 1.285, 2s, 4α-CH_3; 1.39, td, *J* 13.4, 4.7 Hz, H1ax; 1.50, 1.51, 2dd, *J* 12.4, 1.5 Hz, H5; 1.66, dp, *J* 13.9, 3.0 Hz, H2eq; 1.87, qd, *J* 12.6, 5.3 Hz, H6ax; 2.02, qt, *J* 13.9, 3.7 Hz, H2ax; 2.22, m, H1eq, H3eq, H6eq; 2.61, 2.64, 2dd, J 18.7, 2.9 Hz, $(H16)_1$; 2.80, ddd, *J* 17.4, 12.8, 7.9 Hz, H7ax; 2.80, bs, OH; 3.01, 3.02, 2dd, *J* 18.7, 6.9 Hz, $(H16)_1$; 3.50, dd, *J* 17.4, 5.2 Hz, H7eq; 3.670, 3.674, 2s, CO_2CH_3; 3.91, s, $ArOCH_3$; 5.46, dd, *J* 6.9, 3.0 Hz, H17 (stereoisomer); 5.47, dd, *J* 6.0, 2.9 Hz, H17 (stereoisomer); 7.02, s, H11. δ_C 19.9, C2; 20.12, 20.16, C6; 22.8, C19; 27.8, 28.1, C7; 28.4, 4α-CH_3; 37.5, C3; 39.2, C10; 39.9, C1; 43.9, C4; 46.19, 46.27, C16; 51.3, CO_2CH_3; 52.11, 52.24, C5; 55.4, $ArOCH_3$; 65.53, 65.69, C17; 113.1, C11; 127.98, 128.03, C8; 134.6, C13; 142.0, C14; 151.5, C9; 154.66, 154.73, C12; 177.7, CO, ester; 203.94, 204.14, CO, ketone. *m/z* 372 (100, M^+), 357 (4, *M*–Me), 354 (5, *M*–H_2O), 339 (9, 354–Me), 313 (5), 297 (48, 357-CH_3CO_2H).

3.11. Dehydration of methyl 17ξ-hydroxy-12-methoxy-15-oxo-18-nor-5α-androsta-8,11,13-triene-4β-carboxylate (34)

A solution of **34** (16 mg, 0.04 mmol) and *p*-toluenesulfonic acid (1 mg) in benzene (5 ml) was heated to reflux for 30 min. Removal of solvent followed by PLC (hexanes/ether, 3:2) gave methyl 12-methoxy-15-oxo-18-nor-5α-androsta-8,11,13,16-tetraene-4β-carboxylate (**40**) (11 mg, 73%) (Found: $M^{+\bullet}$, 354.1825. $C_{22}H_{26}O_4$ calcd.: M, 354.1831). ν_{max} 1724 (CO, ester), 1699 (CO, ketone), 1616, 1470 (C=C), 1304, 1158 cm^{-1}. δ_H 1.05, s, $(H19)_3$; 1.08, td, *J* 13.5, 4.2 Hz, H3ax; 1.27, s, 4α-CH_3; 1.41, td, *J* 13.9, 4.1 Hz, H1ax; 1.51, dd, *J* 12.5, 1.5 Hz, H5; 1.60, dp, *J* 14.2, 3.3 Hz, H2eq; 1.87, qd, *J* 13.9, 5.3 Hz, H6ax; 2.00, qt, *J* 14.0, 3.7 Hz, H2ax; 2.19, m, H1eq, H6eq; 2.28, bd, *J* 13.3 Hz, H3eq; 2.67, ddd, *J* 18.4, 13.0, 6.5 Hz, H7ax; 3.44, ddd, *J* 18.4, 5.5, 1.4 Hz, H7eq; 3.67, s, CO_2CH_3; 3.83, s, $ArOCH_3$; 5.66, d, *J* 6.0 Hz, H16; 6.85, s, H11; 7.65, d, *J* 6.0 Hz, H17. δ_C 20.0, C2; 20.1, C6; 22.9, C19; 27.3, C7; 28.5, 4α-CH_3; 37.5, C3; 39.4, C10; 40.0, C1; 44.0, C4; 51.3, CO_2CH_3; 52.3, C5; 55.9, $ArOCH_3$; 115.2, C11; 124.9, C16; 129.5, C8; 136.6, C13; 141.9, C14; 145.3, C17; 148.0, C9; 153.7, C12; 176.6, CO, ester; 200.2, CO, ketone. *m/z* 354 (100, M^+), 339 (3, *M*–Me), 322 (4, *M*–MeOH), 294 (51, *M*–CH_3CO_2H), 279 (52, 294–Me), 225 (23).

3.12. Reductive decyanation of a mixture (9:1) of 2-[2'ξ-cyano-2'-(14"-(methyl 12"-methoxypodocarpa-8", 11",13"-trien-19"-oate))ethyl]-1,3-dioxolane (6) and 2-[2'ξ-cyano-2'-(13"-(methyl 12"-methoxypodocarpa-8", 11",13"-trien-19"-oate))ethyl]-1,3-dioxolane (7)

A mixture (9:1) of the dioxolanes **6** and **7** (58 mg, 0.14 mmol) in THF (1 ml) and 2-propanol (1 drop) was added to redistilled (from sodium) liquid ammonia (10 ml) at −78°C. Sodium was added in very small portions in order to just maintain the blue colour. After 1 h, the system was quenched by the addition of solid ammonium chloride, the liquid ammonia was evaporated overnight, and water was added to the residue. Extraction with dichloromethane followed by PLC (hexanes/ether, 7:3, 5 sweeps) gave (i) 2-[2'-(14"-(12"-methoxypodocarpa-8",11",13"-trien-19"-oic acid))ethyl]-1,3-dioxolane (**15**) (42 mg, 80%) as a colourless oil, b.p. 185°C/0.01 mmHg (Kugelrohr) (Found: C, 70.8; H, 8.3. $C_{23}H_{32}O_5$ calcd.: C, 71.1; H, 8.3%) (Found: $M^{+\bullet}$, 388.2256. $C_{23}H_{32}O_5$ calcd.: M, 388.2250). ν_{max} 3300–

2500 (OH broad), 1695 (CO), 1604, 1468 (C=C), 1140 cm^{-1}. δ_H 1.07, td, *J* 13.5, 4.1 Hz, H3″ax; 1.14, s, $(H20'')_3$; 1.33, s, $(H18'')_3$; 1.36, td, *J* 14.2, 4.4 Hz, H1″ax; 1.55, d, *J* 11.8 Hz, H5″; 1.62, bd, *J* 14.2 Hz, H2″eq; 1.98, m, H6″ax, H2″ax, $(H1')_2$; 2.25, m, H6″eq, H1″eq, H3″eq; 2.57, ddd, *J* 16.5, 12.7, 6.3 Hz, H7″ax; 2.67, dd, *J* 16.5, 5.7 Hz, $(H2')_2$; 2.88, dd, *J* 16.5, 4.5 Hz, H7″eq; 3.75, s, $ArOCH_3$; 3.89, 4.02, 2m, $(H4)_2$, $(H5)_2$; 4.94, t, *J* 4.6 Hz, H2; 6.60, d, *J* 2.4 Hz, H11″; 6.70, d, *J* 2.4 Hz, H13″. δ_C 20.0, C2″; 20.8, C6″; 23.0, C20″; 27.4, C2′; 28.2, C7″; 28.6, C18″; 33.9, C1′; 37.2, C3″; 39.1, C10″; 39.8, C1″; 43.0, C4″; 52.4, C5″; 55.1, $ArOCH_3$; 64.9, C4, C5; 104.1, C2; 109.1, C13″; 111.6, C11″; 125.7, C8″; 140.7, C14″; 149.7, C9″; 157.5, C12″; 183.8, CO. *m/z* 388 (19, M^+), 326 (43), 302 (100, $M-H_2CCHOCH_2CH_2O+H$), 254 (8), 185 (10), 135 (38), 73 (15, *M*–diterpenoid–C_2H_4); and (ii) 2-[2′-(13″-(12″-methoxypodocarpa-8″,11″,13″-trien-19″-oic acid)) ethyl]-1,3-dioxolane (**16**) (3 mg, 6%) as a colourless oil, b.p. 185°C/0.01 mmHg (Kugelrohr) (Found: $M^{+\bullet}$, 388.2253. $C_{23}H_{32}O_5$ calcd.: M, 388.2250). ν_{max} 3500-2500 (OH broad), 1698 (CO), 1615, 1576, 1501, 1460 cm^{-1} (C=C). δ_H 1.08, td, *J* 13.6, 4.0 Hz, H3″ax; 1.12, s, $(H20'')_3$; 1.33, s, $(H18'')_3$; 1.41, td, *J* 13.2, 3.8 Hz, H1″ax; 1.54, d, *J* 12.0 Hz, H5″; 1.62, bd, *J* 14.1 Hz, H2″eq; 2.00, m, $(H1')_2$, H2″ax; H6″ax; 2.20, m, H6″eq, H1″eq, H3″eq; 2.68, m, $(H2')_2$, H7″ax; 2.80, dd, *J* 16.5, 4.8 Hz, H7″eq; 3.76, s, $ArOCH_3$; 3.88, 3.99, 2m, $(H4)_2$, $(H5)_2$; 4.90, t, *J* 4.8 Hz, H2; 6.69, s, H11″; 6.81, s, H14″. δ_C 19.9, C2″; 21.0, C6″; 23.0, C20″; 24.5, C2′; 28.7, C18″; 31.1, C7″; 33.7, C1′; 37.3, C3″; 38.7, C10″; 39.1, C1″; 43.9, C4″; 52.9, C5″; 55.3, $ArOCH_3$; 64.8, C4, C5; 104.4, C2; 107.1, C11″; 126.9, C8″; 127.4, C13″; 130.1, C14″; 146.5, C9″; 155.7, C12″; 183.9, CO. *m/z* 388 (65, M^+), 326 (10), 311 (10), 302 (48, $M-H_2CCHOCH_2CH_2O+H$), 285 (50), 100 (100, *M*–diterpenoid–H), 73 (68, *M*–diterpenoid–C_2H_4).

When the sodium was added in one portion, or too quickly, 2-[(14″-(12″-methoxypodocarpa-8″,11″,13″-trien-19″-ol))ethyl]-1,3-dioxolane (**17**) was also obtained as a colourless oil, b.p. 180°C/0.05 mmHg (Kugelrohr) (Found: $M^{+\bullet}$, 374.2445. $C_{23}H_{34}O_4$ calcd.: M, 374.2457). ν_{max} 3521 (OH), 1603, 1469 (C=C), 1293, 1138, 1033 cm^{-1}. δ_H 1.01, td, *J* 13.4, 4.1 Hz, H3″ax; 1.04, s, $(H18'')_3$; 1.19, s, $(H20'')_3$; 1.43, td, *J* 12.9, 5.2 Hz, H1″ax; 1.47, dd, *J* 12.9, 1.2 Hz, H5″; 1.66, m, H2″ax, H2″eq, H6″ax; 1.88, bd, *J* 16.1 Hz, H3″eq; 1.92, m, *J* 5.0 Hz, $(H1')_2$; 2.04, dd, *J* 13.1, 7.5 Hz, H6″eq; 2.27, bd, *J* 12.7 Hz, H1″eq; 2.63, m, H7″ax, $(H2')_2$; 2.82, dd, *J* 17.0, 6.0 Hz, H7″eq; 3.55, 3.87, 2d, *J* 10.9 Hz, $(H19'')_2$; 3.76, s, $ArOCH_3$; 3.89, 4.00, 2m, $(H4)_2$, $(H5)_2$; 4.94, t, *J* 4.6 Hz, H2; 6.60, d, *J* 2.5 Hz, H11″; 6.72, d, *J* 2.5 Hz, H13″. δ_C 19.1, C6″; 19.2, C2″; 25.7, C18″; 26.7, C20″; 27.3, C2′; 27.4, C7″; 33.9, C1′; 35.0, C3″; 38.2, C10″; 38.7, C4″; 39.3, C1″; 50.7, C5″; 55.2, $ArOCH_3$; 65.0, C4, C5; 65.2, C19″; 104.1, C2; 108.3, C13″; 111.5, C11″; 125.2, C8″; 140.7, C14″; 151.5, C9″; 157.5, C12″. *m/z* 374 (22, M^+), 312 (45), 288 (100, $M-H_2CCHOCH_2CH_2O+H$), 135 (32), 100 (5), 73 (18, *M*–diterpenoid–C_2H_4).

The 13″-substituted regioisomer **18** was formed similarly but no spectral data was obtained.

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

Titanium(IV) chloride (24 μl, 0.22 mmol) in dichloromethane (0.1 ml) was added slowly to a cooled (−78°C) solution of **15** (70 mg, 0.18 mmol) in dichloromethane (8 ml). After 30 min the mixture was warmed to room temperature. The mixture was again cooled (0°C). Workup followed by PLC (hexanes/ether, 3:2, 4 sweeps) gave a mixture (50 mg, 5:1) of (i) 12-methoxy-4α-methyl-18-nor-5α-androsta-6,8,11,13-tetraen-4β-oic acid (**43**) (68%) as a colourless oil (Found: $M^{+\bullet}$, 326.1887. $C_{21}H_{26}O_3$ calcd.: M, 326.1882). ν_{max} 3500-2400 (OH), 1695 (CO), 1592, 1464 (C=C), 1298, 1092 cm^{-1}. δ_H 0.95, s, $(H19)_3$; 1.12, td, *J* 13.5, 3.9 Hz, H3ax; 1.36, s, 4α-CH_3; 1.65, td, *J* 13.1, 3.9 Hz, H1ax; 1.68, dp, *J* 13.8, 3.2 Hz, H2eq; 1.98, qt, *J* 13.8, 3.2 Hz, H2ax; 2.07, m, $(H16)_2$; 2.21, bd, *J* 13.4 Hz, H1eq; 2.31, bd, *J* 13.1 Hz, H3eq; 2.35, t, *J* 2.7 Hz, H5; 2.84, m, $(H15)_1$, $(H17)_2$; 2.97, m, $(H15)_1$; 3.81, $ArOCH_3$; 6.39, dd, *J* 9.9, 2.4 Hz, H6; 6.49, dd, *J* 9.9, 3.0 Hz, H7; 6.58, s, H11. δ_C (50 MHz) 19.3, C19; 19.7, C2; 24.7, C16; 28.0, 4α-CH_3; 29.3, C17; 31.2, C15; 36.5, C1; 37.0, C3; 38.4, C10; 43.3, C4; 51.5, C5; 55.2, $ArOCH_3$; 103.2, C11; 121.6, C8; 122.7, C7; 127.0, C6; 129.2, C13; 142.4, C14; 146.4, C9; 155.2, C12; 183.8, CO. *m/z* 326 (100, M^+), 281 (10, *M*–CO_2H), 265 (78), 225 (57) 185 (11), 165 (17); and (ii) 12-methoxy-4α-methyl-18-nor-5α-androsta-8,11,13-trien-4β-oic acid (**35**) (17%) (Found: $M^{+\bullet}$, 328.2033. $C_{21}H_{28}O_3$ calcd.: M, 328.2038). ν_{max} 3500-2400 (OH), 1695 cm^{-1} (CO). δ_H 1.15, s, $(H19)_3$; 1.33, s, 4α-CH_3; 1.55, d, *J* 12.1 Hz, H5; 3.78, s, $ArOCH_3$; 6.62, s, H11. δ_C (50 MHz) 20.0, C2; 20.6, C6; 23.1, C19; 24.4, C16; 28.7, 4α-CH_3, C7; 28.9, C17; 31.7, C15; 37.3, C3; 38.9, C10; 39.8, C1; 43.9, C4; 52.8, C5; 55.2, $ArOCH_3$; 105.3, C11; 123.7, C8; 129.0, C13; 144.5, C14; 147.4, C9; 154.1, C12; 184.1, CO. *m/z* 328 (100, M^+), 313 (70, *M*–Me), 266 (80).

3.14. Reductive decyanation of methyl 15ξ-cyano-17ξ-hydroxy-12-methoxy-4α-methyl-18-nor-5α-androsta-8,11,13-triene-4β-carboxylate (30)

2-Propanol (1 drop) and then a solution of **30** (50 mg, 0.13 mmol) in THF (1 ml) were added to liquid ammonia (8 ml) at − 78°C. Sodium was added in very small portions. After 30 min solid ammonium chloride

was added and the liquid ammonia allowed to evaporate overnight. Work-up followed by PLC (hexanes/ether, 3:2, 3 sweeps) gave (i) methyl 17ξ-hydroxy-12-methoxy-4α-methyl-18-nor-5α-androsta-8,11,13-triene-4β-carboxylate (**36**) (20 mg, 43%) (Found: $M^{+\bullet}$, 358.2150. $C_{22}H_{30}O_4$ calcd.: M, 358.2144). ν_{max} 3480 (OH), 1725 (CO), 1602, 1465, (C=C), 1223, 1141, 1092 cm^{-1}. δ_H 1.05, s, $(H19)_3$; 1.08, td, *J* 13.6, 4.2 Hz, H3ax; 1.28, s, 4α-CH_3; 1.40, td, *J* 13.4, 3.8 Hz, H1ax; 1.51, dd, *J* 12.3, 1.5 Hz, H5; 1.63, dp, *J* 14.2, 2.9 Hz, H2eq; 1.94, qd, *J* 13.7, 5.7 Hz, H6ax; 1.95–2.08, m, H2ax, $(H16)_1$; 2.18–2.31, m, H1eq, H3eq, H6eq; 2.38–2.65, m, $(H15)_2$, $(H16)_1$, OH; 2.72, dd, *J* 16.9, 4.8 Hz, H7eq; 2.97, ddd, *J* 16.9, 8.8, 5.2 Hz, H7ax; 3.67, s, CO_2CH_3; 3.83, s, $ArOCH_3$; 5.44, dd, *J* 7.3, 4.1 Hz, H17; 6.65, s, H11. δ_C 20.0, C2; 20.6, C6; 22.8, C19; 28.5, 4α-CH_3, C7; 29.2, C15; 33.7, C16; 37.6, C3; 38.9, C10; 39.9, C1; 44.0, C4; 51.2, CO_2CH_3; 52.6, C5; 55.0, $ArOCH_3$; 74.6, C17; 105.6, C11; 124.2, C8; 129.5, C13; 144.0, C14; 149.9, C9; 154.4, C12; 177.9, CO. *m/z* 358 (7, M^+), 340 (100, $M-H_2O$), 325 (22, 340-Me), 293 (8), 281 (8), 265 (84), 159 (29); and (ii) the epimer of methyl 17ξ-hydroxy-12-methoxy-4α-methyl-18-nor-5α-androsta-8,11,13-triene-4β-carboxylate (**36**) (19 mg, 40%) (Found: $M^{+\bullet}$, 358.2153. $C_{22}H_{30}O_4$ calcd.: M, 358.2144). ν_{max} 3422 (OH), 1724 (CO), 1601, 1465 (C=C), 1222, 1141, 1092 cm^{-1}. δ_H 1.06, s, $(H19)_3$; 1.09, td, *J* 13.4, 4.3 Hz, H3ax; 1.28, s, 4α-CH_3; 1.40, td, *J* 13.0, 3.8 Hz, H1ax; 1.53, dd, *J* 12.4, 1.6 Hz, H5; 1.64, dp, *J* 14.2, 2.9 Hz, H2eq; 1.93, qd, *J* 13.7, 5.6 Hz, H6ax; 1.96–2.09, m, H2ax, $(H16)_1$; 2.18-2.32, m, H1eq, H3eq, H6eq; 2.41–2.58, m, $(H15)_2$, $(H16)_1$; 2.71, dd, *J* 16.1, 5.1 Hz, H7eq; 2.71, bs, OH; 2.88, ddd, *J* 16.1, 8.9, 4.7 Hz, H7ax; 3.67, s, CO_2CH_3; 3.83, s, $ArOCH_3$; 5.45, dd, *J* 7.3, 4.5 Hz, H17; 6.65, s, H11. δ_C 20.2, C2; 20.6, C6; 22.8, C19; 28.56, 4α-CH_3; 28.59, C7; 29.2, C15; 33.7, C16; 37.6, C3; 39.0, C10; 39.9, C1; 44.0, C4; 51.2, CO_2CH_3; 52.7, C5; 55.1, $ArOCH_3$; 74.6, C17; 105.6, C11; 124.2, C8; 129.6, C13; 143.9, C14; 144.9, C9; 154.4, C12; 177.9, CO. *m/z* 358 (3, M^+), 340 (100, $M-H_2O$), 325 (22, 340–Me), 293 (8), 281 (8), 265 (84), 159 (29).

3.15. Reductive decyanation of 17ξ-hydroxy-12-methoxy-4β-methoxymethyl-4α-methyl-18-nor-5α-androsta-8,11, 13-triene-15ξ-carbonitrile (31)

A solution of **31** (80 mg, 0.22 mmol) in THF (2 ml) containing 2-propanol (1 drop) was added to liquid ammonia (8 ml) at −78°C. Sodium was added in very small portions. After 1 h the system was quenched by the addition of solid ammonium chloride. The liquid ammonia was allowed to evaporate overnight. Work-up followed by PLC (hexanes/ether, 3:2, 2 sweeps) gave (i) 12-methoxy-4β-methoxymethyl-4α-methyl-18-nor-5α-androsta-8,11,13-trien-17ξ-ol (**37**) (54 mg, 72%) as a mixture (1:1) of epimers (Found: $M^{+\bullet}$, 344.2351. $C_{22}H_{32}O_3$ calcd.: M, 344.2355). ν_{max} 3468 (OH), 1602, 1464 (C=C), 1305, 1111 cm^{-1}. δ_H 1.00, td, *J* 13.5, 4.8 Hz, H3ax; 1.035, 1.039, 2s, 4α-CH_3; 1.21, s, $(H19)_3$; 1.41, m, H1ax; 1.43, dd, *J* 12.3, 2.0 Hz, H5; 1.70, m, H2ax, H2eq, H6ax; 1.89, bd, *J* 13.4 Hz, H3eq; 2.02, m, H6eq, $(H16)_1$; 2.29, bd, *J* 13.4 Hz, H1eq; 2.41, m, $(H15)_1$; 2.51–2.74, m, H7eq, $(H15)_1$, $(H16)_1$; 2.82, 2.92, 2ddd, *J* 15.8, 8.9, 5.2 Hz, H7ax; 3.24, 3.56, 2d, *J* 9.1 Hz, CH_2OCH_3; 3.33, s, CH_2OCH_3; 3.83, s, $ArOCH_3$; 5.44, dd, *J* 7.5, 4.1 Hz, H17 (stereoisomer); 5.45, dd, *J* 7.7, 4.4 Hz, H17 (stereoisomer); 6.66, s, H11. δ_C 18.9, C2; 19.2, C6; 25.56, 25.62, C19; 27.6, 4α-CH_3; 27.7, 27.8, C7; 29.0, 29.1, C15; 33.69, 33.72, C16; 35.9, C3; 38.0, C4; 38.2, C10; 39.4, C1; 51.18, 51.22, C5; 55.0, 55.1, $ArOCH_3$; 59.4, CH_2OCH_3; 74.47, 74.49, C17; 75.79, 75.82, CH_2OCH_3; 104.7, C11; 123.6, C8; 129.25, 129.31, C13; 143.9, C14; 151.7, C9; 154.26, 154.29, C12. *m/z* 344 (100, $M^{+\bullet}$), 326 (96, $M-H_2O$), 311 (35, 326–Me), 297 (20), 279 (50), 267 (34), 185 (43); and (ii) 12-methoxy-4β-methoxymethyl-4α-methyl-18-nor-5α-androsta-8,11,13-triene (**38**) (8 mg, 11%) (Found: $M^{+\bullet}$, 328.2395. $C_{22}H_{32}O_2$ calcd.: M, 328.2402). ν_{max} 1598, 1465 (C=C), 1298, 1111 cm^{-1}. δ_H 1.00, td, *J* 13.5, 4.1 Hz, H3ax; 1.04, s, 4α-CH_3; 1.23, s, $(H19)_3$; 1.44, dd, *J* 12.8, 1.8 Hz, H5; 1.48, td, *J* 12.8, 3.6 Hz, H1ax; 1.56–1.82, m, H2ax, H2eq, H6ax; 1.89, dd, *J* 13.5, 1.2 Hz, H3eq; 2.01, dd, *J* 13.4, 7.5 Hz, H6eq; 2.06, m, $(H16)_2$; 2.29, bd, *J* 12.8 Hz, H1eq; 2.57, ddd, *J* 17.3, 11.6, 7.4 Hz, H7ax; 2.63–2.99, m, H7eq, $(H15)_2$, $(H16)_2$; 3.23, 3.56, 2d, *J* 9.1 Hz, CH_2OCH_3; 3.34, s, CH_2OCH_3; 3.80, s, $ArOCH_3$; 6.63, s, H11. δ_C 19.1, C2; 19.3, C6; 24.5, C16; 25.8, C19; 27.6, 4α-CH_3; 28.2, C7; 29.3, C15; 31.7, C17; 35.9, C3; 38.1, C4, C10; 39.5, C1; 51.4, C5; 55.3, $ArOCH_3$; 59.4, CH_2OCH_3; 75.9, CH_2OCH_3; 104.7, C11; 123.4, C8; 128.8, C13; 144.6, C14; 149.4, C9; 154.1, C12. *m/z* 328 (100, M^+), 313 (19, *M*–Me), 297 (1), 281 (55), 201 (31), 187 (55).

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