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Ring A modification of podocarpic acid derivatives: functionalization and cyclopentaannulation of ring C *via* (η^6-arene)tricarbonylchromium(0) complexes

Richard C. Cambie, Peter S. Rutledge, Ralph J. Stevenson and Paul D. Woodgate

Department of Chemistry, University of Auckland, Private Bag 92019, Auckland (New Zealand)

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Abstract

Modification of ring A *via* radical decarboxylation of the 19-carboxylic acid **2** to give the 4(18)-*exo*-methylene diterpenoid **6**, followed by functionalization of ring C *via* addition–oxidation of the (η^6-arene)tricarbonylchromium(0) complex **13**, has been achieved. Further oxidative modifications of ring A followed by titanium(IV) chloride-mediated cyclopentaannulation of ring C produced the ring-C aromatic androstane analogues **17** and **21**, in which the A rings are structurally similar to those in some of the naturally occurring fully alicyclic steroids.

Key words: Chromium; Arene; Ring A modification; Podocarpic acid derivatives; Functionalization; Cyclopentaannulation

1. Introduction

Conversion of derivatives of the tricyclic diterpenoid podocarpic acid (**1**) into ring-C aromatic steroidal analogues [1*–3] requires not only ring D annulation but also ring A modification. Earlier [4–7], we reported the conversion of the 19-carboxylic acid **2** into the enone **5** in 18% overall yield, the decarboxylation being achieved by reaction of **2** with lead tetra-acetate. Recently, Cochrane *et al.* [8], using a diterpenoid substrate, have made use of the highly efficient radical decarboxylation of the ester derived from *N*-hydroxypyridine-2-thione, followed by sulfoxide cyclo-elimination. We have reported [9] that application of this sequence to **2** gives the 4(18)-alkene **6** in high overall yield. We now report the combination of this strategy with the formation of the (η^6-arene)tricarbonylchromium(0) complexes **12** which has allowed functionalization/cyclopentaannulation of ring C to produce ring-C aromatic androstane analogues which contain a number of the key features (in ring A) of some common steroids [10].

Correspondence to: Professor P.D. Woodgate.

* Reference number with asterisk indicates a note in the list of references.

2. Results and discussion

First some significant improvements were made to the procedure reported previously [9]. Thus, the sodium salt **3** of the 19-carboxylic acid **2** was prepared as a suspension in benzene by treatment of the acid with sodium hydride and subsequent addition of oxalyl chloride which resulted in the immediate (*cf.* previously 16 h [9]) formation of the acid chloride **4** (100%). Secondly, formation of an alkene impurity in the next step was minimized by using benzene instead of toluene [9] as the solvent, leading to the required 2′-pyridylthio derivative **15** in 91% yield. Oxidation/cyclo-elimination then gave the 4(18)-alkene **6** (96%).

Treatment of alkene **6** with hexacarbonylchromium(0) [11] gave a mixture (91:9) (90%) of the α/β-diastereoisomers of the (η^6-arene)tricarbonylchromium(0) complex **12** from which the pure α-diastereoisomer **13** was obtained by recrystallization. When the pure α-complex **13** was reacted with the lithio-anion derived from **16** [12] and then iodine in an addition–oxidation sequence, the 14″-substituted dioxolane **7** (92%) was formed as a mixture (2:1) of diastereoisomers at the new (benzylic) stereo centre. Most interesting was the virtual absence ($\leq 1\%$) of any of the

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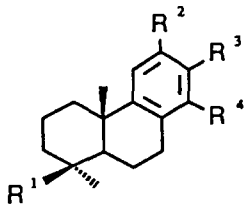
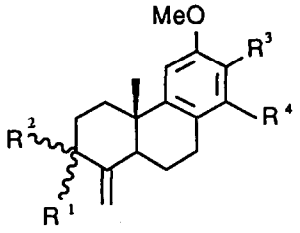


(1:R^1=CO_2H, R^2=OH, R^3=H, R^4=H

2:R^1=CO_2H, R^2=OMe, R^3=H, R^4=H

3:R^1=CO_2Na, R^2=OMe, R^3=H, R^4=H

4:R^1=COCl, R^2=OMe, R^3=H, R^4=H)



(6:R^1=H, R^2=H, R^3=H, R^4=H

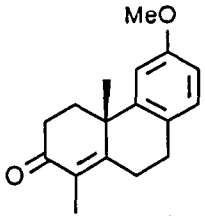
7:R^1=H, R^2=H, R^3=H, R^4=CH(CN)CH_2CHO$(CH_2)_2$O

8:R^1=H, R^2=H, R^3=CH(CN)CH_2CHO$(CH_2)_2$O, R^4=H

9:R^1=H, R^2=H, R^3=H, R^4=OH

10:R^1=H, R^2=α-OH, R^3=H, R^4=CH(CN)CH_2CHO$(CH_2)_2$O

11:R^1/R^2=O, R^3=H, R^4=CH(CN)CH_2CHO$(CH_2)_2$O)



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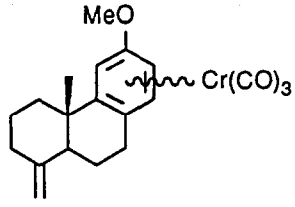

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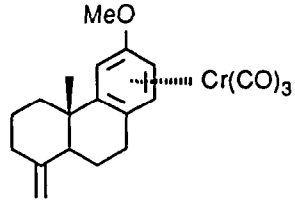

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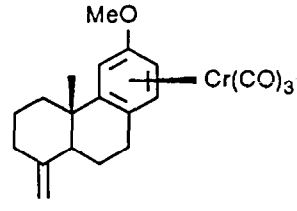

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13″-substituted regioisomers **8**. This isomer was, however, produced (up to 10% yield) when a mixture (5 : 1) of the α/β-diastereoisomers **13**/**14** was reacted with the anion derived from **16**. These results support the view that the α-isomer (in which a carbonyl ligand preferentially eclipses C14 [13]) of such diterpenoid $Cr(CO)_3$ complexes gives predominantly or exclusively the 14-substituted product on reaction with a nucleophile; conversely, the β-isomer (in which C13 is nearly eclipsed by a carbonyl ligand) gives the 13-substituted product [14]. Intriguingly, from some runs of the addition–oxidation sequence, the 14-hydroxy diterpenoid **9** was also isolated [12].

Allylic oxidation of the 4″(18″)-alkene dioxolane **7** with SeO_2/t-BuOOH [15] gave the 3″α-alcohol **10** (68%). Swern oxidation [16] of the 3″α-alcohol **10** gave the 4″(18″)-en-3″-one **11** (95%). Titanium(IV) chloride-mediated cyclization [12] of **11** gave the 4-*exo*-methylene-3-keto androstane analogues **17** (67%) as a mixture (3 : 3 : 2 : 2) of four diastereoisomers.

Barton and Crich [17] have reported the use of pyridineseleninic anhydride (**18**), prepared *in situ* by oxidation of 2,2′-dipyridyl diselenide (**19**) [18] with iodosylbenzene ($PhIO_2$) [19], for the allylic oxidation of alkenes. It effects oxidation directly to α,β-unsaturated ketones, with retention of the initial double-bond regiochemistry. In the present work, reaction between the 4″(18″)-alkene **7** and the $PhIO_2$/2,2′-dipyridyl diselenide system did not give the anticipated 4″(18″)-en-3″-one **11**, but instead afforded the

1″,4″(18″)-dien-3″-one **20** (45%); in some runs a mixture of the enone and the dienone was formed. On the first attempt at this oxidation the reaction went relatively quickly (2 h). However, subsequent experiments resulted in extremely slow reaction. Consideration of the postulated mechanism [17] implies that a proton source is required. It was proposed that the use as a solvent of benzene dried by distillation from sodium was causing this rate retardation. Pleasingly, the addition of a catalytic amount of *p*-toluenesulfonic acid dramatically increased the reaction rate.

Cyclization of the 1″,4″(18″)-dien-3″-one dioxolane **20** promoted by titanium(IV) chloride gave the 1-ene-4-*exo*-methylen-3-one androstane analogues **21** (65%) as a mixture (3:3:2:2) of four diastereoisomers.

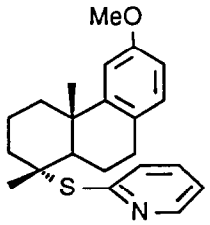
Thus, totally regioselective alkylation of the aromatic ring C of the tricyclic diterpenoid *via* a pure α $Cr(CO)_3$ complex, in combination with the decarboxylation/oxidation methodology applied to ring A, has enabled conversion of some derivatives of podocarpic acid into ring-C aromatic androstane analogues in a straightforward sequence.

3. Experimental details

For general experimental details, see refs. 20 and 21. High-field ^1H 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 a nitrogen atmosphere. Air-sensitive reagents were added by means of a syringe.

3.1. 12-Methoxypodocarpa-8,11,13-trien-19-oyl chloride (4)

Sodium hydride (10 mg, 50% w/w dispersion in oil, 0.42 mmol) was washed with dry hexane (×2) which was then removed with a Pasteur pipette. A solution of **2** (0.10 g, 0.35 mmol) in dry benzene (3 ml) was added to the sodium hydride and the mixture stirred for 30 min. Oxalyl chloride (0.45 ml, 0.52 mmol) was added slowly and stirring continued for a further 1 h. The mixture was then filtered and the solvents removed from the filtrate to give crude 12-methoxypodocarpa-8,11,13-trien-19-oyl chloride (**4**) (0.11 g, 100%). IR ν_{max} (cm^{-1}): 1802; 1778.



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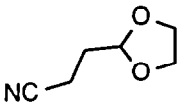

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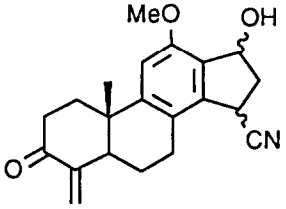

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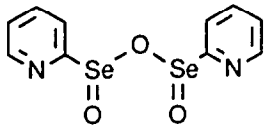

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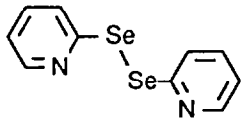

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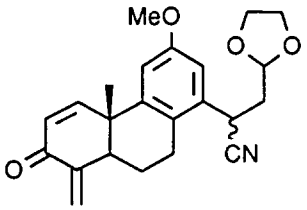

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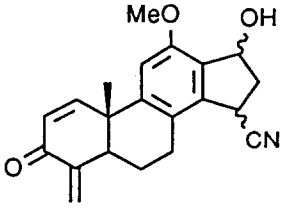

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3.2. 12-Methoxy-4α-(2'-pyridylthio)-18-norpodocarpa-8,11,13-triene (15)

A solution of **4** (0.11 g, 0.35 mmol) in dry benzene (2 ml) was added to an azeotropically-dried suspension of the sodium salt of 2-mercaptopyridine-*N*-oxide (62 mg, 0.42 mmol) and 4-*N*,*N*-dimethylaminopyridine (4 mg, 0.04 mmol) in benzene (6 ml) at reflux. After 1.5 h, the mixture was filtered through Celite. PLC (hexane/ether, 4:1) of the product gave 12-methoxy-4α-(2'-pyridylthio)-18-norpodocarpa-8,11,13-triene (**15**) (0.11 g, 91%) as a white solid [9].

3.3. Tricarbonyl[(8,9,11,12,13,14-η)-12-methoxy-19-norpodocarpa-4(18),8,11,13-tetraene]chromium(0) (12)

The 4(18)-alkene **6** (0.24 g, 0.98 mmol) and hexacarbonylchromium(0) (0.24 g, 1.1 mmol) were heated to reflux in a solution of dibutyl ether (20 ml) and tetrahydrofuran (THF) (2 ml) for 48 h while nitrogen was slowly bubbled through the system. The hot solution was filtered through Celite, and solvents were removed from the filtrate. Flash chromatography (hexane/ether, 4:1) of the product gave (i) starting material (25 mg, 10%) and (ii) tricarbonyl[(8,9,11,12,13,14-η)-12-methoxy-19-norpodocarpa-4(18),8,11,13-tetraene]chromium(0) (**12**) (0.33 g, 90%) (a mixture of α- and β-diastereoisomers, 91:9). Recrystallization from hexane gave the pure α-diastereoisomer **13** as yellow crystals, m.p. 156–159°C. (Found: C, 63.4; H, 5.8%. $C_{20}H_{22}O_4Cr$ calc.: C, 63.5; H, 5.9%) (Found: $M^{+\cdot}$ 378.0915. $C_{20}H_{22}O_4Cr$ calc.: M, 378.0923). IR ν_{max} (KBr disc) (cm^{-1}): 1953; 1876; 1849 (CO); 1645; 1541; 1513 (C=C); 1268. ^1H NMR δ: 1.09 (s, $(H20)_3$) 1.50–1.81 (m, $H2_{ax}$, $H2_{eq}$, $H6_{ax}$, $H6_{eq}$); 2.03 (bd, $J = 12.8$ Hz, $H1_{eq}$); 2.04 (td, $J = 12.9$, 4.1 Hz, $H1_{ax}$); 2.14 (td, $J = 13.0$, 4.5 Hz, $H3_{ax}$); 2.38 (bd, $J = 12.8$ Hz, $H3_{eq}$); 2.49 (bd, $J = 12.1$ Hz, H5); 2.64 (m, $H7_{ax}$, $H7_{eq}$); 3.66 (s, $ArOCH_3$); 4.57, 4.87 (2s, $(H18)_2$); 5.19 (dd, $J = 6.8$, 2.0 Hz, H13); 5.31 (d, $J = 2.0$ Hz, H11); 5.40 (d, $J = 6.8$ Hz, H14) ppm. ^{13}C NMR δ: 20.4 (C6); 23.4 (C2); 24.5 (C20); 26.8 (C7); 36.1 (C3); 36.6 (C1); 38.6 (C10); 44.7 (C5); 55.8 ($ArOCH_3$); 77.9 (C13); 78.7 (C11); 93.8 (C14); 101.8 (C8); 107.3 (C18); 124.4 (C9); 140.4 (C12); 149.2 (C4); 234.3 (CO) ppm. MS *m/z*: 378 (12, M^+); 322 (11, M − 2CO); 294 (100, M − 3CO); 52 (57).

In some cases, the procedure also gave the β-diastereoisomer **14**. ^1H NMR δ: 1.12 (s, $(H20)_3$); 4.59 (s, $(H18)_1$); 5.11 (d, $J = 6.4$ Hz, H14); 5.32 [H13 (superimposed on H11 of the α-diastereoisomer)]; 5.62 (s, H11) ppm. ^{13}C NMR δ: 20.4 [C6 (superimposed on C6 of the α-diastereoisomer)]; 23.8 (C2); 25.0 (C20); 30.1 (C7); 35.5 (C3); 40.2 (C1); 42.5 (C10); 49.1 (C5); 56.4 ($ArOCH_3$); 83.2 (C13); 83.3 (C11); 88.5 (C14); 107.5 (C8); 123.9 (C9); 137.4 (C12); 148.2 (C4); 234.4 (CO) ppm.

3.4. 2-[2'ξ-Cyano-2'-(14"-(12"-methoxy-19"-norpodocarpa-4"(18"),8",11",13"-tetraene))ethyl]-1,3-dioxolane (7)

THF (6 ml) and di-isopropylamine (0.24 ml, 1.7 mmol) were added to the flask and cooled to −78°C. Butyl-lithium (1.41 ml, 1.2 mol l^{-1} in hexane, 1.7 mmol) was added dropwise and the solution was stirred for 30 min. A solution of 2-(2-cyanoethyl)-1,3-dioxolane (**16**) (0.22 g, 1.7 mmol) in THF (0.5 ml) was added and the mixture stirred for a further 30 min. Hexamethylphosphoric triamide (4 ml) was then added, followed by a solution of the α-$Cr(CO)_3$ complex **13** (0.32 g, 0.85 mmol) in THF (6.5 ml) precooled to −78°C. The mixture was then stirred at −78°C for 2 h. A solution of iodine (1.9 g, 7.3 mmol) in THF (5 ml) precooled to −78°C was then added dropwise and the mixture warmed to room temperature overnight. Work-up followed by flash chromatography (hexane/ether, 3:7) of the crude product gave 2-[2'ξ-cyano-2'-(14"-(12"-methoxy-19"-norpodocarpa-4"(18"),8",11",13"-tetraene))-ethyl]-1,3-dioxolane (**7**) (0.28 g, 92%) (diastereoisomeric ratio, 2:1) as a colourless oil, b.p. 180°C/0.1 mmHg (Kugelrohr). (Found: $M^{+\cdot}$, 367.2142. $C_{23}H_{29}NO_3$ calc.: M, 367.2147). IR ν_{max} (cm^{-1}): 2241 (CN); 1607; 1468; 1438 (C=C); 1139. ^1H NMR δ: major diastereoisomer: 1.01 (s, $(H20'')_3$); 1.52 (td, $J = 12.8$, 4.4 Hz, $H1''_{ax}$); 1.75 (m, $H2''_{eq}$, $H2''_{ax}$, $H6''_{ax}$); 2.00 (m, $H6''_{eq}$, $(H1')_1$, $H3''_{ax}$); 2.17 (d, $J = 12.3$ Hz, H5"); 2.23 (d, $J = 12.8$ Hz, $H1''_{eq}$); 2.35 (m, $(H1')_1$, $H3''_{eq}$); 2.70 (ddd, $J = 16.7$, 11.7, 6.7 Hz, $H7''_{ax}$); 2.80 (dd, $J = 16.7$, 5.1 Hz, $H7''_{eq}$); 3.80 (s, $ArOCH_3$); 3.93, 4.04 (2m, $(H4)_2$, $(H5)_2$); 4.18 (dd, $J = 10.6$, 4.5 Hz, H2'); 4.60, 4.88 (2s, $(H18'')_2$); 5.08 (dd, $J = 5.7$, 3.3 Hz, H2); 6.87 (d, $J = 2.5$ Hz, H11"); 6.88 (d, $J = 2.5$ Hz, H13") ppm. ^{13}C NMR (50 MHz) δ: major diastereoisomer: 21.0 (C6"); 22.7 (C20"); 23.6 (C2"); 25.7 (C7"); 28.4 (C2'); 36.0 (C3"); 38.5 (C1"); 38.7 (C1'); 39.9 (C10"); 46.8 (C5"); 55.2 ($ArOCH_3$); 65.1, 65.3 (C4, C5); 101.5 (C2); 106.7 (C18"); 110.3 (C13"); 111.7 (C11"); 121.0 (CN); 124.2 (C8"); 134.8 (C14"); 150.0 (C4", C9"); 157.9 (C12") ppm. MS *m/z*: 367 (13, M^+); 352 (3, M − Me); 305 (15, $M - HOCH_2CH_2OH$); 281 (100, $M - H_2CCHOCH_2CH_2O + H$); 87 (15, M − diterpenoid − CHCN); 73 (28, M − diterpenoid − $CHCNCH_2$).

In some cases, this procedure gave 12-methoxy-19-norpodocarpa-4(18),8,11,13-tetraen-14-ol (**9**) as a major component. (Found: $M^{+\cdot}$, 258.1615. $C_{17}H_{22}O_2$ calc.: M, 258.1620). IR ν_{max} (cm^{-1}): 3421 (OH); 1646; 1618; 1503 (C=C). ^1H NMR δ: 1.01 (s, $(H20)_3$); 1.56 (td, $J = 13.2$, 4.5 Hz, $H1_{ax}$); 1.75 (qt, $J = 13.6$, 4.1 Hz, $H2_{eq}$); 1.79 (m, $H6_{ax}$, $H2_{ax}$); 1.92 (dd, $J = 12.9$, 7.1 Hz, $H6_{eq}$); 2.05 (td, $J = 12.9$, 5.7 Hz, $H3_{ax}$); 2.20 (m, $H1_{eq}$, H5); 2.38 (ddd, $J = 13.0$, 4.0, 2.1 Hz, $H3_{eq}$); 2.54 (ddd, $J = 16.2$, 12.0, 7.2 Hz, $H7_{ax}$); 2.79 (dd, $J = 16.2$, 5.7 Hz,

$H7_{eq}$); 3.76 (s, $ArOCH_3$); 4.61, 4.87 (2d, $J = 1.3$ Hz, $(H18)_2$); 4.72 (s, OH); 6.27 (d, $J = 2.4$ Hz, H11); 6.50 (d, $J = 2.4$ Hz, H13) ppm. ^{13}C NMR δ: 20.5 (C6), 22.4 (C2); 22.7 (C20); 23.7 (C7), 36.3 (C3); 38.5 (C1); 39.6 (C10); 47.2 (C5); 55.2 ($ArOCH_3$); 98.4 (C13); 103.7 (C11); 106.6 (C18); 116.0 (C8); 147.3 (C4), 150.4 (C9); 153.8 (C14); 158.5 (C12) ppm. MS m/z: 258 (100, M^+); 243 (88, M − Me); 215 (18); 187 (13); 137 (49).

When a mixture of α-(**13**) and β-(**14**) diastereoisomers was used 2-[2′ξ-cyano-2′-(13″-(12″-methoxy-19″-norpodocarpa-4″(18″),8″,11″,13″-tetraene))ethyl]-1,3-dioxolane (**8**) (diastereoisomeric ratio, 3:1) was also obtained. ^1H NMR δ: major diastereoisomer: 6.80 (s, H11″); 7.07 (s, H14″) ppm. ^{13}C NMR (50 MHz) δ: major diastereoisomer: 108.0 (C11″); 129.1 (C14″) ppm.

3.5. 2-[2′ξ-Cyano-2′-(14″-(12″-methoxy-19″-norpodocarpa-4″(18″),8″,11″,13″-tetraen-3″α-ol))ethyl]-1,3-dioxolane (10)

Selenium dioxide (21 mg, 0.19 mmol) and t-butyl hydroperoxide (0.14 ml, 8 mol l^{-1} solution in di-t-butyl peroxide, 1.12 mmol) in dichloromethane (3 ml) were stirred for 30 min. A solution of the dioxolanes **7** (0.14 g, 0.37 mmol) in dichloromethane (2 ml) was added slowly to the mixture, which was then stirred at room temperature for 24 h. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium hydrogencarbonate, water and brine, and dried ($MgSO_4$). PLC (hexane/ether, 3:7, two sweeps) of the crude product gave 2-[2′ξ-cyano-2′-(14″-(12″-methoxy-19″-norpodocarpa-4″(18″),8″,11″,13″-tetraen-3″α-ol))-ethyl]-1,3-dioxolane (**10**) (97 mg, 68%) as a colourless oil. (Found: M^+, 383.2103. $C_{23}H_{29}NO_4$ calc.: M, 383.2097). IR ν_{max} (cm^{-1}): 3433 (OH); 2242 (CN); 1608; 1469; 1436 (C=C); 1140; 1056. ^1H NMR δ: major diastereoisomer: 0.99 (s, $(H20'')_3$); 1.63 (bs, OH); 1.70 (m, $H1''_{ax}$, $H6''_{ax}$); 1.58 (m, $H6''_{eq}$ $(H1')_1$, $H1''_{eq}$, $H2''_{eq}$, $H2''_{ax}$); 2.35 (m, $(H1')_1$); 2.72 (bd, $J = 12.2$ Hz, H5″); 2.75 (m, $H7''_{ax}$); 2.82 (dd, $J = 18.1$, 6.5 Hz, $H7''_{eq}$); 3.81 (s, $ArOCH_3$); 3.90, 4.05 (2m, $(H4)_2$), $(H5)_2$; 4.17 (dd, $J = 10.6$, 4.5 Hz, H2′); 4.36 (bs, H3″); 4.76, 5.09 (2t, $J = 1.5$ Hz, $(H18'')_2$); 5.07 (dd, $J = 5.7$, 3.3 Hz, H2); 6.82 (d, $J = 2.6$ Hz, H11″); 6.88 (d, $J = 2.6$ Hz, H13″) ppm. ^{13}C NMR δ: major diastereoisomer: 20.6 (C6″); 22.0 (C20″); 25.6 (C7″); 28.5 (C2′); 30.1 (C1″); 32.7 (C2″); 38.5 (C1′); 39.7 (C10″); 40.5 (C5″); 55.3 ($ArOCH_3$); 65.1, 65.3 (C4, C5); 72.6 (C3″); 101.6 (C2); 110.2 (C18″); 110.5 (C13″); 111.7 (C11″); 120.9 (CN); 124.1 (C8″); 134.9 (C14″); 149.6 (C9″); 151.2 (C4″); 158.0 (C12″) ppm. MS m/z: 383 (13, M^+); 365 (5, $M - H_2O$); 321 (18, $M - HOCH_2CH_2OH$); 297 (100, $M - H_2CCHOCH_2CH_2O + H$); 279 (12); 87 (19, M − diterpenoid − CHCN); 73 (29, M − diterpenoid − $CHCNCH_2$).

3.6. 2-[2′ξ-Cyano-2′-(14″-(12″-methoxy-19″-norpodocarpa-4″(18″),8″,11″,13″-tetraen-3″-one))ethyl]-1,3-dioxolane (11)

Dimethyl sulfoxide (74 μl, 1.05 mmol) was added dropwise to a solution of oxalyl chloride (46 μl, 0.52 mmol) in dichloromethane (8 ml) at −78°C. After 5 min, a solution of the alcohol **10** (0.18 g, 0.48 mmol) in dichloromethane (3 ml) was slowly added. After a further 20 min, triethylamine (0.31 ml, 2.26 mmol) was added dropwise to the suspension. The mixture was stirred for a further 5 min and then warmed to room temperature. Flash chromatography (hexane/ether 1:1, 3:7) of the product gave 2-[2′ξ-cyano-2′-(14″-(12″-methoxy-19″-norpodocarpa-4″(18″),8″,11″,13″-tetraen-3″-one))ethyl]-1,3-dioxolane (**11**) (0.17 g, 95%) as a colourless oil. (Found: M^+, 381.1932. $C_{23}H_{27}NO_4$ calc.: M, 381.1940). IR ν_{max} (cm^{-1}) 2241 (CN); 1695 (CO); 1610; 1583; 1471 (C=C); 1140. ^1H NMR δ: major diastereoisomer: 1.16 (s, $(H20'')_3$); 1.71 (qd, $J = 12.9$, 5.9 Hz, $H6''_{ax}$); 2.00 (m, $H1''_{ax}$, $(H1')_1$); 2.13 (dd, $J = 13.1$, 6.4 Hz, $H6''_{eq}$); 2.41 (m, $H1''_{eq}$, $(H1')_1$); 2.62 (m, H5″, $H2''_{ax}$, $H2''_{eq}$); 2.77 (ddd, $J = 16.7$ 12.0, 6.4 Hz, $H7''_{ax}$); 2.89 (dd, $J = 16.7$, 4.7 Hz, $H7''_{eq}$); 3.82 (s, $ArOCH_3$); 3.94, 4.06 (2m, $(H4)_2$, $(H5)_2$); 4.18 (dd, $J = 10.5$, 4.5 Hz, H2′); 5.08 (dd, $J = 5.6$, 3.3 Hz, H2); 5.13, 6.01 (2bs, $(H18'')_2$); 6.90 (d, $J = 2.5$ Hz, H11″); 6.92 (d, $J = 2.5$, Hz, H13″) ppm. ^{13}C NMR δ: major diastereoisomer: 20.5 (C6″); 22.4 (C20″); 25.5 (C7″); 28.5 (C2′); 36.6 (C1″) 37.8. (C10″); 38.5 (C1′); 45.4 (C5″); 55.3 ($ArOCH_3$); 65.2, 65.3 (C4, C5); 101.5 (C2); 111.0 (C13″); 112.1 (C11″); 118.8 (C18″); 120.8 (CN); 123.9 (C8″); 135.1 (C14″); 147.7 (C4″); 147.8 (C9″); 158.2 (C12″); 201.4 (CO) ppm. MS m/z: 381 (13, M^+); 319 (19, $M - HOCH_2CH_2OH$); 304 (7, 319 − Me); 295 (100, $M - H_2CCHOCH_2CH_2O + H$); 159 (22); 87 (21, M − diterpenoid − CHCN); 73 (35, M − diterpenoid − $CHCNCH_2$).

3.7. Cyclization of 2-[2′ξ-cyano-2′-(14″-(12″-methoxy-19″-norpodocarpa-4″(18″),8″,11″,13″-tetraen-3″-one))ethyl]-1,3-dioxolane (11)

Titanium(IV) chloride (34 μl, 0.32 mmol) in dichloromethane (0.1 μl) was added slowly to a cooled (−78°C) solution of the dioxolanes **11** (0.10 g, 0.26 mmol) in dichloromethane (9 ml). After 40 min, the cooling bath was removed and after a further 30 min aqueous HCl (2 mol l^{-1}) was added to the reddish-brown mixture. The organic layer was washed with saturated aqueous sodium hydrogencarbonate, water and brine, and dried ($MgSO_4$). Flash chromatography (hexane/ether, 1:1, 1:9) gave 17ξ-hydroxy-12-methoxy-4-methylene-18-nor-3-oxo-5α-androsta-8,11,13-triene-15ξ-carbonitrile (**17**) (58 mg, 67%) as a pale yellow solid. (Found: M^+, 337.1673. $C_{21}H_{23}NO_3$ calc.:

M, 337.1678). IR ν_{max} (cm^{-1}): 3488 (OH); 2239 (CN); 1693 (CO); 1609; 1488; 1461 (C=C); 1308; 1269; 1081. ^1H NMR δ: four diastereoisomers: 1.15, 1.16, 1.20, 1.21 (4s, $(H19)_3$); 3.88 (s, $ArOCH_3$); 3.90 (m, H15); 5.27, 6.02, 6.03 (3bs, $=CH_2$); 5.32 (m, H17); 6.82, 6.85, 6.86 (3s, H11) ppm. ^{13}C NMR δ: four diastereoisomers: 20.17, 20.23 (C6); 22.17, 22.29, 22.43, 22.62 (C19); 25.16, 25.28, 26.26, 26.35 (C7); 31.22, 31.51, 31.77, 32.15 (C15); 36.05, 36.38, 36.46, 36.53 (C1, C2); 37.87 (C10); 38.85, 39.10, 39.19 (C16); 45.72, 46.06, 46.44 (C5); 55.31, 55.50 ($ArOCH_3$); 72.24, 72.50, 72.86, 73.00 (C17); 108.11, 108.34, 108.41 (C11); 118.93, 119.06, 119.18 ($=CH_2$); 119.84, 120.02, 120.41, 120.50 (CN); 123.85, 123.91, 123.99, 124.98 (C8); 129.33, 129.41, 130.46, 130.62 (C14); 136.07, 136.53, 136.88, 137.32 (C13); 147.56, 147.69, 147.83 (C4); 148.29, 148.39, 148.57, 148.67 (C9); 154.56, 154.70 (C12); 197.30, 201.22, 201.28, 201.46 (CO) ppm. MS *m/z*: 337 (100, M^+); 322 (69, M − Me); 319 (8, M − H_2O); 310 (15, M − HCN); 304 (22, 319 − Me); 294 (18); 278 (33); 202 (30).

3.8. 2-[2'ξ-Cyano-2'-(14"-(12"-methoxy-19"-norpodocarpa-1",4"(18"),8",11",13"-pentaen-3"-one))ethyl]-1,3-dioxolane (20)

A mixture of the alkenes **7** (90 mg, 0.25 mmol), 2,2'-dipyridyl diselenide (**19**) (8 mg, 0.03 mmol) and iodosylbenzene (0.17 g, 0.74 mmol) in benzene (8 ml) was heated to reflux for 1.5 h. The mixture was cooled to room temperature and filtered through Celite. PLC (hexane/ether, 3:2, five sweeps) gave 2-[2'ξ-cyano-2'-(14"-(12"-methoxy-19"-norpodocarpa-1",4"(18"),8",11",13"-pentaen-3"-one))ethyl]-1,3-dioxolane (**20**) (42 mg, 45%) as a yellow oil. (Found: M^+, 379.1784. $C_{23}H_{25}NO_4$ calc.: M, 379.1784. IR ν_{max} (cm^{-1}): 2241 (CN); 1673 (CO); 1612; 1471 (C=C); 1279; 1140; 1119. ^1H NMR δ: major diastereoisomer: 1.25 (s, $(H20")_3$); 1.88 (qd, J = 12.2, 6.3 Hz, $H6"_{ax}$); 2.02 (ddd, J = 14.2, 10.2, 5.3 Hz, $(H1')_2$); 2.19 (dd, J = 12.3, 6.7 Hz, $H6"_{eq}$); 2.39 (dd, J = 14.0, 3.2 Hz, $(H1')_2$); 2.81 (ddd, J = 16.0, 11.6, 6.5 Hz, $H7"_{ax}$); 2.91 (dd, J = 16.0, 5.9 Hz, $H7"_{eq}$); 3.02 (dd, J = 12.4, 2.2 Hz, H5"); 3.85 (s, $ArOCH_3$); 3.95, 4.06 (2m, $(H4)_2$, $(H5)_2$); 4.18 (dd, J = 10.5, 4.5 Hz, H2); 5.08 (dd, J = 5.5, 3.2 Hz, H2); 5.37 (6.26, 2s, $(H18")_2$); 6.14 (d, J = 10.2 Hz, H2"); 6.96 (d, J = 2.5 Hz, H11"); 7.00 (d, J = 2.5 Hz, H13"); 7.62 (d, J = 10.2 Hz, H1") ppm. ^{13}C NMR δ: major diastereoisomer: 20.2 (C6"); 25.3 (C7"); 27.1 (C20"); 28.5 (C2'); 38.4 (C1'); 41.8 (C10"); 45.7 (C5"); 55.4 ($ArOCH_3$); 65.2, 65.3 (C4, C5); 101.4 (C2); 111.4 (C13"); 112.0 (C11"); 119.5 (C18"); 120.7 (CN); 124.4 (C8"); 128.0 (C2"); 135.9 (C14"); 144.3 (C4"); 145.1 (C9"); 158.2 (C12"); 159.3 (C1"); 188.5 (CO) ppm. MS *m/z*: 379 (10, M^+); 317 (20, M − $HOCH_2CH_2OH$); 302 (22, 317 − Me); 293 (100, M − $H_2CCHOCH_2CH_2O$ + H); 87 (42, M − diterpenoid − CHCN); 73 (41, M − diterpenoid − $CHCNCH_2$).

3.9. Cyclization of 2-[2'ξ-cyano-2'-(14"-(12"-methoxy-19"-norpodocarpa-1",4"(18"),8",11",13"-pentaen-3"-one))ethyl]-1,3-dioxolane (20)

Titanium(IV) chloride (24 μl, 0.22 mmol) in dichloromethane (0.1 ml) was added slowly to a cooled (−78°C) solution of the dioxolanes **20** (70 mg, 0.19 mmol) in dichloromethane (6 ml). After 30 min, the mixture was warmed to room temperature. The mixture was again cooled to −78°C, a further aliquot of $TiCl_4$ (24 μl, 0.22 mmol) added and after 15 min the mixture was warmed to room temperature. Aqueous HCl (2 mol l^{-1}) was added and the mixture diluted with dichloromethane. Work-up followed by flash chromatography (hexane/ether, 3:7, 1:9) gave 17ξ-hydroxy-12-methoxy-4-methylene-18-nor-3-oxo-5α-androsta-1,8,11,13-tetraene-15ξ-carbonitrile (**21**) (40 mg, 65%). (Found: M^+, 335.1527. $C_{21}H_{21}NO_3$ calc.: M, 335.1521). IR ν_{max} (cm^{-1}): 3425 (OH); 2242 (CN); 1672 (CO); 1609; 1470 (C=C); 1276. ^1H NMR δ: major diastereoisomer: 1.25 (s, $(H19)_3$); 3.28 (dd, J = 18.6, 8.8 Hz, $H7_{eq}$); 3.83 (s, $ArOCH_3$); 3.90 (m, H15); 4.60 (dd, J 8.9, 5.0 Hz, H17); 5.38, 6.26 (2bs, $=CH_2$); 6.13 (d, J = 10.2 Hz, H2); 6.86 (s, H11); 7.62 (d, J = 10.2 Hz, H1) ppm. ^{13}C NMR δ: major diastereoisomer: 20.1 (C6); 25.5 (C7); 26.5 (C15); 27.0 (C19); 41.7 (C10); 45.5 (C16); 47.2 (C5); 55.4 ($ArOCH_3$); 72.6 (C17); 112.0 (C11); 119.6 ($=CH_2$); 119.8 (CN); 124.5 (C8); 128.1 (C2); 134.5 (C14); 139.8 (C13); 144.6 (C4); 144.9 (C9); 158.3 (C12); 159.1 (C1); 188.4 (CO) ppm. MS *m/z*: 335 (100, M^+); 320 (25, M − Me); 302 (24, 320 − H_2O); 276 (65); 265 (16).

References and notes

1 For an enyne–alkene approach to this relatively rare class of steroids, see Y.W. Andemichael, Y. Huang and K.K. Wang, *J. Org. Chem., 58* (1993) 1651.
2 R.J. Young, C. Cortez, E. Luna, H. Lee and R.G. Harvey, *J. Org. Chem., 58* (1993) 356.
3 R.G. Harvey, R.J. Young, C. Cortez, H. Lee and E. Luna, *J. Org. Chem., 58* (1993) 361.
4 C.R. Bennett and R.C. Cambie, *Tetrahedron, 23* (1967) 927.
5 R.C. Cambie and W.A. Denny, *Aust. J. Chem., 22* (1969) 1699.
6 R.C. Cambie, R.A. Franich and T.J. Fullerton, *Aust. J. Chem., 24* (1971) 593.
7 R.C. Cambie and T.J. Fullerton, *Aust. J. Chem., 24* (1971) 2611.
8 E.J. Cochrane, S.W. Lazer, J.T. Pinhey and J.D. Whitby, *Tetrahedron Lett., 30* (1989) 7111.
9 R.C. Cambie, M.P. Hay, L. Larsen, C.E.F. Rickard, P.S. Rutledge and P.D. Woodgate, *Aust. J. Chem., 44* (1991) 821.
10 M. Kobayashi, K. Kawzoe, T. Katori and I. Kitagawa, *Chem. Pharm. Bull., 40* (1992) 1773.
11 C.A.L. Mahaffy and P.L. Pauson, *Inorg. Synth., 19* (1979) 154.

12 R.C. Cambie, P.S. Rutledge, R.J. Stevenson, and P.D. Woodgate, *J. Organomet. Chem., 471* (1994) 133.
13 M.F. Semmelhack, in B.M. Trost and I. Fleming (eds.) *Comprehensive Organic Synthesis*, Pergamon, Oxford, 1991, Vol. 4, p. 517.
14 R.C. Cambie, G.R. Clark, A.C. Gourdie, P.S. Rutledge and P.D. Woodgate, *J. Organomet. Chem., 297* (1985) 177.
15 M.A. Umbriet and K.B. Sharpless, *J. Am. Chem. Soc., 99* (1977) 5526.
16 A.J. Mancuso, S.L. Huang and D. Swern, *J. Org. Chem., 43* (1978) 2480.
17 D.H.R. Barton and D. Crich, *Tetrahedron, 41* (1985) 4359.
18 A. Toshimitsu, H. Owada, K. Terao, S. Uemura and M. Okano, *J. Org. Chem., 49* (1984) 3796.
19 D.H.R. Barton, C.R.A. Godfrey, J.W. Morzycki, W.B. Motherwell and S.V. Ley, *J. Chem. Soc., Perkin Trans. 1*, (1982) 1947.
20 R.C. Cambie, P.S. Rutledge, M. Tercel and P.D. Woodgate, *J. Organomet. Chem., 315* (1986) 171.
21 R.C. Cambie, G.R. Clark, S.R. Gallagher, P.S. Rutledge, M.J. Stone and P.D. Woodgate, *J. Organomet. Chem., 342* (1988) 315.