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Synthetic Transformation of Abietic Acid I. Addition of Dienophiles

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Summary Addition of acetylene dicarboxylic acid dimethylester to abietic acid is an en-reaction. The structure of the resulting product was determined. Compounds formally derived from addition of acetylene to levopimaric acid have been synthesized. By a *retro-Diels-Alder* reaction, the B-ring is cleaved and an aromatic system is formed. *Diels-Alder* addition of 2-chloroacrylonitrile to abietic acid gives a tetracyclic α-chloronitrile (**10**). Further transformations of this product are described.

Keywords. Abietic acid; En-reaction of acetylenedicarboxylic acid; 2-Chloroacrylonitrile; *retro-Diels-Alder* reaction.

Synthetische Umwandlung des Abietinsäuregerüsts. Addition von Dienophilen

Zusammenfassung. Die Addition von Acetylendicarbonsäure an Abietinsäure ist eine En-Reaktion. Die Struktur des Reaktionsprodukts wurde aufgeklärt. Formale Dien-Addukte von Acetylen an Laevopimarsäure können durch oxidative Decarboxylierung des Abietinsäure-Fumarsäure-Addukts und Decarbony-Decarboxylierung des Maleinsäureanhydrid-Addukts hergestellt werden. Durch *retro-Diels-Alder*-Reaktion wird anschließend der B-Ring unter Bildung aromatischer Produkte geöffnet. Das Ketenäquivalent 2-Chloracrylnitril liefert als Dien-Addukt ein tetracyclisches α-Chlornitril (**10**), das in verschiedener Weise weiter umgesetzt werden kann.

Introduction

Diels-Alder addition of maleic acid anhydride to abietic acid (**1**) at elevated temperature is very well known and routinely used during industrial utilization of **1** [1]. The product, maleopimaric acid, is formed by addition of the dienophile to levopimaric acid (**3**), which is first generated by isomerization of the double bond system of **1** [2]. *Sandermann* [3] studied the addition of acetylene dicarboxylic acid dimethyl ester to **1**. The structure he deduced for the product (**2**) was corroborated by the fact that pyrolysis of **2** did not give a volatile product. Therefore, he assumed a *retro-Diels-Alder* reaction resulting in product **4**.

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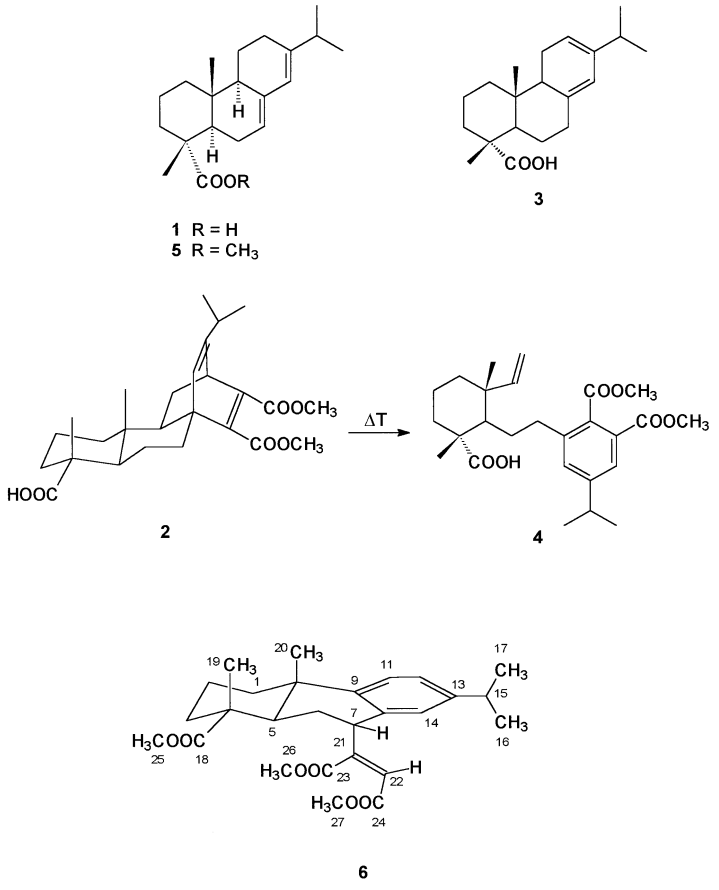


Scheme 1

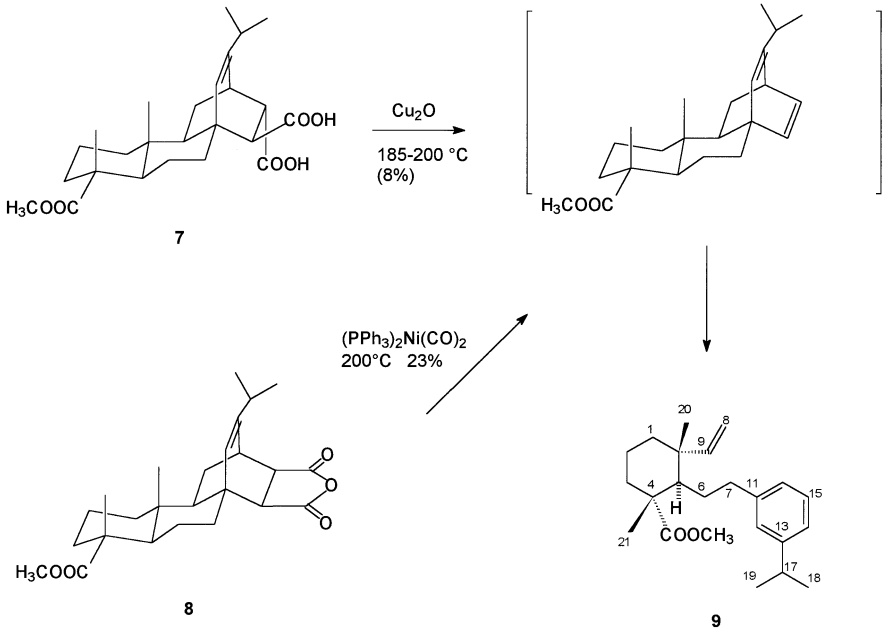
Results and Discussion

Addition of acetylene dicarboxylic acid dimethyl ester

We have studied the addition of acetylene dicarboxylic acid dimethyl ester to **5** under the same conditions as described *Sandermann* [3]. After 3 h at 190°C, no, residual educt (**5**) could be detected. After column chromatography, **6** was obtained in 60% yield. The structure was established by NOE experiments. Irradiating the resonance of the olefinic proton gave enhancements of the signals of H-5, H-7, and H-14, proofing that the olefinic hydrogen is in close spatial proximity to these protons. Therefore, we concluded that the configuration of the double bond is *Z* and that the vinyl substituent is in α-position. Variation of the reaction conditions (temperature, time, or molar ratio of the educts) always lead to the same product. We therefore conclude that compound **4** has the structure given for **6** and that the addition of acetylene dicarboxylic acid dimethyl ester is an en-reaction. The acetylene molecule is the enophile and approaches **5** from the α-side. *Z*-configuration of the double bond in **6** indicates that the course of the reaction is concerted.

Synthesis of diene adducts formally derived from acetylene

To obtain compounds which are formally acetylene adducts on levopimaric acid we tried a decarbony-decarboxylation of maleopimaric acid (**8**) [4, 5] with *bis*-(triphenylphosphine)-nickel dicarbonyl at 200°C.

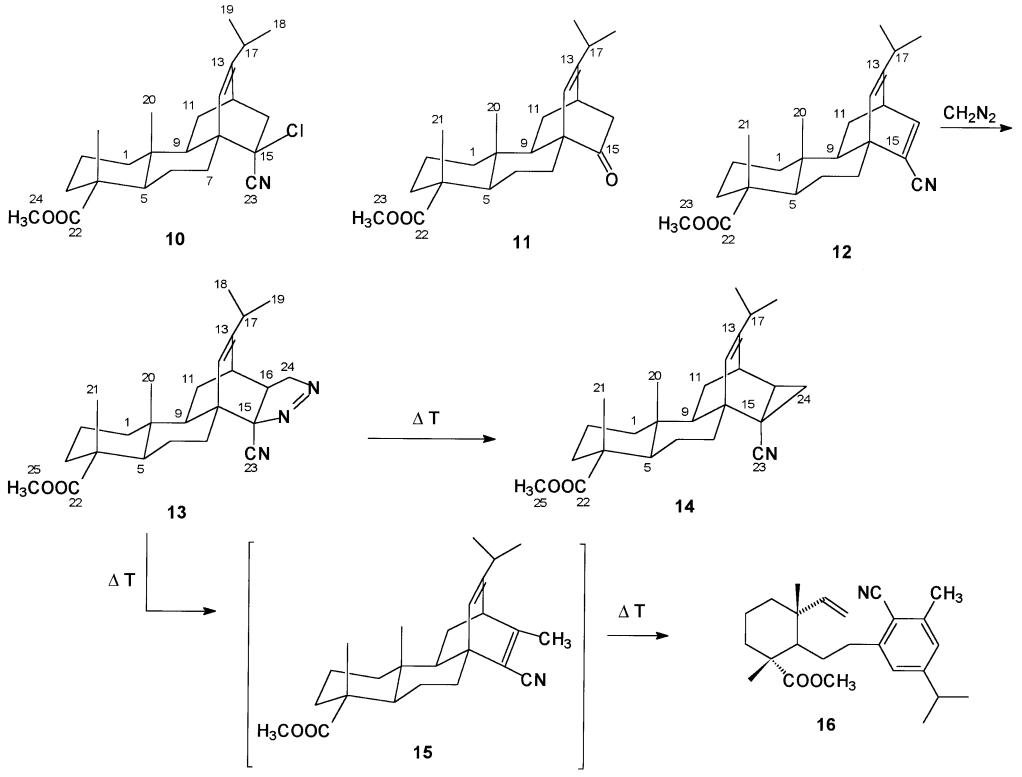


Scheme 2

At this temperature, a *retro-Diels-Alder* reaction is also induced, and the primary product is in turn converted to the aromatic compound **9**. The bisdecarboxylation of the fumaric acid adduct (**7**) [5–7] affords the *retro-Diels-Alder* aromate **9** in 8% yield. The mass spectrum of **9** has its base peak at $m/z = 133$. This ion, an isopropyl substituted tropylium ion, is formed by cleavage at the benzyl position. COSY correlations were observed connecting the aromatic proton H-12 with H-17 and H-7. CH_3-20 has small couplings to the olefinic hydrogens H-9 and H-8_{trans}.

Addition of ketene equivalents

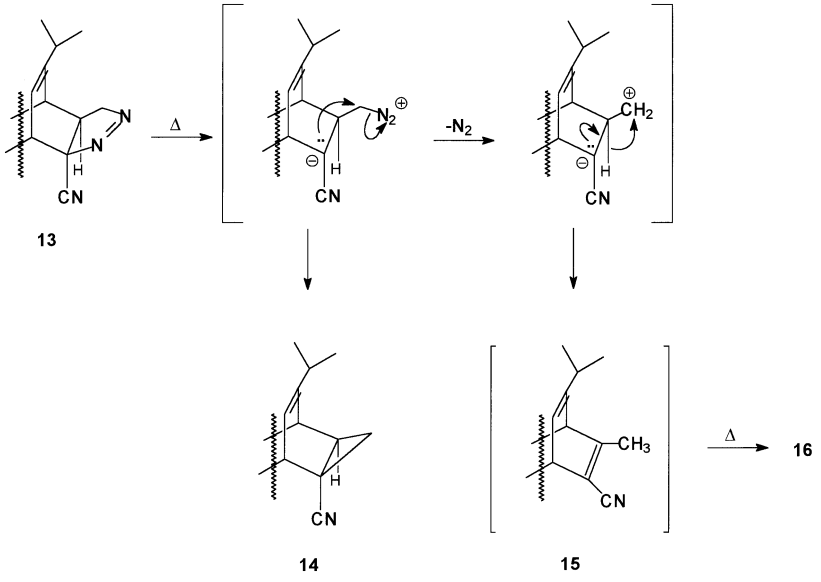
[4+2] addition of ketene equivalents [8] to **5** and further transformation of the primary product should give access to tricyclic molecules with an oxo function which in turn can be used as starting materials for further synthetic transformations. 2-Chloroacrylonitrile has high reactivity and regioselectivity and has been used previously to produce α-chloronitrile adducts which can be easily converted to ketones by KOH in *DMSO* [9–14]. Addition of 2-chloroacrylonitrile to **5** gave **10** in moderate yield which shows an IR absorption at 2237 cm^{-1} (stretching vibration of nitrile). The El-MS exhibits a molecular ion at $m/z = 403$ and a base peak at



Scheme 3

$m/z = 316$ as the result of a *retro-Diels-Alder* fragmentation. The high field shift of CH_3-20 ($\delta = 0.61$ ppm) is induced by the anisotropy of the double bond between C-13 and C-14. The α-orientation of the nitrile group in **10** was determined by X-ray crystallography.

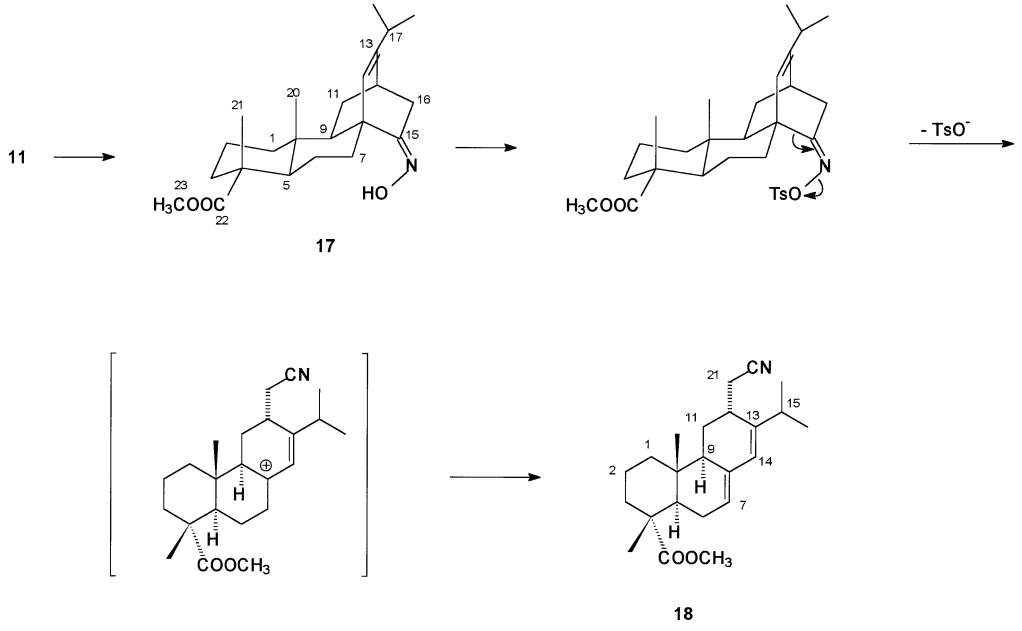
Treatment of **10** with KOH in *DMSO* gave – after usual workup and esterification of the acid with diazomethane – ketone **11** (40%) and pyrazoline **13** (22%). **11** shows a typical ketocarbonyl resonance at $\delta = 212.9$ ppm in the ^{13}C NMR spectrum. In the IR spectrum of compound **13** we found the nitrile absorption at 2230 cm^{-1} and the -N = N-stretching vibration at 1562 cm^{-1} [15]. We assume that **13** was formed by addition of the 1,3-dipole diazomethane to the double bond of **12** during workup. Using KOH in ethanol improved the yield of **11**, and no pyrazoline was observed. Upon thermolysis, compound **13** yields the cyclopropane derivative **14** (51%) and the aromatic compound **16** (39%) which is probably formed by a *retro-Diels-Alder* reaction from intermediate **15** which could not be isolated. The mechanism of thermal decomposition of 1-pyrazolines is not entirely clear; besides ionic intermediates which are shown in Scheme 4, radical intermediates are also discussed in the literature [15–17].



Scheme 4

Ring cleavage by oxime rearrangement

The oxime **17** was obtained in quantitative yield by refluxing **11** and hydroxylamine hydrochloride in EtOH over solid NaOH [18]. The *Z*-oxime is formed exclusively as could be shown by an NOE correlation between the HON-proton and H-7. We planned to introduce a nitrogen function in the terpene skeleton *via* a *Beckmann* rearrangement of the corresponding tosylate [19–21]. **17**



Scheme 5

was treated with an excess of tosylchloride in dry pyridine until no educt could be detected. The product obtained in 85% yield turned out to be the 12-cyanomethyl derivative of abietic acid (**18**).

Treatment of **17** with 72% sulfuric acid [22] or polyphosphoric acid trimethylsilyl-ester [23] (both reagents have been used to induce *Beckmann* rearrangements) also gave nitrile **18** in nearly quantitative yield. We assume that the *tert*-allylkation shown in Scheme 5 is more stable than the carbenium ion which is formed *via* the *Beckmann* rearrangement; therefore, nitrile formation is the main reaction path. The configuration at C-12 was derived from the proton resonance of H-12. Couplings to both H-21 ($^3J = 10.8$ Hz and 4.4 Hz) and two couplings to the protons in position 11 ($^3J = 4.7$ Hz and 1.9 Hz) can be observed. This indicates that H-12 and H-11 are not in an antiperiplanar arrangement. From the reaction mechanism one can also deduce on α-orientation of the cyanomethyl substituent. We therefore assign *R* configuration to C-12.

Further investigations are in progress to clarify how the tetracyclic compounds **10** and **11** can be used as synthons for stereoselective terpene syntheses.

Experimental

Analytical methods

Preparative thin layer chromatography: Chromatotron Harrison Research, 1 mm Kieselgel 60 PF_{254} (Merck) with gypsum; column chromatography (CC): Kieselgel 60 (Merck) (70–230 mesh), pore-diameter 60 Å; thin layer chromatography (TLC): TLC plates (Machery-Nagel) Alugram SIL G/UV_{254} and Polygram SIL G/UV_{254} Kieselgel 60 F_{254} 0.2 mm 200×200 mm; solvents frequently used: cyclohexane (CH) and AcOEt; the substances were detected in UV light at 254 nm and by spraying with molybdatophosphoric acid or methanol/sulfuric acid (9:1) and subsequent heating. Melting points: melting point apparatus SM-LUX (Leitz), uncorrected; optical rotation: polarimeter 241 MC (Perkin Elmer); IR spectra: Perkin-Elmer IR spectrometer 883; UV/Vis: Lambda 17 UV/Vis-spectrometer (Perkin Elmer); NMR spectra: Bruker AC 200 and AMX 500 (300 K), 5 mm tubes, solvent resonance as internal standard. Before NOE experiments were performed, dissolved oxygen was removed by bubbling Ar through the solutions. ^{1}H and ^{13}C resonances were assigned using ^{1}H, ^{1}H and ^{1}H, ^{13}C correlation spectra (sometimes optimized for small CH couplings) and are numbered as given in the formulas. MS: Varian MAT 711 spectrometer (70 eV electron impact and field desorption); elementary analyses: Laboratory for Microanalysis, Institute for Physical Chemistry of the University of Vienna, and Sektion Analytik of the University of Ulm; autoclave: laboratory autoclave, model HR 200 (Berghof).

Abietic acid methyl ester (**5**)

5 was obtained as given in the literature [22].

Dimethyl-(1′R-(1′α,4′aβ,9′α(Z)))-1′-methoxycarbonyl-1′, 4′a-dimethyl-7′-(1-methylethyl)-1′,2′,3′,4′,4′a,9′,10′,10′a-octahydro-9′-phenanthrene-1,2-ethylendicarboxylate (**6**)

A solution of 6.1 g (19 mmol) **5** in 13.5 g (95 mmol) acetylene dicarboxylic acid dimethyl ester was gradually heated to 210°C during 25 h under 80 bar Ar in an autoclave. The pressure went up to 115 bar. After cooling, the Ar pressure was released and the dark resin was dissolved in CH_2Cl_2. This

solution was washed with H_2O and dried over Na_2SO_4. Evaporation and purification by CC over silica (CH/AcOEt = 1:1) gave 5.2 g **5** as a colourless oil (yield: 60%).

$R_f = 0.31$ (CH/AcOEt = 9:1), 0.58 (CH/AcOEt = 1:1); $[\alpha]_D^{20} = +24.7$ ($c = 0.5$, $CHCl_3$); IR (neat): $\nu = 2951$ (m), 1728 (vs), 1434 (m), 1251 (s), 1166 (m) cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 217 (4.156), 265 (3.237) nm; ^1H NMR (C_6D_6): $\delta = 1.05$ (s, 3H, 20-H), 1.12 (d, $J = 6.9$ Hz, 6 H, 16-H, 17-H), 1.30 (s, 3H, 19-H), 1.34 (m, 1 H, 1-H_{ax}), 1.51 (m, 1 H, 3-H_{eq}), 1.3–1.6 (m, 2H, 2-H), 1.71 (d, $J = 14.0$ Hz, 1H, 6-H_{eq}), 1.89 (m, 1H, 3-H_{ax}), 1.98 (m, 1H, 6-H_{ax}), 2.11 (m, 1H, 1H_{eq}), 2.44 (dd, $J =$ 12.3 Hz, $J = 1.8$ Hz, 1H, 5-H), 2.66 (sept, $J = 6.9$ Hz, 1H, 15-H), 3.26 (s, 3H, 27-H), 3.63 (s, 6H, 25-H, 26-H), 4.04 (d, $J = 7.3$ Hz, 1H, 7-H_{eq}), 5.50 (d, $J = 1.1$ Hz, 1H, 22-H), 6.99 (d, $J_{meta} = 2.0$ Hz, 1 H, 14-H), 7.07 (dd, $J_{ortho} = 8.2$ Hz, $J_{meta} = 2.0$ Hz, 1H, 12-H), 7.17 (d, $J_{ortho} = 8.2$ Hz, 1H, 11-H) ppm; ^{13}C NMR (C_6D_6): $\delta = 17.0$ (q, C-19), 18.8 (t, C-2), 23.9 (q, C-16/C-17), 24.1 (q, C-17/C-16), 25.2 (C-6 u. C-20), 33.7 (d, C-15), 36.2 (t, C-3), 37.5 (s, C-10), 38.2 (t, C-1), 39.9 (d, C-5), 43.6 (d, C-7), 47.6 (s, C-4), 51.1 (q, C-27), 51.9 (q, C-25/C-26), 52.0 (q, C-26/C-25), 122.9 (d, C-22), 124.9 (d, C-11), 125.8 (d, C-12), 129.2 (d, C-1), 133.1 (s, C-8), 146.6 (s, C-13), 148.4 (s, C-9), 155.3 (s, C-21), 165.6 (s, C-24), 169.0 (s, C-23), 177.5 (s, C-18) ppm; MS (FD): *m/z* (%) = 456 (100) [M^+]; MS (70 eV): *m/z* (%) = 456 (28), 424 (100), 350 (36), 321 (29), 175 (26), 43 (23); $C_{27}H_{36}O_6$ (456.6); calc.: C 71.03, H 7.95; found: C 71.21, H 7.96.

13-(1-Methylethyl)-17, 18-dinoratis-13-ene-4-methoxycarbonyl-15α, 16β-dicarboxylic acid (**7**)

7 was obtained from **5** as described in the literature [4–6].

Methyl 13-(1-methylethyl)-17, 18-dinoratis-13-ene-4, 15β, 16β-tricarboxylic acid-15, 16-anhydride-4-carboxylate (**8**)

8 was prepared from **5** according to the literature [4, 24].

Methyl-(1R-(1α, 2β, 3α)-1,3-dimethyl-2-(2-(3-(1-methylethyl)-phenyl)-ethyl)-3-vinyl-1-cyclohexane-carboxylate (**9**)

a) 840 mg (2.0 mmol) **8** were dissolved in 6 ml triglyme and stirred under Ar at 220°C. Within 22 h, 1.6 g (2.5 mmol) *bis*-(triphenylphosphino)nickel dicarbonyl were added in small portions. After removing the solvent, a residue was obtained which was refluxed in 12 ml EtOH/CCl_4 (1:1) for 1 h. The solvents were evaporated and the residue was purified by CC over silica (CH/AcOEt = 30:1). Yield: 160 mg **9** (23%), colourless oil.

b) A mixture of 800 mg (1.8 mmol) **7**, 500 mg (3.5 mmol) Cu_2O, 560 mg (3.6 mmol) 2,2′-bipyridyl, 200 mg glass powder, and 5 ml dry quinolin under Ar was heated to 200°C for 7 h. After cooling it was poured in 2 *N* HCl, filtered, and extracted three times with Et_2O. The combined organic phases were washed twice with 2 *N* HCl and twice with H_2O and dried over Na_2SO_4. The solvent was evaporated and the residue purified by CC over silica (CH/AcOEt = 30:1); yield: 50 mg **9** (8%) as a colourless oil.

$R_f = 0.36$ (CH/AcOEt = 30:1); $[\alpha]_D^{20} = -13.8$ ($c = 0.03$, $CHCl_3$); IR (neat): $\nu = 2957$ (s), 1728 (vs), 1460 (m), 1243 (m), 1139 (w) cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 212 (3.788), 259 (2.774) nm; ^1H NMR ($CDCl_3$): $\delta = 0.98$ (s, 3H, 20-H), 1.20 (d, $J = 6.9$ Hz, 6H, 18-H, 19-H), 1.22 (s, 3H, 21-H), 1.31 (m, 2H, 1-H), 1.3–1.7 (m, 2H, 6-H), 1.4–1.6 (m, 2H, 2-H), 1.45 (m, 1H, 3-H_{eq}), 1.77 (m, 1H, 3-H_{ax}), 1.92 (dd, $J = 6.1$ Hz, $J = 4.1$ Hz, 1H, 5-H), 2.38 (m, 2H, 7-H), 2.82 (sept, $J = 6.9$ Hz, 1H, 17-H), 3.63 (s, 3H, 23-H), 4.89 (dd, $J = 17.3$ Hz, $J = 1.2$ Hz, 1H, 8-H_{trans}), 4.93 (dd, $J = 10.9$ Hz, $J = 1.2$ Hz, 1H, 8-H_{cis}), 5.69 (dd, $J = 17.3$ Hz, $J = 10.9$ Hz, 1H, 9-H), 6.89 (dt, $J_{ortho} = 7.7$ Hz, $2\times J_{meta} = 1.4$ Hz, 1H, 14-H/16-H), 6.91 (br s, 1H, 12-H), 6.99 (dt, $J_{ortho} = 7.7$ Hz, $2\times J_{meta} = 1.4$ Hz, 1H, 16H/14H), 7.14 (td, $2J_{ortho} = 7.7$ Hz, $J_{para} = 0.9$ Hz, 1H, 15-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 18.0$ (t, C-2), 18.7

(q, C-21), 19.4 (q, C-20), 24.0 (q, C-18, C-19), 30.7 (t, C-6), 34.1 (d, C-17), 36.4 (t, C-3), 36.9 (t, C-7), 38.2 (t, C-1), 40.8 (s, C-10), 46.6 (s, C-4), 47.8 (d, C-5), 51.7 (q, C-23), 110.9 (t, C-8), 123.7 (d, C-14/C-16), 125.7 (d, C-16/C-14), 126.5 (d, C-12), 128.2 (d, C-15), 143.0 (s, C-11), 148.9 (s, C-13), 150.6 (d, C-9), 179.3 (s, C-22) ppm; MS (70 eV): *m/z* (%) = 342 (52) [M^+], 282 (42), 185 (50), 146 (92), 133 (100), 117 (66), 81 (46), 41 (47); $C_{23}H_{34}O_2$ (342.5); calc.: C 80.66, H 10.01; found: C 80.45, H 9.98.

Methyl-(4α, 15β)-15-chloro-15-cyano-13-(1-methylethyl)-17,19-dinoratis-13-en-4-carboxylate (**10**)

A mixture of 7.1 g (22 mmol) **5**, 9.7 g (111 mmol) 2-chloroacrylonitrile, and a few mg of thiodiphenylamine were heated in an autoclave under Ar to 170°C for 15 h. A brown oil was obtained which was dissolved in 300 ml CH_2Cl_2. 50 g silica were added, and the solvent was evaporated. The cooled silica was moistened with CH/AcOEt (9:1), brought on top of a column containing 300 g silica, and eluted with CH/AcOEt = 9:1.

Yield: 3.1 g **10** (39%); white crystals (petrol ether); m.p.: 133–134°C. Suitable crystals for an X-ray analysis were obtained from AcOEt. Crystal data: orthorhombic, space group $P2_12_12_1$, lattice constants: $a = 11.49(1)$, $b = 16.47(1)$, $c = 12.04\,(1)$Å; $Z = 4$; $D_{calc.} = 1.178$ g/cm^3, $D_{measd.} = 1.17$ g/cm^3; $\mu = 1.48$ cm^{-1}.

$R_f = 0.34$ (CH/AcOEt = 9:1); $[\alpha]_D^{20} = -83.9$ ($c = 0.1$, $CHCl_3$); IR (KBr): $\nu = 2932$ (s), 2237 (w), 1730 (vs), 1448 (m), 1244 (s), 1185 (m) cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 206 (3.720) nm; ^{1}H NMR ($CDCl_3$): $\delta = 0.61$ (s, 3H, 20-H), 0.99 (td, $2\times J = 12.8$ Hz, $J = 3.9$ Hz, 1H, 1-H$_{ax}$), 1.02 (d, $J = 6.9$ Hz, 3H, 18-H/19-H), 1.03 (d, $J = 6.9$ Hz, 3H, 19-H/18-H), 1.14 (s, 3H, 21-H), 1.18 (m, 1H, 11-H$_\beta$), 1.26 (m, 1H, 6-H$_{eq}$), 1.40 (m, 1H, 1-H$_{eq}$), 1.48 (m, 1H, 6-H$_{ax}$), 1.52 (m, 1H, 3-H$_{eq}$), 1.59 (m, 1H, 11 H$_\alpha$), 1.72 (m, 1H, 3-H$_{ax}$), 1.73 (m, 1H, 7-H$_{ax}$), 1.77 (m, 1H, 5-H), 1.80 (dd, $J = 9.5$ Hz, $J = 5.7$ Hz, 1H, 9-H), 1.98 (dt, $J = 14.1$ Hz, $J = 3.0$ Hz, $J_{11\beta,16\beta} = 3.0$ Hz, 1H, 16-H$_\beta$), 2.23 (ddd, $J = 13.4$ Hz, $J = 3.6$ Hz, $J = 3.0$ Hz, 1H, 7-H$_{eq}$), 2.35 (sept, $J = 6.9$ Hz, $J_{14,17} = 1.3$ Hz, 1H, 17-H), 2.56 (dd, $J = 14.1$ Hz, $J = 2.3$ Hz, 1H, 16-H$_\alpha$), 2.57 (br s, 1H, 12-H), 3.65 (s, 3H, 24-H), 5.31 (br s, 1H, 14-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta =$ 15.9 (q, C-20), 16.9 (q, C-21), 17.1 (t, C-6), 20.1 (q, C-18/C-19), 20.2 (q, C-19/C-18), 21.6 (d, C-6), 27.1 (t, C-11), 32.6 (C-7, C-12), 32.7 (d, C-17), 36.5 (t, C-3), 37,9 (t, C-1), 38.0 (s, C-10), 46.1 (s, C-8), 47.1 (s, C-4), 47.5 (t, C-16), 48.9 (d, C-5), 49.8 (d, C-9), 51.9 (q, C-24), 65.2 (s, C-15), 120.5 (s, C-23), 121.7 (d, C-14), 149.7 (s, C-13), 178.8 (s, C-22) ppm; MS (70 eV): *m/z* (%) = 405 (16) [$(M+2)^+$], 403 (43) [M^+], 316 (100), 187 (46), 146 (62), 121 (37), 91 (31), 43 (19); $C_{24}H_{34}ClNO_2$ (404.0); calc.: C 71.35, H 8.48, N 3.47; found: C 71.29, H 8.48, N 3.52.

Methyl-(4α)-13-(1-methylethyl)-15-oxo-17,19-dinoratis-13-en-4-carboxylate (**11**)

A hot saturated solution of 2.8 g (50 mmol) KOH was added to a solution of 2.0 g (5.0 mmol) **10** in EtOH. The mixture became brown and was refluxed for 25 h. After evaporation of the solvent, a yellow oil was obtained. 10 ml ice-cold H_2O was added, and the mixture was acidified with 2 *N* H_2SO_4 and extracted three times with Et_2O. The combined organic phases were dried over Na_2SO_4, and an ethereal diazomethane solution was added until a yellow colour persisted. After evaporation and CC over silica (CH/AcOEt = 9:1), 1.3 g **11** (71%) were obtained as yellow crystals. Further purification for characterization: sublimation at 100°C/0.1 torr.

M.p.: 97–98°C; $R_f = 0.27$ (CH/AcOEt = 9:1), 0.34 (CH/AcOEt = 5:1); $[\alpha]_D^{20} = +170.6$ ($c = 0.05$, $CHCl_3$); IR (KBr): $\nu = 2954$ (s), 1720 (vs), 1466 (m), 1236 (s), 1101 (m) cm^{-1}, UV (MeOH): λ_{max} (lg ε) = 216 (3.394), 297 (2.491) nm; ^{1}H NMR ($CDCl_3$): $\delta = 0.70$ (s, 3H, 20-H), 0.94 (m, 1H, 1-H$_{ax}$), 0.99 (d, $J = 6.8$ Hz, 3H, 18-H/19-H), 1.00 (d, $J = 6.8$ Hz, 3H, 19-H/18-H), 1.13 (s, 3H, 21-H), 1.17 (m, 1H, 6-H$_{eq}$), 1.39 (m, 1H, 11-H$_\beta$), 1.4–1.5 (m, 2H, 2-H), 1.45 (m, 1H, 1-H$_{eq}$), 1.48 (m, 1H, 6-H$_{ax}$), 1.49 (m, 1H, 3-H$_{eq}$), 1.53 (m, 1 H, 9-H), 1.66 (m, 1H, 5-H), 1.68 (m, 1 H, 3-H$_{ax}$), 1.69 (m, 1H,

7-H_{ax}), 1.72 (m, 1H, 11-H_{α}), 1.91 (m, 1H, 7-H_{eq}), 1.94 (dt, $J = 18.1$ Hz, $J = 3.1$ Hz, $J_{11\beta,16\beta} = 3.1$ Hz, 1H, 16-H_{β}), 2.01 (dd, $J = 18.1$ Hz, $J = 2.1$ Hz, 1H, 16-H_{α}), 2.33 (sept, $J = 6.8$ Hz, $J_{14,7} = 1.3$ Hz, 1H, 17-H), 2.80 (m, 1H, 12-H), 3.62 (s, 3H, 23-H), 5.26 (d, $J = 0.7$ Hz, 1H, 14-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.8$ (q, C-20), 16.8 (q, C-21), 17.1 (t, C-2), 20.0 (q, C-18/C-19), 20.1 (q, C-19/C-18), 21.2 (t, C-6), 27.7 (t, C-11), 28.5 (t, C-7), 32.8 (d, C-17), 34.0 (d, C-12), 36.6 (t, C-3), 38.2 (s, C-10) 38.5 (t, C-1), 40.4 (t, C-16), 47.2 (s, C-4), 48.9 (d, C-5), 49.5 (d, C-9), 51.9 (q, C-23), 52.2 (s, C-8), 120.6 (d, C-14), 152.7 (s, C-13), 179.0 (s, C-22), 212.9 (s, C-15) ppm; MS (70 eV): *m/z* (%) = 358 (27) [M^+], 316 (100), 299 (55), 239 (54), 187 (13), 146 (92), 121 (68), 91 (72), 41 (42); $C_{22}H_{34}O_3$ (358.5); calc.: C 77.05, H 9.56; found: C 77.06, H 9.57.

(3aR-(3aα,3bβ,5aα,6α,9aβ,9bα,11β,11aα))-3a-Cyano-6, 9a-dimethyl-12-(1-methylethyl)-3a,3b,4,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-3b,11-etheno-1H-phenanthro-[1,2-c]pyrazol (**13**)

To a solution of 910 mg (2.25 mmol) **10** in 18 ml dry oxygen free *DMSO* under Ar, a hot saturated solution of 630 mg (11.2 mmol) KOH in H_2O was added and this mixture was stirred at 50°C for 10 h. After cooling, 20 ml ice-cold H_2O and *2 N* H_2SO_4 were added and the mixture was extracted three times with Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4, and an ethereal solution of diazomethane was added until a yellow colour persisted. After evaporation of the solvent and CC over silica (CH/AcOEt = 9:1), 90 mg **10**, 320 mg **11**, and 200 mg (22%) **13** were obtained.

13: White crystals, m.p.: 126°C (decomp); $R_f = 0.15$ (CH/AcOEt = 9:1), 0.21 (CH/AcOEt = 5:1); $[\alpha]_D^{20} = +87.7$ ($c = 0.1$, $CHCl_3$); IR (KBr): $\nu = 2944$ (s), 2230 (w), 1721 (vs), 1562 (m), 1448 (m), 1238 (s), 1193 (m) cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 203 (3.714), 325 (2.209) nm; ^{1}H NMR ($CDCl_3$): $\delta = 0.53$ (s, 3H, 20-H), 0.92 (d, $J = 6.8$ Hz, 3H, 18-H/19-H), 0.93 (d, $J = 6.8$ Hz, 3H, 19-H/18-H), 1.00 (m, 1H, 1-H_{ax}), 1.10 (m, 1H, 11-H_{β}), 1.11 (s, 3H, 21-H), 1.23 (m, 1H, 6-H_{eq}), 1.3–1.5 (m, 2H, 2-H), 1.34 (m, 1H, 1-H_{eq}), 1.47 (m, 1H, 3-H_{eq}), 1.53 (m, 1H, 6-H_{ax}), 1.59 (m, 1H, 11-H_{α}), 1.78 (m, 1H, 3-H_{ax}), 1.90 (m, 1H, 9-H), 2.11 (sept, $J = 6.8$ Hz, $J_{14,11} = 1.2$ Hz, 1H, 17-H), 2.3–2.5 (m, 2H, 7-H), 2.37 (m, 1H, 16-H), 2.50 (br s, 1H, 12-H), 3.63 (s, 3H, 25-H), 4.19 (dd, $J = 18.9$ Hz, $J = 3.6$ Hz, 1H, 24-H_{β}), 4.52 (dd, $J = 18.9$ Hz, $J = 9.3$ Hz, 1H, 24-H_{α}), 5.09 (br s, 1H, 14-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.9$ (q, C-20), 16.7 (q, C-21), 16.9 (t, C-2), 19.7 (q, C-18/C-19), 20.6 (q, C-19/C-18), 21.3 (t, C-6), 26.6 (d, C-11), 32.9 (d, C-7), 33.5 (d, C-17), 36.4 (t, C-3), 36.8 (d, C-12), 37.6 (s, C-10), 37.7 (t, C-1), 42.5 (d, C-16), 44.0 (s, C-8), 46.9 (s, C-4), 48.66 (d, C-5), 48.73 (d, C-9), 51.9 (q, C-25), 84.0 (t, C-24), 98.4 (s, C-15), 118.0 (s, C-23), 123.2 (d, C-14), 148.1 (s, C-13), 178.7 (s, C-22) ppm; MS (FD): *m/z* (%) = 381 (100) [($M - N_2$)$^+$], 316 (4); $C_{25}H_{35}N_3O_2$ (409.6); calc.: C 73.30, H 8.61, N 10.26; found: C 73.27, H 8.61, N 10.30.

Methyl-(4α,8α,12α,13R,14S)-14-cyano-16-(1-methylethyl)-13,14-methano-17,19-dinoratis-15-en-4-carboxylate (**14**) *and Methyl-(1R-(1α,2β,3α))-2-(2-(2-cyano-3-methyl-5-(1-methylethyl))-phenyl)-ethyl)-1,3-dimethyl-3-vinyl-1-cyclohexanecarboxylate* (**16**)

110 mg (0.27 mmol) **13** were heated under medium vac. (*ca.* 25 torr) to 140°C for 2 h. CC over silica (CH/AcOEt = 9:1) gave 52 mg (50%) **14** as white crystals.

M.p.: 144–145°C; $R_f = 0.22$ (CH/AcOEt = 9:1); $[\alpha]_D^{20} = +100.8$ ($c = 0.1$, $CHCl_3$); IR (KBr): $\nu = 2946$ (s), 2225 (m), 1727 (vs), 1464 (m), 1243 (s), 1158 (m) cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 204 (3.671) nm; ^{1}H NMR ($CDCl_3$): $\delta = 0.54$ (s, 3H, 20-H), 0.68 (m, 2H, 24-H), 0.93 (d, $J =$ 6.8 Hz, 6H, 18-H, 19-H), 0.98 (m, 1H, 1-H_{ax}), 1.10 (m, 1H, 6-H_{eq}), 1.10 (m, 1H, 11-H_{β}), 1.10 (s, 3H, 21-H), 1.3–1.5 (m, 2H, 2-H), 1.34 (m, 1H, 1-H_{eq}), 1.45 (m, 1H, 3-H_{eq}), 1.49 (m, 1H, 6-H_{ax}), 1.55 (m, 1H, 16-H), 1.62 (m, 1H, 11-H_{α}), 1.69 (m, 1H, 9-H), 1.7–2.0 (m, 2H, 7-H), 1.72 (m, 1H, 3-H_{ax}), 1.80

(m, 1H, 5-H), 2.16 (sept, $J = 6.8$ Hz, $J_{14,17} = 1.2$ Hz, 1H, 17-H), 2.71 (br s, 1H, 12-H), 3.63 (s, 3H, 25-H), 5.01 (br s, 1H, 14-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.7$ (t, C-24), 15.9 (s, C-15), 16.4 (q, C-20), 16.8 (q, C-21), 17.1 (t, C-2), 20.0 (q, C-18/C-19), 20.2 (q, C-19/C-18), 21.7 (t, C-6), 22.0 (d, C-16), 27.2 (t, C-11), 32.2 (d, C-17), 33.1 (d, C-12), 33.8 (t, C-7), 36.5 (t, C-3), 37.6 (s, C-10), 38.1 (t, C-1), 39.6 (s, C-8), 47.2 (s, C-4), 48.9 (d, C-5), 51.9 (q, C-25), 52.1 (d, C-9), 121.4 (d, C-14), 123.4 (s, C-23), 144.3 (s, C-13), 179.0 (s, C-22) ppm; MS (70 eV): *m/z* (%) = 381 (100) [M^+], 321 (48), 306 (29), 171 (51), 81 (44), 55 (51), 41 (66); $C_{25}H_{35}NO_2$ (381.6); calc.: C 78.69, H 9.25, N 3.67; found: C 78.52, H 9.30, N 3.59.

16: 40 mg (39%); colourless oil; $R_f = 0.42$ (CH/AcOEt); $[\alpha]_D^{20} = -11.4$ ($c = 0.1$, $CHCl_3$); IR (neat): $\nu = 2960$ (s), 2218 (m), 1727 (vs), 1606 (m), 1459 (m), 1258 (s), 1245 (s) cm^{-1} ; UV (MeOH): λ_{max} (Ig ε) = 249 (3.452), 279 (3.229), 288 (3.268) nm; ^{1}H NMR ($CDCl_3$): $\delta = 1.03$ (s, 3H, 20-H), 1.21 (d, $J = 6.9$ Hz, 6H, 18-H, 19-H), 1.26 (s, 3H, 21-H), 1.35 (m, 1H, 1-H_{eq}), 1.43 (m, 1H, 6-H), 1.45 (m, 1H, 1-H_{ax}), 1.5–1.6 (m, 2H, 2-H), 1.51 (m, 1H, 3-H_{eq}), 1.59 (m, 1H, 6-H), 1.80 (m, 1H, 3-H_{ax}), 2.03 (dd, $J = 5.7$ Hz, $J = 4.6$ Hz, 1H, 5-H), 2.47 (s, 3H, 24-H), 2.60 (m, $2\times J = 11.9$–13.3 Hz, $J = 5.4$ Hz, 1 H, 7-H), 2.69 (m, $2\times J = 11.9$–13.3 Hz, $J = 5.4$ Hz, 1H, 7-H), 2.84 (sept, $J = 6.9$ Hz, 1H, 17-H), 3.69 (s, 3H, 25-H), 4.94 (dd, $J = 17.5$ Hz, $J = 0.9$ Hz, 1 H, 8-H_{trans}), 4.96 (dd, $J = 10.8$ Hz, $J = 0.9$ Hz, 1 H, 8-H_{cis}), 5.72 (dd, $J = 17.5$ Hz, $J = 10.8$ Hz, 1H, 9-H), 6.86 (s, 1H, 12-H), 6.94 (s, 1H, 14-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.9$ (t, C-2), 18.7 (q, C-21), 19.4 (q, C-20), 20.8 (q, C-24),23.51 (q, C-18/C-19), 23.46 (q, C-19/C-18), 29.8 (t, C-6), 35.5 (d, C-17), 35.5 (t, C-7), 36.4 (t, C-3), 38.0 (t, C-1), 40.6 (s, C-10), 46.6 (s, C-4), 47.5 (d, C-5), 51.9 (q, C-25), 110.0 (s, C-15), 111.2 (t, C-8), 117.4 (s, C-23), 124.8 (d, C-12), 125.6 (d, C-14), 142.1 (s, C-16), 147.2 (s, C-11), 150.2 (d, C-9), 153.6 (s, C-13), 179.1 (s, C-22) ppm; MS (70 eV): *m/z* (%) = 381 (100) [M^+], 321 (30), 172 (29), 136 (28), 81 (37), 41 (33); $C_{25}H_{35}NO_2$ (381.6); calc.: C 78.69, H 9.25, N 3.67; found: C 78.50, H 9.22, N 3.55.

Methyl-(4α,15Z)-15-hydroximino-13-(1-methylethyl)-17,19-dinoratis-13-en-4-carboxylate (**17**)

To a solution of 310 mg (0.86 mmol) **11** in 15 ml EtOH, a conc. aqueous solution of 310 mg (4.5 mmol) $H_2NOH \cdot HCl$ and 390 mg solid NaOH were added. This mixture was refluxed for 7 h. After cooling it was diluted with 20 ml ice-cold water, acidified with 2 *N* H_2SO_4, and extracted three times with Et_2O. The combined organic phases were dried over Na_2SO_4, and a solution of diazomethane in ether was added. Evaporation and CC over silica with CH/AcOEt (2:1) afforded colourless crystals.

Yield: 310 mg **17** (92%); m.p.: 73–75°C; $R_f = 0.45$ (CH/AcOEt = 2:1); $[\alpha]_D^{20} = +74.5$ ($c = 0.1$, $CHCl_3$); IR (KBr): $\nu = 3283$ (m), 2928 (s), 1728 (vs), 1460 (m), 1258 (s), 1076 (m) cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 205 (3.901) nm; ^{1}H NMR ($CDCl_3$): $\delta = 0.64$ (s, 3H, 20-H), 0.89 (m, 1H, 1-H_{ax}), 0.98 (d, $J = 6.8$ Hz, 3H, 18-H/19-H), 0.99 (d, $J = 6.8$ Hz, 3H, 19-H/18-H), 1.13 (s, 3H, 21-H), 1.17 (m, 1H, 6-H_{eq}), 1.25 (m, 1 H, 11-H_β), 1.35–1.55 (m, 2H, 2-H), 1.40 (m, 1H, 1-H_{eq}), 1.48 (m, 1H, 3-H_{eq}), 1.50 (m, 1H, 6-H_{ax}), 1.54 (m, 1 H, 9-H), 1.62 (ddd, $J = 12.8$ Hz, $J = 10.0$ Hz, $J = 2.4$ Hz, 1H, 11-H_α), 1.69 (m, 1 H, 3-H_{ax}), 1.69 (m, 1H, 5-H), 1.83 (dt, $J = 13.5$ Hz, $2\times J = 3.2$ Hz, 1H, 7-H_{eq}), 1.94 (td, $2\times J = 13.5$ Hz, $J = 4.6$ Hz, 1H, 7-H_{ax}), 2.13 (dt, $J = 17.8$ Hz, $J = 3.2$ Hz, $J_{11\beta,16\beta} = 3.2$ Hz, 1H, 16-H_β), 2.26 (dd, $J = 17.8$ Hz, $J = 2.3$ Hz, 1H, 16-H_α), 2.30 (sept, $J = 6.8$ Hz, $J_{14,11} = 1.2$ Hz, 1H, 17-H), 2.74 (br s, 1H, 12-H), 3.63 (s, 3H, 23-H), 5.35 (br s, 1H, 14-H), 8.45 (br s, 1H, NOH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 16.0$ (q, C-20), 16.8 (q, C-21), 17.0 (t, C-2), 20.2 (q, C18/C-19), 20.3 (q, C-19/C-18), 21.5 (t, C-6), 27,7 (t, C-11), 30.3 (t, C-7), 31.8 (t, C-16), 32.7 (d, C-17), 33.2 (d, C-12), 36.6 (t, C-3), 38.0 (s, C-10), 38.2 (t, C-1), 44.0 (s, C-8), 47.3 (s, C-4), 49.3 (d, C-5), 51.8 (d, C-9), 51.9 (q, C-23), 122.5 (d, C-14), 151.5 (s, C-13), 166.5 (s, C-15), 179.2 (s, C-22) ppm; MS (70 eV): *m/z* (%) = 373 (100) [M^+], 356 (69), 330 (42), 296 (77), 181 (52), 139 (70), 121 (93), 43 (41); $C_{23}H_{35}NO_3$ (373.5); calc.: C 73.96, H 9.44, N 3.75; found: C 73.92, H 9.50 N 3.73.

Methyl-(1R-(1α,4aβ,4bα,6α))-6-(cyanomethyl)-1,4a-dimethyl-7-(1-methylethyl)-1,2,3,4,4a,4b,5,6,10,10a-decahydro-1-phenanthrene-carboxylate (**18**)

A mixture of 160 mg (0.43 mmol) **17** and 210 mg (1.10 mmol) *Ts*Cl in 8 ml abs. pyridine was stirred under Ar for 3 days, diluted with 30 ml H_2O, and extracted three times with Et_2O. The combined organic phases were washed with 2 *N* H_2SO_4, $NaHCO_3$, and H_2O, dried over Na_2SO_4, and evaporated. The crude product was air sensitive and purified by prep. TLC under Ar (CH/AcOEt = 3:1).

Yield: 160 mg **18** (85%); colourless air sensitive oil; $R_f = 0.53$ (CH/AcOEt = 3:1); IR (KBr): $\nu = 2950$ (s), 2245 (w), 1726 (vs), 1432 (m), 1246 (s), 1148 (m) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.81$ (s, 3H, 20-H), 1.01 (d, $J = 6.9$ Hz, 3H, 16-H/17-H), 1.05 (d, $J = 6.9$ Hz, 3H, 17-H/16-H), 1.17 (m, 1H, 1-H_{ax}), 1.24 (s, 3H, 19-H), 1.42 (m, 1H, 11-H_{ax}), 1.5–1.6 (m, 2H, 2-H), 1.62 (m, 1H, 3-H_{eq}), 1.76 (m, 1H, 3-H_{ax}), 1.80 (m, 1 H, 6-H_{eq}), 1.87 (m, 1H, 1-H_{eq}), 1.95 (m, 1H, 11-H_{eq}), 2.06 (m, 1H, 9-H), 2.06 (m, 1H, 6-H_{ax}), 2.07 (m, 1H, 5-H), 2.19 (sept, $J = 6.9$ Hz, 1H, 16-H), 2.32 (dd, $J = 17.0$ Hz, $J = 10.8$ Hz, 1H, 21-H), 2.50 (ddd, $J = 17.0$ Hz, $J = 4.4$ Hz, $J_{11ax,21} = 0.7$ Hz, 21-H), 2.62 (m, 1H, 12-H), 3.63 (s, 3H, 23-H), 5.45 (m, 1H, 7-H), 5.82 (br s, 1H, 14-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.9$ (q, C-20), 16.9 (q, C-19), 18.0 (t, C-2), 21.2 (t, C-21), 21.4 (q, C-16/C-17), 22.8 (q, C-17/C-16), 25.9 (t, C-6), 26.4 (t, C-11), 32.5 (d, C-15), 34.3 (s, C-10), 34.5 (d, C-12), 37.2 (t, C-3), 38.1 (t, C-1), 44.6 (d, C-9), 45.4 (d, C-5), 46.6 (s, C-4), 51.8 (q, C-23), 118.8 (s, C-22), 123.6 (d, C-7), 124.7 (d, C-14), 133.9 (s, C-8), 144.2 (s, C-13), 178.7 (s, C-18) ppm; MS (FD): *m/z* (%) = 403 (1) [$(M+48)^+$], 387 (3) [$(M+32)^+$], 371 (23) [$(M+16)^+$], 355 (100) [M^+]; $C_{23}H_{33}NO_2$ (355.5).

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