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Synthetic Transformations of Abietic Acid IV [1]. B- and C-Ring Oxidation

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Summary. Selective oxidations at the B- or C-ring of abietic acid are described. The products can be used as educts for the synthesis of higher terpenes. Carbon side chains are attached to the B-ring *via Michael* additions and *Reformatzky* reactions.

Keywords. Abietic acid; Diterpenes; Oxidation; *Michael* addition; *Reformatzky* reaction.

Synthetische Umwandlungen von Abietinsäure, 4. Mitt. [1]**. B- und C-Ring-Oxidationen**

Zusammenfassung. Es werden selektive Oxidationsreaktionen am Abietinsäuregerüst beschrieben, die zur Einführung von Sauerstoffunktionen am B-bzw. C-Ring führen. Die Oxidationsprodukte können zur Synthese höherer Terpenderivate verwendet werden. An einzelnen Verbindungen werden Aufbaureaktionen beschrieben (*Michael*-Addition, *Reformatzky*-Reaktion), die es gestatten, Kohlenstoffketten an den B-Ring zu knüpfen.

Introduction

Oxidation and subsequent functionalization of abietic acid (**1**) leads to chiral synthons which can be used as starting materials for stereoselective syntheses of bioactive natural compounds [2–5]. Some oxidation products of **1** are powerful allergens [6], and many of them can be used as synthetic precursors for ring cleavage reactions, providing access to chiral degradation products [4, 5]. To induce selective cleavage of ring B or C it is important that only one of the two double bonds of **1** is oxidized by the reagent. It has been shown that osmium tetroxide attacks selectively the double bond of ring C yielding **3** [7]. In this paper we describe reactions which introduce oxygen functions selectively in ring B or C and subsequent transformations which lead to chiral synthons useful for the synthesis of terpene derivatives.

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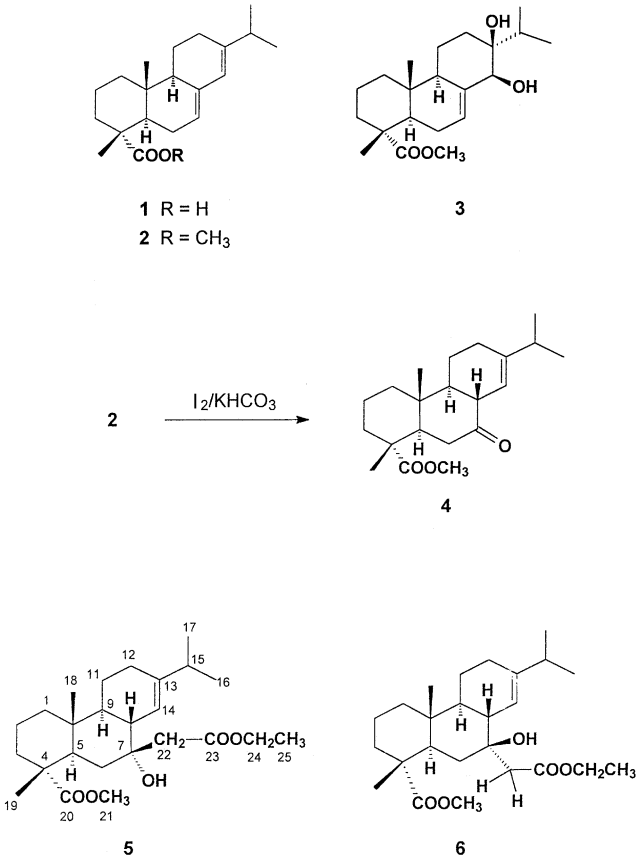
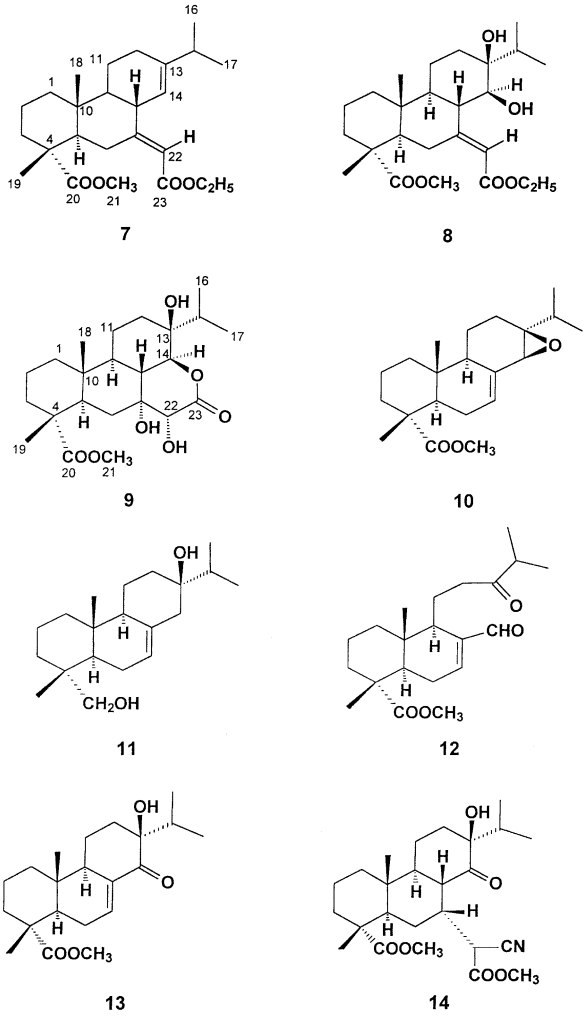


Scheme 1

Results and Discussion

Oxidation of the B-ring

Oxidation of **2** with iodine in aqueous $KHCO_3$ has been described to afford ketone **4** [8]. We found that **10** is a side product obtained in low yield. We further studied the reactivity of the keto function in **4** in order to evaluate the possibility to use this compound as an educt for the synthesis of higher terpene derivatives. *Reformatzky* reaction [9, 10] of **4** with ethyl bromoacetate in *THF* gave a mixture of the diastereomeric compounds **5** (65%) and **6** (16%). The main product (**5**) has *S*-configuration at C-7 as established by NOE measurements which means that the side chain is in equatorial position. Irradiation of 14-H resulted in intensity enhancement of the resonance of both protons in position 22, 15-H, 16/17-H, and 8-H. Irradiation of 14-H in **6** gives NOE enhancement at 15-H, 8-H, and only at one of the two diastereotopic protons attached to C-22 ($\delta = 2.43$ ppm). Irradiation of the other proton at C-22 ($\delta = 2.58$ ppm) gives an NOE at the geminal proton and at H-5. This proves that C-22 is in axial position and indicates restricted rotation about the C-7-C-22 bond. From these experiments we are able to assign the resonances at $\delta = 2.43$ ppm to pro-*R*-H-22 and at $\delta = 2.58$ ppm to pro-*S*-H-22.



Scheme 2

Elimination of the OH-function in **5** gave a mixture of olefinic products. The antiperiplanar relationship of the hydroxyl function to 8-H and 6-H_{ax} directs elimination mainly into the B ring. Product **6** with an axial side chain gives entirely olefin **7** with an exocyclic double bond after elimination. *E*-configuration of this double bond was established by means of a NOESY experiment showing a cross peak connecting 14-H and 22-H.

The double bonds of **7** can be oxidized with OsO_4/trimethylamine N-oxide dihydrate leading to *cis*-diol **8** in 4% and lactone **9** in 39% yield. The ^{1}H NMR spectrum of **8** exhibits a large coupling ($J = 9.2$ Hz) between 8-H and 14-H. Therefore, both protons are in axial positions. Due to the *cis*-addition of osmium tetroxide to double bonds [11], the OH-function at C-13 must be in axial position too.

All rings in **9** are *trans*-annulated as confirmed by selective TOCSY and ROESY experiments. Because of two large diaxial couplings ($J = 11.1$ Hz) to 14-H

and 9-H, the signal of 8-H appears as a *pseudo*-triplett. 14-H shows cross peaks to 9-H and 12-H_{ax}, and 22-H gives a ROE correlation to 8-H.

Oxidation of the C-ring

When the oxidation with iodine and $KHCO_3$ is performed at 50°C in *THF*, **10** is obtained as the main product. Thus, ring B or ring C of abietic acid can be selectively oxidized by choosing the appropriate procedure. A mixture of α- and β-epoxide was obtained earlier by oxidation of **2** with *m*-chloroperbenzoic acid, and the configuration of the oxirane group has been derived [12]. By comparing our NMR spectra to the data given in Ref. [12] we conclude that the epoxide group in **10** is in β-position. Reductive opening of the epoxide ring with $LiAlH_4$ gives diol **11** in 60% yield. We assume the OH-group at C-13 to be in axial position because the reduction with $LiAlH_4$ should not change the configuration of C-13 and cleavage of an epoxide on a substituted cyclohexane ring usually affords an axial alcohol [13].

Oxidation of **1** with osmium tetroxide has been described by *Krohn et al.* [6]. The free acid of diol **3** was obtained as the main product. The configuration of the carbons in positions 13 and 14 was determined by X-ray diffraction and showed clearly that the reagent approaches the C-ring double bond from the β-side. By *Jones* oxidation of **3** we obtained two products: **12** (23%) and **13** (44%). **12** has already been synthesized by cleavage of **3** with $NaIO_4$ [5] and $Pb(OAc)_4$ [7,14]. **13** has a carbonyl function in conjugation to the double bond in ring B. *Michael* addition [15] of methyl cyanoacetate introduces a side chain in position 7. Product **14** (49%), which is a valuable educt for the synthesis of higher terpenes, was obtained as mixture of diastereomeres (4:3). This was established by ^{1}H NMR which shows clearly the resonances of the two diastereomeric compounds. The signal of 22-H of the main component was found at $\delta = 3.65$ ppm and that of the minor product at $\delta = 4.33$ ppm. NOE experiments to determine the configuration of C-7 gave the following results: Irradiation of 3.65 ppm gave intensity enhancement of the signals of 5-H, 6-H, and 7-H, indicating that the side chain in the main diastereomer is in α-position. Irradiation of the resonance at $\delta = 4.33$ ppm gave NOE enhancements at 5-H, 7-H, and 9-H. This experiment proves that the side chain in the minor product is also in α-position. Both compounds have therefore *S*-configuration at C-7 and *R*- or *S*-configuration, respectively, at C-22. We were not able to assign a specific configuration of C-22 to one of the diastereomers.

Experimental

Analytical methods

Melting points: melting point apparatus Dr. Tottoli, uncorrected; optical rotation: polarimeter 241 MC (Perkin-Elmer); MS: Varian MAT 711 spectrometer, EI, 70 eV; IR Spectra: infrared spectrometer System 2000 FT (Perkin-Elmer); UV/Vis: UV-160 A UV-visible recording spectrophotometer (Shimadzu); NMR spectra: Varian Unity Inova 400, 600 (300 K), 5 mm tubes, solvent as internal standard. ^{1}H and ^{13}C resonances were assigned using ^{1}H,^{1}H and ^{1}H,^{13}C correlation experiments: ^{1}H and ^{13}C resonances are numbered as given in the formulas of **5**, **7**, and **9**.

Assignments marked with an asterisk are interchangeable. Before performing NOE experiments, dissolved oxygen was carefully removed by bubbling Ar through the solutions. Elementary analyses: Laboratory for Microanalysis, Institute of Physical Chemistry, University of Vienna. Materials: column chromatography (CC): Kieselgel 60 (Merck, 70–230 mesh), pore diameter 60 Å, solvents: cyclohexane/ethyl acetate (*CH*/EtOAc); thin-layer chromatography (TLC): TLC plates (Merck) Kieselgel 60 F_{254}, 0.2 mm 200 × 200 mm; the substances were detected in UV light at 254 nm and by spraying with molybdatophosphoric acid and subsequent heating with a hot air gun.

Methyl (1R-(1α,4aβ,4bα,7β,8β,10aα))-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydro-7,8-dihydroxy-1,4a-dimethyl-7-(1-methylethyl)-phenanthrene-1-carboxylate (**3**)

3 was prepared from **1** or **2** according to Refs. [7, 16–18].

Methyl (1R-(1α,4aβ,4bα,8aβ,10aα))-1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodeca-hydro-1,4a-dimethyl-7-(1-methylethyl)-9-oxo-phenanthrene-1-carboxylate (**4**)

1.3 g (3.25 mmol) **2** were dissolved in 280 ml Et_2O and 6 ml H_2O, and 6.4 g (64 mmol) $KHCO_3$ and 3.2 g (12.6 mmol) I_2 were added. This mixture was stirred at 30°C for 3 h. It was washed twice with 100 ml H_2O, 100 ml of a 2 *N* $Na_2S_2O_3$, and again three times with 100 ml H_2O, dried over Na_2SO_4, and evaporated. The residue (1.1 g) was purified by CC on silica (*CH*/EtOAc = 5:1) yielding 514 mg (48%) **4** as a colourless oil.

$R_f = 0.32$ (*CH*/EtOAc = 5:1); $[\alpha]_D^{20} = -24.7°$ ($c = 0.30$, CH_2Cl_2); IR ($CHCl_3$): $\tilde{\nu} = 3020$ (s), 2953 (m), 2873 (w), 1720 (s), 1648 (w), 1469 (w), 1460 (w), 1435 (w), 1386 (w), 1215 (vs), 1165 (w) cm^{-1}; UV (CH_2Cl_2): λ_{max} (lgε) = 243 (3.24) nm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.98$ (s, 3H, 18-H), 0.91 (d, $J = 7.0$ Hz, 6H, 16-H, 17-H), 0.98 (m, 1H, 1-H_{ax}), 1.12 (s, 3H, 19-H), 1.30 (m, 2H, 9-H, 12-H_{ax}), 1.57 (m, 3H, 2-H_{ax}, 2-H_{eq}, 3-H_{eq}), 1.74 (m, 1H, 3-H_{ax}), 1.81 (m, 1H, 1-H_{eq}), 1.82 (m, 1H, 12-H_{eq}), 1.86 (dd, $J = 14.0$, 2.7 Hz, 1H, 6-H_{eq}), 1.90 (m, 1H, 11-H), 2.02 (m, 1H, 11-H), 2.09 (dd, $J = 14.0$, 2.7 Hz, 1H, 5-H), 2.12 (sept, $J = 7.0$ Hz, 1H, 15-H), 2.32 (t, $J = 14.0$ Hz, 1H, 6-H_{ax}), 2.84 (d br, $J = 9.1$ Hz, 1H, 8-H), 3.58 (s, 3H, 21-H), 5.72 (s, 1H, 14-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.3$ (q, C-18), 15.6 (q, C-19), 17.5 (t, C-2), 20.8 (q, C-16*), 21.3 (q, C-17*), 22.2 (t, C-12), 26.3 (t, C-11), 34.5 (d, C-15), 35.6 (s, C-10), 36.5 (t, C-3), 37.0 (t, C-1), 40.5 (t, C-6), 46.8 (s, C-4), 48.4 (d, C-8), 48.8 (d, C-5), 51.7 (q, OCH_3), 52.6 (d, C-9), 114.9 (d, C-14), 144.1 (s, C-13), 177.2 (s, C-20), 208.2 (s, C-7) ppm; MS (70 eV): *m/z* (%) = 332 (100) [M^+], 317 (7), 299 (7), 289 (5), 273 (8), 239 (46), 229 (8); $C_{21}H_{32}O_3$ (332.46).

Ethyl (1R-(1α,4aβ,4bα,8aβ,9α,10aα))-1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-9-hydroxy-1,4a-dimethyl-7-(1-methylethyl)-1-methoxycarbonyl-phenanthrene-9β-yl-ethanoate (**5**) *and Ethyl (1R-(1α,4aβ,4bα,8aβ,9β,10aα))-1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-9-hydroxy-1,4a-dimethyl-7-(1-methylethyl)-1-methoxycarbonyl-phenanthrene-9α-yl-ethanoate* (**6**)

Under an Ar atmosphere, a solution of 501 mg (3 mmol) ethyl bromoacetate in 5 ml dry *THF* was added to 502 mg (7.7 mmol) activated Zn and a few crystals of I_2 at 50°C. After stirring at room temperature for 2 h, a solution of 500 mg (1.5 mmol) **4** in 20 ml dry *THF* was added dropwise, and the resulting solution was stirred at 50°C for 90 min. Then, 10 ml H_2O and HCl were added until all Zn hydroxide was dissolved, and a small amount of Et_2O was added. The organic layer was separated and the aqueous phase extracted with three 30 ml portions of Et_2O. The combined organic phases were washed with brine and 1 *N* aqueous $NaHCO_3$, dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by CC over 80 g silica (*CH*/EtOAc = 3:1). The polar fraction gave 410 mg (65%) of **5**, the unpolar fraction yielded 101 mg (16%) of **6**.

5: White crystals; m.p. = 75–77°C; $R_f = 0.29$ (*CH*/EtOAc = 3:1); $[\alpha]_{546}^{20} = -15.9°$ ($c = 0.50$, MeOH); IR (KBr): $\tilde{\nu} = 3529$ (m), 2926 (s), 2870 (m), 2852 (m), 1747 (s), 1245 (m), 1187 (m) cm^{-1}; UV (MeOH): λ_{max} (lgε) = 212 (2.98), 251 (2.86) nm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.79$ (s, 3H, 18-H), 0.94 (d, $J = 6.9$ Hz, 6H, 16-H, 17-H), 1.03 (m, 1H, 1-H$_{ax}$), 1.06 (m, 1H, 11-H$_{ax}$), 1.11 (s, 3H, 19-H), 1.15 (dd, $J = 13.7$, 2.5 Hz, 1H, 6-H$_{eq}$), 1.23 (t, $J = 7.2$ Hz, 3H, 25-H), 1.38 (td, $J = 12.1$, 2.1 Hz, 1H, 9-H), 1.52 (m, 1H, 3-H), 1.54 (m, 2H, 2-H$_{ax}$, 2-H$_{eq}$), 1.64 (t, $J = 13.6$ Hz, 1H, 6-H$_{ax}$), 1.72 (m, 2H, 3-H, 1-H$_{eq}$), 1.74 (m, 1H, 11-H$_{eq}$), 1.95 (m, 2H, 12-H), 2.04 (d, br, $J = 11.1$ Hz, 1H, 8-H), 2.18 (sept, $J = 6.9$ Hz, 1H, 15-H), 2.25 (dd, $J = 13.6$, 2.6 Hz, 1H, 5-H), 2.40 (d, $J = 15.1$ Hz, 1H, 22-H), 2.64 (s br, 1H, OH), 2.74 (d, $J = 15.1$ Hz, 1H, 22-H), 3.62 (s, 3H, 21-H), 4.13 (q, $J = 7.2$ Hz, 2H, 24-H), 5.34 (s br, 1H, 14-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.3$ (q, C-18), 14.2 (q, C-25), 16.5 (q, C-19), 18.0 (t, C-2), 21.2 (q, C-16*), 21.8 (q, C-17*), 21.9 (t, C-11), 26.5 (t, C-12), 35.3 (d, C-15), 35.8 (t, C-6), 36.8 (t, C-3, s, C-10), 37.4 (t, C-1), 43.0 (d, C-5), 43.4 (d, C-8), 44.3 (t, C-22), 47.0 (s, C-4), 47.7 (d, C-9), 51.8 (q, C-21), 60.5 (t, C-24), 71.9 (s, C-7), 117.1 (d, C-14), 147.0 (s, C-13), 172.4 (s, C-23), 178.9 (s, C-20) ppm; MS (70 eV): *m/z* (%) = 420 (1.3) [M^+], 402 (100) [M^+-H_2O], 342 (37.1) [M^+-$C_4H_8O_2$], 327 (25.2) [342-CH_3], 299 (11.9) [342-C_3H_7]; $C_{25}H_{40}O_5$ (420.58); calcd.: C 71.40%, H 9.59%; found: C 71.56%, 9.85%.

6: White crystals; m.p. = 69°C; $R_f = 0.40$ (*CH*/EtOAc = 3:1); $[\alpha]_{546}^{20} = 2.11°$ ($c = 0.52$, MeOH); IR (KBr): $\tilde{\nu} = 3499$ (s), 3010 (s), 2983 (s), 2872 (s), 1717 (vs), 1700 (vs), 1669 (w), 1452 (m), 1382 (m) cm^{-1}; UV (MeOH): λ_{max} (lgε) = 236 (2.26) nm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (s, 3H, 18-H), 0.90 (m, 1H, 9-H), 0.95 (d, $J = 6.8$ Hz, 6H, 16-H, 17-H), 1.00 (m, 1H, 1-H$_{ax}$), 1.10 (m, 1H, 12-H), 1.13 (s, 3H, 19-H), 1.28 (t, $J = 7.1$ Hz, 3H, 25-H), 1.42 (dd, $J = 13.1$, 1.8 Hz, 1H, 6-H$_{eq}$), 1.60 (m, 3H, 3-H$_{ax}$, 3-H$_{eq}$, 6-H$_{ax}$), 1.70 (dd, $J = 13.0$, 1.8 Hz, 1H, 5-H), 1.75 (m, 1H, 11-H), 1.86 (m, 1H, 12-H), 1.94 (m, 1H, 12-H), 2.14 (sept, $J = 6.8$, 1H, 15-H), 2.23 (d br, $J = 11.6$, 1H, 8-H), 2.43 (dd, $J = 17.0$, 0.8 Hz, 1H, 22-H$_{proR}$), 2.58 (d, $J = 17.0$ Hz, 1H, 22-H$_{proS}$), 3.56 (s, 3H, 21-H), 4.11 (m, 2H, 24-H), 4.34 (s br, 1H, OH), 5.50 (s, 1H, 14-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.9$ (q, C-18), 14.1 (q, C-25), 16.4 (q, C-19), 18.0 (t, C-2), 21.3 (q, C-17*), 21.7 (q, C-16*), 21.9 (t, C-11), 26.9 (t, C-12), 34.9 (d, C-15), 36.1 (t, C-22), 36.2 (s, C-10), 37.0 (t, C-3*), 37.1 (t, C-6*), 37.6 (t, C-1), 45.8 (d, C-8), 46.8 (s, C-4), 48.2 (d, C-5), 49.0 (d, C-9), 51.7 (q, C-21), 60.6 (t, C-24), 73.3 (s, C-7), 118.0 (d, C-14), 145.0 (s, C-13), 174.2 (s, C-23), 178.8 (s, C-20) ppm; MS (70 eV): *m/z* (%) = 420 (1.5) [M^+], 402 (100) [M^+-H_2O], 342 (28.9) [M^+-$C_4H_8O_2$], 327 (23.5) [342-CH_3], 299 (12.8) [342-C_3H_7); $C_{25}H_{40}O_5$ (420.58); calcd.: C 71.40%, H 9.59%; found: C 71.10%, 9.41%.

(9E)-Methyl (1R-(1α,4aβ,4bα,8aβ,10aα))-9-(ethoxycarbonylmethylen)-1,2,3,4,4a,4b,5, 6,8a,9,10,10a-dodecahydro-1,4a-dimethyl-7-(1-methylethyl)-phenanthrene-1-carboxylate (**7**)

To a solution of 500 mg (1.22 mmol) **6** in 10 ml dry pyridine, 218 mg (0.13 ml, 1.42 mmol) phosphorus oxychloride were added at 0°C. The mixture was allowed to warm to room temperature and then stirred at 80°C for 18 h. After cooling to room temperature again, the solution was poured on 50 g of ice and extracted three times with 50 ml Et_2O. The organic layer was washed with 2 *N* H_2SO_4 and brine, dried over Na_2SO_4, and evaporated. The residue was purified by CC on 50 g silica (*CH*/EtOAc = 3:1).

Colourless oil; 327 mg (67%); $R_f = 0.52$ (*CH*/EtOAc = 3:1); $[\alpha]_{546}^{20} = -118.4°$ ($c = 0.26$, MeOH); IR (KBr): $\tilde{\nu} = 2956$ (s), 1725 (s), 1644 (s), 1460 (s), 1437 (s), 1385 (s), 1293 (s), 1248 (s), 1173 (s), 1104 (s), 1052 (s), 1047 (s), 858 (m) cm^{-1}; UV (MeOH): λ_{max} (lgε) = 225.0 (3.46) nm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.95$ (s, 3H, 18-H), 0.95 (m, 1H, 1-H$_{ax}$), 0.96 (d, $J = 7.0$ Hz, 6H, 16-H, 17-H), 1.08 (td, $J = 11.5$, 1.9 Hz, 1H, 9-H), 1.19 (s, 3H, 19-H), 1.20 (m, 1H, 11-H$_{ax}$), 1.25 (t, $J = 7.2$ Hz, 3H, 25-H), 1.52 (m, 1H, 3-H), 1.58 (m, 2H, 2-H$_{ax}$, 2-H$_{eq}$), 1.76 (m, 2H, 1-H$_{eq}$, 3-H), 1.77 (m, 1H, 11-H$_{eq}$), 1.85 (dd, $J = 13.2$, 1.5 Hz, 1H, 5-H), 1.87 (m, 1H, 6-H$_{ax}$), 1.92 (m, 1H, 12-H), 1.98 (m, 1H, 12-H), 2.20 (sept, $J = 7.0$ Hz, 1H, 15-H), 2.78 (d br, $J = 11.5$ Hz, 1H, 8-H), 3.51 (dd, $J = 12.1$, 1.4 Hz, 1H, 6-H$_{eq}$), 3.65 (s, 3H, 21-H), 4.10 (q, $J = 7.2$ Hz, 2H, 24-H), 5.33 (s, 1H, 14-H),

5.52 (s, 1H, 22-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$ (q, C-18), 14.4 (q, C-25), 16.4 (q, C-19), 18.0 (t, C-2), 21.1 (q, C-17*), 21.7 (q, C-16*), 22.5 (t, C-11), 26.7 (t, C-12), 29.1 (t, C-6), 35.2 (d, C-15), 36.7 (t, C-3), 37.6 (t, C-1, s, C-10), 43.1 (d, C-8), 47.8 (s, C-4), 52.0 (q, C-21), 52.3 (d, C-5), 55.8 (d, C-9), 59.4 (t, C-24), 110.1 (d, C-22), 118.1 (d, C-14), 145.6 (s, C-13), 165.4 (s, C-7), 166.9 (s, C-23), 178.4 (s, C-20) ppm; MS (70 eV): *m/z* (%) = 402 (16.7) [M^+], 357 (21.6) [M^+-C_2H_5O], 356 (100) [M^+-C_2H_6O], 342 (28.0), 327 (11.3), 299 (13.6), 253 (12.9); $C_{25}H_{38}O_4$ (402.57); calcd.: C 74.59%, H 9.51%; found: C 74.34%, H 9.52%.

(9E)-Methyl (1R-(1α,4aβ,4bα,7β,8β,8aβ,10aα))-9-(ethoxycarbonylmethylen)-perhydro-7,8-dihydroxy-1,4a-dimethyl-7-(1-methylethyl)-phenanthrene-1-carboxylate (**8**) *and Methyl (3S-(3α,3aβ,6β,6aβ,7aβ,8α,11aα,11bβ,11cα))-perhydro-3,6,6a-trihydroxy-8,11a-dimethyl-3-(1-methylethyl)-5-oxo-phenanthro[1,10-bc]pyran-8-carboxylate* (**9**)

500 mg (1.24 mmol) of **7** and 185 mg (1.66 mmol) trimethylamine N-oxide dihydrate were dissolved in 0.6 ml H_2O, 250 µl pyridine, and 10 ml *t*-BuOH under Ar. After addition of 50 µl of a 2.5% solution of OsO_4 in *t*-BuOH, the temperature was raised to 110°C and the mixture was stirred for 24 h. After cooling to room temperature, 5 ml of a 20% solution of Na_2SO_3 were added, and the solvent was partially evaporated and diluted with 5 ml brine. This mixture was extracted five times with $CHCl_3$. The combined organic layers were washed twice with 10 ml 2 *N* H_2SO_4, 10 ml 1 *N* $NaHCO_3$, and 10 ml brine, dried over Na_2SO_4, and evaporated. The residue was purified by CC (*CH*/EtOAc = 1:1). Yield: 22 mg (4%) **8** and 205 mg (39%) **9**.

8: Colourless oil; $R_f = 0.53$ (*CH*/EtOAc = 1:1); $[\alpha]_D^{20} = -79.2°$ ($c = 0.43$, CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu} = 3601$ (m), 3055 (m), 2952 (m), 2874 (m), 1718 (s), 1637 (m), 1390 (m), 1176 (s), 1041 (m), 909 (m), 896 (m) cm^{-1}; UV (CH_2Cl_2): λ_{max} (lgε) = 235.0 (4.06) nm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (d, $J = 7.1$ Hz, 3H, 16-H*), 0.91 (d, $J = 7.1$ Hz, 3H, 17-H*), 0.92 (m, 1H, 1-H_{ax}), 0.99 (m, 1H, 9-H), 1.02 (s, 3H, 18-H), 1.09 (td, $J = 13.5$, 3.9 Hz, 1H, 12-H_{ax}), 1.20 (s, 3H, 19-H), 1.24 (t, $J = 7.1$ Hz, 3H, 25-H), 1.48 (m, 1H, 11-H), 1.52 (m, 5H, 3-H_{ax}, 1-H_{eq}, 11-H, 2-H_{ax}, 2-H_{eq}), 1.68 (m, 1H, 12-H_{eq}), 1.74 (m, 1H, 3-H_{eq}), 1.79 (m, 1H, 5-H), 1.81 (m, 1H, 6-H_{ax}), 2.09 (sept, $J = 7.1$, 1H, 15-H), 2.33 (t br, $J = 9.6$ Hz, 1H, 8-H), 3.59 (d, $J = 11.4$ Hz, 1H, 6-H_{eq}), 3.66 (s, 3H, 21-H), 3.76 (dd, $J = 9.5$, 4.3 Hz, 1H, 14-H), 4.10 (q, $J = 7.1$ Hz, 2H, 24-H), 5.76 (s, 1H, 22-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.3$ (q, C-25), 14.5 (q, C-18), 16.2 (q, C-17*), 16.7 (q, C-19), 17.8 (q, C-16*), 18.0 (t, C-2), 18.6 (t, C-11), 25.7 (t, C-12), 29.3 (t, C-6), 33.4 (d, C-15), 37.1 (s, C-10), 37.6 (t, C-3), 38.2 (t, C-1), 47.3 (s, C-4), 47.8 (d, C-8), 51.9 (d, C-5), 52.1 (s, C-21), 55.4 (d, C-9), 59.6 (t, C-24), 70.2 (d, C-14), 74.7 (s, C-13), 111.1 (d, C-22), 162.7 (s, C-7), 166.5 (s, C-23), 178.4 (s, C-20) ppm; MS (70 eV): *m/z* (%) = 436 (7.9) [M^+], 418 (38.9) [M^+-H_2O], 400 (27.8) [M^+-$2H_2O$], 379 (24.0) [M^+-C_3H_7], 372 (42.3) [406-C_2H_4], 347 (57.4), 312 (41.7), 285 (100), 269 (41.7), 43 (45.5); $C_{25}H_{40}O_6$ (436.58).

9: Colourless crystals; m.p. = 148–151°C; $R_f = 0.44$ (EtOAc); $[\alpha]_{546}^{20} = 60.0°$ ($c = 0.32$, MeOH); IR (KBr): $\tilde{\nu} = 3438$ (s), 2950 (s), 1733 (s), 1724 (s), 1658 (m), 1388 (m), 1262 (s), 1033 (m), 993 (m), 899 (m) cm^{-1}; UV (MeOH): λ_{max} (Igε) = 209.0 (2.64) nm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (d, $J = 6.7$ Hz, 3H, 17-H*), 0.93 (s, 3H, 18-H), 0.94 (d, $J = 6.7$ Hz, 3H, 16-H*), 0.98 (m, 1H, 1-H_{ax}), 1.12 (m, 1H, 9-H), 1.18 (s, 3H, 19-H), 1.28 (m, 2H, 12-H_{ax}, 11-H), 1.50 (m, 2H, 2-H_{ax}, 2-H_{eq}), 1.52 (m, 1H, 11-H), 1.56 (m, 2H, 3-H_{ax}, 3-H_{eq}), 1.68 (m, 1H, 12-H_{eq}), 1.70 (m, 1H, 1-H_{eq}), 1.81 (m, 2H, 6-H_{ax}, 6-H_{eq}), 2.11 (m, 1H, 5-H), 2.15 (m, 1H, C_{13}-OH), 2.16 (m, 1H, 15-H), 2.24 (t, $J = 11.1$ Hz, 1H, 8-H), 3.61 (s, 3H, 21-H), 3.98 (s, 1H, C_{22}-OH), 4.00 (s, 1H, 22-H), 4.79 (d, $J = 10.6$ Hz, 1H, 14-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.5$ (q, C-18), 16.2 (q, C-16*), 16.3 (q, C-19), 17.7 (q, C-17*), 17.8 (t, C-2), 21.9 (t, C-11), 27.7 (t, C-12), 33.7 (d, C-15), 34.9 (s, C-10), 37.1 (t, C-6), 37.5 (t, C-3), 37.9 (t, C-1), 41.9 (d, C-8), 45.2 (d, C-5), 47.0 (s, C-4), 52.2 (q, C-21), 55.0 (d, C-9), 70.2 (s, C-7), 75.2 (s, C-13), 78.9 (d, C-22), 81.2 (d, C-14), 173.3 (s, C-23), 180.0 (s, C-20) ppm; MS (70 eV): *m/z* (%) = 424 (1.5) [M^+], 406 (1.5) [M^+-H_2O], 349 (100) [406-

$C_2H_2O_2$], 331 (23.5), 303 (7.6), 289 (16.4), 275 (20.5), 271 (26.5), 43 (30.3) [$C_3H_7^+$]; $C_{23}H_{36}O_7$ (424.53).

Methyl (1R-(1α,4aβ,4bα,7β,8β,10aα))-7,8-epoxi-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydro-1,4a-dimethyl-7-(1-methylethyl)-phenanthrene-1-carboxylate (**10**)

To 1.03 g (3.25 mmol) **2** dissolved in 280 ml *THF*, 6 ml H_2O, 6.4 g (64 mmol) $KHCO_3$, and 3.2 g (12.6 mmol) I_2 were added. This mixture was stirred at 50°C for 3 h. After cooling to room temperature 300 ml Et_2O were added. Workup and purification were performed as described for compound **4**.

M.p. = 65–67°C; $R_f = 0.46$ (*CH*/EtOAc = 5:1); $[\alpha]_{546}^{20} = 4.58°$ ($c = 0.46$, MeOH); IR (KBr): $\tilde{\nu} = 2951$ (m), 2879 (m), 1708 (s), 1465 (m), 1443 (m), 1259 (m) cm^{-1}; UV (MeOH): λ_{max} (lgε) = 215.0 (2.68) nm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.74$ (s, 3H, 18-H), 0.90 (d, $J = 6.8$ Hz, 3H, 16-H*), 0.94 (d, $J = 6.8$ Hz, 3H, 17-H*), 1.00 (m, 1H, 1-H_{ax}), 1.20 (s, 3H, 19-H), 1.21 (qd, $J = 12.3$, 3.3 Hz, 1H, 11-H_{ax}), 1.35 (dq, $J = 12.3$, 3.3 Hz, 1H, 11-H_{eq}), 1.52 (m, 2H, 2-H_{ax}, 2-H_{eq}), 1.57 (m, 2H, 3-H, 15-H), 1.58 (m, 1H, 12-H), 1.61 (m, 2H, 1-H_{eq}, 3-H), 1.71 (m, 1H, 6-H_{eq}), 1.97 (dt, $J = 14.2$, 3.3 Hz, 1H, 12-H), 1.62 (m, 1H, 9-H), 2.00 (m, 1H, 6-H_{ax}), 2.03 (m, 1H, 5-H), 3.08 (s, 1H, 14-H), 3.60 (s, 3H, 21-H), 5.77 (m, 1H, 7-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$ (q, C-18), 16.1 (t, C-11), 16.6 (q, C-19), 17.6 (q, C-17*), 18.0 (t, C-2), 18.1 (q, C-16*), 24.2 (t, C-12), 25.8 (t, C-6), 33.9 (d, C-15), 34.4 (s, C-10), 37.1 (t, C-3), 37.6 (t, C-1), 45.2 (d, C-5), 46.5 (s, C-4), 50.4 (d, C-9), 51.8 (q, C-21), 60.9 (d, C-14), 64.2 (s, C-13), 129.6 (d, C-7), 132.8 (s, C-8), 178.8 (s, C-20) ppm; MS (70 eV): *m/z* (%) = 332 (44.6) [M^+], 289 (16.9) [M^+-C_3H_7], 273 (6.2) [M^+-$C_2H_3O_2$], 262 (25.1), 247 (100) [M^+-C_5H_9O]; $C_{21}H_{32}O_3$ (332.48); calcd.: C 75.86%, H 9.70%; found: 75.60%, H 9.64%.

Methyl (1R-(1α,4aβ,4bα,7β,10aα))-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydro-7-hydroxy-1,4a-dimethyl-7-(1-methylethyl)-phenanthrene-1-ylmethanol (**11**)

500 mg (1.5 mmol) **10** were dissolved in 15 ml dry Et_2O and added dropwise to a suspension of 90 mg (2.4 mmol) $LiAlH_4$ in 10 ml dry Et_2O. After refluxing for 30 min, the excess of hydride was destroyed by addition of a few drops of water. The reaction mixture was diluted with 10 ml Et_2O, washed with 2 *N* H_2SO_4 and brine, dried over Na_2SO_4, and evaporated. CC of the residue with *CH*/EtOAc (2:1) on 70 g silica gave 276 mg (60%) **11** as a colourless oil.

$R_f = 0.52$ (*CH*/EtOAc = 1:1); $[\alpha]_D^{20} = -19.4°$ ($c = 0.49$, MeOH); $[\alpha]_{546}^{20} = -24.7°$ ($c = 0.49$, MeOH); IR (KBr): $\tilde{\nu} = 3347$ (s), 2926 (s), 2867 (s), 2850 (s), 1724 (w), 1470 (m), 1463 (m), 1443 (m), 1384 (m), 1069 (m), 1048 (m) cm^{-1}; UV (MeOH): λ_{max} (lgε) = 216 (2.87), 245 (2.50) nm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.83$ (s, 3H, 19-H), 0.85 (s, 3H, 18-H), 0.89 (d, $J = 6.8$ Hz, 3H, 17-H*), 0.89 (d, $J = 6.8$ Hz, 3H, 16-H*), 0.97 (td, $J = 12.8$, 4.1 Hz, 1H, 1-H_{ax}), 1.28 (m, 1H, 3-H), 1.32 (m, 1H, 12-H), 1.36 (m, 1H, 3-H), 1.39 (m, 1H, 5-H), 1.46 (m, 2H, 2-H_{ax}, 2-H_{eq}), 1.47 (m, 1H, 11-H), 1.52 (m, 1H, 11-H), 1.56 (m, 1H, 15-H), 1.62 (m, 1H, 12-H), 1.65 (m, 1H, 9-H), 1.82 (m, 1H, 1-H_{eq}), 1.84 (m, 2H, 6-H), 2.04 (s br, 1H, 14-H), 3.08 (d, $J = 10.0$ Hz, 1H, 20-H), 3.33 (d, $J = 10.0$ Hz, 1H, 20-H), 5.43 (s br, 1H, 7-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.7$ (q, C-18), 16.9 (q, C-16*), 17.0 (q, C-17*), 18.1 (t, C-2), 18.2 (q, C-19), 20.2 (t, C-11), 23.4 (t, C-6), 23.8 (t, C-12), 35.2 (s, C-10), 35.5 (t, C-3), 37.3 (s, C-4), 37.7 (d, C-15), 39.5 (t, C-1), 43.2 (t, C-14), 43.5 (d, C-5), 51.8 (d, C-9), 72.1 (t, C-20), 73.3 (s, C-13), 123.5 (s, C-7), 134.9 (d, C-8) ppm; MS (70 eV): *m/z* (%) = 306 (15.2) [M^+], 288 (7.5) [M^+-H_2O], 273 (4.5) [288-CH_3], 263 (14.9) [M^+-C_3H_7], 245 (32.6) [M^+-H_2O-C_3H_7], 227 (9.8) [245-H_2O], 220 (100) [M^+-$C_5H_{10}O$], 109 (37.1); $C_{20}H_{34}O_2$ (306.48).

Methyl (1R-(1α,4aβ,5β,8aα))-6-formyl-1,2,3,4,4a,5,8,8a-octahydro-1,4a-dimethyl-5-(4-methyl-3-oxopentyl)-naphthalene-1-carboxylate (**12**) *and Methyl (1R-(1α,4aβ,4bα,7α,10aα))-1,2,3,4,4a, 4b,5,6,7,8,10,10a-dodecahydro-7-hydroxy-1,4a-dimethyl-7-(1-methylethyl)-8-oxo-phenanthrene-1-carboxylate* (**13**)

Ca. 5.5 ml of *Jones* reagent (2.14 g CrO_3 in 1.9 ml conc. H_2SO_4, H_2O up to 8 ml) were added dropwise to an ice-cooled and stirred solution of 4.0 g (11.4 mmol) **3** in 20 ml acetone until an orange colour persisted. After 15 min, excess reagent was destroyed with a few drops of isopropanol. The solution was filtered over 10 g of silica, diluted with 50 ml water, and extracted five times with Et_2O. The organic phases were washed with brine and dried over Na_2SO_4. Evaporation gave a residue which was purified by CC on 400 g silica (*CH*/EtOAc = 3:1) to yield 914 mg (23%) **12** and 1.75 g (44%) **13**.

12: The NMR-data agree with those given in Ref. [5].

13: $R_f = 0.36$ (*CH*/EtOAc = 3:1); $[\alpha]_D^{20} = 59.6°$ ($c = 0.67$, CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu} = 3490$ (m, br), 2949 (m), 2876 (m), 1684 (m), 1616 (m), 1456 (m), 1125 (s) cm^{-1}; UV (CH_2Cl_2): λ_{max} ($lg\varepsilon$) = 213.5 (3.13), 252.0 (3.71) nm; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.74$ (s, 3H, 18-H), 0.77 (d, $J = 6.7$ Hz, 3H, 16-H*), 0.88 (d, $J = 6.7$ Hz, 3H, 17-H*), 1.13 (m, 1H, 1-H_{ax}), 1.23 (s, 3H, 19-H), 1.29 (td, $J = 11.6$, 5.1 Hz, 1H, 11-H_{ax}), 1.57 (m, 2H, 2-H_{ax}, 2-H_{eq}), 1.65 (m, 2H, 3-H_{ax}, 3-H_{eq}), 1.68 (m, 1H, 11-H_{eq}), 1.79 (m, 1H, 12-H), 1.85 (m, 1H, 15-H), 1.80 (m, 1H, 1-H_{eq}), 1.88 (m, 1H, 12-H), 2.01 (m, 2H, 6-H_{ax}, 6-H_{eq}), 2.05 (m, 1H, 5-H), 2.29 (m, 1H, 9-H), 3.63 (s, 3H, 21-H), 6.98 (s, 1H, 7-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.6$ (q, C-18), 16.2 (q, C-17*), 16.6 (q, C-19, q, C-16*), 17.9 (t, C-2), 19.0 (t, C-11), 26.5 (t, C-6), 31.5 (t, C-12), 34.9 (s, C-10), 35.6 (d, C-15), 37.1 (t, C-3), 37.6 (t, C-1), 44.2 (d, C-5), 46.2 (s, C-4), 50.0 (d, C-9), 52.1 (s, C-21), 77.7 (s, C-13), 135.3 (s, C-8), 137.9 (s, C-7), 178.8 (s, C-20), 204.3 (s, C-14) ppm; MS (70 eV): *m/z* (%) = 448 (15.9) [M^+], 330 (2.7) [M^+-H_2O], 306 (84.3) [M^+-C_2H_2O], 250 (30.8), 245 (100), 43 (38.8); $C_{21}H_{32}O_4$ (348.45).

Methyl (1R-(1α,4aβ,4bα,7β,8aβ,9α,10aα))-perhydro-7-hydroxy-1-methoxycarbonyl-1,4a-dimethyl-7-(1-methylethyl)-8-oxo-phenanthrene-9-yl-cyanoacetate (**14**)

1.85 g (5.30 mmol) **13** and 524 mg (5.3 mmol) cyanoacetic acid methyl ester were dissolved in 40 ml *THF*. After addition of 22 mg activated xonotlite [19], the mixture was heated to 60°C and stirred for 48 h. After evaporation of the solvent, water was added, and the solution was extracted twice with Et_2O. The organic phases were washed twice with 2 *N* H_2SO_4, three times with brine, and dried over Na_2SO_4. After evaporation and CC over silica (*CH*/EtOAc = 2:1), 1.15 g (49%) **14** were obtained as pale yellow crystals containing two diastereomers in a ratio of 4:3 (**14a** and **14b**).

$R_f = 0.27$ (*CH*/EtOAc = 2:1); IR (KBr): $\tilde{\nu} = 3568$ (m), 2953 (s), 2876 (m), 2248 (w), 1748 (s), 1717 (s), 1436 (m), 1153 (m), 909 (m) cm^{-1}; UV (CH_2Cl_2): λ_{max} ($lg\varepsilon$) = 234 (2.35) nm; MS (70 eV): *m/z* (%) = 447 (9.5) [M^+], 419 (8.2) [M^+-CO], 388 (21.6) [M^+-$C_2H_3O_2$], 376 (10.1) [419-C_3H_7], 321 (100), 261 (95.7), 243 (18.1); $C_{25}H_{37}NO_6$ (447.57).

14a (main product): ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (d, $J = 6.4$ Hz, 3H, 16-H*), 0.92 (d, $J = 6.4$ Hz, 3H, 17-H*), 0.99 (s, 3H, 18-H), 1.05 (m, 1H, 1-H_{ax}), 1.18 (s, 3H, 19-H), 1.32 (d br, $J = 14.0$ Hz, 1H, 6-H_{eq}), 1.56 (m, 2H, 2-H_{ax}, 2-H_{eq}), 1.67 (m, 3H, 3-H, 11-H_{ax}, 11-H_{eq}), 1.68 (m, 1H, 12-H), 1.73 (m, 1H, 6-H_{ax}), 1.77 (m, 1H, 3-H), 1.78 (m, 1H, 1-H_{eq}), 1.87 (m, 1H, 5-H), 1.88 (m, 1H, 12-H), 2.09 (m, 1H, 9-H), 2.20 (m, 1H, 15-H), 2.95 (dd, $J = 17.0$, 4.5 Hz, 1H, 8-H), 3.08 (s br, 1H, 7-H), 3.64 (s, 3H, 21-H), 3.65 (s, 1H, 22-H), 3.87 (s, 3H, 24-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.5$ (q, C-18), 15.8 (q, C-17*), 16.6 (q, C-19), 17.9 (q, C-16*, t, C-2), 18.2 (t, C-11), 28.3 (t, C-12), 29.2 (d, C-22), 31.8 (t, C-6, d, C-15), 34.6 (d, C-7), 36.6 (s, C-10), 37.1 (t, C-3), 38.0 (t, C-1), 43.2 (d, C-5), 46.7 (s, C-4), 47.6 (t, C-8), 50.1 (d, C-9), 52.0 (s, C-21), 53.5 (s, C-24), 77.6 (s, C-13), 118.2 (s, C-25), 167.7 (s, C-23), 178.8 (s, C-20), 210.8 (s, C-14) ppm.

14b (minor product): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (d, $J = 6.8$ Hz, 3H, 16-H*), 0.90 (d, $J = 6.8$ Hz, 3H, 17-H*), 0.97 (s, 3H, 18-H), 1.10 (m, 1H, 1-H$_{ax}$), 1.15 (s, 3H, 19-H), 1.32 (d br, $J = 14.8$ Hz, 1H, 6-H$_{eq}$), 1.56 (m, 2H, 2-H$_{ax}$, 2-H$_{eq}$), 1.64 (m, 1H, 12-H), 1.67 (m, 3H, 3-H, 11-H$_{ax}$, 11-H$_{eq}$), 1.70 (m, 1H, 6-H$_{ax}$), 1.76 (m, 1H, 1-H$_{eq}$), 1.77 (m, 1H, 3-H), 1.86 (m, 1H, 12-H), 2.12 (m, 1H, 9-H), 2.20 (m, 1H, 15-H), 2.35 (dd, $J = 13.2$, 1.2 Hz, 1H, 5-H), 2.97 (s br, 1H, 7-H), 3.00 (dd, $J = 13.0$, 5.0 Hz, 1H, 8-H), 3.70 (s, 3H, 21-H), 3.78 (s, 3H, 24-H), 4.33 (d, $J = 6.4$ Hz, 1H, 22-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.2$ (q, C-18), 15.8 (q, C-17*), 16.4 (q, C-19), 17.6 (t, C-2), 17.7 (q, C-16*), 17.9 (t, C-11), 27.4 (t, C-6), 28.3 (t, C-12), 31.6 (d, C-15), 34.4 (d, C-7), 36.7 (d, C-22), 37.3 (t, C-1, s, C-10), 37.5 (t, C-3), 42.3 (d, C-5), 46.7 (t, C-8), 47.1 (s, C-4), 47.9 (d, C-9), 52.2 (s, C-21), 53.3 (s, C-24), 77.4 (s, C-13), 117.6 (s, C-25), 166.9 (s, C-23), 178.3 (s, C-20), 211.8 (s, C-14) ppm.

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