Monatshefte für Chemie 133, 231–239 (2002)

Monatshefte für Chemie
Chemical Monthly

Synthetic Transformations of Abietic Acid V[a]: Structure Modification and Ozonization

Armin Presser*, **Irmgard Pötschger, Ernst Haslinger,** and **Antje Hüfner**

Institute of Pharmaceutical Chemistry, University of Graz, A-8010 Graz, Austria

Summary. Carbon side chains are attached *via Reformatsky* reactions to the B-ring of abietic acid, followed by selective modifications and finally ozonization of the C-ring. The products can be used as educts for the synthesis of highly oxidized terpene derivatives.

Keywords. Abietic acid; Diterpenes; Ozonization; *Reformatsky* reaction.

Introduction

Abietic acid (**1**) is an enantiomerically pure starting material which is cheap and easily available. It can be used for the partial synthesis of biologically active terpene derivatives [2–7]. Especially its oxidative degradation leads to compounds exhibiting interesting biological and pharmacological activities: some oxidation products are powerful allergens [8–10], others have been considered to possess antimalarial activity [11,12]. In this paper, we describe reactions for the modification of ring B and subsequent ozonolysis of the ring C of **1** leading to chiral and highly oxidized terpene derivatives.

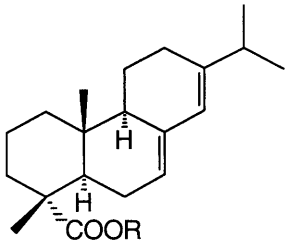
Results and Discussion

Modification of the B-ring

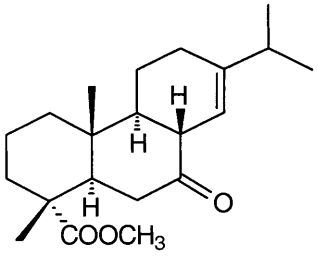
In a previous paper [1] we have described the oxidation of **2** with iodine in aqueous $KHCO_3$ yielding the ketone **3**. We also have reported that the *Reformatsky* reaction of **3** with ethyl bromoacetate in *THF* gave a mixture of the two diastereomeric compounds **4** (16%) and **5** (65%) and that the main product (**5**) is (*S*)-configured at C-7. Reduction of **4** and **5** with $LiAlH_4$ resulted in the corresponding triols **6** and **7**, respectively. The ^{13}C NMR spectra of these products contained three resonances for oxygen-bearing carbons in the region from 58 to 75 ppm. Both compounds gave IR spectra with the typical broad absorption for alcoholic hydroxyl groups between 3200 and 3600 cm^{-1}.

[a] For part IV, see Ref. [1]

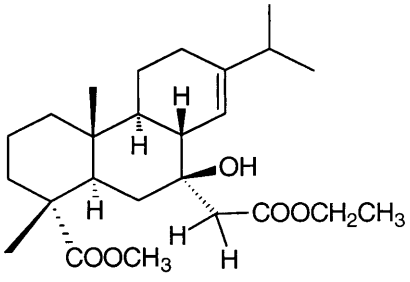
* Corresponding author. E-mail: armin.presser@uni-graz.at



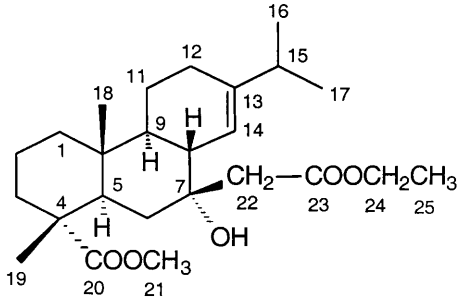
1 $R = H$
2 $R = CH_3$



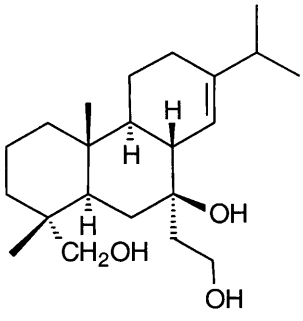
3



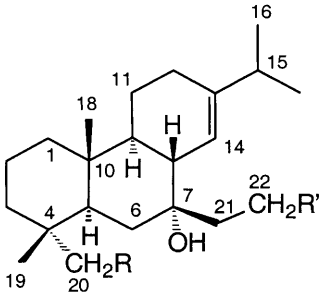
4



5



6



7: $R = R' = OH$
8: $R = R' = OAc$
9: $R = R' = OSO_2CH_3$
10: $R = OSO_2CH_3$ $R' = Cl$

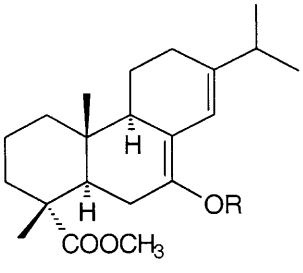
Scheme 1

The tertiary hydroxyl group of **7** was found to be extremely inert. Acetylation of **7** with acetic acid anhydride and 4-(dimethylamino)-pyridine (*DMAP*) in pyridine [13] gave the diacetate **8** (yield: 91%). The ^1H NMR spectrum of **8** showed two overlapping methyl singulets at 2.03 ppm, and the carbon resonances of C-20 and C-22 were shifted to higher frequencies, indicating that acetylation had occurred at these positions.

Reaction of **7** with methanesulfonyl chloride overnight yielded **9** as the main product. **10** was identified as side product. However, **10** was obtained as the sole product after prolonged reaction times. The successful introduction of the methanesulfonyl group was confirmed by NMR spectroscopy. The ^{1}H NMR spectrum of **9** clearly showed two methyl singulets of the methanesulfonyl groups at 3.01 and 3.02 ppm, and the resonances of C-20 and C-22 were shifted significantly to higher frequencies. The mass spectrum (EI) of the halogenated compound **10** showed the molecular peak at $m/z = 446$ as well as characteristic isotope satellite peaks indicating the presence of Cl. In the ^{13}C NMR spectrum, the resonance of C-22 appeared at 40.5 ppm, typical for a CH_2Cl group.

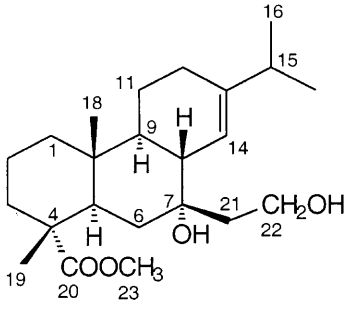
Treatment of **5** with sodium hydride and acetyl chloride yielded after cleavage of the side chain the enol acetate **11**. The mass spectrum of **11** showed a molecular ion at $m/z = 374$ and a peak at $[M - 42]^+$ which resulted from ketene formation, typical for enol acetates. The ^{1}H NMR spectrum showed one singulet at 2.13 ppm (acetate methyl group); four resonances of olefinic carbons were observed in the ^{13}C NMR spectrum. In a similar reaction with *p*-toluenesulfonyl chloride, compound **12** was obtained.

Selective reduction of the ester carbonyl function at the secondary carbon of **5** with $LiAlH_4$ and $AlCl_3$ [14] gave compound **13** in moderate yield. Typical

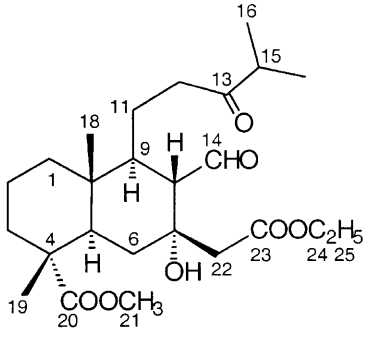


11: *R* = Ac

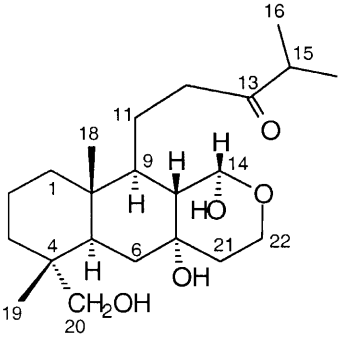
12: *R* = SO_2–C$_6$H$_4$–CH_3



13



14



15

Scheme 2

resonances of the alcohol side chain at 3.71–3.76 ppm (22-H) and 3.97 ppm (22-H′) were obtained.

Cleavage of the C-ring

Oxidative ring opening at the double bond in the C-ring was achieved by ozonolysis. Treatment of **5** with ozone at −70°C provided the aldehyde **14**. Its ^{1}H NMR spectrum showed clearly the resonance of the aldehyde proton as doublet at 9.78 ppm ($J = 4.8$ Hz). The α-proton (8-H) appeared at 2.04 ppm and showed a large diaxial coupling with 9-H ($J = 11.8$ Hz), indicating an axial position of 8-H. The carbonyl resonances were found at 207.3 (CHO) and 213.5 (ketone) ppm.

Ozonolysis of **7** lead to the hemiacetal **15** after reductive work-up with dimethyl sulfide. The proton resonance of the hydroxyl group attached to the acetal carbon appeared at 5.85 ppm ($J = 7.7$ Hz). The equatorial position of 14-H was assigned from the ^{1}H NMR spectrum showing a doublet of doublets with a coupling constant of 7.7 Hz and an additional coupling with 8-H ($J = 2.4$ Hz). The resonance of 8-H showed a large coupling (11 Hz) with 9-H, proving an axial position of this hydrogen atom.

Experimental

Analytical methods

Melting points: Tottoli apparatus, uncorrected. Optical rotation: polarimeter 241 MC (Perkin Elmer). EI-MS: Varian MAT 711 spectrometer, 70 eV, electron impact. ESI-MS: Platform-LCZ (Micromass). CI-MS: Autospec (Micromass), reactant gas NH_3. IR spectra: infrared spectrometer system 2000 FT (Perkin Elmer). UV/Vis: UV-160A UV/Vis recording spectrophotometer (Shimadzu). NMR spectra: Varian Unity Inova 400 (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 spectra. ^{1}H and ^{13}C resonances are numbered as given in the formulas. Assignments marked with an asterisk are interchangeable. Before performing NOE experiments, dissolved O_2 was carefully removed by bubbling Ar through the solutions. Elementary analyses: Laboratory for Microanalysis, Institute of Physical Chemistry, University of Vienna; the data were in satisfactory agreement with the calculated values. Ozonizer: Fischer Ozongenerator 500, operating pressure: 0.5 bar, flow: 45 dm^3/h, ozone production: 1.73 g · dm^{-3}.

Materials: column chromatography (CC): silica gel 60 (Merck, 70–230 mesh), pore diameter: 60 Å; solvents: cyclohexane/ethyl acetate (*CH*/EtOAc), ethyl acetate/ethanol (EtOAc/EtOH); preparative TLC: TLC plates (Merck), silica gel 60 PF_{254}, 1 mm, 200 × 200 mm; thin layer chromatography (TLC): TLC plates (Merck), silica gel 60 F_{254}, 0.2 mm, 200 × 200 mm; the substances were detected using UV light at 254 nm as well as by spraying with molybdatophosphoric acid and by subsequent heating with a heat gun.

2-((1R-(1α,4aβ,4bα,8aβ,9β,10aα))-1,2,3,4,4a,4b,5,6,8a,9,10,10a-Dodecahydro-9-hydroxy-1-hydroxymethyl-1,4a-dimethyl-7-(1-methylethyl)-phenanthren-9-yl)-ethanol (**6**; $C_{22}H_{38}O_3$)

A solution of 500 mg (1.19 mmol) **4** in 15 cm^3 anhydrous Et_2O was added dropwise to a suspension of 119 mg (3.12 mmol) $LiAlH_4$ in 15 cm^3 of the same solvent and refluxed for 1 h. After cooling to room temperature the reaction mixture was quenched with H_2O. The organic layer was separated, and the aqueous phase was extracted with EtOAc and Et_2O. The combined organic layers were washed

successively with 2 *N* H_2SO_4, 1 *N* $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by CC on silica (EtOAc:EtOH = 9:1) yielding 213 mg (51%) **6** as white solid.

M.p.: 150°C; $R_f = 0.51$ (EtOAc:EtOH = 9:1); $[\alpha]_{546}^{21} = -22.7°$ ($c = 0.14$, CH_2Cl_2); IR (KBr): $\tilde{\nu} = 3319$ (s), 2924 (s), 1465 (m), 1381 (m), 1047 (s) cm^{-1}; UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 228.4 (1.97) nm; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.69 (s, 19-CH_3), 0.87 (t, $J = \sim$13 Hz, 1-H_{ax}), 0.88 (s, 18-CH_3), 0.95 (t, $J = \sim$11 Hz, 9-H), 0.95 (d, $J = 6.9$ Hz, 16-CH_3 + 17-CH_3), 1.05–1.15 (m, 11-H), 1.13 (d, $J = \sim$12 Hz, 3-H_{eq}), 1.28 (t, $J = \sim$13 Hz, 6-H_{ax}), 1.34 (d, $J = \sim$14 Hz, 5-H), 1.47–1.53 (m, 2-H), 1.56 (t, $J = \sim$12 Hz, 3-H_{ax}), 1.58–1.65 (m, 2′-H), 1.60–1.67 (m, 21-H), 1.71–1.77 (m, 11′-H), 1.73 (d, $J = \sim$13 Hz, 1-H_{eq}), 1.77–1.85 (m, 21′-H), 1.83–1.97 (m, 12-H_{ax} + 12-H_{eq}), 2.02 (d, $J = \sim$13 Hz, 6-H_{eq}), 2.14 (d, $J = \sim$11 Hz, 8-H), 2.15 (sept, $J = 6.9$ Hz, 15-H), 3.46 (d, $J = 11.4$ Hz, 20-H), 2.82 (d, $J = 11.4$ Hz, 20′-H), 3.79–3.84 (m, 22-H), 3.88–3.94 (m, 22′-H), 5.44 (s, 14-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 14.2 (C-18), 17.8 (C-19), 18.3 (C-2), 21.4 (C-16*), 21.7 (C-17*), 22.2 (C-11), 27.0 (C-12), 32.9 (C-21), 33.6 (C-6), 35.0 (C-15), 35.3 (C-3), 36.6 (C-10), 37.6 (C-4), 38.1 (C-1), 43.1 (C-5), 47.6 (C-8), 49.1 (C-9), 58.9 (C-22), 70.6 (C-20), 75.8 (C-7), 118.0 (C-14), 144.6 (C-13) ppm; EI-MS (70 eV): m/z (%) = 332 (100) [M - H_2O]$^+$, 305 (31).

2-((1R-(1α,4aβ,4bα,8aβ,9α,10aα))-1,2,3,4,4a,4b,5,6,8a,9,10,10a-Dodecahydro-9-hydroxy-1-hydroxymethyl-1,4a-dimethyl-7-(1-methylethyl)-phenanthren-9-yl)-ethanol (**7**; $C_{22}H_{38}O_3$)

In a manner similar to the preparation of **6**, 870 mg (2.07 mmol) **5** were treated with 207 mg (5.44 mmol) $LiAlH_4$ in 30 cm^3 anhydrous Et_2O. Work-up was performed as described for compound **6**. Recrystallization from *CH*:EtOAc = 1:4 gave 421 mg (58%) **7** as white solid.

M.p.: 131–133°C; $R_f = 0.28$ (EtOAc:EtOH = 10:1); $[\alpha]_D^{25} = -18.7°$ ($c = 0.15$, CH_2Cl_2), $[\alpha]_{546}^{25} = -32.0°$ ($c = 0.15$, CH_2Cl_2); IR (KBr): $\tilde{\nu} = 3406$ (s), 2949 (s), 2867 (s), 1656 (w), 1043 (m) cm^{-1}; UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 246.2 (2.77) nm; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.70 (s, 19-CH_3), 0.80 (s, 18-CH_3), 0.89–0.96 (m, 1-H_{ax}), 0.97 (d, $J = 6.8$ Hz, 16-CH_3 + 17-CH_3), 1.01–1.12 (m, 11-H), 1.16–1.20 (m, 3-H), 1.19–1.26 (m, 11′-H), 1.23 (t, $J = \sim$11 Hz, 9-H), 1.24–1.31 (m, 6-H), 1.46–1.55 (m, 21-H), 1.52–1.60 (m, 2-H_{ax} + 2-H_{eq}), 1.56–1.59 (m, 3′-H), 1.63 (dd, $J = 13.1$, 2.3 Hz, 5-H), 1.67–1.72 (m, 1-H_{eq}), 1.68–1.75 (m, 6′-H), 1.77–1.82 (m, 12-H), 1.92–1.98 (m, 12′-H), 1.99 (d, $J = \sim$12 Hz, 8-H), 2.18–2.28 (m, 21′-H), 2.20 (sept, $J = 6.8$ Hz, 15-H), 2.93 (d, $J = 11.3$ Hz, 20-H), 3.45 (d, $J = 11.3$ Hz, 20′-H), 3.73–3.78 (m, 22-H), 3.93–4.00 (m, 22′-H), 5.46 (s, 14-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 13.6 (C-18), 17.6 (C-19), 18.2 (C-2), 21.3 (C-11), 21.9 (C-16, C-17), 26.7 (C-12), 31.5 (C-6), 35.3 (C-3), 35.4 (C-15), 35.9 (C-10), 37.3 (C-4), 37.9 (C-1), 40.7 (C-5), 41.5 (C-21), 44.2 (C-8), 47.7 (C-9), 59.1 (C-22), 70.7 (C-20), 73.9 (C-7), 116.5 (C-14), 149.1 (C-13) ppm; EI-MS (70 eV): m/z (%) = 332 (100) [M - H_2O]$^+$, 304 (13), 279 (14), 209 (13).

(1R-(1α,4aβ,4bα,8aβ,9α,10aα))-1-Acetoxymethyl-1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-9-hydroxy-1,4a-dimethyl-7-(1-methylethyl)-phenanthren-9-yl-ethyl ethanoate (**8**; $C_{26}H_{42}O_5$)

A solution of 500 mg (1.43 mmol) **7** in 10 cm^3 anhydrous triethylamine was stirred with 610 mm^3 (6.45 mmol) acetic acid anhydride and *DMAP* (43 mg) at room temperature for 21 h. The mixture was neutralized with 2 *N* H_2SO_4 and extracted with Et_2O. The extract was washed successively with 1 *N* $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by CC on 50 g silica (*CH*:EtOAc = 2:1) yielding 566 mg (91%) **8** as white crystals.

M.p.: 97°C; $R_f = 0.37$ (*CH*:EtOAc = 2:1); $[\alpha]_D^{23} = -19.0°$ ($c = 0.33$, CH_2Cl_2), $[\alpha]_{546}^{23} = -24.1°$ ($c = 0.33$, CH_2Cl_2); IR (KBr): $\tilde{\nu} = 3525$ (s), 2955 (s), 2923 (s), 1743 (s), 1719 (s), 1380 (m), 1243 (s) cm^{-1}; UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 230.0 (2.02) nm; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.80 (s, 18-CH_3), 0.81 (s, 19-CH_3), 0.92 (td, $J = 12.9$, 3.9 Hz, 1-H_{ax}), 0.96 (d, $J = 7.0$ Hz, 16-CH_3^*), 0.97 (d, $J = 7.0$ Hz, 17-CH_3^*), 1.05–1.10 (m, 11-H), 1.26 (t, $J = 11.6$ Hz, 9-H), 1.33–1.40 (m, 3-H_{ax} +

3-H_{eq}), 1.41 (t, $J = \sim 13$ Hz, 6-H_{ax}), 1.48–1.59 (m, 2-H_{ax} + 2-H_{eq}), 1.51 (d, $J = \sim 13$ Hz, 6-H_{eq}), 1.59 (dd, $J = 12.8$, 2.6 Hz, 5-H), 1.71 (d, $J = 12.9$ Hz, 1-H_{eq}), 1.75–1.80 (m, 11′-H), 1.81–1.89 (m, 21-H), 1.92–1.99 (m, 12-H_{ax} + 12-H_{eq}), 1.96–2.03 (m, 21′-H), 2.00 (d, $J = \sim 11$ Hz, 8-H), 2.03 (s, 2 × CH_3COO), 2.19 (sept, $J = 7.0$ Hz, 15-H), 3.51 (d, $J = 11.0$ Hz, 20-H), 3.94 (d, $J = 11.0$ Hz, 20′-H), 4.13–4.27 (m, 22-H + 22′-H), 5.37 (s, 14-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 13.5 (C-18), 17.4 (C-19), 18.0 (C-2), 21.0 (CH_3COO), 21.1 (CH_3COO), 21.2 (C-16*), 21.8 (C-17*), 21.9 (C-11), 26.7 (C-12), 32.5 (C-6), 35.3 (C-15), 36.1 (C-3, C-4), 36.3 (C-10), 37.8 (C-1), 39.2 (C-21), 42.2 (C-5), 43.1 (C-8), 47.5 (C-9), 61.1 (C-22), 72.0 (C-7), 72.3 (C-20), 116.5 (C-14), 148.6 (C-13), 171.1 (CH_3COO), 171.4 (CH_3COO) ppm; ESI-MS: m/z (%) = 457 (6) $[M + Na]^+$, 435 (22) $[M + H]^+$, 417 (53) $[M + 1 - H_2O]^+$, 357 (100) $[417 - CH_3COOH]^+$.

2-((1R-(1α,4aβ,4bα,8aβ,9α,10aα))-1,2,3,4,4a,4b,5,6,8a,9,10,10a-Dodecahydro-9-hydroxy-1-methanesulfonyloxymethyl-1,4a-dimethyl-7-(1-methylethyl)-phenanthren-9-yl)-ethylmethanesulfonate (**9**; $C_{24}H_{42}O_7S_2$)

550 mm^3 (7.08 mmol) methanesulfonyl chloride were added at 0°C to a solution of 500 mg (1.43 mmol) **7** in 20 cm^3 anhydrous pyridine and stirred for 30 min. The mixture was allowed to warm gradually to ambient temperature and stirred for 16 h in the dark. The solution was concentrated, treated with 2 *N* H_2SO_4, and extracted with Et_2O. The extract was washed successively with 1 *N* $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Recrystallization from *CH*:EtOAc = 1:1 gave 283 mg (39%) **9** as white crystals. CC of the mother liquor on 50 g silica (*CH*:EtOAc = 2:1) provided 100 mg (17%) of the minor product **10**.

9: M.p.: 145°C; $R_f = 0.28$ (*CH*:EtOAc = 2:1); $[\alpha]_D^{22} = -29.7°$ ($c = 0.18$, CH_2Cl_2), $[\alpha]_{546}^{22} = -37.1°$ ($c = 0.18$, CH_2Cl_2); IR (KBr): $\tilde{\nu} = 3564$ (m), 2929 (s), 1351 (s), 1177 (s) cm^{-1}; UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 251.6 (2.02) nm; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.82 (s, 18-CH_3), 0.84 (s, 19-CH_3), 0.93 (t, $J = \sim 13$ Hz, 1-H_{ax}), 0.97 (d, $J = 6.9$ Hz, 16-CH_3 + 17-CH_3), 1.06–1.11 (m, 11-H), 1.27 (t, $J = \sim 11$ Hz, 9-H), 1.34 (d, $J = \sim 13$ Hz, 3-H_{eq}), 1.37 (t, $J = \sim 13$ Hz, 6-H_{ax}), 1.47 (t, $J = \sim 13$ Hz, 3-H_{ax}), 1.50–1.59 (m, 2-H_{ax} + 2-H_{eq}), 1.56 (d, $J = \sim 13$ Hz, 6-H_{eq}), 1.66 (d, $J = \sim 13$ Hz, 5-H), 1.72 (d, $J = \sim 13$ Hz, 1-H_{eq}), 1.76–1.80 (m, 11′-H), 1.84–1.90 (m, 21-H), 1.92–1.99 (m, 12-H_{ax} + 12-H_{eq}), 2.01 (d, $J = \sim 11$ Hz, 8-H), 2.16–2.21 (m, 15-H), 2.20–2.25 (m, 21′-H), 3.01 (s, CH_3–SO_3), 3.02 (s, CH_3–SO_3), 3.60 (d, $J = 9.4$ Hz, 20-H), 4.01 (d, $J = 9.4$ Hz, 20′-H), 4.34–4.38 (m, 22-H), 4.41–4.45 (m, 22′-H), 5.34 (br s, 14-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 13.5 (C-18), 17.1 (C-19), 17.8 (C-2), 21.2 (C-16*), 21.9 (C-11, C-17*), 26.7 (C-12), 32.1 (C-6), 35.3 (C-15), 35.6 (C-3), 36.1 (C-10), 36.5 (C-4), 37.3 (CH_3–SO_3), 37.4 (CH_3–SO_3), 37.6 (C-1), 39.5 (C-21), 41.3 (C-5), 43.7 (C-8), 47.7 (C-9), 66.9 (C-22), 71.9 (C-7), 76.4 (C-20), 115.9 (C-14), 149.4 (C-13) ppm; ESI-MS: m/z (%) = 529 (9) $[M + Na]^+$, 489 (100) $[M + 1 - H_2O]^+$.

(1R-(1α,4aβ,4bα,8aβ,9α,10aα))-9-(2-Chloroethyl)-1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-9-hydroxy-1,4a-dimethyl-7-(1-methylethyl)-phenanthren-1-yl-methylmethanesulfonate (**10**; $C_{23}H_{39}ClO_4S$)

In a manner similar to the preparation of **9**, 270 mg (0.77 mmol) **7** were treated with 270 mm^3 (3.47 mmol) methanesulfonyl chloride in 15 cm^3 anhydrous pyridine. After the mixture reached room temperature, stirring was continued for further 10 days in the dark. Work-up was performed as described for compound **9**. CC of the residue with *CH*:EtOAc = 2:1 on 50 g silica gave 148 mg (45%) **10** as white crystals.

M.p.: 147°C; $R_f = 0.35$ (*CH*:EtOAc = 2:1); $[\alpha]_{546}^{22} = -39.1°$ ($c = 0.20$, CH_2Cl_2); IR (KBr): $\tilde{\nu} = 3520$ (m), 2958 (s), 1352 (s), 1169 (s), 957 (s) cm^{-1}; UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 231.0 (2.26) nm; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.81 (s, 18-CH_3), 0.84 (s, 19-CH_3), 0.93 (td, $J = 12.8$, 4.6 Hz, 1-H_{ax}), 0.97 (d, $J = 6.9$ Hz, 16-CH_3 + 17-CH_3), 1.05–1.10 (m, 11-H), 1.27 (t, $J = \sim 12$ Hz, 9-H), 1.35 (d, $J = \sim 13$ Hz, 3-H_{eq}), 1.38 (t, $J = \sim 13$ Hz, 6-H_{ax}), 1.47 (t, $J = \sim 13$ Hz, 3-H_{ax}),

1.50–1.59 (m, 2-H_{ax} + 2-H_{eq}), 1.52 (d, $J = \sim 13$ Hz, 6-H_{eq}), 1.66 (d, $J = \sim 13$ Hz, 5-H), 1.72 (d, $J =$ 12.8 Hz, 1-H_{eq}), 1.75–1.80 (m, 11′-H), 1.89–1.97 (m, 21-H), 1.92–2.02 (m, 12-H + 12′-H), 2.01 (d, $J = \sim 11$ Hz, 8-H), 2.16–2.22 (m, 15-H), 2.20–2.28 (m, 21′-H), 3.02 (s, CH_3–SO_3), 3.59–3.66 (m, 22-H + 22′-H), 3.61 (d, $J = 9.6$ Hz, 20-H), 4.00 (d, $J = 9.6$ Hz, 20′-H), 5.37 (br s, 14-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 13.5 (C-18), 17.1 (C-19), 17.8 (C-2), 21.3 (C-16*), 21.8 (C-17*), 21.9 (C-11), 26.7 (C-12), 31.8 (C-6), 35.4 (C-15), 35.6 (C-3), 36.1 (C-10), 36.5 (C-4), 37.3 (CH_3–SO_3), 37.6 (C-1), 40.5 (C-22), 41.3 (C-5), 43.4 (C-8), 44.0 (C-21), 47.6 (C-9), 72.5 (C-7), 76.4 (C-20), 115.9 (C-14), 149.4 (C-13) ppm; EI-MS (70 eV): m/z (%) = 446 (56) $[M]^+$, 428 (31) [M - H_2O]$^+$, 383 (59).

Methyl (1R-(1α,4aβ,4bα,10aα))-9-acetoxy-1,2,3,4,4a,4b,5,6,10,10a-decahydro-1,4a-dimethyl-7-(1-methylethyl)-phenanthrene-1-carboxylate (**11**; $C_{23}H_{34}O_4$)

530 mg (1.26 mmol) **5** were dissolved in 10 cm^3 anhydrous *THF* and added dropwise to a suspension of 60 mg (1.51 mmol) NaH (60%, suspension in mineral oil) in 5 cm^3 anhydrous *THF*. After stirring at room temperature for 30 min, 180 mm^3 (2.53 mmol) acetyl chloride were added, and stirring was continued for 3 h. The excess of hydride was destroyed by the addition of approx. 5 cm^3 of H_2O, and the resulting solution was extracted three times with Et_2O. The organic layer was washed with 1 *N* $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The resulting syrup was eluted from a column of silica gel (50 g) with *CH*:EtOAc = 3:1 to give **11** (165 mg, 35%) as a yellowish oil.

$R_f = 0.48$ (*CH*:EtOAc = 3:1); $[\alpha]_{546}^{21} = -69.8°$ ($c = 0.15$, CH_2Cl_2); IR (KBr): $\tilde{\nu} = 2928$ (s), 1728 (s), 1459 (m), 1368 (m) cm^{-1}; UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 248.2 (3.93), 218.0 (3.45) nm; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.88 (s, 18-CH_3), 0.97 (d, $J = 6.8$ Hz, 16-CH_3^*), 0.98 (d, $J = 6.8$ Hz, 17-CH_3^*), 1.06–1.14 (m, 1-H_{ax}), 1.24 (s, 19-CH_3), 1.24–1.27 (m, 11-H), 1.52–1.59 (m, 2-H_{ax} + 2-H_{eq}), 1.59 (d, $J = \sim 12$ Hz, 3-H_{eq}), 1.69–1.75 (m, 6-H), 1.69–1.77 (m, 3-H_{ax}), 1.79–1.83 (m, 11′-H), 1.83 (d, $J = \sim 13$ Hz, 1-H_{eq}), 1.97–2.09 (m, 12-H_{ax} + 12-H_{eq}), 1.98 (d, $J = \sim 13$ Hz, 9-H), 2.13 (d, $J = \sim 13$ Hz, 5-H), 2.13 (s, CH_3COO), 2.24 (sept, $J = 6.8$ Hz, 15-H), 2.26–2.35 (m, 6′-H), 3.61 (s, 21-CH_3), 5.91 (s, 14-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 14.1 (C-18), 17.1 (C-19), 18.0 (C-2), 20.8 (*C*H_3COO), 21.3 (C-16, C-17), 22.3 (C-11), 27.0 (C-12), 27.5 (C-6), 34.9 (C-10), 35.4 (C-15), 36.9 (C-3), 37.9 (C-1), 44.6 (C-5), 46.4 (C-4), 49.7 (C-9), 52.0 (C-21), 114.0 (C-14), 121.6 (C-8), 139.0 (C-7), 147.7 (C-13), 169.3 (CH_3*C*OO), 178.6 (C-20) ppm; EI-MS (70 eV): m/z (%) = 374 (5) $[M]^+$, 346 (44), 332 (41) [M - C_2H_2O]$^+$, 305 (100).

Methyl (1R-(1α,4aβ,4bα,10aα))-1,2,3,4,4a,4b,5,6,10,10a-decahydro-1,4a-dimethyl-7-(1-methylethyl)-9-toluenesulfonyloxy-phenanthrene-1-carboxylate (**12**; $C_{28}H_{38}O_5S$)

500 mg (1.20 mmol) **5** were dissolved in 10 cm^3 anhydrous *THF* and added dropwise to a suspension of 58 mg (1.44 mmol) NaH (60%, suspension in mineral oil) in 5 cm^3 anhydrous *THF*. After stirring at room temperature for 1 h, 458 mg (2.40 mmol) 4-toluenesulfonyl chloride were added, and stirring was continued for 3 h. The reaction mixture was quenched with H_2O, extracted with Et_2O, and worked-up the same way as **11**. The residue was purified by CC on 50 g silica (*CH*:EtOAc = 3:2) to yield 169 mg (29%) **12**.

Yellowish oil; $R_f = 0.45$ (*CH*:EtOAc = 3:1); $[\alpha]_{546}^{21} = -36.0°$ ($c = 0.15$, CH_2Cl_2); IR (KBr): $\tilde{\nu} = 2947$ (m), 1720 (s), 1593 (m), 1373 (s), 1175 (s) cm^{-1}; UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 245.0 (4.34), 218.0 (3.93) nm; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.81 (d, $J = 6.9$ Hz, 16-CH_3^*), 0.82 (s, 19-CH_3), 0.83 (d, $J = 6.9$ Hz, 17-CH_3^*), 0.99–1.06 (m, 11-H), 1.00–1.08 (m, 1-H_{ax}), 1.23 (s, 18-CH_3), 1.49–1.57 (m, 2-H_{ax} + 2-H_{eq}), 1.55–1.70 (m, 3-H_{ax} + 3-H_{eq}), 1.67–1.72 (m, 11′-H), 1.79 (d, $J = \sim 13$ Hz, 1-H_{eq}), 1.85 (d, $J = \sim 12$ Hz, 9-H), 1.85–1.96 (m, 12-H_{ax} + 12-H_{eq}), 1.95–2.03 (m, 15-H), 1.98 (d, $J = \sim 13$ Hz, 6-H_{eq}), 2.04 (d, $J = \sim 12$ Hz, 5-H), 2.39 (s, 7″-CH_3), 2.41 (t, $J = \sim 13$ Hz, 6-H_{ax}), 3.62 (s, 21-CH_3), 5.67 (s, 14-H), 7.27 (d, 2″-H + 6″-H), 7.78 (d, 3″-H + 5″-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 14.1 (C-19), 17.0 (C-18), 17.9 (C-2), 20.7 (C-16*), 21.1 (C-17*), 21.6

(C-7″), 22.2 (C-11), 27.0 (C-12), 28.8 (C-6), 34.6 (C-10), 35.1 (C-15), 37.1 (C-3), 37.8 (C-1), 44.9 (C-5), 46.2 (C-4), 50.1 (C-9), 52.0 (C-21), 114.3 (C-14), 124.9 (C-7), 128.3 (C-2″, C-6″), 129.6 (C-3″, C-5″), 133.8 (C-1″), 138.5 (C-8), 144.7 (C-4″), 148.5 (C-13), 178.4 (C-20) ppm; EI-MS (70 eV): m/z (%) = 486 (15) $[M]^+$, 331 (100) $[M - C_7H_7O_2S]^+$.

Methyl (1R-(1α,4aβ,4bα,8aβ,9α,10aα))-1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-9-hydroxy-9-(2-hydroxyethyl)-1,4a-dimethyl-7-(1-methylethyl)-phenanthrene-1-carboxylate (**13**; $C_{23}H_{38}O_4$)

108 mg (2.85 mmol) $LiAlH_4$ were suspended in 15 cm^3 dry *THF*. After addition of 490 mg (3.67 mmol) anhydrous $AlCl_3$ and 400 mg (0.95 mmol) **5** dissolved in 15 cm^3 dry *THF*, the solution was stirred at 60°C for 45 min. After cooling to room temperature the reaction mixture was quenched with H_2O and extracted with EtOAc and Et_2O. The combined organic layers were washed successively with 2 *N* H_2SO_4, 1 *N* $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. Purification by preparative *TLC* (EtOAc) yielded 147 mg (41%) **13** and 93 mg (28%) **7**.

13: White crystals; m.p.: 162°C; $R_f = 0.55$ (EtOAc); $[\alpha]_D^{24} = -30.6°$ ($c = 0.12$, CH_2Cl_2), $[\alpha]_{546}^{24} = -40.3°$ ($c = 0.12$, CH_2Cl_2); IR (KBr): $\tilde{\nu} = 3402$ (s), 2942 (s), 1730 (s), 1243 (m), 1158 (m) cm^{-1}; UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 274.8 (2.38) nm; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.83 (s, 18-CH_3), 0.99 (d, $J = 6.8$ Hz, 16-CH_3 + 17-CH_3), 1.01–1.11 (m, 1-H_{ax}), 1.17 (s, 19-CH_3), 1.25–1.34 (m, 9-H), 1.30 (t, $J = \sim 11$ Hz, 11-H_{ax}), 1.33–1.46 (m, 6-H_{ax} + 6-H_{eq}), 1.40–1.50 (m, 21-H), 1.49–1.52 (m, 3-H), 1.52–1.62 (m, 2-H_{ax} + 2-H_{eq}), 1.55–1.63 (m, 3′-H), 1.68–1.83 (m, 1-H_{eq}), 1.80 (d, $J = \sim 11$ Hz, 11-H_{eq}), 1.91–2.03 (m, 12-H_{ax} + 12-H_{eq}), 1.97–2.03 (m, 8-H), 2.16 (dd, $J = 12.2$, 3.3 Hz, 5-H), 2.18–2.24 (m, 15-H), 2.21–2.30 (m, 21′-H), 3.67 (s, 23-CH_3), 3.71–3.76 (m, 22-H), 3.97 (td, $J = 10.3$, 4.1 Hz, 22′-H), 5.50 (s, 14-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 13.4 (C-18), 16.5 (C-19), 17.9 (C-2), 21.3 (C-16*), 21.7 (C-11), 21.9 (C-17*), 26.6 (C-12), 34.3 (C-6), 35.4 (C-15), 35.7 (C-10), 36.9 (C-3), 37.5 (C-1), 40.9 (C-21), 43.3 (C-5), 44.5 (C-8), 47.1 (C-4), 47.9 (C-9), 51.9 (C-23), 59.2 (C-22), 73.8 (C-7), 116.4 (C-14), 149.0 (C-13), 178.9 (C-20) ppm; ESI-MS: m/z (%) = 401 (16) $[M + Na]^+$, 361 (100) $[M + 1 - H_2O]^+$.

Ethyl (2S-(2α,3α,4β,4aβ,8α,8aα))-3-formyl-2-hydroxy-8-methoxycarbonyl-4a,8-dimethyl-4-(4-methyl-3-oxopentyl)-perhydro-2-naphthyl-ethanoate (**14**; $C_{25}H_{40}O_7$)

A solution of 450 mg (1.07 mmol) **5** in 30 cm^3 CH_2Cl_2 was cooled at −70°C and treated with a stream of ozone until the characteristic blue colour persisted. The mixture was purged with Ar (5 min) and concentrated. The residue was purified by CC on 50 g silica (CH:EtOAc = 2:1) to give **14** (347 mg, 72%) as a syrup.

$R_f = 0.29$ (*CH*:EtOAc = 2:1); $[\alpha]_D^{21} = -6.3°$ ($c = 0.18$, CH_2Cl_2), $[\alpha]_{546}^{21} = -9.1°$ ($c = 0.18$, CH_2Cl_2); IR (KBr): $\tilde{\nu} = 3499$ (m), 2935 (s), 1715 (s), 1249 (m), 1194 (m) cm^{-1}; UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 291 (1.72), 233 (1.82) nm; ^{1}H NMR (600 MHz, δ, $CDCl_3$): 0.80 (s, 18-CH_3), 0.98–1.07 (m, 11-H), 1.01 (d, $J = 6.8$ Hz, 16-CH_3^*), 1.02 (d, $J = 6.8$ Hz, 17-CH_3^*), 1.06–1.14 (m, 1-H_{ax}), 1.10 (s, 19-CH_3), 1.20 (d, $J = \sim 13$ Hz, 6-H_{eq}), 1.22 (t, $J = \sim 7.5$ Hz, 25-CH_3), 1.46 (t, $J = 13.4$ Hz, 6-H_{ax}), 1.52–1.58 (m, 2-H_{ax} + 2-H_{eq}), 1.56 (d, $J = \sim 11$ Hz, 3-H_{eq}), 1.69–1.77 (m, 3-H_{ax}), 1.73–1.82 (m, 11′-H), 1.79 (d, $J = \sim 13$ Hz, 1-H_{eq}), 1.88–1.92 (m, 9-H), 2.04 (dd, $J = 11.8$, 4.8 Hz, 8-H), 2.23–2.32 (m, 12-H), 2.33 (d, $J = 16.1$ Hz, 22-H), 2.35–2.42 (m, 12′-H), 2.41 (d, $J = \sim 13$ Hz, 5-H), 2.47 (sept, $J = 6.8$ Hz, 15-H), 2.50 (d, $J = 16.1$ Hz, 22′-H), 3.63 (s, 21-CH_3), 4.11 (q, $J = 7.2$ Hz, 24-H + 24′-H), 9.78 (d, $J = 4.8$ Hz, 14-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 13.4 (C-18), 14.0 (C-25), 16.6 (C-19), 17.8 (C-2), 18.1 (C-16*), 18.2 (C-17*), 21.8 (C-11), 35.6 (C-6), 36.7 (C-3), 37.3 (C-10), 37.4 (C-1), 40.7 (C-15), 40.8 (C-12), 42.4 (C-5), 44.6 (C-22), 46.0 (C-9), 46.9 (C-4), 52.0 (C-21), 60.6 (C-8), 60.9 (C-24), 71.6 (C-7), 172.2 (C-23), 178.5 (C-20), 207.3 (C-14), 213.5 (C-13) ppm; CI-MS (NH_3): m/z (%) = 453 (22) $[M + 1]^+$, 452 (21) $[M]^+$, 435 (100) $[M + 1 - H_2O]^+$, 407 (52) $[M - C_2H_5O]^+$, 347 (52), 260 (74).

4-Methyl-1-((1R-(1α,4aα,5aα,6α,9aβ,10β,10aβ))-1,4a-dihydroxy-6-hydroxy-methyl-6,9a-dimethyl-perhydro-naphtho[2,3-c]pyran-10-yl)-3-pentanone (**15**; $C_{22}H_{38}O_5$)

Through a stirred solution of 500 mg (1.43 mmol) **7** in 25 cm^3 CH_2Cl_2 and 5 cm^3 anhydrous MeOH at −70°C, a stream of ozone was bubbled until the characteristic blue colour persisted. The mixture was purged with Ar (5 min), treated with 5 cm^3 H_2O and 2 drops of dimethyl sulfide, and allowed to warm to ambient temperature. After 15 min the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Recrystallization from dioxane:H_2O = 1:1 yielded 449 mg (82%) **15** as a white solid.

M.p.: 85°C; R_f = 0.48 (EtOAc:EtOH = 9:1); $[\alpha]_D^{20} = -11.8°$ (c = 0.30, CH_2Cl_2), $[\alpha]_{546}^{20} = -15.8°$ (c = 0.30, CH_2Cl_2); IR (KBr): $\tilde{\nu}$ = 3398 (s), 2931 (s), 1709 (s), 1055 (m) cm^{-1}; UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 235.0 (1.50), 284.0 (1.58) nm; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.63 (s, 19-CH_3), 0.77 (s, 18-CH_3), 0.92–0.97 (m, 1-H_{ax}), 1.01 (d, J = 6.9 Hz, 16-CH_3^*), 1.02 (d, J = 6.9 Hz, 17-CH_3^*), 1.05–1.08 (m, 3-H), 1.16 (d, J = 15.6 Hz, 11-H_{eq}), 1.25–1.31 (m, 6-H_{ax} + 6-H_{eq}), 1.33 (t, J = ∼11 Hz, 9-H), 1.39–1.47 (m, 21-H), 1.50 (d, J = ∼11 Hz, 8-H), 1.55–1.58 (m, 3′-H), 1.59–1.63 (m, 2-H_{ax} + 2-H_{eq}), 1.65 (t, J = 15.6 Hz, 11-H_{ax}), 1.65–1.75 (m, 21′-H), 1.73–1.77 (m, 1-H_{eq}), 1.88 (dd, J = 11.8, 3.8 Hz, 5-H), 2.40–2.51 (m, 12-H), 2.52 (sept, J = 7.1 Hz, 15-H), 2.69–2.77 (m, 12′-H), 2.81 (d, J = 11.3 Hz, 20-H), 3.36 (d, J = 11.3 Hz, 20′-H), 3.61 (dd, J = 11.4, 4.9 Hz, 22-H_{eq}), 4.20 (td, J = 11.4, 2.3 Hz, 22-H_{ax}), 5.05 (dd, J = 7.7, 2.4 Hz, 14-H), 5.85 (d, J = 7.7 Hz, 14-OH) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 13.2 (C-18), 17.9 (C-2, C-19), 18.2 (C-16, C-17), 20.7 (C-11), 34.8 (C-6), 35.2 (C-3), 37.3 (C-4), 37.6 (C-1), 38.7 (C-10), 39.6 (C-5, C-21), 40.7 (C-15), 41.5 (C-12), 45.9 (C-9), 46.2 (C-8), 55.8 (C-22), 70.0 (C-20), 70.4 (C-7), 93.6 (C-14), 216.0 (C-13) ppm; EI-MS (70 eV): m/z (%) = 364 (8) [M - H_2O]$^+$, 278 (10), 232 (100), 222 (14), 201 (10).

Acknowledgements

We are grateful to Dr. *W. Streicher* and Dr. *H. Steindl* (Krems Chemie) for providing starting material, to Dr. *Günter Michl* (Schering AG, Berlin) and Dr. *J. Reiner* (University of Bayreuth) for recording the mass spectra.

References

[1] Presser A, Haslinger E, Weis R, Hüfner A (1998) Monatsh Chem **129**: 921
[2] Haslinger E, Hüfner A (1995) Monatsh Chem **126**: 1109
[3] Hofner D, Haslinger E (1998) Monatsh Chem **129**: 393
[4] Okawara H, Nakai H, Ohno M (1982) Tetrahedron Lett **23**: 1087
[5] Berettoni M, Dechiara G, Iacoangeli T, Losurdo P, Bettolo RM, Dimirabello LM, Nicolini L, Scarpelli R (1996) Helv Chim Acta **79**: 2035
[6] Buchbauer G, Heneis VM, Krejci V, Talsky C, Wunderer H (1985) Monatsh Chem **116**: 1345
[7] Barrero AF, Alvarez-Manzaneda EJ, Alvarez-Manzaneda R, Chahboun R, Meneses R, Aparicio M (1999) Synlett 713
[8] Krohn K, Budianto E, Florke U, Hausen BM (1992) Liebigs Ann Chem 911
[9] Karlberg AT, Bohlinder K, Boman A, Hacksell U, Hermansson J, Jacobsson S, Nilsson JLG (1988) J Pharm Pharmacol **40**: 42
[10] Mutterer V, Arnau EG, Karlberg AT, Lepoittevin JP (2000) Chem Res Toxicol **13**: 1028
[11] Jefford CW, Vicente MGH, Jacquier Y, Favarger F, Mareda J, Millasson-Schmidt P, Brunner G, Burger U (1996) Helv Chim Acta **79**: 1475
[12] Hofner D (1993) PhD Thesis, University of Ulm, Germany, p 68
[13] Höfle G, Steglich W, Vorbrüggen H (1978) Angew Chem **90**: 602
[14] Brewster JH, Osman SF, Bayer HO, Hopps HB (1964) J Org Chem **29**: 121

Received October 15, 2001. Accepted November 5, 2001