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Stereoselective Synthesis of Taxol Derivatives

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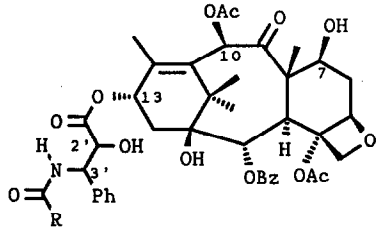
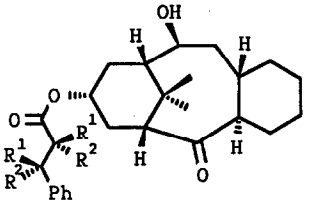
Summary : *The stereoselective synthesis of the tricyclic taxane system with three oxygen centers in ring B is achieved by a photocycloaddition followed by elimination yielding a cyclobutene and oxidative ring expansion. By this strategy a variety of functionalized A,B-ring systems can also be established.*

Introduction:

Due to the promising antitumor activity of taxol **1a** and taxotere **1b**[1] and the limited availability of this type of substances, the synthesis of less functionalized taxol derivates seems especially interesting to us. With our studies we want to contribute to the elucidation of structure-activity-interactions, provide better available biologically active substances, but also work out strategies for the synthesis of taxanes. The diastereomeric mixture of the taxol analogues **2a,b**[2] synthesized by us restricts the depolymerization of tubulin and thus proves that even less functionalized taxanes can be biologically active.

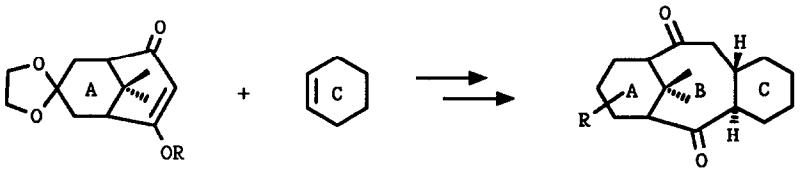


1a: R=Ph taxol
1b: R=O^{t}Bu taxotere



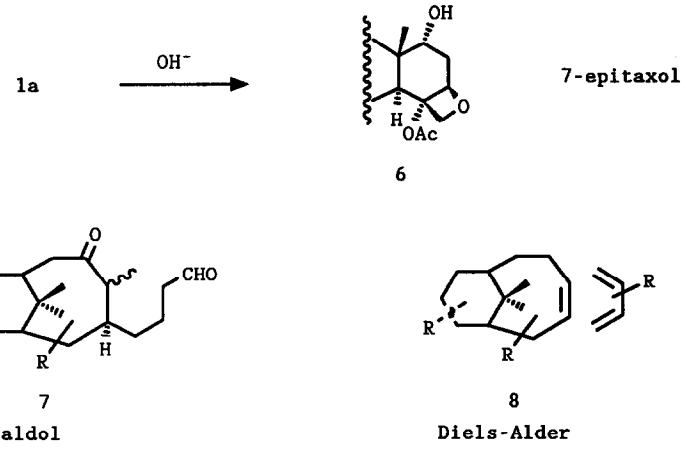
2a: R^1=OH, R^2=H
2b: R^1=H, R^2=OH

These types of compounds are obtained by a stereoselective de Mayo reaction of ring C with a suitably functionalized 1,3-diketone containing ring A.[3]



3 4 5

Additionally a second strategy followed by our group is based on building up the AB-ring system first in order to anellate ring C afterwards. The easy epimerization of taxanes at C-7 is fullfilled by a retro aldol process[4] and thus shows possibilities for ring anellation. Diels-Alder reactions could also be successful. For these reasons we developed several synthetic routes leading to functionalized AB-ring systems.



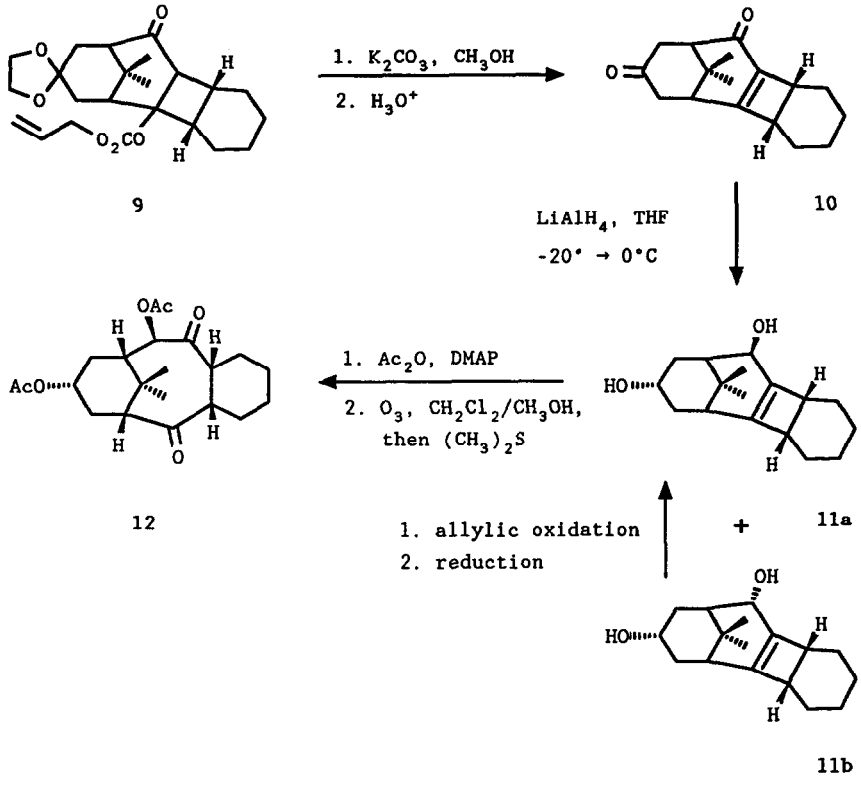
1a 7-epitaxol

6

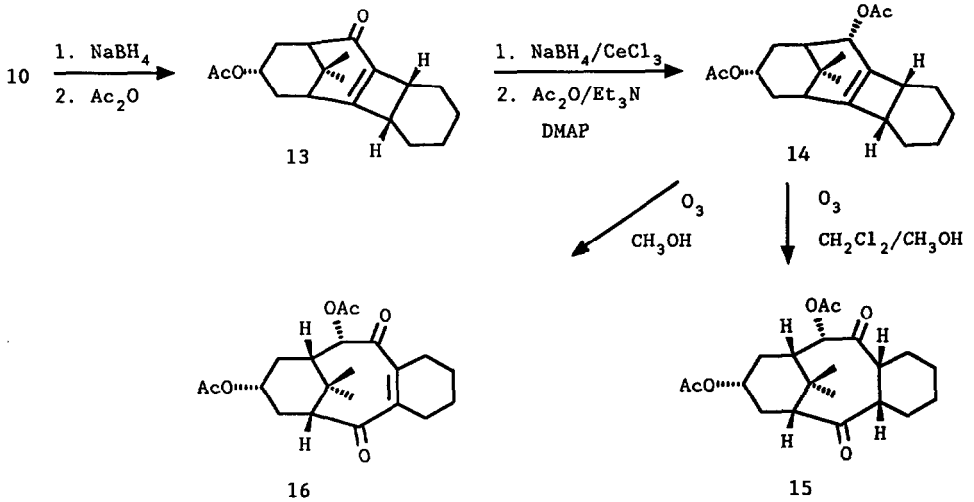
7 aldol 8 Diels-Alder

Results and discussion:

Almost all naturally occuring taxanes bear oxygen functionalities at C-9 like taxol. In addition to studies leading to the synthesis of biologically active taxol analogues we are interested in the introduction of an additional oxygen functionality. After carbonyl oxidation of various derivatives had failed due to steric reasons, the problem was solved by a modification of the de Mayo reaction. The desired functionalization could be achieved by oxidative ring opening of a cyclobutene instead of performing the retro aldol reaction. Enone **10** was obtained from **9**[3] by mild elimination using K_2CO_3 in methanol and consecutive cleavage of the ketal. The stereoselective reduction yielding the "naturally" configurated carbinols was easily achieved at C-13 but difficult at C-10 (taxane numbering). Reduction with $LiAlH_4$ in THF at -20°C and followed by warming up to 0°C led to a mixture of **11a** (38%) and **11b** (33%). The latter could be transformed into **11a** by allylic oxidation with MnO_2 in CH_2Cl_2 and consecutive reduction. The neighbouring effect of a C-13 α-alcohol seems to be responsible for the reduction to the C-10 ß-carbinol **11a**. Acetylation and ozonolysis followed by reductive work-up led to the first taxane skeleton **12** containing three oxygen functionalities in ring B.

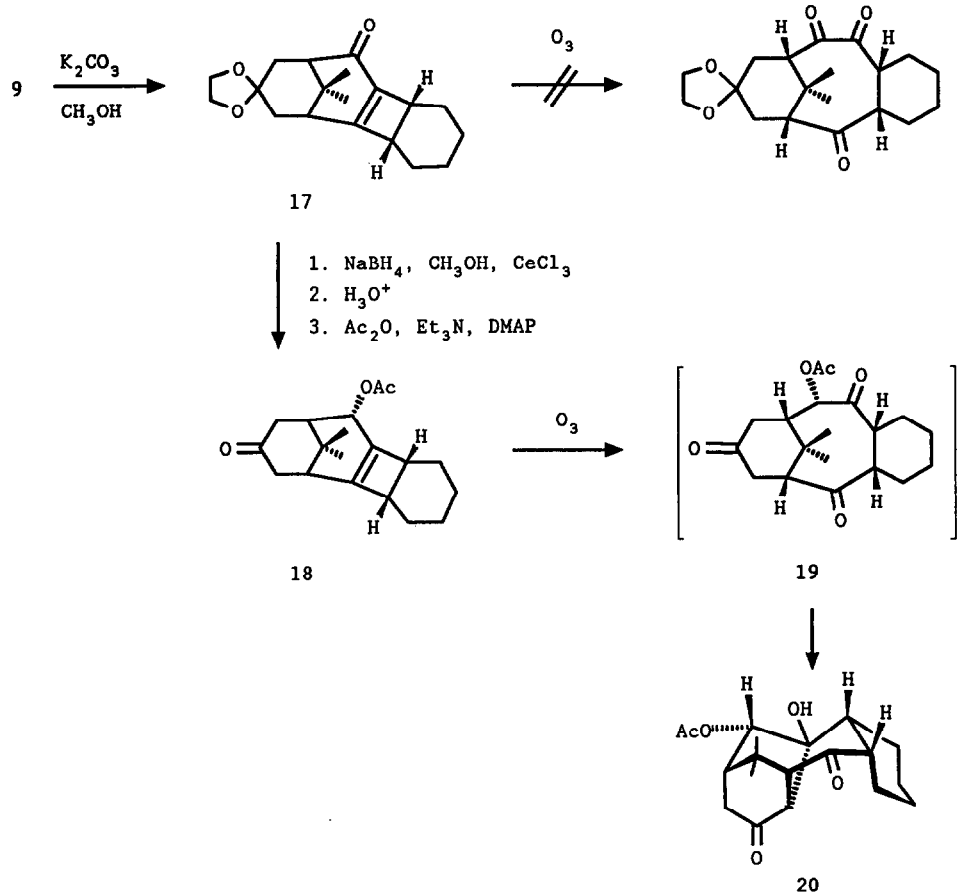


The stereoselective synthesis of taxane derivative **15**, however, is much easier. Reaction of **10** with $NaBH_4$ in methanol at 0°C yields the corresponding alcohol which can be easily esterified to **13**. Further reduction with $NaBH_4/CeCl_3$ led to the allylic carbinol, which was converted into diacetate **14** in the course of model studies. Oxidative cleavage with ozone in CH_2Cl_2/CH_3OH yielded stereochemically uniform compound **15**.

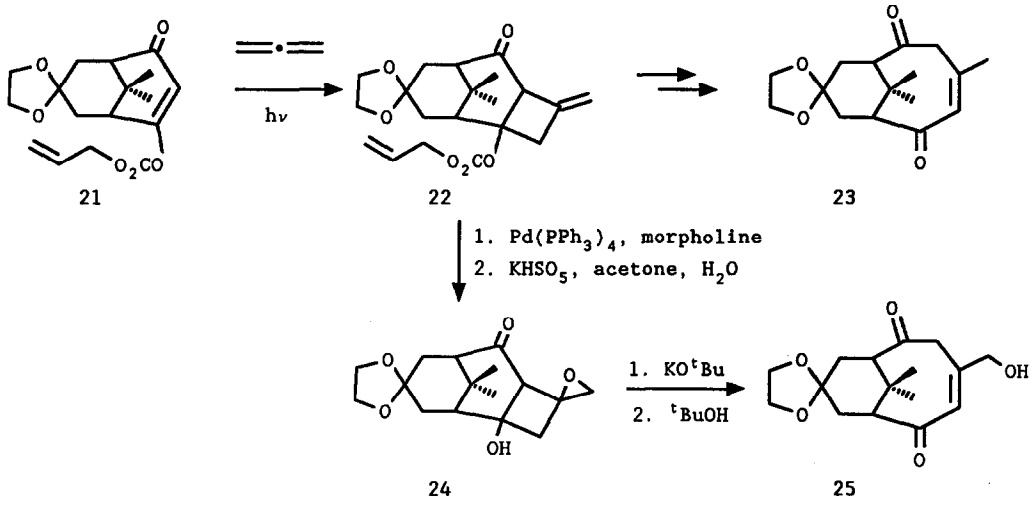


The stereochemistry of all obtained products was determined by the corresponding coupling constants and by NOE-experiments. Irradiation on one of the geminal methyl groups shows a NOE to H-3, H-8 and H-10 of product **15** for example, and confirmes the cis-α-anellation of ring C and the α-position of the acetate. If the ozonolysis of cyclobutene **14** was carried out in methanol, a mixture of **15** (37%) and **16** (44%) was obtained.

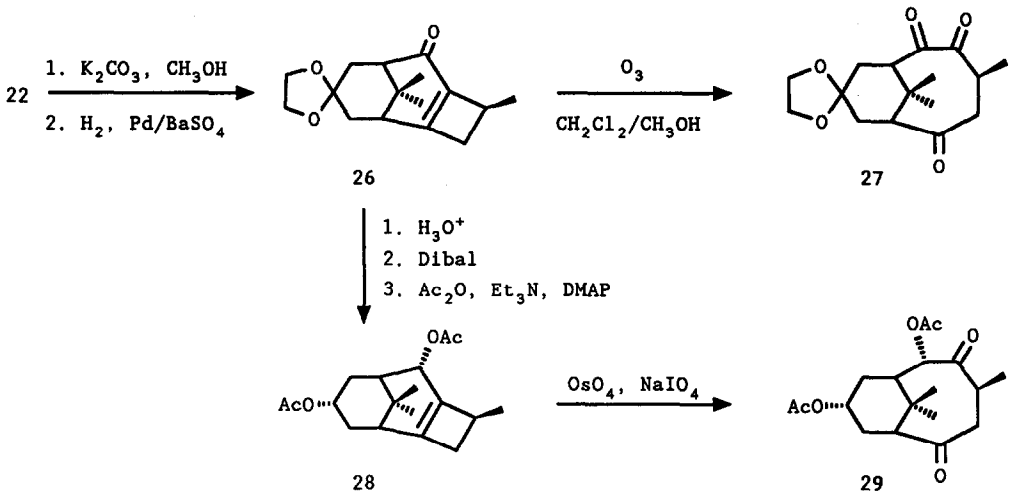
Oxidative ring expansion with the ketal **17**[3] failed in this tricyclic series because the π-system of the double bond is completely shielded. On the other hand the C-13 ketone **18** undergoes an intramolecular ring formation, yielding the corresponding aldol adduct **20** under the conditions of the C-C bond cleavage with ozone or $OsO_4/NaIO_4$.



We synthesized several AB-skeletons which should be of interest for a C-ring anellation by regioselective photoaddition of allene to **21**. Conversion of **22** via deprotection and retro aldol reaction into a functionalized bicyclo[5.3.1]undecane system had already been reported[5]. However, **23** is not suited for Michael additions and Diels-Alder reactions because the conformation of the 8-membered ring disfavours the conjugation of the carbonyl group and the double bond. Epoxidation of the exomethylene group at the aldol step with dimethyldioxirane followed by a retro aldol process yielded the allylic alcohol **25** which was converted into the aldehyde with PDC in CH_2Cl_2. C-C bond formations with this product are currently studied.



The oxidative ring cleavage of a cyclobutene described above led to promising products. Elimination of the allylic carbonate **22** and consecutive hydrogenation of the exomethylene group afforded compound **26** in 70% yield. Ozonolysis yielded triketone **27**. In this series optionally configurated carbinols can be made by variation of the reduction methods as shown in the tricyclic case. The diketone obtained from **26** by hydrolysis was reduced by diisobutylaluminiumhydride to the α-diol and converted into diketone **29** by $OsO_4/NaIO_4$ after acetylation. The presented synthetic strategy offers a high flexibility in the stereoselective construction of various functionalized taxane derivatives by selection of the reaction conditions and variation in the sequence of reactions. In our opinion it is especially interesting for studies on structure-activity interactions.



Experimental:

Infrared spectra were taken on a Perkin-Elmer 157G. ^{1}H-NMR spectra and ^{13}C-NMR spectra were recorded on Bruker AC-200 and WH-400 spectrometers. All chemical shifts are quoted on the δ-scale. Mass spectra were recorded on a Finnigan MAT MS-30 and MS-50. Melting points were determined on a Reichert hot-plate apparatus and are uncorrected. Microanalysis were performed on a C, H, N-Rapid Heraeus apparatus.

15,15-Dimethyl-tetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$]pentadec-2,9-ene-10,13-dione **10**

9 (404 mg, 1 mmol) in 10 ml methanol was stirred with 233 mg (2 mmol) potassium carbonate for 90 minutes at room temperature. After aqueous work-up the reaction mixture was extracted with ether and the crude product was hydrolyzed in 10 ml THF with 1 ml 8N HCl (24 h, TLC-control). After neutralisation, extraction with ether and recrystallisation (ether, hexane) 194 mg (75%) **10** was obtained (mp. 103°C).
^{1}H-NMR ($CDCl_3$): 1.12 (s, 3H), 1.31 (s, 3H), 1.20 - 1.90 (m, 8H), 2.28 - 2.50 (m, 4H), 2.75 (dd, J=18 Hz, J=9 Hz, 1H), 2.83 (dd, J=13 Hz, J=4.5 Hz, 1H), 3.01 (m, 1H), 3.15 (m, 1H)
IR ($CHCl_3$): 2940, 1705, 1675, 1450, 1410, 1390, 1370 cm^{-1}
MS: 258 (M^+, 100%), 243 (28), 229 (29), 215 (14), 201 (17), 173 (13), 161 (76), 133 (15), 105 (29), 91 (39); HRMS: found 258.1623 ($C_{17}H_{22}O_2$) calculated 258.1620

15,15-Dimethyl-tetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$]pentadec-2,9-ene-10β,13α-diol **11a**
15,15-Dimethyl-tetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$]pentadec-2,9-ene-10α,13α-diol **11b**

3.3 ml of a 1M solution of $LiAlH_4$ in THF were added at 0°C to a solution of 716 mg (2.8 mmol) **10** in 50 ml anhydrous THF. Within 20 minutes the reaction mixture was warmed up to room temperature. 1 ml 1n NaOH was added and after 15 minutes the slurry was extracted with ether. The crude product was purified on silica gel (ether/hexane) yielding 290 mg (38%) **11a** and 250 mg (33%) **11b**.

11a:
^{1}H-NMR ($CDCl_3$): 1.02 (s, 3H), 1.08 (s, 3H), 1.10 - 2.40 (m, 15H), 2.70-2.89 (m, 1H), 2.95 - 3.10 (m, 2H), 3.85 (t, J=5.4 Hz, 1H), 4.22 (s, 1H)
^{13}C-NMR ($CDCl_3$): 20.4 (2 x t), 23.9 (t), 24.6 (t), 26.3 (q), 28.7 (q), 31.3 (t), 33.4 (s), 35.0 (t), 38.6 (2 x d), 42.5 (d), 46.9 (d), 65.9 (d), 70.4 (d), 143.6 (s), 157.2 (s)
IR ($CHCl_3$): 3600, 3520, 3000, 2920, 1450, 1380, 1060, 1020 cm^{-1}
MS: 262 (M^+, 16%), 244 (39), 229 (30), 203 (32), 175 (85), 161 (31), 147 (29), 135 (52), 107 (51), 91 (59), 81 (100); HRMS: found 262.1931 ($C_{17}H_{26}O_2$) calculated 262.1933
11b:
^{1}H-NMR ($CDCl_3$): 0.92 (s, 3H), 1.01 (s, 3H), 1.21 - 2.25 (m, 16H), 2.70-2.93 (m, 2H), 2.94 (tt, J=5 Hz, J=1.6 Hz, 1H), 3.93 (tt, J=5 Hz, J=1.6 Hz, 1H), 4.33 (m, 1H)
^{13}C-NMR ($CDCl_3$): 20.3 (t), 20.4 (t), 24.6 (t), 24.7 (t), 26.9 (q), 27.1 (q), 28.2 (t), 34.2 (t), 38.3 (s), 38.7 (d), 40.8 (d), 42.2 (d), 42.4 (d), 65.7 (d), 69.4 (d), 145.7 (s), 156.9 (s)
IR ($CHCl_3$): 3500, 2990, 2930, 1450, 1060, 1030 cm^{-1}
MS: 262 (M^+, 11%), 244 (100), 229 (28), 211 (18), 203 (39), 175 (55), 157 (25), 135 (31); HRMS: found 262.1935 ($C_{17}H_{26}O_2$) calculated 262.1933

(cis-3-4,8,12-Trinortaxan-2,9-dione-10β,13α-diyl)acetate **12**

11a (262 mg, 1mmol) was dissolved in 4 ml triethylamine and 2 ml acetic anhydride and a catalytic amount of DMAP was added. After stirring for 24 h the reaction mixture was poured on 1n HCl and extracted with ether. The crude product was dissolved in 60 ml CH_2Cl_2/CH_3OH (3:1) and treated with ozone at -78°C. After the reaction was completed (TLC-control) the ozone was removed and 0.5 ml of dimethylsulfide were added. After 45 minutes the reaction mixture was warmed up to room temperature. Aqueous work-up and chromatography on silica gel yielded 151 mg (40%) of crystalline **12** (mp. 232° - 234°C).
^{1}H-NMR ($CDCl_3$): 1.25 (s, 3H, H-16), 1.29 (m, 1H, H-6), 1.36 (dt, J=13.6 Hz, J=4.8 Hz, 1H, H-4), 1.43 (s, 3H, H-17), 1.54 (m, 1H, H-5), 1.65 (dd, J=13.6 Hz, J=3.6 Hz, 1H, H-7), 1.78 (ddd, J=16 Hz, J=3.6 Hz, J=1.6 Hz, 1H, H-12α), 1.82 (d, J=13.6 Hz, 1H, H-4'), 1.90 (ddd, J=16 Hz, J=6 Hz, J=4.8 Hz, 1H, H-14β), 1.91 (m, 1H, H-7'), 1.93 (m, 1H, H-6'), 1.95 (m, 1H, H-11), 2.05 (s, 3H, acetate), 2.08 (s, 3H, acetate), 2.14 (dt, J=16 Hz, J=4.8 Hz, 1H, H-12β), 2.23 (dt, J=13.6 Hz, J=4.4 Hz, 1H, H-5'), 2.26 (dt, J=6 Hz, J=1.6 Hz, 1H, H-1), 2.86 (ddd, J=12.8 Hz, J=5.6 Hz, J=3.2 Hz, 1H, H-8β), 3.02 (d, J=26 Hz, 1H, H-14α), 3.52 (t, J=4.8 Hz, 1H, H-3β), 4.98 (tt, J=4.8 Hz, J= 1.6 Hz, 1H, H-13β), 5.65 (d, J=9.1 Hz, 1H, H-10)
^{13}C-NMR ($CDCl_3$): 20.7 (q), 21.8 (q), 21.9 (t), 24.9 (t), 25.8 (t), 27.9 (t), 28.9 (t), 29.3 (t), 32.4 (q), 32.7 (q), 35.5 (s), 43.0 (d), 47.2 (d), 56.4 (d), 58.1 (d), 67.3 (d), 75.2 (d), 169.4 (s), 170.7 (s), 212.3 (s), 213.0 (s)
IR ($CHCl_3$): 3020, 2950, 2930, 1730, 1695, 1375, 1260 1240, 1090, 1020 cm^{-1}
MS: 378 (M^+, 0.03%), 350 (50), 308 (9), 290 (17), 248 (92), 220 (12), 151 (32), 111 (30), 43 (100); HRMS: found 378.2055 ($C_{21}H_{30}O_6$) calculated 378.2042

(15,15-Dimethyl-tetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$]pentadec-2,9-en-10-on-13-yl)acetate **13**

C-10 α-Carbinol (crude product; 400 mg, 1.54 mmol), obtained by reduction of **10** with $NaBH_4$ (cf. **11**), was dissolved in 2 ml triethylamine and 1 ml acetic anhydride and a catalytic amount of DMAP was added. Aqueous acidic work-up and chromatography on silica gel yielded 334 mg (72%) of **13**.
^{1}H-NMR ($CDCl_3$): 1.04 (s, 3H), 1.05 (s, 3H), 1.20 - 2.10 (m, 12H), 1.99 (s, 3H), 2.20 - 2.40 (m, 2H), 2.87 - 3.13 (m, 2H), 5.20 (tt, J=6.6 Hz, J=1 Hz, 1H)
^{13}C-NMR ($CDCl_3$): 20.1 (2 x t), 21.8 (t), 22.8 (t), 23.5 (t), 25.1 (q), 27.7 (q), 28.2 (t), 29.8 (t), 38.5 (d), 39.1 (s), 39.4 (d), 43.7 (d), 52.3 (d), 66.1 (d), 142.8 (s), 170.3 (s), 176.7 (s), 198.2 (s)
IR ($CHCl_3$): 2940, 1720, 1660, 1420, 1360, 1250, 1170, 1040 cm^{-1}
MS: 302 (M^+, 4%), 242 (20), 214 (11), 159 (15), 105 (20), 91 (41), 43 (100); HRMS: found 302.1899 ($C_{19}H_{26}O_3$) calculated 302.1871

(15,15-Dimethyl-tetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$]pentadec-2,9-en-10α,13α-diyl)acetate **14**

Enone **13** (400 mg, 1.32 mmol) was reduced with $NaBH_4$ in a 0.4M solution of $CeCl_3$ in methanol. After aqueous work-up the crude product was acylated as described above. Chromatography on silica gel yielded 320 mg (70%) of **14**.
^{1}H-NMR ($CDCl_3$): 0.99 (s, 6H), 1.20 - 1.71 (m, 9H), 1.73 - 1.84 (m, 2H), 1.90 - 2.25 (m, 3H), 1.99 (s, 3H), 2.02 (s, 3H), 2.60 - 2.82 (m, 2H), 5.00 - 5.09 (m, 1H), 5.31 (ddt, J=6.4 Hz, J=3.2 Hz, J=1 Hz, 1H)
^{13}C-NMR ($CDCl_3$): 20.0 (t), 20.1 (t), 21.2 (q), 21.9 (q), 23.3 (t), 24.0 (t), 25.8 (t), 26.6 (q), 26.7 (q), 30.5 (t), 37.2 (s), 37.7 (d), 39.0 (d), 40.7 (d), 42.4 (d), 66.6 (d), 71.6 (d), 140.5 (s), 153.4 (s), 170.7 (s), 170.9 (s)
IR ($CHCl_3$): 3010, 2920, 1720, 1420, 1365, 1160, 1110, 1015 cm^{-1}
MS: 346 (M^+, 4%), 328 (49), 394 (18), 286 (12), 244 (42), 226 (15), 203 (24), 175 (100); HRMS: found 346.2154 ($C_{21}H_{30}O_4$) calculated 346.2144

(cis-3-4,8,12-Trinortaxane-2,9-dione)-10α,13α-diyl)acetate **15**

14 (346 mg, 1 mmol) was ozonized in 100 ml CH_2Cl_2/CH_3OH (2:1) as described for the preparation of **12**. Chromatography on silica gel yielded 250 mg (64%) of crystalline compound **15** (mp. 188°C).
^{1}H-NMR ($CDCl_3$): 1.23 (s, 3H, H-16), 1.39 (s, 3H, H-17), 1.23 - 1.55 (m, 4H, H-4,5,6,7), 1.68 (dt, J=14.5 Hz, J=10.2 Hz, 1H, H-14), 1.73 - 2.35 (m, 8H, H-4',5',6',7',11,12,12',14'), 2.00 (s, 3H, acetate), 2.07 (s, 3H, acetate), 2.59 (dt, J=9.6 Hz, J=1.2 Hz, 1H, H-1), 2.89 (m, 1H, H-8), 3.46 (m, 1H, H-3), 5.08 (dddd, J=10.2 Hz, J=7.8 Hz, J=6.4 Hz, J=5.4 Hz, 1H, H-13α), 5.40 (d, J=4 Hz, 1H, H-10α)
^{13}C-NMR ($CDCl_3$): 20.7 (q), 21.6 (q), 23.9 (t), 24.2 (t), 24.4 (t), 25.5 (t), 27.2 (t), 27.5 (q), 28.5 (t), 32.8 (s), 36.4 (q), 46.1 (d), 49.7 (d), 50.0 (d), 57.2 (d), 66.6 (d), 77.5 (d), 171.0 (2 x s), 209.6 (s), 211.8 (s)

IR ($CHCl_3$): 3100, 2940, 1730, 1715, 1680, 1450, 1370 1250, 1030 cm^{-1}
MS: 378 (M^+, 0.1%), 350 (48), 318 (7), 308 (5), 290 (20), 258 (33), 248 (100), 193 (92), 168 (85); HRMS: found 378.2010 ($C_{21}H_{30}O_6$) calculated 378.2042

((3,8-Dehydro-4,8,12-trinortaxane-2,9-dione)-10α,13α-diyl)acetate **16**

14 (600 mg, 1.7 mmol) was ozonized in methanol under the reaction conditions described above for compound **15**. 290 mg (44%) **16** (mp. 129°C) and 240 mg (37%) **15** were obtained.
^{1}H-NMR ($CDCl_3$): 1.00 (s, 3H), 1.09 (s, 3H), 1.68 - 1.89 (m, 3H), 1.91 - 2.18 (m, 5H), 1.96 (s, 3H), 1.97 (s, 3H), 2.28 (dt, J=16 Hz, J=5.2 Hz, 1H), 2.37 (dt, J=5 Hz, J=2.4 Hz, 1H), 2.45 (dt, J=13.2 Hz, J=5.2 Hz, 1H), 2.54 (ddd, J=15.6 Hz, J=6.8 Hz, J=4.8 Hz, 1H), 2.61 (ddd, J=15.6 Hz, J=10 Hz, J=4 Hz, 1H), 2.68 (ddd, J=13.2 Hz, J=8.8 Hz, J=5.2 Hz, 1H), 4.96 - 5.00 (m, 1H), 6.11 (d, J=6.8 Hz, 1H)
^{13}C-NMR ($CDCl_3$): 20.6 (q), 21.2 (q), 22.6 (t), 25.6 (t), 25.9 (t), 26.2 (q), 26.6 (q), 27.0 (d), 31.1 (s), 34.5 (t), 37.6 (d), 39.1 (t), 43.4 (t), 67.0 (d), 74.3 (d), 143.4 (s), 144.9 (s), 169.6 (s), 170.3 (s), 203.8 (s), 208.9 (s)
IR ($CHCl_3$): 3000, 2920, 1710, 1670, 1650, 1350, 1250, 1220, 1050, 1030 cm^{-1}
MS: 376 (M^+, 0.2%), 334 (70), 316 (6), 274 (100), 256 (13), 241 (8), 206 (16); HRMS: found 376.1900 ($C_{21}H_{28}O_6$) calculated 376.1886

(15,15-Dimethyl-tetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$]pentadec-2,9-en-13-on-10-yl)acetate **18**

17[3] (309 mg, 1.02 mmol) was reduced with $NaBH_4$ in a solution of $CeCl_3$ in methanol at room temperature. After aqueous work-up the crude product was purified by chromatography. The product was dissolved in dichloromethane and treated with hydrochloric acid. The reaction mixture was sonicated for one hour. After neutralisation with $NaHCO_3$ and extraction with ether the resulting product was acylated as described above (cf. **12**). Yield: 201 mg (65%).

^{1}H-NMR ($CDCl_3$): 1.13 (s, 3H), 1.23 (s, 3H), 1.21 - 1.36 (m, 3H), 1.40 - 1.63 (m, 5H), 2.02 (s, 3H), 2.01 - 2.05 (m, 1H), 2.12 (dddd, J=7 Hz, J=5.6 Hz, J=1.6 Hz, J=1.6 Hz, 1H), 2.29 (dt, J=16.2 Hz, J=2.4 Hz, 1H), 2.37 (dd, J=17.6 Hz, J=7 Hz, 1H), 2.63 (dt, J=17.6 Hz, J=2 Hz, 1H), 2.64 (dd, J=16.2 Hz, J=5 Hz, 1H), 2.71 - 2.83 (m, 2H), 5.36 - 5.40 (m, 1H)
^{13}C-NMR ($CDCl_3$): 19.0 (t), 19.5 (t), 21.4 (q), 23.7 (t), 24.2 (t), 25.3 (q), 26.9 (q), 36.9 (s), 37.9 (t), 40.7 (d), 41.2 (d), 42.0 (t), 42.4 (d), 43.1 (d), 71.2 (d), 140.2 (s), 153.0 (s), 170.9 (s), 210.8 (s)
IR ($CHCl_3$): 2950, 1740, 1710, 1450, 1420, 1380, 1250, 1180, 1120, 1040, 1030 cm^{-1}
MS: 302 (M^+, 19%), 287 (5), 269 (11), 260 (67), 245 (49), 242 (100), 227 (52), 217 (33), 203 (33), 185 (92), 157 (34); HRMS: found 302.1875 ($C_{19}H_{26}O_3$) calculated 302.1882

(9-Hydroxy-15,15-dimethyl-tetracyclo[7.3.1.$2^{11,14}$.$0^{3,8}$]-pentadecane-2,13-dion-10-yl)-acetate **20**

18 (200 mg, 0.7 mmol) was ozonized in methanol under the reaction conditions described above for compound **15**. 140 mg (63%) **20** (mp. 221-225°C) were obtained.

^{1}H-NMR ($CDCl_3$): 1.04 (s, 3H), 1.00 -1.30 (m, 4H), 1.51 - 1.60 (m, 1H), 1.73 - 1.82 (m, 1H), 1.93 (d, J=13.6 Hz, 1H), 2.05 (ddd, J=3.8 Hz, J=2.2 Hz, J=2 Hz, 1H), 2.20 (s, 3H), 2.26 (ddd, J=12.8 Hz, J=6.4 Hz, J=4 Hz, 1H), 2.40 (dt, J=12.8 Hz, J=2 Hz, 1H), 2.43 (d, J=4.4 Hz, 1H), 2.45 (ddd, J=19 Hz, J=3.8 Hz, J=2.2 Hz, 1H), 2.62 (dd, J=19 Hz, J=2 Hz, 1H), 2.89 (t, J=5.6 Hz, 1H), 2.95 (d, J=4.4 Hz, 1H), 5.61 (t, J=2.4 Hz, 1H)
^{13}C-NMR ($CDCl_3$): 21.2 (q), 22.8 (t), 23.3 (q), 24.5 (t), 24.7 (t), 25.3 (t), 31.5 (q), 33.6 (s), 35.0 (t), 44.8 (d), 45.9 (d), 46.3 (d), 52.5 (d), 57.9 (d), 70.9 (d), 72.6 (s), 170.6 (s), 207.9 (s), 210.1 (s)
IR ($CHCl_3$): 3600 - 3200, 3010, 2930, 1730, 1690, 1450, 1370, 1080, 1030 cm^{-1}
MS: 334 (M^+, 24%), 315 (20), 292 (7), 274 (53), 246 (25), 191 (83), 164 (38), 123 (30), 83 (40), 43 (100); HRMS: found 334.1791 ($C_{19}H_{26}O_5$) calculated 334.1780

11,11-Dimethyl-dispiro[oxiran-1,9-1,3-dioxolan-2,9]tricyclo[5.3.1.$0^{2,5}$]undec-2-ol-6-one **24**

24 was obtained by adding dropwise (over 3-4 h) a solution of 0.25 mmol potassium peroxomonosulfate in 5 ml water to a solution of 0.1 mmol of deprotected compound **22** in acetone and water at 0°C. Before starting the reaction the pH was adjusted to 7.0 (buffer system). The aqueous mixture was extracted with ether, the ether extracts were dried over $MgSO_4$ and the solvent was removed in vacuo to give 0.08 mmol (80%) of the colourless crystalline product.
^{1}H-NMR ($CDCl_3$): 1.22 (s, 3H), 1.26 (s, 3H), 1.86 (d, J=15 Hz, 1H), 2.01 (m, 1H), 2.09 (dd, J=15 Hz, J=6 Hz, 1H), 2.18 (d, J=6 Hz, 1H), 2.28 (d, J=3.5 Hz, 2H), 2.58 (d, J=5.5 Hz, 1H), 2.68 (dd, J=15 Hz, J=2 Hz, 1H), 2.84 (dd, J=15 Hz, J=2 Hz, 1H), 3.04 (d, J=5.5 Hz, 1H), 3.22 (m, 1H), 3.80 - 4.04 (m, 4H), 4.05 (s, 1H)
^{13}C-NMR ($CDCl_3$): 28.1 (q), 29.1 (q), 32.8 (t), 34.2 (s), 35.7 (t), 44.3 (t), 45.6 (d), 48.5 (t), 54.5 (d), 59.7 (s), 60.1 (d), 64.1 (t), 64.7 (t), 70.3 (s), 106.9 (s), 214.5 (s)
IR ($CHCl_3$): 3500, 3018-2965, 1697, 1374, 1365, 1264, 1239, 1169, 1114, 1088 cm^{-1}
MS: 294 (M^+, 13%), 264 (44), 234 (46), 167 (55), 141 (74), 99 (49), 86 (100), 83 (62), 69 (60), 55 (60); HRMS: found 294.1467 ($C_{16}H_{22}O_5$) calculated 294.1468

11,11-Dimethyl-4-hydroxymethyl-spiro[1,3-dioxolan-2,9]bicyclo[5.3.$1^{1,7}$]undecen-4-2,6-dione **25**

To 10 mg (0.034 mmol) of **24** in t-BuOH 4.5 mg (0.041 mmol) t-BuOK were added at room temperature. After stirring for 12 h the mixture was hydrolyzed and then extracted with ether. Purification of the crude product by chromatography (ether:hexane 2:1) yielded 7 mg (0.024 mmol, 70%) of colourless crystalline **25**.
^{1}H-NMR ($CDCl_3$): 1.28 (s, 3H), 1.32 (s, 3H), 1.97 (dd, J=16 Hz, J=2 Hz, 1H), 2.02 (t, J=6 Hz, 1H), 2.12 (dd, J=14.5 Hz, J=6.5 Hz, 1H), 2.36 (dd, J=16 Hz, J=8.5 Hz, 1H), 2.38 (d, J=6.5 Hz, 1H), 2.49 (d, J=11.5 Hz, 1H), 2.69 (d, J=6.5 Hz, 1H), 2.72 (dt, J=14 Hz, J=2 Hz, 1H), 3.87 - 4.01 (m, 4H), 4.11 (dd, J=16 Hz, J=5 Hz, 1H), 4.22 (dd, J=16 Hz, J=5 Hz, 1H), 5.06 (d, J=11.5 Hz, 1H), 6.14 (s, 1H)
^{13}C-NMR ($CDCl_3$): 27.8 (q), 31.9 (t), 32.6 (t), 33.2 (s), 33.6 (q), 40.9 (t), 58.0 (d), 60.0 (d), 63.6 (t), 64.1 (t), 66.3 (t), 106.3 (s), 127.4 (d), 138.2 (s), 206.6 (s), 208.0 (s)
IR ($CHCl_3$): 3600-3200, 3010, 2960, 2880, 1691, 1663, 1420, 1300, 1220, 1110, 1080 cm^{-1}

MS: 294 (M^+, 3%), 263 (3), 225 (14), 141 (100), 99 (9), 86 (17); HRMS: found 294.1467 ($C_{16}H_{22}O_5$) calculated 294.1468

4,11,11-Trimethyl-spiro[1,3-dioxolane-2,9-tricyclo[5.3.1.$0^{2,5}$]undec-2,5-en-6-one] **26**

22[5] (480 mg, 1.3 mmol) was dissolved in 10 ml of methanol and stirred with 303 mg (2.6 mmol) potassium carbonate for 90 minutes. After aqueous work-up and extraction with ether the crude product was redissolved in 10 ml methanol and stirred for 5-10 minutes (TLC-control) under H_2-atmosphere with $Pd/BaSO_4$. Purification by chromatography on silica gel yielded 238 mg (70%) **26** (mp. 71°C).
^{1}H-NMR ($CDCl_3$): 1.08 (s, 3H), 1.14 (s, 3H), 1.26 (d, J=7 Hz, 3H), 1.76 (dt, J=14 Hz, J=2 Hz, 1H), 1.84 (dd, J=14.8 Hz, J=2 Hz, 1H), 2.03 - 2.15 (m, 3H), 2.20 (dd, J=14.5 Hz, J=4.5 Hz, 1H), 2.23 (dd, J=15.5 Hz, J=1.8 Hz, 1H), 2.79 (ddd, J=15.5 Hz, J=4.5 Hz, J=1 Hz, 1H), 3.11 - 3.28 (m, 1H), 3.70 - 3.90 (m, 4H)
^{13}C-NMR ($CDCl_3$): 16.3 (q), 25.5 (q), 27.2 (q), 33.9 (t), 35.7 (t), 36.0 (d), 38.0 (s), 38.4 (t), 41.9 (d), 57.5 (d), 63.3 (t), 64.4 (t), 107.1 (s), 144.6 (s), 170.5 (s), 197.1 (s)
IR ($CHCl_3$): 2995, 2980, 1670, 1380, 1270, 1100 cm^{-1}
MS: 262 (M^+, 58%), 249 (10), 192 (37), 161 (13), 113 (100); HRMS: found 262.1577 ($C_{16}H_{22}O_3$) calculated 262.1569

4,11,11-Trimethyl-spiro[bicyclo[5.3.1]undecane-2,9-(1,3)-dioxolane]-2,5,6-trione **27**

26 (260 mg, 1 mmol) was ozonized as described before (compound **12**). Chromatography on silica gel yielded 100 mg (34%) of product **27** (mp. 131°C).
^{1}H-NMR ($CDCl_3$): 1.13 (s, 3H), 1.26 (d, J=7 Hz, 3H), 1.30 (s, 3H), 2.06 (dd, J=15 Hz, J=6.2 Hz, 1H), 2.09 (ddd, J=16 Hz, J=2 Hz, J=1.6 Hz, 1H), 2.37 (dd, J=16 Hz, J=7.6 Hz, 1H), 2.38 (dd, J=8.2 Hz, J=1.4 Hz, 1H), 2.52 (dt, J=6.2 Hz, J=1.8 Hz, 1H), 2.57 (ddd, J=7.6 Hz, J=3 Hz, J=1.6 Hz, 1H), 2.65 (dt, J=15 Hz, J=2 Hz, 1H), 2.80 - 3.00 (m, 1H), 3.80 - 4.00 (m, 5H)
IR ($CHCl_3$): 2940, 1710, 1690, 1450, 1420, 1400, 1000 cm^{-1}
MS: 294 (M^+, 3%), 266 (8), 197 (22), 169 (15), 141 (100), 125 (8); HRMS: found 294.1469 ($C_{16}H_{22}O_5$) calculated 294.1468

[4,11,11-Trimethyl-tricyclo[5.3.1.$0^{2,5}$]undec-2,5-ene-6,9-diyl]acetate **28**

26 (262 mg, 1 mmol) was dissolved in 5 ml THF and hydrolyzed for 24 h by adding 0.3 ml 8N HCl. After aqueous work-up the crystalline ketone (mp. 107°C) was redissolved in 10 ml of toluene and 5 equivalents DIBAL in toluene were added at 0°C. After stirring for 10 minutes the reaction mixture was allowed to warm up to room temperature and stirred for additional 30 minutes. After aqueous work-up the diol was purified on silica gel and acylated as described above (compound **14**). 122 mg (40%) **28** (mp. 77°C) were obtained after chromatography.
^{1}H-NMR ($CDCl_3$): 0.99 (s, 3H), 1.01 (s, 3H), 1.13 (d, J=7 Hz, 3H), 1.56 - 1.65 (m, 1H), 1.65 - 1.83 (m, 2H), 1.94 - 2.04 (m, 2H), 2.01 (s, 3H), 2.02 (s, 3H), 2.06 - 2.20 (m, 2H), 2.57 (ddt,

J=12.8 Hz, J=3.8 Hz, J=0.8 Hz, 1H), 2.86 - 3.02 (m, 1H), 4.97 - 5.05 (m, 1H), 5.30 - 5.40 (m, 1H)
^{13}C-NMR ($CDCl_3$): 17.6 (q), 21.1 (q), 22.1 (q), 25.6 (t), 26.5 (q), 26.8 (q), 29.9 (t), 36.6 (s), 37.4 (d), 37.4 (t), 38.0 (d), 39.2 (d), 66.7 (d), 71.6 (d), 140.9 (s), 148.0 (s), 170.9 ( ), 171.0 (s)
IR ($CHCl_3$): 2940, 1720, 1430, 1375, 1250, 1170, 1020 cm^{-1}
MS: 306 (M^+, 9%), 246 (4), 204 (32), 176 (18), 135 (32), 91 (28), 43 (100); HRMS: found 306.1841 ($C_{18}H_{26}O_4$) calculated 306.1831

[4,11,11-Trimethyl-bicyclo[5.3.1]undecane-2,5-dione-6,9-diyl]acetate **29**

To a solution of 25 mg (0.1 mmol) OsO_4 and 122 mg (0.4 mmol) **28** in 5 ml THF 330 mg $NaIO_4$ dissolved in 3 ml water were added dropwise. After stirring for 30 minutes at room temperature $NaHSO_3$ was added. After aqueous work-up and crystallisation from ether/hexane 54 mg (40%) **29** (mp. 199°C) were isolated.
^{1}H-NMR ($CDCl_3$): 1.17 (d, J=6 Hz, 3H, H-14), 1.21 (s, 3H, H-12), 1.26 (s, 3H, H-13), 1.63 (ddd, J=14.3 Hz, J=9.9 Hz, J=8.7 Hz, 1H, H-10), 1.94 - 2.02 (ddd, J=14.3 Hz, J=9.3 Hz, J=5.4 Hz, 1H, H-10'), 2.02 (s, 3H, H-16), 2.04 (s, 3H, H-18), 2.13 - 2.30 (m, 4H, H-3,7,8,8'), 2.62 (t, J=9 Hz, 1H, H-1), 3.11 (ddt, J=12.5 Hz, J=6 Hz, J=1.8 Hz, 1H, H-3'), 3.17 (t, J=12.5 Hz, 1H, H-4), 5.08 (d, J=4.2 Hz, 1H, H-6), 5.12 - 5.20 (dddd, J=10.2 Hz, J=7.2 Hz, J=7.2 Hz, J=5.4 Hz, 1H, H-9)
^{13}C-NMR ($CDCl_3$): 19.4 (q), 20.5 (q), 21.5 (q), 24.3 (t), 27.8 (t), 28.2 (q), 33.2 (s), 36.4 (q), 42.3 (d), 45.9 (d), 47.2 (t), 56.5 (d), 66.3 (d), 79.6 (d), 170.7 (s), 170.8 (s), 211.5 (s), 211.6 (s)
IR ($CHCl_3$): 3010, 2980, 2930, 1710, 1680, 1450, 1360, 1100 cm^{-1}
MS: 338 (M^+, 5%), 310 (61), 278 (8), 250 (18), 236 (20), 208 (100), 180 (21), 153 (92); HRMS: found 338.1731 ($C_{18}H_{26}O_6$) calculated 338.1729

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