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Novel Tandem Reactions to Taxane A,B-Ring Systems

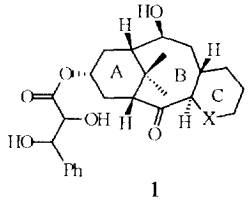
Rolf Jansen, Janna Velder and Siegfried Blechert*

Institut für Organische Chemie, C3, Technische Universität Berlin, Straße des 17. Juni 135, D-10623 Berlin, Germany

Abstract: A novel ring enlargement methodology and its application to taxane A,B-ring synthesis is introduced. In a one pot-procedure an elimination-epoxidation sequence starting from ***5*** *leads to molecules of type* ***6*** *which can be transformed into taxane A,B-ring systems via a tandem reaction. A retroaldol-epoxidation sequence starting from* ***15*** *yields taxane A,B-ring systems suitably functionalized for Diels-Alder reactions.*

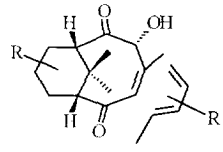
INTRODUCTION

As a part of our investigations on the structure-activity relationship of taxoids we synthesized tricyclic taxoids **1** (Figure 1). We demonstrated their biological activity although these molecules contain major simplifications as compared to natural products.[1,2] A [2+2] photocycloaddition is the key step for the introduction of the C ring in the synthesis of such taxoids. Although the [2+2] photocycloaddition is a reaction of great versatility, access to certain targets proved to be difficult. Aiming at further variation in the C ring portion we have been interested in establishing the C ring by a Diels-Alder reaction between taxane A,B-ring fragments as dienophiles and differentially substituted dienes **2** (figure 1).[3]



1

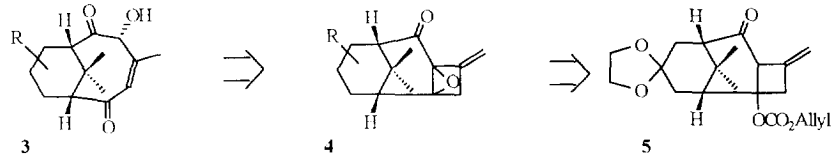
X = O, CH_2



2

Figure 1: Synthetic, biologically active taxoids **1** and the Diels-Alder approach **2** leading to further variation in the C-ring portion.

Accordingly, we developed a methodology leading to suitably functionalized eight-membered rings. They should contain a completely oxygenated B-ring with an activated double bond suitable for the envisioned Diels-Alder reaction. The retrosynthetic analysis of A,B-ring systems of type **3** shows that we could achieve our purpose by developing a ring enlargement. The target can be transformed into epoxides **4** which should be accessible from **5**, a known intermediate from our taxoid synthesis. The allyl carbonate moiety in **5** can be eliminated under basic conditions establishing an α,β-unsaturated ketone which could be selectively epoxidized by nucleophilic attack. The diol available by epoxide opening should furnish **3** under retroaldol conditions.



Scheme 1

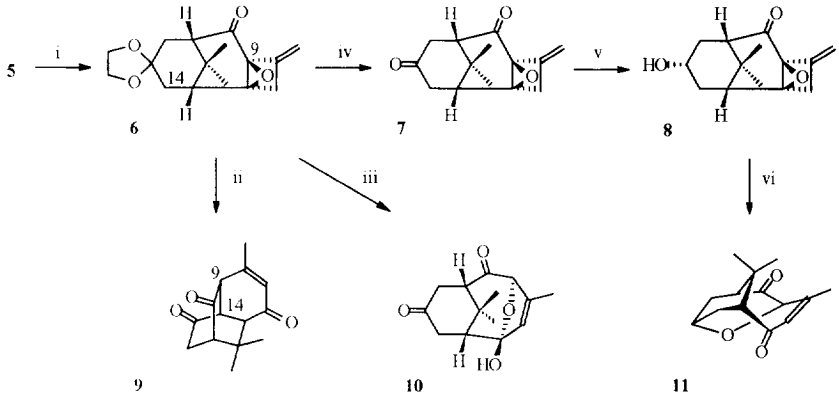
RESULTS AND DISCUSSION

In agreement with our concept the allyl carbonate functionality of **5** was eliminated under basic conditions to create an α,β-unsaturated carbonyl system which was epoxidized using H_2O_2 under basic conditions in a one pot procedure.[4] The epoxidation reaction afforded **6**, exclusively. The stereochemistry was assigned on basis of nuclear Overhauser experiments.

The highly strained skeleton of **6** proved to be unexpectedly stable. Under basic conditions in polar and protic solvents like methanol no epoxide opening could be achieved. Use of a two phase system of dichloromethane and perchloric acid[5] lead to the patchouli type skeleton **9** which can be rationalized by a CC-connection between C-14 and C-9 (taxane numbering) following deketalization.

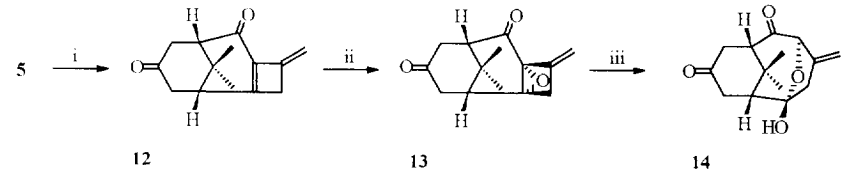
We assume that CC-bond formation is caused by the CH-acidity at C-14. Under similar conditions we isolated the deketalized intermediate **7**. Intramolecular ring closure can be avoided by reduction to **8** using K-Selectride®.[6] Alcohol **8** was treated under the same conditions as **6** affording the bridged taxane A,B-ring system **11**. Although **11** shows the properties required by the retrosynthetic analysis we preferred a process avoiding ether formation, because the ether bridge in the taxane skeleton was assumed to be very stable.

The problem was solved by using trimethylsilyl iodide (TMSI). TMSI as a Lewis acid is able to activate the epoxide. At the same time the iodide anion reacts as a strong nucleophile soluble in dichloromethane which avoids intramolecular reactions and on the other hand is a good leaving group in the subsequent domino process. Thus, aqueous work up results in the completely oxygenated building block **10**.[7]



Scheme 2: i) K_2CO_3, H_2O_2, MeOH, rt ii) $HClO_4$, CH_2Cl_2, heat iii) TMSI, CH_2Cl_2, 0°C iv) HCl, CH_3CN, rt v) K-Selectride^R, THF, -78 °C vi) $HClO_4$, CH_2Cl_2.

In contrast to ketal-bearing **5,** ketone **12** [8] undergoes selective α-epoxidation to **13**. Under Bronsted acidic conditions in acetonitrile at room temperature, epoxide **13** was easily transformed into **14** *via* a tandem reaction. The reaction is initiated by nucleophilic attack of water to the oxirane moiety followed by retroaldol reaction and intramolecular semiketal formation.

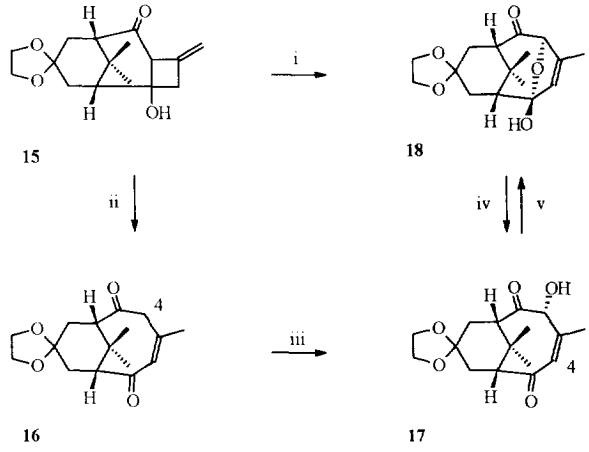


Scheme 3: i) BF_3OEt_2 cat., acetone, rt; $Pd(PPh_3)_4$ cat., morpholine, THF, rt ii) K_2CO_3, H_2O_2, MeOH, rt iii) HCl, CH_3CN, rt.

Although our concept of the synthesis was realized in principle, we had to modify our strategy, because the double bonds in the taxane A,B-ring systems **10** and **14** lacked the activation required for the envisaged Diels-Alder reaction. We decided to invert the sequence epoxidation followed by a retroaldol reaction. The advantage of this strategy should be the conservation of the ketal in ring A which should strain the taxane A,B-ring system and avoid the formation of the semiketal structure in ring B.

The individual steps of the sequence were investigated. The retroaldol reaction from **15** to **16** containing an α,β-unsaturated carbonyl system suitable for nucleophilic epoxidations was known. Epoxidation of **16** under basic conditions yielded **17** directly. In the first step the double bond is selectively attacked from the α-side and in the second step the epoxide is cleaved leading to the stereochemically uniform allyl alcohol structure. The smooth cleavage of the oxirane ring is caused by the CH-acidity at C-4. If the reaction mixture is stirred too long, the formation of semiketal **18** is observed. Because all reactions were carried out under very similar conditions, it was possible to design this four step sequence as a one pot tandem process from **15** to **18** in 70% yield.

The semiketal of **18** could be opened quantitatively under Lewis acidic conditions.[9] The reaction is assumed to be promoted by the additional ringstrain caused from the ketal at ring A. Product **17** contains the substitution pattern of the target structure.



Scheme 4: i) KOH, H_2O_2, EtOH, rt ii) KO^{t}Bu, HO^{t}Bu, rt iii) K_2CO_3, H_2O_2, MeOH, rt iv) $AlEt_3$, CH_2Cl_2, -78 °C v) KOH, EtOH.

In summary we present novel tandem reactions leading to functionalized eight-membered rings useful in the synthesis of taxane A,B-ring systems.

EXPERIMENTAL

General remarks

NMR spectra were taken on Bruker AM 400 and AC 200 spectrometers. ^{13}C multiplicities were determined using DEPT pulse sequences. IR spectra were taken on a Nicolet FTIR 750 spectrometer. Mass spectra were recorded on Varian MAT 711 and 44 S spectrometers. TLC analyses were performed on Merck 60 F 254 silica gel plates. Silica gel 60 (240-400 mesh) was used for silica gel chromatography. THF was freshly distilled from potassium and dichloromethane was freshly distilled from CaH_2.

9-(1,3-Dioxolan)11,11-dimethyl-4-methylene-12β-oxatetracyclo[5.3.1^{1,7}.1^{2,5}.0^{2,5}]dodec-6-one (6): To a solution of **5** (250 mg, 0.69 mmol) in 5 mL methanol were added K_2CO_3 (193 mg, 1.4 mmol) and 0.35 mL 60% H_2O_2. The reaction mixture was stirred overnight at ambient temperature and then poured into brine/CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined oganic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and flash chromatography (petroleum ether PE : tertbutyl methyl ether MTBE 2:1) of the residue gave **6** (155 mg, 0.56 mmol, 82% yield).
^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, CH_3, 3H), 1.24 (s, CH_3, 3H), 1.85 - 1.95 (m, 2H), 2.07 - 2.17 (m, 2H), 2.27-2.37 (m, 2H), 2.35 (ddd, J = 13.0, 1.5, 1.5 Hz, 1H), 2.99 (ddd, J = 13.0, 2.0, 2.0 Hz, 1H), 3.84 (s, 4H), 4.8 (ddb, J = 1.5, 1.5 Hz, 1H), 5.27 (ddb, J = 2.0, 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 28.31 (CH_3), 31.03 (CH_3), 33.80 (C), 33.85 (CH_2), 37.41 (CH), 38.37 (CH_2), 38.65 (CH_2), 54.10 (CH), 60.43 (C), 64.05 (C), 64.12 (CH_2), 64.23 (CH_2), 105.98 (C), 106.59 (CH_2), 144.15 (C), 204.24 (C). IR ($CHCl_3$): ν[cm^{-1}] = 3017 m, 2953 s, 1702 s, 1231 m, 1102 s, 1058 s, 1033 s. HRMS: $C_{16}H_{20}O_4$ calc. 276.1362 found 276.1362 . MS: 276 (M^+, 26), 260 (8), 233 (8), 221 (16), 190 (8), 141 (28), 107 (18), 91 (24), 83 (32), 69 (42), 55 (100).

11,11-Dimethyl-4-methylene-12α-oxatetracyclo[5.3.1^{1,7}.1^{2,5}.0^{2,5}]dodec-6,9-dione (13): To a solution of **12** (300 mg, 1.4 mmol) in 10 mL methanol were added K_2CO_3 (600 mg, 1.8 mmol) and 1 mL 60% H_2O_2.The reaction mixture was stirred overnight at ambient temperature and then poured into brine/CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined oganic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and flash chromatography (PE/MTBE 1:1) of the residue gave **13** (130 mg, 0.56 mmol, 40% yield).
^1H NMR (200 MHz, $CDCl_3$): δ = 1.12 (s, CH_3, 3H), 1.20 (s, CH_3, 3H), 2.20- 2.80 (m, 8H), 5.04 (dd, J = 1.0, 1.0 Hz, 1H), 5.50 (dd, J = 2.0, 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 24.95 (CH_3), 26.29 (CH_3), 37.58 (CH_2), 39.18 (CH), 39.62 (CH_2), 40.04 (CH_2), 42.58 (C), 53.06 (CH), 61.59 (C), 71.63 (C), 110.93 (CH_2), 138.66 (C), 201.03 (C), 205.23 (C). IR ($CHCl_3$): ν[cm^{-1}] = 3024 m, 2967 s, 1706 s, 1670 m, 1409 s, 1232 m, 1032 m. HRMS: $C_{14}H_{16}O_3$ calc. 232.1099 found 232.1099. MS: 232 (M^+, 16), 204 (18), 189 (10), 161 (20), 135 (100), 107 (16), 69 (46), 55 (32).

11,11-Dimethyl-4-methylene-12β-oxatetracyclo[5.3.1^{1,7}.1^{2,5}.0^{2,5}]dodec-6,9-dione (7): To a solution of **6** (55 mg, 0.20 mmol) in 5 mL acetonitrile were added 2 mL 18% aqu. HCl. The reaction mixture was stirred overnight at ambient temperature. The solution was poured into CH_2Cl_2/sat. aqu. $NaHCO_3$, the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and after filtration the solvent was removed under reduced pressure to yield **7** (44 mg, 0.19 mmol, 95% yield).
^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, CH_3, 6H), 2.35 (ddd, J = 17.0, 1.5, 1.5 Hz, 1H), 2.5 (m, 2H), 2.55 ddd, J = 16.5, 2.0, 2.0 Hz, 1H), 2.65 (ddd, J = 5.0, 2.0, 2.0 Hz, 1H), 2.79 (dd, J = 17.0, 7.5 Hz, 1H), 2.9 (ddd, J = 14.0, 2.0, 2.0 Hz, 1H), 2.97 (ddb, J = 16.5, 5.0 Hz, 1H), 4.92 (sb, 1H), 5.29 (ddb, J = 2.0, 2.0 Hz,1H). IR ($CHCl_3$): ν[cm^{-1}] = 3024 m, 2926 s, 1712 s, 1418 m, 1204 s, 1122 m. HRMS: $C_{14}H_{16}O_3$ calc. 232.1099 found 232.1099. MS: 232 (M^+, 22), 216 (3), 189 (6), 175 (4), 161 (10), 147 (5), 135 (100), 69 (52), 55 (46).

9α-Hydroxy-11,11-dimethyl-4-methylene-12β-oxatetracyclo[5.3.1^{1,7}.1^{2,5}.0^{2,5}]dodec-6-one (8): To a solution of 7 (40 mg, 0.17 mmol) in 2 mL dry THF were added dropwise 0.17 mL 1 M K-Selectride at -78°C and it was stirred for 2 h. The reaction was quenched with sat. aqu. NH_4Cl and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried over $MgSO_4$ and after filtration the solvent was removed under

reduced pressure. The residue was purified by flash chromatography (PE/MTBE 1:1) and **8** (17 mg, 0.073 mmol, 43% yield) was isolated.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, CH_3, 3H), 1.26 (s, CH_3, 3H), 1.85 (ddd, J = 15.0, 5.0, 2.0 Hz,1H), 1.98 - 2.08 (m, 2H), 2.2 -2.3 (m, 2H), 2.35 (ddd, 15.0, 6.0, 4.0 Hz, 1H), 2.48 (ddd, J = 13.0, 1.5, 1.5 Hz, 1H), 2.88 (ddd, J = 13.0, 2.0, 2.0 Hz, 1H), 4.05 - 4.1 (m, 1H), 4.8 (ddb, J = 1.5, 1.5 Hz, 1H), 5.28 (ddb, J = 2.0, 2.0 Hz, 1H). IR ($CHCl_3$): ν[cm^{-1}] = 3612 m, 3022 m, 2963 m, 1699 s, 1204 m, 1066 m. HRMS: $C_{14}H_{18}O_3$ calc. 234.1256 found 234.1256. MS: 234 (M^+, 2), 232 (5), 191 (3), 175 (3), 135 (100), 99 (8), 87 (12), 69 (14), 59(22).

4,11,11-Trimethyl-12-oxatricyclo[5.3.1^{1,7}.1^{5,9}]dodec-3-ene-2,6-dione (11): To a solution of **8** (24 mg, 0.12 mmol) in 5 mL CH_2Cl_2 were added 0.1 mL H_2O and 0.1 mL $HClO_4$. The two phase system was stirred 40 min. The reaction was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and after filtration the solvent was removed under reduced pressure. The product was purified by preparative thin layer chromatography (PE/MTBE 1:1) yielding **11** (11 mg, 0.05 mmol, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, CH_3, 3H), 1.26 (s, CH_3, 3H), 2.05 (d, J = 1.5 Hz, CH_3, 3H), 2.1 - 2.4 (m, 5H), 2.75 (db, J = 7.0 Hz, 1H), 4.3 (m, 1H), 4.6 (sb, 1H), 5.85 (qb, J = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 24.24 (CH_3), 26361 (CH_3), 28.04 (CH_2), 30.97 (CH_3), 31.63 (CH_2), 34.39 (C), 53.31 (CH), 56.49 (CH), 65.88 (CH), 80.41 (CH), 127.21 (CH), 150.04 (C), 203.24 (C), 206.34 (C). IR ($CHCl_3$): ν[cm^{-1}] = 3031 m, 2978 s, 1716 s, 1684 s, 1634 m, 1104 m, 909 m. HRMS: $C_{14}H_{18}O_3$ calc. 234.1256 found 234.1256 . MS: 234 (M^+, 22), 232 (18), 206 (28), 178 (10), 161 (12), 137 (83), 109 (98), 98 (90), 69 (100), 67 (100).

4,11,11-Trimethyltricyclo[5.3.1.0^{3,8}]undec-4-ene-2,6,9-trione (9): To a solution of **6** (20 mg, 0.072 mmol) in 5 mL $CHCl_3$ were added 0.1 mL H_2O and 0.1 mL $HClO_4$. The two phase system was refluxed. The deketalization and formation of the product could be monitored by thin layer chromatography (PE/MTBE 1:1). After cooling H_2O was added, the organic layer separated, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and flash chromatography (PE/MTBE 5:1) of the residue gave **9** (8 mg, 0.034 mol, 47% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (s, CH_3, 3H), 1.15 (s, CH_3, 3H), 1.88 (dd, J = 1.5, 1.5 Hz, CH_3, 3H), 2.4 - 2.8 (m, 4H), 3.62 (m, 1H), 3.7 (m, 1H), 5.4 (dq, J = 6.0, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 23.0 (CH_3), 25.1 (CH_3), 28.4 (CH_3), 31.8 (C), 36.7 (CH_2), 51.2 (CH), 53.4 (CH), 54.8 (CH), 68.4 (CH), 121.5 (CH), 139.5 (C), 204.5 (C), 204.7 (C), 205.1 (C). IR ($CHCl_3$): ν[cm^{-1}] = 2961 m, 1744 m, 1712 s, 1414 m, 1378 m, 1250 m, 1141 m, 1016 m. HRMS: $C_{14}H_{16}O_3$ calc. 232.1099 found 232.1099 . MS: 232 (M^+, 62), 204 (18), 189 (14), 176 (14), 161 (42), 141 (56), 133 (32), 121 (28), 108 (86), 96 (94), 83 (98), 69 (100), 55 (66).

2-Hydroxy-4,11,11-trimethyl-12-oxatricyclo[5.3.1^{1,7}.1^{2,5}]dodec-3-ene-6,9-dione (10): To a solution of epoxide **6** (20 mg, 0.07 mmol) in 2 mL $CHCl_3$ were added 0.03 mL trimethylsilyl iodide at ambient temperature. After 20 min the reaction mixture was quenched with 2 mL Na_2SO_3 solution and the two phase system was stirred vigorously for another 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and after filtration the solvent was removed under reduced pressure. The resulting oil was purified by flash chromatography (PE/MBE 1:1). **10** was isolated as a colourless oil (8 mg, 0.032mmol, 45% yield).

^{1}H NMR (400 MHz, C_6D_6): δ = 0.7 (s, CH_3, 3H), 0.85 (s, CH_3, 3H), 1.47 (sb, CH_3, 3H), 1.87 (ddd, J = 6.0, 1.5, 1.5 Hz, 1H), 2.3 (dd, J = 18.0, 6.0 Hz, 1H), 2.32 (dd, J = 18.0, 9.5 Hz, 1H), 2.38 (ddd, J = 9.5, 1.5, 1.0 Hz, 1H), 2.62 (ddd, J = 18.0, 1.5, 1.0 Hz, 1H), 2.78 (sb, OH), 3.45 (ddd, J = 18.0, 1.5, 1.0 Hz, 1H), 4.48 (sb, 1H), 5.0 (qb, J = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 12.6 (CH_3), 28.9 (CH_3), 30.4 (CH_3), 34.1 (C), 37.9 (CH_2), 38.6 (CH_2), 59.4 (CH), 60.6 (CH), 88.5 (CH), 113.1 (C), 130.1 (CH), 139.9 (C), 206.5 (C), 209.4 (C). IR ($CHCl_3$): ν[cm^{-1}] = 3581 m, 3390 m, 3026 m, 2915 s, 1707 s, 1632 m, 1261 m, 1229 m, 1081 m, 1044 s. HRMS: $C_{14}H_{18}O_4$ calc. 250.1205 found 250.1205 . MS: 250 (M^+, 7), 234 (3), 217 (100), 206 (3), 189 (11), 149 (15), 119 (30), 91 (24), 69 (32), 55 (20).

2-Hydroxy-11,11-dimethyl-4-methylene-12-oxatricyclo[5.3.1^{1,7}.1^{2,5}]dodec-6,9-dione (14): A solution of epoxide **13** (20 mg, 0.08 mmol), 5 mL CH_3CN and 0.2 mL 18% aqu. HCl was stirred for 24 h at ambient temperature. The reaction mixture was poured into H_2O/CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and after filtration the solvent was removed under reduced pressure to give **14** (12 mg, 0.05 mmol, 56% yield).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, CH_3, 3H), 1.40 (s, CH_3, 3H), 2.45 (ddd, J = 5.5, 1.5, 1.5 Hz, 1H), 2.57 (dd, J = 18.0, 1.0 Hz, 1H), 2.65 (dd, J = 9.0, 1.5 Hz, 1H), 2.75 (dd, J = 18.0, 9.0 Hz, 1H), 2.82 (dd, J = 18.0, 5.5 Hz, 1H), 3.53 - 3.6 (m, 2H), 5.0 (sb, 1H), 5.15 (ddd, J = 2.0, 2.0, 1.5 Hz, 1H), 5.37 (ddd, J = 2.0, 2.0, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 29.1 (CH_3), 31.9 (CH_3), 34.9 (C), 37.9 (CH_2), 42.1 (CH_2), 47.4 (CH_2), 57.8 (CH), 58.6 (CH), 87.7 (CH), 110.2 (CH_2), 111.1 (C), 142.4 (C), 205.2 (C), 210.6 (C). IR (CCl_4): ν[cm^{-1}] = 2967 s, 1719 s, 1684 s, 1062 s. HRMS: $C_{16}H_{16}O_3$ calc. 232.1099 found 232.1099 . MS: 232 (M$^+$, 66), 217 (9), 204 (12), 189 (16), 161 (14), 150 (22), 135 (60), 101 (86), 69 (100).

9-(1,3-Dioxolan)-5-hydroxy-4,11,11-trimethylbicyclo[5.3.1]undec-3-ene-2,6-dione (17): To a solution of **16** (10 mg, 0.036 mmol) in 2 mL methanol were added K_2CO_3 (20 mg, 0.06 mmol) and 0.1 mL 60% H_2O_2. The reaction mixture was stirred overnight at ambient temperature. The solution was poured into brine/MTBE, the aqueous layer was extracted with MTBE and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure at 40 °C and the residue was purified by flash chromatography (PE/MTBE 1:1). 7 mg (0.024 mmol, 65% yield) of the hydroxylated product **17** were isolated.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, CH_3, 3H), 1.24 (s, CH_3, 3H), 1.98 (d, J = 1.0 Hz, CH_3, 3H), 2.18 - 2.44 (m, 4H), 2.57 (m, 1H), 2.86 (dm, J = 4.0 Hz, 1H), 3.78 (s, 4H), 4.76 (s, 1H), 5.85 (dq, J = 1.1, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 24.06 (CH_3), 25.62 (CH_3), 30.57 (CH_3), 30.79 (CH_2), 34.25 (C), 37.70 (CH_2), 56.1 (CH), 59.73 (CH), 61.73 (CH_2), 62.89 (CH_2), 81.56 (CH), 96.95 (C), 127.39 (CH), 148.24 (C), 203.15 (C), 206.55 (C). IR ($CHCl_3$): ν[cm^{-1}] = 3609 m, 2953 s, 1718 s, 1652 s, 1232 s, 1087 s, 1060 s. HRMS: $C_{16}H_{22}O_4$ calc. 294.1467 found 294.1467. MS: 294 (M$^+$, 25), 233 (30), 169 (57), 141 (57), 125 (100), 10941 (87), 71 (73), 69 (73), 55 (28).

9-(1,3-Dioxolan)-2-hydroxy-4,11,11-trimethyl-12-oxatricyclo[5.3.1^{1,7}.1^{2,5}]dodec-3-ene-6-one (18): To a solution of aldol **15** (191 mg, 0.69 mmol) in 6 mL 1M KOH/Ethanol were added 1mL 60% H_2O_2. The reaction mixture was stirred for 14 h at ambient temperature. The tandem reaction was monitored by thin layer chromatography. The colourless precipitate was filtered off and the filtrate was poured into H_2O/MTBE. The aqueous layer was extracted with MTBE and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and flash chromatography of the residue gave **18** as a colourless foam (140 mg, 0.48 mmol, 70% yield).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, CH_3, 3H), 1.24 (s, CH_3, 3H), 1.8 (sb, CH_3, 3H), 2.0 (db, J = 7.0 Hz, 1H), 2.27 (dd, J = 16.0, 7.0 Hz, 1H), 2.30 (dd, J = 7.0, 7.0 Hz, 1H), 2.42 (db, J = 7.0 Hz, 1H), 2.44 (db, J = 7 Hz, 1H), 2.84 (db, J = 16 Hz, 1H), 3.8 - 4.1 (m, 4H), 4.76 (sb, 1H), 5.62 (sb, 1H). ^{13}C NMR ($CDCl_3$): δ = 12.7 (CH_3), 29.7 (CH_3), 30.9 (CH_3), 33.6 (C), 34.9 (CH_2), 36.1 (CH_2), 50.8 (CH), 59.1 (CH), 63.3 (CH_2), 64.0 (CH_2), 88.5 (CH), 107.5 (C), 112.3 (C), 131.0 (CH), 139.8 (C), 211.0 (C). IR ($CHCl_3$): ν[cm^{-1}] = 3592 w, 3400 m, 2973 m, 1712 s, 1666 m, 1413 m, 1194 m, 1060 m. HRMS: $C_{16}H_{22}O_5$ calc. 294.1467 found 294.1467 . MS: 294 (M$^+$, 18), 267 (21), 205 (10), 180 (100), 141 (100), 86 (94), 57 (82).

Transformation from 18 to 17 : To a solution of **18** (16 mg, 0.054 mmol) in 10 mL dry CH_2Cl_2 were added 0.45 mL 1 M triethylaluminium in hexane (0.45 mmol) at -78°C. After stirring for 2 h the reaction was quenched by 1 M aqueous oxalic acid and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. 15 mg (0.051 mmol, 94% yield) of **17** were isolated.

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