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Synthesis of New Taxoids

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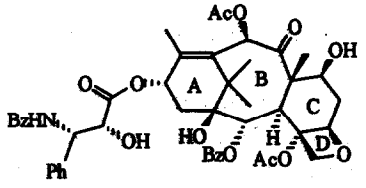
Abstract: *[2+2] Photocycloadditions between enone 2 and 2,3-dihydropyran derivatives lead to a number of interesting intermediates 3a-e for taxoid synthesis. Following this strategy the stereoselective synthesis of a biologically active taxoid mimicking the polarity of the CD ring portion in taxol is reported.*

INTRODUCTION

Investigations on the structure-activity relationship of taxoids are of great interest for drug-design.[1] The availability of taxol from natural sources is very limited and the low solubility of taxol in water means a serious difficulty for its application in cancer therapy.[2,3] Both circumstances can be overcome by the synthesis of easily accessible taxoids with better solubility in water. Recently we reported the first synthesis of a biologically active taxoid.[4] Continuing our program we designed analogues which mimic the polarity of the CD ring portion in taxol. We used our earlier developed modified deMayo methodology[5] to construct the taxane skeleton and introduced ether and ketal functionalities in the C ring at the [2+2] photocycloaddition step. [2+2] Photocycloaddition between enone 2 and dihydropyran derivatives led regiochemically controlled to tetracyclic systems which were transformable into the envisaged structures.



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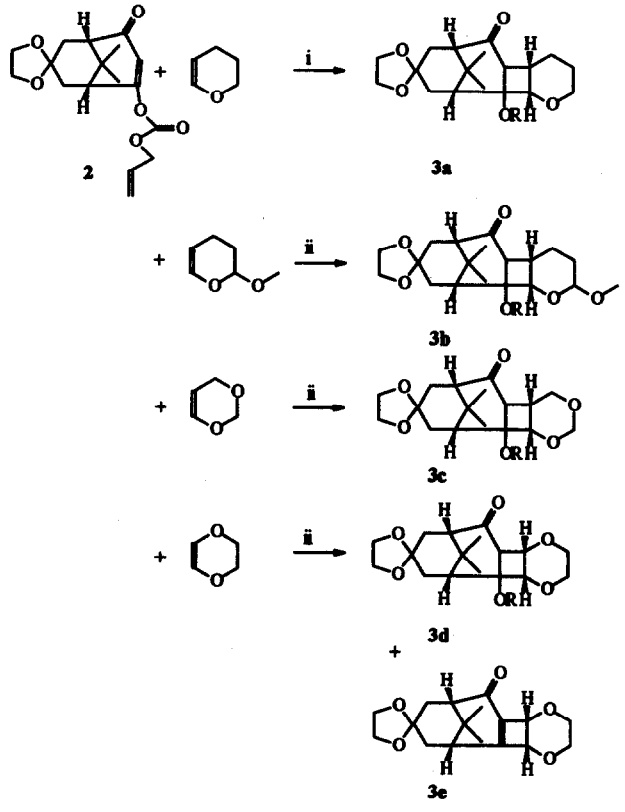
RESULTS AND DISCUSSION

The [2+2] photocycloaddition represents the key step of our strategy to introduce oxygen functionalities in the C ring. To demonstrate the flexibility of this concept enone **2** was irradiated in the presence of several

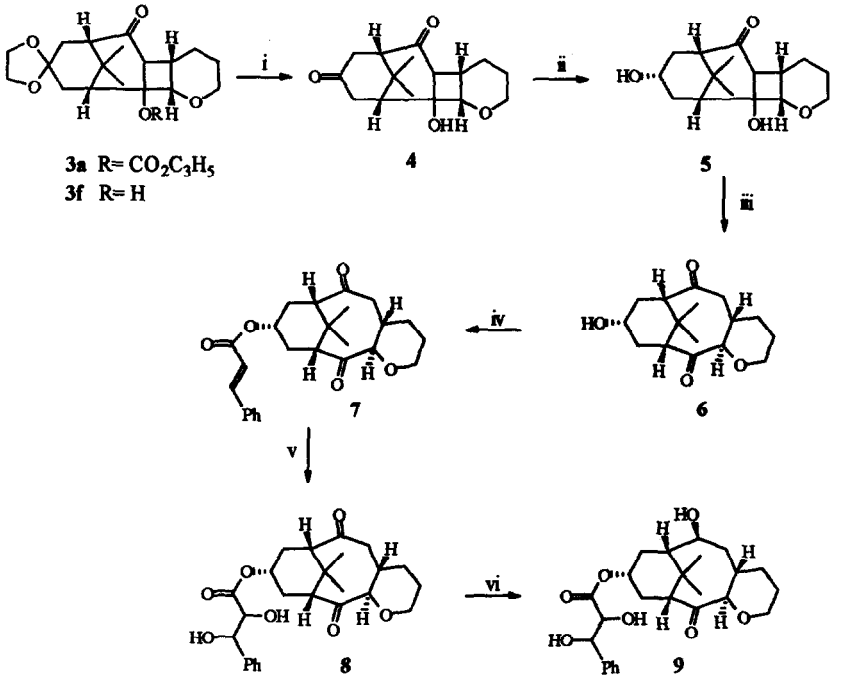
dihydropyrans (Scheme 1) with a high pressure mercury lamp (500 W) or a Xe arc lamp (1000 W, $\lambda > 325$ nm). The [2+2] photocycloaddition of enone **2** with 2,3-dihydropyran was carried out in dichloromethane at -60 °C. 2,3-Dihydropyran was added to **2** regiochemically and stereochemically controlled within 1.5 hours to give **3a** in 84% yield. The regiochemistry of the addition was proved by the ^{1}H NMR spectrum and the stereochemistry was established by Nuclear Overhauser effects between H-3, H-8 (taxane numbering) and the protons of a methyl group. The stereochemistry at C_2 and C_9 (taxane numbering) was not assigned because these stereocenters were planarized in the following retro-aldol reaction.



Scheme 1: i) hν, -60 °C ii) hν, rt, R=$CO_2C_3H_5$, only main diastereomer shown.

2-Methoxy-2,3-dihydropyran reacted with enone **2** in dichloromethane at 15 °C to yield **3b** in 65%. A 3 : 1 ratio from the β- and α-side attack was observed. The stereochemistry was proved by comparison of the ^{1}H NMR data of **3b** with the data of **3a**. Under the same conditions 1,3-dioxene added to enone **2** giving a 3 : 1 mixture of the diastereomers resulting from the β- and α-side attack. The yield of the photocycloaddition based on consumed starting material was good (79%). The reaction rate, however, was quite low compared with the other examples and by longer reaction times the yield dropped. To determine the stereochemistry of **3c**, the allyl carbonate functionality was eliminated and the ketal cleaved. The results of the NOE experiments of the obtained product were consistent with the assigned stereochemistry.[6] 1,4-Dioxene reacted with enone **2** to **3d**. Prolonged

irradiation times led to a photochemically induced elimination of **3d** to **3e** in good yield. Compound **3e** represents another interesting intermediate towards higher functionalized taxoids *via* oxidative cleavage of the double bond.[7] With the compounds of type **3** a number of interesting intermediates for the synthesis of taxoids are described.



Scheme 2: i) $Pd(Ph)_4$cat., morpholine, THF, rt ; BF_3·OEt_2 cat., acetone, rt. ii) L-Selectride^R, THF, -78 °C. iii) KO^{t}Bu/^{t}BuOH, 70 °C. iv) Cinnamoyl chloride, Et_3N, DMAP cat., 0 °C. v) NMO, OsO_4 cat., rt vi) $NaBH_4$, MeOH, rt.

The synthetic potential of these tetracyclic compounds is exemplified by the transformation of **3a** into the taxoid **9** (Scheme 2). The allyl carbonate functionality of compound **3a** was cleaved almost quantitatively using morpholine and catalytic amounts $Pd(PPh_3)_4$ in tetrahydrofuran. Treatment of the resulting alcohol **3f** with BF_3·OEt_2 in acetone gave compound **4** in 78% yield.

Chemoselective and diastereoselective reduction of **4** at C-13 from the β-side could be achieved using L-Selectride^R as the reducing agent. The observed selectivities can be rationalized by sterical hindrance. The following retro-aldol reaction was carried out at 70 °C in ^{t}BuOH/ ^{t}BuOK. Under these conditions C-3 (taxane numbering) was epimerized giving tricyclic compound **6** with the correct *trans*-connected ring C. The *trans*-connection was assigned on the basis of the 10.5 Hz coupling constant between the vicinal protons H-3 and H-8 (taxane numbering). *cis* Hydroxylated cinnamoyl acid was chosen to demonstrate that also in the side chain major simplifications were possible without loss of biological activity. The esterification of compound **6** at C-13 proceeded in 70 % yield after changing the esterification agent from cinnamoyl anhydride to cinnamoyl chloride. The *cis* hydroxylation of compound **7** was carried out with N-methyl morpholine N-oxide (NMO) and

catalytic amounts of OsO_4 to give **8** in 94% yield. The ketone at C-10 was reduced diastereochemically controlled with $NaBH_4$ to β-alcohol **9**, the envisaged taxoid. In contrast to our earlier observations we found only one of the two diastereomers that result from the introduction of the side chain. It was assumed that the hydroxylation of the double bond was directed by complexation of OsO_4 at the oxygen in ring C.

Reports from Nicolaou[8] and our group[4] indicated that only one of the two diastereomers, which are formed when the side chain is established, is biologically active.The *in vitro* tubulin test of taxoid **9** proved that we synthesized the biologically active diastereomer. The biological activity of compound **9** was comparable to the one of our earlier synthesized carbocyclic taxoid.[4]

In summary, a variety of interesting intermediates toward the synthesis of taxoids are accessible and a typical example for the transformation of an intermediate to a biologically active taxoid is given. Further synthetic and biological studies on structure-activity relationship of taxoids are in progress.

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.

Allyl (13-(1,3-dioxolan)-15,15-dimethyl-4-oxatetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$] pentadecan-10-onyl) carbonate 3a: A solution of enone **2** (1.5 g, 4.7 mmol) and dihydropyran (20 mL, 198 mmol) in 200 mL CH_2Cl_2 was degassed by ultrasound while bubbling argon through the reaction mixture for 10 min. The solution was irradiated with a mercury high pressure lamp (500 W) for 1.5 h at -60 °C. Solvent and unchanged dihydropyran were removed by distillation. Flash chromatography (petroleum ether (PE) : ^{t}butyl methyl ether (MTBE) = 1 : 1) of the residue gave **3a** (1.58 g, 3.9 mmol , 84% yield).

^1H-NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, CH_3), 1.24 (s, CH_3), 1.75-1.9 (m, 4H) , 1.95-2.05 (m, 2H), 2.15-2.25 (m, 2H), 2.85 (bs, 1H), 3.08 (bd, J = 5 Hz, 1H), 3.5 (dt, J = 6.5, 11.0, 3.7 Hz, 5H), 4.49 (bd, J = 8.0 Hz, 1H), 4.60 (dddd, J = 13., 5.5, 1.0, 1.0 Hz, 1H), 4.67 (dddd, J = 13.0, 5.5, 1.0, 1.0 Hz, 1H), 5.26 (dddd, J = 10.5, 1.0, 1.0, 1.0 Hz, 1H) , 5.38 (dddd , J = 17.0, 1.0, 1.0, 1.0 Hz, 1H) , 5.95 (ddt , J = 17.0, 10.5, 5.5 Hz, 1H). ^{13}C-NMR ($CDCl_3$): δ = 20.61 (CH_2), 24.51 (CH_2), 27.88 (CH_3), 29.82 (CH_3), 31.73 (CH_2), 34.40 (C), 35.81 (CH), 36.27 (CH_2), 41.85 (CH), 53,80 (CH), 55.05 (CH), 62.99 (CH_2), 63.70 (CH_2), 64.20 (CH_2), 68.04 (CH_2), 73.02 (CH), 87.02 (C), 105.81 (C), 118.45 (CH_2), 131,91 (C), 154.12 (C), 216.31 (C). IR ($CHCl_3$): ν[cm^{-1}] = 2800 - 3000 s , 1745 s , 1695 s , 1367 m , 1249 vs , 1175 m , 1113 m , 1066 m. HRMS : $C_{22}H_{30}O_7$ calc. 406.1992 found 406.1992 . MS: 406 (M^+ , 6), 323 (23), 279 (100), 235 (24), 141 (12), 84 (78), 69 (34).

Allyl (13-(1,3-dioxolan)-4-methoxy-15,15-dimethyl-4-oxatetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$] pentadecan-10-onyl) carbonate 3b: A solution of enone **2** (33 mg, 0,1 mmol) and 2-methoxy-2,3-dihydropyran (2mL, 17.5 mmol) in 8 mL CH_2Cl_2 was degassed by ultrasound while bubbling argon through the reaction mixture for 10 min. The solution was irradiated with a Xe arc lamp (1000 W) at ambient temperature for 55 min. Solvent and unchanged 2-methoxydihydropyran were removed by distillation. After flash chromatography (PE : MTBE = 1 : 1) of the residue two diastereomers **3b** were obtained: 21 mg (0.048 mmol, 48 % yield) product of the β-side addition and 7 mg (0.016 mmol, 16 % yield) product of the α-side addition.

Major diastereomer. ^1H-NMR (400 MHz , $CDCl_3$): δ = 1.16 (s , CH_3 , 3H), 1.24 (s, CH_3, 3H), 1.6 - 2.25 (m, 6H), 2.43 (m, 1H), 2.83 (bs, 1H), 3.09 (bd, J = 5.5 Hz, 1H), 3.31 (s, 3H), 3.7 - 4.0 (m, 4H), 4.53 (bd, J = 7.5 Hz, 1H), 5.57 (dddd, J = 13.0, 5.5, 1.0, 1.0 Hz, 1H), 4.68 (dddd, J = 13.0, 5.5, 1.5, 1.5 Hz, 1H), 4.77 (dd, J = 6.0 , 6.0 Hz , 1H), 5.26 (ddt, J = 10.5, 1.5, 1.5 Hz, 1H), 5.37 (ddt, J = 16.0, 1.5, 1.5 Hz, 1H), 5.95 (ddt , J = 16.0, 10.5, 5.5 Hz).IR ($CHCl_3$): ν[cm^{-1}] = 3015 m, 2800 - 3000 s, 1745 s, 1698 s, 1454 m, 1368 s, 1294 s,

1277 s, 1250 s, 1205 s, 1114 s, 1059 s, 1035 s. HRMS : $C_{23}H_{32}O_8$ calc. 436.2097 found 436.2097 MS: 436 (M^+, 6), 323 (22), 303 (24), 279 (96), 235 (20), 219 (12), 167 (10), 141 (20), 114 (40), 86 (50), 73 (100), 58 (70). **Minor diastereomer.** ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, CH_3, 3H), 1.14 (s, CH_3, 3H), 1.9 - 2.4 (m, 6H), 2.66 (m, 1H), 2.77 (bd, J = 6.5 , 1H), 2.87 (bd, J = 5.5, 1H), 3.14 (s, 3H), 3.85 - 4.0 (m, 4H), 4.57 (dddd, J = 13.0, 5.5, 1.0, 1.0 Hz, 1H), 4.68 (dddd, J = 13.0, 5.5, 1.5, 1.5 Hz, 1H), 4.73 (dd, J = 7.5, 1.5 Hz), 4.78 (dd, J = 5.5, 5.5 Hz, 1H), 5.27 (dddd, J = 10.5, 1.5, 1.5, 1.0 Hz, 1H), 5.38 (dddd, J = 17.5, 1.5, 1.5, 1.0 Hz, 1H), 5.96 (ddt, J = 17.5, 10.5, 5.5 Hz, 1H). IR ($CHCl_3$): ν[cm^{-1}] = 3012 m, 2800 - 3000 s, 1746 s, 1696 s, 1454 m, 1368 s, 1249 s, 1205 s, 1135 s, 1051 s, 1030 s. HRMS : $C_{23}H_{32}O_8$ calc. 436.2097 found 436.2097

Allyl (13-(1,3-dioxolan)-15,15-dimethyl-4,6-dioxatetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$] pentadecan-10-onyl) carbonate 3c: A solution of enone **2** (800 mg, 2.21 mmol) and 1,3-dioxene (6.7 g, 78 mmol) in 7 mL CH_2Cl_2 was degassed by ultrasound while bubbling argon through the reaction mixture for 10 min. The solution was irradiated with a Xe arc lamp (1000 W) at 15 °C for 55 minutes. Solvent and unchanged 1.3-dioxene (bp = 78 °C) were removed by distillation. Flash chromatography (PE : MTBE 1 : 1) of the residue gave 628 mg (1.95 mmol, 78 % yield) starting material and 172 mg of diastereomers **3c:** 128 mg (0.31 mmol, 14 % yield) product of the β-side addition and 44 mg (0.11 mmol, 4.9 % yield) product of the α-side addition. **Major diastereomer:** ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, CH_3, 3H), 1.23 (s, CH_3, 3H), 1.6 - 2.2 (m, 6H), 2.82 (ddt, J = 8.5, 6.0, 6.0 Hz, 1H), 2.97 (bs, 1H), 3.32 (bd, J = 6.0 Hz, 1H), 3.7 - 4.0 (m, 4H), 4.02 (d, J = 6.0 Hz, 2H), 4.61 (dddd, J = 13.0, 5.5, 1.5, 1.5 Hz, 1H), 4.67 (dddd, J = 13.0, 5.5, 1.0, 1.0 Hz, 1H), 4.75 (d, J = 5.0 Hz, 1H), 4.77 (dd, J = 8.5, 1.0 Hz, 1), 5.2 (d, J = 5.0 Hz, 1H), 5.27 (dddd, J = 10.0, 1.0, 1.0, 1.0 Hz, 1H), 5.37 (ddd, J = 17.0, 1.5, 1.5, 1.5 Hz, 1H), 5.95 (ddt, J = 17.0, 10.0, 5.5 Hz, 1H). ^{13}C-NMR ($CDCl_3$): δ = 26.34 (CH_3), 29.62 (CH_3), 32.61 (CH_2), 32.85 (CH_2), 33.65 (C), 37.32 (CH_2), 41.50 (CH), 51.81 (CH), 53.28 (CH), 63.81 (CH_2), 64.15 (CH_2), 68.13 (CH_2), 68.57 (CH_2), 68.98 (CH), 85.15 (C), 90.95 (CH_2), 106.06 (C), 118.73 (CH_2), 131.67 (CH), 153.94 (C), 214.57 (C). IR ($CHCl_3$): ν[cm^{-1}] = 2800-3000 s, 1744 s, 1700 s, 1456 m, 1367 m, 1258 s, 1245 s, 1189 s, 1021 s. HRMS : $C_{21}H_{28}O_8$ calc. 408.1784 found 408.1784 MS: 408 (M^+, 3), 366 (2), 323 (28), 279 (100), 235 (18), 167 (44), 149 (52), 141 (36), 86 (92), 69 (62). **Minor diastereomer:** ^{1}H-NMR (400 MHz , $CDCl_3$): δ = 1.11 (s, CH_3, 3H), 1.15 (s, CH_3, 3H), 1.97 - 2.26 (m, 5H), 2.36 (dd, J = 16.0, 6.5 Hz , 1H), 2.77 (bd, J = 6.5 Hz, 1H), 3.02 (m, 1H), 3.16 (bd, J = 6.5 Hz, 1H), 3.8 - 4.2 (m, 6H), 4.59 (dddd, J = 13.0, 1.5, 1.5, 1.5 Hz, 1H), 4.68 (dddd, J = 13.0, 1.5, 1.5, 1.5 Hz, 1H), 4.71 (d, J = 5.0 Hz, 1H), 5.25 (dd, J = 8.0, 1.5 Hz, 1H), 5.33 (d, J = 5.0, 1H), 5.57 (dddd, J = 10.0, 1.5, 1.5, 1.5 Hz, 1H), 5.68 (dddd, J = 17.5, 1.5, 1.5, 1.5 Hz, 1H), 5.95 (ddt, J = 17.5, 10.0, 5.5 Hz, 1H). ^{13}C-NMR ($CDCl_3$): δ = 27.88 (CH_3), 29.36 (CH_3), 31.92 (CH_2), 34.15 (C), 34.35 (CH), 36.40 (CH_2), 41.92 (CH), 51.81 (CH), 54.92 (CH), 63.83 (CH_2), 64.30 (CH_2), 68.25 (CH_2), 69.14 (CH_2), 70.27 (CH), 86.21 (C), 91.11 (CH_2), 105.69 (C), 119.04 (CH_2), 131.68 (CH), 154.32 (C), 215.72 (C). IR ($CHCl_3$): ν[cm^{-1}] = 2800-3000 s, 1744 s, 1696 s, 1448 m, 142 m, 1240 s, 1204 vs, 1196 s, 1110 s, 1084 s, 1027 s. HRMS : $C_{21}H_{28}O_8$ calc. 408.1784 found 408.1784 MS: 408 (M^+, 2), 323 (44), 306 (16), 279 (94), 235 (16), 211 (18), 167 (52), 149 (58), 129 (56), 86 (100), 73 (100), 69 (60), 57 (72).

Allyl (13-(1,3-dioxolan)-15,15-dimethyl-4,7-dioxatetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$] pentadecan-10-onyl) carbonate 3d and

13-(1,3-dioxolan)-15,15-dimethyl-4,7-dioxatetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$]pentadec-2(9)-ene-10-one 3e: A solution of enone **2** (100 mg, 0,31 mmol) and 1,4-dioxene (420 mg, 4.9 mmol) in 2 mL CH_2Cl_2 was degassed by ultrasound while bubbling argon through the reaction mixture for 10 min. The solution was irradiated with a Xe arc lamp (1000 W) at 15 °C for 6 h.Solvent and unchanged 1,4-dioxene were removed by distillation. Flash chromatography (PE : MTBE = 3 : 1) of the residue gave 18 mg of **3d** (0.04 mmol, 14 % yield) and 49 mg of **3e** (0.16 mmol, 52 % yield) as a mixture of diastereomers. **3d** : ^{1}H-NMR (200 MHz , $CDCl_3$): δ = 0.99 (s, CH_3, 3H), 1.23 (s, CH_3, 3H), 1.7 - 2.3 (m, 5H), 2.9 (bs, 1H), 3.4 - 4.0 (m, 9H), 4.35 (dd, J = 6.0, 3.0 Hz, 1H), 4.55 - 4.7 (m, 3H), 5.25 (dddd, J = 9.0, 1.0, 1.0, 1.0 Hz, 1H), 5.4 (dddd, J = 17.0, 1.5, 1.5, 1.5 Hz, 1H), 5.9 (ddt, J = 17.0, 9.0, 6.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$): δ = 27.7 (CH_3), 29.7 (CH_3), 31.6 (CH_2), 34.2 (C), 35.9 (CH_2), 41.0 (CH), 54.4 (CH), 55.9 (CH), 61.7 (CH_2), 62.7 (CH_2), 63.7 (CH_2), 64.1 (CH_2), 68.1 (CH_2), 69.7 (CH), 71.9 (CH), 87.2 (C), 105.0 (C), 118.9 (CH_2), 131.6 (CH), 153.9 (C), 213,0 (C). IR ($CHCl_3$): ν[cm^{-1}] = 3016 m, 2800 - 3000 s, 1747 s, 1701 vs, 1458 m, 1432 m, 1367 m, 1293 s, 1277 s, 1245 s, 1189 s,

1170 s, 1112 s.HRMS : $C_{21}H_{28}O_5$ calc. 408.1784 found 408.1784 MS: 408 (M^+, 2), 323 (2), 306 (19), 279 (3), 263 (3), 234 (6), 219 (3), 191 (5), 177 (8), 167 (8), 141 (22), 99 (14), 86 (100), 73 (38), 69 (24), 57 (86). **3e major diastereomer:** ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.94 (s, CH_3, 3H), 1.14 (s, CH_3, 3H), 1.6 - 2.4 (m, 6H), 3.8 - 4.0 (m, 8H), 4.82 (d, J = 4.0 Hz, 1H), 5.06 (d, J = 4.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$): δ = 25.1 (CH_3), 27.0 (CH_3), 33.3 (CH_2), 35.8 (CH_2), 36.9 (C), 40.7 (CH), 54.8 (CH), 61.8 (CH_2), 62.6 (CH_2), 63.3 (CH_2), 64.8 (CH_2), 71.0 (CH), 72.1 (CH), 106.7 (C), 145.0 (C), 173.8 (C), 197.6 (C). IR ($CHCl_3$): ν[cm^{-1}] = 2800 - 3000 s, 1682 s, 1453 m, 1429 m, 1362 m, 1231 s, 1227 s, 1175 s, 1160 s, 1110 s, 1052 s, 1032 s. HRMS : $C_{17}H_{22}O_5$ calc. 306.1467 found 306.1467 MS: 306 (M^+, 4), 234 (5), 191 (15), 177 (4), 141 (6), 99 (6), 86 (24), 69 (6), 55 (16). **3e minor diastereomer:** ^{1}H-NMR (200 MHz , $CDCl_3$): δ = 1.16 (s, CH_3, 3H), 1.20 (s, CH_3, 3H), 1.6 - 2.4 (m, 6H), 3.8 - 4.0 (m, 8H), 4.79 (d, J = 4.0 Hz, 1H), 4.91 (d, J = 4.0 Hz, 1H).

13-(1,3-Dioxolan)-2-hydroxy-15,15-dimethyl-4-oxatetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$]pentadecan-10-one : To a solution of **3a** (200 mg, 0.5 mmol) in dry THF were added 5 mol% $Pd(PPh_3)_4$ and 130 mg (1.5 mmol) morpholine at ambient temperature. After 1.5 h the solvent and the morpholine were removed by distillation under reduced pressure. The yellow oil was purified by flash chromatography (MTBE : PE 2 : 1) to give **3f** (153 mg, 0.48 mmol, 95 % yield).^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.1 (s, CH_3, 3H), 1.21 (s, CH_3, 3H), 1.45 - 1.52 (m, H-6, 1H), 1.78 - 1.95 (m, H-6, H-1, H-7, 4H), 2.04 - 2.18 (m, H-12, H-14, 4H), 2.42 -2.58 (m, H-11, H-8, 2H), 2.78 (bd, J = 5.0, H-9, 1H), 3.62 - 3.68 (m, H-5, 1H), 3.82 - 3.96 (m, H-18, H-19, 4H), 4.0 - 4.1 (m, H-5, 1H), 4.12 (s, OH) , 4.3 (dd, J = 8.0, 1.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$): δ = 21.31 (CH_2), 25.18 (CH_2), 27.97 (CH_3), 29.94 (CH_3), 31.67 (CH_2), 34.5 (C), 35.65 (CH), 35.67 (CH_2), 45.20 (CH), 55.45 (CH), 57.11 (CH), 63.32 (CH_2), 63.72 (CH_2), 64.37 (CH_2), 72.60 (CH), 77.18 (C), 106.67 (C), 217.96 (C). IR ($CHCl_3$): ν[cm^{-1}] = 3505 s, 2800 -3000 s, 1697 vs,1372 m,1107 vs. HRMS : $C_{18}H_{26}O_5$ calc. 322.718 found 322.718 MS: 322 (M^+, 7), 239 (100), 195 (60), 84 (80), 69 (54).

2-Hydroxy-15,15-dimethyl-4-oxatetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$]pentadecan-10,13-dione 4: Under an argon atmosphere 25 µL of a half concentrated BF_3·OEt_2 solution (20 mol%) were added to a solution of **3f** (162 mg, 0.5 mmol) in acetone (dried over P_4O_{10}). After stirring for 1 h at ambient temperature the reaction was completed (T.L.C. control) . The reaction mixture was poured into brine/MTBE , the aqueous layer was extracted with MTBE and the combined organic layers were dried over $MgSO_4$. After filtration solvent was removed under reduced pressure and purification by flash chromatography (MTBE : PE = 2 : 1) gave 102 mg of **4** (0.39 mmol, 78 % yield).^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, CH_3, 3H), 1.36 (s, CH_3, 3H), 1.38 -1.5 (m, H-6α, 1H), 1.63 - 1.75 (m, H-7α, 1H), 1.8 -1.92 (m, H-6β, 1H), 1.97 - 2.08 (m, H-7β, H-1, 2H), 2.28 (dt, J = 18.0, 1.5 Hz, H-12α, 1H , 2.33 (dm, J = 5.0 Hz, H-14α, 1H), 2.46 (dm, J = 8.0 Hz, H-12, 1H), 2.48 -2.58 (m, H-14β, H-8, 2H), 2.71 (dd, J = 18.0, 8.0 Hz, H-11,1H), 3.16 (dt, J = 16.0, 3.0 Hz, H-9, 1H), 3.56 - 3.64 (m, H-5α, 1H), 3.93 - 4.0 (m, H-5β, 1H), 4.17 (s, OH), 4.3 (dd, J = 8.0, 1.5 Hz, 1H). ^{13}C-NMR ($CDCl_3$): δ = 21.15 (CH_2), 24.47 (CH_2), 27.97 (CH_3), 29.94 (CH_3), 32.17 (CH_2), 34.31 (C), 36.21 (CH), 36.34 (CH_2), 41.87 (CH), 53.74 (CH), 54.87 (CH), 63.75 (CH_2), 71.98 (CH), 88.09 (CH), 216.32 (C), 217.94 (C). IR ($CHCl_3$): ν[cm^{-1}] = 3505 s, 2800 - 3000 s, 1718 vs, 1698 s, 1372 m, 1106 s, 1043 m. HRMS : $C_{16}H_{22}O_4$ calc. 278.1518 found 278.1526 MS: 278 (M^+, 4), 239 (100), 195 (54), 168 (15), 84 (92), 69 (50), 55 (52).

2,13-Dihydroxy-15,15-dimethyl-4-oxatetracyclo[9.3.1.$0^{2,9}$.$0^{3,8}$]pentadecan-10-one 5: Under an argon atmosphere at -78 °C 1.2 mL (1.2 mmol) of a L-Selectride®/THF solution were added dropwise to a solution of **4** (278 mg, 1 mmol) in 10 mL dry THF. After stirring for 2 h at -78 °C the reaction mixture was poured into brine/MTBE, the aqueous layer was extracted with MTBE and the combined organic layers were dried over $MgSO_4$. After filtration solvent was removed under reduced pressure and purification by flash chromatography (MTBE : PE = 2 : 1) gave 257 mg (0.91 mmol, 92 % yield) of a colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, CH_3, 3H), 1.10 (s, CH_3, 3H), 1.18 - 1.40 (m, H-6α, 1H), 1.38 - 1.47 (m, H-7α, 1H), 1.58 - 1.70 (m, 6-Hβ, 1H), 1.78 - 1.91 (m, H-7β, H-1, 2H), 1.94 - 2.11 (m, H-12, H-14, 4H), 2.38 - 2.50 (m, H-8, H-11, 2H), 2.88 (d, J = 5.5 Hz, H-9, 1H), 3.34 (s, OH), 3.53 - 3.67 (m, H-5α, 1H), 3.97 (bs, H-13, 1H), 3.88 - 4.0 (m, H-5β, 1H), 4.22 (dd, J = 8.0, 1.2 Hz, 1H), 4.54 (s, OH). ^{13}C-NMR ($CDCl_3$): δ = 20.76 (CH_2), 24.31 (CH_2),

27.63 (CH_3), 29.49 (CH_3), 29,95 (CH_2), 33.76 (CH_2), 34.59 (C), 34.83 (CH), 43.28 (CH_2), 53.48 (CH), 57.02 (CH), 62.85 (CH_2), 63.07 (CH), 73.0 (CH), 75.89 (C), 218.27 (C). IR ($CHCl_3$): ν[cm^{-1}] = 3474 s, 2800 - 3000 s, 1696 vs, 1274 m, 1105 m. HRMS : $C_{16}H_{24}O_4$ calc. 280.1675 found 280,1675 MS: 280 (M^+, 7), 260 (50), 197 (100), 179 (80), 109 (30), 84 (90).

13-Hydroxy-15,15-dimethyl-4-oxatricyclo[9.3.1^{1,11}.0^{3,8}]pentadecan-2,10-dione 6: Compound **5** (80 mg, 0.285 mmol) was dissolved in 10 mL ^{t}BuOH/38 mg (0.34 mmol) ^{t}BuOK. The colour of the solution turned into intensive yellow. The reaction mixture was stirred for 1 h at 70 °C and then was poured into brine/MTBE, the aqueous layer was extracted with MTBE and the combined organic layers were dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure and purification by flash chromatography (CH_2Cl_2 : MeOH = 30 : 1) gave 64 mg (0.228 mmol, 80 % yield) of **6**. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.01 (s, CH_3, 3H), 1.20 (s, CH_3, 3H), 1.33 - 1.47 (m, H-6α, 1H), 1.55 - 1.63 (m, H-7β, 1H), 1.75- 1.92 (m, H-6β, H-8, 2H), 1.95 - 2.03 (m, H-6β, 1H), 2.07 (dt, J = 12.0, 2.0 Hz, H-9α, 1H), 2.13 (dm, J = 17.0 Hz, H-12α, 1H), 2.32 -2.4 (m, H-1, H-14α, 2H), 2.47 - 2.56 (m, H-12β, H-14β, 2H), 2.63 (dd, J = 9.0, 4.0 Hz, H-11, 1H), 3.31 (m, H-5β, 1H), 3.52 (dd, J = 12.0, 10.0, H-9α, 1H), 4.03 (s, OH), 4.05 (dm, J = 11.0 Hz, H-5α, 1H), 4.44 - 4.52 (m, H-13, 1H), 5.01 (d , J = 10.5 Hz, H-3, 1H). IR ($CHCl_3$): ν[cm^{-1}] = 3396 s, 2800 - 3000 s, 1696 vs, 1685 s, 1606 m, 1206 s, 1102 s, 793 m. HRMS : $C_{16}H_{24}O_4$ calc. 280.1675 found 280.1675 MS: 280 (M^+, 18), 262 (7), 205 (21), 153 (40), 149 (37), 109 (55), 97 (91), 69 (100).

(15,15-Dimethyl-2,10-dioxa-4-oxatricyclo[9.3.1^{1,11}.0^{3,8}]pentadec-13-yl) 3-phenylacrylate 7: Under an argon atmosphere a solution of **6** (42 mg, 0.15 mmol) and 3.6 mg (0.03 mmol) DMAP in 10 mL dry CH_2Cl_2 was prepared . After cooling down to 0 °C 22 mg (0.3 mmol) Et_3N was added and during 30 minutes 50 mg (0.3 mmol) Cinnamoyl chloride were dropped to the raction mixture. After stirring for 24 h at ambient temperature the reaction mixture was hydrolyzed with 1M HCl , and the aqueous layer was extracted with ether. The combined organic phases were neutralized with $NaHCO_3$ solution and were washed with H_2O , dried over $MgSO_4$ and after filtration the solvent was removed under reduced pressure. Flash chromatography of (MTBE : MeOH = 10 : 1) the residue gave 43.7 mg (0.1 mmol, 71 % yield) of **7**.^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.0 (s, CH_3, 3H), 1.23 (s, CH_3, 3H), 1.38 - 1.51 (m, H-7α, 1H), 1.52 - 1.60 (m, H-7β, 1H), 1.74 - 1.85 (m, H-6α, 1H), 1.85 - 1.91 (m, H-8, 1H), 1.98 - 2.04 (m, H-6β, 1H), 2.11 (dm, J = 12.0 Hz, H-9α, 1H), 2.23 (dm, J = 17.0 Hz, H-14α, 1H), 2.47 (dt, J = 16.0, 4.0 Hz, H-12α, 1H), 2.53 - 2.63 (m , H-12β , H-14β , 2H) , 2.67 (dm , J = 14.0 Hz , H-11 , 1H) , 3.01 (dt , J = 12.0 , 2.0 Hz , H-5α , 1H) , 3.63 (dd , J = 12.0 , 10.0 Hz , H-9β , 1H) , 4.07 (dm , J = 12.0 Hz , H-5β , 1H) , 4.71 (d , J = 10.5 Hz, H-3, 1H), 5.52 - 5.59 (m, H-13, 1H), 6.51 (d, J = 16.0 Hz, H-19, 1H), 7.41 - 7.57 (m, C_6H_5, 5H), 7.8 (d, J = 16.0 Hz, H-20, 1H). ^{13}C-NMR ($CDCl_3$): δ = 25.49 (CH_2), 27.04 (CH_2), 27.24 (CH_3), 27.42 (CH_2), 32.58 (CH_3), 33.98 (CH_2), 34.91 (C), 43.42 (CH_2), 54.47 (CH), 56.75 (CH), 65.02 (CH), 67.68 (CH_2), 82.31 (CH), 117.45 (CH), 128 (CH), 129.5 (CH), 130.75 (CH), 133.93 (C), 145.94 (CH), 165.86 (C), 209.73 (C), 212.6 (C). IR ($CHCl_3$): ν[cm^{-1}] = 2800 - 3000 s, 1698 vs, 1636 m, 1265 m, 908 s. HRMS : $C_{25}H_{30}O_5$ calc. 410.2093 found 410.2093 MS: 410 (M^+, 6), 234 (100), 147 (38), 131 (90), 103 (45), 97 (47), 77 (30).

(15,15-Dimethyl-2,10-dioxa-4-oxatricyclo[9.3.1^{1,11}.0^{3,8}]pentadec-13-yl) 2',3'-dihydroxy-3'-phenylpropionate 8: Compound **7** (140 mg, 0.34 mmol) dissolved in 20 mL ^{t}BuOH was added to a solution of acetone / H_2O (20 L : 40 L), 140 mg NMO and a catalytic amount OsO_4. After stirring for 24 h at ambient temperature the reaction was completed (T.L.C. control). The mixture was diluted with $NaHCO_3$ solution, the aqueous layer was extracted with MTBE and the combined organic phases were dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure and purification by flash chromatography (MTBE) gave 148 mg (0.33 mmol, 98 % yield) of a colourless foam.^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.17 (s, 2 CH_3, 6H), 1.41. - 1.52 (m, H-7α, 1H), 1.52 - 1.59 (m, H-7β, 1H), 1.70 -1.77 (m, H-6α, 1H), 1.77 - 1.82 (m, H-8, 1H), 1.90 -1.97 (m, H-6β, 1H), 2.07 - 2.17 (m, H-12α, 1H), 2.33 -2.45 (m, H-14α, H-1, 2H), 2.47 -2.57 (m, H-12β, H-14β, 2H), 2.64 (dd, J = 10.0, 4.5 Hz, H-11, 1H), 2.94 (bd, J = 6.0 Hz, OH), 3.12 (bd, J = 6.0 Hz, OH), 3.32 (dd, J = 12.0, 2.0 Hz, H-5α, 1H), 3.37 (dd, J = 12.0, 10.0 Hz, H-9β, 1H), 4.07

(dm, J = 12.0 Hz, H-5β, 1H), 4.41 - 4.45 (m, H-20, 1H), 4.50 (d, J = 10.5 Hz, H-3, 1H), 5.06 (m, H-19, 1H), 5.42 - 5,51 (m, H-13, 1H), 7.31 - 7.45 (m, C_6H_5, 5H). ^{13}C-NMR ($CDCl_3$): δ = 25.50 (CH_3), 26.88 (CH_3), 28.21 (CH_2), 33.03 (CH), 33.11 (CH_2), 33.93 (CH), 34.69 (C), 39.11 (CH), 43.09 (CH_2), 54.61 (CH), 56.95 (CH), 67.22 (CH), 67.52 (CH_2), 75.14 (CH), 75.29 (CH), 82.25 (CH), 126.39 (CH), 128.55 (CH), 128.68 (CH), 139.28 (C), 171.89 (C), 209.32 (C), 212.35 (C). IR ($CHCl_3$): ν[cm^{-1}] = 3551 s, 2800 - 3000 s, 1733 s, 1696 vs, 1610 m, 1269 m, 1095 s, 1005 s. MS (FAB): M^+Na^+ = 467.4, M^+H^+ = 445.4, $M\text{-}H_2O+H^+$ = 427.4, $C_{25}H_{32}O_7$ = 444.4.

(10-Hydroxy-15,15-dimethyl-2-oxo-4-oxatricyclo[9.3. $1^{1,11}.0^{3,8}$]pentadec-13-yl) 2',3'-dihydroxy-3'-phenylpropionate 9: Diketone **8** (27 mg, 0.06 mmol) was reduced by a $NaBH_4$/ MeOH solution at 0 °C . The reaction was controlled by T.L.C. . After the reaction was completed the mixture was poured into water. The aqueous layer was extracted with MTBE and the combined organic phases were dried over $MgSO_4$. After filtration solvent was removed under reduced pressure and purification by flash chromatography (MTBE : MeOH = 10 : 1) gave 21 mg (0.047 mmol , 80 % yield).^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, CH_3), 1.17 (s, CH_3), 1.24 - 1.31 (m, H-7α, 1H), 1.44 - 1.51 (m, H-7β, 1H), 1.53 - 1.62 (m, H-6α, H-8, 2H), 1.73 - 2.15 (m, H-12, H-14α, H-9α, H-9β, H-11, H-1, 6H), 2.75 - 2.83 (m, H-12β, H-14β, 2H), 3.29 - 3.37 (m, H-5α, 1H), 3.92 - 3.98 (m, H-10, 1H), 4.13 - 4.18 (m, H-5, 1H), 4.21 (d, J = 10.5 Hz, H-3, 1H), 4.34 - 4.40 (m, H-20, 1H), 4.91 - 4.96 (m, H-19, 1H), 5.32 - 5.47 (m, H-13, 1H), 7.33 - 7.45 (m, C_6H_5, 5H). IR ($CHCl_3$): ν[cm^{-1}] = 3675 s, 3540 vs, 2800 - 3000 vs, 1729 s, 1696 vs, 1264 m, 1097 s. MS (FAB): M^+Na^+ = 469.3, M^+H^+ = 447.3, $M\text{-}H_2O+H^+$ = 429.3, $C_{25}H_{34}O_7$ = 446.3.

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