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Synthetic studies towards D-modified paclitaxel analogues

ZORANA FERJANČIĆ[1]*, RADOMIR MATOVIĆ[2] and RADOMIR N. SAIČIĆ[1]**

[1]Faculty of Chemistry, University of Belgrade, Studentski trg 16, P. O. Box 158, 11000 Belgrade, Serbia and [2]ICTM – Center for Chemistry, Njegoševa 12, 11000 Belgrade, Serbia

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Abstract: A synthetic sequence has been developed for the preparation of 9,10-di-*O*-diacetyl-4-desmethylene-4*β*-(3-butenyl)-4*α*-hydroxy-5-*O*-mesyltaxicin I--1,2-carbonate **3**, an intermediate in an attempted synthesis of a cyclobutane paclitaxel analogue. A series of reactions of **3** were investigated, including the protection of the sterically hindered C-4*α*-hydroxy group and the oxidative cleavage of the terminal double bond. Cyclization of **13** to the cyclobutane-containing intermediate failed due to the unexpected instability of the dimethylsilane protecting group under basic conditions.

Keywords: taxoids; taxanes antitumor agents; radical allylation; silyl protecting groups.

INTRODUCTION

Over the past 25 years, structure–activity relationships (SAR) studies on the antitumor agent paclitaxel have been thoroughly conducted, identifying the major sites involved in its microtubules stabilizing activity.[1] Among these numerous studies, considerable research efforts were directed toward the understanding of the role of the oxetane D-ring in the cytotoxic activity of paclitaxel.[2] The contribution of this ring to the biological activity of paclitaxel is not clear and two hypotheses have been proposed as explanations.[2d,f] The inflexible oxetane ring may force the molecule to adopt a biologically active conformation through its rigidifying effect on the taxane skeleton,[2e,k] or the oxetane oxygen atom might be involved in the stabilizing dipolar or hydrogen bonding interactions with the tubulin protein.[2b,c,h]

In the course of our studies on D-modified 7-deoxypaclitaxel analogues,[2l,n,3] we wished to synthesize analogue **1** in which the oxetane ring would be replaced by cyclobutane, according to the retrosynthetic plan presented in Scheme 1. Analogue **1**, as compared with paclitaxel, possesses a conformationally rigid four-

Corresponding authors: E-mail: *zferjan@chem.bg.ac.rs; **rsaicic@chem.bg.ac.rs
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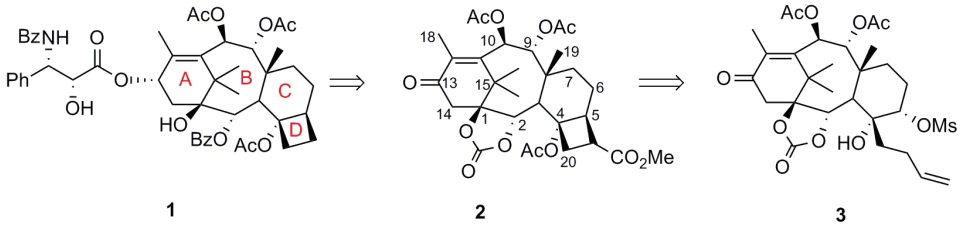
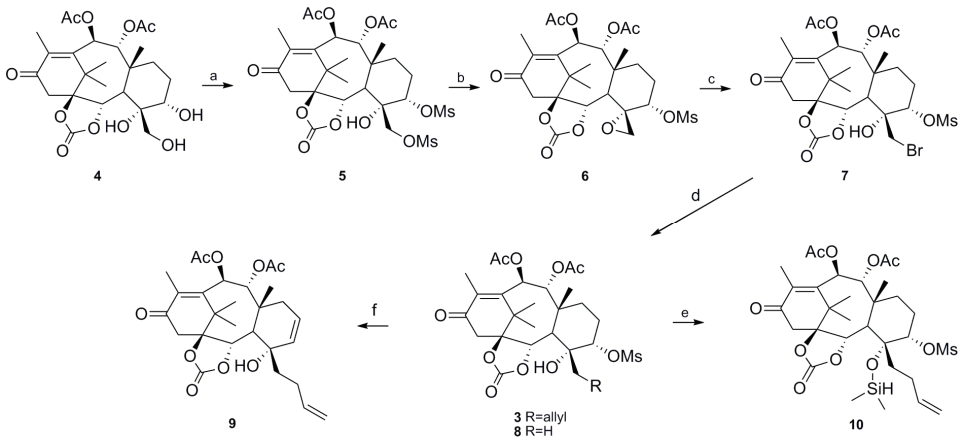
membered D-ring without the electronegative oxygen atom in it. This modification should allow us to determine whether the oxetane ring exerts its influence to the biological activity of taxoids through conformational or electronic effects.



Scheme 1. Retrosynthetic analysis of cyclobutane paclitaxel analogue **1**.

RESULTS AND DISCUSSION

As the starting material for the preparation of analogue **1**, we chose triol **4**, one of the intermediates in our synthesis of 7-deoxy-C,D-*seco*-paclitaxel from taxine B (Scheme 2).[2l,n] Mesylation of the free C-20 and C-5 hydroxyl groups afforded **5** in good yield. Exposure of **5** to the action of the Hunig's base in refluxing toluene furnished epoxymesylate **6**, which was converted to bromohydrin **7** by Lewis acid induced nucleophilic opening of the 4(20)-epoxide. Finally, alcohol **3** was obtained by a free radical allylation of compound **7** with allyltributyltin, using AIBN as initiator. This protocol for elongation of the C-4*β* alkyl chain had already been successfully applied in our synthesis of the C,D-spirolactone analogue of paclitaxel.[2o] It is interesting to note that radical allylation of com-



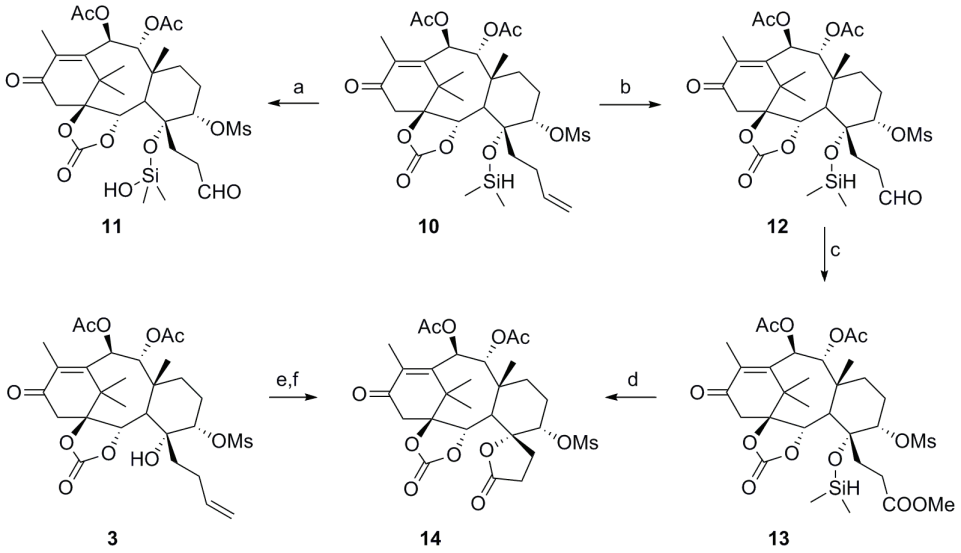
Scheme 2. Conversion of triol **4** into the DMS-protected alcohol **10**. Reagents, conditions and yields: a) MsCl, pyridine, rt, 72 h, 70 %; b) DIPEA, $PhCH_3$, 120 °C, 3 h, 87 %; c) Bu_4NBr, $BF_3{\cdot}OEt_2$, DCM, rt, 15 min, 84 %; d) allyltributyltin, AIBN, PhH, reflux, 3 h, **3** 57 % and **8** 15 %; e) DMSCl, imidazole, DMF, 55 °C, 67 % f) MOMCl, NaI, DIPEA, DME, 86 °C, 26 %.

pound **7** requires the use of a large amount of the initiator: when the standard reaction conditions (catalytic quantities of AIBN) were applied, only the starting material was isolated. However, performing the reaction with 3–4.5 equivalents of the initiator allowed us to obtain alcohol **3** in 57 % yield. Use of such a large amount of the initiator resulted in the formation of side product **8** (15 % yield), probably by reduction of the intermediary C-20 radical with AIBN.

All attempts to protect the tertiary hydroxyl group in **8** were unsuccessful, undoubtedly a direct result of a considerable steric hindrance. For example, treatment of **8** with TMSCl/imidazole in DMF, NaH/MeI in THF or lithium hexamethyldisilazide/methyl chloroformate in THF[2c] led only to the recovery of starting material. Attempted acetylation under forcing conditions with excess Ac_2O/ /DMAP[2i] in toluene at 60 °C also failed to provide the desired product. Interestingly, application of reaction conditions for the protection of tertiary alcohol as a methoxymethyl (MOM) ether (MOMCl, NaI, DMF, *N*,*N*-diisopropylethylamine, reflux)[4] caused only the elimination of C-5 mesylate and the formation of compound **9**. Finally, we found that treatment of **3** with chlorodimethylsilane and imidazole in DMF at 55 °C afforded the dimethylsilane (DMS) protected compound **10** in 67 % yield. Chlorodimethylsilane is a small and reactive reagent and it has already been successively used as a "specific" protecting group for the C-1 tertiary hydroxyl group of taxoids.[5]

We next turned our attention to the oxidative cleavage of the terminal double bond in the silyl ether **10** (Scheme 3). Some preliminary experiments indicated that during the reaction of **10** with a mixture of osmium tetraoxide and sodium periodate in THF/water, oxidation of the DMS protecting group also occurred, resulting in the formation of **11**. The ^{1}H-NMR spectrum exhibited two singlets for the methyls from the DMS group (instead of two doublets) and the absence of the DMS hydrogen atom. The desired transformation could be accomplished by ozonolysis: exposure of **10** to the action of ozone, followed by treatment with dimethyl sulfide to furnish aldehyde **12**. Oxidation of aldehyde **12** with oxone[6] in DMF and subsequent esterification of the carboxylic acid afforded compound **13** in 61 % yield (over two steps). The crucial ring-closure step in the synthesis – formation of the cyclobutane ring – was planned to be effected by the treatment of methyl ester **13** with potassium hexamethyldisilazide in THF at low temperature. However, these conditions proved conducive to the loss of the DMS protecting group and cyclization of thus obtained C-4 alcohol into lactone **14**. The outcome of this reaction was quite unexpected bearing in mind previous work from Chen,[5b] in which the DMS protecting group was unaffected under similar reaction conditions. Alternatively, lactone **14** could also be obtained directly from alcohol **3** by the action of OsO_4 and $NaIO_4$ followed by oxidation of the intermediary hemiacetal with Jones reagent.[2o] Finally, according to the previously observed elimination of the C-5 mesylate in alcohol **3**, we tried to form a

$\Delta^{5,6}$ double bond in **14**. The presence of a 5,6-double bond in the analogue with a C,D-spirolactone moiety could induce a conformational change of the C-ring which positiones the essential C-2, C-13 and C-4 ester groups in the appropriate spatial orientation for the improved biological activity of this type of taxoids.[1b,c] We have previously shown that the C,D-spirolactone paclitaxel analogue was the first D-ring-modified analogue to show significant cytotoxicity, as a result of a different mechanism of action in comparison with paclitaxel, involving mTOR inhibition-dependent autophagy instead of G_2/M cell cycle arrest-dependent apoptosis.[2o] Therefore, elimination of C-5 mesylate in **14** was attempted with several bases (*N*,*N*-diisopropylethylamine, DBU): unfortunately, these experiments led only to the recovery of starting material. Treatment of **14** with a nucleophile, such as the thiophenoxide anion, resulted in the formation of a complex mixture of polar products. The difference in reactivity between compounds **3** and **14** suggests that neighboring free C-4 hydroxyl group in **3** activates the C-5 mesylate toward elimination by intramolecular hydrogen bonding.



Scheme 3. Preparation of intermediate **13** and conversion of **3** and **13** into **14**. Reagents and conditions: a) OsO_4, $NaIO_4$, THF, H_2O, rt, 3 h, 42 %; b) O_3, DCM, –80 °C, then Me_2S, 18 h, 58 %; c) oxone, DMF, rt, 1 h, then CH_2N_2, THF, 0 °C, 1 h, 61 %; d) KHMDS, THF, –78 °C, 30 min, 77 %; e) OsO_4, $NaIO_4$, THF, H_2O, rt, 1 h; f) Jones reagent, acetone, 0 °C, 49 % from **3**.

EXPERIMENTAL

General experimental. All chromatographic separations[7] were performed on silica, 10-18, 60A, ICN Biomedicals. Standard techniques were used for the purification of the reagents and solvents.[8] The NMR spectra were recorded on a Varian Gemini 200 (^{1}H-NMR at 200

MHz, ^{13}C-NMR at 50 MHz, for samples in deuterated chloroform), and on a Bruker Avance III 500 (^{1}H-NMR at 500 MHz, ^{13}C-NMR at 125 MHz). The chemical shifts are expressed in ppm (δ) using tetramethylsilane as an internal standard and the coupling constants (J) are in Hz. The IR spectra were recorded on a Nicolet 6700 FT instrument and are expressed in cm^{-1}. The mass spectra were obtained on Agilent Technologies 6210 TOF LC/MS instrument (LC: series 1200).

*Compound **5***. To a solution of **4** (65 mg; 0.13 mmol) in pyridine (4 mL) at 0° C was added mesyl chloride (222 mg; 1.95 mmol; 15 eq). The reaction mixture was stirred at 0° C for 15 min and then allowed to warm to rt. After 24 h, a second batch of mesyl chloride (222 mg) was added and stirring of the reaction mixture was continued for 24 h. The reaction mixture was diluted with CH_2Cl_2 and the resulting solution was washed successively with ice-cold 2.5% HCl, aq. $NaHCO_3$ and water and dried over anh. $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by dry flash chromatography (eluent: benzene/ethyl acetate = 1/1) to give **5** (60 mg, 70%) as a colorless film. IR (film, cm^{-1}): 3489, 2998, 2937, 1812, 1750, 1686, 1412, 1354, 1237, 1175, 1026; ^{1}H-NMR (200 MHz; $CDCl_3$, δ / / ppm): 6.04 (1H, *d*, *J* = 10.3 Hz), 5.63 (1H, *d*, *J* = 10.0 Hz), 4.92 (1H, *bs*), 4.89 (1H, *d*, *J* = 3.7 Hz), 4.62 (1H, *d*, *J* = 11.4 Hz), 4.48 (1H, *d*, *J* = 11.4 Hz), 3.99 (1H, *s*), 3.90 (1H, *d*, *J* = 19.4 Hz), 3.15 (3H, *s*), 3.00 (3H, *s*), 2.91 (1H, *d*, *J* = 3.67 Hz), 2.86 (1H, *d*, *J* = 19.1 Hz), 2.26 (3H, *s*), 2.11 (3H, *s*), 2.10–1.60 (4H, *m*), 2.05 (3H, *s*), 1.67 (3H, *s*), 1.34 (3H, *s*), 0.97 (3H, *s*); ^{13}C--NMR (50 MHz, $CDCl_3$, δ / ppm): 197.04 (C), 170.17 (C), 169.19 (C), 152.41 (C), 149.83 (C), 143.35 (C), 88.90 (C), 79.58 (CH), 79.13 (CH), 75.00 (CH), 73.70 (C), 72.58 (CH), 68.52 (CH_2), 43.74 (CH), 43.24 (C), 41.44 (C), 40.80 (CH_2), 38.73 (CH_3), 37.27 (CH_3), 32.68 (CH_3), 24.78 (2×CH_2), 20.59 (CH_3), 20.50 (CH_3), 19.92 (CH_3), 18.95 (CH_3), 13.68 (CH_3); HRMS (ESI-TOF high acc) calcd. for $C_{27}H_{39}O_{15}S_2$ (MH^+) 667.1725, found 667.1727.

*Compound **6***. A solution of **5** (134 mg; 0.20 mmol) and DIPEA (181 mg; 1.4 mmol; 7 eq) in anhydrous toluene (21 mL) was heated to reflux with stirring for 3 h. The solvent was removed under reduced pressure and the residue was purified by dry flash chromatography (eluent: benzene/ethyl acetate = 1/1) to give compound **6** (100 mg; 87%) as a colorless film. IR (film, cm^{-1}): 2994, 2939, 1815, 1746, 1688, 1435, 1371, 1236, 1175, 1036; ^{1}H-NMR (200 MHz; $CDCl_3$, δ / ppm): 6.09 (1H, *d*, *J* = 10.3 Hz), 5.72 (1H, *d*, *J* = 10.3 Hz), 4.75 (1H, *d*, *J* = = 4.4 Hz), 4.20 (1H, *bs*), 3.45 (1H, *d*, *J* = 4.0 Hz), 3.23 (1H, *d*, *J* = 4.4 Hz), 3.11 (1H, *d*, *J* = = 19.4 Hz), 3.04 (3H, *s*), 2.94 (1H, *d*, *J* = 19.4 Hz), 2.73 (1H, *d*, *J* = 4.0 Hz), 2.31 (3H, *s*), 2.13 (3H, *s*), 2.13–1.60 (4H, *m*), 2.05 (3H, *s*), 1.63 (3H, *s*), 1.33 (3H, *s*), 1.08 (3H, *s*); ^{13}C-NMR (50 MHz, $CDCl_3$, δ / ppm): 196.20 (C), 170.02 (C), 169.33 (C), 152.12 (C), 150.10 (C), 143.98 (C), 87.78 (C), 85.54 (CH), 77.96 (CH), 74.85 (CH), 72.43 (CH), 59.36 (C), 51.76 (CH_2), 44.30 (C), 41.44 (C), 40.88 (CH_2), 38.69 (CH_3), 37.93 (CH), 32.59 (CH_3), 26.98 (CH_2), 25.33 (CH_2), 20.67 (CH_3), 20.50 (CH_3), 19.92 (CH_3), 17.52 (CH_3), 14.29 (CH_3); HRMS (ESI-TOF high acc) calcd. for $C_{26}H_{35}O_{12}S$ (MH^+) 571.1844, found 571.1834.

*Compound **7***. To a solution of **6** (280 mg, 0.49 mmol) and Bu_4NBr (630 mg, 1.96 mmol, 4 eq) in CH_2Cl_2 (25 mL) was added BF_3•Et_2O (139 mg, 0.98 mmol, 2 eq) dropwise at rt under an argon atmosphere. The reaction mixture was stirred for 15 min and diluted with CH_2Cl_2, washed successively with water and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by dry-flash chromatography (eluent:benzene/ethyl acetate = 7/3) gave compound **7** (255 mg, 80%) as white powder. m.p. 256 °C with decomposition. IR (film, cm^{-1}): 3467, 2928, 1812, 1750, 1686, 1360, 1233, 1173, 1027; ^{1}H-NMR (200 MHz; $CDCl_3$, δ / ppm): 6.04 (1H, *d*, *J* = 10.2 Hz), 5.63 (1H, *d*, *J* = 10.2 Hz), 5.03 (1H, *bs*), 4.83 (1H, *d*, *J* = 4.7 Hz), 4.16 (1H, *d*, *J* = 11.7 Hz), 3.87 (1H, *d*, *J* = 19.3 Hz), 3.79 (1H, *d*, *J* =

= 12.0 Hz), 3.11 (1H, *s*), 3.07 (1H, *d*, *J* = 4.4 Hz), 3.00 (3H, *s*), 2.86 (1H, *d*, *J* = 19.3 Hz), 2.27 (3H, *s*), 2.12 (3H, *s*), 2.12–1.60 (4H, *m*), 2.06 (3H, *s*), 1.67 (3H, *s*), 1.34 (3H, *s*), 1.02 (3H, *s*); ^{13}C-NMR (50 MHz, $CDCl_3$, δ / ppm): 196.95 (C), 170.29 (C), 169.20 (C), 152.12 (C), 149.59 (C), 143.49 (C), 88.82 (C), 80.52 (CH), 79.33 (CH), 75.09 (CH), 73.27 (C), 72.54 (CH), 43.83 (CH), 43.44 (C), 41.48 (C), 40.84 (CH_2), 38.67 (CH_3), 38.33 (CH_2), 32.77 (CH_3), 25.00 (2×CH_2), 20.68 (CH_3), 20.63 (CH_3), 20.05 (CH_3), 19.43 (CH_3), 13.78 (CH_3); HRMS (ESI-TOF high acc) calcd. for $C_{26}H_{36}BrO_{12}S$ (MH^+) 651.1105, found 651.1094.

*Compound **3***. A deaerated solution of **7** (220 mg, 0.34 mmol), allyltributyltin (1.68 g, 5.08 mmol, 15 eq) and AIBN (83 mg, 0.51 mmol, 1.5 eq) in benzene (44 mL) was stirred at 80 °C under an argon atmosphere. After 1 h, AIBN (83 mg) was added and stirring and heating of the reaction mixture were continued for 1 h. After removal of the solvent under reduced pressure, the residue was purified by dry-flash chromatography (eluent: benzene/ethyl acetate = 8/2) to give compound **3** (120 mg, 57%) and compound **8** (29 mg, 15%) as a colorless films. Compound **3**: IR (film, cm^{-1}): 3542, 3439, 2946, 1812, 1750, 1684, 1349, 1234, 1172, 1034; ^{1}H-NMR (500 MHz, $CDCl_3$, δ / ppm): 6.04 (1H, *d*, *J* = 10.5 Hz, H-10), 5.86–5.78 (1H, *m*, H-22), 5.62 (1H, *d*, *J* = 10.5 Hz, H-9), 5.11 (1H, broad *dd*, *J* = 1.0 and 17.0 Hz, H-23), 5.06 (1H, *dd*, *J* = 1.0 and 10.0 Hz, H-23), 4.88 (1H, *d*, *J* = 4.5 Hz, H-2), 4.79 (1H, *bs*, H-5), 3.79 (1H, *d*, *J* = = 19.0 Hz, H-14), 2.97 (3H, *s*, Ms), 2.90 (1H, *s*, OH), 2.84 (1H, *d*, *J* = 19.0 Hz, H-14), 2.78 (1H, *d*, *J* = 4.5 Hz, H-3), 2.32–2.23 (1H, *m*, H-21), 2.26 (3H, *s*, H-18), 2.23––2.13 (2H, *m*, H-20 and H-21), 2.11 (3H, *s*, Ac), 2.05 (3H, *s*, Ac), 2.06–1.98 (1H, *m*, H-6), 1.91–1.85 (1H, *m*, H-6), 1.78–1.68 (3H, *m*, H-20 and 2×H-7), 1.67 (3H, *s*, H-16 or H-17), 1.33 (3H, *s*, H-16 or H-17), 1.03 (3H, *s*, H-19); ^{13}C-NMR (125 MHz, $CDCl_3$, δ / ppm): 197.18 (C, C-13), 170.45 (C, Ac), 169.38 (C, Ac), 152.53 (C, CO), 149.71 (C, C-11), 143.45 (C, C-12), 137.66 (CH, C-22), 116.60 (CH_2, C-23), 89.38 (C, C-1), 81.74 (CH, C-5), 80.41 (CH, C-2), 75.70 (C, C-4), 75.60 (CH, C-9), 72.88 (CH, C-10), 45.23 (CH, C-3), 43.82 (C, C-8), 41.50 (C, C-15), 41.16 (CH_2, C-14), 38.82 (CH_3, Ms), 35.34 (CH_2, C-20), 33.02 (CH_3, C-16 or C-17), 28.24 (CH_2, C-21), 25.52 (CH_2, C-6), 25.44 (CH_2, C-7), 20.90 (CH_3, Ac), 20.81 (CH_3, Ac), 20.27 (CH_3, C-16 or C-17), 19.18 (CH_3, C-19), 13.99 (CH_3, C-18). HRMS (ESI-TOF high acc) calcd. for $C_{29}H_{41}O_{12}S$ (MH^+): 613.2313, found: 613.2318. Compound **8**: IR (film, cm^{-1}): 3500, 2965, 1811, 1750, 1685, 1348, 1237, 1171, 1026; ^{1}H-NMR (500 MHz, $CDCl_3$, δ / ppm): 6.04 (1H, *d*, *J* = 10.5 Hz, H-10), 5.63 (1H, *d*, *J* = 10.5 Hz, H-9), 4.88 (1H, *d*, *J* = 4.5 Hz, H-2), 4.57–4.55 (1H, *m*, H-5), 3.78 (1H, *d*, *J* = 19.5 Hz, H-14), 2.98 (3H, *s*, Ms), 2.85 (1H, *d*, *J* = = 19.0 Hz, H-14), 2.79 (1H, *d*, *J* = 4.5 Hz, H-3), 2.27 (3H, *s*, H-18), 2.11 (3H, *s*, Ac), 2.05 (3H, *s*, Ac), 2.05–2.00 (1H, *m*, H-6), 1.92–1.85 (1H, *m*, H-6), 1.76–1.69 (3H, *m*, 2×H-7), 1.68 (3H, *s*, H-16 or H-17), 1.57 (3H, *s*, H-20), 1.34 (3H, *s*, H-16 or H-17), 1.03 (3H, *s*, H-19); ^{13}C--NMR (125 MHz, $CDCl_3$, δ / ppm): 197.00 (C, C-13), 170.28 (C, Ac), 169.21 (C, Ac), 152.42 (C, CO), 149.52 (C, C-11), 143.40 (C, C-12), 89.21 (C, C-1), 84.93 (CH, C-5), 80.23 (CH, C-2), 75.43 (CH, C-9), 73.38 (C, C-4), 72.68 (CH, C-10), 44.11 (CH, C-3), 43.57 (C, C-8), 41.33 (C, C-15), 40.89 (CH_2, C-14), 38.69 (CH_3, Ms), 32.82 (CH_3, C-16 or C-17), 26.42 (CH_3, C-20), 25.46 (CH_2, C-6), 25.25 (CH_2, C-7), 20.72 (CH_3, Ac), 20.64 (CH_3, Ac), 20.08 (CH_3, C-16 or C-17), 18.57 (CH_3, C-19), 13.83 (CH_3, C-18). HRMS (ESI-TOF high acc) calcd. for $C_{26}H_{37}O_{12}S$ (MH^+): 573.2000, found: 573.1992.

*Compound **9***. A mixture of sodium iodide (12.5 mg, 0.084 mmol) and MOMCl (8.4 mg, 0.104 mmol) in DME (0.2 mL) was stirred for 10 min at rt. Then a solution of **3** (6.4 mg, 0.010 mmol) and DIPEA (14.8 mg, 0.114 mmol) in DME (0.5 mL) was stirred for 20 min at rt and overnight under reflux. A second portion of sodium iodide (25 mg,), MOMCl (17 mg) and DIPEA (30 mg) were added and stirring of the reaction mixture was continued for additional

24 h. The reaction mixture was quenched with saturated $NaHCO_3$ and water and extracted twice with methylene chloride. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: benzene/ethyl acetate = 6/4) to give compound **9** (1.4 mg, 26%) as a colorless film. ^{1}H-NMR (200 MHz; $CDCl_3$, δ / ppm): 6.02 (1H, *d*, *J* = 10.4 Hz), 5.89–5.66 (2H, *m*), 5.70 (1H, *d*, *J* = 10.0 Hz), 5.60–5.52 (1H, *m*), 5.12–4.97 (2H, *m*), 4.92 (1H, *d*, *J* = 6.6 Hz), 3.75 (1H, *d*, *J* = 19.1 Hz), 2.83 (1H, *d*, *J* = 19.5 Hz), 2.40–1.92 (6H, *m*), 2.33 (1H, *d*, *J* = = 6.3 Hz), 2.10 (3H, *s*), 2.08 (3H, *s*), 2.06 (3H, *s*), 1.67 (3H, *s*), 1.31 (3H, *s*), 1.03 (3H, *s*).

*Compound **10***. To a solution of **3** (150 mg, 0.245 mmol) and imidazole (166 mg, 2.45 mmol, 10 eq) in DMF (1.2 mL) was added chlorodimethylsilane (231 mg, 2.45 mmol, 10 eq) dropwise at 0 °C, under an argon atmosphere. The reaction mixture was stirred at 0 °C for 15 min, and then at 55 °C for 1 h. After this period of time, imidazole (166 mg) and chlorodimethylsilane (231 mg) were added and the reaction was stirred at 55 °C for another hour. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by dry-flash chromatography (eluent: benzene/ethyl acetate = 7/3) gave compound **10** (110 mg, 67 %) as a colorless film. IR (film, cm^{-1}): 2964, 1811, 1750, 1685, 1342, 1233, 1173, 1027; ^{1}H-NMR (500 MHz, $CDCl_3$, δ / ppm): 6.02 (1H, *d*, *J* = 10.0 Hz, H-10), 5.77–5.69 (1H, *m*, H-22), 5.62 (1H, *d*, *J* = 10.0 Hz, H-9), 5.05 (1H, broad *dd*, *J* = 1.5 and 17.0 Hz, H-23), 5.02 (1H, *dd*, *J* = 1.0 and 10.5 Hz, H-23), 4.87––4.85 (2H, *m*, H-5 and Si-H), 4.82 (1H, *d*, *J* = 4.5 Hz, H-2), 3.75 (1H, *d*, *J* = 19.0 Hz, H-14), 3.02 (3H, *s*, Ms), 2.80 (1H, *d*, *J* = 19.0 Hz, H-14), 2.72 (1H, *d*, *J* = 4.5 Hz, H-3), 2.29–2.24 (2H, *m*, H-21 and H-20), 2.29 (3H, *s*, H-18), 2.22–2.10 (2H, *m*, H-6 and H-21), 2.10 (3H, *s*, Ac), 2.05 (3H, *s*, Ac), 2.03–1.99 (1H, *m*, H-20), 1.78–1.73 (3H, *m*, H-6 and 2×H-7), 1.66 (3H, *s*, H-16 or H-17), 1.33 (3H, *s*, H-16 or H-17), 1.09 (3H, *s*, H-19), 0.32 (3H, *d*, *J* = 3.0 Hz, Si-CH_3), 0.29 (3H, *d*, *J* = 2.5 Hz, Si-CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$, δ / ppm): 196.99 (C, C-13), 170.44 (C, Ac), 169.42 (C, Ac), 152.78 (C, CO), 150.63 (C, C-11), 142.90 (C, C-12), 136.91 (CH, C-22), 116.03 (CH_2, C-23), 88.83 (C, C-1), 81.13 (CH, C-5), 79.89 (C, C-4), 79.78 (CH, C-2), 75.92 (CH, C-9), 73.20 (CH, C-10), 45.53 (CH, C-3), 44.75 (C, C-8), 41.50 (C, C-15), 41.29 (CH_2, C-14), 39.99 (CH_3, Ms), 35.69 (CH_2, C-20), 33.20 (CH_3, C-16 or C-17), 28.76 (CH_2, C-21), 25.37 (CH_2, C-7), 25.16 (CH_2, C-6), 20.94 (CH_3, Ac), 20.86 (CH_3, Ac), 20.27 (CH_3, C-16 or C-17), 19.64 (CH_3, C-19), 13.80 (CH_3, C-18) 1.04 (CH_3, DMS), 0.95 (CH_3, DMS). HRMS (ESI-TOF high acc) calcd. for $C_{31}H_{47}O_{12}SSi$ (MH^+): 671.2552, found: 671.2530.

*Compound **11***. OsO_4 (30 μL of a 2.5% solution in *t*-BuOH) was added to a solution of **10** (9.6 mg, 0.015 mmol) in a mixture of THF (0.6 mL) and water (0.3 mL), followed by the addition of $NaIO_4$ (16 mg, 0.075 mmol; 5 eq). The reaction mixture was stirred for 1 h at rt, then sodium dithionite (50 mg) was added and stirring was continued for 20 min. The reaction mixture was diluted with CH_2Cl_2, washed with aq. $Na_2S_2O_3$ and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was roughly purified by dry-flash chromatography (eluent: petrol ether/ethyl acetate = 1/1) affording **11** (4.3 mg; 42 %) as a colorless film. ^{1}H-NMR (200 MHz, $CDCl_3$, δ / ppm): 9.81 (1H, *s*), 6.00 (1H, *d*, *J* = 10.0 Hz), 5.63 (1H, *d*, *J* = 10.0 Hz), 4.83 (1H, *d*, *J* = 5.0 Hz), 4.82 (1H, *bs*), 3.73 (1H, *d*, *J* = 19.2 Hz), 3.10 (3H, *s*, Ms), 2.84 (1H, *d*, *J* = 19.2 Hz), 2.99–2.67 (2H, *m*), 2.66 (1H, *d*, *J* = 4.6 Hz), 2.49–2.35 (1H, *m*), 2.26 (3H, *s*, H-18), 2.25–2.11 (2H, *m*), 2.11 (3H, *s*, Ac), 2.06 (3H, *s*, Ac), 1.90–1.66 (3H, *m*), 1.68 (3H, *s*), 1.35 (3H, *s*), 1.13 (3H, *s*), 0.26 (3H, *s*), 0.23 (3H, *s*).

*Compound **12***. Into a cold (–80 °C) solution of **10** (45 mg, 0.067 mmol) in CH_2Cl_2 was bubbled ozone gas until the solution became light blue. Excess ozone was purged from the

reaction by bubbling argon through the cold reaction mixture for 10 min, followed by the addition of dimethyl sulfide (0.2 mL). The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. Purification of the residue by column chromatography (eluent: benzene/ethyl acetate = 7/3) gave compound **12** (27 mg, 58 %) as a colorless film. IR (film, cm^{-1}): 2965, 1810, 1750, 1685, 1341, 1233, 1174, 1031; ^{1}H-NMR (500 MHz, $CDCl_3$, δ / ppm): 9.80 (1H, *s*, CHO), 6.01 (1H, *d*, *J* = 10.5 Hz, H-10), 5.63 (1H, *d*, *J* = 10.0 Hz, H-9), 4.87 (1H, *d*, *J* = 4.5 Hz, H-2), 4.82 (1H, *m*, Si-H), 4.73 (1H, *bd*, *J* = 2.5 Hz, H-5), 3.67 (1H, *d*, *J* = 19.0 Hz, H-14), 3.04 (3H, *s*, Ms), 2.82 (1H, *d*, *J* = 19.0 Hz, H-14), 2.80–2.75 (2H, *m*, 2×H-21), 2.75 (1H, *d*, *J* = 5.0 Hz, H-3), 2.46–2.39 (1H, *m*, H-20), 2.29 (3H, *s*, H-18), 2.25–2.22 (2H, *m*, H-6 and H-20), 2.11 (3H, *s*, Ac), 2.05 (3H, *s*, Ac), 1.90–1.83 (1H, *m*, H-6), 1.76–1.74 (2H, *m*, 2×H-7), 1.67 (3H, *s*, H-16 or H-17), 1.33 (3H, *s*, H-16 or H-17), 1.10 (3H, *s*, H-19), 0.31 (3H, *d*, *J* = 3.0 Hz, Si-CH_3), 0.30 (3H, *d*, *J* = 3.5 Hz, Si-CH_3). ^{13}C--NMR (125 MHz, $CDCl_3$, δ / ppm): 199.99 (C, CHO), 196.54 (C, C-13), 170.15 (C, Ac), 169.17 (C, Ac), 152.29 (C, CO), 150.44 (C, C-11), 142.53 (C, C-12), 88.66 (C, C-1), 81.14 (CH, C-5), 79.45 (C, C-4), 79.19 (CH, C-2), 75.56 (CH, C-9), 72.88 (CH, C-10), 45.30 (CH, C-3), 44.39 (C, C-8), 41.20 (C, C-15), 40.99 (CH_2, C-14), 39.81 (CH_3, Ms), 39.75 (CH_2, C-21), 32.93 (CH_3, C-16 or C-17), 28.46 (CH_2, C-20), 25.24 (CH_2, C-7), 24.77 (CH_2, C-6), 20.65 (CH_3, Ac), 20.56 (CH_3, Ac), 19.99 (CH_3, C-16 or C-17), 19.05 (CH_3, C-19), 13.53 (CH_3, C-18), 0.83 (CH_3, DMS), 0.65 (CH_3, DMS). HRMS (ESI-TOF high acc) calcd. for $C_{30}H_{45}O_{13}SSi$ (MH^+): 673.2345, found: 673.2335.

*Compound **13***. To a solution of **12** (22 mg, 0.032 mmol) in DMF (0.6 mL) oxone (60 mg, 0.098 mmol, 3 eq) was added in one portion and the reaction was stirred at rt for 2 h. The reaction mixture was diluted with ethyl acetate, washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in THF at 0 °C and ethereal solution of diazomethane was slowly added. The reaction mixture was stirred at 0 °C for 1 h and concentrated under reduced pressure. Purification by column chromatography (eluent: benzene/ethyl acetate = 7/3) gave compound **13** (14 mg, 61%) as a colorless film. IR (film, cm^{-1}): 2959, 1809, 1743, 1682, 1373, 1339, 1234, 1174, 1024; ^{1}H-NMR (500 MHz, $CDCl_3$, δ / ppm): 6.01 (1H, *d*, *J* = 10.0 Hz, H-10), 5.63 (1H, *d*, *J* = 10.0 Hz, H-9), 4.85–4.82 (2H, *m*, H-2 and Si-H), 4.76 (1H, *bd*, *J* = 2.0 Hz, H-5), 3.70 (3H, *s*, CO_2Me), 3.68 (1H, *d*, *J* = = 19.0 Hz, H-14), 3.04 (3H, *s*, Ms), 2.82 (1H, *d*, *J* = 19.5 Hz, H-14), 2.74 (1H, *d*, *J* = 4.5 Hz, H-3), 2.57–2.52 (2H, *m*, 2×H-21), 2.49–2.44 (1H, *m*, H-20), 2.29 (3H, *s*, H-18), 2.29–2.24 (2H, *m*, H-6 and H-20), 2.11 (3H, *s*, Ac), 2.06 (3H, *s*, Ac), 1.92–1.85 (1H, *m*, H-6), 1.76–1.72 (2H, *m*, 2×H-7), 1.67 (3H, *s*, H-16 or H-17), 1.33 (3H, *s*, H-16 or H-17), 1.12 (3H, *s*, H-19), 0.33 (3H, *d*, *J* = 2.5 Hz, Si-CH_3), 0.30 (3H, *d*, *J* = 2.5 Hz, Si-CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$, δ / ppm): 196.66 (C, C-13), 172.93 (C, CO_2Me), 170.21 (C, Ac), 169.25 (C, Ac), 152.37 (C, CO), 150.49 (C, C-11), 142.62 (C, C-12), 88.65 (C, C-1), 80.99 (CH, C-5), 79.48 (C, C-4), 79.26 (CH, C-2), 75.60 (CH, C-9), 72.94 (CH, C-10), 52.01 (CH_3, CO_2Me), 45.33 (CH, C-3), 44.43 (C, C-8), 41.23 (C, C-15), 41.01 (CH_2, C-14), 39.87 (CH_3, Ms), 33.00 (CH_3, C-16 or C-17), 31.82 (CH_2, C-20), 29.83 (CH_2, C-21), 25.27 (CH_2, C-7), 24.83 (CH_2, C-6), 20.74 (CH_3, Ac), 20.65 (CH_3, Ac), 20.05 (CH_3, C-16 or C-17), 19.19 (CH_3, C-19), 13.59 (CH_3, C-18) 0.82 (CH_3, DMS), 0.66 (CH_3, DMS). HRMS (ESI-TOF high acc) calcd. for $C_{31}H_{46}O_{14}SSiNa$ (MNa^+): 725.2270, found: 725.2259.

*Compound **14***. OsO_4 (20 μL of a 2.5% solution in *t*-BuOH) was added to a solution of **3** (7 mg, 0.0011 mmol) in a mixture of THF (0.6 mL) and water (0.3 mL), followed by the addition of $NaIO_4$ (12.1 mg, 0.057 mmol; 5 eq). The reaction mixture was stirred for 1 h at rt, then sodium dithionite (40 mg) was added and stirring was continued for 20 min. The reaction

mixture was diluted with CH_2Cl_2, washed with aq. $Na_2S_2O_3$ and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was roughly purified by dry-flash chromatography (eluent: petrol ether/ethyl acetate = 1/1) affording hemiacetal (3.7 mg) that was used in the next step. Jones reagent (25 μL, 0.009 mmol; 1.5 eq) was added to a solution of hemiacetal (3.7 mg, 0.006 mmol) in acetone (0.5 mL) at 0 °C, and the resulting mixture was stirred for 15 min, when isopropanol (100 μL) was added. The reaction mixture was diluted with CH_2Cl_2, washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by coloumn chromatography (eluent: benzene/ethyl acetate = 1/2) gave compound **14** (3.5 mg, 49% over two steps) as a colorless film. IR (film, cm^{-1}): 2993, 2937, 1816, 1746, 1685, 1370, 1353, 1233, 1174, 1024; ^{1}H NMR (500 MHz, $CDCl_3$, δ / ppm): 6.06 (1H, *d*, *J* = 10.5 Hz, H-10), 5.67 (1H, *d*, *J* = 10.0 Hz, H-9), 4.85 (1H, *bd*, *J* = 5.0 Hz, H-2), 4.67 (1H, *bt*, *J* = 2.5 Hz, H-5), 3.54 (1H, *d*, *J* = 19.5 Hz, H-14), 3.06 (1H, *d*, *J* = 5.0 Hz, H-3), 3.01 (3H, *s*, Ms), 2.94 (1H, *dd*, *J* = 19.5 Hz, H-14), 2.82–2.74 (1H, *m*, H-21), 2.67–2.58 (2H, *m*, H-20 and H-21), 2.27 (3H, *s*, H-18), 2.14–2.10 (1H, *m*, H-6), 2.12 (3H, *s*, Ac), 2.06 (3H, *s*, Ac), 1.97–1.91 (2H, *m*, H-6 and H-20), 1.81 (1H, *ddd*, *J* = 2.5, 4.0 and 14.0 Hz, H-7), 1.74 (1H, *dd*, *J* = 3.5 and 13.5 Hz, H-7), 1.68 (3H, *s*, H-16 or H-17), 1.35 (3H, *s*, H-16 or H-17), 1.003 (3H, *s*, H-19); ^{13}C-NMR (125 MHz, $CDCl_3$, δ / ppm): 196.44 (C, C-13), 173.12 (C, C-22), 170.07 (C, Ac), 169.17 (C, Ac), 151.45 (C, CO), 149.82 (C, C-11), 143.32 (C, C-12), 88.65 (C, C-1 or C-4), 85.16 (C, C-1 or C-4), 81.66 (CH, C-5), 78.63 (CH, C-2), 74.59 (CH, C-9), 72.49 (CH, C-10), 43.89 (C, C-8), 41.60 (C, C-15), 41.51 (CH, C-3), 40.53 (CH_2, C-14), 39.10 (CH_3, Ms), 32.79 (CH_3, C-16 or C-17), 28.99 (CH_2, C-20), 27.41 (CH_2, C-21), 24.84 (2×CH_2, C-6 and C-7), 20.71 (CH_3, Ac), 20.58 (CH_3, Ac), 20.07 (CH_3, C-16 or C-17), 18.38 (CH_3, C-19), 13.86 (CH_3, C-18). HRMS (ESI-TOF high acc) calcd. for $C_{28}H_{37}O_{13}S$ (MH^+): 613.1949, found: 613.1922.

CONCLUSIONS

In conclusion, triol **4**, a versatile starting compound in the synthesis of several taxane analogues, was converted into ester **13** – an advanced intermediate in the attempted synthesis of cyclobutane taxane analogue **1**. However, the cyclization failed, due to the unexpected instability of the DMS protecting group in **13** under basic conditions. In addition, useful information was acquired on the reactivity of the obtained taxoid intermediates, as well as on the dimethylsilane (DMS) protecting group. Observation that alcohol **3** has the propensity for elimination of C_5 mesylate and the formation of the $\Delta^{5,6}$ double bond provides a possibility for a future investigation of 5,6-dehydro-C,D-spirolactone analogues. The synthesis and biological evaluation of a novel taxane analogue with a C,D-spirolactone moiety would be of considerable interest, bearing in mind the fact that this type of taxoids show mechanistically different cytotoxic action as compared to paclitaxel.

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ИЗВОД

СИНТЕТИЧКЕ СТУДИЈЕ АНАЛОГА ПАКЛИТАКСЕЛА СА МОДИФИКОВАНИМ D-ПРСТЕНОМ

ЗОРАНА ФЕРЈАНЧИЋ[1], РАДОМИР МАТОВИЋ[2] и РАДОМИР Н. САИЧИЋ[1]

[1]Хемијски факултет Универзитета у Београду, Студентски трг 12–16, п. пр. 158, 11000 Београд и [2]ИХТМ – Центар за хемију, Његошева 12, 11000 Београд

Развијена је синтетичка секвенца за добијање 9,10-ди-*O*-ацетил-4-десметилен-4*β*--(3-бутенил)-4*α*-хидрокси-5-О-мезилтаксицин I-1,2-карбоната (**3**), интермедијера у покушаној синтези циклобутанског аналога паклитаксела. Испитивана је могућност даље хемијске трансформације једињења **3**, као што је заштита стерно изразито заштићене С-4*α* хидроксилне групе и оксидативна фрагментација терминалне двоструке везе. Циклизација једињења **13** није дала жељени резултат – интермедијер са циклобутановим прстеном, што је последица неочекиване нестабилности DMS-заштитне групе у базним реакционим условима.

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