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Synthesis and antitumor activity of 2-(*m*-substituted-benzoyl)baccatin III analogs from taxinine

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Abstract—2-*m*-Azidobenzoyl and 2-*m*-chlorobenzoyl baccatin III analogs were prepared from taxinine, a major component in Japanese yew leaves. In this study, a novel acetyl migration from 13- to 4-hydroxyl group was observed. The antitumor activity of these compounds was evaluated.

1. Introduction

Taxol **1**, first isolated from the Pacific yew tree *Taxus brevifolia*,[1–3] is a powerful therapeutic drug for cancer chemotherapy. It exhibits remarkably high cytotoxicity and strong antitumor activity against different cancers resistant to existing anticancer drugs. Most works have focused on the structure-activity relationships (SAR)[2a,e] of **1** and have revealed that top of the diterpene moiety, C7, C9 and C10, tolerate a wide variety of substituents, while the C2 benzoyloxy group and C4 acetoxy group with the oxetane are essential for the biological activity. In addition the side chain at C13 also has been shown to be essential for biological activity, although it has been reported that 2-(*m*-azidobenzoyl)baccatin III **2b** has taxol-like activity.[4] To obtain more information about SAR, we undertook a synthesis of **2b** analogs.

The methods to synthesize 2-(*m*-substituted-benzoyl)-1,7-dideoxybaccatin III analogs from taxinine **3**,[5] a major taxoid component in Japanese yew leaves, and the evaluation of their antitumor activity is reported herein (Fig. 1).

2. Results and discussion

Deoxygenation of the 1-hydroxyl group of **2a** had been reported to be a difficult procedure,[6] thus we selected taxinine **3** as a starting material (Scheme 1).

In an attempt to construct an oxetane moiety on **3**, treatment of 5-decinnamoyltaxinine[5c] with OsO_4 and NMO in THF was tried. Although only an *exo* double bond was dihydroxylated, the reaction gave an inseparable mixture of 2-*O*-acetate and 20-*O*-acetate. This was due to an

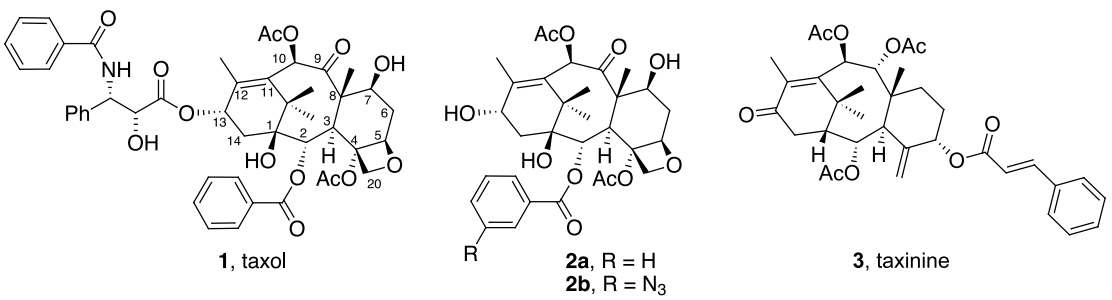

Figure 1.

Keywords: taxol; antitumor activity; taxinine; *m*-azidobenzoyl.

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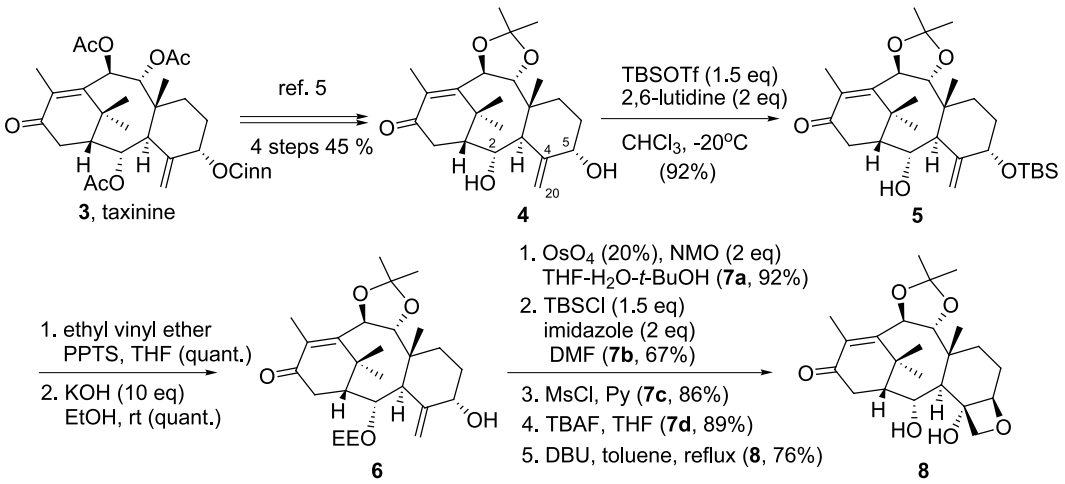


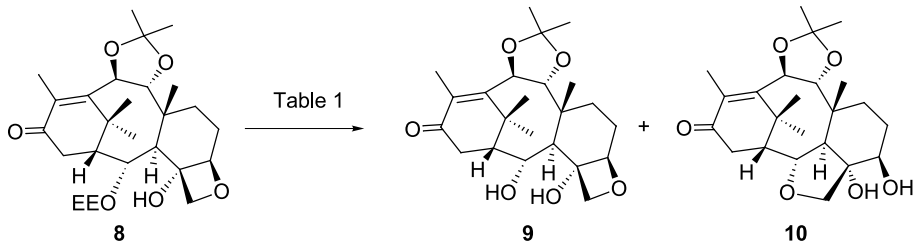
Scheme 1. Modification of taxinine.

intramolecular acetyl migration from the 2-position to a newly formed 20-hydroxyl group. Thus **3** was converted to the 2,5-diol **4** by the known methods.[5] The 5-hydroxyl group was selectively protected as TBS ether with TBSOTf and 2,6-lutidine at −20°C giving alcohol **5**. Attempts to protect the 2-hydroxyl group as TBS ether or MTM ether were unsuccessful and protection as Bn ether (with BnCl, NaH, TBAI, 40°C) was low yielding (40%). Finally, the 2-hydroxyl group could be protected as ethoxyethyl ether (EE) quantitatively. The TBS group was removed under alkaline conditions to give **6** in a quantitative yield. As the 2-hydroxyl group was protected by a non-migrating group, the *exo* olefin was dihydroxylated and the newly formed primary hydroxyl group was selectively protected as TBS ether. Then the secondary hydroxyl group at C5 was mesylated, the TBS group was removed and oxetane ring was formed according to Potier's procedure to give **8**.[7]

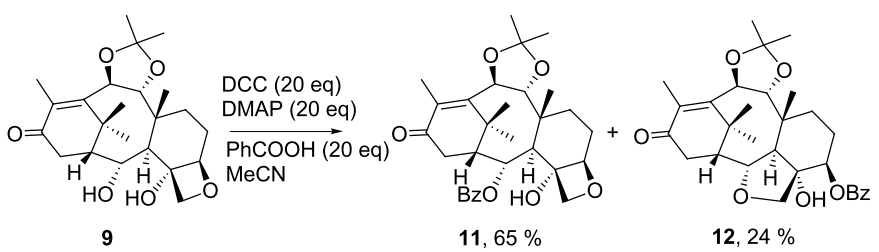
With **8** in hand, conditions to remove the EE group were investigated (Table 1). Under strongly acidic conditions (entries 3–5), the newly formed 2-hydroxyl group of **9** attacked the oxetane ring to form a furan ring (**10**).[8] Under mildly acidic condition (entry 2), **9** was obtained in a 32% yield.

Benzoylation of the 2-hydroxyl group of **9** was then tried. The attempt to introduce a 2,4-cyclic carbodiester using carbonyl diimidazole and pyridine (cat.) in CH_2Cl_2 at −20°C in order to utilize a PhLi-cleavage resulted in immediate isomerization to **10**.[9] Reaction of **9** with

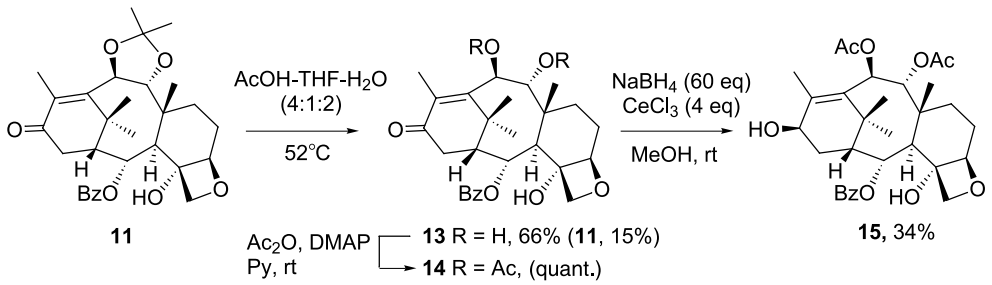
Table 1. Deprotection of the 2-EE group



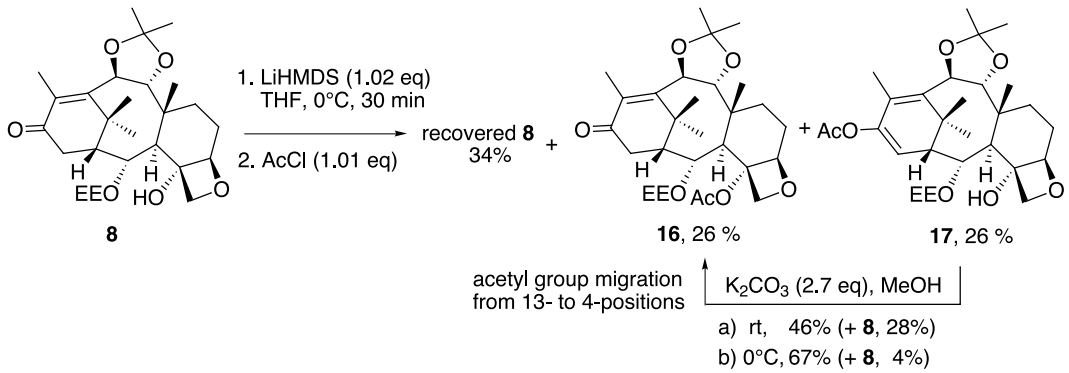
Entry	Conditions	**9** (%)	**10**	Recovery **8**
1	AcOH–THF–H_2O (1/1/1), rt, 3 h	–	–	100
2	AcOH–THF–H_2O (1/1/2), rt, 8 h	32	32	8
3	PPTS, MeOH, rt, 24 h	Trace	63	–
4	0.3% HCl–MeOH, 0°C, 25 min	Trace	74	15
5	2.5% HCl–MeOH, 0°C, 4 min	Trace	61	–



Scheme 2.



Scheme 3.



Scheme 4.

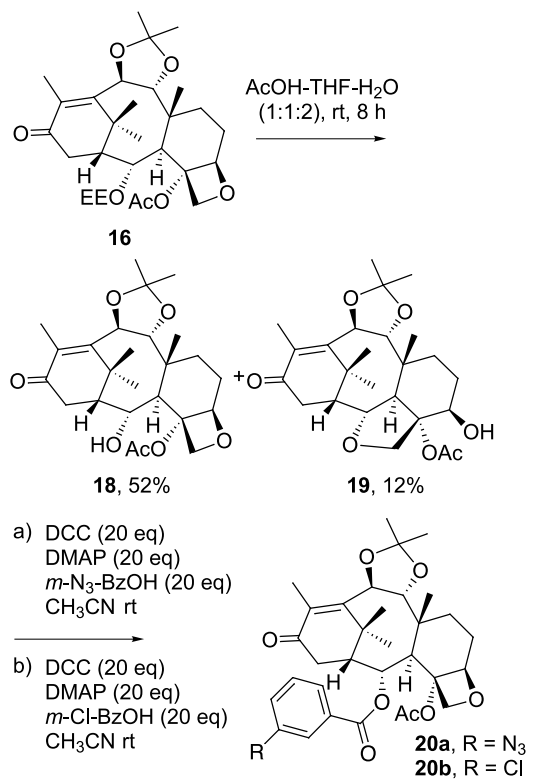
PhCOOH and DCC[10] gave the expected 2-*O*-benzoate **11**, but furan **12** was also formed (Scheme 2).

Next, although acetylation of the 4-hydroxyl group of **11** under a variety of conditions (1.1 equiv. DMAP, 20 equiv. Ac_2O, Py, 50°C), (10 equiv. LiHMDS, DMF, 0°C, 30 min, then 1 equiv. AcBr) etc., were examined, only the starting material was recovered. The acetylation was also tried for 9,10-dihydroxyl or diacetyl derivatives (**13**, **14** and **15**) in which the conformational rigidity could be eased, however, acetylation at 4-position did not occur (Scheme 3).

Finally, the 4-hydroxyl of compound **8** could be acetylated with acetyl chloride after treatment with LiHMDS to give **16** in a low yield, and enol acetate **17** as a by-product (Scheme 4).

This improvement of reactivity might be due to the smaller ethoxyethyl substituent at C2 of **8** relative to the benzoyl group of **11**. Treatment of **17** with K_2CO_3 in MeOH regenerated the enone **8**, and surprisingly, the reaction also gave acetate **16** through the acetyl migration from the 13-hydroxyl to the 4-hydroxyl. The proportion of the migration to the hydrolysis product increased from 65/32 at rt to 94/6 at 0°C (Scheme 4). This migration between the 13-hydroxyl and the 4-hydroxyl was reasonable for the possible conformation in which 13-hydroxyl locates close to the 4-hydroxyl in the molecular model analysis [3.46 Å from 4-oxygen to 13-*O*-acetyl carbonyl carbon at the 3rd stable conformational model of **17** (pc spartan pro 1.0.7 MM2 software)]. This base-catalyzed intramolecular acetyl transfer between the 13-hydroxyl and the 4-hydroxyl is a first example and interesting from a view point of an acetate origin on the 4-acetoxy oxetane biosynthesis.[2a,c,11]

The EE group of **16** was removed under the same condition used on **8**, to give **18** in a good yield. It is noteworthy that relative to the reaction on **8**, the yield of a furan by-product **19** was decreased. This improvement may be due to a conformational change, that is, the distance between generated 2-hydroxyl and C20 in compound **18** became longer than that of compound **9**; or the steric hindrance caused by the 4-*O*-acetyl group. This tendency was also



Scheme 5.

observed in the next reaction; *m*-N_3-Bz and *m*-Cl-Bz group were introduced to the compound **18** to give the compounds **20a** and **20b**, respectively, as a sole product without any production of the corresponding furan compounds (Scheme 5). These final compounds bear least functionalities for the antitumor activity without C_1–OH group: essential 2-*m*-substituted benzoyloxy and 4-acetoxy groups, and D-oxetane ring. As the oxygen functionalities at 7, 9 and 10-positions were known to be dispensable for the activity, the 9,10-acetonide moiety were not modified further.

The antitumor activity of synthesized taxoids (**20a** and **20b**) was evaluated as a function of inhibition of tumor cell growth using a panel screening coupled with a drug sensitivity database, based on the methods of National Cancer Institute.[12] We employed these acetonide compounds because the 9,10-positions were reported to be impartinent to the activity. The screening was accomplished using a sulforhodamine-B assay in 38 human tumor cell lines and mouse P388 leukemia cells. Disappointingly, both compounds exhibited only weak activities. Average concentration required for 50% growth inhibition (GI_{50}) was 48 μm for **20a** and 62 μm for **20b**. Even in the most effective result, GI_{50} was 22 μm for **20a** to SF-268 and 26 μm for **20b** to SNB-75. IC_{50} value of **2b**, drug concentration that inhibits cell division of A549 by 50% after 72 h, was reported as a value of 68 nm (0.068 μm); while GI_{50} values, those after 48 h, were >100 μM for **20a** and 67 μm for **20b**. The differential growth inhibitions were also too weak to guess the mode of action of these compounds by the COMPARE analysis. The reason why these compounds display a reduced activity than **2b** is as yet unclear, but it would be due to the less solubility of **20a** and **20b** with the less number of hydroxyl groups than **2b**.

In conclusion, 1,7-dideoxybacacatin III derivatives have been conveniently prepared in 12 steps in ca. 2.0% overall yield from readily available taxinine, a major taxoid component in Japanese yew leaves. In this study, a novel acetyl migration from 13- to 4-hydroxyl group was observed.

Although these analogs did not show any expected biological activity, the synthetic methodology described here and better understanding chemical reactivity of taxoids would be useful for the preparation of the candidates of biogenetic intermediates of taxol. Among eight oxygen functionalities on taxol, the hydroxyls at C7 and C1 is presumed to be introduced biogenetically at later stage.[13] Since 1,7-dideoxybaccatin III derivatives exist little in nature and is very difficult to prepare through deoxygenation of baccatin III **2a**,[6] this approach from taxinine would be able to apply for the labeled 1,7-dideoxybaccatin III derivatives.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were recorded on a Varian UNITY INOVA 500 and GEMINI 2000 spectrometers (300 and 500 MHz for ^1H and 125 MHz for ^{13}C in $CDCl_3$ unless otherwise noted, TMS as an internal standard). Mass spectra were recorded on a JEOL JMS-700 mass spectrometer. Optical rotation values were measured on a HORIBA SEPA-300 polarimeter. IR spectra were recorded on JASCO IR-Report-100. Merck silica gel 60 (70–230 mesh) was used for column chromatography and Merck silica gel 60 F_{254} was used for preparative thin-layer chromatography (PTLC).

3.2. Materials: isolation of taxinine

The needles of the Japanese yew collected in Sendai or Hokkaido, Japan was dried at rt for 1 month and cut into pieces by GARDEN SHEDDER HG-1500 (Sanyo metal Co. L.T.D). The rough powder was immersed into MeOH for 2 weeks. The organic layer was filtered by the mixture of Celite and Carbon powder (5/1) and the filtrate was concentrated in vacuo. The residue was dissolved into EtOAc and washed with saturated NaCl solution of 1% NaOH and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on column chromatography (EtOAc/hexane, 1/2), yielding crude taxinine (R_f=0.45). The crude was purified by recrystallization (EtOH or EtOAc) to give pure taxinine (ca. 2 g/kg flesh leaves).

3.2.1. Selective protection at 5-OH of diol 4 as TBS ether 5; 20-*t*-butyldimethylsilyloxy-9α,10β-isopropylidendioxy-4 (20),11-taxadien-13-one (5). To a solution of **4** (927 mg, 2.38 mmol) and 2,6-lutidine (510 mg, 4.76 mmol) in dry $CHCl_3$ (3 ml) was added TBSOTf (942 mg, 3.57 mmol) at −20°C. After stirring for 2 h, the mixture was diluted with $CHCl_3$ (30 ml). The reaction mixture was washed with aqueous $NaHCO_3$, aqueous NH_4Cl and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane, 1/2), yielding **5** (1086 mg, 2.21 mmol, 92%) as amorphous solid; $[\alpha]_D^{20}$=+81 (*c* 0.013, $CHCl_3$); ^1H NMR (300 MHz), δ=0.01 (s, 3H, Me_2Si), 0.03 (s, 3H, Me_2Si), 0.86 (s, 9H, *t*BuSi), 1.02 (s, 3H, 19-Me), 1.22 (m, 2H), 1.22 (s, 3H, 17-Me), 1.43 (s, 3H, Me_2CO_2), 1.49 (s, 3H, Me_2CO_2), 1.55–1.70 (m, 2H), 1.66 (s, 3H, 16-Me), 2.06 (s, 3H, 18-Me), 2.20 (d, *J*=19.8 Hz, 1H, 14α-H), 2.20 (m, 1H, OH), 2.40 (dd, *J*=2.5, 7.1 Hz, 1H, 1-H), 2.78 (dd, *J*=7.1, 19.8 Hz, 1H, 14β-H), 3.13 (d, *J*=6.6 Hz, 1H, 3-H), 4.20 (m, 2H, 9-H and 2-H), 4.23 (m, 1H, 5-H), 4.92 (d, *J*=9.3 Hz, 1H, 10-H), 5.10 (s, 1H, 20-H), 5.23 (s, 1H, 20-H); IR (KBr) cm^{-1}: 3600–3200 (s, O–H), 3000–2800 (s), 1660 (s, C=O), 1470 (m), 1460 (m), 1443 (m), 1405 (m), 1380 (s), 1370 (s), 1340 (w), 1305 (w), 1280 (w), 1250 (s), 1230 (s), 1200 (s), 1160 (s), 1140 (s), 1120 (s), 1060 (s), 1040 (w), 1020 (w), 950 (s), 920 (s), 870 (s), 850 (s), 830 (s), 780 (s), 730 (s), 700 (w), 670 (w); ^{13}C NMR (125 MHz, $CDCl_3$), δ=199.71, 150.28, 148.65, 137.91, 113.42, 107.70, 82.01, 76.95, 75.50, 68.01, 51.25, 43.34, 41.32, 38.07, 37.89, 36.21, 32.58, 27.27, 26.81, 26.24, 26.03, 24.48, 18.78, 17.64, 14.17, −4.47, −4.89; HR-FAB-MS, calcd for $C_{29}H_{49}O_5Si$ $(MH)^+$ *m*/*z* 505.3346, found 505.3346.

3.2.2. 2α-Ethoxyethoxy-5α-hydroxy-9α,10β-isopropylidendioxy-4 (20),11-taxadien-13-one (6). To a solution of **5** (300 mg, 0.0589 mmol) and *p*-toluenesulfonic acid (cat.) in THF (2 ml) was slowly added ethyl vinyl ether (0.280 ml,

2.95 mmol) at rt After being stirred for 2 h, the reaction mixture was diluted with EtOAc (30 ml) and the organic layer was washed with aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, and concentrated in vacuo. The residue was filtered by carbon powder, yielding a crude compound (340 mg, 0.583 mmol, 99%). To the compound (340 mg, 0.583 mmol) in EtOH (1 ml) was added KOH [5.89 mmol, in EtOH (20 ml)]. The reaction mixture was stirred at rt for 6 h and was condensed in vacuo. The residue was diluted with $CHCl_3$. To the mixture was added carefully AcOH [0.330 ml, 5.76 mmol in H_2O (10 ml)] at 0°C and the organic layer was washed with aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane, 1/2), yielding **6** quantitatively as amorphous solid; ^{1}H NMR (300 MHz), δ=1.02 and 1.07 (s, each 1.5H, 19-Me), 1.20 and 1.22 (s, each 1.5H, 17-Me), 1.23 and 1.24 (t, J=7.1 Hz, each 1.5H, 4′-Me), 1.31 and 1.34 (d, J=5.5 Hz, each 1.5H, 2′-Me), 1.45 (s, 3H, Me_2CO_2), 1.56–1.63 (m, 2H), 1.71–1.82 (m, 2H), 2.08 and 2.09 (s, each 1.5H, 18-Me), 2.20 and 2.52 (d, J=7.1 Hz, each 0.5H, 3-H), 2.32 and 2.35 (d, J=10.4 Hz, each 0.5H, 14-H), 2.72 and 2.82 (dd, J=7.1, 19.8 Hz, each 0.5H, 14-H), 3.20 (m, 1H, 1-H), 3.49–3.61 (m, 2H, 3′-H), 4.13 (m, 1H, 5-H), 4.25 and 4.16 (m, each 0.5H, 2-H), 4.19 and 4.21 (d, J=5.8 Hz, each 0.5H, 9- or 10-H), 4.64 and 4.70 (q, J=5.2 Hz, each 0.5H, 1′-H), 4.92 and 4.93 (d, J=5.5 Hz, each 0.5H, 9- or 10-H), 5.11, 5.16, 5.29, and 5.65 (m, each 0.5H, 20-H); IR (KBr) cm^{-1}: 3600–3200 (s, O–H), 1670 (s, C=O), 1450 (m), 1370 (s), 1230 (s), 1200 (s), 1040 (s), 870 (m), 810 (m). Anal. calcd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 69.71; H, 9.15.

The pair of diastereomers of **6**, **7a**, **7b**, **7c**, **7d**, **8**, **16** and **17** could not be separated from each other.

3.2.3. Dihydroxylation of 6 to 7a; 2α-ethoxyethoxy-4α,5α,20-trihydroxy-9α,10β-isopropylidendioxy-11-taxen-13-one (7a). To a solution of **6** (439 mg, 0.949 mmol) in THF/H_2O (2 ml/1 ml) were added *N*-methylmorpholine *N*-oxide (1300 mg, 11.1 mmol) and OsO_4 (0.0197 mmol in *t*-BuOH, 9.60 ml) at 0°C. After being stirred for 2 days, $Na_2S_2O_4$ (200 mg) was added to the mixture. After being stirred for additional 1 h, the mixture was diluted with EtOAc (40 ml) and the organic layer was washed with aqueous NH_4Cl and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane, 1/2), yielding **7a** (433 mg, 0.869 mmol, 92%) as amorphous solid; ^{1}H NMR (300 MHz), δ=1.03 and 1.08 (s, each 1.5H, 19-Me), 1.20–1.30 (m, 6H, 17-Me, 4′-Me), 1.35 (d, J=4.9 Hz, 1.5H, 2′-Me), 1.41 (d, J=4.9 Hz, 1.5H, 2′-Me), 1.42 (s, 3H, Me_2CO_2), 1.47 (s, 3H, Me_2CO_2), 1.50–1.63 (m, 2H), 1.65–1.82 (m, 2H), 2.04 (s, 3H, 18-Me), 2.56 (s, 0.5H, OH), 2.68 (s, 0.5H, OH), 2.82 (s, 0.5H, OH), 2.84 (s, 0.5H, OH), 2.86 and 2.93 (d, J=4.7 Hz, each 0.5H, 3-H), 2.65–2.84 (m, 2H, 14-H), 2.22 and 2.59 (m, each 0.5H, 1-H), 3.49 (m, 0.5H, 20-H), 3.51–3.61 (m, 2H, 3′-H; and 0.5H, H-20), 3.56 (m, 1H, 9- or 10-H), 3.64 (m, 0.5H, 20-H), 3.80 (m, 1H, 5-H), 3.96 (s, 0.5H, OH), 4.05 (s, 0.5H, OH), 4.34 (m, 0.5H, 2-H), 4.67 (q, J=5.2 Hz, each 0.5H, 1′-H), 4.83 (d, J=9.3 Hz, 1H, 9- or 10-H), 5.50 (q, J=5.0 Hz, each 0.5H, 1′-H), 4.10 (m, 0.5H, 20-H); IR (NaCl) cm^{-1}: 3600–3200 (s, O–H), 1660 (s, C=O), 1470 (m), 1440 (s), 1370 (s), 1340 (s), 1300 (m), 1270 (m), 1230 (s), 1200 (s), 1160 (s), 1140 (s), 1120 (s), 1080 (s), 1050 (s), 1030 (s), 940 (m), 920 (m), 870 (s), 830 (m), 810 (m), 790 (m), 750 (s), 690 (s). Anal. calcd for $C_{27}H_{44}O_8$: C, 65.30; H, 8.93. Found: C, 64.75; H, 8.33.

3.3. Construction of oxetane ring from 7a to 8a

3.3.1. Silylation of 7a to 7b; 20-*t*-butyldimethylsilyloxy-2α-ethoxyethoxy-4α,5α-dihydroxy-9α,10β-isopropylidendioxy-11-taxen-13-one (7b). To a solution of **7a** (599 mg, 1.21 mmol) in DMF (2 ml) were added imidazole (163 mg, 2.40 mmol) and TBDMSCl (274 mg, 1.82 mmol). After being stirred for 3 h at rt, the mixture was diluted with EtOAc (30 ml). To the mixture was carefully added aqueous $NaHCO_3$ at 0°C. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane, 1/3), yielding **7b** (605 mg, 0.992 mmol, 82%) as amorphous solid; ^{1}H NMR (300 MHz), δ=0.01–0.09 (m, 6H, Me_2Si), 0.88 and 0.89 (s, each 4.5H, *t*BuSi), 1.01 and 1.06 (s, each 1.5H, 19-Me), 1.18–1.28 (m, 3H, 4′-Me; and m, 1.5H, 2′-Me), 1.33 (d, J=5.2 Hz, 1.5H, 2′-Me), 1.42 (s, 3H, Me_2CO_2), 1.48 (s, 3H, Me_2CO_2), 1.50–1.63 (m, 2H),1.61 and 1.62 (s, each 1.5H, 16-Me), 1.65–1.82 (m, 2.5H), 2.03 (s, 3H, 18-Me), 2.10 (m, 0.5H, 1-H), 2.42–2.63 (m, 2H, 3-H and OH), 2.72 (dd, J=8.0, 18.7 Hz, 14β-H), 3.27 (d, J=18.7 Hz, 0.5H, 14α-H), 3.34 (d, J=18.7 Hz, 0.5H, 14α-H), 3.46–3.58 (m, 3H, 3′-H and other), 3.60 (m, 1H, 5-H), 3.89 (d, J=9.6 Hz, 1H), 3.99 (dd, J=2.2, 4.4 Hz, 0.5H, 2-H), 4.13 and 4.14 (d, J=9.1 Hz, each 0.5H, 9-H or 10-H), 4.19 (dd, J=2.5, 4.7 Hz, 0.5H, 2-H), 4.40 (d, J=9.9 Hz, 1H, 9-H or 10-H), 4.55 and 4.70 (q, J=5.2 Hz, each 0.5H, 1′-H), 4.83 (d, J=9.1 Hz, 1H, 9-H or 10-H); IR (neat) cm^{-1}: 3600–3300 (s, O–H), 1670 (s, C=O), 1450 (m), 1370 (s), 1230 (s), 1160 (s), 1120 (s), 1080 (s), 1020 (s), 1000 (s), 930 (m), 870 (s), 830 (s), 770 (m). Anal. calcd for $C_{33}H_{58}O_8Si$: C, 64.88; H, 9.57. Found: C, 64.81; H, 9.57.

3.3.2. Mesylation of 7b to 7c; 20-*t*-butyldimethylsilyloxy-2α-ethoxyethoxy-4α-hydroxy-9α,10β-isopropylidendioxy-5α-methanesulfonyloxy-11-taxen-13-one (7c). To a solution of **7b** (605 mg, 0.992 mmol) in pyridine (3 ml) at 0°C was added MsCl (1.98 mmol, 227 mg). The reaction mixture was stirred for 24 h at rt, after which time EtOAc (15 ml) was added. To the mixture, aqueous $NaHCO_3$ was added at 0°C. The mixture was stirred for 6 h at 0°C. The organic layer was washed with brine, H_2O, aqueous $CuSO_4$, H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane, 1/2), yielding **7d** (589 mg, 0.855 mmol, 86%) as amorphous solid; ^{1}H NMR (300 MHz), δ=0.07 (s, 6H, Me_2Si), 0.85 (s, 9H, *t*BuSi), 1.07 and 1.92 (s, each 1.5H, 19-Me), 1.17–1.27 (m, 6H, 4′-Me, 17-Me), 1.28 (d, 1.5H, J=5.2 Hz, 2′-Me), 1.35 (d, 1.5H, J=5.0 Hz, 2′-Me), 1.41 (s, 3H, Me_2CO_2), 1.47 (s, 3H, Me_2CO_2), 1.50–1.70 (m, 1H), 1.61 and 1.63 (s, each 1.5H, 16-Me), 1.80–2.00 (m, 3H), 2.09 (s, 3H, 18-Me), 2.14 and 2.52 (m, each 0.5H, H-1), 2.46 and 2.47 (d, J=4.4 Hz, each 0.5H, 3-H), 2.74 (dd, J=7.1, 19.5 Hz, 0.5H, 14β-H), 2.80 (dd, J=7.1, 19.8 Hz, 0.5H, 14β-H), 2.98 and 2.99 (s, each 1.5H, $MeSO_3$), 3.15 (d, J=19.8 Hz, 0.5H, 14α-H), 3.17 (d, J=19.5 Hz, 0.5H, 14α-H), 3.34 and 3.36, (s, each 0.5H,

4-OH), 3.40–3.60 (m, 2H, 3′-H), 3.72 (d, J=10.7 Hz, 1H), 3.91 (d, J=11.0 Hz, 0.5H), 4.00 (dd, J=2.2, 4.4 Hz, 0.5H, H-2), 4.13 (d, J=9.34 Hz, 1H), 4.20 (dd, J=2.2, 4.4 Hz, 0.5H, 2-H), 4.32 (d, J=11.0 Hz, 0.5H), 4.56 and 4.69 (q, J=5.2 Hz, each 0.5H, 1′-H), 4.80 (d, J=9.1 Hz, 1H, 9- or 10-H), 4.88 (m, 1H, H-5); IR (neat) cm^{-1}: 3600–3400 (s, O–H), 1670 (s, C=O), 1370 (s), 1350 (s), 1250 (m), 1230 (m), 1200 (m), 1170 (s), 1150 (m), 1080 (s), 1040 (s), 1010 (m), 1000 (m), 970 (m), 960 (m), 930 (s), 900 (m), 840 (s), 770 (m), 750 (m). Anal. calcd for $C_{34}H_{60}O_{10}SSi$: C, 59.27; H, 8.78. Found: C, 59.18; H, 8.78.

3.3.3. Desilylation of 7c to 7d; 2α-ethoxyethoxy-4α,20-dihydroxy-9α,10β-isopropylidendioxy-5α-methanesulfonyloxy-11-taxen-13-one (7d). To a solution of **7c** (589 mg, 0.855 mmol) in THF (2 ml) at 0°C was added tetra-*n*-butylammonium fluoride (1.0 ml, 1.0 mmol in THF). The reaction mixture was stirred for 1 h at rt, after which time EtOAc (50 ml) was added. The mixture was washed with aqueous NH_4Cl and brine. The organic layer was dried over Na_2SO_4 and was concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane, 1/2), yielding **7d** (447 mg, 0.778 mmol, 91%) as amorphous solid; ^1H NMR (300 MHz), δ=1.06 and 1.12 (s, each 1.5H, 19-Me), 1.21–1.29 (m, 3H, 4′-Me), 1.25 (s, 3H, 17-Me), 1.33 (d, 1.5H, J=5.0 Hz, 2′-Me), 1.38 (d, J=5.0 Hz, 1.5H, 2′-Me), 1.30–1.50 (m, 1H), 1.41 (s, 3H, Me_2CO_2), 1.47 (s, 3H, Me_2CO_2), 1.50–1.70 (m, 2H), 1.57 and 1.62 (s, each 1.5H, 16-Me), 1.80–2.00 (m, 2H), 2.10 (s, 3H, 18-Me), 2.50–2.64 (m, 1H), 2.70–2.90 (m, 2H), 2.98 and 2.99 (s, each 1.5H, $MeSO_3$), 2.38, 2.52, 3.97, and 4.08 (m, each 0.5H, OH), 3.42–3.61 (m, 4H, 3′-H, 9-H or 10-H, and 20-H), 4.13 (m, 0.5H, 1H, H-20), 4.13 (dd, J=2.5, 9.1 Hz, 0.5H, 2-H), 4.26 (m, 0.5H, H-20), 4.32 (m, 0.5H, H-2), 4.64 and 4.76 (q, J=5.2 Hz, each 0.5H, 1′-H), 4.82 (d, J=9.3 Hz, 1H, 9-H or 10-H), 4.94 (m, 1H, 5-H); IR (KBr) cm^{-1}: 3600–3200 (s, O–H), 1640 (s, C=O), 1370 (m), 1320 (s), 1230 (m), 1160 (s), 1080 (m), 1050 (s), 1040 (s), 990 (m), 920 (s), 990 (m); HR-FAB-MS, calcd for $C_{28}H_{46}O_{10}SNa$ $(MNa)^+$ m/z 597.2707, found 597.2704.

3.3.4. Construction of oxetane ring: 7d to 8; 5β,20-epoxy-2α-ethoxyethoxy-4α-hydroxy-9α,10β-isopropylidendioxy-11-taxen-13-one (8). To a solution of **7d** (447 mg, 0.778 mmol) in toluene (4 ml) was added DBU (3.89 mmol, 0.580 ml). The mixture was stirred at reflux temperature for 1 h, after which time EtOAc (50 ml) was added. The mixture was washed with aqueous NH_4Cl, aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane, 1/2), yielding **8** (243 mg, 0.507 mmol, 65%) as amorphous solid; ^1H NMR (300 MHz), δ=1.08–1.32 (m, 7H, 19-Me, 4′-Me, 7-H), 1.22 (s, 3H, 17-Me), 1.43 (s, 3H, Me_2CO_2), 1.50 (s, 3H, Me_2CO_2), 1.51 (s, 3H, 2′-Me) 1.65 and 1.67 (s, each 1.5H, 16-Me), 1.82 (d, J=3.5 Hz, 1H), 1.92 (s, 3H, 18-Me), 1.92–2.26 (m, 3H), 2.22 (m, 0.5H, 1-H), 2.60 (m, 0.5H, 1-H), 2.70 (m, 2H, 14-H), 2.93 and 3.00 (s, each 0.5H, 4-OH), 3.45–3.60 (m, 2H, 3′-H), 4.10 (dd, J=2.5, 5.0 Hz, 0.5H, 2-H), 4.20–4.38 (m, 3H), 4.55 (d, J=8.0 Hz, 0.5H), 4.57–4.77 (m, 2.5H), 4.89 (d, J=8.0 Hz, 0.5H); IR (neat) cm^{-1}: 3600–3200 (m, O–H), 1670 (s, C=O), 1450 (m), 1380 (m), 1220 (m), 1170 (s), 1090 (m), 1050 (s), 1000 (m), 970 (m), 870 (m), 750 (m). Anal. calcd for $C_{27}H_{42}O_7$: C, 67.76; H, 8.84. Found: C, 67.47; H, 9.02.

3.3.5. Deprotection of ethoxyethyl group: 5β,20-epoxy-2α,4α-dihydroxy-9α,10β-isopropylidendioxy-11-taxen-13-one (9) and 2α,20-epoxy-4α,5α-dihydroxy-9α,10β-isopropylidendioxy-11-taxen-13-one (10). Compound **8** (243 mg, 0.507 mmol) was dissolved in a mixture of HOAc/THF/H_2O (2 ml/2 ml/4 ml). After being stirred for 24 h at rt, the mixture was diluted with EtOAc (50 ml). The organic layer was washed with aqueous $NaHCO_3$, aqueous NH_4Cl, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography ($CHCl_3$/MeOH, 20/1), yielding **9** (66.0 mg, 0.163 mmol, 32%) as amorphous solid, **10** (65.0 mg, 0.160 mmol, 32%) as amorphous solid, and recovered **8** (19.0 mg, 0.039 mmol, 8.0%).

Compound **9** (*oxetanol*). ^1H NMR (300 MHz), δ=1.22 (s, 3H, 19-Me), 1.15–1.35 (m, 1H, 7-H), 1.43 (s, 3H, Me_2CO_2), 1.49 (s, 3H, Me_2CO_2), 1.66 (s, 3H, 16-Me), 1.65–1.75 (m, 1H, 6-H), 1.75–1.85 (m, 1H, 7-H), 1.78 (d, 1H, J=5.2 Hz, 3-H), 1.9–2.0 (m, 1H, 6-H), 1.92 (s, 3H, 18-Me), 2.28 (m, 1H, 1-H), 2.75 (m, 1H, OH), 2.75 (m, 2H, 14-H), 3.83 (m, 1H, OH), 4.27 (d, J=9.6 Hz, 1H, 9-H), 4.30 (m, 1H, 2-H), 4.36 (d, J=8.5 Hz, 20-H), 4.78 (d, J=8.5 Hz, 1-H, 20-H), 4.70 (m, 1H, 5-H), 4.64 (d, J=9.3 Hz, 1H, 10-H); IR (NaCl) cm^{-1}: 3600–3200 (s, O–H), 1710 (m), 1650 (m), 1450 (m), 1370 (m), 1230 (m), 1170 (m), 1050 (m), 870 (m); HR-FAB-MS, calcd for $C_{25}H_{35}O_6$ $(M+H)^+$ m/z 448.2432, found 448.2436.

Compound **10** (*furanol*). ^1H NMR (300 MHz), δ=1.20 (s, 6H, 17-Me and 19-Me), 1.35–1.45 (m, 1H, 7-H), 1.43 (s, 3H, Me_2CO_2), 1.46 (s, 3H, Me_2CO_2), 1.60 (s, 3H, 16-Me), 1.65–1.75 (m, 1H, 6-H), 1.75–1.85 (m, 1H, 7-H), 1.9–2.0 (m, 1H, 6-H), 1.88 (s, 3H, 18-Me), 2.00 (d, 1H, J=5.5 Hz, 3-H), 2.40 (dd, 1H, J=3.3, 6.9 Hz, 1-H), 2.45 (m, 2H, OH), 2.65 (dd, 1H, J=6.9, 19.7 Hz, 14β-H), 3.03 (d, 1H, J=20.0 Hz, 14α-H), 3.66 (d, 1H, J=11.4 Hz, 20-H), 3.75 (d, 1H, J=11.4 Hz, 20-H), 4.05 (t, 1H, J=6.5 Hz, 5-H), 4.22 (d, 1H, J=9.6 Hz, 9-H), 4.39 (dd, 1H, J=3.9, 4.7 Hz, 2-H), 4.53 (d, 1H, J=9.3 Hz, 10-H); IR (NaCl) cm^{-1}: 3200–3600 (s, OH), 1800 (s), 1760 (s), 1670 (s), 1640 (s), 1390 (w), 1370 (w), 1260 (w), 1230 (s), 1210 (s), 1180 (s), 1080 (s), 1040 (s), 1000 (s), 1000 (s), 870 (w), 760 (w); HR-FAB-MS, calcd for $C_{25}H_{35}O_6$ $(M+H)^+$ m/z 448.2432, found 448.2437.

3.3.6. Benzoylation of 9 to 11 and 12; 2α-benzoyloxy-5β,20-epoxy-4α-hydroxy-9α,10β-isopropylidendioxy-11-taxen-13-one (11) and 5β-benzoyloxy-2α,20-epoxy-4α-hydroxy-9α,10β-isopropylidendioxy-11-taxen-13-one (12). To a solution of **9** (105 mg, 0.259 mmol), benzoic acid (633 mg, 5.18 mmol), and DMAP (632 mg, 5.18 mmol) in dry CH_3CN (10 ml) at 0°C was added DCC [1067 mg, 5.18 mmol in dry CH_3CN (10 ml)]. After being stirring for 24 h, EtOAc (50 ml) was added to the mixture. The organic layer was washed with the solution of HCl (1N, 25 ml), brine, aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography ($CHCl_3$/MeOH, 25/1), yielding **11** (86.0 mg, 0.168 mmol, 65%) as

amorphous solid and **12** (31.0 mg, 0.0608 mmol, 24%) as amorphous solid.

Compound **11**. $[\alpha]_D^{20}$=+39 (*c* 0.017, $CHCl_3$); ^1H NMR (300 MHz), δ=1.25 (m, 1H, H-7), 1.25 (s, 3H, Me-19), 1.43 (s, 3H, Me_2CO_2), 1.44 (s, 3H, Me_2CO_2), 1.57 (s, 3H, 17-Me), 1.50–1.70 (m, 1H), 1.80 (s, 3H, 16-Me), 1.85–2.20 (m, 2H), 1.93 (s, 3H, 18-Me), 2.14 (d, *J*=5.0 Hz, 3-H), 2.21 (d, *J*=2.5 Hz, 1H, 1-H), 2.77 (dd, *J*=7.2, 19.8 Hz, 14β-H), 3.25 (d, *J*=19.8 Hz, 1H, 14α-H), 4.19 (d, *J*=8.2 Hz, 1H, 20-H), 4.37 (d, *J*=8.2 Hz, 1H, 20-H), 4.46 (d, *J*=9.3 Hz, 1H, 9 or 10-H), 4.74 (m, 1H, 5-H), 4.75 (d, *J*=9.3 Hz, 9 or 10-H), 7.45 (m, 2H, arom.), 7.57 (m, 1H, arom.), 8.01 (dd, *J*=8.2, 1.1 Hz, 2H, arom.); IR (neat) cm^{-1}; 3400 (s, O–H), 1710 (s, C=O), 1450 (s, C=O), 1360 (m), 1310 (m), 1050 (s) 1040 (m), 1020 (m), 980 (m), 860 (m), 710 (m); HR-EI-MS, calcd for $C_{30}H_{39}O_7$ $(M+H)^+$ *m/z* 511.2694, found 511.2698.

Compound **12**. $[\alpha]_D^{20}$=+120 (*c* 0.0095, $CHCl_3$); ^1H NMR (300 MHz), δ=1.20–1.40 (m, 1H, 7-H), 1.29 (s, 3H, 17-Me or 19-Me), 1.30 (s, 3H, 17-Me or 19-Me), 1.47 (s, 3H, Me_2CO_2), 1.50 (s, 3H, Me_2CO_2), 1.64 (s, 3H, 16-Me), 1.91–2.00 (m, 2H), 1.96 (s, 3H, 18-Me), 2.20 (m, 2H), 2.42 (m, 1H), 2.68 (dd, *J*=7.1, 19.5 Hz, 1H, 14β-H), 3.19 (m, 2H, 14α-H, 4-OH), 3.59 (d, *J*=10.0 Hz, 1H, 20-H), 3.64 (d, *J*=9.8 Hz, 1H, 20-H), 4.29 (d, *J*=9.5 Hz, 1H, 9- or 10-H), 4.32 (m, 1H, 2-H), 4.64 (d, *J*=9.5 Hz, 1H, 9- or 10-H), 5.27 (m, 1H, 5-H), 7.47 (m, 2H, arom.), 7.62 (m, 1H, arom.), 8.01 (d, *J*=1.2 Hz, 2H, arom.); HR-FAB-MS, calcd for $C_{30}H_{38}O_7Na$ $(M+Na)^+$ *m/z* 533.2513, found 533.2519.

3.4. Trial for acetylation of 11 (method 1)

To a solution of **11** (65.0 mg, 0.127 mmol) in THF (1.0 ml), was added LiHMDS (0.170 ml, 0.170 mmol) at 0°C. After being stirred for 30 min, AcCl (3.1 mg, 0.042 mmol) was added. The mixture was stirred for 1 h, after which time, EtOAc (30 ml) was added. The mixture was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, almost all **11** (62.0 mg, 0.122 mmol, 95%) was recovered.

3.5. Trial for acetylation of 11 (method 2)

To a solution of **11** (4.0 mg, 0.0078 mmol) and DMAP (8.0 mg, 0.065 mmol) in dry pyridine (0.5 ml) was added Ac_2O (20 μl). After the mixture was stirred for 24 h at 50°C, EtOAc (20 ml) was added. The organic layer was washed with brine, H_2O, aqueous $CuSO_4$, H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, almost all **11** was recovered and no acetylated compound was obtained.

3.5.1. Deprotection of isopropylidene group; 2α-benzoyloxy-5α,20-epoxy-4α,9α,10β-trihydroxy-11-taxen-13-one (13). Compound **11** (34.5 mg, 0.0675 mmol) was dissolved in a mixture of AcOH/THF/H_2O (2 ml/0.5 ml/1 ml). After being stirred for 29 h at 52°C, the mixture was diluted with EtOAc (50 ml). The organic layer was washed with aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography ($CHCl_3$/MeOH, 20/1), yielding **13** (21.0 mg, 0.0446 mmol, 66%) as amorphous solid, and recovered **11** (5.3 mg, 0.010 mmol, 15%); $[\alpha]_D^{20}$=+26 (*c* 0.0097, MeOH); ^1H NMR (300 MHz, CD_3OD), δ=1.06 (dt, *J*=12.9, 6.6 Hz, 1H, 7-H), 1.15 (s, 3H, 19-Me), 1.41 (s, 3H, 17-Me), 1.70–1.90 (m, 1H), 1.72 (s, 3H, 16-Me), 1.87 (s, 3H, 18-Me), 2.00–2.20 (m, 3H), 2.35 (d, *J*=5.2 Hz, 1H, 3-H), 2.63 (dd, *J*=6.8, 19.8 Hz, 1H, 14-H), 3.40 (d, *J*=19.5 Hz, 1H, 14-H), 4.12 (d, *J*=9.3 Hz, 1H, 20-H), 4.21 (s, 2H, H-9 and H-10), 4.61 (d, *J*=9.6 Hz, 1H, 20-H), 4.69 (dd, *J*=2.5, 8.8 Hz, 1H, 5-H), 5.81 (m, 1H), 7.47 (m, 2H, arom.), 7.62 (m, 1H, arom.), 8.01 (d, *J*=1.2 Hz, 2H, arom.); IR (neat) cm^{-1}: 3200–3600 (s, O–H), 1710 (s, C=O), 1660 (s, C=O), 1260 (s), 1090 (w), 1050 (w), 705 (m), 1020 (m), 970 (w), 920 (w); HR-FAB-MS, calcd for $C_{27}H_{34}O_7$ M^+ *m/z* 470.2302, found 470.2307.

3.5.2. Acetylation of 13 to 14; 9α,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-4α-hydroxy-11-taxen-13-one (14). To a solution of **11** (19.5 mg, 0.0347 mmol) and DMAP (cat.) in dry pyridine (0.4 ml) was added Ac_2O (50 μl). After the mixture was stirred for 24 h, EtOAc (20 ml) was added. The organic layer was washed with brine, H_2O, aqueous $CuSO_4$, H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, yielding **14** (22.7 mg, 0.0347 mmol, quantitative) as amorphous solid; $[\alpha]_D^{20}$=+14 (*c* 0.011, $CHCl_3$); ^1H NMR (300 MHz), δ=1.15 (m, 1H, 7-H), 1.17 (s, 3H, 19-Me), 1.26 (s, 3H, 17-Me), 1.41 (s, 3H, 16-Me), 1.50–1.70 (m, 2H), 1.85 (s, 3H, 18-Me), 2.09 (s, 3H, MeCO), 2.10 (m, 1H), 2.12 (s, 3H, MeCO), 2.24 (dd, *J*=6.9, 2.7 Hz, 1H, H-1), 2.46 (d, *J*=5.2 Hz, 1H, 3-H), 2.76 (m, 1H, OH), 2.76 (dd, *J*=6.9, 19.8 Hz, 1H, 14-H), 3.40 (d, *J*=19.5 Hz, 1H, 14-H), 4.19 (d, *J*=8.3 Hz, 1H, 20-H), 4.36 (d, *J*=8.5 Hz, 1H, H-20), 4.72 (dd, *J*=3.0, 9.3 Hz, 1H, 5-H), 5.93 (dd, *J*=2.5, 5.5 Hz, 1H, 2-H), 5.98 (d, 2H, *J*=5.5 Hz, 9-H and 10-H), 7.47 (m, 2H, arom.), 7.62 (m, 1H, arom.), 8.01 (d, *J*=1.2 Hz, 2H, arom.); IR (neat) cm^{-1}: 3200–3600 (s, O–H), 1710 (s, C=O), 1660 (s, C=O), 1260 (s), 1090 (w), 1050 (w), 705 (m), 1020 (m), 970 (w), 920 (w); HR-FAB-MS, calcd for $C_{31}H_{39}O_9$ M^+ *m/z* 555.2591, found 555.2588.

3.6. Trial for acetylation of 14

To a solution of **14** (11.7 mg, 0.0211 mmol) in THF (0.5 ml), was added LiHMDS (32 μl, 0.032 mmol) at 0°C. After being stirred for 30 min, AcCl (3.3 mg, 0.042 mmol) was added and the mixture was stirred for 1 h. After which time, the mixture was diluted with EtOAc (20 ml). The mixture was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to recover **14**.

3.6.1. Reduction of 14; 9α,10β-diacetoxy-4α,20-epoxy-2α-ethoxyethoxy-11-taxene-13β-ol (15). A stirred suspension of **14** (22.0 mg, 0.0396 mmol) in dry MeOH (1.5 ml) was treated with $CeCl_3$ (44.0 mg, 0.179 mmol) followed by, portionwise, $NaBH_4$ (90.0 mg, 2.38 mmol). After 25 min, acetone (1 ml) was added and stirring was continued for additional 15 min. The crude reaction product was isolated with Et_2O in usual manner and purified by chromatography ($CHCl_3$/MeOH, 20/1), yielding pure β-alcohol **15** (7.7 mg, 0.014 mmol, 34%) and the inseparable mixture of two compounds (8.7 mg).

Compound **15**. $[\alpha]_D^{20}$=+4.9 (*c* 0.0061, $CHCl_3$); ^1H NMR

(300 MHz), δ=1.30 (m, 1H, 7-H), 1.31 (s, 3H, 19-Me), 1.30 (s, 3H, 17-Me), 1.50–1.60 (m, 1H), 1.78 (s, 3H, 16-Me), 1.80–2.00 (m, 2H), 2.03 (s, 3H, Me-18), 2.04 (s, 3H, MeCO), 2.10 (s, 3H, MeCO), 2.00–2.20 (m, 2H), 2.29 (d, *J*=5.8 Hz, 1H, 3-H), 2.50 (m, 1H, 14-H), 2.70 (m, 1H, 4-OH), 4.18 (d, *J*=8.2 Hz, 1H, 20-H), 4.19 (d, *J*=7.7 Hz, 1H, 20-H), 4.30 (dd, *J*=8.5, 4.1 Hz, 1H, 13-H), 4.76 (m, 1H, 5-H), 5.90 (m, 1H, 2-H), 5.93 (s, 2H, 9- and 10-H), 7.47 (m, 2H, arom.), 7.60 (m, 1H, arom.), 7.98 (d, *J*=1.3 Hz, 2H, arom.); IR (neat) cm^{-1}: 3200–3600 (s, O–H), 1740 (s, C=O), 1710 (s, C=O), 1450 (w), 1370 (s), 1310 (w), 1270 (s), 1240 (s), 1150 (w), 1100 (s), 1060 (m), 1020 (s), 970 (m), 710 (s); FAB-MS, *m/z* $(M+H-H_2O)^+$ 539.

3.6.2. Acetylation of 8 to 16 and 17; 4α-acetoxy-5β,20-epoxy-2-ethoxyethoxy-9α,10β-isopropylidendioxy-11-taxen-13-one (16) and 4α,13-diacetoxy-5β,20-epoxy-2α-ethoxyethoxy-9α,10β-isopropylidendioxy-11,13-taxadiene (17). To a solution of **8** (92.0 mg, 0.192 mmol) in THF (1 ml), was added LiHMDS (0.230 ml of 1 M solution in THF, 0.230 mmol) at 0°C. After being stirred for 30 min, AcCl (18 mg, 0.23 mmol) was added and the mixture was stirred for 1 h. The mixture was diluted with EtOAc (20 ml). The organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, yielding **16** (26.0 mg, 0.050 mmol, 26%) as amorphous solid, **17** (26.0 mg, 0.050 mmol, 26%) and recovered **8** (34.0 mg, 0.0710 mmol, 34%).

Compound **16**. ^1H NMR (300 MHz), δ=1.20–1.30 (m, 7H, 19-Me, 4′-Me, 7-H), 1.43 (s, 3H, 16-Me), 1.48 (s, 3H, Me_2CO_2), 1.49 (s, 3H, Me_2CO_2), 1.50 and 1.52 (s, each 1.5H, 2′-Me), 1.63 and 1.65 (s, each 1.5H, 17-Me), 1.65–1.70 (m, 1H), 1.80–1.90 (m, 1H), 2.00 and 2.03 (s, each 1.5H, MeCO), 2.14–2.26 (m, 1H), 2.19 (dd, *J*=2.5, 7.1 Hz, 0.5H, 1-H), 2.35 (d, *J*=20.1 Hz, 0.5H, 14-H), 2.38 (d, *J*=20.1 Hz, 0.5H, 14-H), 2.49 (d, *J*=4.1 Hz, 0.5H, 3-H), 2.54 (d, *J*=5.0 Hz, 0.5H, 3-H), 2.62 (dd, *J*=2.5, 6.8 Hz, 0.5H, 1-H), 2.66 (dd, *J*=6.9, 20.3 Hz, 0.5H, 14-H), 2.73 (dd, *J*=6.9, 20.1 Hz, 0.5H, 14-H), 3.40–3.60 (m, 2H, 3′-H), 4.01 (dd, *J*=2.5, 5.0 Hz, 0.5H, 2-H), 4.27 (dd, *J*=2.8, 5.5 Hz, 0.5H, 2-H), 4.51 and 4.60 (q, *J*=5.0, 5.2 Hz, each 0.5H, 1′-H), 4.70 (dd, *J*=1.7, 9.3 Hz, 1H, H-5); IR (neat) cm^{-1}: 1720 (s, C=O), 1670 (s, C=O), 1450 (m), 1360 (s), 1220 (s), 1170 (s), 1050 (s), 980 (s), 870 (m), 450 (s); HR-FAB-MS, calcd for $C_{29}H_{44}O_8$ $(M+H)^+$ *m/z* 520.3034, found 520.3037.

3.6.3. 13-Acetoxy-5β,20-epoxy-2α-ethoxyethoxy-9,10-isopropylidendioxy-11,13-taxadien-4-ol (17). ^1H NMR (300 MHz), δ=1.22–1.27 (m, 6H, 19-Me and 4′-Me), 1.43 (s, 3H, Me_2CO_2), 1.44 (m, 1H, 6- or 7-H), 1.44 and 1.45 (s, each 1.5H, 2′-Me), 1.47 and 1.48 (s, each1.5H, Me_2CO_2), 1.52 and 1.61 (s, 1.5H, 17-Me), 1.74 and 1.75 (s, each 1.5H, Me-16), 1.86 (m, 1H, 6- or 7-H), 2.01 (m, 1H, 6- or 7-H), 2.05 (m, 1H, 6-H), 2.06 (m, 0.5H, 1-H), 2.07 and 2.09 (s, each 1.5H, Ac), 2.19 and 2.20 (s, each 1.5H, 18-Me), 2.20 (m, 1H, 3-H), 2.51 (dd, *J*=2.7, 6.1 Hz, 0.5H, 1-H), 3.50–3.60 (m, 2H, 3′-H), 4.01 (dd, *J*=2.7, 4.9 Hz, 0.5H, 2-H), 4.21 (d, *J*=9.3 Hz, 0.5H), 4.22 (d, *J*=9.3 Hz, 0.5H), 4.27 (dd, *J*=2.9, 5.1 Hz, 1H, 2-H), 4.35 (d, *J*=8.3 Hz, 0.5H), 4.45 (d, *J*=8.8 Hz, 0.5H), 4.50 (d, *J*=8.3 Hz, 0.5H), 4.57 (q, *J*=4.9 Hz, 1H, 1′-H), 4.59 (d, *J*=9.3 Hz, 0.5H), 4.60 (d, *J*=9.3 Hz, 0.5H), 4.63 (q, *J*=5.1 Hz, 0.5H, 1′-H), 4.84 (d, *J*=8.8 Hz, 0.5H), 4.95 (m, 1H, 5-H), 5.39 and 5.47 (d, *J*=6.1 Hz, each 0.5H, 14-H). HR-FAB-MS, calcd for $C_{29}H_{44}O_8$ $(M+H)^+$ *m/z* 520.3034, found 520.3037.

3.7. Migration of Ac group from 13-OH to 4-OH

To a solution of **17** (28.0 mg, 0.0539 mmol) in MeOH (1 ml), was added K_2CO_3 (20.0 mg, 0.145 mmol) at rt After being stirred for 30 min, the mixture was diluted with EtOAc (20 ml). The mixture was washed with aqueous NH_4Cl and brine, The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (hexane/EtOAc, 2/1), yielding **16** (13.0 mg, 0.0250 mmol, 46%) and **8** (7.0 mg, 0.015 mmol, 28%).

The same reaction was carried out for **17** (219 mg, 0.422 mmol) at 0°C, yielding **16** (147 mg, 0.283 mmol, 67%) and **8** (8.4 mg, 0.018 mmol, 4%).

3.7.1. Deprotection of ethoxyethyl group; 4α-acetoxy-5β,20-epoxy-2α-hydroxy-9α,10β-isopropylidendioxy-11-taxen-13-one (18) and 4α-acetoxy-2α,20-epoxy-5β-hydroxy-9α,10β-isopropylidendioxy-11-taxene-13-one (19). Compound **16** (243 mg, 0.507 mmol) was dissolved in a mixture of AcOH/THF/H_2O (1 ml/1 ml/2 ml). After being stirred for 50 h at rt, the mixture was diluted with EtOAc (30 ml). The organic layer was washed with aqueous NH_4Cl, aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography ($CHCl_3$/MeOH, 20/1), yielding **18** (40.0 mg, 0.0890 mmol, 52%) and **19** (17.0 mg, 0.0378 mmol, 19%).

Compound **18** (*oxetanol*). $[\alpha]_D^{20}$=+54 (*c* 0.0035, $CHCl_3$); ^1H NMR (300 MHz), δ=1.24–1.30 (m, 1H, 7-H), 1.25 (s, 3H, 19-Me), 1.91 (m, 1H, 6-H), 1.56 and 1.68 (s, each 3H, 16- or 17-Me), 1.46 (s, 3H, Me_2CO_2), 1.51 (s, 3H, Me_2CO_2), 1.94 (s, 3H, 18-Me), 2.08 (s, 3H, MeCO), 2.10 (m, 1H, 6-H), 2.19 (d, *J*=19.8 Hz, 1H, 14-H), 2.20–2.30 (m, 2H, 1-H and 7-H), 2.50 (d, *J*=5.1 Hz, 1H, 3-H), 2.82 (dd, *J*=6.8, 19.8 Hz, 1H, 14-H), 4.27 (d, *J*=9.5 Hz, 1H), 4.34 (m, 1H, H-2), 4.55 (d, *J*=8.8 Hz, 1H), 4.65 (d, *J*=8.8 Hz, 1H), 4.73 (d, *J*=9.3 Hz, 1H), 4.97 (d, *J*=8.0 Hz, 1H, H-5); IR (neat) cm^{-1}: 3600–3200 (m, O–H), 1730 (s, C=O), 1670 (s, C=O), 1460 (m), 1370 (s), 1230 (s), 1200 (m), 1170 (m), 1050 (s), 1030 (s), 1000 (m), 970 (m), 780 (m), 660 (m); HR-FAB-MS, calcd for $C_{25}H_{36}O_7$ $(M+H)^+$ *m/z* 448.2459, found 448.2461.

Compound **19** (*furanol*). $[\alpha]_D^{20}$=+77 (*c* 0.0087, $CHCl_3$); ^1H NMR (300 MHz), δ=1.18–1.23 (m, 1H, H-7), 1.18 (s, 3H, 19-Me), 1.32 (s, 3H, 17-Me), 1.44 and 1.48 (s, each 3H, Me_2CO_2), 1.64 (s, 3H, 16-Me), 1.91 (s, 3H, 18-Me), 1.97 (m, 1H), 2.01 (s, 3H, MeCO), 2.20–2.02 (m, 2H), 2.40 (m, 2H), 2.70 (m, 2H), 3.68 (d, *J*=11.3 Hz, 4-OH), 4.10 (s, 2H, H-20), 4.31 (d, *J*=9.6 Hz, 1H, 9- or 10-H), 4.38–4.31 (m, 2H, 2-H, 5-H), 4.59 (d, *J*=9.6 Hz, 1H, 9- or 10-H); IR (neat) cm^{-1}: 3600–3200 (m, O–H), 3000–2800 (m), 1730 (s, C=O), 1670 (s, C=O), 1650 (s, C=O), 1450 (w), 1390 (s),1370 (s), 1230 (s),1220 (s), 1170 (m), 1065 (s), 1050 (s), 1040 (s), 1020 (s), 1000 (m), 970 (w), 950 (w), 940 (w), 780 (m); HR-FAB-MS, calcd for $C_{25}H_{36}O_7$ $(M+H)^+$ *m/z* 448.2459, found 448.2462.

3.7.2. Introduction of *m*-N_3-benzoyl and *m*-chlorobenzoyl group: 4α-acetoxy-2α-(*m*-azido-benzoyloxy)-5β,20-epoxy-9α,10β-isopropylidendioxy-11-taxene-13-one (20a). To a solution of **18** (39.0 mg, 0.0868 mmol) in dry CH_3CN (10 ml), *m*-N_3-benzoic acid (200 mg, 1.64 mmol), DMAP (200 mg, 1.64 mmol) and DCC (338 mg, 1.64 mmol) were added at 0°C. After being stirring for 24 h at rt, EtOAc (50 ml) was added. The mixture was washed with solution of HCl (1N, 25 ml), brine, aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography ($CHCl_3$/MeOH, 27/1; and hexane/EtOAc, 7/2), yielding **20a** (44.0 mg, 0.0795 mmol, 92%) as amorphous solid: $[\alpha]_D^{20}$=+110 (*c* 0.021, $CHCl_3$); ^{1}H NMR (500 MHz), δ=1.23 (s, 3H, Me-19), 1.47 (s, 3H, Me_2CO_2), 1.55 (s, 3H, Me_2CO_2), 1.55 (s, 3H, Me-17), 1.56 (m, 1H, 7-H), 1.83 (s, 3H, Me-16), 1.87 (m, 1H, 6-H), 1.98 (s, 3H, Me-18), 2.13 (dd, 1H, *J*=7.6, 13.7 Hz, 7-H), 2.18 (s, 3H, MeCO), 2.25 (dd, *J*=2.4, 6.8 Hz, 1H, 1-H), 2.28 (dd, *J*=9.0, 16.6 Hz, 1H, 6-H), 2.44 (d, *J*=19.8 Hz, 1H, 14α-H), 2.80 (dd, *J*=6.8, 20.0 Hz, 1H, 14β-H), 2.84 (d, 1H, *J*=5.9 Hz, 3-H), 4.12 (dd, *J*=1.0, 8.3 Hz, 1H, 20-H), 4.40 (d, *J*=8.1 Hz, 1H, 20-H), 4.44 (d, *J*=9.2 Hz, 1H, 9-H), 4.77 (d, *J*=9.5 Hz, 1H, 10-H), 4.98 (d, 1H, *J*=8.1 Hz, 5-H), 5.85 (dd, *J*=2.7, 5.9 Hz, 1H, 2-H), 7.25 (ddd, 1H, *J*=1.0, 2.4, 8.1 Hz, arom.), 7.48 (dd, 1H, *J*=7.8, 8.1 Hz, arom.), 7.76 (dd, 1H, *J*=1.7, 2.0 Hz, arom.), 7.85 (dt, 1H, *J*=7.8, 1.2 Hz, arom.); ^{13}C NMR (125 MHz), δ=198.10 (C-13), 169.85 (Me*C*O), 163.99 (N_3–Ph*C*O), 152.70 (C-11), 140.84 (arom.) 139.47 (C-12), 131.11 (arom.), 130.16 (arom.), 126.20 (arom.), 124.30 (arom.), 119.69 (arom.), 108.01 (Me_2CO_2), 85.22 (C-5), 82.35 (C-4), 81.25 (C-9), 76.20 (C-20), 75.48 (C-10), 71.00 (C-2), 47.46 (C-1), 41.58 (C-3), 38.91 (C-8), 38.49 (C-15), 38.04 (C-17), 35.41 (C-14), 27.24 (Me_2CO_2), 27.03 (C-6), 26.76 (Me_2CO_2), 26.55 (C-7), 24.36 (C-16), 21.85 (4-Ac), 16.46 (C-19), 14.12 (18-Me); IR (neat) cm^{-1}: 2940, 2120 (s, N_3), 1720 (s, C=O), 1670 (s, C=O), 1580 (m), 1520 (w), 1480 (w), 1440 (w), 1300 (s), 1230 (s), 1170 (m), 1100 (m), 1050 (s), 1020 (s), 990 (m), 940 (w), 890 (w), 880 (w), 810 (w), 760 (s), 670 (m); HR-FAB-MS, calcd for $C_{32}H_{40}N_3O_8$ $(M+H)^+$ *m*/*z* 594.2813, found 594.2814.

The same procedure was used for **18** to give **20b** (4α-acetoxy-2α-*m*-chloro-benzoyloxy-5β,20-epoxy-9α,10β-isopropylidendioxy-11-taxen-13-one: $[\alpha]_D^{20}$=+88 (*c* 0.027, $CHCl_3$); ^{1}H NMR (500 MHz), δ=1.23 (s, 3H, Me-19), 1.47 (s, 3H, Me_2CO_2), 1.55 (s, 3H, Me_2CO_2), 1.55 (s, 3H, Me-17), 1.56 (m, 1H, 7-H), 1.80 (s, 3H, Me-16), 1.88 (m, 1H, 6-H), 1.98 (s, 3H, Me-18), 2.13 (dd, *J*=8.1, 13.7 Hz, 1H, 7-H), 2.19 (s, 3H, MeCO), 2.25 (dd, 1H, *J*=2.7, 6.8 Hz, 1-H), 2.28 (dd, *J*=9.0, 16.6 Hz, 1H, 6-H), 2.43 (d, *J*=20.0 Hz, 1H, 14α-H), 2.80 (dd, *J*=6.8, 20.0 Hz, 1H, 14β-H), 2.85 (dd, 1H, *J*=0.7, 5.9 Hz, 3-H), 4.12 (dd, *J*=0.7, 8.1 Hz, 1H, 20-H), 4.38 (d, *J*=8.1 Hz, 1H, 20-H), 4.43 (d, *J*=9.5 Hz, 1H, 9-H), 4.77 (d, *J*=9.5 Hz, 1H, 10-H), 4.99 (d, 1H, *J*=7.8 Hz, 5-H), 5.83 (dd, *J*=2.9, 5.9 Hz, 1H, 2-H), 7.44 (dd, 1H, *J*=7.8, 8.1 Hz, arom.), 7.60 (ddd, 1H, *J*=1.0, 2.0, 7.8hsp sp=0.25>Hz, arom.), 7.94 (ddd, 1H, *J*=7.8, 1.2, 1.5 Hz, arom.), 8.06 (dd, 1H, *J*=1.7, 2.0 Hz, arom.); ^{13}C NMR (125 MHz, $CDCl_3$), δ=198.10 (C-13), 169.76 (Me*C*O), 163.68 (*m*-Cl–Ph*C*O), 152.70 (C-11), 139.47 (arom.) 139.47 (C-12), 131.11 (arom.), 130.16 (arom.), 126.20 (arom.), 124.30 (arom.), 119.69 (arom.), 108.02 (Me_2CO_2), 85.20 (C-5), 82.36 (C-4), 81.24 (C-9), 76.16 (C-20), 75.48 (C-10), 71.06 (C-2), 47.48 (C-1), 41.60 (C-3), 38.91 (C-8), 38.48 (C-15), 38.06 (C-17), 35.42 (C-14), 27.25 (Me_2CO_2), 27.04 (C-6), 26.77 (Me_2CO_2), 26.58 (C-7), 24.40 (C-16), 21.84 (4-Ac), 16.48 (C-19), 14.12 (18-Me); IR (neat) cm^{-1}: 2940 (m), 1720 (s, C=O), 1670 (s, C=O), 1570 (w), 1530 (w), 1450 (w), 1420 (w), 1370 (m), 1320 (w), 1290 (m), 1230 (w), 1170 (m), 1120 (m), 1100 (m), 1070 (m), 1050 (s), 1020 (m), 990 (m), 970 (w), 940 (w), 890 (w), 880 (w), 810 (w), 760 (s), 670 (m); HR-FAB-MS, calcd for $C_{32}H_{39}O_8Cl$ M^+ *m*/*z* 586.2302, found 586.2330.

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