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$(i\text{PrO})_3\text{TiCl}$-Induced Reactions of α- and β-4(20)-Epoxy -5-Hydroxytriacetyltaxicin I

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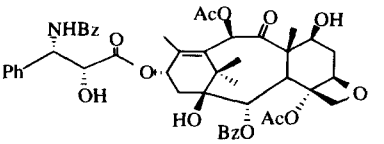
Abstract: Chlorotitanium triisopropoxide-induced reaction of α-4(20)-epoxy-5-hydroxytriacetyltaxicin I **2** gave a 4-hydroxymethylene-5-one **4** and a 4-hydroxy-4-chloromethylene **5**, while the corresponding β-4(20)-epoxide **3** gave a 3,8-cyclopropane **6** and a 6/8/5 ring system **7**. Moreover, boron trifluoride-induced reaction of the α-4(20)-epoxide **2** yielded a 6/8/6/7 ring system **8** and an A-ring contracted alcohol derivative **9**. Plausible mechanisms of these reactions are proposed.

Keywords: *Taxoids; Epoxides; Rearrangements; Chlorotitanium trisopropoxide; Borno trifluoride*

Taxol, first isolated from the Pacific Yew tree *Taxus brevifolia*[1], is a powerful therapeutic drug for cancer chemotherapy[2]. It exhibits remarkably high cytotoxicity and strong antitumor activity against different cancer resistant to existing anticancer drugs[3,4]. Taxol has been approved by the FDA for treatment of advanced ovarian and breast cancer[5,6] and is undergoing clinical trials for other cancers with encouraging results[7]. However, a number of problems[4,8] have been encountered in the pharmaceutical development of taxol including scarcity of the drug owing to a low abundance in yew tissue and a lack of economically-feasible routes to complete or partial synthesis. Althought total syntheses of taxol have been achieved[9], these approaches to supplying the drug are now not commercially viable[10]. Thus, the semi-synthesis of taxol and analogs from more readily available taxoids is still a challenging research area for chemists. In this paper we report six novel compounds obtained from α- and β-4(20)-epoxy-5-hydroxytriacetyltaxicin I in the presence of chlorotitanium triisopropoxide or boron trifluoride in our ongoing chemical conversion of taxoids available from Japanese yew to taxol and its analogs, and propose plausible mechanisms of these reactions.



Taxol

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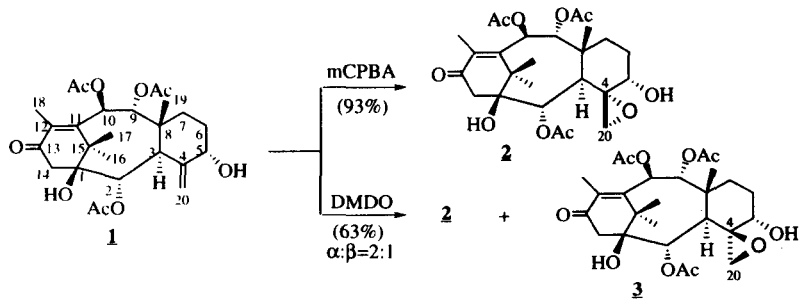
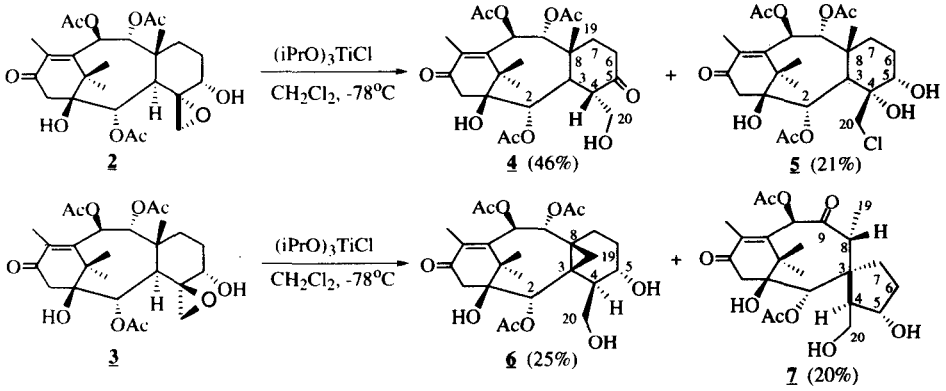


Scheme 1

5-Cinnamoyltriacetyltaxicin I[11], one of the major taxoids isolated from the Japanese yew *Taxus cuspidata*, can be readily converted to 5-hydroxytriacetyltaxicin I **1** in 50% ethanol under reflux in the presence of hydroxyamine hydrochloride[12]. Epoxidation of **1** using *m*-chloroperbenzoic acid (mCPBA)[13] gave a sole product which was determined later to be the α-4(20)-epoxy-5-hydroxytriacetyltaxicin I **2**. Most taxoids isolated from yew trees, however, display the β-4(20)-epoxide functionality[14]. Recently the β-selective epoxidation (α:β=1:4) of the 4(20)-ene moiety in taxoids using dimethyldioxirane (DMDO)[15] has been reported[16]. Epoxidation of **1** using dimethyldioxirane (DMDO) gave the α-4(20)-epoxide **2** and β-4(20)-epoxide **3** in comparatively low stereoselectivity (α:β=2:1). The stereochemistry of **2** and **3** was determined by NOESY experiments: **2** showed correlations of H-20a (δ_H 3.00, d, J =4.5 Hz) to CH_3-19 and H-2, plus H-20b (δ_H 2.48, d, J =4.5 Hz) to H-6β, while **3** displayed NOESY correlations of H-20a (δ_H 3.49, d, J =5 Hz) to H-3 and H-14α.



Scheme 2

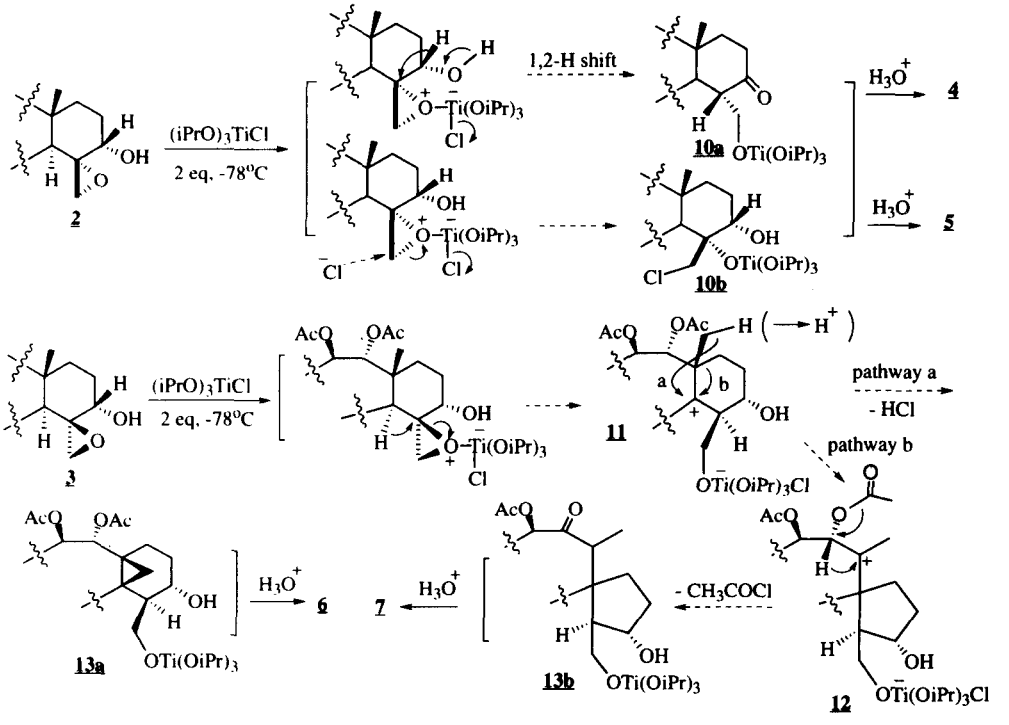
Treatment of **2** with chlorotitanium triisopropoxide (1.0M solution in hexane, 2 equivalents) in CH_2Cl_2 at -78°C for 1h yielded the 4-hydroxymethylene-5-one **4** in 46% yield and the 4,5-dihydroxy-4-chloromethylene **5** in 21% yield (Scheme 2). Similar reaction of **3** afforded the 3,8-cyclopropane derivative **6** in 25% yield and the spiro-cyclopentane derivative **7** in 20% yield. Compound **4** was shown to have the same molecular formula as that of **2**, $C_{26}H_{36}O_{10}$, by HREIMS (*m/z* 508.2310, △ +0.4 mmu). The ^{1}H NMR spectrum of **4** showed signals for H-3 (δ_H 3.12, dd, J =10.5/5.5Hz), H-20a (δ_H 4.19, dd, J =10.5/2.5Hz), and H-20b (δ_H 3.81, dd, J =10.5/3Hz) suggesting the presence of a proton H-4 at (δ_H 2.10, m) possessing a hydroxymethylene group at C-4 which was further confirmed by the ^{1}H-^{1}H COSY connectivites of H-4 to H_2-20 and H-3, and HMBC correlations of H-4 to C-2, C-3, C-8 and C-20, and H-3 to C-20. The ^{13}C NMR and HMQC spectra of **4** also revealed a carbonyl group (C-5) at δ_c 213.55 (s), a secondary carbon (C-20) at δ_c 63.42 (t) and a tertiary carbon

(C-4) at δ_c 52.36 (d). NOESY correlations of H-4 to H-2, H-6β and CH_3-19, and H-20a to H-3 indicated a hydroxymethylene group at C-4 was α-orientated, enabling the tentative stereochemical assignment of H-4β at the outset. The mass spectrum (EI) of compound **5** showed the molecular peak at *m/z* 544 with the 1/3 abundance isotopic peak at *m/z* 546 indicating the presence of a chlorine atom. Moreover, HRFABMS proposed the molecular formula as $C_{26}H_{37}O_{10}Cl$ (MH^+: 545.2157, △ +1.3 mmu). The ^1H and ^{13}C NMR data showed a chloromethyl group (δ_H 3.64, s, H_2-20, δ_c 48.78, t, C-20) was connected to the comparatively downfield quaternary carbon C-4 (δ_c 78.31, s) bearing hydroxy group. This was confirmed by HMBC correlations of H-5 and H-3 to C-20, plus H_2-20 to C-3, C-4 and C-5. The β-orientation of the chloromethylene group at C-4 was supported by NOESY correlations of H-20 to H-2, H-6β and CH_3-19.

Compound **6** was found to have the molecular formula, $C_{26}H_{36}O_{10}$, by HRFABMS (*m/z*, 509.2362, △ +1.4 mmu, calcd for MH^+: 509.2384). The ^1H, ^{13}C NMR and HMQC studies of **6** showed two highfield signals (δ_H 0.48 and 0.79, d, J =5.5Hz, H_2-19; δ_c 21.05, t, C-19, 28.32, s, C-3 and 27.57, s, C-8) indicating the presence of a cyclopropane ring[17]. The C-3 and C-8 fusion of the cyclopropane ring was established by HMBC correlations of: H-2 to C-19; H-4 to C-3 and C-19; H-7 to C-8 and C-19; H-9 to C-19; and H_2-19 to C-8, C-4 and C-2. A hydroxymethylene group (δ_H 3.63, dd, J =10.3/2.5Hz and 3.02, dd, J =10.3/3.7Hz, H_2-20; δ_c 65.87 t, C-20) was connected at C-4 by a HMBC correlation of H-5 to C-20. Finally NOESY correlations of H-19a to H-2 and H-9, H-19b to H-5 and H-7β indicated the cyclopropane ring was β-orientated, while β-orientation of the hydroxymethylene group at C-4 was elucidated by NOESY correlations of H-19b to H-20a, H-20b to H-5, H-4 to H-6α. Overall **6** displayed high structural correlations to a described 1-deoxy-3,8-cyclopropyl system similarly prepared from a taxinine A derivative[17b]. In comparison to the ^1H and ^{13}C NMR of **3**, those of compound **7** indicated the loss of an acetyl groups and this was substantiated by the EIMS of **7** giving the molecular ion at *m/z* 466 and HREIMS suggesting the molecular formula as $C_{24}H_{34}O_9$ for M^+: 466.2179. Two respective singlets at δ_H 6.39 and δ_H 5.68 were assigned for H-10 and H-2 by HMBC correlations of H-10 to C-11 (δ_c 152.43, s), C-15 (δ_c 43.54, s) and C-8 (δ_c 44.72, d). These signals together with a carbonyl group at δ_c 201.14 (C-9), HMBC correlations of H-2 to C-1 (δ_c 74.76), C-15 and C-8, plus a quaternary carbon (C-3) at δ_c 49.82 (s) indicated that a carbonyl group was located at the 9-position as well as a hydrogen (δ_H 2.85, q) connected to C-8[18]. Inaddition, HMBC correlations of: H-8 to C-3, C-4 (δ_c 52.47, d) and C-7 (δ_c 25.57, t); H-4 (δ_H 2.17, m) to C-2, C-3, C-7 and C-8; including H_2-7 (δ_H 1.59-1.63, m) to C-2, C-3, C-4 and C-8 suggested the presence of a spiro-cyclopentane[18] which was fused at C-3 between C-4 and C-7. HMBC correlations of H_2-20 to C-5 and H-5 (δ_H 3.64, ddd, J =9/7/6.5Hz) to C-20 indicated that a hydroxymethylene group was connected at C-4 in the cyclopentane ring. Detailed analysis of a NOESY spectrum established α-orientations for CH_3-19 and the C3–C7 bond on the basis of correlations of CH_3-19 to H-10, H-7 and H-6; H-8 to H-2, H-20; H-7 to H-14α, while a hydroxymethylene group was β-orientated at C-4 by NOESY correlations of H-20 to H-8, H-2 and H-5.

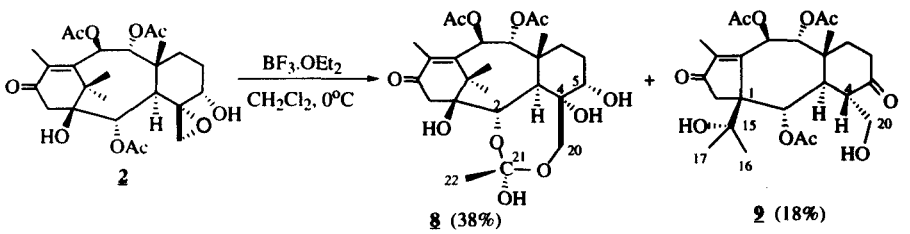
Plausible mechanisms of $(i\text{PrO})_3$TiCl-induced reactions of **2** and **3** in Scheme 3. Formation of **4** or **5** may be simply explained from **2** *via* a 1,2-hydride shift or substitutive epoxide ring opening, respectively. In the first step $(i\text{PrO})_3$TiCl induces fission of the C4–O bond followed by 1,2-hydride shift from C-5 to C-4 and proton loss resulting in formation of the C=O double bond in **10a**, while fission of the C20–O bond, induced by $(i\text{PrO})_3$TiCl, is attacked by chloro anion leading to intermediate **10b**. Hydrolysis of **10a** and **10b** give the final products **4** and

5, respectively. In the case of the β-4(20)-epoxide **3**, $(iPrO)_3TiCl$ induces fission of the C4–O bond followed by 1,2-hydride shift generating the carbocation at C-3 **11**, that can be captured by CH_3-19 followed by proton loss leading to the cyclopropane precursor **13a**[17b,19] (pathway a) to compound **6**. Alternatively, intermediate **12** formed *via* a 1,2-shift rearrangement from **11**, which then undergoes a 1,2 hydride shift from C-9 to C-8 and followed by loss of 9-acetyl group leading to the carbonyl group at the C-9 position in **13b** (pathway b). Finally, acidic hydrolysis of **13b** on workup gives compound **7**. In fact, the facile formation of a five-membered C-ring in this taxoid series has already been reported[18,20].



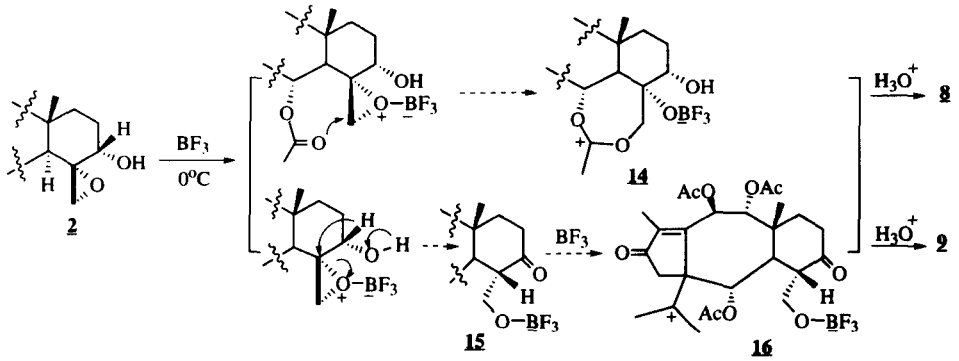
Scheme 3

For further investigation into the lewis acid induced-reaction of α-4(20)-epoxide **2**, the reaction of **2** with boron trifluoride diethyl etherate was carried out. Interestingly, treatment of **2** with boron trifluoride diethyl etherate in CH_2Cl_2 at 0°C for 1h gave the unusual 6/8/6/7 ring system **8** and the A-ring contracted derivative **9** in 38% and 18% yields, respectively. The structures of **8** and **9** were elucidated by spectral data including 2D NMR studies. The HREIMS of **8** gave the molecular peak at *m/z*, 526.2397 to propose the molecular formula $C_{26}H_{38}O_{11}$. The ^1H NMR data showed two protons at (δ_H 3.70, d, J =9Hz and 3.50, d, J =9Hz, H_2-20) suggesting an oxygen-methylene group was connected to C-4. This was confirmed by HMBC correlations of: H-5 (δ_H 3.89, brdd) and H-3 (δ_H 2.70, d, J=3Hz) to C-20 (δ_c 74.62, t) and C-4 (δ_c 78.85, s), and H_2-20 to C-4, C-3 (δ_c 39.81, d) and C-5 (δ_c 70.59, d). Moreover, the NMR data also exhibited onyl two acetyl groups signals (δ_H 2.11, δ_c 20.86, q, 169.46, s; δ_H 2.06, δ_c 20.68, q, 170.21, s) and a new singlet of quaternary carbon (C-21) at downfield (δ_c 120.12, s) due to bearing three oxygen atoms, which were further confirmed by HMBC correlations of H-2 (δ_H, 5.16, d, J =3Hz), H_2-20 and CH_3-22 (δ_H 1.64, s) to C-21. All the above information indicated the presence of a seven-membered ring was fused between C-2 and C-4. NOESY experiment showed



Scheme 4

correlations of H-20a to H-2, H-6β and CH_3-19, H-20b to H-5, and CH_3-22 to H-2 indicated the oxygen-methylene group at C-4 and CH_3-22 both possessing β-orientations. Compound **9** was found to have the same molecular formula $C_{26}H_{36}O_{10}$ by HREIMS as that of **4**. The NMR analysis also gave the similar results of C-ring, for example, a hydroxymethylene group (δ_H 4.02, dd, J=10.2/2.1Hz, δ_H 3.66, dd, J=10.2/4.8Hz, H_2-20) was connected to C-4 possessing α-orientation established by HMBC correlations of H_2-20 to C-4 (δ_c 51.20, d), C-5 (δ_c 213.50, s) and C-3 (δ_c 42.30, d); H-3 (δ_H 2.27, dd, J=11.4/8.1Hz) and H-4 (δ_H 2.11, m) to C-20 (δ_c 64.25, t) together with NOESY correlations of H-4 to H-2, H-6β and CH_3-19, and H-20a to H-3. However, there were some differences of the A-ring between **4** and **9**. The ^{13}C NMR of **9** showed the α,β-unsaturated ketone resonance at δ_c 207.58 and two quaternary carbons at δ_c 63.74 (C-1), 76.38 (C-16). Inaddition, HMBC correlations of H-10 and H-3 to C-1; H-2 to C-1 and C-11; H_2-14 to C-15, CH_3-16, and CH_3-17 to C-15 and C-1 suggested the presence of α,β-unsaturated cyclopentanone and a hydroxyisopropyl locating at C-1. The β-orientation of a hydroxyisopropyl at C-1 was obtained from NOESY experiment.



Scheme 5

Formation of **8** or **9** can be explained by intramolecular 1,2-addition or 1,2-hydride shift along with 1,2-shift rearrangement, respectively (Scheme 5). The most likely first step is the complexation of the lewis acid with the oxygen of α-epoxy-propane, then the oxygen of the acetyl group (C=O) is positioned for nucleophilic attack onto carbon C-20 leading to seven-membered ring bearing the carbocation at C-21 **14**, which is easily to give **8** in the presence of water. Alternatively, intermediate **15** can arise easily from **2** *via* 1,2-hydride shift, which may further undergoes 1,2-shift rearrangement of the A-ring due to fission of C1-O bond, induced by an excess of BF_3, generating the carbocation center at C-15 position in **16**, which readily affords **9** on aqueous workup conditions.

Experimental Section

^1H-NMR, ^{13}C-NMR(125MHz) and 2D NMR were recorded on a Varian Unity INOVA 500 (500MHz)

spectrometers in $CDCl_3$ using TMS as an internal standard. Chemical shifts are expressed in part per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). Optical rorations were recorded on a HORIBA SEPA-300 Polarimeter. UV spectra were carried out on a Shimadzu UV-1600 spectrophotometer in ethanol. MS and HRMS were measured on a JEOL JMS-700 spectrometer using EI and FAB modes. Dichloromethane was refluxed and distilled from CaH_2 under Nitrogen. All commercially available reagents were used without further purification. Chromatography was carried out on a Merck silica gel 60(230-400 mesh). Prepartive TLC were profermed on the 0.85 mm thickness by using Merck silica gel 60 F_{254} plates.

5-hydroxytriacetyltaxicin I (1)[12] To a mixture of 5-cinnamoyltriacetyltaxicin I (0.5 g, 0.8 mmol) and hydroxylamine hydrochloride (0.5 g, 7.2 mmol) in ethanol (50 ml), sodium acetate (1.0 g, 12.2 mmol) in water (50 ml) was added and the reaction mixture was heated at 80°C for 24h. The reaction mixture was cooled to room temperature, diluted with water and extracted with chloroform. The combined organic phase was dried over $MgSO_4$. After removal of solvent, the resulting product was purified by column on silica gel (EtOAc:hexane =1:1) to give 270 mg (67%) of **1**. mp: 208-210°C, $[\alpha]_D^{23}$ +60.1° (c 0.9, $CHCl_3$), ^1H NMR δ: 6.17(d, 1H, *J*=10.5, H-10), 5.90(d, 1H, *J* =10.5, H-9), 5.61(d, 1H, *J*=6.6, H-2), 5.16(s, 1H, H-20), 4.65(s, 1H, H-20), 4.19(brd, 1H, H-5), 3.74(d, 1H, *J*=6.6, H-3), 2.82(d, 1H, *J*=19.8, H-14β), 2.61(d, 1H, *J*=19.8, H-14α), 2.24(s, 3H, CH_3-18), 2.13(s, 3H, Ac), 2.08(s, 3H, Ac), and 2.07(s, 3H, Ac), 1.7-1.85(m, 2H, H-6, H-7), 1.69(s, 3H, CH_3-16), 1.54-1.68(m, 2H, H-6, H-7), 1.21(s, 3H, CH_3-17), 0.90(s, 3H, CH_3-19). HREIMS calcd for $C_{26}H_{36}O_9$(M^+) 492.2357; found 492.2342.

α-4(20)-epoxy-5-hydroxytriacetyltaxicin I (2) To a solution of **1** (100 mg, 0.2 mmol) in CH_2Cl_2 (10 ml), was added *m*CPBA (120 mg, 0.7 mmol) and Na_2HPO_4 (208 mg, 1.46 mmol). The reaction mixture was stirred at room temperature for 3h, amd then extracted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (EtOAc:hexane=2:1) to give 96 mg (93%) of **2** as a colorless amorphous solid. $[\alpha]_D^{23}$ +89° (c 0.8, $CHCl_3$). UV λ_{max}(lgε) 268nm (3.5) and 203nm (3.1). ^1H NMR δ: 6.15(d, 1H, *J*=10.5, H-10), 5.90(d, 1H, *J*=10.5, H-9), 5.59(d, 1H, *J*=4, H-2), 3.62(d, 1H, *J*=4, H-3), 3.11(d, 1H, *J*=19.5, H-14), 3.00(d, 1H, *J*=4.5, H-20a), 3.08(t, 1H, *J*=3, H-5), 2.65(d, 1H, *J*=19.5, H-14), 2.48(d, 1H, *J*=4.5, H-20b), 2.25(s, 3H, CH_3-18), 2.14(s 3H, Ac), 2.10(s, 3H, Ac), 2.06(s, 3H, Ac), 1.93(ddd, 1H, *J*=8.5, 5, 3, H-6), 1.78-1.82(m, 2H, H_2-7), 1.67(m, 1H, H-6), 1.64(s, 3H, CH_3-16), 1.19(s, 3H, CH_3-17), 0.96(s, 3H, CH_3-19). ^{13}C NMR δ: 199.62(s, C-13), 171.72, 169.95, 169.61 (3×s, 3×Ac), 151.56(s, C-11), 141.89(s, C-12), 76.91(s, C-1), 75.70(s, C-4), 75.45(d, C-9), 72.72(d, C-10), 72.34(d, C-2), 63.21(d, C-5), 51.65(t, C-20), 44.51(s, C-8), 44.27(d, C-3), 43.54(s, C-15), 38.47(t, C-14), 33.88(q, C-17), 26.11(t, C-6), 25.36(t, C-7), 21.17, 20.91, 20.69(3×q, 3×Ac), 19.49(q, C-16), 17.37(q, C-19), 14.02(q, C-18). HREIMS calcd for $C_{26}H_{36}O_{10}$ (M^+) 508.2306, found 508.2284.

β-4(20)-epoxy-5-hydroxytriacetyltaxicin I (3) To a solution of **1** (100 mg, 0.2 mmol) in acetone (5 ml) was added DMDO[21] *ca.* 0.28M in CH_2Cl_2 (1.3 ml, 0.36 mmol). The mixture was stirred slowly at room temperature for 36h (monitored by TLC) and concentrated *in vacuo*. The resulting residue was purified by column on silica gel (EtOAc:hexane =2:1) to give 43 mg (42%) of **2** and 22 mg(21%) of **3** as colorless amorphous solids. $[\alpha]_D^{23}$ +107° (c 0.7, $CHCl_3$). UV λ_{max}(lgε) 267nm (3.3) and 204nm (2.9). ^1H NMR δ: 6.12(d, 1H, *J*=10.5, H-

10), 5.91(d, 1H, J=10.5, H-9), 5.61(d, 1H, J=3.5, H-2), 3.49(d, 1H, J=5, H-20a), 3.46(d, 1H, J=3.5, H-3), 3.11(d, 1H, J=19.5, H-14), 2.94(brt, 1H, H-5), 2.66(d, 1H, J=19.5, H-14), 2.31(s, 3H, CH_3-18), 2.16(d 1H, J =5, H-20b), 2.13(s, 3H, Ac), 2.09(s, 3H, Ac), 2.06(s, 3H, Ac), 1.95(m, 1H, H-6), 1.83-1.86(m, 2H, H_2-7), 1.69(m, 1H, H-6), 1.60(s, 3H, CH_3-16), 1.14(s, 3H, CH_3-17), 0.95(s, 3H, CH_3-19). ^{13}C NMR δ: 199.42(s, C-13), 171.52, 170.21, 169.64 (3×s, 3×Ac), 149.96(s, C-11), 140.13(s, C-12), 76.91(s, C-1), 75.70(s, C-4), 75.46(d, C-9), 74.58(d, C-10), 72.58(d, C-2), 62.27(d, C-5), 60.41(t, C-20), 44.51(s, C-8), 43.54(d, C-3), 36.99(s, C-15), 36.11(t, C-14), 35.31(q, C-17), 25.60(t, C-6), 25.27(t, C-7), 21.07, 20.88, 20.70(3×q, 3×Ac), 19.62(q, C-16), 17.41(q, C-19), 14.37(q, C-18). HREIMS calcd for $C_{26}H_{36}O_{10}$ (M^+) 508.2306, found 508.2291.

General procedure for $(iPrO)_3TiCl$-induced reactions. To a solution of **2** (0.1 mmol) in dry CH_2Cl_2 (2 ml), was added (iPrO)$_3$TiCl 1.0M solution in hexane (0.2 ml, 0.2 mmol) at -78°C under nitrogen. The reaction mixture was stirred at -78°C for 1h and then moved to room temperature. The saturated aqueous NH_4Cl (0.5 ml) was added and the resulting mixture was extracted with $CHCl_3$. The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (EtOAc:hexane =2:1) to give **4** (23 mg, 46%) and **5** (11 mg, 21%). **Compd. 4**, $[\alpha]_D^{23}$ +56° (c 0.5, $CHCl_3$). UV λ_{max}(lgε) 240nm (2.7). ^{1}H NMR δ: 6.09(d, 1H, J =10.5, H-10), 6.03(d, 1H, J =10.5, H-9), 5.57(d, 1H, J=5.5, H-2), 4.19(dd, 1H, J=10.5, 2.5, H-20a), 3.81(dd, 1H, J =10.5, 3, H-20b), 3.12(dd, 1H, J =10.5, 5.5, H-3), 2.90(d, 1H, J =19.5, H-14), 2.71(d, 1H, J =19.5, H-14), 2.44(dd, 1H, J =9, 4, H-6), 2.41(brt, 1H, H-6), 2.12(s, 3H, CH_3-18), 2.11(s, 3H, Ac), 2.10(m, 1H, H-4), 2.09(s, 3H, Ac), 2.08(s, 3H, Ac), 2.05(m, 1H, H-7), 1.82(dt, 1H, J=9, 4, H-7), 1.73(s, 3H, CH_3-16), 1.25(s, 3H, CH_3-17), 0.94(s, 3H, CH_3-19). ^{13}C NMR δ: 213.55(s, C-5), 199.36(s, C-13), 171.07, 169.95, 169.54 (3×s, 3×Ac), 150.92(s, C-11), 140.44(s, C-12), 77.58(s, C-1), 74.95(d, C-9), 73.25(d, C-2), 72.16(d, C-10), 63.42(t, C-20), 52.36(d, C-4), 43.17(s, C-8), 43.68(t, C-14), 41.58(s, C-15), 41.19(d, C-3), 36.00(t, C-6), 33.91(q, C-17), 28.05(t, C-7), 20.92, 20.87, 20.67(3×q, 3×Ac), 20.00(q, C-16), 18.10(q, C-19), 13.71(q, C-18). HREIMS calcd for $C_{26}H_{36}O_{10}$(M^+) 508.2306, found 508.2310. **Compd. 5**, $[\alpha]_D^{23}$ +74° (c 0.34, $CHCl_3$). UV λ_{max}(lgε) 239nm (2.9) ^{1}H NMR δ: 6.10(d, 1H, J =10.5, H-10), 5.80(d, 1H, J=10.5, H-9), 5.63(d, 1H, J =5.5, H-2), 3.71(brt, 1H, H-5), 3.64(s, 2H, H_2-20), 3.55(d, 1H, J =20, H-14), 3.32(d, 1H, J =5.5, H-3), 2.59(d, 1H, J =20, H-14), 2.28(s, 3H, CH_3-18), 2.20(s, 3H, Ac), 2.10(s, 3H, Ac), 2.06(s, 3H, Ac), 2.00(m, 1H, H-6), 1.76-1.86(m, 2H H_2-7), 1.68(s, 3H, CH_3-16), 1.59(m, 1H, H-6), 1.23(s, 3H, CH_3-17), 0.85(s, 3H, CH_3-19). ^{13}C NMR δ: 199.82(s, C-13), 171.87, 170.23, 169.36(3×s, 3×Ac), 151.49(s, C-11), 141.38(s, C-12), 78.31(s, C-4), 74.89(s, C-1), 74.84(d, C-9), 73.66(d, C-2), 72.51(d, C-10), 70.18(d, C-5), 48.78(t, C-20), 45.83(d, C-3), 43.38(t, C-14), 43.06(s, C-15), 42.65(s, C-8), 34.28(q, C-17), 24.50(t, C-6), 23.32(t, C-7), 21.19, 20.87, 20.71(3×q, 3×Ac), 19.70(q, C-16), 18.59(q, C-19), 13.36(q, C-18). EI-MS (m/z, %): 544, 546(M+, 14%, 5%) 484(12%), 424(8%). HRFABMS calcd for $C_{26}H_{38}O_{10}Cl$ (MH^+) 545.2151, found 545.2157

Compounds **6** (13 mg, 25%) and **7** (9 mg, 20%) were obtained from **3**. **Compd. 6**, $[\alpha]_D^{23}$ +77° (c 0.2, $CHCl_3$). UV λ_{max}(lgε) 242nm (2.6). ^{1}H NMR δ: 6.25(d, 1H, J =10.5, H-10), 5.94(d, 1H, J =10.5, H-9), 5.64(s, 1H, H-2), 3.65(brt, 1H, H-5), 3.63(dd, 1H, J =10.3, 2.5, H-20a), 3.02(dd, 1H, J=10.3, 3.7, H-20b), 2.62(d, 1H, J=18.6, H-14β), 2.40(m, 1H, H-4α). 2.39(d, 1H, J=18.6, H-14α), 2.15(s, 3H, CH_3-18), 2.11(s 3H, Ac), 2.08(s, 3H, Ac), 2.07(s, 3H, Ac), 1.95(ddd, 1H, J=13, 12, 5, H-6β), 1.70(s, 3H, CH_3-17), 1.68(m,

1H, H-6α), 1.65(s, 3H, CH_3-16), 1.37(m, 1H, H-7β), 1.29(s, 3H, CH_3-17), 1.24(m, 1H, H-7α), 0.79(d, 1H, *J* =5.5, H-19a), 0.48(d, 1H, *J* =5.5, H-19b). ^{13}C NMR δ: 199.56(s, C-13), 170.06, 170.01, 169.24 (3×s, 3×Ac), 151.68(s, C-11), 141.34(s, C-12), 77.52(d, C-9), 74.36(s. C-1), 72.15(d, C-2), 70.82(d, C-10), 65.87(t, C-20), 64.37(d, C-5), 51.45(d, C-4), 43.40(s, C-14), 42.75(t, C-15), 36.02(t, C-6), 33.98(q, C-17), 28.32(s, C-3), 27.57(s, C-8), 25.87(t, C-7), 21.89, 21.43, 21.09(3×q, 3×Ac), 21.05(t, C-19), 19.89(q, C-16), 13.32(q, C-18). HRFABMS calcd for $C_{26}H_{37}O_{10}$ (MH^+) 509.2384, found 509.2362. **Compd. 7**, $[\alpha]_D^{23}$ +134° (c 0.5, $CHCl_3$). UV λ_{max}(lgε) 237nm (3.3). ^{1}H NMR δ: 6.39(s, 1H, H-10), 5.68(s, 1H, H-2), 3.76(dd, 1H, *J* =11, 2.5, H-20a), 3.64(ddd, 1H, *J*=9, 7, 6.5, H-5), 3.14(d, 1H, *J* =20, H-14), 3.01(dd, 1H, *J*=11, 3.5, H-20b), 2.85(q, 1H, *J*=7.0, H-8), 2.72(d, 1H, *J* =20, H-14), 2.17(m, 1H, H-4), 2.16(s, 3H, CH_3-18), 2.13(s, 3H, Ac), 2.07(s, 3H, Ac), 1.94(m, 1H, H-6), 1.78(m. 1H, H-6), 1.59-1.63(m, 2H, H_2-7), 1.57(d, 3H, *J* =7, CH_3-19), 1.31(s, 3H, CH_3-17), 1.23(s, 3H, CH_3-16). ^{13}C NMR δ: 201.14(s, C-9), 199.78(s, C-13), 170.02, 169.46 (2×s, 2×Ac), 152.43(s, C-11), 140.72(s, C-12), 77.52(d, C-10), 74.76(s. C-1), 72.18(d, C-2), 70.52(d C-5), 65.84(t, C-20), 52.47(d, C-4), 49.82(s. C-3), 44.72(d, C-8), 43.54(s, C-15), 43.37(t, C-14), 33.62(q, C-17), 27.25(t, C-6), 25.57)t, C-7), 21.11, 20.87(2×q, 2×Ac), 19.57(q, C-16), 13.74(q, C-18), 10.87(q, C-19).HREIMS calcd for $C_{24}H_{34}O_9$ M^+ 466.2201, found 466.2179.

Boron trifluoride-induced reaction. To an ice-cooled solution of **2** (51 mg, 0.1 mmol) in dry CH_2Cl_2 (2 ml), was added BF_3.OEt_2 (abt. 47% solution, 0.1 ml) under nitrogen. The reaction mixture was stirred for 1h and then partitioned between $CHCl_3$ (10 ml) and saturated aqueous $NaHCO_3$ (2 ml). The organic layer was separated and then washed with water and brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (EtOAc:hexane =2:1) to afford 20 mg (38%) of **8** and 9 mg (18%) of **9**. **Compd. 8**, $[\alpha]_D^{23}$ +205° (c 0.3, $CHCl_3$). UV λ_{max}(lgε) 236nm (2.6). ^{1}H NMR δ: 6.02(d, 1H, *J* =11, H-10), 5.92(d, 1H, *J* =11, H-9), 5.16(d, 1H, *J* =3, H-2), 3.89(brdd, 1H, H-5), 3.70(d, 1H, *J* =9, H-20a), 3.50(d, 1H, *J* =9, H-20b), 3.05(d, 1H, *J* =20, H-14), 2.87(d, 1H, *J* =20, H-14), 2.70(d, 1H, *J* =3, H-3), 2.11(s, 3H, Ac), 2.07(s, 3H, CH_3-18), 2.06(s, 3H, Ac), 2.00(m, 1H, H-6), 1.74-1.77(m, 2H, H_2-7), 1.65(s, 3H, CH_3-16), 1.64(s, 3H, CH_3-22), 1.62(m, 1H, H-6), 1.31(s, 3H, CH_3-17), 1.19(s, 3H, CH_3-19). ^{13}C NMR δ: 200.87(s, C-13), 170.21, 169.46 (2×s, 2×Ac), 154.28(s, C-11), 140.74(s, C-12), 120.12(s, C-21), 78.85(s, C-4), 76.31(s, C-1), 75.52(d, C-9), 74.62(t, C-20), 73.62(d, C-2), 72.44(d, C-10), 70.59(d, C-5), 44.42(t, C-14), 43.72(s, C-8), 41.94(s, C-15), 39.81(d. C-3), 34.18(q, C-17), 26.77(t, C-6), 24.65(t, C-7), 22.92(q, C-22), 20.86, 20.68(2×q, 2×Ac), 20.53(q, C-16), 19.97(q, C-19), 13.24(q, C-18). HREIMS calcd for $C_{26}H_{38}O_{11}$(M^+) 526.2412, found 526.2397. **Compd. 9**, $[\alpha]_D^{23}$ +36.7° (c 0.15, $CHCl_3$). UV λ_{max}(lgε) 239nm (2.2) and 205nm (1.1). ^{1}H NMR δ: 6.27(d, 1H, *J*=10.5, H-10), 6.19(d, 1H, *J*=10.5, H-9), 6.03(d, 1H, *J*=8.1, H-2), 4.02(dd, 1H, *J*=10.2, 2.1, H-20a), 3.66(dd, 1H, *J*=10.2, 4.8, H-20b), 2.64(d, 1H, *J*=18.6, H-14), 2.48(m, 2H, H_2-6), 2.41(d, 1H, *J*=18.6, H-14), 2.27(dd, 1H, *J*=11.4, 8.1, H-3), 2.11(m, 1H, H-4), 2.08(s, 3H, Ac), 2.07(s, 3H, Ac), 2.04(s, 3H, Ac), 2.00(m, 1H, H-7), 1.86(s, 3H, CH_3-18), 1.82(m, 1H, H-7), 1.21(s, 3H, CH_3-16), 1.13(s, 3H, CH_3-17), 1.05(s, 3H, CH_3-19). ^{13}C NMR δ: 213.50(s, C-5), 207.58(s, C-13), 170.68, 170.02, 169.05(3×s, 3×Ac), 162.68(s, C-11), 146.54(s, C-12), 77.12(d, C-9), 76.38(s, C-15), 70.43(d, C-2), 69.17(d, C-10), 64.25(t, C-20), 63.74(s, C-1), 51.20(d, C-4), 44.23(t, C-14), 42.30(d, C-3), 40.21(s, C-8), 36.64(t, C-6), 29.07(t, C-7), 27.91(q, C-16), 27.02(q, C-17), 22.02, 21.39, 21.37(3×q, 3×Ac), 18.51(q, C-19), 9.46(q, C-18). HREIMS calcd for $C_{26}H_{36}O_{10}$(M^+) 508.2306, found 508.2293.

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