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Unusual Boron Trifluoride-catalyzed Reactions of Taxinine Derivatives with α- and β-4(20)-Epoxides

Hirokazu Hosoyama, Hideyuki Shigemori, and Jun'ichi Kobayashi*

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

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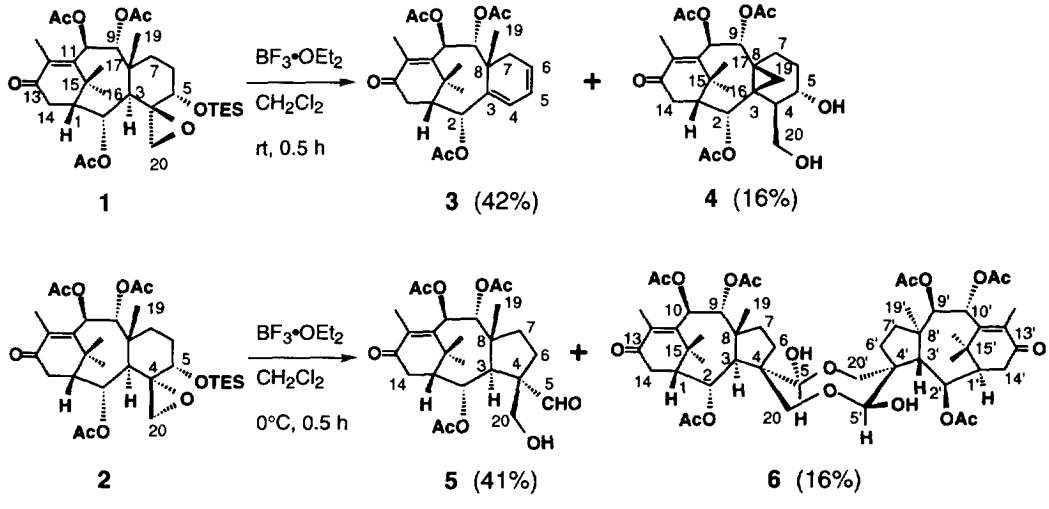
Abstract: Boron trifluoride-catalyzed reaction of β-4(20)-epoxy-5-*O*-triethylsilyltaxinine A (**1**) gave the 3,5-diene (**3**) and the 3,8-cyclopropane (**4**) derivatives, while the similar reaction of the corresponding α-4(20)-epoxide (**2**) afforded the ring contracted derivative (**5**) and its hemiacetal dimer (**6**). Plausible mechanisms of these reactions containing 1,2-hydride shift (**3** and **4** from **1**) or pinacol-type rearrangement (**5** and **6** from **2**) are proposed.

Keywords: boron and compounds; epoxides; rearrangements; taxoids

In our continuing chemical derivatization from taxinine,[1,2] one of major taxoids obtained from the Japanese yew *Taxus cuspidata*,[3-5] we found that boron trifluoride-catalyzed reaction of β-4(20)-epoxy-5-*O*-triethylsilyl (TES) taxinine A (**1**) yielded two unexpected compounds, the 3,5-diene (**3**) and the 3,8-cyclopropane (**4**) derivatives, while the similar reaction of the corresponding α-4(20)-epoxide (**2**) afforded the ring contracted derivative (**5**) and its hemiacetal dimer (**6**). In this paper we describe the formation of **3** and **4** from **1** and that of **5** and **6** from **2**, and propose plausible mechanisms of these reactions.



1 **3** (42%) **4** (16%)

2 **5** (41%) **6** (16%)

Scheme 1

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Treatment of the β-4(20)-epoxy-5-*O*-TES-taxinine A (**1**), which was derived from taxinine A,[1] with boron trifluoride diethyl etherate (BF_3•OEt_2, 2eq.) in CH_2Cl_2 at room temperature for 0.5 h yielded the 3,5-diene (**3**, 42%) and the 3,8-cyclopropane (**4**, 16%) (Scheme 1), while the reaction at 0°C afforded the 3,5-diene (**3**, 47%) but the 3,8-cyclopropane (**4**) was not obtained. When the reaction mixture was treated with 2,4-dinitrophenylhydrazine, formaldehyde-2,4-dinitrophenylhydrazone was obtained, suggesting the liberation of formaldehyde in this reaction. On the other hand, treatment of the α-4(20)-epoxide (**2**), which was also derived from taxinine A,[1] with BF_3•OEt_2 (2 eq.) in CH_2Cl_2 at 0°C for 0.5 h afforded the cyclopentanecarbaldehyde (**5**, 41%) and its hemiacetal dimer (**6**, 16%) (Scheme 1). The structures of **3** ~ **6** were elucidated by spectral data including MS and 2D NMR as follows.[6]

Compound **3** was shown to have the molecular formula, $C_{25}H_{32}O_7$, by HREIMS [*m/z* 444.2150 (M^+), Δ +0.1 mmu]. The ^1H NMR spectrum of **3** showed three olefine proton signals at δ_H 5.58 (H-6), 5.68 (H-4), and 5.75 (H-5). The three olefinic methine carbons (δ_C 119.5, C-4; 122.4, C-5; 123.5, C-6) were indicated by the HMQC spectrum. ^1H-^1H COSY connectivities of H-4 to H-5, H-5 to H-6, and H-6 to H_2-7 and HMBC correlations of H-2 to C-3 and C-4 revealed that **3** possessed a conjugated diene (C-3 ~ C-6) in ring C, which was supported by UV absorption at 258 nm (ε 6800).

The molecular formula, $C_{26}H_{36}O_9$, of compound **4** was established by HREIMS [*m/z* 492.2383 (M^+), Δ +2.3 mmu]. The ^1H and ^{13}C NMR data (δ_H 0.43 and 0.77, d, J = 5.4 Hz, H_2-19; δ_C 21.0, t, C-19, 27.6, s, C-8, and 28.2, s, C-3) of **4** indicated the presence of a cyclopropane ring.[7] The cyclopropane ring was fused between C-3 and C-8 on the basis of HMBC correlations of H-2 to C-19, H-4 to C-3 and C-19, H-7 to C-19, and H-9 to C-8. A hydroxymethylene group (δ_H 2.83 and 3.58, H_2-20; δ_C 65.9, t, C-20) was connected at C-4 by an HMBC correlation between H-5 and C-20. NOESY correlations of H-19a and H_3-16 to H-2 and H-9 indicated that the cyclopropane ring was β-oriented, while β-orientation of the hydroxymethylene group at C-4 was elucidated by NOESY correlations of H-19b to H-20a and H-14a to H-4.

Compound **5** was shown to have the molecular formula, $C_{26}H_{36}O_9$, by HRFABMS [*m/z* 493.2452 $(M+H)^+$, Δ +1.4 mmu]. The ^1H and ^{13}C NMR and HMQC spectra of **5** showed one formyl (δ_H 9.37, s, H-5; δ_C 202.8, d, C-5) and one hydroxymethylene (δ_H 4.19, 3.60, d, J = 11.4 Hz, H_2-20; δ_C 62.6, t, C-20) groups. HMBC correlations of H-3 and H_2-7 to C-4 (δ_C 61.9, s) and H_3-19 to C-3, C-7, and C-8 indicated the presence of a cyclopentane ring (ring C), while the formyl and hydroxymethylene groups were attached at C-4 on the basis of HMBC correlations of H-5 to C-3 and C-20 and H_2-20 to C-6. The β-orientation of the hydroxymethylene group at C-4 was elucidated by NOESY correlations of H_3-19 to H-20a and H-5 to H-3 and H-14b. Thus compound **5** was shown to possess a 6/8/5-ring system with a formyl and a hydroxymethylene groups at C-4.

The molecular formula, $C_{52}H_{72}O_{18}$, of compound **6** was established by HRFABMS [*m/z* 985.4812 $(M+H)^+$, Δ +1.5 mmu], indicating that **6** was a dimer of **5**. The ^1H and ^{13}C NMR data of **6** were very similar to those of **5**, except for resonances of a formyl and a hydroxymethylene groups at C-4 in **5**. The presence of two hemiacetal moieties (δ_H 5.18, brs, H-5; δ_C 99.2, d, C-5; δ_H 4.79, brs, H-5'; δ_C 105.7, d, C-5') was revealed by the HMQC spectrum. HMBC correlations of H-3 and H-5 to C-4, H-5' to C-20, and H-3' to C-5', C-4', and C-20' and a NOESY correlation between H-5 and H-5' indicated the presence of a 1,5-dioxacyclooctane moiety. NOESY correlations of H-5 to H-20a and H-5', H-5' to H-20a and H-

20'a revealed that the 1,5-dioxacyclooctane ring had a chair/chair conformation and the two hydroxy groups at C-5 and C-5' were equatrial. Thus compound **6** was assigned as a dimer of **5**.

The formation of the 3,5-diene (**3**) and the 3,8-cyclopropane (**4**) from the β-4(20)-epoxide (**1**) may be explained by 1,2-hydride shift and then liberation of formaldehyde or cyclopropanation, respectively (Figure 1). In the first step BF_3•OEt_2 induces the fission of C-4 - O bond followed by 1,2-shift of hydride from C-3 to C-4, resulting in generation of the carbocation at C-3 (**a**). Liberation of formaldehyde and dehydration of the allylic functional group at C-5 in **a** give the 3,5-diene (**3**). On the other hand, the 3,8-cyclopropane (**4**) can arise from a trapping of the carbocation center formed at C-3 (**a**) by the methyl (Me-19) followed by loss of a proton.[8,9] In the case of the α-4(20)-epoxide (**2**) BF_3•OEt_2 induces the fission of C-4 - O bond followed by ring contraction through a pinacol-type rearrangement (**b**) to afford the cyclopentanecarbaldehyde (**5**). The pinacol-type rearrangement involving deprotection of the TES group at C-5 accompanies with transfer of the C-6 carbon into C-4 position and generation of an α-oriented formyl group. It is noted that the orientation of the 4(20)-epoxides results in different types of the boron trifluoride - catalyzed reactions.

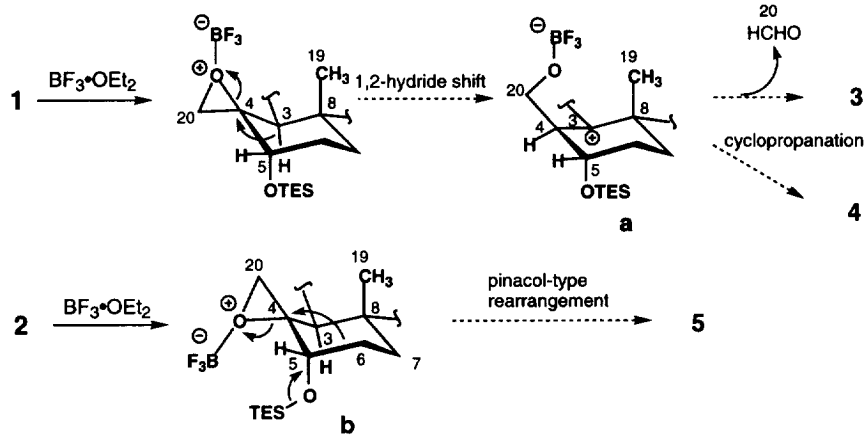

Figure 1. Plausible mechanisms of BF_3•OEt_2-catalyzed reactions of compounds **1** and **2**

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6. Compound **1** (34 mg) was dissolved in dry CH_2Cl_2 (0.4 mL), and then added BF_3•OEt_2 (46% Et_2O solution, 40 µl) under Argon. The solution was stirred at room temperature for 0.5 h, and the reaction mixture was extracted with $CHCl_3$ and saturated aqueous $NaHCO_3$. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was applied to a silica gel column (*n*-Hexane/EtOAc, 4:1) to afford compounds **3** (10.6 mg) and **4** (4.4 mg). According to the same procedure as described above, compounds **5** (3.4 mg) and **6** (1.3 mg), which were separated by a silica gel HPLC (Develosil 60-5, Nomura Chemical; $CHCl_3$/EtOAc, 3:1), were obtained from **2** (10 mg). **Compound 3:** $[\alpha]^{25}_D$ +233° (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 1745, 1674, 1237, 1020 cm^{-1}; UV (MeOH) λ_{max} 258 nm (ε 6800); ^1H NMR ($CDCl_3$): δ_H 6.02 (1H, d, *J* = 10.2 Hz), 5.97 (1H, d, *J* = 10.2 Hz), 5.75 (1H, m), 5.68 (1H, d, *J* = 6.0 Hz), 5.66 (1H, d, *J* = 2.7 Hz), 5.58 (1H, m), 2.74 (1H, dd, *J* = 19.8, 6.0 Hz), 2.69 (1H, m), 2.61 (1H, d, *J* = 19.8 Hz), 2.28 (1H, m), 2.27 (1H, dd, *J* = 18.7, 6.2 Hz), 2.09 (3H, s), 2.06 (3H, s), 2.04 (3H, s), 1.96 (3H, s), 1.73 (3H, s), 1.17 (3H, s), 1.05 (3H, s); ^{13}C NMR ($CDCl_3$): δ_C 198.7, 170.2, 170.1, 169.0, 148.0, 140.3, 139.6, 123.5, 122.4, 119.5, 75.7, 74.6, 69.8, 49.0, 42.0, 37.3, 36.1, 34.2, 31.0, 25.7, 23.6, 21.5, 21.5, 21.0, 14.1. **Compound 4:** $[\alpha]^{24}_D$ +39.1° (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3447, 1741, 1655, 1237, 1021 cm^{-1}; UV (MeOH) λ_{max} 263 nm (ε 2000); ^1H NMR (C_6D_6): δ_H 6.41 (1H, d, *J* = 10.3 Hz), 5.86 (1H, d, *J* = 10.3 Hz), 5.41 (1H, d, *J* = 1.6 Hz), 3.60 (1H, m), 3.58 (1H, dd, *J* = 10.3, 2.5 Hz), 3.36 (1H, d, *J* = 19.9 Hz), 2.83 (1H, m), 2.80 (1H, dd, *J* = 19.9, 7.6 Hz), 2.60 (3H, s), 2.40 (1H, m), 2.13 (1H, dd, *J* = 7.6, 1.6 Hz), 1.93 (1H, ddd, *J* = 13.0, 12.0, 4.9 Hz), 1.87 (3H, s), 1.79 (3H, s), 1.70 (3H, s), 1.67 (1H, m), 1.67 (3H, s), 1.32 (1H, m), 1.26 (1H, m), 0.99 (3H, s), 0.77 (1H, d, *J* = 5.4 Hz), 0.43 (1H, d, *J* = 5.4 Hz); ^{13}C NMR (C_6D_6): δ_C 198.0, 169.5, 169.0, 168.9, 152.1, 139.0, 78.7, 77.9, 74.7, 65.9, 64.3, 51.4, 44.6, 38.1, 37.2, 36.0, 28.2, 27.6, 25.9, 23.4, 21.0, 20.7, 20.4, 20.3, 16.8, 15.2. **Compound 5:** $[\alpha]^{25}_D$ +79.7° (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3489, 1744, 1676, 1233, 1025 cm^{-1}; UV (MeOH) λ_{max} 264 nm (ε 5400); ^1H NMR ($CDCl_3$): δ_H 9.37 (1H, s), 6.05 (1H, d, *J* = 9.4 Hz), 5.87 (1H, d, *J* = 9.4 Hz), 5.46 (1H, dd, *J* = 7.7, 3.7 Hz), 4.19 (1H, d, *J* = 11.4 Hz), 3.60 (1H, d, *J* = 11.4 Hz), 3.27 (1H, d, *J* = 7.7 Hz), 2.71 (1H, dd, *J* = 20.0, 7.5 Hz), 2.31 (1H, d, *J* = 20.0 Hz), 2.26 (1H, dd, *J* = 7.7, 7.5 Hz), 2.26 (1H, m), 2.12 (3H, s), 2.08 (3H, s), 2.06 (3H, s), 2.04 (3H, s), 1.81 (1H, m), 1.68 (3H, s), 1.59 (2H, m), 1.13 (3H, s), 1.11 (3H, s); ^{13}C NMR ($CDCl_3$): δ_C 202.8, 199.3, 170.5, 169.7, 169.0, 150.2, 138.1, 77.3, 73.8, 71.0, 62.6, 61.9, 49.5, 47.7, 46.7, 37.8, 37.6, 35.7, 34.7, 26.0, 25.4, 21.0 (2C), 20.9, 20.6, 13.8. **Compound 6:** $[\alpha]^{26}_D$ +51.1° (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3481, 1748, 1673, 1235, 1083 cm^{-1}; UV (MeOH) λ_{max} 266 nm (ε 8700); ^1H NMR ($CDCl_3$): δ_H 6.38 (1H, d, *J* = 9.9 Hz), 6.32 (1H, d, *J* = 9.9 Hz), 6.17 (1H, d, *J* = 9.9 Hz), 6.13 (1H, d, *J* = 9.9 Hz), 5.83 (1H, dd, *J* = 6.5, 2.8 Hz), 5.82 (1H, dd, *J* = 6.8, 3.1 Hz), 5.18 (1H, brs), 4.79 (1H, brs), 4.12 (1H, d, *J* = 12.0 Hz), 4.02 (1H, d, *J* = 11.8 Hz), 3.81 (1H, d, *J* = 11.8 Hz), 3.73 (1H, brd, *J* = 12.0 Hz), 3.43 (1H, d, *J* = 6.5 Hz), 3.27 (1H, d, *J* = 6.8 Hz), 2.83 (1H, dd, *J* = 19.8, 7.2 Hz), 2.60 (1H, m), 2.59 (1H, dd, *J* = 19.4, 7.1 Hz), 2.51 (1H, d, *J* = 19.8 Hz), 2.50 (3H, s), 2.34 (3H, s), 2.338 (3H, s), 2.32 (1H, m), 2.29 (1H, d, *J* = 19.4 Hz), 2.26 (1H, dd, *J* = 7.2, 2.8 Hz), 2.16 (1H, dd, *J* = 14.4, 9.3 Hz), 2.11 (1H, dd, *J* = 7.1, 3.0 Hz), 1.83 (1H, m), 1.82 (3H, s), 1.81 (3H, s), 1.76 (3H, s), 1.74 (3H, s), 1.72 (2H, m), 1.70 (3H, s), 1.69 (3H, s), 1.68 (3H, s), 1.67 (1H, m), 1.64 (1H, m), 1.25 (3H, s), 1.11 (3H, s), 0.95 (6H, s); ^{13}C NMR ($CDCl_3$): δ_C 200.3, 198.1, 169.9, 169.7, 169.2, 169.1, 168.6, 168.4, 151.3, 151.1, 138.4, 138.2, 105.7, 99.2, 76.4, 76.2, 74.1 (2C), 73.7, 71.6, 71.5, 66.2, 54.7, 51.9, 49.9, 49.8, 47.3 (2C), 46.4, 45.2, 38.2, 38.0, 37.6, 37.5, 36.5, 35.9, 34.2, 33.9, 27.4, 25.1 (2C), 23.1, 21.5, 21.2, 20.3 (2C), 20.2 (2C), 19.3, 13.6, 12.9.
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