

Further unexpected boron trifluoride-catalyzed reactions of taxoids with α - and β -4,20-epoxides

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Three unusual taxinine derivatives, the cyclobutane **3**, the dioxane **4**, and the orthoester **5**, were obtained by boron trifluoride-catalyzed reactions of β - and α -4,20-epoxy-5-*O*-triethylsilyltaxinine A (**1** and **2**, respectively) (**3** and **4** from **1**; **5** from **2**).

Introduction

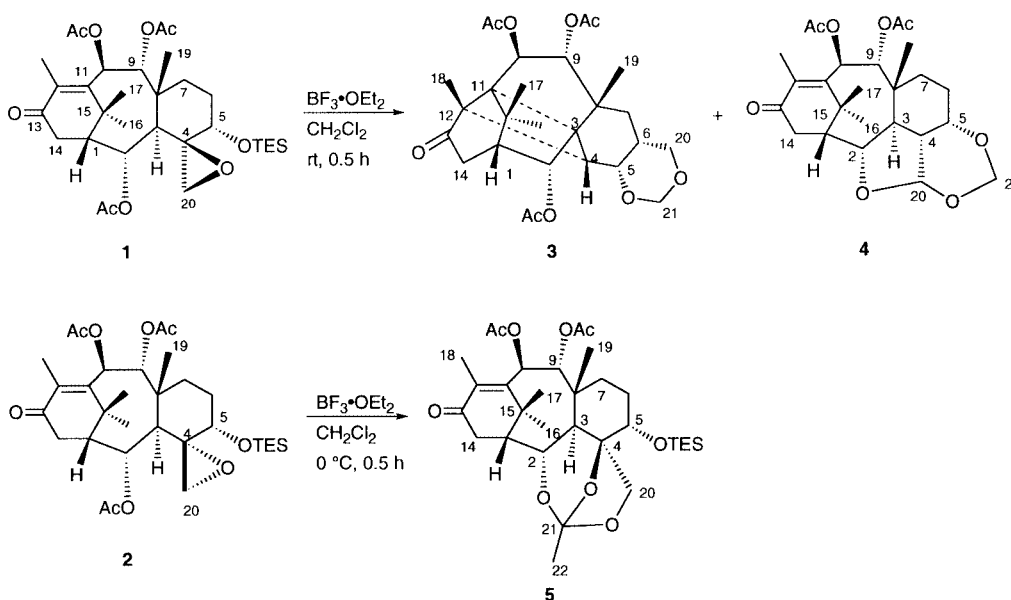
During our studies on chemical modifications of taxinine^{1,2} from the Japanese yew *Taxus cuspidata*,³⁻⁵ we have found that boron trifluoride-catalyzed reaction of β -4,20-epoxy-5-*O*-triethylsilyltaxinine A (**1**) (triethylsilyl = TES) yielded two unexpected compounds, the 3,5-diene and the 3,8-cyclopropane derivatives, while similar reaction of the corresponding α -4,20-epoxide (**2**) afforded the cyclopentanecarbaldehyde derivative and its hemiacetal dimer.⁶ Further investigation on these reaction products led to the isolation of three unusual taxinine derivatives (**3**, **4**, and **5**). In this paper we describe the formation of **3** and **4** from **1** and that of **5** from **2**, and propose plausible mechanisms for these reactions.

Results and discussion

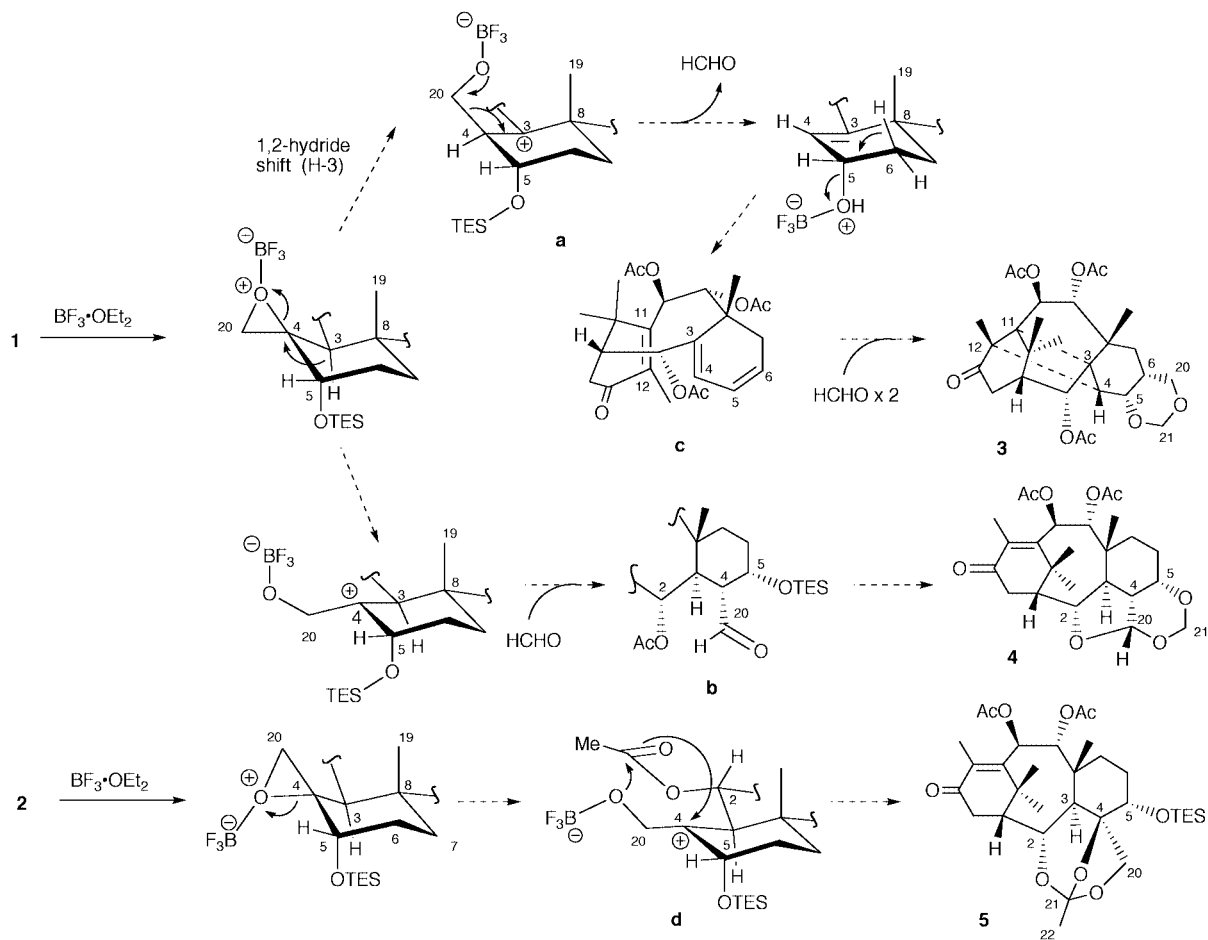
Treatment of the β -4,20-epoxy-5-*O*-TES-taxinine A (**1**) with boron trifluoride-diethyl ether ($\text{BF}_3 \cdot \text{OEt}_2$, 2 equiv.) in CH_2Cl_2 at room temperature for 0.5 h yielded the cyclobutane **3** and the dioxane **4** derivatives (Scheme 1) in addition to the 3,5-diene and the 3,8-cyclopropane derivatives previously reported.⁶ On the other hand, treatment of the α -4,20-epoxide **2** with $\text{BF}_3 \cdot \text{OEt}_2$ (2 equiv.) in CH_2Cl_2 at 0 °C for 0.5 h afforded the orthoester derivative **5** (Scheme 1) together with the cyclopentanecarbaldehyde derivative and its hemiacetal dimer previ-

ously obtained.⁶ The structures of **3**, **4**, and **5** were elucidated on the basis of spectral data including 2D NMR as follows.

Compound **3** was shown to have the molecular formula, $\text{C}_{27}\text{H}_{36}\text{O}_9$, by HREIMS [m/z 504.2386 (M^+), Δ +2.7 mmu]. Analyses of the ^1H and ^{13}C NMR data and HMQC spectrum of **3** provided one ketone, three acetyls, four oxymethines, two oxymethylenes, three methines, two methylenes, five quaternary carbons, and four methyl groups. Detailed analysis of the ^1H - ^1H COSY spectrum revealed connectivities of C-1 to C-2, C-4 to C-7, C-6 to C-20, C-9 to C-10, and C-14 to C-1. In the HMBC spectrum, long-range ^1H - ^{13}C correlations of H-1 to C-11 and C-15, H-14b to C-13, and H_3 -18 to C-11 and C-12 indicated the presence of a cyclohexanone moiety (C-1, C-15, and C-11-C-14), while HMBC correlations of H_3 -19 to C-3, C-7, C-8, and C-9 implied the presence of a cyclohexane moiety (C-3-C-8). The presence of a dioxane ring fused to C-5 and C-6 was revealed by HMBC correlations of H-20b (δ_{H} 3.83) to C-21 (δ_{C} 94.1) and H-21a (δ_{H} 5.15) to C-5 (δ_{C} 75.5). The presence of a cyclobutane ring (C-3, C-4, C-12, and C-11) was deduced from HMBC correlations of H-4 to C-3, C-11, and C-12 and H_3 -18 to C-4. Thus compound **3** was concluded to consist of a 6,5,5,6,4-membered ring system. The relative stereochemistries and ring conformations of **3** were elucidated by NOESY correlations (Fig. 1). NOESY correlations of H-5 to H-20 α and H-21 α indicated a chair conformation of the dioxane ring, while a chair conformation of the cyclohexane moiety was



Scheme 1



Scheme 2

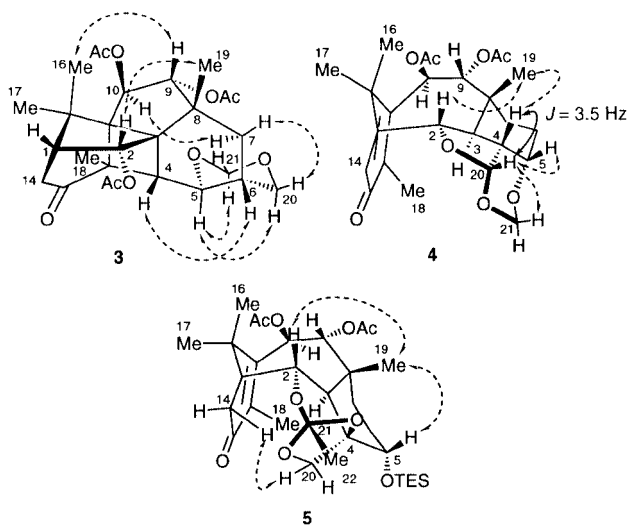


Fig. 1

implied from NOESY correlations of H-4 to H-6 and H-7 to H-10.

The molecular formula, $C_{25}H_{34}O_8$, of compound **4** was established by HRFABMS [m/z 463.2339 ($M + H$)⁺, $\Delta + 0.7$ mmu]. 1H and ^{13}C NMR data (δ_H 4.59 and 4.86, d, $J = 6.9$ Hz, H₂-21; δ_C 90.2, t, C-21 and δ_H 5.09, d, $J = 3.5$ Hz, H-20; δ_C 97.7, d, C-20) indicated the presence of a methylenedioxy and a hemiacetal group. A dioxane ring (C-4, C-5, C-21, and C-20) was deduced from HMBC correlations of H₂-21 to C-5 and C-20, while the HMBC correlation of H-20 to C-2 indicated the presence of a tetrahydrofuran ring (C-2, C-3, C-4, and C-20). NOESY correlations of H₃-19 to H-4, H-20 to H-5 and H-21a,

and the 1H - 1H coupling constant (3.5 Hz) between H-4 and H-20 revealed that H-4, H-5, and H-20 were β -oriented (Fig. 1).

Compound **5** was shown to have the molecular formula, $C_{32}H_{51}O_9Si$, by HRFABMS [m/z 607.3322 ($M + H$)⁺, $\Delta + 2.0$ mmu]. The 1H and ^{13}C NMR and HMQC spectrum of **5** showed the existence of an oxymethyl (δ_H 3.44 and 3.62, d, $J = 8.8$ Hz, H₂-20) and an orthoester (δ_C 120.4, s, C-21) group. HMBC correlations of H-2, H-20, and H-22 to C-21, and H-3 and H-20 to C-4 indicated that the orthoester was formed by C-2, C-4, C-20, C-21, and C-22. The α -orientation of the oxymethyl group at C-4 was elucidated by the NOESY correlation of H-14b to H-20b (Fig. 1).

The formation of the cyclobutane **3** and the dioxane **4** from the β -4,20-epoxide **1** and the orthoester **5** from the α -4,20-epoxide **2** may be explained as follows (Scheme 2). In the first step $BF_3 \cdot OEt_2$ induces the fission of the C-4-O bond of the β -4,20-epoxide **1** followed by the 1,2-shift of the hydride from C-3 to C-4, and then liberation of formaldehyde and dehydration of the allylic functional group at C-5 in **a** give the 3,5-diene (**c**).⁶ 1,4-Michael addition between the α,β -unsaturated ketone (C-11-C-13) and the C-3-C-4 double bond in **c** together with cycloaddition of the C-5-C-6 double bond in **c** with two molecules of the liberated formaldehyde from **a** affords compound **3** (Scheme 2). On the other hand, fission of the C-4-O bond of **1** by $BF_3 \cdot OEt_2$ followed by the 1,2-shift of the hydride from C-20 to C-4 in the carbocation results in generation of an α -oriented formyl group at C-4 (**b**). Furthermore, the concerted reaction (**b**) between the substituents at C-2, C-4, and C-5, and one molecule of the liberated formaldehyde from **a** yields compound **4**. In the case of the α -4,20-epoxide **2**, $BF_3 \cdot OEt_2$ induces the fission of the C-4-O bond and then another concerted reaction (**d**) between O-20, the acetoxy carbonyl at C-2, and the carbocation at C-4 giving the orthoester **5** (Scheme 2).⁷ It is noted that the orientation of the 4,20-epoxides results in the

different types of the boron trifluoride-catalyzed reactions previously reported.⁶

Experimental

General methods

Optical rotations were determined on a JASCO DIP-370 polarimeter. $[\alpha]_D$ has units of 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$. UV and IR spectra were obtained on JASCO Ubest-35 and JASCO FT/IR-230 spectrometers, respectively. ^1H and ^{13}C NMR spectra were recorded on Bruker ARX-500 and AMX-600 spectrometers. The 7.26 ppm resonance of residual CHCl_3 and 77.0 ppm of CDCl_3 were used as internal references, respectively. EIMS was obtained on a JEOL DX-303 spectrometer operating at 70 eV. FABMS were measured on an HX-110 spectrometer by using NBA matrix.

$\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed reactions of β - and α -4,20-epoxy-5-*O*-TES-taxinine A (1 and 2)

Compound **1** (34 mg) was dissolved in dry CH_2Cl_2 (0.4 mL), and then $\text{BF}_3 \cdot \text{OEt}_2$ was added (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** (1.1 mg), **4** (0.8 mg), the 3,5-diene⁶ (10.6 mg), and the 3,8-cyclopropane⁶ (4.4 mg). Compound **2** (18.5 mg) was dissolved in dry CH_2Cl_2 (0.3 mL), and then $\text{BF}_3 \cdot \text{OEt}_2$ was added (46% Et_2O solution, 20 μL) under argon at 0 °C. The solution was stirred at 0 °C 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 silica gel HPLC (Develosil 60-5, Nomura Chemical, CHCl_3 – EtOAc , 3:1) to afford compound **5** (1.6 mg), the cyclopentanecarbaldehyde⁶ (6.6 mg), and its hemiacetal dimer⁶ (2.6 mg).

Compound 3

A colorless amorphous solid; $[\alpha]_D^{24} -29.5$ (*c* 0.40, CHCl_3); IR (film) ν_{max} 1743, 1701, 1235 and 1024 cm^{-1} ; ^1H NMR (CDCl_3): δ 6.20 (1H, d, $J = 9.9$ Hz), 5.69 (1H, d, $J = 6.1$ Hz), 5.42 (1H, d, $J = 9.9$ Hz), 5.15 (1H, d, $J = 6.2$ Hz), 4.59 (1H, d, $J = 6.2$ Hz), 4.21 (1H, m), 3.88 (1H, dd, $J = 11.1, 1.8$ Hz), 3.83 (1H, m), 3.00 (1H, m), 2.77 (1H, d, $J = 9.4$ Hz), 2.76 (1H, d, $J = 19.4$ Hz), 2.48 (1H, dd, $J = 19.4, 6.6$ Hz), 2.39 (1H, m), 2.10 (3H, s), 2.08 (3H, s), 2.01 (3H, s), 1.41 (3H, s), 1.36 (3H, s), 1.15 (3H, s), 1.07 (1H, m), 1.00 (1H, m) and 0.89 (3H, s); ^{13}C NMR (CDCl_3): δ 210.6, 171.2 (2C), 169.8, 94.1, 83.5, 76.8, 76.1, 75.5, 71.4, 57.4, 56.1, 49.1, 47.8, 42.5, 38.1, 36.6, 34.4, 32.0, 29.3, 27.1, 25.1, 21.1, 21.0, 20.8 and 16.4; HREIMS m/z 504.2386 (M^+), calcd. for $\text{C}_{27}\text{H}_{36}\text{O}_9$, 504.2359.

Compound 4

A colorless amorphous solid; $[\alpha]_D^{27} +76.4$ (*c* 1.00, CHCl_3); IR

(film) ν_{max} 1748, 1673, 1235 and 1083 cm^{-1} ; ^1H NMR (CDCl_3): δ 6.09 (1H, d, $J = 10.2$ Hz), 5.97 (1H, d, $J = 10.2$ Hz), 5.09 (1H, d, $J = 3.5$ Hz), 4.86 (1H, d, $J = 6.9$ Hz), 4.59 (1H, d, $J = 6.9$ Hz), 4.50 (1H, dd, $J = 5.6, 10.5$ Hz), 3.99 (1H, m), 3.44 (1H, d, $J = 20.2$ Hz), 2.81 (1H, dd, $J = 10.7, 10.5$ Hz), 2.62 (1H, dd, $J = 20.2, 7.1$ Hz), 2.50 (1H, dd, $J = 7.1, 5.6$ Hz), 2.15 (1H, m), 2.12 (3H, s), 2.09 (3H, s), 2.03 (3H, s), 1.86 (1H, m), 1.81 (1H, m), 1.67 (1H, m), 1.63 (3H, s), 1.51 (1H, m), 1.23 (3H, s) and 0.93 (3H, s); ^{13}C NMR (CDCl_3): δ 201.2, 170.6, 169.6, 150.1, 137.3, 97.7, 90.2, 81.6, 77.1, 74.1, 71.8, 45.8, 45.1, 41.1, 40.4, 38.1, 37.8, 37.5, 35.4, 28.7, 26.3, 25.7, 21.0, 16.9 and 13.0; FABMS m/z 463 ($\text{M} + \text{H}$)⁺, HRFABMS m/z 463.2339 ($\text{M} + \text{H}$)⁺, calcd. for $\text{C}_{25}\text{H}_{35}\text{O}_8$, 463.2332.

Compound 5

A colorless amorphous solid; $[\alpha]_D^{27} +49.3$ (*c* 1.00, CHCl_3); IR (film) ν_{max} 1748, 1673, 1235 and 1083 cm^{-1} ; ^1H NMR (CDCl_3): δ 5.94 (1H, d, $J = 10.7$ Hz), 5.84 (1H, d, $J = 10.7$ Hz), 4.30 (1H, br s), 3.85 (1H, t, $J = 3.0$ Hz), 3.62 (1H, d, $J = 8.8$ Hz), 3.44 (1H, d, $J = 8.8$ Hz), 2.88 (1H, dd, $J = 20.6, 6.1$ Hz), 2.77 (1H, d, $J = 20.6$ Hz), 2.51 (1H, d, $J = 3.1$ Hz), 2.22 (1H, dd, $J = 6.1, 2.0$ Hz), 2.09 (3H, s), 2.06 (3H, s), 2.03 (3H, s), 1.87 (1H, m), 1.75 (1H, dd, $J = 13.6, 3.8$ Hz), 1.71 (3H, s), 1.69 (1H, m), 1.57 (3H, s), 1.57 (1H, m), 1.23 (3H, s), 1.18 (3H, s), 0.94 (9H, m, TES-Me) and 0.56 (6H, m, TES- CH_2); ^{13}C NMR (CDCl_3): δ 200.5, 170.4, 169.5, 152.2, 138.1, 120.4, 79.9, 76.2, 74.7, 73.1, 71.8, 71.5, 48.7, 41.8, 39.5, 38.8, 38.0, 35.9, 26.8, 25.5, 25.3, 23.2, 21.0, 20.9, 20.8, 13.3, 6.9 and 5.2; FABMS m/z 607 ($\text{M} + \text{H}$)⁺; HRFABMS m/z 607.3322 ($\text{M} + \text{H}$)⁺, calcd. for $\text{C}_{32}\text{H}_{51}\text{O}_9\text{Si}$, 607.3302.

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References

- 1 H. Hosoyama, H. Shigemori, Y. In, T. Ishida and J. Kobayashi, *Tetrahedron*, 1998, **54**, 2521.
- 2 H. Hosoyama, H. Shigemori, Y. In, T. Ishida and J. Kobayashi, *Tetrahedron Lett.*, 1998, **39**, 2159.
- 3 D. G. I. Kingston, A. A. Molinero and J. M. Rimoldi, *Prog. Chem. Org. Nat. Prod.*, 1993, **61**, 1 and references cited therein.
- 4 G. Appendino, *Nat. Prod. Rep.*, 1995, **12**, 349.
- 5 J. Kobayashi, A. Ogiwara, H. Hosoyama, H. Shigemori, N. Yoshida, T. Sasaki, Y. Li, S. Iwasaki, M. Naito and T. Tsuruo, *Tetrahedron*, 1994, **50**, 7401.
- 6 H. Hosoyama, H. Shigemori and J. Kobayashi, *Tetrahedron Lett.*, 1999, **40**, 2149.
- 7 S. H. Chen, S. Huang, J. M. Wei and V. Farina, *Tetrahedron*, 1993, **49**, 2805.

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