An Unprecedented Biogenetic-Type Chemical Synthesis of 1(15→11) Abeotaxanes from Normal Taxanes

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A one-pot chemical process using $BF_3 \cdot Et_2O$ for the synthesis of a new class of 1(15→11) abeotaxanes from normal taxanes has been developed. The chemical structures of rearranged 1(15→11) abeotaxane were established by extensive 2D NMR spectroscopic data.

Taxol (**1**), a diterpeno pseudoalkaloid, was first isolated from the bark of the Pacific yew, *Taxus brevifolia*, by Wall and Wani's group in collaboration with the National Cancer Institute (NCI) and is a significant new lead for the treatment of cancer (Figure 1).[1] It has been approved by the FDA for the treatment of advanced ovarian and metastatic breast cancer and is currently in clinical trials for other cancers.[2] The outstanding cytotoxic activity of taxol (**1**) is believed to arise from its unique propensity to hinder cell replication by preventing microtubule depolymerization.[3] The only major source of **1** is from the needles (0.033%) and bark (0.01%) of the Pacific yew tree, *T. brevifolia*, which cannot be considered a renewable source because of its slow growth, and therefore, the supply of **1** is quite limited.[4]

On the other hand, the supply of the key terpenoid fragments baccatin III (**2**) (0.2%) and 10-deacetylbaccatin III (**3**) (0.1%) is readily obtained from the needles, a rapidly renewable resource. The semisynthetic route to the production of Taxol involves the attachment of the *N*-benzoyl-(2*R*,3*S*)-phenylisoserine (**4**) side chain to the main ring of baccatin III (**2**) or 10-deacetylbaccatin III (**3**) (Figure 1).[5] The scarcity of **1** from natural sources and the economic challenges associated with the total synthesis of Taxol[6] have led to the search for an alternative compound.

Extensive chemical studies on other *Taxus* species resulted in the isolation of a large number of taxoids with basic skeletons **I**−**VI** (Figure 2).[7] A normal taxane contains an eight-membered ring sandwiched between two six-membered rings as in **I**. Cyclotaxanes (**II**) are tetracyclic systems with an additional bond between C-3 and C-11 (6/5/5/6 ring system). The rearranged taxanes possessing ring systems **III**−**V** are called 11(15→1) abeotaxane, 2(3→20) abeotaxane, and 11(15→1) and 11(10→9) bisabeotaxane, respectively. Compounds with skeleton **VI** (6/12 ring system) are referred to as pretaxanes since the bond between C-3 and C-8 is not yet formed. It is noteworthy to mention that rearranged taxoids (**II**−**V**) retained the microtubule and multi-drug-resistance (MDR) reversing activities.[8] Thus far, 1(15→11) abeotaxanes (**VII**) with the 5/7/6 ring system have not yet been reported as natural products; therefore their anticancer activity, tubulin-binding activity, and MDR-reversing activities have not yet been studied (Figure 2). Herein we describe an unprecedented chemical synthesis of 1(15→11) abeotaxanes using $BF_3 \cdot OEt_2$.

In continuation of our drug discovery program on anticancer agents we isolated 2-deacetoxytaxinine J (**5**; 2-DAT-J) in reasonably good yield (0.1%) from the Indian *T. baccata* (ssp. *wallichiana*). 2-DAT-J (**5**) was also reported from several other *Taxus* species.[9] It exhibits cytotoxicity against L1210 murine leukemia cells and

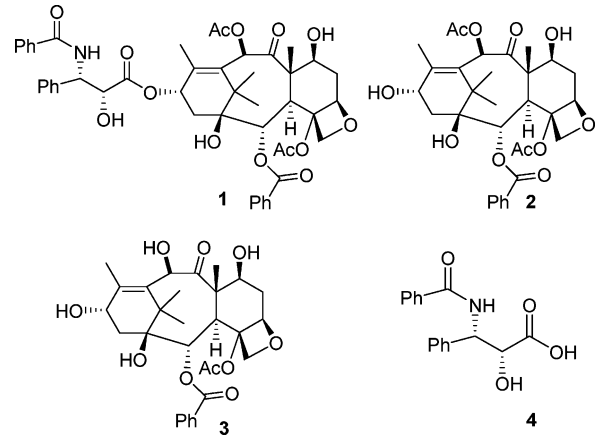

Figure 1. Paclitaxel (**1**, Taxol: BMS-181339); baccatin III (**2**); 10-deacetylbaccatin III (**3**); and phenylisoserine (**4**, Taxol C-13 side chain).

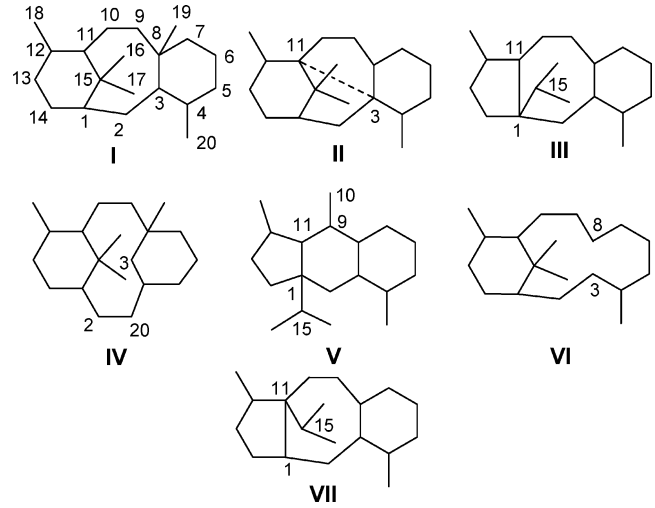

Figure 2. Normal taxoid **I**, rearranged taxoids (abeotaxoids) **II**−**V**, pretaxane **VI**, and chemically synthesized taxoid **VII**.

KB human epidermoid carcinoma cells and has an effect on Ca^{2+}-induced microtubule depolymerization.[9] Taxoid **5** exhibits no cytotoxicity and tubulin affinity and is considered a powerful inhibitor of P-glycoprotein (P-gp) activity, acting as an efficient reversing agent in MDR cancer cells.[10] Botta and co-workers synthesized a small library of analogues of **5** to develop a potential MDR-reversing agent.[11] Recently we also reported the in vitro anticancer activity of **5** and its new derivatives and the in vivo

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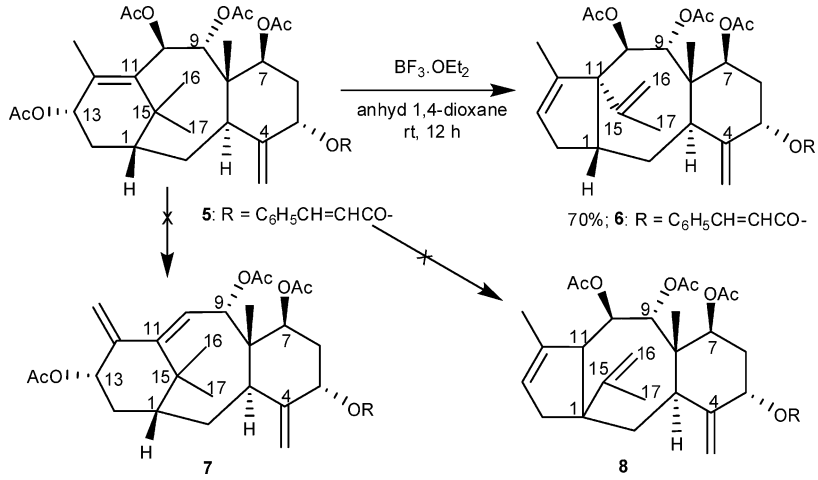
Scheme 1. Synthesis of 1(15→11) Abeotaxane **6** Using $BF_3 \cdot OEt_2$



anticancer activity of **5** in animal models.[12] During this chemical transformation process we attempted to remove the C-13 acetyl group from **5** using $BF_3 \cdot OEt_2$. In our previous studies $BF_3 \cdot OEt_2$ regioselectively deacetylated the polyacetoxyacetophenones.[13] A similar attempt was made on **5**, which surprisingly resulted in the regioselective removal of the acetoxy group followed by an unprecedented rearrangement to provide 1(15→11) abeotaxane **6** (Scheme 1) in reasonably good yield (70%). Extensive 2D NMR studies were carried out to elucidate the structure of **6** (Figure 3). The ESI mass spectrum of **6** showed a molecular ion peak at 613 $[590 + Na]^+$, which clearly gave information on the removal of HOAc (650 − 590 = 60) from **5** (Figure 4). One of the significant differences in the ^1H NMR spectra of **5** and **6** is the appearance of two extra olefinic singlets at 4.59 and 4.83 ppm, an olefinic CH (5.29 ppm), and six methyls in **6** (0.93, 1.41, 1.58, 1.89, 1.96, and 1.99 ppm) instead of eight methyls in **5** (Table 1).

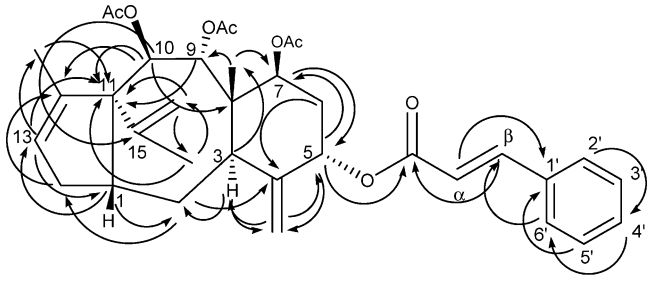


Figure 3. Selected $^1H \rightarrow ^{13}C$ HMBC correlations for **6**.

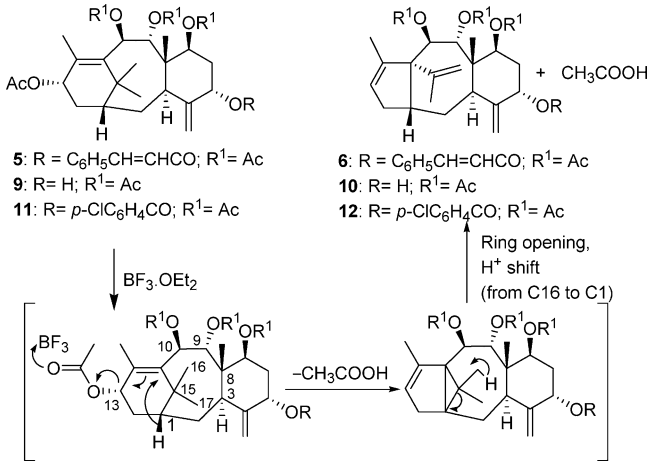


Figure 4. Plausible mechanism for the formation of 1(15→11) abeotaxanes **6**, **10**, and **12**.

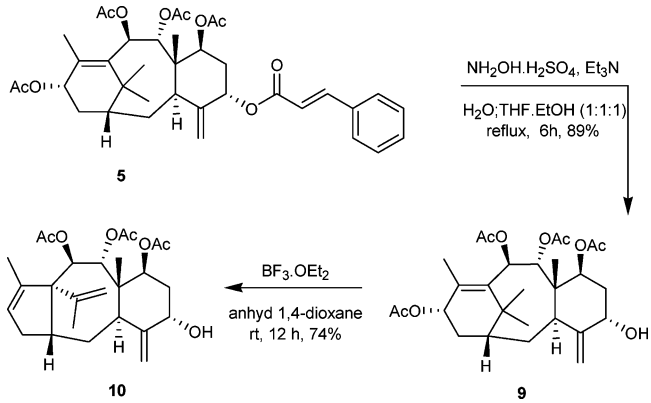
Table 1. Selected $^1H \rightarrow ^{13}C$ HMBC Correlations for **6**

position	δ_H (*J* in Hz)	δ_C	selected HMBC correlations[a]
1	2.92, m	41.4	2, 13
2	1.71, 2.12, m	27.0	4, 14
3	2.91, m	35.0	2, 20
4		146.4	
5	5.44, t (3.6)	74.8	3, 7, 20, CO (cinnamoyl)
6	2.10, 2.24, m	37.1	4, 8
7	5.40, t (3.1)	70.9	3, 5
8		45.7	
9	5.34, t (7.2)	73.5	3, 11
10	5.57, t (7.2)	72.4	8, 11, 12, 15
11		63.7	
12		142.5	
13	5.29, m	126.0	1, 11, 18
14	1.65, 2.22, m	32.3	11, 12
15		145.7	
16	4.59, 4.83, s	112.2	11, 17
17	1.58, s	20.9	11, 16
18	1.41, s	14.8	11, 13
19	0.93, s	13.3	9, 7
20	4.88, 5.24, s	114.2	3, 5
7-$OCOCH_3$	1.89, s	170.1 (CO) 21.2 (CH_3)	7[b]
9- $OCOCH_3$	1.96, s	169.5 (CO) 21.2 (CH_3)	9[b]
10-$OCOCH_3$	1.99, s	169.8 (CO) 21.3 (CH_3)	10[b]
CO cinnamoyl		165.6	
α	6.38, d (15.9)	118.4	1′
β	7.63, d (15.9)	144.9	CO (cinnamoyl), 2′, 6′
1′		134.4	
2′, 6′	7.47, m	128.1	*β*, 4′
3′, 5′	7.33, m	128.9	1′
4′	7.33, m	130.3	2′, 6′

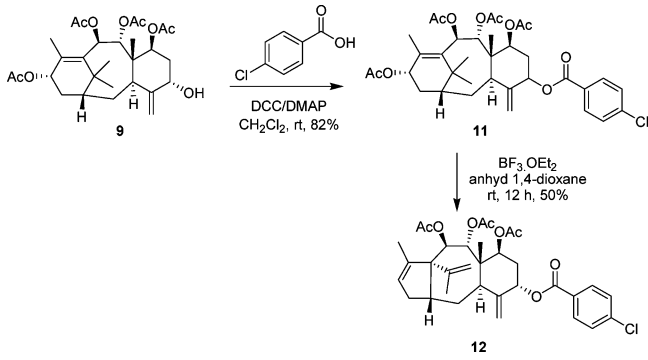
[a] HMBC correlations from proton(s) stated to the indicated carbon. [b] Very weak four-bond correlations.

The ^{13}C NMR spectrum showed a characteristic downfield quaternary carbon at 63.7 ppm. The DEPT-135 and HSQC spectra confirmed the extra olefinic methylene at 112.2 ppm and olefinic methyne at 126.0 ppm (Table 1). In 2-DAT-J (**5**)[14] there were three-bond correlations between H-13 and C-11, which were missing in the rearranged product **6**. In addition to that in **5** H-10 gave three-bond correlations with C-8 (46.3 ppm) as well as C-15 (39.3 ppm). H-9 gave three-bond correlations with C-11 (135 ppm) and two-bond correlations with C-8, whereas in **6** H-10 gave correlations with C-8 (45.7 ppm), C-12 (142.5 ppm), C-15 (145.7 ppm), and C-11 (63.7 ppm) and H-9 also gave correlations with C-11 (63.7 ppm). The newly generated olefinic methylene protons (4.59 and

Scheme 2. Synthesis of 1(15→11) Abeotaxane **10**



Scheme 3. Synthesis of 1(15→11) Abeotaxane **12**



4.83 ppm) gave three-bond correlations with C-11 (63.7 ppm) and a methyl group at 20.9 ppm (C-17) (Figure 3 and Table 1). In addition there were correlations between H-9 (H-5.34: C-73.5 ppm) and H-10 (5.57: 72.4 ppm) in the COSY spectrum to rule out structure **7** (Scheme 1). Attachment of the exocyclic double bond (C-15 and C-16) to C-1 as in **6** or to C-11 as in **8** was confirmed by the HMBC data (Scheme 1). In the HMBC spectrum H-9 (5.34 ppm) and the H-18 methyl (1.41 ppm) gave three-bond correlations with the carbon at 63.7 ppm, which supports the attachment of the exocyclic double bond (C-15 and C-16) to C-11 and not C-1. On the basis of the NMR analysis the structure was assigned as **6** (Figure 3 and Table 1). The relative configuration at C-11 was determined by NOESY data.[15]

To demonstrate the regioselectivity, the C-5 *O*-cinnamoyl group of **5** was selectively removed using NH_2OH to give **9**, which was subsequently reacted with $BF_3 \cdot OEt_2$ to afford the 1(15→11) abeotaxane **10** (Scheme 2). To further study the generality of the reaction, the C-5 *p*-chlorobenzoate **11** was prepared from **9** using the DCC and DMAP protocol and subsequently reacted with $BF_3 \cdot Et_2O$ to give the rearranged 1(15→11) abeotaxane **12** (Scheme 3).

The mechanism for the formation of the 1(15→11) abeotaxane skeleton appears to be the regioselective removal of the C-13 acetoxy group by $BF_3 \cdot OEt_2$ followed by migration of the C-11−C-12 double bond to C-12−C-13. The resultant acetate ion may abstract the C-1 proton, which could lead to a cyclopropyl ring involving C-1, C-11, and C-15. The strain associated with the cyclopropyl ring may lead to ring-opening between C-15 and C-1 and a subsequent Wagner−Meerwein-type H^+ shift from C-16 to C-1 to furnish the required 1(15→11) abeotaxanes **6**, **10**, and **12**. Further studies, however, are required to confirm the exact reaction mechanism (Figure 4).

In conclusion, we discovered a biogenetic-type access for the chemical synthesis of 1(15→11) abeotaxanes from normal taxoids using $BF_3 \cdot OEt_2$. Our simple and convenient method has paved the way toward the synthesis of a new class of 1(15→11) abeotaxanes.

Experimental Section

General Experimental Procedures. Melting points were recorded on a Buchi-530 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer AC-1 spectrometer. ^1H NMR spectra were run on a Bruker Advance DPX 300 MHz in $CDCl_3$, and ^{13}C NMR spectra were recorded at 75 and 50 MHz in $CDCl_3$. COSY, HMBC, and HSQC spectra were recorded at 300 MHz in $CDCl_3$. Chemical shifts are reported in ppm relative to $CHCl_3$ (7.26) in $CDCl_3$, and TMS was used as internal standard. ESIMS were recorded on JEOL SX 102/DA-6000.

Chromatography was done with silica gel (60−120 mesh) using mixtures of EtOAc and *n*-hexane as eluents. EtOAc and *n*-hexane were dried and purified by distillation prior to use. Reactions that required the use of anhydrous and inert conditions were carried out under an N_2 atmosphere. 1,4-Dioxane was distilled over Na.

Representative Procedure for the Synthesis of 1(15→11) Abeotaxane (6). To a magnetically stirred solution of 2-deacetoxytaxinine-J (**5**) (250 mg, 0.38 mmol) in anhydrous 1,4-dioxane (25 mL) was slowly added $BF_3 \cdot OEt_2$ (0.1 mL, 0.76 mmol) at room temperature. The solution was stirred for 12 h at room temperature. After dilution with Et_2O (100 mL), the solution was washed with H_2O (3 × 30 mL) to decompose the $BF_3 \cdot OEt_2$ complex. The solution was dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography using *n*-hexane−EtOAc (70:30) to afford compound **6** (185 mg, 70%): mp 121−123 °C; IR (KBr) ν_{max} 2924, 2854, 1739, 1634, 1446, 1370, 1243, 1166, 1033, 760 cm^{-1}; MS (ESI) *m*/*z* 613.2 $[M + 23]^+$; ^1H NMR and ^{13}CNMR data in Table 1.

1(15→11) Abeotaxane (10): mp 130−132 °C; IR (KBr) ν_{max} 3019, 2924, 2855, 1738, 1632, 1445, 1371, 1249, 1035, 759 cm^{-1}; ^1H NMR data δ 5.63 (d, J = 6.9 Hz, 1H), 5.42 (m, 3H), 5.11 (s, 1H), 4.88 (s, 1H), 4.82 (s, 1H), 4.60 (s, 1H), 4.37 (t, J = 2.9 Hz, 1H), 3.12 (m, 1H), 3.00 (m, 1H), 2.33−2.14 (m, 4H), 2.06 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H), 1.84−1.73 (m, 2H), 1.67 (s, 3H), 1.47 (s, 3H), 0.91 (s, 3H); ^{13}C NMR data δ 170.9, 170.3, 170.2, 151.3, 146.5, 142.4, 126.5, 114.5, 112.1, 73.8, 73.6, 72.9, 71.5, 64.1, 46.4, 41.7, 37.7, 34.7, 34.2, 32.1, 27.7, 21.7, 21.5, 21.1, 15.0, 13.5; MS (ESI) *m*/*z* 478.2 $[M + 18]^+$, 483.3 $[M + 23]^+$.

1(15→11) Abeotaxane (12): ^1H NMR data δ 8.00 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 5.69 (d, J = 6.8 Hz, 1H), δ 5.62 (s, 1H), 5.54 (m, 1H), 5.44 (d, J = 6.8 Hz, 1H), 5.34 (s, 1H), 5.30 (s, 1H), 4.99 (s, 1H), 4.89 (s, 1H), 4.64 (s,1H), 3.05 (m, 1H), 2.98 (m, 1H), 2.34 (m, 4H), 2.08 (s, 3H), 2.04 (s, 3H), 1.97 (s, 3H), 1.79 (m, 2H), 1.66 (s, 3H), 1.49 (s, 3H), 1.04 (s, 3H); ^{13}C NMR data δ 170.2, 169.8, 1969.4, 164.3, 146.3, 146.1, 142.6, 139.5, 130.9 (2C), 128.9, 128.7 (2C), 125.5, 114.1, 111.7, 75.7, 73.2, 72.4, 70.7, 63.8, 45.9, 41.1, 37.5, 35.0, 32.3, 27.3, 21.24, 21.21, 21.15, 20.7, 14.7, 13.0; MS (ESI) *m*/*z* 621.2 $[M + 23]^+$.

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Supporting Information Available: Spectroscopic data of unusual 1(15→11) abeotaxane **6**, 2-DAT-J **5** (2D: HMBC, HMQC, COSY, NOESY, etc.), and **9**−**12** (1D data) and their in vitro anticancer activity are available free of charge via the Internet at http://pubs.acs.org.

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(14) 2DAT-J (**5**): ^{1}H NMR data δ 2.03 (1H, m, H-1), 1.81−1.91 (2H, m, H-2), 2.74 (1H, dd, H-3), 5.58 (1H, dd, H-5), 1.90−1.99 (2H, m, H-6), 5.69 (1H, dd, H-7, 5.95 (1H, d, H-9), 6.31 (1H, d, H-10), 5.81 (1H, dd, H-13), 1,01 and 2.81 (2H, m, H-14), 1.10 (3H, s, H-15), 1.63 (3H, s, H-16), 2.35 (3H, s, H-18), 0.97 (3H, s, H-19), 5.03 and 5.40 (2H, s, H-20); *O*-cinnamoyl: 6.57 (1H, d, H-α), 7.75 (1H, d, H-β), 7.40 (3H, m, H-3′-5′ and H-4′), 7.51 (2H, m, H-2′,6′), *O*-acetyl: 1.72 (3H, s), 2.00 (3H,s), 2.05 (3H, s), 2.08 (3H, s); 13C NMR ($CDCl_3$, 50 MHz) δ 40.1 (C1), 27.2 (C-2), 37.4 (C-3), 146.2 (C-4), 74.8 (C-5), 34.5 (C-6), 70.9 (C-7), 46.3 (C-8), 76.7 (C-9), 71.7 (C-10), 135.0 (C-11), 137.2 (C-12), 70.6 (C-13), 31.8 (C-14), 39.3 (C-15), 27.2 (C-16), 31.1 (C-17), 15.3 (C-18), 13.1 (C-19), 116.0 (C-20); *O*-cinnamoyl: 166.1 (CO), 118.3 (C-α), 145.7 (C-β), 134.0 (C-1′), 129.0 (C-3′,5′), 128.1 (C-2′,6′), 130.6 (C-4′); *O*-acetyl: CO: 169.3, 169.9, 170.2, 170.3, CH_3: 20.8, 21.0, 21.0, 21.4; MS (ESI) *m/z* 673 $[M + 23]^+$.

(15) See the Supporting Information for spectroscopic data and anticancer activity data.

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