A Selective Intramolecular Transacylation of Taxoids Accompanying with the Oxetane Ring Opening

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A selective intramolecular transacylation from C-4 to C-5 of taxoids, which occurred simultaneously with the oxetane D-ring opening and was promoted by $TiCl_4$, was presented. The optimal condition was found to be treatment of substrates in double dose of dichloromethane (per mg of substrate dissolved in 2 mL DCM) with 1 eq of $TiCl_4$ at 25°C for 10 min.

Key words taxane; paclitaxel; titanium tetrachloride; D-ring opening; transacylation

The diterpenoid natural product paclitaxel (Fig. 1) was initially isolated by Wall and Wani from *Taxus brevifolia* and led to the discovery of a new biochemical mechanism.[1,2] Its mechanism of action as a promoter of tubulin assembly has provided the basis of the extensive mechanism-based development of anticancer agents. As two of the most effective drugs for the treatment of cancer, paclitaxel and its analogue docetaxel (Fig. 1) are now used, either as single agents or in combination with other drug, for the treatment of ovarian cancer, breast cancer, and non-small-cell lung cancer.

The oxetane D-ring is one of the unusual features of the paclitaxel structure, and it plays a significant role in paclitaxel's unique activity.[3] A characteristic reaction of the oxetane D-ring of paclitaxel is its opening promoted by Lewis acid, which is accompanied by intramolecular transacylations (Chart 1).[4] The related mechanism was proposed as follows: i) an orthoester between C-4, C-5, and C-20 may be formed promoted by Lewis acid; and ii) this orthoester may be hydrolyzed to afford the C-5 and C-20 acetoxy derivatives, with C-20 acetoxy derivative as the major product.[4] This interesting reaction not only furnished the D-ring opening analogue of paclitaxel, but also acted as a conventional approach to other D-ring modified analogues.[5—13] The biological data of these D-ring modified analogues greatly enriched the structure–activity relationships of paclitaxel.

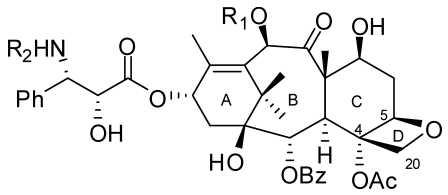

Fig. 1. Structures of Paclitaxel and Docetaxel

To search for novel D-ring modified analogues of paclitaxel, we need an intermediate with an acetoxy group at the C-5 position, which is the minor product from the above-mentioned D-ring opening process.[14] Therefore, we revisited the Lewis acid-promoted oxetane D-ring opening and hoped to search for an unusual and selective transacylation from C-4 to C-5. In this note, we wish to report our observed results in this regard.

Results and Discussion

We began our exploitation with $BF_3{\cdot}OEt_3$ as a Lewis acid because $BF_3{\cdot}OEt_3$ is the most common Lewis acid that was used to promote the D-ring opening of taxoids. Our initial experiment demonstrated that the treatment of an derivative (**3**) of 10-deacetyl Baccatin III (10-DBA, **6**) with $BF_3{\cdot}OEt_3$ at −15°C generated **4** with a C-20 acetoxy group in 65% yield, as well as trace amount of our desired product **5** (10%) (Entry 1, Table 1). Next, we examined the effect of the reaction conditions (such as amount of Lewis acid, reaction time, reaction temperature, and concentration of reaction mixture) on the selectivity of the transacylation from C-4 to C-5 (Table 1). Significantly, it was found that the yield of C-5 acetoxy product **5** was increased from 10 to 25% when the reaction was performed in a highly diluted reaction mixture (Entry 4).

Most importantly, this result encouraged us to further exploit the possibility to increase the yield of the expected product **5** by examining various Lewis acids, including $BF_3{\cdot}OEt_3$, $SnCl_4$, $AlCl_3$, and $TiCl_4$ (Table 1). It was observed: i) that employment of $SnCl_4$ as a Lewis acid in combination with diluted reaction mixture led to slightly improved selectivity for the transacylation from C-4 to C-5 (Entry 9); ii) that $AlCl_3$ is not a good Lewis acid for this reaction in consideration of both

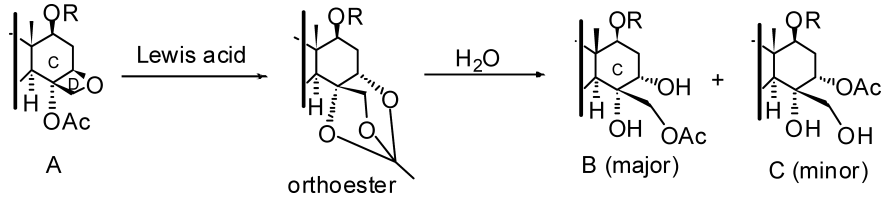

Chart 1. Conventional D-Ring Opening of Taxoids

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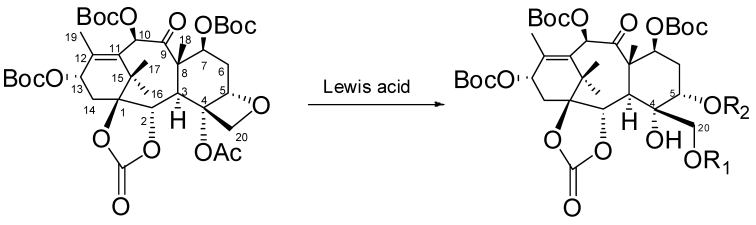
Table 1. Lewis Acid-Promoted Intramolecular Transacylation and D-Ring Opening of **3**



3

4 R_1 = Ac; R_2 = H
5 R_1 = H; R_2 = Ac

Entry	Lewis acid	Reaction temperature	Reaction time	Amount of dichloromethane[a)]	Yield % for **4**	Yield % for **5**
1	$BF_3{\cdot}Et_2O$ (1 eq)	−15°C	10 min	1 mL/mg	65	10
2	$BF_3{\cdot}Et_2O$ (1 eq)	−15°C	30 min	1 mL/mg	50	8
3	$BF_3{\cdot}Et_2O$ (2 eq)	0°C	10 min	1 mL/mg	50	5
4	$BF_3{\cdot}Et_2O$ (1 eq)	−15°C	10 min	4 mL/mg	65	25
5	$BF_3{\cdot}Et_2O$ (1 eq)	25°C	10 min	2 mL/mg	35	5
6	$SnCl_4$ (1 eq)	−15°C	30 min	1 mL/mg	35	30
7	$SnCl_4$ (2 eq)	−15°C	30 min	1 mL/mg	30	20
8	$SnCl_4$ (1 eq)	−15°C	30 min	2 mL/mg	35	35
9	$SnCl_4$ (1 eq)	0°C	30 min	2 mL/mg	45	45
10	$SnCl_4$ (1 eq)	25°C	10 min	2 mL/mg	15	15
11	$AlCl_3$ (1 eq)	0°C	30 min	2 mL/mg	20	5
12	$AlCl_3$ (2 eq)	0°C	30 min	2 mL/mg	20	5
13	$AlCl_3$ (1 eq)	25°C	30 min	2 mL/mg	10	2
14	$TiCl_4$ (1 eq)	25°C	10 min	2 mL/mg	0	93
15	$TiCl_4$ (1 eq)	25°C	30 min	1 mL/mg	15	45
16	$TiCl_4$ (1 eq)	0°C	30 min	2 mL/mg	45	35
17	$TiCl_4$ (2 eq)	25°C	30 min	2 mL/mg	25	60
18	$TiCl_4$ (1 eq)	25°C	10 min	4 mL/mg	0	93

a) 1 mL/mg means that 1 mL of dichloromethane was used for per mg of substrate.

total yield and selectivity (Entry 11); and iii) that $TiCl_4$ was established as an optimal Lewis acid, which might provide an excellent selectivity and yield (Entries 14, 18). It is worth noting that a highly diluted reaction mixture and a relatively higher reaction temperature are very beneficial to the selectivity when using $TiCl_4$ as Lewis acid. However, enhancement of the amount of $TiCl_4$ from 1 to 2 eq is detrimental to the selectivity (Entry 17). To this end, treatment of a highly diluted solution of **3** in double dose of dichloromethane (per mg of substrate dissolved in 2 mL DCM) with 1 eq of $TiCl_4$ at 25°C for 10 min was found to be the optimal condition for the simultaneous ring-D opening and selective transacylation from C-4 to C-5.

The major differences in the ^{1}H-NMR spectra of **4** and **5** (Table 2) occurred at C-5 and C-20, and these differences are consistent with the assignment of the acetoxy group at C-20 for **4** and at C-5 for **5**. Specifically, the chemical shift of the C-20 protons in **4** downshifted from 4.08/3.59 in **5** to 4.52/4.41, indicating that the acetoxy group was transformed to C-20 in **4**. Similarly, the chemical shift of the C-5 proton in **5** downshifted from 3.79 in **4** to 5.32, suggesting the transacylation at C-5.

At this point, we paid our attention to the evaluation of the applicability of this selective transacylation while the D-ring opening. Accordingly, 10-DAB (**6**), Paclitaxel (**1**) and Docetaxel (**2**) possessing free hydroxyl groups was treated with $TiCl_4$ (1 eq) in DCM (2 mL per mg of substrate) at 25°C for 10 min (Chart 2). The selective transacylation from C-4 to C-5 also proceeded smoothly in this case to furnish the D-ring opening products **7**, **8** and **9**, respectively. This indicated that both protected and unprotected hydroxyl groups are perfectly compatible with the aforementioned reaction conditions.

In conclusion, we have developed a regioselective D-ring opening reaction, in which the acetyl group at C-4 could be selectively transferred to C-5 in an excellent yield while the D-ring opening. This reaction is applicable for various taxoids including paclitaxel and docetaxel and highly tolerated to the free hydroxyl groups, which suggested that this selective reaction is particularly useful in the ring D-modifications of taxoids.

Experimental

General ^{1}H- and ^{13}C-spectra were recorded on a Varian Unity INOVA 400/54NMR spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. Chemical shifts are given as δ value and are referenced to residual solvent proton carbon pick. Mass spectra were obtained on a VG Auto spec 3000 or on a Finnigan MAT 90 instrument. Optical rotations were measured on a Perkin-Elmer 341. Silica gel H (Qingdao Sea Chemical Factory, Qingdao, P.R. China) was used for column chromatography. Spots on TLC (silica gel G) were detected with H_2SO_4–EtOH. Commercially available reagents and solvents were used without further purification.

Preparation of the D-Opening Derivate 5 To a stirred

Table 2. NMR Spectroscopic Data for Compounds **4** and **5**

No.	**4**		**5**	
	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR	^{13}C-NMR
1	—	90.2 s	—	90.1 s
2	4.23 d (4.4)	72.1 d	4.24 d (4.8)	72.1 d
3	3.74 d (4.4)	43.4 d	3.50 d (4.8)	45.3 d
4	—	75.4 s	—	74.0 s
5	3.79 t (2.8)	81.1 d	5.32 t (2.8)	81.7 d
6	1.85 m, 2.24 m	30.6 t	2.00 m, 2.12 m	30.0 t
7	5.44 dd (11.2, 4.4)	71.4 d	5.20 dd (11.6, 4.8)	71.6 d
8	—	59.1 s	—	59.0 s
9	—	202.0 s	—	201.9 s
10	6.48 s	78.3 d	6.44 s	78.0 d
11	—	132.0 s	—	132.0 s
12	—	144.2 s	—	143.8 s
13	5.72 dd (10.0, 2.4)	69.8 d	5.82 dd (8.4, 5.6)	71.3 d
14	3.13 dd (15.6, 4.0)	32.5 t	3.13 dd (15.2, 5.6)	32.7 t
	2.64 dd (15.6, 10.0)		2.64 dd (15.2, 10.0)	
15	—	40.6 s	—	41.1 s
16	1.15 s	18.8 q	1.15 s	19.5 q
17	1.22 s	27.1 q	1.28 s	26.0 q
18	2.29 s	16.6 q	2.31 s	16.1 q
19	1.35 s	12.7 q	1.29 s	12.7 q
20	4.52 ABq (12.0)	64.7 t	4.08 ABq (9.2)	62.9 t
	4.41 ABq (12.0)		3.59 ABq (9.2)	
OCOO	—	151.8 s	—	151.9 s
$(CH_3)_3$ C—O	1.44, 1.47, 1.50, s	27.7 q	1.44, 1.47, 1.49, s	27.6 q
	—	82.8 s	—	83.0 s
C=O	—	170.5 s	—	171.0 s
CH_3	2.13 s	20.7 q	2.34 s	21.3 q

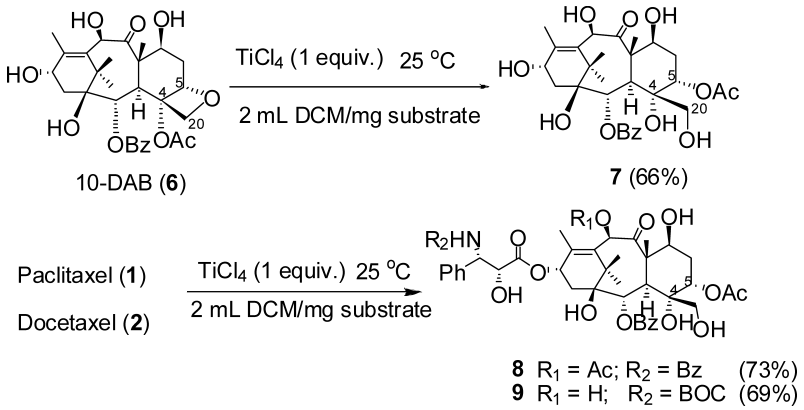


Chart 2. $TiCl_4$-Mediated D-Ring Opening and Transacylation of 10-DAB, Paclitaxel and Docetaxel

solution of compound **3** (100 mg, 0.13 mmol) in CH_2Cl_2 (200 mL) at 25°C, 1 M $TiCl_4$ (in CH_2Cl_2) 0.13 mL was added. The reaction mixture was stirred at 25°C for 10 min, then saturated K_2CO_3 and water were added to quench this reaction. The organic phase was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel (cyclohexane/acetone 6 : 1) to yield compound **5** (96 mg, 93%) as an amorphous powder. $[\alpha]_D^{25}$ −13.2 (c=2.0, $CHCl_3$), MS (electrospray ionization (ESI), MeOH) m/z 785 $[M+H]^+$; HR-ESI-MS: 785.3502 ($M+H^+$, $C_{38}H_{57}O_{17}$, Calcd 785.3517);

Preparation of the D-Opening 10-DAB Derivate 7 To a stirred solution of 10-DAB (**6**, 103 mg, 0.19 mmol) in CH_2Cl_2 (206 mL) at 25°C, 1 M $TiCl_4$ (in CH_2Cl_2) 0.19 mL was added. The reaction mixture was stirred at 25°C for 10 min, then saturated K_2CO_3 and water were added to quench this reaction. The organic phase was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel (petroleum ether/acetone 3 : 1) to yield compound **7** (68 mg, 66%) as an amorphous powder. "Characterization data of compound **7**": $[\alpha]_D^{25}$ −16.6 (c=0.9, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$+CD_3OD) δ: 7.39—7.88

(5H, m), 5.30 (1H, d J=6.4 Hz), 5.21 (1H, br s), 5.16 (1H, br s), 4.16 (1H, ABq, J=9.2 Hz), 3.67 (1H, ABq, J=9.2 Hz), 3.98 (1H, d, J=6.4 Hz), 2.15 (3H, s), 1.99 (3H, s), 1.13 (3H, s), 1.05 (3H, s), 1.00 (3H, s). ^{13}C-NMR ($CDCl_3$+CD_3OD, 100 MHz) δ: 202.3, 170.9, 168.3, 152.8, 152.3, 147.8, 147.8, 129.9, 129.9, 90.3, 83.7, 80.8, 79.3, 77.2, 76.1, 73.7, 66.9, 58.0, 44.2, 40.8, 35.5, 33.8, 27.5, 25.4, 22.4, 20.6, 19.9, 15.7, 10.7. MS (ESI, MeOH) m/z 563 $[M+H]^+$; HR-ESI-MS: 563.2471 ($M+H^+$, $C_{29}H_{39}O_{11}$, Calcd 563.2492).

Preparation of the D-Opening Paclitaxel Derivate 8 To a stirred solution of paclitaxel (**1**, 142 mg, 0.17 mmol) in CH_2Cl_2 (300 mL) at 25°C, 1 M $TiCl_4$ (in CH_2Cl_2) 0.17 mL was added. The reaction mixture was stirred at 25°C for 10 min, then saturated K_2CO_3 and water were added to quench this reaction. The organic phase was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel (petroleum ether/acetone 3 : 1) to yield compound **8** (104 mg, 73%) as an amorphous powder. "Characterization data of compound **8**": $[\alpha]_D^{25}$ +235.2 (c=1.0, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.17—8.05 (15H, m), 6.58 (1H, s), 6.00 (1H, dd, J_1=9.6 Hz, J_2=3.2 Hz), 5.92 (1H, d, J=9.2 Hz), 5.56 (1H, d, J=5.6 Hz), 4.70 (1H, s), 4.50 (1H, m), 4.13 (1H, s), 4.02 (1H, ABq), 3.71 (1H, ABq), 3.04 (1H, dd, J_1=12.0 Hz, J_2=4.4 Hz), 2.21, (1H, s), 2.08 (3H, s), 1.63 (3H, s), 1.24 (3H, s), 1.13 (3H, s), 1.11 (3H, s). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 203.6, 188.6, 171.5, 170.6, 169.6, 167.4, 166.8, 140.3, 138.7, 134.9, 134.1, 133.1, 131.8, 130.0, 128.8, 128.8, 128.7, 128.6, 128.6,128.2, 128.0, 126.9, 126.9, 126.6, 126.6, 77.3, 75.4, 75.2, 74.4, 73.6, 73.2, 71.8, 68.5, 64.1, 60.3, 54.6, 45.7, 42.4, 42.4, 35.0, 31.5, 27.8, 20.7, 19.9, 18.8, 16.2, 10.6. MS (ESI, MeOH) m/z 873 $[M+H]^+$; HR-ESI-MS: 872.3453 ($M+H^+$, $C_{47}H_{54}NO_{15}$, Calcd 872.3493).

Preparation of the D-Opening Docetaxel Derivate 9 To a stirred solution of Docetaxel (**2**, 86 mg, 0.11 mmol) in CH_2Cl_2 (206 mL) at 25°C, 1 M $TiCl_4$ (in CH_2Cl_2) 0.11 mL was added. The reaction mixture was stirred at 25°C for 10 min, then saturated K_2CO_3 and water were added to quench this reaction. The organic phase was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel (petroleum ether/acetone 3 : 1) to yield compound **9** (59 mg, 69%) as an amorphous powder. "Characterization data of compound **9**": $[\alpha]_D^{25}$ +142.5 (c=0.8, CH_3OH), ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.27—8.12 (10H, m), 6.18 (1H, d, J=9.6 Hz), 6.05 (1H, m), 5.59 (1H, d, J=5.2 Hz), 5.55 (1H, br s), 5.39 (1H, br d, J=8.0 Hz), 4.58 (1H, br s), 4.40 (1H, m), 4.12 (1H, ABq), 3.85 (1H, ABq), 2.12, (1H, s), 1.63 (3H, s), 1.44 (9H, s), 1.15 (3H, s), 1.13 (3H, s), 0.86 (3H, s). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 200.1, 176.4, 161.9, 160.0, 139.5, 127.9, 124.3, 122.7, 121.5, 119.6, 119.6, 119.5, 99.9, 99.6, 73.7, 68.7, 68.2, 66.2, 66.1, 65.4, 61.3, 59.5, 59.5, 59.5, 59.2, 50.2, 40.1, 39.9, 39.6, 39.4, 39.2, 34.7, 29.6, 29.4, 23.8, 23.3, 21.0, 20.9, 20.7, 18.6, 17.9, 17.6, 17.0, 14.0, 11.9. MS (ESI, MeOH) m/z 826 $[M+H]^+$; HR-ESI-MS: 826.3613 ($M+H^+$, $C_{43}H_{56}NO_{15}$, Calcd 826.3650).

Acknowledgments We are grateful to the National Natural Science Foundation of China (No. 30873147 and No. 81001383) and the Doctoral Foundation of Ministry of Education, China (No. 20105103120009).

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