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The Seven-Membered Ring Intermediate to Control the Stereochemistry on the Eight-Membered Taxane B Ring Cyclization

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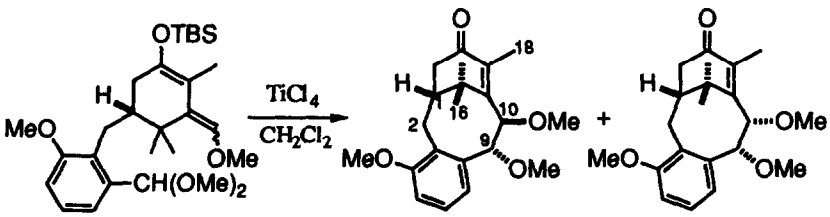
Abstract: On 8-membered ring cyclization of taxane B ring, formation of 7-membered cyclized intermediate has been identified, and the unique cyclization as well as the isomerization mechanism involving several equilibration processes have been proposed.

The remarkable tricarbocyclic skeleton as well as significant biological activities[1] of taxane diterpenoids have attracted increasing interests in synthetic organic chemistry.[2] In connection with construction of the carbon framework, we previously described the direct cyclization of the eight-membered ring to form C-aromatic taxane skeleton with endo conformation.[3] Further, it has also been found that, on performing the reaction at relatively high temperature, stereochemistry at C-9[4] and C-10 (taxane numbering) site can be controlled in the desired manner (9α,10β) irrespective of the geometry of the starting dienol ether (Eq 1, entry 1). From mechanistic viewpoint, there still remains a question how such isomerization of the C-10 stereochemistry takes place.



(Eq 1)

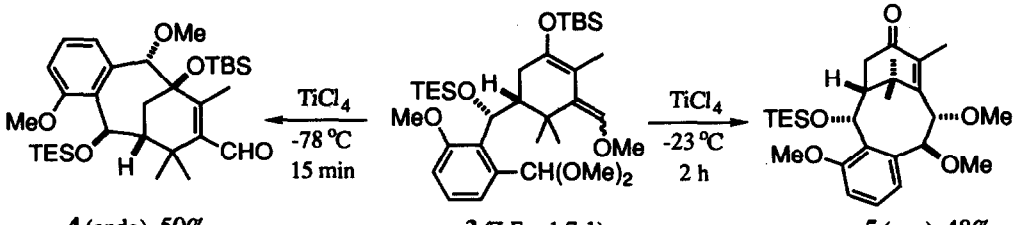
1 **2a** (endo) **2b** (endo)

entry			2a	2b
1	1(*Z*:*E* = 82:18)	-23 ℃, 45 min[a)]	84%	--
2	1(*Z*:*E* = 82:18)	-78 ℃, 15 min[a)]	64%	16%
3	1(*Z*:*E* = 5:95)	-100 ℃, 1 min	28%	22%

a) See ref 3).

To clarify the influence of geometry of dienol ether to the C-10 stereochemistry under kinetic control, we examined cyclization reaction of geometrically homogeneous dienol ether at low temperature. On treating **1** (95% pure *E*) with $TiCl_4$ at -100 °C for 1 min, a mixture of **2a** (endo-9α,10β) and **2b** (endo-9α,10α) was obtained in an almost equal amount (Eq 1, entry 3) along with the recovered **1**, although direct cyclization would give the thermodynamically more stable **2a**.[5] This result implies that the reaction is not kinetically controlled, but proceeds through certain equilibration before the eight-membered ring cyclization even at such low temperature.

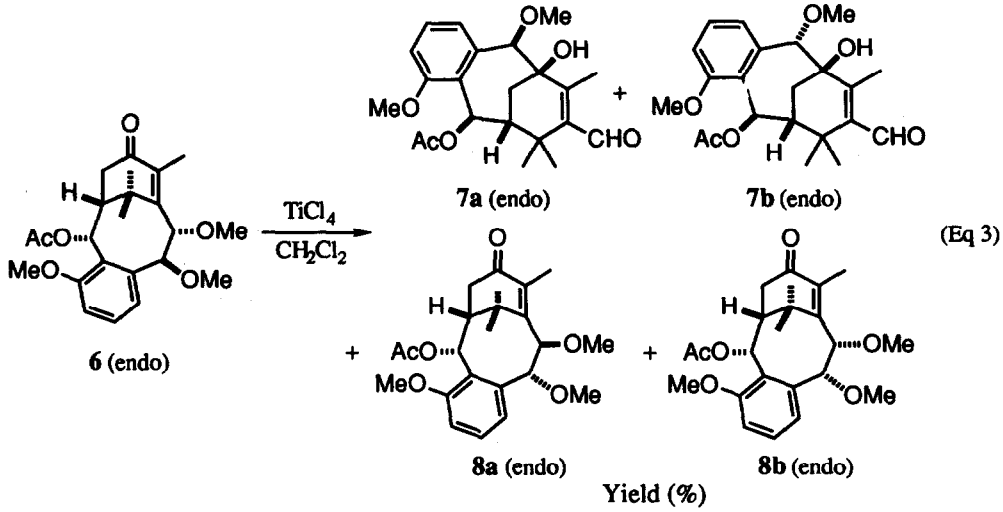
Further, $TiCl_4$ induced cyclization of **3** produced seven-membered cyclization product **4**[6] exclusively at -78 °C, while raising the reaction temperature to -23 °C led to the formation of eight-membered ring product **5**[7,8] (Eq 2).



4 (endo) 50% **3** (*Z*:*E* = 1.7:1) **5** (exo) 48%

(Eq 2)

It should be noted that seven-membered ring intermediates are involved not only during the cyclization step as above, but also in the isomerization process. For instance, an attempt to isomerize C-9 and C-10 sites by



(Eq 3)

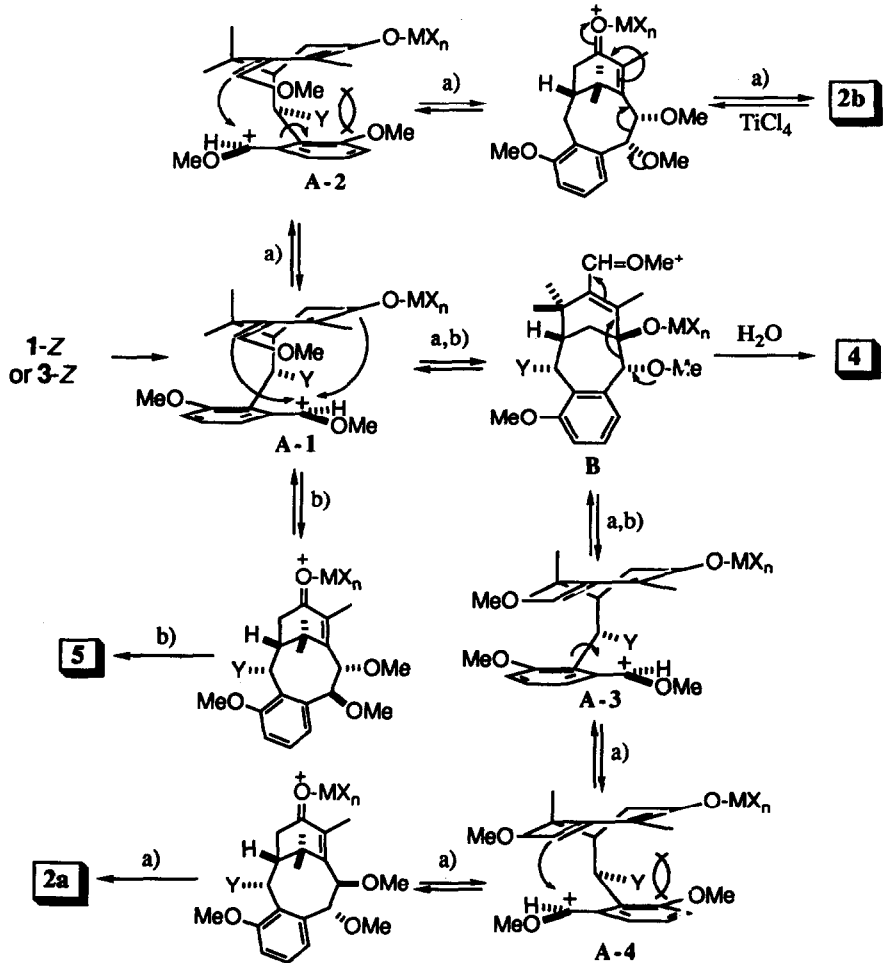
Yield (%)

	6	7a	7b	8a	8b
-100 °C, 15 min	33	58	9	0	0
-45 °C, 45 h	0	22	18	30	6

treating **6** (endo-2α,9β,10α)[9] with $TiCl_4$ at -100 °C resulted in predominant formation of seven-membered tricarbocycles **7a**[6] (58% yield) and **7b**[6] (9% yield), whereas the desired isomerization product **8a**[10] (endo-2α,9α,10β) was obtained in 30% yield by raising the reaction temperature (Eq 3).

Intervention of such seven-membered ring intermediate well accounts for the result of cyclization of **1** (eq 1, entry 3) and stereocontrol at C-10 site at higher temperature. The cyclization mechanism (MX_n = TBS) of **1**- and **3**-*Z* as well as the isomerization process (MX_n = $TiCl_4$) of **2b** to **2a** are depicted in Fig 1. The initially formed cationic species **A-1** rapidly cyclizes to the kinetically favored seven-membered cationic intermediate **B**, which, upon hydrolysis, would yield the aldehyde such as **4**. On performing the reaction at higher temperature, the ring

Fig. 1 Cyclization and Isomerization Mechanism



Cyclization Mechanism: MX_n = TBS Isomerization Mechanism: MX_n = $TiCl_4$

Path a: Y = H, Path b: Y = OTES

opening of **B** is induced to generate both *E*- and *Z*-dienol cationic species **A-2** and **A-4** through **A-1** and **A-3**, and the readily removable property of the silyl group favors the formation of **2**, especially the thermodynamically more stable **2a** (path a: MX_n = TBS, Y = H). On cyclization of **3**, both cationic species **A-2** and **A-4** (MX_n = TBS, Y = OTES) are energetically disfavored by severe steric repulsion between TESO and MeO, and consequently the reaction proceeds preferentially through **A-1** to yield exo cyclized product **5** (path b: MX_n = TBS, Y = H).

Isomerization of **2b** to **2a** may also proceed through equilibration (path a: MX_n = $TiCl_4$, Y = H) due to the great difference of thermodynamic stability.

In summary, the present results have disclosed the unique reaction mechanism of the eight-membered taxane B ring cyclization. The surprisingly high efficiency through such a complicated reaction pathway is noteworthy. We are currently studying total syntheses of natural taxane diterpenes by applying this methodology.

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1) Review on biological activity of taxol: E. K. Rowinsky, L. A. Cazenave, and R. C. Donehower, *J. National Cancer Institute*, **82**, 1247 (1990).

2) Review on synthetic studies on the carbon frameworks: C. S.Swindell, *Org. Prep. Proced. Int.*, **23**, 465 (1991).

3) Y. Horiguchi, T. Furukawa, and I. Kuwajima, *J. Am. Chem. Soc.*, **111**, 8277 (1989). T. Furukawa, K. Morihira, Y. Horiguchi, and I. Kuwajima, *Tetrahedron*, **48**, 6975 (1992).

4) The stereochemistry at C-9 site may be kinetically controlled by steric repulsion of MeO of -CH=O^+Me in the cyclization transition state. See ref 3.

5) By MM2 calculation, **2a** is estimated to be ca. 2.2 kcal/mol more stable than **2b**.

6) The structures of seven-membered products **4**, **7a**, and **7b** were reasonably assigned by NMR analyses, especially by diagnostic NOEs. Further, **4** and **7a** have been confirmed by X ray crystallographic analyses.

7) Due to C-aromatic ring, 18-methyl of endo and 16-methyl of exo isomer appear at higher fields: K. J. Shea and J. W. Gilman, Tetrahedron Lett., **25**, 2451 (1984). The key ^{1}H NMR signals of **5** (270 MHz, $CDCl_3$): 0.10 (s, 3H, 16-Me), 2.04 (s, 3H, 18-Me), 3.99 (d, J = 9.3 Hz, 1H, C(10)-H), 5.23 (d, J = 9.3 Hz, 1H, C(9)-H), and 5.74 (d, J = 5.4 Hz, 1H, C(2)-H).

8) The 2-substituent has a critical influence on endo/exo control. The result and thermal exo/endo isomerization will be described in a separate note.

9) This compound was prepared by thermal isomerization of the exo-2α,9β,10α isomer.

10) The key ^{1}H NMR signals of **8a** (270 MHz, $CDCl_3$): 0.96 (s, 3H, 18-Me), 1.71 (s, 3H, 16-Me), 4.42 (d, J = 9.0 Hz, 1H, C(10)-H), 4.92 (d, J = 9.0 Hz, 1H, C(9)-H).

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