Stereoselective Construction of BC-ring unit of 19-Hydroxytaxol by Samarium(II) Iodide-mediated Double Aldol Cyclization

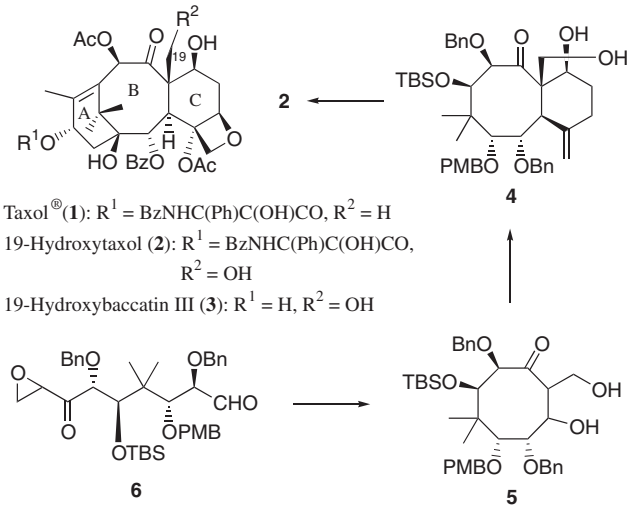
Jun-ichi Matsuo,[†,††] Yasuyuki Ogawa,[†,††] Khanitha Pudhom,[†,††] and Teruaki Mukaiyama*[†,††]
[†]*Center for Basic Research, The Kitasato Institute, 6-15-5 (TCI) Toshima, Kita-ku, Tokyo 114-0003*
[††]*Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641*

(Received October 28, 2003; CL-031029)

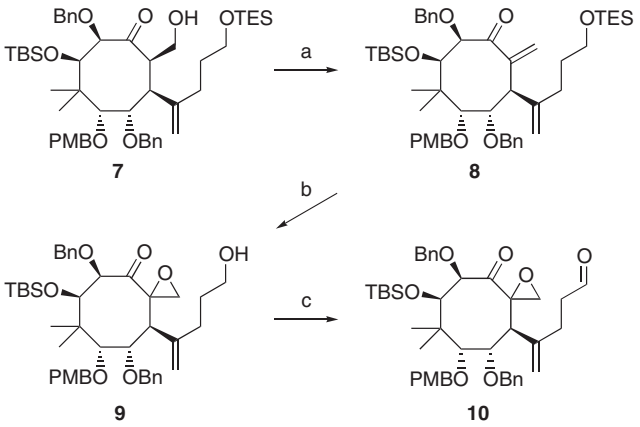
The C-ring of 19-hydroxytaxol is stereoselectively constructed by samarium(II) iodide-mediated intramolecular double aldol cyclization of epoxyketo aldehyde to form the BC-ring unit which has the desired stereochemistry.

To develop a new antitumor agent by synthesizing analogues of a potent anticancer drug, taxol® (**1**), 19-hydroxytaxol (**2**) was chosen as a target molecule on the expectation that its increased solubility in water will improve pharmacokinetics of **1** by introducing a hydroxy group to the 19-position of **1** and further by introducing a hydrophilic molecule to the above 19-hydroxy group (Scheme 1). As 19-hydroxybaccatin III (**3**) is isolated in very small quantities from natural resources, synthesis of **2** and its derivatives in quantities for biological testing is difficult from isolated **3**. It was considered then that our strategy for the total synthesis of **1** from D-pantolactone may be quite practical in synthesizing **2**: that is, to construct B-ring first and then to attach C-ring and A-ring to thus constructed B-ring unit.[1]

In the preceding papers, new and efficient construction of eight-membered B-ring **5** by samarium(II) iodide-mediated intramolecular cyclization of a linear epoxyketo aldehyde **6**,[2] and the subsequent introduction of a side chain for the construction of C-ring by trimethylaluminum-assisted 1,4-addition of higher order cyanocuprate[3] were reported. In the above strategy for the total synthesis of **2**, construction of C-ring will be a key step since a double aldol unit should be prepared stereoselectively at this stage. The synthetic plan is to construct the C-ring by samarium(II) iodide-mediated double aldol cyclization of



Scheme 1.



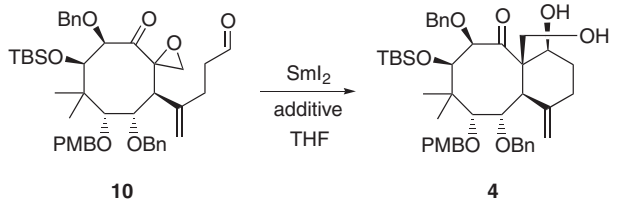
Scheme 2. Reagent and conditions: a) Ac_2O, DMAP, pyridine (89%); DBU, CH_2Cl_2 (75%); b) 0.5N HCl, THF, −20 °C (88%); H_2O_2, NaOH, MeOH, 0 °C (79%); c) PhSNH^{t}Bu, NCS, K_2CO_3, MS4A, CH_2Cl_2 (95%).

epoxyketoaldehyde (**10**) similar to B-ring construction. In this communication, we would like to describe the stereoselective C-ring construction of **2**.

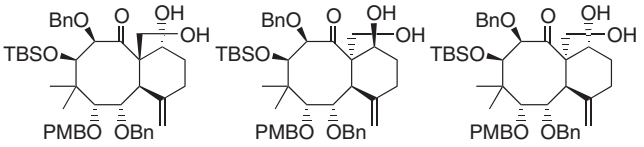
Preparation of the key intermediate, epoxyketo aldehyde **10**, is shown in Scheme 2: namely, hydroxymethyl ketone **7**, prepared by the above-mentioned 1,4-addition of higher order cyanocuprate, was acetylated first, and α,β-unsaturated ketone **8** was obtained by regioselective elimination of the formed α-acetoxymethyl ketone with DBU. After deprotection of triethylsilyl group, epoxidation of enone using H_2O_2 and NaOH gave α-epoxy ketone **9** as a 1:1 mixture of diastereomers. Swern oxidation and tetrapropylammonium perruthenium (TPAP)-catalyzed oxidation of the primary hydroxy group of a diastereomixture of **9** did not give the desired aldehyde **10** whereas sulfenamide-catalyzed oxidation with *N*-chlorosuccinimide[4] oxidized **9** successfully, and **10** was obtained in 95% yield.

Then, samarium(II) iodide-mediated cyclization of **10** was tried (Table 1). First, the reaction was carried out at various temperatures between −100 and −23 °C in the absence of additives (Entries 1–4). The desired isomer **4** was obtained in 71% yield along with diastereomers **12** (10%) and **13** (15%)[5,6] at −100 °C. On the other hand, the yields of both diastereomers **4** and **12** decreased as the reaction temperature rose. In these experiments, a 1:1 diastereomixture of **10** was employed since the results were the same even when a mixture or the single isomer was used. Therefore, it is assumed that the desired facial selectivity of the formed samarium enolate and an aldehyde moiety would be controlled by lowering the reaction temperature. Next, effects of additives were examined.[2b,2c] Contrary to our expecta-

Table 1. SmI_2-mediated intramolecular cyclization of **10**



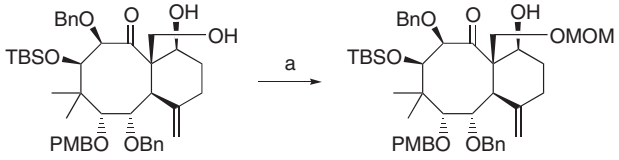
10 **4**



11 **12** **13**

Entry	SmI_2 /equiv.	Additive /equiv.	Temp. /°C	Yield/% 4	11	12	13
1	3.0	-	−100	71	ND[a]	10	15
2	3.0	-	−78	59	ND	9	16
3	3.0	-	−45	42	ND	3	20
4	5.0	-	−23	24	ND	2	16
5	4.0	H_2O (3.0)	−78	45	ND	44	6
6	4.0	MeOH (3.0)	−78	27	ND	38	7
7	3.0	^{i}PrOH (3.0)	−78	41	ND	35	9
8	3.0	HMPA (3.0)	−78	45	ND	24	17

[a] The product was not detected.



4 **14**

Scheme 3. Reagent and conditions; a) MOMCl, ^{n}Bu$_4$NI, ^{i}Pr$_2$NEt, CH_2Cl_2 (76%).

tions, the addition of additives such as H_2O, MeOH, *i*-PrOH, and HMPA showed no improvement in the yield of the desired product **4** while the yield of a diastereomer **12** increased. Formation of diastereomer **11** was not observed through the above mentioned trials.

The stereochemistry of compound **4** was unambiguously identified by X-ray crystal structure analysis of a MOM ether **14** which was obtained by the protection of 19-hydroxy group of **4** with MOM group (Scheme 3, Figure 1).[7]

Currently, the total synthesis of **2** is in progress by utilizing the BC-ring compound **4**, prepared as above.

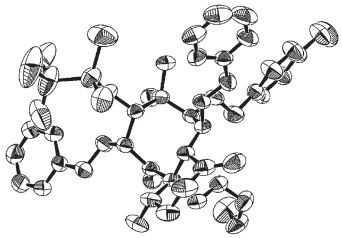


Figure 1. ORTEP drawing of compound **14**.

The present work was partially supported by Grant-in-Aids for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. The authors wish to thank Dr. Youji Furukawa (Sankyo) for his support in X-ray crystal structure analysis.

References and Notes

1 a) T. Mukaiyama, I. Shiina, H. Iwadare, H. Sakoh, Y. Tani, M. Hasegawa, and K. Saitoh, *Proc. Jpn. Acad.*, **73B**, 95 (1997). b) T. Mukaiyama, I. Shiina, H. Iwadare, M. Saitoh, T. Nishimura, N. Ohkawa, H. Sakoh, K. Nishimura, Y. Tani, M. Hasegawa, K. Yamada, and K. Saitoh, *Chem.—Eur. J.*, **5**, 121 (1999).

2 a) T. Mukaiyama, H. Arai, and I. Shiina, *Chem. Lett.*, **2000**, 580. b) T. Mukaiyama, K. Pudhom, K. Yamane, and H. Arai, *Bull. Chem. Soc. Jpn.*, **76**, 413 (2003). c) K. Pudhom, H. Arai, K. Yamane, and T. Mukaiyama, *Chem. Lett.*, **2002**, 82.

3 K. Pudhom, J. Matsuo, and T. Mukaiyama, *Heterocycles*, **59**, 445 (2003).

4 a) J. Matsuo, D. Iida, H. Yamanaka, and T. Mukaiyama, *Tetrahedron*, **59**, 6739 (2003). b) T. Mukaiyama, J. Matsuo, D. Iida, and H. Kitagawa, *Chem. Lett.*, **2001**, 846.

5 In order to make the structures of **12** and **13** clear, the PMB groups of these bicyclic compounds were deprotected with DDQ to lead to bridged tricyclic compounds, and their structures were determined by NOE.

6 After protection of 19-hydroxy group of **12** and **13** with TBS group, isomerization experiment by using NaOMe in MeOH–THF did not give an isomerized product which have the desired stereochemistry suited for synthesize **2**.

7 Crystal data: $C_{46}H_{64}O_9Si$ (FW = 789.09), monoclinic, $P2_1$, $a = 16.051(3)$, $b = 12.914(4)$, $c = 10.915(3)$ Å, $\beta = 93.73(2)^\circ$, $V = 2257$ (1) Å^3, $Z = 2$, $Dx = 1.161$ g cm^{-3}, $T = 298$ K. X-ray intensities were measured on Rigaku AFC7R diffractometer with Cu Kα radiation ($\lambda = 1.54178$ Å), and $R = 0.052$ for 4209 observed reflections.

Published on the web (Advance View) January 8, 2004; DOI 10.1246/cl.2004.124