Stereoselective Synthesis of 19-Hydroxytaxoid Using Intramolecular Pinacol Coupling Reaction

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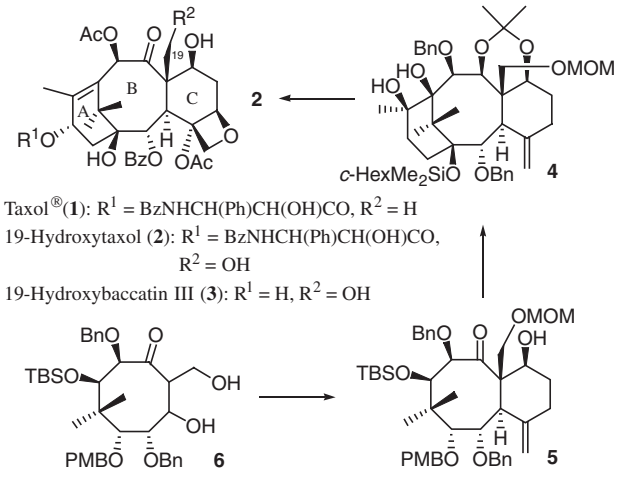
The ABC-ring system of 19-hydroxytaxol is stereoselectively constructed by intramolecular pinacol coupling of diketone **12** with low valent titanium species prepared from $TiCl_2$ and $LiAlH_4$. After manipulations of hydroxy protecting groups, a new 19-hydroxytaxoid **18** was afforded by olefination of vicinal diol part of **17**.

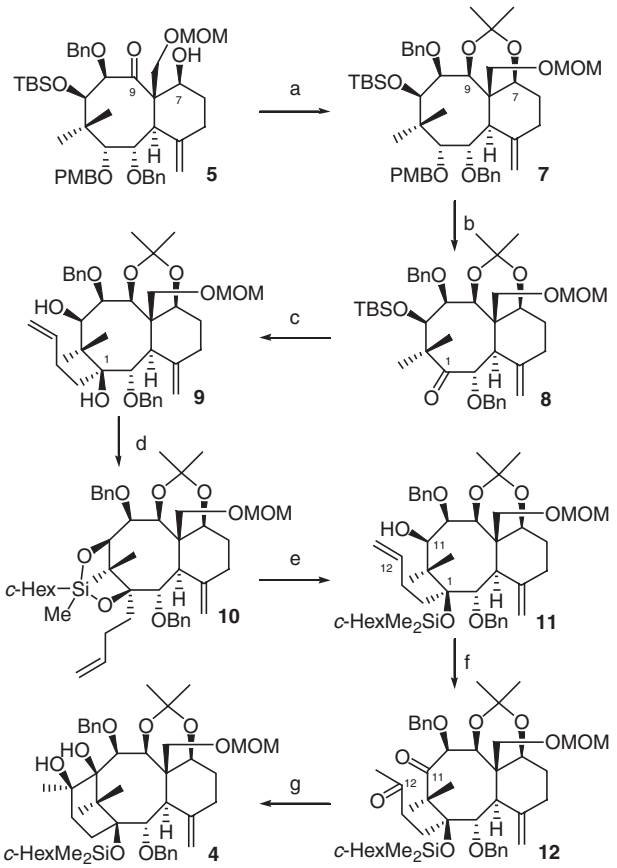
In the course of our synthetic research on preparing a new anticancer agent by chemical modification of a potent anticancer drug, taxol® (**1**), 19-hydroxytaxol (**2**) was chosen so as to improve its pharmacological profile, especially its water-solubility, by putting hydrophilic molecules on its newly-introduced C-19 hydroxy group of **2** (Scheme 1). Although 19-hydroxybaccatin III (**3**) can be isolated from natural resources,[1] quantities of **3** are not sufficient for synthesizing its derivatives **2**. It was then considered to synthesize **2** from D-pantolactone, adapting our strategy for the total synthesis of **1**: that is, to construct B-ring first, and to attach C-ring and A-ring successively to the B-ring.[2]



Scheme 1.

In our preceding papers, a new and efficient method for the construction of BC-ring unit **5** by samarium(II) iodide-mediated intramolecular cyclization of the epoxyketo aldehyde derived from 8-memberd ring **6**, was reported.[3,4] In this communication, we would like to describe the stereoselective construction of ABC-ring system of 19-hydroxytaxol by successive reactions of intramolecular pinacol coupling to form A-ring and of olefination of its diol unit.

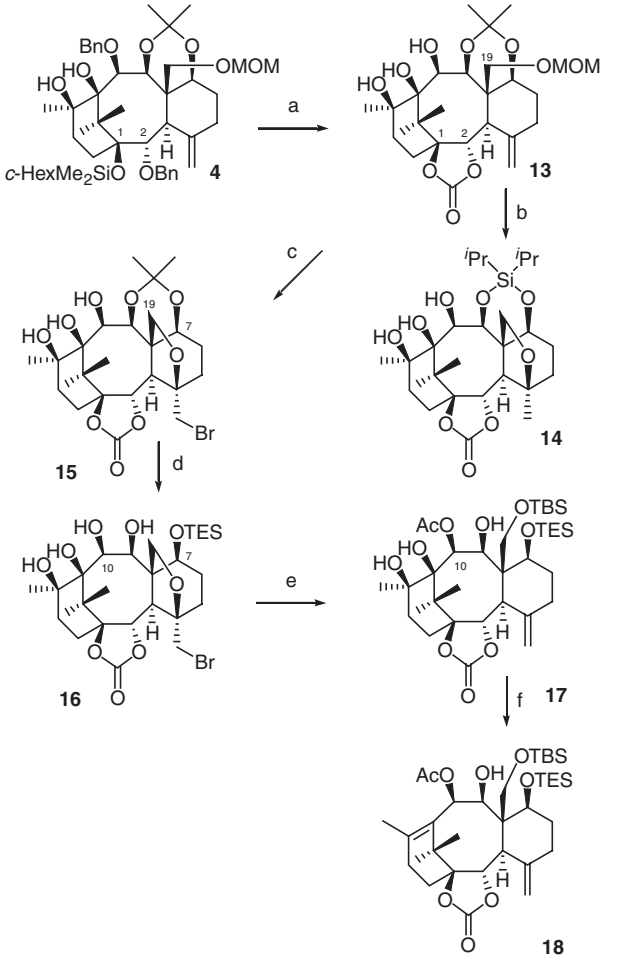
The conversion of **5**, which was prepared by the previously described samarium(II) iodide-mediated double aldol reaction, to the key intermediate diol **4** is shown in Scheme 2. First, MOM-protected double aldol **5** was diastereoselectively reduced with AlH_3 to afford the corresponding C-7,C-9-*cis*-diol preferentially,[5] and protection of thus formed *cis*-diol with isopropylidene acetal provided tricyclic compound **7**. Then it was converted to 8-membered ring ketone **8** by oxidative deprotection of PMB group and by successive oxidation of C-1 hydroxy group with Dess–Martin periodinane. Alkylation of **8** at C-1 position with homoallyllithium[2] in benzene produced the desired β-alcohol in high yield with perfect diastereoselectivity. Deprotection of TBS group resulted in the formation of *cis*-diol **9** and successive treatment of **9** with dichlorocyclohexylmethylsilane yielded silylene **10** in high yield. Alkylaton of **10** with methyllithium



Scheme 2. Reagents and conditions a) AlH_3, THF −23 °C (81%); 2,2-dimetoxypropane, CSA, CH_2Cl_2 rt (92%). b) DDQ, phosphate buffer, CH_2Cl_2 0 °C (quant.); Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2 rt (95%). c) homoallyl lithium, benzene −23 °C to 0 °C (97%); TBAF, THF 50 °C (80%). d) cyclohexylmethyldichlorosilane, imidazole, DMF rt (99%). e) MeLi, THF-HMPA −78 °C (99%). f) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2 0 °C (97%); $PdCl_2$, DMF–H_2O rt (83%). g) $TiCl_2$, $LiAlH_4$, THF (64%) 40 °C.

furnished **11**, which had the desired C-1 siloxy group. Oxidation of thus formed secondary hydroxy group at C-11 with Dess–Martin periodinane gave the corresponding ketone in good yield. The terminal olefin of **11** was then oxidized by using $PdCl_2$ in DMF-H_2O to afford the desired diketone **12** in good yield. By the above sequence of manipulations, compound **12**, a precursor for the construction of ABC-ring system, was efficiently synthesized from BC-ring units. Intramolecular pinacol coupling of diketone **12** using low-valent titanium reagent,[6] prepared form $TiCl_2$ and $LiAlH_4$, gave ABC-ring system of **4** as a main product. Under the pinacol coupling conditions, MOM group of C-19 hydroxy group was not cleaved. On the other hand, the same pinacol coupling reaction using samarium(II) iodide did not give the coupling product.

The conversion of **4** to 19-hydroxytaxoid **18** is shown in Scheme 3. After deprotecting benzyl groups of **4** with Na/NH_3 and of cyclohexyldimethylsilyl group with TBAF, regioselective protection of thus formed pentanol with bis(trichloromethyl)carbonate afforded C-1, C-2 carbonate **13** in high yield.



Scheme 3. Reagents and conditions a) Na, liq. NH_3, THF −78 °C to −45 °C; TBAF, THF rt (94%); triphosgene, pyridine, CH_2Cl_2 −45 °C (95%). b) 6 N HCl, THF 60 °C; *i*-$Pr_2Si(OTf)_2$, pyridine, CH_2Cl_2 −45 °C (37%). c) 6 N HCl, THF rt (quant); NBS, CH_2Cl_2 rt (quant). d) 3 N HCl, THF 60 °C; TESOTf, pyridine −23 °C (91%). e) Zn–Ag, AcOH, EtOH 90 °C (81%); TBSOTf, pyridine −23 °C (83%); Ac_2O, DMAP, pyridine rt (77%). f) Thiophosgene, DMAP, $CHCl_3$ 60 °C; $P(OMe)_3$ 110 °C (43% based on 35% conversion).

Deprotection of both MOM group and isopropylidene acetal under acidic conditions was tried at this point. Acid hydrolysis with 6 N HCl followed by protection with *i*-$Pr_2Si(OTf)_2$ unexpectedly gave cyclic ether **14** in moderate yield. Through careful observation, it was revealed that the deprotection of MOM group and the intramolecular ether formation took place spontaneously while isopropylidene acetal was not completely deprotected. Since it was difficult to suppress the formation of cyclic ether, C-19 hydroxy group, which was formed by selective deprotection of MOM group, was protected by the intramolecular bromo ether formation procedure using *N*-bromosuccinimide (NBS).[7] Isopropylidene acetal of cyclic bromo ether **15** was easily deprotected with HCl, and regioselective protection of hydroxy group at C-7 with TESOTf afforded tetraol **16**. Deprotection of cyclic bromo ether **16** with zinc–silver couple in EtOH,[8] protection of the formed primary hydroxy group with TBSOTf, and the following selective acetylation of hydroxy group at C-10 gave acetate **17**. A novel 19-hydroxytaxoid **18** was synthesized from acetate **17** by two-step procedures. Namely, conversion of the vicinal diol moiety to the corresponding thiocarbonate using thiophosgene, and 19-hydroxytaxoid **18** was afforded by heating the thiocarbonate with trimethylphosphite.[9]

Thus, asymmetric synthesis of the ABC-ring system of 19-hydroxytaxol was completed via two key reactions; namely, intramolecular pinacol coupling and olefination of diol. This is the first report on the synthesis of 19-hydroxytaxoid,[10] and this taxoid is expected to be employed as not only a precursor of 19-hydroxytaxol but also as a starting material for new chemotherapeutic agents.

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References and Notes

1 J. L. McLaughlin, R. W. Miller, R. G. Powell, and C. R. Smith, Jr., *J. Nat. Prod.*, **44**, 312 (1981).
2 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).
3 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).
4 a) K. Pudhom, H. Arai, K. Yamane, and T. Mukaiyama, *Chem. Lett.*, **2002**, 82. b) K. Pudhom, J. Matsuo, and T. Mukaiyama, *Heterocycles*, **59**, 445 (2003). c) J. Matsuo, Y. Ogawa, K. Pudhom, and T. Mukaiyama, *Chem. Lett.*, **33**, 124 (2004).
5 The numbers on each carbon atom of all intermediates are according to IUPAC taxane skeleton nomenclature.
6 $TiCl_2$ was prepared from $TiCl_4$ and $Me_3SiSiMe_3$ by a literature method: a) R. C. Paul, A. Arneja, and S. P. Narula, *Inorg. Nucl. Chem. Lett.*, **5**, 1013 (1969). b) S. P. Narula and H. K. Sharma, *Inorg. Synth.*, **24**, 181 (1986). c) T. Mukaiyama, A. Kagayama, and I. Shiina, *Chem. Lett.*, **1998**, 1107.
7 J. Ishihara, R. Nonaka, Y. Terasawa, R. Shiraki, K. Yabu, H. Kataoka, Y. Ochiai, and K. Tadano, *J. Org. Chem.*, **63**, 2679 (1998).
8 a) J. M. Denis, C. Girard, and J. M. Conia, *Synthesis*, **1972**, 549. b) T. Tokoroyama, K. Matsuo, and R. Kanazawa, *Bull. Chem. Soc. Jpn.*, **53**, 3383 (1980).
9 a) E. Block, *Org. React.*, **30**, 457 (1984). b) E. J. Corey, F. A. Carey, and R. A. E. Winter, *J. Am. Chem. Soc.*, **87**, 934 (1965). c) E. J. Corey and P. B. Hopkins, *Tetrahedron Lett.*, **23**, 1979 (1982).
10 Kuwajima *et al.* already reported this taxoid as an intermediate for synthesis of taxol; H. Kusama, R. Hara, S. Kawahara, T. Nishimori, H. Kashima, N. Nakamura, K. Morihira, and I. Kuwajima, *J. Am. Chem. Soc.*, **122**, 3811 (2000).

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