ORGANIC LETTERS

2006
Vol. 8, No. 14
2973−2976

Synthetic Studies on Taxol: Highly Stereoselective Construction of the Taxol C-Ring via S_N2' Reduction of an Allylic Phosphonium Salt

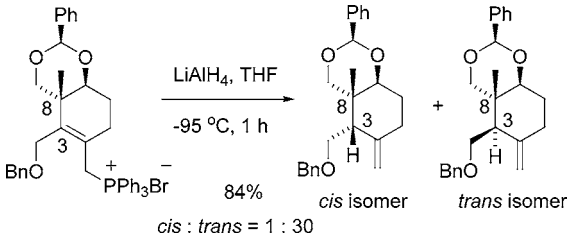
Masayuki Utsugi, Masayuki Miyano, and Masahisa Nakada*

Department of Chemistry, Faculty of Science and Engineering, Waseda University 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

mnakada@waseda.jp

Received April 10, 2006

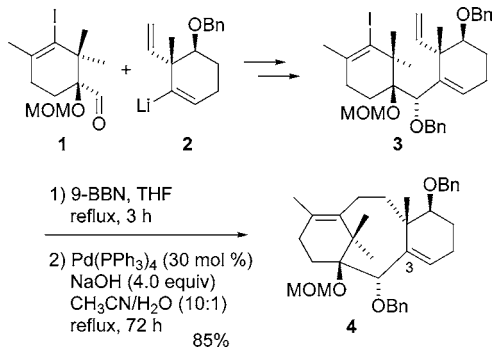
ABSTRACT



The highly stereoselective construction of the C3 stereogenic center of the taxol C-ring is described. The trans isomer at the C3–C8 position of the taxol C-ring, which is required for the total synthesis, as well as its diastereomeric cis isomer were successfully synthesized with highly diastereoselective S_N2' reduction of the allylic phosphonium salts.

Recently, we reported asymmetric synthesis of a taxol model **4** via the *B*-alkyl Suzuki−Miyaura intramolecular coupling of **3**,[1a] which was prepared by coupling of the enantiopure fragments, A-ring **1**, and C-ring **2** (Scheme 1).[1b,c] Although

Scheme 1



compound **4** possesses a taxane skeleton, an alkene is involved at its C3−C4 position, requiring stereoselective introduction of a hydrogen to the C3 position from its α-face to complete the total synthesis of taxol. However, construction of the C3 tertiary stereogenic center with C3α−H was surmised to be difficult because **4** has a cagelike structure, thereby impeding stereoselective introduction of a hydrogen from its α-face, which is the concave side of this molecule.[2] Furthermore, even at the stage before an attempted formation of the B-ring, the stereoselective construction of the C3 stereogenic center starting from the compound with the C3−C4 alkene is limited.[3]

We studied stereoselective construction of the C3 stereogenic center[4] of the taxol C-ring and report herein highly

(1) (a) Kawada, H.; Iwamoto, M.; Utsugi, M.; Miyano, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 4491−4494. (b) Iwamoto, M.; Kawada, H.; Tanaka, T.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 7239−7243. (c) Watanabe, H.; Iwamoto, M.; Nakada, M. *J. Org. Chem.* **2005**, *70*, 4652−4658.

(2) Stereoselective introduction of C3α−H via the elegant intramolecular protonation. See: Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186−9187.

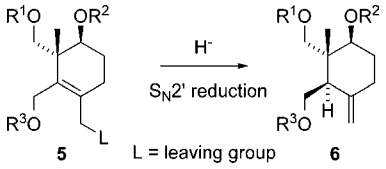
(3) (a) Nakai, K.; Miyamoto, S.; Sasuga, D.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2001**, *42*, 7859−7862. (b) Magnus, P.; Westwood, N. *Tetrahedron Lett.* **1999**, *40*, 4659−4662.

10.1021/ol0608606 CCC: $33.50
Published on Web 06/07/2006

stereoselective construction of the trans isomer at the C3−C8 position of taxol, which is required for the total synthesis, as well as its cis isomer by the diastereoselective S_N2' reduction of the allylic phosphonium salts.

Reduction of the compounds possessing a leaving group at their allylic positions usually affords a S_N2 product and/or a S_N2' product.[5] S_N2' reduction of **5** would produce **6** (Scheme 2), and the trans isomer could be the major

Scheme 2

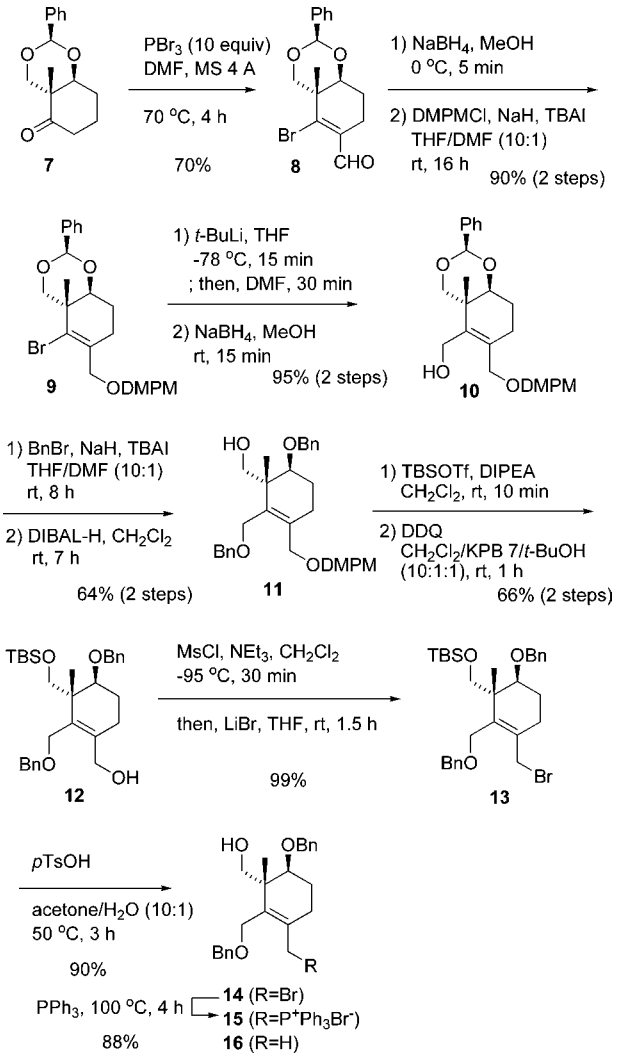


diastereomer by use of a certain substrate and/or under the suitable reaction conditions. Nevertheless, the diastereotropic prochiral C3 position was surmised to be difficult to discriminate if only the steric factors which arose from the substituents at the adjacent C8 quaternary stereogenic center were used to control the stereoselectivity.

Consequently, first, we studied the S_N2' reduction of **5** (R^1 = H) because it would react with the reducing reagent to afford the corresponding alkoxide, which could work as a tethered reducing reagent, delivering a hydride to the desired diastereofacial side at the C3 position to produce **6** (R^1 = H) stereoselectively via the S_N2' pathway. To the best of our knowledge, no precedents exist for this hydroxyl group directed S_N2' reduction.[6]

Preparation of **14**, which corresponds to **5** (R^1 = H, L = Br), commenced with the previously reported enantiopure ketol **7**[1a] (Scheme 3); Vilsmeier reaction[7] of **7** was expected to afford the bromide **8** possessing a one-carbon unit at its C4 position.[4] Preliminary studies on the Vilsmeier reaction of **7** with $POBr_3$/DMF[7c] and PBr_3/DMF[7d] afforded **8** in 57% (at 52% conversion) and 50% yields, respectively. Because benzylidene acetal **7** was sensitive to the acidic conditions, optimization of the reaction conditions was focused on the additive which improved the yield. To this end, we found that 4 Å molecular sieves improved the yield of **8** up to 70%.

Scheme 3



Aldehyde **8** was then converted to the bromide **14** (Scheme 3). Reduction of **8** with $NaBH_4$ produced the corresponding alcohol, which was converted to DMPM (3,4-dimethoxyphenylmethyl)[8] ether **9** in 90% yield (two steps). Reaction of **9** with *t*-BuLi and then with DMF afforded the aldehyde, which was reduced with $NaBH_4$ to afford alcohol **10** in 95% yield (two steps). Benzylation of **10** followed by DIBAL-H reduction produced **11** (64%, two steps). Alcohol **11** was protected as the TBS ether, which was then treated with DDQ to give alcohol **12** in 66% yield (two steps). Direct conversion of **12** to the bromide **13** was fruitless,[9] but this conversion was successfully achieved via the mesylate to produce **13** in 99% yield. The bromide **13** was exposed to acidic conditions to remove the TBS group affording **14** in 90% yield.

Initially, various reagents were surveyed to reduce **14**, but only S_N2 reduction product **16** was obtained. These results suggested that the leaving group should be examined.

(4) Numbering for taxol was applied to the C-ring fragments.

(5) Entwistle, I. D.; Wood, W. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, pp 955−981 and references therein.

(6) For the hydroxyl group directed stereoselective 1,4-reduction of α,β-unsaturated carbonyl compounds, see: (a) Kuethe, J. T.; Wong, A.; Wu, J.; Davies, I. W.; Dormer, P. G.; Welch, C. J.; Hillier, M. C.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5993−6000. (b) Solomon, M.; Jamison, W. C.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702−3704. (c) Salomon, R. G.; Sachinvala, N. D.; Raychaudhuri, S. R.; Miller, D. B. *J. Am. Chem. Soc.* **1984**, *106*, 2211−2213.

(7) For reviews, see: (a) Jones, G.; Stanforth, S. P. *Org. React.* **2000**, *56*, 355−659. (b) Marson, C. M. *Tetrahedron* **1992**, *48*, 3659−3726. For use of $POBr_3$, see: (c) Paquette, L. A.; Johnson, B. A.; Hinga, F. M. *Org. Synth. Collect. Vol.* **1973**, *5*, 215−217. For use of PBr_3, see: (d) Rajamannar, T.; Balasubramanian, K. K. *Tetrahedron Lett.* **1988**, *29*, 5789−5792. (e) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999−10003.

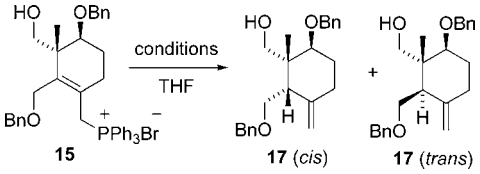
(8) (a) Howell, S. J.; Spencer, N.; Philp, D. *Tetrahedron* **2001**, *57*, 4945−4954. (b) Oikawa, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1985**, *26*, 1541−1544.

(9) Use of CBr_4/PPh_3 gave unidentified products.

Nojima et al. reported that S_N2' reduction proceeded exclusively in the reaction of allylic phosphonium salts.[10] Consequently, we expected that the S_N2' reduction of allylic phosphonium salt **15** could proceed predominantly, so we prepared **15** and examined its S_N2' reduction. Phosphonium salt **15** was easily prepared by **14** and PPh_3 (Scheme 3).

Reduction of **15** with $LiAlH_4$ (1.5 equiv) in THF at 0 °C proceeded in 88% yield (entry 1, Table 1), producing only

Table 1. Diastereoselective Reduction of **15**



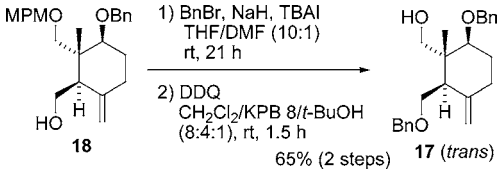
entry	reagent (equiv)	T (°C)	time (h)	yield (%)[a]	cis/trans[b]
1	$LiAlH_4$ (1.5)	0	0.5	88	17:1
2	$LiAlH_4$ (1.5)	−78	1	87	1:0
3	Red-Al (1.2)	−78	1.5	31	1:0

[a] Isolated yields. [b] Ratio determined by 400 MHz ^{1}H NMR.

the S_N2' products with high diastereoselectivity (17:1). Formation of **17** (trans) was not detected if the reduction was performed at −78 °C (entry 2), and the reduction by use of Red-Al at −78 °C also produced only **17** (cis); however, the yield was lower than that of entry 2 (entry 3).

We determined the stereochemistry of the major product in the reduction of **15** as shown in Scheme 4 because we

Scheme 4



had previously reported the highly stereoselective synthesis of **18**.[11] Thus, **18** was successfully converted to **17** (trans) via benzylation, followed by removal of the MPM group, and comparison of their ^{1}H NMR spectra clearly showed that the major product derived from **15** was **17** (cis). This result suggested that the hydroxyl group directed S_N2' reduction of **15** did not occur but rather that the reduction proceeded via the intermolecular process.

The stereoselective reduction of **15** is well explained by the models depicted in Figure 1. Considering that the axial attack is favored in the six-membered ring system,[12] the

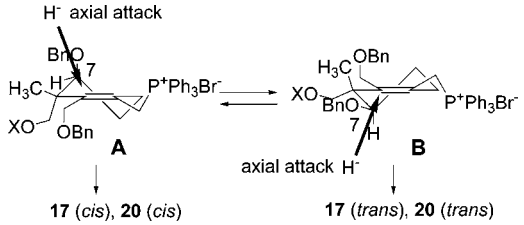


Figure 1. Proposed models **A** and **B**.

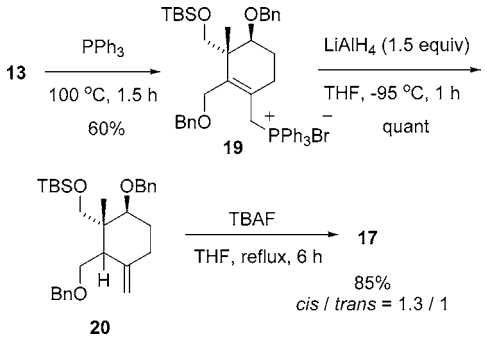
stereoselective reduction of **15** would produce the major product **17** (cis) via model **A**. The benzyloxy group is located at the pseudoaxial position in model **A**, but it is located at the pseudoequatorial position in model **B**, suggesting that model **B** could be energetically more favored. Therefore, it was interesting that **17** (cis), which would form via the less favored model **A**, was formed exclusively. Coordination of the oxygen atom at the C7 position of **15** to the reducing reagent might explain this diastereoselectivity.

The models in Figure 1 also explain the reason for the lack of the desired intramolecular reduction.[13] The hydroxyl group held pseudoaxial in model **A** was unfavorable for the intramolecular axial attack because of the stereoelectronic reason, and the intramolecular reduction was also unfavored in model **B** because the hydroxyl group was held equatorial.

Models **A** and **B** in Figure 1 suggested that protection of the allylic hydroxyl group as a bulky TBS ether would increase the ratio of **17** (trans) because the TBS protected hydroxyl group would take the pseudoequatorial position, rendering model **B** more stable.

Reduction of phosphonium salt **19**, which was easily prepared from **13** (Scheme 5), produced **20** (dr = 1.3:1).

Scheme 5



Conversion of **20** to the known **17** unambiguously determined the stereochemistry of the products from **20**. Although the cis product was still the major product in this reaction,

(10) Hirabe, T.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* **1984**, *49*, 4084−4086.

(11) Nakada, M.; Kojima, E.; Iwata, Y. *Tetrahedron Lett.* **1998**, *39*, 313−316.

(12) For a recent example of the axial addition of cyanide to a cyclohexyl aldehyde derivative, see: Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687−2690.

(13) The hydroxyl group in **15** reacted with the reducing reagent because evolution of hydrogen gas was observed.

this result indicated that the trans selectivity was improved as compared with the results in Table 1.

Studies on the reduction of **15** and **19** strongly suggested that conformation of the substrate was crucial for the stereoselective S_N2' reduction. Therefore, we next examined the S_N2' reduction of **23**, in which the axial attack of a hydride from the bottom face was expected to be dominant because of the rigid conformation of the benzylidene acetal, resulting in the preferential formation of **24** (trans) (Figure 2).

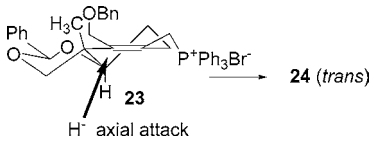
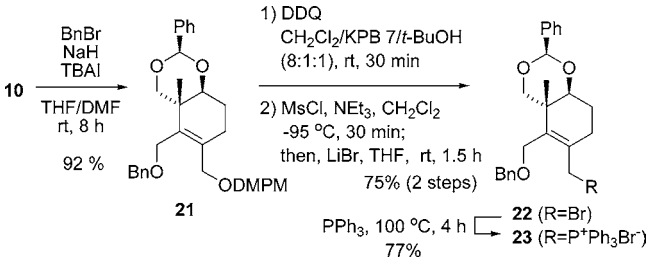


Figure 2. Model for the diastereoselective reduction of **23**.

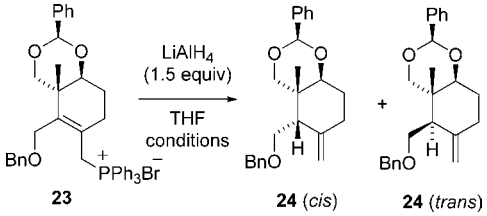
Alcohol **10** was easily converted to benzyl ether **21**, which was treated with DDQ to afford the corresponding alcohol, followed by transformation to the bromide **22** via the mesylate, and finally, treatment of **22** with PPh_3 produced the desired phosphonium salt **23** (Scheme 6).

Scheme 6



Reduction of **23** with $LiAlH_4$ proceeded at ambient temperature to afford products **24** quantitatively with the diastereomer ratio of 1:15 (entry 1, Table 2). The ratio changed according to the reaction temperature; thus, the ratio was 1:20 at 0 °C (entry 2), 1:27 at −78 °C (entry 3), and 1:30 at −95 °C (entry 4). DIBAL-H reduced the major product of **24** to the known **17** (trans) in 73% yield; hence, exclusive formation of **24** (trans) in the reduction of the allylic phosphonium salt **23** occurred as we expected.

Table 2. Diastereoselective Reduction of **23**



entry	T (°C)	time	yield (%)[a]	cis/trans[b]
1	rt	20 min	quantitative	1:15
2	0	1 h	quantitative	1:20
3	−78	1 h	quantitative	1:27
4	−95	1 h	84	1:30

[a] Isolated yields. [b] Ratio determined by 400 MHz ^{1}H NMR.

In conclusion, the highly stereoselective construction of the C3 stereogenic center of the taxol C-ring was achieved. The trans isomer at the C3−C8 position of the taxol C-ring, which is required for the total synthesis of taxol, as well as its cis isomer were successfully synthesized by the diastereoselective S_N2' reduction of the allylic phosphonium salts. To the best of our knowledge, this is the first diastereoselective S_N2' reduction of an allylic phosphonium salt, which constructs a stereogenic tertiary carbon center with high selectivity. This protocol would be applicable for other cyclic systems as well as for acyclic systems to generate a new stereogenic center. Consequently, further studies on this protocol are now underway in our laboratory.

Acknowledgment. We thank Dr. Mitsuhiro Iwamoto for helpful discussions. This work was financially supported in part by a Waseda University Grant for Special Research Projects and a Grant-in-Aid for Scientific Research on Priority Areas (Creation of Biologically Functional Molecules (No. 17035082)) from The Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. We are also indebted to 21COE "Practical Nano-Chemistry".

Supporting Information Available: Spectral data for all new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0608606