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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6868–6872

Construction of the taxane skeleton via the stereoselective conjugate addition of cyanide and the intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction

Masayuki Utsugi, Yasuaki Kamada, Hidetoshi Miyamoto and Masahisa Nakada*

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

Received 9 July 2007; revised 25 July 2007; accepted 26 July 2007
Available online 31 July 2007

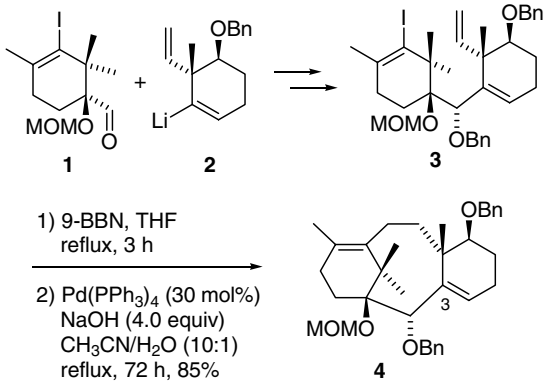
Abstract—Construction of the taxane skeleton via the stereoselective conjugate addition of cyanide and the intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction is described. A conjugate addition of cyanide to enone **17** proceeded diastereoselectively to provide the desired **18** incorporating the correct C3 stereogenic center in the taxol C-ring. The intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction of **22**, which was derived from **18**, successfully furnished the taxol B-ring in 81% yield.

Since its discovery, taxol (Fig. 1) has been a fascinating and synthetically challenging target because of its complex structure and clinically important anticancer activity.[1–7] We have reported asymmetric synthesis of a taxol model **4** (Scheme 1) via the intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction of **3**,[8] which was prepared from the enantiopure fragments, **1** and **2**. Although compound **4** incorporates a taxane skeleton, stereoselective introduction of a hydrogen to the C3 position from its concave α-side is necessary to complete the total synthesis of taxol. However, construction of the C3 tertiary stereogenic center with C3α-H in **4** was surmised to be difficult because of the cage-like structure of **4**.

We report herein a method for constructing the C3 stereogenic center of the taxol C-ring via the stereoselective conjugate addition of cyanide to enone **17**, which was composed of the A- and C-rings of taxol.[9]

We expected that a conjugate addition of cyanide to enone **5** (Scheme 2) would provide stereoselectively the desired product **6** because the transition state derived from model **B** (Fig. 2) would be energetically unfavored due to the three axial substituents (–CN, –OBn, and –CH=CH_2) existing in the transition state. The methyl group in **5** would be axial in the transition state from model **A**, providing enolate **C**. Then, the axial protonation of enolate **C** would occur because the large RCO– group could hardly be axial, affording the desired product **6** as the major diastereomer. Another possible axial attack of cyanide (model **B**, Fig. 2) would lead to the more energetically unfavored transition state as mentioned above, resulting in the formation of enolate **D**, which would afford the undesired product.

Consequently, we undertook to examine the conjugate addition of cyanide to enone **17** possessing the A-ring moiety of taxol.



Scheme 1. Preparation of **4** via the intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction.[8]

* Corresponding author. Tel./fax: +813 5286 3240; e-mail: mnakada@waseda.jp

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doi:10.1016/j.tetlet.2007.07.179

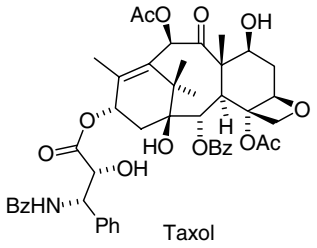
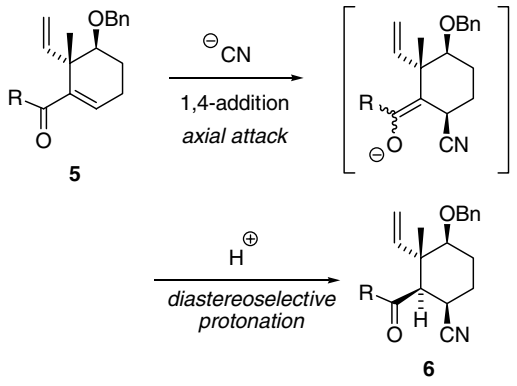


Figure 1. Structure of taxol.



Scheme 2. Construction of the C3 stereogenic center via the stereoselective axial conjugate addition of cyanide to **5**.

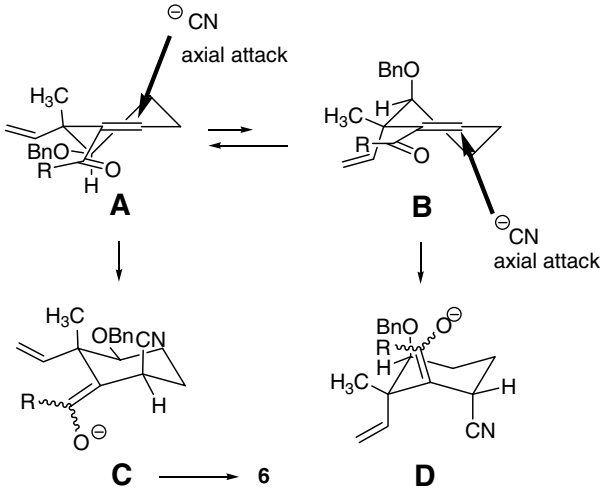
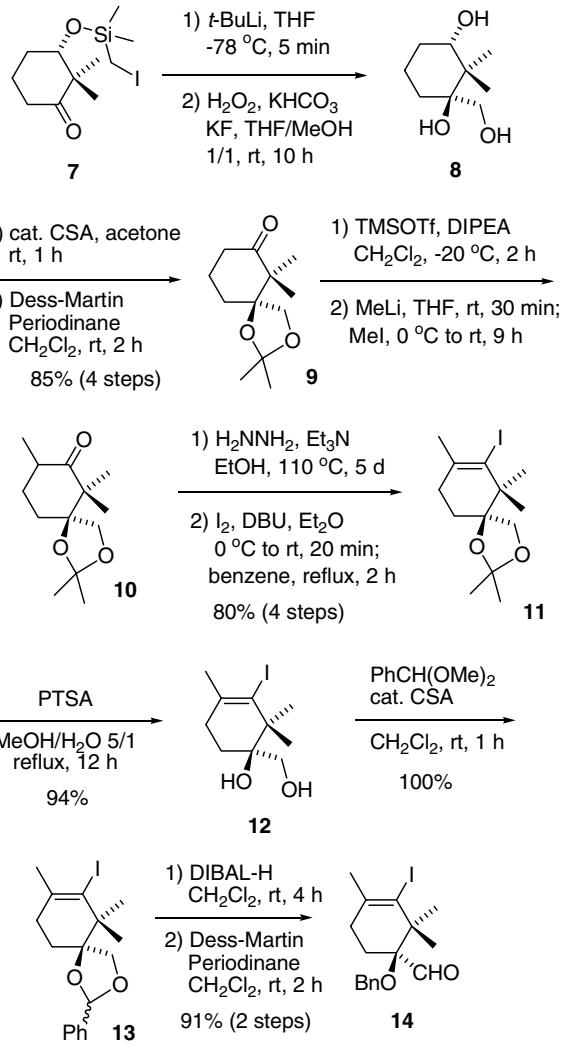
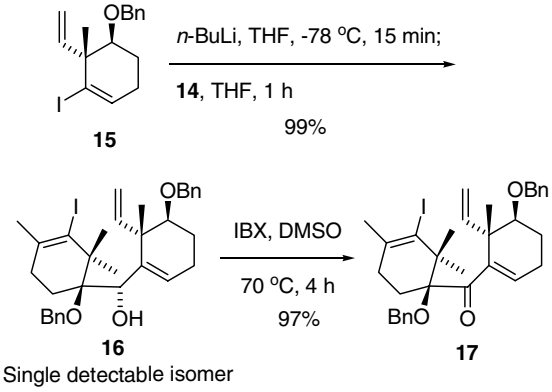


Figure 2. Expected diastereoselective formation of **6** via model **A**.



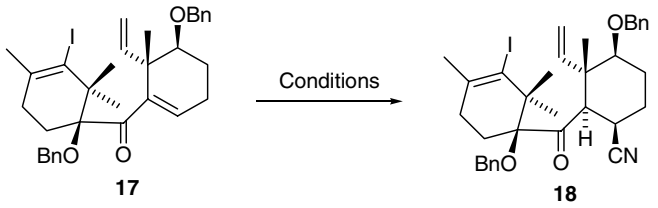
Scheme 3. Preparation of **14** from **7**.



Scheme 4. Coupling reaction of **14** with **15**.

To prepare enone **17** (Scheme 4), fragments **14** and **15** were required. Since **15** is a known compound,[8] preparation of **14** was started for the preparation of enone **17** (Scheme 3). The silicon-tethered intramolecular alkylation of **7**,[10,11] followed by Tamao oxidation,[12] acetonide formation, and Dess–Martin oxidation afforded ketone **9**. Mono-methylation of **9** was troublesome; that is, use of LDA and methyl iodide was unreproducible, and use of methyl iodide and sodium hydride provided **10** with concomitant formation of the corresponding α,α-dimethylated ketone. After surveying various conditions, however, methylation of the lithium enolate generated from the silyl enol ether of **9**[13] successfully provided **10**, which was converted to iodide **11** via a hydrazone of **10**.[14] Acetonide in **11** was replaced by a benzylidene acetal; that is, diol **12** generated by removal of the acetonide in **11** under acidic conditions was then treated with benzaldehyde dimethyl acetal to afford **13**. Finally, regioselective reduction of benzylidene acetal

Table 1. The conjugate addition of cyanide to enone **17**



17 **18**

Entry	Reagents (equiv)	Solvent	Temp (°C)	Time (h)	Yield[a] (%)			
					17	**18**	**19**	**20**
1	KCN (10), NH_4Cl (7.5)	DMF/H_2O (2:1)	100	24	100	0	0	0
2	$AlMe_3$ (4.0), TMSCN (8.0)	Hexane	60	24	100	0	0	0
3	Et_2AlCN (5.0)	Benzene	80	24	100	0	0	0
4	$Yb(CN)_3$ (1.0)	THF	60	12	100	0	0	0
5	$NCCO_2Me$ (7.5), AcOK (5.0), TEA (5.0)	DMF	70	72	10	57	3	7
6	$NCCO_2Me$ (7.5), AcOK (5.0), TEA (5.0)	DMF	100	48	0	71	6	4
7	$NCCO_2Me$ (7.5), TEA (10.0)	DMF	100	72	20	23	0	0
8	$NCCO_2Me$ (7.5), AcOK (10.0)	DMF	100	24	0	65	6	5
9	$NCCO_2Me$ (7.5), AcOK (5.0), TEA (5.0)	DMSO	100	24	22	45	0	0
10	$NCCO_2Me$ (7.5), AcOK (5.0), TEA (5.0)	*n*-PrOH	Reflux	24	100	0	0	0
11	$NCCO_2Me$ (7.5), AcOK (5.0), TEA (5.0)	Toluene	100	24	100	0	0	0
12	KCN (7.5)	DMF	100	24	0	70	6	4

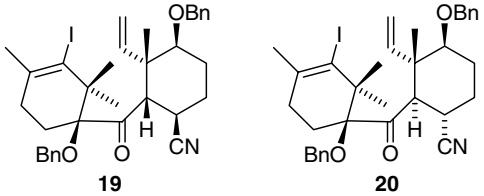
[a] Isolated yield.

13 and the subsequent Dess–Martin oxidation afforded **14**.

The coupling reaction of **14** with **15** was successfully carried out (Scheme 4). That is, the alkenyllithium generated in situ from **15** using *n*-BuLi was reacted with **14** to afford **16** as the single detectable diastereomer. This selectivity would be well explained by the chelation control. IBX oxidation[15] of **16** at 70 °C in DMSO successfully provided **17** with excellent yield (97%).

With enone **17** in hand, a conjugate addition of cyanide to **17** was examined (Table 1). Reaction of the in situ generated hydrogen cyanide[16] with **17** gave no product (entry 1). Then we examined the reaction with various reagents, but no reaction occurred by $AlMe_3$ and TMSCN[17] (entry 2), Et_2AlCN[18] (entry 3), and $Yb(CN)_3$[19] (entry 4).

Fortunately, reaction of **17** with methyl cyanoformate, potassium acetate, and triethylamine in DMF at 70 °C for 72 h (entry 5), which were the conditions reported by Shimizu et al.,[20] provided **18** in 57% along with **19** (3%), **20** (7%) (Fig. 3), and **17** (10%). X-ray crystallographic analysis of **18** clearly determined the structure as shown in Fig. 4,[21] indicating that the conjugate addition of cyanide proceeded stereoselectively, as expected. NOESY spectra of **19** and **20** suggested that **19** and **20**



19 **20**

Figure 3. Structure of **19** and **20**.

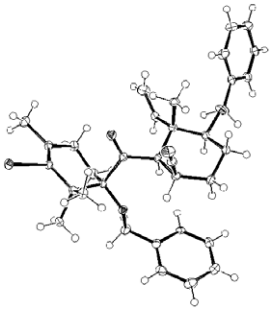
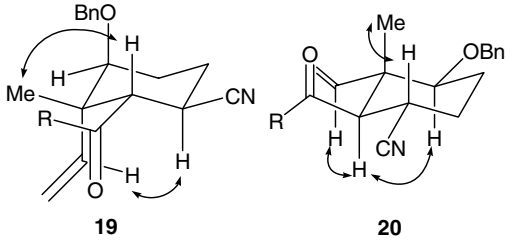


Figure 4. X-ray crystal structure of **18**.

were the diastereomers of **18**, as shown in Figures 3 and 5.

The conjugate addition carried out at 100 °C (entry 6) shortened the reaction time to 48 h, improving the yield to 71%. This result indicated that diastereoselectivity of the conjugate addition was in a ratio of 77:4. The reactions in the absence of AcOK (entry 7) or Et_3N (entry 8) decreased the yield and suggested that AcOK played an important role in this reaction. Change of the solvent to DMSO lowered the yield, too (entry 9). No reaction



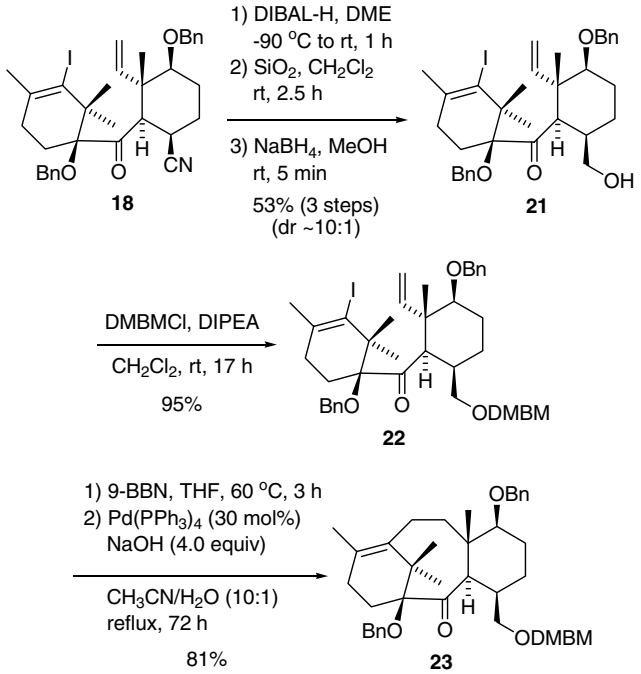
19 **20**

Figure 5. NOE correlations in the NOESY spectra of **19** and **20**. R is A-ring moiety.

occurred in either *n*-propanol (entry 10) or toluene (entry 11). The former would arise from solvation and the latter from insolubility of KCN, which would generate in situ. Finally, we found that the reaction of **17** with potassium cyanide in DMF at 100 °C for 24 h provided **18** in 70% yield along with **19** (6%) and **20** (4%) (entry 12). This result was comparable with that in entry 6, suggesting that the conditions in entry 6 probably generated KCN in situ, which reacted with **17** to afford the products. To the best of our knowledge, a conjugate addition of cyanide has been widely used in a polycyclic system,[18] and the successful example in cyclohexenyl carbonyl compounds is rare.[22]

Next we examined the transformation of **18** (Scheme 5) for the intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction to construct the taxol B-ring.[8] The ketone in **18** was inert to various reducing reagents probably due to its steric hindrance and the nitrile group in **18** was reduced faster to provide the corresponding keto-aldehyde. However, the yield varied depending on the work-up procedure, and the concomitant epimerization at the α position of the aldehyde occurred in part. Fortunately, quenching the DIBAL-H reduction of **18** with THF/AcOH/H_2O (2:1:1) and following silica-gel treatment of the product (a mixture of the aldehyde and its hydrate) reproducibly provided the desired aldehyde. The aldehyde was reduced with $NaBH_4$ to afford **21** in 53% (three steps).

The hydroxyl in **21** was protected as a DMBM (3,4-dimethoxybenzyloxymethyl) ether **22**.[23] Reduction of ketone **22** did not occur even using $LiAlH_4$ probably due to the steric hindrance, resulting in the reduction of the alkenyliodide.



Scheme 5. Conversion of **18** to **23** via the intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction.

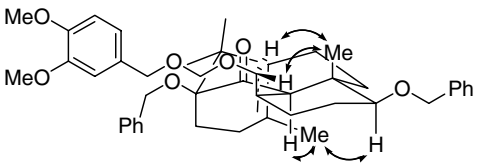


Figure 6. NOE correlations in the NOESY spectrum of **23**.

Consequently, **22** was subjected to the intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction (Scheme 5), and gratifyingly, the product **23** was obtained in high yield (81%).[24] The structure of **23** was confirmed by analyzing its NOESY spectrum (Fig. 6). Although **23** possesses an α-hydrogen adjacent to the ketone, no epimerization was observed during the ring-closing coupling reaction.

In conclusion, we found that the diastereoselective conjugate addition of cyanide to enone **17**, which was presumed to proceed in an axial attack manner, succeeded in the stereoselective construction of the C3 stereogenic center. The intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction of ketone **22** was found to provide **23** incorporating the taxane skeleton without epimerization in high yield, demonstrating its applicability to the eight-membered ring synthesis as well as its mild reaction conditions. The stereoselective reduction[25] and allylic oxidation of **23** are the problems to be solved and now in progress in our laboratory.

Acknowledgments

This work was financially supported in part by a Waseda University Grant for Special Research Projects and a Grant-in-Aid for Scientific Research (C) and Scientific Research on Priority Areas (Creation of Biologically Functional Molecules (No. 17035082)) from MEXT, Japan. We are also indebted to GCOE 'Practical Chemical Wisdom'.

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21. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data centre as supplementary publication number CCDC 653251. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
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24. Compound **23**: IR ($CHCl_3$) ν_{max}: 1700, 1520, 1466, 1380, 1360, 1266, 1160, 1140, 1068, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.19 (m, 10H), 6.90 (d, $J = 1.7$ Hz, 1H), 6.81 (dd, $J = 8.1$, 1.7 Hz, 1H), 6.76 (d, $J = 8.1$ Hz, 1H), 4.72 (d, $J = 6.6$ Hz, 1H), 4.71 (d, $J = 6.6$ Hz, 1H), 4.68 (d, $J = 11.5$ Hz, 1H), 4.48 (d, $J = 11.5$ Hz, 1H), 4.46 (d, $J = 11.7$ Hz, 1H), 4.44 (d, $J = 11.7$ Hz, 1H), 4.44 (d, $J = 11.2$ Hz, 1H), 4.27 (d, $J = 11.7$ Hz, 1H), 4.10 (d, $J = 9.8$ Hz, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 3.67 (dd, $J = 9.8$, 9.3 Hz, 1H), 3.28 (d, $J = 3.9$ Hz, 1H), 3.25 (dd, $J = 11.2$, 4.2 Hz, 1H), 2.73 (m, 1H), 2.33 (ddd, $J = 13.9$, 13.9, 5.4 Hz, 1H), 2.20 (ddd, $J = 14.6$, 9.8, 4.9 Hz, 1H), 2.10–1.79 (m, 8H), 1.73–1.24 (m, 2H), 1.56 (s, 3H), 1.21 (s, 3H), 1.14 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.7, 148.8, 148.5, 139.9, 139.3, 138.7, 130.7, 130.2, 128.3, 128.0, 128.0, 127.6, 126.8, 126.7, 120.4, 111.1, 110.8, 94.6, 91.0, 78.1, 70.5, 69.2, 67.7, 66.0, 55.9, 55.8, 52.4, 43.7, 43.2, 37.8, 34.7, 33.2, 30.5, 28.0, 27.4, 26.0, 25.2, 24.9, 22.7, 22.6, 22.0, 20.6, 20.1; HRMS(FAB)$[M]^+$ calcd for $C_{44}H_{56}O_7$, 696.4026, found, 696.4031; $[\alpha]_D^{22}$ +69.7 (*c* 0.81, $CHCl_3$); $R_f = 0.48$ (hexane/AcOEt = 2:1).
25. Reduction of the ketone at C2 position in the taxane model compounds, see: (a) Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878–5879; (b) Vázquez, A.; Williams, R. M. *J. Org. Chem.* **2000**, *65*, 7865–7869.