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TRIMETHYLALUMINUM-PROMOTED 1,4-ADDITION REACTION OF CUPRATES TO SIX OR EIGHT-MEMBERED 2-HYDROXYMETHYL ENONES†

Khanitha Pudhom, Jun-ichi Matsuo, and Teruaki Mukaiyama*

The Kitasato Institute, Center for Basic Research

6-15-5 (TCI), Toshima, Kita-ku, Tokyo 114-0003, Japan

e-mail: mukaiyam@abeam.ocn.ne.jp

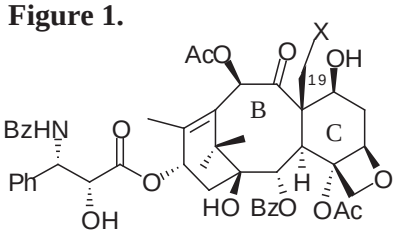
Abstract - 1,4-Addition reaction of higher order cyanocuprates such as $Ph_2Cu(CN)Li_2$ and $[Et_3SiO(CH_2)_3C(=CH_2)]_2Cu(CN)Li_2$ (**3**) to six or eight-membered cyclic 2-hydroxymethyl enones proceeded efficiently by successive treatment with trimethylaluminum and cuprate reagents. A side chain for C-ring of 19-hydroxypaclitaxel (**1**) was introduced in high yields on treating highly functionalized eight-membered cyclic hydroxymethyl enone (**2c**) with trimethylaluminum and cuprate (**3**).

†Dedicated to Professor Yuichi Kanaoka on the occasion of his 75th birthday.

In order to find potent anticancer drugs, synthesis of various taxol derivatives has been studied in our laboratory after our completion of asymmetric total synthesis of taxol® in 1997.[1] A target molecule now

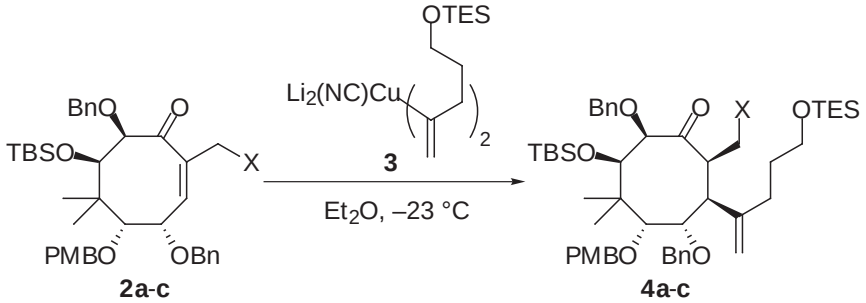
is 19-hydroxypaclitaxel (**1**) which is expected to improve pharmacological features of taxol, especially its water-solubility (Figure 1). Since the transformation of 19-methyl group of taxol or naturally-occurring compounds such as baccatin III to the corresponding 19-hydroxymethyl group is apparently difficult, chemical total synthesis should be a powerful tool for the preparation of such derivative as **1**. Recently, it was reported from our laboratory that a highly functionalized eight-membered B-ring structure had been synthesized by samarium(II) iodide-mediated intramolecular bisaldol forming reaction.[2] In this communication, we would like to report on trimethylaluminum-promoted 1,4-addition reaction of cuprates to 2-hydroxymethyl enones by which a side chain for the construction of C-ring of **1** was introduced efficiently.

Figure 1.



Taxol®: X = H
19-Hydroxypaclitaxel (**1**): X = OH

Table 1. 1,4-Addition reaction of cuprate (**3**) with enones (**2a-c**)



2a-c **4a-c**

Entry	Enone **2**	**3** (equiv.)	Product	Yield/%
1[a]	**2a**: X = H	5.0	**4a**	92
2	**2b**: X = OTES	3.7	**4b**	0
3	**2c**: X = OH	5.0	**4c**	55

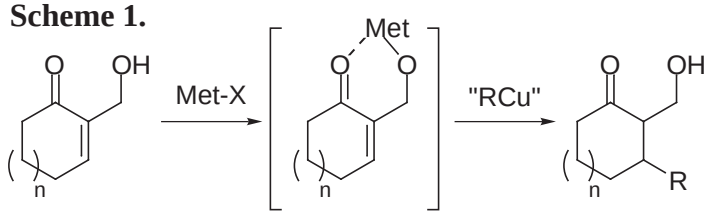
[a]See ref. 1.

In our total synthesis of taxol, a carbon chain for constructing its C-ring was introduced by 1,4-addition of cuprate (**3**) to enone (**2a**), by which the desired stereoisomer (**4a**) was obtained stereoselectively in 92% yield (Table 1, Entry 1).[1] A similar 1,4-addition of cuprate (**3**) to enone (**2b**) having triethylsilyl (TES)-oxy group was tried first to synthesize 19-hydroxypaclitaxel (**1**), but the desired 1,4-adduct was not obtained at all (Entry 2). Also, TES-protected enone (**2b**) did not react with another simple cyanocuprate, $Me_2Cu(CN)Li_2$. Since the protection of hydroxy group was supposed to prevent the present Michael addition reaction, non-protected hydroxymethyl enone (**2c**) was next employed as a

Michael acceptor. The desired Michael addition proceeded by using five equivalents of cuprate (**3**), but the yield of adduct (**2c**) remained low (55%) (Entry 3). Then, it was studied to improve the yield of the desired 1,4-adduct by using less amounts of cuprate (**3**) in the direct Michael addition reaction to 2-hydroxymethyl enones.

It was considered that the Michael addition would proceed more smoothly when the enone moiety was intramolecularly activated:[3] in other words, intramolecular six-membered cyclic chelation would activate the neighboring enone moiety as shown Scheme 1.

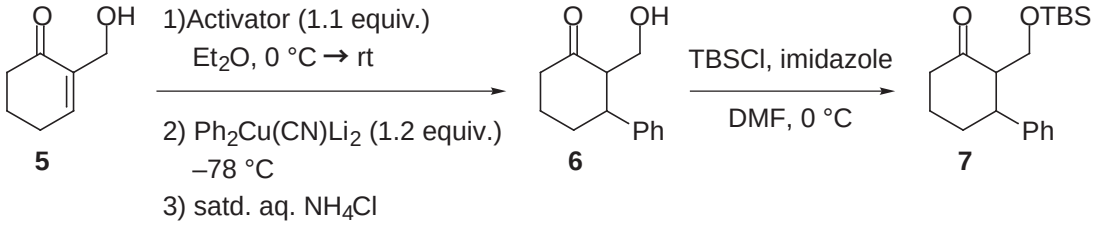
Scheme 1.



In the first place, several alkoxy or alkyl metals were employed as the activating agent in the model Michael addition reaction using 1.2 equivalents of $Ph_2Cu(CN)Li_2$ and 2-hydroxymethylcyclohexenone (**5**)[4] (Table 2). Both yield and *syn*/*anti*-ratio were determined by protecting hydroxylmethyl group of the formed **6** with *t*-butyldimethylsilyl (TBS) group due to its unstability during purification process. It was found there that trimethylaluminum, ethoxydiethylaluminum, tetraisopropoxytitamium, and diethylzinc behaved as activating agents, and Michael adducts were obtained in moderate yields. Quenching the reaction with aqueous ammonium chloride gave *syn*-adduct as a major diastereomer, and *syn*/*anti* -ratio ranged from 73 : 27 to 82 : 18. On the other hand, no *syn*/*anti*-selectivity was observed when the reaction was quenched with aqueous potassium sodium tartrate (Entry 6).

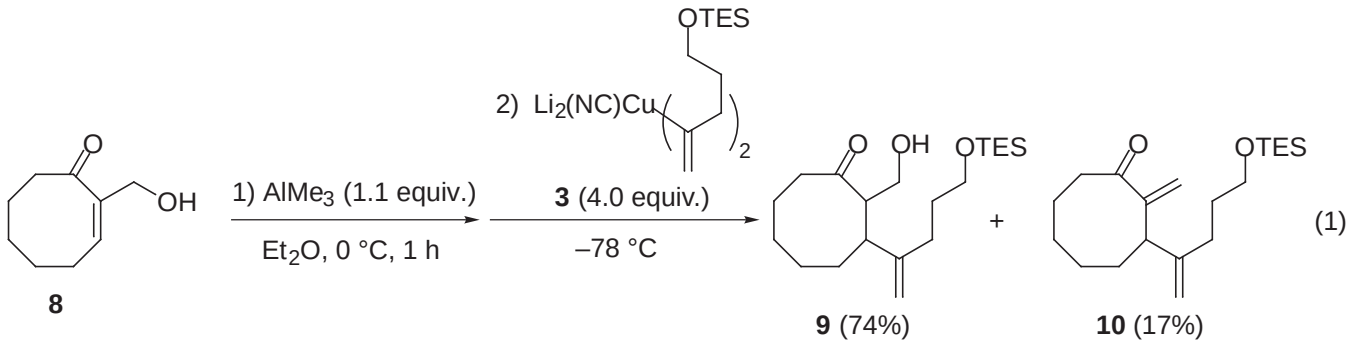
Trimethylaluminum was then chosen as an activating agent, and it was employed in Michael addition of vinylcuprate reagent (**3**) to eight-membered cyclic hydroxymethylenone (**8**) (eq. 1). Trimethylaluminum worked also effectively in this case, and hydroxymethyl ketone (**9**) was obtained in 74% yield along with a dehydrated product (**10**) in 17% yield.

Table 2. Michel addition reaction of $Ph_2Cu(CN)Li_2$ with **5** by intramolecular activation



Entry	Activator	**7** (%)[a]	*syn*/*anti*[b] of **7**
1	none	10	82 : 18
2[c]	none	29	73 : 27
3	BEt_3	12	nd[d]
4	$B(O^iPr)_3$	15	73 : 27
5	$AlMe_3$	70	80 : 20
6[e]	$AlMe_3$	64	50 : 50
7	$Al(OEt)Et_2$	69[f]	nd[d]
8	$Al(O^iPr)_3$	trace	–
9	$Ti(O^iPr)_4$	62[f]	nd[d]
10	$ZnEt_2$	67[f]	nd[d]
11	$Sn(OEt)_2$	trace	–

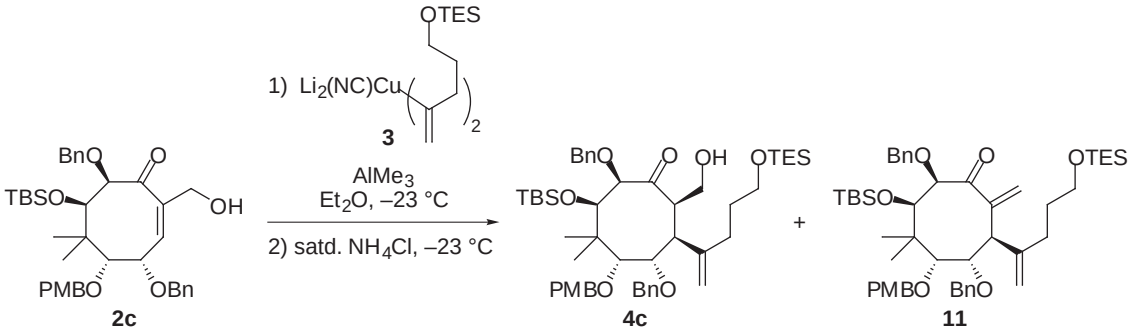
[a]Isolated yields. [b]Determined by ^1H NMR analysis. [c]The cuprate reagent (2.4 equiv.) was employed. [d]Not determined. [e]The 1,4-addition reaction was quenched with aq. potassium sodium tartrate. [f]Isolated yield of **6**.



Since trimethylaluminum-promoted Michael addition of vinylcuprate (**3**) to the model eight-membered hydroxymethyl enone (**8**) proceeded successfully, this method was finally applied to the synthesis of 19-hydroxypaclitaxel (**1**) by the Michael addition of cuprate (**3**) to highly functionalized enone (**2c**). As shown in Table 3, only 2.5 equivalents of the cuprate reagent (**3**) and 1.1 equivalents of trimethylaluminum gave 1,4-adduct (**4c**)[5] in 71% yield (Entry 6) while the use of even five equivalents of cuprate (**3**) gave 1,4-adduct (**4c**) in 55% yield in the absence of trimethylaluminum (Entries 1–3). In

these cases, the dehydrated product (**11**)[5] was also obtained in 17% yield, and both hydroxymethyl ketone (**4c**) and enone (**11**) were utilized as synthetic intermediates in the total synthesis of 19-hydroxypaclitaxel (**1**). Subsequently, trimehylaluminum-promoted Michael addition of **3** to **2c** introduced the side chain in 93% combined yield. It was also found that hydroxy ketone (**4c**) was obtained in better yields when the reaction was quenched with saturated aqueous ammonium chloride at a lower temperature, –78 °C (Entry 4 vs. Entries 5 and 6).

Table 3. Trimethylaluminum-promoted Michael addition reaction of **3** with **2c**



Entry	**3** (equiv.)	$AlMe_3$ (equiv.)	**4c** (%)[a]	**11** (%)[a]	Recovered **2c** (%)[a]
1	2.0	0	–	–	83
2	3.7	0	47	8	41
3	5.0	0	55	26	trace
4	4.0	1.1	28	56	trace
5[b]	3.5	1.1	67	21	trace
6[b]	2.5	1.1	71	22	trace

[a]Isolated yields. [b]The reaction was quenched at –78 °C.

Typical experimental procedure is as follows (Table 3, Entry 6): under an argon atmosphere, *t*-butyllithium (1.51 M in *n*-pentane solution, 1.00 mL, 1.51 mmol) was added dropwise to the solution of 4-bromo-triethylsilyloxypent-4-ene (212 mg, 0.76 mmol) in Et_2O (8 mL) at –78 °C. After stirring the mixture at –78 °C for 25 min, it was transferred through cannula to the suspension of CuCN (33.9 mg, 0.38 mmol) in Et_2O (12 mL) which was cooled down to –78 °C. The reaction mixture was then stirred at –5 °C (ice and NaCl) for 30 min. In another flask, trimethylaluminum (1.08 M in *n*-hexane, 0.15 mL,

0.17 mmol) was added dropwise at 0 °C to the solution of **2c** (100 mg, 0.15 mmol) in Et_2O (3 mL), and the mixture was stirred for 30 min. This solution was cooled down to –78 °C, and was transferred through cannula at –23 °C to the cuprate solution mentioned above. The reaction mixture was stirred at –23 °C for 1 h, quenched by adding saturated aqueous NH_4Cl, and extracted with Et_2O. The combined ether extract was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by preparative thin-layer chromatography (20% ethyl acetate in hexanes) to afford **4c** (102 mg, 71%, *Rf* = 0.28) and **11** (37 mg, 22%, *Rf* = 0.61).

It is noted that trimethylaluminum efficiently promoted 1,4-addition reaction of higher order cyanocuprates such as $Me_2Cu(CN)Li_2$ and vinyl cuprate (**3**) to six or eight-membered 2-hydroxymethyl enones. The present trimethylaluminum-promoted cuprate addition was successfully employed to the introduction of a side chain in constructing C-ring of 19-hydroxypaclitaxel (**1**). Since 2-hydroxymethyl enones employed in this study are grouped into Baylis-Hillman adducts, the present new procedure would be applicable to the Michael addition using other types of Baylis-Hillman adducts, which could be employed extensively in organic synthesis.

ACKNOWLEDGEMENTS

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2. K. Pudhom, H. Arai, K. Yamane, and T. Mukaiyama, *Chem. Lett.*, 2002, 82.
3. For 1,4-addition reaction of organocopper reagents in the presence of Lewis acids, see: B. H. Lipshutz, 'Organometallics in Synthesis: A Manual,' Second Ed., ed. by M. Schlosser, Wiley & Sons, Ltd., West Sussex, 2002, pp. 665-815.
4. F. Rezgui and M. M. E. Gaied, *Tetrahedron Lett.*, 1998, **39**, 5965.
5. In order to clarify the structure of the Michael adducts (**4c** and **11**), these eight-membered ring compounds were transformed into bridged bicyclic compounds by deprotection of PMB group with DDQ, and their structures were determined by NOE: see, ref. 2.