Synthesis of AB Ring Model System of Taxol *via* Allylation of 8-Membered Ring Compound and Intramolecular Aldol Condensation

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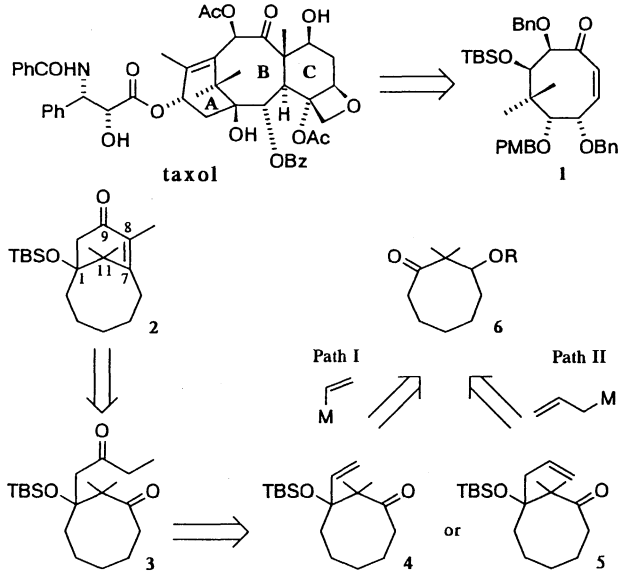
1-*t*-Butyldimethylsiloxy-8,11,11-trimethylbicyclo[5.3.1]undec-7-en-9-one (**2**) has been synthesized via intramolecular aldol condensation of the precursor **3** by combined use of lithium diisopropylamide (LDA) and $CeCl_3$. The dicarbonyl compound **3** was prepared by allylation of 8-membered ring ketone **6b**.

A useful method for the synthesis of optically active 8-membered ring enone (**1**), a new and potential synthetic intermediate of taxol,[1] by way of stereoselective aldol reactions and intramolecular Reformatsky-type reaction was reported in previous communication.[2] In our synthetic strategy, AB ring system of taxol is to be constructed by introducing A ring segment onto 8-membered ring compound **1**, followed by intramolecular cyclization of the precursor as shown in Scheme 1.

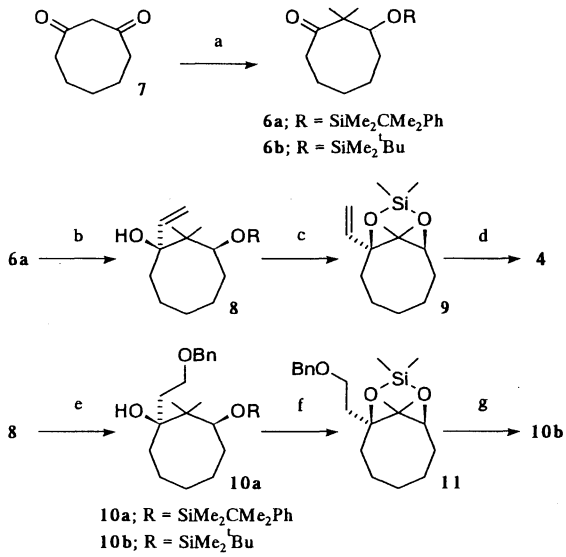
House *et al.* reported an effective method for the synthesis of bicyclo[5.3.1]undec-7-en-9-one skeleton by way of intramolecular aldol-type condensation in the presence of sulfuric acid and acetic acid in 1980.[3] Further, Swindell *et al.* described constructions of AB ring system of taxinine through aldol-type condensation carried out under basic conditions in 1990.[4] In these cases, no oxygenated functions were involved at C-1 position of the synthesized cyclic compounds; therefore, a development of convenient method for the synthesis of **2** which possesses an alkoxy function at C-1 position from 8-membered ring compound **6** is strongly desired in order to complete total synthesis of taxol from 8-membered ring compound **1**.



Scheme 1.

In the first place, starting material **6a** or **6b** was prepared from the known dicarbonyl compound **7**[5] by way of methylation, mono-reduction and protection of resulting alcohol. Though aldol reactions between **6a** or **6b** and the lithium enolate of methyl ethyl ketone, ethyl acetate or ethyl propionate, were attempted in order to introduce carbonyl unit onto 8-membered ring compound, these aldol-type reactions did not proceed at all. To this end, two routes including alkylations of **6** and the subsequent oxygenations were planned as a model synthesis of taxol (Scheme 1, Paths I and II).

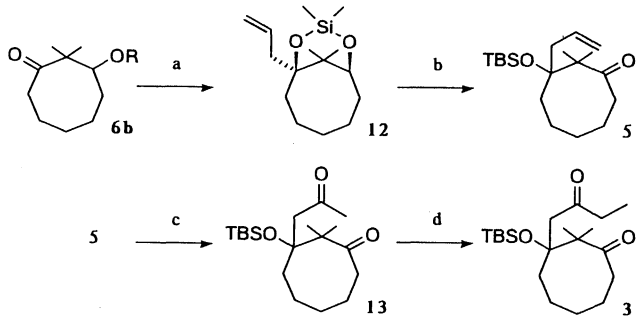
Path I: alkylation of 6a using vinyl cerium reagent proceeded smoothly to give a mixture of siloxy alcohols in good yield (95%, cis / trans = 59 / 41).[6] In attempted protections of resulting allyl alcohols, no desired product was formed because of steric hindrances of the alcohols. On the other hand, cyclic silyl ether **9** was unexpectedly produced when cis-siloxy alcohol **8** was treated with NaH. The corresponding keto *t*-butyldimethylsilyl ether **4** was obtained by regioselective alkylation of cyclic silyl ether **9** with *t*-butyllithium followed by Swern oxidation. Since hydroboration of **4** did not work at all due to bulkiness of the substrate, hydroboration of the cis-siloxy alcohol **8** was investigated at first, and the corresponding diol was formed with good regioselectivity. Silyl ether **10a** was produced by regioselective protection of the diol, then cyclic silyl ether **11** was obtained by deprotection of silyl ether **10a** and protection of resulting cis-diol. Unfortunately, alkylation of **11** with *t*-butyl lithium gave undesired silyl ether **10b** exclusively.



a) K_2CO_3, MeI, acetone, r.t. (97%); $NaBH_4$, EtOH, r.t. (84%); (**6a**) $PhMe_2CMe_2SiCl$, Imidazole, DMAP, DMF, r.t. (99%); (**6b**) TBSCl, Imidazole, DMAP, DMF, r.t. (97%); b) CH_2=CHMgBr, $CeCl_3$, THF, -78 °C (95%, cis / trans = 59 / 41); c) NaH, TESCl, DMF, 0 °C to r.t. (50%); d) ^{t}BuLi, Et_2O, -78 °C (65%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t. (98%); e) $ThexBH_2$, THF; 9N NaOHaq., 30% H_2O_2aq. (80%); NaH, BnBr, THF, 0 °C (97%); f) TBAF, THF, r.t. (99%); Me_2SiCl_2, Imidazole, DMF, r.t. (84%); g) ^{t}BuLi, Et_2O, -78 °C (82%)

Scheme 2.

Path II: then, a route including allylation of 8-membered ring ketone, followed by Wacker oxidation was examined.[7] Allylation of **6b** with allylmagnesium bromide took place smoothly to produce a mixture of siloxy alcohols in excellent yield (97%, cis / trans = 53 / 47). The following treatments of cis-siloxy alcohol, e.g. deprotection of silyl ether and protection of thus formed cis-diol, gave cyclic silyl ether **12**. Further, alkylation of **12** with *t*-butyllithium, followed by Swern oxidation gave desired 8-membered ring ketone **5**. Successive Wacker oxidation of the terminal olefin of **5** and selective methylation of the lithium enolate derived from the diketone **13** afforded dicarbonyl compound **3** in good yield.



a) allylMgBr, THF : Et_2O = 3 : 1, 0 °C (97%, cis / trans = 53 / 47); TBAF, THF, 0 °C (100%); Me_2SiCl_2, Imidazole, DMF, r.t. (89%); b) ^tBuLi, Et_2O, -78 °C (100%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to 0 °C (85%); c) $PdCl_2$, CuCl, O_2, H_2O, DMF, r.t. (62%); d) LHMDS, THF, -78 °C then MeI, HMPA (91%)

Scheme 3.

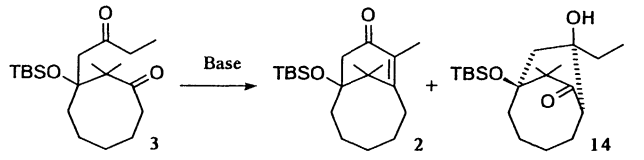


Table 1.

Entry	Base	Solvent	Temp	Yield of 2 / %	Yield of 14 / %
1	NaOMe	MeOH	r.t.	21	-
2	KO^{t}Bu	^{t}BuOH	30 °C	5	-
3	LDA	THF	-78 °C to 0 °C	16	44
4	LDA	THF	0 °C to r.t.	31	44
5	LHMDS	THF	-23 °C to r.t.	29	57
6	LTMP	THF	-23 °C to r.t.	35	59
7	LDA-$CeCl_3$	THF	-23 °C to r.t.	64	15

Next, reaction conditions of cyclization of the precursor **3** were screened as shown in Table 1. It revealed that lithium amides promoted this cyclization smoothly to produce desired bicyclic compound **2**[8] in moderate yields (Entry 3 - 6); however, undesired aldol **14** was also produced under these reaction conditions. On the other hand, elimination of *t*-butyldimethylsilanol proceeded rapidly and the enone **2** was obtained in low yield when NaOMe or KO^{t}Bu was used as a base in a protic solvent. Finally, the best yield was obtained under mild reaction condition when LDA-$CeCl_3$ system was employed (Entry 7).[9]

Thus, convenient synthesis of the enone **2**, the AB ring model system of taxol, was achieved successfully via allylation of 8-membered ring ketone **6b** and intramolecular aldol condensation. A construction of fully functionalized AB ring system of taxol from 8-membered ring enone **1** by the use of above synthetic route II is now in progress.

References and Notes

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8 **2**; ^1H NMR ($CDCl_3$) δ = 0.10 (3H, s), 0.12 (3H, s), 0.88 (9H, s), 0.95 - 1.11 (1H, m), 1.12 (3H, s), 1.29 (3H, s), 1.42 - 2.01 (7H, m), 1.83 (3H, s), 2.33 - 2.71 (2H, m), 2.52 (1H, d, J = 18.8 Hz), 2.93 (1H, d, J = 18.8 Hz); ^{13}C NMR ($CDCl_3$) δ = -2.06 (CH_3, TBS), -1.83 (CH_3, TBS), 12.72 (CH_3), 18.35 (C, ^{t}Bu), 22.07 (CH_3), 25.77 (CH_3*3, TBS), 26.11 (CH_2), 28.20 (CH_2), 28.75 (CH_2), 28.99 (CH_2), 30.95 (CH_3), 44.42 (C), 45.16 (CH_2), 50.30 (CH_2), 79.86 (C), 131.81 (C, enone), 167.31 (C, enone), 198.96 (C, enone); IR (neat) 1660 cm^{-1}; MS (EI) 279 (M^+-^{t}Bu).

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