An Asymmetric Synthesis of the BC Ring System of 8-Epitaxoids by Way of Intramolecular Aldol and Successive Stereoselective Methylation Reactions

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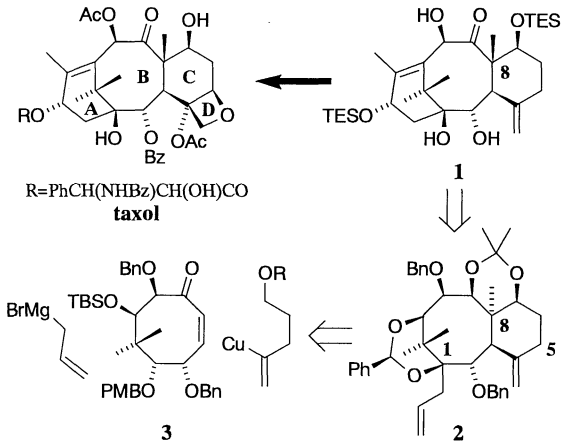
Optically active 1α-allyl-1β,11β-benzylidenedioxy-2α,10β-bis(benzyloxy)-7β,9β-isopropylidenedioxy-8α,12,12-trimethyl-4-methylenebicyclo[6.4.0]dodecane (**2**)[1] which corresponds to BC ring system of 8-epitaxoids was prepared in high yield from ketoaldehyde **8** *via* intramolecular aldol cyclization and successive stereoselective methylation reactions. The ketoaldehyde **8** was synthesized from 8-membered ring compound **3** by stereoselective Michael addition using higher-order cuprate.

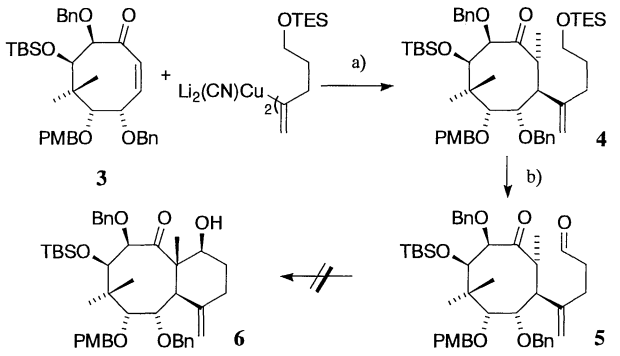
Our recent publications disclosed formal synthesis of taxol from novel synthetic intermediate **1** by way of a new and effective method of constructing oxetane ring onto ABC ring system as well as an asymmetric synthesis of AB ring system of taxol from 8-membered ring compound **3** by way of successive stereoselective allylation and intramolecular aldol reactions.[2-6]

We would like to demonstrate here a method for the synthesis of BC ring system of taxol from the 8-membered ring compound **3** *via* intramolecular aldol cyclization,[7,8] followed by stereoselective methylation with methyl iodide according to a synthetic strategy of constructing A ring system onto the BC ring system of taxol.[4,5,9] An asymmetric synthesis of the tetracyclic compounds **2** which is convertible to the synthetic intermediate **1** is also described.



Scheme 1.

In the first place, three-component coupling reaction of a mixture of two slowly interconverting conformational isomers **3** with a higher-order cuprate reagent,[10] followed by trapping with methyl iodide was studied under several reaction conditions. The Michael reaction proceeded smoothly by employing higher-order cuprate reagent generated in situ from 2 mol of 4-bromo-1-triethylsiloxy-4-pentene with 4 mol of *t*-BuLi and 1 mol of CuCN, and the desired α,β-disubstituted 8-membered ring ketone **4** was obtained in high yield with medium diastereoselectivity (88%, 75 / 25 / 0 / 0). The relative stereochemistry of **4** was



a) THF, -78 °C to -23 °C; then MeI, HMPA, r.t. (59%);
b) TBAF, THF, 0 °C (85%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t. (98%)

Scheme 2.

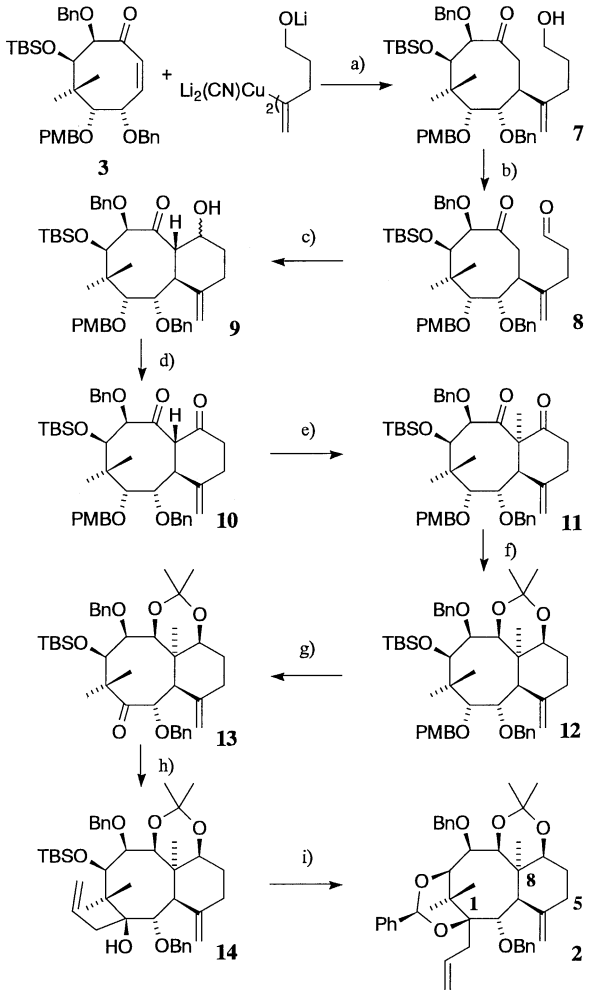
assigned by ^1H NMR measurement of the transformed product. Ketoaldehyde **5**, a precursor of BC ring system of taxol, was obtained in high yield by deprotection of **4** with TBAF, followed by Swern oxidation.

Then, synthesis of bicyclic compound **6** from the precursor **5** which contains all necessary functionalities for constructing taxol was tried under several reaction conditions. However, intramolecular aldol reaction did not proceed at all in any case while ketoaldehyde **5** was recovered almost quantitatively. Since molecular dynamics conformational search with MM2 force field showed that the hydrogen atom at α-position of carbonyl group is located inside of the molecule and the dihedral angle of the C-C bond is nearly planar, it is assumed that generation of the enolate by deprotonation could not take place under the above conditions.

The synthetic strategy was next designed toward the BC ring system of taxol *via* intramolecular aldol cyclization and following stereoselective methylation with methyl iodide. A precursor **8**, having no methyl group at α-position of carbonyl group on 8-membered ring, is expected to generate the enolate which leads to the desired bicyclic compound **9**.

The Michael addition of higher-order cuprate reagent,[11] generated in situ from 2 mol of 4-bromo-4-pentene-1-ol with 6 mol of *t*-BuLi and 1 mol of CuCN, to the 8-membered ring enone **3** proceeded smoothly at -23 °C and the desired β-monosubstituted 8-membered ring hydroxyketone **7** was obtained in high yield with perfect diastereoselectivity, though the 8-membered ring enone **3** was a mixture of two conformational isomers. Ketoaldehyde **8**, a precursor of BC ring system of 8-demethyltaxol, was prepared directly by oxidation of **7** with TPAP and NMO combined system. When intramolecular aldol reaction of the precursor **8** was tried in the presence of NaOMe at room temperature, the desired reaction proceeded smoothly to afford a mixture of bicyclic compounds in nearly quantitative yield with good diastereoselectivity (87 / 13 / 0 / 0). Oxidation of a mixture of **9** and its epimer afforded the corresponding diketone

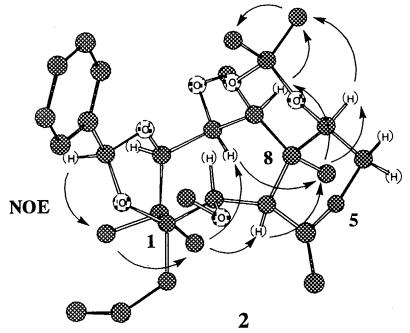
10 in high yield. Methylation of the diketone **10** took place at room temperature by using 1 mol of NaH and excess amount of methyl iodide where the desired methylated compound **11**, corresponding to BC ring system of taxol, was obtained in high yield.[12] The stereochemistry of C-8 position was not yet made clear at this stage. A highly diastereoselective reduction of the diketone **11** with DIBAL in CH_2Cl_2 at -78 °C, followed by protection thus formed diol with isopropylidene acetal provided tricyclic compound **12**. 8-Membered ring ketone **13** was obtained in good yield by DDQ oxidation of the above tricyclic compound **12**, followed by oxidation with PDC. Allylation of **13** by using allylmagnesium bromide afforded homoallyl alcohol **14** as a single stereoisomer in quantitative yield.[13] Since deprotection of TBS group and successive treatment of thus formed diol with benzaldehyde dimethylacetal afforded the desired benzylidene derivative **2**, it was confirmed that the diol had cis configuration.



a) Et_2O, -23 °C (96% based on 85% conversion); b) TPAP, NMO, CH_2Cl_2, MS-4Å, 0 °C (91%); c) NaOMe, MeOH, r.t. (99%, 87 / 13 / 0 / 0); d) TPAP, NMO, CH_2Cl_2, MS-4Å, r.t. (84%); e) NaH, MeI, THF, 0 °C to r.t. (98%); f) DIBAL, CH_2Cl_2, -78 °C (90%); $Me_2C(OMe)_2$, CSA, CH_2Cl_2, r.t. (**12**; 73% plus 20% of desilylated compound which was converted to **12** in 98% yield using TBSOTf and 2,6-lutidine); g) DDQ, H_2O, CH_2Cl_2, r.t. (95%); PDC, CH_2Cl_2, r.t. (85%); h) allylMgBr, THF, -23 °C (100%, **14** only); i) TBAF, THF, r.t. (69%); $PhCH(OMe)_2$, CSA, benzene, azeotrope (85%)

Scheme 3.

Finally, the NOE relationship and conformational analysis by MM2 calculation of the benzylidene derivative **2** showed all stereochemistry of **2** as described in Scheme 3. Based on our preliminary experiments, α-isomer concerning methyl group at C-8 position is likely to be epimerized to more favorable β-isomer by retro-aldol reaction after constructing ABC ring system, though the tetracyclic compound **2** had an opposite configuration to taxol at C-8 position.[14]



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Thus, an asymmetric synthesis of the BC ring system of 8-epitaxoids was accomplished *via* three successive reactions of stereoselective Michael addition, intramolecular aldol cyclization and stereoselective methylation.

Synthetic studies on the ABC ring system of taxol by aldol cyclization from the present BC ring system are in progress and will be reported in due course.

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References and Notes

1 Though this is not a formal nomenclature, the numbering of taxane system is used in this letter to correspond to other references. We thank Prof. N. Inamoto for his kind advice.

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12 **11** (100%ee); $[\alpha]_D^{27}$ +13.4° (c 1.26, benzene).

13 **14** (100%ee); $[\alpha]_D^{23}$ +80.3° (c 1.50, benzene).

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