An Asymmetric Synthesis of the ABC Ring System of 8-Demethyltaxoids from Optically Active 8-Membered Ring Compound *via* Intramolecular Aldol and Pinacol Coupling Reactions

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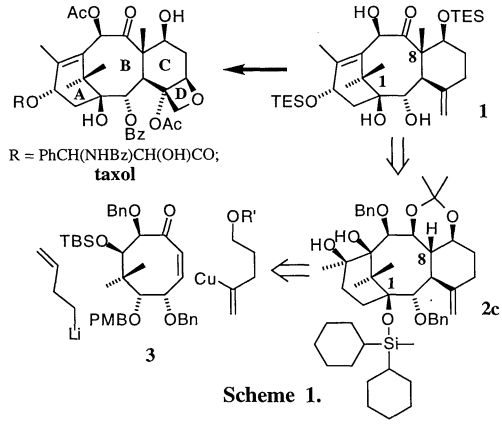
Optically active novel taxoids were efficiently synthesized from 8-membered ring compound **3** by successive constructions of BC and ABC ring systems *via* each intramolecular aldol and intramolecular pinacol coupling reactions.

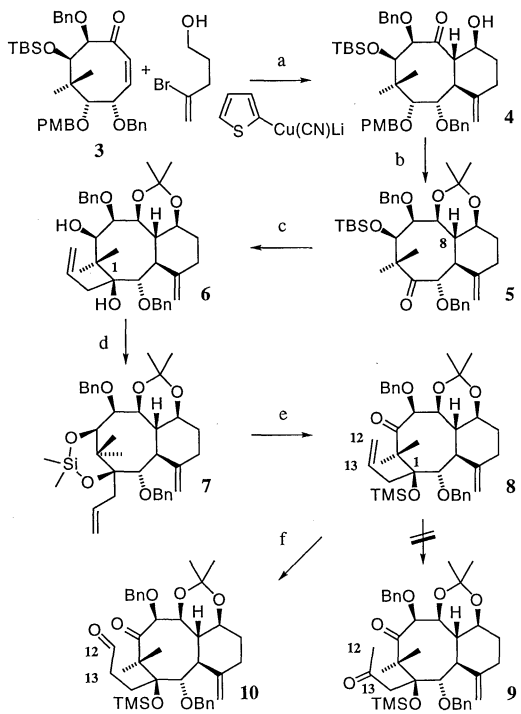
In previous communications, a novel strategy for an asymmetric synthesis of taxol[1] from 8-membered ring compound **3** was shown involving asymmetric syntheses of AB and BC ring systems of taxoids as well as partial synthesis of taxol from a synthetic intermediate **1** by an efficient construction of oxetane ring.[2-7]

Here, we would like to disclose a preparation of BC ring system of 8-demethyltaxoids through highly diastereoselective Michael addition and an effective ring closure to form ABC ring system from the above BC ring system by way of intramolecular pinacol coupling reaction using low-valent titanium reagent.



Scheme 1.

According to our synthetic strategy,[4,5] compound **8** (Scheme 2) was regarded as the initial key precursor to construct the desired ABC ring system of 8-demethyltaxoids. The modified Michael addition to enone **3** using a higher-order cuprate reagent, generated in situ from 1 mol of 4-bromo-4-pentene-1-ol with 3 mol of *t*-BuLi and 1.1 mol of lithium 2-thienylcyanocuprate, gave β-substituted 8-membered ring ketone in high yield with perfect diastereoselectivity. Oxidation of the adduct with TPAP and NMO, followed by intramolecular aldol reaction of the resulted ketoaldehyde afforded the BC ring system of 8-demethyltaxoids in high yield.[6] Diastereoselective reduction of aldol **4** with $LiBH_4$ in THF, followed by protection of thus formed diol with isopropylidene acetal provided tricyclic compound. Then, it was converted to 8-membered ring ketone **5** by deprotection of PMB group and successive oxidation with PDC. Though allylation of **5** using allylmagnesium bromide afforded undesirable homoallyl α-alcohol at C-1 position preferentially, the desired homoallyl β-alcohol was obtained as a single stereoisomer in quantitative yield when **5** was treated with allyllithium reagent. Removal of TBS group gave cis-diol **6** and successive treatment of thus formed diol with Me_2SiCl_2 yielded a silylene compound **7**, which was then converted to trialkylsilylether at C-1 position by way of alkylation of the bridged silicon atom with alkyllithium reagent similar to the previously mentioned result observed in the model synthesis of AB ring system,[4]. Oxidation of thus formed secondary alcohol by PDC gave 8-membered ring ketone **8** in good yield. By the above sequential manipulations, the first target molecule **8** was efficiently synthesized from optically active 8-membered ring enone **3**. In order to prepare C-13 oxygenated compound **9**, a precursor of ABC ring system of 8-demethyltaxoid in our aldol strategy,[4,5] several oxygenation reactions of C-13 position were examined. However, the desired reaction did not take place in any case and C-12 position was regioselectively oxygenated under forced Wacker oxidation conditions.



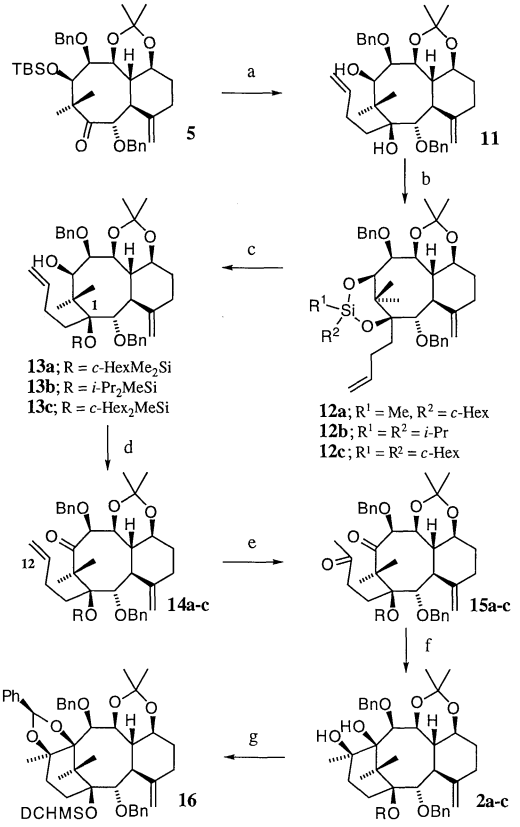
a) *t*-BuLi, Et_2O, -23 °C (90%, β only); TPAP, NMO, MS-4Å, CH_2Cl_2, 0 °C (91%); NaOMe, rt (99%, β-OH / α-OH = 87 / 13);
b) $LiBH_4$, THF, 0 °C to rt (87%); $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt (100%); DDQ, H_2O, CH_2Cl_2, rt (94%); PDC, CH_2Cl_2, rt (97%);
c) allyl-$SnBu_3$, PhLi, THF, -78 °C (100%); TBAF, THF, 50 °C (100%);
d) Me_2SiCl_2, imidazole, DMF, 0 °C; e) MeLi, THF, -78 °C (70% from **6**); PDC, CH_2Cl_2, rt (81%); f) $PdCl_2$, H_2O, DMF, rt (23% of **10**)

Scheme 2.

The ^1H NMR of **8** and MM2 calculation of the conformation indicate that **8** has a rigid tricyclic structure. Comparison of the

environments of C-12 and C-13 positions in the model suggested that C-12 position was relatively easily attacked by H_2O molecule because the C-13 position was considerably shielded by both trialkylsilyl group and exo olefin on the C ring of **8**. Therefore, a new synthetic strategy was designed toward A ring closure forming ABC ring system of 8-demethyltaxoids from intermediate **15** (Scheme 3). According to the above plan, it is assumed that the target molecule **15** can be prepared by the preferential oxygenation of C-12 position of **14** by Wacker oxidation. Further, direct construction of ABC ring system from diketone **15** might be achieved by way of intramolecular pinacol coupling reaction using low-valent metal reagent.

Alkylation of C-1 position of **5** by using homoallyllithium reagent produced the desired bishomoallyl β-alcohol in high yield. Deprotection of TBS group resulted in the formation of cis-diol **11** and successive treatment of thus formed diol with several dialkylsilyl compounds yielded silylene compounds **12a-c** in high yields. Alkylation of these silylene compounds with methyllithium furnished compounds **13a-c** having desired C-1 protected hydroxy group. Oxidation of thus formed secondary alcohols by PDC gave 8-membered ring ketones **14a-c** in good yields. Oxygenation of C-12 positions of **14a-c** proceeded smoothly to produce desired diketones **15a-c** under forced Wacker oxidation conditions as expected.

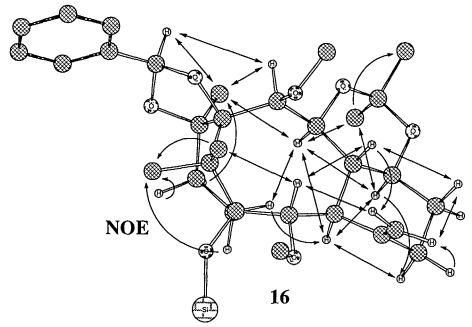


a) homoallyl-Br, *t*-BuLi, THF, -78 °C to rt (89%); TBAF, THF, 50 °C (95%);
b) *c*-HexMeSiCl$_2$, imidazole, DMF, 0 °C (100% of **12a**); *i*-Pr$_2$Si(OTf)$_2$, pyridine, 0 °C (95% of **12b**); *c*-Hex$_2$Si(OTf)$_2$, pyridine, 0 °C (100% of **12c**);
c) MeLi, THF, -78 °C (92% of **13a**); MeLi, THF, 0 °C (91% of **13b**, 98% of **13c**);
d) PDC, CH_2Cl_2, rt (90% of **14a**, 100% of **14b**, 89% of **14c**);
e) $PdCl_2$, H_2O, DMF, rt (90% of **15a**, 100% of **15b**, 90% of **15c**);
f) $TiCl_3$, $LiAlH_4$, THF, 50 °C (40% of **2a**); 60 °C (64% of **2b**); 40 °C (73% of **2c**);
g) PhCH(OMe)$_2$, CSA, benzene, azeotrope (62% based on 75% conversion; from **2c**)

Scheme 3.

Finally, intramolecular pinacol coupling reaction of **15a-c** using low-valent titanium reagent, prepared from $TiCl_3$ and $LiAlH_4$, gave the ABC ring system of 8-demethyltaxoids **2a-c** as shown in Scheme 3. In every case, the desired pinacol was obtained as a main product along with by-products such as rearranged pinacolone type products. Diketone **15c** possessing dicyclohexylmethylsilylether group at C-1 position gave the best result in the above intramolecular pinacol coupling reaction because the silyl group was kept safely under the reaction conditions.[8]

The NOE relationship and conformational analysis by MM2 calculation of the benzylidene derivative **16** showed all stereochemistry of **2c** as described in Scheme 3.



Thus, an asymmetric synthesis of ABC ring system of 8-demethyltaxoids was accomplished *via* successive intramolecular aldol and pinacol coupling reactions from optically active 8-membered ring compound **3**.

Further studies on the synthesis of intermediate **1** from the ABC ring system **2c** and completion of the asymmetric synthesis of taxol are now in progress.

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References and Notes

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8 **2c** (100%ee); $[\alpha]_D^{28}$ +31.1° (c 0.793, benzene).