Total Asymmetric Synthesis of Taxol by Dehydration Condensation between 7-TES Baccatin III and Protected *N*-Benzoylphenylisoserines Prepared by Enantioselective Aldol Reaction

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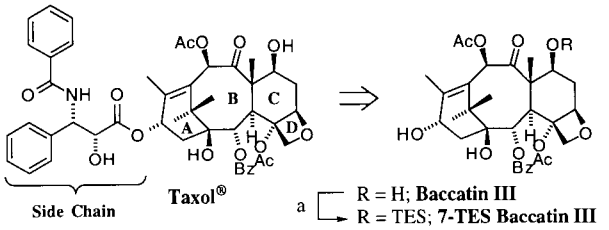
Total asymmetric synthesis of Taxol was completed by dehydration condensation between a protected *N*-benzoylphenylisoserine **4** or **9** and 7-TES baccatin III which was prepared from 8-membered ring enone. Taxol side chains **4**, **7**, **9** and **11**, optically active protected *N*-benzoylphenylisoserines, were successfully synthesized by enantioselective aldol reaction from two achiral starting materials, benzaldehyde and an enol silyl ether derived from *S*-ethyl benzyloxyethanethioate.

In the preceding communication,[1] an asymmetric synthesis of baccatin III *via* the B to BC to ABC to ABCD route was described. In order to complete total synthesis of Taxol, the following two synthetic procedures were investigated: namely, i) asymmetric synthesis of a side chain, a protected *N*-benzoylphenylisoserine, and ii) synthesis of Taxol by dehydration condensation between the side chain and 7-TES baccatin III.

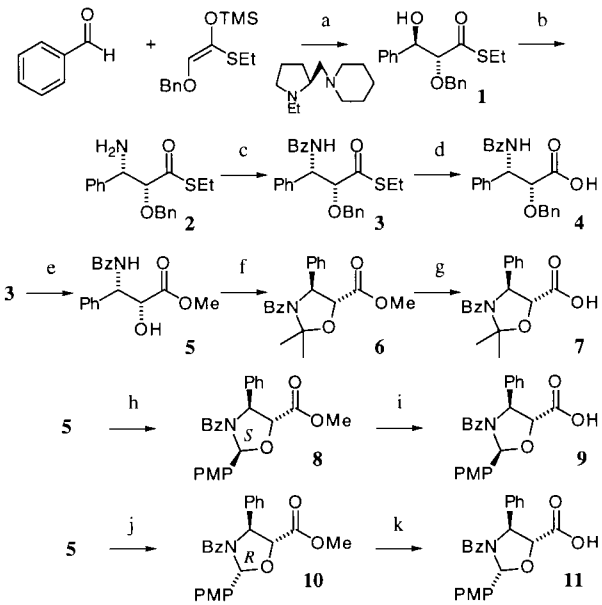


a) TESCl, Py, rt (92% based on 95% conversion)

Scheme 1.

Although several methods for the synthesis of side chains of Taxol were developed in the past decades,[2,10] only a few examples were reported concerning enantioselective synthesis. In this communication, we would like to describe the synthesis of side chain of Taxol, a protected *N*-benzoylphenylisoserine, by enantioselective aldol reaction as a key step from two achiral starting materials. Further, an effective method for the synthesis of Taxol by dehydration condensation of the side chain with 7-TES baccatin III is described.

In the first place, *S*-ethyl (2*R*,3*R*)-2-benzyloxy-3-hydroxy-3-phenylpropanethioate (**1**) was synthesized in high yield with almost perfect stereoselectivity (anti / syn = >99 / 1, 96% ee) by the enantioselective aldol reaction previously reported from our laboratory; that is, the reaction of benzaldehyde with an enol silyl ether prepared from *S*-ethyl benzyloxyethanethioate using a chiral promoter consisting of a chiral diamine, $Sn(OTf)_2$ and $^nBu_2Sn(OAc)_2$.[3] Thus formed aldol product **1** was converted to a C3-inverted azide by Mitsunobu reaction employing hydrogen azide, Ph_3P and DEAD. It was subsequently reduced to amine **2** with Ph_3P according to the method reported by Hanaoka *et al.*[4] Benzoylation of the resulting amine **2** with benzoyl chloride and DMAP gave the desired amide **3** in good yield. (2*R*,3*S*)-3-Benzoylamino-2-benzyloxy-3-phenylpropionic acid (**4**), one of the protected side chains of Taxol, was obtained by hydrolysis of the thiol ester with aqueous silver nitrate. The corresponding *N,O*-acetonide **6** was prepared by successive reactions of debenzylation of **3** with stoichiometric amount of $SnCl_4$ and transesterification with MeOH and $AgOCOCF_3$, followed by treatment of the resulting alcohol **5** with 2-methoxypropene and PPTS. Similarly, 4-methoxybenzylidene *N,O*-acetal **8** was formed by treating **5** with 4-methoxybenzaldehyde dimethyl acetal and CSA. 4-Methoxybenzylidene *N,O*-acetal **10**, the epimer of **8** at the *N,O*-acetal carbon, was obtained by treating **5** with 4-methoxybenzyl methyl ether and DDQ according to a method reported by Greene *et al.*[5] These esters afforded the corresponding carboxylic acids **7**, **9** and **11** in good yields on hydrolysis with aqueous LiOH.



a) $Sn(OTf)_2$, *n*-$Bu_2Sn(OAc)_2$, CH_2Cl_2, -78 °C (96%, 96% ee); b) HN_3, Ph_3P, DEAD, benzene, rt (78%); PPh_3, H_2O, THF, 55 °C (90% based on 82% conversion); c) BzCl, DMAP, CH_2Cl_2, 0 °C (90%); d) $AgNO_3$, H_2O, 1,4-dioxane, reflux (78%); e) $SnCl_4$, CH_2Cl_2, reflux (96%); $AgOCOCF_3$, MeOH, rt (84%); f) $CH_2C(OMe)Me$, PPTS, toluene, 85 °C (89%); g) LiOH, H_2O, MeOH, rt (86%); h) $PMPCH(OMe)_2$, CSA, toluene, azeotrope (79%); i) LiOH, H_2O, MeOH, rt (73%); j) PMBOMe, DDQ, CH_3CN, 60 °C, (69%); k) LiOH, H_2O, MeOH, rt (52%);

Scheme 2.

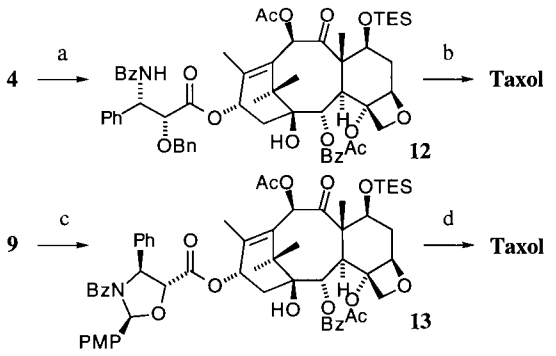
Concerning the preparation of Taxol by introducing side chains to 7-*O*-protected baccatin III, so-called β-lactam method[6] is the most popular and has been utilized in all the reported total syntheses of Taxol.[7] Further, methods for dehydration condensation between carboxylic acids and baccatin III

derivatives were developed by Greene *et al.*[8,5] or by Commerçon *et al.*[9] using DPC (di(2-pyridyl) carbonate) and DMAP or using DCC and DMAP. Recently, Gennari *et al.* reported a transesterification method for the semi-synthesis of Taxol using thiol esters of the side chain.[10] Since both the β-lactam method and the transesterification method were carried out under strongly basic conditions, new method for the direct condensation reaction was studied between 7-TES baccatin III and the side chain as its free carboxylic acid form under rather mild conditions.

Esterification of 3-phenylpropionic acid with cyclohexanol using DPC and DMAP was studied as a model experiment according to a procedure reported by Kim *et al.*,[11] which was later applied to the preparation of protected Taxol *via* condensation between a side chain and baccatin III derivative by Greene *et al.*[8] The corresponding ester was obtained in 74% yield by using DPC as a dehydration reagent while the desired ester was formed in 83% yield when DPTC (di(2-pyridyl) thionocarbonate),[12] a sulfur analog of DPC, was used as a novel coupling reagent. In the second place, dehydration condensation between the side chains and cyclohexanol was studied and, in the presence of DPTC and DMAP, side chains **4**, **7** and **9** reacted smoothly with cyclohexanol to afford the corresponding esters in quantitative yields. On the other hand, the esterification of cyclohexanol with side chain **11** gave the coupling product in moderate yield (53%).

On the basis of these results, dehydration condensation between the side chains and 7-TES baccatin III was tried by using a combination of DPTC and DMAP. 7-TES Baccatin III was synthesized in good yield by monosilylation of baccatin III as shown in Scheme 1. When **4** was used in the above condensation reaction, the corresponding ester **12** was obtained in quantitative yield based on 34% conversion after 2 h at 73 °C in toluene. Further reaction did not proceed even when extra amounts of the side chain **4**, DPTC and DMAP were added to the resulted reaction mixture. However, the rest of 7-TES baccatin III was completely recovered by filtration of the reaction mixture through silica gel chromatography. This suggested that a by-product formed during the above condensation reaction was easily decomposed to 7-TES baccatin III on silica gel. The desired ester **12** was formed by adding the side chain **4**, DPTC and DMAP to the recovered reaction mixture after filtration through silica gel and the overall yield increased by repeating the above procedure. Finally, the condensation product **12** was formed in quantitative yield based on 66% conversion after repeating the above procedure four times. The condensation product **12** was successfully transformed to Taxol after debenzylation using palladium hydroxide on carbon under hydrogen atmosphere and desilylation with HF·pyridine or hydrochloric acid in ethanol (Scheme 3).

In order to increase the reactivity of the side chain, the effect of protecting groups was next examined. Side chains protected as *N,O*-cyclic acetal seemed to be more reactive because of their less hindered structure. In fact, the esterification reaction of side chain **7** with 7-TES baccatin III gave the corresponding ester in quantitative yield at 63% conversion by one operation although the isopropylidene protecting group of the product resisted being deprotected. Condensation reaction between side chain **9** and 7-TES baccatin III also proceeded smoothly to produce the desired coupling product **13** in 95%



a) 7-TES baccatin III, DPTC, DMAP, toluene, 73 °C (100% based on 66% conversion after 4 times operation); b) $Pd(OH)_2/C$, H_2, EtOH, rt (76%); HF·pyridine, THF, rt (100%) or 5% HCl, EtOH, rt (100%); c) 7-TES baccatin III, DPTC, DMAP, toluene, 73 °C (95% based on 93% conversion); d) TFA, H_2O, 0 °C (100%)

Scheme 3.

yield at 93% conversion and, on hydrolysis under acidic conditions, cleavage of the 4-methoxybenzylidene protecting group took place. It is interesting to note that side chain **9** gave the condensation product **13** in high yield while the reaction did not take place when the epimer **11** was used.

Thus, a new method for the synthesis of side chains of Taxol by asymmetric aldol reaction was established. Further, the total synthesis of Taxol was completed by dehydration condensation reaction between the above side chain (**4** or **9**) and 7-TES baccatin III derived from optically active 8-membered ring enone, corresponding to B ring of Taxol. This synthetic method would widely be applicable to the syntheses of derivatives of Taxol and various related taxoids.

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