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Application of Yeast-Catalyzed Reductions to Synthesis of (2*R*,3*S*)-Phenylisoserine

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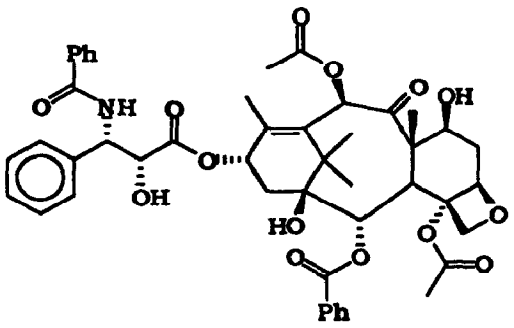
Abstract: A simple synthesis of (2R,3S)-phenylisoserine, a precursor of the C-13 side chain of Taxol®(paclitaxel), utilising yeast-catalyzed reduction to generate a second chiral centre is reported. This short enantioselective series of transformations can be readily adapted to large scale production of a variety of N-substituted paclitaxel analogues.

In the course of our work on yeast-catalyzed reductions of α-keto esters we were able to produce chiral α-hydroxy esters with a high degree of enantiomeric purity. Recognizing the potential of these transformations, we began to apply yeast-catalyzed reductions to the synthesis of compounds with several contiguous chiral centres. One such target molecule is (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine, the C-13 ester side chain of paclitaxel **1**, a compound possessing significant antitumor activity.[2]



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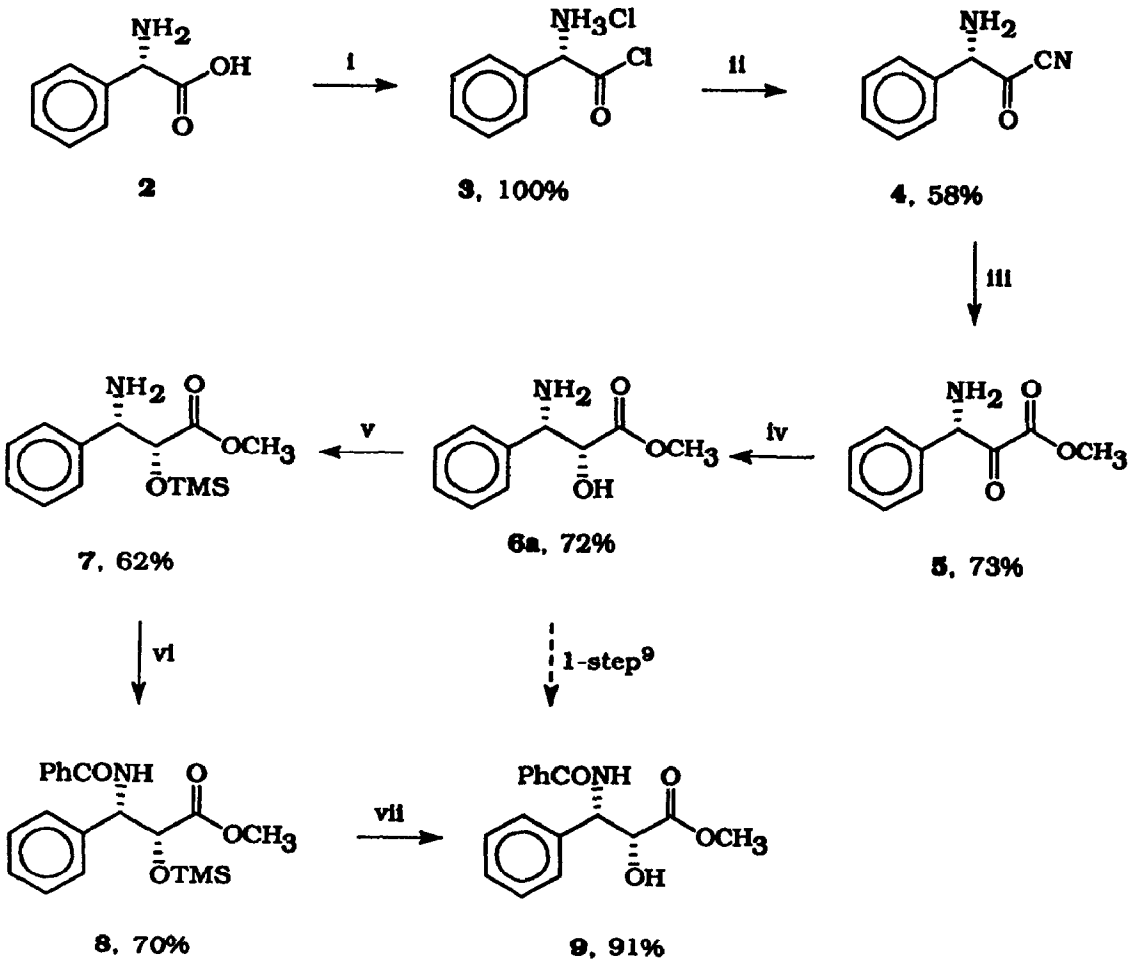
Paclitaxel is a naturally occurring diterpene isolated in minute amounts from the bark of the Pacific yew tree, *Taxus brevifolia*.[3] In view of promising results in cancer treatment, a demand for large quantities of Taxol® is anticipated in the near future.[2,4] The most favourable solution to the supply problem is a semi-synthetic approach involving the synthesis and attachment of (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine to baccatin III obtained from the leaves of readily available *Taxus* species.[5] Several syntheses of chirally pure phenylisoserine are known and a number of procedures for grafting the side chain onto baccatin III have been reported in recent years.[2e,6] Although all approaches produce the side chain of correct stereochemistry in reasonable yields, most are unsuitable for large scale production.

In view of the demand for large quantities of phenylisoserine, we attempted to design a synthesis adaptable to large scale production. Our previous work with α-keto esters has shown that we can generate *R* alcohols with high enantioselectivity in reasonable yields and we felt that this methodology can be used for the production of the paclitaxel side chain. The goal was to employ available and inexpensive reagents and to minimize the number of separation and purification steps. With this in mind we chose natural (2*S*)-phenylglycine as a staring point for the synthesis. The reaction sequence is illustrated in Figure 1.



i. $SOCl_2/Et_2O$, -10°; ii. NaCN, Li_2CO_3/THF; iii. HCl/MeOH; iv. Baker's yeast; v. TMSCl/pyridine; vi. BzCl, K_2CO_3/MeOH,H_2O; vii. KF/H_2O

Although initially we attempted to protect the amino group it turned out that unprotected phenylglycine can be readily converted to phenylglycidylchloride hydrochloride **3** in 100% yield by treatment with thionyl chloride. Several methods for the transformation of the acid chloride to the corresponding nitrile were investigated.[7] The best procedure, which unfortunately gives only a modest yield, involves refluxing **3** with a mixture of potassium cyanide and lithium carbonate in THF for 16 hours. The following step, alcoholysis of the nitrile, is carried out by reacting **4** with methanol in the presence of dry HCl. Although some steps give modest yields, all the reactions thus far are inexpensive and easy to carry out. Furthermore, the only purification required is upon isolation of methyl 3-amino-2-keto-3-phenylpropionate **5** prior to the reduction by yeast and this can be accomplished readily by recrystallization of the hydrochloride salt from dichloromethane.

The following yeast-mediated reduction proceeds smoothly. With the amine (*3S*)-**5** as the substrate, methyl (*2R,3S*)-phenylisoserine **6** is obtained in 72% yield. The crude extraction product contains only a single observable diastereomer as shown by 250 MHz ^{1}H NMR, some ethyl alcohol and a small quantity of contaminating yellow material, which can be readily removed by rapid chromatography over a short column of silica gel. It should be pointed out that the corresponding reduction using sodium borohydride followed by the usual workup produces a diasteromeric mixture of the alcohols (*2S,3S*)-**6** and (*2R,3S*)-**6** in a ratio of 79:21 and 97% total yield.

Although the most recent methods of attaching the side-chain to baccatin are carried out without the benzoyl group,[8] **6** was converted to the paclitaxel side chain in order to allow comparison with data from the literature. This was accomplished by protecting the alcohol with trimethylsilyl chloride, then adding the benzoyl group in the form of benzoyl chloride and removing the protecting group with aqueous fluoride ion. This 3-step sequence can be reduced to a single step by utilising the Schotten-Baumann reaction as decribed by Georg and coworkers.[9]

The isomeric product (*2R,3R*)-**6** was prepared through the same sequence of reactions starting with (*2R*)-phenylglycine. The yield from the yeast-catalyzed reduction of (*3R*)-**5** was slightly diminished (58%) compared to the reduction of (*3S*)-**5** (72%); the isolated product, however, was diastereomerically pure.

In conclusion, the outlined procedure leads to the formation of essentially enantiomerically pure methyl (*2R,3S*)-phenylisoserine in four steps. Although many elegant syntheses of a chirally pure paclitaxel side chain exist, our synthesis is shorter than most reported procedures.[2,6] It is particularly efficient and uses only common, inexpensive reagents and simple purification steps. Furthermore, it is readily adaptable to large scale preparation. The methodology described also gives access to the (*2R,3R*) isomer in good yield. The enantioselective synthesis of the remaining two isomers of phenylisoserine is under investigation.

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