An Efficient Synthesis of Taxotere Side Chain

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Abstract: An efficient synthesis of taxotere side chain has been achieved using Shibasaki's asymmetric Henry reaction as the key step.

Keywords: Taxol, Taxotere side chain, Anticancer agents, Asymmetric synthesis, Asymmetric Henry reaction, La-(*R*)-BINOL.

The celebrity molecule Taxol **1** (Fig. **1**) was isolated [1] in limited quantity from the bark of Pacific yew tree *Taxus bravifolia* and was the most significant discovery ever made in the field of naturally occurring anticancer agents. It has severe water solubility problem for effective drug delivery and therefore requires elaborate secondary treatment. Moreover, the production of taxol from the slow growing yew trees leads to problems of environmental consideration as well as debatibility on the abundance of yew trees. To overcome these problems associated with taxol to be used as a drug; intensive search for suitable taxol analogue has already been initiated. In recent years, more emphasis is being given on the production of 10-DAB III, from which a wide range of semisynthetic taxol analogues such as taxotere **2** can be made. A viable approach for the production of taxotere from simpler 10-DAB III, **3**, by fixing a synthetic 3-phenylisoserine derived side chain has been reported [2].

A number of synthetic approaches for the synthesis of the taxotere side chain are reported in the literature [3]. However, these syntheses involved several steps and also low overall yield. We have long been engaged in the synthesis of bioactive natural products involving nitro aliphatics [4]. In this context and also with our previous experience in the synthesis of taxol side chain [5], we report herein a very short synthesis of the Taxotere side chain starting from phenyl nitromethane in high enantiomeric purity.

Our approach toward the synthesis of taxotere side chain **4** is depicted in Scheme **1**. It is based on the reduction of the nitro alcohol **5**, the synthesis of which is anticipated by Shibasaki's asymmetric Henry reaction of phenyl nitromethane and ethyl glyoxalate.

Accordingly, the synthesis of taxotere side chain commenced with the Shibasaki's asymmetric Henry reaction

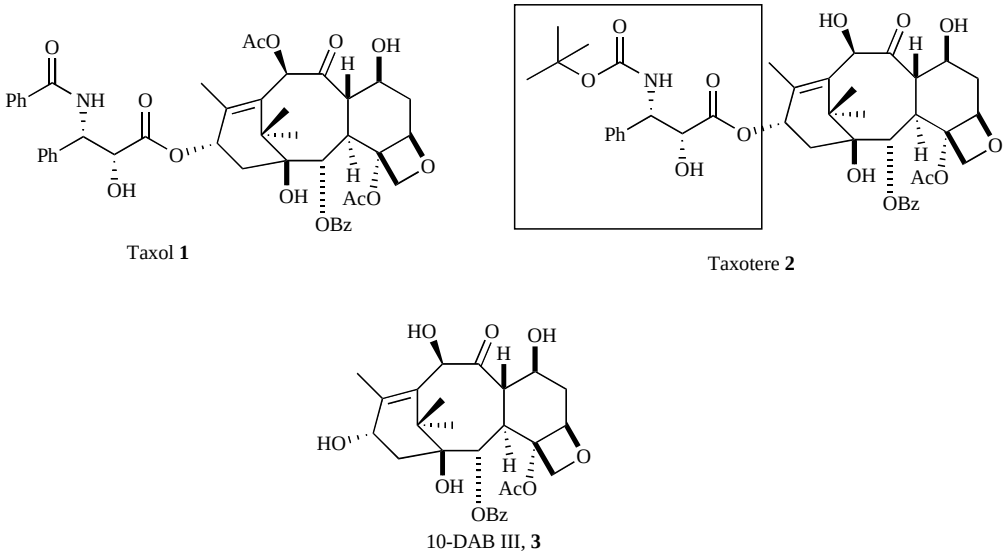

Fig. (1). Structure of Taxol, Taxotere and 10-DAB III.

[6] of Phenyl nitromethane [7] with ethyl glyoxalate in the presence of La-(*R*)-BINOL catalyst at -50 °C in THF to furnish the key intermediate **5** with satisfactory diastereoselectivity (dr = 13:1; syn: anti) in 72% yield and

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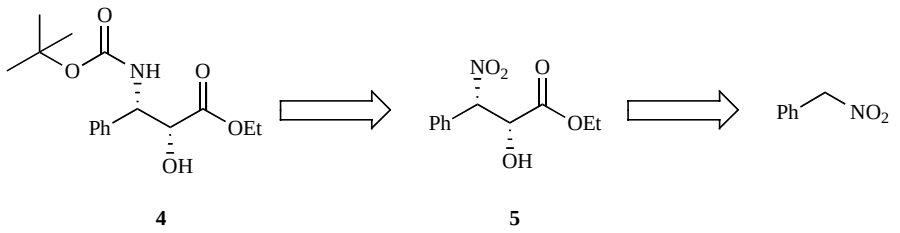
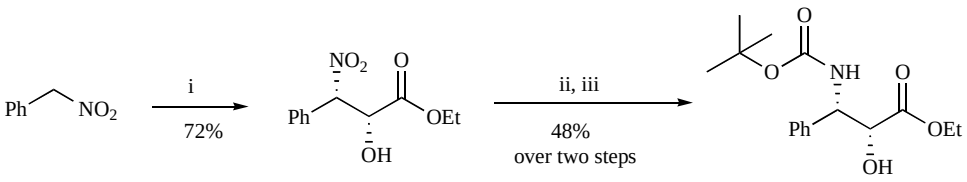


4 **5**

Scheme 1. Retrosynthesis for the synthesis of taxotere side chain.



5 **4**

Scheme 2. Reagents and conditions (i) ethyl glyoxalate, La-(*R*)-BINOL (10 mol%), THF, -50 ^{o}C, 60 h; (ii) H_2/Pd-C, MeOH, rt; (iii) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt.

81% ee [8] (Scheme **2**). Catalytic hydrogenation of the nitro group in **5** followed by protection of the amino group with Et_3N and $(Boc)_2O$ afforded the taxotere side chain in 48 % yield over two steps (89% ee).

In conclusion, we have achieved a very short synthesis of taxotere side chain in 34% overall yield starting from phenyl nitromethane. We have performed this synthesis up to 1 gram level and hence this strategy is adaptable to gram scale synthesis of taxotere side chain (34% yield, 89% ee). The synthesis features an exception to the most other chiral auxillary based approaches to taxotere side chain, reaffirming the versatility of nitro aliphatics.

SPECTRAL DATA OF SELECTED COMPOUNDS

Compound 4

m.p 61-64 ^{o}C $[\alpha]_D^{20}$ = +1.1 (c = 1.0, $CHCl_3$). IR ($CHCl_3$): ν = 3469, 1737, 1558 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53-7.36 (m, 5H), 5.75-5.73 (d, 1H, J = 5.7 Hz), 4.84 (t, 1H, J = 6.3 Hz), 4.23-4.14 (nm 2H), 1.12 (t, 3H, J =6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 131.0, 130.4, 129.5, 128.3, 92.0, 72.6, 63.1, 14.1. MS (ESI): m/z = 239.1 (M^+).

Compound 5

m.p 118-120 ^{o}C. $[\alpha]_D^{20}$ = +6.4 (c = 0.9, $CHCl_3$). IR ($CHCl_3$): ν = 3441, 2979, 1719 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.26 (m, 5H), 5.43-5.40 (d, 1H, J = 9.3), 5.25-5.22 (d, 1H, J = 9.6), 4.46 (bs, 1H), 4.38-4.24 (m, 2H), 3.18 (bs, 1H), 1.41 (s, 9H), 1.35-1.3 (t, 3H, J = 16.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 155.1, 139.2, 128.5, 127.6, 126.7, 79.8, 73.6, 62.5, 55.9, 28.2, 14.1. MS (ESI): m/z = 332.1 (M^++Na).

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[8] The enantiomeric excess (ee) was measured by HPLC analysis carried out using a Waters 510 HPLC system. The HPLC conditions used for analysis were: Chiracel OD column, flow rate 0.8 mL/min, hexane/isopropanol 90 : 10, retention times (2R, 3S) 7.38 min (major isomer), (2S, 3S) 6.61 min (minor isomer).