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First and Stereoflexible Synthesis of Vinylogous Taxol Side Chains

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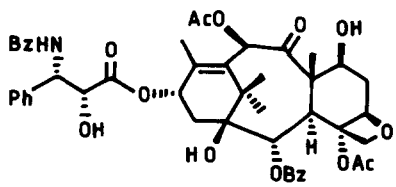
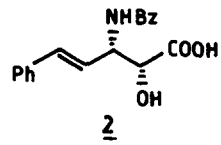
Abstract : First and stereoflexible synthesis of two vinylogous side chains of Taxol from readily available L-arabinose and methyl 3-phenylglycidate as starting materials is described.

Taxol **1**, the most promising anticancer compound especially for breast and ovarian cancers,[1] has been the initial target for synthetic organic chemistry groups.[2] However the poor water solubility of this natural product has engendered more activity in medicinal chemistry laboratories to prepare and study various analogues to address the solubility problem.[3] Thus Taxol derivatives, especially possessing an intact ABC skeleton but carrying simplified and altered side chains at C-13 (Taxol numbering) have been prepared and analysed for SAR studies.[4] The most promising of these has been the N-Boc derivative (Taxotere®[5]) instead of N-Bz (Paclitaxel) as present in the natural product.



1 Taxol



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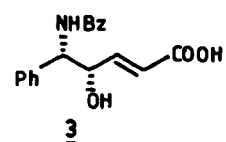

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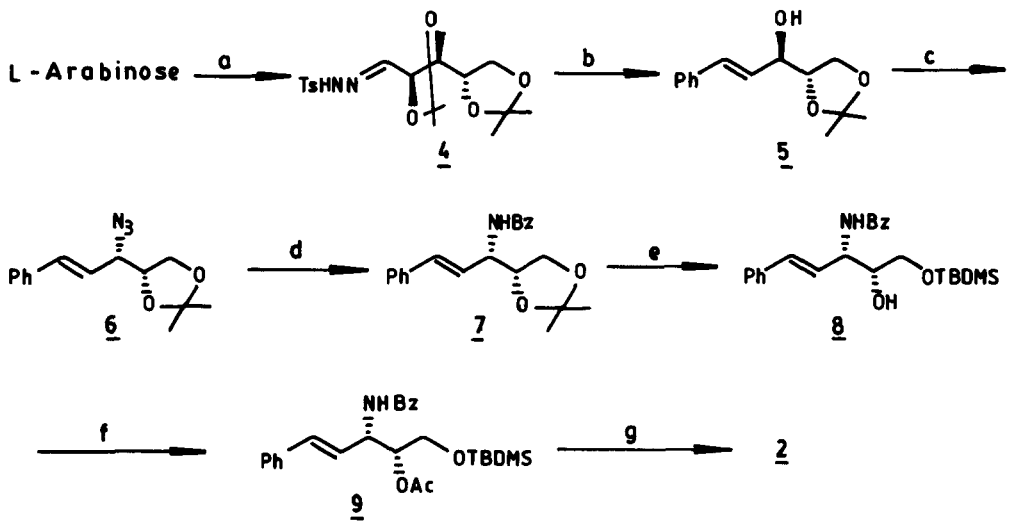
Despite innumerable alterations made to various parts of side chain,[6] it is most surprising to note that, no attempts have been directed to date to synthesize any of the possible vinylogous side chains for this

important molecule. It is well documented in literature that the peptides when incorporated with vinylogous amino acids behave differently in secondary and tertiary structures.[7] To address the issue of preparing vinylogous side chains in a stereodefined manner, herein, we report for the first time the synthesis of 3′ and 1′ vinylogous Taxol side chains **2** and **3** from L-arabinose (involving the recently discovered alkylative fragmentation of the corresponding tosyl hydrazone[8]) and methyl 3-phenylglycidate[9] as starting materials respectively.

The commercially available L-arabinose was converted to the requisite tosyl hydrazone **4** in a standardized four step protocol. Exposure of this hydrazone to PhMgBr in tetrahydrofuran furnished the allyl alcohol **5** in abundant yield (**Scheme 1**). The alcohol was converted to azide with inversion of configuration

Scheme-1



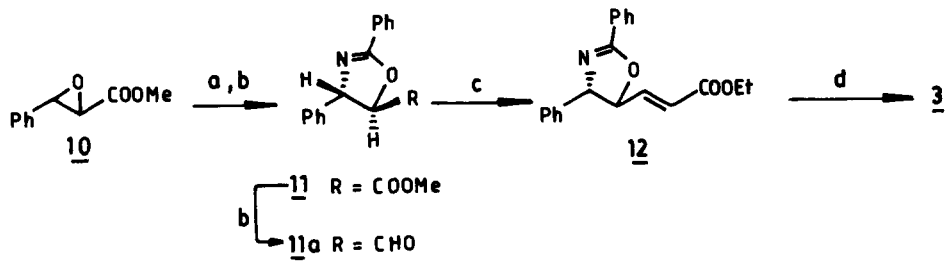
Reagents and Conditions : a) i. EtSH, conc.HCl, 0°C, 6 hr.; ii. Acetone, $CuSO_4$, H_2SO_4 (Cat); iii. $HgCl_2$-HgO, Acetone-H_2O, reflux, 2 hr.; iv. H_2NNHTs, MeOH, RT, 4 hr.; b) PhMgBr (3eq), THF, 15°C, 3 hr.; c) TPP, DEAD, DPPA, THF, -10°C, 3 hr. d) TPP, THF-H_2O, reflux, 2 hr, then at 0°C BzCl, aq. NaOH, 1 hr. e) i. 3N HCl, THF, 2 hr.,RT; ii. TBDMSCl, imidazole, CH_2Cl_2, 0°C, 2 hr.; f) Ac_2O, TEA, DMAP (Cat), CH_2Cl_2, 0°C, 30 min.; g) i. Jone's oxidation ; ii.K_2CO_3, MeOH-H_2O, RT.

under Mitsunobou conditions[10] (DEAD, TPP,DPPA, THF). The resultant azido compound **6** was reduced and derivatized as benzamide (as present in Paclitaxel) in one-pot. For this, azide **6** was reduced to amine using Ph_3P/H_2O condition,[11] which was *in situ* benzoylated (BzCl, aq NaOH) to furnish N-benzoyl derivative **7**. The routine manipulations *viz*, acetonide cleavage (3N HCl in THF) followed by primary O-silylation

(TBDMSCl, imidazole CH_2Cl_2) yielded the silyloxy derivative **8**. Acetylation of the free 2° alcohol for operational simplicity (Ac_2O, Pyridine, DMAP, CH_2Cl_2) and Jone's oxidation[12] of the 1°-silyl ether in **9** produced the required carboxylic acid which on stirring with K_2CO_3 in methanol, uneventfully generated the first 3' vinylogous Taxol side chain **2**, $[\alpha]_D^{28} = 2.4°$ (c 1.1, $CHCl_3$).

Following a more straight forward strategy, the other vinylog of the Taxol side chain *viz*, 1' vinylog is synthesised (**Scheme 2**). The readily available methyl 3-phenylglycidate **10** was converted to the known (+) (4S,5R)-2,4-diphenyl-5-(methoxycarbonyl)-2-oxazoline **11** by a modified procedure.[9b] Careful DIBAL-H reduction of **11** furnished aldehyde **11a** which was immediately homologated using carboethoxy-methylenetriphenylphosphorane to furnish the required intermediate **12** which upon oxazoline ring opening and hydrolysis of ester generated the 1' vinylog of the Taxol side chain **3** in overall 87% yield, $[\alpha]_D^{26} = -10.1°$ (c 1.1, MeOH).

Scheme - 2



Reagents and Conditions : a) Ref. 9; b) DIBAL-H, CH_2Cl_2, - 78°C, 30 min.; c) $Ph_3P{=}CHCO_2Et$, benzene, RT, 12 hr d)i. 1N HCl, EtOH, reflux, 2 hr; ii. K_2CO_3, MeOH-H_2O, RT.

In summary, we have demonstrated for the first time, the synthesis of vinylogous side chains of Taxol in a most practical and efficient manner. These two vinylogous derivatives on dihydroxylation or aminohydroxylation in principle will furnish more hydrophilic derivatives which inturn may act as powerful chemotherapeutic agents. Efforts in this direction are currently underway.[13]

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