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A New Entry to the Stereocontrolled Synthesis of CD Rings of Taxol

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Abstract : Stereocontrolled synthesis of the highly functionalized CD subunit of Taxol utilizing Diels-Alder reaction, Baeyer-Villiger oxidation of bridged keto system, stereodirected hydroboration using thexylborane and stereoselective Sharpless allylic hydroxylation as the key steps is described.
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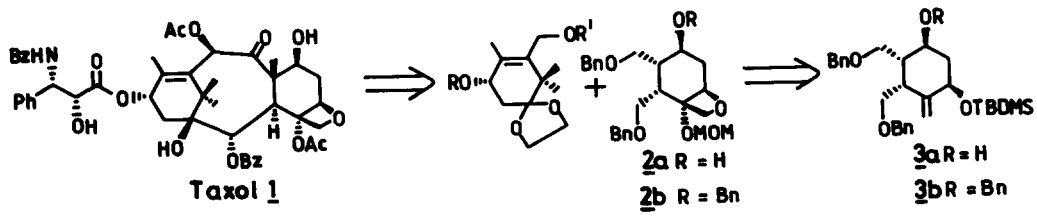
Paclitaxel (Taxol[1]), isolated from the bark[2] of Western yew *Taxus brevifolia*, has become one of the most promising cancer chemotherapeutic agents and has recently been approved for the treatment of cisplatin refractory advanced ovarian cancer and metastatic breast cancer.[3] It is also undergoing clinical trials in nonsmall cell lung cancer (nsclc), head and neck cancer, glioblastoma and oesophageal cancer. Not only due to its antileukemic and tumor-inhibiting activity but also owing to its intricate molecular structure, paclitaxel has become one of the most attractive targets for total synthesis[4] in recent years.

In continuation of our programme on Taxol and its analogues,[5] we report herein an elegant stereocontrolled synthesis of the CD subunit of Taxol.[5c,6] A careful retrosynthetic analysis of Taxol **1** (**Scheme 1**) unravels the CD substructure **2** as the crucial intermediate which can be easily traced from the retron **3**.

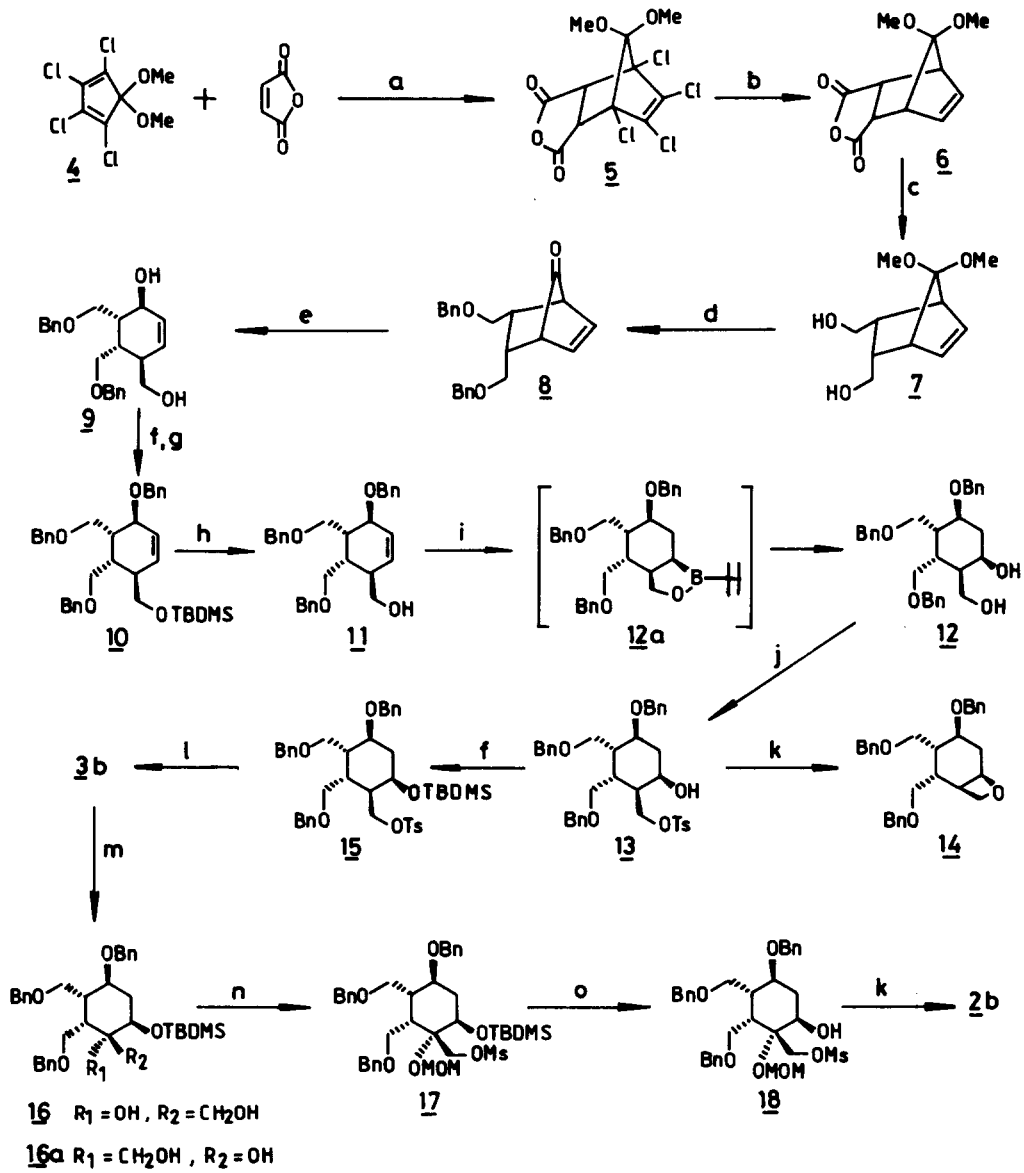
Scheme - 1



The Diels-Alder reaction between maleic anhydride and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene **4**, easily obtained from commerically available hexachlorocyclopentadiene,[7] quantitatively formed the cycloadduct

5. This under sodium-ethanol treatment in liquid ammonia gave dechlorinated product **6** which was reduced with LAH to furnish diol **7** (**Scheme 2**). The crude diol was dibenzylated followed by deketalization to generate

Scheme - 2

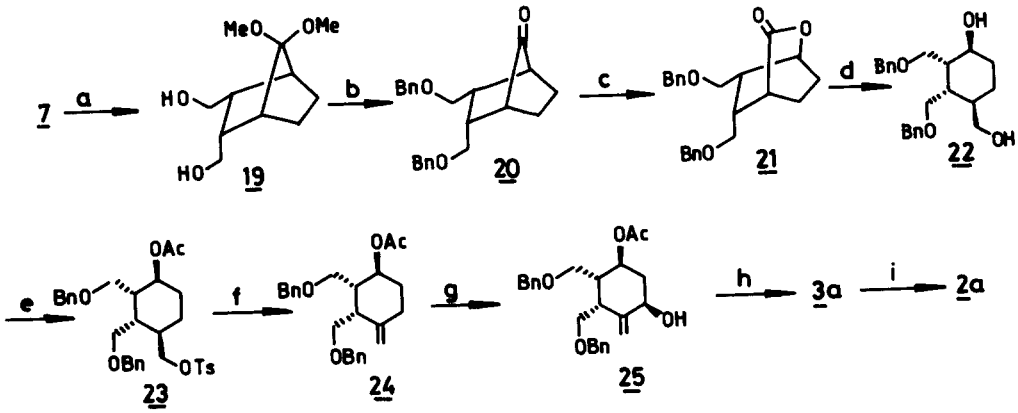


Reagents and Conditions : a) xylene, reflux, 2hr; b) Na, THF-EtOH, liq NH_3; c) LAH, THF, rt; d) i) NaH, THF, BnBr, $^nBu_4NI$ (cat); ii) PTSA, acetone, rt; e) i) H_2O_2, NaOH, MeOH-H_2O (9:1); ii) LAH, THF, 0°C; f) TBDMSCl, imidazole, DCM, 0°C, 1hr; g) NaH, THF, BnBr, $^nBu_4NI$ (cat); h) 3N HCl, THF, rt; i) thexylborane, THF; j) TsCl, Py, DMAP, DCM, 0°C; k) NaH, ether, reflux; l) i) NaI, acetone, reflux 6hr; ii) DBU, benzene, reflux; m) OsO_4 (cat), NMO, acetone-H_2O (9:1); n) i) MsCl,Et_3N, DCM, ii) MOMCl, DIPEA, DCM; o) TBAF, THF, rt, 3hr.

the bridged keto compound **8**. The bridged keto system was subjected to Baeyer-Villiger oxidation[8] with alkaline hydrogen peroxide in methanol followed by LAH reduction to give diol **9**. Primary and secondary alcohols were protected as silyl ether and benzyl ether respectively. After desilylation compound **11** was subjected to hydroboration using thexylborane in THF. The secondary hydroxyl group in compound **12** was introduced in a stereo and regiocontrolled manner due to the formation of intermediate borane chelate **12a**. The position and relative stereochemistry of diol **12** was confirmed by making oxetane ring **14**. For this primary hydroxyl group was tosylated to get compound **13** which on treatment with NaH in THF generated oxetane **14**. The 2° hydroxyl group in compound **13** was protected as the silyl ether **15**. The tosyl group was converted to iodo followed by DBU treatment in refluxing benzene generated the crucial intermediate **3b**. The exocyclic olefin was dihydroxylated to give two regioisomers in 4:1 ratio. The major compound **16** under mesylation of 1° alcohol followed by MOM protection of 3° alcohol generated compound **17** which on desilylation and cyclization produced the highly functionalized CD ring derivative of paclitaxel.

On the other hand compound **7** was converted to saturated diol **19** under hydrogenation conditions (**Scheme 3**). Dibenzylation and deketalization generated bridged keto unit **20** which was oxidized to bridged lactone **21**

Scheme-3



Reagents and Conditions: a) H_2,Pd-C (10%), EtOAc; b) i) NaH, THF, BnBr, $^nBu_4NI$ (cat) , ii) PTSA, acetone, rt; c) mCPBA, DCM, 0°C, 2hr;d) LAH, THF, 0°C; e) i) TsCl, Py, DCM, 0°C, ii) Ac_2O, DMAP, Et_3N, DCM, 0°C; f) i) NaI, acetone, reflux, 6hr, ii) DBU, benzene, reflux; g) SeO_2 (cat), TBHP, HOAc (cat), hexane, rt, 3hr; h) TBDMSCl, imidazole, DCM, 0°C; i) Ref. 5c.

using mCPBA in dichloromethane. Lactone was reduced with LAH in THF to diol **22**. Tosylation followed by acetylation produced compound **23**, which was converted to the key building block **24** in the usual manner. Exocyclic olefin in **24** to the oxetane ring D was employed using stereoselective Sharpless allylic oxidation[9] as the key step. SeO_2 catalysed allylic oxidation of **24** proceeded smoothly to furnish allyl alcohol **25** which was protected as the silyl ether to produce the key retron **3a**. **3a** was successfully converted to oxetane **2a** by a method reported earlier.[5c]

In summary we have developed a new route for the synthesis of functionalized CD substructure of Taxol in a stereocontrolled manner.[10] Further elaboration towards the total synthesis of Taxol is currently being investigated.

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10. a) All compounds were characterised by spectral data. Selected ^{1}H NMR data of some compounds : (200 MHz, $CDCl_3$) **21** : δ 7.40-7.18 (m,10H); 4.71-4.62(m,1H); 4.46-4.37(m,4H); 3.68-3.32(m,4H); 2.74-2.65(m,1H); 2.65-2.45 (m,2H); 1.90-1.65(m,4H). **24** : δ 7.35-7.25(m,10H); 5.20-5.10(dt,J=4.52,9.04 Hz, 1H); 4.80(s,1H); 4.60 (s,1H); 4.44(s,2H); 4.35(s,2H); 3.65-3.30(m,4H); 2.90 (q,J=6.66,11.12 Hz,1H); 2.35-2.20(m,3H); 2.05(s,3H); 1.85-1.60(m,2H). **16** : δ 7.40-7.12(m,15H); 4.58-4.31(m,6H); 4.05-3.90(m,1H); 3.90-3.28(m,7H); 2.84-2.70(m,1H); 2.66-2.55(m,1H); 2.35-2.28(m,1H); 2.01-1.88(m,1H); 0.85(s,9H); 0.1(s,6H). **2b** : δ 7.4-7.2(m,15H); 5.05-4.90(AB_q,J=7.5 Hz, 2H); 4.88-4.70(m,3H); 4.66-4.42(m,6H); 3.78-3.55(m,5H); 3.40(s,3H); 2.68-2.55(m,2H); 2.35-2.02(m,2H).
    b) IICT communication No. 3891

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