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New Strategy for the Synthesis of the Taxane Diterpenes : Formation of the BC-Rings of Taxol *via* a [5+2]-Pyrylium Ylide-Alkene Cyclization, Ring Expansion Strategy

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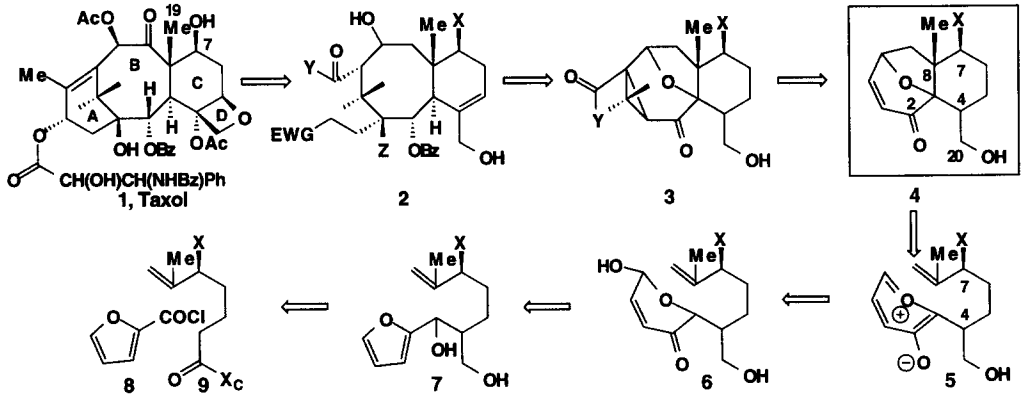
Abstract: The BC-rings of taxol can be synthesized using an intramolecular [5+2]-pyrylium ylide-alkene cyclization, followed by *gem*-methylcyclopropanation and reductive cleavage of the internal cyclopropane bond.

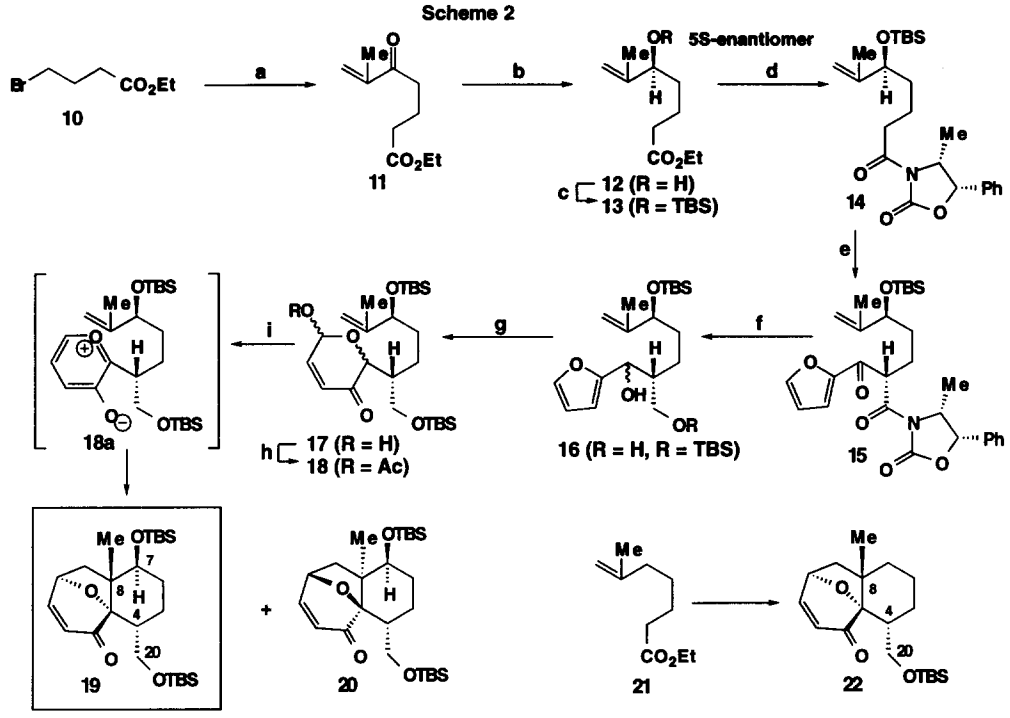
At first sight the synthesis of taxol **1** appears to present some formidable stereochemical problems.[1] Traditionally, quaternary carbon atoms are the most difficult stereogenic centers to install in terpenoid synthesis. Consequently, we considered that the absolute stereochemistry of the C-19 methyl group should be established at an early stage. **Scheme 1** outlines our retrosynthetic analysis.

Scheme 1 (Retrosynthetic Analysis of Taxol)



To implement **Scheme 1** requires Claisen condensation of 2-furoyl chloride **8** with 6-methyl-heptenoate **9** [(Xc is a chiral auxiliary, X = OH or H (7-deoxy series)], followed by reduction to **7**. Oxidative furylcarbinol rearrangement of **7** to **6**, intramolecular pyrylium ylide cyclization[2,3] *via* **5** to **4** and cyclopropanation leads to **3**. Reductive cleavage of the internal cyclopropane bond[4] and alkylation of the C-2 enolate provides the *seco*-ring-A compound **2** (Z = OH or H). Classical Claisen-Dieckmann condensation or more modern methods would complete the A-ring. This letter describes the synthesis of the BC-rings of taxol using this strategy.

Scheme 2



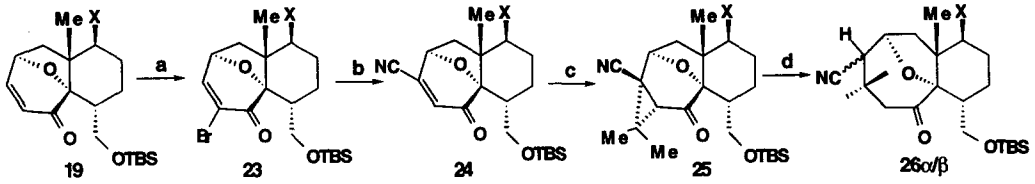
Conditions:-a) *n*-$Bu_4N^+I^-$/Zn dust/TMSCl/1,2-bromoethane/PhMe/*N,N*-dimethylacetamide/85°C/12h, followed by methacryloyl chloride/$Pd(PPh_3)_2Cl_2$/40°C/2h.[5] b) $BH_3.SMe_2$/(*R*)-(-)-diphenyl-2-pyrrolidino methanol oxazaborole (cat)/THF/-20°C/18h, (81%, from **10**). c) TBSCl/Imidazole/DMF/25°C/4h (86%). d) i. NaOH/Me_2CHOH/82°C ii. $(COCl)_2$/PhMe/CH_2Cl_2/DMF (cat)/-10°C to 25°C/12h. iii. LiXc/THF/PhMe/-78°C/4h (99% from **13**). e) $LiN(TMS)_2$/THF/-78°C/2h, followed by 2-furoyl chloride/2h. f) i. $LiBH_4$/MeOH/-20 to 0°C/12h (85%, from **14**). ii. TBSCl/Imidazole/DMF/-18°C/1h (87%). g) $^1O_2$/rose bengal/MeOH/CH_2Cl_2/hv/12h, Me_2S work-up (80%). h) Ac_2O/NEt_3/DMAP/CH_2Cl_2/0°C to 25°C/0.75h (91%). i) DBU/PhMe/110°C/1.5h (77%, **19** and **20**, 10:1).

Scheme 2, outlines the synthesis of the pyrylium-ylide precursor **18** and its cyclization to **19**. Reduction of the enone carbonyl group in **11** with $Me_2S.BH_3$/THF in the presence of a catalytic amount of the chiral reagent (*R*)-(-)-diphenyl-2-pyrrolidino methanol oxazaborole catalyst gave 5*S*-**12** >93%ee (81% from **10**).[6] Treatment of **14** with $LiN(TMS)_2$/THF at -78 °C and quenching the resulting amide enolate with 2-furoyl chloride gave **15**.[7] It proved unnecessary to isolate **15**, which could be reduced *in situ* by the addition of $LiBH_4$/MeOH to give the diol **16** (R = H) (85% from **14**) in a single operation. The chiral auxiliary was recovered (>70%) and recycled. Oxidative rearrangement of **16** (R = TBS) by treatment with singlet oxygen, followed by a reductive work-up gave **17** (80%).[3] Heating **18** in toluene in the presence of DBU gave **19** and **20** (77%, 10:1 respectively). There were other minor components present (<5%) that were clearly diastereoisomers of the major products. The absolute configuration of **19** was confirmed by comparison of the CD/ORD curve with an analog, whose absolute stereochemistry was determined by X-ray crystallography.[8] A similar sequence of transformations allowed us to convert **21** into the 7-deoxy analog **22**. In both cases, the formation of **19** and **22** as the major products,

corresponds to the least strained (MM2) cycloaddition adduct. The C-4 substituent controls the stereochemistry of the C-19 angular methyl group.

Bromination of **19**, and treatment with triethylamine gave the α-bromoenone **23** (100%). Exposure of **23** to an aqueous solution of sodium cyanide under phase transfer conditions gave the β-cyanoenone **24** (96%). Treatment of **24** with isopropylidenetriphenylphosphorane/THF/-78° to 25°C gave **25** (95%) as a single stereoisomer (**Figure 1**, Chem 3D from X-ray coordinates, X = H).[9] Treatment of **25** with sodium naphthalenide/THF/-78°C cleaved the internal cyclopropane bond to generate a dianion, which upon protonation with sat. aq. NH_4Cl gave a mixture of **26**α- and **26**β- (100%, 5:2, for X = H; 95%, 2:1, for X = OTBS).[10]

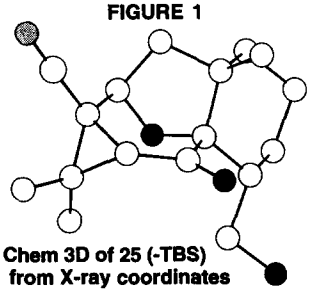
Scheme 3 (X = OTBS or H)



Conditions:-a) $Br_2/Et_3N/CH_2Cl_2$ (100%). b) NaCN/PTC (96%). c) $Me_2C{=}PPh_3$/THF/-78° to 25°C (95%). d) Sodium naphthalenide/THF/-78°C (100%).

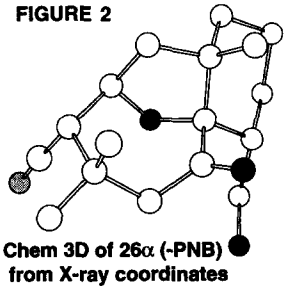
The structure of the derived C-20 *p*-nitrobenzoate of **26**α (X = H) was established by X-ray crystallography (**Figure 2**, Chem 3D from X-ray coordinates). Treatment of the mixture of **26**α and **26**β with MeONa/MeOH resulted in equilibration to give **26**β as the major epimer (*ca.* 10:1).[11]

FIGURE 1



Chem 3D of 25 (-TBS) from X-ray coordinates

FIGURE 2



Chem 3D of 26α (-PNB) from X-ray coordinates

As will be seen in the accompanying paper, both nitrile epimers **26**α/β can be used to construct the A-ring of taxol. This unique strategy for the assembly of the taxol BC-rings with correct absolute stereochemistry is readily amenable to analog variations since the 7-hydroxy, and the 16, 17, and 19 methyl groups can be replaced by other substituents.

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References and footnotes

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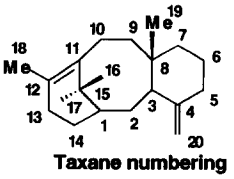
11. All new compounds were purified by chromatography and/or crystallization, and characterized by IR, NMR, MS and HRMS. The numbering system used for the taxanes is as shown.



Taxane numbering

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