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[A0037]

An Asymmetric Synthetic Approach to the A-ring of the Taxol® Family of Anti-Cancer Compounds

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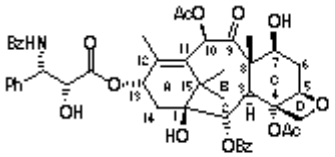
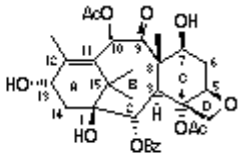
Introduction

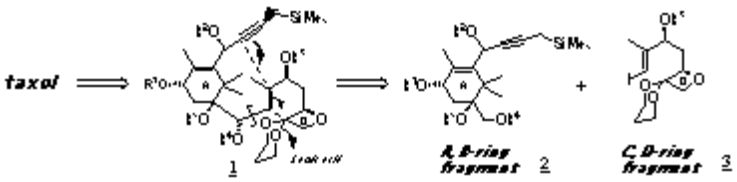
The taxol® family of molecules, exemplified by **taxol®**,[1] and **baccatin III** has commanded the attention of some of the most eminent synthetic organic research teams in the world.[2] This intense interest has been engendered by the unusual tetracyclic structure of this class of compounds, and more importantly, by the use of taxol® in cancer chemotherapy. This outstanding combination of attractive features has stimulated a huge variety of synthetic approaches directed towards the synthesis of taxol® itself, and simpler analogues which may also have desirable anti-cancer properties.





We proposed a versatile strategy for taxol® synthesis in which two major fragments are coupled at a late stage in the synthetic sequence (**Scheme 1**). Our approach is unique in that the C-3-C-4 and C-8-C-9 bonds are formed from a cyclisation precursor containing an intact D-ring. The inception of this approach is based on previously developed Diels-Alder chemistry within the Craig group,[3] especially in the context of tethered intramolecular (IMDA) cycloadditions,[4] and on the studies of cation-mediated intramolecular C-glycosidation processes.[5] Thus, the B- and C-rings are closed in a single step on the coupled product **1** *via* cation-mediated cascade cyclisation. This precursor **1** is obtained by coupling the A,B-ring (**2**) and the C,D-ring (**3**) fragments.

Scheme 1

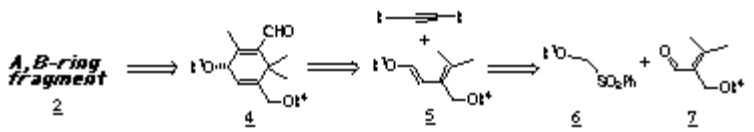


Results and Discussion

In this paper we report the synthetic route developed for the preparation of the A,B-ring fragment **2**. The retrosynthetic analysis we proposed for this fragment is shown in **Scheme 2**. The side chain on C-11 of fragment **2** would be introduced by a nucleophilic addition to an aldehyde moiety existing on this carbon in the cyclohexane **4**. This intermediate would be the result of a Diels-Alder reaction between the diene **5** and

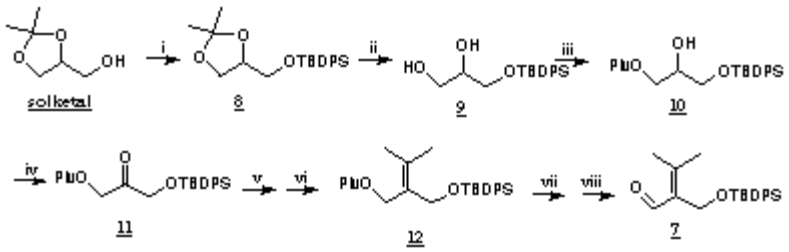
a suitable dienophile. In order to accomplish an asymmetric approach to the A,B-ring fragment we propose to prepare asymmetric dienes and make the first attempts at Diels-Alder reactions with relatively simple dienophiles. These asymmetric dienes **5** would be available by a Julia olefination reaction between the asymmetric sulfones **6** and the aldehyde **7**.

Scheme 2



Therefore, the synthesis begins with the preparation of the aldehyde **7** from the commercially available solketal (**Scheme 3**). Protection of the hydroxyl group of solketal as a TBDPS derivative, followed by deprotection of the diol and subsequent protection of the primary alcohol gave the compound **10**, which was then oxidized to the ketone **11**. Nucleophilic addition of $Me_2C(SeMe)Li$[6] to the carbonyl group of the ketone **11** followed by reductive elimination of the resulting adduct gave the isopropenyl moiety of **12**. Then, reduction of the ester and subsequent oxidation of the alcohol to the corresponding aldehyde gave the desired aldehyde **7**.

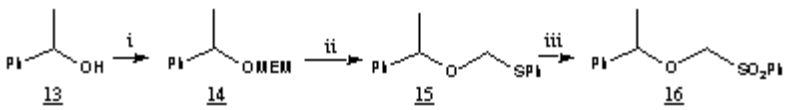
Scheme 3



Reagents and conditions: i) TBDPSCl, TEA, DMAP, 0deg.C then rt; 90%; ii) TFA, MeCN:H_2O (4:1), rt; 99%; iii) Piv-Cl, TEA, DMAP, 0deg.C; 72%; iv) PDC, mol. sieves, rt; 71%; v) $Me_2C(SeMe)Li$, -78deg.C to rt o/n; 99%; vi) PI_3, TEA, 0deg.C; 56%; vii) DIBAL, -78deg.C; 84%; viii) $(COCl)_2$, DMSO, TEA, -60deg.C to rt; 79%

With this aldehyde in hand we examined the options to prepare the above mentioned asymmetric sulfones **6**. For this purpose, the alcohol **13** (**Scheme 4**) was considered to be an attractive starting material since it is commercially available as the racemic mixture as well as in both of the enantiomerically pure forms. Also, it will result in a benzylic protected alcohol which can be differentiated from the alcohol already present in the molecule. First attempts to convert the alcohol **13** to the corresponding chloromethyl derivative by reaction with paraformaldehyde and hydrogen chloride[7] failed, so an alternative route was developed in order to prepare the sulfone **16**. Racemic sec-phenylethyl alcohol **13** was protected as the corresponding MEM-derivative. [8] Reaction of **14** with Me_2BBr[9] followed by addition of thiophenol gave the sulfide **15**.[10] Finally, oxidation under the usual conditions afforded the desired asymmetric sulfone **16**.

Scheme 4

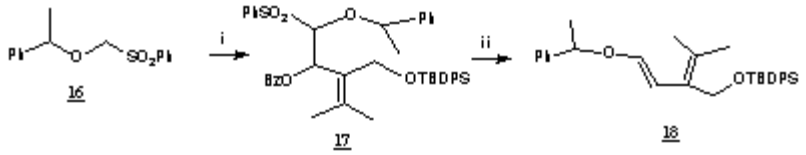


Reagents and conditions: i) MEM-Cl, DIPEA, rt; 86%; ii) Me_2BBr, -78deg.C, then DIPEA, PhSH, -78deg.C; 99%; iii) NaOAc, AcOOH, 0deg.C to rt; 96%

Once the aldehyde **7** and the sulfone **16** had been successfully prepared the next step in our synthesis was

to couple these two fragments (**Scheme 5**). This coupling was achieved by a Julia olefination reaction to give the diastereomeric mixture of adducts **17**, followed by a reductive cleavage of the sulfone and benzoate groups[11] to afford the desired diene **18** as a E:Z mixture in a ratio 9 to 1.

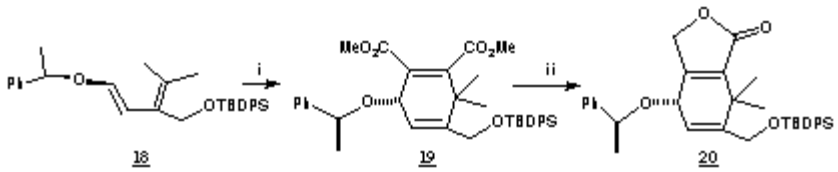
Scheme 5



Reagents and conditions: i) BuLi, -78deg.C, then aldehyde **7**, -78deg.C, then BzOCl, -78deg.C to rt; 88%; ii) SmI_2, DMPU, rt; 90%

Thus, we had achieved the synthesis of the first asymmetric diene which can be used to investigate the asymmetric intermolecular Diels-Alder approach. To test the asymmetric induction of this diene **18**, and, at the same time, avoid problems of regioselectivity in the reaction, the dimethyl ester of the acetylene dicarboxylic acid was chosen as a dienophile. The intermolecular Diels-Alder reaction was carried out at 140deg.C for 67 hours and afforded, in 80% yield, a mixture of diastereoisomers in a ratio 7 to 3 (**Scheme 6**). This successful result proved the asymmetric induction of the diene was possible although it was impossible, at this stage, to assign both diastereoisomers, since they were inseparable by chromatogaphy. Fortunately, we found that after reducing[12] the mixture of adducts **19** to the mixture of lactones **20** enabled easy separation of both diastereoisomers by flash chromatography. The major isomer was obtained as a crystalline solid, and X-ray analysis allowed us to unequivocally assign both compounds.

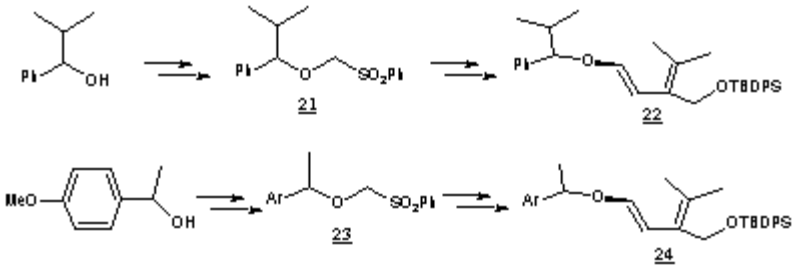
Scheme 6



Reagents and conditions: i) 2. 5 M in PhMe, DMAD, 140deg.C, 67h; 80%; ii) $LiAlH(i\text{-}Bu)_2(n\text{-}Bu)$, THF-hexane, -30deg.C o/n; 40%

After this encouraging Diels-Alder reaction, we explored the possibility of improving the asymmetric induction of the reaction by preparing a more hindered diene and a more electron-rich one. Both dienes (**22** and **24**) were prepared following the synthetic route previously developed (**Scheme 7**). The diene **22** was achieved in a comparable yield to the **18**, whereas the sulfone **23** proved to be very sensitive and it was not possible to obtain the diene **24** as a pure compound in order to carry out a Diels-Alder reaction.

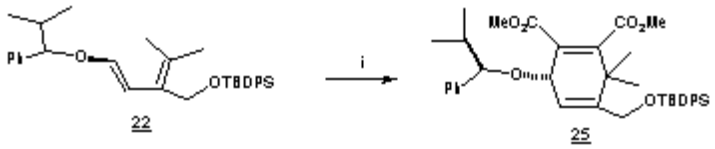
Scheme 7



When the diene **22** was subjected to the same Diels-Alder conditions as above (**Scheme 8**) the desired mixture of diastereoisomers **25** (7:3) were obtained. Unfortunately, no improvement in the selectivity of the reaction was observed and a considerable amount of material was lost due to the lower reactivity of this

more hindered diene. Therefore, subsequent studies on the manipulation of the diesters were carried out using the initial mixture **19**.

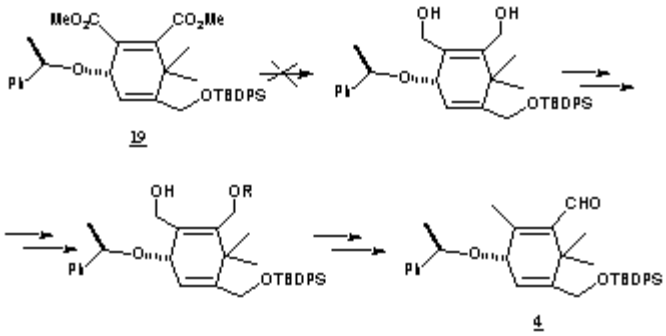
Scheme 8



Reagents and conditions: i) 2. 5 M in PhMe, DMAD, 140deg.C, 67h; 49%

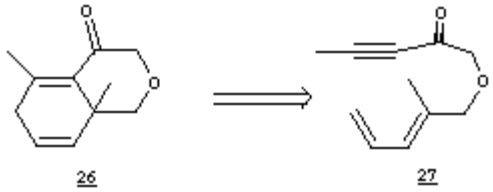
In order to obtain the above mentioned aldehyde **4** a differentiation of the two ester groups in compound **19** was neccesary (**Scheme 9**). The possibility of reducing both ester groups to the corresponding diol and then selectively protecting one of them was investigated. However, after trying several reductions, with varying conditions the diol could not be obtained. The only case of differentiation of the two ester groups that we observed was far the lactones **20** (**Scheme 6**).

Scheme 9



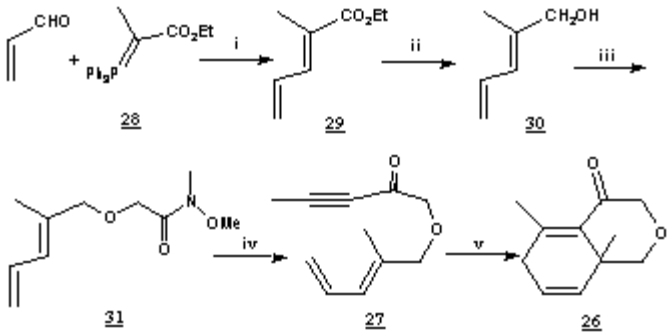
At the same time we are investigating more possibilities of reducing the ester groups, we have started exploring the possibility of preparing the A,B-ring fragment by an intramolecular Diels-Alder reaction (IMDA). We considered, in the first stage, a relatively simple A,B-ring fragment as **26**, that could be obtained by an intramolecular Diels-Alder reaction from **27** (**Scheme 10**).

Scheme 10



To prepare tethered molecule **27** we have developed the synthetic route shown in the **Scheme 11**. This route starts with a Wittig reaction between acrolein and the commercially available phosphorane **28** to give the desired unsaturated ester **29**, which by reduction afforded the alcohol **30**. Coupling between this alcohol and *N*-methoxy-*N*-methyl-2-chloro-acetamide[13] gave the corresponding adduct **31**, that was converted into the mentioned molecule **27** by addition of 1-propynyl magnesium bromide. When a solution of **27** in toluene was heated at 162deg.C for 72 hours the expected Diels-Alder adduct was obtained. Unfortunately, this tethered molecule **27** was not very reactive and the IMDA adduct was obtained in only 5% yield, with the remainder unreacted starting material.

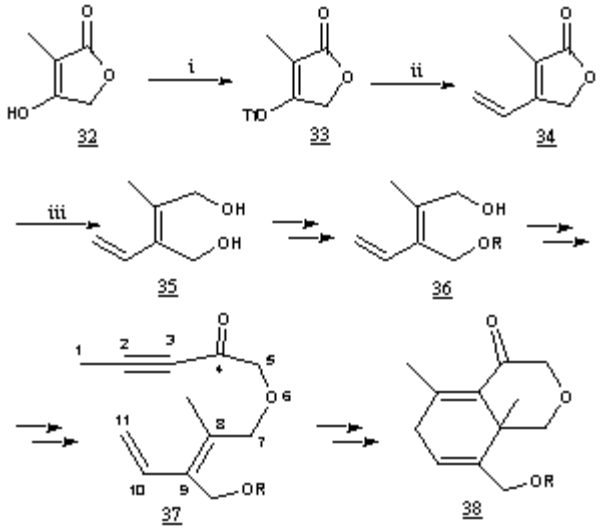
Scheme 11



Reagents and conditions: i) DCM, reflux; 70%; ii) DIBAL, -78deg.C; 91%; iii) NaH, Bu_4NI, *N*-methoxy-*N*-methyl-2-chloro-acetamide, DMF, rt; 60%; iv) 1-Propynyl magnesium bromide, -78deg.C; 82%; v) PhMe, 162deg.C, 72h; 5%

Previous studies have shown that when a side-chain is present on C-9 of the diene used previously for the intermolecular Diels-Alder reactions the reactivity of the diene is significantly increased. Therefore, in order to improve the yield of the IMDA reaction and at the same time introduce functionality that has to be present in the A-ring we decided to prepare the molecule **37**, starting from the already known 2-methyltetronic acid[14] **32** (**Scheme 12**). The corresponding triflate **33**[15] was coupled with tributyl(vinyl)tin to give **34**[16] which has been reduced[17] to the corresponding diol **35**. We now intend to protect one of the two alcohols selectively to give **36**, then apply the chemistry we have already developed in the previous scheme to the unprotected hydroxyl group.

Scheme 12



Reagents and conditions: i) triflic anhydride, DIPEA, DCM, -78deg.C; 92%; ii) tributyl(vinyl)tin, $Pd(PPh_3)_4$, THF, reflux; 91%; iii) DIBAL, Bz, 0deg.C then rt; 60%

In the future we hope to convert the IMDA adduct **38** into the A,B-ring fragment. We also aim to prepare an asymmetric analogue of **37**, which we can then use to prepare an asymmetric A,B-ring fragment **2**.

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