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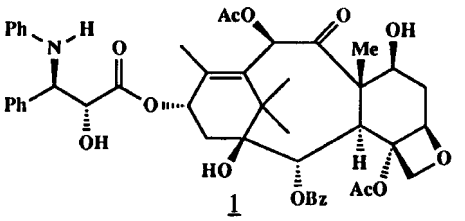
The synthesis of taxoids from glucose

P.R. Jenkins

Chemistry Department, Leicester University, Leicester LE1 7RH.

Abstract: The synthesis of two model compounds of the anti-cancer natural product Taxol is described. The application of these results to the synthesis of chiral taxoids is outlined starting from the Robinson annulation of a protected glucose methyl ketone, further key stages are the Stork silylmethylene radical cyclisation and Vasella fragmentation to give a chiral synthon for the Taxol C-ring, a progress report on the further elaboration of this synthon is given.

The clinical use of Taxol 1(1) and Taxotere (2) in the treatment of solid tumours of the breast and ovary has been one of the most important events in chemotherapy for the past 25 years. The natural source of Taxol is the bark of the pacific yew tree *taxus brevifolia* which has become a threatened species as a result of the enormous demand for Taxol. More recently Taxol has been prepared by semi-synthesis from Baccatin III, (3) a natural product available from the leaves of the european yew tree *taxus baccata.* Taxol has been a very popular target for synthetic chemists over the past five years (4), this wave of activity has resulted in two successful syntheses of Taxol (5). The two synthesese of Taxol are great monuments to the current state of the synthetic art, however it is unlikely that a total synthesis of such a complicated natural product as Taxol could ever compete with semi-synthesis starting from Baccatin III. The development of several efficient routes to taxoids will produce a wide range of structures related to taxol which may show anti-cancer activity similar to or even better than taxol itself. Indeed Taxotere (2) is an analogue of Taxol which is claimed to have equivalent anti-cancer activity.



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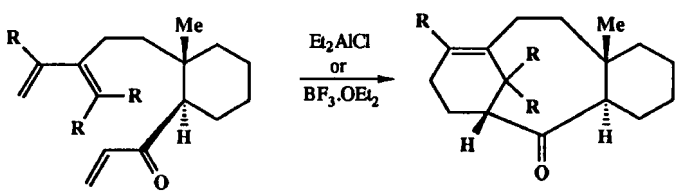
The anti-cancer activity of Taxol has been explained by its interaction with the protein tubulin which is present in all eukaryotic cells. Taxol stimulates the formation of microtubules and prevents their breakdown (6), so preventing normal cell division from occurring. The anti-cancer activity therefore results from this as cancer cells divide more rapidly than normal cells. Action on tubulin is a good indication of possible anti-cancer activity as shown by the fact that Vincristine, Maytansin, Podophylotoxin all act as microtubule poisons (7). Blechert has reported a simple taxoid structure showing tubulin activity (8).

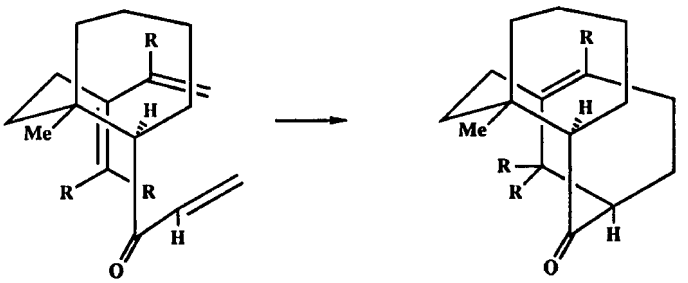
We have published the synthesis of two taxane model systems with a non-aromatic C-ring using a Lewis acid catalysed intramolecular Diels-Alder reaction, 2-3 and 4-5 (9,10). These results show the power of this strategy in the construction of a single diastereomer of the products 3 and 5 in which the new asymmetric centre has the same relative configuration as the natural product taxinine.



2 R = H, 4 R = Me

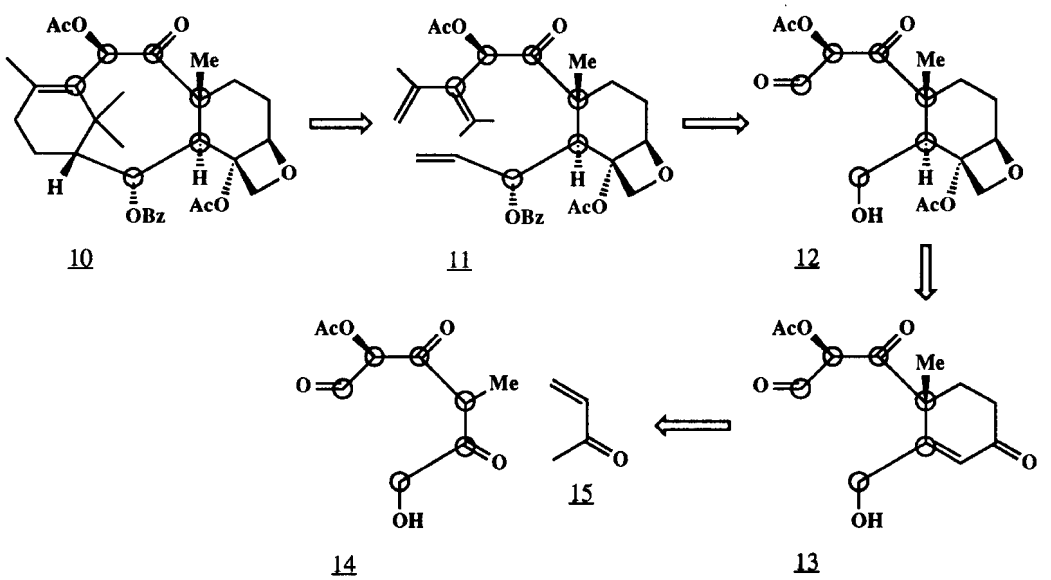
3 R = H, 5 R = Me

The control element in these Diels-Alder cyclisations is the boat-chair conformation of the eight membered ring, this is the conformation observed in the X-ray structure of several taxane natural products (2). We believe that the forming 8-membered ring in the precursors 6 and 7 has a preference for the boat chair conformation and that this is the reason we obtain the observed products. We proved the structure of 8 by X-ray and the structure of 9, which is an oil follows from spectral comparison.



6 R = H, 7 R = Me 8 R = H, 9 R = Me

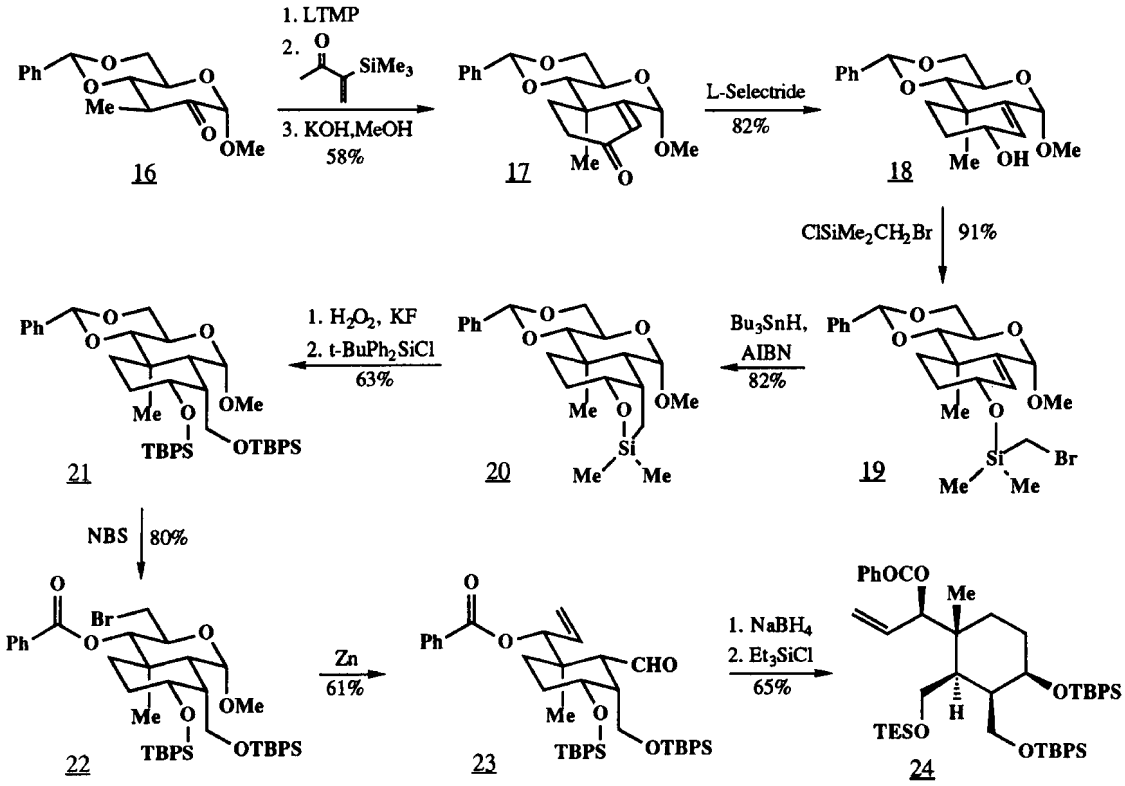
In parallel with our work, Shea (11) has reported the intramolecular Diels-Alder reaction in the synthesis of C-aromatic taxoid structures. Kuwajima (12) and Wender (13) have also prepared C-aromatic taxoids where the C-ring has to be functionalised after cyclisation.
In seeking to exploit our unique strategy using a non-aromatic C-ring in the intramolecular Diels-Alder reaction we embarked on a route to homochiral taxoid structures starting from glucose, the retrosynthetic analysis of this idea is shown in Scheme 1.



Scheme 1

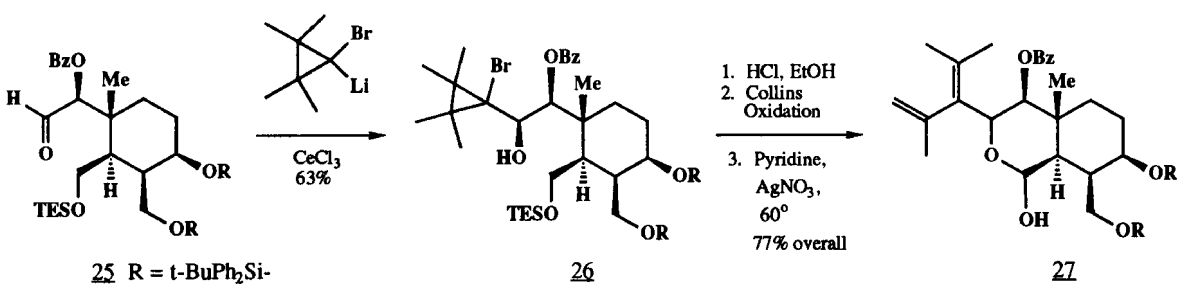
Our target is the homochiral taxoid structure 10, which may be obtained using a Diels-Alder reaction of a precursor such as 11. In the course of our model work we have developed methods for diene synthesis which will be applied to synthetic equivalents of the synthon 12. It may be possible to construct the oxetane ring fom the enone 13 which in turn may be constructed by a Robinson annulation on the sugar methyl ketone synthon 14 and methyl vinyl ketone 15. With this plan in mind we then carried out the following reactions.

The ketone 16 was prepared by the method of Sinay (14) in five steps in an overall yield of 37%. The key points in the route are the Robinson annulation 16-17, (15) stereoselective reduction of 17 to give 18 on which an X-ray crystal structure was carried out (16), Stork radical cyclisation 19-20 (17) followed by oxidation to furnish the tricycle 21, (18) reaction with NBS (19) followed by Vasella fragmentation 21-23 (20) achieved the much sought after carbohydrate to carbocycle conversion (21) reduction and protection of the aldehyde then produced the C-ring synthon 24.



Scheme 2

Ozonolysis of the olefin in 24 gave the aldehyde 25, our first attempt at diene construction is shown in Scheme 3. Conversion of 25 into 26 was a very dificult reaction which required careful control of conditions and a reaction time of several days. Alcohol 26 is obtained as a 2:1 mixture of diastereoisomers the major produt is 26, the stereostructure was proved by an X-ray crystal structure on the minor isomer of 26. Our first successful synthesis of the diene fragment was obtained when the triethylsilyl group was removed, the alcohol was oxidised to an aldehyde and a lactol formed, however rearrangement of the tetramethyl cyclopropane into the diene 27 did indeed occur. The key to success in this synthesis is the conversion of aldehyde 25 into a suitable substrate for intramolecular Diels-alder reaction. The aldehyde is very unreactive in the conversion into 26, there are two major reasons for this; the first is the local steric hindrance of the benzoate on the carbon α to the aldehyde and the second is the remote steric hindrance caused by the extremely large diphenyl tertiary butyl silyl protecting groups. At present we are actively engaged in changing both the ester and the protecting group in order to improve the reactivity of the aldehyde 25. The results indicated in Scheme 3 demonstrate the fact that we are now poised ready to complete the synthesis of a homochiral taxoid structure.



Scheme 3

Acknowledgements

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