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Article

New Synthetic Methods in the Synthesis of Taxoids

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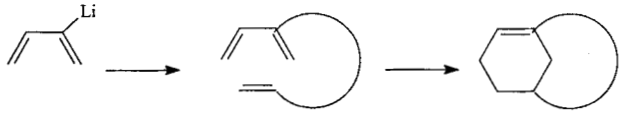
Discute-se uma nova abordagem na síntese de derivados do taxol através de uma reação intramolecular de Diels-Alder.

A new approach to the synthesis of taxoids through an intramolecular Diels- Alder reaction is discussed.

Keywords: *taxoids, Diels-Alder reaction, glucose*

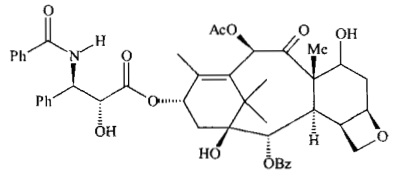
Plans

During my post-doctoral work at ETH Zürich between 1978 and 1980 with Professor Eschenmoser I spent Sunday afternoons in the library working out research proposals which might one day help me to obtain an academic job in a British University. One of the ideas I had was to prepare 2-lithiobutadiene **1**, attach it to a suitable olefin to produce triene **2** and then to carry out an intramolecular Diels-Alder reaction to give a bridge-head olefin **3**.



1 2 3

Like many good ideas other people have already thought of them and the first results on the type-2 Diels-Alder reaction **2-3** appeared from the group of Professor Shea a few months after I wrote my proposal although **2** was not prepared using 2-lithiobutadiene **1**[1]. I next looked for a natural product to prepare by the intramolecular Diels-Alder reaction of a 2-substituted diene and in the book Natural Products Chemistry by Nakanishi, Volume 1, page 281[2] there is a review of the structural elucidation of the Taxane group of Natural Products from the yew tree. These fascinating structures were determined by classical methods by Lithgoe[3] and Nakanishi[4]. Most interesting of all was the compound Taxol which was reported to have antileukemic and antitumour properties[5]. Would it be possible to synthesise taxol using the intra-molecular Diels-Alder reaction?



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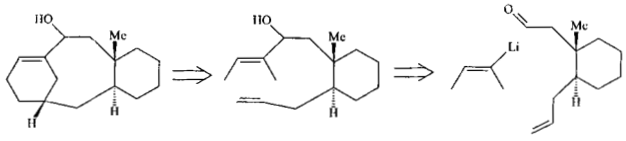
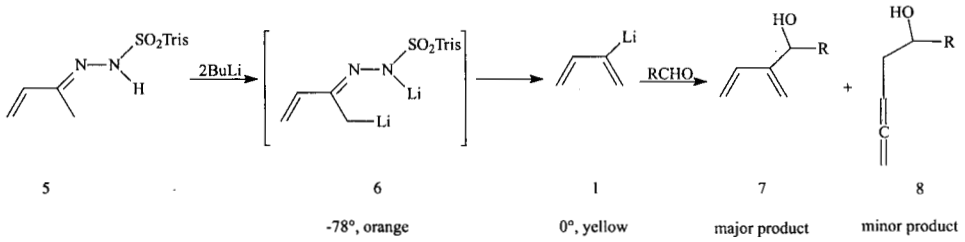
Early Model Studies

After returning from Zürich and spending a year working with Professor Baldwin in Oxford, I was appointed to a lectureship in Leicester University where I could try and put some of my proposals into practice. The first project I worked on was the preparation and reactions of 2-lithio butadiene **1**, Scheme 1. The benzenetriisopropyl hydrazone of 2-butenone **5**, was treated with two equivalents of butyl lithium in dimethoxyethane at -78°, a deep red solution of the dianion **6** formed which gave off nitrogen when it was allowed to warm to room temperature producing a yellow solution of 2-lithiobutadiene **1** by the Shapiro reaction. Addition of an aldehyde gave the diene alcohol **7** as the major product with some allene **8**[6] (see Scheme 1).

Having established a diene synthesis we now needed an appropriate substrate onto which to attatch the diene. The retrosynthetic analysis of a simple taxane model **9** is shown below, the triene **10** may be prepared from the reaction of 2-lithiobutadiene **1** with the C-ring synthon **11**.



9 10 11

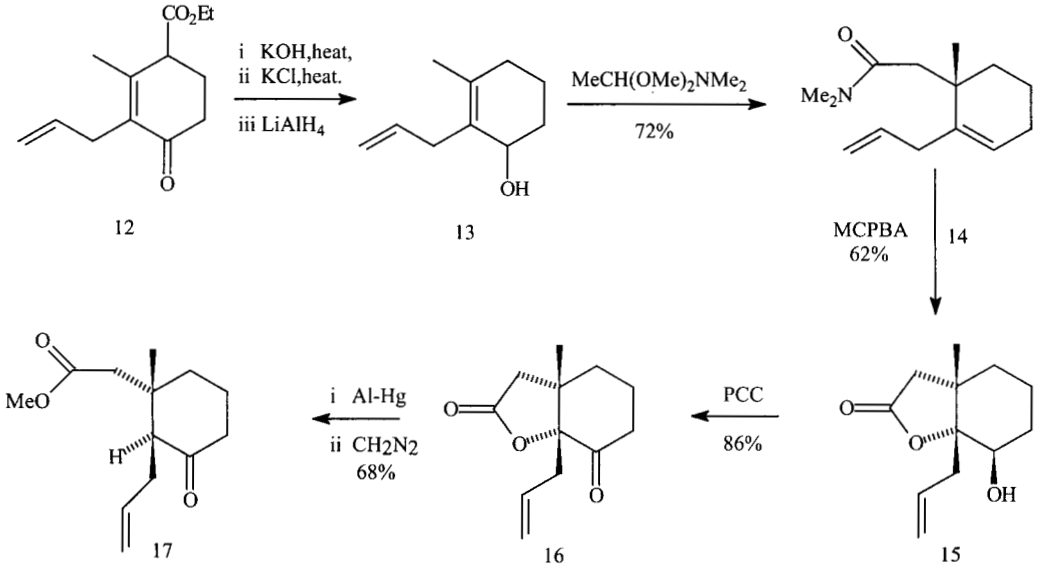


Scheme 1.

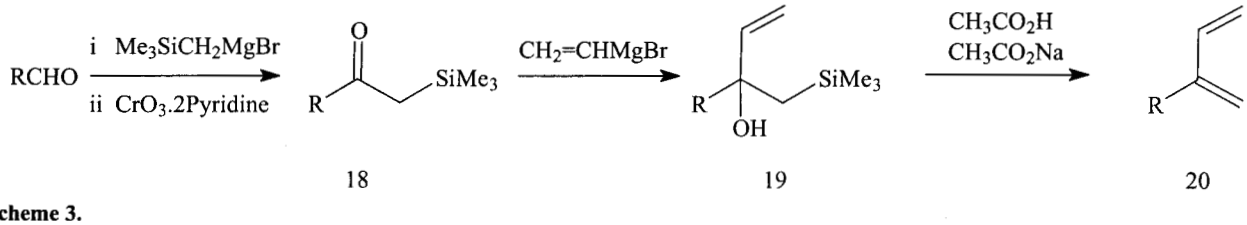
Our first synthetic route to an ester corresponding to **11** is shown in Scheme 2. The starting material for the synthesis is the easily prepared derivative of Hagemann's Ester **12** which was hydrolysed, decarboxylated and reduced to the allylic alcohol **13**. Amide acetal Claisen rearrangement[7] then produced the amide **14** which was subjected to hydroxy-lactonisation to give the hydroxy lactone **15**. This reaction had not previously been reported on an amide. Oxidation to the ketone **15** produced the ketolactone **16** which was cleaved with aluminium amalgam to give the cyclohexanone **17** as a 96-4 mixtue of trans (Structure **17**) to cis isomers[8]. These results illustrate that new synthetic procedures can arise naturally in the synthesis of the taxane natural products. Recently a report on the synthesis of taxane model systems using a 2,3-sigmatropic rearrangement to prepare the C-ring has appeared which is closely related to our earlier concept shown in Scheme 2[9].

We were also making progress in the synthesis of a model taxane structure we were investigating in parallel with the work described so far. The objective of this project was to develop a stepwise diene synthesis from an aldehyde, our first successful route is described in Scheme 3[10].

The aldehyde was first reacted with trimethylsilylmethylmagnesium bromide and oxidised to the β-ketosilane **18**. Addition of vinylmagnesium bromide to the ketone produced the tertiary allylic alcohol **19** which was treated under Peterson Elimination conditions to yield the desired diene **20**. All attempts to prepare **20** without the controling influence of the $SiMe_3$ gave only mixtures of olefins resulting from the loss of every available proton from the cation derived from **19**. Protonation and loss of the OH group in **19** leads to an allylic cation with a β-$SiMe_3$ group which stabilises the cation, and nucleophilic attack at silicon is



Scheme 2.



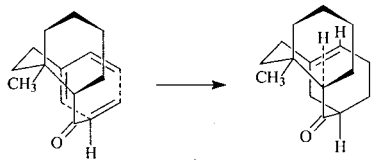
Scheme 3.

faster than attack at a proton, consequently a single isomer of **20** is obtained in agreement with the guidelines for silicon reactivity proposed by Ian Fleming[11].

The Synthesis of a Simple Taxoid Ring System

Armed with an effective way of constructing dienes we next turned our attention to the synthesis of the ring system of the taxane natural products as shown in Scheme 4[12]. The starting point was the Robinson annulation of 2-methyl cyclohexanone and methyl vinyl ketone to give the known decalin **21**[13]. Lithium in ammonia reduction followed by the trapping of the intermediate enloate with trimethyl silyl chloride was carried out following the work of Stork[14], to produce the silyl enol ether **22**, ozonolysis and subsequent methylation produced the ester aldehyde **23** which was reacted with vinyl magnesium bromide and protected as the dimethyl t-butyl silyl ether **24**. Reduction to the corresponding aldehyde **25** was achieved in one step with DIBAH, the product was reacted with trimethylsilylmethylmagnesium chloride to furnish the β-hydroxy silane **26**. Careful oxidation and reaction with vinyl magnesium chloride produced the β-trimethyl silyl allylic alcohol **27**. Treatment of the alcohol **27** under Peterson conditions gave a clean elimination to yield the diene **28**, which was deprotected and oxidised to give the enone **29**.

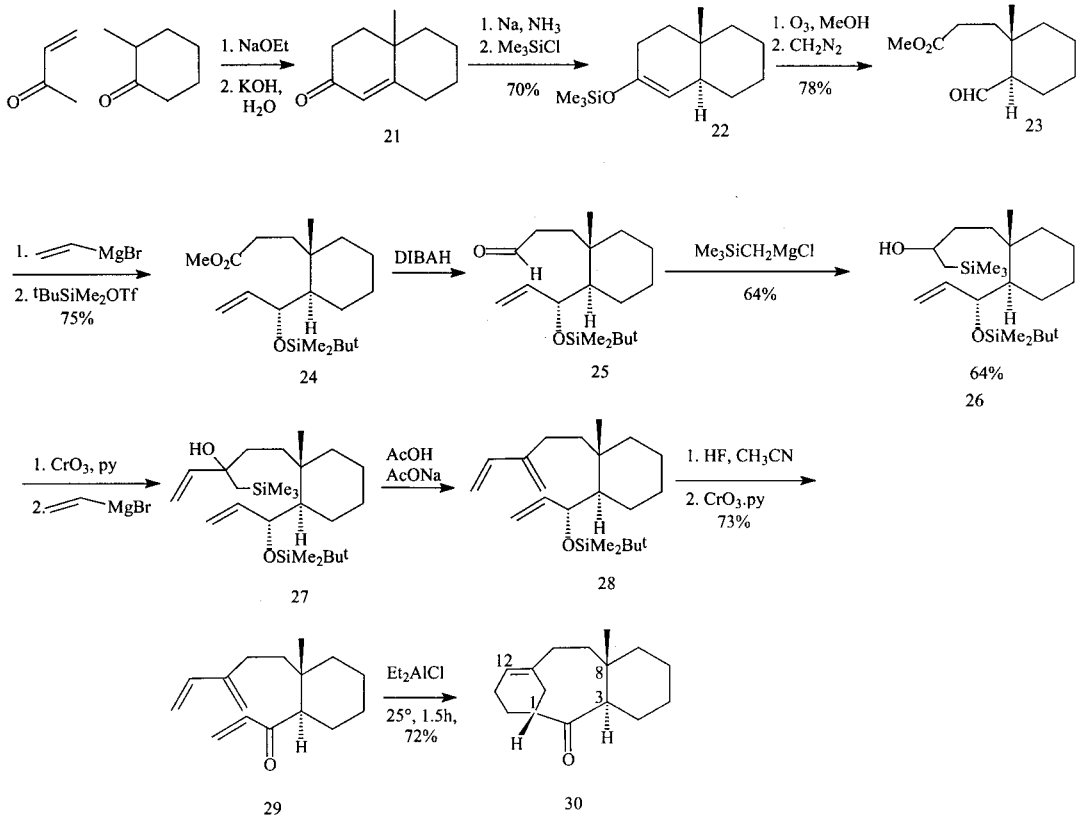
Intramolecular Diels-Alder reaction catalysed by Et_2AlCl then produced the crystalline taxoid ring system **30**. The conformation of the eight membered ring is a boat chair in the X-ray crystal structure of several taxoid structures.[15] We also observed this trend in the X-ray structure of the product **30**, hence we believe the Diels-Alder reaction occurs *via* the transition state **31** to produce the taxoid structure **32** with the eight membered ring in the boat-chair confromation. The overall result of Scheme 4 was the preparation of a racemic taxoid model system with three of the asymmetric centres in the correct relative configuration for the natural products.



31 32

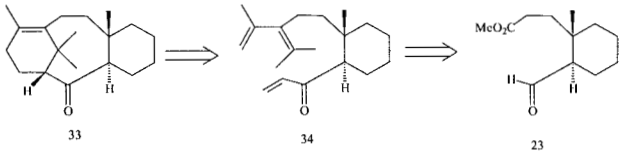
The Synthesis of an Alkylated Taxoid Ring System

Our next objective was to modify our synthetic route to include three further methyl groups in the A-ring of the taxoid strucure as shown in the following retrosynthetic analysis. The

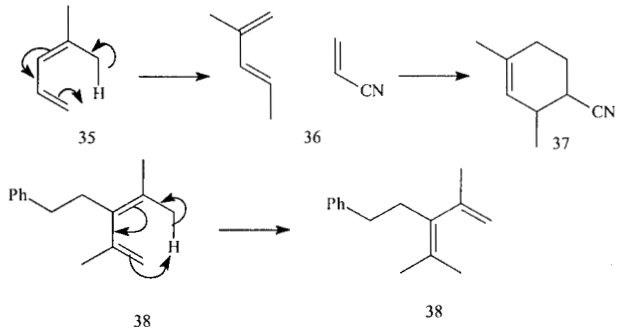


Scheme 4.

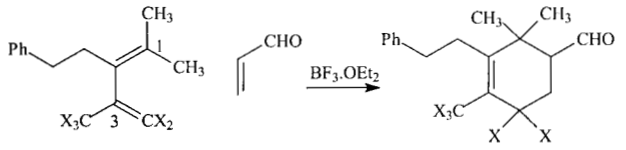
alkylated taxane model **33** may be derived from the triene **34** and this in turn will be obtained from the ester aldehyde **23** already prepared in Scheme 4. The Diels Alder reaction **34** - **33** raises some interesting problems because the diene in **34** has a cis methyl group at its terminal carbon.



It is often stated that Diels-Alder reactions with a cis 1-methyl group are difficult as the required s-*cis* conformation of the diene is hindered by an unfavourable steric interaction between the 1-*cis* methyl and the 4-*cis* hydrogen. Indeed it has been reported that 1,1- dimethyl butadiene **35** undergoes a 1,5-hydrogen shift and the less hindered rearranged product, 1,3-dimethyl butadiene **36** which then undergoes a Diels-Alder Reaction to produce **37**[16]. Using the diene synthesis described in Scheme 3 a range of dienes were prepared[17]. In the case of **38** 1,5-hydrogen shift is degenerate and leads to the same compound.



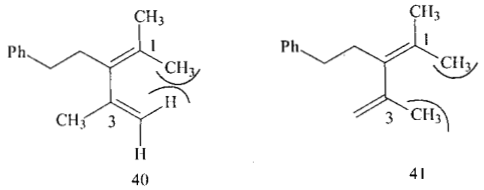
However, when we prepared the diene **38a** with a *cis*-1-methly group and a 3-methyl group the Diels-Alder reaction with acrolein occured readily under Lewis acid catalysis to give the aldehyde **39a** in 52% yield. When we carried this same reaction on a diene lacking the 3-methyl group none of the expected Diels-Alder product was observed.



38a, X= H
38b, X= D

39a, X= H
39b, X= D

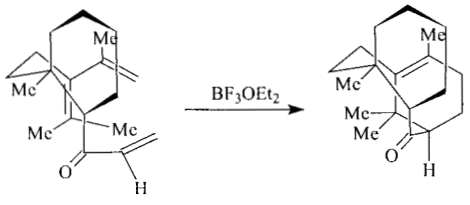
In order to find out if degenerate rearrangement was occurring we prepared the deuterated diene **38b**. In the Diels-Alder reaction with acrolein, the adduct **39b** was produced with no scrambling of label and we conclude from this that no degenerate 1,5-hydrogen rearrangement is taking place. What then is the reason for the 3-methyl group effect? We believe that in the s-*cis* **40** conformation of the diene there is steric interaction between the *cis* methyl group at C-1 and the *cis* hydrogen at C-4, but that in the s-*trans* conformation **41** there is an unfavourable steric interaction between the 1-*cis* methyl group and the 3-methyl group. As a result of this there is sufficient concentration of the s-*cis* conformation for the Diels-Alder reaction to occur[18].



40 41

With this knowledge of the Diels-Alder reaction and of diene synthesis we embarked on our first synthesis of an alkylated taxane ring system (see Scheme 5).

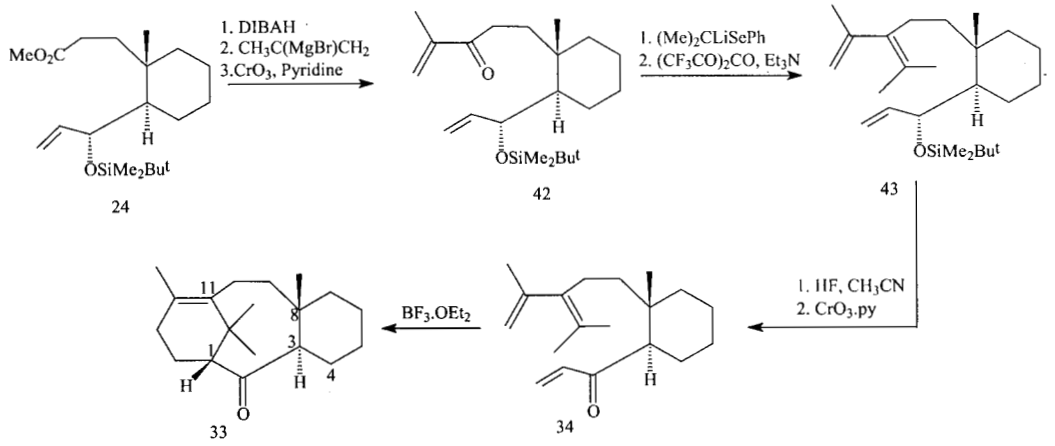
Scheme 5 shows the application of these results on the synthesis of alkylated dienes to a fully alkylated taxane model. Intermediate **24** was reduced to an aldehyde which was reacted with propenyl magnesium bromide and the resulting allylic alcohol was oxidised to the enone **42**. Addition of the anion $Me_2LiSePh$ developed in the work of Krief[19] and Reich[20] followed by elimination gave the triene **43**. Deprotection and oxidation furnished the trienone **34** which readily underwent an intramolecular Diels-Alder reaction catalysed by $BF_3.OEt_2$ to give the alkylated taxane model **33**. This time the product was not crystalline and so a careful nmr analysis was required to show that the cyclisation **44-45** was analogous to the cyclisation **31-32**[21].



44 45

The Synthesis of Chiral Taxoids from Glucose

The next stage in the project was to make oxygen substituted chiral taxoids. Our retrosynthetic plan (Scheme 6) starts from the taxoid structure **46**. At this stage we have assumed that addition of the side chain and oxidation at C-13 will be done using known procedures. We have made two further simplifications at this stage and they are the absence of the OH groups at C-1 and C-7. It should be possible to modify our route to incorporate these groups after we have proved the viability of the route. In fact the

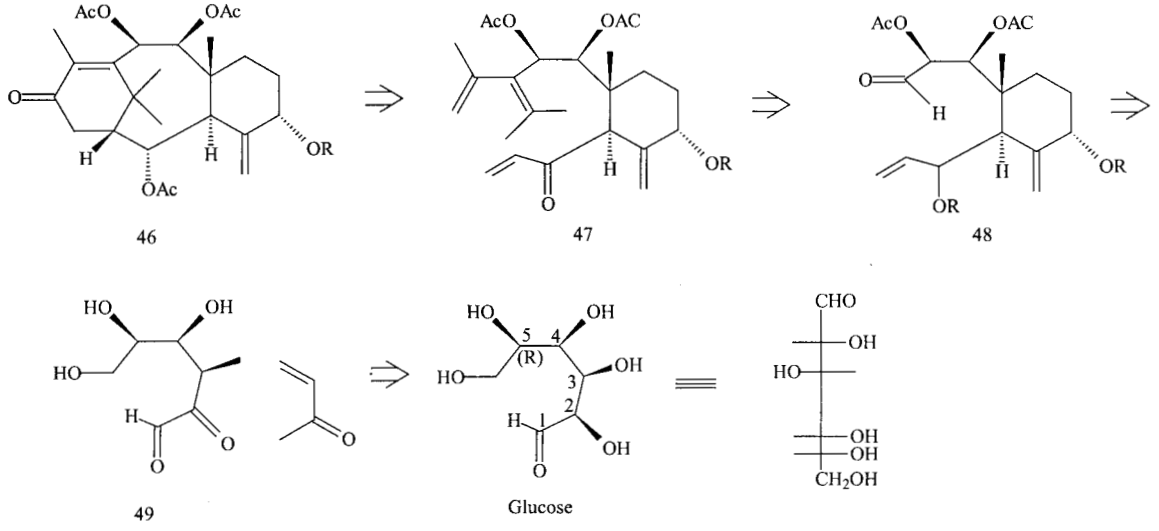


Scheme 5.

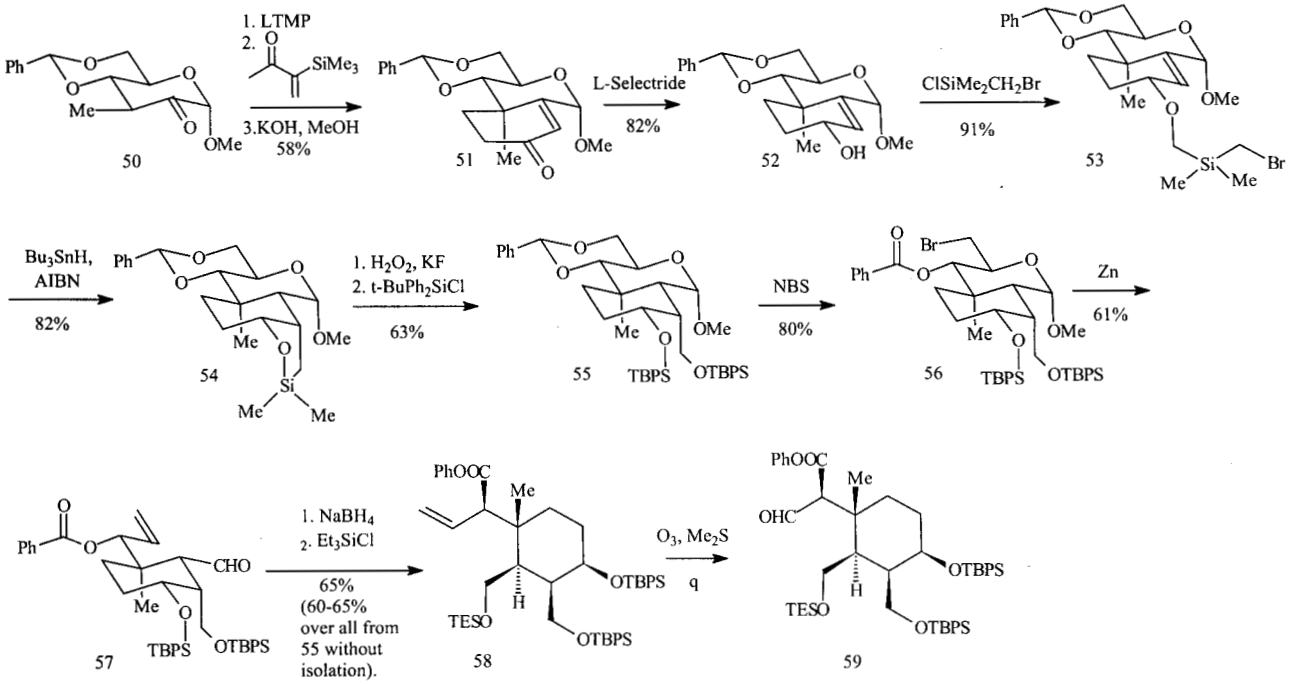
C-7 OH has been shown not to be essential for biological activity. Working back from the target **46** we obtain the triene **47**, the methods for diene construction used in our model work should enable us to make **47** from aldehyde **48**. The Robinson annulation of a protected form of the sugar methyl ketone **49** may then give the C-ring synthon **48**. Our starting point is the sugar glucose and fortunately for us a very efficient preparation of a protected glucose methyl ketone **50** had been published by Professor Sinay[22] (see Scheme 6).

Scheme 7 shows our route in practice starting from the Sinay methyl ketone **50**. The first reaction is the formation of an enolate with lithium tetramethyl piperidide followed by Robinson annulation to produce the enone **51**. There are several points of interest about this reaction, the most important is that it is the first example of a Robinson annulation on a sugar derivative[23]. The second point is that the enolate of **50** has reacted with the enone to give the new bond in the equatorial position. This result was confirmed by X-ray crystallography and is essential for our synthesis as the enone **51** has the correct absolute configuration at the quaternary chiral centre for several taxane natural products. We speculate that the reason for this unusual preference for the formation of the equatorial product may arrise from the conformation of the enolate or that the initial step of the Robinson annulation is reversible which leads to the thermodynamically more stable product **51**. Selective reduction to the equatorial alcohol **52** was achieved with L-Selectride.[R] The next stage was the use of the Stork silyl methylene radical cyclisation[24] to add across the double bond with the correct stereochemistry. The silyl ether **53** was prepared in good yield and it readily cyclised to the tetracyclic compound **54**. Opening of the silicon ring followed by diol protection gave the bis silyl ether **55**[25].

Having used the protected carbohydrate ring as a chiral template for our purposes we next needed to remove it to leave a cyclohexane fragment which will be our chiral C-ring synthon for the synthesis of taxoids. The first step in this process was reaction with NBS following the work



Scheme 6.



Scheme 7.

of Hanessian[26] to produce the bromo ester **56**. Treatment with zinc then produced aldehyde **57** in a Vasella reaction[27], reduction and protection of the aldehyde gave the required chiral C-ring synthon **58** which was converted into the aldehyde **59** by ozonolysis[28].

Addition of all the carbons of the diene as a single unit was achieved using a known tetra methylcyclopropyl reagent[29] and catalysis with $CeCl_3$ (see Scheme 8), the product **60** was rearranged to the diene **61** on a small scale, however these reactions were very dificult and not always reproducible. Our thoughts on the reason for the unreactivity of the aldehyde in structure **59** lead us to the idea that there might be two diferent types of steric hinderance acting on the aldehyde group. Firstly a local steric hinderance by the benzoate ester and secondly a remote steric hinderance by the three large silicon protecting groups as indicated in structure **62**.

The Plate shows a Chem-3D representation of aldehyde **59** we have made a reasonable assumption about the conformation of the aldehyde which fits with the major isomer in the cyclopropane addition **60** which was confirmed by an x-ray crystal structure on the minor isomer. The northern

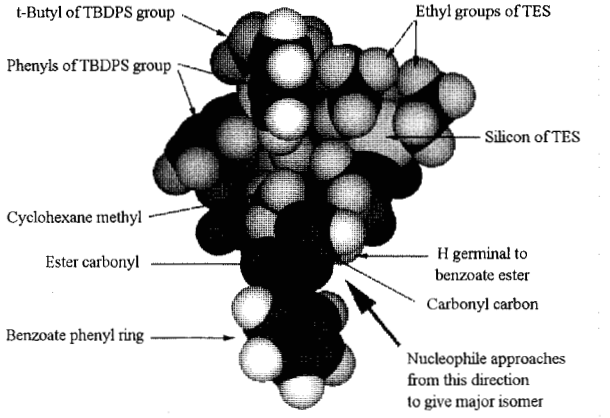
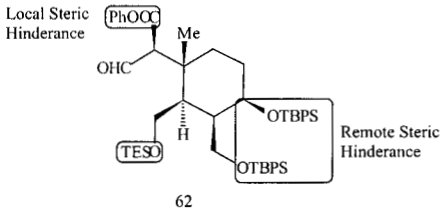
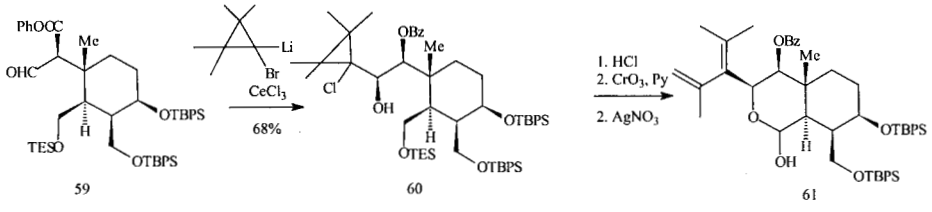


Plate. The picture shows a Chem-3D representation of **59**. We thank Dr Peter Johnson of the University of Leeds for advice and the use of his program.





Scheme 8.

region responsible for the remote steric hinderance from the silicon protecting groups is clearly shown in this picture as is the southern benzoate ester which we have called the local steric hinderance.

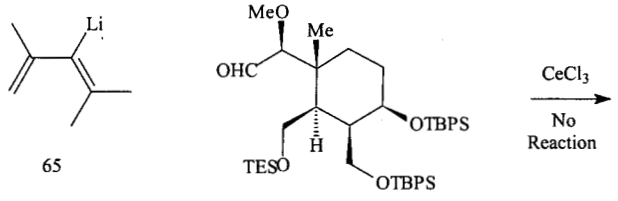
This analysis lead to the following conclusions:

1. The anion which will add to the aldehyde and be transformed to the required diene should be as small as possible.

2. Systematic changes in the remote and local steric hinderance will result in an effective addition of the diene and a solution to the lack of reactivity of the aldehye group in **59**.

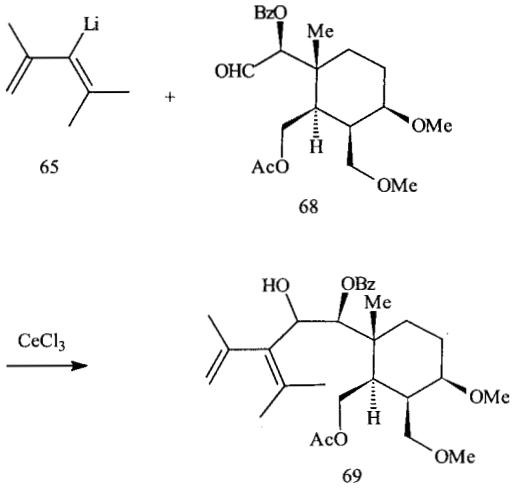
Following the first conclusion we thought it may be better to rearrange the cyclopopane to the diene first before addition. The use of the lithiated cycopropane reagent in Scheme 8 follows from the known preparation of the cyclopropane **63** by dibromocarbene addition to tetramethylethylene and its rearrangement to the bromodiene **64**. Our initial studies on the lithiation of **64** were not sucessful. However, Professor Shea published[30] the formation of the lithiated diene **65** and the addition of the anion to aldehydes catalysed by $CeCl_3$ to produce good yields of the diene product **66** without contamination with the corresponding allene (see Scheme 9).

Our plan was to react aldehyde 59 with the lithiated diene **65** with $CeCl_3$ catalysis this would give us a reagent which may be smaller than the cyclopropane used in Scheme 8. If we could also prepare aldehydes where the remote and local steric hinderance was changed then addition may well occur.



65 67

To test the importance of the local steric hinderance the benzoate group in **58** was removed by DIBAL reduction and the corresponding alcohol was converted into the methyl ether subsequent ozonolysis produced the aldehyde **67**. No reaction took place when the lithiated diene **65** was added to aldehyde **67** in the presence of $CeCl_3$, which indicated that the local steric hinderance is not the most important factor in the reactivity of the aldehyde group in **59**.

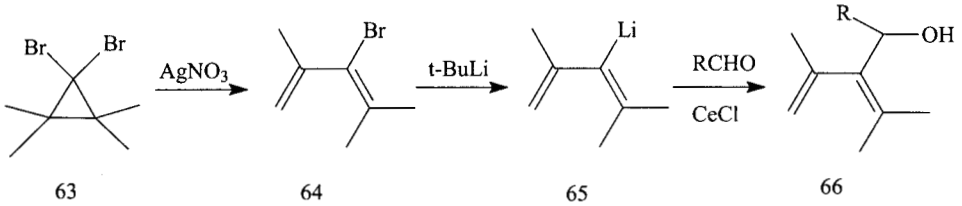


65 68 69

Changing the remote steric hinderance was achieved by synthesising several strucures with alternatives to the silicon portecting groups in **59**. However, only the methyl group was suitable to stand up to the NBS reaction. Methylation of the diol arising from the oxidation of **55**, to give the dimethyl ether coresponding to **56**. The same reaction sequence as for **56** then produced the aldehyde **68** where the large diphenyl tertiarybutyl silyl protecting groups have been repalaced by methyl groups. This time addition of the diene did occur to give the alcohol **69** as a 2:1 mixture of diastereoismers. This result demonstrates that remote steric hinderance by the silicon protecting groups is the most important factor in determining the reactivity of the aldehyde in compound **69**.

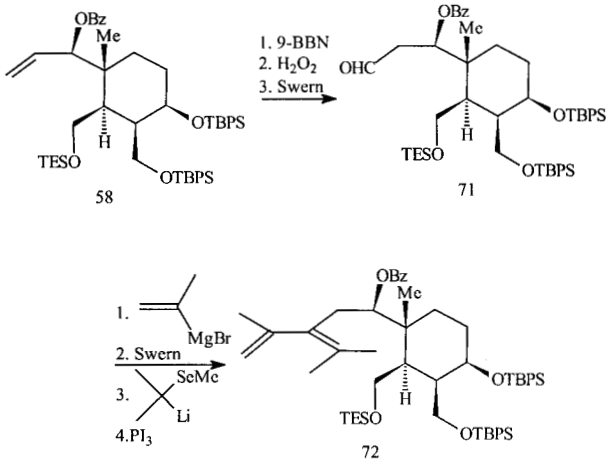
Clearly the methyl groups in **69** are not ideal as they can not be removed to prepare the oxetane ring, however it was a clear step forward to achieve diene addition.

The end game strategy described above was based on the dificulties we had to use the stepwise synthesis described in Scheme 5 in the chiral series. The main reason for this was the failure of the reagent $Me_2CLiSePh$ to add effectively and be converted into the diene. Very recently Professor R.M. Williams published[31] an adaptation of the synthesis described in Scheme 5 to give the first synthesis



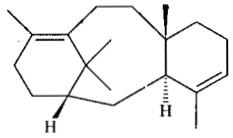
63 64 65 66

Scheme 9.



Scheme 10.

of taxadiene **70**, the proposed first fully cyclised intermediate in the biosynthesis of taxol.



70

The authors of this paper also found dificulties with the stepwise diene synthesis, but they overcame them by carrying out the reaction with $Me_2CLiSeMe$. At the present time we have returned to the stepwise diene synthesis strategy as a means of diene construction with the objective of obtaining a chiral taxoid structure by Diels-Alder cyclisation with protecting groups which can be removed so that oxetane ring formation is possible. The olefin **58** has been converted into the aldehyde **71** which is now being subjected to the four step sequence which may lead to the diene **72** (see Scheme 10).

Acknowledgments

It is a pleasure to acknowledge the contributions of my co-workers to this project, their names are given in the references. I am also grateful to the more recent members, Claire Simons, Gary Tustin, Samantha Hulme, Andrew Wood and Lucy Swallow. Financial support for the work has come from the EPSRC, SERC and Pharmachemie BV of Holland.

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