STUDIES TOWARDS THE TOTAL SYNTHESIS OF TAXOIDS: STRATEGIES BUILT AROUND A MOLECULE AND THE DISCOVERY OF NEW METHODOLOGIES

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This article is dedicated to the memory of Professor Dr Shun-ichi Yamada

Abstract-We describe below the evolution of a three-reaction (aldol-annelation-fragmentation) based strategy as well as the discovery of $Pb(OAc)_4$ mediated cascade reactions towards the total synthesis of the taxoid diterpene skeleton (**1**).

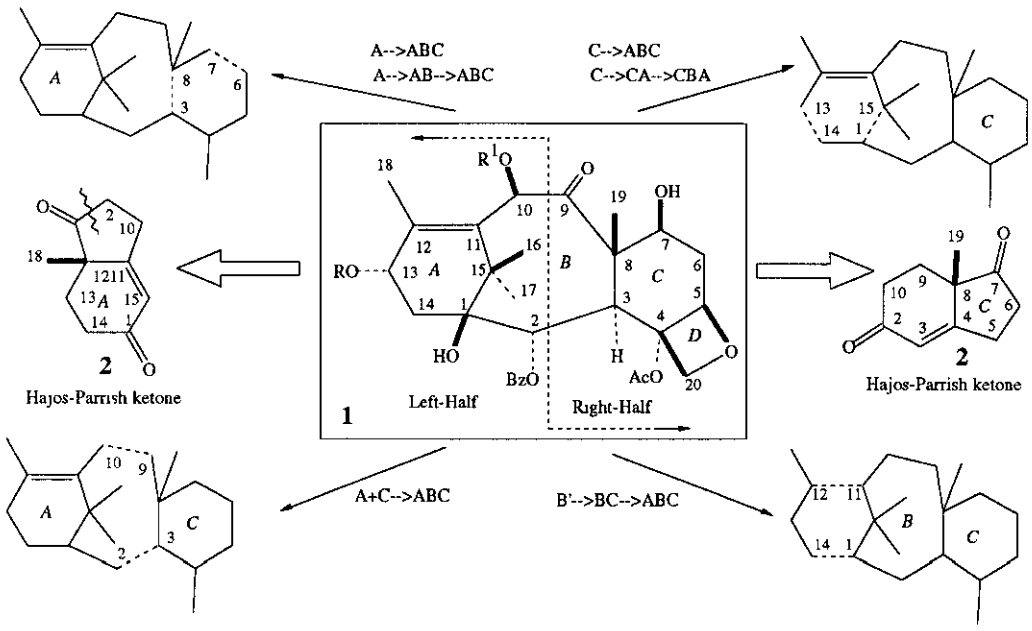
Introduction

The structural complexity of taxol, a promising anticancer drug, continues to challenge synthetic organic chemists three years after the landmark syntheses were reported.[1] While these syntheses are undoubtedly monumental in character, there is little chance for a total synthesis to compete effectively with the partial synthesis developed in our Institute which rests upon baccatin III, collected from yew tree needles, as a renewable raw material.[2] Among the proposed ways for taxol supply, such as semi-synthesis, total synthesis, direct isolation from the bark or leaves of the yew tree and biotechnology, total synthesis still remains impractical. Efforts during the past fifteen years towards the synthesis of both the side chain and the diterpene part of taxoids contributed greatly to the development of new synthetic methodologies and concepts. However, it would certainly be misleading to think that industrial applicability was the reason the numerous strategies were designed and executed for. It is beyond the scope of this review to be generally concerned about the elegant articles published on the area. Several rather comprehensive reviews have been published;[3] thus the purpose of the overview presented here is to highlight the two-year efforts (1992-94) of our laboratory focusing on fast and selective synthesis of key intermediates. The overall objective is to show the development of efficient synthetic routes aimed to improve the

practicability of the construction of the taxoid diterpene part (**1**).

Development of the synthetic plan

At the time that our work was initiated, around February 1992, a large volume of synthetic work, including review articles, had been reported in the literature although no total synthesis had been published and none appeared until we were commited to a promising route. In the event, despite the numerous publications in the area, the method we developed was different from all the other approaches. Guidance on the choice of starting material was provided by earlier work in our laboratory on the synthesis of pentacyclic triterpenes and by the knowledge acquired thereof.[4] The proposed pathway starts from the well-known (S)-(+)-Hajos-Parrish ketone (**2**)[5] as a precursor for the entire taxoid framework and places emphasis on step-efficiency and simplicity. The thought was to utilize a scheme which would provide the 20-carbons of the taxoid diterpene skeleton (**1**) from **2** with the only extra carbons (namely the 16 and 17 carbons) coming from methyl iodide. Thus we needed efficient routes to elaborated taxoid A and B ring building units from the same precursor. Recognition of the pattern that connects this starting material to the target involves an obvious disconnection for the left half, while as far as the right half is concerned there is no direct link between the starting material and the taxoid C-ring. Efforts to link the Hajos-Parrish ketone and its higher homologue, the Wieland-Miescher ketone, to the taxoid right half gave rise to a new ring expansion process, "the one-pot multistage transformations", which led to a number of interesting molecules.



Scheme 1 : Recognition of the key building block and attempted both-sides linking to the target.

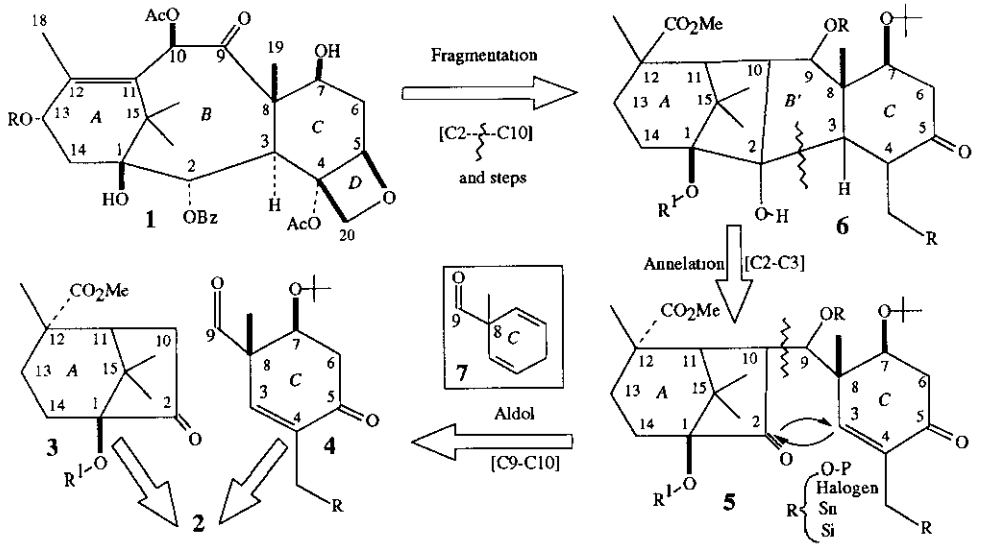
The long term objective was the diterpene part of taxoids (**1**), while the short term goals were A and C-ring fragments obtained from the same precursor (**2**) which should be elaborated in two different ways to

yield the "left" as well as the "right half moieties" of the taxane framework. In other words starting from the same molecule, we aimed to construct fragments then couple them together by incorporating them into one of the four distinct types of taxane construction as shown in Scheme 1. The synthesis of such a complex target molecule (**1**), raises several key issues which will be discussed below in the following order: how we planned to construct the whole taxoid skeleton from the Hajos-Parrish ketone and methyl iodide; how we tried to overcome the encountered difficulties and how these difficulties have been used to synthetic advantage. It is hoped that the information in this review will also be useful to "combined strategies" for taxoid synthesis.

General strategy

Our synthetic plan had to accommodate the requirement that both ring A and C segments be accessible from **2** by redesigning the route for each of them. This feature meant that **2** should be appropriately elaborated to allow access for both left (A) and right half (C) moieties of the taxoid diterpene framework. Linking the A and C ring segments *via* an aldol condensation would then require a procedure for creating the C2-C3 bond, the annelation. We thus elected to develop an approach to the synthesis of **1** that would rely on highly stereoselective aldol and annelation reactions to resolve all stereochemical issues.

Our approach focuses upon three transformations, the two first involve C-C σ-bond formation *via* the aldol-annelation sequence serving to link and then to convert A and C ring segments (**3** and **4** respectively) to a tetracyclic framework (**6**) ; the third is an oxidative cleavage used to generate the eight-membered taxoid B-ring. The key feature of our strategy was the indirect formation of the B-ring, supposedly the most critical to achieve, especially when it contains the appropriate substitution pattern on the periphery.



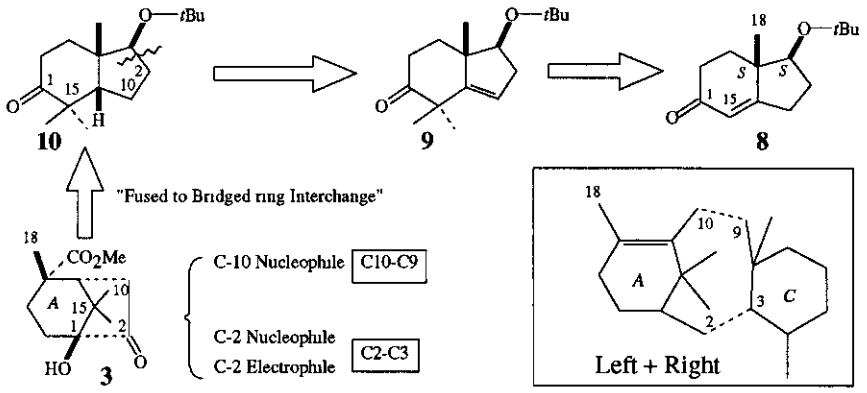
Scheme 2 : Target skeleton (**1**) and strategy

Prior to starting on such a major undertaking we felt it was necessary to test the feasibility of the proposed scheme. To this end we chose to concentrate control elements on the enantiopure enolate "the

left half aldol partner" while simplifying the right half aldol partner. The required achiral aldehyde (**7**) chosen as the model-precursor of ring C in order to simplify the aldol reaction outcome (homotopic faces on the aldehyde), could be prepared on large scale from methyl benzoate using literature conditions (*vide infra*). As we moved forward, things became complicated (as expected) forcing a continuous readjustment of the initial synthetic scheme and this is the main message of the present overview.

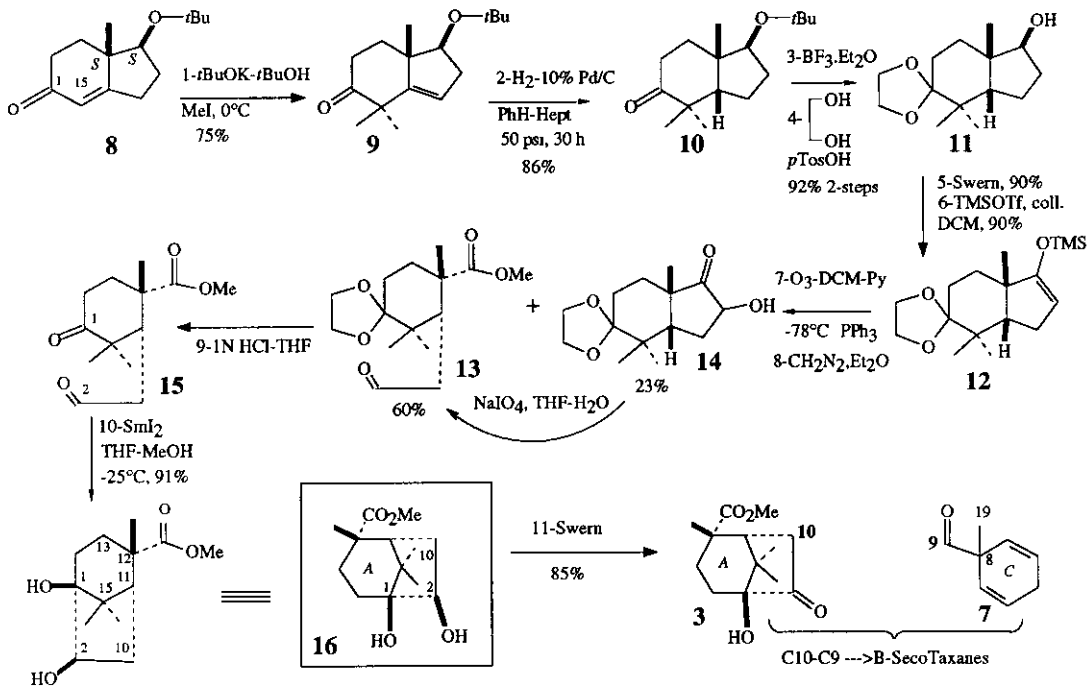
Construction of the "left half"

Retrosynthetic analysis for synthesizing the left-half building block, the bicyclo[3.2.1.]octane unit (**3**) involves the elaboration of the thermodynamically preferred *cis*-fused hydrindane[6] (**10**) and the C1-C2 bond formation leading to the bridged system. The presence of the C-1 oxygen (taxoid numbering) and the potential silyl enol ether formation at C-2 on the *cis*-fused hydrindane (**10**) was suggestive of a pinacol coupling to effect the C1-C2 bonding. This led to the question of how to generate the appropriate stereochemistry, the "*cis*-ring junction", which was simply introduced by catalytic hydrogenation. The two additional carbons at C-15 were provided by methyl iodide, the double bond migrating to the five membered ring (**8** to **9**). Put in this way, the overall transformation needed becomes a "Fused to Bridged Ring System Interchange" (Scheme 3).



Scheme 3 : Retrosynthetic analysis for the left-half building unit (**3**).

Accordingly, we decided to build up the left-half portion, the ring A, as outlined in Scheme 4.[7] gem-Dimethylation followed by catalytic hydrogenation, alcohol deprotection, ketone protection, oxidation and finally treatment with TMSOTf afforded the silyl enol ether (**12**), precursor of the required keto aldehyde (**15**). Once ozonolytic cleavage of the silyl enol ether had been implemented the resulting formyl acid was first exposed to diazomethane and then to dilute acid in tetrahydrofuran to unmask the C-1 carbonyl group. This appropriately set up the C1-C2 bond formation step leading to the bridged system. Conversion of the keto aldehyde (**15**) into bicyclo[3.2.1]octane (**16**) in high yield was achieved by SmI_2 mediated reductive coupling[8] stereospecifically, as a consequence of the *cis*-ring junction in the hydrindanone, fixing the absolute configuration of the C-1 center. The high yield pinacol coupling provided an excellent method for the assembly of the bicyclo[3.2.1]octane ring system (**16**) on multi-gram scale.



Scheme 4 : Setting the bridgehead hydroxyl group at C-1 in the desired absolute stereochemistry.

The significant ^{1}H and ^{13}C NMR (the arcs indicate diagnostic n.O.e.'s) data for the left half aldol partner (**3**) are summarized in Figure 1.

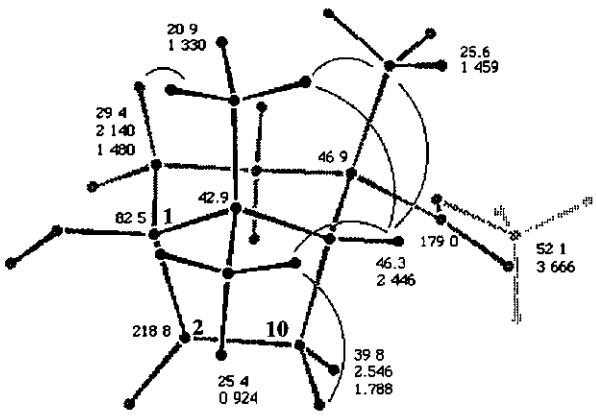
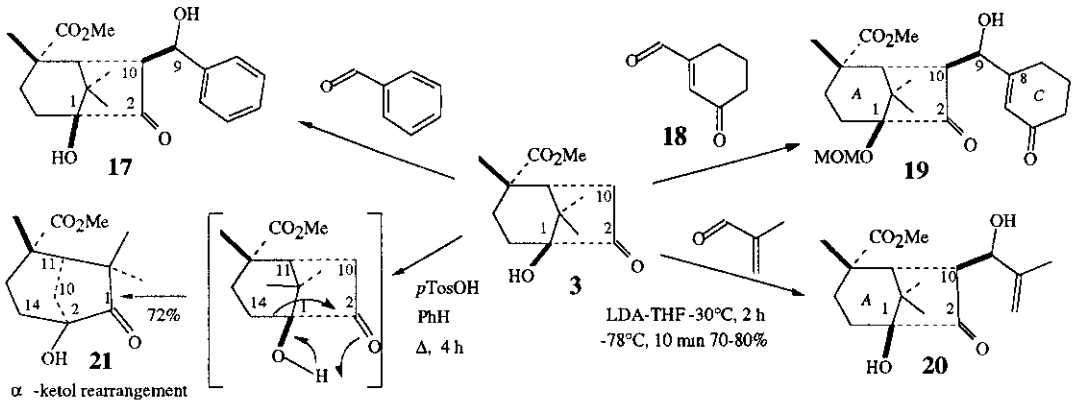


Figure 1: NMR data (chemical shifts and spatial proximities) of **3** shown on the lowest energy conformer as determined by molecular mechanics calculations, using MM2.

C9-C10 bond formation: the A+C linking

A Swern oxidation of the pinacol afforded the "left half" aldol partner (**3**). The aim was to couple this A-ring segment to a C-ring equivalent (**7**) ("right half" aldol partner) using lithium enolate aldol chemistry. But this aldol condensation never worked[9] and the C9-C10 coupling turned out to be more of a problem than we anticipated. Several alternatives were considered (titanium, cerium, boron enolates for example) unsuccessfully, and so we decided to study separately the reactivity of each aldol partner within conceptually similar synthetic schemes. Aldol condensations (LDA, THF, -30°C, 2 h, then addition of the appropriate aldehyde at -78°C, 10 min) with less hindered aldehydes, such as benzaldehyde, aldehyde (**18**) lacking the angular methyl group or just with methacrolein, afforded the B-seco taxane frameworks (**17**), **19** (both devoid of the angular methyl group at C-8) in 70-80 % isolated yields respectively together with recovered starting materials (Scheme 5).



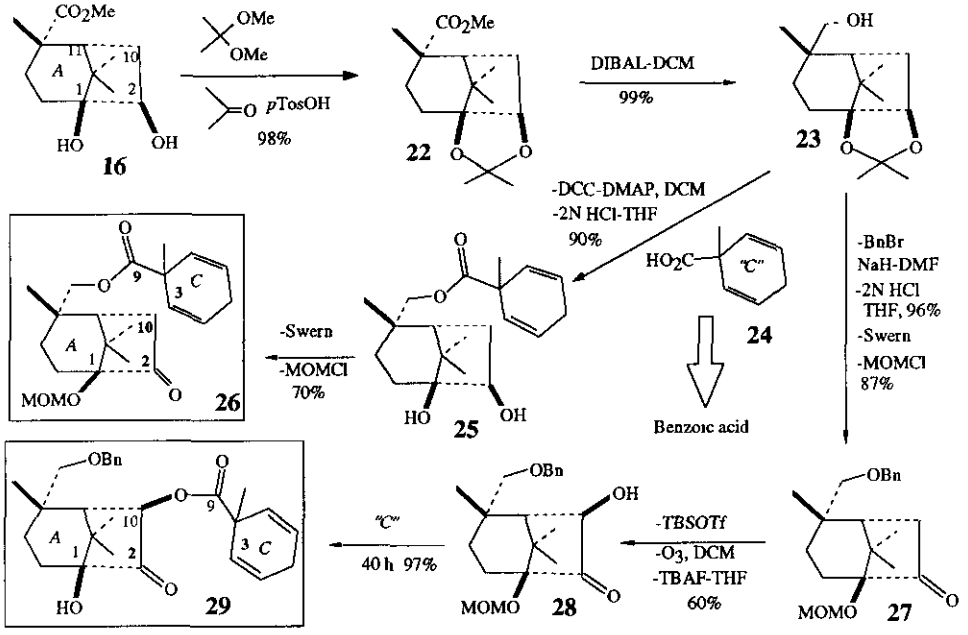
Scheme 5 : Aldol reactions of **3**; the C9-C10 bonding with model, less hindered, aldehydes.

The missing angular methyl group at C-8 could in principle be introduced in further steps either by a Birch reductive alkylation or a conjugate methyl cuprate addition followed by an intramolecular aldolization, but additional steps are needed for protection-deprotection of the existing functionalities. Under more forcing conditions, by heating in benzene in the presence of a catalytic amount of *p*TosOH, **3** was transformed to the ketol (**21**) after an α-ketol rearrangement as a consequence of the C14-C1 bond migration. From these results it became obvious that the left half aldol partner (**3**) behaves normally, the problem being severe steric interactions when put in reaction with its original counterpart (**7**).

Temporary A + C linking: the "indirection" approach

We had not anticipated the above cited problems with the A+C-coupling step, as the model work with benzaldehyde, methacrolein and **18** had not revealed any significant problems, therefore our failure to perform the aldol condensation between **3** and **7** was a severe setback. As the aldol reaction with the hindered aldehyde (**7**), having the angular methyl group at C-8, failed we considered the synthesis of target molecules (**26**) and (**29**), as an alternative sequence (Scheme 6). These molecules contain the left and right half moieties bonded in a way which allows further elaboration towards the taxoid ABC

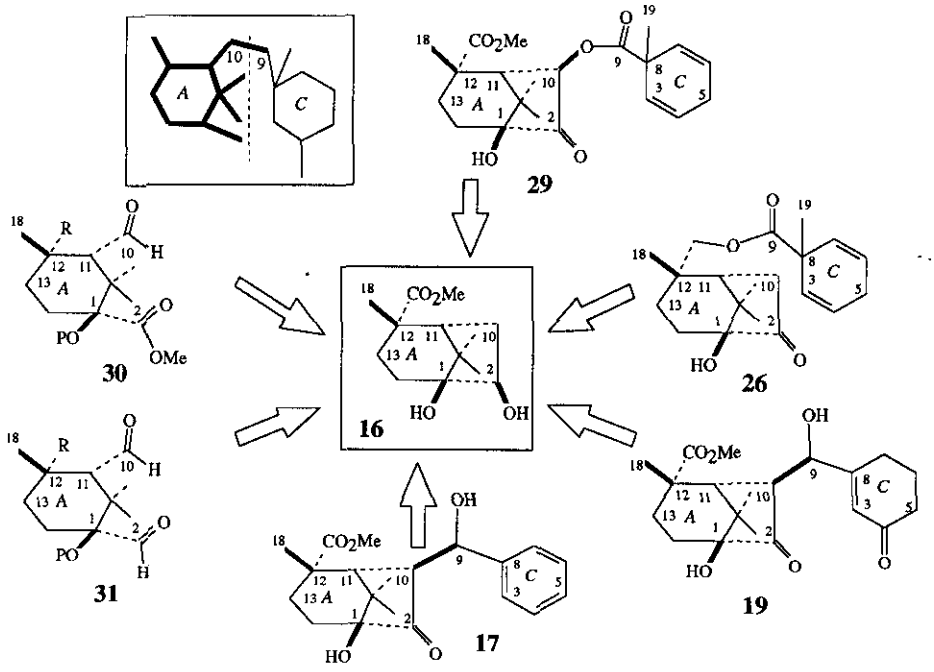
framework, using the same C-C bonding as in the initial strategy. This corresponds to a temporary A-C ring linking *via* an ester linkage, which makes the initial intermolecular A-C ring linking process an intramolecular one.



Scheme 6 : The "indirection" approach; towards a B-seco taxane *via* a dummy bond.

Starting from the pinacol (**16**), acetonide formation (**22**) followed by reduction gave the corresponding alcohol (**23**) in 99% yield. This alcohol was then processed to both target compounds using in both cases the benzoic acid derived C-ring precursor (**24**). Esterification of **23** with the appropriate acid (which corresponds to the right half aldol partner) led to the AC-ring ester (**25**) in 90% yield which after a Swern oxidation and MOM-protection afforded the desired target molecule (**26**) in 70% combined yield. The second target, **29** has also being accessed by a series of conventional functional group manipulations. Benzyl protection of the alcohol (**23**) followed by deprotection of the acetonide and subjection of the resulting diol to Swern oxidation, followed by MOM protection gave the protected α-ketol (**27**) in 80% overall yield. The latter was transformed by a three-step sequence (TBDMSOTf, Et_3N, CH_2Cl_2, rt, 2 h, followed by ozonolysis in CH_2Cl_2 at -78°C and subsequent desilylation with TBAF, THF, rt, 20 min) to the mono-protected bis-α-ketol (**28**) in 60% overall yield, which upon esterification with the same acid (**24**) as above gave a 97% yield of the second target (**29**). Lead tetraacetate mediated oxidative cleavage of the intermediate acyloin or its corresponding pinacol afforded cleanly highly elaborated, homochiral, A-ring segments (**30**) and (**31**) respectively.[10]

So far, investigating the reactivity of the left half aldol partner (**3**), we have succeded in synthesizing step-efficiently, B-seco-taxanes lacking the angular methyl group at C-8 such as **17** and **19**, molecules (**26**) and (**29**) with the A-C-ring linking achieved indirectly and the appropriately functionalized A-ring intermediates (**30**) and (**31**) (Scheme 7).



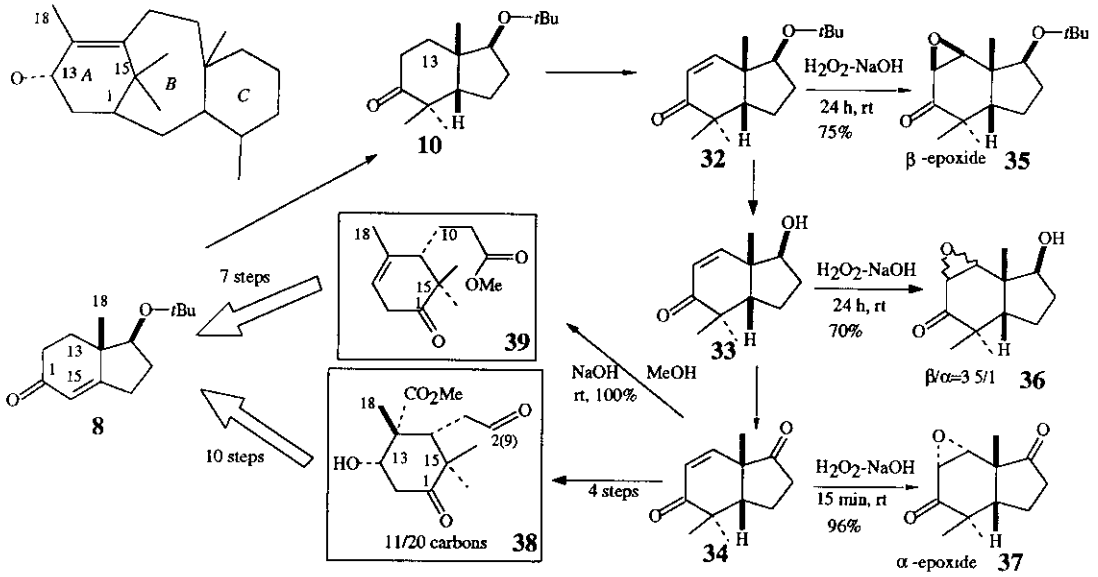
Scheme 7 : The bicyclo[3.2.1]octane unit (**16**) as an "A"-ring precursor.

Thus the bicyclo[3.2.1]octane derivative (**16**), obtained from the Hajos-Parrish ketone, served as starting material to several A-ring substructures for an A--> AC-->ABC mode of taxoid construction. Still at this stage, the C-13 oxygen functionality was missing.

Setting the C-13 center

To install the missing C-13 hydroxy functionality, we studied the nucleophilic epoxidation of three enones (**32**, **33**, and **34**) prepared from a common precursor (**10**), in a three-step sequence: TMS-enol formation by treatment with TMSOTf in collidine at -10°C for 15 min, followed by bromination with NBS-THF, -78°C, 10 min and subsequent dehydrobromination by refluxing for 1 h in dimethylacetamide in the presence of $CaCO_3$ (75% overall yield). With these three enones in hand the targeted diastereoselective epoxidation was then investigated leading to a discovery of a complete facial selectivity reversal going from the *t*Bu-protected enone (**32**) (gives β-epoxidation, as a single isomer) to the ene dione (**34**) (gives α-epoxidation, as a single isomer), while the free hydroxy enone derivative (**33**) gave mixed results (two diastereoisomers, β/α: 3.5/1) under the same reaction conditions. Thus, *t*Bu-protected enone (**32**) upon treatment with 30%-H_2O_2, 6N NaOH, MeOH, at rt for 24 h, afforded a 75% yield of β-epoxide (**35**). In contrast, nucleophilic epoxidation of the ene dione (**34**) was a delightfully fast reaction that was complete after only 15 min at rt affording in 96% yield the desired α-epoxide (**37**). Once **37** had been arrived at, conversion to the A-ring building block (**38**) could next be accomplished using known methodology. Room temperature treatment of α-epoxy diketone (**37**) with TBDMSOTF in CH_2Cl_2 in the presence of collidine followed by a SmI_2 mediated regioselective epoxide ring opening (3 equiv of SmI_2 in THF-MeOH at -90°C, 15 min) led to the corresponding aldol (90%, two steps).

Ozonolysis (O_3, CH_2Cl_2-Py, -78°C then PPh_3) and subsequent esterification (diazomethane, ether, 0°C), afforded **38** (72% from starting ene dione (**34**)), a conveniently functionalized homochiral A-ring component. Thus, appropriate processing of the ene dione (**34**) allowed for access to a C-13 α-hydroxylation as required for the taxoid A-ring.



Scheme 8 : Left-half building units: the C-13 functionalization.

A single step modification of the ene dione (**34**) (trace NaOH-MeOH-H_2O, rt, 2 h) led to compound (**39**) in a quantitative yield as a result of a nucleophilic addition to the non-conjugated carbonyl followed by a ring opening and a double bond migration. Due to allylic 1,2-strain, the chain bearing the C-10 carbon points downward (α-quasiaxial) and it is ideally situated for bottom-face ring closure operations. From molecular mechanics studies it appears that conformations for **32** and **34** , as depicted in Figure 2, are consistent with the observed diastereofacial selectivity.

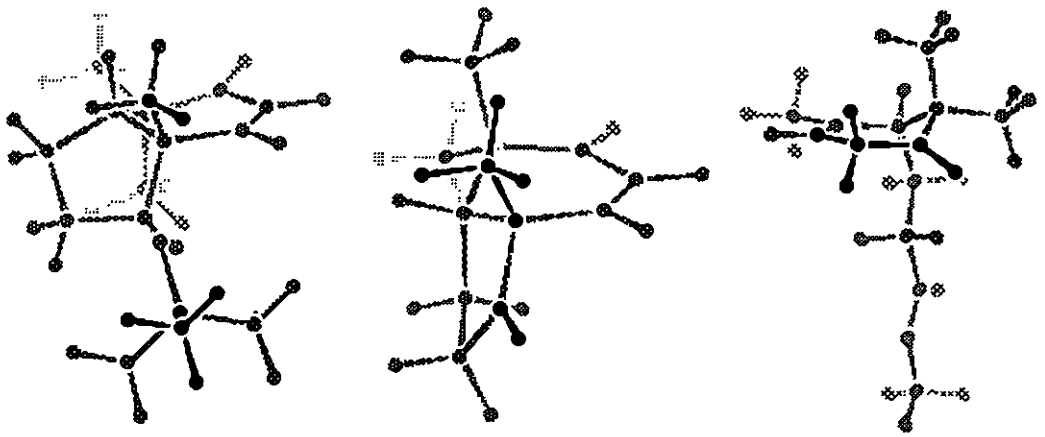


Figure 2 : Lowest energy conformers of **32**, **34** and **39** used to predict face selectivity.

The minimum energy conformations of **32** and **34** calculated by MM2 using Macromodel (in agreement with the observed n.O.e.'s) as shown in Figure 3 gave some insight into the observed stereoselectivity.

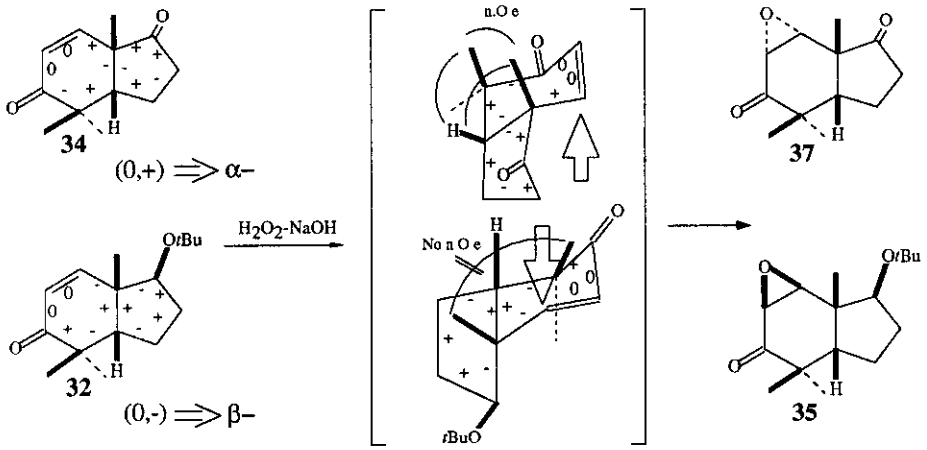
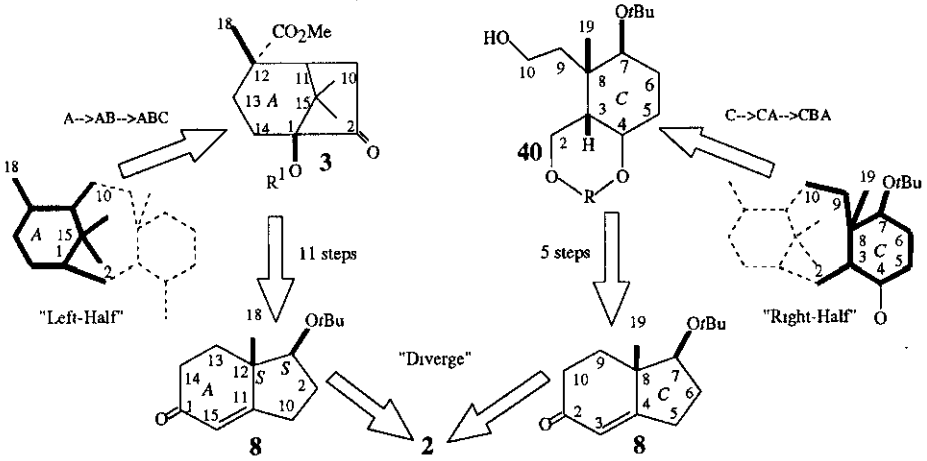


Figure 3 : Rationalization of the facial selectivity reversal using Torsion Angle Notation.

As can be seen from the MM2 calculated lowest energy conformations of the enones and rationalized using the Torsion Angle Notation[11] the stereoselectivity of epoxidation is controlled by the conformational preferences of the *cis*-fused bicyclic systems (**32**) and (**34**). Thus, in contrast to the nucleophilic epoxidation forming exclusively the β-epoxide on **32**, formation of the required α-epoxide occured when the same reaction was applied to **34**. This could be accounted for by the fact that the adopted conformations (confirmed by diagnostic n.O.e.'s) for **34** and **32** favor bottom face attack for the former and top face attack for the latter.

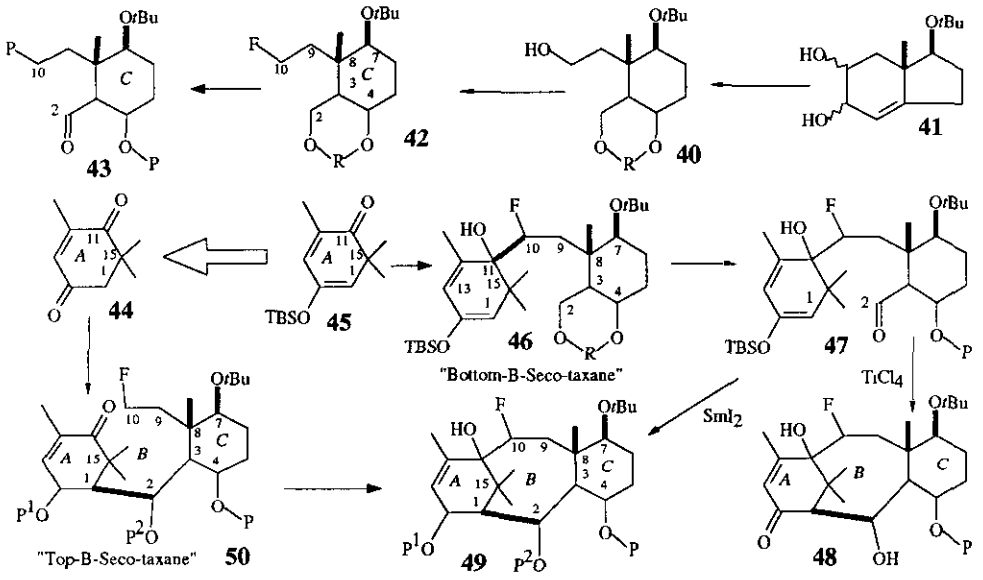
Construction of the "right half"

At this stage, the (S)-(+)-Hajos-Parrish ketone (**2**) has been used to synthesize the bicyclo[3.2.1.]octane derivative (**3**), a homochiral taxoid A-ring precursor (the "left half").



Scheme 9 : Left (**3**) and right-half (**40**) taxoid building units starting from Hajos-Parrish ketone.

To complete our synthetic project we required an enantioselective synthesis of a six-membered ring possessing four contiguous substituents and bearing a quaternary center, such as **40**, the "right half", starting again from the same precursor (**2**). The question raised now is how to go from the same molecule and in a limited number of steps towards the right half, or in other words how to link the same starting material to the taxoid C-ring moiety (Scheme 9). Our efforts to perform this heretofore unprecedented synthetic operation were proven quite successful and will be briefly described below. The basis of this investigation which constitutes the nonobvious disconnection in our retrosynthetic analysis, is the unsuspected course of the oxidative cleavage of *vic*-diols allowing the production in a single operation of a significantly more complex molecule of high synthetic value. Specifically the diols we are considering are derived from the Hajos-Parrish and its higher homologue the Wieland-Miescher ketone. These experiments were designed to explore a stereocontrolled and flexible approach to the taxoid ABC-ring substructure with the intention of subsequently synthesizing taxoid analogues (Scheme 10).



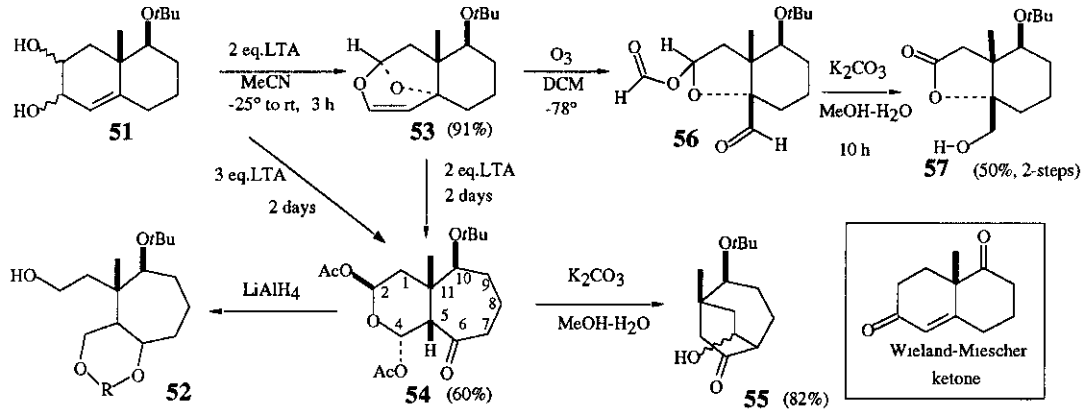
Scheme 10 : Towards a 10-step elaboration of the homochiral ABC taxoid framework.

Following a conventional A-C ring linking (the A-ring precursor (**44**), oxo-isophorone, being a commercial compound) the homochiral ABC-taxoid framework might have been reached in less then ten linear steps. Installation of the oxygen functionalities at C-10, C-9 and C-1 might have been reasonably easy by arranging the C9-C10 part and the mode of bonding at C10-C11 and C1-C2. The key feature of this synthetic scheme is the one-pot multi-stage transformations that occurred upon attempted oxidative cleavage of the starting unsaturated diol (**41**). Initially, the strategy was based on the higher homologue of **41**, the unsaturated diol (**51**) (derived from the Wieland-Miescher ketone). While we were nicely moving forward, the Danishefsky group published an approach starting from the Wieland-Miescher ketone and leading to a CD-intermediate.[12] This led us to reconsider our retrosynthetic scheme, while trying to use at least a part of our efforts, in a different direction. That was the beginning of the discovery

of new cascade type transformations.

One-pot multistage transformations

Let us first examine the outcome of the oxidative cleavage of compound (**51**), easily obtained from the Wieland-Miescher ketone (Scheme 11). The unsaturated diol system is introduced *via* routine methods and the cleavage is effected by use of commercial lead tetraacetate. Thus, treatment of the epimeric mixture (**51**) with 2 equiv of lead tetraacetate in acetonitrile followed by filtration through Celite and silica gel afforded the isolable tricyclic enol ether (**53**) in 91% yield. Upon resubjection of this tricyclic enol ether to LTA or simply upon stirring the starting diol (**51**) and 3 equiv of LTA for a longer period of time (50 h at rt) we obtained straightforwardly the ring enlarged compound (**54**) in 60% isolated yield, together with unreacted tricyclic enol ether (**53**).[13] The LTA mediated one-pot multistage transformations described above have led to an efficient route for the synthesis of seven membered ring compounds possessing functional diversity. The potential of this route to cycloheptane derivatives compares favorably with other reported methods by its mild reaction conditions and a minimum number of synthetic steps.[14]



Scheme 11 : Cascade transformations mediated by lead tetraacetate (LTA) on octalinediols.

Therefore, in three short operations starting from the unsaturated diol (**51**), the bicyclic lactone (**57**) can be obtained while only two steps take us to the ring enlarged-bridged compound (**55**). Thus, base treatment of the ring enlarged compound (**54**) (K_2CO_3-MeOH-H_2O, rt, 16 h) led to the bicyclo[3.2.2]nonane derivative (**55**) as an epimeric mixture in 82% yield. On the other hand, by ozonolysis of **53** in dichloromethane, and subsequent base treatment of the resulting acetal-aldehyde (**56**) (K_2CO_3, MeOH-H_2O, 10 h), the bicyclic lactone (**57**) which can serve as a taxoid C-ring segment was obtained in 50% yield, presumably *via* a Cannizzaro type oxido-reduction. The stereochemistry of the acetal centers at C-2 and C-4 (numbering is arbitrary) in bis-acetoxy acetal (**54**) is as depicted in Scheme 11 and was determined by a comprehensive range of spatial proximity studies using the 1D-NOEDIFF method. For stereoelectronic reasons, at least one of the acetoxy groups (the one at C-2) prefers to adopt an axial arrangement to benefit from the anomeric effect with the ring oxygen. Thus the stereochemical

arrangement at C-2 might have been controlled both by the cavity of the [7+6] *cis*-fused bicyclic ring system and the anomerically more favorable, axially oriented carbon-oxygen bond disposition, while the one at C-4 is controlled by the intramolecular acetate anion delivery (see Figure 4 and Scheme 14).

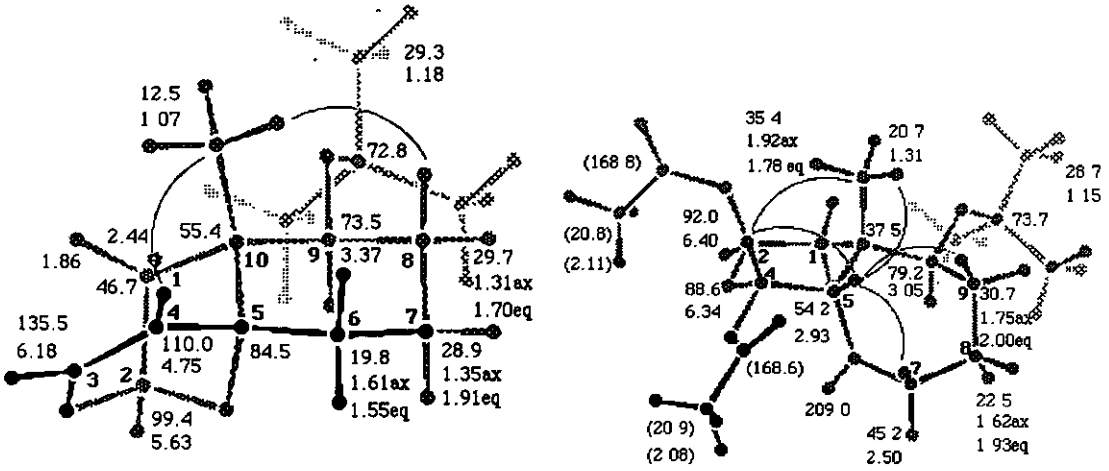
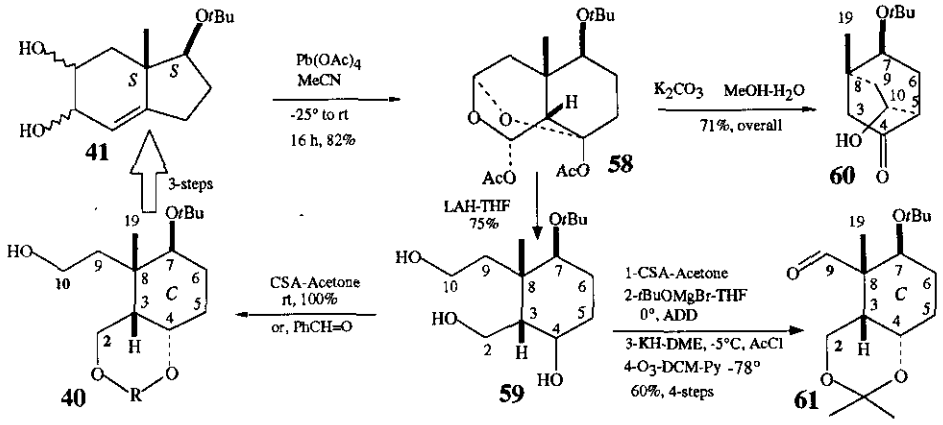


Figure 4 : NMR data and spatial proximities shown on lowest energy conformers of **53** (n=2) and **54**.

The lead tetraacetate mediated ring expansion-skeletal reorganization process could be further extended to prepare seven membered ring containing fused bicyclic compounds or medium size ring systems using known literature procedures (such as Claisen or oxy-Cope); this would offer a route for the easy homochiral preparation of such compounds. Overall, starting from **51** we can efficiently go in three directions: a one step ring expansion followed by rearrangements and leading to the functionalized homochiral 7-membered ring system (**54**); a two-step "Fused to Bridged Ring System Interchange" leading to the bicyclo[3.2.2]nonane framework (**55**); a three-step formation of the rearranged-bicyclic lactone (**57**).

In the Hajos-Parrish series, the lead tetraacetate mediated oxidative cleavage proved also of high synthetic interest. The known unsaturated diol (**41**), obtained according to our previous work, afforded upon treatment with 3 equiv. of LTA in acetonitrile followed by filtration through Celite and silica gel, the ring expanded compound (**58**) in 82% isolated yield. Its conversion to the target (**40**), a useful taxoid C-ring building block containing 10 out of the 20 carbon atoms of taxoid diterpene (**1**), oxygen functionalities at C-2, C-4, C-7, C-10 and the required absolute configuration on C-8, C-7, was straightforward. First, reduction of **58** with excess $LiAlH_4$ afforded **59** as a 9:1 epimeric mixture. Triol differentiation was then effectively achieved *via* the formation of the acetonide. The three steps from **41** to **40** proceeded with an efficiency of 62%. Furthermore, selective differential blocking of the hydroxyl groups may be achieved in various ways, some of them (such as benzylideneacetals, cyclic ketene acetals, stannylene derivatives) offering additional chemoselectivity thus making available the fully functional taxoid C-ring moiety (the right half). Searching for a C-ring component suitable for a C-9/C-10 coupling, we further transformed **40** into the C-9 electrophile (**61**) through the C-10 aldehyde,

obtained by the oxidation of the remaining primary alcohol (*t*BuOMgBr, THF, 0°C, then 1,1'-(azodicarbonyl)dipiperidine ADD, THF, 0°C to rt, 1 h). Conversion to the corresponding enol acetate (KH, DME, -5°C, 15 min for the enolate formation, then AcCl, DME, DMAP, rt, 15 min) and subsequent ozonolysis (O_3, DCM, Py, -70°C, then PPh_3) afforded **61** in 60% combined yield. Base treatment of the first obtained tricyclic intermediate (**58**) (K_2CO_3, MeOH-H_2O, rt, 15 h) led to the bicyclo[2.2.2]octane framework (**60**), a highly elaborated taxoid C-ring precursor, in 92% yield. This again constitutes a 2-step "Fused to Bridged Ring System Interchange" from **41** to **60**.[15]



Scheme 12 : Cascade transformations on hydrindene diols mediated by lead tetraacetate.

The complex structure of **58** was unambiguously established by high field NMR studies using two-dimensional experiments in combination with the 1D NOEDIFF technique, supported by a computer assisted conformational analysis *via* Still's Macromodel program (Figure 5) and finally confirmed by X-ray analysis.

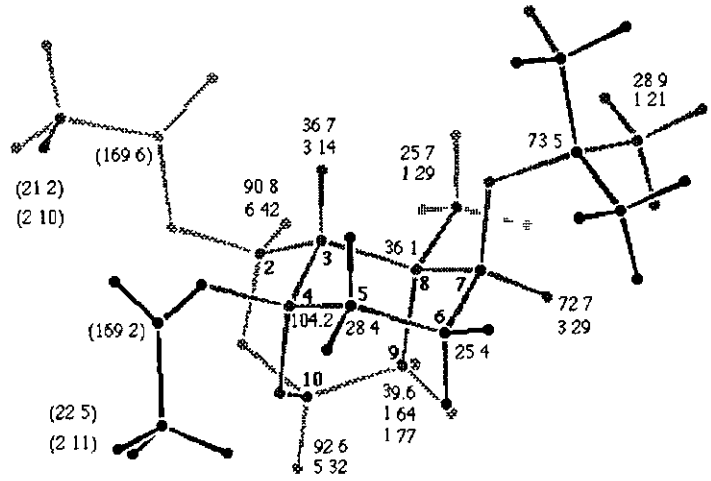
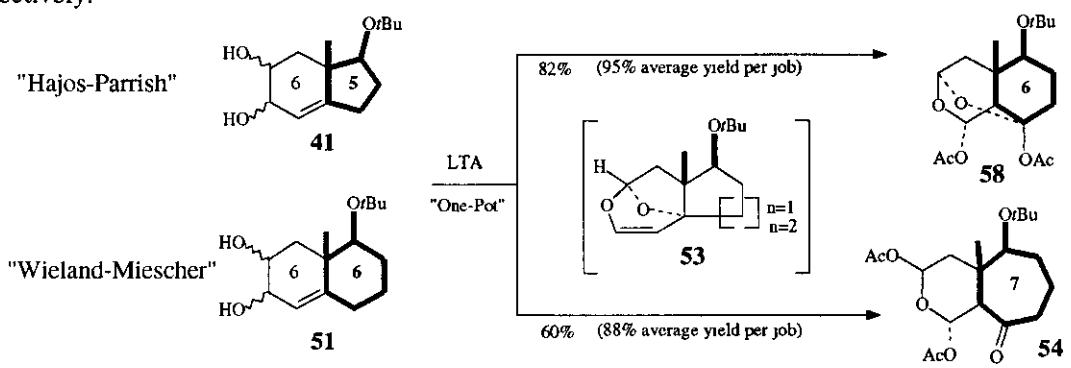


Figure 5 : NMR data (^1H and ^{13}C chemical shifts) of **58** shown on the lowest energy conformer.

In both series, the reaction sequence can be monitored by TLC with all intermediates and the final

product possessing distinct R_f values. In the Hajos-Parrish series, five minutes after addition of the oxidant, two new higher R_f spots appear on the TLC: a UV active spot (dialdehyde) together with a second, higher R_f, non UV active one (tricyclic enol ether (**53**), n=1, see Scheme 13). This nearly 1:1 equilibrium mixture can remain unchanged for months but upon addition of one more equivalent of oxidant (at any time) the first two spots disappear and a third non UV active lower R_f spot (**58**) appears. In the Wieland-Miescher series the dialdehyde initially formed (a higher Rf UV active spot) was entirely transformed to a lower R_f non UV active spot, the tricyclic enol ether (**53**) (n=2), upon 3 h room temperature stirring. One more equivalent of LTA and two more days at room temperature stirring then gave rise to a still lower R_f spot corresponding to **54**.

So far the oxidative cleavage of the unsaturated diols has produced a new straightforward and versatile method for a ring expansion/rearrangement process; four reactions are performed sequentially *via* a tricyclic enol ether intermediate (**53**) which can not be isolated in the Hajos-Parrish series[16] (n=1) but is perfectly stable and thus can be isolated in the Wieland-Miescher series (n=2, Scheme 13). In the Hajos-Parrish series the overall LTA mediated transformation from the starting unsaturated diol (**41**) (in one-pot), was a ring expansion/functional redistribution leading to a tetrasubstituted cyclohexane. In the Wieland-Miescher series the overall LTA mediated transformation starting from the unsaturated diol (**51**), either stepwise through the isolable tricyclic enol ether intermediate (**53**) (n=2) or in one-pot, was again a ring expansion/functional redistribution leading to a tetrasubstituted cycloheptane. The synthetic utility of such a transformation leading to a fully functional optically pure taxoid C-ring offering easy C-10 and C-2 linking in only five steps and high isolated yields is obvious. However, a huge amount of structural analysis and thinking time was devoted to the understanding of these transformations. Usually each reaction step is carried out separately, with its own reaction conditions (temperature, solvent and reagent). The LTA-mediated fragmentations combine multiple bond-forming and bond-breaking sequences into a one pot reaction thus eliminating duplication of steps, reducing protections-deprotections, and the temporary use of functional groups that must be removed later. Only one workup is needed from the unsaturated diols (**41**) and (**51**) to the ring-enlarged compounds (**58**) and (**54**) respectively.



Scheme 13: Time, energy, raw material saving mild transformations at room temperature and atmospheric pressure; lead tetraacetate as a one pot "multi-job" reagent.

The starting diols can be readily assembled and constitute attractive precursors for taxoid building

blocks, highly elaborated cyclohexanes, cycloheptanes and a number of fused and bridged bicyclic systems.

To account for the above transformations we propose to consider the following facts. Of all the elements of Group IV Pb has the largest covalent radius. This leads to large interatomic distances and correspondingly small bonding energies. The divalent state is dominant for Pb having the smallest bonding energies of the carbon family. Inorganic Tl^{3+} salts are Lewis acids and can react as typical electrophiles with unsaturated organic substrates such as olefins. Hg^{2+} and Pb^{4+} are isoelectronic ($5d^0$) and behave in the same way. The most important aspect of lead chemistry is the great facility with which Pb^{4+} undergoes reduction to Pb^{2+}; for the redox potential of Pb^{4+}/Pb^{2+}, Latimer states a value of 1.7V (Figure 6).[17]

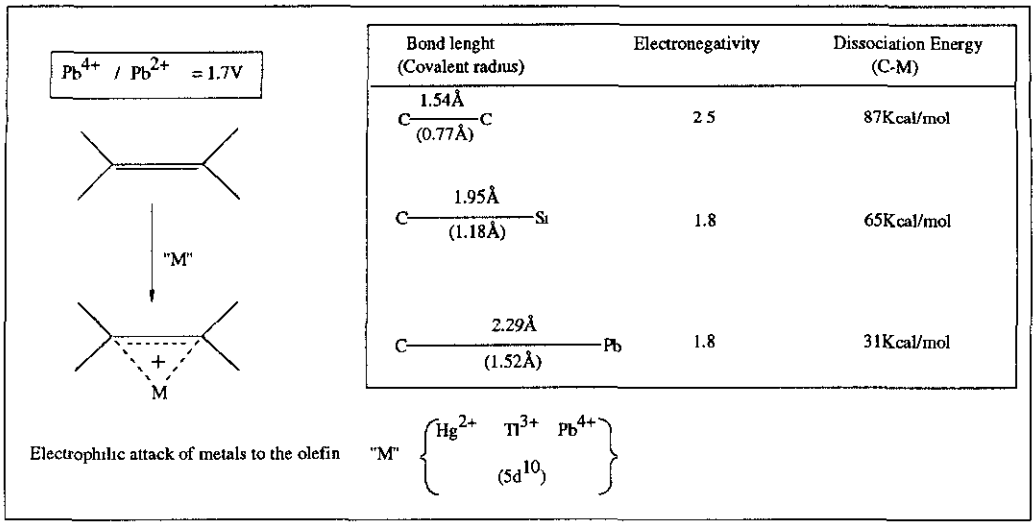
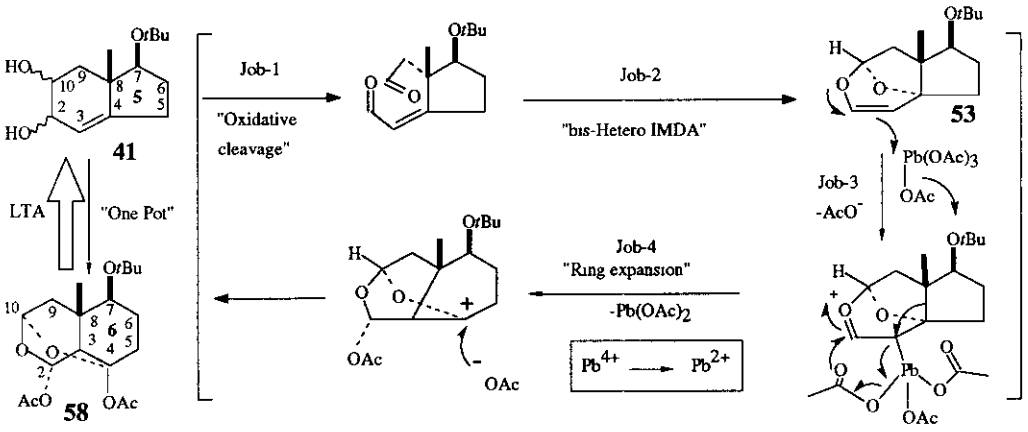


Figure 6 : Some pertinent facts in obtaining a mechanistic rationale.

Insofar as the precise mechanistic details are concerned, the results are consistent with the sequence of events proposed in Scheme 14 (job-1 through job-4) and although they have yet to be rigorously established, most of them can reasonably be rationalized as follows. The final ring-enlarged product (**58**), is obtained *via* the formation of the intermediate dialdehyde (oxidative cleavage, job-1); this collapses to give the tricyclic enol ether **53** *via* an intramolecular bis-hetero-Diels-Alder reaction (job-2), setting the conditions for the next step: an electrophilic attack of the metal on the electron rich olefin (job-3) leading to the formation of a C-Pb bond. The strain associated with the ring system then favors a ring expansion with concomitant loss of $Pb(OAc)_2$ and acylation at C-2 and C-4 (taxoid numbering). The mechanistic picture for these "domino" transformations is portrayed in Scheme 14.[18] The thermodynamically favorable valence change and the ability of Pb^{4+} to act as an oxidizing agent (job-1) and a Lewis acid (job-3 and probably job-2, catalyzing the IMDA) together with the high polarizability of the Pb-C bond, associated with its low dissociation energy, fit with the proposed mechanism of the cascade transformations. At the present time there is ample evidence to support the operation of each of the four

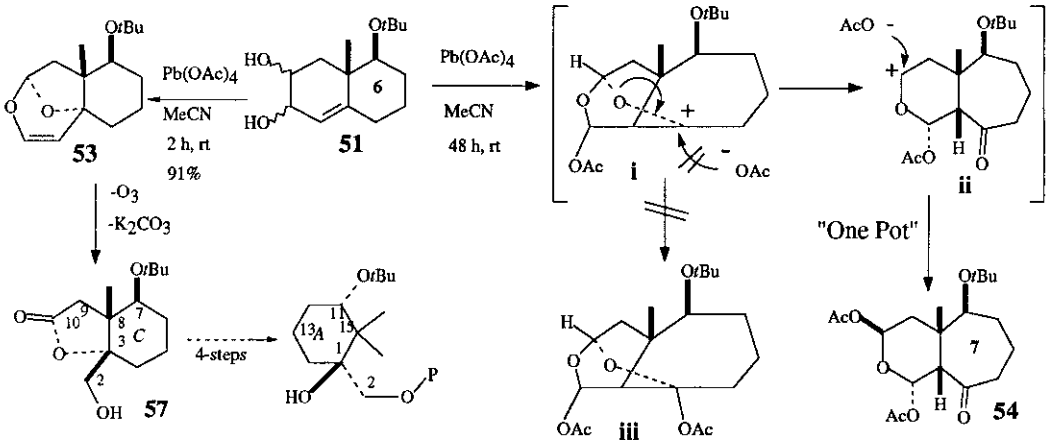
mechanisms proposed in Scheme 14 and no compelling reasons to discount any. The job-1 mechanism is an oxidative cleavage found in textbooks. Job-2 is an intramolecular hetero-Diels-Alder [4+2] cycloaddition where both diene and dienophile components contain a heteroatom. Job-3 is an electrophilic attack on an olefin by a metal and is entirely analogous to the chemistry of thalium, mercury and lead elegantly developed by McKillop,[19] Larock[20] and Rubottom[21] respectively. Finally, the job-4 mechanism which gives rise to a ring expansion (probably with one of the acetates assisting the ring enlargement) is by far the most important of the cascade as it contains the step including the driving force operation.



Scheme 14: A mechanistic rationale for the one-pot multistage transformations in the Hajos-Parrish series.

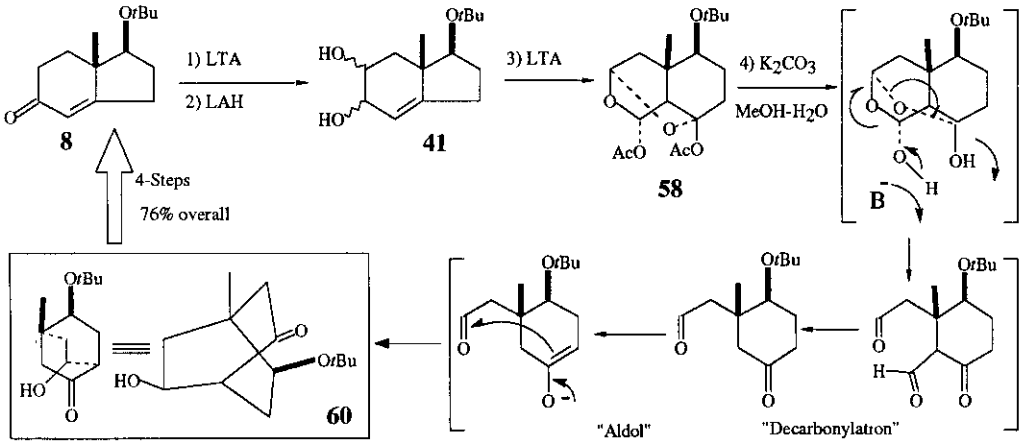
On the Wieland-Miescher series the same mechanistic course would operate to give the bridgehead cation **i** which first undergoes skeletal rearrangement into **ii** and subsequent acetate attack, leading to the ring enlarged compound (**54**). The driving force for the above transformation could be attributed to the enhanced stability of **54** due to the relief of non-bonded interactions accompanying the transformation of a tetrahedral ring atom into a trigonal one. Indeed, in the Hajos-Parrish series, acetate attack on the bridgehead cation leads to a strain-free six-membered ring with a bridgehead acetate as the only product formed. The proposed mechanism for the one-pot transformation of **51** to **54** is summarized in Scheme 15. Product formation for **54** can be explained as arising from the alternative cation **ii** derived from the resonance stabilized cation **i**. In theory, the bridgehead cation **i** could evolve in two ways to yield a ring-expanded product: either by direct attack of the acyl ion yielding an sp^3 center in the seven-membered ring (**iii**) or by forming first the rearranged cation **ii** and subsequent acyl ion attack. The skeletal rearrangement **i-ii**, proposed for the intermediate bridgehead cation is preferred because it releases strain associated with the eclipsing and transannular interactions. A further explanation for the diverging behaviour of the bridgehead cations derived from **41** and **51** is that resonance stabilization at this point would lead to bridgehead double bonds. Due to the relative strain energies of these putative "Anti-Bredt" cations, we can assume that one of these ring systems (the former) could not accommodate a bridgehead double bond. From this point on, the favorable energy features associated with the resonance stabilization

of cations and the thermodynamic stability of the product (introduction of an sp^2 center in the seven-membered ring) dictates the specific reaction outcome.



Scheme 15: A mechanistic rationale for the cascade transformations in the Wieland-Miescher series.

Yet another difference is that the cascade can be interrupted on the Wieland-Miescher series as the tricyclic enol ether (**53**) can be easily isolated thus allowing for a differential functional group interconversion. Even though the LTA mediated cascade transformations starting from **51** can afford both C and A-ring intermediates, the way towards the right half (C-ring) moiety is more attractive.



Scheme 16 : The bicyclo[2.2.2]octane framework *via* two consecutive cascade transformations.

The C-ring taxoid intermediate (**58**) obtained through the LTA mediated cascade afforded again in an one pot operation, after a skeletal reorganization, compound (**60**) which could either be used as a taxoid C-ring precursor or as a precursor for the synthesis of other natural compounds. Thus, basic treatment of **58** led to a suitably functionalized bicyclo[2.2.2.]octane derivative through a decarbonylation and subsequent aldolization as shown in Scheme 16. Extensive ^1H and ^{13}C NMR studies unambiguously established the relative configurations thus providing a complete picture of the structure of **60** as shown

in Figure 7.

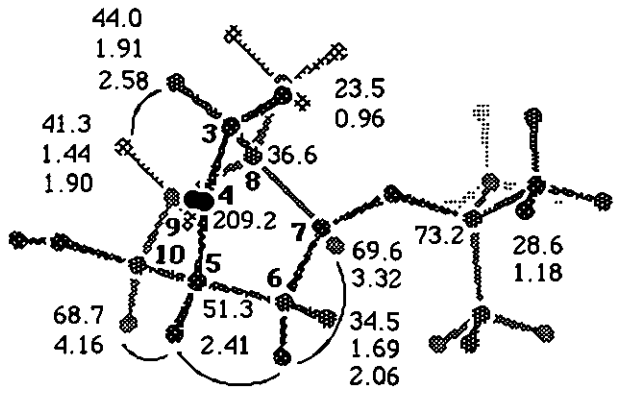
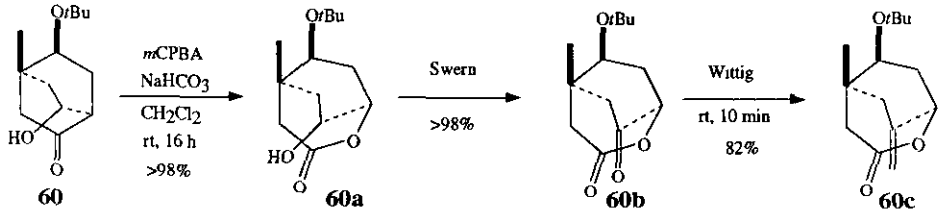


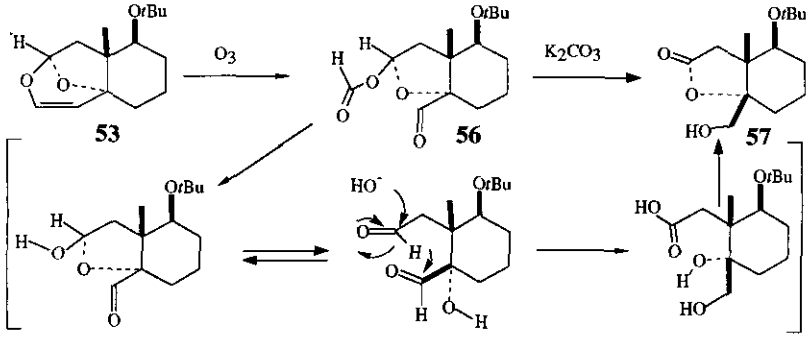
Figure 7 : NMR data and diagnostic n.O.e.'s shown on lowest energy conformer of **60**.

Overall we have a four-step "fused to bridged ring system interchange" ensuring functional diversity and enantiomeric purity. The three functional groups (free hydroxyl, *t*Bu-protected hydroxyl and carbonyl) on each ring offer easy chemodifferentiation for further selective transformations. Thus, following chemoselective functional group manipulation, the optically pure **60c** was obtained in a three-step process and high yield from readily available **60**.



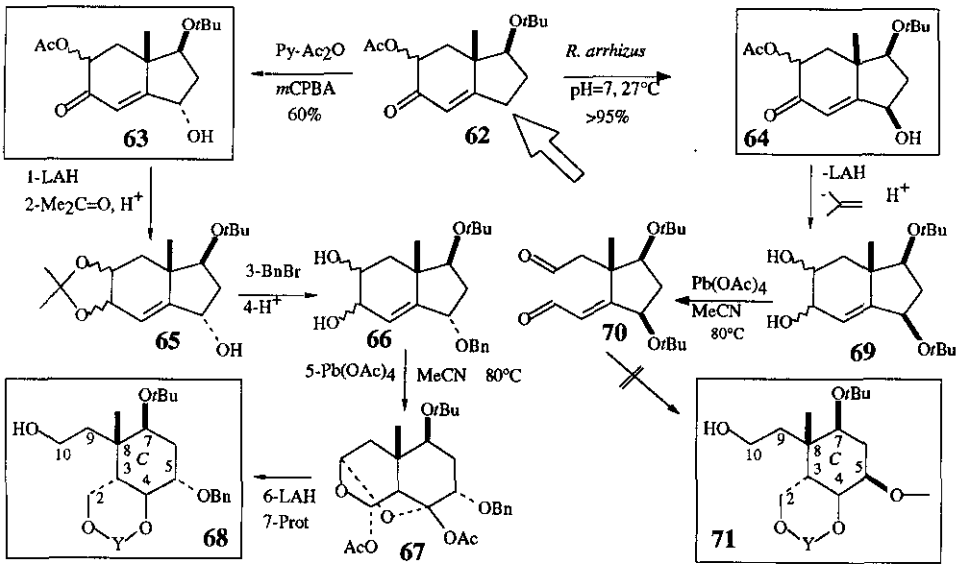
Scheme 17

As in the Hajos-Parrish series one pot multistage transformations continued in the Wieland-Miescher series leading to a new type of taxoid C-ring intermediate.



Scheme 18 : Cannizzaro type oxido-reduction leading to a bicyclic lactone formation.

The isolable tricyclic enol ether (**53**) obtained in one pot with LTA mediated cleavage of **51** afforded, following ozonolysis and basic treatment, the bicyclic lactone (**57**), the overall process being an intramolecular Cannizzaro type oxido-reduction (Scheme 18). The chemistry of this compound is not yet investigated but its straightforward obtention from the unsaturated diol in only three steps is promising.
The ready availability of the above cited building blocks provided incentive for analysis of the scope of this cascade chemistry. Thus, we focused our attention on a brief "scope and limitation" study, based on varying the substitution pattern of the bicyclic framework. For the compounds studied, donor or acceptor substituents such as methyl or ester group on the double bond altered the process which stopped after the second job (tricyclic enol ether stage; incomplete cascade transformation due to steric interference caused by the alkyl or acyl groups). In the context of our above mentioned work on the taxoid studies, we next focused on the synthesis of **66** and **69** to include a route which would be amenable to the fully functional taxoid right half moiety.



Scheme 19 : The allylic hydroxy substitution in Hajos-Parrish series.

Besides the fact that important mechanistic information could be gained by the use of **66** and **69** as cascade precursors, they also were expected to be excellent synthetic intermediates as C-ring components. To this end, **63** and **64**[22] were converted to the corresponding diols (**66**) and (**69**); this was simply performed by starting with the appropriate acetoxyenones (obtained *via* routine methods) and subjecting them to a reduction-protection operation as delineated in Scheme 19. The compound (**69**) containing an allylic β-alkoxy substituent failed to give any rearranged product with the process being stopped at the oxidative fragmentation step leading to the dialdehyde (**70**). On the other hand, α-hydroxy substitution, compound (**66**), slows down the four-job process and lowers the yield. At the best 30% yield of 5-α-alkoxy-substituted taxoid C-ring precursor (**68**) was obtained but under different conditions. Instead of room temperature stirring, the reaction has to be carried out using a pre-heated oil bath at

80°C. Although synthetically less attractive, the last two experiments shed a little more light on the mechanistic aspect of the cascade story.[23] The choice of these substrates was dictated by the extreme importance of target compounds (**68**) and (**71**) in taxoid chemistry (functionalized enantiopure C-ring units). With a β-hydroxy substituent on the allylic position the process was stopped right after the first job, the only observed transformation being the oxidative cleavage affording dialdehyde (**70**).

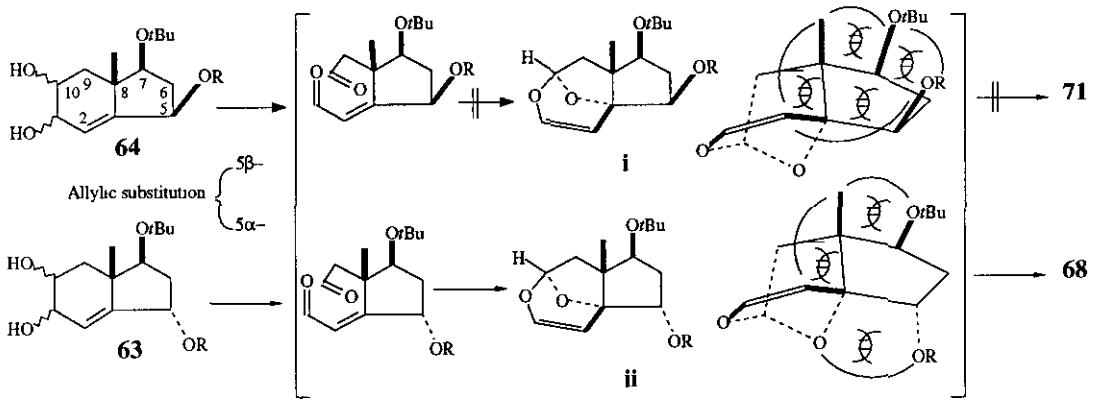
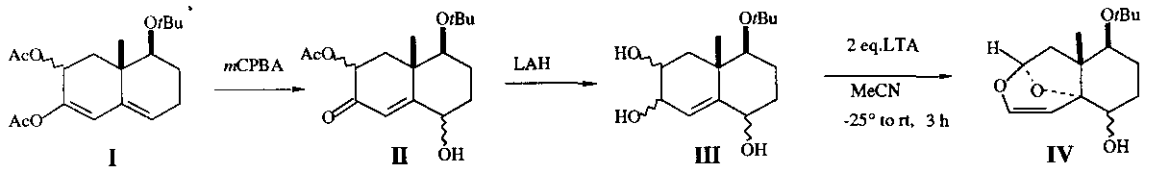


Figure 6 : Rationalizing the effect of α/β-allylic substitution in Hajos-Parrish series.

This could be rationalized with the high degree of steric hindrance on the five membered ring (tricyclic enol ether **i**), which should accommodate four substituents on the β-face. On the other hand, the α-hydroxy substitution slows down the second job (IMDA) by hindering the α-face of the five membered ring (tricyclic enol ether **ii**), but only three substituents are present on the β-face; the same degree of β-face substitution as in **41**, on which the cascade process works perfectly well (Figure 6).

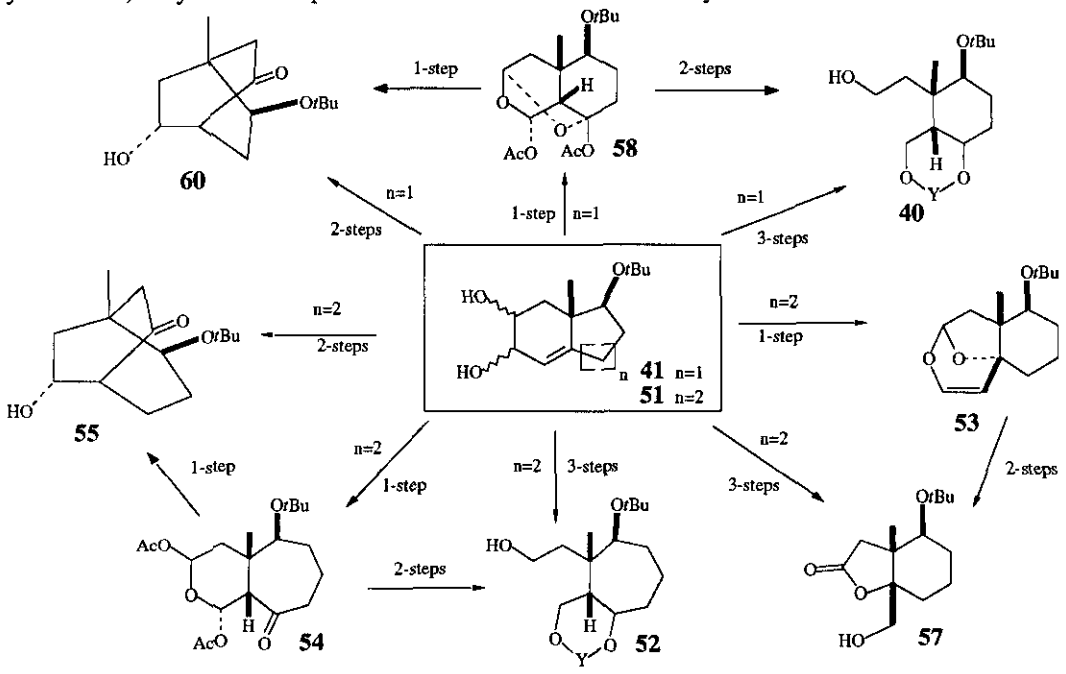
Finally, the allylic substitution on the Wieland-Miescher series is well accepted. Three h room temperature stirring in the presence of LTA gives high yields of the tricyclic enol ether (**IV**) which can be processed further. Protection of the hydroxy substituent (as *t*Bu ether) is useless, free hydroxy group stays intact under the reaction conditions. The same insofar as the hydroxy group stereochemistry is concerned. It works either with α- or β-hydroxy substitution (transformation **III** to **IV**, Scheme 20). Its validity in the synthetic context will be demonstrated hopefully in the near future.[24]



Scheme 20 : The allylic hydroxy substitution in Wieland-Miescher series.

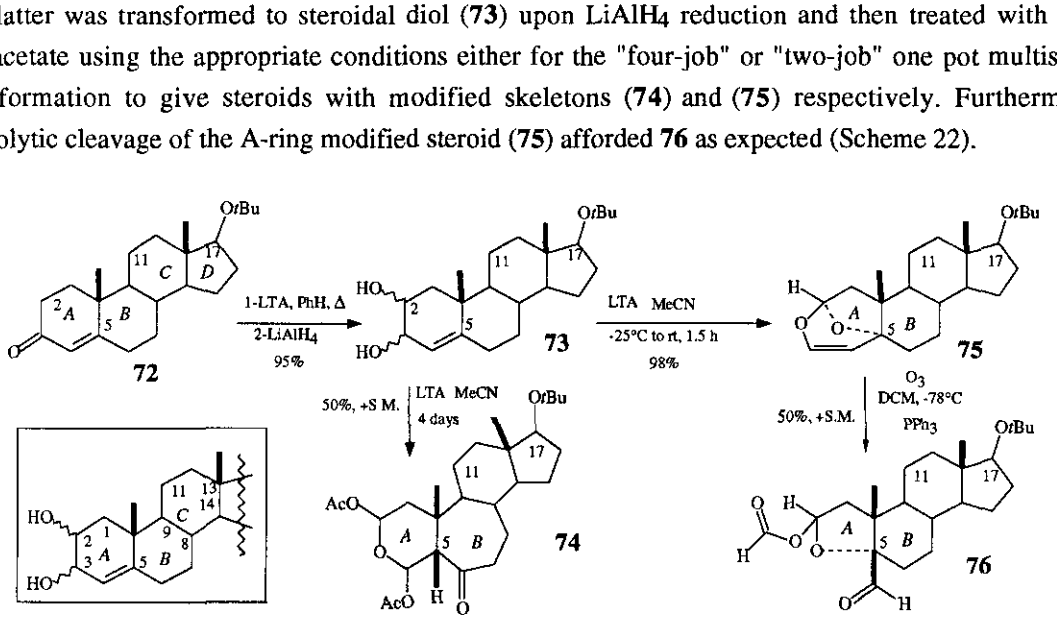
Once in hand the ring-expanded products obtained from the selected unsaturated diols (**41**) and (**51**), were transformed *via* simple operations to a series of novel frameworks. Scheme 21 summarizes some of the versatile synthetic properties exhibited by the readily accessible enantiopure (both antipodes are

easily available) bicyclic diols upon treatment with LTA followed by trivial transformations.



Scheme 21 : Cascade transformations; a novel ring-expansion/rearrangement methodology.

The oxidative cleavage process first investigated with the unsaturated diols obtained from Hajos-Parrish and Wieland-Miescher ketones was than extended to steroidal unsaturated diols; this provided ready access to A and AB-ring modified Homo-steroids (ref. 13). The required building block (**73**) was prepared in a straightforward manner from 17-O*t*Bu-protected testosterone (**72**) using known procedures. The latter was transformed to steroidal diol (**73**) upon $LiAlH_4$ reduction and then treated with lead tetraacetate using the appropriate conditions either for the "four-job" or "two-job" one pot multistage transformation to give steroids with modified skeletons (**74**) and (**75**) respectively. Furthermore, ozonolytic cleavage of the A-ring modified steroid (**75**) afforded **76** as expected (Scheme 22).

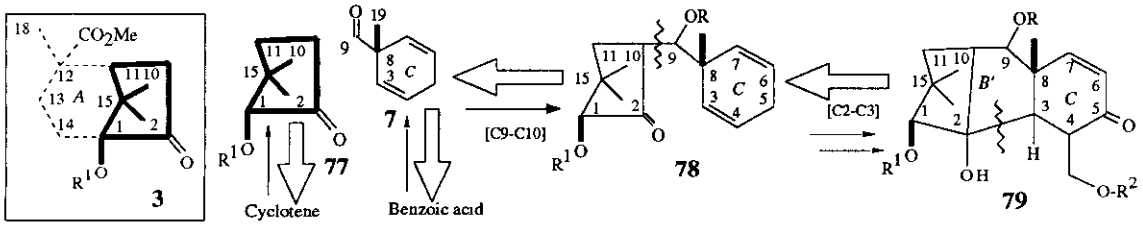


Scheme 22 : Cascade transformations on steroidal unsaturated diols; Homosteroids.

These unique LTA mediated one pot multistage transformations of unsaturated vicinal diols hold considerable potential for the efficient synthesis of a series of complex chiral building blocks. The mild reaction conditions, together with the ease of the experimental and the absence of any detectable side products, constitute the most outstanding feature of this methodology. In summary, studying these one pot multistage transformations, we developed viable processes as a means of achieving short, stereocontrolled syntheses of taxoid precursors and synthetically interesting ring systems by methods that minimize waste while maximizing molecular complexity. Such carbon skeletons form the basic structures of many biologically active natural products. Our excursion into organolead chemistry has resulted in a novel ring expansion methodology; the sequence is now well established and obviously, considerable room for development still exists.

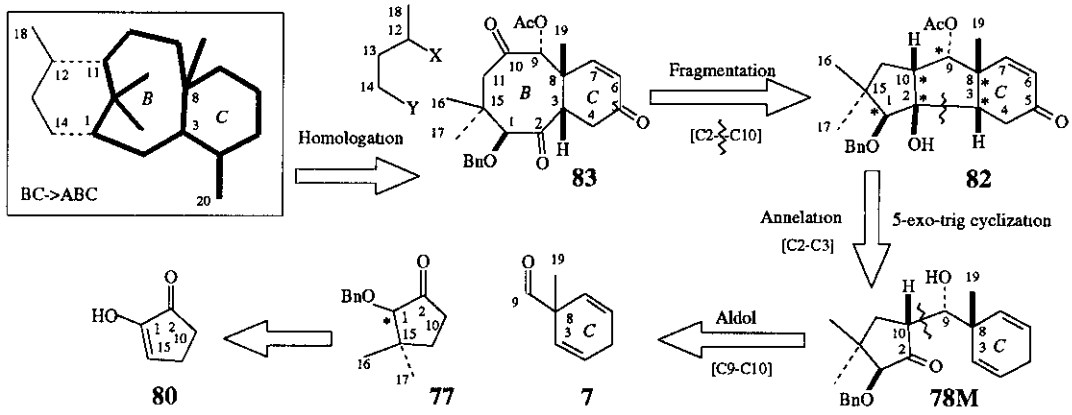
Readjusting the aldol-annelation-fragmentation sequence

Removal of the angular methyl group on the right half aldol partner (**7**) lowered steric hindrance thus making the original aldol reaction possible, but further elaboration of the C-8 quaternary center could have been troublesome (Scheme 5). We felt that the complications discussed above could be conveniently skirted by transforming the A ring component. So we turned our attention to a modified left half aldol partner in order to study its reactivity within a conceptually similar scheme based on the same three reaction-sequence: the aldol-annelation-fragmentation process with the same bond forming (C9-C10 then C2-C3) and breaking (C2-C10) operations.



Scheme 23 : First readjustment of the three reaction sequence on simplified left and right-half models.

As we were convinced that lack of reactivity between the original aldol partners (**3**) and (**7**) was due to steric hindrance we decided to remove the four carbon unit C-18 to C-14, thus removing the cavity with the hope of a better reactivity (Scheme 23). This model study was aimed at the stereochemical evaluation of the strategically crucial aldol-annelation steps and hence setting the stage for the construction of the 6+8 fused BC-subunit of taxoids. In other words it would serve as a typical problem-solving approach, testing the feasibility of our three reaction sequence. In this conceptually similar approach, the left half aldol partner (**3**) was replaced by **77**, a conveniently substituted cyclopentanone synthesized from cyclotene (**80**) *(vide infra)*, a readily available substance of natural occurrence.[25] Starting with only one stereogenic center, the C-1 carbon of the left half aldol partner (**77**), we were planning to end up, after only two key operations, with a molecule containing five more stereogenic centers. That is, the key intermediate (**82**) contains 6 chiral centers and therefore may exist in as many as $2^6 = 64$ stereoisomeric forms or 32 enantiomeric pairs of diastereomers.



Scheme 24 : Looking for control elements on which to base predictions.

For the three reaction process to be successful the first two transformations (aldol-annelation) had to be elaborated to the highest possible degree of stereoselection. The strategy offers high levels of predictability for the newly created stereogenic centers; especially the aldol condensation provides the necessary stereochemical bias for the desired annelation. The chiral enolate from **77** was expected to exhibit excellent levels of selectivity (*E*-geometry, *anti* selective-enolate and facial differentiation due to the benzyl substituent). The tricyclic enone (**82**) would be built "temporarily" to ensure the indirect B-ring formation and guarantee further cavity directed diastereoselective functionalization as required by the structure of the specific target (**1**). To ensure the *cis-syn-cis* stereochemistry, which is crucial for further elaboration, a *trans-threo* aldol (**78M**) was the *sine qua non* of the strategy. The general features of the synthetic plan we have employed are outlined retrosynthetically in Scheme 24. Before progressing to consider the details of functional group manipulations towards the target (**83**), it was worth analyzing the features we had to adress for the stereochemical outcome of the synthetic scheme.

Examining the stereochemical options for the aldol-annelation sequence

The stereostructure of the enolate derived from **77** which can form only anti-selective E-enolates for geometric reasons, determines the relative configuration of the two new chiral centers at C-10 and C-9. A transition state rationale for the Zimmermann-Traxler model[26] as well as the hydrogen-bonded conformations of the major (*threo-trans*) and minor (*threo-cis*) aldol's lowest energy conformers as determined by molecular mechanics calculations are shown in Figure 7. The *threo* (*erythro*) Zimmerman-Traxler transition states that lead to predictably high levels of stereoselection account well for the observed simple diastereoselection and π-facial selectivity.

Concerning the C2-C3 bond formation eneroute for the elaboration of key intermediate (**82**), the projected precursor of the taxoid BC-subunit (**83**), only the three annelated compounds, depicted in Scheme 25 were possible: two from the major *threo* aldol derived intermediate (**84M**), having the *cis-anti-cis* and *cis syn-cis* ring fusion stereochemistry (**I**) and (**82**) respectively, plus one, **II** from the minor *threo* aldol derived intermediate (**84m**), with a *cis-anti-cis* arrangement.

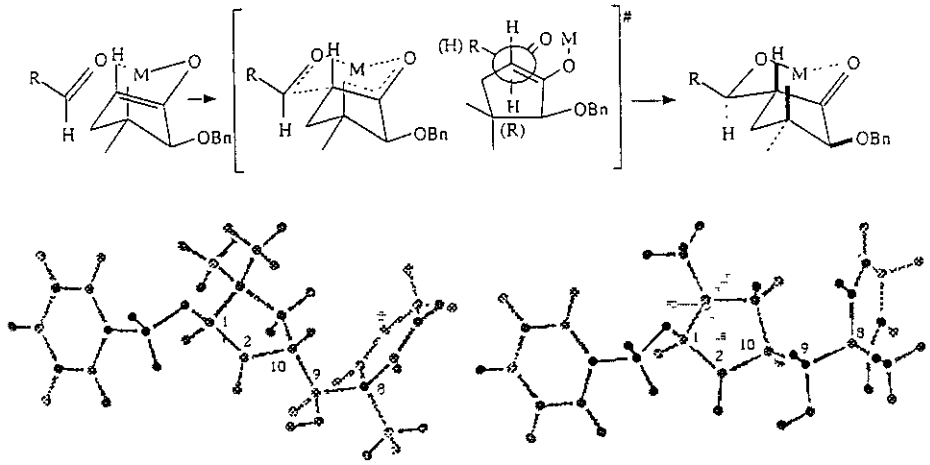
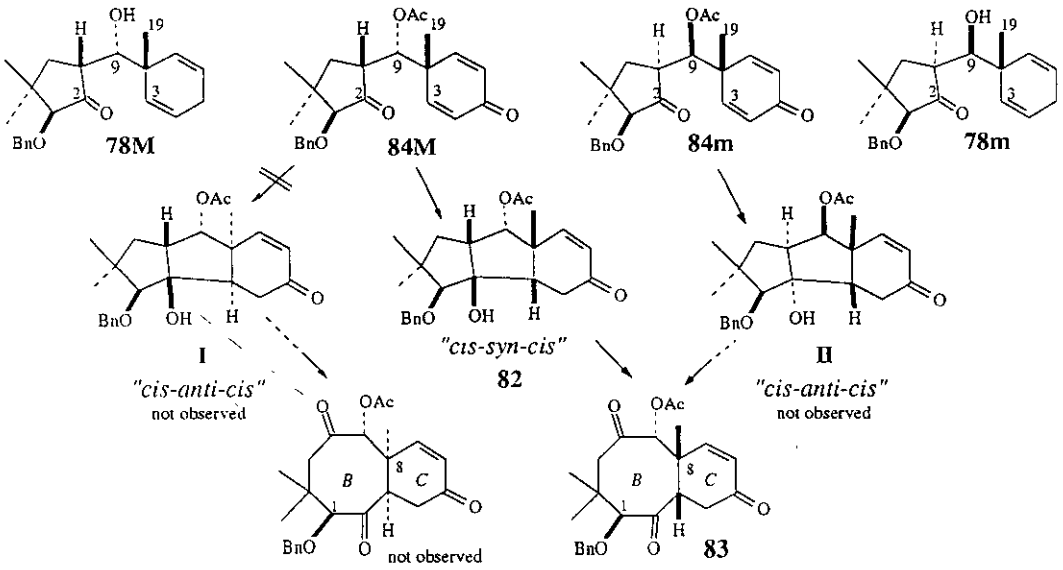


Figure 7 : Stereochemistry of the C9-C10 bond formation

Inspection of Dreiding models showed that annelation on **84M** would mainly result in formation of the *cis-syn-cis* tricyclic ring system which ensures that the chiral centers at C-8 and C-1 have the desired configuration. Contrary to the conformer which might have led to the undesired annelated enone (**I**) (*cis-anti-cis*) from **84M**, the conformer leading to **82** (*cis-syn-cis*) can be cyclized much easier without considerable steric hindrance. The expected selectivity was based on the C-9 acetate/C-19 methyl interactions.



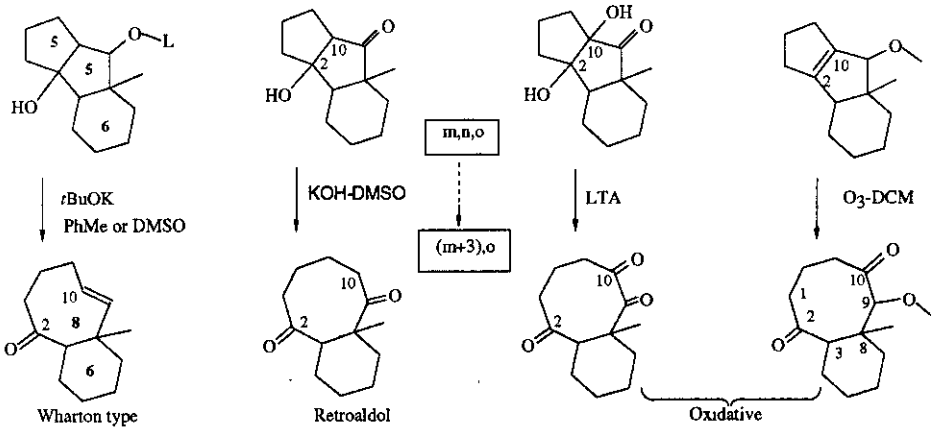
Scheme 25 : Predictions on the stereochemical outcome of the annelation.

Moreover two out of three possible annelated tricyclic intermediates (**82** and **II**), having the desired configuration at C-1 and C-8, would give the same BC-ring subunit given the fact that the stereogenic

centers at C2, C10 and C9 are programmed to become achiral during the following transformations (C-9 will bear a trigonal carbonyl group in the final product). Had the *cis-anti-cis* adduct (**I**) from the major *threo* aldol derived **84M** was obtained, the sequence would certainly have been less attractive. We attribute the expected selective formation of the *cis-syn-cis* (**82**) versus *cis-anti-cis* (**I**) tricyclic intermediate to the significant steric demands which are associated with eclipsing interactions in the transition state; now we can start looking for the appropriate method to effect the C2-C10 cleavage.

Setting the stage for the B-ring formation while securing functional diversity

With the stereochemical issues of the aldol-annelation steps resolved, formation of ring B was then explored. Since ultimate construction of the taxoid ABC framework is necessarily dependent on the nature of the C2-C10 cleavage, efforts were directed to accomplishing this objective so as to acquire the targeted structural unit in the most step efficient manner. Several routes of elaborating the AB, BC or ABC ring system of the taxoid skeleton *via* the fragmentation of smaller fused rings have been published (ref. 3). Some of them were considered for the fragmentation of close derivatives of the tricyclic enone (**82**) into the desired BC-taxoid substructure (Scheme 26) and while a number of methods[27] could eventually be successfully applied (such as Wharton or retro-aldol type fragmentations), we chose the oxidative ring cleavage as the most function rich way for achieving our goal. The Wharton or retro-aldol type fragmentations would result in a net loss of functionality and chemoselectivity in proceeding from the starting material to the products, while an oxidative cleavage, such as ozonolysis for example, would yield the highest number of functional groups and an easy further elaboration next to C-10 carbonyl group. We elected to use the ozonolysis as the cheapest and more efficient way for the C2-C10 cleavage.

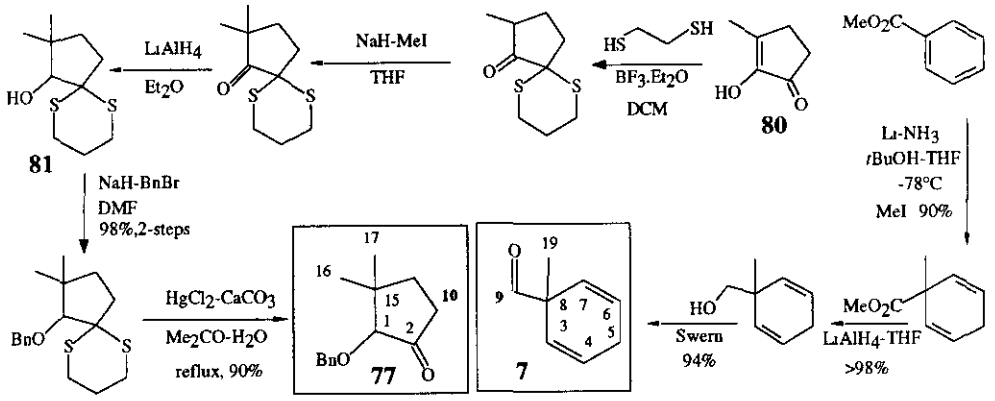


Scheme 26 : Setting the stage for the B-ring formation ; the C2-C10 cleavage.

Elaboration of the key tricyclic intermediate (**82**) into a compound from which the 6+8-fused ring system could in principle be obtained by oxidative ring cleavage would simply require a few trivial transformations. Moreover, the C-10 carbonyl group introduced during the fragmentation step would be well situated for an A-ring formation. We will see below how these distinctions were utilized to synthetic advantage.

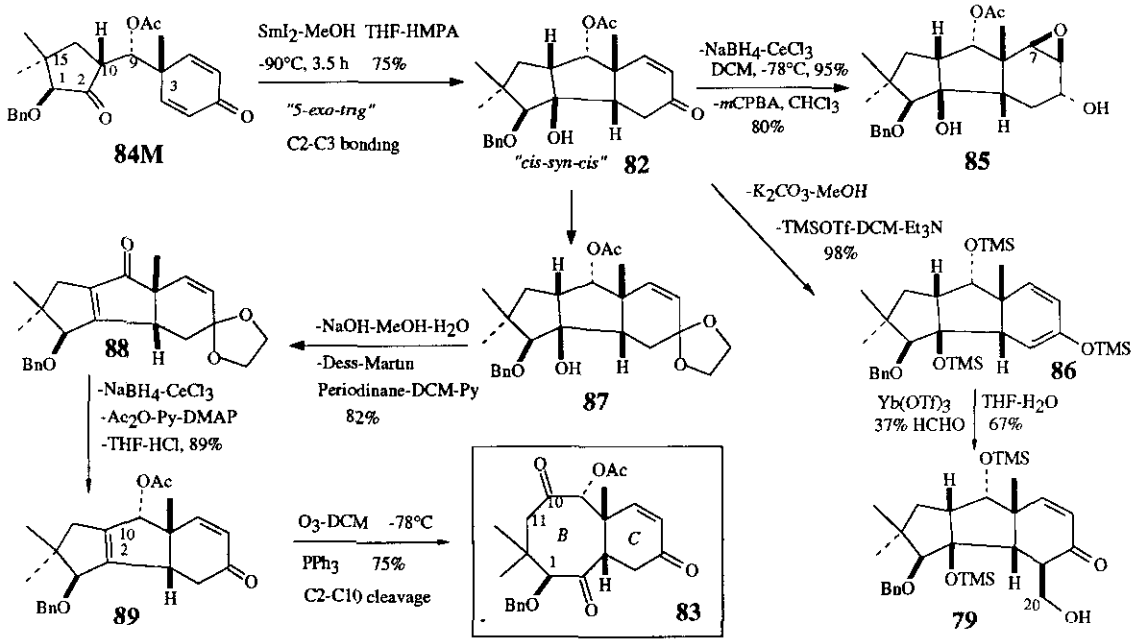
Synthesis of the designed targets

The two aldol partners were synthesized according to slightly improved literature procedures. Cyclotene (**80**) was converted into the left-half aldol component (**77**) using the method developed by Ueda,[28] while either benzoic acid or its methyl ester were converted to the right half aldol partner (**7**) *via* a Birch reductive alkylation by a short route, in high yields (Scheme 27).



Scheme 27: Large scale preparation of the two aldol components.

All of these operations could easily be done on a 100 g scale routinely.[29] With the requisite aldol partners (**7**) and (**77**) in hand, the synthetic plan derived from the above mentioned analysis was executed as outlined in Scheme 28.



Scheme 28 : Testing the feasibility of the three reaction sequence.

The C9-C10 coupling, produced only two *threo* aldols in a 13:1 ratio (*threo-trans* **78M** and *threo-cis*

78m respectively) showing excellent simple diastereoselection and high diastereofacial preference. The stereochemistry of the aldols (**78**) thus obtained was ascertained by conversion to acetonides, as the only use of the magnitude of vicinal coupling constants is subject to care. It is also important to note that the 13:1 (93%:7%) mixture of the two *threo* aldols needs no separation and can be carried forward as such. The pathway leading from the major *threo* aldol (**78M**) derived **84M** to the BC-ring intermediate (**83**) is shown in Scheme 25. The aldol (**78M**) was acetylated prior to allylic oxidation with PDC, *t*BuOOH, in CH_2Cl_2, at -20°C, for 48 h which proceeded in 79% yield. It was hoped that steric factors would permit a selective cyclization to give the requisite ring fusion stereochemistry (*vide supra*). Gratifyingly, treatment of **84M** with SmI_2 in the presence of MeOH as proton source and HMPA at -90°C accomplishes the desired *5-exo-trig* cyclization to give **82**; only one tricyclic intermediate was observed out of three possible. These conditions resulted in the efficient construction of the 5-5-6 framework with exclusive formation of the more sterically congested *cis-syn-cis* isomer; within the limits of detection by 400 MHz NMR spectroscopy, no stereoisomer was produced. Experimental evidence favoring the structure (**82**) came from n.O.e. studies (400 MHz) and was in agreement with molecular mechanics calculations. Irradiation of the angular methyl group 19 (at C-8) provided n.O.e. of H-3, H-4β, H-9, H-10; strong n.O.e.'s were also detected between the protons at C-9, C-10, C-3 and the angular methyl group 19 upon saturation of each one. These results are only consistent with the assigned *cis* orientation of the H-9, H-3, H-10 and Me-19; accordingly these protons must reside in close proximity, as shown in Figure 8, found only in the *cis-syn-cis* ring fused annelated system (**82**). Single-crystal X-ray diffraction analysis of the crystalline tricyclic enone (**82**) enabled unequivocal stereochemical assignment and further confirmed the correctness of previous assignments.

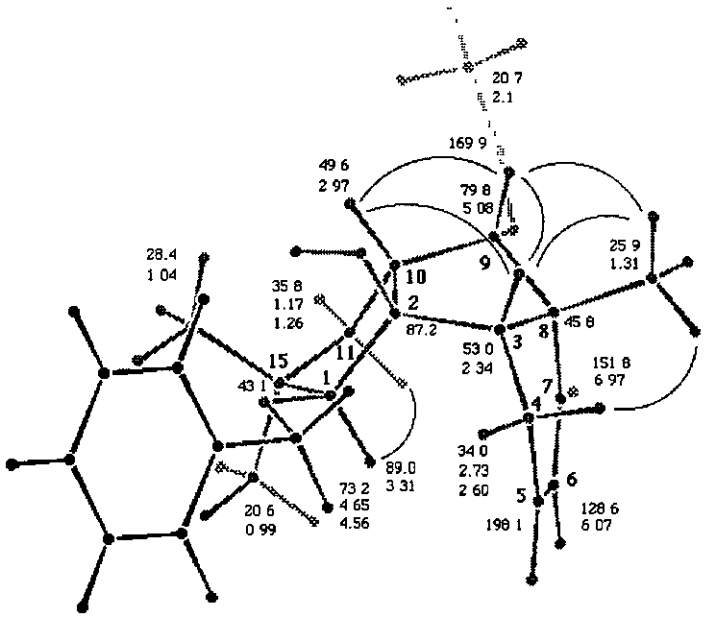


Figure 8 : Lowest energy conformer of key intermediate (**82**). The numerical values indicate the ^1H and ^{13}C NMR assignments; the arcs indicate observed diagnostic n.O.e.'s.

From a preparative standpoint, the presence of the minor *threo* aldol (**78m**) was inconsequential since the annelation carried out on the 13:1 mixture of **84M**:**84m** afforded the desired compound as a single diastereoisomer. This fact constitutes a reaction mediated cleaning of the undesired minor diastereoisomer (from the the *cis-threo* aldol **78m**) present in 7% in the initial aldol mixture.

The small amount of the unwanted *cis-threo* aldol contaminant was readily removed by chromatography for characterization purposes, as in the initial studies the principal objective was to characterize both diastereomeric aldol adducts in order to adress the stereochemical outcome of the annelation. This undesired diastereoisomer did not give any annelated compound when subjected to SmI_2 as above. A few functional group modifications brought **82** forward to the fragmentation precursor (**89**) (Scheme 28). Ketal protection (ethylene glycol, PhH, *p*TsOH, reflux, 3 h) afforded **87** which upon saponification of the C-9 acetyl group (NaOH, MeOH-H_2O, rt, 95%) delivered the free hydroxyl group at C-9. It must be pointed out however that the molecule shows a marked propensity to epimerize at C-9 *via* a ring opening and closing retroaldol-aldol sequence on prolonged reaction time (although inconsequential for the next transformations). Oxidation of the secondary alcohol at C-9 followed by *in situ* dehydration of the resulting hydroxy ketone was then accomplished using the Dess-Martin periodinane (2.17 equiv. in dry dichloromethane and pyridine, rt, 12 h) affording the ketal enone (**88**) in 84% yield (no other oxidant proved as effective as the Dess-Martin reagent). To ensure selective C2-C10 cleavage we further needed three additional steps. Thus $NaBH_4$ reduction of the C-9 carbonyl, reacetylation of the resulting alcohol (Ac_2O, Py, DMAP) afforded the desired compound (**89**) in 89% overall yield from **88**. Transformation of the latter into BC-ring framework (**83**) was achieved by a chemoselective oxidative cleavage of the unconjugated double bond using ozonolysis (O_3, CH_2Cl_2, -78°C, then PPh_3).

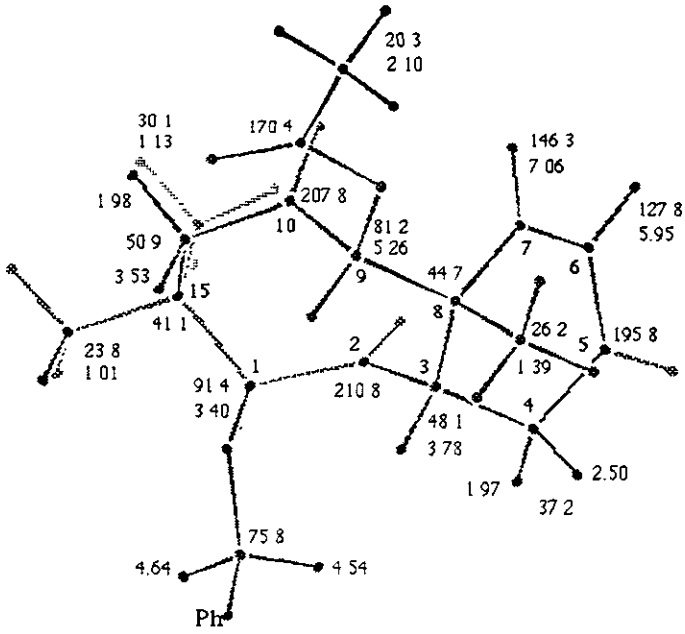


Figure 9 : NMR data of BC-subunit (**83**) shown on the lowest energy conformer (chair-boat conformation). The aromatic ring have been omitted to simplify the presentation.

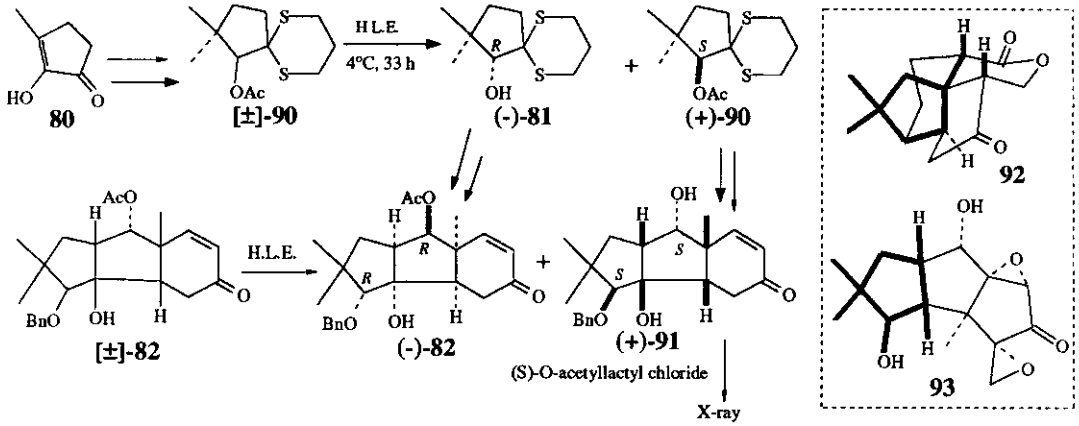
To examine the likely conformation of this molecule a molecular mechanics study was performed; Figure 9 shows a computer drawing of the lowest energy conformer of **83** as derived through use of Allinger's MM2 force field. The [6+8]-*cis*-fused **83** exists in the chair-chair conformation; this assignment was later confirmed by X-ray analysis. Obviously the C-10 carbonyl group in **83** is ideally positioned to facilitate the introduction of the remaining four carbon unit (C12-C13-C14-C18) and provides further coupling possibilities for the construction of the A-ring.

Before commiting valuable material for the remaining steps of the synthesis we undertook a model study to investigate ways for the introduction of the C-7 oxygen and the C-20 unit and to check efficiency and stereocontrol as a consequence of the concave folding of the tricyclic enone (**82**). This would facilitate the further manipulation of the C-ring moiety and in particular would save steps. Thus, the C-7 oxygen functionality and the C-20 hydroxyalkyl group were installed successfully using literature procedures, with the cavity of the *cis-syn-cis* tricyclic system serving as an efficient control element, favouring the natural relative stereochemistry (Scheme 28). The enone (**82**) was reduced to the corresponding allylic alcohol in the usual manner using either $NaBH_4$-$CeCl_3$ in CH_2Cl_2 or L-selectride in THF. Epoxidation with *m*CPBA afforded the epoxide (**85**) with the required configuration at C-7, as a result of a net domination of the conformational shielding (*cis-syn-cis* arrangement) over configurational control (angular methyl group at C-8), with the electrophile approaching exclusively from the convex face of the molecule despite the β-oriented methyl substituent. Incorporation of the C-20 carbon of the diterpene skeleton was achieved by direct treatment with TMSOTf in the presence of collidine or Et_3N (CH_2Cl_2, 0°C) and subsequent aldol condensation of the TMS-dienol ether (**86**) thus obtained with formalin in the presence of $Yb(OTf)_3$, a water tolerant Lewis acid catalyst.[30] Silica gel flash chromatography removed the unreacted starting enone and provided **79** in 67% yield. The configurations at the newly introduced chiral centers C-7, C-4 and C-5 were established using diagnostic n.O.e.'s. These experiments provided three potential precursors (**82, 85, 79**) for the construction of the taxane framework thus illustrating the synthetic utility of the readjusted aldol-annelation-fragmentation approach (**85** and **79** are potentially useful synthetic intermediates although their further elaboration was not progressed at this stage).

Securing optical purity

With a workable racemic synthesis in hand, we turned our attention toward the development of an asymmetric approach to **82**. The need to generate large quantities of the latter dictated the way in which advance was made towards its acquisition. To this end we tried the classical technique of resolution and the enzymatic hydrolysis, with the hope to ensure optical purity as early as possible in the synthetic scheme. The most efficient pathway took advantage of our earlier work using chemobiological transformations (ref. 22). To summarize briefly: the resolution technique worked perfectly on the tricyclic intermediate (after annelation) while the enzyme catalyzed hydrolysis gave very satisfactory results in the beginning of the synthetic scheme (before the aldol condensation). Among several commercially available low-cost lipases examined to secure the appropriately functionalized cyclopentane derivatives in their optically pure (*S*)-form, HLE (Horse liver esterase, acetone powder) gave the best results in terms of chemical yield and enantioselectivity, showing "*R*" specificity at an early

stage of the synthesis. The same enzyme showed the opposite selectivity on the tricyclic intermediate (**82**) hydrolyzing the (*S*)-acetate. The procedure can be scaled up without difficulty; a 5.74 g (22 mmol) conversion in a 2 L Erlenmeyer flask was performed routinely at 4°C for 31 h. The yields are high and the undesired enantiomer can be recycled. The enantiomeric purities were measured on the corresponding lactic esters, obtained by treatment with (*S*)-*O*-acetyllactyl chloride by ^{1}H-NMR and GC analyses. The absolute configuration of the stereochemically encumbered neopentyl acetate ((+)-**90**) was established by X-ray analysis through the correlation studies as shown in Scheme 29.



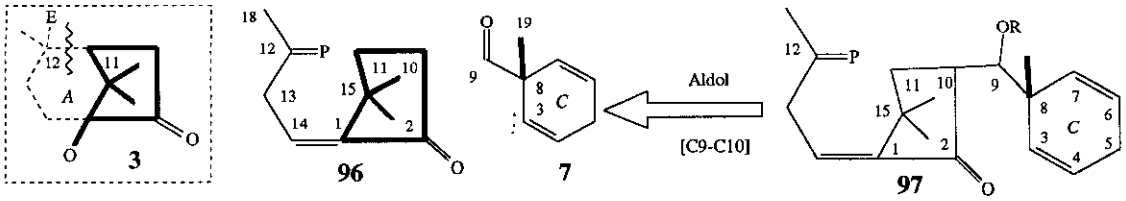
Scheme 29 : Rapid access to enantiopure cyclopentanol derivatives.

A key feature of this enzymatic hydrolysis is that multigram quantities of cyclopentanol derivatives ((±)-**90**) can be easily resolved in high yield and with excellent ee's so that their use as the first step in a synthesis design can be recommended. The functionalized cyclopentane derivatives ((*R*)-(-)-**81**) and ((*S*)-(+)-**90**) obtained in high enantiomeric purity not only possess a number of functional and stereochemical features amenable to an expeditious resolution of the taxoid B-ring problem but, such building blocks could also be used in synthetic approaches leading to quadrone (**92**), tricyclopentanoids like coriolin (**93**) and other interesting molecules. Routes to higher substituted enantiopure cyclopentanones are also possible starting from **77**. Since the biocatalyst is commercially available and rather inexpensive and since we are not dealing with a living organism, reaction conditions as well as the subsequent product isolation techniques fit well in the routine of an organic chemistry laboratory. So the strategy afforded in a reasonable number of steps the enantiopure (natural absolute configuration at C-8) key intermediate (**83**) that allows for incorporation of the missing A-ring component (the four carbons that have been removed to make aldol reaction possible) *via* C11-C12 and C1-C14 linking.

Second readjustment of the aldol-annelation-fragmentation sequence

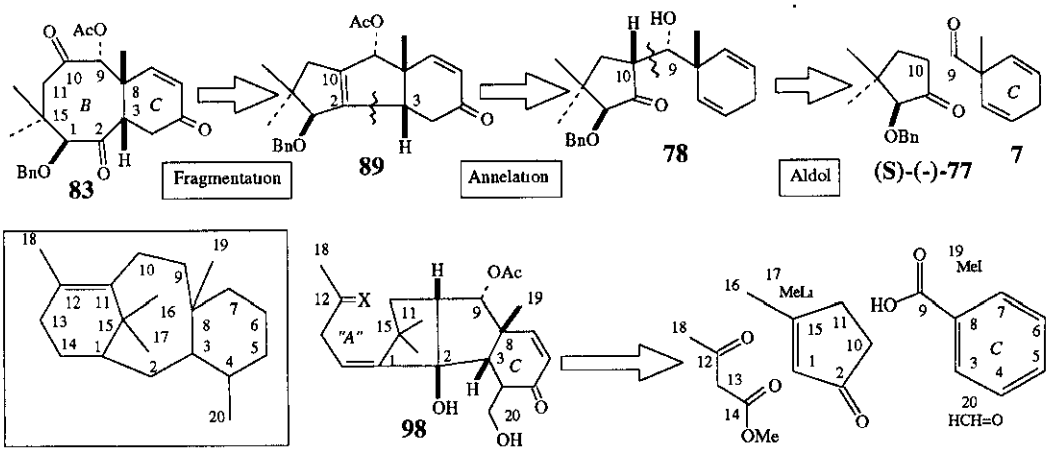
The preliminary investigation described above served to explore a potential route to our target, verified that the aldol-annelation-fragmentation approach was effective for the enantioselective construction of the taxoid BC-subunit (**83**), and above all, helped to define a readjusted strategy whose features have been subject to appropriate tests. The success of the route relied upon the unexpectedly high

stereocontrol in the annelation step leading to the key intermediate (**82**), which established the C-19 methyl bearing quaternary center. This model study identified as a new goal the C11-C12 disconnection on the initial left-half aldol partner (**3**), leading to **96** (Scheme 30) which in turn might be constructed from methylcyclopentenone and methyl acetoacetate. The ready availability of the latter compounds and the experimental precedent for their coupling provided the motivation to explore this route, instead of further pursuing the strategy from **83**. That is, having learned a lot about the reactivity of the left and right half aldol partners and having defined the required reaction conditions for the model system, we moved closer to our original synthetic scheme. To this end we investigated the synthetically more relevant system (**96**) designed from **3** by readjusting the cavity instead of completely removing it. Proceeding this way, we would be better prepared to complete the fully functional ABC-ring substructure of the taxoid backbone; the A-ring annelation, next to fragmentation step, could have been achieved using aldol methodology.



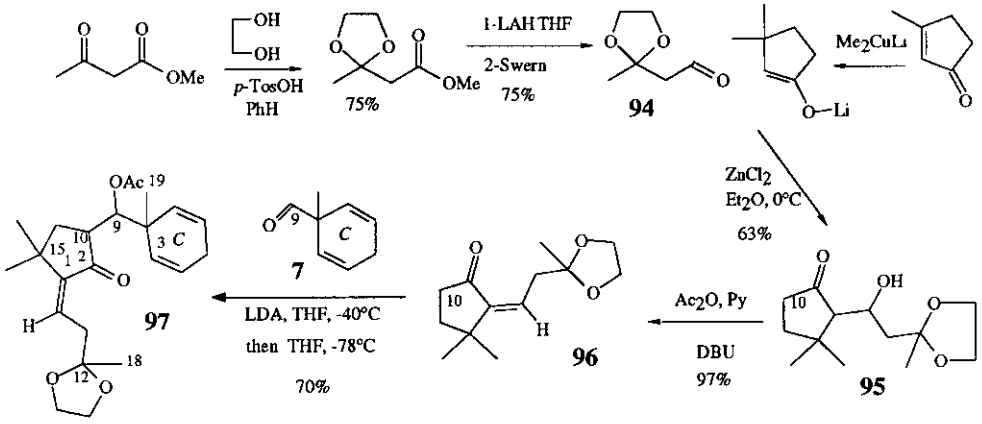
Scheme 30 : Second readjustment of the aldol-annelation-fragmentation sequence.

And so, we next sought to prepare the more advanced compound represented by formula (**97**) which incorporate ring A in its seco form. Overall, in doing so, we keep the original three reaction sequence based strategy for the C-C bonding (aldol-annelation) and C-C bond breaking (fragmentation) but instead of removing the cavity on the original left half aldol partner (**3**), we readjust it by a simple C11-C12 disconnection.



Scheme 31 : Assembling the entire taxoid framework ; "The 20-carbon puzzle".

The approach is now built around a molecule, the methylcyclopentenone, to which were attached the atoms destined to become the taxoid subunit embodying the whole carbon framework and suitable functionalities. Thus, methyl acetoacetate, methyllithium, benzoic acid, methyl iodide and formalin together with methylcyclopentenone would provide the entire taxoid diterpene part using again the same three-reaction sequence. The synthesis of a tricyclic intermediate such as **98** constitutes a formal total synthesis of an A-seco taxane, based on our previous results (Scheme 31). The latter will be the fragmentation precursor which will ultimately close to the bridged/fused ABC ring system; with the taxoid carbon skeleton fully assembled only functional group manipulation would remain.

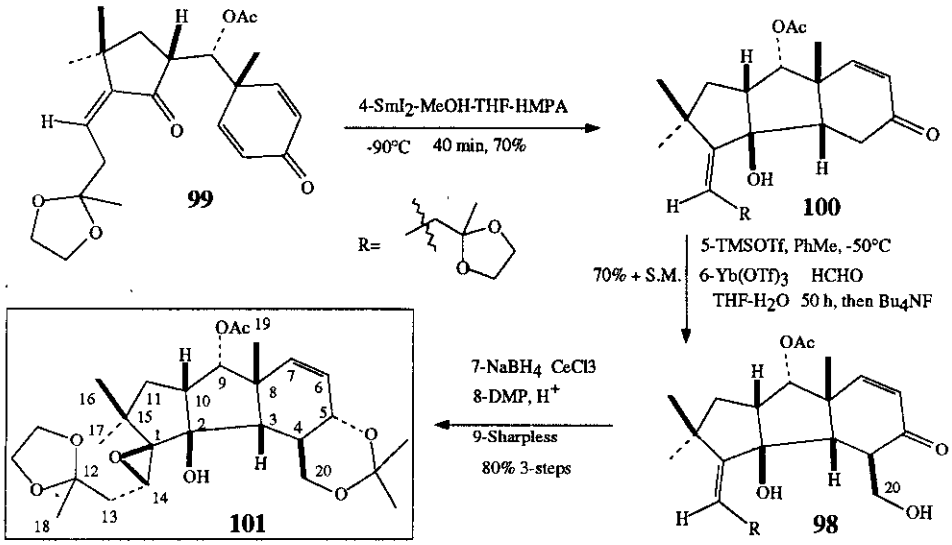


Scheme 32 : The first 19-carbons of the taxoid framework ; 2-steps from aldol partners.

The execution of this strategy culminating in the synthesis of the whole 20-carbon taxane framework (**101**) containing 11 stereogenic centers, as a single diastereoisomer (one out of 1024 possible enantiomeric pairs of diastereoisomers) in only nine steps starting from the two achiral aldol partners (**7**) and (**96**) is described below. Elaboration of the new cyclopentanone derivative (**96**) was accomplished using known methodology from simple fragments which were assembled with an aldol type bond construction as detailed in Scheme 32. The two building blocks, the achiral compounds (**7**) and (**96**) are both readily available and inexpensive. The reaction sequence utilized to achieve the conversion of methylacetoacetate to **96** is very straightforward and does not warrant any special comment.

The new left half aldol partner (**96**) was reacted with the right half partner (**7**) as usual to afford after acetylation **97** as a single aldol which upon treatment with *t*BuOOH and CrO_3 in the presence of 3,5-dimethylpyrazol in CH_2Cl_2, gave ene dione (**99**) in 80% yield.[31] To effect the C2-C3 bond formation on (**99**) thus obtained, we used the SmI_2 mediated reductive coupling as above, in the presence of MeOH as proton source and HMPA, at -90°C thus obtaining, after column chromatography, 70% of the desired tricyclic enone (**100**). In the reaction conditions, at -90°C, the annelation step leads to a single diastereoisomer (within the limits of detection by 400 MHz NMR spectroscopy, no stereoisomer was produced) as a single spot on the TLC plate. The poor material balance obtained, despite efforts devoted in varying the work up conditions, remains unexplained. As for **82**, **100** possess a folded carbon framework to which access on the concave face is highly unfavorable and therefore it is expected to

secure total control over the steric course of the chemical operations on C-ring periphery and for the installation of the C-1 oxygen functionality.



Scheme 33 : A 9-step elaboration of the whole 20-carbon taxoid substructure (**101**).

Guided by the desire to preserve the ring system of the *cis-syn-cis* tricyclic intermediate (**100**) until the complete elaboration of the taxoid substitution pattern, we deferred the C2-C10 cleavage operation to a late stage in the synthesis. The expediency of the overall procedure developed to construct **98** from the 20-carbon puzzle and for its conversion into the fragmentation precursor (**101**), so establishing tricyclic enone (**100**) as a useful relay intermediate for taxoid synthesis is illustrated in Scheme 33. With the intermediate (**101**) in hand, a formal total synthesis of an A-seco taxane is readily achieved. Even though (±)-**100** could be successfully processed *via* optical resolution to the enantiomerically pure tricyclic enone (**100**), for convenience we chose to restrict these exploratory experiments to report the conversion of **100** in the racemic series. From **99**, a straightforward functional group manipulation completed the synthesis of **101**. Briefly, SmI_2 mediated 5-exo-trig cyclization, followed by TMSOTf mediated TMS-dienol ether formation and subsequent ytterbium triflate catalyzed aldol reaction with aqueous formaldehyde led to the C-20 hydroxymethyl group installation. With the tricyclic *cis-syn-cis* system in place and with the C-20 hydroxymethyl functionality also incorporated, enone reduction ($NaBH_4$-$CeCl_3$, CH_2Cl_2 -78°C), acetonide formation (acetone, DMP, *p*TsOH, rt) and epoxidation ($VO(acac)_2$, *t*BuOOH in decane, benzene, 20 min reflux, >98%) afforded the target compound (**101**).[32] The latter obtained as a single diastereoisomer contains the entire carbon skeleton and a large number of oxygen functionalities, with the desired relative stereochemistries. The directed epoxidation using the Sharpless process gave an almost quantitative yield and more importantly set the C-1 oxygen group in its right configuration. The successful construction of **101** reinforced our commitment to the method we developed, the aldol-annelation-fragmentation sequence, which allowed the construction of a highly oxygenated taxoid diterpene precursor. Identification of the stereostructure of **101** was achieved by means of a series of 1

and 2D NMR (400 MHz) experiments and, as usual, n.O.e. studies served to confirm the configurational assignments; the key interactions are indicated in the formula (Figure 10).

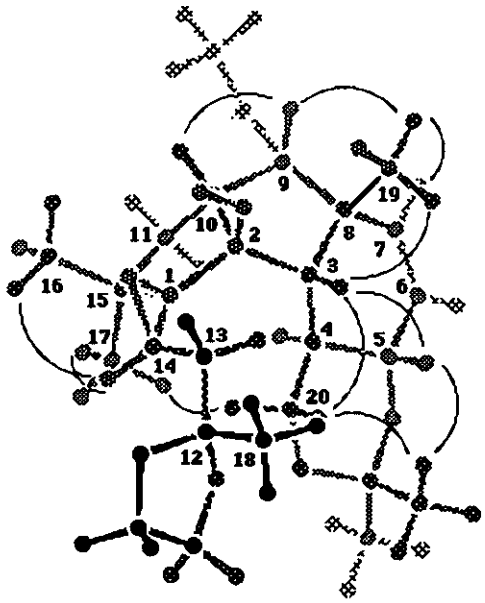


Figure 10 : Diagnostic n.O.e.'s shown on the lowest energy conformer of **101**.

The 9-step preparation of the twenty-carbon unit provides a simple entry to taxoid building blocks; the overall sequence can be readily modified to produce the required carbon/oxygen skeleton offering several distinct ways for further elaboration. We thus have reached an advanced stage in the synthesis and are now in a position to address the stereopure elaboration of the the C-ring moiety into a form suitable for the crucial oxetane D-ring construction, deferred to the end of our synthetic scheme.

This was January 1994, the end of "Taxogossips era". The molecule was already synthesized by Nicolaou, then Holton and later by Danishefsky and from this date on, one could only insist on a new synthesis if its strategy was more practical, offering a much higher milligram to decibel ratio and no more the other way around.

In retrospect, the failure in the original aldol condensation (**3+7**, Scheme 4) was fortunate because it allowed us to develop conceptually similar approaches proving that the aldol-annelation-fragmentation process represents a working method for the taxoid construction and, more importantly, to discover new ring expansion methodologies *via* the lead tetraacetate induced cascade transformations. The task at the present is to combine the most relevant findings into a step-efficient route to taxoids.

CONCLUSION

Over 25 years of research have evolved since the publication of the chemical structure of taxol in 1971,[33] involving an intimate collaboration between universities and industry. However, only after Susan Horwitz's contribution concerning its mode of action[34] in 1979, organic chemists throughout the world

began to adress massively the synthetic questions posed by the diterpene part and the side chain of the taxane skeleton. Taxoids, just as penicillins, steroids, prostaglandins, have served as the focal point for dramatic advances in selectivity and stereocontrol which play a central role in multi-step synthesis. Several new methodologies were developed as a consequence of the stimulus provided by the complex diterpene framework of taxoids. Attempts for the total syntheses of complex natural products will remain a tool for the discovery of new reactions and concepts.[35]

ACKNOWLEDGMENTS

This work owes much to a group of talented coworkers whose names appear in the references and to financial support by CNPq, CAPES (Brazil), Junta de Andalucía (Spain), CNRS and MRT (France).

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32. **101**: mp 140-141°C (ethyl acetate-heptane). **I.R.**(CH_2Cl_2): 3483, 2978, 2876, 1730, 1378, 1244, 1195, 1104, 868. **^{1}H-NMR** ($CDCl_3$, 400 MHz): 0.88 (3H, s, Me-16), 1.16 (3H, s, Me-17), 1.39 (1H, m, H-11), 1.40 (3H, s, Me-19), 1.43 (3H, s, α-equatorial acetonide Me), 1.44 (3H, s, Me-18), 1.50 (3H, s, β-axial acetonide Me), 1.79 (1H, m, H-11), 1.80 (1H, d, J=13.5, H-3), 2.00 (1H, m, H-4), 2.06 (3H, s, $C\underline{H}_3C$=O), 2.07 (2H, m, H-13), 2.83 (1H, m, H-10), 3.17 (1H, s, OH), 3.30 (1H, dd, J=3.7, 8.8, H-14), 3.72 (1H, t, J=11.0, H-20β-ax), 4.01 (4H, m, O-$C\underline{H}_2C\underline{H}_2$-O), 4.14 (1H, br d, J=8.8, H-5), 4.19 (1H, dd, J= 3.6, 11.0, H-20 α-equatorial), 5.12 (1H, d, J=7.8 , H-9), 5.59 (1H, dd, J=2.3, 10.2, H-7), 5.66 (1H, d, J=10.2, H-6). **^{13}C-NMR** ($CDCl_3$, 75.5 MHz): 19.1 (β-axial acetonide $\underline{Me}$), 20.9 ($\underline{C}H_3C$=O), 24.3 (Me-18), 25.8 (Me-16), 27.4 (Me-17), 29.8 (α-equatorial acetonide $\underline{Me}$), 32.0 (Me-19), 37.2 (C-13), 37.7 (C-11), 38.3 (Cq), 41.2 (C-4), 48.6 (Cq), 54.1 (C-3), 55.5 (C-10), 57.5 (C-14), 64.6 and 64.7 (O-$\underline{C}H_2\underline{C}H_2$-O), 65.6 (C-20), 70.0 (C-5), 72.9 (C-1), 81.7 (C-9), 88.2 (C-2), 98.4 (Cq-acetonide), 109.3 (C-12), 126.7 (C-6), 133.1 (C-7), 170.6 (Me$\underline{C}$=O). **E.I.M.S.**: 492 ($M^{+\cdot}$, 2), 491 (4), 477 (6), 417 (4), 311 (55), 113 (34), 87 (100). **Anal.** calcd for $C_{27}H_{40}O_8$: C 65.83, H 8.18, found: C 65.56, H 8.19.

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35. The stereostructures of all new compounds were determined by extensive ^{1}H and ^{13}C-high-field NMR studies and for some of them (**57**, **58**, **82**, **83**, and the 9-O-lactyl derivative of **82**) structural assignments first deduced from NMR analysis using the 1D NOEDIFF technique (L.D. Hall and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1980, **102**, 5703) in combination with 2D experiments were later supported by X-ray crystallography. Molecular mechanics calculations were performed on a Silicon Graphics Work Station (4D25) with Still's Macromodel v4.5 as software using Allinger's basic MM2 force field and Monte Carlo method to generate conformers.

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