Recent progress in the synthesis of taxanes

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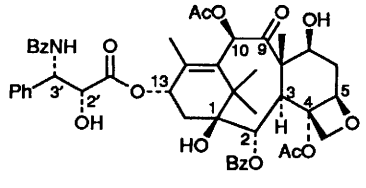
Reviewing the literature published between January 1991 and July 1993. Reference to earlier synthetic work is included where this provides additional perspective

1 Introduction

The highly complex tetracyclic diterpene taxol **1**, first described by Wall and co-workers in 1971,[1] is proving to be of great potential in the successful treatment of many types of cancer.[2] Taxol's unique antimitotic action[3] and remarkable efficacy as an anti-cancer drug has stimulated great biochemical attention.



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Nevertheless the true potential of taxol will only be realized when it is more readily available. The problems associated with its isolation from the bark of the Pacific yew tree *Taxus brevifolia*, have been reported at length.[4] Total[5] and semi-synthesis[6] are just two of the many proposed solutions[7] to increase the supply of taxol without endangering the yew tree. The former approach has proved extremely arduous and, to date,[8] no successful total synthesis of taxol has been published. Nevertheless as a challenging target, taxol has stimulated many elegant synthetic approaches, including the development of new methods that, in addition, have led to the synthesis of many analogues.

We have divided this review into two sections, namely (i) approaches to the total synthesis of taxanes, and (ii) semi-synthesis of taxanes. We have further divided the first section, somewhat loosely, into three parts. The first part (2.1) describes linear approaches that sequentially build the taxane ring from an A-ring precursor (so-called left to right approach) whereas the second part (2.2) details approaches that construct the taxane ring from a C-ring precursor (the right to left approach). The third part (2.3) of the first section includes approaches to taxanes that construct the B-ring, as the final step. from precursors that contain both the A and C-rings. These approaches are summarized diagrammatically in **Figure 1**.

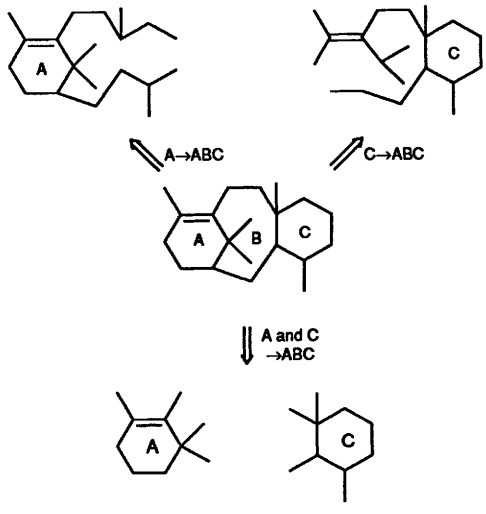
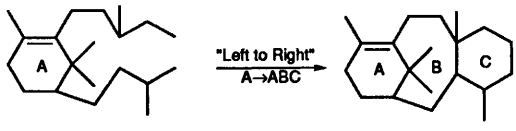


Figure 1 Disconnective approaches towards the synthesis of taxanes.

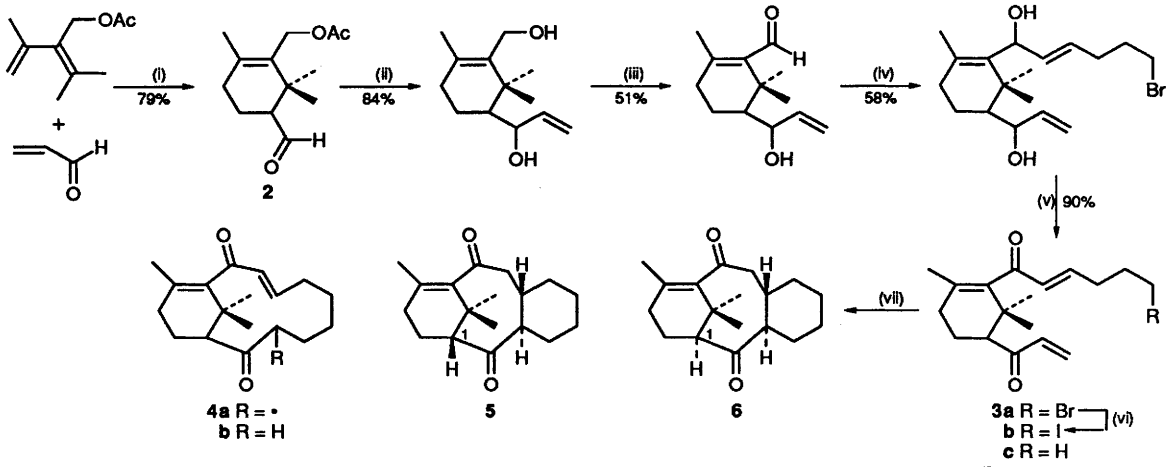
2 Approaches to the total synthesis of taxanes

2.1 From A-ring precursors



Pattenden

Pattenden and Hitchcock[9] have synthesized a compound with the tricyclic ring system common to



Reagents: (i) $BF_3.OEt_2$, −78°C; (ii) 3 eq. $CH_2CHMgBr$; (iii) cat. tetra (n-propyl)ammonium perruthenate, *N*-methylmorpholine oxide; (iv) 2·5eq (*E*)-$Bu_3SnCH{=}CH(CH_2)_3Br$, Bu^nLi, −75°C; (v) $BaMnO_4$; (vi) NaI, MeCOEt; (vii) Bu_3SnH, cat. AIBN, PhH, Δ

Scheme 1

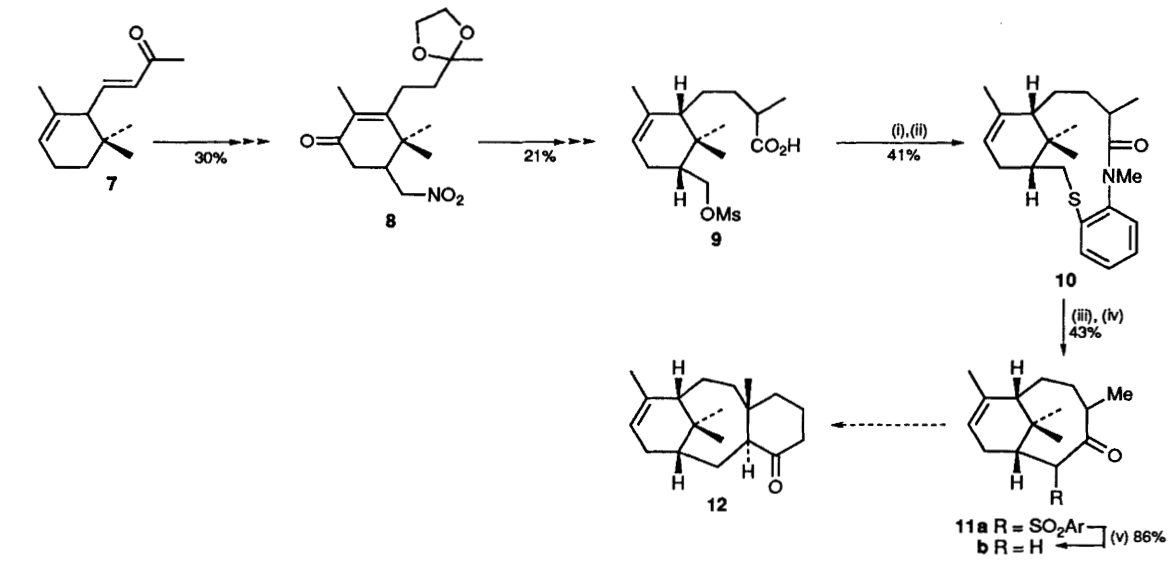
molecules of the taxane group using a powerful tandem radical macrocyclization-transannulation sequence (**Scheme 1**). In this sequence, the functionalized A-ring **2** containing the unsaturation and methyl substitution of the taxane skeleton was obtained from the Diels–Alder reaction between 2,4-dimethyl-3-(acetoxymethyl)-penta-2,4-diene and acrolein, and was then modified to give the radical precursor **3b** as depicted. Upon treatment with tributyltin hydride and α,α'-azoisobutyronitrile (AIBN) the iodo trienedione **3b** gave the two separable C-1 epimers **5** and **6** of the taxane ring system in a 3:1 ratio (25% yield) along with the reduced product **3c** (30%). A second product of reduction **4b** (20%) was isolated, resulting from quenching of the intermediate radical **4a** produced after the initial and impressive 12-*endo* radical macrocyclization step. This ring closure fixes the eventual C-1 ratio of epimers **5** and **6** and is most likely controlled by the conformation of the trienedione **3b** before cyclization. The 6-*exo trig* (transannular) cyclization of **4a** to **5** and **6** led to the desired *trans* fused BC ring junction, in accord with the predictions made using the Beckwith transition state model.

Oishi and Ohtsuka

Oishi and Ohtsuka have developed methodology for the formation of the AB ring system in the taxanes using a strategy based on transannular acylation of sulfone stabilized anion intermediates. Previous reports[10] from their research group had shown that the mesylate **9** can be made from α-ionone **7** as briefly depicted in **Scheme 2**. Macrocyclization of **9** with *o*-(methylamino)thiophenol next gave the 12-membered lactam sulfide **10**, which upon oxidation to the corresponding sulfone and treatment with lithium diisopropylamide (LDA) gave the ring-contracted bicyclic structure **11a**. Reductive cleavage of the sulfone group in **11a** then gave the AB ring system **11b** which has been converted[11] to the tricyclic ABC ring structure **12**. However, as it stood this approach seemed limited since synthesis of the mesylate **9** was rather lengthy (**7**–**9**, 23 steps and 6% overall yield), and the Michael addition of nitromethane anion used in the synthesis of **8** was poor yielding. The chances of overall success in this strategy have recently been greatly increased, however, by a much improved, shorter synthesis (**Scheme 3**).[12] Thus, the monobenzylated 1,5-pentanediol **13** was converted in five steps into the diene **14**, which reacted in a highly stereoselective Diels–Alder reaction with maleic anhydride to give **15** as a single isomer. Direct reduction of **15** with sodium borohydride under various conditions led to mixtures of the isomeric lactones **17** and **18**, with the undesired isomer **18** predominating in most cases. Exclusive conversion of **15** to **17** could be achieved *via* the iodoacid **16**, using a hydrolysis-iodolactonization-reduction sequence. Alkylation of the lactone **17** with LDA and methyl iodide next gave **19** in good yield. The lactone **19** was then converted into mesylate-acid **20** in which the two pendant groups in the A-ring have the *cis* relationship necessary for subsequent macrocyclization. The acid **20** was converted into the AB structure **11b** following much the same sequence summarized in **Scheme 3**. Alkylation of the acid **20** was not effected immediately, that is to give **9**, but was left until after formation of the marocyclic lactam-sulfide ring. This methylation was stereospecific, leading to a single isomer of **10** with undetermined relative configuration.

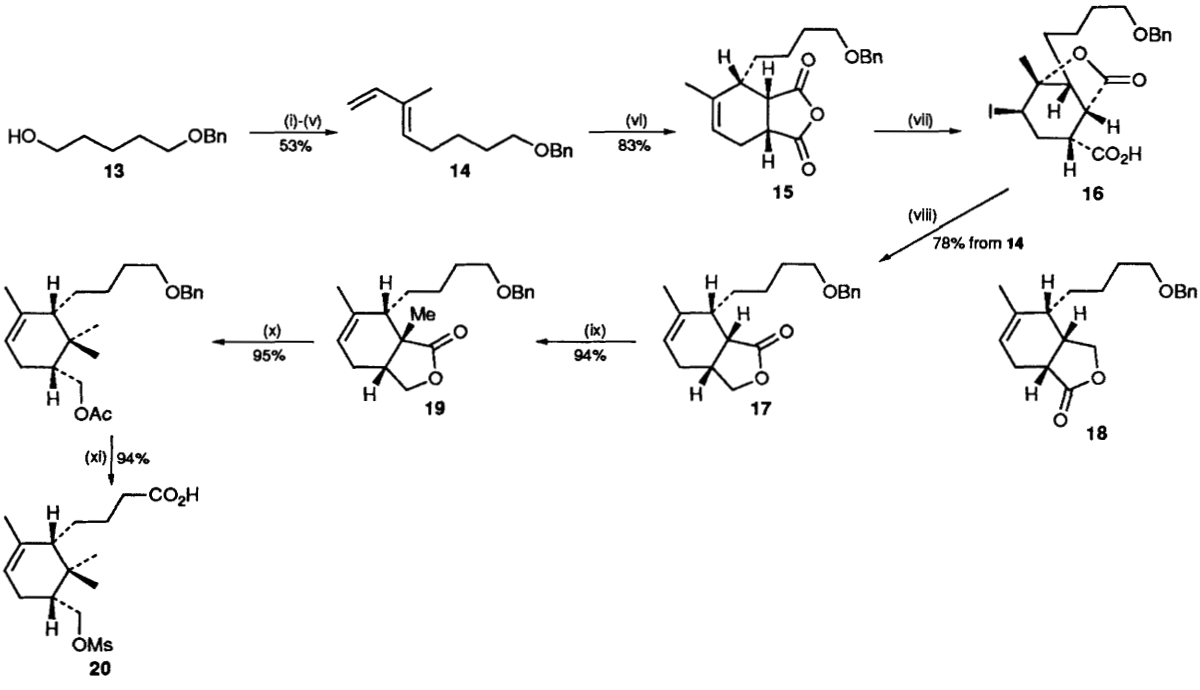
Fetizon

Fetizon has investigated several strategies for the synthesis of taxanes. The first strategy[13] involved coupling of A and C ring fragments, but the subsequent attempted closure to form the B ring was unsuccessful. This work has been reviewed elsewhere.[5] In their most recent report[14] Fetizon and co-workers have shown that the α-fenchol derived enols **21** and **22** undergo photocycloaddition with vinyl acetate to give the



Reagents: (i) $(COCl)_2$, PhH; (ii) (a) 2′-cyanoethyl(2-methylamino)phenyl sulfide; (b) K_2CO_3, $NaBH_4$, DMF; (iii) $NaIO_4$; (iv) LDA, THF; (v) Na–Hg, Na_2HPO_4

Scheme 2

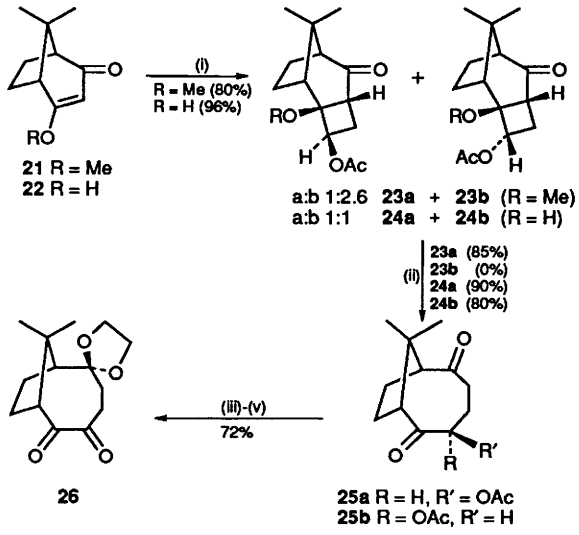


Reagents: (i) PCC, DCM; (ii) $EtO_2CC(=PPh_3)Me$, PhMe; (iii) $LiAlH_4$, Et_2O; (iv) PCC, DCM; (v) Ph_3PMeI, BuLi, THF; (vi) maleic anhydride, PhMe, Δ; (vii) 0·5M $NaHCO_3$ then I_2, KI; (viii) (a) THF–$B(OMe)_3$, $BH_3.Me_2S$, (b) Zn–AcOH; (ix) LDA, MeI; (x) (a) DIBAL-H, PhMe, (b) NH_2NH_2, NaOH, diethylene glycol, (c) Ac_2O, pyridine; (xi) (a) H_2, Raney-Ni, EtOH, (b) 3,4-dihydro-2*H*-pyran, H^+, (c) $LiAlH_4$, (d) MsCl, (e) Jones' oxidation

Scheme 3

cyclobutanes **23a,b** and **24a,b** as a mixture of separable isomers (**Scheme 4**). The boron trifluoride etherate mediated retroaldol reactions of either **23a** or **24a** then gave the bicyclic diketone **25a**; likewise **24b** led to the epimeric diketone **25b**. The *O*-methoxy isomer **23b** on the other hand failed to undergo a retroaldol reaction and was recovered unchanged from the reaction mixture. The products **25** represent contracted AB ring systems in which the A ring is lacking a methylene group. The products **25a,b** have been modified to give the new diketone **26**, and the authors now hope to eventually attach the taxane C ring to **26** *via* an annulation procedure.

In a subsequent report[15] of an AB ring synthesis, Fetizon and his co-workers describe the photochemical cycloaddition route with more complex vinyl acetate derivatives. Thus, the known vinyl acetate **28** was first reacted photochemically with the enol



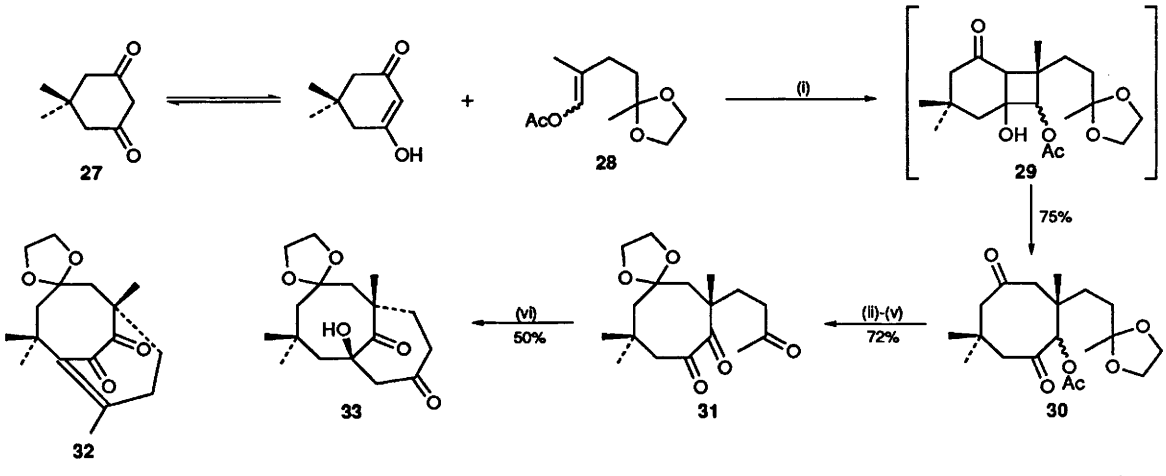
Reagents: (i) CH_2=CHOAc, *hν*, DCM (for **21**) or MeOH (for **22**) (ii) $BF_3.OEt_2$, DCM, 0°C; (iii) $(CH_2OH)_2$, PPTS, PhH, Δ, 48 h; (iv) NaOMe, MeOH, 0°C, 2 h; (v) PDC, DCM, 24 h

Scheme 4

tautomer of dimedone **27**, leading to cyclobutanol **29** (**Scheme 5**), which was not isolated but instead underwent a spontaneous retroaldol reaction to give the diketone **30**. The reaction leading to **30** was found to be regio- and stereo-specific. After various functional group interconversions the triketone **31** was next produced. Upon treatment of **31** with a range of bases (*e.g.* sodium methoxide, potassium-t-butoxide, LDA, and sodium hydride) the dehydrated-cyclized product **32** was then formed. However, treatment of **31** with bromomagnesium diisopropylamide (BMDA) gave the tertiary alcohol **33** in 50% yield. This proved to be very stable under acidic and basic conditions and its structure was determined by *X*-ray analysis.

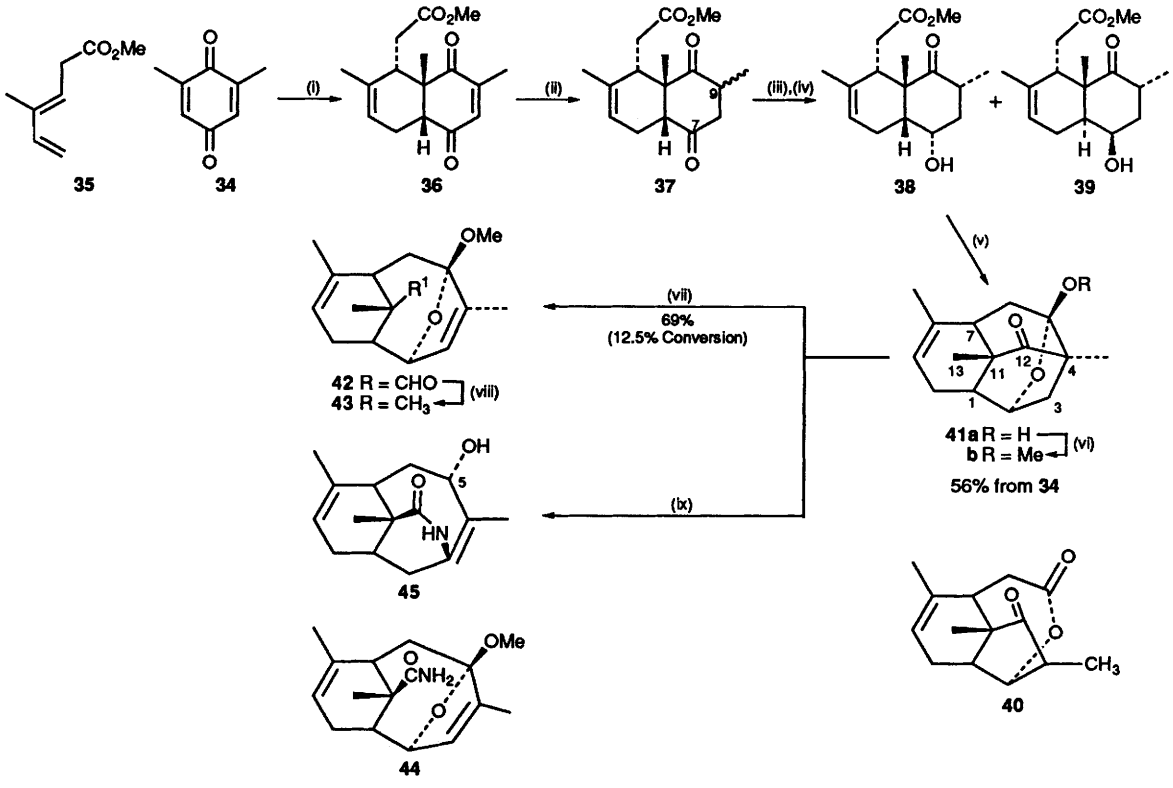
Fetizon and co-workers have recently reported[16] another approach to the taxane AB ring system using a Norrish type II photo-fragmentation strategy (**Scheme 6**). The Diels–Alder cycloaddition of benzoquinone **34** to the diene **35** gave the bicyclic compound **36** as a single regio- and stereo-isomer. This enedione was next reduced to the dione **37**, giving a mixture of epimers at C-9. Further reduction of the C-7 ketone in this mixture with lithium t-butoxy aluminium hydride led to the ketoalcohols **38** and **39** which were easily separated by chromatography. The structure of **38** was proven by *X*-ray crystallography. Treatment of **38** with the non-nucleophilic base sodium hexamethyldisilazide (NaHMDS) produced the hemiacetal **41a**, *via* the lactone **40**. Subsequent methylation of **41a** gave the acetal **41b** in overall 56% yield from **34**. Irradiation of **41b** resulted in homolysis of the C-4–C-12 bond, followed by selective hydrogen migration from C-3 to give the aldehyde **42**. Molecular models showed that, for steric reasons, the homolysis of the C-1–C-12 bond in **41b** cannot be followed by a concerted H-migration from either C-1 or C-7. Unfortunately, the reaction was severely hampered by the appearance of [2 + 2] cycloaddition by-products quite soon after the start of photolysis. The reaction was monitored by TLC and stopped when these by-products built up, typically after only 12% conversion (69% yield based on consumed starting material) to **42**. The starting material could be recovered easily using chromatrography. The aldehyde function in **42** was reduced to a methyl group, so giving the interesting acetal **43**.

In an earlier publication,[17] Fetizon *et al.* showed that application of the Haller–Bauer reaction (sodium amide in toluene) to fragment the acetal **41b** resulted in direct formation of the lactam **45**. After formation of the expected product amide **44**, the strongly basic conditions presumably promoted a ring closure reaction to the acetal functional group in **44**, followed by a reduction of the resulting C-5 ketone. No further elaboration of **45** has been reported, but hydrolysis of the lactam, followed by reduction of the carboxylic acid function to a methyl group could give access to some interesting aza-analogues of the taxane AB ring system.



Reagents: (i) *hν*, MeOH, 0°C; (ii) $(CH_2OH)_2$, PPTS, PhH; (iii) MeONa, MeOH; (iv) PDC, DCM; (v) PPTS, H_2O–acetone (1:9); (vi) $BrMgNPr^i_2$, THF, −78°C

Scheme 5



Reagents: (i) PhH, Δ, 72 h; (ii) Zn, AcOH,))))) ; (iii) lithium t-butoxyaluminium hydride; (iv) chromatography; (v) NaHMDS; (vi) $(MeO)_3CH$, *p*-TsOH; (vii) *hν*, $\lambda \geqslant 254$ nm, MeOH, 0°C; (viii) (a) $LiAlH_4$, (b) MsCl, (c) lithium triethylborohydride; (ix) $NaNH_2$, PhMe

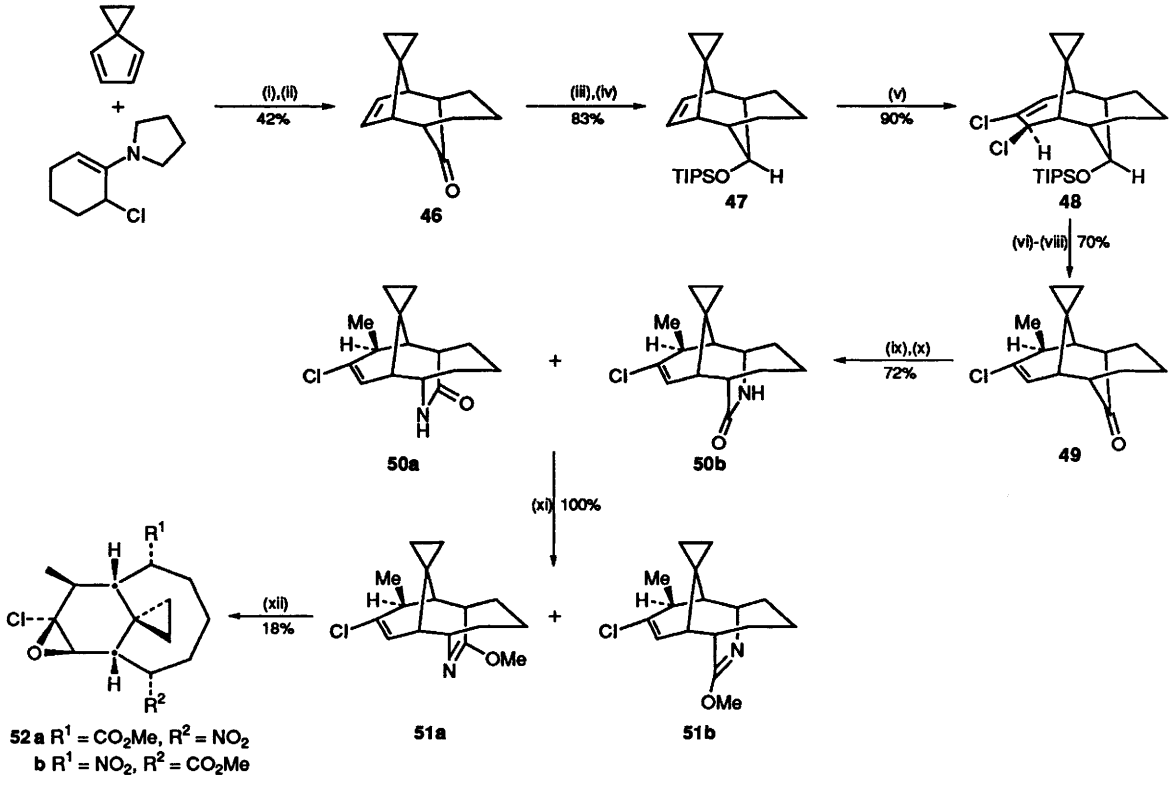
Scheme 6

Cha

Cha has reported[18] a synthesis of the taxane AB ring system based on an initial [4 + 3] diene-oxyallyl cation cycloaddition reaction (**Scheme 7**). Treatment of 3-chloro-2-pyrrolidinocyclohexene and *spiro* [2.4] hepta-4,6-diene with $AgBF_4$ yielded, after basic hydrolysis to the ketone, the cycloadduct **46**. The stereochemical assignment of this compound was based upon the known preference of oxyallyl cations to react in an *endo* mode. Reduction of the ketone functionality in **46** with lithium aluminium hydride occurred stereospecifically to give the corresponding *endo* alcohol which was next protected as its triisopropylsilyl (TIPS) ether. The alkene **47** was then treated with dichlorocarbene generated from ethyl trichloroacetate and sodium methoxide. This reaction gave the ring expanded product **48**; which was modified, after the introduction of a methyl substituent using an S_N2' substitution, to give the ketone **49**. Initially, Cha *et al.* had hoped that this ketone would undergo a Baeyer–Villiger oxidation in order to gain access to the taxane AB skeleton, but unfortunately both of the ketones **49** and **46** proved resistant to this oxidation. This problem was circumvented by using a Beckman reaction. Thus, treatment of the ketone **49** with hydroxylamine hydrochloride led to a 3:2 mixture of oximes, which underwent Beckman rearrangement upon treatment with tosyl chloride in pyridine to give the regioisomeric lactams **50a,b** (3:2 also). After conversion of **50a,b** into the imidates **51a,b** treatment with trifluoroacetic acid (TFA) and *m*-chloroperbenzoic acid (*m*-CPBA) then gave the isomeric nitro esters **52a,b**, but these were isolated in disappointingly low yields (18%). Cha *et al.* hope eventually to extend this approach to give access to the ABC ring system in the taxanes by using the bicyclo oxyallyl cation synthon **53** derived from the optically active Wieland–Miescher ketone.

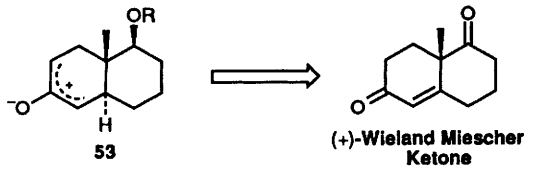
Fallis

Fallis[19] has recently reported an intramolecular Diels–Alder synthesis of the taxane ring system using a suitably functionalized A ring compound. The Diels–Alder precursor **58** was constructed from the aldehyde **54** as shown in **Scheme 8**. Addition of the diene fragment to the aldehyde **54** was achieved using 1-lithio-1,3-butadiene, and led to the diene **55** as the major isomer in 74% yield after hydroxyl group protection. The relative stereochemistry in **55** was determined from an *X*-ray crystallographic structure determination of the derivative **56**. The diene **55** was then taken through to the Diels–Alder precursor **58** *via* compound **57**. It is interesting to note that oxidation of the acetylenic alcohol function in the desilylated derivative of **57** only gave moderate yields in a generally efficient synthesis, and attempts to improve this step by variation of the oxidant were unsuccessful.

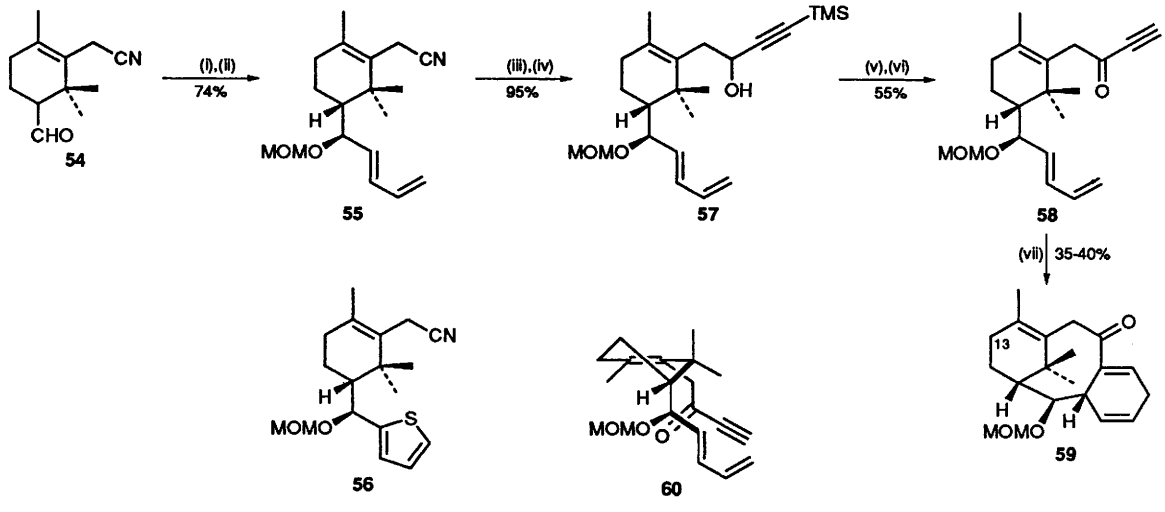


Reagents: (i) $AgBF_4$, DCM; (ii) NaOH, MeOH, Δ; (iii) $LiAlH_4$, Et_2O, 0°C; (iv) TIPSOTf, DCM, 2,6-lutidine; (v) CCl_3CO_2Et, NaOMe, 0°C; (vi) Me_2CuLi, Et_2O; (vii) TBAF, THF, 0°C; (viii) PDC, DCM, 0°C; (ix) $ClH.H_2NOH$, MeOH, py, 80°C; (x) TsCl, py, r.t.→80°C; (xi) $Me_3O.BF_4$, DCM; (xii) mCPBA, TFA, DCM

Scheme 7



Microwave assisted Diels–Alder cyclization of **58** gave the tricyclic taxane ring structure, and the major adduct **59** arose from the *endo* transition state **60**; here the non-bonded interactions are minimized due to alignment of the dienophile on the opposite face of the diene to the *O*-methoxymethyl substituent. An attempted Lewis acid mediated cyclization of **58** proved unsuccessful due to the migration of the cyclohexene double bond into conjugation with the acetylenic ketone. The authors hope that a C-13 carbonyl function, as found in natural taxanes, will suppress this tendency and lead to better yields in the Diels–Alder cycloaddition. Indeed the low yields of



Reagents: (i) (*E*)-$Bu_3SnCH{=}CH{-}CH{=}CH_2$, Bu^nLi, THF, −78°C; (ii) MOM-Cl, DIPEA, DCM; (iii) DIBAL-H; (iv) HC≡CTMS, Bu^nLi, −78°C; (v) KOH, MeOH, DCM; (vi) Dess–Martin oxidation; (vii) 0·05 M in PhMe, microwave, 1 mol% hydroquinone

Scheme 8

the thermal Diels–Alder reaction were also due to this double bond migration and large amounts of uncyclized products were recovered.

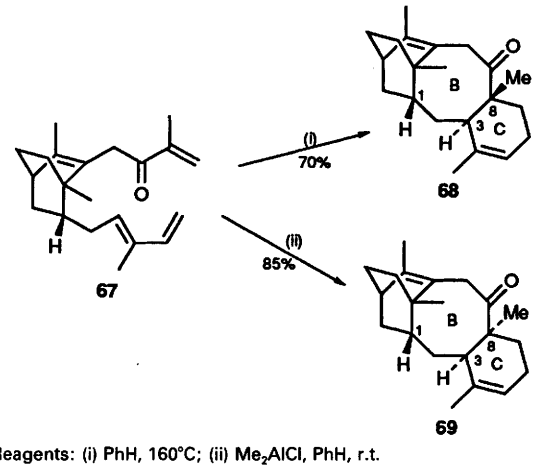
Previous studies provided Fallis *et al.* with a method for introducing the C-13 ketone by allylic oxidation, and the authors also report that the C-1 hydroxyl function can be introduced *via* the corresponding C-2 enolate, in accordance with the results of other researchers.

Wang

Wang's approach[20] to the taxanes also involves the construction of the C-ring by a Diels–Alder reaction, but in an intermolecular sense. The A-ring is derived from the mono protected ketone **61** (**Scheme 9**) which was first subjected to the Shapiro reaction followed by trapping with dimethylformamide and hydrolysis to produce the ketoaldehyde **62**. Acetal formation and subsequent addition of a substituted diene fragment next gave the alcohol **63** which was then subjected to a protection, functional group interconversion sequence to give the aldehyde **64**. Zinc mediated intramolecular cyclization with **64** next provided the AB-ring fragment **65** which was finally converted into the taxoid **66** by an intermolecular Diels–Alder reaction with dimethyl acetylenedicarboxylate.

Sakan

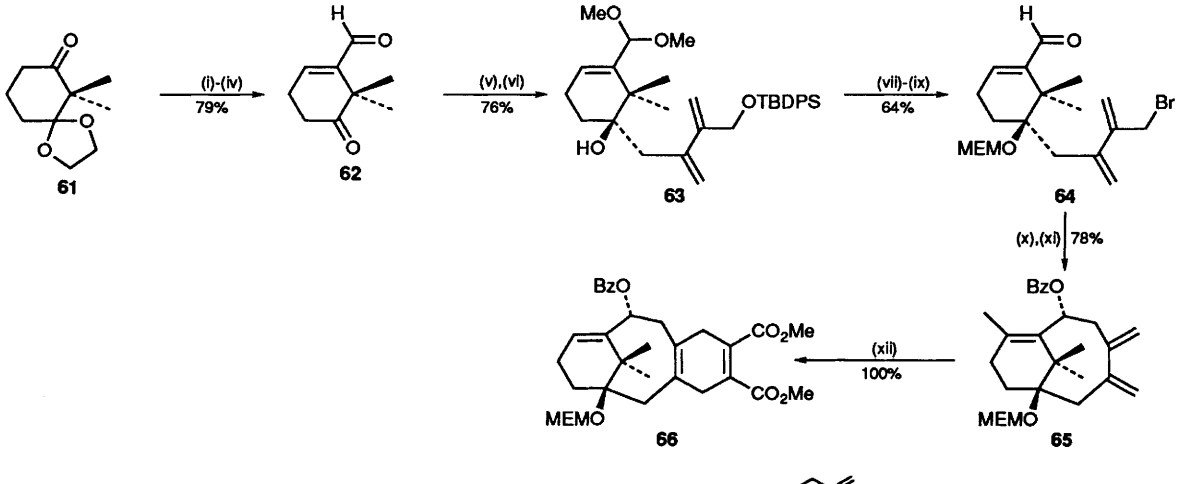
Sakan's approach to the taxanes is similar to that described by Fallis, where a functionalized A-ring is cyclized to create the B and C rings together. In 1983 Sakan and Craven[21] reported a synthesis of the diene **67** and showed that the thermal Diels–Alder reaction gave the *trans* fused ketone **68** (70%), whereas the Lewis acid catalysed cyclization gave the corresponding *cis* fused product **69** (85%) (**Scheme 10**). This observation was unusual, as catalysis of Diels–Alder reactions normally enhances stereoselectivity, but does not reverse it! The outcome is presumably a result of *endo* attack in the Lewis acid mediated reaction giving **69**, and *exo* attack in the thermal reaction giving **68**. Subsequent to this initial observation the stereodirecting effects of alkyl substituents on the diene and dienophile components in **67** were investigated on model systems,[22] and this strategy has now been extended to the taxane system.[23]

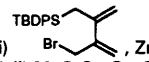


Reagents: (i) PhH, 160°C; (ii) Me_2AlCl, PhH, r.t.

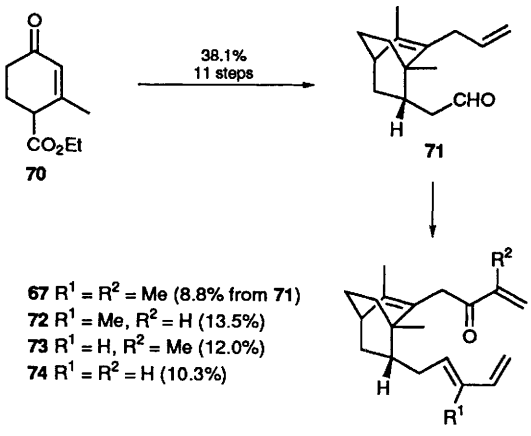
Scheme 10

The aldehyde **71** was prepared from the enone **70**, as previously reported, and was next converted to the diene-enones **67** and **72–74** by standard methods (**Scheme 11**). These compounds were then cyclized under both Lewis acid and thermal conditions, and the ratio of isomers determined. The results are summarized in **Table 1**. In the nomenclature used by Sakan *et al.* the four possible stereoisomers are designated either *cis* or *trans* depending on the relative stereochemistry of the B–C ring junction, and α or β depending on the C-1–C-3 relative configuration. Thus **68** is the *α-trans* isomer (the relative configuration in naturally occurring taxanes) and **69** is the *α-cis* isomer. Where possible the relative configurations were elucidated by *X*-ray crystal structures; otherwise comparison of NMR spectra or



Reagents: (i) *p*-$TsNHNH_2$; (ii) 4 eq., BuLi; (iii) DMF; (iv) HCl, H_2O; (v) *p*-TsOH, MeOH; (vi)  , ZnCu; (vii) MEMCl, Pr^i_2NEt; (viii) Bu_4NF; (ix) CBr_4, Ph_3P then silica gel; (x) Zn–Cu; (xi) PhCOCl, pyridine; (xii) $MeO_2C{-}C{\equiv}C{-}CO_2Me$, Δ

Scheme 9



Scheme 11

chemical correlation methods were used. The authors found that under thermal cyclization conditions a methyl substituent on the diene (R^2 = Me) increases selectivity for the α- over β-isomers, and approximately doubles the *α-trans*: *α-cis* ratio. A methyl substituent on the dienophile (R^2 = Me) decreases the α/β ratio by 40%, but the selectivity for *α-trans* over *α-cis* increases significantly (*ca.* five-fold). In the Lewis acid catalysed reaction only the *α-cis* isomer was formed in all cases, with the exception of **73** where a minor product, tentatively assigned as the *β-cis* isomer, was isolated. The preference of the α stereochemistry at C-3 appears to be a unique feature of this carbon skeleton, and Smith and Houk are currently investigating the molecular mechanics of this system.

Table 1

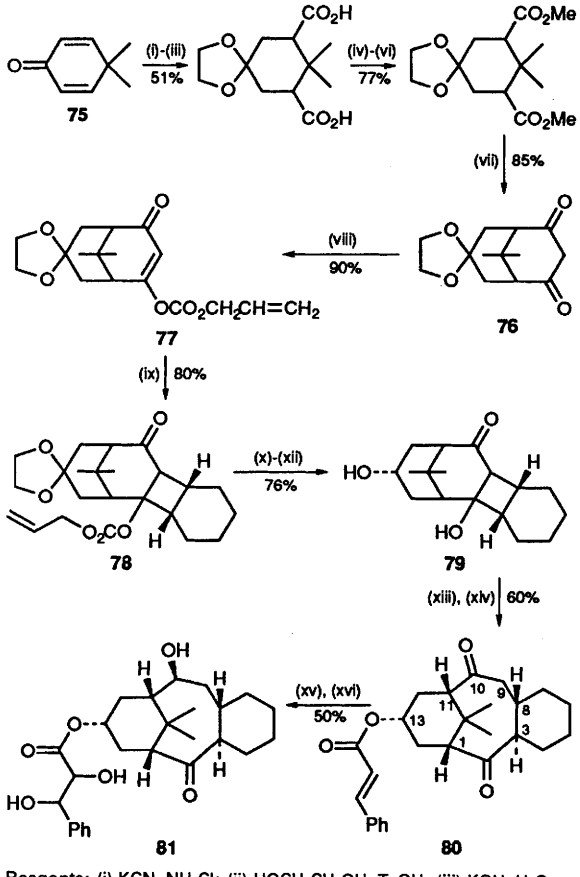
Diels–Alder precursor	*α-trans*[a]	*α-cis*[a]	*β-trans*[a]	*β-cis*[a]
67 thermal	70	0	0	0
catalyzed	0	85	0	0
72 thermal	36	49	15	0
catalyzed	0	97	0	0
73 thermal	38	27	12	13·5
catalyzed	0	80	0	15[b]
74 thermal	17	64	19	0
catalyzed	0	97	0	0

[a]Values are in absolute percentage yield
[b]Structural assignment is tentative

Blechert

Blechert has investigated a photochemical [2 + 2] cycloaddition-retroaldol route to form the eight-membered B ring in the taxanes (**Scheme 12**). Earlier work[24] had shown how the tricyclic ABC skeleton could be built *via* the key dienone **75** and dione **76** intermediates. The allyl carbonate derivative **77** underwent a stereospecific [2 + 2] cycloaddition with cyclohexene leading to cyclobutane **78**. When the analogue of **77** lacking the C-13 ketal protection was subjected to these reaction conditions Blechert found that the reaction occurred without stereoselectivity at the crucial C-8 centre. Another inconvenience was that using 1-methylcyclohexene, with the aim of incorporating the angular C-ring methyl group, gave the wrong regiosiomer, which would have led to a methyl group at C-3 instead of C-8. Blechert is reportedly investigating an alternative route to by-pass this particular problem.[25,26] After deprotecting the tertiary alcohol and ketone functions in **78**, followed by stereoselective reduction of the latter, treatment with potassium t-butoxide gave the retroaldol product (*cf.* **80**) and the ABC tricyclic taxane skeleton. This sequence also effected complete epimerization at C-3 to give the thermodynamically favoured *trans* B/C ring junction. Blechert had found that if the C-13 ketal was left in place, enolization occurred towards C-1, C-9, and C-11 and not C-3. Alternatively, selective reduction of the C-10 carbonyl function allowed epimerization at C-1 as a consequence of altered conformational preferences.

Recently[27] Blechert had taken the cyclobutanol **79** through to the cinnamate ester **80** using the same retroaldol-epimerization sequence.

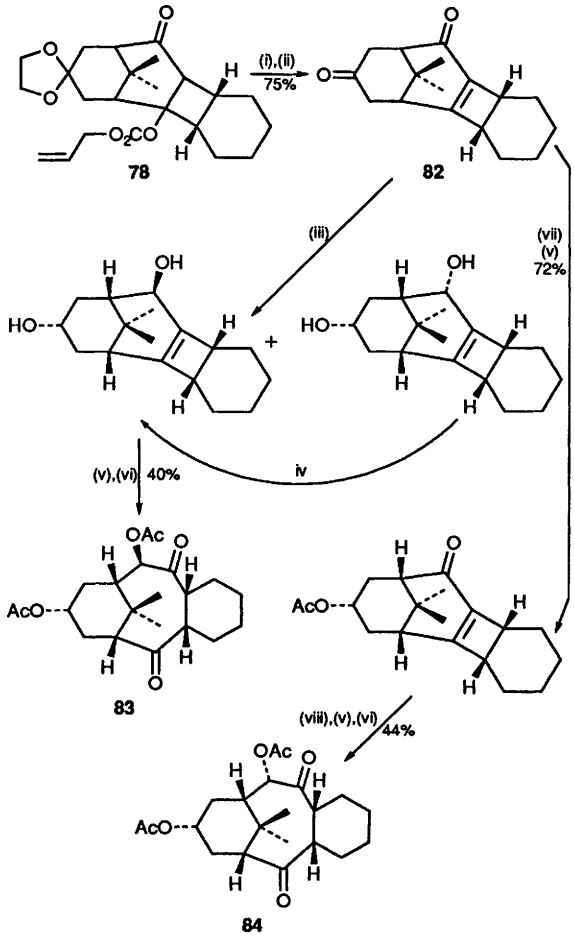


Reagents: (i) KCN, NH_4Cl; (ii) $HOCH_2CH_2OH$, TsOH; (iii) KOH, H_2O_2; (iv) DCC; (v) $LiMe_2Cu$; (vi) CH_2N_2; (vii) KH; (viii) $ClCO_2CH_2CH{=}CH_2$, $NaHCO_3$; (ix) cyclohexene, *hν*; (x) $Pd(PPh_3)_4$, morpholine; (xi) HCl, H_2O, THF; (xii) lithium selectride, −70°C; (xiii) Bu^tOK, Bu^tOH; (xiv) cinnamic acid, dicyclohexylcarbodiimide; (xv) $NaBH_4$, citric acid, CH_3OH, 3 min.; (xvi) OsO_4, *N*-methylmorpholine-*N*-oxide

Scheme 12

cis-Dihydroxylation of the double bond in **80** gave a 1:1 mixture of separable diastereoisomers of **81**. Both isomers were subjected to an *in vitro* tubulin test. The less polar of this pair was shown to inhibit the depolymerization of tubulin. This result is important as it is the first synthetic taxane with action analogous to taxol.

More recent work by Blechert[26] has focused on the intermediate **78**, as a compound to modify in order to introduce oxygen functionalization at C-9 in the B-ring. Thus, deprotection and dehydration of **78** (**Scheme 13**) first gave the dehydro derivative **82**. Various functional group interconversions followed by ozonolysis of the double bond then gave the C-10 epimers **83** and **84**, the first taxanes with three oxygen functionalities in the B-ring.

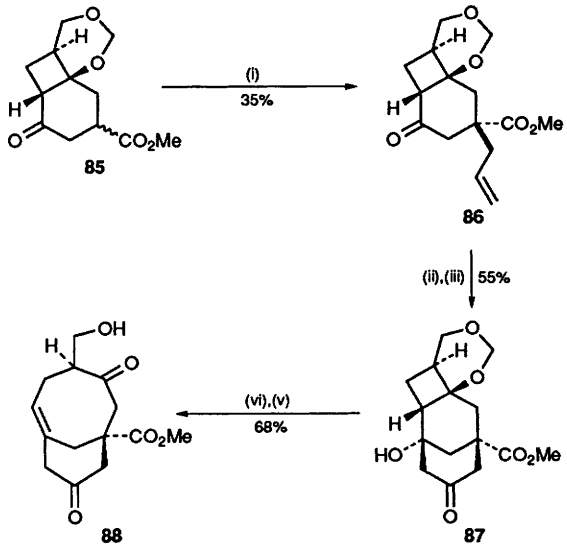


Reagents: (i) K_2CO_3, MeOH; (ii) H_3O^+; (iii) $LiAlH_4$, THF $-20° \rightarrow 0°C$; (iv) (a) MnO_2, DCM, (b) $LiAlH_4$; (v) Ac_2O, DMAP, Et_3N; (vi) O_3, DCM, MeOH then DMS; (vii) $NaBH_4$, MeOH; (viii) $NaBH_4/CeCl_3$, MeOH

Scheme 13

Kraus

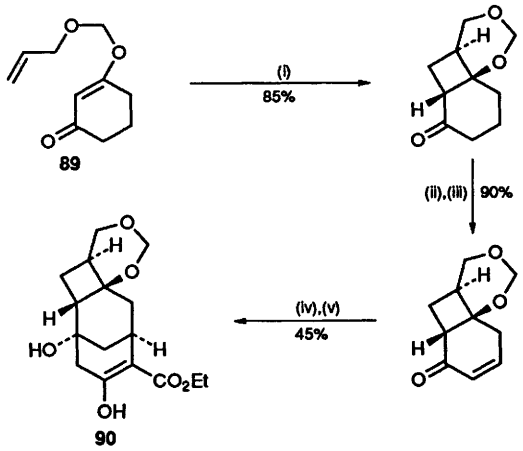
The approach to the taxane AB ring system adopted by Kraus *et al.* involves a similar strategy to that of Blechert and by Fetizon. The common link is the [2 + 2] photocycloaddition of a cyclohexane-1,3-dione enol leading to a [6.4] ring system. The other researchers, as mentioned above, then investigated retroaldol methods to form the B-ring. Kraus, however, has instead employed a fragmentation of the ring system *via* a bridgehead carbocation.[28] The known keto-ester **85** was prepared as a mixture of diastereoisomers, and was allylated to give the derivative **86** (**Scheme 14**). This step was unexpectedly difficult and low yielding (35%), but the product was isolated as a single isomer with the alkylation assumed to have occurred from the *exo* face. Wacker oxidation and cyclization of **86** next gave the bridgehead alcohol **87** which, after bromination, fragmented in the presence of silver tetrafluoroborate to give the AB model compound **88**.



Reagents: (i) 2·2 eq. LDA, allyl bromide; (ii) $PdCl_2$, O_2; (iii) NaOMe, 0°C; (iv) PBr_3; (v) 1·2 eq. $AgBF_4$, 5:1 MeCN/H_2O, 0°C

Scheme 14

An alternative synthesis was investigated in the light of the poor yields for the conversion of **85** into **86**. Thus the enol ether **89** was elaborated as depicted in **Scheme 15**, eventually yielding the tertiary alcohol **90**. The subsequent bromination and fragmentation of this compound has not yet been reported.

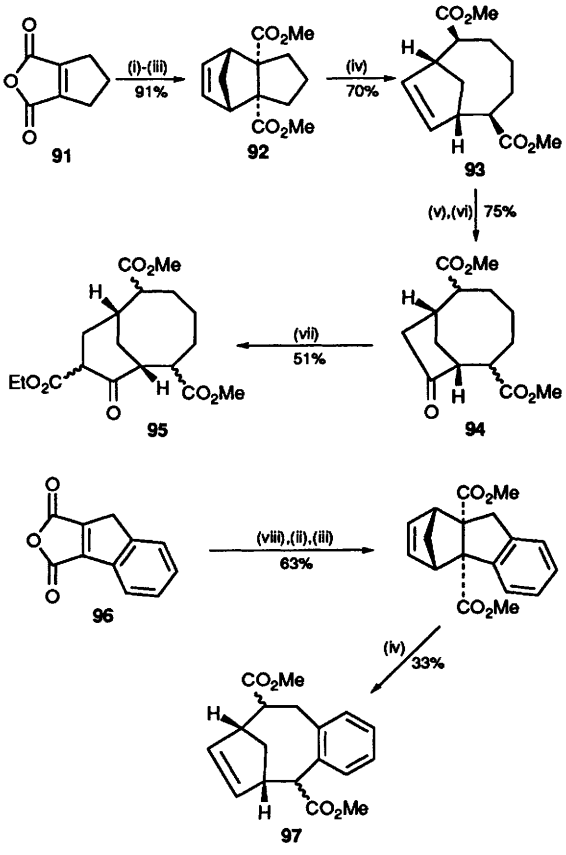


Reagents: (i) *hν*, PhH, 72 h; (ii) LDA, TMS-Cl; (iii) $Pd(OAc)_2$; (iv) Bu^tOK, $Ph_3P{=}CHCOCH_2CO_2Et$, THF, r.t.; (v) 110°C, aq. THF

Scheme 15

Ghosh

In 1990 Ghosh *et al.* reported[29] a Diels–Alder fragmentation sequence in their strategy for making the taxane carbon skeleton. Full details of this work[30] have now appeared. The unsaturated anhydride **91** first underwent a Diels–Alder reaction with cyclopentadiene leading to an adduct which was then modified to give the diester **92** (**Scheme 16**).

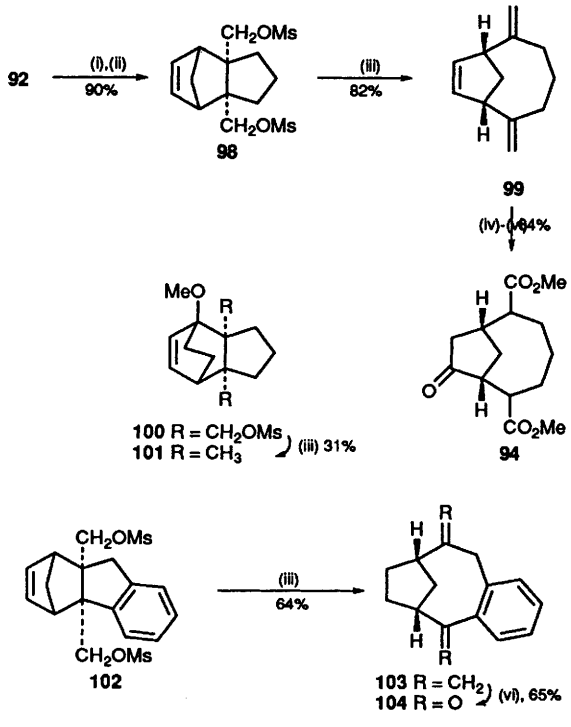


Reagents: (i) cyclopentadiene, THF, $AlCl_3$; (ii) $NaHCO_3$ EtOH, H_2O, Δ; (iii) CH_2N_2, Et_2O; (iv) Na, $NH_3(l)$, −55°C; (v) BH_3, THF, 0°C then NaOH, H_2O_2; (vi) acetone, Jones reagent; (vii) Et_3OBF_4, CH_2Cl_2, N_2CHCO_2Et, 0°C; (viii) cyclopentadiene, PhMe, Δ

Scheme 16

Unfortunately, Ghosh *et al.* found that the analogous reaction with 5,5-disubstituted cyclopentadienes failed to produce any of the expected adducts, and so prevented direct entry to analogues with the functionalization needed to introduce the C-15 (taxane numbering) geminal dimethyl group of the taxane skeleton. He is currently addressing this problem in a number of ways.[31] Reductive cleavage of the strained tricyclic 1,2-diester **92** with sodium in liquid ammonia led to the ring expanded diester **93**. The double bond in **93** was then modified by a hydroboration-oxidation sequence to give the ketone **94**, which then underwent a ring expansion when treated with ethyl diazoacetate, giving the AB analogue **95**. Following a similar strategy, the aromatic C-ring tricyclic model **97** was made from the anhydride **96**; unfortunately the yield of the key C–C bond cleavage was a disappointing 33%.

Recently Ghosh has reported two alternative protocols to replace the sodium-liquid ammonia reductive cleavage step **92**–**93**, again making use of the strain in polycylic systems to help the fragmentation. The first[32] method is shown in **Scheme 17**. The diester **92** was first fully reduced and the resulting diol was then protected as the dimesylate **98**. Treatment of **98** with zinc and sodium iodide in hexamethylphosphoramide (HMPA) next gave the ring expanded triene **99**. Normally this reductive protocol would reduce the mesyloxy function in **98** to a methyl group, but in the strained polycyclic compound **98** an intermediate carbanion at one of these centres triggered the fragmentation to give **99**, in favourable competition with the reduction. In contrast, with the less strained dimesylate **100** the doubly reduced product **101** was isolated from a mixture of products, and no compounds arising from ring cleavage were detected. In a similar fashion the aromatic dimesylate **102** was converted into the diene **103** in 64% yield (*cf.* 33% for the sodium/liquid ammonia mediated fragmentation). Ruthenium tetroxide oxidation of **103** then gave the diketone **104**, so showing the synthetic potential of this protocol.

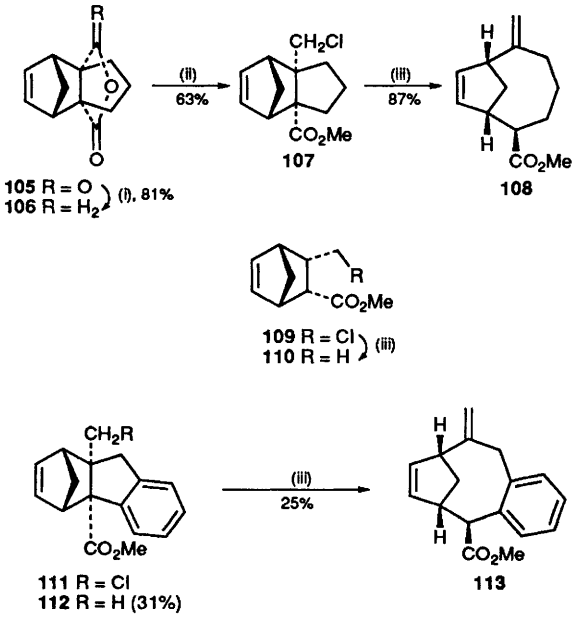


Reagents: (i) $LiAlH_4$, THF, r.t.; (ii) CH_3SO_2Cl, NEt_3, DMAP, DCM, 0°C; (iii) NaI, Zn, HMPA, Δ; (iv) BH_3–THF, 0°C then NaOH, H_2O_2; (v) Jones oxidation, $(CH_3)_2CO$; (vi) CH_2N_2, Et_2O; (vii) $RuCl_3.nH_2O$, CCl_4, MeCN, H_2O, r.t.

Scheme 17

The second alternative cleavage procedure used by Ghosh involved a radical fragmentation.[33] Thus, the anhydride **105** was first reduced to the lactone **106** with sodium borohydride (**Scheme 18**), and **106** was next converted into the chloro ester **107** using thionyl chloride in methanol. Treatment of this chloro ester with tributyltin hydride and catalytic AIBN then initiated a smooth fragmentation to produce the diene

108 in good yield, with only a trace of the directly reduced product detectable in the ^{1}H NMR spectrum. Conversely with the 'strain free' chloro ester **109**, the reduced product **110** predominated. Reduction of the benzo analogue **111** under these conditions, gave only 25% of the fragmented product **113** and 31% of the reduced product **112** even though the tertiary benzylic radical formed after C–C bond cleavage in this case was expected to be more stable than the corresponding debenzo system. Ghosh has speculated that replacement of the hydrogen atoms at C-3 and C-4 with sp^2 carbons in the benzo analogue **111** reduces the non-bonded interactions with the hydrogen atoms at C-10 and so decreases the likelihood of strain-assisted fragmentation. Ghosh has successfully applied many useful protocols and with suitably functionalized precursors a range of interesting ABC taxane compounds should be accessible in the near future.

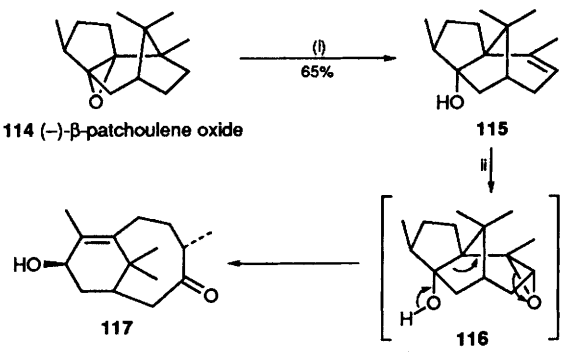


Reagents: (i) $NaBH_4$, THF, 0°C; (ii) $SOCl_2$, MeOH, Δ; (iii) Bu_3SnH, AIBN, PhH, Δ

Scheme 18

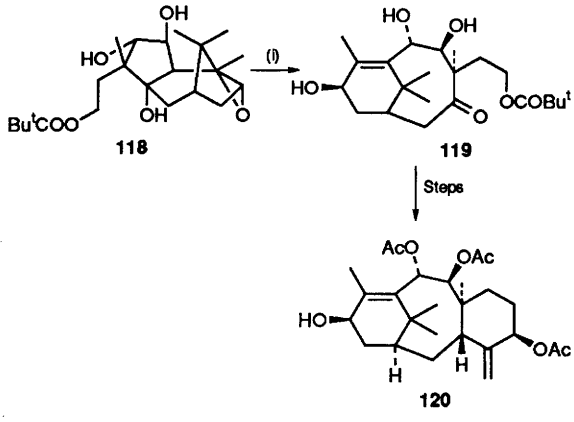
Holton

No review of taxane systems would be complete without mention of the elegant work of Holton. The key steps in the Holton route were first illustrated by the rearrangement of (−)-β-patchoulene oxide **114** into the tertiary alcohol **115** (**Scheme 19**). Subsequent epoxidation and fragmentation of **115** *via* the intermediate **116** then gave the AB-ring system of the taxane structure **117**.[34,35] This result was then extended to produce the functionalized epoxide **118** (**Scheme 20**).[36] Fragmentation of **118** next led to the intermediate **119** which was then elaborated to the unnatural enantiomer of taxusin **120**. At the time of writing this review Holton's approach is the most advanced taxane synthesis. He has recently written an excellent behind-the-scenes account of his work.[37]



Reagents: (i) $BF_3.OEt_2$; (ii) $(Pr^iO)_4Ti$, Bu^tOOH then Me_2S

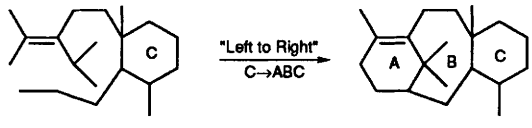
Scheme 19



Reagent: (i) $(Pr^iO)_4Ti$

Scheme 20

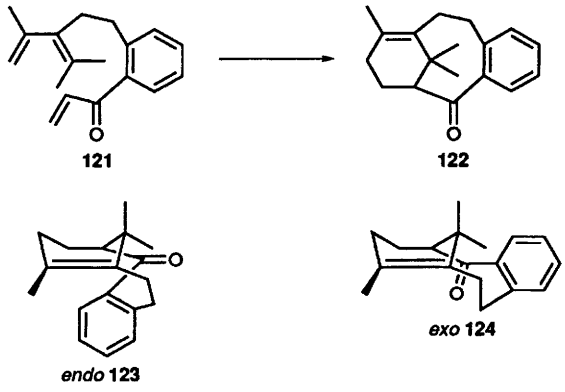
2.2 From c-ring precursors



Shea

The Diels–Alder approach to c-aromatic taxoid structures developed by Shea is an example of a Type II Diels–Alder reaction that he and his colleagues had previously developed in a series of elegant studies.[38] The key step is the intramolecular Diels–Alder reaction of the triene **121** which gives the c-aromatic taxoid **122** under both thermal and Lewis acid conditions. Shea discovered that the product was produced as two atropisomers, *endo* **123** and *exo* **124**, and that the ratio depended upon the conditions used. A strong kinetic preference for the *endo* isomer **123** was observed when the reaction **121** → **122** was carried out in the presence of $AlCl_3$.[39] The phenomenon of atropisomerism in taxoid structures has been studied in detail by Shea,[40] and the results obtained used by all other workers synthesizing c-aromatic taxoid structures.

More recent publications from Shea *et al.*[41] demonstrate developments in converting c-aromatic compounds into structures with a non-aromatic c-ring

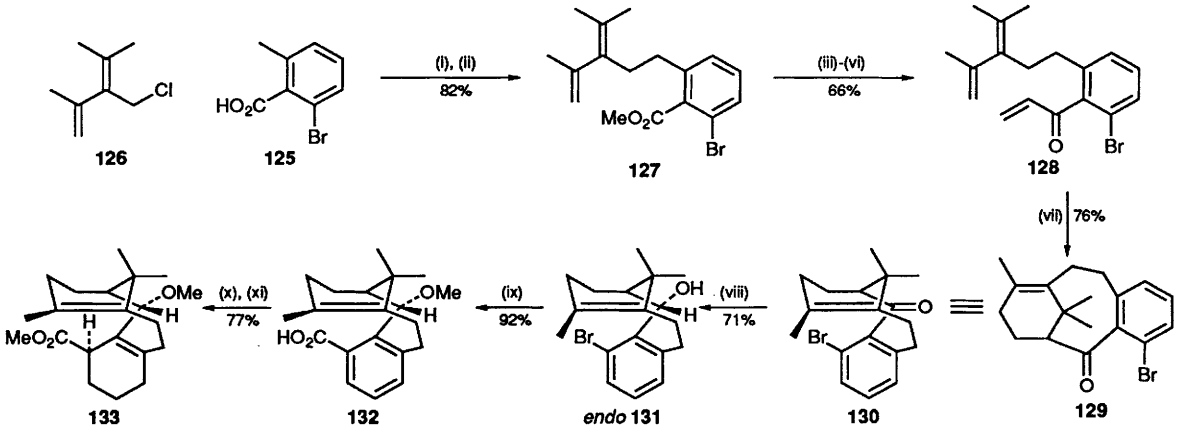


(**Scheme 21**). Thus, the dianion of the aromatic acid **125** was alkylated with the chlorodiene **126** to provide the aromatic diene **127** after esterification. Reduction of the ester **127** to the corresponding aldehyde, followed by addition of vinylmagnesium bromide and oxidation next produced the enone **128**. A Lewis acid catalysed intramolecular Diels–Alder reaction then gave the c-aromatic taxoid structure **129** as the single *endo* product **130**. The reduction of **130**, with DIBAlH, occurred with acceptable stereocontrol to give a 1 : 3.9 mixture of alcohols from which the stereoisomer **131** was isolated in 71% yield. Methylation of the alcohol **131** followed by lithium-halogen exchange and reaction with carbon dioxide next provided the acid **132**. Reduction of the aromatic c-ring in **132** followed by esterification and hydrogenation then yielded the ester **133**. The major step of reduction of the aromatic c-ring has therefore been taken, and clearly further work on this strategy is underway.

Jenkins

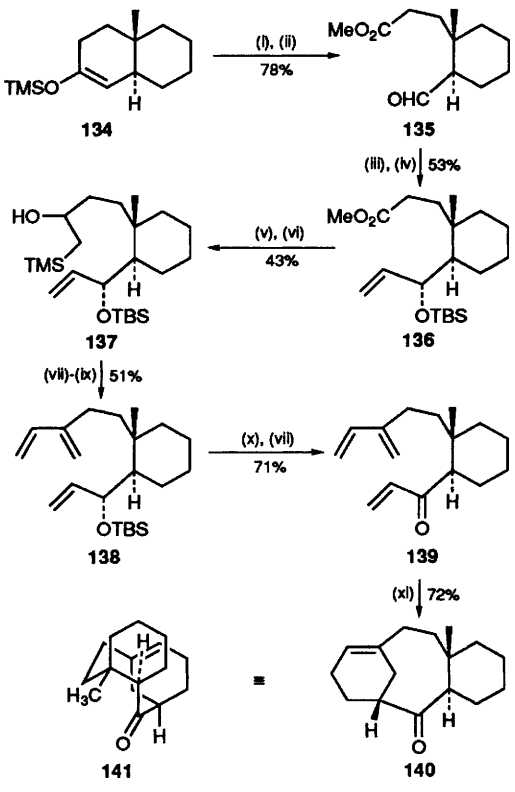
Concurrent with the work of Shea, Jenkins and his group have also investigated the c→ABC Diels–Alder approach to taxanes. The main difference between the two approaches is that Shea *et al.* use an aromatic c-ring precursor which is reduced after cyclization while in the Jenkins route the c-ring precursor is alicyclic. The route of Jenkins *et al.* is illustrated in **Scheme 22**[42] and it starts from the trimethylsilyl enol ether **134**, a compound prepared by the Robinson annulation of 2-methylcyclohexanone and methylvinyl ketone. Ozonolysis of **134** and treatment with diazomethane next gave the ester aldehyde **135**. Addition of vinylmagnesium bromide to **135** followed by protection of the resulting allylic alcohol then led to the ester **136**. Reduction of the ester group in **136** to an aldehyde with DIBAlH followed by addition of trimethylsilylmethylmagnesium chloride next produced the sensitive alcohol **137**. Oxidation of **137** to the corresponding ketone, using a very short reaction time to avoid desilylation, followed by addition of vinylmagnesium bromide and Peterson elimination then provided the key triene **138**. Diels–Alder reaction was not possible without the presence of an electron-withdrawing group in the dienophile; hence the silyl protecting group in **138** was removed and the resulting alcohol was oxidized to give the enone **139**. The intramolecular Diels–Alder reaction with **139** occurred readily with diethylaluminium chloride to produce the tricyclic taxoid structure **140** as a single diastereoisomer. The relative stereochemistry of the three asymmetric centres in the tricycle **140** was shown to be the same as the corresponding centres in the natural taxanes by *X*-ray crystallography, which also proved that the eight-membered ring was in the boat–chair conformation **141**. This is the conformation observed in the *X*-ray crystal structure of a wide range of taxane derivatives.

This Diels–Alder route to the taxanes has been adapted to produce an alkylated taxoid structure as shown in **Scheme 23**.[43] Thus, addition of 2-propenylmagnesium bromide to the aldehyde **142** followed by a Collins oxidation first provided the enone **143**. The selenoacetal of acetone was next lithiated and the resulting anion ($LiCMe_2SePh$)[44] was then added to the enone **143**; subsequent elimination of PhSeOH finally gave the triene **144**. Deprotection and oxidation of **144**, to produce the enone **145**, was



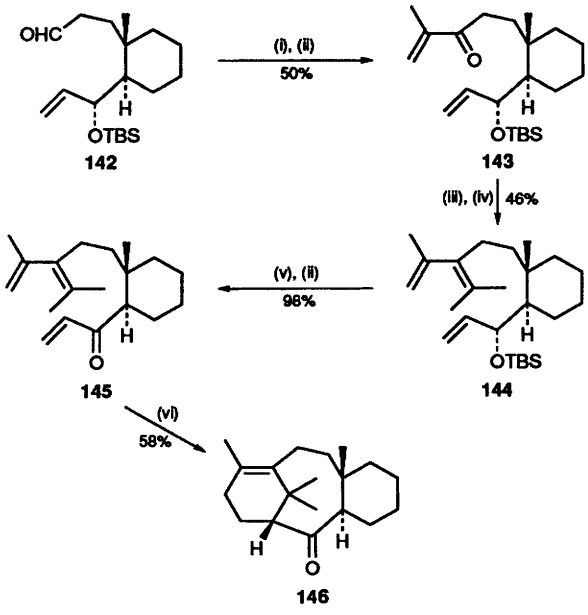
Reagents: (i) LDA, −78°C then the chloride; (ii) CH_2N_2; (iii) DIBAL, C_7H_8, 0°C; (iv) PCC; (v) $CH_2CHMgBr$; (vi) $BaMnO_4$; (vii) Et_2AlCl; (viii) DIBAL, CH_2Cl_2, C_7H_8, −78°C; (ix), NaH, MeI then Bu^{t}Li followed by CO_2; (x) Li, NH_3, EtOH, THF, −78°C then CH_2N_2 followed by H_2, PtO_2

Scheme 21



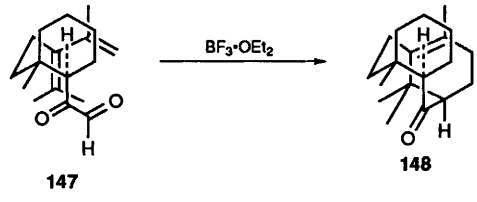
Reagents: (i) O_3, Me_2S; (ii) CH_2N_2; (iii) CH_2=CHMgBr; (iv) TBDMSOTf, 2,6-lutidine; (v) DIBAL; (vi) $TMSCH_2MgCl$; (vii) Collins oxidation; (viii) CH_2=CHMgBr; (ix) NaOAc, HOAc; (x) HF, H_2O, CH_3CN; (xi) Et_2AlCl

Scheme 22



Reagents: (i) $CH_2C(Me)MgBr$; (ii) Collins oxidation; (iii) $Me_2C(SePh)Li$; (iv) $SOCl_2$, Et_3N; (v) HF, H_2O, CH_3CN; (vi) $BF_3.OEt_2$

Scheme 23

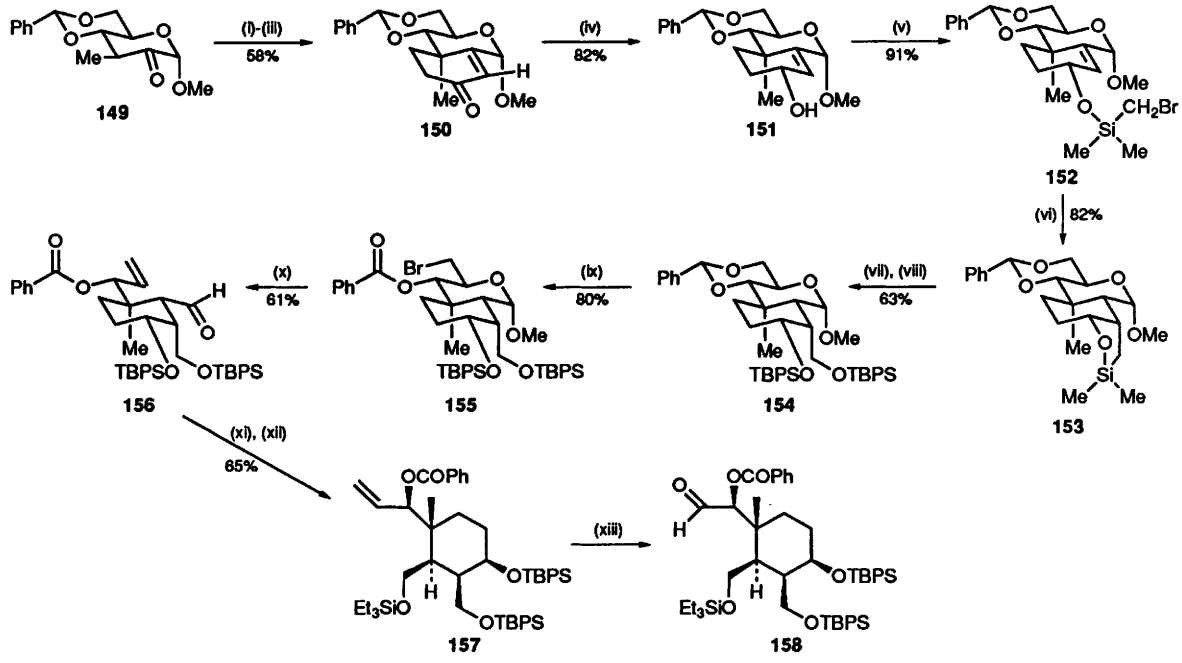


followed by intramolecular Diels–Alder reaction, using $BF_3.OEt_2$ as a catalyst, to give the alkylated taxoid **146**. The product **146** was not crystalline, and so the relative stereochemistry was determined by NOE studies and comparison with the spectra of the unalkylated model compound **141**. The preference for the formation of the eight-membered ring in **146** in the boat–chair conformation is reflected in the transition state of **147** → **148** for the Diels–Alder reaction. The products **141** and **148** correspond to the *endo* isomers observed in the Lewis acid catalysed Diels–Alder cyclization to c-aromatic taxoid structures presented by Shea *et al.*

Jenkins *et al.* have extended their approach to taxanes by using a chiral pool derived c-ring. Thus, the readily available protected glucose methyl ketone **149** (**Scheme 24**) was first subjected to a Robinson annulation to produce the tricyclic enone **150**[45]—the first reported example of the application of this annulation reaction to the synthesis of annulated sugars. Reduction of the ketone group in **150** with L-Selectride® next provided the allylic alcohol **151**, the structure of which was determined by *X*-ray crystallography. The formation of a *trans* ring junction between the carbocyclic ring and the sugar was achieved using the Stork silylmethylene radical cyclization[46] as illustrated in **151** → **152** → **153**.[47] The ring junction between the carbocyclic ring and the sugar ring had now been established with the correct absolute configurations. The next task was to cleave the methoxyacetal group in **153** to leave the highly substituted cyclohexane, the future c-ring.[48] The siloxane ring in **153** proved to be unstable to subsequent reactions, and so it was cleaved oxidatively and then protected to yield the *bis*-silyl ether **154**. Reaction between **154** and *N*-bromosuccinimide caused fragmentation of the benzylidene ring to give the bromoester **155**.[49] A second fragmentation, following the Vasella protocol, was achieved on heating the bromoester **155** with zinc leading to the aldehyde **156**. Reduction and protection of the aldehyde **156** next gave the olefin **157** which was treated with ozone to produce the aldehyde **158**. The aim of Jenkins *et al.* is to construct diene and dienophile components onto the aldehyde **158**, and then to use the intramolecular Diels–Alder reaction to produce the A and B rings of the taxoid structure.

Yadav

An interesting variation on the Diels–Alder approach to the taxanes has been published by Yadav *et al.* (**Scheme 25**).[50] The diol **159** was alkylated selectively with the bromodiene **160** to give the ether **161**. Swern oxidation of **161**, followed by epimerization and addition of vinylmagnesium bromide next gave the alcohol **162**. A further Swern oxidation led to the trienone **163**, which underwent an intramolecular, Lewis acid catalysed Diels–Alder reaction to produce



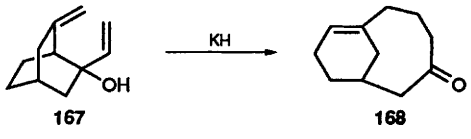
Reagents: (i) Lithium tetramethylpiperidine, Et_2O, 0°C, 1 h; (ii) 3-(trimethylsilyl)but-3-en-2-one, −78°C→r.t., 1 h; (iii) KOH (0·3 mol equiv.), MeOH, 80°C, 6 h; (iv) L-Selectride; (v) $ClSiMe_2CH_2Br$, Et_3N; (vi) Bu_3SnH, azoisobutyronitrile (AIBN); (vii) H_2O_2, KF; (viii) t-butyldiphenylsilyl chloride, CH_2Cl_2, imidazole, r.t., 72 h; (ix) NBS, $BaCO_3$, CCl_4, reflux 3 h; (x) Zn, Pr^iOH, reflux, 5 h; (xi) $NaBH_4$, Pr^iOH, 60°C, 15 min.; (xii) Et_3SiCl, CH_2Cl_2, imidazole, 15 h; (xiii) O_3, CH_2Cl_2, −78°C then dimethyl sulfide

Scheme 24

the tricyclic ether **164**. Reduction of the ketone group in **164** and protection of the resulting alcohol then gave the ether **165** which underwent Wittig rearrangement, using BuLi at −78°C, to produce the tricyclic compound **166**.

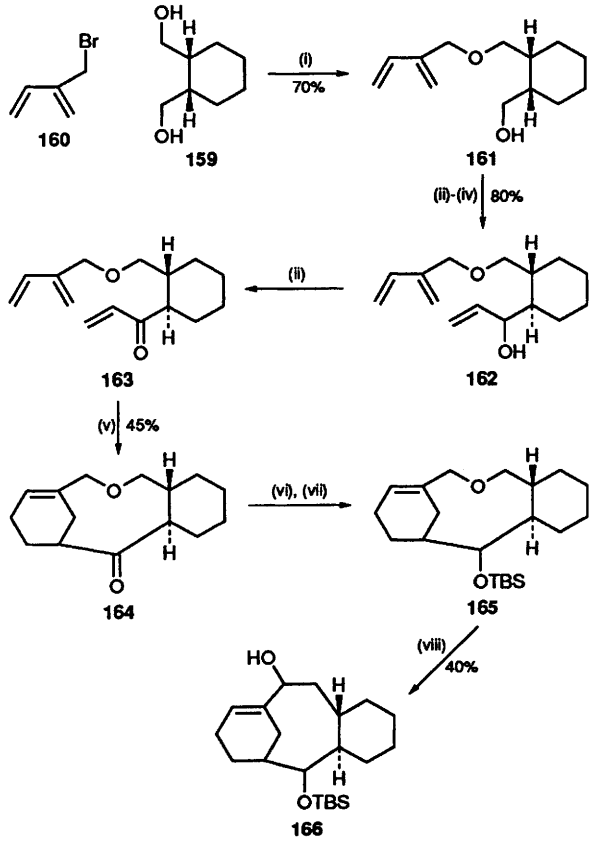
Oxy-Cope routes

The story of the oxy-Cope route to taxanes starts with the publication of the conversion of the diene **167** into the AB-ring fragment **168** by S.F. Martin *et al.*[51] in 1982.



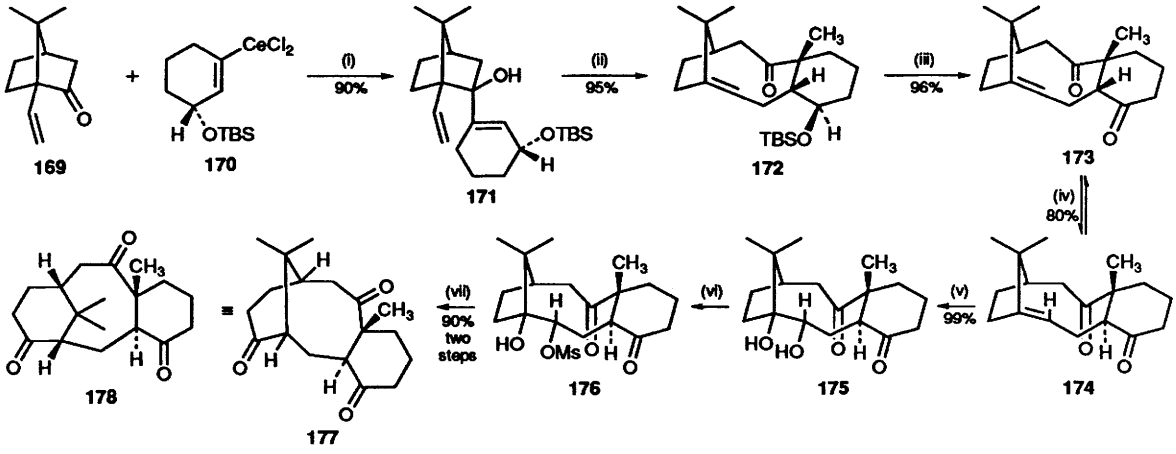
Paquette

The oxy-Cope rearrangement is a key step in Paquette's route to the taxanes. Recent progress on this work is illustrated in **Scheme 26**. The enantiomerically pure ketone **169** is first reacted with the optically enriched cerium reagent **170** to give the alcohol **171**. [3,3] Sigmatropic rearrangement of **171** occurred *via* an *endo* chair transition state, leading to the 'carbonyl down' atropisomer **172**. Deprotection of **172** and oxidation next produced the ketone **173** which was then equilibrated with sodium methoxide to give a 1:1 mixture of ketones with the *cis* and *trans* ring junctions, **173** and **174** respectively. Separation and recycling the *cis* ketone **173** gave the *trans* isomer **174** in 80% yield. Hydroxylation of **174** next provided a



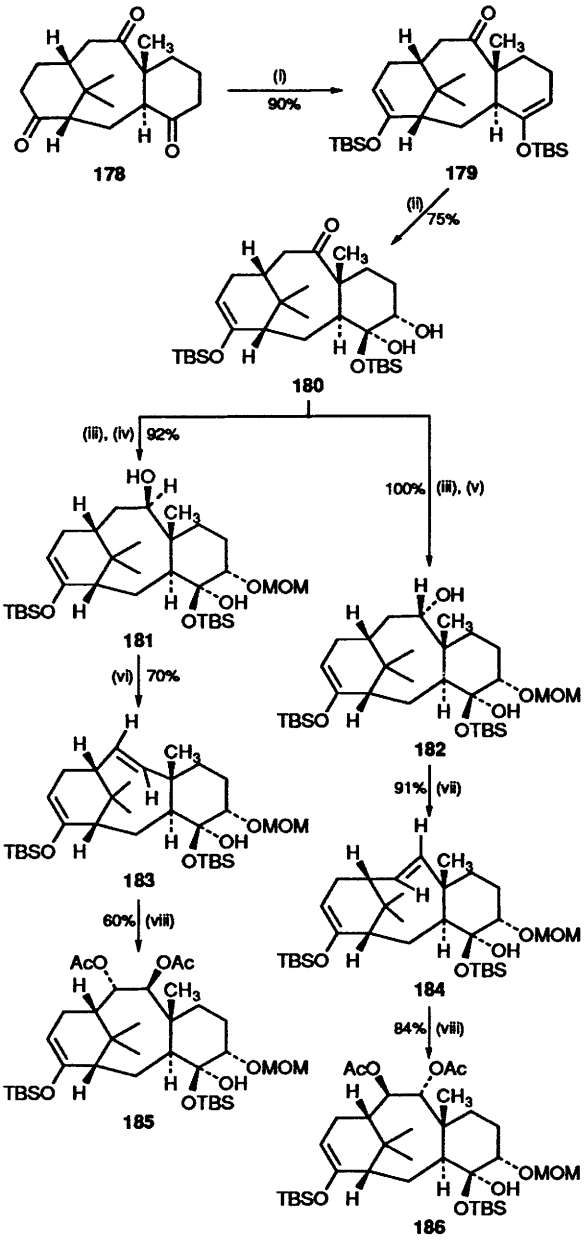
Reagents: (i) NaH; (ii) $(COCl)_2$, Me_2SO, Et_3N, −78°C; (iii) NaOMe, MeOH; (iv) $H_2C{=}CHMgBr$, THF; (v) Et_2AlCl, CH_2Cl_2; (vi) $NaBH_4$, EtOH; (vii) TBDMS-Cl, imidazole, DMF; (viii) BuLi, THF, −78°C

Scheme 25



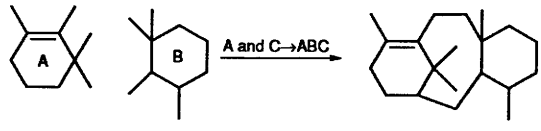
Reagents: (i) THF, −78°C; (ii) KH, 18-crown-6; (iii) Bu_4NF then PDC; (iv) NaOMe, MeOH, separate and recycle; (v) OsO_4, $NaHSO_3$, pyridine, water; (vi) CH_3SO_2Cl, pyridine; (vii) Et_2AlCl

Scheme 26



single diol **175** which was mesylated selectively to yield the secondary mesylate **176**. The second step in this route towards the taxanes is the Et_2AlCl catalysed 1,2-migration of the C_1 bridge in the mesylate **176** to produce the functionalized tricyclo[9.3.1.0.^{3,8}] pentadecane **177**.[52] The alternative depiction **178** gives a representation that is easier to compare with the other taxanes covered in this review. Further transformations of the B and C rings of the triketone **178** are outlined in **Scheme 27**.[53] The three carbonyl groups in **178** are differentiated by first converting the A and C-ring ketones into silyl enol ethers to produce the bis-silyl ether **179**. Steric factors dictate that the C-ring silyl enol ether is more reactive to hydroxylation, which leads to the diol **180**. Protection of **180** followed by low temperature reduction with DIBAlH in hexane provides the β-alcohol **181**, whereas reduction in benzene at 8°C led to the α-alcohol **182**. Dehydration of alcohols **181** and **182** gave the olefins **183** and **184** respectively, which finally produced the respective diacetates **185** and **186**. Clearly this approach is very close to synthesizing some taxane natural products. The main problem to be faced is the introduction of the bridgehead double bond into the A-ring. Once this task has been achieved the route has great potential.

2.3 From A-ring and C-ring precursors



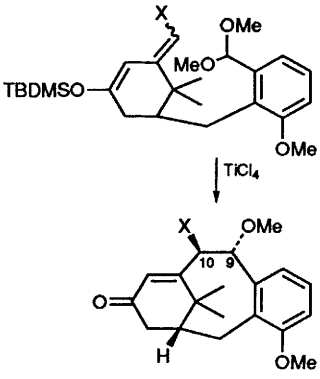
Kuwajima

The key step in the approach to taxanes highlighted by Kuwajima *et al.* is the formation of the 9-10

Reagents: (i) TBSOTf, Et_3N; (ii) Me_2CO_2; (iii) MOMCl, Pr^i_2EtN; (iv) DIBAL, hexane, −78°C to −10°C; (v) DIBAL, benzene, 8°C; (vi) Burgess reagent, benzene, 25–45°C; (vii) $[C_6H_5C(CF_3)_2O]_2SPh_2$, benzene, 25°C; (viii) OsO_4, CH_2Cl_2 then $NaHSO_3$ pyridine followed by Ac_2O, pyridine, DMAP

Scheme 27

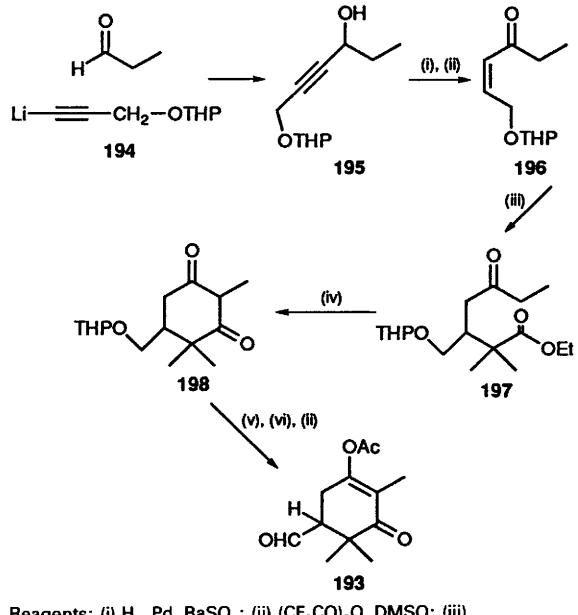
carbon–carbon bond by an intramolecular Lewis acid catalysed cyclization of a dienol silyl ether and an acetal.[54] In the unsubstituted case, **187**, the cyclized product **190** was obtained in 74% yield. Despite the fact that a 1:1 mixture of *E* and *Z* thioethers **188** was used, conditions were varied until a single stereoisomer of **191** was obtained. Similarly, a mixture of the vinyl ethers **189** was converted into one product, the bis-methyl ether **192**. In all cases NOE studies showed that the *endo* product was obtained.



187 X = H
188 X = SPh *E*/*Z* = 1:1
189 X = OMe *E*/*Z* = 1:4.6

190 X = H 74%
191 X = SPh 80%
192 X = OMe 84%

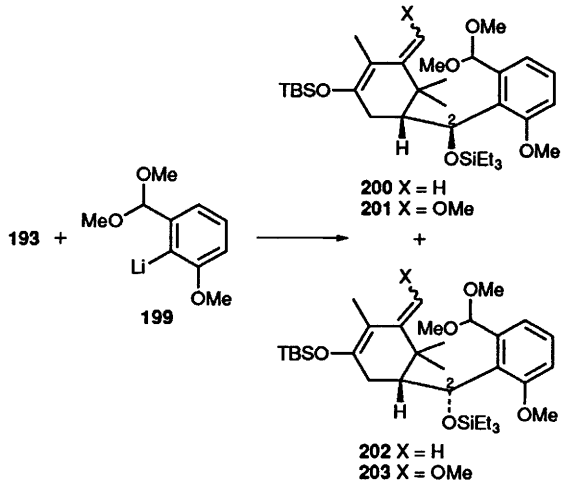
Further progress in this approach is directed towards the introduction of oxygen at C-2 and the synthesis of compounds with a non-aromatic c-ring. Extensive studies on the first problem,[55] were based on an efficient synthesis of the A-ring synthon **197** (**Scheme 28**). Addition of the lithiated THP-propargyl ether **194** to propionaldehyde first produced the alcohol **195**. Lindlar hydrogenation of **195** and Swern oxidation next gave the α,β-unsaturated ketone **196**. Michael addition of lithiated ethyl isobutyrate to **196** then led to the ketoester **197**. Dieckmann-like cyclization of **197** next gave the 1,3-diketone **198** which was subjected to a sequence of acetylation, deprotection, and oxidation leading to the key intermediate **193** in 43% overall yield for the eight-step synthesis.



Reagents: (i) H_2, Pd, $BaSO_4$; (ii) $(CF_3CO)_2O$, DMSO; (iii) $(CH_3)_2CLiCO_2Et$; (iv) Bu^tOK; (v) $(CH_3CO)_2O$, Et_3N; (vi), *p*TsOH, MeOH

Scheme 28

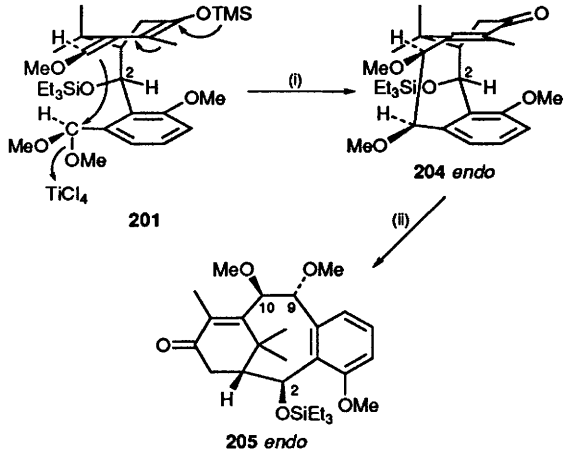
The substituted phenyllithium **199** was now added to the aldehyde **193** in the presence of $CeCl_3$, and a 3:1 ratio of Cram to *anti*-Cram products was obtained. This mixture was separated and converted into the four products **200–203** as illustrated (**Scheme 29**); the vinyl ethers **201** and **203** were obtained as a mixture of *E* and *Z* isomers as in previous cases. The stereochemistry of the C-2 silyloxy group plays a crucial role in the cyclizations of compounds **200–203**. Cyclization of **201** (**Scheme 30**) at −78°C with $TiCl_4$ gave the *endo* product **204**; on separate treatment of **204** with $TiCl_4$ at 0°C epimerization at C-10 produced the *endo* isomer **205**. An unfavourable steric interaction involving the silyloxy group at C-2 causes **203** (**Scheme 31**) to cyclize *via* an *exo* transition state leading to the product **206**.



Reagents: (i) $CeCl_3$; (ii) pyrrolidine, Bu^tMe_2SiCl, Et_3N, separation; (iii) Et_3SiCl, Et_3N; (iv) Me_3SiCH_2Li, Bu^tOK, for **200** and **202**; Me_3Si CH(OMe)Li, Bu^tOK for **202** and **203**

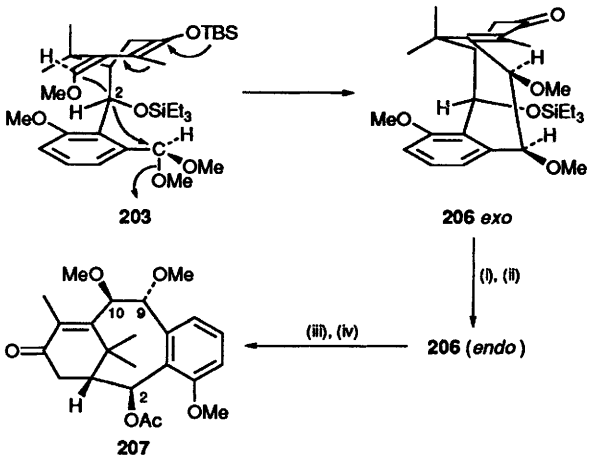
Scheme 29

Isomerization of **206** *exo* to *endo* was achieved by deprotection and heating; epimerization to the desired isomer **207** was realized on acetylation of the OH at C-2 and treatment with $TiCl_4$.



Reagents: (i) $TiCl_4$, −78°C; (ii) $TiCl_4$, 0°C, 30 min.

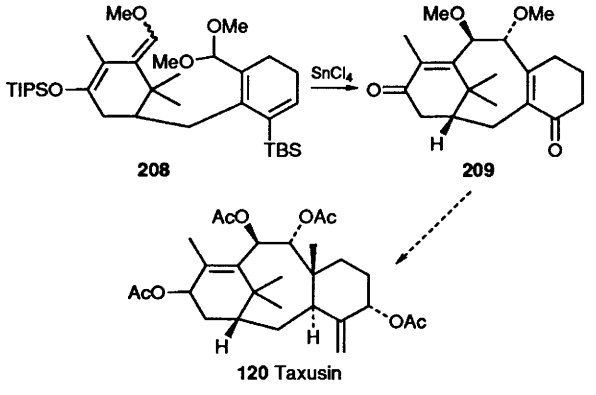
Scheme 30



Reagents: (i) NBu_4F; (ii) heat, 30 min.; (iii) Ac_2O, Et_3N; (iv) $TiCl_4$, −45°C, 45 min.

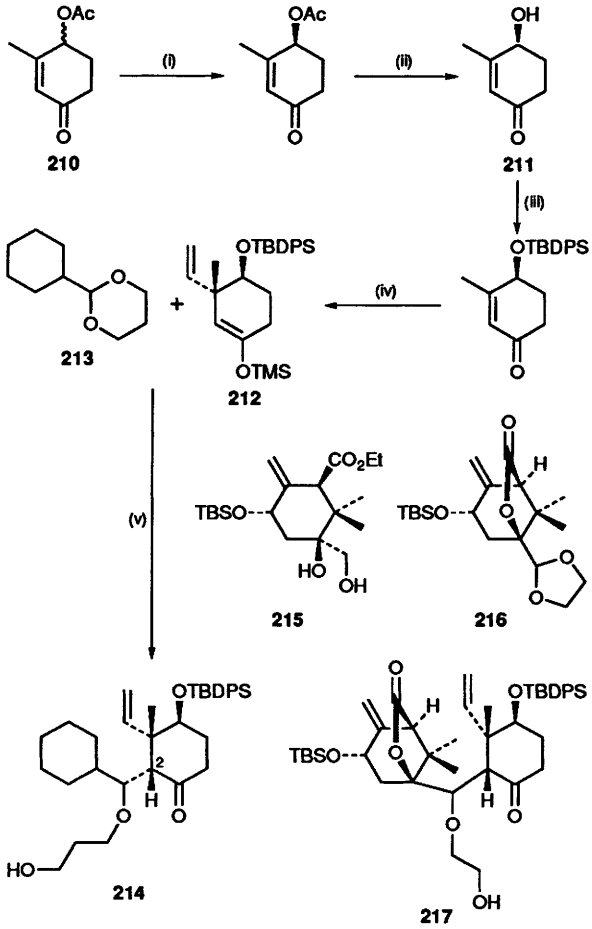
Scheme 31

Two recent publications[56,57] have given further details of these cyclization and isomerization reactions, and studies on the synthesis of a non-aromatic C-ring have been reviewed.[58] The precursor **208** has been synthesized and cyclized to the tricyclic compound **209**, whose stereochemistry was confirmed by *X*-ray crystallography. The objective now is to introduce the C-ring methyl group *via* conjugate addition and to further elaborate the structure to that of taxusin **120**.



Frejd

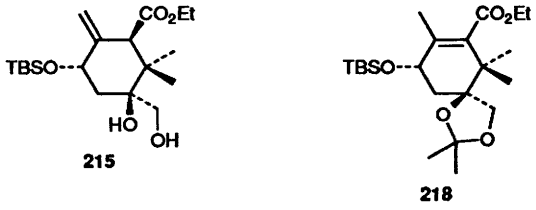
Frejd's approach to the taxane is a convergent strategy in which separate A and C-ring fragments are first synthesized, then coupled to give an A[B]C structure; a final cyclization to form the B ring completes the tricyclic structure. In a recent report[59] Frejd used an enzymic resolution in the synthesis of an optically active C-ring unit. The racemic acetoxy enone **210** was converted into the enantiopure alcohol **211** (> 99% e.e.) using an enzymic resolution/chemical hydrolysis sequence (**Scheme 32**). Elaboration of enone **211** next gave the silyl enol ether **212**, a homochiral taxane C-ring analogue. The enol ether **212** was coupled successfully to the cyclohexane carboxaldehyde derived acetal **213** giving the axially substituted product **214**, which had the incorrect relative configuration at C-2 (C-3 in the eventual taxane skeleton). It is hoped that this can be altered at a later stage. Progressing to a functionalized cyclohexane carboxyaldehyde acetal (A-ring fragment) in place of **213**, Frejd naturally chose the acetal **216**, a derivative of compound **215** and an optically active A-ring unit synthesized from L-arabinose. Unfortunately, attempts to form the coupled product **217** have till now met with failure.

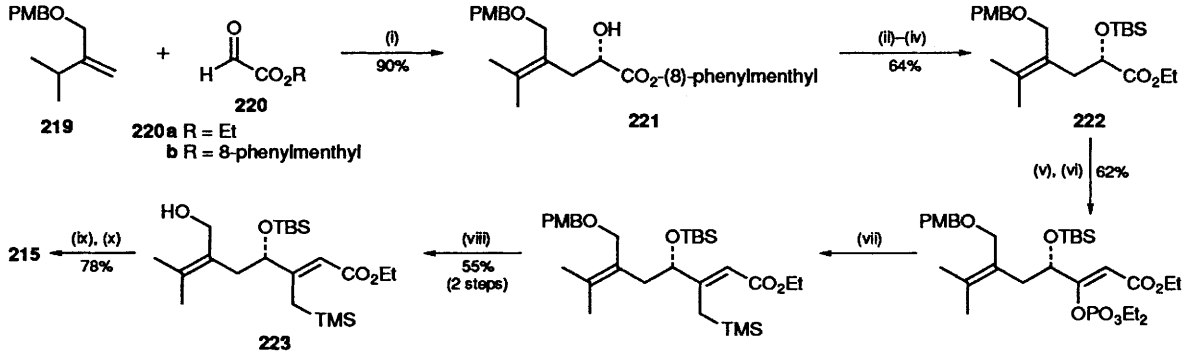


Reagents: (i) PLE; (ii) Na_2CO_3, MeOH; (iii) TBDPSCl, imidazole; (iv) CH_2=CHMgBr, CuBr.Me_2S; then TMSCl, TMEDA; (v) $TiCl_4$, −75°C

Scheme 32

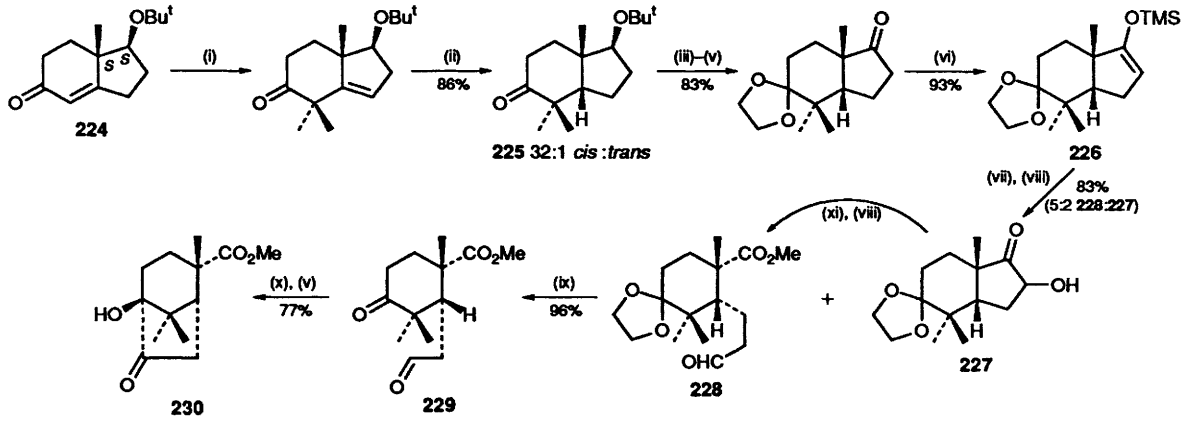
The sequence from L-arabinose to **218** was somewhat arduous (23 steps), and is considered too lengthy to be of practical use. Nevertheless full details have just been reported,[60] and another publication has revealed details of a much improved synthesis of the diol **215**,[61] outlined in **Scheme 33**. The ene reaction between the allylic ether **219** and ethyl glyoxylate **220a** yielded none of the desired allylic alcohol when the reaction was catalysed by the chiral Lewis acid derived from (*S*)-1,1′-binaphthalene-2,2′-diol and $Cl_2Ti(OPr^i)_2$. The reaction of **219** and the phenylmenthyl ester **220b** using $SnCl_4$ as Lewis acid was successful though, and this auxiliary controlled reaction gave yields of the allylic alcohol **221** in excess of 90% with diasteroisomeric excesses greater than 95%. The protected alcohol **222** was homologated by a Claisen ester condensation. Subsequent nickel catalysed coupling of a silyl Grignard reagent and an





Reagents: (i) $SnCl_4$, DCM, −78°C; (ii) 1M NaOH, THF, MeOH; (iii) DBU, EtBr, PhH, Δ; (iv) TBSCl, imidazole, DCM; (v) LiHMDS–EtOAc, TMEDA, THF; (vi) Bu^{t}OK, $ClPO_3Et_2$, THF; (vii) $TMSCH_2MgCl$, $Ni(acac)_2$, Et_2O; (viii) DDQ, DCM, H_2O, 0°C; (ix) Bu$^t O_2H$, $TiOPr^i_4$, (−)-D-diethyl tartrate; (x) $BF_3.OEt_2$

Scheme 33



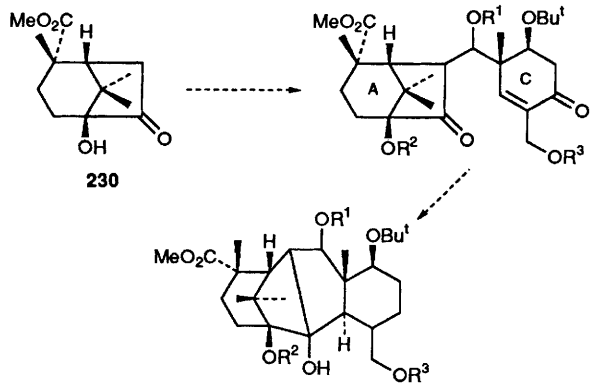
Reagents: (i), Bu^{t}OK, Bu^{t}OH, MeI; (ii) H_2, 10% Pd–C; (iii) $BF_3.OEt_2$, DCM; (iv) $HO(CH_2)_2OH$, *p*-TsOH, PhH, Δ; (v) DMSO, $(COCl)_2$, Et_3N, DCM; (vi) TMSOTf, collidine, DCM; (vii) O_3, DCM, pyridine, −78°C then PPh_3; (viii) CH_2N_2, Et_2O; (ix) 1N HCl, THF, r.t., (x) SmI_2, THF–MeOH, −25°C; (xi) $NaIO_4$, THF, MeOH

Scheme 34

enol phosphate gave, after deprotection, the allylsilane **223**, a precursor to the diol **215**. The stage is now set for coupling the A and C-rings.

Arseniyadas

Arseniyadas[62] has used the derivative **224** of the known lower analogue of the Wieland–Miescher ketone as a precursor in his synthesis of an A-ring equivalent (**Scheme 34**). The homochiral compound **224** was modified, as depicted, in a highly efficient, stereoselective process. The *cis* ring junction in **225** was introduced by catalytic hydrogenation, and only a small percentage of the undesired *trans* isomer was detected. Another interesting point to note in this sequence is the conversion of the silyl enol ether **226** into both the acyloin **227** and the required ester-aldehyde **228** products. The by-product **227** was produced in significant amounts (23%), but could easily be converted into the desired product **228** by periodate cleavage and esterification, so conveniently increasing the yield of the required compound. Conversion of the aldehyde-ketone **229** into bicyclic ketone **230** by a samarium diiodide-mediated reductive coupling followed by oxidation occurred stereospecifically as a consequence of the *cis* ring junction in the hydrindanone **225**, and this importantly fixed the absolute configuration of the C-1 centre. The authors aim to couple this A-ring fragment, **230**, to a C-ring equivalent using enolate chemistry, and then complete the B-ring to form a complete taxane skeleton (**Scheme 35**).



Scheme 35

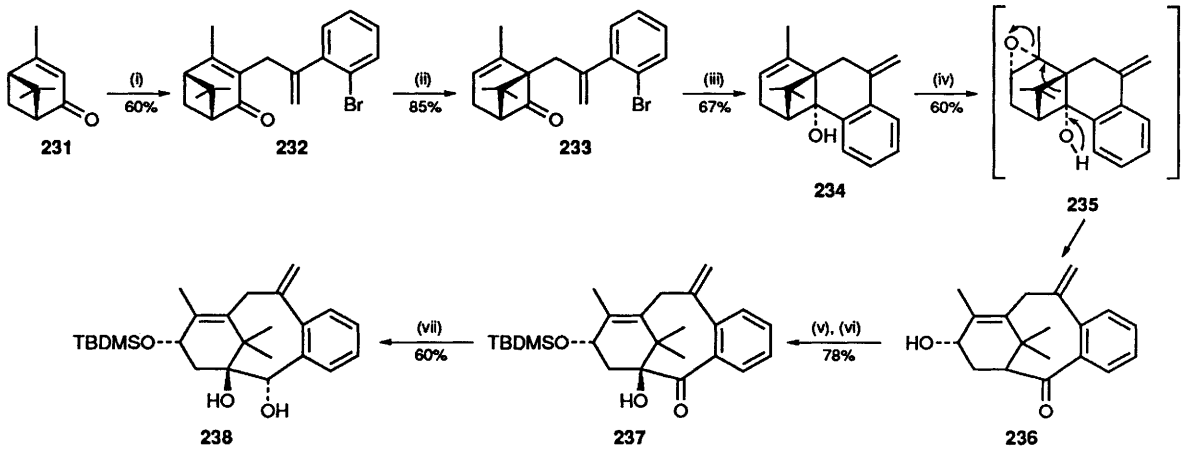
Wender

A very efficient synthesis of a C-aromatic taxane structure has been published by Wender.[63] The key steps of (i) rearrangement to give a quaternary centre in the A-ring precursor and (ii) an hydroxy epoxide fragmentation to produce the B-ring, are related to the Holton synthesis. The starting material for the Wender route (**Scheme 36**) is pinene which is available in both enantiomeric forms and contains ten of the twenty carbon atoms of the taxol skeleton. Pinene was first subjected to air oxidation to give verbenone **231**; deprotonation followed by alkylation next produced the enone **232**. Irradiation of **232** achieved the crucial rearrangement to the ketone **233**. The stereochemistry of the cyclization of ketone **233** is determined by its bicyclic structure, and leads to a single alcohol **234**. Epoxidation of **234** at C-1 led to a single epoxide **235**, which fragmented to the taxoid **236**. Oxidation of **236** α to the carbonyl group occurred under basic conditions and reduction of the resulting hydroxyketone **237** led to the C-aromatic taxoid **238** in enantiomerically pure form. The efficiency of this route shows great potential for further elaboration to taxol and related compounds. Clearly the key question is whether the C-aromatic ring can be fashioned into the functionalized C-ring of taxol.

Nicolaou

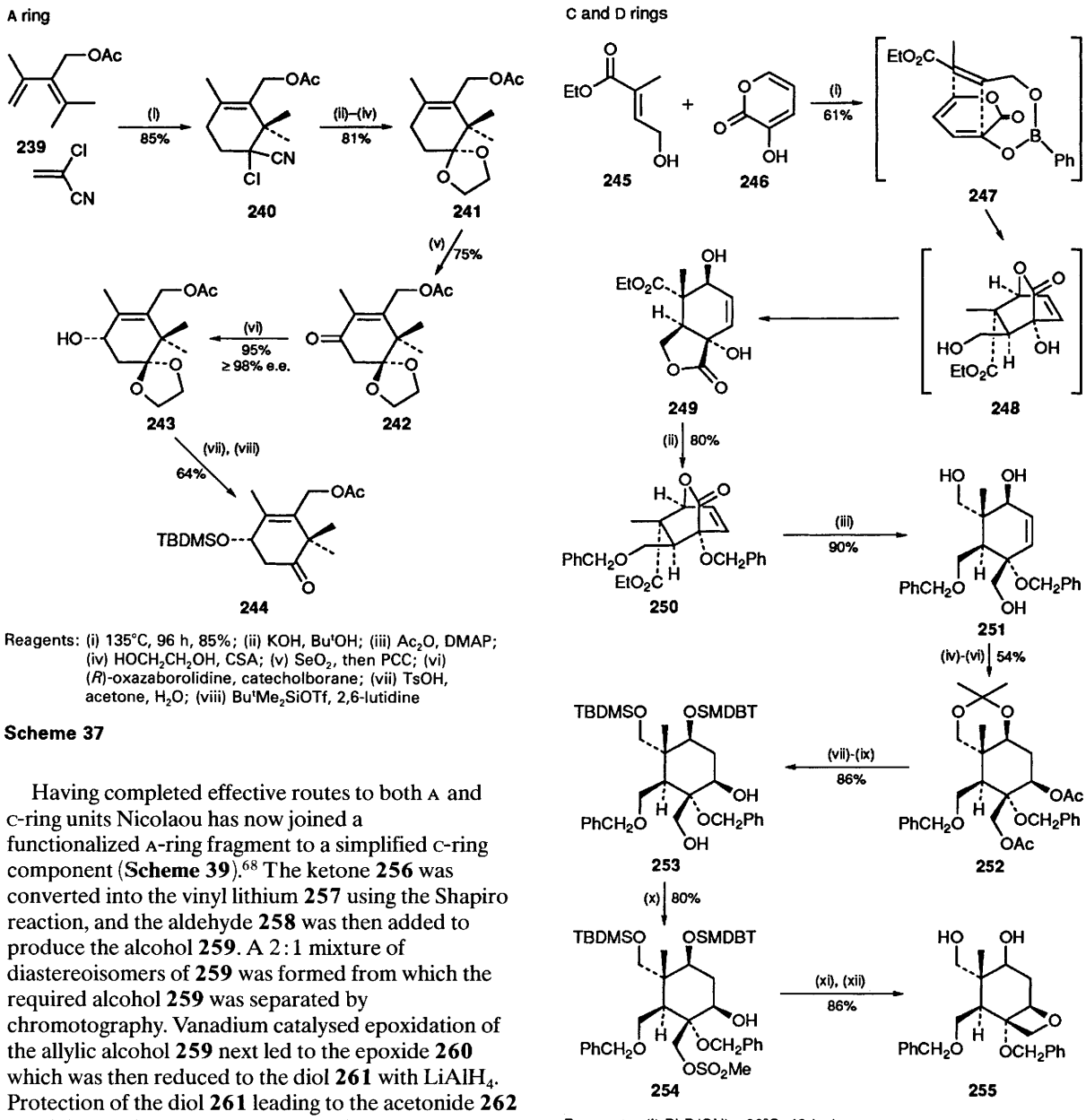
Nicolaou has reported an enantioselective synthesis of the fully functionalized A-ring of taxol,[64] together with the synthesis of the C- and D-rings in racemic form.[65] The diene **239** (**Scheme 37**) was first prepared from the appropriate ester,[66] and then subjected to thermal Diels–Alder reaction with 2-chloroacrylonitrile. The adduct **240** was next treated with base to introduce the carbonyl group which was then converted into the ketal **241** after reacetylation of the alcohol. Regioselective allylic oxidation of **241** with SeO_2 was followed by pyridinium chlorochromate (PCC) oxidation to produce the enone **242**, which with the oxazaborolidine procedure developed by Corey[67] gave the corresponding allylic alcohol **243** in greater than 98% e.e. Removal of the ketal group in **243** and protection of the alcohol function then gave the fully functionalized taxol A-ring **244** in essentially optically pure form.

Nicolaou's synthesis of the taxane C,D-rings is yet again based on the Diels–Alder reaction (**Scheme 38**). The dienophile is the unsaturated ester-alcohol **245**, the diene is 3-hydroxy-2-pyrone **246**, and the reaction is made intramolecular using phenylboronic acid. The presumed intermediate **247**, where the two components are temporarily tethered together, undergoes regioselective cyclization to give **248** as an initial product which rearranges under the reaction conditions to the lactone **249**. Rearrangement back to a bicyclo[2.2.2] lactone **250** occurred under the influence of potassium hydride during the benzylation of **249**. Both the ester and the lactone groups in **250** were reduced with Red-Al to give the triol **251**. Acetal formation, hydroboration, and acetylation of both the primary and the secondary alcohols in **251** next produced the triply protected diacetate **252**. Reorganization of these protecting groups by acetal removal, silylation, and acetate hydrolysis then gave the diol **253** which was converted into the mesylate **254**. The crucial oxetane ring forming reaction proceeded well, and a final desilyation yielded the fully functionalized, racemic taxol C,D-ring fragment **255**.



Reagents: (i) Bu^{t}OK; (ii) *hν*; (iii) Bu^{t}Li, TMEDA; (iv) (a) Ti(OPr^i)$_4$, Bu^{t}OOH; (b) DABCO, heat; (v) Bu^{t}Me$_2$SiCl, imidazole; (vi) KOBu^t, O_2, 60°C; (vii) Na, EtOH

Scheme 36



Reagents: (i) 135°C, 96 h, 85%; (ii) KOH, Bu^{t}OH; (iii) Ac_2O, DMAP; (iv) $HOCH_2CH_2OH$, CSA; (v) SeO_2, then PCC; (vi) (*R*)-oxazaborolidine, catecholborane; (vii) TsOH, acetone, H_2O; (viii) Bu^{t}Me$_2$SiOTf, 2,6-lutidine

Scheme 37

Reagents: (i) $PhB(OH)_2$, 90°C, 48 h then 2,2-dimethylpropane-1,3-diol; (ii) KH, $PhCH_2Br$; (iii) Red-Al; (iv) 2,2-dimethoxypropane, CSA; (v) BH_3.THF then H_2O_2, NaOH; (vi) Ac_2O, DMAP; (vii) CSA, MeOH; (viii) Bu^{t}Me$_2$SiOTf, 2,6-lutidine; (ix) NaOMe, MeOH; (x) $MeSO_2Cl$, DMAP; (xi) NaH, 45°, 12 h; (xii) Bu_4NF

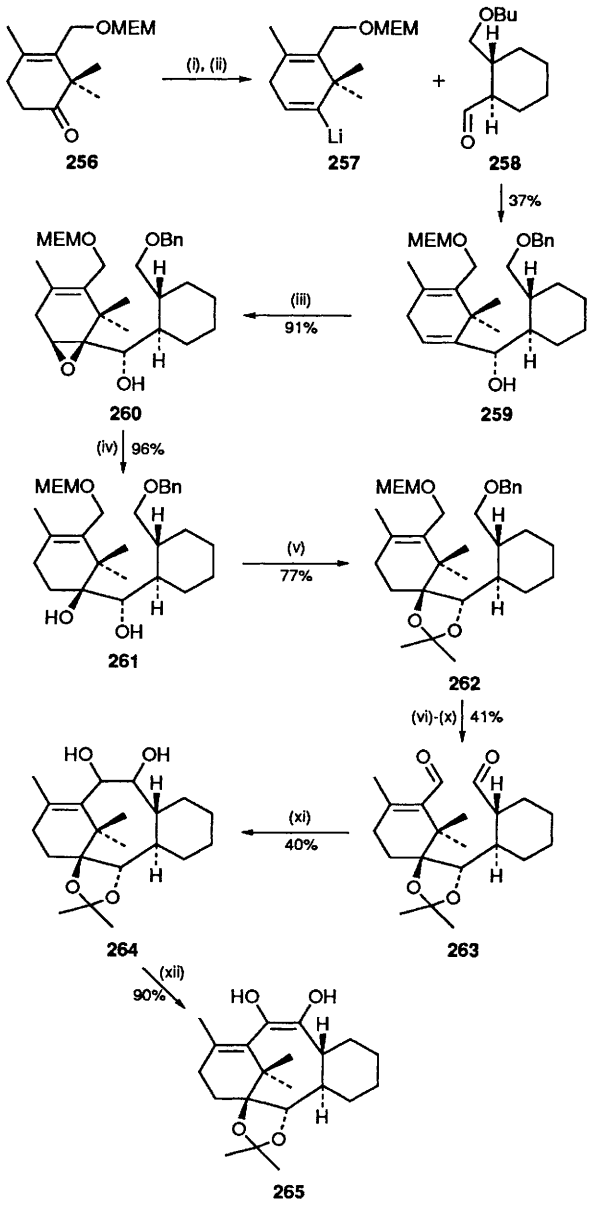
Scheme 38

Having completed effective routes to both A and C-ring units Nicolaou has now joined a functionalized A-ring fragment to a simplified C-ring component (**Scheme 39**).[68] The ketone **256** was converted into the vinyl lithium **257** using the Shapiro reaction, and the aldehyde **258** was then added to produce the alcohol **259**. A 2:1 mixture of diastereoisomers of **259** was formed from which the required alcohol **259** was separated by chromotography. Vanadium catalysed epoxidation of the allylic alcohol **259** next led to the epoxide **260** which was then reduced to the diol **261** with $LiAlH_4$. Protection of the diol **261** leading to the acetonide **262** was followed by a sequence of selective deprotections and oxidations to form the di-aldehyde **263**. McMurry coupling of **263** gave the diol **264** as a 1:1 mixture of diastereoisomers which was then oxidized to the enediol **265** with MnO_2.

2.4 Syntheses starting from the Wieland–Miescher ketone

Danishefsky

The Wieland–Miescher ketone **266** is an important commercially available, enantiomerically pure, starting material. The C and D-rings in the taxanes have been prepared from the Wieland–Miescher ketone as shown in **Scheme 40**.[69] The alcohol **267** was prepared by the method of Heathcock,[70] and protection followed by stereoselective hydroboration and oxidation produced the ketone **268**. Conversion of **268** to the corresponding enol triflate was followed by a palladium-catalysed carbonylation reaction in the presence of methanol to give the ester **269**. Reduction of **269** to the allylic alcohol, then hydroxylation to the olefin led to the triol **270** as the major product. Formation of the D-ring from **270** was achieved by the selective silylation of the primary alcohol group and then conversion into the secondary triflate. Heating the triflate with ethylene glycol caused desilylation and cyclization to the oxetane which was then hydrolysed to the ketone **271**. Deprotonation of **271** with LDA followed by reaction with trimethylsilyl chloride gave the corresponding trimethylsilyl enol ether, which was treated with $Pd(OAc)_2$ according to the method of Ito[71] giving rise to the enone **272**. Formation of a



Reagents: (i) 2,4,6-triisopropylbenzenesulfonyl hydrazine; (ii) BuLi, THF, −78°C then 0°C; (iii) Bu^{t}OOH, $VO(acac)_2$; (iv) $LiAlH_4$; (v) 2,2-dimethoxypropane, camphor sulfonic acid; (vi) H_2, Pd/C; (vii) Ac_2O, 4-DMAP; (viii) $TiCl_4$; (ix) K_2CO_3, MeOH; (x) tetrapropylammonium perruthenate, 4-methylmorpholine-*N*-oxide; (xi) $TiCl_3$-$(DME)_{1.5}$, Zn-Cu; (xii) MnO_2

Scheme 39

trimethylsilyloxy diene from **272** followed by ozonolysis finally gave the dialdehyde **273**; alternatively the enone **272** was hydroxylated to give the hydroxyketone **274**.

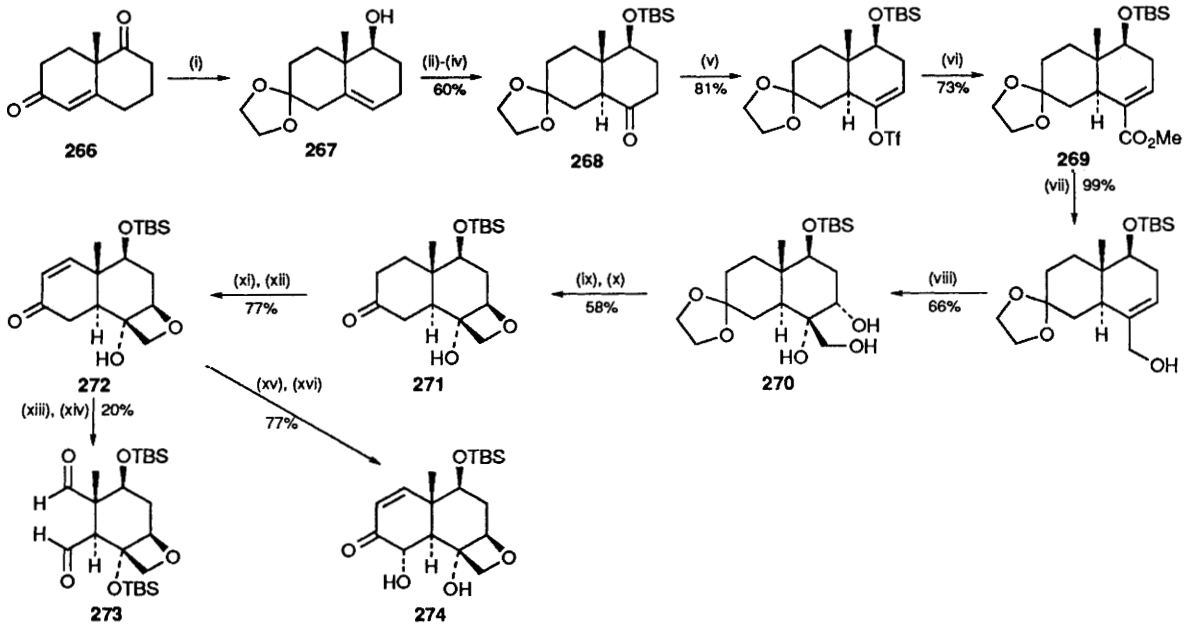
In a separate publication the Sloan–Kettering group have reported the synthesis of other taxane intermediates containing the A-ring.[72] Thus, reaction between 2-methylpentane-3-one **275** and acryloyl chloride was carried out by a known procedure to first give the ketone **276**.[73] Conversion of **276** into the enol triflate **277** and reaction with vinyltributylstannane, with Pd^0 catalysis, followed by the hydroboration next produced the alcohol **278**. Silylation of the alcohol **278**, and regioselective allylic oxidation with chromium trioxide-3,5-dimethylpyrazole then gave the A-ring synthon **279**. The enone **280** was prepared by Swern oxidation of the alcohol **278** followed by addition of 2-propenylmagnesium bromide and a second Swern oxidation. Regioselective Diels–Alder reaction of the enone **280** with the Danishefsky diene next yielded the taxol A,C-ring synthon **281**. Finally, the enolate from **280** was hydroxylated with the Davis oxaziridine,[74] and the product was oxidized to the diketone **282** which led to the A,C-ring synthon **283**. Clearly the Sloan–Kettering group are now poised to combine the work described in **Schemes 40** and **41**.

Watt

The Wieland–Miescher ketone **266** has also been used in an A-ring synthesis (**Scheme 42**).[75] Protection of the α,β-unsaturated carbonyl group in **266** with 1,2-ethanedithiol gave a thioacetal and, despite the fact that the saturated carbonyl group is hindered, addition of t-butyldimethylsilyl cyanide proceeded stereoselectively to produce the protected cyanohydrin **284**. Selective removal of the thioacetal group in **284** occurred with $Tl(NO_3)_2$ leading to the enone **285**. The α-acetoxy ketone corresponding to **286** was prepared by the reaction of **285** with $Pb(OAc)_4$ and this reacted with methanol and potassium carbonate to give the α-hydroxy ketone **286**. Periodate cleavage of **286**, followed by treatment with diazomethane then yielded the ester aldehyde **287**. Finally, decarbonylation with Wilkinson's catalyst provided the A-ring synthon **288**.

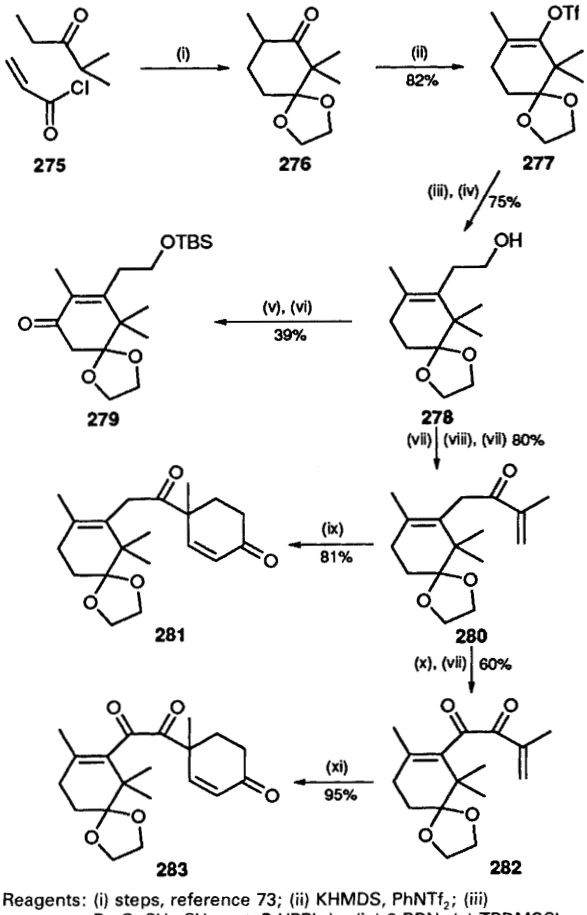
3 Semi-syntheses of taxanes

This approach to taxanes has, to date, been the most successful way of making taxol and biologically active analogues. Potential starting materials for semi-synthesis must be easy to obtain, renewable, and require as little elaboration as possible.[76] 10-Deacetylbaccatin III **289**, first described as a degradation product of taxol,[1] and isolated from needles of the widely distributed *Taxus baccata* (*ca.* 1 g/kg dry leaves)[77] nicely meets these criteria. Synthetic routes to taxanes utilizing **289** have been developed to exploit the differing reactivity of the free hydroxyl groups; 7-OH > 10-OH ≫ 13-OH (the low nucleophilicity of the 13-OH, is due to H-bonding to the C-4 acetyl C = O group and is also on the *endo*-convex face). Sharpless oxyamination[78] of **290**—obtained by sequential protection of **289** and formation of the C-13 cinnamate—gave a mixture of regio- and stereo-isomers with little control (**Scheme 43**). The reaction was later improved[79] by the addition of dihydroquinine *p*-chlorobenzoate and although regiocontrol was again poor the required (2′*R*,3′*S*) stereoisomer **291** was now the major product (d.e. ~ 60%). This isomer was converted into taxol by removal of the t-butyl amido group, followed by benzoylation and removal of the trichloroethoxycarbonyl group. Although the poor control in the oxyamination reaction renders the



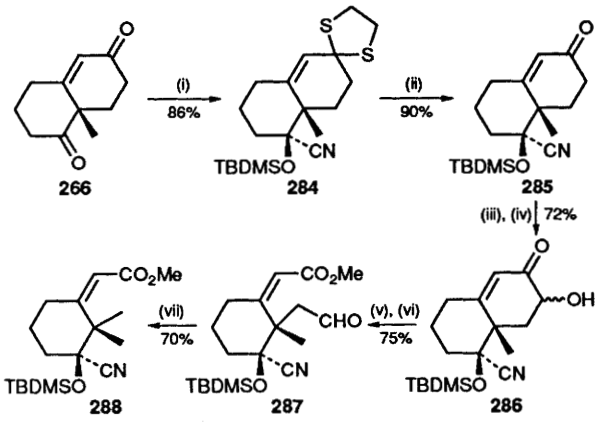
Reagents: (i) steps reference 70; (ii) TBSOTf, 2,6-lutidine; (iii) BH_3–THF then H_2O_2, NaOH; (iv) tetrapropylammonium perruthenate; (v) KHMDS, THF, −78°C then $PhNTf_2$; (vi) $Pd(OAc)_2$, PPh_3, CO, MeOH; (vii) DIBAL, −78°C; (viii) 5 mol% OsO_4, NMMO; (ix) TMSCl, pyridine, −78°C then Tf_2O −78°C→r.t. followed by ethyleneglycol, 40°C, 12 h; (x) collidinium tosylate, acetone, H_2O; (xi) 2 equiv. LDA, −78°C then TMSCl; (xii) $Pd(OAc)_2$ then MeOH, K_2CO_3; (xiii) TBSCl, imidazole; (xiv) LDA, THF, −78°C then TMSCl then O_3, CH_2Cl_2, −78°C then Ph_3P; (xv) TMSCl, pyridine; (xvi) KHMDS, THF, −78°C then 2-(phenylsulfonyl)-3-phenyloxaziridine then H_2O

Scheme 40



Reagents: (i) steps, reference 73; (ii) KHMDS, $PhNTf_2$; (iii) $Bu_3SnCH{=}CH_2$, cat. $Pd(PPh_3)_4$; (iv) 9-BBN; (v) TBDMSCl, Et_3N, DMAP; (vi) CrO_3-3,5-DMP; (vii) Swern oxidation; (viii) $BrMgC(Me){=}CH_2$; (ix) Danishefsky diene, 125°C, then HCl, H_2O; (x) KHMDS, F. Davis oxaziridine; (xi) Danishefsky diene, 80°C, then HCl, H_2O

Scheme 41

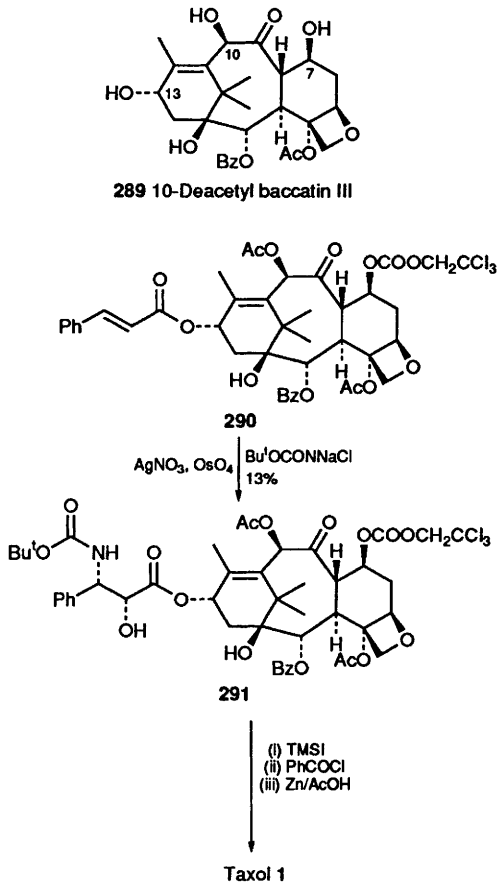


Reagents: (i) $HSCH_2CH_2SH$, *p*-TsOH then TBSCN, ZnI_2; (ii) $Tl(NO_3)_2$, MeOH, H_2O; (iii) $Pb(OAc)_4$; (iv) K_2CO_3, MeOH; (v) $NaIO_4$, H_2O, Bu^tOH; (vi) CH_2N_2; (vii) $RhCl(PPh_3)_3$, 80°C

Scheme 42

approach impractical it has nevertheless given access to many analogues[80] including RP 56976 and taxotère,[81] which has similar pharmacological activity to taxol.

A more direct approach to taxol was first described by the research groups of Potier and Greene,[82] involving the esterification of 7-triethylsilylbaccatin III **292** with the taxol side-chain acid, **Scheme 44**. The use of a large excess of the protected acid **293** (6 eq.), 1,3-dicyclohexylcarbodiimide (DCC), and *N,N*-dimethyl-4-aminopyridine (DMAP) to effect the esterification was followed by deprotection of the silyl and ethylethoxy protecting groups to give taxol (36% from 10-DAB III). Other acyl-activated side chain equivalents have been used in attempts to overcome the problems associated with the low reactivity of the



Scheme 43

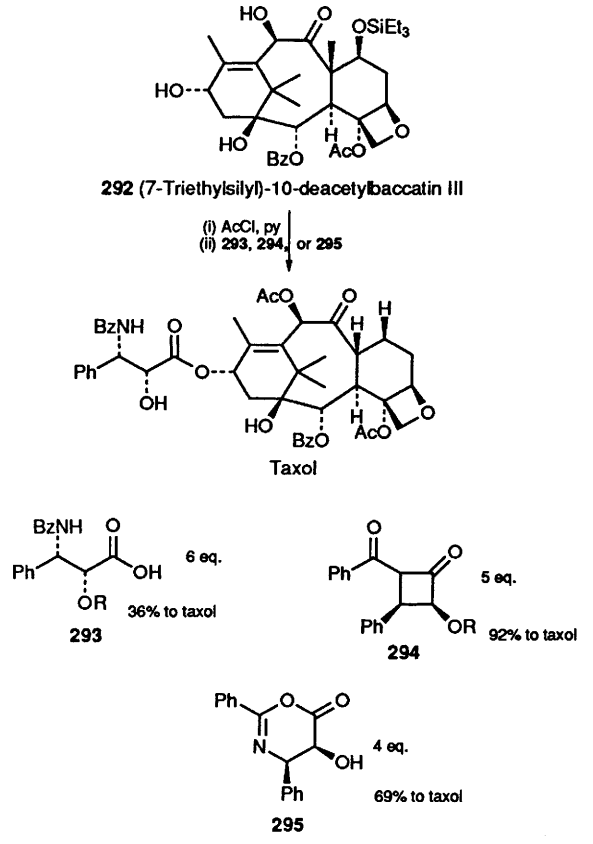
C-13 OH (epimerization of the 2′ centre, and generally low yields)—Ojima[83] and Holton[84] have independently used the β-lactam derivatives **294** to directly couple with 7-TES-10-DAB III **292**. Ojima[85] has further reported a significant improvement to the β-lactam method that avoids large excesses of the β-lactam. A near quantitative coupling can be achieved by sequential treatment of the 7,10-ditroc-10-deacetylbaccatin III (troc = 2,2,2-trichloroethoxylcarbonyl) with sodium hexamethyldisilazide (2.5 equiv.) and the lactam **294**, providing an efficient route to taxotère. Holton[86] has developed another method that utilizes the oxazinone **295** as the acyl equivalent. It is interesting to note that Swindell has also invoked intermediate oxazinone derivatives as coupling agents.[87]

4 Syntheses of the C-13 side chain of taxol

The C-13 side chain in taxol, the (2′*R*,3′*S*)-3′-phenylisoserine unit, presents an interesting and manageable sub-target for asymmetric syntheses, and has consequently seen many elegant approaches. In addition, since the binding of taxol to microtubules[87] is particularly sensitive to changes in the structure of the side-chain, many active analogues of taxol have been made by semi-synthesis.

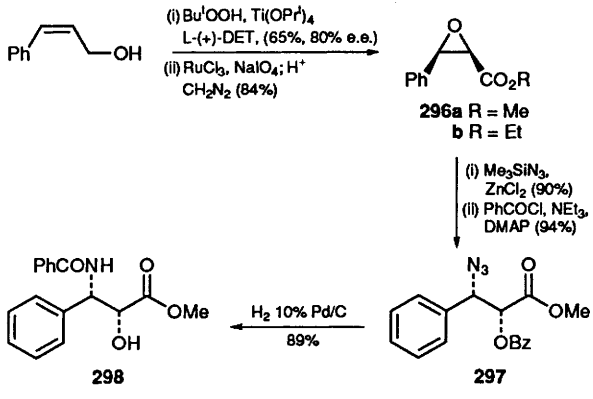
4.1 Phenylglycidate synthon method

In their first synthesis Greene[88] (**Scheme 45**) and his group started with methyl phenylglycidate **296a** which



Scheme 44

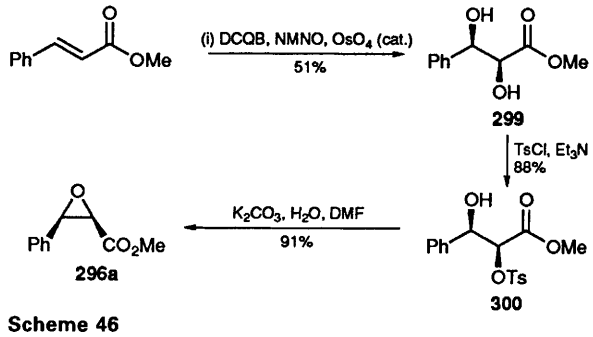
was made by way of Sharpless epoxidation of *cis*-cinnamyl alcohol, followed by oxidation and esterification. The amine group was next introduced stepwise following ring-opening of the epoxide with trimethylsilyl azide (to give a hydroxy azide which was esterified to give the benzoate **297**), and reduction of the azide. The azide reduction was accompanied by O → N migration of the benzoyl group, a procedure followed subsequently by other workers, to give the desired product **298**.



Scheme 45

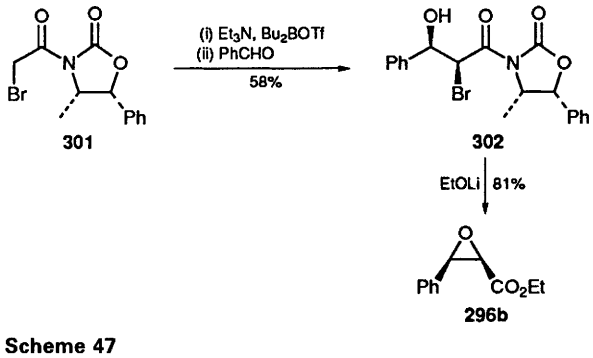
Greene's second and improved[89] synthesis (**Scheme 46**) is essentially a refinement of the synthesis of **296a**. Asymmetric Sharpless dihydroxylation of methyl cinnamate, using dihydroquinidine 4-chlorobenzoate first gave the diol **299**; a new Sharpless procedure[90] gives **299** (ethyl ester) with even higher selectivity (97% e.e.). The diol **299** was next tosylated selectively

to give the 2-tosylate **300** where the high selectivity is thought to be a consequence of strong C-3-OH to ester hydrogen bonding. The epoxide **296a** was then obtained from **300** by treatment with potassium carbonate and elaborated to **293** and the taxotère methyl ester side-chain as described before.



Scheme 46

Commerçon *et al.* have also made the ethyl ester **296b** using Evans chiral-enolate chemistry (**Scheme 47**).[91] Reaction of the boron enolate of the bromoacetyl **301** with benzaldehyde first gave the bromoalcohol **302**, and formation of the epoxide and concomitant removal of the auxiliary then gave the ester **296b**.



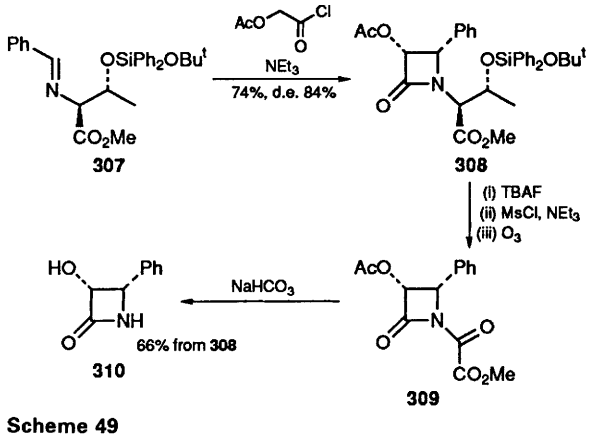
Scheme 47

Jacobsen[92] has reported a similar approach to **306** starting from the epoxide derived from ethyl *cis*-cinnamate (**Scheme 48**). The catalytic epoxidation of ethyl *cis*-cinnamate with 6 mol% (salen)Mn^{III} complex[93] **303** and commercial bleach gave rise to the epoxide **296b** in excellent (95–97%) e.e. A modified procedure whereby the epoxide **296b** was treated with ethanolic ammonia to give the amide **304** followed by hydrolysis with barium hydroxide then gave the acid **305** without epimerization. Generation of the side-chain **306** from **305** was effected by simple treatment with benzoyl chloride.

4.2 The Staudinger synthesis of β-lactams

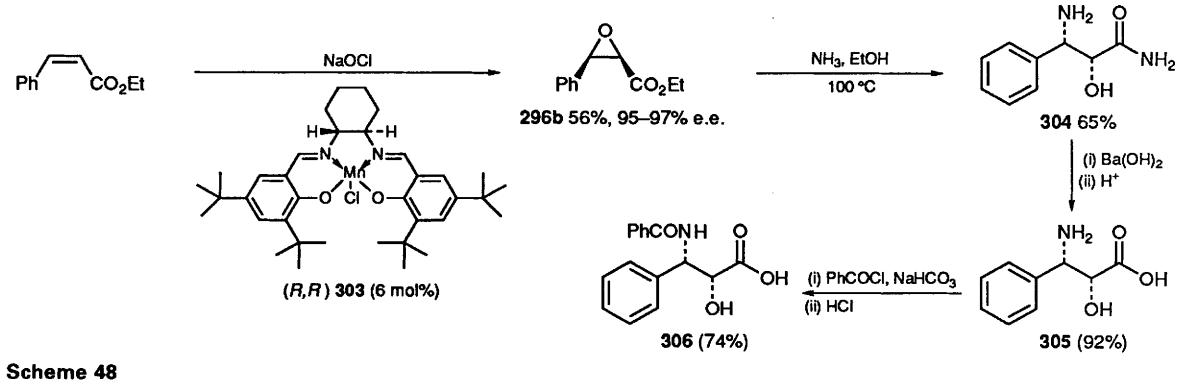
A chiral-pool approach to the C-13 side-chain in taxol is described by Farina and shown in **Scheme 49**.[94] Thus, a highly selective Staudinger reaction between the L-threonine derived imine **307** and acetoxyacetyl chloride first led to the *cis* β-lactam **308** (74%, 84% d.e.). This β-lactam was subsequently converted into the β-lactam **309**, by removal of the silyl group, elimination of water, and ozonolysis to give the corresponding mixed oxalic acid derivative, which was simply hydrolysed to the required β-lactam **310**.

Georg *et al.*[95] have also described a chiral-pool Staudinger reaction (**Scheme 50**) in which the galactose imine **311** and the acid chloride **312** gave a 2:3 mixture of the diastereoisomeric β-lactams **313**. Hydrolysis of both the monosaccharide and the β-lactam groups in **313**, followed by benzoylation then led to the amide **314**. Removal of the hydroxyl protecting group in **314** gave the unnatural (2′*S*,3′*R*) enantiomer **315**. A more detailed study has shown that this poor selectivity is observed with other galactose imines.[96]

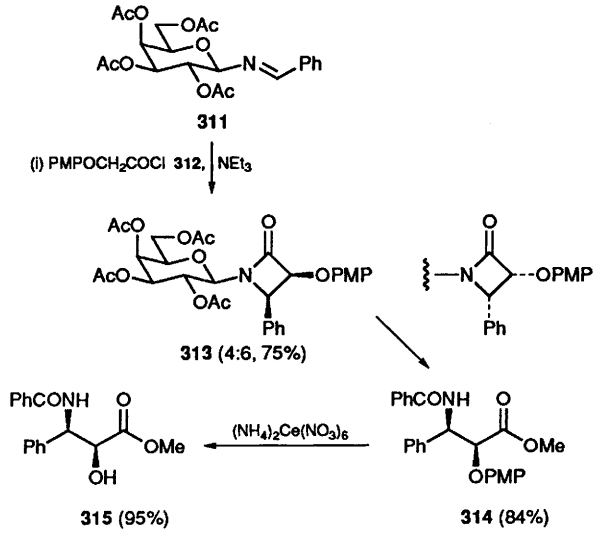


Scheme 49

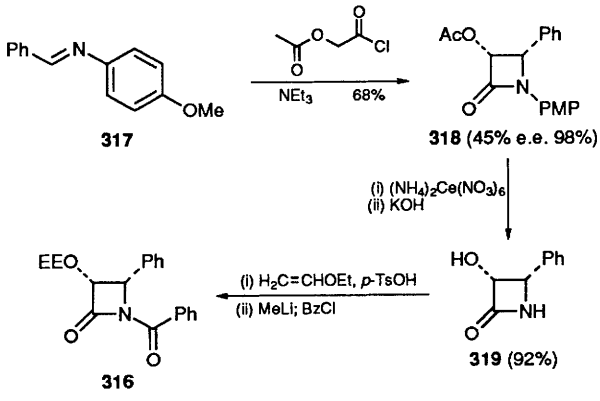
Holton[97] has used the β-lactam **316** to make taxol from 7-triethylsilyl-10-deacetylbaccatin III as described earlier (**Scheme 51**). He made the lactam using the Staudinger reaction between α-acyloxy acetyl chloride and the imine **317** as the key step to



Scheme 48



Scheme 50



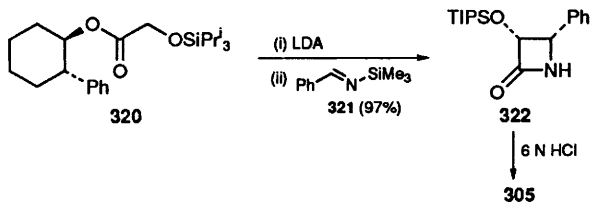
Scheme 51

give the β-lactam **318**, which was converted into **316** using standard transformations. The alcohol **319** was obtained enantiomerically pure by resolution of its 2-methoxy-2-(trifluoromethyl)phenylacetic ester.

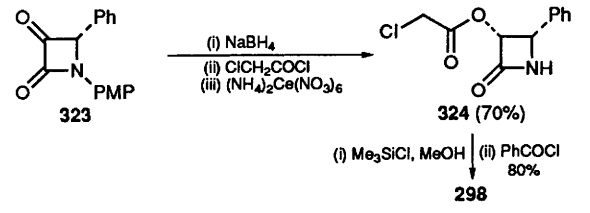
Ojima's[98] strategy, shown in **Scheme 52** is also based on the use of β-lactams, made by a highly selective ester enolate-imine condensation. Thus, deprotonation of the triisopropylsilyl protected ester **320** with lithium diisopropylamide followed by condensation with the imine **321** gave exclusively the *cis* β-lactam **322** (97%). The lactam **322** was then converted into the hydrochloric salt of **305** by treatment with HCl. Palomo[99] has made the related β-lactam derivative **324** by *cis*-selective reduction of **323** (**Scheme 53**).[100] Protection of the hydroxyl group in **323** and *N*-dearylation led to the β-lactam **324** which by standard treatment gave the ester **298**.

4.3 Lithiobenzylamine synthon method

Two approaches that introduce the 3′ carbon in the C-13 side chain of taxanes, from benzylamine have been developed. Thus, Greene *et al.*[101] amongst their many reports have described an alternative synthesis of the side chain of taxotère (**Scheme 54**). In this approach dilithiation of BOC-benzylamine with s-butyllithium first gives the dianion **325** which adds to

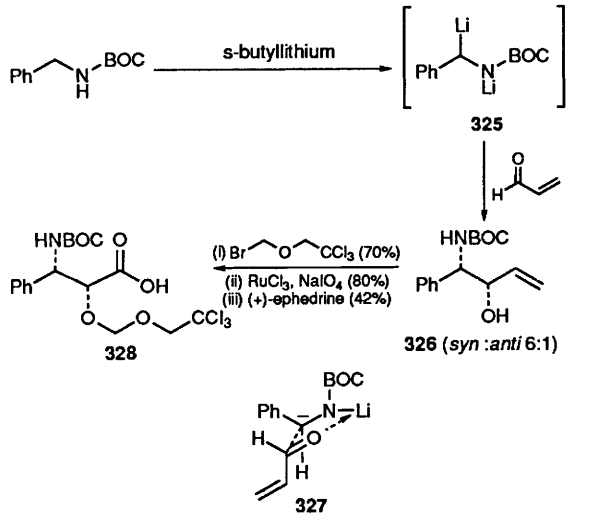


Scheme 52



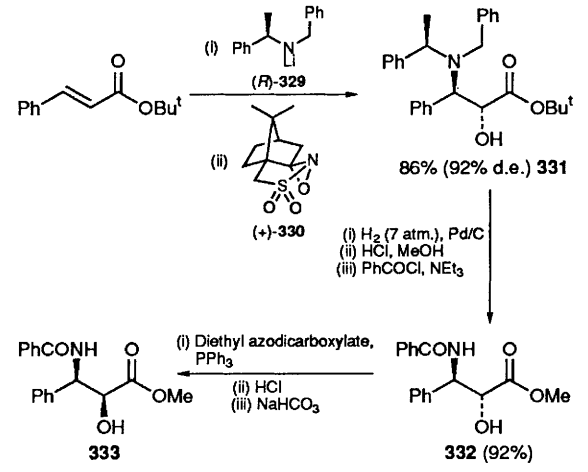
Scheme 53

acrolein to produce the hydroxycarbamate **326** with reasonable selectivity (*syn*:*anti* 6:1). The *syn* preference observed here is consistent with a chelated transition state of the type **327**. Protection of the 2′ OH in the *syn* alcohol **326** as its (trichloroethoxy)methyl ether, followed by oxidative cleavage and resolution using (+)-ephedrine finally gave the protected taxotère side-chain **328**.

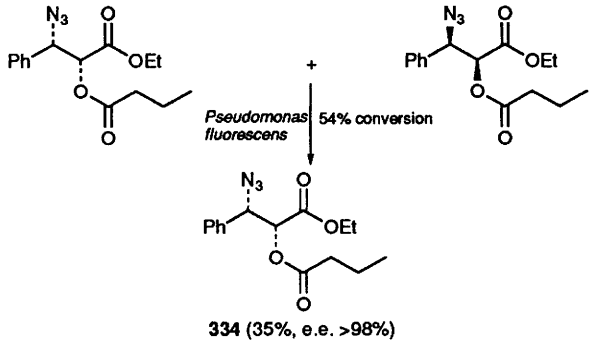


Scheme 54

Davies *et al.*[102] have reported a strategy towards **333** involving conjugate addition of the homochiral lithio (*R*)-(α-methylbenzyl)benzylamide **329** to t-butyl cinnamate followed by hydroxylation of the intermediate enolate with (+)-(camphorsulfonyl)oxaziridine **330** leading to the *anti* hydroxy amine **331** with excellent selectivity (92% d.e.). When **331** was subjected to hydrogenolysis followed by methanolysis and benzoylation the *anti* hydroxy amide **332** was produced which could be converted into the corresponding *syn* (2′*S*,3′*R*) isomer **333** (the enantiomer of **298**) *via* Mitsunobu inversion (**Scheme 55**). Since (*S*)-(α-methylbenzyl)benzylamide is readily available, this method will also produce the taxol side chain with the natural (2′*R*,3′*S*) configuration.



Scheme 55

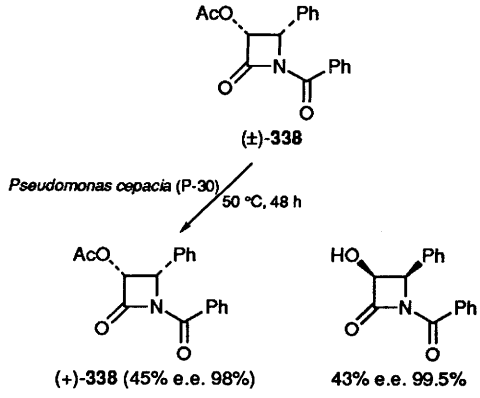


4.4 Enzymic syntheses

The first example of an enzyme-assisted taxol side-chain synthesis came from the group of Hönig,[103] in which the racemic butyryl ester (±)-**334**, obtained from (±)-ethyl *cis*-β-phenylglycidate, was resolved by selective hydrolysis of the (2′*S*,3′*R*) isomer with *Pseudomonas fluorescens*, leaving the required (2′*R*,3′*S*) ester **334** unreacted (e.e. > 98%).

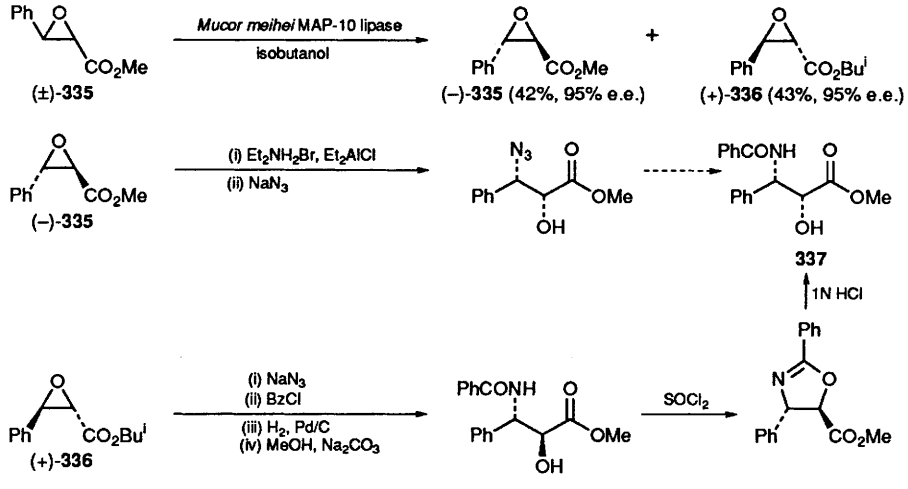
An enzymatic resolution involving lipase-mediated transesterification of methyl *trans*-β-phenylglycidate (±)-**335** has been described by Chen.[104] The best result was obtained with *Mucor miehei* lipase MAP-10 using isobutanol as the acyl acceptor. The (−)-methyl ester **335** (42%,95% e.e.) and the (+)-isobutyl ether **336** (43%, 95% e.e.) could be separated by chromatography or fractional distillation. Interestingly, both **335** and **336** can be converted into the azide **337** in 40% and 38% yields respectively. The route from **335**, illustrated in **Scheme 56**, involves epoxide ring-opening by bromide ion and subsequent displacement with sodium azide with overall retention of configuration at the 3′ position; the same sequence from (+)-**336** results in both the 3′ and 2′ positions being inverted leading to **337**.

Sih[105] has reported a comprehensive study of the lipase-mediated kinetic resolution of β-lactam derivatives. For example, the racemic β-lactam (±)-**338** gives (+)-**338** in high yield, with impressive stereoselection, on treatment with immobilized lipase P-30 (from *Pseudomonas cepacia*).



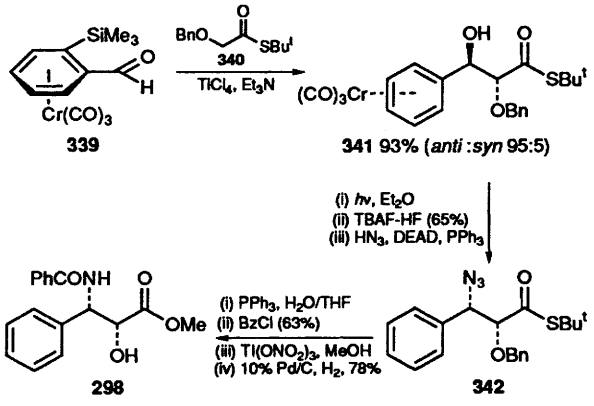
4.5 Aldol reaction approaches

Hanoaka *et al.*[106] have used an asymmetric aldol reaction between the homochiral chromium complex **339** of *o*-trimethylsilyl benzaldehyde and the titanium enolate of **340** (**Scheme 57**). The reaction is highly *anti* selective yielding only the alcohol **341**; interestingly reaction of the corresponding lithium enolate was *syn* selective (*syn*:*anti* 4:1). Sequential decomplexation of the chromium from **341**, followed by deprotection of the silyl group and Mitsunobu



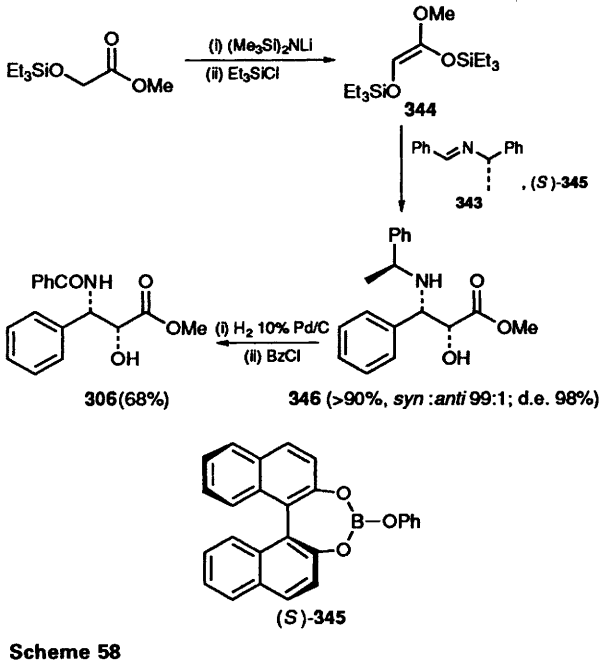
Scheme 56

displacement of the hydroxyl group then led to the azide **342**. Reduction of **342** with wet triphenylphosphine, followed by benzylation, thallium (III) assisted thioester-to-ester interconversion, and deprotection of the benzyl ether finally completed the synthesis of **298**.



Scheme 57

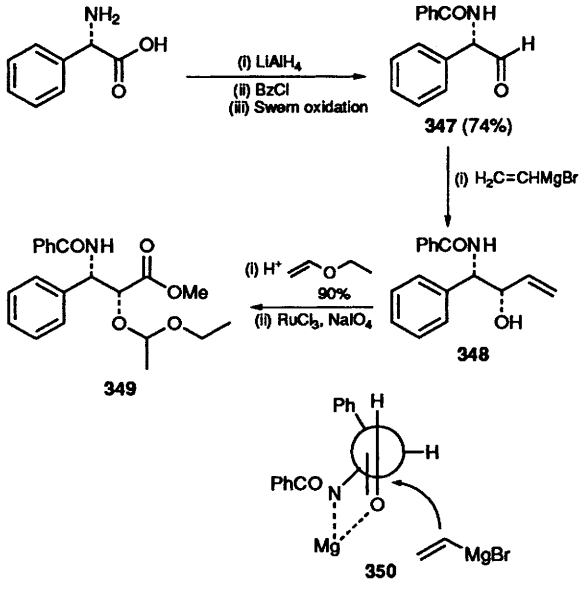
Yamamoto and his colleagues[107] have described an efficient enolate-imine condensation involving the imine **343** and the *Z*-enolate **344**, catalysed by the phenylborate (*S*)-**345**, leading to the (2′*R*,3′*S*) amino alcohol **346** (*syn*:*anti* 99:1; *syn* 98% d.e.). The observed selectivity is only slightly reduced if instead the enantiomer (*R*)-**345** is used (*syn*:*anti* 94:6; *syn* 94% d.e.). Removal of the α-methylbenzylamine group in **346**, followed by selective hydrogenolysis, and Schotten–Baumann benzoylation then produced **306** (**Scheme 58**).



Scheme 58

4.6 A chiral pool approach

Greene *et al.*[108] have reported a synthesis of **349** starting from (*S*)-phenylglycine (**Scheme 59**). Thus, the protected amino aldehyde intermediate **347** was added to vinylmagnesium bromide to give predominantly the *syn* allylic alcohol **348** where the selectivity is explained by chelation controlled addition to **350**. The alcohol **348** was then protected and the alkene group oxidized to give the required acid **349**.



Scheme 59

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