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Recent developments in the synthesis of taxane diterpenes

SUBRATA GHOSH* AND SUBRATA SARKAR
Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 700 032, India.

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Abstract

Recent developments in the synthesis of taxanes mainly during 1991–1993 are reviewed briefly.

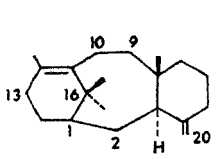
Key words: Taxanes, diterpene.

1. Introduction

Taxane diterpenes[1] are a group of compounds isolated from various yew species (genus Taxus) having the common carbon skeleton **1.** The naturally occurring taxanes differ in degrees of oxygenation as exemplified by taxusin **2**[2], baccatin-I **3**[3], 10-deacetyl baccatin-III **4**[4], taxol 5[5], etc. (Chart 1). Global interest in this family arose from the remarkable potential of a few taxanes, especially taxol, in exhibiting a broad spectrum of activity[6,7] against leukemias and solid tumors through its novel action by promoting the assembly of microtubules inhibiting the normal dynamic reorganisation of the microtubule network required for mitosis and cell proliferation.

The extraction of taxol from the stem bark of the slow-growing yew is tedious and the yield is low. A partial solution to the problem of taxol supply has been offered by Green and Potier[4] through transformation of the more abundant 10-deacetyl baccatin-III **4** isolated from yew leaves. Potier[8] has also transformed **4** to taxotere **6,** a taxol analogue more bioactive than taxol. However, for an uninterrupted supply of taxol, a total synthesis is essential. The carbon network of taxol having a highly strained 8-membered ring B bridged in ring A and tranfused to ring C with a hindering gem-dimethyl group, a bridgehead double bond and an oxetane ring poses considerable challenge to the organic chemists for its total synthesis. Attempts to achieve a total synthesis of taxol have led to the development of a large number of strategies. Although significant progress has been made by several groups, total synthesis of taxol has not been achieved so far.

* For correspondence.



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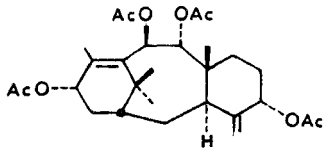

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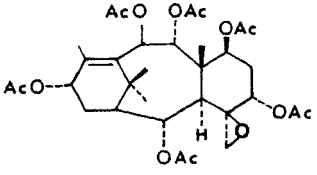

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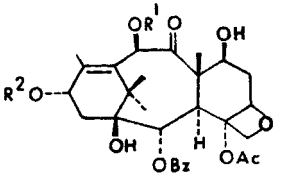
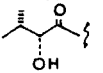


4, $R^1 = R^2 = H$

Taxol, 5, R^1 = Ac, R^2 = Ph



Taxotere, 6, $R^1 = H$, R^2 = Ph

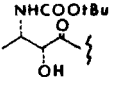


Chart 1.

Initial studies on the synthesis of taxanes were centred mainly on the construction of its tricyclic core. However, recent studies[9–21] aimed at elucidating the structure – activity relation have indicated the importance of the functional groups especially the ester side chain at C-13 and the oxygen functionalities at C-2, C-9 for the biological activity of taxol. Even a less-functionalised taxol analogue synthesised by Blechert[22] has been found to promote microtubule assembly. Hence, more recent studies involve the synthesis of the taxane tricycle with stereocontrolled introduction of the oxygen functionalities and construction of the oxetanol unit[23,24] in order to have access to biologically interesting simpler taxol analogues and finally to taxol. The synthetic strategies developed through early 1991 have been reviewed[25–27] recently. In this account, more recent developments, mainly dealing with the synthesis of tricyclic core, are presented.

2. Synthetic strategies

Various strategies reported so far for the construction of taxane nucleus can be classified based on the type of reaction used for the formation of the 8-membered ring (Chart 2). These include cycloaddition (routes 1–3), intramolecular cyclisation (routes 4–6), anionic oxy-Cope (routes 7–9), and C–C bond fragmentation (routes 10–17) reactions. Carbon atoms involved in bond formation or fragmentation are indicated with dots in Chart 2.

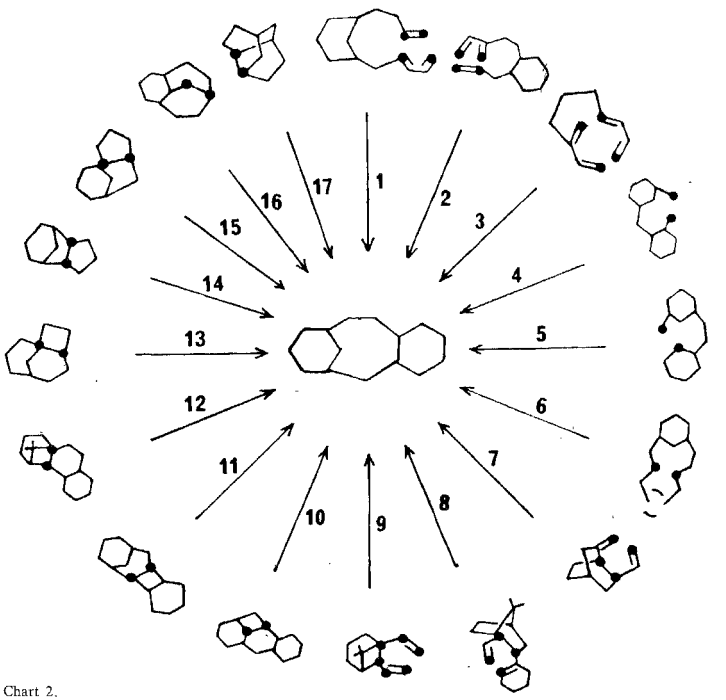
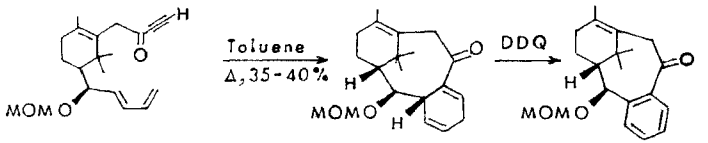


Chart 2.

2.1. *Cycloaddition route*

Intramolecular Diels–Alder cycloaddition constitutes an attractive route for the direct construction of the tricyclic taxane skeleton either through the formation of BC or AB

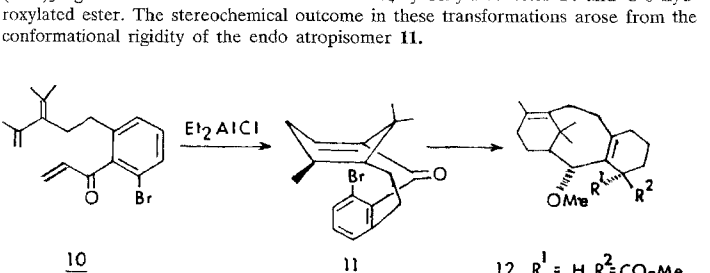
rings. The advantages of this route are easy incorporation of the bridgehead double bond and high stereoselectivity. In addition to Sakan's BC ring approach[28] to taxane nucleus, Fallis[29] has recently reported a thermal intramolecular [4+2] cycloaddition in the enone 7 (Scheme 1) where an acetylene has been used as a dienophile to facilitate cycloaddition. The tricyclic trienone **8** obtained stereoselectively was transformed on DDQ treatment to ring C aromatic taxane analogue **9** as a 1:1 mixture of two atropisomers.



7 8 9

SCHEME 1.

Shea[30] has extended his atropselective Diels–Alder route for introducing functionalities in C ring (Scheme 2). Lewis acid-catalysed intramolecular cycloaddition of the bromotrienone **10** gave rise to the endo tricycle **11.** The bromine atom in the aromatic ring has made possible further functionalisation of this ring to partially saturated C ring through a series of stereoselective reactions to afford **12.** An attempt to introduce the C-8 Me through methylation of the dienolate of **12** led to the C-4 methylation to afford **13,** while trapping of the dienolate with O_2 in the presence of $(EtO)_3P$ gave a diastereoisomeric mixture of C_4-hydroxylated ester **14** and C-8 hydroxylated ester. The stereochemical outcome in these transformations arose from the conformational rigidity of the endo atropisomer **11.**

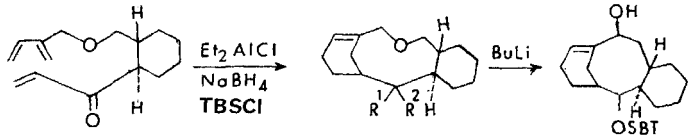


10 11

12, R^1 = H, R^2 = CO_2Me
13, R^1 = Me, R^2 = CO_2Me
14, R^1, R^2 = OH, CO_2Me

SCHEME 2.

Yadav's approach[31] (Scheme 3) to the taxane skeleton involves intramolecular Diels–Alder reaction of the trienone **15** to afford a 9-membered oxygen heterocycle **16.** Reduction of the ketone in **16** followed by silylation gave **17** which on Wittig rearrangement afforded the taxane analogue **18.**



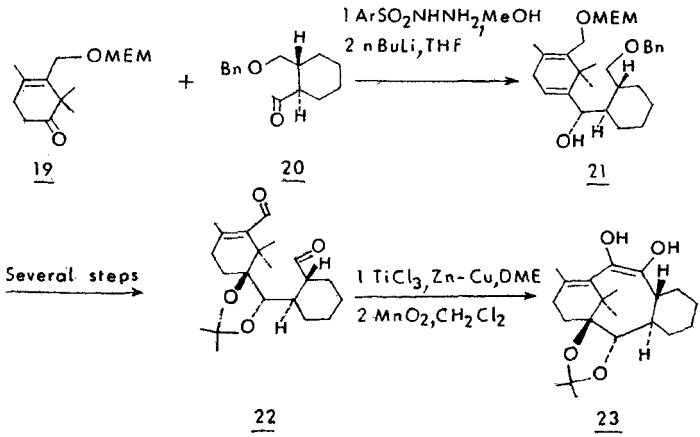
15 16, R^1, R^2 = O 18

17, R^1 = OSBT, R^2 = H

SCHEME 3

2.2. Intramolecular cyclisation route

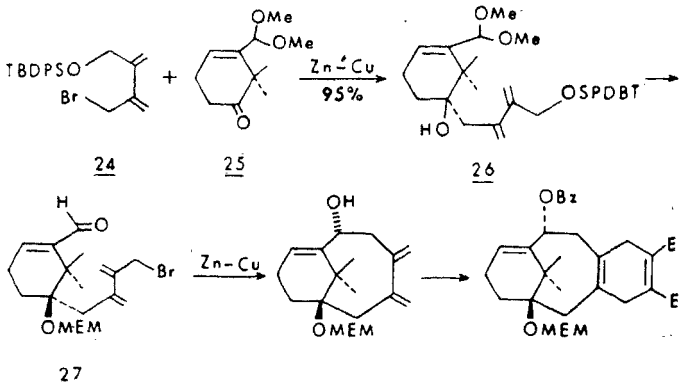
The formation of 8-membered rings by direct ring closure, in general, is not an entropically favourable process due to high degree of ring strain and transannular interactions present in these rings. However, the great advantage of direct ring closure in taxane synthesis lies in its convergency.



SCHEME 4.

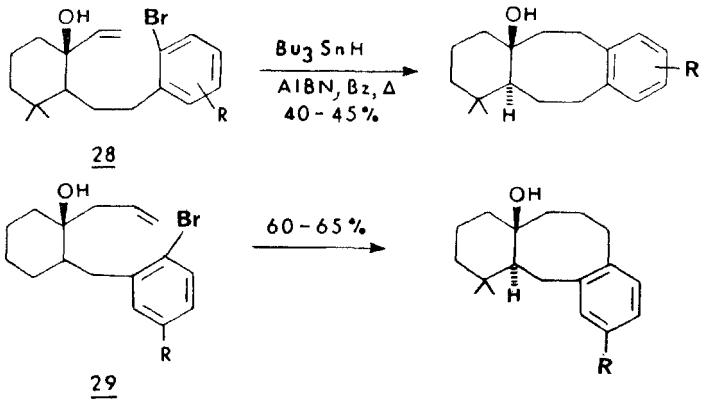
After successful demonstration of Kende[32] and Kuwajima[33] that taxane skeleton could be constructed with stereocontrol by direct ring closure, the most notable achievement came from the laboratory of Nicolaou[34]. In this approach (Scheme 4), coupling of the vinyl anion derived from the cyclohexanone derivative **19**, the ring A precursor, with the aldehyde **20** afforded **21** as the major diastereoisomer. Through a series of functional group manipulations **21** was transformed to the dialdehyde **22**. Intramolecular McMurry coupling of the dialdehyde **22** afforded the taxane analogue **23** having four oxygen functions out of eight oxygen functions present in taxol.

Wang[35] has been able to overcome the unfavoured entropy involved in the 8-membered ring closure through intramolecular coupling of a highly reactive allylzinc with an aldehyde. Addition of allylzinc derived from **24** to the enone **25** afforded the trienol **26** (Scheme 5). Functional group manipulation in **26** led to the allylbromide **27**. Intramolecular coupling in **27** with Zn–Cu couple afforded stereoselectively the AB analogue. Annulation of C ring was accomplished through a Diels–Alder reaction of the diene thus generated, with dimethyl acetylenedicarboxylate to afford the taxane tricyclic core.



SCHEME 5.

Synthesis of 8-membered rings throug radical cyclisation is not a favourable process. However, Ghatak[36a] has recently demonstrated that 8-membered rings can indeed be constructed efficiently through 8-endo-trig-aryl radical cyclisation if the bond-forming carbon atoms are held in a conformation favourable for cyclisation. Thus, tributyltin hydride reaction of the bromoenols **28** produced the cyclised products in 40–45% yield, while the bromoenols **29**, where the olefin and the radical centre are relatively proximal to each other, produced the cyclised products in much better yield (60–65%) (Scheme 6a). Although this investigation has not been aimed at the synthesis

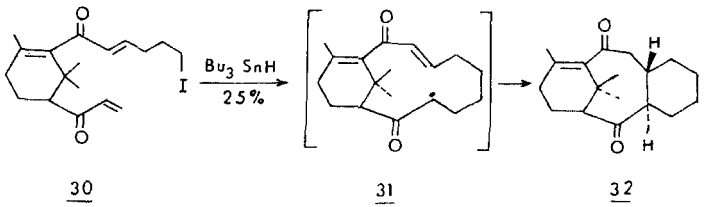


SCHEME 6a.

of taxanes, this radical cyclisation route appears quite attractive to find application in ring C aromatic taxane synthesis.

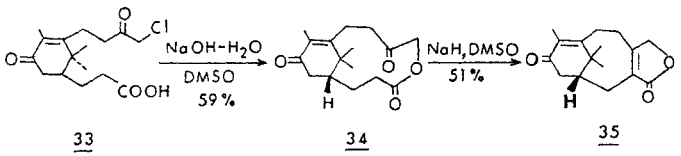
An alternative strategy for constructing taxane B ring involves macrocyclic ring formation–transannular cyclisation protocol.

Pattenden[36b] has demonstrated that tributyltin hydride reaction of the iodo enone **30** led to 12-endo radical macrocyclisation to afford the radical intermediate **31** which after 6-exo-trig transannular cyclisation afforded the tricyclic taxane dione **32** (Scheme 6b).



SCHEME 6b.

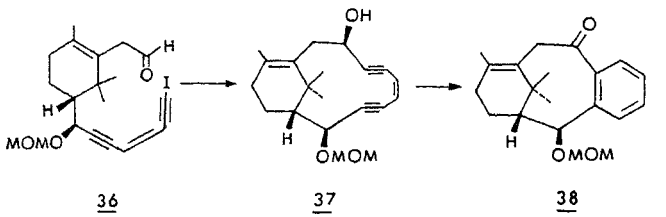
In Sampson's approach[37] (Scheme 7) macrolactonisation of the chloro keto acid **33** afforded the macrolide **34.** Transannular aldol condensation in **34** gave the taxane



SCHEME 7.

AB analogue **35** with suitable functionality in the B ring for further elaboration to a tricyclic nucleus.

Fallis[38] has recently reported an interesting approach for the construction of ring C aromatic taxane *via* cycloaromatisation of an enedyne system incorporated in a seco taxane for which he coined the name taxamycin 12. $CrCl_2$–$NiCl_2$-induced intramolecular coupling between iodo acetylene and aldehyde in **36** afforded stereoselectively the taxamycin analogue **37** (Scheme 8). Cycloaromatisation of **37** followed by oxidation led to the taxane analogue **38** in poor yield.



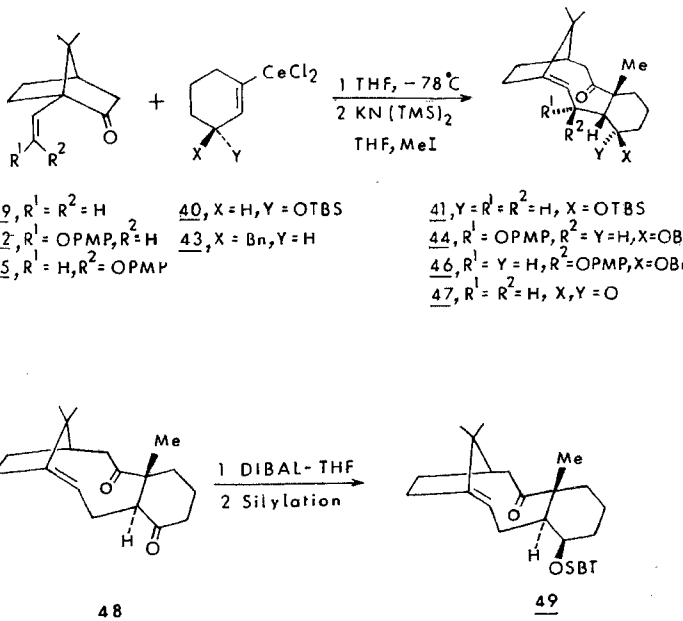
SCHEME 8.

2.3. Anionic oxy-Cope route

Using computer-aided organic synthesis programme SOS, Mehta *et al*[39] have demonstrated the great potential of anionic oxy-Cope reaction for access to taxane skeletons. However, only a limited number of attempts have been made to construct taxane skeleton based on this reaction. Significant progress for the construction of functionalised tricyclo[9.3.1.$0^{3,8}$]pentadecanes has been made by Paquette[40] exploiting this reaction. The special significance of Paquette's approach is the enantiospecificity and the ability to control the oxidation level of bridgehead carbon for taxusin and taxol.

The key concept in Paquette's strategy employs an anionic oxy-Cope rearrangement to construct bridged cyclononene followed by pinacol-like Wagner–Meerwein shift (for taxusin) and α-hydroxy ketone rearrangement (for taxol) to construct the desired

carbon frameworks. The synthesis began with 1,2-addition of optically enriched cerate **40** to optically active **39** and subsequent anionic oxy-Cope rearrangement to afford the (E)-*cis*-ketone **41** after *in situ* methylation (Scheme 9). Coupling of the cerate **43** with the ketone **42** followed by anionic oxy-Cope rearrangement–*in situ* methylation afforded stereoselectively the ketone **44**, offering a possibility for introducing the C-2 oxygen functionality[41]. It is interesting to note that starting with the E-olefinic ketone **45**, the 9-membered ring **46** obtained has opposite stereochemistry at C-2. To establish the *trans*-BC ring juncture, the ketone **41** was desilylated and oxidised to the diketone, **47**, which on equilibration gave a mixture of *cis* and *trans* ketones **47** and **48**. The pure *trans*-diketone **48** was then transformed to the ketone **49**, the precursor for Wagner–Meerwin shift.

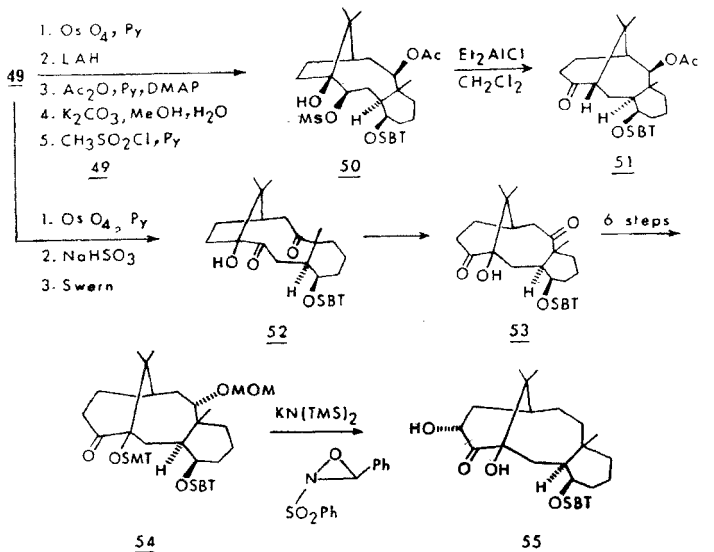


39, $R^1 = R^2 = H$ **40**, X = H, Y = OTBS **41**, $Y = R^1 = R^2 = H$, X = OTBS
42, R^1 = OPMP, $R^2 = H$ **43**, X = Bn, Y = H **44**, R^1 = OPMP, R^2 = Y = H, X = OBn
45, $R^1 = H$, R^2 = OPMP **46**, R^1 = Y = H, R^2 = OPMP, X = OBn
47, $R^1 = R^2 = H$, X, Y = O

48 **49**

SCHEME 9.

For pinacol-like rearrangement, the enone **49** was transformed to the mesylate **50**, Lewis acid treatment of which afforded the taxane derivative **51** without the



SCHEME 10.

bridgehead hydroxyl group (Scheme 10). For α-hydroxy ketone rearrangement to introduce the bridgehead hydroxyl group, the enone **49** was transformed to the hydroxydiketone **52**. Base treatment of **52** effected the rearrangement to afford the taxane nucleus **53** with the bridgehead hydroxyl group. Further, it has also been demonstrated that hydroxylation[42] at C-13 can be achieved through the reaction of the enolate of the C-14 carbonyl group with Davis sulfonyl oxaziridine as exemplified by the transformation of the diketone **53** to the C-13 hydroxylated ketone **55** through the monoketone **54.**

In a recent communication,[43] Paquette has described the stereocontrolled introduction of the C-9, C-10 hydroxyl groups, substitution pattern characteristic of taxusin, through osmylation of a *trans*$\Delta^{9,10}$-tricyclo[9.3.1.$0^{3,8}$]pentadecene diastereoisomeric pair.

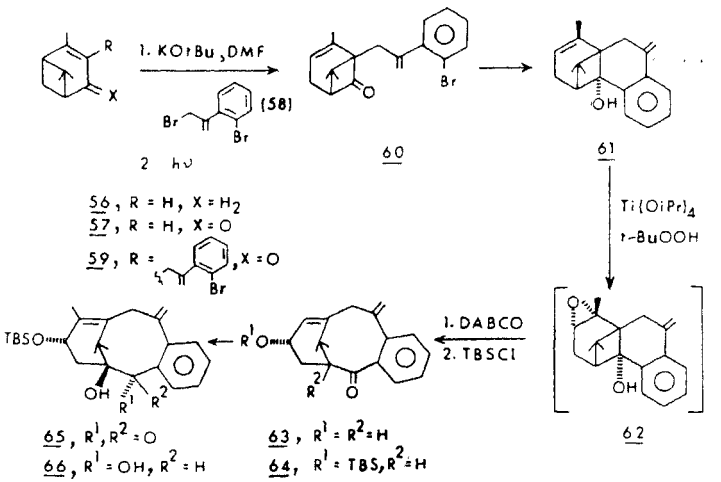
2.4. Fragmentation route

Fragmentation of suitably located C–C bond embodied in a polycyclic system having

A and C ring precursors of taxanes has been extensively used for the construction of tricyclic nucleus of taxanes.

2.4.1. C–C bond cleavage in [4.2.0] derivatives

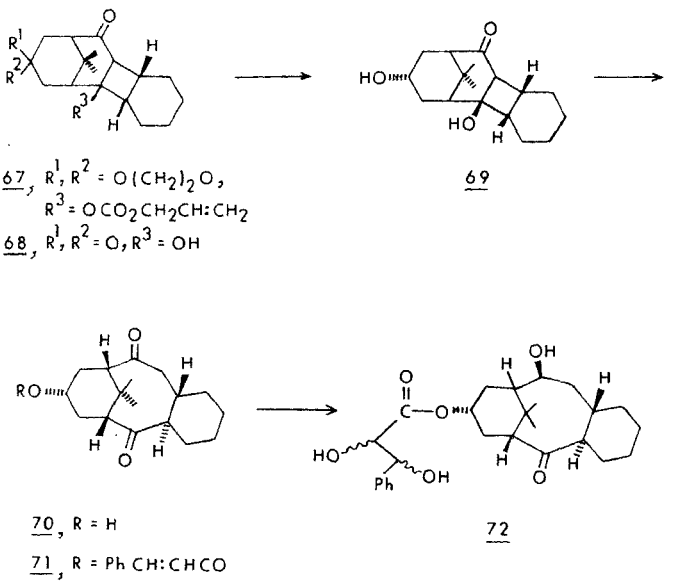
Wender[44] has recently reported a novel and concise route for constructing taxane tricyclic core in the correct enantiomeric form through fragmentation of the strained cyclobutane ring of [4.2.0] system as the key 8-membered ring-forming step. The strategy (Scheme 11) adopted is flexible enough to allow the synthesis of tricyclic analogues of taxol and ultimately taxol itself. The synthesis takes advantage of the use of abundant and inexpensive monoterpene pinene **56** which is available in both enantiomeric form and is used as the A ring precursor of taxane. Attachment of the C ring precursor to R-(+)-verbenone **57** derived from pinene **56** was achieved through enolate alkylation with the dibromide **58** to afford **59.** A photoinduced 1,3-alkyl shift in the alkylated verbenone **59** provided the rearranged pinene nucleus **60**. Intramolecular addition of aryl lithium to the carbonly group accomplished easy fusion of a 6-membered ring on to the 4-membered ring to afford **61.** Stereocontrolled formation of the epoxide **62** set the required stereochemistry at C-13 for attachment of the side chain. Treatment of the epoxide **62** with DABCO effected smooth fragmentation of the 4-membered ring to afford the tricyclic taxane nucleus **63.** Further functionalisation of the taxane nucleus **63** was accomplished through introduction of



SCHEME 11.

bridgehead hydroxyl group *via* enolate oxygenation of the silyl ether **64** to produce the hydroxy ketone **65.** Stereocontrolled reduction of the ketone **65** afforded the diol **66.** The tricyclic taxane derivative **66,** thus obtained in only 7 steps from verbenone, contains the couplete functionality and stereochemistry of the taxol A ring.

Blechert[22] has recently reported the first synthesis of a less-functionalised taxol analogue which has been found to restrict the depolymerisation of tubulin (Scheme 12). The synthesis was achieved through a stereoselective de Mayo reaction of cyclohexene with a suitably functionalised 1,3-diketone. The diketone **68** obtained after Pd^0-catalysed removal of hydroxy protecting group from the photoproduct **67** followed by dekctalisation was stereoselectively reduced to the diol **69.** Retroaldol reaction of **69** afforded a tricyclic diketone **70** with thermodynamically favored *trans*-oriented B/C ring which was transformed to the cinnamic acid ester **71.** The regio- and stereoselective reduction of the sterically more accessible C-10 ketone followed by *cis*-hydroxylation of the side chain double bond in **71** afforded a 1:1 mixture of two



67, $R^1, R^2 = O(CH_2)_2O$, $R^3 = OCO_2CH_2CH{:}CH_2$

68, $R^1, R^2 = O, R^3 = OH$

69

70, R = H

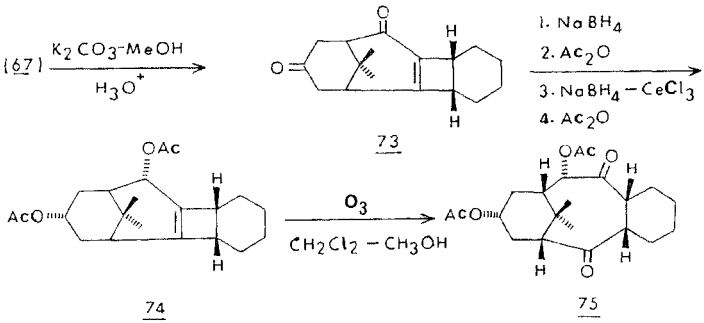
71, R = Ph CH:CHCO

72

SCHEME 12.

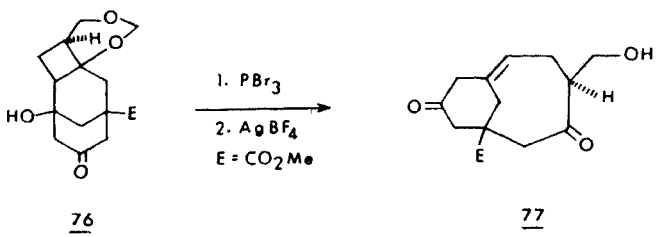
easily separable diastereomers **72**. The less-polar diastereomer in this mixture inhibits depolymerisation of tubulin.

Blechert has also used a modified de Mayo sequence (Scheme 13) for introducing the C-9 functionality through oxidative ring opening of a cyclobutene instead of the retro-aldol reaction. The cyclobutene dione 73 was obtained from the photoproduct **67** through elimination and deketalisation. Stepwise reduction and acetylation gave the diacetate **74** which was oxidatively cleaved to the tricyclic dione **75**. The flexibility of this strategy has allowed synthesis of various functionalised taxane derivatives to elucidate structure–activity interaction and provide better available biologically active taxanes.



73 **74** **75**

SCHEME 13



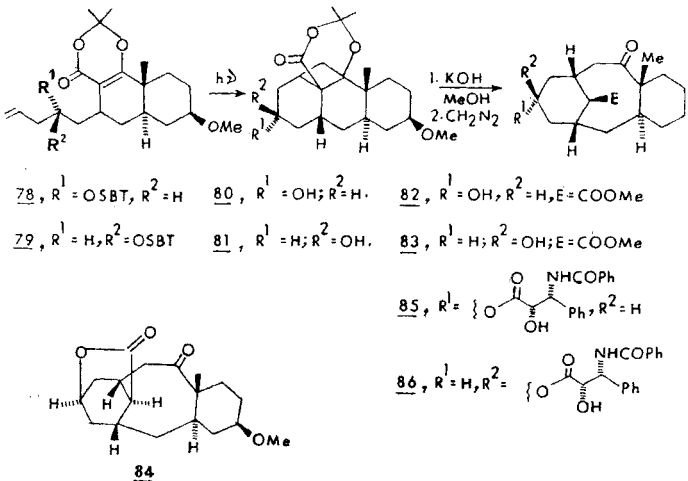
76 **77**

SCHEME 14

The fragmentation of a 4-membered ring fused to a bicyclo[3.3.1]nonane derivative has also been exploited by Kraus[46] to construct taxane AB ring (Scheme 14). Unlike a retro-aldol or alkene oxidation, fragmentation was initiated by a bridgehead

carbocation having an alkoxy group on a carbon atom β to the carbocation, as exemplified by the transformation of **76** to the taxane AB ring **77.**

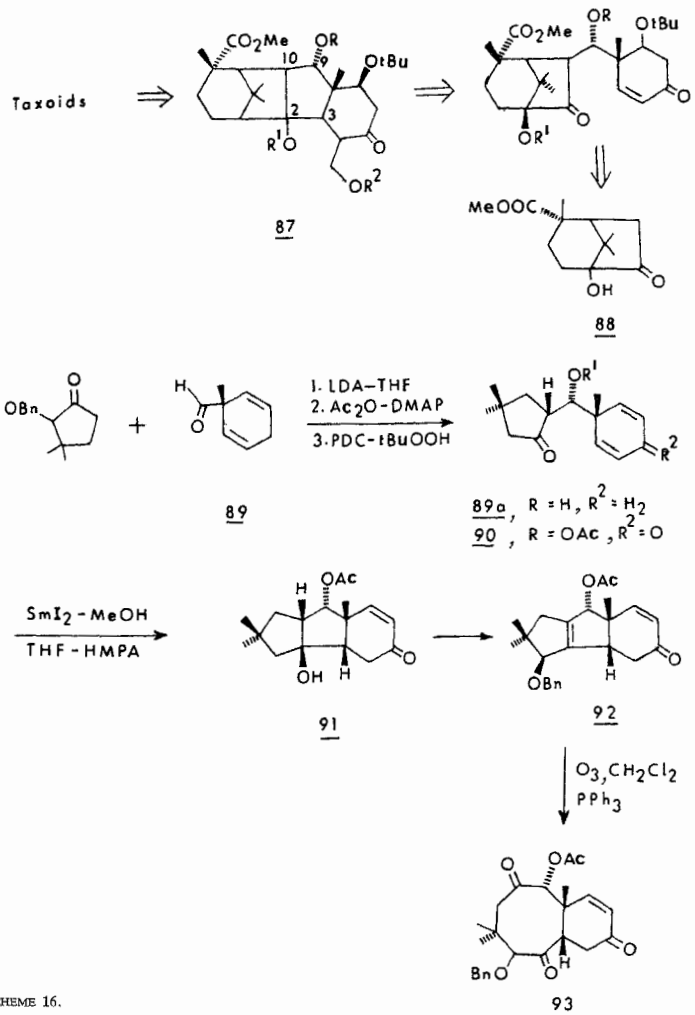
Winkler[47] has extended his earlier strategy involving intramolecular dioxenone photocycloaddition–fragmentation for the synthesis of the C-13 oxygenated taxane analogues (Scheme 15). Intramolecular photocycloaddition of the dioxenones **78** and **79** after desilylation led to the photoadducts **80** and **81.** Fragmentation of cyclobutane was then achieved with base treatment. While **80** gave the tricyclic analogue **82,** the tetracycle **81** gave a 1:1 mixture of the tricycle **83** and the lactone **84.** Attachment of the side chain to **82** and **83** led to the formation of the esters **85** and **86.** The availability of both C-13 oxygenated diastereoisomers is of considerable importance in determining structure–activity relation.



SCHEME 15

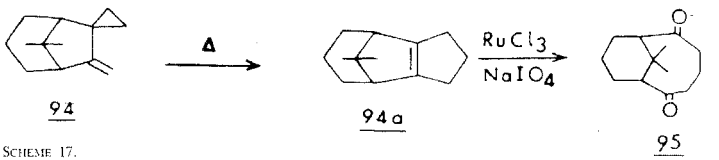
2.4.2. Fragmentation of [3.3.0] derivatives

After demonstration by Trost[48] that taxane AB ring could be constructed by fragmentation of the ring fusion bond of a [3.3.0] system, a few other groups have adopted the same strategy. For example, Arseniyadis[49] has recently adopted a protocol that involves an aldol-type C-10/C-9 bond formation C-2/C-3 annelation to generate the tetracyclic ketone **87** and C-2/C-10 bond fragmentation to lead to the central 8-membered ring. The feasibility of this strategy has been demonstrated by the synthesis of


Taxoids
CO2Me
OR
OtBu
10
9
2
3
R1O
OR2
87
MeOOC
OH
88
OBn
H
O
1. LDA–THF
2. Ac2O-DMAP
3. PDC-tBuOOH
OR1
R2
89
89a, R = H, R2 = H2
90, R = OAc, R2 = O
SmI2 - MeOH
THF - HMPA
OAc
OH
91
OBn
92
O3, CH2Cl2
PPh3
BnO
93

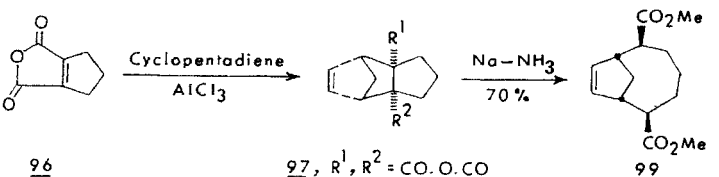
SCHEME 16.

taxane BC framework (Scheme 16). Aldol condensation between 2-benzyloxy-3,3-dimethyl cyclopentanone and the aldehyde **89** gave a mixture of two aldols. The major aldol product **89a** through its acetate was oxidised to the dienone **90**. Samarium(II) iodide-induced intramolecular coupling in **90** provided the enone **91** which was converted to the dienone **92**. Selective oxidative cleavage of the unconjugated

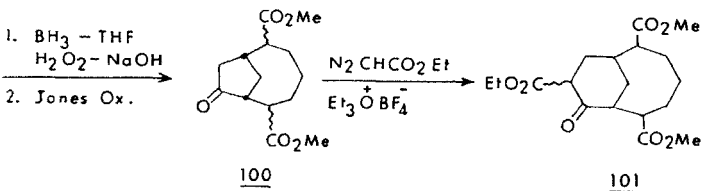


94 94a 95

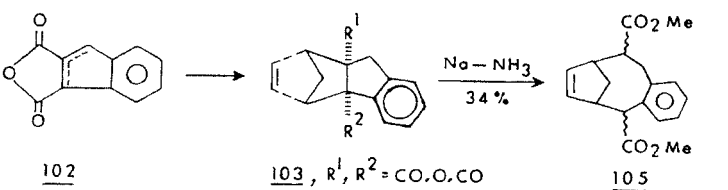
SCHEME 17.



96 97, R^1, R^2 = CO.O.CO 99
98, R^1 = R^2 = CO_2Me



100 101



102 103, R^1, R^2 = CO.O.CO 105
104, R^1, R^2 = CO_2Me

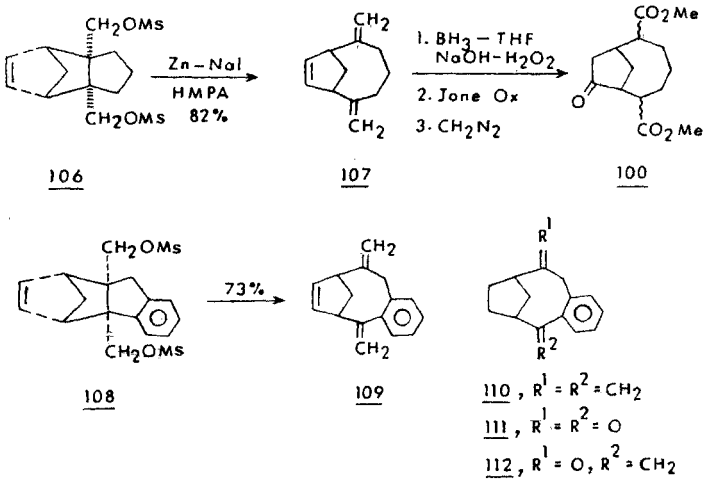
SCHEME 18.

double bond in **92** afforded the BC ring analogue **93** having all the oxygen functionalities of the B ring of taxane. This group has also reported[50] an efficient synthesis of the bicyclo[3.2.1]octane derivative **88** in the optically homogeneous form required for construction of the A ring.

Sonawane's approach[51] (Scheme 17) for constructing AB unit of taxane involves vinylcyclopropane rearrangement in **94** to the cyclopentene **94a** followed by its oxidative cleavage to the dione **95.**

We have developed a convergent approach[52] (Scheme 18) for the construction of taxane framework where a [4+2] cycloaddition was used to bring together A and C ring precursors followed by reductive cleavage of a C–C bond in the resulting adduct to form the B ring. The Diels–Alder reaction of the unsaturated anhydride **96** with cyclopentadiene afforded the adduct **97** which on hydrolysis and esterification gave the diester **98.** C–C bond cleavage in **98** was effected with $Na–NH_3(l)$ to afford stereoselectively the diester **99.** The five-membered ring in **99** was then enlarged through the ketone **100** to afford the taxane AB ring analogue **101.** A similar sequence using the bicyclic unsaturated anhydride **102** led to the synthesis of the ring C aromatic taxane analogue **105.**

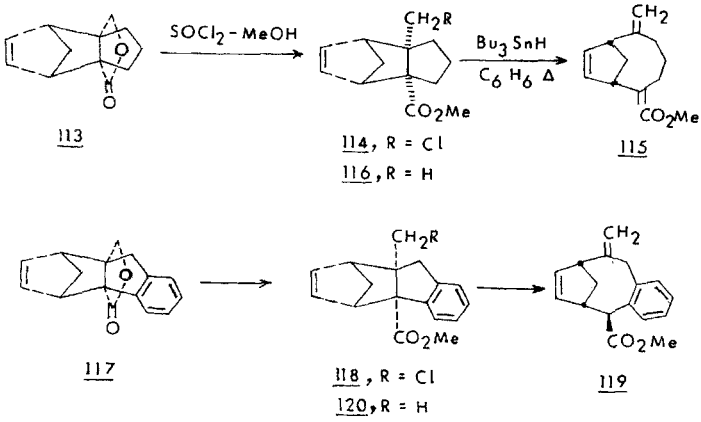
An alternative way[53] for achieving the ring cleavage in the adducts **98** and **103** involves Grob fragmentation induced by a carbanion or a radical generated at one



SCHEME 19.

of the anhydride carbonyl carbon centres. Such a process required transformation of the anhydride moiety of the adducts **97** and **103** to the dimesyl entities **106** and **108**, respectively, through reduction and reaction of the resulting dihydroxy compounds with methanesulfonyl chloride (Scheme 19). Reaction of the dimesyl derivative **106** with Zn–NaI in HMPA effected smooth fragmentation to afford the triene **107.** This triene was easily transformed to the keto-diester **100** which had earlier been transformed to the taxane AB analogue **101.** That this method is more efficient than Na–NH_3 method in cleaving C-C bond is demonstrated by ring cleavage of the tetracycle **108** to afford in much improved yield, a 4:1 mixture of the taxane tricyclic analogue **109** and the reduced product of **108.** In a recent report[54] it has been demonstrated that the delicate balance between the two reaction courses, reduction and C–C bond fragmentation is determined by the strain energies associated with the parent systems and the resultant ring-expanded products. The tricyclic diene **110** obtained from the saturated analogue of the dimesyl derivative **108** was used as a model for 8-membered ring functionalisation. Oxidation of the diene **110** with RuO_4 afforded the tricyclic taxane analogue **111** that contained C-2 and C-10 oxygen functionalities. Interestingly, oxidation of aromatic conjugated olefin with OsO_4 was found to be slow compared to oxidation of the isolated olefin and the tricyclic enone **112** was isolated in excellent yield providing an opportunity for chemoselective functionalisation of the taxane B ring.

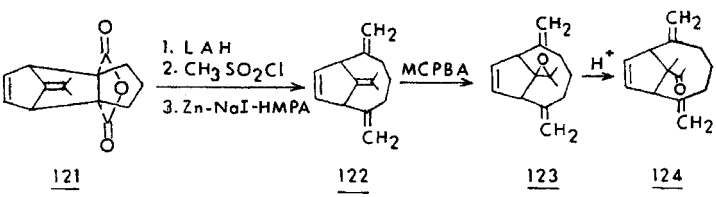
Very recently we have demonstrated[55] that ring cleavage in **97** and **103** can be induced through the intermediacy of carbon-centred radical. The adducts **97** and **103** were converted to the chloro-ester **114** and **118** through the lactones **113** and **117** (Scheme 20). While reaction of the chloro-ester **114** with tributyltin hydride gave the AB analogue



SCHEME 20.

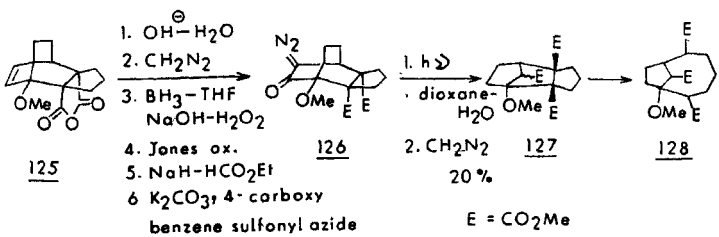
115 with a trace of the reduced product **116,** the chloro-ester **118** produced a 1:1 mixture of the tricyclic analogue **119** and the reduced product **120.** The stereoselectivity observed in the formation of **114** and **118** is notable. This is the first demonstration that C-C bond in ring system larger than 4-membered can be cleaved through a carbon-centred radical and has been attributed to be the result of relief of strain associated with norbornene and that arising through nonbonded interaction of cyclopentane methylene hydrogens with hydrogens at the one carbon bridge.

Attempt to incorporate gem-dimethyl group on the one carbon bridge of the bridged eight-membered rings thus synthesised was initiated[56]according to the plan delineated in Scheme 21. However, the triene-epoxide **123** although obtained in overall excellent yield from the adduct **121,** failed to undergo rearrangement in the desired direction to afford the bicycle **124.**



SCHEME 21.

We have also explored[57] the possibility of introducing the bridgehead oxygen function as portrayed in Scheme 22. The Diels–Alder adduct **125,** obtained in excellent yield from cycloaddition of the unsaturated anhydride **96** with 1-methoxy-1,3-cyclohexadiene, was transformed to the diazoketone **126.** Photolytic Wolf rearrangement of **126** in dioxane–water followed by methylation afforded the triester **127.** Reductive cleavage of the C-2/C-6 bond in **127** is expected to provide the taxane AB ring system with the bridgehead oxygen function. This approach also allows incorporation



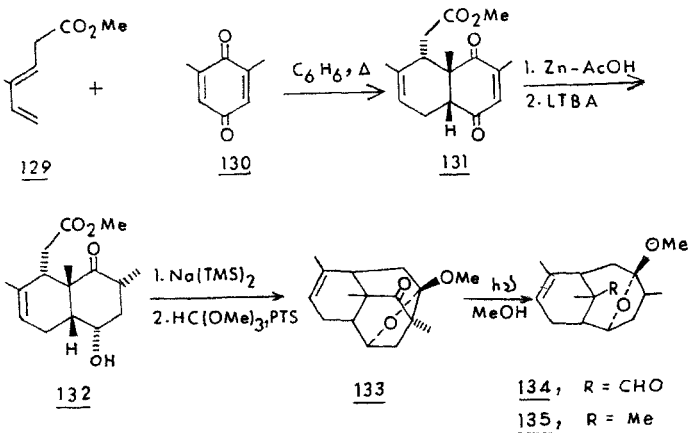
SCHEME 22.

of gem-dimethyl group. However, low yield obtained in the Wolf rearrangement step is a major limitation of this approach.

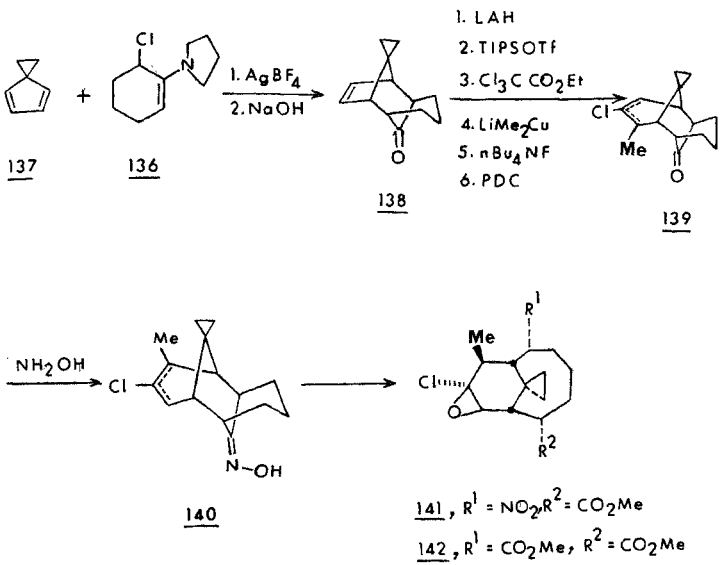
2.4.3. C–C bond cleavage in [3.3.1]nonane derivatives

Cleavage of one of the bonds connecting the one carbon bridge in a [3.3.1]nonane derivative to form 8-membered ring has been used for the construction of taxane AB ring. Such a strategy has recently been reported by Fetizon[58] (Scheme 23). Construction of the [3.3.1]nonane derivative **133** begins with cycloaddition of the diene **129** with 2.6-dimethylbenzoquinone **130** to form the adduct **131.** After two consecutive reductions, **131** was transformed to the hydroxy ester **132** as the major diastereoisomer. Treatment of the keto-ester **132** with base effected ring closure to produce the [3.3.1]nonane derivative **133**. Irradiation of **133** led, through Norrish-II cleavage (C-8/C-17, taxane numbering), the aldehyde **134,** which was finally transformed to the AB ring analogue **135.**

Cha's approach[59] (Scheme 24) employs a [4+3]diene-oxyallyl cycloaddition followed by oxidative cleavage of the resulting one carbon bridge. Cycloaddition of the enamine **136** with the cyclopentadiene derivative **137** followed by basic hydrolysis gave the adduct **138.** The cyclopentene unit in **138** was ring expanded through dichlorocarbene addition to afford the chloro ketone **139** after functional group manipulation. Oxidative cleavage of the one carbon bridge was then effected through the oxime **140** to afford the nitro-ester **141** and **142**, containing the AB ring skeleton of the taxanes.



SCHEME 23.



137 136 138 139 140 141, 142

SCHEME 24.

3. Conclusion

The efforts aimed at total synthesis of taxanes, as summarised above, though, except with one exception[60], did not lead to total synthesis, have enriched the field of organic synthesis with the development of many efficient synthetic methods and novel concepts.

Acknowledgement

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References

1. MILLER, R. W. *J. Nat. Prod.*, 1980, **43**, 425–437.
2. DELLA CASA DE MARCANO, D.P. AND HALSALL, T.G. *J. Chem. Soc., Chem. Commun.*, 1969, 1282–1283.

3. DELLA CASA DE MARCANO, D P. AND HALSALL, T G. — *J. Chem. Soc., Chem. Commun.*, 1970, 1381–1382.
4. DENIS, J.N., GREEN, A.E., GUENARD, D., GUERITTE-VOEGELEIN, F., MANGATAL, L. AND POTIER, P. — *J. Am. Chem. Soc.*, 1988, **110**, 5917–5919.
5. WANI, M.C., TAYLOR, H.L., WALL, M.E., COGGON, P AND MCPHAIL, A.T. — *J. Am. Chem. Soc.*, 1971, **93**, 2325–2327.
6. HOLMES, F.A., WALTERS, R.S., THERIAULT, R.L., FORMAN, A.D., NEWTON, L.K., RABER, M.N., BUZDAR, A.U., FRYE, D.K. AND HORTOBAGYI, G.N. — *J. Natn. Cancer Inst.*, 1991, **83**, 1797–1805.
7. ROWINSKY, E. K., CAZENAVE, L.A. AND DONEHOWER, R.C. — *J. Natn. Cancer Inst*, 1990, **82**, 1247–1259.
8. COLIN, M., GUENARD, D., GUERITTE-VOEGELEIN, F. AND POTIER, P. — *Chem. Abstr.*, 1988, **109**, 22762w.
9. KINGSTON, D.G.I., SAMARANAYAKE, G. AND IVEY, C.A. — *J. Nat. Prod.*, 1990, **53**,1
10. GUERITTE-VOEGELEIN, F., GUENARD, D., LAVELLE, F., LE GOFF, M.T., MANGATAL, L. AND POTEIR, P — *J. Med. Chem.*, 1991, **34**, 992
11. SWINDELL, C.S., KRAUSS, N.E., HORWITZ, S.B. AND RINGEL, I. — *J. Med. Chem.*, 1991, **34**, 1176–1184.
12. WAHL, A., GUERITTE-VOEGELEIN, F., GUENARD, D., Le GOFF, M.T. AND POTEIR, P. — *Tetrahedron*, 1992, **48**, 6965–6974.
13. KLEIN, L.L — *Tetrahedron Lett.*, 1993, **34**, 2047–2050.
14. CHEN, S.H., FAIRCHILD, C., MAMBER, S.W. AND FARINA, V. — *J. Org. Chem.*, 1993, **58**, 2927–2928.
15. CHEN, S H., HUANG, S., WEI, J. AND FARINA, V. — *J. Org. Chem.*, 1993, **58**, 4520–4521.
16. DUBOIS, J., GUENARD, D., GUERITTE-VOEGELEIN, F., GUEDIRA, N., POTIER, P., GILLET, B. AND BELOEIL, J. — *Tetrahedron*, 1993, **49**, 6533.
17. WILLIAMS, H.J., SCOTT, A.I., DIEDEN, R.A., SWINDELL, C.S., CHIRLIAN, L.E., FRANEL, M.M., HEERDING, J.M. AND KRAUSS, N.E. — *Tetrahedron*, 1993, **49**, 6545–6560
18. CHAUDHARY, A.G., RIMOLDI, J.M. AND KINGSTON, D.G.I. — *J. Org. Chem.*, 1993, **58**, 3798–3799.
19. CHAUDHARY, A.G. AND KINGSTON, D.G.I. — *Tetrahedron Lett.*, 1993, **34**, 4921–4924.

20. CHEN, S.H., WEI, J.M AND FARINA, V. *Tetrahedron Lett*, 1993, **34**, 3205–3208.

21. CHEN, S.H., HUANG, S, KANT, J., FAIRCHILD, C., WEI, J AND FARINA, V. *J. Org. Chem.*, 1993, **58**, 5028–5029.

22 BLECHERT, S. AND KLEINE-KLAUSING, A *Angew. Chem Int. Ed. Engl.*, 1991, **30**, 412–414.

23. PAQUETTE, L A AND THOMPSON, R.C *J Org. Chem*, 1993, **58**, 4952–4962 and references cited therin.

24 ISSACS, R.C.A., DI GRAND, M.J. AND DANISHEFSKY, S.J. *J Org. Chem.*, 1993, **58**, 3938–3941 and references cited therein.

25. SWINDELL, C S. *Org. Prep Proc. Int.*, 1991, **23**, 465–543.

26 PETASIS, N.A AND PATANE, M.A. *Tetrahedron*, 1992, **46**, 5757–5821

27 PAQUETTE, L A *Studies in natural products chemistry* (Rahman, A.U. ed.), Vol. 3, pp. 165-197, 1992, Elsevier

28. SAKAN, K, SMITH, D A., BABIRAD, S.A., FRONCZEK, F.R. AND HOUK, K N *J. Org. Chem*, 1991, **56**, 2311–2317.

29. LU, Y.F. AND FALLIS, A.G. *Tetrahedron Lett*, 1993, **34**, 3367–3370.

30. a. JACKSON, R.W, HIGBY, R.G. AND SHEA, K.J. *Tetrahedron Lett.*, 1992, **33**, 4695–4698.

b. JACKSON, R.W., HIGBY, R.G. *Tetrahedron*, 1992, **48**, 7013–7032.

31 YADAV, J.S. AND RAVISHANKAR, R. *Tetrahedron Lett.*, 1991, **32**, 2629–2632.

32. KENDE, A.S., JOHNSON, S., SANFILIPPO, P., HODGES, J.C AND JUNGHEIM, L.N. *J. Am. Chem Soc.*, 1986, **108**, 3513–3515.

33. MORIHIRA, K., SETO, M., FURUKAWA, T., HORIGUCHI, Y. AND KUWAJIMA, I *Tetrahedron Lett.*, 1993, **34**, 345–348

34 NICOLAOU, K.C., YANG, Z., SORENSEN, E.J. AND NAKADA, M. *J. Chem. Soc, Chem. Commun.*, 1993, 1024–1026.

35. WANG, Z, WARDER, S.E, PERRIER, H., GRIMM, E.L., BERNSTEIN, M.A. AND BALL, R.G. *J. Org Chem.*, 1993, **58**, 2931–2932

36. a. GHOSH, K., GHOSH, A.K. AND GHATAK, U.R *J. Chem. Soc., Chem. Commun.* (in press).

b. HITCHCOCK, S.A. AND PATTENDEN, G. *Tetrahedron Lett*, 1992, **33**, 4843–4846

37. CHAI, K.B. AND SAMPSON, P. *J. Org. Chem.*, 1993, **58**, 6807–6813.

38. LU, Y.F., HARWIG, C W. AND FALLIS, A.G. *J. Org Chem.*, 1993, **58**, 4202–4204.

39. MEHTA, G., BARONE, R., AZAIRO, P., BARBERIS, F., ARBELOF, M AND CHANON, M. *Tetrahedron*, 1992, **48**, 8953–8962.

40. a PAQUETTE, L A , ELMORE, S.W , COMBRINK, K.D , HICKEY, E R. AND ROGERS, R.D	*Helv Chim Acta*, 1992, **75**, 1755–1771.
b. PAQUETTE, L.A. COMBRINK, K.D., ELMORE, S.W. AND ZHAO, M.	*Helv. Chim. Acta*, 1992, **75**, 1772–1791.
41. PAQUETTE, L.A., HUBER, S K AND THOMPSON, R C.	*J Org. Chem*, 1993, **58**, 6874–6882.
42. ELMORE, S.W. AND PAQUETTE, L.A.	*J. Org. Chem*, 1993, **58**, 4963–4970.
43. PAQUETTE, L.A. AND ZHAO, M.	*J. Am. Chem. Soc.*, 1993, **115**, 354–356.
44. WENDER, P.A AND MUCCIARO, T.P.	*J. Am Chem. Soc*, 1992, **114**, 5878–5879.
45. BLECHERT, S., MULLER, R. AND BEITZEL, R	*Tetrahedron*, 1992, **48**, 6953–6964
46. KRAUS, G.A AND ZHENG, D.	*Synlett*, 1993, 71–72.
47. WINKLER, J.D AND SUBRAHMANYAM, D.	*Tetrahedron*, 1992, **34**, 7049–7056.
48. a. TROST, B.M. AND HIMESTRA, H	*J. Am. Chem. Soc.*, 1982, **104**, 886–887
b. TROST, B.M. AND FRAY, M.J.	*Tetrahedron Lett.*, 1984, **25**, 4605.
49. ARSENIYADIS, S., YASHUNSKY, D.V., DORADO, M.M., ALVES, R.B., TOROMANOFF, E., TOUPET, L.L. AND POTIER, P.	*Tetrahedron Lett.*, 1993, **34**, 4927–4930
50. ARSENIYADIS, S., YASHUSKY, D.V., PEREIRA DE FREITAS, R., DORADO, M.M., TROMANOFF, E. AND POTIER, P.	*Tetrahedron Lett.*, 1993, **34**, 1137–1140.
51. SONAWANE, H.R , BELLUR, N.S., KULKARNI, D.G. AND AHUJA, J.R.	*Synlett*, 1993, 875–884.
52. a. SAHA, G., BHATTACHARYA, A., SAHA ROY, S., AND GHOSH, S.	*Tetrahedron Lett.*, 1990, **31**, 1483–1484
b. SAHA, G., KARPHA, A., SAHA ROY, S. AND GHOSH, S.	*J. Chem. Soc., Perkin Trans. 1*, 1992, 1587–1591.
53. GHOSH, S., KARPHA, A., SAHA, G. AND PATRA, D.	*Tetrahedron Lett.*, 1992, **33**, 2363–2364.
54 GHOSH, S , SARKAR, S. AND SAHA, G.	*J. Chem. Soc., Perkin Trans. 1*, 1993, 2281–2286.
55. a. SARKAR, S. AND GHOSH, S.	*Tetrahedron Lett.*, 1993, **34**, 2987–2988.
b. SARKAR, S. AND GHOSH, S.	*Tetrahedron*, 1994, **50**, 921–930.
56. BHATTACHARYA, A.	*Synthetic studies in tri- and tetracyclic terpenoids*, Ph.D. Thesis, Jadavpur University, Calcutta, India, 1992.
57. SAHA, G. AND GHOSH, S.	*Synth. Commun.*, 1991, **21**, 2129–2136.
58. BENCHIKH LE-HOCINE, M., KHAC, D.D., FETIZON, M., GUIR, F., GUO, Y. AND PRANGE, T.	*Tetrahedron Lett.*, 1992, **33**, 1443–1446.
59. OH, J., CHOI, J.R. AND CHA, J K.	*J. Org. Chem.*, 1992, **57**, 6664–6667.

60 HOLTON, R.A., JUO, R.R., KIM, H.B., WILLIAMS, A.D., HARUSAWA, S., LOWENTHAL, R.E. AND YOGAI, S. *J Am. Chem. Soc.*, 1988, **110**, 6558–6560.

Note added in proof

A few more approaches to taxane ring system *via* direct ring closure have recently been reported from the laboratories of Swindell[61] (a low-valent Ti-based intramolecular pinacol coupling). Kishi[62] (intramolecular Ni(II)/Cr(II)-mediated coupling of olefin with aldehyde) and Master's[63] (PdCo)-catalysed intramolecular Heck definition). The achievement of the first total synthesis of taxol in enantiomeric from independently by Nicolaou[64] and Holton[65] is a landmark in the area of taxane research and in the history of organic synthesis.

61. SWINDELL, C.S CHANDER, M C., HEERDING, J.M., KLIMKO, P.G., RAHMAN, L.T., RAMAN, J.V AND VENKATARAMAN, H. *Tetrahedron Lett.*, 1993, **34**, 7005–7008.

62. KRESS, M.H., RUEL, R , MILLER, W.H AND KISHI, Y. *Tetrahedron Lett* , 1993, **34**, 6003–6006.

63. MASTERS, J.J., JUNG, D.K , BORNMANN, W G., DANISHEFSKY, S.J. AND DE GALA, S. *Tetrahedron Lett.*, 1993, **34**, 7253–7256.

64. NICOLAOU, K.C. YANG, Z., LIU, J.J. UENO, H., NANTERMET, P.G., GUY, R.K., CLAIBORNE, C.F., RENAUD, J , COULADOUROS, E.A., PAULVANNAN, K. AND SORENSEN, E.J. *Nature*, 1994, **367**, 630–634.

65. HOLTON, R.A., KIM, H B., SOMOZA, C , LIANG, F., BIEDIGER, R.J., BOATMAN, P D., SHINDO, M., SMITH, C C., KIM, S., NADIZADEH, H., SUZUKI, Y., TAO, C., VU, P., TANG, S., ZHANG, P , MURTHI, K.K., GENTILE, L.N. AND LIU, J.H. *J. Am Chem. Soc.*, 1994, **116**, 1599–1600.