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Synthesis of antitumour agents

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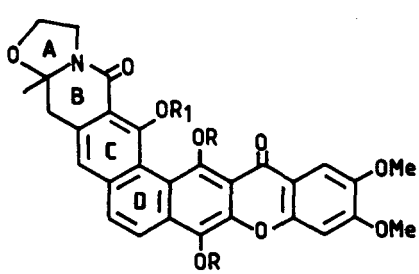
Abstract. A regiocontrolled total synthesis of cervinomycin A_1 and A_2 has been achieved utilizing simple and easily accessible reagents under viable reaction conditions. An approach towards the synthesis of the taxol skeleton using intramolecular Diels-Alder reaction followed by Wittig rearrangement is described.

Cancer, a complex of diseases associated with the abnormal growth of new body tissues, is a most dreadful disease in the world today. About 20% of the deaths in western countries occur due to neoplastic diseases and today, it is one of the third largest killer diseases in India. The most alarming aspects of cancer in India is that it affects the Indian 15-20 years earlier than their counterpart in western countries. This could be due to the climatic conditions. Radiation and surgery are the effective tools to combat it as long as this disease is detected early and localized. However, by the time it is detected it often spreads to other parts of the body. Chemotherapy or its combination with the radiation is the only solution. Realising the need and problem, we initiated a programme to develop chemotherapeutic agents. The synthesis of Cervinomycin **1** & **2** and Taxol **4** will be discussed.

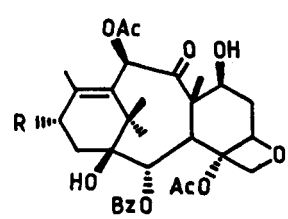


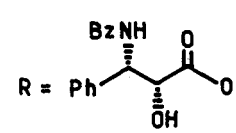
1 R = H , R_1 = H

2 E ring quinone , R_1 = H

3 R = R_1 = Ac

29 R_1 = CH_3 , Ring E quinone





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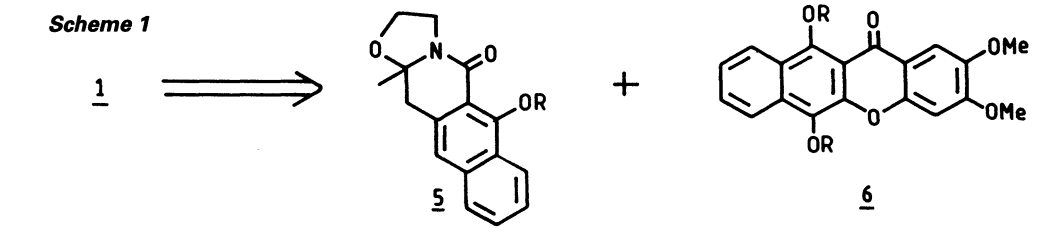
A. CERVINOMYCIN A_1 **1** AND A_2 **2**

Cervinomycin, produced by *Streptomyces cervinus sp. nov.*, is an antibiotic possessing (ref.1) strong inhibitory activity against anaerobic bacteria and mycoplasma Cervinomycin consists of two components A_1 **1** and A_2 **2** which are insoluble in most of the organic solvents. However, triacetyl cervinomycin **3**, has high solubility and is developed as a drug because of its low toxicity and enhanced activity. Cervinomycin's unique structure, which possesses a sensitive isoquinolone moiety fused angularly with a novel and highly functionalized xanthone unit makes it a synthetically challenging target. A programme was therefore initiated on its total synthesis (ref. 2,3) with the aim to prepare chemical variants of **1** to further examine therapeutic efficacy.

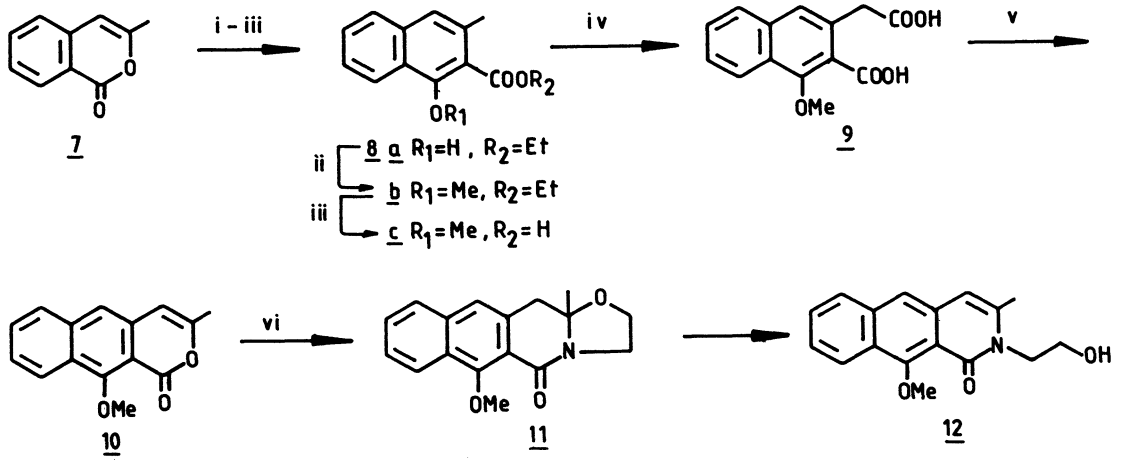
Incisive architectural scrutiny of target molecule **1** unfolds that it is a heptacyclic aromatic compound with extended conjugation. ABC and EFG rings are angularly fused to central D ring, giving a shape of extended phenanthrene. ABC rings consist of the xanthone moiety of the molecule. D is the central ring, whose substitution pattern imparts an "elbow bend" to the molecule. The location of the carbonyl group in pyron F ring imposes regiospecificity to the molecule, which can be characterised as an "upward" xanthone.

Before embarking on the total synthesis of any complex molecule such as cervinomycin, it is important to conduct crucial reactions on model compounds so as to gain expertise in executing key reactions, which will not only provide an insight into the reactions and conditions to determine the sensivity of the molecule but also help in the visualization of suitable precursors making the retrosynthetic plan easier. The major strategic concern, therefore, would be the identification of suitable methodologies for both the fragments oxazolidine **5** and xanthone **6** fragments corresponding to ABCD and DEFG rings of cervinomycins (scheme 1).

Scheme 1



Scheme 2

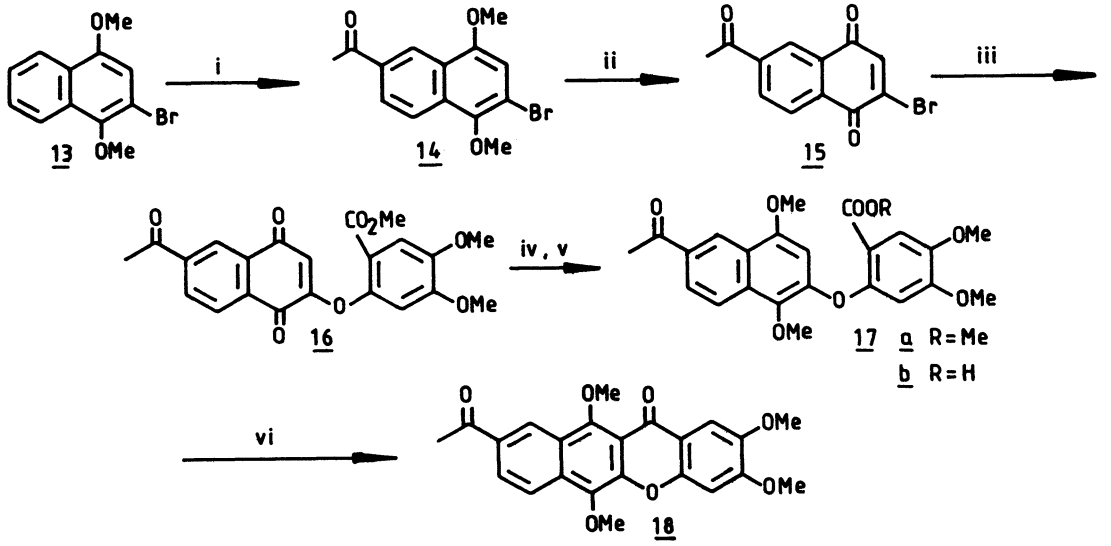


Reagents: i. Zn, $BrCH_2COOEt$, Benzene; ii. NaH, Me_2SO_4, DMF; iii. KOH, aq. DMSO; iv. LDA, $(EtO)_2CO$, THF; v. Ac_2O, Pyridine, 10% aq. NaOH, Ac_2O, $HClO_4$(Cat); vi. $H_2NCH_2CH_2OH$, MeOH

At the first instance, we planned to develop the methodology for the preparation of the oxazolidine unit which is very sensitive to acids, bases and heat. It was envisaged that this moiety can be prepared from the corresponding isocoumarin **10** by the action of 2-amino-ethanol. The isocoumarin, prepared as depicted in the scheme 2, when treated with 2-amino-ethanol in refluxing methanol produced **12** as the sole product. However, when the reaction was carried out (ref.4) at room temperature, the desired oxazolidine unit **11** could be obtained in 80% yield.

Our next attention was drawn to develop the methods for the preparation of the xanthone moiety, which was achieved by the sequence of reactions as delineated in scheme 3. Thus, the known (ref.5) 2-bromo-1,4-dimethoxynaphthalene **13**, on Friedel-Crafts acylation afforded (ref.6) the 6-acetyl derivative **14** regioselectively which on oxidative demethylation gave rise to 2-bromo-naphthoquinone **15**. Treatment of **15** with methyl-2-hydroxy-4,5-dimethoxybenzoate (ref. 7) in presence of K_2CO_3 produced **16** which was hydrolysed and cyclized to xanthone **18**.

Scheme 3

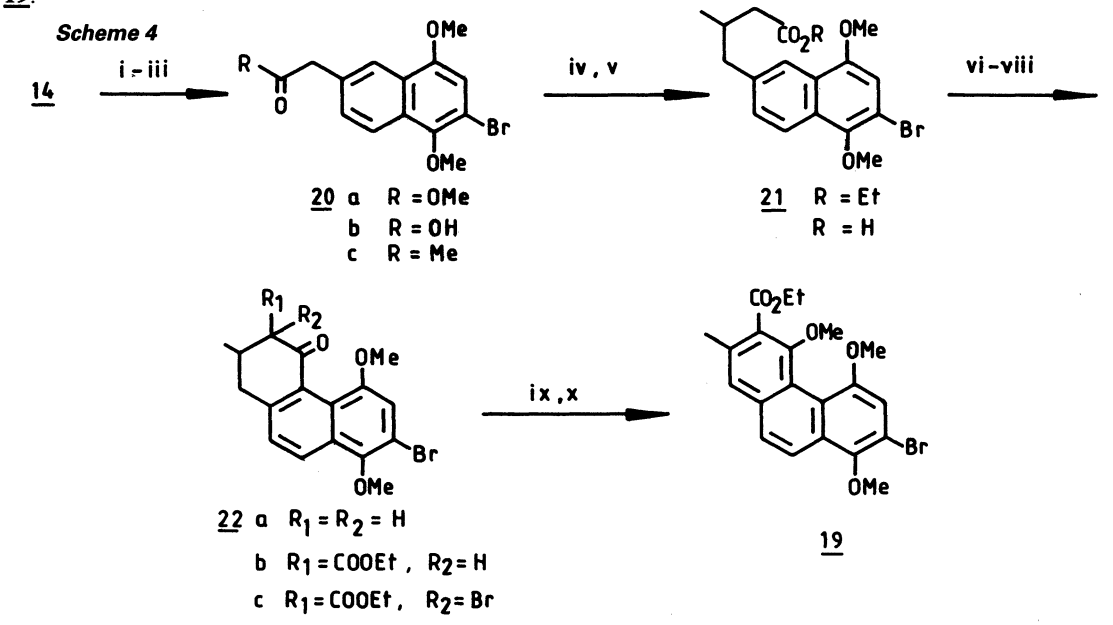


Reagents: i. Ac_2O, $AlCl_3$, CH_2ClCH_2Cl; ii. $(NH_4)_2Ce(NO_3)_{6,aq.}$ CH_3CN; iii. Methyl 2-hydroxy-4,5-dimethoxybenzoate; iv. $Na_2S_2O_4$,$(MeO)_2SO_2$-K_2CO_3; v. KOH,C_2H_5OH; vi. PPE, $CHCl_3$

After establishing the methods for the preparation of the oxazolidine and xanthone moieties, we imagined that **19** would be the ideal synthon having CDE rings of cervinomycin built in it. It has a toluic acid portion for the elaboration to theoxazolidine unit and a bromosubstituent to stitch the xanthone unit. Thus, the attention was now focused to prepare the key intermediate **19**.

Thus, an efficient approach for the synthesis of **19** was developed as depicted in scheme 4 starting from **14**. **14** on treatment with thallium trinitrate in acidic medium produced (ref. 8) **20a** which was transformed to **20c** in two steps. **20c** was olefinated with Ph_3P=CHCOOEt and hydrogenated over Adam's catalyst to afford **21**, which after hydrolysis, was cyclized (ref.9) to **22a** in overall good yield. The ester functionality was introduced in **22a** to get **22b** which was aromatized and methylated to get the key synthon **19**.

Scheme 4



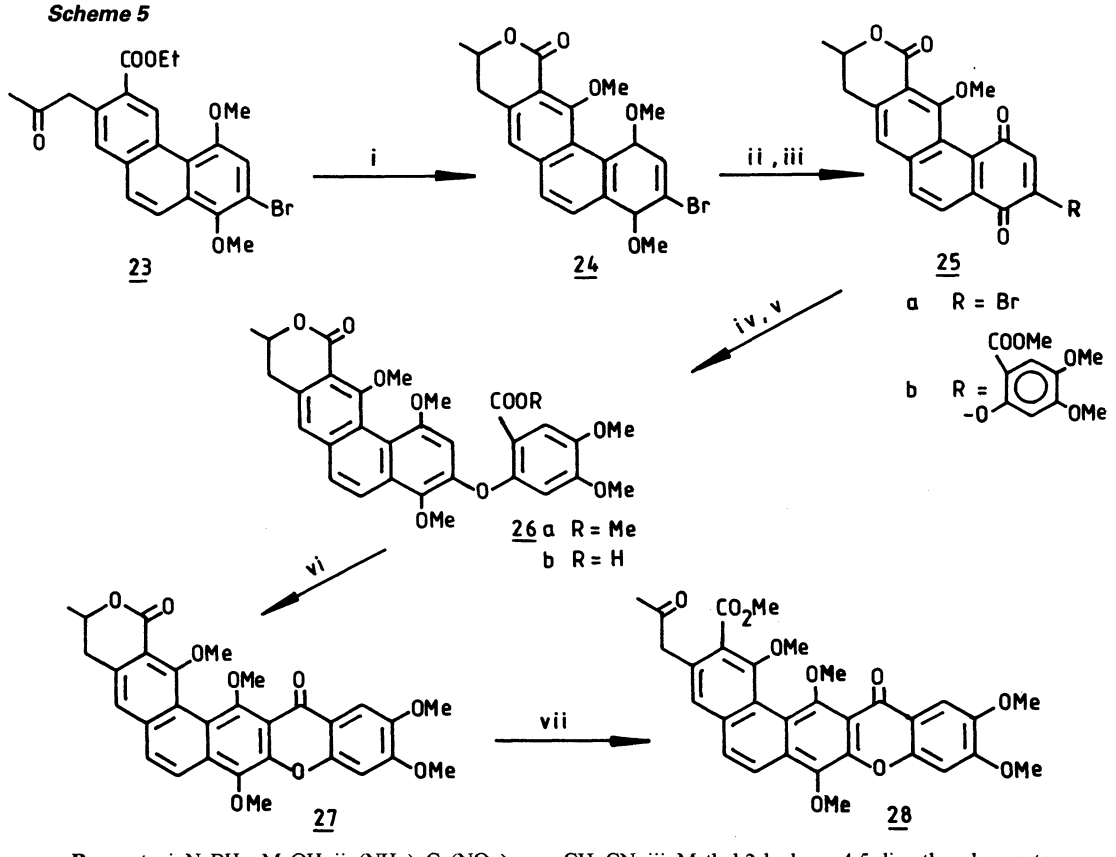
Reagents: i. TTN, $HClO_4$, MeOH; ii. KOH-C_2H_5OH; iii. MeLi ether; iv. Ph_3P=$CHCO_2Et$, PtO_2-H_2; v. KOH, C_2H_5OH; vi. PPE, $CHCl_3$; vii. NaH,$CO(OEt)_2$, THF; viii. $C_5H_5NHBr_3$,AcOH; ix. DBU, $CHCl_2$; x. $(MeO)_2SO_2$ K_2CO_3, CH_3COCH_3

Having the pivotal intermediate **19** in hand with the required substituents for a regiospecific annulation of the xanthone and oxazolo-isoquinolone units, the next concern was to acetylate the aromatic methyl first, then to construct the xanthone. Accordingly, **19** was converted to **23** using LDA and excess N-methoxy-N-methyl acetamide (ref.10) in THF at -78°C. Here, the oxazolidine ring was intended to be built at a later stage of the synthetic planning because it would not stand the reaction conditions employed in the preparation of the xanthone.

The ketone **23** on reduction with $NaBH_4$ in methanol afforded lactone **24** in 80% yield. **24** on oxidative demethylation furnished quinone **25a**, which was stirred with excess methyl 2-hydroxy-4,5-dimethoxy benzoate (ref. 7) in presence of anhydrous K_2CO_3 in DMF to afford **25b** in 65% yield (scheme 5). Quinone **25b** on reduction with sodium dithionite and subsequent O-methylation of the resultant hydroquinone using potassium carbonate and dimethyl sulphate in an inert atmosphere furnished **26a**. The ester **26a** on hydrolysis with ethanolic KOH afforded a diacid, which on subsequent crystallization with PPE furnished the hexacyclic xanthone **27.**

Although we had developed the method for the formation of the oxazolidine ring by reacting 2-aminoethanol with an isocoumarin, it was envisaged, keeping in view the mechanistic consideration for the formation of oxazolidine, that a ketoester would serve as a better substrate in comparison to the isocoumarin (scheme 6).

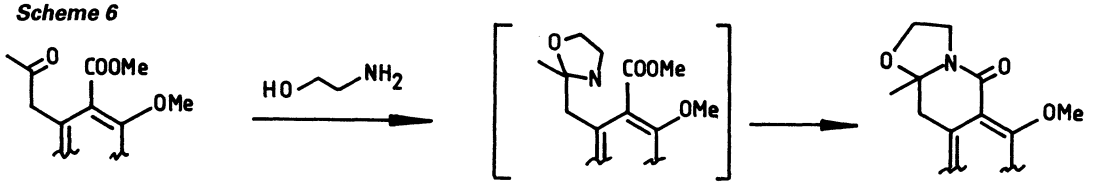
Scheme 5



Reagents: i. $NaBH_4$, MeOH; ii. $(NH_4)_2Ce(NO_3)_6$, aq. CH_3CN; iii. Methyl 2-hydroxy-4,5-dimethoxybenzoate, K_2CO_3, DMF; iv. $Na_2S_2O_4$,$(MeO)_2SO_2$-K_2CO_3; v. KOH, EtOH; vi. PPE, $CHCl_3$; vii. KOH-EtOH, CH_2N_2-ether, PCC-CH_2Cl_2

Thus, lactone **27** was hydrolysed with alcoholic KOH and the hydroxy acid thus obtained was esterified with diazomethane. The alcohol functionality was oxidized to get the keto ester **28**, which on treatment with 2-aminoethanol in refluxing MeOH in presence of K_2CO_3 afforded **29** having the complete skeleton of cervinomycin.

Scheme 6

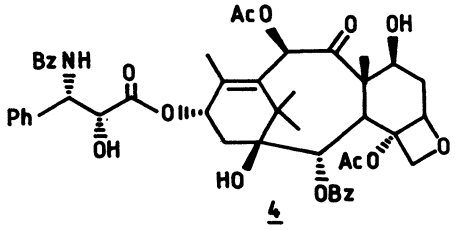


Having obtained **29** successfully, the only remaining task was to strip off three methyl ethers to generate cervinomycin A_1, **1**. When **29** was subjected to oxidative demethylation (ref. 11) using ceric ammonium nitrate in aq. acetonitrile, the E ring methyl ethers were cleaved chemoselectively to afford O-methyl cervinomycin A_2 **29** in 95° yield, mp 300°C dec. [lit. (ref.1b), mp, 300°C dec.]. After several unsuccessful attempts with various reagents, $Et_3N{:}BCl_3$ was found to be an optimum reagent to cleave the methyl ether of ring C (1 eq. of boron trichloride in presence of 1.1 eq. of triethylamine in DCM at 0°C) to afford (±) cervinomycin A_2 **2** in 85% yield, mp 280°C dec [lit. (ref. 12) mp 279-284°C dec.]. The (±) **2** so obtained was identical (ref.1) with an authentic sample of (-) cervinomycin A_2 by direct comparison. Reduction of (±) cervinomycin A_2 **2** with $NaBH_4$ afforded cervinomycin A_1 **1**.

In conclusion, a regiocontrolled total synthesis of cervinomycin A_1 and A_2 has been achieved utilizing simple and easily accessible reagents under viable reaction conditions. This strategy would also facilitate the preparation of its analogues in the development of effective chemotherapeutic agents. An, effective and efficient methodology, hitherto unknown in the literature for the annulation of oxazolidine unit with a suitable treatise on mechanism of its formation was also unfurled.

B. TAXOL *4*

Taxol **4**, a highly oxygenated complex diterpenoid isolated (ref.12) from the bark of the western yew plant, *Taxus brevifolia*, is an exceptionnally promising cancer chemotherapeutic agent. Taxol, apart from showing a broad spectrum of potent antileukemic and tumor inhibiting activity (ref. 13), has driven the attention (ref. 14) of scientists the world over owing to its tremendous structural complexity and also being the drug of choice for ovarian cancer.



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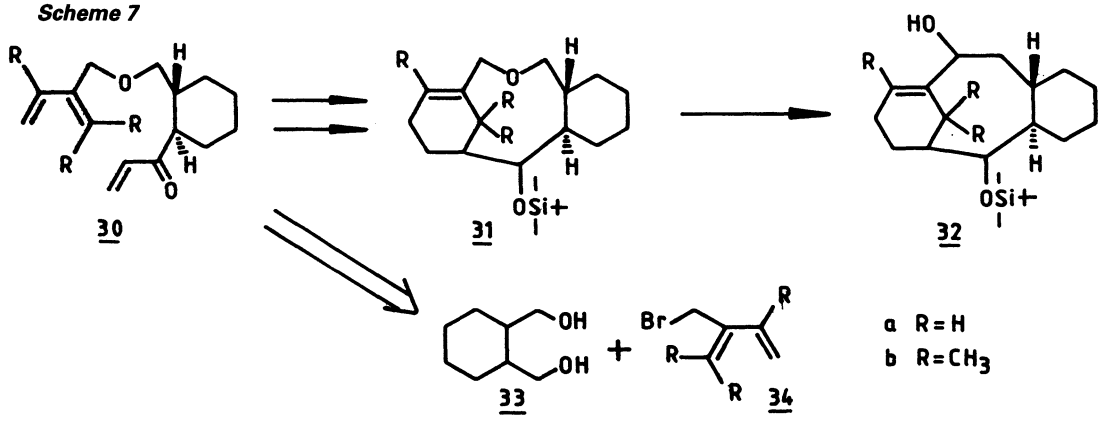
We have started earnestly, in our laboratory, a feasible approach to the major tricyclic framework of Taxol which could pave the way ultimately to Taxol. Hitherto approaches (ref. 14, 15) were there for Taxol

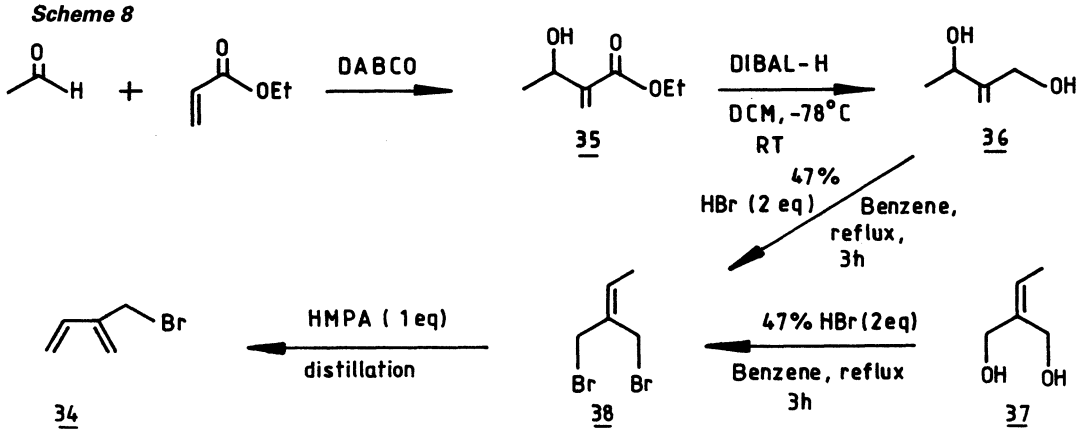
Scheme 7



a R=H
b R=CH_3

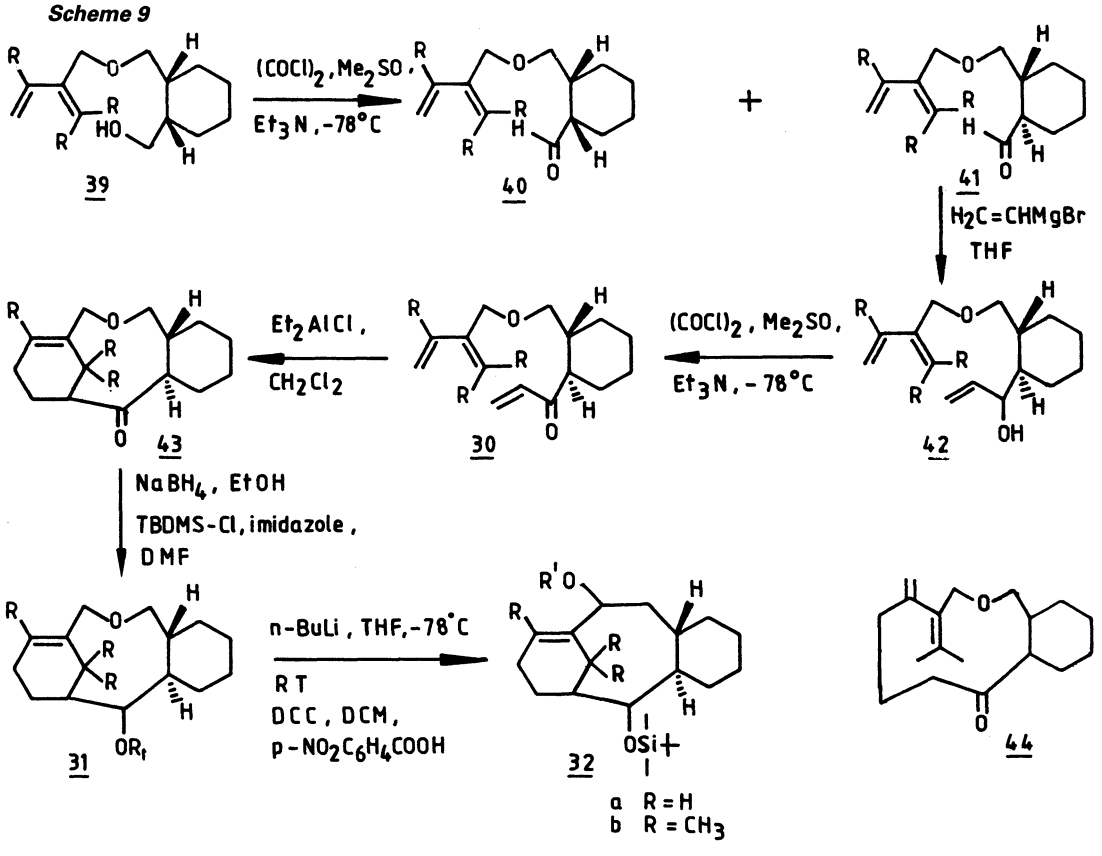
which lead to an unfunctionalized or partly functionalized central eight membered ring. Our approach centres around an intramolecular Diels -Alder reaction of **30a** whose retroanalysis leads to the diol **33** and the diene unit **34**. After unsuccessful attempts to obtain the diene unit by the reported procedures (ref. 17) involving didebromination of 2-bromoethyl-1,2-butene with zinc dust, we looked for an alternative approach as shown in scheme 8.

Scheme 8



Condensation of a homogenous mixture of freshly distilled acetaldehyde and ethyl acrylate using DABCO as catalyst afforded (ref.18) the olefin ester **35** in 90% yield. Treatment of the ester with DIBAL-H DIBAL-H gave the allylic diol **36** which was subsequently treated with hydrobromic acid in refluxing benzene to furnish the dibromide **38** which can also be obtained from diol **37**. Mono dehydrobromination of the dibromide by distilling with 1 eq. of HMPA gave the diene **34** in quantitative yield.

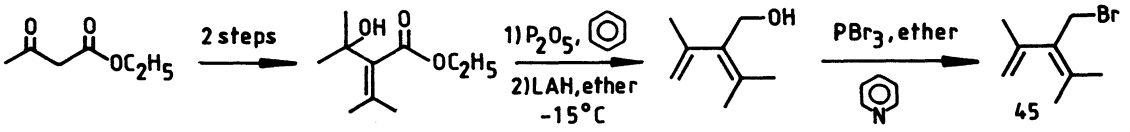
Scheme 9



Thus, selective mono O-alkylation of the diol **33** with the bromodiene **34** using one equivalent of NaH in THF gave the monoalcohol **39** in 70% yield (scheme 9). Swern oxidation of the alcohol **39** afforded a mixture of aldehydes in the ratio of 3:1. The aldehyde mixture was stirred overnight with sodium methoxide in methanol which gave a single isomer **41**. Treatment of the aldehyde **41** with vinyl magnesium bromide gave the allylic alcohol **42** which was then subjected to a Swern oxidation to realize ketone **30a**. IMDA reaction of the triene **30a** system using diethyl aluminium chloride at 0°C for ten minutes gave the tricyclic system in 45% yield. Prior to the Wittig rearrangement the ketone was reduced with sodium borohydride to the alcohol and later protected as its silyl ether **31a**. The key intramolecular Wittig rearrangement was performed with n-butyl lithium in THF to furnish **32a** the desired tricyclic framework of taxol.

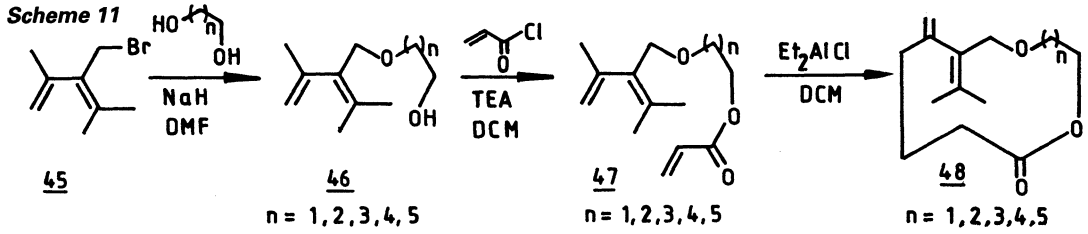
After obtaining the taxol skeleton through intramolecular Diels-Alder followed by Wittig rearrangement, we now aimed to make the fully functionalized taxol skeleton by using the same synthetic strategy as shown in scheme 7 and 9.

Scheme 10

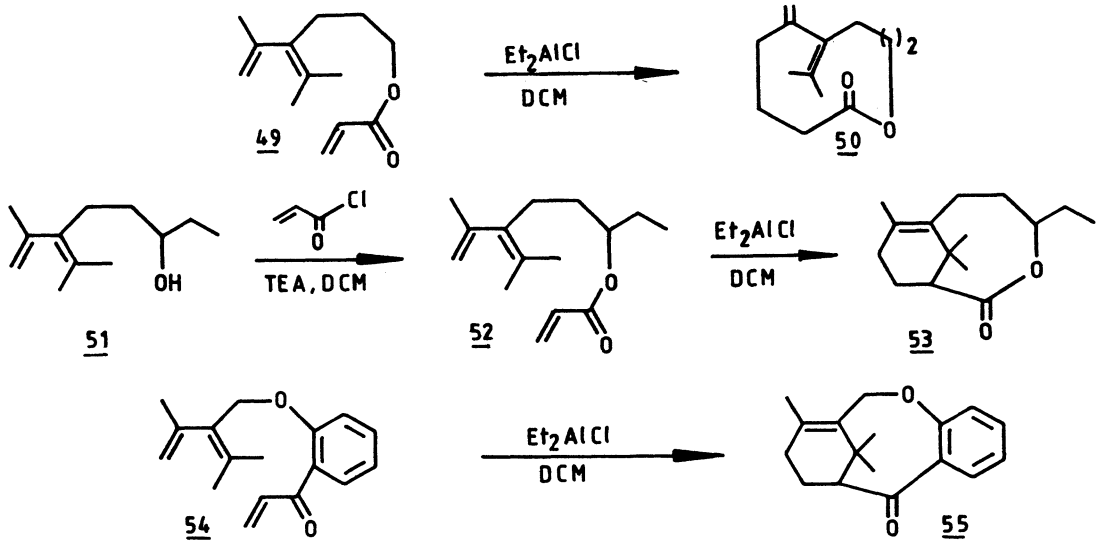


Diol **33** was mono-O-alkylated using diene bromide **45** (prepared as depicted in scheme 10), NaH and DMF, followed by Swern's oxidation, and vinyl Grignard gave **42b**, which on Jone's oxidation gave **30b**. Compound **30b** was subjected to IMDA reaction. But all efforts to cyclize **30b** (both thermal and catalytic methods under different conditions) to **43b** failed. Surprisingly, we have observed an intramolecular ene reaction leading to **44**.

Scheme 11



With the above result in hand, we have studied the ene vs. Diels-Alder reaction by preparing several substrates **47** (n=1, 2, 3, 4, 5) and subjecting them to the intramolecular reaction. In all the cases the reactants underwent the ene reaction, instead of the desired Diels-Alder reaction. Even **49** where the outer



ring would have been an eight membered ring also underwent the ene reaction. A close scrutiny of the literature (ref. 20, 21) suggests that the substituents at α and β to carbonyl of the dienophile induce the Diels-Alder reaction when the ring size formed is precisely eight membered. We, therefore, put a substituent at the β carbon atom with respect to the carbonyl of the dienophile as in **52** which underwent the Diels-Alder reaction. Likewise, **54** also underwent the Diels-Alder reaction leading to **55**. Now, we are doing theoretical calculations to rationalise these results.

We have now initiated a programme for a fully functionalized taxol skeleton employing an intramolecular Diels-Alder reaction based on the above results.

Acknowledgements

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REFERENCES

1. a) S. Omura, A. Nagakawa, K. Kushida, G. Lukacs, *J. Am. Chem. Soc.* **108**, 6088 (1986).
   b) S. Omura, A. Nagakawa, K. Kushida, H. Shimizu, G. Lukacs, *J. Antibiot.* **40**, 301 (1987)
2. T.R. Kelly, C. Jagoe, Q. Li, *J. Am. Chem. Soc.* **111**, 4522 (1989)
3. a) G. Mehta, Y. Venkateswarlu, *J. Chem. Soc., Chem. Commun.* 1200 (1988)
   b) K.A. Parkar, S.M. Ruder, *J. Am. Chem. Soc.* **111**, 5948 (1989)
   c) R.O. Duthaler, C. Heuberger, U.H.-U. Wegmann, V. Scherrer, *Chimia*, **39,** 174 (1985)
4. a) A.V. Rama Rao, K.K. Reddy, J.S. Yadav, A.K. Singh, *Tetrahedron Lett.* **32**, 5199 (1991)
5. J.B. Data, R.D. Bannett, *J; Med. & Pharm. Chem.* **4**, 327 (1961)
6. U. Lauk, P. Skrabal, H. Zollinger, *Helv. Chim. Acta* **66**, 1574 (1983)
7. Prepared from Asaronaldehyde (Fluka) by oxidation ($NaClO_2$, NH_2SO_3H), esterification (CH_2N_2) and selective mono demethylation to obtain the product in 65% yield.
8. A. McKillop, M.P. Swann, E.C. Taylor, *J. Am. Chem. Soc.* **93**, 4919 (1971)
9. a) W.S. Johnson, *Org. React.* **2**, 114 (1944)
   b) I. Agranat, Y.S. Shih, *Synthesis* 875, (1974) and references cited therein
10. a) C.N. Lewis, P.L. Spargo, J. Staunton, *Synthesis*, 944 (1986)
    b) S. Nahm, S.M. Weinreb, *Tetrahedron Lett.* **22**, 3815 (1981)
11. P. Jacob (III), P.S. Callery, A.T. Shulgin, N. Castagnoli Jr. *J. Org. Chem.* **41**, 3627 (1976)
12. M.C. Wani, H.L. Taylor, M.E. Wall, P. Coggon, A.I. McPhail, *J. Am. Chem. Soc.* **93**, 2325 (1971)
13. a) M.B. Lythgoe in "*The Alkaloids*" ed. R.H.E. Manske, **X**, 597 (1968), Academic Press.
    b) R.W. Miller, *J. Nat. Prod.* **43**, 425 (1980)
14. For extensive review on its synthesis see: C.S. Swindell, *Org. Prep. Proc. Int.* **23**, 465 (1991) and references cited therein.
15. a) P.A. Wender and T.P. Mucciaro, *J. Am. Chem. Soc.* **114**, 5878-79 (1992) and references cited therein
    b) Y. Queneau, W.J. Kroll, W.G. Bornmann and S.J. Danishefsky, *J. Org. Chem.* **57**, 4043-47 (1992)
    c) S.A. Hitchkock and G. Pattenden, *Tetrahedron Lett.* **33**, 4843 (1992) and references cited therein.
16. J.S. Yadav and R. Ravishankar, *Tetrahedron Lett.* **32**, 2629 (1991)
17. A.G. Martinez and J.L.M. Contelles, *Synthesis*, 742 (1982)
18. D. Basavaiah, T.K. Bharathi and V.V.L. Gowriswari, *Tetrahedron Lett.* **28**, 4351 (1987)
19. A.V. Rama Rao, J.S. Yadav, A.M. Naik and A.G. Chaudhary, *Tetrahedron Lett.* **27**, 933 (1986)
20. K.J. Shea, J.W. Gilman, C. D. Haffner and T.K. Dougherty, *J. Am. Chem. Soc.* **108**, 4953 (1986) and references cited therein.
21. R.V. Bonnert and P. Jenkins, *J. Chem. Soc., Chem. Commun.* 1540 (1987)