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A NOVEL APPROACH TOWARDS THE SYNTHESIS OF FUNCTIONALIZED TAXANE SKELETON EMPLOYING WITTIG REARRANGEMENT

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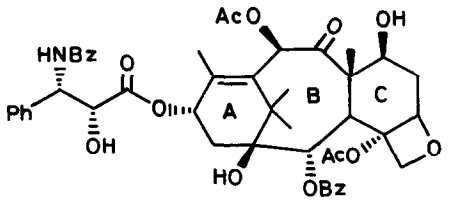
Abstract An expeditious synthesis of Taxol skeleton is described utilizing the combination of intramolecular Diels-Alder (IMDA) and Wittig rearrangement reactions.

Taxane class of compounds belonging to the group of diterpenoids[1] have been isolated from Taxus family, and are known for their structural complexity and powerful anti-tumor activity. Among those, Taxol (**1**)[2], isolated from the bark of western yew Taxus brevifolia, is an exceptionally promising cancer chemotherapeutic agent with a broad spectrum of potent antileukemic and tumor inhibiting activities and is currently undergoing phase II clinical trials.[3] Complex structural features of Taxol with a tricyclic ring system having 6+8+6 carbon framework possesses an unusual bridgehead olefinic bond and a plethora of functional groups which have made it a challenging synthetic target. Several elegant approaches have been reported[4,5,6] for its preparation. However, all of them are devoid of the proper functionalities in the central eight membered ring. We have now developed a method employing intramolecular Diels-Alder (IMDA)[7] reaction followed by Wittig rearrangement[8] rendering strategically situated hydroxy functionality in the central ring for the eventual elaboration.



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Central to our synthetic strategy is the intramolecular Wittig rearrangement of the oxatricyclic intermediate **3** to construct the taxane skeleton **4**. Our approach is delineated in Scheme I. The intermediate **3** could be obtained by the intramolecular Diels-Alder (IMDA) reaction of **2** which retrosynthetically leads to the known diol **5** and diene **6**.

Our attempts to prepare 2-bromomethyl butadiene **6** by reported procedure[9] involving reductive didebromination of 2-bromomethyl 1,4-dibromo-2-butene with zinc dust resulted in the forma-

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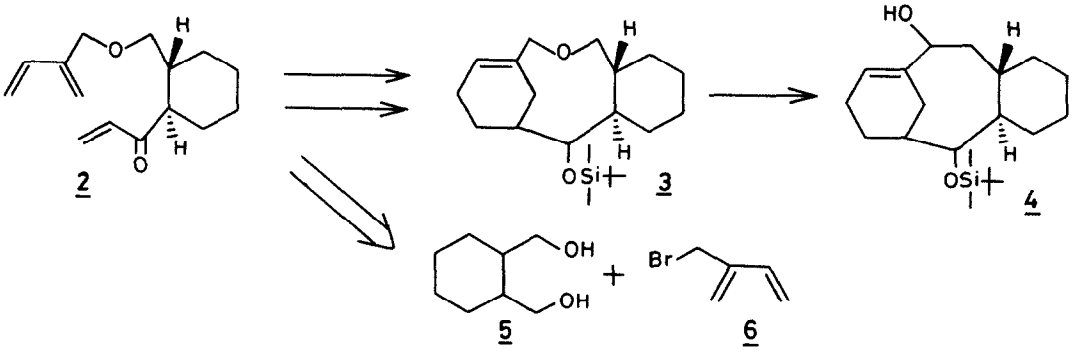
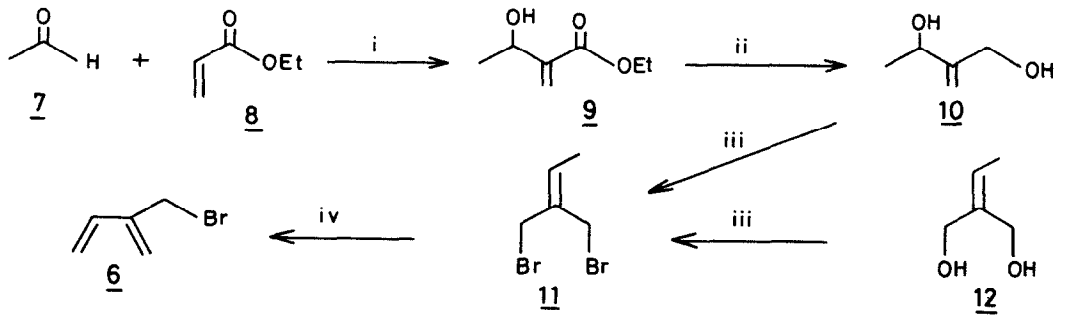
tion of mostly volatile materials and **6** could not be isolated in an acceptable yield. This prompted us to look for an alternative and efficient approach, which is elaborated in Scheme II.

Scheme I



Condensation of a homogeneous mixture of molar equivalent of freshly distilled acetaldehyde **7**, and ethyl acrylate **8** using DABCO[10a,b] as catalyst for seven days at room temperature afforded the olefin ester **9** in 90% yield. Treatment of the ester **9** with DIBAL-H gave the allylic diol **10** which was treated with hydrobromic acid in refluxing benzene to furnish the dibromide **11**. The intermediate **11** can also be obtained from the diol **12** reported by us earlier.[10c] Monodehydrobromination of the dibromide **11** by distilling with 1 eq. of HMPA gave the diene **6** in quantitative yield.

Scheme II

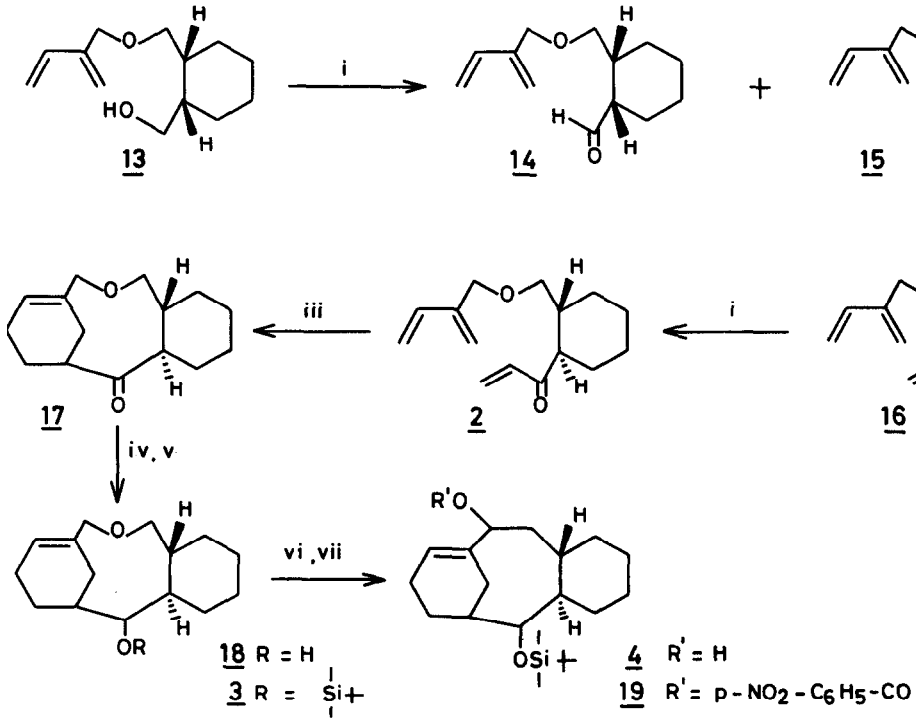


Reagents: i) DABCO ii) DIBAL-H, DCM, -78°C RT iii) 47% HBr(2 eq), Benzene, reflux, 3 h iv) HMPA (1 eq), distillation.

The approach for the intermediate **3** is shown in Scheme III. Selective mono O-Alkylation of diol **5** with diene **6** using one equivalent of NaH in THF gave the monoalcohol **13** in 70% yield. The efficacy of the diene unit in **13** is revealed by the fact that it serves dual purposes, as a protecting group for one of the alcohol moieties and as a diene unit for the construction of ring A at a later stage during IMDA reaction, thus avoiding the extra steps of protection and deprotection. Swern oxidation of the hydroxy function in **13** afforded a mixture of aldehydes[11] **14** and **15** in the ratio of 75:25. The aldehyde mixture was stirred overnight with sodium methoxide in methanol

which gave exclusively single isomer corresponding to the aldehyde **15**.

Scheme III



Reagents: i) $(COCl)_2$, Me_2SO, Et_3N, -78°C; ii) $H_2C{=}CHMgBr$, THF; iii) Et_2AlCl, CH_2Cl_2; iv) $NaBH_4$, EtOH; v) TBDMS-Cl, imidazole, DMF; vi) n-Buli, THF, -78°C RT; vii) DCC, DCM, p-$NO_2C_6H_4COOH$.

Treatment of the aldehyde **15** with vinyl magnesium bromide gave the allylic alcohol **16** in 80% yield which was subjected to Swern oxidation to realize ketone[12] **2**. IMDA reaction was best performed using diethyl aluminium chloride at 0°C during 10 minutes to give rise to the adduct[12] **17** in 45% yield. Prior to the Wittig rearrangement the ketone was reduced with sodium borohydride to the alcohol **18** which was later protected as its silyl ether **3**. The key Wittig rearrangement was performed with n-butyllithium in THF which furnished the anticipated product **4**[12] in 40% yield. Alcohol **4** was derivatized as p-nitrobenzoate (DCC, p.NO_2-$C_6H_4CO_2H$, DCM, rt, 12 h) which was crystallized twice to get m.p. 174°-175°C.

In conclusion, we have demonstrated here the preparation of Taxane skeleton by a novel and operationally feasible approach. This methodology may find wide applicability in the preparation of functionalized Taxane skeleton.

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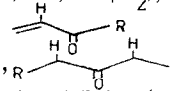
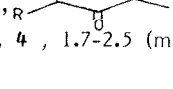
11. In the PMR spectrum ($CDCl_3$) the aldehyde protons were observed at 9.80 and 9.60 ppm integrating in the ratio of 3:1 for **14** and **15** respectively. Treatment of the above mixture with sodium methoxide in methanol afforded single isomerized product **15**.
12. Selected PMR data (90 MHz, $CDCl_3$, , J in Hz) : **2** (3.3 m, 2H, $-OCH_2$), 4.05 s, 2H, OCH_2), 5.0-5.5 (m, 4H, olefinic), 5.75 (dd, H, J = 9.6 and 3.0 Hz, ), 6.0-6.8 (m, 3H, olefinic). **17**, 2.05-2.80 (m, 4H, allylic), 2.85-3.07 (br, t, 2H, ), 3.10-3.75 (m, 2H, OCH_2), 3.87 (s, 2H, OCH_2), 5.95 (br d, olefinic), **4** , 1.7-2.5 (m, 4H, allylic), 4.07 (br s, -CHOTBDMS), 4.8 (br d, H, -CHOH).

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