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Selective Bond Cleavage of [5.3.1]Propellanes by Lead Tetraacetate : A Facile Entry into the Carbocyclic Frame [A,B Ring] of Taxol

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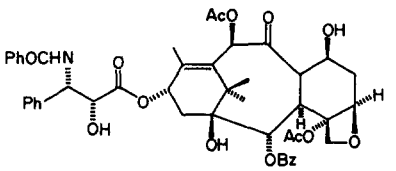
Abstract : *[5.3.1] Propellanes e.g., the tricyclo[5.3.1.0^{1,7}]undeca-2,4-dien-10-one* **8** *and the corresponding methylidene compound* **10** *were prepared from methyl cinnamate* **2** *in several steps involving rhodium(II) acetate mediated cyclization of* **4** *to* **6** *as a key step. The selective central cyclopropyl bond cleavage in* **8** *and* **10** *by lead tetraacetate provides the basis of a new approach to the construction of carbocyclic frame of A,B ring of Taxol.*

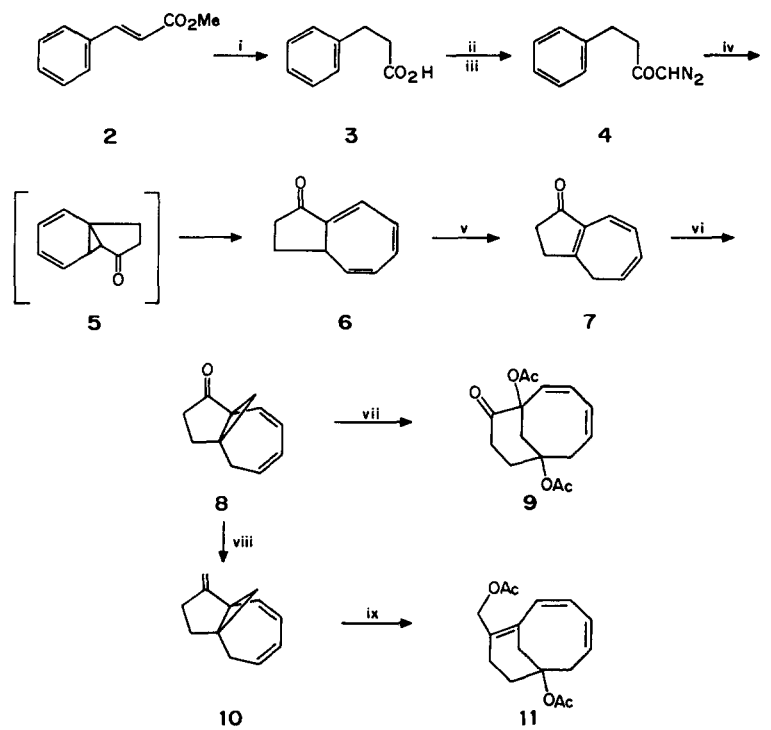
Taxol **1** is recognised worldwide as a promising antitumour chemotherapeutic lead, because of its successful clinical trials for the treatment of breast, head, neck and ovarian cancers. Recently, numerous synthetic strategies for its partial or total synthesis have been reported.[1-3] Its limited availability and synthetically challenging complex structure stimulated us to initiate a modest approach towards synthesising Taxol and/or its potent analogues. Herein, we wish to report a new route to the model A,B rings of carbocyclic frame of Taxol via propellanes where the issues of C-1 hydroxylation and bridgehead double bond are addressed.

The synthetic strategy for the preparation of [5.3.1]propellanes is illustrated in Scheme 1. Thus, methyl cinnamate **2** was subjected to catalytic hydrogenation using 10% Pd-C in ethylacetate, followed by ester hydrolysis to give 3-phenylpropionic acid **3** in quantitative yield.[4] Alternatively, **3** can be prepared from **2** under reflux in methanol : water mixture using Raney Nickel. The dihydrocinnamic acid **3** was converted into acid chloride by treatment with thionyl chloride. The subsequent treatment with diazomethane furnished the diazoketone **4** in 93% yield. When diazoketone **4** was heated with catalytic amount of rhodium(II) acetate in refluxing dichloromethane followed by treatment with triethylamine, the desired 3,4-dihydroazulene-1(2H)-one **7** was obtained in 89% yield.[5] The formation of **7** can be explained via **5** by initial intramolecular carbene addition to benzene, followed by base induced bond organisation of **6**. The nucleophilic cyclopropanation[6] of the trienone **7** using Corey's ylide in dimethyl sulfoxide gave the desired tricyclo[5.3.1.0^{1,7}]undeca-2,4-dien-10-one **8** in 76% yield; the structure of which was established based on analytical and spectroscopic evidences.



Scheme 1

1



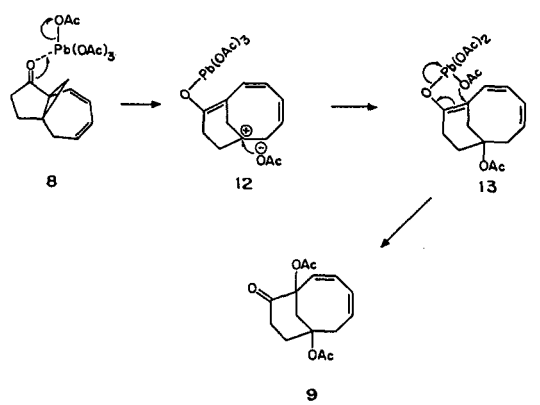
Scheme 1 *Reagents and conditions* : i, Raney Nickel, MeOH/H_2O, 10h, reflux or 10% Pd-C, EtOH, 30psi, 16h, 90%, aq.KOH-MeOH, 10h, reflux, 97% ; ii, $SOCl_2$, DMF, 2h, reflux, 97% ; iii, CH_2N_2, O°C then room temp., 4h, 93% ; iv, $[Rh(OAc)_2]_2$, CH_2Cl_2, reflux, 93% ; v, Et_3N, CH_2Cl_2, 1h, room temp., 89% ; vi, $(CH_3)_3SOI$, NaH, DMSO, 76% ; vii, LTA, AcOH, C_6H_6, 6h, reflux, 45% ; viii, Zn-CH_2Br_2-$TiCl_4$, THF, -20°C, 81% ; ix, LTA, AcOH, C_6H_6, O°C, then room temp., 3h, 35% .

Selective ring opening of activated cyclopropanes is useful tool in organic synthesis. It readily offers access to intermediates with a high degree of functionalisation and with efficient stereo- and regioselection. Our strategy towards creating A,B rings of carbocyclic frame of Taxol is mainly based on the central cyclopropyl bond cleavage in [5.3.1] propellanes by electrophile - assisted nucleophilic addition. A variety of reagents e.g., TMSOTf,[7] AcOH-NaOAc,[8] Na-Liq.NH_3,[9] $Br_2/NaOCH_3$[10] and Zn-AcOH[11] have been employed for this purpose. Thus, when compound **8** was subjected to treatment with trimethylsilyl triflate in toluene at low temparature, the desired product could not be obtained. The Warner's method[8] of central propellane bond cleavage by sodium acetate/acetic acid under varying reaction conditions did not yield the desired product. Alternatively, the reductive cleavage by zinc /acetic acid[11]

and photo-induced electron transfer method[12] were also a failure. However, the reaction of **8** with lead tetraacetate and acetic acid in refluxing benzene afforded the 1,7-diacetoxy bicyclo[5.3.1]undeca-2,4-diene-10-one **9**[13] in 45% yield.

Similarly, the selective bond cleavage of propellane was also examined with another model 8-methylidene tricyclo[5.3.1.0^{1,7}]undeca-3,5-diene **10**[13] which in turn was prepared from **8** by treatment with zinc dust, titanium tetrachloride and dibromo methane (Lombardo reaction)[14] in tetrahydrofuran in about 81% yield. Compound **10**, being unstable, was used without further purification. The treatment of **10** with lead tetraacetate in acetic acid in benzene at O°C afforded the desired 1-acetoxy-8 methylacetoxy bicyclo[5.3.1]undeca-3,5,7-triene **11**[13] in 35% yield along with some unidentified impurities which could not be separated even with repeated column chromatography.

A plausible mechanism for the cyclopropyl bond cleavage with lead tetraacetate is delineated in scheme 2. Presumably, the cleavage reaction proceeds via the ion pair $Pb^{+}(OAc)_3$ ^{-}OAc as described by Robins et al.[15] in oxidation studies with $Hg(OAc)_2$ and $Tl(OAc)_3$. The reaction of **8** with lead tetraacetate following a SN_2 displacement mechanism by the loss of acetate ion may in fact be more of a concerted process. As a result, the departing acetate ion becomes attached to the developing carbonium ion centre at the tertiary carbon (bridgehead carbon) in **12** and back to polarisation gives diacetate compound **9**.



Scheme - 2

In summary, the selective bond scission of [5.3.1]propellanes has been successfully demonstrated which provides an easy access to the A,B ring of Taxol. The strategy described here has significant potential of creating highly advanced skeletons for Taxol. Thus, we are currently investigating the application of this process for the carbocyclic frame of Taxol from the appropriately functionalised and substituted benzene ring of **4**.

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13. All new compounds were fully characterised on the basis of their spectra and analytical data. Selected spectral data : **9** (semi-solid) ; IR ν_{max}/cm^{-1}($CHCl_3$), 3000(s), 2930(s), 1760(vs), 1730(s), 1480(s), 1450(m) ^1H NMR(200 MHz;$CDCl_3$) : δ 2.05(s,6H,2 OAc), 2.1(m,2H), 2.4-2.6(m,4H), 2.7(m,2H), 4.9(m,1H), 5.5-5.62(m,2H), 5.9(m,1H). ^{13}C NMR(200 MHz;$CDCl_3$) : δ208.97(CO,s), 170.36(s), 169.74(s), 129.09(d), 128.02(d), 127.00(d), 123.30(d), 72.20(s), 71.44(s), 31.64(t), 36.76(t), 35.31(t), 32.31(t), 20.94(q,2C,$COCH_3$). MS : m/z(%) 219(5), 203(16), 172(35), 144(50), 129(100), 117(68), 91(27). **10** : ^1H NMR(200 MHz;$CDCl_3$) : δ 0.9(d,1H), 1.7(d,1H), 1.72-2.2(m,4H), 2.6(d,2H), 5.6(m,2H), 5.9(m,1H), 6.4(d,1H). MS : m/z(%) 158(M^+,34), 143(100), 129(70), 117(27). **11**(colorless oil) ; IR ν_{max}/cm^{-1}($CHCl_3$), 2985(s), 1740(vs), 1445(m), 1380(s). ^1H NMR(200 MHz;$CDCl_3$) : δ 1.95-2.1(m,6H), 2.15(s,6H,OAc), 2.4(m,2H), 4.55(m,2H), 5.5-5.8(m,3H), 6.25(m,1H). MS : m/z(%) 217(18,-OAc), 190(14), 157(20), 144(51), 117(100),79(10).
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