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Taxol Synthesis : Synthesis of A-ring and a Methodology for Substituted cyclohexadienes

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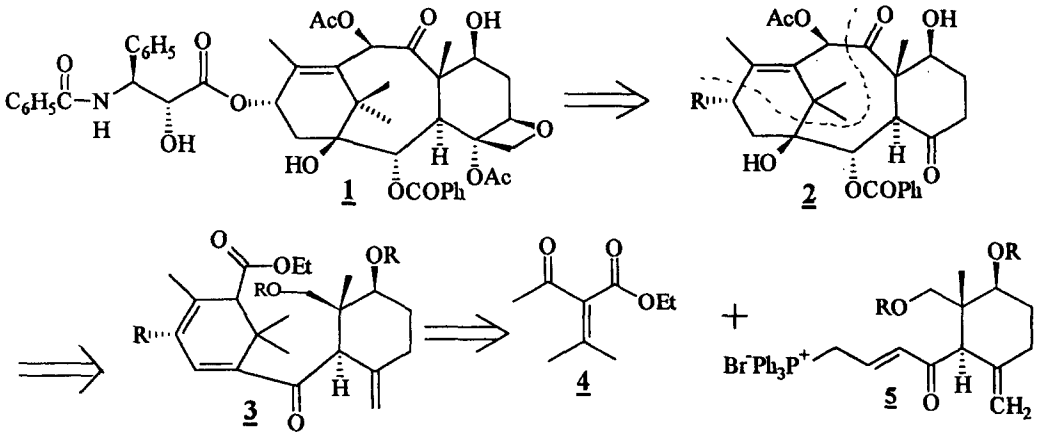
Abstract: A fully functionalised synthesis of taxol A-ring, through Michael/Wittig reaction and regioselective opening epoxide as key steps and also a methodology for substituted cyclohexadienes through tandem Michael/Wittig reaction is described.

Taxol, a substance originally isolated[1] from the Pacific yew tree Taxus brevifolia, more than two decades ago, has recently been approved for the clinical treatment of cancer and is considered as one of the most significant advances in chemotherapy. This molecule exerts its anti cancer activity by inhibiting mitosis through enhancement of the polymerisation of tubulins and consequent stabilization of microtubules. The scarcity of Taxol and the ecological impact of harvesting it have prompted an extensive search for alternative sources including semisynthesis, cell culture and chemical synthesis. Apart from its activity, it has gained prominence owing to its extremely complex structure with a plethora of functionalities, prominently the bridgehead olefin in ring A, highly functionalized ring B and the very sensitive oxetane ring D fused to ring C. Several strategies towards taxol synthesis proceeding from A to ABC rings have been reported.[2,3] Herein,

Scheme-1



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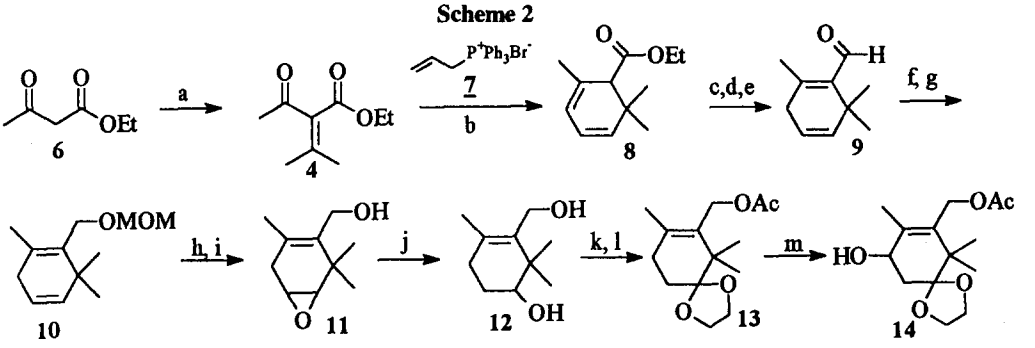
we report a strategy proceeding from right to left (C to A ring), to the functionalised tricyclo (9,3,1,0) pentadecene skeleton of taxol making use of the Michael/Wittig and pinacol coupling as the key steps. The retrosynthetic analysis is depicted in scheme 1 where in the functionalised A ring of the key intermediate can be elaborated from a Michael/Wittig reaction of the fragment 4 with the fragment 5.

This communication details, our efforts towards the synthesis of substituted cyclohexadienes and its further transformation into fully functionalised A ring of taxol[4] (scheme.2)

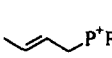
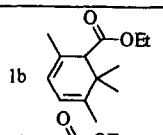
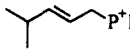
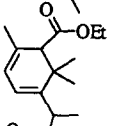
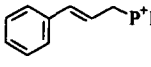
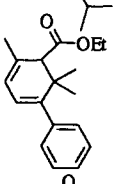
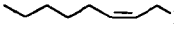
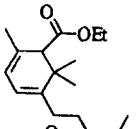
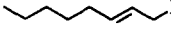
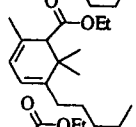
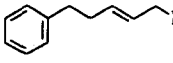
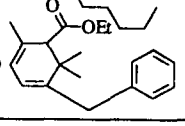
Scheme 2



a) $(CH_2)_2C{=}O/Ac_2O/Zn/ZnCl_2$ 48% b) n-BuLi/Et_2O 85% c) DIBAL-H/DCM 72% d) $(COCl)_2$, DMSO/Et_3N/THF 68% e) DBU/DCM 89% f) $NaBH_4/CeCl_3.7H_2O$/MeOH 90% g) MOM-Cl/Et_3N/DCM 95% h) mCPBA/DCM 85% i) *PTSA*/MeOH 90% j) LAH/THF 77% k) Ac_2O/Et_3N/DCM 95% l) PTSA/$(CH_2{-}OH)_2$/Ph-H 88% m) SeO_2/Dioxane/H_2O (5:1) 73%

Ethyl acetoacetate was condensed with acetone in the presence of $ZnCl_2$ and Ac_2O to furnish 4

Table

Entry	Wittig salt	Product	Yield %
1.		 1b	90
2.			85
3.		 3b	75
4.			69
5.			70
6.		 6b	62

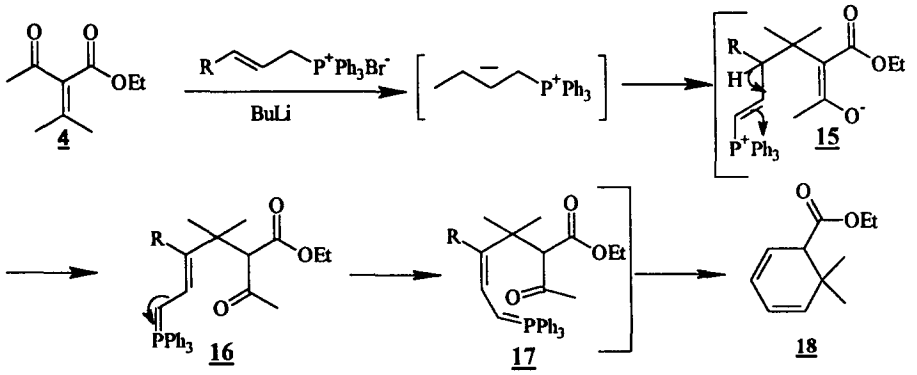
which was reacted with the allyl anion generated from the allyl Wittig salt by reaction with n-BuLi to afford 8. The compound 8 was then converted to the aldehyde in a two step sequence and isomerised using DBU to afford the conjugated aldehyde 9. The aldehyde 9 was converted to alcohol which was protected as its MOM ether 10. Epoxidation with mCPBA followed by MOM deprotection using *P*TSA/MeOH afforded the less substituted epoxide 11. Regioselective opening of the epoxide using LAH conditions afforded 12. The primary alcohol was protected as its acetate and the secondary alcohol functionality oxidised under Swern conditions to the ketone and protected as its ketal using *P*TSA/ethylene glycol afforded 13. Finally oxidation of 13 using SeO_2 afforded the functionalised A ring[4] 14.

In the above scheme 2, the second step is the tandem Michael/Wittig reaction. Even though it was reported by Alkonyi et al (1967) and Wuest et al (1971),[5] as an extension of their method, here, we have carried out a reaction with substituted allylbromide Wittig salt to give a substituted cyclohexadiene which would serve for the functionalisation of C_1 of taxol. Thus crotyl bromide Wittig salt, treated with n-BuLi at 0 °C with 5 afforded the substituted cyclohexadiene in excellent yield. In order to generalise the reaction and check the functional group compatibility, different allylbromide Wittig salts were prepared and subjected to Michael/Wittig reaction and the corresponding cyclohexadienes were obtained in good yields.[6] (Table)

The possible mechanism is depicted in scheme 3. The generated allyl anion undergoes Michael addition with compound 4 to give the intermediate 15 and it further rearranges[5] through 1,5 sigmatropic shift may afford the phosphonium betaine, proton transfer to the ylide followed by intramolecular Wittig condensation could afford the substituted cyclohexadienes.

Scheme-3

Mechanism



Thus, in conclusion it has been amply demonstrated that this new strategy definitely helps to make analogues of taxol. Based on the above strategy the synthetic studies on taxol are currently underway in our laboratory.

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Reference and notes :

1. Wani, M.C.; Taylor, H.L.; Wall, M.E.; Coggon, P.; McPhail, A.T. *J. Am. Chem. Soc.* **1971,** *93*, 2325-2327.
2. The total syntheses of taxol have recently appeared: a) Nicolaou, K.C.; Yang, Z; Liu, J.; Ueno, H.; Nantermat, P.; Guy, R.; Claiborne, C.; Reneaud, J.; Couladouros, E.; Paulvannan, K.; Sorensen, E. *Nature* **1994**, 367, 630. b) Holton, R.A. ; Somoza, C.; Kim, H.; Liang, F.; Biediger, R.; Boatman, P.; Shindo, M.; Smith, C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K.; Gentile, L.; Liu, J. *J. Am. Chem. Soc.* **1994**, 116, 1597. c) Danishefsky, S.J.; Masters, J.J.; Young, W.B.; Link, J.T.; Synder, L.B.; Magee, T.V.; Jung, D.K.; Isaacs, R.C.A.; Bornmann, W.G.; Alaimo, C.A.; Coburn, C.A. and Di Grandi, M.J. *J. Am. Chem. Soc.* **1966**, 118, 2843. d) Wender, P.A.; Badham, N.F.; Conway, S.P.; Florancig, P.E.; Glass, T.E.; Houze, J.B.; Krauss, N.E.; Lee, D.; Marquess, D.G.; McGrane, P.L.; Meng, W.; Natchus, M.G.; Shuker, A.J.; Sutton, J.C. and Taylor, R.E.; *J. Am. Chem. Soc.* **1997**, 119, 2757; e) Nicolaou, K.C.; Nantermet, P.G.; Ueno, H.; Guy, R.K.; Couladouros, E.A.; Sorensen, E.J.; *J.Am. Chem. Soc.* **1995**, 117, 624. f) Nicolaou, K.C.; Liu, J.J.; Yang, Z.; Ueno, H.; Sorenson, V.J.; Claiborne, C.F.; Guy, R.K.; Hwang, C.K.; Nakada, M.; Nantermet, P.G.; *J. Am. Chem. Soc.* **1995**, 117, 634; g) Nicolaou, K.C.; Yang, Z.; Liu, J.J.; Nantermet, P.G.; Claiborne, C.F.; Renaud, J.; Guy, R.K.; Shibayama, K.; *J. Am. Chem. Soc.* **1995**, 117, 645; h) Nicolaou, K.C.; Ueno, H.; Liu, J.J.; Nantermet, P.G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R.; *J. Am. Chem. Soc.* **1995**, 117, 653 and references cited therein.
3. For excellent recent reviews on the synthesis taxanes, see a) Boa, A.N.; Jenkins, P.R.; Lawrence, N.J. *Contemporary Organic Synthesis* **1994**, 47. b) Nicolaou, K.C.; Dai, W.; Guy, R. *Angew. Chem. Intl. Ed.* **1994**, 33, 15. c) Swindell, C.S. *Org. Prep. Proc. Intl.* **1992**, 23, 465.
4. a) Nicolaou, K.C.; Hwang, C.K.; Sorensen, E.J. and Clairborne, J. *Chem. Soc. Chem. Commun.* **1992**, 1117. c) Queneau, Y.; Krol, W.J.; Bornmann, W. J. and Danishefsky, S.J.; *J. Org. Chem.*, **1992**, 57, 4043. d) Kitagawa, I.; Shibuya, H.; Fujioka, M.; Kajiwara, A.; Tsuji, S.; Yamamoto, Y. and Takagi, A. *Chem. Lett.*, **1980**, 1001. e) Pettersson, L.; Frejd, T.; Magnusson, G.; *Tetrahedron Lett.*, **1987**, 28, 2753. f) Lin, J.; Nikaido, M.M. and Clark, G. *J. Org. Chem.* **1987**, 52, 3745. g) Yuding and Jiang, X.R.; *J. Chem. Soc. Chem. Commun.* **1995**, 1693. h) Alcarag, L.; Harnett, J.J.; Mioskowski, C.; Gall, L.J.; Shin, D.S. and Falck, J.R. *J. Org. Chem.* **1995**, 60, 7209. i) Koskinon. *Tetrahedron*, **1995**, 51, 7555. j) Kishi, Y; Kregs, H.M.; *Tetrahedron Lett.*, **1995**, 36, 4583.
5. a) Alkonyi, I. and Szabo, D. *Chem. Ber.* **1967**, 100, 2773. b)Wuest, H. and Buchi, G. *Helv. Chim. Acta*, **1971**, 54, 1765. c)Youssef, L.B. and Marcus, F.B. *J.Org. Chem.* **1995**, 60, 1195.
6. Notes : Compound ^{1}H NMR ($CDCl_3$) : δ a) **1b** 1.02 -1.2 (2 s, 6 H), 1.3 (t, 3 H), 1.9 (s, 3 H), 2.3 (S, 1 H), 4.2 (q, 2 H), 5.3- 5.5 (two doublets, 2 H, J=4.5 Hz), b) **3b** 1 -1.2 (2 s, 6 H), 1.3 (t, 3 H), 1.7-1.8 (s, 6 H), 2.3 (s, 1 H), 4.2 (q, 2 H), 5.3 - 5.4 (d, 2 H, J=10.17, 13.55), 7.1 (m, 5 H). c) **6b** 1.02 -1.2 (2 s, 6 H), 1.3 (t, 3 H), 1.8 (s, 3 H), 2.3-2.4 (m, 3 H), 4.2 (q, 2 H), 5.4 - 5.5 (two doublets, 2 H, J=4.66), 7.1 (m, 5 H) d) **14** 1.01 (s, 3H), 1.09 (s, 3H), 1.09 (s, 3H), 1.5-1.65 (m, 2H), 1.85 (s, 3H), 2.07 (s, 3H), 3.80-3.95 (m, 1H), 3.97-4.10 (m, 4H), 4.6 (s, 2H)

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