Pergamon

Tetrahedron Letters, Vol. 35, No. 21, pp. 3617-3620, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

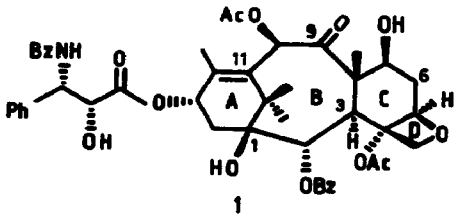
0040-4039(94)E0606-X

First and Stereocontrolled Entry to C-7 Hydroxy Functionality of Taxanes Employing Boord Reaction

Yadav, J S*, Ravishankar Renduchintala and Lakshman Samala
Indian Institute of Chemical Technology, Hyderabad-500007, India

Abstract: *Synthesis of a highly functionalized taxol skeleton core making use of Diels-Alder and a novel oxygen bridge opening strategies leading to functionalized C-ring is described.*

Taxol **1**, an antineoplastic agent belonging to a class of diterpenoids was isolated from the bark of pacific yew, Taxus brevifolia.[1] Eversince the serendipitous discovery of its activity, taxol has occupied the centre stage among scientific circles owing to its exceptional cancer chemotherapeutic activity against various cancer types in addition to possessing complex structural and stereochemical features. At the conclusion of Phase II clinical trials, it has demonstrated remarkable degree of activity in patients with advanced refractory ovarian cancer[2] resistant to cisplatin and is being developed as a drug in the management of epithelial ovarian cancer. Among the parameters for the potent biological activity of taxol are the unique C-ring features which constitute the extremely labile C-7 hydroxy functionality[3] and highly sensitive oxetane ring D fused to ring C. Lack of any of these C-ring features results in much lowered activity of the molecule. Construction of the C-ring functionalities has become an ardous task and a matter of synthetic challenge. Of the strategies mentioned hitherto on Taxanes[4] with particular reference to taxol, approach for the formation of C-7 hydroxy functionality received much less attention.



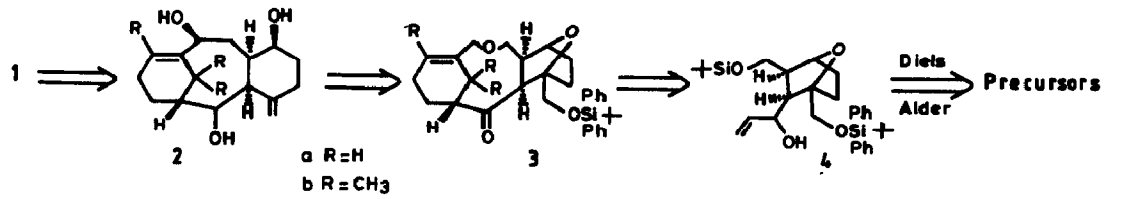
1

In continuation of our taxol synthesis programme,[5] we relied on a method to construct the C-7 hydroxy group and concurrent formation of exocyclic olefin on C-ring **2** which provides a perfect handle for further manoeuvre to the four membered oxetane ring. To this end, we report an elegant stereocontrolled formation of C-7 hydroxy group on C-ring with the concomitant formation of exocyclic olefin via a Zn dust induced[6] opening of oxygen bridged tetracyclic system **20** leading to **21**, the first such report on taxol.

IICT Communication No.3330.

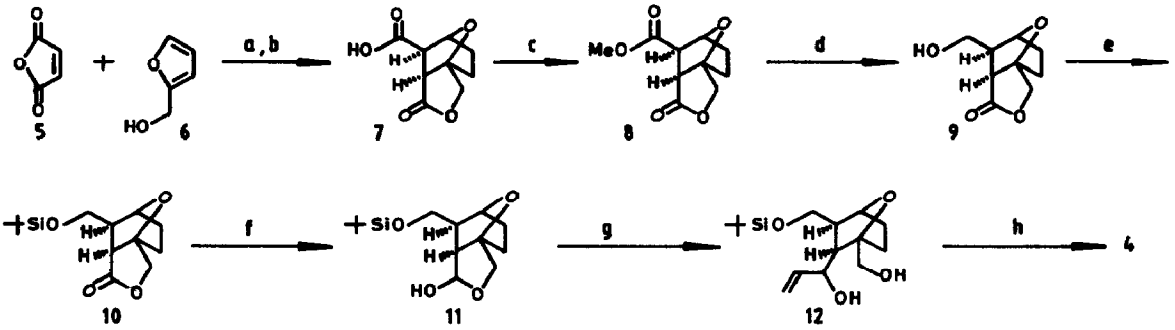
Accordingly, the following retrosynthetic disconnection reveals our strategy (scheme 1).

Scheme 1



The initial efforts were directed towards synthesising the intermediate 4 starting from Diels-Alder precursors 5 and 6 (scheme 2). Thus, cyclisation[7] between furfuryl alcohol 5 and maleic anhydride 6 by stirring in anhydrous ether for 24 h followed by immediate hydrogenation of the unstable adduct afforded the oxabicyclic system 7.

Scheme 2



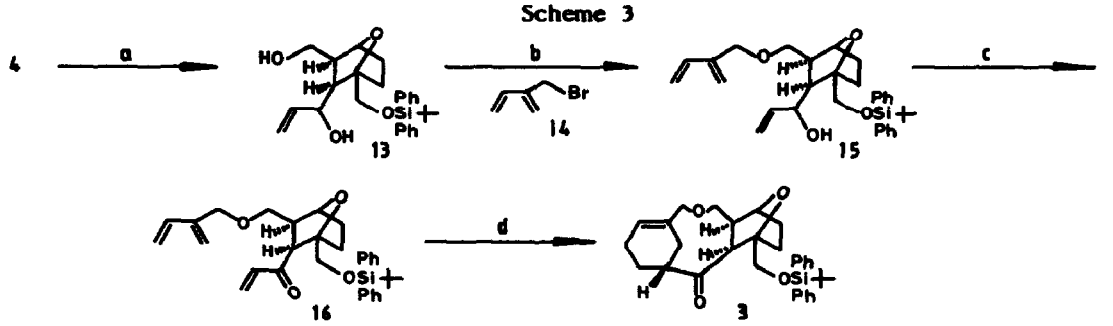
Reagents and conditions: a) Anhydrous ether, 25°C, 24 h; b) H_2/Pd-C, EtOH; c) CH_3COCl:MeOH (1:20), 12 h; d) $NaBH_4$ (1.1 eq), EtOH, rt, 3 h; e) TBDMS-Cl/ imidazole, DCM, 1 h; f) DIBAL-H (1 eq), DCM-78°C; g) MgBr/THF; h) TBDPS-Cl/ imidazole, DCM, 2 h.

The acid group of 7 was converted in quantitative yield to its methyl ester 8 on treatment with methanolic HCl. Methyl ester was selectively reduced[8] without affecting the lactone functionality to its corresponding alcohol 9 with $NaBH_4$ in ethanol in 65% yield. The primary alcohol of 9 was then protected as its silyl ether 10 by treating with TBDMS-Cl using imidazole in dry DCM. Lactone 10 was reduced to lactol 11, then vinyl Grignard treatment of 11 afforded the diol 12. Primary alcohol of 12 was protected with TBDPS-Cl using imidazole in dry DCM, which yielded compound 4#.

After obtaining intermediate 4, the route for compound 3 is delineated in scheme 3. Thus, selective deprotection of TBDMS group without affecting the TBDPS group in 4 was performed by treating with catalytic amount of PPTS in absolute ethanol[9] at 50°C for 1 h to provide synthon 13# in 70% yield. Treatment of diol 13 with one equivalent

of NaH in dry THF and then quenching the anion with diene **14** gave the mono-O-alkylated product **15** in 75% yield. Swern oxidation of the secondary alcohol **15** afforded trienone **16**. IMDA reaction of **16** using diethyl aluminium chloride at -78°C resulted in the Diels-Alder product **3**# in 60% yield.

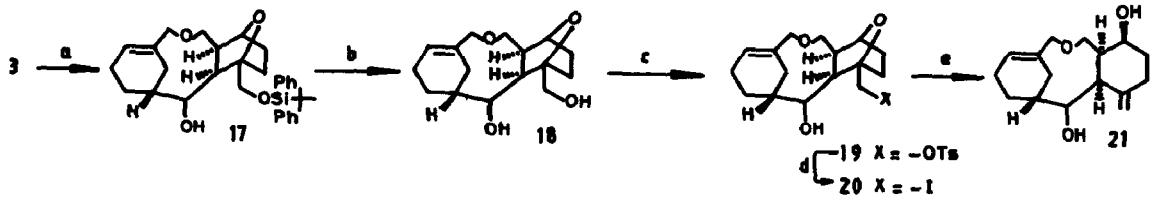
Scheme 3



Reagents and conditions: *a) PPTS (Cat), EtOH (abs), 50°C, 1 h; b) NaH (1 eq), THF, then 14; c) $(COCl)_2$, DCM, -78°C, DMSO, TEA; d) Et_2AlCl, DCM, -78°C*

The final efforts towards obtaining C-ring functionalities is shown in scheme 4.

Scheme 4



Reagents and conditions: *a) $NaBH_4$/MeOH; b) n-Bu_4NH, THF; c) PTS-Cl (1 eq), TEA, DCM; d) NaI (1.2 eq), CH_3CN, reflux; e) Zn dust, EtOH (abs), reflux, 1 h.*

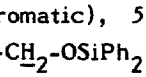
Before performing the key Boord reaction, ketone of **3** was reduced to the secondary alcohol **17** using $NaBH_4$ in methanol. Silyl group deprotection of **17** using n-Bu_4NF in aq THF gave diol **18**, primary alcohol of which was converted to the iodide **20** via the tosylate **19** by treating **19** with NaI in refluxing acetonitrile. Finally, refluxing the iodo compound **20** with freshly activated Zn dust in absolute ethanol for 1 h delivered the tricyclic system **21**# with a stereocontrolled formation of the C-7 hydroxy and the simultaneous formation of exocyclic olefin. Ring contraction of the central nine membered ring to the required eight membered ring found in taxanes was already demonstracted in our earlier communication.[5] Further work for the fully methylated A-ring and elaboration of the exocyclic olefin to four membered oxetane ring is under progress.

Acknowledgements: This project is generously funded from a grant No.DST/N-USHRF-(138)/86 of PL 480 (NIH) and CSIR, New Delhi.

References:

1) Wani, M.C.; Taylor, H.L.; Wall, M.E.; Coggon, P.; McPhail, A.I. *J. Am. Chem. Soc.* **1971**, *93*, 2325.
2) McGuir, W.P.; Rowinsky, E.K.; Rosenshein, B.B.; Grumbine, F.C.; Ettinger, D.S.; Armstrong, D.K. and Donehower, R.C. *Ann. Int. Med.* **1990**, *111*, 273, Holmes, F.A.; Walters, R.S.; Rheriault, P.C.; Forman, A.O.; Newton, K.; Raber, M.N.; Buzdar, A.V.; Frye, D.K.; Hortobagyi, G.N. *J. Natl. Cancer Inst.* **1991**, *83*, 1797 and references cited therein.
3) Kingston, D.G.I. *Pharmac. Ther.* **1991**, *52*, 1.
4) (a) For review on synthetic approaches to taxol and related compounds, see: Swindel, C.S. *Org. Prep. Proc. Intl.* **1991**, *23*, 245.
   (b) Swindel, 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.
5) Yadav, J.S. and Ravishankar, R. *Tetrahedron Lett.* **1991**, *32*, 2629.
6) Soday, F.J. and Boord, C.E. *J. Am. Chem. Soc.* **1933**, *55*, 3293.
7) Pelter, A.; and Singaram, B. *Tetrahedron Lett.* **1982**, *23*, 245.
8) Tauiguchi, M.; Koga, K.; Yamoka, S. *Tetrahedron* **1974**, *30*, 3547.
9) Chandrapraksh, Senior Salen and Blair, I.*Tetrahedron Lett.* **1989**, *30*, 19.

#Selected ^{1}H-NMR data: (200 MHz, $CDCl_3$, ,J in Hz):

3: 7.6 (m,5H,aromatic), 7.3 (m,5H,aromatic), 5.65 (brd,1H,olefinic), 4.1 (d,J=4.44 Hz,-C<u>H</u>-C-O-C), 4.0-3.4 (m,6H,C=C-C<u>H</u>$_2$-OSiPh$_2$), 2.9-2.8 (m,2H, ), 2.4-2.05 (m,4H,allylic), 1.7-1.45 (m,6H,3x-C<u>H</u>$_2$-), 1.2 [s,9H,SiC(C<u>H</u>$_3$)$_3$].

4: 7.55 (m,5H,aromatic), 7.25 (m,5H,aromatic), 5.7-5.55 (dd,J=4.1,5.7,4.1,1H,HOCH-C<u>H</u>=CH$_2$-OH), 4.05-3.85 [ABq,J=11.4 Hz,2H,<u>H</u>C-OSi(Ph)$_2$], 3.85-3.80 (ddd,J=3.4,5.3 Hz), 2.15-1.95 (m,2H,C-C<u>H</u>-C-), 1.7-1.45 (m,4H,2xC<u>H</u>$_2$-), 0.95 [s,9H,Ph$_2$Si-C(C<u>H</u>$_3$)$_3$], 0.8 [s,9H(CH$_3$)$_2$-Si(C<u>H</u>$_3$)$_3$], 0.1 [s,6H,H-Si(C<u>H</u>$_3$)$_2$].

13: 7.4 (m,5H,aromatic), 7.2 (m,5H,aromatic), 5.90-5.70 (ddd,J=4.60,5.40 Hz,1H, HOHC-C<u>H</u>=CH$_2$-), 5.2-4.90 (m,2H,-HC=C<u>H</u>$_2$), 4.55 (d,J=5.83 Hz,1H,-C-C<u>H</u>-O-C-), 4.5 (m,1H,HO-C<u>H</u>-CH=C<u>H</u>$_2$-), 4.1-3.9 [ABq,J=4.0 Hz,4H,C<u>H</u>$_2$-O-Sil(Ph)$_2$,C<u>H</u>$_2$-OH], 2.3-2.1 (m,2H,C-C<u>H</u>-C-), 1.85-1.55 (m,4H,-C<u>H</u>$_2$-C<u>H</u>$_2$-), 1.08 [s,9H,SiC(C<u>H</u>$_3$)$_3$].

21: 5.58 (brd,1H,CH$_2$-C<u>H</u>-), 4.79 (s,1H,-C<u>H</u>=C-), 4.72 (s,1H,-<u>H</u>C=C-), 4.0 (dt,J=5.2, 10.4 Hz,1H,-CH-C<u>H</u>-OH-CH$_2$-), 3.65-3.45 (m,5H,-C=C-C<u>H</u>$_2$-O,HC-C<u>H</u>-OH-CH,O-C<u>H</u>$_2$-C-), 2.8 (dd,1H,C=C-C<u>H</u>-), 2.5-2.0 (m,9H,allylic 3xC=C-C<u>H</u>$_2$-,3xC-C<u>H</u>-C), 1.45-1.25 (m,4H,2x-C<u>H</u>$_2$-).

All the intermediates gave expected spectral data including HRMS.

(*Received in UK* 20 *December* 1993; *revised* 7 *March* 1994; *accepted* 24 *March* 1994)