Pergamon

Tetrahedron Letters, Vol. 35, No. 21, pp. 3621-3624, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0607-Y

A Facile Stereocontrolled Synthesis of Taxol CD Rings

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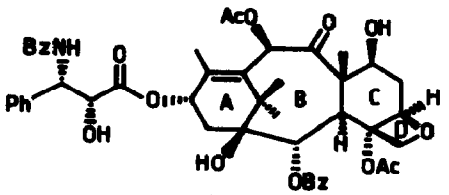
Abstract: *The crucial highly functionalized CD substructure of taxol has been synthesized featuring a stereocontrolled Boord reaction and stereoselective Sharpless allylic oxidation sequence leading to oxetane formation.*

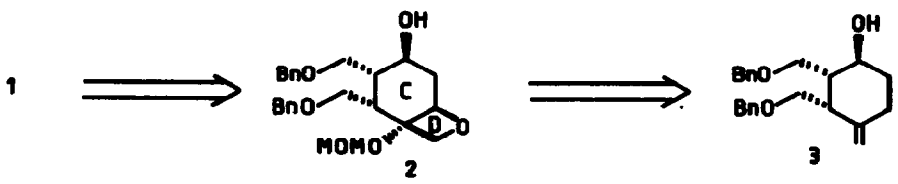
In the preceding communication,[1] we demonstrated the taxane tricycle synthesis encompassing an exocyclic double bond on ring C as a strategically situated appendage for the transformation to oxetane ring, which is structurally unique and a requisite system for the biological activity of taxol 1. Chemically sensitive oxetane formation has been the subject of intense independent synthetic studies,[2] leading to some effective methods. In the present communication, we report an expedient synthesis of the highly functionalized system 2 corresponding to the CD rings of taxol.



1

A careful retrosynthetic disconnection of taxol 1 outlined in scheme 1 unravels the CD substructure 2 as the crucial intermediate which could then be retrosynthetically traced to the key building block 3.

Scheme 1

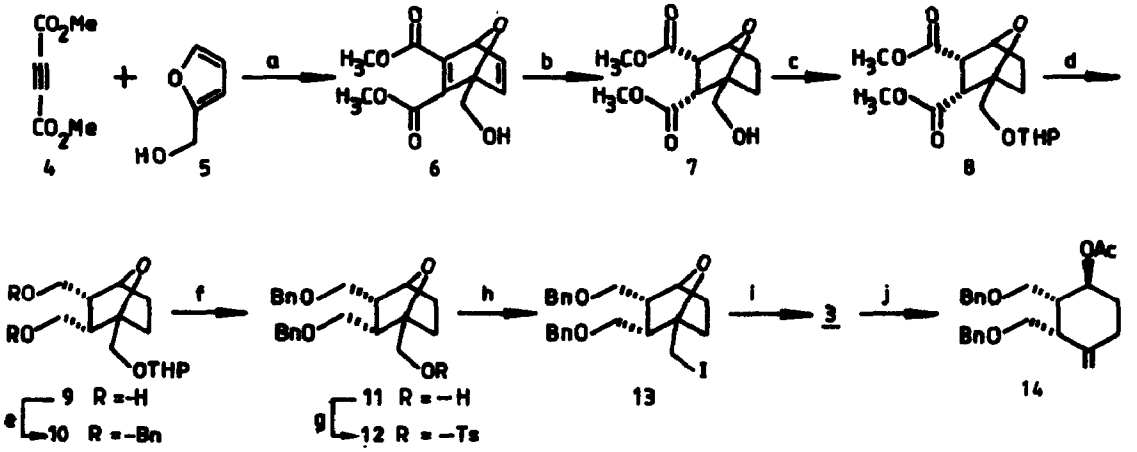


The origin of retron 3 could be traced to simple precursors via Diels-Alder

IICT Communication No.3331.

reaction. Accordingly, 3 was synthesized in 95% yields starting from acetylenic dienophile 4 and furfuryl alcohol 5 as summarized in scheme 2.

Scheme 2



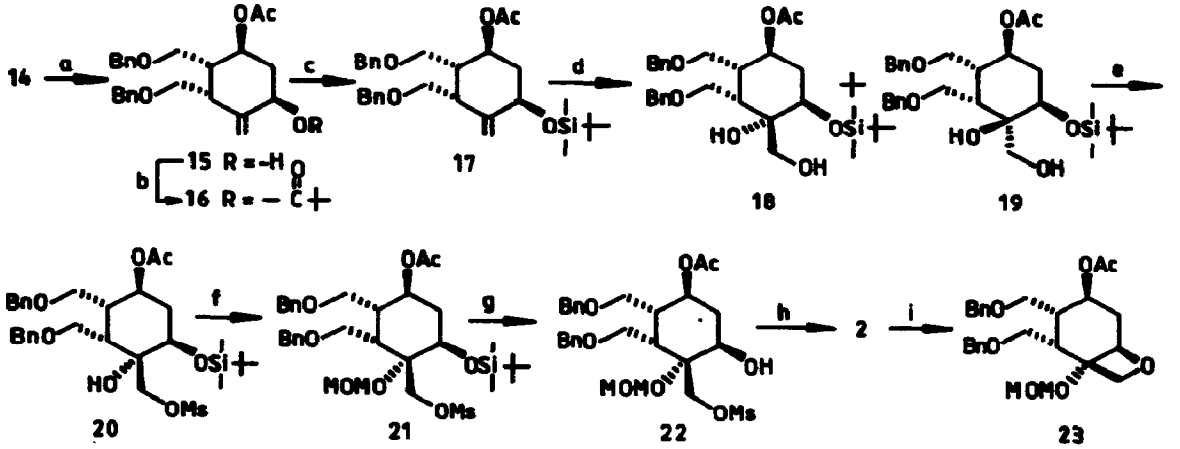
Reagents and conditions: a) Toluene, reflux, 4 h; b) Pd-C/H_2, MeOH, 4 h; c) PTSA (Cat), DCM, DHP, 0°C rt; d) LAH, THF, 0°C; e) NaH (2 eq), THF, BnBr (2 eq); f) PTSA (Cat), MeOH, 1 h; g) PTS-Cl, TEA, DMAP (Cat), DCM, 0°C rt, 2 h; h) NaI (1.2 eq), CH_3CN, reflux 4 days, i) Zn dust (1.1 eq), EtOH, reflux 1 h; j) Ac_2O, DMAP (Cat), TEA, DCM, 0.5 h.

Thus, Diels-Alder cyclization between 4 and 5 in refluxing toluene for 4 hours led to the oxabicyclic system 6 in quantitative yields. Compound 6 was converted to its saturated system 7 by hydrogenation over Pd-C in anhydrous methanol. The alcohol 7 was then protected as its THP-ether on treatment with dihydropyran under catalytic PTSA conditions, which gave 8 in 90% yields. The ester groups in 8 were reduced to the corresponding alcohol groups 9 and later protected as their benzyl ethers to give 10 in overall 80% yields. The THP group of 10 was deprotected and the free alcohol group in 11 was converted to its tosylate 12 on treatment with tosyl chloride and triethylamine. Refluxing 12 with NaI in acetonitrile converted the tosylate to its Iodo compound 13 in 80% yields. Employing Boord[3] conditions of refluxing compound 13 with Zn dust in absolute ethanol delivered the key building block 3 in quantitative yield with a stereocontrolled formation of the newly formed secondary hydroxy group, characterized by the ^{1}H-NMR spectrum of its acetate 14#.

The final process involving conversion of the exocyclic olefin in 14 to the oxetane ring D employing regioselective Sharpless allylic oxidation[4] as the keystep

leading to stereospecific product 15 is delineated in scheme 3.

Scheme 3



Reagents and conditions: a) SeO_2 (Cat), t-BHP (3 eq), AcOH (drop), hexane, 3 h; b) $(CH_3)_3CCOCl$ (1.2 eq), DMAP (Cat), TEA, DCM, 0.5 h; c) t-BDMSCl, imidazole, DCM, 1 h; d) OsO_4 (Cat), NMO, CH_3COCH_3:H_2O (9:1), 20 h; e) MSCl, TEA, DCM, 0°C rt, 1 h; f) DIPEA, MOM-Cl (2 eq), DCM, 20 h; g) n-Bu_4NF, THF, 1 h; h) NaH, ether, 6 h; i) Ac_2O, DMAP (Cat), TEA, DCM, 0.5 h.

SeO_2 catalysed allylic oxidation of 14 proceeded smoothly to furnish the regio- and stereoselective product 15 in 65% yield which was supported by the ^{1}H-NMR spectral data of its pivolate derivative 16#. Conversion of 15 to its silyl ether 17 was achieved in 95% yields on treatment with imidazole and TBDMS-Cl. The latter compound 17 was then dihydroxylated using catalytic OsO_4 and NMO conditions,[5] which led to separable diastereomers 18 and 19 with the major isomer (80%) corresponding to synthon 18#. The primary hydroxy group of 18 was converted to its mesylate 20 on treatment with Ms-Cl and triethylamine. To avoid any undesired possibilities, the tertiary alcohol in 20 was protected as its MOM-ether by treating with MOM-Cl using diisopropylethylamine over a period of 24 hours which gave 21 (80%). Silyl group of 21 was removed by the action of n-Bu_4NF to afford the compound 22 (85%). Finally, treatment of 22 with NaH in dry THF at 60°C for 12 hours gave the pivotal oxetane system 2#. The cyclisation was accompanied by the downfield shift of dd pattern of CH-OTBDMS proton in 20 from 4.1 to 4.8 ppm in 2. Conversion of the free hydroxy group of 2 to its acetate 23 resulted in the disappearance of the dt pattern of the methine proton at 3.8 ppm and consequent downfield shift to 4.7 ppm.

The above chemistry would prove of significant value in our efforts directed towards the total synthesis of taxol and/or its analogues or mimics.

Acknowledgements:

Authors are indebted to Dr A C Kunwar for fruitful discussions on ^{1}H-NMR spectra of some intermediates. This project is generously funded from a grant No.DST/N-USHRF-(138)/86 of PL 480 (NIH) and CSIR, New Delhi.

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   c) Lin, J.; Nikaido, M.M. and and Clark, G. *J. Org. Chem.* **1987,** *52,* 3745.
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Selected ^{1}H-NMR data: (200 MHz,$CDCl_3$, ,J in Hz):

14: 7.35-7.25 (m,10H,ArH), 5.20-5.10 (dt,J=4.5,9.0 Hz,1H,-C<u>H</u>-OAc), 4.8 (s,1H, C=C<u>H</u>), 4.6 (s,1H,C=C<u>H</u>), 4.45-4.35 (ABq,J=11.5 Hz,4H,benzylic), 3.65-3.30 (m,4H,2x-C<u>H</u>$_2$OBn), 2.9 (q,J=6.66 and 11.12,1H,H<u>C</u>-C=CH_2), 2.35-2.20 (m,3H,<u>H</u>C-CHOAc and C<u>H</u>$_2$-C=CH_2), 2.05 (s,3H,-OAc), 1.85-1.60 (m,2H,C<u>H</u>$_2$-CHOAc).

16: 7.35-7.20 (m,10H,ArH), 5.60 (dd,J=4.5 and 9.0 Hz,1H,C<u>H</u>-OPiv), 5.35-5.25 (dt, J=4.5 and 9.0 Hz,1H,C<u>H</u>OAc), 4.98 (s,1H,C=C<u>H</u>), 4.85 (s,1H,C=C<u>H</u>), 4.6-4.45 (ABq,2H,J=10.8 Hz,2H,benzylic), 4.45-4.35 (ABq,J=10.8 Hz,2H,benzylic), 3.65-3.35 (m,4H,2xC<u>H</u>$_2$-OBn), 3.0 (quart,J=6.55 and 11.12,1H,<u>H</u>C-C=CH_2), 2.3-2.2 (m, 2H,H_2C-<u>H</u>C-OAc and -<u>H</u>C-CHOAc), 2.0 (s,3H,-OAc), 1.7-1.5 (m,1H,<u>H</u>C-CHOAc), 1.25 (s,9H,-OCO(C<u>H</u>$_3$)$_3$.

18: 7.35-7.30 (m,10H,ArH), 5.15-4.95 (dt,J=4.5 and 9.0 Hz,1H,-C<u>H</u>-OAc), 4.50-4.30 ABq,J=10.90 Hz,benzylic), 4.10-3.95 (dd,J=4.70 and 9.45 Hz,1H,C<u>H</u>-OTBDMS), 3.70-3.40 (m,4H,-C<u>H</u>$_2$-OBn), 2.60-2.40 (m,3H,2x-C-C<u>H</u>-C- and -C<u>H</u>-CHOAc), 2.0 (s,3H,-OAc), 1.70 (m,1H,-C<u>H</u>-CHOAc), 0.85 [s,9H,-SiC(C<u>H</u>$_3$)$_3$], 0.1 [s,6H, Si(C<u>H</u>$_3$)$_2$].

2: 7.35-7.20 (m,10H,ArH), 4.98-4.83 (ABq,J=7.5 Hz,2H,-OC<u>H</u>$_2$OC<u>H</u>$_3$], 4.82-4.78 (dd,J=4.6 and 9.2 Hz,1H,C<u>H</u>O), 4.75-4.45 (ABq,J=7.1,2H,C<u>H</u>$_2$O), 4.45-4.38 (ABq,J=11.5 Hz,4H,benzylic), 3.80 (dt,J=4.5 and 9.0 Hz,1H,C<u>H</u>OH), 3.65-3.40 (m,4H,2xC<u>H</u>$_2$-OBn), 3.55 (s,3H,-OCH$_2$-OC<u>H</u>$_3$), 2.45-2.40 (m,2H,2xC<u>H</u>), 2.3 (m, 1H,-CH_2), 2.25 (m,1H,-CH_2).

All the intermediates gave expected spectral data including HRMS.

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