Pergamon

Tetrahedron Letters, Vol. 38, No. 8, pp. 1341-1344, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00094-4

Enantioselective Synthesis of a Taxane C-Ring Component Using the Schultz Asymmetric Birch Reduction Methodology

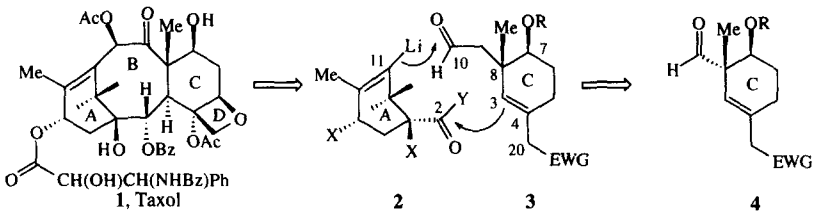
Philip Magnus,* Francis Tavares and Nicholas Westwood

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712.

Abstract: The asymmetric Birch reduction methodology has been used to develop two complementary routes to the taxane C-ring component in an enantioenriched form.

While there have been a number of strategies reported for the synthesis of the C-ring portion of the taxane diterpenes,[1] none have taken advantage of the Schultz asymmetric Birch reduction methodology which would appear to be ideally suited for the synthesis of **3** or **4**, **Scheme 1**.[2] We envisioned that **4** would serve as a convenient precursor to **3**, and the construction of **1** could be brought about by the union of **2** and **3** (or equivalents to both).[3]

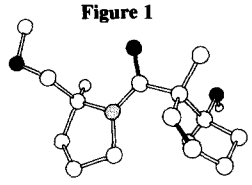
Scheme 1



1, Taxol 2 3 4

The amide **5** was reduced with K/NH_3/THF and **6** was isolated as a 4:1 mixture of diastereomers.

Figure 1

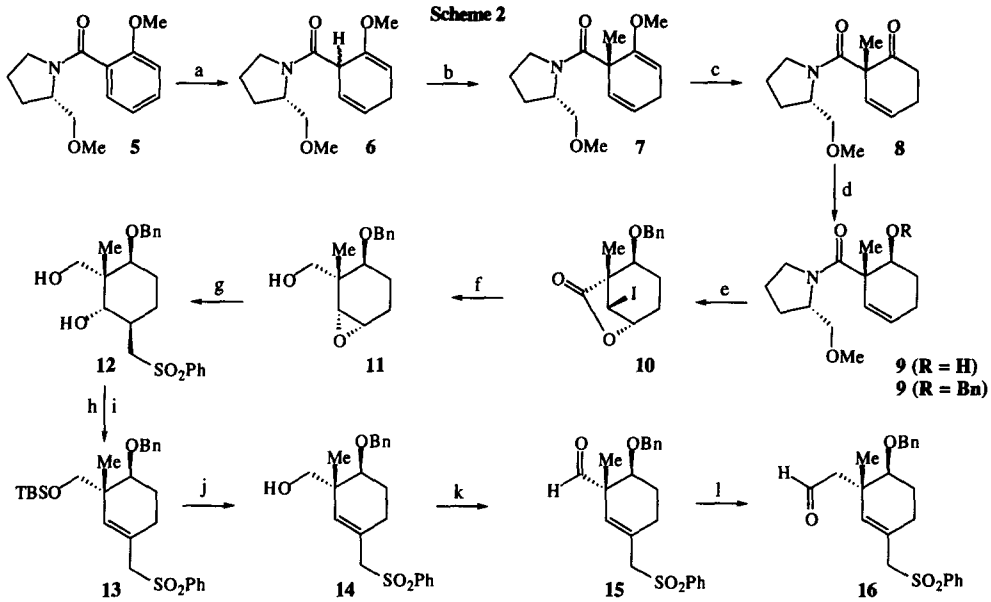


Chem 3D of **9** (R = H) from X-ray coordinates

Treatment of **6** with *n*-BuLi at -78°C, warming to 25°C and cooling to 0°C, followed by addition of HMPA, and recooling to -78°C followed by addition of MeI gave the correct diastereomer **7** (>99:1).[4] If the amide enolate is not brought to 25°C, then the incorrect diastereomer is the major product. After acid hydrolysis the ketone **8** was reduced with $Zn(BH_4)_2/Et_2O$, and the resulting alcohol **9** (R = H) protected as the benzyl ether **9** (R = Bn). The configuration of **9** (R = H) was determined by X-ray crystallography, and **Figure 1** shows a Chem 3D representation. The reduction is highly stereoselective, only traces (>99:1) of the other diastereomer were detected. Reduction of **8** with $NaBH_4$ gave a mixture (2.4:1, β:α) of both alcohols. Iodolactonization of **9** gave **10**, which on treatment with $LiBH_4$ followed by exposure of the iodohydrin to DBU resulted in the epoxy alcohol **11**.[5] Regioselective opening of the epoxide **11** was accomplished by treatment with $PhSO_2CH_2Li$/THF/HMPA to give **12** (98%); the primary alcohol was selectively protected as its -TBS ether, and dehydration using the Burgess reagent resulted in **13**. Deprotection

and oxidation of **13** provided **15** *via* **14**, and standard Wittig homologation[6] gave the desired C-ring component **16**.

Scheme 2



Conditions: a) K/NH_3/*t*-BuOH/-78°C, **6** (99%, 4:1). b) *n*-BuLi/THF/-78°C to 0°C, HMPA, cool to -78°C add MeI, **7** (85%, >99:1). c) THF/HCl/25°C, **8** (95%). d) i. $Zn(BH_4)_2/Et_2O$, >99:1. ii. BnBr/THF/KI (cat)/KH/25°C, **9** (91%). e) I_2/THF/H_2O (1:1)/25°C, **10** (76%). f) $LiBH_4$/THF/-5°C, followed by DBU/CH_2Cl_2/25°C, **11** (89%). g) THF/$PhSO_2Me$/*n*-BuLi/HMPA/-78° to 25°C, **12** (98%). h) TBSCl/DMF/Imidazole/25°C, **13** (86%). i) Burgess reagent/PhMe/110°C, **14** (56%). j) TBAF/THF/25°C, **15** (86%). k) SO_3.py/DMSO/NEt_3/CH_2Cl_2/0° to 25°C, **16** (92%). l) $MeOCH_2PPh_3^+Cl^-$/KN(TMS)$_2$/THF/-78° to 0°C (84%), followed by 2N HCl/THF, **16** (87%).

An alternative synthesis of **14** was examined to avoid the difficult dehydration of **12**, and allow more flexibility in the choice of substituents at C-20. Again using the Schultz asymmetric Birch reduction methodology **17** was converted into **18**. Iodolactonization of **18** proceeded cleanly to give **19**, whose structure and absolute configuration was confirmed by X-ray crystallography, **Figure 2** shows a Chem 3D representation from the X-ray coordinates, **Scheme 3**. Reduction of the lactone using $LiBH_4$ followed by elimination of HI gave the epoxide **20**. Exposure of **20** to the classical Crandall[7] epoxide elimination conditions ($LiNEt_2/Et_2O$) proceeded slowly even at reflux to give a mixture of allylic alcohols **21** and **22** (1:3).[8] Whereas, treatment of **20** with Olofson's "Harpoon" base[9] at 25°C cleanly produced **21** and **22** (1:6) in 84% yield. It is necessary to conduct the above epoxide rearrangement on the unprotected primary alcohol **20** because the corresponding TBS derivative does not undergo any conversion into an allylic alcohol. This suggests that lithium alkoxide coordination to the adjacent epoxide oxygen atom lone pair of electrons greatly facilitates the endo- and exocyclic elimination process.

The TBS protected exocyclic allylic alcohol **23** was surprisingly reluctant to participate in [2.3]-sigmatropic rearrangement chemistry. For example, treatment of **23** with PhSCl/*n*-BuLi/Et_2O/-78°C gave the rearranged sulfoxide in low yield, and surprisingly **22** did not react with PhSsuccinimide/PBu_3 at all. This

problem was readily solved by making use of standard S_N2' chemistry. Treatment of **23** with thionyl chloride/pyridine cleanly gave the rearranged allylic chloride **24**, which was converted directly into the sulfone **13** (84% from **23**) by exposure to $PhSO_2Na/NaI/DMF$. Alternatively, treatment of **24** with PhSH/NaH/THF gave the sulfide **25**, which was converted into the homologous aldehyde **26** using the same sequence of transformations as before.

Scheme 3

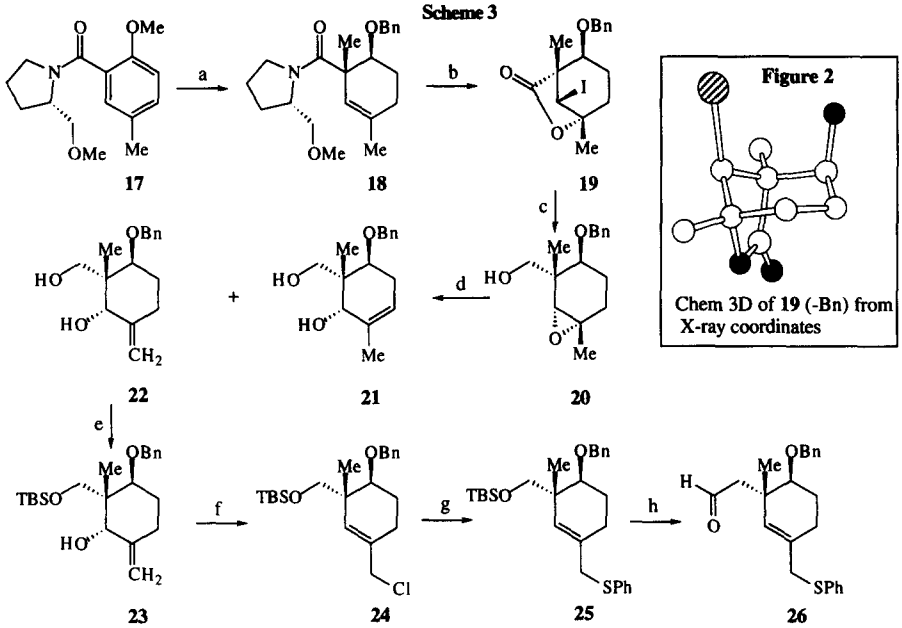


Figure 2

Chem 3D of **19** (-Bn) from X-ray coordinates

Conditions: a) Same as for **9**, **Scheme 2** (77% over 5 steps). b) $I_2/THF/H_2O$ (1:1)/25°C, **19** (84%). c) $LiBH_4/THF$/0°C, followed by DBU/CH_2Cl_2/25°C, **20** (78%). d) 2,2,6,6-Tetramethylpiperidine/*n*-BuLi/0° to 25°C, **21**:**22** (1:6, 84%). e) $TBSCl/NEt_3/DMAP/CH_2Cl_2$/25°C, **23** (95%). f) $SOCl_2/py/Et_2O$/0°C. g) PhSH/NaH/THF/25°C, **25** (92% from **23**). h) i. TBAF/THF/25°C, (92%). ii. SO_3.py/DMSO/NEt_3/CH_2Cl_2/0° to 25°C, (86%). iii. $MeOCH_2PPh_3^+Cl^-/KN(TMS)_2$/THF/-78° to 0°C (69%), followed by 2N HCl/THF, **26** (97%).

The sequence of reactions outlined in **Scheme 2** is the preferred route to the C-ring sulfone **16**, but the alternative route in **Scheme 3** to the C-ring sulfide **26** also allows access to the C-20 sulfoxide. The Schultz asymmetric Birch reduction methodolgy provides a very direct way to control the absolute stereochemistry at C-7 and C-8 in the taxol C-ring, and the compounds **16** and **26** are appropriately functionalized for attachment of the A-ring portion by the reaction processes indicated in **Scheme 1** (**2** + **3**).

Acknowledgments. The National Institutes of Health, National Science Foundation, Welch Foundation and Merck Frosst are thanked for their support of this research. N. W. thanks NATO for a post-doctoral fellowship.

References and Footnotes

1. Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15. Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634. Nicolaou, K. C.; Liu, J. J.; Dai, W.-M.; Guy, R. K. *J. Chem. Soc. Chem. Commun.* **1992**, 1118. Magee, T. V.; Bornmann, W. G.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274. Swindell, C. S.; Patel, B. P.; deSolms, S. J. *J. Org. Chem.* **1987**, *52*, 2346. Bauta, W.; Booth, J.; Bos, M. E.; DeLuca, M.; Diorazio, L.; Donohoe, T.; Magnus, N.; Magnus, P.; Mendoza, J.; Pye, P.; Tarrant, J.; Thom, S.; Ujjainwalla, F. *Tetrahedron Lett.* **1995**, *36*, 5327.

2. Schultz, A. G.; Macielag, M.; Sundaraaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828.

3. Magnus, P.; Frost, C.; Linnane, P.; Spyvee, M. *Tetrahedron Lett.* **1996**, *37*, 9139.

4. Professor Schultz is thanked for information concerning this procedure.

5. Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 6210.

6. Wittig, G.; Boll, W.; Kruck, K-H. *Chem. Ber.* **1962**, *95*, 2514.

7. Crandall, J. K.; Chang, L-H. *J. Org. Chem.* **1967**, *32*, 435.

8. Dutcher, J. S.; MacMillan, J. G.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 2663.

9. Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 583.

(*Received in USA* 19 *November* 1996; *revised* 13 *January* 1997; *accepted* 14 *January* 1997)