Construction of a Key Intermediate in the Asymmetric Synthesis of Chiral Taxanes

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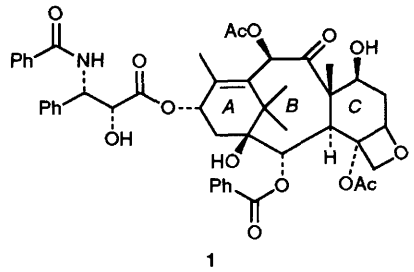
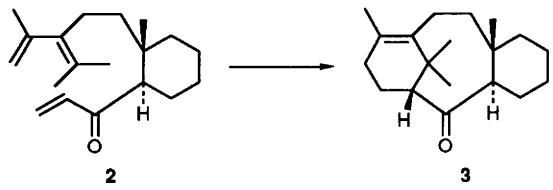
The radical bromination of acetal **5** followed by zinc-promoted fragmentation gives the highly functionalised, homochiral cyclohexane **7**, which possesses the carbon skeleton of the *C*-ring of taxol; nucleophilic addition of dimethyllithium cuprate to **8**, followed by ozonolysis gives aldehyde **10**, ozonolysis of **8** gives aldehyde **9**.

Taxol[1] **1**, isolated from the bark of the Pacific Yew tree *Taxus brevifolia*, is a highly functionalised diterpene possessing exciting antitumour activity.[2] It is presently being tested in phase II clinical trials in the treatment of ovarian and breast cancer. The projected demand for taxol has caused concern for the survival of the yew species; indeed there may not be enough trees to meet future needs. Proposed solutions to this problem have been reviewed,[3] and an efficient, practical total synthesis is seriously considered to be one such answer.

We have reported[4] a synthesis of the taxane skeleton **3** in which the *A* and *B* rings were constructed by an intramolecular Diels–Alder reaction of a suitable functionalised cyclohexane **2** (Scheme 1). Since then we have been adapting this approach to incorporate a higher degree of functionality starting from a homochiral *C*-ring derivative. Following recent reports concerning the syntheses of taxol *C*-rings in enantiomerically pure[5] and racemic forms,[6,7] we are now prompted to reveal our results in this area. We have already described the synthesis of the diol[8] **4**, and now report of its successful conversion to three substituted cyclohexanes **8**, **9** and **10** which we believe will be useful for the syntheses of taxanes.

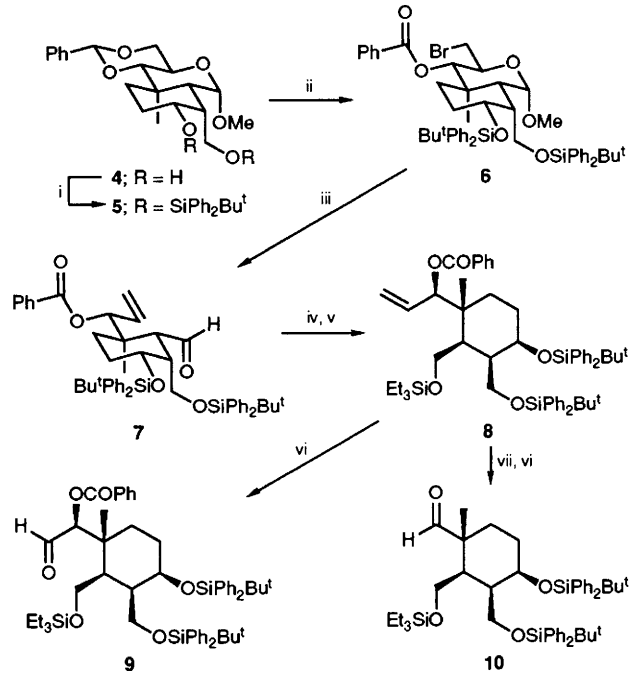


1



2 3

Scheme 1



Scheme 2 *Reagents and conditions*: i, *tert*-butyldiphenylsilyl chloride, CH_2Cl_2, imidazole, room temp., 72 h, 77%; ii, NBS, $BaCO_3$, CCl_4, reflux 3 h, 80%; iii, Zn, Pr^iOH, reflux, 5 h, 61%; iv, $NaBH_4$, Pr^iOH, 60 °C, 0.25 h, 73%; v, Et_3SiCl, CH_2Cl_2, imidazole, 15 h, room temp., 89%; vi, O_3, CH_2Cl_2, −78 °C then dimethyl sulfide; vii, Me_2CuLi, Et_2O, 0 °C, 3 h, 71%

We attempted to open the sugar-like ring of the protected methoxypyranose **5** under a variety of acid-catalysed conditions,[9] but met with little success even when different protecting groups were used. As an alternative strategy we embarked upon a sequential fragmentation to cleave both of the acetal rings of **5** (Scheme 2). Following the method described by Hanessian and Plessas,[10] reaction of **5** with *N*-bromosuccinimide (NBS) (CCl_4, reflux, 3 h) gave the bromoester **6** in 80% yield, and this was converted to the aldehyde **7** in 61% yield by a Vasella fragmentation.[11] Reduction and protection of the resulting alcohol gave the cyclohexane **8**.

To facilitate diene synthesis by a number of different methods,[12] the three-carbon side chain of **8** can be shortened to a two-carbon chain by ozonolysis, leading to **9**, or by alkyl cuprate addition followed by ozonolysis to give the one-carbon side chain in aldehyde **10**.

In conclusion, cyclohexane **8** is a versatile intermediate for the chiral synthesis of taxanes starting from the *C*-ring, and we are actively pursuing this objective using the Diels–Alder strategy for the construction of the *A* and *B* rings.[4]

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References

1 M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggan and A. T. McPhail, *J. Am. Chem. Soc.*, 1971, **93**, 2325.
2 P. H. Wiernik, E. L. Schwartz, J. J. Strauman, J. P. Dutcher, R. B. Lipton and E. Paietta, *Cancer Res.*, 1987, **47**, 2486.
3 S. M. Edgington, *Bio-Technology*, 1991, **9**, 993; *J. Nat. Cancer Inst.*, 1989, **81**, 1122; S. Borman, *Chem. Eng. News*, 1991, September 2, 11.
4 P. A. Brown and P. R. Jenkins, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1303; R. V. Bonnert and P. R. Jenkins, *J. Chem. Soc., Perkin Trans. 1*, 1989, 413. A related Diels–Alder approach has been pursued concurrently by K. J. Shea and C. D. Haffner, *Tetrahedron Lett.*, 1988, **29**, 1367; R. W. Jackson, R. G. Highby, J. W. Gilman and K. J. Shea, *Tetrahedron*, 1992, **48**, 7013.
5 T. V. Magee, W. G. Bornmann, R. C. A. Isaacs and S. J. Danishefsky, *J. Org. Chem.*, 1992, **57**, 3274.
6 K. C. Nicolaou, J. J. Lui, C.-K. Hwang, W.-M. Dai and R. K. Guy, *J. Chem. Soc., Chem. Commun.*, 1992, 1118.
7 P. A. Wender and D. B. Rawlins, *Tetrahedron*, 1992, **48**, 7033.
8 R. V. Bonnert, J. Howarth, P. R. Jenkins and N. J. Lawrence, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1225; R. V. Bonnert, M. J. Davies, J. Howarth, P. R. Jenkins and N. J. Lawrence, *J. Chem. Soc., Perkin Trans. 1*, 1992, 27.
9 J. Howarth, PhD Thesis, University of Leicester, 1990.
10 S. Hanessian and N. R. Plessas, *J. Org. Chem.*, 1969, **34**, 1035.
11 B. Bernet and A. Vasella, *Helv. Chim. Acta*, 1979, **62**, 1990; M. Nakane, C. R. Hutchinson and H. Gollman, *Tetrahedron Lett.*, 1980, **21**, 1213.
12 P. A. Brown and P. R. Jenkins, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1129; R. V. Bonnert, P. A. Brown, P. R. Jenkins, N. J. Lawrence and M. R. Selim, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1893.