A concise stereoselective synthesis of the C-aromatic taxane skeleton: an application of novel sequential transacetalation oxonium ene cyclization

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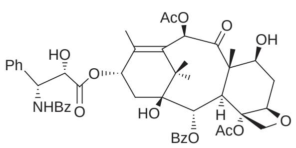
A three-step sequence for the construction of the C-aromatic taxane nucleus from easily available A-ring unit 2 and C-aromatic unit 3 is reported; $SnCl_4$ promoted reaction of 4, presumably *via* the diastereoselective oxonium ene cyclisation reaction of 6a formed *in situ*, delivers cyclic ether 5a which on treatment with Bu^nLi provides C-aromatic taxane skeleton 8.

The remarkable chemotherapeutic potential and the unique molecular framework of taxol[1] **1** have stimulated enormous synthetic efforts towards the synthesis of taxane diterpenoids.[2] Although five different total syntheses of **1** have been reported[3] in recent years, interest towards the development of new synthetic methods to acquire potent taxol analogues continues to grow. In this context, one of the long standing problems has been the construction of the sterically congested central eight-membered B-ring. In view of the known difficulties stemming from the high degree of ring strain and the transannular interactions associated with the direct cyclooctane annulation process, a recourse to indirect methods such as fragmentation of bicyclic systems, ring contraction and ring expansion have been developed.[4] For the purposes of construction of the taxane skeleton, particularly *via* C_{10}–C_{11} bond formation as the key step, the methods available are limited to the Heck reaction,[5] the Kishi–Nozaki coupling reaction[6] and the intramolecular nitrile oxide cyclization reaction.[7] Moreover, the application of these methods is severely restricted due to their substrate-specific nature and also the difficulty encountered in deriving the required substrates. In this context, we have initiated a new convergent approach starting with B-*seco*-taxane **A** wherein the critical bond connection between C_{10}–C_{11} was envisioned to arise from the α-alkoxycarbenium ion generated from **B** *via* treatment with a Lewis acid (Scheme 1). This approach was expected to help overcome the known unfavorable entropic and transannular interactions associated with the direct cyclooctane annulation using an acyclic precursor. We report herein our successful preliminary results for the construction of taxane skeleton **8** *via* the oxonium ene cyclisation reaction of **4** as the key step.



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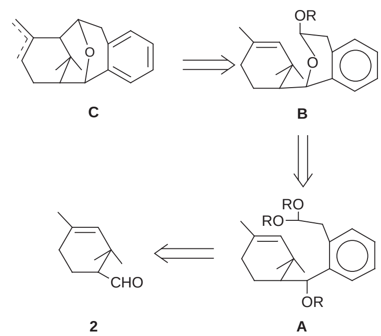
The precursor compound **4** was readily assembled by the reaction of aryllithium reagent **3**, prepared *via* the reductive metalation of the diethylacetal of 2-iodophenylacetaldehyde[8] using Bu^nLi, with compound **2** (Scheme 2). The utility of chiral A-ring unit **2** derived from α-pinene in the preparation of B-*seco*-taxanes has recently been reported by us.[9] The substrate **4** (75%) was found to be a mixture of **4a** (1*R**,2*R**) and **4b** (1*R**,2*S**) in the ratio of 3.4:1, established from the ¹H NMR spectral data.[10] Since the separation of individual diastereomers

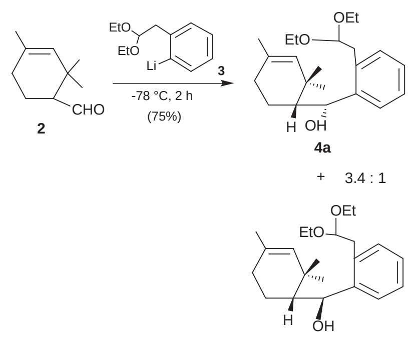


Scheme 1

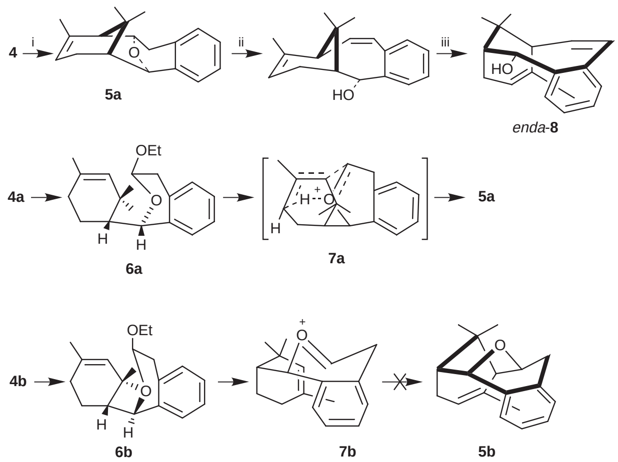
was found to be difficult, it was decided to use the mixture of isomers for the next step.

Addition of $SnCl_4$ (2.5 equiv.) to a stirring solution of **4** in CH_2Cl_2 at −60 °C for 3 h, followed by quenching of the reaction mixture with saturated aqueous NH_4Cl, usual workup and purification *via* silica gel column chromatography, afforded compound **5a** in 32% yield (Scheme 3). The ¹H and ¹³C NMR spectra of **5a** confirmed its structure and indicated that it possessed a complete taxane core incorporating an *endo*-ether linkage connecting C_2 and C_{10} in the central eight-membered B-ring. The structural assignment was further supported by comparing the ¹H NMR data from the structurally related C-aromatic *exo/endo* atropisomeric taxanes reported by Shea.[11]

In order to understand the mode of formation of **5a** from **4**, the reaction was also examined using two more Lewis acids, *i.e.* $TiCl_4$ and $BF_3{\cdot}Et_2O$ (Table 1). It was noticed that these Lewis acids are equally effective in promoting the formation of **5a**. For example, the reaction of 1 equiv. of $SnCl_4$ with **4** provided transacetalation product **6** in good yield (65–74%) as a mixture of diastereomers (suggested on the basis of the ¹H NMR spectrum). Interestingly, when **6** was separately treated with $SnCl_4$ (1.5 equiv.), it was readily transformed to compound **5a**, thus, revealing the nature of the overall transformation[12] (Scheme 3). The only other report that deals with a similar type of strategy for the construction of the taxane skeleton is from Hitchcock and Pattenden,[13] who demonstrated the efficacy of a



Scheme 2



Scheme 3 *Reagents and conditions*: i, $SnCl_4$ (2.5 equiv.), −60 °C, 3 h, CH_2Cl_2; ii, Bu^nLi, THF, room temp., 7 h; iii, heat

Table 1 Results of Lewis acid-promoted cyclisations

Compound	Lewis acid (equiv.)	*T*/°C	Product	Yield (%)
4	$SnCl_4$ (2.5)	−60	**5a**	32
4	$SnCl_4$ (1.1)	−78	**6**	74
6	$SnCl_4$ (1.5)	−60	**5a**	41
4	$TiCl_4$ (1.1)	−78	**6**	72
4	$BF_3{\cdot}Et_2O$ (1.1)	−78	**6**	65

tandem radical macrocyclization–transannular sequence using an appropriately functionalised A-ring unit.

Initially, the high stereoselectivity observed in the overall cyclization process, *viz.* **4**→**5a**, appeared somewhat intriguing. However, mechanistic considerations along with an examination of the molecular models helped us greatly in increasing our understanding. Mechanistically, in analogy with Overman's proposal,[14] a concerted oxonium ion ene cyclization may well be visualized in the formation of *exo*-**5a** from oxonium ion **7a**, derived from the major isomer **6a** involving a favorable six-membered transition state. The lack of the possibility of such a transition state, due to the unfavorable geometry of the oxonium ion **7b**, from the minor isomer **6b** precludes it from undergoing an analogous type of cyclization that would lead to **5b**.

In order to transform **5a** into a molecule having taxane skeleton **8** it was treated with Bu^nLi[15] at room temperature, which furnished crystalline compound *endo*-**8**[16] (78%; mp 141 °C), instead of the corresponding *exo*-**8**. This observation may possibly be explained by considering a thermal *exo* to *endo* atropisomerization[17] during the work-up stage. The structure and stereochemical assignment of *endo*-**8** follows from a detailed ^{1}H NMR decoupling experiment and selected coupling constants. Finally, the structure was confirmed by a 2D-COSY NMR experiment.

In conclusion, we have described a facile entry into a functionalized C-aromatic taxane ring system employing an oxonium ene cyclization reaction as the key step for the first time. The potential of this method to construct the ABC system of taxol is under investigation.

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Notes and References

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1 M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon and A. T. McPhail, *J. Am. Chem. Soc*., 1971, **93**, 2325.
2 K. C. Nicolaou, M-W. Dai and R. K. Guy, *Angew. Chem., Int. Ed. Engl*., 1994, **33**, 15; A. N. Boa, P. R. Jenkins and N. J. Lawrence, *Contemp. Org. Synth.*, 1994**,** 47.
3 I. Shiina, H. Iwadare, H. Sakoh, M. Hasegawa, Y. Tani and T. Mukaiyama, *Chem. Lett*., 1998., 1 and references cited therein.
4 N. A. Petasis and M. A. Patane, *Tetrahedron*, 1992, **48,** 5757.
5 J. J. Masters, J. T. Link, L. B. Snyder, W. B. Young and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1723.
6 M. H. Kress, R. Ruel, W. H. Miller and Y. Kishi, *Tetrahedron Lett*., 1993**, 34,** 5999.
7 Y. Hirai and H. Nagaoka, *Tetrahedron Lett.*, 1997, **38**, 1969.
8 J. E. leffler and A. F. Wilson, *J. Org. Chem*., 1960, **25**, 424.
9 H. R. Sonawane, S. G. Sudrik, M. M. Jakkam, A. Ramani and B. Chanda, *Synlett.*, 1996, 175. In the present work the experiment was carried out with (±)-**2** which was prepared by the Diels–Alder reaction of 2,4-dimethylpenta-1,3-diene and acrolein catalysed by $BF_3{\cdot}OEt_2$.
10 Separation of **4a** and **4b** *via* derivatisation and cyclisation is underway. *Selected data* for **4**: ν_{max}($CHCl_3$)/cm^{-1} 3450, 2900, 1360, 1210; δ_H($CDCl_3$, 200 MHz) 7.6–7.1 (m, 4H), 5.3 (s, 0.77H), 5.05 (s, 1H), 4.85 (d, *J* 10.8, 0.23H), 4.7–4.55 (m, 1H), 3.8–3.55 (m, 2H), 3.55–3.3 (m, 2H), 3.2–2.9 (m, 2H), 2.0–1.5 (m, 8H), 1.4–1.0 (m, 12H) (Calc. for $C_{22}H_{34}O_3$: C, 76.30; H, 9.82. Found: C,75.99; H, 9.43%).
11 R. W. Jackson, R. G. Higby, J. W. Gilman and K. J. Shea, *Tetrahedron*, 1992, **48**, 7013.
12 L. F.Tietze, *Chem. Rev*., 1996, **96**, 115.
13 S. A. Hitchcock and G. Pattenden, *Tetrahedron Lett*., 1992, **33**, 4843.
14 For an elegant application of this concept in the synthesis of Δ^4-oxocene, see T. A. Blumenkopf, G. C. Look and L. E. Overman, *J. Am. Chem. Soc*., 1990, **112**, 4399.
15 M. E. Jung and S. J. Miller, *J. Am. Chem. Soc.*, 1981, **103**, 1984.
16 *Selected data* for **8**: ν_{max}(Nujol)/cm^{-1} 3273, 2950, 2800, 1254, 1021; δ_H($CDCl_3$, 200 MHz) 7.55 (d, *J* 7.6, 1H), 7.2 (dt, *J* 6.4, 1.2, 1H); 7.1 (dt, *J* 6,1.2, 1H), 7.0 (d, *J* 7.4, 1H), 6.6 (d, *J* 10.7, 1H), 6.0 (dd, *J* 11.7, 1H), 5.1 (s, 1H), 4.55 (br s, 1H), 2.35 (d, *J* 9.2, 1H), 2.1 (br s, 2H), 1.7 (br s, 1H), 1.3 (s, 3H), 1.2 (d, *J* 1.2, 3H), 1.05 (s, 3H); δ_C($CDCl_3$, 50 MHz) 142.8, 135.9, 133.5, 132.1, 129.9, 126.5, 126.1, 125.6, 124.6, 120.5, 70.1, 49.9, 46.7, 32.9, 29.7, 26.1, 24.2, 22.8 (Calc. for $C_{18}H_{22}O$: 254.1670 (M+). Found: 254.1666).
17 M. Seto, K. Morihira, Y. Horiguchi and I. Kuwajima, *J. Org. Chem*., 1994, **59**, 3165.

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