Synthesis of a Highly Functionalised AB Taxane Ring System: Formation of the Eight-membered Ring by an Efficient 8-*exo*-tet Alkylation of an α-Sulfonyl Anion

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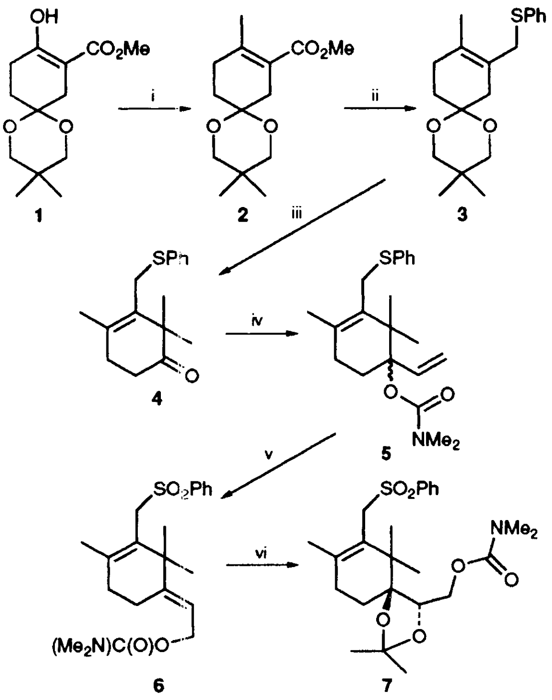
An efficient, scalable route to a Taxol A ring synthon has been developed; its successful elaboration to a highly functionalized AB system by means of a novel nucleophilic ring closure is described.

Presently, there is considerable interest in developing efficient routes towards the synthesis of taxane diterpenoids.[1] The convergent synthesis of Taxol being pursued in this laboratory entails construction of A and C/D ring moieties followed by their coupling with the formation of the B-ring. This poses two significant problems: (*a*) construction of the hindered C1–C2 bond, bringing the A-ring and C-ring synthons together, followed by installation of the diol functionality with the correct stereochemistry, and (*b*) an efficient ring-closure reaction across C9–C10 forming the requisite eight-membered ring of the taxoid skeleton. The present high level of interest in convergent strategies is attested by a number of papers describing methodology for closure of the B-ring.[2] Despite the recent successful convergent total synthesis of Taxol by Nicolaou *et al.*,[3a] there still remains much room for development. Here we disclose our synthesis of a highly functionalised taxane AB ring system that effectively addresses the key factors outlined above.

Scheme 1 summarises the synthesis of the taxane A-ring, formation of the C1–C2 bond and introduction of the diol functionality. β-Keto ester **1** was prepared easily on a scale of several hundred grams following the procedure of Fuchs and coworkers.[4] In order to introduce the methyl group on C12, **1** was first converted to its enol phosphate, followed by conjugate addition using $Me_2CuCNLi_2$ essentially according to the procedure of Weiler and coworkers,[5] to provide **2** in 65% yield.

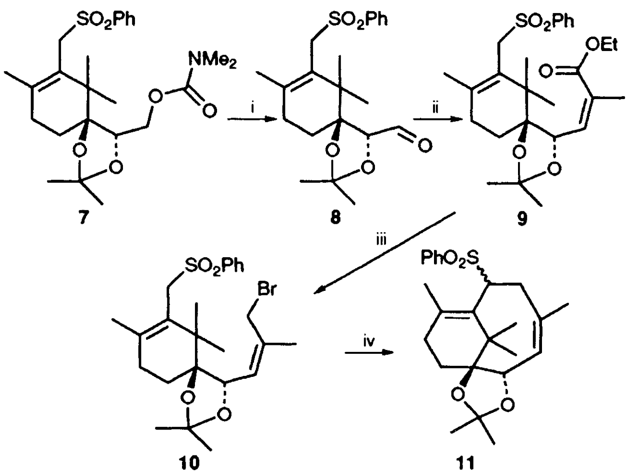


Scheme 1 *Reagents and conditions*: i, NaH, $ClP(O)(OMe)_2$ then $Me_2CuCNLi_2$, 65%; ii, Dibal–H, −78 °C then Bu^nLi, TsCl then PhSLi, 0 °C, 67%; iii, TsOH, acetone, H_2O then Bu^tOK, MeI, −15 °C, 86%; iv, $CH_2CHCeCl_2$, 83% then KH, Me_2NCOCl, 92% then MMPP, 90%; v, cat. $Hg(OTFA)_2$, 96%, >95:5 (*E*):(*Z*); vi, OsO_4, NMO then 2-methoxypropene, TsOH, 40%

The α,β-unsaturated ester **2** was then reduced with 2 equiv. of Dibal–H and the resulting allylic alcohol was converted to the phenyl sulfide **3** *via* its tosylate in 67% yield for the two steps. Deprotection of **3**, followed by deconjugative alkylation with methyl iodide at −15 °C, provided the A-ring synthon **4** in 86% yield.

Previously,[6] we had successfully achieved olefination of a related C1 ketone by means of the Meyer–Schuster reaction. However, concerns about the use of ethoxyacetylene on a large scale lead us to seek an alternative protocol. In the event, **4** was treated with vinylcerium dichloride,[7] at −78 °C to give the desired allylic alcohol cleanly. This alcohol was converted to its carbamate under standard conditions using potassium hydride as the base and quenching the alkoxide with dimethyl carbamoyl chloride. Oxidation of the phenyl sulfide to the corresponding sulfone with magnesium monoperphthalate[8] (MMPP) gave **5** and set the stage for a 1,3-oxygen transposition. Pleasingly, the Hg^{2+}-catalysed allylic rearrangement[9] gave exclusively the desired (*E*)-olefin **6** in almost quantitative yield. The geometry of the olefin was proven by appropriate NOE studies. The exocyclic alkene **6** was then subjected to dihydroxylation under the standard Van Rheenan conditions[10] and the resulting diol was converted to its acetonide **7** in 40% overall yield from **6**. The conversion of the diol to the acetonide served two purposes in that it functions as a protecting group and importantly restricts the conformation of the acyclic precursor so as to facilitate ring-closure reactions across C9 and C10.

Scheme 2 summarises the sequence adopted to form the required eight-membered taxane B-ring. Thus, **7** was subjected to base hydrolysis followed by oxidation of the resulting alcohol using Ley's tetrapropylammonium perruthenate/*N*-methylmorpholine-*N*-oxide (TPAP/NMO) protocol[11] giving the aldehyde **8** in 74% yield from **7**. The cyclisation precursor was synthesized by subjecting **8** to a (*Z*)-selective Horner–Emmons olefination[12] reaction giving the (*Z*)-α,β-unsaturated ester **9**. Attempted ring



Scheme 2 *Reagents and conditons*: i, KOH, MeOH, 83% then TPAP, NMO, 89%; ii, $(CF_3CH_2O)_2P(O)CHMeCO_2Et$, KHMDS, 18-crown-6, −78 °C, 52%; iii, Dibal–H, 73% then PPh_3, CBr_4, 60%; iv, LiHMDS, 0 °C, 88%

closure on this system was ineffective. Therefore the ester was reduced using Dibal–H to the allylic alcohol which was subjected to bromination using PPh_3 and CBr_4 to give the bromide **10** in good yield. The crucial cyclisation step was carried out by slow addition of a 0.1 mol dm^{-3} solution of LiHMDS (2 equiv.) in THF to a 5 mmol dm^{-3} solution of the bromide at 0 °C and gave **11**, in a clean reaction, as a 1 : 1 mixture of diastereoisomers in 88% yield. Although, much progress has been made in recent years towards the construction of eight-membered rings,[13] the 8-*exo*-tet alkylation of α-sulfonyl anions appears to be unprecedented.[14]

In conclusion we have described a facile entry into a highly functionalized Taxol AB ring system by means of a novel nucleophilic ring closure. Further progress toward the synthesis of Taxol will be reported in due course.

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Footnote

† All new compounds exhibited satisfactory spectral, analytical and/or exact mass data. Yields refer to chromatographically and spectroscopically homogenous materials. Taxol numbering is used throughout.

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