A Direct Carbometallation-Stereoselective Cycloaddition-Ring Closing Metathesis Route to the Tricyclic ABC Core of Taxoids

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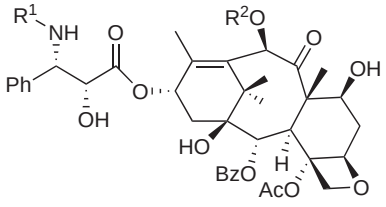
Received 11 November 2002

This paper is dedicated to Professor Raymond U. Lemieux to celebrate his lifetime achievements. Presented with respect and gratitude for his significant contributions to organic chemistry and our friendship.

Abstract: The synthesis of the tricyclic ABC ring-system of Taxol® (paclitaxel) is described. This direct route involves sequential reactions employing the carbometallation of a propargyl alcohol, followed by a *cis*-alkene tether controlled stereoselective intramolecular Diels–Alder reaction to generate the AB-ring system and ring closing metathesis (RCM) of the pendant allyl substituents to construct the C ring.

Key words: carbometallation, Diels–Alder, taxanes, ring closing metathesis (RCM)

Taxol® (paclitaxel) and Taxotere® (docetaxel) are established chemotherapeutic agents particularly for treating ovarian and breast cancer (Figure 1). They are also useful for a variety of other cancers as mixed chemotherapy. These drugs operate by a novel mechanism of action that differs from other spindle poisons such as vincristine. Thus taxoids provide a different method to attack cancer cells. The challenge of total synthesis has been surmounted by six different groups.[1] However, new efficient strategies are still required if we are to make new analogues efficiently with better solubility and improved therapeutic profiles. Consequently, this challenging skeleton continues to elicit considerable medicinal and synthetic interest.[2]



Paclitaxel (Taxol®) R^1 = Bz, R^2 = Ac
Docetaxel (Taxotere®) R^1 = Boc, R^2 = H

Figure 1

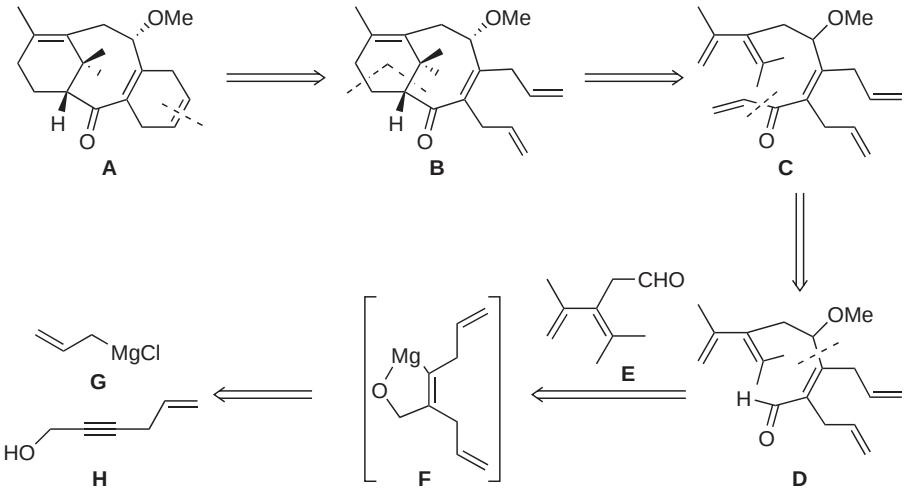
We wish to report an extension of our ongoing research into taxane synthesis[3] which has evolved into a direct synthesis of the tricyclic ABC ring-system (tricyclo[9.3.1.$0^{3,8}$]pentadecane core) of Taxol® (paclitaxel) via a carbometallation-cycloaddition-ring closing metathesis (RCM) sequence. This strategy has arisen from our earlier studies in two areas. The carbometallation of propargyl alcohols,[4] and the development of stereoselective Lewis acid catalyzed and chelation controlled intramolecular Diels–Alder cycloadditions (IMDA) for eight membered rings.[5] With the correct substitution pattern and a *cis*-alkene in the tether cyclization proceeded easily to generate the AB-ring system by a type 2 cycloaddition.[6] The C ring was constructed in a straightforward manner by ring closing metathesis (RCM). Previous reports have described (RCM) routes to both the AB[7] and BC[8] taxane ring systems respectively. Our strategy is illustrated retrosynthetically in Scheme 1.

For reasonable biological activity the C7 hydroxyl and C10 acetate can be omitted without compromising efficacy.[2,9] The C9 hydroxyl is not essential but it increases activity slightly, and acts as a useful handle for the formation of resolvable derivatives[10] or the introduction of solubilizing groups.[11] In contrast the C2 benzoate, and related oxetane substituents on the molecule's 'southern' perimeter are more important. With a view to the future and to take advantage of the rapid AB-ring assembly afforded by an intramolecular Diels–Alder strategy, we elected to employ diene aldehyde **E** as a source of the future C9 oxygen. The propargyl alcohol **H** contributes the C2 benzoate. Thus generation of the magnesium chelate **F** from the addition of **G** to **H**, condensation with the diene aldehyde **E** in situ and subsequent elaboration would give hexaene **C**. It was anticipated that Lewis acid catalyzed cycloaddition to the AB-ring system in **C** would afford a single diastereomer due to favorable complexation with a Lewis acid and finally ring closing metathesis would generate **A**.

Our magnesium mediated carbometallation reaction of propargyl alcohols is a versatile multi-component coupling protocol (dienes, furans, etc.) that may be varied depending upon the synthetic objective and the substrates employed. The sequential combination of **1** and **2** generated the magnesium chelate of type **F** followed by in situ condensation with aldehyde **3** to afford the diol **4** (Scheme 2). Selective protection of primary alcohol with TBSCl afforded **5**, which was treated with MeI to generate

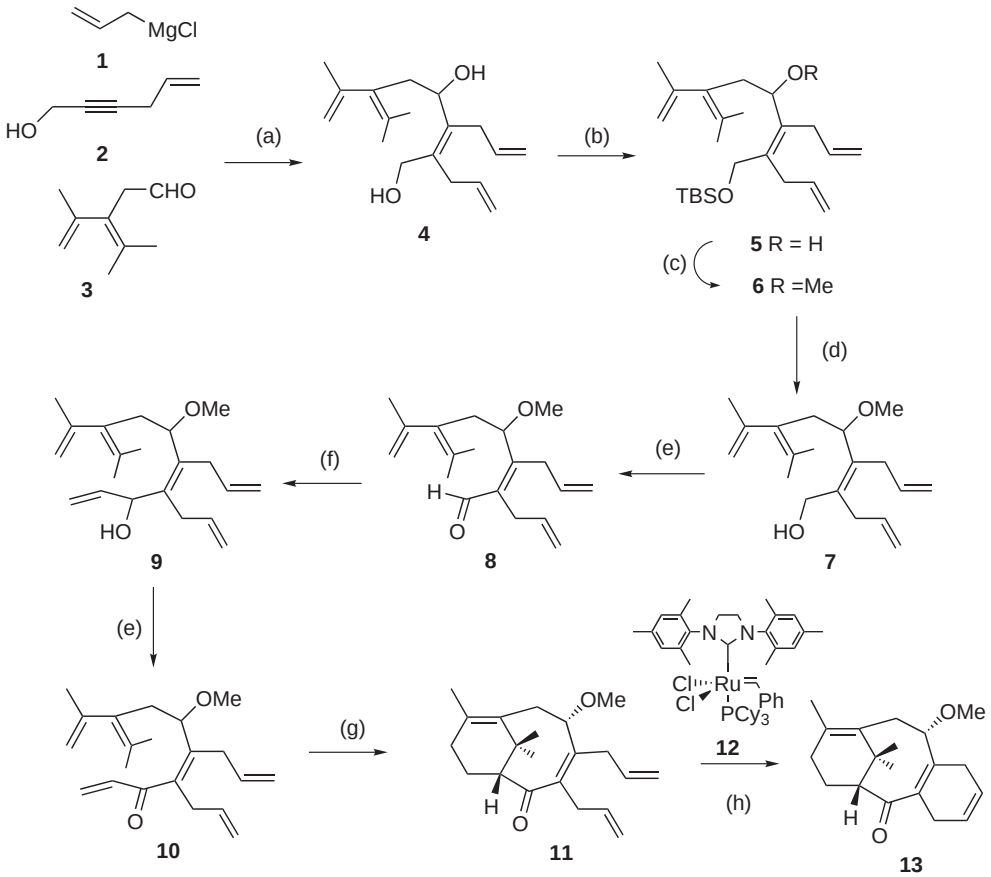
Synlett 2003, No. 9, Print: 11 07 2003.
Art Id.1437-2096,E;2003,0,09,1263,1266,ftx,en;S10403ST.pdf.

ISSN 0936-5214



Scheme 1 Retrosynthetic analysis for the ABC ring-system of Taxol®

the methoxy ether of the secondary alcohol **6**. Deprotection of the silyl ether with *n*-Bu_4NF released the primary alcohol **7**. Oxidation with IBX/DMSO/THF afforded the corresponding aldehyde **8**. Vinyl Grignard addition to this aldehyde furnished the vinylic alcohol **9** followed by a second IBX oxidation to provide the Diels–Alder precursor **10**. Exposure of this α,β-unsaturated ketone to either diethylaluminum chloride (–78 °C to 22 °C, 10 min) or boron trifluoride etherate (–78 °C to 22 °C, 2 h) afforded the AB ring adduct **11**, as a single diastereomer with the C9 methoxy group positioned below the ring. This was confirmed by the X-ray structure in Figure 2.



Scheme 2 Synthesis of the tricyclic ABC ring-system.
Reagents and conditions: (a) **1** (2.5 equiv), $MgCl_2$ (1 equiv), **2** (1 equiv, cyclohexane), reflux 18 h, **3** (1.3 equiv, ether) –78 °C, 1 h, 0 °C, 1 h, 22 °C, 1 h, 64%. (b) TBSCl, DMAP, CH_2Cl_2, 22 °C, 6 h, 81%. (c) NaH, MeI, THF, 0 °C to 22 °C, 6 h, 89%. (d) TBAF, THF, 22 °C, 3 h, 93%. (e) IBX/DMSO, THF, 0 °C to 22 °C, 3 h, 67–86%. (f) C_2H_3MgCl, THF, –78 °C, (1 h) to 0 °C (1 h), 60%. (g) $BF_3{\cdot}(OEt)_2$ (1 equiv) or Et_2AlCl (1 equiv), CH_2Cl_2, –78 °C, 2 h, 70–72%. (h) **11** (0.2 M CH_2Cl_2), **12** (5 mol%), 22 °C, 2 h, 93%.

The observed stereoselectivity arose from the chelation control provided by complexation of the Lewis-acid between the C2 carbonyl and C9 methoxy substituens as illustrated in Scheme 3. This forms a seven membered 'cycloheptene-like' arrangement that appears to be particularly favorable and may also be partially stabilized by association with the π-system of the double bond to facilitate achievement of the *endo* transition state and control the orientation of the ether group. Related Lewis acid mediated chelation effects are known to control the selectivity of both intermolecular[14] and intramolecular cycloadditions.[15]

Exposure of this diallyl compound **11** to the Grubbs catalyst **12**[12] under mild conditions at room temperature (22 °C, 2 h) afforded the desired ring C diene **13** in 93% yield and completed a concise route to the tricyclic nucleus in nine steps.

The X-ray structure illustrates the concave nature of this tricyclic skeleton and the close proximity of the C13 centre of the A ring with the ring C C4 methylene, a key stereochemical component of paclitaxel. Snyder and coworkers[9] have suggested the oxetane ring is not essential, however a replacement hydrogen bond acceptor is desirable. They have also noted that a C3-C8 double bond imparts increased rigidity to maintain Taxol®-like activity. These features are apparent in Figure 2. Consequently, selective functionalization of the C ring may lead to the introduction of therapeutically useful substituents.

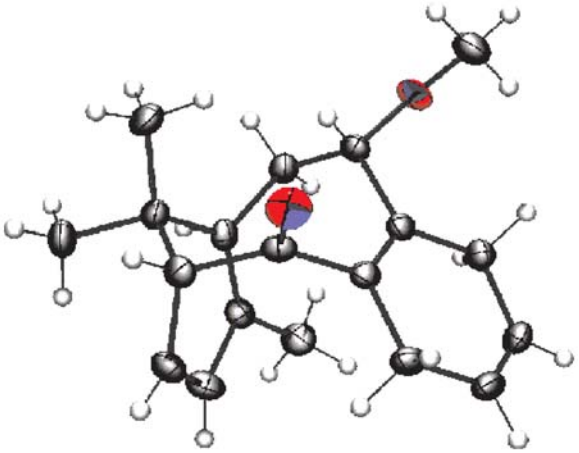


Figure 2 X-Ray structure of **13**.

In conclusion, we have established a direct carbometallation-cycloaddition-ring closing metathesis route to the tricyclic ABC taxane core in which the C ring diene is quite stable. The twisted nature of the cyclohexadiene inhibits its facile transformation to an aromatic ring. This suggests that further functional group manipulation will be feasible, in order to introduce useful functionality for further chemical transformations to induce the requisite biological activity. In addition, the starting materials are readily available and our propargyl alcohol based coupling protocol can be adapted to a variety of substitution patterns depending upon the synthetic objective.

Acknowledgement

We are grateful to the Canadian Breast Cancer Research Initiative (CBCRI, NCI, Canada) for financial support of this research. N. P. Villalva-Servín thanks the Government of Mexico and the University of Ottawa for Graduate Scholarships.

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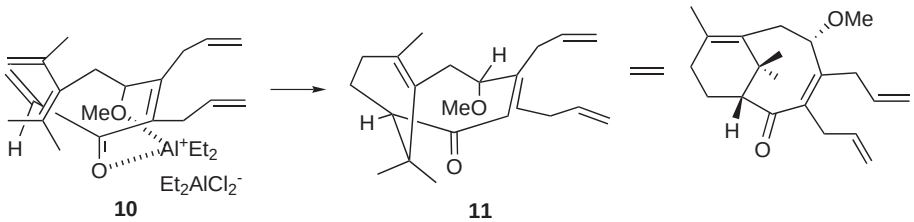

Scheme 3 Chelation control of IMDA transition state.

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